in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Maiwenn Al acted as health economic project lead, contributed to the writing of the report and supervised the health economic part of the project. Nasuh Büyükkaramikli, Saskia de Groot, Ching-Yun Wei and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Debra Fayter and Piet Portegijs acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission 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.

Abbreviations

AE	Adverse Events
AI	Aromatase Inhibitor
AIC	Akaike's Information Criterion
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BI	Budget impact
BIC	Bayesian Information Criterion
BIRC	Blinded independent review committee
BNF	British National Formulary
CBR	Clinical benefit rate
CDF	Cancer Drugs Fund
CDK4/6	Cyclin-dependent kinase 4 and 6
CE	Cost effectiveness
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CHF	Swiss Franc
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute)
DSU	Decision Support Unit
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-3L	European Quality of Life-5 Dimensions, three-level scale
ERG	Evidence Review Group
ESO-ESMO	European School of Oncology-European Society for Medical Oncology
EUR	Erasmus University Rotterdam
FBC	Full blood count
FDA	Food and Drug Administration
G1	Gap1
G2	Gap2
GHS/QoL	Global Health Status/Quality of Life
HER2-	Human epidermal growth factor receptor 2-negative
HR	Hazard Ratio
HR+	Hormone receptor-positive
HRQoL	Health-related quality of life
HSU	Health state utility
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
INK4	Inhibitor of CDK4
IPD	Individual Patient Data
ITT	Intention-to-treat
KM	Kaplan–Meier

KSR	Kleijnen Systematic Reviews
LFT	Liver function test
LYG	Life year gained
M	Mitosis
MeSH	Medical Subject Headings
MHRA	Medicines and Healthcare Products Regulatory Agency
MRU	Medical resource utilisation
MTD	maximum tolerated dose
NA	Not applicable
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIHR	National Institute for Health Research
NR	Not Reported
NR	Not Reached
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PFS1	First-line PFS
PFS2	Second-line PFS
PR	Partial Response
PRESS	Peer Review of Electronic Search Strategies
PRO	Patient-reported outcome
PS	Performance Status
PSA	Probabilistic Sensitivity Analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QoL	Quality of life
QTcF	QT interval corrected for heart rate as per Fridericia's formula
Rb	Retinoblastoma
RCT	Randomised Controlled Trial
RDE	Recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumours
S	DNA synthesis
SAE	Serious Adverse Event
ScHARR	School of Health and Related Research
SD	Standard Deviation
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SPC	Summary of product characteristics
STA	Single Technology Appraisal
TdP	Torsade de Pointes
TTD	Time to Treatment Discontinuation
UMC	University Medical Centre
UK	United Kingdom
WHO	World Health Organisation

Table of Contents

Table of Tables

Table of Figures

1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The NICE scope describes the decision problem as ribociclib in combination with an aromatase inhibitor for postmenopausal women with advanced or metastatic hormone receptor positive, HER2 negative breast cancer previously untreated in the advanced setting. The comparators are described as: aromatase inhibitors (such as letrozole or anastrozole).

Ribociclib is indicated for use in combination with an aromatase inhibitor, for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer as initial endocrine-based therapy. An opinion from the EMA is anticipated in August 2017.

In the company submission ribociclib in combination with letrozole is compared with letrozole alone. This is in line with the NICE scope. However, other aromatase inhibitors (such as anastrozole) have not been considered. In addition, the population included in the main trial may not be fully representative of the UK patient population. Only [redacted] were included and [redacted].

1.2 Summary of clinical effectiveness evidence submitted by the company

One Phase 3 trial, MONALEESA-2, with 668 patients was presented as the main source of evidence. The MONALEESA-2 study included postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease.

The trial was conducted at 223 trial centres in 29 countries including [redacted] patients from England and Wales. Patients were randomised 1:1 to receive ribociclib (600 mg once daily, days 1–21 of a 28-day cycle) plus letrozole (2.5 mg once daily, continuous treatment) or placebo plus letrozole (2.5 mg once daily, continuous treatment). Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage adverse events (AEs); no dose reductions were permitted for letrozole and no crossover between treatment arms was allowed. Patients who discontinued ribociclib or placebo could continue receiving letrozole. Treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of ribociclib or letrozole.

The primary outcome was progression-free survival (PFS) as per RECIST version 1.1 criteria, based on local radiological assessment; assessments were also carried out by blinded independent review committee (BIRC). The key secondary endpoint was OS (defined as the time from date of randomisation to date of death due to any cause). Other secondary outcomes included objective response rate (ORR; complete response [CR] or partial response [PR]), Clinical benefit rate (CBR, overall response plus stable disease lasting 24 weeks or more), time to deterioration of ECOG Performance Status (PS), safety and health-related quality of life (HRQoL).

A total of 668 patients were randomised to ribociclib (n=334) or placebo (n=334) in the intention to treat (ITT) population. At the time of data cut-off (29 January 2016), a total of 349 patients (52.2%) were still receiving treatment (ribociclib, n=195; placebo, n=154). The rates of discontinuation were 41.6% in the ribociclib group compared with 53.9% in the placebo group. The most frequent reason for discontinuation was disease progression in both groups (ribociclib, 26.0%; placebo, 43.7%).

Discontinuations due to AEs were 7.5% in the ribociclib group and 2.1% in the placebo group. The median duration of follow-up from randomisation to data cut-off was 15.3 months.

The CS presents data from the first interim analysis only (cut-off January 2016) and focuses on results based on local assessment. Median PFS was significantly longer and was not reached in the ribociclib group (95% confidence interval [CI]: 19.3–not reached [NR]) versus 14.7 months (95% CI, 13.0–16.5) in the placebo group. The addition of ribociclib to letrozole reduced the risk of death or progression by 44% (HR = 0.56; 95% CI: 0.43–0.72).

The primary efficacy outcome was further supported by significant improvements in ORR (40.7% versus 27.5%, $p < 0.001$) and clinical benefit rate (79.6% vs. 72.8%, p=0.018) in the full analysis set, as well as in the subgroup of patients with measurable disease at baseline (ORR 52.7% vs. 37.1%; CBR 80.1% vs. 71.8%). OS data were not mature at the time of the first pre-planned interim analysis; at that time 43 patients had died (23 in the ribociclib group and 20 in the placebo group).

Quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms.

Subgroup analyses showed that results for PFS favour ribociclib for all subgroups including both those with newly diagnosed disease and those with existing disease and those who have received prior therapy and patients who have not. Nevertheless, there are differences in effectiveness. Most noticeably, results for ribociclib are more favourable for younger patients (<65 yr), newly diagnosed patients (vs not newly diagnosed), not ER- and PR-positive (vs other hormone-receptor status), and not bone-only disease (vs. bone-only disease).

Although occurrence of any adverse events were overall similar in ribociclib and placebo groups, a greater number of adverse events and severe adverse events were attributable to ribociclib. [redacted] The most common event was neutropenia. Gastrointestinal events such as nausea, vomiting and diarrhoea occurred more frequently in the ribociclib group.

A similar number of patients died in the two groups in the June 2016 cut-off although data were not mature.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches. A good range of databases were searched, and additional searches of conference proceedings were conducted. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal sections 5.2.2 and 5.2.4. However, no literature searches were conducted to identify adverse events data, indirect and mixed treatment comparisons or non-randomised and non-controlled evidence.

The clinical effectiveness evidence in the submission is based on one trial, the MONALEESA-2 study. The ERG is not aware of any other evidence relevant to the decision problem. However, the ERG noticed on the FDA website that two more recent interim analyses from the MONALEESA-2 trial were available (June 2016 and January 2017), and requested these data as part of the clarification process. These data are presented in this report together with the first interim analysis (January 2016).

Overall, the MONALEESA-2 trial is a good quality randomised controlled trial. Patient baseline characteristics seem well balanced between treatment groups in terms of demographics and disease characteristics. However, increased rates of adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients. Therefore, results based on independent review are more reliable.

The main concern regarding the methodology of the MONALEESA-2 trial is that the use of an interim analysis for PFS meant that the initial results presented in the company submission were based on the data available at the time of this analysis (January 2016) for PFS. At this point the OS data were immature as the required number of deaths had not been reached, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off.

Results are available for three time points:

1. The first planned interim analysis performed at the data cut-off on 29 January 2016 after observing 243 of the planned 302 events, the median duration of follow up was 15.3 months.
2. A second interim analysis on 22 June 2016 based on 297 local PFS and 147 central PFS events, the median duration of follow up was 20.1 months.
3. A third interim analysis on 2 January 2017 based on 345 local PFS events, the median duration of follow up was 26.4 months.

In this report we have focused on the most recent data available.

In addition, PFS results can be based on local and central (BIRC) assessment, we have focused on BIRC results, partly because the NICE committee preferred these data in a recent related technology appraisal, and partly because adverse events could have unblinded physicians and/or patients, thus making results based on independent review more reliable.

Table 1.1: Comparison of preferred PFS and OS results from the company and ERG

	Ribociclib + letrozole (n = 334) versus Placebo + letrozole (n = 334)	
	Company preference	**ERG preference**
PFS HR (95% CI)[a]	0.56 (0.43–0.72)[1]	[redacted][2]
OS HR (95% CI)[a]	[redacted][3]	0.746 (0.517-1.078)[4]

Source: CS, Novartis MONALEESA-2 ribociclib June 2016 CSR update and Novartis MONALEESA-2 ribociclib January 2017 CSR data cut

a) HR obtained from COX PH model stratified by liver and / or lung metastasis as per IRT

1. Based on local assessment and first interim analysis (January 2016)
2. Based on central assessment and most recent analysis (June 2016)
3. Based on first interim analysis (January 2016, after 43 deaths)
4. Based on most recent analysis (January 2017, after 116 deaths)

As can be seen from the results presented in Table 1.1 PFS results are [redacted] for ribociclib in the company preferred results; while OS results are more favourable for ribociclib in the ERG preferred results. It should be kept in mind that the economic model is informed by the PFS results from the MONALEESA-2 trial, but not by the OS results from the MONALEESA-2 trial. The OS treatment effect in the economic model is based on the idea of surrogacy i.e. that a gain in PFS predicts a gain in OS. In the base-case, the assumption is that the gain in OS is identical to the gain in PFS.

[redacted]

[redacted]

1.4 Summary of cost effectiveness evidence submitted by the company

The company developed an individual patient simulation model following a state-transition approach, to assess the cost effectiveness of ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic HR+/HER2- breast cancer. In the model, simulated patients move through a series of health states; these include first-line PFS (PFS1), second-line PFS (PFS2), progressed disease (later lines) and death.

All patients start in the PFS1 state, in which they receive either ribociclib in combination with letrozole or letrozole alone. Patients stay in this state until they progress and move to PFS2 state, or until they die. PFS2 represents the time between disease progression in first-line and second-line treatment cessation (as a proxy for disease progression). In the PFS2 state, patients receive one of the following treatments: everolimus in combination with exemestane, exemestane (representative of a single-agent endocrine therapy) or capecitabine (representative of chemotherapy). Patients stay in this state until they progress and move to the "progressed disease" state, or until they die. The progressed disease state represents the time from second-line therapy cessation (as a proxy for progression) until death, and in this state patients receive subsequent treatments and/or supportive/palliative care. The death state is an absorbing state.

The length of the PFS during the first-line is informed by the MONALEESA-2 trial. The benefit in PFS in the first-line is transferred to OS using an OS surrogacy approach (due to immaturity of OS data from the MONALEESA-2 trial). In the base-case it is assumed that the PFS benefit will lead to an OS benefit the same as the PFS benefit. TTD was independently modelled from the PFS in the first-line and used in drug acquisition cost calculations. Parametric models were used for both PFS and TTD following NICE DSU guidelines. Treatment received in the first-line determines the distribution of treatments received in the second line. TTD and post-discontinuation survival from PFS2 were derived from the BOLERO-2 trial in which everolimus in combination with exemestane was compared to exemestane alone. The hazard ratios from Li et al. 2015 were used to model the effect of chemotherapy.

Utility values of patients in the PFS1 state were derived from the MONALEESA-2 trial. Utility values for PFS2 were taken from Lloyd et al. 2006 adjusted for age and treatment response (the latter based on the BOLERO-2 study). For patients treated with second-line chemotherapy a utility decrement was applied, in line with the findings of Peasgood et al.2010 Utility values for the progressed disease state were also taken from Lloyd et al. 2006 adjusted for age.

Treatment costs (e.g. technology acquisition costs of first, second, third and later line treatments), drug administration costs, monitoring costs and health state costs are included. Additionally the costs of adverse events associated to first-line treatment were incorporated.

Without the patient access scheme, incremental QALYs are 0.96 and incremental costs are [redacted]. The corresponding ICER is [redacted] for ribociclib plus letrozole compared to letrozole monotherapy. With the patient access scheme, incremental costs reduce to [redacted], and the corresponding ICER is [redacted]. QALYs are predominantly gained within the PFS1 health state. The increase in costs is mainly caused by the increase in first-line treatment costs.

The probabilistic sensitivity analysis showed that the probability that ribociclib in combination with letrozole is cost effective compared to letrozole alone is [redacted] at a willingness-to-pay threshold of £30,000/QALY. With the patient access scheme this likelihood increases to [redacted]

Within the deterministic sensitivity analyses, the company varied some of the input parameters to its upper and lower limits. This analysis showed that the ICER was most sensitive to the discount rates.

Furthermore, the company performed several scenario analyses. A time horizon of five or 10 years (instead of 40 years), the use of a Weibull or Gompertz parametric function for first-line PFS (PFS1 health state) (instead of an Exponential function) and the use of lower post-progression treatment costs for the progressed disease health state (i.e. £1,000, £425, or £0 per month instead of £2,000 per month) had the largest impact on the ICER. This was observed both with and without the patient access scheme.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The cost effectiveness searches in the CS were well documented and reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal.

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a large extent, and the impact of deviations (mostly regarding valuation of post first-line health states) was found to be small. The ERG confirmed that there was no existing cost effectiveness model for ribociclib plus letrozole for the current indication.

One of the main concerns of the ERG with the company submission was the assumption in the model that any gain in PFS is 100% translated into OS gain in the base-case. The ERG considers this assumption speculative, as there are studies indicating that duration of PFS gain would translate into an OS gain that is shorter, especially in HER2-negative patients. This trend can be also observed in the PALOMA-1 trial (comparing palbociclib plus letrozole vs letrozole) where a "gain in median OS/gain in median PFS" ratio close to 38.5% was observed. The ERG considered the observed ratio of 38.5% more evidence-based than the completely arbitrary 100% that the company assumed.

In addition, the ERG base-case included the company provided PFS data as per January 2017. This PFS assessment was based on local assessment, rather than the central assessment, which would have been the ERG's preference. The company stated that the observed hazard ratio for PFS was approximately the same for both methods of assessment. [redacted] If the same is true for the data as per January 2017, this would most likely increase the ICER. Unfortunately, the ERG could not confirm this as only summary data and Kaplan-Meier curves for the PFS based on central assessment from the June 2016 dataset was provided.

For the estimation of drug acquisition costs in the progression health state the company used expert opinion. However, hardly any information was provided on the details of what was suggested by the experts to arrive at these costs. Thus, the ERG was not able to assess the validity of this cost estimate (approximately £2,000 per month).

To choose a parametric distribution for the PFS curves, the company did not only look at the statistical goodness-of-fit of various distributions, but also compared the extrapolated parts of the curves to external data. When the PFS extrapolations (January 2017) were compared with the KM curves from external trials, it was observed by the ERG that the exponential distribution extrapolations were closer to the KM curves from the LEA and ALLIANCE trials, whereas the extrapolations from the Weibull and Gompertz distributions were closer to the KM curves from PALOMA-2 and MONALEESA-2 trials. Thus, according to the ERG the choice of the company to use an exponential distribution can be considered to be just as plausible as an Weibulll distribution.

In addition to the more major issues discussed above, other issues might potentially be relevant. This is for instance true for the inclusion of wastage in treatment costs (since dispensed packages cannot be used for other patients once a patient discontinues treatment) and the modelling of the post-treatment discontinuation survival after chemotherapy, where an approach was used that could be seen as 'the best possible' for a cohort model but was unnecessary in the context of a simulation model. Also potentially relevant was the proportions of patients receiving one of three treatment options as second-line treatment; in the model these proportions were assumed to be different depending on the treatment received in first-line, whereas the ERG questioned if this is indeed the case.

Finally, some issues that the ERG considered of potential importance could not be addressed quantitatively in the current assessment. For example, although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER.

Another example relates to the approach of modelling PFS2 and PD using data from the BOLERO-2 study. The OS and PFS results from the BOLERO-2 trial were used in the model without any adjustments, as if the BOLERO-2 trial was conducted subsequent to the MONALEESA-2 trial population upon their disease progression. Instead of this approach followed by the company, the ERG would have preferred an approach where the OS and PFS parametric functions used from the BOLERO-2 trial were adjusted based on the patient characteristics at disease progression from the first-line treatment (e.g. age, previous treatment, ECOG disease status, time since diagnosis at the time of first line treatment progression etc.). The use of such adjusted OS and PFS survival functions from BOLERO-2 might have changed the ICER.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Searches were carried out in line with the NICE guide to the methods of technology appraisal and included a good range of databases and conference proceedings searches.

The clinical evidence is based on one good quality randomised controlled trial including 668 patients. The comparator arm of the MONALEESA-2 trial was letrozole, an aromatase inhibitor used to treat patients with untreated MBC in NHS clinical practice, that is a valid comparator for this appraisal. It seems reasonable to generalise the clinical effectiveness results associated with letrozole to other commonly used aromatase inhibitors in NHS clinical practice (i.e. exemestane and anastrozole).

An important strength of the HE model submitted by the company is the patient-level simulation approach. When modelling multiple lines of treatment, this approach offers the needed flexibility. In this regard it is quite fortunate that estimates for the second-line treatment could be derived from a previous study done by the same manufacturer, as it enabled analyses based on individual patient data.

Additionally, the use by the company of external long-term PFS data to inform the choice of parametric distribution for the PFS curves is undoubtedly a strength, as this reduces the structural uncertainty.

1.6.2 Weaknesses and areas of uncertainty

The ERG was concerned about the language bias of restricting searches to English language only, as this is not in line with current best practice. Date limits were imposed on all literature searches. The clinical effectiveness searches were conducted in June 2016 and the cost effectiveness searches in

August 2016 for the initial CS; searches were updated for the company response to clarification. Searches for adverse events data, non-randomised and non-controlled evidence, and indirect and mixed treatment comparisons were not conducted. It is possible that relevant evidence may have been missed as a consequence of this.

The population included in the MONALEESA-2 trial may not be fully representative of the UK patient population. In addition, adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients in the MONALEESA-2 trial.

The main concern regarding the MONALEESA-2 trial is that the use of an interim analysis for PFS meant that the initial results presented in the company submission were based on the data available at the time of the interim analysis for PFS. At this point the OS data were immature as the required number of deaths had not been reached, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off.

The main weakness of the HE model lies in the need to make an assumption regarding the relation between PFS gain and OS gain. Unfortunately, the ERG does not agree with the assumption made by the company, i.e. a gain in the PFS would lead to an equal gain in the OS. No data are available to support this relationship. A review by Davis et al. (2012) has shown that a relationship between PFS/TTP and OS varies considerably by cancer type and is not always consistent even within one specific cancer type. Data from a drug in the same class as ribociclib is therefore preferred to study the relationship between PFS and OS (given the immaturity of the OS data in the MONALEESA-2 trial). The ERG base-case therefore assumes an OS surrogacy similar to the relationship between median PFS and OS as observed in the PALOMA-1 trial (comparing palbociclib and letrozole with letrozole alone). Although the data from the PALOMA-1 trial have their limitations, that trial is the only one currently available for providing insight in the association between PFS and OS of patients treated with a CDK 4/6 inhibitor.

In the ERG base-case, PFS data (local assessment) from the January 2017 data cut-off were used, as these data were the most recent. Although PFS data from the central assessment were preferred over the local assessment, these data were unavailable at the most recent data cut-off. In their response to the clarification letter, the company indicates that they are willing to update the model with PFS data from the January 2016 data cut-off, the most recent date for which central assessment data are available (no central assessment was performed at the January 2017 data cut-off).

Although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG has incorporated various adjustments to the company base-case. Ideally, the adjustments would have included the model inputs based on blinded independent central review (BIRC) PFS assessment based on the latest data cut-off date (January 2017). However, this data was not ready at the time of the company submission.

The ERG base-case resulted in an ICER of [redacted] per QALY gained without the PAS price and [redacted] with the PAS price. The most influential adjustments/corrections made by the ERG were: 1) Changing the full OS surrogacy approach to a partial OS surrogacy approach, using median OS and PFS data from the PALOMA-1 trial; 2) Using model inputs derived from the most recent PFS dataset

of the MONALEESA-2 trial (data cut-off January 2017) and; 3) Using a third-line treatment related cost estimate from a published NICE appraisal (TA239, fulvestrant). From the PSA results, the probability that ribociclib plus letrozole therapy is cost effective compared to letrozole monotherapy is approximately [redacted] at a £30,000 per QALY gained threshold (with the PAS price). The key findings from company and ERG preferred analyses are given in Table 1.2.

Table 1.2: Key finding from company and ERG analyses

(with PAS)	ribociclib plus letrozole		letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(without PAS)	**ribociclib plus letrozole**		**letrozole monotherapy**		**Incr. costs**	**Incr. QALYs**	**ICER**
	Total costs	**Total QALYs**	**Total costs**	**Total QALYs**			
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

CS = company submission; ERG = expert review group; ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years.

The ERG conducted some additional scenario analyses on their preferred base-case to assess structural uncertainty.

In one of the scenarios, the ERG explored the impact of using a Weibull distribution instead of exponential in generating time to event for PFS in the first-line. The ERG considers the Weibull distribution to be as plausible as an exponential distribution as discussed in the critique, yielding an ICER of [redacted] without PAS and [redacted] with PAS.

Similarly, the decision on the third-line treatment-related cost has a big impact on the ICER; the ICER ranges from [redacted] per QALY gained to [redacted] per QALY gained (without PAS) and from [redacted] per QALY gained to [redacted] per QALY gained (with PAS) when the cost estimate is varied from £0 to £2,000 per month.

Scenarios with more modest impact on the ICER included changing the drug acquisition costs from cycle 11 onwards to the mean costs of cycle 11 to 26, instead of the costs at cycle 10, and second-line treatment that is independent of the technology used in first line.

In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around [redacted] per QALY gained without PAS, compared to [redacted] with PAS. This latter ICER value is [redacted]. In addition, due to several assumptions e.g. regarding PFS/OS surrogacy and regarding the choice of parametric distribution to extrapolate PFS, the ERG deems that the uncertainty around the cost effectiveness of ribociclib is substantial.

2. BACKGROUND

In this section the ERG provides a review of the evidence submitted by Novartis in support of ribociclib (LEE 011), trade name Kisqali® in combination with an aromatase inhibitor for the treatment of previously untreated advanced or metastatic breast cancer. The population under consideration is patients with metastatic hormone-receptive, HER2- negative breast cancer. We outline and critique the company's description of the underlying health problem and the overview of current service provision. The information is taken mainly from Chapter 3 of the company submission (CS) with sections referenced as appropriate.

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

The underlying health problem of this appraisal is advanced or metastatic hormone receptor-positive (HR+) HER2- negative breast cancer in postmenopausal women previously untreated in the advanced setting.

The company describes the heterogeneity of breast cancer as a disease. The CS goes on to state that '*Around 75% of postmenopausal women with breast cancer have tumours that are HR+[1] and HR+/HER2- is the most common form of breast cancer.*'[2, 3]

The CS states that '*Most cases of advanced or metastatic HR+/HER2- breast cancer represent recurrent disease*'.[4] The company add that '*As many as 50% of women with early disease eventually develop or progress to advanced breast cancer or metastatic disease*'[5, 6] The CS states that '*In the UK, 13% of newly diagnosed breast cancers are found to be HR+/HER2- advanced cancers at initial presentation*'[7]

The CS emphasises the role of endocrine therapies such as aromatase inhibitors in the management of HR+ breast cancers in both early and advanced disease. The CS also states that '*Despite an initial response to such endocrine therapies, many patients will experience disease progression'.*[1]

The CS outlines the impact of advanced or metastatic breast cancer on patients and their families and carers. For patients, this includes the symptoms of disease such as fatigue, the effects of treatment for advanced or metastatic disease, deleterious effect on quality of life, associated psychological distress and impact on daily activities and work productivity.

The CS states that '*disease progression has been found to be the factor having the greatest impact on HRQoL in patients with metastatic cancer.*'[8] The company adds that '*prolonging PFS is an important goal for endocrine therapy in patients with advanced or metastatic disease, thus preserving HRQoL and delaying the need to progress to chemotherapy*'[4] which '*is generally associated with significant toxicity which further reduces HRQoL*'.[9, 10]

The company emphasises the poorer outlook of patients with advanced cancer compared to those diagnosed early. The CS states '*The median survival of patients with advanced breast cancer is just 2-3 years.*'[11]

The CS states that '*accumulating evidence indicates that improvements in PFS may be also associated with prolonged OS.*' The company cites three studies to demonstrate correlation between the two outcomes.[12-14]

ERG comment:
The ERG checked the references cited by the company to support the statements made above and considered the company to have given overall an appropriate description of the underlying health problem.

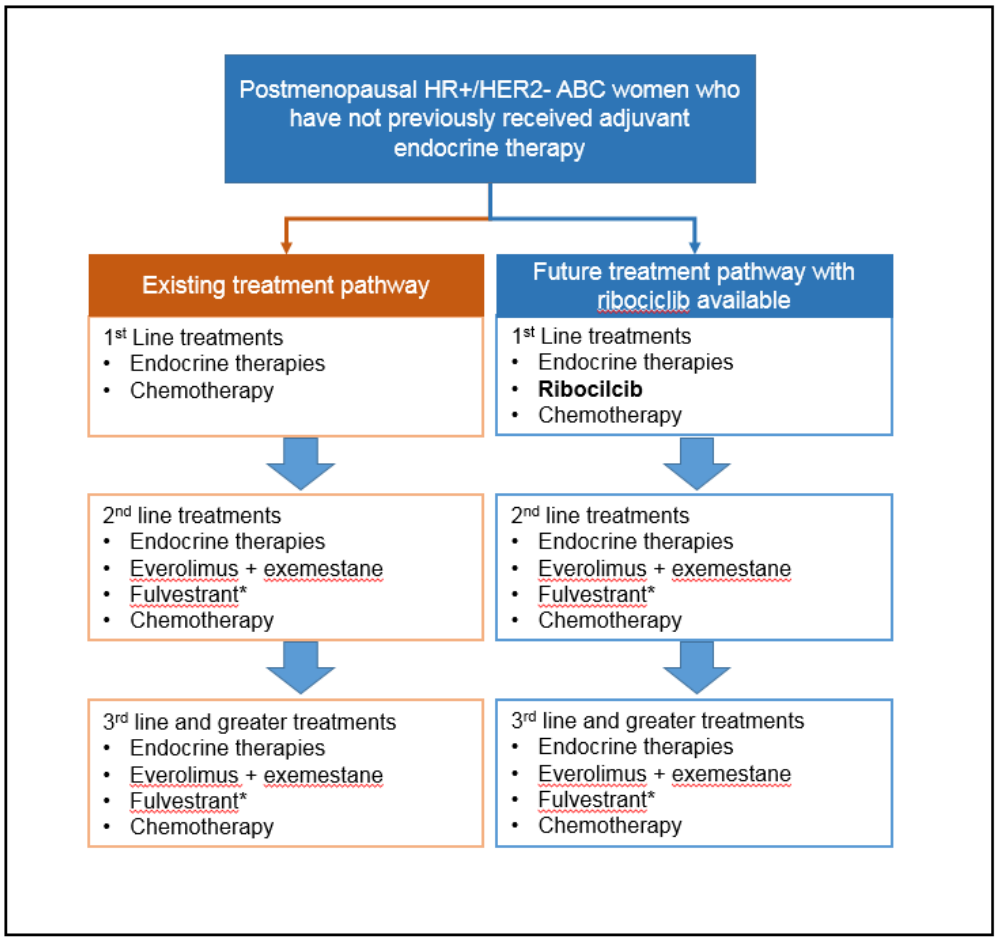
We identified some discrepancies which we investigated further.

- The statement that '*As many as 50% of women with early disease eventually develop or progress to advanced breast cancer or metastatic disease'* did not appear to be supported by the reference cited. It has been estimated that approximately 35% of those with early or locally advanced diseases will progress to metastatic breast cancer in the 10 years following diagnosis.[15]
- The statement that '*In the UK, 13% of newly diagnosed breast cancers are found to be HR+/HER2- advanced cancers at initial presentation*' was not supported in the article cited.[7] It is not clear where this statistic is taken from.
- The reference supporting the statement that '*disease progression has been found to be the factor having the greatest impact on HRQoL in patients with metastatic cancer*' is from a sample of the general public not from patients with advanced or metastatic breast cancer.[8] The exact role of progression in relation to HRQoL in postmenopausal women with HR+ HER2- negative breast cancer is not clear. The MONALEESA-2 trial generally suggested that, despite improvements in progression-free survival, for HRQoL there were no clinically meaningful changes from baseline and no meaningful differences between treatment arms. However information from Breast Cancer Now states that '*Delaying progression means more quality time with family and loved ones as well as a delay to other therapies and ultimately, starting on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients.*'[16]
- The statement in the CS that '*accumulating evidence indicates that improvements in PFS may be also associated with prolonged OS*' is fair, but among the three studies cited by the company the ERG found variation in the correlation according to HER2 status and setting. The ERG could not in the available timeframe conduct a systematic review of the correlation between the two outcomes of PFS and OS. However two further sources were investigated.[17, 18] The aim of the first (a NICE Decision Support Unit document) was to examine the evidence available on the relationship between PFS/TTP and OS in advanced or metastatic cancer.[17] It included 19 papers covering eight different tumour types. The review concluded that that the level of evidence available to support a relationship between PFS/TTP and OS varies considerably by cancer type and is not always consistent even within one specific cancer type.[17] A further review assessed approaches to surrogate-endpoint validation based on meta-analysis in various advanced tumour settings.[18] The two surrogates, PFS and time-to-progression [TTP], were assessed for suitability using three validation frameworks. The authors found that PFS was not judged to be a valid surrogate for OS according to the three evaluation frameworks used.[18]
- The committee will need to consider whether delaying progression of disease without clear knowledge of the effect on overall survival is in itself a worthwhile outcome. The information from Breast Cancer Now states that '*Delay to progression of disease can also have benefits for the mental health of patients, as lack of progression indicates that the medicine is working. A longer time to progression may mean that the patient is able to lead a more or less normal daily life throughout this time. Lack of progression of a metastatic cancer is also likely to bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness*.'

2.2 Critique of company's overview of current service provision

Figure 2.1 shows the current and proposed treatment pathway for postmenopausal women with advanced HR+/HER2- breast cancer. In the proposed pathway, the company submission (CS) specifies ribociclib as first-line treatment.[4]

Figure 2.1: Current and anticipated future treatment pathway of postmenopausal women with advanced HR+/HER2- breast cancer not previously treated with adjuvant endocrine therapy



Source: Section 3.3 of the CS; Based on NICE pathway 2016[19]

AI, aromatase inhibitor; BC, breast cancer; CT, chemotherapy; ET, endocrine therapy, HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; Ribociclib in combination with AI

Everolimus + exemestane TA421[20]

*Fulvestrant TA239[21] is not NICE recommended, however clinical feedback demonstrates usage as per licence

The company quote the NICE guidance for postmenopausal women with HR-positive and HER2-negative disease. They state that '*The specific recommendations in NICE pathways of care regarding first-line endocrine therapy for women with advanced HR+/HER2- disease vary according to the patient's menopausal status and prior treatment of earlier stage cancer.*'[4] More specifically NICE guidance (CG81) states:

'Offer endocrine therapy as first-line treatment for the majority of patients with ER-positive advanced breast cancer.

Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity.'[22]

In terms of endocrine therapy NICE guidance states:

'Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- *postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy*
- *postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.'*[22]

In addition to citing existing NICE guidance, the CS also refers to European School of Oncology / European Society for Medical Oncology (ESO-ESMO) international consensus guidelines for advanced breast cancer.[11] The company notes that according to these guidelines '*real-world studies show that many patients still receive chemotherapy as their first treatment despite its lower efficacy*.'[4]

The company states that '*The availability of ribociclib for use, together with an aromatase inhibitor, may deepen and prolong responses in first-line treatment of advanced disease – both for newly diagnosed advanced disease and metastatic advanced disease previously treated adjunctively – through actions that complement the antiproliferative effects of endocrine therapy and that potentially prolong and restore sensitivity to endocrine therapies*.'[23]

The CS further states that '*Improved PFS can be expected to prolong OS, however data for ribociclib are as yet too immature to demonstrate an OS benefit*.'[4] In addition '*ribociclib may …. allow more postmenopausal women with advanced HR+/HER2- breast cancer to delay the need for chemotherapy to control PD*.'[4]

In section 2.4 of the CS changes to current service provision and management are highlighted. The company state that '*No additional tests beyond those currently used in clinical practice are needed for the selection of patients for treatment with ribociclib*' Prior to the administration of ribociclib, '*it is recommended that a FBC, LFTs and an ECG are performed…….FBC and LFTs should be monitored every 2 weeks for the first two cycles, at the beginning of each subsequent 4 cycles and then as clinically indicated, and an ECG assessment should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, and then as clinically indicated*.'[24]

ERG comment:
The company's description of the treatment pathway and options was based on existing NICE guidance which is appropriate and relevant to the decision problem. The company also cited supporting guidance from several other sources including ESO/ESMO.

- The NICE guidance cited refers to women who are 'ER positive'. However the NICE scope and the CS refers to 'Hormone receptor-positive breast cancer'. Breast cancer can be oestrogen receptor positive (ER+) or progesterone receptor positive (PR+) or both. In practice most are ER+. This report will use the terminology 'hormone receptor-positive' or HR+ unless otherwise indicated.
- The guidance by ESMO cited by the company stating that '*real-world studies show that many patients still receive chemotherapy as their first treatment despite its lower efficacy'* is based on a study conducted in The Netherlands.[25]
- The relationship of PFS to OS has been discussed in section 2.1. As the company notes, data on OS in relation to ribociclib are not yet mature.

- The details of the extra monitoring required for ribociclib as detailed by the company above are drawn to the attention of the committee.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population (s)	Postmenopausal women with advanced or metastatic HR^+ / $HER2^-$ breast cancer previously untreated in the advanced setting	Postmenopausal women with HR+/ HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy	N.A.	In line with the scope of the decision problem.
Intervention	Ribociclib in combination with an aromatase inhibitor	Ribociclib in combination with letrozole	N.A.	In line with the scope of the decision problem.
Comparator (s)	Aromatase inhibitors (such as letrozole or anastrozole)	Letrozole	N.A.	In line with the scope of the decision problem. However, other aromatase inhibitors (such as anastrozole) have not been considered.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • progression-free survival • overall survival • objective response rate • clinical benefit rate • adverse effects of treatment • health-related quality of life.	CBR, which captures CR, PR and as well as the absence of progression (stable disease) for at least 24 weeks, is regarded as a well-established robust measure of anti-tumour activity that is well suited to measure benefit in breast cancer particularly for breast cancer drugs. In this submission, CBR outcomes are presented alongside ORR outcomes in order to demonstrate the superior antitumour activity of ribociclib over standard of care.	In line with the scope of the decision problem.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of		-	In line with the scope of the decision problem.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.			The cost effectiveness of treatments were expressed in terms of cost per quality-adjusted life year gained and a time horizon of a life-time was assumed. An NHS and Personal Social Services perspective was adopted.
Subgroups to be considered		None	No subgroup identified as ribociclib in combination with letrozole benefited all patients regardless of subgroup in MONALEESA-2	In line with the scope of the decision problem.
Special considerations including issues related to equity or equality		None	N.A.	

Source: CS, Table 1, page 14-15.

CBR = clinical benefit rate; CR = complete response; $HER2^-$ = human epidermal growth factor receptor 2-negative; HR^+ = hormone receptor-positive; N.A.= not applicable; ORR = objective response rate; PR = partial response

3.1 Population

The population is in line with the scope. However, the submission relies on one trial only, the MONALEESA-2 trial, and this trial included only [redacted] The trial was considered by the company's clinical experts to be in general representative of the aBC population in England and Wales.[26] However the ERG draws to the attention of the committee that the MONALEESA-2 trial may not be totally representative of the population in the scope in England and Wales because [redacted][26] Further details of the population of the MONALEESA-2 trial will be discussed in section 4 of this report.

3.2 Intervention

The intervention is in line with the scope. The intervention described in the scope is 'ribociclib in combination with an aromatase inhibitor'. The intervention in the CS and the main trial is 'ribociclib in combination with letrozole'. The company does not provide any evidence for ribociclib in combination with other aromatase inhibitors (AIs).

A marketing authorisation application for ribociclib, for use in combination with an AI, for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer as initial endocrine-based therapy was submitted to the European Medicines Agency (EMA) in [redacted]. An opinion from the EMA is anticipated in August 2017.

Ribociclib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Ribociclib is an oral therapy formulated as 200 mg tablets. The recommended dose of ribociclib is 600 mg (three 200 mg film-coated tablets) taken orally once daily for 21 consecutive days followed by seven days off treatment, resulting in a complete cycle of 28 days. Ribociclib can be taken with or without food. Ribociclib should be given together with an AI. An AI should be taken once daily throughout the 28-day cycle.

3.3 Comparators

The NICE scope mentions two possible aromatase inhibitors as comparators: letrozole or anastrozole. The company submission presents evidence for one comparator only: letrozole. It does not provide any evidence for the effectiveness of ribociclib versus any other aromatase inhibitors or for the relative effectiveness of letrozole versus anastrozole.

The company was asked to provide evidence that letrozole and anastrozole are equally effective as comparators for the population of this scope.[26] In response to the letter of clarification the company stated that '*There have been no substantive head to head randomized controlled studies of letrozole compared with anastrozole…. for the first line treatment of patients with HR+, HER2-ve advanced breast cancer*.' Furthermore they replied that NICE guideline (CG81) does not distinguish between aromatase inhibitors in its recommendations for the first line treatment of HR+/HER2- advanced breast cancer due to assumptions of equal effectiveness. Finally, they stated the NICE appraisal of palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, HR+, HER2- breast cancer (ID915) only included a comparison with letrozole.[26]

The ERG believes that the company has provided justification for generalisability of the letrozole comparator to other aromatase inhibitors such as anastrozole.

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- overall survival
- progression free survival
- response rate
- adverse effects of treatment
- health-related quality of life.

These outcomes are reported in the CS. However, as the results are based on one clinical trial, MONALEESA-2, and results from the first interim analysis only (29 January 2016) are presented in the CS, data for OS were not mature at the time of the interim analysis. The company was asked if any more up-to-date survival data were available.[26] A second interim OS analysis was provided with a cut-off of 2 January 2017. However the company stated that the OS data remain immature at the second interim analysis.[26]

3.5 Other relevant factors

The submission includes a Patient Access Scheme (PAS). The PAS is a [redacted].

The use of ribociclib will require additional monitoring. As stated by the company: "*prior to the administration of ribociclib, it is recommended that a FBC, LFTs and an ECG are performed. Thereafter, in patients initiating ribociclib, FBC and LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and then as clinically indicated, and an ECG assessment should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, and then as clinically indicated.*[24]" (CS, page 27).

The company pointed out that "*almost half (46%) of female breast cancer cases in the UK are diagnosed in women aged 65 years and older.*[27] *Providing access to appropriate therapies for elderly individuals is recognized by the UK Department of Health as an important priority to counter concerns regarding undertreatment of the elderly*." (CS, page 38).

The company also claims that ribociclib is an innovative therapy, which targets key mechanisms that are dysregulated in breast cancer and which also appear to play a role in the loss of response or poor response to endocrine therapy in HR+ disease (see CS, section 2.5).

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[28] _ENREF_14 The submission was also checked against the Single Technology Appraisal (STA) specification for company/sponsor submission of evidence.[29]

The CS stated that searches for systematic reviews and trials were conducted in June 2016. Search strategies were reported in detail in Appendix 2 of the CS for the following databases: MEDLINE, MEDLINE in-Process, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE). The host provider for each database was listed. The date span of the databases searched and the specific date the searches were conducted were provided. Searches utilised study design filters based on the BMJ Clinical Evidence MEDLINE and Embase filters for RCTs.[30]

Additional searches of the following conference proceedings were reported for 2013-2016: American Society for Clinical Oncology (ASCO), American Association for Cancer Research (AACR), ASCO Breast Cancer Symposium (ASCO BC), San Antonio Breast Cancer Symposium (SABCS), European CanCer Organisation (ECCO), European Breast Cancer Conference (EBCC) and European Society of Medical Oncology (ESMO).

ERG comment:

- The database searches were clearly structured (population, intervention, study design), using a combination of subject heading indexing and free text terms, with synonyms, adjacency operators and truncation.
- The search strategy provided in Appendix 2 of the CS reports a simultaneous search across six different databases using the Ovid interface: MEDLINE, MEDLINE In-Process, Embase, CENTRAL, CDSR and DARE. This approach was not transparent, as it was unclear how successfully the searches were executed in each individual database. Furthermore, the results per search line and per database were not reported, in line with current best practice, meaning that it was difficult to appraise the search strategy with confidence.
- The ERG was concerned that limiting the clinical effectiveness searches to English language studies may have introduced potential language bias. Current best practice states that *'Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication'*.[31] During the clarification process, the ERG queried the rationale for applying an English language limit. In response to clarification the company referred to the Cochrane Handbook for Systematic Reviews of Interventions[32], which infers that the *'potential impact of studies published in languages other than English in a meta-analysis may be minimal because of the shift towards publication of studies in English'*.[26] The Cochrane Handbook does however follow this up by stating that *'it is difficult to predict in which cases this exclusion may bias a systematic review'*.[33] Furthermore, the Cochrane Handbook states clearly that *'no language restrictions should be included in the search strategy'*.[31] The company response cited another study[34] as further justification for limiting their searches to English language only, *'which found no evidence of a systematic bias from the use of language restrictions in systematic review-based meta-analyses in conventional medicine'*.[26] Once again however, the authors of this study

qualified this conclusion by stating that their *'findings do not rule out the potential for language bias when language restrictions are used"* and that *"searches should include LOE (languages other than English) studies when resources and time are available to minimize the risk of a biased summary effect'*.[34] The company also referred to previous NICE appraisals excluding non-English language publications from their searches and that based on this *'a pragmatic decision to not expand the search to non-English language articles was made"*[26]. Finally, the company conducted a search of PubMed *"for ribociclib NOT English[language] on 4th May 2017 found only 2 publications not in English, neither of which were RCTs, so we are confident that no relevant studies have been excluded or missed in this review due to not being published in English'*.[26]

- The ERG remains concerned that the English language restrictions applied to the searches were too restrictive and not in line with current best practice.
- The date limit used in the searches, 2007-2016, was justified by the CS as *'HER2 testing was standardized since 2007'*.[4] The reference cited in the section 4.1.1 of the CS to support this justification was incorrect.[35] The correct citation was provided in section 8.2.1 of the CS Appendix.[36] Despite this justification, it is possible that potentially useful studies published before 2007 were not included in the review.
- The search strategy included a facet of drug search terms (search line #62: lapatinib, trastuzumab, pertuzumab) that, via the Boolean operator NOT, had been used to remove database records including these search terms. This is not recommended practice: *'The 'NOT' operator should be avoided where possible to avoid the danger of inadvertently removing from the search set records that are relevant'*[37] and *'NOT should be used with great care because it may have a larger effect than anticipated; a record may well discuss both the concept of interest and the one to be excluded'*.[38]
- It was unclear if the RCT filters for MEDLINE and Embase included in the search strategy were also used in the Cochrane Library search. As the Cochrane Library databases are pre-filtered to include trials and systematic reviews, a study design filter was not necessary and may have adversely affected the results.
- Search terms used to limit the search to retrieve human only studies appear four times in the search strategy.
- The searches were conducted in June 2016, meaning that they were nine months out of date when the report was submitted to NICE in March 2017. The ERG asked why the searches had not been updated, and in response, the company conducted an update of the searches in May 2017. Full details of the update searches were provided: search strategies, date of searches, date span, and results. Seven records were identified that met the inclusion criteria: six were publications derived from the MONALEESA-2 trial;[39] and one was the protocol for the MONALEESA-3 trial[40], for which no results have been reported yet.
- For the searches of conference proceedings the CS did not provide full details of the search terms used, the precise date of the searches or the results. Full details were provided for the update searches conducted in May 2017.
- A search of trials registers, such as ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for unpublished and ongoing trials would have been a useful addition to the literature searches.
- Section 4.12 of the CS states that safety data were derived from the MONALEESA-2 trial.[39] No literature searches to identify other adverse events data were reported in 4.12 or Appendix 9. The ERG queried this omission and asked for confirmation that there had been no literature searches for adverse events. CRD guidance[38] recommends that if searches have been limited by

a study design filter, additional searches should be undertaken to ensure that adverse events that are long-term, rare or unanticipated are not missed. When the ERG queried this omission, the clarification response confirmed that safety data were only derived from the MONALEESA-2 trial,[39] and the following reasons were given for limiting the literature search to RCTs only:

- 'The NICE Guide to the methods of technology appraisal recommend that RCTs are considered to be the most appropriate source for measures of relative treatment effect due to minimising potential external influences when assessing an effect on one or more interventions on outcomes.
- NICE consider non-randomised and non-controlled evidence have the potential to contain multiple biases and may lead to difficulty in interpreting the true treatment effect and providing valid conclusions.
- Currently there are no non-randomised trial outcomes available for the intervention treatment, ribociclib, which would provide more robust clinical information over and above the pivotal phase III MONALEESA-2 trial.
- The non-randomised trials listed in Table 15 of the CS[4] are included based on internal knowledge and as context and confirmation for the RCT MONALEESA-2 trial. The non-RCTs were not used to drive the submission.
- The availability of patient level data for the pivotal trial data, MONALEESA-2, enables the most robust analysis of the trial data, strengthening the conclusions that can be made of the treatment effect.
- Clinical expert validation supported MONALEESA-2 as being a clinically relevant study that provides robust data on the effect of ribociclib + letrozole in patients with aBC'.[26]

- Searches were not conducted for indirect and mixed treatment comparisons (4.10) or for non-randomised and non-controlled evidence (4.11). The CS states that an indirect comparison was not performed as the economic analysis used data from the one relevant RCT identified, MONALEESA-2.[41] Although three non-randomised trials provided information relevant to the dosing regimen and schedule selected for investigation in the MONALEESA-2 trial, there was no indication of how these trials were identified. Appendix 5, where the search strategy for indirect and mixed treatment comparisons would have been reported, was left blank. The company responded by confirming that clinical efficacy and safety data were derived from the MONALEESA-2 trial,[41] and that as no indirect or mixed treatment comparisons were performed there was no need for searches to be conducted.

4.1.2 Inclusion criteria

A review of the literature was conducted to identify systematic reviews and trials of interventions in patients with HR+ HER2- advanced breast cancer.

The eligibility criteria used in the search strategy for clinical effectiveness is presented in Table 4.1.

Table 4.1: Eligibility criteria used in search strategy for clinical effectiveness

	Inclusion criteria	Exclusion criteria
Population	Women with hormone receptor-positive (HR+), HER2 negative (HER2-) advanced breast cancer (ABC) who had received no systemic anti-cancer treatment for advanced disease	Women whose cancer was not HR+ HER2- or no outcomes were presented for this subtype Women whose cancer was not advanced or a mixed population with no separate results for ABC Women who had received systemic anti-cancer treatment for advanced disease
Interventions	Ribociclib as monotherapy or as part of combination therapy	Not including the drug of interest
Outcomes	At least one of the following outcomes: **Efficacy** Overall survival (OS) Progression-free survival (PFS) Time to progression (TTP) Overall response rate (ORR) Clinical benefit rate (CBR) **Safety** Adverse events (AEs) Serious adverse events (SAEs) All-cause discontinuation Discontinuation due to AE	No outcomes of interest
Study design	Randomised controlled trials (RCTs)	Single-arm trials Case reports Editorials and opinion pieces Reviews
Language restrictions	English language only	Non-English
Publication year	2007 – current	Published before 2007
Source: CS, Table 7, pages 39-40		

ERG comment:

- The population of the systematic review is in line with the NICE scope. However, the intervention is not. Regarding interventions, only studies that included a ribociclib arm were included. Therefore the company did not attempt to compare different types of aromatase inhibitors (AIs) with each other to allow an indirect comparison of ribociclib plus letrozole versus other AIs.
- Health-related quality of life was not included as a relevant outcome in the systematic review. However in response to clarification the company stated that '*No trials were excluded in their entirety for this reason*.'[26]
- The study design was restricted to RCTs. The company were asked if any non-randomised evidence was available particularly in relation to adverse events (see also section 4.1.1 of this

report). The company provided justification for limiting the evidence to RCTs (see also section 4.1.1 of this report).

4.1.3 Critique of data extraction

In response to clarification, the company stated that '*Two reviewers screened, extracted, and assessed the quality of each record in parallel. If there was a discrepancy, a third reviewer reviewed and resolved the discrepancy.*'[26]

ERG comment: The ERG believes that overall the data extraction was carried out appropriately.

4.1.4 Quality assessment

Quality assessment of MONALEESA-2 was performed using the clinical study report and published paper. Elements assessed were randomisation, allocation concealment, comparability of groups, blinding of care providers, patients and outcome assessors and drop out, selective reporting of outcomes and use of intention to treat analysis and appropriate methods for dealing with missing data.

ERG comment: Study quality appeared to have been assessed using appropriate tools.

4.1.5 Evidence synthesis

No meta-analysis or indirect comparison could be performed as only one trial was found eligible for inclusion in the submission.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the evidence in the submission

The CS was based on one trial (MONALEESA-2) which will be discussed in detail in this section. Three non-randomised trials were included to '*provide information relevant to the dosing regimen and schedule selected for investigation in the phase 3 MONALEESA-2 trial'*.[42-44] These will be discussed more briefly in this report. Ongoing trials will be discussed in section 4.2.4.

ERG comment: The ERG was provided with a list of excluded studies. It did not appear that any studies were excluded inappropriately.

4.2.2 The MONALEESA-2 trial

4.2.2.1 Methodology of the MONALEESA-2 trial

The MONALEESA-2 study included postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. Patients were required to have either measurable disease (according to RECIST version 1.1 criteria) or at least one predominantly lytic bone lesion, along with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and adequate bone marrow and organ function. Exclusion criteria included previous treatment with a CDK4/6 inhibitor or any systemic chemotherapy or endocrine therapy for metastatic disease. Previous neoadjuvant or adjuvant therapy with a non-steroidal aromatase inhibitor agent was allowed when the disease-free interval was more than 12 months. Patients with inflammatory breast cancer, central nervous system metastases, a history of cardiac disease or dysfunction (including a QTcF of >450 msec at screening) or impaired gastrointestinal function that altered drug absorption were excluded. The use of concomitant medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes (TdP) was not permitted.[23]

Table 4.2: Methodology of the MONALEESA-2 trial

PICO	Description
Population	Postmenopausal women with HR+/ HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy
Intervention	Ribociclib (600 mg once daily on days 1–21 of a 28-day cycle) in combination with letrozole (2.5 mg once daily, continuous therapy)
Comparator	Placebo in combination with letrozole (2.5 mg once daily, continuous therapy)
Outcomes	Primary: PFS based on local and BIRC assessment Secondary: OS, ORR, CBR, Safety (AEs, biomarker analysis, vital signs, time to definitive deterioration of ECOG PS) and Quality of life, evaluated using the EORTC QLQ-C30, EQ-5D-5L and breast cancer module EORTC QLQ-BR23
Study design	Randomised, double-blind, placebo-controlled phase 3 trial

AE = Adverse events; BIRC = blinded independent review committee; CBR = clinical benefit rate; ECOG PS = Eastern Cooperative Oncology Group performance status; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer; EQ-5D-5L = European quality of life-5 dimensions-5 levels; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; MONALEESA-2 = mammary oncology assessment of LEE011's efficacy and safety-2; RCT = randomised controlled trial; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

The methodology of the trial is summarised in Table 4.2. The trial was conducted at 223 trial centres in 29 countries including [redacted] patients from England and Wales. Patients were randomised 1:1 to receive ribociclib (600 mg once daily, days 1–21 of a 28-day cycle) plus letrozole (2.5 mg once daily, continuous treatment) or placebo plus letrozole (2.5 mg once daily, continuous treatment). Randomisation was stratified according to the presence or absence of liver or lung metastases. Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage AEs; no dose reductions were permitted for letrozole and no crossover between treatment arms was allowed. Patients who discontinued ribociclib or placebo could continue receiving letrozole. Treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of ribociclib or letrozole.[23]

The primary outcome was PFS as per RECIST version 1.1 criteria, based on local radiological assessment. The key secondary endpoint was OS (defined as the time from date of randomisation to date of death due to any cause). Other secondary outcomes included objective response rate (ORR; complete response [CR] or partial response [PR]), CBR (overall response plus stable disease lasting 24 weeks or more), time to deterioration of ECOG PS, safety and HRQoL.[23]

Tumour assessments were based on computed tomography scanning or magnetic resonance imaging of the chest, abdomen and pelvis performed at baseline and every eight weeks during the first 18 months, and every 12 weeks thereafter until disease progression. Tumour response was assessed using RECIST version 1.1.[23]

HRQoL was evaluated every eight weeks during the first 18 months and every 12 weeks thereafter until disease progression and at end of study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0), European quality of life-5 dimensions-5 levels (EQ-5D-5L, version 4.0) and the breast cancer-specific EORTC QLQ-BR23 (version 1.0). Time to definitive deterioration (10%) in the global health status on the EORTC QLQ-

C30 scale as well as in each of the three functional scales (emotional, physical, and social functioning) was compared between the two treatment groups.

AEs were recorded throughout the study. Haematological laboratory tests were performed at screening, on day 15 of cycle 1, and on day 1 of subsequent cycles until the end of treatment. ECG assessments were performed at screening, on day 15 of cycle 1, and on day 1 of cycles 2 and 3 in all patients. Following a protocol amendment, in order to enhance and clarify the cardiac safety monitoring specifically for cases of QTc prolongation, additional ECG assessments were performed on day 1 of cycles 4 through 9 in all patients and on day 1 of subsequent cycles in patients with a mean QTcF interval of >480 msec or more at any time before cycle 10.

Pre-specified subgroup analyses of the primary outcome measure, PFS, were conducted along with the planned interim analysis. A total of 19 subgroup analyses were performed based on patient and disease characteristics and prior therapies. The categories included: age (less than 65 years and 65 years or older); race (Asian, non-Asian); baseline ECOG status (0 or 1); hormone-receptor status (ER+ and progesterone receptor-positive or other); liver or lung metastases (yes or no); bone-only disease (yes or no); number of metastatic sites (<3 vs. ≥3); newly diagnosed disease (yes or no); prior adjuvant or neoadjuvant chemotherapy (yes or no); previous endocrine therapy (non-steroidal AIs and others, tamoxifen or exemestane, none).[23]

4.2.2.2 Statistical analysis of the MONALEESA-2 trial

The objective of the MONALEESA-2 trial was to evaluate the efficacy and safety of the combination of ribociclib plus letrozole and placebo plus letrozole in postmenopausal women with HR+, HER2-, recurrent or metastatic breast cancer who had received no prior systemic therapy for advanced breast cancer.

The primary outcome was progression free survival (PFS) and progression was classified using the Investigator's review of radiology data using the RECIST version 1.1 criteria. PFS was defined as the time from the randomisation date to the date of the first documented disease progression or death due to any cause. There were two PFS analyses: an interim analysis after approximately 211 PFS events and a final analysis after 302 PFS events had occurred. The sample size calculation was based on a 2-look group sequential design using the Haybittle–Peto efficacy stopping boundary.[45, 46] At the interim analysis the observed p-value had to be $< 1.29 \times 10^{-5}$ (HR = 0.56) to conclude superior efficacy of ribociclib to placebo for PFS. It was determined that 302 PFS events were required to detect a hazard ratio of 0.67 with a power of 93.5% at a one-sided alpha level of 0.025 using this 2-look sequential design. Allowing for 10% of patients lost to follow-up it was planned to recruit a total of 650 patients and the 302nd PFS event was estimated to occur at approximately 20 months from the date of the first randomisation.[45, 46]

For the primary efficacy analysis, PFS was compared between the two groups using a log-rank test stratified according to the presence or absence of liver or lung metastases at a one-sided 2.5% significance level. A Cox proportional hazards model stratified according to the presence or absence of liver or lung metastases was also performed to estimate the hazard ratio (HR) with 95% confidence interval (CI). An additional Cox proportional hazards model was used to evaluate the impact of other baseline or disease characteristics on the estimated HR. For PFS missing scans were assessed using the 'actual event' and 'backdating' approaches. The 'actual event' approach took the PFS event date whenever it occurred, after two or more missing tumour assessments. The 'backdating' approach used the date of next scheduled assessment as the PFS event date whenever it occurred after a missing tumour assessment. Sensitivity analysis was performed, including these events, in the assessment of PFS.

Overall survival (OS) analyses were only performed if the primary endpoint of PFS was statistically significant and favoured ribociclib plus letrozole over placebo plus letrozole. Four OS analyses were planned: at the time of the interim (after 76 expected deaths) and final analyses for PFS (after 120 expected deaths), after 300 deaths and after 400 deaths (at approximately 65 months from the date of the first randomisation. OS was defined as the time from the date of randomisation to the date of death from any cause. As there were multiple analyses the type I error rate was controlled using a 4-look sequential design using a Lan and Demets α-spending function.[47] The sample size for OS assumed that the median OS in the placebo plus letrozole group would be 34 months and treatment with ribociclib would increase this to 47.2 months. A total of 400 deaths would be needed to detect a HR of 0.72 with 90% power at a one-sided 2.5% significant level.

OS between the two treatment groups was compared using a stratified log-rank test at a one-sided 2.5% significance level and the HR with 95% CI was estimated using a stratified Cox proportional hazards model, using the presence or absence of liver or lung metastases as the stratification factor. For OS analysis, in the rare cases when either the day was missing or both month and day were missing for the date of death, imputation rules were implemented based on the date of the last patient contact.

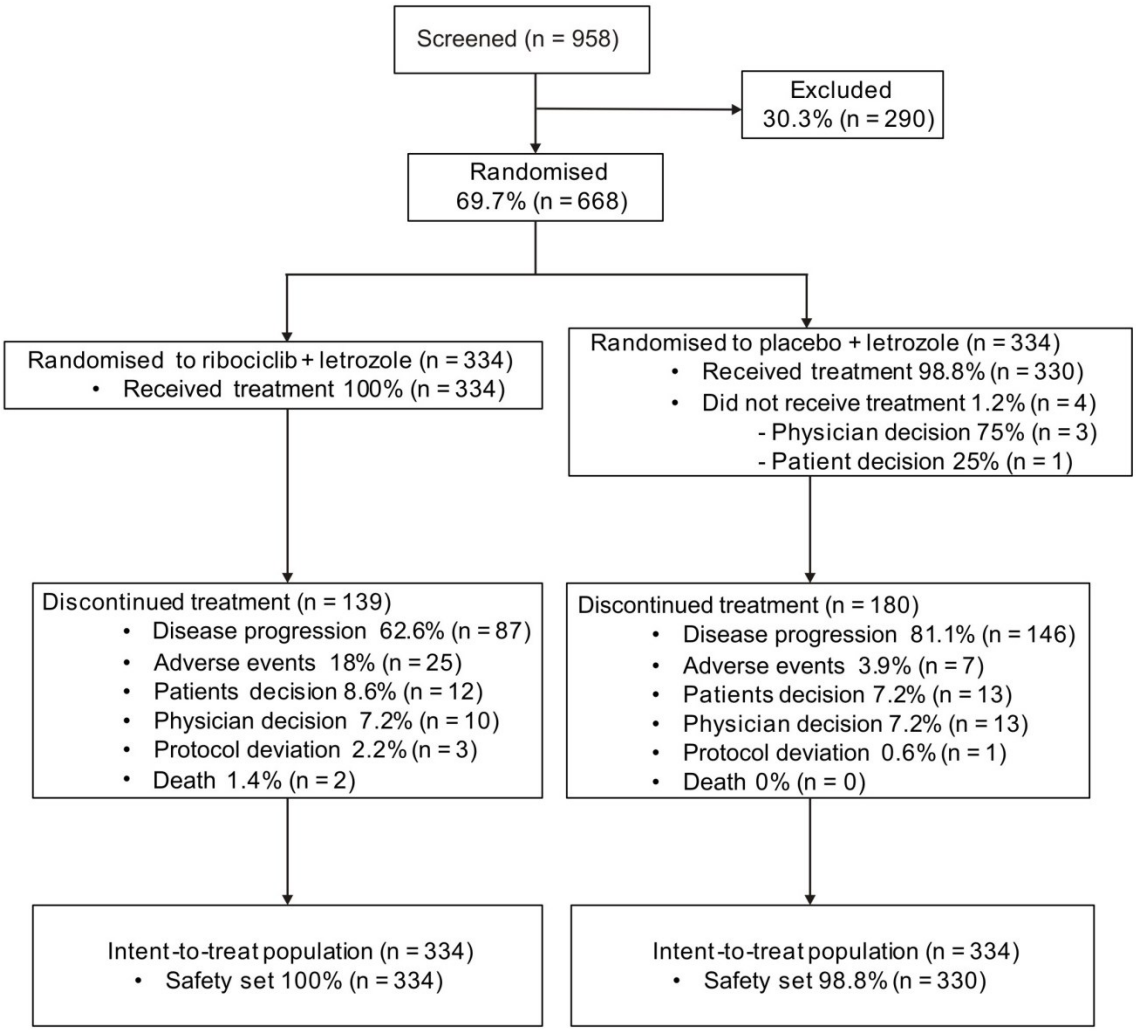
Efficacy analyses were performed in the ITT population which was all randomised patients who were analysed according to the treatment and stratum assigned at randomisation. Safety analyses were performed in the safety population which was defined as all patients who received at least one dose of study treatment and had at least one post-baseline safety assessment. Safety population data were analysed according to the treatment received.

ERG comment: The methods used for the design and statistical analysis of this trial appear to be appropriate. It was designed using group sequential trial methods which accounted for interim analyses by applying a stopping boundary which used a very small p-value to prevent erroneously concluding a treatment benefit which did not exist. The statistical analysis methods also appear to be appropriate. The main concern is that the use of an interim analysis for PFS meant that the initial results presented in the company submission were based on the data available at the time of the interim analysis for PFS. At this point the OS data were immature as the required number of deaths had not been reached. Additional OS results for later data cut-offs were provided by the company and are discussed in the results section below.

4.2.2.3 Participants in the MONALEESA-2 trial

A participant flow diagram for the MONALEESA-2 trial as of the data cut-off date for the interim analysis (29 January 2016) is provided in Figure 4.1.

Figure 4.1: CONSORT diagram for MONALEESA-2



Source: CS, Figure 6, page 47

A total of 668 patients were randomised to ribociclib (n=334) or placebo (n=334) in the ITT population. At the time of data cut-off (29 January 2016), a total of 349 patients (52.2%) were still receiving treatment (ribociclib, n=195; placebo, n=154). The rates of discontinuation were 41.6% in the ribociclib group compared with 53.9% in the placebo group. The most frequent reason for discontinuation was disease progression in both groups (ribociclib, 26.0%; placebo, 43.7%). Discontinuations due to AEs were 7.5% in the ribociclib group and 2.1% in the placebo group. The median duration of follow-up from randomisation to data cut-off was 15.3 months.[23]

Demographic and clinical characteristics of the patients enrolled in the MONALEESA-2 trial are summarised in Table 4.3.

Table 4.3: Participant characteristics of the MONALEESA-2 TRIAL

Baseline characteristics	Ribociclib group (n = 334)	Placebo group (n = 334)
Age, years Median (range)	62 (23–91)	63 (29–88)
Race, n (%)[a] White Asian Black Others or unknown	 269 (80.5) 28 (8.4) 10 (3.0) 27 (8.1)	 280 (83.8) 23 (6.9) 7 (2.1) 24 (7.2)
ECOG PS, n (%) 0 1	 205 (61.4) 129 (38.6)	 202 (60.5) 132 (39.5)
Disease stage, n (%) III IV	 1 (0.3) 333 (99.7)	 3 (0.9) 331 (99.1)
Disease-free interval, n (%) Newly diagnosed Existing disease ≤12 months >12 to ≤24 months >24 months Unknown	 114 (34.1) 220 (65.9) 4 (1.2) 14 (4.2) 202 (60.5) 0	 113 (33.8) 221 (66.2) 10 (3.0) 15 (4.5) 195 (58.4) 1 (0.3)
HER2 receptor status, n (%) Positive Negative	 1 (0.3) 333 (99.7)	 1 (0.3) 333 (99.7)
Oestrogen receptor positive, n (%) Progesterone receptor positive, n (%)	332 (99.4) 271 (81.1)	333 (99.7) 278 (83.2)
Number of metastatic sites, n (%) 0 1 2 ≥3	 2 (0.6) 100 (29.9) 118 (35.3) 114 (34.1)	 1 (0.3) 117 (35.0) 103 (30.8) 113 (33.8)
Site of metastases, n (%) Breast Bone Any Only Visceral[b] Lymph nodes Other	 8 (2.4) 246 (73.7) 69 (20.7) 197 (59.0) 133 (39.8) 35 (10.5)	 11 (3.3) 244 (73.1) 78 (23.4) 196 (58.7) 123 (36.8) 22 (6.6)

Baseline characteristics	Ribociclib group (n = 334)	Placebo group (n = 334)
Prior therapy, n (%)[c]		
Radiotherapy	178 (53.3)	167 (50.0)
Neoadjuvant or adjuvant chemotherapy	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Tamoxifen	140 (41.9)	145 (43.4)
Anastrozole	47 (14.1)	42 (12.6)
Letrozole	34 (10.2)	25 (7.5)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Other	2 (0.6)	4 (1.2)
Source: CSR, Table 11, pages 48-49 a. Race was self-reported; b. Visceral involvement included liver, lung and other visceral metastases; c. Some patients received both chemotherapy and endocrine therapy as neoadjuvant or adjuvant treatment. ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2.		

Almost all patients (≥ 99%) had stage IV disease and were ER+/HER2-, with more than 80% being positive for progesterone receptors. Thirty-four percent of the patients in both groups had newly diagnosed advanced or metastatic disease, and most of those with recurrent disease had been disease-free for at least 24 months. Approximately one-third of patients had three or more metastatic sites and similar proportions had one or two metastatic sites. Visceral disease (including liver, lung and other visceral metastasis) was present in 58.8%, and 22.0% had bone-only disease. Approximately half of the patients had received prior radiotherapy half had received prior neo-adjuvant or adjuvant chemotherapy and approximately 40% had received prior neo-adjuvant or adjuvant endocrine therapy.

Approximately 45% of patients were aged 65 years or older, and the median age was 62 and 63 years in the two groups. The ERG asked for further breakdown of patient age in MONALEESA-2. This is shown in Table 4.4.

Table 4.4: Age breakdown in the MONALEESA-2 TRIAL

Age group	Ribociclib group (n = 334)	Placebo group (n = 334)	All patients (n = 668)
20 - < 30	[redacted]	[redacted]	[redacted]
30 - < 40	[redacted]	[redacted]	[redacted]
40 - < 50	[redacted]	[redacted]	[redacted]
50 - < 60	[redacted]	[redacted]	[redacted]
60 - < 70	[redacted]	[redacted]	[redacted]
70 - < 80	[redacted]	[redacted]	[redacted]
80 - < 90	[redacted]	[redacted]	[redacted]
90 - < 100	[redacted]	[redacted]	[redacted]
Source: CLEE011A2301 - Additional analyses (Cut-off date: 04JAN2017) – provided by the company			

The company also confirmed in response to clarification that '[redacted]

[redacted] The applicability of the trial to a population in England and Wales was considered by the company's clinical experts to be in general representative of the aBC population in England and Wales.[26] However the ERG draws to the attention of the committee that the MONALEESA-2 trial may not be totally representative of the population in the scope in England and Wales.

[redacted]'[26]

ERG comment:

- Overall, patient baseline characteristics seem well balanced between treatment groups in terms of demographics and disease characteristics.
- The trial includes both patients with de novo disease and those who have received previous adjuvant/neoadjuvant therapy. The ERG asked for results separately for these patient groups and these are provided in the results section.

4.2.2.4 Quality assessment of the MONALEESA-2 trial

Quality assessment of the MONALEESA-2 study is described in Table 4.5.

Table 4.5: Quality of the MONALEESA-2 TRIAL

Question	Company assessment and explanation	ERG assessment and explanation
Was randomisation carried out appropriately?	Yes, randomisation of patients in a 1:1 ratio to study interventions was carried out using an IRT system	Yes
Was the concealment of treatment allocation adequate?	Yes, randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone involved in the study	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced between treatment groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, patients, investigators, study team and anyone involved in the study conduct were blinded to the identity of the treatment from the time of randomisation until database lock An independent statistical group, pharmacokinetics bio analyst and clinical pharmacology expert, not involved in the study conduct, prepared data reports	Unclear. Adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and or patients. Therefore, results based on independent review are more reliable.

Question	Company assessment and explanation	ERG assessment and explanation
Were there any unexpected imbalances in drop-outs between groups?	No, disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo plus letrozole arm compared to the ribociclib plus letrozole arm	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The CSR provides details of all outcomes assessed. The primary endpoint and most secondary endpoints are reported in the primary publication.	A summary version of the CSR was provided as part of the CS. However, the ERG is not aware of any missing results for any outcomes. OS results are not mature.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for the data?	Yes, the FAS consisted of all randomised patients. Following the ITT principle, patients were analysed according to the treatment and stratum they were assigned to at randomisation; data from the FAS were the primary basis for all efficacy analyses Missing data were appropriately handled as mentioned below: PFS: Actual event and backdating Missing scans were assessed using the 'actual event' and 'backdating' approaches. The 'actual event' approach took the PFS event date whenever it occurred, after two or more missing tumour assessments. The 'backdating' approach used the date of the next scheduled assessment as the PFS event date whenever it occurred after a missing tumour assessment. Sensitivity analysis was performed including these events in the assessment of PFS For OS analysis, in rare cases when either the day was missing or both month and day were missing for the date of death, imputation rules were implemented	Yes.
Source: CS, Table 12, pages 49-50 CSR = clinical study report; FAS = full analysis set; IRT = Interactive Response Technology; ITT = intention-to-treat; OS = overall survival, PFS = progression-free survival		

ERG comment: Adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients. Therefore, results based on independent review are more reliable. In addition, overall survival results were not mature at the time of the first interim analysis, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off. The study remains blinded for follow-up of overall survival.[23]

4.2.2.5 Efficacy results of the MONALEESA-2 trial

Results of the planned interim analysis of MONALEESA-2 (performed at the data cut-off on 29 January 2016 after observing 243 of the planned 302 events) demonstrated superior PFS with ribociclib plus letrozole compared with placebo plus letrozole as first-line treatment of postmenopausal women with

HR+/HER2- recurrent or metastatic breast cancer. The PFS benefit for ribociclib was observed across all pre-planned subgroups and as per local and central assessment (see Table 4.6). However, results from the blinded independent review committee (BIRC) were [redacted] for ribociclib than those based on local assessment; especially for results [redacted] when comparing the two treatment groups. Furthermore, ribociclib was associated with a statistically significant improvement in ORR and CBR. The study has a median follow-up of 15.3 months, which is insufficient to demonstrate effects on OS; 43 patients died (23 in the ribociclib group and 20 in the placebo group).[23]

Table 4.6 summarises the key efficacy data for this study.

Table 4.6: Summary of efficacy data for MONALEESA-2 (29 January 2016 cut-off)

Endpoint	Ribociclib + letrozole (n = 334)	Placebo + letrozole (n = 334)
PFS (local)		
Median PFS, (95% CI), months	NR (19.3–NR)	14.7 (13.0–16.5)
6-month PFS, % (95% CI)	[redacted]	[redacted]
12-month PFS, % (95% CI)	72.8 (67.3–77.6)	60.9 (55.1–66.2)
18-month PFS, % (95% CI)	63.0 (54.6–70.3)	42.2 (34.8–49.5)
HR (95% CI)[a]	0.56 (0.43–0.72)	
PFS (central)		
Median PFS, (95% CI), months	[redacted]	[redacted]
6-month PFS, % (95% CI)		
12-month PFS, % (95% CI)		
18-month PFS, % (95% CI)		
HR (95% CI)[a]	0.59 (0.41–0.85)	
OS		
Median OS, months	NR	NR
12-month OS, % (95% CI)	[redacted]	[redacted]
HR (95% CI)[a]		
Response rate (all patients), n (%)		
Response rate (all patients), n (%)		
Complete Response	9 (2.7)	7 (2.1)
Partial Response	127 (38.0)	85 (25.4)
Stable Disease	95 (28.4)	111 (33.2)
Neither complete response nor progressive disease*	66 (19.8)	75 (22.5)
Progressive Disease	19 (5.7)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)
ORR[b]	136 (40.7), p<0.001	92 (27.5)
CBR[c]	266 (79.6), p=0.018	243 (72.8)

Endpoint	Ribociclib + letrozole (n = 334)	Placebo + letrozole (n = 334)
Source: Table 13 and 14 of the CS and Hortobagyi et al., 2016[23] a. HR obtained from Cox proportional hazards model stratified by liver and/or lung metastases as per the IRT; b. Overall response included a complete or partial response (P<0.001 for the comparison with placebo); c. Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting 24 weeks or more, or neither a complete response nor progressive disease lasting 24 weeks or more (P=0.02 for the comparison with placebo). * In this category, the best overall response was evaluated only among patients who had no measurable disease at baseline, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. One patient with measurable disease in the placebo group was misclassified as having a best overall response of neither complete response nor progressive disease. CBR = clinical benefit rate; CI = confidence interval; HR = hazard ratio; HRQoL = Health-related quality of life; IRT = Interactive Response Technology; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.		

ERG comment: The company was asked to clarify the differences observed in results between local and central assessment. They stated that '*In clinical practice PFS is a combined end point that may include symptomatic progression (e.g. pain due to bone metastasis) in addition to radiologic progression. Symptomatic deterioration may be a reason to discontinue or alter therapy*.' They further stated that '[redacted]'[26]

The company was asked if more up-to-date data were available than that presented in the CS (29 January 2016) as overall survival data were not mature at the time of interim analysis. The company provided details of two further analyses providing data on PFS and OS (22 June 2016 and 2 January 2017).

By 22 June 2016 the median duration of follow up was 20.1 months as opposed to 15.3 months at the interim analysis. The efficacy analyses were based on 297 local PFS and [redacted] central PFS events. Overall survival was not assessed. [redacted] of patients were still continuing treatment with ribociclib and [redacted] continued on placebo. Results are presented in the table below alongside the 29 January 2016 data presented in the submission.

By 2 January 2017 the median duration of follow up was 26.4 months. The efficacy analyses were based on 345 local PFS events only. Overall survival was also assessed. One hundred and thirty-one (39.2%) of patients were still continuing treatment with ribociclib and 88 (26.3%) continued on placebo. Results are presented in the table below alongside the 29 January 2016 data presented in the submission.

In a recent related technology appraisal ('Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer' [ID915]), the NICE committee "concluded that the BIRC results would be more appropriate for decision-making." (See ACD, point 4.3, page 7).[48] Therefore, in this report we have focused on the BIRC results.

Table 4.7: Comparison of PFS and OS for the three data cut-off points in the MONALEESA-2 trial

Endpoint	29 January 2016		22 June 2016		2 January 2017	
	Ribociclib + letrozole (n = 334)	Placebo + letrozole (n = 334)	Ribociclib + letrozole (n = 334)	Placebo + letrozole (n = 334)	Ribociclib + letrozole (n = 334)	Placebo + letrozole (n = 334)
PFS (local)						
Median PFS, (95% CI), mnths	NR (19.3–NR)	14.7 (13.0–16.5)	22.4 (20.8-NE)	15.3 (13.4-16.7)	25.3 (23.0 -30.3)	16.0 (13.4-18.2
6-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12-month PFS, % (95% CI)	72.8 (67.3–77.6)	60.9 (55.1–66.2)	[redacted]	[redacted]	[redacted]	[redacted]
18-month PFS, % (95% CI)	63.0 (54.6–70.3)	42.2 (34.8–49.5)	[redacted]	[redacted]	[redacted]	[redacted]
24-month PFS, % (95% CI)	NA	NA	NA	NA	54.7 [redacted]	35.9 [redacted]
30-month PFS, % (95% CI)	NA	NA	NA	NA	[redacted]	[redacted]
HR (95% CI)[a]	0.56 (0.43–0.72)		0.559 (0.443-0.706)		0.568 (0.457-0.704)	
PFS (central)						
Median PFS, (95% CI), mnths	22.9	NR	[redacted]	[redacted]	[redacted]	
6-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]		
12-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]		
18-month PFS, % (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]		
HR (95% CI)[a]	0.59 (0.41–0.85)		[redacted]			
OS	**Based on 43 deaths**				**Based on 116 deaths**	
Median OS, months	NR	NR	Not assessed		NR	33.0 (33.0-NE)
12-month OS, % (95% CI)	[redacted]	[redacted]			[redacted]	[redacted]
18-month OS, % (95% CI)					[redacted]	[redacted]
24-month OS, % (95% CI)					86.7 [redacted]	84.8 [redacted]
30-month OS, % (95% CI)					[redacted]	[redacted]
HR (95% CI)[a]	[redacted]				0.746 (0.517-1.078)	

Source: CS, Novartis MONALEESA-2 ribociclib June 2016 CSR update and Novartis MONALEESA-2 ribociclib January 2017 CSR data cut
a) HR obtained from COX PH model stratified by liver and / or lung metastasis as per IRT
NA = not assessed, NE = not estimable, NR = Not reached

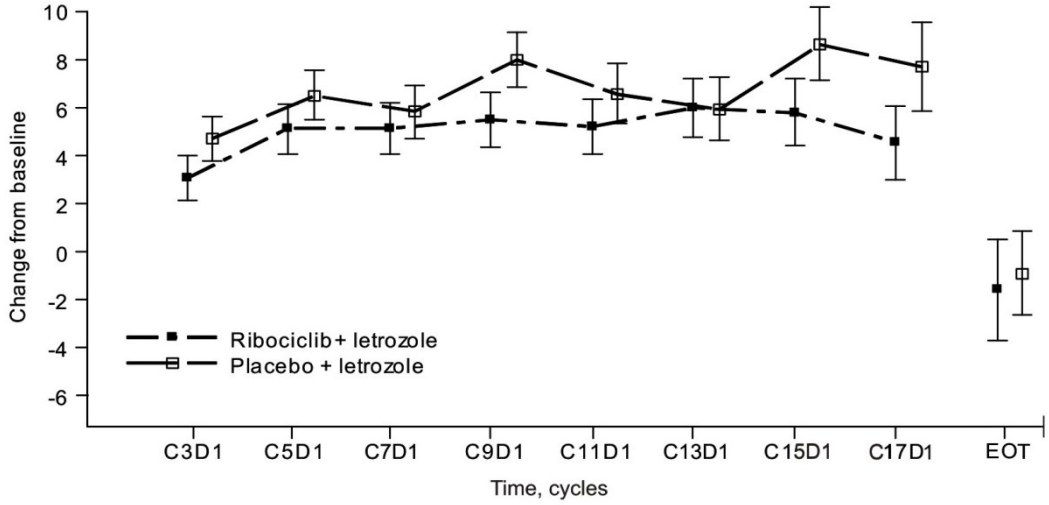
4.2.2.6 HRQoL results of the MONALEESA-2 trial

The global health status/global QoL scale score of the EORTC QLQ-C30 was the primary patient reported outcome (PRO) variable of interest. Physical functioning, emotional functioning and social functioning sub-scale scores of the EORTC QLQ-C30, the breast cancer symptoms scale of the EORTC QLQ-BR23, and the VAS of the EQ-5D-5L were secondary PRO variables of interest.

Measures of HRQoL (QLQ-C30, QLQ-BR23 and EQ-5D-5L) were obtained for most patients (>90%) throughout the first year of treatment.

Scores for QLQ-C30 GHS/QoL domain were similar in the two groups throughout the study and showed a slight improvement over the course of the study (See Figure 4.2).

Figure 4.2: Change from baseline in EORTC QLQ-C30 GHS/QOL scores over time



Ribociclib	n =	285	262	249	232	223	203	152	108	97
Placebo	n =	285	254	248	219	193	177	129	80	142

Source: MONALEESA-2 CSR 2016.[41]

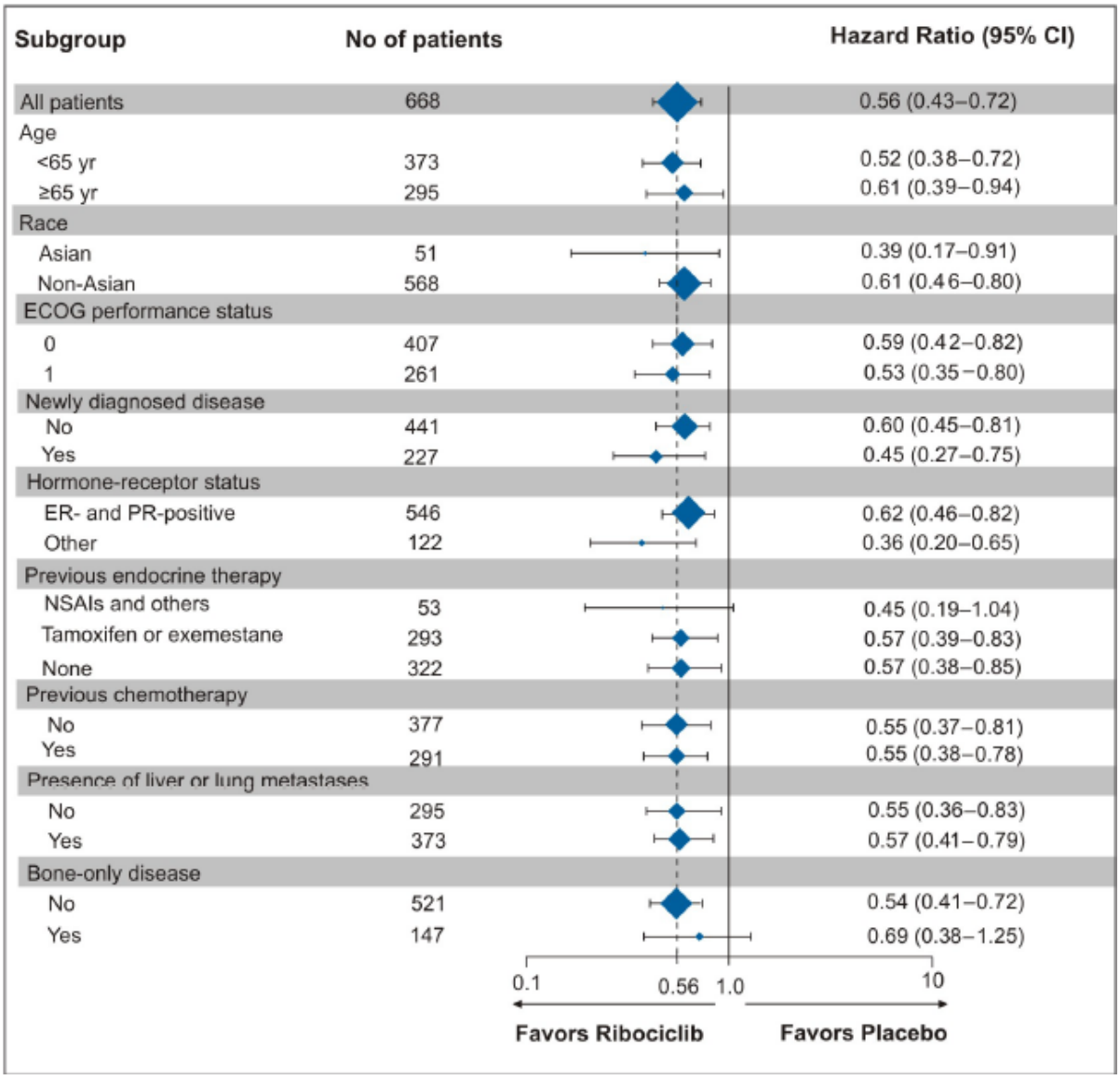
C3D1 = cycle 3 day 1; EORTC QLQ-C30 GHS/QOL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Global Health Status/Quality of Life; EOT = end of therapy, LS = least squares; SEM = standard error of the mean.

Analyses of functional scales and symptom scales/items of EORTC QLQ -C30 suggest no clinically meaningful changes from baseline and no meaningful differences between treatment arms [redacted] mean change from baseline scores of QLQ-BR23 [redacted] suggest no clinically meaningful changes from baselines and no meaningful differences between treatment arms.

4.2.2.7 Subgroup analyses of the MONALEESA-2 trial

Results for ribociclib plus letrozole versus letrozole were similar across subgroups based on different patient baseline characteristics, including the presence or absence of liver or lung involvement, as can be seen in Figure 4.3.

Figure 4.3: PFS across various selected subgroups



Source: Hortobagyi et al. 2016[23] and CS, Figure 16, page 62.

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor; NSAI = non-steroidal aromatase inhibitor; PFS = progression-free survival; PR = progesterone receptor; yr = years.

ERG comment:

The ERG notes that results for PFS favour ribociclib for all subgroups including both those with newly diagnosed disease and those with existing disease and those who have received prior therapy and patients who have not, although in some cases results are not statistically significant. Nevertheless, there are differences in effectiveness. Most noticeably, results for ribociclib are more favourable for younger patients (<65 yr), newly diagnosed patients (vs not newly diagnosed), not ER- and PR-positive (vs other hormone-receptor status), and not bone-only disease (vs. bone-only disease).

4.2.2.8 Safety results of the MONALEESA-2 trial

Data regarding the safety profile of ribociclib in combination with letrozole in patients with HR+/HER- advanced breast cancer that are provided in the CS were based on the phase 3 MONALEESA-2 trial.

The data presented were based on a median exposure to treatment at data cut-off of 13 months in the ribociclib group and 12.4 months for the placebo group. Median relative dose intensity was 87.5% for ribociclib, 100% for placebo, and 100% for letrozole (in both treatment groups).

The most common reasons for discontinuation were progressive disease in 87 patients (26.0%) in the ribociclib group and in 146 (43.7%) in the placebo group; a decision by the patient or physician in 22 (6.6%) and in 26 (7.8%), respectively; and adverse events in 25 (7.5%) and 7 (2.1%), respectively.[23]

Interruptions in the dose of ribociclib occurred in 257 patients (76.9%), and letrozole was interrupted in 132 patients (39.5%) in the ribociclib group. Among the 330 patients in the placebo safety population, placebo was interrupted in 134 (40.6%), and letrozole was interrupted in 107 (32.4%). Dose reductions occurred in 53.9% of the patients in the ribociclib group and in 7.0% of those in the placebo group, most commonly for adverse events (in 169 patients [50.6%] and 14 [4.2%], respectively). The most frequent adverse event leading to dose reduction was neutropenia (in 104 patients receiving ribociclib and in no patients receiving placebo).[23]

Tables 4.8, 4.9 and 4.10 summarise the incidence of AEs reported in the two treatment groups.

Table 4.8: Incidences of adverse events and death in MONALEESA-2

Events	Ribociclib + letrozole (N=334)			Placebo + letrozole (N=330)		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
[redacted]	[redacted]			[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 16, page 68
AE = Adverse event; SAE = Severe adverse event
a All deaths, including those occurring >30 days after the last study treatment.
b Deaths occurring >30 days after the last study treatment were not included.
c Study drug discontinuation refers to discontinuation of ribociclib/placebo only or both ribociclib/placebo and letrozole.

In the safety population (334 patients in the ribociclib group and 330 in the placebo group), adverse events of any grade that occurred in at least 35% of the patients in either group were neutropenia (74.3% in the ribociclib group and 5.2% in the placebo group), nausea (51.5% and 28.5%, respectively), infections (50.3% and 42.4%), fatigue (36.5% and 30.0%), and diarrhoea (35.0% and 22.1%) (See Table 4.9). Nausea, infections, fatigue, and diarrhoea were mostly grade 1 or 2. The most common grade 3 or 4 adverse events (≥5% of the patients in either group) were neutropenia (59.3% in the ribociclib group and 0.9% in the placebo group), leukopenia (21.0% and 0.6%, respectively), hypertension (9.9% and 10.9%), increased alanine aminotransferase level (9.3% and 1.2%), lymphopenia (6.9% and 0.9%), and increased aspartate aminotransferase level (5.7% and 1.2%). Febrile neutropenia occurred in five patients (1.5%) in the ribociclib group and in none in the placebo group.[23]

Table 4.9: Overview of adverse events in MONALEESA-2*

Adverse event	Ribociclib + letrozole (n =334)			Placebo + letrozole (n =330)†		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any adverse event	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
Neutropenia‡	248 (74.3)	166 (49.7)	32 (9.6)	17 (5.2)	3 (0.9)	0
Nausea	172 (51.5)	8 (2.4)	0	94 (28.5)	2 (0.6)	0
Infections	168 (50.3)	12 (3.6)	2 (0.6)	140 (42.4)	7 (2.1)	1 (0.3)
Fatigue	122 (36.5)	7 (2.1)	1 (0.3)	99 (30.0)	3 (0.9)	0
Diarrhoea	117 (35.0)	4 (1.2)	0	73 (22.1)	3 (0.9)	0
Alopecia	111 (33.2)	NA	NA	51 (15.5)	NA	NA
Leukopenia	110 (32.9)	66 (19.8)	4 (1.2)	13 (3.9)	2 (0.6)	0
Vomiting	98 (29.3)	12 (3.6)	0	51 (15.5)	3 (0.9)	0
Arthralgia	91 (27.2)	2 (0.6)	1 (0.3)	95 (28.8)	3 (0.9)	0
Constipation	83 (24.9)	4 (1.2)	0	63 (19.1)	0	0
Headache	74 (22.2)	1 (0.3)	0	63 (19.1)	1 (0.3)	0
Hot flush	70 (21.0)	1 (0.3)	0	78 (23.6)	0	0
Back pain	66 (19.8)	7 (2.1)	0	58 (17.6)	1 (0.3)	0
Cough	65 (19.5)	0	NA	59 (17.9)	0	NA
Anaemia§	62 (18.6)	3 (0.9)	1 (0.3)	15 (4.5)	4 (1.2)	0
Decreased appetite	62 (18.6)	5 (1.5)	0	50 (15.2)	1 (0.3)	0
Rash	57 (17.1)	2 (0.6)	0	26 (7.9)	0	0
Increased alanine aminotransferase	52 (15.6)	25 (7.5)	6 (1.8)	13 (3.9)	4 (1.2)	0
Increased aspartate aminotransferase	50 (15.0)	16 (4.8)	3 (0.9)	12 (3.6)	4 (1.2)	0

Source: Hortobagyi et al. 2016[23]

NA = not applicable, since grade 4 cough and grade 3 and 4 alopecia are not included in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

* Listed are events that were reported in at least 15% of the patients in any group. One event of interest (hypertension) fell below the reporting threshold listed here.

† Four patients who were randomly assigned to the placebo group did not receive either placebo or letrozole.

‡ Neutropenia includes a decreased neutrophil count and granulocytopenia.

§ This category includes both anaemia and a decreased haemoglobin level.

Four patients (1.2%) in the ribociclib group were confirmed as having met the biochemical definition of Hy's law (concomitant increases in aminotransferase and bilirubin levels in the absence of cholestasis). Three of the four cases in the ribociclib group were suspected by the investigator to be related to the study treatment. None of these cases resulted in death, and aminotransferase and bilirubin levels returned to normal in all four patients after the discontinuation of ribociclib.[23]

Infections were reported in 168 patients (50.3%) in the ribociclib group and in 140 (42.4%) in the placebo group; of these infections, the most common were urinary tract infections (10.8% and 8.2%, respectively) and upper respiratory tract infections (10.5% and 10.6%), predominantly of grade 1 or 2. The only grade 3 infections were reported in the ribociclib group, with grade 3 urinary tract infection in 2 patients (0.6%); there were no grade 4 infections in either group.[23]

Serious adverse events occurred in 71 patients (21.3%) in the ribociclib group and in 39 (11.8%) in the placebo group (See Table 4.10). Of these events, 25 (7.5%) in the ribociclib group and 5 (1.5%) in the placebo group were deemed to be related to the study regimen. There were four deaths (three [0.9%] in the ribociclib group and one (0.3%) in the placebo group) during treatment. One patient in each group died from the progression of underlying breast cancer. The remaining two deaths in the ribociclib group were due to sudden death and death from an unknown cause. The case of sudden death was considered to be related to ribociclib and occurred on day 11 in cycle 2 in association with grade 3 hypokalemia (treated with oral potassium supplements) and a grade 2 prolongation in the QTcF interval on day 1 of cycle 2; the patient had taken a prohibited concomitant medication with a known risk for QT prolongation (methadone) during cycle 1. The patient who died from an unknown cause received ribociclib for four days before withdrawing consent and discontinuing the study treatment; her death was reported 19 days later and was not considered to be related to ribociclib by the investigator.[23]

Table 4.10: Serious adverse events (>1 patient in either arm), regardless of relationship to study drugs

Adverse event	**Ribociclib + letrozole (n =334)**			**Placebo + letrozole (n =330)***		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Abdominal pain	5 (1.5)	3 (0.9)	0	0	0	0
Vomiting	5 (1.5)	3 (0.9)	0	2 (0.6)	2 (0.6)	0
ALT increased	4 (1.2)	1 (0.3)	3 (0.9)	0	0	0
Anemia	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Constipation	4 (1.2)	2 (0.6)	0	0	0	0
Dyspnea	4 (1.2)	3 (0.9)	0	1 (0.3)	1 (0.3)	0
Febrile neutropenia	4 (1.2)	2 (0.6)	1 (0.3)	0	0	0
Nausea	4 (1.2)	2 (0.6)	0	2 (0.6)	2 (0.6)	0
AST increased	3 (0.9)	1 (0.3)	1 (0.3)	0	0	0
Back pain	3 (0.9)	2 (0.6)	0	1 (0.3)	0	0
Dizziness	3 (0.9)	0	0	0	0	0
General physical health deterioration	3 (0.9)	3 (0.9)	0	1 (0.3)	1 (0.3)	0
Hepatotoxicity	3 (0.9)	3 (0.9)	0	0	0	0

Adverse event	Ribociclib + letrozole (n =334)			Placebo + letrozole (n =330)*		
Pneumonia	3 (0.9)	2 (0.6)	0	1 (0.3)	1 (0.3)	0
Sepsis	3 (0.9)	1 (0.3)	2 (0.6)	0	0	0
Syncope	3 (0.9)	3 (0.9)	0	0	0	0
Ascites	2 (0.6)	2 (0.6)	0	0	0	0
Cholecystitis	2 (0.6)	2 (0.6)	0	0	0	0
Dehydration	2 (0.6)	1 (0.3)	0	1 (0.3)	1 (0.3)	0
Diarrhoea	2 (0.6)	0	0	0	0	0
Femur fracture	2 (0.6)	2 (0.6)	0	0	0	0
Hepatic failure	2 (0.6)	2 (0.6)	0	0	0	0
Hypotension	2 (0.6)	2 (0.6)	0	0	0	0
Mental status changes	2 (0.6)	1 (0.3)	0	1 (0.3)	0	0
Neutropenia	2 (0.6)	0	2 (0.6)	0	0	0
Non-cardiac chest pain	2 (0.6)	1 (0.3)	0	0	0	0
Pleural effusion	2 (0.6)	1 (0.3)	0	4 (1.2)	3 (0.9)	0
Pulmonary embolism	2 (0.6)	1 (0.3)	1 (0.3)	0	0	0
Pyrexia	2 (0.6)	1 (0.3)	0	0	0	0
Urinary tract infection	2 (0.6)	2 (0.6)	0	0	0	0
Spinal compression fracture	0	0	0	2 (0.6)	2 (0.6)	0

Source: Hortobagyi et al. 2016[23]
ALT = alanine aminotransferase; AST = aspartate aminotransferase.
*Four patients were randomized to the placebo arm but did not receive study treatment.

[redacted]

[redacted]

Results of adverse events for the June 2016 cut-off point are provided in Table 4.11.

Table 4.11: Incidences of adverse events and death in MONALEESA-2 (June 2016 cut-off)

Events	Ribociclib + letrozole (N=334)			Placebo + letrozole (N=330)		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						
[redacted]						

Source: CS, Table 16, page 68
AE = Adverse event; SAE = Severe adverse event
a All deaths, including those occurring >30 days after the last study treatment.
b Deaths occurring >30 days after the last study treatment were not included.
c Study drug discontinuation refers to discontinuation of ribociclib/placebo only or both ribociclib/placebo and letrozole.

The adverse events at the June 2016 cut-off are similar to those at the interim analysis shown in Table 4.8.

[redacted].

At the final cut of 2 January 2017, a total of 50 (15.0%) and 65 (19.7%) patients died in the ribociclib and placebo arms respectively, with seven (2.1%) and three (0.9%) up to 30 days after the last study treatment One patient in the placebo arm who never took any study treatment (thus not in safety set) also died. The causes of on-treatment deaths (up to 30 days after the last study treatment) on ribociclib and placebo arms, respectively, were study indication (0.6% vs. 0.6%), acute respiratory failure (0.6% vs. 0%), death (sic) (0.3% vs. 0%), pneumonia (0.3% vs. 0%), sudden death (0.3% vs. 0%) and subdural haematoma (0% vs. 0.3%)

ERG comment: The ERG draws to the attention of the committee that although occurrence of any adverse events were overall similar in ribociclib and placebo groups, [redacted]

[redacted]The most common event was neutropenia. Gastrointestinal events such as nausea, vomiting and diarrhoea occurred more frequently in the ribociclib group.

4.2.3 A similar number of patients died in the two groups in the June 2016 cut-off although data were not mature.

[redacted]**Overview of the non-randomised evidence**

Three non-randomised trials were included to '*provide information relevant to the dosing regimen and schedule selected for investigation in the phase 3 MONALEESA-2 trial*'.[42-44] The company was asked how the studies were selected for inclusion given that the inclusion criteria for the review specified RCTs only. The company responded that they were included '*based on internal knowledge and as context and confirmation for the RCT MONALEESA-2 trial. The non-RCTs were not used to drive the submission.'* The company confirmed that *t*wo trials (CLEE011X2107 and CLEE011X2108) were reported only as poster publications.[43, 44] The methodology and results of the three non-randomised studies is given in Tables 4.12 and 4.13.

Table 4.12: Methodology of the non-randomised evidence

Trial name	Participants	Interventions	Primary outcome
CLEE011X2101[42] Phase 1 study	Adults with advanced solid tumours or lymphoma failing standard therapy for whom no further effective standard therapy exists	Dose escalation: ribociclib 50 to 1200 mg/day 3 weeks on / 1 week off Continuous dose ribociclib 600 mg/day	To determine the maximum tolerated dose (MTD) and recommended dose for expansion for ribociclib
CLEE011X2107[43] Phase 1b / 2 study	Postmenopausal women with metastatic or locally advanced HR+/HER2- breast cancer	1. Ribociclib 600 mg (3 weeks on/ 1 week off) + letrozole 2.5 mg once daily 2. Alpelisib 300 mg daily + letrozole 2.5 mg once daily (cohort 1: both given in the morning; cohort 2; alpelisib given in the evening and letrozole in the morning) 3. Ribociclib 400 mg (3 weeks on/ 1 week off) + alpelisib 100 mg + letrozole 2.5 mg once daily 4. Ribociclib 200 mg continuous once daily + alpelisib 200 mg + letrozole 2.5 mg once daily 5. Ribociclib 300 mg (3 weeks on/ 1 week off) + alpelisib (3 weeks on/ 1 week off) + letrozole 2.5 mg once daily Each arm included dose escalation and dose expansion	To determine the recommended dose of the phase 2 study To evaluate safety and tolerability.
CLEE011X2108[44] Phase 1b / 2 study	Postmenopausal women with metastatic or locally advanced HR+/HER2- breast cancer. Patients had to have progressed during or within 12 months of prior adjuvant AI therapy or during or within 1 month of AI therapy for metastatic disease and to have received ≤ 2 prior lines of chemotherapy for advanced disease.	1. Ribociclib 400 mg[a] + buparlisib 20 mg daily + fulvestrant 500 mg[b] 2. Ribociclib 400 mg + alpelisib 100 mg daily + fulvestrant 500 mg[b] 3. Ribociclib 600 mg[a] + fulvestrant 500 mg[b] 3A. Ribociclib 400 mg daily + fulvestrant 500 mg[b]	Phase 1b: To determine the MTD and/or recommended phase 2 dose Phase 2: To compare PFS

Source: Table 15 of CS
MTD = maximum tolerated dose; PFS = progression-free survival
a. 3 weeks/1 week off
b. every 28 days with 1 additional dose on day 15 of cycle 1

Table 4.13: Results of the non-randomised evidence

Trial name	Main findings
CLEE011X2101[42]	132 patients were included in the study and dose escalation proceeded to a dose of 1200 mg/day at 3 weeks on/1 week off. A continuous regimen of 600 mg / day was investigated but 6 of 7 patients required dose reductions so this was not explored further. MTD was 900 mg once daily at 3 weeks on/1 week off 600 mg once daily identified for further investigation **% of patients with adverse events** 46% neutropenia (27% grade 3 / 4) 43% leukopenia (17% grade 3 / 4) 45% fatigue (2% grade 3 / 4) 42% nausea (2% grade 3 / 4) 9% grade 3 / 4 thrombocytopaenia 9% QTc prolongation at doses of ≥ 600 mg / day 33% QTc prolongation at doses of > 600 mg / day
CLEE011X2107[43]	Results were reported for Arm 1 only (Ribociclib 600 mg (3 weeks on/ 1 week off) + letrozole 2.5 mg once daily) (47 patients) **Advanced setting treatment naïve patients** (n = 28) 2 CR, 11 (39%) PR, median PFS 25.3 months **Advanced setting previously treated patients** (n = 19) [redacted] 34 patients discontinued treatment due to disease progression (57%) and 2 patients due to adverse events. [redacted] **% of patients with adverse events** 83% neutropenia (60% grade 3 / 4) 49% nausea 34% fatigue 38% diarrhoea 32% arthralgia 30% alopecia
CLEE011X2108[44]	Results were reported for Arms 3 and 3a only (Ribociclib 600 mg intermittent + fulvestrant 500 mg and Ribociclib 400 mg daily continuous+ fulvestrant 500 mg (28 patients) **Intermittent** (n = 13) 3 (23.1%) PR, 9 (69.2%) stable disease **Continuous** (n = 15) 2 (13.3%) PR, 7 (46.7%) stable disease **% of patients with adverse events (suspected to be drug related)** 64.3% neutropenia (46.4% grade 3 / 4) 42.9% fatigue 42.9% nausea
CR = complete response, MTD = maximum tolerated dose, PD = progressive disease, PFS = progression-free survival, PR = partial response, QTcF or QT = interval corrected for heart rate as per Fridericia's formula	

The most relevant of the non-randomised trials is the CLEE011X2107 study. In this trial, which most closely represents MONALEESA-2, patients received ribociclib and letrozole. Twenty-eight of 47 patients were treatment-naïve in the advanced setting. In this group of patients two patients had a complete response, 11 (39%) had a partial response and median PFS was 25.3 months. Adverse events were similar to MONALEESA-2.

ERG comment: Details of the three non-randomised trials are presented in this report as they are included in the submission. However they represent supporting evidence only and were not retrieved in a systematic way.

4.2.4 Ongoing trials

Three further trials were listed in the CS as ongoing (MONALEESA-3, MONALEESA-7 and COMPLEEMENT-1). The CS noted that the trials '*involve different patient populations from those relevant to this submission and investigate treatment with ribociclib in combination with other endocrine therapies*.' Details of these trials are provided in Table 4.14.

Table 4.14: Ongoing trials

Trial name	Participants	Interventions	Primary outcome	Estimated completion dates
MONALEESA-3[49] Phase 3 randomised, double-blind trial	Men and postmenopausal women with HR+/HER2- advanced breast cancer who have received no or one line of prior endocrine treatment	Ribociclib[a] in combination with fulvestrant (440) vs. Placebo + fulvestrant (220)	PFS according to local assessment	February 2020
MONALEESA-7[50] Phase 3 randomised, double-blind trial	Premenopausal women with HR+/HER2- advanced breast cancer	Ribociclib[a] in combination with either tamoxifen plus goserelin or a non-steroidal AI (letrozole or anastrozole) plus goserelin (330) vs. Placebo in combination with either tamoxifen plus goserelin or a non-steroidal AI (letrozole or anastrozole) plus goserelin (330)	PFS according to local assessment	February 2018
COMPLEEMENT-1[51] Phase 3 open label single arm study	Men and postmenopausal women with HR+/HER2- advanced breast cancer having received no prior endocrine therapy for advanced disease	Ribociclib in combination with letrozole vs. Placebo + letrozole (Approx 3000)	Overall safety and tolerability	November 2020
Source: Section 4.14 and Table 20 of CS AI = aromatase inhibitor; PFS = progression-free survival a) 600 mg, once daily, day 1-21 of each 28 day cycle,				

ERG comment:

- As stated in the CS, none of the three ongoing trials directly match the population and intervention of this appraisal. Of the three, COMPLEEMENT-1 is most relevant to this appraisal. The population includes postmenopausal women and ribociclib is given in conjunction with letrozole. Furthermore the CS states that the study will involve 30 UK sites and aims to enrol [redacted] UK patients. However this study is open label which is less reliable than a blinded RCT particularly for efficacy data. Nevertheless, it will be important for the assessment of long-term safety of ribociclib. The study is due to finish in November 2020.
- The company confirmed in response to clarification that no relevant interim data were available from any of the three ongoing trials at the time of the appraisal.[26]
- The ERG identified that the FDA had recommended two trials as a post-marketing requirement for ribociclib. One of these was to assess the efficacy and safety of an alternative dosing regimen after evaluation of ECG, PK and efficacy data from on-going MONALEESA-3 and MONALEESA-7 studies. This was to mitigate the risks for QT prolongation without compromising efficacy. The second was to complete an on-going pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment. As these trials were not listed under ongoing studies in the CS, the ERG queried their current status. The company confirmed that '[redacted]'[26]

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

Only one trial is included in the CS: the MONALEESA-2 trial. No indirect comparisons and/or multiple treatment comparisons were performed.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

Only one trial is included in the CS: the MONALEESA-2 trial. No indirect comparisons and/or multiple treatment comparisons were performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

Ribociclib is indicated for use in combination with an aromatase inhibitor, for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer as initial endocrine-based therapy.[4] An opinion from the EMA is anticipated in August 2017.

The company conducted a systematic review to identify studies of ribociclib as monotherapy or as part of combination therapy. The NICE scope specified ribociclib in combination with an aromatase inhibitor as the intervention, and aromatase inhibitors (such as letrozole or anastrozole) as the comparator. No attempt was made to look for evidence for the comparability of different aromatase inhibitors and the effectiveness of other AIs in combination with ribociclib. Nevertheless, the ERG believes that the company has provided justification for generalisability of the letrozole comparator to aromatase inhibitors such as anastrozole normally offered to the population of the scope.

One Phase 3 trial, MONALEESA-2, with 668 patients was presented as the main source of evidence. The MONALEESA-2 study included postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease.

The trial was conducted at 223 trial centres in 29 countries including [redacted] patients from England and Wales. Patients were randomised 1:1 to receive ribociclib (600 mg once daily, days 1–21 of a 28-day cycle) plus letrozole (2.5 mg once daily, continuous treatment) or placebo plus letrozole (2.5 mg once daily, continuous treatment). Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage AEs; no dose reductions were permitted for letrozole and no crossover between treatment arms was allowed. Patients who discontinued ribociclib or placebo could continue receiving letrozole. Treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of ribociclib or letrozole.

The primary outcome was PFS as per RECIST version 1.1 criteria, based on local radiological assessment; assessments were also carried out by BIRC. The key secondary endpoint was OS (defined as the time from date of randomisation to date of death due to any cause). Other secondary outcomes included objective response rate (ORR; complete response [CR] or partial response [PR]), CBR (overall response plus stable disease lasting 24 weeks or more), time to deterioration of ECOG PS, safety and HRQoL.

A total of 668 patients were randomised to ribociclib (n=334) or placebo (n=334) in the ITT population. At the time of data cut-off (29 January 2016), a total of 349 patients (52.2%) were still receiving treatment (ribociclib, n=195; placebo, n=154). The rates of discontinuation were 41.6% in the ribociclib group compared with 53.9% in the placebo group. The most frequent reason for discontinuation was disease progression in both groups (ribociclib, 26.0%; placebo, 43.7%). Discontinuations due to AEs were 7.5% in the ribociclib group and 2.1% in the placebo group. The median duration of follow-up from randomisation to data cut-off was 15.3 months. Patient baseline characteristics seem well balanced between treatment groups in terms of demographics and disease characteristics.

Overall, the MONALEESA-2 trial is a good quality randomised controlled trial. However, adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients. Therefore, results based on independent review are more reliable. In addition, overall survival results were not mature at the time of the first interim analysis, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off.

Results are available for three time points:

1. The first planned interim analysis performed at the data cut-off on 29 January 2016 after observing 243 of the planned 302 events, the median duration of follow up was 15.3 months.
2. A second interim analysis on 22 June 2016 based on 297 local PFS and [redacted] central PFS events, the median duration of follow up was 20.1 months.
3. A third interim analysis on 2 January 2017 based on 345 local PFS events, the median duration of follow up was 26.4 months.

In this report we have focused on the most recent data available.

In addition, PFS results can be based on local and central (BIRC) results. As mentioned before, we have focused on BIRC results, partly because the NICE committee preferred these data in a recent related technology appraisal, and partly because adverse events could have unblinded physicians and/or patients, thus making results based on independent review more reliable.

Table 4.15: Comparison of preferred PFS and OS results from the company and ERG

	Ribociclib + letrozole (n = 334) versus Placebo + letrozole (n = 334)	
	Company preference	**ERG Preference**
PFS HR (95% CI)[a]	0.56 (0.43–0.72)[1]	[redacted][2]
OS HR (95% CI)[a]	[redacted][3]	0.746 (0.517-1.078)[4]

Source: CS, Novartis MONALEESA-2 ribociclib June 2016 CSR update and Novartis MONALEESA-2 ribociclib January 2017 CSR data cut

a) HR obtained from COX PH model stratified by liver and / or lung metastasis as per IRT

1. Based on local assessment and first interim analysis (January 2016)
2. Based on central assessment and most recent analysis (June 2016)
3. Based on first interim analysis (January 2016, after 43 deaths)
4. Based on most recent analysis (January 2017, after 116 deaths)

As can be seen from the results presented in Table 4.15 PFS results are more favourable for ribociclib on the company preferred results; while OS results are more favourable for ribociclib in the ERG preferred results. It should be kept in mind that the economic model is informed by the PFS results from the MONALEESA-2 trial, but not by the OS results from the MONALEESA-2 trial. The OS treatment effect in the economic model is based on the idea of surrogacy i.e. that a gain in PFS predicts a gain in OS. In the base-case, the assumption is that the gain in OS is identical to the gain in PFS.

Quality of life scores showed no clinically meaningful changes from baseline and no meaningful differences between treatment arms.

Subgroup analyses showed that results for PFS favour ribociclib for all subgroups including both those with newly diagnosed disease and those with existing disease and those who have received prior therapy and patients who have not. Nevertheless, there are differences in effectiveness. Most noticeably, results for ribociclib are more favourable for younger patients (<65 yr), newly diagnosed patients (vs not newly diagnosed), not ER- and PR-positive (vs other hormone-receptor status), and not bone-only disease (vs. bone-only disease).

Although occurrence of any adverse events were overall similar in ribociclib and placebo groups, a greater number of adverse events and severe adverse events were attributable to ribociclib. [redacted] The most common event was neutropenia. Gastrointestinal events such as nausea, vomiting and diarrhoea occurred more frequently in the ribociclib group.

A similar number of patients died in the two groups in the June 2016 cut-off although data were not mature.
[redacted]

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

Searches for cost effectiveness analysis review

A systematic literature review was conducted to identify evidence to support the cost-effectiveness model for ribociclib. Searches were conducted to identify studies reporting economic evaluations as well as resource use and costs. The search strategies for cost-effectiveness studies were reported in detail in Appendix 11 for MEDLINE, MEDLINE In-Process, Embase and the NHS Economic Evaluation Database (NHS EED). The host provider for each database was listed and the date the searching was conducted was provided. Additional searches of the NICE website for relevant manufacturer submissions and ERG reports were conducted, as well as searches of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) European and International congresses for 2014-2016. The searches met the requirements detailed in the NICE guide to the methods of technology appraisal.[52]

ERG comment:

The ERG considered the concurrent MEDLINE and Embase searches to be satisfactory in structure in addressing retrieval of economic evaluations and cost studies. There were numerous redundant search terms included in the search strategies, but these would have had no impact on the final results.

The ERG was also concerned that limiting the MEDLINE and Embase cost effectiveness searches to English language may have introduced potential language bias. Current best practice states that "*Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication"*.[31] During the clarification process, the ERG queried the rationale for applying an English language limit. The company did not clarify specifically why the cost-effectiveness searches were limited to English language, but did respond in detail about this issue in 'Section A Clarification on effectiveness data' of the response to clarification.[26]. See Section '4.1.1. Searches' for details of the company response to clarification and ERG comments.

Searches for cost effectiveness evidence were limited to 2000-2016. The date limit used in the searches was justified as "*The search was focused on identifying recent studies in advanced breast cancer on the basis that economic studies conducted prior to January 2000 are unlikely to accurately represent contemporary clinical practice"*.[4] It is possible that potentially useful studies published before 2000 were not included in the review. In the response to clarification the company further justified the use of a date limit by stating that they wanted to "*selectively identify economic evaluations that assess current treatment modalities for the target population*" and that studies published before 2000 "*are unlikely to provide additional relevant information that would support decision-making for ribociclib"*.[26]

It was not clear to the ERG whether a validated study design search filter was used for the cost effectiveness facet of search terms. The searches excluded conference abstracts from the results. It is not clear why this limit was included in the search strategy.

The database and ISPOR conference searches for the initial CS were conducted in August 2016, meaning that they were seven months out of date when the report was submitted to NICE in March 2017. The search of the NICE website was conducted in March 2017. In response to the ERG querying this time lag the company conducted update searches for Embase and PubMed in April 2017. Full details of these two update searches were provided: search strategies, date of searches, date span, and results. Three studies identified in the update searches presented the results of cost effectiveness analysis in subjects with HR+/HER2- advanced breast cancer, and Table 8 of the response to clarification detailed the key characteristics of these studies.[26] The company excluded the studies as none "*were UK specific and were therefore, not deemed relevant to the decision problem*".[26]

The CS did not provide full details of the search terms used, the precise date of the searches or the results for the searches of conference proceedings and the NICE website. It would have been useful if the conference proceedings searched for clinical effectiveness evidence had also been searched for cost effectiveness evidence. Furthermore, a search of health economic databases, such as Cost Effectiveness Analysis (CEA) Registry (www.cearegistry.org) and ScHARRHUD (http://www.scharrhud.org/), would have been a useful addition to the literature searches.

Measurement and valuation of health effects

A separate search was conducted for Section 5.4.3 to identify studies with health state utility (HSU) values. Searches were reported in detail in Appendix 13 for MEDLINE, MEDLINE In-Process, Embase and the NHS Economic Evaluation Database (NHS EED). The host provider for each database was listed and the date the searching was conducted was provided, as well as the date span. Additional searches of the NICE website and ISPOR conference proceedings (2014-2016) were conducted.

ERG comment:

For the most part, the database searches were clearly structured and used combinations of index terms appropriate to the resource searched, as well as free text and synonyms. However, it was not clear to the ERG whether a validated search filter was used for the health state utility values facet of search terms.

The ERG has similar concerns to those addressed in the comments for the cost effectiveness searches regarding the use of English language limits, date limits (2000-2016), exclusion of conference abstracts, lack of update searches, and that full details for ISPOR and NICE searches were not reported. The company updated the PubMed search in April 2017, and reported details of the date span, search strategy and results in the response to clarification.[26] One study with information relevant to the ribociclib cost-effectiveness analysis was identified, and the key characteristics of this study were reported in Table 16.[26] Details of the search terms used, date searched and results of the NICE website search were provided in the response to clarification, and the company confirmed that "*bibliographic searching refers to the reviewing of secondary studies cited in primary studies identified through literature searches"*.[26]

Searching for health state utilities in databases of cost-utility analyses, such as Cost Effectiveness Analysis (CEA) Registry (www.cearegistry.org) and ScHARRHUD (http://www.scharrhud.org/), would have been a useful addition to the literature searches.

Cost and healthcare resource identification, measurement and valuation

A systematic review was conducted to identify studies reporting healthcare resource use and cost data (Section 5.5.1 of the CS).

ERG comment:

It was not clear what searches the company used to identify studies for the systematic review of healthcare resource use and cost data. The CS refers to the methods used being described in 'section 0'. In response to clarification the company confirmed that "*resource utilization studies were identified as part of the economic evaluation review (i.e. cost-effectiveness searches). Of the 30 economic studies identified, 13 reported cost and resource use data. Of these 13, only four reported costs relevant to the UK healthcare system"*.[26]

Appendix 14 of the CS, where the full details of the searches should have been reported, was left blank. In response to clarification letter, the company confirmed that searches conducted for the cost effectiveness analysis review (Section 5.1.1.) were used to inform this review.[26]

5.1.2 Inclusion/exclusion criteria used in the study selection

Table 5.1. below presents an overview of inclusion criteria used by the company for the review.

Table 5.1: Inclusion criteria for the study selection

Criteria	Inclusion
Patients	Studies including advanced breast cancer, female, adult (≥18 years) patients
Interventions	No restrictions
Comparators	No restrictions
Outcomes	• Cost of illness analyses, • Cost utility analyses, • Cost effectiveness analyses, • Cost benefit analyses, • Cost minimisation analyses, • Budget impact analyses and • Cost consequence analyses
Geography	No restrictions
Language	English only
Date restriction	For electronic databases: from 1 January 2000 to 5 August 2016 For ISPOR conference proceedings: 2014-2016 For NICE website: 1 January 2000 to 1 March 2017

ERG comment:

In the company submission, the electronic database search for cost effectiveness evidence was limited to English language with a date restriction from 1 January 2000 to 5 August 2016. After the ERG asked for the rationale for these restrictions, the company updated the literature search from 5 August 2016 to 26 April 2017 in its response to the clarification letter document.[26] The company mentioned that among the identified cost effectiveness, healthcare utilisation, and quality of life studies from the search conducted in EMBASE (n=269 studies) and in PubMED (n=61 studies), none were deemed relevant for UK clinical practice based on screening of the titles by a single reviewer.

In the company submission, besides the data restriction, further details of the search strategy conducted on the ISPOR conference proceedings database and the NICE website (e.g. search strings) were not given.

5.1.3 Included/excluded studies in the cost effectiveness review

The CS mentions that the literature search identified a total of 2,110 articles for abstract screening. After abstract screening, 559 publications were included for full-text review. The full text review and additional ISPOR conference proceedings' database search identified a total of 34 publications from 30 unique studies, which were deemed relevant for this appraisal by the company. It was further stated by the company that, out of these 30 identified studies, only 21 were economic evaluations and the rest were on the costs/resource use for HR+/HER2- advanced breast cancer. The summary of these 21 economic evaluations was provided in Table 7 of Appendix 11 of the CS[53], whereas the summary results from the NICE website search were reported separately in Table 23 of the CS[4].

The identified 21 economic evaluation studies were further filtered according to the treatment line of the interventions, and as a result, the company selected eight studies out of 21 as the most relevant for ribociclib and its target indication, which is the first-line treatment of HR+/HER2- advanced breast cancer. The summary of these eight studies was given in Table 22 of the CS.[4]

Among these eight evaluations, three were from the US[54-56], and the others were from the UK[57], France[58], Switzerland[59], Canada[60] and Italy[61], respectively. Four of the evaluations were classified as cost effectiveness analysis[54-56, 59], three of the evaluations were categorised as cost-utility evaluation[57, 60, 61], and the remaining one[58] was considered as a cost-minimisation study. The effectiveness of the interventions was evaluated using various outcomes including quality adjusted life years (QALYs), life years (LYs) or quality-adjusted progression-free months. All of the studies adopted a payer perspective, including two studies from the US with a private payer perspective[54, 55], and the remaining six studies having national healthcare system perspectives[56-61]. The company stated that none of the studies incorporated indirect costs from a societal perspective.

Two of the eight studies[55, 58] were not model-based evaluations, and were solely based on the analysis of collected patient level data. Among the model-based economic evaluations, three of the studies were reported to have their analyses based on Markov state transition models[54, 59, 61], one study was reported to follow a partitioned survival approach[57], one was reported to be based on a decision-node structure[60] and one was reported to follow a regression modelling methodology[55].

Among these eight identified studies, the predominant model structure was the conventional three-state model with progression-free, progressed disease and death states, most with a cycle length of one month, whereas more complex model structures incorporating line specific treatment states were also present.

One of the identified studies was a cost-minimisation analysis comparing the costs of different combination therapies including bevacizumab and a chemotherapy.[58] Five of the identified economic evaluations were comparing tamoxifen versus anastrazole or letrozole.[55, 56, 60 57, 61] Among these comparisons, the company deemed only Das et al.2013[57] as relevant to the decision problem, which reported the cost effectiveness of fulvestrant, letrozole, and anastrozole from the UK National Health Service (NHS) perspective. However, the company also noted that this study was not fully representative of the decision problem, as the cost effectiveness analysis was conducted for the second-line treatment of HR+/HER2- advanced breast cancer patients. The remaining two studies compared palbociclib plus letrozole versus letrozole or anastrazole alone.[54, 59] In Matter-Walstra et al. 2016,[59] the lifetime cost effectiveness of palbociclib plus letrozole versus letrozole alone was assessed from Swiss healthcare system perspective, using a conventional three state Markov model with progression-free, progressed disease and death states. In Bhattacharya et al.2016,[54] a more involved decision analytical model with treatment-line specific states was used to compare the cost effectiveness of palbociclib plus

letrozole and anastrazole alone and letrozole alone from a US third-party payer perspective. In both studies, palbociclib plus letrozole were not considered to be cost effective versus either letrozole or anastrazole monotherapy, with ICERs far beyond the acceptable thresholds, when the palbociclib drug costs were based on wholesale US prices.

The NICE website search of the company yielded two finished single technology appraisals, TA421 (everolimus in combination with exemestane after endocrine therapy) and TA239 (fulvestrant), which reported economic data in patients with HR+/HER2- advanced breast cancer.[20, 21] There is a superseded appraisal for everolimus in combination with exemestane (TA295),[62] and the company refers to both of these appraisals (TA421 and TA295) interchangeably while summarising the results of these appraisals. Furthermore, the company identified another ongoing appraisal on the NICE website, i.e. the appraisal of palbociclib (ID915) for HR+/HER2- advanced breast cancer patients.[63]

A detailed comparison of survival and health economic modelling approaches, assumptions surrounding adverse events, costs/resource utilisations, and health utility valuations between the fulvestrant appraisal (TA239) and everolimus plus exemestane appraisals (TA421 or TA295) was given in section 5.1.3 of the company submission. Even though there are some differences, the approaches/assumptions followed in the appraisals were broadly in line with each other. An overview table of the approaches followed in TA239, TA295 and ID915 was provided by the company in the response to the clarification document, upon the ERG's request, which is given below.

Table 5.2: Comparison of key model characteristics as reported in TA239, TA295 and ID915.

Characteristics	TA 239	TA 295	ID915
Model structure and simulation	Three state partitioned survival model comprising of pre-progression, post-progression and Death state.	Three state partitioned survival model comprising of PFS, PD and Death state.	Three state partitioned survival Markov model comprising of PFS, PD and Death state. The PD includes three tunnel states.
Healthcare costs	Resource data for pre-progression state were based on expert opinion, as no studies were identified in the literature review • Resource data for post-progression states was treatment dependent and based on feedback from clinical experts. The post-progression treatment pathway options included: Third line hormonal therapy, supportive palliative care • Chemotherapy, supportive palliative care • Third line hormonal therapy, chemotherapy, supportive palliative care • Supportive palliative care Resource use for third line hormonal therapy was assumed to be the same as that during second line hormonal therapy.	Monthly resource use in stable disease health state comprised of: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, and 1 social worker visit lasting 1 hour Monthly resource use in stable disease health state comprised of: community nurse home contact lasting 40 minutes, 1 GP home visit, clinical nurse specialist contact lasting 4.5 hrs, and social worker contact lasting 2.5 hrs Terminal care costs was considered in the analysis, but subsequent therapy costs were not considered	**Pre-progression state resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, and 1 consultant visit (oncologist) once every 6 moths lasting 1 hour **2nd line post progression (subsequent treatment 1) resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins and 1 CT scan **3rd line post progression (subsequent treatment 2) resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, 1 CT scan, Therapist lasting 30 mins and Physiotherapist lasting 30 mins

Characteristics	TA 239	TA 295	ID915
			4th line post progression (subsequent treatment 3) resource use: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, 1 CT scan, Therapist lasting 30 mins and Physiotherapist lasting 30 mins **BSC resource use:** 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, Therapist lasting 30 mins, Physiotherapist lasting 30 mins and lymphoedema nurse lasting 20 mins
Health benefits	Health benefits using quality adjusted life years (QALYs), assessed via EQ-5D was incorporated in the cost-effectiveness analysis.	Health benefits using quality adjusted life years (QALYs), assessed using EORTC QLQ-C30 at 7 12 and 18 months was incorporated in the cost-effectiveness analysis.	Health benefits using quality adjusted life years (QALYs), assessed via EQ-5D was incorporated in the cost-effectiveness analysis.
PFS = progression-free survival; PD = progressive disease; GP = general practitioner; CT = computerised tomography; QALY = quality-adjusted life year.			

ERG comment:
In the company submission, it is mentioned that 21 of the 30 included studies reported the results of economic evaluations, but the company considered only eight studies to be relevant for the indication of the ribociclib submission. The reasons for exclusion of the remaining 13 studies were not clear to the ERG. In the company submission, it was suggested that these eight studies were selected on the basis of being economic evaluations for first-line breast cancer treatments. However, the company later discussed that Das et al.2013,[57] which was one of these eight included studies, was not fully representative of the indication of ribociclib, because the cost effectiveness analysis in Das et al.2013[57] was conducted for second-line treatment of breast cancer. It would be more transparent if the company had provided the reasons for exclusion for each of the 13 excluded studies that led to the short list of eight studies.

In addition to this electronic database search, the company also hand-searched the NICE website and identified the following previous/ongoing technology appraisals as relevant in the company submission: TA295 (everolimus in combination with exemestane), TA239 (fulvestrant) and ID915 (palbociclib).[20, 21, 63] In the NICE scope,[64] other technology appraisals such as TA263, TA214 and TA116 were also mentioned, however it was not clear to the ERG why these appraisals were not taken into consideration.[65-67] The company, in its response to the clarification letter,[26] explained that these appraisals were not considered relevant as the population of these appraisals were different from that of the ribociclib (i.e. HR+/HER2- advanced breast cancer). Despite the differences in target population, the ERG thinks there could be some relevant information in these previously published appraisals.

Finally, the ERG noted that the quality assessment of the selected cost effectiveness studies was not conducted by the company. A quality assessment of the studies identified in the cost effectiveness literature review based on available checklists (e.g. Philips et al. 2004[68]) is necessary to critically appraise the published cost effectiveness evidence. The ERG could not conduct the quality assessments due to time limitations.

5.1.4 Conclusions of the cost effectiveness review
Besides the descriptive summary of the identified studies and comparison of approaches/data inputs of the relevant technology appraisals, no specific conclusions from the economic review were provided in the CS.

5.2 Summary and critique of company's submitted economic evaluation by the ERG
Table 5.3 presents a summary of the de novo economic model developed by the company.

Table 5.3: Summary of the company submission economic evaluation

	Approach	Source/Justification	Signpost (location in CS)
Model	An individual patient simulation model with state-transition approach was developed. Simulated patients entering the model are postmenopausal women with advanced or metastatic HR+/HER2- breast cancer that were previously untreated in the advanced setting (first line). Simulated patients move through a series of health states until death. Time horizon in the base-case was lifetime.		Section 5.2.1 and 5.2.2
States and events	Four health states were defined based on the line of each treatment: First-line PFS (PFS1), second-line PFS (PFS2), progressed disease (later lines) and death states. In the PFS1 state, patients receive either ribociclib in combination with letrozole or letrozole alone. Patients in this state are starting at the stable disease stage and stay in this state until they progress and move to PFS2 state, or until they die. PFS2 represents the time between disease progression in first-line and second-line treatment cessation (as a proxy for disease progression). In the PFS2 state, patients receive one of the following treatments: everolimus in combination with exemestane, exemestane (representative of a single-agent endocrine therapy) and capecitabine (representative of chemotherapy). Patients stay in this state until they progress and move to the "progressed disease" state or until they die. Progressed death state represents the time from second-line therapy cessation (as a proxy for progression) until death, and in this state patients receive subsequent treatments and/or supportive/palliative care. Death state is an absorbing state.	In the CS, it was stated that the model structure and the health states in this submission were chosen to reflect the UK treatment pathway in advanced breast cancer, to make the best use of data from the MONALEESA-2[23] trial and make the best use of the evidence available in second-line (from BOLERO-2[69] trial) to model the OS appropriately, accounting for the immaturity of the OS data from the MONALEESA-2[23] trial.	Section 5.2.2
Comparators	Letrozole monotherapy	Letrozole was the only comparator in the MONALEESA-2[23] trial. Other aromatase inhibitors like anastrazole were not included due to absence of data and expert opinion that they are equivalent in terms of effectiveness and interchangeable.	Section 5.2.3
Natural History	In advanced or metastatic breast cancer, patients receive consecutive treatments until death. Choice of the treatment determines the time to progression and overall survival.		Section 5.3

	Approach	Source/Justification	Signpost (location in CS)
Treatment effectiveness	Treatment (letrozole monotherapy or in combination with ribociclib) influences the length of the PFS during the first-line. The benefit in PFS in the first-line is transferred to OS using an OS surrogacy approach. In the base-case it is assumed that the PFS benefit will lead to an OS benefit the same as the PFS benefit. Time to treatment discontinuation (TTD) was independently modelled from the PFS in the first-line and used in drug acquisition cost calculations. Parametric models were used for both PFS and TTD following NICE DSU guidelines[70] Treatment choice in the first-line determines the distribution of treatments received in the second line.	OS, post treatment-discontinuation survival and TTD data from the BOLERO-2 trial and HR from Li et al. 2015[71] for chemotherapy were used to use TTD and post treatment discontinuation survival in the second-line treatment, OS surrogacy was assumed due to immaturity of OS data from the MONALEESA-2 trial.	Section 5.2.2 and 5.3
Adverse events	The model includes the following grade 3 and 4 adverse events: diarrhoea, fatigue, infection, nausea, febrile neutropenia, pulmonary embolism and vomiting. Neutropenia was not included in the model, even though it was reported in approximately [redacted] of the patients.	In the CS, it was mentioned that the included AEs were the ones which require additional NHS resource use for their management.	Section 5.3.7
Health related QoL	The health state utilities used during the first-line treatment were derived from the patients in the MONALEESA-2 study. The utility values for the second line PFS and progressed disease states were taken from Lloyd et al. 2006[8] and a decrement of utility was assumed for chemotherapy, which was derived from Peasgood et al. 2010[72]. No utility decrements were assumed for the adverse events.	EQ-5D estimates were from the MONALEESA-2 trial and Lloyd et al. 2006[8] and they are weighted according to the UK tariff. As the utility values from MONALEESA-2 involve patients with AEs, in the CS, it was argued that the effects of AEs on health states were already captured.	Section 5.4
Resource utilisation and costs	Treatment costs (e.g. technology acquisition costs of first, second, third and later line treatments), drug administration costs, monitoring, resource use and health state unit costs and unit costs for adverse event management are included. Dose intensity/treatment discontinuation issues for ribociclib are included in the model	Based on literature and UK reference costs.	Section 5.5
Discount rates	A 3.5% discount rate was used for both costs and effects.	According to NICE reference case. Continuous discounting is applied for costs/QALYs that are accumulating continuously.	Section 5.2.2

	Approach	Source/Justification	Signpost (location in CS)
Sensitivity analysis	One-way deterministic sensitivity analysis, scenario analyses and probabilistic sensitivity analysis	Ranges/scenarios based on observed confidence intervals and different assumptions.	Section 5.8

HR+ = hormone receptor-positive; HER2- = human epidermal growth factor receptor 2 negative; PFS = progression-free survival; OS = overall survival; CS = company submission; TTD = time to treatment discontinuation; HR = hazard ratio; AE = adverse event; NHS = National Health Service; QALY = quality-adjusted life year.

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.4: Comparison of the CS model with the NICE reference case

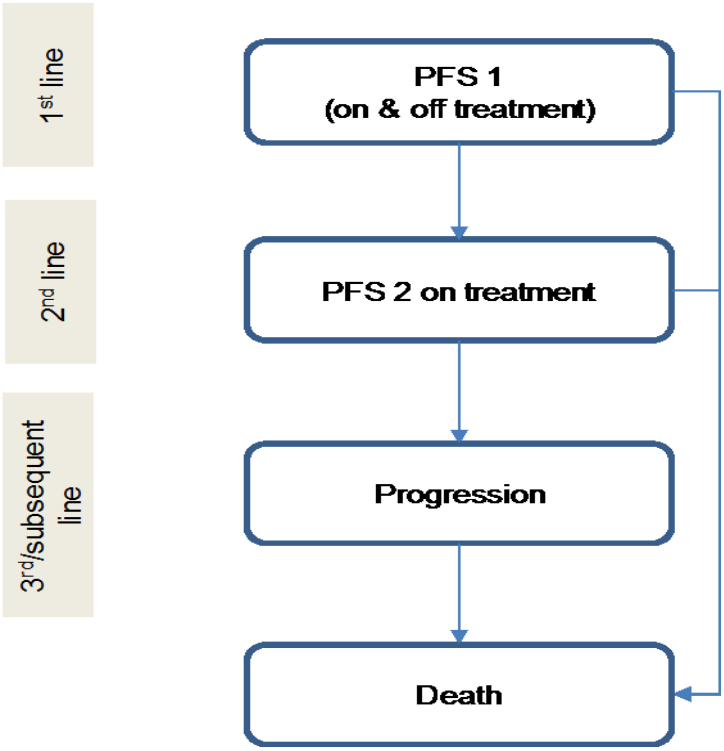
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	Only letrozole was considered as a comparator. Other aromatase inhibitors such as anastrazole were not included.
Type of economic evaluation	Cost effectiveness analysis	Yes	
Perspective on costs	NHS and PSS	Yes	
Perspective on outcomes	All health effects on individuals	Yes	
Time horizon	Sufficient to capture differences in costs and outcomes	Yes	Time horizon is considered to be lifetime.
Synthesis of evidence in outcomes	Systematic review	No	The effectiveness of the intervention was based on a single trial, MONALEESA-2.
Measure of health effects	QALYs Life-years	Yes	
Source of data for measurement HRQOL	Reported directly by patients and/or carers.	Yes	EQ-5D data were directly collected from the patients in the MONALEESA-2 trial and used for PFS in first-line. Health state utility values from the publication by Lloyd et al.[8] were used for the PFS in the second-line and the progressed disease health state.
Source of preference data for valuation of changes in HRQOL	Sample of public	Yes	EQ-5D-5L social UK tariff was applied to the data obtained from the MONALEESA-2 trial. In the study by Lloyd et al.[8] vignettes were used to describe health states and then members of the general public in the United Kingdom rated them using standard gamble to determine utilities.
Discount rate	Annual rate of 3.5% on costs and health effects	Yes	
Equity weighting	No special weighting	Yes	
Sensitivity analysis	Probabilistic sensitivity analysis	Yes	In addition, univariate sensitivity and scenario analyses were performed.

NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; PFS = progression-free survival.

5.2.2 Model structure

An individual patient simulation model following a state-transition approach was developed in Visual Basic for Excel. In the model, the simulated patients may move through three health states until death as depicted in Figure 5.1.

Figure 5.1: De novo model structure



Source: CS, Figure 18, page 99
PFS = progression-free survival

In the first-line PFS state (PFS1), patients receive either ribociclib in combination with letrozole or letrozole alone. Patients starting at this state are assumed to be in stable disease. They stay in this state until they progress and move to the second-line PFS state (PFS2) or until they die.

In the PFS1 state, a patient can be either on-treatment or off-treatment. Time to treatment discontinuation (TTD) determines the duration that a patient is on-treatment and is modelled independent from the PFS in the economic model. For the PFS1 state, the relevant clinical model inputs are TTD, PFS and proportion of death among the PFS events. These inputs are derived from the analysis of data from the MONALEESA-2 trial, which will be explained further in section 5.2.6.

The PFS2 state represents the time between disease progression after the first-line treatment until the second-line treatment cessation (as a proxy for disease progression, due to data unavailability). In the second-line, patients are assumed to receive one of the following treatments: everolimus in combination with exemestane, exemestane (representative of a single-agent endocrine therapy) and capecitabine (representative of chemotherapy). The probability of receiving each of these treatments in the second-line is dependent on the treatment that was received in the first-line (ribociclib and letrozole or letrozole only) and is based on expert opinion. Patients are assumed to stay in the PFS2 state until they progress and move to the "progressed disease" state or until they die.

The progressed disease state represents the time from second-line therapy cessation until death, and in this state the patients are assumed to receive subsequent treatments and other supportive/palliative care.

In the model, separate third-line treatments were not explicitly modelled but a separate third-line treatment cost was incorporated. Death state is an absorbing state.

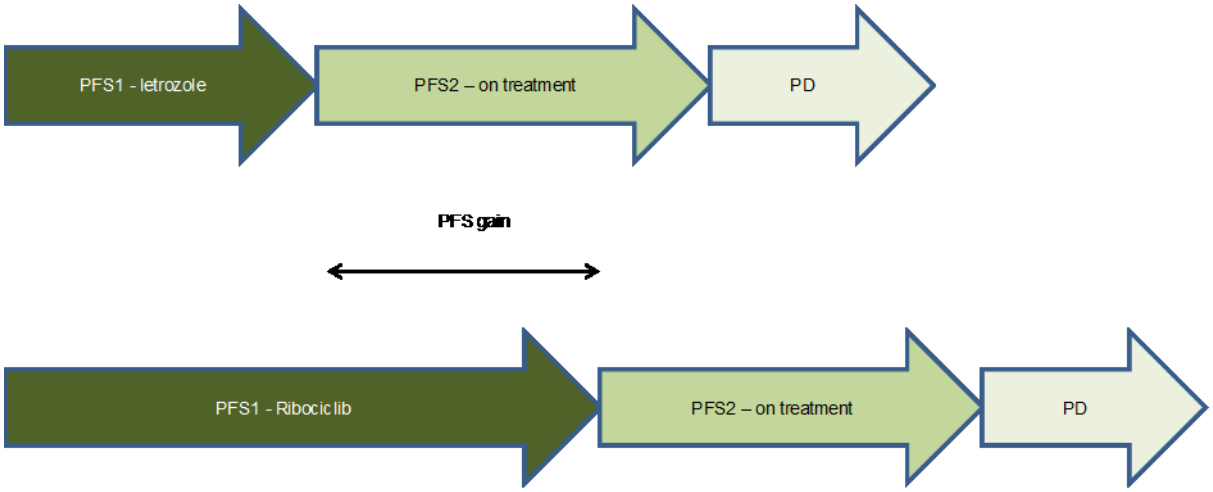
For the patients who received exemestane monotherapy or everolimus in combination with exemestane in the second-line, relevant model clinical inputs like TTD and the probability of death before treatment discontinuation in the second-line, and time to death after TTD are derived from the analysis of the patient level data from the BOLERO-2 trial. For the patients who received chemotherapy in the second-line, OS and TTD HRs from Li et al. 2015[71] with other additional assumptions are used.

In contrast with the majority of the models published in the cost effectiveness of oncology treatments literature, the model in this submission did not use a partitioned survival approach, discussing that this would be inappropriate considering the immaturity of the OS data from the MONALEESA-2 trial. The model is individual-patient based, and uses a time to event approach, hence it has no time cycles. This approach was preferred by the company over the conventional cohort modelling approach, as it provides more flexibility in modelling different OS surrogacy scenarios, where the OS estimates were dependent on the PFS history of the patient. In the deterministic base-case analysis, 5,000 simulation runs were taken to ensure stable results while incorporating the first order uncertainty.

5.2.2.1 Modelling of the OS

In the model, OS is modelled indirectly, and is a function of the time spent in each of the alive health states (PFS1, PFS2 and progressed disease). In the model, in the base-case, it is assumed that a gain in the PFS would lead to an equal gain in the OS, for the patients who did not die upon progression. The perfect OS-surrogacy approach used in the base-case is depicted below in Figure 5.2:

Figure 5.2: Illustration of the perfect OS surrogacy approach

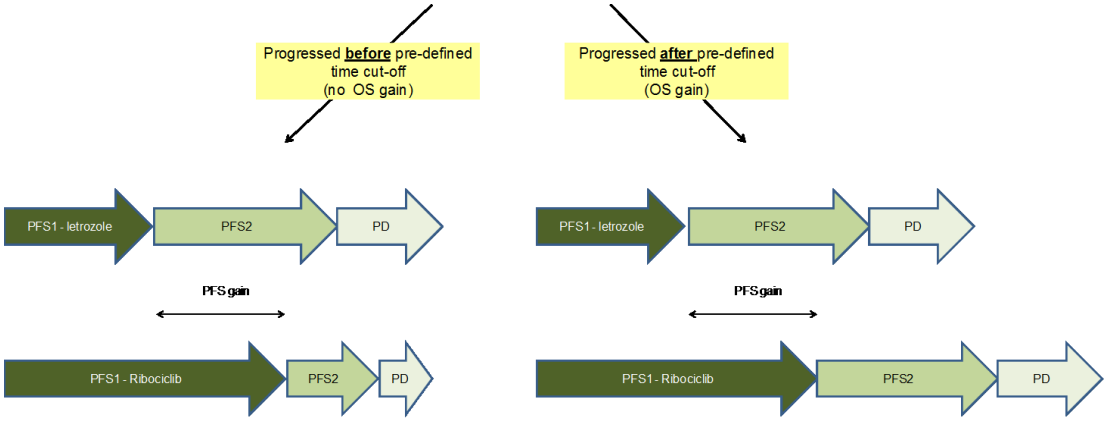


Source: CS, Figure 20, page 102
PFS = progression-free survival; PD = progressive disease.

In addition to the base-case, a range of threshold-based OS surrogacy scenarios (from four months to 24 months) were conducted. In these scenarios, a gain in the PFS is translated into an equivalent gain in the OS only if a pre-defined threshold is exceeded. The threshold was defined either in terms of the absolute PFS under ribociclib with letrozole or in terms of PFS gain of ribociclib in combination with letrozole compared to letrozole monotherapy.

A schematic illustration of the patient flow based on an absolute PFS based threshold scenario is given below in Figure 5.3.

Figure 5.3: Illustration of the patient flow in an absolute PFS based threshold scenario



Source: CS, Figure 21, page 103
OS = overall survival; PFS = progression-free survival; PD = progressive disease.

ERG comment:
In the economic model, a patient cannot move to the "progression" state and receive BSC after the first-line treatment without receiving a second-line treatment. The ERG asked the company if there are any patients in the MONALEESA-2 trial or in any other trial/breast cancer registry, who did not receive any further treatment after the first-line advanced breast cancer treatment. In its response to the clarification letter, the company stated that the proportion of patients who did not receive any further treatment among the patients who discontinued active first-line therapy in advanced breast cancer was [redacted] Even though the proportion of patients who received BSC after first-line treatment in the MONALEESA-2 trial is [redacted], the ERG considers that confirmation of these estimates from the MONALEESA-2 trial with real world data derived from the registries in UK clinical practice might be useful.

Although the NICE clinical guideline for advanced breast cancer (CG81)[22] recommends anthracyclines and then docetaxel as chemotherapy options, the health economic model assumes that patients will be treated with capecitabine (based upon clinician validation), as the company argues that this chemotherapy is widely used due to the convenience of administration and the preferable side effect profile. The ERG considers that confirmation of the clinical expert opinions on this issue with real world data from patient registries or audits conducted in UK might be useful.

In the company's base-case health economic model, it was assumed that only the second-line treatment choice affected the prognosis of the patients after they progressed from their first-line treatment (letrozole monotherapy or combination therapy with ribociclib). Furthermore, the OS and PFS results from the BOLERO-2 trial were used in the model without any adjustments, as if the BOLERO-2 trial was conducted subsequent to the MONALEESA-2 trial population upon their disease progression. Instead of this approach followed by the company, the ERG would have preferred an approach where the OS and PFS parametric functions used from the BOLERO-2 trial were adjusted based on the patient characteristics at the disease progression from the first-line treatment (e.g. age, previous treatment, ECOG disease status, time since diagnosis at the time of first-line treatment progression etc.). The use of such adjusted OS and PFS survival functions from BOLERO-2 might have provided more refined simulation estimations.

The current surrogacy approaches followed in the company submission assumed that the gain in PFS is 100% translated into OS gain in the base-case, and in some scenarios only if PFS/TTP (gain) is above a certain predefined threshold. The ERG considers that 100% translation of PFS gain into OS gain might not be plausible, as there are studies indicating that duration of PFS gain would translate into an OS gain that is shorter, especially in HER2-negative patients.[12, 73-75] This trend can be also observed in the PALOMA-1 trial, which is the only randomised trial that studied a CDK 4/6 inhibitor drug and reported median PFS and OS for both intervention and control arms. In this trial, the median PFS for palbociclib and letrozole arms were 25.7 and 14.8 months (according to the BIRC assessment), whereas the median OS were 37.5 and 33.3 months, which resulted in a "gain in median OS/gain in median PFS" ratio close to 38.5% (4.2 months/10.9 months). Due to these figures from the literature, the ERG asked the company to include a scenario where the gain of PFS is translated into an OS gain with a factor less than 100%. The company incorporated this scenario in the new economic model attached to its response to the clarification letter; however the ERG identified some inconsistencies in the implementation of this scenario, which resulted in negative time spent in PPS or PFS2 states for some patients, which led to negative cost and utility estimates in some simulation runs. Therefore, the ERG followed a different approach in its base-case and all the time spent in the post-progression states (PFS2 and PD) was multiplied with a constant scaling factor that is less than one in the ribociclib arm. This constant scaling factor is derived from a model calibration exercise, where different scaling factors were explored and the one that achieved a targeted "gain in median OS/gain in median PFS" ratio from the simulation outcomes was chosen. The details of this scenario will be discussed further in section 5.3.

In their submission, the company mentioned that several threshold-based OS surrogacy scenarios were conducted, in which the PFS gain was not translated to an OS gain if the defined outcome (e.g. absolute PFS/TTD or PFS/TTD gain) was below a certain threshold. However, in the actual simulation implementation, if the PFS of the ribociclib arm is greater than the OS of the letrozole monotherapy, then it is assumed that the PFS event of that patient is death and a gain in OS might be still implemented despite the predetermined outcome is below the threshold. Furthermore, due to this implicit assumption in the implementation of the threshold scenarios, the proportion of patients died before progression can be unlikely high (up to 30%) for some scenarios in the ribociclib arm.

5.2.3 Population

The population of interest for the economic model was defined as women with advanced or metastatic HR+/HER2- breast cancer previously untreated in the advanced setting (i.e. first-line). It is assumed that the patient population from the MONALEESA-2 clinical trial is representative for the population of interest. It is further assumed that the baseline patient characteristics in the BOLERO-2 trial reflect the characteristics of those patients who progress after the first-line treatment either with ribociclib in combination with letrozole or with letrozole monotherapy.

ERG comment:

The generalisability of the results of the MONALEESA-2 trial to the total population with HR+/HER2- treatment-naïve advanced or metastatic breast cancer in the UK is discussed in section 3.1. Baseline characteristics of the patients in the BOLERO-2 trial are comparable to the baseline characteristics of the patients in the MONALEESA-2 trial, with respect to age, ECOG performance status and disease-free interval. A difference was found in the proportion of Asian people within both trials; 8% in the MONALEESA-2 trial and 20% in the BOLERO-2 trial.

It was not clear to the ERG to what extent the baseline characteristics of the patients in the BOLERO-2 trial would reflect the characteristics of the population of HR+/HER2- advanced breast cancer patients

in the UK who progressed on treatment with ribociclib in combination with letrozole or letrozole monotherapy.

In response to the clarification letter, the company explained that within the economic model the median age at first line progression was [redacted] and [redacted] for patients treated with ribociclib in combination with letrozole and patients treated with letrozole monotherapy, respectively (based on the modelled median PFS from the January 2016 data cut). The median age of patients in the BOLERO-2 trial starting treatment with everolimus in combination with exemestane or exemestane monotherapy was 62 and 61, respectively.

Additional data regarding characteristics of patients (e.g. ECOG status) with HR+/HER2- advanced breast cancer who progressed on treatment with ribociclib in combination with letrozole or letrozole monotherapy were unavailable to the ERG. As a consequence, the ERG cannot conclude whether or not the patients in the BOLERO-2 trial would reflect the characteristics of the population of HR+/HER2- advanced breast cancer in the UK who progressed on treatment with ribociclib in combination with letrozole or letrozole monotherapy.

5.2.4 Interventions and comparators

In the economic evaluation, ribociclib in combination with letrozole, at dosages equivalent to the dosages used in MONALEESA-2, was considered as the intervention. Patients who enrolled in the MONALEESA-2 trial received ribociclib at a fixed dose (daily 600 mg in the first 21 days of a 28-day cycle) in combination with letrozole (2.5 mg once daily each day in a 28-day cycle).

Dose reductions for ribociclib were allowed (400mg or 200 mg per day). The model considers dose distribution while calculating the drug acquisition costs as will be discussed in section 5.2.9.

Letrozole monotherapy was considered as the only comparator (2.5 mg once daily each day in a 28-day cycle).

ERG comment:

Aromatase inhibitors other than letrozole were not included in the economic evaluation. It is implicitly assumed that all aromatase inhibitors are equivalent and letrozole is representative for the other aromatase inhibitors. In response to the clarification letter, the company argued that the NICE clinical guideline[22] makes no distinction between aromatase inhibitors for the first line treatment of HR+/HER2- advanced breast cancer patients either (see also section 3.3).

5.2.5 Perspective, time horizon and discounting

In the cost effectiveness analysis, a lifetime horizon was used. The analysis adopted the perspective of the NHS/PPS and a discount rate of 3.5% was applied for both costs and effects. The discounting was applied continuously for the cost/QALY items, which are assumed to accumulate in a continuous manner (e.g. resource use costs).

ERG comment:

The ERG has no specific comments on these choices for perspective, time horizon and the discount rates. In the economic model, half cycle corrections were not applied, as the model follows a time-to-event patient level based simulation approach, therefore not using time cycles. The rationale of the choice for the cost/QALY items that were discounted continuously was not always very clear to the ERG. For instance, it was assumed that the drug acquisition costs for everolimus and exemestane, which were used daily in the second-line, were continuously accruing and hence continuous discounting was

applied for these costs. However, for the drug acquisition costs of the oral chemotherapy in the second-line (capecitabine), which is also taken daily for two weeks in each three-week cycle, continuous discounting was not considered. It would have been more transparent if the company had provided the discounting approach (continuous or discrete) for each cost/QALY item as well as the rationale of the discounting approach that is followed.

5.2.6 Treatment effectiveness and extrapolation

In this section, the treatment effectiveness related inputs for the economic model will be summarised. The clinical model inputs (PFS, TTD, proportion of death among PFS events) related to the first-line treatment with either ribociclib in combination with letrozole or letrozole monotherapy were derived from the analysis of the IPD from the MONALEESA-2 trial. For validation purposes, survival results from other clinical trials, in which letrozole monotherapy was a comparator, were used as well.

5.2.6.1 PFS in the first-line therapy

The PFS for ribociclib in combination with letrozole and letrozole monotherapy in the first-line were based on IPD from the MONALEESA-2 trial from the dataset of January 2016 cut-off.[23] The progression was measured according to local assessment. The company discussed that the methodology used to select the survival model for the PFS in the first-line was in line with the NICE DSU guidance[70] and the steps are as explained below.

First, the plausibility of the proportional hazard assumption for the PFS in the first-line (ribociclib in combination with letrozole vs. letrozole monotherapy) was assessed using the log-cumulative hazard plots for PFS (based on local assessment) as shown in Figure 24 of the CS.[4] In that figure it can be seen that the plots cross each other at the beginning indicating a violation of the proportional hazard assumptions in the [redacted]. However, after the curves cross each other the plots seemed to be parallel to each other. As the curves crossed each other, the company argued that fitting separate models for ribociclib plus letrozole and letrozole would be most appropriate. Nevertheless, the company also provided scenario analyses in which HR was used, since its use might be justifiable as the curves seemed to be parallel after two to three months.

Next, the company generated Kaplan-Meier curves for both the letrozole monotherapy and letrozole plus ribociclib arms. A range of parametric survival models (Weibull, exponential, Gompertz, log-normal and log-logistic) were considered for extrapolation. The most appropriate distribution for the parametric survival model was selected based on the assessment of the statistical goodness-of-fit, the visual fit to the observed KM and the plausibility of the long-term extrapolation to the external clinical data from other trials in which letrozole monotherapy was a comparator.

The assessment of the statistical goodness-of-fit was performed via Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the parametric models fitted to the PFS data from MONALEESA-2. The company warned that extra caution should be taken while interpreting the goodness-of-fit results, since they provide indications over the observed period and the PFS data over the observed period can be considered still as immature. The AIC and BIC statistics given in Table 29 of the CS[4] suggested that the AIC and BIC values were similar for all different distributions used in the parametric survival models, and that the lognormal distribution provided the best statistical fit to the data for both letrozole monotherapy and letrozole plus ribociclib arms. For letrozole monotherapy, the Weibull distribution provided the second best statistical fit to the data both in terms of AIC and BIC. For ribociclib in combination with letrozole, the log-logistic distribution provided the second-best statistical fit to the data according to the AIC and the exponential distribution provided the second-best statistical fit to the data according to the BIC.

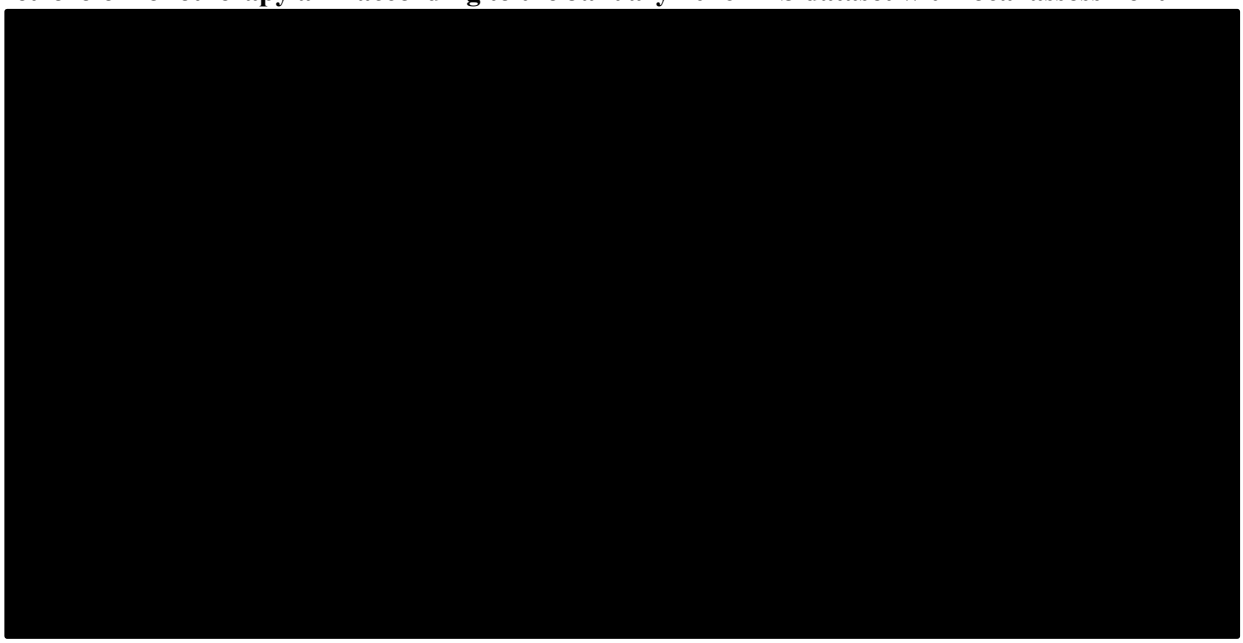
The visual assessment of fit for the parametric survival models to the observed PFS data was conducted by plotting the overlaid estimated survival curves for each distribution on top of the corresponding Kaplan-Meier curve, for both ribociclib plus letrozole and letrozole monotherapy, as presented in Figure 5.4 and Figure 5.5, respectively. From these figures, the company concluded that all distributions provided a reasonable fit to the KM curve during the observed period. However, the long-term extrapolations of these distributions varied extensively, which is why the company argued that the validation of the long-term extrapolation from these models was essential.

Therefore, the company presented a comparison of the parametric survival models against the KM of the PFS data of letrozole monotherapy from MONALEESA-2[23], PALOMA-2[73], LEA[76] and ALLIANCE[77] trials in Figure 5.6. From this figure, the company concluded that the exponential distribution provided a more plausible long-term extrapolation for the letrozole monotherapy, compared to other distributions, and was therefore selected as the base-case.

Figure 5.4: Parametric survival curves and the non-parametric PFS Kaplan-Meier plots for ribociclib plus letrozole arm according to the January 2016 PFS dataset with local assessment

Source: CS, Figure 25, page 110
PFS = progression-free survival.

Figure 5.5: Parametric survival curves and the non-parametric PFS Kaplan-Meier plots for letrozole monotherapy arm according to the January 2016 PFS dataset with local assessment



Source: CS, Figure 26, page 111
PFS = progression-free survival.

Figure 5.6: Comparison of the KM curves for PFS for letrozole in the MONALEESA-2, PALOMA-2, LEA and ALLIANCE trials and parametric functions based on MONALEESA-2 (data cut-off January 2016)

Source: CS, Figure 27, page 113
KM = Kaplan-Meier; PFS = progression-free survival.

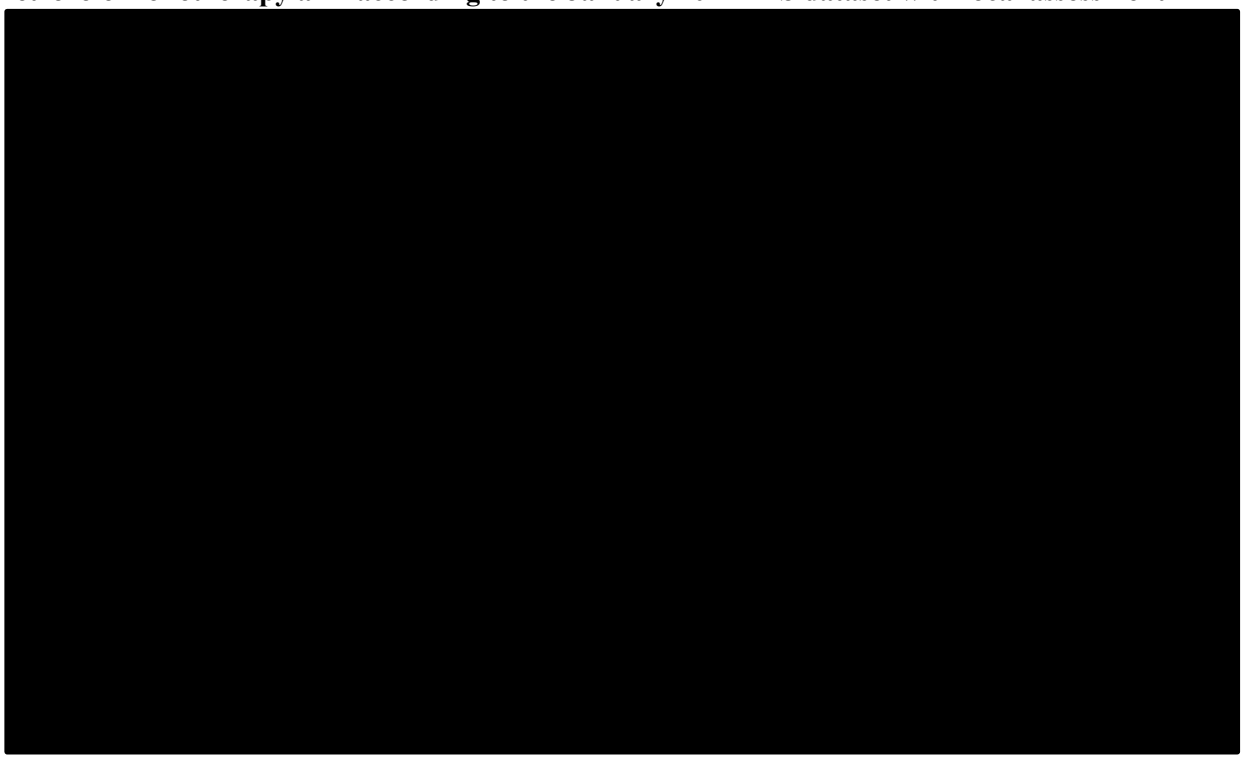
In line with the DSU guidance,[70] which recommends that the same distribution parametric models should be selected for all treatment arms, the exponential distribution was also chosen for ribociclib plus letrozole arm in the base-case. The impact of choosing other parametric functions for the survival modelling of the PFS were explored in the scenario analyses which will be elaborated on further in section 5.2.11.

The company mentioned that additional external validation efforts were conducted with clinical experts, who confirmed that the model estimates for the proportion of progression-free patients at certain time points with letrozole monotherapy (three, five and 10 years) were in line with the clinical expectations.

ERG comment:

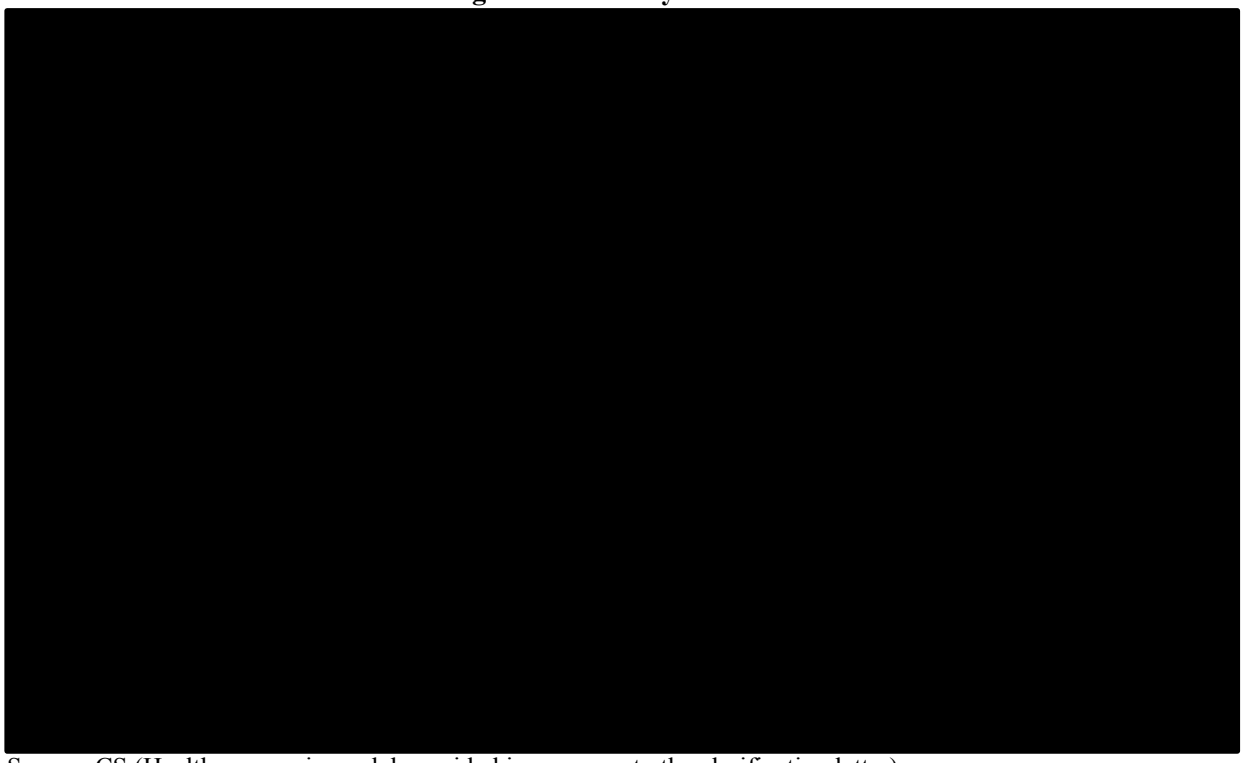
The survival analyses conducted in the CS were based on the PFS dataset from the first interim analysis (January 2016) and the local assessment of the PFS events. As discussed previously in section 4.2, the ERG considers PFS results from central assessment to be more plausible compared to the local assessment. Furthermore, the ERG became aware of two later data cut-offs (June 2016 and January 2017). Therefore, the ERG asked the company to provide survival analyses from the PFS dataset from the latest data cut-off date (January 2017) in which the PFS events were centrally assessed. In its response to the clarification letter, the company stated that the central assessment was not performed for the PFS dataset from the January 2017 cut-off because the additional time required for the central assessment was not available. Instead, the company incorporated the survival analysis results conducted on the PFS dataset from January 2017 cut-off in which PFS events were assessed locally. Only summary data and Kaplan-Meier curves for the PFS based on central assessment from the June 2016 dataset was provided. The assessment of the statistical goodness-of-fit was performed via AIC and BIC for the parametric models fitted to the PFS data from the latest data cut-off of the MONALEESA-2 trial were provided in the economic model. The AIC and BIC values were [redacted] different distributions used in the parametric survival models, and the [redacted] provided the best and the second best statistical fit to the data for letrozole monotherapy. For ribociclib the AIC and BIC values of the Weibull, Gompertz and exponential were very similar. From the visual fit assessment (Figure 5.7 and Figure 5.8), which was provided in the economic model, it can be seen that the parametric extrapolations [redacted] the progression-free survival according to the KM curves for both ribociclib and letrozole monotherapy arms. When the PFS extrapolations based on the more recent cut-off (January 2017) were compared with the KM curves from external trials, it can be seen [redacted] to the KM curves from LEA and ALLIANCE trials, whereas extrapolations from [redacted] to the KM curves from PALOMA-2 and MONALEESA-2 trials. (See Figure 5.9)

Figure 5.7: Parametric survival curves and the non-parametric PFS Kaplan-Meier plots for letrozole monotherapy arm according to the January 2017 PFS dataset with local assessment



Source: CS (Health economic model provided in response to the clarification letter)
PFS = progression-free survival.

Figure 5.8: Parametric survival curves and the non-parametric PFS Kaplan-Meier plots for ribociclib and letrozole arm according to the January 2017 PFS dataset with local assessment



Source: CS (Health economic model provided in response to the clarification letter)
PFS = progression-free survival.

Figure 5.9: Comparison of the KM curves for PFS for letrozole in the MONALEESA-2, PALOMA-2, LEA and ALLIANCE trials and parametric functions based on MONALEESA-2 (data cut-off January 2017)

Source: CS (Health economic model provided in response to the clarification letter)
KM = Kaplan-Meier; PFS = progression-free survival.

In the NICE DSU guidance for survival analysis,[70] for the survival plots whose log-log cumulative hazard plots do not approximate straight lines, it is recommended that piecewise or other more flexible models (e.g. splines) are fitted individually to the survival data from each treatment arm. From Figure 24 in the CS, it can be seen that the log-log cumulative hazard plots for PFS were not [redacted], but rather seemed to be [redacted] in time. Therefore, in line with the NICE DSU guidance,[70] the ERG considers that piecewise or more flexible models might have been more plausible.

In the economic model, the ERG identified a small error in the VBA module which estimates time to event for the PFS under letrozole monotherapy based on the KM curve. The percentage of patients who were still progression free in the last two event times were entered incorrectly. The ERG corrected this error in the base-case. This change does not affect the base-case results as KM-based extrapolation was used only in scenario analyses in the CS.

In the light of discussions above, the ERG concurs with the choice of the January 2017 PFS dataset based on local assessment in the base-case and an extrapolation based on the [redacted] distribution. However, since the Weibull distribution can be considered to be as plausible as an exponential distribution for PFS extrapolation, the ERG will provide the results of using a Weibull distribution in its exploratory analyses.

5.2.6.2 Proportion of patients for whom the PFS event was death on first-line therapy

In Table 5.5, the number and proportion of deaths among the PFS events are given for letrozole monotherapy and letrozole combination therapy with a CDK4/6 inhibitor (ribociclib or palbociclib) from MONALEESA-2[23] and PALOMA-2[73] trials, respectively.

Table 5.5: Proportion of deaths among PFS events in the first line therapy (January 2016 cut-off PFS dataset)

Trial	Event	Letrozole monotherapy	Letrozole combination therapy with a CDK4/6 inhibitor
MONALEESA-2	PFS events, n	[redacted]	[redacted]
	Deaths, n (%)	[redacted]	[redacted]
PALOMA-2	PFS events, n	137	194
	Deaths, n (%)	3 (2.2%)	11 (5.7%)
Pooled data	PFS events, n	[redacted]	[redacted]
	Deaths, n (%)	[redacted]	[redacted]
Source: CS, Table 30, page 114 CDK4/6 = cyclin-dependent kinase 4 and 6; PFS = progression-free survival.			

Out of the [redacted] patients in the MONALEESA-2 trial who initiated letrozole monotherapy and had a PFS event, [redacted] patients died. Out of the [redacted] patients who initiated ribociclib plus letrozole and had a PFS event, [redacted] patients died before progression [redacted]. The figures from the MONALEESA-2 trial were used in the economic model in the base-case and the pooled results from the MONALEESA-2 and PALOMA-2 trial were used in the scenario analysis.

ERG comment:

In the economic model, for each PFS event, a treatment specific probability of death (given a PFS event) was applied for letrozole monotherapy and ribociclib in combination with letrozole. These probabilities were constant in time, and the same for all patients. However, these probabilities might be dependent on PFS time as well as other patient characteristics. The patient level data and the PFS events (whether it is a death or progression) could have been analysed by using binomial regression models and a predictive model for death probability could have been used with more covariates than only the treatment used in the first line (ribociclib in combination with letrozole or letrozole monotherapy).

Furthermore, the ERG noted that in the most recent (data cut-off January 2017) PFS dataset, more recent deaths have occurred before progression. The updated number and proportion of deaths among PFS events based on January 2017 cut-off dataset is given in Table 5.6. These updated figures will be used in the ERG base-case.

Table 5.6: Proportion of deaths among PFS events in the first line therapy (January 2017 dataset)

Trial	Event	Letrozole monotherapy	Letrozole combination therapy with a CDK4/6 inhibitor
MONALEESA-2	PFS events, n	[redacted]	[redacted]
	Deaths, n (%)	[redacted]	[redacted]
PALOMA-2	PFS events, n	137	194
	Deaths, n (%)	3 (2.2%)	11 (5.7%)
Pooled data	PFS events, n	[redacted]	[redacted]
	Deaths, n (%)	[redacted]	[redacted]
Source: Derived from the response to the clarification letter and company submission CDK4/6 = cyclin-dependent kinase 4 and 6; PFS = progression-free survival.			

5.2.6.3 TTD in the first-line therapy

The TTD for ribociclib in combination with letrozole and letrozole monotherapy in the first-line were modelled independent from PFS and were also based on IPD from the MONALEESA-2[23] trial. The steps that were taken to select the survival model for the TTD is similar to the steps that were taken for PFS, as explained in Section 5.2.6.1.

The implausibility of the proportional hazard assumption was already ascertained by the company from the crossing KM curves of the TTD depicted in Figure 28 from the CS.[4] Hence, the company argued that fitting individual models for the TTD curves from ribociclib plus letrozole and letrozole arms would be more appropriate.

A range of parametric survival models (Weibull, exponential, Gompertz, log-normal and log-logistic) were considered for extrapolation. The most appropriate distribution for the parametric survival model was selected based on the assessment of the statistical goodness-of-fit, the visual fit to the observed KM and the plausibility of the long-term extrapolation.

The assessment of the statistical goodness-of-fit was performed via Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the parametric models fitted to the TTD data from MONALEESA-2. Similar to the PFS, the company warned that extra caution should be taken while interpreting the goodness-of-fit results, as the TTD data can be considered still as immature. The AIC and BIC statistics given in Table 31 of the CS[4] suggested that the lognormal distribution provided the best statistical fit to the data for the letrozole monotherapy arm and Gompertz distribution provided the best fit to the letrozole plus ribociclib arm. According to the AIC and BIC statistics, the second-best distribution was Weibull for the letrozole monotherapy and log-normal for the ribociclib with letrozole arm.

The visual assessment of fit for the parametric survival models to the observed TTD data was conducted by plotting the overlaid estimated survival curves for each distribution on top of the corresponding Kaplan-Meier curve, for both ribociclib plus letrozole and letrozole monotherapy arms, as presented in Figure 29 and 30 in the CS[4], respectively. From these figures and the selected distribution for the PFS extrapolation ([redacted]), the company concluded that only [redacted] distributions were plausible for the ribociclib in combination with letrozole arm, and [redacted] distributions were plausible for the letrozole monotherapy arm. All the other distributions that were deemed implausible for TTD were all crossing the corresponding PFS curve at some point. Based on clinical expert opinion and model predictions, the company selected the exponential distribution for the base-case and alternative distributions were explored in the scenario analyses (elaborated further in Section 5.2.11) taking into account a time constraint, which assured that TTD was never greater than PFS.

ERG comment:

It was not clear to the ERG whether the treatment discontinuation in the ribociclib arm meant treatment discontinuation of both ribociclib and letrozole at the same time or only discontinuation from ribociclib only (i.e. letrozole is administered until progression even after discontinuation from ribociclib). In the company submitted economic model, it seems like the former (i.e. discontinuation of both treatments simultaneously) was assumed, however in Hortobagyi et al. 2016[78] it was mentioned that "*Patients who discontinued either ribociclib or placebo were permitted to continue receiving letrozole*". If some of the patients indeed continued to receive letrozole after ribociclib discontinuation (until disease progression) in the MONALEESA-2 trial, the economic model seems to overlook a part of the drug

acquisition costs in the ribociclib arm. Incorporating this cost would increase the ICER, however considering the low prices of letrozole, the impact of this correction on ICER is anticipated to be low.

In the CS economic model, TTD and PFS were modelled independently but while simulating PFS and TTD time to events, the same random numbers were used for both times. This approach ensured that the TTD is always lower than the PFS in the base-case. However, TTD can be the same as the PFS in many cases. Furthermore, some clinicians might choose the continuation of the same treatment even after the disease progression.[79] The joint analysis of TTD and PFS would have resulted in more reliable and robust TTD estimates.

Finally, as discussed in Section 5.2.6.1 of this report, the results from the latest PFS data cut-off (January 2017) were provided, however the TTD used in the model is still based on the January 2016 cut-off PFS dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date, despite the fact that it was clearly requested in the clarification letter.

5.2.6.4 Distribution of treatments received in the second-line

In the base-case, the distribution of treatments received in the second-line were different for ribociclib in combination with letrozole and letrozole monotherapy arms as given in Table 5.7 below.

The company mentioned that these base-case distribution estimates were based on clinical opinion and the impact of assuming different treatment distributions was explored in scenario analyses (Section 5.2.11).

Table 5.7: Distribution of second-line treatments assumed in the base-case

Second-line therapies	Proportion of patients receiving each treatment (%)	
	Ribociclib in combination with letrozole	Letrozole monotherapy
Everolimus + exemestane	70%	30%
Single-agent endocrine therapy	5%	40%
Chemotherapy	25%	30%
Source: CS, Table 32, page 121		

ERG comments:

In the economic model, the distribution of the treatments received in the second-line differed between the ribociclib and the letrozole arms. The company stated that the probability estimates given in Table 5.7 were based on the proportions provided by clinical experts. However, in the communication documents provided by the company at the ERG's request (e.g. minutes of the ad-board meetings, questionnaires filled in by experts, etc.), the ERG came across various estimates (e.g. one expert gave different proportions for the second-line treatment after letrozole arm than the ones in Table 5.7 and the same expert declined to give estimates for second-line treatment proportions after ribociclib arm). Furthermore, in the provided documents, the ERG could not find any justification for the different estimates of second-line treatments after ribociclib and after letrozole. Therefore, it is still not clear to the ERG how the estimates in Table 5.7 were generated (i.e. was the average of all proportions from the experts taken? How many experts answered this question? Were the proportions varying significantly?). Since the ERG cannot provide a better estimate, the estimates in the CS will not be changed in the ERG base-case, but several scenarios with different second-line treatment proportions will be conducted in section 5.3.

Furthermore, in the economic model, it was assumed that these proportions do not change over time and are the same for all patients. The choice of second-line treatment might be dependent on other factors than the first-line treatment, e.g. a specific treatment might be chosen more frequently for the patients who progressed earlier or for the patients who are younger. Ideally, statistical analysis of patient level data (e.g. a multinomial regression model) should have been conducted to generate a predictive function that estimates the second-line treatment choice probability based on all relevant factors (e.g. choice of the first-line treatment, time of PFS, treatment related AE history, baseline characteristics etc.) and that predictive function might have been used in the simulation.

5.2.6.5 PFS, TTD and OS in the second-line therapy

PFS, TTD and OS in the second-line therapy for everolimus in combination with exemestane and exemestane monotherapy (representative of the single-agent endocrine therapy) were based on the analysis of the IPD from the BOLERO-2 trial, whereas for the chemotherapy, the treatment effect was modelled by applying the adjusted HRs reported in Li et al.2015,[71] to the survival models chosen for the extrapolation of the PFS, OS and TTD data from the everolimus and exemestane arm of the BOLERO-2 trial.

The BOLERO-2 trial included 724 postmenopausal women with HR+/HER2- advanced breast cancer, who had recurred or progressed following prior treatment with the nonsteroidal aromatase inhibitors (letrozole or anastrozole), and who received exemestane 25 mg/day in combination with either everolimus 10 mg/day or with placebo. The company used the TTD data as a proxy for PFS, since the PFS and TTD curves from the BOLERO-2 trial were deemed to be very similar (from Figure 31 and 32 in the CS), and the data cut-off date for the PFS (December 2011) was much earlier than the data cut-off date of OS and TTD (October 2013).

Despite the fact that the crossing KM curves in Figure 33 of the CS suggested the violation of the proportional hazard assumption, the company chose to model the survival of the exemestane monotherapy arm by applying the HR ([redacted] monotherapy vs. everolimus plus exemestane combination therapy from BOLERO-2 trial) on top of the modelled survival curve of the combination therapy. A range of parametric survival models were fitted to the data and the Weibull distribution was chosen to model the TTD of the everolimus plus exemestane combination therapy arm based on the visual fit (Figure 34 of the CS); alternative distributions for the modelling of the TTD (as a proxy for PFS) were explored in the scenario analyses which will be elaborated on further in section 5.2.11.

Five (1.06%) patients died upon discontinuation out of the 471 patients who initiated everolimus with exemestane and discontinued the treatment, whereas no deaths (0%) occurred upon treatment discontinuation among the patients who initiated exemestane monotherapy and discontinued the treatment in the BOLERO-2 trial. It is assumed that no patients died upon discontinuation under chemotherapy. These probabilities were implemented in the economic model.

The company used the post-treatment discontinuation survival data as a proxy for the post-progression survival in the BOLERO-2 trial. For the modelling of the post-treatment discontinuation survival, the company pooled the post-discontinuation survival data from both monotherapy and combination therapy arms, based on the observed similarity of the KM curves in Figure 35 of the CS. Afterwards, a range of parametric survival models were fitted to the data and the Weibull distribution was chosen to model the post-discontinuation survival based on the statistical fit (Table 34 of the CS) and the visual fit (Figure 36 of the CS). Alternative distributions for the modelling of the post-discontinuation survival were explored in the scenario analyses which will be elaborated on further in section 5.2.11.

For the clinical model inputs for chemotherapy, the company identified a retrospective study, Li et al.2015[71], in which the effectiveness of everolimus-based therapy (n=234 patients) was compared with chemotherapy (n=137 patients) in community-based oncology practices between January 2012 and April 2013 after failure of a non-steroidal aromatase inhibitor therapy. The study presented PFS (HR=0.61, 95% CI: 0.32-1.17), OS (HR=0.53, 95% CI: 0.20-1.39) and TTD (HR=0.3, 95% CI: 0.17-0.52) hazard ratios (everolimus versus chemotherapy), derived from adjusted Cox models, for the second-line treatment patients.

The company applied the inverse of the TTD HR to the TTD curve fitted for the everolimus plus exemestane arm of the BOLERO-2 trial.

For the post-discontinuation survival under chemotherapy, the company estimated the mean OS and the mean TTD under chemotherapy, using the HRs from Li et al.2015,[71] and afterwards fitted a Weibull distribution to the difference between OS and TTD, assuming an arbitrary shape parameter of 0.0375 based on the Weibull shape parameter of the PPS calculated from pooled data from patients receiving everolimus in combination with exemestane and exemestane in the BOLERO-2 trial. The company discussed that this approach was taken in TA386.[80]

ERG comment:

In section 5.2.2 it was discussed that the OS and PFS results from the BOLERO-2 trial were used in the model without any adjustments, as if the BOLERO-2 trial was conducted subsequent to the MONALEESA-2 trial population upon their disease progression. Besides the potential problems that might arise with this approach, the ERG was unsure if the BOLERO-2 trial and Li et al.2015[71] were the only relevant studies to model the treatment effectiveness of the second-line HR+/HER2- patients. In the CS, the ERG could not find any systematic review for identifying studies on the clinical effectiveness of the second-line treatments in HR+/HER2- advanced breast cancer patients.

Regarding the modelling of the TTD, PFS and OS from the BOLERO-2 survival data, the ERG has the following concerns. Firstly, by using the TTD as a proxy for PFS, the company might have underestimated the time spent in the PFS2 state, since there is a visible gap between the TTD and PFS curves of the everolimus and exemestane arms from the BOLERO-2 trial (Figure 31 of the CS). Secondly, it was not clear why the company decided to apply the HR (derived from the Cox PH model) to the TTD curve of the everolimus arm in order to model the exemestane monotherapy TTD, despite the fact that the crossing KM curves (Figure 33 in the CS) suggested the violation of the proportional hazard assumption. Since the log-cumulative hazard plots were not provided for the TTD data from the BOLERO-2 trial, the ERG could not suggest an appropriate alternative for the modelling of the TTD of the exemestane monotherapy according to the NICE DSU guidance for survival analysis.[70] Finally, the pooled post treatment discontinuation survival (from both the everolimus and exemestane arms) in the BOLERO-2 trial was used as a proxy for the post progression survival of both treatment arms. The ERG considers that by using the post treatment discontinuation survival data from the BOLERO-2 trial, the company might have overestimated the actual post-progression survival times (since TTD data from BOLERO-2 seems to be smaller than PFS). Furthermore, the ERG considers that before pooling the post-treatment discontinuation survival times from everolimus and exemestane arms, a statistical test (i.e. to check if these times were coming from the same distribution) should have been conducted.

The probability of death among TTD events for the second-line treatments (everolimus in combination with exemestane and exemestane monotherapy) was calculated in a similar way as described in section 5.2.6.2. The critique given in section 5.2.6.2 (i.e. that the death probability is dependent only on the

treatment received but not on other patient level characteristics) holds for the calculation of death among TTD events in the second-line, as well.

In the CS, for chemotherapy in the second-line, TTD was again used as a proxy for PFS. The ERG is concerned about the plausibility of this assumption. Furthermore, in the modelling of TTD and post-progression survival of the chemotherapy in the second-line, adjusted hazard rates from Li et al.2015[71] study were used, however, in the CS, neither the covariates used in the adjustment nor the methods of adjustment conducted in the Li et al.2015[71] study were explained. Additionally, in the Li et al.2015[71] study, the efficacy of the chemotherapy was compared with the efficacy of the *"everolimus-based therapy"*. It was not clear to the ERG what *"everolimus-based therapy"* is in the Li et al.2015[71] study (i.e. if it exactly refers to the everolimus in combination with exemestane as in the BOLERO-2 trial, or if it includes everolimus monotherapy or other combination therapies with everolimus, as well). Also, the ERG noted that no death probability is applied before time to treatment discontinuation under chemotherapy in the second-line in the economic model; however this assumption was not justified in the company submission.

Finally, the ERG considers that using the Weibull shape parameter for the post-treatment discontinuation survival from the BOLERO-2 might be unnecessary while modelling (as a Weibull function) the post-progression survival of chemotherapy based on the mean difference of OS and TTD. Instead, the ERG considers sampling the post-progression survival from the parametric functions for OS and TTD under chemotherapy in the second-line would be more suitable. These functions can be derived from the OS and TTD parametric functions fitted to the OS and TTD data from the everolimus arm of the BOLERO-2 trial and the HRs from Li et al.2015[71] study. If the same random number is used while sampling TTD and OS for the chemotherapy, the issue the company defined in the CS (i.e. the sampled OS is smaller than the sampled TTD) can be avoided. The ERG changed the way chemotherapy post-progression survival times are sampled in the ERG base-case so that the arbitrary scale parameter for a distribution is no longer needed.

5.2.7 Adverse events

The grade 3/4 adverse events that were included in the model and their probabilities from the MONALEESA-2 trial are given in Table 5.8 below. In the CS, it is mentioned that the AEs that required additional NHS resource use in their management were included in the model

Table 5.8: Probability of grade 3/4 AEs according to treatment in MONALEESA-2.

Grade 3/4 AE	Ribociclib + letrozole	Letrozole
Diarrhoea	1.2%	0.9%
Fatigue	2.4%	0.9%
Infection	4.2%	2.4%
Nausea	2.4%	0.6%
Febrile neutropenia	0.0%	0.0%
Pulmonary embolism	0.0%	0.3%
Vomiting	3.6%	0.9%
Source: CS, Table 36, page 134 AE = adverse events		

ERG comment:

Although 59.3% of the patients treated with ribociclib combined with letrozole within the MONALEESA-2 trial experienced grade 3/4 neutropenia compared to 0.3% of the patients in the

letrozole only arm, costs associated to neutropenia were not taken into account. The company argues that these costs were not incorporated in the health economic model, because neutropenia is managed through treatment interruptions or dose reduction. The ERG further noticed that, beside neutropenia, additional adverse events were not taken into account (e.g. grade 3/4 leukopenia [21.0% versus 0.6%] and back pain [2.1% versus 0.3%]). The reasoning for excluding these adverse events was lacking, and should have been given.

According to Table 36 in the CS (and Table 53 in the CS) the probabilities of grade 3/4 febrile neutropenia and pulmonary embolism were equal to 0%. The ERG noticed that these probabilities were inconsistent with the probabilities used within the health economic model. In the model it is assumed that the probability of grade 3/4 febrile neutropenia was 1.2% and the probability of grade 3/4 pulmonary embolism was 0.9% for patients treated with ribociclib combined with letrozole. These probabilities were equal to 0.0% and 0.3% for patients treated with letrozole alone.

5.2.8 Health-related quality of life

The company carried out a systematic literature review to identify studies on health-related quality of life relevant to the decision problem, and included 31 studies. Details relating to these studies are provided in the CS (Table 40).

ERG comment:

The company argued that only five of the 31 studies were useful for the HE model as they reported health state utility values for both progression-free and progressed disease. The ERG noticed that the study by Lloyd et al.2006[8] was the only one used, and it was unclear to the ERG what the limitations of the alternative publications were.

5.2.8.1 Pre-progression utility values

In section 5.4 of the CS,[4] the measurement and valuation of health effects is described. Utilities were derived by combining the answers to the EQ-5D-5L, as collected in the MONALEESA-2 trial, with the UK EQ-5D-5L tariff. A repeated measures mixed effects model was fitted to these data with disease status as an independent variable (either progression-free or progressed disease). Health state utilities of PFS 1 (on and off treatment) are shown in Table 5.8. No disutilities due to adverse events were applied, as the company argues that these were incorporated in the health state utility of PFS 1 (on and off treatment). [redacted] was found in the MONALEESA-2 trial between the utilities of patients treated with ribociclib in combination with letrozole and letrozole monotherapy (and between the period on and off treatment), and [redacted]

5.2.8.2 Post-progression (including PFS2) utility values

Although the EQ-5D-5L was completed [redacted] times during progressed disease (in the MONALEESA-2 trial), a utility value for the PFS 2 (on treatment) health state was derived from a publication by Lloyd et al. 2006.[8] These values were then adjusted for age and treatment response (the latter based on the BOLERO-2 trial), in line with the NICE appraisal of everolimus + exemestane [TA421][20] (Table 5.9). The company argues that this value better reflects the utility of patients receiving second-line therapy (than the utility as observed in the MONALEESA-2 trial), given the treatment pathway within the health economic model. Similar health state utilities were used for patients treated with everolimus in combination with exemestane and exemestane monotherapy (for simplicity). For patients treated with second-line chemotherapy, a utility decrement of 0.113 was applied, in line with the findings of Peasgood et al.2010.[72]

The health state utility for the progressed disease health state was also derived from the publication by Lloyd et al. 2006[8] in line with the approach taken by the ERG in the NICE appraisal of palbociclib (ID915)[63] (see Table 5.9).

Table 5.9: Health state utilities, as used within the base-case of the health economic model

Health state	Mean estimate	Standard error	Source
PFS1 on treatment	[redacted]	[redacted]	MONALEESA-2[23]
PFS1 off treatment	[redacted]	[redacted]	MONALEESA-2[23]
PFS2 – on treatment	0.774	Assumed to be 20% around the mean	Lloyd et al 2006[8]; NICE TA421[20]
PD	0.5052	Assumed to be 20% around the mean	Lloyd et al 2006[8]; NICE ID915[63]
Decrement in utility associated with chemotherapy	-0.113		Peasgood et al. 2010[72]

Source: CS, Table 41, page 149
PFS = progression-free survival; PD = progressed disease.

ERG comments:

It was not clear to the ERG which value set the company has used to calculate utilities from the answers to the EQ-5D-5L, since they only refer to Devlin et al. (without providing a full reference). Nevertheless, the ERG assumes that the EQ-5D-5L value set by Devlin et al. 2016[81] have been used (and not a preliminary UK tariff or the crosswalk). Although the mean utility of patients within the PFS1 health state seems relatively high, the estimation is in line with the NICE reference case. Nevertheless, the ERG wants to emphasise that there are differences between the UK EQ-5D-3L and English EQ-5D-5L value sets. Mulhern et al. 2017 concluded that "the EQ-5D-5L values for matched states are higher, and the overall range and therefore change between adjacent states is smaller than for the EQ-5D-3L".[82]

As there was [redacted] found within the MONALEESA-2 trial between the utilities of patients treated with ribociclib in combination with letrozole and letrozole monotherapy, no disutilities due to adverse events were applied in order to avoid double counting. Although the ERG agreed with this approach, they requested a scenario analysis to explore its impact. In their response, the company showed that the impact on the ICER [redacted] when adding disutilities for adverse events.

The utility values for PFS2 and PD were based on a publication by Lloyd et al. 2006,[8] and the values for PFS2 were adjusted based on BOLERO-2. In the study by Lloyd et al. 2006[8] vignettes were used to describe health states and then members of the general public in the UK rated them using standard gamble to determine utilities. In the clarification letter the ERG requested why the utility values, as observed during progressed disease in the MONALEESA-2 trial, were not used for the PFS2 health state. In their response, the company argued that [redacted] Additionally, they showed that assuming a utility value of 0.774 [redacted] can be considered a conservative approach; [redacted] The ERG is aware that health state utilities from the publication by Lloyd et al. 2006[8] were also used in previous appraisals of breast cancer therapies by NICE (including TA239; TA421 and ID915).[20, 21, 63]

A utility decrement of 0.113 was applied to patients treated with second-line chemotherapy based on a study by Peasgood et al. 2010.[72] In this study, data regarding a large number of utility values were synthesised by meta-regression. The ERG agrees that it is likely that patients treated with chemotherapy have a lower utility compared to patients treated with everolimus in combination with exemestane or single-agent endocrine therapy, but was unable to verify this disutility of 0.113. Nevertheless, the impact is rather small, given that only a proportion of patients receive second-line chemotherapy (25% in the ribociclib + letrozole arm and 30% in the letrozole monotherapy arm) and the time spent in PFS2 is relatively small.

Whereas a decrement in utilities is assumed if patients are treated with chemotherapy, the utility values of patients treated with everolimus plus exemestane and single-agent endocrine therapy are assumed the same (in PFS2). The ERG requested information regarding the difference in utility values. The company explained that the utility value of patients treated with exemestane, in the NICE appraisal of everolimus plus exemestane, was assumed to be 0.760. Given the small difference with the utility value of patients treated with everolimus plus exemestane (i.e. 0.774), the impact on the ICER is small.

5.2.9 Resources and costs

In section 5.5 of the CS[4] the identification, measurement and valuation of costs and healthcare resource use are described. The following cost components were included in the analysis: drug acquisition costs (including administration costs), costs of monitoring, health state costs (including terminal care costs), and the costs of adverse events.

5.2.9.1 Drug acquisition costs

To calculate drug acquisition costs of ribociclib, the company [redacted]

Drug acquisition costs for letrozole (2.5 mg) were estimated to be £0.05 per day and £1.52 per 28-day cycle, based on the eMIT.[83]

For the second-line treatment, within the health economic model, 25% of the patients in the ribociclib plus letrozole arm and 30% of the patients in the letrozole monotherapy arm received chemotherapy. Although NICE clinical guidelines[22] recommend anthracyclines and then docetaxel as chemotherapy options, the health economic model assumes that patients will be treated with capecitabine (based upon clinician validation), as the company argues that this chemotherapy is widely used due to the convenience of administration and the preferable side effect profile. Drug acquisition costs for capecitabine (1250 mg/m^2 twice daily for 14 days followed by a rest day of seven days[22, 84]) were estimated to be £145.69 per 21-day cycle (based on a body surface area of 1.74m^2[85]). In a scenario-analyses, the impact of alternative second-line chemotherapies (including paclitaxel, docetaxel and doxorubicin) was tested.

Everolimus plus exemestane is assumed to be given to 70% of the patients in the ribociclib plus letrozole arm and to 30% of the patients in the letrozole monotherapy arm as second-line treatment. Drug

acquisition costs for everolimus (10 mg daily) were estimated to be [redacted] per week (taking into account the Patient Access Scheme). Drug acquisition costs for exemestane (25 mg daily[86]) were estimated to be £1.39 per week.

For simplicity, the company did not take dose intensities of letrozole, everolimus plus exemestane, single-agent endocrine therapy (i.e. exemestane) and chemotherapy into account.

For the progression health state drug acquisition costs were estimated to be £461.54 per week (i.e. £2,000 per month). These costs include all future treatment-related costs following second-line treatment, but excludes the costs of terminal care. This estimate has been established taken into account the progression treatment-related costs in previous NICE appraisals (i.e. TA239, TA421 and ID915), [20, 21, 63] and was validated based on expert opinion. In scenario-analyses, the impact of alternative progression treatment-related costs was tested.

ERG comment:

In the CS it was stated that the drug acquisition costs of ribociclib [redacted] Thus, the ERG explored the impact of [redacted] but found that the impact was minimal.

Ribociclib is available in cycle packs (21 days). Once a pack has been opened, another patient cannot use the same pack. [redacted] drug acquisition costs are not corrected for wastage, i.e. the fact that if the patient ceases treatment at any point before the end of that cycle any unused treatment is wasted (note that wastage may only occurs at treatment cessation and not at dose adjustments, since ribociclib is delivered in packages with 200 mg tablets). Additionally, the company failed to take into account the costs of unused treatment within the second-line (i.e. the costs of unused tablets of everolimus, exemestane and capecitabine). In the ERG base-case costs of wastage are incorporated. Furthermore, the ERG identified an error in the wastage costs if a chemotherapy other than capecitabine was selected as second-line therapy. This error does not have an impact on the ICER as presented in the CS base-case and ERG base-case.

Costs of capecitabine were used in order to reflect the costs of chemotherapy in second-line, whereas NICE clinical guidelines recommend anthracyclines as the chemotherapy of first choice. Nevertheless, the company explored the impact of alternative second-line chemotherapies including anthracyclines in scenario-analyses, and showed that the impact was small. According to the CS, the costs of capecitabine were based on a daily dose of 4,350 mg (two times 2,175 mg). The ERG noticed that within the health economic model this dose was rounded down, i.e. in the model it is assumed that a patient needs eight 500 mg tablets and two 150 mg tablets per day (adding up to 4,300 mg). Nevertheless, the ERG did not change the implementation of the costs of capecitabine, because it assumed that the recommended dose per administration for a patient with a bsa of 1.74 is 2,150 (instead of 2,175) in line with the eMC website.[84]

In the CS, the explanation of the drug acquisition costs in the progression health state is very limited. The ERG therefore requested the details of these costs. In their response, the company argued that these costs were based on expert opinion, but a foundation was lacking. Nevertheless, the company found support in the NICE appraisal of fulvestrant (TA239)[21] in which an overview of treatment pathways was provided during post-progression, as well as average cost post-progression per month amounting to £1,084 (excluding costs associated to adverse events). Although the ERG realises that TA239 was

published in 2011, and the treatment pathway will have changed, the ERG considers the costs as estimated within TA239 more reliable than the costs based on expert opinion (given that the details of what was suggested by the experts to arrive at these costs are lacking). Therefore, in the ERG base-case post-progression costs (of third-line and subsequent lines of treatment) were based on TA239. Additionally, the ERG explored the impact of different assumptions regarding the costs of third-line and greater treatment cost in scenario-analyses.

5.2.9.2 Administration costs

The health economic model does not include drug administration costs for ribociclib, letrozole, everolimus plus exemestane and single-agent endocrine therapy (i.e. exemestane), since they are all administered orally. In contrast, administration costs for capecitabine were assumed to be £181.27.[87] Additionally, the costs of premedication were taken into account for patients receiving docetaxel; these cycle-costs were taken from TA416.[88]

5.2.9.3 Monitoring costs

The costs of monitoring were included for patients receiving ribociclib (for a maximum of six cycles). These costs include the costs of full blood counts, liver function tests and electrocardiograms, based on the anticipated license for ribociclib. No monitoring costs were assumed for letrozole, everolimus plus exemestane, single-agent endocrine therapy (i.e. exemestane) and chemotherapy. Costs were estimated at £89.26, £48.91, and £4.28 for the first, second, and third to sixth cycle, respectively (see Table 48 CS)

5.2.9.4 Health state costs

Table 5.10 (Table 52 CS) shows the health state costs. Health state costs of PFS1 and PFS2 include the costs of general practitioner visits (once every month), oncology consultant office (once every six months), community nurse (once every quarter), clinical nurse specialist (once every month) and computer tomography scan (once every quarter). In addition to these costs, costs of a social worker (once every two months) are included in the health state costs of progressed disease.

With respect to terminal care it is assumed that 50% of the patients receive terminal care at home (with community support), 40% receive terminal care in the hospital, and 10% in a Marie Curie hospice.

Table 5.10: Health state costs

Health state	Cost per month (£) (unless stated)	Reference in CS
Progression Free (PFS1) on and off treatment -1st line	£155.73	Table 49
Progression Free (PFS2) on treatment -2nd line	£155.73	Table 49
Progressed disease	£195.23	Table 50
Terminal care (one-time)	£4,379.03	Table 51
Source: CS, Table 52, page 160 CS = company submission; PFS = progression-free survival.		

5.2.9.5 Costs of adverse events

The costs of the management of adverse events associated with ribociclib and letrozole were estimated by multiplying the probability of grade 3 and 4 adverse events by the unit costs of the management of these adverse events (Table 5.11). Then, the sum of these costs were divided by the time patients were

exposed to either ribociclib or letrozole (as observed in the MONALEESA-2 trial). This resulted in total costs of [redacted] (ribociclib) and £0.65 (letrozole) per patient per week.

Costs of the management of grade 3 and 4 neutropenia were not taken into account, as it was assumed that these adverse events do not consume NHS resources, but lead to dose interruptions or reductions instead.

Table 5.11: Probabilities of grade 3 and 4 adverse events and the associated unit costs

Adverse event	Ribociclib	Letrozole	Unit cost	Resource use assumption (comments)
Diarrhoea	1.2%	0.9%	£461.17	FZ36G to FZ36Q - Gastrointestinal Infections non-elective short stay (weighted average) - NHS reference costs 2015-2016
Fatigue	2.4%	0.9%	£508.67	SA04K - Iron Deficiency Anaemia with CC Score 2-5 non-elective short stay - NHS reference costs 2015-2016
Infection	4.2%	2.4%	£518.34	WH07A to WH07G - Infections or Other Complications of Procedures (weighted average) - NHS reference costs 2015-2016
Nausea	2.4%	0.6%	£557.45	JA12D to JA12L - Malignant Breast Disorders (weighted average) - NHS reference costs 2015-2017
Febrile neutropenia	0.0%	0.0%	£2,383.80	SA35A to SA35E - Agranulocytosis non-elective long stay (weighted average) - NHS reference costs 2015-2016
Pulmonary embolism	0.0%	0.0%	£499.38	DZ09J to DZ09Q - Pulmonary Embolus (weighted average) - NHS reference costs 2015-2017
Vomiting	3.6%	0.9%	£557.45	JA12D to JA12L - Malignant Breast Disorders (weighted average) - NHS reference costs 2015-2017
Source: CS, Table 53 and 54, page 160 and 161				

ERG comments:

In contrast to the zero probabilities of grade 3/4 febrile neutropenia and pulmonary embolism in Table 5.11, the ERG noticed that in the health economic model these probabilities are equal to 1.2% and 0.0% (grade 3/4 febrile neutropenia), and 0.9% and 0.3% (grade 3/4 pulmonary embolism).

5.2.10 Cost effectiveness results

Table 5.12 and Table 5.13 present the total costs, life years and QALYs for both ribociclib plus letrozole and letrozole monotherapy with and without the patient access scheme (PAS) under the base-case analysis. Without the PAS, incremental QALYs are 0.96 and incremental costs are [redacted]. The corresponding ICER is [redacted] per QALY gained for ribociclib plus letrozole compared to letrozole monotherapy. With the PAS, incremental costs reduce to [redacted], and the corresponding ICER is [redacted] per QALY gained.

Table 5.12: Base-case cost effectiveness results (without patient access scheme)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]

Source: CS, Table 58
ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

Table 5.13: Base-case cost effectiveness results (with patient access scheme)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]

Source: Company PAS submission, Table 5
ICER = incremental cost-effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

In the CS, the company attempted to compare the clinical outcomes from the MONALEESA-2 trial and the model outcomes for the two main outcome measures, OS and PFS. This was however not possible due to the data being immature. Only the median PFS for the letrozole arm from the trial could be compared with the median PFS from the model (14.7 months vs. [redacted] months, respectively).

Disaggregated results (in terms of QALYs and costs [without PAS]) from the base-case analysis are given in Table 5.14 and Table 5.15 below. The difference in total QALYs between the two technologies mostly resulted from the gain in PFS1 for patients on ribociclib plus letrozole compared to the patients on letrozole only. Similarly for the difference in total costs, higher drug acquisition costs were incurred for patients on ribociclib plus letrozole for a longer time compared to the patients on letrozole only.

Table 5.14: Disaggregated QALYs by health state

Health state	QALY intervention (ribociclib plus letrozole)	QALY comparator (letrozole monotherapy)	Increment	Absolute increment	% absolute increment
PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	0.96	[redacted]

Source: CS, Table 60
QALYs, quality-adjusted life years; PFS = progression-free survival; PD = progressed disease.

Table 5.15: Disaggregated costs by health state

Health state	Cost intervention (ribociclib plus letrozole)	Cost comparator (letrozole monotherapy)	Increment	Absolute increment	% absolute increment
Treatment acquisition – PFS1 health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment acquisition – PFS2 health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state resource use costs (PFS1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state resource use costs (PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression health state related costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 61
PFS = progression-free survival.

ERG comments:

In the CS, the company attempted to compare the model outcomes for median PFS and OS with the median PFS and OS derived from the MONALEESA-2 trial dataset with the January 2016 data cut-off. Since most of the median/mean estimates were not available for the January 2016 data cut-off dataset, this comparison attempt was not very informative. After the company provided the results from the January 2017 data cut-off at the ERG's request, the ERG was able to make a comparison table based on the updated data as given in Table 5.16 below. [redacted]

Table 5.16: Comparison of the clinical outcomes from the trial with the base-case model outcomes based on dataset from January 2017 cut-off

Outcomes per treatment	Clinical trial result		Model result	
	Median	Mean	Median	Mean
Ribociclib				
First-line progression-free survival (PFS1)	25.3	Not reached, not reported	[redacted]	[redacted]
Overall survival	Not reached, not reported	Not reached, not reported	[redacted]	[redacted]
Letrozole				
First-line progression-free survival (PFS1)	16	Not reached, not reported	[redacted]	[redacted]
Overall survival	33	Not reached, not reported	[redacted]	[redacted]
PFS = progression-free survival.				

5.2.11 Sensitivity analyses

Probabilistic sensitivity analyses (PSA)

To examine the impact of the joint uncertainty across all model inputs, probabilistic sensitivity analyses were conducted. According to the CS (Table 56 in CS[4]), the following category of inputs were varied simultaneously, based upon their corresponding distribution given between brackets.

- Survival function parameters of the first line PFS, TTD for ribociclib or letrozole arms (normal or multivariate normal distributions)
- Proportion of death among PFS events for ribociclib and letrozole arms (beta distribution)
- Survival function parameters for the second-line PFS, TTD for everolimus and exemestane therapy and for the second-line PPS for pooled everolimus and exemestane arms (multivariate normal distribution)
- Proportion of death among PFS events for second-line everolimus and exemestane patients (beta distribution)
- Treatment effect for exemestane monotherapy vs. everolimus in combination with exemestane (log-normal)
- Utility values for PFS (on- and off-treatment) in the first and second lines (beta distribution)
- Health state management costs for PFS in first and second-line, in progressed disease and terminal care costs (gamma distribution)

The results of 1,000 PSA iterations are shown in the figures below. The cost effectiveness planes show the incremental QALYs and costs of ribociclib plus letrozole relative to the letrozole monotherapy (Figure 5.10 [without PAS] and Figure 5.11 [with PAS]). Additionally, the cost effectiveness acceptability curves (CEAC) are presented, showing the likelihood of ribociclib plus letrozole being cost effective at different willingness-to-pay thresholds (Figure 5.12 [without PAS] and Figure 5.13 [with PAS]).

The cost effectiveness results of the PSA without PAS and with PAS are given in Table 5.17 and in Table 5.18 below. Mean incremental QALYs from ribociclib plus letrozole were around 0.98. Mean incremental costs were [redacted]. The resulting probabilistic ICER from 1,000 iterations was [redacted] (comparable to the deterministic, base-case ICER of [redacted]). When taking into account the patient

access scheme, the incremental costs reduces to [redacted], and the corresponding probabilistic ICER was [redacted] (comparable to the deterministic, base-case ICER of [redacted]).

Table 5.17: PSA cost effectiveness results without PAS, mean (95% percentile interval)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	[redacted]

Source: CS, Table 62
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

Table 5.18: PSA cost effectiveness results with PAS, mean (95% percentile interval)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]

Source: Company PAS submission, Table 6
ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.

The CEAC in Figure 5.12 suggests that there is a [redacted] likelihood of ribociclib plus letrozole cost effectiveness at a willingness-to-pay threshold of £30,000/QALY; when taking into account the PAS (Figure 5.13), this likelihood is [redacted].

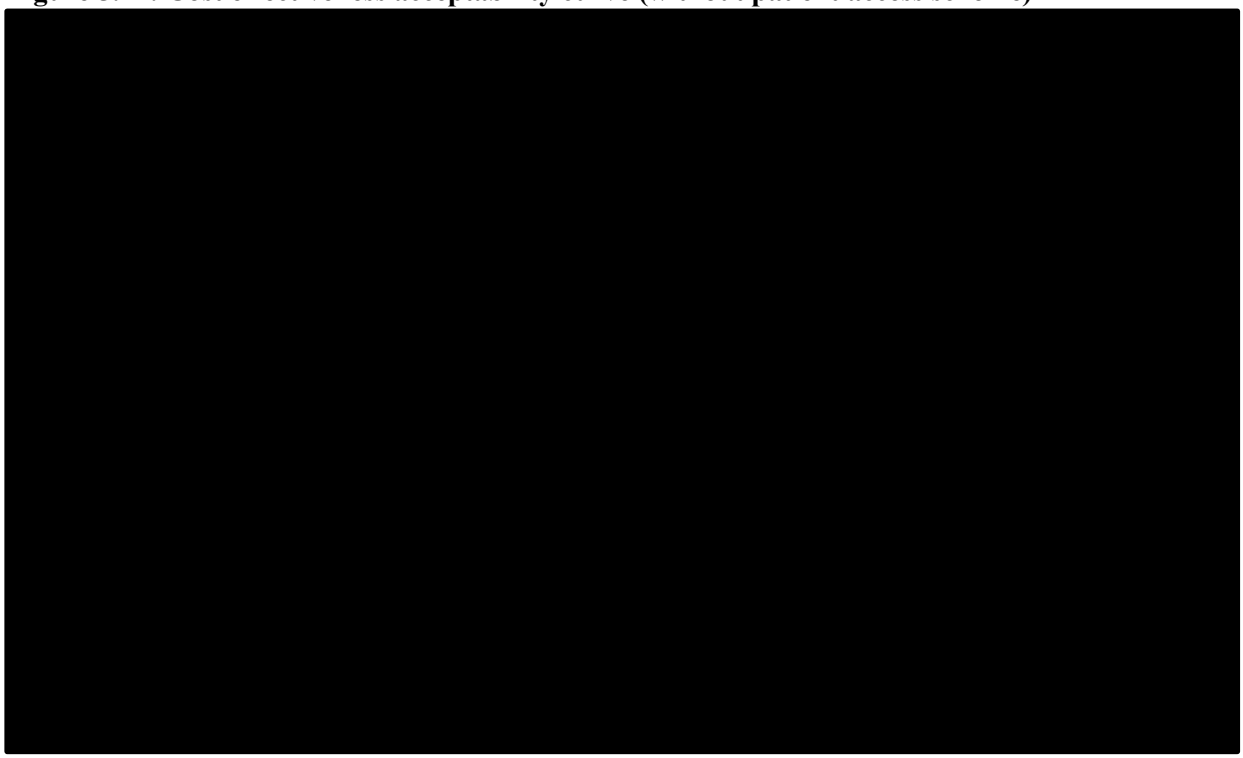
Figure 5.10: Cost effectiveness plane (without patient access scheme)

Source: CS, Figure 40
QALYs = quality-adjusted life years.

Figure 5.11: Cost effectiveness plane (with patient access scheme)

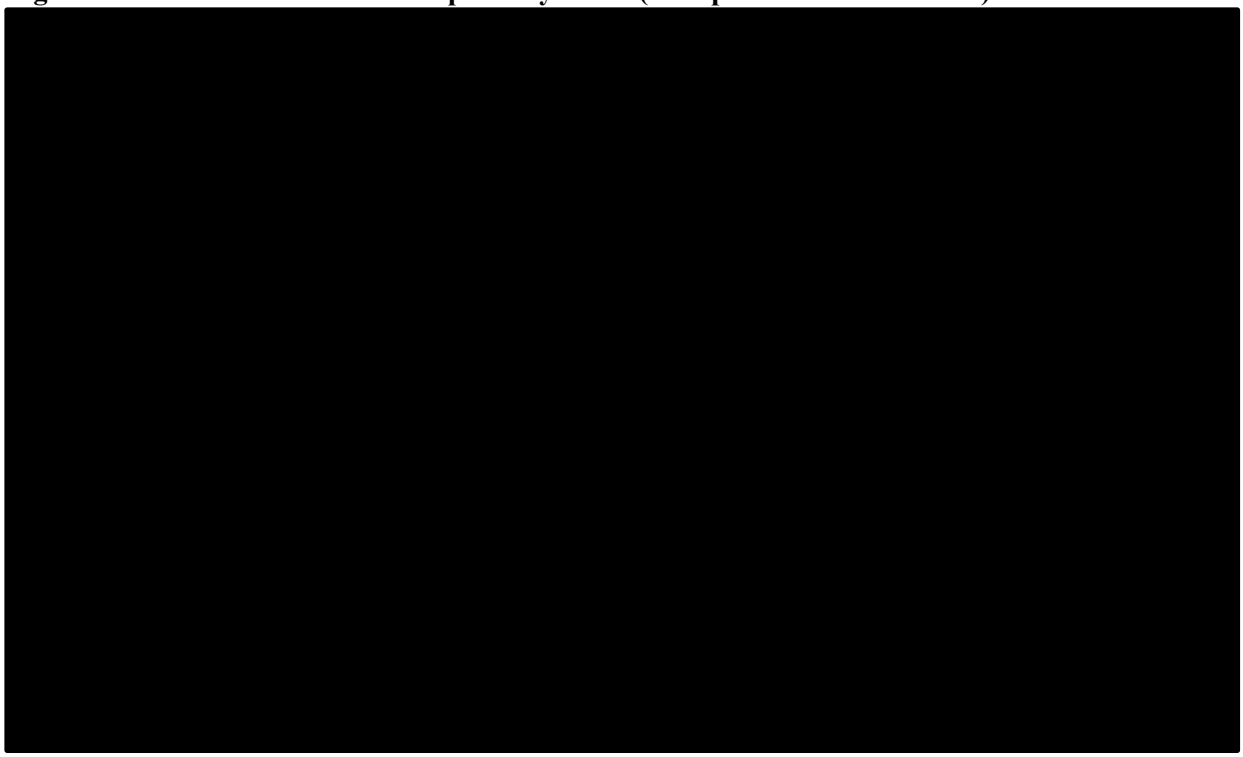
Source: Company PAS submission, Figure 2
QALYs = quality-adjusted life years.

Figure 5.12: Cost effectiveness acceptability curve (without patient access scheme)



Source: CS, Figure 41
QALYs = quality-adjusted life years.

Figure 5.13: Cost effectiveness acceptability curve (with patient access scheme)



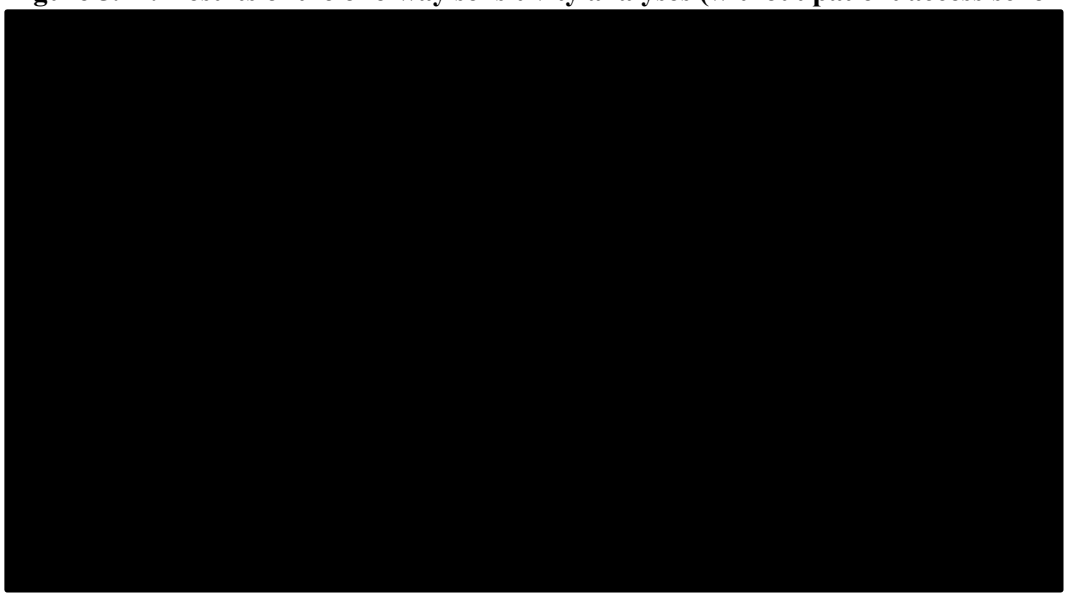
Source: Company PAS submission, Figure 3
QALYs = quality-adjusted life years.

Deterministic sensitivity analyses

The company included the parameters presented in Table 5.19 (with their corresponding upper and lower range values) in the one-way sensitivity analysis.

Figure 5.14 displays a tornado diagram showing the 10 parameters that had the largest impact on the ICER. The tornado diagram in Figure 5.15 takes into account the patient access scheme. The ICER was most sensitive to the discount rates. The probability of death among first-line PFS events in the ribociclib arm, third-line treatment costs, and the HR for exemestane TTD (vs. everolimus TTD) in second line seem to have visible impacts on ICER, as well.

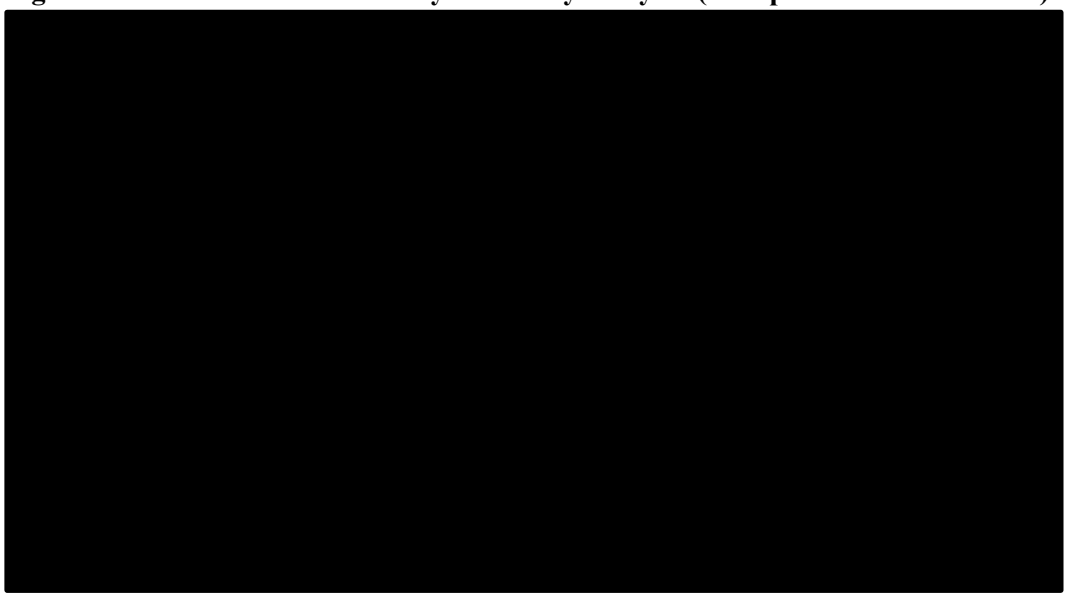
Figure 5.14: Results of the one-way sensitivity analyses (without patient access scheme)



Source: CS, Figure 42

HR = hazard ratio; TTD = time to treatment discontinuation; Dth = death; PFS = progression-free survival; Rib = ribociclib; HS = health state; trt = treatment; CES = Treatment cessation.

Figure 5.15: Results of the one-way sensitivity analyses (with patient access scheme)



Source: Company PAS submission, Figure 1

Dth = death; PFS = progression-free survival; Rib = ribociclib; HR = hazard ratio; TTD = time to treatment discontinuation; HS = health state; trt = treatment; OS = overall survival.

Table 5.19: Parameters used in the one-way sensitivity analysis

Parameter	Parameter values			Reference
	Lower value	Base-case	Upper value	
Discount costs	1.5%	3.50%	5.0%	Fixed to 1.5% and 5%
Discount benefits	1.5%	3.50%	5.0%	Fixed to 1.5% and 5%
HR exemestane TTD	[redacted]	[redacted]	[redacted]	Lognormal (95% CI)
Cost progression health state	£369.23	£461.54	£553.85	Assume -/+20%
Utility value - 1st line PFS	[redacted]	[redacted]	[redacted]	Beta (estimated 95% CI)
% death upon PFS 1st line ribociclib	[redacted]	[redacted]	[redacted]	Beta (estimated 95% CI)
Utility value – progressed	0.46	0.51	0.55	Beta (estimated 95% CI)
Cost HS PFS1 - Off treatment	£28.75	£35.94	£43.13	Assume -/+20%
Utility value - 2nd line PFS	0.69	0.77	0.85	Beta (estimated 95% CI)
% death upon PFS 1st line letrozole[#]	[redacted]	[redacted]	[redacted]	Beta (estimated 95% CI)
HR Chemo 2nd TTD	0.17	0.30	0.52	Lognormal (95% CI)
HR Chemo 2nd OS	0.30	0.56	1.02	Lognormal (95% CI)
Cost HS PD	£36.04	£45.05	£54.06	Assume -/+20%
Cost HS PFS1 - On treatment	£28.75	£35.94	£43.13	Assume -/+20%
Cost AE ribociclib	£1.66	£2.07	£2.48	Assume -/+20%

Source: CS, Table 63
HR = hazard ratio; TTD = time to treatment discontinuation; PFS = progression-free survival; HS = health state; OS = overall survival; PD = progresses disease; AE = adverse event.
# One way sensitivity analysis was not run for % death upon PFS 1st line letrozole due to the 0% used in the base-case and the results have no impact on the ICER in one way. This variable has been explored in scenario analysis.

Scenario analyses

The company conducted several scenario analyses exploring the impact of structural or remaining uncertainties on the incremental results of the economic evaluation. The following scenario analyses were conducted in the CS[4]:

- Different time horizons (5, 10, 15, 20, 25 and 30 years, where 40 years was the base-case)
- Different (partially) parametric extrapolation functions for the PFS in the first-line (Weibull, Gompertz, Log-normal, Log-logistic and Kaplan-Meier until last event followed by parametric extrapolation, where the exponential distribution was assumed as the base-case)
- Modelling the PFS of ribociclib and letrozole arms jointly by applying the HR for PFS in first-line from MONALEESA-2 trial (where independent modelling of different arms was the base-case)
- Different OS surrogacy thresholds (Full OS surrogacy is assumed if PFS of ribociclib or the PFS gain under ribociclib is above a certain threshold, i.e. 4, 8, 10, 12 and 28 months, where in the base-case full OS surrogacy is always assumed)
- Choice of the chemotherapy agent in the second-line (paclitaxel, docetaxel and doxorubicin were explored, where capecitabine was assumed in the base-case)
- Different distributions for the second-line treatment (same treatment pathways for both arms were applied, where 100% chemotherapy, 100% everolimus in combination with exemestane, 100% exemestane and another distribution [50% chemotherapy, 25% everolimus in

combination with exemestane and 25% exemestane]) were explored, whereas in the base-case different distributions for the second-line treatments were assumed based on clinical expert opinion.

- Different parametric extrapolation functions for the PFS, TTD, PPS and OS in the second-line (Exponential, Gompertz, Log-normal and Log-logistic, where Weibull distribution was assumed as the base-case)
- Different third-line treatment costs (£1,000, £425, £0 per month were explored whereas it was assumed £2,000 in the base-case)
- Different probability of death among PFS events (pooled results from MONALEESA-2 and BOLERO-2 trials were used whereas in the base-case only the results from MONALEESA-2 trial was used)

Table 5.20 shows the results of these scenario analyses, not taking into account the patient access scheme. The company concluded that the ICERs are all close to the results of the base-case analysis. Scenarios with the largest impact on the ICER (i.e. ICER > [redacted]) are:

- a time horizon of 5 and 10 years (instead of 40 years);
- the use of a Weibull or Gompertz parametric function for first-line PFS (PFS1 health state) (instead of an Exponential function);
- the threshold defined on ribociclib PFS to have an OS gain = 28 months, threshold defined on PFS gain = 12 months and 28 months (instead of full OS surrogacy);
- the use of £425 per month or £0 per month for third-line treatment costs (during the progression health state) (instead of £2,000 per month).

Table 5.21 shows the results of the scenario analyses, taking into account the patient access scheme. Scenarios with the largest impact on the ICER (i.e. ICER > [redacted]) are:

- a time horizon of five years (instead of 40 years);
- the use of a Weibull or Gompertz parametric function for first-line PFS (PFS1 health state) (instead of an Exponential function);
- the use of £1,000 per month, £425 per month or £0 per month for third-line treatment costs (progression health state) (instead of £2,000 per month).

Table 5.20: Results of the scenario analyses (without patient access scheme)

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base-case = 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Time horizon = 5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.42	[redacted]
Time horizon = 10 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81	[redacted]
Time horizon = 15 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93	[redacted]
Time horizon = 20 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Time horizon = 25 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Time horizon = 30 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS (parametric function)							
Base-case = Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.80	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.76	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.74	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1.31	[redacted]
Use of HR for PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	[redacted]
KM plus parametric PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]
Overall survival: Surrogacy assumption							
Base-case = full OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Threshold PFS to have OS gain = 4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]
Threshold PFS to have OS gain = 8 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	[redacted]
Threshold PFS to have OS gain = 10 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	[redacted]
Threshold PFS to have OS gain = 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93	[redacted]

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Threshold PFS to have OS gain = 28 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.84	[redacted]
Threshold PFS gain = 4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	[redacted]
Threshold PFS gain = 8 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
Threshold PFS gain =10 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.87	[redacted]
Threshold PFS gain =12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]
Threshold PFS gain =28 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.67	[redacted]
Chemotherapy used in second-line							
Base-case = capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Treatment pathway – second-line treatment used							
Base-case = different treatment pathways	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Same treatment pathway: Eve + exe = 25% Single agent endocrine therapy = 25% Chemotherapy = 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
Same pathway: Eve + exe = 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]
Same pathway: Single agent endocrine therapy = 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.87	[redacted]
Same pathway: Chemotherapy = 100%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.91	[redacted]

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Parametric functions used in 2nd line							
Base-case = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
TTD Eve = Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	[redacted]
PFS Eve = Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PPS Eve = Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PPS Eve = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
PPS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.92	[redacted]
PPS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93	[redacted]
OS Eve = Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Third line (progression HS) costs							
Base-case = £2,000 per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
£1000 per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
£425 per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
£0 per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Death before first line progression							
Base-case = MONALEESA-2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Pooled 1st line progression %	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]

Source: CS, Table 65
QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; Eve = everolimus; exe = exemestane; HS = health state.

Table 5.21: Results of the scenario analyses (with patient access scheme)

Scenario	ICER per QALY gained (£)	Scenario	ICER per QALY gained (£)
Time horizon		*Treatment pathway – second-line treatment used*	
Base-case = 40 years	[redacted]	**Base-case = different treatment pathway***	[redacted]
Time horizon = 5 years	[redacted]	Same treatment pathway: Eve + exe = 25% Single agent endocrine therapy = 25% Chemotherapy = 50%	[redacted]
Time horizon = 10 years	[redacted]	Same pathway: Eve + exe = 100%	[redacted]
Time horizon = 15 years	[redacted]	Same pathway: Single agent endocrine therapy = 100%	[redacted]
Time horizon = 20 years	[redacted]	Same pathway: Chemotherapy = 100%	[redacted]
Time horizon = 25 years	[redacted]	*Parametric functions used in 2nd line*	
Time horizon = 30 years	[redacted]	**Base-case = Weibull**	[redacted]
PFS (parametric function)		TTD Eve = Exponential	
Base-case = Exponential	[redacted]	TTD Eve = Gompertz	[redacted]
Weibull	[redacted]	TTD Eve = Log-Normal	[redacted]
Gompertz	[redacted]	TTD Eve = Log-logistic	[redacted]
Log-normal	[redacted]	PFS Eve = Exponential	[redacted]
Log-logistic	[redacted]	PFS Eve = Gompertz	[redacted]
Use of HR for PFS	[redacted]	PFS Eve = Log-Normal	[redacted]
KM plus parametric PFS	[redacted]	PFS Eve = Log-logistic	[redacted]
Overall survival: Surrogacy assumption		PPS Eve = Exponential	[redacted]
Base-case = full OS surrogacy	[redacted]	PPS Eve = Gompertz	[redacted]
Threshold PFS to have OS gain = 4 months	[redacted]	PPS Eve = Log-Normal	[redacted]
Threshold PFS to have OS gain = 8 months	[redacted]	PPS Eve = Log-logistic	[redacted]
Threshold PFS to have OS gain = 10 months	[redacted]	OS Eve = Exponential	[redacted]
Threshold PFS to have OS gain = 12 months	[redacted]	OS Eve = Gompertz	[redacted]
Threshold PFS to have OS gain = 28 months	[redacted]	OS Eve = Log-Normal	[redacted]
Threshold PFS gain = 4 months	[redacted]	OS Eve = Log-logistic	[redacted]
Threshold PFS gain = 8 months	[redacted]	*Third line (progression HS) costs*	
Threshold PFS gain = 10 months	[redacted]	**Base-case = £2,000 per month**	[redacted]
Threshold PFS gain = 12 months	[redacted]	£1000 per month	[redacted]
Threshold PFS gain = 28 months	[redacted]	£425 per month	[redacted]
Chemotherapy used in second-line		£0 per month	[redacted]
Base-case = capecitabine	[redacted]	*Death before first line progression*	

Scenario	ICER per QALY gained (£)	Scenario	ICER per QALY gained (£)
Paclitaxel	[redacted]	**Base-case = MONALEESA-2**	[redacted]
Docetaxel	[redacted]	Pooled 1st line progression %	[redacted]
Doxorubicin	[redacted]		

Source: Company PAS submission, Table 7
QALYs = quality-adjusted life years; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; HR = hazard ratio; KM = Kaplan-Meier; OS = overall survival; Eve = everolimus; exe = exemestane; HS = health state.

ERG comment:

The ERG noted that more parameters than it was stated in the CS (Table 56)[4] were included in the PSA, such as the TTD, PFS and OS HRs (vs. everolimus) for the treatment effect of chemotherapy in the second-line. Unfortunately, besides the assumed functional form of the distributions, there was no information in the CS on how the probabilistic samples for these parameters are generated in the CS (e.g. mean and standard error for each parameter and the calculations conducted to estimate PSA samples were lacking). However, from the economic model, the ERG still noticed that some of the key parameters were not included to the PSA, such as the third-line treatment costs, disutility due to chemotherapy, and the distribution of second-line treatments. This of course leads to an underestimation of the total parameter uncertainty.

Regarding the deterministic sensitivity analysis, the ERG noticed that the company included different parameters than in the PSA. Some of the parameters that may be expected to have a large impact on the overall uncertainty were not included into the deterministic sensitivity analysis, such as the ribociclib treatment effect parameters. In the CS, it was stated that these parameters were addressed in scenario analyses. The justification for the parameter inclusion criteria used by the company for deterministic sensitivity analysis is not clear to the ERG, and similarly the details on the calculations of the lower and upper bounds were lacking in the company submission (e.g. for some parameters, ±20% was assumed for lower and upper bounds, but for the other 95% CI estimates, the details of the calculations were missing).[4] Taking into consideration the rather limited set of parameters varied in the deterministic one-way sensitivity analyses and the rather narrow confidence intervals used for some input parameters, the results presented in the tornado diagrams should be interpreted with care.

Overall, given the lack of details provided in the CS, the ERG cannot assess the quality and reliability of the PSA and the one-way sensitivity analysis implementations.

In the scenario analyses, the ERG identified some minor programming errors, for instance in the scenario analysis where the PFS in the first line was sampled from the KM curve until the last event and a parametric function afterwards, the ERG noticed that the KM probabilities were not correctly entered for the last two events (based on PFS 2017 cut-off dataset) for the letrozole arm. Another error was in the scenario analysis where another chemotherapy agent was selected for the second-line other than capecitabine. The final (incomplete) cycle drug acquisition costs were always calculated under the capecitabine regimen assumptions, even if another chemotherapy agent was selected. These errors do not have any impact on the company base-case and ERG base-case analyses, and have minor impact on the relevant scenario analysis results.

Another inconsistency was identified in the threshold-based OS surrogacy scenarios. As discussed in section 5.2.2.1 of this report, in the actual simulation implementation, if the PFS with ribociclib is larger than the OS with letrozole monotherapy, even if the gain in PFS (or the PFS of the ribociclib arm) is

below the pre-defined threshold, it is assumed that the PFS event of that patient is death and a gain in OS is still implemented. Due to this implicit assumption, the proportion of death among PFS events in the first-line can be unlikely high (up to 30%) for some thresholds in the ribociclib arm. Due to this inconsistency, the ERG followed a different approach while modelling OS surrogacy as will be described in section 5.3 of this report.

5.2.12 Model validation and face validity check

The company mentioned that both internal and external validation efforts were conducted for the cost effectiveness model.

As part of the internal validation efforts, the company stated that the model went through a quality control check by an internal health economist team and another independent health economist to ensure that the model was reliable and producing robust and expected results.

Furthermore, the OS and PFS model predictions for the letrozole monotherapy were compared with the OS and PFS data for the letrozole monotherapy as a first-line treatment for advanced HR+/HER2- breast cancer patients from MONALEESA-2 and other two identified trials, LEA[76] and ALLIANCE[77] (For PFS, Figure 44 in the CS; for OS, Figure 45 in the CS).

Additionally, as part of external validation efforts, the company declared that clinical expert meetings were organised, during which the relevance of the MONALEESA-2 trial to the UK clinical practice, the appropriateness of the economic model in terms of representing the natural history of the disease and representing the disease management pathway, and the plausibility of the clinical inputs of the model as well as the model outputs were discussed. According to the company, the experts concluded that the MONALEESA-2 trial was robust and relevant to the UK and the structure of the economic model was deemed as representative of the clinical pathway for advanced HR+/HER2- breast cancer patients in the UK. The clinical experts expressed their anticipation of different treatment pathways after progression with ribociclib in combination with letrozole and with letrozole monotherapy. The model predictions for PFS and OS of letrozole monotherapy at three, five and 10 years were considered to be reasonable. The clinical experts expressed no concerns about the additional monitoring requirements of ribociclib and QTcF prolongation.

Finally, the company presented a detailed comparison between the evidence presented in the CS and the evidence presented in the ID915 NICE technology appraisal[63] for palbociclib, since both appraisals are for the same indication, i.e. first-line treatment for HR+/HER2- advanced breast cancer patients, and both treatments are considered to be in the same class of therapies, i.e. CDK4/6 inhibitors.

One of the key differences between the evidence in these two appraisals was found to be in the model structure. Whilst the current submission employs a patient level simulation approach, in the palbociclib appraisal a partitioned survival Markov model approach was followed with post-progression tunnel states for second, third and fourth treatments and best supportive care. In both appraisals, the comparator was the same, letrozole monotherapy. The clinical data used for ID915[63] were from PALOMA-2 for PFS and utilities, and PALOMA-1 for OS. Only neutropenia costs were incorporated in ID915 among all grade 3/4 adverse events. The results of the cost effectiveness analysis differed between the two appraisals, especially in terms of life years gained; the economic model of this submission estimated the LYG for letrozole monotherapy [redacted] than ID915.[63] The company argued that the gap between the LYG estimates from the two appraisals arose from the differences in the modelling approaches (i.e. patient level simulation vs. partitioned survival Markov). The company further argued that the LYG results from the previous appraisals for the other treatments in HR+/HER2- advanced breast cancer

(everolimus, TA421[20] and fulvestrant, TA239[21]) were more in line with the LYG results from the evidence presented in this appraisal.

ERG comment:

The ERG found the list of programming error checks provided in company's response to the clarification letter document useful, however considered that the reporting of these error checks did not provide sufficient information. When reporting verification efforts, in addition to the qualitative description, a technical description of each effort (e.g. which cell or programming lines were modified and from which cells/output lines the model outcome could be assessed) should be also reported to facilitate the reproducibility of verification test results.

Since the detailed explanation of the codes and functions used in the simulation was provided only in the response to the clarification letter document, the ERG could not conduct the steps of their in-house technical verification checklist (TECH-VER checklist) to verify whether the model was correctly implemented and whether the report (description of the model as well as the results) and the model (calculations and results) were consistent or not. However, the validation exercise followed by the company (reprogramming a part of the simulation in Excel using partitioned survival approach) is appreciated.

The ERG also appreciated the provision of some of the communication details with the clinical experts in response to the clarification letter, and believes they include valuable insights and information. However, the ERG noticed that consensus among the experts on the inputs used in the model was lacking (e.g. second-line treatment choice and third-line treatment costs). Given the lack of transparency and details on how these estimates were derived, it is difficult to judge the robustness of these estimates.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Based on all considerations from section 5.2, the ERG defined a new base-case. This base-case includes multiple adjustments to the original base-case presented in the CS. The ERG will use the updated CS base-case as a starting point for its analysis. These adjustments made by the ERG/provided in the updated company base-case form the ERG base-case and were subdivided into three categories (derived from Kaltenthaler 2016[89]):

- Fixing errors (correcting the model were the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model were the ERG considers that reasonable alternative assumptions are preferred)

After the ERG base-case analysis, additional scenario analyses were performed by the ERG in order to examine the potential impact of alternative assumptions on the cost effectiveness estimates.

5.3.1 Explanation of the ERG adjustments

Fixing errors

Since the detailed explanation of the codes and functions used in the simulation code were provided only in the response to the clarification letter document, the ERG did not have enough time to conduct the steps of their in-house technical verification checklist (TECH-VER checklist) systematically, to verify whether the model was correctly implemented and whether the report (description of the model as well as the results) and the model (calculations and results) were consistent or not.

Nevertheless, the ERG still was able to identify the following programming errors in the company base-case:

- In the scenario analysis where the PFS in the first line was sampled from the KM curve derived from the MONALEESA-2 trial until the last event and a parametric function afterwards, the ERG noticed that the KM probabilities were not correctly entered for the last two events (based on the PFS 2017 cut-off dataset) for the letrozole monotherapy arm.
- In the scenario analysis where another chemotherapy agent was selected for the second-line other than capecitabine, the final (incomplete) cycle drug acquisition costs were still calculated under the capecitabine regimen assumptions.
- In the scenario analysis in which equal treatment pathways were assumed in the second-line, the treatment percentages in the model implementation (50% everolimus in combination with exemestane and 50% chemotherapy) were different from the reported treatment percentages (25% everolimus in combination with exemestane, 25% exemestane monotherapy and 50% chemotherapy).

1. The errors listed above were fixed in the ERG base-case. Fixing these errors/inconsistencies did not affect the cost effectiveness results from the company base-case.

Fixing violations

2. Updating the PFS related clinical model inputs with the data from the dataset pertaining to the most recent data cut-off date (January 2017).

The ERG incorporated this change to the model to be in line with good modelling practice to use the most recently available clinical data. The (partially) parametric functions fitted to the most recent (January 2017 cut-off date) dataset were used while sampling time to event for PFS and updated figures were used (from Table 5.6) to estimate the probability of death among PFS events.

3. Incorporating the wastage costs (for the unused tablets in the last treatment cycle)

In the model, the costs for the unused tablets in the last treatment cycle were not incorporated for letrozole, ribociclib, exemestane, everolimus and capecitabine treatments. The ERG incorporated expected approximate wastage costs in its base-case to be in line with good modelling practice to include all relevant costs in the cost effectiveness calculations.

Matters of judgement

4. Using the post-progression treatment related cost estimate from the fulvestrant TA239[21] for monthly third-line treatment costs

In the CS, a monthly third-line treatment related cost estimate of £2,000 was used, which was based on clinical expert opinion. The details on how this cost estimate had been derived were not provided. Therefore, the ERG believes the inflation adjusted cost estimate from TA239,[21] £1,140 to be a more plausible and a more transparent estimate. The details on how this estimate was derived can be traced in the TA239[21] as well as in the company's response to the clarification letter document[26] (question B16).

5. Changing the modelling of the post-treatment discontinuation survival after second-line chemotherapy

In the CS, while modelling the post-treatment discontinuation survival after second-line chemotherapy as a Weibull function, it is explicitly assumed that the shape parameter of the Weibull distribution will

be the same as the shape parameter of the Weibull distribution fitted to the pooled post-treatment discontinuation survival data from the BOLERO-2 trial. The ERG considers this assumption might be unnecessary because the post-treatment discontinuation survival time can be sampled from the parametric functions fitted for the OS and TTD under chemotherapy in the second-line. These functions can be obtained by applying the HRs from Li et al[71] study to the OS and TTD parametric functions fitted to the OS and TTD data from the everolimus arm of the BOLERO-2 trial. If the same random number is used while sampling TTD and OS for the chemotherapy, the issue the company defined in the CS (i.e. the sampled OS smaller than the sampled TTD) can be avoided. The ERG changed the way chemotherapy post-progression survival times are sampled in the ERG base-case so that the arbitrary scale parameter is no longer needed.

6. Assuming partial OS surrogacy

In the company base-case, it was assumed that any gain in the PFS would translate into an equivalent gain in the OS, however there are studies indicating that duration of PFS gain might translate into an OS gain that is shorter, especially for HER2-negative patients.[12, 73-75]

Actually, in the PALOMA-1 trial, which is the only randomised trial that studied a CDK 4/6 inhibitor treatment and reported median PFS and OS for both intervention and control arms, the median PFS for palbociclib and letrozole arms were reported to be 25.7 and 14.8 months (according to the BIRC assessment), whereas the median OS were reported to be 37.5 and 33.3 months. This would result in a "gain in median OS/gain in median PFS" ratio close to 38.5% (4.2 months/10.9 months). Even though the ERG is aware of the limitations of the PALOMA-1 trial, which were elaborately discussed in ID914[63], it still constitutes the only evidence for the relation between PFS gain and OS gain under a CDK 4/6 inhibitor treatment for HR+/HER2- advanced breast cancer patients.

Therefore, the ERG uses that "gain in median OS/gain in median PFS" ratio of 38.5% from PALOMA-1, and for the patients receiving ribociclib, all the time spent in the post-progression states (PFS2 and PD) was multiplied with [redacted], which is the constant scaling factor that is derived from model calibration that achieved the targeted "gain in median OS/gain in median PFS" ratio of 38.5% from the simulation outcomes. Note that this scaling factor should be recalibrated if any of the PFS related assumptions are updated.

Additional scenarios

The ERG conducted additional scenario analyses to explore further the structural uncertainties in the economic evaluation in the ERG preferred base-case. These additional scenarios are listed as below.

Scenario 1. Weibull distribution for PFS1 and TTD

In both the company base-case and the ERG base-case, an exponential distribution is used to estimate PFS1 and TTD. In this exploratory scenario analysis, a Weibull distribution is used for PFS1 and TTD, as it appeared to be an equally plausible distribution based on the external PFS data.

Scenario 2a. Third-line treatment costs = £0

In the company base-case, third-line treatment costs are assumed to be £2,000 per month. In the ERG base-case, third-line treatment costs are estimated to be £1,140 (2016 value) per month in line with the post-progression costs in the NICE appraisal of fulvestrant (TA239).[21] In this scenario, third-line treatment costs are assumed to be £0.

Scenario 2b. Third-line treatment costs = £2,000

In this scenario, third-line treatment costs are assumed to be £2,000 as per the CS.

Scenario 3. Drug acquisition costs from cycle 11 onwards based on mean costs of cycle 11 to 26
In both the company and the ERG base-case, drug acquisition costs of cycle 10 were used for the subsequent cycles. The impact of applying mean drug acquisition costs of cycle 11 to 26 to the subsequent cycles was explored in this scenario analysis.

Scenario 4. Full OS surrogacy
Whereas the company base-case assumes a full OS surrogacy (i.e. a gain in the PFS would lead to an equal gain in the OS), the ERG base-case assumes an OS surrogacy similar to the relationship between gain in the median PFS and gain in the median OS as observed in the PALOMA-1 trial.[73] In this scenario-analysis, a full OS surrogacy is assumed, while the other changes made to the company base-case remain.

Scenario 5. Full OS surrogacy and Weibull function for PFS 1 and TTD
This scenario combines scenario 1 and 5. A Weibull distribution is used for PFS1 and TTD and a full OS surrogacy is assumed.

Scenario 6. Similar second-line treatments
Both in the company and the ERG base-case, it is assumed that different second-line therapies were received after the ribociclib combined with letrozole treatment and after the letrozole monotherapy. In this scenario analysis, similar second-line treatments are assumed, i.e. 25% everolimus plus exemestane, 50% single-agent endocrine therapy and 25% chemotherapy.

5.3.2 Results from the ERG preferred base-case and probabilistic sensitivity analysis

Table 5.22 and Table 5.23 present the total costs, life years and QALYs for both ribociclib plus letrozole and letrozole monotherapy with and without the patient access scheme under the ERG base-case analysis. Without the patient access scheme, incremental QALYs are 0.53 and incremental costs are [redacted]. The corresponding ICER is [redacted] per QALY gained for ribociclib plus letrozole compared to letrozole monotherapy. With the patient access scheme, incremental costs reduce to [redacted], and the corresponding ICER is [redacted] per QALY gained.

Table 5.22: ERG base-case cost effectiveness results (without patient access scheme)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 5.23: ERG base-case cost effectiveness results (with patient access scheme)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Disaggregated results (in terms of QALYs and costs [without patient access scheme]) from the base-case analysis are given in Table 5.24 and Table 5.25 below. Difference in total QALYs between two arms mostly resulted from the fact that in the ribociclib arm, patients stayed longer in the PFS1 state compared to the patients in the letrozole arm. Similarly for the difference in total costs, higher drug acquisition costs were incurred for patients in the ribociclib arm for a longer time compared to the patients in the letrozole arm.

Table 5.24: Disaggregated QALYs by health state

Health state	QALY intervention (ribociclib plus letrozole)	QALY comparator (letrozole monotherapy)	Increment	Absolute increment	% absolute increment
PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	0.53	[redacted]

Table 5.25: Disaggregated costs by health state

Health state	Cost intervention (ribociclib plus letrozole)	Cost comparator (letrozole monotherapy)	Increment	Absolute increment	% absolute increment
Treatment acquisition – PFS1 health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment acquisition – PFS2 health state	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state resource use costs (PFS1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Health state resource use costs (PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Progression health state related costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

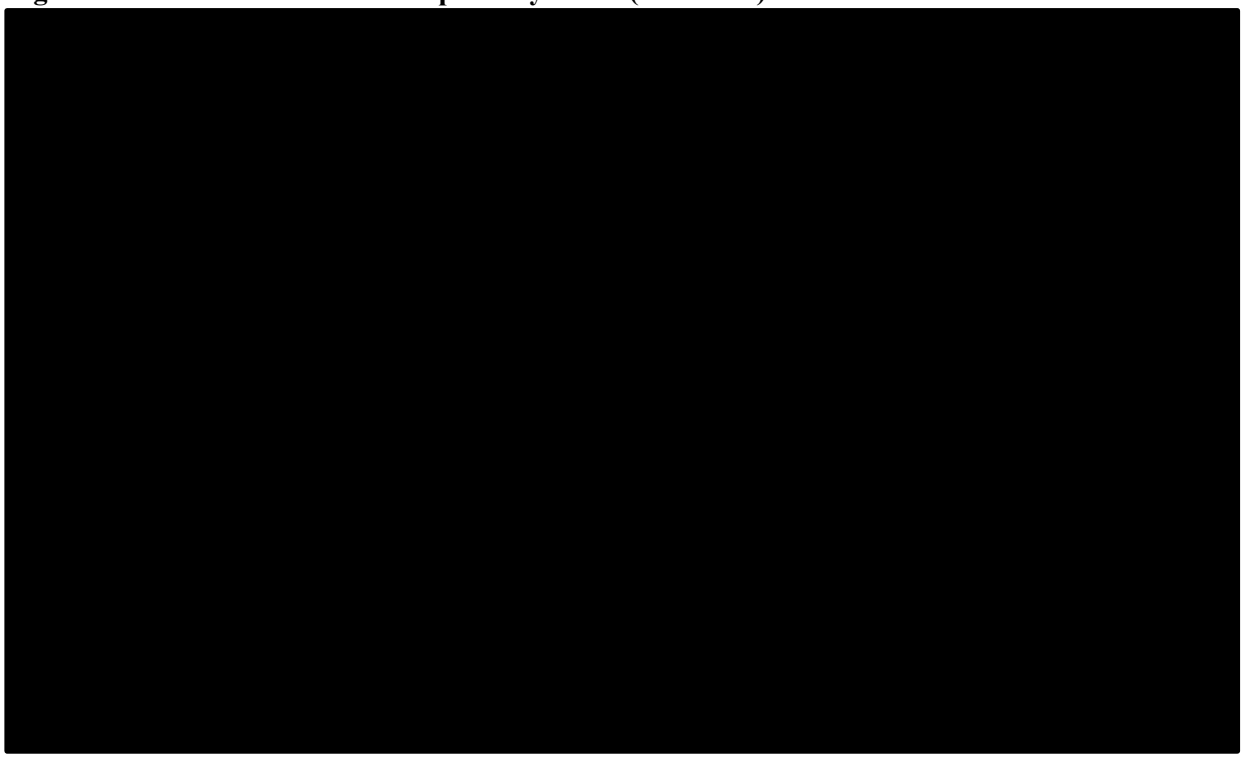
The results of 1,000 PSA iterations are shown in the figures below. The cost effectiveness planes show the incremental QALYs and costs of ribociclib plus letrozole relative to the letrozole monotherapy (Figure 5.16 [with PAS]). Additionally, the cost effectiveness acceptability curves (CEAC) are presented, showing the likelihood of ribociclib plus letrozole being cost effective at different willingness-to-pay thresholds (Figure 5.17 [with PAS]).

Mean incremental QALYs from ribociclib plus letrozole were around 0.53. When taking into account the patient access scheme, the incremental costs reduces to [redacted], and the corresponding probabilistic ICER was [redacted] (comparable to the deterministic, base-case ICER of [redacted]).

Figure 5.16: Cost effectiveness plane (with PAS)

[redacted]

Figure 5.17 Cost effectiveness acceptability curve (with PAS)



5.3.3 Results from the ERG additional exploratory scenario analyses

The results of the additional scenarios described in section 5.3.1 of this report, which were performed on the ERG preferred base-case with and without PAS prices, are provided in Table 5.26 and Table 5.27 below.

Table 5.26: Results from the additional scenario analyses conducted on the ERG preferred base-case (with PAS price)

Scenarios	Ribociclib in combination with letrozole		Letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 1 (Weibull function for PFS1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
Scenario 2a (Third-line treatment costs = £0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 2b (Third-line treatment costs = £2,000 per month)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

Scenarios	Ribociclib in combination with letrozole		Letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
Scenario 3 (Drug acquisition costs from cycle 11 onwards based on mean costs of cycle 11 to 26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 4 (Full OS surrogacy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
Scenario 5 (Full OS surrogacy and Weibull function for PFS 1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]
Scenario 6 (similar second-line treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.50	[redacted]
QALYs = quality adjusted life years; ICER = incremental cost effectiveness ratio; CS = company submission; PFS = progression-free survival; TTD = time to treatment discontinuation.							

Table 5.27: Results from the additional scenario analyses conducted on the ERG preferred base-case (without PAS prices)

Scenarios	Ribociclib in combination with letrozole		Letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 1 (Weibull function for PFS1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
Scenario 2a (Third-line treatment costs = £0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 2b (Third-line treatment costs = £2,000 per month)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

Scenarios	Ribociclib in combination with letrozole		Letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
Scenario 3 (Drug acquisition costs from cycle 11 onwards based on mean costs of cycle 11 to 26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 4 (Full OS surrogacy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
Scenario 5 (Full OS surrogacy and Weibull function for PFS 1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]
Scenario 6 (similar second-line treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.50	[redacted]
QALYs = quality adjusted life years; ICER = incremental cost effectiveness ratio; CS = company submission; PFS = progression-free survival; TTD = time to treatment discontinuation.							

Among the scenarios above, in both settings (with PAS price or without PAS price), the largest impact on the ERG base-case ICER occurred in scenario 1, i.e. when the base-case PFS/TTD distributions for the first-line were changed from exponential to Weibull. In both settings, the choice of Weibull distribution led to a substantial increase in ICER. Since in section 5.2.6.1, it was previously discussed that the Weibull distribution can be as plausible as the company's preferred exponential distribution, the ERG stresses that this scenario might be reflective of the uncertainty of the cost effectiveness of ribociclib.

Using higher (£2,000) or none (£0) third-line treatment costs resulted in substantial changes in ICER as well. A higher third-line treatment cost decreases the ICER.

Finally, assuming full OS surrogacy instead of partial OS surrogacy also decreases the ICER considerably.

5.4 Conclusions of the cost effectiveness section

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a large extent, and the impact of deviations (mostly regarding valuation of post first-line health states) was found to be small. The ERG confirmed that there was no existing cost effectiveness model for ribociclib plus letrozole for the current indication.

The company submitted a HE model that was based on the results of the MONALEESA-2 trial, comparing ribociclib plus letrozole with letrozole monotherapy for the PFS1 health state. In the PFS2 state, patients receive either everolimus in combination with exemestane, exemestane (representative of a single-agent endocrine therapy) or capecitabine (representative of chemotherapy). In the progressed disease state (representing the time from second-line therapy cessation until death) patients receive

subsequent treatments and/or supportive/palliative care. TTD and post-discontinuation survival from PFS2 were derived from the BOLERO-2 trial and Li et al. 2015.[69, 71]

The company's base-case ICER without PAS amounts to [redacted], compared to [redacted] with PAS.

One of the main concerns of the ERG with the company submission was the assumption in the model that any gain in PFS is 100% translated into OS gain in the base-case. The ERG considers this assumption speculative, as there are studies indicating that duration of PFS gain would translate into an OS gain that is shorter, especially in HER2-negative patients.[12, 73-75] This trend can be also observed in the PALOMA-1 trial (comparing palbociclib plus letrozole vs letrozole) where a "gain in median OS/gain in median PFS" ratio close to 38.5% was observed. The ERG considered the observed ratio of 38.5% more evidence-based than the completely arbitrary 100% that the company assumed, and hence this ration of 38.5% was incorporated into the ERG base-case.

In addition, the ERG base-case included the company provided PFS data as per January 2017. This PFS assessment was based on local assessment, rather than the central assessment, which would have been the ERG's preference.

For the estimation of drug acquisition costs in the progression health state the company used expert opinion. However, hardly any information was provided on the details of what was suggested by the experts to arrive at these costs. Thus, the ERG was not able to assess the validity of this cost estimate (approximately £2,000 per month). Consequently, in the ERG base-case post-progression costs (of third-line and subsequent lines of treatment) were based on TA239, the NICE appraisal of fulvestrant (2011)[21] which included as average costs post-progression per month £1,084 (excluding costs associated to adverse events). Although the ERG realises that TA239 was published in 2011, and the treatment pathway will have changed, the ERG considers the costs as estimated within TA239 more reliable than the cost estimate based on (ill-documented) expert opinion.

In addition to the three more major issues discussed above, two smaller issues were also addressed in the ERG base-case, i.e. inclusion of wastage in treatment costs and changing the modelling of the post-treatment discontinuation survival after chemotherapy. With these changes, the ERG arrived at an alternative base-case ICER without PAS amounts to [redacted] with PAS.

Several other issues were addressed through exploratory scenario analyses.

To choose a parametric distribution for the PFS curves, the company did not only look at the statistical goodness-of-fit of various distributions, but also compared the extrapolated parts of the curves to external data. When the PFS extrapolations (January 2017) were compared with the KM curves from external trials, it was observed by the ERG that the [redacted] to the KM curves from the LEA and ALLIANCE trials, whereas the extrapolations from the [redacted] to the KM curves from PALOMA-2 and MONALEESA-2 trials (See Figure 5.9). Thus, according to the ERG the choice of the company to use an exponential distribution can be considered to be as plausible as a Weibull distribution. Therefore, the ERG used a Weibull distribution in its exploratory analyses, yielding an ICER of [redacted] without PAS and [redacted] with PAS.

Similarly, the decision on the third-line treatment related cost has a big impact on the ICER, the ICER ranges from [redacted] per QALY gained to [redacted] per QALY gained (without PAS) and from [redacted] per QALY gained to [redacted] per QALY gained (with PAS) when the cost estimate is varied from £0 to £2,000 per month.

Scenarios with more modest impact on the ICER included changing the drug acquisition costs from cycle 11 onwards to the mean costs of cycle 11 to 26, instead of the costs at cycle 10, and second-line treatment that is independent of the technology used in first-line.

Finally, some issues that the ERG considers of potential importance could not be addressed quantitatively. For example, although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER.

Also, the ERG base-case is based on the PFS data from January 2017, based on local assessment rather than the central assessment, which would have been the ERG's preference. The company stated that the observed hazard ratio for PFS was approximately the same for both methods of assessment. However, in an economic evaluation the area between the PFS curves for both treatment arms is usually the driver of the results, and this area is noticeably [redacted] for the central assessment (as per June 2016) than for the local assessment. If the same is true for the data as per January 2017, this would most likely increase the ICER. Unfortunately, the ERG could not confirm this as [redacted]

A final example relates to the approach of modelling PFS2 and PD using data from the BOLERO-2 study. The OS and PFS results from the BOLERO-2 trial were used in the model without any adjustments, as if the BOLERO-2 trial was conducted subsequent to the MONALEESA-2 trial population upon their disease progression. Instead of this approach followed by the company, the ERG would have preferred an approach where the OS and PFS parametric functions used from the BOLERO-2 trial were adjusted based on the patient characteristics at disease progression from the first-line treatment (e.g. age, previous treatment, ECOG disease status, time since diagnosis at the time of first line treatment progression etc.). The use of such adjusted OS and PFS survival functions from BOLERO-2 might have changed the ICER.

In conclusion, based on the ERG base-case analysis, the ICER is estimated to be around [redacted] per QALY gained without PAS, compared to [redacted] with PAS. [redacted]. In addition, due to several assumptions e.g. regarding PFS/OS surrogacy and regarding the choice of parametric distribution to extrapolate PFS, the ERG deems that the uncertainty around the cost effectiveness of ribociclib is substantial.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

In section 5.3 of this report the ERG base-case was presented, which was based on various changes compared to the company base-case. Table 6.1 and Table 6.2 show how each individual change impacts the ICER plus the combined effect of all changes simultaneously with and without the PAS, respectively. The analyses numbers in Table 6.1 and Table 6.2 correspond to the analyses numbers reported in section 5.3.

In the tables below, most results are quite intuitive, but this may not be true for combination 1+6, where we now assume that any gain in PFS will only partially lead to a gain in OS. At first glance, one might expect the ICER to increase, as fewer life-years and QALYs will be gained. This is indeed observed in the tables below, where the incremental QALYs go from 0.96 to 0.58. However, due to the high treatment costs associated with being in the progression state, the decreased time in PD with ribociclib reduces the total costs to such extend, that overall the ICER decreases.

However, once all changes are made together, the treatment costs in PD are now much lower, meaning that the smaller gain in QALYs is no longer compensated for by the decrease in incremental costs.

Table 6.1: Revised base-case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG (with PAS)

Scenarios	Ribociclib plus letrozole		letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
1. Fixing errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+2). Fixing errors and using the results from PFS data cut-off January 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
(1+3). Fixing errors and including the costs of wastage (i.e. unused tablets)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+4). Fixing errors and using post-progression costs from TA239 (fulvestrant)[21]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+5). Fixing errors and changing the modelling of the post-treatment discontinuation survival after chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]
(1+6). Fixing errors and changing full PFS-OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]
(1 to 6 all): ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

CS = Company submission; ERG = Evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality adjusted life years.

Table 6.2: Revised base-case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG (without PAS)

Scenarios	Ribociclib plus letrozole		letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
1. Fixing errors	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+2). Fixing errors and using the results from PFS data cut-off January 2017	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
(1+3). Fixing errors and including the costs of wastage (i.e. unused tablets)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+4). Fixing errors and using post-progression costs from TA239 (fulvestrant)[21]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
(1+5). Fixing errors and changing the modelling of the post-treatment discontinuation survival after chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]
(1+6). Fixing errors and changing full PFS-OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]
(1 to 6 all): ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

CS = Company submission; ERG = Evidence review group; ICER = incremental cost effectiveness ratio; Incr. = incremental; LYG = life years gained; QALYs = quality adjusted life years.

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

The company conducted a systematic review to identify studies of ribociclib as monotherapy or as part of combination therapy. The NICE scope specified ribociclib in combination with an aromatase inhibitor as the intervention, and aromatase inhibitors (such as letrozole or anastrozole) as the comparator. No attempt was made to look for evidence for the comparability of different aromatase inhibitors and the effectiveness of other AIs in combination with ribociclib. Nevertheless, The ERG believes that the company has provided justification for generalisability of the letrozole comparator to aromatase inhibitors such as anastrozole normally offered to the population of the scope.

One Phase 3 trial, MONALEESA-2, with 668 patients was presented as the main source of evidence. The MONALEESA-2 study included postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease.

The trial was conducted at 223 trial centres in 29 countries including [redacted] patients from England and Wales. Patients were randomised 1:1 to receive ribociclib (600 mg once daily, days 1–21 of a 28-day cycle) plus letrozole (2.5 mg once daily, continuous treatment) or placebo plus letrozole (2.5 mg once daily, continuous treatment). Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage AEs; no dose reductions were permitted for letrozole and no crossover between treatment arms was allowed. Patients who discontinued ribociclib or placebo could continue receiving letrozole. Treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of ribociclib or letrozole.

The primary outcome was PFS as per RECIST version 1.1 criteria, based on local radiological assessment; assessments were also carried out by BIRC. The key secondary endpoint was OS (defined as the time from date of randomisation to date of death due to any cause). Other secondary outcomes included objective response rate (ORR; complete response [CR] or partial response [PR]), CBR (overall response plus stable disease lasting 24 weeks or more), time to deterioration of ECOG PS, safety and HRQoL.

A total of 668 patients were randomised to ribociclib (n=334) or placebo (n=334) in the ITT population. At the time of data cut-off (29th January 2016), a total of 349 patients (52.2%) were still receiving treatment (ribociclib, n=195; placebo, n=154). The rates of discontinuation were 41.6% in the ribociclib group compared with 53.9% in the placebo group. The most frequent reason for discontinuation was disease progression in both groups (ribociclib, 26.0%; placebo, 43.7%). Discontinuations due to AEs were 7.5% in the ribociclib group and 2.1% in the placebo group. The median duration of follow-up from randomisation to data cut-off was 15.3 months. Patient baseline characteristics seem well balanced between treatment groups in terms of demographics and disease characteristics.

Overall, the MONALEESA-2 trial is a good quality randomised controlled trial. However, adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients. Therefore, results based on independent review are more reliable. In addition, overall survival results were not mature at the time of the first interim analysis, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off.

Results are available for three time points:

1. The first planned interim analysis performed at the data cut-off on 29 January 2016 after observing 243 of the planned 302 events, the median duration of follow up was 15.3 months.
2. A second interim analysis on 22 June 2016 based on 297 local PFS and [redacted] central PFS events, the median duration of follow up was 20.1 months.

3. A third interim analysis on 2 January 2017 based on 345 local PFS events, the median duration of follow up was 26.4 months.

In this report we have focused on the most recent data available.

In addition, PFS results can be based on local and central (BIRC) results. As mentioned before, we have focused on BIRC results, partly because the NICE committee preferred these data in a recent related technology appraisal, and partly because adverse events could have unblinded physicians and/or patients, thus making results based on independent review more reliable.

Table 7.1: Comparison of preferred PFS and OS results from the company and ERG

	Ribociclib + letrozole (n = 334) versus Placebo + letrozole (n = 334)	
	Company preference	**ERG Preference**
PFS HR (95% CI)[a]	0.56 (0.43–0.72)[1]	[redacted][2]
OS HR (95% CI)[a]	[redacted][3]	0.746 (0.517-1.078)[4]

Source: CS, Novartis MONALEESA-2 ribociclib June 2016 CSR update and Novartis MONALEESA-2 ribociclib January 2017 CSR data cut

a) HR obtained from COX PH model stratified by liver and / or lung metastasis as per IRT

1. Based on local assessment and first interim analysis (January 2016)
2. Based on central assessment and most recent analysis (June 2016)
3. Based on first interim analysis (January 2016, after 43 deaths)
4. Based on most recent analysis (January 2017, after 116 deaths)

As can be seen from the results presented in Table 7.1 PFS results are more favourable for ribociclib on the company preferred results; while OS results are more favourable for ribociclib in the ERG preferred results. It should be kept in mind that the economic model is informed by the PFS results from the MONALEESA-2 trial, but not by the OS results from the MONALEESA-2 trial. The OS treatment effect in the economic model is based on the idea of surrogacy i.e. that a gain in PFS predicts a gain in OS. In the base-case, the assumption is that the gain in OS is identical to the gain in PFS.

Quality of life scores showed [redacted]

Subgroup analyses showed that results for PFS favour ribociclib for all subgroups including both those with newly diagnosed disease and those with existing disease and those who have received prior therapy and patients who have not. Nevertheless, there are differences in effectiveness. Most noticeably, results for ribociclib are more favourable for younger patients (<65 yr), newly diagnosed patients (vs not newly diagnosed), not ER- and PR-positive (vs other hormone-receptor status), and not bone-only disease (vs. bone-only disease).

Although occurrence of any adverse events were overall similar in ribociclib and placebo groups, a greater number of adverse events and severe adverse events were attributable to ribociclib. [redacted]

The most common event was neutropenia. Gastrointestinal events such as nausea, vomiting and diarrhoea occurred more frequently in the ribociclib group.

A similar number of patients died in the two groups in the June 2016 cut-off although data were not mature.

[redacted]

The economic model described in the CS is considered by the ERG to meet the NICE reference case to a reasonable extent and is in line with the decision problem specified in the scope. According to the CS, [redacted]

Although some of the individual ERG's revisions lead to a decrease in the ICER, most revisions increased the company base-case ICER. Also the combined ERG's revisions increased the ICER. The incremental QALYs according to the ERG base-case were 0.53 [redacted]

7.2 Strengths and limitations of the assessment

The searches for eligible studies in the CS were well documented and reproducible. Searches were carried out on all databases recommended in the NICE 2013 guide to the methods of technology appraisal sections 5.2.2 and 5.2.4.[52] The clinical effectiveness search strategies utilised recognised study design filters developed by the BMJ Clinical Evidence group.[30] Additional searches of conference proceedings and organisation websites were conducted by the company in order to identify additional studies not retrieved by the main database searches. Date and language limits used in the search strategies may have led to relevant evidence being missed. No searches were conducted to identify adverse events data, indirect and mixed treatment comparisons or non-randomised and non-controlled evidence.

The clinical evidence is based on one good quality randomised controlled trial including 668 patients. The comparator arm of the MONALEESA-2 trial was letrozole, an aromatase inhibitor used to treat patients with untreated MBC in NHS clinical practice that is a valid comparator for this appraisal. It seems reasonable to generalise the clinical effectiveness results associated with letrozole to other commonly used aromatase inhibitors in NHS clinical practice (i.e. exemestane and anastrozole).

The population included in the MONALEESA-2 trial may not be fully representative of the UK patient population. In addition, adverse events, such as neutropenia (74% in the ribociclib group vs. 5% in the letrozole group), could have unblinded physicians and/or patients in the MONALEESA-2 trial.

The main concern regarding the MONALEESA-2 trial is that the use of an interim analysis for PFS meant that the initial results presented in the company submission were based on the data available at the time of the interim analysis for PFS. At this point the OS data were immature as the required number of deaths had not been reached, with 43 deaths (23 in the ribociclib group and 20 in the placebo group) at the time of data cut-off.

One of the main concerns of the ERG regarding the economic analyses is the full OS surrogacy assumption in the CS (i.e. a gain in the PFS would lead to an equal gain in the OS). However, no data are available supporting this relationship. A review by Davis et al. 2012[17] has shown that a relationship between PFS/TTP and OS varies considerably by cancer type and is not always consistent even within one specific cancer type. Data from a drug in the same class as ribociclib is therefore preferred to study

the relationship between PFS and OS (given the immaturity of the OS data in the MONALEESA-2 trial). The ERG base-case therefore assumes an OS surrogacy similar to the relationship between median PFS and OS as observed in the PALOMA-1 trial (comparing palbociclib and letrozole with letrozole alone).[73] As a consequence incremental QALYs decreased from 0.96 to 0.58, and the ICER [redacted] Although the data from the PALOMA-1 trial have its limitations, the PALOMA-1 trial is the only one trial currently available providing insight in the association between PFS and OS of patients treated with a CDK 4/6 inhibitor.

In the ERG base-case, PFS data (local assessment) from the January, 2017 data cut-off were used, as these data were the most recent. Although PFS data from the central assessment were preferred over the local assessment, these data were unavailable at the most recent data cut-off. In their response to the clarification letter, the company indicates that they are willing to update the model with PFS data from the June 2016 data cut-off (no central assessment was performed at the 2 January 2017 data cut-off).

Although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER.

7.3 Suggested research priorities

As mentioned in section 7.2 of this report one of the research priorities is an update of the model with PFS data (central assessment) from the June 2016 data cut-off. Additionally, more insight is needed in the treatment pathway of patients with previously untreated advanced or metastatic hormone receptor-positive, HER2- breast cancer. Since the post-progression treatment costs are uncertain and have a large impact on the ICER, this information can help to derive a better estimate of these costs.

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