# 6.09 RIBOCICLIB
## Tablet 200 mg,
## Kisqali®,
## NOVARTIS PHARMACEUTICALS AUSTRALIA PTY LIMITED.

## 1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule, Authority Required (telephone/online) listing for ribociclib, in combination with adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), resected early breast cancer (eBC) at high risk of disease recurrence. Ribociclib was recommended for listing at the November 2024 PBAC meeting for patients with ≥4 positive axillary lymph nodes (ALNs), or 1–3 positive ALNs and either grade 3 disease (on the Nottingham grading system) or tumour size ≥ 5 cm. This submission requested the listing be expanded to include the complement sub-group of high-risk eBC patients who were not included in the recommendation for ribociclib at the November 2024 PBAC meeting.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus adjuvant ET alone. The key components of the clinical issue addressed by the submission are presented in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

| Component | Description |
|---|---|
| Population | Adult patients with HR positive, HER2 negative eBC with (a) stage II or III disease with 1–3 positive ALNs with grade ≤ 2 histology and tumour size < 5 cm, or (b) stage IIB or III node-negative disease, or (c) stage IIA node-negative disease with (i) histological grade 3 or (ii) histological grade 2 with a positive molecular diagnostic outcome. |
| Intervention | Ribociclib 400 mg orally, once daily on days 1–21 of each 28-day cycle for up to 3 years, plus adjuvant ET. |
| Comparator | Adjuvant ET alone as standard of care |
| Outcomes | Primary efficacy outcome: iDFS<br>Patient-relevant secondary efficacy outcomes: RFS, DDFS, DRFS, OS and time to subsequent antineoplastic therapy<br>HRQoL<br>Safety |
| Clinical claim | Ribociclib + adjuvant ET is superior to adjuvant ET alone with respect to efficacy and inferior with respect to safety. |

Source: Section 1.1, p3 of the submission.
ALNs = axillary lymph nodes; cm = centimetre; DDFS = distant disease free-survival; DRFS = distant recurrence-free survival; eBC = early breast cancer; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HRQoL = health-related quality of life; iDFS = invasive disease-free survival; mg = milligram; OS = overall survival; RFS = recurrence-free survival

# 2 Background

## *Registration status*

2.1 Ribociclib in combination with an aromatase inhibitor (AI) received TGA registration in eBC on 7 March 2025 for the adjuvant treatment of patients with HR+, HER2-, stage II and III eBC at high risk of recurrence.

## *Previous PBAC consideration*

2.2 At its November 2024 meeting, the PBAC recommended the PBS listing of ribociclib, in combination with standard adjuvant ET, for the treatment of HR+, HER2-, lymph node positive, invasive, resected eBC at high risk of disease recurrence. This included patients with ≥ 4 positive ALNs, or 1–3 positive ALNs and either grade 3 disease (on the Nottingham grading system) or tumour size ≥ 5 cm. Ribociclib was PBS-listed for this indication on 1 July 2025. The listing was recommended on the basis of a cost-minimisation analysis comparing ribociclib versus abemaciclib (para. 7.1, ribociclib Public Summary Document [PSD], November 2024). The proposed PBS population for the current submission corresponds to the complement sub-group of high-risk eBC patients who were not included in the recommendation for ribociclib at the November 2024 PBAC meeting. The ESC noted the complement subgroup has a lower risk of disease recurrence.

2.3 Ribociclib is also currently PBS-listed for use in combination with either a non-steroidal aromatase inhibitor (AI) (if never treated with prior endocrine therapy) or fulvestrant (250 mg/5 mL injection) for the treatment of patients with HR+, HER2- advanced or metastatic breast cancer.

# 3 Requested listing

3.1 The submission requested the following new listing. Suggested additions are in italics and deletions are in strikethrough.

| MEDICINAL PRODUCT medicinal product pack | Dispensed Price for Max. Qty | Max. qty packs | Max. qty units | №.of Rpts | Available brands |
|---|---|---|---|---|---|
| RIBOCICLIB | | | | | |
| Ribociclib 200 mg tablet, 21 | $1,847.51 published price<br>$[redacted] effective price | 1 | 21 | 5 | Kisqali<br>Novartis<br>Pharmaceuticals<br>Australia Pty. Ltd. |
| Ribociclib 200 mg tablet, 42 | $3,557.28 published price<br>$[redacted] effective price | 1 | 42 | 5 | |
| **Category / Program:** General Schedule (Code GE) | | | | | |
| **Prescriber type:** ☒Medical Practitioners | | | | | |
| **Restriction type:** ☒Authority Required (telephone/online PBS Authorities system) | | | | | |
| **Indication:** Early breast cancer | | | | | |
| **Treatment Phase:** ~~Initial treatment~~ | | | | | |
| **Clinical criteria:** | | | | | |
| The treatment must be adjuvant to surgical resection | | | | | |
| **AND** | | | | | |
| The condition must not have been treated with adjuvant endocrine therapy for more than 12 months prior to commencing this drug | | | | | |
| **AND** | | | | | |
| The condition must be human epidermal growth factor receptor 2 (HER2) negative | | | | | |
| **AND** | | | | | |
| The condition must be hormone receptor positive | | | | | |
| **AND** | | | | | |
| Patient must have Stage II or III disease plus all of: (a) 1–3 positive axillary lymph nodes, (b) histological grade ≤ 2, (c) tumour size < 5 cm; or | | | | | |
| Patient must have Stage IIB or III disease with no positive lymph nodes; or | | | | | |
| Patient must have Stage IIA disease with no positive lymph nodes plus either: (a) grade 3 histology or (b) grade 2 histology with a positive molecular diagnostic outcome. | | | | | |
| **AND** | | | | | |
| The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 3 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression | | | | | |
| **AND** | | | | | |
| The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) olaparib, (iii) pembrolizumab | | | | | |
| **AND** | | | | | |
| **Treatment criteria:** | | | | | |
| Patient must be undergoing concurrent treatment with a non-steroidal aromatase inhibitor where this drug is being prescribed as a PBS-benefit | | | | | |
| **Administrative Advice:** Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole. | | | | | |
| **Administrative Advice:** Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib. | | | | | |
| **Administrative Advice:** The Nottingham grading system is the histologic grading system developed by Elston and Ellis as a modification of the Scarff-Bloom-Richardson grading system. See the following literature publication for details: Elston, CW, Ellis, IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991 Nov;19(5):403-10. | | | | | |
| **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
| **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. | | | | | |

| |
|---|
| **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:** Special Pricing Arrangements apply. |
| **Prescribing Instructions:** Retain all pathology imaging and investigative test results in the patient's medical records. |
| **Caution:** QT interval monitoring is required for patients treated with this drug. |
| |
| **Indication:** Early breast cancer |
| **Treatment Phase:** ~~Grandfathered treatment~~ *Transitioning from non-PBS to PBS subsidised treatment – 'Grandfather' treatment* |
| **Clinical criteria:** |
| The treatment must have been adjuvant to surgical resection prior to receiving non-PBS-subsidised therapy with this drug. |
| **AND** |
| **Clinical criteria:** |
| The condition must not have been treated with adjuvant endocrine therapy for more than 12 months prior to commencing this drug |
| **AND** |
| **Clinical criteria:** |
| The condition must be human epidermal growth factor receptor 2 (HER2) negative |
| **AND** |
| **Clinical criteria:** |
| The condition must be hormone receptor positive |
| **AND** |
| **Clinical criteria:** |
| Patient must have had, prior to receiving non-PBS-subsidised therapy with this drug, Stage II or III disease plus all of: (a) 1–3 positive axillary lymph nodes, (b) histological grade ≤ 2, (c) tumour size < 5 cm; or |
| Patient must have had, prior to receiving non-PBS-subsidised therapy with this drug, Stage IIB or III disease with no positive lymph nodes; or |
| Patient must have had, prior to receiving non-PBS-subsidised therapy with this drug, Stage IIA disease with no positive lymph nodes plus either: (a) grade 3 histology or (b) grade 2 histology with a positive molecular diagnostic outcome. |
| **AND** |
| **Clinical criteria:** |
| The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 3 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression. |
| **AND** |
| **Clinical criteria:** |
| The treatment must not be in combination with any of the following: (i) abemaciclib, (ii) olaparib, (iii) pembrolizumab |
| **AND** |
| **Treatment criteria:** |
| Patient must be undergoing concurrent treatment with a non-steroidal aromatase inhibitor where this drug is being prescribed as a PBS-benefit |
| **Administrative Advice:**<br>Non-steroidal aromatase inhibitors for the purposes of this restriction are anastrozole and letrozole. |
| **Administrative Advice:**<br>Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors for the purposes of this restriction are abemaciclib, palbociclib and ribociclib. |

| |
|---|
| **Administrative Advice:** The Nottingham grading system is the histologic grading system developed by Elston and Ellis as a modification of the Scarff-Bloom-Richardson grading system. See the following literature publication for details: Elston, CW, Ellis, IO. Pathological prognostic factors in breast cancer. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991 Nov;19(5):403-10. |
| **Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. |
| **Administrative Advice:** No increase in the maximum quantity or number of units may be authorised. |
| **Administrative Advice:** No increase in the maximum number of repeats may be authorised. |
| **Administrative Advice:** Special Pricing Arrangements apply. |
| **Prescribing Instructions:** Retain all pathology imaging and investigative test results in the patient's medical records. |
| **Caution:** QT interval monitoring is required for patients treated with this drug. |

3.2 The submission proposed a published ex-manufacturer price (EMP) $[redacted] per pack of 21 tablets, and $[redacted] for a pack of 42 tablets. The submission requested a special pricing arrangement (SPA) with effective EMPs of $[redacted] per pack of 21 tablets, and $[redacted] for a pack of 42 tablets. These prices were higher than the effective prices for ribociclib in eBC from the November 2024 consideration (Table 2). The ESC noted higher prices are inconsistent with a proposed listing for a lower risk population for which use would be less cost-effective.

**Table 2: Effective prices for ribociclib for treatment of early breast cancer (November 2024 consideration)**

| | Pack size | Ex-manufacturer price | Dispensed price for maximum quantity |
|---|---|---|---|
| Ribociclib | 21 tablets | $[redacted] | $[redacted] |
| Ribociclib | 42 tablets | $[redacted] | $[redacted] |

3.3 The submission requested that patients be eligible for ribociclib if they have initiated adjuvant ET no more than 12 months prior to initiation of ribociclib. The submission stated there was a clinical need for flexibility in the timing of initiation of ribociclib, as there is a subset of patients who require additional time to recover from surgery and resolve existing infections prior to initiating ribociclib. It would also allow more time for clinicians to assess response to ET. For the ribociclib population considered at the November 2024 PBAC meeting, the PBAC considered that an interval of up to 12 months between initiation of adjuvant ET and ribociclib was not appropriate given that: (1) in the NATALEE trial, more patients commenced therapy ≤6 months (49.4%) after starting ET than > 6 months (21.5%); (2) the mean time to initiate ribociclib treatment in the NATALEE trial was only 3.5 months; and (3) there is a clinical imperative to start timely therapy with a CDK4/6 inhibitor given patients have a high risk of BC recurrence (para 3.5, ribociclib PSD, November 2024). The PBAC previously recommended the timeframe should match the current 6-month requirement for abemaciclib in eBC (para 7.4, ribociclib PSD, November 2024). The Pre-Sub Committee Response (PSCR) maintained that a 12-month initiation interval was appropriate and stated that Australian medical oncologists report a need for greater flexibility to assess

a patient's response to ET before introducing a CDK4/6 inhibitor. However, the ESC considered that the clinical imperative to start timely therapy with a CDK4/6 inhibitor was particularly relevant to this subgroup of patients who likely have a lower risk of disease recurrence compared to the subgroup of patients considered for ribociclib in November 2024. The ESC considered that the timeframe should match the current 6-month requirement for abemaciclib in eBC. The Pre-PBAC Response argued this requirement was arbitrary and inconsistent with the evidence in the NATALEE trial that allowed ribociclib to commence within 12 months of starting ET and maintained that the requirement creates inequities for patients who may require a longer period due to reasons such as complications, surgery, or fertility planning.

3.4 The submission also proposed an amendment to the PBS restriction criteria for ribociclib in HR+, HER2-, inoperable, locally advanced or metastatic breast cancer to allow for retreatment with ribociclib or other CDK4/6 inhibitors, if the relapse occurred at least 12 months after completing adjuvant treatment. This was proposed to replace the lifetime restriction of a single line of CDK4/6 therapy. The submission referred to the postMONARCH trial to support its request. The PBAC previously considered this request at its November 2024 meeting and did not support the removal of the lifetime restriction of a single line of CDK4/6 therapy. The PBAC considered that the postMONARCH trial did not provide evidence to support removal of this condition, noting that only 1% of the metastatic BC patients had received prior adjuvant CDK4/6 inhibitor treatment and the trial did not have a suitable design to allow conclusions with respect to retreatment (para. 7.4 ribociclib PSD, November 2024). The ESC noted that the evidence presented in the submission to justify the request was not substantially different to the previous submission and did not address the PBAC's previous concerns. For this reason, the ESC considered that the removal of the lifetime restriction of a single line of CDK4/6 therapy was likely not appropriate. The impact of the proposed restriction change was also not addressed in the economic or financial analyses.

3.5 The proposed restriction does not define 'positive molecular diagnostic outcome' for the subgroup of patients with grade 2 histology eligible for ribociclib treatment. In the NATALEE trial, this was defined as Ki67 ≥ 20% or high-risk categorisation by a gene expression profiling test (e.g. Oncotype DX score ≥26 or Prosigna, MammaPrint or EndoPredict high-risk). At the March 2022 PBAC meeting, the PBAC considered that Ki67 may not be adequately validated in Australia for use in a PBS restriction (para. 3.5, abemaciclib PSD, March 2022 PBAC meeting). One gene expression profiling test is available on the MBS (EndoPredict, MBS item 73306). However, the item descriptor specifies that the service is not administered for the purpose of altering treatment decisions (such as determining access to ribociclib treatment); EndoPredict or other gene expression profiling may alternately be privately funded ($3,300–$6,150 per test). The PSCR stated that molecular diagnostic testing is routinely performed as part of a patient's standard prognostic evaluation, and that clinicians are able to interpret the meaning of a 'positive molecular diagnostic outcome' in relation to the patient's future risk of disease. The ESC considered that the proposed wording could be

interpreted in a number of ways and considered that this may allow ribociclib to be used outside of the intended patient population. However, due to the lack of a standardised and subsidised test, the ESC did not consider that a specific test or result should be included in the proposed PBS restriction.

3.6 The submission also requested a grandfathered listing for patients who are currently receiving ribociclib through a Novartis funded access program. The proposed grandfathered listing was aligned with the proposed PBS listing.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 4 Population and disease

4.1 Breast cancer is the most commonly diagnosed cancer among women in Australia, with over 20,000 new cases expected annually.[1] Screening programs such as BreastScreen Australia have significantly improved early detection rates, meaning most cases are diagnosed at stage I or II, when the cancer is still confined to the breast and regional lymph nodes.[2] In Australia, approximately 70 to 75 percent of early breast cancers are HR+ and HER2-.[3] The primary treatment for this population is surgery with intent to cure. Despite a generally favourable prognosis, patients with HR+, HER2- early breast cancer may experience recurrence.

4.2 The ribociclib submission considered by the PBAC in November 2024 included a sub-population of the NATALEE trial that aligned with the eBC PBS population for abemaciclib. The proposed PBS population includes the complement of the subgroup considered in November 2024, i.e. the remainder of the NATALEE trial population with a lower risk of recurrence.

4.3 Ribociclib is an orally bioavailable and highly selective small molecule inhibitor of the CDK 4/6 enzyme complex, which directly targets the retinoblastoma protein to block cell cycle progression and cancer cell proliferation.[4]

4.4 The proposed use of ribociclib is in combination with ET. The proposed TGA Product Information (PI) does not specify which non-steroidal aromatase inhibitor (NSAI) must be used with ribociclib, however the NATALEE trial used either letrozole or anastrozole. In men and pre-menopausal women, ET is ineffective unless administered with ovarian suppression (e.g. goserelin or triptorelin); in the NATALEE trial, patients were given goserelin, administered as a 3.6 mg subcutaneous implant once every 28 days. Patients may have had neoadjuvant or adjuvant radiotherapy and/or chemotherapy prior to ribociclib plus adjuvant ET.

[1] Australian Institute of Health and Welfare, 2024. Cancer data in Australia. Canberra.
[2] Australian Institute of Health and Welfare, 2024. BreastScreen Australia monitoring report 2024. Canberra.
[3] Orrantia-Borunda E A-NP, Acuña-Aguilar LE, et al, 2022. Subtypes of Breast Cancer. In: HN M, editor. Breast Cancer: Exon Publications.
[4] Braal CL, Jongbloed EM, Wilting SM, Mathijssen RHJ, Koolen SLW, Jager A, 2021. Inhibiting CDK4/6 in Breast Cancer with Palbociclib, Ribociclib, and Abemaciclib: Similarities and Differences. *Drugs*. 81(3):317-31

4.5 Ribociclib is also listed for the treatment of HR+, HER2-, locally advanced or metastatic breast cancer. The PBS listing states 'PBS-subsidised treatment with CDK 4/6 inhibitors is restricted to one line of therapy at any disease staging for breast cancer (i.e. if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available).'

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 5 Comparator

5.1 The submission nominated adjuvant ET alone as the comparator. This was appropriate as ET alone is the current standard of care (SoC) for the nominated population. For the purposes of the submission, ET was assumed to be treatment with an AI (either letrozole or anastrozole). The submission did not consider an oestrogen receptor modulator (tamoxifen) as part of the comparator. The submission stated that this was consistent with the pivotal NATALEE trial, and ribociclib may not be used with tamoxifen.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

# 6 Consideration of the evidence

## *Sponsor hearing*

6.1 The Sponsor requested a hearing for this item. The clinician was supportive of the proposed PBS listing of ribociclib, noting the positive results of the clinical trial among a patient group classified as having a high risk of recurrence. The clinician discussed how high risk of recurrence was typically determined in practice, stating that it was primarily based on size and nodal status. The clinician also considered that biological characteristics, such as the grade of the tumour and the percentage of cells that are Ki-67 positive, were key determinants. The clinician also considered that genomic testing was useful to help inform the decision to use chemotherapy.

6.2 The clinician noted that a 12-month initiation window for ribociclib following the introduction of ET was consistent with the NATALEE trial and discussed the benefits that a longer window would have for patients, allowing them to adjust to changing treatments, including managing the side effects associated with ET.

6.3 The clinician discussed the importance of effective cure and prevention of cancer recurrence to patients and discussed the positive results of the clinical trial, highlighting that while longer-term data continues to be collected for CDK4/6 inhibitors, the currently available data continues to show a benefit over ET alone. In addition, the clinician highlighted the anxiety and fear associated with the risk of recurrence experienced by patients and noted that most patients, post-surgery consider self-funding treatment with a CDK4/6 inhibitor, but noted that their current cost was a significant barrier to treatment.

## *Consumer comments*

6.4 The PBAC noted and welcomed the input from health professionals (3), individuals who would like access to ribociclib (3), the Medical Oncology Group Australia (MOGA) and consumer organisations (4), including Rare Cancers Australia, Breast Cancer Network Australia (BCNA), So Brave and Inherited Cancers Australia.

6.5 The PBAC acknowledged the input from health professionals discussed the treatment of early breast cancer, which aims to reduce the risk of recurrence and increase the proportion of cured individuals. The input also noted the importance of ribociclib as an additional treatment option to reduce recurrence rates, whilst noting that ribociclib had side effects, but that they were usually able to be managed. The input also noted that the current cost of ribociclib was a barrier to treatment.

6.6 The PBAC also acknowledged the input from individuals who would like access to ribociclib but have not used the medicine. The input discussed the devastating impact of a breast cancer diagnosis and the difficult side effects associated with current treatments, including fatigue, pain, brain fog, mobility issues and significant emotional impacts. The input also described the fear and anxiety related to the risk of recurrence. The Committee noted the comments from individuals regarding the peace of mind that would be offered by additional treatment options and called for broader access for patients.

6.7 The PBAC noted the input from Rare Cancers Australia discussed the devastating impacts of a diagnosis of this form of breast cancer on patients and their loved ones, with many undergoing mastectomies and facing ongoing physical and mental health challenges, as well as facing loss of income and inability to work, further compounding these issues. The Committee also noted the input discussed the side effects of current treatments and the appeal of a simpler tablet treatment that could provide reassurance and maintain good quality of life.

6.8 The PBAC noted the input from BCNA supporting the requested listing, which highlighted the positive results of the NATALEE trial showing an invasive disease-free survival benefit for the node-negative cohort, and stated that adding ribociclib to standard hormone therapy offers a new treatment option that may better prevent cancer recurrence in people at moderate-high risk who are not eligible for abemaciclib. The input also highlighted the psycho-social impacts of having more treatments that improve disease-free survival and reduce the risk of recurrence and considered that ribociclib would likely provide patients with greater confidence and peace of mind about their long-term outlook.

6.9 The PBAC noted the input from So Brave focusing on the impacts of HR+, HER2- breast cancer on young women, and highlighted the importance of issues related to a delayed diagnosis, fertility preservation treatment delays, financial impact, risk of recurrence and personalised medicine to patients. The input also outlined that young women diagnosed with breast cancer in Australia are health literate and confident in their ability to understand and participate in their healthcare decision-making,

deserve all available treatment options to be presented, count on a good quality of life and the best possible health outcomes, and deserve equitable and affordable access to breast cancer treatments. A letter from a Patient Advisory Committee member accompanied the So Brave input. The individual was diagnosed with HR+, HER2- Stage II breast cancer and discussed the back-to-back procedures and treatments they had undergone. The individual emphasised the distress caused by the potential failure to meet the PBS restriction criterion for initiating treatment with a CDK4/6 inhibitor, due to the delays associated with fertility preservation. The individual noted that without PBS reimbursement, the cost of CDK4/6 inhibitor medicines would be unaffordable.

6.10 The PBAC noted the input from Inherited Cancers Australia discussed the population requested for listing in the current submission (lower lymph node involvement) and highlighted the fear of recurrence experienced by these patients, who still remain at a high risk. The input also discussed the Project Shirley study that investigated the experiences of women with early-stage breast cancer and their psychosocial needs, which found that 97% of patients reported their breast cancer diagnosis had a negative effect on their ability to plan for the future, with more than 80% reporting a negative impact on family and social relationships, with ongoing fear of recurrence a major factor. The input also discussed the results of the NATALEE trial showing a benefit in disease-free survival and highlighted the positive impact expanded access to this treatment would likely have to a broader community of breast cancer patients.

6.11 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the ribociclib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the full population NATALEE trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for ribociclib the highest grade 'A', categorising it as a treatment with substantial benefit in the curative setting[5]. While this input was based on the intention-to-treat (ITT) population of the trial, the PBAC noted that it also included data which appeared specific to the subgroup requested in the current submission.

## *Clinical trials*

6.12 The submission was based on a subgroup of patients (n=1,794) from a randomised trial comparing ribociclib + ET to ET alone (NATALEE) (N=5,101) (hereafter referred to as 'the PBS subgroup'). The PBAC previously considered the complement subgroup of the NATALEE trial in November 2024 (patients with ≥ 4 positive ALNs, or 1–3 positive ALNs and histological grade 3 disease and/or tumour size ≥ 5 cm).

6.13 Details of the NATALEE trial and associated reports presented in the submission are provided in Table 3.

[5] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

**Table 3: Trial and associated reports presented in the submission**

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|---|
| NATALEE<br>NCT03701334 | A phase III, multicenter, randomised, open-label trial to evaluate efficacy and safety of Ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer (New Adjuvant TriAl with Ribociclib [LEE011]: NATALEE). | CSR<br>Data cut-off date: 11 January 2023<br>Report date: 2 August 2023 |
| | A phase III, multicenter, randomised, open-label trial to evaluate efficacy and safety of Ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: efficacy analysis and safety update Final iDFS Analysis. | Data cut-off date: 21 July 2023<br>Report date: 23 November 2023 |
| | A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: End of Ribociclib Analysis Report. | Data cut-off date: 29 April 2024<br>Report date: 12 September 2024 |
| | A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer (New Adjuvant TriAl with Ribociclib [LEE011]: NATALEE). | Clinical Trial Protocol<br>Version 3.0, 23 January 2020 |
| | Hortogagyi G.N., Lacko A., *et al.* A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival from the NATALEE trial. | *Ann Oncol* 2025, 36, 149-157 |
| | Slamon D., Lipatov O., *et al.* Ribociclib plus Endocrine Therapy in Early Breast Cancer. | *N Engl J Med*, 2024, 390, 1080-1091 |
| | Slamon D.J., Fasching P.A., *et al.* Rationale and trial design of NATALEE: a Phase III trial of adjuvant ribociclib + endocrine therapy versus endocrine therapy alone in patients with HR+/HER2- early breast cancer. | *Ther Adv Med Oncol*, 2023, 15 |

Source: Table 2.3, pp44-45 of the submission.
CSR = clinical study report; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; ID = Identifier; iDFS = invasive disease-free survival

6.14 The key features of the NATALEE trial are summarised in Table 4. By the April 2024 cut-off, all patients in the ribociclib arm had either completed treatment or had discontinued ribociclib.

**Table 4: Key features of the included evidence**

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcomes |
|---|---|---|---|---|---|
| **Ribociclib plus adjuvant ET vs ET alone** | | | | | |
| NATALEE | ITT = 5101<br>Proposed PBS subgroup = 1794 | R, OL, MC<br><br>DCO April 2024: 49.6 months | *Low* | HR+, HER2-, resected eBC,<br>Stage II or III<br>Regardless of nodal disease | iDFS, DRFS, OS, DDFS, RFS, PROs, safety |

Source: Compiled during evaluation
DCO = data cut-off; DRFS = distant recurrence-free survival; eBC = early breast cancer; ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor positive; iDFS = invasive disease-free survival; ITT = intention-to-treat; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; RFS = recurrence-free survival.

6.15 The PBAC previously considered the NATALEE trial (ribociclib Public Summary Document [PSD], November 2024 PBAC Meeting). The subgroup of the NATALEE trial that aligned with the proposed PBS population had similar baseline characteristics across treatment arms. The evaluation considered that it was reasonable that the risk of bias for the proposed PBS subgroup would be considered the same as for the overall NATALEE trial. However, the ESC noted that the subgroup was not prespecified in the NATALEE trial.

## *Comparative effectiveness*

6.16 Table 5 summarises the results for invasive disease-free survival (iDFS), distant recurrent-free survival (DRFS) and overall survival (OS) from the NATALEE trial (ITT, proposed PBS subgroup and currently PBS listed population [calculated as the difference between the ITT population and proposed PBS subgroup]). The results for the key outcomes of iDFS and DRFS indicate a statistically significant benefit for ribociclib plus adjuvant ET compared to ET alone in the ITT population and proposed PBS subgroup.

**Table 5: Summary of survival outcomes in NATALEE (ITT and PBS subgroup, DCO April 2024; currently listed PBS subgroup)**

| Outcome | Ribociclib plus adjuvant ET n/N (%) | ET alone n/N (%) | Hazard Ratio (95% CI) |
|---|---|---|---|
| **iDFS** | | | |
| ITT | 263/2549 (10.3%) | 340/2552 (13.3%) | **0.715 (0.609, 0.840)**<br>**p < 0.0001** |
| Proposed PBS subgroup | 55/891 (6.2%) | 78/903 (8.6%) | **0.665 (0.469, 0.944)**<br>**p = 0.011** |
| Listed PBS subgroup | 208/1658 (12.5%) | 262/1649 (15.9%) | Not reported |
| **DRFS** | | | |
| ITT | 210/2549 (8.2%) | 276/2552 (10.8%) | **0.705 (0.589, 0.844)**<br>**p < 0.0001** |
| Proposed PBS subgroup | 39/891 (4.4%) | 57/903 (6.3%) | **0.637 (0.421, 0.965)**<br>**p = 0.016** |
| Listed PBS subgroup | 171/1658 (10.3%) | 219/1649 (13.3%) | Not reported |
| **OS** | | | |
| ITT | 105/2549 (4.1%) | 121/2552 (4.7%) | 0.827 (0.636, 1.074)<br>p = 0.0766 |
| Proposed PBS subgroup | 19/891 (2.1%) | 20/903 (2.2%) | 0.871 (0.460, 1.652)<br>p = 0.336 |
| Listed PBS subgroup | 86/1658 (5.2%) | 101/1649 (6.1%) | Not reported |

Source: Table 2.16, p65, Table 2.20, p68, Table 2.22, p70 of the submission, listed PBS subgroup calculated as the difference between ITT and proposed PBS subgroup.

CI = Confidence Interval; DCO = data cut-off; DRFS = distant recurrence-free survival; ET = endocrine therapy; iDFS = invasive disease-free survival; ITT = intention-to-treat; OS = overall survival; PBS = Pharmaceutical Benefits Scheme

**Bold** = statistically significant results.

Note that the results presented in Table 5 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

6.17 In the ITT population, with a median follow-up of 44.2 months (data cut-off [DCO] April 2024), ribociclib plus adjuvant ET showed a 28.5% relative reduction in the hazard of

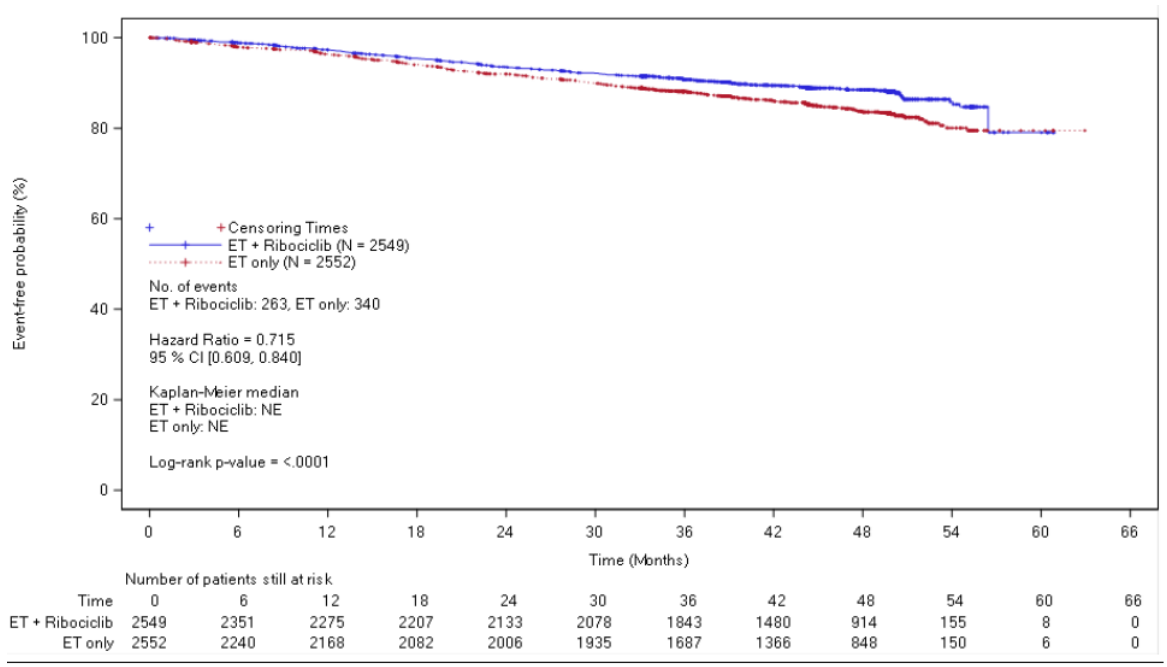
invasive disease recurrence, as evidenced by a hazard ratio of 0.715 (95% confidence interval [CI]: 0.609, 0.840; p < 0.0001) for iDFS and a 29.5% relative reduction in the hazard of distant disease recurrence with a hazard ratio of 0.705 (95% CI: 0.589, 0.844 p < 0.0001) for DRFS. The risk reduction was similar in the PBS subgroup, with a hazard ratio of 0.67 (95%CI: 0.47, 0.94; p = 0.011) for iDFS and a hazard ratio of 0.64 (95% CI: 0.42, 0.97; p = 0.016) for DRFS. The ESC noted the confidence intervals of the iDFS HR for the PBS subgroup were wide and considered that the point estimate was likely subject to some uncertainty.

6.18 The Kaplan-Meier (KM) curves for the primary outcome, iDFS for the ITT population and PBS subgroup in NATALEE are presented in Figure 1 and Figure 2, respectively.

6.19 The absolute benefits were smaller in the PBS population than in the ITT population. The PBAC previously considered that an iDFS benefit of 3.5% was modest but may be clinically meaningful in the adjuvant setting where the intention is cure (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting). The absolute iDFS benefit at 4 years was reported as 3.7% in the PBS subgroup.

6.20 The results for OS showed no significant difference between the two arms in the ITT population or PBS subgroup population. The PBAC previously considered that the outcome of iDFS is an uncertain, but generally plausible surrogate for OS in this setting. However, the PBAC also noted that the relationship between iDFS and OS is uncertain (for abemaciclib), given the OS data were immature and no difference in OS was observed at the most recent data cutoff (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting). The evaluation noted that the OS was immature in this submission, and therefore considered the relationship between iDFS and OS for ribociclib to also be uncertain.

**Figure 1: KM curve for iDFS in the ITT population in NATALEE at April 2024 DCO**

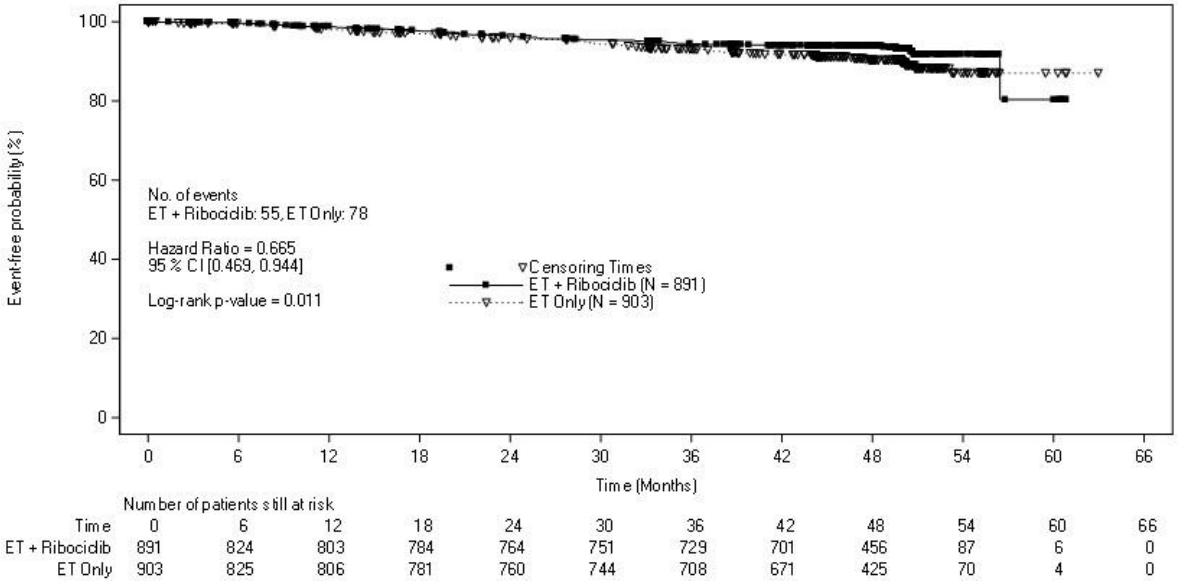



Source: Figure 2-1, p8, NATALEE CSR 12 Sep 2024

CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; iDFS = invasive disease-free survival; ITT = intention-to-treat; KM = Kaplan-Meier.

*Note that the results presented in Figure 1 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Figure 2: KM curve for iDFS in the proposed PBS population in NATALEE at the April 2024 DCO**




Source: Figure 2.5 p66 of the submission

CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; iDFS = invasive disease-free survival; KM = Kaplan-Meier; PBS = Pharmaceutical Benefit Scheme.

*Note that the results presented in Figure 2 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.21 The submission presented the results of the patient reported outcomes for the NATALEE trial. Health related quality of life (HRQoL) was assessed as a secondary outcome at the April 2024 DCO using the physical functioning subscale score and the global health status/QoL score of the European Organization for Research and Treatment of Cancer's Core Quality of Life Questionnaire – C30 (EORTC QLQ-C30).

6.22 The EORTC QLQ-C30 physical functioning and quality of life scores were similar across the treatment arms; and the submission concluded that adding ribociclib to ET treatment does not result in any notable deterioration in HRQoL compared with current standard of care. The submission stated that there was no meaningful difference between the two treatment arms for the reported outcomes from baseline, at each visit and at the end of treatment. The evaluation noted that there was a slight decline in physical functioning in both treatment arms post-baseline.

### *Comparative harms*

6.23 A summary of adverse events (AEs) for ribociclib + ET and ET alone is presented in Table 6. The safety outcomes were presented for the patients in the NATALEE safety set[6] who would be eligible for the PBS population. Patients in the PBS subgroup who received ribociclib + ET experienced more treatment-emergent adverse events (TEAEs) than patients who received ET alone (97.4% vs. 88.3%). This included the ribociclib arm experiencing over three times the risk of a Grade ≥3 TEAE (61.5% vs. 19.1%), more discontinuations due to AEs (22.6% vs. 6.7%), and more AEs of special interest (84.7% vs. 47.7%). The most common Grade ≥3 AE in the PBS subgroup treated with ribociclib + ET was neutropenia (27.4%) while in the patients treated with ET alone it was hypertension (2.6%). The safety profile of the proposed PBS subgroup from the NATALEE trial was similar to the whole safety set population from the NATALEE trial.

[6] The safety set was defined as patients who received at least one dose of any study treatment

**Table 6: Summary of key adverse events in the trial**

| Trial ID / AEs | Ribociclib + ET<br>n with event/N (%) | ET alone<br>n with event/N (%) | RR (95% CI) |
|---|---|---|---|
| Mean duration of exposure months (SD) | 39.7 (16.09) | 38.3 (17.3) | - |
| **NATALEE (safety set population) April 2024 DCO (median follow-up 49.6 months)** | | | |
| Any TEAE | 2478/2526 (98.1%) | 2155/2441 (88.3%) | **1.11 (1.09, 1.13)** |
| Grade ≥ 3 TEAE | 1622/2526 (64.2%) | 481/2441 (19.7%) | **3.26 (2.99, 3.55)** |
| Any SAE | 375/2526 (14.8%) | 267/2441 (10.9%) | **1.36 (1.17,1.57)** |
| Treatment related - SAE | 71/2526 (2.8%) | 13/2441 (0.5%) | **5.28 (2.93, 9.51)** |
| Discontinuation due to AEs | 534/2526 (21.1%) | 130/2441 (5.3%) | **3.97 (3.30, 4.77)** |
| AEs of special interest | 2195/2526 (86.9%) | 1201/2441 (49.2%) | **1.28 (1.25, 1.32)** |
| All deaths | 104/2526 (4.1%) | 122/2441 (5.0%) | 0.82 (0.64, 1.06) |
| On treatment deaths | 20/2526 (0.8%) | 9/2441 (0.4%) | **0.43 (0.20, 0.95)** |
| **NATALEE (safety set matching PBS subgroup) April 2024 DCO (median follow-up 49.6 months)** | | | |
| Any TEAE | 859/882 (97.4%) | 777/880 (88.3%) | 1.07 (0.99, 1.16) |
| Grade ≥ 3 TEAE | 542/882 (61.5%) | 168/880 (19.1%) | **3.22 (2.78, 3.72)** |
| Any SAE | 125/882 (14.2%) | 87/880 (9.9%) | **1.39 (1.06, 1.82)** |
| Treatment related - SAE | 26/882 (2.9%) | 3/880 (0.3%) | **8.65 (2.63, 28.46)** |
| Discontinuation due to AEs | 199/882 (22.6%) | 59/880 (6.7%) | **3.26 (2.45, 4.33)** |
| AEs of special interest | 747/882 (84.7%) | 420/880 (47.7%) | **1.72 (1.55, 1.91)** |
| All deaths | 19/882 (2.2%) | 20/880 (2.3%) | 0.92 (0.49, 1.72) |
| On treatment deaths | 7/882 (0.8%) | 3/880 (0.3%) | 2.25 (0.58, 8.71) |

Source: Table 2.27, p75 and Table 2.8 p54 of the submission, RRs calculated during evaluation

CI = Confidence Interval; DCO = data cut-off; ET = endocrine therapy; ID = Identifier; PBS = Pharmaceutical Benefits Scheme; RR = relative risk; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event.

**Bold** = statistically significant results

*Note that the results presented in Table 6 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

**Table 7: Summary of Grade ≥ 3 AEs (safety set)**

| Trial ID / AEs | Ribociclib + ET<br>n with event/N (%) | ET alone<br>n with event/N (%) | RD (95% CI) |
|---|---|---|---|
| **NATALEE (safety set population) April 2024 DCO (median follow-up 49.6 months)** | | | |
| Neutropenia | 710/2525 (28.1%) | 13/2442 (0.5%) | **0.28 (0.26, 0.29); p < 0.0001** |
| Neutrophil count decreased | 448/2525 (17.7%) | 8/2442 (0.3%) | **0.17 (0.16, 0.19); p < 0.0001** |
| Alanine aminotransferase increased | 194/2525 (7.7%) | 17/2442 (0.7%) | **0.07 (0.06, 0.08); p < 0.0001** |
| Aspartate aminotransferase increased | 117/2525 (4.6%) | 14/2442 (0.6%) | **0.04 (0.03, 0.05); p < 0.0001** |
| White blood cell count decreased | 95/2525 (3.8%) | 6/2442 (0.2%) | **0.04 (0.03, 0.04); p < 0.0001** |
| Leukopenia | 94/2525 (3.7%) | 2/2442 (0.1%) | **0.04 (0.03, 0.04); p < 0.0001** |
| Diarrhoea | 368/ 2525 (14.6%) | 13 /2442 (5.53%) | NR |
| **NATALEE (safety set matching the PBS subgroup) April 2024 DCO (median follow-up 49.6 months)** | | | |
| Neutropenia | 242/882 (27.4%) | 8/880 (0.9%) | NR |
| Leukopenia | 33/882 (3.7%) | 0/880 (0%) | NR |
| Diarrhoea | 9/882 (1.0%) | 1/880 (0.1%) | NR |
| Alanine aminotransferase increased | 77/882 (8.7%) | 5/880 (0.6%) | NR |
| Aspartate aminotransferase increased | 45/882 (5.1%) | 5/880 (0.6%) | NR |
| White blood cell count decreased | 18/882 (2.0%) | 2/880 (0.2%) | NR |
| Hypertension | 18/882 (2.0%) | 23/880 (2.6%) | NR |
| Arthralgia | 6/882 (0.7%) | 10/880 (1.1%) | NR |

Source: Table 11, p19, Attachment 6, Table 12-4h, pp1-2, Attachment 7, of the submission, Table 4-6 pp49-50 CSR DCO April 2024
AEs = adverse events; CI = confidence interval; DCO = data cut-off; ET = endocrine therapy; n = number of participants with event; N = total participants in group; NR = not reported; RD = risk difference; SAE = serious adverse events; TEAE = treatment-emerging emerging adverse event; SAE = serious adverse event
^One person had grade 5 diarrhoea.
**Bold** = statistically significant results
*Note that the results presented in Table 7 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

## *Benefits/harms*

6.24 A summary of the comparative benefits and harms for ribociclib plus ET versus ET alone is presented in Table 8.

**Table 8: Summary of comparative benefits and harms for Ribociclib and ET and ET alone (NATALEE trial, proposed PBS population, April 2024 DCO)**

| Event | Ribociclib + ET | ET alone | Absolute Difference | Hazard Ratio (95% CI) |
|---|---|---|---|---|
| **Benefits** | | | | |
| **iDFS (median duration of follow up 49.6 months)** | | | | |
| Invasive disease or death, n/N (%) | 55/891 (6.2%) | 78/903 (8.6%) | NA | **0.67 (0.47, 0.94) p = 0.011** |
| Median iDFS (95% CI) | Not yet met | Not yet met | - | - |
| % alive without invasive disease at 1 year (95% CI) | 98.8% (97.8, 99.3) | 98.1% (96.9, 98.8) | 0.7% | - |
| % alive without invasive disease at 2 years (95% CI) | 96.4% (94.9, 97.5) | 95.9% (94.2, 97.0) | 0.5% | - |
| % alive without invasive disease at 3 years (95% CI) | 94.4% (92.6, 95.8) | 93.1% (91.1, 94.6) | 1.3% | - |
| % alive without invasive disease at 4 years (95% CI) | 93.9% (92.0, 95.3) | 90.2% (87.8, 92.2) | 3.7% | - |
| **DRFS (median duration of follow up 49.6 months)** | | | | |
| Distant disease or death, n/N (%) | 39/891 (4.4%) | 57/903 (6.3%) | NA | **0.64 (0.42, 0.97) p = 0.016** |
| Median DRFS (95% CI) | Not yet met | Not yet met | - | - |
| % alive without distant disease at 1 year (95% CI) | 99.4% (98.5, 99.7) | 98.6% (97.5, 99.2) | 0.8% | - |
| % alive without distant disease at 2 years (95% CI) | 98.1% (96.9, 98.9) | 97.6% (96.2, 98.4) | 0.5% | - |
| % alive without distant disease at 3 years (95% CI) | 96.3% (94.8, 97.4) | 95.0% (93.3, 96.3) | 1.3% | - |
| % alive without distant disease at 4 years (95% CI) | 95.7% (94.0, 96.9) | 92.9% (90.8, 94.6) | 2.8% | - |
| **Overall survival (median duration of follow up 49.6 months)** | | | | |
| Deaths, n/N (%) | 19/891 (2.1%) | 20/903 (2.2%) | NA | 0.87 (0.46, 1.66) p = 0.34 |
| Median OS, months (95% CI) | Not yet met | Not yet met | - | - |
| % Alive at 1 year (95% CI) | 100.0% (100.0,100.0) | 99.8% (99.0, 99.9) | 0.2% | - |
| % Alive at 2 years (95% CI) | 99.6% (98.9, 99.9) | 99.4% (98.5, 99.7) | 0.2% | - |
| % Alive at 3 years (95% CI) | 98.8% (97.7, 99.3) | 98.1% (96.9, 98.9) | 0.7% | - |
| % Alive at 4 years (95% CI) | 97.8% (96.5, 98.6) | 97.5% (96.1, 98.4) | 0.3% | - |

| **Harms** | | | | | | |
|---|---|---|---|---|---|---|
| **Adverse event** | **Ribociclib + ET n/N** | **ET alone n/N** | **RR (95% CI)** | **Event rate/100 patients*** | | **RD** |
| | | | | **Ribociclib + ET** | **ET alone** | |
| Grade ≥ 3 TEAE | 542/882 | 168/880 | **3.22 (2.78, 3.72)** | 61.5 | 19.1 | **0.42 (0.38, 0.46)** |
| Neutropenia | 383/882 | 33/880 | **11.58 (8.22, 16.32)** | 43.4 | 3.8 | **0.40 (0.36, 0.43)** |
| Alanine aminotransferase increased | 193/882 | 41/880 | **4.70 (3.40, 6.50)** | 21.9 | 4.7 | **0.17 (0.14, 0.20)** |
| Leukopenia | 126/882 | 21/880 | **5.99 (3.81, 9.41)** | 14.3 | 2.4 | **0.12 (0.09, 0.14)** |
| Diarrhoea | 136/882 | 53/880 | **2.56 (1.89, 3.47)** | 15.4 | 6.0 | **0.09 (0.07, 0.12)** |

Source: Table 2.16, p65, Table 2.17, p66 of the submission, Table 2.22 and Table 2.23, p70 of the submission.

CI = Confidence Interval; DCO = data cut-off; ET = endocrine therapy; DRFS = distant recurrence free survival; iDFS = invasive disease-free survival; OS = overall survival; PBS = Pharmaceutical Benefits Scheme; HR = hazard ratio; PBO = placebo; RD = risk difference; RR = risk ratio; NA = not applicable
* Median duration of follow-up: 49.6 months
**Bold** = statistically significant results
*Note that the results presented in Table 8 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.25 On the basis of direct evidence presented by the submission, for every 100 patients treated with ribociclib plus ET in comparison with ET alone:

- Approximately 4 additional patients would remain invasive-disease-free after 4 years, however, there would be no difference in overall survival.
- Approximately 3 additional patients would remain distant-disease-free after 4 years.
- Approximately 42 patients would experience a grade ≥3 treatment-emergent AE over 4.1 years.
- Approximately 40 additional patients would experience neutropenia (abnormally low neutrophils, a type of white blood cell that helps fight infections, all grades) over 4.1 years.
- Approximately 12 additional patients would experience leukopenia (abnormally low leukocytes, another type of white blood cell that help fight infections) over 4.1 years.
- Approximately 17 additional patients would have alanine aminotransferase increased (indicating liver damage or injury) over 4.1 years.
- Approximately 9 additional patients would have diarrhoea over 4.1 years.

## *Clinical claim*

6.26 The submission described ribociclib plus adjuvant ET as superior in terms of effectiveness compared to adjuvant ET alone.

6.27 The ESC considered the claim was adequately supported for iDFS, however considered that the absolute benefit was modest. In the PBS subgroup of the NATALEE trial, treatment with ribociclib + ET, in comparison to ET alone, resulted in an absolute benefit of iDFS of 1.3% at 3 years and 3.7% at 4 years and an absolute benefit of DRFS of 1.3% at 3 years and 2.8% at 4 years. It was noted that the PBAC previously considered that a 3.5% absolute difference in iDFS may be clinically meaningful in the adjuvant eBC setting where the goal is cure (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting). However, it was noted that the clinical data at the 4-year follow-up point may be subject to reduced reliability due to a lower number of patients remaining at risk (approximately 50% of the original cohort). The ESC also noted the risk of recurrence in the ET alone arm was substantially lower in the proposed PBS population (8.6%) than the complement group which reflects the current PBS

population ((340-78)/(2552-903) = 15.9%). The Pre-PBAC Response reiterated the iDFS benefit was greater than the 3.5% previously considered by the PBAC to be clinically meaningful and argued the recurrence rate of 8.6% in the ET alone arm reinforces the clinical need for improved treatments to reduce the risk of recurrence.

6.28 In the NATALEE trial, both the iDFS and OS data were immature. The results for OS showed no significant difference between the two arms in the ITT population or PBS subgroup population. Due to this the submission used iDFS as a surrogate for OS. The ESC noted that the PBAC previously considered that iDFS being employed as a surrogate for OS was an uncertain, but generally plausible surrogate for OS in the eBC setting. However, the PBAC also noted that the relationship between iDFS and OS was uncertain (for abemaciclib), given the OS data were immature and no difference in OS was observed at the most recent data cutoff (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting). As OS was immature in this submission, the relationship between iDFS and OS for ribociclib is also uncertain. The PSCR stated that the immaturity of the data should be viewed in the context of an adjuvant treatment, where patients have undergone surgery with curative intent. Many patients are therefore likely to remain free of invasive disease long-term and a difference in OS may not be observed within the duration of a clinical trial.

6.29 The submission described ribociclib plus adjuvant ET as inferior in terms of safety compared to ET alone. The ESC considered that this claim was adequately supported. Patients in the PBS subgroup who received ribociclib + ET experienced more TEAEs than patient who received ET alone (97.4% vs. 88.3%). This included the ribociclib arm experiencing more Grade ≥3 TEAEs (61.5% vs. 19.1%), more discontinuations due to AEs (22.6% vs. 6.7%), and more AEs of special interest (84.7% vs. 47.7%).

6.30 Overall, the ESC considered that when considering the drug toxicity associated with ribociclib and the relatively low risk of recurrence in the proposed incremental population, the benefit-harm profile of ribociclib as adjuvant therapy is uncertain. In this context, the ESC advised that the use of adjuvant ribociclib should be considered carefully in the context of the 'Once in a lifetime' rule for CDK4/6 inhibitors as its use in eBC would prevent patients from using ribociclib in the advanced setting where it is currently PBS listed. The Pre-PBAC response disagreed that the benefit-harm profile was uncertain, noting that the TGA had previously considered that ribociclib had a favourable benefit-harm profile in this population. The Response argued that the decision to treat eBC ultimately rests with the individual patient and clinician, who are best positioned to assess and determine the benefit-risk of available treatment options. It was noted that the TGA approved population related to the ITT population of the NATALEE trial, and was not specific to the lower risk subset of patients being considered in this submission.

6.31 The PBAC noted that whilst the reductions in iDFS and DRFS were statistically significant, they were smaller than observed for the currently listed eBC patients. In the context of the increase in the number adverse events reported, and that patients treated in the adjuvant setting forego treatment with a CDK4/6 in the metastatic

setting, the PBAC considered the overall benefit associated with adding ribociclib to ET in node negative/low patients had not been demonstrated to be clinically meaningful.

6.32 The PBAC considered that the claim of inferior comparative safety was reasonable.

## *Economic analysis*

6.33 The submission presented a stepped economic evaluation comparing adjuvant ribociclib plus ET with ET alone, based on a subgroup of patients in the NATALEE trial in line with the proposed PBS population. The key components of the economic evaluation are summarised in Table 9.

**Table 9: Summary of model structure, key inputs and rationale**

| Component | Description |
|---|---|
| Treatments | Adjuvant treatment with ribociclib + ET vs ET |
| Time horizon | 30 years in the base case *versus* a median follow-up of 49.6 months in the NATALEE trial |
| Outcomes | LYs and QALYs |
| Methods used to generate results | Cohort expected value analysis (Markov model) |
| Health states | 6 health states: iDF, NMR, remission, SPM, DR, and death |
| Cycle length | 28 days |
| Transition probabilities | iDF: Probabilities of transitioning from the iDF health state to the NMR, DR, SPM, and death health states were estimated based on the iDFS KM curves by treatment up to 48 months from the PBS subgroup in the NATALEE trial, and the distribution of first iDFS events observed in this subgroup.<br>NMR: The probability of transitioning from the NMR to death was based on the age-specific general population mortality (ABS Life Tables 2020-2022). All patients remaining in the NMR health state after 1 year transitioned to the remission health state.<br>Remission: The probability of DR in patients in the remission health state was sourced from the NICE technology appraisal and the PBAC submission for abemaciclib + ET for eBC (based on Hamilton *et al* 2015[a]). The transition probability from remission to death was based on the age-specific general population mortality.<br>DR: Absorbing health state (with two substates: ET-sensitive and ET-resistant) with patients entering this state receiving one-off payoffs of costs and LYs from embedded PSMs (with 3 health states: PFS, PPS, and death) on transition, based on external studies in advanced BC. Costs and health outcomes for each metastatic treatment option were weighted by the distribution of use with and without ribociclib in the adjuvant setting.<br>SPM: All patients with a SPM were assumed to exit the model with a cost for diagnosis but no QALYs applied to these patients.<br>TTD: Ribociclib: KM estimates from the PBS subgroup in the NATALEE trial used up to 36 months without extrapolation. ET (alone and in combination with ribociclib): KM estimates used up to 60 months with no need for extrapolation. |
| Extrapolation method | iDF: Trial-based KM were used until 48 months, after which data were extrapolated using restricted exponential functions fitted to the observed KM estimates for both ribociclib + ET and ET alone. The distribution of iDFS events was assumed to remain constant beyond the trial duration. The treatment effect of ribociclib in terms of the hazard of iDFS events and the distribution of iDFS events were assumed to wane between Years 8 and 16, after which no treatment benefits were assumed.<br><br>LYs gained in the extrapolation period: 83% for ribociclib + ET and 81% for ET alone. The incremental survival benefits associated with ribociclib adjuvant were accrued entirely during the extrapolation period. |
| Health related quality of life | iDF: 0.8877 for ribociclib + ET on-treatment, 0.8857 for ET on-treatment, 0.8412 for off-treatment, based on QoL data from NATALEE. However, as the trial on-treatment utilities were higher than the utility of the general Australian population (0.87 for the age category of 45-54 years, McCaffrey et al 2016), the utility of the general population was used for patients receiving adjuvant treatment in the iDF health state instead.<br>NMR: 0.8222, based on NATALEE.<br>Remission: same as the general population.<br>DR: 0.7867 for PFS (based on NATALEE) and 0.7508 for PPS (based on NATALEE and MONALEESA-2)<br>All health state utilities were age-adjusted over time using the Australian general population utility by age category for the EQ-5D-5L (McCaffrey et al 2016). |

Source: Table 3-1, pp90-91 of the submission.

ABS = Australian Bureau of Statistics; BC = breast cancer; DR = distant recurrence; eBC = early breast cancer; EQ-5D-5L = EuroQoL 5-dimension 5-level; ET = endocrine therapy; iDF = invasive disease-free; iDFS = invasive disease-free survival; KM = Kaplan-Meier; LYs = life years; NICE = National Institute for Health and Care Excellence; NMR = non-metastatic recurrence; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; PPS = post-progression survival; PSM = partitioned survival model; QoL = quality of life; QALYs = quality-adjusted life years; SPM = second primary malignancy; TTD = time to treatment discontinuation

[a] Hamilton SN, Tyldesley S, *et al*. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? *Int J Radiat Oncol Biol Phys*. 2015;91(5):977-85.

6.34 The economic evaluation adopted a Markov model. A total of six health states were included, of which three were non-absorbing health states: invasive disease-free (iDF), non-metastatic recurrence (NMR), and remission; and three were absorbing health states: second primary malignancy, distant recurrence (DR), and death. The DR health state was divided into two substates based on whether patients were resistant to ET (those who developed DR while on, or within 12 months of completion of, adjuvant ET) or who were sensitive to ET. The structure of the ribociclib economic model was generally consistent with the economic models for abemaciclib previously considered by the PBAC (abemaciclib PSDs, March 2022, March 2023 and November 2023 PBAC meetings). The ESC previously agreed with the evaluation that the two metastatic recurrence sub-states in the economic model added unwarranted complexity, and their inclusion was not well justified (para. 6.31, abemaciclib PSD, March 2022 PBAC meeting).

6.35 The starting age of the model population was assumed to be 53.5 years, based on the PBS subgroup in the NATALEE trial. The submission acknowledged that the PBAC previously considered that the starting age for the modelled cohort in the abemaciclib for eBC economic evaluation should be approximately 60 years, based on data from the Chan et al (2021) study (abemaciclib PSDs, March 2023 and November 2023 PBAC meetings). This study included patients diagnosed with eBC included in BreastSurgANZ, which reported a mean age of 61.4 years.[7] The submission argued that this is likely an overestimate, as a real-world analysis of patients enrolled in the Australian Capital Territory (ACT) and South-Eastern (SE) New South Wales (NSW) Breast Cancer Treatment Group (BCTG) showed that the median age of the NATALEE eligible cohort was 56 years.[8] The mean age of the NATALEE eligible cohort from the ACT and SE NSW BCTG registry was not reported. The PBAC previously noted the mean age reported by Chan et al (2021) was based on approximately 100,000 patients diagnosed with eBC from 2002 to 2016 and that it included patients with triple negative breast cancer who are approximately 10 years younger at diagnosis. In addition, the PBAC previously noted the abemaciclib sponsor's analysis of Scottish Registry data reported a median age of diagnosis of 59 years (para. 7.12, abemaciclib PSD, March 2023 PBAC meeting). Furthermore, the Chan et al study cited by the PBAC reported a trend of increase in the mean age at diagnosis of eBC in Australia, from

[7] Chan A, O'Neil N, *et al*. BreastSurgANZ members recommendations for adjuvant systemic treatment and patient compliance in Australian breast cancer patients. *ANZ Journal of Surgery*. 2021;91(11):2418-24.

[8] Kanjanapan Y, Anderson W, *et al*. Real-World Analysis of Breast Cancer Patients Qualifying for Adjuvant CDK4/6 Inhibitors. *Clin Breast Cancer*. 2025;25(2):e159-e69.e2.

59.0 years in 2002−2006, to 60.1 years in 2007−2011 to 61.4 years in 2012−2016. Considering the time period when the patients in the ACT and SE NSW BCTG registry were enrolled (between 1997 and 2017), it is likely that the patient age in this real-world evidence has underestimated the age of the target population in the current Australian setting. Overall, the evaluation considered that the age of patients entering the economic model was younger than expected in the context of Australian practice, and the model was sensitive to the change of this variable (Table 15). The PSCR stated that Chan et al (2021) did not distinguish by molecular subtype of eBC or risk profile and was therefore not representative of the proposed PBS population. The Response considered that the only relevant data sources that could accurately inform the average age of model entry were NATALEE and the ribociclib eligible cohort in the ACT & South-East NSW BCTC registry (Kanjanapan et al., 2024). However, the ESC agreed with the evaluation that the starting age of the model population should be consistent with previous considerations in eBC (61.4 years) and advised that this should be included in a respecified base case. The ESC noted that using a model entry age of 61.4 years increased the incremental cost-effectiveness ratio (ICER) by [redacted]% ($35,000 to < $45,000 per quality adjusted life year [QALY] gained). The Pre-PBAC Response argued that the starting age proposed by the ESC does not represent the totality of patients in the study and is confounded by changes in national breast cancer screening that occurred at that time, and that it is more appropriate to use an age aligned with the NATALEE trial (53.5 years). The Response also noted two retrospective studies reporting the median age at diagnosis as 50 years among women with node negative/low eBC[9] and 55 years among women with HR+ eBC[10].

6.36 The OS benefit from adjuvant ribociclib was modelled indirectly through iDFS. The submission modelled both a reduction in the hazard of iDFS events with ribociclib and a lower proportion of iDFS events that were deaths or DRs (52.7% with ribociclib + ET vs. 59.0% with ET) based on data from the proposed PBS subgroup in NATALEE. Trial iDFS KM curves were used until Month 48, after which data were extrapolated using parametric models. The truncation time point was selected on the basis that less than 10% of patients in either treatment arm were at risk of an iDFS event at the next available time point. At Month 48, around half of patients in each treatment arm remained at risk (456 patients in the ribociclib + ET arm and 425 patients in the ET arm), which resulted in the exclusion of an amount of observed trial data before they became unreliable. Using a later time point for extrapolation (e.g. 54 weeks; number of patients at risk: 87 patients in the ribociclib + ET arm vs. 70 patients in the ET arm), however, did not have a big impact on the result (Table 15).

6.37 Restricted (dependent) exponential distributions were selected to extrapolate iDFS curves in the base case, on the basis of goodness of fit statistics, visual inspection, and clinical plausibility. The submission also assumed that the distribution of iDFS events

[9] Dogan I, Aydin E, et al. Long-term outcomes and predictors of recurrence in node-negative early stage breast cancer patients. JCRCO. 2023; 149:14833-14841.
[10] EBCTCG. Reductions in recurrence in women with early breast cancer entering clinical trials between 1990 and 2009: a pooled analysis of 155 746 women in 151 trials. Lancet. 2024; 404:1407-18.

would remain constant beyond the trial period until the treatment effect was assumed to wane from Year 8 to Year 16. At the latest data cutoff, less than 10% of patients in the PBS subgroup in NATALEE experienced an iDFS event (6.2% [n=55] for ribociclib + ET and 8.6% [n=78] for ET alone). The iDFS data were immature and not likely to provide a reliable basis both for the long-term extrapolation of iDFS curves and for the determination of the distribution of iDFS events over time. The evaluation considered that the selection of restricted parametric functions for extrapolation were not well justified. The results from transformation diagnostics and Schoenfeld residuals suggest the violation of the proportional hazards assumption. Of the diagnostic plots presented in the submission, the log-log survival curves of the two treatment arms were not parallel over time, and the Schoenfeld residuals plot clearly showed a non-zero slope over time. These do not support use of restricted parametric models. Based on the goodness of fit statistics, exponential, Weibull, log-logistic and gamma distributions were the best fitting restricted distributions. Visual inspection indicated that all parametric functions provided a good and very similar fit to the KM data before trial data became unreliable (Figure 3).

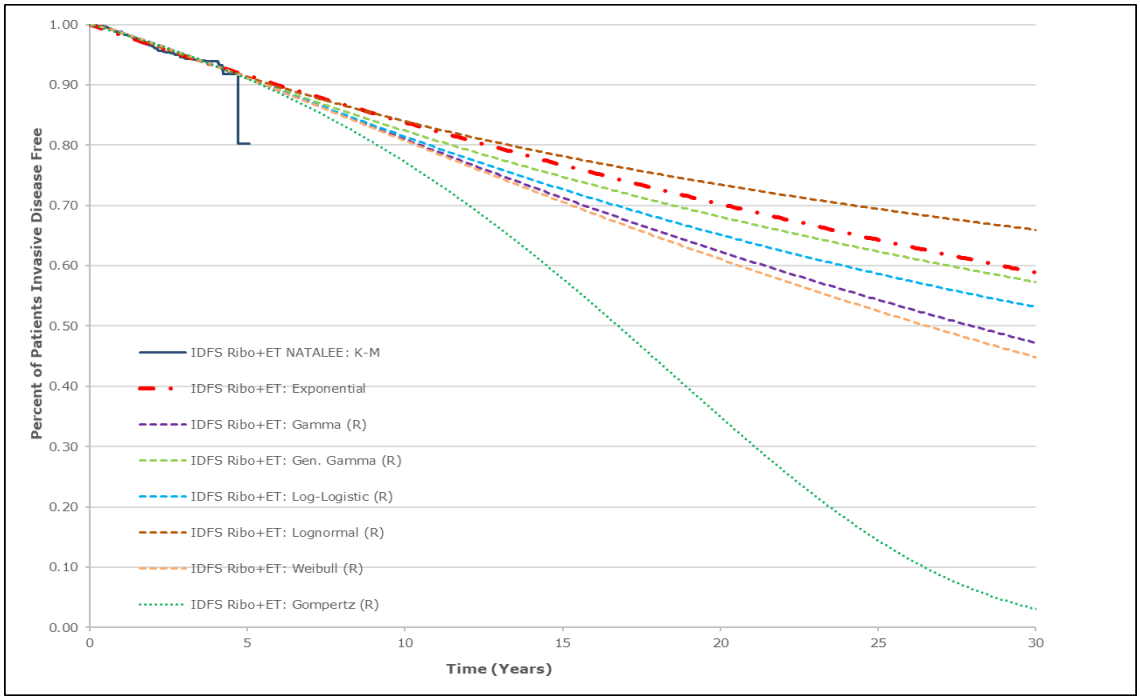
6.38 The submission selected the exponential function for long-term extrapolation of iDFS based on the iDFS data in patients from the ACT and SE NSW BCTG registry[8] who were found to meet the NATALEE trial eligibility criteria. It was noted that the NATALEE eligible cohort from the BCTG registry included patients outside the proposed PBS population for ribociclib, e.g. with ≥4 ALNs, tumour size of > 5 cm, histological grade ≥3, but the proportion of these patients in the NATALEE-eligible cohort was unknown. This limited the use of the external data from the ACT & SE NSW BCTG to validate the long-term extrapolation of iDFS for ET. The PSCR maintained that the extrapolation of iDFS in the economic model was reasonable and clinically plausible. The PSCR noted that the long-term extrapolation of iDFS for ET alone aligned with that reported by the ACT & South-East NSW BCTC for the NATALEE eligible population up to approximately 15 years, and the 3-, 5- and 7-year recurrence rates reported in Jhaveri et al 2024[11]. It was noted that the actual recurrence rates modelled in the ET alone arm of the ribociclib economic evaluation appeared to be lower than presented in the PSCR and that reported in the Jhaveri et al (2024) data. Overall, the ESC considered that a more conservative parametric function should be applied to the extrapolation of ribociclib + ET iDFS. The ESC advised that the restricted Weibull function for the ribociclib + ET arm would be more appropriate and considered that the extrapolation for ET should remain unchanged from the original base case. The ESC noted that this increased the ICER by [redacted]% ($45,000 to < $55,000/QALY). The Pre-PBAC Response stated that the proportional hazards assumption had not been violated, based on Schoenfeld residuals test, and maintained that the exponential (restricted) function was best

[11] Jhaveri, K., Pegram M. 292P Real-world evidence on risk of recurrence (ROR) in patients (pts) with node-negative (N0) and node-positive HR+/HER2- early breast cancer (EBC) from US electronic health records (EHR). *Annals of Oncology*, 35, 2024;S337-S338

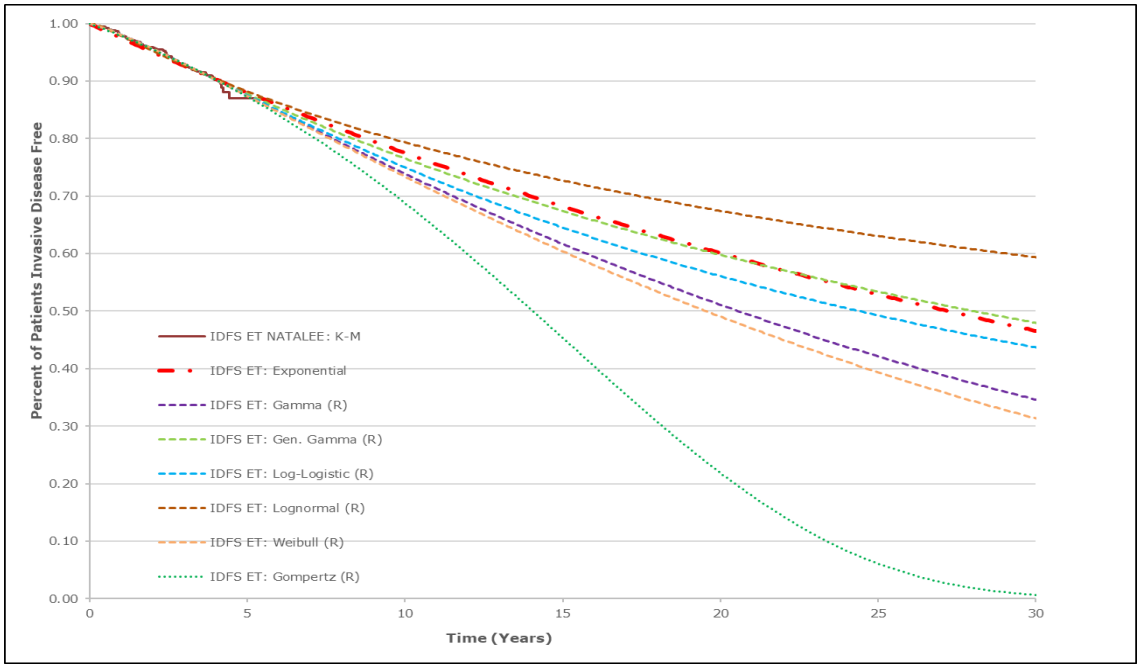
supported by the evidence. The visual signs of non-proportionality noted by the evaluation were not discussed in the response.

**Figure 3: Long-term iDFS projections for (A) ribociclib + ET and (B) ET alone**

**A**




**B**



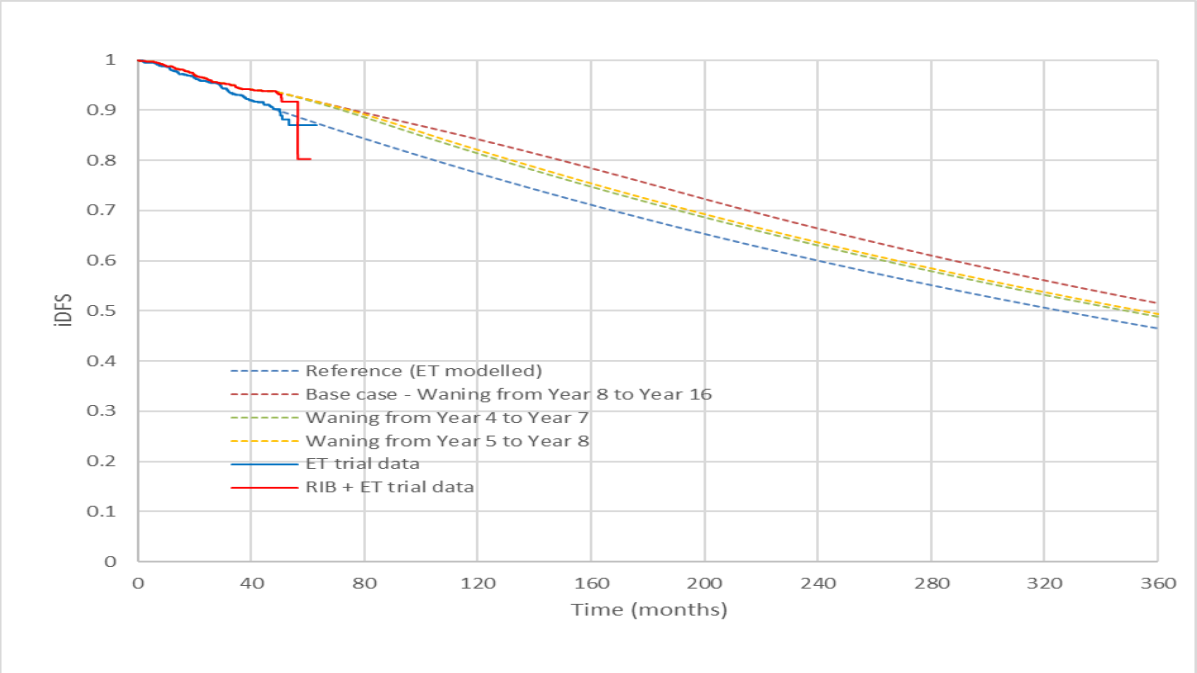

Source: Revised from Figure 3.11, p109 of the submission.
ET = endocrine therapy; iDFS = invasive disease-free survival; K-M = Kaplan-Meier; R = restricted
*Note that the results presented in Figure 3 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.39 As restricted parametric survival models were used, the extrapolations effectively assumed an ongoing treatment effect of ribociclib + ET over ET. Although ribociclib has a limited duration of treatment (maximum of 3 years), this treatment effect was assumed to last for 8 years, after which, the effect of ribociclib was assumed to wane until the beginning of Year 16 (duration of waning: 8 years). Treatment effect waning was implemented such that the hazard of an iDFS event for ribociclib + ET linearly decreased to that of ET alone starting at Year 8 and reaching the same hazard for iDFS between the two treatment arms after 8 years. The time point for treatment effect waning was based on the treatment effects for tamoxifen/anastrozole (endocrine inhibitor).[12,13] The evaluation considered that this was unlikely to be applicable to the duration of the treatment effect of ribociclib (a CDK4/6 inhibitor) in addition to ET. The PBAC previously considered that a treatment waning period of 5−8 years would be appropriate for abemaciclib in eBC, based on a median follow-up of 54 months in the pivotal trial (para. 7.10, abemaciclib PSD, November 2023 PBAC meeting). The evaluation noted that considering the available trial data for ribociclib (median follow-up in NATALEE: 49.5 months), a treatment effect waning assumption from Year 5 to Year 8 may be more reasonable and consistent with previous PBAC advice. A comparison of the modelled curves with various assumptions regarding treatment waning is presented in Figure 4. The ICER was very sensitive to this assumption. The PSCR noted that treatment with ribociclib was likely to be longer than treatment with abemaciclib and therefore considered treatment waning should start later than considered for abemaciclib. The PSCR maintained that the proposed waning period was appropriate and was supported by the results of the NATALEE trial showing a continued divergence of the ribociclib + ET and ET alone iDFS curves and improved HRs in subsequent data cuts. However, the ESC advised that in consideration of the available trial data for ribociclib, a more conservative treatment waning, from year 5 to year 8 (as previously accepted by the PBAC for abemaciclib), should be included in a respecified base case. The ESC noted that reducing the treatment waning period from 8−16 years to 5−8 years increased the ICER by [redacted]% ($45,000 to < $55,000/QALY). The Pre-PBAC Response argued the monarchE 5-year iDFS data for abemaciclib demonstrates that waning does not start at year 5 and while the 5-year data cut for NATALEE are pending, the Response considered the NATALEE data to be consistent and more favourable compared to monarchE. The Response also noted the longer treatment duration of abemaciclib vs ribociclib and reiterated the submission input of 8 years was appropriate.

[12] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687-717.

[13] Howell A, Cuzick J, *et al*. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet.* 2005;365(9453):60-2.

**Figure 4: Modelled iDFS showing effect of alternative assumptions around treatment effect waning**




Source: Figure constructed during the evaluation using "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook.
ET = endocrine therapy; iDFS = invasion disease-free survival; RIB = ribociclib
*Note that the results presented in Figure 4 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.40 The submission nominated a 30-year time horizon in the base case analysis. The submission considered this to be an appropriate time horizon as it was aligned with that recommended by the PBAC for abemaciclib for eBC (para. 7.13, abemaciclib PSD, March 2023 PBAC meeting). The PBAC previously considered that a 20-year time horizon would be more reasonable for the abemaciclib model, however, the 30-year time horizon would be reasonable in the context of a more conservative treatment waning (4 to 7 years) and older age at model entry (61.4 years) (para. 6.37, abemaciclib PSD, November 2023 PBAC meeting). As previous discussed, the ribociclib model assumed an optimistic waning assumption and a younger age of the model population, therefore, an extended time horizon of 30 years was not consistent with previous PBAC advice. The PSCR stated that given the generally favourable prognosis of patients with eBC and the need to capture the long-term benefit of adjuvant treatment with ribociclib + ET and ET alone on disease recurrence, a 30-year time horizon was appropriate and previously supported by the PBAC. While the ESC agreed in principle, a time horizon should capture all costs and outcomes in alignment with the disease's natural course but noted that it should also consider the decision context. Shorter time horizons may be preferred for decision making when the long-term projections of model parameters are highly uncertain.

6.41 All patients who experienced a DR in a cycle transitioned to one of two absorbing DR health substates: DR ET-sensitive and DR ET-resistant, with one-off costs and health

outcomes applied on transitioning depending on whether the patients entered the DR ET-sensitive or DR ET-resistant substate. The applied discounted cost and outcome payoffs were estimated from embedded partitioned survival models (PSMs). The progression-free survival (PFS), OS and time to treatment discontinuation (TTD) curves for ribociclib + NSAI for the treatment of ET-sensitive DR were based on the MONALEESA-2 trial, which formed the basis of the PBS listing for ribociclib + NSAI for first-line treatment of patients with HR+, HER2- advanced breast cancer (ribociclib PSDs, July 2017, November 2017, March 2018 PBAC meetings). The submission further assumed identical PFS, OS and TTD estimates for ribociclib + fulvestrant in the DR ET-resistant PSM to those for ribociclib + NSAI in the DR ET-sensitive PSM, as the PBAC previously accepted that ribociclib + fulvestrant is non-inferior to ribociclib + NSAI in terms of PFS and safety, based on the clinical evidence from the treatment-naïve subgroup in MONALEESA-3 (for ribociclib + fulvestrant) and the MONALEESA-2 trial (for ribociclib + NSAI) in the first-line advanced setting (ribociclib PSD, July 2020 PBAC meeting). The survival curves of other metastatic breast cancer treatments were estimated by applying hazard ratios, which were sourced from published studies and previous PBAC considerations, to the survival curves for ribociclib + NSAI/fulvestrant. Results of the external metastatic breast cancer studies may not be applicable to the economic model. For example, the treatment-naïve subgroup in MONALEESA-3 does not represent patients with ET-resistant DR as defined in the submission, as the vast majority (78.5% [237 out of 302]) of patients in this MONALEESA-3 subgroup were first-line ET-sensitive, i.e. de novo or patients who had relapsed ≥ 12 months after receiving ET in the (neo)adjuvant setting (Table 3, ribociclib PSD, July 2020 PBAC meeting). This is likely to result in an overestimate of survival associated with ribociclib + fulvestrant in the DR ET-resistant PSM.

6.42 Costs and outcomes attributed to DRs were assumed to vary by the treatment received in the adjuvant setting, as the submission assumed that use of a CDK4/6 inhibitor in the adjuvant setting would preclude its use in the metastatic setting. This, although aligns with current PBS CDK4/6 once per lifetime restrictions, does not reflect the requested restriction changes in the submission. In addition, this was not consistent with previous PBAC consideration. The PBAC previously considered that for metastatic recurrence, some CDK4/6 inhibitor re-challenge would be likely post adjuvant abemaciclib treatment, but it may also be reasonable to assume differences in use across model arms (para. 6.33, abemaciclib PSD, March 2022 PBAC meeting; para. 6.39, abemaciclib PSD, March 2023 PBAC meeting). The impact of re-challenging CDK4/6 inhibitors on the ICER cannot be reliably estimated, given the lack of clinical efficacy data to model associated health outcomes.

6.43 The modelled ICERs from the DR ET-resistant and ET-sensitive PSMs were calculated during the evaluation and are presented in Table 10, based on a discount assumption regarding the prices for abemaciclib and palbociclib. The results of DR PSMs reflect a mixture of treatment options for the treatment of advanced breast cancer, of which CDK4/6 inhibitors were used in around one-third of patients in the first-line DR ET-resistant setting and in around three-fourths of patients in the first-line DR ET-

sensitive setting following adjuvant ET alone, but no patients were retreated with CDK4/6 inhibitors for the treatment of DR following ribociclib adjuvant therapy. Of note, the ICER of CDK4/6 inhibitor + ET (NSAI or fulvestrant) versus ET alone for the treatment of metastatic breast cancer as modelled in the economic evaluation varied between $55,000 to < $75,000/quality-adjusted life year (QALY) to $75,000 to < $95,000/QALY, higher than what the PBAC had previously considered cost-effective ($15,000-$45,000) (para. 6.10, palbociclib PSD, March 2018 PBAC meeting). The incorporation of the less cost-effective treatment for advanced breast cancer in the comparator arm favoured ribociclib adjuvant therapy.

6.44 Of note, the submission erroneously applied the undiscounted, instead of discounted, cost and outcome payoffs to patients transitioning into the DR ET-resistant substate (Cells H16:I669, 'ET-Resistant PSM' spreadsheet, "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook). The results herein are revised and correct for this mistake.

**Table 10: Incremental cost-effectiveness of modelled DR PSMs, with and without adjuvant ribociclib (discounted)**

| | ET | Ribociclib + ET | Increment |
|---|---|---|---|
| **ET – resistant**<br>Assuming 34.8% use of CDK4/6 inhibitor + fulvestrant after adjuvant ET, the remaining 65.2% in the ET arm and 100% in the ribociclib + ET arm using a mix therapies (fulvestrant, everolimus + exemestane, exemestane, tamoxifen and capecitabine) for the treatment of DR | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| QALYs | 3.65 | 3.41 | 0.24 |
| **ICER per additional QALY gained** | | | **$[redacted][1]** |
| **ET – sensitive**<br>Assuming 73.4% use of CDK4/6 inhibitor + NSAI after adjuvant ET, the remaining 26.6% in the ET arm and 100% in the ribociclib + ET arm using a mix therapies (letrozole, anastrozole, exemestane, tamoxifen, fulvestrant, and capecitabine) for the treatment of DR | | | |
| Costs | $[redacted] | $[redacted] | $[redacted] |
| QALYs | 3.98 | 3.64 | 0.34 |
| **ICER per additional QALY gained** | | | **$[redacted][2]** |

Source: Analyses performed during the evaluation using "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook.
CDK4/6 = cyclin-dependent kinase 4 and 6; DR = distant recurrence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; NSAI = non-steroidal aromatase inhibitor; PSM = partitioned survival model; QALY = quality adjusted life year
Note: Analyses were revised during the evaluation to correct the fixed outcome and cost payoffs from the DR ET-resistant PSM, using the discounted payoffs instead of undiscounted payoffs.
*The redacted values correspond to the following ranges:*
*[1] $45,000 to < $55,000*
*[2] $75,000 to < $95,000*

6.45 The health state utilities were initially estimated based on the EQ-5D-5L data collected in the PBS subgroup in NATALEE, mapped into utilities using the Australian value set by Norman et al (2023).[14] All health state utilities were capped and age-adjusted over time using the Australian general population utilities by age category for the EQ-5D-5L as reported in McCaffrey et al (2016).[15] Given that the trial-based utilities for iDFS on-treatment were higher than the utility for the general Australian population

[14] Norman R, Mulhern B, *et al*. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. *Pharmacoeconomics*. 2023;41(4):427-38.
[15] McCaffrey N, Kaambwa B, *et al*. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. 2016;14(1):133.

(0.8857−0.8877 vs. 0.8702), the general population utility was used as the health state utility for iDF in patients who were on adjuvant therapy. The ESC agreed with the evaluation that the HRQoL data collected in NATALEE likely lacked face validity and use of the utility in the general population as a proxy for the iDF on-treatment utility overestimated the utility value of this health state. The health state utilities used in the abemaciclib eBC model previously accepted by the PBAC were consistently lower than the utilities applied to the ribociclib model (e.g. 0.841−0.870 vs. 0.785 for iDF, 0.787 vs. 0.748 for PFS in the DR PSMs) and these estimates were used in univariate and multivariate sensitivity analyses, however the model was not very sensitive to these utility inputs (Table 15). The ESC considered that the utilities applied to the base case of the economic model likely lacked face validity and alternate utilities should be applied. The ESC advised the use of the utilities applied to the previous abemaciclib eBC model would likely be appropriate. The Pre-PBAC Response argued the utilities should be informed by the ribociclib data, rather than rely on those previously accepted for abemaciclib.

6.46 A summary of the key drivers of the model is shown below.

**Table 11: Key drivers of the model**

| Description | Method/Value | Impact<br>Base case ICER: $[redacted][1]/QALY (revised) |
|---|---|---|
| Duration of treatment effect | The treatment effect based on the restricted parametric extrapolations was assumed to continue beyond the trial period from 4 years until 8 years. Thereafter, a waning of the treatment effect was implemented until Year 16. At this point the hazard of iDFS events in the ribociclib + ET arm equalled that in the comparator ET alone arm. The time points in the treatment effect waning assumption were not adequately justified. | High, favours ribociclib. Assuming that the treatment effect wanes from Year 5 to Year 8 increases the ICER to $[redacted][2]/QALY. |
| Time horizon | 30 years in the base case. This was too long given the optimistic assumption of treatment effect waning, and the younger age of the model population. | High, favours ribociclib. Reducing the time horizon to 20 years increases the ICER to $[redacted][2]/QALY. |
| Extrapolation of iDFS | The trial iDFS curves for ribociclib + ET and for ET were extrapolated using restricted exponential distributions. The selection of the extrapolation function, especially for iDFS in the ribociclib + ET arm, was not adequately justified in the submission primarily due to the immaturity of the iDFS data from NATALEE. | High, possibly favours ribociclib. Using a Weibull extrapolation function for ribociclib + ET but leaving the parametric function for ET unchanged from the base case increases the ICER to $[redacted][2]/QALY. |
| Distribution of iDFS events | The submission assumed a lower proportion of iDFS events that were DRs or deaths (52.7% for ribociclib + ET vs. 59.0% for ET) in the ribociclib + ET arm compared with the ET alone arm, and this difference maintained over time until the start of the treatment effect waning. This was inadequately supported given the low number of iDFS events at the latest data cutoff in the trial. | High, possibly favours ribociclib. Using identical distribution of iDFS events between the two treatment arms increases the ICER to $[redacted][2]/QALY. |
| Starting age of the model patients | 53.5 years. This is likely an underestimate of the age of the patients who are eligible for ribociclib adjuvant therapy in Australian clinical practice. | Moderate, favours ribociclib. Assuming a starting age of 61.4 years increases the ICER to $[redacted][1]/QALY. |
| Fixed payoffs applied to patients transitioning into DR | The distribution of treatments for DR in Australian clinical practice with and without adjuvant ribociclib was uncertain. In addition, the populations in advanced breast cancer studies used to estimate the fixed payoffs may not be applicable to the modelled population. | Unclear impact. Assumptions in relevant sensitivity analyses cannot be determined based on evidence presented. |

Source: Constructed during the evaluation.

DR = distant recurrence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; iDFS = invasive disease-free survival; PSM = partitioned survival model; QALY = quality adjusted life year

Note: The health outcomes and costs in the DR ET-resistant PSM were undiscounted (Cells H16:I669, 'ET-Resistant PSM' spreadsheet in the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook). This was corrected during the evaluation.

*The redacted values correspond to the following ranges:*

[1] *$35,000 to < $45,000*

[2] *$45,000 to < $55,000*

6.47 The results of the stepped economic analysis are presented in Table 12. Results of the economic evaluation were corrected during the evaluation by incorporating a 5% annual discounting rate for health outcomes and costs accrued in the DR ET-resistant PSM.

6.48 Results presented in the table below were based on the prices for abemaciclib and palbociclib for the treatment of advanced breast cancer assumed by the submission ([redacted]% discount on the published prices for abemaciclib and palbociclib).

**Table 12: Results of the stepped economic evaluation**

| Step and component | Ribociclib + ET | ET alone | Increment |
|---|---|---|---|
| **Step 1: trial-based economic evaluation (drug costs only, a time horizon of 4 years, applying a 5% discount rate for both costs and health outcomes)** | | | |
| Costs | $[redacted] | $4,741 | $[redacted] |
| LYs gained | 3.77 | 3.81 | -0.05 |
| Incremental cost/extra LY gained | | | Dominated |
| **Step 2: Time horizon extended to 30 years** | | | |
| Costs | $[redacted] | $5,550 | $[redacted] |
| LYs gained | 13.83 | 13.28 | 0.55 |
| Incremental cost/extra LY gained | | | $[redacted][1] |
| **Step 3: Incorporation of medical resource costs** | | | |
| Costs | $[redacted] | $26,185 | $[redacted] |
| LY gained | 13.83 | 13.28 | 0.55 |
| Incremental cost/extra LY gained | | | $[redacted][2] |
| **Step 4: Utility weights applied** | | | |
| Costs | $[redacted] | $26,185 | $[redacted] |
| QALYs | 11.87 | 11.38 | 0.49 |
| Incremental cost/extra QALY gained | | | $[redacted][2] |
| **Revised[a]** | | | |
| Costs | $[redacted] | $24,854 | $[redacted] |
| QALYs | 11.85 | 11.33 | 0.52 |
| **Incremental cost/extra QALY gained** | | | **$**[redacted][2] |

Source: Table 3.22, p141 of the submission.

DR = distant recurrence; ET = endocrine therapy; LY = life year; PSM = partitioned survival model; QALY = quality adjusted life year

[a] The health outcomes and costs in the DR ET-resistant PSM were undiscounted (Cells H16:I669, 'ET-Resistant PSM' spreadsheet in the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook). This was corrected during the evaluation.

*The redacted values correspond to the following ranges:*

[1] *$35,000 to < $45,000*

[2] *$25,000 to < $35,000*

6.49 The disaggregated results of the economic evaluation in terms of costs and health outcomes are summarised in Table 13.

**Table 13: Disaggregated summary of cost impacts and health outcomes (discounted)**

| | Ribociclib + ET | ET alone | Incremental | % incremental |
|---|---|---|---|---|
| **Costs** | | | | |
| Drug acquisition | $[redacted] | $12,003 | $[redacted] | [redacted]% |
| Adjuvant therapy in iDF | $[redacted] | $5,550 | $[redacted] | [redacted]% |
| NMR | $[redacted] | $16 | $[redacted] | [redacted]% |
| DR | $[redacted] | $6,438 | -$[redacted] | -[redacted]% |
| Disease management and monitoring | $4,830 | $6,407 | -$1,576 | -9.1% |
| iDF | $767 | $726 | $41 | 0.2% |
| NMR | $352 | $337 | $15 | 0.1% |
| Remission | $98 | $95 | $4 | 0.0% |
| DR | $3,608 | $5,244 | -$1,635 | -9.4% |
| SPM transition | $5 | $6 | -$1 | 0.0% |
| AEs | $2,832 | $189 | $2,643 | 15.2% |
| Terminal care | $5,524 | $6,255 | -$731 | -4.2% |
| From iDF, NMR and remission | $2,408 | $2,113 | $295 | 1.7% |
| Within DR PSMs | $3,116 | $4,143 | -$1,026 | -5.9% |
| **Total costs** | **$[redacted]** | **$24,854** | **$[redacted]** | **100.0%** |
| **LYs** | | | | |
| iDF | 12.73 | 11.84 | 0.89 | 150.4% |
| NMR | 0.06 | 0.06 | 0.00 | 0.4% |
| Remission | 0.33 | 0.32 | 0.01 | 1.9% |
| DR ET-resistant | 0.20 | 0.41 | -0.20 | -34.5% |
| DR ET-sensitive | 0.48 | 0.59 | -0.11 | -18.3% |
| **Total LYs** | **13.80** | **13.21** | **0.59** | **100.0%** |
| **QALYs** | | | | |
| iDF | 10.99 | 10.24 | 0.75 | 144.7% |
| NMR | 0.05 | 0.05 | 0.00 | 0.4% |
| Remission | 0.28 | 0.27 | 0.01 | 1.8% |
| DR ET-resistant | 0.16 | 0.32 | -0.16 | -30.4% |
| DR ET-sensitive | 0.36 | 0.45 | -0.09 | -16.5% |
| **Total QALYs** | **11.85** | **11.33** | **0.52** | **100%** |

Source: Table compiled during the evaluation, based on Table 3.23 and Table 3.24, p142 of the submission, and the 'Results' spreadsheet in the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook

AEs = adverse events; DR = distant recurrence; ET = endocrine therapy; iDF = invasive disease-free; LYs = life years; NMR = non-metastatic recurrence; PSM = partitioned survival model; QALYs = quality-adjusted life years; SPM = second primary malignancy

Note: Costs and health outcomes were revised during the evaluation to correct the fixed outcome and cost payoffs from the DR ET-resistant PSM, using the discounted payoffs instead of undiscounted payoffs.

6.50 The incremental costs were driven by the drug acquisition cost of adjuvant ribociclib followed by costs for treatment of AEs associated with adjuvant therapy, with cost offsets mainly due to a reduction in the treatment of DR. The life years (LYs) and QALYs gained were predominantly accrued in the iDF health state, with a reduction in health outcomes gained in the DR health state. Table 14 summarises the recurrence rates and LY gained at 4 years (data truncation time point) and at the end of 30-year time horizon. The proportion of patients experiencing a DR event as modelled in the economic evaluation was 29.1% for ribociclib + ET versus 34.8% for ET at 30 years, equal to 5.7 DR events avoided per 100 patients treated with adjuvant ribociclib in addition to ET. This compared with 3.1 DR events avoided per 100 patients at Year 4.

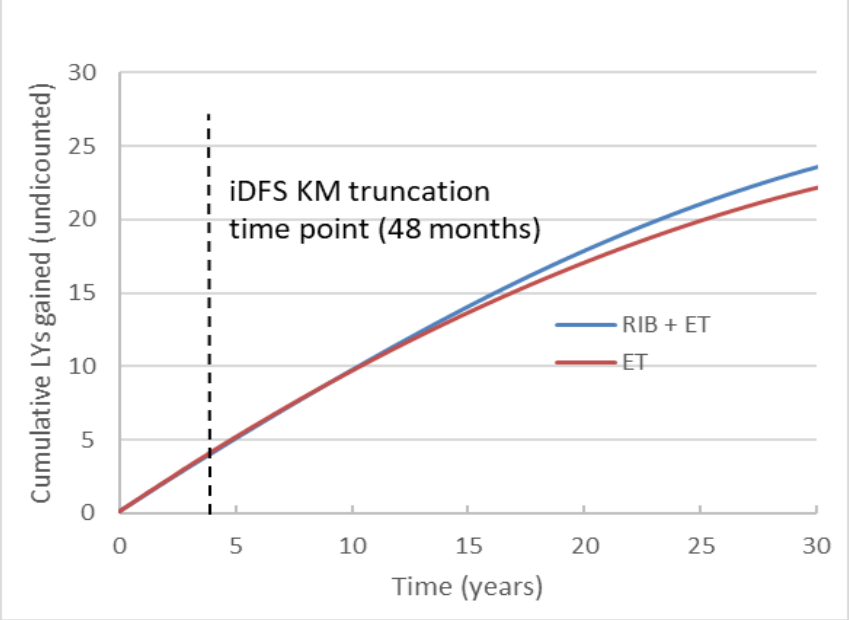
**Table 14: Recurrence events and LYs gained (undiscounted)**

| | Ribociclib + ET | ET | Difference |
|---|---|---|---|
| **At 4 years** | | | |
| Distant recurrence | 2.5% | 5.7% | -3.1% |
| Non-metastatic recurrence | 1.7% | 1.9% | -0.2% |
| LYs | 4.07 | 4.17 | -0.10 |
| **At 30 years** | | | |
| Distant recurrence | 29.1% | 34.8% | -5.7% |
| Non-metastatic recurrence | 10.3% | 9.6% | 0.7% |
| LYs | 23.59 | 22.15 | 1.44 |

Source: Calculated during the evaluation, based on the 'Comp1.Calc' and 'Comp2.Calc' spreadsheets in the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook
ET = endocrine therapy; LYs = life years

6.51 The accumulation of undiscounted LYs gained over the model time horizon is depicted in Figure 5. For both treatment arms, the majority of the LYs gained were accrued in the extrapolated period. The accumulative LYs gained were slightly lower in patients receiving ribociclib + ET than those treated with ET alone in the first 8.5 years. This was primarily due to the greater proportion of patients treated with ribociclib + ET for whom the first iDFS event was death (14.5%) compared with that observed for those treated with ET alone (2.6%) in NATALEE. After 8.5 years, the additional use of adjuvant ribociclib generated survival benefits, resulting in a survival gain of 1.4 years (undiscounted) in a 30-year time horizon.

**Figure 5: Cumulative LYs gained over the time horizon of the model (undiscounted)**




Source: Constructed during the evaluation, using the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook
ET = endocrine therapy; iDFS = invasive disease-free survival; KM = Kaplan-Meier; LYs = life years; RIB = ribociclib.
*Note that the results presented in Figure 5 are derived from ad-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.*

6.52 Results of key univariate and multivariate sensitivity analyses, based on the revised base case, are summarised in Table 15.

**Table 15: Key sensitivity analyses**

| Analyses | Incremental cost | Incremental QALY | ICER | % change |
|---|---|---|---|---|
| **Base case** | **$[redacted]** | **0.52** | **$[redacted][1] (revised)** | **–** |
| **Time horizon (base case 30 years)** | | | | |
| 20 years[a] | $[redacted] | 0.37 | $[redacted][2] | [redacted]% |
| **Discount rate (base case: 5%)** | | | | |
| 0% | $[redacted] | 1.15 | $[redacted][3] | [redacted]% |
| 3.5% | $[redacted] | 0.65 | $[redacted][1] | [redacted]% |
| **Model starting age (base case: 53.5 years)** | | | | |
| 55 years | $[redacted] | 0.50 | $[redacted][1] | [redacted]% |
| 60 years[a] | $[redacted] | 0.46 | $[redacted][4] | [redacted]% |
| 61.4 years **#2** | $[redacted] | 0.45 | $[redacted][4] | [redacted]% |
| **iDFS data truncation point (base case: 48 weeks in both treatment arms)** | | | | |
| 54 weeks in both treatment arms[a] | $[redacted] | 0.55 | $[redacted][1] | [redacted]% |
| **iDFS parametric distribution (base case: restricted exponential for both arms)** | | | | |
| Restricted Weibull for both arms[b] | $[redacted] | 0.56 | $[redacted][1] | [redacted]% |
| Restricted gamma for both arms[a,b] | $[redacted] | 0.55 | $[redacted][1] | [redacted]% |
| Restricted gamma for RIB + ET, with parametric function for ET unchanged from base case[a,b] | $[redacted] | 0.39 | $[redacted][2] | [redacted]% |
| Restricted Weibull for RIB + ET, with parametric function for ET unchanged from base case[a,b] **#4** | $[redacted] | 0.37 | $[redacted][2] | [redacted]% |
| **Distribution of iDFS events (based case: RIB + ET: 27.3% NMR, 14.5% death, 38.2% NMR, 20.0% SPM; ET alone: 19.2% NMR, 2.6% death, 56.4% NMR, 21.8%)** | | | | |
| Identical distribution of iDFS events between the two treatment arms[c] **#5** | $[redacted] | 0.36 | $[redacted][2] | [redacted]% |
| **Treatment effect waning (base case: from Year 8 to Year 16)** | | | | |
| From Year 5 to Year 8 (previously accepted by the PBAC for abemaciclib) [a] **#1** | $[redacted] | 0.34 | $[redacted][2] | [redacted]% |
| From Year 4 to Year 7[a] | $[redacted] | 0.29 | $[redacted][5] | [redacted]% |
| **Health state utilities (base case: 0.870 for iDF on-treatment and for remission, 0.841 for iDFS off-treatment, 0.822 for NMR, 0.787 for PFS in the DR ET-resistant and ET-sensitive PSMs, 0.751 for PPS in the DR ET-resistant and ET-sensitive PSMs, mainly based on QoL data from NATALEE)** | | | | |
| Assumed based on the abemaciclib model[a,d] **#3** | $[redacted] | 0.50 | $[redacted][1] | [redacted]% |
| **Multivariate analyses** | | | | |
| #1 AND #2 | $[redacted] | 0.31 | $[redacted][5] | [redacted]% |
| #1 AND #2 AND #3 | $[redacted] | 0.30 | $[redacted][5] | [redacted]% |
| **ESC advised sensitivity analysis: #1 AND #2 AND #3 AND #4** | **$[redacted]** | **0.26** | **$[redacted][5]** | **[redacted]%** |
| #1 AND #2 AND #3 AND #5 | $[redacted] | 0.18 | $[redacted][6] | [redacted]% |

Source: Adapted from Table 3-25, pp144-145 of the submission, and the "Kisqali (ribociclib) - eBC N0N1 - CEA" Excel workbook

DR = distant recurrence; ET = endocrine therapy; ICER = incremental cost-effectiveness ratio; iDF = invasive disease-free; iDFS = invasive disease-free survival; NMR = non-metastatic recurrence; PFS = progression-free survival; PPS = post-progression survival; PSM = partitioned survival model; QALY = quality adjusted life year; QoL = quality of life; RIB = ribociclib

Note: Analyses were performed during the evaluation based on the corrected base case where the fixed outcome and cost payoffs from the DR ET-resistant PSM have been corrected, using the discounted payoffs instead of undiscounted payoffs.

[a] Additional sensitivity analyses performed during the evaluation.

[b] The Weibull and gamma functions provided the most conservative long-term projections of the four best fitting distributions according to goodness of fit statistics.

[c] For both arms: 23.3% NMR, 8.6% death, 47.3% DR, 20.9% SPM

[d] 0.785 for iDF, 0.779 for NMR, 0.748 for PFS in the DR ET-resistant and ET-sensitive PSMs, 0.476 for PPS in the DR ET-resistant and ET-sensitive PSMs.

*The redacted values correspond to the following ranges:*

[1] *$25,000 to < $35,000*
[2] *$45,000 to < $55,000*
[3] *$5000 to < $15,000*
[4] *$35,000 to < $45,000*
[5] *$55,000 to < $75,000*
[6] *$95,000 to < $115,000*

6.53 Results from sensitivity analyses showed that the treatment effect waning had the biggest impact on the ICER, followed by age of the patients on model entry, time horizon, iDFS extrapolation function, distribution of iDFS events, and discount rate. When the inputs of the treatment effect waning assumption and the age of the modelled patients were revised for consistency with previous PBAC consideration on the abemaciclib for eBC economic evaluation, and the health state utilities from the abemaciclib model were applied, the ICER increased from $35,000 to < $45,000/QALY gained (revised base case) to $55,000 to < $75,000 /QALY. Applying conservative assumptions in terms of iDFS extrapolation and iDFS distribution increased the ICER further, possibly above $100,000/QALY.

6.54 When the abemaciclib for eBC submissions were considered, the PBAC considered that an ICER of up to $30,000/QALY gained would account for the uncertainty regarding the modelled OS in the context of more conservative treatment waning (5−8 years) and an older age at model entry (61.4 years) (paras. 7.10−7.11, abemaciclib PSD, November 2023 PBAC meeting; para. 7.13, abemaciclib PSD, March 2023 PBAC meeting).

6.55 The ESC noted the modelled incremental QALYs gained (0.52) were higher than accepted by the PBAC for the currently listed PBS population (between 0.266 and 0.407, exact estimate not provided in PSD) (Table 13, abemaciclib PSD, November 2023). Given the proposed population has a lower risk of recurrence, the ESC noted the QALYs gained should be smaller than previously accepted.

6.56 The ESC considered a respecified base case was required to address primary issues related to the economic model. The ESC advised revision to the following inputs:

- the starting age of the model population should be increased to 61.4 years (para. 6.35);
- a more conservative parametric function should be applied to the extrapolation of ribociclib + ET iDFS. The ESC advised the restriction Weibull function for ribociclib + ET and considered that the extrapolation for ET should remain unchanged from the original base case (paras. 6.37−6.38);
- in consideration of the available trial data for ribociclib, a more conservative treatment waning, from year 5 to 8, should be included in the model (para. 6.39); and
- the use of alternate health state utilities. The ESC advised that the utilities applied to the previous abemaciclib eBC model would likely be appropriate (para. 6.45).

The ESC noted that these revisions resulted in 0.26 incremental QALYs and an ICER of $55,000 to < $75,000/QALY (Table 15).

## *Drug cost/patient/course*

6.57 The per patient cost of ribociclib based on use in the clinical evidence, the economic model and the financial estimates are presented in Table 16. While the average dose applied was similar across the economic and financial analyses, the cost applied varied. The economic evaluation estimated the cost for ribociclib, based on a planned dose intensity of 400 mg per day, applying a relative dose intensity (RDI) of 83.4%[16] as reported in the NATALEE clinical study report (CSR). In the financial analysis, the submission used a compliance of 96.5%, which differed to the RDI reported in the NATALEE trial (83.4%). As the cost impact for use of both the 400 mg and 200 mg daily strengths was presented, compliance was estimated from the mean dose intensity reported in the trial (333.58 mg per day)[16] as a proportion of a planned dose intensity per day derived in the submission to account for dose reductions (345.61 mg per day)[17]. This therefore assumed that dose reductions that were observed in the trial occurred from treatment initiation, which may not be reasonable. Further, the trial estimates of dose reductions applied included those due to dosing and dispensing errors and technical problems (approx. 4 of 27 percentage points). The permanence of such dose reductions and whether these would be observed in practice was not certain.

**Table 16: Drug cost per patient for ribociclib**

| | Ribociclib<br>Trial dose and duration | Ribociclib<br>Economic model | Ribociclib<br>Financial estimates |
|---|---|---|---|
| Mean dose | 334 mg | 334 mg per day | 334 mg per day |
| Mean duration (28-day cycles) | 28.9 cycles [a] | 28.9 cycles [a] | 28.6 scripts [b] |
| Cost/patient/cycle | $ [redacted] [c] | $ [redacted] [c] | $ [redacted] [d] |
| Cost/patient/course | $ [redacted] | $ [redacted] | $ [redacted] |

Source: Constructed during the evaluation from the "Kisqali (ribociclib) - eBC N0N1 - CEA" and 'Kisqali (ribociclib) - eBC N0N1 – UCM.xlsx' workbooks included in the submission.

[a] At the April 2024 data cutoff in the NATALEE trial, all patients in the ribociclib + ET arm either completed or discontinued ribociclib adjuvant therapy. The treatment duration for ribociclib was estimated based on the time to treatment discontinuation curve from the trial and was half-cycle adjusted.

[b] Based on 118.19 weeks of treatment, equivalent to 2.27 years on treatment, assuming 12.59 scripts per year (13.04 28-day cycles per year, assuming 96.52% compliance).

[c] The average cost per 28-day cycle was estimated by applying trial reported relative dose intensity (83.4%) to the cost per pack of 42 × 200 mg ribociclib ($[redacted])

[d] The average cost per script was estimated assuming 27.2% of scripts were for the lower pack size i.e. 27.2% × $[redacted] + 72.8% × $[redacted]

6.58 Use of ET was assumed to vary with or without ribociclib use. In the economic evaluation, the drug cost for ET was estimated to the $[redacted] in the ribociclib + ET arm and $[redacted] in the ET alone arm. This was based on the trial TTD curve for ET after half-cycle adjustment (215.3 weeks in the ribociclib + ET arm and 210.9 weeks in the ET alone arm), the distribution of ET agents, and the RDI of ET agents, with and without

[16] 83.4% = 333.58 mg / 400 mg, where 400 mg was the planned dose intensity, and 333.58 mg was the mean dose intensity (defined as actual cumulative dose / duration of exposure).

[17] 72.8% × 400 mg + 27.2% × 200 mg

ribociclib use. The average cost per course for ET as estimated in the financial analysis was slightly higher than that in the economic evaluation, being $[redacted] in the ribociclib + ET arm and $[redacted] in the ET alone arm. This was primary due to the removal of the half-cycle correction in the financial estimates. Due to the benefit of ribociclib in extending iDFS observed in the trial, the evaluation considered that a longer duration of ET appeared reasonable, however it was not clear whether the differences observed in the trial with respect to distribution of agent or compliance would be realised.

## *Estimated PBS usage & financial implications*

6.59 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the number of incident patients each year who would be eligible for the proposed ribociclib treatment. A summary of the data sources and parameter values used to estimate the utilisation and financial implications associated with the proposed listing of ribociclib for the adjuvant treatment of eBC is presented in Table 17.

**Table 17: Key inputs for financial estimates**

| Parameter | Value applied and source | Comment from the evaluation |
|---|---|---|
| Breast cancer incidence (in women), 2016 and 2020 | 2016: 17,354 (reported)<br>2020: 19,807 (projected)<br>(BreastScreen Australia monitoring report 2020)[18] | A more recent AIHW[19] report published breast cancer incidence projections to 2024 which may be more reliable, as it is based on latest population estimates and incidence of breast cancer. |
| Annual breast cancer incidence growth rate | 3.36%, calculated from reported and projected incidence 2016–2020 (BreastScreen Australia monitoring report 2020)[18] | This estimate has been presented in previous submissions to the PBAC (Table 16, ribociclib PSD, November 2024 PBAC meeting; Table 15, abemaciclib PSD, November 2023 PBAC meeting). However, growth in annual incidence based on more recent AIHW data[19] may be more appropriate. |
| Proportion of patients with Stage I–III disease | 95.0% (National Cancer Control Indicators 2018)[20] | This was similar to 95.3% applied previously for abemaciclib (Table 15, abemaciclib PSD, November 2023 PBAC meeting). |
| Proportion of patients who are HR+/HER2- | 72.9% (Schaffler 2023)[21] | This was slightly higher than 70.0% applied previously for abemaciclib (Table 15, abemaciclib PSD, November 2023 PBAC meeting), though may be reasonable. |

[18] Australian Institute of Health and Welfare. BreastScreen Australia monitoring report 2020 Canberra: AIHW; 2020; Available from: https://www.aihw.gov.au/reports/cancer-screening/breastscreen-australia-monitoring-report-2020/summary.

[19] Australian Institute of Health and Welfare. Cancer Data in Australia. Book 1a – Cancer incidence (age-standardised rates and 5-year age groups). Canberra: AIHW; 2024 [cited 2025 March]; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/.

[20] National Cancer Control Indicators. Distribution of cancer stage. Cancer Australia; 2018 [cited 2025 Apr]; Available from: https://ncci.canceraustralia.gov.au/diagnosis/distribution-cancer-stage/distribution-cancer-stage.

[21] Schaffler H, Mergel F, Pfister K, Lukac S, Fink A, Veselinovic K, et al. The Clinical Relevance of the NATALEE Study: Application of the NATALEE Criteria to a Real-World Cohort from Two Large German Breast Cancer Centers. *Int J Mol Sci*. 2023 Nov 15;24(22).

| Parameter | Value applied and source | Comment from the evaluation |
|---|---|---|
| Proportion of patients who meet the high risk criteria | 26.5% (Schaffler 2023[21]; and Toi 2023[22]) | A lower estimate (23.9%) was derived from an alternate Australian study[8] identified in the submission. This estimate was not used in the submission due to the exclusion of Ki67 and genomic assay criteria. However, given the limitation on tests subsidised (and used) through the MBS, this justification may not be reasonable. |
| Proportion of patients who do not receive tamoxifen | Increasing from 85.6% in Year 1 to 90.6% in Year 6 based on linear forecast of 10% PBS sample data analysis. | Projections of current PBS data may overestimate the tamoxifen market share if ribociclib listing affects tamoxifen use due to patients opting for hormone therapies which may be used with ribociclib. |
| Grandfathered patients | None. | This was not reasonable given the current access program and proposed listing for grandfathered patients. |
| Uptake rate | Increasing from [redacted]% in Year 1 to [redacted]% in Year 5 (Assumption). | This was overestimated given that the PBAC previously considered the maximum uptake rate of [redacted]% applied in a higher-risk population to be an overestimate, given that 20% of patients eligible for an CDK4/6i in this setting decline use (para. 6.64 ribociclib PSD, November 2024 PBAC meeting). |
| Duration of (adjuvant) ribociclib treatment | 118.19 weeks (equivalent to 2.27 years), based on the complete time-to-treatment discontinuation curve from the PBS-subgroup of the NATALEE trial. | Given that patients in practice are likely to be older than the trial, a reduced duration of treatment may be expected. Due to similar concerns, the PBAC previously considered that abemaciclib use would be less than reported in the trial and that a mean treatment duration of 18 months was more reasonable (para. 7.13, abemaciclib PSD, November 2023 PBAC meeting). |
| Compliance<br>No. (adjuvant) ribociclib scripts per year | 12.59, based on 13.04 28-day cycles per year, assuming 96.52% compliance, where compliance was based on the mean dose intensity (334 mg, NATALEE) as a proportion of planned dose intensity (346 mg), adjusted in the submission for dose reductions.[a] | The RDI reported in the NATALEE trial was 83.4%, however was derived assuming planned dose intensity of 400 mg per day. This was more consistent with previous PBAC advice which suggested compliance be less than reported for hormonal therapy (84%) (para. 7.14, abemaciclib PSD, March 2023 PBAC meeting). |
| Reduction in metastatic breast cancer incidence | 19 cases in Year 1, increasing to 177 cases (revised: 164) in Year 6 based on extrapolations of iDFS from the NATALEE trial, assuming 38.2% and 56.4% of events, respectively following ribociclib + ET and ET alone, were metastatic breast cancer events. | Given the low number of iDF events in the NATALEE trial, differences in incidence of mBC across treatment arms are uncertain. |

[22] Toi M, Boyle F, Im YH, Reinisch M, Molthrop D, Jiang Z, et al. Adjuvant Abemaciclib Combined with Endocrine Therapy: Efficacy Results in monarchE Cohort 1. *Oncologist*. 2023 Jan 18;28(1):e77-e81.

| Parameter | Value applied and source | Comment from the evaluation |
|---|---|---|
| Duration of metastatic breast cancer treatment | CDK4/6i + fulvestrant: 104.7 weeks<br>Fulvestrant (monotherapy): 63.9 weeks<br>Everolimus + exemestane: 105.5 weeks<br>Exemestane (monotherapy), tamoxifen or capecitabine: 47.7 weeks<br>Based on hazard ratios applied to data for patients with ET-sensitive metastatic breast cancer | For CDK4/6i, the hazard ratio applied was 1, which was not likely to be reasonable as patients who experience distant recurrence within the projected period have ET-resistant disease and would likely have a shorter duration of treatment than those who are ET-sensitive . |
| Ribociclib (adjuvant) | 42-pack: $[redacted]<br>21-pack: $[redacted] | |
| Affected MBS items | | |
| ECG | $206.96[b] (MBS item 55129)<br><br>Ribociclib (adjuvant or metastatic): 2 services in the first year of treatment | The cited item is for a transthoracic ECHO, rather than ECG, and so may not be appliable. MBS item 11704 (schedule fee: $35.60) may be more appropriate and was used in previous analyses presented to the PBAC (para. 6.40, abemaciclib PSD, March 2019 PBAC meeting). Use per patient may be underestimated as some patients with prolonged QT may require additional ECGs (Table 16, ribociclib PSD November 2024 PBAC meeting). |
| FBC | $13.56 [b] (MBS item 65070)<br><br>Ribociclib (adjuvant or metastatic) or palbociclib: 6, 4 and 3 services respectively in the first, second and third years of treatment.<br><br>Abemaciclib: 7 services in the first year of treatment | Reasonable. |
| Electrolytes | $12.52[b] (MBS item 66509)<br><br>Ribociclib (adjuvant or metastatic): 3 services in the first year of treatment | Reasonable. |
| LFT | $14.16[b] (MBS item 66512)<br><br>Ribociclib (adjuvant or metastatic): 6, 4 and 3 services respectively in the first, second and third years of treatment. | Reasonable. |
| ALT and AST | $9.32[b] (MBS item 66503)<br><br>Abemaciclib: 7 services in the first year of treatment | Reasonable. |

Source: Adapted from Table 4.1, pp149–151 of the submission.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; CDK4/6i = cyclin-dependent kinases 4 and 6 inhibitor; ECG = electrocardiogram; ECHO = echocardiogram; ET = endocrine therapy; FBC = full blood count; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; iDF = invasive disease-free; iDFS = invasive disease-free survival; LFT = liver function test; PSD = public summary document; RDI = relative dose intensity
[a] 72.8% × 400 mg + 27.2% × 200 mg
[b] Assuming an 80% level of rebate

6.60 The estimated use and financial implications associated with the listing of ribociclib is presented in Table 18.

**Table 18: Estimated use and financial implications**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| Breast cancer incidence (3.36% growth) | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| No. patients with Stage I–III disease (95.0%) | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][1] |
| No. patients who are HR+ / HER2- (72.9%) | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] | [redacted][2] |
| No. patients who meet proposed high-risk criteria (26.5%) | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][4] |
| Proportion who do not receive tamoxifen | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% |
| No. patients who do not receive tamoxifen | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| Proportion who uptake treatment | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% | [redacted]% |
| No. patients who initiate treatment each year | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] | [redacted][3] |
| No. patient-years on treatment [a] | [redacted][3] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] | [redacted][4] |
| No. scripts (12.59 per patient-year on treatment) [b] | [redacted][5] | [redacted][6] | [redacted][7] | [redacted][8] | [redacted][9] | [redacted][10] |
| • 42-tablet pack (72.8%) | | | | | | |
| ○ No. RPBS scripts | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] |
| ○ No. PBS scripts | [redacted][1] | [redacted][12] | [redacted][13] | [redacted][13] | [redacted][6] | [redacted][6] |
| • 21-tablet pack (27.2%) | | | | | | |
| ○ No. RPBS scripts | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] | [redacted][11] |
| ○ No. PBS scripts | [redacted][2] | [redacted][1] | [redacted][1] | [redacted][1] | [redacted][5] | [redacted][5] |
| Cost of ribociclib (42-pack) ($[redacted] per script) | $[redacted][14] | $[redacted][15] | $[redacted][16] | $[redacted][17] | $[redacted][17] | $[redacted][18] |
| Cost of ribociclib (21-pack) ($[redacted] per script) | $[redacted][19] | $[redacted][20] | $[redacted][20] | $[redacted][20] | $[redacted][20] | $[redacted][20] |
| **Cost to the PBS/RPBS, less copayments** | **$**[redacted][21] | **$**[redacted][16] | **$**[redacted][17] | **$**[redacted][18] | **$**[redacted][18] | **$**[redacted][22] |
| Cost to the PBS/RPBS for increase in adjuvant ET due to ribociclib listing | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] |
| Cost to the PBS for treatment of mBC | –$[redacted][19] | –$[redacted][19] | –$[redacted][19] | –$[redacted][19] | –$[redacted][19] | –$[redacted][19] |
| **Net cost to the PBS/RPBS** | **$**[redacted][21] | **$**[redacted][16] | **$**[redacted][17] | **$**[redacted][18] | **$**[redacted][18] | **$**[redacted][22] |
| Net cost to the MBS | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] | $[redacted][19] |
| Net cost to Government health budgets | $[redacted][21] | $[redacted][16] | $[redacted][17] | $[redacted][18] | $[redacted][18] | $[redacted][22] |

Source: Constructed during the evaluation from the '3a. Scripts - proposed' and '3c. Impact - proposed (eff)' worksheets in the 'Kisqali (ribociclib) - eBC N0N1 – UCM.xlsx' workbook included in the submission.

ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; mBC = metastatic breast cancer.

Note: Estimates were revised during the evaluation to correctly multiply the number of patients who initiate ribociclib treatment in Year 6 by the incidence of mBC in the first (rather than sixth) year following treatment initiation.

[a] Based on an average duration of treatment of 118.19 weeks, implemented as 100% patient-years on treatment in first and second years following initiation, with 27.3% of a year on treatment in the third year. This is equivalent to 28.6 scripts per patient who initiates treatment.

[b] 13.04 scripts per year on treatment (365.25/28), assuming 96.52% compliance

*The redacted values correspond to the following ranges:*

*[1] 20,000 to < 30,000*

*[2] 10,000 to < 20,000*

[3] *500 to < 5,000*
[4] *5,000 to < 10,000*
[5] *30,000 to < 40,000*
[6] *80,000 to < 90,000*
[7] *90,000 to < 100,000*
[8] *100,000 to < 110,000*
[9] *110,000 to < 120,000*
[10] *120,000 to < 130,000*
[11] *< 500*
[12] *50,000 to < 60,000*
[13] *70,000 to < 80,000*
[14] *$20 million to < $30 million*
[15] *$50 million to < $60 million*
[16] *$60 million to < $70 million*
[17] *$70 million to < $80 million*
[18] *$80 million to < $90 million*
[19] *$0 to < $10 million*
[20] *$10 million to < $20 million*
[21] *$30 million to < $40 million*
[22] *$90 million to < $100 million*

6.61 The total cost to the PBS/RPBS of listing ribociclib was estimated to be $30 million to < $40 million in first year of listing, increasing each year to $90 million to < $100 million in Year 6, totalling $400 million to < $500 million during the first 6 years of listing.

6.62 Breast cancer incidence was estimated over the projected period by applying an annual incidence growth rate (3.36%, based on breast cancer incidence projections between 2016–2020) (AIHW, 2020)[18] to the number of new cases of breast cancer diagnosed in women in Australia in 2016 (AIHW, 2020)[18]. While this was consistent with previous submissions presented to the PBAC (Table 16, ribociclib PSD, November 2024 PBAC meeting; Table 15, abemaciclib PSD, November 2023 PBAC meeting), recent data published by the AIHW (2024)[19] reported actual and projected estimates of breast cancer incidence to 2024, suggesting that incidence in the submission may have been overestimated (Table 19). Using projections of AIHW (2024)[19] data resulted in an annual 9–14% decrease in the estimated financial impact to the PBS/RPBS (Table 20). The PSCR acknowledged that more recent projections have been published. However, the PSCR argued that the incidence projections should be estimated using the same data source and methods as was used previously for abemaciclib and ribociclib. The ESC considered it would be preferable to estimate incidence using the most recent projections.

**Table 19: Breast cancer incidence estimated in the submission relative to those reported by the AIHW[19]**

| | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|---|---|---|
| Breast cancer incidence (assuming 3.36% annual growth) | 17,354 | 17,937 | 18,540 | 19,163 | 19,807 | 20,472 | 21,160 | 21,871 | 22,606 |
| AIHW breast cancer incidence counts [a] | 17,409 | 17,715 | 18,209 | 18,497 | 17,984 | 19,637 | 20,016 | 20,461 | 20,973 |

Source: Constructed during the evaluation.
[a] The AIHW report actual cancer incidence counts until 2020, with projections reported for 2021–2024.

6.63 Other key areas of uncertainty identified during the evaluation included the proportion of patients who meet the proposed eligibility criteria[23], rate of uptake of ribociclib, and ribociclib compliance. The submission assumed that 26.5% of patients would meet the proposed eligibility criteria, based on a retrospective analysis of German patients who meet the criteria for the NATALEE (ribociclib) trial, after excluding patients who would also have met the criteria for PBS-funded abemaciclib (Schaffler et al. 2023)[21]. While this approach was reasonable, a larger study was identified using a retrospective analysis of Australian patients (Kanjanapan et al. 2025)[8]. The submission stated that this reference was not used in the analysis due to incomplete reporting of Ki67 or genomic assays. Given concerns raised regarding the use of Ki67 as part of PBS restriction criteria (para. 3.5, abemaciclib PSD, March 2022 PBAC meeting), and as limited genomic assays are subsidised (and used) through the MBS (74 services of EndoPredict claimed in the 12-month period March 2024–February 2025), the proportions reported in Kanjanapan et al. (2025)[8] may be more representative of the Australian setting. This study reported that 41.3% (1,587/3,840) of HR+, HER2- patients would meet the eligibility criteria for NATALEE and 17.5% (671/3,840) would be eligible for monarchE, resulting in 23.9% ([1,587 – 671]/3,840) of HR+, HER2– patients who meet the proposed PBS criteria for ribociclib. The ESC considered 23.9% was likely to be a more reasonable estimate and noted that applying this estimate resulted in an annual 10% decrease in the estimated financial impact to the PBS/RPBS (Table 20).

6.64 The Pre-PBAC Response argued that since the proposed PBS population corresponds to the difference between the monarchE cohort 1 and NATALEE ITT populations, it remains appropriate to align the incidence projections and eligibility using this same data source and methods.

6.65 Uptake was assumed to increase from [redacted]% in Year 1 to [redacted]% in Year 5. The evaluation considered that this was likely an overestimate, given that the PBAC previously considered that of patients eligible, 20% would decline use of CDK4/6 inhibitors in the high-risk eBC setting due to risk of toxicities, age, frailty and the current restriction that permits one course of CDK4/6 inhibitors per lifetime (para. 6.64, ribociclib PSD, November 2024 PBAC meeting). The PSCR maintained that uptake would be high and closer to [redacted]%. The ESC agreed with the evaluation that uptake was likely overestimated by the submission and considered a maximum uptake rate of [redacted]% would be more appropriate. The ESC noted that the estimated financial impact to the PBS/RPBS decreased by 6–16% each year when an [redacted]% uptake was applied (Table 20). The Pre-PBAC Response argued that given the rapid uptake of abemaciclib for eBC, a very high uptake is anticipated.

[23] HR positive, HER2 negative Stage II–III disease with 1–3 positive lymph nodes and histological grade ≤2 and tumour size < 5 cm; HR positive, HER2 negative Stage IIB or III disease with no positive lymph nodes; or HR positive, HER2 negative Stage IIA disease with no positive lymph nodes, with either (a) grade 3 histology, or (b) grade 2 histology with a positive molecular diagnostic outcome.

6.66 Compliance to ribociclib was estimated to be 96.5%, based on the mean dose intensity observed in the trial (334 mg) as a proportion of planned dose intensity, adjusted in the submission for dose reductions (346 mg)[24]. The PSCR maintained this calculation was an accurate reflection of compliance. However, the ESC considered that while the dose assumed in the financial estimates was consistent with the trial, a compliance rate less than for hormonal therapy (84%) would be more consistent with what would be expected in practice (paras. 6.65 and 7.10, ribociclib PSD, November 2024 PBAC meeting) (annual 14% decrease in the estimated financial impact to the PBS/RPBS, Table 20). The Pre-PBAC Response argued the compliance rate in the abemaciclib submission was based on an analysis of US patients and given the differences in health systems, argued compliance would likely be higher in the Australian setting.

6.67 The submission expected that the proposed listing of ribociclib would lead to an increase in the use and cost of adjuvant ET (due to a longer duration of treatment and changes in the distribution and compliance to ET) and a net reduction in the use and cost of treatments for metastatic breast cancer (due to reduced incidence derived from extrapolations of iDFS from the PBS-subgroup of NATALEE, assuming 38.2% and 56.4% of events, respectively following ribociclib + ET and ET alone, were metastatic breast cancer events). Due to the benefit of ribociclib in extending iDFS observed in the NATALEE trial, a longer duration of ET may be reasonable, however whether the differences observed in the trial with respect to distribution of agent or compliance were significant was not reported (and so differences applied may not be realised). The evaluation considered that given the low number of iDF events in the NATALEE trial, differences in incidence of metastatic breast cancer across treatment arms are uncertain, and it was not clear if these represent an avoidance of recurrence or delay over the projected period.

6.68 Use in grandfathered patients was not considered. The evaluation considered that this was not reasonable given that the submission noted that there are patients who currently receive ribociclib through the sponsor's funded access program and given that the submission has proposed a listing for grandfathered patients. The PSCR stated that grandfathered patients were included in the incident population. Thus, separately including this cohort would result in double counting. The ESC considered that grandfathered patients who accessed ribociclib prior to year 1 of the utilisation estimates would not be included in the incident population. The ESC considered grandfathered patients should be included as a separate subgroup to account for (i.e. remove from the estimates) the treatment received prior to PBS listing. The Pre-PBAC Response acknowledged this issue and agreed to work to determine more accurate grandfather patient numbers in the event of a positive recommendation.

6.69 The submission assumed that listing of ribociclib would affect the use of electrocardiograms and blood tests (electrolytes, FBC, LFT and ALT/AST) due to increased monitoring requirements associated with adjuvant ribociclib treatment, with offsets due to reduced CDK4/6 inhibitor use in the metastatic setting. In general,

[24] 72.8% × 400 mg + 27.2% × 200 mg

the evaluation considered that the approach used to estimate the impact to the MBS was reasonable, however the item fee assumed for ECG use (MBS item 55129, fee: $258.70) was for transthoracic ECHO, rather than MBS item 11704 (fee: $35.60). As the cost of ECG was the main driver of the estimated costs to the MBS, the cost to the MBS estimated in the submission has been substantially overestimated. While the PBAC previously considered that some patients with prolonged QT may require additional ECGs, cardiology reviews and oncologist consultations for treatment cessation ± monitoring, the impact was noted to be small given the rarity of the event (Table 16, ribociclib PSD, November 2024 PBAC meeting).

6.70 Multivariate analyses conducted during the evaluation including changes described in paras. 6.61–6.66 resulted in a decrease in the estimated financial impact to the PBS/RPBS by 33–44% each year (Table 20). The ESC considered that overall the submission had likely overestimated the utilisation of ribociclib and considered it was likely more appropriate to amend the proportion eligible to 23.9% (SA 2#), apply the incidence estimates projected from AIHW data (SA 3#), apply an uptake rate of [redacted]% (SA #4), and apply a compliance of 83.4% (SA 5#) (see Table 20).

**Table 20: Sensitivity analyses**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|---|---|---|---|---|---|---|
| **Base case impact to the PBS/RPBS** | **$[redacted]**[1] | **$[redacted]**[2] | **$[redacted]**[3] | **$[redacted]**[4] | **$[redacted]**[4] | **$[redacted]**[5] |
| Proportion eligible for ribociclib (base case: 26.5%) | | | | | | |
| 1. 25.5% | $[redacted][6] | $[redacted][2] | $[redacted][3] | $[redacted][3] | $[redacted][4] | $[redacted][4] |
| 2. 23.9% | $[redacted][6] | $[redacted][7] | $[redacted][2] | $[redacted][3] | $[redacted][3] | $[redacted][4] |
| Breast cancer incidence (base case: 2016 incidence, assuming 3.36% annual growth) | | | | | | |
| 3. Projected from AIHW data | $[redacted][6] | $[redacted][7] | $[redacted][2] | $[redacted][3] | $[redacted][3] | $[redacted][3] |
| Uptake (base case: Increasing from [redacted]% in Year 1 to [redacted]% in Year 5) | | | | | | |
| 4. [redacted]% | $[redacted][6] | $[redacted][7] | $[redacted][2] | $[redacted][3] | $[redacted][3] | $[redacted][3] |
| Ribociclib compliance, (base case: 96.5%) | | | | | | |
| 5. 83.4% | $[redacted][6] | $[redacted][7] | $[redacted][2] | $[redacted][2] | $[redacted][3] | $[redacted][3] |
| **Multivariate analysis** | | | | | | |
| #3 and #4 | $[redacted][6] | $[redacted][7] | $[redacted][2] | $[redacted][2] | $[redacted][2] | $[redacted][2] |
| #3, #4 and #2 | $[redacted][6] | $[redacted][8] | $[redacted][7] | $[redacted][7] | $[redacted][7] | $[redacted][7] |
| **ESC advised sensitivity analysis: #3, #4, #2 and #5** | **$[redacted]**[6] | **$[redacted]**[8] | **$[redacted]**[8] | **$[redacted]**[8] | **$[redacted]**[8] | **$[redacted]**[7] |

Source: Constructed during the evaluation from Table 4.27, p166 of the submission and the 'Kisqali (ribociclib) - eBC N0N1 – UCM.xlsx' workbook.

mBC = metastatic breast cancer.

Note: The base case impact includes the correct multiplication of the number of patients who initiate ribociclib treatment in Year 6 by the incidence of mBC in the first year following treatment initiation.

*The redacted values correspond to the following ranges:*

[1] *$30 million to < $40 million*

[2] *$60 million to < $70 million*

[3] *$70 million to < $80 million*

[4] *$80 million to < $90 million*

[5] *$90 million to < $100 million*

[6] *$20 million to < $30 million*

[7] *$50 million to < $60 million*

[8] *$40 million to < $50 million*

### *Financial Management – Risk Sharing Arrangements*

6.71 The sponsor proposed that should a listing of ribociclib be recommended for the proposed population, a concomitant increase in the risk-sharing caps should also be established.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

7.1 The PBAC did not recommend the listing of ribociclib, as combination therapy with adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), resected early breast cancer (eBC) with stage II or III disease with 1−3 positive axillary lymph nodes (ALNs) meeting specific histological and tumour size criteria, stage IIB or III disease with no positive lymph nodes or Stage IIA disease with no positive lymph nodes meeting specific histological criteria[25] (for brevity referred to below as 'node negative/low' patients). The PBAC noted the risk of recurrence is lower in the proposed population compared with the HR+, HER2- adjuvant population already funded through the PBS (patients with ≥4 positive ALNs, or 1–3 positive ALNs and either grade 3 disease or tumour size ≥ 5 cm; referred to below as 'node positive' patients). The PBAC noted that whilst the reductions in invasive disease-free survival (iDFS) and distant recurrence-free survival (DRFS) were statistically significant, reflecting the overall low rate of recurrence for node negative/low patients, the reductions were small and smaller than observed for the currently listed node positive patients. In the context of the increase in the number of adverse events reported with the addition of ribociclib to ET, and that patients treated in the adjuvant setting forego treatment with a CDK4/6 in the metastatic setting, the PBAC considered the overall benefit associated with adding ribociclib to ET in node negative/low patients had not been demonstrated to be clinically meaningful. The PBAC noted the economic model presented in the submission estimated that the benefit (incremental quality adjusted life years [QALYs]) in node negative/low patients would be greater than that previously accepted for node positive patients and considered this result to be implausible.

7.2 The PBAC considered the primary reason for this outcome was due to the proposed place in therapy.

7.3 The Committee acknowledged the input from health professionals, individuals and consumer organisations, including Rare Cancers Australia, Breast Cancer Network

[25] (a) stage II or III disease with 1–3 positive ALNs with grade ≤ 2 histology and tumour size < 5 cm, or (b) stage IIB or III node-negative disease, or (c) stage IIA node-negative disease with (i) histological grade 3 or (ii) histological grade 2 with a positive molecular diagnostic outcome.

Australia (BCNA), So Brave and Inherited Cancers Australia, expressing their support for the proposed listing for ribociclib. The PBAC noted the input emphasising the risk and fear of disease recurrence for this population and the need for additional therapies. The input outlined the clinical benefit associated with ribociclib, based on the results of the NATALEE trial. The PBAC also noted the input describing the serious side effects associated with current care; however, the PBAC noted treatment with ribociclib was additive to ET, which would further increase the risk of adverse events. In addition, the PBAC noted the Medical Oncology Group Australia's support for the submission.

7.4 With regards to the requested restriction, the PBAC advised that:

- The timeframe between the initiation of adjuvant ET and ribociclib should match the current 6-month requirement for abemaciclib in eBC (para 3.3);
- Given that there is currently no evidence of a clinical benefit from CDK4/6 retreatment in the metastatic setting after use in the adjuvant setting, the lifetime restriction of a single line of CDK4/6 therapy should remain included in the restriction (para 3.4); and
- A definition for a 'positive molecular diagnostic outcome' for the subgroup of patients with grade 2 histology and/or requirement for a molecular diagnostic test would not be required (para 3.5).

7.5 The PBAC considered the nominated comparator of standard of care comprising of adjuvant ET was reasonable.

7.6 The PBAC noted the submission was supported by the randomised open-label NATALEE trial, which it had considered in November 2024 for the listing for node positive patients. The evidence for the current submission for node negative/low patients was from a post-hoc subgroup analysis in 1,794 patients (approximately 35% of the intention-to-treat [ITT] population). The PBAC noted the reductions in iDFS (hazard ratio [HR] 0.665, 95% confidence interval [CI] 0.469, 0.944) and DRFS (HR 0.637, 95% CI 0.421, 0.965) were statistically significant, however the absolute reductions in the number of recurrence events were small and smaller than for the node positive patients. The PBAC noted the Kaplan-Meier (KM) plot for iDFS illustrates the small difference in this outcome for the node negative/low patients (see Figure 1). Over a median follow-up of 49.6 months, an iDFS event was reported in 8.6% of node negative/low patients in the ET alone arm compared with 6.2% of patients in the ribociclib + ET arm (difference of 2.4%). Although not reported in the submission, based on the number of events in the node negative/low and the ITT populations, the corresponding percentages for node positive patients were 12.5% and 15.9% (difference of 3.4%). Similarly, for DRFS, the proportion of node negative/low patients with events was lower and the absolute difference was smaller than for node positive patients (6.3% vs 4.4%, difference 1.9%; 13.3% vs 10.3%, difference 3.0%).

7.7 The PBAC acknowledged it had previously considered that a 3.5% absolute difference in iDFS may be clinically meaningful in the adjuvant eBC setting where the goal is cure (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting). The PBAC noted that the

estimated reduction in iDFS at 4 years with the addition of ribociclib to ET in node negative/low patients was 3.7%. However, the PBAC noted that the clinical data at the 4-year follow-up point was subject to reduced reliability due to a lower number of patients remaining at risk (approximately 50% of the node negative/low subgroup, equivalent to approximately 18% of the total population), the reduction in iDFS at 3 years was lower (1.3%), and the reduction in DRFS at 3 and 4 years was less than 3.5% (1.3% and 2.8%, respectively).

7.8 The PBAC noted the overall survival (OS) data were immature and there was no significant difference between the two arms in the ITT population or the node negative/low population. The PBAC noted the economic model relied on iDFS being a surrogate for OS. The PBAC recalled it had previously considered that iDFS was generally a plausible surrogate for OS in the eBC setting (para. 7.8, abemaciclib PSD, March 2022 PBAC meeting), however considered that the relationship between iDFS and OS was uncertain given the OS data were immature and a statistically significant difference in OS was not observed in the trial.

7.9 The PBAC agreed with the submission's claim that ribociclib added to ET is of inferior comparative safety to ET alone. The PBAC noted treatment with ribociclib was associated with a substantially higher risk of grade 3 or higher treatment-emergent adverse events (TEAEs, relative risk [RR] 3.22, 95% CI 2.78, 3.72), treatment-related serious adverse events (SAEs, RR 8.65, 95% CI 2.63, 28.46) and higher rates of neutropenia. In addition, the Committee noted treatment discontinuation due to adverse events (AEs) was significantly higher in the ribociclib arm of the trial (RR 3.26, 95% CI 2.45, 4.33).

7.10 The PBAC noted the submission claimed superior comparative effectiveness for ribociclib plus ET compared with ET alone. The PBAC noted that whilst the reductions in iDFS and DRFS were statistically significant, they were smaller than observed for the currently listed node positive patients. In the context of the increase in the number adverse events reported, and that patients treated in the adjuvant setting forego treatment with a CDK4/6 in the metastatic setting, the PBAC considered the overall benefit associated with adding ribociclib to ET in node negative/low patients had not been demonstrated to be clinically meaningful.

7.11 The PBAC noted, given the lower risk of recurrence in node negative/low patients, that the magnitude of the incremental QALYs in node negative/low patients would be expected to be less than for node positive patients. However, the economic model presented in the submission estimated 0.52 incremental QALYs gained which was higher than accepted by the PBAC for the node positive patients (between 0.266 and 0.407, exact estimate not provided in PSD) (Table 13, abemaciclib PSD, November 2023). Given this, the PBAC did not consider the results of the economic model, as presented in the submission, to be a reliable estimate of the cost-effectiveness of ribociclib when added to ET for patients with node negative/low disease.

7.12 The PBAC noted the submission estimated that the number of node negative/low patients that would be treated with ribociclib was considerably larger than the node

positive population treated with CDK4/6. However, the PBAC noted the advice from the ESC and agreed the utilisation of ribociclib for the node negative/low population was likely overestimated due to overestimates in breast cancer incidence (para. 6.62), proportion eligible (paras. 6.63−6.64), and the expected uptake and compliance (paras. 6.65−6.66).

7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**
Not recommended

# 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

# 9 Sponsor's Comment

Novartis believes all Australians with early breast cancer at high risk of recurrence should have equitable access to effective treatment options. The PBAC's decision not to recommend Kisqali leaves some women with HR+/HER2- high-risk early breast cancer without access to a treatment that can reduce their risk of disease recurrence. Novartis will continue to partner with the breast cancer community to advance care through collaboration and innovation.