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ORIGINAL RESEARCH ARTICLE

Evaluation of Cost-Effectiveness of Adjuvant Osimertinib in Patients with Resected EGFR Mutation-Positive Non-small Cell Lung Cancer

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Abstract

Background For many patients with resected epidermal growth factor receptor mutation-positive (EGFRm) non-small cell lung cancer (NSCLC), current standard of care (SoC) is adjuvant chemotherapy; however, disease recurrence remains high. Based on positive results from ADAURA (NCT02511106), adjuvant osimertinib was approved for treatment of resected stage IB−IIIA EGFRm NSCLC.

Objective The aim was to assess the cost-effectiveness of adjuvant osimertinib in patients with resected EGFRm NSCLC.

Methods A five-health-state, state-transition model with time dependency was developed to estimate lifetime (38 years) costs and survival of resected EGFRm patients treated with adjuvant osimertinib or placebo (active surveillance), with/without prior adjuvant chemotherapy, using a Canadian Public Healthcare perspective. Transitions between health states were modeled using ADAURA and FLAURA (NCT02296125) data, Canadian life tables, and real-world data (CancerLinQ Discovery®). The model used a 'cure' assumption: patients remaining disease free for 5 years after treatment completion for resectable disease were deemed 'cured.' Health state utility values and healthcare resource usage estimates were derived from Canadian real-world evidence.

Results In the reference case, adjuvant osimertinib treatment led to a mean 3.20 additional quality-adjusted life-years (QALYs; (11.77 vs 8.57) per patient, versus active surveillance. The modeled median percentage of patients alive at 10 years was 62.5% versus 39.3%, respectively. Osimertinib was associated with mean added costs of Canadian dollars (C$)114,513 per patient and a cost/QALY (incremental cost-effectiveness ratio) of C$35,811 versus active surveillance. Model robustness was demonstrated by scenario analyses.

Conclusions In this cost-effectiveness assessment, adjuvant osimertinib was cost-effective compared with active surveillance for patients with completely resected stage IB−IIIA EGFRm NSCLC after SoC.

1 Introduction

Approximately 30% of patients with non-small cell lung cancer (NSCLC) present with resectable disease [1–3], for whom primary treatment is surgical removal of the primary tumor [4]. Platinum-based chemotherapy regimens are recommended as post-operative adjuvant therapy for patients with stage II−IIIA disease and select patients with stage IB disease [5, 6]. Standard practice in Canada reflects European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology/Cancer Care Ontario (ASCO/CCO) treatment guidelines [5, 6], with most jurisdictions recommending adjuvant chemotherapy for stage II−IIIA patients. After resection and receiving adjuvant chemotherapy, patients undergo a 'watch and wait' or active surveillance period.

Although treatment for patients with stage IB−IIIA NSCLC is of curative intent, a high proportion of patients have disease recurrence or die. Five-year survival rates range from 36% for stage IIIA NSCLC to 68% for stage IB disease [7]. Disease recurrence rates after adjuvant chemotherapy range from approximately 45% for stage IB to 76% in stage III NSCLC, over a median follow-up of 5.2 years [8]. The risk of dying increases greatly after disease recurrence in all stages of resected NSCLC, so delaying or preventing recurrence is crucial to improving long-term outcomes [9].

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Key Points for Decision Makers

The cost-effectiveness of osimertinib in Canada for the adjuvant treatment of patients with stage IB–IIIA non-small cell lung cancer (NSCLC) was assessed using a state-transition model with time dependency based on data from the ADAURA trial. FLAURA trial and real-world patient population data were also used because of the immaturity of ADAURA's overall survival data. The model structure and selected data sources were deemed appropriate by several health technology assessment agencies globally.

Our model estimated that more patients would be alive at 10 years on osimertinib (62.5%) versus active surveillance (39.3%); adjuvant osimertinib was cost-effective in resected epidermal growth factor receptor mutation-positive NSCLC, with an incremental cost-effectiveness ratio of 35,811 Canadian dollars versus active surveillance.

Results presented here differ markedly from analyses completed by the Canadian Agency for Drugs and Technologies in Health (CADTH). Differences in assumptions regarding cure and long-term disease-free survival recurrence rates drove model result differences. Scenario analyses are presented here to better characterize the heterogeneity in model setup and resulting outcomes.

As with metastatic epidermal growth factor receptor mutation-positive (EGFRm) NSCLC, targeted therapies in the resectable setting may offer an improvement in survival [10].

Osimertinib is a third-generation, irreversible, central nervous system (CNS)-active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), and has demonstrated benefit in progression-free survival (PFS) and overall survival (OS) in patients with EGFRm metastatic NSCLC [11–16]. The pivotal study supporting osimertinib as an adjuvant therapy is the phase III, double-blind ADAURA trial (NCT02511106) [10], which demonstrated a statistically significant disease-free state (DFS) benefit with osimertinib versus placebo in patients with completely resected stage IB–IIIA EGFRm NSCLC (hazard ratio [HR] 0.20; 99.12% confidence interval [CI] 0.14–0.30, $p < 0.001$; 11% and 46% maturity for osimertinib and placebo, respectively). OS data were immature (4%) at the time of the unplanned interim exploratory analysis.

Based on ADAURA data, osimertinib was approved by the Food and Drug Administration (FDA) [17], European Medicines Agency (EMA) [18], and other global authorities as adjuvant treatment after tumor resection in patients with EGFRm (ex19 del or L858R) NSCLC. A critical question in all regions is what is the incremental value of the treatment regimen containing adjuvant osimertinib. To estimate incremental value, payers often require estimates of the survival benefits of novel oncology treatments to inform reimbursement decisions; modeling long-term survival benefits of treatments can also be valuable for clinical decision-making. Adjuvant osimertinib was approved by Health Canada on January 18, 2021 [19]; we present the economic evaluation from a Canadian perspective in this setting, which was submitted by the sponsor to support a Canadian health technology assessment (HTA). The objective was to evaluate osimertinib's cost-effectiveness as an adjuvant treatment for patients with EGFRm NSCLC after complete tumor resection (with or without prior adjuvant chemotherapy), with costs and efficacy associated with subsequent treatments for patients with disease progression or relapse being estimated.

2 Methods

2.1 Model Structure

A state transition model with time dependency was developed (Excel®, Microsoft, Washington, USA), using a cycle length of 1 month, to estimate the costs and survival of patients with resectable EGFRm NSCLC based on the ADAURA trial. The model structure comprised five mutually exclusive health states: 'disease free' (DF), 'local/regional recurrence' (LRR), 'first-line treatment for distant metastatic NSCLC' (1L DM), 'second-line treatment for distant metastatic NSCLC' (2L DM), and 'Death' as the absorbing state (Fig. 1a). Assumptions in the model, model structure and treatment pathway were reviewed and validated with clinical experts (authors PC, BM, and BS, through advisory board and consultation).

Patients in the DF state were modeled to transition to distant metastatic disease, local/regional disease (which can be treated with curative intent again), relapse with distant metastatic disease or be cured in stage IB–IIIA and remain DF indefinitely. Distant metastatic disease required two health states as costs and efficacy of drugs in 1L DM (osimertinib) varied markedly from 2L DM (platinum doublet chemotherapy [PDC] or taxanes).

2.2 Treatment Pathway

The modeled treatment pathway compared two different adjuvant treatment arms following complete tumor resection: the osimertinib arm and the active surveillance arm

(Fig. 1b). Further details are available in 'Supplementary Methods' (see the electronic supplementary material).

Data from ADAURA were used to inform the transitions out of the DF health state. Given the earlier than expected read-out of ADAURA [10], limited long-term follow-up data were available; therefore, data were supplemented with an 'ADAURA-like' cohort of patients with resected EGFRm NSCLC who had relapsed into the LRR state. Data for these patients were obtained from the US electronic medical record CancerLinQ Discovery® database [20–22] (see 'Supplementary Methods'), and this modeled population was used to inform transitions out of the LRR health state. The CancerLinQ cohort had comparable patient demographic characteristics to patients in the ADAURA trial, with similar proportions of patients across disease stages (Supplementary Table S1, see the electronic supplementary material). Data from the phase III, double-blind trial FLAURA (NCT02296125) [11, 16], which evaluated first-line osimertinib versus comparator EGFR-TKI (erlotinib or gefitinib) in patients with EGFRm advanced NSCLC, was used to inform transitions in the 1L DM and 2L DM health states. Time to treatment discontinuation was used as a proxy for progression as longer follow-up data were available for this parameter than for PFS. Therefore, time to treatment discontinuation was used to model progression from 1L DM to 2L DM. For patients expected to receive osimertinib on relapse to 1L DM from DFS, data from the osimertinib arm of the FLAURA trial were used (Supplementary Table S1).

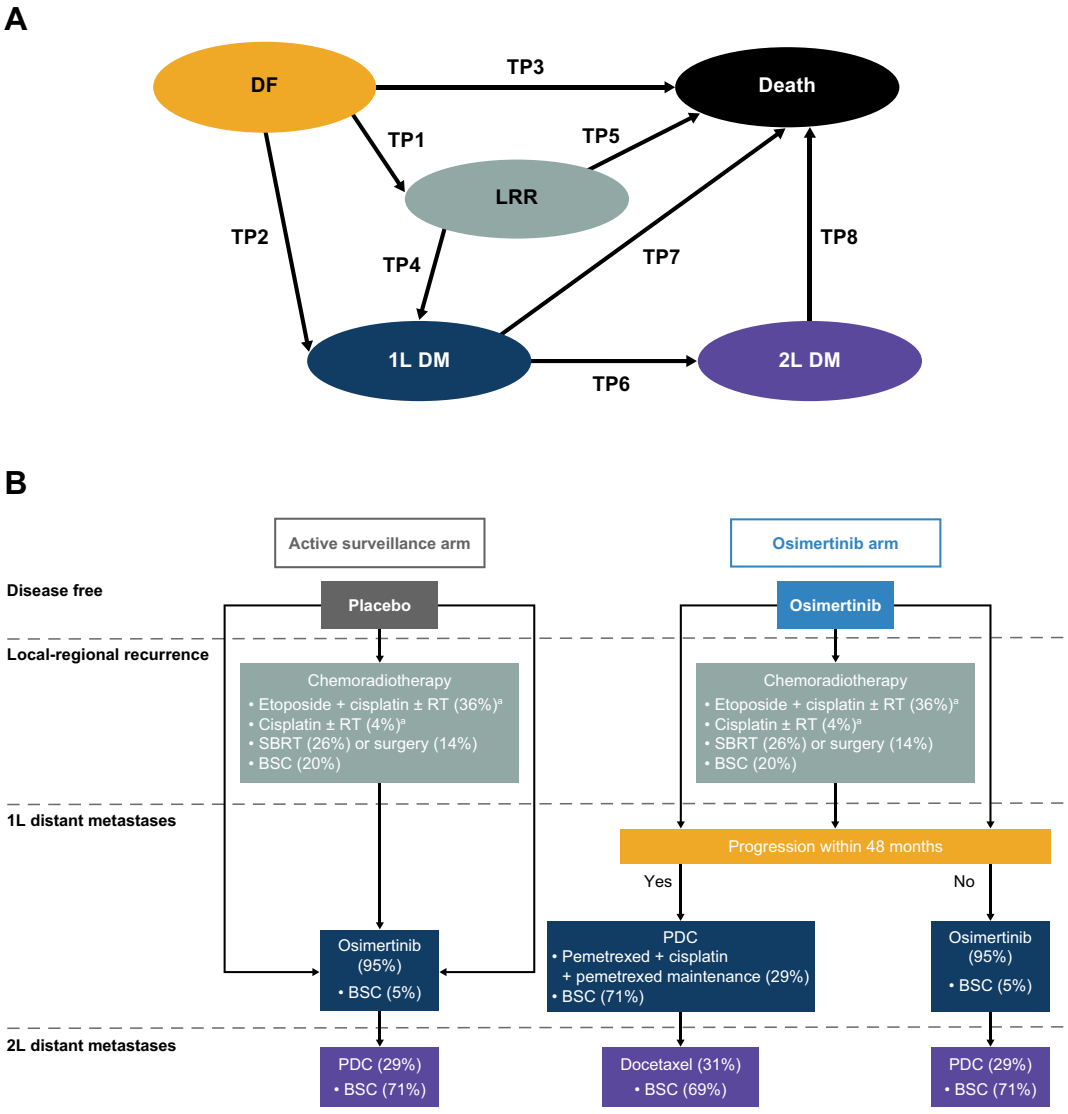

Fig. 1 Model and treatment pathway. **a** Five-health-state model structure and **b** treatment pathway modeled. *1L* first-line, *2L* second-line, *BSC* best supportive care, *DF* disease free, *DM* distant metastases, *LRR* local/regional recurrence, *PDC* platinum doublet chemotherapy, *RT* radiotherapy, *SBRT* stereotactic body radiation therapy, *TP* transition probability. [a]Of which, 55% of patients received radiotherapy

Patients not expected to receive osimertinib on relapse (see Fig. 1b, patients in the osimertinib arm who progressed within 48 months) were modeled using the comparator EGFR-TKI arm, with an HR [23] applied to correct for the use of PDC instead of comparator EGFR-TKI. The HR for 2L DM to Death is recalibrated to ensure that the combined HR for 1L DM to 2L DM and 2L DM to Death reflects the OS HR from 1L DM to Death in Holleman et al. [23]. Validation of the modeling of the placebo arm of the ADAURA trial versus Canadian real-world data [24] was assessed by calculation of the mean absolute percentage error (MAPE) and correlation coefficient (R^2). Key clinical inputs are listed in Supplementary Table S3.

Competing risk events were censored for each transition throughout the model [25]. As an example, for the transition from DF to LRR, DM and death events were censored. Cause-specific hazards for each transition were calculated and applied by state-transition modeling to derive overall state-transition probabilities for each of the five states in the model.

Standard parametric survival modeling was used to model the transitions between health states. For all transitions to 'death', the maximum hazard from the selected distribution or general population mortality (GPM) was utilized. Data from each source (ADAURA for DF, CancerLinQ for LRR, and FLAURA for 1L DM and 2L DM) were extrapolated using standard parametric survival modeling to the lifetime horizon and assessed for 'goodness of fit' using visual inspection further informed by insights of clinical experts, the Akaike information criterion, Bayesian information criterion, and Schoenfeld residuals test [26, 27]. The generalized gamma distribution was selected as the preferred curve fit for the reference case analysis. Given that the proportional hazards assumption did not hold for all transitions, only individual fits were applied. The parametric models used are provided in Supplementary Table S2, extrapolations are provided in Supplementary Figures S1–S3, and goodness-of-fit information for each transition is supplied in Supplementary Tables S4–S9.

2.3 Outcomes

In the model, cost-effectiveness was measured both in costs (total and incremental) and health outcomes: quality-adjusted life-years (QALYs) and life-years (LYs). The incremental cost-effectiveness ratio (ICER) both of incremental cost/QALY and incremental cost/LY were calculated.

2.4 Time Horizon

Patients randomized in ADAURA had a mean age of 62 years, and clinical experts anticipated resection to lead to cure in some patients, so a lifetime was defined as the time required to achieve < 1% survival in both treatment arms, which was estimated to be 100 years of age. Therefore, the model considered a lifetime horizon of 38 years.

2.5 Assumptions

Based on clinical expert feedback, 95% of patients who remained DF for 5 years after the completion of treatment for resectable EGFRm NSCLC were deemed 'cured.' For the adjuvant osimertinib arm, this was after 3 years of adjuvant osimertinib treatment plus 5 years of no treatment; for the active surveillance arm, this was 5 years after the start of placebo ('no') treatment. Implementation of this assumption was based on long-term DFS results from the POTENT real-world study, a retrospective chart review in patients with resected stage IB−IIIA EGFRm NSCLC from three Canadian cancer centers [24] and the preference of clinical experts. The POTENT study showed the rate of relapse to markedly decrease at year 4 then to plateau in all treatment groups by year 6. The resulting model implementation is a linear increase from 0% 'cured' at year 4 to 95% 'cured' at the beginning of year 6 in the active surveillance arm, and a similar transition from 0% 'cured' at year 4 to 95% 'cured' at the end of year 8 in the osimertinib arm in the DF health state. Patients predicted to be 'cured' are assumed to be at no elevated risk of death due to NSCLC.

GPM from Canadian life tables [28] supplemented data sources where extrapolations for the transitions to 'death' had lower probability of death from the trial data than the national average (corrected for age and sex), or when patients were assumed to be 'cured.' A standardized mortality rate was applied to the GPM hazard to account for additional deaths that may occur due to the higher risk of death among patients in the LRR and DM health states; this was estimated based on excess mortality associated with BRCA mutation in other cancer types [29]. For 'cured' patients in the DF health state, GPM without adjustment was considered.

Based on expert opinion, it was assumed that patients who received adjuvant osimertinib could receive retreatment with osimertinib in the 1L DM health state if disease progression took place ≥ 48 months from the start of adjuvant osimertinib treatment. No efficacy data are available for patients retreated with osimertinib in the 1L DM health state, the efficacy is assumed to be the same as for patients receiving osimertinib for the first time. This assumption was validated by clinical experts.

2.6 Perspective

The analysis was conducted from a Canadian Public Healthcare perspective. Model requirements were aligned to Canadian Agency for Drugs and Technologies in Health

(CADTH) guidelines [30]. Ontario costs were used in the reference case analysis.

2.7 Health State Utility Values

The reported utility value for osimertinib used in the metastatic setting in patients with stable disease was 0.85 (standard error [SE] 0.027), which had been previously accepted by the Institute National d'Excellence en Santé et en Services Sociaux (INESSS) and the pan-Canadian Oncology Drug Review (pCODR) in the HTA assessment for first-line osimertinib [31]. It was therefore assumed that patients receiving osimertinib in an earlier stage setting must have a utility that is no lower than for the metastatic setting, and thus the utility of 0.85 was used as the reference case value for osimertinib and active surveillance for the DF and LRR states. Disutilities for grade ≥ 3 adverse events (AEs) were applied to the DF state, with no differentiation in AEs assumed in later states. An age-adjustment to the utility in every state was applied [32]. Literature-based health state utility values (HSUVs) for the DF and DM health states were available from Canadian real-world evidence (RWE) [24, 33] and are used as the reference case. Utility data in ADAURA were collected in the Short Form 36 Health Survey Questionnaire (SF-36) and needed to be mapped to the EuroQoL 5-dimensions (EQ-5D) before a Canadian tariff could be applied. Since there was no direct mapping algorithm available from SF-36 to EQ-5D, an intermediate step had to be performed, mapping SF-36 to SF-12. SF-12 was then mapped to EQ-5D-3L answers, on which the Canadian tariff was applied. The many intermediate steps did make the results unreliable and not suited for the reference case. Therefore, the results are only used in scenario analyses. HSUVs are supplied in Supplementary Table S3 (see the electronic supplementary material).

2.8 Healthcare Resource Usage

The model included costs associated with drug acquisition, treatment administration, healthcare resource use, subsequent therapy and AEs. Key costs are shown in Supplementary Table S3 (see the electronic supplementary material). For resource use, in addition to costing inputs by expected utilization and unit costs, the model also allows costing of resource utilization and administration costs through a 'top-down' approach using data from a recent Institute for Clinical Evaluative Sciences (ICES) costing analysis of real-world management for patients who were DF, patients with LRR, and metastatic NSCLC in Ontario [31]. In the reference case analysis, costs for drug acquisition (at list price), AE management and EGFR mutation testing were micro-costed, while all other costs were derived from ICES costing studies [34]. Costs and effects were discounted at 1.5% per year, in accordance with CADTH guidelines [30]. Drug costs and other model inputs were obtained from Ontario databases, where possible, and publications. All costs are provided in Canadian dollars (C$). Costs from the past were inflated to 2020 using the Canadian Consumer Price Index.

2.9 Reference Case

The reference case was conducted as a probabilistic analysis to account for uncertainty of the underlying parameter estimates [30]. The choice of distribution was selected based on recommendations of Briggs et al. [35].

When possible, the reported SEs from the data sources, or alternatively standard deviation (SD) or 95% CIs used to calculate an SE, were used to define parameter uncertainty. Otherwise, when not reported, the SE was estimated as 10% of the default value. The probabilistic analyses used 1500 iterations, as this gave less than 1% deviation in the mean ICER.

2.10 Sensitivity Analyses and Scenario Analyses

One-way deterministic sensitivity analysis was performed to identify key model drivers. Parameters were varied one at a time between their upper and lower 95% CIs, which were determined using SEs when available (e.g., for utilities), or using SEs estimated as ± 10% the mean where measures of variance were not available.

Probabilistic scenario analyses were conducted as for the reference case to explore parameter uncertainty and test model robustness.

3 Results

3.1 Reference Case Analysis

The model predicted that patients with completely resected stage IB−IIIA EGFRm NSCLC who received adjuvant osimertinib treatment would have an increased life expectancy compared with patients with active surveillance. Patients who received adjuvant osimertinib were predicted to spend longer in the DF health state than those in the active surveillance arm, and this was estimated to result in a longer OS. Patients who received placebo and underwent active surveillance were more likely to transition directly to the 1L DM health state, thus leading to a shorter OS compared with patients who received adjuvant osimertinib.

In the reference case, adjuvant osimertinib treatment was predicted to lead to a clinically meaningful gain in QALYs

of a mean 11.77 (95% CI 8.58–14.95) QALYs per patient compared with 8.57 (95% CI 7.24–10.05) for active surveillance, that is 3.20 mean additional QALYs per patient (Table 1). Adjuvant osimertinib treatment was predicted to lead to a mean 14.02 (95% CI 10.38–17.65) LYs compared with 10.32 (95% CI 8.78–12.03) for active surveillance. Collectively, adjuvant osimertinib treatment was predicted to nearly double the QALYs and LYs accrued in the DF state. In the DF state, mean 10.31 (95% CI 6.71–14.37) versus 5.97 (95% CI 4.14–7.95) QALYs and mean 12.13 (95% CI 7.89–16.91) versus 7.03 (95% CI 4.88–9.36) LYs were estimated in the osimertinib and the active surveillance arms, respectively. This predicted increase in the proportion of time spent DF led to a modeled median percentage of patients alive at 5 years of 84.1% (95% CI 65.1−94.6) for osimertinib versus 69.8% (95% CI 61.7−77.4) for active surveillance. There was an estimated 23.2% absolute improvement in patients alive at 10 years: the modeled median percentage of patients alive at 10 years was 62.5% (95% CI 42.3−79.3) for osimertinib versus 39.3% (95% CI 30.5−49.2) for active surveillance. Adjuvant osimertinib was associated with mean added costs of C$114,513 per patient (Table 1). Supplementary Table S10 shows a breakdown per category (see the electronic supplementary material). The resulting probabilistic ICER (incremental cost per QALY) for adjuvant osimertinib versus the active surveillance arm was C$35,811, with 95% CI of 59,565–164,779 for the incremental cost and 95% CI of − 0.28 to 6.79 for the QALY. The deterministic sensitivity analysis showed a similar ICER of C$37,028, indicating the robustness of the model. The importance of the parameters in the model on the ICER are summarized in Fig. 2a.

The robustness of the model is also highlighted when comparing modeled DFS and OS rates with RWE; the model-derived DFS and OS rates were validated by real-world DFS and OS rates in patients with EGFRm NSCLC in Ontario (Fig. 3). Modeled placebo arm survival aligned well to real-world data, with an MAPE of 22.5% and an R^2 of 0.98. This validation also supports the lifetime horizon as applied within the model. At a willingness-to-pay threshold

Table 1 Reference case cost-effectiveness analysis

	Active surveillance	(95% CI)	Osimertinib	(95% CI)
Costs per health state (C$)[a]				
DF	18,118	(14,761–21,475)	277,744	(273,558–281,929)
LRR	22,595	(9198–35,992)	15,900	(902–30,898)
1L DM	170,522	(137,272–203,773)	52,646	(30,357–74,936)
2L DM	36,265	(27,164–45,367)	15,724	(6489–24,959)
Total costs (C$)[a]	247,501	(188,394–306,607)	362,014	(311,306–412,722)
Incremental costs (C$)[a]			114,513	
LY per health state				
DF	7.03	(4.88–9.36)	12.13	(7.89–16.91)
LRR	0.92	(0.35–1.48)	0.64	(0.02–1.26)
1L DM	1.50	(1.21–1.79)	0.55	(0.31–0.79)
2L DM	0.88	(0.64–1.12)	0.70	(0.2–1.21)
Total LYs	10.32	(8.78–12.03)	14.02	(10.38–17.65)
Incremental LYs			3.70	
QALY per health state[a]				
DF	5.97	(4.14–7.95)	10.31	(6.71–14.37)
LRR	0.78	(0.3–1.26)	0.54	(0.02–1.07)
1L DM	1.22	(0.98–1.46)	0.44	(0.25–0.63)
2L DM2	0.60	(0.44–0.76)	0.48	(0.14–0.82)
Total QALYs[a]	8.57	(7.24–10.05)	11.77	(8.58–14.95)
Incremental QALYs[a]			3.20	
Patients 'cured' (%)[b]	29.1		49.4	
ICER (incremental cost/LY)			30,971	
ICER (incremental cost/QALY)			35,811	

1L first-line, *2L* second-line, *C$* Canadian dollars, *CI* confidence interval, *DF* disease free, *LRR* local/regional recurrence, *DM* distant metastasis, *ICER* incremental cost-effectiveness ratio, *LY* life-year, *QALY* quality-adjusted life-year

[a]Costs and effects discounted at 1.5% per year

[b]The percentage cure is determined by the percentage of DF patients after 95% cure has been reached

of C$50,000 per QALY gained [36], adjuvant osimertinib was cost-effective in 66.3% of iterations (Fig. 2b).

3.2 Scenario Analyses

Probabilistic scenario analyses were conducted to explore uncertainty of the model parameters (Table 2). For all scenarios explored, ICERs ranged from C$22,396 to C$64,911. A scenario analysis shortening the time horizon to 15 years resulted in the highest ICER (C$64,911). Allowing no retreatment with osimertinib resulted in the lowest ICER of C$22,396. The ICER was minimally affected by using mapped EQ-5D utilities derived from the ADAURA trial data. Changing the 'cure' assumption in the osimertinib arm so that the model transitioned patients without recurrence to 'cured' over a shorter time (from year 4 to end of year 7, instead of end of year 8) resulted in a 18% smaller ICER. A scenario without cure (which

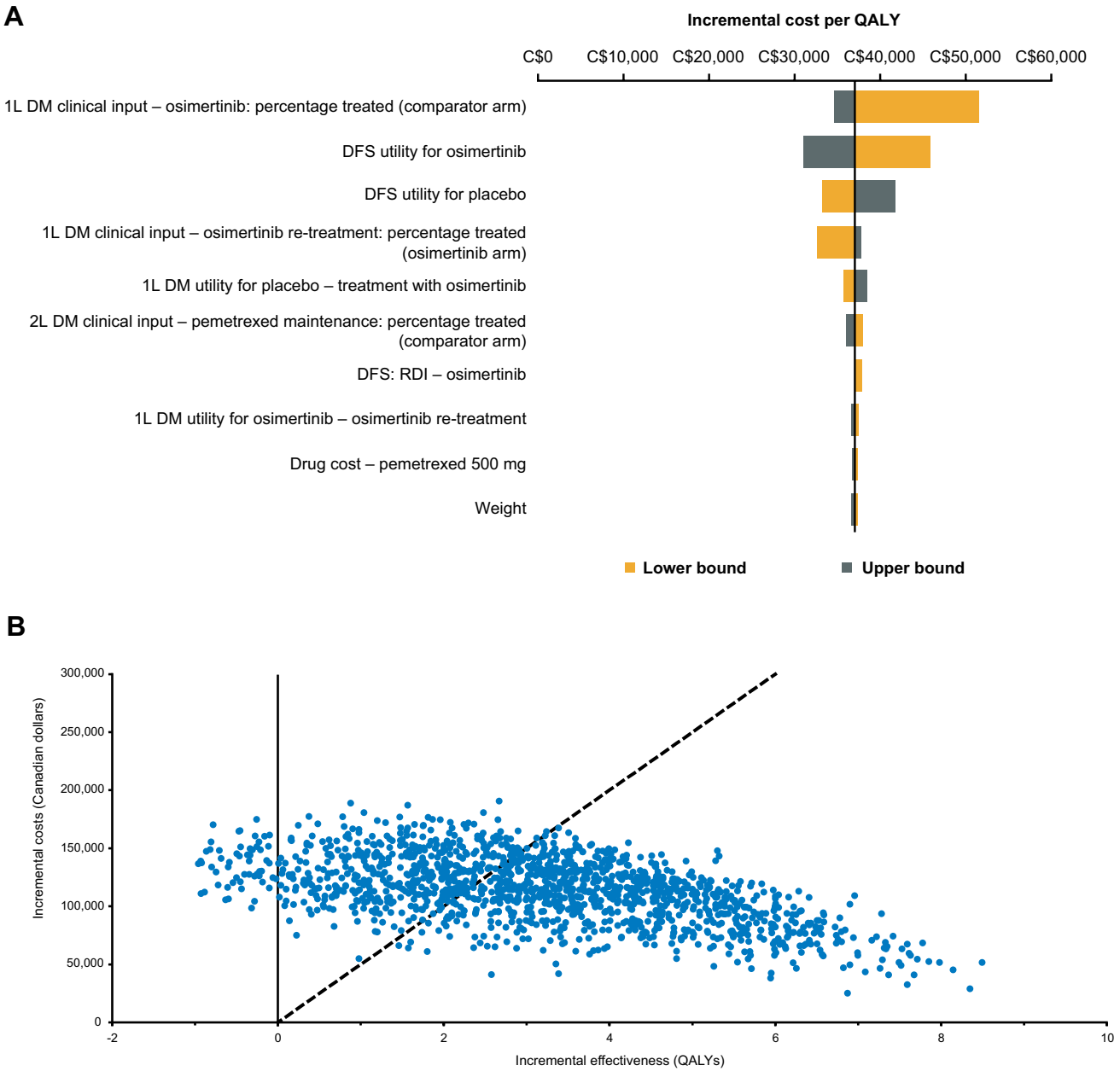

Fig. 2 **a** Tornado plot of the effect of one-way sensitivity analyses on model parameter uncertainty. **b** Probabilistic scatterplot of incremental cost-effectiveness ratio between treatment with adjuvant osimertinib and active surveillance. The broken line indicates the willingness-to-pay threshold of C$50,000/QALY. *1L* first-line, *C$* Canadian dollars, *DFS* disease-free state, *DM* distant metastases, *QALY* quality-adjusted life-year, *RDI* relative dose intensity

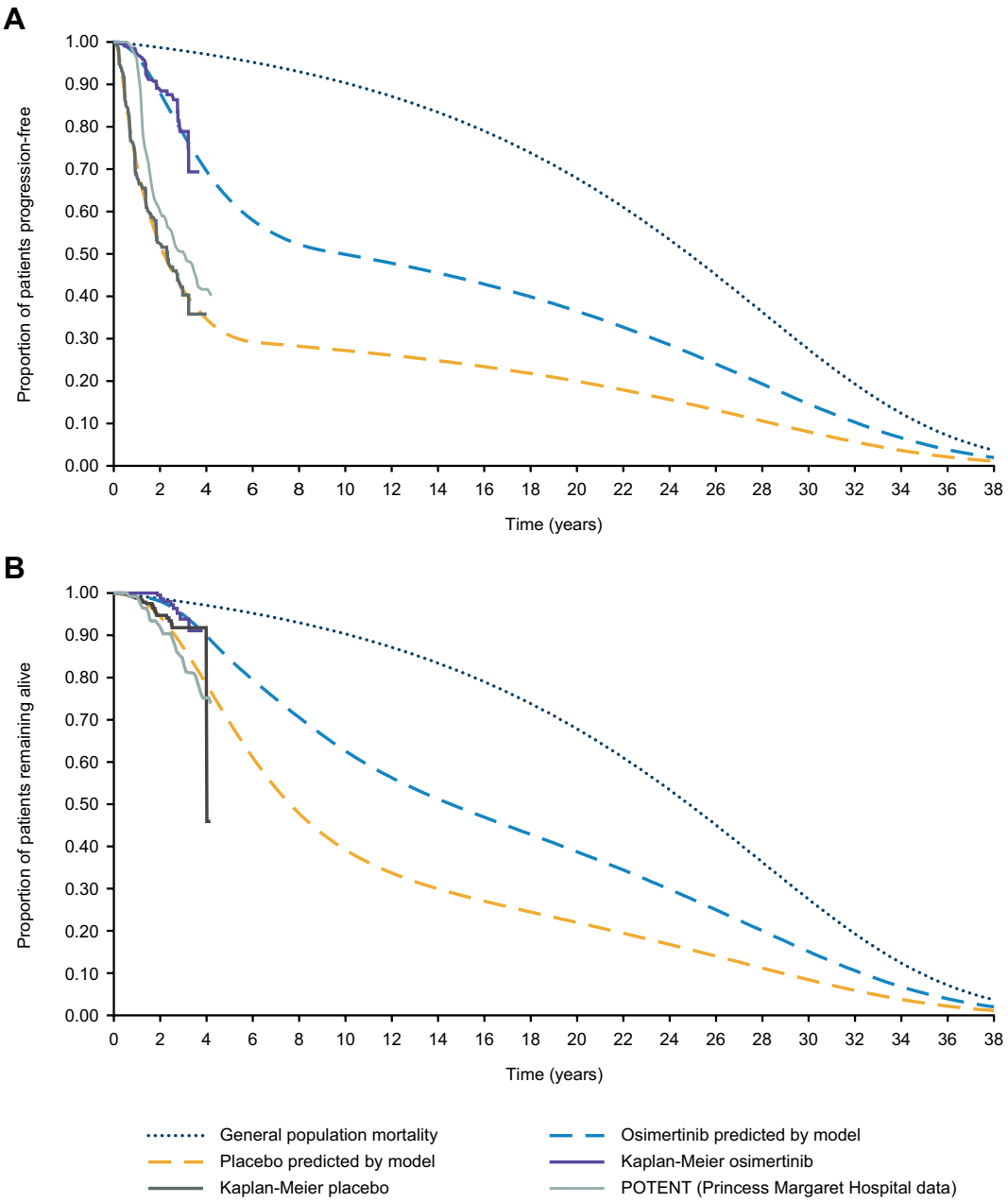

Fig. 3 Modeled reference case long-term survival. **a** Disease-free survival and **b** overall survival

clinical experts advised was an implausible scenario) led to an ICER of C$61,977, corresponding to a 73% increase. In another 'cure' scenario, the standardized mortality ratio was applied to the transitions from DF and LRR to 'Death,' leading to an ICER increase of 16%. Scenarios included alternatives for parametric distribution modeling of the transitions between health states. Choosing loglogistic as an alternative curve fit for the transition probability (TP) from DF to LRR (DF → LRR) resulted in an 11% greater ICER; choosing lognormal as an alternative curve fit for DF → LRR resulted in a 7% smaller ICER. Choosing an alternative curve fit for 2L DM → Death minimally impacted the ICER (~ 0.1% lower). Scenario analyses demonstrated that the conclusions from the reference case analysis remained robust in terms of the cost-effectiveness of osimertinib versus active surveillance.

Table 2 Scenario analyses to assess model robustness

Scenario	ICER (incremental cost/QALY)
Reference case	C$35,811
Time horizon 15 years	C$64,911
Discount rate 0%	C$28,118
Discount rate 3%	C$45,305
No costs for subsequent IV treatments	C$38,876
DF → LRR curve fit loglogistic	C$39,442
DF → LRR curve fit lognormal	C$34,581
DF → 1L DM curve fit loglogistic	C$58,656
DF → 1L DM curve fit lognormal	C$45,696
DF → LRR curve fit loglogistic + DF → 1L DM curve fit loglogistic[a]	C$64,152
DF → LRR curve fit lognormal + DF → 1L DM curve fit lognormal[a]	C$46,259
2L DM → Death curve fit exponential	C$36,791
dF → LRR curve fit loglogistic + 2L DM → Death curve fit exponential	C$39,431
dF → LRR curve fit lognormal + 2L DM → Death curve fit exponential	C$34,370
Utility LRR similar to DM	C$34,792
Utility source trial-based utilities	C$36,872
Utility source alternative literature source DM	C$35,071
Retreatment after 6 months (42 months after resection)	C$37,178
Retreatment after 18 months (56 months after resection)	C$33,358
No retreatment	C$22,396
No SMR applied to general population mortality	C$36,244
SMR = 2 applied to general population mortality	C$35,016
Treatment effect waning applied	C$38,343
'Cure' transition period for osimertinib arm begins at 36 months[b]	C$29,217
No cure assumption applied[a]	C$61,977
SMR applied to all transitions to Death (SMR of 1.26)[a]	C$41,584

1L first-line, *2L* second-line, *C$* Canadian dollar, *DF* disease free, *DM* distant metastases, *ICER* incremental cost-effectiveness ratio, *IV* intravenous, *LRR* local/regional recurrence, *LY* life-year, *QALY* quality-adjusted life-year, *SMR* standardized mortality ratio

[a]These scenarios were run deterministically

[b]Patients in the osimertinib arm without recurrence were modeled to transition to 'cured' from the end of year 4 to the end of year 7, instead of from the end of year 4 to the end of year 8 as in the reference case

4 Discussion

As in patients unselected for EGFR mutations [8], the rates of disease recurrence remain high in completely resected patients with EGFRm NSCLC following surgery with curative intent [37], and survival outcomes are poor [7, 38]. There has been little innovation in this treatment setting in the past 15 years; chemotherapy was the only adjuvant treatment option to improve DFS after surgery, and its incremental benefit is low [8, 39, 40]. There is a clear unmet need for a targeted, efficacious, and well-tolerated treatment option for patients with EGFRm NSCLC following complete tumor resection. Following the positive DFS findings from the ADAURA trial, osimertinib has been approved as an adjuvant treatment in this disease setting [10, 17, 18]. This economic evaluation based on the Canadian HTA submission indicated that adjuvant osimertinib is predicted to increase life expectancy versus placebo for stage IB–IIIA EGFRm NSCLC, with patients predicted to spend a substantial proportion of time DF, resulting in an estimated 23.2% absolute improvement in OS at 10 years and a mean 3.20 additional QALYs per patient. Additional data cuts with more mature data from the ADAURA trial will inform long-term survival outcomes in the future.

Adjuvant osimertinib treatment was associated with a probabilistic ICER of C$35,811 versus active surveillance. The ICER was most sensitive to clinical assumptions pertaining to the percentage of patients that received treatment

upon relapse to metastatic disease and the quality of life of patients in the DF and DM health states. At a willingness-to-pay threshold of C$50,000 per QALY gained, osimertinib was cost-effective in 66.3% of iterations.

In this analysis, the model used five health states to cover the possible clinical outcomes observed after complete resection and adjuvant treatment in EGFRm NSCLC. A key assumption is that patients in the DF state can transition to LRR or distant metastases, with the former state being treated in a curative manner. Another consideration is that the lifetime horizon used was 38 years. CADTH requires a time horizon of lifetime, often defined as the time until < 1% of patients are alive. Shorter time horizons were included in the scenario analyses; the time horizon of 15 years may have resulted in a larger ICER than in the reference case because the full benefits of cure could not be realized within this shortened time horizon.

At the unplanned interim analysis for ADAURA, maturity of the OS data was 4%, so a non-direct method was applied, using CancerLinQ and FLAURA data to extrapolate outcomes to model a lifetime horizon. Methodological best practices were followed for extrapolation and for choosing the most clinically valid distributions. In addition, clinical experts provided validation to confirm that the predicted estimates were plausible and clinically relevant. Survival in the modeled active surveillance arm was well-aligned with real-world data [24]. Model goodness of fit increases as MAPE approaches 0 and R^2 approaches 1. A MAPE of 22.5% compared well with established, respected health economic models in other fields [41]. There are challenges around using real-world data rather than rigorously collected data from clinical trials; however, the CancerLinQ cohort had comparable patient demographics to the ADAURA trial, including the proportion of patients at each disease stage, with a limitation regarding the index date being diagnosis compared with post-surgery within the ADAURA trial. Besides OS data, there remains uncertainty regarding the current DFS data, more specifically on the impact of treatment cessation on DFS. Several scenario analyses were conducted with alternative parametric survival functions to account for the uncertainty regarding extrapolation of survival outcomes. The results of those scenario analyses showed that adjuvant osimertinib treatment consistently provided increased QALYs and LYs versus active surveillance following complete resection. A scenario with the risk of relapse for the osimertinib arm was set equal to the risk of relapse for the placebo arm (treatment arm) after year 3, but had no significant impact on the ICER. Collectively, scenario analyses have highlighted the model's robustness and demonstrated that osimertinib remained cost-effective across most scenarios. As well as the need to use other sources to extrapolate OS data, health-related quality of life assessment in the ADAURA trial did not readily support the creation of HSUVs for Canada. This was because the trial took place in many other countries; thus, HSUVs were assumed from real-world data from Canada [33, 42].

Another limitation is the validation of the cure assumption, as the long-term cure rate for both trial arms remains uncertain. The definition of cure in resected EGFRm NSCLC, is as yet unclear. While patients were deemed 'cured' after being DF for 5 years after the end of treatment, thus 8 years in the osimertinib arm compared with 5 years in the active surveillance arm, by beginning to transition patients in both arms to cure at 4 years, we ensured that a proportion of patients in the model were cured at 5 years. The time it took to transition patients to 'cure' was based on RWE that showed DFS plateauing in resected EGFRm NSCLC retrospective cohorts, and validated by the clinical experts, thus minimizing this limitation.

It should be noted that in the Canadian HTA submission, CADTH made several changes to the model and reanalyzed the data. The reanalysis resulted in a substantially higher ICER of C$328,026 for adjuvant osimertinib versus active surveillance [36]. The key difference between the CADTH reanalysis and our model was the survival distribution used to model TPs for DF → LRR and DF → 1L DM for osimertinib: Gompertz by CADTH [36] and generalized gamma by our model. TPs for DF → LRR and DF → 1L DM are critical parameters of the model; selection of the Gompertz curve assumes near complete loss of benefit within 2 years of completing adjuvant treatment (Supplementary Figures S1A and S2A, see the electronic supplementary material). While data post-discontinuation of adjuvant osimertinib remain immature, the Gompertz curve in the CADTH reanalysis assumed a 15-times increase in rate of relapse after year 3, which is not supported by current evidence from the clinical trial. CADTH opted not to model indefinite benefit in the reference case. CADTH assumed that there was no DFS benefit from osimertinib by year 5; the updated ADAURA data with 2 years additional follow-up from the data published in 2020 highlighted a sustained DFS benefit, as the DFS HR was 0.27 (95% CI 0.21–0.34) for patients with stage IB–IIIA EGFRm NSCLC [43]. The model used for the CADTH submission has been submitted in England, Scotland, the Netherlands, and Canada to support HTAs by the National Institute for Health and Care Excellence, Scottish Medicines Consortium, Zorginstituut Nederland, and INESSS, respectively, for whom the selected TPs aligned more closely with the reference case TPs [36, 44–46]. In addition, ADAURA data have been in other independent cost-effectiveness models of adjuvant osimertinib, published in a peer-reviewed manuscript [47] as well as presented at congress [48]. The models produced different ICERs due to different structures without the potential for cure, shorter time horizons, different retreatment assumptions, and extrapolation of OS data assuming 5% benefit. The methods employed in our analysis

are robust and aligned to HTA and academic expectations, and as noted above, the modeled OS data aligned well with real-world data.

Osimertinib is a highly efficacious and well-tolerated treatment that can play a role in an adjuvant treatment regimen with a potentially curative intent [10]. Osimertinib for patients with completely resected EGFRm NSCLC represents a paradigm shift to patients and healthcare providers in a disease area with significant unmet needs. Further to the important clinical benefits of osimertinib to patients, adjuvant osimertinib was found to be a cost-effective treatment when compared with established clinical management, reporting an ICER of C$35,811 per QALY versus active surveillance, with a 95% CI of 59,565–164,779 for the incremental cost and a 95% CI of − 0.28 to 6.79 for the QALY.

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Availability of data and material Provision of standard data underlying the findings described in this article may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. The code for the model is not available publicly.

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