

**6.01 ABEMACICLIB,
Tablet 50mg,
Tablet 100mg,
Tablet 150mg,
Verzenio[®],
Eli Lilly Australia PTY LTD.**

1 Purpose of submission

- 1.1 The Category 2 submission requested a General Schedule Authority Required (Telephone/Online) listing for abemaciclib (ABE), in combination with standard adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), lymph node positive, invasive, resected early breast cancer (EBC) at high risk of disease recurrence.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus ET alone.

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

Component	Description
Population	Adult patients with HR+, HER2- lymph node-positive, invasive, resected, EBC and high risk of recurrence
Intervention	ABE, 150mg twice daily (recommended dose) in combination with standard adjuvant ET
Comparator	Standard adjuvant ET alone, presenting SoC
Outcomes	Primary endpoint: IDFS Secondary endpoints: DRFS, HRQoL, OS
Clinical claim	In the target population described above: <ul style="list-style-type: none"> • ABE + ET provides superior effectiveness to ET alone; and • ABE + ET provides monitorable and manageable safety to ET alone

Source: Table 11, p24 of the submission.

ABE = abemaciclib; EBC = early-stage breast cancer; ET = endocrine therapy, DRFS = distant relapse-free survival, HER2- = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive; HRQoL = health-related quality of life, IDFS = invasive disease-free survival, mg= milligram, OS = overall survival, SoC = standard of care.

Bold text indicates changes from previous submission. The current submission included the word “standard” to “adjuvant ET alone” and the word “monitorable” to “manageable safety to ET alone”.

2 Background

Registration status

- 2.1 ABE in combination with ET received Therapeutic Goods Administration (TGA) registration in EBC on the 9 June 2022 for the adjuvant treatment of patients with HR+, HER2-, node positive EBC at high risk of recurrence.
- 2.2 ABE also has TGA registration for the treatment of HR+, HER2- locally advanced or metastatic breast cancer in combination with an aromatase inhibitor (AI) or fulvestrant as initial endocrine-based therapy or following prior ET.

Previous PBAC consideration

- 2.3 This is the third consideration of ABE in combination with ET for the adjuvant treatment of patients with HR+, HER2-, node-positive, invasive, resected EBC at high risk of recurrence. The initial submission for ABE was considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in March 2022 but was not recommended. In March 2023, ABE received a positive recommendation that was contingent on addressing the remaining concerns held by the PBAC. The current submission sought to address those concerns using alternate approaches to those recommended by the PBAC at the March 2023 meeting. Previous concerns and how they were addressed in the current submission are summarised in Table 2.
- 2.4 The initial submission for ABE is referred to as ‘March 2022 submission’. The first resubmission is referred to as ‘March 2023 resubmission’, while the November 2023 submission is referred to as the ‘current submission’ herein.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the current submission addresses it
Clinical place in therapy	The PBAC recommended flow on changes for all currently PBS-listed CDK4/6 inhibitors in the advanced/metastatic treatment context to prohibit sequential application (i.e. use in EBC and then use in advanced/metastatic breast cancer) due to the absence of safety or efficacy data supporting repeated use of CDK4/6 inhibitors (para 7.5, abemaciclib, PSD, March 2023 PBAC Meeting).	Not addressed. The sequential impact of ABE in EBC to metastatic disease has not been captured in the clinical management algorithm of the current submission.
Clinical effectiveness	The PBAC considered that due to immature OS data there remained an unclear relationship between IDFS/DRFS and OS (para 7.7, abemaciclib, PSD, March 2023 PBAC Meeting).	No new clinical data was presented since the March 2023 resubmission. The economic model has been updated to use the July 2022 data cut.
Economic evaluation	The PBAC considered the treatment waning effect should be from Year 4 to Year 7 (para 7.11, abemaciclib, PSD, March 2023 PBAC Meeting).	Treatment waning has been changed from Year 7 to Year 28.9 (March 2023 resubmission) to Year 7 to Year 10 in the current submission. This was further revised to 6-9 years in the pre-PBAC response.
	The PBAC considered the starting age for the modelled cohort should be approximately 60 years (para 7.12, abemaciclib, PSD, March 2023 PBAC Meeting).	Starting age has been changed from 52.2 years (March 2023 resubmission) to 56 years in the current submission. This was further revised to 58.5 years in the pre-PBAC response.
	The PBAC previously considered that a 20-year time horizon would be more reasonable, 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 7.13, abemaciclib, PSD, March 2023 PBAC Meeting).	Time horizon remains unchanged at 30 years. The 30-year time horizon was combined with treatment waning from Year 7 to Year 10, and an age at model entry of 56 years in the submission, and with treatment waning from Year 6 to Year 9, and an age at model entry of 58.5 years in the pre-PBAC response.

Public Summary Document – November 2023 PBAC Meeting

Component	Matter of concern	How the current submission addresses it
	The PBAC noted the economic model assumed that treatment with ABE would reduce the risk of recurrence and would result in an increase in OS. The PBAC further noted a relationship between DFS and OS had not been consistently demonstrated with other treatments for HR+ EBC, thus considered the modelled OS gain to be highly uncertain (para 7.9, abemaciclib, PSD, March 2023 PBAC Meeting). Additionally, the PBAC considered that an ICER of up to \$30,000/QALY gained would account for the uncertainty regarding the modelled OS (para 7.13, abemaciclib, PSD, March 2023 PBAC Meeting).	The current submission's economic model maintained the assumption that treatment with ABE would reduce the risk of recurrence resulting in an increase in OS (OS benefit modelled indirectly through IDFS). The current submission presented a revised economic analysis with updated data from the July 2022 data cut-off of the monarchE trial, however, the modelled OS gain remained highly uncertain.
Financial estimates	The PBAC previously considered that the assumed maximum uptake of █████% was too high and considered that a maximum uptake rate of █████% would be reasonable (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting).	Partially addressed. The current submission applied a constant uptake rate (█████%) from Year 1 to Year 6. This was changed from the March 2023 resubmission that used █████% in Year 1 increasing to █████% in Years 3-6. This was further revised in the pre-PBAC response to █████% in Year 1 increasing to █████% in Year 2 and █████% in Years 3-6.
	The PBAC recommended a compliance rate that is less than reported for hormonal therapy (84%) (para 7.14, abemaciclib, PSD, March 2023 PBAC meeting).	Addressed. The current submission used 83% compliance. This has been updated from 100% compliance over 24 months in the March 2023 resubmission.
	The PBAC previously considered the assumed treatment duration of 24 months was too long. The PBAC considered abemaciclib use in clinical practice was likely to be less than the mean treatment duration reported in the monarchE trial (82.7 weeks, 20.7 months) due to the toxicity associated with abemaciclib and the likely older cohort treated through the PBS. The PBAC considered that a mean treatment duration of 18 months was a more reasonable estimate (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting).	Not addressed. The assumed length of therapy in the financial estimates was unchanged in the submission (24 months) The assumed length of therapy in the financial estimates was unchanged in the submission (24 months) and revised to 21 months in the pre-PBAC response. The mean length of therapy modelled in the economic evaluation was also 21 months (based on a K-M TTD curve).
	The PBAC considered that a RSA with financial caps based on revised estimates would be required to manage the risk of utilisation in patients with a lower risk of recurrence where use would be less cost-effective. The PBAC considered a rebate of 80% for use exceeding the financial caps would be appropriate noting that the cost effectiveness of such use would be unknown (para 7.15, abemaciclib, PSD, March 2023 PBAC meeting).	Addressed. The current submission proposed a RSA with annual subsidisation caps with a rebate of █████% for use exceeding the financial caps.

Source: Abemaciclib Public Summary Document, March 2023; Abemaciclib, DUSC Advice, March 2022 PBAC Meeting
 ABE = abemaciclib, CDK = cyclin dependent kinases, DRFS = distance relapse-free survival, DUSC = drug utilisation sub-committee, EBC = early breast cancer, IDFS = invasive disease-free survival, KM = Kaplan-Meier; OS = overall survival, PBAC = pharmaceutical benefits advisory committee, PBS= Pharmaceutical Benefits Scheme, PSD= public summary document, RSA = risk sharing arrangement.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ABEMACICLIB					
abemaciclib 150 mg tablet, 56	\$4249.98 published price \$ [REDACTED] effective price	1	56	5	Verzenio
abemaciclib 100 mg tablet, 56	\$4249.98 published price \$ [REDACTED] effective price	1	56	5	Verzenio
abemaciclib 50 mg tablet, 56	\$4249.98 published price \$ [REDACTED] effective price	1	56	5	Verzenio
Indication: Early breast cancer					
Clinical criteria:					
The treatment must be adjuvant to surgical resection					
AND					
Clinical criteria:					
The condition must not have been treated with endocrine therapy for more than 6 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:					
The condition must be at high risk of recurrence at treatment initiation with this drug, with high risk being any of: (a) cancer cells in at least 4 positive axillary lymph nodes, (b) cancer cells in 1 to 3 positive axillary lymph nodes plus at least one of: (i) tumour size of at least 5 cm in size, (ii) grade 3 tumour histology (on the Nottingham grading system)					
AND					
Clinical criteria:					
The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 2.00 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression					
Treatment criteria:					
Patient must be undergoing concurrent treatment with endocrine therapy where this drug is being prescribed as a PBS-benefit					
Prescribing Instructions:					
Retain all pathology imaging and investigative test results in the patient's medical records.					
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.					
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:					
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. <i>Histopathology</i> . 1991 Nov;19(5):403-10.					

Source: Table 14, p7 of the submission.

cm = centimetre, HER2- = human epidermal growth factor receptor 2 negative, max = maximum, mg = milligram, no. = number, PBS = Pharmaceutical Benefits Scheme, qty = quantity, rpts = repeats.

- 3.1 The proposed effective dispensed price for maximum quantity (DPMQ) is \$ [REDACTED] lower than proposed in the March 2023 submission ([REDACTED] % reduction).
- 3.2 The proposed published price matches the published price of ABE for use in locally advanced or metastatic HER2- breast cancer in combination with an aromatase inhibitor or fulvestrant. The proposed effective AEMP for ABE in EBC is \$ [REDACTED] ([REDACTED] %) lower than the existing effective price of ABE for locally advanced or metastatic HER2- breast cancer with the same dosages and quantities available.
- 3.3 The Economic Sub-Committee (ESC) noted that the primary change to the proposed restriction was the addition of a requirement for patients to have been treated with ET for no longer than 6 months prior to the initiation of ABE. The submission stated it was included to minimise the risk of use of ABE in a population for which the cost-effectiveness has not been determined. The monarchE trial eligibility criteria allowed patients to have received ET for up to 12 weeks prior to randomisation. The patient also must have been randomised within 16 months from the time of definitive breast cancer surgery.
- 3.4 Further, the current submission stated that the addition of the Nottingham tumour grading system will avoid ambiguity. The use of the Nottingham tumour grading system is consistent with the monarchE trial.
- 3.5 The current submission also clarified in the requested listing that concurrent treatment with ET must be prescribed as a PBS-benefit.
- 3.6 The PBAC considered that the proposed restriction was appropriate, however noted that it should include a criterion that prevented use with other PBS-subsidised therapies for this condition.
- 3.7 The implementation of the requested PBS listing for ABE may lead to partial replacement of treatment with CDK4/6 inhibitors in combination with fulvestrant in later stages of disease, potentially leading to a reduction in future treatment options. Currently, ABE is PBS listed in combination with an aromatase inhibitor or fulvestrant for the treatment of locally advanced, metastatic breast cancer and is restricted to patients who have not previously received a CDK4/6 inhibitor. The PBAC recalled it had previously recommended flow on changes to all CDK4/6 inhibitors currently PBS listed in the advanced/metastatic treatment setting to exclude sequential use (i.e. use in EBC and then use in advanced/metastatic breast cancer) as there was no safety or efficacy data for repeated use of CDK4/6 inhibitors (para 7.5, abemaciclib, Public Summary Document (PSD), March 2023 PBAC meeting). The PBAC advised that flow on changes to all CDK4/6 inhibitors to exclude sequential use remained appropriate.
- 3.8 As in the March 2023 resubmission, the submission requested that ‘new item codes for each dose form are included, with restriction criteria that are separate and independent of the existing ABE items (11868P, 11871T, 11876C).’ Creating new PBS item codes for the early stage breast cancer indication, would enable the Department

to more easily distinguish between expenditure on advanced/metastatic breast cancer versus early stage breast cancer.

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

4 Population and disease

- 4.1 The proposed population of the current submission was adult patients with HR+, HER2-, lymph node positive, invasive, resected, EBC and high risk of recurrence. This has not changed from the March 2023 resubmission.
- 4.2 EBC was defined in the current submission as stages 1-3 breast cancer (early or locally advanced), which has not spread beyond the breast tissue or nearby lymph nodes. This definition of EBC is unchanged from the March 2023 resubmission. However, the Cancer Australia definition of EBC is stage I to IIB (early) whereas stages IIB (advanced) to IIIC are considered as advanced breast cancer¹.
- 4.3 HR+, HER2- breast cancer is the most common form of breast cancer, accounting for 70% of all cases². Approximately 30% of patients who have early-stage breast cancer will experience a recurrence³.
- 4.4 ABE is a cyclin D-dependent kinase 4 and 6 (CDK4/6) inhibitor, preventing the phosphorylation of growth suppressor retinoblastoma.
- 4.5 ABE in combination with ET has been proposed to replace ET alone in the treatment of patients with invasive, resected HR+, HER2-, lymph node positive EBC at high risk of recurrence. Treatment consists of twice daily 150mg doses of ABE administered orally for up to two years, in combination with an orally administered ET of physician's choice taken for at least five years continuously, if deeming medically appropriate.

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

5 Comparator

- 5.1 ET alone is the nominated comparator, represented in the current submission as the standard of care (SoC). PBS-listed ET treatment options for the adjuvant treatment of patients with HR+ breast cancer include aromatase inhibitors (letrozole, anastrozole or exemestane) or selective oestrogen receptor modulators (tamoxifen). This has not changed from the March 2023 resubmission. The PBAC previously considered single

¹ Cancer Australia, (2021), 'Stages of breast cancer', <https://www.canceraustralia.gov.au/cancer-types/breast-cancer/symptoms-and-diagnosis/stages-breast-cancer#:~:text=Stages%20of%20breast%20cancer%20are%20numbered%20from%200,%28locally%20advanced%20breast%20cancer%20or%20metastatic%20breast%20cancer%29>

² American Cancer Society, (2019), 'Breast Cancer Facts & Figures 2019-2020', <https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html>

³ O'Shaughnessy, J. (2005). Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*, 10(Suppl 3), 20-29. [https://doi: 10.1634/theoncologist.10-90003-20](https://doi:10.1634/theoncologist.10-90003-20).

agent ET alone as the appropriate comparator (para 7.6, abemaciclib PSD, March 2023 PBAC meeting). The evaluation considered ET alone remains an appropriate comparator for ABE based on the current clinical management of EBC in Australia.

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 noted that longer follow-up data from the monarchE trial were available⁴. The clinician stated that improvement in invasive disease free survival (IDFS) and distant relapse free survival (DRFS) is sustained up to 5 years of follow-up and argued that the benefit from ABE is maintained over time. The clinician acknowledged that while fewer deaths were reported in the abemaciclib + ET arm (8.6%) compared to ET alone (10.3%), the difference in overall survival (OS) was not statistically significant (HR=0.903; 95% CI: 0.749–1.088; p=0.284). The clinician also noted that it was unclear what proportion of patients who develop metastatic disease will receive a CDK4/6 inhibitor as part of their first line metastatic treatment and that it may be several years before a difference between arms in OS is observed. The clinician considered that based on patients entering the Australian Patient Familiarisation program (mean age = | years) and the KARMA registry (mean age = 54 years)⁵, that the age of patients in the monarchE trial (mean age = 52 years) were representative of Australian patients with high risk HR+ breast cancer. With respect to adverse events, the clinician stated that in their experience side effects and dose adjustments tend to occur early, and the current clinical infrastructure have well developed processes to support patients manage the toxicity related to abemaciclib and assist patients to maintain adherence for 2 years. The clinician also noted that the cut off for entry in the monarchE trial was 12 weeks after the commencement of ET, however stated that a wider time frame would assist clinicians in identifying patients who may benefit, but may take longer to recover from their previous therapy. The PBAC considered that the hearing, provided as a letter with a question and answer format, was informative as it provided a clear clinical perspective of the meaningfulness of the results reported in the monarchE trial.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from 1 individual and 4 organisations via the Consumer Comments facility on the PBS website.

⁴ Rastogi et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk breast cancer: results from a monarchE overall survival interim analysis, including 5-year efficacy outcomes. ESMO and JCO October 2023.

⁵ Wong, V., de Boer, R., Baron-Hay, S., Blum, R., Boyle, F., Chua, S. et al (2022). Real-World Outcomes of Ribociclib and Aromatase Inhibitor Use in First Line Hormone Receptor Positive, HER2-Negative Metastatic Breast Cancer. Clin Breast Cancer, 22(8), 792-800.

- 6.3 The individual stated they would like access to abemaciclib and noted the improvement in IDFS and DRFS reported for abemaciclib patients compared with ET alone in the monarchE trial. The individual considered abemaciclib would likely reduce their risk of disease recurrence and a terminal diagnosis. However, the individual considered the current cost of abemaciclib (calculated as \$4,500 per 28 day script) was a significant barrier to treatment.
- 6.4 The PBAC noted the advice received from 4 organisations (Medical Oncology Group of Australia [MOGA], MOGA Breast Cancer Special Interest Group, Pink Hope, Breast Cancer Network Australia [BCNA]) supporting the PBS listing of abemaciclib for the treatment of HR+, HER2- lymph node positive, invasive resected early breast cancer. The organisations outlined the clinical benefits associated with the treatment of abemaciclib based on the monarchE trial and emphasised the need for additional therapy options for patients with HER2-/HR+ breast cancer. The organisations also emphasised the psycho-social benefits associated with reducing the fear of disease recurrence and the likely associated improvements to overall wellbeing and quality of life.
- 6.5 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the use of abemaciclib in early breast cancer at high risk of recurrence, categorising it as one of the therapies of ‘highest priority for PBS listing’ on the basis of the monarchE trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for abemaciclib the highest grade ‘A’, categorising it as a treatment with substantial benefit in the curative setting.⁶
- 6.6 The MOGA Breast Cancer Special Interest Group emphasised the clinical need for reducing the risk of recurrence for patients diagnosed with early breast cancer at high risk of recurrence. The Special Interest Group expressed support for access to CDK4/6 inhibitor therapy for these patients, noting clinical trial results from NATALEE, also demonstrating a clinical improvement to IDFS for EBC patients treated with ribociclib in combination with ET versus ET alone.

Clinical trial

- 6.7 The current submission was based on one head-to-head trial comparing ABE + ET to ET alone (n=5,637): the monarchE trial. Cohort 1 of the monarchE trial included patients at high risk of recurrence (defined as ≥ 4 axillary lymph nodes (ALNs); or 1-3 ALNs and tumour ≥ 5 cm or grade 3 disease) which accounted for 91% of the intention to treat (ITT) population in the monarchE trial. Cohort 1 reflects the proposed PBS population. The current submission presented results from the monarchE trial at the

⁶ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017.

additional follow-up 2 data cut-off (AFU2 DCO) (July 2022) with a median follow up of 42 months. This has not changed from the March 2023 resubmission.

6.8 Details of the trial presented in the current submission are provided in Table 3.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
monarchE / I3Y-MC-JPBL (NCT03155997) (JPRN0JapicCTI- 173668) EUCTR2016-004362- 26-DE) CTRI/2017/10/010017)	Clinical Study Report A Randomized, Open-Label, Phase 3 Study of Abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, hormone receptor positive, human epidermal receptor 2 negative, breast cancer.	CSR approval date: 30-Nov-2020; CSR approval date: 28-Jun-2021
	Protocol I3Y-MC-JPCF. Amendment (e)	Approval date: 18-Sept-2020
	Statistical Analysis Plan I3Y-MC-JPC, version 5.	Approval date: 05-Jun-2020
	Statistical Analysis Plan I3Y-MC-JPC, PRO version 2	Approval date: 06-May-2020
	Statistical Analysis Plan I3Y-MC-JPC, Addendum for OS Analyses	Approval date: 15-Dec-2020
	Cohort 1 additional tables. Additional analyses of Cohort 1.	Approval date: April 2021
	Statistical tables – confidential Statistical tables and figures for key outcomes for ITT and Cohort 1 (CSR not yet available)	Approval date: July 2022
	Publications Rastogi, P., Toi, M. et al. MonarchE: a randomized, open-label, phase 3 study of ABE combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, HR+, HER2-breast cancer.	<i>Cancer Research</i> 2018; 78 (4).
	Johnston, S., Harbeck, N. et al. 2MO ABE in high-risk early breast cancer.	<i>Annals of Oncology</i> 2020; 31:S1242-S1243.
	Johnston, S. R. D., Harbeck, N. et al. ABE Combined with Endocrine Therapy for the Adjuvant Treatment of HR+, HER2-, Node-Positive, High-Risk, Early Breast Cancer (monarchE).	<i>Journal of clinical oncology</i> 2020
	Johnston, S. R. D., Harbeck, N. et al. ABE in high-risk early breast cancer.	<i>Annals of Oncology</i> 2020; 31:S1143-S1144
	Jiang, Z., Nakayama, T. et al. LBA 1 Baseline characteristics of patients from Asia enrolled in monarchE, evaluating ABE in high-risk early breast cancer.	<i>Annals of oncology</i> 2020; 31:S1241.
	Harbeck N., Rastogi P., et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study	2021 (<i>in press</i>)
	Harbeck N., Rastogi P., et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study	2021 (<i>in press – supplementary data</i>)
	Harbeck N., Rastogi P., et al. Letter to the Editor for "Adjuvant Abemaciclib Combined With Endocrine Therapy for High-Risk Early Breast Cancer: Updated Efficacy and Ki-67 Analysis From the monarchE Study"	2021 (<i>in press</i>)
	M. Martin, R. Hegg, S. B. Kim, M. Schenker, D. Grecea, J. A. Garcia-Saenz, et al. Abemaciclib combined with adjuvant endocrine therapy in patients with high-risk early breast cancer who received neoadjuvant chemotherapy (NAC).	<i>Journal of clinical oncology</i> 2021 Vol. 39 Issue 15 SUPPL
	S. Zhimin, Q. Zhang, C. G. Song, Q. Ouyang, Z. Liu, Q. Liu, et al. Efficacy and safety analysis of Chinese patients in monarchE:	<i>Journal of clinical oncology</i> 2021 Vol. 39 Issue 15 SUPPL.

Trial ID	Protocol title/ Publication title	Publication citation
	abemaciclib combined with adjuvant endocrine therapy for high risk HR+, HER2-early breast cancer.	
	Y. S. Yap, S. B. Kim, J. W. Y. Chiu, E. Lim, R. Broom, Z. Liu, et al. 48P Abemaciclib combined with adjuvant endocrine therapy in patients from Asia with high-risk early breast cancer: monarchE.	<i>Annals of oncology</i> 2021 Vol. 32 Pages S41-S42.
	S. Tolaney, I. Blancas, Y. Im, P. Rastogi, J. Brown, A. Shahir, et al. Patients' quality of life and side effect perceptions in monarchE, a study of abemaciclib plus endocrine therapy in adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer.	<i>Breast</i> (Edinburgh, Scotland) 2021 Vol. 56 Pages S20-S21.
	M. Toi, F. Boyle, Y. H. Im, M. Reinisch, D. Molthrop, Z. Jiang, et al. 59MO Adjuvant abemaciclib combined with endocrine therapy (ET): efficacy results in monarchE Cohort 1.	<i>Annals of oncology</i> 2022 Vol. 33 Page S149.
	S. Paluch-Shimon, P. Neven, J. Huober, I. Cicin, Z. Jiang, M. P. Goetz, et al. 63P Efficacy and safety results by menopausal status in monarchE: adjuvant abemaciclib combined with endocrine therapy in patients with HR+, HER2- high-risk early breast cancer.	<i>Annals of oncology</i> 2022 Vol. 33 Page S151.
	S. Paluch-Shimon, H. Lueck, J. Beith, E. Tokunaga, J. R. Contreras, R. O. de Sant'Ana, et al. Adjuvant endocrine therapy combined with abemaciclib in monarchE patients with high-risk early breast cancer: disease characteristics and endocrine therapy choice by menopausal status.	<i>Annals of oncology</i> 2021 Vol. 32 Pages S427-S428.
	J. O'Shaughnessy, S. Johnston, N. Harbeck, M. Toi, Y. Im, M. Reinisch, et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib plus adjuvant endocrine therapy for high-risk early breast cancer.	<i>Tumori</i> 2021 Vol. 107 Issue 2 SUPPL Pages 11-12.
	J. A. O'Shaughnessy, S. Johnston, N. Harbeck, M. Toi, Y. H. Im, M. Reinisch, et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer.	<i>Cancer Research</i> 2021 Vol. 81 Issue 4 SUPPL
	M. Martin, R. Hegg, S. B. Kim, M. Schenker, D. Grecea, J. A. Garcia-Saenz, et al. Treatment With Adjuvant Abemaciclib Plus Endocrine Therapy in Patients With High-risk Early Breast Cancer Who Received Neoadjuvant Chemotherapy: a Prespecified Analysis of the monarchE Randomized Clinical Trial.	<i>JAMA oncology</i> 2022.
	N. Harbeck, P. Rastogi, M. Martin, S. M. Tolaney, Z. M. Shao, P. A. Fasching, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study.	<i>Annals of oncology</i> 2021 Vol. 32 Issue 12 Pages 1571-1581.
	N. Harbeck, S. Johnston, P. Fasching, M. Martin, M. Toi, P. Rastogi, et al. High Ki-67 as a biomarker for identifying patients with high risk early breast cancer treated in monarchE.	<i>Cancer Research</i> 2021 Vol. 81 Issue 4 SUPPL.
	P. Fasching, N. Harbeck, S. Johnston, M. Martin, M. Toi, P. Rastogi, et al. High Ki-67 as a biomarker for identifying patients with high-risk early breast cancer treated in monarchE.	<i>Oncology research and treatment</i> 2021 Vol. 44 Issue SUPPL 2 Page 244.
	Johnston SRD, Toi M, O'Shaughnessy J, Rastogi P, et al.: Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial.	<i>Lancet Oncol.</i> 2023 Jan;24(1):77-90.
	Meirson T, Goldstein DA, Gyawali B, Tannock IF. Review of the monarchE trial suggests no evidence to support use of adjuvant	<i>Lancet Oncol.</i> 2023 Jun;24(6):589-593.

Trial ID	Protocol title/ Publication title	Publication citation
	abemaciclib in women with breast cancer.	

Source: Table 2-5, pp60-61 of the March 2023 resubmission, and Table 21, p30 of the current submission and updated during the evaluation. ABE = abemaciclib, CSR = clinical study report, Dec = December, ET= endocrine therapy, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, ITT= intention-to-treat, JAMA= Journal American Medical Association, Jun = June, NAC = neoadjuvant chemotherapy, Nov = November, Sept = September, SUPP = supplementary, Vol.= volume.

Blue shading indicates data previously seen by the PBAC.

Publication identified during the evaluation and was not included in the current submission.

6.9 Meirson et al. (2023)⁷ was identified during the evaluation and presented a re-analysis of the monarchE trial primary outcome, IDFS, and OS. Analyses were adjusted to account for uneven study discontinuation between the treatment arms using the reverse Kaplan-Meier (KM) method where censoring is considered the event of interest. The results of this analysis showed a smaller treatment difference in IDFS between the study groups (compared to monarchE, July 2022, ITT analysis) and potentially less favourable OS for ABE + ET compared to ET alone.

6.10 The key features of the direct randomised trial are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation ^d
ABE+ET versus ET alone						
monarch E	ITT: 5637	R, OL 42 mths	Low/some concerns ^a	HR+, HER2- resected EBC, ALN+ with high risk of recurrence ITT: both cohort 1 and cohort 2	IDFS, DRFS, OS, HR-QoL and safety	Not used
	Cohort 1: 5120			Cohort 1: high risk of recurrence: ≥4 ALNs; or 1-3 ALNs and tumour ≥5cm or grade ≥3 disease	IDFS, DRFS, OS	IDFS ^b , DRFS ^b , OS without distant recurrence ^{b,c} , HR-QoL ^b , and safety ^b
	Cohort 2: 517			Cohort 2: 1-3 ALNs and high Ki-67 index (≥20%), not meeting eligibility for cohort 1 due to tumour <5cm and grade <3 disease	IDFS, DRFS, OS	Not used

Source: Figure 2-3, p64, Table 2-6, p64, Table 2-7, p65 and Table 2-22, p83 of the March 2023 resubmission.

ABE = abemaciclib, ALN = axillary lymph node, DRFS = distant relapse free survival, EBC = early breast cancer, ET= endocrine therapy, HER2- = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, HR-QoL = health-related quality of life, IDFS = invasive disease-free survival, ITT= intention-to-treat, mths, months, OL = open label, OS = overall survival, R = randomised.

^a The evaluation considered that informative censoring may have put the analysis at risk of attrition bias, consequently meaning an overall assessment of low/some concerns.

^b The economic model used the trial data on IDFS, DRFS, and OS without distant recurrence from the most recent July 2022 data cutoff (median follow-up: 42 month) from Cohort 1

^c OS without distant recurrence was not a pre-specified outcome.

^d Data previously seen by the PBAC but were not used in modelled evaluation in the March 2023 resubmission.

Blue shading indicates data previously seen by the PBAC.

6.11 The evaluation considered that the potential impact of monarchE trial attrition bias and informative censoring likely favours ABE + ET and overestimates the magnitude

⁷ Meirson, T., Goldstein, D. A., Gyawali, B., & Tannock, I. F. (2023). Review of the monarchE trial suggests no evidence to support use of adjuvant abemaciclib in women with breast cancer. *The Lancet. Oncology*, 24(6), 589–593. [https://doi.org/10.1016/S1470-2045\(23\)00165-1](https://doi.org/10.1016/S1470-2045(23)00165-1)

of the effect⁸. The risk of bias for monarchE trial was therefore changed from low to low/some concerns.

Comparative effectiveness

- 6.12 No updated clinical evidence was presented in the current submission.
- 6.13 The Pre-Sub Committee Response (PSCR) provided additional follow-up data from monarchE interim analysis 3 (OS interim analysis 3 [OS IA3], July 2023) for the ITT population and Cohort 1. The data include an additional 12 months of follow-up data (median = 54 months).
- 6.14 Table 5 summarises the results of the primary outcome of IDFS and secondary outcomes of distant relapse-free survival (DRFS) and OS outcomes from the monarchE trial ITT population alongside the subgroups Cohort 1 and Cohort 2 (AFU2 only). Figure 1, Figure 2, and Figure 3 present the Kaplan-Meier curves for IDFS, DRFS, and OS for the ITT population, respectively. Figure 4, Figure 5, and Figure 6 present the Kaplan-Meier curves for IDFS, DRFS, and OS for Cohort 1, respectively.

Table 5: Summary of survival outcomes in monarchE, OS IA3 (July 2023) and AFU2 (July 2022)

	Arm A ABE + ET n with event/N (%)	Arm B ET n with event/N (%)	HR (95% CI)
OS IA3 (July 2023)			
Invasive disease or death			
ITT population	407/2808 (14.5%)	585/2829 (20.7%)	0.68 (0.60, 0.77)
Cohort 1	382/2555 (15.0%)	553/2565 (21.6%)	0.67 (0.59, 0.77)
Distant relapse or death			
ITT population	345/2808 (12.3%)	501/2829 (17.7%)	0.68 (0.59, 0.78)
Cohort 1	325/2555 (12.7%)	477/2565 (18.6%)	0.67 (0.58, 0.77)
Death			
ITT population	208/2808 (7.4%)	234/2829 (8.3%)	0.90 (0.75, 1.09)
Cohort 1	197/2555 (7.7%)	223/2565 (8.7%)	0.89 (0.74, 1.08)
AFU2 (July 2022)			
Invasive disease or death			
ITT population	336/2808 (12.0%)	499/2829 (17.6%)	0.66 (0.58, 0.76)
Cohort 1	317/2555 (12.4%)	474/2565 (18.5%)	0.65 (0.57, 0.75)
Cohort 2 ^a	19/253 (7.5%)	25/264 (9.5%)	0.77 (0.42, 1.42)
Distant relapse or death			
ITT population	281/2808 (10.0%)	421/2829 (14.9%)	0.66 (0.57, 0.77)
Cohort 1	267/2555 (10.5%)	402/2565 (15.7%)	0.65 (0.56, 0.76)
Cohort 2 ^a	14/253 (5.5%)	19/264 (7.2%)	0.76 (0.38, 1.53)
Death			
ITT population	157/2808 (5.6%)	173/2829 (6.1%)	0.93 (0.75, 1.15)
Cohort 1	147/2555 (5.8%)	168/2565 (6.6%)	0.89 (0.71, 1.11)
Cohort 2 ^a	10/253 (4.0%)	5/264 (1.9%)	2.20 (0.75, 6.46)

⁸ Meirson, T., Goldstein, D. A., Gyawali, B., & Tannock, I. F. (2023). Review of the monarchE trial suggests no evidence to support use of adjuvant abemaciclib in women with breast cancer. *The Lancet. Oncology*, 24(6), 589–593. [https://doi.org/10.1016/S1470-2045\(23\)00165-1](https://doi.org/10.1016/S1470-2045(23)00165-1)

Source: Table 2-24, p92 of the March 2023 resubmission, Table 2-66, p152 of the March 2023 resubmission, and Table JPCF.5.10. of the monarchE CSR AFU2 July 2022; PSCR, Attachment 1

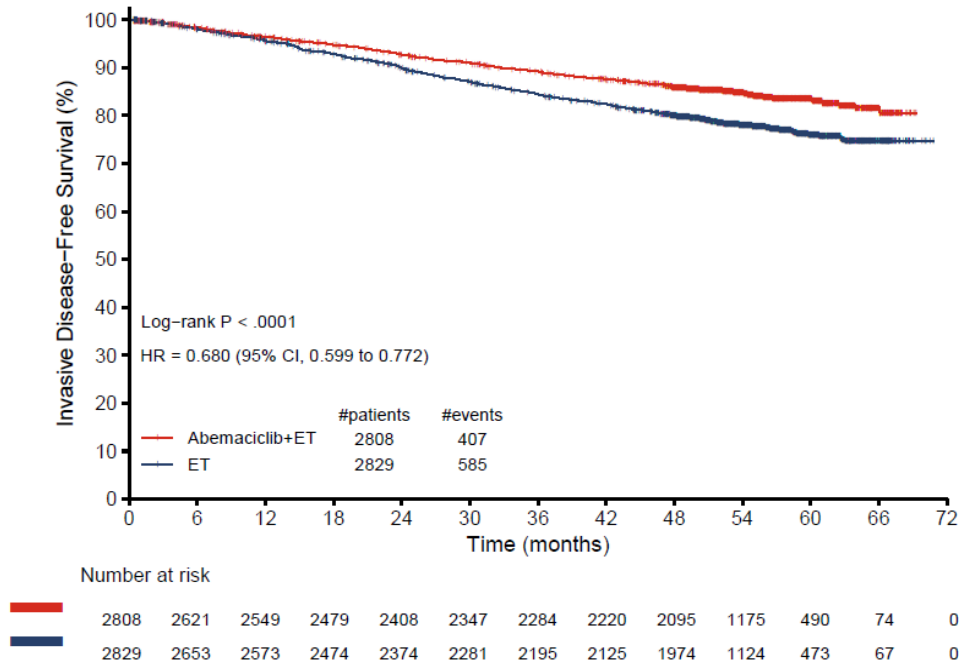
ABE = abemaciclib, AFU2=additional follow up 2, CI = confidence interval, DRFS= distant relapse-free survival, ET = endocrine therapy, HR = hazard ratio, ITT = intention-to-treat, n = number of participants reporting data, N = total participants in group, OS=overall survival.

^a Cohort 2 had a median follow-up of 38.6 months in Arm A and 39.1 months in Arm B (vs. 42 months for Cohort 1).

Bold indicated statistically significant results.

Blue shading indicates data previously seen by the PBAC.

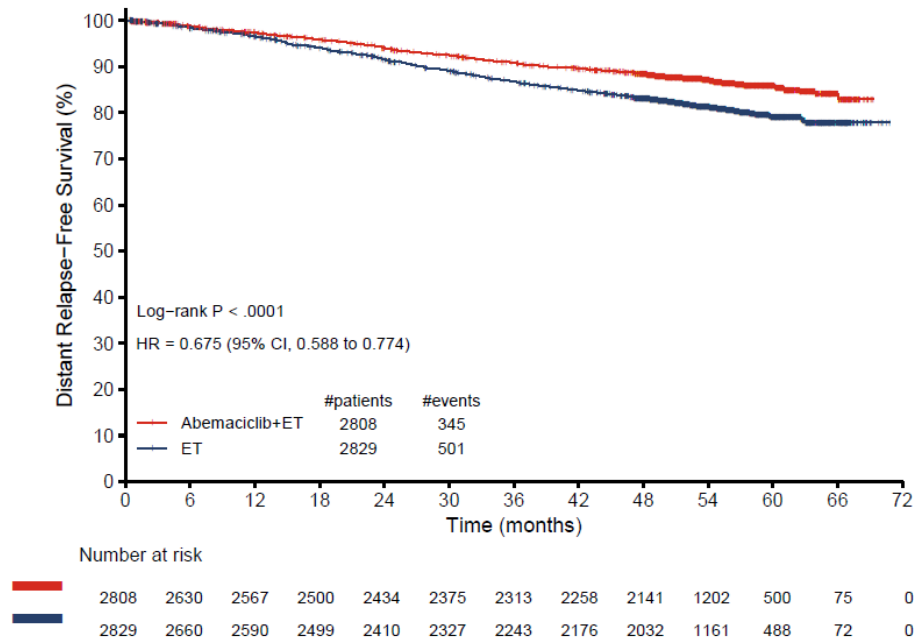
Figure 1: K-M plot of IDFS, ITT population, OS IA3 (July 2023)



Source: PSCR, Attachment 1

AFU2 = additional follow up 2, CI = confidence interval, ET = endocrine therapy, HR = hazard ratio, IA1 = interim analysis1, IDFS = invasive disease-free survival, ITT = intention-to-treat, K-M= Kaplan-Meier, OS = overall survival.

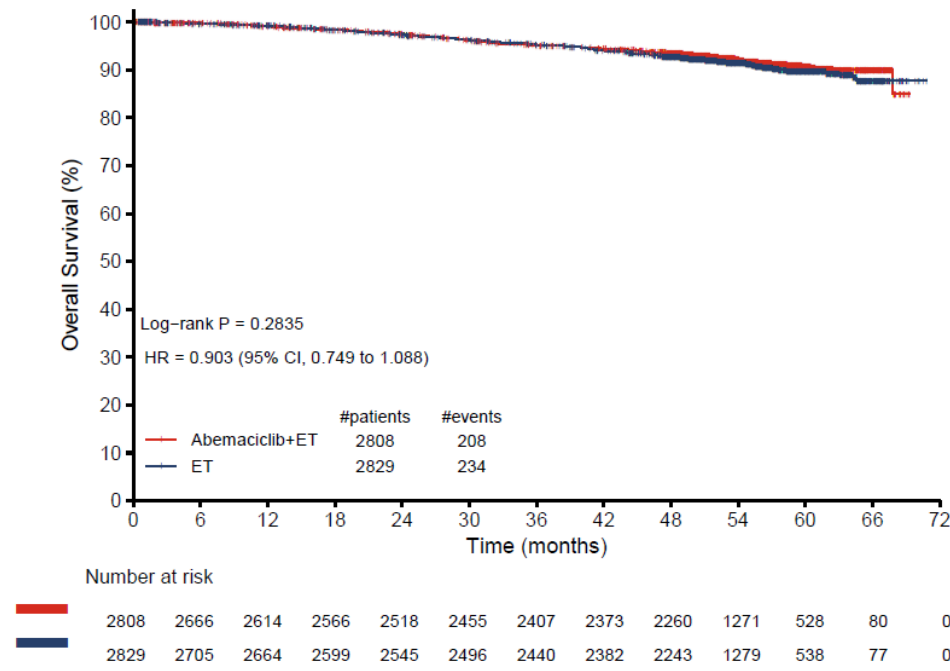
Figure 2: K-M plot of DRFS, ITT population, OS IA3 (July 2023)



Source: PSCR, Attachment 1

AFU2= additional follow up 2, CI = confidence interval, DRFS = distant relapse-free survival, ET = endocrine therapy, HR = hazard ratio; IA1= interim analysis 1, ITT = intention-to-treat, K-M= Kaplan-Meier, OS = overall survival.

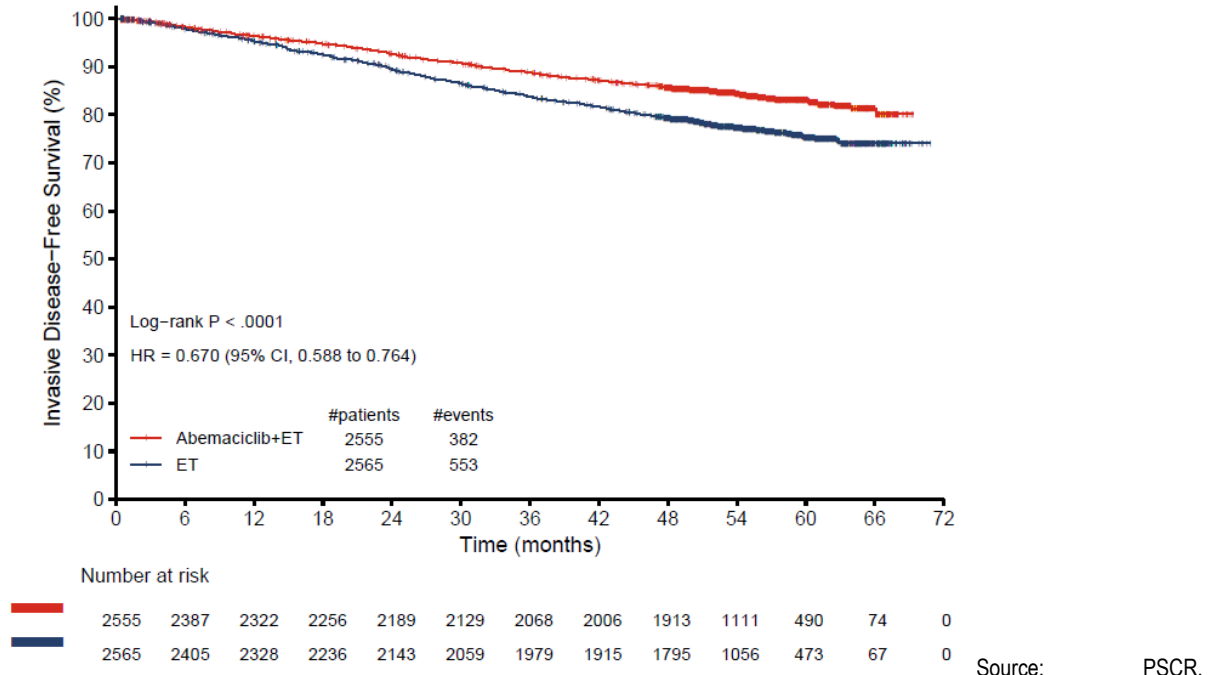
Figure 3: K-M plot of OS, ITT population, OS IA3 (July 2023)



1

AFU2 = additional follow up 2, CI = confidence interval, ET = endocrine therapy, HR = hazard ratio, ITT= intention-to-treat, K-M= Kaplan-Meier, n = number of participants with event; N = total participants in group; OS = overall survival.

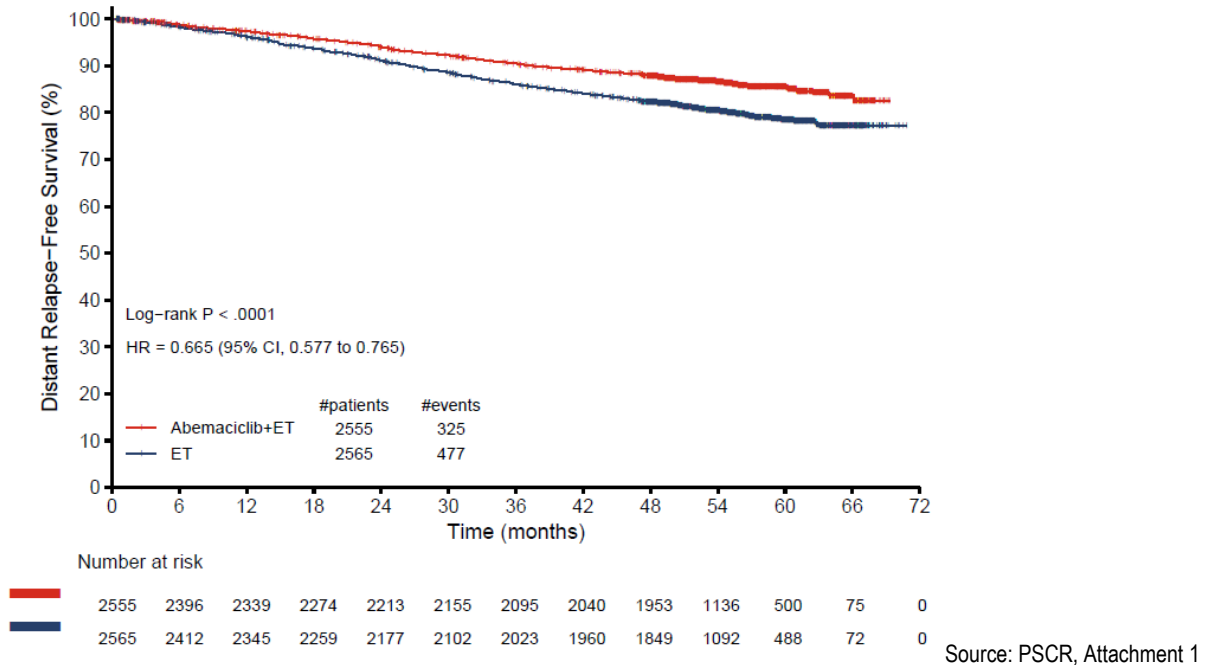
Figure 4: K-M plot of IDFS, Cohort 1, OS IA3 (July 2023)



Attachment 1

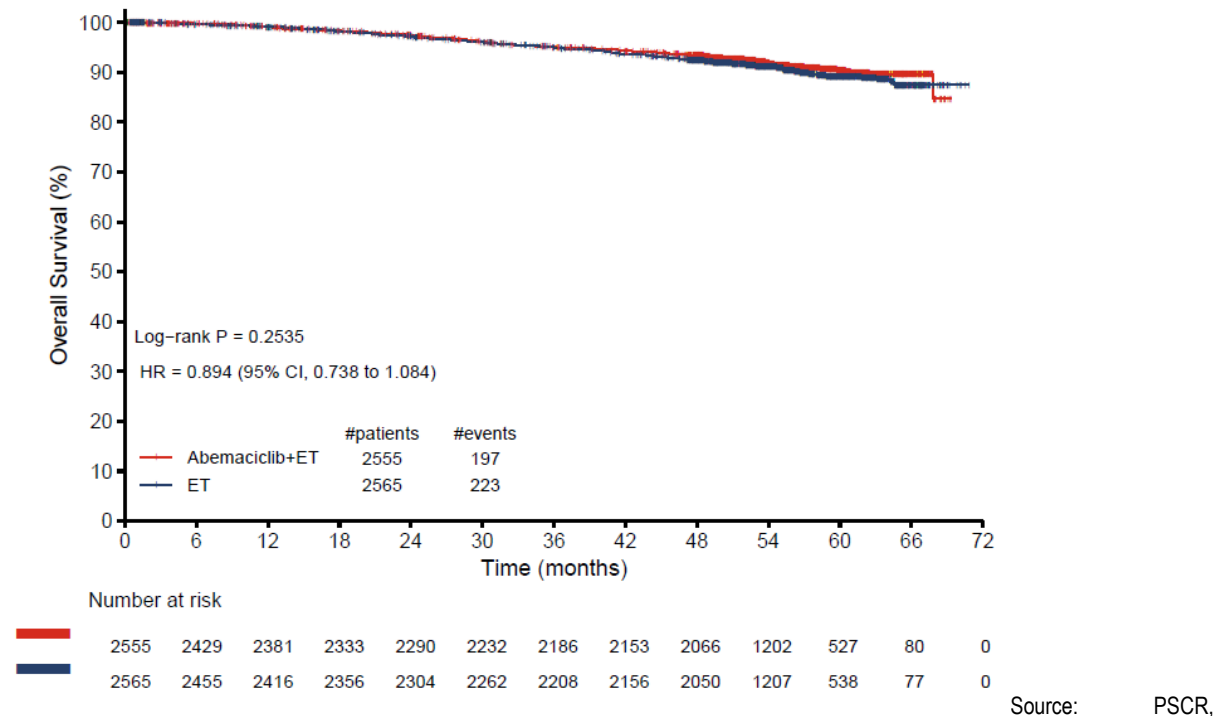
AFU2 = additional follow up 2, CI = confidence interval, ET = endocrine therapy, HR = hazard ratio, IA1 = interim analysis1, IDFS = invasive disease-free survival, ITT = intention-to-treat, K-M= Kaplan-Meier, OS = overall survival.

Figure 5: K-M plot of DRFS, Cohort 1, OS IA3 (July 2023)



AFU2 = additional follow up 2, CI = confidence interval, ET = endocrine therapy, HR = hazard ratio, IA1 = interim analysis1, DRFS = distant relapse-free survival, ITT = intention-to-treat, K-M= Kaplan-Meier, OS = overall survival.

Figure 6: K-M plot of OS, Cohort 1, OS IA3 (July 2023)



Attachment 1

AFU2 = additional follow up 2, CI = confidence interval, ET = endocrine therapy, HR = hazard ratio, ITT= intention-to-treat, K-M= Kaplan-Meier, n = number of participants with event; N = total participants in group; OS = overall survival.

- 6.15 In the ITT population with a median follow-up of 42 months (AFU2, July 2022), ABE + ET showed a 34% relative reduction in the hazard of IDFS compared to ET alone (hazard ratio [HR] = 0.66; 95% CI: 0.58, 0.76). With a median follow-up of 54 months (OS IA3, July 2023), ABE + ET showed a 32% relative reduction in the hazard of IDFS compared to ET alone (HR = 0.68; 95% CI: 0.60, 0.77).
- 6.16 The OS data showed no significant difference between the two arms in the ITT population at AFU2 (HR = 0.93; 95% CI: 0.75, 1.15) or OS IA3 (HR = 0.90; 95% CI: 0.75, 1.09).
- 6.17 Cohort 1 of the monarchE trial (defined as ≥ 4 ALNs; or 1-3 ALNs and tumour ≥ 5 cm or grade ≥ 3 disease) accounted for 91% of the ITT population. Cohort 1 represented the target population of the requested listing. This is unchanged from the previous submission. The IDFS results for Cohort 1 at median follow up 42 months (AFU2, July 2022) and 54 months (OS IA3, July 2023) were similar to the ITT population (Table 5).
- 6.18 There were no updated data for health-related quality of life at data cut-off (AFU2) (July 2022). The March 2023 resubmission presented EuroQol 5D 5-level version (EQ-5D-5L) change from baseline in both the ABE + ET arm and the ET alone arm and reported that the differences were smaller than the specified minimal clinically important difference (MCID) of 0.5 of the baseline standard deviation (July 2020).

- 6.19 The results of the Meirson et al (2023) re-analysis demonstrated a smaller treatment difference in IDFS and potentially less favourable OS with ABE + ET compared with ET alone. The PSCR argued that study discontinuation rates were low and well-balanced between treatment groups in the monarchE trial, with the majority of patients remaining in active follow-up to evaluate longer-term efficacy. The PSCR argued that an analysis of censoring, in the context of low numbers, is not statistically sound. The ESC noted the publication of an authors' response to Meirson et al (2023) (Johnston et al 2023⁹) and advised that the accuracy of the analysis conducted by Meirson et al (2023) was uncertain and considered the analysis should be interpreted with some caution, as it appeared to be a non-peer-reviewed essay and was conducted with reconstructed data from a .pdf image, not patient-level data.

Comparative harms

- 6.20 The safety data has not been updated since the March 2023 resubmission. The PSCR stated that the safety data at the July 2022 data-cut were considered final, however stated that at OS IA3 the safety data remained consistent with prior monarchE analyses and the known safety profile of abemaciclib. The updated safety data was stated by the PSCR to be 'on file' and was not provided with the PSCR.

⁹ Johnston, S. R. D., Tolaney, S. M., O'Shaughnessy, J., Rastogi, P., Harbeck, N., & Martin, M. (2023). Review of the monarchE trial suggests no evidence to support use of adjuvant abemaciclib in women with breast cancer - Authors' reply. *Lancet Oncol*, 24(6), e238.

Table 6: Summary of key adverse events in the trials in the monarchE trial at AFU2, safety population

Trial ID	Arm A ABE + ET n with event/N (%)	Arm B ET n with event/N (%)	RD % (95%CI)	RR (95% CI)
monarchE				
Patients with ≥ 1 TEAE	2746/2791 (98.4)	2488/2800 (88.9)	9.5 (8.28, 10.79)	1.11 (1.09, 1.12)
Patients with ≥ 1 CTCAE Grade ≥ 3 TEAE	1393/2791 (49.9)	472/2800 (16.9)	33.1 (30.74, 35.37)	2.96 (2.71, 3.24)
Patients with ≥ 1 TE-SAE	433/2791 (15.5)	256/2800 (9.1)	6.4 (4.66, 8.09)	1.70 (1.47, 1.96)
Patients who discontinued all study treatment due to AE	180/2791 (6.4)	30/2800 (1.1)	5.4 (4.39, 6.37)	6.02 (4.10, 8.82)
Patients who died due to AE on study therapy or ≤ 30 days of discontinuation from study treatment	15/2791 (0.5)	11/2800 (0.4)	0.1 (-0.21, 0.50)	1.37 (0.63, 2.97)
Patients who discontinued ABE due to AE ^a	515 (18.5)	NA	NA	NA
Grade ≥ 3 diarrhoea ^a	219/2791 (7.8)	6/2800 (0.2)	7.63 (6.62, 8.64)	36.62 (16.30, 82.26)
Grade ≥ 3 neutropenia ^a	546/2791 (19.6)	23/2800 (0.8)	18.74 (17.23, 20.24)	23.82 (15.74, 36.03)
Grade ≥ 3 leukopenia ^a	317/2791 (11.4)	11/2800 (0.4)	10.96 (9.77, 12.16)	28.91 (15.89, 52.62)
Grade ≥ 3 lymphopenia ^a	151/2791 (5.4)	13/2800 (0.5)	4.95 (4.07, 5.82)	11.65 (6.63, 20.48)

Source: Table 2-51, p133 of the March 2023 resubmission, and Table 2-53, p135 of the March 2023 resubmission..

ABE = abemaciclib, AE = adverse event, AFU2= Additional follow up 2, CI = confidence interval, CTCAE = common terminology criteria for adverse events, ET= endocrine therapy, n = number of participants reporting data, N = total participants in group, NA= not applicable, RD = risk difference, RR = relative risk, TEAE = treatment emergent adverse event, TE-SAE = treatment emergent serious adverse event.

Notes: **Bold** indicates statistically significant results.

Blue shading indicates data previously seen by the PBAC.

Benefits/harms

6.21 The comparative benefits and harms remain unchanged from the March 2023 resubmission.

Table 7: Summary of comparative benefits and harms for ABE + ET vs ET, ITT, OS IA3 (July 2023) and AFU2 (July 2022)

Invasive disease-free survival (IDFS; median duration of follow up 54 months)						
Event	ABE + ET	ET	Absolute Difference		HR (95% CI)	
Invasive disease or death, n/N (%)	407/2808 (14.5%)	585/2829 (20.7%)			0.68 (0.60, 0.77)	
Median IDFS, months (95% CI)	NA	NA	NA		-	
% alive without invasive disease at 36 months (95% CI)	89.2 (88.0, 90.4)	84.4 (83.0, 85.8)	4.8 (3.0, 6.6)		-	
% alive without invasive disease at 48 months (95% CI)	86.0 (84.6, 87.3)	80.0 (78.5, 81.5)	6.0 (3.9, 8.0)		-	
% alive without invasive disease at 60 months (95% CI)	83.6 (82.0, 85.1)	76.0 (74.1, 77.8)	7.6 (5.2, 10.0)		-	
Distant relapse-free survival (DRFS; median duration of follow up 54 months)						
Distant relapse or death, n/N (%)	345/2808 (12.3%)	501/2829 (17.7%)			0.68 (0.59, 0.78)	
Median DRFS, months (95% CI)	NA	NA	NA		-	
% alive without distant relapse at 36 months (95% CI)	90.9 (89.7, 91.9)	86.7 (85.4, 88.0)	4.1 (2.4, 5.8)		-	
% alive without distant relapse at 48 months (95% CI)	88.4 (87.1, 89.6)	83.1 (81.6, 84.5)	5.3 (3.4, 7.2)		-	
% alive without distant relapse at 48 months (95% CI)	86.0 (84.5, 87.4)	79.2 (77.4, 80.9)	6.7 (4.5, 9.0)		-	
Overall survival (OS; median duration of follow up 54 months)						
Deaths, n/N (%)	208/2808 (7.4%)	234/2829 (8.3%)			0.90 (0.75, 1.08)	
Median OS, months (95% CI)	NA	NA	NA		-	
% alive at 36 months (95% CI)	95.1 (94.2, 95.9)	95.3 (94.4, 96.0)	-0.2 (-1.3, 1.0)		-	
% alive at 48 months (95% CI)	93.6 (92.6, 94.5)	92.8 (91.7, 93.7)	0.8 (-0.5, 2.2)		-	
% alive at 60 months (95% CI)	90.7 (89.3, 92.0)	89.6 (88.2, 90.9)	1.1 (-0.8, 3.0)		-	
Harms (median duration of follow up 42 months)						
	ABE + ET n/N	ET n/N	RR (95% CI)	Event rate/100 patients^a		RD (95% CI)
				ABE + ET	ET	
Grade ≥ 3 TEAE	1393/2791	472/2800	2.96 (2.71, 3.24)	49.9	16.9	33.1 (30.74, 35.37)
TE-SAE	433/2791	256/2800	1.70 (1.47, 1.96)	15.5	9.1	6.4 (4.66, 8.09)
Discontinuation due to AE	180/2791	30/2800	6.02 (4.10, 8.82)	6.4	1.1	5.4 (4.39, 6.37)
Grade ≥ 3 diarrhoea ^b	219/2791	6/2800	36.62 (16.30, 82.26)	7.8	0.2	7.63 (6.62, 8.64)
Grade ≥ 3 neutropenia ^b	546/2791	23/2800	23.82 (15.74, 36.03)	19.6	0.8	18.74 (17.23, 20.24)

Source: Table 2-51, p133 of the March 2023 resubmission, Table 2-52, p135 of the March 2023 resubmission, PSCR (Attachment 1)
 ABE = abemaciclib, CI = confidence interval, DRFS = distant relapse-free survival, ET = endocrine therapy, HR = hazard ratio, IDFS = invasive disease-free survival, n = number of participants reporting data, N = total participants in group, NA = not available (not reached),

OS = overall survival, RD = risk difference, RR = risk ratio, TEAE = treatment emergent adverse event, TE-SAE = treatment emergent serious adverse event.

Notes: **Bold** indicated statistically significant results.

Blue shading indicates data previously seen by the PBAC.

^a Median 42 months duration of follow-up

^b No updated data was provided at AFU2.

6.22 Based on direct evidence presented in the PSCR, for every 100 patients with HR+, HER2-, EBC with a high risk of recurrence, treated with ABE + ET instead of ET alone for a median follow-up duration of 54 months:

- Approximately 8 fewer patients would experience invasive disease or death at 54 months.
- No difference in OS.

During a median follow-up of 42 months:

- Approximately 33 additional patients would experience a grade ≥ 3 TEAE.
- Approximately 6 additional patients would experience a treatment-emergent serious adverse event.
- Approximately 5 additional patients would discontinue all study treatment due to adverse events.

Additionally, during a median follow up of 27 months:

- Approximately 8 additional patients would experience grade ≥ 3 diarrhoea.
- Approximately 19 additional cases of neutropenia.

Clinical claim

6.23 The current submission described ABE + ET as superior in terms of effectiveness compared with ET alone and with a monitorable and manageable safety profile.

6.24 The ESC noted that the PBAC previously considered that the claim of superior comparative effectiveness of ABE + ET over ET alone was supported (para 7.7, abemaciclib, PSD, March 2023 PBAC meeting). However, the PBAC noted that a benefit in terms of OS had not been demonstrated in the clinical trial and therefore remained uncertain (para 7.1, abemaciclib, PSD, March 2023 PBAC meeting). The PSCR argued that longer-term follow-up data from OS IA3 (July 2023) confirm that DRFS benefit translates into a more favourable OS benefit, with HRs remaining below 1.0, 95% CIs continuing to narrow and p-values evolving favourably. The PSCR also argued that the previously observed imbalance of incurable metastatic disease recurrence between the two treatment arms has been reinforced at OS IA3 (July 2023) and has translated into incremental differences of patients dying from disease in the ET arm compared with the ABE+ET arm, which is increasing with each data-cut (OS IA1 (April 2021): 76 vs 72 patients (difference = 4 patients); OS IA2 (July 2022): 139 vs 118 patients (difference = 21 patients); OS IA3 (July 2023): 187 vs 154 patients (difference

= 33 patients). The PSCR stated that it is expected that this clinical benefit will continue to mature favourably with longer follow-up.

- 6.25 The PBAC noted additional follow-up data for the monarchE trial was provided in the PSCR, which increased the median duration of follow-up from 42 months of data included in the submission to 54 months. The PBAC also noted that updated annualised HRs were not available. The PBAC considered the magnitude of relative treatment effect appears to be maintained up to the most recent data cut-off (median follow-up = 4.5 years). However, the PBAC noted that the OS data remained immature, and agreed with the ESC that there remains an unclear relationship between IDFS/DRFS and OS.
- 6.26 The PBAC recalled it had previously considered that the difference in IDFS and DRFS was likely to represent a clinically meaningful benefit. The PBAC also recalled it considered that overall the claim of superior comparative effectiveness of abemaciclib + ET over ET alone was supported (para 7.7, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC considered that the updated efficacy results remain consistent with this conclusion.
- 6.27 ABE in combination with ET was associated with inferior safety compared to ET alone with higher rates of grade ≥ 3 treatment emergent adverse events (TEAEs), treatment emergent serious adverse event (TE-SAEs), and adverse events (AEs) leading to discontinuation in patients taking ABE. The ESC noted that the PBAC previously considered that a claim of inferior, yet manageable safety was reasonable and that the safety profile of ABE is manageable with monitoring and dose modifications (para 7.9, abemaciclib, PSD, March 2022 PBAC meeting; para 7.8, abemaciclib, PSD, March 2023 PBAC meeting).
- 6.28 The PBAC considered the safety claim of inferior yet monitorable and manageable safety compared to ET alone was reasonable.

Economic analysis

- 6.29 The current submission presented a modelled economic evaluation comparing ABE + ET to ET alone based on the monarchE randomised control trial. The type of economic evaluation presented was a cost-utility analysis (CUA). The approach remained unchanged from the March 2023 resubmission.
- 6.30 The economic model presented in the submission was a cohort state transition model (Markov) with five health states. The health states were IDFS, non-metastatic recurrence, remission, metastatic recurrence, and death. Death and metastatic recurrence were modelled as absorbing health states. The structure of the economic model including health states remained unchanged from the March 2023 resubmission.
- 6.31 The current submission did not present a stepped economic evaluation. This is not reasonable, given the analysis continues to rely heavily on modelled assumptions, including extrapolation of IDFS and generation of outcomes in metastatic recurrence.

6.32 Key changes from the March 2023 resubmission include:

- Incorporation of July 2022 data-cut of the monarchE trial, including updated curve fitting analyses;
- Increasing the cohort starting age from 52.2 to 56 years;
- A reduction in the treatment effect waning period (from Year 7-28.9 to Year 7-10);
- Drug costs, effective price \$ | reduced from \$ | per 56 tablets (DPMQ) for 50 mg, 100 mg, 150 mg strengths;
- Updated life tables (ABS 2019-21).

6.33 The key components of the economic evaluation comparing ABE + ET with ET alone are presented in Table 8.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	ABE+ ET vs ET
Time horizon	30 years versus 42-month median follow up in the monarchE trial (July 2022 data cut).
Outcomes	QALYs and LYs.
Methods used to generate results	A cohort state-transition model (Markov model).
Health states	Five health states: Invasive disease-free survival; Non-metastatic recurrence (including three sub-states: second primary neoplasm [a], locoregional recurrence and contralateral recurrence); Remission; Metastatic recurrence (including two sub-states: endocrine-resistant and endocrine-sensitive) [a]; and Dead [a].
Cycle length	28 days.
Transition probabilities or Allocation to health states (if partitioned survival model)	IDFS, recurrence type, OS without metastatic recurrence and TTD were sourced from Cohort 1 monarchE (July 2022 data cut; AFU2).
	The probability of recurrence in remission was based on Hamilton (2015).
	As metastatic recurrence was modelled as an absorbing health state, one-off costs and QALYs were applied on the transition to this health state. These were based on LYs, by progression status, generated in external workbooks of ABE in the metastatic setting for each first-line metastatic treatment option included (and subsequently weighted by the distribution of use with and without ABE in the adjuvant setting).
Extrapolation method	The current submission presented a revised economic analysis with updated data from the July 2022 data cut-off of the monarchE trial
	Observed KM data were used in the model with extrapolation of Cohort 1, monarchE KM IDFS, OS without distant recurrence and TTD for ET (with or without adjuvant ABE) data.
	Updated data were used, however the type of parametric function chosen to extrapolate IDFS and OS were unchanged from the March 2023 resubmission. Parametric model selection was based on an assessment of proportional hazards, goodness of fit statistics, clinical plausibility and previous PBAC consideration. <ul style="list-style-type: none"> - IDFS: a jointly fitted log-logistic distribution was used from month 48. - OS without metastatic recurrence: a jointly fitted exponential distribution was used from month 48. - IDFS and OS without metastatic recurrence were adjusted for a waning of the ABE treatment effect (from Year 7–10). - ET TTD: independently fitted models were used after all of the observed K-M TTD. Hazards spline models with two knots were used for both arms. All extrapolations were adjusted for background mortality using the 2019-2021 Australian Bureau of Statistics (ABS) life tables.
Health related quality of life	Derived from monarchE Cohort 1 (IDFS and remission: 0.785), MONARCH-2 (ET-resistant PFS and ET-sensitive PFS2: 0.748), MONARCH-3 (ER-MBC PFS1: 0.724) and published literature (Lidgren 2007 ^a and Lloyd 2006 ^b).
Cohort start age	56 years.

Source: Compiled during evaluation from Section 3 of the current submission and Table 3-2, p182 of the March 2023 resubmission. ABE= abemaciclib, AFU2 = additional follow-up 2, ET= endocrine therapy, ESC= Economic Sub Committee, ICER= Incremental Cost Effectiveness Ratio, IDFS = invasive disease-free survival, K-M = Kaplan Meier, LY = life years, OS = overall survival, PBAC= Pharmaceutical Benefits Advisory Committee, PFS= progression-free survival, QALY = quality-adjusted life year, TTD = time to treatment discontinuation.

^a Modelled as absorbing health states.

^b The Cohort 1 patient criteria matches the proposed PBS patient criteria. This represents 91% of the ITT population.

Blue shading indicates these data sources and key inputs were unchanged from the March 2023 resubmission.

- 6.34 The economic model presented in the current submission was informed by updated clinical inputs from the monarchE trial (July 2022 data cut). It applied parametric extrapolation for IDFS, TTD, and OS without distant recurrence; the proportion of IDFS events that are metastatic; distribution of types of non-metastatic recurrence (NMR) events; and adverse event incidence.
- 6.35 As with the March 2023 resubmission, the OS benefit of ABE was modelled indirectly through IDFS, where an improvement in IDFS was assumed to reduce the number of recurrences, in particular metastatic recurrences, and therefore mortality due to metastatic recurrence. The current submission updated the economic model to incorporate additional data for OS, however no OS benefit was observed at the July 2022 data cut of the monarchE trial. At the March 2023 meeting, the PBAC noted that the economic model assumed that treatment with ABE would reduce the risk of recurrence and that this would result in an increase in OS (para 7.9, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC also considered that it is unclear if treatment with ABE results in recurrence being avoided in a proportion of patients and hence a permanent cure as claimed, or if ABE delays micro-metastases progressing to macro-metastases and hence delays when recurrence occurs (para 7.9, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC further noted that a relationship between IDFS and OS had not been consistently demonstrated with other treatments for HR+ EBC, and overall, the PBAC considered the modelled OS gain to be highly uncertain (para 7.9, abemaciclib, PSD, March 2023 PBAC meeting). These issues remain despite the addition of the updated July 2022 data cut from monarchE. The ESC noted no new data reporting an OS benefit was provided in the current submission and considered the modelled OS gain remained highly uncertain.
- 6.36 The ESC considered issues previously raised by the PBAC remain unaddressed, including the model time horizon (para 6.37), treatment waning (para 6.38–6.39) and the cohort starting age (paras 6.40), detailed below.
- 6.37 The current submission nominated a time horizon of 30 years. This remained unchanged from the March 2023 resubmission. The PBAC previously considered that a 20-year time horizon would be more reasonable, 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 7.13, abemaciclib, PSD, March 2023 PBAC Meeting). The submission neither applied the 20-year time horizon nor a 30-year time horizon with more conservative assumptions regarding treatment waning and the model starting age. The PSCR argued that the time horizon remains unchanged as the PBAC considered that a 30-year time horizon was reasonable given the aim of treatment in the EBC setting is cure (para 7.13, abemaciclib PSD, March 2023 PBAC Meeting). The PSCR argued that based on modelled estimates 27% of ABE + ET patients and 23% of ET patients remain in IDFS at year 30 and applying a 30-year time horizon is considered conservative, as it does not represent a lifetime for this patient cohort.

- 6.38 The current submission applied a waning of the treatment effect from Year 7 to Year 10 (reduced from Year 7 to Year 28.9 previously). No new evidence was provided in the submission to support the applied treatment waning period from Year 7 to Year 10. The submission justified the applied treatment waning period based on the PBAC's consideration of trastuzumab emtansine (T-DM1; Kadcyla®) in EBC. The submission argued that:
- Evidence from the pivotal trial, KATHERINE, demonstrated a reduction in the magnitude of benefit of T-DM1 treatment on IDFS as early as Year 2 and continuing to reduce through Year 4 of the study. However, the patient populations eligible for TDM-1 and ABE differ. T-DM1 was recommended by the PBAC for the treatment of adjuvant therapy of patients with HER2 positive EBC with residual disease following HER2-targeted neoadjuvant therapy (para 7.1, trastuzumab emtansine, PSD, November 2019 PBAC meeting). As such, the duration and treatment effect of TDM-1 does not provide a basis for ABE.
 - Results of monarchE did not indicate a reduction in the benefit of ABE based on the annual HR over the first 3 years. However, data from KATHERINE indicated a reduction in benefit starting as early as Year 2 and continuing to reduce through Year 4. These arguments were made previously by the sponsor (para 6.37, abemaciclib, PSD, March 2023). The ongoing treatment effect of T-DM1 beyond the observed data was supported by longer-term trials (HERA and BCIRG-006). In contrast, the current submission did not provide further evidence to support the maintenance of ABE treatment effect beyond the observed data at 48 months (approximately 4 years). Annualised hazard rates over a short period of time, as provided by the submission, may not adequately represent a long-term maintenance of treatment effect.
- 6.39 The PBAC previously noted the piecewise hazard ratios for IDFS and DRFS suggested that the magnitude of relative treatment effect appears to be maintained to approximately 4 years, however agreed with ESC that using 4 years of data to predict the next 25 years of treatment effect is highly uncertain. The PBAC previously agreed with the ESC and considered that the waning of the treatment effect from Year 4 to Year 7 would be a more reasonable assumption (para 7.11, abemaciclib, PSD, March 2023 PBAC Meeting). The evaluation noted that the start of the treatment effect waning period (from Year 7 to Year 10) applied in the current economic model extends beyond that recommended (from Year 4 to Year 7). The PSCR argued that treatment waning should not start earlier than the timepoint of the latest clinical data. The PSCR stated that at the July 2023 data-cut, a continued benefit of ABE treatment on IDFS (n = 141 patients) and DRFS (n = 147 patients) is demonstrated at 66 months of follow-up, with KM data available up to 72 months (6 years). Therefore, the PSCR considered that starting treatment waning at Year 7 was a conservative approach, as a rapid decline in treatment benefit was not likely. The PSCR argued that the results from the latest July 2023 data-cut provides evidence of a continued benefit and thus additional certainty of the magnitude and duration of treatment benefit beyond 5 years. The pre-

PBAC response maintained that the treatment waning assumed in the submission was appropriate, however in order to reduce uncertainty beyond the last clinical datapoint reported, the sponsor stated it would accept reducing the treatment waning period from 7–10 years to 6–9 years over a 30-year time horizon.

- 6.40 The current submission revised the cohort starting age by increasing the mean age presented in March 2023 resubmission (52.2 years) to 56 years. The submission noted that the PBAC previously considered the starting age for the modelled cohort should be approximately 60 years based on data from the Chan et al. (2021) study, which reported a mean age of 61.4 years between 2012 and 2016. The submission reiterated that this study did not distinguish by molecular sub-type of EBC or risk profile, therefore is not representative of the proposed PBS population for ABE. However, the PBAC previously noted the mean age reported by Chan et al. (2021) was based on approximately 100,000 patients diagnosed with EBC from January 2002 to December 2016 and that it included patient with triple negative breast cancer who are approximately 10 years younger at diagnosis. In addition, the PBAC previously noted the 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). The current submission did not justify why 56 years was chosen and did not provide any new data or evidence to support the proposed starting age. The PBAC previously considered that the starting age for the modelled cohort should be approximately 60 years (para 7.12, abemaciclib, PSD, March 2023 PBAC Meeting). The PBAC noted in their previous consideration that no evidence or biological rationale was provided to support that high-risk patients are on average younger (para 7.12, abemaciclib, PSD, March 2023 PBAC Meeting). The PSCR maintained that a starting age of 56 years was appropriate and argued that the estimates from Australian patients enrolled in the monarchE trial (n = 217, mean age = 52.5 years) and the Verzenio Patient Familiarisation Program (n = < 500, mean age = 54.3, ‘data on file’) represent the most valid sources of evidence to inform the starting age of patients in the economic model. The PSCR argued that the study period of Chan et al. 2021 includes a time period when treatments such as CDK4/6 inhibitors were not available. The PSCR also argued that most patients recorded in this database were node-negative, with a median number of positive lymph nodes being zero and were therefore not reflective of the proposed high risk target population.
- 6.41 The PSCR further argued that based on the evidence, that patients with high risk EBC may be younger than the proposed age of 56 years. The PSCR noted a registry of Australian patients receiving first-line treatment with ribociclib and an aromatase inhibitor for HR+, HER2- metastatic breast cancer (KARMA; Wong et al 2022¹⁰). The average age of patients in the KARMA registry was 54.3 years. The PSCR argued that

¹⁰ Wong, V., de Boer, R., Baron-Hay, S., Blum, R., Boyle, F., Chua, S. et al (2022). Real-World Outcomes of Ribociclib and Aromatase Inhibitor Use in First Line Hormone Receptor Positive, HER2-Negative Metastatic Breast Cancer. Clin Breast Cancer, 22(8), 792-800.

given patients must have had EBC prior to developing metastatic disease, it considered that based on this data it is implausible for EBC patients to be approximately 60 years of age. The pre-PBAC response maintained that data from Australian patients enrolled in monarchE and in the Verzenio Patient Familiarisation Program represent the most valid sources of evidence to inform the starting age of patients in the economic model. The Response also stated that of the 342,149 patients with EBC (Stage I–IIIC) in the Surveillance, Epidemiology, and End Results (SEER) database, 238,222 (69.6%) patients had HR+/HER2- EBC and among patients who met the monarchE clinicopathologic high-risk criteria, the mean age reported was 58.5 years (Nelson 2022¹¹, Table 3). Based on the totality of evidence presented and for the purpose of finding a path forward, the pre-PBAC response stated that the starting age of the modelled cohort should be no more than 58.5 years.

6.42 A summary of the key drivers of the model is described in Table 9.

¹¹ Nelson DR, Brown J, Morikawa A, Method M. Breast cancer-specific mortality in early breast cancer as defined by high-risk clinical and pathologic characteristics. PLoS One. 2022 Feb 25;17(2):e0264637.

Table 9: Key drivers of the model

Description	Method/Value	Impact Base case: \$ [redacted] /QALY gained
Duration of treatment effect	The treatment effect based on the jointly-fitted parametric model extrapolations was assumed to continue beyond the trial period (median follow-up of 42 months) until Year 7. A waning of the treatment effect was implemented until the extrapolated comparator IDFS hazard rate equalled background mortality (at Year 10). This approach is not well justified. The PBAC previously considered the treatment waning effect should be from Year 4 to Year 7 (para 7.11, abemaciclib, PSD, March 2023 PBAC Meeting).	High, favours ABE. Assuming that the treatment effect wanes over the period from the end of the observed data (Year 4) to Year 7 increases the ICER to \$ [redacted] ² .
Time horizon	30 years in the base case. The PBAC previously considered that a 20-year time horizon would be more reasonable, 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 7.13, abemaciclib, PSD, March 2023 PBAC Meeting).	High, favours ABE. Reducing the time horizon to 20 years increases the ICER to \$ [redacted] ² .
Age of modelled patients	56 years. This is lower than the mean age of diagnosis of early breast cancer in Australia (61.4 years) reported by Chen et al 2021 ¹² . The PBAC previously considered that the starting age for the modelled cohort should be approximately 60 years (para 7.12, abemaciclib, PSD, March 2023 PBAC Meeting).	Moderate, favours ABE. Increasing the starting age of patients in the model to 61.4 years increases the ICER to \$ [redacted] ³ .
Extrapolation of IDFS	Jointly-fitted log-logistic extrapolation from month 48. The monarchE IDFS data were immature and may not provide a reliable basis for extrapolation. For both the intervention arm (ABE+ET) and comparator arm (ET), all curves appear to fit the observed data reasonably well within the trial data period, however, there is substantial variation in the curves over the time horizon. There is also a significant difference in log-logistic curves (the best-fitting curve by AIC/BIC) and Weibull curves (the second-best fitting curve by AIC/BIC).	Unknown, due to immaturity of the data and resultant variation in the curves, and uncertainty related to the duration of treatment effect.

Source: Constructed during the evaluation using 'A5.1_Abemaciclib Section 3 workbook November 2023.xlsm' workbook of the submission
 AIC = Akaike's Information Criterion, ABE = abemaciclib, BIC = Bayesian Information Criterion, ET = endocrine therapy, ICER = incremental cost-effectiveness ratio, IDFS = invasive disease-free survival, OS = overall survival, PBAC= pharmaceutical benefits advisory committee, QALY= quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$35,000 to < \$45,000

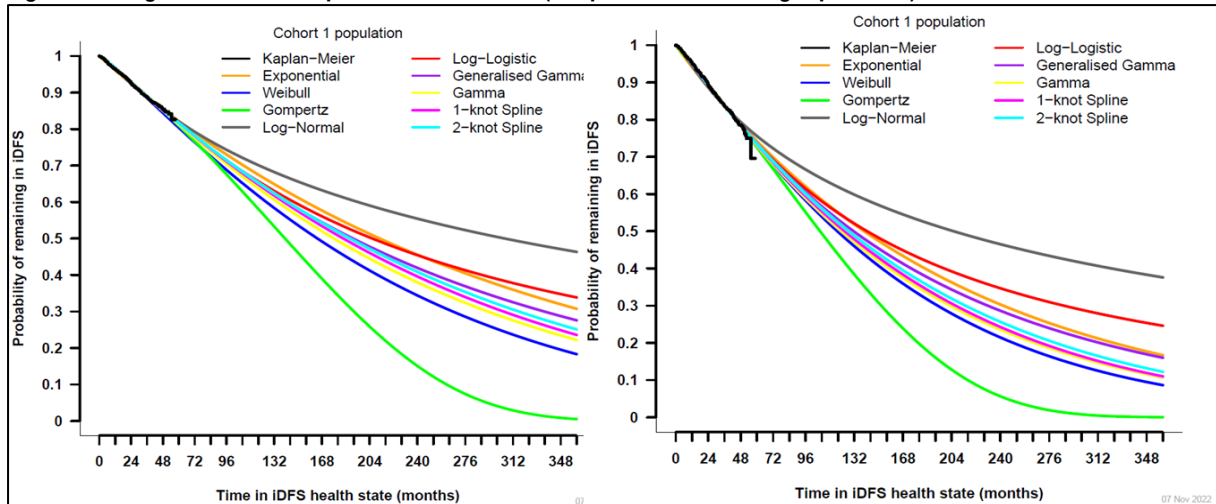
³ \$25,000 to < \$35,000

6.43 The current submission's economic analysis utilised the patient-level IDFS data (up to 48 months) from the AFU2 (July 2022) data-cut from Cohort 1 of the monarchE trial. After this time, IDFS was extrapolated using a dependant parametric model (Figure 7). The modelled IDFS data were based on a small number of events (12.4% in the intervention arm and 18.5% in the comparator) and may not provide a reliable basis for extrapolation. A jointly-fitted log-logistic parametric model was chosen for IDFS extrapolation. In the March 2023 resubmission, a jointly-fitted log-logistic parametric model was selected for IDFS extrapolation. The log-logistic model is a reasonable

¹² Chan A, O'Neil N, Lomma C, Chih H, Willsher P. BreastSurgANZ members recommendations for adjuvant systemic treatment and patient compliance in Australian breast cancer patients. ANZ J Surg. 2021 Nov;91(11):2418-2424.

choice as this was based on an assessment of proportional hazards, goodness of fit statistics, clinical plausibility and previous PBAC consideration. Furthermore, the projected estimates in the ET arm were consistent with external studies for both IDFS at 5 years (Smith 2017), and metastatic recurrence at 5–20 years (Pan 2017).

Figure 7: Long-term IDFS extrapolations – Cohort 1 (left panel ABE+ET – right panel ET)



Source: Figure 3-7, p20 of the submission.

ABE = abemaciclib, ET = endocrine therapy, IDFS = invasive disease-free survival.

- 6.44 The ESC agreed with the evaluation that for both the intervention arm (ABE+ET) and comparator arm (ET), all curves appear to fit the observed data reasonably well within the trial data period. However, noted that there is substantial variation in the curves over the remaining time horizon. There is also a significant difference in log-logistic curves (the best-fitting curve by AIC/BIC) and Weibull curves (the second-best fitting curve by AIC/BIC). The current submission presented a scenario analysis employing the dependent Weibull curve, which lowered the incremental cost-effectiveness ratio (ICER) to \$15,000 to < \$25,000/quality adjusted life year (QALY) (27.2% reduction). The ICER is sensitive to the selection of the distribution model of IDFS extrapolation.
- 6.45 Comparison of modelled outcomes for IDFS and metastatic recurrence (MR) with external data is presented in Table 10. The submission compared 5-year and 10-year IDFS rates (in the comparator arm) between what was reported in the FACE trial and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2022 meta-analysis. The FACE trial compared letrozole to anastrozole in postmenopausal patients with HR+ node-positive early breast cancer, while the EBCTCG 2022 conducted a meta-analysis of individual patient data from randomised trials comparing aromatase inhibitors (anastrozole, exemestane, or letrozole) versus tamoxifen for 3 or 5 years in premenopausal women with oestrogen receptor (ER)-positive breast cancer receiving ovarian suppression (goserelin or triptorelin) or ablation. Results from studies were consistent with what was modelled for IDFS in the ET arm at 5 years in the submission's base case (73.8%). The current submission also compared 5, 10, 15, and 20-year MR rates (in the comparator arm) to the risk of distant recurrence reported at 20 years in a population of patients who had completed 5 years of ET reported in

the Pan et al. 2017 study. This is also consistent with what was modelled in the current submission's base case.

Table 10: Comparison of modelled outcomes for IDFS and MR with external data

	IDFS ET		MR ET			
	5 years	10 years	5 years	10 years	15 years	20 years
External data						
A5.11_Study Report 2019-9068 Table 5	76%	59%	-	-	-	-
FACE* (Smith et al 2017)	70.9% - 75.1%	-	-	-	-	-
Meta-analysis* (EBCTCG, 2022)	~75%	~60%	-	~ 8 years 29.1-30.1%	-	-
Pan et al 2017*	-	-	22%	36%	45%	52%
Modelled						
Exponential	74.1%	55.0%	18.6%	33.4%	44.7%	53.0%
Gamma	73.6%	53.3%	18.9%	34.7%	46.4%	54.6%
Generalised gamma	73.6%	53.3%	18.9%	34.7%	46.4%	54.6%
Gompertz	74.1%	55.0%	18.6%	33.4%	44.7%	53.0%
Log-logistic	73.8%	55.0%	18.8%	33.4%	43.1%	49.4%
Log-normal	74.9%	61.3%	18.0%	28.4%	35.2%	39.2%
Weibull	73.2%	50.1%	19.2%	37.2%	51.1%	60.9%
Hazard spline 1 knot	73.5%	51.8%	19.0%	35.9%	48.9%	58.2%
Hazard spline 2 knots	73.7%	53.1%	18.8%	34.9%	47.3%	56.3%

Source: Table 3-6, p21 of the submission.

EBCTCG= Early Breast Cancer Trialists' Collaborative Group, ET= endocrine therapy, IDFS= invasive disease-free survival, MR-ET= metastatic recurrence endocrine therapy

Notes: Treatment waning not applied.

*subgroup results for N4-9.

6.46 As with the March 2023 resubmission, the current submission applied fixed payoffs that represent the expected costs and QALYs in metastatic disease on transition into the health state due to limited follow-up in monarchE. These were based on estimates of life years gained from analyses that explored the cost-effectiveness of ABE in the metastatic setting based on the MONARCH-2 and MONARCH-3 trials (and associated network meta-analyses). The approach of assigning one-time costs and life years (LYs) upon the onset of metastatic disease is the same approach from the March 2023 resubmission. Consequently, previously raised concerns regarding the complexity and transitivity, due to differences in therapy types received and patient characteristics between monarchE and the MONARCH-2 and MONARCH-3 studies (para 6.38, abemaciclib, PSD, March 2023 PBAC Meeting), continue to be relevant. Transitivity issues had an unclear effect on the results of the analysis.

6.47 The results of the economic analysis are presented in Table 11.

Table 11: Results of the economic evaluation

	March 2023 resubmission ^a			Current submission		
	ABE + ET	ET	Increment	ABE + ET	ET	Increment
Costs	\$ █	\$39,238	\$ █	\$ █	\$39,783	\$ █
QALYs	9.317	8.881	0.436	9.210	8.803	0.407
Incremental cost per additional QALY gained						
			\$ █ ¹			\$ █ ²

Source: Table 3-14, p28 of the submission, Table 3-66, p275 of the March 2023 resubmission, and Table 12, p27 of abemaciclib PSD, March 2023 PBAC Meeting.

ABE = abemaciclib, ET = endocrine therapy, QALY = quality-adjusted life year.

^a Obtained from the 'A6.1_Abemaciclib Section 3 workbook 2022.xlsm' corrected workbook of the March 2023 resubmission. Included correction of errors identified during the March 2023 resubmission evaluation.

Blue shading indicates results previously seen by the PBAC.

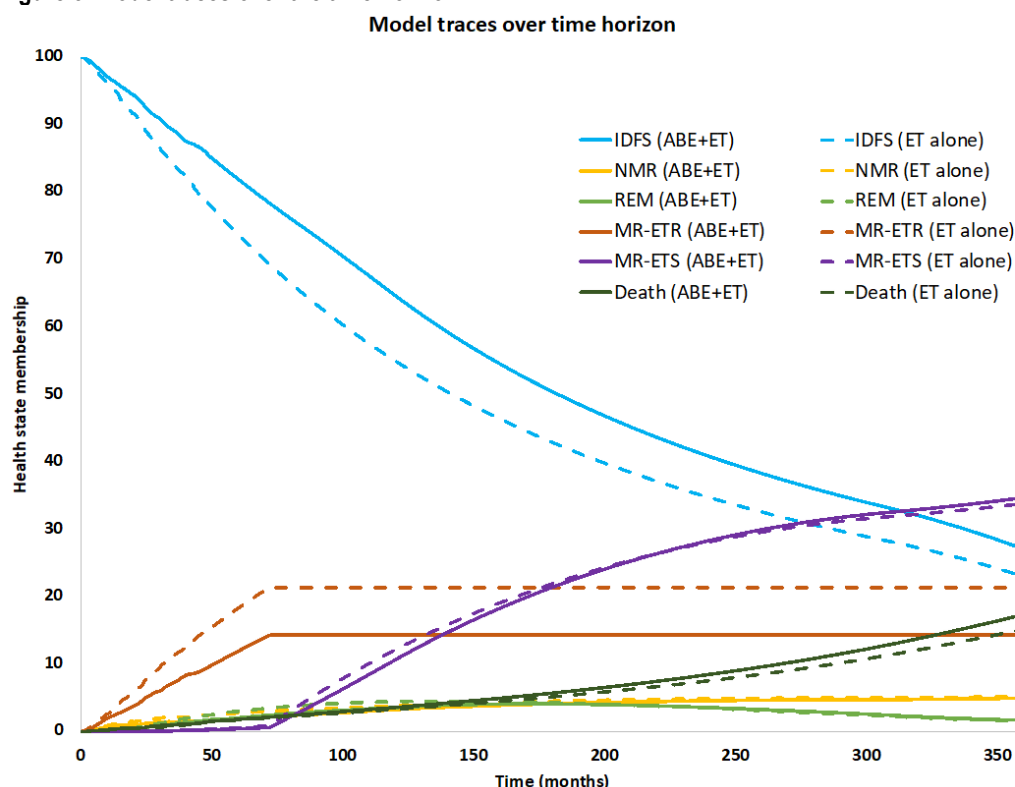
The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$15,000 to < \$25,000

6.48 Traces for the model results were constructed during the evaluation and are presented in Figure 8. As with the March 2023 resubmission, time spent in IDFS is the key driver of the clinical benefits modelled.

Figure 8: Model traces over the time horizon



Source: Constructed during the evaluation from the submission's base case parameters the 'A5.1_Abemaciclib Section 3 workbook November 2023.xlsm' workbook included in the current submission.

ABE = abemaciclib, ET = endocrine therapy, IDFS = invasive disease-free survival, NMR = non-metastatic recurrence, MR-ETR = metastatic recurrence endocrine therapy resistant, MR-ETS = metastatic recurrence endocrine therapy sensitive, REM = remission.

6.49 As for the March 2023 resubmission, the LYs and QALYs gained were predominantly accrued in the IDFS health state, with a reduction in QALYs related to non-metastatic and metastatic recurrences. This is consistent with the claim that ABE improves IDFS

and leads to a reduction in metastatic recurrences. The LYs and QALYs gained with ABE treatment are likely to be an overestimate due to the approach used to wane the treatment effect of ABE beyond the observed period (from Year 7 to Year 10) and the time horizon chosen (30 years). Most of the life years gained with ABE treatment were accrued in the extrapolated period, beyond 4 years. The estimation of LYs in metastatic disease remains uncertain in the current submission due to transitivity issues between the monarchE and the metastatic trials, and the Australian population.

- 6.50 The number of recurrence events and resulting number of recurrences avoided with ABE treatment in combination with ET compared with ET alone for the July 2022 data cut and the submission’s time horizon are presented in Table 13. Consistent with the March 2023 resubmission, the submission’s ICER relies on avoiding metastatic recurrence in 6.1% of patients over the 30-year time horizon. Over the 30-year time horizon, patients treated with ABE obtained an additional 1.175 life years which equates to 16.8 (117.5/7) life years gained per recurrence avoided (previously 15.9) or 18.1 (117.5/6.5) life years gained per metastatic recurrence avoided (previously 16.2).

Table 12: Recurrence events (undiscounted)

Recurrence event	ABE + ET		ET		Incremental outcome	
	March 2023 resubmission	Current submission	March 2023 resubmission	Current submission	March 2023 resubmission	Current submission
LYG (base case)	20.127	19.875	18.795	18.700	1.332 (133.2 per 100 patients)	1.175 (117.5 per 100 patients)
Cohort 1, monarchE						
Non-metastatic recurrence ^a	2.4%	2.2%	3.2%	3.2%	-0.8	-1.0
Metastatic recurrence	5.7%	8.4%	9.1%	13.5%	-3.4	-5.1
Any recurrence	7.9%	11.4%	12.0%	17.7%	-4.1	-6.3
Model time horizon (30 years)						
Non-metastatic recurrence ^a	17.2%	15.4%	17.4%	16.2%	-0.2	-0.8
Metastatic recurrence	51.1%	49.0%	59.3%	55.1%	-8.2	-6.1
From IDFS	41.9%	41.4%	50.0%	46.8%	-8.1	-5.4
From Remission	9.2%	7.7%	9.7%	8.4%	-0.5	-0.7
Any recurrence	68.3%	64.4%	76.7%	71.4%	-8.4	-7.0

Source: Constructed from the 'A6.1_Abemaciclib Section 3 workbook 2022.xlsm' workbook included with the March 2023 resubmission and the 'A5.1_Abemaciclib Section 3 workbook November 2023.xlsm' workbook of the submission.

ABE = abemaciclib; ET = endocrine therapy; IDFS = invasive disease-free survival; LYG = life years gained.

^a Combining the occurrences of local/regional recurrence and contralateral recurrence.

- 6.51 The results of key univariate and multivariate sensitivity analyses are summarised in Table 13.

Table 13: Sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change to ICER
Base case		0.407	1	█ %
Time horizon (base case: 30 years)				
25 years		0.363	2	█%
40 years		0.443	1	- █%
Model starting age (base case: 56 years)				
61.4 years		0.387	2	█%
Discount rate (base case: 5% per annum)				
0.0%		0.927	3	- █%
3.5%		0.516	1	- █%
Treatment waning (base case: from Year 7 to Year 10)				
No waning		0.547	1	- █%
Year 4 to Year 7		0.279	4	█%
No effect beyond the observed data (month 48)		0.183	5	█%
IDFS extrapolation (base case: log-logistic in both arms)				
Dependant Weibull (in both arms); second-best fitting		0.372	1	- █%
Dependent Exponential (in both arms); third-best fitting		0.412	1	- █%
Independent Log-logistic (in both arms)		0.488	1	- █%
Proportion of NMR (base case: ABE+ET: 27.1%, ET: 25.8%)				
28% (pooled trial data) in ABE + ET and ET		0.394	2	█%
60% in both arms		0.358	4	█%
10% in both arms		0.414	1	- █%
Proportion of NMRs that are second primary neoplasms (base case: 31.5% both arms)				
33.7% in ABE + ET and 29.7% in ET (ITT trial data)		0.377	2	█%
ET treatment duration				
ET treatment duration (base case: 5 years), 10 years		0.407	2	█%
Sensitivity analyses based on assumptions suggested by PBAC				
Time horizon 30 years + treatment waning from Year 4 to Year 7 + starting age of 61.4 years		0.266	4	█%

Source: Constructed during the evaluation from the 'A5.1_Abemaciclib Section 3 workbook November 2023.xlsm' workbook of the submission.

ABE = abemaciclib, ET = endocrine therapy; DPMQ = dispensed price for maximum quantity, ICER = incremental cost-effectiveness ratio, IDFS = invasive disease-free survival, ITT= intention-to-treat, N/A = not applicable, NMR = non-metastatic recurrence, PBAC = Pharmaceutical Benefits Advisory Committee, QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$15,000 to < \$25,000

² \$25,000 to < \$35,000

³ \$0 to < \$5,000

⁴ \$35,000 to < \$45,000

⁵ \$55,000 to < \$75,000

6.52 A multivariate analysis conducted during the evaluation including a 30-year time horizon, treatment waning from Year 4 to Year 7, and a cohort start age of 61.4 years (based on previous PBAC recommendations) resulted in an increase in the ICER from \$15,000 to < \$25,000 to \$35,000 to < \$45,000 per quality adjusted life year (QALY).

The ESC accepted that this multivariate analysis provides an appropriate re-specified base case to address the previous concerns of the PBAC (March 2023 PBAC meeting).

- 6.53 The ESC noted the proposed DPMQ of \$ [REDACTED] would need to be reduced to \$ [REDACTED] (by 12.7%) for the ICER of \$35,000 to < \$45,000 per QALY to reduce to \$30,000 per QALY, the threshold recommended by the PBAC in March 2023. The ESC noted this is higher than the DPMQ required to meet the PBAC’s March 2023 recommendation (DPMQ \$ [REDACTED]) as a result of applying the clinical trial data from the later data cut. The pre-PBAC response revised assumptions and inputs for the starting cohort age (58.5 years) and treatment waning (6–9 years). Changing these inputs increased the ICER from \$15,000 to < \$25,000 to \$25,000 to < \$35,000. The pre-PBAC response argued that the resulting ICER remained below the threshold of \$30,000 per QALY, previously accepted by the PBAC.

ABE cost/patient/course

- 6.54 The per patient costs of ABE + ET and ET alone as used in the monarchE trial, the economic model, and the financial analysis, are presented in Table 14. The cost/patient/course was slightly higher in the financial estimates compared with the economic model due to differences in treatment durations applied.
- 6.55 The assumed treatment duration of the economic model (21 months) and the financial estimates model (24 months) were not consistent in the submission. The pre-PBAC response reduced the mean duration of treatment in the financial model to 21 months, resulting in a cost/patient/course of \$ [REDACTED]¹³. A difference in the cost/patient/course between the economic and financial models is likely due to the application of the K-M TTD curve in the economic model.

Table 14: Drug cost per patient for ABE + ET and ET alone

	ABE + ET monarchE	ABE + ET Model	ABE + ET Financial estimates	ET monarchE	ET Model	ET Financial estimates
Mean duration in 28-day cycle	ABE: 20.68 ^a ET: 22.75 ^b	ABE: 21.01 ET: 38.7	ABE: 24.00 ^c ET: NE	ET: 23.30 ^d	37.8	NE
Cost/patient/28-day cycle (\$)	ABE: \$ [REDACTED] ET: \$28 ^e	ABE: \$ [REDACTED] ET: \$28 ^e	ABE: \$ [REDACTED] ET: NE	ET: \$28 ^e	\$28 ^e	NE
Cost/patient/course (\$)	ABE: \$ [REDACTED] ET: \$628	ABE: \$ [REDACTED] ET: \$1082	ABE: \$ [REDACTED] ^c ET: NE	ET: \$643	\$1058	NE

Source: Constructed during the evaluation based on Tables on pp37-40 of “A2.16 monarchE_AFU2 (July 2022) Statistical tables – CONFIDENTIAL”, “A5.1_Abemaciclib Section 3 Workbook November 2023” Excel workbook, and “A6.1_Cost and utilisation model abemaciclib EBC November 2023” Excel workbook.

ABE = abemaciclib, ET = endocrine therapy, NE = not estimated.

^a Mean duration of treatment was 82.70 weeks at the July 2022 data cut.

^b Mean duration of treatment was 91.01 weeks at the July 2022 data cut.

^c Calculated as (365.25/12 x 24 months x 83% compliance)/28 days x \$ [REDACTED]

^d Mean duration of treatment was 93.18 weeks at the July 2022 data cut.

^e Weighted using the ET comparator percentages (letrozole 26%, anastrozole 25%, tamoxifen 43%, and exemestane 5%).

¹³ Calculated as (365.25/12 x 21 months x 83% compliance)/28 days x \$ [REDACTED]

Estimated PBS usage & financial implications

- 6.56 This submission was not considered by the Drug Utilisation Sub-Committee (DUSC).
- 6.57 As in the March 2023 resubmission, an epidemiological approach was taken to estimate the financial impact of the proposed listing of ABE.
- 6.58 The current submission presented revised utilisation estimates, alongside an updated effective AEMP for ABE and a Risk Sharing Arrangement (RSA) proposal. The key inputs in the financial analysis are summarised in Table 15.

Table 15: Key inputs for financial estimates

Data	Value applied, and Source		Comment
Eligible population			
Incident patients with breast cancer	22,606 in Year 1 (2024) of listing, increasing to 26,668 in Year 6 (2029) BreastScreen Australia monitoring report (AIHW 2020), assuming a linear projection applying an annual growth rate of 3.36%.		In the March 2023 resubmission, the number of incident patients with breast cancer in the first 6 years of listing were underestimated by assuming that the first year of listing would be Year 2022. The current submission updated the first year of listing to 2024.
Proportion of EBC (including inflammatory breast cancer)	100% (abemaciclib PSD, March 2022 PBAC meeting)		Remained unchanged.
% incident breast cancer cases of Stage 1-3	95.3% NCCI data on distribution of cancer stage (2018)		Remained unchanged.
% HR+/HER2-	70% everolimus PSD, March 2013 PBAC meeting; Nelson et.al. 2022		Remained unchanged.
% node-positive EBC	24.6%	US SEER Registries Research Data Nelson et.al. 2022	Remained unchanged.
% meeting high risk criteria	48.8%		
Uptake rate ABE	█% in Year 1 to Year 6 Assumption		The PBAC previously considered that a maximum uptake rate of █% would be reasonable noting the rapid uptake of ABE in the Australian patient familiarisation program (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting). The DUSC suggested that a range of █% in Year 1 moving to █-█% by Year 6 would be more reasonable noting that the patient group is mostly older and frailer (abemaciclib, DUSC Advice, March 2022 PBAC Meeting). Considering both the PBAC and DUSC recommendations, an uptake of █% in Year 1, gradually increasing to a maximum of █% by Year 6 may have been more appropriate. This was revised in the pre-PBAC response to █% in Year 1 increasing to █% in Year 2 and █% in Years 3-6.
Length of therapy	24 months Based on median treatment duration in monarchE clinical trial (23.8 months)		Remained unchanged and does not align with the previous PBAC advice. The PBAC considered that the assumed treatment

Data	Value applied, and Source	Comment
		duration of 24 months was too long. The PBAC considered ABE use in clinical practice is likely to be less than the mean treatment duration reported in the monarchE trial (82.7 weeks, 20.7 months) due to the toxicity associated with abemaciclib and the likely older cohort treated through the PBS. The PBAC previously considered that a mean treatment duration of 18 months was a more reasonable estimate (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting). The assumed length of therapy was revised to 21 months in the pre-PBAC response. The mean length of therapy modelled in the economic evaluation was also 21 months (based on a K-M TTD curve).
Compliance	83% Assumption	This is consistent with previous PBAC advice (less than 84% for hormonal therapy; para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting).
Utilisation across ABE dose forms (150mg vs. 100mg vs. 50mg)	50.1%:37.9%:12.0% PBS script data for ABE relating to locally advanced or metastatic HR+/HER2- breast cancer	Remained unchanged.
ABE price (150mg, 100mg, or 50mg, 56 tablets)	AEMP: \$ [REDACTED] DPMQ: \$ [REDACTED] Proposed by the current submission	The updated effective AEMP represents a [REDACTED]% reduction to that proposed in the March 2023 resubmission.
Patient co-payment	PBS: \$22.57 (99.46%) RPBS: \$7.30 (0.54%) Medicare data on trastuzumab for early HER2+ breast cancer in 2022.	The January 2023 ^a updated co-payments were reflected in the financial analysis.

Source: Compiled during the evaluation from "A6.1_ Cost and utilisation model abemaciclib EBC November 2023" Excel workbook. ABE = abemaciclib, AEMP= approved ex manufacturer price, AIHW = Australian Institute of Health and Welfare, DUSC = Drug Utilisation Sub-committee, DPMQ = dispensed price for maximum quantity, EBC = early breast cancer, HER2- = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, NCCI = National Cancer Control Indicators, PBAC = Pharmaceutical Benefits Advisory Committee, PBS = Pharmaceutical Benefits Scheme, PSD = public summary document, RPBS = Repatriation Pharmaceutical Benefits Scheme, SEER = Surveillance, Epidemiology and End Results, US= United States.

^a Reduction in general patient co-payment from \$42.50 to \$30.00 and an increase in concessional patient co-payment from \$6.80 to \$7.30. Blue shading indicates data previously seen by the PBAC.

6.59 The submission stated that given that ABE has also recently been accepted on the eviQ adjuvant breast cancer protocol (eviQ, 2022), which is widely accepted across Australia as the preferred provider of evidence-based cancer treatment information, and in line with the March 2023 PBAC outcomes, the model assumes uptakes rates of [REDACTED]% in Year 1 to Year 6. This was reduced from the March 2023 resubmission which applied an uptake rate of [REDACTED]% in Year 1 rising to [REDACTED]% in Years 3-6. The PBAC considered that a maximum uptake rate of [REDACTED]% would be reasonable, noting the rapid uptake of ABE in the Australian patient familiarisation program (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting). Moreover, the DUSC suggested that a range of [REDACTED]% in year 1 moving to [REDACTED]-[REDACTED]% by year 6 would be more reasonable noting that the patient group is mostly older and frail (abemaciclib, DUSC Advice, March 2022 PBAC Meeting).

Considering both, the PBAC and DUSC recommendations, an uptake of 10% in Year 1, gradually rising to 15% by Year 6 may have been more appropriate. This assumption was tested in the uncertainty analysis conducted during the evaluation resulting in a 16% reduction in financial estimates over 6 years. The ESC noted the PSCR maintained that the uptake rate of 10% from Year 1 onwards was appropriate and argued it reflects the high unmet clinical need seen in this patient population in Australia. The PSCR noted that since starting the patient familiarisation program (PFP), it has rapidly reached its quota, and the sponsor stated it is receiving ongoing requests from clinicians to enrol additional patients in the PFP. Given this strong demand, the sponsor is currently exploring the possibility of expanding access to patients with high risk EBC. The PSCR argued that the proposed uptake rates are also consistent with clinical expert opinions that expect 10% of eligible patients will be offered abemaciclib in combination with ET. The ESC suggested that whether the submission had adequately addressed this previous concern remained for PBAC consideration.

- 6.60 The pre-PBAC response maintained that rapid uptake from Year 1 is reasonable in the context of ongoing strong demand in the Australian patient familiarisation program, however proposed revised uptake rates of 10% in Year 1, 15% in Year 2 and 15% as of Year 3, to address any outstanding concerns.
- 6.61 The current submission applied a compliance rate of 83%. This is consistent with the PBAC advice of less than 84% for hormonal therapy (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting).
- 6.62 The submission proposed an assumption that, on average, a real-world high-risk EBC patient will fill 83% of their total prescriptions based on a combination of length of therapy and compliance (i.e. 24 months length of treatment and 83% compliance). The submission stated that applying 83% compliance and a shorter duration of treatment to utilisation estimates would constitute double-counting and is not reflective of the real-world evidence cited by the PBAC (Zhao et al., 2021). Based on the sponsor's assumption, the applied compliance rate of 83% over a 24-month length of therapy results would be an 'average duration of treatment' of 19.9 months, which remains higher than the previous PBAC recommendation. The PBAC previously considered ABE use in clinical practice is likely to be less than the mean treatment duration reported in the monarchE trial (82.7 weeks, 20.7 months) due to the toxicity associated with ABE and the likely older cohort treated through the PBS and considered that a treatment duration of 18 months was a more reasonable estimate (para 7.14, abemaciclib, PSD, March 2023 PBAC Meeting). The assumption for treatment duration was tested during the evaluation in the sensitivity analyses. The PSCR maintained that applying a compliance rate of 83% over a 24-month length of therapy is equivalent to an average duration of treatment of 19.9 months and considered that this estimate was conservative. The ESC noted the PSCR argued that it is not justified to assume that abemaciclib would have a shorter treatment duration than that reported in the monarchE trial due to toxicity. The PSCR argued that ribociclib, which has previously demonstrated non-inferior safety to abemaciclib in the

metastatic setting, was shown to have a longer treatment duration in the real-world setting compared to its pivotal clinical trial (24.5 months in the real world versus 20.2 months in MONALESSA-2) (Wong et al., 2022¹⁴). However, the ESC considered the comparison inappropriate, as data from the metastatic setting is not likely to reflect the adjuvant setting and considered that the treatment duration assumed in the submission remained overestimated. The pre-PBAC response reduced the treatment duration in the financial estimates to 21 months, consistent with the economic model.

- 6.63 The current submission's estimates for use and financial impacts of listing ABE are summarised in Table 16. The financial estimates provided with the pre-PBAC response with amendments to treatment duration (21 months) and uptake rates (|% in Year 1, |% in Year 2 and |% as of Year 3) are also shown in Table 16.

¹⁴ Wong, V., de Boer, R., Baron-Hay, S., Blum, R., Boyle, F., Chua, S. et al (2022). Real-World Outcomes of Ribociclib and Aromatase Inhibitor Use in First Line Hormone Receptor Positive, HER2-Negative Metastatic Breast Cancer. *Clin Breast Cancer*, 22(8), 792-800.

Table 16: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated ^a	1	1	1	1	1	1
Number of scripts dispensed ^b	2	6	6	6	6	6
Estimated financial implications of ABE						
Cost to PBS/RPBS less co-payments	3	7	7	7	7	7
Estimated financial implications for other medicines						
Cost to PBS/RPBS less co-payments	4	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS	3	7	7	7	7	7
Net cost to MBS	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS	3	7	7	7	7	7
Pre-PBAC response						
Net cost to PBS/RPBS	5	8	9	9	7	7
March 2023 resubmission						
Net cost to PBS/RPBS	3	7	10	11	11	11

Source: Table 4-2, p35 of the submission; pre-PBAC response (pp2-3) and accompanying workbook 'A6.1_ Cost and utilisation model abemaciclib EBC November 2023_updated.xlsx'

MBS= Medicare Benefits Scheme, PBAC= Pharmaceutical Benefits Advisory Committee, PBS= Pharmaceutical Benefits Scheme, RPBS= Repatriation Pharmaceutical Benefits Scheme.

Blue shading indicates data previously seen by the PBAC.

^a From Year 2, the number of treated patients includes patients who initiate abemaciclib therapy in the previous year and continue on their second year of treatment.

^b Assuming 13.04 (=365.25/28) scripts per patient per year as estimated by the submission.

The redacted values correspond to the following ranges:

- ¹ 500 to < 5,000
- ² 20,000 to < 30,000
- ³ \$20 million to < \$30 million
- ⁴ \$0 to < \$10 million
- ⁵ \$10 million to < \$20 million
- ⁶ 40,000 to < 50,000
- ⁷ \$50 million to < \$60 million
- ⁸ \$30 million to < \$40 million
- ⁹ \$40 million to < \$50 million
- ¹⁰ \$60 million to < \$70 million
- ¹¹ \$70 million to < \$80 million

6.64 The total cost to the PBS/RPBS of listing ABE was estimated in the pre-PBAC response to be \$50 million to < \$60 million in Year 6, and a total of \$200 million to < \$300 million in the first 6 years of listing. This was reduced from a total cost to the PBS/RPBS of \$50 million to < \$60 million in Year 6, and a total of \$300 million to < \$400 million in the first 6 years of listing estimated in the submission.

6.65 The sensitivity analyses performed during evaluation are presented in Table 17, which includes revisions for uptake rates (|% in Year 1, increasing by |% per year up to |% in Year 6) and treatment duration (18 months). The cumulative effect of these changes is a decrease in the financial impact to the PBS/RPBS in the first six years of listing from \$300 million to < \$400 million in the base case to \$200 million to < \$300 million (34% reduction). When assuming the revised uptake and the mean treatment duration assumed in the economic model (21 months), the financial impact to the PBS/RPBS in the first six years of listing is \$200 million to < \$300 million (25% reduction).

Table 17: Uncertainty analyses: net financial impacts to the PBS/RPBS (performed during the evaluation)

Assumption	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	% change over 6 years
Base case	█ ¹	█ ³	█ ³	█ ³	█ ³	█ ³	-
Uptake rate of ABE (base case: █% in Years 1-6)							
█% in Year 1, increasing by 5% per year up to █% in Year 6 (SA.1)	█ ²	█ ⁴	█ ⁵	█ ⁵	█ ³	█ ³	-15.5%
Treatment duration (base case: 24 months)							
Treatment duration of 18 months (consistent with previous PBAC advice) (SA.2)	█ ¹	█ ⁴	█ ⁵	█ ⁵	█ ⁵	█ ⁵	-22.5%
Treatment duration of 21 months (consistent with economic model) (SA.3)	█ ¹	█ ⁵	█ ⁵	█ ⁵	█ ³	█ ³	-11.3%
Multivariate analyses							
(#1, #2)	█ ²	█ ¹	█ ⁴	█ ⁴	█ ⁵	█ ⁵	-34.2%
(#1, #3)	█ ²	█ ⁴	█ ⁴	█ ⁵	█ ⁵	█ ³	-24.9%

Source: Conducted during evaluation using "A6.1_Cost and utilisation model abemaciclib EBC November 2023" Excel workbook.

ABE = abemaciclib; DoT = duration of treatment; DUSC = Drug Utilisation Sub-Committee; EBC = early breast cancer; NA = not applicable; SA = sensitivity analysis.

The redacted values correspond to the following ranges:

¹ \$20 million to < \$30 million

² \$10 million to < \$20 million

³ \$50 million to < \$60 million

⁴ \$30 million to < \$40 million

⁵ \$40 million to < \$50 million

Quality Use of Medicines

- 6.66 The current submission did not provide information regarding quality use of medicines (QUM). However, activities outlined in the March 2023 resubmission to promote safe and effective use of ABE in clinical practice included online medical education modules, scientific meetings, health education symposia, and conferences.
- 6.67 The PBAC previously considered that there was unlikely to be new QUM issues given ABE is an existing therapy with a known safety profile. As such, the PBAC had agreed with the current submission that the AEs associated with adjuvant abemaciclib could be monitored and managed with dose modifications (paras 7.8 and 7.9, abemaciclib, PSD, March 2022 PBAC Meeting).
- 6.68 The March 2023 resubmission stated that the sponsor will continue to support a patient program that supplies loperamide free of charge to patients on PBS-subsidised treatment for the management of the most common AE, diarrhoea, associated with ABE treatment. The details of the provision of a loperamide support program were not described in the March 2023 resubmission nor in the current submission.

Financial Management – Risk Sharing Arrangements

6.69 The PBAC previously noted that there was significant risk in use outside the proposed restriction to patients with lower risk of recurrence than seen in the monarchE trial (para 7.14, abemaciclib, PSD, March 2022 PBAC meeting). The current submission proposed a Risk Sharing Agreement with annual subsidisation caps (SCs) with a rebate of █% for use exceeding the financial caps. The PBAC previously considered a rebate of █% for use exceeding the financial caps would be appropriate (para 7.15, abemaciclib, PSD, March 2023 PBAC Meeting).

6.70 The subsidisation cap structure provided in the pre-PBAC response for ABE over 6 years at effective AEMP is presented in Table 18.

Table 18: Subsidisation cap (SC) structure for ABE in early breast cancer (effective AEMP)

	Year 1 (2024) ^a	Year 2 (2025) ^a	Year 3 (2026) ^a	Year 4 (2027) ^a	Year 5 (2028) ^a	Year 6 (2029) ^a
Cap (\$) ^b	█	█	█	█	█	█

Source: Pre-PBAC response (pp2-3) and accompanied workbook 'A6.1_ Cost and utilisation model abemaciclib EBC November 2023_updated.xlsx'

ABE = abemaciclib; AEMP = approved ex-manufacturer price, SC= subsidisation cap.

^a Based on effective AEMP-based Commonwealth expenditure.

^b There is no discount applied up to the specified cap, and an █% discount is applied beyond that cap.

6.71 The PBAC noted the submission proposed a Risk Sharing Arrangement (RSA) with annual subsidisation caps with a rebate of █% for use exceeding the financial caps. The PBAC noted this was aligned with its March 2023 advice and considered the rebate level reasonable. However, the PBAC also noted that a shared cap for the CDK4/6 inhibitors across the adjuvant and metastatic settings may be appropriate given that the cost-effectiveness for abemaciclib in the adjuvant setting relies on reduced costs in the metastatic setting due to no repeated use of CDK4/6 inhibitors. The PBAC noted that the caps would need to be increased to account for additional patients treated with abemaciclib in the adjuvant setting, with offsets for reduced use of CDK4/6 inhibitors in the metastatic setting, consistent with the economic model.

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

7 PBAC Outcome

7.1 The PBAC recommended the General Schedule Authority Required listing of abemaciclib, in combination with standard adjuvant endocrine therapy (ET), for the treatment of hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-), lymph node positive, invasive, resected early breast cancer (EBC) at high risk of disease recurrence. The PBAC considered the evidence presented demonstrated an invasive disease-free survival (IDFS) benefit over the comparator ('ET alone') but noted that a benefit in terms of overall survival had not been demonstrated in the updated clinical trial data and therefore remained uncertain. The PBAC noted that changes to the economic evaluation and financial estimates had partially addressed the Committee's previous concerns. The PBAC advised that revisions should be made to the duration of treatment effect and the

patient age assumed in the economic model and that the listing of abemaciclib would be considered cost-effective with a price reduction. The PBAC also considered that the financial estimates remained overestimated and advised the assumed uptake rates should be reduced.

- 7.2 The PBAC noted the consumer comments emphasising the clinical need for reducing the risk of recurrence for patients diagnosed with high risk EBC and emphasising the likely clinical benefit associated with access to cyclin-dependent kinase (CDK)4/6 inhibitor therapy for these patients. The PBAC noted the consumer comments outlining the disease free survival benefits associated with abemaciclib, based on the results of the monarchE trial. The PBAC noted comments stating that the private cost of abemaciclib remained a financial burden to patients and that a PBS listing would ensure equity of access.
- 7.3 The PBAC considered that there remained a moderate clinical need for effective treatments for patients with this condition.
- 7.4 The PBAC noted that the sequential impact of listing abemaciclib in EBC to metastatic disease had not been captured in the clinical management algorithm included in the submission. The PBAC reiterated that flow on changes to all CDK4/6 inhibitors currently PBS listed in the advanced/metastatic treatment setting was required to exclude sequential use (i.e. use in early breast cancer and then use in advanced/metastatic breast cancer) as there are currently no safety or efficacy data for repeated use of CDK4/6 inhibitors.
- 7.5 The PBAC considered that the proposed restriction was appropriate, however noted that it should include a criterion that prevented use with other PBS-subsidised therapies for this condition.
- 7.6 The PBAC noted the nominated comparator, ET alone, was the same as for the March 2023 submission and considered it remained appropriate.
- 7.7 The PBAC noted additional follow-up data for the monarchE trial was provided in the Pre-Sub Committee Response (PSCR), which increased the median duration of follow-up from 42 months of data included in the submission to 54 months. The PBAC noted that the addition of abemaciclib resulted in a statistically significant reduction in IDFS (HR 0.67, 95% CI 0.59, 0.77) and distant-relapse free survival (DRFS) (HR 0.67, 95% CI 0.58, 0.77). The PBAC noted that the magnitude of relative treatment effect appears to be maintained up to the recent data cut-off (median follow-up = 4.5 years). The PBAC recalled it had previously considered that the difference in IDFS and DRFS was likely to represent a clinically meaningful benefit. The PBAC also recalled it considered that overall the claim of superior comparative effectiveness of abemaciclib + ET over ET alone was supported (para 7.7, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC considered that the updated efficacy results remain consistent with this conclusion. However, the PBAC considered that due to immature overall survival (OS) data there remained an unclear relationship between IDFS/DRFS and OS.

- 7.8 The PBAC recalled it had previously considered that abemaciclib in combination with ET was associated with inferior safety compared to ET alone, and while the risk of adverse events was likely to be greater outside the controlled clinical trial environment, the adverse events associated with abemaciclib could be monitored and managed with dose modifications (para 7.8, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC considered the claim of inferior yet monitorable and manageable safety was reasonable.
- 7.9 The PBAC noted the economic model maintained its assumption that treatment with abemaciclib would reduce the risk of recurrence and that this would result in an increase in OS. The PBAC recalled it had previously considered that it was unclear if treatment with abemaciclib results in recurrence being avoided in a proportion of patients and hence a permanent cure as claimed, or if abemaciclib delays micro-metastases progressing to macro-metastases and hence delays when recurrence occurs (para 7.9, abemaciclib, PSD, March 2023 PBAC meeting). Overall, the PBAC considered the modelled OS gain remained highly uncertain.
- 7.10 The PBAC recalled that in March 2023 it had considered that abemaciclib could be considered cost-effective if changes were made to the economic model in combination with an incremental cost effectiveness ratio (ICER) of up to \$30,000 per quality adjusted life year (QALY). The PBAC considered these amendments would account for the uncertainty regarding the modelled OS. The PBAC noted that the submission presented a revised economic evaluation and proposed further revisions in the pre-PBAC Response. The PBAC noted issues previously raised by the PBAC that remained partially addressed were:
- the treatment waning period had been reduced from 7–28.9 years (March 2023 resubmission) to 6–9 years, instead of 4–7 years as requested by the PBAC (para 6.39). The PBAC noted that the magnitude of relative treatment effect appears to be maintained with the recent July 2023 data cut-off (median follow-up = 4.5 years), and therefore considered that a treatment waning period of 5–8 years would be appropriate. The PBAC noted this length of treatment waning increased the ICER to \$25,000 to < \$35,000 per QALY.
 - The cohort starting age was increased from 52.2 years (March 2023 resubmission) to 58.5 years, instead of approximately 60 years as previously requested by the PBAC (para 6.40). The PBAC considered the cohort starting age in the model remained underestimated, and noted that an appropriate starting age of 61.4 years, based on the mean age reported in Chan et al 2021¹⁵, increased the ICER to \$25,000 to < \$35,000 per QALY.
- 7.11 The PBAC noted that the changes to treatment waning and cohort starting age

¹⁵ Chan A, O'Neil N, Lomma C, Chih H, Willsher P. BreastSurgANZ members recommendations for adjuvant systemic treatment and patient compliance in Australian breast cancer patients. ANZ J Surg. 2021 Nov;91(11):2418-2424.

outlined in paragraph 7.10 increased the base case ICER from \$15,000 to < \$25,000 per QALY to \$35,000 to < \$45,000 per QALY. The PBAC recalled it previously considered that an ICER of up to \$30,000 per QALY would be required to account for the uncertainty regarding the modelled OS (para 7.13, abemaciclib, PSD, March 2023 PBAC meeting), and noted that a further price reduction would be required to maintain an ICER of \leq \$30,000 per QALY. The PBAC also recalled it had previously considered that the cost-effectiveness of abemaciclib relied on a gain in OS and reiterated that if listed, the sponsor should provide the PBAC with the final overall survival results (or any further interim analyses) from the monarchE trial when available (planned at 650 events, or 10 years).

- 7.12 The PBAC noted that changes were made in the submission to the financial estimates that were consistent with its March 2023 advice and that further revisions were proposed in the pre-PBAC response, however considered the patient numbers estimated in the pre-PBAC response remained overestimated due to the assumed uptake rates. The submission reduced the uptake of abemaciclib from █% in Year 1 increasing to █% in Years 3–6 (March 2023 resubmission), to █% in Year 1 increasing to █% in Year 2 and █% in Years 3–6. The PBAC recalled it had previously considered a maximum uptake rate of █% would be reasonable (para 7.14, abemaciclib, PSD, March 2023 PBAC meeting) and considered that it would take longer than estimated in the pre-PBAC response to reach a level of █%. The PBAC considered an uptake of █% in Year 1 gradually increasing to █% in Year 6 would be appropriate.
- 7.13 The PBAC noted that the treatment duration was reduced from 24 months to 21 months in the pre-PBAC response, consistent with the treatment duration modelled in the economic evaluation. The PBAC recalled it had previously considered that a treatment duration of 18 months was a more reasonable estimate, as it considered abemaciclib use in clinical practice would likely be less than the mean treatment duration reported in the monarchE trial (82.7 weeks, 20.7 months) due to toxicity and the likely older cohort treated through the PBS (para 7.14, abemaciclib, PSD, March 2023 PBAC meeting). The PBAC accepted a treatment duration of 21 months to be appropriate to inform the financial estimates given consistency with the economic model, and in the context of a reduced treatment uptake (as outlined in paragraph 7.12).
- 7.14 The PBAC noted the submission proposed a Risk Sharing Arrangement (RSA) with annual subsidisation caps with a rebate of █% for use exceeding the financial caps. The PBAC noted this was aligned with its March 2023 advice and considered the rebate level reasonable. However, the PBAC also noted that a shared cap for the CDK4/6 inhibitors across the adjuvant and metastatic settings may be appropriate given that the cost-effectiveness for abemaciclib in the adjuvant setting relies on reduced costs in the metastatic setting due to no repeated use of CDK4/6 inhibitors. The PBAC noted that the caps would need to be increased to account for additional patients treated with abemaciclib in the adjuvant setting, with offsets for reduced use of CDK4/6 inhibitors in the metastatic setting, consistent with the economic model.

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for abemaciclib:

- a) The treatment is expected to provide a moderate improvement in efficacy over the comparator (ET alone) on the basis of the clinical evidence considered at the March 2023 meeting;
- b) The treatment is not expected to address a high and urgent unmet clinical need;
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items with new indication as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	Rpts	Available brands
ABEMACICLIB					
abemaciclib 150 mg tablet, 56	NEW 1 MP	1	56	5	Verzenio
abemaciclib 100 mg tablet, 56	NEW 2 MP	1	56	5	Verzenio
abemaciclib 50 mg tablet, 56	NEW 3 MP	1	56	5	Verzenio
Safety Net Rule Penalty Applies? Yes					
Restriction Summary / Treatment of Concept: [New 1]: Authority Required					
Category / Program: GENERAL – General Schedule (Code GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction Type – <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Indication: Early breast cancer					
Clinical criteria:					
The treatment must be adjuvant to surgical resection					
AND					
Clinical criteria:					

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	The condition must not have been treated with endocrine therapy for more than 6 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:
	The condition must be at high risk of recurrence at treatment initiation with this drug, with high risk being any of: (a) cancer cells in at least 4 positive axillary lymph nodes, (b) cancer cells in 1 to 3 positive axillary lymph nodes plus at least one of: (i) tumour size of at least 5 cm in size, (ii) grade 3 tumour histology (on the Nottingham grading system)
	AND
	Clinical criteria:
	The treatment must not be a PBS-subsidised benefit beyond whichever comes first: (i) a total of 2 years of active treatment (this includes any non-PBS subsidised supply if applicable), (ii) disease recurrence/progression
	AND
	Clinical criteria:
	<i>The treatment must be the sole PBS-subsidised therapy for this condition</i>
	AND
	Treatment criteria:
	Patient must be undergoing concurrent treatment with endocrine therapy where this drug is being prescribed as a PBS-benefit
	Prescribing Instructions: Retain all pathology imaging and investigative test results in the patient's medical records.
	Prescribing instructions: 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 advance or metastatic disease is no longer available).
	Administrative advice: Special Pricing Arrangements apply.
	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: 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: 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. <i>Histopathology</i> . 1991 Nov;19(5):403-10.

Flow on changes to limit subsidy of CDK4/6i therapy to once per lifetime, irrespective if prescribed for early disease or late stage disease. These include:

- Abemaciclib (11868P, 11871T, 11876C)
- Palbociclib (12822W, 12819Q, 12818P)

- Ribociclib (11385F, 11386G, 11397W)

The following prescriber instruction will be added to these listings:

Prescribing instructions: 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).
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These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

The sponsor had no comment.