NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer [ID3755]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer [ID3755]

Contents:

The following documents are made available to consultees and commentators:

The **final scope and final stakeholder list** are available on the NICE website. This is a review of TA593.

1. **Company submission** from **Novartis**
2. **Company response to NICE's request for clarification**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Now
4. **Evidence Review Group report** prepared by **BMJ Group**
5. **Evidence Review Group – factual accuracy check**
6. **Public Health England Study Report**
7. **Technical engagement response** from **Novartis**
   a. Technical engagement response from company
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8. **Technical engagement responses from experts:**
   a. Holly Heath, Policy Manager at Breast Cancer Now – patient expert, nominated by Breast Cancer Now
9. **Evidence Review Group critique of company response to technical engagement** prepared by **BMJ Group**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cancer Drugs Fund Review of TA593

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (ID3755)

Company evidence submission for committee

September 2020

File name	Version	Contains confidential information	Date
ID3755	Final	Yes	24th September 2020

Contents

Tables and figures

List of Abbreviations

AE, adverse event
AIC, akaike information criterion
B2, BOLERO-2
BIC, bayesian information criterion
CDF, Cancer Drugs Fund
CDK4/6, cyclin-dependent kinase 4 and 6
CI, confidence interval
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
ICER, incremental cost-effectiveness ratio
ITC, indirect treatment comparison
ITT, intention to treat
KM, Kaplan-Meier
LHRH, luteinizing hormone-releasing hormone
LYG, life years gained
M3, MONALEESA-3
MAPK, mitogen-activated protein kinase
mTOR, mammalian target of rapamycin
NE, not evaluable
NHS, National Health Service
NICE, National Institute for Health and Care Excellence
NMA, network meta-analysis
OS, overall survival
PAIC, population-adjusted indirect comparison
PAS, patient access scheme
PD, progressive disease
PgR, progesterone receptor
PFS, progression-free survival
PFS2, progression-free survival after next line of therapy
RMST, restricted mean survival times
QALY, quality-adjusted life years
Rb, retinoblastoma
RCS, restricted cubic spline.
RCT, randomized controlled trial
RDI, relative dose intensity
SACT, Systemic Anti-Cancer Treatment

SERD, selective oestrogen receptor degrader
SLR, systematic literature review
TTP, time to treatment progression
WTP, willingness to pay

Cancer Drugs Fund review submission

A.1 Background

Ribociclib in combination with fulvestrant is currently recommended under the Cancer Drugs Fund (CDF; TA593[1]) for the treatment of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–), locally advanced or metastatic breast cancer in patients who have received previous endocrine therapy if: (1) exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor, and (2) the conditions in the managed access agreement for ribociclib with fulvestrant are followed. The managed access agreement informing TA593 consisted of i) a patient access scheme (PAS) in the form of a simple discount on the list price of ribociclib ([redacted]), and ii) an additional [redacted] discount on the list price of ribociclib via a confidential commercial access arrangement.[1,2] An overall discount of [redacted] was considered by the committee for the CDF recommendation only, which resulted in an incremental cost-effectiveness ratio (ICER) below the threshold of £30 000 per quality-adjusted life year (QALY) gained.[2]

As part of the CDF recommendation, the Appraisal Committee highlighted some uncertainties in the clinical data, detailed in Table 1, which are addressed in this review.

A.2 Key committee assumptions

The assumptions preferred by the Appraisal Committee addressed in this review are summarised in Table 1.

Table 1. Key committee assumptions.

Area	Committee preferred assumptions
Population	Women with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with fulvestrant who have received previous endocrine therapy. This population is covered by subpopulation B of the MONALEESA-3 RCT (as per CDF entry [TA593][1], see Figure 2) and is the relevant population for the CDF review.
Comparator	The CDF review should only include a comparison with exemestane plus everolimus.
NMA	The company should update the NMA and should explore the most appropriate trials and methods to compare PFS and OS across treatments.
Time to treatment discontinuation	The company should update the time-on-treatment data and, unless the new data suggest otherwise, use the ERG's unrestricted model approach.
ECG costs	The committee agreed that resting ECG costs should be used.
Post-progression survival assumption	The company should explore the most appropriate approach for estimating and extrapolating post-progression survival.
Most plausible ICER	The Committee concluded that the company's revised base case included its preferred assumptions as stated in the appraisal consultation document, and considered that the most plausible ICER was £21,068. The committee noted that there remained a high level of uncertainty in the clinical evidence and that the ICERs were based on small incremental gains, and are therefore highly sensitive to change. The direction of the effect of the uncertainty on cost-effectiveness results is unknown.
End of life	Ribociclib plus fulvestrant does not meet the end-of-life criteria.

CDF, Cancer Drugs Fund; ECG, electrocardiogram; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.
Source: Terms of engagement of CDF review (TA593).[2]

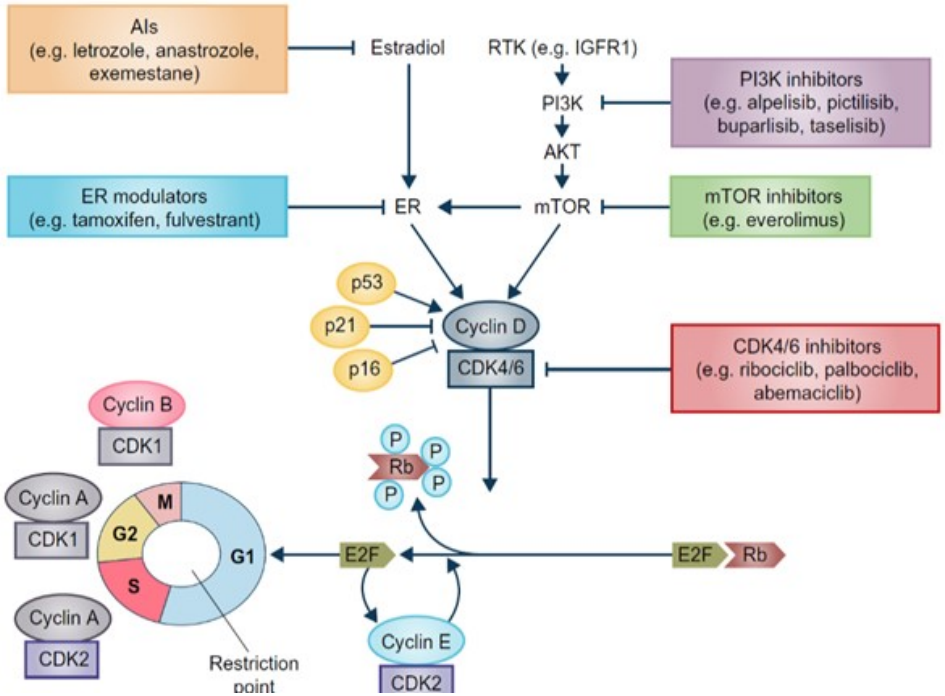
A.3 Other agreed changes

It was agreed that requested changes to the model that impact other assumptions may be updated, but should be explicitly highlighted to NICE and the committee. These include some model corrections, in response to Committee comments during TA593 (see Section A.8.1.4 and Table 16 for full details).[2]

A.4 The technology

An overview of the technology (ribociclib in combination with fulvestrant) under review is summarised in Table 2.

Table 2. Technology being reviewed.

UK approved name and brand name	UK approved name: Ribociclib Brand name: Kisqali®
Mechanism of action	Ribociclib is a selective inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6).[3-5] CDK4/6 are members of a family of enzymes involved in regulation of the G1–S phase of the cell cycle.[3] Imbalance of the cyclin D–CDK pathway is known to be associated with a proliferative phenotype in cancer cells.[4] Figure 1 shows the mechanism of action of ribociclib and other relevant treatments. **Figure 1. Regulation of cell-cycle progression through the CDK4/6 pathway.** 

	CDK, cyclin-dependent kinase; E2F, elongation factor 2; ER, endocrine receptor; HER2, human epidermal growth factor receptor-2; IGF1R, insulin-like growth factor 1 receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; Rb, retinoblastoma; RTK, receptor tyrosine kinase. Tripathy *et al.*, 2017.[6] By preventing interaction between CDK4/6 and cyclin D, ribociclib inhibits the phosphorylation and inactivation of the retinoblastoma (Rb) tumour suppressor protein. Consequently, progression from the G1 to the S phase of the cell cycle does not occur, and cells become quiescent.[4] Ribociclib's mechanism of action may be particularly important in hormone receptor-positive (HR+) breast cancer, in which responsiveness and resistance to endocrine therapies is understood to be linked to CDK/cyclin D/Rb activity. CDK4/6 inhibition has been shown to block cell cycle progression in endocrine-resistant breast cancer cells.[7] Fulvestrant is a selective oestrogen receptor degrader (SERD) that acts by targeting and blocking endocrine receptors in tumour cells.[8] The combined use of ribociclib with fulvestrant therefore employs the dual approach of inhibiting cellular proliferation[9] and reducing oestrogen signalling.[8]
Marketing authorisation/CE mark status	The EMA marketing authorisation for ribociclib covers the following indications:[10] • Ribociclib is indicated for the treatment of women with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based, or in women who have received prior endocrine therapy. • In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.
Indications and any restriction(s) as described in the summary of product characteristics	Ribociclib is indicated for the treatment of women with hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based, or in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.[10]
Method of administration and dosage	Ribociclib is administered orally. The recommended regimen is 600 mg, once daily for 21 consecutive days, followed by 7 days off treatment (28-day cycle) in combination with fulvestrant 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter.
Additional tests or investigations	Regular blood tests are required before and during treatment with ribociclib to monitor liver function, blood cell (red, white and platelets) count and electrolyte levels. Cardiac monitoring via electrocardiogram is required before and during treatment with ribociclib.[10] No additional testing is associated with fulvestrant.

<table>
<tr><td>List price and average cost of a course of treatment</td><td>The list prices per pack for ribociclib are reported below:[11]

<table><tr><th>Drug</th><th>Pack size (200 mg tablets)</th><th>List price, £</th></tr><tr><td>Ribociclib 600 mg</td><td>63</td><td>2950.00</td></tr><tr><td>Ribociclib 400 mg</td><td>42</td><td>1966.67</td></tr><tr><td>Ribociclib 200 mg</td><td>21</td><td>983.33</td></tr></table>
The list price for fulvestrant is £522.41 for 2 x 5 ml (250 mg) prefilled syringes. Fulvestrant requires an additional loading dose of 500 mg on day 15 of the first cycle, resulting in a cost of £1044.82 for month 1, and a monthly cost of £522.41 from month 2.[12,13]
Patients should be treated until disease progression, unless there is unacceptable toxicity. The median duration of treatment with ribociclib plus fulvestrant in the overall MONALEESA-3 study population (the pivotal clinical trial for ribociclib plus fulvestrant in this indication) was [redacted] months with ribociclib plus fulvestrant and [redacted] months with placebo plus fulvestrant.[14]
The mean number of packs of ribociclib and fulvestrant received during the MONALEESA-3 study was [redacted] and [redacted], respectively (calculation based upon mean study treatment exposure at a treatment cycle length of 28 days). Based upon these values, the average cost of a course of treatment with ribociclib 600 mg plus fulvestrant at full list price is [redacted][a]</td></tr>
<tr><td>Commercial arrangement (if applicable)</td><td>A confidential simple patient access scheme (PAS) exists for ribociclib, which enables the NHS to procure ribociclib at net prices lower than the list price. Ribociclib is provided to the NHS with a [redacted] discount off the current list price. As such, the confidential PAS net price for ribociclib are reported below.
<table><tr><th>Drug</th><th>Pack size (200 mg tablets)</th><th>List price with PAS applied, £</th></tr><tr><td>Ribociclib 600mg</td><td>63</td><td>[redacted]</td></tr><tr><td>Ribociclib 400mg</td><td>42</td><td>[redacted]</td></tr><tr><td>Ribociclib 200mg</td><td>21</td><td>[redacted]</td></tr></table></td></tr>
<tr><td>Date technology was recommended for use in the CDF</td><td>July, 2019[1]</td></tr>
<tr><td>Data collection end date</td><td>January, 2020[14]</td></tr>
</table>

[a] When 10% fulvestrant discount is applied (see Table 16)
CDF, cancer drugs fund; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LHRH, luteinising hormone-releasing hormone; PAS, patient access scheme; SERD, selective oestrogen receptor degrader; Rb, retinoblastoma.

A.5 Clinical effectiveness evidence

The evidence supporting this review is derived from an updated data cut (3 June 2019)[15] from the international phase 3, multicentre, randomised, double-blind, placebo-controlled MONALEESA-3 trial[14] that provided the evidence base for NICE appraisal TA593[1] (data cut: 3 November 2017), and the extension to the EMA label (Table 3).[10] Data on ribociclib plus fulvestrant use within NHS England as part of the Systemic Anti-Cancer Therapy (SACT) data collection are also presented (Table 4).

The ITT population of MONALEESA-3 comprised two subpopulations as summarised in Figure 2.[15,16] The population covered under TA593,[1] as well as considered relevant by the committee[2] is **subpopulation B**, i.e. patients who experienced an early relapse or receiving second-line treatment for $HR^+/HER2^-$ locally advanced or metastatic breast cancer.

Figure 2. MONALEESA-3 population assessed within this submission

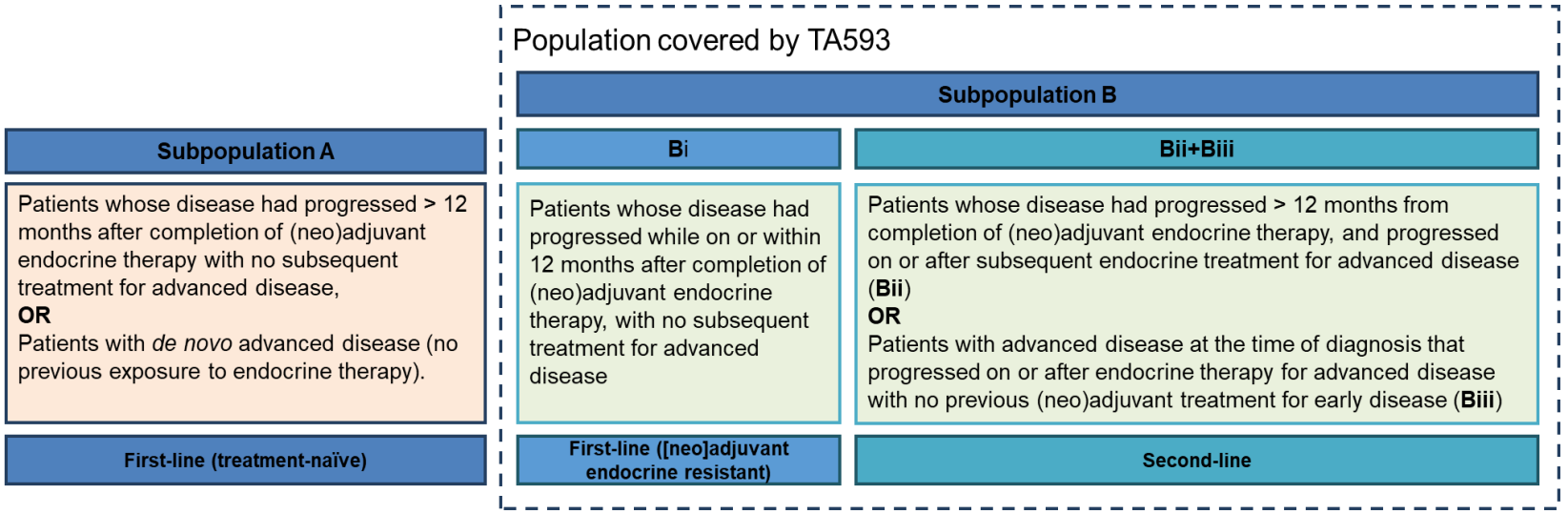


Table 3. Primary source of clinical effectiveness evidence (used in model)

Study title	**Slamon *et al*, 2020[14]**
Study design	Phase 3, multicentre, randomised (2:1), double-blind, placebo-controlled study
Population	Post-menopausal women and men with histologically and/or cytologically confirmed $HR^+/HER2^-$ advanced breast cancer.
Intervention(s)	Ribociclib plus fulvestrant
Comparator(s)	Placebo plus fulvestrant
Outcomes collected that address committee's key uncertainties	OS, PFS, TTD/time to chemotherapy and safety
Reference to section in appendix	Section A.6 and Appendix E

CDK4/6, cyclin-dependent kinase 4/6; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.

Table 4. Secondary source of clinical effectiveness evidence (not modelled)

Study title	**SACT data cohort study[17]**
Study design	SACT data cohort study
Population	Patients with HR+/HER2–, locally advanced or metastatic breast cancer who have had previous endocrine therapy and for whom exemestane plus everolimus is the most appropriate alternative to CDK4/6 inhibitors.
Intervention(s)	Ribociclib plus fulvestrant
Comparator(s)	Not applicable
Outcomes collected that address committee's key uncertainties	Treatment utilisation
Reference to section in appendix	SACT data report for TA593[18]

CDK4/6, cyclin-dependent kinase 4/6; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival; SACT, Systemic Anti-Cancer Therapy.

A.6 Key results of the data collection

The evidence base for this review is provided by the final analysis of the MONALEESA-3 trial (3 June 2019 data cut) where the median duration of follow up for all patients was 39.4 months. This data cut provides an additional 19.0 months of follow up compared to the first interim OS analysis which was considered in the initial appraisal.[14,19] Median treatment duration was 15.8 months in ribociclib + fulvestrant arm, 12.0 months in placebo + fulvestrant arm. Key outcomes from the final analysis of MONALEESA-3 are summarised in Table 5.

Table 5. Summary of the final analysis of MONALEESA-3 (3 June 2019 data cut-off).

Endpoint	ITT population[a]		Subpopulation B[b]	
	Events, n (%)	Ribociclib plus fulvestrant vs fulvestrant (months)	Events, n (%)	Ribociclib plus fulvestrant vs fulvestrant (months)
Investigator assessed PFS, months (95% CI)	283 (58.5) vs 193 (79.8)	20.6 (95%CI, 18.5–23.5) vs 12.8 (95%CI, 10.9–16.3) HR, 0.59 (95% CI, 0.48–0.73)	167 (70.5) vs 95 (87.2)	14.6 (95%CI, 12.5–18.5) vs 9.1 (95%CI, 6.1–11.1) HR, 0.57 (95% CI, 0.43–0.74)
OS, months (95% CI)	167 (34.5) vs 108 (44.6)	Not reached (NE–NE) vs 40.0 (37.0–NE) HR, 0.72 (95% CI, 0.57–0.92); *p* = 0.00455	102 (43.0) vs 60 (55.0)	40.2 (37.4–NE) vs 32.5 (27.8–40.0) HR, 0.73 (95% CI, 0.53–1.00)

[a] Randomisation 2:1 (N = 726), ribociclib + fulvestrant (N =484) and placebo + fulvestrant (N = 242).
[b] ribociclib + fulvestrant (N =237) and placebo + fulvestrant (N = 109).
CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival; PFS, progression-free survival.

No new safety concerns were highlighted in the extended follow up period of MONALEESA-3, nor in the Systemic Anti-Cancer Treatment (SACT) data, which was based on the real-world usage of ribociclib plus fulvestrant between 17 July 2019 and 16 January 2020. Neutropenia is a known safety concern of CDK4/6 inhibitors including ribociclib and palbociclib.[1,20,21] Although not

necessarily symptomatic, neutropenia may lead to dose interruptions and discontinuations,[20] and patients receiving ribociclib receive additional monitoring in line with its marketing authorisation.[10]

It is widely recognised that CDK4/6 inhibitors differ in terms of their safety profiles.[1,20,22] While ribociclib and palbociclib are associated with neutropenia (grade 3–4; ribociclib + fulvestrant, 57%;[14] palbociclib + fulvestrant, 65%;[23] abemaciclib + fulvestrant, 23.6%[22]), abemaciclib has an increased incidence of diarrhoea (grade 3–4; ribociclib + fulvestrant, 0.6%;[15] palbociclib + fulvestrant, 0;[23] abemaciclib + fulvestrant, 13.4%[22]), and the combination of everolimus and exemestane is also associated with significant toxicity.[1,20,22]

Given the differences in safety profiles, clinical and patient opinion consistently raises the importance and value of a range treatment options: the choice of CDK4/6 inhibitor used in clinical practice can be based upon the ability of the patient to tolerate treatment.[1,20,22]

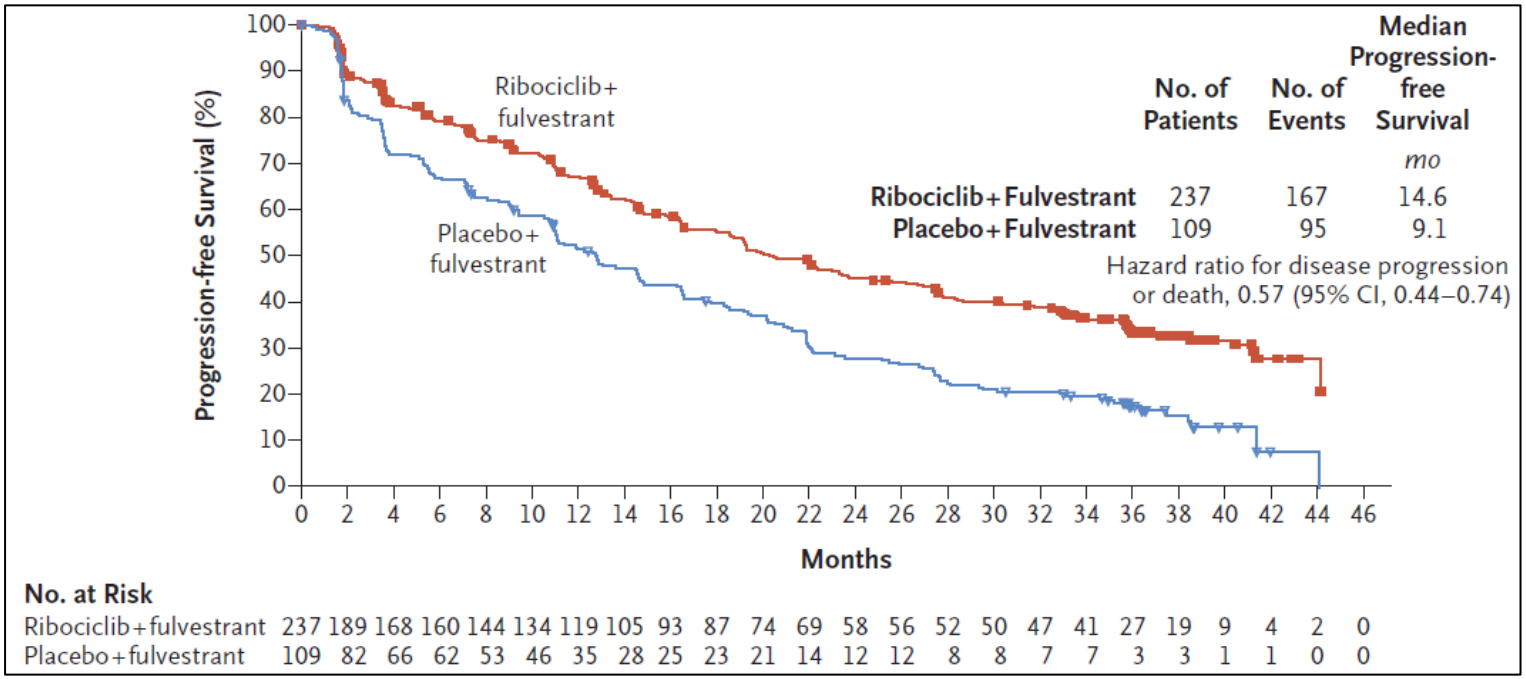
A.6.1 *Progression-free survival (primary endpoint)*

The update (data cut-off: 3 June 2019) of investigator assessed PFS (progression or death, whichever came first) in the ITT population was consistent with that of the primary analysis. A total of 283 PFS events in 484 patients (58.5%) had occurred in the ribociclib + fulvestrant arm and 193 PFS events in 242 patients (79.8%) in the placebo + fulvestrant arm (Table 5). Ribociclib + fulvestrant was associated with a 7.8-month PFS benefit compared with placebo + fulvestrant (median, 20.6 months [95%CI, 18.5–23.5] vs 12.8 months [95%CI, 10.9–16.3]). This equated to 41% reduction in risk of progression or death (HR, 0.59 [95% CI, 0.48–0.73]).[19]

In **subpopulation B** (patients with early relapse or receiving second-line treatment), a total of 167 PFS events in 237 patients (70.5%) had occurred in the ribociclib + fulvestrant arm and 95 events in 109 patients (87.2%) in the placebo + fulvestrant arm (84% data maturity). Ribociclib + fulvestrant was associated with a 5.5-month PFS benefit compared with placebo + fulvestrant

(median PFS, 14.6 [95%CI, 12.5–18.5] months vs 9.1 [95% CI, 6.1–11.1] months; Figure 3). This equated to a 43% reduction in risk of progression or death (HR, 0.57 [95% CI, 0.43–0.74]).[14,19]

Figure 3. Kaplan–Meier plot of investigator-assessed PFS for subpopulation B (data cut 3 June 2019)



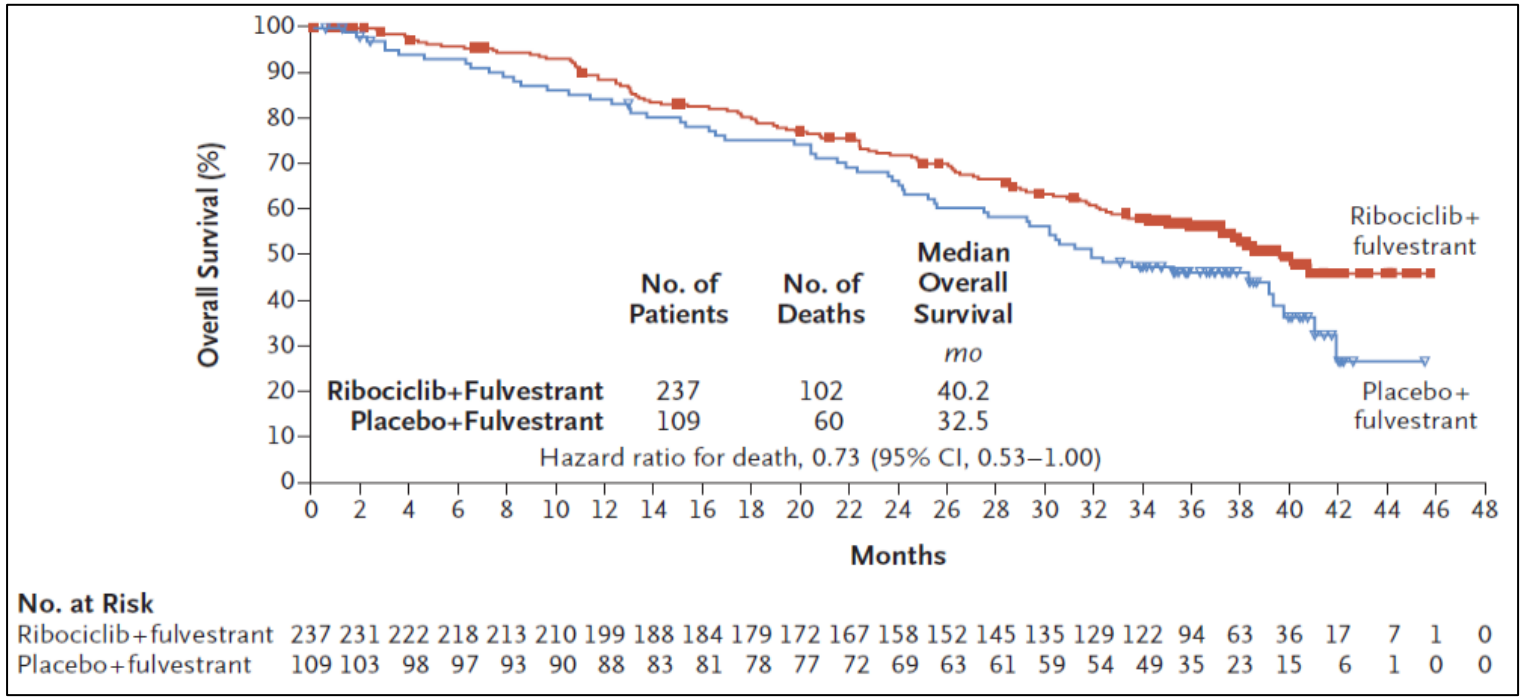
CI, confidence interval; PFS, progression-free survival.
Source: Slamon *et al*, 2019.[14]

A.6.2 *Overall survival (secondary endpoint)*

At the 3 June 2019 data cut off (second pre-specified analysis), a total of 275 deaths had occurred in the ITT population (ribociclib + fulvestrant, 167 deaths in 484 patients [34.5%]; placebo + fulvestrant, 108 deaths in 242 patients [44.6%]) (Table 5). The one-sided stratified log-rank test *p* value (0.00455) crossed the prespecified O'Brien-Fleming stopping boundary to claim superior efficacy.[14,19]

In **subpopulation B**, 102 deaths in 237 patients (43.0%) occurred in the ribociclib + fulvestrant arm and 60 deaths in 109 patients (55.0%) in the placebo + fulvestrant arm. Ribociclib + fulvestrant was associated with a 7.7-month OS benefit compared with placebo + fulvestrant (median OS, 40.2 months [95% CI, 37.4–not estimable (NE)] vs 32.5 months [95% CI, 27.8–40.0]; Figure 4). This equated to a 27% reduction in risk of death (HR, 0.73 [95% CI, 0.53–1.00]; Figure 4).[14,19]

Figure 4. Kaplan–Meier plot of investigator-assessed OS for subpopulation B (data cut 3 June 2019)



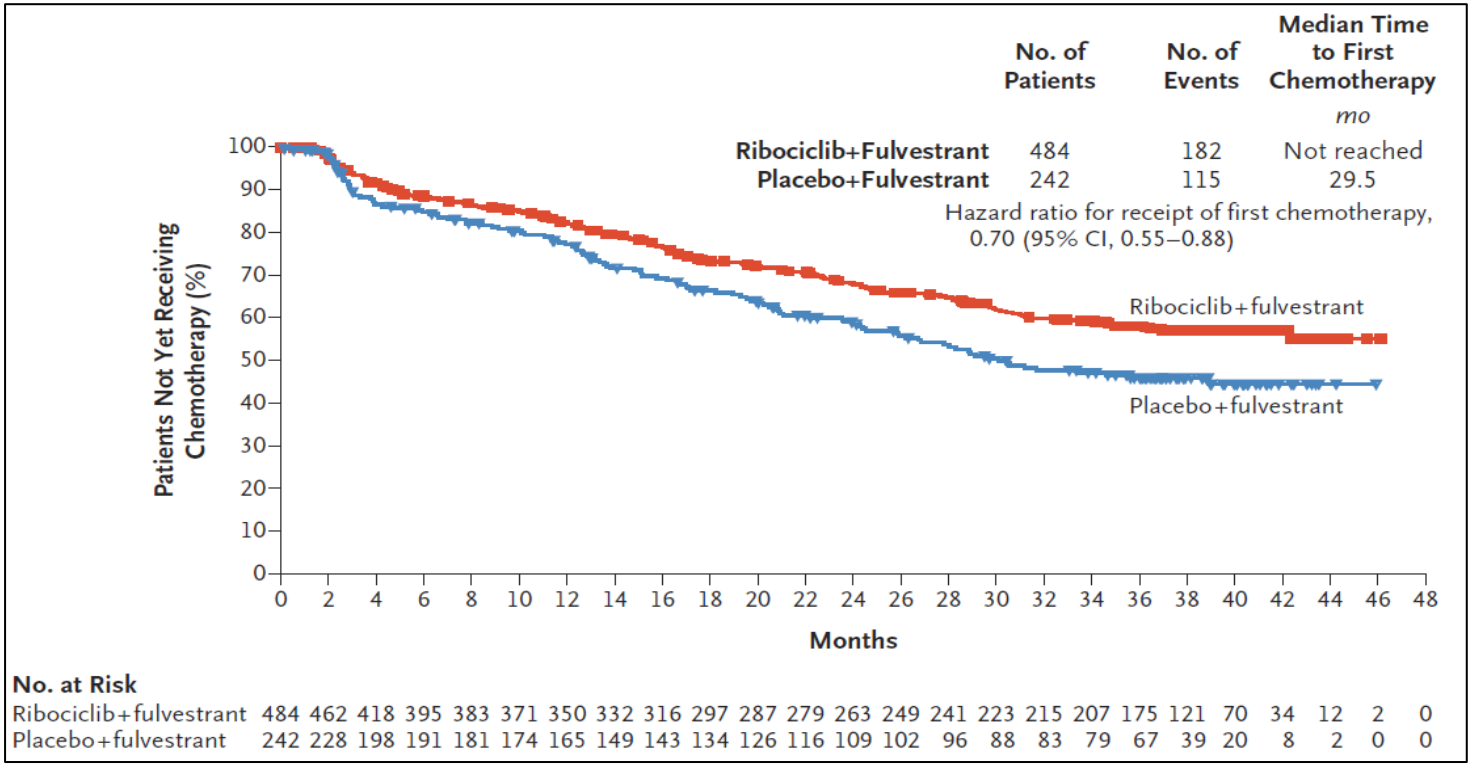
CI, confidence interval; OS, overall survival.
Source: Slamon *et al*, 2019.[14]

A.6.3 *Time to first chemotherapy*

In total, 362 patients (74.8%) in the ribociclib + fulvestrant group and 209 patients (86.4%) in the placebo + fulvestrant group discontinued trial treatment. Subsequent antineoplastic therapies were received by 295 of 362 patients (81.5%) in the ribociclib +

fulvestrant group and 177 of 209 patients (84.7%) in the placebo + fulvestrant group. Subsequent CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib, were received by 40 of 362 patients (11.0%) in the ribociclib group and 53 of 209 patients (25.4%) in the placebo group. Chemotherapy, alone or in combination, was received as the first subsequent therapy by 205 of the 571 patients who discontinued trial treatment (130 of 362 patients [35.9%] in the ribociclib group and 75 of 209 patients [35.9%] in the placebo group). Estimates for the percentage of patients who had not yet received chemotherapy at 42 months were 56.4% (95% CI, 51.3-61.1) in the ribociclib group and 43.7% (95% CI, 36.3-50.8) in the placebo group (Figure 5).

Figure 5. Time to first chemotherapy after discontinuation (overall population)



CI, confidence interval, *mo*, months.
Source: Slamon *et al*, 2019.[14]

A.6.4 *Other endpoints*

MONALEESA-3 endpoints updated at the 3 June 2019 data cut but not used in the economic model, are shown in Appendix E.

A.6.5 *Safety*

Safety data were comparable with those in the first interim analysis, with no new safety signals observed. Treatment discontinuations were reported in 74.8% of patients in the ribociclib + fulvestrant arm and 86.4% of the placebo + fulvestrant arm (safety population, Appendix E).[19] AEs occurred more frequently in the ribociclib + fulvestrant arm compared with the placebo + fulvestrant arm: neutropenia (57.1% vs 0.8%) and leukopenia (15.5% vs 0%) were the most frequently reported grade 3 or 4 AEs.[15] Other AEs of special interest included hepatobiliary toxic effects (ribociclib + fulvestrant, 13.7% vs placebo + fulvestrant, 5.8%) and prolonged QT interval (3.1% vs 1.2%).[15] Grade 3 or 4 interstitial lung disease was observed in a single patient in the ribociclib + fulvestrant arm, with no patients in the placebo arm.[15]

A.6.6 *SACT data collection*

SACT data were collected on the real-world usage of ribociclib plus fulvestrant between 17 July 2019 and 16 January 2020. During this time, 221 applications for ribociclib in combination with fulvestrant were identified by NHS England and NHS improvement, three of which were duplicate applications and one that was excluded as the patient had received ribociclib with fulvestrant previously. Of the 217 relevant applications, an analysis was conducted on data from 187 patients (97%): 8 patients died before treatment, 16 did not receive treatment, and data were missing for 6 patients. All of the 187 patients receiving ribociclib plus fulvestrant were female; 82% of included patients were aged 50–79 years and 82% had an ECOG performance status 0–2. Full patient characteristics and methodology are reported in the SACT data report for TA593.[18]

By 31 January 2020, median follow-up time was 3.7 months (112 days): 141 patients (75%) remained on treatment and 46 patients (25%) had completed treatment (includes patients who died or had received no treatment in at least 3 months). Median treatment duration for all patients was 9.4 months (95% CI not calculable; 286 days) and 72% (95% CI, 63%–78%) of patients were still

receiving treatment at six months. Of the patients who stopped treatment, 30% (14 patients) was due to disease progression, 24% (11 patients) to death while not on treatment, 15% (7 patients) to acute chemotherapy toxicity, 9% (4 patients) to death while on treatment, 4% to patient choice (2 patients). Full results are reported in the SACT data report for TA593.[18]

A.7 Evidence synthesis

A.7.1 *Network meta-analysis (NMA)*

HRs for PFS for everolimus + exemestane (BOLERO-2[24]) versus ribociclib + fulvestrant (MONALEESA-3[14]) were derived by a network meta-analysis (NMA) using RCTs previously identified by systematic literature review (SLR) in TA593 and updated data from MONALEESA-3.[18] An OS comparison was not generated as the model uses PPS equivalency assumption (see section A.8.2.2). NMA methodological details and supporting data are shown in Appendix F.

Table 6 shows the PFS HRs generated by NMA for subpopulation B. HR values were incorporated directly into the pharmaco-economic model base case (see section A.8).

Table 6 Derived HRs for PFS from subpopulation B NMA

Comparator	HR (95% CI) vs fulvestrant	HR (95%CI) vs ribociclib + fulvestrant
Fulvestrant	1.00 (n/a , n/a)	1.75 (1.36, 2.26)
Ribociclib + fulvestrant	0.57 (0.44 , 0.74)	1.00 (n/a , n/a)
Everolimus + exemestane	0.59 (0.45 , 0.77)[a]	**1.03 (0.71, 1.49)[b]**

[a] used in scenario analysis (see section A.11.3).
[b] used in base case (see section A.10.4).
HRs for full network are given in Appendix F. Data in bold and shaded are used in the economic model.
CI, confidence interval; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival.

A.7.1 *Population-adjusted indirect comparison (PAIC)*

As the NMA was identified as a source of uncertainty in TA593,[18] an alternative ITC comparing PFS between MONALEESA-3 and BOLERO-2 directly using population-adjusted indirect comparison (PAIC) was performed, in line with NICE Decision Support Unit (DSU) 18 (see appendix F for methodological details).[25] 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. PFS HR values derived by this PAIC (Table 7) were used in additional pharmacoeconomic model scenario analyses (presented in section A.11.3).

Table 7 Cox proportional hazards regressions from PAIC

Endpoint	HR (95% CI)	p-value[c]
PFS (unweighted)	0.622 (0.495–0.781)	< 0.001
PFS (weighted)[a,b]	0.633 (0.486–0.824)	< 0.001

[a] see appendix F.1.2 for details of weighting methodology.
[b] these data were applied to a scenario analysis (see section A.11.3).
[c] not adjusted for weighting.
CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival.

A.8 Incorporating collected data into the model

A.8.1 *Model structure*

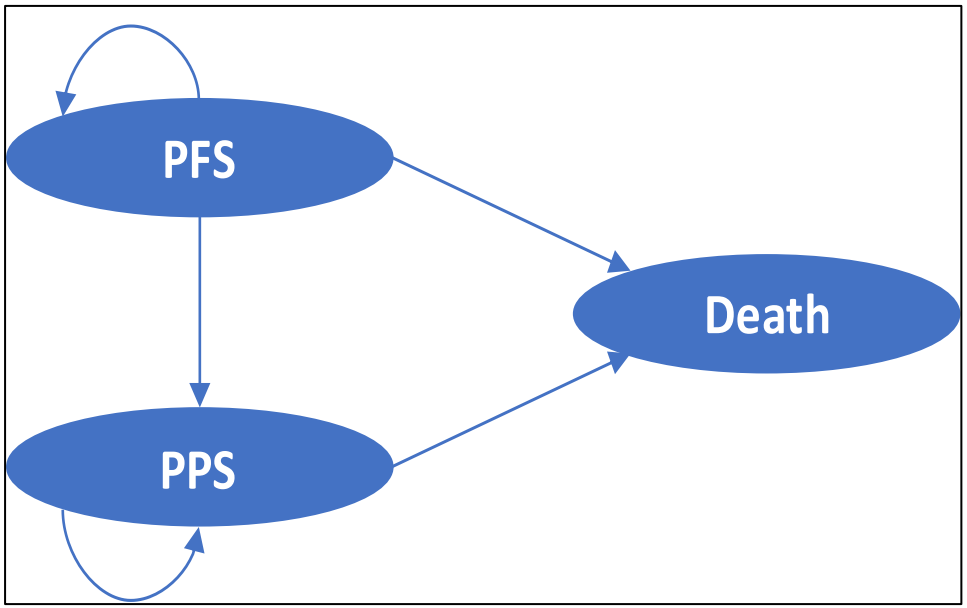
A non-homogenous semi-Markov model was developed in Microsoft Excel® to reflect the natural history of disease for breast cancer and the current clinical pathway. This is the same model as used in TA593, with updates as agreed with NICE / outlined below in Section A.8.1.4 and Table 16.

Consistent with the model used to inform decision making in TA593, the model used in this review consists of three mutually exclusive health states: PFS, post-progression survival (PPS) and death (separated into death from metastatic breast cancer and death from other causes), appropriately capturing the patient journey and the clinical pathway of care. Transition probabilities required for the Markov cohort model include the following:

- Probabilities of transition from the PFS state to the PPS state;
- Probability of transition from the PFS state to the death state; and
- Probability of transition from the PPS state to the death state.

The structure of the model is shown in Figure 6. Health-state transition probabilities, utility values, duration and intensity of treatment, and probability of AEs were based on data from the MONALEESA-3 study and other published sources. Cost parameters were estimated based on data from secondary sources. Since the model does not include states for “on” and “off” treatment, transition probabilities are not conditional on whether patients are on or off therapy. Costs and utilities, however, are dependent on whether patients are on therapy and are calculated by combining information on time to treatment discontinuation by time in state with cost and utility values conditioned on whether patients are on or off therapy.

Figure 6 TA593 model structure



PFS, progression-free survival; PPS, post-progression survival.

A.8.1.1 Progression-free survival

Patients in this health state are free from progression and can either (a) remain in this health state in the absence of disease progression (or death), (b) move to PPS health state or (c) die. The probabilities of transition from the PFS state to the PPS state and the death state are calculated by combining estimates of the probability of PFS events with estimates of the probability that a PFS event is death.

A.8.1.2 Post-progression survival

Patients in this health state have progressive disease and can either remain in this health state or progress to death. Probabilities of death following progression, or PPS, were estimated using individual patient failure time data from MONALEESA-3. PPS was estimated separately for patients randomised to ribociclib + fulvestrant and fulvestrant monotherapy, as well as for all patients

pooled across treatment arms. OS is the summation of PFS and PPS. Please see section A.8.2.4 for information on how everolimus + exemestane was incorporated into the model.

A.8.1.3 Death state

The model includes two death states: one for death due to breast cancer, and another for death due to other causes. Probabilities of death following progression, or PPS, were estimated using individual patient failure time data from MONALEESA-3.

A.8.1.4 Corrections to original CDF entry model

In response to ERG comments in TA593 (regarding inconsistent application of mortality between PFS and PPS, and half-cycle correction issues), the following model issues were identified and changed:

- On Survcalc in the columns labelled “Tunnel” for the PFS distributions (e.g., W31:W555), changed the formula to include general population mortality in the complement of transitions probabilities for PFS
- On each of the “CompX.Calc” worksheets, modified the formulas in cells H31:K554 such that general population mortality is considered in addition to mortality from breast cancer represented by the hazard rate for PFS
- On the medcalc sheet in cells GV11:HL534, 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

In addition, for base case scenario 2 (replication of CDF model with new data cut), it was not possible to precisely replicate the model used by the ERG (CDF model). In the CDF model, extrapolations based on the old data (ERG ribo, ERG ful, ERG ever[vs ribo]) were manually entered survivor functions. Scenario 2 was therefore run using an RCS3 Weibull parameterisation for PFS, based on the fact that the model most likely used a PH treatment effect since the name of the curve for everolimus ERG ever (vs ribo) implies it was derived by applying the HR for everolimus to the PFS curve for ribociclib.

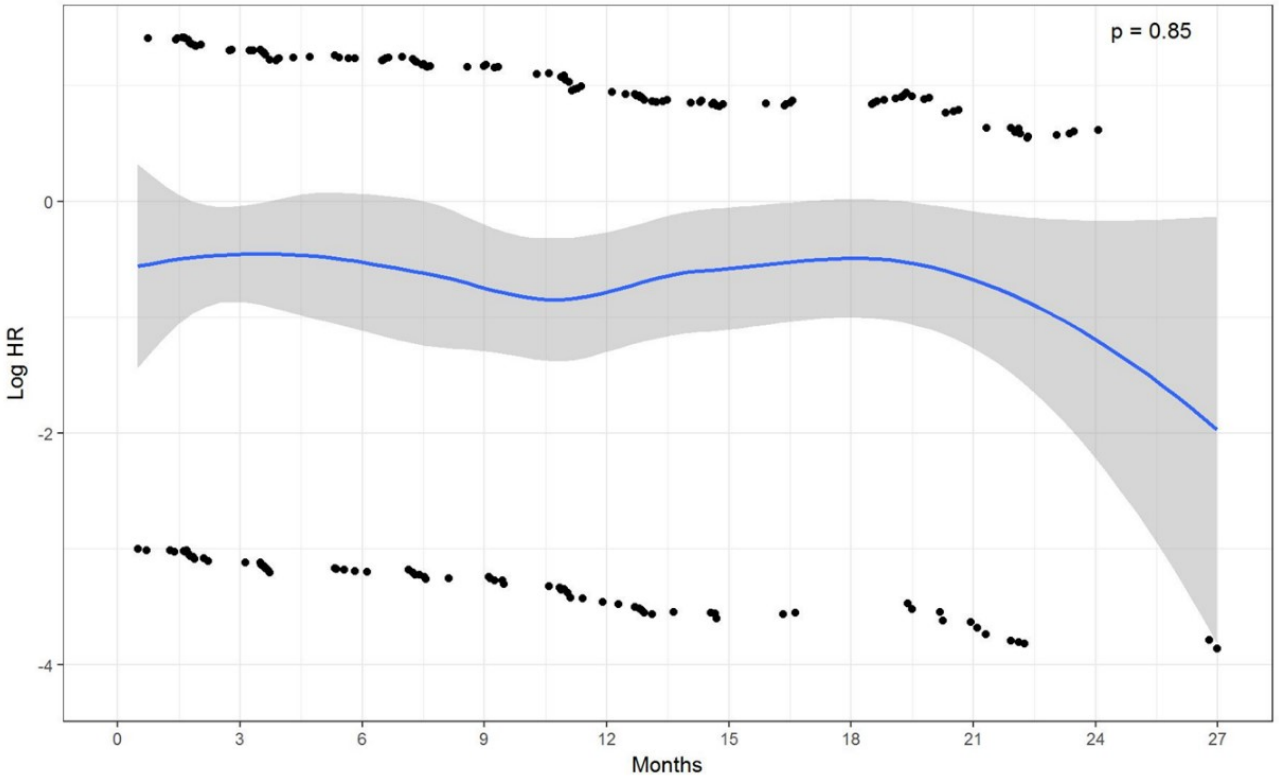
A.8.2 *Clinical parameters and variables*

A.8.2.1 Progression-free survival (PFS)

For patients receiving ribociclib plus fulvestrant or fulvestrant monotherapy, probabilities of PFS events were estimated by fitting parametric survival distribution to the individual patient failure time data from MONALEESA-3. Curves were fit to PFS time-to-event data for patients in both treatment arms simultaneously, stratified by treatment arm. Long-term PFS estimations for ribociclib + fulvestrant and fulvestrant alone were based on parametric survival distributions fit to MONALEESA-3 patient level data. A plot of a smoothed curve fit to the scaled Schoenfeld residuals for the treatment group covariate in a Cox proportional hazard regression model is provided in Figure 7. In order to test proportionality of hazards, the slope of the scaled Schoenfeld residuals was tested and was found to not deviate significantly from zero (p=0.85), suggesting that a proportional hazards assumption may be appropriate. We also present additional scenario analysis to further support this in section A.11.3 .

The methodology for fitting and selecting survival functions was based on NICE DSU guidance.[26]

Figure 7. Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS in Subpopulation B

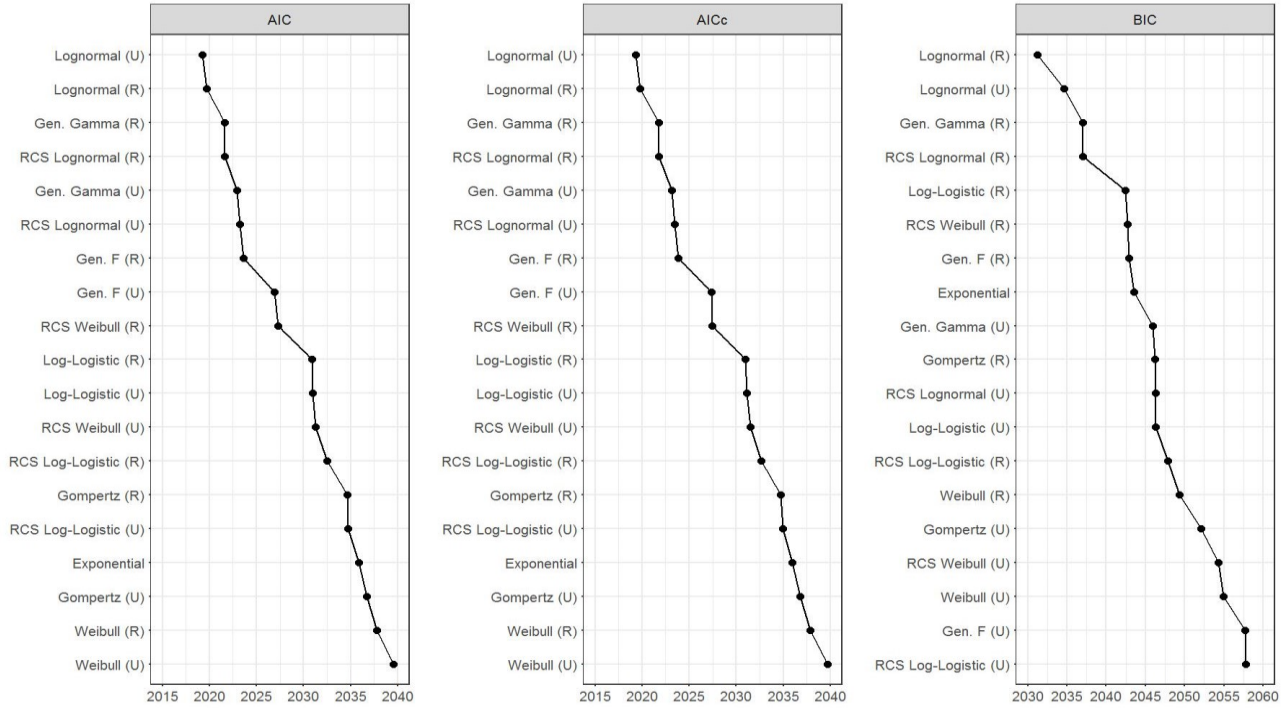


PFS, progression-free survival.
Source: PAI Analyses of MONALEESA-3 data.

The visual fit of the parametric distributions to the KM curves are all reasonably good for the ribociclib plus fulvestrant arm (Figure 10 and Appendix G.1.12), however the visual fit for these distributions KM is less consistent with KM PFS for the fulvestrant arm. Hazard rates during the trial follow-up for the best fitting parametric survival distributions for PFS are compared with non-parametric hazards (Appendix G.1.12). Given that the RCS 3 Weibull (R) model is one of the better fits according to BIC (Figure 8, Figure 9

and Table 8, see also Appendix G.1.1.2), has a good visual fit to the updated MONALEESA-3 KM data (Figure 12), 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, it was utilised for the base case (Figure 12). Table 9 provides predicted data (% patients remaining over time) based on different functional forms.

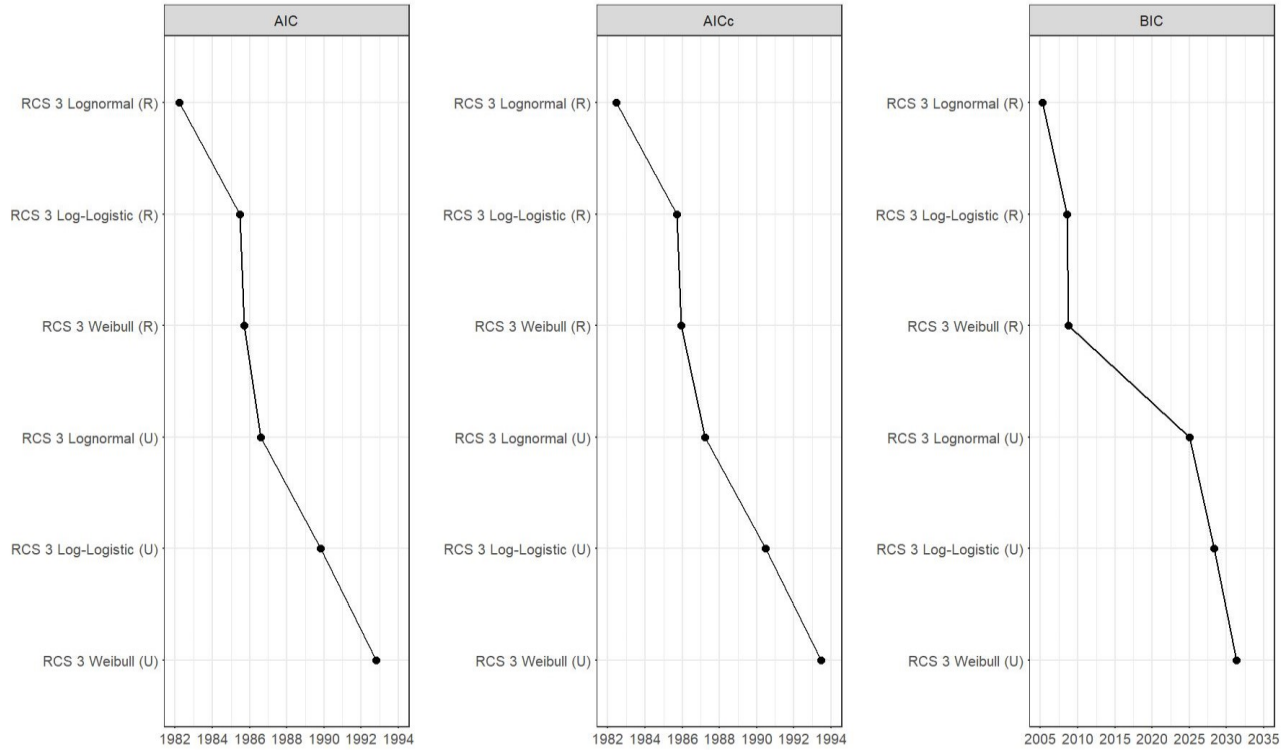
Figure 8 Fit statistics for PFS



AIC, Akaike information criterion; BIC: Bayesian Information criterion; PFS, progression-free survival.

* Novartis clinical validation (25th June 2020, data on file). Validation was limited to PFS and TTD extrapolations (PPS was not presented).

Figure 9. Fit statistics for PFS (RCS models)



AIC, Akaike information criterion; BIC: Bayesian Information criterion; PFS, progression-free survival.

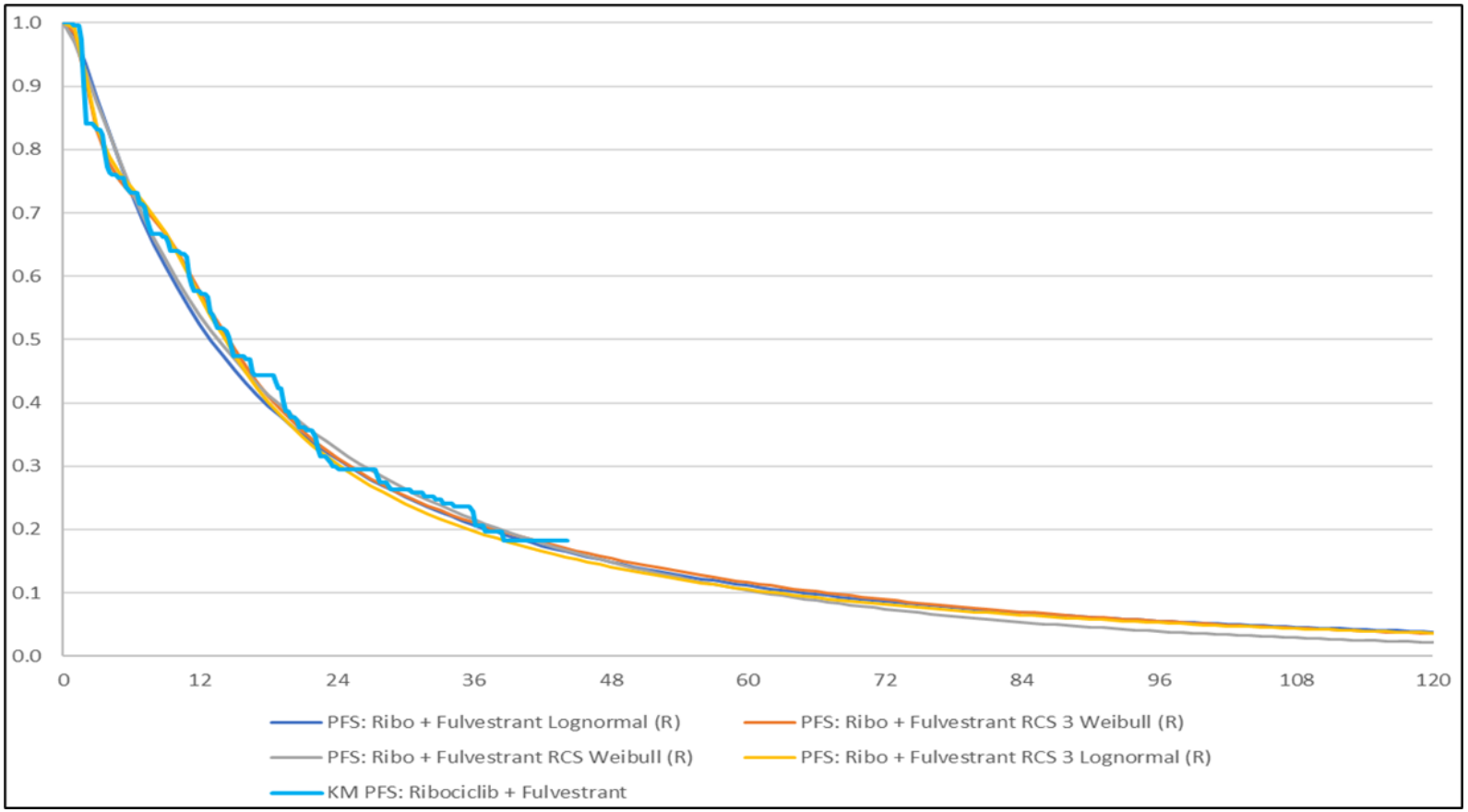
Table 8. Fit statistics for PFS parametric curves

Distribution	Converged	DF	-2LL	AIC	AICc	BIC
RCS 3 Lognormal (R)	TRUE	6	1970.2	1982.2	1982.4	2005.3
RCS 3 Log-Logistic (R)	TRUE	6	1973.5	1985.5	1985.7	2008.5
RCS 3 Weibull (R)	**TRUE**	**6**	**1973.7**	**1985.7**	**1985.9**	**2008.8**
RCS 3 Lognormal (U)	TRUE	10	1966.6	1986.6	1987.2	2025.0
RCS Log-Logistic (U)	TRUE	10	1969.8	1989.8	1990.5	2028.3
Lognormal (R)	TRUE	3	2013.7	2019.7	2019.8	2031.2
RCS Weibull (U)	TRUE	10	1972.8	1992.8	1993.5	2031.3
Lognormal (U)	TRUE	4	2011.2	2019.2	2019.3	2034.6
Gen. Gamma (R)	TRUE	4	2013.6	2021.6	2021.8	2037.0
RCS Lognormal (R)	TRUE	4	2013.6	2021.6	2021.8	2037.0
Log-Logistic (R)	TRUE	3	2024.9	2030.9	2030.9	2042.4
RCS Weibull (R)	TRUE	4	2019.3	2027.3	2027.4	2042.7
Gen. F (R)	TRUE	5	2013.6	2023.6	2023.8	2042.9
Exponential	TRUE	2	2031.9	2035.9	2035.9	2043.6
Gen. Gamma (U)	TRUE	6	2010.9	2022.9	2023.2	2046.0
Gompertz (R)	TRUE	3	2028.7	2034.7	2034.7	2046.2
RCS Lognormal (U)	TRUE	6	2011.2	2023.2	2023.5	2046.3
Log-Logistic (U)	TRUE	4	2023.0	2031.0	2031.1	2046.4
RCS Log-Logistic (R)	TRUE	4	2024.5	2032.5	2032.6	2047.9
Weibull (R)	TRUE	3	2031.8	2037.8	2037.9	2049.3

Gompertz (U)	TRUE	4	2028.7	2036.7	2036.8	2052.1
RCS Weibull (U)	TRUE	6	2019.2	2031.2	2031.5	2054.3
Weibull (U)	TRUE	4	2031.6	2039.6	2039.7	2055.0
Gen. F (U)	TRUE	8	2010.9	2026.9	2027.4	2057.7
RCS Log-Logistic (U)	TRUE	6	2022.7	2034.7	2035.0	2057.8

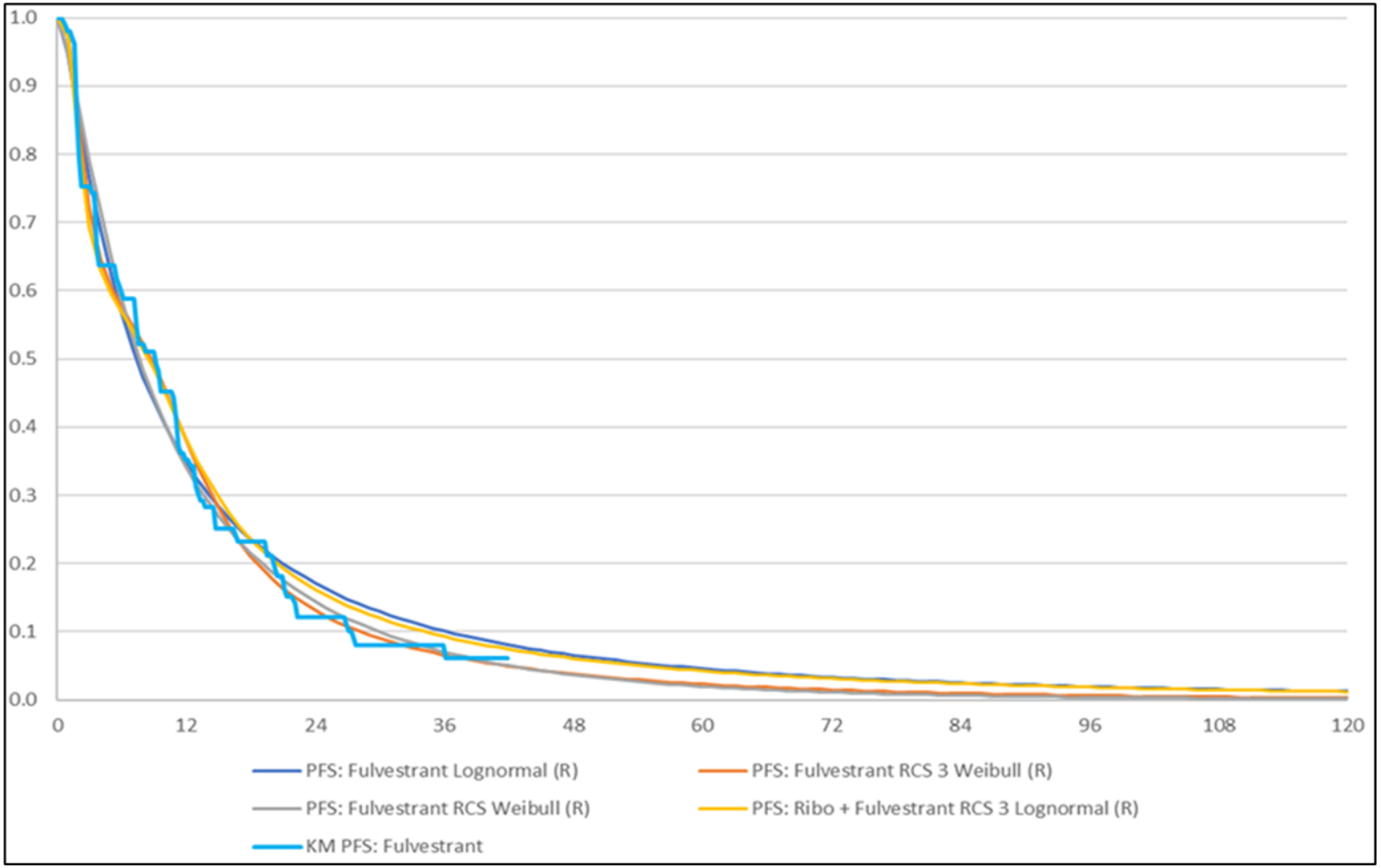
AIC, Akaike information criterion; BIC: Bayesian Information criterion; PFS, progression-free survival; RCS, restricted cubic spline.
RCS Weibull (R) shown in bold.

Figure 10. 10-year PFS projections (ribociclib + fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay



KM, Kaplan Meier; PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; Ribo, ribociclib.

Figure 11. 10-year PFS projections (fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay



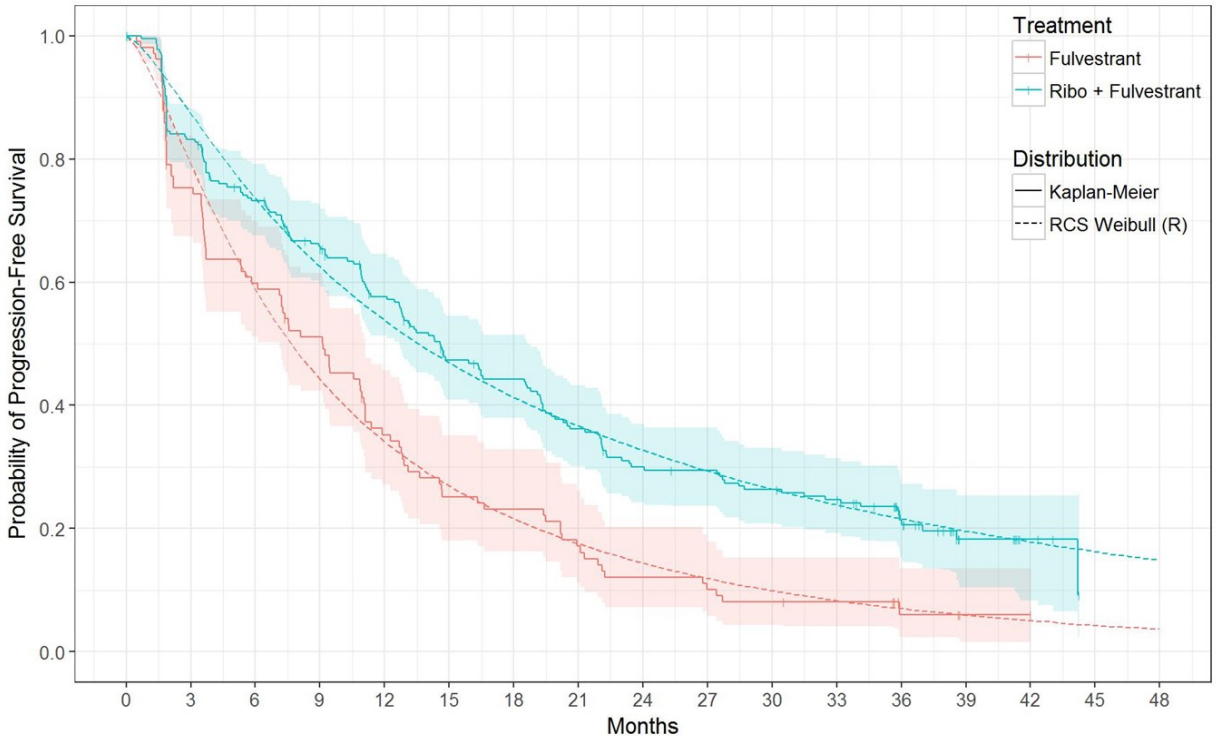
KM, Kaplan Meier; PFS, progression-free survival; R, restricted; RCS, restricted cubic spline.

Table 9. Predicted proportion (%) of patients remaining over time for PFS parametric curves (ribociclib + fulvestrant)

Time	Kaplan-Meier	Ribo + Fulvestrant Lognormal (R)	Ribo + Fulvestrant RCS 3 Weibull (R)	Ribo + Fulvestrant RCS Weibull (R)	Ribo + Fulvestrant RCS 3 Lognormal (R)
2-Year	30.00%	32.28%	32.63%	33.95%	31.64%
3-Year	22.88%	21.24%	21.71%	22.32%	20.37%
5-Year	---	11.15%	11.91%	10.72%	10.79%
10-Year	---	3.72%	3.64%	2.22%	3.71%

KM, Kaplan-Meier; PFS, progression-free survival; RCS, restricted cubic spline.

Figure 12. PFS to end of trial follow-up using RCS Weibull (R)



PFS, progression-free survival; R, restricted; RCS, restricted cubic spline; Ribo, ribociclib.

A.8.2.2 Post progression survival (PPS)

Probabilities of death following progression, or post-progression survival (PPS), for patients receiving ribociclib plus fulvestrant or fulvestrant monotherapy were estimated using individual patient failure time data from MONALEESA-3 using methods similar to those described above for PFS and accepted as part of TA593. PPS from MONALEESA-3 was based on the June 3, 2019 data cut-off. Analyses of PPS stratified by randomised treatment revealed that PPS for patients in subpopulation B was not statistically different between the two patient groups (logrank p-value=0.3583). Accordingly, PPS was estimated for all patients pooled across treatment arms for the base case analysis (an assumption accepted in NICE TA593). This can be considered a conservative simplification and is likely to result in minimal bias since the same pooled PPS is applied to both the ribociclib plus fulvestrant and placebo plus fulvestrant treatment arms.

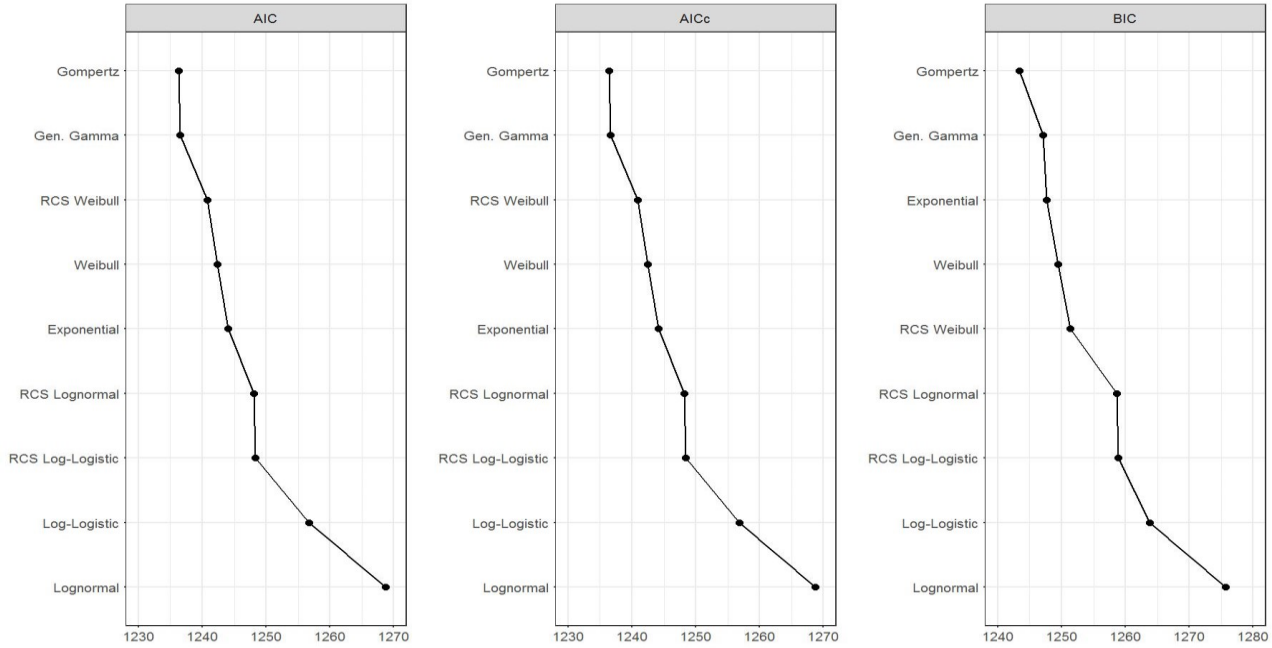
Long-term PPS estimations for ribociclib + fulvestrant and fulvestrant alone were based on parametric survival distributions fit to MONALEESA-3 patient level data. The Gompertz, generalised gamma, and RCS Weibull distributions all have good visual fit to the KM data during trial follow-up (Appendix G.1.2). Projections based on the exponential, Weibull, and RCS lognormal distributions tend to overestimate KM PPS by the end of follow-up (see Appendix G.1.2).

The Gompertz, generalised gamma, Weibull, and RCS Weibull distributions yield hazards that increase consistently over the duration of follow-up, which are generally consistent with the observed nonparametric hazards (see Appendix G.1.2). The exponential model is characterised by constant hazards, which greatly underestimated the nonparametric hazard rates after 24 months. Hazard rates in the RCS lognormal model are increasing until month 21 but then begin decreasing thereafter, which is inconsistent with the nonparametric hazard rates. Using long-term projections of PPS for these five distributions (Figure 14 and Appendix G.1.2), the Gompertz and generalised gamma models yield projected PPS reaching zero at around 60 months, while the exponential, Weibull, and RCS Weibull models reach zero between 90 and 120 months The RCS lognormal model yields the most

optimistic projection of PPS, reaching zero at 180 months. It should be noted that these projections do not include general population mortality, which is captured separately in the model.

Given that the Gompertz model has the best fit according to BIC (Figure 13 and Table 10) excellent visual fit (Figure 15), and projected hazards that are consistent with nonparametric hazard rates, it has been utilised for the base case.

Figure 13 Fit statistics for PPS (both arms together)



AIC, Akaike information criterion; BIC: Bayesian Information Criterion; PPS, post-progression survival.

Table 10. Fit statistics for PPS parametric curves

Distribution	Converged	DF	-2LL	AIC	AICc	BIC
Gompertz	**TRUE**	**2**	**1232.3**	**1236.3**	**1236.4**	**1243.4**
Gen. Gamma	TRUE	3	1230.5	1236.5	1236.6	1247.1
Exponential	TRUE	1	1242.1	1244.1	1244.1	1247.6
Weibull	TRUE	2	1238.4	1242.4	1242.4	1249.5
RCS Weibull	TRUE	3	1234.8	1240.8	1240.9	1251.4
RCS Lognormal	TRUE	3	1242.1	1248.1	1248.1	1258.7
RCS Log-Logistic	TRUE	3	1242.3	1248.3	1248.4	1258.9
Log-Logistic	TRUE	2	1252.7	1256.7	1256.8	1263.8
Lognormal	TRUE	2	1264.7	1268.7	1268.7	1275.7

AIC, Akaike information criterion; BIC: Bayesian Information Criterion; PPS, post-progression survival.
Gompertz is shown in bold.

Figure 14 [redacted]

[redacted]

Table 11. [redacted]

[redacted]

Figure 15. [redacted]

[redacted]

A.8.2.3 Time to treatment discontinuation (TTD)

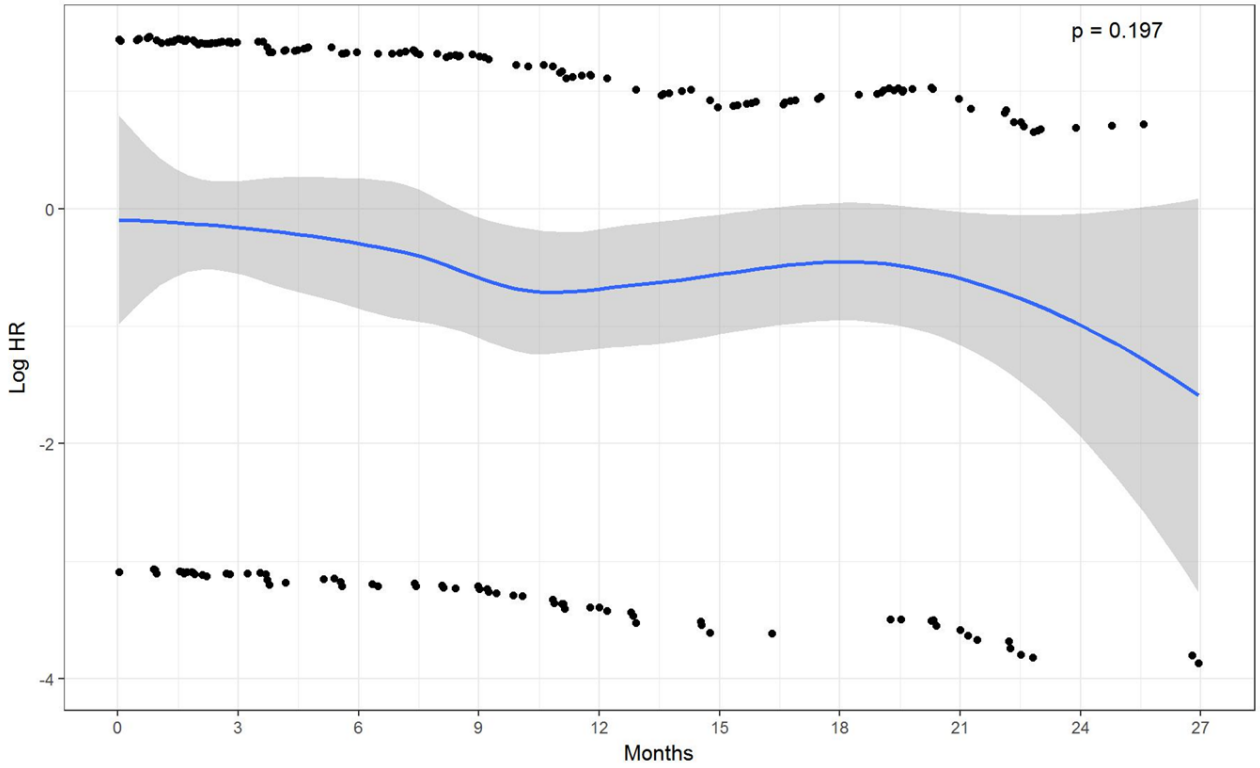
Probabilities of treatment discontinuation, or time-to-treatment discontinuation (TTD), were estimated using individual patient failure time data from patients in subpopulation B in MONALEESA-3 using methods similar to those described previously for PFS and PPS and accepted in TA593. Long-term TTD estimations for ribociclib + fulvestrant and placebo + fulvestrant were based on parametric survival distributions fit to MONALEESA-3 patient level data. Based on BIC (Figure 17, Figure 18 and Table 10) and visual fit (Figure 19 and Figure 20), Gompertz (R) is the best fit for both curves.

However, the use of an (R) model for TTD may be biased since it assumes a treatment effect on one of the parameters of the distribution, consequently a (U) model is preferable. Whilst this would mean selecting Gompertz (U) for TTD, the down side of this is that it produces the greatest amount of time on treatment among all of the models considered (Figure 21**Error! Reference source not found.**). The tail on the Gompertz (U) model suggests that all patients remaining on ribociclib at approximately 8 years would continue to receive ribociclib and never discontinue (i.e., they would not discontinue if they hadn't done so by year 8), which is not clinically plausible. The large time on treatment for Gompertz (U) is also reflected in a comparison of the restricted mean survival times (RMST) for the models (Table 14), which is calculated as the area under the curve and represents the mean time (months) on treatment (before adjusting for general population mortality). The time on treatment with ribociclib based on the Gompertz (U) is nearly double that of the median time on treatment and a full 6 months greater than the next closest model, the Gompertz (R). Based on these data, we argue that Gompertz (U) overestimates the time on treatment for ribociclib and that a Gompertz (R) should be avoided for the reasons given above and expectations of the terms of engagement.

Therefore, taking into account BIC, the next best fit (U) model would be RCS Lognormal (U). The difference between RCS Lognormal (U) and either Gompertz is relatively small (<10; i.e no strong evidence for a significantly better fit between them[27]). Furthermore, RCS Lognormal (U) does not suffer from the clinically implausible tail seen with Gompertz (U). As shown in Figure 22, RCS Lognormal (U) provides a good visual fit to the clinical KM data, and is highly similar to that achieved using Gompertz (U).

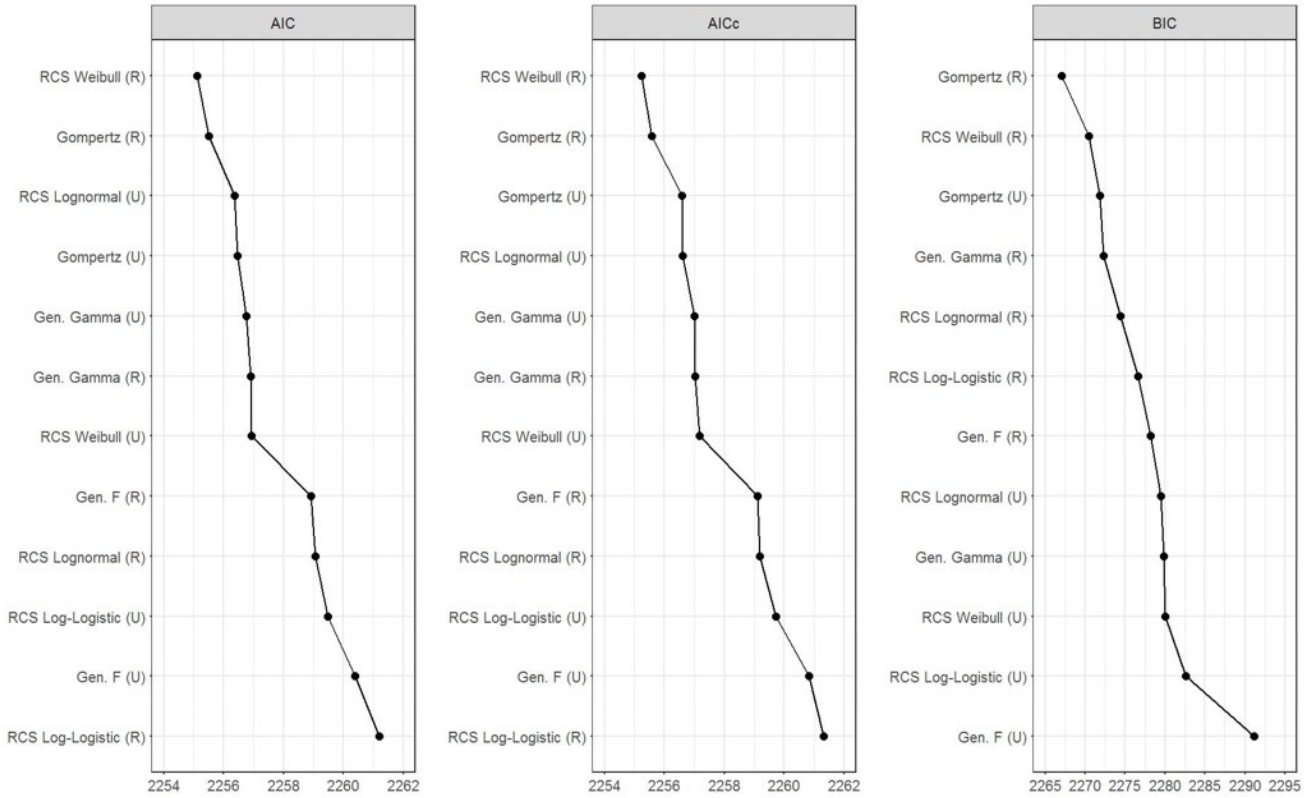
In summary, when we consider the three main criteria (BIC, visual fit, clinical plausibility), for two of them, the statistical and visual fit, there are no major differences between the Gompertz (U) and RCS lognormal (U). However, the Gompertz (U) leads to a clinically implausible model, thus RCS lognormal (U) was selected as the base case.

Figure 16. Plot of Smoothed Curve fit to Schoenfeld Residuals for TTD in Subpopulation B



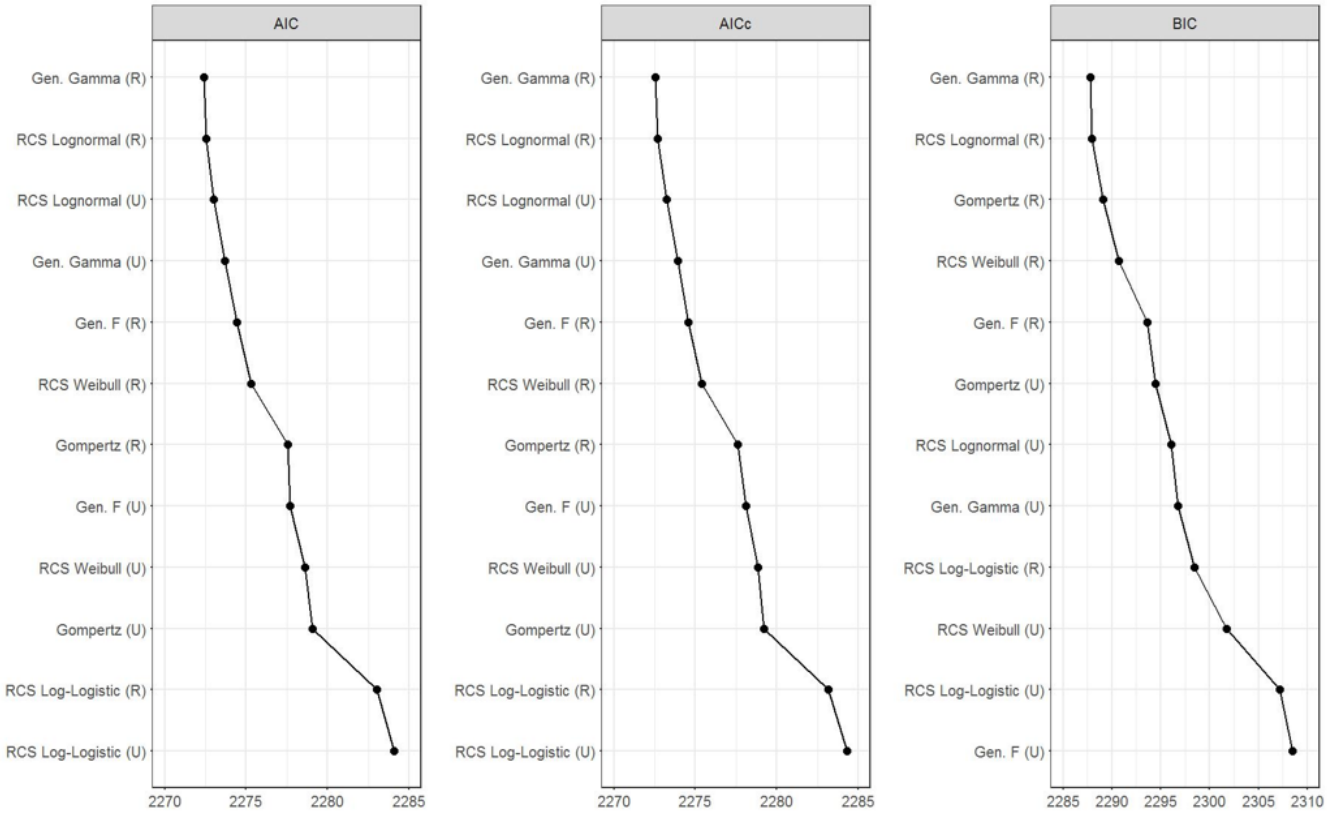
TTD, time to treatment discontinuation.

Figure 17. Fit statistics for TTD (ribociclib plus fulvestrant)



AIC, Akaike information criterion; BIC: Bayesian Information criterion; R, restricted; TTD, time to discontinuation; U, unrestricted.

Figure 18 Fit statistics for TTD (fulvestrant)



AIC, Akaike information criterion; BIC: Bayesian Information criterion; R, restricted; TTD, time to discontinuation; U, unrestricted.

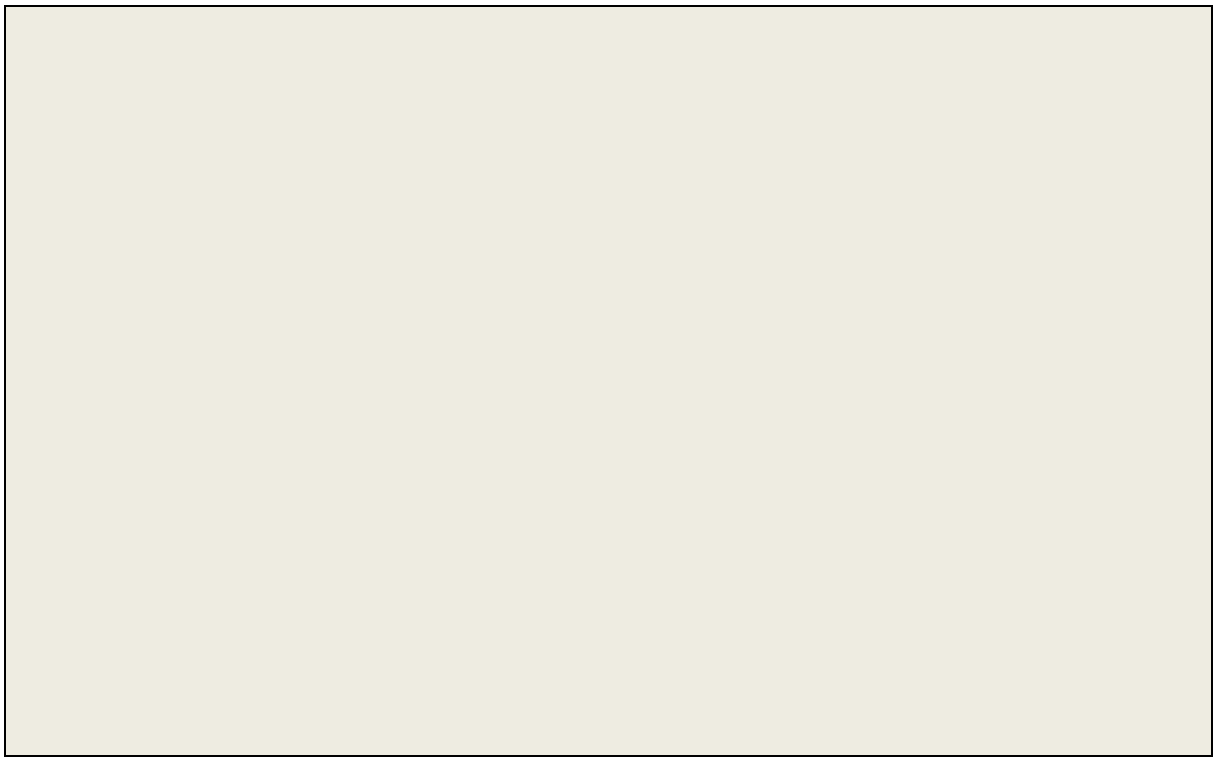
Table 12. Fit statistics for TTD parametric curves

Distribution	AIC	AICc	BIC
Ribociclib + fulvestrant			
Gompertz (R)	2255.5	2255.6	2267.1
RCS Weibull (R)	2255.1	2255.2	2270.5
Gompertz (U)	2256.5	2256.2	2271.8
Gen. Gamma (R)	2256.9	2257.0	2272.3
RCS Lognormal (R)	2259.1	2259.2	2274.5
RCS Log-Logistic (R)	2261.2	2261.3	2276.6
Gen. F (R)	2258.9	2259.1	2278.2
RCS Lognormal (U)	**2256.4**	**2256.6**	**2279.4**
Gen. Gamma (U)	2256.7	2257.0	2279.8
RCS Weibull (U)	2256.9	2257.2	2280.0
RCS Log-Logistic (U)	2259.5	2259.7	2282.6
Gen. F (U)	2260.4	2260.8	2291.2
Fulvestrant			
Gen. Gamma (R)	2272.4	2272.5	2287.8
RCS Lognormal (R)	2272.5	2272.7	2287.9
Gompertz (R)	2277.5	2277.6	2289.1
RCS Weibull (R)	2275.3	2275.4	2290.7
Gen. F (R)	2274.4	2274.6	2293.6

Gompertz (U)	2279.1	2279.2	2294.5
RCS Lognormal (U)	**2273.0**	**2273.2**	**2296.1**
Gen. Gamma (U)	2273.7	2273.9	2296.8
RCS Log-logistic (R)	2283.0	2283.2	2298.4
RCS Weibull (U)	2278.6	2278.9	2301.7
RCS Log-Logistic	2284.1	2284.3	2307.2
Gen. F (U)	2277.7	2278.1	2308.6

AIC, Akaike information criterion; BIC: Bayesian Information criterion; R, restricted; TTD, time to discontinuation; U, unrestricted.

Figure 19. [redacted]



[redacted]

Figure 20. [redacted]

[redacted]

Table 13. [redacted]

[redacted]

[redacted]

Figure 21. [redacted]

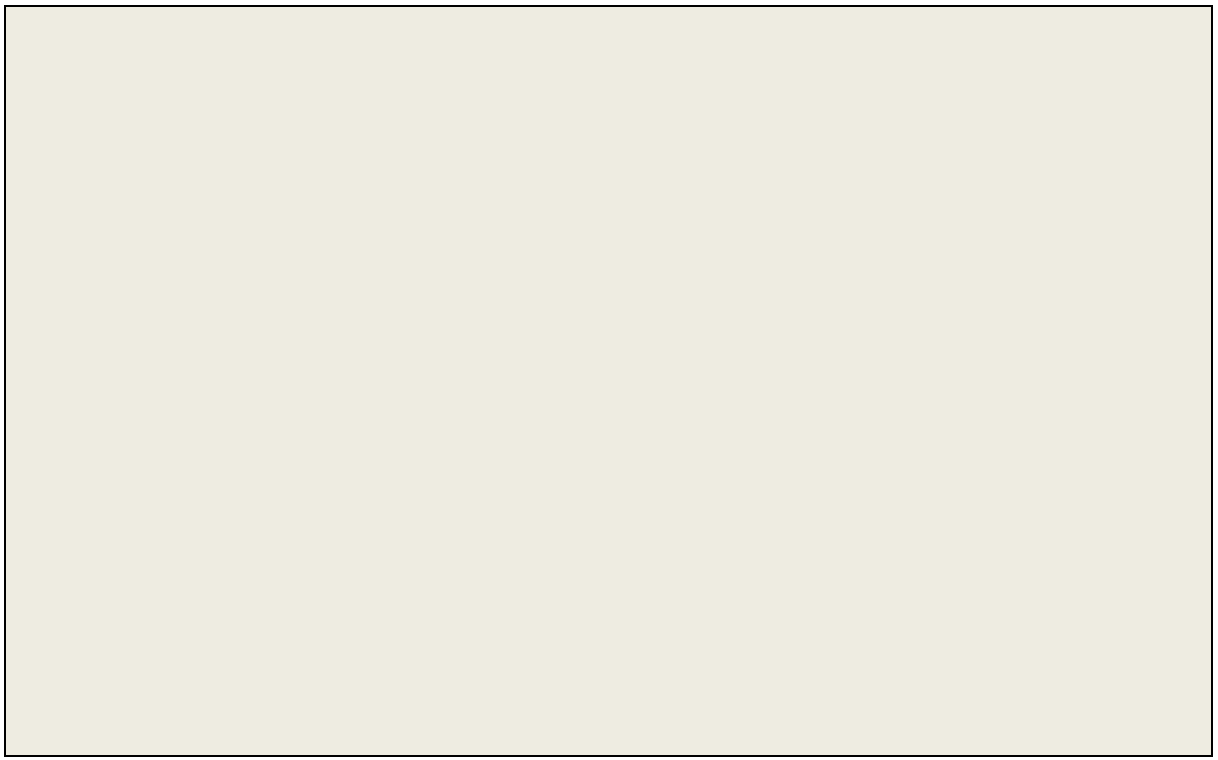
[redacted]

Table 14. RMST for Models Fitted to TTD in subpopulation B

Distribution	Ribociclib + Fulvestrant	Fulvestrant	Difference
Gen. F (R)	20.6	13.9	6.7
Gen. F (U)	23.4	12.2	11.2
Gen. Gamma (R)	20.0	13.3	6.7
Gen. Gamma (U)	22.6	11.9	10.7
Gompertz (R)	37.2	17.2	20.0
Gompertz (U)	43.9	12.5	31.4
RCS Log-Logistic (R)	26.3	19.8	6.5
RCS Log-Logistic (U)	30.6	14.3	16.3
RCS Lognormal (R)	21.0	15.1	5.9
RCS Lognormal (U)	24.1	12.2	11.9
RCS Weibull (R)	20.0	12.4	7.6
RCS Weibull (U)	21.0	11.8	9.2

AIC, Akaike information criterion; BIC: Bayesian Information criterion; R, restricted; RMST, restricted mean survival time analysis; TTD, time to discontinuation; U, unrestricted.

Figure 22 [redacted]



[redacted]

A.8.2.4 Comparator modelling

The model comparator was everolimus + exemestane using data from the BOLERO-2 RCT, as per the terms of engagement document. Long-term PFS estimations for everolimus + exemestane were based on comparative PFS data generated by ITC as described in section A.7 .

Long-term PPS estimations for everolimus + exemestane was assumed to be equivalent to ribociclib plus fulvestrant. This assumption was questioned in TA593 and reiterated in the terms of engagement. To address this, we show in Figure 23 that the PPS KM plots for ribociclib + fulvestrant from MONALEESA-3 and everolimus + exemestane from BOLERO-2 visually look very similar and are well within the 95% CIs, and cross at multiple points. It can also be seen that the curve for everolimus is initially slightly higher than the curve for ribociclib until approximately 7 months, but from month 8 through to month 35 the ribociclib curve is slightly higher. Taken together, we argue that these observations support the assumption that PPS is equivalent for the two therapies. Long term TTD was assumed to be equivalent to PFS, as accepted in TA593.

Figure 23. [redacted]

[redacted]

Additionally, we present output from a cox regression of the PPS curves both with and without weights from SAS (Table 15). For the unweighted analysis, the HR was 0.978 (p = 0.8778). For the weighed analysis the Hazard rate was 0.918 (p = 0.6006). The results would suggest that there is no statistically significant difference between the two curves (the 95% CI span 1.0), which is consistent with a visual assessment of the curves in Figure 23.

Table 15. Cox Regression of MONALESSA-3 and BOLERO-2 PPS curves

RIB+FUL M3 vs EVE+EXE B2: Unweighted[a]					
Description	**Parameter Estimate**	**Point Estimate**	**95% Wald Confidence Limits**		**p-value[a]**
treatment RIB+FUL M3 vs EVE+EXE B2	-0.02189	0.978	0.740	1.293	0.8778
RIB+FUL M3 vs EVE+EXE B2: Weighted[a]					
treatment RIB+FUL M3 vs EVE+EXE B2	-0.08564	0.918	0.666	1.265	0.6006

[a] we used the curves after weighting in the curve-fitting, the Cox regression of unweighted curves is provided for context.
[b] Chi-square test
B2, BOLERO-2; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; M3, MONALEESA-3; PPS, post-progression survival; RIB, ribociclib.

A.8.2.5 Probability of adverse events

AEs from the full MONALEESA-3 trial were considered in the model as there were not expected to be any differences in the events seen in the different subpopulations. In the base-case, the model incorporates 81 AEs for ribociclib + fulvestrant, and 141 for everolimus + exemestane.

A.9 Key model assumptions and inputs

Table 16 summarises the main model inputs and assumptions, indicating where these have changed since the TA593 submission.

Table 16. Changes in the key model assumptions and inputs

Model input [a]	Original parameter /assumption	Updated parameter /assumption	Source/Justification
Comparators	Exemestane + everolimus	Exemestane + everolimus	No change
Population	Subpopulation B	Subpopulation B	No change

Model structure	Four state semi-Markov model (PFS1, PFS2, progression and death)	Four state semi-Markov model (PFS1, PFS2, progression and death) Correction of three 'issues' with model from TA593, two of which flagged by ERG / Committee, and the third identified during rectification process. See section A.8.1.4 for further details	No change These address ERG observations in TA593.
Time horizon	40 years	40 years	No change
Cycle length	28-days, half-cycle correction	28-days, half-cycle correction	No change
Discount rate	3.5%	3.5%	No change
ITC HRs for exemestane and everolimus	Derived by NMA	Derived by NMA	Same network as TA593 but generated updated HR values for comparison through the use of updated MONALEESA-3 PFS and OS data, BOLERO-2 and other network trial inputs unchanged. The previous NMA did not generate OS HR values due to data immaturity. An alternative ITC (PAIC) was also carried out and included as a scenario analysis (see section A.11.3 and Appendix F.1.). The PFS and OS HR values derived from this analysis suggest that the original (and updated) NMA HRs may be under-estimating the efficacy of ribociclib plus fulvestrant relative to everolimus plus exemestane. As this method utilises IPD from both MONALEESA-3 and BOLERO-2 trials, both sets of IPD will be supplied as part of this submission (the latter was not supplied in TA593 as there were several

			comparators and the NMA relied on aggregate data rather than IPD.
PFS probability calculations	Probabilities of PFS events for patients receiving ribociclib with fulvestrant and fulvestrant monotherapy were estimated from MONALEESA-3 based on the November 3, 2017 data cut-off. 3-knot spline extrapolation used for both arms	Probabilities of PFS events for patients receiving ribociclib with fulvestrant and fulvestrant monotherapy were estimated from MONALEESA-3 based on the **June 3, 2019** data cut-off. RCS 3 Weibull (R) for both arms	Included the most up to date PFS data cut RCS 3 Weibull (R) extrapolation represents the best fitting curve using updated MONALEESA-3 data and was clinically validated
PPS probability calculation	Derived from pooled ribociclib + fulvestrant and fulvestrant arms of MONALEESA-3 3-knot spline extrapolation used for pooled arms Assumed equivalent between ribociclib + fulvestrant and everolimus + exemestane	Derived from pooled ribociclib + fulvestrant and fulvestrant arms of MONALEESA-3 Gompertz (R) extrapolation used for pooled arms Assumed equivalent between ribociclib + fulvestrant and everolimus + exemestane. A MONALEESA-3/BOLERO-2 PPS comparison supports this assumption (see Section A.8.2.4).	Used the most up to date OS data cut Gompertz (R) extrapolation represents the best fitting curve using updated MONALEESA-3 data
TTD probability calculations	RCS 3 Weibull (R) extrapolation used for both arms	RCS lognormal (U) extrapolation used for both arms	RCS lognormal (U) extrapolation represents the best fitting curve, that does not overestimate TTD, using updated MONALEESA-3 data (see section A.8.2.3 for detailed argument)

Utility values	Healthy-state utility values were directly derived from EQ-5D-5L assessment on MONALEESA-3 (2017). [redacted] [redacted] EQ-5D collected in MONALEESA-3, mapped to EQ-3L	Healthy-state utility values were directly derived from EQ-5D-5L assessment on MONALEESA-3 (2019). [redacted] [redacted] EQ-5D collected in MONALEESA-3, mapped to EQ-3L	Utilities updated in line with updated MONALEESA-3 data
Cost and healthcare resource use	See TA593	As per TA593 with following exceptions: Updated unit costs but not frequencies of healthcare services for follow-up and monitoring 10% discount for fulvestrant used in base case	Frequencies have stayed the same since CDF model **Fulvestrant pricing**: the patent for fulvestrant is due to expire in [redacted]. Whilst the future cost of fulvestrant is unknown, it is felt that a 10% reduction in average selling price compared to current list price would represent a conservative estimate of the price reduction. This estimate is based on the average selling prices of other molecules, following their loss of exclusivity. Novartis are aware of at least 7 licence applications by manufacturers for the future supply of fulvestrant in the UK (see Appendix H). Note: several scenario analyses were performed taking into account a range of possible cost discounts related to fulvestrant's generic status and multiple new market entries (see section A.11 and Appendix H)

[a] Model inputs as per revised base case for TA593.
ERG, Evidence Review Group; HR, hazard ratio; NMA, network meta-analysis; PAIC, population-adjusted indirect comparison; PAS, patient access scheme; PFS, progression-free survival; PPS, post-progression-free survival; RCS, restricted cubic spline.

A.10 Cost-effectiveness results (deterministic)

Confidential PAS's (both in the form of simple discounts) are already in place for ribociclib and everolimus in their licensed indications, and the same schemes are available for the indication in this current appraisal. Four cost-effectiveness scenarios are presented, methodologically summarised in Table 17 and results in Table 18. The assessments performed are:

- Scenario 1.1 (replication of model at CDF entry);
- Scenario 1.2 (replication of model at CDF entry but with several corrections made to the model [see section A.8.1.4]);
- Scenario 2 (scenario 1.2 with updated clinical data from MONALEESA-3), and;
- Scenario 3 (scenario 2 with updated costs i.e. the new base case).

Table 17. Key methodological details of presented cost-effectiveness analyses

	½ cycle correction[a]	Mortality application correction for PPS[a]	Removal of programming bugs[a]	Application of new MONALEESA-3 data	Application of new costs, utilities and parameterisation
CEA 1.1[b]	✗	✗	✗	✗	✗
CEA 1.2	✓	✓	✓	✗	✗
CEA 2	✓	✓	✓	✓	✗
CEA 3 (new base case)	✓	✓	✓	✓	✓

[a] detailed in section A.8.1.4.
[b] replication of most plausible CEA at CDF entry
CDF, Cancer Drug Fund; CEA, cost-effectiveness analysis.

A.10.1 *Cost-effectiveness analysis 1.1: cost-effectiveness analysis that demonstrated plausible potential for cost-effectiveness at CDF entry*

In the published NICE TA593 (i.e. at CDF entry) over a lifetime horizon, the total costs associated with ribociclib plus fulvestrant were estimated to be [redacted] compared to [redacted] for those receiving everolimus and exemestane (an incremental cost of £1,498) (Table 18). The total QALYs for patients receiving ribociclib plus fulvestrant were estimated to be 2.55 compared to 2.48 for those receiving everolimus and exemestane (an incremental QALY gain of 0.07).

As such, the ICER for ribociclib plus fulvestrant in patients with HR+/HER2– advanced breast cancer, who have received prior endocrine therapy in the advanced setting or relapsed on or within 12 months of completing (neo)adjuvant endocrine treatment, was £21,068/QALY when compared with everolimus plus exemestane. This is a precise replication of the ICER, based on Committee-preferred assumptions from TA593.

A.10.2 *Cost-effectiveness analysis 1.2: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with model corrections*

Based on the analysis 1.1, and recognising the concerns raised by the ERG in TA593, the model was also run based on the corrections identified in section A.8.1.4. Using the clinical data available at the time of the TA593 submission (and all other committee-preferred parameter values), this analysis results in total costs associated with ribociclib plus fulvestrant of [redacted], compared to [redacted] for those receiving everolimus and exemestane (a cost difference of £1,478, Table 18). The total QALYs for patients receiving ribociclib plus fulvestrant are estimated to be 3.60 compared to 3.49 for those receiving everolimus and exemestane (an incremental QALY gain and 0.07).

As such, the ICER for ribociclib plus fulvestrant in this scenario is £20,412/QALY, when compared with everolimus plus exemestane, which is broadly consistent with the scenario 1.1 (£21,068/QALY).

A.10.3 *Cost-effectiveness analysis 2: cost-effectiveness analysis used at CDF entry incorporating updated clinical analysis*

Updating the CDF entry model with clinical data from the 3 June 2019 data cut along with model corrections (CEA 1.2), whilst retaining all other Committee-preferred model parameter and input values from TA593, leads to an estimated total cost for ribociclib plus fulvestrant of [redacted], and [redacted] for those receiving everolimus and exemestane (a cost difference of –£1,129 [saving]). The total QALYs for patients receiving ribociclib plus fulvestrant are estimated to be 3.01, and 2.93 for those receiving everolimus and exemestane (an incremental QALY gain of 0.08; Table 18).

In this scenario, ribociclib plus fulvestrant is estimated to dominate everolimus plus exemestane.

A.10.4 *Cost-effectiveness analysis 3: new company base case*

An updated base case was developed, based on the specification outlined in Table 16. This analysis estimates total costs associated with ribociclib plus fulvestrant of [redacted], compared to [redacted] in the everolimus and exemestane arm (an incremental cost of £1,478, Table 18). The total QALYs for patients receiving ribociclib plus fulvestrant are estimated to be 2.80, compared to 2.71 for those receiving everolimus and exemestane (an incremental QALY gain of 0.09).

As such, based on the latest available clinical data, the ICER for ribociclib plus fulvestrant in patients with HR+/HER2– advanced breast cancer, who have received prior endocrine therapy in the advanced setting or relapsed on or within 12 months of completing (neo)adjuvant endocrine treatment, is £23,022/QALY when compared with everolimus plus exemestane.

Table 18. Cost-effectiveness results (deterministic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental. costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Cost-effectiveness analysis 1.1: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry[a]								
Ribociclib + Fulvestrant	[redacted]	3.56	2.55	–	–	–	–	–
Everolimus + Exemestane	[redacted]	3.46	2.48	1,498	0.10	0.07		21,068
Cost-effectiveness analysis 1.2: Replication of analysis that demonstrated plausible potential for cost-effectiveness at CDF entry, with model corrections[a,b]								
Ribociclib + Fulvestrant	[redacted]	3.60	2.55	–	–	–	–	
Everolimus + Exemestane	[redacted]	3.49	2.48	1,478	0.10	0.07		20,412
Cost-effectiveness analysis 2: Analysis that demonstrated plausible potential for cost-effectiveness at CDF entry – incorporating updated clinical evidence[a]								
Ribociclib + Fulvestrant	[redacted]	4.21	3.01	–	–	–	–	–
Everolimus + Exemestane	[redacted]	4.09	2.93	-1,129	0.12	0.08		Dominant
Cost-effectiveness analysis 3: New company base-case								
Ribociclib + Fulvestrant	[redacted]	3.87	2.80	–	–	–	–	–
Everolimus + Exemestane	[redacted]	3.76	2.71	2,003	0.11	0.09		23,022

[a] This scenario is based on the extrapolations exponential for PPS, Gompertz (U) for ribociclib +fulvestrant, and RCS Weibull for fulvestrant, used in the CDF entry model. From the model entering the CDF we cannot be certain of which 3 knot spline was chosen without further information. We chose to run the RCS3 Weibull based on the suggestion of using a 3-knot spline and using the PH assumption.
[b] See section A.8.1.4 for a description of model corrections
CDF, Cancer Drug Fund; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PH, proportional hazards; PPS, post-progression survival; RCS, restricted cubic spline; QALYs, quality-adjusted life years; U, unrestricted.

A.11 Key sensitivity and scenario analyses

A.11.1 *Probabilistic sensitivity analysis*

Probabilistic sensitivity analyses were conducted to take into account the simultaneous effect of uncertainty relating to model parameter values. A total of 1,000 simulations were performed in order to provide sufficient information on uncertainty. Uncertainty surrounding all important model parameters were described by probability distributions (gamma for costs, beta for binomial and Dirichlet for multinomial proportion, multivariate normal for regression models) and propagated through the model using Monte Carlo sampling. The choice of distribution was based on consideration of the properties of the parameters and data informing the parameters. These parameters were the same ones used in TA593, save for one change (current PSA varied cost parameters with a lognormal distribution, whereas in the CDF entry model PSA, they were not varied). The results of the probabilistic sensitivity analysis are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (Figure 24 and Figure 25, respectively) and summarised in Table 19.

Over a lifetime, patients receiving ribociclib in combination with fulvestrant accrue more QALYs (2.78 QALYs) than patients initiating everolimus + exemestane (2.73 QALYs), but at a greater cost ([redacted] vs. [redacted] respectively). The ICER is £13,816/QALY gained in the probabilistic sensitivity analysis. Importantly, although the final ICER generated by the PSA is lower than the base case (£13,816/QALY and £23,022/QALY, respectively i.e. ~40%), total costs, LYGs and QALYs generated in the PSA (Table 19) are similar (variation < 1%) to those of the base case (Table 18). Therefore, small changes in total costs or QALYs can have a relatively large impact on the ICER.

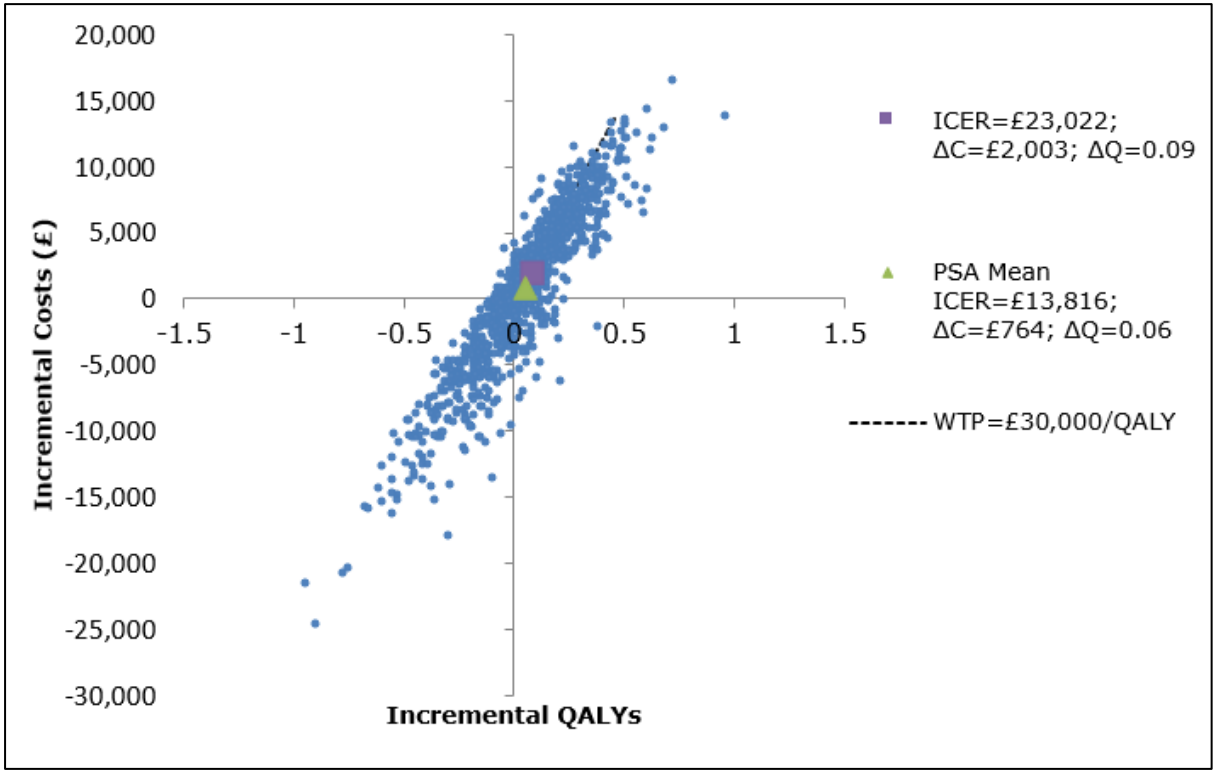
The cost-effectiveness plane and cost-effectiveness acceptability curves for comparisons against everolimus plus exemestane are presented below in respective order. The probability of ribociclib plus fulvestrant being a cost-effective strategy is 60.9% when using a threshold of £30,000/QALY when compared to everolimus plus exemestane.

Table 19. Updated base-case results (probabilistic)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)	Incremental ICER (£/QALY)
Ribociclib + fulvestrant	[redacted]	3.86	2.78					
Everolimus + exemestane	[redacted]	3.79	2.73	764	0.06	0.06		13,816

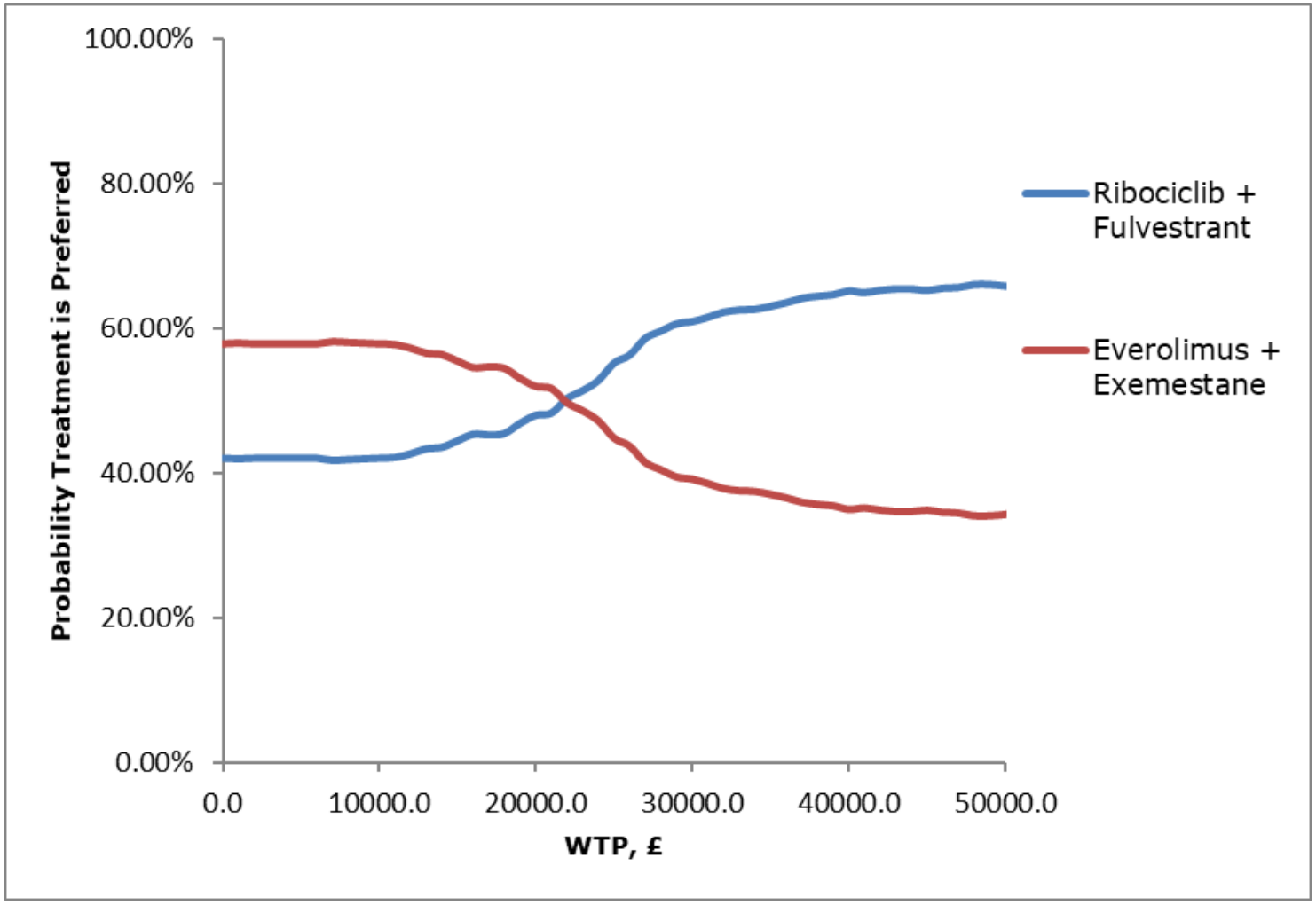
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Figure 24. Cost-effectiveness plane ribociclib plus fulvestrant vs everolimus plus exemestane



C, cost; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; Q, QALY, QALYs, quality-adjusted life years; WTP, willingness to pay.

Figure 25. Cost-effectiveness acceptability curve ribociclib plus fulvestrant vs everolimus plus exemestane

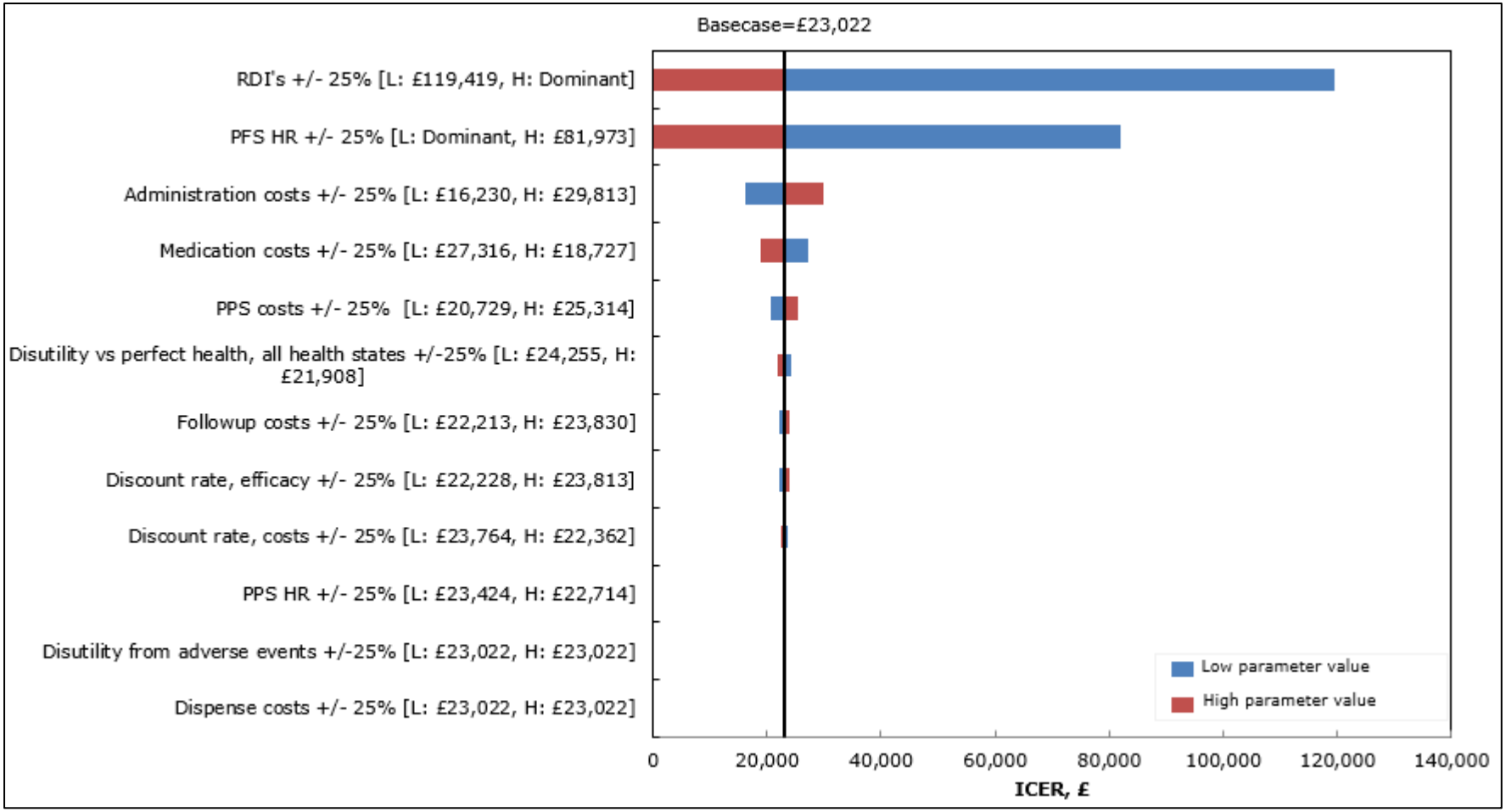


WTP, willingness to pay.

A.11.2 *Deterministic sensitivity analysis*

A Tornado diagram is presented in Figure 26 for the parameters that had the largest impact on the base case ICER.

Figure 26. Tornado diagram for the updated base case



ICER, incremental cost-effectiveness ratio; H, high; HR, hazard ratio; L, low; PFS, progression-free survival; PPS, post-progression survival; RDI, relative drug intensity.

A.11.3 *Scenario analyses*

Important variables in the model were varied in scenario analyses (these are the same variables run in the CDF entry model for MONALEESA-3 subpopulation Bi and Bii+Biii plus the inclusion of several key ITC variations). Results from these scenarios are presented in Table 20. The scenario analyses indicated that, even when a wide number of variables are considered, the resulting ICERs are similar to the base case analysis and can be considered supportive of a robust base case analysis.

Table 20. Key scenario analyses

Scenario	Total cost (£) ribociclib + fulvestrant	Total cost (£) everolimus + exemestane	Total QALYs ribociclib + fulvestrant	Total QALYs everolimus + exemestane	Incremental costs (£)[a]	Incremental QALYs	ICER per QALY gained (£)
Base case 40 years	[redacted]	[redacted]	**2.80**	**2.71**	**2,003**	**0.09**	**23,022**
Time horizon 5 years	[redacted]	[redacted]	2.33	2.28	1,382	0.06	24,196
Time horizon 10 years	[redacted]	[redacted]	2.69	2.61	1,627	0.08	20,368
Time horizon 20 years	[redacted]	[redacted]	2.79	2.71	1,969	0.09	22,746
EQ-5D-5L utility values	[redacted]	[redacted]	3.07	2.97	2,003	0.09	21,363
Lloyd *et al.* PPS utility value	[redacted]	[redacted]	2.46	2.38	2,003	0.08	25,534
PFS - Lognormal (R)	[redacted]	[redacted]	2.77	2.69	2,753	0.09	31,839
PFS - Lognormal (U)	[redacted]	[redacted]	2.86	2.77	774	0.09	8,391
PFS - General Gamma (R)	[redacted]	[redacted]	2.79	2.70	2,362	0.09	26,937
PFS - General Gamma (U)	[redacted]	[redacted]	2.93	2.83	-942	0.10	Dominant
PFS - Log-Logistic (R)	[redacted]	[redacted]	2.87	2.78	359	0.09	3,827
PFS - Log-Logistic (U)	[redacted]	[redacted]	2.94	2.84	-1,328	0.10	Dominant
PFS - Gompertz (R)	[redacted]	[redacted]	2.79	2.70	2,348	0.09	26,521
PFS - Gompertz (U)	[redacted]	[redacted]	2.78	2.70	2,484	0.09	28,206
PFS - Weibull (R)	[redacted]	[redacted]	2.61	2.53	2,512	0.08	32,266

PFS - Weibull (U)	[redacted]	[redacted]	2.62	2.54	2,582	0.08	32,904
PFS - General F (R)	[redacted]	[redacted]	2.79	2.70	2,360	0.09	26,913
PFS - General F (U)	[redacted]	[redacted]	2.93	2.83	-954	0.10	Dominant
PPS - Exponential	[redacted]	[redacted]	3.02	2.93	2,172	0.09	23,470
PPS Gen. Gamma	[redacted]	[redacted]	2.76	2.67	1,971	0.09	22,936
PPS Weibull	[redacted]	[redacted]	2.92	2.83	2,098	0.09	23,278
TTD Ribo Gen. Gamm (U)	[redacted]	[redacted]	2.80	2.71	1,521	0.09	17,478
TTD Ribo RCS Weibull (U)	[redacted]	[redacted]	2.80	2.71	783	0.09	9,004
TTD Ribo RCS Log-Logistic (U)	[redacted]	[redacted]	2.80	2.71	2,883	0.09	33,793
TTD Ful Gen. Gamma (U)	[redacted]	[redacted]	2.80	2.71	2,007	0.09	23,070
TTD Ful RCS Weibull (U)	[redacted]	[redacted]	2.80	2.71	1,022	0.09	11,660
TTD Ful RCS Log-Logistic (U)	[redacted]	[redacted]	2.80	2.71	2,453	0.08	28,892
Fulvestrant no discount	[redacted]	[redacted]	2.80	2.71	3,293	0.09	37,853
Fulvestrant (-20%)	[redacted]	[redacted]	2.80	2.71	713	0.09	8,190
Fulvestrant (-30%)	[redacted]	[redacted]	2.80	2.71	-578	0.09	Dominant
Fulvestrant (-40%)	[redacted]	[redacted]	2.80	2.71	-1,868	0.09	Dominant
Fulvestrant (-50%)	[redacted]	[redacted]	2.80	2.71	-3,159	0.09	Dominant
Fulvestrant (-60%)	[redacted]	[redacted]	2.80	2.71	-4,449	0.09	Dominant
PAIC PFS HR values	[redacted]	[redacted]	2.80	2.16	15,281	0.64	23,778
NMA for PFS anchored on fulvestrant PFS	[redacted]	[redacted]	2.80	2.71	2,005	0.09	23,022
PPS curves estimated with data from BOLERO-2	[redacted]	[redacted]	2.74	2.61	3,417	0.14	25,231

[a] Due to rounding, some incremental costs do not exactly match difference between comparator costs.
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; R, restricted; U, unrestricted.

A.12 End-of-life criteria

Based on updated MONALEESA-3 data,[14] ribociclib does not meet end of life criteria.

Table 21 End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	MONALEESA-3 comparator arm median OS was 32.5 months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	Yes

NHS, National Health Service; OS, overall survival.

A.13 Key issues and conclusions based on the data collected during the CDF review period

At TA593 CDF entry,[1] several parameters were identified by the Appraisal Committee as likely sources of uncertainty in the original model, and consequently the resulting base case.

Below, we set out the key uncertainties identified by the Appraisal Committee, as captured within the current Terms of Engagement document for this CDF review (first bullet text in italics),[2] followed by our approach to reducing these uncertainties in this submission (second bullet, not italicised):

- *The committee considered that the results of the network meta-analysis 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 proportional hazards assumption had not been met in the MONALEESA-3 trial, so using a hazard ratio dependent on this trial is likely to be unreliable.* ***The***

company should update the network meta-analysis and should explore the most appropriate trials to include and the most appropriate method to compare progression-free survival and overall survival across the treatments.[2]

- In this update, the NMA has been strengthened by the incorporation of mature OS data from MONALEESA-3 (Section A.7.1 and Appendix F.1.1). Analysis of Schoenfeld residuals based on the updated data suggests that the PH assumption is not violated and therefore supports the use of the hazard ratio from this trial in comparisons with other trials in the network (Section A.8.2.3). Whilst some uncertainty remains due to the heterogenous nature of some of the studies included, the inclusion of a second ITC (PAIC) using IPD directly from both MONALEESA-3 and BOLERO-2 (Section A.7.1 Appendix F.1.2, and presented as a scenario analysis (Section A.11.3) suggest that the residual uncertainty in the NMA is in the form of under-estimating the treatment effectiveness (in terms of PFS) of ribociclib plus fulvestrant relative to everolimus plus exemestane. However, if the PAIC comparative data for PFS were applied to the base case, the resulting QALY gain would be expected to be fairly similar to the base case (£23,778/QALY) as a result of increased drug costs over a longer time to PFS (and a similar underlying HR).

- *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.[2]***

  - The parametric extrapolation applied to modelled TTD was RCS Lognormal (U) (Section A.8.2.3).

- *The company used data from the MONALEESA-3 trial to estimate post-progression survival for ribociclib and fulvestrant. Because no exemestane with everolimus post-progression survival data were available, the company assumed that post-progression survival 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 post-progression survival was the same for exemestane with everolimus and ribociclib with fulvestrant. ***The company should explore the most appropriate approach for estimating and extrapolating post-progression survival.***

- To address this issue, we have presented a PPS comparison between these interventions (see section A.8.2.3) and show that this assumption is reasonable.

Therefore, based upon these methodological updates (and others identified by the ERG in TA593), along with the updated MONALEESA-3 data cut, we consider there is greater certainty around the comparison between ribociclib + fulvestrant and everolimus + exemestane within this analysis. Moreover, when comparing the different PFS/OS HRs generated by the NMA and PAIC analyses,† it is likely that the base case incremental QALY is an underestimation of the true effectiveness of ribociclib plus fulvestrant compared to everolimus plus exemestane. This is demonstrated in the PAIC scenario analysis where the incremental QALY was 0.64 in favour of ribociclib + fulvestrant (although this led to a similar ICER [£23,778] due to increased drug costs to progressive disease).

The analyses presented in this submission are a focused update to those preferred by the Appraisal Committee in their consideration of TA593, which ultimately resulted in the inclusion of ribociclib and fulvestrant on to the CDF.[1] The assessment considers a distinct and clinically relevant patient subpopulation (subpopulation B) from the pivotal RCT MONALEESA-3, which now has mature OS (and longer-term PFS) data (3 June 2019 data cut).[15] These updated data were not available at the time of the CDF entry, but are consistent with the data reported in the data cut (3 November 2017)[14] used to inform the earlier assessment, along with data generated and captured within the SACT dataset (17 July 2019 and 16 January 2020).[17]

†A more direct form of ITC that makes use of IPD and thus avoids the issues of intervening trial issues described in TA593 and the terms of engagement.

No new safety signals were observed in either MONALEESA-3,[15] or the SACT data (although this data set currently represents a shorter treatment median duration [9.4 months] relative to MONALEESA-3 [15.8 months for ribociclib arm], see section A.6.6).[17] These safety data are typical for toxicity generated for CDK4/6 inhibitors to date, and consistent with emerging real-world evidence showing that key AEs such as neutropenia are similar between ribociclib and palbociclib.[21]

The updated base case shows that ribociclib plus fulvestrant is associated with a higher QALY gain than everolimus plus exemestane, with an ICER of £23,022/QALY. These results include the currently agreed PAS for both ribociclib and everolimus. This outcome is also based on an assumed average selling price of fulvestrant which is 10% below the prevailing list price. This is justified as fulvestrant is set to become a generic drug from [redacted], with multiple (7 known), rapid market entries expected (see appendix H), with a resultant significant price cut anticipated. Thus, we believe a 10% discount applied to the base case can be considered a conservative assumption. This variable is further explored in the scenario analyses (section A.11.3), where we used a range of likely fulvestrant price reductions, derived from past precedents within the generics market (which suggest reductions of 20–60%), to show that the likely base case ICER for ribociclib plus fulvestrant relative to everolimus plus exemestane may fall between £8,190/QALY and dominant.

There is a clear unmet need for clinically effective and cost-effective treatments for patients with endocrine resistant advanced HER2-/HR+ breast cancer, recognising that the current standard of care (CDK4/6i's) are only available through the CDF. The MONALEESA-3 trial is a large well designed RCT with a patient cohort (subpopulation B), which is highly applicable to patients treated second line in England, and broadly consistent with SACT data collection. The availability of ribociclib provides clinicians and patients with a wider choice of therapeutic options in this difficult to treat disease, increasing the likelihood of a meaningful clinical response in as many patients as possible.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Cancer Drugs Fund Review of TA593

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (ID3755)

Clarification questions

October 2020

File name	Version	Contains confidential information	Date
ID3755 Ribociclib clarification questions to PM for company [ACIC]	1	Yes	23rd October 2020

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Network meta-analysis

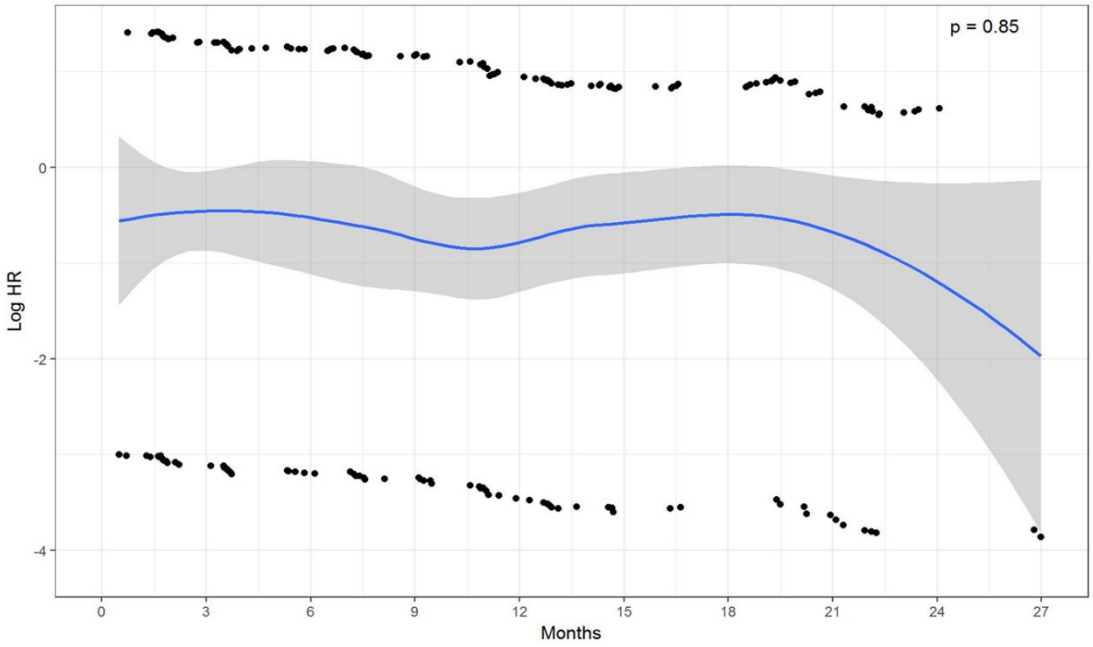
A1. Please provide your assessment of proportional hazards for progression-free survival (PFS) for the trials used in the network meta-analysis.

Plots of Schoenfeld residuals were generated to assess the proportional hazards (PH) assumption. In order to test the PH assumption, the slope of the scaled Schoenfeld residuals was tested using linear regression.

MONALEESA-3 (Group B Patients)

A plot of a smoothed curve fit to the scaled Schoenfeld residuals for the treatment group covariate in a Cox proportional hazard regression model is provided in Figure 1. The slope of the scaled Schoenfeld residuals was tested and was found to not deviate significantly from zero (p=0.85), suggesting that a proportional hazards assumption may be appropriate.

Figure 1: Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS for Patients in Group B of MONALEESA-3



BOLERO-2

A plot of a smoothed curve fit to Schoenfeld residuals for PFS for patients in BOLERO-2 is shown in Figure 2.The p-value on the test of non-proportionality is statistically significant (p=0.005), suggesting that the PH assumption may be violated. This may bias the comparison using the HRs from the Bucher NMA in favour of everolimus + exemestane, as the HR for everolimus + exemestane vs exemestane appears to be increasing over time, as shown in Figure 3.

Figure 2: Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS for Patients in BOLERO-2

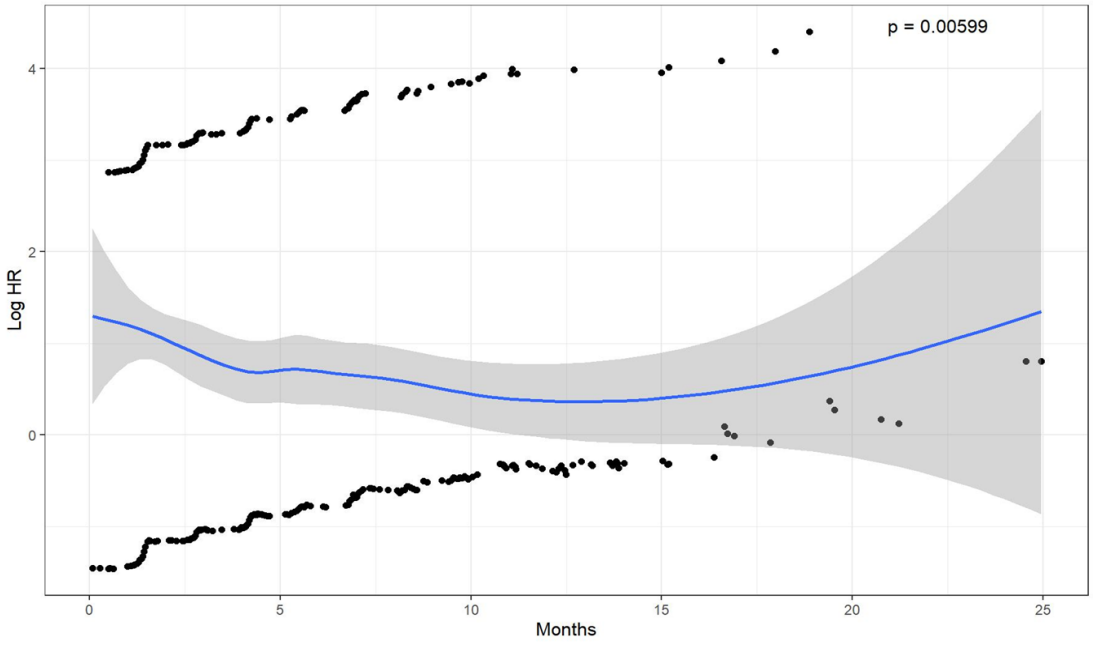
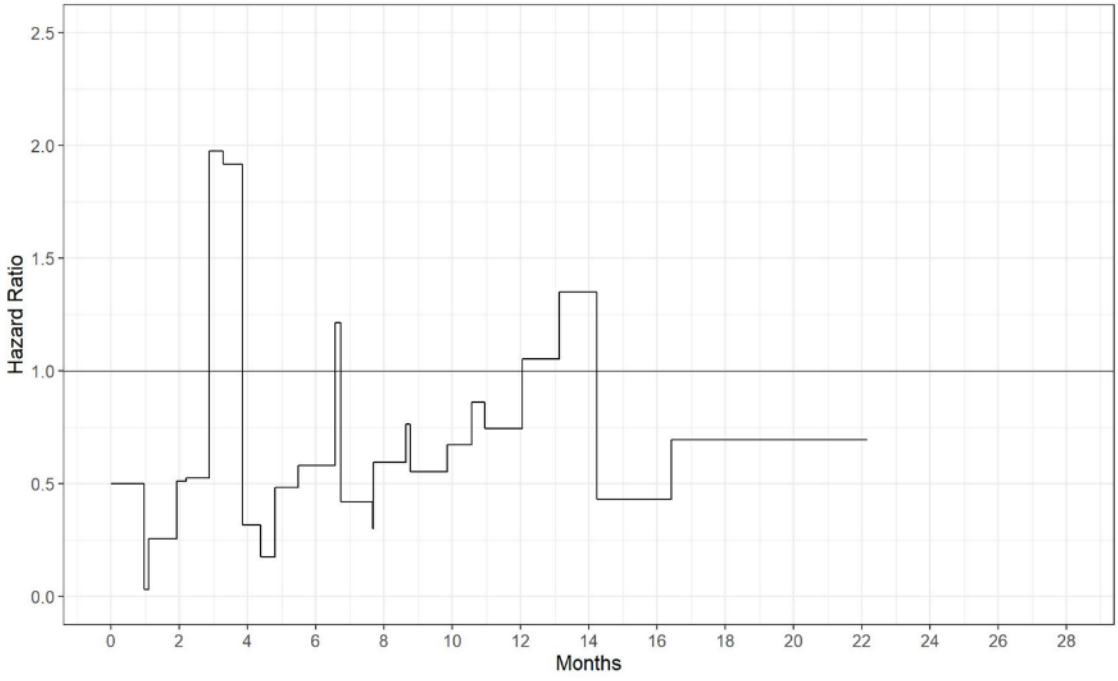


Figure 3: Plot of HR for PFS for Everolimus + Exemestane vs Exemestane in BOLERO-2



CONFIRM, EFECT, SoFEA. A plot of a smoothed curve fit to Schoenfeld residuals for PFS for patients in the CONFIRM, EFECT and SoFEA trials are shown in Figures 4, 5 and 6, respectively. The p-value on the test of non-proportionality for

each of these trials is not significant, suggesting that the PH assumption is not unreasonable.

Figure 4: Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS for Patients in CONFIRM

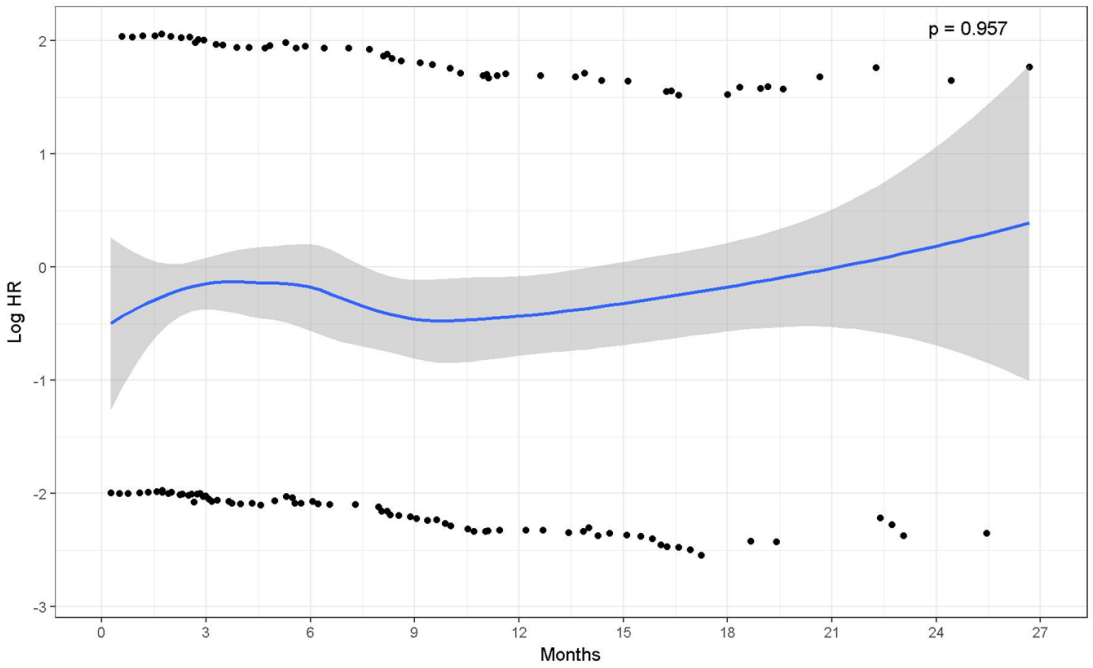


Figure 5: Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS for Patients in EFECT

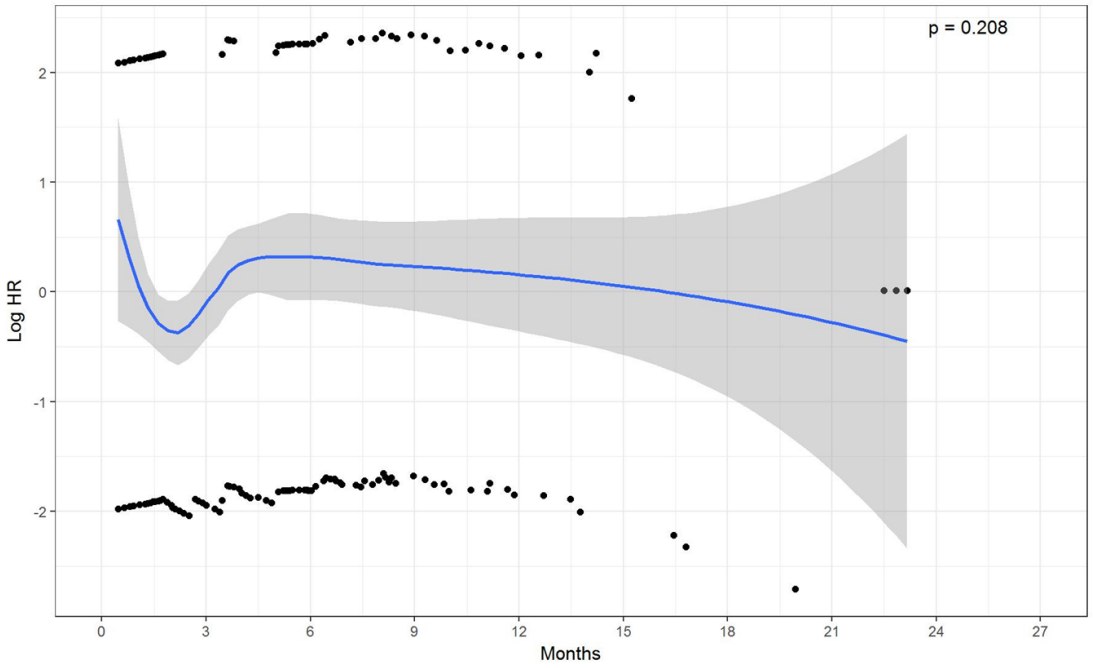
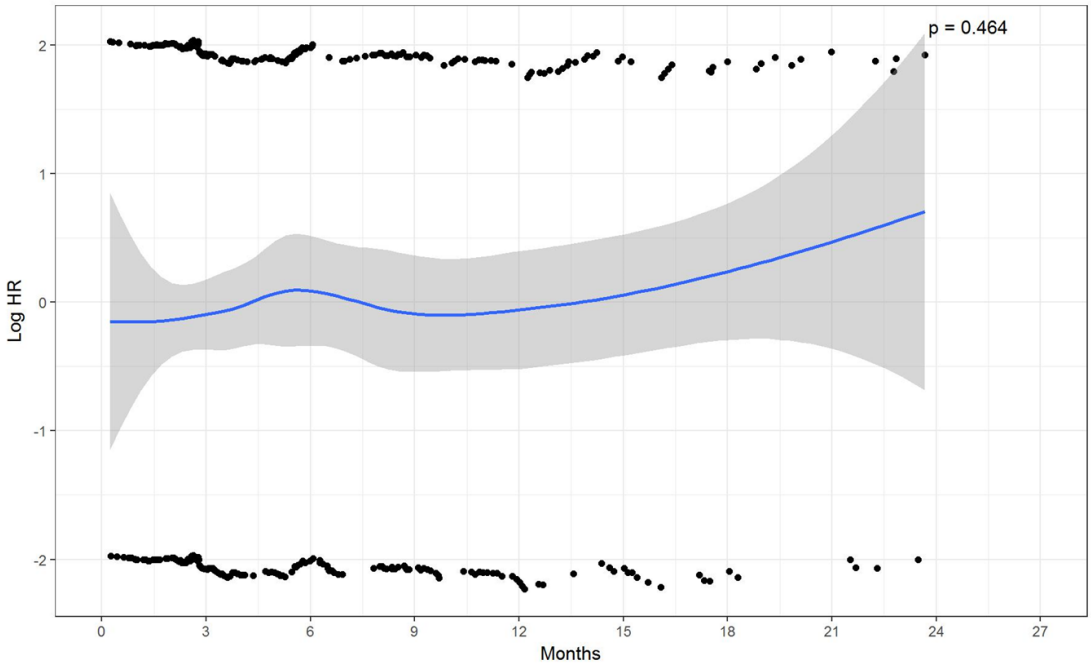


Figure 6: Plot of Smoothed Curve fit to Schoenfeld Residuals for PFS for Patients in SoFEA



Based on the result of the assessment for BOLERO-2, Novartis will be exploring the use of alternative approaches to estimate time-dependent HRs (e.g. hazards characterized as fractional polynomials). It has not been possible to provide these assessments as part of this response, due to the time available.

A2. Priority question: The preferred committee assumptions ask the company to explore the most appropriate methods to compare overall survival across the treatments. In light of this, please conduct a network meta-analysis (NMA) for overall survival and provide the results along with details of the methodology used.

The type of analysis will be determined by whether the proportional hazards (PH) assumption holds for each trial in the network. If PH hold, please provide details of your assessment of PH. If PHs are shown not to hold, please consider an alternative method that can more appropriately account for a variable hazard, for

example, fractional polynomial (FP) NMA (Jansen BMC Medical Research Methodology 2011, 11: 61). Please also see question B6.

Schoenfeld residual plots were generated for all four trials used in the network (see Figure 7 below [while the EFECT trial was included in the PFS NMA, OS was not reported and therefore it was not included in the OS NMA]). The tests of linearity of the Schoenfeld residuals was not statistically significant for any trial suggesting that the assumption of PH is not unreasonable. For BOLERO-2, although the p-value on the test of non-proportionality was not significant (p = 0.161), the smoothed curve fit to the residuals has a decreasing slope. Fuller details are presented in Figures 8-11 for MONALEESA-3, BOLERO-2, CONFIRM and SoFEA, respectively.

Figure 7: NMA Network

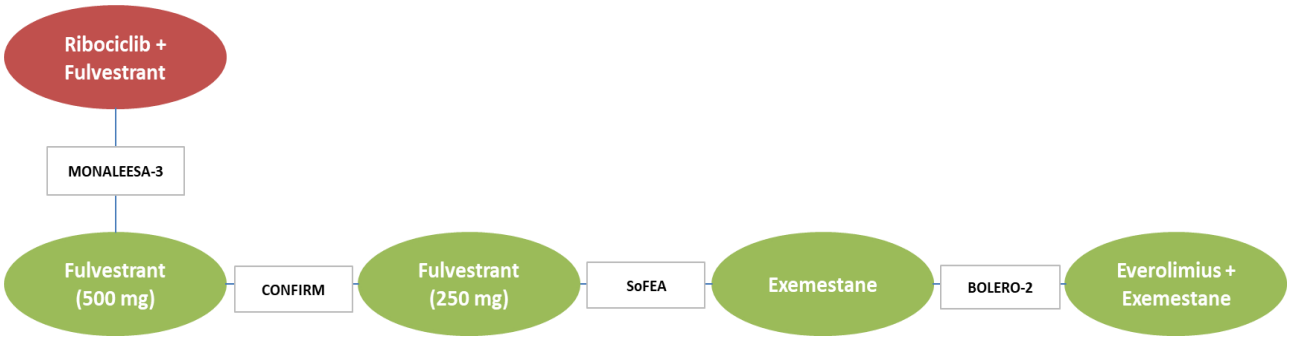


Figure 8: Plot of Smoothed Curve fit to Schoenfeld Residuals for OS for Patients in Group B of MONALEESA-3

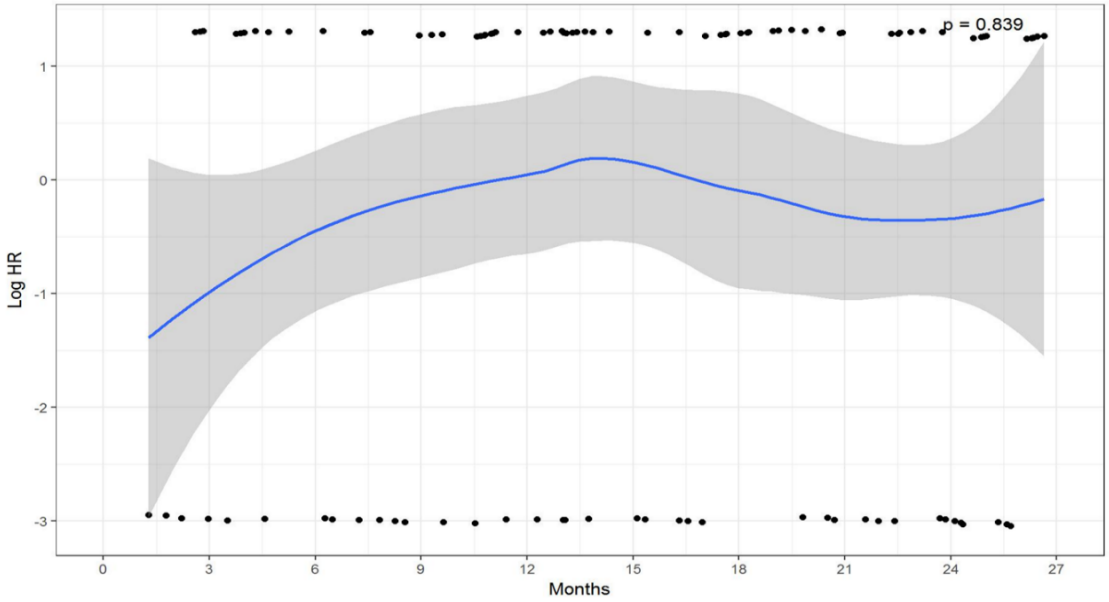


Figure 9: Plot of Smoothed Curve fit to Schoenfeld Residuals for OS for Patients in BOLERO-2

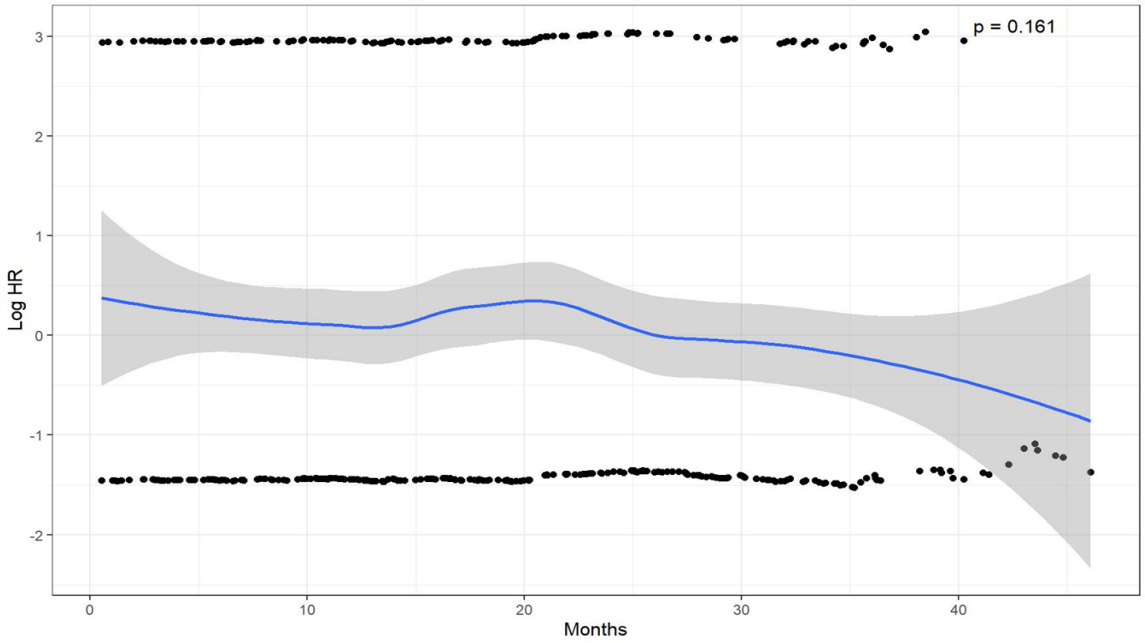


Figure 10: Plot of Smoothed Curve fit to Schoenfeld Residuals for OS for Patients in CONFIRM

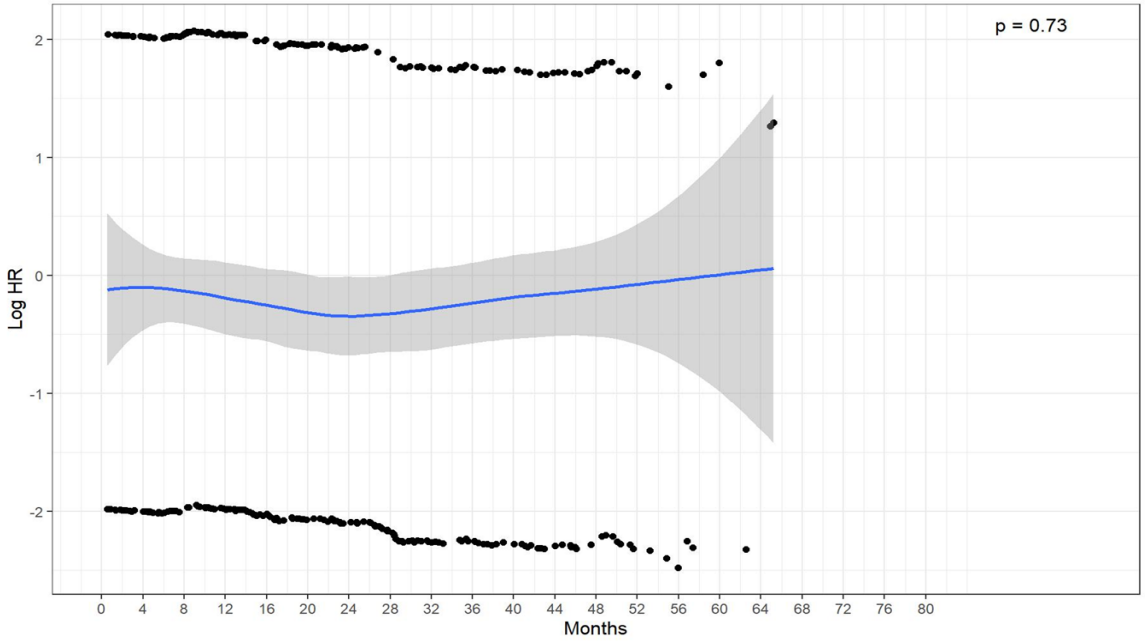
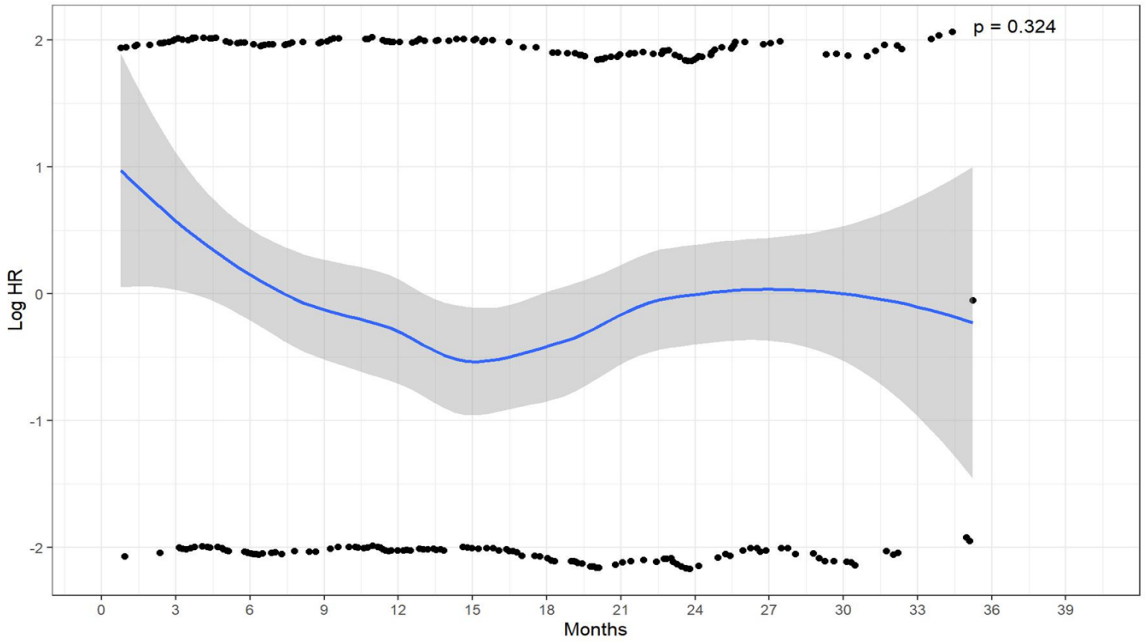


Figure 11: Plot of Smoothed Curve fit to Schoenfeld Residuals for OS for Patients in SoFEA



Based on the analyses of Schoenfeld residuals suggesting that the PH assumption is not violated for any of the comparisons in the network, the use of an alternative approach that accounts for variable hazard ratios, such as the use of fractional polynomials as proposed by Janssen (2011), is unnecessary.

The OS NMA based on the Bucher method was carried out at the same time as the PFS NMA based on the Bucher method. Results of the former analysis were not included in the CDF submission as OS was not used in the semi-Markov economic model. Results of the OS NMA based on the Bucher method are as shown in the table below.

The OS NMA based on the Bucher method was carried out at the same time as the PFS NMA based on the Bucher method. Results of the former analysis were not included in the CDF submission as OS was not used in the semi-Markov economic model. Results of the OS NMA based on the Bucher method are as shown in the table below.

Estimated HRs for OS for Subpopulation B based on Bucher NMA

	HR, Treatment vs. Fulvestrant 500mg		HR, Treatment vs. Ribociclib + Fulvestrant		HR, Ribociclib + Fulvestrant vs Treatment	
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]

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

As noted above, while the test of non-linearity of Schoenfeld residuals were not statistically significant for any of the trials included in the NMA of OS, the p-value for BOLERO-2 was trending towards significance (p=0.161) and the smoothed curve of the residuals was decreasing, providing some evidence of non-PH for OS in this trial. Accordingly, Novartis will be exploring alternative methods for estimating time dependent HRs.

A3. On page 20 of the Appendix it states "HRs for PFS for other comparators versus fulvestrant were based on an ITC of RCTs of the comparators of interest identified by SLR conducted in April 2018 and supplemented with a targeted, non-systematic review conducted in July and August of 2018". Please explain why the search dates were not updated in the systematic literature review to 2020.

An full SLR update was performed to 06 March 2019 (this text was erroneously not updated in Appendix G). The same twenty-one studies were identified as a potential evidence base for constructing a NMA for subpopulation B (table below).

Based on this SLR, and likely future studies identified (e.g. as congress abstracts or grey literature searches of clinicaltrials.gov), as well as *ad hoc* pubmed searches, Novartis are not aware of any new studies or relevant updates to existing studies up to the CDF submission of September 2020.

Studies Identified by SLR (to 06 March 2019)

Trial/Source	Treatment	Control	Source/Notes
ANZBCTG COSA	Anthracyclines	Tamoxifen	Only 25% had known HR status (ER+). HRs for PFS and OS in ER+ subgroup were not reported. HR assumed to be 1.0.
BOLERO-2	Everolimus + Exemestane	Exemestane	PAI analyses of BOLERO-2 data for patients receiving second-line treatment of metastatic disease using Cox proportional hazards regression.
BOLERO-6	Everolimus + Exemestane	CAP	Includes first- and subsequent-line ABC patients. Phase II trial, however, it is the only direct comparison of capecitabine and everolimus + exemestane.
CONFIRM	Fulvestrant 500 mg	Fulvestrant 250 mg	HER2 status was not evaluated.
EFECT	Fulvestrant 250 mg	Exemestane	Includes first- and second-line ABC patients, however, at least 90% were second-line.
FALCON	Fulvestrant 500 mg	AI	Only first-line. Less than 1% of patients were ER-, and <1% were HER2+.
FIRST	Fulvestrant 500 mg	AI	Only first-line. Approximately 19% of patients had HER2 status 2+/3+, while ~47% were HER2-, and 34% had unknown HER2 status.
MONALEESA-2	Ribociclib + AI	AI	Only first-line.
MONALESSA-3	Ribociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	PAI analyses of MONALEESA-3 Data
MONARCH-2	Abemaciclib + Fulvestrant 500 mg	Fulvestrant 500 mg	Includes both first- and second-line patients, as well pre- and postmenopausal women. At least 40% of patients were receiving second-line treatment for ABC. Approximately 80% of patients were postmenopausal. HRs of PFS for abemaciclib vs placebo, by line of therapy were not provided.

Trial/Source	Treatment	Control	Source/Notes
MONARCH-3	Abemaciclib + AI	AI	Only first-line.
North American	Tamoxifen	AI	39% of patients had unknown HR status (HER2 status was not evaluated)
PALOMA-2	Palbociclib + AI	AI	Only first-line.
PALOMA-3	Palbociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	Includes both first- and subsequent-line patients, as well pre- and postmenopausal women. Approximately 45% of patients were receiving second-line treatment for ABC; corresponding values for first-line and greater than second-line were ~25% and ~30%, respectively. Approximately 80% of patients were postmenopausal. HRs of PFS for placebo vs placebo, by line of therapy were not provided in this paper
Piccart-Gebhart NMA	Paclitaxel	Anthracyclines	Meta-analysis of single agent taxanes vs. single agent anthracycline in 1st line MBC; In taxane trials, approximately 90% of patients received paclitaxel; 10% docetaxel
PO25	AI	Tamoxifen	Only first-line. 33% of patients had unknown HR status (HER2 status was not evaluated). Cox's regression (univariate); Interval between randomization and earliest date of disease progression (increase of 25% or more in size of measurable lesions, an estimated increase in non-measurable lesions of the appearance of new lesions). Progression free survival not reported
SoFEA	Fulvestrant 250 mg	Exemestane	Includes first- and second-line ABC patients, however, at least 80% were second-line. Approximately 7% of patients were HER2+, while ~33% had unknow status
TAMRAD	Everolimus + Exemestane	Tamoxifen	Approximately 95% of patients were HER2-and 100% were ER and/or PgR positive

Trial/Source	Treatment	Control	Source/Notes
TARGET	Tamoxifen	AI	Only first-line. 39% of patients had unknown HR status (HER2 status was not evaluated)
Tax 311	Docetaxel	Paclitaxel	Approximately 50% were receiving 1st line therapy. Patients were HER2+ or -. HR was based on Log rank statistics (Cox HR not reported)
Trial 0021	Fulvestrant 500 mg	AI	Only second-line treatment. Approximately 80% of patients were ER and/or PgR positive. HER2 status was not evaluated

n.b. trials not used in the NMA are highlighted in grey

ABC, advanced breast cancer; AI, aromatase inhibitor, ER, oestrogen receptor; HER2−, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; MBC, metastatic breast cancer; NMA, network meta-analysis; OS, overall survival; PAI, Policy Analysis Inc.; PFS, progression-free survival; PgR, progesterone receptor.

Population-adjusted indirect comparison

A4. Priority question: The Cox regression analysis results in Table 15 for post progression survival (PPS) appear similar to the population-adjusted indirect comparison (PAIC) conducted for PFS. Please provide more detail of the methods and results of this analysis, including whether this analysis is a PAIC and the matched variables adjusted for. If this analysis differs from the PAIC conducted for PFS, please provide a rationale for this.

In table 15 of the CDF submission (reproduced below), results of Cox regression on PPS are reported using the unweighted (i.e., no PAIC or other adjustments performed) and weighted (i.e., based on the PAIC) samples from BOLERO-2. The methods employed for the PAIC of PPS, including the covariates used to construct the weights, were identical to those employed for the PAIC of PFS.

Table 15. Cox Regression of MONALESSA-3 and BOLERO-2 PPS curves

RIB+FUL M3 vs EVE+EXE B2: Unweighted[a]					
Description	**Parameter Estimate**	**Point Estimate**	**95% Wald Confidence Limits**		**p-value[a]**
treatment RIB+FUL M3 vs EVE+EXE B2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RIB+FUL M3 vs EVE+EXE B2: Weighted[a]					
treatment RIB+FUL M3 vs EVE+EXE B2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] we used the curves after weighting in the curve-fitting, the Cox regression of unweighted curves is provided for context.
[b] Chi-square test
B2, BOLERO-2; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; M3, MONALEESA-3; PPS, post-progression survival; RIB, ribociclib.

A5. Priority question: Please provide updated PFS data as assessed by the blinded independent review committee (BIRC) for subpopulation B of MONALEESA-3, at the latest data cut-off.

BIRC assessment for PFS was only performed up to the point of study unblinding (i.e. 03 November 2017 data cut used in the original submission). An update to these data is therefore not available for the current data cut (03 June 2019).

A6. Please attempt a PAIC analysis for OS, as has been conducted for PFS. Please provide full details of methods and results as provided for the PAIC of PFS in the company submission.

A PAIC of OS for ribociclib + fulvestrant vs. everolimus + exemestane was carried out at the same time as the PFS analysis, but not included in the prior submission as OS was not used in the Markov cohort model. The HRs for OS from the PAIC are shown alongside those for PFS in the table below. The methodology used for the PAIC of OS is the same as that used for the PAIC of PFS as described in the appendix F.

Cox proportional hazards regressions from PAIC

Endpoint	HR (95% CI)	p-value[c]
PFS (unweighted)	[redacted]	< 0.001
PFS (weighted)[a,b]	[redacted]	< 0.001
OS (unweighted)	[redacted]	0.008
OS (weighted)[a,b]	[redacted]	0.025

[a] see appendix F for details of weighting methodology.
[b] these data were applied to a scenario analysis (see section **Error! Reference source not found.**).
[c] not adjusted for weighting.
CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival.

A7. BOLERO-6 (everolimus + exemestane compared with everolimus or capecitabine) has not been included in the network meta-analysis. Please state whether BOLERO-6 could be used in the PAICs for PFS, PPS and OS, and if not, provide the reasons for this.

BOLERO-6 was not included in the NMA because it did not inform the estimation of the HRs for PFS for everolimus + exemestane vs. ribociclib + fulvestrant (see Figure below). The PAIC of PFS for ribociclib plus fulvestrant vs. everolimus, based on data from MONALEESA-3 and BOLERO-2, that was provided as a response to a request for this analysis in the terms of engagement. While it might be feasible to combine the data on everolimus + exemestane from BOLERO-2 and BOLERO-6

and conduct an unanchored PAIC of everolimus + exemestane vs. ribociclib + fulvestrant using the pooled data from the BOLERO trials, these analyses have not been conducted at this time.

A8. Please confirm whether the data used for the PFS PAIC from MONALEESA-3 is investigator-assessed rather than BIRC.

The PFS data used in the PAIC were based on investigator assessment. PFS based on BIRC were not available for this data cut (see response to question A5)

MONALEESA-3

A9. Priority question: The data cut-off used in the submission was June 2019, by which time 275 overall survival events had occurred, and a final data cut-off can be expected when 351 overall survival events have occurred. Is a later data cut-off now available for overall survival? If so, please provide this data and updated analyses.

At the June 2019 data cut-off (second OS analysis), there was a statistically significant difference in OS in the ITT population following 275 deaths. This is the final OS analysis in line with the protocol that states that a third OS analysis at approximately 351 events should only be performed if a statistically significant difference in OS was not observed at the second OS analysis. Since the OS was statistically significant based on the June 2019 data cut-off with 275 events, no further analyses of OS are planned.

A10. Please provide the latest clinical study report (CSR) or addendum for MONALEESA-3 that incorporates the data from the most recent cut-off, including updated information regarding protocol violations and amendments.

No updated CSR was available for the 3 June data cut-off; in lieu of a CSR, we have provided an addendum that summarises the 'First Interpretable Results' (FIR)

from the second overall survival interim analysis (CLEE011F2301 FIR – 2nd OS IA.docx), and includes the final OS analysis, first subsequent neoplastic therapies and the number of protocol deviations. Updated data pertaining to safety and subsequent therapies were taken from the study publication (Slamon *et al*, 2020 *NEJM*: 382: 514–24).

A11. Please provide a table with the numbers at risk, along with the number of patients censored and number with an event for each of the timepoints in:

a) *Figure 3 Kaplan-Meier plot of investigator-assessed PFS for subpopulation B (data cut 3 June 2019)*

b) *Figure 4 Kaplan-Meier plot of investigator assessed OS for subpopulation B (data cut 3 June 2019)*

c) *Figure 5 for time to first chemotherapy after discontinuation*

The requested information is provided in the tables below.

Table for Figure 3

Investigator-assessed PFS – subpopulation B		
	Ribociclib + fulvestrant	**Placebo + fulvestrant**
Number of patients at risk, n	237	109
Number of patients censored, n (%)	Refer to accompanying .rtf file / excel worksheet	
Number of patients with an OS event, n (%)	167 (70)	95 (87)

Table for Figure 4

OS – subpopulation B		
	Ribociclib + fulvestrant	**Placebo + fulvestrant**
Number of patients at risk, n	237	109
Number of patients censored, n (%)	Refer to accompanying .rtf file / excel worksheet	
Number of patients with an OS event, n (%)	102 (43)	62 (57)

Table for Figure 5

Time to first chemotherapy – ITT population		
	Ribociclib + fulvestrant	**Placebo + fulvestrant**
Number of patients at risk, n	484	242
Number of patients censored, n (%)	Refer to accompanying .rtf file	
Number of patients with an OS event, n (%)	182 (38)	115 (48)

A12. Please provide separate KM data of TTD for (1) ribociclib (2) fulvestrant (in combination) and (3) fulvestrant (monotherapy) for subpopulation B of MONALEESA-3. Similarly to question A11 please provide a table with the numbers at risk, along with the number of patients censored and number with an event for each of the timepoints.

Kaplan–Meier data of TTD for ribociclib

TTD - ribociclib	
	Ribociclib
Number of patients at risk, n	Refer to accompanying excel worksheet
Number of patients censored, n (%)	
Number of patients with an OS event, n (%)	

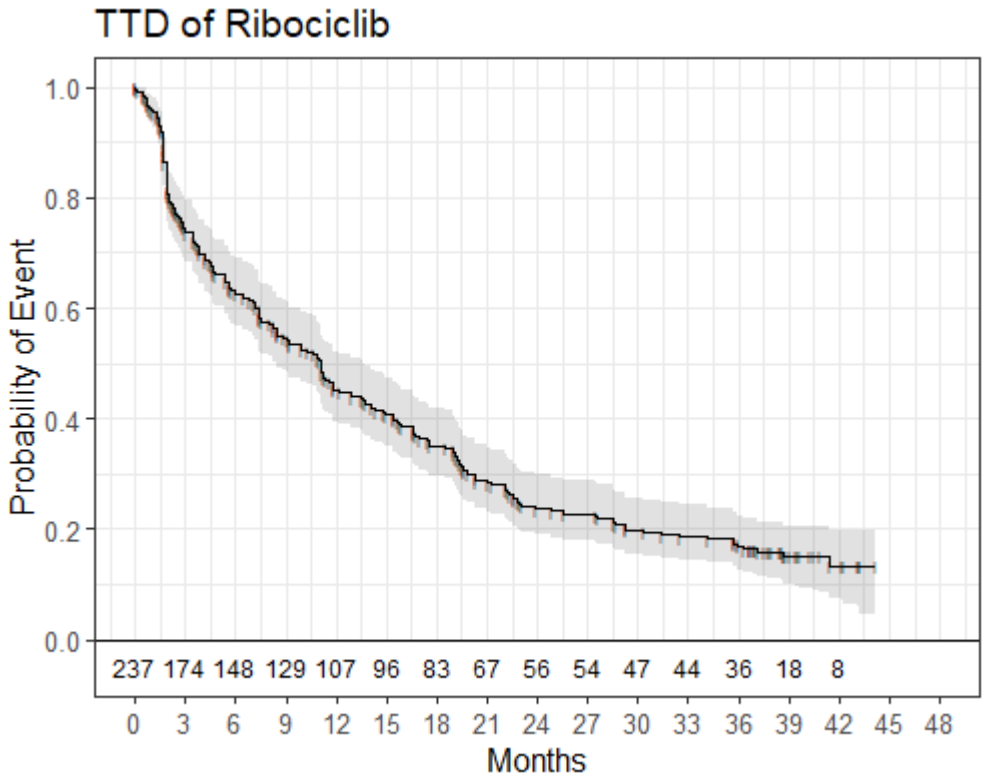
Kaplan–Meier data of TTD for ribociclib plus fulvestrant

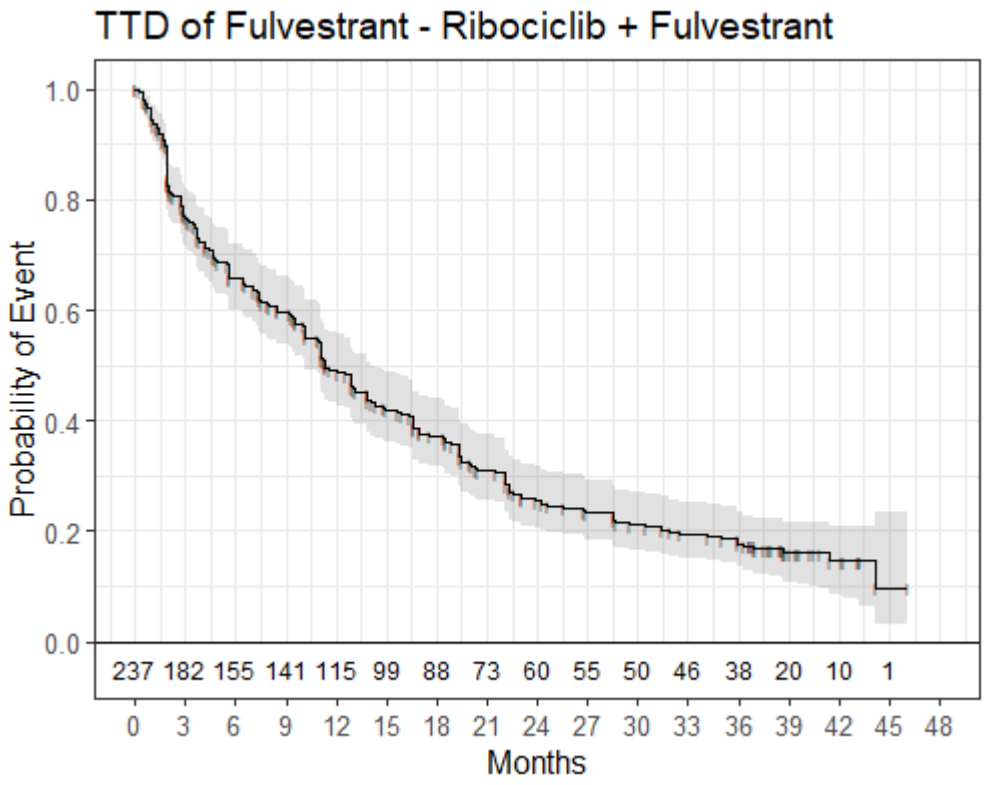
TTD – ribociclib plus fulvestrant	
	Ribociclib plus fulvestrant
Number of patients at risk, n	Refer to accompanying excel worksheet
Number of patients censored, n (%)	
Number of patients with an OS event, n (%)	

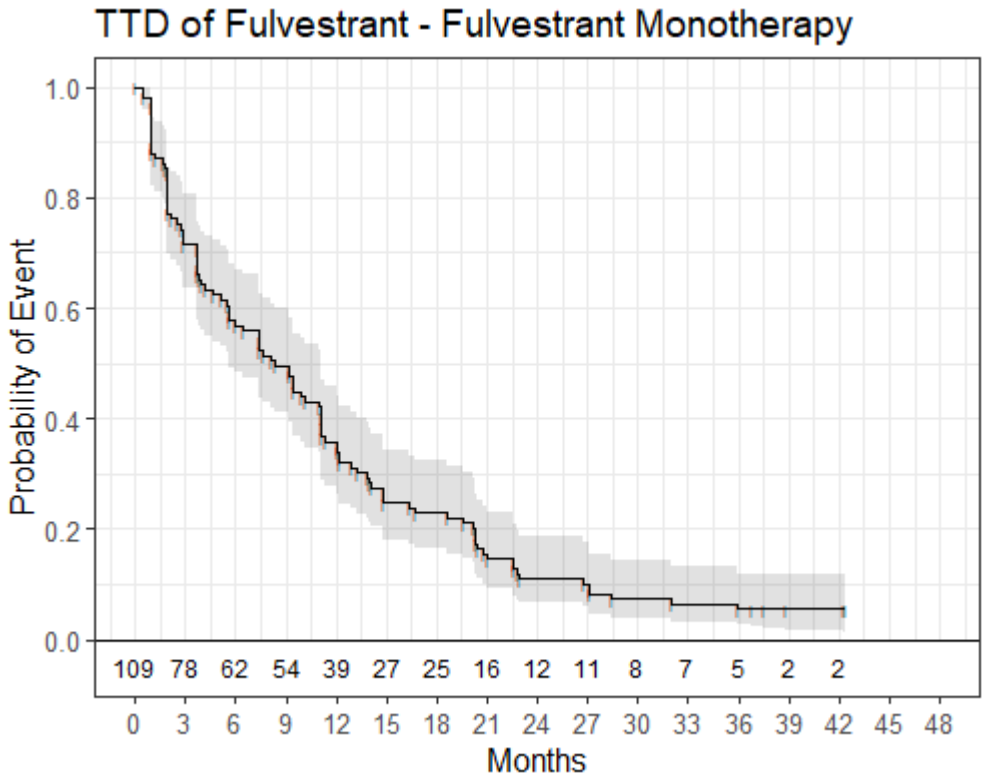
Kaplan–Meier data of TTD for fulvestrant monotherapy

TTD – fulvestrant monotherapy	
	Fulvestrant
Number of patients at risk, n	Refer to accompanying excel worksheet
Number of patients censored, n (%)	
Number of patients with an OS event, n (%)	

In response to the updated request from the ERG, the Kaplan-Meier plots for TTD for (1) ribociclib (2) fulvestrant (in combination) and (3) fulvestrant (monotherapy) for subpopulation B of MONALEESA-3 are provided in the Figures below. Numbers at risk are displayed above the months, and the shaded area represents the 95% CIs:




TTD of Fulvestrant - Ribociclib + Fulvestrant
Probability of Event
1.0
0.8
0.6
0.4
0.2
0.0
237 182 155 141 115 99 88 73 60 55 50 46 38 20 10 1
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months


TTD of Fulvestrant - Fulvestrant Monotherapy
Probability of Event
1.0
0.8
0.6
0.4
0.2
0.0
109 78 62 54 39 27 25 16 12 11 8 7 5 2 2
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48
Months

A13. Please provide the following for overall survival in ribociclib + fulvestrant vs fulvestrant in subpopulation B of MONALEESA-3:

a) *A test to assess statistical significance between the two treatment arms*

b) *A critique and discussion of the maturity of the data.*

Reply to (a): Statistical significance for OS in MONALEESA-3 (subpopulation B)

The study is powered to demonstrate a statistically significant difference between ribociclib plus fulvestrant and placebo plus fulvestrant in the ITT population, but not in subpopulation B. The HR estimates for subpopulation A and subpopulation B are consistent with the ITT population.

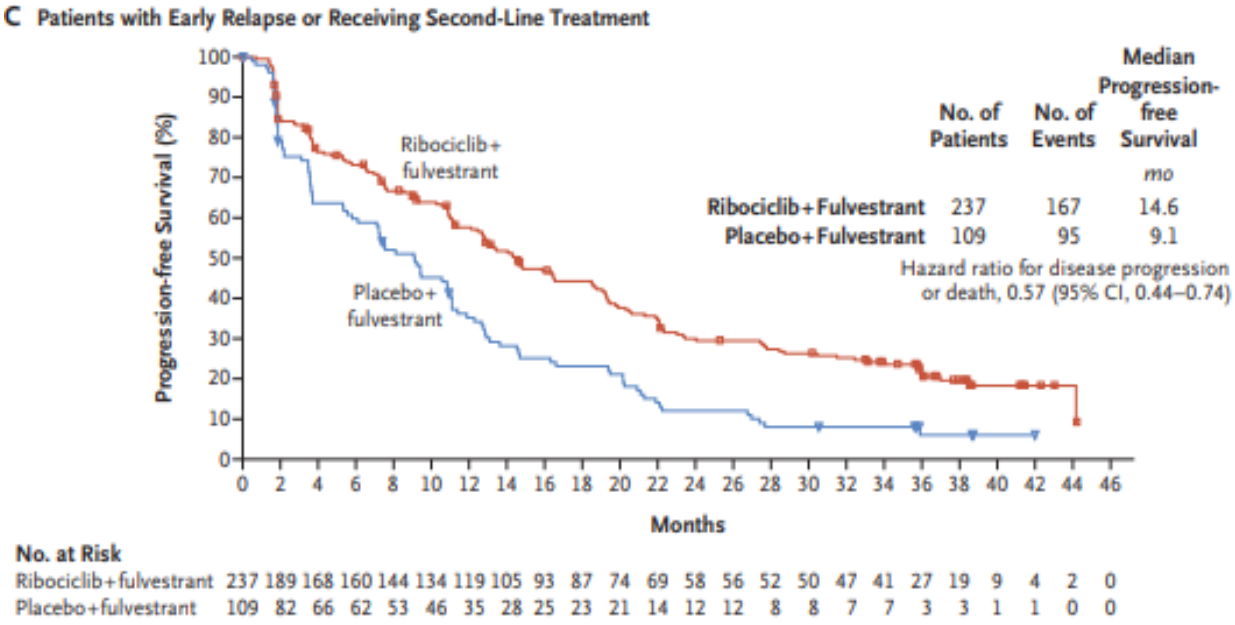
Population	No. of events (data maturity, %)	HR for OS (95% CI)	Powered to detect a change
ITT	275 (78)	0.72 (0.57–0.92)	✓ (p = 0.00455)
Subpopulation A	110 (30)	0.70 (0.48–1.02)	×
Subpopulation B	162 (47)	0.73 (0.53–1.00)	×

Reply to (b): critique and discussion of data maturity in MONALEESA-3

Owing to the design of the MONALEESA 3 trial, which is powered to detect a survival difference in the ITT population rather than the individual subpopulations, data maturity is linked to the number of events in the ITT population. At the second interim analysis, a total of 275 deaths had occurred in the ITT population corresponding to ~78% data maturity, which met the criteria for the final analysis at a median follow-up of 39.4 months (minimum follow-up, 35.8 months) as summarised A.9. The extent and maturity of the trial data ensured that the data were adequate to provide a thorough and robust assessment of OS. Furthermore, the stopping boundary guidelines for the interim analysis are based on the conservative Lan-DeMets (O'Brien-Fleming) α-spending function (Lan and DeMets 1983), meaning that the study would only be declared positive for OS if the results were statistically significant and clinically compelling.

A14. Priority question. The KM data of PFS for subpopulation B of MONALEESA-3 in Figure 3 does not match the KM data of PFS for subpopulation B of MONALEESA-3 in Figures 10, 11 or 12. Please explain these discrepancies and update as necessary.

Figure 3 in the CDF submission was based on Figure 3C from the December 11, 2019 online publication by Slamon et al. based on the June 2019 data cut-off of MONALEESA-3. However, this figure was in error as it is identical to the KM PFS for the overall population. An updated publication in June 2020 has the correct PFS curves for population B, as shown below. The model uses the data corresponding to the corrected figure.



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

Other

A15. Please discuss the SACT data in further detail, including a critique of:

a) *Differences and similarities in the population between SACT and MONALEESA-3; and*

b) *A comparison of treatment duration between SACT and MONALEESA-3.*

Reply to (a): Differences and similarities between SACT and MONALEESA-3 populations

A comparison of patient characteristics from the ITT population of MONALEESA-3 and the real-world population from which SACT data were collected is summarised below. The table below shows a comparison of baseline characteristics between MONALEESA-3 and SACT. For some characteristics, the data categories aren't fully aligned, in which case an approximate / overlapping range was used.

Reply to (b): Comparison of baseline characteristics between MONALEESA-3 and SACT

Ribociclib plus fulvestrant	**MONALEESA-3 (n = 484) ITT population**	**SACT data (n = 187)**
Sex, n (%)		
Female	484 (100)	187 (100)
Age, years, n (%)		
< 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)	–
ECOG 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 while receiving adjuvant therapy	138 (28.5)[c]	84 (45%)
PD ≤ 12 months of completing adjuvant therapy[d]	98 (20.2)	6 (3%)
PD on first line endocrine therapy	110 (22.7)[b]	97 (57%)

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

The real-world population from SACT was older than the population of MONALEESA-3 with only 38% of the population aged under 60 years compared with 53% of patients enrolled in MONALEESA-3 aged 65 years and under. At the upper threshold, 67% of patients were under 70 and 86.6% aged 75 years and under in the SACT population and MONALEESA-3, respectively. It should be noted, however, that this is an approximation as the data is not fully aligned between studies.

A higher proportion of patients enrolled in MONALEESA-3 had an ECOG performance status 0 than in the real-world population (64.0% vs 41%); however, data was missing from approximately 20% of patients in the SACT population, which may confound the data. It should also be noted that an ECOG performance status of 0–1 was a criterion of MONALEESA-3, whereas a performance status of 0–2 was permitted for the SACT population; although only a minority of patients had a performance status of 2 (7 patients; 14%). In general, the eligibility criteria for the MONALEESA-3 trial was more stringent than the eligibility for treatment under SACT. A comparison of the eligibility criteria for MONALEESA-3 and treatment under SACT are summarised below.

Comparison of study eligibility criteria used in MONALEESA-3 and SACT

MONALEESA-3	Eligibility for treatment under SACT
Inclusion criteria	
• Adult male/female ≥ 18 years old at the time of informed consent and has signed informed consent before any	• Patient has histologically or cytologically documented oestrogen

trial-related activities and according to local guidelines. • Female patients must be postmenopausal • Histologically and/or cytologically confirmed diagnosis of oestrogen receptor positive and/or progesterone receptor positive breast cancer by local laboratory and has HER2− breast cancer • Measurable disease by RECIST 1.1 or at least one predominately lytic bone lesion, advanced (locoregionally recurrent not amenable to curative therapy [e.g. surgery and/or radiotherapy] or metastatic) breast cancer • Patients may be: newly diagnosed advanced/metastatic breast cancer, treatment-naïve • Relapsed with documented evidence of relapse more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease • Relapsed with documented evidence of relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced/metastatic disease • Relapsed with documented evidence of relapse more than 12 months from completion of adjuvant endocrine therapy and then subsequently progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-oestrogen or an aromatase inhibitor) for advanced/metastatic disease • Newly diagnosed advanced/metastatic breast cancer at diagnosis that progressed with documented evidence of progression after one line of endocrine therapy (with either an anti-oestrogen or an aromatase inhibitor); patient has an ECOG PS of 0 or 1	receptor positive and HER-2 negative breast cancer • Patient has metastatic breast cancer or locally advanced breast cancer which is not amenable to curative treatment • Patient is male or is female and if female is either post-menopausal or if pre- or perimenopausal has undergone ovarian ablation or suppression with LHRH agonist treatment • Patient has an ECOG performance status of 0 or 1 or 2 • Patient has received previous endocrine therapy according to one of the three populations as set out below as these are the groups on which the NICE Technology Appraisal for ribociclib plus fulvestrant focused. Please record which population the patient falls into: ○ Patient has progressive disease whilst still receiving adjuvantor neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or ○ Patient has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or ○ Patient has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression • Patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib (in combination with fulvestrant) or palbociclib (in combination with fulvestrant) has had to be stopped within 3 months of its start solely as a consequence of dose

• Patient has adequate bone marrow and organ function.	limiting toxicity and in the clear absence of disease progression or ribociclib has been received as part of an early access scheme for the combination of ribociclib plus fulvestrant and the patient meets all the other criteria set out in this form • Patient has had no prior treatment with fulvestrant • Patient has had no prior treatment with everolimus • Ribociclib will only be given in combination with fulvestrant • Treatment will continue until there is progressive disease or excessive toxicity or until the • patient chooses to discontinue treatment, whichever is the sooner • Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle • Ribociclib and fulvestrant will be otherwise used as set out in their Summaries of Product • Characteristics (SPC) including the need for ECGs to be performed prior to treatment, after 2 weeks of treatment and after 4 weeks of therapy
Exclusion criteria	
• Patients with symptomatic visceral disease or any disease burden that makes the patient ineligible for endocrine therapy per the investigator's best judgement • Patient has received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant or any CDK4/6 inhibitor • Patient with inflammatory breast cancer at screening • Patient with CNS involvement unless they are at least 4 weeks from completion of prior therapy at the time of starting treatment and have stable CNS tumour at the time of screening and not receiving steroids and/or	• None

enzyme-inducing anti-epileptic medications for brain metastases • Clinically significant, uncontrolled heart disease and/or cardiac repolarization abnormality • Patient is currently receiving any of the following substances and cannot be discontinued 7 days prior to the start of treatment: known strong inducers or inhibitors of CYP3A4/5 • Substances that have a known risk of prolongation of the QT interval or induction of Torsades de Pointes • Substances that have a narrow therapeutic window and are predominantly metabolized through CYP3A4/5 • Herbal preparations/medications, dietary supplements.	

The distribution of previous therapy varied between MONALEESA-3 and SACT populations. Over half of patients in the SACT population received ribociclib plus fulvestrant as second-line therapy (57%), with few patients receiving treatment following disease progression within 12 months of completing adjuvant therapy (6 patients; 3%). The remaining patients received ribociclib plus fulvestrant following disease progression during adjuvant therapy (45%). In the MONALEESA-3 trial, the distribution of patients was broadly similar between patients who experienced progressive disease while receiving adjuvant therapy (28.5%), within 12 months of receiving adjuvant therapy (20.2%) and on first-line therapy (22.7%).

Reply to (b): A comparison of treatment duration between SACT and MONALEESA-3.

The duration of treatment with ribociclib plus fulvestrant was 6.4-months longer in the MONALEESA-3 trial than in the SACT data collection. Based on the data available, it is difficult to provide a fuller critique of these data, or discussion of an informed comparison between them.

Duration of treatment in MONALEESA-3 and SACT

Population	Duration of treatment, months
SACT data	9.4
MONALEESA-3 (ribociclib plus fulvestrant arm)	15.8

SACT, Systemic Anti-Cancer Therapy.
Source: Slamon *et al*, 2020.*NEJM*:382:514–24. SACT data collection report. TA593.

Section B: Clarification on cost-effectiveness data

Please note:

If in your response to Question A9 a later data cut-off is available, please update the extrapolations as appropriate.

If as a result of the responses to the clarification questions the company base case analysis is revised, please indicate what other assumptions are considered for the revised base case and provide updated results, probabilistic sensitivity analyses and deterministic sensitivity analyses.

Please provide all requested scenario analyses as options in the economic model and results on top of any revised assumptions.

Reply to above notes:

Not applicable – the June 2019 data cut-off is the most recent available, with no further planned analyses for OS.

Progression-free survival

B1. Priority question: The model used in the committee's decision-making in TA593 applied independently fitted curves to each treatment arm because the cumulative hazard plots for MONALEESA-3 did not demonstrate PHs (i.e. the

curves crossed). According to the updated cumulative hazard plots (Figure G2 of Appendix G), the curves also cross.

a) ***Please provide a rationale for using jointly fitted curves in the CDF review submission.***

b) ***Please provide a scenario where independent parametric models are fit to each treatment arm. Please provide AIC/BIC statistics for each distribution as well as graphs of the distributions compared against KM data.***

Reply to (a): Rationale for use of jointly fitted curves

While the ACD states that the ERG's preferred distribution for PFS was a 3-knot spline model, it wasn't clearly stated in TA593 that the curves were fitted independently. For the CDF review submission, the population differed from that examined in TA593 in that the former focused on Group B from MONALEESA-3 whereas the latter focused on Group Bii + Biii. Additionally, the CDF review submission was based on a more recent data cut (03 June 2019). For this updated analysis, the same distribution was employed as suggested by the ERG (i.e., 3-knot spline model).

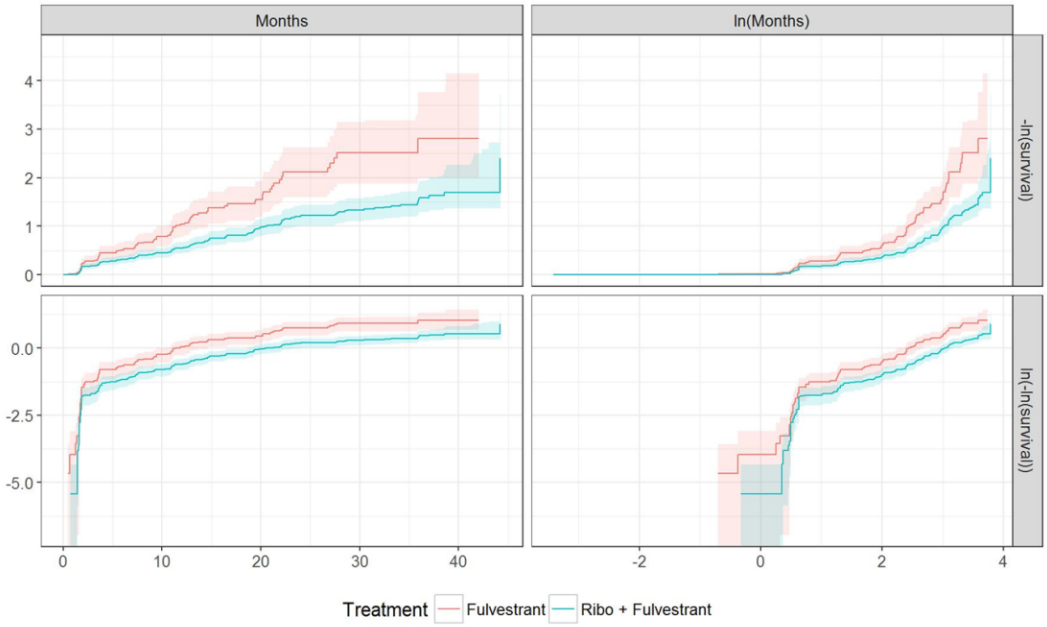
The jointly- rather than independently-fitted model was used for several reasons:

- First, the test of Schoenfeld residuals did not provide strong evidence of non-proportionality of hazards.
- Second, with the exception of the first month after randomization, the cumulative hazards plot for PFS for Group B using the updated data do not cross, as shown in Figure G2A of the appendices of the CDF submission (reproduced below).
- Third, in the plot of ln(-ln(survival) and ln(time), the curves are approximately linear and parallel after ln(t)= ~0.5, or t= ~1.6 months. These findings suggest that a Weibull model using the PH assumption may be appropriate.

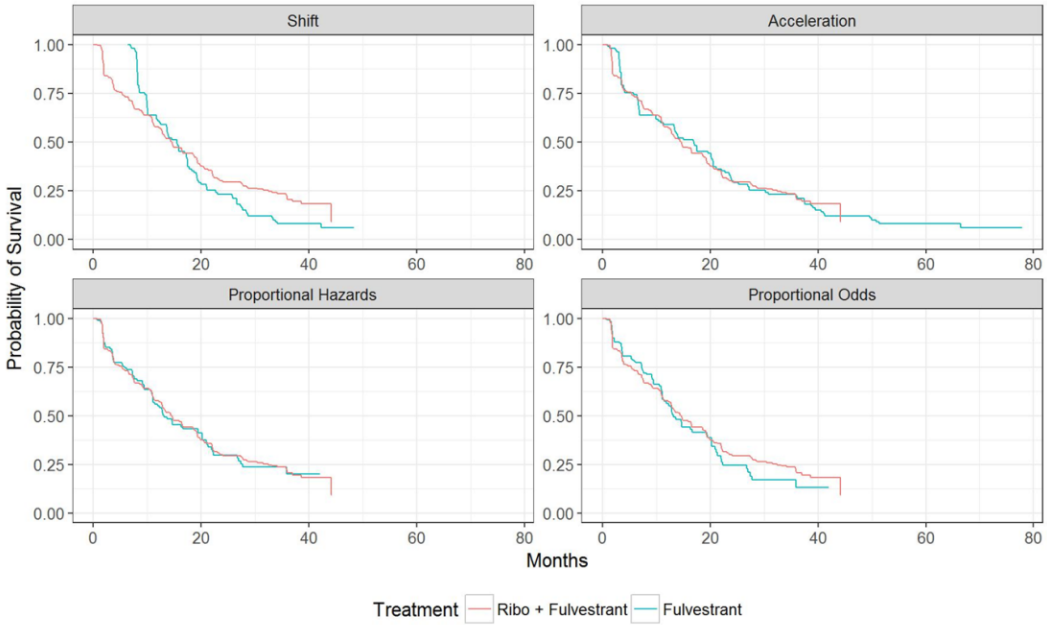
- Fourth, the treatment effect diagnostic plots (Figure G2B) demonstrate that the counterfactual KM curve for fulvestrant for the PH assumption overlaps the KM curve for ribociclib + fulvestrant, again suggesting the PH assumption is reasonable.

Appendix Figure G2. Transformation and Treatment Effect Diagnostic Plots for Progression-Free Survival in Group B of MONALEESA-3, by Randomized Treatment

A. Transformation Diagnostics



B. Treatment Effect Overlay Diagnostic Plots



Finally, as noted in the CDF submission, the best-fitting RCS 3-knot models were all restricted (i.e., jointly-fitted) models. Taken as a whole, these analyses therefore suggest that selection of the 3-knot RCS Weibull (R) was (a) consistent with the ERG preferred use of a 3-knot spline model but also (b) consistent with the updated data for Group B.

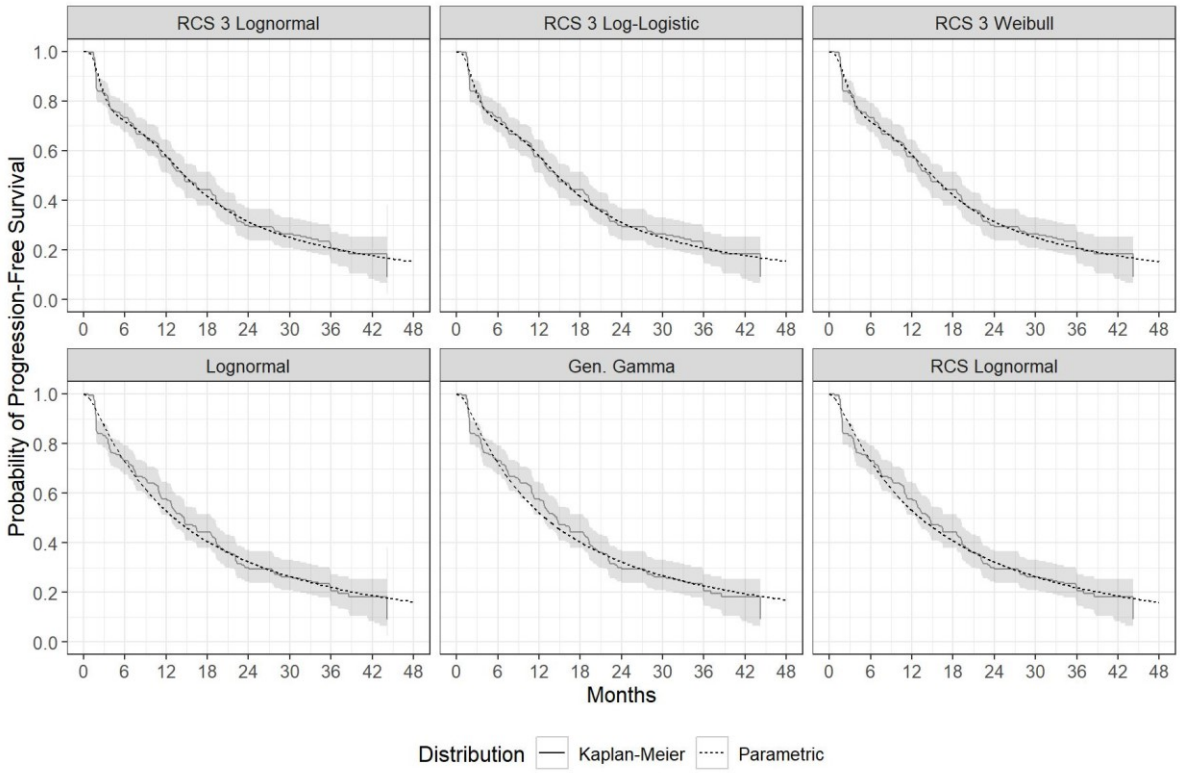
Reply to (b): Scenario where independent parametric models are fitted to each treatment

Results of such a scenario have been added to the model using the RCS 3 lognormal distribution, the ICER generated is [redacted]. This distribution was chosen based on fit statistics and visual fit, as shown in the table below:

Fit Statistics for Independently fitted parametric distributions – Ribociclib + Fulvestrant PFS

Distribution	AIC	AICc	BIC
RCS 3 Lognormal	1336.3	1336.6	1353.7
RCS 3 Log-Logistic	1341.3	1341.5	1358.6
RCS 3 Weibull	1343.4	1343.6	1360.7
Lognormal	1358.5	1358.5	1365.4
Gen. Gamma	1360.2	1360.3	1370.6
RCS Lognormal	1360.5	1360.6	1370.9
Exponential	1368.3	1368.3	1371.7
Log-Logistic	1365.6	1365.7	1372.6
Gompertz	1368.1	1368.1	1375.0
Gen. F	1362.2	1362.4	1376.1
RCS Weibull	1365.9	1366.0	1376.3
Weibull	1370.0	1370.0	1376.9
RCS Log-Logistic	1367.6	1367.7	1378.0

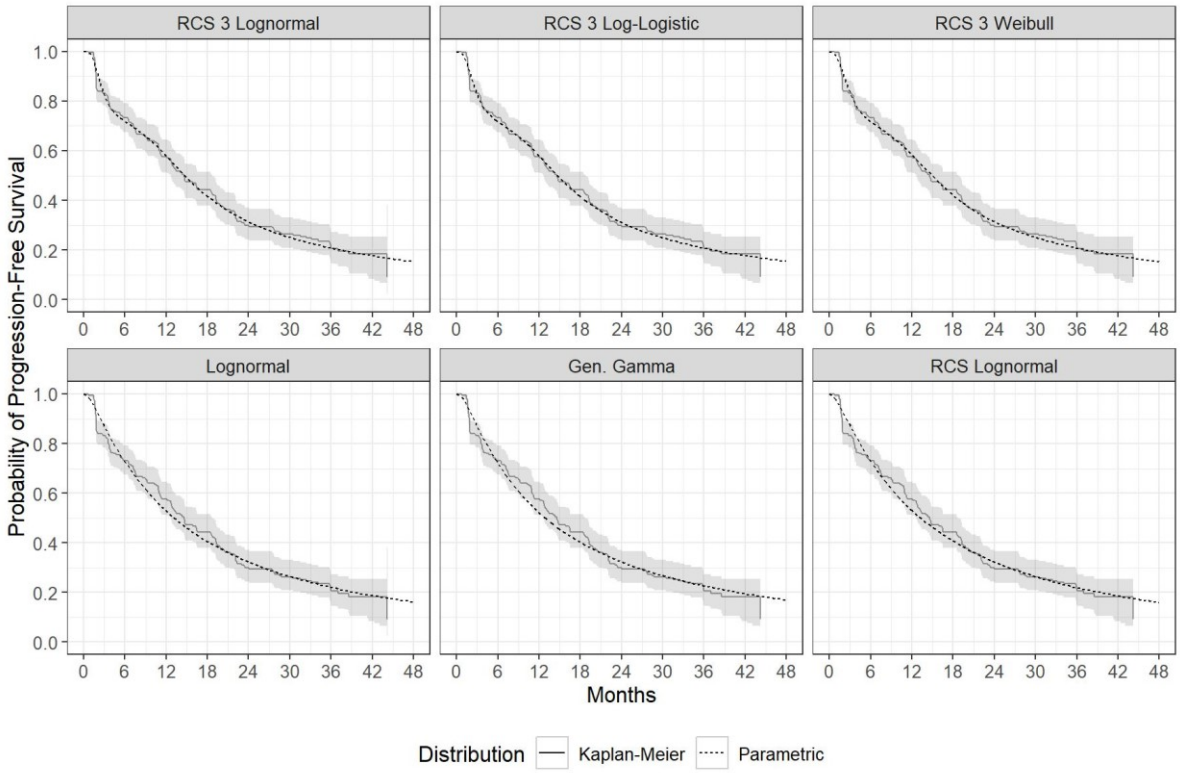
Comparison of independently fitted parametric distributions vs. KM data – Ribociclib + Fulvestrant PFS



Fit Statistics for Independently fitted parametric distributions –Fulvestrant PFS

Distribution	AIC	AICc	BIC
RCS 3 Log-Logistic	649.8	650.4	663.2
RCS 3 Weibull	649.8	650.4	663.3
Lognormal	660.7	660.8	666.1
RCS 3 Lognormal	653.4	654.0	666.8
Exponential	667.6	667.7	670.3
Log-Logistic	665.3	665.4	670.7
Gen. Gamma	662.7	662.9	670.7
RCS Lognormal	662.7	663.0	670.8
Gompertz	668.6	668.7	674.0
RCS Weibull	665.9	666.2	674.0
Weibull	669.6	669.7	675.0
RCS Log-Logistic	667.3	667.6	675.4
Gen. F	664.7	665.1	675.4

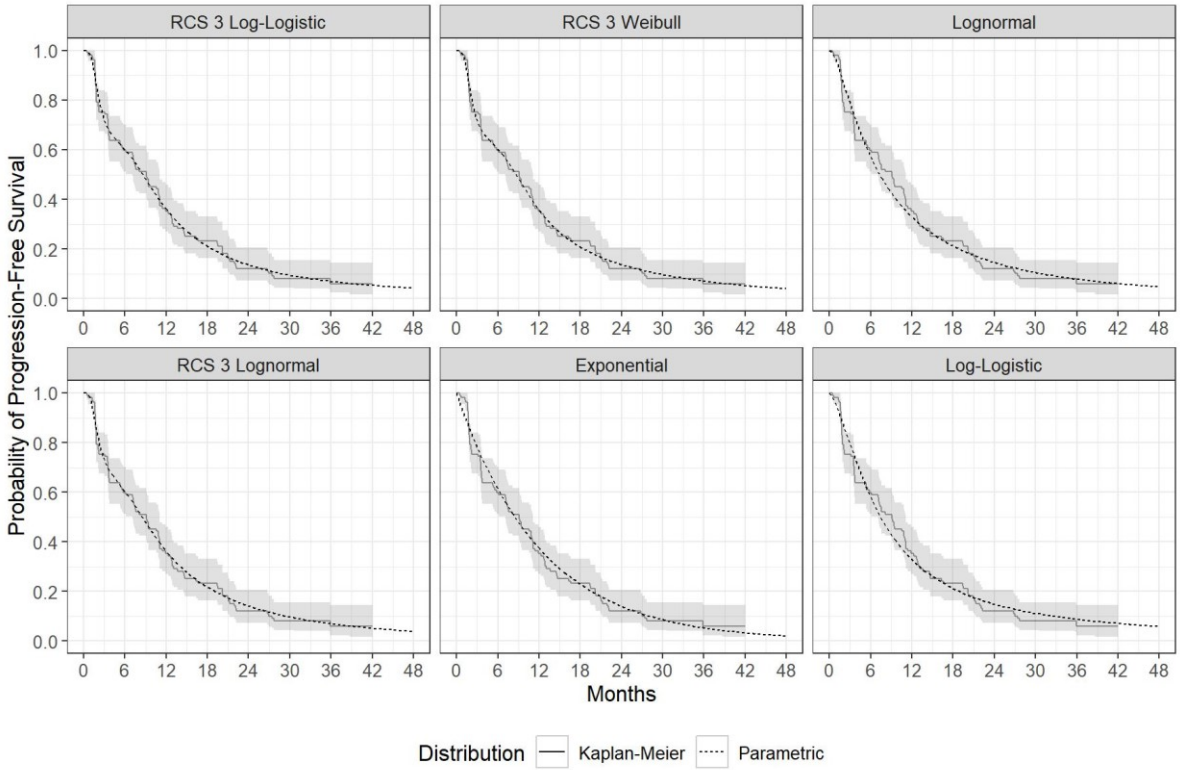
Comparison of independently fitted parametric distributions vs. KM data – Ribociclib + Fulvestrant PFS



Fit Statistics for Independently fitted parametric distributions –Fulvestrant PFS

Distribution	AIC	AICc	BIC
RCS 3 Log-Logistic	649.8	650.4	663.2
RCS 3 Weibull	649.8	650.4	663.3
Lognormal	660.7	660.8	666.1
RCS 3 Lognormal	653.4	654.0	666.8
Exponential	667.6	667.7	670.3
Log-Logistic	665.3	665.4	670.7
Gen. Gamma	662.7	662.9	670.7
RCS Lognormal	662.7	663.0	670.8
Gompertz	668.6	668.7	674.0
RCS Weibull	665.9	666.2	674.0
Weibull	669.6	669.7	675.0
RCS Log-Logistic	667.3	667.6	675.4
Gen. F	664.7	665.1	675.4

Comparison of independently fitted parametric distributions vs. KM data – Fulvestrant PFS



B2. Priority question: As PH do not appear to hold in MONALEESA-3, please use the fulvestrant monotherapy arm in MONALEESA-3 as the baseline to which the HRs derived from the NMA are applied.

a) Please explain why the company's scenario analysis (NMA for PFS anchored on fulvestrant PFS in Table 20 of the CDF review submission) produces an identical ICER to the base case in the CDF review submission, but a similar scenario carried out by the ERG during TA593 saw a profound increase in the ICER ([redacted]). Please note that the

ERG is also unable to replicate the ICER produced by the company for this scenario in its submission for the CDF review.

Reply to priority question: 'Use of fulvestrant monotherapy as baseline for NMA HR'

A scenario was provided in which fulvestrant monotherapy arm in MONALEESA-3 was used as the baseline to which the HRs derived from the NMA were applied.

Reply to (a): Explanation for identical ICER in scenario analysis

The scenario analysis "NMA for PFS anchored on fulvestrant PFS" produces an identical ICER because the only assumption that is changed is that the HR for PFS for everolimus is applied to the fulvestrant PFS curve as opposed to being applied to the ribociclib + fulvestrant PFS curve. Since the fitted distribution used for PFS has a PH treatment effect (RCS Weibull 3 restricted), the projected PFS for everolimus + exemestane based on the ITC did not change materially, and thus the ICER would not be expected to change.

It is possible that the ERG scenario finding (referenced above) was obtained because the ERG used independently-fitted curves for PFS, in which case the application of the HR for everolimus + exemestane vs. fulvestrant to the fulvestrant curve will yield a curve with a different shape than that which is obtained when one applies the HR for everolimus + exemestane vs. ribociclib + fulvestrant to the ribociclib + fulvestrant curve. If the independently-fitted curves for ribociclib + fulvestrant and fulvestrant converge over time, then so too will the curves for ribociclib + fulvestrant and everolimus + exemestane. The curve for everolimus + exemestane may in fact cross that for ribociclib + fulvestrant, which might result in a dramatically different ICER.

B3. Please add predictions from the Restricted Cubic Spline (RCS) 3 log-logistic (R) distribution to Figure 10, Figure 11 and Table 9.

Figure 10. 10-year PFS projections (ribociclib + fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay

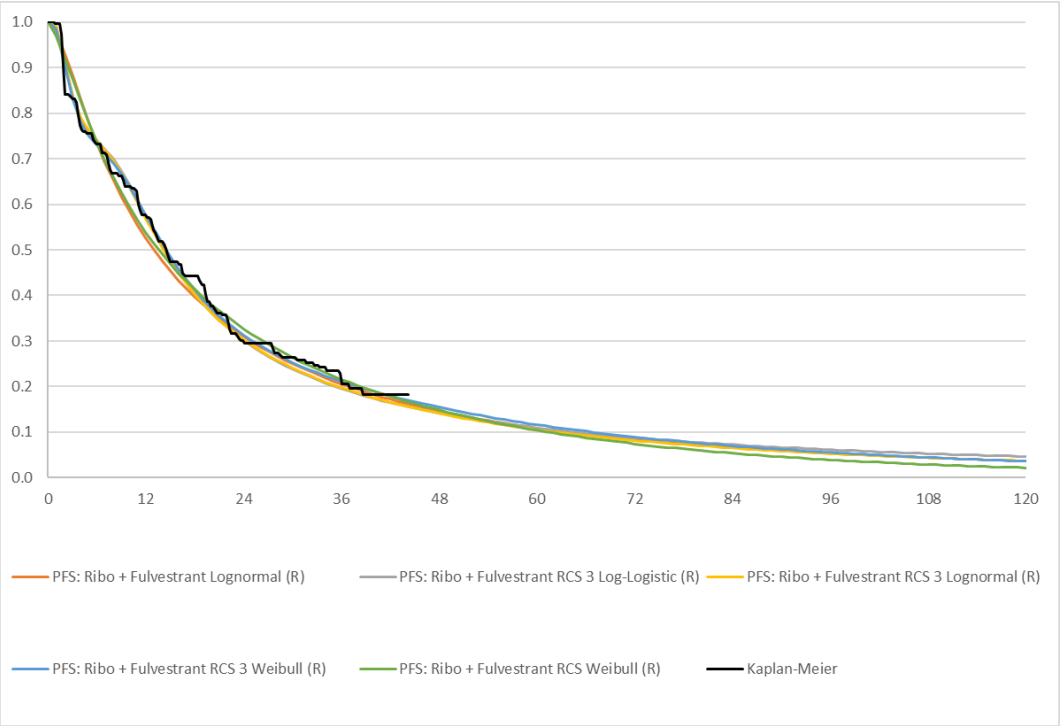
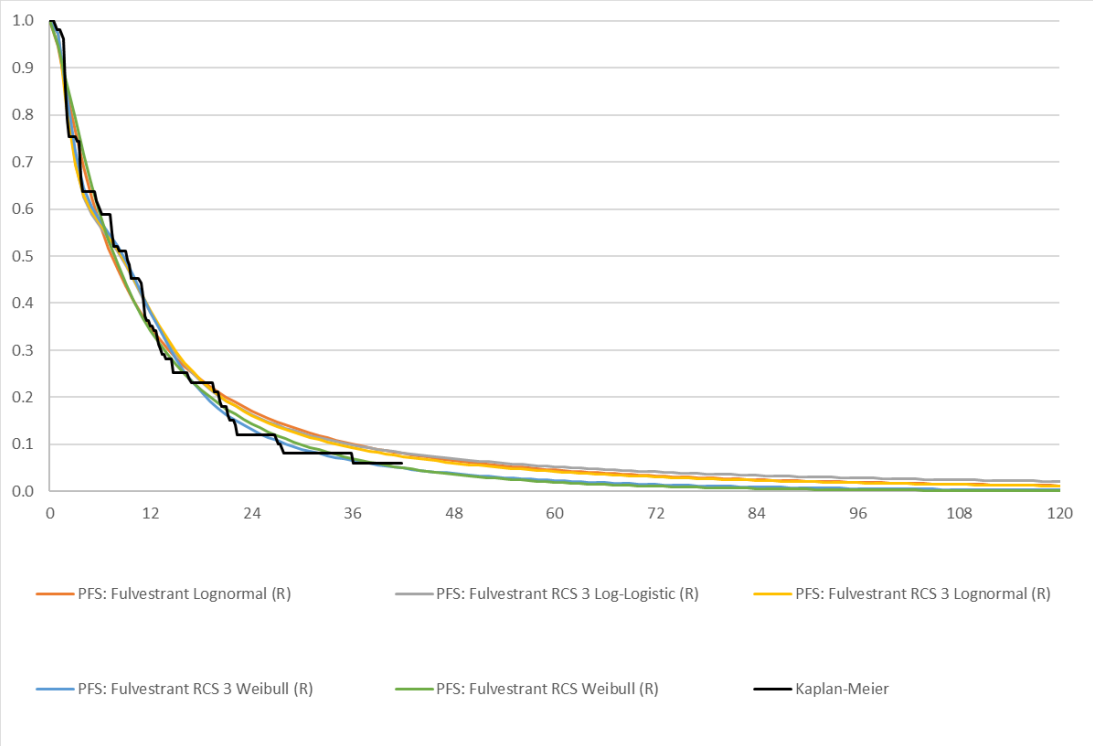


Figure 11. 10-year PFS projections (fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay



Tale 9. Predicted proportion (%) of patients remaining over time for PFS parametric curves (ribociclib + fulvestrant)

Time	Kaplan-Meier	Ribo + Fulvestrant Lognormal (R)	Ribo + Fulvestrant RCS 3 Log-Logistic (R)	Ribo + Fulvestrant RCS 3 Lognormal (R)	Ribo + Fulvestrant RCS 3 Weibull (R)	Ribo + Fulvestrant RCS Weibull (R)
2-Year	30.00%	32.28%	31.46%	31.64%	32.63%	33.95%
3-Year	22.88%	21.24%	20.19%	20.37%	21.71%	22.32%
5-Year	--	11.15%	11.16%	10.79%	11.91%	10.72%
10-Year	--	3.72%	4.68%	3.71%	3.64%	2.22%

B4. Please provide scenario analyses using the following distributions to inform PFS:

a) *RCS Weibull (R): Generates an ICER of* [redacted]

b) *RCS 3 Log-Logistic (R): Generates an ICER of* [redacted]

Both of these scenarios have been added to the model

Post-progression survival

B5. Priority question: Table 16 of the CDF review submission makes several references to using OS data in the model, these include hazard ratios for OS and OS data cuts for PPS calculations. Please provide the hazard ratios for OS, detailing the methods of how they were derived, and clarify how OS data from MONALEESA-3 has been used in the PPS calculations.

The references to “PFS and OS data” and “OS data cut” in Table 16 refer to the data on time to progression and time to death from the June 2019 data cut-off of the MONALEESA-3 trial in general terms. Since the submitted model employs a Markov cohort approach (per the Terms of Engagement), data on the OS endpoint are not used *per se*. Rather, the data on time to progression and time to death are used to construct the PPS endpoint. Specifically, PPS was defined as the time from disease progression until death or loss to follow-up, and was calculated for only

those patients who progressed during follow-up. For these patients, the PPS endpoint was calculated as the difference between the months for the OS endpoint and the months for the PFS endpoint. Patients who were censored for OS were also censored for PPS.

The OS HR referred to in Table 16 relates to that from the PAIC. The unweighted and weighed HRs for this analysis are provided in response to question A6. The HR for OS for ribociclib + fulvestrant vs. fulvestrant in Group B of MONALEESA-3 was 0.73 (95% CI 0.53, 1.00) (Slamon, 2020).

B6. Priority question: Please justify the decision to use PPS rather than OS in the health economic model.

a) As a scenario analysis, please use the NMA for OS requested in Question A2 to estimate cost-effectiveness.

I. Please provide details of OS extrapolations, including how the best fitting curve was chosen.

II. When using the derived HRs for OS from the NMA, please consider the proportionality of the hazards between everolimus + exemestane (using KM data from BOLERO-2) and each of the baseline treatment options (ribociclib + fulvestrant and fulvestrant) to determine the most suitable

baseline OS curve.fulvestrant and fulvestrant) to determine the most suitable baseline OS curve.

b) ***As a scenario analysis, please use the PAIC for OS requested in Question A6 to estimate cost-effectiveness.***

    I. ***Please provide details of OS extrapolations, including how the best fitting curve was chosen.***

c) ***If the company cannot provide the aforementioned scenarios, please explore other ways to demonstrate if using OS would provide similar results to using PPS.***

Reply to priority question: Justification of decision to use PPS rather than OS in model

The decision to use PPS rather than OS (i.e., a Markov cohort rather than partitioned survival approach) in the CDF submission was based on the instructions provided to the manufacturer (terms of engagement) that the same modelling approach should be used in the CDF submission (Markov cohort) as was used in TA593 (also Markov cohort). This was discussed with members of the NICE and ERG teams during the clarification questions call on 9 October.

Reply to (a): request for scenario analysis based on NMA OS

Since the economic model uses a Markov cohort approach, it is not feasible to use the OS data from MONALEESA-3 directly, as this would require the model to be restructured to use a partitioned survival approach. As discussed during the clarification questions call with members of NICE and the ERG on 9 October, this was not feasible within the limited timeframe provided for this response, and – as suggested by the ERG – approaches to validate / compare this approach have been made (presented below). Novartis will be exploring the use of a partitioned survival model to evaluate cost-effectiveness.

Reply to (b): request for PAIC scenario analysis

As noted above, the model uses a Markov cohort approach and it therefore is not feasible to use OS from the PAIC directly.

Reply to (c): request to explore other ways of using OS

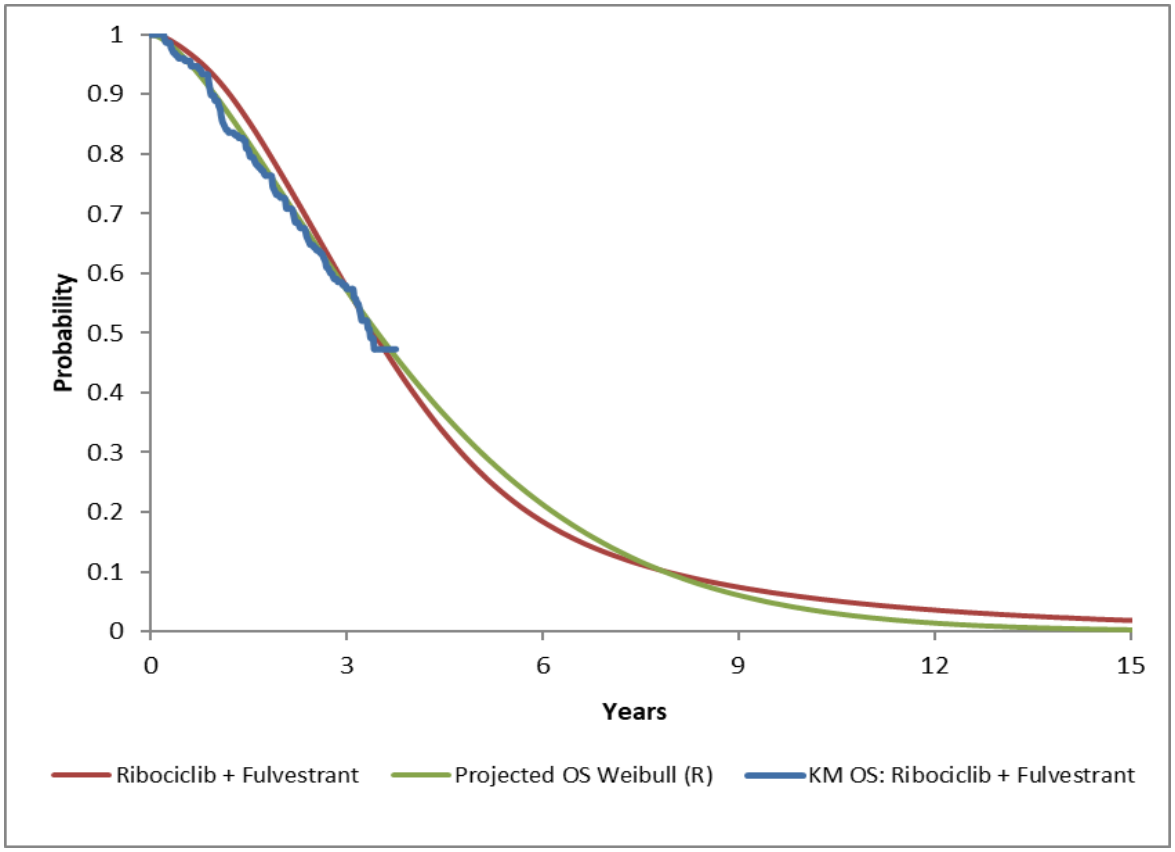
While it was not feasible to develop a *de novo* partitioned survival model within the time provided for a response, it can be shown that projections of OS for ribociclib plus fulvestrant in Group B based on the Markov cohort model are consistent with the corresponding KM OS data from the MONALEESA-3 trial. Additionally, we can also compare the projected OS generated by the Markov model against corresponding parametric distributions fit to OS for Group B from MONALEESA-3. For this analysis, the Weibull distribution was used for OS based on assessment of fit statistics and visual fit. Fit statistics for parametric distributions fitted to OS for Group B of MONALEESA-3 are shown in the table below (sorted in ascending order).

Distribution	AIC	AICc	BIC
Weibull (R)	1625.1	1625.2	1636.6
Log-Logistic (R)	1627.8	1627.9	1639.4
Gompertz (R)	1628.9	1628.9	1640.4
Weibull (U)	1626.9	1627.0	1642.3
RCS Weibull (R)	1627.1	1627.2	1642.4
Gen. Gamma (R)	1627.1	1627.2	1642.5
RCS Lognormal (R)	1627.7	1627.8	1643.1
Lognormal (R)	1632.0	1632.1	1643.5
RCS Log-Logistic (R)	1629.1	1629.2	1644.4
Log-Logistic (U)	1629.7	1629.8	1645.1
Gompertz (U)	1630.8	1630.9	1646.2
Gen. F (R)	1629.1	1629.3	1648.3
Lognormal (U)	1633.6	1633.7	1648.9
Gen. Gamma (U)	1627.9	1628.1	1651.0
RCS Weibull (U)	1629.2	1629.4	1652.2
RCS Lognormal (U)	1630.6	1630.8	1653.7

RCS Log-Logistic (U)	1631.4	1631.6	1654.4
Exponential	1647.5	1647.5	1655.1

As shown in the figure below, projected OS for ribociclib +fulvestrant from the Markov model is generally consistent with KM estimates of OS and OS based on the Weibull distribution.

Projected OS ribociclib +fulvestrant

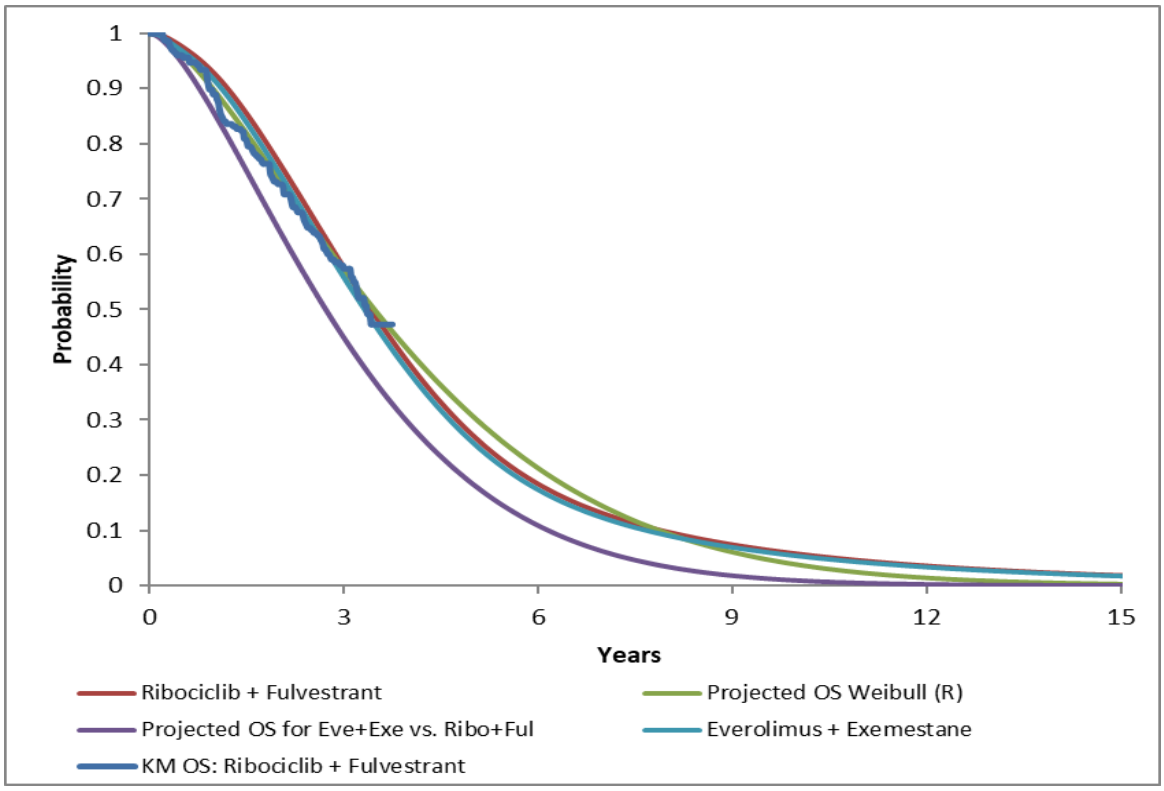


In the base case, the Markov model generates estimates of [redacted] discounted LYs for ribociclib + fulvestrant. In comparison, the OS based on a Weibull distribution yields an estimated [redacted] discounted LYs, or a relatively small absolute (percentage) difference of [redacted] in discounted LYs. These findings demonstrate that use of a partitioned survival model would yield estimated LYs for ribociclib + fulvestrant that are similar to those generated using the Markov cohort approach.

In the response to question A2, a Bucher ITC of OS was conducted in which the HR for OS was estimated to be [redacted] for everolimus + exemestane vs. ribociclib +

fulvestrant and [redacted] for everolimus + exemestane vs. fulvestrant (compared with [redacted] for ribociclib + fulvestrant vs. fulvestrant). Applying this HR to the Weibull distribution for OS for ribociclib + fulvestrant yields the OS distribution for everolimus + exemestane that would be obtained in a partitioned survival model. As shown in the figure below, the OS for everolimus + exemestane based on this approach and set of assumptions is less favourable than that obtained using the Markov model approach.

Applying NMA HR to OS curves for ribociclib + fulvestrant and everolimus + exemestane (Weibull distribution)



The discounted LYs for everolimus + exemestane using the OS curve/partitioned survival approach is [redacted], or [redacted] less than that for ribociclib + fulvestrant. This compares with a gain of [redacted] discounted LYs based on the Markov approach in the current base case. This analysis demonstrates that the projected gain in OS for ribociclib + fulvestrant vs. everolimus + exemestane based on the Markov cohort model is conservative relative to that which would be obtained using a partitioned survival model under the set of assumptions described above.

B7. Priority question: Please explain how the scenario "PPS curves estimated with data from BOLERO-2" has been conducted.

Parametric distributions were fitted to data on PPS for ribociclib + fulvestrant from Group B on MONALEESA-3 and for everolimus + exemestane from the PAIC-adjusted population of BOLERO-2. The methods for constructing the PAIC of PPS were identical to those employed in the PAIC of PFS. The Gompertz (R) distribution fitted to these data was selected based on statistical fit and visual comparisons of projected PPS compared with KM PPS.

B8. Priority question: Figure 23 of the CDF review submission presents a comparison of post-progression survival for ribociclib + fulvestrant (MONALEESA-3) compared with everolimus + exemestane (BOLERO-2). Please clarify if this a naive comparison or if the data have been adjusted.

Figure 23 is based on an unanchored comparison of PPS for ribociclib + fulvestrant vs. PAIC-adjusted PPS for everolimus + exemestane. The methods for conducting the PAIC of PPS are the same as those which were employed for the PAIC of PFS.

B9. Priority question: Please clarify why the HR for the PAIC scenario in the model ([redacted] in Scenario_Inputs!G116) does not reflect the value in Table 7 of the CDF review submission ([redacted] for ribociclib + fulvestrant versus everolimus + exemestane, the inverse of which is [redacted] for everolimus + exemestane compared with ribociclib + fulvestrant).

The value [redacted] is correct (it is the inverse of [redacted] [after rounding]). This has been confirmed verbally with the ERG.

Time to treatment discontinuation

B10. Priority question: Please provide a scenario analysis using the best fitting (U) TTD curve (Gompertz (U)) for ribociclib + fulvestrant and cap this TTD curve to the PFS curve to avoid including treatment costs beyond progression.

A scenario analysis using this approach has been included in the model. The ICER for this scenario is [redacted]

B11. Priority question: Please provide a scenario analysis assuming ribociclib + fulvestrant (both drugs in the combination treatment) are given until progression.

A scenario analysis assuming TTD is equal to PFS has not been included in the model as it is not clinically plausible because TTD was less than PFS for both ribociclib and fulvestrant in MONALEESA-3. Also, this scenario would yield estimates of treatment costs that are inconsistent with estimates of efficacy and therefore lacks internal validity.

B12. Priority question: The ERG acknowledges that TTD for everolimus + exemestane is assumed to be equivalent to PFS, as accepted in TA593. However, current clinical advice to the ERG is that this is not the case in clinical practice. The ERG's clinical adviser stated that around 20% of people discontinue before progression and 30% of patients receive a 10 mg daily dose of everolimus and 70% receive a 5 mg daily dose of everolimus. Therefore, please provide the following scenario analyses:

a) ***Use the IPD TTD data from BOLERO-2 to fit separate TTD curves to everolimus and exemestane (i.e. one TTD curve for everolimus and one***

TTD curve for exemestane). Please provide details of TTD extrapolations, including how the best fitting curve was chosen.

b) ***Fit separate TTD curves to everolimus and exemestane and assume TTD for everolimus is 80% of PFS (i.e. 20% of patients discontinue everolimus before progression) and TTD for exemestane is equal to PFS. Please provide details of TTD extrapolations, including how the best fitting curve was chosen.***

c) ***Assume 30% of patients receive a 10 mg daily dose of everolimus and 70% receive a 5 mg daily dose of everolimus. Assume TTD is equal to PFS in this scenario.***

d) ***Combine parts b) and c) above and fit separate TTD curves to everolimus and exemestane and assume TTD for everolimus is 80% of PFS (i.e. 20% of patients discontinue everolimus) and TTD for exemestane is equal to PFS. For those 80% that remain on everolimus treatment, assume 30% of patients receive a 10 mg daily dose of everolimus and 70% receive a 5 mg daily dose of everolimus.***

Overall reply to question B12

As discussed with members of the NICE and ERG teams during the clarification questions call on 9 October, this issue related to TTD was not raised during the Terms of Engagement meeting, and represents a significant departure from the approach used in TA593.

Given the time constraints of this initial clarification step, we have not included any new analyses, but we are willing to explore this in next steps (included in specific replies below). This would need to encompass a validation of the clinical opinion referred to in the ERG question – where important information is based on a single source – relative to what data are currently available.

Reply to point (a)

While it might be feasible to fit parametric distributions to TTD from BOLERO-2 and to use these in the model, this would be inappropriate as it would amount to an

unanchored and unadjusted ITC of TTD for everolimus + exemestane vs. ribociclib + fulvestrant. Accordingly, to address this issue, a scenario could be conducted in which TTD for everolimus and TTD for exemestane are estimated by applying to the model-estimated PFS for everolimus + exemestane estimates of the HR for TTD vs. PFS for everolimus and the HR for TTD vs. PFS for exemestane.

Reply to point (b)

Since the scenario involves using PFS for both everolimus and exemestane, we assume that the phrase "*Fit separate TTD curves to everolimus and exemestane and*" is not relevant to this question, and that "*Please provide details of TTD extrapolations, including how the best fitting curve was chosen*" is redundant of what is requested in part (a) of this question.

The clinical input that 20% of patients discontinue before disease progression does not imply that TTD is equal to 80% of PFS. We believe that such information requires further validation. For example, it might be the case that 20% of patients discontinue treatment before progression but that on average the time between discontinuation and progression is very short (e.g., one day). In this case, the TTD curve would be very similar to the PFS curve and much greater than 80% of PFS. Also, while clinicians may believe that this is representative of patients receiving everolimus + exemestane in their practice, it is not consistent with what was observed in BOLERO-2 and does not reflect the efficacy data from the trial which is used in the estimation of the model. Accordingly, we have not added this scenario to the model. Rather, we would propose a scenario in which TTD for everolimus would be calculated by applying to PFS for everolimus + exemestane the HR for TTD vs. PFS and assume that TTD for exemestane is equal to PFS for exemestane (i.e., HR TTD vs. PFS = 1.0).

Reply to point (c)

The assumptions above that 30% of patients receive 10mg everolimus and 70% would receive 5mg corresponds to an average RDI of 0.65 relative to a planned dose of 10mg daily. Using these assumptions would yield estimates of exposure that are inconsistent with the clinical trial data on efficacy. We would propose a scenario analysis using the RDI from the BOLERO-2 trial.

Reply to point (d)

Consistent with the discussion above, we would propose conducting a scenario in which the TTD for everolimus is calculated using the HR for TTD vs. PFS from BOLERO-2, TTD for exemestane is assumed to be equal to PFS, and the RDIs for everolimus is based on the value obtained from the BOLERO-2 trial.

B13. Priority question: In the model, TTD is estimated separately for ribociclib and fulvestrant (the combination treatment). In the submission it is unclear which treatments in the combination are being referred to (Figures 17 to 22 and Tables 12 to 13 of the CDF submission). Please review and clarify how TTD has been presented in submission, specifically:

a) ***Please clarify if the fulvestrant TTD estimates in the submission are taken from the fulvestrant + placebo arm of MONALEESA-3 or the ribociclib + fulvestrant arm of MONALEESA-3. Please provide the fulvestrant TTD estimates from the ribociclib + fulvestrant arm of MONALEESA-3 if these are not presented.***

b) ***Please clarify if the ribociclib and fulvestrant TTD estimates in the submission reflect the combination treatment as a whole, or only the ribociclib TTD estimates from the ribociclib + fulvestrant arm of MONALEESA-3. Please provide the ribociclib TTD estimates from the ribociclib + fulvestrant arm of MONALEESA-3 if these are not presented.***

c) ***Please provide the equivalent of Table 13 for the fulvestrant TTD estimates from the ribociclib + fulvestrant arm of MONALEESA-3. Also confirm if Table 13 currently represents ribociclib TTD estimates from the ribociclib + fulvestrant arm of MONALEESA-3.***

d) ***In Figure 19, the legend relates to fulvestrant, but the plot is for ribociclib + fulvestrant. In Figure 20, the legend relates to ribociclib, but***

the plot is for fulvestrant. Please clarify if the graphs are assigned to the right treatment and correctly labelled

e) ***In Figures 21 and 22, the treatments in the legend include fulvestrant and ribociclib + fulvestrant, please clarify if these represent the separate treatments in the combination treatment, or the two treatment arms in MONALEESA-3.***

f) ***In Figure G8 of Appendix G, the treatments in the legend include fulvestrant and ribociclib + fulvestrant but the plot is for ribociclib or blinded placebo. In Figure G12 of Appendix G, the treatments in the legend include fulvestrant and ribociclib + fulvestrant but the plot is for fulvestrant. Please clarify if the graphs are assigned to the right treatment and correctly labelled?***

General note: We agree that there appears to be some ambiguity and typographical errors in the titles of Figures 17-22 and Tables 12-13.

Reply to point (a)

TTD fulvestrant for patients receiving ribociclib + fulvestrant is presented in the submission. However, Figures 19 and 20 are mislabelled. Figure 19 shows the TTD fulvestrant (for patients receiving ribociclib and fulvestrant in combination) while Figure 20 shows the TTD ribociclib.

Reply to point (b)

The “ribociclib and fulvestrant” TTD estimates as they are described in Figure 17, Table 12, Figure 21, and Figure 22 represent the TTD of ribociclib (i.e., **not** the combination treatment as a whole) for the ribociclib + fulvestrant treatment arm. However, Figure 19 was mislabelled and represents the TTD of fulvestrant for ribociclib + fulvestrant (note that TTD of ribociclib is shown in Figure 20, which was also mislabelled). Table 13 shows the TTD of fulvestrant for ribociclib + fulvestrant. The correct table for TTD of ribociclib is provided below:

Time	Kaplan-Meier	RCS Weibull (R)	RCS Lognormal (U)	RCS Lognormal (R)	Gompertz (U)	Gompertz (R)	Gen. Gamma (U)	Gen. Gamma (R)	Gen. F (R)
2-Year	23.73%	26.04%	25.84%	24.35%	25.30%	25.34%	25.94%	25.31%	25.09%
3-Year	17.37%	16.35%	17.14%	15.13%	16.78%	16.28%	17.01%	15.54%	15.56%
5-Year	--	7.25%	9.21%	7.27%	10.12%	9.09%	8.76%	6.92%	7.21%
10-Year	--	1.30%	3.27%	2.11%	6.56%	5.12%	2.71%	1.48%	1.82%

Reply to point (c)

Table 13 was mislabelled and represents TTD of fulvestrant for ribociclib + fulvestrant. The equivalent of Table 13 for TTD of ribociclib is shown above.

Reply to point (d)

The titles for Figures 19 and 20 are incorrect. Figure 19 shows TTD of fulvestrant while Figure 20 shows TTD of ribociclib.

Reply to point (e)

In Figures 21 and 22, “Treatment” in the legend represents the treatment arm to which patients were randomized. The outcome in both figures is TTD of ribociclib (i.e., time until discontinuation of ribociclib). For patients randomized to fulvestrant, they are actually receiving a placebo but patients and investigators were blinded to which patients were receiving a placebo and which were receiving active treatment.

Reply to point (f)

In Figure G8, “Treatment” in the legend refers to the treatment arm to which patients were randomized. The outcome depicted in figure G8 is TTD of ribociclib. TTD of ribociclib was defined as the time until discontinuation of the medication ribociclib, or for patients randomized to fulvestrant, placebo. In Figure G12, the outcome depicted is TTD of fulvestrant. TTD of fulvestrant was defined as the time until discontinuation of the medication fulvestrant.

Other

B14. Priority question: The model used in the committee's decision-making in TA593 at the point of CDF entry applied a single health-state utility value to PFS. Please provide a rationale for using different PFS utilities for patients who are on or off treatment in the CDF review model.

a) ***Please test for a statistically significant difference between the PFS utilities derived for patients who are on and off treatment in MONALEESA-3.***

b) ***Please provide a scenario analysis using a single health-state utility value for PFS***

Reply to priority question: Rationale for using different PFS utilities

The treatment regimens being received by patients in the MONALEESA-3 trial are associated with adverse events which may impact patients' quality of life. As such, it is reasonable to expect that patients residing in PFS who have permanently discontinued treatment may have different (i.e., higher) utility values compared with patients who were residing in the PFS state and still receiving treatment. If patients who discontinue have higher utility values than those remaining on treatment and the proportion of patients in the PFS state who remain on treatment varies over time, then using the average utility value for on- and off-treatment observed during the trial may yield biased projections (e.g., if the percentage of patients off-treatment increases over time, then using the average on- and off-treatment during the trial underestimates utility during the period after the trial). Thus, there is a strong methodological rationale for estimating separate utility values for on- vs. off-treatment.

Results of the GEE regression model with separate covariates for PFS on-treatment and PFS off-treatment for Group B yielded results that were consistent with this expectation. Namely, that patients who were in PFS and on-treatment had a lower utility compared with those off-treatment [redacted] suggesting that adverse events experienced by patients while on-treatment have important impacts on quality of life.

While the QIC statistic is smaller for the GEE regression model where there is no difference for PFS on-treatment vs. off-treatment the difference in the QIC statistic compared with that for the GEE regression model with separate covariates for PFS on-treatment and PFS off-treatment is not material. Accordingly, it is reasonable to use a model which captures this aspect of the patient experience.

Reply to point (a)

The table below shows outputs from the GEE regression model with covariates for baseline utility value, PFS off-treatment (referent state), PFS on-treatment, and PPS.

Analysis	Intercept	Baseline Utility	PFS-Off Tx	PFS-On Tx	PPS
Model 3:					
Estimate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%Low	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
95%High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
p-value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
QIC/QICu	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Reply to point (b)

A scenario analysis with a single health state utility value for PFS has been added to the model consistent with TA 593 (HSU value for PFS = [redacted]). The ICER for this scenario with a single health state utility value is [redacted].

B15. Priority question: Please amend the base case analysis to include the list price of fulvestrant

This was provided as a scenario analysis along with a range of discounts ranging from 20% to 60% in the company submission. Including a fulvestrant discount of 10% was raised at the Terms of Engagement meeting and was agreed to be

reasonable, as long as we presented the full range of ICERs based on 0% to 60% discount.

B16. Priority question. Page 24 of the CDF review submission lists corrections to the original CDF entry model "in response to ERG comments in TA593 (regarding inconsistent application of mortality between PFS and PPS, and half-cycle correction issues". Please provide citations for the comments you are addressing in the committee papers for TA593.

We believed that the ERG had made these comments regarding the model submitted in TA593, however we are not able to find any reference to the comments in the committee papers. It is therefore possible that the issues were discovered by internal reviewers and not the ERG. Regardless, these issues did merit being corrected.

B17. Priority question. Please enable the model corrections described in section A.8.1.4 to be turned on and off in the model.

As discussed with members of the NICE and ERG teams during the clarification questions call on 9 October, it was not feasible to enable this feature within the Excel model within the available timeframe. There would also be a detrimental impact on the performance of the model.

As such, and as considered acceptable by the ERG, a separate version of the model has been provided without the corrections described in A.8.1.4.

B18. Priority question. Please add the before and after model input values to *"[ID3755] Ribociclib - Novartis Changes between Model Versions - Post Technical Eng. compared with Updated Model - MP 240920 [CIC]*"

See excel changes between model versions – Post Technical Eng. Compared with Updated Model- Input values.xlsx

B19. Priority question. Where model inputs have been updated to reflect more recent cost information from NHS Reference Costs 2018/2019, please provide the currency code/description and service code/description used to inform the more recent cost.

The following tables identify all the model inputs that have been updated to recent NHS reference costs.

Healthcare services for follow-up and monitoring

Service	Cost (£) Value 2018/2019	Source
General practitioner visits	39.2	PSSRU 2019 Table 10.3b
Oncology consultant office	150.2	Weighted average of CL WF01B (Non-Admitted Face-to-Face Attendance, First) 800-Clinical Oncology and CL WF01A (Non-Admitted Face to Face Attendance, Follow-Up) 800-Clinical Oncology (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)
Community nurse	60.0	PSSRU 2019 Table 10.1 band 5
Clinical nurse specialist	84.0	PSSRU 2019 Table 10.1 band 6
Social worker	51.0	PSSRU 2019 Table 11.1 cost per hour including qualifications
Computer tomography scan	103.5	IMAG RD24Z -- Computerised Tomography Scan of Two Areas, with Contrast (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)
Liver function test	1.1	DAPS DAPS04 -- Clinical biochemistry (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)
Complete blood count	2.8	DAPS DAPS05 -- Haematology (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)
ECG	48.8	DADS EY51Z -- Electrocardiogram Monitoring or Stress Testing (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)

Ultrasound	57.4	Weighted average of: IMAG RD40Z -- Ultrasound Scan with duration of less than 20 minutes, without Contrast; IMAG RD42Z -- Ultrasound Scan with duration of 20 minutes and over, without Contrast (National Schedule of Reference Costs - Year 2018/2019 - NHS trusts and NHS foundation trusts)

Administration costs

Drugs	Admin Cost (£)	Source and Description
Fulvestrant, loading	167.12	1st administration: NHS Reference Costs 2018/2019 - CL WF01B (£244.84) + 2nd administration: NHS Reference Costs 2018/2019 - CL WF01A (£194.17; outpatient assumed to be 33.3%) + PSSRU Table 10.1 Band 5, Curtis & Barnes, 2019 (£37.00; primary care assumed to be 66.7% Divided by 2 to reflect that the loading dose is administered twice in the first cycle: (244.84 + [194.17 * 0.33 + 37.00 * 0.67]) / 2 = 167.12
Fulvestrant	89.39	NHS Reference Costs 2018/2019 - CL WF01A (£194.17; outpatient assumed to be 33.3%) + PSSRU Table 10.1 Band 5, Curtis & Barnes, 2019 (£37.00; primary care assumed to be 66.7% 194.17 * 0.33 + 37.00 * 0.67 = 89.39

Costs of treating adverse events

Adverse Event	Cost (£)	Source Code
Abnormal LFTs	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Anemia	526.26	Weighted average NES SA44A & NES SA45A Single plasma exchange or other intravenous blod transfusion, 19 years and over AND Injection of Rh immune globulin or other blood transfudion, 19 years and over
Decreased leukocyte count	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Diarrhea	432.62	Weighted average NES FD01A - FD01J Gastrointestinal infections with/without intervetion
Fatigue	475.29	NES SA04K Iron Deficiency Anaemia with CC Score 2-5
Hypertension	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up

Increased ALT	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Increased GGT	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Infection	463.04	Weighted average NES WH07A - WH07G Infections or Other Complications of Procedures, with Multiple or Single Interventions
Febrile neutropenia	2398.73	SA35A to SA35E - Agranulocytosis non-elective long stay (weighted average)
Pain	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
Pneumonia	661.23	Weighted average NES DZ23H - DZ23K Bronchopneumonia with multiple/single intervention
PNNs	142.73	CL WF01A (service code 800 [Clinical Oncology (Previously Radiotherapy)]) Non-admitted face to face attendance, follow-up
PPE syndrome	1281.26	Weighted average NES JD07A - JD07D Skin disorders with interventions
Stomatitis	391.93	Weighted average NES CB02A - CB02F Non-malignant, ear, nose, mouth, throat or neck disorders, with or without interventions
Nausea	566.07	JA12D to JA12L - Malignant Breast Disorders (weighted average)
Vomiting	566.07	JA12D to JA12L - Malignant Breast Disorders (weighted average)
Pulmonary embolism	505.21	DZ09J to DZ09Q - Pulmonary Embolus (weighted average)
Pneumonitis	521.82	SA12G to SA12K - Thrombocytopenia (weighted average non-elective short stay)

Terminal care costs

Service	Cost (£)	Source
Terminal care costs	5715.95	Source for setting and cost based on NICE CG 81: Setting: Hospital, 40%; hospice, 10%; home, 50%; Costs (2006/7): Hospital £4,706; hospice £5,867; home £2,428; Adjusted to 2018/2019

B20. Priority question. Please provide more detail on the parameters changed between scenarios 2 and 3. If only costs and utilities are changed (as inferred by

*the text) there should be no change in life years between scenarios 2 and 3. Please provide a log of changes similar to "**[ID3755] Ribociclib - Novartis Changes between Model Versions - Post Technical Eng. compared with Updated Model - MP 240920 [CIC]**" if this is possible.*

We would like to clarify the nature of the scenarios presented in Section A.10 of the company submission:

- The first scenario (CEA 1.1 and 1.2) were based on the data available at time of CDF entry: whilst 1.1 was entirely in line with the model specification at CDF entry (and replicates the ICER precisely), 1.2 updated the model corrections discussed in A.8.1.4 in the company submission.

- Scenario 2 (CEA 2) was based on the same specification as 1.2, 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 (and 1.1 & 1.2).

- Scenario 3 built upon scenario 2, by reassessing the functional forms of the best fitting curves, based on the updated data (along with cost updates etc).

Based on the re-parameterisation of the clinical data for the extrapolated period, it would be expected that there would be a change in life year and QALY yield.

If we have misunderstood the nature of the analyses requested within the CDF template, we are happy to provide an updated scenario,

Section C: Textual clarification and additional points

C1. Please explain what "OS - KM" is labelling in Results_Figures!DB14. The values below this appear to be calculations not Kaplan Meier data

This cell is mislabelled. The heading has been corrected in the revised model.

C2. Please explain the headings "KM - Ribociclib + NSAI + Goserelin TTD" and "KM - NSAI TTD" in Regimens_Disc!CP51:CX5

This cell is mislabelled. The heading has been corrected in the revised model.

C3. Figure 4 refers to the OS data as 'investigator-assessed' yet this is not stated anywhere else in the company submission. Please clarify if there are any other assessments of OS.

This is a typo. It should read "Kaplan-Meier plot of OS …".

C4. Please explain the differences between the restricted and unrestricted distributions used in the company's model. Please explain what an unrestricted RCS distribution involves.

Survival distributions for the two treatment groups were estimated using two alternative approaches for parameterizing the effect of treatment on survival times:

- "Restricted" (R) models in which a single parameter of the survival distribution is allowed to differ between groups
- "Unrestricted" (U) models in which all parameters of the survival distribution are allowed to differ between groups

With both approaches, the distributions of survival for the treatment and control groups were assumed to be of the same type of distribution (e.g., both are Weibull). However, with the first approach (restricted models), in which the effect of treatment is restricted to a single distributional parameter (e.g. the scale parameter of the Weibull distribution), projections of survival are consistent with the PH assumption, accelerated failure time (AFT), or other univariate treatment effect models, depending on the underlying distribution (e.g., the Gompertz is a proportional hazards model, the lognormal and log-logistic are AFT models, and the exponential and Weibull are both PH and AFT models). The second approach (unrestricted models) places no such restrictions on the distributional parameters or the assumed

nature of treatment effect within the class of distributions. Therefore, the jointly fitted unrestricted models are identical to those which are obtained by fitting the curves to each treatment arms independently. The difference is that the fit statistics for the jointly fitted unrestricted models can be compared to those for the jointly fitted restricted models. Conversely, the fit statistics obtained when fitting curves independently cannot be compared with those for the restricted models fit jointly.

For example, a Weibull distribution has two parameters: a scale parameter and shape parameter. With the restricted Weibull distribution, the scale parameter is permitted to differ between arms but the shape parameter is assumed to be the same. With an unrestricted Weibull distribution, both the shape and the scale parameters are permitted to differ between arms. The restricted Weibull is a PH model whereas the unrestricted Weibull is not. The use of this approach for parameterizing treatment effects permits the comparison of models in which the effect of treatment is and is not interacted on different distributional parameters using conventional fit statistics such as the BIC.

For restricted cubic spline (RCS) distributions, the difference between “restricted” (i.e., [R]) and “unrestricted” (i.e., [U]) models is the same as for the other distributions with respect to the parameterization of the treatment effects. Note that the term “restricted” in the term “restricted cubic spline” refers to the fact that the splines are constrained (i.e., “restricted”) to be linear in the two tails.

C5. Please clarify if the distributions in Tables 10 and 11 of the CDF review submission are restricted models or unrestricted models. If only one of these types has been explored, please explain why.

Table 10 and Table 11 are for models fitted to PPS with both groups combined. Hence, there are no treatment effects to be parameterized. The distinction between restricted and unrestricted is irrelevant.

C6. In "[ID3755] Ribociclib - Novartis Changes between Model Versions - Post Technical Eng. compared with Updated Model - MP 240920 [CIC]", please clarify if cell address F17:24 in the Costs_drug sheet should actually reflect column H (Admin Cost (£)) rather than column F (mg/ug per Pack)

Yes, the admin costs in Column H were updated, the units (mg per pack) were not updated.

C7. On page 20 of Appendix G it states "*In the base case, PFS for other comparators was estimated by applying to the estimated PFS for fulvestrant the estimated HRs for the other comparators versus fulvestrant*". Please explain this statement as HRs versus ribociclib + fulvestrant have been applied in the main CDF review submission (Table 6) and model (Efficacy_PFS!F18)

This is a typo. The sentence should read "… *estimated by applying to the estimated PFS for* ***ribociclib****+fulvestrant the estimated HRs for the other comparators versus* ***ribociclib****+fulvestrant.*" (emphasis added).

NICE National Institute for Health and Care Excellence

Patient organisation submission

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (CDF review of TA593) [ID3755]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. Full details on our income can be found in our annual reports, which are available on our website at http://breastcancernow.org/about-us/what-we-do/annual-report-and-accounts.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. In 2019/20 Breast Cancer Now has either received or been pledged the following funding from pharmaceutical companies which are listed in the matrix for this appraisal: - Novartis, £17,835 grant towards our Helpline - Novartis, £2,580, UK Interdisciplinary Breast Cancer Symposium 2020 Sponsorship

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Secondary (also known as advanced, metastatic or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for secondary breast cancer. Treatment aims to control and slow the spread of the cancer, relieve any symptoms, and maintain health, wellbeing and a good quality of life for as long as possible. A patient can be diagnosed with secondary breast cancer right from the start, or they can develop the condition months or years after treatment for their primary breast cancer has ended. Being diagnosed with secondary breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as

	angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. People living with secondary breast cancer have told us: "How confused and scared I am all the time; even when I'm happy it's always there in the back of your mind". "It is scary. I am permanently scared about my future and what my family will have to deal with without me". As well as the huge emotional toll of living with secondary breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, which may include working, household and parental responsibilities as well as travelling to and from hospital appointments. People living with secondary breast cancer have shared the following: "It totally and completely affects your life after diagnosis. Endless doctors' appointments can begin to wear you down in no time at all". "My treatment goes on for as long as it works and this is my life now. Constant 'scanxiety', endless hospital appointments and the struggle with day to-day living that others either don't see or understand". The symptoms of secondary breast cancer can vary depending on where the cancer has spread to. For example, if it has spread to the bones the main symptoms can include pain in the bones or bone fractures. If breast cancer has spread to the lungs, someone may experience symptoms such as breathlessness or continuous pain and tightness in the chest. Also all breast cancer treatments can cause some side effects

	and although everyone reacts differently to drugs, for those people who experience more side effects than others, it can cause a significant impact on their day to day lives and health and wellbeing. Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients when considering their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	The introduction of ribociclib with fulvestrant (and other CDK 4/6 inhibitors) into NHS use via the Cancer Drugs Fund was hugely welcomed by the patient community. These offer a new treatment option for patients with hormone receptor positive, HER2 negative locally-advanced or metastatic breast cancer after prior endocrine therapy. CDK 4/6 inhibitors with fulvestrant opened the door for thousands of women who had received prior endocrine therapy to benefit from the innovative CDK 4/6 inhibitor which had previously only been available to newly diagnosed patients with locally advanced or metastatic breast cancer. Prior to CDK 4/6 inhibitors, this patient group could receive exemestane, tamoxifen or exemestane plus everolimus. However, the clinical community has previously suggested in NICE appraisals that exemestane plus everolimus can have adverse events which may limit its use in clinical practice.
8. Is there an unmet need for patients with this condition?	Yes there was as an unmet for this patient group. Patients who progressed on an AI could not benefit from the introduction of CDK 4/6 inhibitors. Treatments that improve the time before progression, delay chemotherapy are much needed for this group of patients. Interim analysis also now suggests this treatment combination could improve overall survival.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	For patients, the advantages of ribociclib in combination with fulvestrant are: • Improved overall survival which is significant for this patient group, with the latest data suggesting median overall survival of 40.2 months with ribociclib with fulvestrant vs 32.5 months for fulvestrant alone when this treatment is used as a second-line treatment. • The MONALEESA-3 study demonstrated for the overall population that ribociclib plus fulvestrant improves progression free survival (PFS) compared with fulvestrant alone, with a median PFS of 20.5 months, versus 12.8 months respectively. Those receiving it as second line treatment had median PFS of 14.6 versus 9.1 months. • Patients value this extra time, as it means more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group as metastatic breast cancer is not curable. • Delaying progression and improving overall survival can also have a positive impact on patients' emotional wellbeing and mental health, as it may mean that a patient can continue doing the activities they enjoy and leading a more or less normal daily life. • These outcomes are also likely to bring some comfort to their relatives and friends. This in turn could help to reduce any stress the patient is experiencing as a result of worrying about any burden placed on their friends and family. • The use of this technology could also delay patients having to use other therapies and ultimately, starting on systemic (non-targeted) chemotherapy. Chemotherapy is traditionally associated with more severe and gruelling side effects which can result in a poorer quality of life for patients and people are often particularly fearful and anxious about being moved onto chemotherapy

10. What do patients or carers think are the disadvantages of the technology?	Ribociclib plus fulvestrant is associated with some increased side effects, compared to fulvestrant alone. According to MONALEESA-3 the most common all grade adverse events include neutropenia, nausea, fatigue and leukopenia, whilst the most common grade 3 or grade 4 events are neutropenia or leukopenia. Although neutropenia was the most common of all-grade and grade 3 or 4 adverse events, the trial reports that the events were generally uncomplicated. It would be important that patients receiving this treatment are given accessible information about neutropenia, including the signs to look out for and when to seek prompt medical advice. Every treatment for breast cancer has some side effects and each patient's situation will be different and the side effects will affect some patients more than others. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice as to the level of risk they will be willing to take. As outlined in the summary of product characteristics for ribociclib, there is some extra monitoring required for patients taking ribociclib. This is mostly in the form of regular blood tests rather than lengthy trips to hospital. Patients will also need to attend hospital or in some places a GP surgery for fulvestrant to be administered, as this is given as an injection. However, for many patients, any inconvenience caused by attending hospital appointments for monitoring or the administration of fulvestrant will be outweighed by an increase in progression free survival.

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- In the MONALEESA-3 trial, ribociclib in combination with fulvestrant showed significant benefits in progression-free survival and overall survival compared to fulvestrant alone.
- These outcomes are important to patients as it enables patients to spend quality time with their friends and families as well as continue with their daily activities, which can improve the emotional wellbeing of both patients and their loved ones.
- There are some increased side effects from ribociclib in combination with fulvestrant, compared to fulvestrant alone. However, not all patients will experience side effects. As long as the benefits and risks of a treatment are clearly discussed with the patient, they can make the decision that is right for them.
- This treatment adds to the drug options available for patients with this type of breast cancer which cannot be cured. Any new treatments that can delay the need to start on chemotherapy which is generally associated with more severe side effects and a poorer quality of life is welcomed by patients.
- The introduction of this treatment into NHS practice (via the Cancer Drugs Fund) was a significant step forward in the treatment of this type of breast cancer and was welcomed amongst patients and the clinical community. It is critical we now do not take a step back and that this treatment is able to be routinely approved for NHS use.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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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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Contribution of authors:

Steve Edwards	Critical appraisal of the company's submission; provided feedback on all versions of the report. Guarantor of the report
Rebecca Boffa	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted the summary, background and clinical results sections
Victoria Wakefield	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and assisted with drafting the clinical results sections
Gemma Marceniuk	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; critical appraisal of the economic evidence; and assisted with carrying out the economic analyses

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

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List of Tables

List of Figures

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]

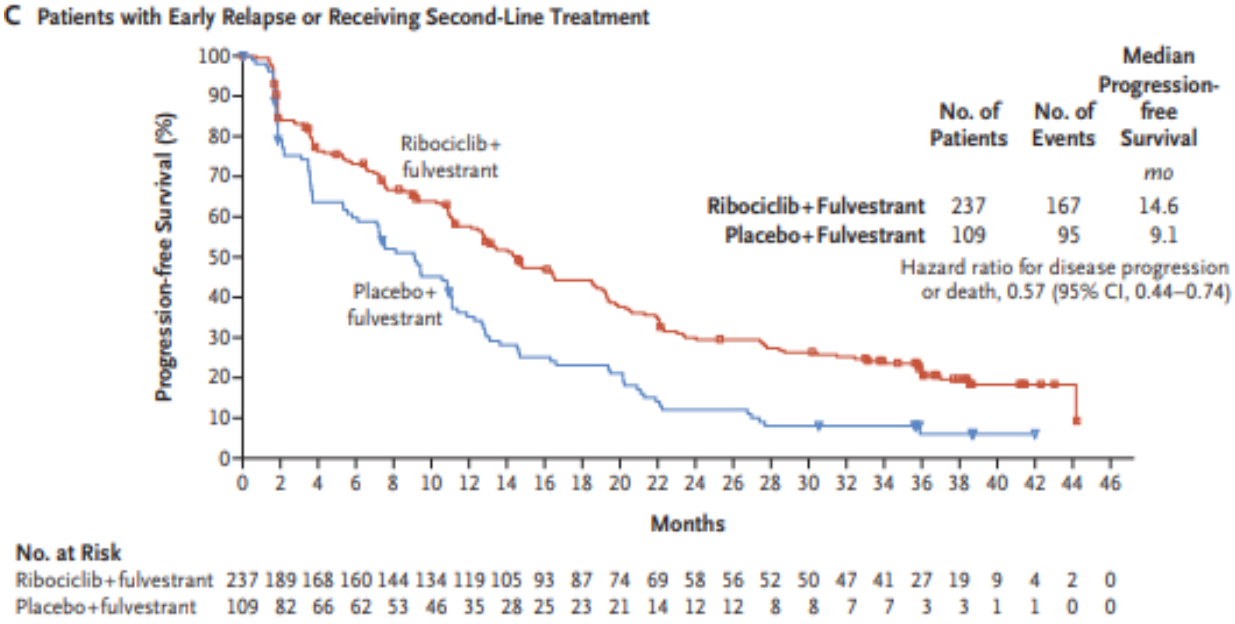
[redacted]. MONALEESA-3 was assessed in TA593 to be of high methodological quality and low risk of bias by the company. Although the ERG predominantly agreed with this assessment, the ERG had concerns that due to the association of ribociclib with prolongation of the QT interval, it is possible that 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.

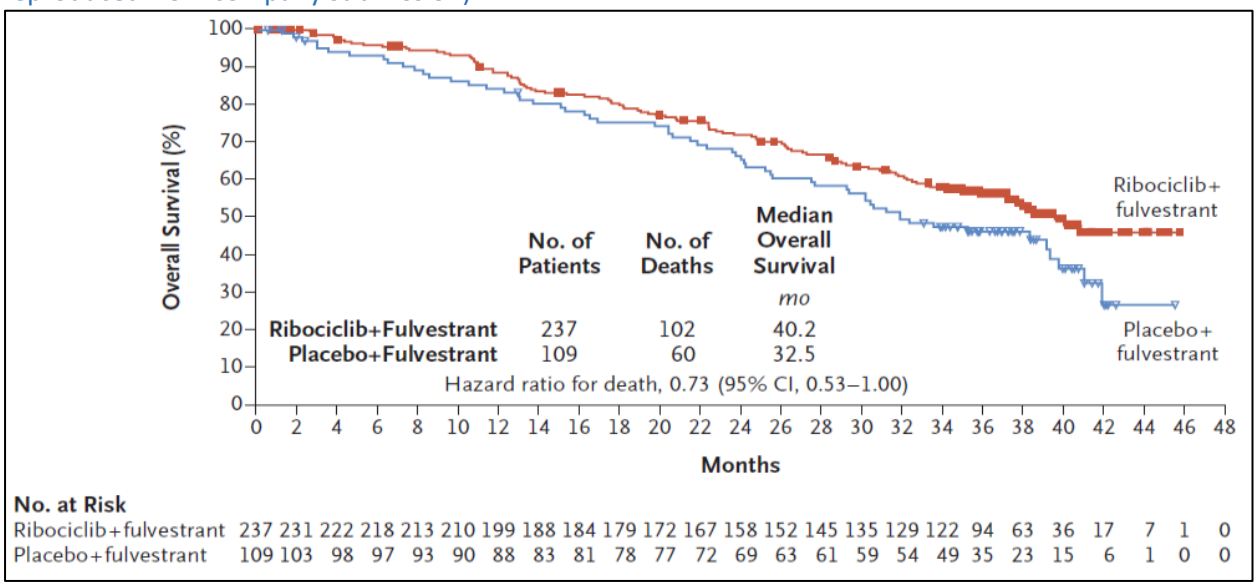
The company provided forest plots with summary data for PFS in various subgroups including line of endocrine therapy, region of metastases, site of metastasis, most recent therapy, age, ECOG score, race, geographic region, progesterone receptor (PgR) status and HR status (see Section E.1.2 of the company 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)

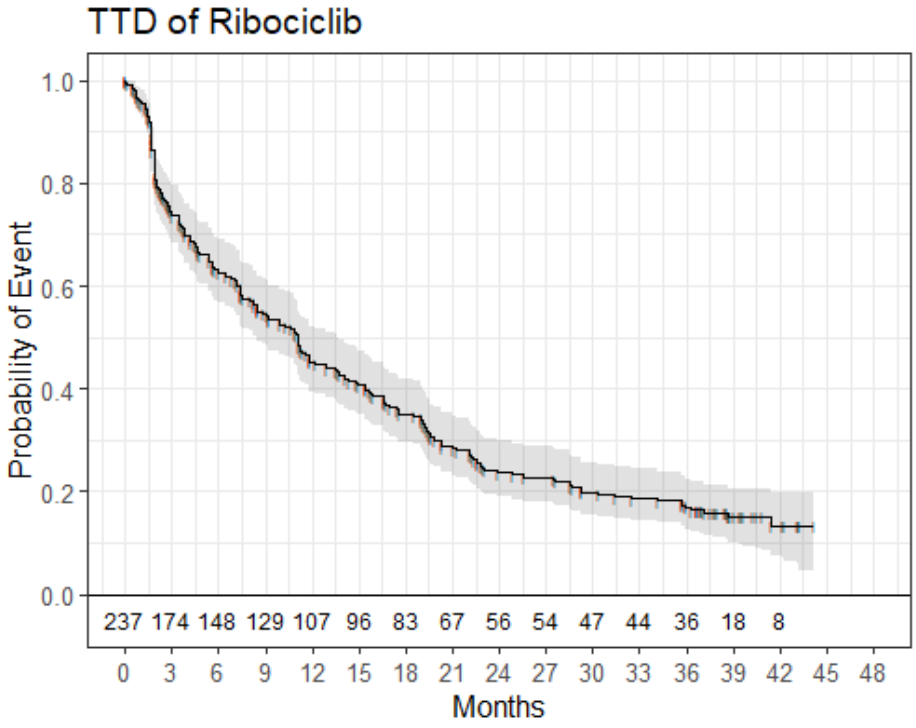


Figure 4. Time to treatment discontinuation for fulvestrant (combination) in MONALEESA-3 subpopulation B (3 June 2019 data-cut, reproduced from clarification question A12)

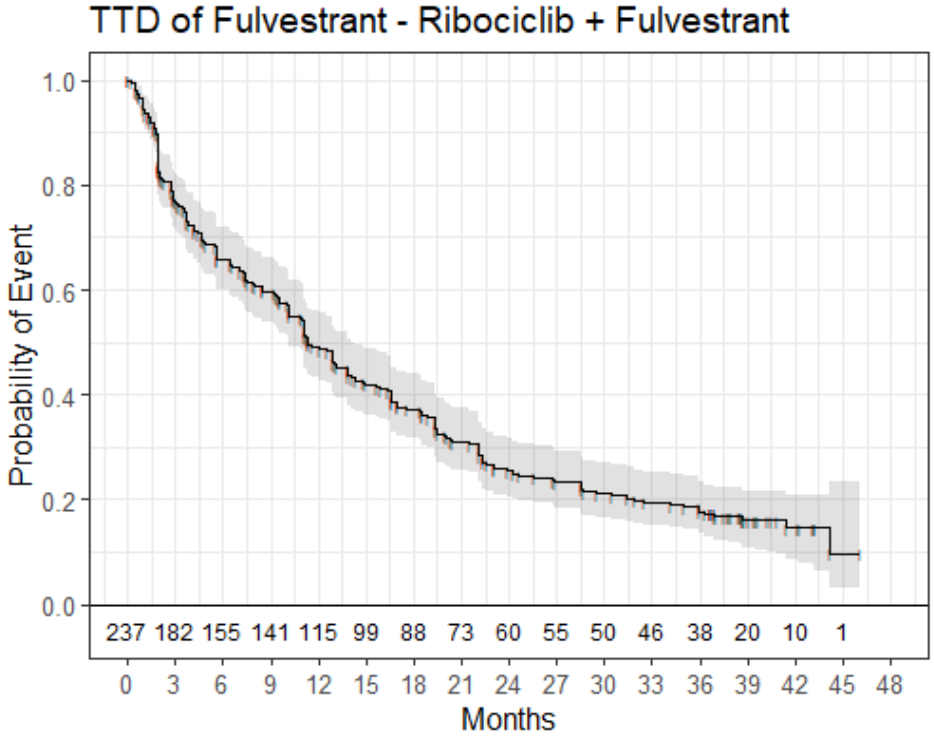
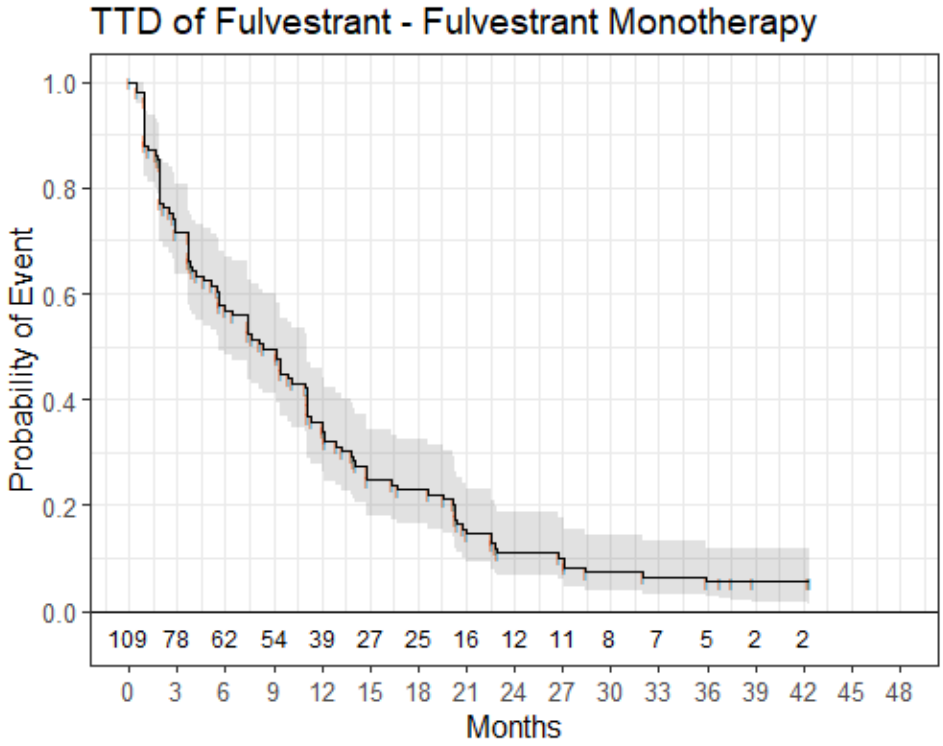


Figure 5: Time to treatment discontinuation for fulvestrant (monotherapy) in MONALEESA-3 subpopulation B (3 June 2019 data-cut, reproduced from clarification question A12)



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)

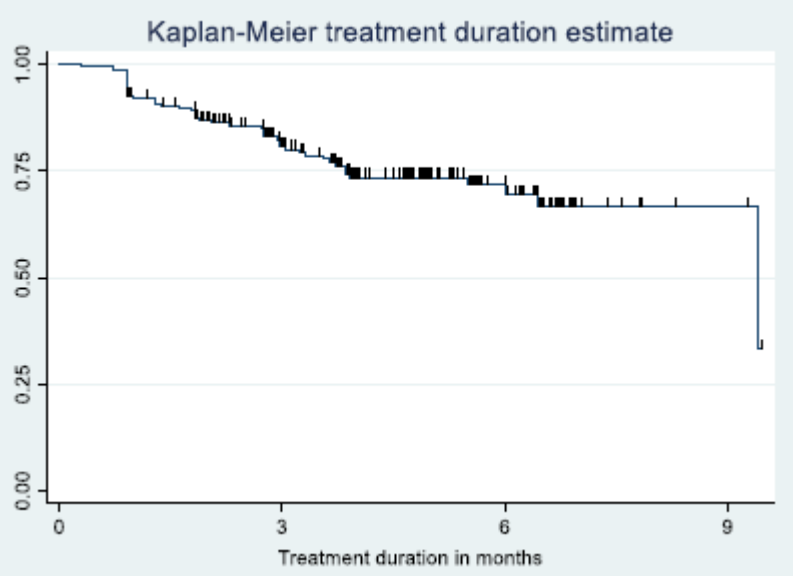


Table 11. Number of patients at risk and censored in the analysis of time to treatment discontinuation for the SACT cohort (Adapted from the SACT report, table 8 and table 9)(11)

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)

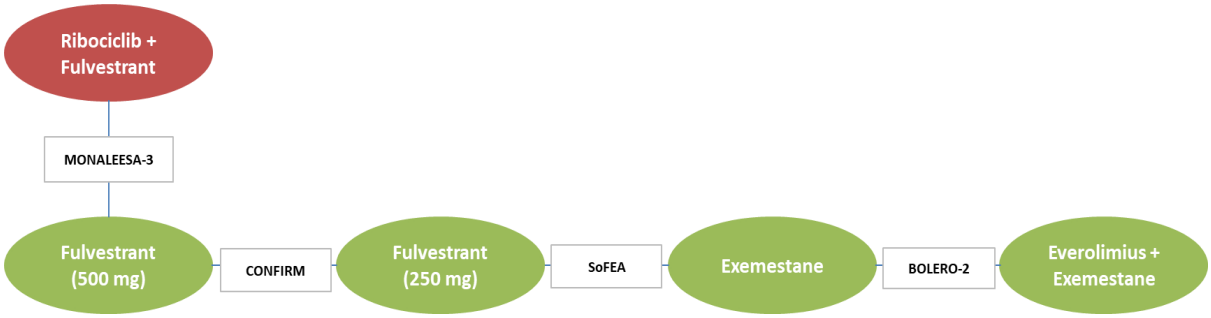


Figure 8 shows the model structure of the NMA for OS, which is consistent with the NMA for PFS, with the exception that EFECT was not included because it did not report OS. Table 14 shows the OS HRs generated by the NMA for subpopulation B. The ERG independently validated the company's analysis and obtained 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.

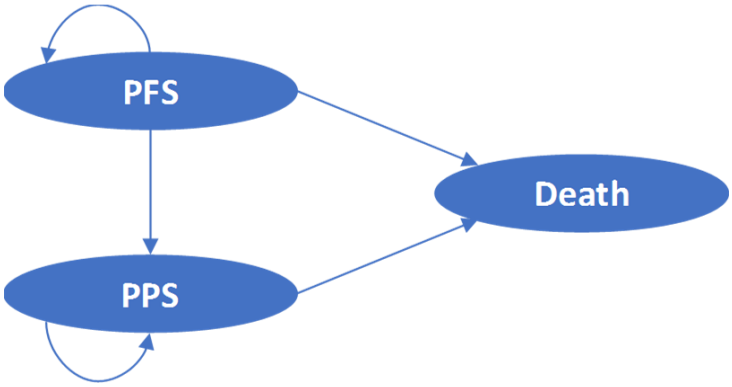
4.1.2 Interventions and comparators

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)

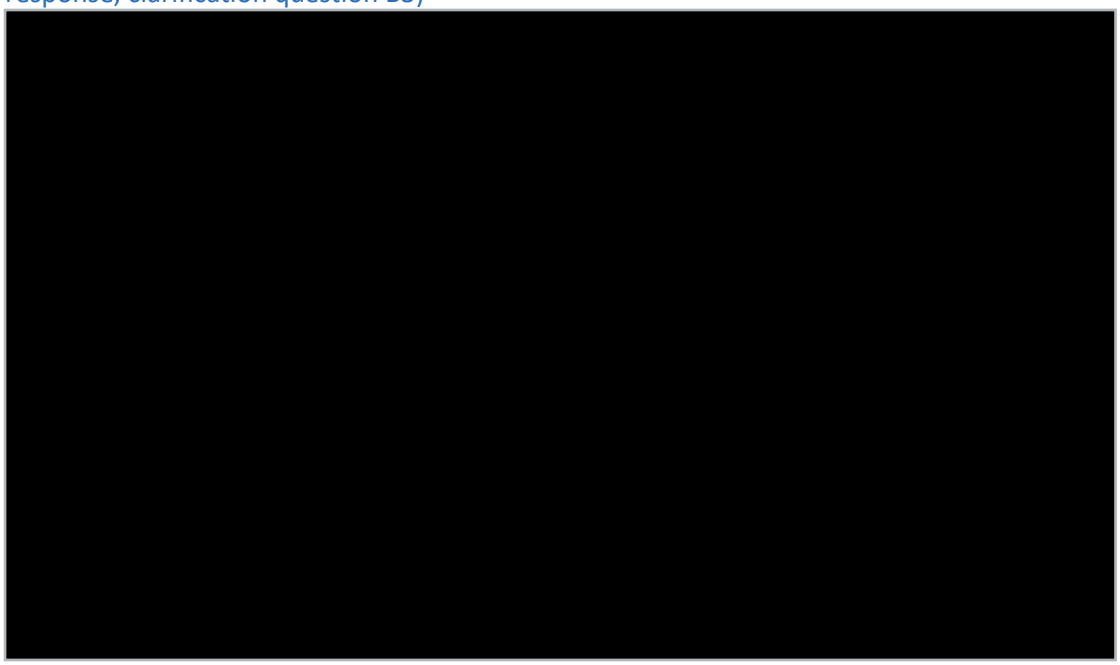


Figure 11. 10-year PFS projections (fulvestrant) using curve extrapolations with MONALEESA-3 trial KM plot overlay (reproduced from Figure 11 of the company's clarification response, clarification question B3)

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.

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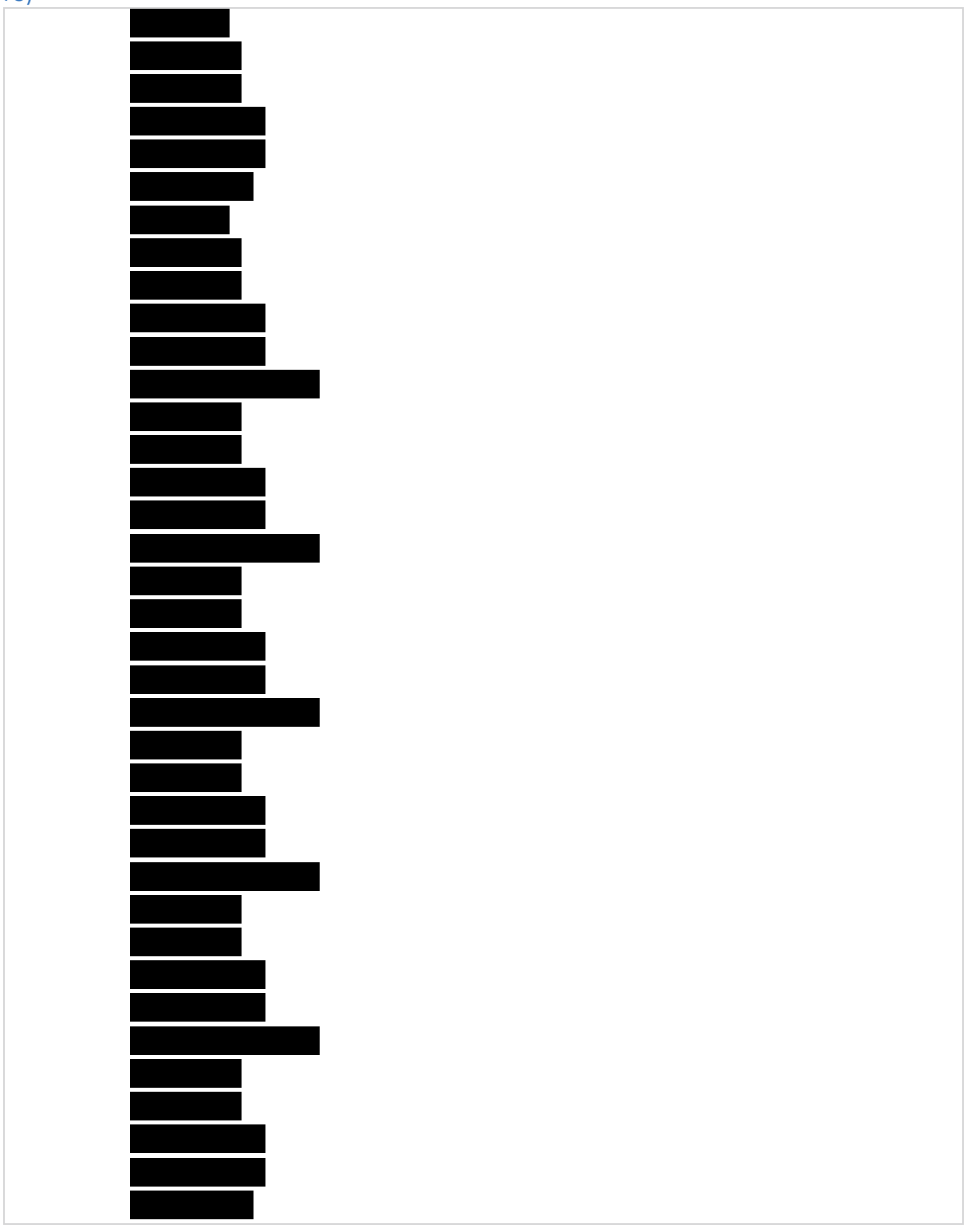
9 Appendices

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.)

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer [ID3755]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **4 November 2020** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Proposal to supply further analyses (FP NMA and PSM)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
ERG suggestion on further analyses based on FP NMA* (for both PFS/OS comparisons between MONALEESA-3 and BOLERO-2) and the possible application of these data to a partition survival model (PSM) • PH assumption violation points raised: Page 25 (table 6), 39, 40, 50, 52 and 53 • PSM: Pages 15, 16 (table 1), 19 (table 4), 26 (table 6), 49, 57, 63, 64, 77 and 78	Should NICE and the Appraisal Committee wish to consider some of the ERG's proposed amendments, we request permission to supply further analyses, which will allow these changes to be properly considered (see accompanying cover letter)	The FP NMA (for PFS) would: • Solve the issue of PH assumption violation for PFS in BOLERO-2 (and MONALEESA-3, see Issue 5 below) A PSM will: • Avoid a full surrogacy assumption between PFS and OS. The ERG points to assumptions around PPS and OS as key uncertainties remaining unresolved. The model relies on a "full surrogacy" assumption in the semi-Markov model, in which gains in PFS translate into OS gains, given the assumption no difference in PPS. While we do believe that the current approach is conservative, we agree that a PSM analysis would reduce uncertainty (although outside of the initial Terms of Engagement) • Realise a more standard and appropriate approach to modelling, when mature OS results are available from a pivotal trial (i.e. the updated OS data cut from MONALEESA-3) • Align the pharmacoeconomic analysis	The ERG would welcome the additional analyses suggested by the company.

		of ribociclib with other members of the CDK4/6 class abemaciclib (TA579) and palbociclib (TA619) for this patient group, both currently funded by CDF	

* This suggestion (FP NMA) was made at the clarification questions stage

Issue 2 MONALEESA-3 OS maturity

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Claim that MONALEESA-3 OS data is immature • Page 15, 19 (table 4), 22, 26 (table 6), 46, 51, 78	Suggested removal of inaccurate immaturity statements	Novartis consider the MONALEESA-3 OS data to be final (i.e. mature) and would like to note the following: • The MONALEESA-3 study was powered to detect differences in both PFS and OS using the intention-to-treat (ITT) population, as detailed in Table 1. • A statistically significant difference in the primary endpoint (PFS) in favour of the test arm (ribociclib + fulvestrant) occurred in the ITT population at the primary analysis (first interim OS analysis). At the second OS analysis (June 2019), there was superior OS result, following 275 deaths in the ITT population. In line with the predefined statistical analysis plan, the trial was stopped at this point given that a superior PFS and OS (p = 0.00455) result was achieved; based on the number of deaths observed; the p value threshold was 0.01129 at the second interim analysis. Thus, it is misleading to ascribe data maturity based on % of planned events for OS. A third OS analysis will be performed once approximately 351 events have	This is not a factual inaccuracy and therefore no changes to the report are required. While the ERG appreciates that the ITT analysis for overall survival may be considered more mature, this analysis was not critiqued in the ERG report given that it was not relevant to the decision problem, as outlined in section 2.2. The ERG notes that the company has stated in their comment that they

		occurred at the cut-off date; however, as statistical significance has already been reached, this is an *ad-hoc*, exploratory analysis, and the June 2019 analysis is regarded as final as per the protocol. • Finally, it should be noted that MONALEESA-3 was powered to detect a difference in the ITT population. Subpopulation B is a subpopulation analysis; therefore, the OS data for this subpopulation is not powered to detect a difference irrespective of the maturity of the OS data. There is, however, consistency in OS outcomes between subpopulation B (0.73 [95% CI, 0.53–1.00] and the ITT population (0.72 [95% CI, 0.57–0.92]) for which the study is powered **Table 1. MONALEESA-3 statistical power calculations (from statistical Analysis Plan)** OS was defined as the time from the date of randomization to the date of death due to any cause. OS was one of the secondary endpoint. A hierarchical testing strategy, where OS was to be statistically evaluated and interpreted only if the primary efficacy endpoint of PFS was significantly different between the two treatment arms, was used to control the overall type-I error rate. A maximum of three analyses were planned for OS: at the time of the PFS analysis (provided PFS was significant), at which point a total of 161 deaths (46% of OS events) were expected; after 263 events (75% of OS events) were documented; and a final OS analysis when 351 deaths (100% of OS events) were expected (expected 56 months from date of first patient to be randomized). The type I error rate was controlled by using a 3-look group sequential design using a Lan-DeMets alpha spending function which approximates O'Brien-Fleming type stopping boundaries. The distribution function of OS was estimated using Kaplan-Meier methodology. The two treatment arms were compared using a stratified log-rank test at an overall one-sided 2.5% level of	will be performing an additional analysis of OS once 351 events have occurred. Given the incomplete OS data for the subgroup of interest, the ERG requests that the company provides this analysis when it is available (as previously requested in clarification question A9). The ERG has amended the ERG report to reflect this (see Table 2 of the ERG report).

		significance. A stratified Cox regression was to be used to estimate the OS hazard ratio and the associated 95% CI. **The trial allows for the stopping of the study for a superior OS result, provided the primary endpoint PFS has already been shown to be statistically significant favouring the test treatment arm (fulvestrant + ribociclib). Furthermore, the exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses.** **Projected timelines for interim and final analyses** **Months after randomization of the first patient** / **PFS events, (%)** / **Cumulative power (%) against a hazard ratio of 0.67** / **OS events, (%)** / **Cumulative conditional power (%) against hazard ratio of 0.71** 26 / 364 (100) / 95 / 161 (46) / 14 39 / -- / -- / 263 (75) / 60 56 / -- / -- / 351 (100) / 85	

Issue 3 Systemic Anti-Cancer Therapy (SACT) data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"*the CDF SACT data collection period was subsequently amended*	Remove this statement	Whilst Novartis have been engaged in calls with Public Health England, NICE and NHSE regarding the SACT data being collected as	The ERG thanks the company for identifying the error; the ERG based its original text on information provided by

to end in January 2020, at the company's request" (Page 35)		part of the CDF agreement, there has never been a request to terminate the data collection process made by Novartis. We are unclear on the origins of this statement, and it should be removed.	Public Health England in the SACT report. The affected text on pages 14 and 35 of the ERG report has been amended to reflect the company's comments.

Issue 4 Data cut used to generate utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
MONALEESA-3 data cut used to generate utilities (page 47)	Reword to correct data cut	The data cut used for calculation of utility values is the same as in TA593. The change listed under Table 7 of the company submission ("Changes in the key model assumptions and inputs") relates to changes in the GEE regression model used. The confusion likely arises as the text in the source/justification column indeed indicates that the utilities were "updated in line with updated MONALEESA-3 data", which suggests a new data cut being used. Our apologies for any confusion this may have caused.	The ERG thanks the company for identifying the error. The ERG report has been amended.

Issue 5 PH assumption violation (MONALEESA-3 PFS)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
"*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*" (page 52)	None (agreement and clarification)	Novartis accepts that the PH assumption may not hold based on log-cumulative hazard plots. As pointed out by the ERG, the curves appear to meet or cross, although the latter is in our opinion debatable (Figure G2 in the CDF submission appendix). Similarly, we also note that the PH assumption does not appear to hold for BOLERO-2. Given this level of uncertainty regarding PH, we agree that the use of FP NMA analysis may be warranted, as suggested at the clarification stage (see 0 & cover letter)	This is not a factual inaccuracy and therefore no changes to the report are required. The ERG thanks the company for their clarification.

Issue 6 Time-to-discontinuation (TTD) for everolimus (+ exemestane)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
In the penultimate paragraph of page 61, there is a statement that the BOLERO-2 trials report dose interruptions or reductions (to 5mg) for	Data correction and re-analysis	This statement is erroneous as the BOLERO-2 clinical study report, Table 12-3 states that 'reduction and/or interruptions were 58.5% for everolimus and 19.9% for exemestane. Reductions alone were 33.4% for everolimus and 0.4% for exemestane.	This is not a factual inaccuracy and therefore no changes to the report are required. The statement is based on Yardley *et al.* and was referenced in the report as such. The ERG also notes that the BOLERO-2 CSR was not supplied as part of the company's

66.8% of patients on everolimus (page 61)		Similarly, on page 62, “Based on clinical expert opinion, 70% of patients are assumed to dose reduce in this scenario.“ Correspondingly, the ERG performs a scenario where 20% of patients discontinue everolimus at month 6, and a scenario in which 70% of patients dose reduce from 10mg to 5mg at month 6. While Novartis recognizes the importance of incorporating treatment discontinuation and dose reductions in these analyses, there are several problems with these assumptions. First, assuming that 70% of patients dose reduce to 5mg at month 6 is more than twice the reported proportions from the BOLERO-2 CSR. Second, where the CSR reports reductions and/or interruptions for 58.5% of patients, interruptions do not necessarily translate to full treatment discontinuation. To better account for the available evidence regarding use of everolimus, we have conducted analyses on the BOLERO-2 data to allow a scenario where dosage matches empirical dosage distributions The mean dose intensity for everolimus in BOLERO-2 was 7.89 mg/day. The dose intensity is calculated as the cumulative dose received divided by the duration of exposure. The mean relative dose intensity for everolimus in BOLERO-2 was 0.79, which is	submission. Additionally, the ERG’s scenario analysis was based on clinical expert opinion and the ERG has emphasised in its report that the company can perform a more robust analysis using the data available to the company from BOLERO-2. 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.

		calculated as the dose intensity divided by the planned dose (i.e., 7.89 mg daily / 10 mg daily). The assumption that 70% of patients remaining on everolimus would dose reduce to 5mg daily would effectively yield a relative dose intensity of 0.65 (30% x 1.0 + 70% x 0.5 = 0.65). This assumption is therefore inappropriate because the observed efficacy in BOLERO-2 reflects the observed mean relative dose intensity of 0.79 and not the assumed relative dose intensity of 0.65.	

Issue 7 ERG base case

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
We note that the ERG base case ICER presented in Table 5 ([redacted]) • Page 68	Request removal of this analysis or wording that it is an alternative to the agreed base case parameters at Terms of Engagement	We would like to point out that the 10% fulvestrant discount was agreed as part of the Terms of Engagement. That aside, we confirm that our model matches the ERG output given in Table 5 when the 10% discount is removed.	This is not a factual inaccuracy and therefore no changes to the report are required. On page 47 of the ERG report it clearly states that, "*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*."

Issue 8 PPS validation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The ERG notes that PFS and TTD extrapolations from MONALEESA-3 were validated with clinical experts, and query why this was not done for PPS (page 73)	None (clarification)	Under the assumption that there is no difference in PPS, such a validation was not considered relevant as this would not have a significant impact on the results	This is not a factual inaccuracy and therefore no changes to the report are required. The ERG thanks the company for their clarification.

Public Health England

Protecting and improving the nation's health

Ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer – data review

Commissioned by NHS England and NHS Improvement

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

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Contents

Executive summary

Introduction

The National Institute for Health and Care Excellence (NICE) appraised the clinical and cost effectiveness of ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer. The appraisal committee highlighted clinical uncertainty around estimates of overall survival (OS) in the evidence submission. As a result, they recommended commissioning of ribociclib in combination with fulvestrant through the Cancer Drugs Fund (CDF) to allow a period of managed access, supported by additional data collection to answer the clinical uncertainty.

NHS England and NHS Improvement commissioned Public Health England (PHE) to evaluate the real-world treatment effectiveness of ribociclib in combination with fulvestrant in the CDF population during the managed access period. This report presents the results of the use of ribociclib in combination with fulvestrant in clinical practice, using the routinely collected Systemic Anti-Cancer Therapy (SACT) dataset.

This report, and the data presented, demonstrate the potential within the English health system to collect real-world data to inform decision-making about patient access to cancer treatments via the CDF. The opportunity to collect real-world data enables patients to access promising new treatments much earlier than might otherwise be the case, whilst further evidence is collected to address clinical uncertainty.

The NHS England and NHS Improvement and PHE partnership for collecting and following up real-world SACT data for patients treated through the CDF in England has resulted in analysis being carried out on 97% of patients and 70% of patient outcomes reported in the SACT dataset. PHE and NHS England and NHS Improvement are committed to providing world first high-quality real-world data on CDF cancer treatments to be appraised alongside the outcome data from the relevant clinical trials.

Methods

NHS England and NHS Improvement's Blueteq® system was used to provide a reference list of all patients with an application for ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in the CDF. Patient NHS numbers were used to link Blueteq applications to PHE's routinely collected SACT data to provide SACT treatment history.

Between 17 July 2019 and 16 January 2020, 221 applications for ribociclib in combination with fulvestrant were identified in NHS England and NHS Improvement's Blueteq system. Following appropriate exclusions (see Figures 1 and 2), 187 unique patients who received treatment were included in these analyses. All patients were traced to obtain their vital status using the personal demographics service (PDS)[1].

Results

187 (97%) unique patients with CDF applications were reported in the SACT dataset.

Median treatment duration was 9.4 months[a], (286 days). 72% [95% CI: 63%,78%] of patients were receiving treatment at 6 months.

At data cut off, 25% (N=46) of patients were identified as no longer being on treatment; 30% (N=14) of patients stopped treatment due to progression, 15% (N=7) of patients stopped treatment due to acute toxicity, 4% (N=2) of patients chose to end their treatment, 24% (N=11) of patients died not on treatment, 9% (N=4) of patients died on treatment and 17% (N=8) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

A secondary analysis was conducted for each of the Blueteq populations showing treatment duration for each of the previous endocrine therapy options.

Conclusion

This report analyses SACT real world data for patients treated with ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in the CDF. It evaluates treatment duration and treatment outcomes for all patients treated with ribociclib in combination with fulvestrant for this indication.

[a] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Introduction

Breast cancer (C50) accounts for 15% of all cancer diagnoses in England. In 2017, 46,109 patients were diagnosed with breast cancer (females 45,790, males 319)[2].

Ribociclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy only if:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor and
- the conditions in the managed access agreement for ribociclib with fulvestrant are followed[3].

Background to this report

The Public Health England and NHS England and NHS Improvement partnership on cancer data – using routinely collected data to support effective patient care

High quality and timely cancer data underpin NHS England NHS Improvement and Public Health England's (PHE's) ambitions of monitoring cancer care and outcomes across the patient pathway. The objective of the PHE and NHS England and NHS Improvement partnership on cancer data is to address mutually beneficial questions using Systemic Anti-Cancer Therapy (SACT) data collected by PHE. This includes NHS England and NHS Improvement commissioning PHE to produce routine outcome reports on patients receiving treatments funded through the Cancer Drugs Fund (CDF) during a period of managed access.

The CDF is a source of funding for cancer drugs in England[4]. From the 29th July 2016 NHS England implemented a new approach to the appraisal of drugs funded by the CDF. The new CDF operates as a managed access scheme that provides patients with earlier access to new and promising treatments where there is uncertainty as to their clinical and cost effectiveness. During this period of managed access, ongoing data collection is used to answer the uncertainties raised by the NICE committee and inform drug reappraisal at the end of the CDF funding period[5].

PHE will analyse data derived from patient-level information collected in the NHS, as part of the care and support of cancer patients. The data is collated, maintained, quality-assured and analysed by the National Cancer Registration and Analysis Service, which is part of PHE.

NICE Appraisal Committee review of ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer [TA593].

The NICE Appraisal Committee reviewed the clinical and cost effectiveness of ribociclib in combination with fulvestrant (Novartis) in treating advanced hormone-receptor positive, HER2-negative breast cancer [TA593] and published guidance for this indication in August 2019[6].

Due to the clinical uncertainties identified by the committee and outlined below, the committee recommended commissioning of ribociclib in combination with fulvestrant through the CDF for a period of seventeen months, from July 2019 to December 2020. The CDF SACT data collection period was subsequently amended to end in January 2020, at the company's request, due to the primary data source (MONALEESA-3 clinical trial) reporting earlier than anticipated.

During the CDF funding period, results from ongoing clinical trials evaluating ribociclib in combination with fulvestrant in the licensed indication are likely to answer the main clinical uncertainties raised by the NICE committee. The ongoing trial to support the evaluation of ribociclib with fulvestrant is MONALEESA-3[7]. Data collected from the MONALEESA-3 clinical trial would be the primary source of data collection.

Analysis of the SACT dataset would provide information on real-world treatment patterns and outcomes for ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer in England, during the CDF funding period. This would act as a secondary source of information alongside the results of the MONALEESA-3[7].

The committee identified the key areas of uncertainty below for re-appraisal at the end of the CDF data collection;

- **overall survival data**
- **progression-free survival**
- **post-progression survival**

Results for the clinical uncertainty mentioned above will come from the MONALEESA-3 clinical trial. PHE has carried out analyses on regimen outcomes and treatment duration. Given the short data collection period there was no meaningful data from SACT to produce overall survival.

Approach

Upon entry to the CDF, representatives from NHS England and NHS Improvement, NICE, PHE and the company (Novartis) formed a working group to agree the Data Collection Agreement (DCA)[6]. The DCA set out the real-world data to be collected and analysed to support the NICE re-appraisal of ribociclib in combination with fulvestrant. It also detailed the eligibility criteria for patient access to ribociclib in combination with fulvestrant through the CDF and CDF entry and exit dates.

This report includes patients with approved CDF applications for ribociclib in combination with fulvestrant, approved through Blueteq® and followed-up in the SACT dataset collected by PHE.

Methods

CDF applications - identification of the cohort of interest

NHS England and NHS Improvement collects applications for CDF treatments through their online prior approval system (Blueteq®). The Blueteq application form captures essential baseline demographic and clinical characteristics of patients needed for CDF evaluation purposes. Where appropriate, Blueteq data are included in this report.

Consultants must complete a Blueteq application form for every patient receiving CDF funded treatment. As part of the application form, consultants must confirm that a patient satisfies all clinical eligibility criteria to commence treatment. PHE has access to the Blueteq database and key data items such as NHS numbers, primary diagnosis and drug information of all patients with an approved CDF application (which therefore met the treatment eligibility criteria).

The lawfulness of this processing is covered under Article 6(1)(e) of the EU General Data Protection Regulations (GDPR) (processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller). The processing of special categories of personal data is also covered under article 9(2)(h) of EU GDPR (processing is necessary for the purposes of preventive or occupational medicine). As NHS E & I do not have an exemption to the Common Law Duty of Confidentiality, NHS E & I cannot access the identifiable data directly. PHE, through the National Cancer Registration and Analysis Service have permission to process confidential patient information though Regulation 2 of The Health Service (Control of Patient Information) Regulations 2002.

PHE collates data on all SACT prescribed drugs by NHS organisations in England, irrespective of the funding mechanism. The Blueteq extract is therefore essential to identify the cohort of patients whose treatment was funded by the CDF.

Ribociclib in combination with fulvestrant clinical treatment criteria

- Patient has histologically or cytologically documented oestrogen receptor positive and HER-2 negative breast cancer
- Patient has metastatic breast cancer or locally advanced breast cancer which is not amenable to curative treatment
- Patient is male or is female and if female is either post-menopausal or if pre- or peri-menopausal has undergone ovarian ablation or suppression with LHRH agonist treatment
- Patient has an ECOG performance status of 0 or 1 or 2
- Patient has received previous endocrine therapy according to one of the three populations as set out below as these are the groups on which the NICE Technology Appraisal for ribociclib plus fulvestrant focused. Please record which population the patient falls into:
    - Patient has progressive disease whilst still receiving adjuvantor neoadjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - Patient has progressive disease within 12 or less months of completing adjuvant endocrine therapy for early breast cancer with no subsequent endocrine therapy received following disease progression or
    - Patient has progressive disease on 1st line endocrine therapy for advanced/metastatic breast cancer with no subsequent endocrine therapy received following disease progression
- Patient has had no prior treatment with a CDK 4/6 inhibitor unless either abemaciclib (in combination with fulvestrant) or palbociclib (in combination with fulvestrant) has had to be stopped within 3 months of its start solely as a consequence of dose limiting toxicity and in the clear absence of disease progression or ribociclib has been received as part of an early access scheme for the combination of ribociclib plus fulvestrant and the patient meets all the other criteria set out in this form
- Patient has had no prior treatment with fulvestrant
- Patient has had no prior treatment with everolimus
- Ribociclib will only be given in combination with fulvestrant
- Treatment will continue until there is progressive disease or excessive toxicity or until the patient chooses to discontinue treatment, whichever is the sooner
- Treatment breaks of up to 6 weeks are allowed, but solely to allow toxicities to settle

- Ribociclib and fulvestrant will be otherwise used as set out in their Summaries of Product Characteristics (SPC) including the need for ECGs to be performed prior to treatment, after 2 weeks of treatment and after 4 weeks of therapy

CDF applications - de-duplication criteria

Before conducting any analysis on CDF treatments, the Blueteq data is examined to identify duplicate applications. The following de-duplication rules are applied:

- If two trusts apply for ribociclib in combination with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer for the same patient (identified using the patient's NHS number), and both applications have the same approval date, then the record where the CDF trust (the trust applying for CDF treatment) matches the SACT treating trust is selected.

- If two trusts apply for ribociclib in combination with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer for the same patient, and the application dates are different, then the record where the approval date in the CDF is closest to the regimen start date in SACT is selected, even if the CDF trust did not match the SACT treating trust.

- If two applications are submitted for ribociclib in combination with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer and the patient has no regimen start date in SACT capturing when the specific drug was delivered, then the earliest application in the CDF is selected.

Initial CDF cohorts

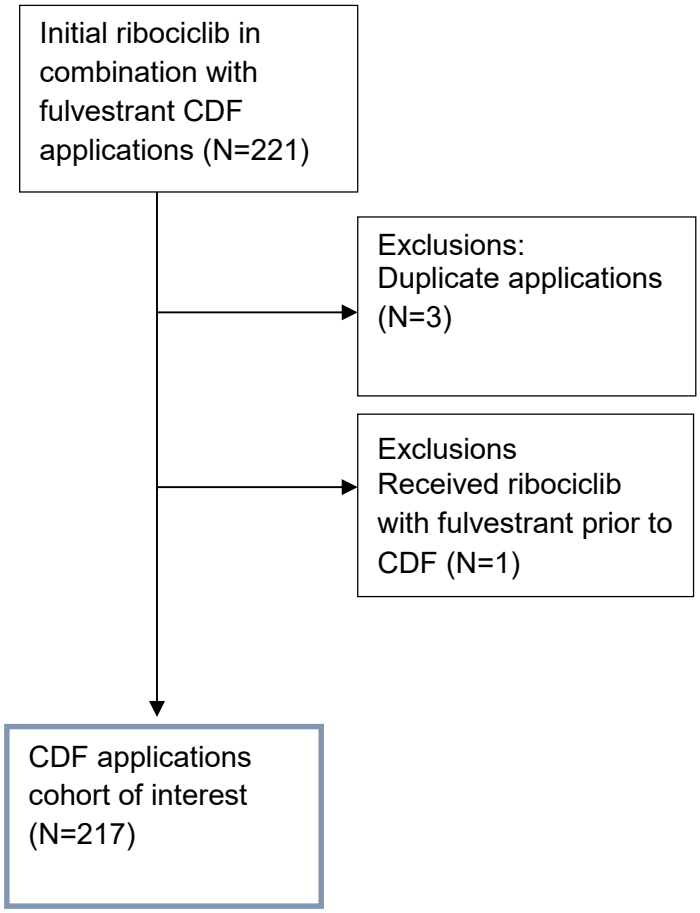
The analysis cohort is limited to the date ribociclib in combination with fulvestrant entered the CDF for this indication, onwards. Any treatments delivered before the CDF entry date are excluded as they are likely to be patients receiving treatment via an Early Access to Medicines Scheme (EAMS) or a compassionate access scheme run by the pharmaceutical company. These schemes may have different eligibility criteria compared to the clinical treatment criteria detailed in the CDF managed access agreement for this indication.

The CDF applications included in these analyses are from 17 July 2019 to 16 January 2020. A snapshot of SACT data was taken on 2 May 2020 and made available for analysis on 11 May 2020. The snapshot includes SACT activity up to the 31 January 2020. Tracing the patients' vital status was carried out on 29 June 2020 using the personal demographics service (PDS)[1].

There were 221 applications for CDF funding for ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer between 17 July 2019 and 16 January 2020 in the NHS England and NHS Improvement Blueteq database. Following de-duplication this relates to 218 unique patients.

One patient was excluded from these analyses as they appeared to have received ribociclib in combination with fulvestrant prior to the drug being available through the CDF.

Figure 1: Derivation of the cohort of interest from all CDF (Blueteq) applications made for ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer between 17 July 2019 and 16 January 2020



Linking CDF cohort to SACT

NHS numbers were used to link SACT records to CDF applications for ribociclib in combination with fulvestrant in NHS England and NHS Improvement's Blueteq system. Information on treatments in SACT were examined to ensure the correct SACT treatment records were matched to the CDF application; this includes information on treatment dates (regimen, cycle and administration dates) and primary diagnosis codes in SACT.

Addressing clinical uncertainties

Treatment duration

Treatment duration is calculated from the start of a patient's treatment to their last known treatment date in SACT.

Treatment start date is defined as the date the patient started their CDF treatment. This date is identified as the patient's earliest treatment date in the SACT dataset for the treatment of interest. Data items[8] used to determine a patient's earliest treatment date are:

- Start date of regimen – SACT data item #22
- Start date of cycle – SACT data item #27
- Administration date – SACT data item #34

The earliest of these dates is used as the treatment start date.

The same SACT data items (#22, #27, #34)[8] are used to identify a patient's final treatment date. The latest of these three dates is used as the patient's final treatment date.

Additional explanation of these dates is provided below:

Start date of regimen
A regimen defines the drugs used, their dosage and frequency of treatment. A regimen may contain many cycles. This date is generally only used if cycle or administration dates are missing.

Start date of cycle
A cycle is a period of time over which treatment is delivered. A cycle may contain several administrations of treatment, after each treatment administration, separated by an appropriate time delay. For example; a patient may be on a 3-weekly cycle with treatment being administered on the 1st and 8th day, but nothing on days 2 to 7 and days 9 to 20. The 1st day would be recorded as the "start day of cycle". The patient's next cycle would start on the 21st day.

Administration date
An administration is the date a patient is administered the treatment, which should coincide with when they receive treatment. Using the above example, the administrations for a single 3-week cycle would be on the 1st and 8th day. The next administration would be on the 21st day, which would be the start of their next cycle.

The interval between treatment start date and final treatment date is the patient's time on treatment.

All patients are then allocated a 'prescription length' which is a set number of days added to the final treatment date to allow for the fact that they are effectively still 'on treatment' between administrations. The prescription length should correspond to the typical interval between treatment administrations.

If a patient dies between administrations, then their censor date is their date of death and these patients are deemed to have died on treatment unless an outcome summary is submitted to the SACT database confirming that the patient ended treatment due to disease progression or toxicity before death.

Ribociclib in combination with fulvestrant is administered orally, treatment is generally prescribed in a healthcare facility and healthcare professionals are able to confirm that the prescribing of treatment has taken place on a specified date. A duration of 28-days has been added to final treatment date for all patients; this represents the duration from a patient's last cycle to their next[9]. Ribociclib in combination with fulvestrant is a 28-day cycle consisting of one administration.

Treatment duration is calculated for each patient as:
Treatment duration (days) = (Final treatment date – Treatment start date) + prescription length (days).

Once a patient's treatment duration has been calculated, the patient's treatment status is identified as one of the following:

No longer receiving treatment (event), if:

- the patient has died.
- the outcome summary (SACT data item #41) detailing the reason for stopping treatment has been completed.
- there is no further SACT records for the patient following a three-month period.

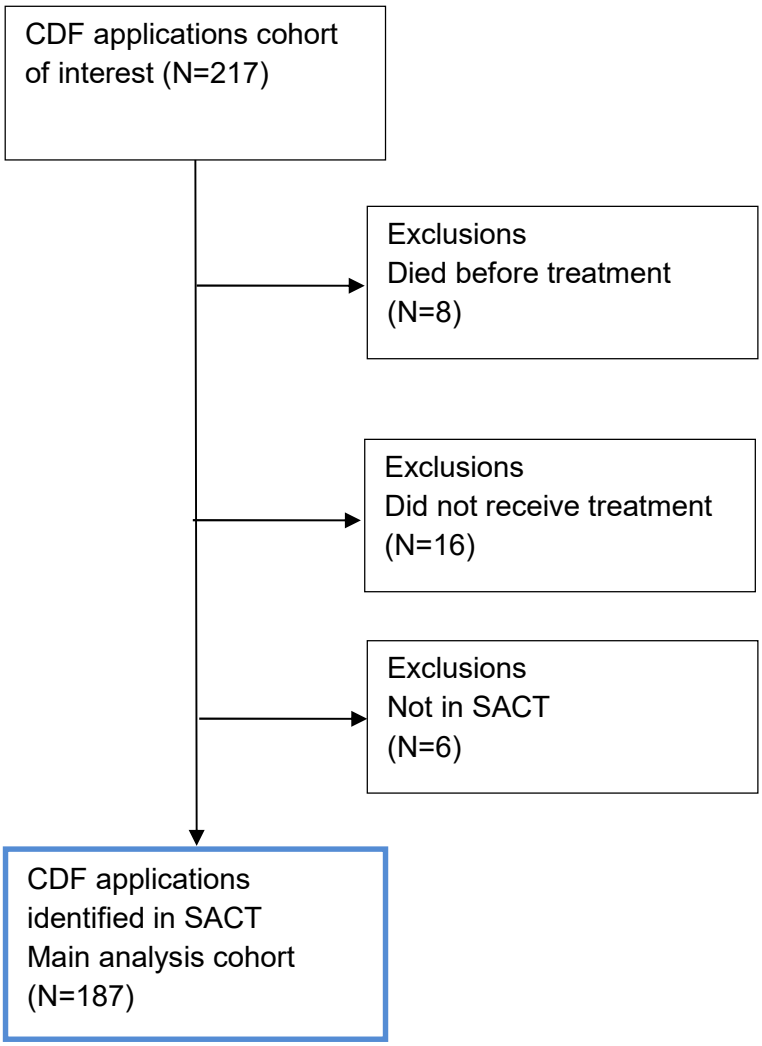
If none of the above apply, the patient is assumed to still be on treatment and is censored.

Results

Cohort of interest

Of the 217 new applications for CDF funding for ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer, eight patients died before treatment, 16 patients did not receive treatment and six patients were missing from SACT[b] (see Figure 2).

Figure 2: Matched cohort - SACT data to CDF (Blueteq®) applications for ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer between 17 July 2019 and 16 January 2020



[b] The 16 patients that did not receive treatment were confirmed by the relevant trust by the PHE data liaison team. Of the eight that died before treatment, five have been confirmed by the relevant trusts by the PHE data liaison team.

A maximum of 193 ribociclib in combination with fulvestrant records are expected in SACT for patients who were alive, eligible and confirmed to have commenced treatment (Figure 2). 97% (187/193) of these applicants for CDF funding have a treatment record in SACT.

Completeness of SACT key variables

Table 1 presents the completeness of key data items required from SACT. Completeness is 100% for primary diagnosis, date of birth, gender and treatment dates. Performance status at the start of regimen is 82% complete.

Table 1: Completeness of key SACT data items for the ribociclib in combination with fulvestrant cohort (N=187)

Variable	Completeness (%)
Primary diagnosis	100%
Date of birth (used to calculate age)	100%
Sex	100%
Start date of regimen	100%
Start date of cycle	100%
Administration date	100%
Performance status at start of regimen	82%

Table 2 presents the completeness of regimen outcome summary. A patient's outcome summary, detailing the reason why treatment was stopped, is only captured once a patient has completed their treatment. Therefore, the percentage completeness provided for outcome summary is for records where we assume treatment has stopped and an outcome is expected. Outcomes are expected if a patient has died, has an outcome in SACT stating why treatment has ended or has not received treatment with ribociclib in combination with fulvestrant in at least three months. These criteria are designed to identify all cases where a patient is likely to have finished treatment. Based on these criteria, outcomes are expected for 46. Of these, 31 (67%) have an outcome summary recorded in the SACT dataset.

Table 2: Completeness of outcome summary for patients that have ended treatment (N=46)

Variable	Completeness (%)
Outcome summary of why treatment was stopped	67%

Completeness of Blueteq key variables

Table 3 presents the completeness of key data items required from Blueteq. Previous endocrine therapy is 100% complete (187/187).

Table 3: Previous endocrine therapy (N=187)

Variable	Completeness (%)
Previous endocrine therapy	100%

Patient characteristics

The median age of the 187 patients receiving ribociclib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative breast cancer was 64 years, all patients were female.

Table 4: Patient characteristics (N=187)

Patient characteristics[c]		N	%
Sex	Female	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%
Performance status	0	76	41%
	1	64	34%
	2	14	7%
	3	0	0%
	4	0	0%
	Missing	33	18%

[c] Figures may not sum to 100% due to rounding.

Blueteq data items

Previous endocrine therapy

The distribution of previous endocrine therapy in Table 5 shows that 52% (N=97) of patients have progressive disease on 1st line endocrine therapy, 45% (N=84) of patients have progressive disease whilst still receiving adjuvant therapy and 3% (N=6) of patients have progressive disease within 12 months or less of completing adjuvant endocrine therapy.

Table 5: Distribution of previous endocrine therapy in Blueteq (N=187)

Previous endocrine therapy	N	%
Has progressive disease on 1st line endocrine therapy	97	52%
Has progressive disease whilst still receiving adjuvant therapy	84	45%
Has progressive disease within 12 or less months of completing adjuvant endocrine therapy	6	3%
Total	**187**	**100%**

Treatment duration

Of the 187 patients with CDF applications, 46 (25%) were identified as having completed treatment by 31 January 2020 (latest follow up in SACT dataset). Patients are assumed to have completed treatment if they have died, have an outcome summary recorded in the SACT dataset or they have not received treatment with ribociclib in combination with fulvestrant in at least three months (see Table 9). The median follow-up time in SACT was 3.7 months (112 days).

Presently, 94% (N=132) of trusts submit their SACT return to the submission portal two months after the month's treatment activity has ended; this provides a maximum follow-up period of nine months. 6% (N=9) of trusts submit their SACT return to the submission portal one month after the month's treatment activity has ended; this provides the maximum follow-up period of ten months. SACT follow-up ends 31 January 2020.

Table 6: Breakdown by patients' treatment status[d,e,f]

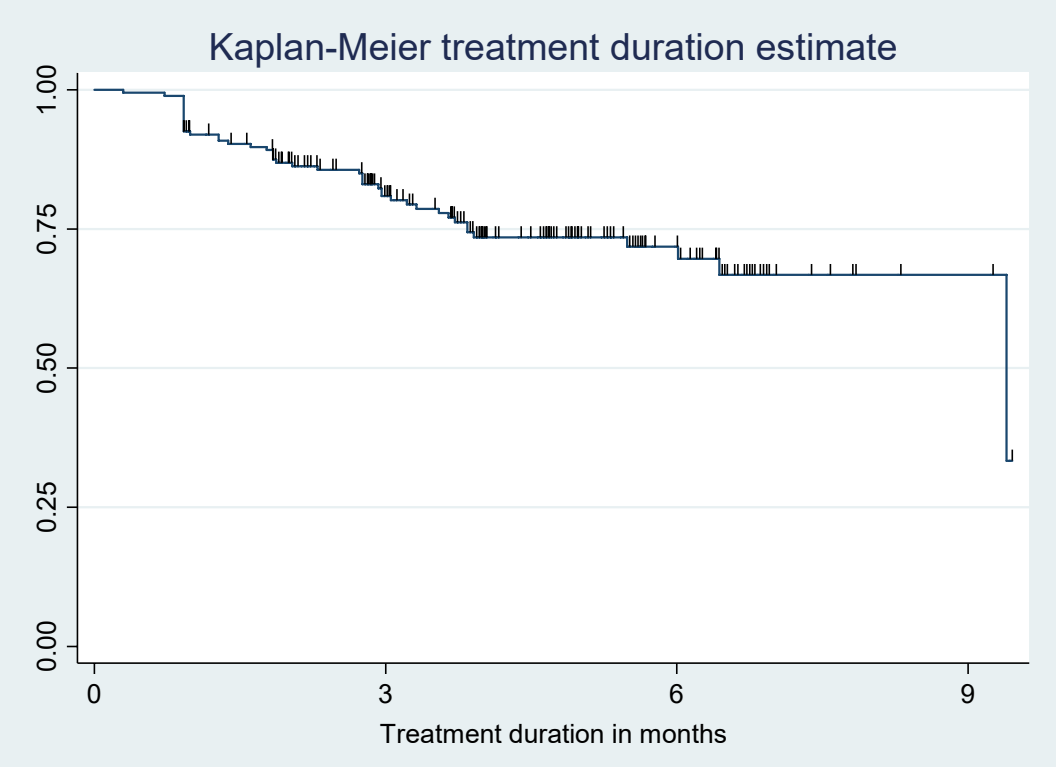
Patient status	Frequency (N)	Percentage (%)
Patient died – not on treatment	27	14%
Patient died – on treatment	4	2%
Treatment stopped	15	8%
Treatment ongoing	141	75%
Total	**187**	**100%**

[d] Figures may not sum to 100% due to rounding.
[e] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[f] '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/

The Kaplan-Meier curve for ongoing treatment is shown in figure 3. The median treatment duration for all patients was 9.4 months[g] (286 days) (N=187).

72% of patients were still receiving treatment at six months [95% CI: 63%,78%].

Figure 3: Kaplan-Meier treatment duration (N=187)



Tables 7 and 8 show 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. The maximum follow-up period for all patients for treatment duration was 6.5 months (197 days). SACT contains more follow-up for some patients.

Table 7: Number of patients at risk, by quarterly breakpoints.

Time intervals (months)	0 - 12	3 - 12	6 - 12	9 - 12
Number at risk	187	111	33	3

[g] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Table 8 shows that for all patients who received treatment, 141 were still on treatment (censored) at the date of follow-up and 46 had ended treatment (events).

Table 8: Number of patients at risk, by quarterly breakpoints split between patients that have ended treatment (events) and patients that are still on treatment (censored).

Time intervals (months)	0 - 12	3 - 12	6 - 12	9 - 12
Censored	141	98	30	2
Events	46	13	3	1

Table 9 gives a breakdown of a patient's treatment outcome recorded in SACT when a patient's treatment has come to an end. 25% (N=46) of patients had ended treatment at 31 January 2020.

Table 9: Treatment outcomes for patients that have ended treatment (N=46)[h,i]

Outcome	Frequency (N)	Percentage (%)
Stopped treatment – progression of disease	14	30%
Stopped treatment – acute chemotherapy toxicity	7	15%
Stopped treatment – patient choice	2	4%
Stopped treatment – died not on treatment[j]	11	24%
Stopped treatment – died on treatment	4	9%
Stopped treatment – no treatment in at least 3 months	8	17%
Total	**46**	**100%**

[h] Figures may not sum to 100% due to rounding.
[i] Table 9 presents the outcome summary data reported by trusts. This includes patients from Table 6 who 'died on treatment', 'died not on treatment' and 'stopped treatment'.
[j] '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/

Table 10: Treatment outcomes and treatment status for patients that have ended treatment (N=46)

Outcome[k]	Patient died [l] not on treatment	Treatment stopped	Patient died on treatment
Stopped treatment – progression of disease	9	5	
Stopped treatment – acute chemotherapy toxicity	5	2	
Stopped treatment – patient choice	2		
Stopped treatment – died not on treatment	11		
Stopped treatment – died on treatment			4
Stopped treatment – no treatment in at least 3 months		8	
Total	**27**	**15**	**4**

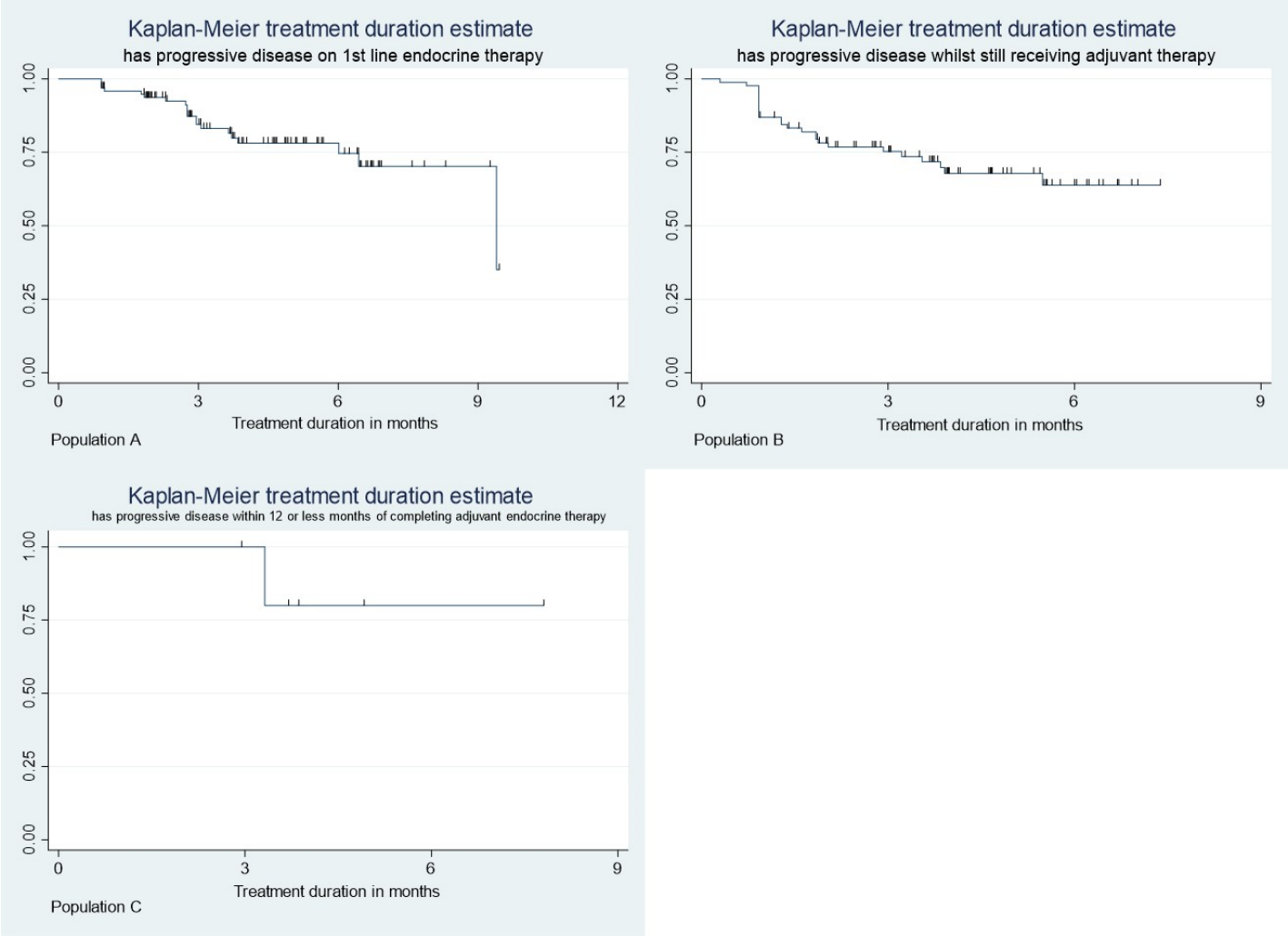
[k] Relates to outcomes submitted by the trust in table 9.
[l] Relates to treatment status in table 6 for those that have ended treatment.

Treatment duration by Blueteq previous endocrine therapy

The median treatment duration for population A[m] was 9.4[n] months (286 days). The median treatment duration was not reached for populations B and C.

The Kaplan-Meier curve for ongoing treatment is shown in figure 4 for each population.

Figure 4: Kaplan-Meier treatment duration plot by previous endocrine therapy population in Blueteq (N=187)



[m] Population A - has progressive disease on 1st line endocrine therapy. Population B - has progressive disease whilst still receiving adjuvant therapy. Population C - has progressive disease within 12 or less months of completing adjuvant endocrine therapy

[n] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced

Conclusions

193 patients received ribociclib in combination with fulvestrant for the treatment of advanced hormone-receptor positive, HER2-negative breast cancer [TA593] through the CDF in the reporting period (17 July 2019 and 16 January 2020). 187 patients were reported to the SACT dataset, giving a SACT dataset ascertainment of 97%. An additional 16 patients with a CDF application did not receive treatment and eight patients died before treatment. Not all were confirmed by the trust responsible for the CDF application by the team at PHE.

Patient characteristics from the SACT dataset show that all patients (N=187) that received ribociclib in combination with fulvestrant for advanced hormone-receptor positive, HER2-negative breast cancer were female. Most of the cohort was aged between 50 and 79 years (82%, N=153) and 82% (N=154) of patients had a performance status between 0 and 2 at the start of their regimen.

At data cut off, 25% (N=46) of patients were identified as no longer being on treatment; 30% (N=14) of patients stopped treatment due to progression, 15% (N=7) of patients stopped treatment due to acute toxicity, 4% (N=2) of patients chose to end their treatment, 24% (N=11) of patients died not on treatment, 9% (N=4) of patients died on treatment and 17% (N=8) of patients did not have a treatment record in SACT in at least three months and are assumed to have completed treatment.

Median treatment duration was 9.4 months[o], (286 days). 72% [95% CI: 63%,78%] of patients were receiving treatment at six months.

[o] Confidence intervals could not be produced as there was an insufficient number of events at the time this report was produced.

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Technical engagement response form

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (ID3755)

As a stakeholder you have been invited to comment on the ERG report for this appraisal. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the key issues below. You do not have to provide a response to every issue. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be included in the committee papers in full and may also be summarised and presented in slides at the appraisal committee meeting.

Deadline for comments Guidance paragraphs follow. At the end of each recommendation, insert a cross-reference to the corresponding paragraph number(s) in the considerations section (4).] [Paragraph 4.x].

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Notes on completing this form

- Please see the ERG report which summarises the background and submitted evidence, and presents the ERG's summary of key issues, critique of the evidence and exploratory analyses. This will provide context and describe the questions below in greater detail.
- Please ensure your response clearly identifies the issue numbers that have been used in the executive summary of the ERG report. If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.
- If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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About you

Your name	
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	Novartis Pharmaceuticals UK Ltd.
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

Please use the table below to respond to questions raised in the ERG report on key issues. You may also provide additional comments on the key issue that you would like to raise but which do not address the specific questions.

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Maturity of overall survival (OS) data	NO	We are pleased to note the general acknowledgement from the ERG, that the company have adhered to the committee's preferred assumptions from the terms of engagement (ToE, page 14).[1] It was highlighted during the technical engagement clarification call with NICE (24 November 2020) that Novartis consider that the MONALEESA-3 OS data cut of 3 June 2019 is mature.[2] Novartis do not anticipate submitting any further OS data from MONALEESA-3, as part of this CDF review. The OS data from the 03 June 2019 data cut have been used in the updated partitioned survival model (PSM), described in Key_issue_4.
Key issue 2: Parametric survival distribution fitted to time to treatment discontinuation (TTD) data in MONALEESA-3 [Company's preferred unrestricted restricted cubic spline (RCS) lognormal *vs* ERG's	YES (see addendum)	Novartis have analysed both the ERG's preferred Gompertz (U) as well several of the suggested 3-knot spline models for MONALEESA-3 TTD (ribociclib + fulvestrant) and we have made the following observations and subsequent decisions: • Using Gompertz (U) leads to a clinically implausible curative 'tail' with the TTD curve crossing that of progression-free survival (PFS) (see also clarification question B10 where a scenario analysis was requested to cap the Gompertz (U) TTD curve to the PFS curve). As stated in the ERG's report (pages 18, 20, 58-59, 77 and 80), capping the extrapolated TTD by the PFS curve prevents the potentially implausible treatment beyond progression. However, the Gompertz

preferred unrestricted Gompertz *vs* other 3-knot spline models]		(U) may still overestimate acquisition costs to the extent that patients who discontinue either ribociclib or fulvestrant may remain in PFS after stopping treatment. To assess this potential bias, we estimated PFS from the time of discontinuation of study medication in MONALEESA-3 among patients who discontinued treatment before the date of disease progression and for reasons other than progression or death. Approximately 25% of patients remained in PFS 24 months after treatment was discontinued. This suggests that the TTD curve remains below the PFS curve well beyond the end of follow-up in the trial and thus, the Gompertz (U) distribution overestimates time on treatment with ribociclib (see addendum section 2.2.1 for full details of this analysis). • Among the 3-knot spline models that were fit to data on TTD from MONALEESA-3, the 3-knot log-logistic ("RCS 3 Log-Logistic (U)") had the best fit according to BIC. This distribution also had the best visual fit to the TTD Kaplan-Meier (KM) from among all of the parametric distributions tested (i.e., among 3-knot spline as well as "standard" distributions). In particular, the visual fit for the RCS 3 Log-logistic (U) was considered to be better than either the Gompertz (U) – preferred by the ERG – or the RCS lognormal (U) – considered by the company to be more appropriate than the Gompertz (U). Finally, the RCS 3 Log-logistic (U) is considered to have clinical validity. Based on these considerations, we have used the 3-knot spline log-logistic model fit to TTD for the PSM base case described in Key_issue_4; scenario analyses with the Gompertz (U) and RCS lognormal (U) also have also been performed, in the updated base case analyses supplied as part of the addendum to our initial submission.
Key issue 3: Time to treatment discontinuation (TTD) assumptions for everolimus plus exemestane for patients	YES (see addendum)	Novartis have attempted to inform the TTD assumptions for everolimus using individual patient data (IPD) from BOLERO-2. However, a major issue in generating usable data is that treatment discontinuation in BOLERO-2 was only recorded when treatment with both of everolimus (or placebo) and exemestane was permanently stopped (i.e. treated as a 2-drug unit), not for each drug separately (see section 2.3.1 of addendum for details).

receiving everolimus plus exemestane, is treatment (in particular, everolimus) given until progression? If not, what proportion of patients stops taking treatment before progression? 20% or other? For patients who continue taking treatment until progression, is the dose the same? If not, what proportion continues having a reduced dose? What reduced dose is given to these patients?		Given this limitation, we have decided to employ the clinical assumptions provided by the ERG for TTD for everolimus (described in pages 62–64 of the ERG report) in the PSM base case, itself described in Key issue 4. The ERG assumptions are: (1) that 80% of patients would discontinue from 6 months (after treatment initiation), as published by Yardley et al, 2010,[3] and; (2) of the remaining 80% of patients still on treatment, it is then assumed that 70% of them (0.56 of study total) would be treated with 5 mg of everolimus daily whilst the other 30% (0.24 of study total) would receive 10mg of everolimus daily. Finally, we have employed an off treatment utility value when patients discontinue everolimus even if they have continued on exemestane. This is consistent with ERG statements on exemestane and off treatment utility values (ERG report page 63).
Key issue 4: Including OS data in a partitioned survival model (preferred by ERG) rather than the company's semi-Markov model	YES (see addendum)	Novartis agree with this suggestion and thus we have constructed a *de novo* PSM which has been submitted and described in an accompanying addendum document. We believe that the PSM approach allows for OS to be modelled directly, rather than assuming surrogacy (inherent in the previous semi Markov model) where OS gains are equal to PFS gains. Key features of the PSM base case are as follows: • The model uses updated MONALEESA-3 (subpopulation B) PFS and OS data (3 June 2019 data cut) as per the original semi-Markov model described in the technical engagement document.

		• The model compares ribociclib + fulvestrant (MONALEESA-3) to everolimus + exemestane (BOLERO-2) as per the original semi-Markov model • The base case retains the PFS RCS 3 Weibull (R) distribution used in the semi-Markov model, as detailed in the ERG report section 4.1.5 • The base case OS was modelled using a Weibull (R) distribution, based on statistical fit, visual fit to the KM data, and with clinical experts' expectations. • The base case TTD for ribociclib + fulvestrant was modelled using a 3-knot spline log logistic curve fit, as described in Key issue 2. • Everolimus + exemestane TTD discontinuation and dose modification clinical assumptions are those preferred by the ERG, as detailed in Key issue 3. • Off treatment, utility values were used for patients when they discontinue everolimus even though they continue on exemestane, as described in in Key issue 3. • The comparative hazard ratio (HR) for ribociclib + fulvestrant (MONALEESA-3) vs. everolimus + exemestane (BOLERO-2) PFS was made using a fractional-polynomial (FP) Network Meta-analysis (NMA), as suggested by the ERG at clarification stage. This was done to account for the violation of the proportional hazards (PH) assumption in BOLERO-2. Details of this FP NMA analysis are given below in the 'additional issues' section. Full details are included in the model addendum submitted alongside this response. • The comparative HR for ribociclib + fulvestrant (MONALEESA-3) vs. everolimus + exemestane (BOLERO-2) OS was made using a Bucher NMA. The Bucher methodology was deemed appropriate as: (1) the PH assumptions were not violated for MONALEESA-3, BOLERO-2, nor any of the trials in the network allowing this comparison to be made, and; (2) a FP NMA of OS was explored but estimated data was not deemed clinically viable, as detailed in the 'additional

issues' section (see addendum section 2.4.1.2 for more details). The comparative OS HRs using the Bucher NMA are shown in the ERG report.

- The base case continues to use a 10% discount for fulvestrant as agreed in the terms of engagement. Further to this, we are aware that the Commercial Medicines Unit within NHS England are currently inviting tender submissions for fulvestrant. All submissions are due on 8 December 2020, with an award notification to offerors due to be issued 9 December 2020. The schedule advises that the agreement would commence ASAP (which we assume to be the time of loss of exclusivity for fulvestrant on [redacted]). The agreement is expected to be in place until 1st May 2021, with an option to extend for periods up to 24 months.
- Patient access scheme (PAS) of [redacted] is applied to ribociclib.
- PAS of [redacted] is applied to everolimus.
- We have removed the model 'fix' on ribociclib monitoring costs to reflect that patient monitoring only continues until cycle 7 of treatment (see ERG report page 68).

Using these parameters, the revised company base case is shown in Table 1.

Table 1. Revised base case

	Costs, (£)	LYs	QALYs	Incremental costs, (£)	Incremental LYs	Incremental QALYs	ICER, £/QALY
Ribo + Ful	[redacted]	3.76	2.72				

Eve + Exe	[redacted]	3.02	2.17	17,628	0.75	0.55	32,074

ICER, incremental cost-effectiveness; Eve, everolimus; Exe, exemestane; Ful, fulvestrant; LY, life year; Ribo, ribociclib; QALY, quality-adjusted life year.

Given the residual uncertainty around the fixed point estimate base case, Novartis believe that the ICER generated by the probabilistic sensitivity analysis (PSA), shown in Table 2, is more appropriate as the preferred base case. Probabilistic estimates of cost effectiveness base cases have been accepted in previous NICE reviews of company submissions.[4]

Table 2. Probabilistic sensitivity analysis

	Costs, (£)	LYs	QALYs	Incremental costs, (£)	Incremental LYs	Incremental QALYs	ICER, £/QALY
Ribo + Ful	[redacted]	3.76	2.72				
Eve + Exe	[redacted]	3.01	2.16	16,297	0.75	0.56	29,570

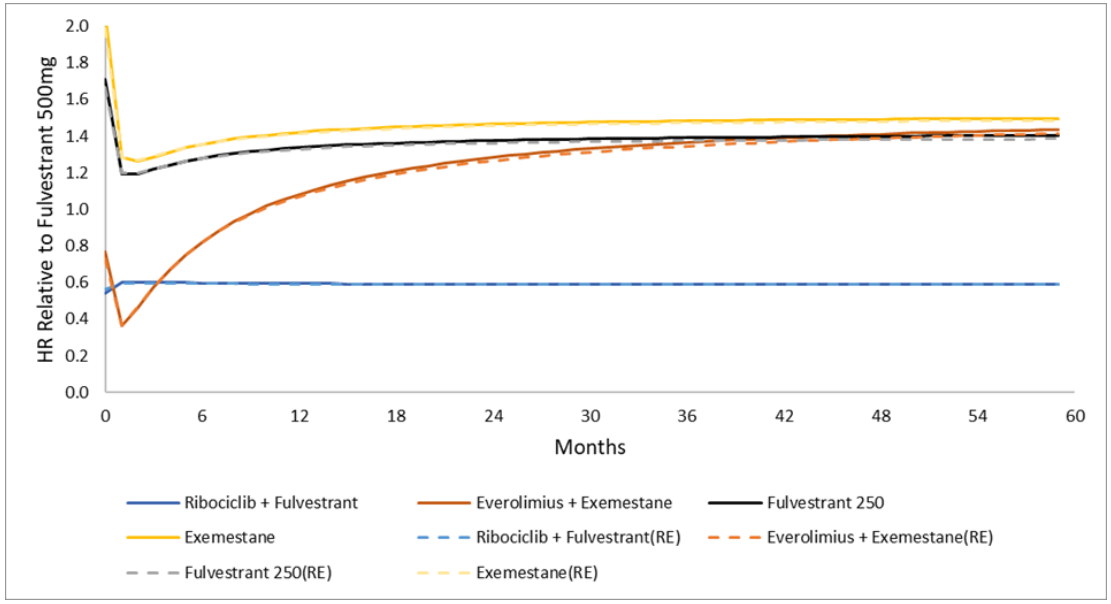
Note: the PSA involved running a sufficient number of simulations for the mean ICER to converge, as described by Hatswell et al.[5]

ICER, incremental cost-effectiveness; Eve, everolimus; Exe, exemestane; Ful, fulvestrant; LY, life year; Ribo, ribociclib; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.

Additional issues

Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (e.g. at the clarification stage).

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: PH assumption violation for everolimus + exemestane (BOLERO-2) PFS and subsequent use of a FP-NMA to generate comparative HR values for PFS	Page 26 and pages 40–43	Yes (see addendum)	The PH assumption was violated for PFS in BOLERO-2 (subpopulation B equivalent i.e. second line patients). As such, an NMA with hazards characterized as FP (FP NMA[6]), which allows for modelling of time-varying HRs, was performed to account for this uncertainty (see section 2.1.9 of addendum). This methodology was suggested by the ERG in clarification question A1. Different parametrisations were explored, including fixed-effect and random-effects with informative priors. The fixed-effect model was utilised based on the Deviance Information Criterion (DIC), visual comparison of estimated survival distributions with KM PFS from MONALEESA-3, and the fact that the HRs based on the random-effects model were virtually identical to those based on the fixed-effect (i.e., the impact in the model would be minimal). The same network was described in the ERG report (Figure 7, page 42). The survival data used in the FP NMA were based on individual patient failure-time data for the MONALEESA-3 and BOLERO-2 trials. For CONFIRM, SoFEA, and EFECT trials, published KM survival curves were digitised and reconstructed failure time data were generated using a published algorithm.[7] Results of the Bayesian FP NMA using fixed-effect were validated using frequentist approach with methods as described by

			Wiksten et al.[8] HRs for PFS for each treatment vs fulvestrant 500 mg are shown in are shown in Figure 1. **Figure 1 Estimated HRs for PFS for subpopulation B based on FP NMA**  FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival. The HRs for ribociclib plus fulvestrant and fulvestrant 250mg versus fulvestrant 500mg are relatively constant throughout the 60-month projection period. Those for everolimus plus exemestane and exemestane drop initially then increases rapidly throughout the projection, especially for everolimus plus exemestane. The estimated HRs for OS for ribociclib plus fulvestrant versus fulvestrant 500mg and for fulvestrant 250mg versus fulvestrant 500mg based on random-effects with informative priors are

			virtually identical to those based on the fixed-effect. However, the estimated HRs for OS for everolimus plus exemestane versus fulvestrant 500mg and exemestane versus fulvestrant 500mg based on the random-effects model with informative priors are higher (i.e., less favourable for these treatments compared with fulvestrant 500mg) than those based on the fixed-effect model. Therefore, fixed effects were utilised in the PSM base case. An FP NMA of subpopulation B OS was also explored. However, FP NMA generated 10 year OS data for ribociclib plus fulvestrant based that significantly exceeded the estimated landmark OS that clinical experts advised was reasonable based on the Weibull (R) distribution fit directly to data on OS for ribociclib plus fulvestrant in MONALEESA-3 (as used in the PSM described in Key issue 4). Additionally, projected OS for everolimus plus exemestane based on the FP NMA was lower than that for exemestane alone, which did not reflect the findings of the BOLERO-2 trial. The comparative OS HRs derived by the Bucher NMA are presented in the ERG report table 14 on page 43 (and response to clarification question A2). Fuller details for the FP (and Bucher) NMAs for PFS and OS are provided in the addendum document.

Summary of changes to the company's cost-effectiveness estimate(s)

Company: If you have made changes to the company's preferred cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes.

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case ICER
Updates relating to key issues 1-4 and additional issue.	Given that we have switched from a semi-Markov model to the ERG's preferred PSM, the tabular entries here are redundant save the company's preferred base case, as detailed below.		
Company's preferred base case following technical engagement	**Incremental QALYs: 0.56**	**Incremental costs: £16,297**	**New base case: £29,570/QALY**

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7. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
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Addendum to Manufacturers Submission

Model Modification in Response to Cancer Drug Fund Questions and ERG Report

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2 negative advanced breast cancer [ID3755]

Title Cost-Effectiveness of Ribociclib in Combination with Fulvestrant for the Treatment of Men and Postmenopausal Women with HR+/HER2- Advanced Breast Cancer Who Have Received No or Only One Prior Line of Endocrine Therapy

Date December 2020

Version 2

TABLE OF CONTENTS

1 INTRODUCTION

This report describes modifications to an economic model to evaluate the cost-effectiveness of ribociclib and fulvestrant in combination as treatment in patients with HR+/HER2- advanced breast cancer (aBC) who have received previous endocrine therapy (ET), based on Group B of the MONALEESA-3 trial and other sources. This model was included in Novartis's submissions to the National Institute for Health and Care Excellence (NICE) in response to a technology appraisal of this technology (TA593) and subsequent submission for Cancer Drugs Fund (CDF) review (ID3755). The submitted model used a semi-Markov state-transition (STM) approach to compare the cost-effectiveness of ribociclib plus fulvestrant versus fulvestrant 500mg (the comparator in the MONALEESA-3 trial) and everolimus plus exemestane. Progression-free survival (PFS) for ribociclib plus fulvestrant and fulvestrant 500mg were estimated by fitting parametric survival distributions to patient level failure time data from MONALEESA-3. PFS for everolimus plus exemestane was obtained by estimating the HR for PFS for everolimus plus exemestane versus ribociclib plus fulvestrant, based on a Bucher network meta-analysis (NMA) of randomized controlled trials (RCTs) in patients with aBC. This HR was then applied to the PFS for ribociclib plus fulvestrant. Post-progression survival (PPS) was assumed to be equal for all treatments, and was estimated based on parametric survival distributions fit to data from Group B of MONALEESA-3.

Revisions to the model were implemented to address three key concerns raised by the Evidence Review Group (ERG) during their review of the model submitted to the CDF. First, the ERG commented that the assumption of proportional hazards (PH) for PFS in the BOLERO-2 trial of everolimus plus exemestane versus exemestane appeared to be violated based on a statistically significant result for the test of linearity of Schoenfeld residuals for PFS in this trial. Based on this finding, the ERG suggested that it would be more appropriate to conduct the NMA of PFS using a method that allows for time-varying HR, as opposed to the Bucher method, which assumes that HRs are constant with respect to time. To address this concern, the model estimates of PFS have been modified to utilise estimates derived from a Bayesian NMA of PFS with hazards characterised by fractional polynomials ("FP NMA") and which yields time-varying HRs [1].

Second, whereas it was assumed in the submitted model that treatment with everolimus and exemestane would continue until disease progression and that the relative dose intensity (RDI) for everolimus plus exemestane would be 100% (i.e., that all patients would remain on the recommended 10mg daily dose), the ERG noted that clinical expert opinion supported assuming that time to treatment discontinuation (TTD) of everolimus would be less the PFS and that some proportion patients would have dose reductions, and therefore that the RDI would be less than 100%. The ERG suggested scenarios for the economic model in which it would be assumed that 20% of patients receiving treatment with everolimus plus exemestane would discontinue everolimus at six months – but continue on treatment with exemestane – and that 70% of patients remaining on treatment with everolimus would dose reduce from 10mg daily to 5mg.

To address this issue, the model was modified as follows: (a) TTD for everolimus was estimated by assuming that 80% of patients remaining in PFS after month 6 would discontinue treatment, and; (b) assuming that 70% of those remaining on treatment would dose reduce to 5mg daily. Although use of data from BOLERO-2 to estimate TTD for everolimus and exemestane was explored, because information

on time to discontinuation was not collected separately for everolimus and exemestane in the BOLERO-2 trial, it was infeasible to use information from the trial to estimate duration of exposure to the individual components of the combination. The approach proposed by the ERG was therefore used. Additionally, data on dosages for everolimus and exemestane from the BOLERO-2 trial were analyzed in an attempt to inform the proportion of patients receiving everolimus at a reduced dose. However, because TTD could not be estimated for everolimus and exemestane separately with data from BOLERO-2, the assumptions related to dose reductions of everolimus were based on clinical expert opinion for consistency. There were also adjustments to the approach taken to assumed utility levels for on- and off-treatment whilst in the PFS state, consistent with the requests from the ERG.

Third, the ERG suggested that due to the availability of OS results from the June 2019 data cut of the MONALEESA-3 trial, a partitioned survival model (PSM) approach might be preferred to the STM approach that was employed in the submitted model. Accordingly, the model was modified to permit the estimation of cost-effectiveness using either an STM or PSM approach, with OS for ribociclib plus fulvestrant and fulvestrant in the latter estimated by fitting parametric survival distributions to patient-level OS data from the June 2019 data cut of MONALEESA-3. For the PSM, OS for everolimus plus exemestane was obtained by applying to the OS for ribociclib plus fulvestrant an estimate of the HR for OS for everolimus plus exemestane versus ribociclib plus fulvestrant based on and Bucher NMA of RCTs. The use of the Bucher NMA for OS was considered appropriate because, unlike PFS, there was no evidence of non-proportionality of hazards for OS for any trial contributing to the NMA. For completeness, however, the model also includes the facility to estimate OS for all treatments based on results of an FP NMA with time-varying HRs.

Our preferred base case following technical engagement and includes all the above mentioned changes results in an ICER for ribociclib plus fulvestrant estimated of £30,479 per QALY gained compared with everolimus plus exemestane based on the probabilistic sensitivity analysis (PSA).

2 METHODS

2.1 Bayesian NMA of PFS with Hazards Characterized as Fractional Polynomials

2.1.1 Evidence Network

A diagram depicting the evidence network for the ITC of PFS is presented in Figure 1.

Figure 1. Evidence Network for ITC of PFS for Treatments of HR+/HER2- ABC

The patient characteristics of these trials have been compared previously in response to clarification questions from the ERG in TA593. Importantly, SoFEA and CONFIRM trials included HER2+ patients (7% and not reported, respectively) while MONALEESA-3 and BOLERO-2 enrolled only HER2- patients [2-5]. Additionally, SoFEA enrolled patients from the UK and South Korea, while all other trials in the NMA network enrolled patients internationally. These differences and other unreported differences between patient populations might bias the anchored NMAs of PFS (and OS) to the extent that these factors might modify the treatment effects.

2.1.2 Assessment of PH Assumption

Plots of Schoenfeld residuals were generated to assess the proportional hazards (PH) assumption. Schoenfeld residuals are calculated at each failure time by taking the difference of the covariate value for the patient and a weighted average covariate value of patients remaining in the risk set at that time. The scaled residuals are then obtained by multiplying the vector of unscaled residuals by the inverse of their covariance matrix. The scaled residuals can then be used as a time-dependent measure of the treatment effect. An increasing or decreasing trend in the Schoenfeld residuals can be used to detect a deviation from the PH assumption. Because the treatment group covariate is a binary variable, the scaled residuals will either appear well above or below the mean, depending on the group in which the failure occurred. In order to make the pattern of these residuals easier to visualize, a kernel-smoothed estimate was provided. In order to test the PH assumption, the slope of the scaled Schoenfeld residuals was tested using linear regression. Plots of smoothed curves fit to scaled Schoenfeld residuals for PFS for each trial contributing to the indirect treatment comparison (ITC) of PFS for treatments for HR+/HER2- aBC were provided to the ERG in response to clarification questions received on the manufacturer submission for this CDF review. Results of the PH assessment for PFS are summarised in Table 1, below. A statistically significant finding on the test of linearity, defined as a p-value less than 0.05, suggests that the PH assumption may be violated. As shown in the table below, the PH assumption appears to be violated for PFS for BOLERO-2.

Table 1. Results of Assessment of PH Assumption for PFS based on Test of Linearity of Schoenfeld Residuals

Trial	P-Value for Test of PH Assumption
MONALEESA-3	0.85000
BOLERO-2	**0.00599***
CONFIRM	0.95700
EFECT	0.20800
SoFEA	0.46400

*Indicates statistically significant finding

2.1.3 Approach

To reflect a non-proportional hazards for comparisons of PFS, a fractional polynomial (FP) was used to define the hazard functions over time, by which the treatment effect is represented with multiple parameters and changes over time. The method follows the procedure described in Chapter 10 of Dias et

al., *Network Meta-Analysis for Decision Making* [6] and in the publication by Jansen, *Network Meta-Analysis of Survival Data with Fractional Polynomials* [1].

2.1.4 Data

The survival data used in the FP NMA were based on individual patient failure-time data for MONALEESA-3 and BOLERO-2 trials. For CONFIRM, SoFEA, and EFECT trials, published Kaplan-Meier (KM) survival curves were digitised and reconstructed failure time data were generated using a published algorithm [7]. The survival data were then reorganised by time interval with the following parameters:

- s – study;
- r - number of events;
- z - number at risk at the beginning of the interval;
- a - treatment arm;
- t -the end of the interval, in months); and
- dt - length between the interval).

Intervals were defined with monthly intervals if possible (i.e., dt=1) but with longer intervals if needed to ensure at least 1 event within each interval.

2.1.5 Model

The model for the FP NMA of survival data assumes similarity and consistency regarding the estimated model parameters. FPs of 1st and 2nd order were considered. The equation for a 2nd order FP and for k treatments (A, B, C, etc.) is described by **Equation 1** below:

Equation (1):

$$ln(\mathrm{h}_{jkt}) = \begin{cases} \mathrm{alpha0}_{jk} + \mathrm{alpha1}_{jk}t^{p1} + \mathrm{alpha2}_{jk}t^{p2} & with\ t^0 = log(t), p1 \neq p2 \\ \mathrm{alpha0}_{jk} + \mathrm{alpha1}_{jk}t^{p} + \mathrm{alpha2}_{jk}t^{p}log(t) & p = p1 = p2 \end{cases}$$

$$\begin{pmatrix} \mathrm{alpha}_{0jbk} \\ \mathrm{alpha}_{1jbk} \\ \mathrm{alpha}_{2jbk} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix}, if\ k = b, b = A, B, C, etc. \\ \begin{pmatrix} \mu_{0jb} \\ \mu_{1jb} \\ \mu_{2jb} \end{pmatrix} + \begin{pmatrix} \partial_{0jbk} \\ \partial_{1jbk}. \\ \partial_{2jbk} \end{pmatrix}, \quad if\ k\ after\ b \end{cases}$$

For a 1st order FP model, the alpha2 terms are removed from the equation.

In **Equation 1**, h_{jkt} reflects the underlying hazard rate in trial j for intervention k at time t. Vector μ is trial-specific and reflects the parameters alpha0, alpha1 and alpha2 of the comparator treatment, and the vector ∂ reflects the study specific difference in alpha0, alpha1 and alpha2 of the log hazard curve for treatment k relative to comparator treatment b and are drawn from a multivariate normal distribution with vague priors with the pooled estimates expressed in terms of the overall reference treatment A

(baseline) with d_{0AA}, d_{1AA} and d_{2AA} =0, while, for example, $d_{0BC} = d_{0AC} - d_{0Ab}$, $d_{1BC} = d_{1AC} - d_{1Ab}$ and $d_{2BC} = d_{2AC} - d_{2Ab}$.

Depending on the type of model used (random-effects or fixed-effect), heterogeneity can be assumed on the parameters of vector ∂. Under the random-effects model, the heterogeneity was assumed on the parameter ∂_{0jbk} such that:

$$\partial_{0jbk} \sim \text{Normal}(d_{0Ak}-d_{0Ab}, sd^2) \text{ and } \begin{pmatrix}\partial_{1jbk}\\ \partial_{2jbk}\end{pmatrix} = \begin{pmatrix}d_{1Ak} - d_{1Ab}\\ d_{2Ak} - d_{2Ab}\end{pmatrix}.$$

In the base case, a vague prior was used for the heterogeneity parameter (sd ~ Uniform (0,2)).

For the fixed-effect model, no heterogeneity is assumed so the vector ∂ is:

$$\begin{pmatrix}\partial_{0jbk}\\ \partial_{1jbk}.\\ \partial_{2jbk}\end{pmatrix} = \begin{pmatrix}d_{0Ak} - d_{0Ab}\\ d_{1Ak} - d_{1Ab}\\ d_{2Ak} - d_{2Ab}\end{pmatrix}.$$

The log HR between each treatment at every time points is calculated with **Equation 2** below. As an example, and assuming A versus B and A versus C trials are comparable on effect modifiers, the equation can be described as follows:

Equation (2):

If $p1 \neq p2$

$$\ln(HR_{BC}(t)) = (alpha0_{AC} - alpha0_{AB}) + (alpha1_{AC} - alpha1_{AB})\, t^{p1} + (alpha2_{AC} - alpha2_{AB})\, t^{p2}$$

or

$$\ln(HR_{BC}(t)) = (d_{0AC} - d_{0AB}) + (d_{1AC} - d_{1AB})\, t^{p1} + (d_{2AC} - d_{2AB})\, t^{p2}$$

If $p = p1 = p2$

$$\ln(HR_{BC}(t)) = (alpha0_{AC} - alpha0_{AB}) + (alpha1_{AC} - alpha1_{AB})\, t^{p} + (alpha2_{AC} - alpha2_{AB})\, t^{p} \log(t)$$

or

$$\ln(HR_{BC}(t)) = (d_{0AC} - d_{0AB}) + (d_{1AC} - d_{1AB})\, t^{p} + (d_{2AC} - d_{2AB})\, t^{p} \log(t)$$

Finally, the hazard rate function for each treatment at every time point is obtained with **Equation 3** below:

Equation (3):

$$ln(h_{kt}) = \begin{cases} alpha0_k + alpha1_k t^{p1} + alpha2_k t^{p2} & with\ t^0 = log(t), p1 \neq p2 \\ alpha0_k + alpha1_k t^{p} + alpha2_k t^{p} log(t) & p = p1 = p2 \end{cases}$$

$$\begin{pmatrix} \text{alpha}_{0k} \\ \text{alpha}_{1k} \\ \text{alpha}_{2k} \end{pmatrix} = \begin{cases} \begin{pmatrix} \mu_0 \\ \mu_1 \\ \mu_2 \end{pmatrix}, & if\ k = A\ (baseline\ treatment) \\ \begin{pmatrix} \mu_0 \\ \mu_1 \\ \mu_2 \end{pmatrix} + \begin{pmatrix} \partial_{0k} \\ \partial_{1k.} \\ \partial_{2k} \end{pmatrix}, & otherwise \end{cases}$$

In **Equation 3**, the vector μ reflects the parameters alpha0, alpha1 and alpha2 of the baseline treatment, and the vector ∂ reflects the treatment specific difference in alpha0, alpha1 and alpha2 of the log hazard curve for treatment k relative to the baseline comparator.

It is recommended that the baseline (i.e., referent) treatment should be the "standard" treatment or, in larger networks, a relatively central treatment [6]. For this analysis, we considered fulvestrant 500mg to be the standard, since it is the control arm in MONALEESA-3. Also, to ensure that the survival distributions for ribociclib plus fulvestrant and fulvestrant 500mg from the NMA matched the KM distributions for these two treatments in Group B of MONALEESA-3, hazard rates for all treatments were estimated by applying HRs from the FP NMA to the estimated baseline survival distribution for fulvestrant 500mg from MONALEESA-3. Although, fulvestrant 250mg could be construed as the most 'central' treatment, using this as the baseline yields survival distributions for ribociclib plus fulvestrant and fulvestrant 500mg that do not match well to the KM survival from MONALEESA-3. While it may have been feasible to use ribociclib plus fulvestrant as the baseline treatment, an approach consistent with that which was used when applying HRs from the Bucher method, this would have yielded results similar to those obtained using fulvestrant 500mg in MONALEESA-3 as the baseline. To estimate the hazard rate function of each treatment for **Equation 3**, the μ vector was obtained by performing the model with only the study of interest (MONALEESA-3).

2.1.6 Software

Model parameters were estimated using a Bayesian Framework with Markov Chain Monte Carlo (MCMC) simulations, which allows reproduction of the model several times until convergence. The model was performed with 2 chains, with 50,000 burn-in iterations for PFS and 50,000 simulations for each chain. Convergence of the models were assessed with Gelman Rubin Statistics. WinBUGs software was used for all analyses. The code used is part of Dias, Ades, Welton, Jansen and Sutton (2018) Network Meta-Analysis for Decision Making [6].

2.1.7 Model Choice

For the fixed-effects model, all possible unordered combinations of p1 and p2 with values for p1 and p2 taken from the set of {-2, -1, -0.5, 0, 0.5, 1, 2, 3} were considered (Table 2). Note that it is unnecessary to consider all the combinations of p1 and p2, as p1=*x* and p2=*y* yields the same result as p1=*y* and p2=*x*.

Table 2. FP models considered in analysis

p2	p1							
	-2	**-1**	**-0.5**	**0**	**0.5**	**1**	**2**	**3**
-2	✓	✓	✓	✓	✓	✓	✓	✓
-1	--	✓	✓	✓	✓	✓	✓	✓
-0.5	--	--	✓	✓	✓	✓	✓	✓
0	--	--	--	✓	✓	✓	✓	✓
0.5	--	--	--	--	✓	✓	✓	✓
1	--	--	--	--	--	✓	✓	✓
2	--	--	--	--	--	--	✓	✓
3								✓

Model fit was assessed using the Deviance Information Criterion (DIC). DIC is equal to the posterior mean deviance (Dbar) plus the effective number of parameters (pD), given by the posterior mean of the deviance (Dbar) minus the deviance of the posterior mean (Dhat) [8] The model with the smallest DIC is the one that best replicates the input data [8]. If the DICs were similar for multiple models, survival distributions were overlaid with KM survival and the model was selected that provided the best visual fit to the KM data. A random-effect model also was estimated for the best fitting model. A sensitivity analysis was conducted for the random-effects model using informative priors for between study variability (τ) with these informative priors based on the estimated predictive distributions for between-study heterogeneity for a semi-objective outcome for a comparison of pharmacological treatments ($\tau \sim$ log-normal (-3.23, 1.88^2) [9].

2.1.8 Model Validation

Results of the Bayesian FP NMA using fixed-effect were validated using frequentist approach with methods as described by Wiksten et al. [10]. This frequentist fixed-effect framework enables rapid estimation of different models, the best fitting of which can be assessed further in a Bayesian framework [10].

2.1.9 FP NMA Results

Dbar and Dhat, pD, and DIC for each model considered are shown in Table 3. Combinations of p1 and p2 that did not converge are not shown in the table. The selected fixed-effect model was 2nd order FP with p1 = -2 and p2 =-1 (DIC =1536.4). The DIC for the random-effects model with p1= -2 and p2=-1 was not as good as the corresponding fixed-effect model.

Table 3. Model Choice for FP NMA of PFS Based on DIC

p1*	p2*	Dbar	Dhat	pD	DIC
1st Order Fixed-effect					
-2	-	1862.8	1845	17.8	1880.6

-1	-	1992.7	1974.7	18	2010.7
-0.5	-	2049.8	2032	17.8	2067.6
0	-	2079	2061	18	2096.9
0.5	-	2078.3	2060.5	17.9	2096.2
2nd Order, Fixed-effect					
-2	-2	1520.6	1494.2	26.4	1546.9
-2	**-1**	**1510.1**	**1483.7**	**26.3**	**1536.4**
-2	-0.5	1517.9	1491.2	26.7	1544.5
-2	0	1539.6	1512.6	27	1566.6
-2	0.5	1573.6	1546.9	26.7	1600.3
-2	1	1614.7	1587.9	26.7	1641.4
-1	-1	1527.5	1500.9	26.6	1554.1
-1	-0.5	1557.3	1531.4	25.9	1583.1
-1	0	1602.7	1576.2	26.6	1629.3
-1	0.5	1658.2	1631.2	27	1685.1
-1	1	1714.3	1687.5	26.8	1741.1
-0.5	-0.5	1600.5	1575.3	25.2	1625.7
-0.5	0	1656.4	1632.3	24.2	1680.6
-0.5	0.5	1719.9	1694	25.9	1745.8
-0.5	1	1780.9	1754.6	26.3	1807.2
0	0	1722.3	1696.1	26.2	1748.6
0	0.5	1789.1	1763.3	25.8	1814.9
0	1	1849.1	1822.7	26.4	1875.4
0.5	0.5	1853.3	1829.9	23.5	1876.8
0.5	1	1911.1	1884.5	26.6	1937.6
2nd Order Random-effects					
-2	-1	1511.4	1483.9	27.5	1538.9

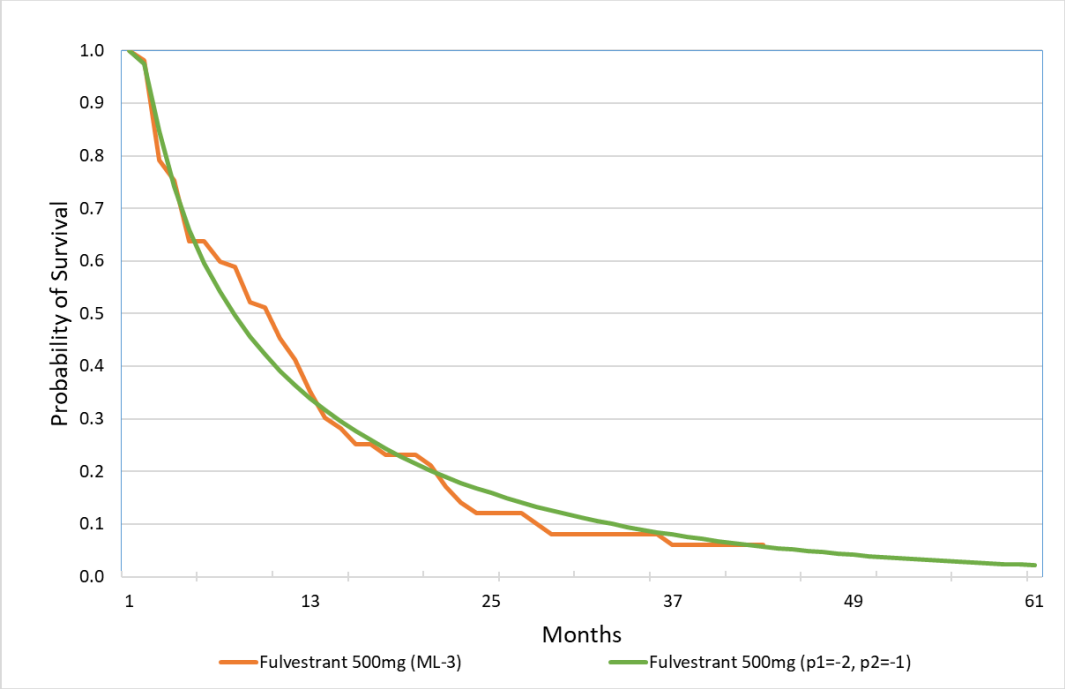
*Other combinations not included in this table were not converging well.

To estimate the hazard rate function for each treatment using **Equation 3**, the μ vector was obtained by estimating the model with p1 = -1 and p2 = -2 only using only data on PFS for the ribociclib plus fulvestrant and fulvestrant arms of MONALEESA-3. These values were then applied to other parameters derived from the full NMA to complete **Equation 3**.

The distribution of μ has the following parameters in the PFS model and visually fits the data (Figure 2):

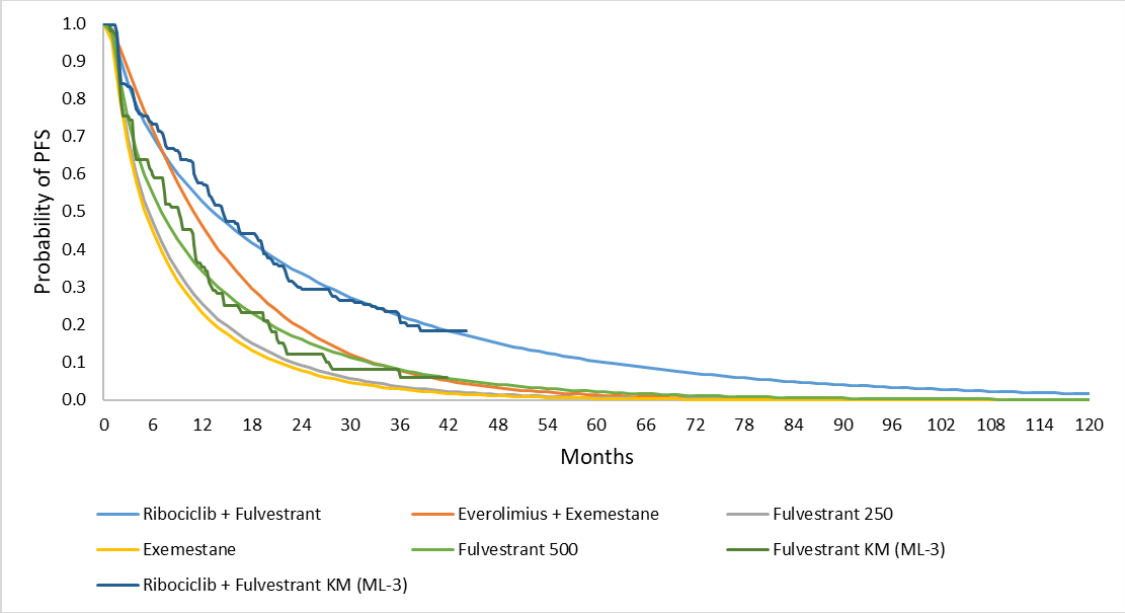
$$\begin{pmatrix}\mu_0\\ \mu_1\\ \mu_2\end{pmatrix} \sim Normal\left(\begin{pmatrix}-3.0\\ -5.5\\ 4.8\end{pmatrix}, T_\mu\right), T_\mu = \begin{pmatrix}0.04 & 0.21 & -0.23\\ 0.21 & 2.38 & -1.94\\ -0.23 & -1.94 & 1.84\end{pmatrix}$$

Figure 2. PFS Distribution Based on FP NMA for Fulvestrant in Group B of MONALEESA-3



Survival distributions for PFS from the FP NMA with time-varying hazards for all comparators contributing to the NMA network are shown in Figure 3. The visual fit for ribociclib plus fulvestrant and fulvestrant monotherapy is good as a result of using fulvestrant 500mg in MONALEESA-3 as the referent treatment. While the visual fit is not as good as that obtained using the 3-knot restricted cubic spline (RCS) Weibull restricted (R) distribution used in the base-case in the model submitted to the CDF, this is to be expected as that distribution has a total of 10 parameters including the knot locations.

Figure 3. PFS Distributions Based on FP NMA for All Treatments



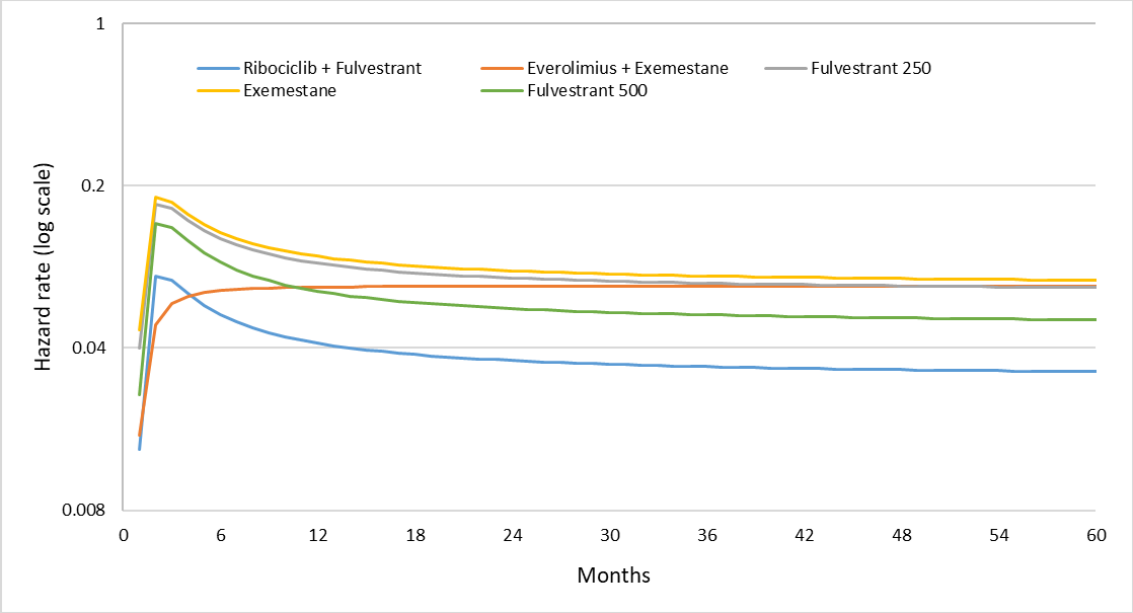
Landmark projections of PFS for survival distributions based on the FP NMA are shown in Table 4. Landmark PFS at 10 years for ribociclib plus fulvestrant based on the FP NMA (1.67%) is just slightly lower than with the RCS 3 Weibull (R) model fit to OS data for Group B in MONALEESA-3 (3.64%), which was clinically validated as described in the manufacturer submission for this CDF review, and therefore can be considered clinically reasonable.

Table 4. Predicted Landmark PFS for Treatments of HR+/HER2- ABC Based on FP NMA

Years	Ribociclib + Fulvestrant KM	Ribociclib + Fulvestrant RCS 3 Weibull (R)	Ribociclib+ Fulvestrant FP NMA	Everolimus + Exemestane FP NMA	Fulvestrant 250mg FP NMA	Exemestane FP NMA	Fulvestrant 500 mg FP NMA
2	30.00%	32.63%	34.86%	20.59%	10.07%	8.57%	17.05%
3	22.88%	21.71%	23.11%	8.47%	3.95%	3.13%	8.57%
5	--	11.91%	10.63%	1.43%	0.66%	0.46%	2.34%
10	--	3.64%	1.67%	0.02%	0.01%	0.00%	0.11%

Plots of the estimated hazard functions for PFS based on the FP NMA are shown in Figure 4 (on the log scale). For all treatments except for everolimus plus exemestane, the time-varying hazard functions increase initially then decrease over time. For everolimus plus exemestane, the hazards increase monotonically over time.

Figure 4. Estimated Hazard Functions for PFS Based on FP NMA



HRs for PFS for each treatment versus fulvestrant 500 mg are shown in Figure 5. The HR for ribociclib plus fulvestrant versus fulvestrant 500 mg is relatively constant throughout the 60-month projection period. The HR for everolimus plus exemestane versus fulvestrant 500 mg drops initially in the first month or so and then increases throughout the projection. HRs for exemestane and fulvestrant 250 drop initially then increase relatively little over the projection period. The estimated HRs for PFS using the fixed-effect model are virtually identical to those based on the model with random-effects and informative priors. However, the 95% confidence intervals of the HRs based on random-effects with informative priors on between study heterogeneity were wider than those based on the fixed effect model (Figure 6). The random-effects model with vague priors (not shown) yielded HRs that were similar to the fixed-effects and the random-effects with informative priors).

Figure 5. Estimated HRs for PFS for Treatments versus Fulvestrant 500mg Based on FP NMA with Fixed-effect and with Random-effects with Informative Priors

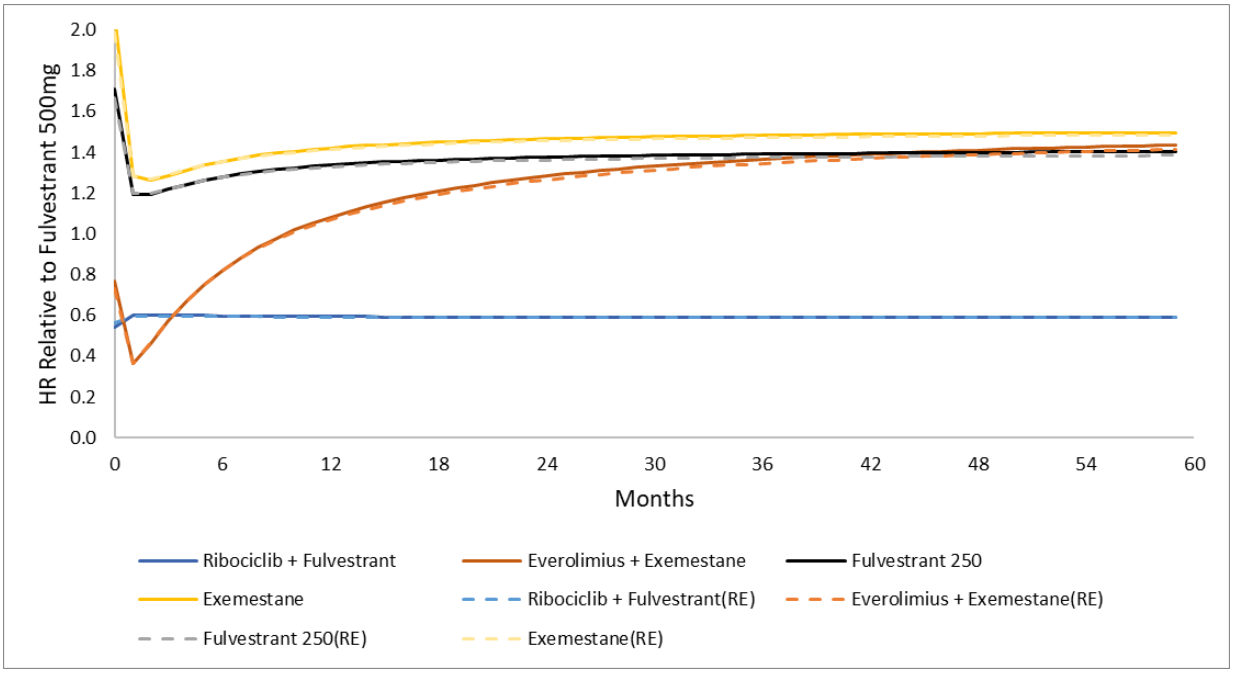
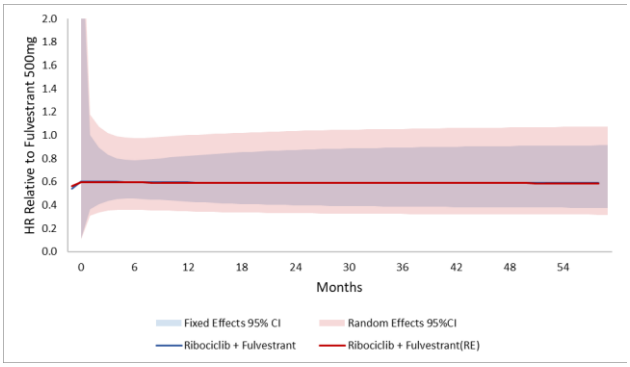
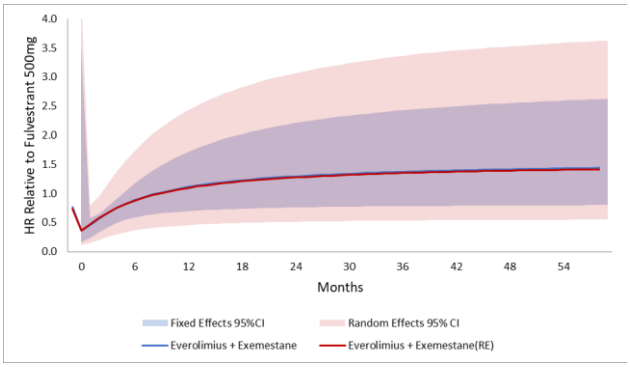


Figure 6. Estimated HRs and 95% CI for PFS for Treatments versus Fulvestrant 500mg Based on FP NMA with Fixed-effect and Random-effects with Informative Priors

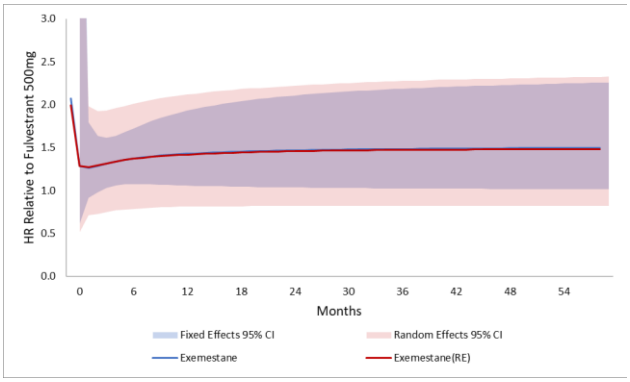
A. Ribociclib + Fulvestrant



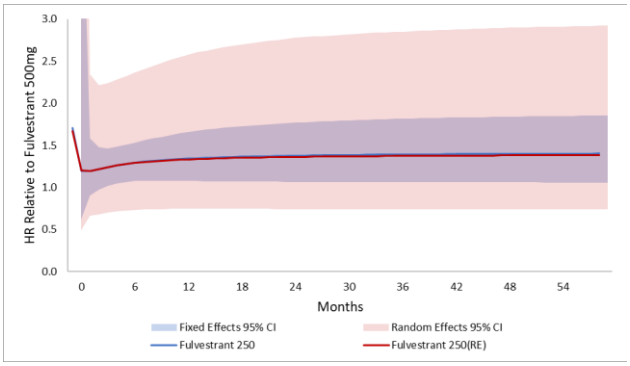
B. Everolimus + Exemestane



C. Exemestane



D. Fulvestrant 250mg



Due to time constraints, and in response to a specific request from the ERG during the Technical Engagement clarification call on 24 November, coefficients for the other parameterizations of first- and second-order models (i.e., those other than p1 = -1 and p2 = -2) were generated using the frequentist approach so that all of the possible parametrizations could be implemented in the economic model.

Table 5. Coefficients for FP NMA Models of PFS Based on Frequentist Approach

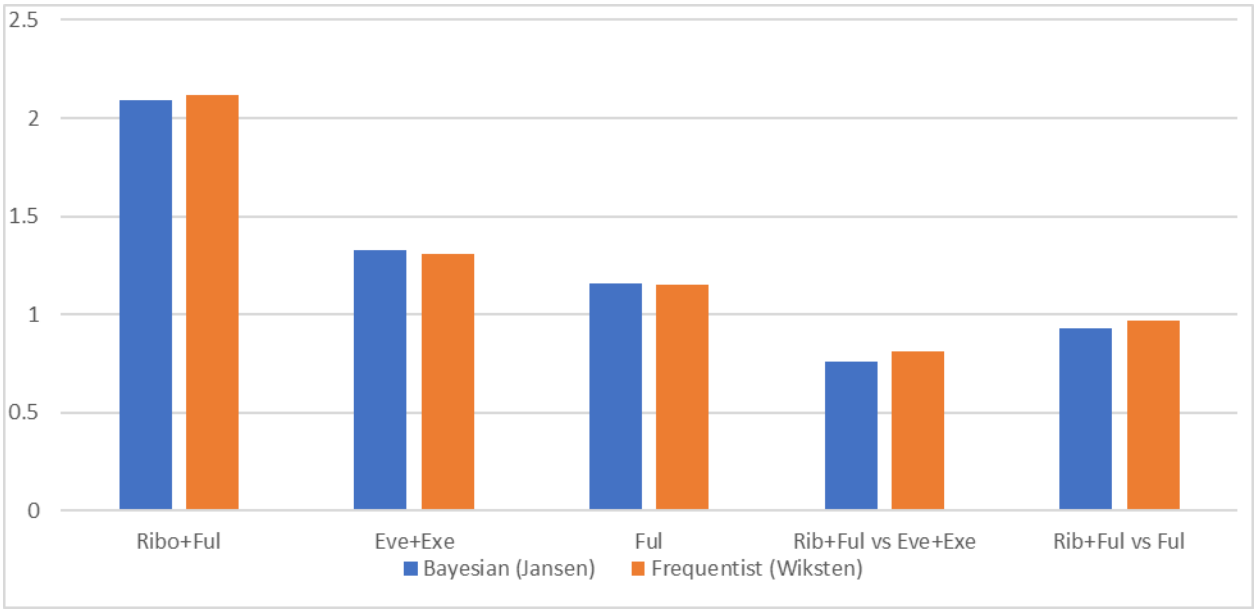
p1*	p2*	Alpha0	Alpha1	Alpha2
Fulvestrant 500mg				
1st order, fixed effects				
-2	-	-2.4506	-0.5990	-
-1	-	-2.4848	-0.1379	-
-0.5	-	-2.5719	0.1314	-
0	-	-2.3287	-0.0955	-
0.5	-	-2.1931	-0.1082	-
2nd Order, fixed effects				
-2	-2	-2.7969	-1.0078	7.3030
-2	-1	-3.0229	-5.4654	4.8741

p1*	p2*	Alpha0	Alpha1	Alpha2
-2	-0.5	-3.4915	-3.1111	3.1086
-2	0	-1.3640	-2.0156	-0.4749
-2	0.5	-1.5691	-1.4560	-0.2641
-2	1	-2.0270	-1.1674	-0.0336
-1	-1	-3.3285	-0.0036	3.4607
-1	-0.5	-3.9588	-5.6683	6.4458
-1	0	-0.7115	-2.3392	-0.6492
-1	0.5	-1.3008	-1.3474	-0.3049
-1	1	-1.9166	-0.9346	-0.0360
-0.5	-0.5	-4.9495	1.9218	2.5941
-0.5	0	1.3043	-4.2055	-1.0396
-0.5	0.5	-0.6585	-1.7818	-0.3698
-0.5	1	-1.6352	-1.0749	-0.0395
0	0	-2.7847	0.6497	-0.2096
0	0.5	-2.1028	0.7061	-0.6029
0	1	-2.6065	0.3168	-0.0493
0.5	0.5	-3.6285	0.9876	-0.2567
0.5	1	-2.9841	0.4664	-0.0857
Everolimus plus Exemestane				
1st order, fixed effects				
-2	-	-2.9443	-1.0140	-
-1	-	-2.8779	-0.7198	-
-0.5	-	-2.7695	-0.5974	-
0	-	-3.1664	0.0876	-
0.5	-	-3.0798	0.0418	-
2nd Order, fixed effects				
-2	-2	-2.6841	-1.2420	0.5686
-2	-1	-2.5756	-1.0769	-0.2496
-2	-0.5	-2.3713	-0.9779	-0.5794
-2	0	-2.9807	-0.9775	0.2046
-2	0.5	-3.1928	-1.0111	0.2253
-2	1	-2.9874	-1.0552	0.0510
-1	-1	-2.4692	-1.4353	0.3111
-1	-0.5	-2.2647	-1.2984	-0.3292
-1	0	-2.8341	-1.0287	0.2066
-1	0.5	-3.0836	-0.9814	0.2345
-1	1	-2.8697	-0.9870	0.0524
-0.5	-0.5	-2.0637	-1.7771	0.2247
-0.5	0	-2.4527	-1.3271	0.1910
-0.5	0.5	-2.7847	-1.1745	0.2331
-0.5	1	-2.5754	-1.1603	0.0512
0	0	-3.6973	0.5918	-0.0146
0	0.5	-3.8334	0.3390	0.2039
0	1	-3.6225	0.3182	0.0461
0.5	0.5	-4.2098	0.6588	-0.0396

p1*	p2*	Alpha0	Alpha1	Alpha2
0.5	1	-3.8818	0.3663	0.0275
Ribociclib plus Fulvestrant				
1st order, fixed effects				
-2	-	-3.0473	-0.5091	-
-1	-	-3.0937	0.0270	-
-0.5	-	-3.1965	0.2845	-
0	-	-2.8648	-0.1020	-
0.5	-	-2.8162	-0.0816	-
2nd Order, fixed effects				
-2	-2	-3.3825	-1.3316	8.7175
-2	-1	-3.5733	-5.8235	5.1367
-2	-0.5	-3.9635	-3.0382	2.9575
-2	0	-2.0748	-1.7991	-0.3957
-2	0.5	-2.3593	-1.2111	-0.1891
-2	1	-2.7400	-0.9304	-0.0207
-1	-1	-3.7799	0.0040	3.1435
-1	-0.5	-4.2175	-4.5803	5.2303
-1	0	-1.7794	-1.6269	-0.4584
-1	0.5	-2.3279	-0.7847	-0.1840
-1	1	-2.7585	-0.4514	-0.0186
-0.5	-0.5	-4.7925	1.4222	1.8329
-0.5	0	-0.8125	-2.4082	-0.6213
-0.5	0.5	-2.1968	-0.7410	-0.1830
-0.5	1	-2.7681	-0.2758	-0.0163
0	0	-3.0857	0.2426	-0.0927
0	0.5	-2.8035	0.1718	-0.1983
0	1	-2.9438	0.0086	-0.0124
0.5	0.5	-2.9803	0.0423	-0.0287
0.5	1	-2.8526	-0.0557	-0.0038

As stated above, the frequentist approach was used to validate results using the Bayesian approach, and it was determined that model coefficients for the two approach were similar and yielded similar model results for life expectancy as shown below.

Figure 7. Comparison of model projections of life expectancy using FP NMA of PFS with p1 = -1 and p2 = -2 based on Bayesian vs. Frequentist Methods



2.2 TTD for Ribociclib and Fulvestrant

As requested by the ERG during the technical engagement stage, the fit of 3-knot spline models to TTD for ribociclib and fulvestrant from MONALEESA-3 was explored in order to improve the visual fit of the parametric distribution for TTD to the KM data. These curves were estimated using the same methods as those employed for the other parametric survival distributions considered in the CDF review submission document, which have been described previously.

2.2.1 TTD for Ribociclib

Rankings of the 3-knot spline models based on statistical measures of goodness of fit are shown in Figure 8. Among these models, the unrestricted (U) models (i.e., independently fitted models) are consistent with the committee's preferred assumptions in TA593. Among these, the RCS 3 log-logistic (U) has the best statistical fit based on the BIC. In Table 6, fit statistics for the 3-knot spline models are compared against those for the "standard" parametric distributions included in the CDF review submission document.

Figure 8. Fit Statistics for 3-Knot Spline Model fit to TTD for Ribociclib for Patients in Group B of MONALEESA-3

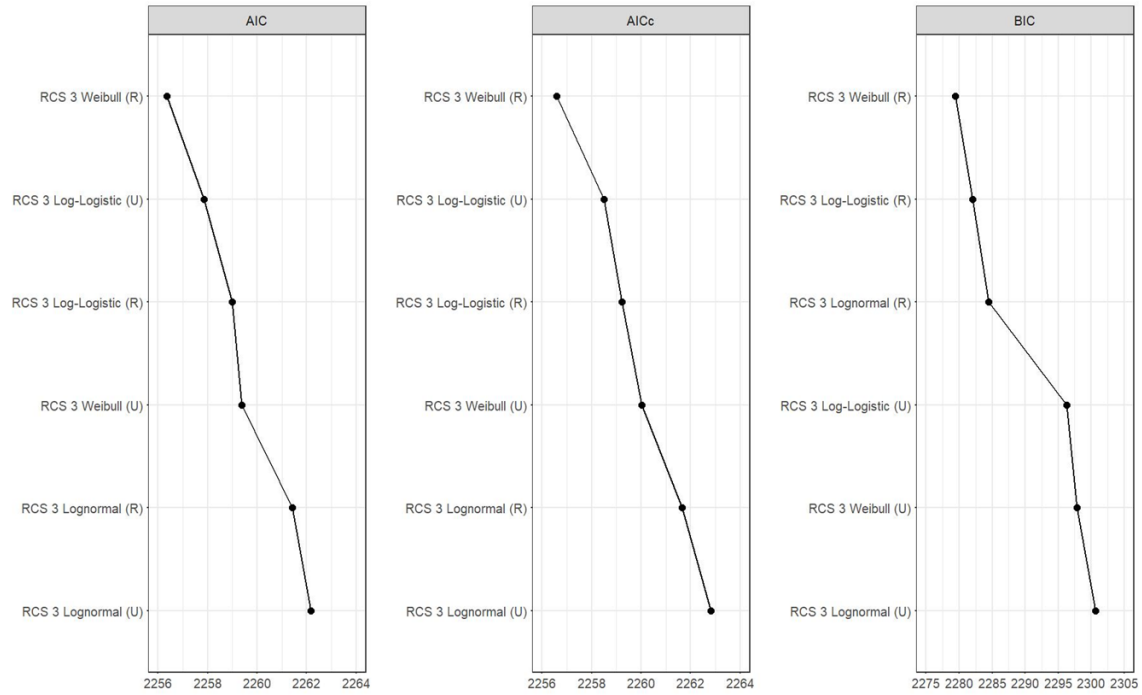


Table 6. Fit Statistics for all Parametric Distributions fit to TTD for Ribociclib for Patients in Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Gompertz (U)	2256.5	2256.6	2271.8
RCS Lognormal (U)	2256.4	2256.6	2279.4
Gen. Gamma (U)	2256.7	2257	2279.8
RCS Weibull (U)	2256.9	2257.2	2280
RCS Log-Logistic (U)	2259.5	2259.7	2282.6
Gen. F (U)	2260.4	2260.8	2291.2
RCS 3 Log-Logistic (U)	2257.8	2258.5	2296.3
RCS 3 Weibull (U)	2259.4	2260	2297.8
RCS 3 Lognormal (U)	2262.2	2262.8	2300.6

Visual comparisons of the goodness of fit for the unrestricted 3-knot spline models fit to TTD for ribociclib are shown in Figure 9. The 3-knot spline models have improved visual fit compared with either of the RCS lognormal (U) or Gompertz (U). The best visual fit is the RCS 3 log-logistic (U) model, which is compared against KM TTD for ribociclib from MONALEESA-3 over the duration of trial follow-up in Figure 10.

Figure 9. 10-Year Projections of TTD for Ribociclib Based on 3-Knot Spline Models Compared Against KM from Group B of MONALEESA-3

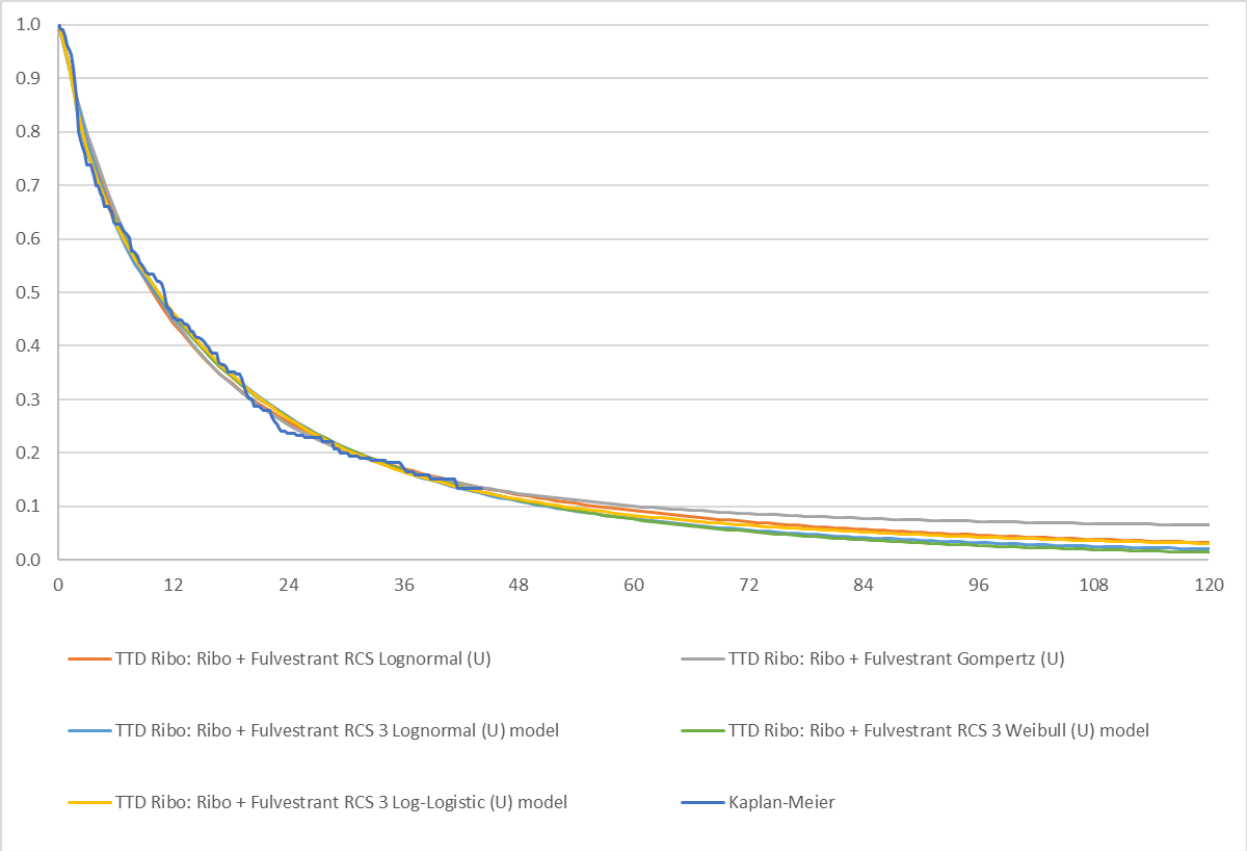
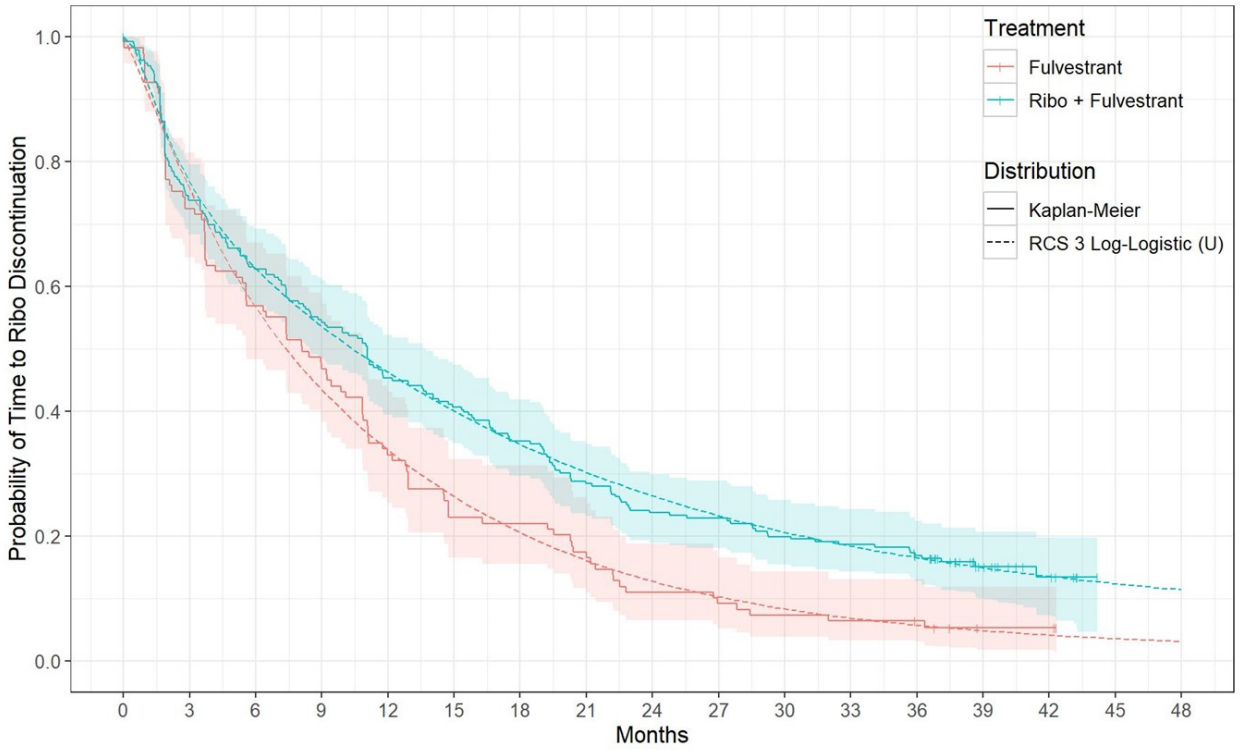


Figure 10. TTD for Ribociclib to End of Trial Follow-up Based on the RCS 3 Log-Logistic (U)



Predicted landmark TTD for ribociclib based on the 3-knot spline models are compared against the company's preferred parametric distribution in the CDF review submission document – the RCS lognormal (U) – and the ERG's preferred parametric distribution – the Gompertz (U) – are show in Table 7.

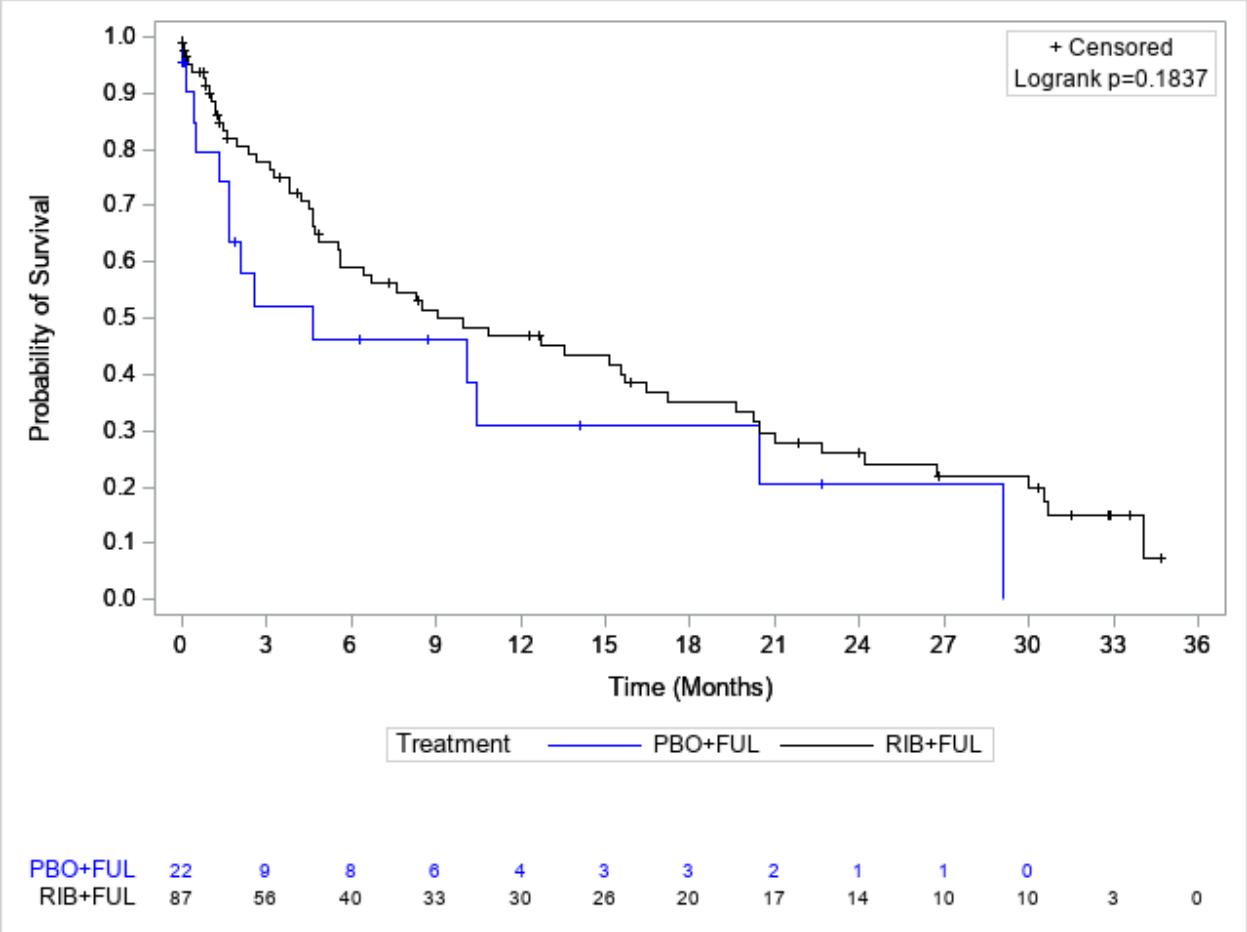
Table 7. Predicted Landmark TTD for Ribociclib based on 3-Knot Spline Models fit to TTD Data for Group B of MONALEESA-3

Time	KM	RCS Lognormal (U)	Gompertz (U)	RCS 3 Log-Logistic (U)	RCS 3 Lognormal (U)	RCS 3 Weibull (U)
2-Year	23.73%	25.84%	25.30%	26.44%	26.74%	26.56%
3-Year	17.37%	17.14%	16.78%	16.54%	16.58%	16.87%
5-Year	--	9.21%	10.12%	8.40%	7.70%	7.67%
10-Year	--	3.27%	6.56%	3.12%	2.06%	1.46%

As stated in the CDF review submission document, the Gompertz (U) model for TTD was considered to be implausible because of the long tail of the distribution, which would effectively be a cure model resulting in a proportion of patients who would continue receiving treatment indefinitely. The ERG had suggested this could be remedied by capping the TTD by the PFS curve, so that patients would not receive treatment

after disease progression. However, this would still potentially overestimate costs for ribociclib to the extent that patients who discontinue treatment may remain in PFS for an extended period of time. To assess the magnitude of this potential bias, we estimated PFS from the time of discontinuation of study medication in MONALEESA-3 (i.e., ribociclib or blinded placebo) among patients who discontinued the medication before the date of disease progression and for reasons other than progression or death. As shown in Figure 11, the median time from discontinuation of ribociclib until disease progression (black curve) was approximately 8 months, compared with approximately 5 months for placebo. Approximately 25% of patients remained in PFS 24 months after treatment was discontinued. This analysis would suggest that the TTD curve may remain below the PFS curve well beyond the end of follow-up in the trial and support the hypothesis that the Gompertz (U) distribution for TTD overestimates time on treatment with ribociclib.

Figure 11. Time from Discontinuation of Ribociclib or Placebo to Progression



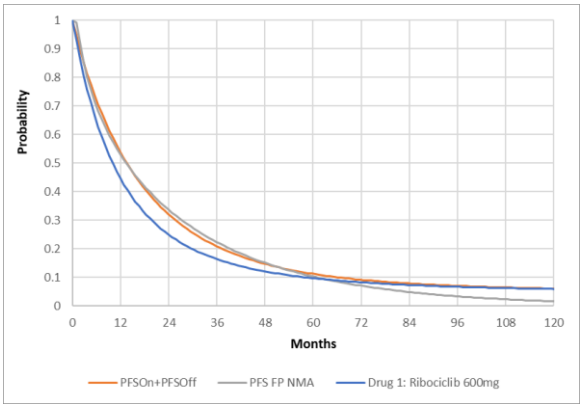
To further explore this issue we developed a simple Markov model with states for PFS on treatment, and PFS off treatment, and post progression. The probability of remaining in the PFS on treatment state was based on the assumed TTD distribution, for which we alternately used the Gompertz (U) and the RCS 3 Log-logistic (U). The proportion of patients in the PFS off treatment state was derived by first assuming

161/585=27.5% of patients who discontinue do so for reasons other than progression (the remainder are assumed to move to post-progression state upon discontinuation). Those entering the PFS off treatment state were assumed to transit to the post-progression state based on the distribution of PPS given discontinuation as shown above. For simplicity, we assumed an exponential distribution with the monthly rate of progression equal to 0.06396, which we derived from the 36 months probability of PFS in the chart above (approximately 10%).

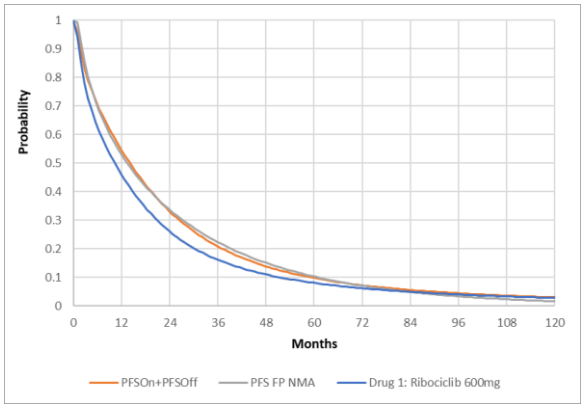
As shown in the figures below, combining TTD based on the RCS 3 Loglogistic (U) with the PFS given discontinuation distribution as described above yields projections of PFS that are much more consistent with the projections obtained using the TTD based on the Gompertz (U). This analysis therefore provides additional support for using the RCS 3 Loglogistic (U) for PFS.

Figure 12. Residence in PFS Off Treatment and PFS On Treatment Based on Parametric Distributions Fit to TTD for Ribociclib

A. Gompertz (U) for TTD



B. RCS 3 Log logistic (U) for TTD



2.2.2 TTD for Fulvestrant

Rankings of the 3-knot spline models based on statistical measures of goodness of fit are shown in Figure 13. Among the unrestricted 3-knot models, the RCS 3 log-logistic (U) had the best fit according to the BIC. In Table 8, fit statistics for the 3-knot models are compared with the “standard” parametric distributions included in the CDF review submission document.

Figure 13. Fit Statistics for 3-Knot Spline Model fit to TTD for Fulvestrant for Patients in Group B of MONALEESA-3

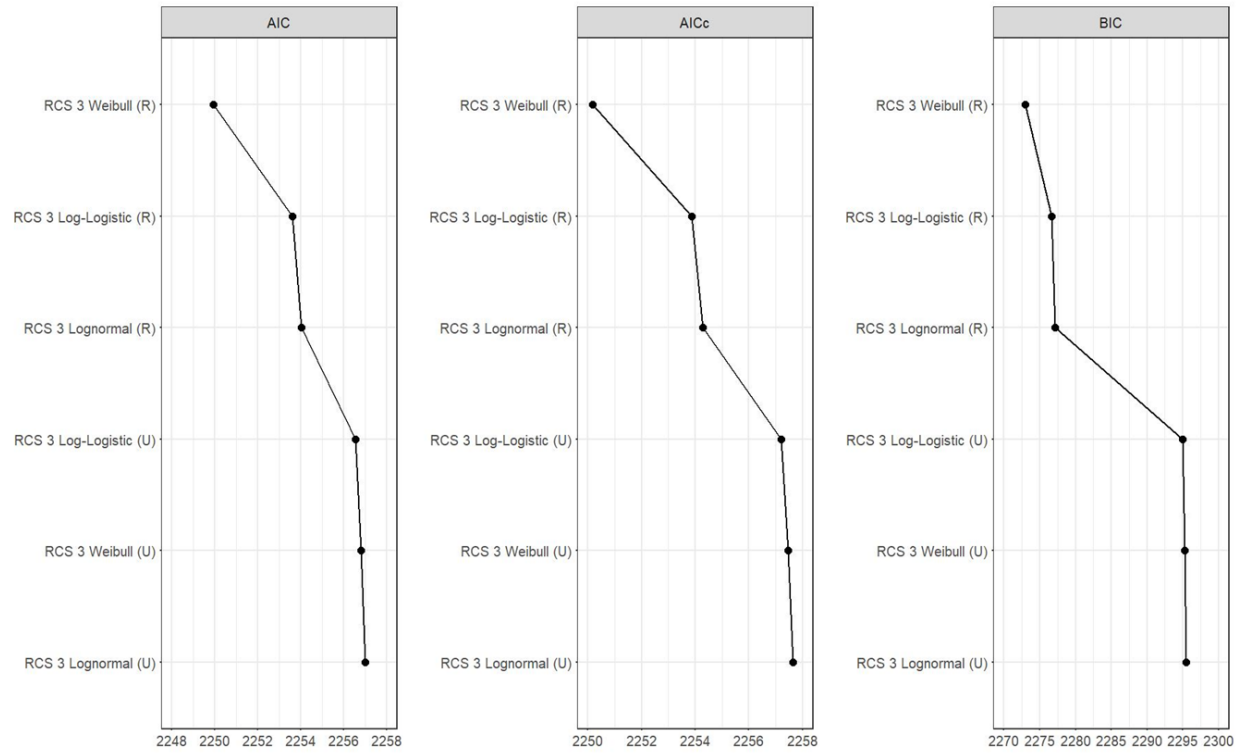


Table 8. Fit Statistics for all Parametric Distributions fit to TTD for Fulvestrant for Patients in Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Gompertz (U)	2279.1	2279.2	2294.5
RCS 3 Log-Logistic (U)	2256.5	2257.2	2295
RCS 3 Weibull (U)	2256.8	2257.5	2295.3
RCS 3 Lognormal (U)	2257	2257.6	2295.5
RCS Lognormal (U)	2273	2273.2	2296.1
Gen. Gamma (U)	2273.7	2273.9	2296.8
RCS Weibull (U)	2278.6	2278.9	2301.7
RCS Log-Logistic (U)	2284.1	2284.3	2307.2
Gen. F (U)	2277.7	2278.1	2308.5

Visual comparisons of the goodness of fit for the 3-knot spline models fit to TTD for fulvestrant are shown in Figure 14 for patients receiving fulvestrant with ribociclib and in Figure 15 for patients receiving fulvestrant monotherapy in MONALEESA-3. The RCS 3 log-logistic (U) has the best visual fit for both treatment arms, as shown in Figure 16.

Figure 14. 10-Year Projections of TTD for Fulvestrant for Patients Receiving it with Ribociclib Based on 3-Knot Spline Models Compared Against KM from Group B of MONALEESA-3

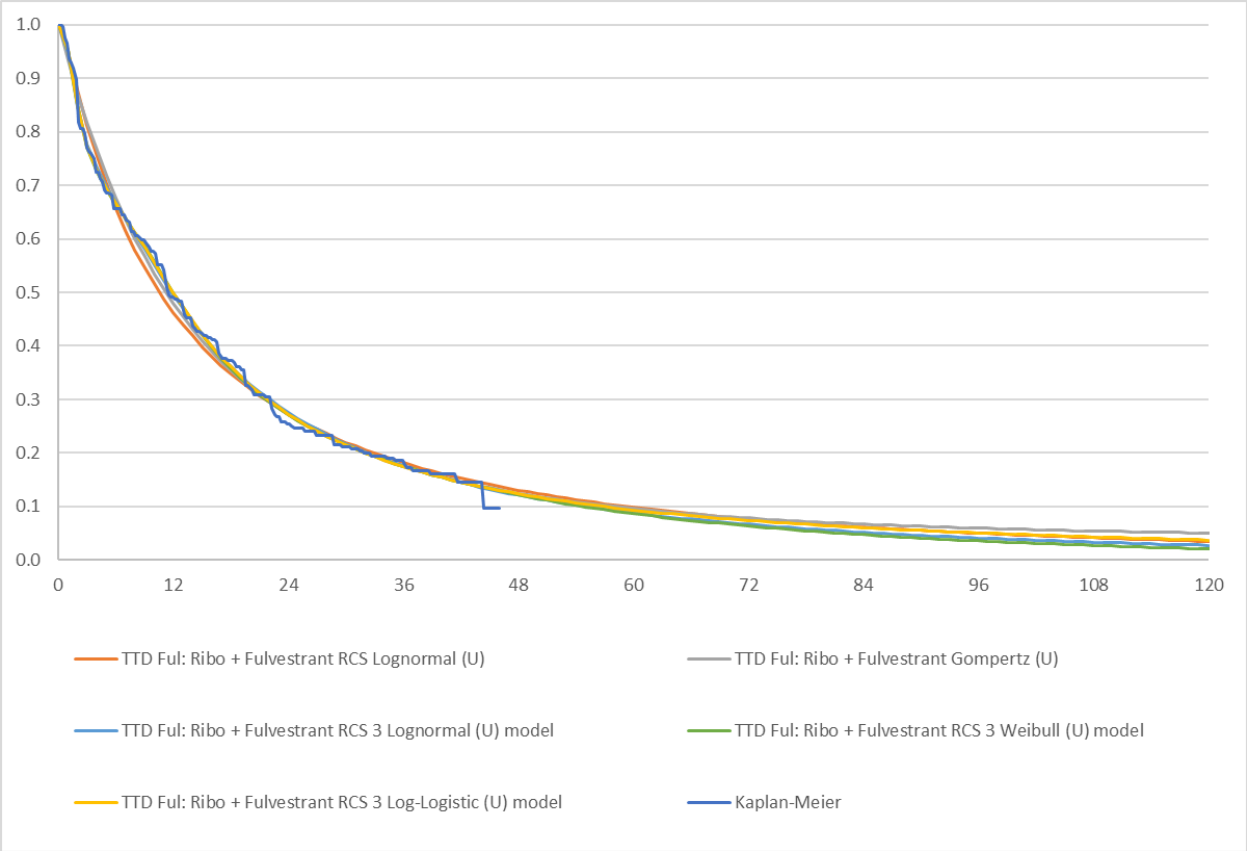


Figure 15. 10-Year Projections of TTD for Fulvestrant for Patients Receiving it as Monotherapy Based on 3-Knot Spline Models Compared Against KM from Group B of MONALEESA-3

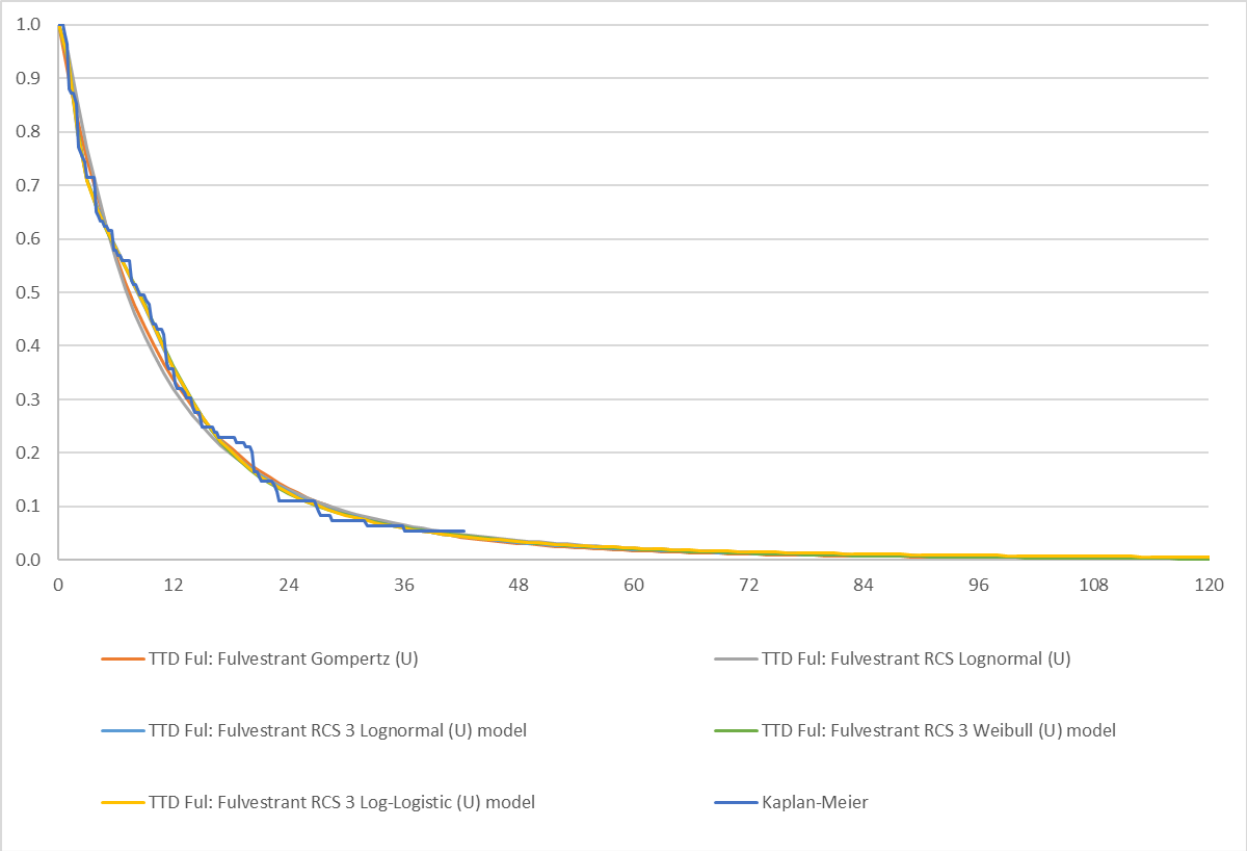
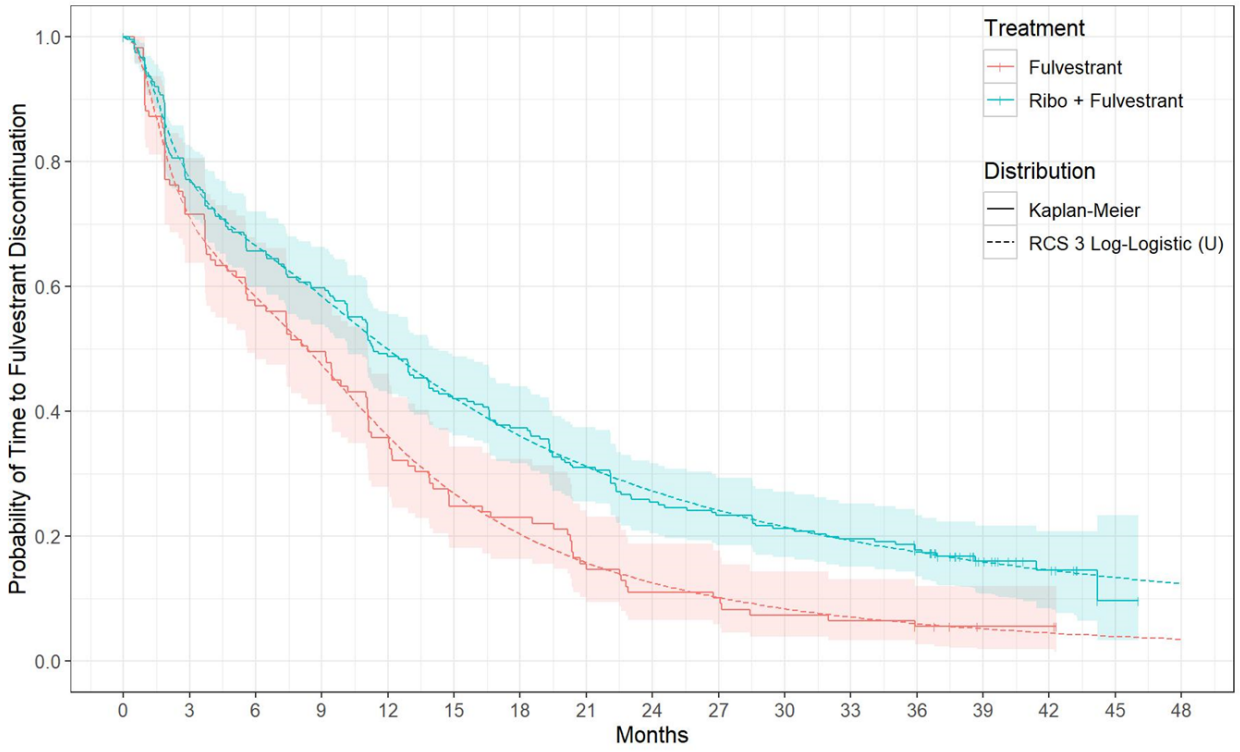


Figure 16. TTD for Fulvestrant to End of Trial Follow-up Based on the RCS 3 Log-Logistic (U)



Predicted landmark TTD for fulvestrant among patients receiving fulvestrant in combination with ribociclib are shown in Table 9. Corresponding estimates for those receiving fulvestrant as monotherapy are shown in Table 10.

Table 9. Predicted Landmark TTD for Fulvestrant for Patients Receiving it with Ribociclib based on 3-Knot Spline Models fit to TTD Data for Group B of MONALEESA-3

Time	KM	RCS Lognormal (U)	Gompertz (U)	RCS 3 Log-Logistic (U)	RCS 3 Lognormal (U)	RCS 3 Weibull (U)
2-Year	25.42%	27.26%	27.16%	27.26%	27.53%	27.15%
3-Year	18.20%	18.20%	17.52%	17.48%	17.57%	17.54%
5-Year	--	9.84%	9.61%	9.37%	8.84%	8.70%
10-Year	--	3.51%	5.05%	3.76%	2.75%	2.11%

Table 10. Predicted Landmark TTD for Fulvestrant for Patients Receiving it as Monotherapy based on 3-Knot Spline Models fit to TTD Data for Group B of MONALEESA-3

Time	KM	RCS Lognormal (U)	Gompertz (U)	RCS 3 Log-Logistic (U)	RCS 3 Lognormal (U)	RCS 3 Weibull (U)
2-Year	11.01%	13.42%	13.13%	12.54%	12.72%	12.42%

3-Year	6.42%	6.13%	6.56%	6.00%	6.04%	6.11%
5-Year	--	1.80%	2.26%	2.25%	1.99%	2.07%
10-Year	--	0.31%	0.38%	0.57%	0.31%	0.24%

2.3 TTD and Daily Dose Reductions for Everolimus

Scenario analyses were conducted to account for TTD based on clinical assumptions and dose reductions of everolimus based on data from BOLERO-2. Methods for estimating TTD and dose reductions for everolimus are described below

2.3.1 Time to Treatment Discontinuation

The use of patient-level data from the BOLERO-2 study to model TTD for patients receiving everolimus and exemestane was explored. However, because of how data on treatment discontinuation were recorded in BOLERO-2, this proved to be infeasible. Specifically, per the BOLERO-2 protocol, the date of study treatment discontinuation was recorded when ***both*** drugs (i.e., everolimus/blinded placebo and exemestane) were permanently discontinued. The date of discontinuation for individual components of the combination was not available in the data sets Similarly, data on adverse event (AEs) include information on whether this led to discontinuation to one or more of the study drugs, not the individual components of the combination. While data on daily dosages for each dispensation of everolimus and exemestane were captured separately, these data do not provide information on the date when receipt of a specific drug was stopped. Therefore, the last date with daily dose recorded for a given drug does not necessarily reflect the date when the patient stopped receiving that drug. Rather, it only reflects that last daily dose observed during follow-up (i.e., it is not possible to determine whether the patient continued receiving the drug after the last follow-up).

As it was not practically feasible, within the time available to conduct these analyses, to estimate TTD separately for everolimus and for exemestane using data from the BOLERO-2 study, TTD for everolimus and exemestane was therefore modelled based on clinical feedback provided to the ERG, as described in the ERG report. Specifically, it was assumed that 20% of patients receiving everolimus would discontinue that drug at month 6, whereas exemestane would be received until disease progression [11]. The PFS off-treatment utility value was applied to the 20% of patients who discontinue everolimus, as any effects of exemestane on utility values are likely to be small.

The user can turn TTD for everolimus based on clinician feedback on or off from the “Regimens_Disc” input sheet. TTD for everolimus based on clinician feedback is applied in the model by default. To turn this off, the user would select “No” (Override TTD Curve with % Discontinuing) in cell F40. The user also can modify the percentage of patients assumed to discontinue and the time at which discontinuation occurs.

2.3.2 Dose Reductions

Based on clinical feedback provided to the ERG, some proportion of patients receiving treatment with everolimus plus exemestane in clinical practice would be expected to have their daily doses reduced from 10mg to 5mg [11]. Since it was not feasible to estimate TTD for everolimus and exemestane separately,

the base case utilised the ERG's preferred assumptions for dose reductions: that 70% of patients remaining on everolimus after month 6 would reduce dose of to 5mg daily [11]. Consistent with the price used by the ERG in a similar analysis, the list price of the 5 mg tablet of everolimus was based on the list price of for a 30-tablet pack of Afinitor 5 mg (Novartis) from the British National Formulary (NHS indicative price of £2,250.00) and was adjusted for a [redacted] PAS discount.

As a scenario analysis, the proportion of patient days on treatment with everolimus at each daily dose (i.e., 0mg, 2.5mg, 5mg, and 10mg) was estimated based on patient-level data on treatment exposure from BOLERO-2, as shown in Table 11. Daily doses of 0mg reflect temporary dose interruptions.

Table 11. Distribution of Dosages of Everolimus in BOLERO-2

	0mg	2.5mg	5mg	10mg	Total
Number of days	8,343	2,476	30,792	86,182	127,793
Percent of days	6.5%	1.9%	24.1%	67.4%	100.0%

Consistent with clinical feedback provided to the ERG, only dose reductions from 10mg to 5mg daily were considered [11]. Because a small proportion of days on treatment were at a dose of 2.5mg (1.9%), this proportion was uniformly allocated to 5mg and 10mg. It was therefore estimated that 68.4% of treatment days would have a dose of 10mg (67.4% + [1.9% / 2] = 68.4%), 25.1% would have a dose of 5mg (24.1% + [1.9% / 2] = 25.1%), and 6.5% would have a dose of 0mg.

The user can turn everolimus down dosing based on clinician feedback on or off from the "Regimens_Dose" input sheet. Everolimus down dowsing is applied by default in the model. To turn everolimus down dosing off, the user would select "No" (delay application of reduced dose) from the dropdown in cell F40 and also set the RDI for the everolimus reduced dose to 0 in cell L26.

2.4 Partitioned Survival Model

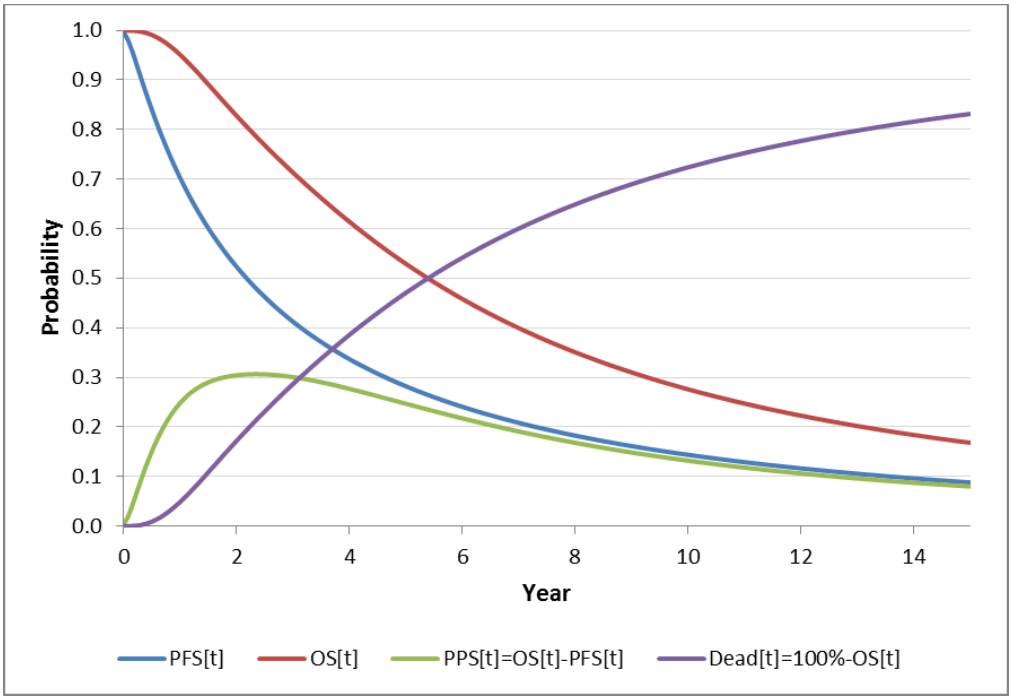
The model used in the original submission to the CDF was modified to permit the use of two alternative modeling approaches, including:

1. STM approach; and
2. PSM approach.

This is implemented with two separate calculation engines within the model workbook used to calculate the model trace—i.e., the probabilities of residing in each mutually exclusive health state across model cycles. With either approach, health states in the model include PFS, PPS, and dead. Users can toggle between modeling approaches using a control variable located on the "Model Settings" worksheet. In order to avoid excessively large file size, all model inputs are used by both calculation engines (i.e., the model does not have separate input parameters for the STM and PSM engines), with one exception; while the STM engine uses efficacy parameters for PFS and PPS, the PSM engine uses efficacy parameters for PFS and OS.

The model structure for the STM has been described previously in the company's submission. With the PSM approach, patients who are alive are "partitioned" according to progression status (i.e., progression-free or post-progression) under the assumption that progression has implications for QOL and costs. Membership in the three states over time is determined by efficacy parameters – in the form of survival curves – for PFS and OS. The survival curve for PFS provides the proportion of patients remaining in the PFS state over time. The survival curve for OS acts as a ceiling for PFS, meaning that the model assumes PFS at any point in time cannot exceed OS. Membership in the dead state is calculated as the complement of the OS survival curve over time. Membership in the PPS state is calculated as the difference between PFS and OS over time. The process of deriving membership in the PFS state and the dead state (PFS[t] and Dead[t], respectively) is illustrated in Figure 17.

Figure 17. Simplified Schematic of PSM Model



This approach does not include explicit states for "on" and "off" treatment. Hence probabilities of PFS are not conditioned on whether patients are on or off therapy. However, costs and utilities are allowed to depend on whether patients are on therapy in the PFS state based on estimated distributions of time to discontinuation (TTD). Expected costs and QALYs are therefore calculated by combining information on time to discontinuation by time in state with cost and utility values conditioned on whether patients are on or off therapy.

2.4.1 Overall Survival

For patients receiving ribociclib plus fulvestrant and fulvestrant monotherapy, probabilities of OS were estimated using a similar approach employed for the estimation of PFS in the model submitted for in the CDF review dossier. Specifically, OS was estimated by fitting parametric survival distributions to the individual patient failure time data from Group B of MONALEESA-3. Parametric survival distributions fitted

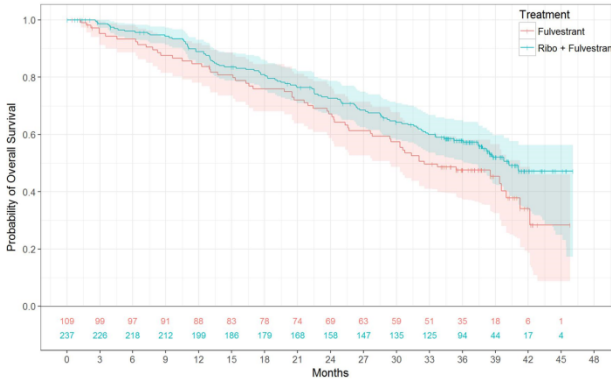
to OS data were evaluated using the same methodology employed for PFS to select the most appropriate model.

2.4.1.1 OS for Ribociclib plus Fulvestrant and Fulvestrant

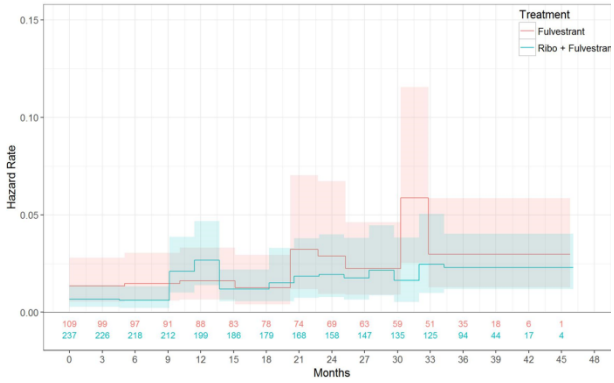
KM survival and hazard rates by treatment group, the hazard ratio for ribociclib plus fulvestrant versus fulvestrant, and restricted mean survival time (RMST; i.e., area under the curve, which provides an estimate of the expected survival) for Group B patients in MONALEESA-3 are displayed in Figure 18. The plot of hazard rates over time shows there is a slight increasing pattern for the hazards both treatment arms. The plot of the HR over time oscillates up and down without a clear pattern of increasing or decreasing.

Figure 18. Overall Survival in Group B of MONALEESA-3, by Randomized Treatment

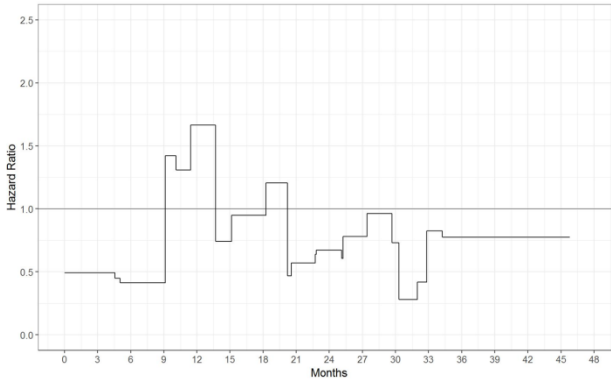
A. Kapan-Meier Survival Distribution



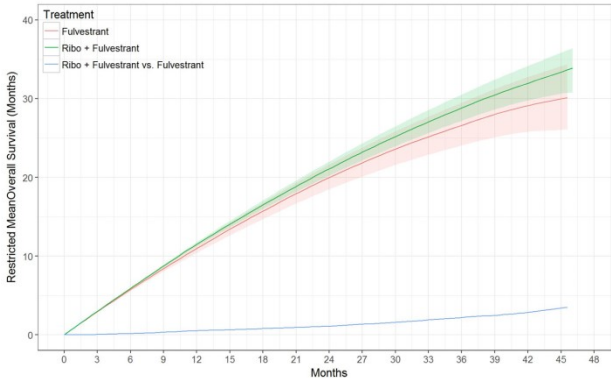
B. Hazard rates



C. Hazard ratio



D. Restricted Mean Survival Time



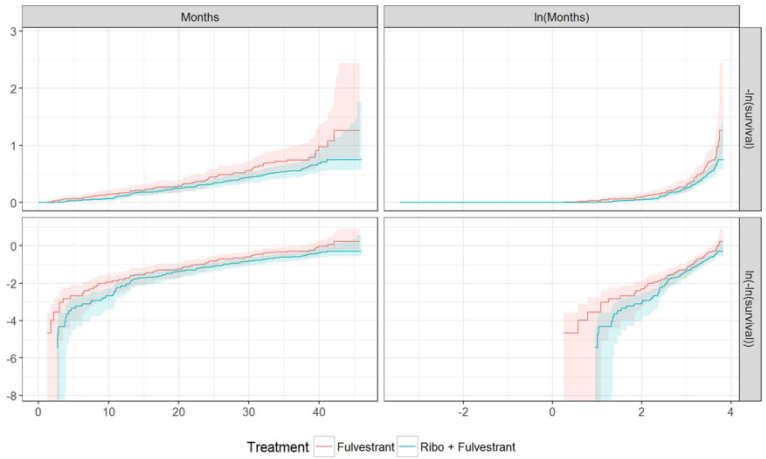
PAI Analyses of MONALEESA-3 data

Transformation and treatment effect diagnostic plots for OS for Group B of MONALEESA-3 are shown in Figure 19. The plots of the –ln(survival) versus months, representing the cumulative hazard function, do not appear to cross, suggesting the PH assumption is not violated. The plots of ln(-ln(survival)) against ln(months) are approximately linear and parallel after ln(months)=0.5 (months=1.6) suggesting the Weibull distribution, which has a PH treatment effect, may be an appropriate survival distribution. The treatment effect diagnostic plots for the PH and proportional odds assumptions both are overlapping,

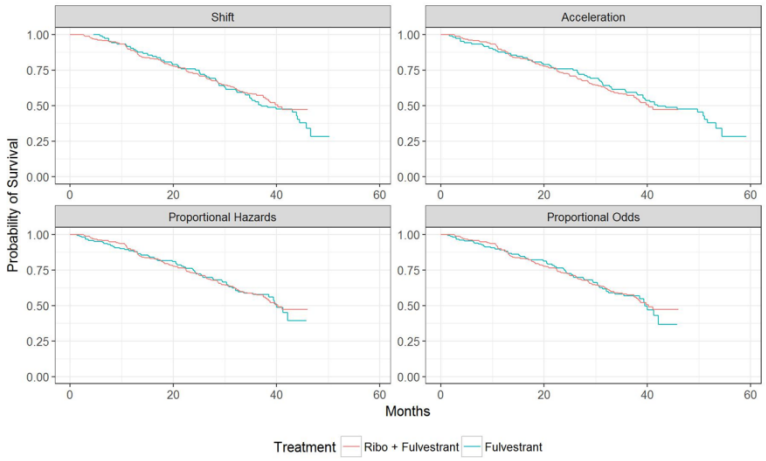
suggesting that models employing these treatment effect assumptions (e.g., the exponential or Weibull for PH and the log-logistics for proportional odds) would be consistent with the data.

Figure 19. Transformation and Treatment Effect Diagnostic Plots for Overall Survival in Group B of MONALEESA-3, by Randomized Treatment

A. Transformation Diagnostics



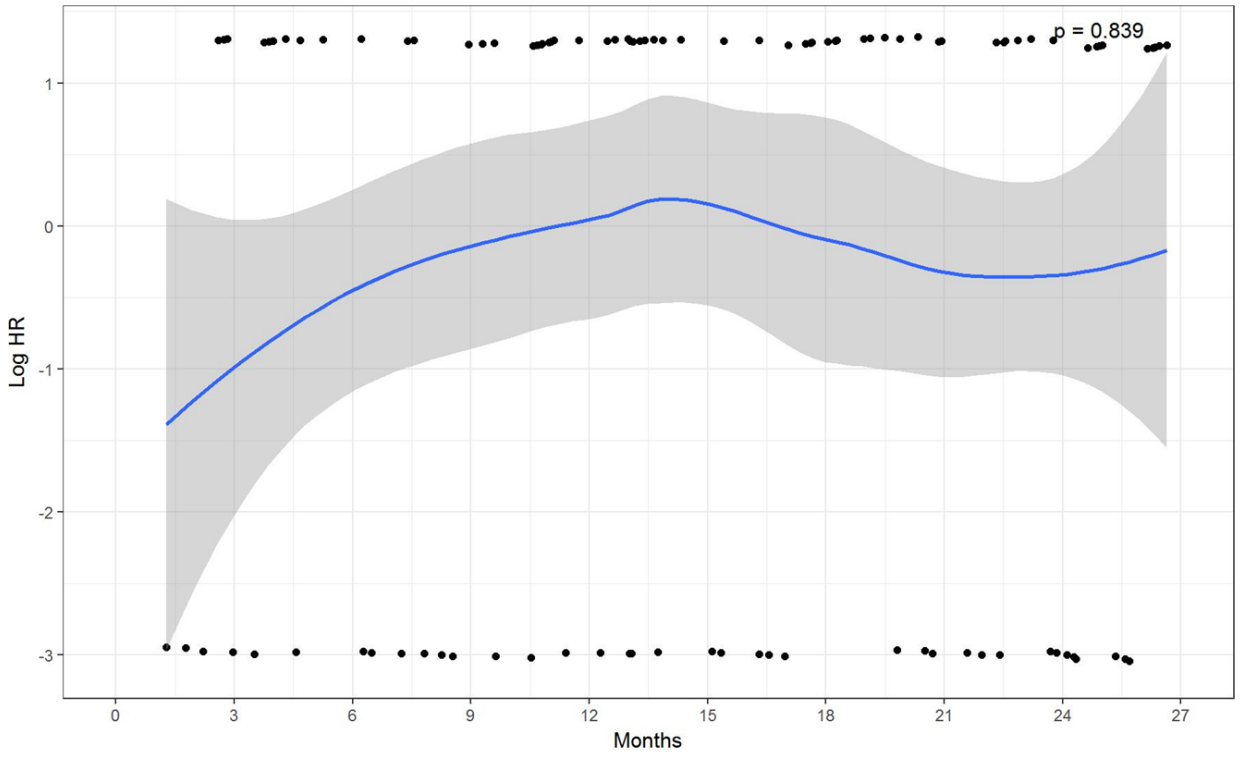
B. Treatment Effect Overlay Diagnostic Plots



PAI Analyses of MONALEESA-3 data

A plot of a smoothed curve fit to Schoenfeld residuals for OS for Group B of MONALEESA-3 is shown in Figure 20. The p-value on the test of non-proportionality is not significant suggesting that the PH assumption is not unreasonable.

Figure 20. Plot of Smoothed Curve fit to Schoenfeld Residuals for OS in Group B of MONALEESA-3



PAI Analyses of MONALEESA-3 data

Rankings of parametric distributions fit to OS according to statistical measures of goodness of fit are shown in Figure 21 and Table 12. The best fitting parametric distributions according to the BIC statistic were as follows:

- Weibull restricted;
- Log-logistic restricted;
- Gompertz restricted;
- Weibull unrestricted;
- RCS Weibull restricted; and
- Generalized gamma restricted.

The top fitting distributions based on the AIC and AICc were generally similar to those based on the BIC.

Figure 21. Fit Statistics for Parametric Distributions fit to OS for Patients in Group B of MONALEESA-3

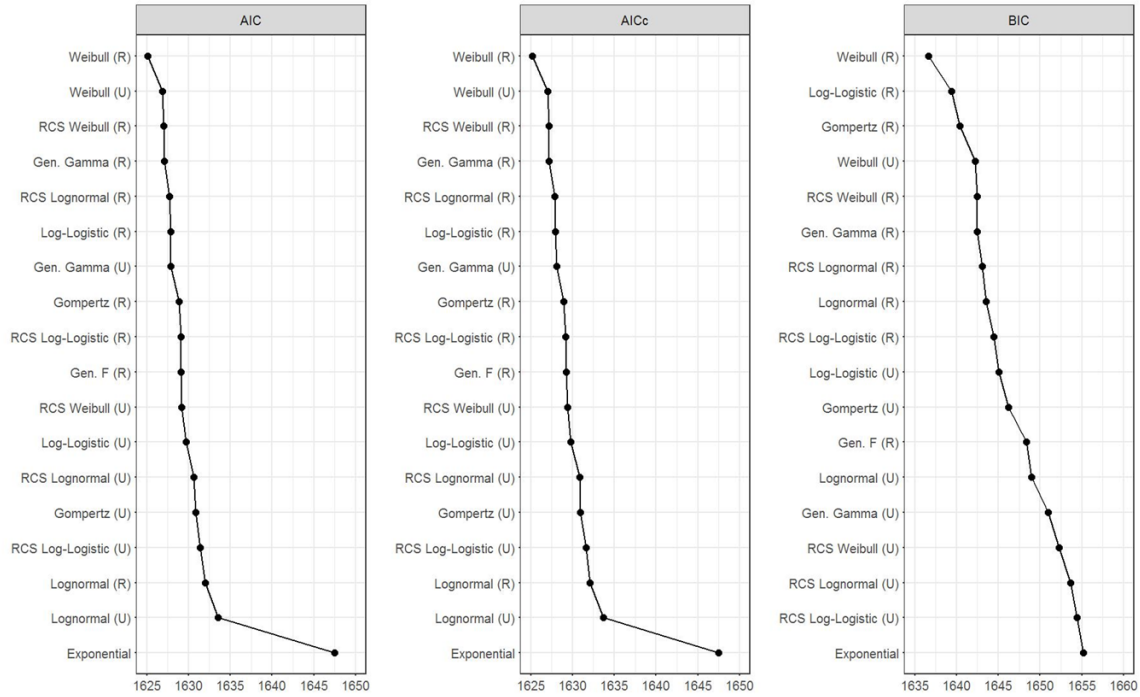


Table 12. Fit Statistics for Parametric Distributions fit to OS for Patients in Group B of MONALEESA-3

Distribution	AIC	AICc	BIC
Weibull (R)	1625.1	1625.2	1636.6
Log-Logistic (R)	1627.8	1627.9	1639.4
Gompertz (R)	1628.9	1628.9	1640.4
Weibull (U)	1626.9	1627.0	1642.3
RCS Weibull (R)	1627.1	1627.2	1642.4
Gen. Gamma (R)	1627.1	1627.2	1642.5
RCS Lognormal (R)	1627.7	1627.8	1643.1
Lognormal (R)	1632.0	1632.1	1643.5
RCS Log-Logistic (R)	1629.1	1629.2	1644.4
Log-Logistic (U)	1629.7	1629.8	1645.1
Gompertz (U)	1630.8	1630.9	1646.2
Gen. F (R)	1629.1	1629.3	1648.3
Lognormal (U)	1633.6	1633.7	1648.9
Gen. Gamma (U)	1627.9	1628.1	1651.0
RCS Weibull (U)	1629.2	1629.4	1652.2
RCS Lognormal (U)	1630.6	1630.8	1653.7
RCS Log-Logistic (U)	1631.4	1631.6	1654.4
Exponential	1647.5	1647.5	1655.1

Visual comparisons of the goodness of fit for parametric distributions fit to OS versus KM survival for Group B in MONALEESA-3 are shown in Figure 22 for ribociclib plus fulvestrant and in Figure 23 for fulvestrant monotherapy. The visual fit during trial follow-up all appear to be relatively good for each of the best-fitting distributions according to the BIC. Generally, the best-fitting distributions according to the BIC are restricted (R)—i.e., jointly fitted—models, with the exception of the Weibull unrestricted (U) —i.e., independently fitted—model. However, and as shown in the figures below, the projected survival for four of the six best-fitting distributions, including the Weibull (R) and Weibull (U), are virtually identical in the period after trial follow-up. The log-logistic (R) is one exception, which yields greater projected survival for both treatment arms compared with the other distributions, while the Gompertz (R) yields lower projected survival.

Figure 22. 10-Year Projections based on Parametric Distributions fit to OS for Ribociclib plus Fulvestrant Compared Against MONALEESA-3 Group B KM

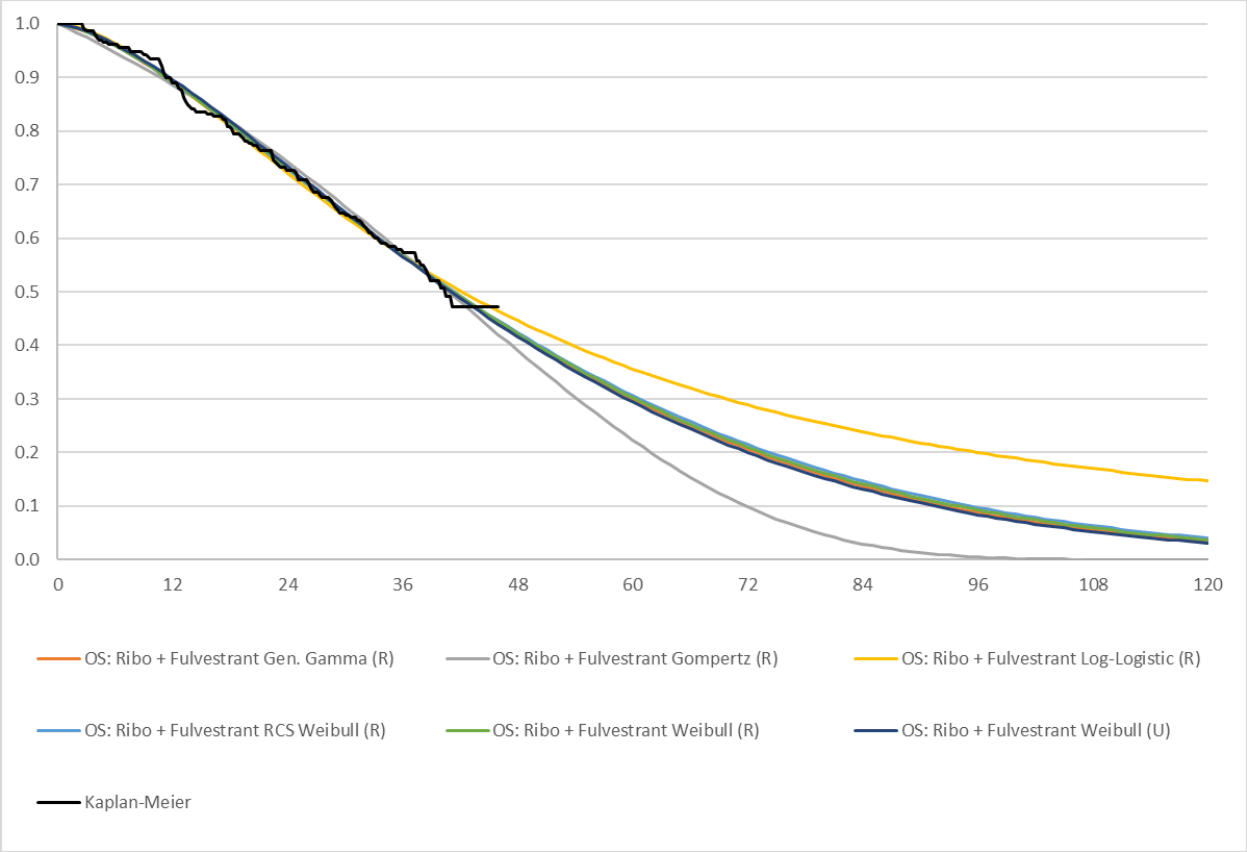
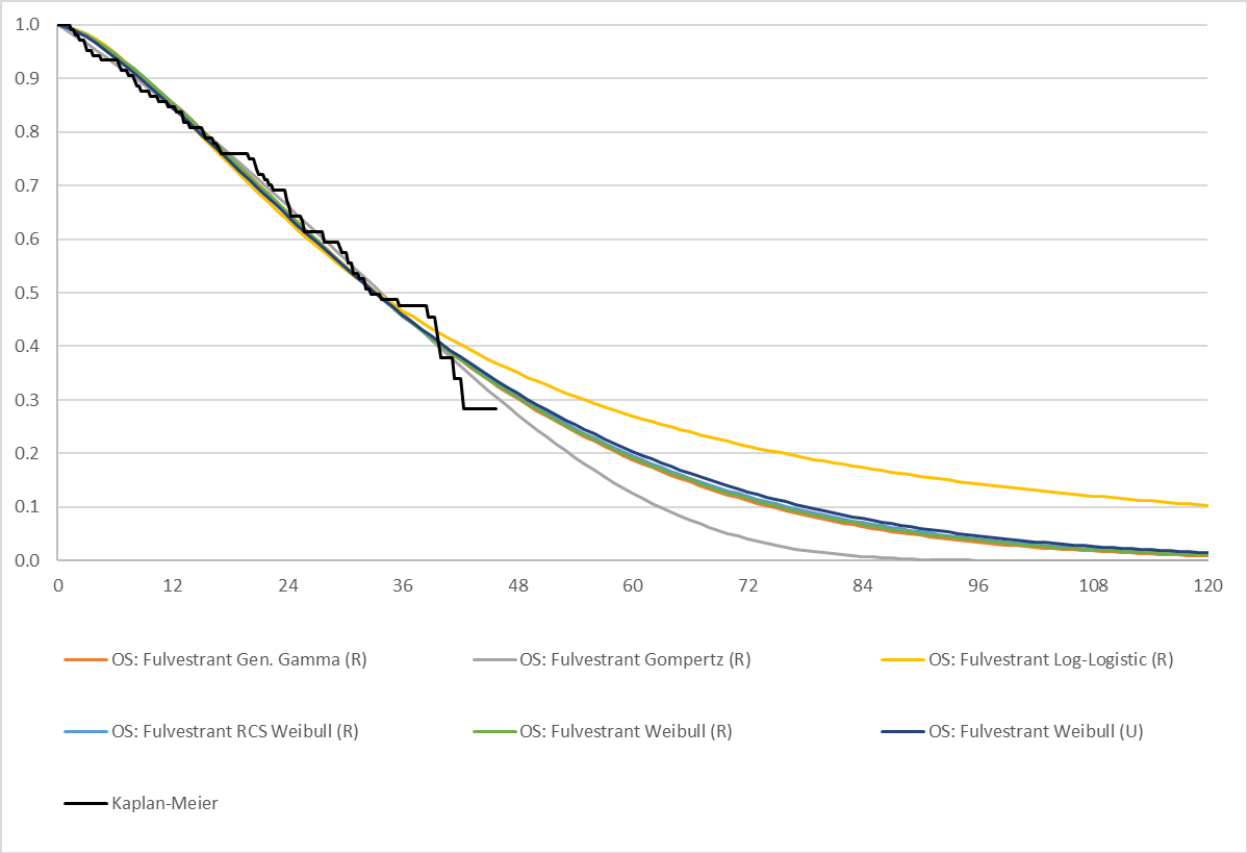


Figure 23. 10-Year Projections based on Parametric Distributions fit to OS for Fulvestrant Monotherapy Compared Against MONALEESA-3 Group B KM



Predicted landmark OS for the best-fitting parametric distributions fit to ribociclib plus fulvestrant in Group B of MONALEESA-3 are displayed in Table 13, below. These parametric distributions fit to OS were validated by clinical experts, who advised that the projected landmark OS based on the Weibull (R) distribution was consistent with their expectations based on clinical practice.

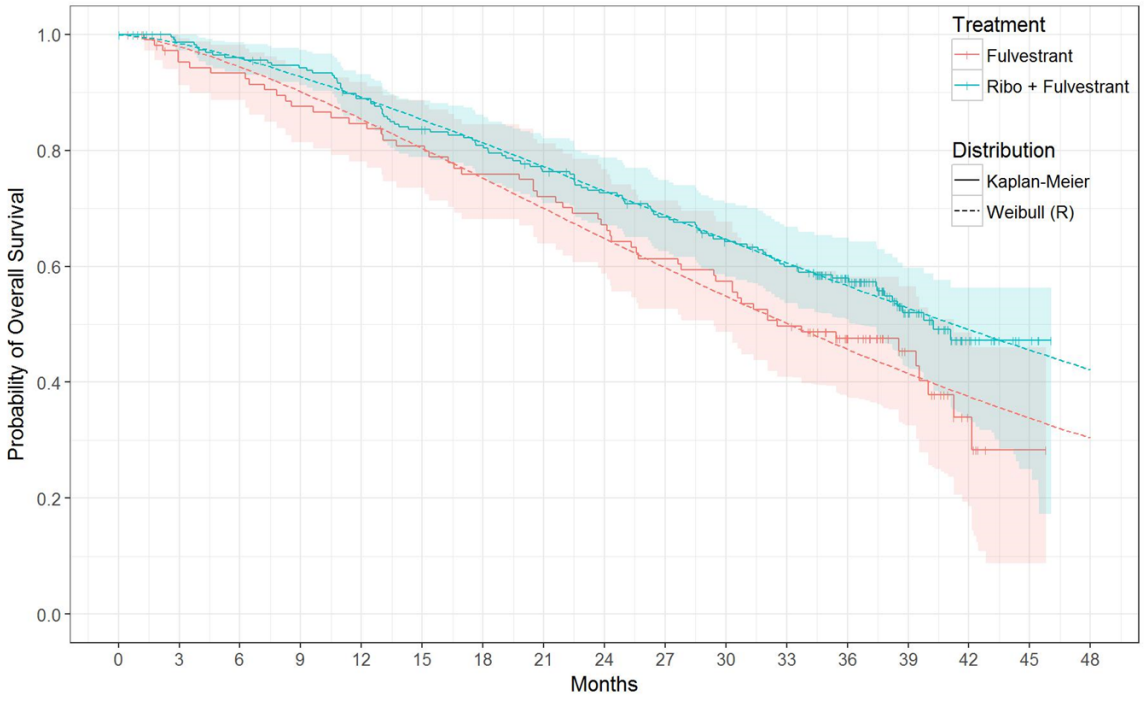
Table 13. Predicted Landmark OS for Parametric Distributions Fit to Ribociclib Plus Fulvestrant in Group B of MONALEESA-3

Time	KM	Gen. Gamma (R)	Gompertz (R)	Log-Logistic (R)	RCS Weibull (R)	Weibull (R)	Weibull (U)
2-Year	72.66%	74.47%	75.46%	73.54%	74.25%	74.41%	74.75%
3-Year	57.95%	57.99%	58.64%	57.80%	57.95%	57.97%	57.94%
5-Year	--	30.84%	23.59%	36.24%	31.49%	31.10%	30.32%
10-Year	--	3.54%	0.00%	14.84%	4.21%	3.88%	3.29%

The base case utilized the Weibull (R) distribution for OS because it had the best statistical fit, excellent visual fit to the KM data, and yielded projected OS that was consistent with clinical experts' expectations. It should be noted that the Weibull (R) distribution slightly overestimates OS for the fulvestrant arm and

slightly underestimates the OS for the ribociclib plus fulvestrant arm at the very end of follow-up. Scenario analyses were explored using alternative distributions fit to data on OS, including the independently fitted Weibull (U).

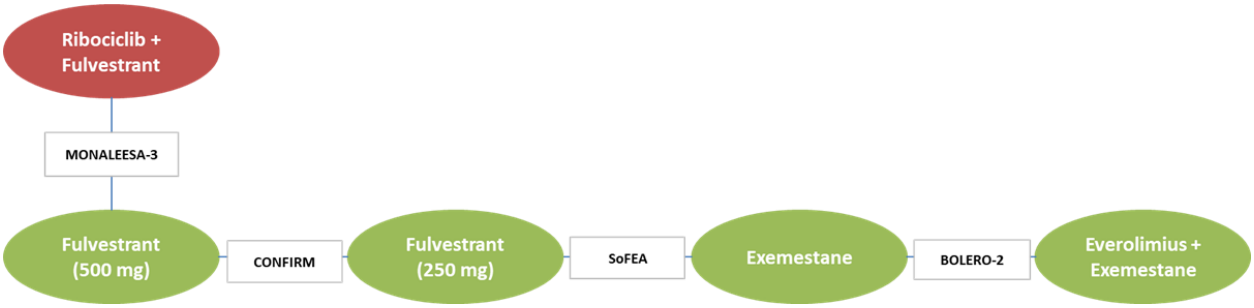
Figure 24. OS to End of Trial Follow-Up Based on Weibull (R) Distribution



2.4.1.2 NMAs of OS

A diagram depicting the evidence network for the ITC of OS is presented in Figure 25. While the EFECT trial was included in the evidence network for PFS, OS was not reported for this trial and it is therefore omitted from the network for OS [12].

Figure 25. Evidence Network for ITC of OS for Treatments of HR+/HER2- ABC



Results of the assessments of PH assumption for trials included in the NMA of OS based on the test of linearity of Schoenfeld residuals are shown in Table 14 below. These analyses suggest that the PH assumption was not violated for any of the trials contributing to the NMA and therefore a Bucher NMA using time-independent HRs is not unreasonable.

Table 14. Results of Assessment of PH Assumption for PFS based on test of Linearity of Schoenfeld Residuals

Trial	P-Value for Test of PH Assumption
MONALEESA-3	0.839
BOLERO-2	0.161
CONFIRM	0.730
SoFEA	0.324

2.4.1.2.1 Bucher NMA of OS

Because analyses of Schoenfeld residuals suggests that the PH assumption is not violated for any of the comparisons in the network, a Bucher NMA using time-independent HRs was considered appropriate [13-15]. HRs used in the ITC for OS for treatments of HR+/HER2- aBC are shown in Table 15, below.

Table 15. HRs for OS Used in the Bucher Method ITC of Treatments for HR+/HER2- ABC

Trial	Study Arm		HR (95%CI)	Source
	Experimental	Control		
MONALEESA-3	Ribociclib + Fulvestrant 500 mg	Fulvestrant 500 mg	0.73 (0.53, 1.00)	[16]
CONFIRM	Fulvestrant 500 mg	Fulvestrant 250 mg	0.81 (0.69, 0.96)	[17]
SoFEA	Fulvestrant 250 mg	Exemestane	1.05 (0.84, 1.29)	[2]
BOLERO-2	Everolimus + Exemestane	Exemestane	0.89 (0.73, 1.10)	[18]

Results of the ITC using the Bucher method for treatments of HR+/HER2- aBC are shown in Table 16.

Table 16. Results of HRs for OS from Bucher Method ITC of Treatments for HR+/HER2- ABC

Treatment	HR (95% CI) Treatment versus		HR (95%CI) Ribociclib + Fulvestrant vs Treatment
	Fulvestrant 500mg	Ribociclib + Fulvestrant	
Ribociclib + Fulvestrant	0.73 (0.53, 1.00)	1.00 (n/a, n/a)	1.00 (n/a, n/a)
Fulvestrant	1.00 (n/a, n/a)	1.37 (1.00, 1.89)	0.73 (0.53, 1.00)
Everolimus + Exemestane	1.05 (0.75, 1.47)	1.43 (0.90, 2.28)	0.70 (0.44, 1.11)

Exemestane	1.18 (0.90, 1.54)	1.61 (1.06, 2.45)	0.62 (0.41, 0.94)

2.4.1.2.2 Bayesian NMA of OS with Hazards Characterized as Fractional Polynomials

The methodology employed for the FP NMA of OS was the same as that described in the FP NMA of PFS.

2.4.1.2.2.1 Model Choice

The model selection process for the FP NMA of OS was identical to that used for the FP NMA of PFS, as described in Section 2.4.1.2.2.1. A sensitivity analysis was conducted for the random-effects model using informative priors for between study variability with these informative prior based on the estimated predictive distributions for between-study heterogeneity for mortality for a comparison of pharmacological treatments (sd ~ log- normal (-4.27, 1.48^2) [9].

2.4.1.2.2.2 FP NMA Results

Dbar and Dhat, pD, and DIC for each model considered for OS are shown in Table 17. Combinations of p1 and p2 that did not converge are not shown in the table. A 2nd order FP fixed-effect model with p1 = 0.5 and p2 = 0 was selected based on the lowest DIC (885.6). A sensitivity analysis with the chosen combination of p (p1 = 0.5 and p2 =0) using a random-effects model was also conducted. The DIC for the random-effects model was not as good as that for the corresponding fixed-effect model.

Table 17. Model Choice for FP NMA of OS Based on DIC

p1*	p2*	Dbar	Dhat	pD	DIC
1st Order Fixed-Effect Model					
-2	-	921.5	906.6	14.9	936.4
-1	-	913.2	897.5	15.7	928.9
-0.5	-	918.9	903.5	15.4	934.4
0	-	931.3	915.8	15.5	946.8
0.5	-	942.9	927.5	15.4	958.3
2nd Order Fixed-Effect Model					
-2	-2	913.8	895	18.8	932.6
-2	-1	912	891.3	20.6	932.6
-2	-0.5	909.5	888.1	21.3	930.8
-2	0	906.3	883.6	22.7	929
-1	-1	907	885.4	21.6	928.7
-1	-0.5	901.9	881.5	20.3	922.2
-1	0	893.9	872.2	21.7	915.7
-1	1	874.5	851.1	23.3	897.8
-0.5	-0.5	895	873	22.1	917.1
-0.5	0	885.7	865.2	20.5	906.2
-0.5	0.5	876.4	853	23.4	899.8
0	0	877.6	854.6	23	900.6
0.5	0	865.5	845.3	20.1	885.6

2nd Order-Random-Effects Model					
0.5	0	866.1	845	21.1	887.2

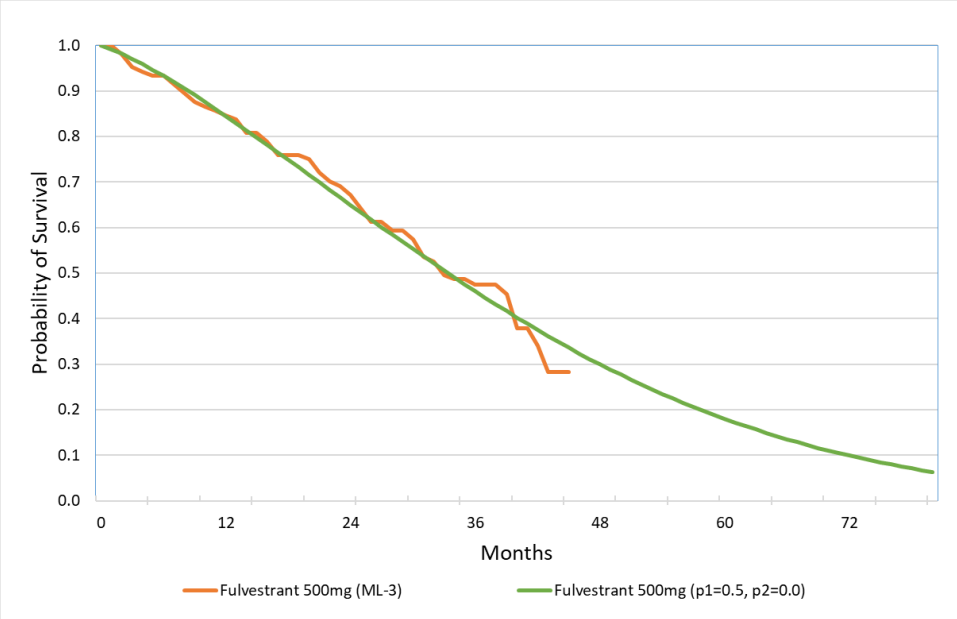
*Other combinations not included in this table were not converging well.

To estimate the hazard rate function of each treatment for **Equation 3**, the μ vector was obtained by performing the model with only the study of interest (MONALEESA-3) with p1= 0 and p2=0.5 for OS. These values were then combined with other parameters derived from the full NMA to complete **Equation 3**.

The distribution of μ has the following parameters in the OS model and fits the data (Figure 26).

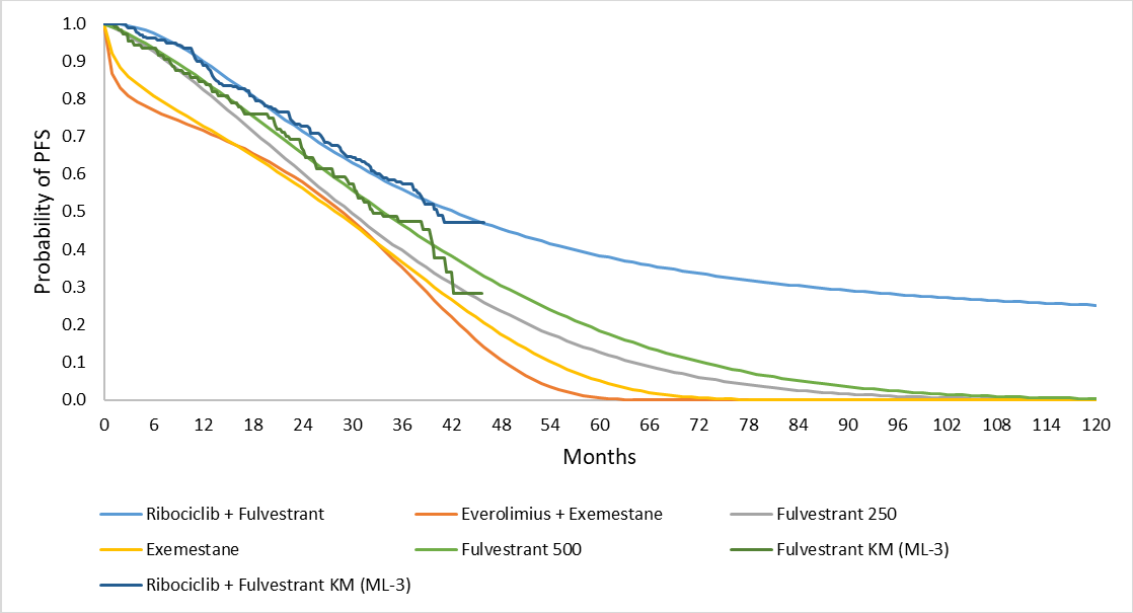
$$\begin{pmatrix}\mu_0\\ \mu_1\\ \mu_2\end{pmatrix} \sim Normal\left(\begin{pmatrix}-4.9\\ 0.2\\ 0.1\end{pmatrix}, T_\mu\right), T_\mu = \begin{pmatrix}0.41 & 0.15 & -0.37\\ 0.15 & 0.19 & -0.35\\ -0.37 & -0.35 & 0.67\end{pmatrix}$$

Figure 26. OS Distribution Based on FP NMA for Fulvestrant in Group B of MONALEESA-3



Survival distributions for OS from the FP NMA with time-varying hazards for all comparators contributing to the NMA network are show in Figure 27.

Figure 27. OS Distributions Based on FP NMA for All Treatments



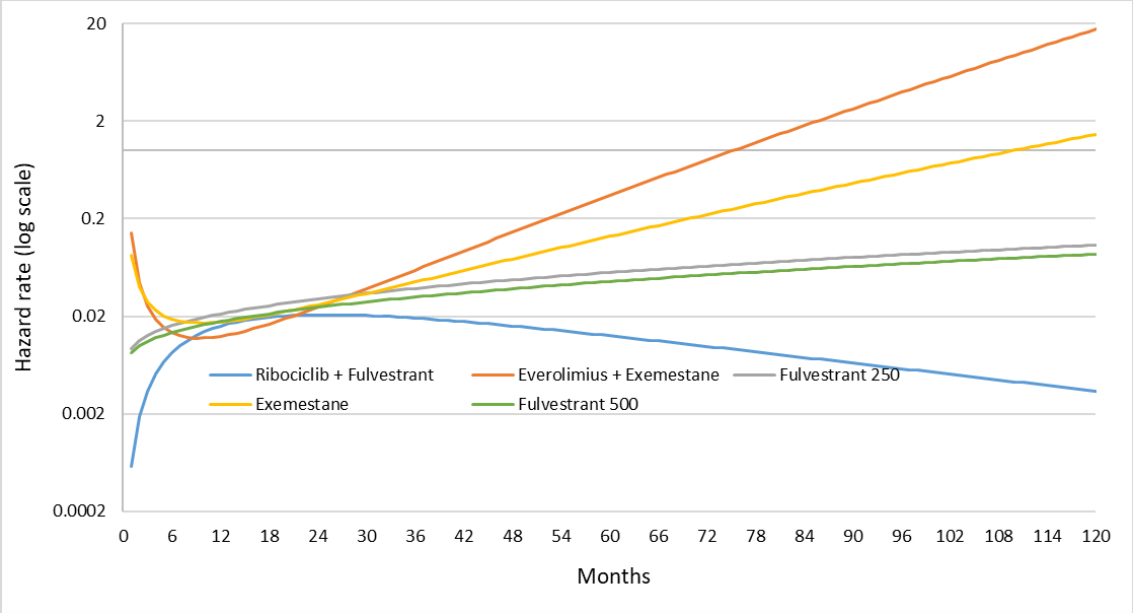
During the follow-up period of MONALEESA-3, the visual fit for ribociclib plus fulvestrant and fulvestrant monotherapy is very good. However, long-term projections of OS appear to be highly optimistic for ribociclib plus fulvestrant. This is reflected in Table 18, which compares predicted landmark OS for treatments of HR+/HER2- aBC based on the FP NMA against KM OS for ribociclib plus fulvestrant in Group B of MONALEESA-3 and the Weibull (R) distribution fit to OS for ribociclib plus fulvestrant. As stated previously, clinical experts advised that the Weibull (R) was consistent with their expectations. Importantly, OS for ribociclib plus fulvestrant based on the FP NMA is considerably higher at 10 years (25.3%) compared with the Weibull (R) distribution (3.88%). Additionally, projected OS for everolimus plus exemestane after 2 years is lower than that for exemestane based on the FP NMA. While everolimus plus exemestane did not demonstrate a statistically significant improvement in OS compared with exemestane in BOLERO-2, OS for the former treatment was numerically greater than for the latter (HR = 0.89, 95% CI 0.73-1.10, log-rank *P* = 0.1426) [18]. As such, it would not be expected that OS with everolimus plus exemestane would be lower than that for exemestane alone.

Table 18. Predicted Landmark OS for Treatments of HR+/HER2- ABC Based on FP NMA

Time	Ribociclib + Fulvestrant KM	Ribociclib + Fulvestrant Weibull (R)	Ribociclib+ Fulvestrant FP NMA	Everolimus + Exemestane FP NMA	Fulvestrant 250mg FP NMA	Exemestane FP NMA	Fulvestrant 500 mg FP NMA
2-Year	72.66%	74.41%	72.87%	59.24%	62.15%	57.75%	67.18%
3-Year	57.95%	57.97%	57.14%	37.53%	41.31%	38.43%	48.12%
5-Year	--	31.10%	38.88%	0.84%	13.38%	5.74%	19.29%
10-Year	--	3.88%	25.27%	0.00%	0.11%	0.00%	0.39%

Plots of the estimated hazard functions for PFS based on the FP NMA are shown in Figure 28. Projected hazards for ribociclib plus fulvestrant are increasing until approximately 15 months, after which point, they are decreasing steadily. For all of the other treatments, the hazard rates are increasing over time. Hazards for everolimus plus exemestane are highest among the treatments included in the FP NMA.

Figure 28. Estimated Hazard Functions for OS Based on FP NMA



HRs for OS each treatment versus fulvestrant 500 mg are shown in Figure 29. The HRs for ribociclib plus fulvestrant and fulvestrant 250mg versus fulvestrant 500mg are relatively constant throughout the 60-month projection period. Those for everolimus plus exemestane and exemestane drop initially then increases rapidly throughout the projection, especially for everolimus plus exemestane. The estimated HRs for OS for ribociclib plus fulvestrant versus fulvestrant 500mg and for fulvestrant 250mg versus fulvestrant 500mg based on random-effects with informative priors are virtually identical to those based on the fixed-effect. However, the estimated HRs for OS for everolimus plus exemestane versus fulvestrant 500mg and exemestane versus fulvestrant 500mg based on the random-effects model with informative priors are higher (i.e., less favorable for these treatments compared with fulvestrant 500mg) than those based on the fixed-effect model.

Figure 29. Estimated HRs for OS for Treatments versus Fulvestrant 500mg Based on FP NMA with Fixed-effect and with Random-effects with Informative Priors

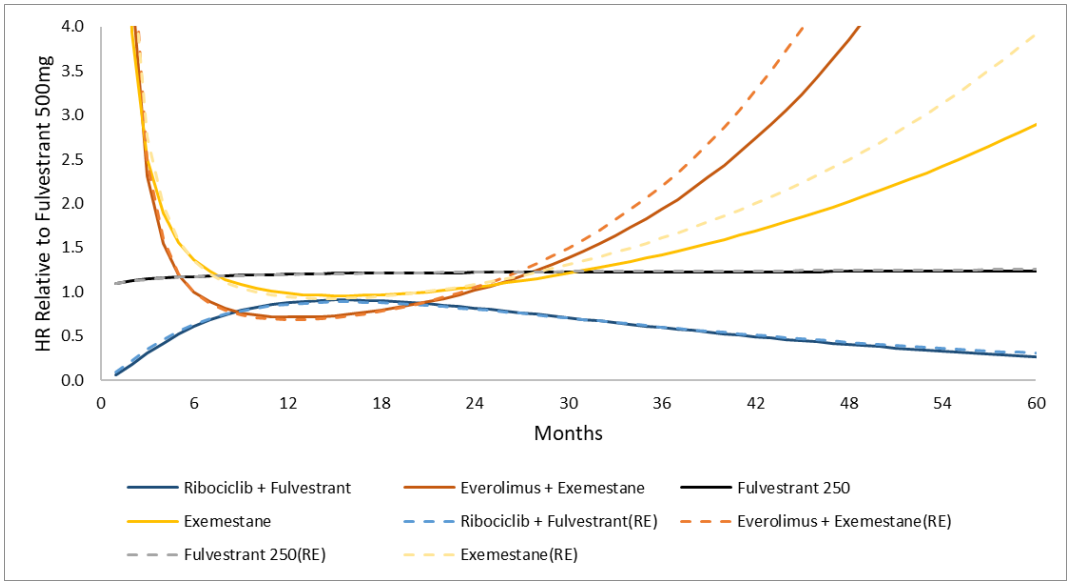
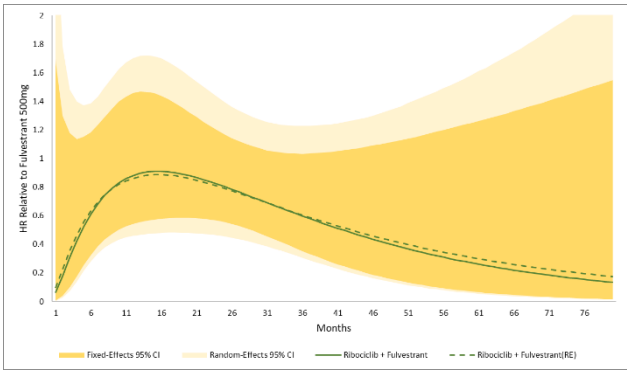
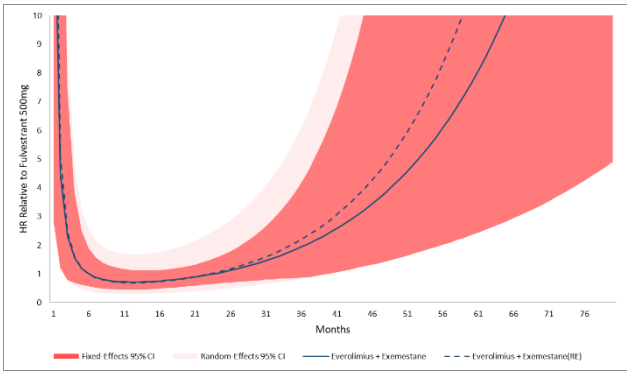


Figure 30. Estimated HRs and 95% CI for OS for Treatments versus Fulvestrant 500mg based on FP NMA with Fixed-effect and Random-effects with Informative Priors

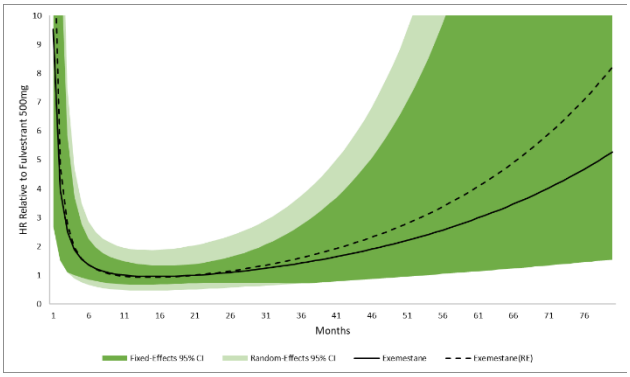
A. Ribociclib + Fulvestrant



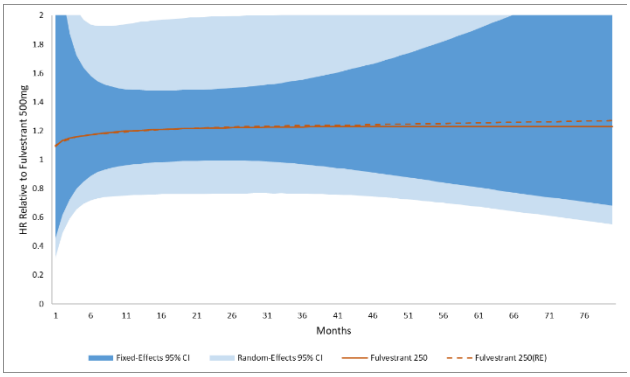
B. Everolimus + Exemestane



C. Exemestane



D. Fulvestrant 250mg



Due to time constraints, and again consistent with the ERG request during the Technical Engagement call on 24 November, coefficients for the other parameterisations of first and second order models (i.e., those other than p1 = 0.0 and p2 = 0.5) were generated using the frequentist approach so that all of the possible parametrisations could be implemented in the economic model. As stated above, the frequentist approach was used to validate results using the Bayesian approach, and it was determined that model coefficients for the two approaches are similar.

Based on a lack of evidence that the PH assumption was violated for OS based on assessment of Schoenfeld residuals and the long-term projected OS for ribociclib plus fulvestrant based on the FP NMA being inconsistent with clinical expert feedback, the Bucher method NMA for OS was used in the base case.

Table 19. Model Coefficients for FP NMA Models for OS Based on Frequentist Approach

p1*	p2*	Alpha0	Alpha1	Alpha2
Fulvestrant 500mg				
1st order, fixed effects				
-2	-	-3.8194	-4.0066	-
-1	-	-3.6676	-2.5027	-
-0.5	-	-3.2840	-2.2448	-
0	-	-4.9974	0.3974	-
0.5	-	-4.8550	0.2242	-
2nd Order, fixed effects				
-2	-2	-3.6816	6.3706	-14.3999
-2	-1	-3.4689	8.7784	-6.5474
-2	-0.5	-3.0135	3.8213	-3.5119
-2	0	-5.1930	1.3102	0.4585
-2	0.5	-4.8367	-0.1647	0.2207
-2	1	-4.3664	-1.0939	0.0243
-1	-1	-3.2037	0.1615	-3.9568
-1	-0.5	-2.6423	5.3805	-6.4055
-1	0	-5.5957	1.4356	0.5656
-1	0.5	-4.8967	0.1236	0.2313
-1	1	-4.3203	-0.5366	0.0234
-0.5	-0.5	-1.8560	-2.1546	-2.2147
-0.5	0	-6.7708	2.4820	0.7927
-0.5	0.5	-5.0162	0.2593	0.2454
-0.5	1	-4.2077	-0.5018	0.0222
0	0	-4.4087	-0.1572	0.1142
0	0.5	-4.7999	-0.1147	0.2857
0	1	-4.6216	0.1211	0.0193
0.5	0.5	-4.5792	0.0466	0.0374
0.5	1	-4.7090	0.1443	0.0097
Everolimus plus Exemestane				
1st order, fixed effects				

p1*	p2*	Alpha0	Alpha1	Alpha2
-2	-	-3.9048	6.2141	-
-1	-	-3.8254	-0.1684	-
-0.5	-	-3.4832	-1.3880	-
0	-	-4.9418	0.3857	-
0.5	-	-5.0333	0.2711	-
2nd Order, fixed effects				
-2	-2	-3.5890	27.6593	-31.9908
-2	-1	-3.1324	32.2247	-14.0988
-2	-0.5	-2.1379	21.7457	-7.5977
-2	0	-6.9070	16.6902	1.0125
-2	0.5	-6.1938	13.8805	0.5054
-2	1	-5.1702	12.2122	0.0585
-1	-1	-2.2889	9.4558	-13.1780
-1	-0.5	-0.5067	25.8604	-20.6564
-1	0	-9.9224	12.7783	1.7998
-1	0.5	-7.7085	8.4662	0.7438
-1	1	-5.8963	6.3385	0.0778
-0.5	-0.5	2.8877	-0.4775	-9.9425
-0.5	0	-18.4503	19.1908	3.4125
-0.5	0.5	-10.7558	9.2550	1.0488
-0.5	1	-7.3239	5.9342	0.0973
0	0	-0.7379	-3.5027	0.8074
0	0.5	-3.7018	-3.0399	1.9622
0	1	-2.5481	-1.4175	0.1359
0.5	0.5	1.3873	-3.9454	0.9097
0.5	1	-1.6634	-1.6642	0.2503
Ribociclib plus Fulvestrant				
1st order, fixed effects				
-2	-	-4.0161	-20.5210	-
-1	-	-3.7916	-5.5993	-
-0.5	-	-3.3280	-3.4490	-
0	-	-5.5155	0.4581	-
0.5	-	-5.1339	0.2108	-
2nd Order, fixed effects				
-2	-2	-3.8486	35.1301	-39.7559
-2	-1	-3.7390	5.6856	-7.0226
-2	-0.5	-3.5203	-6.7381	-2.4470
-2	0	-4.7113	-12.5104	0.2177
-2	0.5	-4.3881	-15.6472	0.0747
-2	1	-4.1691	-17.5073	0.0060
-1	-1	-3.7759	-5.3677	-0.1900
-1	-0.5	-3.8522	-6.2934	0.4399
-1	0	-3.5117	-6.4275	-0.0766
-1	0.5	-3.5470	-6.4378	-0.0416
-1	1	-3.6248	-6.4211	-0.0051

p1*	p2*	Alpha0	Alpha1	Alpha2
-0.5	-0.5	-4.5334	-4.3913	2.1761
-0.5	0	-0.1505	-8.2628	-0.6836
-0.5	0.5	-1.8012	-6.0792	-0.1954
-0.5	1	-2.4885	-5.3429	-0.0171
0	0	-7.5191	2.0788	-0.3051
0	0.5	-6.3206	1.7580	-0.6624
0	1	-6.6089	1.1455	-0.0415
0.5	0.5	-8.8380	2.4796	-0.4669
0.5	1	-7.0747	1.2004	-0.1146

2.5 Ribociclib Monitoring Costs

As described in the CDF review submission document, a correction was implemented in the model that added ribociclib monitoring costs to all cycles. In Section 6.1 of the ERG report for the CDF review, the ERG states that monitoring costs for ribociclib should be incurred up to cycle 7 as this was based on the ribociclib licence and was accepted in the original submission. In recognition of the ERG's statement, the correction has been removed from the model. Accordingly, and consistent with the ERG's changes, cells HD18:534 on the MedCalc sheet were modified so that ribociclib monitoring costs were no longer applied after cycle 7 (monitoring costs in PFS that were not specific to ribociclib are still applied after cycle 7, this is consistent with the SmPC).

2.6 Key Model Assumptions and Inputs

The main model inputs and assumptions have been described in the CDF review submission. Key model assumptions that have been changed in the revised model are summarised in Table 20, indicating where these have been changed since the CDF review submission.

Table 20. Changes in the Revised Base Case

Assumption	Original Assumption	Updated Assumption	Rationale
Modelling approach	STM	PSM	OS data based on the 3 June 2019 data cut-off of MONALEESA-3 were more mature than the data previously reported for the November 2017 data cut-off. The PSM approach allows for OS to be modelled directly, rather than assuming surrogacy where OS gains are equal to PFS gains.
PFS probabilities	Bucher Method ITC	FP NMA with time-varying hazard functions	The PH assumption was violated for PFS in BOLERO-2. As such, an NMA with hazards characterised

Assumption	Original Assumption	Updated Assumption	Rationale
			as FP, which allows for modelling of time-varying HRs, was performed to account for this uncertainty. Different parametrisations were explored, including fixed-effect and random-effects with informative priors. The fixed-effect model was utilised based on the DIC, visual comparison of estimated survival distributions with KM PFS from MONALEESA-3, and the fact that the HRs based on the random-effects model were virtually identical to those based on the fixed-effect (i.e., the impact in the economic model would be minimal).
OS for ribociclib plus fulvestrant	The STM approach used surrogacy for PFS and OS, whereby estimated PFS benefits for ribociclib plus fulvestrant corresponded to equivalent gains in OS.	Weibull (R) parametric distribution fit to data on OS for ribociclib plus fulvestrant from Group B in MONALEESA-3.	Use of the PSM approach allowed for modelling of OS for ribociclib plus fulvestrant directly by fitting parametric distributions to data on OS from MONALEESA-3. This accounts for potential uncertainty associated with the surrogacy assumption for PFS and OS with the semi-Markov model. The chosen distribution, the Weibull (R), had the best statistical fit, excellent visual fit, and was validated by clinical experts.
OS for everolimus plus exemestane	N/A	An ITC based on the Bucher method was performed to estimate the relative treatment effect expressed as a HR for everolimus plus exemestane versus ribociclib plus fulvestrant. The estimated HR for OS for everolimus plus exemestane was then applied to the	Assessment of the PH assumption for OS based on Schoenfeld residuals revealed that the PH assumption appeared to be appropriate for all of the trials contributing to the evidence network for the NMA. An FP NMA of OS was explored but estimated landmark OS at 10 years for ribociclib plus fulvestrant based on this approach greatly exceeded the

Assumption	Original Assumption	Updated Assumption	Rationale
		estimated OS curve for ribociclib plus fulvestrant.	estimated landmark OS that clinical experts advised was reasonable based on the Weibull (R) distribution fit directly to data on OS for ribociclib plus fulvestrant in MONALEESA-3. Additionally, projected OS for everolimus plus exemestane based on the FP NMA was lower than that for exemestane alone, which did not reflect the findings of the BOLERO-2 trial.
TTD for ribociclib and fulvestrant	RCS lognormal (U)	RCS 3 log-logistic (U)	We explored 3-knot spline models fit to TTD as suggested by the ERG. The 3-knot RCS log-logistic (U) model had the best visual fit to the TTD curves, and therefore was used in the revised base case.
TTD for everolimus	Received until progression	Assumed that 80% discontinue treatment at month 6, 70% of patients remaining on treatment receive 5mg daily, the remaining patients receive 10mg daily.	The ERG's preferred assumptions for TTD and dose reductions of everolimus were used. Estimation of TTD separately for everolimus and exemestane was not feasible.
Ribociclib plus fulvestrant monitoring costs	A "fix" was applied to ribociclib monitoring costs that resulted in costs of healthcare services for monitoring of patients on ribociclib to extend beyond cycle 7.	The "fix" was removed, resulting in ribociclib monitoring costs to no longer be applied after cycle 7.	As described in the ERG report, it was agreed that ribociclib monitoring costs would continue only until cycle 7 (consistent with the SmPC).
Everolimus plus exemestane health state utility value in PFS	PFS off-treatment utility value was applied when patients were not receiving everolimus or exemestane.	PFS off-treatment utility value is applied when patients discontinue everolimus, even if they continue to receive exemestane.	The health state utility value for PFS off-treatment was estimated to be greater than that for PFS on-treatment. Everolimus is associated with toxicities that may impact patients' QOL. Therefore, if everolimus is discontinued, QOL for these patients might be expected to improve. Any

Assumption	Original Assumption	Updated Assumption	Rationale
			effects on utility are likely to be small.

3 ECONOMIC MODEL RESULTS

3.1 Partitioned Survival Model

The revised base case was estimated based on the assumptions outlined in Table 20. The impact on the ICER from changing these assumptions is described in the APPENDIX. Total costs with ribociclib plus fulvestrant were estimated to be [redacted] compared with [redacted] for everolimus plus exemestane (incremental £17,628). Total QALYs for ribociclib plus fulvestrant were estimated to be 2.72 compared with 2.17 for everolimus plus exemestane (incremental QALY gain of 0.55). The ICER for ribociclib plus fulvestrant was therefore estimated to be £32,074 per QALY gained compared with everolimus plus exemestane. The base case model results are summarized in Table 21.

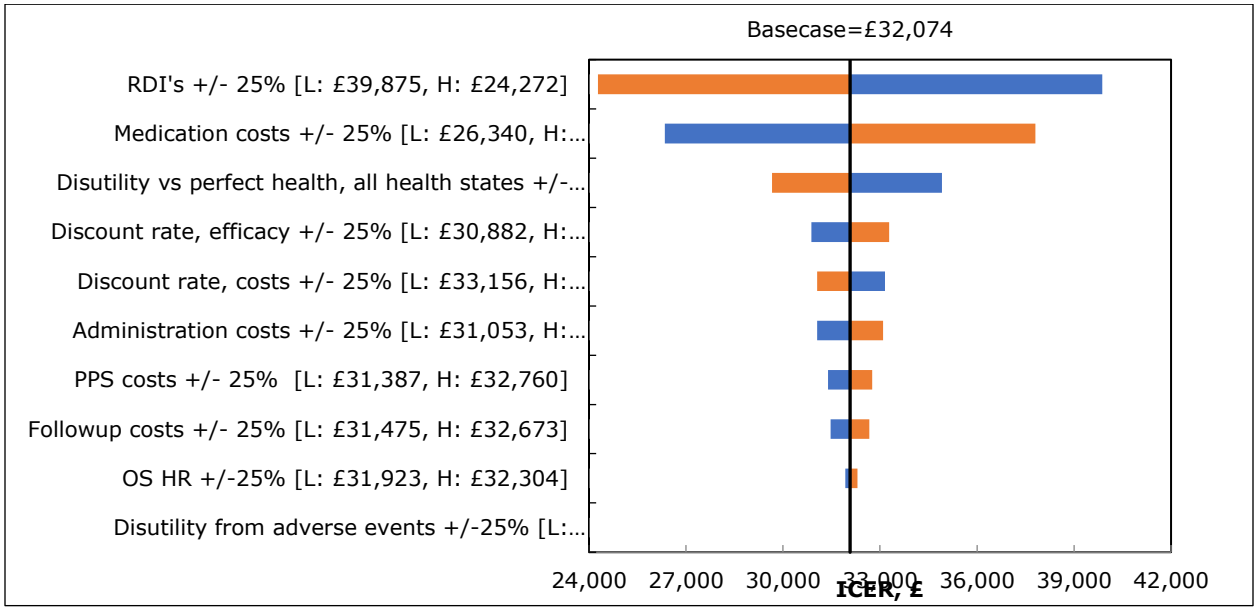
Table 21. Cost-Effectiveness Results for Revised Base Case Based on the PSM

Comparator	Costs, (£)	Life-years (LYs)	QALYs	ΔCosts, (£)	ΔLYs	ΔQALYs	ICER (QALY)
Ribociclib + Fulvestrant	[redacted]	3.76	2.72				
Everolimus + Exemestane	[redacted]	3.02	2.17	17,628	0.75	0.55	32,074

3.1.1 Deterministic Sensitivity Analyses

Model results of varying input parameters by +/-25% of the base case value are displayed as a tornado diagram in Figure 31. The model is most sensitive to varying RDIs for all medications, followed by the medication costs, and the disutility versus perfect health for all health states. The model is more sensitive to variation of the RDIs than medication costs because the dosing for ribociclib is based on the average dose received over time, and therefore is held constant when the former parameters are varied.

Figure 31. Tornado Diagram of One-Way Sensitivity Analyses Based on the PSM



3.1.2 Scenario Analyses

Alternative assumptions for key parameters in the model were explored in scenario analyses. Alternative time horizons of 5, 10, and 20 years (base case assumption = 40 years), utility values estimated based on EQ-5D-5L (base case used EQ-5D-3L), use of a Bucher method for the NMA of PFS (revised base case used an FP NMA), and alternative parametric distributions fit to data on OS and TTD from MONALEESA-3 yielded ICERs that were generally consistent with the base case. If TTD and dose adjustments for everolimus are not considered, the ICER is estimated to be £24,491.

Table 22. Results of Scenario Analyses Based on the PSM

Scenario	ICER (£ per QALY gained) Ribociclib plus Fulvestrant versus Everolimus plus Exemestane
Base case	**32,074**
Timeframe - 5 years	33,446
Timeframe - 10 years	32,003
Timeframe - 20 years	32,073
EQ-5D-5L utility values	29,356
Lloyd et, al. PPS utility values	33,047
Fulvestrant generic - discount 20%	29,852
Fulvestrant generic - discount 30%	27,630

Scenario	ICER (£ per QALY gained) Ribociclib plus Fulvestrant versus Everolimus plus Exemestane
Fulvestrant generic - discount 40%	25,409
Fulvestrant generic - discount 50%	23,187
Fulvestrant generic - discount 60%	20,965
Fulvestrant no discount to list price	34,295
Single health state utility value for PFS	32,177
Everolimus dose based on BOLERO-2 data	33,434
No TTD or dose reduction for Everolimus	24,491
PAIC of PFS MONALEESA-3 vs. BOLERO-2	28,952
Bucher NMA of PFS with RCS Weibull (R)	42,259
Bucher NMA of PFS with RCS 3 Log-logistic (R)	40,787
Bucher NMA of PFS with RCS 3 Lognormal	40,741
Bucher NMA of PFS with RCS 3 Weibull (R)	40,453
Bucher NMA of PFS with RCS 3 Weibull (R), anchored on fulvestrant PFS	40,452
Bucher NMA of PFS with RCS 3 Weibull (R), no TTD or down-dosing for Everolimus	26,161
OS Log-Logistic (R)	31,996
OS Gompertz (R)	33,218
OS Weibull (U)	32,138
FP NMA of OS	31,123
FP NMA of OS, no TTD or dose reduction of everolimus	29,491
TTD Ribo + Fulvestrant Gompertz (U)	32,604
TTD Ribo + Fulvestrant RCS Lognormal (U)	32,252
TTD Ribo Gen. Gamm (U)	32,099
TTD Ribo RCS Weibull (U)	31,740
TTD Ribo RCS Log-Logistic (U)	32,900
TTD Ful Gen. Gamma (U)	32,042
TTD Ful RCS Weibull (U)	31,505
TTD Ful RCS Log-logistic (U)	32,387
KM PFS for 42 months followed by FP NMA	31,868

3.1.3 Probabilistic Sensitivity Analyses

Probabilistic analyses (PSAs) were generated by simultaneously sampling from estimated probability distributions of model parameters. For selected parameters derived from MONALEESA-3 (i.e., survival parameter distributions for TTD and OS as well as distributions of events by type) the model samples from the joint bootstrap distributions for these parameter estimates that were derived from bootstrap samples of data from the MONALEESA-3 trial. For the PFS distributions estimated based on the FP NMA of PFS, model coefficients used to calculate the survival curves were chosen at random from among the 50,000 MCMC simulations.

For each simulation, expected costs and QALYs were calculated for each comparator, along with the differences between comparators in expected costs and QALYs. Descriptive statistics were generated based on the simulated values for costs, QALYs, incremental costs, and incremental QALYs. Ninety-five percent credible intervals were calculated for these outcomes based on the 2.5 and 97.5 percentiles of the simulations. The probabilistic ICER was calculated based on the ratio of the mean incremental cost to the mean incremental QALYs.

Based on 1,000 PSA simulations, total costs with ribociclib plus fulvestrant were estimated to be [redacted] compared with [redacted] for everolimus plus exemestane (incremental £16,297). Total QALYs for ribociclib plus fulvestrant were estimated to be 2.72 compared with 2.16 for everolimus plus exemestane (incremental QALY gain of 0.56). The ICER for ribociclib plus fulvestrant was therefore estimated to be £29,570 per QALY gained compared with everolimus plus exemestane.

Table 23. Mean Cost-Effectiveness Results from 1,000 PSA Simulations Based on the PSM

Comparator	Costs, (£)	Life-years (LYs)	QALYs	ΔCosts, (£)	ΔLYs	ΔQALYs	ICER (QALY)
Ribociclib + Fulvestrant	[redacted]	3.76	2.72				
Everolimus + Exemestane	[redacted]	3.01	2.16	16,297	0.75	0.56	29,570

In general, the probabilistic mean ICER (£29,570) was consistent with the deterministic ICER (£32,074). A scatter plot of PSA simulations is displayed in Figure 32 along with a comparison of the mean probabilistic ICER and deterministic ICER. The acceptability curve (Figure 33) shows that ribociclib plus fulvestrant is more likely to be cost effective compared with everolimus plus exemestane at willingness-to-pay thresholds of £30,000 per QALY or greater.

Figure 32. Scatter Plot of PSA Simulations for Ribociclib plus Fulvestrant versus Everolimus plus Exemestane Based on the PSM

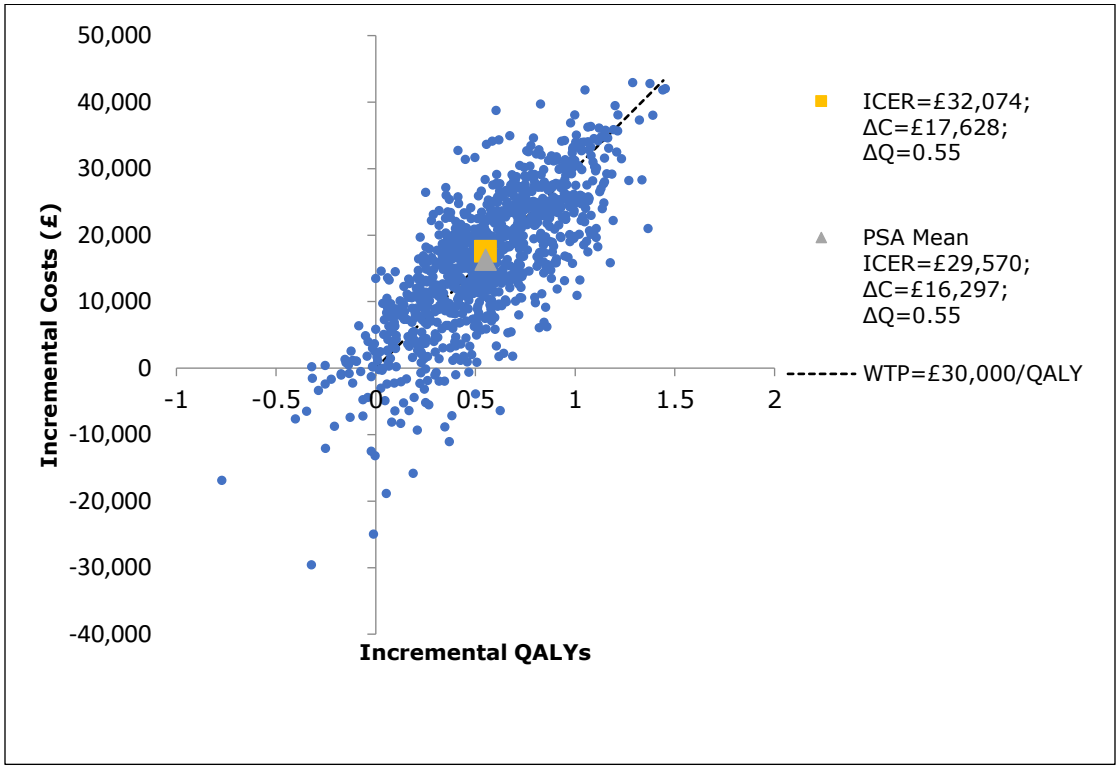
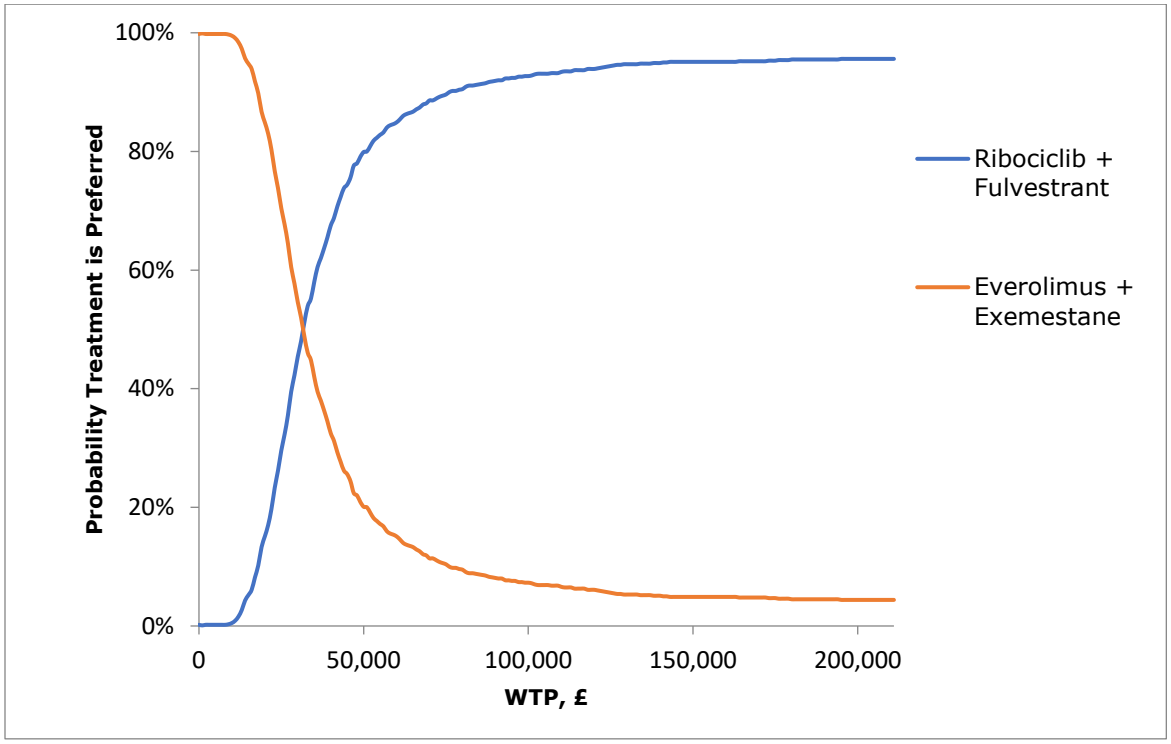


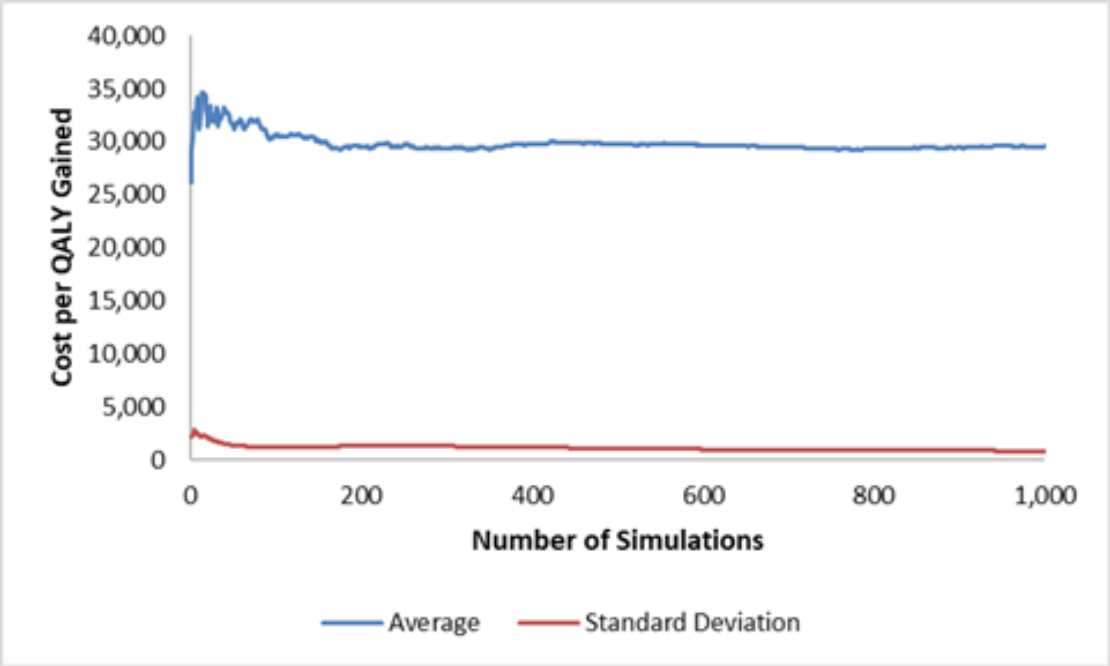
Figure 33. Cost-Effectiveness Acceptability Curve Based on the PSM



3.1.3.1 Test of Convergence of the Probabilistic Analyses

A test of convergence of the mean ICER based on simulations of the probabilistic analyses (PA) using the PSM approach is provided in Figure 34. Analyses of the mean ICER by number of simulations indicates that the PA was virtually unchanged after approximately 200 simulations. The standard deviation of the mean ICER by number of PA simulations is relatively flat after approximately 100 simulations. This would suggest that the 1,000 simulations performed for the PA are adequate.

Figure 34. Plot of PA Mean and Standard Deviation ICER for Ribociclib plus Fulvestrant vs. Everolimus plus Exemestane by Number of Simulations Based on the PSM



3.2 Semi-Markov STM

The semi-Markov STM approach was evaluated based on the FP NMA for PFS with all other assumptions unchanged from the CDF review submission document [11]. Total costs with ribociclib plus fulvestrant were estimated to be [redacted] compared with [redacted] for everolimus plus exemestane (incremental £16,168). Total QALYs for ribociclib plus fulvestrant were estimated to be 2.69 compared with 2.20 for everolimus plus exemestane (incremental QALY gain of 0.50). The ICER for ribociclib plus fulvestrant was therefore estimated to be £32,496 per QALY gained compared with everolimus plus exemestane. This result is similar to that obtained with the PSM .

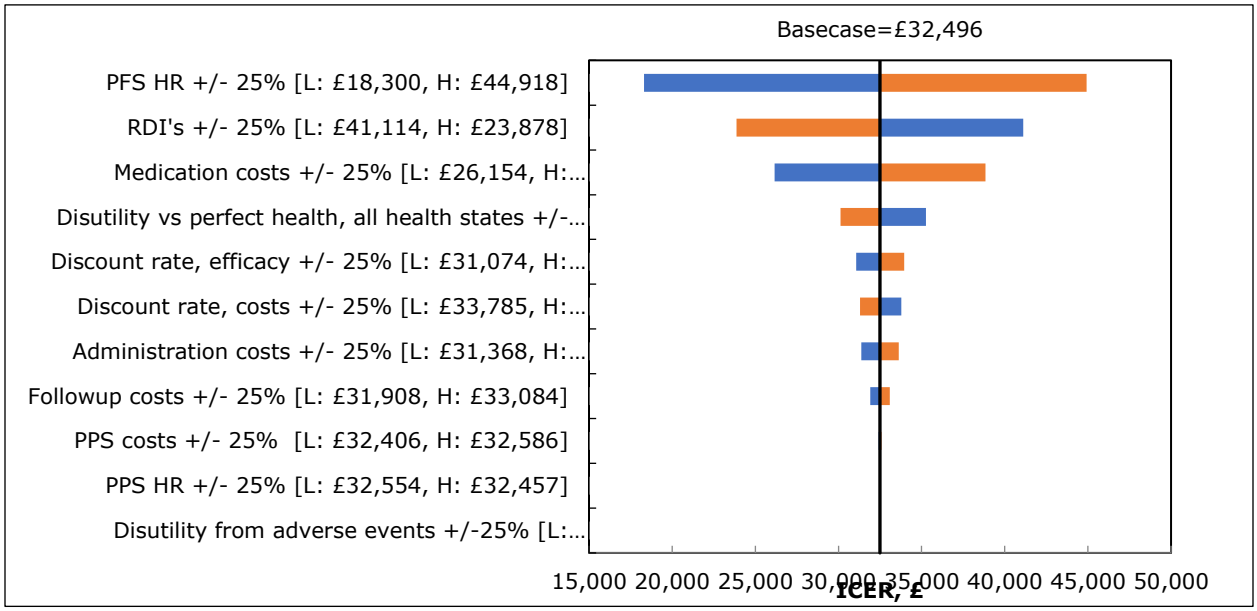
Table 24. Cost-Effectiveness Results for Revised Base Case with STM

Comparator	Costs, (£)	Life-years (LYs)	QALYs	ΔCosts, (£)	ΔLYs	ΔQALYs	ICER (QALY)
Ribociclib + Fulvestrant	[redacted]	3.73	2.69				
Everolimus + Exemestane	[redacted]	3.05	2.20	16,168	0.67	0.50	32,496

3.2.1 Deterministic Sensitivity Analyses

Model results of varying input parameters by +/-25% of the base case value are displayed as a tornado diagram in Figure 35. The model is most sensitive to varying the hazard rates in PFS, followed by the RDIs for all medications, and the medications costs.

Figure 35. Tornado Diagram of One-Way Sensitivity Analyses Based on the STM



3.2.2 Scenario Analyses

Results of scenario analyses with the STM are shown in Table 25.

Table 25. Results of Scenario Analyses Based on the STM

Scenario	ICER (£ per QALY gained) Ribociclib plus Fulvestrant versus Everolimus plus Exemestane
Base case	32,496
Timeframe - 5 years	35,215
Timeframe - 10 years	32,425
Timeframe - 20 years	32,491
EQ-5D-5L utility values	29,759
Lloyd et, al. PPS utility values	32,622

Scenario	ICER (£ per QALY gained) Ribociclib plus Fulvestrant versus Everolimus plus Exemestane
PPS exponential	32,560
Fulvestrant generic - discount 20%	30,041
Fulvestrant generic - discount 30%	27,585
Fulvestrant generic - discount 40%	25,130
Fulvestrant generic - discount 50%	22,674
Fulvestrant generic - discount 60%	20,218
Fulvestrant no discount to list price	34,952
PPS curves estimated with data from BOLERO-2	32,162
Everolimus dose based on BOLERO-2 data	33,998
No TTD or dose reduction for Everolimus	24,124
PAIC of PFS MONALEESA-3 vs. BOLERO-2	29,008
Bucher NMA of PFS with RCS Weibull (R)	122,726
Bucher NMA of PFS with RCS 3 Log-logistic (R)	110,013
Bucher NMA of PFS with RCS 3 Lognormal	119,462
Bucher NMA of PFS with RCS 3 Weibull (R)	117,285
Bucher NMA of PFS with RCS 3 Weibull (R), anchored on fulvestrant PFS	117,192
Bucher NMA of PFS with RCS 3 Weibull (R), no TTD or down-dosing for Everolimus	13,967
TTD Ribo + Fulvestrant Gompertz (U)	33,082
TTD Ribo + Fulvestrant RCS Lognormal (U)	32,693
TTD Ribo Gen. Gamm (U)	32,525
TTD Ribo RCS Weibull (U)	32,127
TTD Ribo RCS Log-Logistic (U)	33,410
TTD Ful Gen. Gamma (U)	32,461
TTD Ful RCS Weibull (U)	31,867
TTD Ful RCS Log-logistic (U)	32,843
KM PFS for 42 months followed by FP NMA	32,223

3.2.3 Probabilistic Sensitivity Analyses

Based on 1,000 PSA simulations, total costs with ribociclib plus fulvestrant were estimated to be [redacted] compared with [redacted] for everolimus plus exemestane (incremental £14,858). Total QALYs for ribociclib plus fulvestrant were estimated to be 2.71 compared with 2.20 for everolimus plus exemestane (incremental QALY gain of 0.51). The ICER for ribociclib plus fulvestrant was therefore estimated to be £29,141 per QALY gained compared with everolimus plus exemestane.

Table 26. Mean PSA Results for 1,000 PSA Simulations Based on the STM

Comparator	Costs, (£)	Life-years (LYs)	QALYs	ΔCosts, (£)	ΔLYs	ΔQALYs	ICER (QALY)
Ribociclib + Fulvestrant	[redacted]	3.76	2.71				
Everolimus + Exemestane	[redacted]	3.07	2.20	14,858	0.69	0.51	29,141

In general, the probabilistic mean ICER (£29,141) was consistent with the deterministic ICER (£32,496). A scatter plot of PSA simulations is displayed in Figure 36. The cost-effectiveness acceptability curve (Figure 37) shows that ribociclib plus fulvestrant is more likely to be cost effective compared with everolimus plus exemestane at willingness-to-pay thresholds of approximately £25,000 per QALY or greater.

Figure 36. Scatter Plot of PSA Simulations for Ribociclib plus Fulvestrant versus Everolimus plus Exemestane Based on the STM

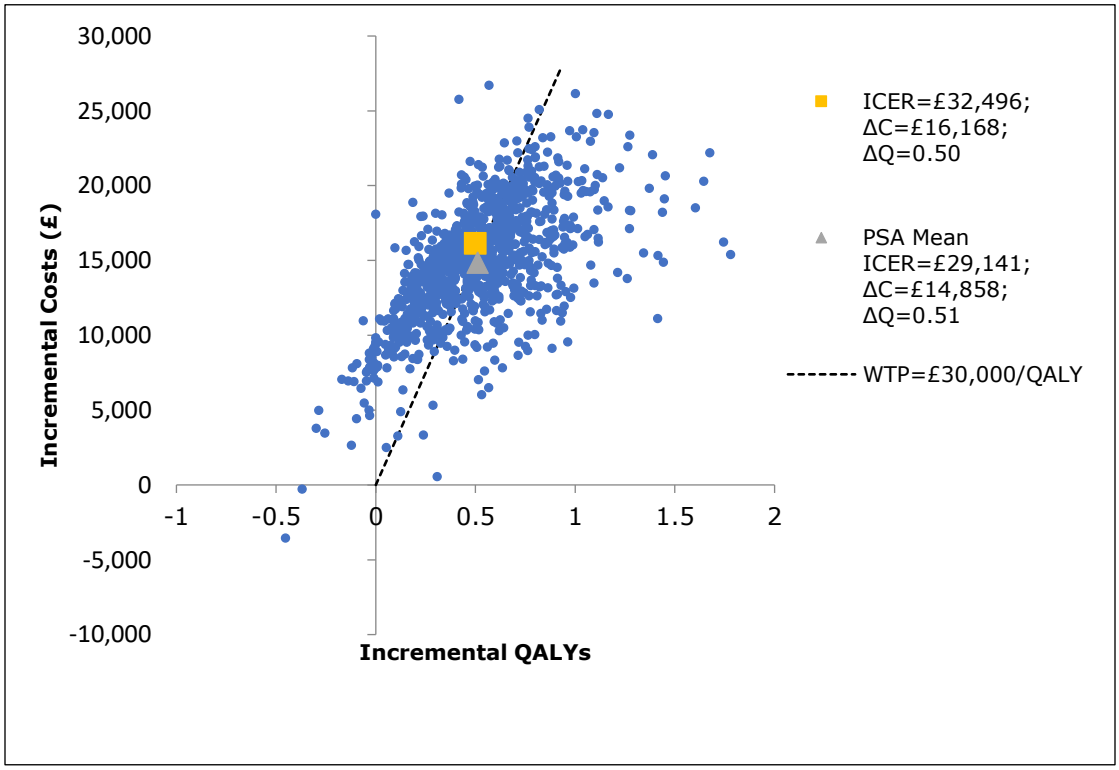
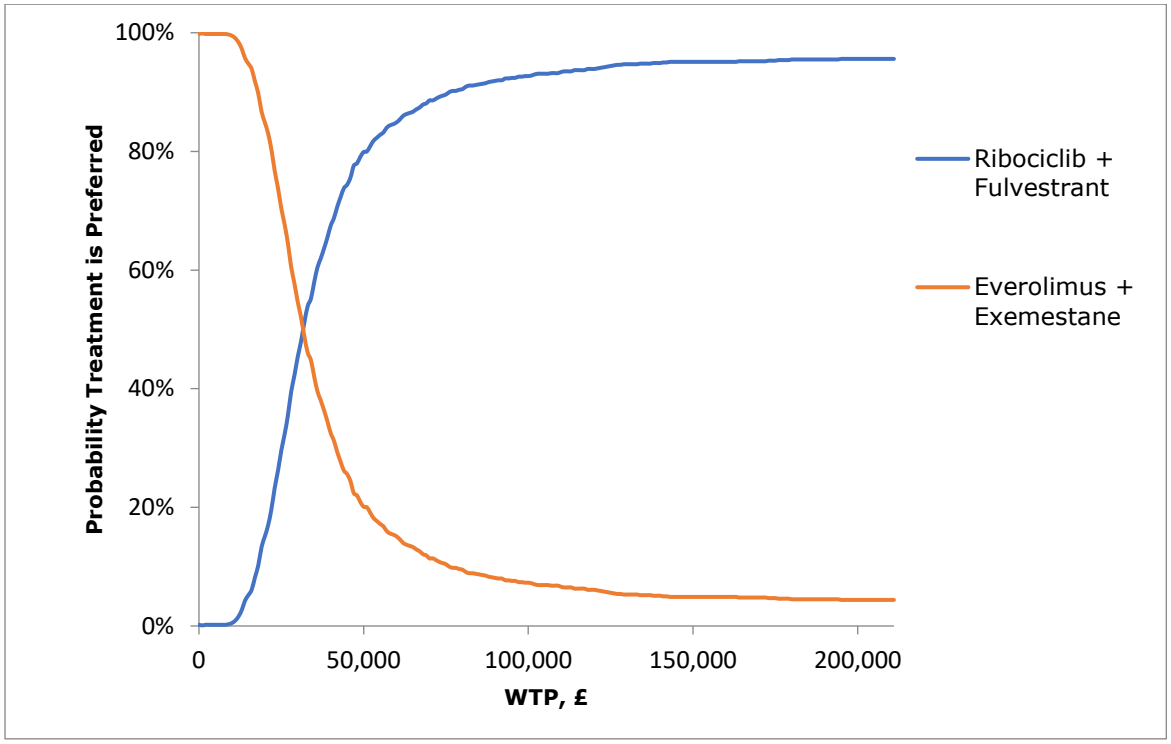


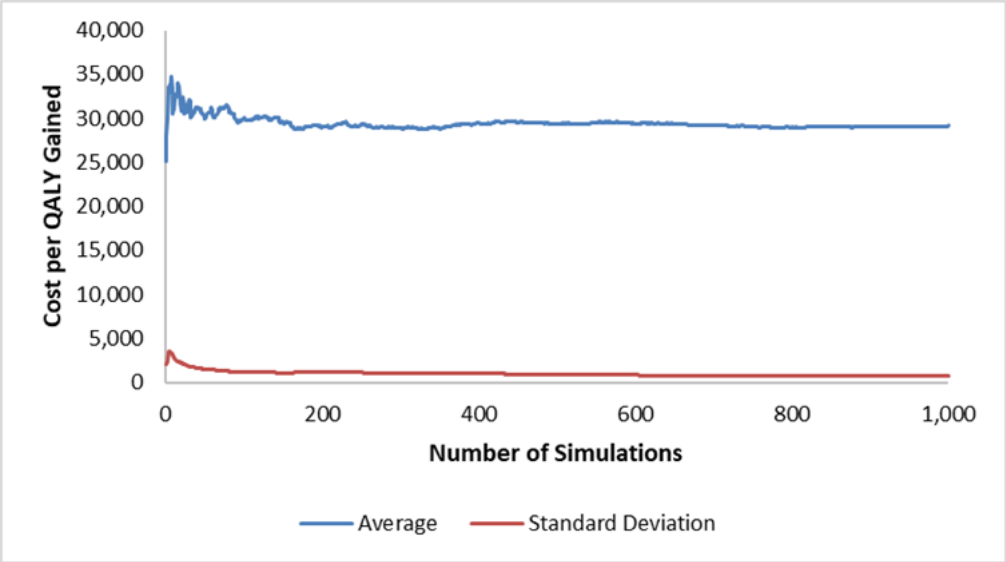
Figure 37. Cost-Effectiveness Acceptability Curve Based on the STM



3.2.3.1 Test of Convergence of Probabilistic analyses

A test of convergence of the mean ICER based on PA simulations using the semi-Markov STM is shown in Figure 38. Analyses of the mean ICER by number of simulations indicates that the PA was virtually unchanged after approximately 200 simulations. The standard deviation of the mean ICER by number of PA simulations is relatively flat after approximately 100 simulations. This would suggest that the 1,000 simulations performed for the PA are adequate.

Figure 38. Plot of PA Mean and Standard Deviation ICER for Ribociclib plus Fulvestrant vs. Everolimus plus Exemestane by Number of Simulations Based on the STM



3.3 Scenario 2: Cost-Effectiveness Analysis used at CDF Entry Incorporating Updated Clinical Analysis

Cost-effectiveness results generated by updating the CDF entry model based on the semi-Markov STM and which estimated PFS distributions based on a Bucher NMA with clinical data from the 3 June 2019 data cut along with model corrections was demonstrated in the CDF review submission document. If this analysis is further revised to utilise the FP NMA for PFS, ribociclib plus fulvestrant is expected to yield total costs of [redacted] compared with [redacted] for everolimus plus exemestane (incremental £9,998). Total QALYs with ribociclib plus fulvestrant are estimated to be 2.91 compared with 2.42 for everolimus plus exemestane (gain of 0.50). The ICER based on the STM is therefore estimated to be £20,158 for ribociclib plus fulvestrant versus everolimus plus exemestane.

Based on the PSM and FP NMA for PFS, ribociclib plus fulvestrant is expected to yield total costs of [redacted] compared with [redacted] for everolimus plus exemestane (incremental £11,437). Total QALYs with ribociclib plus fulvestrant are estimated to be 2.71 compared with 2.17 for everolimus plus exemestane (gain of 0.55). The ICER for ribociclib plus fulvestrant versus everolimus plus exemestane is therefore estimated to be £20,874 per QALY gained.

Table 27. Cost-Effectiveness Results for Analysis at CDF Entry Incorporating Updated Clinical Evidence

Comparator	Costs, (£)	Life-years	QALYs	ΔCosts, (£)	ΔLife-years	ΔQALYs	ICER (QALY)
STM Approach and FP NMA for PFS							
Ribociclib + Fulvestrant	[redacted]	4.07	2.91				
Everolimus + Exemestane	[redacted]	3.39	2.42	9,998	0.67	0.50	20,158
PSM Approach and FP NMA for PFS							
Ribociclib + Fulvestrant	[redacted]	3.76	2.71				
Everolimus + Exemestane	[redacted]	3.02	2.17	11,437	0.75	0.55	20,874

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APPENDIX

Impact of Changes to Key Model Assumptions on Model Results

Deterministic cost-effectiveness results presented in the original CDF review submission document were based on a semi-Markov state-transition model (STM) with PFS estimated using a Bucher method NMA. The revised base case modified those two key assumptions, as described above. This appendix provides an explanation of the impact on the ICER from changing both of these key assumptions as well as the combined impact on the ICER when the assumptions are employed together. As shown in Table 28, either of these changes have a relatively minor impact on the ICER.

Row 1 in the table shows the base case results presented by the company in the CDF review submission document. With a PAS of [redacted] for ribociclib and keeping all other assumptions unchanged results in an ICER of £16,644. Keeping the semi-Markov modelling approach but using the FP NMA to estimate survival distributions for PFS (Row 2 vs. Row 1) in lieu of the Bucher method results in a 3.7% reduction in total LYs for ribociclib plus fulvestrant (3.87 versus 3.73, respectively), a 3.7% reduction in QALYs (2.80 versus 2.69, respectively), and a 2.2% reduction in total costs ([redacted], respectively). For everolimus plus exemestane, total LYs are reduced by 18.9% (3.76 versus 3.05, respectively), total QALYs are reduced by 19.2% (2.71 versus 2.19, respectively), and total costs are reduced by 16.4% ([redacted] versus [redacted], respectively). Use of the FP NMA for PFS has a relatively minor impact on aggregate totals for LYS, QALYs, and costs for ribociclib plus fulvestrant compared with the Bucher method. LYs are slightly lower due to survival curve estimated based on the FP NMA for PFS being slightly below that for the RCS 3 Weibull (R) fit to PFS that is used with the semi-Markov approach (Table 4). However, the impact for everolimus plus exemestane is much greater. This is reflected by the projected hazards in PFS for everolimus plus exemestane based on the FP NMA, which are increasing over time (Figure 4). In contrast, the Bucher method assumes PH for everolimus plus exemestane versus ribociclib plus fulvestrant, which consequently would cause the slope of the projected hazard rates for everolimus plus exemestane to follow the same pattern as the slope of the hazards for ribociclib plus fulvestrant (i.e., decreasing). As such, estimated time in PFS (PFS LYs) for everolimus plus exemestane is lower with the FP NMA compared with the Bucher method. Costs and QALYs are similarly reduced as these outcomes are sensitive to changes in LYs.

Compared with the Row 1, if the Bucher method NMA for PFS is used but the modelling approach is changed from semi-Markov to a PSM (Row 7), the result is a 2.8% reduction in total LYs for ribociclib plus fulvestrant (3.87 versus 3.76, respectively), a 2.5% reduction in QALYs (2.80 versus 2.73, respectively), and a 2.6% reduction in total costs, ([redacted] versus [redacted], respectively). For everolimus plus exemestane, total LYs are reduced by 19.8% (3.76 versus 3.02, respectively), total QALYs are reduced by 18.7% (2.71 versus 2.21, respectively), and total costs are reduced by 19.0% ([redacted] versus [redacted] respectively). In general, total LYs, QALYs, and costs for ribociclib plus fulvestrant are similar for the PSM approach compared with the semi-Markov; small differences are observed because projected OS with the PSM based on the Weibull (R) fit directly to OS data from MONALEESA-3 is slightly lower than that based on

the semi-Markov, which relies on a surrogacy assumption for PFS and OS. For everolimus plus exemestane, total LYs with the PSM are lower as a consequence of the Bucher NMA of OS, which yields an estimated HR for OS for everolimus plus exemestane versus ribociclib plus fulvestrant of 1.43 (Table 16), or a 43% increase in the risk of death. Consequently, the OS curve for everolimus plus exemestane with this combination of assumptions is lower than with the semi-Markov approach, which assumes surrogacy between PFS and OS.

Table 28. Steps to Obtain Revised Base Case Cost-Effectiveness Results

Comparator	Costs, (£)	Life-years	QALYs	ΔCosts, (£)	ΔLife-years	ΔQALYs	ICER (QALY)
1. Semi-Markov model and Bucher Method NMA for PFS							
Ribociclib + Fulvestrant	[redacted]	3.87	2.80				
Everolimus + Exemestane	[redacted]	3.76	2.71	1,448	0.11	0.09	16,644
2. Semi-Markov model and FP NMA for PFS							
Ribociclib + Fulvestrant	[redacted]	3.73	2.69				
Everolimus + Exemestane	[redacted]	3.05	2.19	12,308	0.67	0.50	24,439
3. Semi-Markov model and Bucher Method NMA for PFS, remove 'fix' for ribociclib monitoring							
Ribociclib + Fulvestrant	[redacted]	3.87	2.80				
Everolimus + Exemestane	[redacted]	3.76	2.71	1,384	0.11	0.09	15,904
4. Semi-Markov model and Bucher Method NMA for PFS, RCS 3 Log-logistic distribution for ribociclib + fulvestrant TTD							
Ribociclib + Fulvestrant	[redacted]	3.87	2.80				

Everolimus + Exemestane	[redacted]	3.76	2.71	1,277	0.11	0.09	14,716
5. Semi-Markov model and Bucher Method NMA for PFS, TTD and dose reductions for everolimus based on clinician feedback							
Ribociclib + Fulvestrant	[redacted]	3.87	2.80				
Everolimus + Exemestane	[redacted]	3.76	2.72	9,097	0.11	0.08	120,061
6. Semi-Markov model and FP NMA for PFS, RCS 3 Log-logistic for ribociclib TTD, and everolimus TTD and down dosing based on clinician feedback*							
Ribociclib + Fulvestrant	[redacted]	3.73	2.69				
Everolimus + Exemestane	[redacted]	3.05	2.20	16,168	0.67	0.50	32,496
7. PSM and Bucher Method NMA for PFS							
Ribociclib + Fulvestrant	[redacted]	3.76	2.73				
Everolimus + Exemestane	[redacted]	3.02	2.21	13,916	0.75	0.52	26,618
8. PSM and FP NMA for PFS, RCS 3 Log-logistic for ribociclib TTD, and everolimus TTD and down dosing based on clinician feedback ()*							
Ribociclib + Fulvestrant	[redacted]	3.76	2.72				
Everolimus + Exemestane	[redacted]	3.02	2.17	17,628	0.75	0.55	32,074

* Deterministic Results

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer (ID3755)

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

About this Form

In **part 1** we are asking you to complete questions about living with or caring for a patient with the condition.

In **part 2** we are asking you to give your views on key issues in the Evidence Review Group (ERG) report that are likely to be discussed by the committee. An overview of the key issues are summarised in the executive summary at the beginning of the ERG report.

The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. In part 2 of this form we have included any of the issues raised by the ERG where we think having a patient perspective could help either:

- resolve any uncertainty that has been identified
  or
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.
-

In **part 3** we are asking you to provide 5 summary sentences on the main points contained in this document.

If you have any questions or need help with completing this form please email the public involvement team via pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please return this form by **5pm** on **Tuesday 1st December 2020**

Completing this form

Part 1 can be completed anytime. We advise that the final draft of part 2 is completed after the expert engagement teleconference (if you are attending/have attended). This teleconference will briefly summarise the key issues, any specific questions we would like you to answer and the type of information the committee would find useful.

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee. The text boxes will expand as you type.

Important information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 15 pages.

PART 1 – Living with or caring for a patient with hormone receptor-positive, HER2-negative advanced breast cancer and current treatment options	
About you	
1.Your name	**Holly Heath**
2. Are you (please tick all that apply):	☐ a patient with hormone receptor-positive, HER2-negative advanced breast cancer? ☐ a patient with experience of the treatment being evaluated? ☐ a carer of a patient with hormone receptor-positive, HER2-negative advanced breast cancer? ☒ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation.	Breast Cancer Now
4. Has your nominating organisation provided a submission? Please tick all options that apply.	☐ No, (please review all the questions below and provide answers where possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement

	☐ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience. ☐ I have other relevant knowledge/experience (e.g. I am drawing on others' experiences). Please specify what other experience: ☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
Living with the condition	
6. What is your experience of living with hormone receptor-positive, HER2-negative advanced breast cancer? If you are a carer (for someone with hormone receptor-positive, HER2-negative advanced breast cancer) please share your experience of caring for them.	

Current treatment of the condition in the NHS	
7a. What do you think of the current treatments and care available for hormone receptor-positive, HER2-negative advanced breast cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of **current NHS treatments** for hormone receptor-positive, HER2-negative advanced breast cancer (for example how everolimus plus exemestane is given or taken, side effects of treatment etc) please describe these.	
Advantages of this treatment	
9a. If there are advantages of ribociclib with fulvestrant over current treatments on the NHS please describe these. For example, the impact on your Quality of Life, your ability to continue work, education, self-care, and care for others?	

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does ribociclib with fulvestrant help to overcome/address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these.	
Disadvantages of this treatment	
10. If there are disadvantages of ribociclib with fulvestrant over current treatments on the NHS please describe these? For example, are there any risks with ribociclib with fulvestrant? If you are concerned about any potential side affects you have heard about, please describe them and explain why.	
Patient population	
11. Are there any groups of patients who might benefit more from ribociclib with fulvestrant or any	

who may benefit less? If so, please describe them and explain why. Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering hormone receptor-positive, HER2-negative advanced breast cancer and ribociclib with fulvestrant? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	

More information on how NICE deals with equalities issues can be found in the NICE equality scheme. More general information about the Equality Act and equalities issues can be found at https://www.gov.uk/government/publications/easy-read-the-equality-act-making-equality-real and https://www.gov.uk/discrimination-your-rights.	
Other issues	
13. Are there any other issues that you would like the committee to consider?	

PART 2 – Technical engagement questions for patient experts
Issues arising from technical engagement
We welcome your response to the questions below, but you do not have to answer every question. If you think an issue that is important to patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section. The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the patient organisation that nominated you has been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, these will also be considered by the committee.	
14a. **Key issue 1:** Maturity of overall survival (OS) data 14b. **Key issue 2:** Parametric survival distribution fitted to time to treatment discontinuation (TTD) data in MONALEESA-3 [Company's preferred unrestricted restricted cubic spline (RCS) lognormal vs ERG's preferred unrestricted Gompertz vs other 3-knot spline models] 14c. **Key issue 3:** Time to treatment discontinuation (TTD) assumptions for everolimus plus exemestane	We are aware through anecdotal evidence that given the adverse effects associated with everolimus such as mouth ulcers that the clinical use of this treatment combination can be limited in practice or patients may stop with everolimus soon after commencing treatment or experience a dose reduction. If people are unable to tolerate everolimus they may have exemestane monotherapy.

[For patients receiving everolimus plus exemestane, is treatment (in particular, everolimus) given until progression? If not, what proportion of patients stops taking treatment before progression? 20% or other? For patients who continue taking treatment until progression, is the dose the same? If not, what proportion continues having a reduced dose? What reduced dose is given to these patients?] 14d. **Key issue 4:** Including overall survival (OS) data in a partitioned survival model	

(preferred by ERG) rather than the company's semi-Markov model.	
15. Are there any important issues that have been missed in ERG report?	As set out in the technical engagement call in response to a question, it is crucial that a number of CDK 4/6 inhibitors are available given the different side effect profile. Having this choice is crucial for clinicians and patients and we now hope this treatment will be able to be approved for routine use on the NHS.

PART 3 -Key messages

16. In up to 5 sentences, please summarise the key messages of your statement:

- As set out in our patient organisation submission.
-
-
-
-

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

.....

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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Ribociclib with fulvestrant for treating hormone receptor-positive, HER2 negative advanced breast cancer [ID3755]

ERG response to technical engagement

December 2020

Source of funding

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 131562T.

1 Introduction

This document provides the Evidence Review Group's (ERG's) critique of the company's response to technical engagement (TE) for the appraisal of ribociclib with fulvestrant for treating hormone receptor-positive, HER2 negative advanced breast cancer [ID3755]. Each of the issues outlined in the TE report are discussed in further detail in Section 3. The company's updated base case analyses are outlined in Section 2 while the ERG's updated base case analyses are given in Section 4.

2 Company's revised cost-effectiveness results

In response to the TE report, the company presented updated base case analyses. The changes that have been made to the company's base case analyses include the model correction suggested by the ERG (including monitoring costs for ribociclib up to cycle 7) and some of the ERG's preferred assumptions or proposals in the main ERG report related to:

- The parametric survival distribution fitted to time to treatment discontinuation (TTD) data from MONALEESA-3 (Issue 2);
- TTD for everolimus plus exemestane (Issue 3);
- Including overall survival (OS) data in a partitioned survival model (PSM) rather than a semi-Markov state transition model (STM) (Issue 4).

Additionally, the company generated a fractional polynomial network meta-analysis (FP NMA) to account for the violation of proportional hazards (PH) for progression free survival (PFS) in BOLERO-2 (see additional Issue 1). The company's revised base case results for the PSM are presented in Table 1. The company also presented results revised base case using a STM which includes all other revised assumptions, these results can be found in Section 3.2 of the company's addendum.

As per the company's original Cancer Drugs Fund (CDF) review, 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. [redacted]. Results including this discount can be found in the confidential appendix.

Finally, results also include a simple patient access scheme (PAS) discount of [redacted] for ribociclib and [redacted] for everolimus (the marketing authorisation for everolimus is also held by Novartis).

Table 1. Company's revised base case results using the partitioned survival model (list price for fulvestrant)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
EVE+EXE	[redacted]	3.02	2.17	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.72	19,372	0.75	0.55	35,247

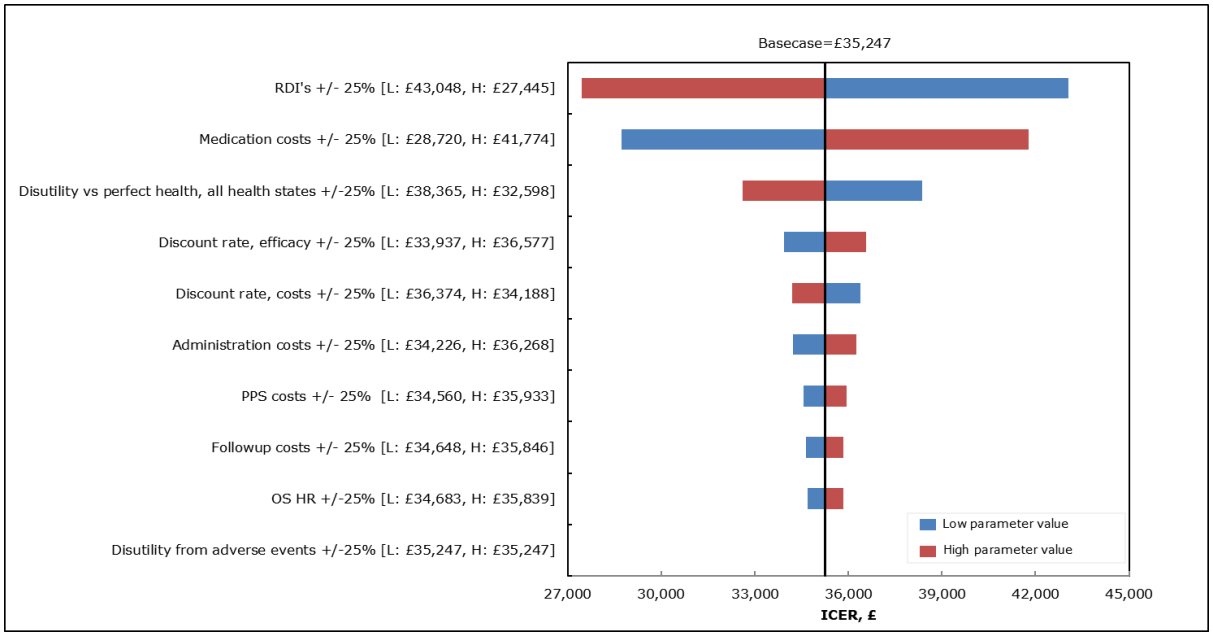
Abbreviations: EVE, everolimus; EXE, exemestane; FUL, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RIBO, ribociclib

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 1. Results of key scenario analyses conducted by the company are presented in Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

Table 2. The ERG considers it important to note that the company has not provided cost-effectiveness results using alternative FP NMA models for PFS. Furthermore, the company has not assessed the uncertainty around its preferred FP NMA model using any measure of uncertainty (e.g. sampling from the CODA for their estimation of the "alphas" specifying the FP curves produced by the NMA). Due to time constraints, the ERG has been unable to produce cost-effectiveness results for the alternative FP NMAs presented by the company. Cost-effectiveness results using the ERG's preferred FP NMAs are given in Section 4.

Figure 1. Results of the one-way sensitivity analysis using the partitioned survival model



Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

Table 2. Results of the scenario analysis based on the partitioned survival model

Scenario	ICER (£/QALY)
Base case	35,247
Timeframe - 5 years	38,309
Timeframe - 10 years	35,295
Timeframe - 20 years	35,247
EQ-5D-5L utility values	32,260
Lloyd *et al.* 2006 PPS utility values[1]	36,317
Fulvestrant generic - discount 20%	30,804
Fulvestrant generic - discount 30%	28,582
Fulvestrant generic - discount 40%	26,360
Fulvestrant generic - discount 50%	24,139
Fulvestrant generic - discount 60%	21,917
Fulvestrant no discount to list price	35,247

Single health state utility value for PFS	35,361
Everolimus dose based on BOLERO-2 data	36,607
No TTD or dose reduction for Everolimus	27,630
PAIC of PFS MONALEESA-3 vs BOLERO-2	32,143
Bucher NMA of PFS with RCS Weibull (R)	45,738
Bucher NMA of PFS with RCS 3 Log-logistic (R)	44,284
Bucher NMA of PFS with RCS 3 Lognormal	44,244
Bucher NMA of PFS with RCS 3 Weibull (R)	43,955
Bucher NMA of PFS with RCS 3 Weibull (R), anchored on fulvestrant PFS	43,954
Bucher NMA of PFS with RCS 3 Weibull (R), no TTD or down-dosing for Everolimus	29,593
OS Log-Logistic (R)	33,939
OS Gompertz (R)	37,361
OS Weibull (U)	35,406
FP NMA of OS	31,813
FP NMA of OS, no TTD or dose reduction of everolimus	30,179
TTD Ribo + Fulvestrant Gompertz (U)	35,793
TTD Ribo + Fulvestrant RCS Lognormal (U)	35,427
TTD Ribo Gen. Gamm (U)	35,274
TTD Ribo RCS Weibull (U)	34,904
TTD Ribo RCS Log-Logistic (U)	36,101
TTD Ful Gen. Gamma (U)	35,212
TTD Ful RCS Weibull (U)	34,624
TTD Ful RCS Log-logistic (U)	35,590
KM PFS for 42 months followed by FP NMA	35,033

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.

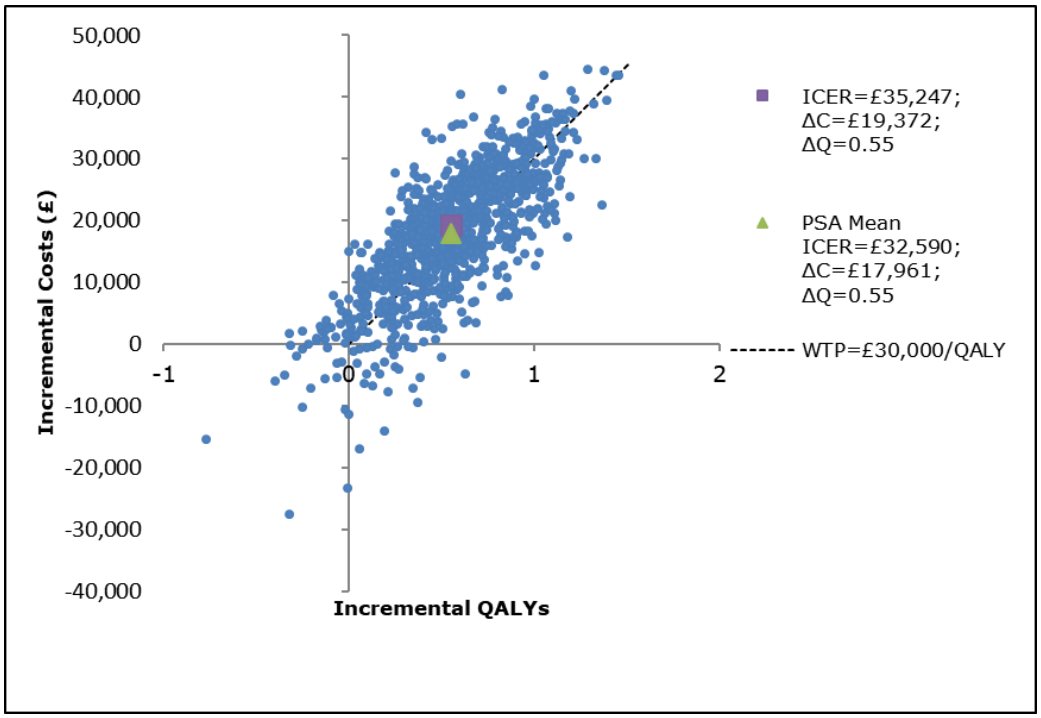
The company provided a probabilistic sensitivity analysis (PSA) based on 1,000 samples, to assess the impact of parameter uncertainty when all parameters are varied simultaneously in the economic model. For the PFS distributions estimated based on the FP NMA of PFS, model coefficients used to calculate the survival curves were chosen at random from among the 50,000 Markov chain Monte Carlo (MCMC) simulations. The results of the PSA (generated by the ERG) are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (Figure 2 and Figure 3, respectively) and summarised in Table 3.

Table 3. Probability sensitivity analysis based on the partitioned survival model

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
EVE+EXE	[redacted]	3.01	2.16	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.72	17,961	0.75	0.55	32,590

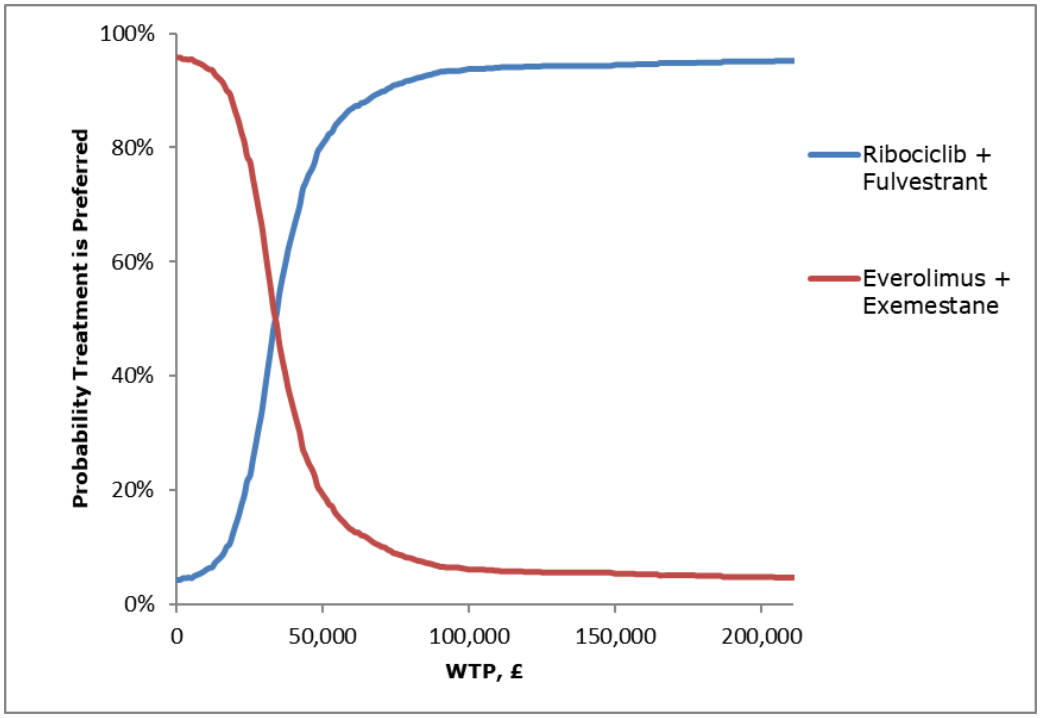
Abbreviations: EVE, everolimus; EXE, exemestane; FUL, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years; RIBO, ribociclib

Figure 2. Cost-effectiveness plane



Abbreviations: ΔC, incremental costs; ICER, incremental cost-effectiveness ratio; ΔQ, incremental QALY; QALY, quality-adjusted life year; WTP, willingness-to-pay

Figure 3. Cost-effectiveness acceptability curve



Abbreviations: WTP, willingness-to-pay

3 Key issues for engagement

3.1 Additional key issue: PH assumption violation for everolimus + exemestane (BOLERO-2) and subsequent use of a FP-NMA

As discussed in the ERG report, it is unclear if proportional hazards (PHs) assumptions hold for the progression-free survival (PFS) and overall survival (OS) Bucher method network meta-analyses (NMAs) presented in the company submission (CS). At the clarification stage, the company highlighted that they were exploring alternative methods for estimating time dependent hazard ratios (HRs), and in response to the technical engagement report, the company reported that they would conduct fractional polynomial (FP) NMAs. This is in line with the committee's preferred assumptions for this Cancer Drugs Fund (CDF) review (i.e., to explore the most appropriate methods of comparing PFS and OS).

The company reported that the results of the FP NMA for OS were not clinically plausible compared to the Weibull (R) distribution fit and that projected OS for everolimus plus exemestane based on the FP NMA was lower than that for exemestane alone, which did not reflect the findings of the BOLERO-2 trial. Due to time constraints, the ERG has been unable to validate the FP NMA for OS. Nonetheless, the ERG maintains that while there may have been some uncertainty around the PHs for OS, there was not clear evidence to suggest a violation of the PH assumptions and so it would not be unreasonable to use the Bucher NMA results for OS in the economic model. Conversely, the Bucher method NMA for PFS showed a clearer violation of proportional hazard assumptions, with a statistically significant finding on the test of linearity for BOLERO-2. Hereafter the ERG focuses on a critique and validation of the FP NMA provided by the company for PFS.

3.1.1 Methods

The company based their methods for the FP NMA on those described by Chapter 10 of Dias *et al.* 2018[2] and Jansen 2011.[3] More details of the methods are provided in the company addendum, Section 2.1. The network for PFS was identical to the original network in the company submission (see Figure 4).

Figure 4. Evidence Network for NMA of PFS for Treatments of HR+/HER2- advanced breast cancer (reproduced from company addendum, Figure 1)

Overall, the ERG considers the company's methodology to be generally appropriate, with the key aspects of the company's approach being:

- The data used in the FP NMA were based on individual patient failure-time data for MONALEESA-3[4] and BOLERO-2[5] trials. For the CONFIRM[6], EFECT[7] and SoFEA[8] trials, published Kaplan-Meier (KM) survival curves were digitised and reconstructed failure time data were generated. The survival data were organised by monthly time intervals where possible, but with longer intervals if needed to ensure at least 1 event within each interval.

- The model was performed with 2 chains, with 50,000 burn-in iterations for PFS and 50,000 simulations for each chain. Convergence of the models were assessed with Gelman Rubin Statistics.
- The company considered both FPs of 1st and 2nd order using fixed effect models, testing p1 and p2 combinations of 0.5, 0, -0.5, -1 and -2. The company selected the model with the best statistical fit based on the DIC values, and also explored the corresponding random effects model for the best statistical fit.

The ERG agrees with the company's decision to focus on fixed-effect models, given that the NMA consists of a linear network predominantly connected by single trials, and so data on possible between-study heterogeneity is limited.

The ERG notes that the company included in the NMA informative priors for the chosen baseline treatment (fulvestrant 500mg) with no further explanation. The ERG is concerned about this because:

- It is not part of the methodology described by Jansen 2011;[3]

- While the use of informative priors may be reasonable in some circumstances, the challenges in justifying their use means that "standard practice" is to use uninformed or "vague" priors;
- The company uses the fulvestrant 500mg data from MONALEESA-3[4] as the source of the informed priors which is inappropriate since MONALEESA-3 is part of the dataset informing the analysis – this could result in a form of confirmation bias (i.e. the resulting FP curves may be constrained to be the best fit for MONALEESA-3 but not the "average" best fit for all of the data included in the analysis).

The company also provided a sensitivity analysis of the random-effects model results using informative priors based on estimated predictive distributions from Turner *et al.* 2012.[9] However, the study cited only provided estimations for within pairwise meta-analysis comparisons, and the ERG considers it inappropriate to use these distributions to estimate between-study heterogeneity in the company's NMA.

Due to the uncertainty surrounding the company's use of priors, the ERG decided to run its own analyses using the code from Jansen 2011[3] with no informed priors. A comparison of the results of the company's model with informative priors and the ERG's with uninformed priors is described below. The ERG also reran and independently validated the company's model and results.

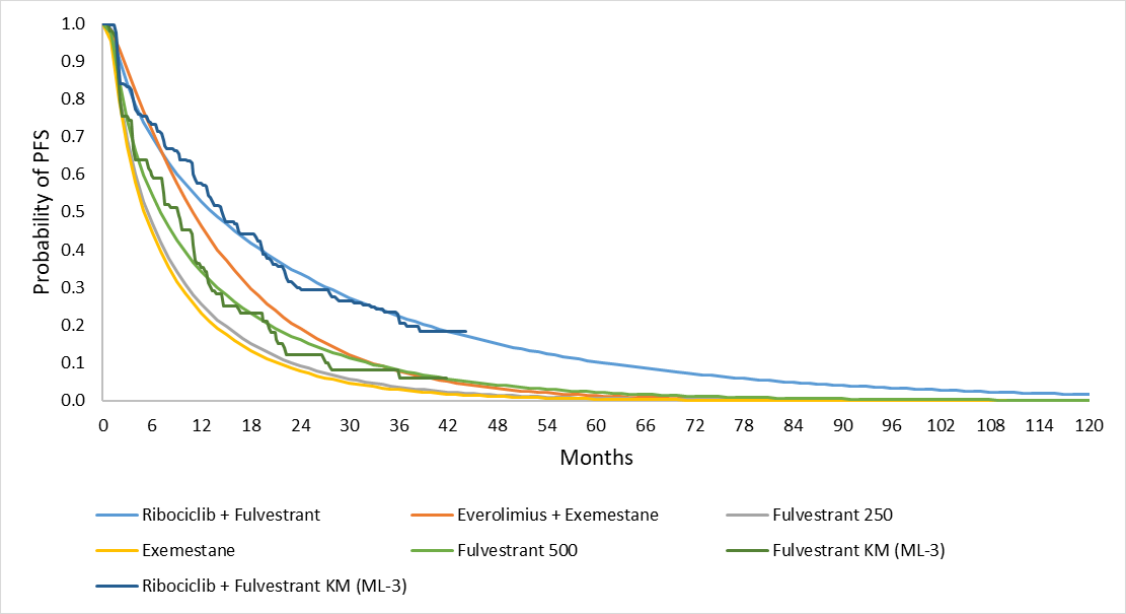
3.1.2 Results

Among the models that were indistinguishable from each other in terms of statistical fit (i.e., within 5 DIC from the best statistical fit) and were considered clinically plausible, the company reported that the 2nd order, fixed effect (FE) models p1 = −2 and p2 = −1 showed best fit for PFS (DIC 1,536). Conversely, based on the ERG's NMA, the best 1st order statistical fit was p1=-4 (DIC 1,756), and the best 2nd order statistical fit was p1=−2, p2=0 (DIC 1,572).

The fitted PFS curves generated from each model were superimposed on the trial Kaplan-Meier data to observe the visual fit of trial data versus modelled data. The company's selected model appeared to be a good fit for both ribociclib plus fulvestrant and fulvestrant 500mg (Figure 5), yet not for the key comparator, everolimus plus exemestane. The ERG considers that a good visual fit for fulvestrant 500mg would be expected, given that data from this treatment arm was used to inform the prior, and that this would naturally lead to a good fit for ribociclib plus fulvestrant. The ERG also considers there to be a large amount of uncertainty in the estimates of PFS, whereby the 95% credible intervals for ribociclib plus fulvestrant versus everolimus plus exemestane overlap (Abbreviations: FP NMA, fractional polynomial network meta-analysis; KM, Kaplan-Meier; ML-3, MONALEESA-3; PFS, progression free survival.

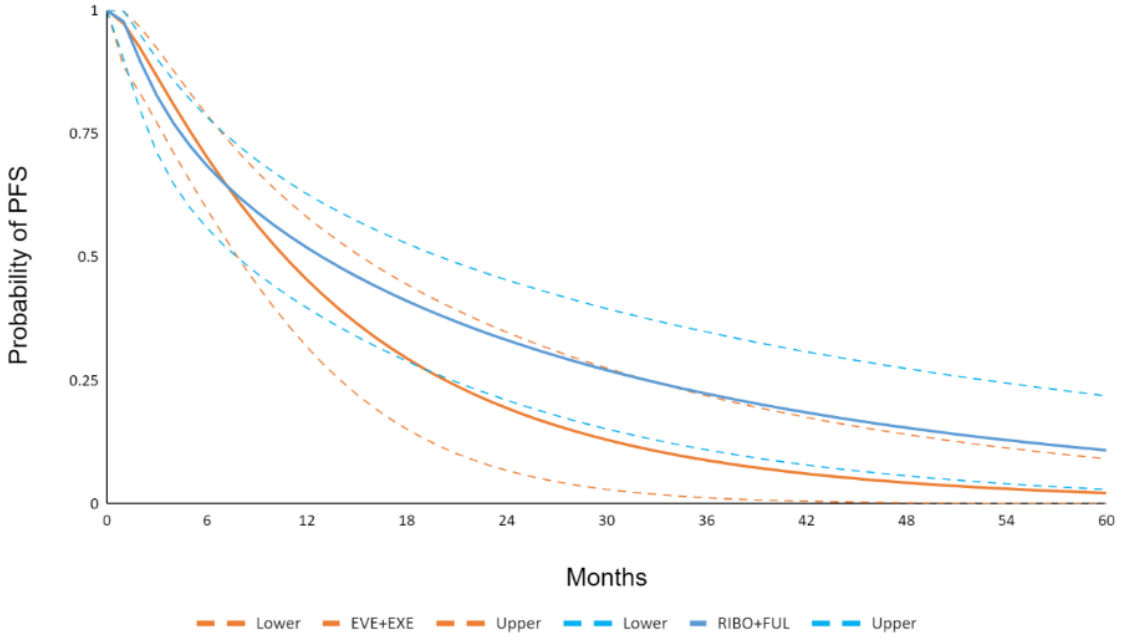
Figure 6).

Figure 5. PFS distributions based on company's FP NMA for all treatments (reproduced from company addendum, Figure 3)



Abbreviations: FP NMA, fractional polynomial network meta-analysis; KM, Kaplan-Meier; ML-3, MONALEESA-3; PFS, progression free survival.

Figure 6. PFS distributions for ribociclib plus fulvestrant and everolimus plus exemestane (based on the company's FP NMA with 95% credible intervals)



Abbreviations: EVE+EXE, everolimus plus exemestane; FP NMA, fractional polynomial network meta-analysis; KM, Kaplan-Meier; PFS, progression free survival; RIBO+FUL, ribociclib plus fulvestrant.

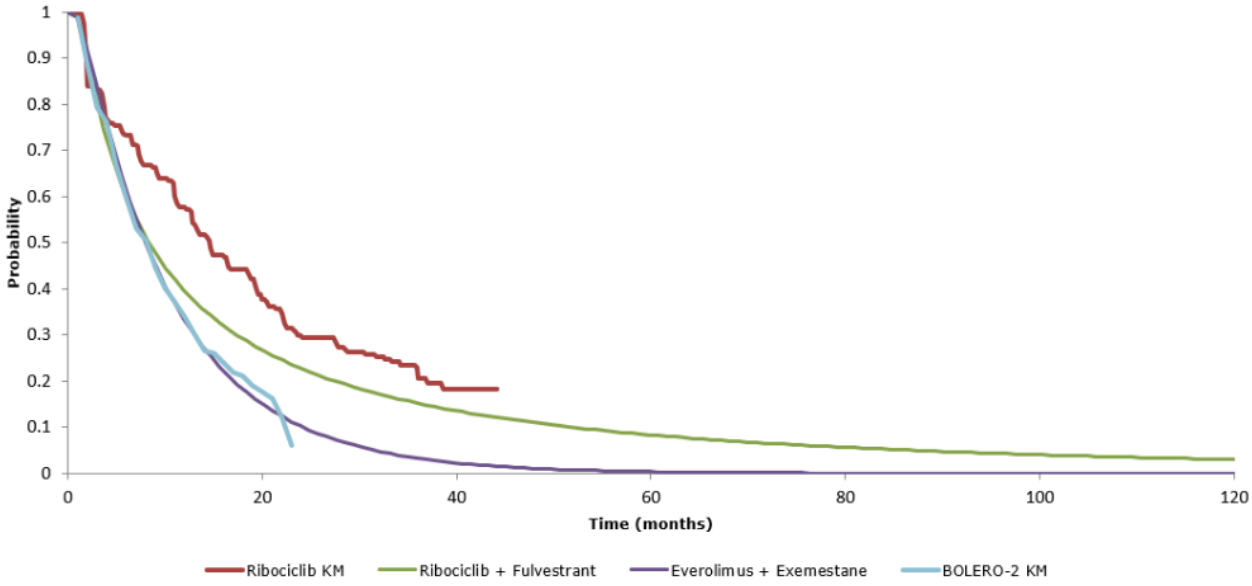
Conversely, the ERG's preferred models did not include an informed prior for any treatment and the results indicate a good fit for the everolimus plus exemestane KM data from BOLERO-2 but a poor fit for ribociclib plus fulvestrant (Figure 7 and Figure 8). The difference in fit for ribociclib plus fulvestrant is likely due to fulvestrant 500mg being informed by MONALEESA-3[4] and CONFIRM[6], where the latter observed a substantially lower median PFS (6.5 vs 9.1 months for CONFIRM and MONALEESA, respectively); a synthesis of the two in the NMA would result in a lower estimate than that observed in MONALEESA-3 alone. As fulvestrant 500mg is the "reference" treatment, the impact of this would be to also "lower" the treatment effect for ribociclib plus fulvestrant.

The ERG selected the 2nd order model over the 1st order model, due to the closer fit to the everolimus plus exemestane KM data in the former, as well as more clinically reasonable extrapolations of the data. Furthermore, the ERG notes that, while there is still uncertainty present, the 95% credible intervals are narrower and overlap to a lesser extent than the company's PFS estimates (

Figure 9). On visual inspection it appears that the company's and ERG's NMAs produce similar curves with the exception of the initial period, where there is a more rapid drop in PFS in the results of the ERG's NMA than in the company's NMA.

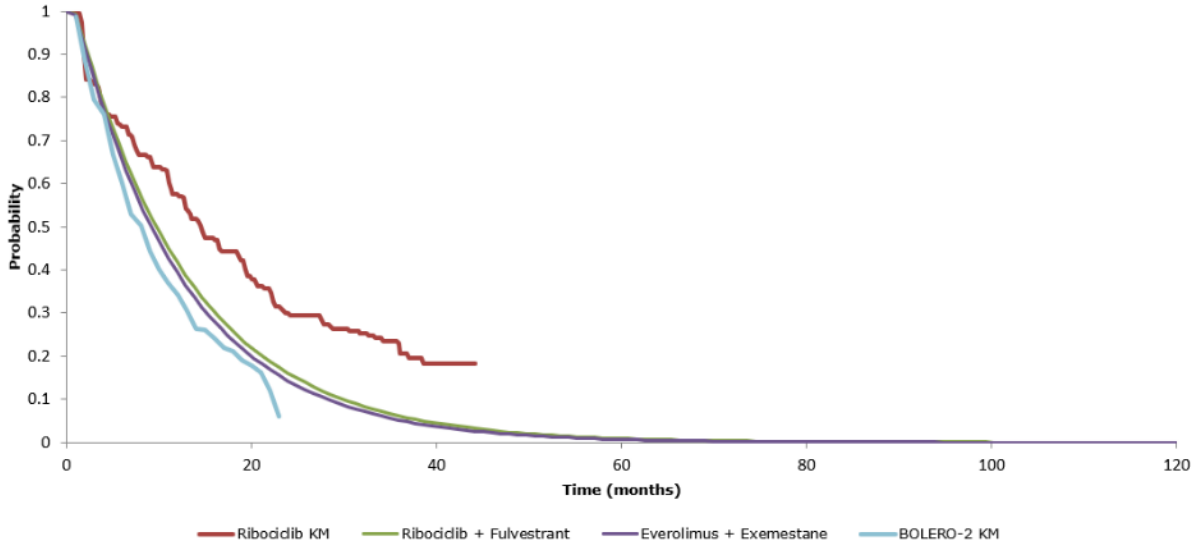
The ERG also considers that both the company's preferred 1st order models and the ERG's preferred 1st order models produce results that are much more similar to the results of the Bucher method used in the company's original submission. This could be due to the inflexibility of the 1st order models or conversely the 2nd order models could be "overfitting" to the heavily censored "tails" of the KM data, while appearing to be a better statistical fit. Unfortunately, due to time constraints the ERG could not explore this issue further.

Figure 7. PFS Distributions Based on ERG's best fitting 2nd order FP NMA for all treatments



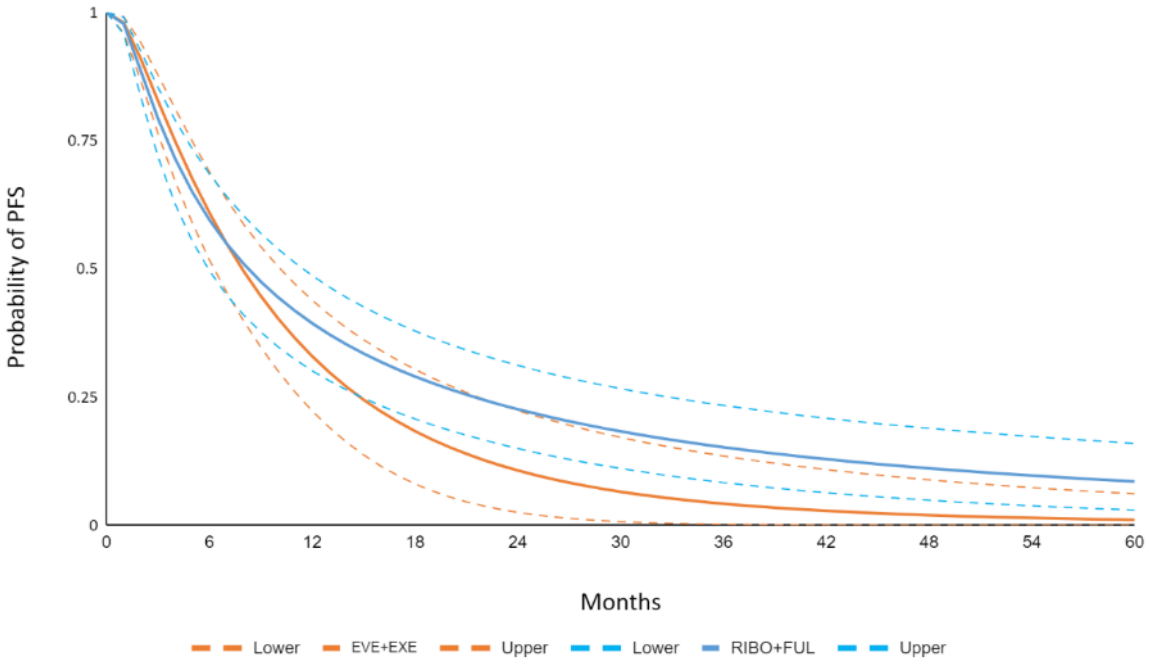
Abbreviations: FP NMA, fractional polynomial network meta-analysis; KM, Kaplan-Meier; PFS, progression-free survival

Figure 8. PFS distributions based on ERG's best fitting 1st order FP NMA for all treatments



Abbreviations: FP NMA, fractional polynomial network meta-analysis; KM, Kaplan-Meier; PFS, progression-free survival

Figure 9. PFS distributions for ribociclib plus fulvestrant and everolimus plus exemestane (based on ERG's FP NMA with 95% credible intervals)



Abbreviations: EVE+EXE, everolimus plus exemestane; FP NMA, fractional polynomial network meta-analysis; PFS, progression free survival; RIBO+FUL, ribociclib plus fulvestrant.

3.1.3 Conclusion

While FP NMAs allow for a change of hazards over time and are thus more flexible than standard parametric curves, the ERG emphasises the challenges of selecting the most appropriate model based on the fit of the results to the KM data for a specific comparator. As the NMA is adjusting the data to a set of FP curves with the best "average" fit it is unlikely that the resulting curves will be a good fit for any underlying KM curve – particularly if there is more than one trial potentially informing the "baseline" curve as is the case in the current analysis for fulvestrant 500mg. It would appear that the company has tried to resolve this by providing an informed prior for fulvestrant 500mg based on MONALEESA-3 but, as explained earlier, the ERG is concerned that this may be methodologically inappropriate. The ERG considers that had the company used ribociclib plus fulvestrant as the "reference" treatment instead of fulvestrant 500mg, as this is only informed by MONALEESA-3, it may have achieved the desired result without the use of informed priors. However, due to time constraints the ERG was unable to explore this option further. In any event, the ERG considers that the statistical fit of any model should be weighed against what would be considered clinically plausible, which is not necessarily the same as choosing a single underlying trial to inform that clinical judgement.

Due to time constraints, the ERG has been unable to explore more model options, but the best fitting models based on the DIC appear to be a reasonable visual fit of the data. The ERG considers the company's NMA to be more uncertain due to the wider credible intervals for ribociclib plus fulvestrant and everolimus plus exemestane. Due to this, and coupled with concerns related to the use of MONALEESA-3 data to inform the prior for fulvestrant 500mg, the ERG has limited confidence in the company's FP NMA. While the ERG considers the 2nd order ERG model to be a more robust and conservative analysis, it notes that there is still uncertainty surrounding the estimates.

Overall, the ERG considers that the following comparisons consistently suggest a numerical (but non-significant) benefit for PFS for ribociclib plus fulvestrant compared to everolimus plus exemestane:

- Bucher method;
- Company's preferred 1st order (p1=−2) and 2nd order FP NMAs (p1 =−2, p2 =−1);
- ERG's preferred 1st order (p1=−4) and 2nd order FP NMAs (p1=−2, p2=0).

As such, the ERG considers it reasonable to assume that there is a benefit in PFS for ribociclib plus fulvestrant over everolimus plus exemestane but that the magnitude of the benefit is highly uncertain. As such, the ERG has chosen the Bucher approach as a conservative estimate for benefit as its base case, with other options provided as scenarios (including a scenario of "no difference" to reflect the lack of statistical significance in all of the analyses). This is explored further in Section 4.

3.2 Key issue 1: Maturity of OS data

At the factual accuracy check stage, the company highlighted that a later data cut for OS data from MONALEESA-3 may be available. The ERG responded highlighting that these data would be useful, to reduce the uncertainty surrounding the relatively immature OS data for subpopulation B of MONALEESA-3. However, the company highlighted during the technical engagement call (24 November 2020) that no further OS data from MONALEESA-3 are available as part of this CDF review.

The ERG maintains the view held in the ERG report, that OS for subpopulation B of MONALEESA-3 from the June 2019 data-cut remains somewhat immature, given that median OS was only just reached and the upper bound confidence intervals were not estimable. Nonetheless, the data are at least more mature than the previous data-cut from November 2017, whereby median OS was not reached. Taking this into account, the ERG requested a new model structure utilising these OS data,

rather than assuming equivalency of post-progression survival between ribociclib plus fulvestrant and everolimus plus exemestane (see Section 3.5).

3.3 Key issue 2: Parametric survival distribution fitted to TTD data in MONALEESA-3

Following a suggestion from the ERG, the company explored unrestricted (U) 3-knot spline models to improve the visual fit of the parametric distribution for TTD to the KM data. Among the unrestricted 3-knot spline models, the RCS 3 log-logistic (U) had the best fit according to the AIC and BIC statistic for ribociclib and fulvestrant (in the combination arm) (Table 4). The company also noted that the RCS 3 log-logistic (U) had the best visual fit to the KM data and the most plausible long-term predictions (Figure 10 and

Figure 11).

The company considered the ERG's preferred curve in the main ERG report, the Gompertz (U), to overestimate time on treatment with ribociclib as TTD was capped by PFS too soon. To substantiate this, the company estimated that approximately 25% of patients in the ribociclib plus fulvestrant arm of MONALEESA-3 remained in PFS 24 months after treatment was discontinued (

Figure 12). Therefore, a TTD curve such as the RCS 3 log-logistic (U) or RCS lognormal (U), which remains below the PFS curve beyond the end of trial follow-up is plausible.

For these reasons, the RCS 3 log-logistic (U) was used to inform the company's revised base case analyses. The ERG considers the company's revised parametric survival distribution to be a reasonable choice. Additionally, using the Gompertz (U) in the economic model leads to a minimal increase in the ICER (see Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

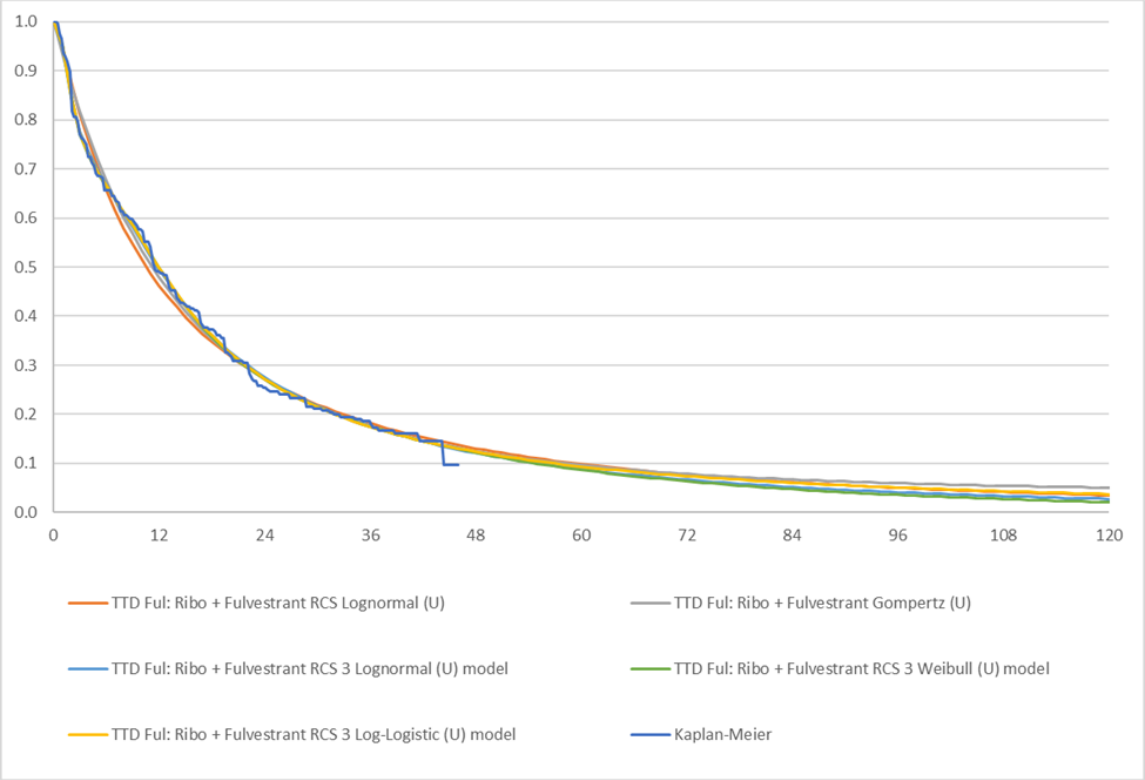
Table 2 in Section 2).

Table 4. Fit Statistics for key parametric distributions fitted to TTD for Patients in Group B of MONALEESA-3

Distribution	AIC	BIC
Ribociclib		
Gompertz (U): ERG CDF review	2256.5	**2271.8**
RCS Lognormal (U): Company CDF review	**2256.4**	2279.4
RCS 3 Log-Logistic (U)	2257.8	2296.3
RCS 3 Weibull (U)	2259.4	2297.8
RCS 3 Lognormal (U)	2262.2	2300.6
Fulvestrant in the combination arm		
Gompertz (U): ERG CDF review	2279.1	**2294.5**
RCS 3 Log-Logistic (U)	**2256.5**	2295.0
RCS 3 Weibull (U)	2256.8	2295.3
RCS 3 Lognormal (U)	2257.0	2295.5
RCS Lognormal (U): Company CDF review	2273.0	2296.1

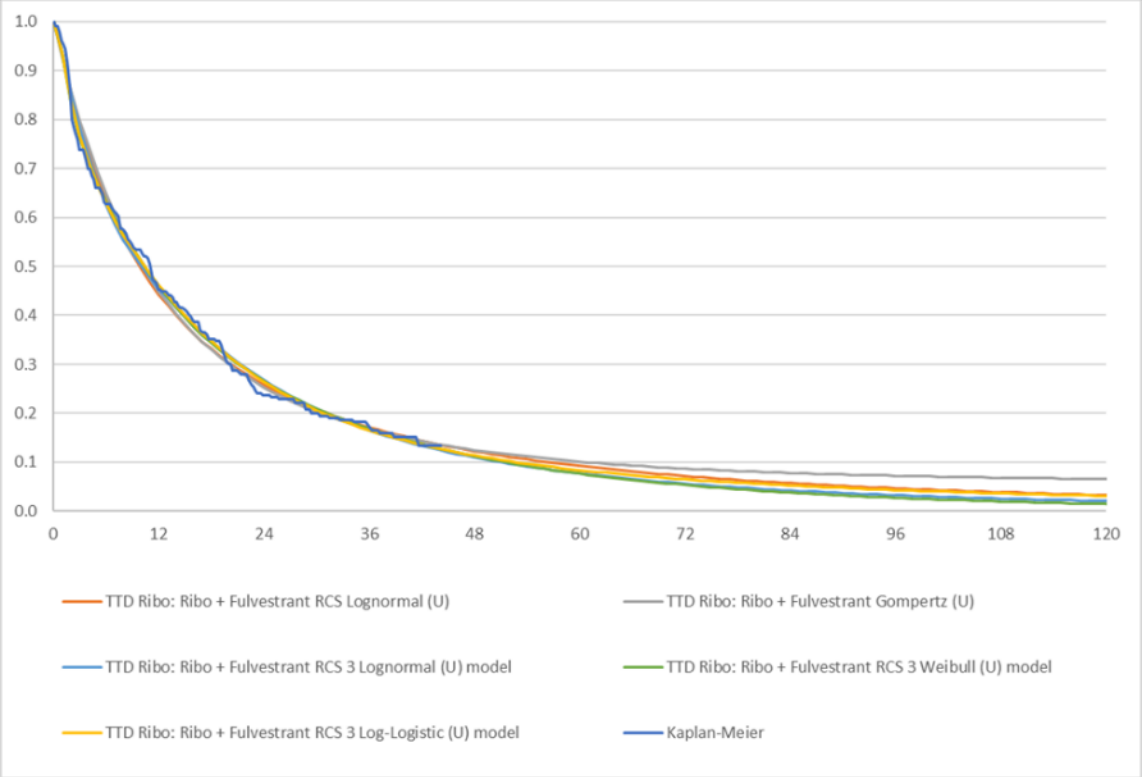
Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; CDF, Cancer Drugs Fund; restricted, (R), restricted, RCS, restricted cubic spline; TTD, time to treatment discontinuation; (U), unrestricted

Figure 10. 10-year projections of TTD for fulvestrant for patients receiving it with ribociclib based on 3-Knot Spline models compared against KM from Group B of MONALEESA-3 (reproduced from Figure 14 of the company's addendum)



Abbreviations:(RCS, restricted cubic spline; TTD, time to treatment discontinuation; (U), unrestricted.

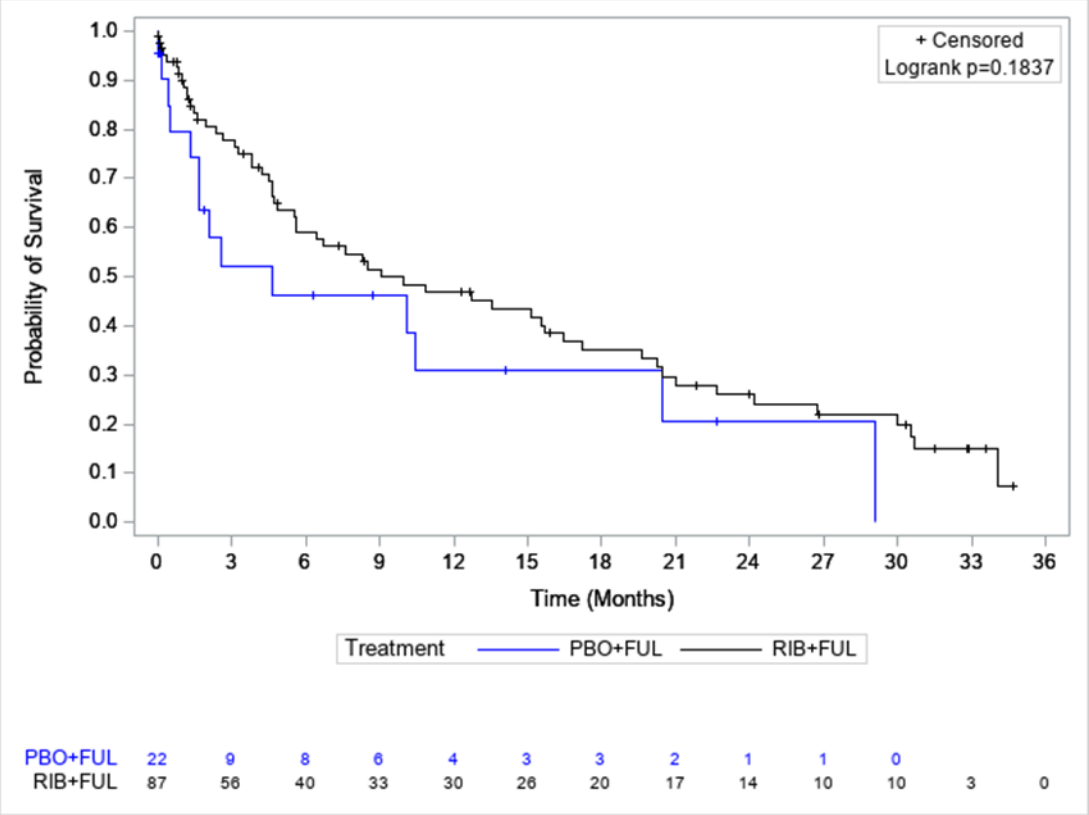
Figure 11. 10-year projections of TTD for ribociclib based on 3-Knot Spline models compared against KM from Group B of MONALEESA-3 (reproduced from Figure 9 of the company's addendum)



Abbreviations: RCS, restricted cubic spline; Ribo, ribociclib; TTD, time to treatment discontinuation; (U), unrestricted.

Figure 12. PFS from the time of discontinuation of study medication in MONALEESA-3 among patients who discontinued treatment before the date of disease progression and for reasons other

than progression or death (reproduced from Figure 11 of the company's addendum)



Abbreviations: FUL, fulvestrant; PBO, palbociclib; RIBO, ribociclib.

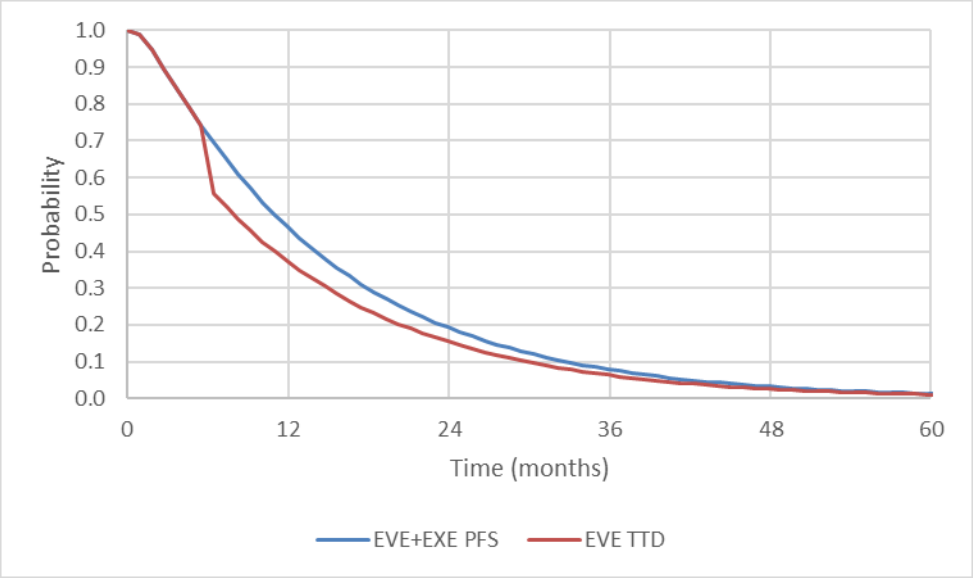
3.4 Key issue 3: TTD assumptions for everolimus plus exemestane

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 was based on clinical expert opinion. This assumption consisted of a proportion of patients (20%) who discontinue everolimus at month 6 and a proportion of patents (70%) who dose reduce from 10 mg daily to 5 mg daily at month 6. However, as noted in the main ERG report, the ERG would prefer an analysis which reflects the TTD data in BOLERO-2 to match the source of effectiveness data used in the analysis for everolimus plus exemestane.

During the clarification stage, the company noted that they planned to provide an analysis during TE where TTD for everolimus and TTD for exemestane were 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. However, in the company's response to TE, it was found that treatment discontinuation in BOLERO-2 was only recorded when treatment with both of everolimus (or placebo) and exemestane was permanently stopped (i.e. treated as a 2-drug unit), not for each

drug separately. As a result, the company employed the ERG's scenario based on clinical expert opinion in their revised base case. The company also employed an off-treatment utility value when patients discontinue everolimus, even if they have continued on exemestane, as per the recommendation in the ERG report. Figure 13 shows what the TTD curve for everolimus looks like compared to the PFS curve when 20% of patients are assumed to discontinue everolimus at month 6.

Figure 13. 5-year projections of TTD for EVE assuming 20% discontinue at month 6



Abbreviations: EVE, everolimus; EXE, exemestane; PFS, progression-free survival; TTD, time to treatment discontinuation

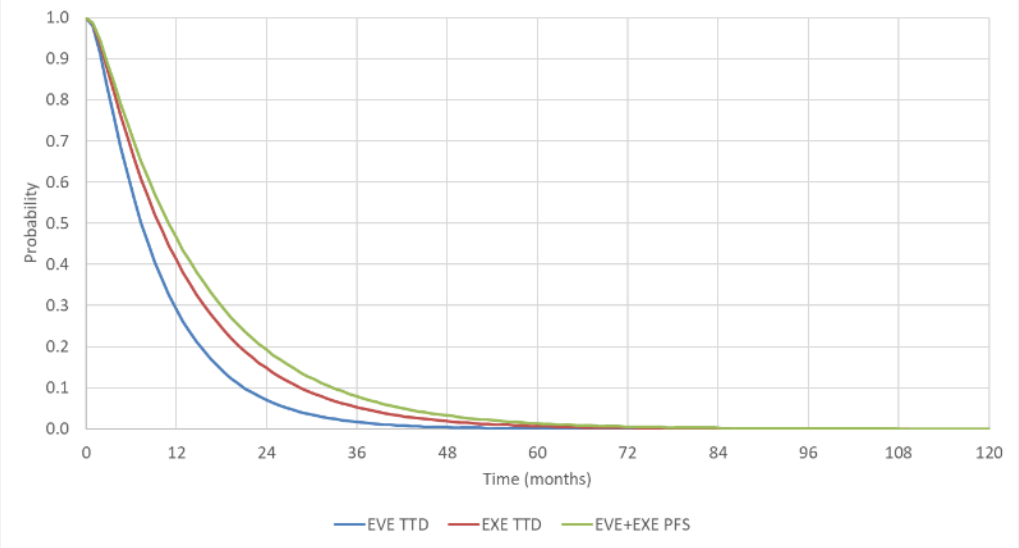
The ERG is somewhat surprised by the company's finding regarding the IPD in BOLERO-2 given that Yardley *et al.* 2013[5] (BOLERO-2, cut-off date for the final PFS analysis, December 15, 2011) reported the time to treatment exposure separately for everolimus and exemestane in the combination arm. In the absence of IPD data from BOLERO-2 the ERG considers the data in Yardley *et al.* 2013 an important alternative to explore. Additionally, this source would better match the TTD data employed in the NICE submission for abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (TA579)[10] and provide committee with a more consistent approach for decision making.

In Yardley *et al.* 2013, the median duration of exposure for everolimus and exemestane in the combination arm was 5.5 (23.9) and 6.8 months (29.5 weeks), respectively. As noted in TA579, a HR can be derived by dividing the cumulative hazard for median TTD (i.e. log(0.5)) by the cumulative hazard on the PFS curve at the time of median TTD.

For everolimus the calculation would be log(0.5)/log(0.65) = 1.61; where 0.65 represents the percentage of patients in the KM PFS curve for the combination treatment at 5.5 months. For exemestane, the calculation would be: log(0.5)/log(0.58) = 1.27; where 0.58 represents the percentage of patients in the KM PFS curve for the combination treatment at 6.8 months. These estimates were obtained by digitising the PFS KM data from BOLERO-2 using GetData Graph Digitizer.

Figure 14 shows that when the aforementioned HRs used in the model, the TTD curve for everolimus lies below the TTD curve for exemestane and the PFS EXE-EVE curve, which satisfies the ERG's clinical experts' opinion that patients usually discontinue treatment with everolimus before progression, given the drug's toxicity profile. Furthermore, the ERG has employed an off-treatment utility value when patients discontinue everolimus even if they have continued on exemestane as any effects of exemestane on utility values are likely to be small.

Figure 14. 10-year projections of TTD for EVE+EXE calculated using Yardley *et al.* 2013



Abbreviations: EVE, everolimus; EXE, exemestane; PFS, progression-free survival; TTD, time to treatment discontinuation

Finally, in the company's response to TE, the proportion of patient days on treatment with everolimus at each daily dose was estimated based on IPD on treatment exposure from BOLERO-2 (Table 5). As a small proportion of days on treatment were at a dose of 2.5mg (1.9%), the company considered it reasonable to allocate these days to doses of 5mg and 10mg. The company explored these adjusted proportions in a scenario analysis (see Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

Table 2). These proportions have also been added to the ERG's alternative TTD scenario using Yardley *et al.* 2013 in order to provide a scenario, which is a closer match to the TTD data in BOLERO-2. Results of the ERG's analyses are given in Section 4.

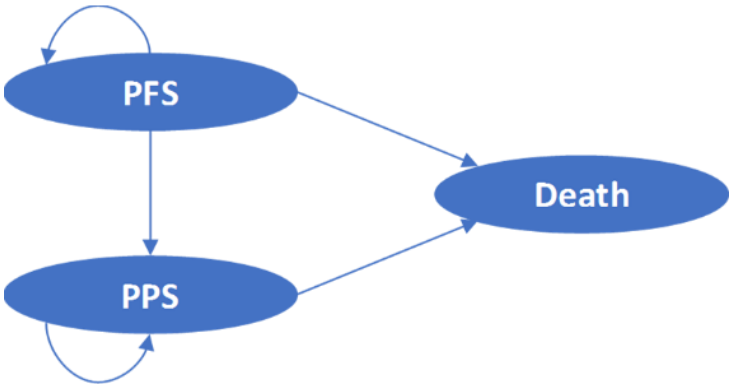
Table 5. Distribution of dosages of everolimus in BOLERO-2

	0mg	2.5mg	5mg	10mg	Total
Number of days	8,343	2,476	30,792	86,182	127,793
Percent of days	6.5%	1.9%	24.1%	67.4%	100.0%
Adjusted percent of days	6.5%	0%	25.1%	68.4%	100.0%

3.5 Key issue 4: Model structure

The ERG considered that as more mature OS data were available from the June 2019 data cut from MONALEESA-3 (subpopulation B), a more appropriate structure for the cost-effectiveness analysis would be to use a PSM approach, which utilises OS data directly instead of the company's original surrogacy approach. In response to TE, the company supplied an updated economic model, which includes an option to switch between the original STM and the company's new PSM. The structure of the company's new PSM is still based on a three-health state approach, which includes PFS, PPS and death (Figure 15).

Figure 15. Partitioned survival model structure.

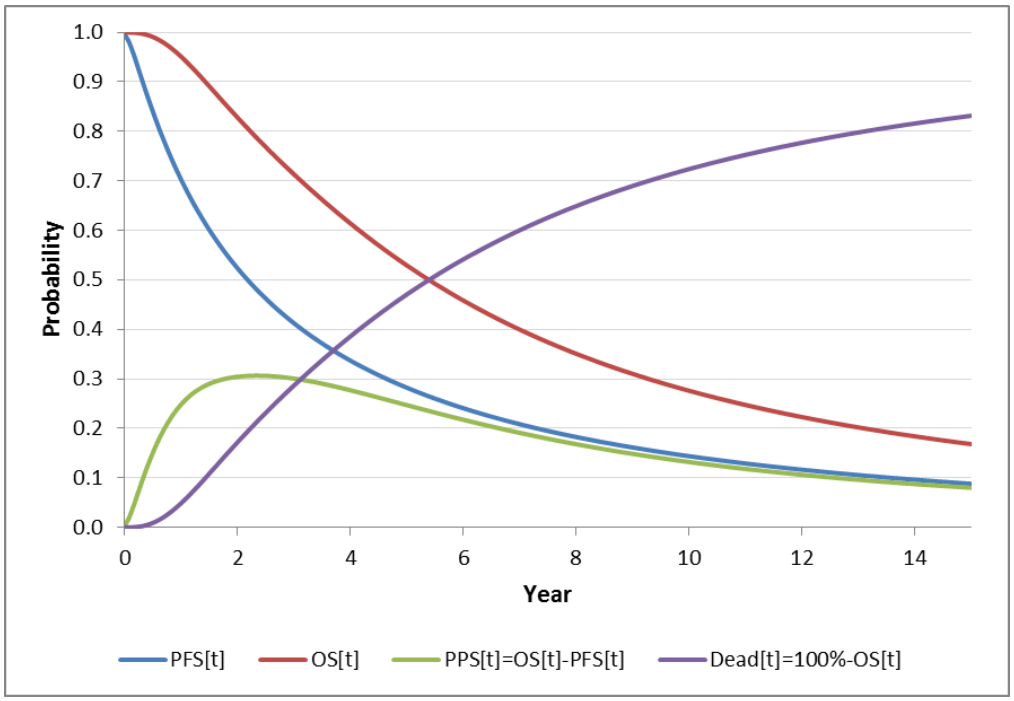


Abbreviations: PFS, progression-free survival; PPS, post-progression survival.

All patients enter the model in the progression-free health state and are assumed to start treatment on ribociclib + fulvestrant or everolimus + exemestane. During each model cycle, patients in the progression-free health state can be either on-treatment or off-treatment if they are experiencing unacceptable toxicity. Furthermore, from the progression-free health state, patients can transition to either the post-progression health state when they experience disease progression or die (thus transitioning to the death health state). When patients transition to the post-progression health state, they remain there until death.

Extrapolations of clinical outcomes data, PFS and OS, using parametric curves are implemented in the model to estimate the proportion of patients occupying a health state in any given model cycle. PFS is used to estimate the proportion of patients occupying the progression-free health state, OS is used to model the death state and TTD is used to estimate the proportion of patients who are progression-free and on-treatment. The proportion of patients occupying the post-progression health state for any given cycle is calculated as the difference between OS and PFS per cycle. Please refer to Figure 16 for an overview of the health state occupancy over time in the PSM. A detailed description of how the PFS and OS curves are estimated and implemented in the model for each treatment arm is provided in Section 3.1 and 3.5.1.

Figure 16. Health state occupancy of the company's partitioned survival model (Figure 17 of the addendum to the company submission).



Abbreviations: PFS, progression-free survival; PPS, post-progression survival; OS, overall survival; t, time.

A model cycle length of 28-days with half-cycle correction applied was implemented in the model. The model time horizon was set to 40 years, considered by the company to be sufficiently long enough to capture a lifetime as the mean age in MONALEESA-3 at baseline was 63 years. The perspective of the analysis was based on the UK national health service (NHS), with costs and benefits discounted using a rate of 3.5%, as per the NICE reference case.

Aside from updated methods for estimating treatment effectiveness, cost and utility parameters remain unchanged from the original economic model submitted for the CDF review. However, the company did remove the fix they applied for the costs of monitoring patients receiving ribociclib, as per the recommendation in the ERG report.

The ERG considers the structure of the company's model is appropriate, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other appraised oncology models. The 28-day cycle length used in the model is suitable to capture important changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. Half-cycle correction has been appropriately applied in the model to prevent over or under-estimation of costs and quality-adjusted life-years (QALYs).

3.5.1 Overall survival (OS)

The probabilities of OS for ribociclib plus fulvestrant and fulvestrant were estimated by fitting parametric survival distributions to the IPD from subpopulation B of MONALEESA-3. According to the hazard profiles for ribociclib plus fulvestrant and fulvestrant, the hazard rates show no clear pattern of increasing or decreasing. Furthermore, the log-cumulative hazard plots (a plot of: log [-log of the survivor function] against log [time]) and the slope of the scaled Schoenfeld residuals suggest that the PH assumption is not unreasonable (Figures 18, 19 and 20 of the company's addendum).

Based on the company's evaluation of the survival curves, the company selected the Weibull (R) (R referring to a jointly fitted model) to extrapolate OS data from subpopulation B of MONALEESA-3. According to the company, the Weibull (R) had the best fit statistical fit, excellent visual fit to the KM data, yielded projected OS that was consistent with clinical experts' expectations and meets PH assumptions. The ERG also notes that the Weibull (R) is consistent with the company's chosen parametric distribution during the clarification stage (the parametric distribution that would be used if a PSM was undertaken) (CQ B6).

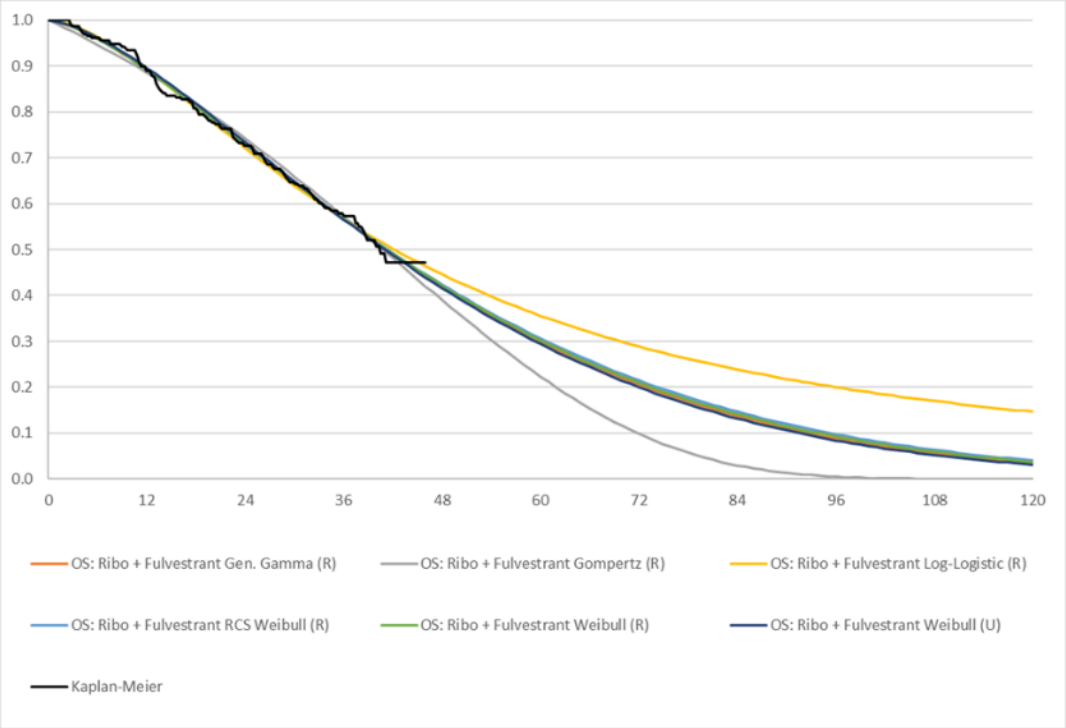
Fit statistics for the top 6 parametric distributions are given in Table 6. Those parametric distributions fit to the KM data are shown in Figure 17 for ribociclib plus fulvestrant and in Figure 18 for fulvestrant monotherapy.

Table 6. Fit statistics for the top 6 parametric distributions fit to OS for patients in Group B of MONALEESA-3

Distribution	AIC	BIC
Weibull (R)	**1625.1**	**1636.6**
Log-Logistic (R)	1627.8	1639.4
Gompertz (R)	1628.9	1640.4
Weibull (U)	1626.9	1642.3
RCS Weibull (R)	1627.1	1642.4
Gen. Gamma (R)	1627.1	1642.5

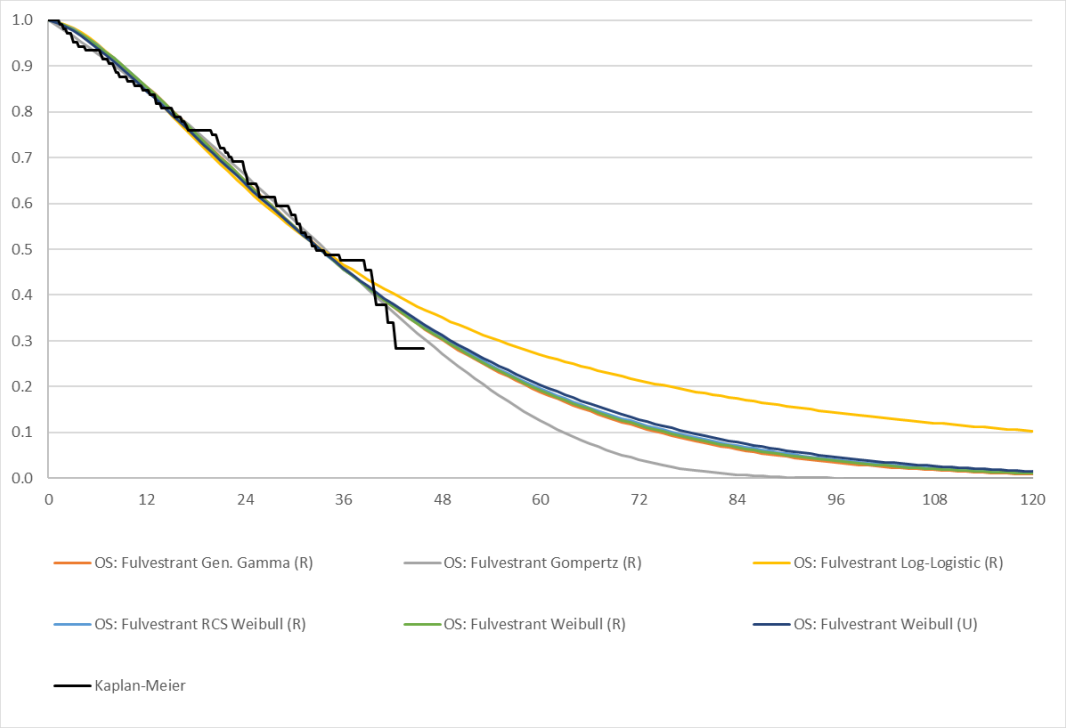
Abbreviations: AIC, Akaike information criterion, BIC, Bayesian information criterion; OS, overall survival; (R), restricted; RCS, restricted cubic spline; (U), unrestricted

Figure 17. 10-year projections based on parametric distributions fit to OS for ribociclib plus fulvestrant compared against MONALEESA-3 Group B KM (reproduced from Figure 22 of the company's addendum)



Abbreviations: OS, overall survival; (R), restricted; Ribo, ribociclib; (U), unrestricted

Figure 18. 10-year projections based on parametric distributions fit to OS for fulvestrant monotherapy compared against MONALEESA-3 Group B KM (reproduced from Figure 23 of the company's addendum)



Abbreviations: OS, overall survival; (R), restricted; (U), unrestricted

To yield the OS curve for everolimus plus exemestane, the company applied the HR obtained from the Bucher NMA ([redacted] for everolimus plus exemestane versus ribociclib plus fulvestrant) to the Weibull (R) distribution for OS for ribociclib plus fulvestrant. The Bucher NMA is unchanged from the original CDF review and is described in detail in Section 3.2.2 of the main ERG report. As mentioned in Section 3.1, the company also explored a FP NMA to estimate comparative HRs for OS. These results were implanted in the model as a scenario analysis, the results of which are given in Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

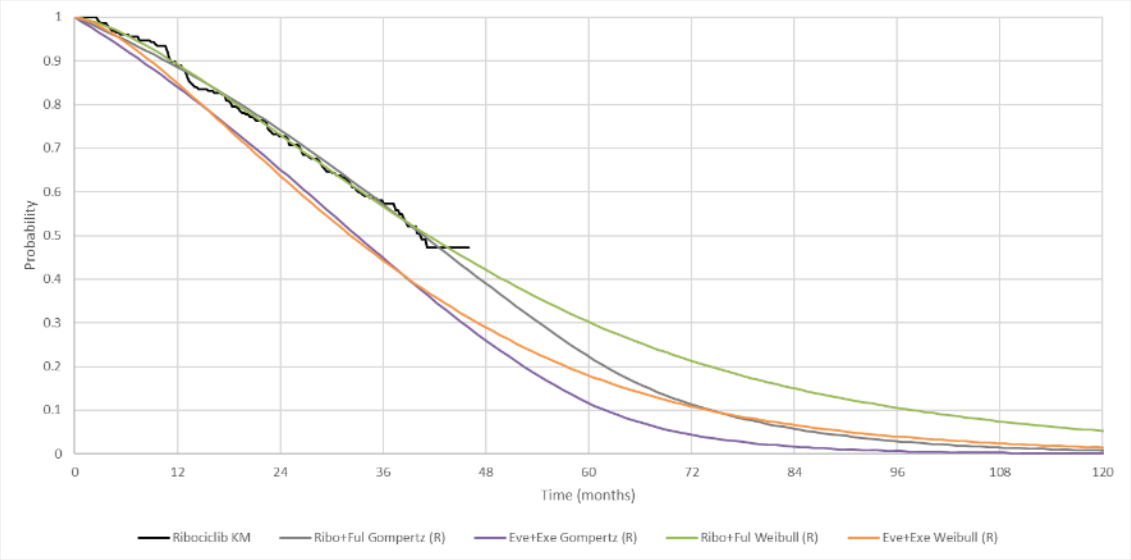
Table 2.

A key factor in considering the suitability of the baseline OS curve is the proportionality of the hazards between everolimus plus exemestane and each of the baseline treatment options (ribociclib plus fulvestrant or fulvestrant). The company appears to have overlooked this in their response and only tested for PH between the treatment arms in MONALEESA-3. Nonetheless, changing the baseline OS curve from ribociclib plus fulvestrant to fulvestrant had a negligible impact on the ICER.

The ERG has a few reservations with using the Weibull (R) to inform the base case analysis. One clinical expert advising the ERG considered the Gompertz (R) curve to produce the most plausible predictions as they expected at least 90% of patients on fulvestrant monotherapy or everolimus plus exemestane to have died by 5 years (60 months) and at least 95% to have died by 10 years (120 months). The ERG also considers the Gompertz (R) to provide a better visual fit to the KM data in the fulvestrant monotherapy arm, this is important because the company choose a jointly-fitted model (Figure 18). Furthermore, as noted in the main ERG report, there is heavy censoring present at the

end of the KM curve of OS for subpopulation B of MONELEESA-3 from 34 months onward and data beyond this point may be unreliable. Additionally, the Gompertz (R) is a PH model which can incorporate the constant hazard rates observed in MONALEESA-3. For these reasons, the ERG considers the Gompertz (R) model more appropriate, if, conservative choice. A comparison of the Weibull (R) and Gompertz (R) curves is given in Figure 19. Results of the ERG's analyses are given in Section 4.

Figure 19. 10-year OS projections based on Gompertz (R) and Weibull (R) distributions (generated by the ERG)



Abbreviations: EVE+EXE, everolimus plus exemestane; KM, Kaplan-Meier; OS, overall survival; (R), restricted; RIBO+FUL, ribociclib plus fulvestrant.

4 ERG's cost-effectiveness results

In Section 3, the Evidence Review Group (ERG) has described several scenarios that warrant further exploration in addition to the company's supplied scenario and sensitivity analyses to ascertain the impact of these changes on the incremental cost-effectiveness ratio (ICER). The scenarios that the

ERG has produced are applied to the company's revised base case in the partitioned survival model (PSM) and include:

- Alternative fractional polynomial (FP) network meta-analyses (NMAs) models for progression-free survival (PFS) (Additional Issue 1, see Section 3.1):
    - Company's preferred 1st order FP NMA (p1=-2);
    - ERG's preferred 1st order and 2nd order FP NMAs (p1=-4 and p1=−2, p2=0, respectively);
- Assuming everolimus plus exemestane PFS is equal to ribociclib plus fulvestrant PFS to reflect the lack of statistical significance in all of the PFS analyses (Additional Issue 1, see Section 3.1);
- Alternative time to treatment discontinuation (TTD) assumptions: published trial data on time to treatment exposure in BOLERO-2 (Yardley *et al.* 2013)[5] to inform TTD for everolimus plus exemestane and individual patient0level data (IPD) in BOLERO-2 to inform the distribution of dosages for everolimus (Issue 3, see Section 3.4).

Results of these scenario analyses are provided in Table 7. For ease of comparison, the ERG has also included the company's results using the Bucher NMA of PFS and the Gompertz (R) distribution for overall survival (OS) in Table 7 (previously given in Abbreviations: HR, hazard ratio; ICER, incremental cost-effectiveness ratio; OS, overall survival; PPS, post-progression survival RDI, relative dose intensity;

Table 2 of Section 2).

Table 7. Results of ERG scenario analyses (list price for fulvestrant)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Company's revised base case (company's preferred 2nd order FP NMA (p1=-2, p2=-1)							
EVE+EXE	[redacted]	3.02	2.17	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.72	19,372	0.75	0.55	35,247
Bucher NMA of PFS with RCS 3 Weibull (R) (HR of [redacted] for EVE+EXE versus RIBO+FUL)							
EVE+EXE	[redacted]	3.02	2.22	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.73	22,516	0.75	0.51	43,955
Company's preferred 1st order FP NMA (p1=-2)							

EVE+EXE	[redacted]	3.02	2.20	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.71	22,154	0.75	0.51	43,393
ERG's preferred 1st order FP NMAs for PFS (p1=-4)							
EVE+EXE	[redacted]	3.02	2.16	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.66	21,290	0.75	0.50	42,272
ERG's preferred 2nd order FP NMAs for PFS (p1=-2, p2=0)							
EVE+EXE	[redacted]	3.02	2.15	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.69	22,144	0.75	0.54	40,836
PFS equal (RCS 3 Weibull (R) applied to MONALEESA-3 and HR 1 for EVE+EXE vs RIVO+FUL)							
EVE+EXE	[redacted]	3.02	2.22	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.73	22,832	0.75	0.51	44,881
Gompertz (R) parametric survival distribution fitted to OS data in MONALEESA-3							
EVE+EXE	[redacted]	2.79	2.02	-	-	-	-
RIBO+FUL	[redacted]	3.32	2.42	14,961	0.53	0.40	37,361
Alternative TTD assumptions for EVE+EXE using BOLERO-2							
EVE+EXE	[redacted]	3.02	2.18	-	-	-	-
RIBO+FUL	[redacted]	3.76	2.72	23,958	0.75	0.54	44,345

Abbreviations: EVE, everolimus; EXE, exemestane; FP, fractional polynomial; FUL, fulvestrant; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; LYG, life years gained; NMA, network meta-analysis; PFS, progression free survival; QALYs, quality-adjusted life years; RCS, restricted cubic spline; RIBO, ribociclib TTD, time to treatment discontinuation

In this section of the report the ERG also presents its preferred base case ICER. The ERG also presents an alternative base case ICER, which reflects a different scenario on TTD for everolimus plus exemestane.

The ERG caveats this alternative analysis of TTD (using published trial data on time to treatment exposure TTD in BOLERO-2) with the company's finding that the date of study treatment discontinuation in BOLERO-2 was only recorded when both drugs (i.e., everolimus/blinded placebo and exemestane) were permanently discontinued. The company noted that while data on daily dosages for each dispensation of everolimus and exemestane were captured separately, these data do not provide information on the date when receipt of a specific drug was stopped. Therefore, the

last date with daily dose recorded for a given drug does not necessarily reflect the date when the patient stopped receiving that drug. Rather, it only reflects that last daily dose observed during follow-up (i.e., it is not possible to determine whether the patient continued receiving the drug after the last follow-up). The ERG appreciates the challenges in interpreting the data captured as presented by the company and considers this to mean that the company deems it inappropriate to use the time to treatment exposure data in Yardley *et al.* 2013. Nonetheless, the ERG considers this alternative analysis to be one step closer to aligning the source of cost data with the source of effectiveness data.

The key changes and assumptions made to the ERG's updated base case ICER are:

- Bucher NMA of PFS with restricted cubic spline (RCS) 3 Weibull (R) (see Section 0);
- TTD assumptions for everolimus plus exemestane (see Section 3.4):
    - Base case: clinical expert opinion (described in the main ERG report and included in the company's revised base case);
    - Alternative base case: published trial data on time to treatment exposure in BOLERO-2 (Yardley *et al.* 2013) to inform TTD for everolimus plus exemestane and IPD in BOLERO-2 to inform the distribution of dosages for everolimus;
- Gompertz (R) parametric survival distribution fitted to OS data in MONALEESA-3 (see Section 3.5.1).

However, as noted in Section 0, the ERG considers it reasonable to assume that there is a benefit in PFS for ribociclib plus fulvestrant over everolimus plus exemestane but that the magnitude of the benefit is highly uncertain. As such, the ERG has chosen the Bucher approach as a conservative estimate for benefit as its base case. Likewise, as noted in Section 3.5.1, the ERG considers the Gompertz (R) a more appropriate distribution to extrapolate OS data, if, a conservative choice.

The ERG's revised base case results using the list price for fulvestrant are given in Table 8. Due to time constraints, the ERG has been unable to produce probabilistic results. As noted in Section 2, results including the discount on the list price of fulvestrant agreed [redacted] can be found in the confidential appendix.

Table 8. ERG's revised base case results using the partitioned survival model (list price for fulvestrant)

Interventions	Total Costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
ERG base case							
EVE+EXE	[redacted]	2.79	2.05	-	-	-	-
RIBO+FUL	[redacted]	3.32	2.42	17,794	0.53	0.37	48,463
ERG alternative base case							
EVE+EXE	[redacted]	2.79	2.07	-	-	-	-
RIBO+FUL	[redacted]	3.32	2.42	23,957	0.53	0.35	67,794

Abbreviations: EVE, everolimus; EXE, exemestane; FUL, fulvestrant; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; RIBO, ribociclib.

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