Technology Guidance

Olaparib

for treating germline BRCA-mutated HER2-negative high-risk early breast cancer

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Olaparib 100 mg and 150 mg tablets as adjuvant treatment of patients with germline BRCA-mutated, HER2-negative, high-risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy. Maximum duration of treatment: 1 year.

Funding status

Olaparib 100 mg and 150 mg tablets are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 March 2024.

Clinical indication, subsidy class and MediShield Life claim limit for olaparib are provided in the Annex.

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Factors considered to inform the recommendations for funding

Company-led submission

1.1. At the June 2023 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence submitted by the company and a review of the submission by one of ACE's evidence review centres for the technology evaluation of adjuvant olaparib for treating germline breast cancer gene mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative, high-risk early breast cancer (EBC) in patients previously treated with neoadjuvant or adjuvant chemotherapy. The company's requested listing was in line with the HSA-approved indication for olaparib.

1.2. Expert opinion was obtained from the MOH Cancer Drug Subcommittee and patient experts from local patient and voluntary organisations, who assisted ACE to ascertain the clinical value of olaparib.

1.3. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.4. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

1.5. Following a negative recommendation during the June 2023 meeting, based on uncertain clinical benefit and unfavourable cost-effectiveness, the company submitted a revised proposal, which the Committee considered at the October 2023 DAC meeting.

Clinical need

2.1 The Committee noted that approximately 26 patients with gBRCAm, HER2-negative, high-risk EBC require adjuvant treatment each year in Singapore. The Committee acknowledged that breast cancers with germline BRCA mutations are generally more aggressive, with higher recurrence risk.

2.2 In local clinical practice, the choice of adjuvant treatment for high-risk EBC is dependent on hormone receptor (HR) status, HER2 expression and prior treatment with neoadjuvant or adjuvant chemotherapy. Most patients with triple-negative breast cancer (TNBC) receive neoadjuvant chemotherapy, followed by adjuvant

capecitabine if they have residual disease. Patients with HR-positive, HER2-negative EBC receive adjuvant abemaciclib with endocrine therapy. For a minority of patients with TNBC who receive adjuvant chemotherapy, current clinical management is watchful waiting. Therefore, the Committee considered the nominated comparators in the submission, capecitabine for the TNBC subgroup and abemaciclib for the HR-positive, HER2-negative subgroup, as reasonable.

2.3 The Committee considered testimonials from local patient experts about how breast cancer had negatively impacted their daily lives, physically, mentally, and emotionally, especially in the first few years after diagnosis. They noted that many patients experience stress, insomnia, family-planning challenges and fatigue, with fear of disease recurrence as their greatest concern. The Committee acknowledged that patients welcomed new treatments that are effective, affordable and have manageable side effects.

Clinical effectiveness and safety

Olaparib versus capecitabine and abemaciclib

3.1 The Committee noted there were no head-to-head trials comparing olaparib with either capecitabine or abemaciclib. Based on indirect treatment comparisons (ITCs) of olaparib (OlympiA), capecitabine (CIBOMA, CREATE-X) and abemaciclib (monarchE), olaparib did not result in statistically significant differences in iDFS or DFS relative to capecitabine in patients with TNBC (Table 1) or to abemaciclib in patients with HR-positive, HER2-negative EBC (Table 2).

3.2 The Committee acknowledged that differences in patient ethnicity, prior treatment with (neo)adjuvant chemotherapy and definition of high-risk for disease recurrence between olaparib and comparator trials limited the findings from the ITCs. The Committee also noted that OlympiA recruited only patients with gBRCA mutations, while comparator trials included patients regardless of gBRCA mutation status. Taken together, the Committee considered the ITC results to be uncertain.

3.3 The Committee acknowledged that the available evidence was inadequate to support a reliable assessment of the comparative safety of olaparib relative to capecitabine or abemaciclib.

3.4 Overall, the Committee considered that the submitted evidence did not show that olaparib was superior in terms of effectiveness or safety compared with capecitabine and abemaciclib, and any clinical benefit relative to the two nominated comparators was uncertain. The Committee concluded that at best, olaparib could be considered non-inferior to capecitabine in patients with TNBC, and non-inferior to abemaciclib in the patients with HR-positive, HER2-negative EBC.

Table 1: Indirect comparisons of the primary endpoint, iDFS (OlympiA)/DFS (CREATE-X, CIBOMA) in the TNBC subgroup

Olaparib trial and population	Capecitabine trials and populations	Hazard ratio (95% CI)		
		Olaparib *vs.* placebo	Capecitabine *vs.* observation/SoC	ITC: Olaparib *vs.* capecitabine
OlympiA TNBC (N=1509)	CREATE-X TNBC (N=286)	0.62 (0.49 to 0.79)	0.58 (0.39 to 0.87)	1.07 (0.67 to 1.70)
	CIBOMA all patients (TNBC) (N=876)		0.82 (0.63 to 1.06)	0.76 (0.53 to 1.08)
	CREATE-X TNBC + CIBOMA all patients (N=1162)		0.71 (0.51 to 1.00)[a]	0.87 (0.58 to 1.31)[b]
	CREATE-X TNBC + CIBOMA high-risk TNBC (N=416)		0.78 (0.41 to 1.49)[a]	0.79 (0.40 to 1.58)[b]
OlympiA TNBC neoadjuvant (N=722)	CIBOMA high-risk TNBC (N=130)	0.63 (0.46 to 0.85)	1.12 (0.64 to 1.97)	0.56 (0.30 to 1.06)

Abbreviations: DFS, disease-free survival; iDFS, invasive disease-free survival; ITC, indirect treatment comparison; SoC, standard of care; TNBC, triple-negative breast cancer.

[a] Meta-analysis performed using a random effects model.

[b] ITCs conducted based on meta-analysis of capecitabine trial results using a random effects model.

Table 2: Indirect comparisons of the primary endpoint, iDFS (OlympiA, monarchE) in the HR-positive, HER2-negative subgroup

Olaparib trial and population	Abemaciclib trial and populations	Hazard ratio (95% CI)		
		Olaparib *vs.* SoC	Abemaciclib *vs.* SoC	ITC: Olaparib *vs.* abemaciclib
OlympiA HR-positive (N=325)	monarchE all patients (HR-positive) (N=5637)	0.68 (0.40 to 1.13)	0.70 (0.59 to 0.82)	0.97 (0.56 to 1.69)
	monarchE Ki-67-high (N=2003)		0.63 (0.49 to 0.80)	1.08 (0.60 to 1.93)

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone-receptor; iDFS, invasive disease-free survival; ITC, indirect treatment comparison; SoC, standard of care.

Olaparib versus placebo

3.5 The Committee reviewed the clinical evidence in the submission from OlympiA, an ongoing phase III randomised controlled trial comparing olaparib and placebo.

3.6 In the intention-to-treat (ITT) population at median follow-up of 3.5 to 3.6 years (OlympiA's second data cut-off; July 2021), adjuvant olaparib was associated with a statistically significant improvement in the primary efficacy endpoint of invasive disease-free survival (iDFS) compared with placebo (HR 0.63; 95% CI 0.50 to 0.78) (Table 1). This reduction in hazard was numerically smaller than was observed for the first data cut-off (HR: 0.58; 99.5% CI 0.41 to 0.82).

3.7 Compared with placebo, olaparib was also associated with statistically significant improvements in the secondary efficacy endpoints of distant disease-free survival (DDFS) and overall survival (OS) (Table 3).

Table 3: Results of iDFS, DDFS and OS in OlympiA (ITT population) (Data cut-off 12 July 2021)

	Olaparib (N=921)	Placebo (N=915)
Invasive disease-free survival (iDFS)		
No. of events, n (%)	134 (14.5)	207 (22.6)
Median iDFS, months	Not reached	Not reached
Hazard ratio (95% CI)	0.63 (0.50 to 0.78)	
Distant disease-free survival (DDFS)		
No. of events, n (%)	107 (11.6)	172 (18.8)
Median DDFS, months	Not reached	Not reached
Hazard ratio (95% CI)	0.61 (0.48 to 0.77)	
Overall survival (OS)		
No. of events, n (%)	75 (8.1)	109 (11.9)
Median OS, months	Not reached	Not reached
Hazard ratio (98.5% CI)	0.68 (0.47 to 0.97)	

Abbreviations: CI, confidence interval; ITT, intention-to-treat.

3.8 At follow up, there were no clinically meaningful between-group differences reported for changes of Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scores and European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire – Core Questions 30 (EORTC QLQ-C30) global health status and functioning scores from baseline. Compared with placebo, EORTC QLQ-C30 nausea and vomiting symptom scores were increased in the olaparib arm at months 6 and 12 and returned to baseline at months 18 and 24.

3.9 In terms of safety, the Committee noted the incidence of adverse events (AEs) of any grade (91.8% versus 83.8%), grade ≥3 AEs (24.5% vs 11.3%), and AEs leading to treatment discontinuation (10.8% vs 4.6%) were consistently higher in patients treated with olaparib than those receiving placebo.

3.10 Overall, the Committee noted that long-term data was required to reliably determine the magnitude of the treatment benefits associated with olaparib. In addition, the higher proportion of patients with TNBC in OlympiA, compared with local clinical practice, might overestimate the treatment benefit of olaparib over placebo.

Cost effectiveness

Olaparib versus capecitabine and abemaciclib

4.1 In view of the non-inferiority claim between olaparib and its nominated comparators, the Committee agreed that a cost-minimisation approach was appropriate to assess the cost-effectiveness of olaparib. They acknowledged that the submission's cost-minimisation analysis (CMA) was overly complex and could not be independently verified. The Committee noted that a revised CMA was conducted to estimate the cost-neutral price of olaparib if it replaced capecitabine, abemaciclib or a weighted combination of both.

4.2 Using available data from relevant trials, the revised CMA estimated equi-effective doses as olaparib 300 mg twice a day for 10.21 months, capecitabine 1,250 mg/m^2 twice a day for 14 days in a 21-day cycle for 4.59 months and abemaciclib 150 mg twice a day for 21.69 months. Costs from drug administration, treatment monitoring and adverse events were also incorporated into the revised CMA.

4.3 The Committee noted the revised CMA results showed that a significant price reduction was required for olaparib to achieve price neutrality, when the price was weighted against both capecitabine and abemaciclib.

Olaparib versus placebo

4.4 The Committee also considered the results of the submission's cost-utility analysis (CUA) that compared olaparib with placebo based on OlympiA trial for the small TNBC subgroup who receives adjuvant chemotherapy. Key components of the economic evaluation provided in the submission are summarised in Table 4.

Table 4: Key components of the company-submitted economic evaluation

Component	Description
Type of analysis	Cost-utility analysis
Population	Patients with gBRCAm, HER2-negative, high-risk early triple negative early breast cancer
Outcomes	Total and incremental direct medical costs; total and incremental LY gained; total and incremental QALYs; ICER
Perspective	Singapore healthcare system
Type of model	Semi-Markov model
Time horizon	20 years in the base case 10 years, 15 years, 25 years and 57 years modelled in sensitivity analysis
Health states	Five health states: iDFS, non-metastatic breast cancer (non-mBC), early-onset mBC (onset during first 2 years), late-onset mBC (onset beyond the first 2 years), death
Cycle length	30.4375 days (1 month)
Transition probabilities	iDFS to non-mBC & iDFS to mBC: Parametric survival curves applied to OlympiA iDFS curves (arm-specific hazards). The transition probabilities from iDFS to non-mBC and iDFS to mBC health states were determined by the proportion of patients experiencing a non-distant recurrence event and distant recurrence event respectively, based on OlympiA trial data. Metastatic recurrences occurring prior to 2 years transition to the early-onset mBC health state, otherwise recurrences are late-onset mBC. iDFS to death: External all-cause mortality matched to the age and gender distribution in OlympiA – adjusted to incorporate excess mortality associated with BRCA mutations versus the general population. Both arms have same hazards. Non-mBC to mBC & non-mBC to death: Parametric survival curve applied to the time to event data from OlympiA (adjusted for competing events). Both arms have same hazards. Early-onset mBC to death & late-onset mBC to death: For early-onset mBC to death transition, parametric survival curves applied to the time to event data from OlympiA (arm-specific hazards). For late-onset mBC to death transition, external survival data using OlympiAD study (mBC) was incorporated in deriving the arm-specific hazards.

Health-related quality of life	• iDFS and non-mBC state utilities were derived from OlympiA trial and mapped to EQ-5D (UK tariffs) using Crott and Briggs algorithm = 0.869 (for both treatment arms) • Early-onset and late-onset mBC states utilities were literature-based, informed by Lidgren et al 2007 = 0.685 (for both treatment arms)
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Healthcare resource use • Subsequent treatment costs • AE management costs

Abbreviations: 1L, first-line; AE, adverse event; CUA, cost-utility analysis; gBRCAm, germline breast cancer gene mutated; EQ-5D, EuroQol-5 dimensions; HER2, human epidermal growth factor receptor 2; iDFS, invasive disease-free survival; ICER, incremental cost-effectiveness ratio; LY, life-year; mBC, metastatic breast cancer; QALY, quality-adjusted life-year.

4.5 The base-case incremental cost-effectiveness ratio (ICER) in the submission was between SG$15,000 and SG$45,000 per quality-adjusted life year (QALY) gained. However, the Committee considered the ICER to be highly uncertain and likely underestimated, in view of the following:

- The submission applied a time horizon of 20 years in the base case economic model. Given the median follow-up in the OlympiA trial was 3.5 to 3.6 years, the model implemented a substantial proportion of extrapolation.

- The model applied a restriction on the hazards for iDFS in the olaparib arm, which prevented the olaparib and placebo iDFS curves from converging. This was inconsistent with the observed data in the OlympiA trial that appeared to indicate some convergence from about 4 years onwards. The Committee acknowledged that by removing this restriction, the revised model permitted the curves to converge, which was in better alignment with the observed Kaplan-Meier data.

- The submission included the use of olaparib as post-progression treatment in the placebo arm for the metastatic breast cancer (mBC) health states. While some use of olaparib in mBC may occur, there is uncertainty in the extent of use and overall cost of olaparib treatment in the post-progression health states. The Committee acknowledged that it was reasonable to exclude the use of olaparib in mBC health states.

4.6 The Committee considered the revised base case, which accounted for the uncertainties in the company's model. Key changes to the economic model included applying a shorter time horizon, removing the hazard restriction on olaparib's iDFS curve and excluding the use of olaparib in downstream health states. These changes increased the ICER to between SG$45,000 and SG$75,000 per QALY gained. Scenario analyses exploring the influence of olaparib's price on the ICER showed that further price reductions were required to achieve reasonable ICERs.

4.7 Overall, based on the analyses incorporating both CMA and CUA results, the Committee concluded that olaparib did not represent a cost-effective use of healthcare resources at the price proposed by the company.

4.8 In October 2023, following a revised pricing proposal by the company, the Committee considered olaparib to be an acceptable use of healthcare resources for treating gBRCAm HER2-negative high-risk EBC.

Estimated annual technology cost

5.1 Using an epidemiological approach, the submission estimated that the annual cost impact to the public healthcare system would be between SG$1 million and SG$3 million over the first five years of listing olaparib on the MOH List of Subsidised Drugs for adjuvant treatment of gBRCAm, HER2-negative high-risk EBC in patients who have previously been treated with neoadjuvant or adjuvant chemotherapy.

5.2 The Committee considered that the submission estimates and price volume agreement (PVA) caps were high due to an overestimation of eligible patients and optimistic uptake rate of olaparib. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be less than SG$1 million.

5.3 In October 2023, the Committee considered the revised PVA adequate to manage the uncertainty of overall budget impact.

Additional considerations

6.1. The Committee acknowledged that, contingent on funding listing, the company had agreed to expand the existing patient assistance programme (PAP) for olaparib, which would provide further savings to patients in addition to MAF financial assistance.

Recommendations

7.1. In June 2023, based on the evidence submitted, the Committee recommended not listing olaparib on the MOH List of Subsidised Drugs as adjuvant treatment for gBRCAm, HER2-negative, high-risk early breast cancer due to uncertain clinical benefit and unfavourable cost-effectiveness at the price proposed by the company compared with alternative treatments.

7.2. In October 2023, the Committee recommended olaparib 100 mg and 150 mg tablets to be listed on the MAF for the adjuvant treatment of patients with gBRCAm, HER2-

negative, high-risk EBC. The Committee considered that the revised pricing proposal adequately addressed the issues in cost-effectiveness and budget certainty.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Olaparib 100 mg and 150 mg film-coated tablet	Adjuvant treatment of patients with germline BRCA-mutated, HER2-negative, high-risk early breast cancer who have previously been treated with neoadjuvant or adjuvant chemotherapy. Maximum duration of treatment: 1 year.	MAF (1 Mar 2024)	$1600 (1 Mar 2024)

Abbreviation: BRCA, breast cancer gene; HER2, human epidermal growth factor receptor 2.

VERSION HISTORY

Guidance on olaparib for treating germline BRCA-mutated HER2-negative high-risk early breast cancer

This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**
   Date of Publication 1 Sep 2023

2. **Guidance updated with revised MOH DAC recommendations for olaparib**
   Date of Publication 2 Jan 2024

Agency for Care Effectiveness - ACE Agency for Care Effectiveness (ACE)

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

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