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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Ribociclib plus an Aromatase Inhibitor (AI) Versus AI Alone in the Adjuvant Treatment of Stage II and III Pre- and Postmenopausal Women with HR+/HER2− Early Breast Cancer (EBC): A Canadian Payer Perspective

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Abstract

Background Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors have transformed the treatment of hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2−) breast cancer. Ribociclib plus an aromatase inhibitor (AI) was approved in Canada as adjuvant treatment for high-risk stage II–III early breast cancer (EBC) based on the phase 3 NATALEE trial, demonstrating improved invasive disease-free survival (iDFS) versus AI treatment alone. This study evaluated the cost-effectiveness of ribociclib plus AI versus AI alone and tamoxifen from a Canadian public payer perspective.

Methods A non-homogeneous, semi-Markov cohort model with six health states (iDFS, second primary malignancy, non-metastatic recurrence, remission, distant recurrence [DR], and death) was developed, using Ontario-based costs (Canadian dollars) and a lifetime horizon. Transition probabilities from iDFS were derived from NATALEE trial data; other transitions were informed by published sources. DR was stratified by endocrine therapy (ET) sensitivity based on recurrence timing (≤ 12 months post-ET: resistant; > 12 months: sensitive), with outcomes and costs informed by prior health technology assessment evidence in metastatic disease. Results were reported as incremental cost-effectiveness ratios (ICERs) per quality-adjusted life-year (QALY) gained.

Results Ribociclib plus AI yielded a probabilistic ICER of $45,097/QALY versus AI alone; tamoxifen was dominated by AI alone. Sensitivity analyses showed results were most sensitive to iDFS hazard rates and ribociclib drug costs. In the probabilistic analysis, ribociclib was preferred in 58.5% of simulations at a $50,000 willingness-to-pay threshold.

Conclusion Ribociclib plus AI is cost-effective for HR+/HER2− EBC with an ICER of $45,097, below the $50,000 willingness-to-pay threshold versus AI or tamoxifen alone.

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Key Points for Decision Makers

Ribociclib plus endocrine therapy is likely cost-effective for high-risk early breast cancer in Canada, falling below the commonly accepted willingness-to-pay threshold of $50,000 (Canadian dollars) per quality-adjusted life-year gained.

Although ribociclib increases upfront drug costs, it reduces the risk of breast cancer recurrence, leading to significant savings on expensive advanced cancer treatments over a patient's lifetime.

Results are most sensitive to the duration of ribociclib's benefit over time and its drug price, which are key considerations for reimbursement decisions.

1 Introduction

Breast cancer is the second leading cause of cancer deaths among women in Canada, with an estimated 30,500 new diagnoses and 5,500 deaths among women in 2024 [1]. Most newly diagnosed cases are early stage: approximately 63% are localized disease and 28% involve regional lymph nodes, with 5-year relative survival rates of 99% and 86%, respectively [2]. Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) is the largest subtype of breast cancer, accounting for 69% of cases [2].

Early-stage breast cancer (EBC) is more commonly diagnosed in older women, likely due to increased screening uptake [3]. Treatment of EBC aims to cure disease and improve disease-free survival (DFS) and overall survival (OS) while minimizing long-term sequelae and recurrence [3].

Treatment options for stage II–III EBC include surgery, postoperative radiation therapy, and pre- and/or postoperative systemic therapy [4, 5]. In patients with HR+/HER2− breast cancer, endocrine therapy (ET) is recommended as adjuvant to surgery. In Canada, tamoxifen is the most commonly used estrogen receptor (ER) modulator for EBC and may be replaced or followed by aromatase inhibitor (AI) treatment [6].

Ribociclib is a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor approved in Canada in combination with an AI as adjuvant treatment for patients with HR+/HER2− stage II–III EBC at high risk of recurrence, based on results from the phase 3 NATALEE trial [7]. NATALEE demonstrated a sustained and statistically significant improvement in invasive disease-free survival (iDFS) with ribociclib plus AI compared with AI alone [7] (iDFS hazard ratio 0.72; 95% CI 0.61–0.84) [8]. Despite the availability of adjuvant ET, a substantial proportion of patients with HR+/HER2− stage II/III EBC remain at high risk of disease recurrence. Healthcare costs are approximately three times higher in the metastatic versus early-stage setting in Ontario, highlighting the clinical and economic burden of recurrence in this population [9].

Although the cost-effectiveness of ribociclib has been evaluated by the Canada's Drug Agency (CDA-AMC) [10], no published Canadian cost-effectiveness analysis of ribociclib as adjuvant treatment for HR+/HER2− EBC currently exists. This study evaluates the cost-effectiveness of ribociclib plus AI compared with AI alone and compared with tamoxifen as adjuvant therapy for stage II–III EBC from the Canadian public healthcare system perspective.

2 Methods

2.1 Overview

An economic model was developed in Microsoft Excel® to evaluate the cost-effectiveness of ribociclib plus AI versus AI alone and versus tamoxifen as adjuvant treatment for HR+/HER2− EBC in Canada. The model was evaluated from the perspective of the Canadian healthcare system and was designed to adhere to guidelines for economic evaluations from CDA-AMC [11]. Cost-effectiveness was assessed against a willingness-to-pay (WTP) threshold of $50,000 (Canadian dollars [CAD]) per quality-adjusted life-year (QALY) gained, which is commonly used in Canadian economic evaluations [11].

The population evaluated in the model consisted of adult (aged ≥ 18 years) men and women receiving adjuvant treatment for stage II–III HR+/HER2− EBC, consistent with the inclusion criteria of the phase 3 NATALEE trial [12]. Comparators included treatments approved and reimbursed in Canada for this indication: AI monotherapy (i.e., letrozole, anastrozole, or exemestane) and tamoxifen. Ribociclib was assumed to be administered at a dosage of 400 mg once daily (QD) by mouth (PO) for 3 weeks followed by a 1-week break, in a 28-day cycle, for up to 36 months or until disease recurrence or unacceptable toxicity, whichever occurred first. Letrozole (2.5 mg QD PO), anastrozole (1 mg QD PO), exemestane (25 mg QD PO), and tamoxifen (20 mg QD PO) were all administered orally. Goserelin 3.6 mg subcutaneous (SC) injection once every 28 days, for men and premenopausal women only, was administered for up to 60 months or until disease recurrence or unacceptable toxicity, whichever occurred first.

Only direct healthcare costs associated with EBC and its treatment were considered, including drug acquisition, drug administration and/or dispensing, treatment of adverse events (AEs), routine follow-up and monitoring, and subsequent treatment following disease recurrence. Outcomes evaluated in the model included life-years (LYs) and quality-adjusted life-years (QALYs). Cost-effectiveness was based on the incremental cost-effectiveness ratio (ICER), expressed in terms of the cost per LY gained and the cost per QALY gained. A lifetime time horizon was used (i.e., 49 years) based on an assumed starting age of 52.8 years, with future costs and effects discounted at 1.5% annually [11]. A PICOT (patient, intervention, comparators, outcomes, timeframe) framework describing the economic model is shown in Table 1.

2.2 Model Structure

A non-homogeneous semi-Markov cohort model (MCM) was developed to evaluate the cost-effectiveness of ribociclib plus AI versus AI alone and versus tamoxifen. The model incorporated time-dependent transition probabilities and tunnel states to reflect age-specific mortality and time since entering health states. Six health states were included: iDFS, second primary malignancy (SPM), non-metastatic recurrence (NMR), remission, distant recurrence (DR), and death (Fig. 1).

All patients entered the model in the iDFS state. Transition risks from iDFS were estimated using NATALEE trial data. The model has a cycle length of 28 days, and in each cycle, patients could remain disease-free or transition to NMR, SPM, DR, or death. Treatment exposure within iDFS was captured using time-to-treatment discontinuation (TTD) curves and stopping rules (36 months for ribociclib; 60 months for AI).

SPM was modeled as an absorbing state, and future outcomes (e.g., LYs) after transition to the SPM state were not tallied in the model, consistent with prior Canadian Health Technology Assessment (HTA) evaluations [13]. Patients with NMR could transition to DR or death within 1 year; those remaining after 1 year entered remission, where they could remain, progress to DR, or die.

DR was stratified by endocrine sensitivity based on the timing of recurrence relative to ET. Patients entering either of the DR states received fixed payoffs of LYs and time on treatment. LYs and time on treatment in DR were based on

Table 1 PICOT framework

Patients	Patients receiving adjuvant treatment for HR+/HER2− high-risk EBC who, after surgical resection, had complete tumor removal, and who met one of the following staging criteria: • Stage IIA with N1, or • Stage IIA with N0 and Grade 3, or • Stage IIA with N0 and Grade 2 with additional high-risk features, defined as at least one of the following: o Ki-67 ≥ 20% o Oncotype DX Breast Recurrence Score ≥ 26, or o High risk by genomic risk profiling • Stage IIB, or • Stage III
Intervention	Ribociclib 400 mg plus AI (letrozole 2.5 mg or anastrozole 1 mg) and, for men and pre-menopausal women only, goserelin 3.6 mg
Comparators	• AIs o Anastrozole o Letrozole o Exemestane • Tamoxifen
Outcomes	• Expected direct costs associated with EBC and its treatment • Life expectancy or LYs • QALYs • ICER
Model inputs	• Clinical data from the NATALEE trial • Published or publicly available sources for resource use and unit costs
Perspective	Canadian healthcare system perspective
Timeframe	Lifetime (i.e., 49 years)
Modeling approach	Non-homogenous semi-MCM
Discount rate	Costs and effects discounted at 1.5% annually

AI aromatase inhibitor, *EBC* early breast cancer, *HR+/HER2−* hormone receptor-positive/human epidermal growth factor receptor 2-negative, *ICER* incremental cost-effectiveness ratio, *LY* life-year, *MCM* Markov cohort model, *PICOT* patient, intervention, comparators, outcomes, timeframe, *QALY* quality-adjusted life-year

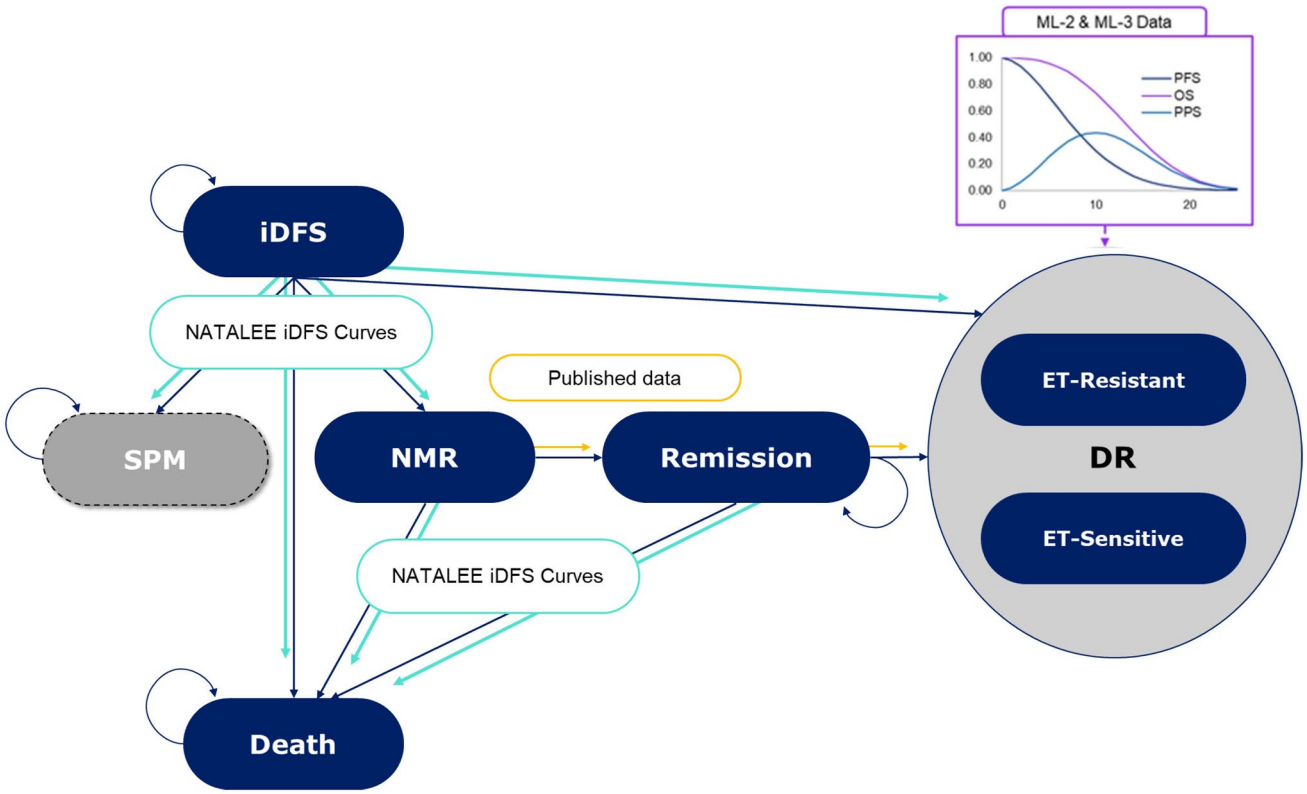


Fig. 1 Simplified schematic of model structure. Cyan and yellow arrows denote the sources of the transition probability inputs. *DR* distant recurrence, *ET* endocrine therapy, *iDFS* invasive disease-free survival, *ML* MONALEESA, *NMR* non-metastatic recurrence, *OS* overall survival, *PFS* progression-free survival, *PPS* post-progression survival, *SPM* second primary malignancy

estimates from a previous CDA evaluation of ribociclib as treatment for metastatic HR+/HER2− breast cancer [14]. The main parameters of the model are presented in Table 2.

2.3 Transition Probabilities

2.3.1 Invasive Disease-Free State

For patients receiving ribociclib plus AI and AI alone, iDFS transition probabilities (to SPM, NMR, DR, and death) were estimated using parametric survival distributions fitted to patient-level failure time data from the NATALEE trial (data cut-off April 29, 2024). In each model cycle, probabilities of transitioning from iDFS to the SPM, NMR, DR, and death health states for a given comparator were calculated by multiplying the iDFS hazard rate by the distribution of iDFS events by type (i.e., with types of events corresponding to the model health states). For patients receiving AI alone or tamoxifen alone, the distribution of iDFS events was assumed to be constant over time aside from adjustments for background mortality as the model population aged. Specifically, it was assumed that the risk of death in any model cycle could not be lower than age-matched general population mortality. For patients receiving ribociclib plus AI, a treatment effect waning assumption was applied and incorporated into the distribution of iDFS events.

Parametric survival distributions were fitted in R, using FlexSurv [15]. Candidate distributions included exponential, Weibull, log-logistic, lognormal, Gompertz, generalized gamma, gamma, generalized F, and restricted cubic spline (RCS) forms with up to three knots. For RCS specifications, Weibull, log-logistic, and lognormal baseline forms were evaluated; models included a single interior knot in addition to the two boundary knots, with boundary knots at the minimum and maximum failure times and the interior knot at the median failure time. Model selection considered statistical fit, visual inspection of survival and hazard functions, time-dependent hazard ratios, treatment-effect diagnostics, and clinical plausibility. The Bayesian information criterion (BIC) was used as the primary fit statistic because it penalizes model complexity and limits undue influence of tail behavior on long-term projections. The proportional hazards assumption was assessed using Schoenfeld residual tests.

A Weibull distribution fitted to iDFS was selected for the model base case. This distribution ranked among the best in goodness of fit based on BIC and had excellent visual fit to the Kaplan-Meier (KM) iDFS for both arms in NATALEE (Fig. 2). The Weibull was also relatively conservative in

Table 2. Main model input parameters

Parameter	Base-case value	Probabilistic variation	Source
General population mortality			
Life tables	N/A	Not varied	Statistics Canada [20]
iDFS distributions			
Ribociclib + AI	Weibull restricted	Bootstrapped values	NATALEE trial data on file
AI			
Distribution of iDFS events			
Ribociclib + AI		Bootstrapped values	NATALEE trial data on file
NMR	16.3%		
Death	6.5%		
DR	62.4%		
SPM	14.8%		
AI		Bootstrapped values	NATALEE trial data on file
NMR	19.5%		
Death	3.2%		
DR	65.5%		
SPM	11.8%		
Treatment effect waning			
Ribociclib + AI	Treatment waning began at 8 years, with the ribociclib iDFS hazard converging to AI until matching general population mortality at 32 years	Not varied	NICE TA810 evaluation of abemaciclib in EBC [17]
Transition probabilities in other states			
Remission to DR	0.0076 (monthly)	Not varied	NICE TA810 and Hamilton et al. 2015 [17, 19]
Stopping rules in iDFS			
Ribociclib	36 months	Not varied	Slamon et al. 2024 [12]
All ETs	60 months	Not varied	
TTD distributions			
Ribociclib	RCS Weibull	Bootstrapped values	NATALEE trial data on file
AI	Weibull restricted		
Health state utilities			
On-Treatment iDFS	0.8264	Multivariate normal distribution	NATALEE trial data on file
Off-Treatment iDFS	0.8050		
NMR	0.7683		
DR	0.7169		
AE-related disutilities in iDFS			
ALT increased	−0.005	Lognormal distribution	NICE TA810 [17]
Diarrhea	−0.103		
Leukopenia	−0.003		
Lymphopenia	0.000		
Neutropenia	−0.007		
Ratio of utilities in PPS to PFS in DR			
ET-resistant	0.930	Not varied	MONALEESA-2 and MONALEESA-3 trial data on file
ET-sensitive	0.960		

Table 2. (continued)

Parameter	Base-case value	Probabilistic variation	Source
Medication acquisition costs (list price per unit in 2023 CAD)			
Ribociclib 200 mg (42 capsules, oral)	$94.13	Gamma distribution	IQVIA Health Care Database
Letrozole 2.5 mg (30 tablets, oral)	$1.38		
Anastrozole 1 mg (30 tablets, oral)	$0.95		
Goserelin 3.6 mg (1 vial, SC)	$422.68		
Exemestane 25 mg (30 tablets, oral)	$1.33		
Tamoxifen 20 mg (30 tablets, oral)	$0.35		
Fulvestrant 500 mg (2 vials, SC)	$58.29		
Palbociclib 100 mg (21 capsules, oral)	$253.91		
Everolimus 10 mg (30 tablets, oral)	$172.26		
Capecitabine 150 mg (60 tablets, oral)	$0.46		
Paclitaxel 300 mg (1 vial, IV)	$74.80		

AE adverse event, *AI* aromatase inhibitor, *ALT* alanine aminotransferase, *CAD* Canadian dollars, *DR* distant recurrence, *EBC* early breast cancer, *ET* endocrine therapy, *iDFS* invasive disease-free survival, *IV* intravenous, *N/A* not applicable, *NICE* National Institute for Health and Care Excellence, *NMR* non-metastatic recurrence, *PFS* progression-free survival, *PPS* post-progression survival, *RCS* restricted cubic spline, *SC* subcutaneous, *SPM* second primary malignancy, *TTD* time-to-treatment discontinuation

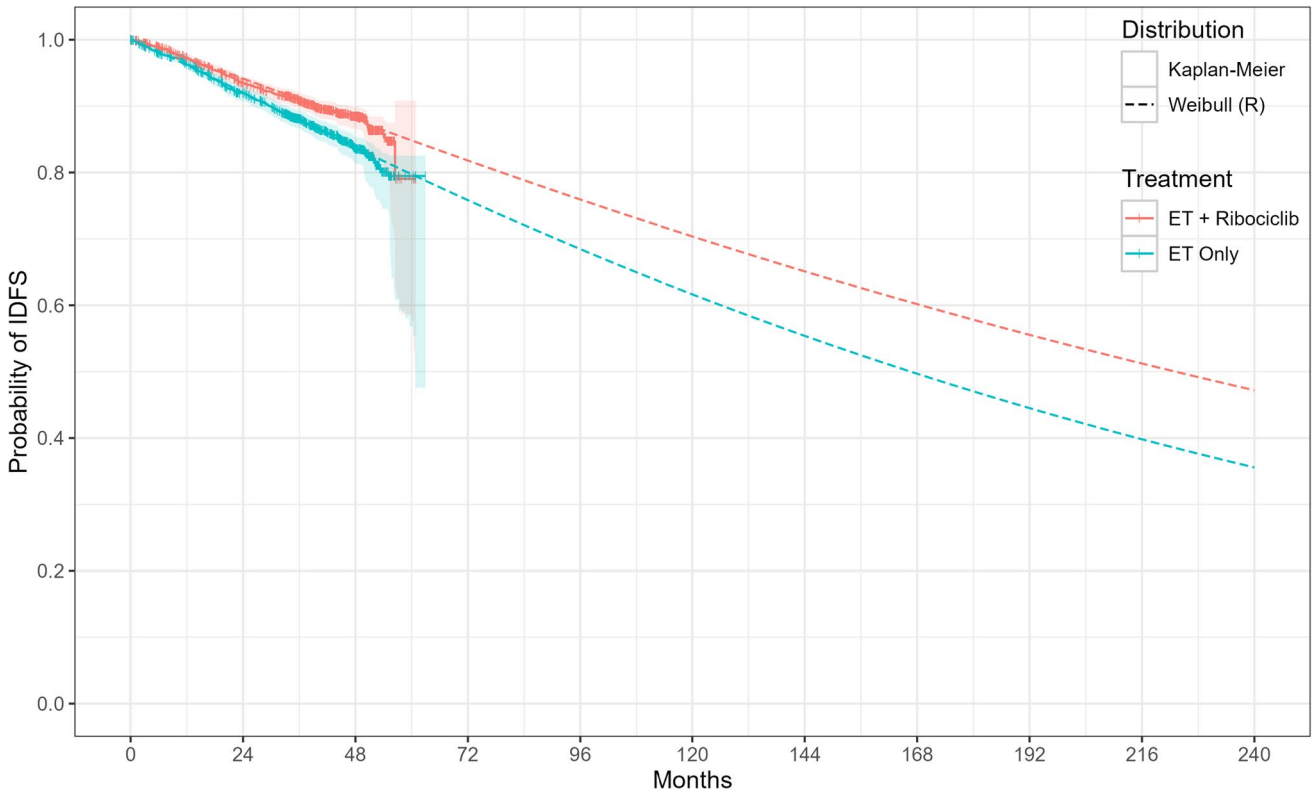


Fig. 2 iDFS of ribociclib + AI vs. AI alone with restricted Weibull distribution. *AI* aromatase inhibitor, *ET* endocrine therapy, *iDFS* invasive disease-free survival

terms of overall iDFS projections; the restricted mean survival time (RMST) was 171.8 months (range 162.6–187.3) for ribociclib plus AI and 153.3 months (range 137.2–174.3) for AI alone. Furthermore, the Weibull distribution had an estimated difference in RMST of 18.5 months (range 12.3–42.3), which can be used as a proxy for the projected benefit on iDFS. It should be noted, however, that the projected RMSTs were based on the extrapolated curves only and did not account for background mortality or treatment effect waning. The full set of candidate distributions is presented in Supplementary Fig. 1 (see the electronic supplementary material).

Transition probabilities for tamoxifen were estimated by applying to the iDFS curve for AI alone an estimate of the hazard ratio for tamoxifen versus AI based on a systematic review and meta-analysis presented at the San Antonio Breast Cancer Symposium [16]. Among pre-menopausal patients receiving adjuvant treatment, the pooled hazard ratio for ET versus tamoxifen was 0.66 (95% CI 0.54–0.79), equivalent to a hazard ratio of 1.52 for tamoxifen versus ET.

2.3.2 Non-metastatic Recurrence and Remission States

Transition probabilities from the NMR state to death were assumed to be the same as the probability of death for the general population, using the probability of death estimated from the iDFS curve as a floor. This assumption was made on the basis that patients in the NMR state have not yet experienced DR and are therefore not expected to face excess mortality beyond that of the general population.

One year after entry into the NMR state, all those remaining in the state were assumed to transition to remission, reflecting the clinical observation that patients who do not progress to DR within 1 year are likely to achieve disease control. Similarly, the probability of death in the remission state was assumed to be equal to that of the general population, using the iDFS probability of death as a floor, on the basis that patients in remission who have not progressed to metastatic disease would not be expected to experience mortality rates substantially different from those of the age- and sex-matched general population. The probability of DR within the remission state was estimated consistently with that in the National Institute for Health and Care Excellence (NICE) Technology Appraisal TA810 appraisal of abemaciclib [17]. The primary source for this parameter was the NICE TA632 of trastuzumab, which used a published study of 12,836 EBC patients and estimated the risk of the incidence of a second malignancy after receipt of adjuvant therapy [18]. The monthly transition probability of 0.0076 was calculated from a mean time until progression of 7.6 years [19].

2.4 Time to Treatment Discontinuation

For patients residing in the iDFS state, probabilities of remaining on treatment by time since treatment initiation were based on estimated TTD curves until a maximum duration based on corresponding stopping rules. A 36-month stopping rule was assumed for ribociclib in the adjuvant setting, and a 60-month stopping rule was assumed for all other treatments (Table 2).

TTD curves were estimated independently for ribociclib and AI using patient-level data from the NATALEE trial based on KM methods and fitted parametric distributions. For patients receiving ribociclib and AI in combination, the model includes one TTD curve to estimate time on treatment with ribociclib and a separate TTD curve to estimate time on treatment with AI. This reflects a component of the trial design whereby patients who discontinued ribociclib could continue receiving treatment with AI. TTD was not a predefined endpoint in NATALEE and was calculated based on post-hoc analyses of patient-level exposure data. TTD was defined as the time from randomization until the last date of treatment exposure for patients who permanently discontinued for any reason. Patients who were still receiving treatment by the data cut-off date were censored for TTD at the date of censoring for iDFS.

2.5 Treatment Effect Waning

Treatment effect waning was applied to iDFS starting 8 years after treatment initiation with ribociclib. Eight years was chosen based on the evaluation of abemaciclib as treatment for EBC that was submitted to CDA, as well as the NICE TA810 evaluation of abemaciclib, and was used recently in the NICE TA1086 of ribociclib [13, 17, 21]. Treatment effect waning was implemented such that the hazard of recurrence for ribociclib plus AI in iDFS linearly approached that of AI alone over a specified waning duration period. Specifically, the hazard rate for ribociclib after 8 years was calculated as a weighted average of the hazard rate from the parametrized ribociclib iDFS curve and that of the AI-alone iDFS curve. The weights were adjusted during each period of the specified waning duration such that the weight applied to the hazard rates of the AI-alone arm was equal to one at the end of the waning period. Additionally, the same waning assumptions were applied to the distribution of iDFS events for ribociclib plus AI, which approached the distribution of iDFS events for AI alone over the waning duration.

2.6 Adverse Events (AEs)

Treatment-emergent AEs considered in the model included all-cause grade 3+ AEs with an incidence $\geq$ 5% for any of the comparators of interest. Grade 1–2 events were not

considered because they are generally self-limited and are therefore not likely to be associated with substantial treatment costs or reductions in health-related quality of life. The incidences of AEs for patients receiving ribociclib plus AI and AI alone were based on data from the NATALEE trial [12]. For modeling purposes, a conservative assumption was made that the AE profile of tamoxifen is equivalent to that of AI alone. AE rates used in the model are shown in Supplementary Table 1 (see the electronic supplementary material).

2.7 General Population Mortality

The probability of death in any given model cycle was assumed to not be lower than the age- and sex-matched mortality probabilities for the general population, which were based on data from Statistics Canada, assuming a mean starting age of 52.8 years and that 99.6% of patients are female at entry into the model, based on baseline demographic characteristics of patients in NATALEE [12, 20].

2.8 Utility Values

2.8.1 Health State Utilities and AE Utility Decrements

Health state utilities were estimated with EQ-5D-5L assessments of the NATALEE trial. Dimension scores for the five domains of the EQ-5D-5L assessments collected in NATALEE were converted to index utility scores with Canadian tariffs using the 'eq5d' package in R [22, 23]. EQ-5D-5L index scores were analyzed using generalized estimating equations (GEEs) (an extension of generalized linear model regression for analyzing data with correlation of the dependent variable across observations) in order to obtain utility values for model health states, controlling for EQ-5D index values at baseline. GEE regressions were conducted using the SAS PROC GENMOD procedure with the REPEATED statement. Estimated health state utilities used in the base case for the evaluation of the intention-to-treat population are shown in Table 2.

Health state utilities in iDFS while on treatment were estimated using the utility value for AI alone and applying AE-related utility decrements. AE-related utility decrements for each comparator were calculated as the incremental AE rate for that comparator versus AI alone multiplied by the corresponding AE disutility. All AEs were assumed to have a duration of 1 month. Lacking estimates for Canada-specific disutility values for AEs, these parameters were sourced from the NICE technology assessment of abemaciclib in the UK [17].

Utility values for patients in remission were assumed to be the same as those of the general population. Utility values in the progression-free survival (PFS) substates for the DR ET-resistant and DR ET-sensitive health states were both assumed to be 0.7169, as estimated from NATALEE. However, as information regarding subsequent progressions after metastatic recurrence was not captured in NATALEE, utilities for DR post-progression survival (PPS) could not be directly estimated. Therefore, relative decreases between PFS and PPS utilities observed in MONALEESA-3 and MONALEESA-2 were applied to the ET-resistant and ET-sensitive PPS states, respectively. These relative decreases were 7.02% for ET-resistant and 3.96% for ET-sensitive [14, 24]. Health state utilities were adjusted for age-related declines in health-related quality of life using age- and sex-matched general population utilities for Canada [25]. Age-specific declines in utility were applied weighted by proportions of males and females for the current age versus the age at entry into the model.

In the probabilistic sensitivity analysis, health state utilities were varied assuming a multivariate normal distribution to account for correlations across health states, using the variance-covariance matrix from the GEE regression.

2.9 Fixed Payoffs for Distant Recurrence Health States

Subsequent transitions after entry into either DR substate were not modeled explicitly. Instead, the model calculated fixed payoffs for LYs, QALYs, and costs based on the following: the mix of DR treatments received; undiscounted LYs in PFS and PPS by DR treatment; time on treatment (months); drug acquisition, administration, and dispensing costs; follow-up and monitoring costs; terminal care costs; and health state utilities.

Payoffs for LYs were calculated by multiplying the DR treatment mix by estimated LYs in PFS and PPS for each treatment (Supplementary Table 2; see the electronic supplementary material). PFS and PPS LYs and time on treatment were derived from the CDA economic evaluation of ribociclib plus fulvestrant for HR+/HER2− advanced breast cancer, which was estimated primarily using data from the MONALEESA-3 trial [14]. Payoffs for QALYs were calculated by multiplying the PFS and PPS LY payoffs by the corresponding health state utilities (Supplementary Table 2).

Costs in DR were comprised of drug acquisition, administration, dispensing, follow-up, monitoring, and terminal care costs. Drug costs were calculated by multiplying the treatment mix by time on treatment, unit costs of medication, and dosages (Supplementary Table 2). Follow-up and monitoring costs were estimated by multiplying LY payoffs by healthcare resource utilization rates and corresponding unit costs (Supplementary Tables 3 and 4). Terminal care costs were assigned to all patients entering either DR substate.

All payoffs were calculated on an undiscounted basis, with discounting applied at the time of entry into the DR state. Total LYs, QALYs, and costs in DR were then

calculated by multiplying the fixed payoff values by the proportion of patients transitioning into the corresponding DR substate in each model cycle. The mix of treatments received in DR was assumed to vary by type of DR (i.e., ET-resistant, ET-sensitive) and by the treatment received in the adjuvant setting (Supplementary Table 2). Proportions of patients receiving each treatment in DR were based on assumptions, due to the lack of evidence for CDK4/6 inhibitor re-treatment in the metastatic/advanced setting following CDK4/6 inhibitor adjuvant therapy.

2.10 Costs

All costs are presented in 2023 CAD, consistent with the ribociclib CDA submission [10]. Drug costs, a key model driver, have remained unchanged since 2023 and are reflective of 2026 prices.

2.10.1 Medication Acquisition Costs

Costs of medications were extracted from the IQVIA Healthcare Database and costs for Ontario province [26]. Medication costs were applied while patients remained on treatment in the iDFS state (i.e., TTD up until the stopping rule). While in the NMR state, patients were assumed to receive either letrozole or anastrozole. Costs of treatment in DR were assigned based on the mix of DR treatments and duration of treatment. Costs per unit (e.g., capsule, tablet, vial) of medication were calculated as the price per package of medication divided by the number of units in package (Table 2). Dosages for medications were based on clinical trials [12].

2.10.2 Administration Costs and Dispensing Fees

For any intravenous (IV) treatments, the cost of administration was assumed to be $75, based on the Schedule of Benefits unit cost for "Complex single agent or multi-agent therapy—chemotherapy and/or biologic agent(s) that can cause vesicant damage, infusion reactions, cardiac, neurologic, marrow or renal toxicities that may require immediate intervention by the physician" (Code G345). This cost is not incurred by any regimens in the base case as none of the drugs included require IV administration. The cost of SC injection administration was assumed to be zero. Dispensing fees for oral medications were assumed to be $11.04 based on Canadian Institute for Health Information (CIHI) pharmaceutical data tool [27].

2.10.3 Costs of Follow-Up and Monitoring

Unit costs of healthcare services and frequency of utilization by health state were based on data from the 2023 Ontario Schedule of Benefits [28]. Lacking information on healthcare resource utilization for follow-up and monitoring of breast cancer patients in Canadian clinical practice, annual frequencies of services received and the percentage receiving each service were based on the NICE TA612 appraisal of neratinib [29]. Detailed unit costs and resource use assumptions for follow-up and monitoring are provided in Supplementary Table 3 (see the electronic supplementary material). Additional treatment-specific monitoring resources for ribociclib were based on Canadian product monographs (Supplementary Table 5).

2.10.4 Costs of Treating AEs

AE treatment costs were calculated by multiplying the incidence of AEs by the expected cost per event and summing across all events to obtain a total per patient cost. Treatment costs per event were estimated from a survey of medical oncologists in Canada providing breast cancer care, regarding healthcare resource utilization for AE management [30]. Estimated AE costs can be found in Supplementary Table 6 (see the electronic supplementary material).

2.10.5 Terminal Care Costs

A published study by Yu and colleagues (2015) estimated the public cost of terminal care in Canada to be $15,976 (2012 CAD) [31]. After adjustment for inflation using Canadian consumer price index, the cost of terminal care was calculated to be $20,531 in 2023 CAD [32]. This cost was applied to all persons entering the death state excluding those who enter the SPM absorbing state, as death is not modeled for that population.

3 Analyses

Base-case results were generated using probabilistic analyses, based on second-order Monte Carlo simulations with model inputs sampled from bootstrapped values or varied according to assumed probability distributions. Parameters are sampled simultaneously; for correlated parameters, joint bootstrap distributions derived from NATALEE data are used. The probabilistic analysis is "seeded," whereby a fixed seed value generates a pre-determined sequence of random numbers, ensuring reproducibility of results.

Deterministic sensitivity analyses were conducted to assess the impact of key parameter assumptions on the ICER and were depicted with tornado plots. In tornado plots, each parameter was varied by ± 25% of its base-case value, or within its 95% CI where available. Probabilistic scenario analyses were also conducted to evaluate results under alternative sets of assumptions and parameter estimates.

Table 3 Summary of probabilistic cost-effectiveness results

Outcome	Ribociclib + AI	AI
Total, discounted		
Costs ($)	$150,824	$113,167
Life-years	18.00	16.99
QALYs	14.22	13.39
Difference (ribociclib + AI vs. comparator)		
Costs ($)	–	$37,657
Life-years	–	1.02
QALYs	–	0.84
ICER (ribociclib + AI vs. comparator)		
Cost per life-year gained	–	$37,090
Cost per QALY gained	–	$45,097
QALY breakdown		
iDFS	12.30	10.80
NMR	0.08	0.10
Remission	0.59	0.76
DR ET-resistant	0.29	0.47
DR ET-sensitive	0.97	1.25
T otal	14.22	13.39
Costs breakdown ($) discounted		
Drug acquisition	$104,971	$10,450
Administration and dispensing	$1,642	$1,526
Follow-up and monitoring	$3659	$2,719
AEs	$294	$9
Terminal care	$4,390	$3,600
SPM transition	$14	$13
DR (ABC-related healthcare)	$35,854	$94,851
Total	$150,824	$113,167
Scenario analyses (ICER [ribociclib + AI vs. comparator])		
Base case	–	$45,097
No treatment effect waning	–	$34,744
Discount rate of 0% for costs and efficacy	–	$23,490
Discount rate of 3% for costs and efficacy	–	$74,044

Results presented in 2023 Canadian dollars

ABC advanced breast cancer, *AE* adverse event, *AI* aromatase inhibitor, *DR* distant recurrence, *ET* endocrine therapy, *ICER* incremental cost-effectiveness ratio, *iDFS* invasive disease-free survival, *NMR* non-metastatic recurrence, *QALY* quality-adjusted life-year, *SPM* second primary malignancy

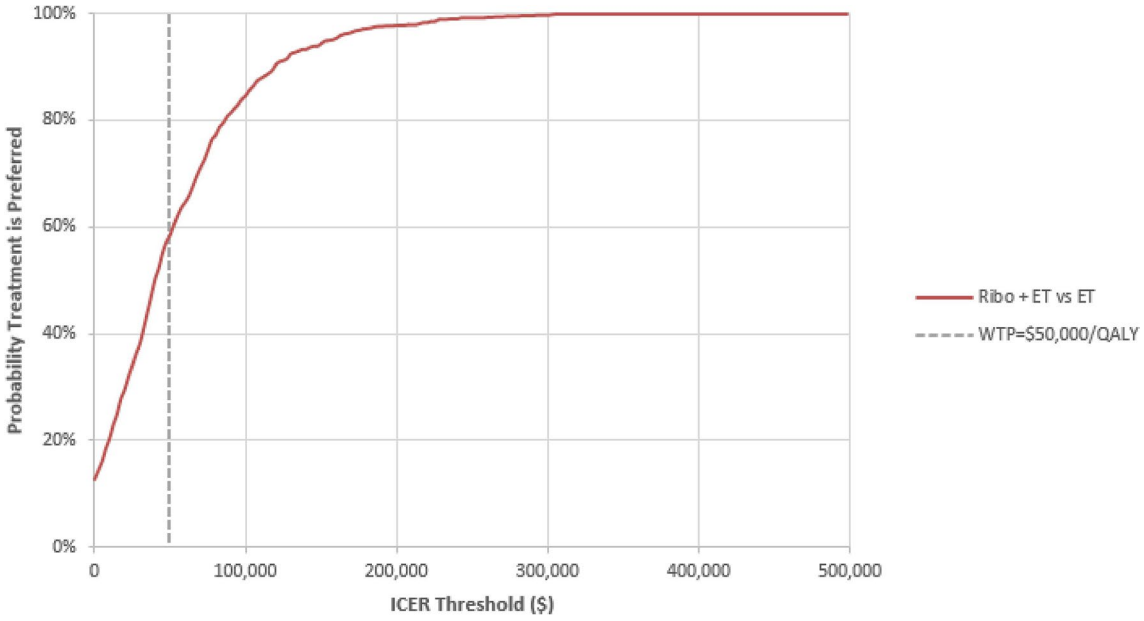


Fig. 3 Pairwise cost-effectiveness acceptability curve. *ET* endocrine therapy, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year, *Ribo* ribociclib, *WTP* willingness to pay

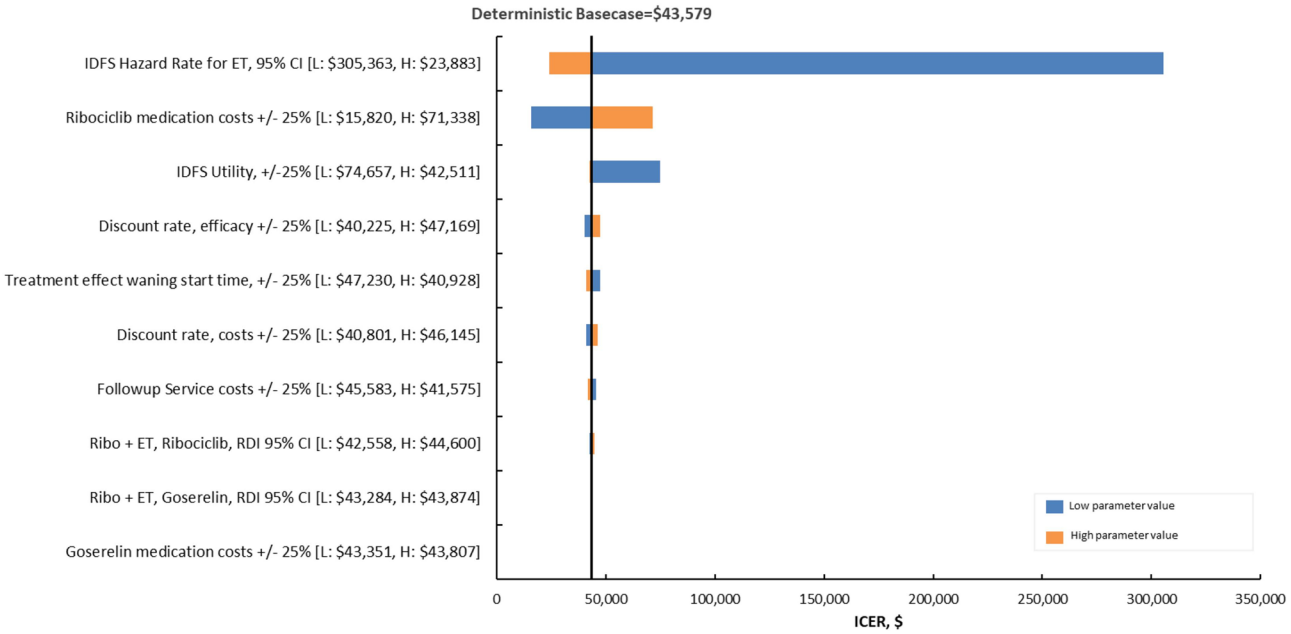


Fig. 4. Deterministic sensitivity analysis results for the comparison against AI alone. *AI* aromatase inhibitor, *CI* confidence interval, *ET* endocrine therapy, *H* high, *ICER* incremental cost-effectiveness ratio, *iDFS* invasive disease-free survival, *L* low, *RDI* relative dose intensity, *Ribo* ribociclib

4 Results

The probabilistic base case was estimated using 1,000 Monte Carlo simulations, and the results are summarized in Table 3. Tamoxifen was dominated by AI alone, and therefore it was decided to only present results comparing ribociclib + AI versus AI alone. The probabilistic ICER of ribociclib plus AI versus AI alone was $45,097 per QALY

gained, consistent with the deterministic base-case ICER of $43,579 per QALY gained.

Disaggregated healthcare costs are also summarized in Table 3. Medication acquisition costs were the driver of total costs for ribociclib plus AI ($104,971), whereas such costs were much lower for AI alone ($10,450). Additionally, post-DR healthcare costs (i.e., treatment of advanced breast cancer, follow-up and monitoring, and terminal care) were the driver of total costs for AI alone ($94,851), but were markedly lower for ribociclib ($35,854). This latter finding reflects not only the delay of DRs associated with ribociclib but also that the lifetime risk of DR with ribociclib (i.e., as estimated by the model) was 39% compared with 47% for AI alone. The cost-effectiveness acceptability curve of the probabilistic analysis is shown in Fig. 3. The probability that ribociclib plus AI was preferred over AI at a WTP threshold of $50,000 was 58.50%.

A tornado plot presenting the deterministic sensitivity analysis results for the comparison against AI alone is shown in Fig. 4. The ICER per QALY gained of ribociclib plus AI versus AI alone was most sensitive to variations in the iDFS hazard rates for AI, which resulted in an ICER of $305,363 for the lower bound and $23,883 for the upper bound. In the base case, iDFS transition probabilities for AI were estimated from extrapolations of iDFS survival data for patients randomized to AI in the NATALEE trial. Rather than varying parameters of the extrapolated distribution, the hazard rate for AI in the tornado analysis was estimated by applying the estimated hazard ratio for AI versus ribociclib to the projected iDFS curve for AI in the model. The hazard ratio for AI was then varied by the lower and upper bounds of the corresponding 95% CI.

Table 3 shows the results of the probabilistic scenario analyses. When assuming no treatment effect waning, the ICER was $34,744 for ribociclib plus AI versus AI alone. Scenarios with alternative discount rates of 0% and 3% were also explored and resulted in ICERs of $23,490 and $74,044, respectively.

5 Discussion

The objective of this analysis was to evaluate the cost-effectiveness of ribociclib plus AI versus AI alone and versus tamoxifen in persons with HR+/HER2− EBC receiving adjuvant therapy from a Canadian healthcare system perspective.

In the base case, the probabilistic ICER of ribociclib plus AI versus AI alone was $45,097 per QALY gained, and treatment with tamoxifen was dominated by treatment with AI alone. Deterministic sensitivity analyses showed that the ICER was most sensitive to variations in iDFS hazard rates for AI and the medication costs of ribociclib.

The findings of the present analysis are broadly consistent with cost-effectiveness evaluations of ribociclib and other CDK4/6 inhibitors in the adjuvant setting conducted in other countries, though important differences exist across healthcare systems. In England, NICE TA1086 concluded that ribociclib plus an AI is a cost-effective use of National Health Service (NHS) resources for adjuvant treatment of HR+/HER2− EBC at high risk of recurrence, and recommended it for routine NHS funding [21]. Further, a cost-effectiveness analysis from the Greek healthcare system perspective reported a probabilistic ICER of €7928 per QALY gained for ribociclib plus ET versus ET monotherapy, also concluding that ribociclib is cost-effective [33]. These findings reinforce the clinical and economic value of ribociclib as a cost-effective adjuvant treatment for HR+/HER2− EBC, supporting its broader adoption for patients at high risk of recurrence.

The CDA's reanalysis of the abemaciclib submission, another CDK4/6 inhibitor approved in the adjuvant setting in Canada, estimated an ICER of $133,903 per QALY gained versus ET alone [13]. The more favorable ICER for ribociclib may reflect differences in drug pricing, treatment duration (3 years for ribociclib versus 2 years for abemaciclib), and the broader eligible patient population under NATALEE compared with the more restrictive monarchE criteria.

The model predicts that ribociclib plus AI reduces the lifetime risk of DR from 47% to 39% compared with AI alone, translating into meaningful reductions in the use of expensive metastatic breast cancer treatments. These downstream cost savings partially offset the higher upfront drug acquisition costs of ribociclib, an important consideration for decision makers assessing the overall budget impact of reimbursement.

As with all economic evaluations, the methods implemented in the present set of analyses are subject to limitations. First, there is uncertainty in extrapolating outcomes from the NATALEE trial with a median follow-up of 49.6 months to a lifetime time horizon. As such, results of these analyses could vary with alternative parametric distributions used to extrapolate iDFS. Second, outcomes of patients in controlled settings such as clinical trials tend to be more favorable than those in the real world, due to selection bias, where enrolled patients are typically healthier, more adherent, and more closely monitored than the broader population eligible for treatment, and due to factors related to access to medical care. Results of this analysis may therefore differ when using efficacy outcomes examined in real-world clinical practice. Additionally, there is uncertainty surrounding the durability of the treatment effect observed with ribociclib plus AI in the NATALEE trial. At the time of writing, the treatment effect on iDFS observed with ribociclib plus AI versus AI alone in the NATALEE trial was durable up until the latest publicly available data cutoff of July 9, 2025 [35].

Consistent with recent HTA assessments of other treatments for EBC, the model assumed this treatment effect would begin to wane 8 years after treatment initiation. However, as follow-up is ongoing in NATALEE, it is possible that some future analysis may provide additional insights on the durability and duration of the treatment effect. As such, the assumptions surrounding treatment effect waning employed in this model may be biased to the extent that the duration of the treatment effect associated with ribociclib plus AI may vary in a real-world setting. Finally, while model input values were sourced from publicly available Canadian sources wherever possible, certain inputs (AE utility decrements, and healthcare resource utilization of follow-up medical services) were informed by published economic models developed for the UK healthcare system perspective, as reliable estimates from the Canadian setting were unavailable at the time of model development.

6 Conclusion

Results of this study suggest that ribociclib plus AI as adjuvant treatment for patients with HR+/HER2− EBC is expected to yield substantial gains in LYs and QALYs compared with AI alone and tamoxifen in Canada. While total breast cancer-related healthcare costs are higher with ribociclib than with current comparators, this is primarily driven by increased drug acquisition costs. Importantly, the model predicts reduced lifetime risk of DR with ribociclib plus AI, with consequent cost savings from avoided advanced or metastatic breast cancer treatment. This is consistent with the sustained reduction in disease recurrence risk observed in the NATALEE trial, which represents a critical benefit for patients with EBC. Overall, findings from this study support that ribociclib is cost-effective at the commonly used WTP threshold of $50,000 per QALY gained in Canada.

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Declarations

Conflict of Interest Dr. Sandeep Sehdev previously acted as research support in advisory boards and other consultations for Novartis, Eli Lilly, AstraZeneca, Merck, Daiichi Sankyo, and Roche, and previously received speaking fees from Novartis, Eli Lilly, AstraZeneca, Knight, Gilead, Daiichi Sankyo, and Roche. Dr. Christine Brezden-Masley received research grants and participated in clinical trials receiving funding from Pfizer, AstraZeneca, Novartis, Eli Lilly, Gilead Sciences, Astellas, Daiichi Sankyo, and Merck. Dr. Brezden-Masley also previously received speaker fees from Amgen, Pfizer, AstraZeneca, Novartis, Knight, Eli Lilly, Gilead, Astellas, BMS, Merck, Daiichi Sankyo, and Roche, and acted as a medical advisory consultant for Amgen, Pfizer, AstraZeneca, Novartis, Knight, Eli Lilly, Gilead, Astellas, BMS, Duchesnay, Merck, Daiichi Sankyo, and Roche. N. Sabater Anaya, D. Soliman, K. El Ouagari, D. Stellato, and T. Vincken have no conflicts of interest to declare.

Author Contributions N. Sabater Anaya, D. Soliman, K. El Ouagari, D. Stellato, and T. Vincken were involved with the study conception, analysis interpretation, manuscript drafting, and revision. C. Brezden-Masley, K. El Ouagari, and S. Sehdev were involved with analysis interpretation, manuscript drafting, and revision.

Data Availability This article utilized secondary analyses of NATALEE trial data provided by Novartis.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication (From Participants) Not applicable.

Code Availability Not applicable.

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