# CONFIDENTIAL UNTIL PUBLISHED

## Evidence Review Group Report commissioned by the NIHR HTA Programme on behalf of NICE

**Abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive, HER2-negative breast cancer**

## ERRATUM

Replacement pages following the factual accuracy check by Eli Lilly and Company


**Produced by** Southampton Health Technology Assessments Centre (SHTAC)

**Authors**
Dr Jonathan Shepherd, Principal Research Fellow
Mr Olu Onyimadu, Research Fellow (Health Economics)
Dr Jill Colquitt, Senior Researcher, Effective Evidence LLP
Ms Petra Harris, Research Fellow
Dr Emma Loveman, Senior Researcher, Effective Evidence LLP
Professor Joanne Lord, Professorial Fellow in Health Economics

**Correspondence to**
Dr Jonathan Shepherd
Southampton Health Technology Assessments Centre (SHTAC)
Wessex Institute
Alpha House
Enterprise Road, University of Southampton Science Park
Southampton SO16 7NS
www.southampton.ac.uk/shtac


**Date completed** 17th August 2018

## SUMMARY

### Scope of the company submission

The company submission (CS) assesses the clinical effectiveness and cost effectiveness of abemaciclib (ABE) in combination with a non-steroidal aromatase inhibitor (NSAI) in women with hormone-receptor positive (HR+), human epithelial growth factor receptor 2-negative (HER2-) advanced breast cancer. The comparators are palbociclib with an NSAI and ribociclib with an NSAI.

The decision problem accords with the NICE scope.

### Summary of submitted clinical effectiveness evidence

A good quality systematic literature review of clinical effectiveness identified one randomised controlled trial (RCT) of abemaciclib relevant to the decision problem. The MONARCH 3 trial was a double blind, phase III RCT of abemaciclib (150 mg taken orally twice daily) and NSAI (ABE+NSAI) versus (vs) placebo+NSAI (n=493 patients randomised). The NSAIs used were either letrozole or anastrozole (investigator choice). A small number of patients from the UK ([redacted]) were enrolled in the trial. MONARCH 3 was judged by the ERG to be of reasonable methodological quality, though the possibility of unblinding, imbalance in drop-outs and selective reporting of outcomes increasing the risk of bias. The ERG believes that the company has identified all the relevant available RCTs of abemaciclib.

The CS presents interim results from MONARCH 3 (pre-specified and previously published) at a median follow-up of 17.8 months (data cut-off 31st January 2017), and results at the final progression free survival (PFS) assessment (from a confidential clinical study report) at a median follow-up of [redacted] months (data cut-off 3rd November 2017). Analyses were from an intention-to-treat (ITT) population for the majority of outcomes. The primary outcome of PFS (defined as the date of randomisation to objective progression or death) was investigator-assessed at the interim and final analysis. An independent review of PFS was also undertaken at both assessments.

There are no known trials of ABE+NSAI compared with the scoped comparators palbociclib (PAL) and ribociclib (RIBO). The CS present a Bayesian network meta-analysis (NMA) using published methods to perform indirect comparisons with these (and other) comparators (we refer to this as the 'first-line treatment NMA' in this report). A broad range of (non-scoped) comparator treatments were eligible from the SLR informing the NMA to allow a fully connected network. The NMA included a total of 18 RCTs, though only four of these were directly relevant to the decision problem: The MONARCH 3 trial of abemaciclib; the MONALEESA-2 trial of ribociclib; the PALOMA-1/TRIO-18 and PALOMA-2 trials of palbociclib (all with respective NSAIs). The ERG believes the SLR has identified all relevant RCTs. OS and PFS results from this NMA are used to inform the economic model: PFS results inform the time to first progression estimate and OS results inform the estimate of deaths before first progression (see below for a description of the economic model).

The company also briefly presents an additional NMA (in an appendix) to provide relative OS and PFS estimates for second line treatments included in the cost-effectiveness model. The phase III MONARCH 2 RCT, which compares abemaciclib and fulvestrant to placebo and fulvestrant, is indirectly compared with trials of other endocrine therapies for patients who have progressed following first-line treatment for advanced breast cancer. This NMA (referred to in this report as the 'second-line treatment' NMA) was necessary as the OS data from the MONARCH 3 trial are immature and the economic model therefore includes a PFS2 health state to estimate OS from abemaciclib indirectly via the effects of second-line and subsequent treatment lines.

*In the MONARCH 3 trial at the final PFS analysis:*
Investigator assessed median PFS was [redacted] months in the ABE+NSAI group compared with [redacted] in the placebo+NSAI group; HR [redacted] (95% CI [redacted], 2-sided [redacted]), giving a reduction in the risk of progression of disease or death of 46%. Expert clinical advice to the ERG is that these results are clinically meaningful.

Median OS was [redacted], HR [redacted] (95% CI [redacted] 2-sided stratified log-rank [redacted]). [redacted] the OS rate at 24 months (ABE+NSAI [redacted] vs placebo+NSAI [redacted] OS data are currently immature ([redacted] events recorded, with final OS analysis to be done after 315 events)

- progression on first-line treatment. We note, however, that the first line NMA indicated similar treatment effects for abemaciclib, ribociclib and palbociclib. This conflicts with the larger advantage predicted for abemaciclib when estimated directly from MONARCH 3 data. A similar issue arises when estimating the first-line pre-progression death rate, but in the opposite direction: direct estimation from MONARCH 3 for ABE+NSAI (jointly estimated with NSAI) gives a higher mortality rate than when this parameter is estimated from the NMA relative effects. Given that the decision problem is focussed on comparison between abemaciclib, ribociclib and palbociclib, it is important that comparators are modelled in a consistent way, and the NMAs are best source of evidence to judge relative treatment effects.
- At second-line, the company use data from a sub-set of patients in the MONARCH 2 trial to estimate PFS and OS for second-line fulvestrant, with other drugs modelled relative to these survival curves using NMA results. As noted above, we have concerns over heterogeneity of the second-line trials and hence over the robustness of the NMA.
- The company choose to model second-line OS with an exponential curve fitted to the fulvestrant arm of MONARCH 2, and long-term extrapolation based on the CONFIRM trial. We disagree with this approach. Firstly, because the exponential curve had a poor fit to the MONARCH 2 data. Secondly, because very little information is provided to justify the fitting of the Weibull survival curve to the CONFIRM trial data. Based on evidence of goodness-of-fit and consideration of the plausibility of extrapolations, we consider the Gompertz or Log-logistic curves fitted to MONARCH 2 data are likely to be more reliable.
- Regarding the company's utility estimates in the base case, we suggest that the value used for second-line progression-free survival (0.69) in the final version of the TA496 appraisal looks more realistic than the original estimate, which is higher than the company's estimated for first-line utility.
- Our main concern over resource use assumptions: that the estimated use of second and third-line treatments does not reflect current NHS practice. In particular, the company includes fulvestrant which is not recommended by NICE in this context.

**Summary of additional work undertaken by the ERG**

We identified four minor errors in the coding of the model, which we correct. These made very little difference to the company's results. We also ran a range of scenario analyses to test

# 1 Introduction to the ERG Report

This report is a critique of the company's submission (CS) to NICE from Eli Lilly and Company Limited on the clinical effectiveness and cost effectiveness of abemaciclib with an aromatase inhibitor for untreated advanced hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer. It identifies the strengths and weaknesses of the CS. Clinical experts were consulted to advise the Evidence Review Group (ERG) and to help inform this report.

Clarification on some aspects of the CS was requested from the company by the ERG via NICE on (11th July 2018). A response from the company via NICE was received by the ERG on 26th July 2018 and this can be seen in the NICE committee papers for this appraisal.

# 2 BACKGROUND

## 2.1 Critique of company's description of underlying health problem

The company presents an accurate overview of breast cancer and its pathogenesis in CS section B.1.3. Breast cancer is the most common cancer amongst women in the UK (age-standardised incidence rate of 95.0 per 100,000[1]) and is responsible for 7% of all cancer deaths in the UK (mortality rate of 17.1 per 100,000[1, 2]). The annual breast cancer incidence in England and Wales is 0.08% (~46,700 women),[3-5] of which approximately 90% of patients are diagnosed with invasive breast cancer.[3] The majority of these women (95%) are estimated to have early and locally advanced disease,[3] in which the cancer has not spread to other parts of the body. Approximately 35% of these women progress to advanced metastatic breast cancer,[3] where the disease has spread (metastasised) to other parts of the body (e.g. bones, liver, and lungs) or has grown into tissues and is unable to be removed completely by surgery.[6] An estimated 13% of women in the UK have advanced breast care at diagnosis.[3, 7] Advanced breast cancer is associated with poorer outcomes and is incurable, with a median overall survival (OS) of 2–3 years.[8]

The population of relevance to this appraisal is people with untreated advanced HR+ and HER2- breast cancer. Breast tumours are tested for oestrogen receptors (ER) and progesterone receptors (PgR), which stimulate tumour growth. ER+ or PgR+ tumours are commonly referred to as being HR+. The majority of HR+ tumours are both ER+ and PgR+, while around 15% to 20% are ER+ only. Patients with HR+ breast cancer generally have an improved prognosis.

The ERG queried with clinical experts whether the inclusion of locoregionally recurrent breast cancer would potentially exclude patients with newly occurring (de novo) locally advanced breast cancer. The experts clarified that in routine practice the majority of these patients would be treated with chemotherapy in an attempt to downstage them and they would then receive surgery. The patients are unlikely to be entered into palliative treatment trials such as those relevant to this appraisal.

The company's decision problem reflects the patient population in the pivotal clinical trial of abemaciclib included in the CS (MONARCH 3[13] - see Table ).

### 2.3.2 Intervention

The description of the intervention (abemaciclib + non-steroidal AI [ABE+NSAI]), is appropriate to the NHS and the NICE scope. Abemaciclib is a selective dual inhibitor of cyclin-dependent kinase 4 and 6 (CDK4 and 6). The starting dose of abemaciclib is 150 mg twice daily, reflecting the recommended dose of abemaciclib in the draft Summary of Product Characteristics (SmPC) when used in combination with endocrine therapy.[14] Abemaciclib should be taken continuously as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs. Dose interruption and/or dose reduction due to adverse events are recommended (see Table 1), such as for hematologic toxicities, diarrhoea and increased alanine aminotransferase levels.

**Table 1 Dose adjustment recommendations for adverse reactions**

| **Draft SmPC[14]** | **Abemaciclib dose combination therapy** |
|---|---|
| Recommended dose | 150 mg twice daily |
| 1st dose adjustment | 100 mg twice daily |
| 2nd dose adjustment | 50 mg twice daily |
| 3rd dose adjustment | - |

The decision problem states that either anastrozole or letrozole can be chosen as the NSAI to be used in combination with abemaciclib.

### 2.3.3 Comparators

The comparators are palbociclib + NSAI (PAL-NSAI) (letrozole) and ribociclib + NSAI (RIB+NSAI) (letrozole). These are appropriate for the NHS and reflect the NICE scope. Clinical experts advising the ERG consider palbociclib and ribociclib equivalent in effectiveness and safety, and the choice between them would be down to patient and clinician preference.

### 2.3.4 Outcomes

The outcomes stated in the CS scope are overall survival (OS), progression-free survival (PFS), tumour response rate, adverse effects of treatment and health-related quality of life (HRQoL). These are standard outcomes measured in cancer treatment trials and reflect those in the NICE scope.

### 2.3.5 Economic analysis

The economic analysis described in the decision problem is appropriate for the NHS. Cost-effectiveness is expressed in terms of the incremental cost per quality-adjusted life years (QALY) and costs are considered from the perspective of the NHS and personal social services (PSS), with a 35-year time horizon, using a Markov state-transition model with a fixed 'pay-off' for post-progression survival (see section **Error! Reference source not found.** of this report for further description of the economic analysis).

### 2.3.6 Other relevant factors

The NICE scope does not contain any patient subgroups. The CS presents a summary of subgroup analyses of PFS and OS from the MONARCH 3 trial of abemaciclib (CS Appendix E). These are discussed in further detail in section 3.1.6 and section 3.3.6 of this report.

The company does not identify inequality issues that could be associated with the introduction or provision of abemaciclib (CS Section B.1.4).

Around 40% of patients had de novo metastatic disease (slightly higher in the ABE+NSAI arm, Table 3) and approximately 44% had prior endocrine therapy in the neo(adjuvant) setting (slightly higher use of (neo)adjuvant NSAI in the placebo+NSAI arm).

The CS summarises selected categories of concomitant medication use (Table 3). Nearly all the patients received concomitant medication regardless of treatment allocation (ABE+NSAI [redacted], placebo+NSAI [redacted]), with details only reported for treatment received in [redacted] of patients. Differences between the treatment arms existed in the use of loperamide (an antidiarrhoeal) (ABE+NSAI [redacted] vs placebo+NSAI [redacted]) and therefore also in the antidiarrhoeal category (ABE+NSAI [redacted] vs placebo+NSAI [redacted], both [redacted] in patients receiving abemaciclib. Use of ≥1 antiemetics + anti-nauseants, erythropoietic agents, granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor [redacted] in patients receiving abemaciclib compared with placebo.

**Table 2 Population as defined in the NICE scope, MONARCH 3, company decision problem and anticipated marketing authorisations**

| NICE final scope | Trial inclusion (MONARCH 3) | Company decision problem | Anticipated EMA marketing authorisation (CS p10)[b] |
|---|---|---|---|
| People with advanced HR+/HER2− breast cancer that has not been previously treated with endocrine therapy | Postmenopausal women (≥18 years) with HR+/HER2− locoregionally recurrent or metastatic breast cancer who had no prior systemic therapy in the advanced setting<br><br>Exclusion criteria: prior (neo) adjuvant ET with a disease free interval of ≤12 months from completion of treatment | Postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease (patients who have received treatment with endocrine therapy in the (neo)adjuvant [a] setting with a disease-free interval >12 months from completion of ET are included). | Abemaciclib is expected to be indicated for the treatment of women with HR+/HER2− locally advanced or metastatic breast cancer:<br>• in combination with an aromatase inhibitor as initial endocrine-based therapy (current appraisal) or in women who have received prior endocrine therapy<br>• in combination with fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy" |

[a] As defined in the MONARCH 3 trial

[b] Updated from the CS following the positive opinion for abemaciclib from the Committee for Medicinal Products for Human Use (CHMP) on 26th July 2018.

[a] Race was self-reported; [b] Data was missing for remaining patients; [c] Percentage does not equal 100% as the result of rounding; [d] For one patient in the placebo+NSAI arm, HR status and HER2 status were missing. The patient was not treated; [e] Treatment-free interval was calculated only for patients with prior endocrine therapy.

### 3.1.4 Description and critique of the approach to validity assessment

Quality assessment of MONARCH 3 was undertaken by the company using NICE recommended criteria. A comparison of the company and ERG judgements for MONARCH 3 can be seen in Table 4.

**Table 4 Company and ERG assessment of trial quality for MONARCH 3**

| NICE QA Criteria for RCT[a] | CS response | ERG response |
|---|---|---|
| 1. Was the method used to generate random allocations adequate? | Low | Low |
| 2. Was the allocation adequately concealed? | Low | Low |
| 3. Were the groups similar at the outset of the study in terms of prognostic factors, e.g. severity of disease? | Low | Low (for most characteristics but not duration of disease or treatment-free interval, see section 3.1.1) |
| 4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)? | Low | Unclear: adequate blinding described but high frequency of adverse events such as diarrhoea in the ABE+NSAI arm could lead to unblinding. |
| 5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for? | Low | High: [redacted] |
| 6. Is there any evidence to suggest that the authors measured more outcomes than they reported? | Low | Low. However, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast 23 (EORTC QLQ-BR23) was measured in MONARCH 3, but this is not mentioned in the CS or trial publication (mentioned in the CSR). |
| 7. Did the analysis include an intention to treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? | Low | Low |

[a] Low = low risk of bias, high = high risk of bias, unclear = uncertain risk of bias.

The ERG agrees with most of the company's judgements for MONARCH 3, but notes that the higher frequency of adverse events such as diarrhoea in the ABE+NSAI arm could have led to unblinding of patients and care providers. This may potentially increase the risk of performance bias and detection bias (particularly affecting self-reported outcomes such as HRQoL). The reasons for discontinuation were not presented by trial arm in the CS; these were requested by the ERG and provided in clarification response A3. [redacted]

[redacted]. The ERG judged the MONARCH 3 trial to have a risk of selective reporting bias, as the EORTC QLQ-BR23 trial was measured but not reported. The ERG obtained these results from the CSR.

### 3.1.5 Description and critique of company's outcome selection

The outcomes selected by the company are appropriate to the NICE scope and are commonly measured in a cancer trial. The details in the CS generally concur with those reported in the MONARCH 3 trial publication[13] and CSR except where stated below. The ERG consider that the outcomes appear to have been predefined.

The primary outcome of the MONARCH 3 trial was investigator-assessed PFS as defined by RECIST (RECIST: Response Evaluation Criteria in Solid Tumours) version 1.1.[15] PFS was measured from the date of randomisation to the date of objective progression or death due to any cause. A randomly selected subset of scans (number of scans not stated) was independently and blindly reviewed by a panel of radiologists at the interim analysis, and at the final analysis a full independent review of PFS was performed. The CS provides results for both investigator and independently reviewed PFS at both interim and final analysis, which the ERG considers appropriate.

Baseline tumour measurements (RECIST 1.1) were performed within 28 days of randomisation and then on Day 21–28 of every second cycle (approximately every eight weeks) between cycle 2 and cycle 18 and on day 21–28 of every third cycle (approximately every 12 weeks) after cycle 18, and then within 14 days of clinical progression. The finding of a new lesion was required to be unequivocal and not attributable to something other than a tumour. In the non-measurable, bone only disease cases, appearance of one or more new lesions (in bone or outside of bone), or unequivocal progression of existing bone lesions was required.

- For those patients with locoregionally recurrent disease (around 3%) the CS states that in those in whom surgery was performed while on study with evidence of residual disease postoperatively, new baseline measurements should have been assessed. The CSR also describes that in [redacted]

- Proportions with at least one TEAE related to treatment as judged by the investigator ([redacted] abemaciclib + NSAI vs [redacted] placebo + NSAI);
- Proportions with grade ≥3 TEAEs (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted], with [redacted] and [redacted] considered related to study treatment as judged by the investigator, respectively);
- Proportions with at least one serious adverse event (SAE) (abemaciclib + NSAI arm [redacted] vs placebo + NSAI arm [redacted]);
- Serious adverse events considered related to study treatment as judged by the investigator (abemaciclib + NSAI group [redacted] placebo + NSAI group [redacted];
- Discontinuations of all study treatments (abemaciclib plus NSAI arm [redacted] vs placebo plus NSAI arm 3.1%).

The CS provides details of TEAEs (grades 1-4 and all grades) occurring in at least 15% of participants in CS Table 16 (CS p69), not reproduced here. All TEAS, with the exception of arthralgia and back pain, occurred more frequently in the abemaciclib + NSAI arm. At any grade, diarrhoea ([redacted]), infections/infestations ([redacted]), neutropenia ([redacted]), fatigue ([redacted]) and nausea ([redacted]) were the most frequently experienced TEAEs in the abemaciclib plus NSAI arm. Infections/infestations ([redacted]), fatigue ([redacted]), diarrhoea ([redacted]), nausea ([redacted]) and arthralgia ([redacted]) were the most frequently experienced TEAEs of any grade in the placebo plus NSAI arm. At grade 3 or higher, the most commonly experienced TEAEs in the abemaciclib + NSAI arm were neutropenia ([redacted] grade 3 / [redacted] grade 4); diarrhoea ([redacted] grade 3 / [redacted] grade 4, see below for more details of diarrhoea); leukopenia ([redacted] grade 3 / [redacted] grade 4); infections and infestations ([redacted] grade 3 / [redacted] grade 4) and anaemia ([redacted] grade 3 / [redacted] grade 4) Table 14. Rates of grade 3 or 4 TEAEs in the placebo + NSAI arm were low; there were no events that were reported more commonly than others, see **Error! Reference source not found.** for those most commonly reported in the abemaciclib + NSAI arm.

Specific TEAEs related to study treatment were not reported in the CS but were identified in the CSR addendum from the final analysis. Any grade diarrhoea made up the majority of these events in both the abemaciclib + NSAI arm ([redacted]) and the placebo + NSAI arm ([redacted]); the majority of which were grade 1 or 2. Rates of other TEAEs related to study treatment that were commonly experienced included any grade neutropenia ([redacted] and [redacted] in the abemaciclib + NSAI arm and placebo + NSAI groups respectively, with [redacted] of ≥grade 3 in the former group) fatigue ([redacted] and [redacted] in the abemaciclib + NSAI arm and

### 4.3.2 Decision problem

#### 4.3.2.1 Population

While the NICE scope considers a broad population of people with advanced HR+/HER2- breast cancer, the decision problem addressed by the company is narrowed to address postmenopausal women with advanced HR+/HER2− locoregionally recurrent or metastatic breast cancer who have had no prior systemic therapy for advanced disease. No patient subgroups are included in the NICE scope of the CS.

The modelled cohort is women of 65 years and above. To estimate drug doses for intravenous treatments, a body surface area (BSA) of 1.70 $m^2$ was calculated indirectly. Given that BSA data were not collected directly from the MONARCH 3 trial, height and body weight were used to estimate BSA using a published formula. An average weight of 67.99kg and a height of 158.41cm were used for this estimation.

#### 4.3.2.2 Interventions and comparators

The comparators in the model are palbociclib or ribociclib with an aromatase inhibitor, which are currently licensed for use in the UK NHS and correspond to the NICE scope.

The first-line NMA and economic model treat the NSAIs letrozole and anastrozole as a single class (i.e. similar in efficacy and safety). This reflects conclusions in previous NICE appraisals that in clinical practice AIs are considered to be equivalent, with similar effectiveness and acquisition costs (NICE TA495 and TA496).

In the previous NICE appraisals TA495 and TA496, the committees also considered NSAI monotherapy as a comparator for ribociclib + NSAI and palbociclib + NSAI. However, NSAI monotherapy is not specified as a comparator in the scope for this current appraisal. The company includes NSAI as a reference treatment in the first-line NMA and in the economic model. We therefore report input parameters and results for NSAI to provide context for the included comparators.

#### 4.3.4.3.4 Overall survival calibration

A 'partial surrogacy' assumption is applied by calibrating the time spent in the fixed-pay-off sub-model until a desired ratio between median PFS gain and median OS gain for the first-line comparators relative to NSAI is achieved. The target for the calibration is 27.5% in the company base case. To achieve this target, the calibration weights are: 1.22 for ABE+NSAI; 1.16 for PAL+NSAI; 1.25 for RIBO+NSAI; and 1 for the reference treatment NSAI (CS Table 25, CS section B.3.3.7). For each comparator, the same weight is applied to all second-line event rates (progressions, deaths before progression and deaths after progression), thus holding the proportion of time spent in the three second-line health states (PFS2, PPS and death) constant. The calibration is implemented using the Excel 'goal seek' function. This is also applied within each PSA iteration; so, a different set of calibration factors is estimated for each iteration. Uncertainty over the calibration target itself is not reflected in the PSA. The company conducts a scenario analysis with 'full surrogacy' (i.e. calibration weights of 1 for all comparators).

The base case target of 27.5% surrogacy reflects the 'lower bound' specified by the committee for the NICE appraisal of palbociclib (TA495), based on fitting an exponential curve to final OS and PFS data from the PALOMA-1 trial. The TA495 committee concluded that the extension of PFS1 is likely to result in some improvement in OS, although the choice between the lower bound (27.5%) and upper bound (100%) is a source of uncertainty. The NICE DSU reviewed evidence on the relationship between PFS and OS, concluding that evidence on full surrogacy is 'inconclusive'.[39] Similarly, the NICE committee for appraisal TA496 concluded that ribociclib + NSAI improves PFS, that this is likely to result in some improvement in OS, that a degree of partial surrogacy is 'probably more likely' than full surrogacy, but that the magnitude of the relationship is highly uncertain.

> **ERG conclusion**: We consider that the company have correctly implemented the calibration and that they test an appropriate the range of assumptions about the magnitude of the surrogacy relationship between OS and PFS, as requested by previous NICE appraisal committees TA495 and TA496 (from 27.5% to 100% surrogacy). We also test the conservative assumption of no surrogacy and other intermediate values in our analyses.

### 4.3.5 Health related quality of life

#### 4.3.5.1 Health state utilities

The company report a systematic literature review of utility studies (CS B.3.4.1 and Appendix H) but conclude that studies found were not representative of the population of interest. Instead, utilities for the model are estimated from analysis of EQ-5D-5L data from MONARCH 3 and MONARCH 2 and from previous NICE appraisals – reported in CS Tables 26, 27 and 28 (B.3.4.2). We summarise sources in Table 23 and discuss further below.

**Table 23 Health state utility estimates**

| Source | PFS1 | PFS2[a] | PPS | Comments |
|---|---|---|---|---|
| **Company analysis** | | | | |
| **Base case** | [redacted] Overall | 0.745[a] | [redacted] | MONARCH 3 Model 1 for PFS1. Others from TA496 |
| Scenario 1 | [redacted] NSAI<br>[redacted] Other | 0.745[a] | 0.505 | Treatment specific PFS1 from MONARCH 3 (Model 2) |
| Scenario 2 | 0.774 | 0.745[a] | 0.505 | PFS1 assumed equal to PFS2 (without chemotherapy) |
| Scenario 3 | [redacted] | [redacted][a] | 0.505 | PFS2 from MONARCH 2 pre-progression utility |
| Scenario 4 | [redacted] | 0.745[a] | [redacted] | PPS estimated from MONARCH 3 progression disutility applied to PFS1[c] |
| **Company estimates form trial data** [b] | | | | |
| **MONARCH 3** | [redacted] Overall<br>[redacted] NSAI<br>[redacted] ABE+NSAI | [redacted] | | EQ-5D-5L adjusted for repeated measures, baseline utility and progression, with / without treatment arm |
| **MONARCH 2** | | [redacted] | [redacted] | As above, without treatment |
| **Previous NICE appraisals** | | | | |
| **TA495** (palbociclib) | 0.72 Overall<br>0.71 NSAI<br>0.74 PAL+NSAI | 0.505 | 0.505 | PALOMA 2 EQ-5D-3L, mean baseline values for PFS1. Estimated from Lloyd et al.[37] by ERG.[51] |
| | | | | |
| **TA496** (ribociclib) | Redacted in committee papers | 0.774 initial<br><br>0.690 final, suggested by DSU | 0.505 | PFS1 from MONALEESA-2 EQ-5D-5L mixed model for repeated measures. PFS2 based on Lloyd et al. model [37] adjusted for BOLERO-2 age and response. DSU proposed reduction.[39] |

| | | | | |
|---|---|---|---|---|
| Exemestane | 37.0% | 6.2% | 15% | 5% |
| Tamoxifen | 18.5% | 7.7% | 20% | 10% |
| **Everolimus + exemestane** | **8.0%** | **0.0%** | **40%** | **10%** |
| **No treatment** | **0.0%** | **45.6%** | **0%** | **15%** |

These are based on assumptions in the NICE appraisal of fulvestrant for untreated HR+ advanced breast cancer (TA503)[57] and the company's assumption that NSAIs would not be used following use at first line.

**ERG conclusion**: Clinical advice to ERG suggests that these distributions do not reflect current NHS practice and policy. Fulvestrant is not used at second or third line, because it is not recommended by NICE (TA239) and fewer patients have exemestane monotherapy now that everolimus + exemestane are recommended by NICE (TA421). At third-line, a greater proportion of patients have chemotherapy (around 50%), with few patients receiving no treatment (10-15%). NSAIs may also be used sometimes at third-line. We test the impact of a scenario based on this clinical advice in ERG analyses.

#### 4.3.6.2 Duration of treatment

We summarise methods used to model treatment duration in Table 26. For first- and second -line treatments, similar methods are used as for TTP and PFS: with parametric survival curves fitted to MONARCH 3 (NSAI and ABE+NSAI) and MONARCH 2 (FUL), adjusted for other comparators with hazard ratios. However, as time to discontinuation is not reported in trial publications, hazard ratios were estimated based on reported median treatment durations. Third line treatment is only included in the model as a cost, applied for a fixed proportion of time spent in the PPS health state.

**Table 26 Time to treatment discontinuation**

| | | **Treatment** | **Base case** | | **Source** |
|---|---|---|---|---|---|
| TTD1 | Time to discontinuation of first-line treatment | NSAI<br>ABE+NSAI | Gamma survival curves (joint fit) | | MONARCH 3, IC-adjusted (CS Figures 24 & 25) |
| | | [redacted] | [redacted] | | Hazard ratios estimated from median times on treatment (CS Appendix M Table 68 M.2.4) |
| | | [redacted] | [redacted] | [redacted] [a] | |
| | | PAL+NSAI | 19.8 months | HR 0.81 [b] | |
| | | RIBO+NSAI | 20.3 months | HR 0.79 [b] | |
| TTD2 | Time to discontinuation of second-line treatment | FUL | | | |
| | | [redacted] | [redacted] | | Hazard ratios relative to fulvestrant, estimated from median times on treatment (CS Appendix M Table 78 M.2.4) |
| | | ANAS | 5.6 months | HR 1.43 | |
| | | LTZ | 5.9 months | HR 1.36 | |
| | | EXE | 4.4 months | HR 1.84 | |
| | | TMX | 4.4 months | HR 1.84 | |
| | | EVE+EXE | 7.8 months | HR 1.03 | |
| | | CAP | 4.8 months | HR 1.66 | |

| | | | | | |
|---|---|---|---|---|---|
| | | PAC | 4.8 months | HR 1.66 | |
| | | DOC | 4.8 months | HR 1.66 | |
| Third line: proportion of time in PPS spent on treatment | | | 37% | | |

[a] Relative to NSAI. Not used in company base case (included here for reference).

[b] Relative to ABE+NSAI.

Time to discontinuation of first-line treatment (TTD1) with ABE+NSAI and NSAI is estimated using parametric survival models fitted to MONARCH 3. Estimation methods are similar to those for TTP1 (see CS section B.3.3.5 and CS Appendix M.1.2 and M.2.4). The company concludes that treatment effects are multiplicative over time, rather than proportional, and that the log-normal, gamma and Gompertz models provide a good fit to the observed data. However, as treatment continuation is constrained by progression (modelled as an exponential), the company ruled out the log-normal and Gompertz curves for the base case (they 'overshoot' progression). They therefore chose the gamma distribution for TTD1, with log-normal, Gompertz and exponential curves used as scenarios. Note the model does also constrain time to discontinuation to not exceed time to progression. Time to discontinuation of the other first-line comparators (PAL+NSAI and RIBO+NSAI) was estimated relative to NSAI using hazard ratios estimated from median times to discontinuation. The resulting TTD1 extrapolation curves are shown in CS Figure 26.

The process for fitting time to discontinuation of second-line treatment (TTD2) was similar to that for PFS2 (CS section B.3.3.6 and CS Appendix M.1.5 and M.2.8). Joint parametric survival curves were fitted to MONARCH 2 data, although only the curve for the fulvestrant curve was used in the model. The company concluded that there was no evidence of violation of the proportional hazards assumption and that the Gompertz curve has the best fit to trial data. However, this overshoots progression, modelled with an exponential curve. The company decided to use an exponential curve for TTD2 in the base case and Gompertz and log-logistic curves for scenario analysis. Consideration of CS Figure 37, which shows the fitted parametric curves in relation to the Kaplan-Meier curve for the fulvestrant arm of MONARCH 2, indicates that exponential does provide a reasonable fit for TTD2.

#### 4.3.6.2.1 Duration of third-line treatment

The company estimates time on third-line therapy, calculated based on an assumption that patients spend approximately 37% of their time on treatment after progression from second-

**Table 35 Company scenario results (ERG corrected)**

| Scenarios | Treatments | Total costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICER ABE+NSAI vs. comparator |
|---|---|---|---|---|---|
| **Discount rates: 0.00%** | NSAI | 63,783 | 3.381 | Referent | £212,804 |
| | PAL+NSAI | 170,307 | 3.721 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 172,946 | 3.735 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 144,531 | 3.760 | £212,804 | - |
| **Discount rates: 6.00%** | NSAI | 51,717 | 2.774 | Referent | £279,586 |
| | PAL+NSAI | 141,688 | 3.014 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 120,879 | 3.021 | £279,586 | - |
| | RIBO+NSAI | 143,775 | 3.025 | £6,988,613 | £6,988,613 |
| **ABE+NSAI treatment effects for PFS: NMA** | NSAI | 56,152 | 2.997 | Referent | £341,663 |
| | ABE+NSAI | 130,514 | 3.215 | £341,663 | - |
| | PAL+NSAI | 152,268 | 3.273 | Ex Dominated | £376,720 |
| | RIBO+NSAI | 154,559 | 3.285 | £343,915 | £343,915 |
| **Interval censoring unadjusted** | NSAI | 56,152 | 2.997 | Referent | £250,352 |
| | PAL+NSAI | 152,268 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.291 | £250,352 | - |
| **Covariate and interval censoring adjusted** | NSAI | 58,122 | 3.127 | Referent | £223,086 |
| | RIBO+NSAI | 161,058 | 3.400 | Dominated | ABE+NSAI Dominant |
| | PAL+NSAI | 159,934 | 3.400 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 142,262 | 3.504 | £223,086 | - |
| **TTP1 Weibull** | NSAI | 56,305 | 3.018 | Referent | £240,299 |
| | PAL+NSAI | 155,494 | 3.311 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,213 | 3.322 | £240,299 | - |
| | RIBO+NSAI | 158,148 | 3.327 | £5,606,781 | £5,606,781 |
| **TTP1 Gompertz** | NSAI | 56,506 | 3.051 | Referent | £215,479 |
| | ABE+NSAI | 127,893 | 3.382 | £215,479 | - |
| | PAL+NSAI | 162,059 | 3.396 | £2,469,570 | £2,469,570 |
| | RIBO+NSAI | 165,016 | 3.399 | £935,832 | £2,184,412 |
| **PFS2 Weibull** | NSAI | 55,987 | 3.007 | Referent | £256,648 |
| | PAL+NSAI | 152,229 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,529 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,528 | 3.294 | £256,648 | - |
| **PFS2 Gompertz** | NSAI | 55,226 | 3.045 | Referent | £278,905 |
| | PAL+NSAI | 152,010 | 3.284 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,329 | 3.295 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,214 | 3.310 | £278,905 | - |
| **OS2 Exp.** | NSAI | 71,084 | 3.584 | Referent | £282,820 |
| | RIBO+NSAI | 167,238 | 3.801 | Dominated | ABE+NSAI Dominant |
| | PAL+NSAI | 165,287 | 3.804 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 142,943 | 3.838 | £282,820 | - |
| **OS2 Log-logistic** | NSAI | 57,047 | 3.031 | Referent | £246,160 |
| | PAL+NSAI | 153,251 | 3.322 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 155,397 | 3.327 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 130,419 | 3.329 | £246,160 | - |
| | NSAI | 40,049 | 2.350 | Referent | £197,123 |

| Scenarios | Treatments | Total costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICER ABE+NSAI vs. comparator |
|---|---|---|---|---|---|
| **OS2 Gompertz** | ABE+NSAI | 117,466 | 2.743 | £197,123 | - |
| | RIBO+NSAI | 142,614 | 2.750 | Dominated | £3,292,916 |
| | PAL+NSAI | 140,748 | 2.761 | £1,250,081 | £1,250,081 |
| **TTD1 Gompertz** | NSAI | 56,150 | 2.997 | Referent | £263,915 |
| | PAL+NSAI | 151,324 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 153,716 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 133,567 | 3.291 | £263,915 | - |
| **TTD1 Log-normal** | NSAI | 56,152 | 2.997 | Referent | £254,995 |
| | PAL+NSAI | 152,038 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,263 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 130,952 | 3.291 | £254,995 | - |
| **TTD1 Exp** | NSAI | 56,148 | 2.997 | Referent | £224,015 |
| | PAL+NSAI | 136,447 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 139,204 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 121,861 | 3.291 | £224,015 | - |
| **TTD2: Log-logistic** | NSAI | 56,152 | 2.997 | Referent | £250,352 |
| | PAL+NSAI | 152,268 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.291 | £250,352 | - |
| **TTD2 Gompertz** | NSAI | 56,152 | 2.997 | Referent | £250,352 |
| | PAL+NSAI | 152,268 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.291 | £250,352 | - |
| **TTD2 vs 2nd line PFS** | NSAI | 56,728 | 2.997 | Referent | £248,834 |
| | PAL+NSAI | 152,179 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,444 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,720 | 3.291 | £248,834 | - |
| **Treatment specific utility** | NSAI | 56,152 | 3.009 | Referent | £270,232 |
| | PAL+NSAI | 152,268 | 3.263 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.275 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.281 | £270,232 | - |
| **PPS MONARCH 2** | NSAI | 56,152 | 3.425 | Referent | £412,280 |
| | PAL+NSAI | 152,268 | 3.597 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.603 | £412,280 | - |
| | RIBO+NSAI | 154,559 | 3.608 | £5,621,400 | £5,621,400 |
| **PFS utility MONARCH 2** | NSAI | 56,152 | 2.992 | Referent | £249,002 |
| | PAL+NSAI | 152,268 | 3.269 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.281 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.287 | £249,002 | - |
| **PPS LOS MONARCH 3** | NSAI | 57,858 | 2.997 | Referent | £248,787 |
| | PAL+NSAI | 153,562 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 155,846 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 130,836 | 3.291 | £248,787 | - |

| Scenarios | Treatments | Total costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICER ABE+NSAI vs. comparator |
|---|---|---|---|---|---|
| **Relative dose intensity** | NSAI | 55,697 | 2.997 | Referent | £196,802 |
| | PAL+NSAI | 145,059 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 141,672 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 113,427 | 3.291 | £196,802 | - |
| **PFS1 utility = PFS2 utility** | NSAI | 56,152 | 3.077 | Referent | £209,834 |
| | PAL+NSAI | 152,268 | 3.406 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.419 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.427 | £209,834 | - |
| **PPS BOLERO-2** | NSAI | 49,909 | 2.660 | Referent | £183,093 |
| | ABE+NSAI | 122,096 | 3.055 | £183,093 | - |
| | PAL+NSAI | 144,078 | 3.113 | Ex Dominated | £372,986 |
| | RIBO+NSAI | 145,475 | 3.138 | £278,607 | £278,607 |
| **Full surrogacy** | NSAI | 56,152 | 2.997 | Referent | £159,395 |
| | ABE+NSAI | 133,339 | 3.481 | Ex Dominated | - |
| | PAL+NSAI | 159,387 | 3.633 | Ex Dominated | £171,930 |
| | RIBO+NSAI | 162,269 | 3.674 | £156,794 | £150,253 |
| **Utility source EQ5D-5L** | NSAI | 56,152 | 2.997 | Referent | £250,352 |
| | PAL+NSAI | 152,268 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,559 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,590 | 3.291 | £250,352 | - |
| **Diarrhoea Hosp. and loperamide** | NSAI | 56,196 | 2.997 | Referent | £251,371 |
| | PAL+NSAI | 152,320 | 3.273 | Dominated | ABE+NSAI Dominant |
| | RIBO+NSAI | 154,648 | 3.285 | Dominated | ABE+NSAI Dominant |
| | ABE+NSAI | 129,933 | 3.291 | £251,371 | - |

### 4.4.3 ERG preferred assumptions and scenario analyses

**Error! Reference source not found.** below summarises ERG preferred assumptions and scenario analyses, as discussed earlier in this report

### 4.4.4 Results from ERG analysis

#### 4.4.4.1 ERG preferred assumptions

Table 37 reports the company's original base case results, the ERG's corrected company base case results and, cumulatively, a series of ERG preferred assumptions. The final part of the table (labelled 'ERG 2L drug use') represents the ERG's base case results. As can be seen, abemaciclib + NSAI remains dominant.

**Table 37 Cumulative ERG assumptions – deterministic at list prices**

| Analysis | Treatments | Total costs | Total QALYs | Incremental ICERs (£/QALY) | Pairwise ICERs ABE vs. comparator |
|---|---|---|---|---|---|
| **Company original base case** | NSAI | £56,449 | 2.997 | Referent | £250,065 |
| | PAL+NSAI | £145,266 | 3.225 | Dominated | ABE+NSAI dom. |
| | RIBO+NSAI | £148,170 | 3.222 | Dominated | ABE+NSAI dom. |
| | ABE+NSAI | £129,803 | 3.291 | £250,065 | - |
| **ERG corrected company base case** | NSAI | £56,152 | 2.997 | Referent | £250,352 |
| | PAL+NSAI | £152,268 | 3.273 | Dominated | ABE+NSAI dom. |
| | RIBO+NSAI | £154,559 | 3.285 | Dominated | ABE+NSAI dom. |
| | ABE+NSAI | £129,590 | 3.291 | £250,352 | - |
| **+ ABE+NSAI TTP1 from NMA** | NSAI | £56,152 | 2.997 | Referent | £341,663 |
| | ABE+NSAI | £130,514 | 3.215 | £341,663 | - |
| | PAL+NSAI | £152,268 | 3.273 | Ext. dom. | £376,720 (SW) |
| | RIBO+NSAI | £154,559 | 3.285 | £343,915 | £343,915 (SW) |
| **+ ABE+NSAI PFD1 from NMA** | NSAI | £56,152 | 2.997 | Referent | £289,982 |
| | PAL+NSAI | £152,268 | 3.273 | Dominated | ABE+NSAI dom. |
| | ABE+NSAI | £138,597 | 3.282 | £289,982 | - |
| | RIBO+NSAI | £154,559 | 3.285 | £4,909,402 | £4,909,402 (SW) |
| **+ OS2 Gompertz** | NSAI | £40,049 | 2.350 | Referent | £208,333 |
| | RIBO+NSAI | £142,614 | 2.750 | Dominated | ABE+NSAI dom. |
| | PAL+NSAI | £140,748 | 2.761 | Dominated | ABE+NSAI dom. |
| | ABE+NSAI | £127,062 | 2.768 | £208,333 | - |
| **+ PFS2 utility 0.69 (TA496 final value)** | NSAI | £40,049 | 2.283 | Referent | £192,356 |
| | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dom. |
| | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dom. |
| | ABE+NSAI | £127,062 | 2.735 | £192,356 | - |

SW = South West quadrant of the cost-effectiveness plane (ABE+NSAI less expensive and less effective than comparator).

Table 2 reports the results of the ERG's scenario analyses.

**Table 2 ERG preferred assumptions - deterministic**

| ERG scenario | | Treatment | Total Costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICERs ABE+NSAI vs. comparator |
|---|---|---|---|---|---|---|
| **ERG preferred** | | NSAI | £40,049 | 2.283 | Referent | £192,356 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,062 | 2.735 | £192,356 | - |
| 1 | **Not IC adjusted** | NSAI | £40,049 | 2.283 | Referent | £192,356 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,062 | 2.735 | £192,356 | - |
| 2 | **IC and baseline adjusted** | NSAI | £41,483 | 2.389 | Referent | £201,960 |
| | | ABE+NSAI | £128,490 | 2.820 | £201,960 | - |
| | | RIBO+NSAI | £149,959 | 2.875 | Dominated | £386,131 |
| | | PAL+NSAI | £148,835 | 2.875 | £365,922 | £365,922 |
| 3 | **TTP1 - Joint model (M3)** | NSAI | £40,049 | 2.283 | Referent | £156,468 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,711 | 2.843 | £156,468 | - |
| 4 | **TTP1 - Weibull** | NSAI | £40,247 | 2.306 | Referent | £177,263 |
| | | PAL+NSAI | £144,368 | 2.785 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £147,055 | 2.802 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £128,583 | 2.804 | £177,263 | - |
| 5 | **TTP1 - Gompertz** | NSAI | £40,542 | 2.343 | Referent | £153,780 |
| | | PAL+NSAI | £151,630 | 2.903 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £129,688 | 2.922 | £153,780 | - |
| | | RIBO+NSAI | £154,998 | 2.926 | £6,462,870 | £6,462,870 (SW) |
| 6 | **PFS1 HRs - CS Figure 10** | NSAI | £40,049 | 2.283 | Referent | £192,356 |
| | | RIBO+NSAI | £142,106 | 2.721 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,062 | 2.735 | £192,356 | - |
| | | PAL+NSAI | £141,488 | 2.742 | £2,106,830 | £2,106,830 (SW) |
| 7 | **PFS1 HRs - ABE+NSAI 0.5** | NSAI | £40,049 | 2.283 | Referent | £174,272 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,141 | 2.783 | £174,272 | - |
| 8 | **PFS1 HRs - ABE+NSAI 0.55** | NSAI | £40,049 | 2.283 | Referent | £198,512 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £126,886 | 2.720 | £198,512 | - |
| | | PAL+NSAI | £140,748 | 2.727 | £1,983,190 | £1,983,190 (SW) |
| 9 | **PFS1 HRs - ABE+NSAI: 0.60** | NSAI | £40,049 | 2.283 | Referent | £258,764 |
| | | ABE+NSAI | £124,830 | 2.611 | Ex Dominated | - |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | £163,426 (SW) |
| | | PAL+NSAI | £140,748 | 2.727 | £226,580 | £136,293 (SW) |
| 10 | **PF Deaths** | NSAI | £40,049 | 2.283 | Referent | £192,356 |
| | | RIBO+NSAI | £142,614 | 2.719 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,748 | 2.727 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,062 | 2.735 | £192,356 | - |

| ERG scenario | | Treatment | Total Costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICERs ABE+NSAI vs. comparator |
|---|---|---|---|---|---|---|
| 11 | **PFS2 Weibull** | NSAI | £39,910 | 2.286 | Referent | £195,229 |
| | | RIBO+NSAI | £142,600 | 2.716 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,735 | 2.724 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,049 | 2.732 | £195,229 | - |
| 12 | **PFS2 Gompertz** | NSAI | £39,369 | 2.289 | Referent | £197,231 |
| | | RIBO+NSAI | £142,595 | 2.717 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £140,713 | 2.725 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £127,034 | 2.733 | £197,231 | - |
| 13 | **OS2 Log-logistic** | NSAI | £57,047 | 2.963 | Referent | £259,329 |
| | | PAL+NSAI | £153,251 | 3.273 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £155,397 | 3.278 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £139,562 | 3.281 | £259,329 | - |
| 14 | **OS2 Exp + CONFIRM** | NSAI | £56,152 | 2.929 | Referent | £269,236 |
| | | PAL+NSAI | £152,268 | 3.226 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £138,597 | 3.236 | £269,236 | - |
| | | RIBO+NSAI | £154,559 | 3.238 | £5,455,056 | £5,455,056 (SW) |
| 15 | **BOLERO 2 PFS2 & OS2** | NSAI | £49,909 | 2.610 | Referent | £187,366 |
| | | PAL+NSAI | £144,078 | 3.027 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £130,558 | 3.041 | £187,366 | - |
| | | RIBO+NSAI | £145,475 | 3.042 | £13,923,475 | £13,923,475 (SW) |
| 16 | **OS/PFS surrogacy - 10%** | NSAI | £40,049 | 2.283 | Referent | £221,645 |
| | | PAL+NSAI | £138,769 | 2.633 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £141,012 | 2.644 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £125,673 | 2.669 | £221,645 | - |
| 17 | **OS/PFS surrogacy - 50%** | NSAI | £40,049 | 2.283 | Referent | £165,508 |
| | | PAL+NSAI | £142,126 | 2.801 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £144,299 | 2.801 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £128,643 | 2.818 | £165,508 | - |
| 18 | **OS/PFS surrogacy - 100%** | NSAI | £40,049 | 2.283 | Referent | £125,080 |
| | | PAL+NSAI | £144,768 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £147,146 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £131,236 | 3.012 | £125,080 | - |
| 19 | **TTD1 lognormal** | NSAI | £40,049 | 2.283 | Referent | £126,355 |
| | | PAL+NSAI | £144,538 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £146,851 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,166 | 3.012 | £126,355 | - |
| 20 | **TTD1 Gompertz** | NSAI | £40,048 | 2.283 | Referent | £129,407 |
| | | PAL+NSAI | £143,824 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £146,304 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £134,389 | 3.012 | £129,407 | - |
| 21 | **TTD1 exp.** | NSAI | £40,046 | 2.283 | Referent | £111,295 |
| | | PAL+NSAI | £128,947 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £131,792 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £121,182 | 3.012 | £111,295 | - |

| ERG scenario | | Treatment | Total Costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICERs ABE+NSAI vs. comparator |
|---|---|---|---|---|---|---|
| 22 | **TTD2 log-logistic** | NSAI | £40,049 | 2.283 | Referent | £125,080 |
| | | PAL+NSAI | £144,768 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £147,146 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £131,236 | 3.012 | £125,080 | - |
| 23 | **TTD2 Gompertz** | NSAI | £40,049 | 2.283 | Referent | £125,080 |
| | | PAL+NSAI | £144,768 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £147,146 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £131,236 | 3.012 | £125,080 | - |
| 24 | **TTD3 - 10%** | NSAI | £37,754 | 2.283 | Referent | £125,391 |
| | | PAL+NSAI | £142,660 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £144,985 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £129,167 | 3.012 | £125,391 | - |
| 25 | **TTD3 - 50%** | NSAI | £41,154 | 2.283 | Referent | £124,931 |
| | | PAL+NSAI | £145,782 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.012 | £124,931 | - |
| 26 | **AE rates diarrhoea** | NSAI | £41,154 | 2.283 | Referent | £124,931 |
| | | PAL+NSAI | £145,782 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.012 | £124,931 | - |
| 27 | **AE rates leukopenia** | NSAI | £41,154 | 2.283 | Referent | £124,935 |
| | | PAL+NSAI | £145,782 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,235 | 3.012 | £124,935 | - |
| 28 | **AE rates neutropenia** | NSAI | £41,154 | 2.283 | Referent | £124,941 |
| | | PAL+NSAI | £145,782 | 2.998 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.001 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,240 | 3.012 | £124,941 | - |
| 29 | **Utility PFS1 0.69** | NSAI | £41,154 | 2.229 | Referent | £131,629 |
| | | PAL+NSAI | £145,782 | 2.909 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 2.911 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 2.921 | £131,629 | - |
| 30 | **Utility PFS1 0.774** | NSAI | £41,154 | 2.363 | Referent | £116,113 |
| | | PAL+NSAI | £145,782 | 3.131 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.136 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.147 | £116,113 | - |
| 31 | **Utility PFS2 (ET/ targeted) 0.505** | NSAI | £41,154 | 2.173 | Referent | £124,549 |
| | | PAL+NSAI | £145,782 | 2.889 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 2.898 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 2.905 | £124,549 | - |
| 32 | **Utility PFS2 (ET/ targeted) 0.724** | NSAI | £41,154 | 2.303 | Referent | £125,000 |
| | | PAL+NSAI | £145,782 | 3.018 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.020 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.031 | £125,000 | - |

| ERG scenario | | Treatment | Total Costs (£) | Total QALYs | Incremental ICER (£/QALY) | Pairwise ICERs ABE+NSAI vs. comparator |
|---|---|---|---|---|---|---|
| 33 | **Utility PFS2 (chemotherapy) 0.505** | NSAI | £41,154 | 2.318 | Referent | £125,053 |
| | | PAL+NSAI | £145,782 | 3.033 | Dominated | ABE+NSAI Dominant |
| | | RIBO+NSAI | £148,187 | 3.034 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.046 | £125,053 | - |
| 34 | **Utility PFS2 (chemo) 0.724** | NSAI | £41,154 | 2.363 | Referent | £125,210 |
| | | RIBO+NSAI | £148,187 | 3.076 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £145,782 | 3.078 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,232 | 3.090 | £125,210 | - |
| 35 | **Second and third line therapies** | NSAI | £48,437 | 2.399 | Referent | £129,215 |
| | | PAL+NSAI | £152,351 | 3.094 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £138,626 | 3.097 | £129,215 | - |
| | | RIBO+NSAI | £155,046 | 3.111 | £1,200,827 | £1,200,827 (SW) |
| 36 | **Hospitalisation for diarrhoea** | NSAI | £41,199 | 2.350 | Referent | £125,576 |
| | | RIBO+NSAI | £148,277 | 3.064 | Dominated | ABE+NSAI Dominant |
| | | PAL+NSAI | £145,835 | 3.065 | Dominated | ABE+NSAI Dominant |
| | | ABE+NSAI | £132,575 | 3.078 | £125,576 | - |

# 5 END OF LIFE

The CS does not present a justification for NICE's end of life criteria to be applied.

# 6 INNOVATION

The company provides a justification for abemaciclib to be considered a treatment innovation on the following basis:

- Abemaciclib delays disease progression and thus the need for cytotoxic chemotherapy to be given. Expert clinical opinion to the ERG is that the increase in PFS is clinically meaningful.
- Abemaciclib has a favourable safety profile which permits continuous dosing. The CS notes that palbociclib and ribociclib are associated with higher levels of neutropenia which requires regular blood count monitoring and treatment gaps at the end of each 21 day cycle. Expert clinical advice to the ERG is that reduced neutropenia-associated myelosupression would be a minor advantage when choosing a between abemaciclib and palbociclib / ribociclib.

# 7 DISCUSSION

## 7.1 Summary of clinical effectiveness issues

The MONARCH 3 trial showed a gain of [redacted] months in median PFS for the combination of abemaciclib and NSAI compared to NSAI alone. This is regarded to be a clinically meaningful benefit and is in-keeping with PFS gains for the other CDK 4/6 inhibitors ribociclib (and NSAI) (median difference 9.3 months[19, 29]) and palbociclib (and NSAI) (median difference 13.1 months[21, 49]). The indirect comparison of these treatments showed no statistically significant differences between them.

Abemaciclib can therefore be considered similar in effects to existing NICE recommended treatments in delaying cancer progression, one of the key treatment goals for patients with advanced breast cancer. The effect of abemaciclib on overall survival is currently unclear, as the duration of follow-up is not yet long enough to have measured the required number of events (deaths) needed for the analysis (the estimated study completion date is July 2021). A similar lack of follow-up of survival also applies to the palbociclib and ribociclib pivotal phase III trials. Thus, the clinical effectiveness of these CDK 4/6 inhibitors in

treatments based on the odds of an event is given for the response outcomes of ORR and CBR in Appendix G).[17] The networks comprise comparisons that are informed by both direct and indirect evidence (closed loops) as well as comparisons only informed by indirect evidence.

### 9.2.3 Statistical methods

The statistical approach used is similar to that used to conduct the first-line treatment NMA (as described in more detail in section 3.1.7 of this report). In brief:

- A Bayesian generalised linear model is used, based on NICE DSU guidelines.[24]
- Fixed and random effects modelling is undertaken with selection of model according to best fit (based on DIC values). Both random effects and fixed effects model are presented for PFS, but only fixed effects results are presented for OS as there was evidence of the prior around the random effects standard deviation dominating the posterior estimates (it is not stated why). Given the observed clinical heterogeneity in the networks (see section 9.2.4 below) the ERG considers the random effects model would have been more appropriate in principle.
- Vague prior distributions were chosen for treatment and study-specific term, in accordance with DSU methodological guidance.[24]
- OpenBUGS software was used to run the analysis (the code is provided in Appendix E the NMA report). A Markov chain Monte Carlo simulator was run for 50,000 burn-in simulations with a further 100,000 simulations for convergence to the posterior distribution (Brooks-Gelman-Rubin plots).

The ERG notes that OS data are immature (median OS not reached in at least one arm) in eight of the trials, including the MONARCH 2 trial. (The final OS analysis of this trial will be conducted at 441 OS events. The estimated study completion date is July 2021.[16] However, none of the remaining seven trials included comparisons that were used in the economic model.

An inconsistency assessment was performed to determine the level of consistency between direct and indirect evidence in the NMA networks, based on the approach recommended by the NICE DSU.[26] For PFS and OS both the total residual deviance and DIC values remained similar (<5 point difference) between consistency and inconsistency models, indicating no inconsistency.