Technology Guidance

Ribociclib

for the adjuvant treatment of HR-positive, HER2-negative stage II and III early breast cancer at high risk of recurrence

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

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

- ✓ Ribociclib 200 mg tablet, in combination with an aromatase inhibitor, for the adjuvant treatment of patients with HR-positive, HER2-negative stage II and III early breast cancer at high risk of recurrence. Maximum treatment duration: 3 years.

  Patients with anatomic stage group IIA and node-negative disease must have one additional risk factor:
  - Grade 3 tumour; or
  - Grade 2 tumour and Ki-67 ≥20%; or
  - Grade 2 tumour and high risk by gene signature testing.

Funding status

Ribociclib 200 mg tablet is recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indication from 1 April 2026.

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

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Technology evaluation

1.1. At the November 2025 meeting, the MOH Drug Advisory Committee ("the Committee") considered the technology evaluation of ribociclib, in combination with an aromatase inhibitor (AI), for adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer (EBC) at high risk of recurrence. The evaluation comprised the evidence submission for ribociclib (Kisqali) submitted by Novartis, and a review conducted by one of ACE's evidence review centres.

1.2. Expert opinion from clinicians at public healthcare institutions and the MOH Cancer Drug Subcommittee, and patient experts from local patient and voluntary organisations helped ACE ascertain the clinical value of ribociclib.

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.

Clinical need

2.1. Approximately 1,100 patients are diagnosed with HR-positive, HER2-negative stage II and III EBC each year in Singapore. Current standard of care includes adjuvant endocrine therapy (ET), comprising tamoxifen or an AI, plus a luteinising hormone-releasing hormone agonist (for pre- or perimenopausal women and men). For patients with node-positive disease at high risk of recurrence, adjuvant abemaciclib, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) may be added to ET for up to 2 years, based on evidence from Cohort 1 of the monarchE trial. The Committee noted that ribociclib, also a CDK4/6i, in combination with an AI would replace ET alone and, in a subset of patients with node-positive disease, would also replace abemaciclib in combination with ET.

2.2. The Committee considered testimonials from local patients about their lived experiences with EBC. The submission included four testimonials from patients who were compensated for interviews, and 20 patients submitted their testimonials to ACE. The Committee heard that breast cancer had negatively impacted patients' daily activities, such as work, and their ability to care for their loved ones. Having breast cancer also affected patients' relationships with others and raised concerns about potential loss of fertility. The Committee noted the impact of the condition on patients' emotional and mental wellbeing, particularly regarding fear of disease recurrence.

2.3. The Committee heard that these patients had received treatments including abemaciclib, AIs, and tamoxifen and had experienced side effects such as a compromised immune system, joint and muscle pain, fatigue, and diarrhoea. The Committee noted that while these patients were not familiar with ribociclib, they most valued new treatments for breast cancer that have manageable side effects and improve quality of life.

Clinical effectiveness and safety

Ribociclib plus AI versus AI alone

3.1. The Committee reviewed the clinical evidence from a phase III open-label randomised controlled trial (NATALEE) that investigated ribociclib plus AI versus AI alone as adjuvant treatment in patients with HR-positive, HER2-negative stage II and III EBC. Patients with anatomic stage group IIA node-negative disease were required to have either histologic grade 3 tumours, or histologic grade 2 tumours with either Ki-67 ≥20% or high risk by gene signature testing. In the ribociclib plus AI arm, treatment with ribociclib was continued until first disease recurrence, unacceptable toxicity, or completion of 3 years of treatment, whichever was earlier.

3.2. Table 1 summarises the efficacy results in the NATALEE intention-to-treat (ITT) population at the Apr 2024 data cut-off (median follow-up of 49.6 months). Outcomes include the primary outcome of invasive disease-free survival (iDFS), and the secondary outcomes of distant disease-free survival (DDFS), recurrence-free survival (RFS), and overall survival (OS).

Table 1: Summary of survival outcomes in NATALEE (ITT population; data cut-off 29 Apr 2024)

Outcome, n (%)	Ribociclib + AI (N=2,549)	AI alone (N=2,552)	HR (95% CI); p-value
iDFS	263 (10.3)	340 (13.3)	0.715 (0.609, 0.840); p<0.0001
DDFS	240 (9.4)	311 (12.2)	0.715 (0.604, 0.847); p<0.0001
RFS	224 (8.8)	298 (11.7)	0.695 (0.584, 0.827); p<0.0001
OS	105 (4.1)	121 (4.7)	0.827 (0.636, 1.074); p=0.0766

Abbreviations: AI, aromatase inhibitor; CI, confidence interval; DDFS, distant disease-free survival; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; RFS, recurrence-free survival.

3.3. While ribociclib plus AI was associated with statistically significant improvements in iDFS, DDFS, and RFS compared to AI alone, the Committee considered these results were immature due to the small number of events and censoring observed.

3.4. The Committee noted that OS results were immature, with no statistically significant difference between treatment arms. In the absence of mature OS data, the submission proposed iDFS as a surrogate for OS. The Committee considered that DDFS would have been a more appropriate proxy for OS, as it specifically captures distant metastasis, which is a stronger indicator of long-term benefit.

3.5. In terms of safety, the incidences of grade ≥3 adverse events (AEs), serious AEs, and AEs that led to treatment discontinuation were consistently higher in patients receiving ribociclib plus AI compared with AI alone.

3.6. The Committee reviewed a post hoc subgroup analysis in patients who were ineligible for monarchE Cohort 1 (low-risk subgroup), which represented 35% of the ITT population. The Committee noted that absolute improvements in iDFS and DDFS with the addition of ribociclib were smaller in this subgroup compared to the overall ITT population, and the incidence of adverse events was consistent with the ITT population.

3.7. Based on the available evidence, the Committee concluded that the submission's clinical claim of superior efficacy (in terms of iDFS, DDFS, and RFS) for ribociclib plus AI versus AI alone was reasonable, but considered that the magnitude of long-term benefits remained uncertain given immaturity of the data. Whilst safety data were consistent with ribociclib's known profile, the Committee concluded that ribociclib plus AI was inferior in safety compared with AI alone given the significantly higher rates of treatment discontinuation due to AEs.

<u>Ribociclib plus AI versus abemaciclib plus ET</u>

3.8. The Committee heard that no head-to-head trial was conducted comparing ribociclib plus AI with abemaciclib plus ET, and therefore reviewed an unanchored matching-adjusted indirect comparison (MAIC) from the submission. This MAIC compared the abemaciclib plus ET arm from monarchE Cohort 1 with a post hoc subgroup of NATALEE patients who met monarchE Cohort 1 eligibility criteria (high-risk subgroup).

3.9. The Committee heard that this high-risk subgroup represented 65% of the NATALEE ITT population, and the effective sample size (ESS) was considerably reduced after matching.

3.10. The primary MAIC analysis showed that ribociclib plus AI demonstrated comparable efficacy in terms of iDFS, distant relapse-free survival (DRFS) and OS compared to abemaciclib plus ET in these patients.

3.11. The MAIC showed that ribociclib plus AI was associated with reduced odds of diarrhoea, leukopenia, and lymphopenia compared to abemaciclib plus ET, but increased odds of neutropenia and elevated alanine aminotransferase.

3.12. The submission described that ribociclib plus AI and abemaciclib plus ET have comparable treatment effects and different safety profiles. The Committee acknowledged that the ESS reduction increased uncertainties in the MAIC results and their generalisability to the local setting, but overall considered the submission's claims to be reasonable.

Cost effectiveness

Ribociclib plus AI versus ET alone

4.1. The submission presented two cost-utility analyses (CUA) that compared ribociclib plus AI with ET alone as adjuvant treatment, based on data from the NATALEE ITT population and the low-risk subgroup. Key components of the economic evaluation in the NATALEE ITT population are summarised in Table 1.

Table 1: Key components of the company-submitted base-case economic evaluation (NATALEE ITT population)

Component	Description
Type of analysis	Cost-utility analysis
Populations	Patients with HR-positive, HER2-negative stage II and III EBC
Outcomes	Total and incremental costs, LY gained and QALY gained; ICER, NHB and NMB
Perspective	Singapore healthcare system
Type of model	Semi-Markov model
Time horizon	20 years in base case Lifetime time horizon (31 years) modelled in scenario analysis
Health states	Six health states: Invasive Disease-Free (IDF), Second Primary Malignancy (SPM), Non-Metastatic Recurrence (NMR), Remission, Distant Recurrence (DR), Death. SPM, DR and Death are absorbing health states. The DR health state is split into two substates based on timing of recurrence following completion of the ET component: ET-resistant (≤12 months) and ET-sensitive (>12 months). Each substate was modelled using a partitioned survival framework, with patients being progression-free, post-progression or dead.
Cycle length	28 days
Transition probabilities	• IDF to SPM, NMR, DR and Death: Based on NATALEE data. • NMR to Remission: Transit after remaining in the NMR state for 12 months (assumption). • Remission to DR: Based on transitions from NICE TA810. • Within DR health state: Based on MONALEESA-3 (ET-resistant) and MONALEESA-2 (ET-sensitive) data. All-cause age-related mortality was informed by Singapore life tables.
Extrapolation methods used to generate results	Extrapolated curves estimated using parametric and spline models were used. Curves were selected based on statistical fit (AIC, AICc and BIC values), visual fit and clinical plausibility of the modelled outcomes. The selected models were: IDF health state

Component	Description
	• iDFS (both treatment arms) = Log-logistic restricted (jointly-fitted) • TTD (ribociclib) = RCS Weibull • TTD (ET component in both treatment arms) = Weibull restricted for AI (jointly-fitted) <u>DR (ET-resistant) health state</u> • PFS, OS, TTD (fulvestrant) = Weibull restricted • TTD (ribociclib) = RCS Weibull restricted <u>DR (ET-sensitive) health state</u> • PFS, TTD (letrozole) = Exponential • OS = Gamma • TTD (ribociclib) = Generalised Gamma Treatment waning of iDFS was modelled starting at 8 years in the base case.
Health-related quality of life	• IDF on-treatment: 0.7620 (NATALEE April 2024 DCO) • IDF off-treatment: 0.7367 (NATALEE April 2024 DCO) • NMR: 0.6818 (NATALEE April 2024 DCO) • Remission: 0.7367 (Assumed equal to IDF off-treatment) • DR (ET-resistant) progression-free: 0.6190 (NATALEE April 2024 DCO) • DR (ET-resistant) post-progression: 0.5755 (Calculated) • DR (ET-sensitive) progression-free: 0.6190 (Assumed equal to DR (ET-resistant) progression-free) • DR (ET-sensitive) post-progression: 0.5944 (Calculated)
Types of healthcare resources included	• Drug and drug administration • Disease management cost • Subsequent treatment costs • AE management costs • End-of-life costs

Abbreviations: AE, adverse event; AI, aromatase inhibitor; AIC, Akaike information criterion; AICc, AIC corrected; BIC, Bayesian information criterion; CDA, Canada's Health Agency; DCO, data cut-off; DR, distant recurrence; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICER, incremental cost-effectiveness ratio; IDF, invasive disease-free; iDFS, invasive disease-free survival; ITT, intention-to-treat; LY, life year; NHB, net health benefit; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; NMR, non-metastatic recurrence; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; RCS, restricted cubic splines; SPM, second primary malignancy; TTD, time to discontinuation.

4.2. The submission's base-case incremental cost-effectiveness ratio (ICER) for ribociclib plus AI versus ET alone in the NATALEE ITT population was between SG$15,000 and SG$45,000 per quality-adjusted life year (QALY) gained. The Committee considered the ICER to be uncertain and likely underestimated, due to the following key reasons:

- The log-logistic restricted distribution selected for iDFS extrapolation likely overestimated the benefit for ribociclib plus AI, as other distributions with similar fit to the available Kaplan-Meier data provided estimates that were more aligned with those from local clinical experts.

- There was uncertainty whether the assumed 16.7% tamoxifen use in the ET alone arm reflected local practice, and whether patients who would have received tamoxifen would switch to an AI for combination with ribociclib. Given that tamoxifen monotherapy is less effective than AIs in reducing disease recurrence, a higher proportion of tamoxifen use in the ET alone arm would favour the ribociclib plus AI arm.

- The submission modelled treatment waning of iDFS as starting at 8 years, based on results from the ATAC trial. The Committee noted there was uncertainty in extrapolating these findings, given the different interventions and treatment durations between ATAC and NATALEE.

- The appropriateness of using MONALEESA-2 and MONALEESA-3 data to model outcomes after distant recurrences in the ribociclib plus AI arm was uncertain, given that these trials excluded patients with prior CDK4/6 inhibitor use.

4.3. The Committee considered the revised base case, which applied the lognormal restricted distribution to extrapolate iDFS and incorporated adjustments to other assumptions. These changes increased the ICER, which remained between SG$15,000 and SG$45,000 per QALY gained. The Committee noted that scenario analyses, which assumed an earlier treatment waning effect and 0% tamoxifen use in the ET alone arm, increased the ICER to between SG$45,000 and SG$75,000 per QALY gained. Overall, the Committee considered that the ICERs were uncertain and likely underestimated given the inherent data immaturity of the NATALEE trial and other limitations.

4.4. The Committee also noted the incremental QALYs gained with ribociclib plus AI in the low-risk subgroup was higher compared with the ITT population, and considered this finding to be implausible as it contradicted the clinical evidence presented. The Committee also heard that the results were highly uncertain due to a lack of model validation and justifications for model assumptions. They did not consider these results to be informative for decision-making.

<u>Ribociclib plus AI versus abemaciclib plus ET</u>

4.5. The submission presented a cost-minimisation analysis (CMA) between ribociclib and abemaciclib based on a claim of comparable efficacy and assuming similar costs of AI and ET. The revised base case incorporated AE and treatment monitoring costs due to their different safety profiles, and showed that total healthcare costs with ribociclib plus AI were lower compared to abemaciclib plus ET over a three-year time horizon.

4.6. Based on findings from the CUA (NATALEE ITT population) and the CMA, the Committee considered ribociclib plus AI to be an acceptable use of healthcare resources when used as adjuvant treatment of patients with HR-positive, HER2-negative stage II and III EBC at high risk of recurrence.

Estimated annual technology cost

5.1. Using an epidemiological approach, the submission estimated that listing ribociclib on the MOH List of Subsidised Drugs for the adjuvant treatment of patients with HR-positive, HER2-negative stage II and III EBC at high risk of recurrence would result in an annual cost impact to the public healthcare system from between SG$1 million and SG$3 million in the first year to between SG$5 million and SG$10 million in the fifth year.

5.2. The Committee considered that the submission estimates were high due to an overestimation of eligible patients and an optimistic uptake rate of ribociclib. Based on the revised budget impact model, the annual cost impact to the public healthcare system was estimated to be between SG$1 million and SG$3 million in the first year, increasing to between SG$3 million and SG$5 million in the fifth year of listing.

5.3. The Committee considered the company's price-volume agreement (PVA) caps, which included use of ribociclib in the metastatic setting, to be unacceptably high and thereby did not provide budget certainty to payors.

Recommendations

6.1. Based on available evidence and the company's pricing proposal, the Committee indicated that ribociclib could be considered for listing on the MOH List of Subsidised Drugs contingent upon the company agreeing to an improved PVA to manage the overall budget uncertainty. The company subsequently submitted a revised pricing proposal with an improved PVA to address the Committee's concerns. Accordingly, the Committee recommended ribociclib 200 mg tablet be listed on the Medication Assistance Fund (MAF) for use in combination with an AI for the adjuvant treatment of patients with HR-positive, HER2-negative stage II and III EBC at high risk of recurrence, for a treatment duration of up to 3 years. Patients with anatomic stage group IIA and node-negative disease must have one additional risk factor:

- Grade 3 tumour; or
- Grade 2 tumour and Ki-67 ≥20%; or
- Grade 2 tumour and high risk by gene signature testing.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Approved clinical indication	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Ribociclib 200 mg tablet	Ribociclib in combination with an aromatase inhibitor for the adjuvant treatment of patients with HR-positive, HER2-negative stage II and III early breast cancer at high risk of recurrence. Maximum treatment duration: 3 years. Patients with anatomic stage group IIA and node-negative disease must have one additional risk factor: - Grade 3 tumour; or - Grade 2 tumour and Ki-67 ≥20%; or - Grade 2 tumour and high risk by gene signature testing.	MAF (1 April 2026)	$800 (1 April 2026)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; MAF, Medication Assistance Fund.