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REVIEW ARTICLE

Abemaciclib in Combination with Endocrine Therapy for Adjuvant Treatment of Hormone Receptor-Positive, HER2-Negative, Node-Positive Early Breast Cancer: An Evidence Review Group Perspective of a NICE Single Technology Appraisal

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Abstract
The National Institute for Health and Care Excellence (NICE) invited the manufacturer (Eli Lilly) of abemaciclib (Verzenios) to submit evidence for the clinical and cost effectiveness of this drug in combination with endocrine therapy (ET) for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence, as part of the Institute's Single Technology Appraisal (STA) process. Kleijnen Systematic Reviews Ltd, in combination with Newcastle University, was commissioned to act as the independent Evidence Review Group (ERG). This paper summarised the Company Submission (CS), presents the ERG's critical review of the clinical and cost-effectiveness evidence in the CS, highlights the key methodological considerations, and describes the development of the NICE guidance by the Appraisal Committee. The ERG produced a critical review of the evidence for the clinical and cost-effectiveness evidence in the CS and also independently searched for relevant evidence and modified the manufacturer decision analytic model to examine the impact of altering some of the key assumptions. A systematic literature review identified the MonarchE trial, an ongoing, open-label, randomised, double blind trial involving 5637 people comparing abemaciclib in combination with ET versus ET alone. The trial included two cohorts that used different inclusion criteria to define high risk of recurrence. The ERG considered Cohort 1 as an adequate representation of this population and the AC concluded that Cohort 1 was generalisable to National Health Service clinical practice. Trial results showed improvements in invasive disease-free survival for the abemaciclib arm, which was considered an appropriate surrogate outcome. The ERG believed that the modelling structure presented in the *de novo* economic model by the company was appropriate but highlighted several areas of uncertainty that had the potential to have a significant impact on the resulting incremental cost-effectiveness ratio (ICER). Areas of uncertainty included the extrapolation of long-term survival curves, the duration of treatment effect and treatment waning, and the proportion of patients who receive other CDK4/6 treatments for metastatic disease after receiving abemaciclib. ICER estimates were £9164 per quality-adjusted life-year gained for the company's base-case and £17,810 for the ERG's base-case. NICE recommended abemaciclib with ET as an option for the adjuvant treatment of HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.

1 Introduction

Abemaciclib, tradename Verzenios, in combination with standard endocrine therapy (ET), was appraised within the National Institute for Health and Care Excellence (NICE) Single Technology Appraisal (STA) process. Health technologies must be shown to be clinically effective and to represent a cost-effective use of National Health Service (NHS) resources in order to receive a recommendation by NICE. Within the STA process, the company (Eli Lilly) provided NICE with a written submission and a mathematical health economic model, summarising the company's estimates of the clinical effectiveness and cost effectiveness of abemaciclib in combination with ET for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, early breast cancer at high risk of recurrence. The Company Submission (CS) was

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Key Points for Decision Makers

The National Institute for Health and Care Excellence (NICE) recommended abemaciclib with endocrine therapy (ET) as an option for the adjuvant treatment of hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence.

Cohort 1 of the MonarchE trial was considered an adequate representation of this population and generalisable to National Health Service (NHS) clinical practice.

Abemaciclib in combination with ET improved invasive disease-free survival and distant relapse-free survival results compared with ET alone. Abemaciclib also presented increases in adverse events related to gastrointestinal disorders and increases in severe adverse events, but the safety profile was deemed acceptable to patients given the potential benefits.

The most plausible incremental cost-effectiveness ratio was uncertain, but unlikely to be above what NICE normally considers an acceptable use of NHS resources. The ERG identified the immaturity of the clinical evidence and the lack of evidence around treatment waning over the long-term to be key sources of uncertainty.

reviewed by an Evidence Review Group (ERG) independent of NICE. The ERG, Kleijnen Systematic Reviews, in collaboration with Newcastle University, produced an ERG report [1]. After consideration of the evidence submitted by the company and the ERG report, the NICE Appraisal Committee (AC) issued guidance to recommend the technology by means of the Final Appraisal Determination (FAD), which is open for appeal. This paper presents a summary of the ERG report and the development of the NICE guidance. Furthermore, it highlights important methodological issues that were identified that may help in future decision making.

Full details of all appraisal documents (including the appraisal scope, CS, ERG report, consultee submissions, technical engagement, FAD and comments from consultees) can be found on the NICE website [2].

2 The Decision Problem

The CS and the scope used the same definition for the population, i.e. "adults with hormone-receptor positive, HER-2 negative,node-positive early breast cancer after definitive surgery of the primary risk tumour at high risk of recurrence" [3]. The MonarchE trial, an open-label, phase III study comparing abemaciclib plus ET versus ET alone [4], was used as the pivotal trial to derive the evidence for this submission. However, the intention to treat (ITT) population in the MonarchE trial was composed of two cohorts split by different definitions of 'high risk' of recurrence:

- Cohort 1 enrolled 5120 patients considered at high risk of recurrence based on pathological tumour involvement in the axillary lymph nodes (ALNs), the Bloom Richardson disease grading system, and tumour size.
- Cohort 2 enrolled 517 patients defined as high risk of recurrence based on pathological tumour involvement in ALNs and Ki-67 index scores.

The ERG requested the company to provide an operational definition of 'high risk' and to clarify which of the two cohorts in the MonarchE trial [4] is most consistent with this definition in NHS clinical practice. In its response, the company argued that 'high risk' will be defined in clinical practice based on a combination of clinical and pathological features, and that this was in line with Cohort 1 of the MonarchE trial. Furthermore, at the time of writing, the Ki-67 index was not being routinely used in the NHS for early breast cancer, therefore Cohort 2 was deemed outside the scope of analysis by the ERG and NICE (see Sect. 3.2). Although the company maintained that the ITT population was the most generalisable source of evidence, the ERG requested efficacy and cost-effectiveness analysis for Cohort 1 to best represent the NHS population.

Despite no subgroup analysis being specified by the NICE scope, the ERG requested subgroup analyses for effectiveness and cost effectiveness in pre- or postmenopausal groups of patients due to potential differences in treatment pathways, and given that the MonarchE trial randomisation was stratified by this factor [5]. The company provided results for invasive disease-free survival (IDFS) and distant relapse-free survival (DRFS) analyses for both menopausal status subgroups but not for the overall survival (OS) subgroup analysis. The company argued that results from the ITT population were still applicable for both menopausal status subgroups as the difference in hazard ratios (HRs) was not statistically significant between pre- and postmenopausal patients. However, the HR and 95% confidence intervals (CI) were higher for postmenopausal patients in the intervention arm, which the ERG highlighted as a key issue.

The intervention and comparator described in the CS were in line with the NICE scope; however, the ERG was concerned that the administration of ET might have deviated from NHS clinical practice, particularly across subgroups according to menopausal status.

3 Independent Evidence Review Group (ERG) Review

The ERG reviewed the clinical-effectiveness and cost-effectiveness evidence of abemaciclib alongside ET for this indication. As part of the STA process, the ERG and NICE had the opportunity to ask for clarification on specific issues in the CS, in response to which the company provided additional information [3]. The ERG also produced an ERG base-case to assess the impact of alternative assumptions and parameter values on the model results, by modifying the health economics model submitted by the company. Sections 3.1–3.6 summarise the evidence presented in the CS, as well as the review from the ERG.

3.1 Clinical Effectiveness Evidence Submitted by the Company

The company conducted two systematic literature reviews (SLRs) to identify relevant clinical evidence from randomised controlled trials (RCTs) and observational studies, respectively. The SLR search of RCTs was conducted in July 2019 and updated in October 2020 and December 2020. An SLR search of observational studies was conducted in August 2020. The SLR identified one RCT, the MonarchE trial, for which published literature was available [4]. Moreover, the company reported holding further unpublished data from this trial, which was presented in the appraisal.

Results for the primary outcome (IDFS) and secondary outcomes (DRFS, OS, and patient-reported outcomes) were provided in the CS. The CS and the ERG analyses focused primarily on the most recent data cut available (April 2021). The HR estimates for IDFS from Cohort 1 data alone showed higher IDFS for patients receiving abemaciclib + ET compared with ET alone. Subgroup analyses by menopausal status carried out on the ITT population suggested improvements in IDFS across both subgroups for the intervention arm. However, differences in stratified HRs for premenopausal patients relative to postmenopausal patients suggested lower IDFS in the latter subgroup, with an overlap in the 95% CIs between pre- and postmenopausal patients.

The DRFS was a measure of time spent free from metastatic recurrence (MR) of disease. Cohort 1 data suggested higher DRFS for the abemaciclib + ET arm compared with ET alone. For the menopausal status subgroup analysis on the ITT population, stratified HRs for DRFS in the abemaciclib + ET arm were lower in premenopausal patients compared with postmenopausal patients with an overlap in the 95% CIs.

The HR estimates for OS did not suggest a difference between treatment groups for the ITT population even after censoring for suspected or reported coronavirus disease 2019 (COVID-19)-related deaths. Separate data reporting HRs for OS split by menopausal status were not provided.

Data for adverse events (AEs) were derived from the latest cut of the data; with the CS, emphasising its maturity given that 90% of patients had completed or discontinued abemaciclib by this point. The incidence of grade 3 treatment-emergent AEs (TEAEs) was greater in the abemaciclib + ET arm (46%) than in the ET-alone arm (15.5%). The most frequently reported class of TEAEs for the abemaciclib + ET arm were gastrointestinal disorders, and musculoskeletal and connective tissue disorders for the ET-alone arm. Diarrhoea of any grade was the most common TEAE in the abemaciclib + ET arm (83.5%) compared with the ET-alone arm (8.6%). Severe AEs were more common in the abemaciclib + ET arm (15.2%) compared with the ET-alone arm (8.8%), with venous thromboembolic events being the most common severe AE.

3.2 Critique of Clinical Effectiveness Evidence and Interpretation

The company performed two SLRs. The first sought to identify RCTs, and the second focused on observational studies. The first review searched a comprehensive set of databases but the second only searched two databases. Full details on the searches were provided in response to the ERG clarification letter. Separate searches for safety data were not conducted.

In the first SLR, only one RCT was identified. In this RCT, participants were randomised to either placebo + ET or abemaciclib + ET across two cohorts. This trial, the MonarchE trial [4], was the basis of the clinical effectiveness evidence. The comparators in this trial were largely in line with NHS clinical practice. However, there were discrepancies between the definitions of 'high risk of recurrence' across the two cohorts: Cohort 2 was a smaller group that enrolled people using a Ki-67 index value of at least 20%. At the time of writing, the Ki-67 index score was not routinely used for early breast cancer in the NHS and its introduction was not part of the scope.

The differences between the high risk of recurrence definition in cohort 2 and in NHS clinical practice made the generalisability of the ITT population of MonarchE [4] a key issue for the ERG. Cohort 1 enrolled patients at high risk of recurrence based on clinical features that more accurately represented UK clinical practice, therefore the ERG considered results from analysis using Cohort 1 data to be more suitable for decision making.

Another key issue identified by the ERG was the high proportion of patients receiving an aromatase inhibitor instead of tamoxifen/toremifene in the ET-alone arm. This appeared inconsistent with the recommendations from NG101 [6]. Consequently, the ERG recommended a subgroup analysis

by menopausal status, as this is a determinant factor for receiving each treatment.

The company preferred the ITT population as the most generalisable source of evidence [7]. Results using Cohort 1 data alone showed higher IDFS and DRFS rates for abemaciclib + ET versus ET alone compared with results using the ITT population, but the size of the difference across both datasets was small.

The subgroup analysis by menopausal status for IDFS and DRFS was run using data from the ITT population, as Cohort 1 data were not made available. Results showed lower IDFS and DRFS for postmenopausal patients compared with premenopausal patients; however, the 95% CIs overlap. No subgroup analysis by menopausal status was performed for OS at the latest data cut because data were stated by the company as being immature.

3.3 Cost-Effectiveness Evidence Submitted by the Company

An SLR was conducted by the company to identify cost-effectiveness studies. The CS provided sufficient detail for the ERG to be able to appraise the searches conducted. A further targeted literature review (TLR) was conducted to identify UK-specific data on health-related quality of life (HRQoL) and healthcare resource use. The TLR comprised of searches of HTA websites, with an emphasis on the NICE website to retrieve relevant TA submissions reported within the previous 5 years.

The company developed a de novo model in Microsoft Excel [8], described as a cohort state transition model with five health states (see Fig. 1). Patients enter the model in (1) the IDFS state and receive ET for 5 years, plus abemaciclib for a maximum of 2 years if they are in the intervention arm; patients can remain in this state until they (2) die, experience (3) an MR, or (4) a non-MR (NMR) where patients move through this tunnel state to (5) a remission state. Patients in remission stay in this state until they die or experience an MR and move to MR. MR was modelled as an absorbing state, with cost and quality-adjusted life-year (QALY) payoffs assigned.

The NMR state is split into two substates (not shown in Fig. 1): second neoplasm, which functions as an absorbing state, and locoregional/contralateral neoplasm, which is a tunnel state. The MR state is also split into two sub-states: (1) endocrine-resistant metastasis for metastasis occurring during ET treatment or up to 12 months after treatment completion; and (2) endocrine-sensitive metastasis for metastasis occurring 12 months or onwards after ET treatment completion.

The population in the base-case model was patients with HR-positive, HER2-negative, node-positive early breast cancer. This was in line with the final NICE scope and the population of the MonarchE trial [4]. The ERG requested a subgroup cost-effectiveness analysis by menopausal status, but the company insisted that menopausal status was not an appropriate subgroup to include in the economic analysis due to between-group differences not being statistically significant [7], therefore making the assumption that absence of evidence is the same as evidence of absence.

For the intervention arm, the treatment consisted of abemaciclib 150 mg twice daily for a maximum of 2 years in combination with standard ET for up to 5 or 10 years. Patients remained on abemaciclib until disease progression or toxicity in line with the proposed license and dose received in the MonarchE trial [4, 5]. The comparator was standard ET treatment for 5 years, which consisted of aromatase inhibitors or tamoxifen. ET comprised physician's choice of standard ET used in routine clinical practice, which was costed in the model as a weighted average of these treatments, based on the proportion of patients receiving each treatment in the MonarchE trial [3]. The analysis was performed from a UK NHS and Personal Social Services (PSS) perspective. The time horizon in the model was 49 years from the starting age of 52.1 years. Discount rates at 3.5% were applied to both costs and benefits. A 28-day cycle length was implemented in the model and the half-cycle correction was applied.

The MonarchE trial [4] was the primary source of treatment effectiveness, used to inform parameters on time-to-treatment discontinuation (TTD), IDFS, and OS (without distant recurrence) curves that determined the transitions across the model. The model used parametric extrapolations to generate long-term outcomes beyond trial follow-up. A set of seven parametric distributions (exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma) and two hazard splines distributions with one or two knots were fitted to Kaplan–Meier data to generate different extrapolations. These were assessed using goodness-of-fit statistics (Akaike information criterion/Bayesian

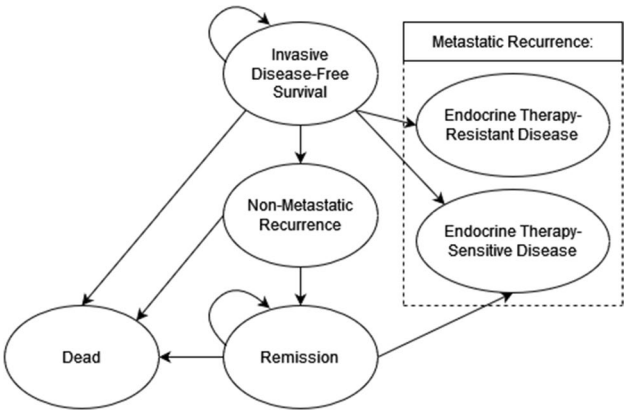

Fig. 1 Model structure

information criterion), visual assessments of the survival curves, hazard plots and comparisons with data in the published literature to determine the most appropriate model to use in the base-case.

Proportional hazards assumptions between treatment arms were tested using a log-cumulative plot, the Grambsch and Therneau test and Schoenfeld residuals visualisation, based on NICE Technical Support Document 14 [9]. For IDFS, the company found no violation of the proportional hazards assumption; hence, a single model for IDFS was selected for both arms using an adjustment factor (the HR) for the treatment effect. The 5- and 10-year IDFS rate extrapolations in the ET-alone control arm from the model were compared with estimates from the literature.

The treatment effect of abemaciclib was modelled with a fixed-effect duration lasting 8 years from treatment start, which is based on the company piecemeal analysis suggesting a treatment-effect duration beyond the end of treatment and an estimate from the literature [10]. Following this period, treatment effect begins to wane until the hazard rates of IDFS and OS (without distant recurrence) are equivalent based on TA612 [11]; full waning occurs around year 27 in the base-case model [3].

Treatment duration was determined by the TTD curves for abemaciclib and ET, respectively, in each treatment arm. TTD was based on the MonarchE trial [4, 5], where patients remained on treatment until they (1) reached a limit defined by a clinical stopping rule; (2) discontinued treatment due to toxicity; or (3) withdrew from the study or experienced recurrence. Following the same analysis steps as IDFS, the company found the proportional hazards assumption was not appropriate and instead modelled TTD independently for each treatment arm. The hazards spline 2 knots distribution was chosen as the most appropriate distribution.

OS (without distant recurrence) followed the same statistical tests and data visualisation analyses. The company assumed proportional hazards to be appropriate and a single model was fitted. The exponential distribution was chosen to extrapolate survival based on statistical fit. OS data from the MonarchE trial [4] were considered immature as the trial duration was too short to detect differences in survival across the treatment arms. OS from the UK general population [12] was used as a lower limit of the mortality rate for OS (without distant recurrence).

Once patients reach the remission state in the model, there was a probability that they suffer an MR; this was modelled from TA632 [13] and was assumed to stay constant over time based on expert opinion. In the absence of clinical data for the distant recurrence, data from TA725 based on the Monarch2 trial were used for ET-resistant metastasis, and TA563 based on the Monarch3 trial for ET-sensitive metastasis [14, 15] were assigned to the metastatic state. Finally, it was assumed that treatment arm patients receiving abemaciclib cannot receive any CKD 4/6 inhibitor treatment during an MR.

The base-case included grade III/IV and grade I/II AEs, which had an incidence of ≥ 50% (only grade I/II diarrhoea had an incidence of ≥ 50%). AE probabilities were informed by the latest cut of the MonarchE dat a[4, 5] and were assumed to occur once within the first cycle of the model for patients receiving treatment. Therefore, AEs were modelled as one-off costs and disutility values, which were then multiplied by incidence for each AE.

As no cost-effectiveness studies were identified, a further TLR was carried out to elicit potential utility data for the model. Utility values for IDFS were sourced from the MonarchE trial [4] using the EQ-5D-5L with responses cross-walked to the EQ-5D-3L value set in line with the NICE reference case [16]. Responses were collected at months 3, 9, 12, and 18; 30 days post treatment discontinuation; and during the first and second long-term follow-up visits. As the data showed no significant difference between treatment arms, the CS assumed that overall utilities were appropriate to be applied to both treatment arms instead of using treatment-specific utilities. Mean index scores were estimated using a mixed-effect model repeat measurement (MMRM) regression. The remission health state assumed that patient utility returns to the IDFS baseline. Utility data for other health states could not be sourced from the MonarchE trial.

For the NMR health state, a 3-month disutility weight was applied sourced from Lidgren et al. [17], after which patients return to the baseline IDFS utility. Utilities for the MRs were sourced from Monarch2 for ET-sensitive and Monarch3 for ET-resistant recurrences (except at the progression-free survival second-line therapy stage, which was taken from Mitra et al. [18], in line the ERG's suggestion in TA563 [14]. Baseline utility values were adjusted by age using the values reported by Szende et al. [19].

The cost categories included in the model were drug acquisition and administration, and medical procedure costs for (1) one-off interventions at the start of the treatment; (2) at the IDFS health state; (3) at the ET-resistant MR health state; and (4) at the ET-sensitive MR state in the model. A targeted review of previous technology appraisals (TAs) in early breast cancer was conducted to identify the relevant costs and four relevant technology assessment reviews (TARs) [11, 13, 20, 21]. Resource use was derived from the MonarchE trial [4] and unit costs were sourced from UK national available sources, including eMIT [22], the BNF [23] and NHS reference costs [24]. Abemaciclib was offered with a confidential Patient Access Scheme (PAS) discount.

In the company's original base-case analysis, total life-years and total QALYs gained were larger for the abemaciclib + ET arm than for ET alone. The QALY gains were mainly

driven by a larger proportion of patients staying in the IDFS state with abemaciclib + ET. Total costs were also higher for abemaciclib + ET; incremental costs mainly resulted from higher drug acquisition costs at the start of the treatment. The CS base-case incremental cost-effectiveness ratio (ICER) was £3786 per QALY gained. The company subsequently made changes to the model (correcting errors and incorporating some, although not all, ERG-recommended changes). The company's final ICER was £9164 per QALY gained. This estimate was obtained using Cohort 1 data from the MonarchE trial [4], including the PAS discount for abemaciclib but listed prices for ET in both arms. The company undertook several sensitivity scenario analyses. The scenario analysis results were most sensitive to the proportion of patients receiving CDK 4/6 inhibitors during MR, the treatment waning assumption, and the extrapolation of the IDFS curve.

3.4 Critique of Cost-Effectiveness Evidence and Interpretation

The ERG considered the range of databases searched for the SLR of cost-effectiveness studies was comprehensive. The CS also provided sufficient detail for the ERG to appraise the searches conducted. The TLR searches appeared to have been conducted as part of the SLR. The searches were conducted in August 2020; an update prior to the date of submission to NICE could have identified potentially relevant studies published between these two dates. Furthermore, the search could have included NICE TAs for other CDK 4/6 inhibitors in this setting.

The ERG and the company debated over the categorisation of the model as purely a state transition model, as its core structure shares elements of a partitioned survival model where state transitions from IDFS towards non-MR states are determined by the IDFS and OS (without distant recurrence) curves extrapolated from the MonarchE trial [4].

The ERG considered the data used to analyse the treatment effects were premature considering that the MonarchE trial is due to end in 2029 [5], and the latest cut of the data provided in the CS was from April 2021, where the proportion of participants who had completed 2 years of the study period was 72.2% [3].

The CS suggested that IDFS extrapolations for the ET-alone arm in the model presented a pessimistic scenario where predictions of patients remaining progression-free up to year 5 in the base-case were lower relative to estimates of 84.9% and 82.9% DFS rates sourced from the literature [25], with the caveat that studies from the literature were not identified systematically. The ERG found a separate systematic review and meta-analysis [26] reporting a 5-year probability of breast cancer recurrence of 17.2%, which further suggests that the company base-case model uses pessimistic assumptions for IDFS.

Following the request by the ERG to use Cohort 1 of MonarchE, the company presented their economic analysis based on this population. An economic analysis for menopausal status subgroups was not performed as subgroup data based on Cohort 1 alone were not provided despite being requested by the ERG. Furthermore, non-adherence to adjuvant hormonal therapy is a concurrent issue in this patient population [27]; the ERG felt its effect (and the impact of abemaciclib on it) was overlooked in the CS analysis.

The ERG noted there is considerable uncertainty that remains in the long-term effectiveness of abemaciclib + ET versus ET alone in extending IDFS and OS. Some uncertainties were deemed unresolvable at this time. These included:

- the functional form for treatment waning (assumed to be linear but could take other forms, yet it was not possible to determine the most appropriate functional form from the evidence presented);
- the choice of the distribution used to predict IDFS (based primarily on statistical fit rather than predictive ability, given the lack of comparable external evidence and the long period of the extrapolation relative to the trial duration; hence, most distributions presented pessimistic predictions on disease-free survival);
- the proportion of patients receiving CKD 4/6 treatments for an MR (the model assumes that patients receiving abemaciclib cannot receive CKD 4/6 treatment at recurrence anytime into the future, which was considered a strong assumption with little to no data to back it).

The health state utility values used in the economic model were considered appropriate by the ERG, the main exception was the choice by the company to use utilities for IDFS derived from the combined treatment arms instead of treatment-specific utilities. The ERG felt that this assumption was unnecessary given the format of the model. The ERG considered that different utility values should be used for different treatment arms, with the imprecision surrounding estimates explored within a probabilistic sensitivity analysis.

The MonarchE trial was likely the best available evidence for AEs [4, 5], and the ERG considered the inclusion thresholds used in the model to be acceptable. The company's approach to including disutility values for AEs was deemed consistent with previous TARs. Nevertheless, the assumption of one-off AEs in the model may underestimate the impact of AEs. The ERG disagreed in particular with the assumption of venous thromboembolic events causing no

disutility in the CS base-case model, but replacing this with a value sourced from the literature had a negligible effect on the ICER due to the low frequency of this AE. The ERG also noted a discrepancy in the cost of "delivery of subsequent elements of a chemotherapy cycle" between the CS base-case and the literature available; this was addressed in the ERG base-case and had a negligible impact on the ICER.

3.5 Additional Work Undertaken by the ERG

Based on the considerations highlighted in the ERG critique, the ERG defined a new base-case model in which various adjustments were made to the company's base-case after correcting for errors. These included:

- changing the cohort being modelled to Cohort 1 rather than the ITT population as it was deemed a more appropriate representation of the UK clinical population;
- decreasing the assumption of fixed treatment effect duration to 3 years, with linear treatment waning until year 8 and no treatment effect afterwards;
- having the probability of MR converge in both arms and reach parity as the treatment effect wanes;
- using Kaplan-Meier curves to model the TTD of abemaciclib;
- presenting a scenario analysis with a log-normal IDFS extrapolation giving less pessimistic predictions than the base-case log-logistic IDFS extrapolation;
- exploring differences in the assumptions for fixed-effect duration, treatment-effect waning, IDFS extrapolations and patients receiving CKD 4/6 treatments at MR in the scenario analysis.

The ERG did not expect large differences in utility values across treatment arms during IDFS; however, the ERG was concerned with the approach used by the company of pooling utility estimates rather than providing treatment-specific estimates and standard errors.

The ERG's final base-case ICERs for the population defined in Cohort 1 of the MonarchE trial [4], including the PAS discount for abemaciclib but list prices for all other treatments, was £17,810 per QALY gained. Caution is advised at interpreting the company and ERG's ICERs considering the large unresolved uncertainties. ERG scenarios where the treatment effect was < 3 years or where the proportion of MR patients treated with CKD 4/6 is equal in both arms increased the ICER just above £30,000. Nonetheless, the lack of evidence to accurately inform these scenarios could not be reflected in the ERG base-case.

3.6 Conclusion of the ERG Report

The ERG considered that the company complied with the majority of the NICE reference case criteria. However, at the time of writing, the ERG considered the cohort 1 population of the pivotal MonarchE trial [4] as more representative of the UK patient population than the ITT population of the trial. Furthermore, the ERG considered that a subgroup analysis for pre- and postmenopausal patients remains necessary to better understand the clinical benefits and cost effectiveness of abemaciclib + ET and help make results more generalisable. Data necessary to conduct this have not been made available. There was a large uncertainty around the ICER estimated as a product of issues with data maturity, the lack of appropriate evidence to compare the model predictions against, and the model assumptions used.

4 Key Methodological Issues

The list of key methodological issues following technical engagement was:

- *Generalisability of MonarchE results to clinical practice:* From the two cohorts composing the MonarchE trial [4], the definition of high risk of recurrence used in Cohort 1 is more likely to reflect NHS NG101 [6].
- *Lack of recognition that comparators depend on menopausal status leading to biases in the cost effectiveness:* ET treatment pathways depend on menopausal status; bias may be introduced by pooling all groups together as IDFS and DRFS outcomes are potentially better for premenopausal patients.
- *Selection of IDFS curves for treatment and comparators:* MonarchE trial data were deemed immature, leading to considerable uncertainty over the appropriate long-term survival functions included in the model.
- *Lack of long-term evidence for assumptions of fixed treatment effect duration and treatment waning:* Assumptions in the model were made under considerable uncertainty and deemed too optimistic by the ERG.

- *Medication adherence to ET not modelled:* This remains a concern in clinical practice and was potentially overlooked in the economic model.
- *The proportion of patients who receive CDK 4/6 inhibitors to treat MR disease:* Abemaciclib is a CDK 4/6 inhibitor, therefore the company assumed that patients who had abemaciclib as adjuvant therapy would not have another CDK 4/6 inhibitor later in the treatment pathway. The ERG carried out a scenario analysis where patients are equally likely to receive a CDK 4/6 inhibitor in each arm. Both scenarios were considered highly unlikely, with the true proportion deemed to be uncertain.

5 National Institute for Health and Care Guidance

On 20 July 2022, NICE recommended the use of abemaciclib with ET, within its marketing authorisation, as an option for adjuvant treatment of HR-positive, HER2-negative, node-positive early breast cancer in adults with disease at high risk of recurrence as pathological tumour involvement in at least four ALNs, or one to three ALNs and at least one of grade 3 disease or primary size tumour size of at least 5 cm [28].

5.1 Considerations of Clinical Effectiveness

On the concern raised by the ERG on the generalisability of the overall trial population from MonarchE [4] to clinical practice, the AC noted that the marketing authorisation was granted only for Cohort 1 from the trial, and concluded it is generalisable to the NHS practice. The AC also considered that abemaciclib with ET improves IDFS, which was deemed as an appropriate surrogate outcome in the absence of mature OS data; however, it recognised that the extent to which IDFS translates into OS benefits is unknown. On the issue of differences in treatment effect based on menopausal states and type of ET used, the AC concluded these were minimal and that the MonarchE Cohort 1 population is suitable for decision making. The AC also noted that for many patients, the potential benefits of abemaciclib outweigh the risk of adverse effects. The clinical experts agreed that these adverse effects are generally well tolerated but noted that they potentially increase treatment delays and burden on general practitioners and oncologists. The AC concluded that the safety profile of abemaciclib + ET is acceptable to patients.

5.2 Considerations of Cost Effectiveness

The AC concluded that the extrapolation of long-term IDFS using the log-logistic curve is a source of uncertainty, but in the absence of an alternative option, is suitable for decision making. On the assumptions for treatment effect duration and waning effect, the AC concluded that the actual duration of these that would be seen in clinical practice remains highly uncertain, hence a range of potentially plausible estimates were taken into consideration. The clinical expert considered that medication adherence rates are likely to be the same for ET alone or in combination with abemaciclib. The AC concluded that adherence to ET was not critical for decision making, and that subsequent treatment for MR disease may include a proportion of people who have another CDK 4/6 treatment, but the proportion remained unknown [28].

6 Conclusions

Both the company's and ERG's base-case results were within the range NICE normally considers an acceptable use of NHS resources. The AC was aware of the uncertainty associated with the extrapolation of IDFS data over a lifetime time horizon, treatment effect duration, and treatment waning assumptions. Therefore, the most plausible ICER was deemed uncertain; however, it was agreed that the most plausible ICER was unlikely to be above what NICE normally considers an acceptable use of health resources. Therefore, abemaciclib in combination with ET was recommended by NICE as an option for the adjuvant treatment of HR-positive, HER2-negatice, node-positive early-breast cancer at high risk of recurrence.

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Declarations

Authors' contributions The draft of this manuscript was written by Giovany Orozco Leal and all authors had the chance to comment on previous versions of the manuscript. All authors contributed to the study conception and design and all authors were involved with the work of the ERG. Nigel Armstrong acted as project lead, health economist and systematic reviewer on this assessment, critiqued the clinical effectiveness and cost effectiveness methods and evidence, and contributed to the writing of the report. Luke Vale acted as health economic project lead, critiqued the company's economic evaluation, and contributed to the writing of the report. Giovany Orozco Leal, Diarmuid Coughlan, Tomos Robinson, Asheigh Kernohan and Charlotte Ahmadu acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Susan O'Meara and Kevin McDermott acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence, and contributed to the writing of the report. Steven Duffy critiqued the search methods in the submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision

problem and their description of the underlying health problem and current service provision, contributed to the writing of the report, and supervised the project.

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Conflicts of interest Giovany Orozco Leal, Nigel Armstrong, Asheigh Kernohan, Charlotte Ahmadu, Diarmuid Coughlan, Kevin McDermott, Steven Duffy, Susan O'Meara, Tomos Robinson, Luke Vale, and Jos Kleijnen have no conflicts of interest to declare.

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References

1. Armstrong N, Vale L, Coughlan D, Orozco Leal G, Robinson T, Kernohan A, et al. Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]. York: Kleijnen Systematic Reviews Ltd; 2022.
2. National Institute for Health and Care Excellence. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence (review of TA810) [ID3857]: Committee Papers. 2022. https://www.nice.org.uk/guidance/ta810/evidence. Accessed 11 Jan 2023
3. Eli Lilly and Company Limited. Abemaciclib for adjuvant treatment of hormone receptor positive, HER2-negative, node-positive early breast cancer [ID3857]. Document B. Company evidence submission. Single technology appraisal (STA). Eli Lilly and Company Limited; 2021.
4. Johnston SRD, Harbeck N, Hegg R, Toi M, Martin M, Shao ZM, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol. 2020;38(34):3987–98.
5. ClinicalTrials.gov. Endocrine therapy with or withoutabemaciclib (LY2835219) following surgery in participants with breast cancer (monarchE). https://clinicaltrials.gov/ct2/show/NCT03155997. Accessed 11 Jan 2023.
6. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. NICE guideline 101. 2018. https://www.nice.org.uk/guidance/ng101. Accessed 11 Jan 2023.
7. Eli Lilly and Company Limited. Abemaciclib in combination with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer [ID3857]. Clarification questions. Eli Lilly and Company Limited; 2021.
8. Corporation M. Microsoft Excel. Redmond: Microsoft Corporation; 2018.
9. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data. 2011. http://www.nicedsu.org.uk. Accessed 11 Jan 2023.
10. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11(12):1135–41.
11. National Institute for Health and Care Excellence. Neratinib for extended adjuvant treatment of hormone receptor-positive, HER2- positive early stage breast cancer after adjuvant trastuzumab. Technology appraisal guidance 612. 2019. https://www.nice.org.uk/guidance/TA612. Accessed 11 Jan 2023.
12. National life tables: UK. Office for National Statistics. 2021. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed 11 Jan 2023.
13. National Institute for Health and Care Excellence. Trastuzumab emtansine for adjuvant treatment of HER2-positive early breast cancer. Technology appraisal guidance 632. 2020. https://www.nice.org.uk/guidance/TA632. Accessed 21 Dec 2022.
14. National Institute for Health and Care Excellence. Abemaciclib with an aromatase inhibitor for untreated advanced hormone-receptor positive, HER2-negative breast cancer ID1227. Technology appraisal guidance TA563. 2019. https://www.nice.org.uk/guidance/TA563. Accessed 21 Dec 2022.
15. National Institute for Health and Care Excellence. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy. Technology appraisal guidance 725. 2021. https://www.nice.org.uk/guidance/TA725. Accessed 21 Dec 2022.
16. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal. 2013. https://www.nice.org.uk/process/pmg9. Accessed 21 Dec 2022.
17. Lidgren M, Wilking N, Jönsson B, Rehnberg C. Health related quality of life in different states of breast cancer. Qual Life Res. 2007;16(6):1073–81.
18. Mitra D, Wood R, De Courcy J, Iyer S. Patient reported health utility in HR+/HER2-advanced/metastatic breast cancer. Value Health. 2016;19(7):A749.
19. Szende A, Janssen B, Cabases J. Self-reported population health: an international perspective based on EQ-5D. Dordrecht (NL): Springer; 2014. https://www.ncbi.nlm.nih.gov/books/NBK500356/. Accessed 21 Dec 2022.
20. National Institute for Health and Care Excellence. Pertuzumab for adjuvant treatment of HER2- positive early stage breast cancer. Technology appraisal guidance 569. 2019. https://www.nice.org.uk/guidance/TA569. Accessed 21 Dec 2022.
21. National Institute for Health and Care Excellence. Intrabeam radiotherapy system for adjuvant treatment of early breast cancer. Technology appraisal guidance 501. 2018. https://www.nice.org.uk/guidance/ta501. Accessed 21 Dec 2022.
22. Drugs and pharmaceutical electronic market information tool (eMIT). Department of Health and Social Care; 2018. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 21 Dec 2022.
23. British National Formulary. BMJ Group and Pharmaceutical Press. 2021. https://bnf.nice.org.uk/. Accessed 21 Dec 2022.
24. NHS Improvement, NHS England. National schedule of reference costs—year 2019/2020 - NHS trust and NHS foundation trusts.

2019. https://www.england.nhs.uk/national-cost-collection/. Accessed 21 Dec 2022.
25. Smith I, Yardley D, Burris H, De Boer R, Amadori D, McIntyre K, et al. Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor-positive, node-positive early breast cancer: final results of the randomized phase III Femara versus Anastrozole Clinical Evaluation (FACE) trial. J Clin Oncol. 2017;35(10):1041–8.
26. Salvo EM, Ramirez AO, Cueto J, Law EH, Situ A, Cameron C, et al. Risk of recurrence among patients with HR-positive, HER2-negative, early breast cancer receiving adjuvant endocrine therapy: a systematic review and meta-analysis. The Breast. 2021;57:5–17.
27. Yussof I, Tahir NAM, Hatah E, Shah NM. Factors influencing five-year adherence to adjuvant endocrine therapy in breast cancer patients: a systematic review. The Breast. 2022;62:22–35.
28. National Institute for Health and Care Excellence. Abemaciclib with endocrine therapy for adjuvant treatment of hormone receptor-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. Technology appraisal guidance TA810. 2022. https://www.nice.org.uk/guidance/ta810. Accessed 21 Dec 2022.

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