CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

A cost–utility analysis of atezolizumab in the second-line treatment of patients with metastatic bladder cancer

A. Parmar MD,*† M. Richardson MSc,† P.C. Coyte MA PhD,†‡ S. Cheng MD,*
B. Sander RN MBA MEcDev PhD,†‡§|| and K.K.W. Chan MD MSc PhD*†#

ABSTRACT

Background Despite initial promising results, the IMvigor211 clinical trial failed to demonstrate an overall survival (OS) benefit for atezolizumab compared with chemotherapy as second-line treatment for metastatic bladder cancer (mBC). However, given lessened adverse events (AEs) and preserved quality of life (QOL) with atezolizumab, there might still be investment value. To evaluate that potential value, we conducted a cost–utility analysis (CUA) of atezolizumab compared with chemotherapy from the perspective of the Canadian health care payer.

Methods A partitioned survival model was used to evaluate atezolizumab compared with chemotherapy over a lifetime horizon (5 years). The base-case analysis was conducted for the intention-to-treat (ITT) population, with additional scenario analyses for subgroups by IMvigor-defined PD-L1 status. Health outcomes were evaluated through life–year gains and quality-adjusted life–years (QALYs). Cost estimates in 2018 Canadian dollars for systemic treatment, AEs, and end-of-life care were incorporated. The incremental cost-effectiveness ratio (ICER) was used to compare treatment strategies. Parameter and model uncertainty were assessed through sensitivity and scenario analyses. Per Canadian guidelines, cost and effectiveness were discounted at 1.5%.

Results For the ITT population, the expected QALYs for atezolizumab and chemotherapy were 0.75 and 0.56, with expected costs of $90,290 and $8,466 respectively. The resultant ICER for atezolizumab compared with chemotherapy was $430,652 per QALY. Scenario analysis of patients with PD-L1 expression levels of 5% or greater led to a lower ICER ($334,387 per QALY). Scenario analysis of observed compared with expected benefits demonstrated a higher ICER, with a shorter time horizon ($928,950 per QALY).

Conclusions Despite lessened AEs and preserved QOL, atezolizumab is not considered cost-effective for the second-line treatment of mBC.

Key Words Cost–utility analyses, health technology assessments, atezolizumab, immunotherapy, metastatic bladder cancer

Curr Oncol. 2020 August:27(4)e386–e394 www.current-oncology.com

INTRODUCTION

The treatment of metastatic bladder cancer (mBC) represents a significant challenge, with 5-year survival rates of less than 5% in untreated disease and historically poor outcomes with systemic therapy[1]. Although first-line systemic treatment for mBC with cisplatin-based chemotherapy is associated with a high objective response rate, long-term survival gains are poor, with 5-year survival rates up to 15%[2]. Accordingly, many patients ultimately require second-line systemic treatment that, until recently, was associated with disappointing outcomes, including objective response rates of less than 30% and progression-free survival (PFS) benefits of only 2–3 months[3,4]. Further, given that mBC is largely a disease of patients who are elderly, with comorbidities, concern attends the use of cytotoxic chemotherapy in this population, particularly in the setting of an expected low benefit[5–7].

Correspondence to: Kelvin K.W. Chan, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Room T2-058, Toronto, Ontario M4N 3M5. E-mail: kelvin.chan@sunnybrook.ca ■ **DOI:** https://doi.org/10.3747/co.27.5459
Supplemental material available at http://www.current-oncology.com

Advances in immuno-oncology have revolutionized the treatment paradigm for patients with mBC. Given observed improvements in patient outcomes, systemic treatment with immunotherapy is proving to be a promising option for those patients[8–12]. For instance, KEYNOTE-045 established the efficacy of second-line immunotherapy with pembrolizumab, with a 27% reduction in the risk of mortality, translating to a 2.9-month improvement in median overall survival (OS)[9]. Further, given that, compared with cytotoxic chemotherapy, immunotherapy is typically associated with lesser toxicities, interest is growing in its use as a therapeutic option with potentially lessened adverse events (AEs) and an improved quality of life (QOL) profile in a patient population that is elderly and has comorbidities. However, with an annual cost upward of $100,000 per patient, the cost-effectiveness of immuno-oncology treatments becomes critical to evaluate.

Atezolizumab is a novel monoclonal antibody targeting PD-L1. It gained early Health Canada approval for use in patients with cisplatin-refractory mBC after phase II evidence demonstrated an objective response rate of up to 20% and promising survival outcomes[8]. Despite those initial encouraging results, the recently published phase III IMvigor211 trial failed to demonstrate an OS benefit[11]. However, given lower rates of AEs and a trend for improved QOL, use of atezolizumab might still be preferred over cytotoxic chemotherapy.

Accordingly, a cost–utility analysis (CUA) of atezolizumab from the Canadian health care payer perspective was conducted to evaluate whether improvements in the toxicity profile and QOL alone, in the absence of an OS benefit, could demonstrate cost-effectiveness. Further, scenario analyses were conducted to evaluate the influence of biomarker stratification (by PD-L1 expression level) and expected (compared with observed) treatment outcomes on cost-effectiveness.

METHODS

A CUA was conducted to compare atezolizumab with standard cytotoxic chemotherapy (that is, docetaxel, paclitaxel) as second-line systemic therapy for mBC. The Canadian health care payer perspective was adopted for the analysis. All model parameters were informed by the IMvigor211 trial, which evaluated those two strategies in patients with mBC who had progressed on first-line cisplatin-based chemotherapy. From the perspective of the Canadian health care payer, only costs associated with publicly funded medical interventions were incorporated into the model, including the costs of systemic therapy, selected AEs, and end-of-life care. Health outcomes of interest included life–year gains (LYGs) and quality-adjusted life–years (QALYs). Per Canadian guidelines, health outcomes and costs were discounted at 1.5%[13].

Model Structure

A partitioned survival model including 3 mutually exclusive health states—progression free, progressive disease, and death—was used to evaluate the two therapeutic strategies. Figure 1 outlines the partitioned survival model. Health outcomes and costs were calculated in 1-month time steps (cycle length) over a lifetime horizon of 5 years. The model was implemented using the TreeAge 2018 software application (TreeAge Software, LLC, Williamstown, MA, U.S.A.).

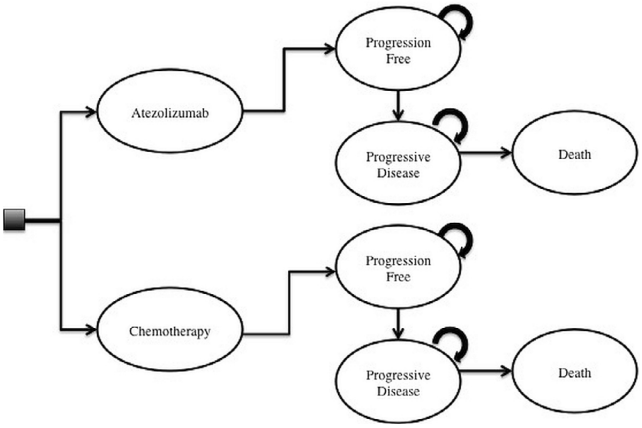

FIGURE 1 Partitioned survival model used for the cost–utility analysis of atezolizumab compared with chemotherapy for second-line systemic therapy in metastatic bladder cancer.

Progression and Survival Estimates

The published IMvigor211 PFS and OS curves were used to inform the probabilities for transition between health states[11]. The curves were digitized using the Plot Digitizer software application (http://plotdigitizer.sourceforge.net) to derive estimates of pseudo-individual patient data. Those data were then used to generate Kaplan–Meier (KM) survival curves.

Flexible spline-based parametric models based on the Royston–Parmar technique were used to fit the KM survival curves (with 95% confidence intervals) for both PFS and OS[14]. That technique has been shown to provide good fit to trial data in the evaluation of immunotherapy, given the unique KM curves and the potential for durable responses seen with those therapies[15,16]. The best-fit curve was derived based on visual inspection, statistical fit, and assessment for clinical plausibility. The best-fit curve was extrapolated to a lifetime horizon (supplemental Figure 1). The statistical analysis for curve generation and model fitting was completed using the R software application (R Foundation for Statistical Computing, Vienna, Austria)[17,18].

Utility Estimates

Utility estimates for the health states of progressive disease and progression free for both treatment strategies were derived from the IMvigor211 randomized controlled trial's EQ-5D (EuroQol Research Foundation, Rotterdam, Netherlands) preference-based estimates, as published in the U.K. National Institute for Health and Care Excellence economic evaluation report for the use of atezolizumab in mBC[11,19]. Because the EQ-5D utility estimates were derived from trial-based estimates over the course of treatment, disutilities associated with AEs were assumed to be included in the overall health-state utility estimate. Therefore, no additional disutilities were applied for AEs.

Cost Estimates

Costs for paclitaxel and docetaxel chemotherapy were derived from list price estimates, as reported in the published

recommendations from the pan-Canadian Oncology Drug Review's Expert Review Committee for pembrolizumab for the same indication[20]. Because cytotoxic chemotherapy is dosed by body surface area (BSA), cost estimates for an average BSA of 1.8 m^2 were used for the base-case analysis. For additional scenario analyses that included vinflunine, the cost estimate per cycle at a BSA of 1.8 m^2 was derived from the single-technology appraisal for vinflunine from the U.K. National Institute for Health and Care Excellence[21], converted to 2018 Canadian dollars. For atezolizumab, the recommended dose is a fixed dose for treatment in various cancer indications. The cost estimate for atezolizumab was therefore derived from the final pan-Canadian Oncology Drug Review's Expert Review Committee recommendations for atezolizumab in the treatment of metastatic non-small-cell lung cancer[22]. Systemic therapy costs for post-progression treatment were incorporated into the respective progressive disease health states, per rates informed by the IMvigor211 randomized controlled trial.

Costs for treatment-related AEs associated with hospital admission and documented medical costs were incorporated. Those costs included estimates for grade 3 or 4 anemia and febrile neutropenia, as derived from the published literature and the Canadian Institute for Health Information's patient cost estimator[23]. (https://www.cihi.ca/en/patient-cost-estimator)

Treatment with immunotherapy can be associated with unique immune-related AEs (irAEs). Because the IMvigor211 trial did not report specific rates of irAEs, rates and costs were derived from the published literature[24,25]. A one-time cost for end-of-life care in hospital was incorporated into our model as a terminal cost for the progressive disease health state. Given that many patients receive their end-of-life care in hospital, the associated cost estimate was derived from the published literature based on the reported mean length of stay in hospital at the end of life for Canadian patients with a diagnosis of cancer[26]. Costs associated with physician visits and routine diagnostic imaging were also included (supplemental Table I). All costs were inflated to 2018 Canadian dollars using the Canadian Health Consumer Price Index on 28 February 2019[27].

Base-Case Analysis

The base-case analysis was evaluated for patients in the trial intention-to-treat (ITT) analysis. Given that the CUA was conducted from the Canadian health care payer perspective, the base-case analysis was completed with the assumption that patients in the chemotherapy treatment arm received either docetaxel or paclitaxel chemotherapy, because vinflunine is not available in North America. Further, given the absence of approved immunotherapy for patients who progress on second-line treatment in Canada, chemotherapy was considered to be the only post-progression therapy, per the post-progression treatment rates informed by the IMvigor211 trial.

A probabilistic analysis was conducted to derive the expected health outcomes and lifetime costs of atezolizumab and chemotherapy. Cost estimates were characterized using gamma distributions, as derived by the mean and standard error (SE). Health state utility estimates and probabilities for events were characterized by beta distributions, as derived from the mean and SE. Estimates that did not have a value for SE (that is, costs of systemic therapy, grades 3 and 4 anemia and febrile neutropenia) were allocated at 25% of the expected range (supplemental Table I).

Scenario Analyses

Scenario analyses were conducted to explore model uncertainty, including analyses of patient subgroups according to PD-L1 expression level. The IMvigor211 trial represented their patient cohorts as ITT (PD-L1 staining on tumour infiltrating cells at ≥0%), IC1/2/3 (immune cell PD-L1 expression ≥1%), and IC2/3 (immune cell PD-L1 expression ≥5%). To evaluate changes in cost-effectiveness with enrichment based on PD-L1 expression level, scenario analyses for patients in the IC1/2/3 and IC2/3 populations were therefore conducted.

An additional scenario analysis was completed to evaluate the difference in observed compared with expected survival outcomes, through variation of the time horizon to 2 years (that is, within trial timelines) and to 10 years (that is, expected long-term survival benefit). Such an analysis is of particular importance in the evaluation of immunotherapy, given the notable "tail-on-the-curve" effect that is seen in many immunotherapy trials. Accordingly, to understand the effect of extrapolation of benefit beyond the observed effectiveness estimates, this scenario analysis generates a more accurate representation of potential benefit.

Further, a scenario analysis using standard parametric survival distributions to explore outcomes was also conducted. The best-fit parametric curve was derived according to the best statistical fit (Akaike information criterion), visual inspection, and clinical plausibility. Using that approach, the best-fit parametric survival distribution was log-logistic for PFS with atezolizumab and for OS with chemotherapy, and log-normal for PFS with chemotherapy and for OS with atezolizumab. The best-fit parametric curves were used to extrapolate survival beyond the 2-year trial duration to estimated lifetime horizons of 5 and 10 years (supplemental Figure 2).

Additional scenario analysis inclusive of vinflunine chemotherapy and post-progression use of immunotherapy in the chemotherapy arm, per trial specifics, was also conducted, because inclusion of those therapies might have influenced the effectiveness estimates.

Sensitivity Analyses

One-way sensitivity analyses of all costs associated with treatment (including drug costs, physician visits, and routine diagnostic imaging), probability and costs of AEs, and health-state utility estimates were conducted. Sensitivity analyses for chemotherapy drug cost estimates associated with BSAs of 1.5 m^2 and 2.2 m^2 were completed for paclitaxel and docetaxel. To understand the influence of the price of atezolizumab on cost-effectiveness, the cost of atezolizumab was varied to 20%, 50%, and 75% of base-case estimates. A sensitivity analysis for the cost of end-of-life care was conducted with estimates for in-hospital admission at the end of life ranging from 0 to 14 days[26]. The cost for anemia was varied from zero to the cost associated with 2 transfusions. For febrile neutropenia, the sensitivity analysis was conducted with costs ranging from a 2-night to an 8-night

stay in hospital. For irAEs, the sensitivity analysis was conducted for the cost of hospital lengths-of-stay of 4 through 8 days[24]. Sensitivity analyses were also conducted for the health state utilities, based on the SE noted in the EQ-5D estimates from the IMvigor211 trial[19] (supplemental Table I).

RESULTS

Base-Case Analysis

Table I outlines the expected health outcomes and lifetime costs for the base-case analysis. Atezolizumab was associated with an expected LYG of 1.25 compared with 0.97 for chemotherapy. The QALYs for atezolizumab and chemotherapy were 0.75 and 0.56 respectively. The expected costs associated with treatment with atezolizumab and chemotherapy over a lifetime horizon were $90,290 and $8,466 respectively. The resultant incremental cost-effectiveness ratio (ICER) for atezolizumab compared with chemotherapy was $430,652 per QALY. Figure 2 represents the cost-effectiveness acceptability curve and supplemental Figure 3 represents the incremental cost-effectiveness scatterplot for atezolizumab compared with chemotherapy.

Scenario Analyses

Biomarker Stratification

When the analysis was conducted by PD-L1 expression level, the ICERs for the IC1/2/3 and IC2/3 populations were $539,120 per QALY and $334,387 per QALY respectively. The lower ICER in the IC2/3 population appeared to be driven by greater derived benefit in the biomarker-selected population, as demonstrated by the larger QALY gain from treatment with atezolizumab in biomarker-selected populations (0.33 for the IC2/3 group compared with 0.19 for the ITT group and 0.15 for the IC1/2/3 group, Table II).

Observed and Expected Outcomes

The scenario analyses by time horizon also demonstrated variation in generated ICERs. In the ITT population, within the trial timeline (that is, 2 years), atezolizumab and chemotherapy generated QALYs of 0.57 and 0.51 respectively, resulting in an incremental QALY gain of 0.06 with atezolizumab. The incremental cost was $55,737 for atezolizumab compared with chemotherapy, resulting in an ICER of $928,950 per QALY (Table III).

Conversely, adoption of a long-term time horizon of 10 years generated QALYs of 0.90 (atezolizumab) and 0.56 (chemotherapy). The incremental cost was $103,839, resulting in an ICER of $305,408 per QALY (Table III). The improvement in ICER with adoption of a longer time horizon appears to be driven by differences in expected health outcomes, given the larger difference noted between the incremental QALYs (0.34, 10-year lifetime horizon; 0.19, 5-year lifetime horizon; and 0.06, within-trial horizon) and the lower difference noted in incremental costs ($103,839, 10-year lifetime horizon; $81,824, 5-year lifetime horizon; and $55,737, within-trial horizon). Further, the finding of a larger QALY gain for atezolizumab (Δ0.33 between the 10-year lifetime horizon and the within-trial horizon) than for chemotherapy (Δ0.05) through the use of a longer time horizon (up to 10 years), highlights the substantial effect that immunotherapy durable responses could have on the cost-effectiveness of those agents.

Scenario analyses using best-fit parametric survival curves for progression and survival estimates revealed an ICER of $383,807 per QALY for the ITT population over a 5-year time horizon (supplemental Table II). However, visual inspection of the parametric survival curves fitted to IMvigor211 KM PFS curves for atezolizumab revealed poor fit (supplemental Figure 2).

Scenario analysis with the inclusion of vinflunine and post-progression immunotherapy revealed an ICER of $321,610 per QALY in the ITT population. The lower ICER seen in that scenario analysis is likely secondary to the higher cost of chemotherapy with the inclusion of vinflunine, and the higher cost of post-progression immunotherapy after chemotherapy (supplemental Table III).

Sensitivity Analyses

Figure 3 presents the results of the deterministic sensitivity analysis, represented by a tornado diagram. The drug cost of atezolizumab and the health utility of the progression

TABLE I Base-case results[a]

Variable	Atezolizumab	Chemotherapy	Incremental
Expected cost (CA$)	90,290	8,466	81,824
Progression free	88,574	6,896	81,678
Progressive disease	1,716	1,570	146
Life year gain (LYG)	1.25	0.97	0.28
Progression free	0.72	0.52	0.20
Progressive disease	0.53	0.45	0.08
Quality-adjusted life years (QALYs)	0.75	0.56	0.19
Progression free	0.47	0.32	0.15
Progressive disease	0.28	0.24	0.04
Cost (CA$)			
Per LYG	—	—	292,228
Per QALY	—	—	430,652

[a] Health outcomes and costs for atezolizumab and chemotherapy for the base-case analysis. All costs are presented in 2018 Canadian dollars (CA$).

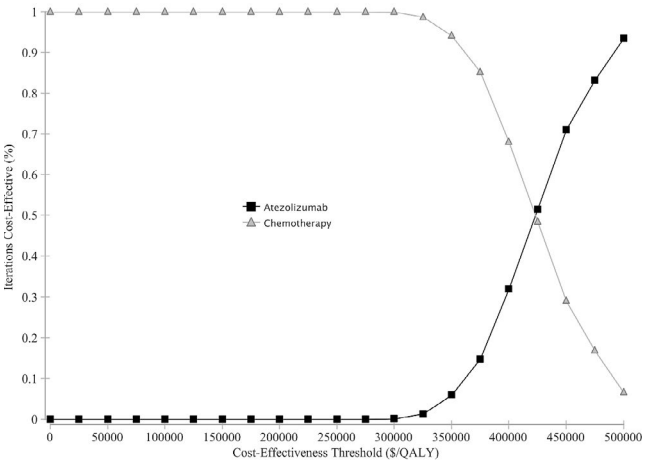

FIGURE 2 Cost-effectiveness acceptability curve for the base-case analysis. QALY = quality-adjusted life-year.

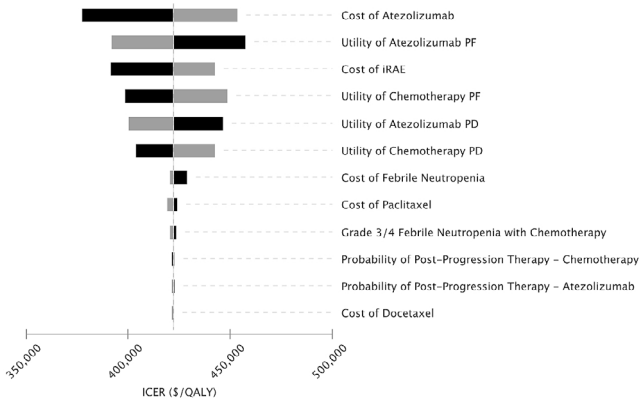

FIGURE 3 Tornado diagram of the one-way deterministic sensitivity analysis for the base case. PF = progression-free; iRAE = immune-related adverse event; PD = progressive disease; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

free health state for atezolizumab generated the greatest range of uncertainty in the cost-effectiveness of atezolizumab compared with chemotherapy. Sensitivity analyses with the cost of atezolizumab at 20%, 50%, and 75% of list price generated ICERs of $354,289, $232,784, and $133,400 per QALY respectively.

DISCUSSION

Through a CUA of atezolizumab for the second-line treatment of mBC from the Canadian health care payer perspective, atezolizumab, compared with standard-of-care cytotoxic chemotherapy, demonstrated an ICER of $430,652 per QALY. Therefore, despite lessened AEs and preserved QOL, at a cost-effectiveness threshold of $100,000 per QALY, atezolizumab is not considered cost-effective.

The treatment of mBC remains a challenge, given relatively ineffective and toxic therapies in a target population that is generally older and has comorbidities. Indeed, age and comorbidities have been shown to negatively affect the likelihood of receiving second-line chemotherapy in mBC[6,7,28]. Given the risks associated with platinum-based chemotherapy, it is clear that there is a fine balance between improving cancer-related outcomes and mitigating potential toxicities from systemic treatment[5,7]. Given a low perceived benefit with currently available regimens, together with the high likelihood of patients with mBC having risk factors for chemotherapy toxicity, clinicians and patients often make decisions to forego second-line chemotherapy, leading to poorer cancer-specific outcomes[6,28,29].

Accordingly, alternative systemic therapies such as immunotherapy offer hope to address the critical lack of reasonable systemic therapy options for patients with mBC. Although the demonstrated improvements in patient outcomes are modest with the use of immunotherapy in the second-line, the improvements in toxicity rates offer a foreseeable benefit for a larger proportion of patients with mBC[9,11]. Accordingly, evaluation of those agents has attracted ongoing interest[9–12].

The positive initial results demonstrated in the phase II IMvigor210 trial generated public interest, leading to Health Canada approval of atezolizumab in April 2017, less than 1 year after release of the results[8]. Although the subsequent phase III trial failed to demonstrate an OS benefit for immunotherapy compared with chemotherapy, the notable improvements in AE rates and the preserved QOL underscored the rationale for the present consideration of the potential investment value for atezolizumab[11]. Consideration of the trade-offs between survival benefits, QOL gains, and cost are evidently an important need when dealing with decisions in a patient population that has minimal reasonable alternatives. However, despite atezolizumab's favourable QOL and toxicity profile, the present analysis highlights the inability to justify investment in this agent.

The present analysis considered important exploratory analyses specific to the economic evaluation of immunotherapy. First is a consideration of biomarker-driven patient selection to enrich for patient response. In the current immuno-oncology landscape, PD-L1 status is a biomarker commonly used for patient stratification. Although PD-L1 expression level has not been shown to predict response with immunotherapy treatment across all cancer subtypes, clinically relevant differences in outcomes have been demonstrated for certain disease sites[30]. In the current literature of immunotherapy in the second-line treatment of mBC, a trend toward improvements in response and survival are seen with higher levels of PD-L1 expression[9,11,12,30]. That differential response affected our scenario analysis stratified by PD-L1 expression level, with the most favourable ICER seen in the subgroup with a PD-L1 expression level of 5% or greater as compared with an unselected population. In the absence of significant differences in clinical outcome by PD-L1 stratification, it is unclear whether stratification by that biomarker will influence Canadian drug funding and reimbursement decisions.

Further, the exploratory analyses by time horizon highlight the need for careful interpretation of CUAs for immunotherapy, given the differences in outcome related to the time horizon adopted. Best practice for evaluating

cost-effectiveness includes using a time horizon that encompasses a period sufficient to incorporate all relevant costs and outcomes associated with a particular intervention[31]. For most CUAs, extension of a time horizon typically leads to improvements in the generated ICER[32]. In the presence of real-world data, a CUA over a lifetime horizon provides important information about the true implications of an intervention with respect to real-world costs and outcomes. However, in the setting of extrapolated benefits, such as in a CUA modelled from trial data, the use of longer time horizons warrants caution, particularly in the setting in which expected survival is short[16,32].

Those concerns are exemplified in our scenario analyses by time horizon, demonstrating a difference in the generated ICERs for the scenarios by trial timeline and by estimated 10-year lifetime horizon. As shown by the larger difference in the incremental QALY gain (an increase by a factor of 5.7 from the within-trial to the 10-year lifetime horizon) than in the incremental cost (an increase in cost by a factor of 1.9 from the within-trial to the 10-year lifetime horizon), the variation in ICER by time horizon appears to be driven more by expected differences in health outcomes. Accordingly, in the era of immunotherapy, extrapolated effectiveness must be carefully interpreted, given the unique potential for long-term durable responses.

Ultimately, long-term real-world data will be required to better inform any significant differences that might exist in long-term expected and observed effectiveness estimates. However, until those long-term data for immunotherapy are available, consideration should be given to standardizing the reporting of CUAs with respect to within-trial and extrapolated lifetime time horizons such that information about the potential uncertainty in expected benefits is provided.

Our data also highlight the need for careful consideration of the methods used to generate progression and survival estimates for time-to-event data. Flexible spline-based modelling has previously been shown to be more representative for estimating survival in immunotherapy evaluations, underscoring our rationale for using that method in our base-case analysis[15,16,33]. However, despite the cumulative literature supporting use of those methods, few CUAs for immunotherapy in MBC have used them, generating their progression and survival estimates by standard best-fit parametric survival distributions instead[34]. Our exploratory analyses using best-fit parametric survival distributions generate some concern with the use of such methods, given that our data demonstrated an imperfect fit to the observed PFS data, and thus a potential to misrepresent the benefit for immunotherapy treatment. Future work characterizing the presence and magnitude of differences

TABLE II Scenario analyses by PD-L1 expression level[a]

Variable	Atezolizumab	Chemotherapy	Incremental
IC1/2/3 subgroup			
Expected cost (CA$)	90,198	9,330	80,868
Progression free	88,168	7,179	80,989
Progressive disease	2,030	2,151	–121
Life-year gain (LYG)	1.34	1.12	0.22
Progression free	0.72	0.54	0.18
Progressive disease	0.62	0.58	0.04
Quality-adjusted life years (QALYs)	0.80	0.65	0.15
Progression free	0.46	0.33	0.13
Progressive disease	0.34	0.32	0.02
Cost (CA$)			
Per LYG	—	—	367,581
Per QALY	—	—	539,120
IC2/3 subgroup			
Expected cost (CA$)	119,659	9,311	110,348
Progression free	117,507	7,531	109,976
Progressive disease	2,152	1,780	372
Life year gain (LYG)	1.56	1.06	0.50
Progression free	0.95	0.56	0.39
Progressive disease	0.61	0.50	0.11
Quality-adjusted life years (QALYs)	0.95	0.62	0.33
Progression free	0.62	0.35	0.27
Progressive disease	0.33	0.27	0.06
Cost (CA$)			
Per LYG	—	—	220,696
Per QALY	—	—	334,387

IC1/2/3 = PD-L1 positivity ≥ 1%; IC2/3 = PD-L1 positivity ≥ 5%.

[a] Subgroups by PD-L1 expression level, as defined in the IMvigor211 trial. All costs are presented in 2018 Canadian dollars (CA$).

TABLE III Scenario analyses by time horizon[a]

Variable	Atezolizumab	Chemotherapy	Incremental
Within-trial timeline			
Expected cost (CA$)	64,159	8,422	55,737
Progression free	62,207	6,678	55,529
Progressive disease	1,952	1,744	208
Life year gain (LYG)	0.96	0.88	0.08
Progression free	0.53	0.51	0.02
Progressive disease	0.43	0.37	0.06
Quality-adjusted life years (QALYs)	0.57	0.51	0.06
Progression free	0.33	0.31	0.02
Progressive disease	0.24	0.20	0.04
Cost (CA$)			
Per LYG	—	—	696,712
Per QALY	—	—	928,950
10-Year lifetime horizon			
Expected cost (CA$)	112,310	8,471	103,839
Progression free	110,288	6,900	103,388
Progressive disease	2,022	1,571	451
Life year gain (LYG)	1.48	0.97	0.51
Progression free	0.88	0.52	0.36
Progressive disease	0.60	0.45	0.15
Quality-adjusted life years (QALYs)	0.90	0.56	0.34
Progression free	0.58	0.32	0.26
Progressive disease	0.32	0.24	0.08
Cost (CA$)			
Per LYG	—	—	203,605
Per QALY	—	—	305,408

[a] Scenario analyses by time horizons of 2 years (that is, within trial) and 10 years. All costs are presented in 2018 Canadian dollars (CA$).

in outcomes between those methods should generate guidance for standardizing CUAs for immunotherapy.

Nevertheless, in all exploratory analyses of atezolizumab compared with cytotoxic chemotherapy, cost-effectiveness was not demonstrated, producing ICERs consistently greater than $100,000 per QALY and highlighting the lack of investment value in atezolizumab therapy. In particular, in the presence of a reasonable alternative (pembrolizumab, which demonstrated a significant OS benefit in the second line for patients with mBC), the availability of atezolizumab is unlikely to offer any additional benefit in this therapeutic space[9]. Furthermore, CUAs of pembrolizumab have demonstrated cost-effectiveness from the U.S. perspective at a cost-effectiveness threshold of $100,000–$150,000 per QALY (2017 U.S. dollars)[34]. In the analysis by Sarfaty *et al.*[34], who used historical thresholds of up to $100,000 per QALY, pembrolizumab was found not to be cost-effective from the Canadian health care perspective; however, it might be cost-effective when considered at cost-effectiveness thresholds up to $150,000 per QALY. In the United States, cost-effectiveness thresholds of up to $150,000 per QALY are now being considered, given the rising costs of novel efficacious therapies[35]. Yet concerns have been raised about the effect that adoption of higher cost-effectiveness thresholds might have for population-level health benefits, with growing discussion about the need for cost-effectiveness thresholds that also reflect country-specific resource constraints[36,37]. In Canada, no explicit threshold currently guides drug funding decisions, with ongoing discussion about to how to best promote individual patient access to efficacious therapies while reducing potential disinvestment to other health care sectors because of the funding of high-cost therapeutics[36].

With respect to our study assumptions, given that the analysis was conducted from the perspective of the Canadian health care payer, vinflunine and post-progression immunotherapy treatment were omitted from the included cost data. Although that assumption was necessary given the absence of those therapies from the Canadian perspective, the effectiveness estimates obtained from the trial data might have been influenced by incorporation of those therapies. However, given a large retrospective analysis demonstrating no significant difference in survival between second-line taxane and vinflunine chemotherapy, our assumption is considered to have had minimal impact[38]. Further, given that less than 25% of the patient population received post-progression immunotherapy after chemotherapy, the influence of the incremental effectiveness of post-progression immunotherapy compared with post-progression chemotherapy is felt to have been minimal. Moreover, our assumption to include AE costs for

only select grades 3 and 4 toxicities might have underrepresented the costs of AEs.

Notable limitations of our study include the absence of granular data to inform all estimates of cost and effectiveness. For instance, utilities from the appraisal of atezolizumab by the U.K. National Institute for Health and Care Excellence were used in our model; those utilities were based on United Kingdom–specific utility estimates, which might not be entirely representative of estimates for the Canadian population[39,40]. In addition, given the availability only of PFS and OS KM curves, a traditional Markov model was not possible, prompting the use of a partitioned survival analysis. A concern arising from our model is the existence of a post-progression survival benefit, as evidenced in our results, in which a LYG was observed in the post-progression health state. One clinical possibility that can be used to justify that finding is the possibility of pseudo-progression, which has been described in mBC treated with immunotherapy[41] and, accordingly, might be a contributing factor to the LYG observed in the progressed period. Despite that limitation, the use of a partitioned survival analysis for the analysis of oncology trials has not been shown to lead to substantially different results: available data have supported close approximation of trial outcomes[15,42,43]. Finally, despite the use of flexible spline-based models to estimate progression and survival estimates, an imperfect fit was noted in the early part of the generated OS curve. Although that imperfect fit might have influenced the pre-progression estimates for both chemotherapy and atezolizumab, the more accurate fit to the IMvigor211 PFS and OS curves obtained with the use of that method (compared with best-fit parametric survival distributions) highlights its preferential suitability to derive those estimates.

CONCLUSIONS

Despite observed improvements in AEs and preserved QOL, atezolizumab as second-line systemic therapy in the management of mBC was not found to be cost-effective from a Canadian health care payer perspective based on its current price. Given the effect of PD-L1 expression level on the generated ICER, stratification by biomarker selection might be considered for future CUAs of immunotherapy. Further, the variation observed with adopted time horizons warrants ongoing caution in the conduct and interpretation of CUAs of immunotherapy.

ACKNOWLEDGMENTS

The Canadian Centre for Applied Research in Cancer Control (ARCC) is funded by Canadian Cancer Society Research Institute grant no. 2015-703549.

Components of the present study are informed by data compiled and provided by the patient cost estimator at the Canadian Institute for Health Information (CIHI). The analyses, conclusions, and opinions expressed herein are those of the listed authors and not of CIHI.

This work was presented in part at the 2019 ARCC conference; Halifax, NS; 27–28 May 2019; and at the 2019 American Society of Clinical Oncology annual meeting; Chicago, IL, U.S.A.; 31 May–4 June 2019.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SC has received honoraria from Hoffman–La Roche AG, Merck and Co., and AstraZeneca. SC has also received fees as an advisory board member for Merck and Co. and AstraZeneca. MR has stock ownership in Veru. The remaining authors have no conflicts of interest to disclose.

AUTHOR AFFILIATIONS

*Odette Cancer Centre, Sunnybrook Health Sciences Centre, †Institute of Health Policy, Management and Evaluative Sciences, University of Toronto, ‡Toronto Health Economics and Technology Assessment Collaboration, University Health Network, §ICES, University of Toronto, ‖Public Health Ontario, and #Canadian Centre for Applied Research in Cancer Control, Toronto, ON.

REFERENCES

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. *Canadian Cancer Statistics 2017.* Toronto, ON: Canadian Cancer Society; 2017.
2. von der Maase H, Sengelov L, Roberts JT, *et al.* Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602–8.
3. Bellmunt J, Theodore C, Demkov T, *et al.* Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454–61. [Erratum in: *J Clin Oncol* 2010;28:182]
4. Vaughn DJ, Broome CM, Hussain M, Gutheil JC, Markowitz AB. Phase II trial of weekly paclitaxel in patients with previously treated advanced urothelial cancer. *J Clin Oncol* 2002; 20:937–40.
5. Bellmunt J, Mottet N, De Santis M. Urothelial carcinoma management in elderly or unfit patients. *EJC Suppl* 2006;14:1–20.
6. Galsky MD, Pal SK, Lin SW, *et al.* Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. *Bladder Cancer* 2018;4:227–38.
7. Galsky MD, Hahn NM, Rosenberg J, *et al.* Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. *J Clin Oncol* 2011;29:2432–8.
8. Rosenberg JE, Hoffman-Censits J, Powles T, *et al.* Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. *Lancet* 2016;387:1909–20.
9. Bellmunt J, de Wit R, Vaughn DJ, *et al.* Pembrolizumab as second-line therapy for advanced urothelial carcinoma. *N Engl J Med* 2017;376:1015–26.
10. Patel MR, Ellerton J, Infante JR, *et al.* Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. *Lancet Oncol* 2018;19:51–64.
11. Powles T, Duran I, van der Heijden MS, *et al.* Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. *Lancet* 2018;391:748–57.
12. Sharma P, Retz M, Siefker-Radtke A, *et al.* Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2017;18:312–22.
13. Canadian Agency of Drugs and Technology in Health (CADTH). *Guidelines for the Economic Evaluation of Health Technologies.* Ottawa, ON; CADTH: 2017.
14. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival

data, with application to prognostic modelling and estimation of treatment effects. *Stat Med* 2002;21:2175–97.
15. Gibson EJ, Begum N, Koblbauer I, *et al.* Modeling the economic outcomes of immuno-oncology drugs: alternative model frameworks to capture clinical outcomes. *Clinicoecon Outcomes Res* 2018;10:139–54.
16. Gibson E, Koblbauer I, Begum N, *et al.* Modelling the survival outcomes of immuno-oncology drugs in economic evaluations: a systematic approach to data analysis and extrapolation. *Pharmacoeconomics* 2017;35:1257–70.
17. Jalal H, Pechlivanoglou P, Krijkamp E, Alarid-Escudero F, Enns E, Hunink MGM. An overview of R in health decision sciences. *Med Decis Making* 2017;37:735–46.
18. Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Myriam Hunink MG, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: a tutorial. *Med Decis Making* 2018;38:400–22.
19. National Institute for Health and Care Excellence (NICE). *Single Technology Appraisal: Atezolizumab for Treating Metastatic Urothelial Cancer After Platinum-Based Chemotherapy.* London, U.K.: NICE; 2017.
20. pan-Canadian Oncology Drug Review (pCODR). *pCODR Expert Review Committee: Final Recommendation* [re: pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy]. Ottawa, ON: pCODR; 2018.
21. U.K. National Institute for Health and Care Excellence (NICE). *Final Appraisal Determination: Vinflunine for the Treatment of Advanced or Metastatic Transitional Cell Carcinoma of the Urothelial Tract.* London, U.K.: NICE; 2011.
22. pan-Canadian Oncology Drug Review (pCODR). *pCODR Expert Review Committee: Final Recommendation* [re: atezolizumab for the treatment of patients with locally advanced or metastatic non–small cell lung cancer who have progressed on or after systemic chemotherapy until loss of clinical benefit]. Ottawa, ON: pCODR; 2018.
23. Lagerquist O, Poseluzny D, Werstiuk G, *et al.* The cost of transfusing a unit of red blood cells: a costing model for Canadian hospital use. *Blood Transfus* 2017;12:375–80.
24. Chu JN, Choi JG, Ostvar S, *et al.* Cost of inpatient admissions for immune-related adverse effects from immune checkpoint inhibitor therapy: a single center experience [abstract 3060]. *J Clin Oncol* 2018;36:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.3060; cited 30 June 2020]
25. Maughan BL, Bailey E, Gill DM, Agarwal N. Incidence of immune-related adverse events with program death receptor-1– and program death receptor-1 ligand–directed therapies in genitourinary cancers. *Front Oncol* 2017;7:56.
26. Bekelman JE, Halpern SD, Blankart CR, *et al.* Comparison of site of death, health care utilization, and hospital expenditures for patients dying with cancer in 7 developed countries. *JAMA 2016;*315:272–83.
27. Consumer Price Index [supplement dated 18 January 2019]. In: Statistics Canada. *The Daily.* Ottawa, ON: Statistics Canada; 2019.
28. Noon AP, Albertsen PC, Thomas F, Rosario DJ, Catto JWF. Competing mortality in patients diagnosed with bladder cancer: evidence of undertreatment in the elderly and female patients. *Br J Cancer* 2013;108:1534–40.
29. Hurria A, Togawa K, Mohile SG, *et al.* Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011;29:3457–65.
30. Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis. *BMJ* 2018; 362:k3529.
31. Sanders GD, Neumann PJ, Basu A, *et al.* Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *JAMA* 2016;316:1093–103.
32. Kim DD, Wilkinson CL, Pope EF, *et al.* The influence of time horizon on results of cost-effectiveness analyses. *Expert Rev Pharmacoecon Outcomes Res* 12017;7:615–23.
33. Guyot P, Ades AE, Beasley M, Lueza B, Pignon JP, Welton NJ. Extrapolation of survival curves from cancer trials using external information. *Med Decis Making* 2017;37:353–66.
34. Sarfaty M, Hall PS, Chan KKW, *et al.* Cost-effectiveness of pembrolizumab in second-line advanced bladder cancer. *Eur Urol* 2018;74:57–62.
35. Institute of Clinical and Economic Review (ICER). *Overview of the ICER Value Assessment Framework and Update for 2017–2019.* Boston, MA: ICER; n.d.
36. The Working Group to Inform the Patented Medicine Prices Review Board (PMPRB). *PMPRB Steering Committee on the Modernization of Price Review Guidelines.* Ottawa, ON: PMPRB; 2019.
37. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016;19:929–35.
38. Barwitz L, Berger A, Zschaebitz S, *et al.* Efficacy of different second-line therapy regimens in metastatic urothelial carcinoma. *Open Urol Nephrol J* 2017;10:52–8.
39. Fang M, Oremus M, Tarride JE, *et al.* A comparison of health utility scores calculated using United Kingdom and Canadian preference weights in persons with Alzheimer's disease and their caregivers. *Health Qual Life Outcomes* 2016;14:105.
40. Lien K, Tam VC, Ko YJ, Mittmann N, Cheung MC, Chan KKW. Impact of country-specific EQ-5D-3L tariffs on the economic value of systemic therapies used in the treatment of metastatic pancreatic cancer. *Curr Oncol* 2015;22:e443–52.
41. Soria F, Beleni AI, D'Andrea D, *et al.* Pseudoprogression and hyperprogression during immune checkpoint inhibitor therapy for urothelial and kidney cancer. *World J Urol* 2018;36:1703–9.
42. Briggs A, Baker TM, Gilloteau I, *et al.* Partitioned survival versus state transition modeling in oncology: a case study with nivolumab in advanced melanoma [abstract RM3]. *Value Health* 2015;18:A338.
43. Goeree R, Villeneuve J, Goeree J, *et al.* Economic evaluation of nivolumab for the treatment of second-line advanced squamous NSCLC in Canada: a comparison of modeling approaches to estimate and extrapolate survival outcomes. *J Med Econ* 2016; 19:630–44.