EE317

Cost-effectiveness of Adjuvant Olaparib in Germline BRCA1/2-mutated, High-risk, Human Epidermal Growth Factor-2-negative Early Breast Cancer: A Canadian Perspective

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Introduction

- Breast cancer (BC) is the most common cancer in females in Canada, with an estimated incidence of 27,725 new cases in 2021. It is the third-leading cause of cancer mortality in the country, with 5,400 deaths annually, despite a relatively high five-year survival rate (89% across stages) due to the majority of patients being diagnosed in early stages.[1,2]
- Approximately 5–10% of patients with BC carry germline BRCA gene mutations (gBRCAm).[3]
- The current treatment landscape for early BC in Canada is informed by provincial and international guidelines[4-6] and until recently, there were no recommended adjuvant therapy options specific to patients with human epidermal growth factor-2-negative (HER2-) BC and a gBRCAm.
- In 2022, olaparib, a first-in-class poly(ADP)-ribose polymerase inhibitor (PARPi), and the first targeted adjuvant therapy for patients with gBRCAm, high-risk, human epidermal growth factor receptor 2 (HER2)-negative early BC (eBC), was approved.
- Approval was informed by the results of the OlympiA trial,[7] where 1 year of olaparib demonstrated significant improvement in invasive disease-free survival (iDFS) vs placebo in high-risk, HER2- (triple-negative BC [TNBC] or hormone receptor-positive [HR+]) gBRCAm stage I to III BC (hazard ratio [HR] 0.58; 99.5% confidence interval [CI]: 0.41, 0.82, p<0.001). In the second interim analysis, olaparib significantly improved overall survival vs placebo (HR 0.68; 98.5% CI: 0.47, 0.97; P=0.009).

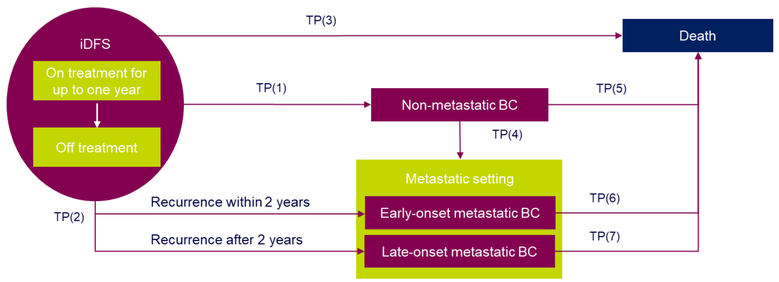
Objective

- This evaluation examined the cost-effectiveness of adjuvant olaparib vs Watch and Wait ([W&W], proxied by placebo), in gBRCAm1/2, high-risk, HER2- eBC previously treated with adjuvant or neoadjuvant chemotherapy, from a Canadian healthcare perspective.

Methods

- A cost-utility analysis was conducted, with outcomes expressed as incremental costs per quality-adjusted life year (QALY) as recommended by the Canadian Agency for Drugs and Technologies in Health guidelines.[8] Cost-effectiveness was also reported as incremental costs per life year (LY) gained.
- The target population aligned with the intent-to-treat population of the OlympiA trial[7] (adults [≥18 years] with gBRCAm, high-risk, HER2- eBC who have received prior adjuvant or neoadjuvant chemotherapy).
- To account for differences in future treatment and recurrence risk by HER2- status, total costs and outcomes were estimated separately for TNBC and HER2-/HR+, and combined to calculate an overall population incremental cost-effectiveness ratio (ICER), using the weights per the ITT population of OlympiA (82.3% TNBC and 17.7% HER2-/HR+, median age of 42-43 years)
- A semi-Markov state transition model was developed in Microsoft Excel® with five health states: iDFS, non-metastatic BC, early-onset metastatic BC, late-onset metastatic BC, and death (Figure 1).

Figure 1. Model structure (Semi-Markov model with 1-month cycle length)



Abbreviations: BC, breast cancer; iDFS, invasive disease-free survival; TP, transition probability

- Consistent with approaches used in past economic models in eBC, and supported by clinical literature and expert opinion, the risk of death after metastatic cancer was assumed to differ based on the timing of recurrence, defined as early-onset transition probability (TP6) and late-onset TP (TP7).
- The data sources informing TP1 to TP7 are summarized in Table 1.
- Due to low event numbers for pre-recurrence deaths in OlympiA (n=2), the risk of death from iDFS (TP3) was modelled using age- and gender-matched Canadian lifetable statistics adjusted for excess mortality risk of gBRCA mutation.[9,10]
- For TP1, TP2 and TP4 to TP7, standard parametric models (including exponential, lognormal, Weibull, loglogistic, Generalized Gamma, Gompertz and Gamma) were fit to the clinical data informing each transition probability to extrapolate clinical outcomes beyond the trial period. TP5 to TP7 were adjusted to ensure death risks remained above the age/gender/BRCA-adjusted lifetable statistics.
- The model assumed patients with TNBC who remain disease free for five years are at zero risk of recurrence, thereafter, supported by Canadian clinical experts and eBC long-term study data.[11,12]
- Based on Canadian clinical opinion, the model assumed that patients with HER2-/HR+ experience a lifetime risk of recurrence; however, it was acknowledged that limited data exist in this setting.
- Modelled costs included drug acquisition (including up to one year of olaparib) and administration, subsequent therapies, adverse events, hospitalization, and physician visits. QALYs were calculated using literature utility values.
- In the probabilistic base case, costs and outcomes were estimated over a lifetime horizon (57 years) with an annual discount rate of 1.5%. Deterministic and sensitivity analyses were performed.

Methods (cont.)

Table 1. Data sources informing each transition

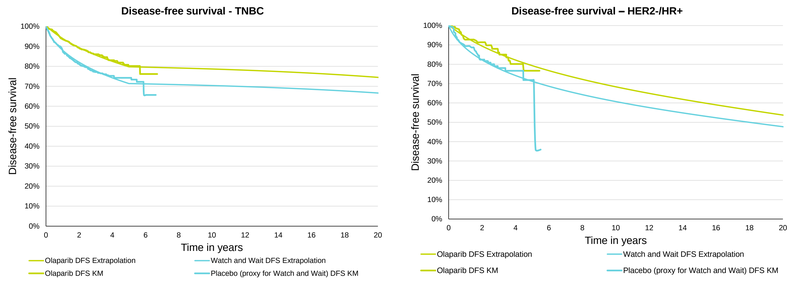
TP	Data source	Risk by treatment arm
TP1 and TP2: iDFS to disease recurrence	OlympiA, DCO2	Different
TP3: iDFS to death	Canadian general population mortality[9] Adjusted for excess mortality risk in patients with gBRCA[10]	Same
TP4: NM BC to metastatic BC	OlympiA, DCO2	Same
TP5: NM BC to death	OlympiA, DCO2	Same
TP6: EOM BC to death (recurrence within 2 years)	OlympiA, DCO2	Different, based on data from OlympiA
TP7: LOM BC to death (recurrence after 2 years)	Final OS analysis of OlympiAD	Same

Sources: 8. Mai et al., 2009; 9. Statistics Canada
Abbreviations: BC, breast cancer; DCO, data cutoff; EOM, early-onset metastatic; gBRCA, germline BRCA gene; iDFS, invasive disease-free survival; LOM, late-onset metastatic; NM, non-metastatic; OS, overall survival; TP, transition probability

Results

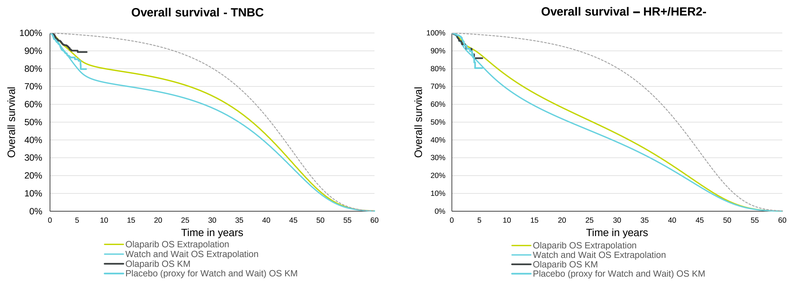
- In the TNBC population, over a 57-year time horizon, total discounted costs were $139,026 for olaparib and $74,685 for W&W; total discounted QALYs were 19.47 and 17.81, respectively. The resulting ICER was $40,654 per QALY gained for olaparib vs W&W.
- In the HER2-/HR+ population, total discounted costs were $191,945 for olaparib and $117,703 for W&W; total discounted QALYs were 16.17 and 14.81, respectively. The resulting ICER was $54,744 per QALY gained for olaparib vs W&W.
- The modelled survival curves are shown in Figure 2 and Figure 3.
- Based on a weighted average of the results for the TNBC and HR-positive/HER2-negative populations, in the HER2-negative ITT population, adjuvant olaparib was associated with an incremental gain in LYs and QALYs (1.50 and 1.61, respectively) vs W&W, and incremental costs of $68,563 vs W&W. The resulting ICER was $42,668 per QALY gained for olaparib vs W&W.

Figure 2. iDFS extrapolation and Kaplan-Meier curves



Abbreviations: DFS, disease-free survival; EOM, early-onset metastatic; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KM, Kaplan-Meier; TNBC, triple-negative breast cancer

Figure 3. OS extrapolation and Kaplan-Meier curves



Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; KM, Kaplan-Meier; OS, overall survival; SMR, standardized mortality rate; SoC, standard of care; TNBC, triple-negative breast cancer

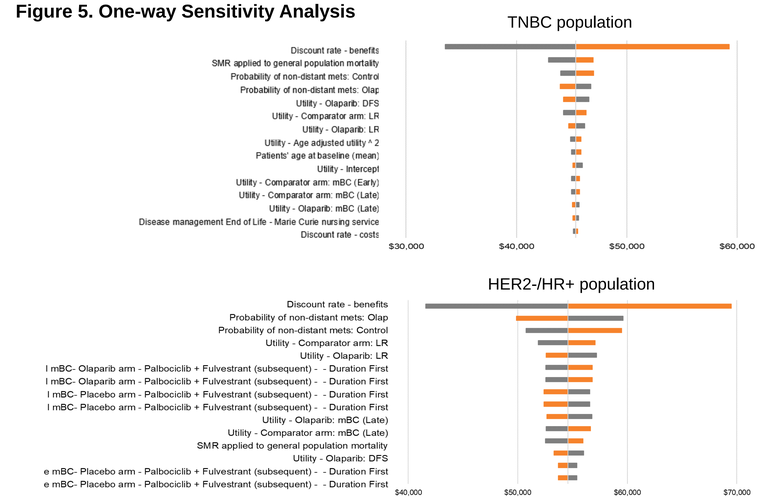
- Results were consistent across HER2-negative subgroups (Figure 2, 3, and 4) and scenario analyses.
- In the one-way sensitivity analysis, the ICER was most sensitive to changes in the discount rates on QALYs and the SMR applied to the general population mortality (Figure 5) in both subpopulations.
- For TNBC, all scenarios except one (discounting for health benefits of 3.0%) were below the willingness-to-pay (WTP) threshold of $50,000 in Canada.

Results (cont.)

Figure 4. Cost-effectiveness planes

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; QALY, quality-adjusted life year; TNBC, triple-negative breast cancer

Figure 5. One-way Sensitivity Analysis



Abbreviations: BC, breast cancer; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LR, locoregional recurrence; SMR, standardized mortality rate; TNBC, triple-negative breast cancer

Discussion

- Our results suggest that over a lifetime horizon, 1 year of adjuvant olaparib would yield substantial health benefits vs. W&W, with meaningful improvements in LYs and QALYs and a weighted ICER for the HER2-negative population (including HER2-/HR+ and TNBC) that is below the WTP threshold in Canada.
- The strengths of the analysis include the extensive use of the large, well-designed, OlympiA trial (n=1,836) to inform model extrapolations, and the modeling of results by histology status to capture differences in outcomes between the TNBC and HER2-/HR+ populations. Clinical experts consulted during model development advised that the OlympiA trial results are generalizable to Canadian practice.
- Key limitations include the need to extrapolate short-term trial outcomes to a lifetime horizon which led to uncertainty in results, and the absence of other potential adjuvant options (capecitabine, pembrolizumab or abemaciclib) from the analysis due to a lack of efficacy data in gBRCA eBC. Despite these limitations, sensitivity analyses suggest that results were robust to uncertainty in most model parameters.

Conclusion

- Adjuvant olaparib is a cost-effective alternative to W&W in the treatment of patients with gBRCAm, high-risk, HER2-negative, eBC from a Canadian healthcare perspective

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