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# Cost–utility of adjuvant zoledronic acid in patients with breast cancer and low estrogen levels

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## ABSTRACT

**Background** Adjuvant zoledronic acid (ZA) appears to improve disease-free survival (DFS) in women with early-stage breast cancer and low levels of estrogen (LLE) because of induced or natural menopause. Characterizing the cost–utility (CU) of this therapy could help to determine its role in clinical practice.

**Methods** Using the perspective of the Canadian health care system, we examined the CU of adjuvant endocrine therapy with or without ZA in women with early-stage endocrine-sensitive breast cancer and LLE. A Markov model was used to compute the cumulative costs in Canadian dollars and the quality-adjusted life-years (QALYs) gained from each adjuvant strategy, discounted at a rate of 5% annually. The model incorporated the DFS and fracture benefits of adjuvant ZA. Probabilistic and one-way sensitivity analyses were conducted to examine key model parameters.

**Results** Compared with a no-ZA strategy, adjuvant ZA in the induced and natural menopause groups was associated with, respectively, $7,825 and $7,789 in incremental costs and 0.46 and 0.34 in QALY gains for CU ratios of $17,007 and $23,093 per QALY gained. In one-way sensitivity analyses, the results were most sensitive to changes in the ZA DFS benefit. Probabilistic sensitivity analysis suggested a 100% probability of adjuvant ZA being a cost-effective strategy at a threshold of $100,000 per QALY gained.

**Conclusions** Based on available data, adjuvant ZA appears to be a cost-effective strategy in women with endocrine-sensitive breast cancer and LLE, having CU ratios well below accepted thresholds.

**Key Words** Adjuvant therapy, zoledronic acid, breast cancer, bone health, cost–utility, economic analyses

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## INTRODUCTION

More than 50% of breast cancer patients present with early-stage endocrine-sensitive disease. In that group, breast cancer outcomes have improved significantly over time partly because of increasingly efficacious adjuvant therapies[1]. Based on favourable preclinical data[2], mitigation of therapy-related bone density loss in the adjuvant setting[3–5], and prevention of skeletal events in the metastatic setting[6], the intravenous bisphosphonate zoledronic acid (ZA) has been investigated as an adjuvant therapy for breast cancer.

Marked methodologic heterogeneity has complicated the interpretation of trials examining adjuvant ZA in early breast cancer. Many of the completed trials investigated adjuvant bisphosphonate therapy for its effect on bone health[7–12]. Those trials often compared early with delayed bisphosphonate therapy rather than adjuvant ZA with no bisphosphonate, or considered primary endpoints that were unrelated to breast cancer outcomes. The only two phase III trials that considered cancer-specific primary endpoints and compared adjuvant therapy with and without ZA (ABCSG-12 and AZURE) independently suggested that adjuvant ZA improves breast cancer outcomes in patients with low circulating estrogen levels secondary to induced or natural menopause[13,14]. Meta-analyses of adjuvant ZA and adjuvant bisphosphonate trials as a whole appear to confirm the benefit in that subgroup of patients[6,15–17].

In many jurisdictions, the adoption of adjuvant ZA into routine clinical practice will depend on its "value for money" in addition to its clinical benefit. To further inform

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treatment and regulatory decisions, we performed a cost–utility (CU) analysis of the incremental cost per quality-adjusted life-year (QALY) gained associated with adjuvant ZA in patients with early-stage endocrine-sensitive breast cancer and low levels of estrogen (LLE).

## METHODS

### Cohort

Our study examined two hypothetical cohorts of women undergoing adjuvant therapy after initial surgical resection of early-stage endocrine-sensitive breast cancer. The first cohort (induced menopause) assumed an average age of 40 years and included women treated with adjuvant ovarian suppression using a luteinizing-hormone releasing-hormone agonist for 3 years, as in the ABCSG-12 trial[13]. Adjuvant tamoxifen was given concurrently for a total of 5 years. The second cohort (natural menopause) assumed an average age of 60 years and included postmenopausal women treated with adjuvant endocrine therapy for a total of 5 years.

In the induced menopause group, adjuvant endocrine therapy consisted of tamoxifen (because the aromatase inhibitor arm was not superior to tamoxifen in the ABCSG-12 trial[13]). The distribution of adjuvant endocrine therapy in the natural menopause group was based on expert opinion representing common Canadian practice.

### Markov Model

The analysis took a Markov approach by defining a number of possible health states and modelling the probability of transition from one state to another in monthly cycles (Figure 1). The model was developed in Excel (Microsoft Corporation, Redmond, WA, U.S.A.) to examine the CU of adjuvant ZA in addition to endocrine therapy ("ZA strategy") relative to adjuvant endocrine therapy alone ("no-ZA strategy").

In the primary analysis, ZA was given per the AZURE schedule (4 mg by intravenous infusion every 1 month for 6 doses, followed by every 3 months for 8 doses, followed by every 6 months for 5 doses)[14]. Cumulative costs and outcomes associated with each strategy were determined over a defined number of cycles, reflecting a lifetime horizon. Costs and outcomes were both discounted by 5% annually. The analysis reported per-patient cumulative and incremental costs in Canadian dollars and outcomes in QALYs gained. The CU was then expressed as the cost per QALY gained—that is, the incremental CU ratio (ICUR)—for a ZA strategy compared with a no-ZA strategy. The analysis took a probabilistic approach and used 5000 iterations per cohort to estimate the uncertainty related to costs and effects.

### Health States

The model incorporated 7 distinct health states (Figure 1). All patients entered the model in the "On therapy" state after surgical resection and could transition to other states based on event rates derived from the literature and described in the Event Rates subsection (next). Only patients treated with ZA could transition into the "Osteonecrosis of the jaw" state[18]. All patients were subject to state-specific and age-specific background mortality based on Canada life tables[19].

### Event Rates

Table I shows key model parameters. The risks of recurrence in the absence of adjuvant systemic therapy over model years 0–15 was derived from the Early Breast Cancer Trialists' Collaborative Group meta-analysis[1]. The specific risk in each year was modelled using a beta distribution, but the resulting lifetime risk was nonparametric. The relative DFS benefit with the addition of adjuvant ZA to endocrine therapy was pooled from the ABCSG-12 and AZURE trials (Table I)[6]. The primary analysis assumed no carryover benefit for adjuvant ZA beyond the 5 years of therapy.

Osteonecrosis of the jaw necessitating discontinuation of ZA developed in 1.6% of the patients in AZURE (Table I)[18]. Of those patients, 46% required minor surgical procedures[25]. Although no other specific adverse effects were modelled, adjuvant ZA was assumed to be associated with a small utility deficit applied uniformly during ZA therapy (Table II).

Baseline fracture rates and the anatomic distribution of fractures were estimated from the trials of adjuvant endocrine therapies in the relevant setting (Table I)[13,21–24]. The reduction in fracture risk associated with ZA therapy was based on ABCSG-12 in the induced menopause cohort (hazard ratio: 0.71) and the published literature in the natural menopause cohort (hazard ratio: 0.65)[6,13].

For other parameters that did not vary between the treatment strategies, please refer to our previously published work[26,27]. Table III shows a list of model assumptions.

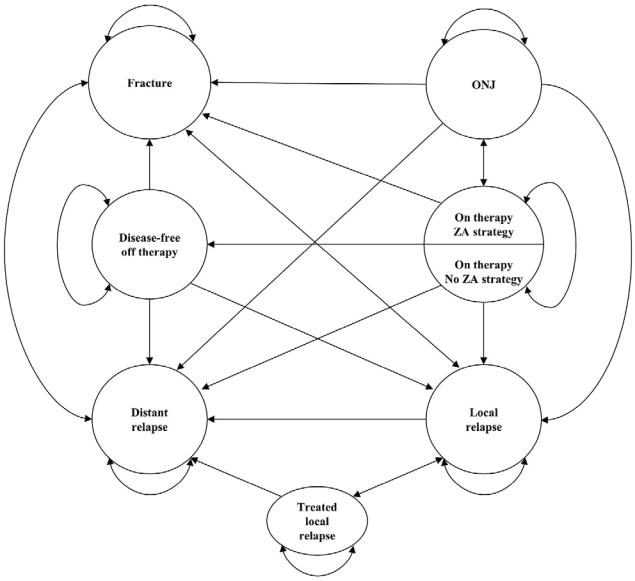


**FIGURE 1** Markov model schema. Health states are shown in circles, and possible transitions between health states are depicted by arrows. All patients enter the model in either the "On therapy – ZA strategy" or "On therapy – No ZA strategy" state and move to other health states according to transition probabilities. Only patients treated with ZA can transition into the "ONJ" state. Patients were subject to mortality in all states based on state-specific and age-adjusted background probabilities. ZA = zoledronic acid; ONJ = osteonecrosis of the jaw

**TABLE I** Key model parameters

| Parameter | Distribution | Point estimate | Standard deviation | Reference |
|---|---|---|---|---|
| *Natural history* | | | | |
| Risk of relapse[a] | | | | |
| Induced menopause | Nonparametric | 31.6% | 0.5 | EBCTCG, 2005[1] |
| Natural menopause | | | | |
| Tamoxifen | Nonparametric | 30.5% | 0.5 | EBCTCG, 2005[1] |
| Aromatase inhibitor | Nonparametric | 26.5% | 0.7 | EBCTCG, 2005[1] |
| Sequential combinations | Nonparametric | 27.5% | 0.5 | EBCTCG, 2005[1] |
| Distant relapse survival | Poisson | 21 Months | 6 | Hillner[20] |
| Fracture risk | | | | |
| Induced menopause | Beta | 2% | 0.6 | Gnant *et al.*, 2009[13] |
| Natural menopause | | | | |
| Tamoxifen | Beta | 4% | 0.3 | Baum *et al.*, 2003[21]; Howell *et al.*, 2005[22] |
| Aromatase inhibitor | Beta | 6% | 0.3 | Coombes *et al.*, 2004[23]; Goss *et al.*, 2005[24] |
| *Zoledronic acid* | | | | |
| Hazard ratio for DFS | Beta | 0.71 | 0.01 | Wong *et al.*, 2012[6] |
| Hazard ratio for fracture | | | | |
| Induced menopause | Beta | 0.71 | 0.07 | Gnant *et al.*, 2009[13] |
| Natural menopause | Beta | 0.65 | 0.07 | Wong *et al.*, 2012[6] |
| Osteonecrosis of the jaw | | | | |
| Risk | Beta | 1.6% | 0.3 | Rathbone *et al.*, 2013[18] |
| Resolution rate | Beta | 35% | 9 | Rathbone *et al.*, 2013[18] |

[a] Calculated from a uniform risk of relapse, with application of the benefit from each individual endocrine therapy.
EBCTCG = Early Breast Cancer Trialists' Collaborative Group; DFS = disease-free survival.

## Costs and Utilities

The analysis took a direct health system payer perspective and considered the costs associated with administration of all adjuvant therapies, as well as the downstream costs of follow-up and breast cancer recurrence (Table II). Up-front costs were estimated based on local unit costs at the QEII Health Sciences Centre in Halifax, Nova Scotia. The costs of managing adverse effects, breast cancer follow-up, and treatment of recurrent disease have previously been reported and were derived from the literature[28,29]. The average cost for management of osteonecrosis of the jaw during the first month was calculated assuming that all patients underwent conservative treatment and that a proportion also required surgical intervention. The cost of conservative treatment was estimated based on expert opinion, and the cost of surgical procedures was derived from the literature[30]. All costs were adjusted to 2014 Canadian dollars using the Consumer Price Index (health care component)[31]. Utility weights for individual health states were multiplicative and derived from a published database (https://research.tufts-nemc.org/cear4/Default.aspx) and from the literature (Table II)[32].

## Sensitivity Analyses

Cost-effectiveness acceptability curves generated through probabilistic sensitivity analyses are presented to illustrate the probability of a ZA strategy being cost-effective across a range of willingness-to-pay thresholds. Tables I and II show the distribution and ranges of individual model parameters tested in the probabilistic sensitivity analyses. One-way sensitivity analyses were also performed to determine the effect of individual model parameters and assumptions on outcomes. The latter analyses included scenarios in which ZA DFS and fracture benefits were individually eliminated, and a scenario in which ZA was dosed using the less-frequent ABCSG-12 schedule[13]. Finally, although adjuvant ovarian suppression is not routine practice in our jurisdiction[33], the primary analysis assumed that adjuvant treatment for premenopausal women included ovarian suppression using an luteinizing-hormone releasing-hormone agonist in both the ZA and no-ZA strategies. Another scenario was therefore included in which ovarian suppression was administered only in the ZA strategy. The remaining one-way sensitivity analyses are described in the Results section.

**TABLE II** Model costs and utilities

| Parameter | Point estimate | Standard deviation | Duration | Reference |
|---|---|---|---|---|
| *Cost (dollars)*[a] | | | | |
| Zoledronic acid (per dose) | 543 | 136 | 5 Years | QEII HSC[b] |
| LHRH agonist (per year) | 3,150 | 788 | 3 Years | QEII HSC[b] |
| Tamoxifen (per month) | 11 | 3 | 5 Years | QEII HSC[b] |
| AI (per month) | 161 | 40 | 5 Years | QEII HSC[b] |
| Fracture | 6,484 | 1,621 | — | 29 |
| Osteonecrosis of the jaw | | | | |
| First month | 2,045 | 511 | 1 Month | 30 |
| Subsequent months | 100 | 25 | Variable | — |
| Follow-up | | | | |
| Years 1–2 | 61 | $15 | 2 Years | 28 |
| Subsequent years | 38 | $9 | Variable | 28 |
| Distant relapse | $37,700 | 1,724 | 21 Months | 28 |
| Local relapse | $12,344 | 1,756 | 4 Months | 28 |
| *Utilities*[c] | | | | |
| Zoledronic acid | 0.99 | 0.00 | 5 Years | — |
| Endocrine therapies | 0.95 | 0.01 | 5 Years | 32 |
| Fracture | | | | |
| Acute phase | 0.80 | 0.02 | 1 Year | 32 |
| Chronic phase | 0.98 | 0.00 | Life | 32 |
| Osteonecrosis of the jaw | 0.67 | 0.09 | Variable | 33 |
| Disease-free | 0.95 | 0.00 | Life | 32 |
| Distant relapse | 0.60 | 0.04 | 21 Months | 32 |
| Local relapse | | | | |
| First | 0.70 | 0.03 | 4 Months | 32 |
| Second | 0.50 | 0.05 | 4 Months | 32 |
| Treated local relapse | 0.85 | 0.01 | Life | 32 |
| Death | 0.00 | — | — | 32 |

[a] In probabilistic sensitivity analysis, all costs were assumed to have log-normal distribution.
[b] Derived from local unit costs at the QEII Health Sciences Centre (QEII HSC).
[c] In probabilistic sensitivity analysis, all utility weights were assumed to have 1 log-normal distribution.
LHRH = luteinizing-hormone releasing-hormone; AI = aromatase inhibitor.

## RESULTS

Table IV shows the per-patient cumulative costs and QALY gains in each cohort. Relative to the no-ZA strategy, adjuvant ZA was associated with incremental costs and QALY gains in both the induced and natural menopause cohorts. In the induced menopause group, ZA was associated with a per-patient incremental cost of $7,825 [95% confidence interval (CI): $6,875 to $8,554] and 0.46 QALYs gained (95% CI: 0.25 to 0.64 QALYs gained), leading to an ICUR of $17,007 (95% CI: $10,742 to $34,216) per QALY gained. In the natural menopause group, ZA was associated with a per-patient incremental cost of $7,789 (95% CI: $6,792 to $8,342) and 0.34 QALYs gained (95% CI: 0.20 to 0.49 QALYs gained), leading to an ICUR of $23,093 (95% CI: $13,861 to $41,710) per QALY gained.

The cost-effectiveness acceptability curves suggested that the probability of adjuvant ZA being a cost-effective strategy relative to no-ZA at a threshold of $100,000 per QALY gained was 100% in both the induced and the natural menopause groups (Figure 2).

Figure 3 shows the one-way sensitivity analyses, which demonstrated that the CU of ZA was most sensitive to changes in its DFS benefit, dosing schedule (AZURE vs. ABCSG-12), and elimination of adjuvant ovarian suppression in patients treated on the no-ZA strategy. Overall, the CU results were robust to reasonable ranges of uncertainties. A scenario in which the ZA DFS benefit was eliminated (leaving only a fracture benefit) showed ICURs of $102,169 and $117,066 per QALY gained in the induced and natural menopause groups respectively. When the less-frequent dosing schedule from ABCSG-12 was considered, the ICURs

**TABLE III** Primary analysis model assumptions

| |
|---|
| Chemotherapy, endocrine therapy, and radiation treatment were similar for both strategies[a]. |
| Treatment and survival after relapse were similar for both strategies[a]. |
| Nonparametric breast cancer recurrence rates were derived from Early Breast Cancer Trialists' Collaborative Group data[1]. |
| The ratio of local to distant relapse was 1:2[a]. |
| Locoregional relapse and new contralateral cancers were combined as local relapse[a]. |
| Patients with local relapse were treated for 4 months, and then entered the treated local relapse state[a]. |
| Patients with local relapse were at risk of synchronous distant relapse and had double the risk of subsequent relapse events[a]. |
| The instant rate of distant relapse in patients with local relapse was 20%. |
| Patients could experience only two local relapses. Subsequent relapses were distant[a]. |
| Patients with distant relapses had a median survival of 21 months[20]. |
| Patients could transition into the death state from any other state based on state-specific and background age-adjusted mortality probabilities[19]. |
| Adjuvant endocrine therapy in the naturally menopausal cohort included 40% aromatase inhibitor alone, 20% tamoxifen alone, and 40% sequential combination strategies[b]. |
| Adjuvant luteinizing-hormone releasing-hormone agonist therapy consisted of leuprolide 45 mg by subcutaneous injection every 6 months[b]. |
| The utility penalty associated with zoledronic acid was calculated as one fifth that of endocrine therapy[b]. |
| Patients could transition into the osteonecrosis of the jaw state only during zoledronic acid treatment[b]. |
| Osteonecrosis of the jaw resolved in 35% of affected patients after a median duration of 803 days[18]. |
| The fracture state included acute and chronic phases with different costs, utilities, and durations[a]. |

[a] Per our previous work[26,27].
[b] Expert opinion.

**TABLE IV** Cumulative results

| Cohort | Zoledronic acid strategy | Cumulative | |
|---|---|---|---|
| | | Cost ($) | QALYs gained |
| Induced menopause | No | 26,606 | 12.4 |
| | Yes | 34,431 | 12.9 |
| Natural menopause | No | 21,448 | 10.9 |
| | Yes | 29,238 | 11.3 |

QALY = quality-adjusted life-year.

associated with adjuvant ZA were $3,899 and $5,506 per QALY gained in the induced and natural menopause groups respectively[13]. In a one-way sensitivity analysis in which ovarian suppression was administered only in the ZA strategy, adjuvant ZA remained cost-effective, with an ICUR of $35,139 per QALY gained.

## DISCUSSION

Pharmacoeconomic evaluations are important considerations in the assessment of novel medical therapeutics and novel indications for established interventions[34,35]. Our CU evaluation suggests that adjuvant ZA is an economically favourable therapy in women with early-stage endocrine-sensitive breast cancer and LLE. The ICURs of $17,007 and $23,093 per QALY gained in the primary analysis are considered "highly cost-effective" by the World Health Organization and are well within the commonly cited North American threshold of $100,000[36–38].

The present pharmacoeconomic study is the first to consider both the fracture prevention and DFS benefits associated with adjuvant ZA. Our results accord with the limited data published to date, including two industry-funded CU analyses[39,40]. Logman *et al.*[39] performed a CU analysis of upfront and delayed ZA strategies for the prevention of adjuvant aromatase inhibitor–induced bone loss among postmenopausal women with breast cancer. Treatment with ZA consisted of 4 mg intravenous infusions every 6 months for up to 5 years during therapy with adjuvant aromatase inhibitor. The study took the perspective of the United Kingdom's National Health Service and was based on interim results from the ZO-FAST study, considering only the fracture benefit of adjuvant ZA[41]. Compared with adjuvant treatment omitting ZA, upfront and delayed ZA resulted in ICURs of £21,973 and £16,069 per QALY gained—both considered "highly acceptable"[39]. Lux *et al.*[40] published a second CU analysis of adjuvant ZA from the perspective of the German health care system. That study was based on the ZA dosing and results from ABCSG-12 and considered only the DFS benefit[13]. The results suggested that adjuvant ZA was less costly and more effective (that is, dominant) when incorporated into adjuvant treatment including ovarian suppression in women with endocrine-sensitive breast cancer. These industry-sponsored studies used efficacy data from single trials[39,40]; by contrast, our study used pooled efficacy results from all trials of adjuvant ZA in the relevant setting.

Our study has several limitations that are partly a result of the significant methodologic heterogeneity of the adjuvant ZA trials. Where possible, those limitations were addressed in specific one-way sensitivity analyses. In the primary analysis, the hazard ratio for DFS with the use of adjuvant ZA was taken from a pooled efficacy analysis of phase III clinical trials. However, uncertainty about the true breast cancer recurrence benefit of adjuvant ZA remains, and in our study, the ZA CU was most sensitive to changes in that parameter. In the scenario in which the ZA DFS benefit was eliminated entirely, the resultant ICURs rose above commonly accepted thresholds. That observation suggests that, for adjuvant ZA to be cost-effective, it must provide some improvement in DFS.

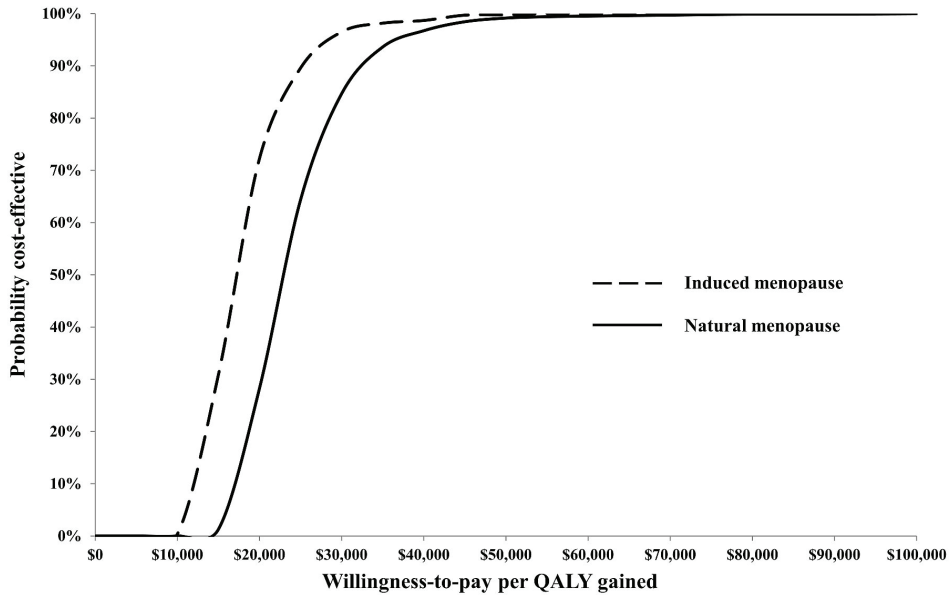


**FIGURE 2** Cost-effectiveness acceptability curves. The *x* axis shows the willingness-to-pay per quality-adjusted life-year (QALY) gained in Canadian dollars, and the *y* axis shows the probability that the strategy of therapy with zoledronic acid is cost-effective. The likelihood that that strategy is cost-effective at various willingness-to-pay thresholds is shown for both the induced and the natural menopause groups, based on probabilistic sensitivity analysis.

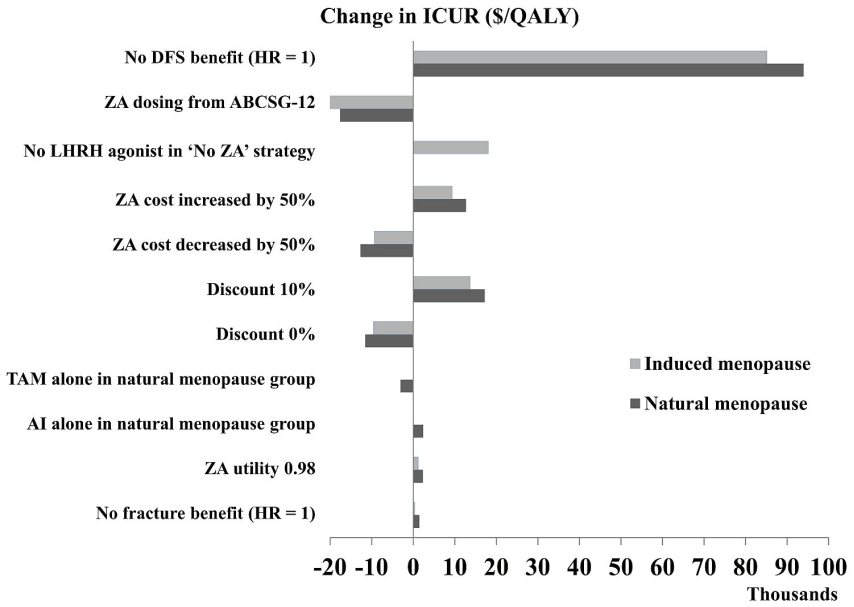


**FIGURE 3** Results of the one-way sensitivity analysis. The *y* axis shows the parameters and values tested in the one-way sensitivity analysis; the *x* axis reflects the resultant change in incremental cost-utility ratio (ICUR) in Canadian dollars per quality-adjusted life-year (QALY) gained (primary analysis results). Results are shown for the induced and natural menopause groups separately. DFS = disease-free survival; HR = hazard ratio; ZA = zoledronic acid; LHRH = luteinizing-hormone releasing-hormone; TAM = tamoxifen; AI = aromatase inhibitor.

Beyond those specific limitations, our hypothetical economic modelling study depends on multiple assumptions. Our probabilistic sensitivity analyses attempted to control for all possible uncertainties in the assumptions, and those analyses showed our results to be robust to reasonable changes in the model parameters. In the end, the CU results depend on model input and are, therefore, jurisdiction-specific. The ZA drug acquisition cost used

in the analysis could change in future when generic ZA becomes available. As that change occurs, the CU of adjuvant ZA will become more favourable.

## CONCLUSIONS

Compared with a no-ZA strategy of endocrine therapy, a strategy of adjuvant ZA plus endocrine therapy is associated with increased costs and QALY gains in women with early-stage endocrine-sensitive breast cancer and LLE. The resultant ICURS are considered highly cost-effective and would likely remain cost-effective even if the current evidence overestimates the DFS benefit of adjuvant ZA in the relevant setting[36]. It therefore appears that, economically, adjuvant ZA offers good value for money, further supporting its incorporation into routine clinical care for women with early-stage endocrine-sensitive breast cancer and LLE.

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### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none. This CU study was neither supported nor reviewed by industry.

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