Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer (CDF review of TA593)

Cancer Drugs Fund Review

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All authors read and commented on draft versions of the ERG report.

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List of Abbreviations

aBC	Advanced breast cancer
AE	Adverse event
AIC	Akaike information criterion
B2	BOLERO-2
BIC	Bayesian information criterion
BICR	Blinded independent review committee
CDF	Cancer Drugs Fund
CDK4/6	Cyclin-dependent kinase 4 and 6
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CS	Company submission
CSR	Clinical study report
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
ERG	Evidence Review group
EMA	European Medicines Agency
EQ-5D-5L	5-dimension EuroQoL questionnaire
HER2−	Human epidermal growth factor receptor 2 negative
HR	Hazard ratio
HR+	Hormone receptor positive
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient level data
ITC	Indirect treatment comparison
ITT	Intention to treat

KM	Kaplan-Meier
LHRH	Luteinizing hormone-releasing hormone
LYG	Life years gained
M3	MONALEESA-3
NA	Not applicable
NE	Not evaluable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression-free survival
PHE	Public Health England
PPS	Post-progression survival
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RCS	Restricted cubic spline.
RCT	Randomised controlled trial
RDI	Relative dose intensity
SACT	Systemic Anti-Cancer Treatment
SD	Standard deviation
SE	Standard error

SERD	Selective oestrogen receptor down-regulators
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology appraisal
ToE	Terms of engagement
TTD	Time to treatment discontinuation
WTP	Willingness-to-pay

1 Executive summary

This summary provides a brief overview of the key issues identified by the Evidence Review Group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report (Section 2 onwards).

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 Critique of the adherence to committees preferred assumptions from the Terms of Engagement in the company's submission

In general, the ERG considers that the company have adhered to the committee's preferred assumptions from the terms of engagement (ToE), although the updated overall survival (OS) data from MONALEESA-3[(1)] remain relatively immature (see Section 3.1.1.2). The clinical data presented by the company includes the ToE required later data-cut from the company's randomised controlled trial (RCT) of ribociclib plus fulvestrant versus placebo plus fulvestrant, MONALEESA-3. In addition, the company presented a summary of the observational data that were also required to be collected by Public Health England during the period of managed access for ribocilclib plus fulvestrant, hereafter referred to as the Systemic Anti-Cancer Therapy (SACT) data set. The ERG, however, considers the SACT data set to be immature as it was terminated earlier than originally planned and, as it comprises only data on treatment duration and not PFS or OS, it is unfortunately of limited value.

The ERG is satisfied that the population both within MONALEESA-3 and the SACT cohort are representative of people with advanced breast cancer (aBC) in England who are likely to be eligible for treatment with ribociclib plus fulvestrant, and the company have adhered to the committee's preferred assumptions by focusing on subpopulation B of the previous appraisal (TA593), which comprises of patients who experienced an early relapse or those receiving second-line treatment for aBC (see Section 2.2 for further details). The ERG is also satisfied that the company has focused on the key comparator identified by the committee, everolimus plus exemestane. Although the key trial informing the company submission, MONALEESA-3, does not include this comparator, the company have provided indirect treatment comparisons to inform the comparison of ribociclib plus

fulvestrant to everolimus plus exemestane. The company have revised their original network meta-analysis (NMA) for progression-free survival (PFS) with the updated data-cut of MONALEESA-3, and have conducted a new search to ensure all relevant studies were included in the NMA. On request from the ERG, the company have further provided an NMA for OS, as well as population-adjusted indirect comparisons (PAICs) for PFS, post-progression survival (PPS) and OS using individual patient data (IPD) from the everolimus plus exemestane arm of BOLERO-2 and the ribociclib plus fulvestrant arm of MONALEESA-3. While the results for OS remain uncertain (see Section 3.1.1.2) the ERG considers that the company has sought to reduce the uncertainty in the estimation of PPS by assuming this to be equivalent between the two treatments, despite identifying a numerical advantage for OS in their NMA (see Section 3.2).

Furthermore, the company have adhered to the committee preferred assumptions by updating time to treatment discontinuation (TTD) data for ribociclib and fulvestrant and using unrestricted models (unrestricted RCS lognormal) to extrapolate the data. However, the ERG considers that the unrestricted Gompertz model may be more appropriate.

The ERG also notes that, as per the company's original submission, the company assumed everolimus plus exemestane was given until progression. Although this assumption was not questioned by the committee in TA593, the clinical experts in attendance did state that ribociclib plus fulvestrant would be considered a more appropriate treatment for patients due to tolerability concerns with the everolimus component of everolimus plus exemestane. Clinical experts advising the ERG for this CDF review have supported the view presented at committee that in clinical practice patients may discontinue everolimus due to tolerability issues but continue with exemestane until progression. Given that differences in TTD are key drivers in the ICER, the ERG considers that TTD warrants exploration in the CDF review.

Additionally, as outlined in the ToE, the company used the same modelling approach in the CDF submission as was used in TA593. This approach consisted of a semi-Markov model where PFS and PPS are extrapolated. However, in the ToE, it is also noted that the most appropriate methods should be used to compare OS across treatments. Since the OS results from the June 2019 data-cut are more mature than the data previously reported from the November 2017 data-cut, the ERG considers that a PSM would be preferred to the company's semi-Markov model because this enables the OS data from the MONALEESA-3 trial to be used directly in the model, rather than having to make additional assumptions (i.e. having to estimate PPS rather than directly using OS and having to conduct the analysis assuming full surrogacy: where OS gains are equal to PFS gains).

Finally, the company adhered to the committee's preferred assumption and used resting ECG costs in the model.

1.2 Overview of the ERG's key issues

Table 1 provides a summary of the ERG's key issues.

Table 1. Summary of key issues

ID	Summary of issue	Report sections
1	OS from MONALEESA-3 remains immature	3.1.1.2
2	Parametric survival distribution fitted to TTD in MONALEESA-3	4.1.5.3
3	TTD assumptions for everolimus plus exemestane	4.1.5.3
4	Including OS in a PSM	4.1.5.4

Abbreviations: OS, overall survival; PSM, partitioned survival model; TTD, time to treatment discontinuation

The key differences between the company's preferred assumptions and the ERG's preferred assumptions include the TTD assumptions for everolimus and the parametric survival distribution fitted to TTD from MONALEESA-3 (for ribociclib and fulvestrant in the treatment arm).

1.3 Overview of key model outcomes

The company has modelled ribociclib plus fulvestrant to affect quality adjusted life years (QALYs) by:

- Reducing the time on treatment while in the progression-free health state compared with everolimus plus exemestane (progression free patients on treatment have a lower quality of life than progression free patients off treatment); and,
- Increasing the time in the progression-free health state compared with everolimus plus exemestane (although there is no statistically significant difference in PFS between the two treatments, i.e. the 95% confidence interval crosses 1)

The company has modelled ribociclib plus fulvestrant to affect costs by:

- Its higher unit price compared with everolimus plus exemestane;
- Its additional monitoring (electrocardiograms, blood counts and liver function blood tests) compared with everolimus and exemestane during the first few treatment cycles;
- Being administered intravenously in hospital (fulvestrant only) (everolimus and exemestane are administered orally);

- Being discontinued prior to disease progression (everolimus plus exemestane are assumed to be given until disease progression).

The modelling assumptions that have the greatest effect on the ICER are:

- related to TTD; and,
- the quality of life experienced during while progression-free and off treatment.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

Table 2 presents the key issues of the company's clinical effectiveness evidence.

Table 2. Issue 1: Data maturity OS

Report section	Section 3.1.1.2
Description of issue and why the ERG has identified it as important	OS from MONALEESA-3 remains relatively immature, median OS has only just been reached. The ERG notes that OS is not a clinical outcome used to inform the clinical effectiveness of ribociclib plus fulvestrant in the economic model.
What alternative approach has the ERG suggested?	The ERG has no suggested alternative approach as the issue is a result of immature clinical data and so the ERG's preference would be to wait until a later data cut from MONALEESA-3 with mature data for OS available.
What is the expected effect on the cost-effectiveness estimates?	Immature overall survival data has not influenced the cost-effectiveness estimates because the company assumed post-progression survival to be equivalent between the two treatments.
What additional evidence or analyses might help to resolve this key issue?	According to the statistical plan of MONALEESA-3, no further analyses would be expected given that the OS analysis for the ITT population reached significance. Nonetheless, the company has highlighted to the ERG during the factual inaccuracy stage that they will be conducting a further exploratory analysis of OS once more events have occurred. The ERG considers that this analysis could reduce the uncertainty caused by relatively immature OS data. The company should therefore provide this data when it is available and update analyses accordingly.

Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; PPS, post-progression survival; OS, overall survival.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

Table 3 to Table 5 present the ERG's key issues of the company's cost-effectiveness evidence.

Table 3. Issue 2: Parametric survival distribution fitted to TTD in MONALEESA-3

Report section	4.1.5.3
Description of issue and why the ERG has identified it as important	The company disregarded the best fitting curve (unrestricted Gompertz) based on a lack of plausibility in the extrapolation. The ERG considers this curve to be a better fit to the KM data than the company's chosen curve. This issue is important because differences in TTD are key drivers in the ICER.
What alternative approach has the ERG suggested?	The ERG considers a more appropriate method would be to choose the best fitting curve for TTD (unrestricted Gompertz) and cap the extrapolation by the PFS curve to prevent the potentially implausible treatment beyond progression. The company provided this scenario during the clarification stage.
What is the expected effect on the cost-effectiveness estimates?	Implementing the scenario above [redacted]
What additional evidence or analyses might help to resolve this key issue?	In addition to the scenario provided by the company at the clarification stage, the company should explore 3-knot spline models to improve the fit to the KM data.

Abbreviations: ICER, incremental cost-effectiveness ratio; KM, Kaplan Meier; PFS, progression-free survival; TTD, time to treatment discontinuation

Table 4. Issue 3: TTD assumptions for everolimus plus exemestane

Report section	4.1.5.3
Description of issue and why the ERG has identified it as important	As per the company's original submission, the company assumed everolimus plus exemestane was given until progression. Although this assumption was not questioned by the committee in TA593, the ERG has had a clear direction from its clinical experts for the CDF review that patients may discontinue everolimus before progression due to tolerability issues. Furthermore, using utility estimates that depend on when a patient is on or off treatment is only reasonable when TTD is accurately represented for everolimus plus exemestane (i.e. either revised to reflect BOLERO-2 or based on clinical expert opinion). Otherwise, as with drug costs, [redacted] ribociclib plus fulvestrant.
What alternative approach has the ERG suggested?	During the clarification stage, the company was asked to explore a scenario which used the IPD TTD data from BOLERO-2 to fit separate TTD curves to everolimus and exemestane. The company was also asked to explore scenarios where TTD for everolimus was based on clinical expert opinion to the ERG. The company was unable to provide these scenarios due to time constraints.
What is the expected effect on the cost-effectiveness estimates?	Based on clinical expert feedback, the ERG implemented a scenario where 20% of patients discontinue everolimus from month 6. This scenario increased the company's corrected base case ICER from [redacted]. However, of those 80% who remain on everolimus, the ERG's clinical experts considered that a large proportion will dose reduce from 10 mg daily to 5mg daily. The ERG implemented another scenario where the dose of everolimus is reduced from 10mg daily to 5mg daily at month 6, for 70% of patients. This increased the company's corrected base case ICER from [redacted]. As these scenarios are coexisting, the ERG combined them and produced an ICER of [redacted].
What additional evidence or analyses might help to resolve this key issue?	The company should explore the scenario requested during the clarification stage: using the IPD TTD from BOLERO-2 to fit separate TTD curves to everolimus and exemestane. Additional clinical expert input would be helpful to verify the ERG's scenarios (which were informed by two experts) and obtain a view on the most plausible scenario.

Abbreviations: CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; IPD, individual patient level data; PFS, progression-free survival; TTD, time to treatment discontinuation

Table 5. Issue 4: Including OS in a PSM

Report section	4.1.5.4
Description of issue and why the ERG has identified it as important	The OS results from MONALEESA-3 at the June 2019 data-cut are more mature than the data previously reported from the November 2017 data-cut. For this reason, the ERG considers that an alternative model structure should have been considered by the company; that is, a PSM. A PSM would be preferred to the company's semi-Markov model because this enables the OS data from the MONALEESA-3 trial to be used directly in the model, rather than having to make additional assumptions (i.e. having to estimate PPS rather than directly using OS and having to conduct the analysis assuming full surrogacy: where OS gains are equal to PFS gains). A PSM would directly inform if the full surrogacy assumption is true or whether in fact there is just partial surrogacy.
What alternative approach has the ERG suggested?	During the clarification stage, the company was asked to use the latest OS data-cut to implement data on OS in the model directly. In their response, the company provided a NMA on OS, but due to time constraints, it was not possible for the company to restructure the semi-Markov model into a PSM.
What is the expected effect on the cost-effectiveness estimates?	The company demonstrated that the projected gain in OS for ribociclib plus fulvestrant compared with everolimus plus exemestane based on the semi-Markov model is conservative relative to that which would be obtained using a PSM. However, until the ERG is able to make a direct comparison between the two models, it is speculative to say that the semi-Markov model will produce conservative cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	As noted in Table 3 the company will be conducting a further exploratory analysis of OS once more events have occurred. The company should therefore provide this data when it is available and update the economic analysis using a PSM.

Abbreviations: NMA, network meta-analysis; OS, overall survival; PPS, post-progression survival; PSM, partitioned survival model

1.6 Summary of ERG's preferred assumptions and resulting ICER

One of the key uncertainties made apparent to the ERG during the CDF review was the company's assumption that everolimus is given until progression. In the absence of IPD TTD data from BOLERO-2, the ERG's preferred assumption to model TTD for everolimus is based on clinical expert opinion. This assumption consists of a proportion of patients who discontinue everolimus at month 6 and a proportion of patents who dose reduce from 10 mg daily to 5 mg daily at month 6.

The ERG also disagrees with the company's chosen curve fitted to TTD from MONALEESA-3 (for ribociclib and fulvestrant in the treatment arm). The ERG considers a more appropriate method would be to choose the best fitting curve for TTD and cap the extrapolation by the PFS curve to prevent the potentially implausible treatment beyond progression.

In the semi-Markov model, the ERG has no major issues with the company's approach to model PFS and PPS. The ERG's clinical experts were also of the opinion that ribociclib plus fulvestrant is non-inferior to everolimus plus exemestane. As such, the ERG's preferred assumptions are contained to TTD. Results using the ERG's preferred assumptions are given in Table 6.

Table 6. ERG's preferred assumptions and resulting ICER

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	[redacted]
Company's corrected base case (ribociclib monitoring costs)	[redacted]	[redacted]	[redacted]
Gompertz (U) extrapolation of TTD for ribociclib and fulvestrant	[redacted]	[redacted]	[redacted]
At month 6, 20% of patients discontinue everolimus and 70% of those 80% who continue dose reduce from 10 mg daily to 5 mg daily	[redacted]	[redacted]	[redacted]
ERG's preferred base case	[redacted]	[redacted]	[redacted]

Abbreviations:

Modelling errors identified and corrected by the ERG are described in Section 6.1. For further details of the exploratory and sensitivity analyses done by the ERG, see Section 6.2.

2 Introduction and background

2.1 Introduction

Breast cancer is one of the most common cancers diagnosed in England and Wales, with most cases (approximately 99%) occurring in women. A small proportion of patients are diagnosed in the advanced stages, when the tumour has spread significantly within the breast or to other organs of the body, and there are a significant number of women who have been previously treated with curative intent who subsequently develop either a local recurrence or metastases. Advanced breast cancer (aBC) encompasses both patient groups, with locally advanced and metastatic cancer.[2],[3]

Advanced breast cancer is currently incurable, yet multiple treatments are available to improve quality of life and increase the time in which patients live with the disease. Breast cancer is a heterogeneous disease and treatment options depend on multiple histological and genetic factors, including the expression of hormone receptors (HRs) and overexpression of human epidermal growth factor receptor 2 (HER2). HR-positive (HR+), HER2-negative (HER2-) is the most common form of breast cancer, accounting for approximately 73% of cases (in which HR/HER2 status is known).[4], [5] These tumours are typically slow growing in comparison with other subtypes[4], yet prognosis is poor where disease is advanced.[6]

For HR+/HER2- breast cancer the treatment strategy comprises endocrine therapies such as tamoxifen, fulvestrant and aromatase inhibitors (AIs), that disrupt hormone production or otherwise interfere with intracellular oestrogen signalling.[7] Some HR+ tumours do not respond to initial endocrine therapy or develop resistance over time. For people with endocrine-resistance (see Section 2.2) the predominant treatment of choice that is available through routine commissioning is everolimus plus exemestane. Ribociclib plus fulvestrant is proposed as a treatment alternative for patients who have relapsed or progressed on or after prior endocrine therapy, for whom everolimus plus exemestane would be the most appropriate alternative. Ribociclib plus fulvestrant is currently recommended for use within the Cancer Drugs Fund (CDF) for this indication (TA593) and has been available for use in this indication since August 2019.[8]

Ribociclib is a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor that prevents the formation of cyclin D-CDK4/6 complex and subsequent cell-cycle progression, and fulvestrant is a selective oestrogen receptor down-regulators (SERD), that targets and blocks endocrine receptors in tumour cells.[9] Other CDK 4/6 inhibitors, palbociclib and abemaciclib, in combination with fulvestrant are also available through the CDF for this patient population but as they are not available through routine

commissioning, they are not considered relevant comparators for this review. Here, this report comprises a review of the latest clinical and cost-effectiveness evidence for ribociclib plus fulvestrant in advanced HR+, HER2- breast cancer.

2.2 Background

The clinical-effectiveness evidence for ribociclib plus fulvestrant in the original company submission (CS) for TA593 were derived from one randomised controlled trial (RCT), MONALEESA-3. MONALEESA-3 was designed to assess the efficacy and safety of ribociclib plus fulvestrant versus fulvestrant plus placebo in people with HR+/HER2- aBC. MONALEESA-3 comprises of two cohorts of patients: those who were treatment-naïve in the advanced setting or had relapsed after 12 months of completing endocrine therapy, with no treatment for advanced or metastatic disease (subpopulation A), and subpopulation B, which consists of patients with endocrine-resistant disease, including:

- Early relapse on first-line neoadjuvant endocrine therapy (during or within 12 months of completion), with no treatment for advanced or metastatic disease (TA593 subpopulation Bi);
- Advanced or metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy (TA593 subpopulation Bii);
- Relapsed >12 months from completion of adjuvant or neoadjuvant endocrine therapy with subsequent progression after one line of endocrine therapy for advanced or metastatic disease (TA593 subpopulation Biii).

In the original appraisal of TA593 the committee agreed to focus on subpopulation B as the relevant population for NHS clinical practice and the most appropriate positioning of ribociclib plus fulvestrant. Accordingly, hereafter this ERG report will focus only on updated data for subpopulation B of MONALEESA-3 only. Patient and disease characteristics of those enrolled in MONALEESA-3 are discussed in greater detail in section 3.1.1.

In their appraisal of TA593, committee concluded that there was uncertainty in the clinical evidence due mainly to immature OS data and a relatively short follow-up for PFS available from the clinical trial. Due to these limitations, the cost-effectiveness estimates were very uncertain and were above the range normally considered an acceptable use of NHS resources. The committee, therefore, agreed to recommend ribociclib plus fulvestrant within the CDF, to allow for further data collection from MONALEESA-3. A Terms of Engagement was agreed between the company and NHS England

(NHSE) for Public Health England (PHE) to undertake a retrospective collection of data for patients that receive ribociclib plus fulvestrant for this indication through the CDF.

The ERG notes that committee also concluded that everolimus plus exemestane is the most relevant comparator for ribociclib plus fulvestrant. The ERG notes that there is no direct trial evidence for this comparator. A critique of the indirect comparisons made by the company between MONALEESA-3 and other trials is therefore a key focus of this report (see Sections 3.2 to 3.3).

2.3 Critique of company's adherence to committees preferred assumptions from the Terms of Engagement

In general, the ERG considers that the company has adhered to the committees preferred assumptions from the Terms of Engagement. The ERG's critique of the company's adherence to the committees preferred assumptions from the Terms of Engagement is provided in Table 7.

Table 7. Preferred assumptions from Terms of Engagement

Assumption	Terms of Engagement	Addressed by the company submission	Rationale if different	ERG comment
Population	Results were presented separately for a subgroup of patients who had had previous endocrine therapy (n=345). This subgroup was considered in the company's submission as population B. The committee concluded that population B was the relevant population to this appraisal Committee preferred this approach rather than the company's initial suggestion of further splitting population B into 2 subpopulations: 1 with disease that has progressed at or within 12 months after neoadjuvant or adjuvant endocrine therapy, and another with disease that has progressed after 1 line of endocrine therapy in the advanced setting. **Population B is the relevant population for the CDF review**	Y	N/A	In the original appraisal of TA593, the committee agreed that ribociclib plus fulvestrant use would be most appropriate for people with endocrine-resistance, which is represented in subpopulation B of MONALEESA-3.
Comparator	The committee concluded that exemestane with everolimus is the key comparator for population B, the relevant subgroup from the MONALEESA-3 trial. The committee recommended that ribociclib with fulvestrant should be used within the CDF only if everolimus plus exemestane is the most appropriate alternative to a CDK 4/6 inhibitor. **The CDF review should only include a comparison with exemestane with everolimus**	Y	N/A	The company have updated their NMA, which compares ribociclib plus fulvestrant to everolimus plus exemestane, for both PFS and OS. In addition, the company have also provided a PAIC based on IPD of MONALEESA-3 and BOLERO-2, that compares ribociclib plus fulvestrant to everolimus plus exemestane.

NMA	The committee considered that the results of the NMA were highly uncertain, and that the effect of this uncertainty on the cost-effectiveness results was likely to be high. There were substantial differences in the baseline characteristics of the patients included in the studies and the ERG highlighted that the PHs assumption had not been met in the MONALEESA-3 trial, so using a HR dependent on this trial is likely to be unreliable. **The company should update the NMA and should explore the most appropriate trials to include and the most appropriate method to compare PFS and OS across the treatments.**	Y	N/A	The company explored PH assumptions for the trials within the NMAs and concluded PH assumptions were met and so the Bucher method was appropriate. The ERG considers that the assumption of PH might be acceptable but cautions, as per the original appraisal of TA593, that there is uncertainty around the HRs derived from the indirect comparisons.
TTD	Because time on treatment was shorter for ribociclib than it was for fulvestrant in the treatment arm, the company originally modelled time-to-treatment stopping for ribociclib and fulvestrant monotherapy (in the treatment arm) separately in its base case. The ERG explained that restricted models assume a common shape parameter across different treatment groups. It further explained that unrestricted models, determined only by the treatment group in which the curves are applied, were a more appropriate method to use in this instance. The committee agreed that unrestricted models were more suitable **The company should update the time-on-treatment data and, unless the new data suggests otherwise, use the ERG's unrestricted model approach**	Y	N/A	The company updated time-on-treatment data for ribociclib and fulvestrant and used unrestricted models (unrestricted RCS lognormal) to extrapolate the data. However, the ERG considers that the unrestricted Gompertz model may be more appropriate. As per the company's original submission, the company assumed everolimus plus exemestane was given until progression. Although this assumption was not questioned by the committee in TA593, the ERG has had a clear direction from its clinical experts for the CDF review that patients may discontinue everolimus before progression due to tolerability issues. Given that differences in TTD are key drivers in the ICER, the ERG considers that TTD warrants exploration in the CDF review.

ECG costs	The company suggested that the cost of an ECG is not as high as suggested by the ERG, and a simple resting ECG should be included. **Committee agreed resting ECG costs should be used**	Y	N/A	The company adhered to the committee's preferred assumption and used resting ECG costs.
PPS assumption	The company used data from the MONALEESA-3 trial to estimate PPS for ribociclib and fulvestrant. Because no exemestane with everolimus PPS data were available, the company assumed that PPS for exemestane with everolimus was the same as it was for ribociclib and fulvestrant. The committee concluded that no evidence had been presented to support the assumption that PPS was the same for exemestane with everolimus and ribociclib with fulvestrant **The company should explore the most appropriate approach for estimating and extrapolating PPS.**	Y	N/A	Using IPD from BOLERO-2 and MONALEESA-3 the company provided further support for the assumption that PPS is equivalent between ribociclib plus fulvestrant versus everolimus plus exemestane, in the form of PAICs. However, since the OS results from the June 2019 data-cut are more mature than the data previously reported from the November 2017 data-cut, the ERG considers that an alternative model structure should have been considered by the company; that is, a PSM where OS is applied directly in the model.
Most plausible ICER	The committee concluded that the company's revised base case included its preferred assumptions as stated in the appraisal consultation document The committee considered that the most plausible ICER, excluding comparator discounts, was [redacted] per QALY gained The committee recognised that there remained a high level of uncertainty in the clinical evidence They noted that the ICERs were based on small incremental gains and therefore were extremely sensitive to change.	N	N/A	The ERG considers that because OS data is still relatively immature, the uncertainty in the ICERs presented in TA593 that was to be addressed by the CDF review still remains. Additionally, the company has not used to most appropriate methods to directly compare OS across treatments (a PSM). The ERG also notes that TTD for everolimus is a key issue that warrants further exploration and the ERG's scenarios around this issue increase the ICER above [redacted]. Finally, in [redacted], fulvestrant is expected to go through loss of exclusivity and the ICER is highly variable to the discount on the list price of

	They recognised that the direction of the effect of the uncertainty on cost-effectiveness results is unknown			fulvestrant. The company's base case ICER for the CDF review was [redacted] per QALY gained using the list price for fulvestrant.
End of life	Ribociclib and fulvestrant does not meet the end-of-life criteria	N/A	N/A	N/A

Abbreviations: CDF, Cancer Drugs Fund; CDK, cyclin-dependent kinase; ECG, electrocardiogram; ERG, Evidence Review Group; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; IPD, individual patient-level data; N/A, not applicable; NMA, network meta-analysis; OS, overall survival; PAIC, population adjusted indirect comparison; PFS, progression free survival; PH, proportional hazards; PPS, post progression survival; PSM, partitioned survival model; QALY, quality adjusted life year; RCS, restricted cubic spline; ToE, terms of engagement; TTD, time to treatment discontinuation.

3 Clinical effectiveness

3.1 Critique of new clinical evidence

The new clinical data provided by the company for this Cancer Drugs Fund (CDF) review comprise updated overall survival (OS), progression free survival (PFS), post-progression survival (PPS) and time to treatment discontinuation (TTD) data from MONALEESA-3, a randomised controlled trial (RCT) of ribociclib in combination with fulvestrant in patients with advanced breast cancer (aBC). The company submission (CS) included new clinical data both for the full ITT population and for subpopulation B. In addition, the company provides data from the Systemic Anti-Cancer Therapy (SACT) database on the duration of treatment for patients receiving ribociclib plus fulvestrant within the National Health Service (NHS).

The data provided for MONALEESA-3 are from the 3 June 2019 data-cut and include 39.4 months median follow-up for all patients, compared to 20.4 months in the original company submission (CS) for TA593 (data-cut 3 November 2017). The ERG asked the company whether data from a more recent data-cut were available, given that the clinical study report (CSR) of MONALEESA-3 states a final data-cut would occur when 351 OS events had occurred, which the company estimates to be towards the end of 2020. The company replied that further data will not be available because the June 2019 data-cut showed a statistically significant benefit of ribociclib plus fulvestrant over fulvestrant alone, and so further data analyses will not be conducted. Furthermore, the data from the SACT database comprise 187 patients and 3.7-months median follow-up. Further details of both studies are discussed below.

The company has also updated the network meta-analysis (NMA) for PFS, which was presented in the original review of TA593, with the new data from MONALEESA-3, and has also produced NMA results for OS. The NMAs are discussed further in Section 3.2.

3.1.1 MONALEESA-3

MONALEESA-3 is an international, double-blind, phase III RCT of ribociclib plus fulvestrant compared to fulvestrant (plus placebo). Ribociclib was administered at a dose of 600 mg, orally once daily for 21 consecutive days, followed by 7 days off, for a complete cycle of 28 days. Fulvestrant (in both treatment arms) was administered at a dose of 500 mg, administered intramuscularly on day 1 of each 28-day cycle, with an additional dose on day 15 of cycle. [redacted]

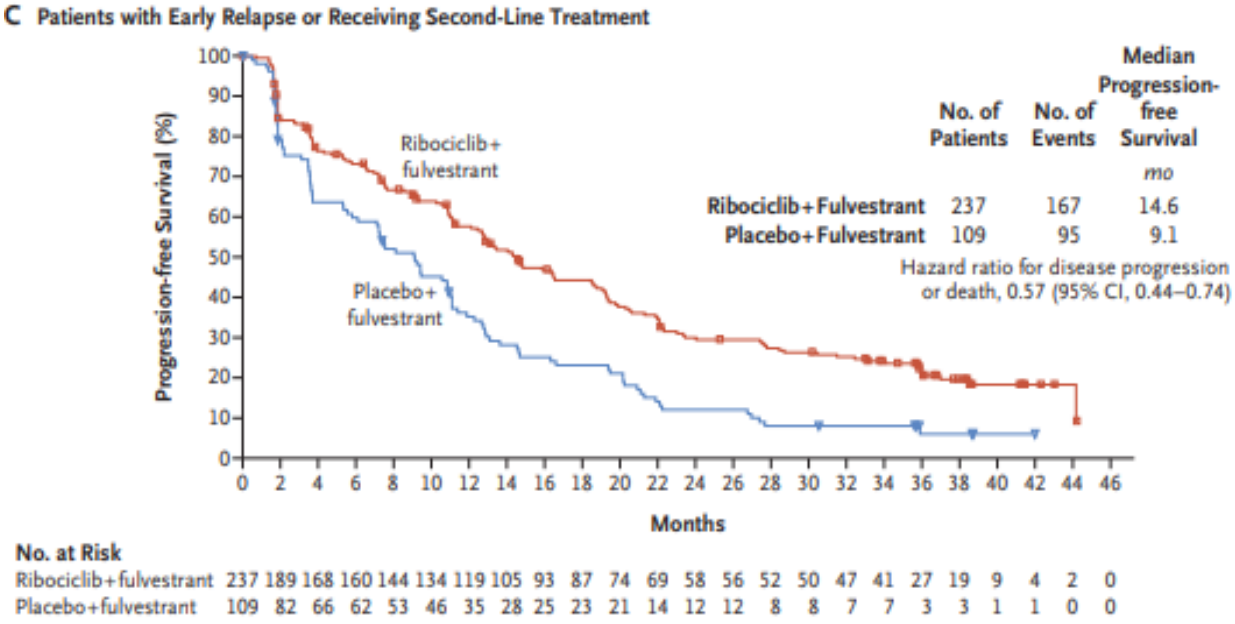
[redacted]. MONALEESA-3 was assessed in TA593 to be of high methodological quality and low risk of bias by the company. Although the ERG predominantly agreed with this assessment, the ERG had concerns that due to the association of ribociclib with prolongation of the QT interval, it is possible that detection of prolonged QT interval could have compromised masking of those allocated to ribociclib plus fulvestrant, which could have influenced investigator-assessed PFS. Nonetheless, with this exception, the ERG agreed that blinding of care providers, participants and outcome assessors in the trial appeared generally sufficient.

Patients enrolled in MONALEESA-3 (n=726) had a median age of 63 years, with histologically or cytologically confirmed HR+/HER2- aBC (metastatic or locoregionally recurrent disease not amenable to curative treatment). Only patients with an Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1 were included in the trial. The ERG's clinical experts fed back that the baseline characteristics of those enrolled in MONALEESA-3 are representative of people with aBC in England who are likely to be eligible for treatment with ribociclib plus fulvestrant. See Section 3.2 for a comparison of the population within MONALEESA-3 and the other trials in the indirect treatment comparisons.

3.1.1.1 Progression-free survival

In the original appraisal, subpopulation B was split into two separate groups (see Section 2.2), both of which demonstrated [redacted]. The PFS results from the June 2019 data-cut are [redacted] with the data previously reported from the November 2017 data-cut, with ribociclib plus fulvestrant demonstrating an improvement in PFS compared with fulvestrant plus placebo in subpopulation B (HR: 0.57, 95% CI: 0.43 to 0.74, Figure 1 and Table 8). As per the original appraisal, the ERG notes that, as subgroups, results should be interpreted with some degree of caution as the study was not powered to detect a difference between treatments in the defined groups.

Figure 1. Kaplan–Meier plot of investigator-assessed PFS for subpopulation B of MONALEESA-3 (data-cut 3 June 2019, reproduced from clarification response A14)



Source: Slamon *et al*. *NEJM* 2020;382:514–24.

Table 8. PFS final analysis of MONALEESA-3 in subpopulation B[a] (3 June 2019 data-cut, adapted from company submission, Table 5).

Endpoint	Events, n (%)	Ribociclib plus fulvestrant vs fulvestrant (months)
Investigator assessed PFS, months (95% CI)	167 (70.5) vs 95 (87.2)	14.6 (95%CI: 12.5 to 18.5) vs 9.1 (95%CI: 6.1 to 11.1) HR, 0.57 (95% CI:0.43 to 0.74)

[a]Ribociclib plus fulvestrant (N =237) and placebo plus fulvestrant (N = 109).

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

In the June 2019 data-cut of MONALEESA-3, median PFS was 14.6 months (95% CI: 12.5 to 18.5) in the ribociclib plus fulvestrant arm, and 9.1 months (95% CI: 6.1 to 11.1) in the fulvestrant plus placebo arm for subpopulation B. However, the ERG notes that there is heavy censoring present at the end of the Kaplan–Meier curve (from month 32) and so the data at this point may be unreliable.

At the clarification stage, the ERG requested updated results of the audit-based central assessment by the blinded independent review committee (BIRC), given that there were concerns related to blinding in MONALEESA-3 which could have influenced investigator-assessed PFS. The company responded that further PFS BIRC data were not available, as blinded review had not been conducted since the last data-cut. The ERG notes that differences between investigator-assessed PFS and BIRC

PFS in the previous appraisal were minimal, and so although further BIRC data would have been preferred, the ERG does not see this as a major issue.

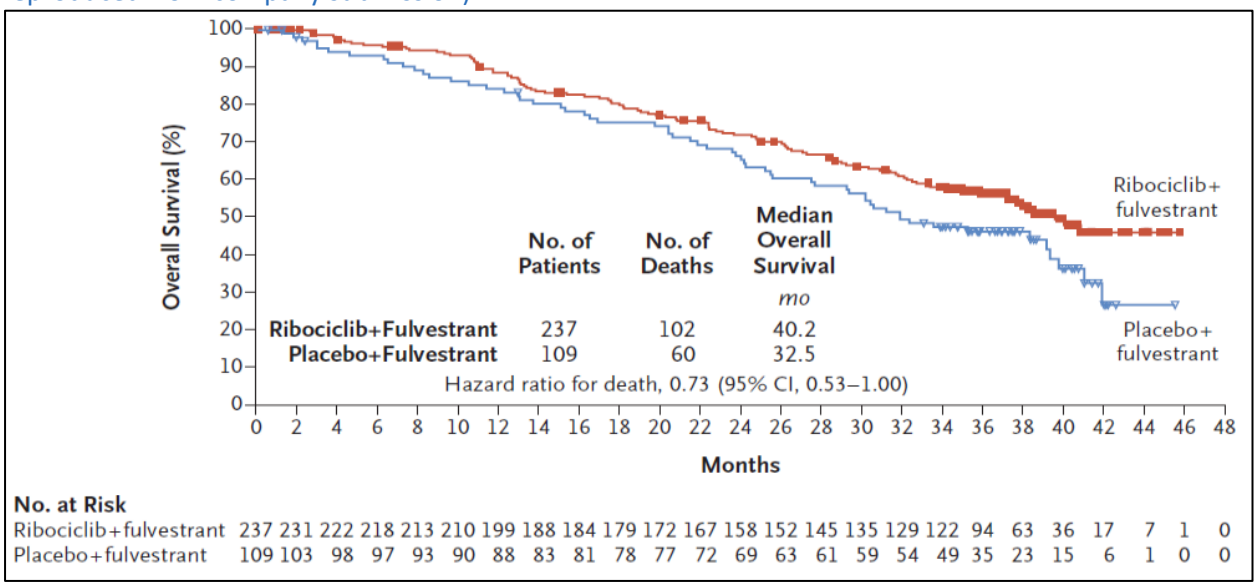
The company provided forest plots with summary data for PFS in various subgroups including line of endocrine therapy, region of metastases, site of metastasis, most recent therapy, age, ECOG score, race, geographic region, progesterone receptor (PgR) status and HR status (see Section E.1.2 of the company submission appendices). The ERG generally agree that results were consistent across the subgroups, and note that where effect estimates appear to differ across subgroups, these results were very uncertain due to small sample sizes and wide confidence intervals.

3.1.1.2 Overall survival

In the original appraisal, OS for the subpopulations presented by the company were immature. [redacted], the ERG considered that results for each subgroup should be interpreted with caution. Ribociclib plus fulvestrant compared to fulvestrant plus placebo was associated with a HR [redacted] in subpopulation Bi and HR [redacted] in subpopulation Bii+Biii.

The OS results from the June 2019 data-cut are more mature than the data previously reported from the November 2017 data-cut, although the ERG is still concerned with the data maturity, given that median OS was only just reached and the upper bound confidence intervals were not estimable. Nonetheless, ribociclib plus fulvestrant demonstrated an improvement in OS compared with fulvestrant plus placebo in subpopulation B (HR: 0.73, 95% CI: 0.53 to 1.00, Figure 2 and Table 9). Median OS was 40.2 months in the ribociclib plus fulvestrant arm (95% CI: 37.4 to NE [not reached]) compared to 32.5 months in the fulvestrant plus placebo arm (95% CI: 37.4 to NE). In the ribociclib plus fulvestrant arm there were 102 deaths in 237 patients (43.0%) and 60 deaths in 109 patients (55.0%) in the fulvestrant plus placebo arm. However, the ERG notes that there is heavy censoring present at the end of the Kaplan–Meier curve from 34 months onward. The ERG therefore cautions that data beyond this point may be unreliable.

Figure 2. Kaplan–Meier plot of investigator-assessed OS for subpopulation B (data-cut 3 June 2019, reproduced from company submission)



Abbreviations: CI, confidence interval; OS, overall survival.

Source: Slamon *et al.* 2019.(10)

Table 9. OS final analysis of MONALEESA-3 in subpopulation B[a] (3 June 2019 data-cut, adapted from company submission, Table 5).

Endpoint	Events, n (%)	Ribociclib plus fulvestrant vs fulvestrant (months)
OS, months (95% CI)	102 (43.0) vs 60 (55.0)	40.2 (37.4 to NE) vs 32.5 (27.8 to 40.0) HR, 0.73 (95% CI, 0.53 to1.00)

[a]Ribociclib plus fulvestrant (N =237) and placebo plus fulvestrant (N = 109).

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival.

At the clarification stage, the ERG requested the results for the significance test for OS in subpopulation B. The company did not provide this analysis, stipulating that MONALEESA-3 was not designed nor powered to identify a statistically significant difference in subpopulation B. The ERG agrees that any test for significance would need to be interpreted with caution due to it not being appropriately prespecified in the statistical analysis plan for the trial.

The ERG further notes that OS was not used in the economic model produced by the company, either in the original CS for TA593 or for this CDF review. Instead, post-progression survival (PPS), or death following progression, was used. This was estimated using individual patient failure time data from MONALEESA-3, which was used to generate PPS KM curves for each treatment arm. See

Section 4.1.5.2 for full details of how PPS was estimated within the economic model, as well as Section 3.3 which critiques the PAIC results for PPS.

3.1.1.3 Time to treatment discontinuation

At the clarification stage, the ERG requested separate Kaplan-Meier data for: ribociclib, fulvestrant (in combination), and fulvestrant (monotherapy) for subpopulation B of MONALEESA-3, given that ribociclib and fulvestrant may not be discontinued at the same time and the clinical inputs of the economic model include separate data for each drug. The ERG presents the separate Kaplan-Meier plots provided by the company (Figure 3-Figure 5). The ERG estimates median time to discontinuation to be 8.4 months for fulvestrant monotherapy, compared to 11 months for ribociclib and 11.4 months for fulvestrant in the combination arm, but advises caution when interpreting these data due to possible imprecision in estimates (although 95% CIs are presented as grey shading in each graph). The ERG notes that in the economic model, TTD for everolimus plus exemestane was estimated from the BOLERO-2 trial (see Section 4.1.5.3 for further details of TTD within the economic model).

Figure 3. Time to treatment discontinuation for ribociclib in MONALEESA-3 subpopulation B (3 June 2019 data-cut, reproduced from clarification question A12)

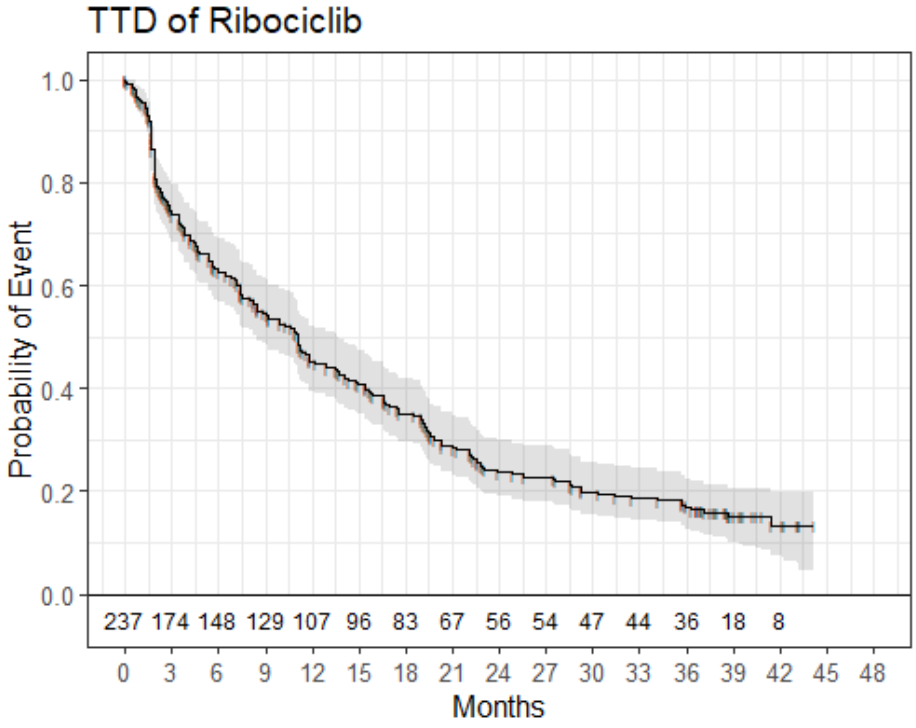


Figure 4. Time to treatment discontinuation for fulvestrant (combination) in MONALEESA-3 subpopulation B (3 June 2019 data-cut, reproduced from clarification question A12)

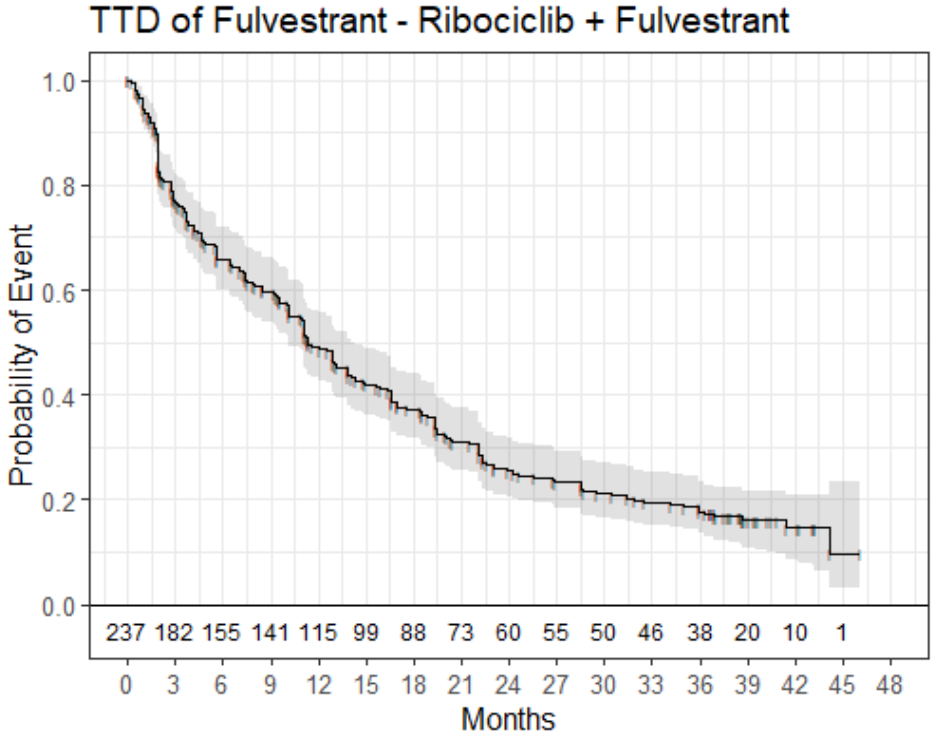
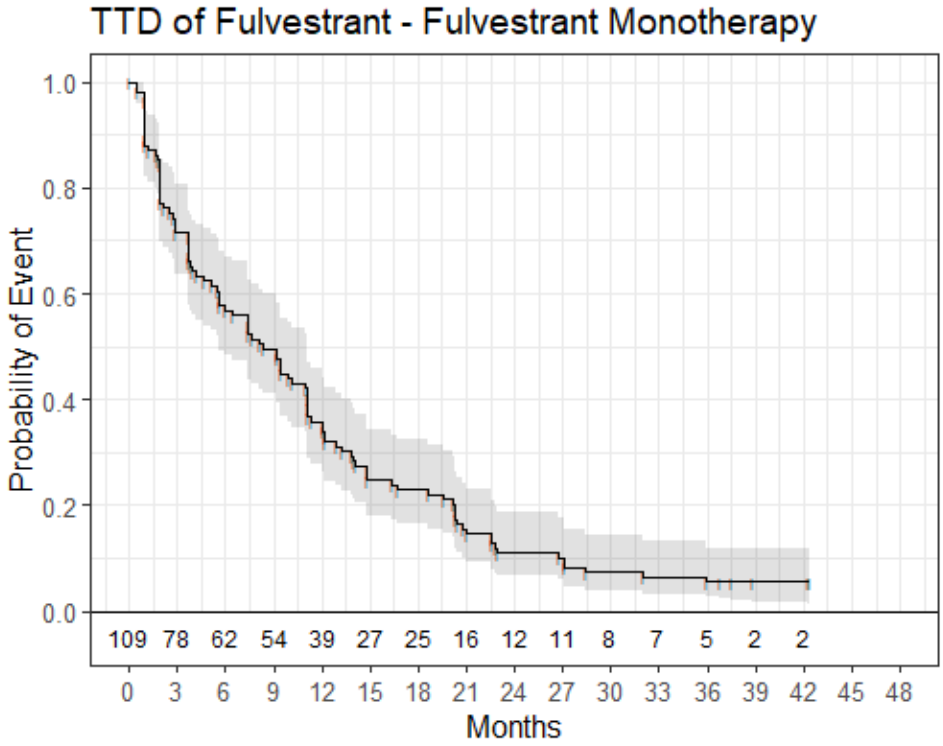


Figure 5: Time to treatment discontinuation for fulvestrant (monotherapy) in MONALEESA-3 subpopulation B (3 June 2019 data-cut, reproduced from clarification question A12)



3.1.1.4 Adverse events

The company reported no new safety concerns related to ribociclib plus fulvestrant, and provided rates of adverse events that occurred more frequently in the ribociclib plus fulvestrant arm compared with the fulvestrant plus placebo arm from the June 2019 data-cut. The ERG agree that these rates are similar to the previous November 2017 data-cut (see Section A.6.5 of the company submission for further details). The ERG further notes that adverse events were not updated in the economic model (see Section 4.1.6).

3.1.2 Systemic Anti-Cancer Therapy (SACT)

Due to the clinical uncertainties identified by the committee of TA593, ribociclib plus fulvestrant was commissioned through the Cancer Drugs Fund (CDF) for a period of 17 months, from July 2019 to December 2020. However, Public Health England reported that the CDF systemic anti-cancer therapy (SACT) data collection period was subsequently amended to end in January 2020 which they attributed as being due to the primary data source (MONALEESA-3 clinical trial)[(1)], reporting earlier than anticipated. The resulting SACT data that were collected by Public Health England (PHE) on the real-world usage of ribociclib plus fulvestrant comprised of 187 patients who received treatment between 17 July 2019 and 16 January 2020.[(11)] In general, the ERG note that SACT data is limited due to a relatively short-follow up and lack of comparative data to other treatments.

PHE reported that they carried out analyses on regimen outcomes and treatment duration for patients in the SACT cohort. PHE also reported that given the short data collection period it was not feasible to conduct analyses for OS using the SACT data set.

3.1.2.1 Baseline characteristics for the SACT cohort

Baseline characteristics of patients from the SACT cohort and MONALEESA-3 are presented in Table 10. In response to clarification the company provided a comparison of the baseline characteristics of patients in MONALEESA-3 and those in the SACT cohort and highlighted that for some characteristics (e.g. age), the data categories aren't fully aligned and so a direct comparison is not possible. All of the 187 patients receiving ribociclib plus fulvestrant in the SACT cohort were female and the median age was 64 years. In MONALEESA-3 (full ITT population)[(1)]; all patients were female, and the median age was 63 years, with the age range extending from 31 to 89 years. The company reported that patients in the SACT cohort may be older compared to MONALEESA-3 patients which the ERG notes is often the case in real world data sets compared to clinical trial populations.

In contrast to MONALEESA-3, patients with an ECOG performance status of 2 were eligible for inclusion in SACT and 7% of patients included in the SACT cohort were classed as ECOG 2. The ERG notes that performance status at baseline details were missing for 18% of patients in the SACT cohort and so the proportion with ECOG 2 may in fact be higher. The ERG also notes that the proportion of patients with ECOG 0 was higher in MONALEESA-3 compared with the SACT cohort (64.0% vs 41%); however, this could be partly related to the large proportion of patients with missing data in the SACT cohort (18%). The ERGs clinical experts reported that they would expect some ECOG performance status 2 patients to be eligible to receive ribociclib plus fulvestrant in clinical practice and therefore the SACT cohort is perhaps slightly more reflective of clinical practice. The ERG also notes that 97% of the patients in the SACT cohort had progressive disease on first line endocrine therapy or while still receiving adjuvant therapy. The data on previous therapy from MONALEESA-3 are possibly not directly comparable with the SACT data due to differences in the data categories (further details in Table 10).

Table 10. Baseline characteristics of patients in MONALEESA-3 and the SACT cohort (reproduced from company response to clarification question A15)

Ribociclib plus fulvestrant	MONALEESA-3 (n = 484) ITT population	SACT data (n = 187)
Sex, n(%)		
Female	484 (100)	187 (100%)
Age		
<40	–	8 (4%)
40-49	–	15 (8%)
50-59	–	49 (26%)
60-69	–	54 (29%)
70-79	–	50 (27%)
80+	–	11 (6%)
< 65	258 (53.3)	–
< 75	149 (86.6)	–
Performance status		
0	310 (64.0)	76 (41%)
1	173 (35.7)	64 (34%)
2	–[a]	14 (7%)

Missing	1 (0.2)	33 (18%)
Distribution of previous endocrine therapy		
PD on first line endocrine therapy	110 (22.7)[b]	97 (57%)
PD while receiving adjuvant therapy	138 (28.5)[c]	84 (45%)
PD ≤ 12 months of completing adjuvant therapy[d]	98 (20.2)	6 (3%)

Note: Figures may not sum to 100% due to rounding.

[a] Eligible patients had an ECOG score of 0–1.

[b] Assumed equivalent to same as second-line patients.

[c] Progression on or within 12 months of the end of (neo)adjuvant therapy.

[d] Source: MONALEESA-3 CSR final April 2018 and SACT data collection report. TA593.

Abbreviations: CSR, Clinical Study Report; ECOG, eastern Cooperative Oncology Group; PD, progressive disease; SACT, Systemic Anti-Cancer Therapy.

3.1.2.2 Time to treatment discontinuation and treatment outcome for the SACT cohort

Treatment discontinuation in the SACT cohort is reported for overall treatment with ribociclib plus fulvestrant. However, in practice ribociclib and fulvestrant can be discontinued at different times, and therefore TTD of each drug within MONALEESA-3 was analysed separately and incorporated separately within the economic model (see Section 4.1.5.3). Nonetheless, a total of 46 (25%) of the 187 patients who received ribociclib plus fulvestrant via the CDF had discontinued treatment by 31 January 2020 (latest follow up in SACT dataset and includes patients who have not received treatment for at least 3 months). The median follow-up time was 3.7 months (112 days) and the median treatment duration was 9.4 months (286 days). In contrast, the median treatment duration in MONALEESA-3 for the ribociclib plus fulvestrant study arm was 15.8 months although the ERG notes that this was for the full population and not population B which is the population of interest for this review. The ERG agrees with the company that the shorter treatment duration and follow-up for the SACT cohort make it difficult to compare the TTD data with that from MONALEESA-3. However, a summary of the TTD data from the SACT cohort is provided below.

The Kaplan-Meier plot for time to treatment discontinuation for patients in the SACT cohort is shown in Figure 6, and Table 11 shows a breakdown of the number of patients at risk, the number of patients that were censored and the number of patients that ended treatment (events) from the time patients started treatment to the end of the follow-up period in the CDF. The ERG notes that it is reported in the SACT report that 72% of patients were still receiving treatment at six months (95%

confidence interval: 63% to 78%) and at 31 January 2020 there were 141 patients (75%) still receiving treatment. The ERG notes from the Kaplan–Meier plot there is heavy censoring beyond 3 months and the ERG therefore considers the SACT data to be immature and unreliable for drawing conclusions on treatment duration or outcomes with ribociclib plus fulvestrant.

Figure 6. Kaplan-Meier plot of time to treatment discontinuation for the SACT cohort (Reproduced from SACT report, Figure 3)(11)

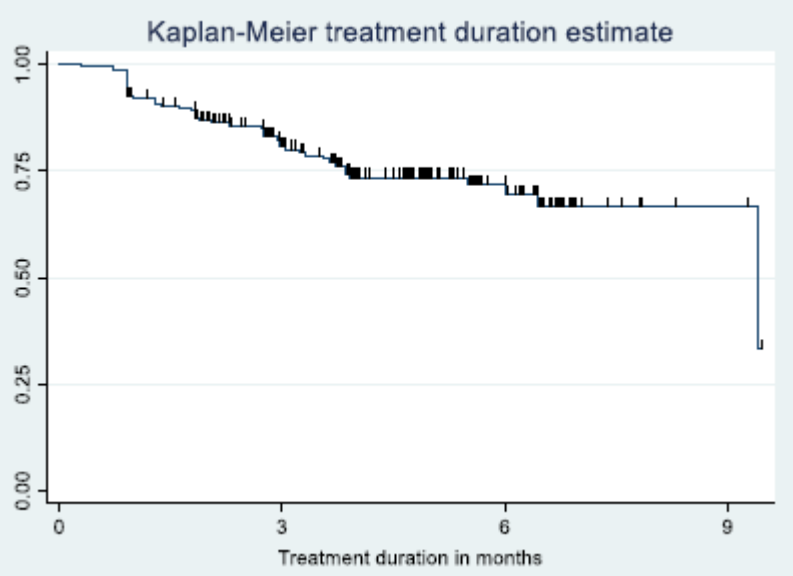


Table 11. Number of patients at risk and censored in the analysis of time to treatment discontinuation for the SACT cohort (Adapted from the SACT report, table 8 and table 9)(11)

Time intervals (months)	0 - 12	3 - 12	6 - 12	9 - 12
Number at risk	187	111	33	3
Censored	141	98	30	2
Events (ended treatment)	46	13	3	1

Table 12 provides a breakdown of each patient's treatment outcome for the 46 patients who had ended treatment at the 31 January 2020 data-cut. The ERG notes that 15 (33%) of these patients remain alive and the reason for treatment discontinuation was acute chemotherapy toxicity in 7 (15%) of the patients who had discontinued treatment.

Table 12. Treatment outcomes for patients in the SACT cohort that have ended treatment (reproduced from SACT report, Table 6)(11)

Outcome or reason for stopping treatment	N (%)
Progression of disease	14 (30%)
Acute chemotherapy toxicity	7 (15%)
Patient choice	2 (4%)
Died not on treatment[a]	11 (24%)
Died on treatment[a]	4 (9%)
No treatment in at least 3 months	8 (17%)

Notes: Figures may not sum to 100% due to rounding.

[a] 'Deaths on treatment' and 'deaths not on treatment are explained in the methodology paper available on the SACT website: http://www.chemodataset.nhs.uk/nhse_partnership/

3.2 Network-meta analysis

The company updated the original network meta-analysis (NMA) for PFS with data from the June 2019 data-cut of MONALEESA-3. The company reported that they used the same methodology for the NMAs as they used in their original submission for TA593. In the original appraisal, the Bucher method was used to calculate hazard ratios (HRs), which the company previously considered appropriate, citing that the Schoenfeld residuals suggested that proportional hazard (PH) assumption was not violated for any of the comparisons in the network. During the previous appraisal, the ERG considered the assumption of PH might be acceptable but cautioned that there was uncertainty around the HRs derived from the indirect comparisons, given that, for MONALEESA-3, the log-cumulative hazards cross at the beginning (see Section 4.1.5.1 for further details). Furthermore, at the clarification stage for this CDF review, the company further highlighted that PH assumptions may be violated for one of the trials in the network (BOLERO-2), given that the p-value on the test of non-proportionality was statistically significant (p=0.005). The company stated that due to this uncertainty, they would be exploring alternative NMA methods. Similar, to the previously submission, the ERG considers that PHs may hold but cautions that there is uncertainty around the HRs derived from the Bucher method.

At the clarification stage, the ERG requested the company conduct an NMA for OS in order to meet the committee preferred assumptions of exploring the most appropriate methods to compare OS across treatments, as outlined in the ToE. The company provided this analysis, highlighting that the same trials were included as per the NMA PFS, with the only exception being that EFECT(12) did not report OS and therefore was not included. For this analysis, the company concluded that the assumptions of PH were not unreasonable, given that the tests of linearity of the Schoenfeld residuals was not statistically significant in any trial. The ERG agrees that assumptions of PH might be acceptable but again cautions that there is some uncertainty, given that the smoothed curve fit to the residuals for BOLERO-2 has a decreasing slope.

The company performed an updated search for studies on 6 March 2019 to determine if new studies were available to include in the network. The company did not identify any new studies, and the ERG is satisfied that all relevant studies have been included in the NMA, with the clinical experts advising the ERG also being unaware of any new studies being published. The ERG notes that the population differences between MONALEESA-3 and other trials in the network are consistent with the original submission, whereby the ERG concluded that population differences between trials were minimal and unlikely to produce substantial bias in the effect estimates. In general, inclusion criteria of the trials were similar; all studies included postmenopausal women who had aBC that had recurred or progressed during treatment with an endocrine therapy, either as an adjuvant treatment or as a treatment for advanced disease. All studies required people to have HR+ aBC. However, HER2– status was not a requirement for enrolment in CONFIRM[13], EFECT[12], or SoFEA[14], and the proportion of women with HER2– disease is unclear in these studies. The ERG notes that in the previous NMA, the proportion of patients in each trial who came under subpopulation Bi (early relapse), or Bii/Biii (relapse or progression after first-line treatment) differed across trials. However, the ERG considers that, as in the original appraisal, this is unlikely to produce bias in the effect estimates. In TA593, the subgroup analysis of MONALEESA-3 showed minimal differences in the effect of ribociclib plus fulvestrant across these subgroups, and for this reason the committee decided to combine the groups into one population (subpopulation B).

3.2.1 *Progression-free survival*

Figure 7. MONALEESA-3 subpopulation B network (PFS) (reproduced from company submission appendices)

Abbreviation: PFS, progression-free survival.

Figure 7 shows the model structure of the NMA for PFS, which is consistent with the previous appraisal of TA593. Table 13 shows the PFS HRs generated by NMA for subpopulation B. The ERG independently validated the company's analysis and obtained the same effect estimates as the company. HR values were incorporated directly into the economic model base case (see Section 4.1.5.1). Overall, the ERG considers the result to be consistent with the previous appraisal, with everolimus plus exemestane versus ribociclib plus fulvestrant demonstrating a HR [redacted] (95% CI [redacted]), compared to HR 1.04 (95% CI: 0.70 to 1.41) in the previous submission (note that the latter HR has been inverted by the ERG to allow comparison).

Table 13. Derived HRs for PFS from subpopulation B NMA (reproduced from company submission, Table 6)

Comparator	HR (95% CI) vs fulvestrant	HR (95%CI) vs ribociclib + fulvestrant
Fulvestrant	[redacted]	[redacted]
Ribociclib + fulvestrant	[redacted]	[redacted]
Everolimus + exemestane	[redacted]	[redacted]

Note: Data in bold are used in the economic model.
Abbreviations: CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

3.2.2 *Overall survival*

Figure 8. OS NMA network (reproduced from clarification responses, Figure 7)

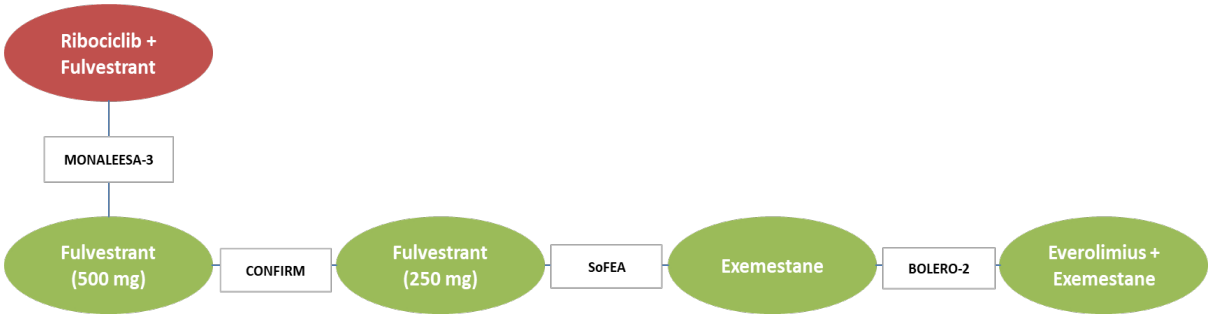


Figure 8 shows the model structure of the NMA for OS, which is consistent with the NMA for PFS, with the exception that EFECT was not included because it did not report OS. Table 14 shows the OS HRs generated by the NMA for subpopulation B. The ERG independently validated the company's analysis and obtained the same effect estimates as the company. The ERG notes that OS was not incorporated into the economic model, whereby instead post-progression survival was assumed to be equivalent between treatments (see 4.1.5.2 for further details). The ERG considers the result of the NMA to suggest a [redacted] ribociclib plus fulvestrant compared to everolimus and exemestane, with a HR [redacted]. However, this result is uncertain, with [redacted]. See below Table 14 for full results of the NMA.

Table 14. Estimated HRs for OS for Subpopulation B based on Bucher NMA (reproduced from company response to clarification question A2)

Treatment	HR, Treatment vs Fulvestrant 500mg		HR, Treatment vs Ribociclib + Fulvestrant		HR, Ribociclib + Fulvestrant vs Treatment	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Ribociclib+Fulvestrant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fulvestrant 500mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus+Exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; vs, versus.

3.3 Population-adjusted indirect comparisons

The company conducted population-adjusted indirect comparisons (PAICs) using individual patient data (IPD) from the ribociclib plus fulvestrant arm of MONALEESA-3 and the everolimus plus

exemestane arm of BOLERO-2[15], following guidance from the NICE Decision Support Unit (DSU) on PAICs[16]. The PAIC for progression-free survival (PFS) was used to support the PFS results from the NMA. NMAs that consist of only one or two trials per treatment are vulnerable to systematic variation (bias) resulting from imbalances in effect modifier distributions. In these cases, PAICs may support decision-making by providing insight into results whereby population differences are reduced. The PAICs for overall survival (OS) and post-progression (PPS) were also used to validate the methods of estimating PPS used in the economic model (see Section 4.1.5.2 for further details).

The ERG emphasises that the PAICs conducted are unanchored and based on single arms of trials without a common comparator. Due to this, randomisation is effectively 'broken', resulting in a non-randomised comparison, whereby it is assumed that absolute outcomes can be predicted from the covariates and that all effect modifiers and prognostic factors are accounted for. The DSU guidance for PAICs highlights that this assumption is very strong, and largely considered impossible to meet [16]. Failure to meet this assumption leads to an unknown amount of bias in the unanchored estimate and the ERG therefore advises caution when interpreting the results of the PAICs, although notes that the clinical experts advising the ERG reviewed the variables adjusted for (appendix 9.1) and confirmed that these were reasonable. At the clarification stage, the ERG asked the company to add BOLERO-6[17] to the PAICs, a trial comparing everolimus plus exemestane to everolimus alone. The company responded that while this may be feasible, they could not conduct this analysis in the time available. The ERG therefore has concerns related to the omission of this study, and considers this to add further uncertainty to the effect estimates derived from the PAIC, given that the estimates could have differed on inclusion of an additional study.

At the clarification stage, the company also confirmed that the methods were identical for the OS, PFS and PPS PAICs. Patients in the BOLERO-2 trial were weighted such that the baseline characteristics of the weighted patients in BOLERO-2 match the baseline characteristics of the unweighted patients in MONALEESA-3, using inverse probability of treatment weighting (IPTW) methods. Weights were calculated using logistic regression analyses with covariates for baseline demographic and clinical characteristics. Outcomes included PFS, PPS and OS and were analysed using Kaplan Meier methods, Cox proportional hazards regression, and parametric survival distributions. All covariates adjusted for were identical in the 3 PAICs (see appendix 9.1).

Results are presented in Table 15, and show a statistically significant benefit of ribociclib plus fulvestrant compared to everolimus plus exemestane for PFS (Weighted HR [redacted], 95% CI: [redacted]

[redacted], p<0.001) and OS (Weighted HR [redacted], 95% CI: [redacted], p=0.025). Results for PPS, however, did not show a statistically significant difference between the two arms (HR [redacted] 95% CI: [redacted]), thus supporting extrapolation of PPS used within the economic model (where it is assumed that PPS is equivalent between the two arms).

Table 15. Cox proportional hazards regression results from PAIC (adapted from clarification responses and company submission)

Endpoint	HR (95% CI); ribociclib plus fulvestrant versus everolimus plus exemestane	p-value
PFS (unweighted)	[redacted]	< 0.001
PFS (weighted)	[redacted]	< 0.001
PPS (unweighted)	[redacted]	[redacted]
PPS (weighted)	[redacted]	[redacted]
OS (unweighted)	[redacted]	0.008
OS (weighted)	[redacted]	0.025

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival.

3.4 Summary: indirect treatment comparisons

The ERG notes that the OS PAIC results differ to the OS NMA results, whereby the results of the NMA did not demonstrate a statistically significant difference between treatments, whereas the estimate derived from the PAIC did (See Table 16 below). The ERG advises caution when interpreting the results from the PAICs, given the methodological limitations of the analysis, and considers the results of the NMA to be more reliable. Nonetheless, the ERG reasons that the results of both the PAIC, coupled with the NMA, support the extrapolation of PPS used within the model; both results show a numerical trend towards a benefit of ribociclib plus fulvestrant, and suggest that it is unlikely that everolimus plus exemestane has a survival benefit over ribociclib plus fulvestrant.

Similarly, the ERG notes that the results of the PFS NMA remain uncertain, with wide confidence intervals crossing the line of no effect, whereas the PAIC results show a statistically significant benefit for ribociclib plus fulvestrant. The ERG considers the results from the NMA to be more robust and therefore consider the company's approach of using the PFS NMA results in the model to be

appropriate. The ERG notes that the PFS PAIC results support this approach to some extent, given that the estimates of effect suggest everolimus plus exemestane is unlikely to have a PFS benefit over ribociclib plus fulvestrant.

Table 16. Comparison of NMA and PAIC results (adapted from clarification responses and company submission)

	NMA results		PAIC results	
Endpoint	HR (95% CI); ribociclib plus fulvestrant versus everolimus plus exemestane	p-value	HR (95% CI); ribociclib plus fulvestrant versus everolimus plus exemestane	p-value
PFS (weighted)	0.97 (0.67 to 1.41)	NA	[redacted]	< 0.001
PPS (weighted)	[redacted]	[redacted]	[redacted]	[redacted]
OS (weighted)	0.70 (0.43 to 1.11)	NA	[redacted]	0.025

Abbreviations: CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PAIC, population-adjusted indirect comparison; PFS, progression-free survival; PPS, post-progression survival.

3.5 Conclusions of the clinical effectiveness section

In general, the ERG considers that the company has adhered to the committee's preferred assumptions from the ToE, although the updated OS data from MONALEESA-3 has not reached maturity. The uncertainty from TA593 in terms of the effect of ribociclib plus fulvestrant on OS that was to be resolved during the CDF data collection period has therefore not been fully resolved. The clinical data presented by the company includes the ToE required later data-cut from MONALEESA-3 for OS, PFS and TTD, and the observational SACT data that were also required to be collected by Public Health England during the period of managed access for ribociclib plus fulvestrant. The ERG agrees that the company has focussed on the required population (subpopulation B) and the key comparator of everolimus plus exemestane. However, the ERG notes subpopulation B to be a *post-hoc* subgroup analysis of the original trial, which was not powered to detect a difference between treatments in this subgroup alone. The ERG therefore advises, as detailed in the original ERG report, caution to be taken when interpreting the results of this subgroup analysis.

MONALEESA-3 now comprises 39.4 months median follow-up (compared to 20.4 months in the previous appraisal) and includes later data-cuts for OS, PFS and TTD. However, the ERG notes that

the updated data from MONALEESA-3 remain immature for OS. The SACT data set comprises data on treatment duration for 187 patients, yet is also immature due to data collection ending earlier than expected. The SACT data is therefore unfortunately of limited value and the short data collection period has resulted in a lack of suitable data to conduct analyses of OS. The ERG considers there is still some uncertainty in the clinical data, despite the later data-cut from MONALEESA-3 and new data from the SACT. In terms of population, the clinical experts advising the ERG were satisfied that the population in MONALEESA-3 and SACT are broadly consistent with expected clinical practice in England, although MONALEESA-3 does not contain any patients with ECOG performance status 2 due to the study inclusion criteria.

In addition to an updated NMA for PFS, the company have conducted further analyses for this review, including an NMA for OS and PAICs for PFS, PPS and OS. These clinical analyses support the company's assumptions of no difference in PFS or PPS in the economic model. Although the PAICs demonstrate a benefit for PFS and OS, the ERG has concerns about the reliability of these estimates due to the methodological limitations of the analysis. Nevertheless, the ERG stipulates that the PAIC OS and PFS results do not conflict with the company's assumptions in the economic model, given that they at least show a numerical trend towards a benefit for ribociclib plus fulvestrant, meaning it is unlikely that everolimus and exemestane has a survival benefit over ribociclib plus fulvestrant.

In summary, the ERG considers the results of the analyses of OS with ribociclib plus fulvestrant compared to everolimus plus exemestane still to be uncertain due to the relative immaturity of the data from MONALEESA-3. The ERG considers the NMA analysis presented by the company for OS, coupled with the results of the PAICs, to support the company's clinical inputs in the economic model.

4 Cost effectiveness

4.1 Summary and critique of the company's submitted economic evaluation by the ERG

The key updates made in the company's economic evaluation were as follows:

- A more recent data-cut (June 3, 2019) of progression-free survival (PFS) from MONALEESA-3 has been used to update the indirect treatment comparison (ITC) (network meta-analysis, NMA) and parametric survival curves for ribociclib plus fulvestrant and fulvestrant monotherapy;
- A more recent data-cut (June 3, 2019) of post-progression survival (PPS) from MONALEESA-3 has been used to update the parametric survival curves for ribociclib plus fulvestrant (and everolimus plus exemestane due to the equivalency assumption);
- A more recent data-cut (June 3, 2019) of time to treatment discontinuation (TTD) from MONALEESA-3 has been used to update the parametric survival curves for ribociclib and fulvestrant (treatment arm);
- Utilityvalues for PFS are now based on whether a patient is on or off treatment;
- The additional [redacted] discount on the list price of ribociclib via a confidential commercial access arrangement has been removed, thus the Patient Access Scheme (PAS) for ribociclib 600 mg has been reduced from [redacted] to [redacted];
- Costs have been revised to reflect a 2018/19 cost year.

In addition to the key changes, the company made some minor corrections that were identified when updating the economic model for the CDF submission:

- Modified formulas to apply general population mortality; and,
- Removed programming bugs that assigned treatment initiation costs in cycles 2-7.

Finally, the company applied a discount of 10% to the list price of fulvestrant to account for the upcoming loss of exclusivity. However, in agreement with NICE, the ERG generated results using the list price of fulvestrant.

The results of the company's analysis from the point of entry to the Cancer Drugs Fund (CDF) to the CDF review are summarised in Table 17. Detailed results at each stage can be found in Appendix 9.2.

These results include a simple PAS discount of [redacted] for everolimus (the marketing authorisation for everolimus is also held by Novartis).

Table 17. Summary of the company's results from the point of CDF entry to the CDF submission, list price for fulvestrant

Interventions	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA593, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final base case results from TA593, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* excluding corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* including corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's updated base case results† including corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; ribo, ribociclib

* based on the same specification as the final base case results but updated the clinical data as per the 3 June 2019 cut-off. No other inputs were changed, including parameterisation of the curves (i.e. the functional form of PPS, PPS etc were as specified in the model at time of CDF entry)

†includes reassessing the functional forms of the best fitting curves, based on the updated data (along with cost updates, etc.)

4.1.1 Population

The population in the company's economic evaluation remains unchanged from that accepted by the committee in TA593 (population B including subpopulations Bi and Bii+Biii). Briefly, this

population includes patients who experienced an early relapse or receiving second-line treatment for HR+/HER2– locally advanced or metastatic breast cancer.

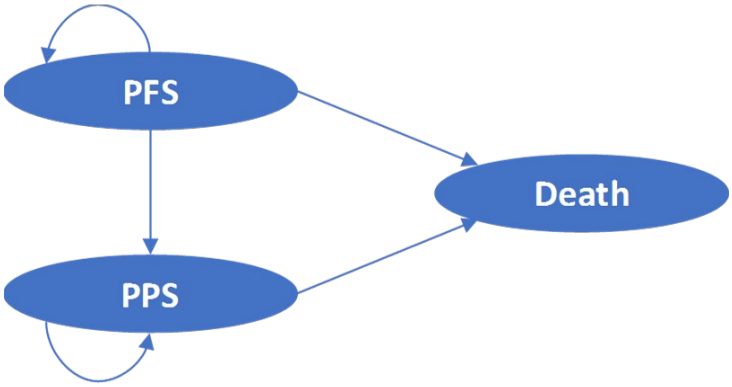
4.1.2 Interventions and comparators

The intervention included in the company's economic evaluation is ribociclib plus fulvestrant and this has remained unchanged from the original submission. The comparator is everolimus plus exemestane. This was the key comparator for population B considered by the committee in TA593.

4.1.3 Modelling approach and model structure

The model structure used for this CDF review is unchanged from that used in the original submission. This structure was accepted by the committee as being suitable for decision making. Briefly, this structure was a semi-Markov state-transition model with three health-states: PFS; PPS; and death (Figure 9). The semi-Markov property means that, between the health state transitions the model uses tunnel states to account for all-cause mortality.

Figure 9. Model structure



As described in Section 3, the overall survival (OS) results from the June 2019 data-cut are more mature than the data previously reported from the November 2017 data-cut. For this reason, the ERG considers that an alternative model structure should have been considered by the company; that is, a partitioned survival model (PSM) where OS is applied directly. The company's semi-Markov model extrapolates PFS and PPS then uses the sum of these outcomes to estimate OS. During the clarification stage, the company was asked to use the latest OS data-cut to implement data on OS in the model using an ITC. The methods and results of the company's ITC are given in Section 3. Due to time constraints, the company could not restructure the model to implement these results in the model, this point is discussed further in Section 4.1.5.4.

4.1.4 Perspective, time horizon and discounting

The perspective of the economic analysis is the same as in the original submission; that is, from the perspective of the NHS and personal social services. The time horizon of the model is 40 years, which is considered to cover a lifetime. This was accepted by committee and the ERG considers it to be reasonable. Discounting was applied at an annual rate of 3.5% for both costs and QALYs as per the NICE reference case.

4.1.5 Treatment effectiveness

4.1.5.1 Progression-free survival (PFS)

Using the later data-cut for PFS from MONALEESA-3 (June 3, 2019) in population B, the company updated their NMA (see Section 3.2.1) and produced revised parametric survival curves for use in the economic analysis. The company highlighted that their methods for fitting and selecting survival curves was based on NICE DSU guidance.[18]

As per the original submission, probabilities of PFS events for patients receiving ribociclib plus fulvestrant or fulvestrant monotherapy, were estimated by fitting parametric survival distributions to the individual patient level data (IPD) from MONALEESA-3. Considering the potential issue of violation of proportional hazards (PHs), the company produced a Schoenfeld residuals plot for the treatment group covariate in the Cox PH model. The company considered [redacted]. For this reason, the company considered it appropriate to fit one parametric model to the entire dataset, with treatment group included as a covariate in the analysis. The ERG notes that the company refers to these jointly-fitted type models as restricted (R) models.

Based on the company's re-evaluation of the survival curves, the company selected the restricted cubic spline (RCS) 3 Weibull (R) to model PFS for ribociclib plus fulvestrant and fulvestrant monotherapy. According to the company, the [redacted] model has one of the better fits according to BIC (Table 18), has a good visual fit to the updated MONALEESA-3 Kaplan-Meier (KM) data (Figure 10 and Figure 11), meets clinical expectations of this population (curves shape over time and proportion of patients alive at 10 years), has projected hazards that are consistent with nonparametric hazard rates and finally meets the PH assumptions.

Table 18. Fit statistics for the top 5 PFS distributions

Distribution	DF	-2LL	AIC	AICc	BIC
RCS 3 Lognormal (R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS 3 Log-Logistic (R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS 3 Weibull (R)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS 3 Lognormal (U)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCS Log-Logistic (U)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; DF, degrees of freedom; LL, log-likelihood; (R), restricted, (U), unrestricted

Figure 10. 10-year PFS projections (ribociclib + fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay (reproduced from Figure 10 of the company's clarification response, clarification question B3)

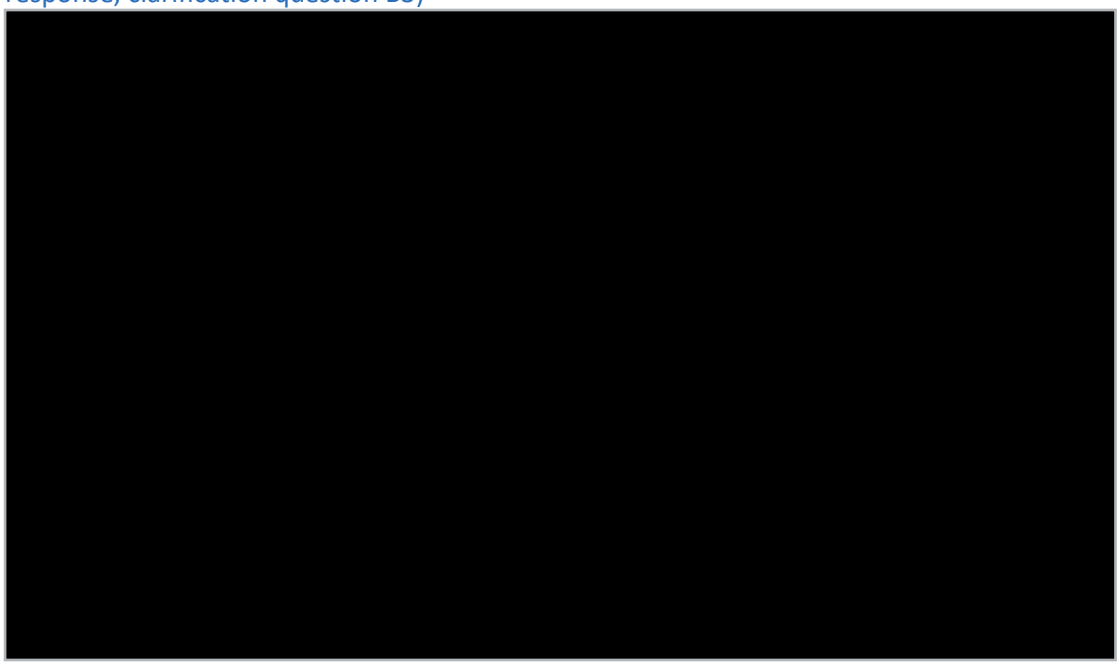


Figure 11. 10-year PFS projections (fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay (reproduced from Figure 11 of the company's clarification response, clarification question B3)

The ERG agrees with the company that the [redacted] has a good visual fit and allows for the changing hazards to be sufficiently well modelled. Furthermore, based on the feedback obtained from the ERG's clinical experts, most patients (around 95%) on fulvestrant monotherapy in subpopulation B are expected to have progressed by year 5. Thus, the best fitting models according to fit statistics [redacted] would not be suitable due to their longer tails.

However, the ERG considers it important to note that independently fitted curves were opted by the company in their original submission, and by the ERG in response to technical engagement (i.e. the model at the point of CDF entry). The decision to use independently fitted models in the original submission appeared to be because the curves in the log-cumulative hazard plots for MONALEESA-3 crossed at the beginning, indicating that PH may not hold. The ERG for this CDF review has made a similar observation based on the log-cumulative hazard plots provided in the CDF submission (Figure G2 of the company's appendix). In response to a clarification question, the company provided a scenario analysis using independently fitted curves. The company's chosen curve for this scenario was the [redacted], which had the best fit statistics and visual fit. However, as shown in Section 5.1.2, the impact of using independently fitted models on the ICER was minimal. In their response, the company also noted that the best-fitting RCS 3-knot models were all restricted models (jointly-

fitted models) and with the exception of the first month after randomisation (after the point at which the log-log plots cross) the assumption of PHs may be appropriate.

As for patients receiving everolimus plus exemestane, the probabilities of PFS events was estimated by using the fulvestrant plus ribociclib treatment arm in MONALEESA-3 as the baseline to which the HRs derived from the NMA are applied. The company also provided a scenario analysis where the fulvestrant monotherapy arm in MONALEESA-3 was used as the baseline PFS curve, but the impact of changing the baseline PFS curve had a minimal impact on the results (see Section 5.1.2). The methods and results of the NMA are given in detail in Section 3.2.1.

Additionally, the company conducted a scenario analysis which included the PFS hazard ratio (HR) derived by the population adjusted indirect comparison (PAIC) (a HR of [redacted] for everolimus plus exemestane vs ribociclib plus fulvestrant was applied to the baseline PFS curve). As shown in Section 5.1.2, this scenario [redacted]. The methods and results of the PAIC are given in detail in Section 3.3.

Finally, as noted in Section 3.2, the PH assumption may be violated in BOLERO-2, thus the company agreed to explore alternative approaches to estimate time-dependent HRs (e.g. hazards characterized as fractional polynomials). At the time of writing, these analyses were still underway. Should the company perform the analysis in sufficient time prior to the committee meeting, the ERG will provide an assessment of it in the form of an addendum.

Overall, the ERG has no major issues with the company's implementation of PFS in the model given the current evidence base. The ERG's clinical experts were also of the opinion that ribociclib plus fulvestrant is non-inferior to everolimus plus exemestane.

4.1.5.2 Post-progression survival (PPS)

Ribociclib plus fulvestrant

Using the later data-cut for PPS from MONALEESA-3 (June 3, 2019), the company updated their analysis of PPS data in subpopulation B by treatment group. As per the company's original submission, the company found [redacted]. For this reason, the company maintained their original approach to pool the data from both treatment arms. This approach was accepted by the committee for TA593.

The company fitted parametric survival distributions to the pooled data and followed the same process as for PFS in determining the most plausible curve. The company's chosen curve was the [redacted], which had the best BIC, an "excellent" visual fit, and projected hazards that are consistent with nonparametric hazard rates (hazards that increase consistently over the duration of follow-up). Fit statistics are given in Table 10 of the CDF submission while a plot of the hazard rates is given in Figure G5.

The ERG considers the [redacted] to be a reasonable choice for the base case analysis. However, it is important to note that the ERG's clinical experts were divided in their opinion on the best fitting curve. One expert considered the second-best fitting curve, the [redacted], to produce the most plausible predictions ([redacted]) while another expert was content with the company's chosen curve ([redacted]). Thus, the ERG considers the [redacted] to be a suitable model to explore in scenario analysis. However, as shown in Section 5.1.2, this scenario has a minimal impact on the results ([redacted]).

Figure 12. 10-year projections of PPS for pooled ribociclib plus fulvestrant in patients in subpopulation B of MONALEESA-3 KM plots and parametric functions (reproduced from Figure 14 of the CDF submission)

[redacted]

Everolimus plus exemestane

As per the company's original submission, it was assumed that PPS for everolimus plus exemestane was the same as it was for ribociclib plus fulvestrant. As a result, the company is assuming a "full surrogacy" approach; i.e. any gains in PFS would directly translate into an OS gain as PPS is assumed to be the same.

To address committee concerns from TA593 that no evidence had been presented to support this assumption, the company accessed IPD data from BOLERO-2 for the CDF submission. Following this, the company showed that the PPS KM plots for ribociclib plus fulvestrant from MONALEESA-3 and everolimus plus exemestane from BOLERO-2 looked very similar, are well within the 95% CIs, and cross at multiple points (Figure 13). In response to a clarification question, the company noted that Figure 13 is based on an unanchored PAIC-adjusted comparison of PPS for ribociclib plus fulvestrant and everolimus plus exemestane.

Figure 13. PPS KM comparisons for ribociclib + fulvestrant (MONALEESA-3) and everolimus + exemestane (BOLERO-2) intervention arms (reproduced from Figure 23 of the CDF submission)

The company also presented a weighted and unweighted Cox regression analysis of the PPS KM plots from MONALEESA-3 and BOLERO-2. The methods and results of this analysis are described further in Section 3.3. Overall, these results suggest that there is no statistically significant difference in PPS between ribociclib plus fulvestrant and everolimus plus exemestane, which is consistent with the company's visual assessment of the curves.

As a scenario analysis, the company implemented a PPS curve for everolimus plus exemestane based on the KM data from BOLERO-2. In response to a clarification question as to how this scenario was undertaken, the company explained that parametric distributions were fitted to data on PPS for everolimus plus exemestane from the PAIC-adjusted population of BOLERO-2. The company also noted that methods for constructing the PAIC of PPS were identical to those employed in the PAIC of PFS. Then, the Gompertz distribution was fitted to both treatment arms and was selected based on statistical fit and visual comparisons of projected PPS compared with KM PPS (Figure 14). As shown in Section 5.1.2, this scenario [redacted].

Figure 14. 10-year projections of PPS used in the company's scenario analysis using PPS curves estimated from BOLERO-2 for everolimus plus exemestane, generated by the ERG

In light of the company's response, the ERG is unclear why the company took different approaches to model the results obtained from the PAIC for PFS and PPS. For PFS, the company applied the HR for everolimus plus exemestane vs ribociclib plus fulvestrant to the baseline PFS curve (see Section 4.1.5.1). Nonetheless, when the ERG explored using the HR for PPS in the model, the ICER was similar to the company's analysis based on the extrapolation of PPS from BOLERO-2. Results of the ERG's scenario analysis can be found in Section 6.3.

Finally, the ERG sought clinical expert advice on the company's assumption that PPS for everolimus plus exemestane was the same as it was for ribociclib plus fulvestrant. The ERG's clinical experts did not have any reservations with the company's assumption.

Overall, the ERG agrees that if ribociclib plus fulvestrant can be considered equivalent to everolimus plus exmestane based on similarities in the PPS gain then the assumption of full surrogacy may be plausible. However, as explained in Section 4.1.5.4, a PSM would directly inform if the full surrogacy assumption is true or whether in fact there is just partial surrogacy.

4.1.5.3 Time to treatment discontinuation (TTD)

4.1.5.3.1 Ribociclib plus fulvestrant

As per the original submission, the company modelled TTD for ribociclib and fulvestrant (treatment arm) separately in its base case (despite some labelling in the CDF submission suggesting otherwise) because time on treatment was shorter for ribociclib than it was for fulvestrant. In line with the committee's preferred assumptions in TA593, the company considered unrestricted (U) models (i.e. independently fitted models) when selecting the best fitting TTD curves.

According to the fit statistics, the Gompertz (U) was the best fitting unrestricted curve. However, the company considered this curve to overestimate the time on treatment for ribociclib. Fit statistics are given in Table 12 of the CDF submission while 10-year projections for TTD are given in Figure 19 of the CDF submission for ribociclib and Figure 20 of the CDF submission for fulvestrant (treatment arm). In consequence, the company considered the next best fitting unrestricted curve, the RCS Lognormal (U), to inform the base case analysis. The company presented Figure 15 to show that the RCS Lognormal (U) provides a good visual fit to the KM data and produces very similar predictions to the Gompertz (U). The company also noted that the RCS Lognormal (U) curve does not suffer from the clinically implausible tail seen with the Gompertz (U).

Figure 15. TTD to end of trial follow-up using Gompertz (U) and RCS lognormal (U), taken from Figure 22 of the CDF submission

The ERG assessed the extrapolations of the RCS Lognormal (U) and Gompertz TTD (U) curves and compared them to the PFS extrapolations for plausibility (Figure 16 and Figure 17). The ERG determined that the RCS Lognormal (U) TTD curve for ribociclib crossed the fitted PFS curve much later than the Gompertz (U) TTD curve ( ). Additionally, the RCS lognormal TTD curve was capped by the PFS curve at the point of crossing to prevent the potentially implausible treatment beyond progression.

However, the best fitting curve for TTD (Gompertz (U)) was disregarded by the company because, "*all patients remaining on ribociclib at approximately 8 years would continue to receive ribociclib and never discontinue*". The ERG considers the company's rationale to be somewhat contradictory to using the minimum of TTD and PFS in the base case. A more appropriate method would be to choose the best fitting curve for TTD (Gompertz (U)) and cap the extrapolation by the PFS curve. As touched upon in Section 4.1.7, this scenario would also be one step closer to clinical expert opinion that patients would be expected to continue ribociclib and fulvestrant treatment until progression because they are well tolerated. Furthermore, any intolerabilities or toxicities are likely to be seen in the first few months of treatment.

Figure 16. 10-year projections of PFS and TTD using the RCS lognormal (U) curve for TTD, generated by the ERG

Figure 17. 10-year projections of PFS and TTD using the Gompertz (U) curve for TTD, generated by the ERG

The ERG also disagrees with the company that the RCS lognormal (U) distribution is flexible enough to capture the shape of the KM data for fulvestrant (treatment arm). The figures produced by the ERG using the TTD data in the model for fulvestrant (treatment arm) show a clear separation between the KM data and extrapolations between 6 and 18 months, which is likely to cause an underestimation of drug acquisition costs (Figure 18). Following this, the ERG found that the

company presented KM data for the fulvestrant monotherapy arm in the CDF submission despite the write-up suggesting otherwise (Figure 15). The ERG considers it methodologically flawed to use extrapolations in the monotherapy arm to justify extrapolations in the combination arm.

Finally, although the Gompertz (U) curve appears to be a better fit to the KM data included in the model, a better fit might be achieved using a 3-knot spline model (used for PFS). Unfortunately, the company did explore these types of models for TTD. As shown in Section 5.1.2, using the Gompertz (U) curve to inform TTD [redacted].

Figure 18. TTD to end of trial follow-up using Gompertz (U) and RCS lognormal (U), generated by the ERG

4.1.5.3.2 Everolimus plus exemestane

As per the company's original submission, the company assumed everolimus plus exemestane was given until progression. Although this assumption was not questioned by the committee in TA593, the clinical experts in attendance did state that ribociclib plus fulvestrant would be considered a more appropriate treatment for patients due to tolerability concerns with the everolimus component of everolimus plus exemestane. Clinical experts advising the ERG for this CDF review have supported the view presented at committee that in clinical practice patients may discontinue everolimus due to tolerability issues but continue with exemestane until progression. The clinical experts advised the ERG that around 20% of patients would discontinue everolimus before

progression due to intolerability and toxicity. Additionally, most patients who continue with everolimus during PFS are likely to reduce their dose from 10mg daily to 5mg daily. The clinical experts also considered that ribociclib and fulvestrant were more likely to be given until progression than everolimus and exemestane.

The ERG also notes that the findings from the BOLERO-2 trial are in keeping with the ERG's clinical expert opinion: in the everolimus plus exemestane treatment arm, 66.8% of patients required dose interruptions or reductions (to 5 mg daily) for everolimus while 23.9% of patients required dose interruptions or reductions for exemestane. Additionally, the median duration of exposure to everolimus was shorter than exemestane (23.9 weeks compared with 29.5 weeks).[15]

Given that differences in TTD are key drivers in the ICER, the ERG considers that TTD warrants exploration in the CDF review. During the clarification stage, the company was asked to explore a scenario using the IPD TTD from BOLERO-2 to fit separate TTD curves to everolimus and exemestane. The company was also asked to explore scenarios using the treatment discontinuation assumptions suggested by the ERG's clinical experts. Due to time constraints, the company did not provide the scenarios requested. In their response, the company also noted that an unanchored and unadjusted ITC of TTD would be inappropriate. However, the ERG envisaged that the company would extrapolate the PAIC-adjusted population of BOLERO-2 (to match the methodology used to assess PPS in BOLERO-2). The ERG also notes that the approach outlined by the company in their clarification response sounds like a reasonable alternative if their approach can account for non-monotonic hazards: TTD for everolimus and TTD for exemestane are estimated by applying to the model-estimated PFS for everolimus plus exemestane estimates of the HR for TTD vs PFS for everolimus and the HR for TTD vs PFS for exemestane.

As noted in the company's clarification response, it is unclear when patients would discontinue everolimus due to intolerability or toxicity. In order to answer this, the ERG contacted its clinical experts to ascertain when this would usually happen. Clinical experts advised the ERG that patients could be considered for a dose reduction between 6 weeks and 6 months and could discontinue within 2 weeks for mucositis and within 6 months for pneumonitis. Based on this information the ERG considers it reasonable to perform scenarios where patients discontinue, or dose reduce from month 6.

The ERG then ran three scenario analyses to reflect the uncertainty around TTD for everolimus. Each of these is described in turn below (and are similar to those outlined in the clarification letter for the company).

Based on clinical expert feedback, the ERG performed a scenario where 20% of patients discontinue everolimus at month 6. The remaining 80% are assumed to remain on the 10 mg daily dose of everolimus. Additionally, the costs of exemestane are continued until progression. As this scenario affects the TTD curve, the (higher) PFS off-treatment utility value is applied to 20% of patients in the treatment arm (i.e. including patients who continue with exemestane). The ERG considers this to be reasonable given that exemestane is not associated with the intolerability and toxicities that would lead to a lower quality of life.

However, according to the ERG's clinical experts, a large proportion of patients who remain on everolimus will dose reduce from 10 mg daily to 5mg daily. To address this, the ERG implemented another, separate scenario, where the dose of everolimus is reduced from 10mg daily to 5mg daily at month 6. Based on clinical expert opinion, 70% of patients are assumed to dose reduce in this scenario. This scenario does not affect utility values. The acquisition cost of the 5 mg preparation is based on the same brand at the 10 mg preparation (Afinitor, produced by Novartis) and includes the simple PAS discount of [redacted] on the list price (NHS indicative price of £2,250.00 for a 30-tablet pack).[19]

During the ERG's discussions with its clinical experts it was also made clear that these are coexisting scenarios. In clinical practice, there will be a mix of patients who discontinue, and dose reduce. As such, the ERG combined the scenarios. As shown in Section 6.3, all aforementioned scenarios increased the ICER above [redacted].

4.1.5.4 Overall survival (OS)

In response to a clarification question, the company compared OS between the treatments under consideration (see Section 3.2.2). Due to time constraints it was not possible to use the OS data directly in the model as this would require the model to be restructured to use a partitioned survival approach. Instead, the company explored other ways to demonstrate that a PSM which implements OS directly would provide similar results to the company's semi-Markov model where OS is the sum of PFS and PPS.

The company compared the OS estimates for ribociclib plus fulvestrant obtained from the semi-Markov model with the KM OS data from MONALEESA-3 and the parametric distributions fitted to KM OS data from MONALEESA-3 (that would be employed in a PSM). For this analysis, the Weibull (R) distribution was chosen based on an assessment of fit statistics and visual fit. These OS estimates are illustrated in Figure 19.

The ERG notes that the OS estimates for ribociclib plus fulvestrant obtained from the semi-Markov model (red curve) cross the curve fitted to the KM OS data from MONALEESA-3 (green curve) at multiple points. The ERG also notes that the curve fitted to the KM OS data from MONALEESA-3 is a closer match to the KM data than the estimates from the semi-Markov model. Additionally, the curve fitted to the KM OS data from MONALEESA-3 addresses clinical expert concerns that survival beyond 10 years is very speculative. Nonetheless, the discounted LYs obtained from each approach are similar ([redacted] in the semi-Markov model and [redacted] using the PSM approach).

As for everolimus plus exemestane, the company applied the HR obtained from the NMA ([redacted] for everolimus plus exemestane versus ribociclib plus fulvestrant) to the Weibull distribution for OS for ribociclib plus fulvestrant (green curve) to yield the OS curve for everolimus plus exemestane that would be employed in a PSM (purple curve). As shown in Figure 19, the curve estimated for everolimus plus exemestane using this approach is less favourable than that obtained in the semi-Markov model. As such, the ERG agrees with the company that this analysis demonstrates that the company's current model structure is likely to produce more conservative cost effectiveness estimates than using a PSM.

Even so, the ERG considers it is important to highlight that a PSM would be preferred to the company's semi-Markov model because this enables the OS data from the MONALEESA-3 trial to be used directly in the model, rather than having to make additional assumptions (i.e. having to estimate PPS rather than directly using OS and having to conduct the analysis assuming full surrogacy: where OS gains are equal to PFS gains). A PSM would directly inform if the full surrogacy assumption is true or whether in fact there is just partial surrogacy. Furthermore, as outlined in the ToE, the company should use the most appropriate methods to compare OS across treatments.

Therefore, until the ERG is able to make a direct comparison between the two models, it is speculative to say that the semi-Markov model will produce conservative cost effectiveness estimates.

Figure 19. Company's response to CQ B6, OS curve comparison

4.1.6 Adverse events

Adverse events (AEs) were included in the model based on ≥ grade 3 AEs that were experienced by at least 5% of patients in either the MONALEESA-3 (for ribociclib plus fulvestrant) or BOLERO-2 (for everolimus plus exemestane) trials. This approach was used in the original submission and was accepted by the committee. The ERG considers the company's approach to be reasonable and also notes that AEs are not a key driver of the cost effectiveness results.

4.1.7 Health-related quality of life

The company updated utilities in line with the updated EQ-5D data collected in MONALEESA-3. What the company did not mention in their CDF submission was that this entailed using a PFS off treatment utility that was [redacted] the PFS on treatment utility (Table 19). The model used in the committee's decision-making at the point of CDF entry applied a single health-state utility value to PFS.

As a result of the factual inaccuracy check, the company noted that the updated EQ-5D data was taken from the same data cut as the original submission and that the change for the CDF review was related to a change in how that data was analysed. The ERG notes that this change to utilities was not raised during the ToE meeting and represents a significant departure from the approach used in TA593.

This change is important for the company's base case analysis because progression free patients in the comparator arm (everolimus plus exemestane) [redacted] because treatment is assumed to be given until progression.

The ERG consulted with its clinical experts to ascertain if discontinuing treatment during PFS could have a positive impact on a patient's quality of life. The ERG's clinical experts unanimously agreed that patients would have a better quality of life once they discontinue everolimus because everolimus is highly intolerable and toxic. The ERG's clinical experts also reported that they did not expect patients to have a better quality of life when they discontinue ribociclib or fulvestrant because both of these drugs are well tolerated. As such, the ERG's clinical experts disagreed with some of the company's assumptions regarding TTD. These concerns are discussed further in Section 4.1.5.3.

Table 19. HSUVs applied in the model

HSUV	Original submission	CDF submission
PFS on treatment	[redacted]	[redacted]
PFS off treatment	[redacted]	[redacted]
PPS	[redacted]	[redacted]

Abbreviations: CDF, cancer drugs fund; HSUV, health state utility value; PFS, progression free survival; PPS, post-progression survival

*Taken from the model, only PFS on treatment and PPS HSUVs reported in the CDF submission

In response to a clarification question, the company provided the results of a scenario analysis using a single HSUV for PFS. As shown in Section 5.1.2, applying a single HSUV of [redacted] to all progression free patients [redacted]. To mitigate the ERG's concerns around assuming everolimus plus exemestane are given until progression (see Section 4.1.5.3), the ERG's preference is to use a single HSUV for PFS. The ERG considers that using utility estimates that depend on when a patient is on or off treatment is only reasonable when TTD is accurately represented for everolimus plus exemestane (i.e. either revised to reflect BOLERO-2 or based on clinical expert opinion). Otherwise, as with drug costs, [redacted] ribociclib plus fulvestrant.

4.1.8 *Resource use and costs*

The company's approach to estimating resource use and costs was largely the same as the approach used in the original submission, which was accepted by the committee. Three key aspects which have now changed include the cost year, the list price of fulvestrant and the formulas used to assign drug monitoring costs. Each of these is described in turn below.

Firstly, the company updated their submission to reflect a 2018/19 cost year (previously a 2016/17 cost year). These costs were either obtained from NHS Reference Costs 2018/2019 or inflated to a 2019 cost year using the consumer price index.[20, 21]

Secondly, in [redacted], fulvestrant is expected to go through loss of exclusivity. For this reason, the company applied a discount of 10% to the list price of fulvestrant and presented results including this discount. However, the future cost of fulvestrant is unknown. Therefore, in agreement with NICE, the ERG presents results using the list price of fulvestrant. Removing this discount increased the company's base case ICER by approximately £15,000.

Finally, the company, "*modified the formulas to remove a bug that inappropriately assigns costs of healthcare resources that should be incurred only upon treatment initiation to be incurred in other cycles beyond treatment initiation, specifically, cycles 2-7*." The ERG notes that these costs include the costs of monitoring patients receiving ribociclib. The ERG disagrees with the intended correction because full blood counts and liver function tests should be completed in cycles 2-7 because this was accepted in the original submission and based on the marketing authorisation for ribociclib (Table 20).[22] Furthermore, the correction implemented by the company added monitoring costs to all cycles and not only to the cycle upon treatment initiation. For these reasons, the ERG removed the company's correction (see Section 6.1).

Table 20. Unit costs for monitoring (adapted from Table 42 of the original submission)

Monitoring resource	Unit cost, 2016/17	Unit cost, 2018/19	Numbers per first cycle	Numbers per subsequent cycles	Total number per patient
Complete blood count	£3.06	£2.79	2	6	8
Liver function tests	£1.13	£1.13	2	6	8

5 Cost effectiveness results

As noted in Section 4.1.8, the company applied a discount of 10% to the list price of fulvestrant throughout the economic analysis to reflect the anticipated price following loss of exclusivity. However, in agreement with NICE, the ERG generated results using the list price of fulvestrant.

5.1.1 Company's cost effectiveness results

The company's updated base case results are given in Table 21.

Table 21. Company's base case results

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ribo, ribociclib

5.1.2 Company's sensitivity analyses

The company conducted a range of one-way sensitivity analyses to assess the impact of varying each parameter individually. The results of these are shown in the tornado plot in Figure 20. Results of key scenario analyses conducted by the company are presented in Table 21.

Figure 20. Results of OWSA, generated by the ERG

Table 22. Results of scenario analysis, generated by the ERG

Scenario Name	ICER (£/QALY)
Base case	[redacted]
Timeframe - 5 years	[redacted]
Timeframe - 10 years	[redacted]
Timeframe - 20 years	[redacted]
EQ-5D-5L utility values	[redacted]
Lloyd et al.[23] PPS utility values	[redacted]
CQ B14. Single health state utility value for PFS	[redacted]
PFS lognormal restricted	[redacted]
PFS lognormal unrestricted	[redacted]
PFS Gen. Gamma restricted	[redacted]
PFS Gen. Gamma unrestricted	[redacted]
PFS log-logistic restricted	[redacted]
PFS log-logistic unrestricted	[redacted]
PFS Gompertz restricted	[redacted]
PFS Gompertz unrestricted	[redacted]
PFS Weibull restricted	[redacted]
PFS Weibull unrestricted	[redacted]
PFS Gen. F restricted	[redacted]

PFS Gen. F unrestricted	[redacted]
CQ B4. PFS RCS Weibull restricted	[redacted]
CQ B4. PFS RCS 3 Log-logistic restricted	[redacted]
CQ B1. PFS RCS 3 Lognormal	[redacted]
PPS exponential	[redacted]
PPS Gen. Gamma	[redacted]
PPS Weibull	[redacted]
Fulvestrant generic - discount 10% (company's base case in the CDF submission)	[redacted]
Fulvestrant generic - discount 20%	[redacted]
Fulvestrant generic - discount 30%	[redacted]
Fulvestrant generic - discount 40%	[redacted]
Fulvestrant generic - discount 50%	[redacted]
Fulvestrant generic - discount 60%	[redacted]
PAIC of MONALEESA-3 vs BOLERO-2	[redacted]
NMA for PFS anchored on fulvestrant PFS	[redacted]
PPS curves estimated with data from BOLERO-2	[redacted]
TTD Ribo Gen. Gamm (U)	[redacted]
TTD Ribo RCS Weibull (U)	[redacted]
TTD Ribo RCS Log-Logistic (U)	[redacted]

TTD Ful Gen. Gamma (U)	[redacted]
TTD Ful RCS Weibull (U)	[redacted]
TTD Ful RCS Log-logistic (U)	[redacted]
CQ B10. TTD Gompertz (U)	[redacted]

Abbreviations: CQ, clarification question; EQ-5D, 5-dimension EuroQoL questionnaire; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PFS, progression-free survival; PH, proportional hazard; PPS, post-progression survival; QALYs, quality-adjusted life years; RCS, restricted cubic spline; TTD, time to treatment discontinuation; U, unrestricted.

The company provided a PSA based on 1,000 samples, to assess the impact of parameter uncertainty when all parameters are varied simultaneously in the economic model. The results of the PSA (generated by the ERG) are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (Figure 21 and Figure 22, respectively) and summarised in Table 23. A limitation of the PSA is that it takes around 2 hours to run. Additionally, small changes in total costs or QALYs can have a relatively large impact on the ICER (because there is a non-significant difference in PFS between the treatments and an equivalency assumption for PPS). As such, the PSA results should be interpreted with caution.

Table 23. PSA results, generated by the ERG

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; ribo, ribociclib

Figure 21. Cost-effectiveness plane, generated by the ERG

Figure 22. CEAC, generated by the ERG

5.1.3 *Model validation and face validity check*

The company provided their updated analyses for the CDF review in a new version of the economic model. This included corrections to general population mortality and treatment initiation costs. The ERG considers the corrections to general population mortality to be appropriate, but the ERG disagrees with the correction to treatment initiation costs (see Section 4.1.8).

In the company's response to clarification, the company noted that if these corrections were added as executable options to the original version of the economic model, "*there would also be a detrimental impact on the performance of the model*." Given that the company provided supporting documents to outline where inputs and formula had been revised, the ERG does not consider this to be a major issue. However, the new version of the economic model is still extremely complex and a PSA of 1,000 samples takes around 2 hours to run.

Finally, the company validated the PFS and TTD extrapolations from MONALEESA-3 with its clinical experts. The ERG is unclear why PPS was not validated as part of this discussion. The ERG is also unclear if the company's assumption that everolimus and exemestane are given until progression has been validated with the company's clinical experts.

6 Additional economic analysis undertaken by the ERG

6.1 Model corrections

As described in Section 4.1.8, the company included a correction so that ribociclib monitoring costs were only incurred in the first treatment cycle. However, the correction implemented by the company added ribociclib monitoring costs to all cycles. Furthermore, the ERG disagrees with the intended correction because ribociclib monitoring costs should be incurred up to cycle 7 because this was accepted in the original submission and based on the ribociclib licence.

The company's correction made changes to cells GV11:HL534 of the MedCalc worksheet. Due to time constraints, the ERG made changes to cells HD18:534 which are the cells specific to ribociclib. The ERG considers that both approaches will provide the same result (Table 24).

Table 24. Company's corrected base case results

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ribo, ribociclib

6.2 Exploratory and sensitivity analyses undertaken by the ERG

The company was asked to perform a number of scenarios during the clarification stage. These included alternative progression free survival (PFS) and time to treatment discontinuation (TTD) curves, and one single health state utility value (HSUV) for PFS, which the company provided (see Table 22 in Section 5.1.2). However, the ERG's requests to use alternative assumptions to model TTD for everolimus plus exemestane were not provided by the company (see Section 4.1.5.3). The ERG considers that this still warrants further exploration as TTD is a key model driver. Following the clarification stage, the ERG also considered alternative approaches to model estimates from the population adjusted indirect comparison (PAIC) for post-progression survival (PPS) (see Section 4.1.5.2). The results of the ERG's scenario analysis are given in Section 6.3.

6.3 ERG scenario analysis

Results of the ERG's scenario analysis are given in Table 25.

Table 25. Results of the ERG's scenario analyses

	Results per patient	Intervention	Comparator	Incremental value
0	Company's corrected base case			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
1	At month 6, 20% of patients discontinue everolimus			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
2	At month 6, 70% of patients on everolimus dose reduce from 10 mg daily to 5 mg daily			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
3	At month 6, 20% of patients discontinue everolimus and 70% of those 80% who continue dose reduce from 10 mg daily to 5 mg daily			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]
4	PPS HR derived by the PAIC included in the model			
	Total costs	[redacted]	[redacted]	[redacted]
	QALYs	[redacted]	[redacted]	[redacted]
	ICER (£/QALY)	-	-	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; HR, hazard ratio; PAIC, population adjusted indirect comparison; PFS, progression free survival; PPS, post-progression survival; QALY, quality adjusted life year

6.4 ERG preferred assumptions

One of the key uncertainties made apparent to the ERG during the Caner Drugs Fund (CDF) review was the company's assumption that everolimus is given until progression. In the absence of

individual patient level data (IPD) TTD data from BOLERO-2, the ERG's preferred assumption to model TTD for everolimus is based on clinical expert opinion. This assumption consists of a proportion of patients who discontinue everolimus at month 6 and a proportion of patents who dose reduce from 10 mg daily to 5 mg daily at month 6. The ERG considers that the company has more robust ways to assess this uncertainty using the IPD TTD data from BOLERO-2. As such, the ERG's analysis should be interpreted as an exploratory analysis.

The ERG also disagrees with the company's chosen curve fitted to TTD from MONALEESA-3 (for ribociclib and fulvestrant in the treatment arm). The ERG considers a more appropriate method would be to choose the best fitting curve for TTD and cap the extrapolation by the PFS curve to prevent the potentially implausible treatment beyond progression.

The ERG's preferred assumptions and cumulative incremental cost-effectiveness ratios (ICERs) are given in Table 26. The ERG's base case results are given in more detail in Table 27. To account for the upcoming loss of exclusivity for fulvestrant, results using the ERG's preferred assumptions are given in Table 28 using different discounts on the list price of fulvestrant.

Table 26. Cumulative results using the ERG's preferred model assumptions

Preferred assumption	Section in ERG report	Cumulative ICER (£/QALY)
Company base case	-	[redacted]
Company corrected base case	4.1.8	[redacted]
Gompertz (U) extrapolation of TTD for ribociclib and fulvestrant	4.1.5.3	[redacted]
At month 6, 20% of patients discontinue everolimus and 70% of those 80% who continue dose reduce from 10 mg daily to 5 mg daily	4.1.5.3	[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year; TTD, time to treatment discontinuation; (U), unrestricted

Table 27. ERG's deterministic base case ICER

Interventions	Total Costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ribo, ribociclib

Table 28. Results using the ERG's preferred model assumptions and different discounts on the list price of fulvestrant

Discount on the list price of fulvestrant	ICER (£/QALY)
0% (ERG's base case)	[redacted]
10%	[redacted]
20%	[redacted]
30%	[redacted]
40%	[redacted]
50%	[redacted]
60%	[redacted]
70%	[redacted]

Abbreviations: ERG, evidence review group; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life year

Like the company's probabilistic sensitivity analysis (PSA), the ERG notes that small changes in total costs or quality-adjusted life years (QALYs) can have a relatively large impact on the probabilistic ICER. Additionally, a limitation of the PSA is that it takes round 2 hours to run and, due to paucity of time, a wide range of PSA of ICERs cannot be presented. As such, the ERG does not see the value in presenting a PSA result using its preferred assumptions.

6.5 Conclusions of the cost effectiveness sections

One of the key uncertainties expected to be resolved during the time ribociclib was in the CDF was PPS and overall survival (OS). While the company has provided an update to PPS and OS from MONALEESA-3, PPS has been used to inform the economic analysis. Due to time constraints it was not possible to for the company to use the OS data directly in the model as this would require the model to be restructured to use a partitioned survival approach. Instead, the company demonstrated that the projected gain in OS for ribociclib plus fulvestrant compared with everolimus plus exemestane based on the semi-Markov model is conservative relative to that which would be obtained using a partitioned survival model (PSM). Although this is one step closer to resolving the uncertainties relating to OS, the conclusions are speculative without access to a PSM.

The ERG also considers it important to highlight that the company is assuming a "full surrogacy" approach in the semi-Markov model; i.e. any gains in PFS would directly translate into an OS gain as

PPS is assumed to be the same. A PSM would directly inform if the full surrogacy assumption is true or whether in fact there is just partial surrogacy. This is important because the non-significant benefit of the PFS HR ([redacted]) is still generating [redacted] additional life years (LYs) for ribociclib plus fulvestrant. These benefits would be much more transparent in a PSM as the company wouldn't have to make a surrogacy assumption.

However, the ERG acknowledges that a PSM may not help to resolve all uncertainties relating to OS because the OS data from MONALEESA-3 are still considered relatively immature.

Considering the semi-Markov model, the ERG has no major issues with the company's approach to model PFS and PPS. The ERG also considers that the company has taken conservative approaches to model PFS and PPS in the base case as alternative ITCs produced more favourable estimates for ribociclib plus fulvestrant compared with everolimus plus exemestane. The ERG's clinical experts were also of the opinion that ribociclib plus fulvestrant is non-inferior to everolimus plus exemestane.

Differences in TTD are key drivers in the ICER and one of the key uncertainties made apparent to the ERG during the CDF review was the company's assumption that everolimus is given until progression. During the clarification stage, the company was asked to address this uncertainty by exploring scenarios based on the IPD TTD from BOLERO-2 and clinical expert opinion obtained from the ERG. However, the company could not provide these scenarios due to time constraints. As such, the ERG ran scenario analysis around the TTD estimates for everolimus, based on clinical expert opinion. In each of these scenarios, the ICER was above [redacted]. However, the ERG considers it important to reiterate that these are exploratory analysis to demonstrate what the impact on the ICER could be based on the available data to the ERG. The ERG considers that the company has more robust ways to assess this uncertainty using the IPD TTD data from BOLERO-2.

The ERG also notes that differences in TTD are important due to the company's revised utility estimates. The model used in the committee's decision-making at the point of CDF entry applied a single HSUV to PFS. For the CDF review, the company applied a PFS off treatment utility [redacted] the PFS on treatment utility. This change is important for the company's base case analysis because progression free patients on everolimus plus exemestane always incur the [redacted] because these treatments are assumed to be given until progression. The ERG considers that using utility estimates that depend on when a patient is on or off treatment is only

reasonable when TTD is accurately represented for everolimus plus exemestane (i.e. either revised to reflect BOLERO-2 or based on clinical expert opinion). Otherwise, as with drug costs, [redacted] ribociclib plus fulvestrant.

Another concern of the ERG's is the company's parametric survival distribution fitted to TTD from MONALEESA-3 (for ribociclib and fulvestrant in the treatment arm). The ERG considers a more appropriate method would be to choose the best fitting curve for TTD and cap the extrapolation by the PFS curve to prevent the potentially implausible treatment beyond progression.

Finally, in [redacted], fulvestrant is expected to go through loss of exclusivity and the ICER is highly variable to the discount on the list price of fulvestrant.

7 End of Life

The company has not made a case for ribociclib plus fulvestrant meeting the end of life criteria and the ERG agrees with this assessment.

8 References

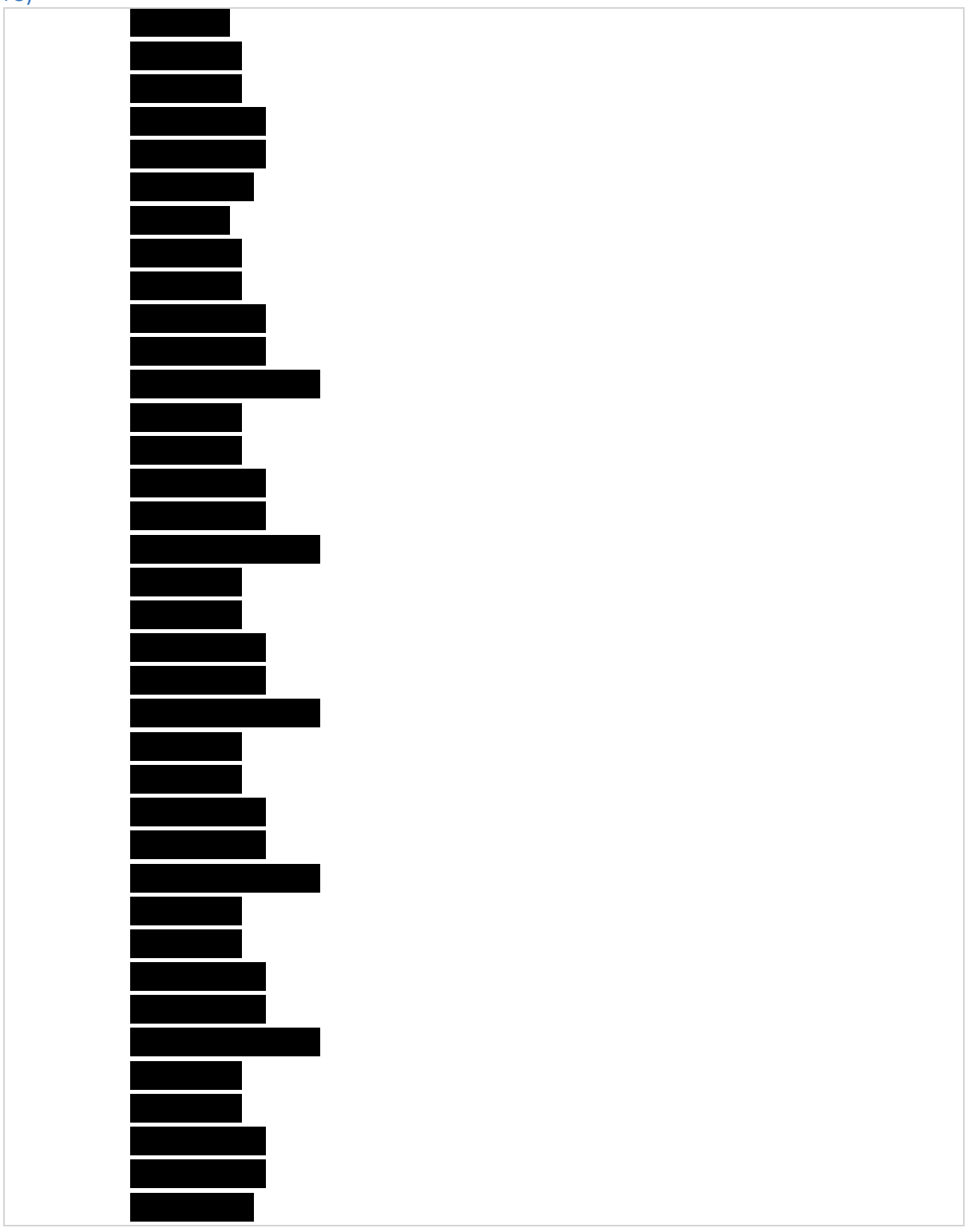
1. Novartis. Clinical Study Report LEE011F2301 (MONALEESA-3), 25 April 2018.
2. Cancer Research UK. TNM breast cancer staging. 2017. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/tnm-staging. (Accessed 17 July 2018).
3. Cancer Research UK. Number stages of breast cancer. 2017. Available from: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/number-stages. (Accessed 17 July 2017).
4. Howlader N, Altekruse SF, Li CI, Chen VW, Clarke CA, Ries LA, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst. 2014;106(5).
5. Vidula N, Rugo HS. Cyclin-Dependent Kinase 4/6 Inhibitors for the treatment of breast cancer: a review of preclinical and clinical data. Clinical breast cancer. 2016;16(1):8–17.
6. O'Sullivan CC. Overcoming Endocrine Resistance in Hormone-Receptor Positive Advanced Breast Cancer-The Emerging Role of CDK4/6 Inhibitors. Int J Cancer Clin Res. 2015;2(4).
7. F. Cardoso SP-S ES, G. Curigliano, M.S. Aapro, F. André, C.H., Barrios JB, G.S. Bhattacharyya, L. Biganzoli, F. Boyle, M.-J. Cardoso, L.A., Carey JC, N.S. El Saghir, M. Elzayat, A. Eniu, L. Fallowfield, P.A. Francis,, K. Gelmon JG, R. Haidinger, N. Harbeck, X. Hu, B. Kaufman, R. Kaur,, B.E. Kiely S-BK, N.U. Lin, S.A. Mertz, S. Neciosup, B.V. Offersen, S. Ohno,, O. Pagani AP, F. Penault-Llorca, H.S. Rugo, G.W. Sledge, C. Thomssen, D.A., et al. . 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol; 2020.
8. National Institute for Health and Care Excellence (NICE). Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer: technology appraisal guidance [TA593] 2019.
9. Carlson RW. The history and mechanism of action of fulvestrant. Clinical breast cancer. 2005;6 Suppl 1:S5-8.
10. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im S-A, et al. Overall Survival with Ribociclib plus Fulvestrant in Advanced Breast Cancer. New England Journal of Medicine. 2019;382(6):514-24.
11. Public Health England. Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer – data review. 2020.
12. Chia Y, Ma C. Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFECT: Chia S, Gradishar W, Mauriac L, et al (Univ of British Columbia, Vancouver, Canada) J Clin Oncol 26: 1664-1670, 2008 §. Breast Diseases: a YB Quarterly. 2009;20(1):94-5.
13. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(30):4594-600.
14. Johnston SR, Kilburn LS, Ellis P, Dodwell D, Cameron D, Hayward L, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol. 2013;14(10):989–98.
15. Yardley DA, Noguchi S, Pritchard KI, Burris HA, 3rd, Baselga J, Gnant M, et al. Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther. 2013;30(10):870-84.

16. National Institute of Health and Care Excellence. NICE DSU TECHNICAL SUPPORT DOCUMENT 18: METHODS FOR POPULATION-ADJUSTED INDIRECT COMPARISONS IN SUBMISSIONS TO NICE. Available at, http://nicedsu.org.uk/wp-content/uploads/2018/08/Population-adjustment-TSD-FINAL-ref-rerun.pdf (accessed 21/9/20). Note: code adapted from appendix: http://nicedsu.org.uk/wp-content/uploads/2017/05/TSD18-Appendix-D-Worked-example-of-MAIC-and-STC.pdf 2016.
17. Jerusalem G, de Boer RH, Hurvitz S, Yardley DA, Kovalenko E, Ejlertsen B, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor–Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. JAMA Oncology. 2018;4(10):1367-74.
18. (ScHARR). DSU. Ribociclib in combination with an aromatose inhibitor for previously untreated advanced or metastatic hormone receptor-positve, HER-negative breast cancer: a review of the model structure, inputs and assumptions, August 20172017 Oct 2020. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/11/Aug-2017-Ribociclib-DSU-Report.pdf.
19. Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press2020 Oct 2020. Available from: https://bnf.nice.org.uk/drug/everolimus.html#indicationsAndDoses.
20. Curtis LB, A. Unit Costs of Health and Social Care 20192019 Oct 2020. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/.
21. Improvement N. National Cost Collection: National Schedule of NHS costs - Year 2018-19 - NHS trust and NHS foundation trusts2020 Oct 2020. Available from: https://www.england.nhs.uk/national-cost-collection/.
22. European Medicines Agency. Kisqali Summary of Product Characteristics. March 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kisqali. (Accessed 12 June 2020).
23. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683–90.

9 Appendices

9.1 Matched covariates in the population-adjusted indirect comparisons

Table 29. Matched covariates in the PAICs (reproduced from company submission appendices, Table F3)



[redacted]

9.2 Company's cost-effectiveness results from the point of CDF entry

Table 30. Company's results from the point of CDF entry to the CDF submission, list price for fulvestrant

Interventions	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Final base case results from TA593, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Final base case results from TA593, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* excluding corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* excluding corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* including corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated clinical data from MONALEESA-3* including corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's updated base case results† excluding corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Company's updated base case results† including corrections, [redacted] PAS for ribociclib 600 mg							
Eve+exe	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribo+ful	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: eve, everolimus; exe, exemestane; ful, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALYs, quality-adjusted life years; ribo, ribociclib

* based on the same specification as the final base case results but updated the clinical data as per the 3 June 2019 cut-off. No other inputs were changed, including parameterisation of the curves (i.e. the functional form of PPS, PPS etc were as specified in the model at time of CDF entry)

†includes reassessing the functional forms of the best fitting curves, based on the updated data (along with cost updates, etc.)