Cost Utility of Nivolumab Versus Observation for the Adjuvant Treatment of Urothelial Carcinoma for Patients Who Are at High Risk of Recurrence: A Canadian Public-Payer Perspective

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INTRODUCTION

Urothelial Carcinoma

- Urothelial carcinoma (UC) is the growth of abnormal tissues in the urothelial cells lining the mucosal surfaces of the lower urinary tract (including the urethra and bladder) and upper urinary tract (including the renal pelvis and ureters).
- UC is the eighth most common cancer in Canada, leading to approximately 2,600 deaths each year. In Canada, approximately 12,500 new cases of bladder cancer are diagnosed each year.[1]

Nivolumab

- Nivolumab (NIVO) monotherapy is the first and thus far the only immuno-oncology treatment to demonstrate through a phase 3 study (CheckMate-274) a statistically significant improvement in disease-free survival (DFS) when compared with placebo (PBO) for patients with muscle-invasive UC at high risk of recurrence.[2-4]
- After a minimum follow-up time of 11.0 months in CheckMate-274, when compared with PBO, NIVO significantly improved DFS, with a hazard ratio (HR) of 0.70 (95% confidence interval [CI], 0.57-0.85) in the intention-to-treat (ITT) population.[3] Median DFS for the ITT population was 22.01 months (95% CI, 17.68-36.93) for the NIVO arm and 10.87 months (95% CI, 8.28-13.96) for the PBO arm.
- Extended follow-up results from the study confirm the benefit of NIVO compared with PBO after 31.6 months of minimum follow-up time.[4]
- The presented analysis is based on 11-month data instead of the extended follow-up, as these were the data available at the time of analysis. Overall survival data from the trial were still immature and not available.
- NIVO is approved by Health Canada and is recommended for reimbursement by the Canadian Agency for Drugs and Technologies in Health (CADTH) as a monotherapy for the adjuvant treatment of adult patients with UC who are at high risk of recurrence after undergoing radical resection.[5]

OBJECTIVE

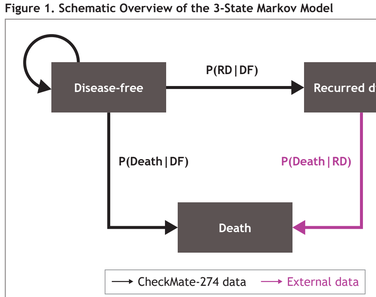
- To estimate the cost-utility of adjuvant UC treatment with NIVO versus observation (OBS) after radical resection from a Canadian public-payer perspective.

METHODS

Model Structure

- A 3-state Markov model was developed to evaluate incremental cost-effectiveness ratios (ICERs) and incremental cost-utility ratios (ICURs). The model states were labeled as disease-free (DF), recurred disease (RD) (consisting of local recurrence and distant recurrence), and death. The model spans a 30-year time horizon and evaluates discounted total costs, life-years (LYs) and quality-adjusted life-years (QALYs) (Figure 1).
- OBS was chosen as the comparator as patients are usually untreated in this setting.

Figure 1. Schematic Overview of the 3-State Markov Model

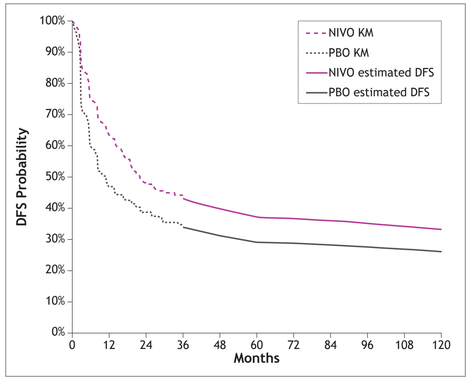


Note: Arrows represent the directions of possible transitions in the Markov model; Death is an absorbing state. P(RD|DF) = probability of moving from DF to RD; P(Death|DF) = probability of moving from DF to Death; P(Death|RD) = probability of moving from RD to Death.

Efficacy and Survival

- The main head-to-head efficacy measure for NIVO and OBS in the model was DFS based on the CheckMate-274 ITT population's 11-month data.
- A nonparametric approach was employed to predict the transitions from the DF state and the long-term DFS rates beyond the trial follow-up period to estimate the cumulative DFS over the 30-year time horizon. This differs from the conventional approach based on methods guidance from the Decision Support Unit at the National Institute for Health and Care Excellence,[6,7] where the Kaplan-Meier (KM) curves for DFS could be dressed with standard parametric and spline-based models.
- Baseline characteristics of patients in the deferred chemotherapy arm of the EORTC-30994 study[8] were similar with those of the PBO arm in CheckMate-274. There were also overlaps between the KM curves and the smoothed hazards of the DFS from the comparator arms of these trials. Another rationale behind the nonparametric approach was the difficulty of capturing the tail and the protocol-driven early behavior of the KM curves with standard parametric and spline-based models.
  - Due to limited follow-up in CheckMate-274, where KM curves extended only to month 54, the observed DFS data from the trial were used for the first 3 years.
  - Between years 3 and 5, the DFS rates for NIVO and OBS were predicted using their observed DFS rates at year 3 and assuming their DFS hazard trends to be identical to those in the control arm of EORTC-30994.
  - Patients who were DF at 5 years from randomization are considered functionally cured (i.e., not at risk of recurrence but only at risk of death according to general population mortality sourced from Canadian life table data[9]).
  - Relative proportions of deaths and recurrences among the first recurrence events along with the estimated DFS rates were used to derive the transitions from DF to RD and death until functional cure of the disease. The distribution of first recurrence events in the model were assumed to be constant until year 5.

Figure 2. Predicted Long-Term DFS for NIVO and OBS



- Due to a lack of overall survival data from CheckMate-274, transitions from the RD state were informed by the modeled survival data from the literature of the first-line metastatic UC (1L mUC).
  - Subsequent treatments for cisplatin-eligible patients included cisplatin plus gemcitabine, and carboplatin plus gemcitabine.
  - Long-term survival for cisplatin-eligible patients was estimated by fitting an exponential distribution to the data from clinical literature.[8,10] Selection of the exponential distribution instead of more complex parametric survival models was not expected to impact cost-effectiveness results.
  - In addition, to account for the fraction of cisplatin-ineligible patients who may receive pembrolizumab upon recurrence, the estimated long-term survival for patients receiving carboplatin plus gemcitabine was adjusted by an HR estimated from an indirect treatment comparison (ITC).[11]
  - Subsequent treatment shares from CheckMate-274 (specific to NIVO and OBS) were used to aggregate the long-term, treatment-specific post-recurrence survival (PRS) estimates to derive the transitions from the RD health state.

Inputs and Settings

- The analyses were performed from the perspective of a Canadian publicly funded healthcare payer.
- The model included costs of drug acquisition, administration, monitoring, subsequent therapies, adverse events (AEs), routine disease management, and end-of-life care.
- Drug acquisition costs were obtained from a previous pan-Canadian Oncology Drug Review (pCODR) guidance report.[12-14]
- Unit costs for drug administration, drug monitoring, and disease management were derived from the Ontario Schedule of Benefits 2021 cost data.[15]
- Canadian-specific terminal care costs were taken from the published literature.[16]
- Disease management resource use (outpatient visits, monitoring tests, surgery, and terminal care) was based on clinical expert input.[17]
- Only treatment-related grade 3/4 AEs for NIVO and OBS from CheckMate-274 were included. Canadian-specific AE costs were derived from published literature and publicly available data.[18-20]
- Time on treatment for NIVO was informed by the mean number of doses reported from CheckMate-274. In line with the protocol-mandated stopping rule, all acquisition costs were incurred within the first year.
- Patients in the RD state were assumed to receive subsequent radiotherapy, surgery, and/or active systemic anticancer therapy.
  - Proportion of patients receiving pembrolizumab therapy was sourced from the Checkmate-274. The remaining patients were distributed across chemotherapy regimens (cisplatin plus gemcitabine, and carboplatin plus gemcitabine) on the basis of market research conducted in Canada.
- Health state utility values were derived from CheckMate-274 using the EQ-5D-3L questionnaire and a Canadian value set.[21,22]
- QALY decrements due to grade 3/4 AEs were also included.
- An annual discount rate of 1.5% was applied for both costs and QALYs, and expected cost were estimated for base-case and scenario analyses using a probabilistic analysis that took the form of a Monte Carlo simulation, in line with CADTH guidelines.[23]
- The base-case settings for key model parameters are presented in Table 1.

Table 1. Key Base-Case Model Settings for Key Parameters

Parameter	Base-case value
Time horizon	30 years
Perspective	Canadian publicly funded healthcare payer
Population	Patients with UC at high risk of recurrence after undergoing radical resection
Cycle length	Weekly with half-cycle correction
Discounting	Annual 1.5% for costs and outcomes (QALYs, LYs)
Patient characteristics (baseline mean age, gender, BSA)	Average baseline characteristics of CheckMate-274 population 65.6 years, 76.2% male, 1.79 m^2
Survival extrapolation	
DFS	• Up to year 3: Reported KM data from CheckMate-274 • Between years 3 and 5: Hazard adjustment from EORTC 30994 • Beyond year 5: Background mortality adjustment from 5 years assuming functional cure of the disease
PRS	• Cis + Gem: OS data from EORTC 30987 trial[8] fitted with exponential distribution • Carb + Gem: OS data from EORTC 30986 trial[10] fitted with exponential distribution • Pembrolizumab: Modeled by applying an HR estimated by an ITC[11] to the Carb + Gem OS curve
Health state utilities	
DF	0.851
RD	0.769
Subsequent treatment	Subsequent treatment distribution was informed by CheckMate-274 data and local market research
Resource use	Based on clinical expert opinion[17]
Unit cost for resource use	Ontario Schedule of Benefits 2021 cost data[15]

BSA = body surface area; Carb + Gem = carboplatin and gemcitabine; Cis + Gem = cisplatin and gemcitabine; OS = overall survival.

RESULTS

Base Case

- Long-term mean survival was substantially higher for NIVO, with a 1.37 LY differential (total LYs: 7.86 vs. 6.49, respectively) compared with OBS (Table 2).
- Treatment with NIVO was associated with greater total QALYs compared with OBS (total QALYs: 6.64 vs. 5.46, respectively), resulting in an incremental QALY of 1.18.
- ICER and ICUR between NIVO and OBS were estimated as CAD 54,814/LY and CAD 64,046/QALY, respectively.

Table 2. Base-Case Probabilistic Results (Costs and Outcomes, Discounted)

Settings	NIVO	OBS
Total costs (CAD, $)	$100,458	$25,097
Drug acquisition	$79,273	$0
Drug administration	$1,262	$0
Monitoring	$967	$0
Disease management	$7,654	$8,007
Subsequent treatment	$3,386	$9,256
Surgery and radiotherapy	$28	$20
Terminal care	$7,335	$7,388
AEs	$553	$426
Total QALYs	6.64	5.46
DF health state	6.02	4.77
RD health state	0.62	0.69
Decrement due to AEs	−0.00379	−0.00216
Total LYs	7.86	6.49
DF health state	7.08	5.61
RD health state	0.78	0.88
ICER vs. OBS	$54,814/LY	
ICUR vs. OBS	$64,046/QALY	

Sensitivity Analysis

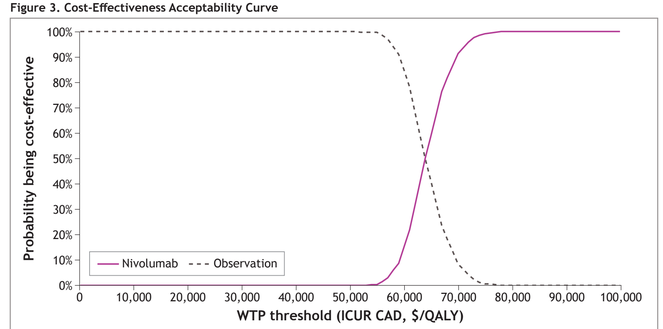
- Deterministic sensitivity analysis (DSA) was completed on key parameters using their 95% confidence intervals (when available), or plausible ranges, or varying base-case values by ± 20.
- The DSA showed that the parameters with the largest impact on the ICURs were the annual discount rate for QALYs (approximately −14% to +15% impact) followed by the utility value for NIVO patients in DF state (approximately −8% to +9% impact) and the utility value for OBS in DF state (approximately −6% to 7% impact). The remaining parameters that were tested in the DSA did not lead to more than 2% variation in the ICURs.
- The probabilistic sensitivity analysis confirmed the robustness of the model results. NIVO reaches almost 100% probability of cost-effectiveness at a willingness-to-pay (WTP) threshold of $76,000 and maintains cost-effectiveness at all WTP levels beyond this threshold (Figure 3).
- Scenario analyses with respect to PRS and model structure were explored. More specifically, scenario analyses included the following: (1) shortening the time horizon to 15 years; (2) assuming functional cure from year 4 and applying general population mortality hazards accordingly from year 4; (3) modeling DFS from baseline by best-fitting standard parametric model; (4) doubling the rate of the exponential distribution used to estimate PRS; (5) reducing the rate of the exponential distribution used to estimate PRS by half; and (6) including productivity losses associated with NIVO administration.
- Results from scenario analyses are presented in Table 3.
  - Doubling or halving the rate of the exponential distribution for PRS altered the ICUR by −1.2% and 5.3%, respectively, which shows paratremization of RD state limited impact on results.

Table 3. Results From Scenario Analyses

Settings	ICUR	
	Value (CAD, $/QALY)	% Change
Base case	64,046	N/A
15-year time horizon	84,794	+32.36%
General population mortality hazards applied from year 4	61,936	−3.89%
Independent generalized gamma model for DFS extrapolation from baseline[a]	67,001	+4.77%
PRS with double hazard rate	63,244	−1.20%
PRS with halved hazard rate	67,426	+5.34%
Productivity losses due to NIVO administration	64,340	+0.46%

[a] Generalized gamma was the best fit for both NIVO and OBS. Proportional hazards assumptions were violated. Therefore, independent models were fit. DFS rates from the fitted models were used up to year 5. Beyond year 5, background mortality adjustment from 5 years was used assuming functional cure of the disease.

Figure 3. Cost-Effectiveness Acceptability Curve



Note: Cost-effectiveness likelihoods stay constant beyond the WTP threshold $100,000.

CONCLUSIONS

- NIVO is estimated to be a life-extending treatment option compared with OBS for UC in Canada, which results in a compelling ICUR that is robust to uncertainties in the data.
- The majority of the health benefits of NIVO and OBS (86%-90% of total LYs and QALYs) were accrued in the DF state. Assumptions around the modeling of PRS did not have substantial impact on the health outcomes or ICURs.
- The functional cure assumption enables the nonparametric DFS modeling approach to be free of potential bias due to model selection.
  - With longer follow-up from CheckMate-274, the functional cure assumption can be validated, and dependency on EORTC-30994 can be minimized in nonparametric extrapolations of DFS.

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