NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee papers

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SINGLE TECHNOLOGY APPRAISAL

Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer [ID1026]

Contents:

- ERG addendum based on updated PAS

13. Evidence Review Group report – factual accuracy check

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

Pre-meeting briefing

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

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

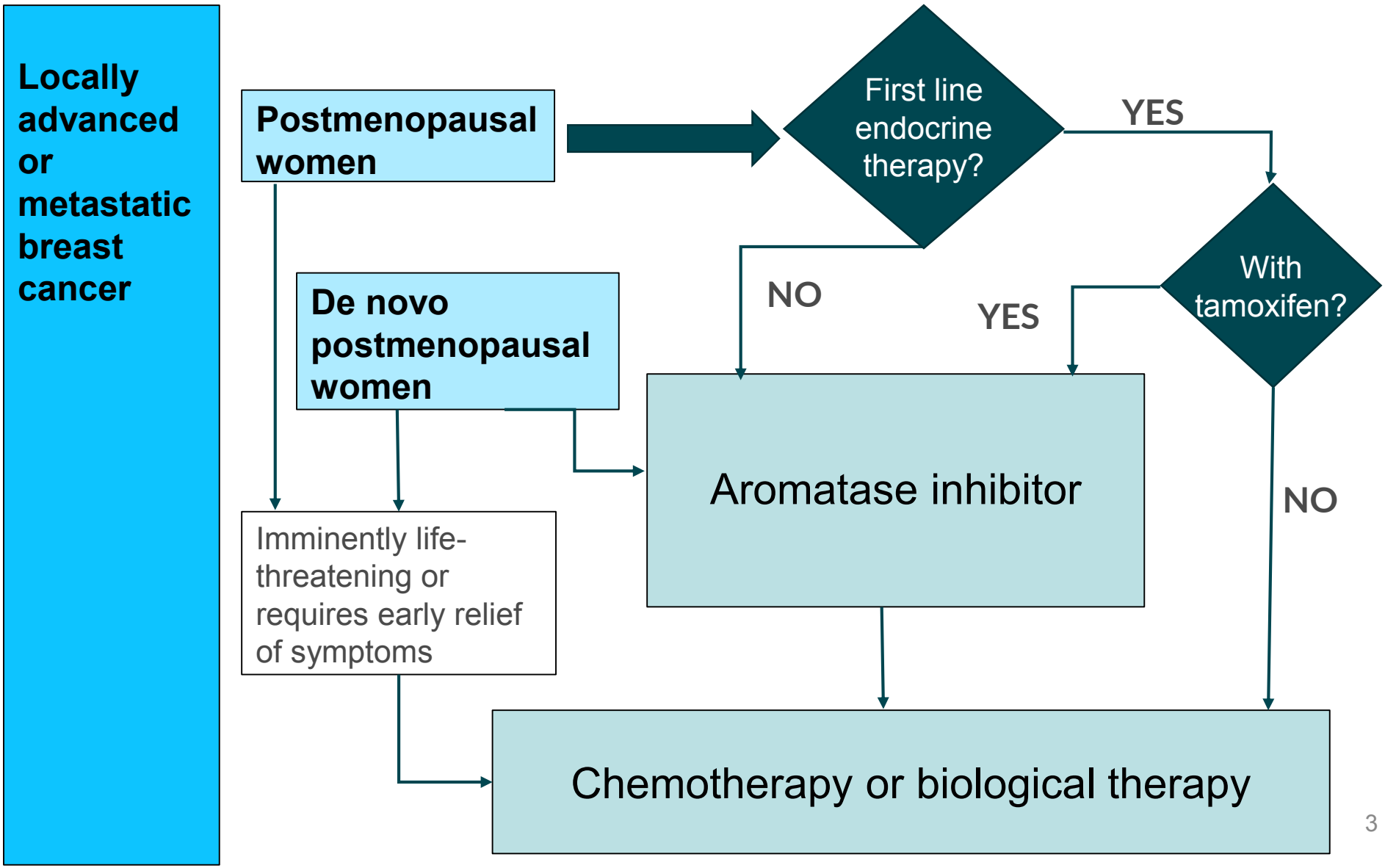
The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Advanced breast cancer (ABC) background

- Cancer Research UK describes breast cancer as the most common cancer in the UK and reported 53,696 new cases of invasive breast cancer in 2013
- HR+/HER2- is the most common form of breast cancer (approximately 73% of breast cancers)
- 30 - 50% of women with early disease eventually develop or progress to advanced breast cancer or metastatic disease
- almost half (46%) of women diagnosed with breast cancer in the UK each year are aged 65 years and over at the time of diagnosis, therefore the majority are postmenopausal
- The company estimated that there are 8,380 postmenopausal women eligible for first-line treatment for advanced HR+/HER2- breast cancer in England and Wales

Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Treatment pathway
ER+/HER- breast cancer (CG81)

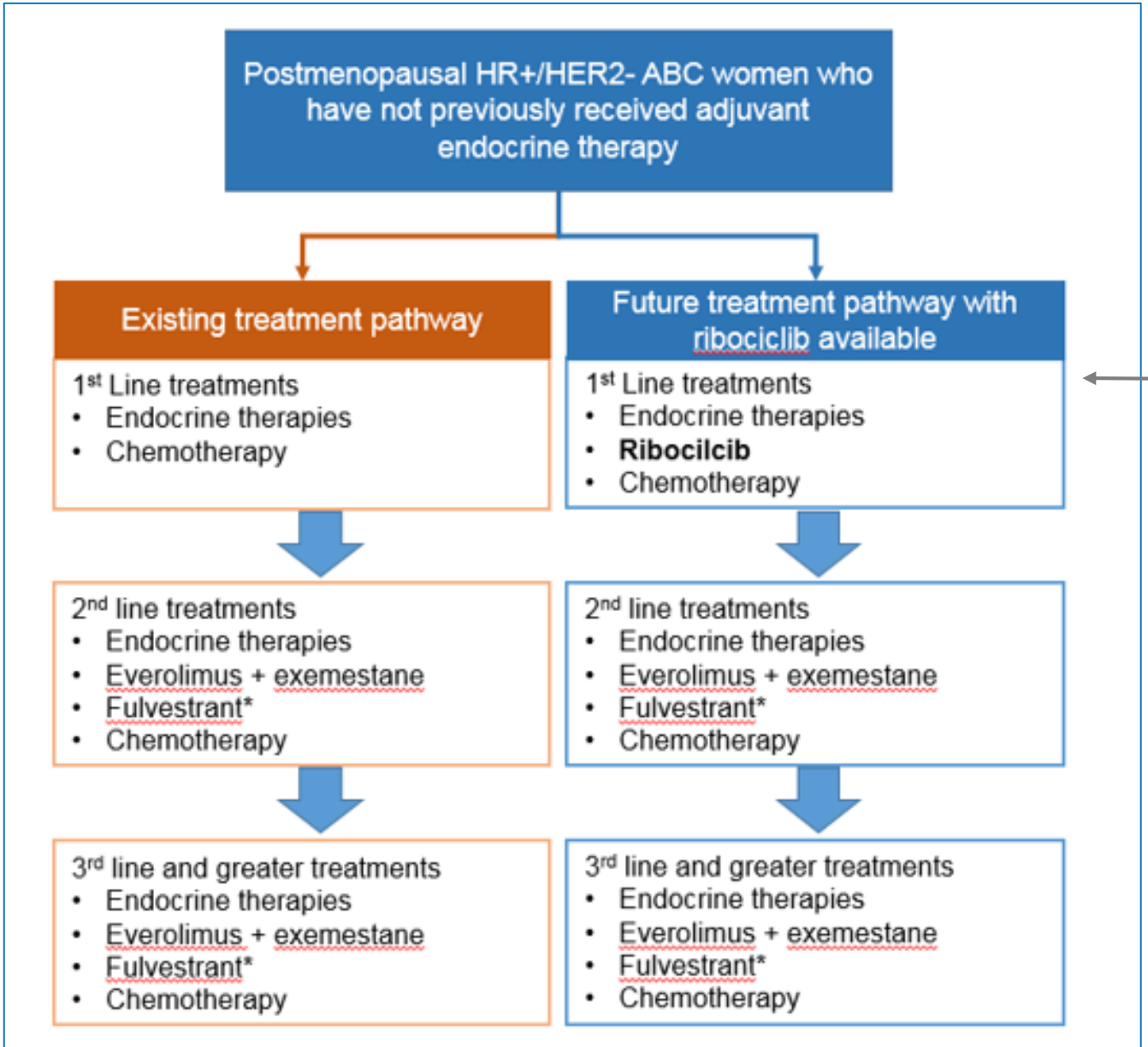


Ribociclib (Kisqali, Novartis)

Positive CHMP opinion	Kisqali in combination with an aromatase inhibitor is indicated for the treatment of postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer as initial endocrine based therapy.
Mechanism of action	Ribociclib is a selective cyclin-dependent-kinase 4 and 6 (CDK4/6) inhibitor. When either of these two proteins are activated they can cause the cancer cells to grow and divide too quickly.
Administration	600 mg (3 x 200 mg tablets) once daily for 21 days of 28-day cycle 400 - 200 mg/day dose reductions to manage treatment-related AEs taken orally (film-coated tablets)
Acquisition cost	600 mg £2,950 400 mg £1,966.67 200 mg £983.33
Cost of a course of treatment	[redacted] anticipated number of repeat courses of treatments: [redacted] Simple PAS discount submitted

Key: AE, adverse events; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Company - Treatment pathway



Decision problem

	NICE scope	Company	ERG
Population	Postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in the advanced setting		MONALEESA-2 may not be totally representative of the scope
Intervention	Ribociclib in combination with an aromatase inhibitor	Ribociclib in combination with letrozole	in line with scope
Comparators	Aromatase inhibitors (such as letrozole or anastrozole)	• letrozole • letrozole and anastrazole assumed equally effective	Accepts the generalisability assumption
Outcomes	progression free survival, overall survival, response rate, adverse effects of treatment, health-related quality of life	in addition, clinical benefit rate to demonstrate the ribociclib's antitumour activity	in line with scope

Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Patients and carers comments

- *This class of drug is innovative*
- *Ribociclib could benefit a large proportion of the advanced breast cancer population, as the largest proportion of breast cancers are hormone positive, HER2 negative.*
- *The key benefit of ribociclib is a prolonged period of PFS*
- *Ribociclib can allow people to delay having chemotherapy for a substantial amount of time*
- *This drug is given in oral form, which makes it simple for patients to take. Apart from short-stay, regular blood tests, patients are not required to spend long lengths of time at the hospital, so it is unlikely that this will place a significant additional burden on patients and their families.*
- *Ribociclib can cause liver problems and a heart problem called QT prolongation. Healthcare professionals should monitor patients to ensure these adverse effects are identified swiftly and managed appropriately*
- *However not all patients will experience side effects. The benefits and risks of a treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them*.

Key: HER2 negative, human epidermal growth factor receptor 2-negative.

Clinical-effectiveness evidence

Company submission section 4

Preview: clinical effectiveness and treatment pathway issues

1. How will ribociclib fit into the current treatment pathway?
2. What are the appropriate comparators?
3. Can equivalent efficacy between aromatase inhibitors be assumed?
4. Is a class effect for CDK 4/6 inhibitors likely?
5. How generalisable are MONALEESA-2 results?
   - Is MONALEESA-2 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in advanced setting?
6. Local versus central PFS assessment
   - Central assessment not available at the longest follow-up
   - Difference between local and central PFS assessment
7. When can interim and mature OS data from MONALEESA-2 be expected?

Key: HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; PFS, progression free survival.

Company: overview of clinical evidence

- **Phase III RCT MONALEESA-2**, a placebo-controlled evaluation of ribociclib with letrozole in postmenopausal women with HR+/HER2- ABC
- Ongoing studies:
  - MONALEESA-3: placebo-controlled RCT of ribociclib with fulvestrant in men and postmenopausal women with HR+/HER2- ABC with one or none prior endocrine therapy ([redacted])
  - MONALEESA-7: placebo-controlled RCT of ribociclib with tamoxifen or non-steroidal aromatase inhibitor (letrozole or anastrozole), plus goserelin in premenopausal women with HR+/HER2- ABC ([redacted])
  - COMPLEEMENT-1: open label single arm safety and efficacy assessment of ribociclib with letrozole in men and postmenopausal women with HR+/HER2- ABC with no prior endocrine therapy (expected in November 2020)

Key: ABC, advanced breast cancer; Q, quarter; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive.

Clinical evidence: MONALEESA-2

Design	Double blind placebo-controlled phase 3 RCT
Location (sites)	223 sites in 29 countries • [redacted]
Population	Post-menopausal women with ER+ and/or PR+, HER2- recurrent or metastatic breast cancer who had not received systemic therapy for advanced breast cancer *Exclusion criteria*: e.g. history of cardiac disease or dysfunction, irregular heart beat, and prior treatment with CDK4/6 inhibitor or systemic chemotherapy or endocrine therapy for advanced disease
Intervention and comparator	Ribociclib (n=334): ribociclib 600 mg/day on a 3 weeks on/1 week off 28-day treatment cycle in combination with letrozole (2.5 mg/day) Placebo (n=334): matched placebo with letrozole
Outcomes	Primary: PFS based on local assessment Secondary: OS, ORR, CBR, safety, EORTC QLQ-C30, EQ-5D, safety and breast cancer module EORTC QLQ-BR23 Supportive analysis: Central PSF (blinded independent review)

Key: CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4 and 6; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ BR23, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer; ER+, oestrogen receptor-positive; EQ-5D-5L, European quality of life-5 dimensions-5 levels; HER2-, human epidermal growth factor receptor 2-negative; OS, overall survival; ORR, objective response rate; PFS, progression free survival; PR+, progesterone receptor-positive.

MONALEESA-2 baseline characteristics

Baseline characteristics		Ribociclib group N=334	Placebo group N=334
Age, years	Median (range)	62 (23–91)	63 (29–88)
ECOG PS, n (%)	0	205 (61.4)	202 (60.5)
	1	129 (38.6)	132 (39.5)
Disease stage, n (%)	III	1 (0.3)	3 (0.9)
	IV	333 (99.7)	331 (99.1)
Disease-free interval, n (%)	Newly diagnosed	114 (34.1)	113 (33.8)
	Existing disease	220 (65.9)	221 (66.2)
HER2 receptor status, n (%)	Positive	1 (0.3)	1 (0.3)
	Negative	333 (99.7)	333 (99.7)
Oestrogen receptor positive, n (%)		332 (99.4)	333 (99.7)
Progesterone receptor positive, n (%)		271 (81.1)	278 (83.2)
Site of metastases, n (%)	Breast	8 (2.4)	11 (3.3)
	Bone (any)	246 (73.7)	244 (73.1)
	Bone (only)	69 (20.7)	78 (23.4)
	Visceral[b]	197 (59.0)	196 (58.7)
	Lymph nodes	133 (39.8)	123 (36.8)
	Other	35 (10.5)	22 (6.6)
Prior therapy, n (%)[c]	Radiotherapy	178 (53.3)	167 (50.0)
	Neo/adjuvant chemotherapy	146 (43.7)	145 (43.4)
	Neo/adjuvant endocrine therapy	175 (52.4)	171 (51.2)

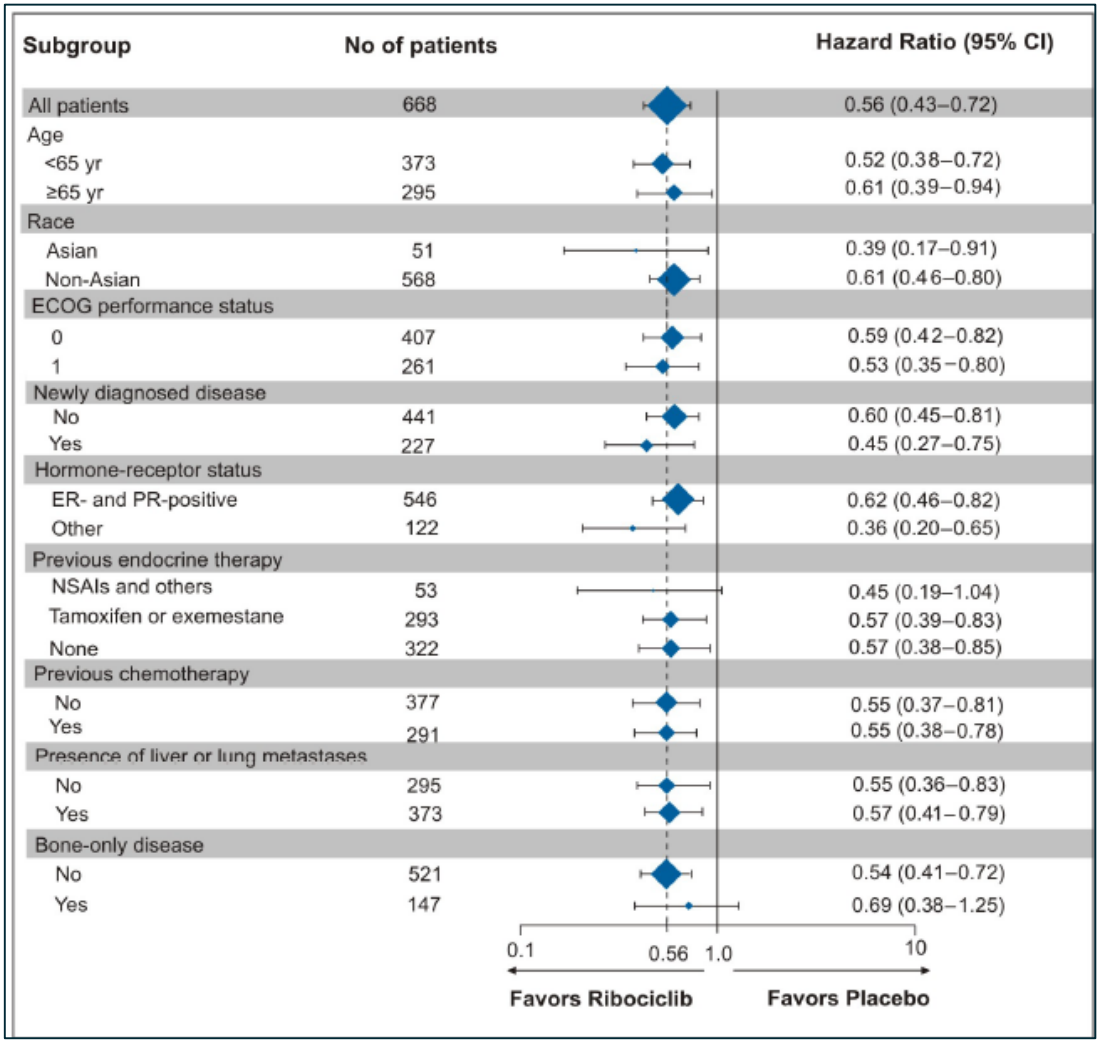
MONALEESA-2 PFS (I)

(months)	Local assessment		Central assessment	
	Ribo & Let n=334	Pbo & Let n=334	Ribo & Let n=334	Pbo & Let n=334
January 2016 data cut-off				
Median (95 CI)	NR (19.3–NR)	14.7 (13.0–16.5)	[redacted]	[redacted]
HR	0.56 (0.43–0.72) p<0.001		0.59 (0.41–0.85) p=0.002	
KM 18 months (95%CI)	63.0 (54.6–70.3)	42.2 (34.8–49.5)	[redacted]	[redacted]
June 2016 data cut-off				
Median (95 CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR	[redacted]		[redacted]	
KM 18 months (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
January 2017 data cut off				
Median (95 CI)	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)	[redacted]	
HR	0.568 (0.457, 0.704) p<0.001			
KM 18/30 months (95%CI)	[redacted]	[redacted]		

Key: Let, letrozole; NE, not estimable; NR, not reached; Pbo, placebo; Ribo, ribociclib.

MONALEESA-2 PFS (II)

PFS across selected subgroups local assessment January 2016 cut-off

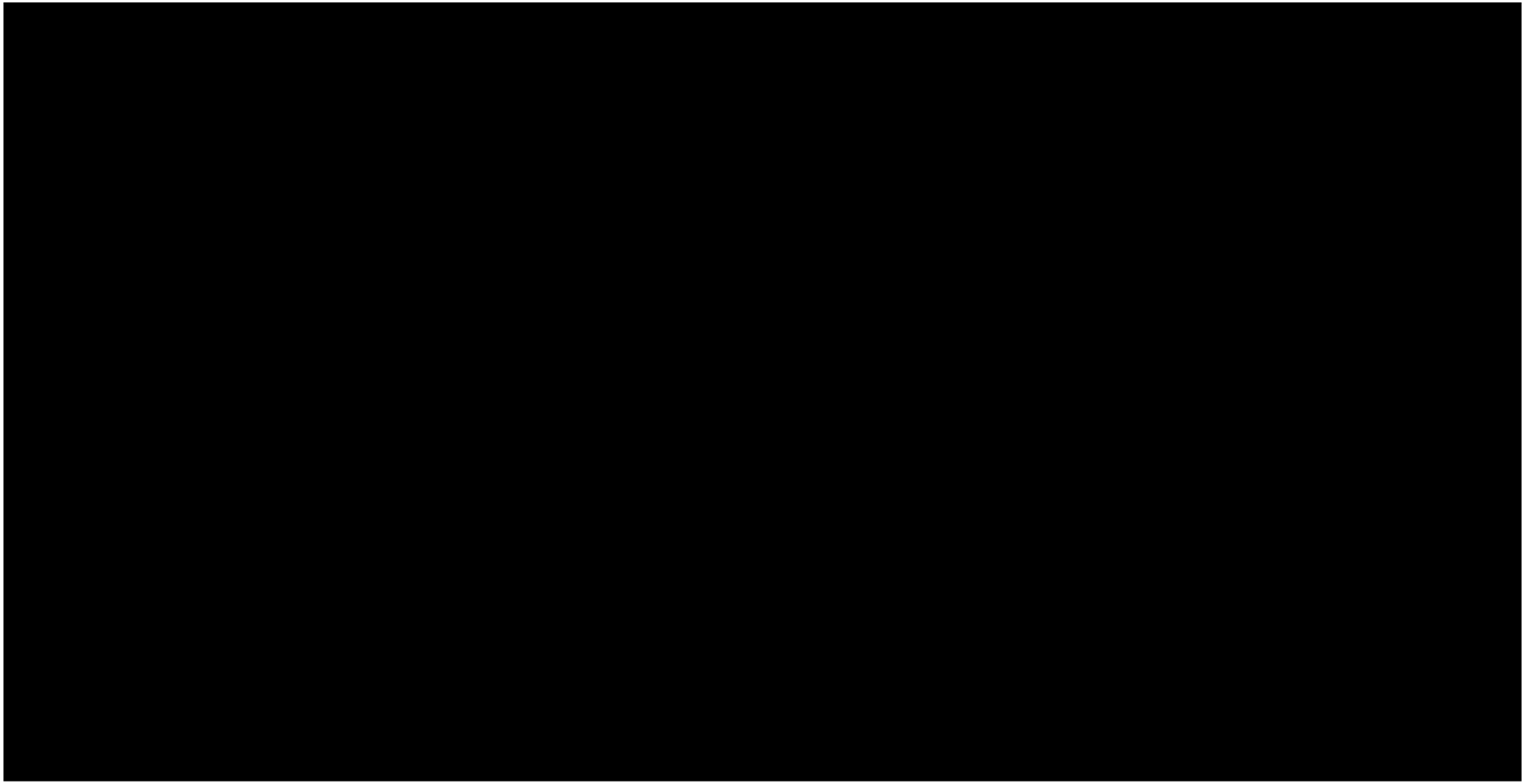


- The PFS benefit for ribociclib was observed across all pre-planned subgroups and as per local and central assessment

Key: ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; NSAI, non-steroidal aromatase inhibitor; PR, progesterone receptor; yr, years .

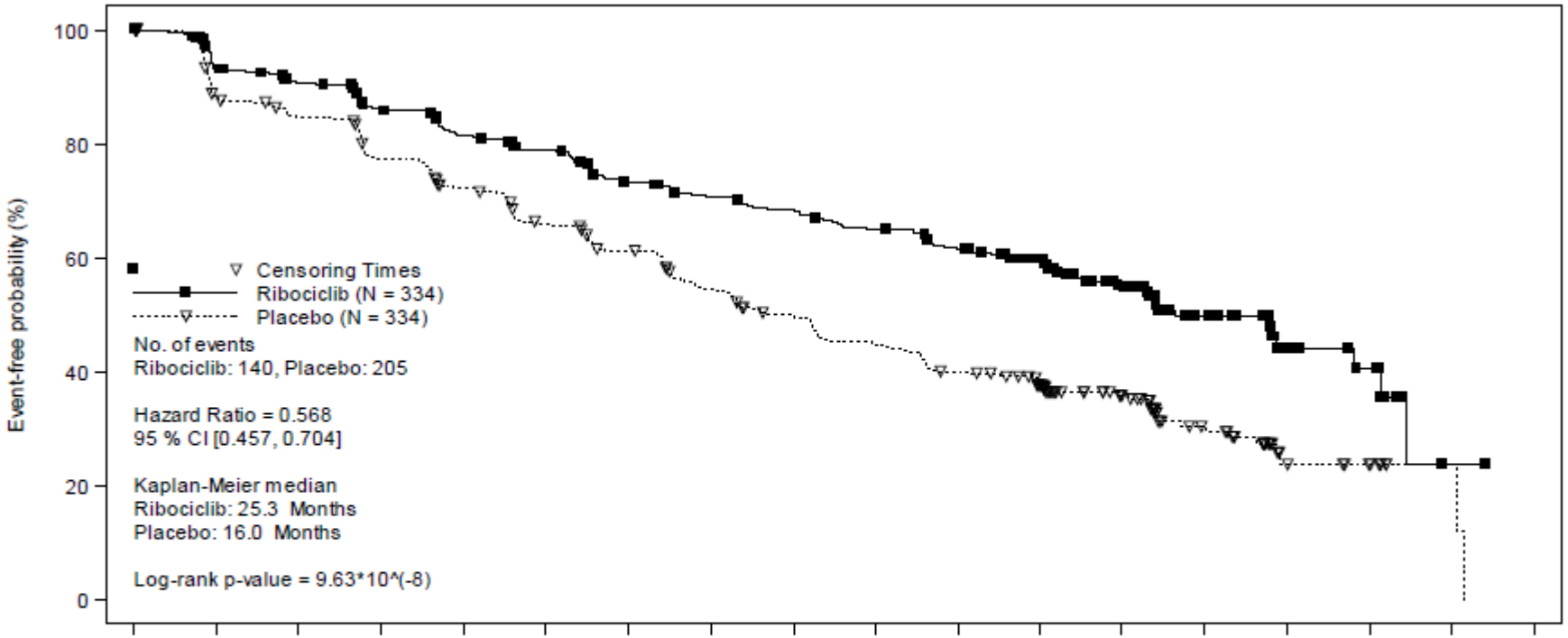
MONALEESA-2 PFS (III)

Kaplan-Meier plot: central assessment June 2016 cut-off



MONALEESA-2 PFS (IV)

Kaplan-Meier plot: local assessment January 2017 cut-off



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ribociclib	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
Placebo	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

- Using January 2016 data: the overall concordance between local and central assessment was [redacted] in ribociclib and [redacted] in letrozole group.

MONALEESA-2 OS (I)

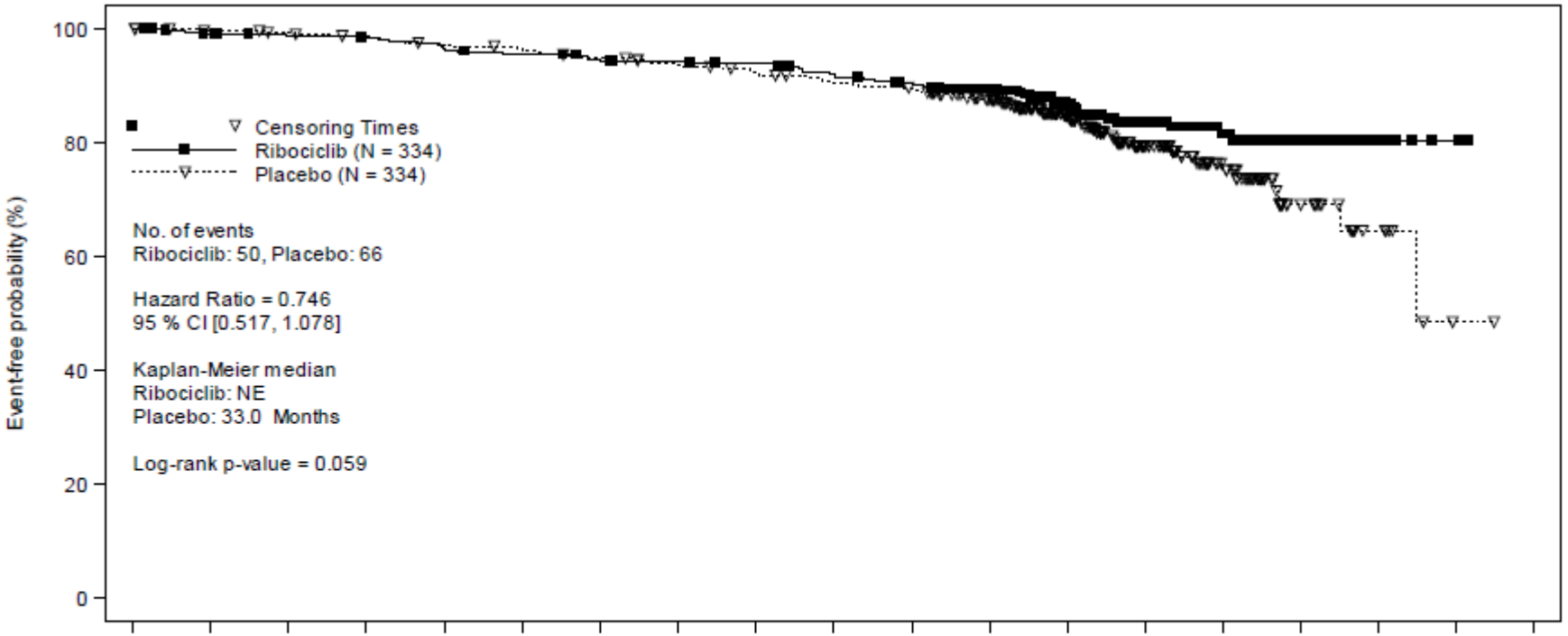
	Ribo & Let n=334	Pbo & Let n=334
January 2016 data cut-off		
Median (95 CI) months	NR	NR
HR	[redacted]	
KM 12 months (95%CI)	[redacted]	[redacted]
Deaths n (%)	23/334 (6.9)	20/330 (6.1)
January 2017 data cut off		
Median (95 CI) months	NE (NE, NE)	33.0 (33.0, NE)
HR	0.746 (0.517, 1.078)	
KM 12/30 months (95%CI)	[redacted]	[redacted]
Deaths n (%)	50 (15)	65 (19.7)

- January 2016 interim analysis: [redacted]

Key: Let, letrozole; NE, not estimable; NR, not reached; Pbo, placebo; Ribo, ribociclib.

MONALEESA-2 OS (II)

Kaplan-Meier plot: January 2017 cut-off



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Ribociclib	334	327	323	321	315	310	304	302	299	291	284	266	191	123	63	25	9	2	0
Placebo	334	329	326	322	316	312	306	299	293	286	282	259	185	107	57	22	8	1	0

MONALEESA-2 response rate

n (%; CI)	Local assessment		Central assessment	
	Ribo & Let n=334	Pbo & Let n=334	Ribo & Let n=334	Pbo & Let n=334
January 2016 data cut-off				
CR	9 (2.7)	7 (2.1)	[redacted]	[redacted]
ORR (=CR + PR)	136 (40.7), p<0.001	92 (27.5)	[redacted]	[redacted]
CBR (=CR+PR+[SD or Non-CR/Non-PD>=24 weeks])	266 (79.6; 75.3, 84.0), p=0.018	243 (72.8; 68.0, 77.5)	[redacted]	[redacted]
June 2016 data cut-off				
CR	[redacted]	[redacted]	[redacted]	[redacted]
ORR (=CR + PR)	[redacted]	[redacted]	[redacted]	[redacted]
CBR (=CR+PR+[SD or Non-CR/Non-PD>=24 weeks])	[redacted]	[redacted]	[redacted]	[redacted]

Key: CBR, clinical benefit rate; CR, complete response; Let, letrozole; NR, not reported; Pbo, placebo; PR, partial response; SD, stable disease; ORR, objective response rate; Ribo, ribociclib.

MONALEESA-2 EQ-5D 5-level and AEs
January 2016

EQ-5D 5-level

- Quality of life scores showed that there was no significant difference between the two treatment groups and HRQoL was sustained over the course of the study
- EQ-5D-5L collected at screening, every 8 weeks for 18 months, every 12 weeks afterwards, until disease progression and at end of treatment

AE

- protocol amendment: cardiac safety monitoring (QTc prolongation) additional ECG assessments (day 1 of cycles 4 - 9) in all patients, and in patients with a mean QTcF interval of ≥480 msec before cycle 10 (day 1 of subsequent cycles).
- QTc prolongation events more frequent in ribociclib compared with letrozole [redacted]

Key: EEC, Electrocardiogram; QTcF, QT interval corrected for heart rate as per Fridericia's formula.

MONALEESA-2 AEs January 2016

Any grade AEs n (%)	Ribo + let N=334	Placebo + let N=330[a]
Any AE	329 (98.5)	320 (97.0)
Neutropenia[b]	248 (74.3)	17 (5.2)
Nausea	172 (51.5)	94 (28.5)
Infections	168 (50.3)	140 (42.4)
Fatigue	122 (36.5)	99 (30.0)
Diarrhoea	117 (35.0)	73 (22.1)
Alopecia	111 (33.2)	51 (15.5)
Leukopenia	110 (32.9)	13 (3.9)
Vomiting	98 (29.3)	51 (15.5)
Arthralgia	91 (27.2)	95 (28.8)
Constipation	83 (24.9)	63 (19.1)
Headache	74 (22.2)	63 (19.1)
Hot flush	70 (21.0)	78 (23.6)
Back pain	66 (19.8)	58 (17.6)
Cough	65 (19.5)	59 (17.9)
Anaemia[c]	62 (18.6)	15 (4.5)
Decreased appetite	62 (18.6)	50 (15.2)
Rash	57 (17.1)	26 (7.9)
Increased ALT	52 (15.6)	13 (3.9)
Increased AST	50 (15.0)	12 (3.6)

January 2016

- More patients discontinued due to AEs with ribociclib (7.5% vs. 2.1%) and
- [redacted]

June 2016 data available

- [redacted]

January 2017 data not available

ERG: available evidence MONALEESA-2

- all relevant evidence had been included
- MONALEESA-2 trial is a good quality RCT [redacted]
- patients mostly endocrine sensitive (disease free interval > 12 months) whereas UK patients are somewhat more likely to be moderately sensitive
- [redacted]
- Difference between local and central PFS assessment explained by company:
  - *PFS is a combined end point that may include symptomatic progression (e.g. pain due to bone metastasis) in addition to radiologic progression. Symptomatic deterioration may be a reason to discontinue or alter therapy*.'
  - [redacted]
- CS focused on January 2016 cut-off and local PFS assessment (updated submission used 2017 PFS data)
- ERG considered more recent data and central assessment more appropriate (increased rates of AEs e.g. neutropenia 74% with ribociclib vs. 5% in letrozole, could have unblinded physicians/patients)

Clinical effectiveness and treatment pathway issues

1. How will ribociclib fit into the current treatment pathway?
2. What are the appropriate comparators?
3. Can equivalent efficacy between aromatase inhibitors be assumed?
4. Is a class effect for CDK 4/6 inhibitors likely?
5. How generalisable are MONALEESA-2 results?
   - Is MONALEESA-2 population representative of postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in advanced setting?
6. Local versus central PFS assessment
   - Central assessment not available at the longest follow-up
   - Difference between local and central PFS assessment
7. When can interim and mature OS data from MONALEESA-2 be expected?

Key: HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; PFS, progression free survival.

Cost-effectiveness evidence

Company submission section 5

Preview: cost-effectiveness issues

1. Is the assumption that any gain in PFS is 100% translated into OS gain in the base-case appropriate?
2. Is the PFS local assessment from January 2017 data cut-off appropriate for the modelling?
   - What is the most suitable distribution for PFS modelling?
3. Does the committee accept the relatively high utility value for *PFS1*, compared with previous appraisals in the same disease area?
4. Is the choice of second line treatments appropriate?
5. Is BOLERO-2 representative of HR+/HER2- ABC patients who progressed on ribociclib with letrozole or letrozole monotherapy?
   - Is modelling of OS, PFS and TDD in *PFS2* appropriate?
6. Is the drug acquisition costs estimate in *Progression* of £2,000 per month appropriate?
7. The company has provided a comparison of the inputs and ICERs for ribociclib and the palbociclib appraisal, what is the committee's view of this comparison?

Key: HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative;OS, overall survival; PFS, progression free survival; TTD, time to disease discontinuation.

Company: model structure

Individual patient based state-transition model (life time horizon of 40 years):

PFS1

- ribociclib & letrozole compared with letrozole
- TTD and PFS are modelled independently
- IPD from MONALEESA-2
- base-case: PFS gain = OS gain
- patients cannot move to *Progression* directly

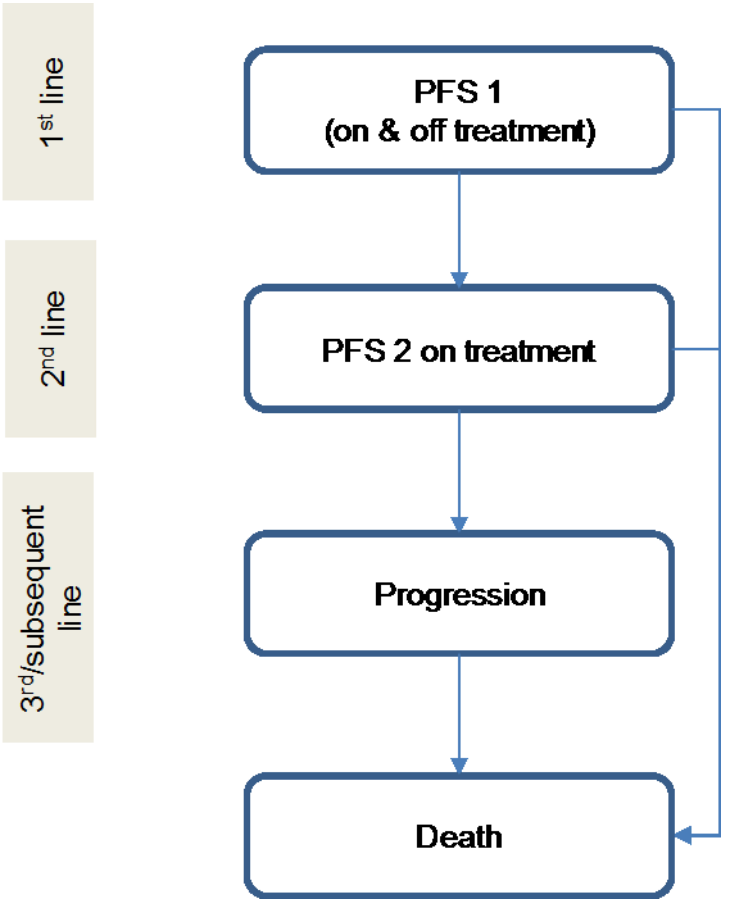
PFS2

- everolimus & exemestane, exemestane monotherapy or capecitabane therapy
- IPD from BOLERO-2: placebo controlled RCT of everolimus & exemestane in postmenopausal women with ER+/HER2- ABC with recurrence/progression on nonsteroidal AIs or to treat advanced disease (or both)

Progression

- subsequent therapies not modelled directly
- cost of £2,000 per month assumed

Death: absorbing state



Key: ABC, advanced breast cancer; AIs, aromatase inhibitors; ER+, estrogen-receptor positive; HER2-, human epidermal growth factor receptor 2-negative; IPD, individual participant data; PFS 1, first-line progression-free survival; PFS 2, second-line progression-free survival; TTD, time to treatment progression.

ERG: model structure

PFS1

- OS is modelled indirectly, and is a function of the time spent in each of the alive health states (*PFS1*, *PFS2* and *Progression*).
- 100% translation of PFS gain into OS gain is not plausible
  - ERG: ratio close to PALOMA-1 trial of 38.5% is more plausible

PFS2

- assumed that only second-line treatment affected the prognosis of patients after they progressed from first-line treatment
- Is BOLERO-2 representative of HR+/HER2- ABC patients who progressed on ribociclib with letrozole or letrozole monotherapy?
- baseline characteristics of MONALEESA-2 and BOLERO-2 comparable, but proportion of Asian people 8% and 20% respectively

Progression

- [redacted]
- Company: [redacted]
- ERG: no confirmation of the results with real world data derived from registries in UK clinical practice provided

Key: HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; PFS, progression free survival.

Company: *PFS1* state (I)
PFS local assessment January 2016 cut-off

PFS modelling:

- Letrozole: lognormal and Weibull distributions = best and second best statistical fit
- Ribociclib: AIC & BIC for Weibull, Gompertz and exponential very similar
- comparison of parametric survival models and KM data of letrozole monotherapy from PALOMA-2, LEA and ALLIANCE trials conducted to explore the plausibility of long-term extrapolation (Figure 5.6 in CS)
- exponential distribution was chosen for PFS extrapolation

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan–Meier; PFS, progression free survival.

Company: *PFS1* state (II) Predicted and observed PFS

Modelled PFS extrapolation against the observed KM: MONALEESA-2 local assessment January 2017 cut-off

Key: KM, Kaplan–Meier; PFS, progression free survival.

ERG: *PFS1* state progression free survival

PFS Central assessment

- Central assessment for latest data follow-up would be preferred
- Company: [redacted]

PFS Local assessment

- Company: in response to clarification questions provided survival analysis based on local assessment of PFS from January 2017 cut-off
- In the absence of central assessment ERG agrees that local assessment from the January 2017 cut-off is appropriate for modelling

PFS Modelling

- log-log cumulative hazard plots were not approximating straight lines: ERG considers piecewise or more flexible models more plausible
- [redacted]
- [redacted]
- [redacted]

Company: *PFS1* state TTD and proportion of deaths amongst PFS events

TTD: **January 2016 data**

- Ribociclib: AIC & BIC: Gompertz distribution is the best fit
  - Exponential distribution deemed better clinical fit and used in base-case
- Letrozole: AIC & BIC: log-normal distribution is the best fit
  - Exponential distribution used in base-case

Proportion of deaths among PFS events: updated to **January 2017 data**

Trial	Event	Letrozole	CDK4/6i
MONALEESA-2 January 2017 cut-off	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
PALOMA-2	Progression events, n	137	194
	Death, n (%)	3 (2.2)	11 (5.7)
Pooled data	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; TTD, time to disease discontinuation.

ERG: *PFS1* state
TTD and proportion of death in PFS events

TTD data
- were not updated using 2017 data.
- The ERG could not assess the impact of using 2017 data to model TDD.
- However, changing PFS inputs from January 2016 to January 2017 had a great impact on the model.

TTD modelling
- TTD and PFS modelled independently but same random numbers used to simulate PFS and TTD time to events (TTD < PFS, but TTD can = PFS in many cases. Joint TTD & PFS analysis would be more robust.

Letrozole discontinuation
- If some MONALEESA-2 patients had letrozole after ribociclib discontinuation, company's ICER may be marginally underestimated

Proportion of deaths among PFS events
- binomial regression and a predictive model for death probability with more covariates than only first line treatment could be used

Key: PFS, progression free survival; TTD, time to disease discontinuation.

Clinical evidence *PFS2* state: BOLERO-2

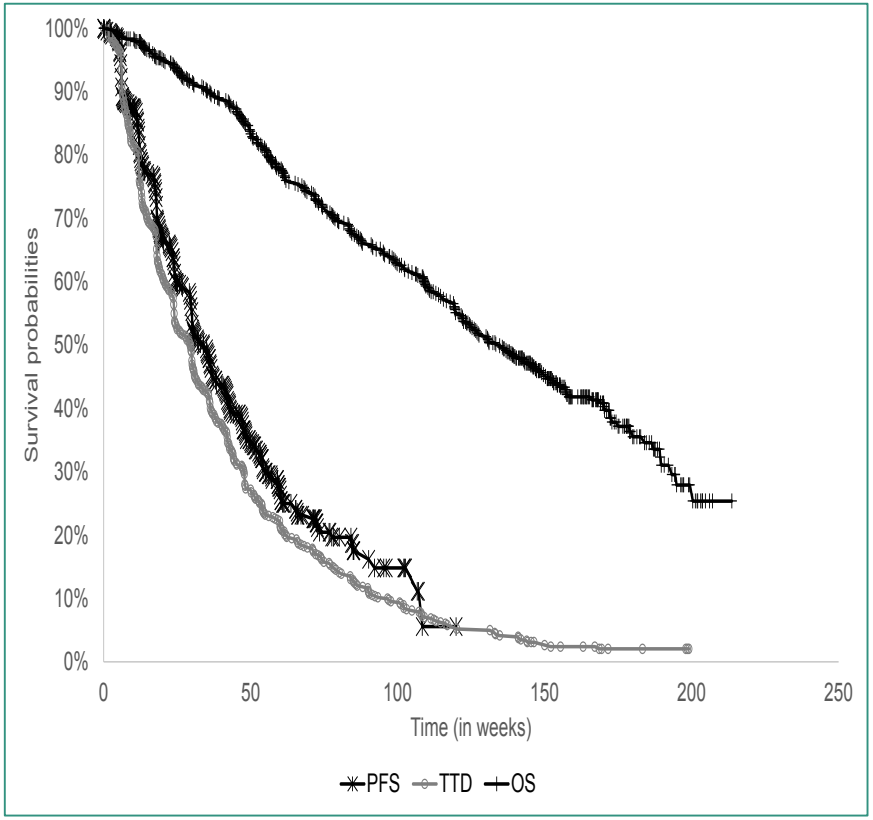
Design	Placebo-controlled phase 3 RCT (randomised on visceral metastasis and sensitivity to endocrine therapy)
Location	Multinational
Population	N=724; postmenopausal women with HR+/HER2- advanced breast cancer refractory to letrozole or anastrozole
Intervention and comparator	• Everolimus 10 mg/day with exemestane 25 mg/day • Placebo with exemestane 25 mg/day
Primary outcome	PFS based on local assessment: the latest data cut-off is December 2011 (no data for PFS collected after this date).
Secondary outcome	• TTD and OS: the latest data cut-off is October 2013. • Overall response rate, clinical benefit rate (proportion of patients with a CR, PR, or stable disease), safety, bone turnover markers and EORTC QLQ-C30 and breast module until disease progression.

Key: EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; OS, overall survival; PFS, progression free survival; TTD, time to disease discontinuation.

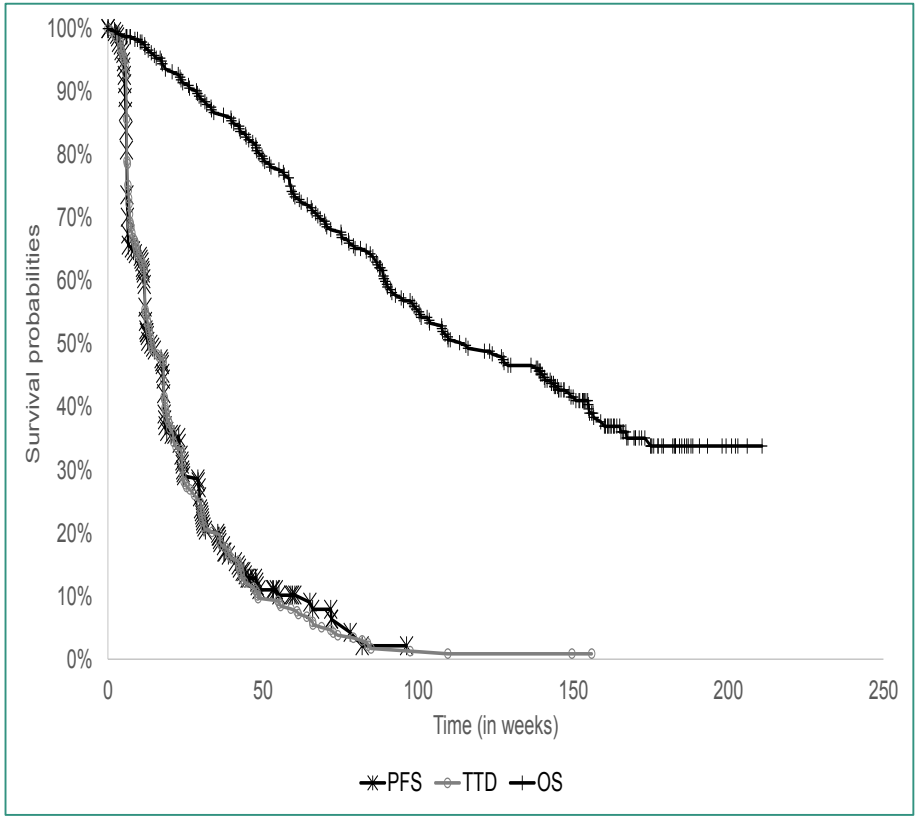
BOLERO-2: PFS, OS and TDD

OS and TTD data: October 2013 cut-off, PFS data: December 2011 cut-off

Everolimus & exemestane BOLERO-2



Exemestane monotherapy BOLERO-2



- TTD and PFS in both arms are relatively similar.
- But slight inconsistency at the end of the curves (where PFS crosses TTD) due to early censoring of PFS; attributable to different cut-off dates.

Key: OS, overall survival; PFS, progression free survival; TTD, time to disease discontinuation.

Company: *PFS2* state (I)

Second-line treatments based on clinical expert opinion:

	Proportion of patients receiving each treatment (%)	
	Ribociclib with letrozole	Letrozole monotherapy
Everolimus + exemestane	70%	30%
Exemestane	5%	40%
Chemotherapy	25%	30%

Time to treatment discontinuation is a proxy for disease progression:

- Everolimus and exemestane:
  - Parametric models fitted to BOLERO-2 KM data, AIC & BIC: log-logistic and log-normal are the best fit & Weibull as in TA421 used in base-case
- Exemestane monotherapy:
  - [redacted]
- Chemotherapy:
  - Inverse HR of 0.30 (95% CI: 0.17 – 0.52) from Li et al. 2015 was applied to curve for everolimus and exemestane

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan–Meier; PFS, progression free survival.

Company: *PFS2* state (II)

Time to death from treatment discontinuation (post-discontinuation survival curve) estimates the time patients spend in progressive disease; this includes:

- the period when patients are progression-free off treatment (*PFS2* off treatment) and
- the period during which patients are in progressive disease (*progression*).

- Everolimus and exemestane pooled
  - AIC & BIC: Gompertz and exponential are the best fit
  - Weibull used in base-case
- Chemotherapy
  - mean post-discontinuation survival estimated as the difference between the mean OS (estimated using an HR) and the mean TTD (estimated using an HR) from Li et al. 2015

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression free survival; TTD, time to disease discontinuation.

ERG: *PFS2* state (I)

Second line treatments

- CG81 recommends anthracyclines and then docetaxel, but based on clinical opinion capecitabine modelled
  - The ERG is still unclear how the proportions were estimated
  - no confirmation of clinical expert's opinions with real world data from UK registries or audits provided
- Choice of second line do not depend only on first-line therapy
- Could be based on MONALEESA-2

BOLERO-2

- No systematic review conducted to identify studies of second-line treatments in HR+/HER- ABC patients
  - The ERG is unsure if the BOLERO-2 trial and Li et al. 2015 were the only relevant studies to inform *PFS2*
- Results with no adjustments used, as BOLERO-2 was conducted in MONALEESA-2 population upon their disease progression

Proportion of deaths

- Company calculated probabilities in a similar way as in *PFS1,* but probabilities depend on many patient characteristics, not only on treatments received

Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PFS, progression free survival.

ERG: *PFS2* state (II)

TTD as a proxy for PFS

- Time spent in *PFS2* may be underestimated because of a gap between TTD and PFS curves of the everolimus and exemestane arm in BOLERO-2
- The ERG question plausibility of this assumption for chemotherapy

Appling HR to TTD curve

- Despite violation of the proportional hazard assumption, survival of exemestane monotherapy is modelled by applying HR from BOLERO-2 trial to everolimus arm
- Adjusted HR of chemotherapy versus "everolimus-based therapy" (Li et al. 2015) used for chemotherapy, but the adjustments & comparator are not explained

Pooled post treatment discontinuation survival

- from BOLERO-2 used as a proxy for the post progression survival
- BOLERO-2 TTD data seems smaller than PFS potentially overestimating survival
- Weibull shape parameter from BOLERO-2 used to model post progression survival for chemotherapy
  - The ERG changed the way chemotherapy post-progression survival times are sampled so the scale parameter is no longer needed

Key: PFS, progression free survival; TTD, time to disease discontinuation.

Company: utilities

Health state	Mean estimate	Standard error	Source	Justification
PF1 on treatment	[redacted]	[redacted]	MONALEESA-2	EQ-5D-5L direct elicitation from study
PF1 off treatment	[redacted]	[redacted]	MONALEESA-2	
PFS2 – on treatment	0.774	Assumed to be 20% around the mean	Lloyd et al. 2006 BOLERO-2 adjusted	EQ-5D sourced directly from NICE TA421
	Chemotherapy decrement of -0.113		Derived from Peasgood et al.	Publication; chemotherapy versus endocrine therapy
PD	0.5052	Assumed: 20% around mean	Lloyd et al 2006	accepted in NICE TA915

PFS1:

- data derived directly from MONALEESA-2 accounting for the impact of AEs associated with the intervention and comparators

Key: AEs, adverse events**;** PD, progressed disease; PF, progression-free.

ERG: utilities

PFS1: EQ5D-5L used in MONALEESA-2

- the mean utility of [redacted] seems high
- The utility of women aged 60 and 65 is 0.81 and 0.78 respectively [redacted]. These utilities were derived from 3L instrument, and 5L values for matched states are higher.
- no statistically significant difference for utilities in MONALEESA-2: disutilities due to AEs not included. Adding the disutilities [redacted] the company's base case ICER (including PAS) [redacted]

Utilities in *PFS2*

- the company did not used utility for PD because [redacted]
- using PD utility from MONALEESA-2 [redacted] the company's base case ICER (including PAS) [redacted]
- Same utility for everolimus and exemestane assumed (0.774). Using separate utilities [redacted] respectively [redacted] the company's base case ICER (including PAS) [redacted]

Key: PD, progressed disease; PF, progression-free.

ERG: costs and AE

AE

- Company: neutropenia (grade ¾) was reported in approximately [redacted] of patients. It was not included in the economic model because:
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- In addition, grade 3/4 leukopenia (21.0% versus 0.6%) and back pain (2.1% versus 0.3%) were not included in model with no explanation.

Wastage cost

- the costs for the unused tablets in the last treatment cycle for letrozole, ribociclib, exemestane, everolimus and capecitabine not included
  - The ERG incorporated expected approximate wastage costs in its base-case to include all relevant cost

3rd-line cost (in *Progression* state)

- a monthly cost of £2,000 based on clinical expert opinion assumed
  - details on how this cost estimate had been derived were not provided.
  - ERG believes the inflation adjusted estimate from TA239,21 of £1,140 to be a more plausible

Company: original base-case results including initial PAS

	Total costs (£)	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
January 2016 cut-off							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
January 2017 cut-off*							
Letrozole	[redacted]	-	[redacted]	-	-	-	-
Ribociclib	[redacted]	-	[redacted]	[redacted]	-	0.90	[redacted]

Probabilistic analyses using 2016 data

	Total costs (£)	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
-							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]

- The probability of ribociclib being cost-effective at £30,000/QALY is [redacted]

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

ERG: Company results

Given the lack of details, the ERG cannot assess the quality and reliability of the PSAs and the one-way sensitivity analysis:

- Company PSAs: key parameters not included (3rd-line costs, chemotherapy disutility, second-line treatments distribution) underestimating the total parameter uncertainty
- Company deterministic sensitivity analysis: Justification of parameters and details of lower/upper bounds calculations are unclear.
  - Tornado diagrams should be interpreted with caution

ERG adjustments

- PFS and proportion of deaths among PFS events based on 2017 data
- fixing programming errors
- incorporating the wastage costs
- using 3rd-line inflation adjusted costs from TA239 (£1,140)
- changing modelling of post-treatment discontinuation survival after second-line chemotherapy
- OS surrogacy based on PALOMA-1 (ratio of 38.5%)

Key: OS, overall survival; PFS, progression-free survival; PSAs, probabilistic sensitivity analyses.

ERG: deterministic results with initial PAS (January 2017 data)

Changes	Ribociclib		letrozole alone		Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs		
1. CS base-case with fixed errors (January 2016 data)	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
1+2: January 2017 PFS	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
1+3: wastage cost	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
1+4: 3rd-line costs from TA239	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
1+5: changing modelling of post-treatment discontinuation survival after chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]	0.95	[redacted]
1+6: changing full PFS-OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	0.58	[redacted]
1 to 6 all: ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

Key: CS, company submission; ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; QALYs, Quality-Adjusted Life Year .

ERG: probabilistic analyses including initial PAS (January 2017 data)

January 2017 cut-off	Total costs (£)	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Deterministic							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Probabilistic							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

[redacted]

The probability of ribociclib being cost-effective at £30,000/QALY is [redacted]

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

ERG: scenario analyses with initial PAS (January 2017 data)

Scenarios	Ribociclib		Letrozole alone		Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs		
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
1: Weibull function for PFS1 and TTD	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
2a: 3rd-line costs costs = £0	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
2b: 3rd-line costs = £2,000 per month	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
3: ribo cost from cycle 11 based on mean costs of cycles 11 to 26	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
4: Full OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
5: 1 & 4	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]
6: similar second-line treatments	[redacted]	[redacted]	[redacted]	[redacted]	0.50	[redacted]

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation. QALYs, Quality-Adjusted Life Year .

ERG: Clinical outcomes from the model
January 2017 data

January 2017	Clinical trial result		Model result	
	Median	Mean	Median	Mean
Ribociclib				
First-line progression-free survival (PFS1)	25.3	Not reached, not reported	[redacted]	[redacted]
Overall survival	Not reached, not reported	Not reached, not reported	[redacted]	[redacted]
Letrozole				
First-line progression-free survival (PFS1)	16	Not reached, not reported	[redacted]	[redacted]
Overall survival	33	Not reached, not reported	[redacted]	[redacted]

- [redacted]

Key: OS, overall survival; PFS, progression-free survival.

Company: Revised base case

Changes to company base case in addition to fixing errors and using 2017 PFS data (changes 1 and 2 in ERG analyses):

- Enhanced PAS
- including the costs of wastage (change 3 in ERG analyses)
- changing the modelling of the post-treatment discontinuation survival after chemotherapy (change 5 in ERG analyses)

Scenario analyses with the remaining changes suggested by ERG were performed:

- Cost of 3rd line therapy based on TA239 (change 4 in ERG analyses)
- PFS-OS surrogacy based on PALOMA-1 (change 6 in ERG analyses)

Key: OS, overall survival; PFS, progression-free survival.

Company: revised base case with enhanced PAS

	Total costs (£)	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
January 2017 cut-off							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]

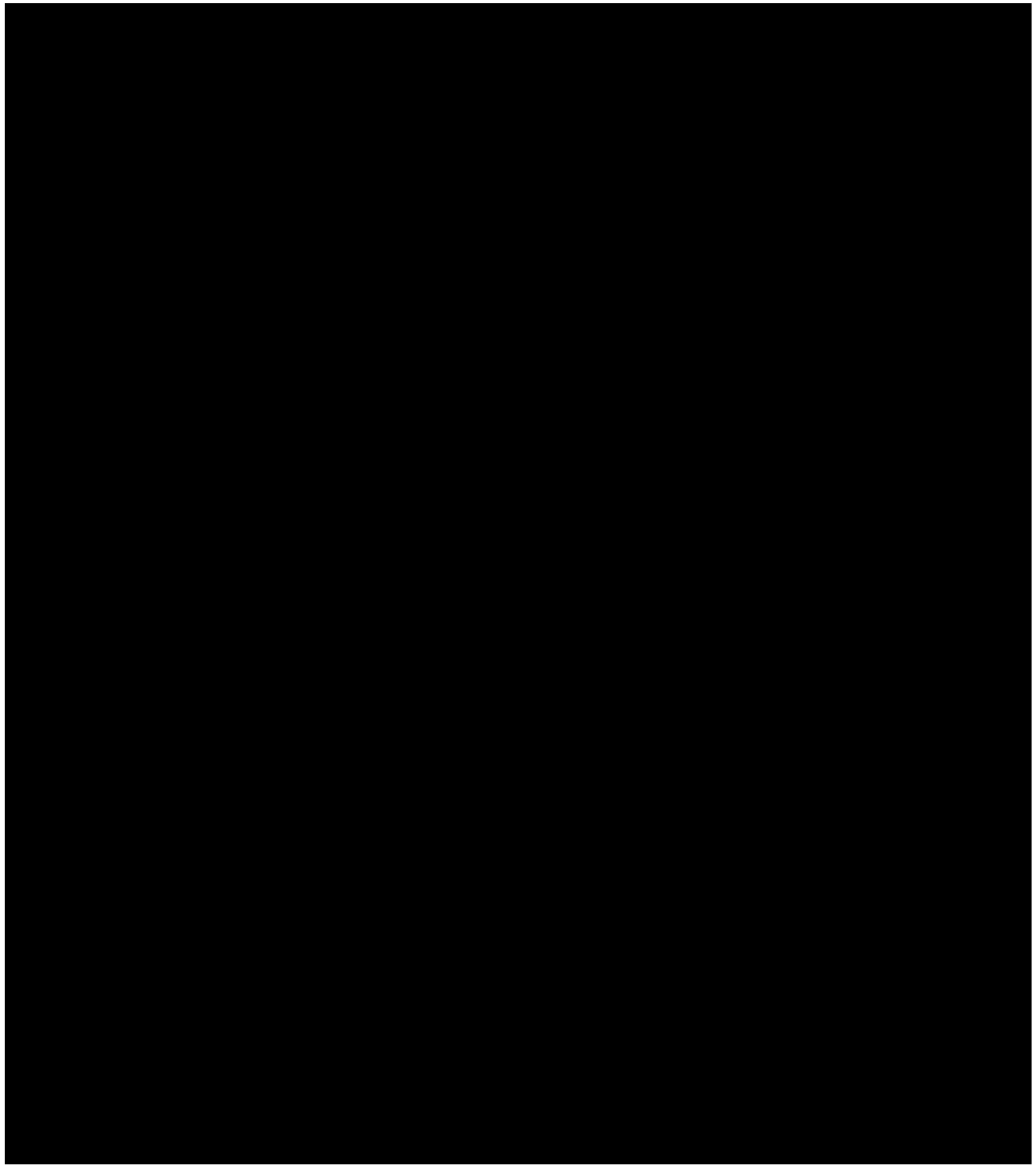
Probabilistic analyses

	Total costs (£)	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
January 2016 cut-off							
Letrozole	[redacted]	[redacted]	[redacted]	-	-	-	-
Ribociclib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.88	[redacted]

- The probability of ribociclib being cost-effective at £30,000/QALY is [redacted]

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

Company: one-way sensitivity analyses with enhanced PAS



Company: scenario analyses including enhanced PAS

Scenarios	Ribociclib		Letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. Base-case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 1) adding ERG post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 2) ERG PFS-OS ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 3) £1,500 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 to 2) Base-case and ERG post-progression costs and PFS-OS ratio Incorporates all ERG's preferred base-case modifications	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 2 + 3) Base-case, ERG PFS-OS ratio and £1,500 3rd line costs: all ERG's changes but 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

Key: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival QALYs, quality-adjusted life years.

ERG: scenario analyses with enhanced PAS

Scenario analyses	Ribociclib		letrozole alone		Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs		
• New CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	**0.89**	[redacted]
a) CS + 3rd line cost from TA421	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
b) CS + PALOMA-1 OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
• ERG base-case (CS + a & b)	[redacted]	[redacted]	[redacted]	[redacted]	**0.53**	[redacted]
• ERG PSA	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
1: Weibull for PFS1 and TTD	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
2a: 3rd-line costs = £0	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
2b: 3rd-line costs = £2,000	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
3: ribo cost from cycle 11 based on mean costs of cycles 11 to 26	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
4: Full OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
5: 1 & 4	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]
6: similar second-line treatments	[redacted]	[redacted]	[redacted]	[redacted]	0.50	[redacted]
7: PFS1 utility = 0.72	[redacted]	[redacted]	[redacted]	[redacted]	0.44	[redacted]

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation. QALYs, Quality-Adjusted Life Year .

Company- End of life criteria

This submission does not meet the criteria for end-of-life as the life expectancy for patients with newly diagnosed HR+/HER2- advanced breast cancer is greater than 24 months.

Equality

- No equality issues were raised.

Company: differences between ribociclib and palbociclib NICE appraisals

(using 2016 data and no PAS)

	Ribociclib ID1026	Palbociclib ID915
Model	IPD simulation State-transition model: *PFS1* (on and off treatment) – 1st line treatment, *PFS2* – 2nd line treatment, *Progressio*n – post second line progression treatments, *Death*	Partitioned survival Markov model: • *Pre-Progression* (1st line treatment), *Post-Progressio*n including tunnel states for 2nd, 3rd, 4th treatments and BSC, *Death*
PFS	MONALEESA-2 clinical trial	PALOMA-2 clinical trial
OS	OS is modelled based on IPD simulation through the state transition model as follows: *PFS2:* everolimus + exemestane & exemestane monotherapy from BOLERO-2 IPD, and HR from Li et al. 2015 used for chemotherapy *Progression:* Modelled based upon BOLERO-2 OS IPD data, Hazard Ratio applied Li et al. 2015	PALOMA-1 clinical trial data (base case analysis)
HRQoL	*PFS1*: MONALEESA-2 clinical trial – EQ-5D-L *PFS2*: Lloyd et al. 2006 & BOLERO-2 adjusted *PD*: Lloyd 2006	PALOMA-2 – EQ-5D *PD*: Lloyd 2006
Utilities	[redacted] *PFS2: 0.774; Progression* : 0.5052 Chemotherapy disutility: -0.113	*PFS*: **0.72*** *Post-Progression*: 0.4492 (all lines)
AE	Grade 3 and 4 adverse events from MONALEESA-2	Only neutropenia
LYG	[redacted]	3.79 palbo & 3.02 let: **difference:0.77**
QALYs	[redacted]	2.40 palbo & 1.77 let: **difference:0.63**
Total costs	[redacted]	Palbociclib: 116,696 & Letrozole: **£21,843**
ICER	[redacted]	**£150,869**

Cost-effectiveness issues

1. Is the assumption that any gain in PFS is 100% translated into OS gain in the base-case appropriate?
2. Is the PFS local assessment from January 2017 data cut-off appropriate for the modelling?
   - What is the most suitable distribution for PFS modelling?
3. Does the committee accept the relatively high utility value for *PFS1*, compared with previous appraisals in the same disease area?
4. Is the choice of second line treatments appropriate?
5. Is BOLERO-2 representative of HR+/HER2- ABC patients who progressed on ribociclib with letrozole or letrozole monotherapy?
   - Is modelling of OS, PFS and TDD in *PFS2* appropriate?
6. Is the drug acquisition costs estimate in *Progression* of £2,000 per month appropriate?
7. The company has provided a comparison of the inputs and ICERs for ribociclib and the palbociclib appraisal, what is the committee's view of this comparison?

Key: HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative;OS, overall survival; PFS, progression free survival; TTD, time to disease discontinuation.

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- **Joanna Richardson**
  Technical Adviser
- with input from the Lead Team: Brian Shine, Mohit Sharma and Pamela Rees

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

Company evidence submission

23 March 2017

File name	Version	Contains confidential information	Date
		Yes	**01/09/17**

Novartis Pharmaceuticals UK Limited

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

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List of figures

Abbreviations

AE	AE
AI	aromatase inhibitor
AIC	Akaike's Information Criterion
ALT	alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BIC	Bayesian Information Criterion
BNF	British National Formulary
CBR	clinical benefit rate
CDK4/6	cyclin-dependent kinase 4 and 6
CI	confidence interval
CHF	Swiss Franc
CR	complete response
DSU	Decision Support Unit
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC QLQ Questionnaire	European Organization for Research and Treatment of Cancer Quality of Life
ESO-ESMO	European School of Oncology-European Society for Medical Oncology
FBC	full blood count
G1	gap1
G2	gap2
GHS/QoL	Global Health Status/Quality of Life
HER2-	human epidermal growth factor receptor 2-negative
HR	hazard ratio
HR+	hormone receptor-positive
HRQoL	health-related quality of life
HSU	health state utility
ICER	incremental cost-effectiveness ratio
INK4	inhibitor of CDK4
IPD	Individual Patient Data
ITT	intention-to-treat
KM	Kaplan–Meier
LFT	liver function test
LYG	life year gained
M	mitosis
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NICE	National Institute of Health and Care Excellence
NHS	National Health Service
NR	not reached
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS1	first-line PFS
PFS2	second-line PFS
PR	partial response
PS	performance status
PSSRU	personal social services research unit
QALY	quality-adjusted life year
QTcF	QT interval corrected for heart rate as per Fridericia's formula
Rb	retinoblastoma
RCT	randomised controlled trial
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumors
S	DNA synthesis

SAE	serious AE
SD	standard deviation
TdP	Torsade de Pointes
TTD	time to treatment discontinuation

1 Executive summary

Breast cancer is one of the most common cancers affecting women worldwide and a leading cause of cancer deaths.[3] Despite advances in the understanding of different forms of breast cancer and improvements in the treatment and management of patients, breast cancer remains a potentially life-threatening diagnosis, in large part because of breast cancer recurrence and the incurability of advanced disease; both remain major clinical challenges.[4] Advanced breast cancer is considered to include both locally advanced and stage IV (metastatic) cancer,[5,6] and the median survival of patients with advanced breast cancer is just 2–3 years.[7]

Breast cancer is a heterogeneous disease and there are a number of recognisable histological and intrinsic subtypes distinguished by the expression of oestrogen receptors, progesterone receptors and epidermal growth factor receptors (HER2), and by distinct gene profiles that affect prognosis and outlook.[8-10] This submission concerns the management of patients found to have HR+/HER2- breast cancer.[10] Around 75% of postmenopausal women with breast cancer have tumours that are hormone receptor positive (HR+),[11] and HR+/HER2- is the most common form of breast cancer.[10,12]

Tumours that are HR+/HER2- tend to be slow growing, but while the expression of hormone receptors is predictive of a response to endocrine therapy, progression of these tumours is almost inevitable and cure rates are low.[10,13] There is thus a need for therapies to improve the initial response to endocrine therapy and to reduce the risk, or delay the development, of resistance, thus prolonging the duration of remission achieved with endocrine therapy. This in turn delays the need to progress to chemotherapy and helps preserve health-related quality of life (HRQoL) and reduce the burden on carers.

Ribociclib is an innovative therapy which targets a key pathway in the cell cycle that is dysregulated in breast cancer and appears to play a role in poor responses to endocrine therapy in HR+ disease. [12,14-17] Ribociclib inhibits cyclin-dependent kinases (CDK4/6) thus preventing the phosphorylation of retinoblastoma (Rb) protein and restoring the growth-inhibitory effects of this cell-cycle regulator. Ribociclib thus directly targets a driver of tumourigenesis in breast cancer – the dysregulation of CDK-driven control of normal cell cycling. This innovative mechanism of action appears particularly important in HR+ breast cancers where changes in CDK/cyclin D1/Rb activity and interactions can affect responsiveness to endocrine therapy in metastatic disease.[12,15,16,18] Aromatase inhibitors such as letrozole are believed to act through decreasing the activity or expression of cyclin D1, leading to reduced phosphorylation (and hence reduced activity) of Rb (in addition to direct effects on gene transcription). By inhibiting CDK4/6, ribociclib thus acts synergistically with aromatase inhibitors, restoring sensitivity to endocrine therapy. Indeed, the 2016 European School of Oncology-European Society for Medical Oncology (ESO-ESMO) international consensus guidelines state that the introduction of selective CDK4/6 inhibitors such as ribociclib represent the most important therapeutic advance in the management of breast cancer in recent years.[7] These agents are considered to have the potential to change the therapeutic landscape for HR+ disease.[13-15]

The current NICE pathway of care and guidance regarding the therapeutic management of advanced breast cancer and the ESO-ESMO consensus guidelines for advanced breast cancer (ABC3), recommend endocrine therapy as the first-line treatment for the majority of patients.[7,19] The 2016 ESO-ESMO international consensus guidelines in addition recommend use of a CDK4/6 inhibitor in combination with aromatase inhibitors as a preferred option, whenever available.[7] According to the NICE pathway of care and the ESO-ESMO guidelines, chemotherapy should only be a first-line option in patients whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement. In such patients, endocrine therapy should then be offered on completion of chemotherapy.[19] Ribociclib may thus have a major role in the management of patients with HR+/HER2- advanced breast cancer.

1.1 Statement of decision problem

Table 1 summarises the decision problem relating to this submission.

Table 1 The decision problem

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

Economic analysis	The reference case stipulates that the cost-effectiveness of treatments, should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.		-
Subgroups to be considered		None	No subgroup identified as ribociclib in combination with letrozole benefited all patients regardless of subgroup in MONALEESA-2
Other considerations		None	N.A.

1.2 Description of the technology being appraised

As summarized in Table 2, the anticipated indication for ribociclib is for use in combination with an aromatase inhibitor, for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer as initial endocrine-based therapy. Ribociclib is administered orally once daily. Dose reductions are permitted to manage treatment-related adverse events (AEs).

Table 2 Technology being appraised

UK approved name and brand name	Approved name: Ribociclib (LEE011) Brand name: Kisqali™
Marketing authorization	Ribociclib received Marketing Authorisation on on 22nd August 2017
Indications and any restriction(s) as described in the summary of product characteristics	Ribociclib is indicated for use in combination with an aromatase inhibitor for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer as initial endocrine-based therapy.

	Ribociclib is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.
Method of administration and dosage	Oral The recommended regimen is 600 mg (three 200 mg tablets) once daily for 21 days of a 28-day cycle.[20] Dose reductions from 600 mg to 400 mg to 200 mg per day are permitted to manage treatment-related AEs

1.3 Summary of the clinical effectiveness analysis

Evidence for the efficacy and safety of ribociclib in combination with an aromatase inhibitor is largely based on the results of a large multicentre randomised double-blind, placebo controlled phase 3 study – the MONALEESA-2 study – which compared ribociclib plus letrozole versus letrozole alone.[21] In this study, the primary endpoint, progression-free survival (PFS), was met at the planned interim analysis; the interim results demonstrated statistically significant improvement in PFS for the combination over letrozole alone, ribociclib plus letrozole reduced the risk of death or progression by 44% (HR 0.56; 95% CI: 0.43–0.72; p=3.29×10-6). The regimen investigated in the phase 3 study – 600 mg once daily given according to the 3 weeks on/1 week off schedule – was chosen based on the results of a phase 1 dose-escalation study of single-agent ribociclib in patients with solid tumours (CLEE011X2101, NCT01237236),[22] and is supported by results from a phase 1b/2 study of ribociclib in combination with letrozole in patients with advanced HR+ breast cancer (CLEE011X2107, NCT01872260).[23] These two studies thus provide further data regarding the safety profile of ribociclib. The phase 1b/2 study ((CLEE011X2108, NCT02088684)[24] has reported safety data and preliminary data regarding clinical activity for ribociclib in combination with fulvestrant and thus provides supporting evidence for the clinical value of adding ribociclib to endocrine therapy in patients with HR+/HER2- advanced breast cancer.

1.3.1 Efficacy

Evidence for the efficacy and safety of ribociclib in combination with an aromatase inhibitor for the management of HR+/HER2- breast cancer comes from the pre-planned interim analysis of a large multicentre randomised double-blind, placebo-controlled phase 3 study – the MONALEESA-2 study.[21] This study was conducted in postmenopausal women with HR+/HER2- advanced or metastatic breast cancer (n=668) who had received no prior therapy for advanced disease. The study randomised patients 1:1 to receive ribociclib (600 mg once daily, days 1–21 of a 28-day cycle) plus letrozole (2.5 mg once daily, continuous treatment) or placebo plus letrozole (2.5 mg once daily, continuous treatment). Dose reductions for ribociclib (from 600 mg to 400 mg to 200 mg per day) were permitted to manage AEs. Treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of ribociclib or letrozole.

The primary outcome measure was PFS as per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, based on local radiological assessment and the study was powered for significance. The key secondary endpoint was overall survival (OS) and other secondary outcomes included objective response rate (ORR, complete or partial response), clinical benefit rate (CBR, overall response plus

stable disease lasting 24 weeks or more), safety, and health-related quality of life (HRQoL). A pre-specified interim analysis was planned after 70% of PFS events (i.e. after 211 or 302 events) and the superiority of ribociclib was defined as a hazard ratio (HR) of 0.56 or less with $p<1.29\times10^{-5}$. The final analysis was planned after 302 PFS events with 93.5% power to detect a 33% risk reduction (HR, 0.67) with a one-sided α of 2.5%. Up to four analyses were planned for OS with the first being performed at the time of the interim analysis for PFS (provided PFS was significant).

A total of 668 patients were randomised (intention-to-treat [ITT] population) and at the time of data cut-off for the interim analysis, a total of 349 patients (52.2%) were still on treatment (ribociclib, n=195; placebo, n=154). Almost all (≥99% patients) had stage IV disease, approximately 34% were newly diagnosed and all were HR+/HER2-. Approximately 45% of patients were ≥ 65 years, Visceral disease (including liver, lung and other visceral metastasis) was present in 58.8%, and 22.0% had bone-only disease. The median duration of follow-up from randomisation to data cut-off for the interim analysis was 15.3 months.

The study achieved its primary objective, demonstrating superior PFS for ribociclib plus letrozole over placebo plus letrozole. Median PFS was significantly longer and was not reached in the ribociclib group (95% confidence interval [CI]: 19.3–not reached [NR]) versus 14.7 months (95% CI, 13.0–16.5) in the placebo group. The addition of ribociclib to letrozole reduced the risk of death or progression by 44% (HR 0.56; 95% CI: 0.43–0.72; p=3.29×10-6). The Kaplan–Meier (KM) PFS curves diverged from the time of first tumour assessment at week 8 onwards with the PFS probability remaining higher for ribociclib plus letrozole relative to placebo plus letrozole at any subsequent time point indicating an early and sustained advantage for the ribociclib combination.

Good agreement between the central radiology review of tumour response and local assessment, together with a sensitivity analysis based on the per protocol set, demonstrated that this observed improvement in PFS was robust. Further, the improvement in PFS was consistent across all pre-defined subgroups, including patients expected to be sensitive to endocrine therapy (i.e. newly diagnosed disease and those who had not received prior endocrine therapy) and patients with visceral metastases or with bone-only metastases.[21,25,26]

The primary efficacy outcome was further supported by significant improvements in ORR (40.7% versus 27.5%, p < 0.001) and clinical benefit rate (79.6% vs. 72.8%, p=0.018) in the full analysis set, as well as in the subgroup of patients with measurable disease at baseline (ORR 52.7% vs. 37.1%; CBR 80.1% vs. 71.8%).[21] OS data were not mature at the time of the pre-planned interim analysis. The study remains blinded for follow-up of OS and three further analyses of OS are planned.

Taken together, the results from this trial provided robust evidence for the benefits of ribociclib in patients receiving first-line endocrine therapy for advanced HR+/HER2- breast cancer.

1.3.2 Safety

The safety profile of ribociclib in combination with a non-steroidal aromatase inhibitor has been conclusively demonstrated in the results of the phase 3 MONALEESA-2 study,[21] and is supported by

data from a phase 1 study of ribociclib monotherapy in patients with solid tumours or lymphoma,[22] and a phase 1b/2 study of ribociclib plus letrozole in patients with advanced HR+/HER2- breast cancer.[23]

Ribociclib was generally well tolerated in MONALEESA-2. The incidence of grade 3/4 AEs and serious AEs (SAEs) was higher for patients receiving treatment with ribociclib plus letrozole than placebo plus letrozole, but most of the AEs were successfully managed with dose reductions or interruptions. Few patients discontinued therapy for AEs; the incidence was 7.5% for ribociclib plus letrozole and 2.1% for placebo plus letrozole.[21] The incidence of on-treatment deaths was low in both the treatment groups.

The majority of patients in both treatment groups experienced at least one AE (98.5% vs. 97%) and approximately 81% (ribociclib) and 33% (placebo) experienced grade 3/4 AEs. SAEs considered related to treatment were reported in 7.5% of patients receiving ribociclib (compared with 1.5% of patients in the placebo group). Most non-haematological AEs were grade 1 or 2 in severity, although grade 3/4 elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were reported for 31 (9.3%) and 19 (5.7%) of patients, respectively, receiving ribociclib.

Haematologic AEs reflected the effect of ribociclib on bone marrow stem cells, with neutropenia being the most frequently reported grade 3/4 AE, reported in approximately 60% of patients (compared with 1% for placebo). Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 16 days, and the median time to resolution of grade ≥3 (to normalisation or grade ≤2) was 15 days following treatment interruption and/or dose reduction.[20,21] CDK4/6 inhibitors induce bone marrow suppression through cell-cycle arrest and, as such, the neutropenia is readily reversible upon withdrawal of the CDK4/6 inhibitor.[27] This was observed in MONALEESA-2 where the median time to resolution of grade 3/4 neutropenia was 15 days. Thus, only 3 (<1%) patients discontinued ribociclib therapy due to neutropenia. The reversible nature of the neutropenia induced by ribociclib is also the rationale for the 3 weeks on/1 week off regimen chosen for investigation in the phase 1 study and subsequently used in the phase 1b/2 CLEE011X2107 study and MONALEESA-2. Only 5 (1.5%) patients experienced febrile neutropenia in MONALEESA-2 and no patients discontinued therapy due to febrile neutropenia; 7.8% of patients in the ribociclib group received granulocyte-colony stimulating factor. In the phase 1b/2 CLEE011X2107 study, neutropenia was the only grade 3/4 AE reported in > 5% of patients, occurring in 60% of patients, thus being consistent with the results for MONALEESA-2.[23]

Grade 3/4 elevation of liver enzymes was observed in approximately 15% (9.3% ALT and 5.7% AST) of patients receiving ribociclib in MONALEESA-2 and was consistent with observations in other studies of CDK4/6 inhibitors given in conjunction with aromatase inhibitors (AIs).[28] Most grade 2 or worse transaminases elevations occurred within the first six months of treatment. The median time to onset was 57 days for the ribociclib plus letrozole treatment group and the median time to resolution (to normalisation or grade ≤2) was 24 days. Treatment discontinuation due to elevation of liver enzymes of hepatotoxicity occurred in 6% of patients. Most cases were asymptomatic and reversible, being managed by dose adjustment or treatment interruptions. Five cases (four in ribociclib plus letrozole group and one in placebo plus letrozole group) of biochemical Hy's Law (with ALT or AST>3×ULN and

total bilirubin >2×ULN and ALP <2×ULN) were reported in the study. None of the Hy's law cases were fatal and the liver parameters for all the cases returned to normal ranges within five months.

Nonclinical studies with ribociclib suggest that ribociclib has the potential to delay ventricular repolarization in humans and thus, may contribute to QT interval corrected for heart rate as per Fridericia's formula (QTcF) prolongation. The potential for QTcF prolongation with ribociclib was assessed in the phase 1 study and contributed to the choice of 600 mg once daily as the dose for further investigation as it was noted that the incidence of QTcF prolongation was dose dependent at doses above 600 mg.[22] In the absence of substantial accumulation of ribociclib and its metabolite over time, dose interruption and/or reduction thus appears to be an effective way to manage QT interval prolongation in patients during treatment with ribociclib. In MONALEESA-2, QTcF prolongation to >480 msec occurred in 3.3% of patients receiving ribociclib, with a median time to onset of 15 days. All cases resolved with appropriate management; only 0.9% of patients required dose interruptions/adjustments and one (0.3%) discontinued due to QTcF interval prolongation; there were no cases of Torsade de Pointes (TdP). Patients with QTcF >450 msec were excluded from MONALEESA-2.

Four deaths occurred in patients on treatment, three in the ribociclib group and one in the placebo group. One death in each group were considered to be related to primary disease or disease progression. The remaining two deaths in the ribociclib group were due to sudden death (considered related to ribociclib and occurring on day 11 in cycle 2 in association with grade 3 hypokalaemia and grade 2 prolongation in the QTcF interval, probably due to intake of a prohibited concomitant medication with a known risk for QT prolongation), and death from unknown cause (not related to ribociclib).[21] Deaths occurring beyond the treatment period were considered to be related to the underlying disease.

Thus, safety data from MONALEESA-2, supported by data from the phase 1b/2 CLEE011X2107 study, suggest that ribociclib is well tolerated and AEs are generally manageable with dose reductions or treatment interruptions; monitoring for QTcF prolongation is required at the beginning of treatment.

1.3.3 HRQoL during treatment with ribociclib

HRQoL was assessed in the MONALEESA-2 study and was found to be generally sustained or to show a slight improvement in both groups over the course of the study, thus suggesting that AEs associated with ribociclib did not compromise on HRQoL or effects were outweighed by improvements associated with disease remission. Scores for the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 Global Health Status/Quality of Life (GHS/QoL) were similar in the two groups throughout the study and showed a slight improvement over the course of the study. At 10 months, a 10% deterioration in QLQ-C30 GHS/QoL score was observed in 21.4% and 25.3% of patients in the ribociclib and placebo groups, respectively. The time to 10% deterioration in GHS/QoL did not differ significantly between the two groups (HR 0.890; 95% CI: 0.670–1.182). No clinically meaningful changes from baseline and no clinically meaningful differences between treatment groups were observed for EORTC QLQ-C30 sub-scales (functional or symptom scales), QLQ-BR23 and EQ-5D-5L scores. [redacted]

[redacted]

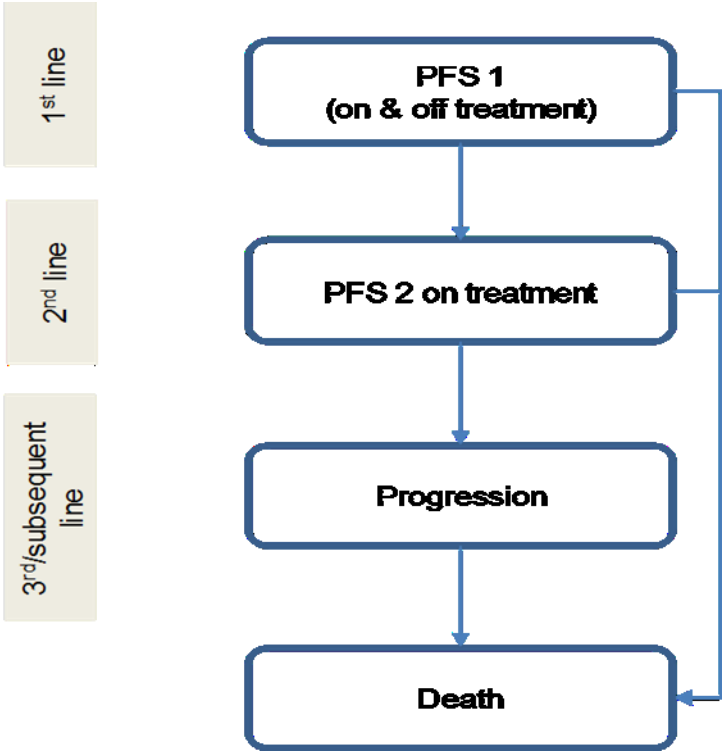
1.3.4 Conclusions

Results from the phase 3 MONALEESA-2 study, supported by those of the phase 1b/2 CLEE011X2107 study, demonstrate that the addition of ribociclib to the non-steroidal aromatase inhibitor, letrozole, significantly improves outcomes for patients with HR+/HER2- advanced or metastatic breast cancer. The significant prolongation in PFS translates into risk reduction of death or progression by 44% (HR 0.56; 95% CI: 0.43–0.72; p=3.29×10-6), these results can be expected to provide clinically meaningful benefits for patients, extending their duration of remission and delaying the need to progress to chemotherapy with sustained HRQoL during treatment. Benefits were observed in all patient subgroups considered, including those with *de novo* disease (as well as those who had received therapy in the adjuvant setting), and in patients with visceral metastases and those with bone-only metastases. Few patients died during the median follow-up of 15.3 months and hence OS data are as yet immature. Therapy was generally well tolerated with most AEs being successfully managed with dose reductions or treatment interruptions. Few patients (7.5%) discontinued therapy for AEs and the incidence of on-treatment deaths was low (n=3, 0.9%). These data suggest that the addition of ribociclib to standard-of-care endocrine therapy represents a significance advance in the management of HR+/HER2- advanced or metastatic breast cancer.

1.4 Summary of the cost-effectiveness analysis

A de novo individual patient based state-transition model consisting of four health states (First-Line PFS, Second-Line PFS, Progression and Death) compared ribociclib in combination with letrozole versus letrozole monotherapy in postmenopausal HR+/HER2- advanced/metastatic breast cancer patients who had not previously received adjuvant endocrine treatment. For both costs and health benefits, in line with NICE guidance, an annual discount rate of 3.5%, the base case analysis time horizon was lifetime (40 years). There was no cycle length applied in the model, as it was individual patient based with a time to event approach.

Figure 1 Cost-effectiveness model structure



PFS data was modelled for both PFS1 and PFS2 health states using parametric survival function best fits and extrapolated, while OS data was modelled using parametric survival function best fits from the progression health state. The model was used as it allowed for greater incorporation of the patient pathway while accounting for immature MONALEESA-2 OS data. The clinical data informing the first-line PFS for both ribociclib plus letrozole and letrozole monotherapy came from the most recent available Individual Patient Data (IPD) from the pivotal MONALEESA-2 clinical study. Second-line treatment PFS and OS was modelled on IPD from the final data cut of the BOLERO-2 trial. A further study, Li et al, 2015, was utilised to allow for chemotherapy treatments to be incorporated in the model. The choice of survival extrapolation was based on NICE Decision Support Unit (DSU) guidance for both data modelled using parametric functions.

In the base case analysis, first-line PFS was modelled using the Exponential function as based on visual inspection, statistical goodness-of-fit and external clinical expert validation, which provided the most clinically plausible modelled prediction values. In particular, clinical validation for the letrozole arm, which has longer real world usage.

In the base case analysis, OS is modelled indirectly through applying the appropriate patient pathway and modelling the second-line PFS and subsequent survival (OS) curve from the BOLERO-2 clinical data. The Weibull parametric function is applied to both PFS and OS for PFS2 health state and the Progression Health State. This was based upon visual inspection, statistical goodness-of-fit and

previous NICE appraisal recommendations. The model allows for patients to experience one of three second-line treatments, everolimus + exemestane, single agent endocrine therapy (exemestane used) and chemotherapy. The everolimus + exemestane arm and exemestane only arms where modelled directly from the BOLERO-2 IPD, however a further study Li et al, 2015 provided Hazard Ratios for the chemotherapy versus everolimus, these HRs were thus applied for chemotherapy.

The results from the base case analysis are summarised in Table 3, where the Exponential distribution for first-line PFS and Weibull distribution, second-line PFS and subsequent survival, were used for survival extrapolation.

Limitations of the cost-effectiveness analysis relate to immaturity of the survival data and gaps in the evidence base as follows:

- MONALEESA-2 OS data are currently immature and not used to model survival.
- The individual patient based State-Transition model differs from the traditional cohort based partitioned-survival models used in oncology appraisals. The model used also requires a number of assumptions, although these were informed through expert clinical validation.

The presented cost-effectiveness analysis indicates that at current NICE thresholds and at list price, ribociclib in combination with letrozole would [redacted] the significant benefit in progression free survival demonstrated in the MONALEESA-2 clinical study. The strengths of the modelling approach are:

- Allows for a more detailed modelling of the patient pathway through inclusion of treatments patients would receive post first-line treatment progression
- Utilises the most amount of long-term, mature clinical data to inform the model.
- Allows for flexibility to approach the relationship of PFS to OS without multiple tunnel states
- The model was developed through clinical validation and thus presents a robust patient pathway approach
- A number of sensitivity analyses have been performed and support the robustness of the base case analysis

Table 3 Incremental cost-effectiveness results

Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline (letrozole)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib in combination with letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]

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

2 The technology

2.1 Description of the technology

- Brand name: Kisqali®[20]
- Approved name: Ribociclib (LEE011)
- Pharmacotherapeutic group: not yet assigned

Ribociclib is a highly selective small molecule inhibitor of cyclin-dependent kinase

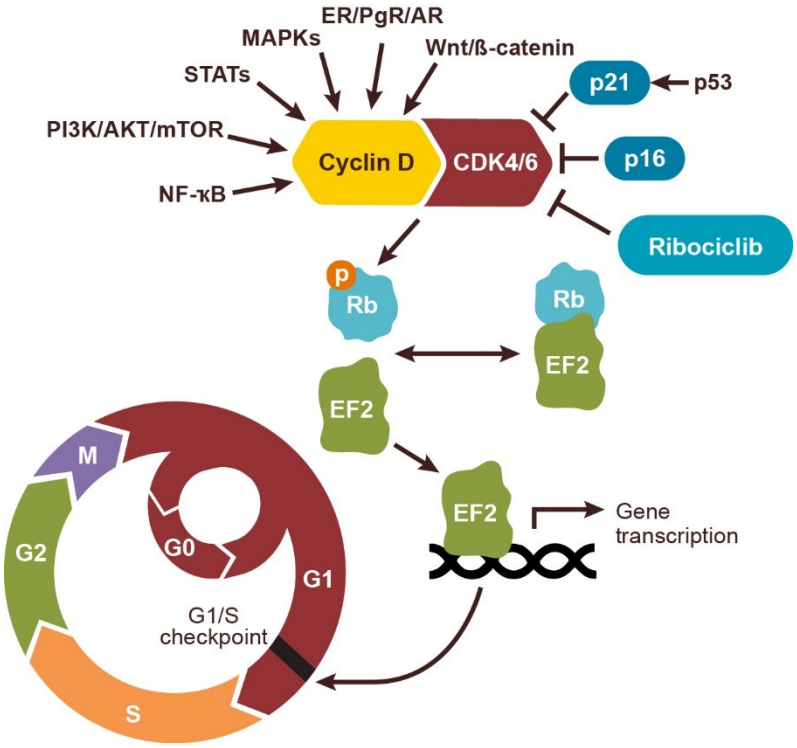
Ribociclib is an orally bioavailable, potent and selective inhibitor of cyclin-dependent kinase 4 and 6 (CDK4/6).[14,15,20] Agents that act as CDK4/6 inhibitors are a new class of therapeutic agent with the potential to improve outcomes in patients with hormone receptor-positive (HR+) breast cancer.[12-14,18]

Cancer cells exhibit sustained, chronic proliferation and often evade normal growth-suppressor signals due to disruption of normal cell-cycle regulation.[14,29] The cell cycle involves four recognised phases that a cell must pass through in order to divide and replicate: the gap1 (G1) phase, the DNA synthesis (S) phase, the gap2 (G2) phase and the mitosis (M) phase.[14,29] Progression from the G1 to the S phase involves a restriction point that determines whether a cell continues to divide or becomes quiescent.[15] CDK4/6 are members of a family of enzymes that play a key role in governing and controlling this step in cell cycling (Figure 2).[14] In normal cells, the interaction of CDK4 and CDK6 with cyclin D1 leads to the phosphorylation and inactivation of an antigrowth agent – the Rb tumour suppressor protein. By inactivating Rb, CDK4 and CDK6 enzymes promote progression from the G1 to the S phase of the cell cycle.[14,15]

Research has shown that an imbalance of the cyclin D and CDK pathway in cancer cells is associated with a proliferative phenotype.[15] Indeed, a number of genetic and epigenetic mechanisms have been linked with deregulation of the CDK4/6-Rb pathway in cancers, including loss or mutation of Rb; amplification of CDK4 or gene encoding-type cyclins such as *CCND1* (which encodes cyclin D1); overexpression of D-cyclins; and loss of function of endogenous CDK4/6 inhibitors.[12,14,15,29] In human breast cancers, *CCND1* amplification and CDK4 overexpression are common.[15] Further evidence for the importance of the cyclin D-CDK4/6-Rb pathway in breast cancer comes from research suggesting that aromatase inhibitors may effect their actions on HR+ breast cancer cells by decreasing cyclin D1 expression and activity,[30] and from the finding that cyclin D-CDK4/6-inhibitor of CDK4 (INK4)-Rb pathway activation is associated with a poor response of breast cancer cells to endocrine therapy.[17] HR+ breast cancer appears to be particularly dependent on CDK/cyclin D1/Rb interactions and there is evidence that CDK4/6 inhibitors are more potent in HR+ cancer cell lines.[12] Furthermore, it is thought that resistance to endocrine therapy in HR+ tumours may be linked with cyclin D overexpression,[13,14] and it has been shown that CDK4/6 inhibition blocks cell-cycle progression in endocrine-resistant breast cancer cells.[31]

Pharmacological inhibition of CDK4/6 can prevent the phosphorylation of the Rb protein – restoring and reactivating Rb anti-growth signalling – resulting in cell-cycle arrest in the G1-S phase.[15]

Figure 2 Regulation of cell-cycle progression through the CDK4/6 pathway and inhibition by ribociclib



AKT, protein kinase B; AR, androgen receptor; CDK, cyclin-dependent kinase; EF2, E2 transcription factor; ER, oestrogen receptor; G1, gap 1; G2, gap 2; M, mitosis; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PgR, progesterone receptor; PI3K, phosphatidylinositol-3-kinase; Rb, retinoblastoma; S, DNA synthesis; STAT, signal transducer and activator of transcription; Wnt, Wingless-type MMTV integration site family member.
Lehn *et al*. 2011;[32] Thangavel *et al*. 2011.[17]

The highly selective CDK4/6 inhibitor, ribociclib, has demonstrated antitumour activity *in vitro* and *in vivo* – causing cell-cycle arrest in Rb-positive cell lines and showing antitumour activity in a variety of xenograft tumour models, including phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)-mutant breast cancer and HR+ models. This has been demonstrated for ribociclib as a single agent, and in combination with the AI letrozole and with phosphatidylinositol 3-kinase (PI3K) inhibitors[14,15,29,33] (see also section 2.5).

2.2 Marketing authorisation/CE marking and health technology assessment

A marketing authorisation application for ribociclib, for use in combination with an AI, for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer as initial endocrine-based therapy was submitted to the European Medicines Agency (EMA) in September 2016. A positive opinion from the EMA was received on 22nd August 2017 for use in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy.

The anticipated UK launch for ribociclib, in combination with an aromatase inhibitor, for the treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy is August 2017.

[redacted]

2.3 Administration and costs of the technology

Considerations related to the cost of ribociclib therapy are summarized in Table 4.

Table 4 Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Film-coated tablet	SmPC[20]
Acquisition cost (excluding VAT)[a]	600 mg £2,950 400 mg £1,966.67 200 mg £983.33	Novartis data on file
Method of administration	Oral	SmPC[20]
Doses	600 mg (three 200 mg tablets) once daily for 21 days of 28-day cycle	SmPC[20]
Dosing frequency	See above	
Average length of a course of treatment	[redacted] months	CSR Treatment exposure
Average cost of a course of treatment	[redacted]	
Anticipated average interval between courses of treatments	Given continuously until disease progression	SmPC[20]
Anticipated number of repeat courses of treatments	[redacted]	
Dose adjustments	Dose reductions from 600 mg to 400 mg to 200 mg per day are permitted to manage treatment-related AEs	SmPC[20]
Anticipated care setting	Secondary	

[a] Indicate whether this acquisition cost is list price or includes an approved patient access scheme. When the marketing authorisation or anticipated marketing authorisation recommends the intervention in combination with other treatments, the acquisition cost of each intervention should be presented.

SmPC, Summary of Product Characteristics.

Ribociclib is an oral therapy formulated as 200 mg tablets. The recommended dose of ribociclib is 600 mg (three 200 mg film-coated tablets) taken orally once daily for 21 consecutive days followed by 7 days off treatment, resulting in a complete cycle of 28 days. Ribociclib can be taken with or without food. Ribociclib should be given together with an AI. An AI should be taken once daily throughout the 28-day cycle. Patients should be encouraged to take their dose of ribociclib and an AI at approximately the same time each day, preferably in the morning.[20]

In the treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy, ribociclib is to be administered in combination with an aromatase inhibitor, that is, as an add-on therapy to standard-of-care endocrine therapy. Therefore,

while the overall costs of treatment will be higher for the combination regimen, the costs of treatment-administration are not anticipated to increase over those already incurred during first-line treatment of this patient group.

There are no additional diagnostic test costs associated with the selection of patients to receive ribociclib treatment, and no biomarkers have been identified that predict response to ribociclib. Assessment of HER2 and HR status is part of the standard assessment of all patients with newly diagnosed invasive breast cancer and those with recurrent breast cancer in the UK, as advised in National Institute of Health and Care Excellence (NICE) breast cancer quality standards, NICE pathways and current guidelines followed in the UK.[7,34-36]

Table 5 summarises the recommendations for monitoring patients receiving ribociclib therapy. A full blood count (FBC) and liver function tests (LFTs) are routinely measured at each clinic visit in patients receiving endocrine therapy. In addition, an electrocardiogram (ECG) should be performed prior to initiation of ribociclib treatment. Treatment with ribociclib should be initiated only in patients with a QT interval corrected for heart rate as per Fridericia's formula (QTcF) of <450 msec. In patients receiving ribociclib, an ECG assessment should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated. In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended. All monitoring related costs are captured in the economic model (See Section 5.5.5).

Aromatase inhibitors lower circulating oestrogen levels and this may cause a reduction in bone mineral density possibly resulting in an increased risk of fracture; additionally up to 75% of patients with advanced breast cancer present bone metastasis.[37-39] ESMO guidelines therefore recommend initiating bone-targeted therapy in these patients and continuing treatment indefinitely including throughout the course of the disease.[40] Bisphosphonates and denosumab have become established as a valuable addition to current therapy. Both bisphosphonates and denosumab are generally well tolerated treatments. However they are associated with renal dysfunction and hypocalcaemia. In current clinical practice it is thus recommended to monitor renal function and standard hypercalcaemia-related metabolic parameters before starting therapy and during treatment with either agent.[41,42]

Table 5 Recommended monitoring during therapy with ribociclib plus a non-steroidal aromatase inhibitor

Test	Before initiating treatment	Cycle 1, 2 (every 2 weeks)			Cycle 3-6 (beginning of each cycle)	After Cycle 6
		Week 2	Week 4	Week 6		
FBC	X	X	X	X	X	As clinically indicated
LFTs	X	X	X	X	X	As clinically indicated
ECG	X	X	X	As clinically indicated		

ECG, electrocardiogram; FBC, full blood count; LFTs, liver function tests.

2.4 Changes in service provision and management

No additional tests beyond those currently used in clinical practice are needed for the selection of patients for treatment with ribociclib, in combination with an aromatase inhibitor, as initial endocrine therapy for the treatment of postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer. As noted in section 2.3, prior to the administration of ribociclib, it is recommended that a FBC, LFTs and an ECG are performed. Thereafter, in patients initiating ribociclib, FBC and LFTs should be monitored every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and then as clinically indicated, and an ECG assessment should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, and then as clinically indicated.[20]

Whilst the use of ribociclib will require additional monitoring within this indication, it is not expected that this will significantly impact or alter current infrastructure and service provision requirements.

2.5 Innovation

Ribociclib targets key mechanisms that drive breast cancer progression and acts in synergy with aromatase inhibitors

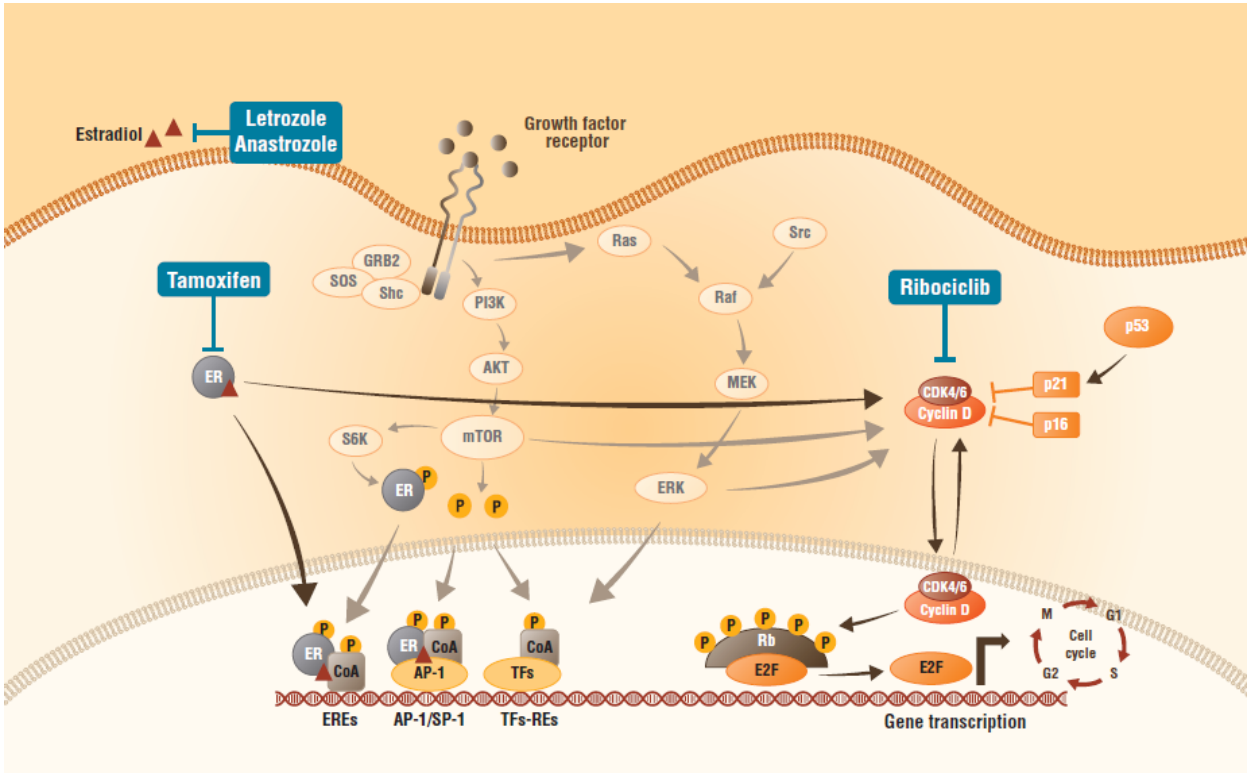
Ribociclib is an innovative therapy, which targets key mechanisms that are dysregulated in breast cancer and which also appear to play a role in the loss of response or poor response to endocrine therapy in HR+ disease (see section 2.1).[12,14-17] Ribociclib inhibits CDK4/6, thus preventing the phosphorylation of Rb and restoring the growth inhibitory effects of this cell-cycle regulator (see Figure 2). Ribociclib thus directly targets a driver of tumourigenesis in breast cancer – the dysregulation of CDK-driven control of normal cell cycling – and this innovative mechanism of action appears particularly important in HR+ breast cancers in which changes in CDK/cyclin D1/Rb activity and interactions can affect responsiveness to endocrine therapy in metastatic disease and/or underlie resistance to endocrine therapies.[12,14-16,18] Aromatase inhibitors such as letrozole are believed to act by decreasing the activity or expression of cyclin D1, leading to reduced phosphorylation (and hence reduced activity) of Rb (in addition to direct effects on gene transcription) (see Figure 3). By inhibiting CDK4/6, ribociclib acts synergistically with aromatase inhibitors, restoring sensitivity to endocrine therapy.[17,32] Ribociclib and other selective CDK4/6 inhibitors are thus considered to represent an important therapeutic advance in breast oncology, with the potential to change the therapeutic landscape of HR+ breast cancer.[13-15]

Ribociclib offers a new treatment option for women living with HR+/HER2- locally advanced or metastatic breast cancer

Breast cancer recurrence and the incurability of advanced disease remain major clinical challenges.[4] Advanced breast cancer comprises both locally advanced and metastatic breast cancer.[7] Development of new treatments for advanced breast cancer is considered a research priority given the high incidence of disease progression and recurrence despite treatment involving standard therapies,[13] and the poor prognosis associated with advanced or metastatic forms of breast cancer (see section 3.1).[16] In

particular, the identification of effective treatment options that prolong or restore sensitivity to standard-of-care endocrine therapies is important.[21]

Figure 3 The cyclin D-CDK4/6-Rb and oestrogen receptor signalling pathways



AKT, protein kinase B; AP-1, activator protein 1; CDK, cyclin-dependent kinase; CoA, co-activator; E2F, E2 transcription factor; ER, oestrogen receptor; EREs, oestrogen response elements; ERK, extracellular signal-regulated kinase; G1, gap 1 phase; G2, gap 2 phase; GRB2, growth factor receptor-bound protein 2; INK4, inhibitor of CDK4; M, mitotic phase; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P, phosphate; PI3K,phosphatidylinositol 3-kinase; Rb, retinoblastoma; RE, response element; S, synthesis phase; S6K, S6 kinase; Shc, Src homology 2 domain-containing protein; SOS, Son of sevenless; SP-1, specificity protein 1; TF, transcription factor.
Lehn *et al*. 2011;[32] Thangavel *et al*. 2011.[17]

Women with advanced or metastatic HR+/HER2- breast cancer comprise both patients with disease that was detected early, who develop recurrent advanced disease or metastatic disease, and patients with an initial diagnosis of advanced disease.[43,44] The current first-line treatment options for women in the UK with advanced or metastatic HR+/HER2- breast cancer who are post-menopausal are limited to treatment with standard-of-care endocrine therapies (In these patients, the use of chemotherapy should be reserved for rapidly progressive disease (PD), rapid visceral recurrence or proven endocrine resistance – see section 3.3.)[19,34,35,45,46]

Ribociclib offers a new treatment option for women living with HR+/HER2- locally advanced or metastatic breast cancer, which acts in synergy with initial standard-of-care endocrine therapy for patients with recurrent or metastatic disease who have not had previous systemic therapy for advanced or metastatic disease. Evidence supporting the use of ribociclib treatment in combination with an aromatase inhibitor comes from a phase 3, randomised, double-blind, placebo controlled study – the

MONALEESA-2 study – conducted in postmenopausal women with HR+/HER2- advanced or metastatic breast cancer who had received no prior therapy for advanced disease.[21]

In MONALEESA-2, the addition of ribociclib to the aromatase inhibitor, letrozole, significantly improved the primary endpoint of PFS over use of letrozole alone (placebo group) (see section 4.7.2). PFS per investigator assessment was significantly longer in the ribociclib plus letrozole arm, where the median was not reached (95% CI: 19.3-NR), versus 14.7 months (95% CI: 13.0-16.5) in the placebo plus letrozole arm, corresponding to an estimated 44% reduction in the risk of death or progression (HR 0.556; 95% CI: 0.429-0.720; stratified log-rank $p=3.29\times10^{-6}$). The robustness of this primary analysis was confirmed by results of the PFS analysis per central review. Results yielded a 40.8% relative risk reduction (HR 0.592; 95% CI: 0.412-0.852; p=0.002).

Prolonging PFS, i.e. the duration of remission, is highly meaningful for patients and their families. In women with HR+ advanced breast cancer, PFS is generally 1 year with current endocrine therapy as has been demonstrated in a number of studies.[47,48] For example a recent review of studies in post-menopausal women with advanced breast cancer treated with various endocrine therapies reported that median time to progression or PFS for patients receiving first-line endocrine therapy less than 12 months in one or both treatment groups in most studies identified. Prolonging PFS is especially clinically meaningful as HRQoL is preserved during remission and declines dramatically on disease progression.[49] Furthermore on progression, patients generally proceed to chemotherapy which can be associated with severe AEs that adversely impact on HRQoL[50] and may well reduce the patient's ability to work and continue with a normal lifestyle.[51,52] There is also increasing evidence to suggest that prolonging PFS or time to progression is associated with prolonged OS.[53-55] Thus improving PFS is an important treatment goal for patients with advanced breast cancer.

The benefits of the combination of ribociclib plus letrozole on PFS were evident across patient subgroups including those with newly diagnosed or pre-treated metastatic disease and those with or without metastases. The study also found that the combination of ribociclib plus letrozole was associated with significant improvements compared with placebo in overall response rate and in CBR, in both the ITT population and in patients with measurable disease.

In addition to the potential to extend PFS over endocrine therapy alone, ribociclib offers an oral route of administration and with an acceptable safety profile, making this agent attractive to patients with advanced HR+/HER2- breast cancer.[13,15]

3 Health condition and position of the technology in the treatment pathway

3.1 Disease overview and pathogenesis

Breast cancer is a common cancer and a heterogeneous disease

Breast cancer is one of the most common cancers affecting women worldwide and a leading cause of cancer deaths.[3] Data from the GLOBOCAN series of the International Agency for Research on Cancer for the year 2012 record that, worldwide, breast cancer is the second most common cancer overall and the most common cancer diagnosed in women in developed countries. Despite advances in understanding of different forms of breast cancer and improvements in the treatment and management of patients, breast cancer remains a potentially life-threatening diagnosis. This is in large part because of breast cancer recurrence, and the incurability of advanced disease remains a major clinical challenge.[4]

When diagnosed at its earliest stage, 5-year survival rates for women with breast cancer are almost 100%. However a late diagnosis, made when disease has already advanced, or cases where disease has advanced or metastasised following treatment, by contrast have a much poorer outlook.[56] Advanced breast cancer is considered to include both locally advanced and stage IV (metastatic) cancer.[5,6] The median survival of patients with advanced breast cancer is just 2–3 years.[7]

Breast cancer is a heterogeneous disease and there are a number of recognisable histological and intrinsic subtypes distinguished by the expression of oestrogen receptors, progesterone receptors and epidermal growth factor receptors (HER2), and by distinct gene profiles that affect prognosis and outlook.[8-10] This submission focuses on aspects of the management of patients found to have HR+/HER2- breast cancer.[10] Around 75% of postmenopausal women with breast cancer have tumours that are HR+,[11] and HR+/HER2- is the most common form of breast cancer.[10,12] Tumours that are HR+/HER2- tend to be slow growing, but while the expression of hormone receptors (HRs) is predictive of a response to endocrine therapy, progression of these tumours is almost inevitable and cure rates are low.[10,13] Other types of breast cancer, not reviewed or discussed further in this submission, include HR-/HER2- (triple negative), HR+/HER2+ (Luminal B) and HR-/HER2+ (HER2 enriched) disease.

Most cases of advanced or metastatic HR+/HER2- breast cancer represent recurrent disease

Most patients with advanced (or metastatic) breast cancer are patients who received an initial diagnosis of early disease that has now progressed or recurred. As many as 50% of women with early disease eventually develop or progress to advanced breast cancer or metastatic disease.[16,43] A smaller group of patients with advanced HR+/HER2- breast cancer are those where disease is recognised late. In the UK, 13% of newly diagnosed breast cancers are found to be HR+/HER2- advanced cancers at initial presentation[44] (see also section 3.4).

HR+ breast cancer has a complex pathogenesis

The specific triggers and drivers of cancer initiation, progression, metastases and drug resistance are largely unknown and research continues to try to understand cancer pathogenesis and the many complex tumour- and host-related factors and interactions with normal biological pathways that underlie different types of breast cancer.[4]

By definition, HR+ breast cancer is influenced by ovarian hormones, with cells essentially being programmed to respond to oestrogen. Consequently endocrine therapies such as aromatase inhibitors have an established and major role in the management of HR+ breast cancers and have contributed significantly to reducing mortality in advanced breast cancer.[4,11,57] There are two main recognised mechanisms by which endocrine therapies act in HR+ breast cancer.

a) The agent tamoxifen blocks oestrogen receptor activity within tumour cells and is effective in premenopausal women. Tamoxifen may also be effective in postmenopausal women.
b) AIs inhibit the production of oestrogen through the aromatase pathway and are used in management of postmenopausal women.[58]

Despite an initial response to such endocrine therapies, many patients will experience disease progression.[11] In fact around 50% of patients with advanced disease do not respond to first-line tamoxifen and ~40% of patients who receive adjuvant tamoxifen experience tumour relapse. [57] Response rates for AIs are only slightly higher than those for tamoxifen in patients with advanced disease, and mechanisms of resistance clearly affect their efficacy, as with tamoxifen.[57]

Similar results from aromatase inhibitors in HR+ advanced breast cancer have been shown in different clinical studies. Efficacy of anastrozole and letrozole was compared in a phase IIIb/IV study in first-line or second-line therapy for advanced breast cancer (patients who had progressed on first-line antiestrogen or were clinically resistant to adjuvant tamoxifen). The primary end point, time to progression (TTP), was 5.7 months in both arm and the overall response rate (ORR) was was significantly higher in the letrozole arm (19.1% vs. 12.3%; p=0.013). [57]

In the search to better understand other drivers of breast cancer and disease progression in HR+ breast cancer, research has focused on pathways that interact with those mediated by the oestrogen receptor, such as growth factor pathways and control of the cell cycle.[4] As discussed in detail in section 2.1, a number of genetic and epigenetic mechanisms are linked with deregulation of the cell cycle in HR+ breast cancer cells and, in particular, with increases in cyclin D-dependent activity and cyclin D-CDK4/6-INK4 pathway alterations. For example amplification of the *CCND1* gene is common across breast cancer subtypes, including in luminal A cancers, as is CDK4 overexpression,[15] and there is evidence to show that in HR+ breast cancer, poor responses and resistance to endocrine therapies are linked with cyclin D1 overexpression and Rb phosphorylation.[14]

3.2 Effects of breast cancer on patients and carers

Pain, discomfort and distress impact on quality of life in patients with advanced or metastatic breast cancer

Advanced or metastatic breast cancer is a life-limiting disease and as such is likely to have a major impact on patients and their families and carers. A number of symptoms of disease, as well as the effects of treatments for advanced or metastatic disease, pose appreciable burdens to patients. Patients with metastatic breast cancer report decreased overall health-related quality of life (HRQoL) in the first year after receiving the news that their condition is metastatic, with the change in HRQoL often being linked directly with disease-related or treatment-related symptoms, including pain and discomfort. Indeed, many of the symptoms faced by patients with advanced disease meet the criteria for causing psychological distress in the form of anxiety and depression.[59,60] Very often, symptoms such as fatigue, disturbed sleep, emotional distress, drowsiness and decreased sexual interest are described by patients with locally recurrent or metastatic disease as severe, Women with locally recurrent or metastatic disease receiving treatment have reported that the symptom burden impacts negatively on their daily activities and work productivity,[50] and in one observational study, 30% of patients felt daily living was impaired and work impairment ranged from 20–40% across different indices of work function among employed patients.[50]

As with many serious diagnoses, breast cancer is also associated with appreciable levels of absenteeism from work[61] and, for patients with advanced disease, the condition can also impact on the patient's carers and family, affecting their work attendance and productivity.[62] Partners and family members of breast cancer patients have to support the person given a diagnosis of advanced disease, as well as dealing with understanding and coming to terms with what the diagnosis means for the broader family – factors that contribute to the wider impact of this condition on family and carers.[63] Indeed, carers have been shown to be at increased risk of depression and a reduced HRQoL compared with the general population.[64] The burden on carers is likely to increase with disease progression as the patient's health and HRQoL of life deteriorates, and as more aggressive interventions such as chemotherapy are offered.

In the face of the symptoms associated with metastatic disease and the psychological impact on patients and their families, achieving and sustaining remission is an important goal for patients with advanced breast cancer. Remission is associated with relief from many of the symptoms and this results in improved HRQoL and allows patients to continue with as normal a lifestyle as possible. Indeed, disease progression has been found to be the factor having the greatest impact on HRQoL in patients with metastatic cancer.[49] Furthermore, following progression on endocrine therapy, chemotherapy is generally associated with significant toxicity which further reduces HRQoL[65,66] and the ability patients to continue working and function normally.[51,52] Indeed, the prospect of chemotherapy has been reported to induce fear and anxiety in many patients.[67] Thus prolonging PFS is an important goal for endocrine therapy in patients with advanced or metastatic disease, thus preserving HRQoL and delaying the need to progress to chemotherapy. In addition, accumulating evidence indicates that improvements in PFS may be also associated with prolonged OS. Indeed correlations between PFS or TTP and OS have been demonstrated for patients with metastatic breast cancer in an analysis of the results for phase 3 trials of first-line therapy,[53] a trial-level analysis of PFS and OS for patients receiving anthracyclines, taxanes, or targeted therapies,[68] and an analysis involving 144 studies in patients with metastatic breast cancer.[54]

3.3 Clinical pathway, current guidelines and the role of ribociclib

Current therapeutic management of advanced or metastatic HR+/HER2- breast cancer in the UK follows NICE pathways, guidance and quality standards on the care of patients with breast cancer (see also section 3.5).[19,34,35,45,46] The NICE guidance and the recently updated recommendations of the UK National Coordinating Committee for Breast Pathology state that HER2 status should be determined in all newly diagnosed and in recurrent and metastatic breast cancers.[19,35,36] Knowing the HR and HER2 status of the tumour is important for prognostication and for making treatment and management decisions.[34,69] The requirement for testing again in the event of recurrence or when disease is metastatic reflects the fact that if breast cancer recurs, the HR and HER status can be different from that of the original primary tumour – factors that again affect and influence treatment choice.[34]

The NICE guidelines and pathways regarding the therapeutic management of advanced breast cancer broadly reflect the principles and recommendations in the current ESO-ESMO international consensus guidelines for advanced breast cancer (ABC3), and the guidelines of the American Society of Clinical Oncology (ASCO) and the American National Comprehensive Cancer Network (NCCN), including those for inoperable locally advanced breast cancer and oestrogen receptor-positive (HR+)/HER2- advanced breast cancer.[7,70,71] Across such guidelines, the general goals of first-line treatment of advanced disease are to prolong PFS and minimise toxicities, so that treatment can be delivered at full dose and on schedule, while maintaining or improving patient HRQoL.

Current guidelines recommend first-line treatment with AIs in postmenopausal women with advanced HR+/HER2- breast cancer

The NICE pathway of care and guidance for women with advanced HR+/HER2- disease recommend endocrine therapy as the first-line treatment for the majority of patients.[19] Of note, some patients with advanced disease may have previously received endocrine therapy as adjuvant treatment during an early stage in their disease course.

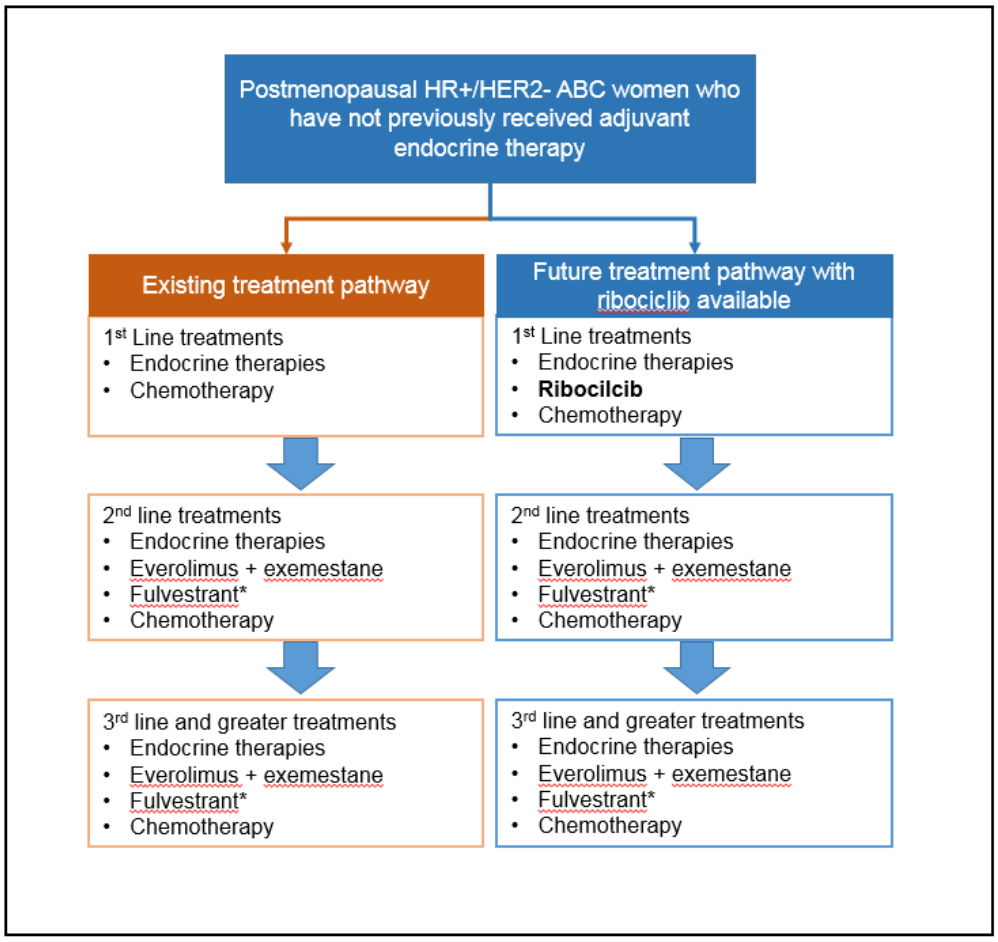
As described in section 3.1 there are two main types of endocrine therapy – oestrogen-receptor blockers such as tamoxifen and AIs.[58] The specific recommendations in NICE pathways of care regarding first-line endocrine therapy for women with advanced HR+/HER2- disease vary according to the patient's menopausal status and prior treatment of earlier stage cancer (Figure 4). Postmenopausal women with HR+ breast cancer and no prior history of endocrine therapy, and postmenopausal women with HR+ breast cancer that was previously treated with tamoxifen, should be offered an AI as first-line endocrine therapy for their advanced disease. Pre- and peri-menopausal women who were not previously treated with tamoxifen, should be offered tamoxifen and ovarian suppression as first-line treatment.

The 2016 ESO-ESMO international consensus guidelines similarly recommends endocrine therapy as the first-line treatment for women with advanced HR+/HER2- disease with the choice of therapy depending on the type and duration of adjuvant endocrine therapy. These guidelines additionally state that the most important advance in the management of HR+/HER2- advanced breast cancer in recent years is the introduction of CDK4/6 inhibitors for use in combination with an endocrine agent, and recommend this as a preferred option where available.[7]

According to the NICE pathway of care and the ESO-ESMO guidelines, chemotherapy should only be a first-line option in patients whose disease is imminently life threatening or requires early relief of symptoms because of significant visceral organ involvement. In such patients, endocrine therapy should then be offered on completion of chemotherapy. However, the current ESO-ESMO international consensus guidelines highlight that real-world studies show that many patients still receive chemotherapy as their first treatment despite its lower efficacy.[7]

In patients who progress after a non-steroidal aromatase inhibitor, the addition of everolimus to an aromatase inhibitor is a valid option for some postmenopausal patients, according to the ESO-ESMO guidelines. This is also supported by NICE based on the technology assessment for everolimus plus exemestane published in December 2016[72] (although not included in the current NICE guidelines as these were last updated in September 2016). Chemotherapy is an alternative option in patients after progression on endocrine therapy.

Figure 4 Current and anticipated future treatment pathway of postmenopausal women with advanced HR+/HER2- breast cancer based on NICE guidelines



AI, aromatase inhibitor; BC, breast cancer; CT, chemotherapy; ET, endocrine therapy, HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive
Ribociclib in combination with AI
Everolimus + exemestane TA421[72]
*Fulvestrant TA239[73] is not NICE recommended, however clinical feedback demonstrates usage as per licence
Based on NICE pathway 2016.[19]

Ribociclib has the potential to change the treatment paradigm for first-line management of locally advanced or metastatic HR+/HER2- breast cancer in postmenopausal women

Ribociclib, in combination with current standard-of-care treatment, offers improved outcomes over standard-of-care endocrine therapy alone in postmenopausal women with locally advanced or metastatic HR+/HER2- breast cancer.[21] The availability of ribociclib for use, together with an aromatase inhibitor, may deepen and prolong responses in first-line treatment of advanced disease – both for newly diagnosed advanced disease and metastatic advanced disease previously treated adjunctively – through actions that complement the antiproliferative effects of endocrine therapy and that potentially prolong and restore sensitivity to endocrine therapies.[21] In postmenopausal women with locally advanced or metastatic HR+/HER2- breast cancer who had received no prior therapy for advanced disease, ribociclib, given together with letrozole, improved median PFS over letrozole and placebo and the combination had low and manageable haematological and liver toxicities (see section 4.12).[21] This represents an important advance for a group of patients considered to have a poor prognosis, where median survival can be as little as 2–3 years.[69] Improved PFS can be expected to prolong OS; however, data for ribociclib are as yet too immature to demonstrate an OS benefit.

Ribociclib has the potential to change the treatment paradigm for first-line management of advanced HR+/HER2- breast cancer in postmenopausal women. Ribociclib treatment has been shown, in combination with endocrine therapy, to lower the relative risk of disease progression by 44%.[21] Given in addition to standard-of-care therapy, ribociclib may thus allow more postmenopausal women with advanced HR+/HER2- breast cancer to delay the need for chemotherapy to control PD. There is also emerging evidence that CDK4/6 inhibitors such as ribociclib may affect pathways involved in the development of resistance to endocrine therapy and potentially delay the development of resistance to an otherwise valuable class of drugs.[14] These potential benefits of using ribociclib, with a standard-of-care therapy, represent a step change and innovation in the initial management of advanced HR+/HER2- disease in the postmenopausal patient population.

3.4 Life expectancy and potential patient population

The potential patient population for ribociclib is postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer who have received no prior endocrine therapy for advanced disease.

Exact estimates of the numbers of postmenopausal women who have HR+/HER2- breast cancer requiring initial endocrine-based therapy for locally advanced or metastatic disease in the UK are not available; however, consideration of the epidemiology of breast cancer provides some insights into the population potentially eligible for ribociclib. Global cancer statistics suggest that the annual incidence of breast cancer in the UK in 2012 was 129.2 per 100,000.[74] Cancer Research UK describes breast cancer as the most common cancer in the UK and reported 53,696 new cases of invasive breast cancer in 2013.[56] It is projected that the age-standardised rate of breast cancer in 2030 in the UK will decline slightly as compared with 2012 values, and be 111.5 per 100,000.[75] An additional epidemiological

observation of relevance to the potential patient population for ribociclib is that almost half (46%) of women diagnosed with breast cancer in the UK each year are aged 65 years and over at the time of diagnosis,[56] and therefore the same proportion or more are likely to be postmenopausal.

Available epidemiological data indicate that ~73% of breast cancers are HR+ and HER2-.[10] Data from the UK suggests that ~ 13% of newly diagnosed breast cancers are HR+/HER2- advanced cancers at first presentation.[44] It is also reported that around 30–50% of women with early disease eventually develop advanced breast cancer or metastatic disease.[16,43] Thus, current epidemiological data indicate that the majority of breast cancer cases are HR+/HER2- disease, that a substantial number of such cases are locally advanced or metastatic disease, and at least half are in postmenopausal women. Table 6 summarises the number of patients in England and Wales likely to require first-line therapy for postmenopausal HR+/HER2- advanced breast cancer.

Table 6 Estimated population of patients in England and Wales with postmenopausal HR+/HER2- breast cancer requiring first-line therapy

Population	Proportion of patients	Number of patients (incident)	References
Breast cancer diagnosed in 2015 in postmenopausal women[#]		45,118	ONS England Wales cancer intelligence
Postmenopausal women with invasive breast cancer	90%	40,606	NICE CG81[46] NICE, Early and locally advanced breast cancer costing template and NICE clinical guidelines 80 and 81[45,46]
Postmenopausal women with early and locally advanced invasive breast cancer	95%	38,575	
Postmenopausal women with early and locally advanced invasive breast cancer who will not die before disease progression	70%	27,002	
Postmenopausal women with early breast cancer who will develop advanced cancer	35%	9,450	
Postmenopausal women with advanced invasive breast cancer at diagnosis	5%	2,030	
Total number of postmenopausal women with locally advanced or metastatic breast cancer		11,480	
Postmenopausal women who are HR+/HER2-	73%	8,380	Howlander et al 2014[10]
Total number of postmenopausal women eligible for ribociclib first-line treatment		8,380	

[#]Postmenopausal is defined as women aged 50 years old and greater.

Patients with advanced or metastatic breast cancer have a poor prognosis

The life of expectancy of patients with advanced or metastatic disease varies according to a number of factors, including patient age and stage of cancer at diagnosis, but prognosis and outlook is often poor and is worse in women who present with advanced disease.[16] The median survival of patients with advanced breast cancer (advanced or metastatic) is 2–3 years.[69]

3.5 NICE guidance

Current NICE guidance relating to the care and therapeutic management of women with advanced breast cancer includes NICE guidelines 80 and 81 and related NICE pathways on the management of locally advanced disease and advanced disease (see section 3.3).[19,34,35,45,46] Furthermore, recently published health technology assessment for everolimus plus exemestane recommends this combination therapy as an additional option for postmenopausal women with HR+/HER2- advanced disease who progress after a non-steroidal aromatase inhibitor.[72]

3.6 Clinical guidelines

As discussed in section 3.3, guidelines for the management of advanced breast cancer are provided by NICE, ESO-ESMO, ASCO and NCCN.[7,19,34,35,45,46,70,71] All four guidelines make similar recommendations regarding the role of endocrine therapy and chemotherapy in the management of advanced and metastatic breast cancer, while those provided by ESO-ESMO, ASCO and NCCN all make mention of the role of CKD4/6 inhibitors as a recommended option as part of first-line endocrine therapy.[7,70,71]

3.7 Issues relating to current clinical practice

In recent years, the ESO-ESMO guidelines have noted that patients with advanced breast cancer were a neglected population, for whom advances in survival outcomes have been slow. The 2014 ESO-ESMO guidelines also noted that there have been few proven standards of care in management of advanced breast cancer,[69] and stated that there has been a tendency to withhold therapy from older patients because of concern about comorbidities and fear of treatment toxicity,[69] underscoring the many unmet needs of older patients with advanced breast cancer. The 2016 updated ESO-ESMO guidelines on the management of advanced or metastatic breast cancer highlight an important issue, and gap, between evidence-based recommendations and the actual practices and clinical management of patients with advanced or metastatic HR+/HER2- breast cancer. These guidelines describe as ‘unfortunate’ the fact that real-life data studies show that most of these patients still receive chemotherapy as their first treatment, despite the lower efficacy of this treatment approach as compared with the preferred, and guidelines-recommended treatment, which in the majority of cases guidelines agree should be endocrine therapy (excepting those patients with visceral crisis and concern or proof of endocrine resistance).[7,70,76] In this context, the 2016 guidelines also note the clinical advance represented by the introduction of CDK4/6 inhibitors, further highlighting the gap between current practice and the potential benefits of endocrine therapy-based regimens.

Women in the UK with advanced cancer at diagnosis have traditionally had poorer survival than that reported in other European countries,[77] particularly older women, perhaps reflecting the fact that treatment recommendations are less well defined for older women, who often have more complex comorbidities. Another issue affecting current practice and the management options for postmenopausal women with advanced disease is the lack or loss of response to endocrine therapy, which is a major concern affecting treatment choice and the effectiveness of the current first-line therapy options for advanced disease. [7]

3.8 Equality

Many patients diagnosed with advanced breast cancer are elderly. Almost half (46%) of female breast cancer cases in the UK are diagnosed in women aged 65 years and older.[56] Providing access to appropriate therapies for elderly individuals is recognized by the UK Department of Health as an important priority to counter concerns regarding undertreatment of the elderly.

4 Clinical effectiveness

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

A series of literature searches were performed to identify systematic reviews and trials of interventions in diagnosed hormone receptor positive (HR+)/human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. The main search concepts included the disease (advanced breast cancer), interventions (endocrine therapy [i.e. letrozole, anastrozole, exemestane, tamoxifen and fulvestrant], targeted therapy [i.e. palbociclib, everolimus, ribociclib and abemaciclib] or chemotherapy [i.e. capecitabine, doxorubicin, paclitaxel, docetaxel, cyclophosphamide and eribulin]) and study design (randomised controlled trial [RCT]). The search was restricted to 2007 and onwards, because HER2 testing was standardized since 2007.[3] For MEDLINE, EMBASE, Cochrane Library where Boolean operations were available, disease, interventions, and study design were searched using exact, refined keywords. Keywords for study design were constructed according to the British Medical Journal (BMJ) filters. For searches in the conference proceedings databases where the search engines supported fewer search options and where Boolean operations could not be performed, the search concepts were applied in a case-specific manner to the extent feasible given these limitations. The detailed search strategy is presented in Appendix 1.

4.1.2 Study selection

The inclusion and exclusion selection criteria are presented in Table 7.

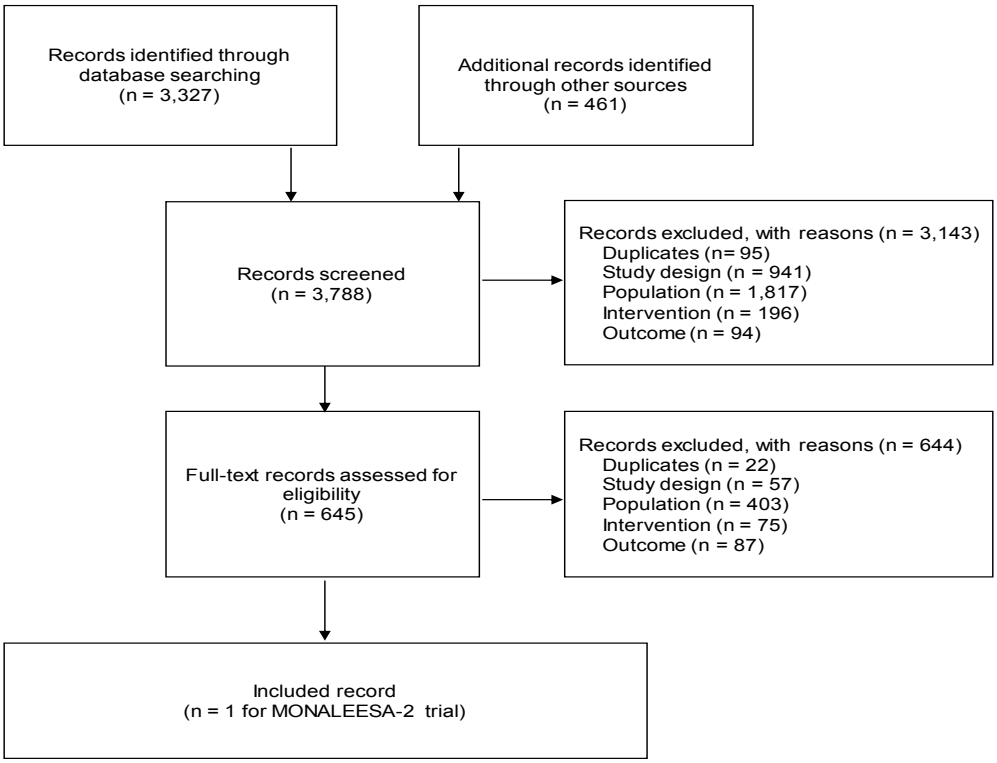
Table 7 Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Women with HR+ HER2- ABC • Received no systemic anti-cancer treatment for advanced disease	• Not HR+ HER2- subtype, or no outcomes separately for this subtype • Not ABC, or mixed population, but no results separately for ABC • Received systemic anti-cancer treatment for advanced disease
Interventions	• Ribociclib as monotherapy or as part of a combination therapy	• Not include the drug of interest
Outcomes	At least one of the following outcomes is reported: Efficacy outcomes • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP)	• No outcomes of interest

	• Overall response rate (ORR) • Clinical benefit rate (CBR) Safety outcomes • AEs (AEs) • Serious AEs (SAEs) • All-cause discontinuation • Discontinuation due to AE	
Trial design	• RCT	• Single-arm trials • Case reports • Editorials & opinion pieces • Reviews
Language restrictions	• English	• Non-English
Publication year	• 2007 – current	• Published before 2007

A PRISMA diagram describing the study selection process is presented in Figure 5.

Figure 5 PRISMA diagram of included and excluded studies in the systematic review



4.2 List of relevant randomised controlled trials

A single RCT, MONALEESA-2, directly relevant to the submission was identified, see Table 8.

MONALEESA-2 was a phase 3 study conducted in postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease and compared ribociclib, in combination with letrozole, with placebo, in combination with letrozole.[21] After 2 years, the planned interim analysis demonstrated that the primary end point had been met. The study continues to explore the secondary objectives.

Table 8 List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
CLEE011A2301 (MONALEESA-2) NCT01958021	Postmenopausal women with HR+/ HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy	Ribociclib (600 mg once daily on days 1–21 of a 28-day cycle) in combination with letrozole (2.5 mg once daily, continuous therapy)	Placebo in combination with letrozole (2.5 mg once daily, continuous therapy)	Hortobagyi *et al.* 2016[21]

MONALEESA-2, mammary oncology assessment of LEE011's efficacy and safety-2; HR+, hormone receptor-positive; HER2-, human epidermal growth factor receptor 2-negative; RCT, randomised controlled trial.

4.3 Summary of methodology of the MONALEESA-2 study, the pivotal phase 3 RCT

Table 9 summarises the methodology of the MONALEESA-2 trial.[21,78,79]

4.3.1 Design

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

4.3.2 Patients

Inclusion and exclusion criteria are listed in Table 9. The study included postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease. Patients were required to have either measurable disease RECIST version 1.1 criteria) or at least one predominantly lytic bone lesion, along with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; and adequate bone marrow and organ function. Exclusion criteria included previous treatment with a CDK4/6 inhibitor or any systemic chemotherapy or endocrine therapy for metastatic disease. Previous neoadjuvant or adjuvant therapy with a non-

steroidal aromatase inhibitor agent was allowed when the disease-free interval was more than 12 months. Patients with inflammatory breast cancer, central nervous system metastases, a history of cardiac disease or dysfunction (including a QTcF of >450 msec at screening) or impaired gastrointestinal function that altered drug absorption were excluded. The use of concomitant medications with a known risk of prolonging the QT interval or inducing TdP was not permitted. [21]

Table 9 Comparative summary of trial methodology

Trial number (acronym)	**MONALEESA-2 (NCT01958021, CLEE011A2301)**
Location	International (223 centres in 29 countries)
Trial design	Randomised, double-blind, placebo-controlled phase 3 trial
Eligibility criteria for participants	Post-menopausal women with ER+ and/or PR+, HER2- recurrent or metastatic breast cancer who had not received systemic therapy for advanced breast cancer Measurable disease, i.e. at least one measurable lesion as per RECIST 1.0; or at least one predominantly lytic bone lesion ECOG PS of 0 or 1 Adequate bone marrow and organ function *Exclusion criteria*: Patients with a history of cardiac disease or dysfunction (LVEF <50%), bradycardia, tachycardia, PR interval >220 msec, QRS interval >109 msec or QTcF >450 msec Prior treatment with CDK4/6 inhibitor or systemic chemotherapy or endocrine therapy for advanced disease. Currently receiving other anticancer therapy or systemic corticosteroids or with inflammatory breast cancer, recurrent malignancy, central nervous system metastases or impaired gastrointestinal function
Settings and locations where the data were collected	Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Korea, Lebanon, Netherlands, Norway, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom and United States of America
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) Intervention(s) (n=[x]) and comparator(s) (n=[x]) Permitted and disallowed concomitant medication	Ribociclib arm (n=334): Ribociclib 600 mg/day on a 3 weeks on/1 week off 28-day treatment cycle in combination with letrozole (2.5 mg/day) Placebo arm (n=334): Matched placebo (600 mg/day on a 3 weeks on/1 week off 28-day treatment cycle in combination with letrozole (2.5 mg/day) The use of concomitant medications with a known risk of prolonging the QT interval or inducing TdP was not permitted
Primary outcomes (including scoring methods and timings of assessments)	PFS based on local and BIRC assessment Pre-planned analyses of PFS were to be undertaken after 211 and 302 local PFS events Tumour assessments based on the RECIST v1.1 criteria were carried out locally every 8 weeks during the first 18 months, and every 12 weeks thereafter until disease progression

Trial number (acronym)	MONALEESA-2 (NCT01958021, CLEE011A2301)
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	OS (time frame: up to approximately 65 months) ORR (time frame: up to approximately 20 months) CBR (time frame: up to approximately 20 months) Safety (AEs, biomarker analysis, vital signs, time to definitive deterioration of ECOG PS) Quality of life, evaluated using the EORTC QLQ-C30, EQ-5D-5L and breast cancer module EORTC QLQ-BR23
Pre-planned subgroups	*Efficacy subgroups*: Age (<65 years and ≤65 years); race (Asian, non-Asian); geographical region (Asia, Europe, North America, Latin America and other); baseline ECOG PS (0 or 1); hormone-receptor status (ER+, PR+ or other); liver or lung metastases (yes or no); bone-only disease (yes or no); number of metastatic sites (<3 vs. ≥3); Ki67 (≤14% vs. >14%); cyclin D1 (≤2001.6 vs. >2001.6); total Rb by H-score (low (<100) vs. high (≥100)); P16 mRNA by nanostring (≤31.5 vs. >31.5); P16 protein by H-score (low (<50) vs. medium (≥50 – <150) vs. high (≥150)); newly diagnosed disease (yes or no); prior adjuvant or neoadjuvant chemotherapy (yes vs. no); previous endocrine therapy; de novo disease (yes or no) *Safety subgroup:* Safety subgroup analyses were based on baseline ECOG PS, age, race and region

AE, AE; BIRC, blinded independent review committee; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4 and 6; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC QLQ BR23, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer; ER+, oestrogen receptor-positive; EQ-5D-5L, European quality of life-5 dimensions-5 levels; HER2-, human epidermal growth factor receptor 2-negative; LVEF, left ventricular ejection fraction; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR+, progesterone receptor-positive; QTcF, QT interval corrected for heart rate as per Fridericia's formula; Rb, retinoblastoma; RECIST, Response Evaluation Criteria In Solid Tumors; TdP, Torsades de Pointes.

4.3.3 Outcomes

The primary and secondary outcomes are summarised in Table 9. The primary outcome was PFS as per RECIST version 1.1 criteria, based on local radiological assessment. The key secondary endpoint was OS (defined as the time from date of randomisation to date of death due to any cause). Other secondary outcomes included objective response rate (ORR; complete response [CR] or partial response [PR]), CBR (overall response plus stable disease lasting 24 weeks or more), time to deterioration of ECOG PS, safety and HRQoL.[21]

Tumour assessments were based on computed tomography scanning or magnetic resonance imaging of the chest, abdomen and pelvis performed at baseline and every 8 weeks during the first 18 months, and every 12 weeks thereafter until disease progression. Tumour response was assessed using RECIST version 1.1.[21]

HRQoL was evaluated every 8 weeks during the first 18 months and every 12 weeks thereafter until disease progression and at end of study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3.0), European quality of life-5 dimensions-5 levels (EQ-5D-5L, version 4.0) and the breast cancer-specific EORTC QLQ-BR23

(version 1.0). Time to definitive deterioration (10%) in the global health status on the EORTC QLQ-C30 scale as well as in each of the three functional scales (emotional, physical, and social functioning) was compared between the two treatment groups.

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

4.3.4 Subgroup analysis

Pre-specified subgroup analyses of the primary outcome measure, PFS, were conducted along with the planned interim analysis. A total of 19 subgroup analyses were performed based on patient and disease characteristics and prior therapies. The categories included: age (less than 65 years and 65 years or older); race (Asian, non-Asian); baseline ECOG status (0 or 1); hormone-receptor status (ER+ and progesterone receptor-positive or other); liver or lung metastases (yes or no); bone-only disease (yes or no); number of metastatic sites (<3 vs. ≥3); newly diagnosed disease (yes or no); prior adjuvant or neoadjuvant chemotherapy (yes or no); previous endocrine therapy (non-steroidal AIs and others, tamoxifen or exemestane, none).[21]

4.4 Statistical analysis and definition of study groups in MONALEESA-2

An overview of statistical analyses used in the RCT is provided in Table 10.

A pre-specified interim analysis was planned after disease progression or death was reported in 211 of 302 patients (70%) and the final analysis was to be performed after 302 events. The superiority of ribociclib plus letrozole versus placebo plus letrozole was defined as an HR of 0.56 or less with $p<1.29\times10^{-5}$.[21] A maximum of four analyses were planned for OS; at the time of the interim and final analysis for PFS (provided PFS was significant), at which point a total of [redacted] and [redacted] deaths were expected; after [redacted] deaths were documented; and a final analysis when [redacted] deaths were expected (expected [redacted] months from the date of the first patient to be randomised).

Table 10 Summary of statistical analyses in MONALEESA-2

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
MONALEESA-2 (CLEE011A2301) NCT01958021	To evaluate the efficacy and safety of the combination of ribociclib plus letrozole and placebo plus letrozole in postmenopausal women with HR+, HER2-, recurrent or metastatic breast cancer who had received no prior systemic therapy for advanced breast cancer	The primary end-point of the study was PFS, defined as the time from the date of randomisation to the date of the first documented progression or death due to any cause. PFS was assessed via a local assessment and determined using a log-rank test stratified according to the presence of liver and/or lung metastases. The secondary outcome measure OS was defined as the time from date of randomisation to the date of death from any cause. Kaplan Meier methodology was used to estimate PFS survival distribution, distribution functions for OS, time and duration of response (CR or PR) and ECOG PS A pre-specified interim analysis was planned after disease progression or death was reported in 211 of 302 patients (70%). The superiority of ribociclib plus letrozole versus placebo plus letrozole would be defined as an HR of 0.56 or less with $p<1.29\times10^{-5}$.[21] A maximum of four analyses were planned for	Based on an estimated median PFS of 9.0 months in the control group and an estimated 33% reduction in the hazard rate with ribociclib, 302 PFS events were calculated for the final analysis, in order to detect an HR of 0.67 with 93.5% power at a one-sided alpha level of 0.025 with the use of a log-rank test and a two-look Haybittle-Peto boundary at a one-sided overall 2.5% level of significance to reject the null hypothesis (HR=1). Assuming a rate of patient recruitment of 37 patients/month over 16 months, 592 patients would be needed to be randomised to two treatment arms in a 1:1 ratio Assuming approximately 10% of patients are lost to follow-up, it was estimated that a total of	Patients who discontinued the study treatment for any reason other than disease progression were required to follow the same schedule of assessment The full analysis set consisted of all randomised patients PFS: Actual event and backdating Missing scans were assessed using the 'actual event' and 'backdating' approaches. The 'actual event' approach took the PFS event date whenever it occurred, after 2 or more missing tumour assessments. The 'backdating' approach used the date of next scheduled assessment as the PFS event date whenever it occurred after a missing tumour assessment. Sensitivity analysis was performed, including these events, in the assessment of PFS

Trial number (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		OS; at the time of the interim and final analysis for PFS (provided PFS was significant), at which point a total of [redacted] and [redacted] deaths were expected; after [redacted] deaths were documented; and a final analysis when [redacted] deaths were expected (expected [redacted] months from the date of the first patient to be randomised). A hierarchical testing strategy (where OS was to be statistically evaluated and interpreted only if the primary efficacy endpoint PFS was significantly different between the two treatment groups) was used to control the overall type I error rate A stratified (stratum using IRT data) Cox proportional hazards model was used to derive the OS HR with two-sided 95% confidence interval Cochran-Mantel-Haenszel chi-square test (strata based on the randomisation stratification factor) was used to compare the two treatment groups with respect to ORR and CBR at one-sided 2.5% level of significance	650 patients would need to be randomised	OS analysis-missing month/day in date of death For rare cases when either the day was missing or both month and day were missing for the date of death, imputation rules were implemented

CBR, clinical benefit rate; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2-, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; IRT, Interactive Response Technology; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

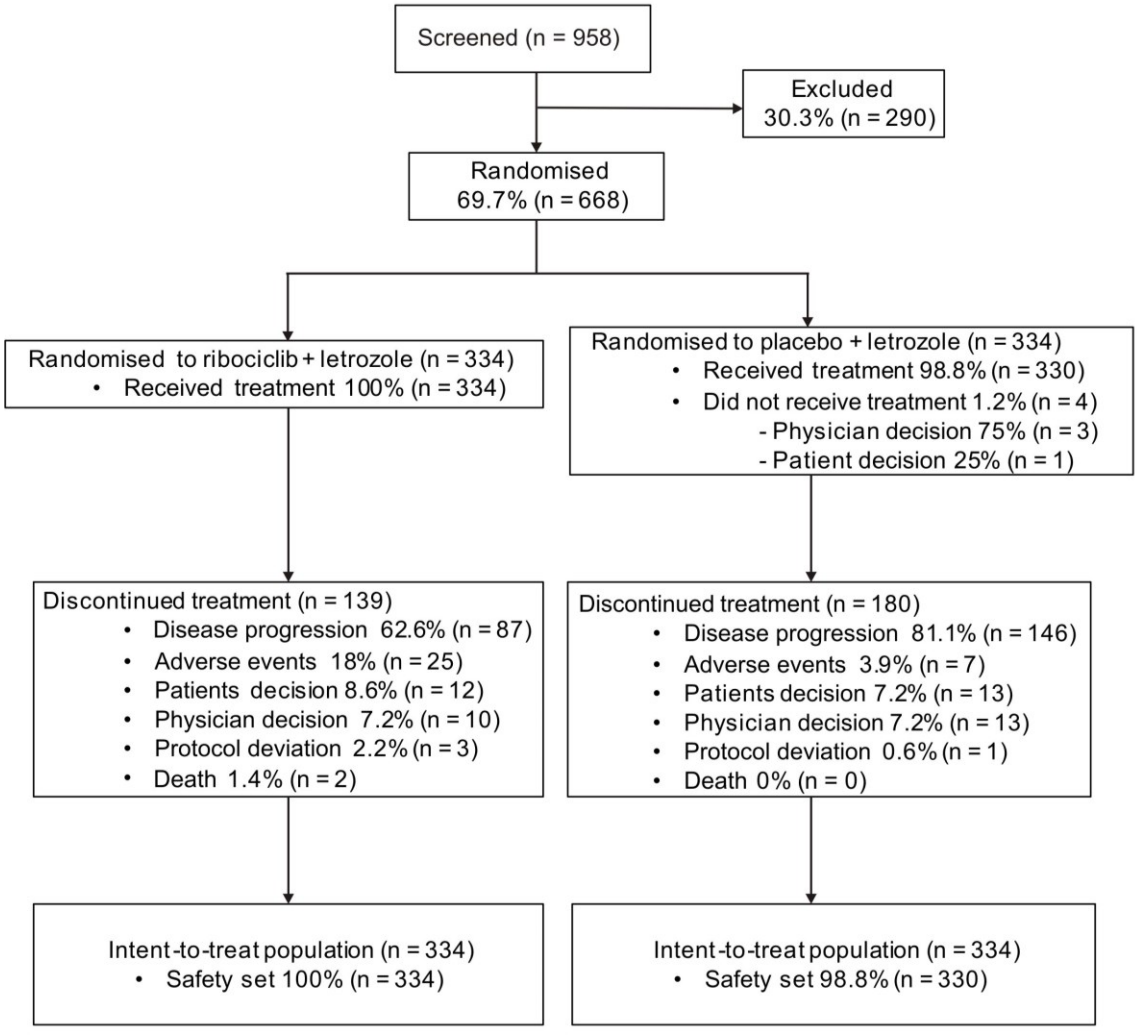
Efficacy analyses were performed in the ITT population. Safety analyses were performed in patients who received at least one dose of a study regimen and had at least one post-baseline safety assessment.

4.5 Participant flow in the relevant RCTs

4.5.1 Patient disposition

A Consolidated Standards of Reporting Trials (CONSORT) participant flow diagram for MONALEESA-2 as of the data cut-off date for the interim analysis (29 January 2016) is provided in Figure 6.

Figure 6 CONSORT diagram for MONALEESA-2



Hortobagyi *et al*. 2016[79]

A total of 668 patients were randomised to ribociclib (n=334) or placebo (n=334) in the ITT population. At the time of data cut-off, a total of 349 patients (52.2%) were still receiving treatment (ribociclib, n=195; placebo, n=154). The rates of discontinuation were lower in the ribociclib group compared with the placebo group (41.6% vs. 53.9%, respectively). The most frequent reason for discontinuation was PD in both groups (ribociclib, 26.0%; placebo, 43.7%). Discontinuations due to AEs were low in both

groups: 7.5% in the ribociclib group and 2.1% in the placebo group. The median duration of follow-up from randomisation to data cut-off was 15.3 months.[21]

4.5.2 Baseline patient demographics and clinical characteristics

Demographic and clinical characteristics of the patients enrolled in MONALEESA-2 are summarized in Table 11. Patient baseline characteristics were well balanced between treatment groups. Almost all (≥99% patients) had stage IV disease and were ER+/HER2-, with more than 80% being positive for progesterone receptors. Approximately 45% of patients were aged 65 years or older, and the median age was 62 and 63 years in the two groups. Thirty-four percent of the patients in both the groups had newly diagnosed advanced or metastatic disease, and most of those with recurrent disease had been disease-free for at least 24 months. Approximately one-third of patients had 3 or more metastatic sites and similar proportions had 1 or 2 metastatic sites. Visceral disease (including liver, lung and other visceral metastasis) was present in 58.8%, and 22.0% had bone-only disease.[21] Approximately half of the patients had received prior radiotherapy, half had received prior neo-adjuvant or adjuvant chemotherapy and approximately 40% had received prior neo-adjuvant or adjuvant endocrine therapy.

Table 11 Characteristics of participants in the MONALEESA-2 study[21]

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

Baseline characteristics	Ribociclib group N=334	Placebo group N=334
Any	246 (73.7)	244 (73.1)
Only	69 (20.7)	78 (23.4)
Visceral[b]	197 (59.0)	196 (58.7)
Lymph nodes	133 (39.8)	123 (36.8)
Other	35 (10.5)	22 (6.6)
Prior therapy, n (%)[c]		
Radiotherapy	178 (53.3)	167 (50.0)
Neoadjuvant or adjuvant chemotherapy	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Tamoxifen	140 (41.9)	145 (43.4)
Anastrozole	47 (14.1)	42 (12.6)
Letrozole	34 (10.2)	25 (7.5)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Other	2 (0.6)	4 (1.2)

[a] Race was self-reported.
[b] Visceral involvement included liver, lung and other visceral metastases.
[c] Some patients received both chemotherapy and endocrine therapy as neoadjuvant or adjuvant treatment.
ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2.
Hortobagyi *et al.* 2016;[21] CSR 2016[78].

4.6 Quality assessment of MONALEESA-2

Quality assessment of the MONALEESA-2 study is described in Table 12. The critical appraisal of MONALEESA-2 was based on the clinical study report and published paper.[21,78,79] Randomisation, concealment of allocation and blinding of the care providers, participants and everyone involved in the study were adequate. The patient groups were well balanced with respect to baseline characteristics. More patients discontinued in the placebo group compared with the ribociclib group, as might be expected given that the main reason for discontinuation was disease progression. Patients were analysed as per ITT and all patients were accounted for in the primary analysis and those secondary analyses using KM methods. Adequate detail was included in the clinical study report describing the interim analysis to suggest there was no selective reporting. The primary paper reports the primary endpoint and some of the secondary endpoints, namely ORR and safety.

Table 12 Quality assessment for the MONALEESA-2 study

Was randomisation carried out appropriately?	Yes, randomisation of patients in a 1:1 ratio to study interventions was carried out using an IRT system
Was the concealment of treatment allocation adequate?	Yes, randomisation data were kept strictly confidential until the time of unblinding and were not accessible by anyone involved in the study
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, baseline characteristics were well balanced between treatment groups
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, patients, investigators, study team and anyone involved in the study conduct were blinded to the identity of the treatment from the time of randomisation until database lock

	An independent statistical group, pharmacokinetics bio analyst and clinical pharmacology expert, not involved in the study conduct, prepared data reports
Were there any unexpected imbalances in drop-outs between groups?	No, disease progression was the primary reason for treatment discontinuation and was more frequent in the placebo plus letrozole arm compared to the ribociclib plus letrozole arm
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The CSR provides details of all outcomes assessed. The primary endpoint and most secondary endpoints are reported in the primary publication.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, the FAS consisted of all randomised patients. Following the ITT principle, patients were analysed according to the treatment and stratum they were assigned to at randomisation; data from the FAS were the primary basis for all efficacy analyses Missing data were appropriately handled as mentioned below: PFS: Actual event and backdating Missing scans were assessed using the 'actual event' and 'backdating' approaches. The 'actual event' approach took the PFS event date whenever it occurred, after two or more missing tumour assessments. The 'backdating' approach used the date of the next scheduled assessment as the PFS event date whenever it occurred after a missing tumour assessment. Sensitivity analysis was performed including these events in the assessment of PFS For OS analysis, in rare cases when either the day was missing or both month and day were missing for the date of death, imputation rules were implemented

CSR, clinical study report; FAS, full analysis set; IRT, Interactive Response Technology; ITT, intention-to-treat; OS, overall survival, PFS, progression-free survival.

4.7 Clinical effectiveness results of the relevant RCTs

4.7.1 Overview of efficacy data

Results of the planned interim analysis of MONALEESA-2 (performed at the data cut-off on 29 January 2016 after observing 243 of the planned 302 events) have demonstrated a substantial reduction in the risk of disease progression for the addition of ribociclib to letrozole as first-line treatment of postmenopausal women with HR+/HER2- recurrent or metastatic breast cancer. The PFS benefit for ribociclib was observed across all pre-planned subgroups and as per local and central assessment. Furthermore, ribociclib was associated with a statistically significant improvement in ORR and CBR and a trend towards providing a more rapid and durable response. HRQoL was maintained in most patients over the first year of treatment in both groups. The study has a median follow-up of 15.3 months, which is insufficient to demonstrate effects on OS; few patients died in either treatment group.[21]

Table 13 summarises the key efficacy data for this study.

Table 13 Summary of efficacy data for MONALEESA-2

Endpoint	Ribociclib + letrozole N=334	Placebo + letrozole N=334
PFS (local)		

Endpoint	Ribociclib + letrozole N=334	Placebo + letrozole N=334
Median PFS, (95% CI), months	NR (19.3–NR)	14.7 (13.0–16.5)
6-month PFS, % (95% CI)	[redacted]	[redacted]
12-month PFS, % (95% CI)	72.8 (67.3–77.6)	60.9 (55.1–66.2)
18-month PFS, % (95% CI)	63.0 (54.6–70.3)	42.2 (34.8–49.5)
HR (95% CI)[a]	0.56 (0.43–0.72) $p=3.29\times10^{-6}$	
PFS (central)		
Median PFS, (95% CI), months	[redacted]	[redacted]
6-month PFS, % (95% CI)	[redacted]	[redacted]
12-month PFS, % (95% CI)	[redacted]	[redacted]
18-month PFS, % (95% CI)	[redacted]	[redacted]
HR (95% CI)[a]	0.59 (0.41–0.85) p=0.002	
OS		
Median OS, months	NR	NR
12-month OS, % (95% CI)	[redacted]	[redacted]
HR (95% CI)[a]	[redacted]	
Response rate (all patients), n (%)		
CR	9 (2.7)	7 (2.1)
ORR[b]	136 (40.7), p<0.001	92 (27.5)
CBR[c]	266 (79.6), p=0.018	243 (72.8)

[a] HR obtained from Cox proportional hazards model stratified by liver and/or lung metastases as per the IRT.
[b] Overall response included a complete or partial response (P<0.001 for the comparison with placebo).
[c] Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting 24 weeks or more, or neither a complete response nor progressive disease lasting 24 weeks or more (P=0.02 for the comparison with placebo).
CBR, clinical benefit rate; CI, confidence interval; CR, complete response; HR, hazard ratio; IRT, Interactive Response Technology; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.
Hortobagyi *et al.* 2016[21]; CSR 2016[78].

4.7.2 Primary endpoint, PFS

Ribociclib plus letrozole significantly improved PFS over letrozole alone

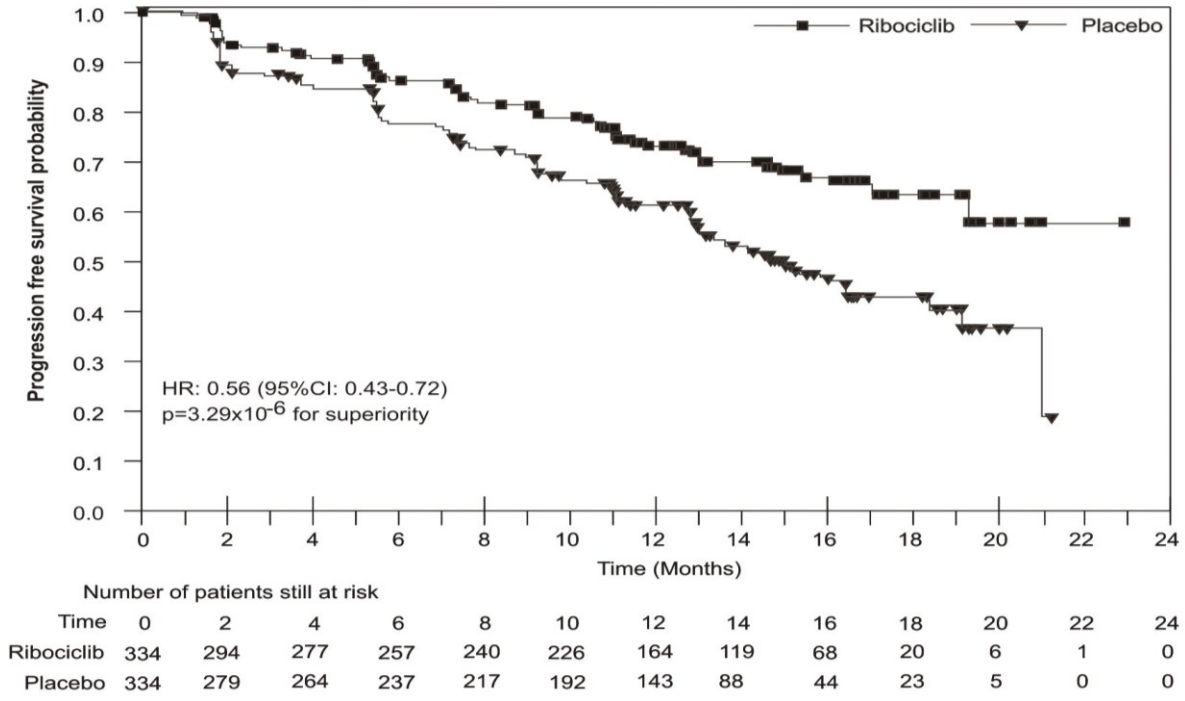
The MONALEESA-2 study achieved its primary objective by demonstrating superior PFS for ribociclib plus letrozole over placebo plus letrozole (

Table 13). According to local assessment, median PFS was significantly longer and was not reached in the ribociclib group (95% CI: 19.3–NR) versus 14.7 months (95% CI, 13.0–16.5) in the placebo group. The addition of ribociclib to letrozole reduced the risk of death or progression by 44% (HR 0.56; 95% CI: 0.43–0.72; p=3.29×10-6). The KM PFS curves diverged from the time of first tumour assessment at week 8 onwards with the PFS probability remaining higher for ribociclib plus letrozole relative to placebo plus letrozole at any subsequent time point indicating an early and sustained advantage for the ribociclib combination (Figure 7). The estimated PFS rates were 72.8% (95% CI: 67.3–77.6) versus 60.9% (95% CI: 55.1–66.2) at 12 months and 63.0% (95% CI: 54.6–70.3) versus 42.2% (95% CI: 34.8–49.5) at 18 months, in the ribociclib plus letrozole versus placebo plus letrozole arms, respectively.

Results for central assessment were generally in good agreement with local evaluation. The central assessment reported a 41% reduction in the risk of death or progression (HR 0.59; 95% CI: 0.412–0.852; p=0.002). PFS was [redacted] and [redacted] at 12 months and [redacted] and [redacted] at 18 months, respectively, in the ribociclib plus letrozole group and the placebo plus letrozole group. [redacted]

The overall concordance rate between the local assessment and central assessment was [redacted] in the ribociclib plus letrozole group and [redacted] in the placebo plus letrozole group, respectively. [redacted]

Figure 7 Kaplan-Meier plot for PFS according to local assessment (primary endpoint)



PFS, progression-free survival.
Hortobagyi *et al.* 2016;[21] CSR 2016[78].

4.7.3 Key secondary endpoint, OS

Results for the effect of ribociclib on OS were immature at the time of the interim analysis

A maximum of four analyses were planned for OS; at the time of the interim and final analysis for PFS (provided PFS was significant), at which point a total of [redacted] and [redacted] deaths were expected; after [redacted] deaths were documented; and a final analysis when [redacted] deaths were expected (expected [redacted] from the date of the first patient to be randomised). Results for the first interim analysis are summarised here.

Data for OS were not mature at the time of the interim analysis, with only 43 deaths having occurred (23 in the ribociclib plus letrozole arm and 20 in the placebo plus letrozole arm).[21] [redacted] (Table 13). At a median follow up of 15.3 months, the OS results [redacted] (Figure 8).

Figure 8 Overall survival (full analysis set) in MONALEESA-2

Hortobagyi *et al.* 2016;[21] CSR 2016[78].

4.7.4 Other secondary endpoints

Ribociclib was associated with higher ORR and CBR compared to letrozole alone

Treatment with ribociclib in combination with letrozole was associated with marked improvement in ORR and CBR relative to placebo plus letrozole, both for the ITT population and for the subgroup of patients with measurable disease at baseline. In the ITT population, the ORR was significantly greater for patients receiving ribociclib plus letrozole compared with those receiving placebo plus letrozole (40.7% vs. 27.5%; p<0.001), as was the CBR (79.6% vs. 72.8%; p=0.018) (Table 14). The proportion of patients achieving a CR was comparable for the two groups, i.e. 9 patients (2.7%) in the ribociclib

group versus 7 patients (2.1%) in the placebo group.[21] Furthermore, tumour shrinkage was observed in [redacted] of patients in the ribociclib plus letrozole arm compared with [redacted] of patients in the placebo plus letrozole arm (

Figure 9). In patients with measurable disease at baseline, the ORR and CBR were 52.7% (ribociclib) vs. 37.1% (placebo) (p<0.001) and 80.1% (ribociclib) vs. 71.8% (placebo) (p=0.020), respectively.

[redacted]

Table 14 Best overall response as per local assessment (full analysis set)

Response	Ribociclib + letrozole	Placebo + letrozole
All patients	334	334
Confirmed best overall response, n (%)		
Complete response	9 (2.7)	7 (2.1)
Partial response	127 (38.0)	85 (25.4)
Stable disease	95 (28.4)	111 (33.2)
Non-complete response/Non-progressive disease[a]	66 (19.8)	75 (22.5)
Progressive disease	19 (5.7)	40 (12.0)
Unknown	18 (5.4)	16 (4.8)
Overall response[b]		
No. of patients	136	92
Percentage of patients (95% CI)	40.7 (35.4–46.0)	27.5 (22.8–32.3)
Clinical benefit[c]		
No. of patients	266	243
Percentage of patients (95% CI)	79.6 (75.3–84.0)	72.8 (68.0–77.5)
Patients with measurable disease at baseline	256	245
Confirmed best overall response, n (%)		
Complete response	8 (3.1)	6 (2.4)
Partial response	127 (49.6)	85 (34.7)
Stable disease	95 (37.1)	111 (45.3)
Progressive disease	13 (5.1)	31 (12.7)
Unknown	13 (5.1)	11 (4.5)
Overall response[b]		
No. of patients	135	91
Percentage of patients (95% CI)	52.7 (46.6–58.9)	37.1 (31.1–43.2)
Clinical benefit[d]		
No. of patients	205	176
Percentage of patients (95% CI)	80.1 (75.2–85.0)	71.8 (66.2–77.5)

[a] In this category, the best overall response was evaluated only among patients who had no measurable disease at baseline, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. One patient with measurable disease in the placebo group was misclassified as having a best overall response of neither complete response nor progressive disease.
[b] Overall response included a complete or partial response (p<0.001 for the comparison with placebo).
[c] Clinical benefit in the overall population was defined as a complete or partial response, stable disease lasting 24 weeks or more, or neither a complete response nor progressive disease lasting 24 weeks or more (p=0.02 for the comparison with placebo).
[d] Clinical benefit among patients with measurable disease at baseline was defined as a complete or partial response or stable disease lasting 24 weeks or more (p=0.02 for the comparison with placebo).
CI, confidence interval.
Hortobagyi *et al.* 2016;[21] CSR 2016[78].

Figure 9 Tumour shrinkage: best percentage change from baseline – full analysis set; a) ribociclib + letrozole, b) placebo + letrozole

Response	Ribociclib + letrozole	Placebo + letrozole
Decrease in best percent change from baseline, %		
Increase or no change in best percent change from baseline, %		
Percent change in target lesion contradicted by overall lesion response being equivalent to progressive disease, %		

MONALEESA-2 CSR 2016[78].

Ribociclib in combination with letrozole was associated with trends in favour of a shorter time to response and a longer duration of response

Ribociclib was associated with a shorter time to response as evident from a KM analysis (Figure 10). At 6 months, an objective response was achieved in of patients in the ribociclib group compared with in the placebo group. Furthermore, the response in the ribociclib group was as evident from the rate of progression at 12 months being compared with (

Figure 11). [78]

Figure 10 Kaplan-Meier plot of time to response according to local assessment

MONALEESA-2 CSR 2016[78].

Figure 11 Kaplan-Meier plot of duration of response according to local assessment

MONALEESA-2 CSR 2016[78].

Ribociclib maintained the ECOG PS of patients when compared to placebo

Time to deterioration in ECOG PS was similar in the two treatment groups. At 6, 12 and 18 months the proportion of patients with no deterioration in ECOG PS was [redacted] in the ribociclib vs. placebo group, respectively. [redacted] was observed for time to deterioration of ECOG PS (

Figure 12).

Figure 12 Kaplan-Meier plot of time to definitive deterioration in ECOG performance status (FAS)

MONALEESA-2 CSR 2016[78].

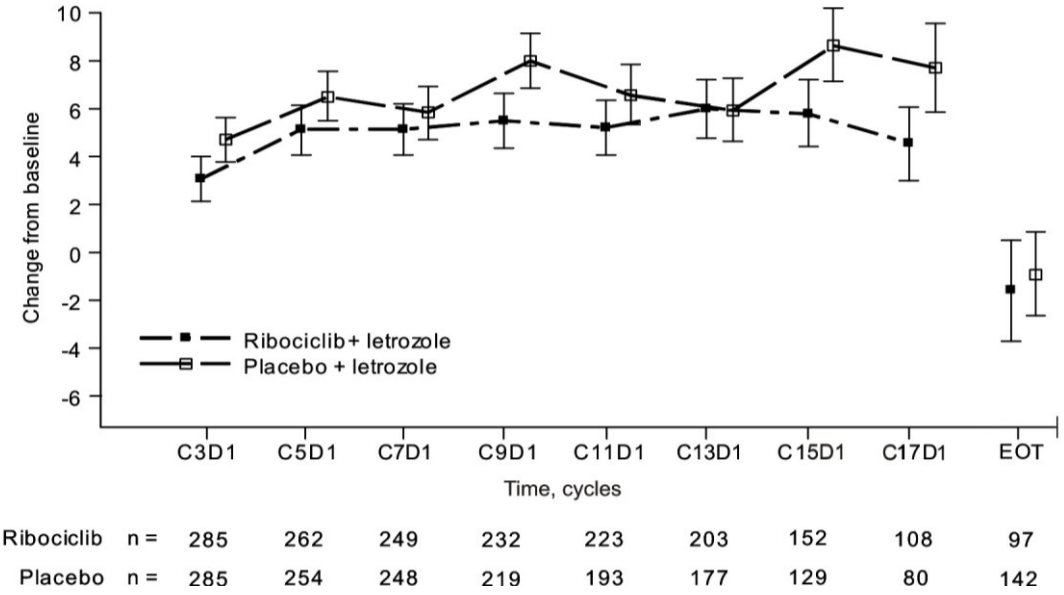
4.7.5 Health-related quality of life

HRQoL was generally sustained during the study in both treatment groups

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

Scores for QLQ-C30 GHS/QoL domain were similar in the two groups throughout the study and showed a slight improvement over the course of the study. (Figure 13).

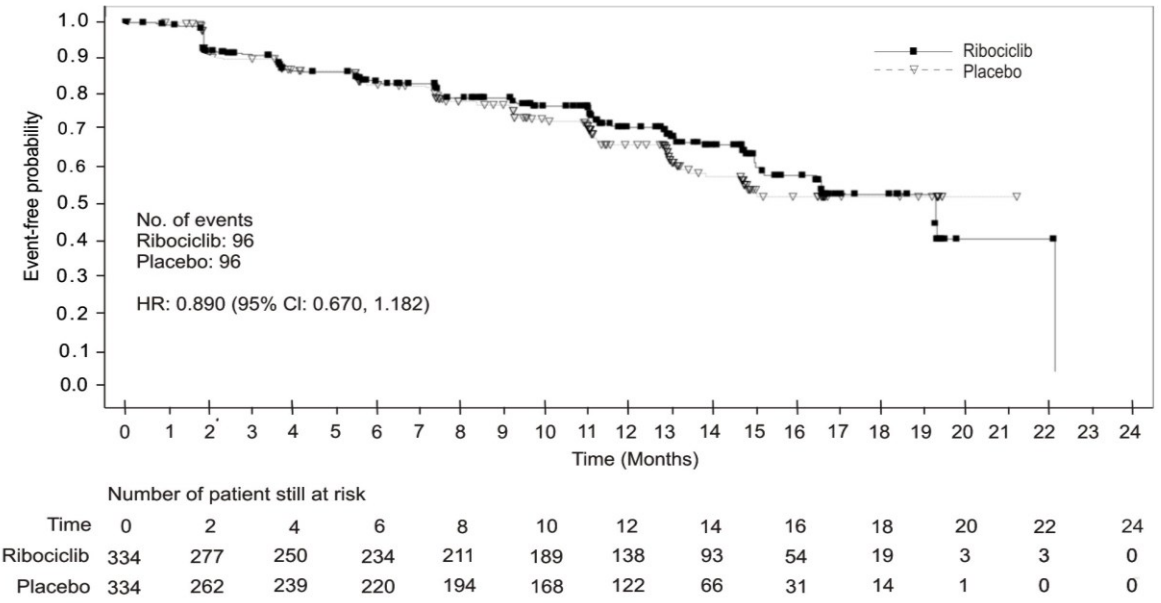
Figure 13 Change from baseline in EORTC QLQ-C30 GHS/QOL scores over time



C3D1, cycle 3 day 1; EORTC QLQ-C30 GHS/QOL, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Global Health Status/Quality of Life; EOT, end of therapy, LS, least squares; SEM, standard error of the mean.
MONALEESA-2 CSR 2016[78].

At 10 months, a 10% deterioration in QLQ-C30 GHS/QoL score was observed in 21.4% and 25.3% of patients in the ribociclib and placebo groups, respectively (Figure 14). The time to 10% deterioration in GHS/QoL was similar between treatment groups, slightly favouring the ribociclib plus letrozole group (HR 0.890; 95% CI: 0.670–1.182).

Figure 14 Kaplan-Meier plot of time to definitive 10% deterioration of the global health status/QOL scale (EORTC QLQ-C30)



MONALEESA-2 CSR 2016[78].

No clinically meaningful changes from baseline and no clinically meaningful differences between treatment groups were observed for EORTC QLQ-C30 sub-scales (functional or symptom scales), QLQ-BR23 [redacted]. In particular, no statistically or clinically relevant differences were observed for key symptoms according to EORTC QLQ-C30 scores, including for fatigue, nausea, and vomiting. There was a clinically relevant (>5 points) improvement in pain from baseline to post-baseline (up to cycle 15) in the ribociclib + letrozole group while there was only mild improvement (<5 points) observed in the placebo + letrozole group.

Data for EQ-5D-5L were also collected in the study. Figure 15 plots mean score over time for the two treatment groups and [redacted]

Figure 15 Mean HSU by time since randomisation (by study group)

4.8 Subgroup analysis

Benefits for the addition of ribociclib to letrozole were seen irrespective of patient baseline characteristics, including the presence or absence of liver or lung involvement.

Ribociclib in combination with letrozole benefited all patients regardless of characteristics, including age, race, ECOG PS, hormone-receptor status, presence of metastases, presence of bone-only disease and newly diagnosed disease versus

Furthermore, the benefit of ribociclib was observed regardless of receipt of prior endocrine therapy or prior chemotherapy (

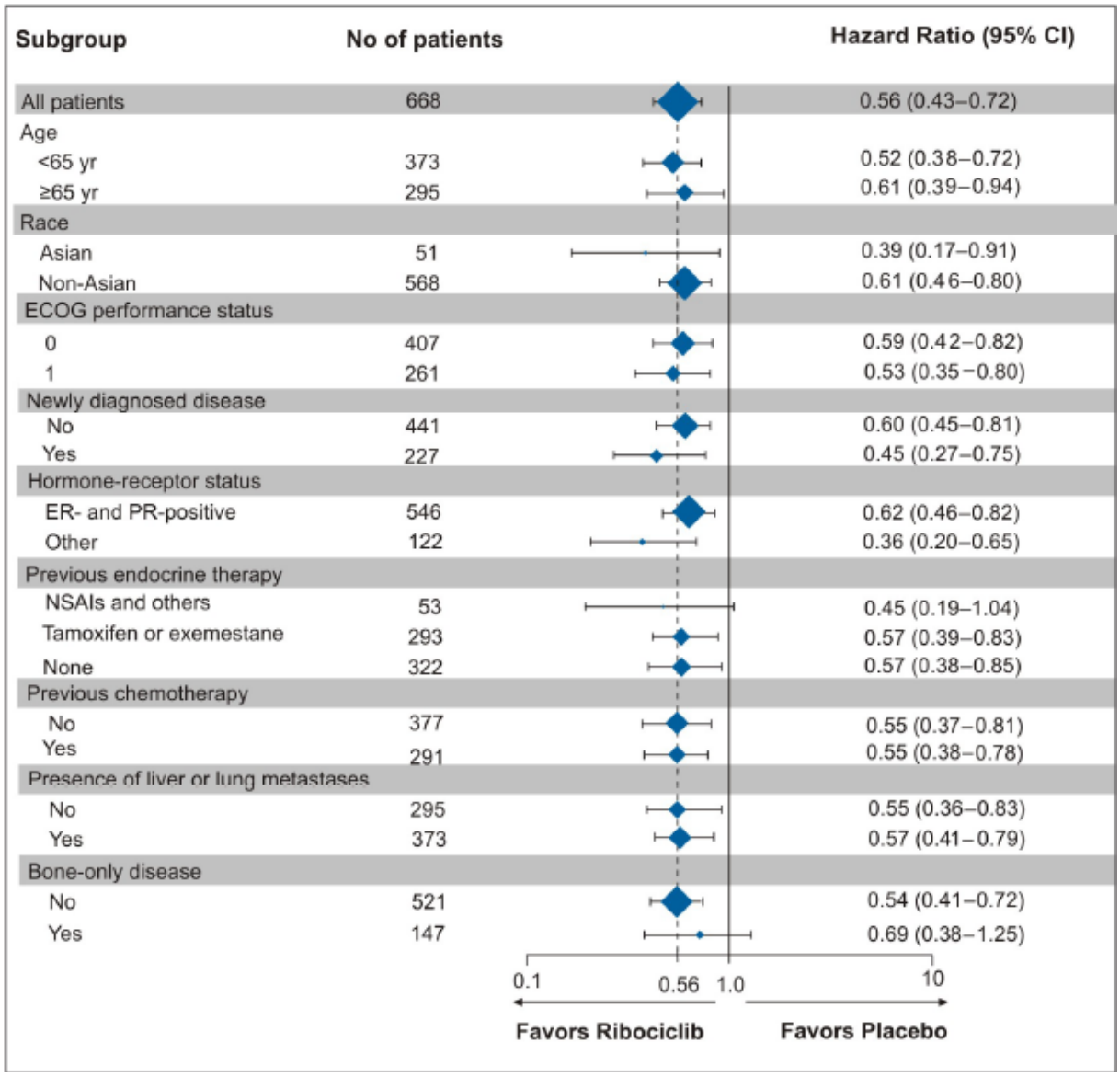
Figure 16).

In particular, approximately a third (34%, n=227) of patients included in the study had *de novo* advanced breast cancer. In this sub-group median PFS was not reached in the ribociclib arm vs. 16.4 (95% CI 13.4–NR) months in placebo arm and 12-month PFS was 81.6% vs. 65.7% in ribociclib and placebo, respectively, representing a 55% reduction in the risk of progression or death (HR, 0.448, 95% CI 0.267–0.750).[26] The best overall clinical responses per local assessment were better in the ribociclib versus placebo arm. The ORR was 47.4% vs. 33.6%, and CBR was 83.3% vs. 77.0% in ribociclib and placebo arms, respectively. Analysis of the de novo breast cancer patient subgroup population showed an ORR of 56.3% vs. 44.6% and CBR of 82.3% vs. 77.1% in the ribociclib and placebo arms respectively. Treatment was generally well tolerated, showing a similar safety profile to that observed for the overall study population.

Approximately 60% of patients (n=393) had visceral metastases and 22% (n=147) had bone-only disease.[25] In visceral metastases sub-groups (including liver, lung, and/or other metastatic sites), median PFS was not reached (95% CI 19.3–not reached) in the ribociclib arm vs. 13.0 months (95% CI 12.6–16.5) in the placebo arm (HR: 0.535; 95% CI 0.385–0.742). CR was achieved in 3 (6%) of patients in both treatment groups while the proportion who achieved PR was higher in the ribociclib group (42%

vs. 32%). Among patients with bone-only disease, there were few PFS events at the cut-off date, with 18 events being reported in the ribociclib arm and 32 events in the placebo arm. The median PFS was not reached in ribociclib arm versus 15.3 months in the placebo arm (HR: 0.690; 95% CI 0.381–1.249). No patients achieved CR and 10% (ribociclib) and 4% (placebo) achieved a PR. Ribociclib plus letrozole was generally well tolerated in both patient subgroups, with a similar safety profile to that observed in the full population.

Figure 16 PFS across various selected subgroups



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival; PR, progesterone receptor; yr, years. Hortobagyi *et al.* 2016.[21]

4.9 Meta-analysis

Only one relevant RCT was identified which directly compared ribociclib plus an aromatase inhibitor with an aromatase inhibitor as monotherapy. Thus a meta-analysis could not be performed.

4.10 Indirect and mixed treatment comparisons

The economic analysis compares ribociclib plus letrozole with letrozole as monotherapy. Clinical data for this comparison are based on the data for ribociclib plus letrozole versus letrozole reported for MONALEESA-2. Thus an indirect comparison was not performed.

4.11 Non-randomised and non-controlled evidence

Three non-randomised controlled trials provide information relevant to the dosing regimen and schedule selected for investigation in the phase 3 MONALEESA-2 trial (Table 15).

Table 15 Overview of dose-escalation studies for ribociclib

Study number (acronym)	Intervention	Population	Objective
Phase I study CLEE011X2101[22] (NCT01237236)	Dose escalation: ribociclib 50 to 1200 mg/day 3 weeks on/ 1 week off Continuous dose: ribociclib 600 mg/day	Adults with advanced solid tumours or lymphoma failing standard therapy for whom no further effective standard therapy exist.	Primary objective: • To determine the MTD and the recommended dose for expansion for ribociclib Secondary objectives: • To evaluate the safety and tolerability of ribociclib • To evaluate the pharmacokinetics of ribociclib • To evaluate the antitumour activity associated with ribociclib • To investigate the relationship between QTc prolongation and exposure to ribociclib
Phase 1b/2 study CLEE011X2107 (NCT01872260)[23]	Arm 1. Ribociclib 600 mg (3 weeks on/ 1 week off) + letrozole 2.5 mg once daily Arm 2, Alpelisib 300 mg daily + letrozole 2.5 mg once daily (cohort 1: both given in the morning; cohort 2; alpelisib given in the evening and letrozole in the morning) 3. Ribociclib 400 mg (3 weeks on/ 1 week off) + alpelisib 100 mg + letrozole 2.5 mg once daily 4. Ribociclib 200 mg continuous once daily + alpelisib 200 mg + letrozole 2.5 mg once daily 5. Ribociclib 300 mg (3 weeks on/ 1 week off) + alpelisib	Postmenopausal women with metastatic or locally advanced HR+/HER2- advanced breast cancer.	Primary outcome measures: • To determine the recommended dose of the phase 2 study • To evaluate safety and tolerability. Secondary outcome measures include: • ORR, duration of response and PFS. • Safety and tolerability of ribociclib, plus letrozole

Study number (acronym)	Intervention	Population	Objective
	(3 weeks on/ 1 week off) + letrozole 2.5 mg once daily Each arm included dose escalation and dose expansion		
Phase 1b/2 study CLEE011X2108 (NCT02088684)[24]	Arm 1: Ribociclib 400 mg[a] + buparlisib 20 mg daily + fulvestrant 500 mg[b] Arm 2: Ribociclib 400 mg* + alpelisib 100 mg daily + fulvestrant 500 mg[b] Arm 3: Ribociclib 600 mg[a] + fulvestrant 500 mg[b] Arm 3A: Ribociclib 400 mg daily + fulvestrant 500 mg[b]	Postmenopausal women with HR+/HER2- metastatic or locally advanced breast cancer.	Primary objectives • Phase Ib: To determine the MTD and/or recommended phase 2 dose • Phase 2: To compare PFS Secondary objectives included • Safety and tolerability • Anti-tumour activity

[a]3 weeks / 1 week off; [b]every 28 days with 1 additional dose on day 15 of cycle 1
HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; MTD, maximum tolerated dose; ORR, objective response rate; PFS, progression-free survival

4.11.1 Phase 1 dose-escalation study in patients with solid tumours, CLEE011X2101

A phase 1 dose-escalation study (CLEE011X2101, NCT01237236) of single-agent ribociclib in adult patients with solid tumours expressing the Rb protein was performed to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE) for ribociclib.[22] Based on the results of preclinical studies, a dose of 50 mg/day given on a 3 weeks on/1 week off schedule was selected as the starting dose and was given until disease progression, unacceptable toxicity, death or consent withdrawal. [22]

A total of 132 patients were included in the study and dose escalation proceeded to a dose of 1200 mg/day given according to the 3 weeks on/1 week off schedule. A continuous regimen of 600 mg/day was also explored, but 6 of the 7 patients who received this regimen required dose reductions and hence continuous dosing was not explored further. The MTD was identified as 900 mg once daily given on a 3 weeks on/1 week off schedule, and a dose of 600 mg once daily given on a 3 weeks on/1 week off schedule was identified as an appropriate regimen for further investigation.[22]

Nine dose-limiting toxicities were observed during cycle 1 among 70 evaluable patients who received the MTD or RDE, most commonly neutropenia (n=3) and thrombocytopenia (n=2). Common treatment-related AEs were (all-grade/grade 3/4): neutropenia (46%/27%), leukopenia (43%/17%), fatigue

(45%/2%) and nausea (42%/2%). The onset of neutropenia occurred by approximately day 15 and typically resolved 7–14 days after dose interruption and infrequently required growth factor support. Grade 3/4 thrombocytopenia occurred in 9% of patients. Myelosuppression was self-limiting and readily reversible, and was the most common reason for dose interruption or reduction. Fatigue, nausea and vomiting were common, but were mostly grade 1/2 and rarely necessitated dose modification. QTc prolongation was observed at doses of ≥600 mg/day (9% of patients at 600 mg/day; 33% at doses >600 mg/day), but was always asymptomatic and reversible on stopping therapy.[22]

4.11.2 Phase 1b/2 dose escalation/expansion study in patients with advanced HR+/HER2- breast cancer, CLEE011X2107

The ribociclib dose of 600 mg once daily was investigated further in a phase 1b/2 dose escalation/expansion study in patients with advanced HR+ breast cancer (CLEE011X2107, NCT01872260).[23] The dose escalation used an open label, dose escalation design to establish the MTD/RP2D of three combination regimens. There were five arms in the study, i.e.

- Arm 1: ribociclib 600 mg (3 week on / 1 week off) in combination with 2.5 mg letrozole (daily);
- Arm 2: alpelisib 300 mg once daily (Cohort 1 evening, Cohort 2 morning) in combination with 2.5 mg letrozole (daily);
- Arm 3: ribociclib 400 mg (3 week on / 1 week off) in combination with alpelisib 300 mg once daily and 2.5 mg letrozole (daily);
- Arm 4: ribociclib 200 mg daily in combination with alpelisib 200 mg (daily) and letrozole 2.5 mg (daily); and
- Arm 5: ribociclib 300 mg (3 week on / 1 week off) in combination with alpelisib 200 mg once daily and 2.5 mg letrozole (daily).

The five combination regimens evaluated in the dose escalation phase of the study were also evaluated in the dose expansion phase at the respective recommended phase 2 dose.

Results are reported only for the ribociclib plus letrozole group.

Dose-limiting toxicity was observed in 3 patients receiving the ribociclib starting dose of 600 mg once daily and hence this was the dose investigated further in the phase 2 part of the study.

At the time of analysis, 47 patients had received this regimen, 28 of whom were treatment-naïve for advanced breast cancer. In total 34 patients discontinued treatment, largely due to disease progression (57%). Only 2 patients discontinued due to AEs. [redacted]

Considering the subgroup of patients who were treatment-naïve, two patients achieved a CR and 11 (39%) achieved a PR, resulting in an ORR of 46%. A CBR (confirmed CR + PR + stable disease ≥24 weeks + non-CR/non-PD ≥24 weeks) of 79% was reported. In the previously treated group, [redacted]

[redacted]. The median PFS for this group of patients was 25.3 months and 5.5 months in the first-line group and previously treated group, respectively.

The most common (>30% of patients) AEs (any grade) regardless of the relationship to study medication were neutropenia (83%), nausea (49%]), fatigue (34%), diarrhoea (38%), arthralgia (32%) and alopecia (30%), and the only grade 3/4 AEs regardless of relationship to study medication reported in >5% of patients was neutropenia (60%).

The results of this study thus suggested that ribociclib at a dose of 600 mg once daily given on days 1–21 of a 28-day cycle in combination with letrozole is generally well tolerated and has clinical activity against HR+/HER2- breast cancer, particularly in patients who are treatment-naïve. The safety profile was consistent with that observed with other CDK4/6 inhibitors and AEs were generally manageable through dose reductions and interruptions.

4.11.3 Phase 1b/2 study of ribociclib plus fulvestrant in patients with HR+/HER2- advanced breast cancer, CLEE011X2108

Further evidence for the efficacy and tolerability of ribociclib added to endocrine therapy is available from a phase 1b/2 study investigating ribociclib + fulvestrant along with buparlisib and alpelisib in patients with HR+/HER2- advanced breast cancer (CLEE011X2108).[24] The two treatment groups investigating ribociclib plus fulvestrant involved administration of ribociclib at a dose of 600 mg/day (3 weeks on/1 week off) or 400 mg/day given continuously, while fulvestrant was administered at a dose of 500 mg on days 1 and 15 of cycle 1 and day 1 of subsequent cycles. (Two further treatment groups investigated the addition of buparlisib 20 mg/day or alpelisib 100 mg/day to ribociclib plus fulvestrant but are not reported here.) Patients must have progressed during or within 12 months of prior adjuvant AI therapy or during or within 1 month of AI therapy for metastatic disease and to have received ≤2 prior lines of chemotherapy for advanced disease.

At the time of analysis, 28 patients had received therapy, 13 with intermittent dosing and 15 with continuous ribociclib dosing. Both regimens were found to have a manageable safety profile and demonstrated clinical activity. Of 13 evaluable patients who received ribociclib on an intermittent schedule, 3 (23.1%) patients had a confirmed PR and 9 (69.2%) had stable disease, The best overall responses in the 7 patients who had received prior fulvestrant were 2 confirmed PRs and 5 SDs. Of 15 evaluable patients treated with continuous ribociclib, 2 (13.3%) had a confirmed PR and 7 (46.7%) had stable disease, while the best overall responses in the 6 patients who had received prior fulvestrant were 1 confirmed PR, 3 stable disease, 1 neither complete response nor progressive disease, and 1 PD. Both ribociclib once-daily continuous and intermittent dosing schedules were associated with acceptable safety profiles. Lower rates of grade 3/4 neutropenia were observed with continuous dosing than with intermittent dosing. The most common AEs (any grade) suspected to be study drug-related (≥30% of all patients) were neutropenia (64.3%), fatigue (42.9%), and nausea (42.9%). The most common grade 3/4 AEs suspected to be study drug-related (≥10% of all patients) were neutropenia (46.4%) and white blood cell count decreased (10.7%).

4.11.4 Implications for further studies

Results from the phase 1 study in patients with solid tumours was used to determine the dose and regimen for investigating ribociclib in combination with letrozole in the phase 3 MONALEESA-2 trial (as described in sections 4.3 to 4.9 and section 4.12). The phase 1b/2 CLEE011X2107 study in patients with HER+/HER2- breast cancer provides supporting evidence to that provided by MONALEESA-2 for the efficacy and safety of ribociclib in combination with letrozole in this patient population. These studies together with the phase 1b/2 CLEE011X2108 study of ribociclib plus fulvestrant provide the rationale for phase 3 studies of ribociclib in combination with endocrine therapy in two further breast cancer indications, namely in men and postmenopausal women with HR+/HER2- advanced breast cancer who have received no or only one line of prior endocrine therapy for advanced disease (MONALEESA-3: endocrine therapy, fulvestrant),[80] and in newly diagnosed women with advanced HR+/HER2- breast cancer aged less than 50 years (pre- or peri-menopausal) in MONALEESA-7 (endocrine therapy: goserelin plus tamoxifen or goserelin plus letrozole or anastrozole)[81] (see section 4.14).

4.12 Adverse reactions

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

The median relative dose intensity was almost 90% for ribociclib suggesting that the majority of the patients were able to receive most of the planned dose

The median exposure to treatment at data cut-off was 13 months in the ribociclib group and 12.4 months for the placebo group, thus allowing for an adequate assessment of safety. Median relative dose intensity was 87.5% for ribociclib, 100% for placebo, and 100% for letrozole (in both treatment groups). About half (n=180; 53.9%) of patients in the ribociclib arm and 7% (n=22) in the placebo arm required at least one dose reduction and most (n=169 (50.6% of the treatment group) receiving ribociclib and 14 (4.2 % of the treatment group) receiving placebo) of these were attributable to AEs.[21]

Dose interruptions were more frequent in the ribociclib plus letrozole treatment group than in the placebo plus letrozole group. At least one dose interruption of therapy with ribociclib occurred in 257 patients (76.9% of the treatment group) while placebo treatment was interrupted in 134 (40.6%) patients. The proportions of patients requiring dose interruptions for letrozole were comparable in the ribociclib and placebo groups (39.5% vs. 32.4%). The major reason for interruption of ribociclib was AEs (68.0%), [redacted] also being reasons for interruption of ribociclib therapy in [redacted] and AEs (13.3%) were the main reasons for interruption of placebo and were also the main reasons for interruption of letrozole therapy in the ribociclib group [redacted]

AEs observed were consistent with the known safety profile of ribociclib

Table 16, Table 17 and Table 18 summarise the incidence of AEs reported in the two treatment groups.

Most patients in both treatment groups experienced at least one AE (98.5% vs. 97.0%). The most frequently reported AEs of any grade reported in ≥35% of patients in either group (ribociclib vs. placebo group, respectively) were: neutropenia (74.3% vs. 5.2%), nausea (51.5% vs. 28.5%), infections (50.3% vs. 42.4%), fatigue (36.5% vs. 30.0%) and diarrhoea (35.0% vs. 22.1%) (Table 17). Nausea, infections, fatigue and diarrhoea and were mostly grade 1 or 2 in severity.[21]

Table 16 Incidences of AEs and death in MONALEESA-2

Events	Ribociclib + letrozole N=334			Placebo + letrozole N=330		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
All deaths[a] On-treatment deaths[b]	23 (6.9) 3 (0.9)			20 (6.1) 1 (0.3)		
AEs Suspected to be drug related	329 (98.5)	221 (66.2)	50 (15.0)	320 (97.0)	105 (31.8)	3 (0.9)
SAEs Suspected to be drug related	71 (21.3) 25 (7.5)			39 (11.8) 5 (1.5)		
AEs leading to discontinuation[c] Suspected to be drug related						
AEs requiring dose interruption and/or change Suspected to be drug related						
AEs requiring additional therapy Suspected to be drug related						

[a] All deaths, including those occurring >30 days after the last study treatment.
[b] Deaths occurring >30 days after the last study treatment were not included.
[c] Study drug discontinuation refers to discontinuation of ribociclib/placebo only or both ribociclib/placebo and letrozole.
AE, AE; SAE, serious AE.
Hortobagyi *et al.* 2016;[21] CSR 2016[78].

Grade 3/4 AEs were more frequent in the ribociclib arm (grade 3, 66.2%; grade 4, 15.0%) than in the placebo arm (grade 3, 31.8; grade 4, 0.9%). The most frequently reported grade 3/4 AEs in ≥5% of the patients in either group (ribociclib vs. placebo group, respectively) were: neutropenia (59.3% vs. 0.9%), leukopenia (21.0% vs. 0.6%), hypertension (9.9% vs. 10.9%), increased ALT level (9.3% vs. 1.2%), lymphopenia (6.9% vs. 0.9%), and increased AST level (5.7% vs. 1.2%).[21] However, few patients in either group discontinued treatment due to grade 3/4 AEs (ribociclib, 7.5%; placebo, 2.1%), reflecting the fact that most grade 3/4 events were reversible by dose reduction or treatment interruptions.

Table 17 Most frequently reported AEs in MONALEESA-2 (reported in ≥15% of patients in either treatment group)

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

Listed are events that were reported in ≥15% of the patients in any group. One event of interest (hypertension) fell below the reporting threshold listed here. NA denotes not applicable, since grade 4 cough and grade 3 and 4 alopecia are not included in the National Cancer Institute Common Terminology Criteria for AEs, version 4.03.
[a] Four patients who were randomly assigned to the placebo group did not receive either placebo or letrozole.
[b] Neutropenia includes a decreased neutrophil count and granulocytopenia.
[c] This category includes both anaemia and a decreased haemoglobin level.
AE, AE; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Hortobagyi *et al.* 2016.[21]

AEs leading to discontinuation in ≥1% of patients in the ribociclib group were [redacted] The most commonly occurring AEs (>5%) that necessitated dose interruption for the ribociclib plus letrozole group were [redacted]. AEs leading to dose reduction were reported in 50.6% of the ribociclib group (vs. 4.2% of the placebo group) [redacted]

The incidence of SAEs was higher in the ribociclib plus letrozole than in the placebo plus letrozole group (21.3% and 11.8%, respectively). Of these, 25 events (7.5%) in the ribociclib group were considered

related to the study treatment compared with 5 (1.5%) in the placebo group. Febrile neutropenia was the only treatment-related SAE reported in >1% of patients, occurring in 5 (1.5%) patients receiving ribociclib (vs. no patients in the placebo group) and all events occurred in the first 4 weeks of treatment.[21]

Table 18 Treatment-related AEs reported in ≥5% of patients in either arm in MONALEESA-2

AE[a]	Ribociclib + letrozole N=334			Placebo + letrozole N=330		
	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	[redacted]					
Neutropenia						
Nausea						
Alopecia						
Fatigue						
Diarrhoea						
Neutrophil count decreased						
Vomiting						
White blood cell count decreased						
Hot flush						
Arthralgia						
Leukopenia						
Anaemia						
Rash						
Increased ALT						
Constipation						
Decreased appetite						
Increased AST						
Stomatitis						
Pruritus						
Asthenia						
Headache						
Dysgeusia						
Dry mouth						
Dizziness						
Thrombocytopenia						
Lymphocyte count decreased						

[a] AEs up to 30 days after last study treatment.
AE, AE; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
MONALEESA-2 CSR 2016[78].

Neutropenia was reported in three-quarters of patients receiving ribociclib plus letrozole, but only 1.5% experienced febrile neutropenia

The characteristics of neutropenia in the group receiving ribociclib plus letrozole are summarised in Table 19. Neutropenia was the most frequently reported AE (any grade and grade 3/4) in the ribociclib group, and neutropenia-grouped AEs were reported more frequently in the ribociclib plus letrozole group

(any grade, 74.3%; grade 3/4, 59.6%) relative to the placebo plus letrozole group (any grade, 5.2%; grade 3/4, 0.9%). Among the patients who had grade 2, 3 or 4 neutropenia, the median time to onset was 16 days for those patients who had an event. The median time to resolution of grade ≥3 (to normalisation or grade <3) was 15 days in the ribociclib plus letrozole treatment group following treatment interruption and/or reduction and/or discontinuation.[20,21,78]

Discontinuation of treatment with ribociclib plus letrozole due to neutropenic events was low, occurring in only 3 patients (0.9%), and the incidence of neutropenia as a SAE was also low (ribociclib, 1.8%; placebo, 0%).

Five patients (1.5%) experienced febrile neutropenia (all in the ribociclib plus letrozole group) and all were determined by the investigators to be related to study treatment. Of these, four patients had grade 3/4 febrile neutropenia requiring dose interruptions (n=3) or reductions (n=1) and four were considered to be SAEs. However, there were no discontinuations due to febrile neutropenia. Overall, 26 patients (7.8%) in the ribociclib plus letrozole group and one patient (0.3%) in the placebo plus letrozole group received colony-stimulating factors (primarily filgrastim).

Table 19 Characteristics of neutropenia in patients receiving ribociclib plus letrozole in MONALEESA-2

Parameter	**Ribociclib + letrozole N=334**
Median onset time of neutropenia in patients with grade 2–4 neutropenia from start of treatment	16 days
Median time to resolution of neutropenia (from grade ≥3 to grade <3)	15 days
Patients discontinuing treatment due to neutropenia, n (%)	3 (0.9)
[redacted] Febrile neutropenia, n (%)	[redacted] 1 (0.3)
[redacted] Febrile neutropenia, n (%)	[redacted] 3 (0.9)
Patients requiring granulocyte-colony stimulating factors for treatment of neutropenia, n (%)	26 (7.8)

Hortobagyi *et al.* 2016;[21] CSR 2016[78]. Kisqali SmPC[20]

Grade 3/4 elevation of liver enzymes occurred in approximately 10% of patients receiving ribociclib, but most were asymptomatic and reversible with dose adjustment

Elevation in liver enzymes (ALT and AST)[21] were the only grade 3/4 AEs, in addition to neutropenia and leukopenia, reported in ≥5% of patients receiving ribociclib and were reported more frequently with ribociclib than placebo: ALT[20]: 10.2% versus 1.2% and AST: 6.9% versus 1.5%. Most grade 3/4 ALT or AST elevation events occurred within the first 6 months of treatment; the median time to onset was 57 days for the ribociclib plus letrozole treatment group. The median time to resolution (to normalisation or grade ≤2) was 24 days in the ribociclib plus letrozole group. Elevation of liver enzymes meeting

criteria for Hy's law (i.e. concurrent elevations in ALT or AST >3 times the upper limit of normal and total bilirubin >2 times the upper limit of normal, with alkaline phosphatase < 2 times the upper limit of normal) occurred in 4 (1.2%) patients and all patients recovered to normal levels within 154 days after treatment with ribociclib was discontinued. Dose interruptions and/or adjustments due to hepatotobiliary toxicity events were reported in 8.4% of ribociclib plus letrozole-treated patients, primarily due to elevated ALT (5.7%) and/or elevated AST (4.5%). Discontinuation of treatment due to abnormal liver function tests or hepatotoxicity occurred in [redacted] of patients. Thus, most cases were asymptomatic and reversible with dose adjustment.

Less than 5% of patients experienced QTcF prolongation to >480 msec and there were no cases of TdP during therapy with ribociclib

QTc interval prolongation events (overall and grade 3/4) were more frequent in the ribociclib group compared to the placebo group (any AE: 7.5% versus 2.4%; [redacted] Dose interruption or adjustments due to ECG QT prolongation and syncope were required by 3 patients (0.9%) in the ribociclib group. [redacted] An increase of more than 60 msec from baseline in the QTcF interval occurred in 9 patients (2.7%) in the ribociclib group and in no patient in the placebo group. Eleven patients (3.3%) in the ribociclib group had at least one average QTcF interval of greater than 480 msec, including 6 who had an increase of >60 msec from baseline. Amongst these patients, the median time to onset was 15 days and these changes were reversible with dose interruption and/or dose reduction and were not related to clinical manifestations. There were no reported cases of TdP.[20,21,78]

Most deaths in both treatment groups were due to underlying disease

[redacted] The incidence of on-treatment death was low in both groups (3 in the ribociclib group and 1 in the placebo group), with 1 in each group considered to be related to primary disease or disease progression. The remaining 2 deaths in the ribociclib group were due to sudden death (considered related to ribociclib and occurring on day 11 in cycle 2 in association with grade 3 hypokalaemia and grade 2 prolongation in the QTcF interval, probably due to intake of a prohibited concomitant medication with a known risk for QT prolongation, methadone, during cycle 1), and death from unknown cause (patient received ribociclib for 4 days before withdrawing consent and discontinuing the study treatment; her death was reported 19 days later and was not considered to be related to ribociclib by the investigator).[21,78] Deaths occurring beyond the treatment period were considered to be related to the underlying disease.

In conclusion, the safety profile for ribociclib plus letrozole, as observed in MONALEESA-2, was consistent with that previously observed for ribociclib in the phase 1 and phase 1b/2 studies (see section

4.11). Ribociclib plus letrozole was generally well tolerated and AEs were largely managed by dose reductions and interruptions. Few patients discontinued therapy because of AEs.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Efficacy

The addition of ribociclib to current standard of care provides clinically meaningful and statistically significant improvements in PFS for patients with HR+/HER2-, advanced breast cancer receiving first-line therapy

Ribociclib added to standard of care AI therapy is an effective and well-tolerated treatment for patients requiring first-line therapy for advanced HR+/HER2- breast cancer. As demonstrated in the pre-planned interim analysis of the international multicentre phase 3 trial, MONALEESA-2, which involved 668 patients followed up for 15.3 months, ribociclib significantly prolongs PFS and improves response rates over those achieved with letrozole alone.

Two PFS analyses were planned for the MONALEESA-2 trial: an interim analysis after approximately 211 (70% information fraction) of the total events and a final analysis after 302 local PFS events. At the interim analysis, a 2-look group sequential design with Haybittle-Peto boundary was used to determine the significance level threshold; the observed p value had to be less than $p=1.29\times10^{-5}$ (or Z=4.2077, HR=0.56) in order to conclude superior efficacy.[82]

The trial met its primary endpoint and demonstrated a clinically meaningful and statistically significant improvement in PFS for ribociclib plus letrozole over letrozole alone, corresponding to a 44% reduction in the relative risk of progression (HR 0.556; 95% CI: 0.429–0.720; one-sided $p=3.29\times10^{-6}$). Thus, the data indicate that the addition of ribociclib to endocrine therapy provided a clinically meaningful reduction in the risk of disease progression.

Good agreement between the central radiology review of tumour response and local assessment, together with a sensitivity analysis based on the per protocol set, demonstrates that this observed improvement in PFS was robust. Further, the improvement in PFS was consistent across all pre-defined subgroups, including patients expected to be sensitive to endocrine therapy (i.e. newly diagnosed disease and those who had not received prior endocrine therapy) and patients with or without lung or liver metastases.

The primary efficacy outcome was further supported by significant improvements in ORR (40.7% vs. 27.5%; p<0.001) and clinical benefit rate (79.6% vs. 72.8%; p=0.018) in the full analysis set as well as in the subgroup of patients with measurable disease at baseline (ORR 52.7% vs. 37.1%; CBR 80.1% vs. 71.8%). HRQoL was generally sustained or showed a slight improvement over the course of the study in both groups, suggesting that AEs associated with ribociclib did not compromise HRQoL or their effects were outweighed by improvements associated with disease remission. The OS data were not mature at the time of the pre-planned interim analysis and no difference in OS was evident between the treatment groups. The study remains blinded for follow-up of OS and 3 further analyses of OS are planned.

Taken together, the results from this trial provided robust evidence for the benefits of ribociclib in patients receiving first-line endocrine therapy for advanced HR+/HER2- breast cancer.

4.13.2 Safety

Ribociclib is well tolerated and the AEs were generally manageable with dose reductions

Safety data for ribociclib added to letrozole in patients with advanced breast cancer was available for 334 patients in the phase 3 MONALEESA-2 trial who received ribociclib for up to 23 months, and further supporting evidence is provided by a phase 1 study of ribociclib monotherapy in patients with solid tumours or lymphoma,[22] and a phase 1b/2 study of ribociclib plus letrozole in patients with advanced HR+/HER2- breast cancer.[23]

Ribociclib was generally well tolerated in MONALEESA-2. The incidence of grade 3/4 AEs and SAEs was higher for patients receiving treatment with ribociclib plus letrozole than placebo plus letrozole, but most of the AEs were successfully managed with dose reductions or interruptions. Few patients discontinued therapy for AEs and the incidence was similar in both treatment groups (ribociclib 7.5%; placebo 2.1%).[21] The incidence of on-treatment deaths was low in both the treatment groups.

The majority of patients in both treatment groups experienced at least one AE (98.5% vs. 97%) and approximately 80% (ribociclib) and 33% (placebo) experienced grade 3/4 AEs. SAEs considered related to treatment were reported in 7.5% of patients receiving ribociclib (compared with 1.5% of patients in the placebo group), but febrile neutropenia was the only SAE reported in more than 1% of patients. Most non-haematological AEs were grade 1 or 2 in severity, although grade 3/4 elevations of ALT and AST were reported for 31 (9.3%) and 19 (5.7%) of patients, respectively, receiving ribociclib. [redacted] Grade 3 and 4 infections occurred in [redacted] and [redacted] patients receiving ribociclib (compared with [redacted] and [redacted] for placebo), respectively, and [redacted]

Haematologic AEs reflected the effect of ribociclib on bone marrow stem cells, with neutropenia being the most frequently reported grade 3/4 AE, reported in approximately 60% of patients (compared with 1% for placebo). Most cases of neutropenia occurred within the first 4 weeks of treatment. Only 5 (1.5%) patients experienced febrile neutropenia and no patients discontinued therapy due to febrile neutropenia; [redacted].

Neutropenia associated with ribociclib therapy is readily reversed as it reflects the effects of cell-cycle arrest, not DNA damage or induction of apoptosis in bone marrow precursor cells

Neutropenia is a common grade 3/4 AE associated with many therapies for breast cancer. However the characteristics of the neutropenia observed with CDK4/6 inhibitors differ significantly to those observed with chemotherapy and some other targeted therapies. CDK4/6 inhibitors induce bone marrow

suppression through cell-cycle arrest and, as such, the neutropenia is readily reversible upon withdrawal of the CDK4/6 inhibitor.[27] This was observed in MONALEESA-2 where the median time to resolution of grade 3/4 neutropenia was 15 days. Thus, only 3 (<1%) patients discontinued ribociclib therapy due to neutropenia. The reversible nature of the neutropenia induced by ribociclib is also the rationale for the 3 weeks on/1 week off regimen chosen for investigation in the phase 1 study and subsequently used in the phase 1b/2 study and MONALEESA-2. In contrast, chemotherapeutic agents result in DNA damage and induce apoptosis in bone marrow mononuclear cells. As a result of this permanent DNA damage or apoptosis in bone marrow precursor or progenitor cells, recovery from the myelosuppressive effects of chemotherapy is less rapid and may necessitate dose reductions, interruption and/or treatment discontinuations in more patients than is observed with CKD4/6 inhibitors such as ribociclib.

Elevations of liver enzymes were observed during therapy with ribociclib, but were largely asymptomatic and reversible

Grade 3/4 elevation of liver enzymes was observed in approximately 10% of patients receiving ribociclib in MONALEESA-2 and was consistent with observations in other studies of CDK4/6 inhibitors given in conjunction with AIs.[28] Treatment discontinuation due to elevation of liver enzymes of hepatotoxicity was [redacted] Most cases were asymptomatic and reversible, being managed by dose adjustment or treatment interruptions.

QTcF prolongation, a common AE associated with tyrosine kinase inhibitors, is effectively managed during ribociclib therapy by careful monitoring and dose adjustment or interruption

QTcF prolongation is a recognised AE associated with tyrosine kinase inhibitors such as ribociclib. It results from inhibition of the ion channel involved in conducting the major ventricular repolarising potassium current during phases 2–3 of the action potential and results in prolongation of the ventricular action potential duration.[83] Although QTcF interval prolongation is not in itself harmful, it can induce potentially fatal ventricular tachyarrhythmias. The ventricular tachyarrhythmia most typically triggered is known as TdP.

The potential for QTcF prolongation with ribociclib was assessed in the phase 1 study and contributed to the choice of 600 mg once daily as the dose for further investigation as the incidence of QTcF prolongation increased at doses above 600 mg.[22] The phase 1 study also indicated that QTcF prolongation was dose dependent and therefore suggested that this effect can be managed by careful monitoring and dose reduction. In MONALEESA-2, QTcF prolongation to >480 msec occurred in 3.3% of patients receiving ribociclib. Only 0.9% of patients required dose interruptions/adjustments and one (0.3%) discontinued due to QTcF interval prolongation. There were no cases of TdP in MONALEESA-2 or the phase 2 study.

Patients at high risk for QTcF prolongation were excluded from MONALEESA-2. This is reflected in the Summary of Product Characteristics, which states that treatment with ribociclib should be initiated only

in patients with QTcF values <450 msec.[20] Furthermore, an ECG assessment should be repeated at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

Ribociclib was well tolerated in de novo advanced breast cancer patients with visceral metastases and those with bone-only disease patient subgroups

Treatment with ribociclib was well tolerated in patient subgroups including patients with visceral metastases, with bone-only disease and in patients with *de novo* advanced breast cancer. A similar safety profile was observed in these groups as for the full population.

Thus, safety data from MONALEESA-2, supported by data from the phase 1b/2 study, suggest that ribociclib is well tolerated and AEs are generally manageable with dose reductions or treatment interruptions; monitoring for QTcF prolongation is required during treatment.

4.13.3 Strengths of the evidence base

Evidence for the efficacy and safety of ribociclib in combination with letrozole is based on results from a large, international, double-blind, placebo-controlled, phase 3 study. The results of this study provide robust evidence for the clinical efficacy and safety of ribociclib in combination with letrozole in postmenopausal women with HR+/HER2- advanced or metastatic breast cancer based on the rigorous design of the study, inclusion of appropriate endpoints, and the duration of follow-up. Further supporting evidence regarding the safety profile of ribociclib plus letrozole are provided by the phase 1b/2 study, which involved a further 47 patients.

The phase 3 MONALEESA-2 study involved 668 patients from 223 centres in 29 countries, and was double-blind with respect to treatment with ribociclib or placebo. PFS was the primary endpoint and the study was powered for significance. PFS is particularly relevant in this setting as it is correlated with OS, and is not confounded by subsequent treatment after disease progression. The trial was also powered to detect significant differences in OS between treatment groups and OS was included as a secondary endpoint. No crossover between treatment groups was allowed during the study; therefore OS will not be confounded. Tumour response was determined by RECIST v1.1 criteria by both local and central assessment, and good agreement was observed between assessments. HRQoL was measured using the validated EORTC QLQ-C30, QLQ-BR23 and EQ-5D-5L tools at 8-week intervals.

Median follow-up at the interim analysis was 15.3 months and was thus long enough to demonstrate clinically meaningful effects of treatment on disease progression. Similarly, median exposure to ribociclib was 13 months and is thus long enough to assess the safety profile of ribociclib plus letrozole in the target population.

Reported efficacy results consistently demonstrated benefits for the addition of ribociclib to letrozole. Clinically meaningful prolongation of PFS was observed according to the primary endpoint (local assessment) as well as for central assessment, for all subgroups considered and for a sensitivity analyses based on the per protocol set. Statistically significant improvements in ORR and CBR were also observed.

Safety data from MONALEESA-2 provide a robust assessment of the safety profile of ribociclib plus letrozole in the relevant patient population and are supported by data from the phase 1b/2 study.

4.13.4 Shortcomings of available evidence

There are shortcomings relating to the clinical evidence for ribociclib plus letrozole for management of advanced HR+/HER2- breast cancer. Firstly, data are only available from a single RCT. However, a second large, phase 3b study, COMPLEEMENT-1, is currently underway and will provide additional data for ribociclib plus letrozole in patients with HR+/HER2- advanced breast cancer (see section 4.14 for further details). [redacted]

Secondly, although the median follow-up of 15.3 months was sufficient to demonstrate statistically significant benefit for PFS, longer follow-up is required for OS data to become mature and hence determine the impact of ribociclib on OS. Three further analyses of OS are planned.

4.13.5 Relevance of the evidence to the decision problem

Data from MONALEESA-2 are highly relevant to the decision problem. MONALEESA-2 provides evidence for the comparative efficacy and safety of ribociclib in combination with letrozole (endocrine therapy) and one of the comparators of interest, letrozole. Furthermore letrozole is a current standard of care in England and Wales.

Patients included in MONALEESA-2 are representative of patients expected to receive ribociclib in routine clinical practice in England and Wales, including the involvement of patients with newly diagnosed disease (34%) – expected to be responsive to endocrine therapy, but who still benefitted from the addition of ribociclib.

Efficacy and safety data from MONALEESA-2 are directly used in the model. The efficacy endpoint, PFS, is used to model disease progression and grade 3/4 AEs recorded during the study are included in the economic model. Use of G-CSF was recorded during the trial and these data are also included in the economic model. Two centres in England were included in MONALEESA-2 (Royal Cornwall Hospital, Truro, Cornwall, and Freeman Hospital, Newcastle-upon-Tyne).

4.13.6 End-of-life criteria

This submission does not meet the criteria for end-of-life as the life expectancy for patients with newly diagnosed HR+/HER2- advanced breast cancer is greater than 24 months.

4.14 Ongoing studies

Three further phase 3 trials of ribociclib for the treatment of breast cancer are ongoing and form part of the clinical trial programme for ribociclib in the management of advanced breast cancer (Table 20). These trials involve different patient populations from those relevant to this submission and investigate treatment with ribociclib in combination with other endocrine therapies. However, the results from these studies will provide supporting evidence regarding the efficacy and safety of ribociclib in conjunction with endocrine therapy.

- MONALEESA-3 (NCT02422615) is a randomised double-blind, placebo-controlled study 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 line of prior endocrine treatment.[80] The primary endpoint is PFS according to local assessment, and secondary endpoints include OS, PFS according to central assessment, ORR and safety.
- MONALEESA-7 (NCT02278120) is a double-blind, placebo-controlled evaluation of ribociclib in combination with either tamoxifen plus goserelin or a non-steroidal AI (letrozole or anastrozole) plus goserelin in premenopausal women with HR+/HER2- advanced breast cancer.[81] The primary outcome measure is PFS according to local assessment, and secondary endpoints include PFS according to central assessment, ORR, CBR and safety and tolerability.
- COMPLEEMENT-1 (NCT02941926) is an open-label, single-arm, multicentre study to assess the safety and efficacy of ribociclib in combination with letrozole for the treatment of men and postmenopausal women with HR+/HER2- advanced breast cancer having received no prior endocrine therapy for advanced disease. This study aims to collect additional safety and efficacy data for the regimen investigated in MONALEESA-2 in a broader patient population (i.e. including men with HR+/HER2- advanced breast cancer and patients treated with prior chemotherapy for advanced disease).[84] The study will involve 30 UK sites and aims to enrol approximately 100 patients in the UK.

Table 20 Ongoing phase 3 clinical trials of ribociclib in patients with advanced breast cancer

Study	Description	No. of patients	Primary outcome	Estimated completion dates
MONALEESA-3 (NCT02422615)[80]	Phase 3, randomised, double-blinded Ribociclib + fulvestrant vs. Placebo + fulvestrant	Ribociclib arm: 440 Placebo arm: 220	PFS	Primary completion: February 2020 Study completion: February 2020
MONALEESA-7 (NCT02278120)[81]	Phase 3, randomised, double-blinded Ribociclib + goserelin + tamoxifen or NSAI (letrozole or anastrozole) vs. Placebo + goserelin + tamoxifen or NSAI (letrozole or anastrozole)	Ribociclib arm: 330 Placebo arm: 330	PFS	Primary completion: February 2018 Study completion: February 2018
COMPLEEMENT-1 (NCT02941926)[84]	Phase 3, open-label Ribociclib + letrozole vs. Placebo + letrozole	Approximately 3000	Overall safety and tolerability	Primary completion: November 2020 Study completion: November 2020

NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival.

5 Cost effectiveness

- A *de novo* cost-utility analysis was undertaken to assess the cost-effectiveness of ribociclib in combination with letrozole for the treatment of first-line postmenopausal women with HR+/HER2- advanced breast cancer.
- The economic model used an individual patient based state-transition model consisting of four health states (first-line progression-free PFS1, second-line progression-free PFS2, progressed disease and death) to determine the time spent in each health state by each patient over the lifetime horizon (40 years). This model approach has been used in previous NICE appraisals (TA386); however, it differs from the more traditional cohort-based partitioned-survival models used in oncology.
- A time horizon of 40 years (equivalent to lifetime) was applied to ensure that all relevant costs and outcomes were captured, a discount rate of 3.5% was applied to costs and outcomes, and an NHS and personal social services perspective was used. Therefore, the economic analysis was consistent with the NICE reference case.
- In line with the NICE decision problem, the base case analysis compares ribociclib in combination with letrozole with letrozole monotherapy.
- The clinical efficacy data for first-line PFS comes from the MONALEESA-2 clinical study IPD, the clinical efficacy data for second-line PFS and progression survival (i.e. post-second-line treatment) comes from BOLERO-2 IPD and Li et al, 2015.[1]
- Health-state utilities in the model were EQ-5D-5L values and were calculated directly from the MONALEESA-2 study for first-line PFS, the BOLERO-2 study for second-line PFS and sourced directly from NICE appraisals for progression.
- In the base case, first-line PFS was modelled based on the exponential parametric function as this was recommended in NICE appraisal ID915,[2] provided a plausible fit and clinical expert validation supported this predictions; second-line PFS was modelled on the Weibull parametric function, as this provided both plausible fit and NICE has previously recommended this function.
- The base case deterministic ICER was [redacted] per QALY gained for ribociclib in combination with letrozole compared with letrozole alone.
- The probabilistic ICER was [redacted] per QALY gained for ribociclib in combination with letrozole compared with letrozole alone
- Sensitivity analysis suggest that results of the model are most sensitive to the parametric function applied to first-line PFS and the time horizon.

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

A systematic literature review was conducted to identify evidence to support the cost-effectiveness model for ribociclib, which focuses on patients with locally advanced or metastatic HR+/HER2- breast cancer. A structured review process was conducted to identify studies reporting economic evaluations as well as resource use and costs. The primary objective of the economic review was to assess the cost-effectiveness associated with pharmacological interventions for first-line treatment of patients with advanced or metastatic HR+/HER2- breast cancer.

The literature was searched in the biomedical electronic literature databases recommended by health technology assessment agencies, including NICE,[85] and summarised in Table 21.

The NICE website was also hand-searched to identify relevant manufacturer submissions and evidence review group documents from 1 January 2000 to 1 March 2017. (See Appendix 11 for further details of the methodology.)

Table 21 Search strategies for systematic literature review

1. Search strategy component	2. Sources	3. Data limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE In-Process® Excerpta Medical Database (Embase®) NHS Economic Evaluation Database (NHS EED)	1 January 2000 to 5 August 2016
HTA bodies	NICE	1 January 2000 to 1 March 2017
Conference proceedings	ISPOR	2014–2016

5.1.2 Description of identified studies

The literature search identified a total of 2,110 articles for abstract screening of which 1,940 were unique publications (duplicate publications n=170). Following review of the abstracts, 559 publications were identified as potentially relevant references and were included for full-text review for more detailed evaluation (Figure 17). Following detailed examination of the full-text publications, a further 535 publications were excluded, leaving a total of 24 publications relevant for this appraisal. In addition, 10 ISPOR abstracts were identified resulting in a total of 34 publications reporting economic data for 30 unique studies.

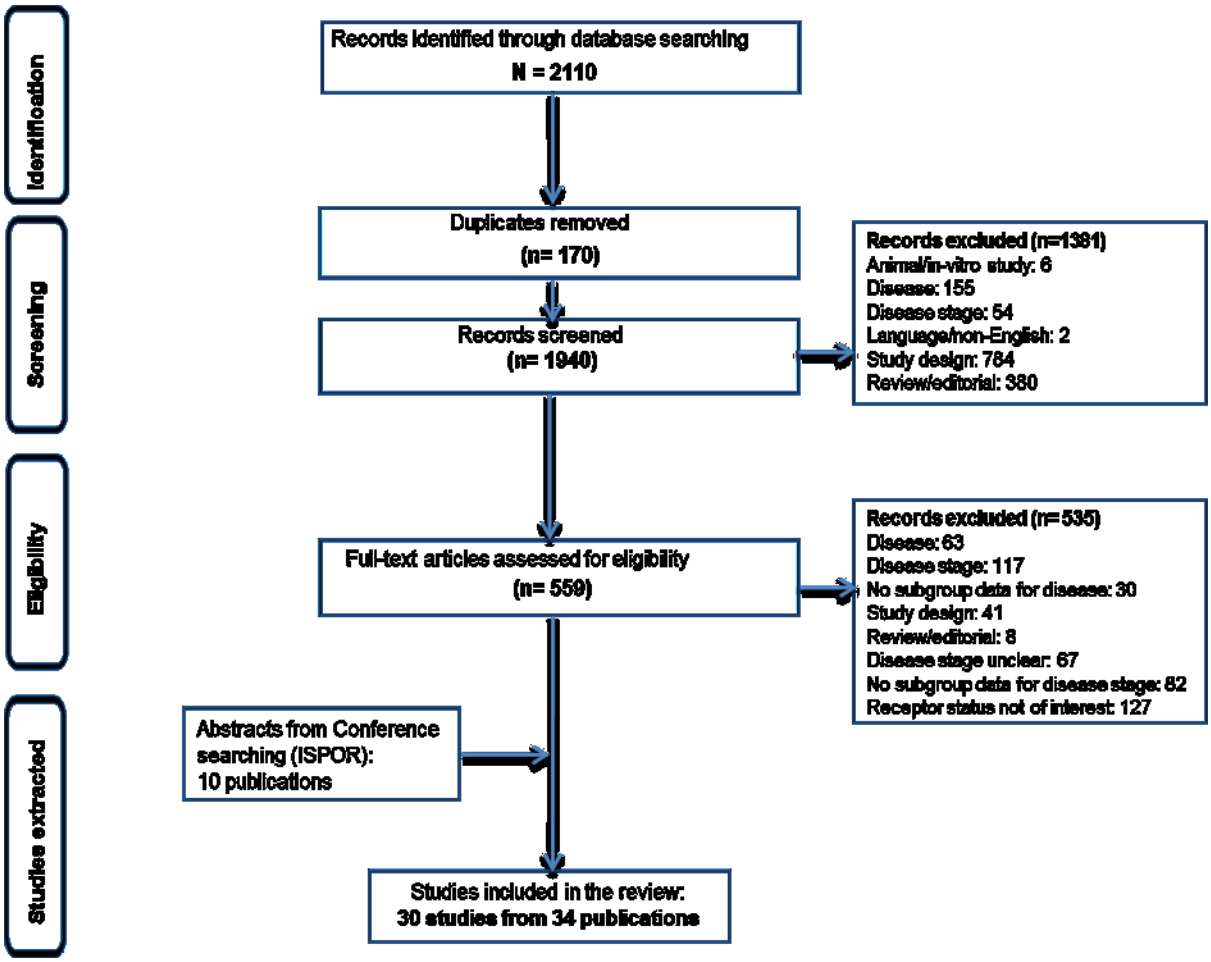
Three NICE appraisals were identified that reported economic data in patients with advanced breast cancer:

- TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer[73]
- TA295: Everolimus with exemestane for treating advanced breast cancer after endocrine therapy[86]

- TA421: Everolimus with exemestane for treating advanced breast cancer after endocrine therapy[72] (it should be noted that TA421 supersedes TA295)
- ID915: Palbociclib for treating breast cancer (HR+/HER2-).[2]

Of the 30 included studies, 21 reported the results of economic evaluations and nine reported costs or resource use data in HR+/HER2- advanced breast cancer. A summary of the included economic studies and the two health technology assessments is provided in Appendix 11. Further detail on the cost and resource use studies is provided in section 5.5.1

Figure 17 PRISMA flow diagram of identified studies in the cost-effectiveness systematic review.



Published economic evaluations in first-line advanced breast cancer

The studies of most relevance to ribociclib and its target indication are those reporting treatment in the first-line setting. These studies reported evaluations from the US (n=3), UK, France, Switzerland, Canada, and Italy. Table 22 summarises these studies.

Of the eight studies, four were classified as cost-effectiveness evaluations[87-90] three were cost-utility evaluations (including one that also reported budget impact),[91-93] and one reported a cost-minimisation

analysis.[94] The effectiveness of therapies was evaluated in various ways including in terms of quality-adjusted life years (QALYs), life years gained (LYGs) and quality-adjusted progression-free months or years. All eight studies reported costs from a payer perspective, including private (n=2)[88,89] and national healthcare systems (n=6).[87,90-92,94] None of the studies identified considered indirect costs in line with a societal perspective.

The majority of studies were model-based evaluations (n=6), with the exception of the cost-minimisation analysis[94] and one of the cost-effectiveness studies,[89] both of which reported evaluations based on patient-level data. Of the model-based evaluations, three reported the use of Markov state transition models,[87,88,92] one reported a decision-node structure,[91] one reported a time-in-state method,[93] which is equivalent to the partitioned survival approach, and one reported a regression-based methodology.[89] The structures of the models included conventional three-state structures comprising health states for progression-free, progressed disease, and death, and more complex structures involving states representing different lines of therapy. For models that used cycle periods, a 1-month cycle period was the preferred option.

Five of the eight studies reported the economic evaluation of tamoxifen versus anastrozole or letrozole.[89-93] A further two studies reported the evaluation of palbociclib plus letrozole versus letrozole or anastrozole alone,[87,88] and one study reported a cost-minimisation analysis comparing the costs of bevacizumab given in combination with different chemotherapies.[94] Further details for these studies are provided in the following sections.

Table 22 Results of the first-line studies in advanced breast cancer

No.	Lead author – year (country)	Modelling method	Patient population (average age in years)	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)
1	Nerich *et al*., 2012[94] (France)	Retrospective cost-minimisation analysis based on patient-level data from 83 patients consecutively treated with bevacizumab plus docetaxel (n=35) or bevacizumab plus paclitaxel (n=49). Only direct medical costs were considered including costs for drug, administration, hospitalization for serious AEs and healthcare travel (cost of trip to treatment is borne by the health care system in France)	Bevacizumab plus docetaxel regimen [Median] 57 Bevacizumab plus paclitaxel regimen [Median] 60	2011	Bevacizumab plus docetaxel regimen: total costs [mean (SD)] €53,093 (34,395) Bevacizumab plus paclitaxel regimen: total costs [mean (SD)] €60,196 (48,766)	-	Cost difference €7,103 (paclitaxel combination versus docetaxel combination)
2	Matter-Walstra *et al*., 2016[87] (Switzerland)	Markov model comprising states for progression-free, progressed disease, and death. Clinical outcomes were modelled based on data from PALOMA-1. Outcomes were modelled over a 4 week cycle period assuming a constant hazard rate over time. The base case analysis was conducted assuming 0% discounting of costs and outcomes	-	2015	Palbociclib + Letrozole CHF501,105 Letrozole CHF158,665	Palbociclib + Letrozole QALY: 3.33 Letrozole QALY: 2.19	CHF301,227/QALY (Palbociclib + Letrozole versus letrozole alone)
3	Bhattacharya *et al*., 2016[88] (abstract) (US)	Markov disease-state transition model was developed to estimate the cost-effectiveness of anastrozole, letrozole, and combination letrozole and palbociclib	-	2014	Palbociclib + Letrozole US$203,867 Letrozole US$21,322	Palbociclib + Letrozole LYG: 1.82 Letrozole LYG: 1.47	US$21,824/LYG (Letrozole versus anastrozole) US$510,356/LYG

No.	Lead author – year (country)	Modelling method	Patient population (average age in years)	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)
					Anastrozole US$19,982	Anastrozole LYG: 1.40	(Palbociclib+Letrozole versus anastrozole)
4	Simons *et al*., 2003[89] (US)	Healthcare resource utilisation data were collected prospectively in the North American trial and used to estimate resource consumption in the analysis. The incremental cost-difference per patient after disease progression to death was estimated using a 2-stage model comprising probit and tobit regressions. Effectiveness was measured using the Q-TWiST method, and included quality-adjusted time to disease progression	-	2000	Tamoxifen: Indemnity Insurer (Total) US$28,521 Anastrozole: Indemnity Insurer (Total): US$18,843 Tamoxifen: POS Insurer (Total): US$34,301 Anastrozole: POS Insurer (Total): US$21,587 Tamoxifen: HMO Insurer (Total): US$27,495 Anastrozole: HMO Insurer (Total): US$18,431	-	Difference in cost: US$9,678 (Tamoxifen versus anastrozole - Indemnity) Difference in cost: US$12,715 (Tamoxifen versus anastrozole - POS) Difference in cost: US$9,064 (Tamoxifen versus anastrozole - HMO)
5	Dranitsaris *et al*., 2003[91] (Canada)	Decision analytical model based on decision nodes for response status that were evaluated at 3-monthly intervals until disease	-	2003	(Canadian dollars)	Letrozole: Quality-adjusted progression-free benefit (years):	Cost per quality-adjusted progression-free year gained: Can$12,500/QALY

No.	Lead author – year (country)	Modelling method	Patient population (average age in years)	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)
		progression. Therapy was continued whilst responding, and up to disease progression. Failure to respond resulted in chemotherapy treatment. Effectiveness was measured in terms of the quality-adjusted progression-free survival benefit			Letrozole: Average cost/patient Can$2,883 Tamoxifen: Average cost/patient Can$2,258 Anastrozole: Average cost/patient Can$2,847	0.49 Tamoxifen: Quality-adjusted progression-free benefit (years): 0.44 Anastrozole: Quality-adjusted progression-free benefit (years): 0.47	(Letrozole versus Tamoxifen) Cost per quality-adjusted progression-free year gained: Can$19,600/QALY (Anastrozole versus Tamoxifen)
6	Marchetti *et al*., 2004[92] (Italy)	Markov model comprising states for 1st through 3rd line hormone therapy, 1st through 3rd line chemotherapy, palliative therapy and death. Clinical outcomes were modelled based on pooled data from four randomised trials for hormone therapy. Outcomes were modelled over a 1-month cycle period for a time horizon of 8.3 years. Costs and outcomes were discounted at 3% per annum	-	2003	Letrozole: Average cost/patient €23,777 Tamoxifen: Average cost/patient €20,076 Anastrozole: Average cost/patient €22,505	Letrozole: Quality-adjusted progression-free benefit (months): 18.73 Tamoxifen: Quality-adjusted progression-free benefit (months): 16.10 Anastrozole: Quality-adjusted progression-free benefit (months): 18.80	Cost per quality-adjusted survival gained (months) €/QALY (95% CI): 16,886 (9,117-15,465) (Letrozole versus Tamoxifen) Cost per quality-adjusted survival gained (months) €/QALY (95% CI): 10,795 (7,737-12,899) (Anastrozole versus Tamoxifen)
7	Das *et al*., 2013[93] (UK)	Time in state (or partitioned survival) model comprising three states for pre-progression, post-progression, and death. Clinical	-	2010/2011	Fulvestrant: Total discounted cost on average	Fulvestrant: QALY 1.638	£34,528/QALY (Fulvestrant versus letrozole)

No.	Lead author – year (country)	Modelling method	Patient population (average age in years)	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)
		outcomes were modelled based on data from 7 randomised controlled trials identified through a systematic review. Costs and outcomes were discounted at annual rates of 3.5% over a lifetime horizon of 13.5 years			per patient: £38,224 Anastrozole: Total discounted cost on average per patient: £28,976 Letrozole: Total discounted cost on average per patient: £23,841	Anastrozole: QALY 1.334 Letrozole: QALY 1.211	£41,862/QALY (Anastrozole versus letrozole) £31,468/QALY (Fulvestrant versus Anastrozole)
8	Cressman *et al*., 2015[90] (US)	The additional costs and benefits gained from oncology drugs over time was assessed using treatment protocols and efficacy results from US FDA records to calculate cost-effectiveness ratios for drugs approved for multiple cancers, including breast cancer. Benefits were measured in terms of the difference in progression-free survival	-	2013	-	-	(First-line and HER2-only reported) Cost per efficacy progression-free life year gained (versus tamoxifen) US$3,846 (Anastrozole) Cost per efficacy progression-free life year gained (versus tamoxifen) US$5,124 (Letrozole) Cost per efficacy progression-free life year gained (unclear comparison) US$178,249

No.	Lead author – year (country)	Modelling method	Patient population (average age in years)	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)
							(bevacizumab and paclitaxel)

CHF: Swiss Francs; HMO: health maintenance organization; CI: confidence interval; EUR: Euros; FDA: Food and Drug Administration; HER: human epidermal growth factor receptor; LY: life-year; POS: point of service; QALY: quality-adjusted life-year SD: standard deviation; US: United States

Evaluations of anastrozole and letrozole

Five studies reported the economic evaluation of tamoxifen versus anastrozole or letrozole.[89-93] This included a cost difference study and a cost-effectiveness study conducted from the US healthcare perspective, and three cost-effectiveness studies that reported economic evaluations from Canadian, Italian, and UK healthcare perspectives. Of the five identified economic evaluation studies identified, only one publication was considered to be of direct relevance to the appraisal of ribociclib, which is that of Das *et al.*,[93] since this reported the cost-effectiveness of fulvestrant, letrozole, and anastrozole from the UK National Health Service (NHS) perspective. However, it should also be noted that the reported cost-effectiveness analysis was in respect of second-line treatment in HR+/HER2- advanced breast cancer patients. Thus, this study does not fully represent the decision problem, although it does offer a wider perspective that is relevant for the appraisal.

Das *et al.* reported the cost-effectiveness of fulvestrant, letrozole, and anastrozole in terms of the cost per QALY gained from a UK NHS perspective.[93] The analysis was performed using a conventional three-state progression-free, progressed disease, and death model using a time-in-state approach to estimate transitions over time. The clinical efficacy of therapy was estimated from a meta-analysis, and costs included drug acquisition, administration and monitoring, patient monitoring, and the costs of serious AEs. Both costs and outcomes were discounted at rates of 3.5% per annum in line with standard practice for evaluations in the UK.

Over a time horizon of 13.5 years, the mean total costs (discounted) for fulvestrant were £38,224, versus £28,976 for anastrozole and £23,841 for letrozole. The corresponding mean total QALYs were 1.638 for fulvestrant, 1.334 for anastrozole, and 1.211 for letrozole. A fully incremental analysis was performed using letrozole as the reference as it was the treatment associated with the lowest cost. The next most costly intervention to letrozole was anastrozole, with an incremental cost-effectiveness ratio (ICER) of £41,862/QALY gained (versus letrozole). The next most costly intervention was fulvestrant. The incremental cost-effectiveness ratio for fulvestrant versus letrozole was £31,468/QALY gained.[93]

In summary, whilst Das *et al*.[93] reported the cost-effectiveness of letrozole and anastrozole in respect of the UK, the results were based on second-line HR+/HER2- advanced breast cancer treatment i.e. not the decision problem of consideration in this appraisal; however, the publication provides value in consideration of the economic modelling approach and resource use costs captured.

Evaluations of palbociclib plus letrozole

Two studies reported the results of evaluations comparing palbociclib plus letrozole versus letrozole or anastrozole alone.[87,88]

Matter-Walstra *et al.* reported the lifetime cost-effectiveness of palbociclib plus letrozole versus letrozole alone from the perspective of the Swiss health care system.[87] A Markov model with a 4-week period and comprising three mutually exclusive states for progression-free, progressed disease, and death was developed. Clinical outcomes were modelled based on data from the PALOMA-1 study. Hazards

were assumed to be constant over time and for letrozole, were estimated from the median time spent progression-free and alive (e.g. OS). Transition probabilities for palbociclib plus letrozole were estimated by applying the hazard ratios from PALOMA-1 to the rates obtained from the letrozole arm of PALOMA-1. The effectiveness of therapy was modelled in terms of QALYs, with health state utilities derived from a mapping analysis reported in a previous economic evaluation by Delea *et al.* The same utilities were assumed to apply to both arms of the evaluation. Costs comprised study medication, follow-up treatment and costs for neutropenia. The cost of palbociclib was based on US prices converted to Swiss Francs (CHF).

Matter-Walstra *et al.* reported that palbociclib cannot be considered a cost-effective treatment strategy from the Swiss healthcare system perspective when priced at parity with US costs.[87] In the base case (0% discounting), there were 1.14 incremental QALYs comparing palbociclib plus letrozole versus letrozole alone. When combined with an incremental cost of CHF342,440, the resulting incremental cost-effectiveness ratio was CHF301,227/QALY gained. The authors state that this cost-effectiveness ratio exceeds commonly accepted thresholds in the UK and US, and is above a recently proposed threshold of CHF100,000 for reimbursement in Switzerland. It was reported that a 75% price reduction for palbociclib would yield a cost-effectiveness ratio below CHF100,000, with an 18% probability of being cost-effective at a threshold of CHF50,000 per QALY gained.[87]

Similar outcomes were reported in the conference abstract by Bhattacharya *et al*., who developed a Markov disease-state transition model in TreeAge Pro 2015 to compare the cost-effectiveness of anastrozole, letrozole and palbociclib plus letrozole.[88] The disease states in the model comprised first-line therapy, no disease progression, disease progression, chemotherapy and palliative care, and death. Transition probabilities were obtained from published clinical trials; no detail was provided for the data sources. Literature-based costs included drug acquisition derived from wholesale prices, and literature costs were used for chemotherapy and palliative care. The incremental cost-effectiveness ratio reported in the poster (5% discounting of cost and benefits) was $510,356/LYG comparing palbociclib and letrozole versus anastrozole alone (incremental LYG of 0.42 versus anastrozole).[88]

In summary, the two studies reported that palbociclib plus letrozole is not cost-effective versus either letrozole monotherapy or anastrozole monotherapy when based on wholesale prices in the US. In the study by Matter-Walstra *et al.,* it was reported that a 75% reduction in the price of palbociclib would yield cost-effectiveness ratios below a maximum threshold of CHF100,000, with a one in five chance of it being cost-effective at a threshold of CHF50,000. The results of these studies should be viewed in the light of their limitations, given that both studies only considered a limited range of costs and employed various assumptions when modelling outcomes (e.g. constant hazard rate over time) that may underestimate long-term survival benefits of therapy.

5.1.3 Description of health technology appraisals in advanced breast cancer

Two single technology appraisals were identified that reported economic data in patients with HR+/HER2- advanced breast cancer.[72,73]

A summary of the results of the cost-effectiveness analyses reported in these appraisals and their outcomes is given in Table 23.

In both appraisals, the manufacturer drugs were deemed cost-ineffective versus standard of care and were not recommended as treatment options in their respective marketing authorizations. Further details of the modelling methods adopted in these appraisals are provided in the following sections.

Table 23 Summary of the results of the health technology appraisals in advanced breast cancer

TA/Title	Modelling method	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)	Committee conclusion
TA239, Fulvestrant for the treatment of locally advanced or metastatic breast cancer[73]	Time in state model comprising three states for pre-progression, post-progression, and death. The model calculated the proportion of patients in each health state according to the estimated survival functions for TTP and overall survival. Clinical outcomes were modelled based on data from 8 randomised controlled trials identified through a systematic review. Costs and outcomes were discounted at annual rates of 3.5% over a lifetime horizon of 13 years	2010/11	Fulvestrant (500 mg): Costs per patient £35,576 Fulvestrant (250 mg): Costs per patient £30,849 Anastrozole: Costs per patient £27,453 Letrozole: Costs per patient £27,357	Fulvestrant (500 mg): 1.6966 Fulvestrant (250 mg): 1.4896 Anastrozole: 1.4644 Letrozole: 1.3822	£34,972 (Fulvestrant 500 mg versus anastrozole) £134,703 (Fulvestrant 250 mg versus anastrozole) £26,137 (Fulvestrant 500 mg versus letrozole) £32,519 (Fulvestrant 250 mg versus letrozole) £1,162 (Anastrozole versus letrozole)	Not recommended

TA/Title	Modelling method	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)	Committee conclusion
TA295, Everolimus in combination with exemestane for treating advanced HER2- negative hormone receptor positive breast cancer after endocrine therapy[72]	State transition Markov model comprising three health states: stable disease, progressed disease and death. Transition of patients was calculated using the proportion of patients in each health state according to the survival functions for progression-free survival and overall survival. A total of 7 treatments were considered including 3 chemotherapy agents (docetaxel, doxorubicin or capecitabine). Both costs and outcomes were discounted at annual rates of 3.5% over a lifetime horizon of 10 years		Everolimus + Exemestane £46725 Exemestane: Costs per patient £21736	Everolimus + Exemestane: 1.931 Exemestane: 1.306	£39,978 (Everolimus + Exemestane vs. Exemestane)	Not recommended
TA421, Everolimus in combination with exemestane for treating advanced HER2- negative hormone receptor positive breast cancer after endocrine therapy[72]	TA421 supersedes TA295 in which the cost-effectiveness comparison was everolimus + exemestane vs. everolimus					Everolimus + exemestane was recommended as a treatment option within its marketing authorisation

TA/Title	Modelling method	Cost year	Costs (intervention, comparator)	QALYs (intervention, comparator)	ICER (per QALY gained, unless otherwise stated)	Committee conclusion
ID915, Breast cancer (hormone-receptor positive, HER2-negative) – palbociclib[a]	Partitioned survival Markov model comprising of three health states: pre-progression, post-progression (including three tunnel states) and death. Transition of patients was calculated using the proportion of patients in each health state according to the survival functions for progression-free survival (PFS) and overall survival (OS). Base case analysis applied survival functions as per the following: • PFS – PALOMA-2 trial data • OS – PALOMA-1 trial data (with an applied factor) The comparator treatment considered was letrozole. Both costs and outcomes were discounted at annual rates of 3.5% over a lifetime horizon of 40 years	2014/15	Palbociclib: £116,696 £2,950 proposed monthly cost per patient (Letrozole: £21,843 £1.52 monthly cost per patient	Palbociclib: 2.40 Letrozole: 1.77	£150,869 (palbociclib + letrozole vs. letrozole)	Not recommended at first ACD

ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year; TA, technology assessment; TTP, time to progression.
[a]NICE technology appraisal ID915 was identified through an update hand search. The appraisal is currently still ongoing and the final appraisal determination (FAD) is yet to be published.

Model structure and simulation methodology

In TA295, now superseded by TA421, and TA239 appraisals, cost-effectiveness was estimated using a three-state cohort model that contained health states for progression-free disease, progressed disease, and death. State occupancy in the models was estimated via a partitioned survival analysis, which involves the direct modelling of PFS and OS data to estimate the numbers in each state. Costs and outcomes were discounted at rates of 3.5% per year, and evaluated over monthly cycle periods for time horizons of 10 (TA239) and 12.5 (TA295) years.

PFS and OS were modelled using conventional parametric survival function (e.g. Weibull) fitted to individual patient data from the manufacturer's primary clinical trials; CONFIRM (TA239) and BOLER02 (TA295). The selection of best fitting function was based on a combination of statistical goodness-of-fit, inspection of the visual fit of each function to the KM plot, and consideration of the clinical plausibility of lifetime function predictions judged through consultation with clinical experts. In both appraisals, the preferred parametric function for OS was the Weibull distribution, with the Weibull preferred for PFS in TA421 and log-normal in TA239. The approaches adopted follow the methods recommended in NICE technical support document 14.[95]

AE-related costs and outcomes were considered in both appraisals, see Table 24. The costs and health consequences of these events were modelled as one-off cost and QALY adjustments were applied at the start of the simulation. A more extensive list of AEs was considered in TA421 than in TA239, with only cough, diarrhoea, fatigue, and nausea being considered in both appraisals.

Table 24 AEs considered in each appraisal

List of AEs	TA239[a]	TA295[b]
Anorexia	✓	×
Arthralgia	✓	×
Asthenia	✓	×
Back pain	✓	×
Bone pain	✓	×
Cough	✓	✓
Decreased appetite	×	✓
Diarrhoea	✓	✓
Fatigue	✓	✓
Headache	✓	×
Hot flush	✓	×
Hypertension	✓	×
Hyperglycaemia	×	✓
Injection site pain	✓	×
Nasopharyngitis	✓	×
Nausea	✓	✓
Pain in extremity	✓	×
Pneumonitis	×	✓

List of AEs	TA239[a]	TA295[b]
Rash	×	✓
Stomatitis	×	✓
Vomiting	✓	×
Weight decreased	×	✓

[b]The manufacturer submission for TA295 (now replaced by TA421) used serious AEs rather than the conventional grade 3 or 4 AEs.
[b]TA295 incorporated costs for AEs in the sensitivity analysis only.
Bold text indicates
AE, adverse event; TA, technology appraisal.
NICE TA239;[73] NICE TA421[72]

Costs and resource utilization

In both appraisals, cost inputs included drug acquisition and administration, progression-free and progressed disease state costs and AE costs. A summary of the monthly resource utilization rates assigned to the progression-free and progressed disease states are shown in Table 25 and Table 26.

Table 25 Healthcare resource use the progression-free and progressed disease state used in TA239

Resource type	Proportion of patients	Units of resource consumed
Progression-free state		
Oncology visit	33%	1 visit per cycle
GP visit	10%	1 visit lasting 11.7 minutes per cycle
Radiographer	4%	1 visit lasting 1 hour per cycle
Biochemistry test	33%	1 test per cycle
Blood test	30%	1 test per cycle
Bone scintigraphy	8%	1 test per cycle
CT scan	20%	1 scan per cycle
Chest X-ray	3%	1 X-ray scan per cycle
Bone X-ray	3%	1 bone x-ray scan per cycle
Hospitalization (general medicine)	1%	6 days
Hospitalization (oncology)	1%	8 days
Nurse, day ward	99%	1 visit lasting 15 minutes per cycle
Progressed disease state		
Community nurse home visits	33%	4 visits lasting 20 minutes per cycle
Clinical nurse specialist: 1 hour	10%	4 visits lasting 1 hour per cycle
GP contact: 1 hour	4%	2 visits per cycle
Therapist: 1 hour	33%	2 visits per cycle

CT, computed tomography; GP, general practitioner.
NICE TA239[73]

The monthly resource utilisation rates were estimated from different sources in the two appraisals.[72,73] A review of the NICE CG81 treatment pathway was used in TA421 and expert clinical opinion was used in TA239. Modelled healthcare costs in TA239 comprised resources relating to disease monitoring (e.g. tests), and supportive care (e.g. nursing). In TA421, only costs relating to healthcare practitioners were included.

Table 26 Healthcare resource use for the progression-free and progressed disease state used in TA421

Resource type	Units of resource consumed
Progression-free state	
Community nurse home visits	1 visits lasting 20 min per cycle
Clinical nurse specialist	1 visit lasting 1 hr per cycle
GP contact	1 surgery visit per cycle
Social worker	1 visit per cycle
Progressed disease state	
Community nurse home visits	2 visits lasting 20 min per cycle
Clinical nurse specialist	4 visit lasting 1 hr per cycle
GP contact	1 home visit per cycle
Therapist	1 visit per cycle

GP, general practitioner.
NICE TA421[72]

Unit costs were identified from conventional sources including the British National Formulary (BNF) for drug unit costs, the NHS reference costs for hospitalization events, and the personal social services research unit (PSSRU) for practitioner costs.

Valuation of health benefits

In line with the NICE methods guide,[85] the health benefits of treatment were modelled in terms of the QALY. In both appraisals, patient-related HRQoL (utilities) was modelled using data from Lloyd *et al*.,[49] which reports societal preferences for metastatic breast cancer and six common toxicities. The utilities reported in this study were elicited from 100 members of the general public using the standard gamble method. This study was considered the best source of data on utilities available at the time of appraisal. The NICE reference case requires that utilities are estimated using the EQ-5D questionnaire, mapped to utilities based on UK social preferences.

A summary of the utilities applied in each appraisal is presented inTable 27.

The negative impact of AE on utilities was not incorporated in the base case analyses for TA239 and TA421. This was justified on the basis that only a small number of events were observed in the clinical trials.

Table 27 Health state utility values used in TA239 and TA421

	TA239	TA421
Values used in manufacturer submission	PFS, 0.72 (SE = 0.014) PD, 0.44 (SE = 0.016)	PFS, 0.798 (SE = 0.014) PD, 0.496 (SE = 0.016)
Re-estimated values used in ERG model	TTP/PFS, 0.7733 PD (without AE), 0.4964	PFS (Everolimus), 0.798 PFS (Exemestane), 0.7571
Notes	The manufacturer used the utility values reported in the Lloyds study. However, the values used in the MS did not account for the response to therapy in its estimation. The ERG used the response to therapy data collected during the trials and re-estimated the utility scores	The manufacturer used the utility values reported in the Lloyds study. However, the values used in the MS did not account for the different levels of response in the BOLERO trial. The ERG used these values and re-estimated treatment-specific utility scores for the PFS health state

AE, adverse event; ERG, evidence review group; MS, manufacturer submission; PFS, progression-free survival; PD, progressed disease; TTP, time to progression.
NICE TA239,[73] NICE TA421.[72]

5.2 De novo analysis

The objective of the economic evaluation was to assess the cost-effectiveness of ribociclib in combination with letrozole for the first-line treatment of advanced or metastatic HR+/HER2- breast cancer from the perspective of the NHS, versus letrozole as per the NICE scope (see section 1.1).

5.2.1 Patient population

The economic evaluation considers patients that reflect the decision problem, postmenopausal women with advanced or metastatic HR+/HER2- breast cancer previously untreated in the advanced setting (i.e. first-line), which is consistent with the population from the MONALEESA-2 clinical trial[21] used to support the EU marketing authorisation submission for ribociclib and the anticipated licence.

5.2.2 Model structure

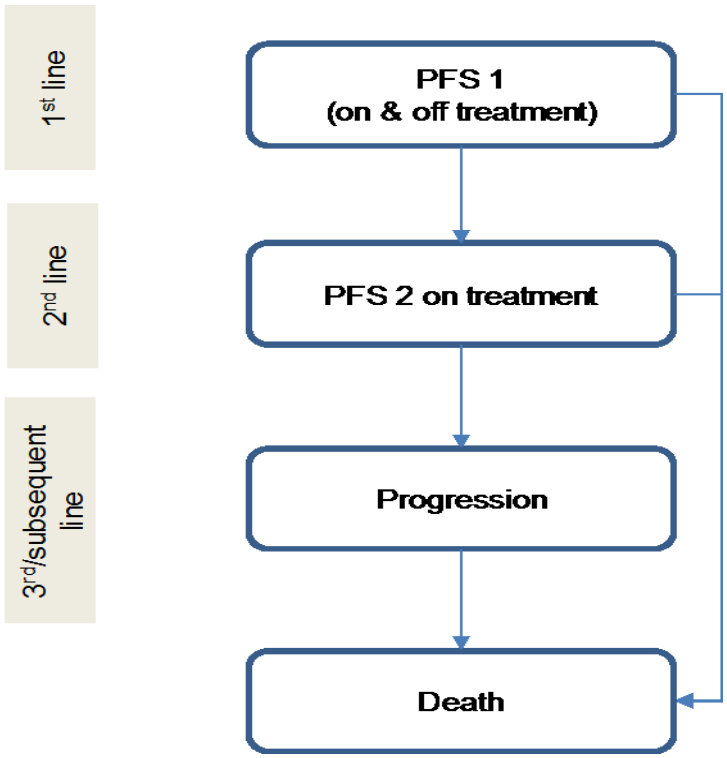
A state-transition approach model was developed based upon clinical validation through advisory board discussions and individual discussions with clinical experts and supplemented by our understanding of the natural history of advanced or metastatic breast cancer through detailed review of published literature and previously used economic models in oncology. The de novo economic model structure was chosen to:

- reflect the UK treatment pathway in advanced breast cancer by incorporating therapies used following progression of first-line treatment in UK clinical practice
- make the best of use of data from the MONALEESA-2 trial, which provided a direct comparison with the appropriate comparator

- make the best use of the evidence available in second-line (which is mature) to model OS to account for the immaturity of the OS data from the MONALEESA-2 trial.

A state-transition approach model was developed in Visual Basic for Excel whereby individuals move through a series of four health states, reflected in Figure 18.

Figure 18 De novo model structure



PFS, progression-free survival.

Movements through the model and health states definition are described below.

First-line PFS (PFS1) health state: Individuals enter the model in the "first-line PFS" health state where they receive one of the following treatments:

- ribociclib in combination with letrozole
- letrozole alone.

Patients in this health state are free from progression and can either (a) remain in this health state in the absence of progression (or death), (b) move to second-line treatment in the "second-line PFS (PFS2) on treatment" health state or (c) die. It should be noted that patients are unable to move directly to the "progressive disease" (progression) health state. This is a simplification due to the lack of data available to model the outcomes of people who receive no further treatment following first-line progression.

In the economic model, "first-line PFS" encompasses both the period on and off treatment. Therefore, "first-line PFS" is sub-divided into on-treatment and off-treatment phases to capture

the differences in associated drug acquisition costs as well as to reflect the treatment duration in the MONALEESA-2 trial, for which the efficacy data for the economic model is derived. In the economic model, for simplicity, time to treatment discontinuation (TTD) and PFS are modelled independently (i.e. they are not linked) from each other. It should be noted that this approach resembles the assumption made within a partitioned-survival approach.

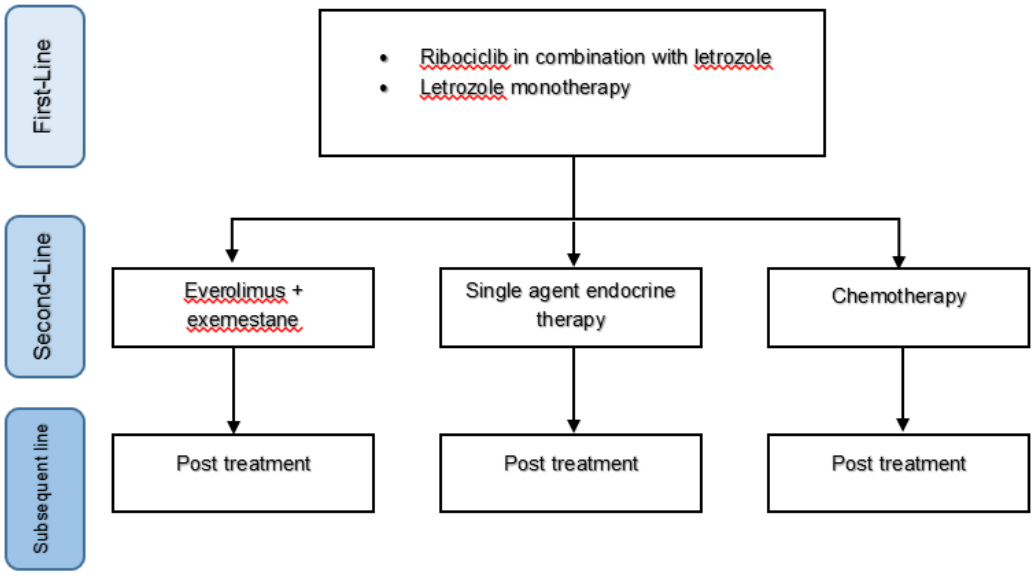
Second-line PFS on treatment (PFS2) health state: This represents the time between disease progression in first-line and second-line treatment cessation (used as a proxy for progression due to data availability – see section 5.3.5 for further details). Patients entering this health state can (a) remain in this health state, (b) move to the "progressed disease" (progression) health state or (c) die.

Patients entering the "second-line PFS on treatment" health state are assumed to be treated with one of the following active second-line treatments. The choice of therapy was based on treatments that are available (NHS reimbursed), and widely used following discussion with clinical experts and appropriate clinical data was available (illustrated in Figure 19):

- everolimus + exemestane
- single-agent endocrine therapy (exemestane monotherapy is used in the model)
- chemotherapy (assumed to be capecitabine).

It should be noted that the treatment pathway in post-menopausal women with HR+/HER2- is a difficult and complex process with a multitude of treatments available (single agents or combination therapies). The choice of second-line therapy depends on several factors including patient choice, time to progression and response to prior therapy, the type of therapy previously received and the disease characteristics. This makes the accurate modelling of the treatment pathway particularly challenging. Therefore, assumptions were made based upon clinical validation. The base case analysis considers that ribociclib in combination with letrozole patients follow a different treatment pathway to letrozole monotherapy patients following first-line treatment progression. This is based upon clinical expert validation; however, there is still uncertainty regarding the true clinical pathway patients will follow once ribociclib is introduced to the NHS as a first-line treatment. This is because CDK4/6 inhibitors are a new class of therapy and there still remains limited long-term real-world usage. This assumption is explored in scenario analysis where patients follow the same treatment pathway irrespective of first-line treatment (see section 5.8.3).

Figure 19 Treatment pathway assumed in the economic model



Progressed disease health state: This represents the time from cessation of second-line therapy (used as a proxy for progression) to death. In this health state, patients are in a progressive health state and receive subsequent treatments and/or supportive/palliative care.

It should be noted that third-line therapies are not explicitly modelled due to the absence of data. Thus, a separate cost (based on assumption – see section 5.5.2 for further details) is added in the base case in the progressed disease health state to reflect the drug acquisition and resource use costs for subsequent lines of therapies.

Death state: absorbing health state.

Type of model and justification

There are two key characteristics of this model:

1) A state-transition approach was employed in order to use external data to account for the immaturity of the OS in the MONALEESA-2 trial. The use of MONALEESA-2 data would make the direct estimation of OS challenging. The use of external sources also allowed the model to incorporate the effect of second-line therapies that are reflective of UK practice and the rapidly changing environment in breast cancer. Owing to the immaturity of the OS data in the MONALEESA-2 trial, a partitioned survival approach is likely to be considered inappropriate, as any long-term extrapolation to the observed KM could be considered arbitrary.

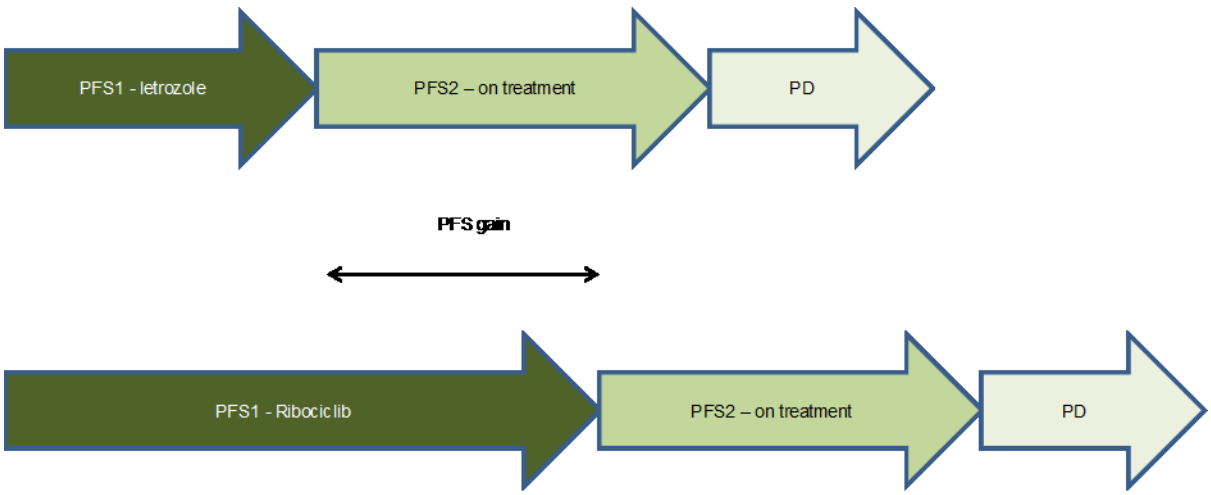
2) Furthermore, in contrast to many submissions to NICE, the model is individual-patient based and uses a time to event approach; thus, there are no time cycles. This approach was chosen over a cohort approach in order to incorporate time and flexibility and

explore the impact of different structural assumptions when modelling OS in scenario analysis. Standard cohort models are inflexible and require the use of tunnel states, which can be convoluted and time consuming to implement. In contrast, individual-based approaches provide more flexibility and are easier to implement. OS in the MONALEESA-2 trial[21] is immature, which makes the estimate of OS challenging with conventional modelling approaches. Additionally, it is felt that the use of a Markov model would not optimally capture the pathway of care experienced by the patient, especially as first-line patients would typically go on to receive a number of future lines of treatment post-progression. The use of the state-transition model means that the additional lines of treatments and related HRQoL and costs associated with these treatments are more accurately captured.

Modelling of OS

As depicted in Figure 20, the economic model uses a state-transition approach whereby individuals move through a series of health states. Thus, OS is modelled indirectly and is a function of the time spent in each of the modelled health states. Similar to the assumption used in many state-transition models, a shift in PFS in the first line would lead to a commensurate shift in OS (with the exception of patients who die upon progression). This is a simplification given the immaturity of the OS data from MONALEESA-2 and challenges/uncertainty when modelling the surrogacy between PFS and OS.

Figure 20 Illustration of assumption of perfect surrogacy



Due to immaturity of OS data from the MONALEESA-2 trial, it is difficult to predict the level of OS benefit. Clinical expert opinion at the palbociclib appraisal committee[2] considered that the gain in PFS shown would translate into a gain in OS. However, in the absence of data a base case assumption has been made that PFS benefit will translate into an equivalent OS gain.

In addition to our base case, a range of scenario analyses have been conducted for the estimation of OS around the surrogacy between PFS and OS and the impact that this has on the resulting ICER. In brief, in contrast to our base case, in scenario analyses, we assume that a shift in PFS for ribociclib (in combination with letrozole) compared with letrozole monotherapy translates into an equal shift in OS in only a proportion of patients. The proportion of patients experiencing the PFS to OS translational shift is defined by (a) their time to progression, i.e. only patients for whom their time to progression is greater or equal to 6 months or (b) their PFS gain, i.e. only patients who experience 6 months of PFS gain compared with letrozole.

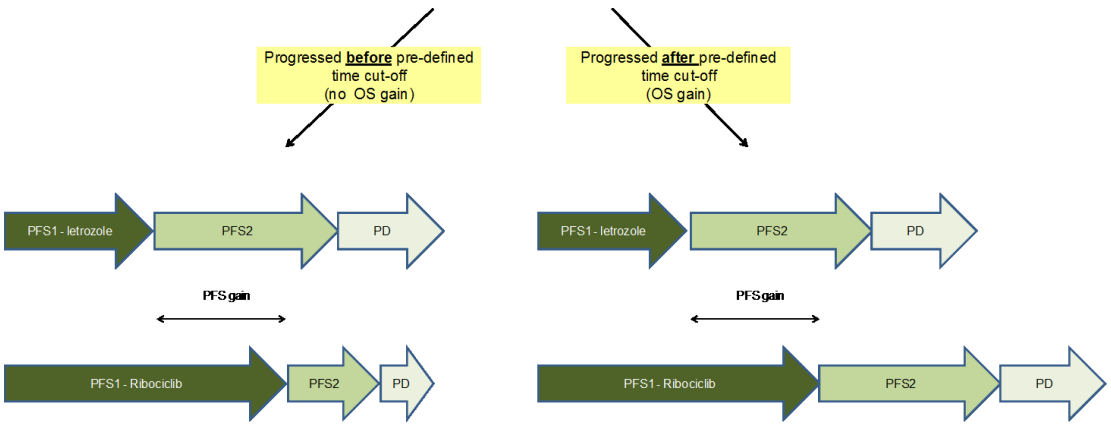
Figure 21 presents a graphical representation for the patient flow in the economic model in defining patients who experience a PFS to OS surrogacy compared with patients who experience no OS gain.

A range of scenario analyses are conducted using different PFS to OS surrogacy assumptions as follows:

- scenarios matching (a) above where patients PFS ≥ 4, 8, 12, 16, 20 and 24 months
- scenarios matching (b) above where patients experience 4, 8, 12, 16, 20 and 24 months of PFS gain compared to letrozole.

It should be noted that modelling the surrogacy between PFS and OS is challenging and therefore a number of simplifications and assumptions are required as it is not possible to model accurately the patient's experience. In particular, in addition to the surrogacy to apply to a proportion of patients, in patients for whom a shift in PFS translate into a shift in OS, the shift in OS may not be equal to the shift in PFS. Similarly, in patients for whom we assumed no shift in OS, these patients may still experience a shift in OS, not commensurate to their shift in PFS. Thus, these scenario analyses have to be considered with caution and with respect to the assumptions made. These scenarios are presented for transparency and completeness. We believe, as discussed earlier that the most reliable approach will be to assume that a PFS gain will result in a gain in OS as per our base case.

Figure 21 Schematic illustrating patient flow based on PFS to OS surrogacy definition



The key features of the de novo economic analysis are presented in

Table 28.

In order to address the decision problem and provide both the cost per QALY and cost per LYG, the economic model, in line with the NICE reference case,[85] adopts an NHS/personal social services perspective and includes the resource use and costs associated with disease management, treatment acquisition, administration, and AEs. In order to fully capture the benefits of ribociclib and comparator treatments, a lifetime time horizon of 40 years is used in the base case analysis. Costs and health-state utility values are allocated to each health state and multiplied by state occupancy to calculate the weighted costs and QALYs per cycle. In line with the NICE reference case, an annual discount rate of 3.5% is applied to costs and outcomes (Table 28). Different scenarios have been tested (see section 5.8) in which to explore the impact of different assumptions considered, including shorter time horizons and different discount rates.

Table 28 Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	Lifetime (40 years)	NICE reference case[85]
Cycle length	No cycle length	Individual-based approach – time is sampled directly
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case[85]
Discount of 3.5% for utilities and costs	Yes	NICE reference case[85]
Perspective (NHS/PSS)	Yes	NICE reference case[85]

PSS, personal social services; QALYs, quality-adjusted life years.

5.2.3 Intervention technology and comparators

As discussed in section 1.1, the base case analysis addresses the decision problem through considering the treatment intervention, ribociclib in combination with letrozole, and the comparator treatment, non-steroidal AI (letrozole). A detailed description of how both the intervention and comparator are incorporated into the economic model is presented below.

Intervention: ribociclib in combination with letrozole

The economic analysis uses evidence from the MONALEESA-2 trial[21] whereby ribociclib was prescribed in accordance with its anticipated license, i.e. in combination with letrozole. Patients enrolled in the MONALEESA-2 trial received ribociclib at a flat-fixed dose (600 mg once daily [per protocol], days 1–21 of a 28-day cycle) in combination with letrozole (2.5 mg once daily, days 1–28 of a 28-day cycle). It should be noted that in the MONALEESA-2 trial,[21] patients were allowed to appropriately dose reduce to either 400 mg or 200 mg ribociclib daily (see

section 4.3.1). The economic model takes into account dose distribution experienced by patients in the MONALEESA-2 study and discussed further in section 5.5.2.

In the MONALEESA-2 trial,[21] patients were treated with the study treatment until disease progression, unacceptable toxicity, death, or discontinuation due to any other reason, including loss to follow up or withdrawal of consent. Thus, no stopping rule is included in the economic model to reflect the treatment duration from the MONALEESA-2 trial.[21]

Comparator: non-steroidal aromatase inhibitors (AIs)

The AI, letrozole, as monotherapy (2.5 mg once daily days 1–28 of a 28-day cycle continuously) is included as a comparator in this economic evaluation as this is the comparator in the MONALEESA-2 trial[21] and as per the decision problem (see section 1.1). Anastrozole, another widely used AI, is not included as a comparator given the absence of robust data, and the expert clinical validation that letrozole and anastrozole are equivalent and interchangeable (section 3.3).

5.3 Clinical parameters and variables

As summarized in section 4.3, the clinical efficacy and safety of ribociclib plus letrozole as a first-line treatment of HR+/HER2- advanced breast cancer is currently being investigated in the MONALEESA-2 trial. IPD for ribociclib plus letrozole and letrozole monotherapy were obtained from this trial.[21,96] In addition, a systematic literature review was carried out to identify published survival data for letrozole monotherapy to be used for validation of long-term outcomes. IPD were also obtained for the Novartis BOLERO-2 trial, which compared everolimus + exemestane versus exemestane alone and provides robust long-term clinical efficacy data to be used for modelling second-line treatment.

The clinical data used within the model are listed below, and described in detail in the following sections:

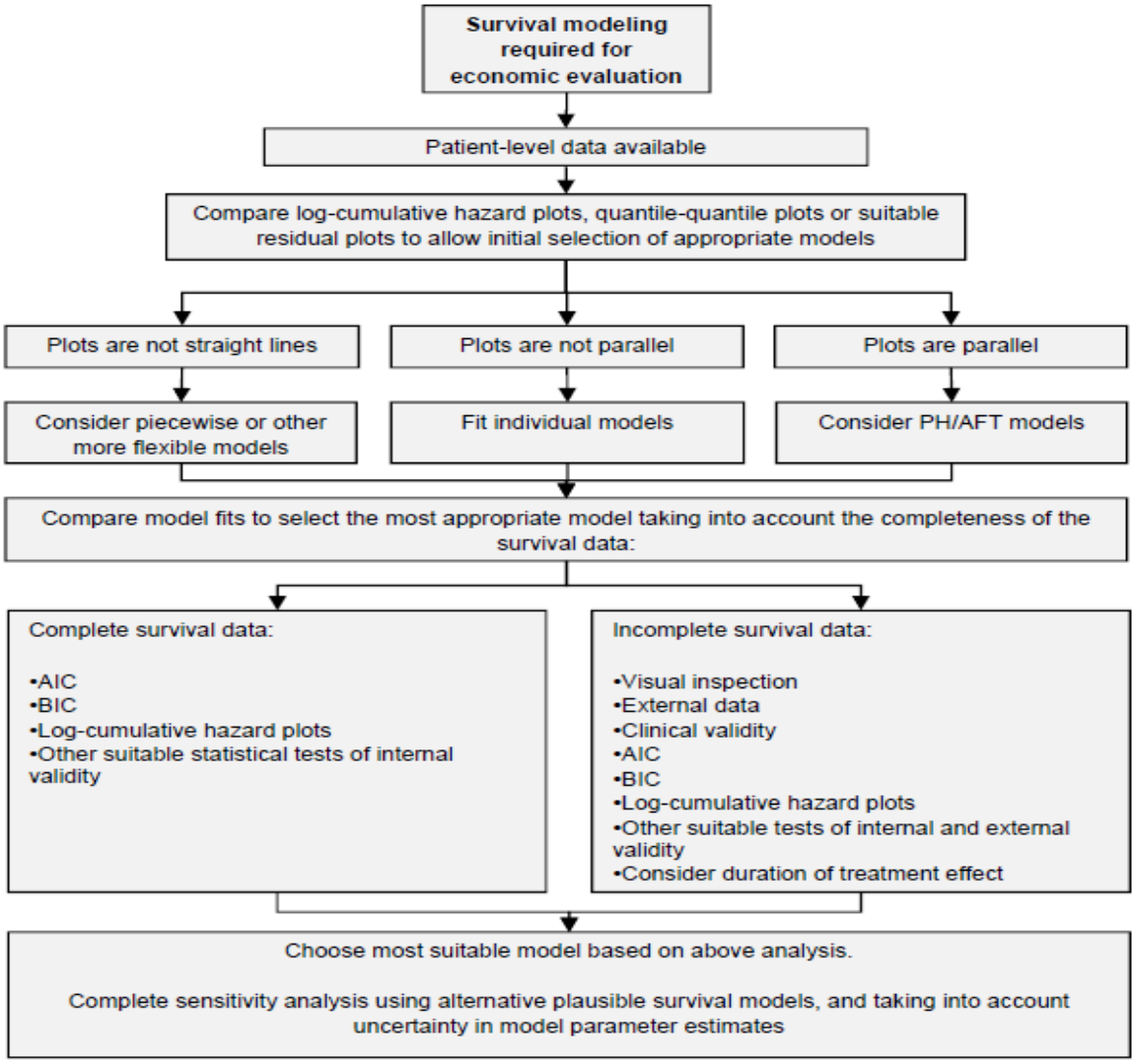
- PFS in patients on first-line therapy
- proportion of patients for whom the progression event on first-line therapy was death
- TTD in first-line
- distribution of treatments received in second-line
- modelling the effect of second-line treatment for everolimus + exemestane and exemestane monotherapy
- estimating TTD, PFS and OS in patients receiving second-line chemotherapy
- TTD in patients receiving second-line therapy
- safety.

5.3.1 Progression-free survival in patients on first-line therapy

In line with the decision problem, the base case analysis focuses on a comparison of ribociclib in combination with letrozole versus letrozole alone as the first-line treatment based on data from the MONALEESA-2 clinical trial. Standard guidance for fitting and selecting survival

functions was used and a full step-wise description of the statistical analysis based on the NICE DSU guidance[95] is provided in Figure 22. Due to the immaturity of the survival data currently available from MONALEESA-2 study, the assumption of proportional hazards is difficult to test. This section describes the methodology used to select the survival model to be used for first-line treatment PFS (PFS1 health state) in the model.

Figure 22 Selection of the survival model as recommended by the NICE DSU



Assessment of the proportional hazard assumption based MONALEESA-2

PFS for first-line treatment (ribociclib plus letrozole or letrozole alone) was assessed as recommended by the NICE DSU to explore whether it is appropriate to use proportional hazards or independent survival models.

The PFS KM curves (local assessment) from the MONALEESA-2 study[21] for both ribociclib plus letrozole and letrozole monotherapy are shown in Figure 23. A plot showing the log cumulative hazard versus log-time for PFS (local assessment) is shown in

Figure 24. It can be seen that the curves cross at the beginning, indicating a violation of the proportional hazard assumption during the initial months. Thus, PFS data were fitted separately for ribociclib plus letrozole and letrozole monotherapy. Furthermore, as the key comparison of interest is ribociclib plus letrozole versus letrozole monotherapy, the use of individual curves provided a more accurate estimation of the difference between the two treatments. However, it should be noted that whilst the curves cross at the beginning, the assumption of proportional hazards appear to hold thereafter and therefore the use of a HR is debatable and explored in scenario analysis for transparency and completeness.

Figure 23 Kaplan-Meier plot for PFS according to local assessment (primary endpoint) in MONALEESA-2

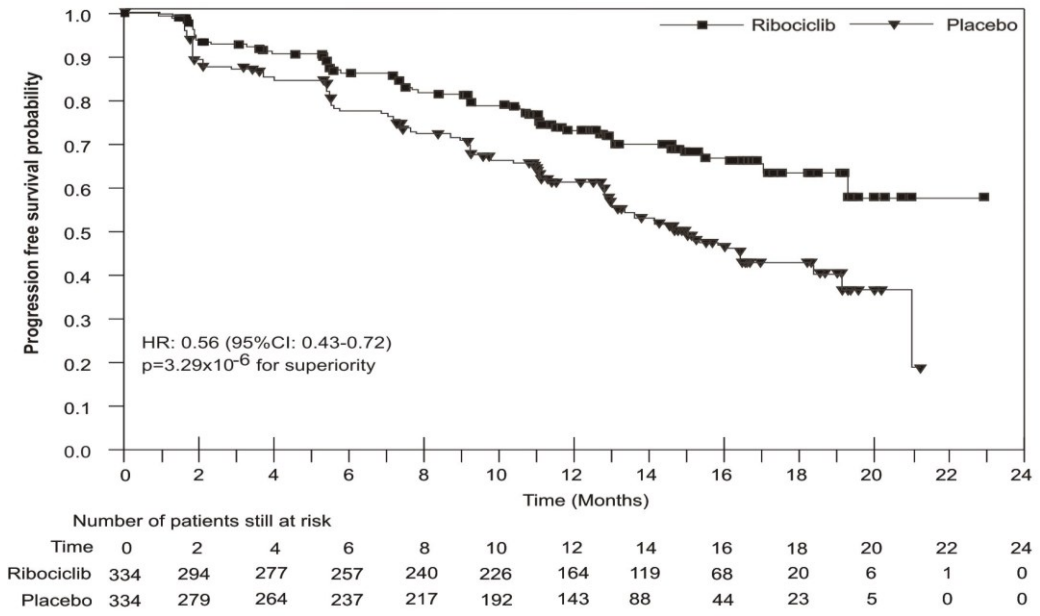


Figure 24 Log cumulative hazard plot for PFS (local assessment) in MONALEESA-2

Selection of a parametric survival function for PFS

IPD from MONALEESA-2[21] for both treatment arms, ribociclib in combination with letrozole (n=334) and letrozole monotherapy (n=334), were analysed to generate PFS KM curves for each treatment arm. A range of parametric survival models – Weibull, exponential, Gompertz, log-normal and log-logistic – were considered for extrapolation. The most appropriate distribution was selected using the following process: (a) assessment of the visual fit to the

observed KM, (b) assessment of the statistical goodness-of-fit, and (c) external clinical validation to assess the plausibility of the long-term extrapolation.

Visual assessment of fit

The KM data and overlaid extrapolated parametric survival models for all candidate survival functions for ribociclib plus letrozole and letrozole monotherapy are presented in Figure 25 and Figure 26. It can be seen that all of the distributions tested provided a reasonable visual fit to the observed period for both ribociclib (in combination with letrozole) and letrozole monotherapy. However, they provided different long-term extrapolation following the observed period.

Figure 25 Modelled parametric curves and the non-parametric PFS Kaplan–Meier plots for ribociclib plus letrozole

Figure 26 Modelled parametric curves and the non-parametric PFS Kaplan–Meier plots for letrozole

Assessment of statistical goodness-of-fit Table 29 summarises the statistical goodness-of-fit using both the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC) for the PFS estimates. However, goodness-of-fit criteria only provide an indication of the goodness-of-fit to the observed period and do not categorically indicate that one distribution should be preferred over the remaining distributions. Although caution should be taken when interpreting the goodness-of-fit statistics, the following conclusions can be made:

- based on the AIC and BIC of the PFS curves the log-normal distribution provides the best (statistical) fit to the data for both treatment arms
- based on the AIC and BIC, the Weibull distribution provides the next best fit for letrozole monotherapy, whilst for ribociclib plus letrozole, the exponential distribution provides the next best fit (in terms of BIC)
- it should be noted, however, that values for AIC and BIC were similar for all the different distributions tested for both treatment arms.

Table 29 Goodness-of-fit statistics for PFS for ribociclib in combination with letrozole and letrozole monotherapy from MONALEESA-2

	Progression-free survival			
	Ribociclib plus letrozole		Letrozole monotherapy	
Model	**AIC (#)**	**BIC (#)**	**AIC (#)**	**BIC (#)**
Exponential	553.24 (4)	557.06 (2)	716.71 (5)	720.52 (4)
Weibull	553.05 (3)	560.67 (4)	711.28 (2)	718.90 (2)
Gompertz	554.73 (5)	562.36 (5)	713.31 (4)	720.93 (5)
Log-normal	**548.89 (1)**	**556.52 (1)**	**708.41 (1)**	**716.03 (1)**
Log-logistic	552.02 (2)	559.64 (3)	712.79 (3)	720.41 (3)

Validation assessment of the plausibility of the long-term extrapolation

The selection of which parametric survival function should be used for PFS in first-line treatment is challenging as visual and statistical inspection suggest that more than one survival function provides a plausible extrapolation for the MONALEESA-2 clinical data,[21] but the different curves differ in shape. Consequently, assessing the plausibility of the long-term extrapolation is crucial. This was done by a) comparing the parametric functions for PFS against three external data sources in similar populations that had a longer follow-up period, namely the PALOMA-2,[97] LEA[98] and ALLIANCE[99] trials, and b) external validation with clinical experts.

In addition to the PALOMA-2 trial,[97] two additional studies, LEA[98] and ALLIANCE,[99] were identified that reported the PFS in people initiating letrozole monotherapy in a population that was considered close to the population included in the MONALEESA-2 trial.[21] It should be noted that whilst there were slight variations between the populations included, these studies (PALOMA-2, LEA, and ALLIANCE) provide an indication of the anticipated long-term PFS curve (shape) in people initiating letrozole monotherapy.

Figure 27 presents a comparison of the parametric functions against the KM for PFS from the MONALEESA-2,[21] PALOMA-2,[97] LEA,[98] and ALLIANCE[99] trials. It can be seen that the exponential distribution provides a more plausible extrapolation to the longer-term external data sources compared with the Weibull or Gompertz distributions for the letrozole monotherapy arm. Thus, the exponential distribution is used in the base case. Scenario analyses are conducted using alternative distributions (see section 5.8.3). Additional consideration is given to the recent NICE appraisal committee conclusions of palbociclib (ID915),[2] in which the evidence review group suggested that the exponential parametric function is more appropriate than the Weibull function.

Further external validation was conducted with clinical experts who validated the portions of patients alive and progression-free at certain time points (3, 5, and 10 years). Given the length of time that letrozole has been an available treatment, the clinical experts were able to provide detailed understanding of expected patients being alive and progression-free at each of the time points. Clinical validation supported the model survival predictions.

In accordance with NICE DSU guidelines,[95] the same parametric models were selected for both treatment arms.

In addition to using parametric functions for PFS (from the start), scenario analyses (see section 5.8.3) are conducted using (a) the KM up to the last event, followed by extrapolation using any of the parametric functions examined or (b) the HR applied to the ribociclib plus letrozole arm based upon the MONALEESA-2 study.

Figure 27 Comparison of the Kaplan–Meier curves for PFS for letrozole in the MONALEESA-2, PALOMA-2, LEA and ALLIANCE trials and parametric functions based on MONALEESA-2

5.3.2 Proportion of patients for whom the progression event on first-line therapy was death

As discussed in section 2.1, there is growing body of evidence for CDK4/6 inhibitors in breast cancer and based upon the additional maturity of the PALOMA-2 study (CDK4/6i palbociclib), the model has included the PALOMA-2 data. This allows for CDK4/6 data to be pooled for the proportion of patients who died as their progression event. This is explored further in scenario analysis (see section 5.8).

Out of the [redacted] patients who initiated letrozole monotherapy in MONALEESA-2[21] who had a progression event, [redacted] patients died (Table 30). In contrast, of the [redacted] patients who initiated ribociclib plus letrozole in MONALEESA-2[21] who had a progression event, [redacted] patients died upon progression (Table 30). However, the data from MONALEESA-2 are relatively immature.

To reflect this, in the economic model base case analysis we assumed that:

- [redacted] of progression events in patients initiating letrozole monotherapy would be attributable to death based on the pooled number of events in the MONALEESA-2[21] trials
  [redacted] of progression events in patients initiating ribociclib (CDK4/6i) in combination with letrozole would be attributable to death based on the number of events in the MONALEESA-2.[21]

Table 30 Proportion of progression events that are deaths in patients progressing on first-line therapy

Trial	Event	Letrozole	CDK4/6i
MONALEESA-2	Progression events, n	[redacted]	[redacted]
	Deaths, n (%)	[redacted]	[redacted]
PALOMA-2	Progression events, n	137	194
	Death, n (%)	3 (2.2)	11 (5.7)
Pooled data	Progression events	[redacted]	[redacted]
	Death	[redacted]	[redacted]

MONALEESA-2;[21] PALOMA-2[97]

Data from the MONALEESA-2[21] and PALOMA-2[97] were pooled and explored the scenario analysis (Table 30) to increase the sample size and reflect the immaturity of the MONALEESA-2 trial. This was felt to be a reasonable sensitivity analysis to consider given that palbociclib is a CDK4/6 inhibitor and both PALOMA-2 and MONALEESA-2 used letrozole as the placebo arm and combination therapy for the intervention arm. It should also be noted that both trials

have similar trial protocols. Scenario analyses (see section 5.8.3) are conducted using the proportion from the MONALEESA-2 trials separately. In the absence of direct data for chemotherapy, we assumed that patients initiating chemotherapy have the same probability of death as for patients initiating ribociclib.

5.3.3 Time to treatment discontinuation in first-line

Assessment of the proportional hazard assumption based on MONALEESA-2

IPD from the MONALEESA-2 trial[21] were analysed for patients enrolled in the letrozole monotherapy arm (n=334) and ribociclib plus letrozole arm (n=334) to generate the KM curve for TTD (Figure 28). It can be seen that the curve crosses suggesting that the assumption of proportional hazard is violated. Therefore, individual curves were fitted to both arms separately based on IPD from MONALEESA-2.[21]

Selection of a parametric survival function for TTP

For both arms, a range of parametric survival models (Weibull, exponential, Gompertz, log-normal and log-logistic) was considered (Table 31). The most appropriate distribution was selected using the following process: (a) assessment of the visual fit to the observed KM, (b) assessment of the statistical goodness-of-fit (measured using the AIC and BIC), and (c) assessment of the plausibility of the long-term extrapolation.

Figure 28 Kaplan-Meier plot for TTD in MONALEESA-2

Statistical assessment of goodness-of-fit

The AIC and BIC are presented in Table 31 and were similar for all survival models. The results suggest that the log-normal distribution provides the best (statistical) fit to the data for letrozole monotherapy. The best statistical fit for the ribociclib plus letrozole arm was using the Gompertz distribution. However, as previously mentioned, goodness-of-fit criteria only provide an indication of the goodness-of-fit to the observed period and do not categorically indicate that one distribution should be preferred to the remaining distributions.

Table 31 Goodness-of-fit statistics for TTD for ribociclib plus letrozole and letrozole monotherapy from MONALEESA-2

	Time to treatment discontinuation			
	Ribociclib plus letrozole		**Letrozole monotherapy**	
Model	**AIC (#)**	**BIC (#)**	**AIC (#)**	**BIC (#)**
Exponential	895.46 (5)	899.27 (5)	820.25 (5)	824.05 (3)
Weibull	890.85 (4)	898.48 (4)	816.42 (2)	824.02 (2)
Gompertz	**886.22 (1)**	**893.84 (1)**	818.65 (4)	826.25 (5)
Log-normal	886.28 (2)	893.90 (2)	**815.64 (1)**	**823.24 (1)**
Log-logistic	886.97 (3)	894.59 (3)	817.83 (3)	825.43 (4)

Visual assessment of fit

The observed KM was plotted (

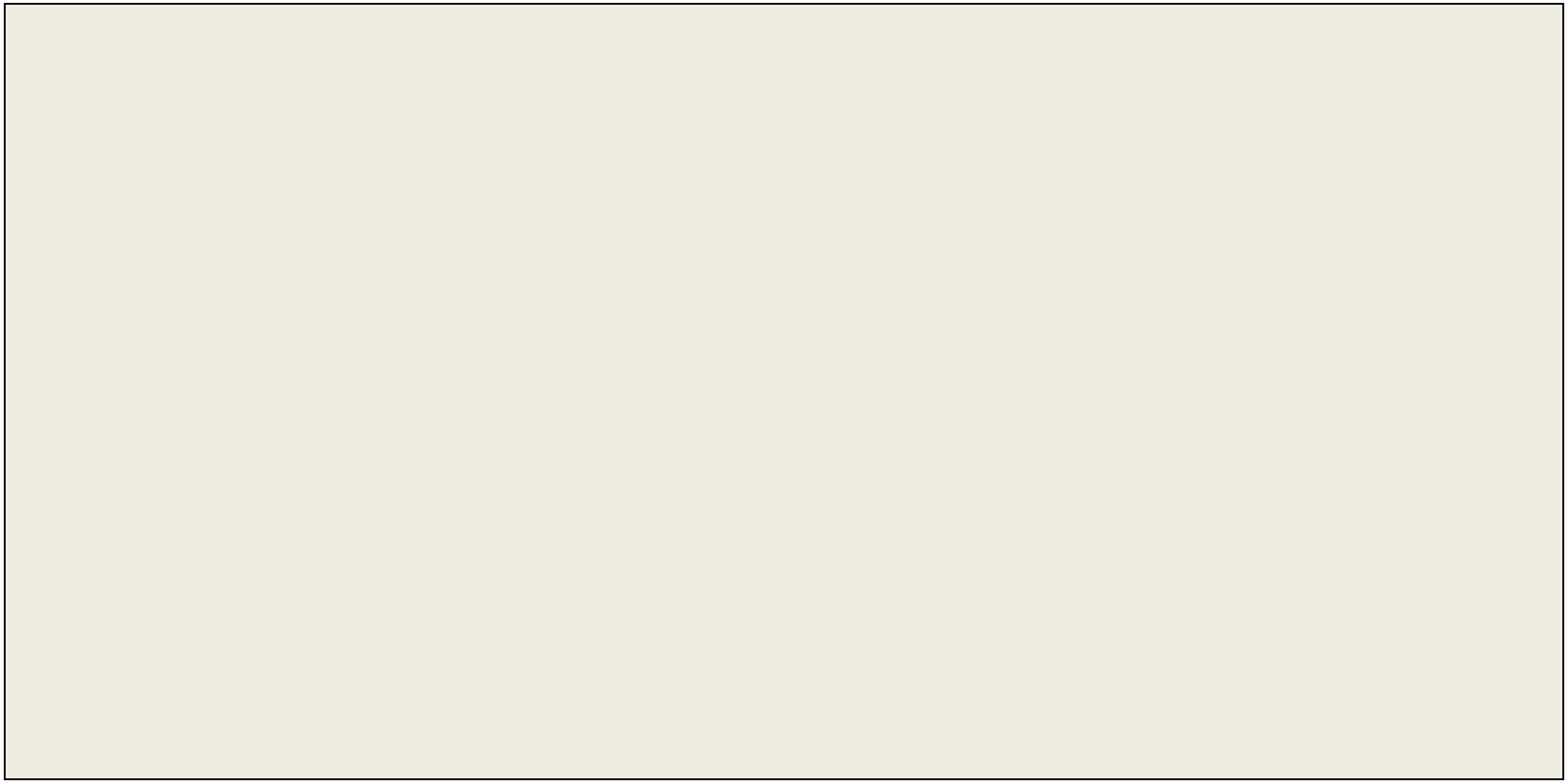
Figure **29** and Figure 30) against the fitted parametric distributions for TTD and the exponential function selected for PFS to ensure that the TTD extrapolation is consistent with the PFS extrapolation. For the ribociclib arm (in combination with letrozole), only the exponential and Weibull distribution provided a reasonable fit to the observed period and a plausible and consistent extrapolation with PFS, and as can be seen, the log-normal, log-logistic and Gompertz all cross the PFS curve (

Figure **29**). The choice between Weibull and exponential is challenging and both could be considered plausible. Following clinical expert opinion, the exponential was used in the base case in response to clinical validation of the model predictions for survival and clinical experience of letrozole in the real world and to remain consistent with letrozole. Given that ribociclib and CDK4/6i are a new class of therapy and there has been limited long-term experience in the UK, expert clinical validation was considered stronger for assessing model predictions of letrozole monotherapy. Alternative distributions were explored in scenario analyses (see section 5.8.3), with the time constraint when the TTD is greater than PFS.

For the letrozole monotherapy arm, only the Gompertz, Weibull, and exponential distribution provided a good fit to the observed data and a plausible and consistent extrapolation with PFS (Figure 30). Again, the choice of distribution is challenging. Following clinical opinion, the exponential distribution is used in the base case in response to clinical validation of the model predictions for survival and clinical experience in the real world. Alternative distributions were explored in scenario analyses (see section 5.8.3), with the time constraint when the TTD is greater than PFS.

Figure 29 Kaplan–Meier curve for TTD (taken from MONALEESA-2) and selected parametric distributions for ribociclib plus letrozole

Figure 30 Kaplan–Meier curve for TTD (taken from MONALEESA-2) and selected parametric distributions for letrozole



5.3.4 Distribution of treatments received in second-line

The distribution of second-line therapies assumed in the model is shown in Table 32 are based on proportions provided through clinical expert validation. However, through further conversations with clinicians it was clear that the treatment pathway advanced HR+/HER2- advanced breast cancer patients follow is complex and based on a number of variables, including previous treatments received, patient preference, toxicities associated with available treatment options, and funding status of treatments. Given the variability of treatment pathways patients may experience, the proportions are varied in scenario analyses (see section 5.8.3) to explore the potential impact on the ICER.

Table 32 Distribution of second-line treatment assumed in the base case

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

5.3.5 Modelling the effect of second-line treatment for everolimus + exemestane and exemestane monotherapy

Description of the BOLERO-2 data

IPD from the BOLERO-2 trial were obtained. The BOLERO-2 trial was conducted in 724 postmenopausal women with HR+/HER2- advanced breast cancer that had recurred or progressed following prior treatment with the non-steroidal AIs, letrozole or anastrozole, and compared the combination treatment of everolimus 10 mg/day in combination with exemestane 25 mg/day with that of placebo in combination with exemestane 25 mg/day.[100] The primary endpoint was PFS based on local and central radiological assessment. Secondary endpoints included OS, CBR (defined as the proportion of patients with a CR, PR, or stable disease), ORR, HRQoL outcomes evaluated using the EORTC QLQ-C30, safety, and bone turnover markers.

For the economic model, data on PFS, TTD, and OS were sought. Data were available for different cut-off dates. For TTD and OS, the latest data cut-off is October 2013. In contrast, for PFS, the latest data cut-off is December 2011 with no data for PFS collected after this date. This is a challenge for the economic model when modelling the correlation between these three outcomes.

Figure 31 and Figure 32 present the plot for OS (cut-off date: October 2013), TTD (cut-off date: October 2013) and PFS (cut-off date: December 2011) using local assessment. It can be seen than the TTD and PFS for both everolimus + exemestane (Figure 31) and exemestane monotherapy (Figure 32) are relatively similar. Of note, given the different cut-off date between PFS and TTD, a slight inconsistency can be seen in the data at the end of the curves (where

PFS crosses TTD) due to early censoring of PFS. This is not a matter of concern and is attributable to using different cut-off dates.

Figure 31 OS, PFS and TTD for everolimus + exemestane from BOLERO-2

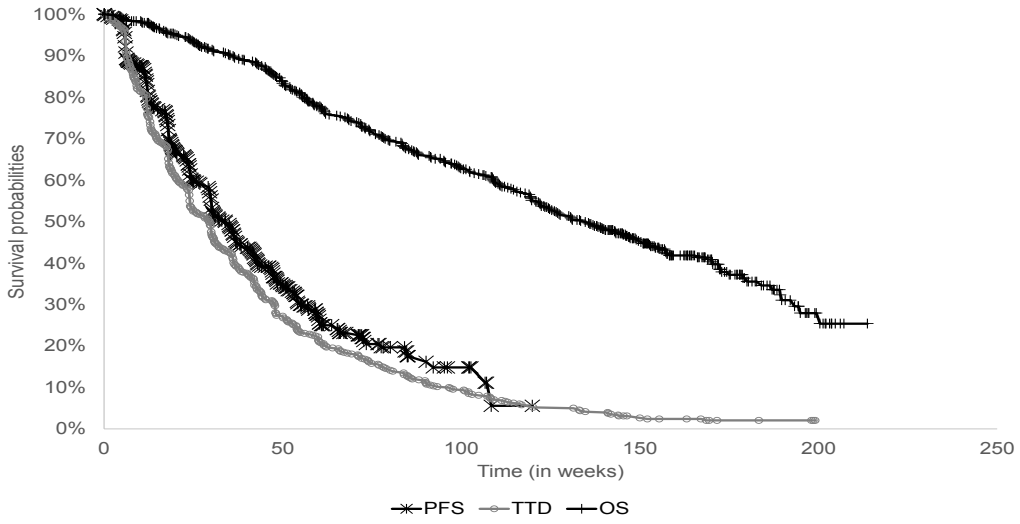
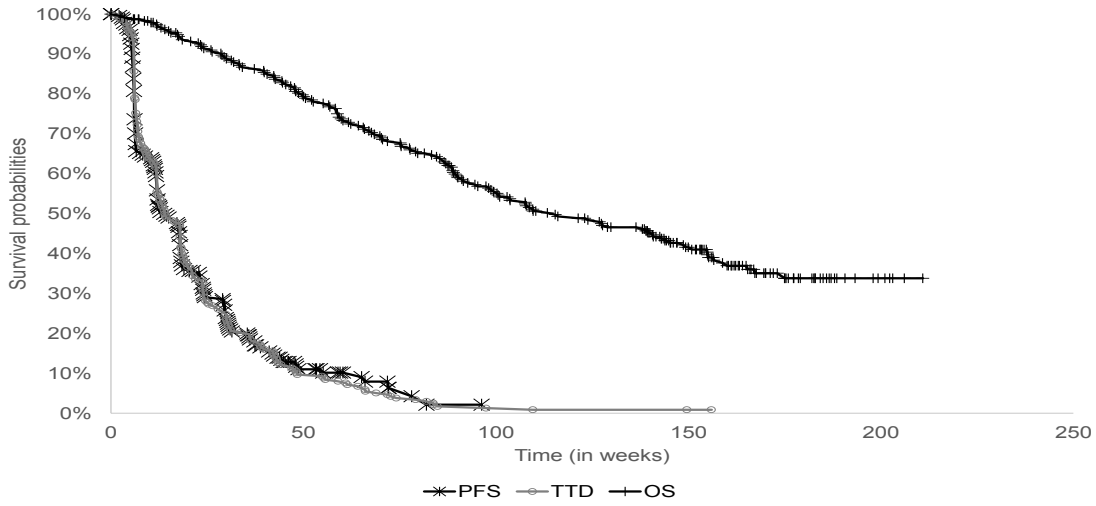


Figure 32 OS, PFS and TTD for exemestane monotherapy from BOLERO-2



Data used in the economic model and general approach to modelling

Given the absence of data for PFS, TTD, and OS from the same cut-off and the expected small differences between PFS and TTD, a simple approach, which has been applied in this model, is to assume that patients move to the progressive health state directly following treatment cessation. Therefore, TTD is used as a proxy for PFS. This is a simplification, as some patients could remain progression-free (with good quality of life) without incurring drug costs. However, whilst this is a simplification, data from the BOLERO-2 indicated that TTD was relatively close to PFS, therefore any biases are likely to be minimal. Furthermore, as this is applied to both arms, the impact of such an assumption is likely to be very limited.

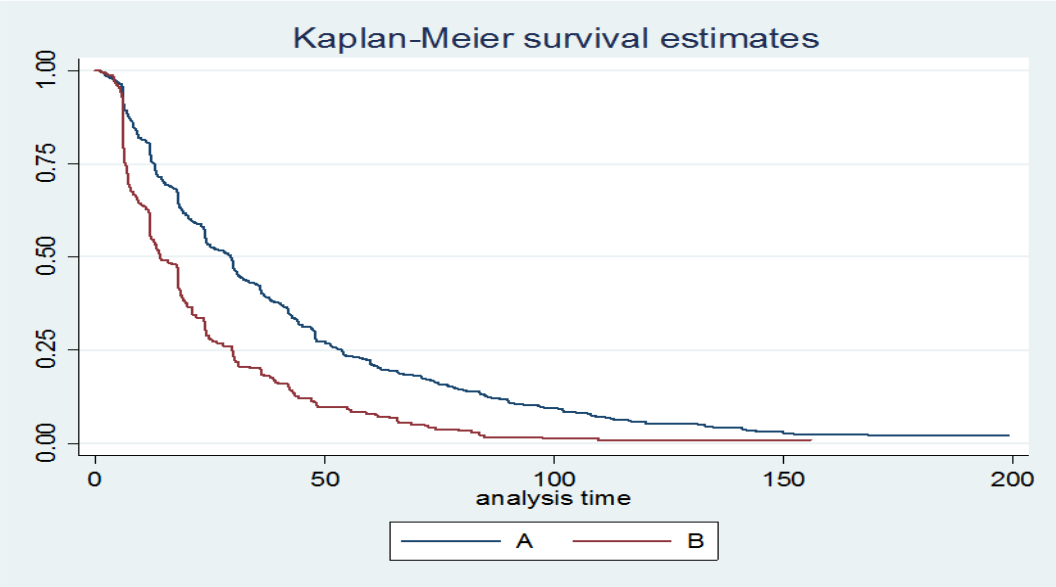
The economic model uses two key outcomes from BOLERO-2:[100]

- Data for TTD to model the TTD and (as proxy) for disease progression in patients progressing on second-line for patients receiving everolimus + exemestane or exemestane monotherapy second-line.
- The post-discontinuation survival curve from PFS2, (i.e. time to death from treatment discontinuation) to estimate the time patients spend in progressive disease (progression health state). It should be noted that post-discontinuation survival includes both the period during which patients are progression-free off treatment (PFS2 off treatment) and the period during which patients are in progressive disease (progression health state). Therefore, in scenario analysis, we attempted to include the period of time in PFS off treatment i.e. PFS2 health state – off treatment, the time in progressed disease is split between PFS2 off treatment and progressive disease (progression health state).

Estimating TTD (used as a proxy for PFS) in people initiating everolimus + exemestane

IPD from the BOLERO-2 trial were analysed for patients enrolled in the everolimus + exemestane arm (n=482) and exemestane monotherapy (n=238) to generate a KM curve for TTD (Figure 33). Although data were virtually complete, a range of parametric survival functions (Weibull, exponential, Gompertz, log-normal and log-logistic) were fitted to the data given that a minority of patients were still on treatment (n=17) at the latest data cut-off, and in order to vary this parameter in the probabilistic sensitivity analysis.

Figure 33 Kaplan–Meier for TTD for everolimus + exemestane (A) and exemestane monotherapy (B) in BOLERO-2



It can be seen that the curves cross slightly at the beginning, indicating that the assumption of proportional hazard may be violated (at the beginning). However, despite this, for simplicity, an HR was used and applied to the everolimus + exemestane arm to estimate the TTD for patients initiating exemestane monotherapy. The rationale for using an HR approach is in order to (a) minimise the number of inputs, (b) simplify the model, (c) be in line with the assumption used for chemotherapy, and (d) the aim of the model is not to estimate accurately the difference between treatment in second-line. Furthermore, whilst this may be a limitation, the impact is likely to be minimal as all arms are impacted equally.

The AIC and BIC for the everolimus arm are presented in
Table **33**. The results suggest that the log-logistic and log-normal distribution provides the best (statistical) fit to the data for everolimus + exemestane.

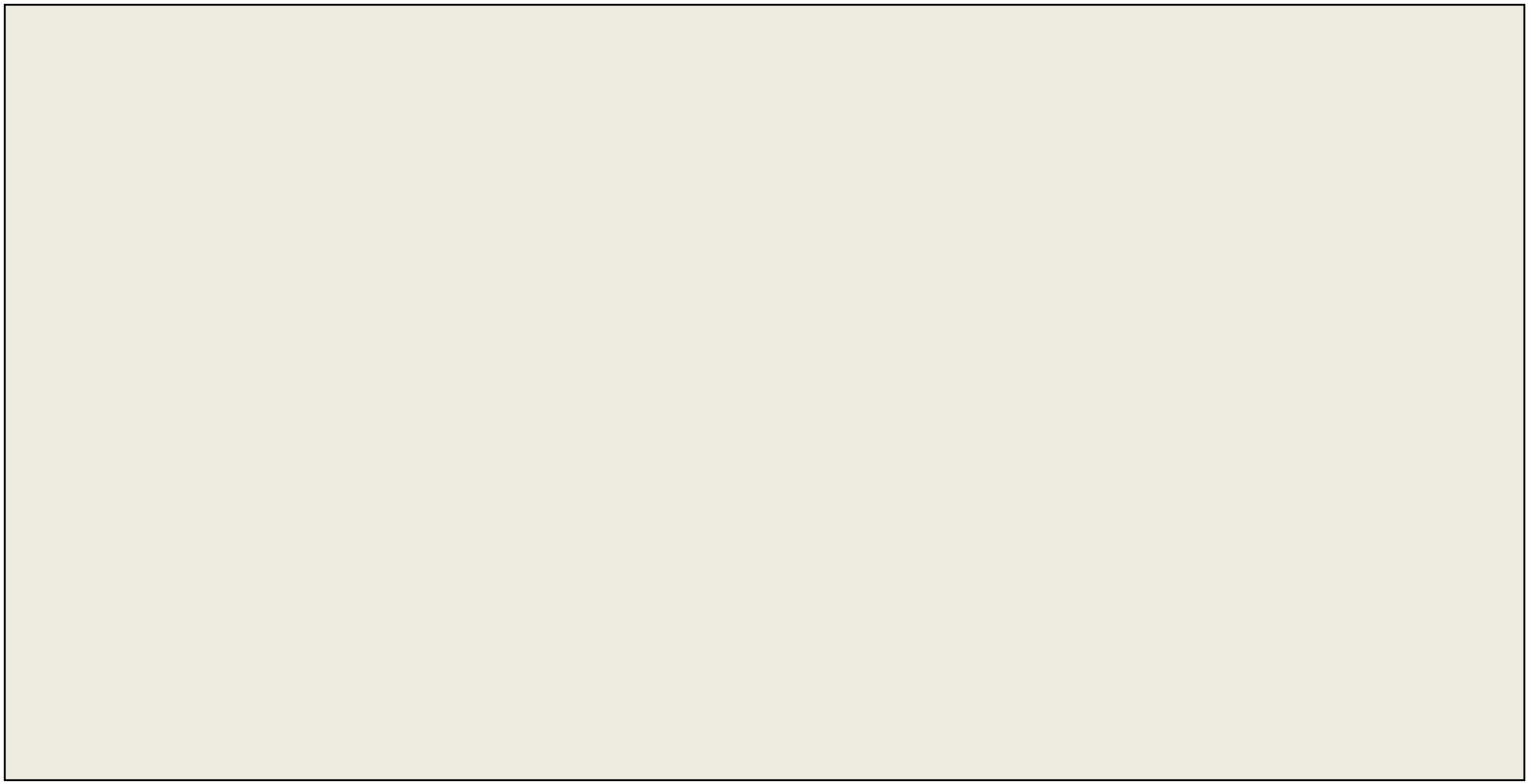
Table 33 Goodness-of-fit statistics for tested survival functions for TTD for everolimus + exemestane based on data from BOLERO-2

Model	AIC	BIC
Exponential	1419.90	1424.08
Weibull	1416.07	1424.43
Gompertz	1421.59	1429.95
Log-normal	1381.66	1390.02
Log-logistic	1394.02	1402.38

The observed KM was also plotted against the fitted parametric distributions (

Figure **34**). It can be seen that all of the distributions tested provided a good visual fit to the observed period and plausible extrapolations. However, as expected the log-normal and log-logistic had long tails and appeared to plateau. Thus, in the base case, we used the Weibull distribution, as in the previous NICE appraisal of everolimus TA421. Alternative distributions are tested in scenario analyses (see section 5.8.3).

Figure 34 Kaplan–Meier for TTD and fit of parametric distributions for everolimus + exemestane from BOLERO-2



Estimating TTD in patients initiating exemestane monotherapy

[redacted]

Death upon treatment discontinuation

Out of the 471 patients who initiated everolimus + exemestane in BOLERO-2 and who discontinued the trial, 5 (1.06%) patients died upon discontinuation. In contrast, of the 236 patients who initiated exemestane monotherapy in BOLERO-2 who discontinued, 0 (0%) patients died upon discontinuation. This is incorporated in the model.

Time to death from treatment discontinuation

IPD from the BOLERO-2 trial were analysed for patients enrolled in the everolimus + exemestane arm (n=466) and exemestane monotherapy (n=236) to generate a KM curve for time to death from treatment discontinuation (Figure 35). It should be noted that this outcome is different to the usual post-progression survival used in the economic model, as this is the time from treatment discontinuation to death rather than the time from progression (i.e. PFS or TTP) to death. This was necessary to account for the fact that only data on OS and TTD were available from the same cut-off date.

Figure 35 Kaplan-Meier plot comparing time to death from treatment discontinuation for everolimus plus exemestane (A) and exemestane monotherapy (B) in BOLERO-2.

It can be seen in Figure 35 that the post-discontinuation survival is relatively similar between patients initiating everolimus + exemestane and exemestane monotherapy. Thus, for simplicity, data from both arms were pooled, and the same post-discontinuation survival was assumed in patients initiating everolimus + exemestane and exemestane monotherapy. This is a simplification and was done to limit the number of inputs. However, whilst this is a simplification, any biases are likely to be minimal as this is applied to both the ribociclib (in combination with letrozole) and letrozole arms.

A range of parametric survival models (Weibull, exponential, Gompertz, log-normal, and log-logistic) were fitted to the data. The AIC and BIC are presented in Table 34. The AIC and BIC were similar for the Weibull, exponential, and Gompertz distributions.

Table 34 Goodness-of-fit statistics for survival from TTD for everolimus + exemestane/exemestane from BOLERO-2

Model	AIC	BIC
Exponential	1170.05	1174.20
Weibull	1171.34	1179.62
Gompertz	1168.46	1176.75
log-normal	1208.69	1216.98
log-logistic	1189.35	1197.64

The observed KM was also plotted (

Figure **36**) against the fitted parametric distributions. Only the exponential, Weibull and Gompertz distribution provided a good fit to the observed data and a plausible extrapolation. The Weibull distribution is used in the base case. Alternative distributions are tested in scenario analyses (see section 5.8.3).

Figure 36 Kaplan–Meier for time to death from treatment discontinuation and fit of parametric distributions for everolimus + exemestane/exemestane from BOLERO-2

5.3.6 Estimating TTD, PFS and OS in patients receiving second-line chemotherapy

In the absence of patient-level data for second-line chemotherapy, we modelled the effect of chemotherapy by applying HRs to the baseline curves for PFS, TTD, and OS estimated for everolimus + exemestane from the BOLERO-2 trial.[100] HRs were taken from Li *et al.*,[1] described below.

Effect of chemotherapy compared with everolimus-based therapy

A retrospective study was identified that reported the HR for chemotherapy versus everolimus-based therapy. In brief, the study compared the effectiveness of everolimus-based therapy and chemotherapy in postmenopausal women with HR+/HER-2- metastatic breast cancer in community-based oncology practices treated between January 2012 and April 2013 after failure of a non-steroidal AI.[1]

The study included 234 patients treated with everolimus-based therapy and 137 patients treated with chemotherapy. The authors further reported that patients treated with everolimus-based therapy tended to have less aggressive disease than patients treated with chemotherapy and, therefore, multivariate adjusted Cox models were conducted to account for the differences in baseline characteristics.

Overall, the authors reported that everolimus-based therapy was associated with significantly longer OS (HR = 0.37, 95% CI: 0.22–0.63), PFS (HR = 0.70, 95% CI: 0.50–0.97), and time on treatment (HR = 0.34, 95% CI: 0.25–0.45) compared with chemotherapy. In second-line, the authors reported HRs of 0.53 (95% CI: 0.20–1.39) for OS, 0.61 (95% CI: 0.32–1.170) for PFS and 0.30 (95% CI: 0.17–0.52) for TTD.

The HRs estimated for the second-line setting and used in our base case analysis are presented in Table 35.

Table 35 Summary of HRs used for chemotherapy in second-line (vs. everolimus)

Comparator (vs. everolimus)	Mean hazard ratio effect size	Lower 95% credible interval	Upper 95% credible interval
OS	0.53	0.20	1.39
PFS	0.61	0.32	1.17
TTD	0.30	0.17	0.52

It should be noted that the retrospective design of this study is an important limitation, in particular with respect to selection biases. Despite the attempts made by the authors to adjust for baseline characteristics, biases may still exist, as there may be unobservable confounding factors. The sample size is also relatively small, which may limit the ability to properly adjust for confounding factors. Thus, findings from this study need to be considered with caution.

However, it is important to consider that there are limited clinical trial data for the comparison of everolimus + exemestane versus chemotherapy.

Estimating TTD in patients receiving second-line chemotherapy

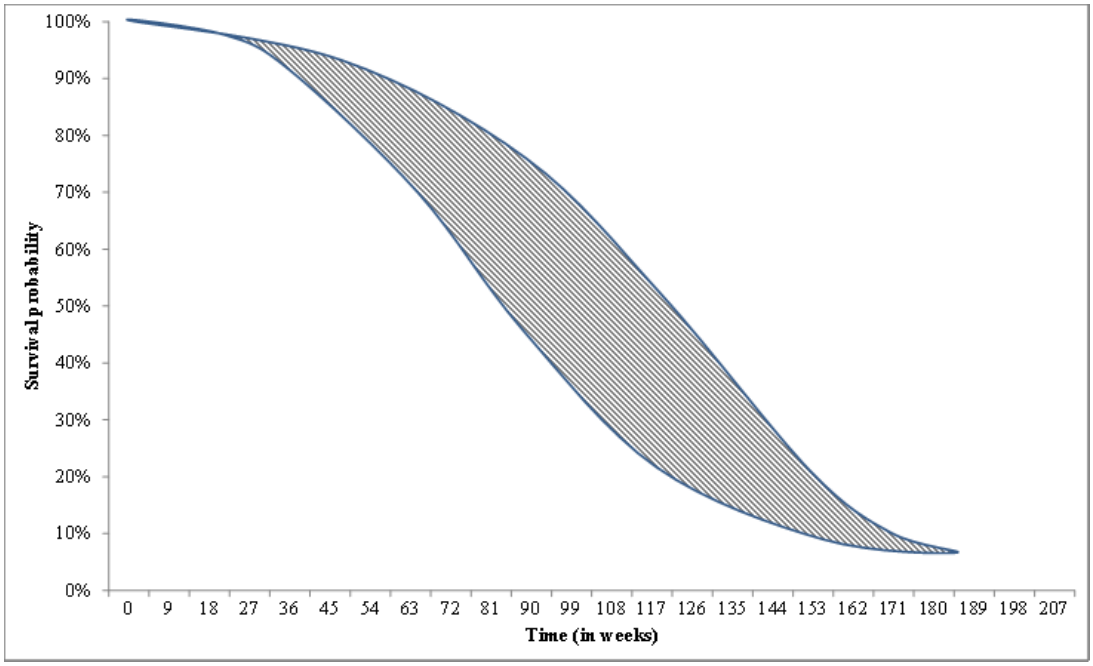
The TTD in patients receiving second-line chemotherapy was estimated by applying the inverse of the HR reported by Li *et al*.[1] to the TTD curve for everolimus + exemestane from BOLERO-2.

Estimating the time to death following treatment discontinuation

A key challenge in the economic model is to preserve the correlation that exists between the time to discontinuation (of treatment) and the time to death. Sampling distributions for OS (after applying an HR to the everolimus arm) and TTD (after applying an HR to the everolimus arm) separately would lead to inconsistencies (e.g. time to discontinuation being longer than time to death) as these parameters are correlated. Ideally, the post-discontinuation survival time would be estimated directly. However, this is not possible as we do not have access to data for chemotherapy. The only option was to use an HR for OS and TTD to be applied to the everolimus arm.

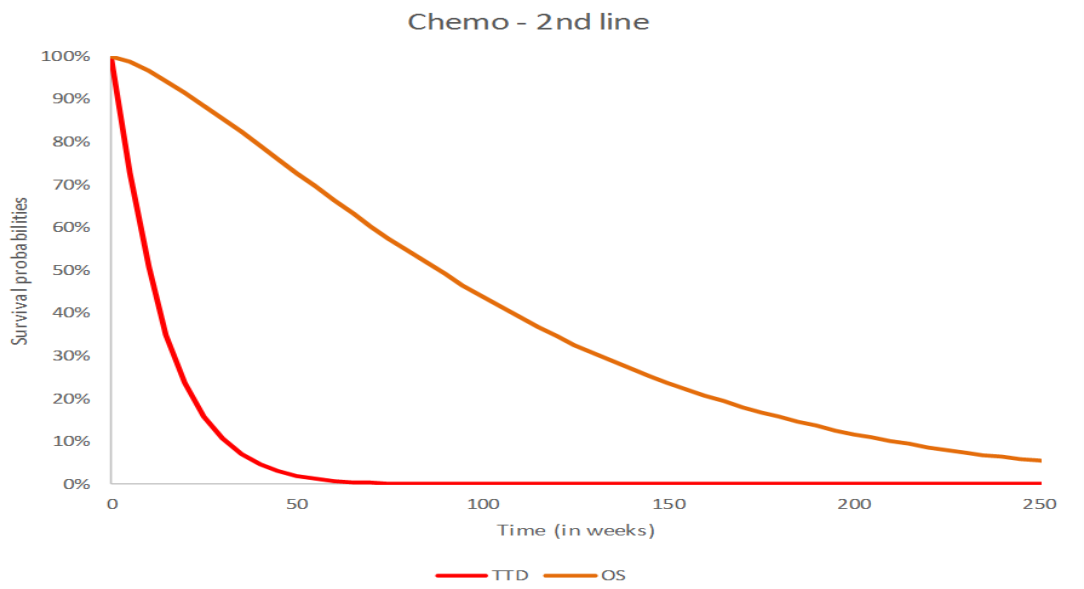
Thus, a similar approach to NICE TA386[101] was used. In traditional cohort models (notably partitioned-survival or area under the curve models), this is less of an issue as, typically, parametric curves would be fitted to the time to discontinuation (of chemotherapy) and the OS data, with the post-discontinuation survival (of chemotherapy) being estimated indirectly from the difference in the area under the two curves, as illustrated in Figure 37 (shaded area).

Figure 37 Illustration of the difference in the area under the two curves



Inspired by this approach, we estimated the 'expected' mean post-discontinuation survival (with chemotherapy) as the difference between the mean OS (estimated using an HR) and the mean TTD (estimated using an HR). Figure 38 presents the OS and TTD curves used for chemotherapy following application of the HR.

Figure 38 TTD, PFS, and OS estimated for chemotherapy following application of HR



Knowing the mean post-discontinuation survival for chemotherapy (difference between mean TTD and mean OS), we then made an assumption about the distribution and its shape. In the base case we assumed that the post-discontinuation survival followed a Weibull distribution (with the given calculated mean). An arbitrary shape of 0.0375 was chosen based on the shape of the PPS calculated for everolimus + exemestane from the BOLERO-2 trial. It should be noted that this approach is similar to the approach traditionally used in cohort models where the time alive post-progression is estimated as the area under the two curves. However, it was necessary to make an assumption regarding the distribution and shape of the curve. Although this is an unknown, the shape of the curve is likely to have a limited impact on the ICER given that the mean remains unchanged as illustrated in TA386.[101] However, small differences could occur due to discounting.

5.3.7 Safety

Table 36 presents the probability of grade 3/4 AEs as per the MONALEESA-2 study for both first-line treatments, ribociclib plus letrozole and letrozole monotherapy. While neutropenia of grade 3/4 was reported in approximately [redacted] of patients, this AE was not included in the economic model. The reasons for not including neutropenia are as follows: the early onset of neutropenia and time to resolve (see section 4.12), the monitoring requirements for ribociclib

(see section 2.4, Table 5) and that patients who experienced neutropenia would be managed through treatment interruption of approximately 14 days (as discussed in section 4.12). The included AEs are those of grade 3 and 4 severity, which require additional NHS resource use as management.

Table 36 Probability of grade 3/4 AEs according to treatment in MONALEESA-2.

Grade 3/4 AE	Ribociclib + letrozole	Letrozole
Diarrhoea	1.2%	0.9%
Fatigue	2.4%	0.9%
Infection	4.2%	2.4%
Nausea	2.4%	0.6%
Febrile neutropenia	0.0%	0.0%
Pulmonary embolism	0.0%	0.0%
Vomiting	3.6%	0.9%

5.4 Measurement and valuation of health effects

The NICE methods guide[85] stipulates that data obtained using the EQ-5D preference-based measure is the preferred choice for use in economic evaluations when available, although other preference-based instruments (such as the Short-Form Health Survey-6D), the Health Utilities Index or other condition specific measure) may be used in submissions if generic utility data are not available or appropriate. In addition, when utility data from generic validated instruments are not available, then methods can be used to estimate EQ-5D utility data by mapping (also known as 'cross-walking').

5.4.1 Health-related quality-of-life data from clinical trials

In line with the requirements of NICE, the health state utilities (HSU) applied in the model were identified through a systematic literature review and the analysis of patient-reported outcome data from MONALEESA-2. The methods and results of the review and patient-level statistical analysis are detailed in the following sections.

The MONALEESA-2 study included EQ-5D-5L collected during the screening phase, every 8 weeks during the first 18 months, and then every 12 weeks thereafter until disease progression with a final collection at the end of treatment. All domain responses collected in MONALEESA-2 up to the data cut-off on 29 January 2016 were analysed for input into the cost-effectiveness analysis.

HSU values were calculated using the EQ-5D-5L UK social tariff reported by Devlin *et al.* Any questionnaires that had missing domain scores or were missing in their entirety were excluded from the analysis on the basis that responses to all five domains are required to generate HSU values. To provide inputs for the model, the imputed HSU values were mapped to treatment, progression, and response health states. Statistical analyses were performed using summary

statistics and a series of repeated measures mixed effects regression models. Further detailed analysis is presented in Appendix 13. Although analysis of the EQ-5D-5L utility values were also analysed by treatment response, this was not utilised in the economic model and only HRQoL utility values by health states (PFS1 health state) were applied. Table 37 summarises the utility values used in the model.

Table 37 Health state utilities according to status

	Progressed disease	PF
Overall		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Ribociclib plus letrozole		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Placebo plus letrozole		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]

PD, progressed disease; PF, progression-free; n, number of observations; SD, standard deviation; IQR, inter-quartile range.

EQ-5D-5L values were collected until end of treatment and a small number of values were collected once patients had progressed on disease; however, the number of patients and values collected were small. HSU in patients with progression-free disease is [redacted] than that observed in patients with progressed disease [redacted] The difference in mean HSU is [redacted] when considered at a threshold of 0.05.[102] It should also be noted that HRQoL utility values from BOLERO-2 were deemed more appropriate based on the treatment pathway followed in the model.

The precision of the mean HSU may be overestimated through the averaging of HSU across repeated measures over time. A more robust approach is to use a repeated measures mixed effects model fitted to all observations of HSU taking into account the repeated structure of observations. This is a valid approach to estimating mean HSU under the assumption that data are missing at random. The mean HSU estimated through the repeated measures mixed effects model for each health state is shown in

Table 38. The utility values used for the PFS1 health state is based on the mean estimation by progression-free status by least squares means presented in

Table 38.

Table 38 Least squares means for HSU by progression status

Status	Mean estimate	Standard Error	DF	t Value	Pr > |t|
PD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PF	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

PD, progressed disease; PF, progression-free; DF, degrees of freedom; Pr > |t|, p-value based on the t-test.

5.4.2 Mapping

Mapping was not required to estimate HSU values as EQ-5D data were derived directly from the underlying phase 3 trials, MONALEESA-2 and BOLERO-2, and the NICE appraisal of palbociclib ID915.[2]

5.4.3 Health-related quality-of-life studies

A systematic literature review, in line with the economic review described in section 5.1.1, was conducted to identify HRQoL and utility studies relevant to the decision problem. The utility review was conducted based on the PRISMA standards and related health technology assessment guidance for identifying HSU studies for economic models. The literature was searched in biomedical electronic literature databases recommended by health technology assessment agencies, including NICE,[85] and summarised in Table 39. The NICE website was also hand-searched to identify relevant manufacturer submissions and evidence review group documents from 2000 to 1 March 2017. (See Appendix 13 for further details of the methodology.)

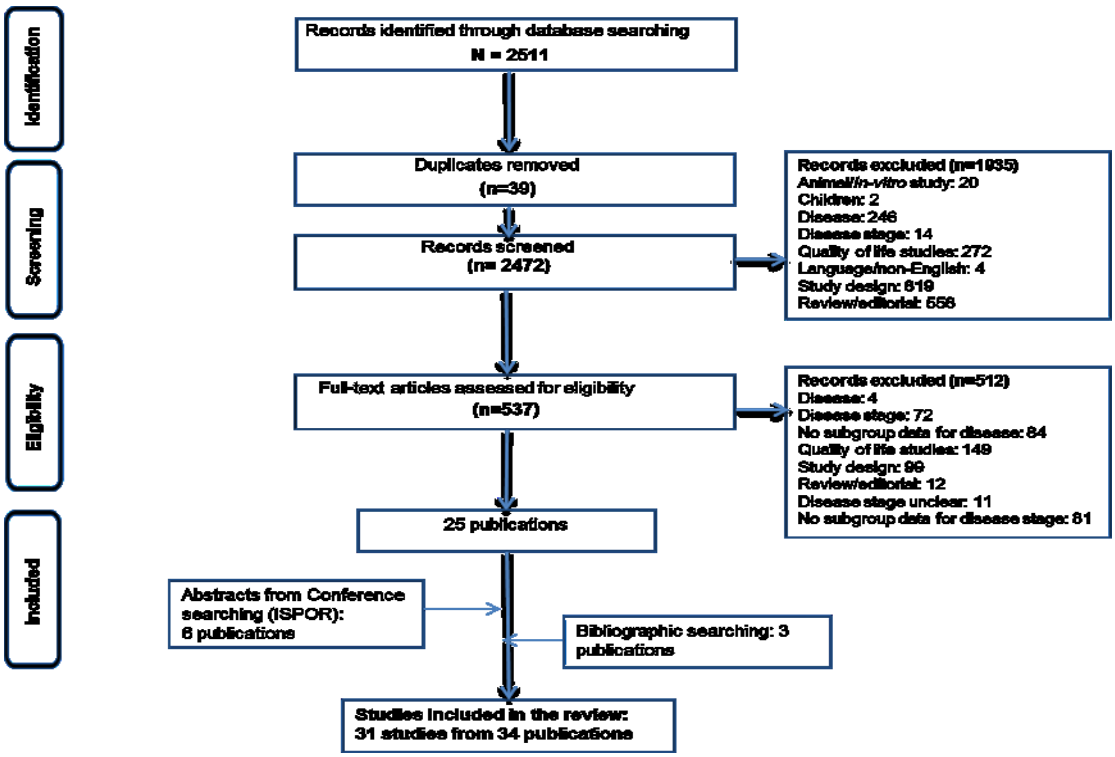
Table 39 Search strategies for the systematic literature review

1. Search strategy component	2. Sources	3. Data limits
Electronic database searches Key biomedical electronic literature databases recommended by HTA agencies	MEDLINE® MEDLINE In-Process® Excerpta Medical Database (Embase®) NHS Economic Evaluation Database (NHS EED)	1 January 2000 to 5 August 2016
Conference proceedings	ISPOR	2014–2016

HTA bodies	NICE	1 January 2000 to 1 March 2017

The database searches identified a total of 2,511 citations, of which 2,472 were unique publications (duplicate publications n=39). Following abstract screening a total of 1,935 publications were excluded, leaving a total 537 publications for full text review (Figure 39). A further 512 publications were excluded upon full text review, resulting in 25 publications relevant for this appraisal. After full text screening, an additional six publications were identified through review of abstracts at conference proceedings. Additionally, three publications were identified through bibliographic searching. In total 31 unique published studies from 34 publications were included.

Figure 39 PRISMA flow diagram of identified studies in the HRQoL systematic review



A summary of the 31 included studies is presented in Table 40.

A variety of elicitation methods were employed to estimate HSU values across the 31 studies included in the review. The majority of studies reported utilities elicited using an indirect method (n=15), such as the EQ-5D and Health Utilities Index questionnaire (n=14 and n=1, respectively). Of the 14 EQ-5D studies, four reported the use of the UK social tariff in generating HSU from the domain responses. Two EQ-5D studies also reported the mapping of disease specific EORTC QLQ instrument to EQ-5D using either published or de novo mapping

algorithms. Direct elicitation methods such as time trade off (n=7), standard gamble (n=4), and visual analogue scales (n=2) were reported in 16 studies. There were also studies reporting HSU elicited via expert opinion (n=2), the chained gamble method (n=1), and the UBC-Q questionnaire (n=1).

Not all of the studies identified in the review reported HSU values that can be directly mapped to the health states in the model; namely progression-free with response, progression-free with stable disease, and progressed disease. Of the 31 included studies, five reported HSU for both progression-free and progressed disease states. The HSUs reported in these studies were included in the model. Studies reporting HSU for progression-free only or progressed disease only were not considered in the model given that their application would require the mixing of data from disparate studies that may yield implausible estimates of HSU.

Table 40 Summary of the included studies (n=31) reporting health state utility values

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	**Study author, year**	**Study title**	**Country**	**Study design**	**Sample size**	**HER2-status, menopausal status, N (%)**			
Studies that reported HSU considered relevant to the model (EQ-5D)									
1	Hudgens *et al*., 2016[103]	Real-world evidence on health states utilities in in metastatic breast cancer patients: data from a retrospective patient record form study and a cross-sectional patient survey	France, Germany, Italy, Spain and UK	Analysis of retrospective patient record forms and cross-sectional patient survey	788	-	EQ-5D	HSU reported for patients in stable disease, tumour response and progressed-disease	UK
2	Hudgens *et al*., 2014[104]	Comparison of methods to estimate health state utilities in metastatic breast cancer	-	Comparison of values from mapping algorithm and vignette study in patients enrolled in a clinical trial	750	-	Mapped EQ-5D using Crott 2013 algorithm	HSU reported stable disease, tumour response and progressed-disease	Unclear
3	Shiroiwa *et al*., 2017 [105]	Long-term health status as measured by EQ-5D in patients with metastatic breast cancer: comparison of first-line oral S-1 and taxane therapies in the randomised phase 3 SELECT BC trial	Japan	Clinical trial	618	HER2- : 192 (92.3%)	EQ-5D	HSU reported for progression-free and post-progression reported at different follow-up time-points	Japan
Studies that reported HSU considered relevant to the model (other indirect methods)									

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	**Study author, year**	**Study title**	**Country**	**Study design**	**Sample size**	**HER2-status, menopausal status, N (%)**			
4	Reed *et al*., 2009 [106]	Cost effectiveness of ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment	Canada, the UK and US	Cost-effectiveness analysis	-	-	HUI-3	Treatment specific HSU for complete or partial response, stable disease and progressed disease	-
Studies that reported HSU considered relevant to the model (direct methods)									
5	Lloyd *et al*., 2006b[49]	Health state utilities for metastatic breast cancer	UK	Cross-sectional study	100	-	Standard gamble	HSU reported for stable disease, treatment response and disease progression	-
Studies that reported HSU that were not considered relevant to the model (EQ-5D)									
6	Zhou *et al*., 2009 [107]	Lapatinib plus capecitabine versus capecitabine alone for HER2+ (ErbB2+) metastatic breast cancer: Quality-of-life assessment	-	Analysis of quality of life data from clinical trial	331	-	EQ-5D, VAS	Treatment specific HSU	UK

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	Study author, year	Study title	Country	Study design	Sample size	HER2-status, menopausal status, N (%)			
7	Sherrill *et al*., 2008[108]	Q-TWiST analysis of lapatinib combined with capecitabine for the treatment of metastatic breast cancer	-	Analysis of quality of life data from clinical trial	399	HER2+ women who had been previously treated for metastatic breast cancer	EQ-5D	Treatment specific HSU for progression free disease, state with toxicity, post-progression	US
8	Eyles *et al*., 2015[109]	Mindfulness for the self-management of fatigue, anxiety, and depression in women with metastatic breast cancer: A mixed methods feasibility study	UK	Longitudinal study	19	-	EQ-5D-3L	HSU is not reported for specific health states but for patients undergoing psychological supportive stress reduction therapy	Unclear
9	Pickard *et al*., 2016[110]	Using Patient-reported Outcomes to Compare Relative Burden of Cancer: EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer	US	Retrospective analysis of data collected in clinical trial	52	-	EQ-5D-3L/FACT-B	HSU is not reported for specific health states	US

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	**Study author, year**	**Study title**	**Country**	**Study design**	**Sample size**	**HER2-status, menopausal status, N (%)**			
10	Lidgren *et al*., 2007[111]	Health related quality of life in different states of breast cancer	Sweden	Cross-sectional study	345	-	EQ-5D, TTO	HSU is not reported but values at different time points during follow-up (i.e. 1st year after diagnosis of breast cancer, 1st year after recurrence, 2+ years after recurrence, metastatic breast cancer	UK
11	Von *et al*., 2015[112]	Bone pain and bone targeting agent treatment patterns in patients with bone metastases from breast cancer in real world setting in Europe	Belgium, France, Germany, Italy, Spain and UK	Cross-sectional study	754	Post-menopausal: 655 (86.9%)	EQ-5D	HSU is not reported but values are reported for subjects with breast cancer who had bone metastases and visceral metastases	Unclear

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	**Study author, year**	**Study title**	**Country**	**Study design**	**Sample size**	**HER2-status, menopausal status, N (%)**			
12	Kim *et al*., 2012[113]	Mapping the cancer-specific EORTC QLQ-C30 and EORTC QLQ-BR23 to the generic EQ-5D in metastatic breast cancer patients	Korea	Retrospective analysis, mapping study	199	Post-menopausal: 140 (70.4%)	Mapped EQ-5D	HSU is not reported, study reported development of mapping algorithm for subjects in metastatic breast cancer	Korea
13	Crott *et al*., 2010[114]	Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences	Belgium, France, the Netherlands, Switzerland, and The UK	Retrospective analysis of clinical trial data, mapping study	448	-	Mapped EQ-5D	HSU is not reported, study reported development of mapping algorithm for subjects in metastatic breast cancer	
Studies that reported HSU that were not considered relevant to the model (Indirect methods)									
14	Oh *et al*., 2012[115]	Evaluation of the willingness-to-pay for cancer treatment in Korean metastatic breast cancer patients: A multicentre, cross-sectional study	Korea	Cross-sectional study	188	Post-menopausal: 134 (71.3%)	EQ-5D, VAS, EORTC QLQ-C30	Values presented were not specific to any health states	Korea

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	**Study author, year**	**Study title**	**Country**	**Study design**	**Sample size**	**HER2-status, menopausal status, N (%)**			
15	Garcia *et al*., 2012[116]	Priority Symptoms in Advanced Breast Cancer: Development and Initial Validation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Breast Cancer Symptom Index	US	Observational study	52	-	VAS	HSU not reported	Unclear
16	Milne *et al*., 2006[117]	Quality-of-life valuations of advanced breast cancer by New Zealand women	New Zealand	Cross-sectional study	50	-	VAS, TTO	HSU reported for hormonal therapy, chemotherapy, radiotherapy, hypocalcaemia	UK New Zealand
17	Nooij *et al*., 2003[118]	Continuing chemotherapy or not after the induction treatment in advanced breast cancer patients: Clinical outcomes and oncologists` preferences	Belgium, Denmark, Italy, The Netherlands, Poland, Spain and The United Kingdom	Cross-sectional study	196	Post-menopausal: 143 (72.9%)	VAS	HSU not reported	-
Studies that reported HSU that were not considered relevant to the model (Direct method)									

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	Study author, year	Study title	Country	Study design	Sample size	HER2-status, menopausal status, N (%)			
18	Schleinitz *et al*., 2006[119]	Can differences in breast cancer utilities explain disparities in breast cancer care?	US	Utility assessment study	156	-	Standard gamble	HSU reported for Stage 1, Stage II, Stage III, Stage IV (ER+), Stage IV (ER-), chemotherapy, hormonal therapy and radiation therapy	-
19	Wittenberg *et al*., 2005[120]	Patient utilities for advanced cancer: effect of current health on values	US	Cross-sectional study	51	-	Chained gamble	HSU reported for very good , good, moderate and poor health state	-
20	Brown *et al*., 2001[121]	Cost effectiveness of treatment options in advanced breast cancer in the UK	UK	Cost-effectiveness analysis	180	-	Standard gamble method applied to proxy utility data collected from specialised oncology nurses and nurses	Treatment specific HSU reported for partial/complete response, stable disease, progressed disease, terminal disease	-

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	Study author, year	Study title	Country	Study design	Sample size	HER2-status, menopausal status, N (%)			
21	Songtish *et al*., 2014[122]	A cost-utility analysis comparing standard axillary lymph node dissection with sentinel lymph node biopsy in patients with early stage breast cancer in Thailand	Thailand	Cost-effectiveness analysis	110	-	Standard gamble	HSU reported for early and advanced breast cancer stages	-
22	Hildebrandt *et al*., 2014[123]	Health utilities in gynaecological oncology and mastology in Germany	Germany	Utility assessment study	80	-	TTO	HSU not reported	-
23	Lewis *et al*., 2014[124]	Budget impact analysis of everolimus for the treatment of hormone receptor positive, human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer in Kazakhstan	Kazakhstan	Budget impact analysis based on data from clinical trial	-	-	-	HSU not reported but treatment specific values were reported	-
24	Dranitsaris *et al*., 2000[125]	Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: A comparison of two aromatase inhibitors to megestrol acetate	Canada	Cost-effectiveness analysis	50	-	TTO	HSU reported for response and progression	-

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	Study author, year	Study title	Country	Study design	Sample size	HER2-status, menopausal status, N (%)			
25	Dranitsaris *et al*., 2009[126]	Economic analysis of albumin-bound paclitaxel for the treatment of metastatic breast cancer	Canada	Meta-analysis of clinical trial data	-	-	TTO	HSU not reported but treatment specific values were reported	-
26	Nafees *et al*., 2016[127]	An assessment of health-state utilities in metastatic breast cancer in the United Kingdom	UK	Cross-sectional survey	12	-	TTO	HSU reported for stable and progressed disease	-
27	Dranitsaris *et al*., 2015[128]	Nab-paclitaxel, docetaxel, or solvent-based paclitaxel in metastatic breast cancer: A cost-utility analysis from a Chinese health care perspective	China	Cost-effectiveness analysis	28	-	TTO	HSU not reported but treatment specific values were reported	-
28	Frederix *et al*., 2013[129]	Utility and Work Productivity Data for Economic Evaluation of Breast Cancer Therapies in the Netherlands and Sweden	Netherlands and Sweden	Utility assessment study	200	HER2+ (100%)	TTO/VAS	HSU reported for stable and progressed disease	-
Other studies that were not considered relevant to the model									

	Study characteristics				Population characteristics		Method of elicitation	Comment on health states	Social preference weights
No.	Study author, year	Study title	Country	Study design	Sample size	HER2-status, menopausal status, N (%)			
29	Grimison *et al*., 2009[130]	Preliminary validation of an optimally weighted patient-based utility index by application to randomised trials in breast cancer	Australia and New Zealand	Analysis of data collected in clinical trial	325	-	Using algorithmic conversion of UBQ-C scores	HSU not reported	-
30	Lux *et al*., 2009b[131]	Cost-utility analysis for advanced breast cancer therapy in Germany: Results of the fulvestrant sequencing model	Germany	Cost-effectiveness analysis	Not reported	-	Expert opinion VAS	HSU not reported but treatment specific values were reported	
31	Hillner *et al*., 2000[132]	Pamidronate in prevention of bone complications in metastatic breast cancer: A cost-effectiveness analysis	USA	Cost-effectiveness analysis	752	-	Expert opinion	HSU reported for radiation, surgery, hypercalcaemia and other fractures	-

EORTC-QLQ-C30 and –BR23, breast cancer module of the EURTC-QLQ-C30; EQ-5D, Euro-Qol-5 dimensions; EQ-5D-3L, EQ-5D 3 response levels; ER, estrogen receptor; FACT-B, Functional Assessment of Canter Therapy; HER2, human epidermal growth factor receptor; HSU, health state utility; HUI-3, health utilities index-3; TTO, time trade-off; UK, United Kingdom; UQB-C, utility based questionnaire-cancer, US, United States; VAS, visual analogue scale.

5.4.4 Adverse Events

The impact of ribociclib in combination with letrozole therapy on HRQoL is reflected in the findings of the MONALEESA-2 trial and discussed in detail in section 4.7.5. Assessments in the trials were not undertaken in such a way that any impact on HRQoL could be directly associated with a particular AE. Overall, the HRQoL analysis in the MONALEESA-2 trial demonstrated that there is [redacted] in HSU across different treatment groups or by time in the MONALEESA-2 study, confirming that the potential exposure to more AEs through receiving the two drugs does not negatively impact on HRQoL.

In the economic model, the health states are valued using utility data derived directly from the MONALEESA-2 trial and as such they indirectly account for the impact of AEs associated with the intervention and comparators.

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

Table 41 summarises HRQoL values used within the economic model by health state.

Table 41 Health state utilities used in the economic model

Health state	Mean estimate	Standard error	Source	Reference in submission (section and page number)	Justification
PF1 on treatment	[redacted]	[redacted]	MONALEESA-2[21]		EQ-5D-5L direct elicitation from study[21]
PF1 off treatment	[redacted]	[redacted]	MONALEESA-2[21]		
PFS2 – on treatment	0.774	Assumed to be 20% around the mean	BOLERO-2[72]		EQ-5D sourced directly from NICE TA421[72]
PD	0.5052	Assumed to be 20% around the mean	Lloyd et al 2006;[49] NICE ID915[2]		Previously accepted in NICE TA915
Decrement in utility associated with chemotherapy	-0.113		Derived from Peasgood et al.[133]		Decrement value sourced from publication and associated with chemotherapy versus endocrine therapy

NICE appraisal of everolimus + exemestane TA421 supersedes TA295

Health state utility value in patients initiating first-line treatment

EQ-5D data were directly collected in the MONALEESA-2 trial[21] and therefore used for PFS in first-line. Data were analysed as described in section 5.4.1. In brief, the analysis shows that for PFS, [redacted]

[redacted] were observed between treatment arms and between the period on and off treatment. Further details are provided in section 4.7.5.

Given that [redacted] between the treatment arms in MONALEESA-2, (ribociclib in combination with letrozole and letrozole monotherapy), were observed, [redacted] is used in the PFS1 health state in our base case. The mean HSU was estimated through a mixed effects model to account for repeated measures. It should be noted that this value incorporates the effect of AEs.

HSU value in PFS in second-line

HSU value for PFS in second-line is taken directly from the EQ-5D estimated from BOLERO-2 and used in the previous submission for everolimus + exemestane (0.774).[72] For simplicity, the same utility value was assumed for everolimus + exemestane and for exemestane monotherapy. It should be noted that this value already incorporates the effect of AEs. For patients initiating chemotherapy in second-line, a decrement in utility is applied. A scenario analysis is conducted using the utility value estimated at the point of progression from the MONALEESA-2 trial (see section 5.8.3).

Health state utility value in progressed disease

The utility value for patients entering the progressed disease health state (0.5052) was taken from the NICE appraisal of palbociclib, ID915[2] and based on Lloyd *et al*.[49] It should be noted that whilst the MONALEESA-2 trial[21] collected EQ-5D-5L at the point of progression, the utility value for progression from the MONALEESA-2 trial is reflective of second-line treatment, i.e. the PFS2 health state, rather than the progressed disease (progression health state). Furthermore, the utility value for progression from MONALEESA-2 does not capture advanced stages of disease progression.

Decrement in utility associated with chemotherapy

For chemotherapy, a decrement in utility of 0.113 was applied to the on-treatment phase based on the decrement in utility associated with chemotherapy compared with endocrine therapy estimated from Peasgood *et al*.[133]

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

A systematic literature review was conducted to identify studies reporting healthcare resource use and cost data in patients with advanced breast cancer, as described in section 0.

In total 30 studies were identified, of which 13 reported cost and resource use data. Of these 13, four reported costs relevant to the healthcare setting in the UK base case (two posters and two journal articles).

A summary of the key costing studies identified in the review is provided in Appendix 13.

5.5.2 Intervention and comparators' costs and resource use

Drug acquisition costs for first-line treatments

Ribociclib in combination with letrozole

Drug acquisition costs were calculated based on available formulations, pack sizes, unit costs, and price per week for the combination of treatment included in the model. The dosing information for ribociclib + letrozole was based on the MONALEESA-2 trial protocol and the anticipated EMA licence. The ribociclib drug acquisition costs provided in this submission are provisional, based upon anticipated Department of Health price approval.

Patients enrolled in the MONALEESA-2 trial[21] received ribociclib at a dose of 600 mg once daily (per protocol), on days 1–21 of a 28-day cycle. However, a proportion of patients had dose reductions, firstly to 400 mg, then to 200 mg daily.

To account for dose reductions, although a typical approach in economic models is to calculate the drug costs based on the mean daily dosage [redacted] and cost per mg, this approach could be considered biased because tablets cannot be split. Consequently, an alternative approach was employed based on the proportion of dosage received per cycle of treatment.

[redacted]Table 42[redacted]

Table 42 Dosage of ribociclib received in MONALEESA-2 in patients initiating therapy with ribociclib plus letrozole

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 43 summarises the cost per 28-day cycle used in our base case.

Table 43 Drug acquisition cost per cycle for ribociclib

[redacted]

A scenario analysis was conducted calculating the distribution of dose across all cycles, rather than being cycle specific.

Letrozole

Letrozole was assumed to be given once daily at a dose of 2.5 mg, days 1–28 of a 28-day cycle. Based on the eMIT,[134] we estimated the drug acquisition cost per day for letrozole (2.5 mg) to be £0.05 and £1.52 per 28-day cycle.

Table 44 summarizes the drug acquisition costs for first-line therapies.

Table 44 Summary of drug acquisition inputs for first-line therapies

	Ribociclib	Letrozole
Dosage regimen	600 mg daily on days 1 to 21 of 28 day cycle (400 mg and 200 mg also available)	2.5 mg once daily, days 1–28 of a 28-day cycle
Administration method	Oral	Oral
Formulation	200 mg tablets	2.5 mg
Pack size	63 tablets (600 mg dosage regimen)	28 tablets
	42 tablets (400 mg dosage regimen)	
	21 tablets (200 mg regimen)	
Price per pack	£2,950.00	£1.52
	£1,966.67	
	£983.33	
Dosing in the model	See section 5.5.2*Drug acquisition costs – ribociclib in combination with letrozole*	2.5 mg daily
Total drug cost per cycle (28 days)	[redacted]	£1.52

Drug acquisition costs for second-line treatments

Chemotherapies

Capecitabine is the chosen chemotherapy used as the chemotherapy treatment option for second-line based upon clinician validation. Whilst the recommendation from NICE clinical guidelines[46] suggest that anthracyclines should be the first chemotherapy option used, and then docetaxel is the next recommended chemotherapy, capecitabine was validated as being widely used as a preferred second-line treatment option due to the convenience of administration (oral) and the preferable side effect profile compared with other chemotherapy options. However, since there is a number of chemotherapy options available, including paclitaxel, docetaxel, and doxorubicin in addition to capecitabine, scenario analysis presented in section 5.8.3 considers the impact on the ICER of different second-line chemotherapies used.

We assumed that single-agent capecitabine is administered at a dose of 1250 mg/m^2 twice daily for 14 days followed by a rest of 7 days, as per licence[135] and NICE clinical guidelines 81 (Table 45).[46] A body surface area of 1.74 m^2 was used.[136]

Table 45 Drug acquisition cost for capecitabine

	Chemotherapy (capecitabine)	Value used in model
Dosage regimen	1250 mg/m^2 twice daily	-
Daily dose required	4,350 mg	-
Total days of treatment	14 days	-
Administration method	oral	-
Formulations	150 mg	-
	500 mg	

	Chemotherapy (capecitabine)	Value used in model
Pack size	60 tablets (150 mg)	112 tablets
	120 tablets (500 mg)	28 tablets
Price per pack	£20.20 (150 mg)	-
	£146.00 (500 mg)	-
Price per tablet	£0.34 (150 mg)	£9.43
	£1.22 (500 mg)	£136.27
Total drug cost per cycle (21 days)		**£145.69**

Source: BNF
BSA = 1.74[136]
Values used in model represent tablets per cycle and cost per tablet multiplied by total tablets per cycle.

Everolimus

Everolimus is administered once daily at a dose of 10 mg. The cost of everolimus was assumed based on the BNF (NHS indicative price = £2673.00 for 30 tablets). It should be noted that according to NICE guidance "*Everolimus is recommended only if the company provides it with the discount agreed in the patient access scheme*". Whilst the discount is confidential, this has been incorporated within the model as the drug is produced by Novartis (see Table 46).

Exemestane monotherapy

Exemestane is assumed to be administered once daily at a dose of 25 mg as per licence,[137] see Table 46.

Table 46 Drug acquisition cost of everolimus and exemestane

	Everolimus	Exemestane
Dosage regimen	10 mg daily	25 mg daily
Administration method	Oral	oral
Formulation	10 mg tablets	25 mg tablets
Pack size	30 tablets	30 tablets
Price per pack	£2,673.00	£5.96
[redacted]	[redacted]	-
Dosing in the model	10 mg daily	25 mg daily
Total drug cost per week	[redacted]	£1.39

Source: BNF
Everolimus cost per week includes the cost per week of exemestane

Drug acquisition costs for progression health state (i.e. third-line and greater)

The drug acquisition costs applied to the progression health state in the model is [redacted], which is [redacted] per month. This cost is based upon expert clinical validation and consideration of previous NICE appraisals (TA239, TA421, and ID915) in advanced breast cancer.

The progression health state captures all future treatments patients will receive following second-line treatment progression and, as such, is required to capture all future treatment related costs a patient will experience (excluding terminal care associated costs). The treatment pathway that patients follow in advanced breast cancer is varied and will depend on a number of different factors. Given the level of complexity required in deriving a specific treatment flow for the progression health state, it was considered that a simple fixed cost, elicited through clinical validation, would be a reasonable approach. A specific point made through clinical expert validation regarding the future treatment-related costs (progression health state) was that of the costs associated with chemotherapy, both delivery and acquisition, along with AE management costs of chemotherapy.

When considering previous NICE technology appraisals (TA239, TA421, and ID915) it should be noted that the progression health state in the model is representative of the post-progression for the NICE TAs reviewed. It can be seen that the post-progression treatment-related costs in the reviewed appraisals ranged from approximately £800 to over £2,000; however, these figures were at different yearly values and with different treatments available. Given that the treatment-related costs for the progression health state is an assumption with expert validation, further scenario analyses are presented in section 5.8.3 which considers different progression health state drug-related costs and the impact this variable has on the ICER.

5.5.3 Drug administration costs

Ribociclib, letrozole, everolimus, and exemestane are all administered orally. Therefore, no additional administration resource cost is required.

In contrast, chemotherapy incurs administration costs. The administration costs for capecitabine are sourced directly from NHS reference costs 2015–16 for outpatient delivery of exclusively oral chemotherapy[138] (see Table 47).

Along with administrations costs, patients receiving chemotherapy often require premedication. Patients receiving docetaxel monotherapy require premedications. The premedication costs per cycle were taken from NICE TA416.[139]

Table 47 presents the chemotherapy-related administration and premedication costs used in the economic model.

Table 47 Chemotherapy related administration cost

Treatment	Cost item	Unit cost (£)
Chemotherapy (capecitabine)	Oral chemotherapy – First attendance (SB11Z - Deliver Exclusively Oral Chemotherapy)	£181.27
	Oral chemotherapy – Subsequent attendance (SB11Z - Deliver Exclusively Oral Chemotherapy)	£181.27

Source: NHS reference costs 2015–2016[138]

5.5.4 Dose intensity

Dose intensity for ribociclib is already included in the model as described in section 5.5.2.

For letrozole, given the low cost and the fact that ribociclib is an add-on, dose intensity was not considered. Similarly, for simplicity, dose intensity was not considered for everolimus + exemestane, single-agent endocrine therapy (exemestane), and chemotherapy.

5.5.5 Monitoring

Monitoring was included for ribociclib only. No monitoring was assumed for letrozole monotherapy or for any post first-line treatment, including everolimus, single-agent endocrine therapy, and chemotherapy. This is a conservative simplification, as monitoring for second-line treatments would be expected.

The following monitoring was assumed for ribociclib based on the anticipated license for ribociclib:

- Full blood counts (FBCs) before initiating treatment, every 2 weeks for the first 2 cycles, and at the beginning of each subsequent 4 cycles.
- Liver function tests (LFTs) before initiating treatment, every 2 weeks for the first 2 cycles, and at the beginning of each subsequent 4 cycles.
- Electrocardiogram before initiating treatment, repeated at approximately day 14 of the first cycle and at the beginning of the second cycle.

Unit costs applied in the economic model are presented in Table 48.

Table 48 Unit costs for monitoring

Monitoring resource	Unit cost	Numbers per first cycle	Numbers per subsequent cycles	Total number per patient	Source
Complete blood count	£3.10	2	6	8	Haematology (DAPS05)
Liver function test	£1.18	2	6	8	Clinical Biochemistry (DAPS05)
Electrocardiogram	£40.35	2	1	3	Electrocardiogram Monitoring or Stress Testing (EY51Z)

Source: NHS reference costs 2015–2016[138]

5.5.6 Health state unit costs and resource use

The costs associated with the management of the disease costs were estimated based on the package of resource use for advanced breast cancer recommended in the NICE clinical guideline 81, previous NICE technology appraisals in HR+/HER2- advanced breast cancer (TA421, and ID915) and validation through clinical experts. The resource use for both PFS1 and PFS2 health states are presented in Table 49, Table 50 presents resource use for the progression health state and Table 51 summarises terminal

care costs. All resource use data were sourced from NHS reference costs (2015–2016)[138] and PSSRU.[39,140]

Costs per week for each health state used in the economic model are summarised below in Table 52.

Table 49 Background health state resource use unit costs (PFS1 and PFS2 health states)

Resource item	Frequency/length of visit	Proportion of patients (%)	Usage per month	Unit cost	Source/notes
General practitioner visits	Once every month	100%	0.3	£36.0	PSSRU 2016 (10.3b – Per surgery consultation lasting 9.22 minutes including qualifications) NICE ID915[2] NICE CG8[146]
Oncology consultant office	Once every six months	100%	0.2	£133.38	NHS reference costs 2015-2016 WF01A – WF01B Non-Admitted Face to Face Attendance (first/follow up) – 800 Clinical Oncology (Previously Radiotherapy) Average of one WF01B Non-Admitted Face to Face Attendance (First) and five WF01A Non-Admitted Face to Face Attendance (Follow-up)
Community nurse	Once every quarter	100%	0.3	£36.0	PSSRU 2016 (10.1 band 5 – cost per working hour)
Clinical nurse specialist	Once every month	100%	1.0	£44.0	PSSRU 2016 (10.1 band 6 – cost per working hour)
Computer tomography scan	Once every quarter	100%	1.0	£111.2	RD24Z - Computerised Tomography Scan of two areas, with contrast - NHS reference costs 2015-2016

Table 50 Background health state resource use unit costs (progression health state)

Resource item	Frequency/length of visit	Proportion of patients (%)	Usage per month	Unit cost	Source/notes
General practitioner visits	Once every month	100%	0.3	£36.0	As per Table 49
Oncology consultant office	Once every 6 months	100%	0.2	£133.38	As per Table 49
Community nurse	Once every quarter	100%	0.3	£36.0	As per Table 49
Clinical nurse specialist	Once every month	100%	1.0	£44.0	As per Table 49
Computed tomography scan	Once every quarter	100%	1.0	£111.2	As per Table 49
Social worker	Once every 2 months	100%	0.5	£79.0	PSSRU 2016 (11.2 – cost per hour of client related work including qualifications)

Table 51 Terminal care resource use and unit costs

Resource use	% of patients in each care setting	Source for clinical setting	Unit cost (£)	Source for unit costs
Hospital	40%	NICE CG81 Package 3 [39,140]	£5,595.20	NICE CG 81 Package 3 unit costs, inflated from 2006/07 to 2015/16 Values[39,140]
Marie Curie hospice	10%		£6,975.58	
At home (with community support)	50%		£2,886.78	

Table 52 provides a summary of the health state resource costs by health state implemented in the economic evaluation.

Table 52 List of health states and associated costs in the economic model

	Cost per month (£) (unless stated)	Cost per week (£)	Reference in submission
Progression Free (PFS1) on and off treatment -1st line	£155.73	£36	Table 49
Progression Free (PFS2) on treatment -2nd line	£155.73	£36	
Progressed disease	£195.23	£45	Table 50
Terminal costs	£4,379.03	-	Table 51

5.5.7 Management of AEs

AEs were entered in the model as the probability of experiencing a grade 3/4 AE (Table 53) multiplied by the cost associated with the AE management (Table 54) and finally taking into consideration the exposure to treatment from the MONALEESA-2 study. The resulting cost per week is presented in Table 55. This means that the incidence data used is for the whole treatment period and the unit costs are per event. While serious grade 3 or 4 neutropenia was experienced in approximately [redacted] of patients in MONALEESA-2, neutropenia was not included in the economic model; this is because the management of neutropenia was through dose interruption or dose reduction, rather than use of NHS resources. Additionally, the time to onset was quick, with a median time to onset of 16 days and the time to resolve was quick, with a median time to resolve 15 days (See section 4.12).

Table 53 Probability of grade 3 and 4 adverse events per treatment in MONALEESA-2

	Ribociclib	Letrozole
Diarrhoea	1.2%	0.9%
Fatigue	2.4%	0.9%
Infection	4.2%	2.4%
Nausea	2.4%	0.6%
Febrile neutropenia	0.0%	0.0%
Pulmonary embolism	0.0%	0.0%
Vomiting	3.6%	0.9%

Table 54 Adverse event unit costs and associated resource utilisation

AE	Unit cost	Resource use assumption (comments)
Diarrhoea	£461.17	FZ36G to FZ36Q - Gastrointestinal Infections non-elective short stay (weighted average) - NHS reference costs 2015-2016
Fatigue	£508.67	SA04K - Iron Deficiency Anaemia with CC Score 2-5 non-elective short stay - NHS reference costs 2015-2016
Infection	£518.34	WH07A to WH07G - Infections or Other Complications of Procedures (weighted average) - NHS reference costs 2015-2016

AE	Unit cost	Resource use assumption (comments)
Nausea	£557.45	JA12D to JA12L - Malignant Breast Disorders (weighted average) - NHS reference costs 2015-2017
Febrile neutropenia	£2,383.80	SA35A to SA35E - Agranulocytosis non-elective long stay (weighted average) - NHS reference costs 2015-2016
Pulmonary embolism	£499.38	DZ09J to DZ09Q - Pulmonary Embolus (weighted average) - NHS reference costs 2015-2017
Vomiting	£557.45	JA12D to JA12L - Malignant Breast Disorders (weighted average) - NHS reference costs 2015-2017

Table 55 Adverse event management cost per treatment arm in MONALEESA-2

	Total cost per patient per week
Ribociclib in combination with letrozole	£2.07
Letrozole monotherapy	£0.65

5.5.8 Miscellaneous unit costs and resource use

None applicable.

5.6 Summary of base case de novo analysis inputs and assumptions

5.6.1 Summary of base case de novo analysis inputs

Details of all of the values used in the economic model are provided in Table 56.

Table 56 Summary of variables applied in the economic model

Area	Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model settings/ patient characteristics	Time horizon	Lifetime (assumed to be 40 years)		5.2
	Discount rate	3.5%		
	Cycle length	No cycle length		
Clinical data efficacy – first-line treatment	First-line PFS - ribociclib in combination with letrozole	[redacted]	Normal	5.3
	Time to treatment cessation – ribociclib in combination with letrozole	[redacted]	Normal	

	Proportion of death upon progression – ribociclib in combination with letrozole	[redacted]	Beta	
	First-line PFS – letrozole monotherapy	[redacted]	Normal	
	Time to treatment cessation – letrozole monotherapy	[redacted]	Normal	
	Proportion of death upon progression – letrozole monotherapy	[redacted]	Beta	
Distribution of second-line treatments – ribociclib in combination with letrozole	Everolimus + exemestane	70%	Not varied	
	Chemotherapy (capecitabine)	25%		
	Single-agent endocrine therapy (exemestane)	5%		
Distribution of second-line treatments – letrozole monotherapy	Everolimus + exemestane	30%	Not varied	
	Chemotherapy (capecitabine)	30%		
	Single-agent endocrine therapy (exemestane)	40%		
Clinical data efficacy – second-line treatment	Second-line PFS – everolimus + exemestane	[redacted]	Multivariate normal	
	Time to treatment cessation – everolimus + exemestane	[redacted]	Multivariate normal	
	Overall survival – everolimus + exemestane	[redacted]	Multivariate normal	
	Proportion of death upon progression – everolimus + exemestane	[redacted]	Beta	
	Post-discontinuation survival – pooled everolimus + exemestane and exemestane	[redacted]	Multivariate normal	
	Treatment effect for exemestane monotherapy (vs. everolimus + exemestane)	[redacted]	Log-normal	
Utility values	PFS – on treatment ribociclib in combination with letrozole	[redacted]	Beta	5.4
	PFS – on treatment letrozole monotherapy	[redacted]	Beta	
	First-line PFS (PFS1) – off treatment	[redacted]	Beta	
	Second-line PFS: everolimus + exemestane	0.774	Beta	

	single-agent endocrine therapy (exemestane monotherapy)			
	Decrement in utility associated with chemotherapy	-0.113	Not varied	
Resource use and costs	Ribociclib treatment cost per pack			
	Ribociclib 600 mg	£2,950.00	Fixed	5.5
	Ribociclib 400 mg	£1,966.67		
	Ribociclib 200 mg	£983.33		
	Other treatment costs			
	Letrozole 2.5 mg, 28 tablets per pack	£1.52		
	Everolimus price per pack (list price)	£2,673.00	Fixed	
	[redacted]	[redacted]	[redacted]	
	Exemestane	£5.96		
	[redacted]	[redacted]		
	Exemestane monotherapy – total drug cost per week	[redacted]		
	Chemotherapy (capecitabine) – cost per 21 day cycle	£145.69		
	Chemotherapy – administration cost per first visit	£181.27		
	Chemotherapy – administration cost per subsequent visit	£181.27		
	Health state management costs (per week unless stated)			
	PFS1 – on treatment	£36	Gamma (SE assumed to be 20% around the mean)	
	PFS1 – off treatment	£36		
	PFS2	£36		
	Progressed disease	£45		
	Terminal care off cost per month	£4,379.03		
	Treatment related AE management costs (per week unless stated)			
	Ribociclib	£2.07		
	Letrozole monotherapy	£0.65		

CI, confidence interval

5.6.2 Assumptions

The key assumptions applied in the base case analysis are described in Table 57 below.

Table 57 Overall summary of assumptions in the base case analysis

Assumption	Justification
Comparators	
• Letrozole monotherapy	Letrozole monotherapy is widely used in the UK and is a direct comparator in the MONALEESA-2 trial[141]
Model structure & modelling approach	
State-transition approach	To reflect 2nd line treatments used in the UK and enable the use of external OS data as data from MONALEESA-2 is too immature[21]
Four health states	Represents the treatment pathway and natural history of BC. Third/subsequent lines of treatments are not modelled due to the absence of data
Individual based approach	This approach was chosen over a cohort approach in order to incorporate time and flexibility to explore the impact of different structural assumptions when modelling OS
Modelling of OS	
Base-case analysis assuming full PFS to OS surrogacy	OS data from the MONALEESA-2 trial is currently too immature
We assumed that individuals would experience the same proportion of time in the subsequent health states as they would have otherwise if they would have initiated on letrozole monotherapy	Absence of data Explored in addition to assuming that the surrogacy between PFS and OS is applied to only a proportion of patients
Movement through the model	
PFS1 separated into on and off treatment	This was done to capture the differences in treatment related associated costs as well as reflect the treatment duration in the trial (from which the efficacy is derived from) The time to treatment discontinuation and time to progression are modelled independently (i.e. they are not linked) from each other using the same random number rather than modelling a phase on and off treatment. This is a simplification
Treatment pathway	
patients follow the same treatment pathway independent of the first-line treatment received	The treatment pathway in post-menopausal women with ER+/HER2- is a difficult and complex process with a multitude of treatments available (single agents or

Assumption	Justification
	combination therapies). The choice of second-line therapy depends on patient's choice, the time to progression and response to prior therapy, the type of therapy previously used and the disease characteristics. This makes the accurate modelling of the treatment pathway particularly challenging. Therefore, simplifications were made
Second-line treatment assumed to consist of (a) everolimus + exemestane, (b) chemotherapy and (c) exemestane monotherapy	Assumption based on treatment available and clinical expert validation Assumption that exemestane representative of single agent endocrine therapies in second-line based on available data, IPD available from BOLERO-2 study,[72] clinical validation that this treatment would be a reasonable representation of single agent endocrine therapies. It was mentioned that fulvestrant is a treatment option that could be considered; however, this would cause additional uncertainty due to weak indirect treatment comparison data
No modelling of third-line/subsequent lines of treatment	Absence of data Mature long term OS data available from studies for second-line treatments included[72]
PFS extrapolation in first-line	
Exponential distribution used in base case	Provides a good visual and statistical fit to the observed KM for letrozole monotherapy and plausible extrapolation to external sources[97-99] External clinical expert validation confirmed the model predictions were representative of real world clinical outcomes Exponential used for ribociclib for consistency
Death upon progression in first-line	
Data from MONALEESA-2 and PALOMA-2 are pooled	This was done to increase the most use of clinical evidence available for both CDK4/6 inhibitors and letrozole by increasing the sample size
TTD in first line	
Same random number used for PFS and TTD	Because PFS and TTD are sampled independently of each other. This avoids inconsistencies. Also a constraint is added to avoid TTD to be greater than PFS
Exponential distribution used in base case	The choice between the Weibull and exponential distribution is challenging. The exponential distribution is used in the base case following clinical expert advice.

Assumption	Justification
	The exponential distribution is used for letrozole monotherapy for consistency
Second-line treatments	
HR applied to everolimus + exemestane (despite curves for TTD crossing at the beginning between everolimus and exemestane)	This was done to (a) minimise the number of inputs, (b) simplify the model, (c) be in line with the assumption use for chemotherapy and (d) the aim of the model is not to estimate accurately the difference between treatment in second-line. Whilst this is a limitation, the impact is likely to be minimal as all arms are impacted equally
Weibull distribution used for TTD	The log-normal and log-logistic had long tails
Post-discontinuation survival pooled across arms in BOLERO-2	No evidence of difference and for simplicity
Weibull distribution used in the base case for post-discontinuation survival	The exponential and Gompertz are equally plausible and explored in scenario analysis
Post-discontinuation survival for chemotherapy assumed to take a Weibull distribution with the same shape as everolimus + exemestane	Assumption in the absence of data
Health state utility values	
Utility value in PFS taken from MONALEESA-2, assumed to be the same between arms and on and off treatment phase	No differences observed in MONALEESA-2 by treatment arm or off and on treatment
Utility value in PD taken from NICE TA915 based on Lloyd et al (2006)	Whilst utility at the point of progression were collected in MONALEESA-2, the utility value for progression from the MONALEESA-2 trial is more reflective of second-line rather than the progressed disease. Furthermore, the utility value for progression from MONALEESA-2 does not capture advanced stages of disease progression following two treatments
Drug acquisition costs	
Drug acquisition costs taken from eMIT when possible	
Dose reduction included	A large proportion of patients treated with ribociclib in the MONALEESA-2 trial had dose reductions
Management of breast cancer	
The same cost was assumed in PFS1 and PFS2 on and off treatment	Assumption

5.7 Base-case results

5.7.1 Base-case incremental cost-effectiveness analysis results

Total costs, LYG, QALYs, and incremental cost per QALY for ribociclib in combination with letrozole versus letrozole monotherapy are presented in Table 58. As described previously, the base case analysis is based on first-line advanced or metastatic breast cancer patients who are HR+/HER- from the MONALEESA-2 study. The Exponential distribution was used to extrapolate the PFS and the OS was informed based on the patient pathway followed in the economic model (Weibull extrapolation for both PFS and OS used for everolimus + exemestane arm PFS2) in the base case analysis. In the base case analysis, ribociclib in combination with letrozole generates 0.96 incremental QALYs and [redacted] incremental costs over a lifetime horizon compared with letrozole monotherapy, resulting in an ICER of [redacted] per QALY gained.

Table 58 Base case results

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

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

5.7.2 Clinical outcomes from the model

Treatment with ribociclib in combination with letrozole is associated with an expected mean LYG of [redacted] ([redacted]) compared with [redacted] ([redacted]) when patients received letrozole monotherapy.

The mean and median time to disease progression in first-line treatment (PFS1), time to progression in second-line treatment (PFS2), time in progressed disease (third-line and subsequent line treatments) and time alive (OS) for each arm of the simulation are summarized in Table 59. The predicted median and mean time in PFS are [redacted] and [redacted] months for ribociclib in combination with letrozole, compared with [redacted] and [redacted] months for letrozole monotherapy.

It should be noted that due to the immaturity of the clinical data no OS data has been presented and thus it is not fully possible to fully validate the estimated survival for both arms against the MONALEESA-2 data. Further validation discussion is presented in section 5.10

Table 59 Summary of model results compared with clinical data

Outcome for ribociclib	Clinical trial result		Model result	
	Median	Mean	Median	Mean
Ribociclib				
First-line progression-free survival (PFS1)	Not reached	Not reached, not reported	[redacted]	[redacted]
Overall survival	Not reached, not reported	Not reached, not reported	[redacted]	[redacted]
Letrozole				
First-line progression-free survival (PFS1)	14.7	Not reached, not reported	[redacted]	[redacted]
Overall survival	Not reached, not reported	Not reached, not reported	[redacted]	[redacted]

5.7.3 Disaggregated results of the base case incremental cost-effectiveness analysis

Table 60 summarises the breakdown of QALYs for each health state over the model time horizon in the base case analysis. Treatment with ribociclib in combination with letrozole is associated with more QALYs in the pre-progression (first-line PFS1) and the second-line PFS (PFS2) health states compared with letrozole monotherapy.

Table 60 Summary of QALY gain by health state

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

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

QALY, quality-adjusted life year; HS1, health state 1; HS2, health state 2.

Table 61 summarises the breakdown of costs in the base case analysis.

Table 61 Summary of costs by health state

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

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was 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 was 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. The results of the probabilistic sensitivity analysis are presented as cost-effectiveness planes and cost-effectiveness acceptability curves. The choice of distribution is described in Table 56.

The results of the probabilistic sensitivity analyses using 1,000 iterations are shown below (Table 62). Over a lifetime, patients receiving ribociclib in combination with letrozole accrue more QALYs ([redacted] QALYs) compared with patients initiating letrozole monotherapy ([redacted] QALYs), but at a greater cost ([redacted] respectively). The ICER is [redacted] per QALY gained in the probabilistic sensitivity analysis.

Table 62 Results of the probabilistic sensitivity analysis

	LYs (undiscounted)	QALYs (discounted)	Costs (discounted)	ICER
Letrozole	[redacted]	[redacted]	[redacted]	
Ribociclib	[redacted]	[redacted]	[redacted]	
Incremental	[redacted]	0.98	[redacted]	[redacted]

Figure 40 and [redacted] show the cost-effectiveness plane and cost-effectiveness acceptability curve using results generated over a lifetime horizon. The curves show the probability of being cost-effective for different levels that the decision maker may be willing to pay for an additional QALY. The cost-effectiveness acceptability curves show that the probability of ribociclib in combination with letrozole being a cost-effective strategy is [redacted] when using a threshold of £30,000, £40,000, £50,000, £60,000, and £100,000 per QALY, respectively.

Figure 40 Cost-effectiveness plane

Figure 41 Cost-effectiveness acceptability curve

5.8.2 Deterministic sensitivity analysis

The majority of inputs to the model were included in a one-way sensitivity analysis. Inputs not varied in one-way sensitivity analysis were varied in scenario analysis. Parameters were varied within the reported range, CI or within reasonable range as shown in Table 63. The results are given in Table 64.

A Tornado diagram is presented in Figure 42 for the [redacted] that had the largest impact on the ICER. As expected, the ICER was mostly sensitive to the discount rates. Other input parameters had a limited impact in the ICER ([redacted]).

Table 63 Parameters used in the deterministic sensitivity analysis

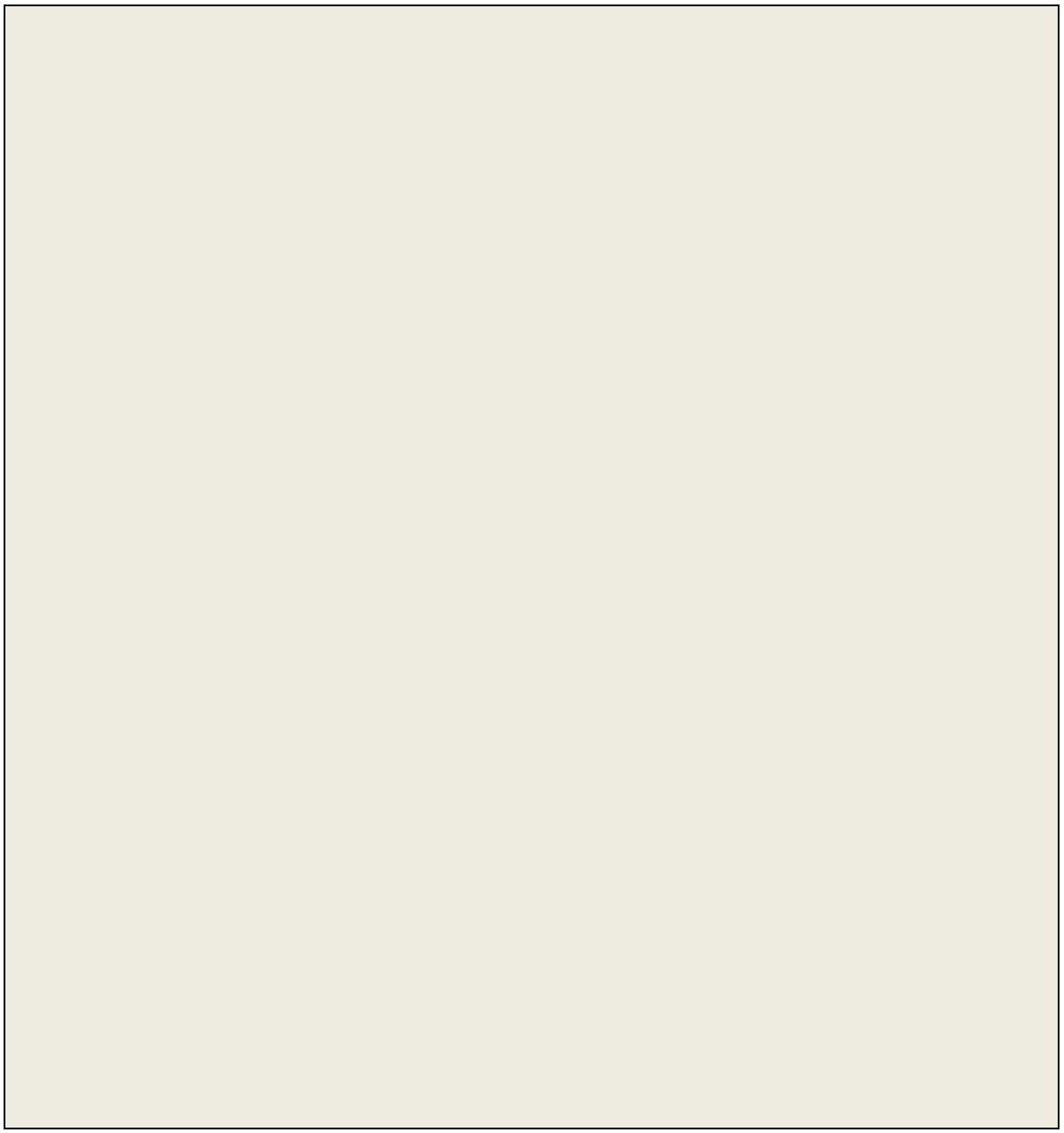
Parameter	Parameter values			Reference
	Lower value	Base case	Upper value	
Discount costs	1.5%	3.50%	5.0%	Fixed to 1.5% and 5%
Discount benefits	1.5%	3.50%	5.0%	Fixed to 1.5% and 5%
HR exemestane TTD	[redacted]	[redacted]	[redacted]	Lognormal (95% CI)
Cost progression health state	£369.23	£461.54	£553.85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

[#]One way sensitivity analysis was not run for % death upon PFS 1st line letrozole due to the 0% used in the base case and the results have no impact on the ICER in one way. This variable has been explored in scenario analysis.

Table 64 Results of deterministic sensitivity analysis

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

Figure 42 One-way sensitivity analysis Tornado plot



5.8.3 Scenario analysis

Important variables in the model were varied in scenario analysis. The results of the tested scenarios are presented below.

It can be seen in Table 65 that after presenting over 40 scenario analyses that the ICERs are close to the presented base case analysis. This would validate the robust structure of the model. Only the time horizon of 5 and 10 years, the use of [redacted]

[redacted] shifted the ICER [redacted]. However, it is important to consider which of these scenarios are validated. It would be unrealistic to expect [redacted] for all patients, as would it be to have a time horizon of 5 or 10 years for this patient population. The [redacted] was not considered a viable parametric survival function as through clinical validation the predictions were lower than expected in the real world. While the [redacted] could be seen as more plausible, again clinical validation supported the model predictions using the exponential function along with the NICE and evidence review group acceptance for using an exponential survival function for this patient population in appraisal ID915.[2]

Conclusions of the scenario analysis are 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 65 Results of the scenario analysis

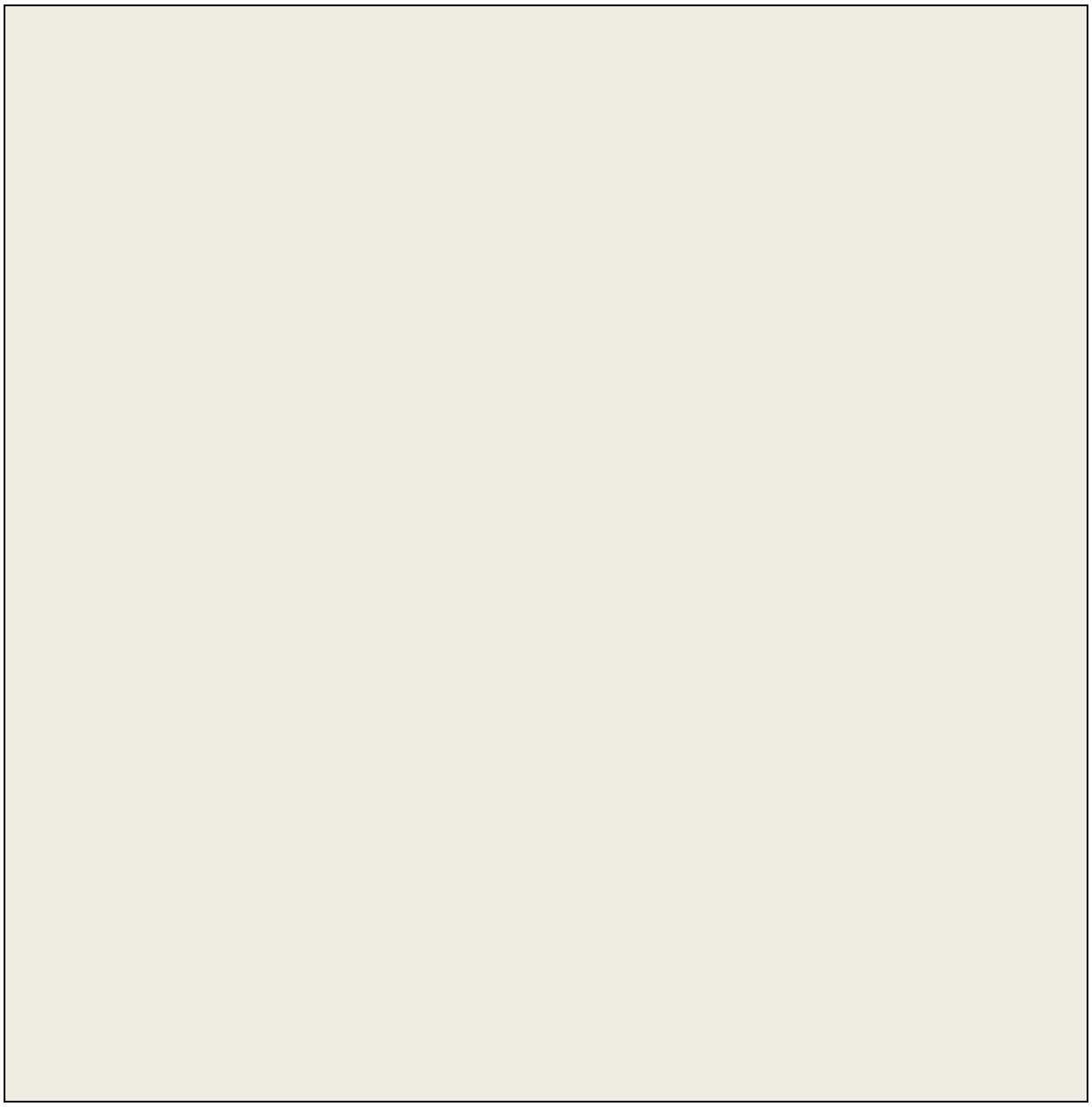
Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Base case = 40 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Time horizon = 5 years	[redacted]	[redacted]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

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
Threshold PFS to have OS gain = 10 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	[redacted]
Threshold PFS to have OS gain = 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93	[redacted]
Threshold PFS to have OS gain = 28 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.84	[redacted]
Threshold OS gain = 4 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.94	[redacted]
Threshold OS gain = 8 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
Threshold OS gain = 10 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.87	[redacted]
Threshold OS gain = 12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]
Threshold OS gain = 28 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.67	[redacted]
Chemotherapy used in second-line							
Base case = capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
Paclitaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Docetaxel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Doxorubicin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Treatment pathway – second-line treatment used							
Base case = different treatment pathway*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.85	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.87	[redacted]

Scenario	Total cost (£) ribociclib	Total cost (£) letrozole	Total QALYs ribociclib	Total QALYs letrozole	Incremental costs (£)	Incremental QALYs	ICER per QALY gained (£)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.91	[redacted]
Parametric functions used in 2nd line							
Base case = Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
TTD Eve = Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Gomp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
TTD Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	[redacted]
PFS Eve = Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Gomp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PFS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PPS Eve = Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
PPS Eve = Gomp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
PPS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.92	[redacted]
PPS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.93	[redacted]
OS Eve = Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Gomp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
OS Eve = Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.96	[redacted]
Third line (progression HS) costs							
Base case = £2,000 per month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**0.96**	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Figure 43 Graphical representation of scenario analyses performed



5.8.4 Summary of sensitivity analyses results

A range of sensitivity and scenario analyses were conducted to test the robustness and structural assumptions of the model inputs. Overall, results were robust to most parameters and structural assumptions.

Based on the sensitivity analyses run, and assuming the treatments are at list price, the results suggest that the model is most sensitive to a time horizon of 5 years and the choice of parametric function used to estimate PFS for first-line treatment; however, only a limited set of assumptions were plausible. While this model has the flexibility to explore a PFS to OS surrogacy relationship for a defined population, the

scenario results indicate that this relationship has a limited impact on the ICER. See Table 62, Table 64, Table 65 and Figure 42 and Figure 43.

5.9 Subgroup analysis

Subgroups were not explored in this analysis, as ribociclib in combination with letrozole showed a benefit over letrozole in all predefined subgroups from the MONALEESA-2 study.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

Validation of the de novo cost-effectiveness analysis consisted of both internal and external level validation. The levels of validation aimed to:

- validate that the economic model developed was robust in representing the disease, advanced breast cancer, and the management pathway of the patient population relevant to the decision problem, HR+/HER2- advanced breast cancer patients
- validate the model inputs used
- validate the clinical and economic outputs being derived by the de novo model.

A series of validation steps were performed and are discussed in further detail.

Internal validation

The economic model was quality control checked by the independent health economist developing the model and an internal health economic modelling team at Novartis to ensure the model was reliable, and producing robust results as would be expected. In consideration of the clinical data and model predictions, internal validation consisted of sourcing additional long-term letrozole monotherapy trial/study evidence in a population that is considered representative to the population reviewed in this appraisal. Two studies were identified, the LEA[98] and ALLIANCE[99] studies. These studies are both recent and provided both PFS and OS data for letrozole monotherapy in first-line advanced breast cancer HR+/HER2-. Overlaying the available data from both these studies showed that the model produced predictions for letrozole monotherapy that are in line with mature trial data.

Additional internal validation was conducted to ensure that the cost, health state utilisation and utility inputs used in the model were representative of the UK. This consisted of reviewing previous NICE appraisals in the disease area and utilisation of NICE clinical guideline recommendations where possible.

External validation

Further validations were performed with clinical and health economic experts through individual validation meetings with two experts and an advisory board meeting consisting of a further three clinical experts. These validation meetings covered a number of detailed questions consisting of the relevance of the MONALEESA-2 study to UK practice, the economic model and appropriate representation of the disease area and disease management pathway, and the clinical data input (in the model) and the model outputs.

Clinical experts concluded that the MONALEESA-2 study was robust and relevant to the UK. The structure of the economic model was discussed in detail and feedback was that it does represent the clinical pathway for advanced breast cancer patients who are HR+/HER2-.

A particular input to the model in respect of the management pathway was that of the post-progression treatment patients would receive. It was clear from feedback that the choice of breast cancer treatment depends on a number of aspects, and differs by locality and availability of treatments. However, it was clear that there is an anticipation of a different treatment pathway post-progression on ribociclib in combination with letrozole compared with letrozole monotherapy.

The validation with the experts was presented with model predications for both PFS and OS, at 3, 5 and 10 years for ribociclib in combination with letrozole and letrozole monotherapy. While all experts found it difficult to validate the predictions for ribociclib, given that it is a new treatment and currently under assessment for a licence, they were able to validate the letrozole predictions. All experts considered that the model predications for letrozole were very close to the survival proportions they would expect in clinical practice. See Figure 44 and

Figure 45

All clinical experts were presented with the MONALEESA-2 study publication and the safety results used in the submission. A particular question related to the interpretation and impact in future impact of QTcF prolongation and other treatment monitoring that may be required with ribociclib. The clinical experts confirmed that any additional monitoring was not a concern when considering the use of ribociclib and that the ability to perform any required monitoring is currently available. It was mentioned that clinicians are already used to managing the toxicities associated with chemotherapy.

Figure 44 PFS: comparison of predicted vs. actual in MONALEESA-2, ALLIANCE and LEA

Figure 45 OS: comparison of predicted vs. actual in MONALEESA-2, ALLIANCE and LEA

5.11 Interpretation and conclusions of economic evidence

The systematic literature review undertaken for this appraisal identified a number of cost-effectiveness analyses; however, almost all were in different treatment lines, i.e. second-line, thus, meaning any direct comparisons would not be appropriate. However, one NICE cost-effectiveness appraisal was identified, Breast cancer (hormone-receptor positive, HER2-negative) – palbociclib. [ID915].[2] This appraisal can be considered directly relevant for comparisons to the appraisal of ribociclib due to the similarity of the licenced indication, i.e. first-line HR+/HER2- advanced breast cancer in combination with an AI, the indication under appraisal, same as this appraisal (see section 1.1), and class of therapy, CDK4/6 inhibitor. The key differences between both these appraisals are presented in Table 66. It should be noted that a final appraisal determination (FAD) has not been published for ID915.[2]

Table 66 Key differences between ribociclib and palbociclib NICE appraisals

	NICE appraisal	
	Ribociclib ID1026	**Palbociclib ID915**
Economic model structure	Individual patient simulation State-transition approach with the following four health states: • PFS1 (on and off treatment) – 1st line treatment • PFS2 – 2nd line treatment • Progression – post second line progression treatments • Death	Partitioned survival Markov model including the following health states: • Pre-Progression (1st line treatment) • Post-Progression including tunnel states for 2nd, 3rd, 4th treatments and BSC • Death
Treatment comparator	Letrozole (NSAI)	Letrozole (NSAI)
Clinical data used		
Progression-Free Survival (PFS)	MONALEESA-2 clinical trial	PALOMA-2 clinical trial
Overall Survival	OS is modelled based on individual patient simulation through the state transition model as follows: **PFS2 HS** – second line treatment is either: • everolimus + exemestane (BOLERO-2 clinical trial IPD) • Single-agent endocrine therapy, exemestane (BOLERO-2 clinical trial IPD) • Chemotherapy, capecitabine for base case analysis – Hazard Ratio based on Li et al, 2015[1] Progression HS – post second line treatments i.e. third line and greater • Modelled based upon BOLERO-2 OS IPD data	PALOMA-1 clinical trial data (base case analysis)

	NICE appraisal	
	Ribociclib ID1026	**Palbociclib ID915**
	• Hazard Ratio applied Li et al. 2015[1]	
HRQoL data source	MONALEESA-2 clinical trial – EQ-5D-5L BOLERO-2 clinical trial and TA421 ID915 (based on Lloyd 2006[49])	PALOMA-2 – EQ-5D Lloyd 2006
Utility values used	[redacted] PFS2 HS: 0.774 Progression HS: 0.5052 Chemotherapy disutility: -0.113	PFS HS: marked confidential Post-Progression HS: 0.4492 (all lines)
Costs		
Year base	2015-16	2014-15
Health state resource costs	Based upon NICE CG81 care packages	Based upon NICE CG81 care packages
Adverse events	Grade 3 and 4 adverse events from MONALEESA-2	Only neutropenia
Results		
Life Years Gained (LYG) Base case analysis (deterministic values)	[redacted]	Palbociclib: 3.79 Letrozole monotherapy: 3.02
QALYs	[redacted]	Palbociclib: 2.40 Letrozole monotherapy: 1.77
Total costs	[redacted]	Palbociclib: 116,696 Letrozole monotherapy: £21,843
ICER	[redacted]	£150,869

[redacted] as compared with ID915,[2] it is pertinent to consider differences in modelling approaches between the two appraisals, state-transition (individual based) versus partitioned survival (cohort based), and for wider validation, consideration for previous NICE appraisals specifically for HR+/HER2- advanced breast cancer.

Modelling approaches

As presented (see section 5.2.2), a state-transition approach based on individual patient simulation has been used. The strengths of using such an approach allows for the model to reflect in greater detail the HR+/HER2- advanced breast cancer treatment pathway, with second-line treatments directly used. The state-transition approach used a time to event method, which allows flexibility and greater sensitivity for when each individual patient experiences an event (e.g. first-line treatment progression). A partitioned survival (cohort) model approach requires that all of the cohort population experience the same treatment pathway.

Partitioned survival models are more widely used in oncology appraisals, given their simple approach, minimal assumptions required and the direct modelling of OS, based upon the OS KM curves from clinical trials. However, it was felt that given the level of immaturity of the MONALEESA-2 trial,[21] any direct estimation of OS could be seen as very uncertain. The state-transition approach allows for the use of more robust long term clinical data to estimate survival. Additionally, the state-transition model used allowed for exploratory analysis to consider only a proportion of patients achieving survival advantage.

Previous NICE appraisals

When considering the key differences presented in Table 66, the resulting LYG appear [redacted] when using the state-transition modelling approach. However, when considering previous NICE appraisals for HR+/HER2- advanced breast cancer, specifically the NICE appraisal for everolimus TA421[72] and the appraisal of fulvestrant TA239,[73] the total LYG presented for each appraisal was [redacted] and 2.62, respectively. While both these appraisals were in second-line HR+/HER2- advanced breast cancer, it could be considered that ID915[2] LYG were [redacted] than might be expected.

The economic evaluation presented in this appraisal has a number of key strengths, as listed below.

Strengths

- The economic evaluation directly addresses the appraisal decision problem (see section 1.1).
- The modelling approach, state-transition (individual based) approach (see section 5.2.2) allows for use of the most available long-term clinical data across the treatment pathway of patients.
- The state-transition approach, while not typically utilised in oncology, is an established modelling methodology used in previous NICE assessments of medicines.
- Utilises IPD from a high-quality robust clinical study, MONALEESA-2, for informing the first-line treatment pre-progression health state (PFS1 health state).
- Utilises IPD from a high-quality robust clinical study, BOLERO-2, for informing the second-line treatment pre-progression health state (PFS2 health state).
- The model was developed through clinical validation in order to accurately reflect the HR+/HER2- advanced breast cancer patient pathway, with validation of the model predictions.
- The model provides additional flexibility which is typically complex and convoluted when considering the more traditional partitioned survival approach.
- The model allows for more accurate costing of post-first-line progression treatment, i.e. second-line treatment.
- The health state resource use costs utilised are consistent with previous NICE appraisals and are based upon NICE clinical guidelines.
- EQ-5D-5L utility data were derived for the intervention and comparator directly from the core clinical phase III study MONALEESA-2;[21] this eliminates the need to model impact of AEs as these are already incorporated.
- Post-progression health state utility values used remain consistent with previous NICE technology appraisals.

- Wider validation considering previous NICE appraisals in HR+/HER2- advanced breast cancer demonstrates that the model results can be considered reasonable.
- The costs incorporated into the economic model are specific to practice in the UK and based on NHS reference costs. As such, the analysis is generalizable to the populations of England and Wales and addresses fully the specifications in the decision problem.
- The model incorporates probabilistic sensitivity analysis.

Limitations of the economic evaluation are listed below:

Limitations:

- The state-transition model requires a number of assumptions to be made, as opposed to a partitioned survival mode. While the assumptions made are validated through clinical experts, clinical expert opinion will vary based on local guidelines.
- The link between PFS and OS is uncertain, and while the model aims to test the impact through sensitivity analysis, only long term clinical data will provide the answer.
- The clinical data for MONALEESA-2 was based upon a pre-specified interim analysis and, thus, the immaturity of the data does not allow for direct model validation to the clinical data.
- Estimates of AEs were limited to grade 3 and 4 for ribociclib and letrozole from the MONALEESA-2 study only. The model does not account for AEs on second-line treatments (everolimus + exemestane, single-agent endocrine therapy exemestane and chemotherapy).
- The model applies an assumption of the monthly cost for third-line treatment, although this was validated through clinical experts.

6 Assessment of factors relevant to the NHS and other parties

6.1 Number of eligible patients in England and Wales

The estimated number of total HR+/HER2- advanced breast cancer patients in England and Wales who are eligible for ribociclib as first-line treatment is summarised in Table 67.

Table 67 Estimated number of patients with HR+/HER2- advanced breast cancer in England and Wales eligible to receive ribociclib

Population	Number of patients (incident)	References
Total number of patients eligible for endocrine based therapies	[redacted]	Novartis data on file

Patient numbers and drug acquisition costs calculated through a prevalence based forecast model.

6.2 Assumptions made about current treatment options and associated costs

An assumption made in the budget impact analysis is that ribociclib would displace non-steroidal AI therapies (letrozole and anastrozole) only, and the non-steroidal AI therapy used for the budget impact analysis is letrozole. Whilst this is a simplification, this was made given that the current treatments available to the NHS for first-line HR+/HER2- advanced breast cancer are either endocrine therapies (non-steroidal AI or tamoxifen) or chemotherapy. Since clinical guidelines recommended that chemotherapy should only be a first-line option in patients whose disease is imminently life threatening or requires early relief of symptoms because of significant visceral organ involvement (see section 3.3) it was not seen as appropriate to include in the budget impact calculations. However, it should be noted that expert feedback suggests that chemotherapy is used more widely than clinical guidelines and, as such, the assumption made could be seen as conservative.

Since both ribociclib and letrozole are oral therapies no administration costs are considered. There are no companion diagnostic testing costs associated with ribociclib and all diagnostic tests associated with advanced breast cancer are already routine clinical practice.

Assumptions about the duration of therapy are based upon the median TTD results from the economic model for ribociclib plus letrozole (see Section 5.3.3) and the published median PFS from the, MONALEESA-2 study, for letrozole. Table 68 summarises the cost per treatment cycle per patient associated with ribociclib in combination with letrozole and letrozole monotherapy.

Table 68 Total annual cost per patient associated with ribociclib in combination with an AI

Treatment	Duration of therapy[#]	Cost per treatment cycle (28 days)
Ribociclib	[redacted]	[redacted]

#Duration of therapy for ribociclib plus letrozole is based on the median Time to Treatment Discontinuation (TTD), as per the economic model

6.3 Estimated annual budget impact on the NHS in England and Wales

The budget impact is estimated as the number of eligible patients and associated costs for treating those patients according to the assumed market share associated with the uptake of ribociclib in the NHS. The estimated net cumulative annual budget impact to the NHS in England and Wales of introducing ribociclib in combination with letrozole for first-line HR+/HER2- advanced breast cancer patients over the period of 2017–2019 is approximately [redacted] and is presented in Table 69.

Table 69 Estimated annual budget impact to the NHS in England and Wales of introducing ribociclib in combination with an AI for first-line HR+/HER2- advanced breast cancer

	Y1 (2017)	Y2 (2018)	Y3 (2019)
Total estimated postmenopausal women eligible for ribociclib treatment	[redacted]	[redacted]	[redacted]
Estimated ribociclib market share %	[redacted]	[redacted]	[redacted]
Total estimated patients treated with ribociclib + letrozole	[redacted]	[redacted]	[redacted]
Drug acquisition costs			
Total ribociclib + letrozole drug acquisition costs	[redacted]	[redacted]	[redacted]

Patient numbers and drug acquisition costs calculated through a prevalence based forecast model.
#Estimated ribociclib market share is of the total first line treated patients.
Novartis data on file.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

April 2017

File name	Version	Contains confidential information	Date
		Yes	**27/10/2017**

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2104) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company/ of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Name of technology: Kisqali® (ribociclib)

The anticipated marketing authorisation: Kisqali (ribociclib) in combination with an aromatase inhibitor for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) locally advanced or metastatic breast cancer as initial endocrine-based therapy.

Following a positive recommendation by NICE for ribociclib for the treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer as initial endocrine-based therapy, the patient access scheme (PAS) will be applied to all supplies and preparations of ribociclib and is applicable to all current and future indications.

3.2 Please outline the rationale for developing the Patient Access Scheme.

The simple discount PAS is a mechanism through which the NHS will be able to procure ribociclib at net prices lower than the current list prices. The discount result in a price that is cost-effective versus current treatment alternatives.

The proposed patient access scheme is a simple discount to the ribociclib list price. The discount will apply at the point of invoicing for ribociclib. The scheme for ribociclib will only be implemented upon publication of positive NICE guidance.

Should the list prices of ribociclib change, the percentage discount will change accordingly to maintain a fixed net price.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include

details of the list price and the proposed percentage discount/fixed price.

Financially-based scheme: simple discount to list price. The amount of discount and net price will remain commercial in confidence.

Table 1 Ribociclib list price per pack

Formulation	Pack size (# tablets)	Price per pack
200mg tablets	63	£2,950.00
200mg tablets	42	£1,966.67
200mg tablets	21	£983.33

Table 2 Ribociclib net price [redacted]

Formulation	Pack size (# tablets)	Price per pack
200mg tablets	63	[redacted]
200mg tablets	42	
200mg tablets	21	

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the entire anticipated licensed population for ribociclib, namely postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Following positive NICE guidance for ribocilcib the PAS will apply to all supplies and preparations of ribociclib and is applicable to all current and future indications. No additional criteria will need to be met.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme is applicable to 100% of the population treated with ribociclib in the NHS in England and Wales.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

[redacted] The amount of discount and net price will remain commercial in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

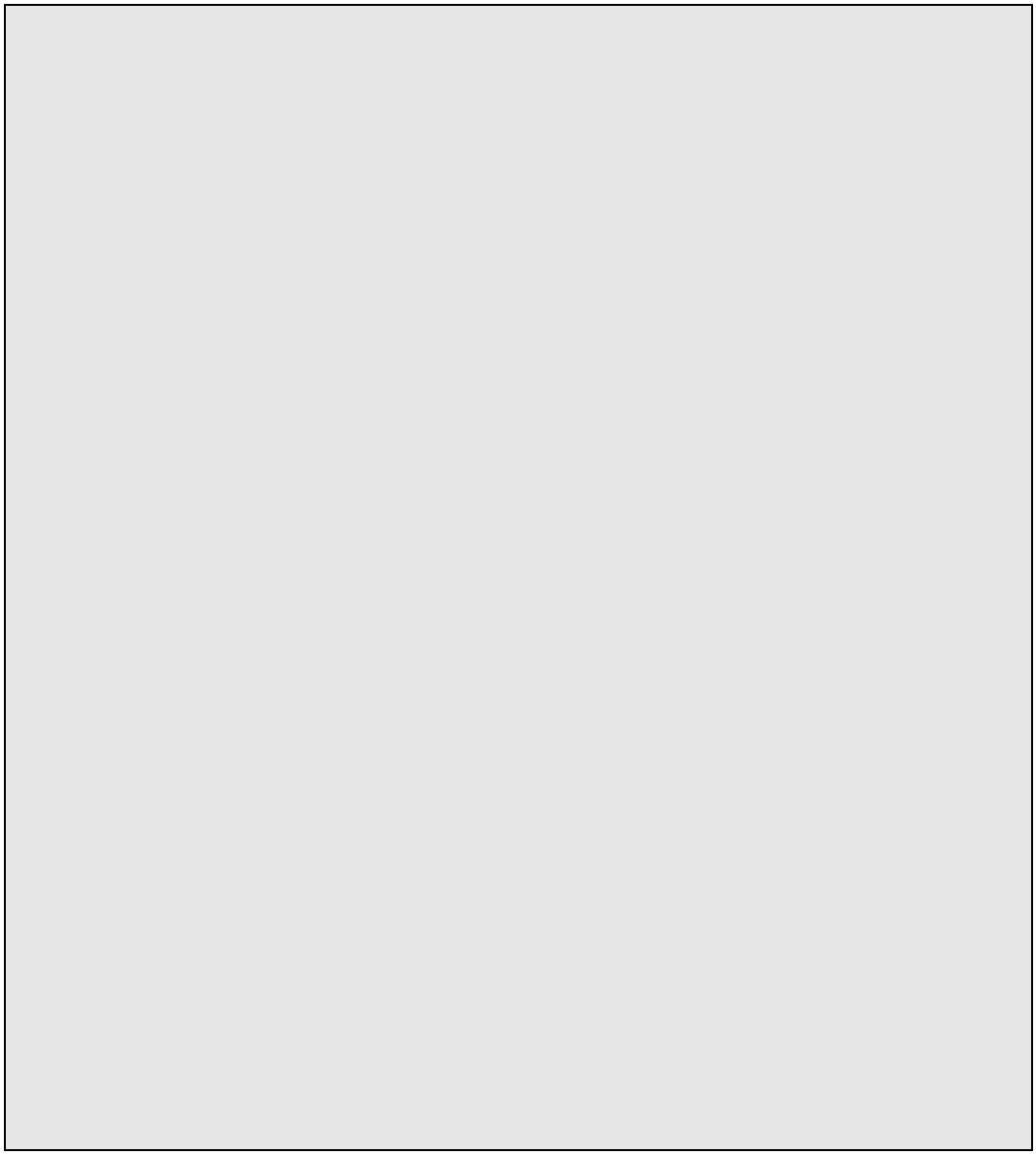
There will be no need to collect any additional information.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The scheme will not require any additional NHS resource to access the PAS net price [redacted]

[redacted]

[redacted]



3.10 Please provide details of the duration of the scheme.

Subject to positive NICE guidance for ribociclib, the proposed scheme will be in place until NICE review of the guidance, subject to the usual NICE review process.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to this scheme.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company/sponsor submission of evidence'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The population to whom the scheme applies has been presented in the main submission of evidence.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

N/A – this patient access scheme is being submitted for consideration alongside the main submission in this technology appraisal.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the main submission document, list prices are used for ribocilcib.

[redacted]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

A simple scheme/discount is used; only drug acqusition cost for ribociclib is changed by the patient access scheme.

The clinical effectiveness data presented in the main submission of evidence is used in the economic model including the Patient Access Scheme.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 5.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The proposed scheme consists of simple discounts, and therefore there will be no additional costs associated with its implementation and operation in NHS England and Wales.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Table 3 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Ribociclib without PAS		Ribociclib with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Treatment acquisition – PFS1 health state	£2,950* [redacted]	[redacted]	[redacted]	[redacted]	Economic model
Treatment acquisition – PFS2 health state	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Health state resource use costs (PFS1)	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Health state resource use costs (PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Progression health state related costs	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Total treatment-related costs	N/A	[redacted]	N/A	[redacted]	Economic model

Note: *Ribociclib 600mg - £2,950, ribociclib 400mg - £1,966.67, ribociclib 200mg - £983.33

**[redacted]

Treatment acquisition – PFS1 health state includes the total combination cost of ribociclib in combination with letrozole

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 4).

The base case results for ribociclib in combination with letrozole versus letrozole monotherapy with and without the patient access scheme are presented below

Table 4 Base-case cost-effectiveness results

	Ribociclib in combination with letrozole	**Letrozole monotherapy**
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.96
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 5 Base-case cost-effectiveness results using the Patient Access Scheme

	Ribociclib in combination with letrozole	Letrozole monotherapy
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.96
ICER (£)	N/A	[redacted]

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

The table above contains the only results, as the comparison is ribociclib in combination with letrozole versus letrozole monotherapy only and therefore no incremental analysis is required.

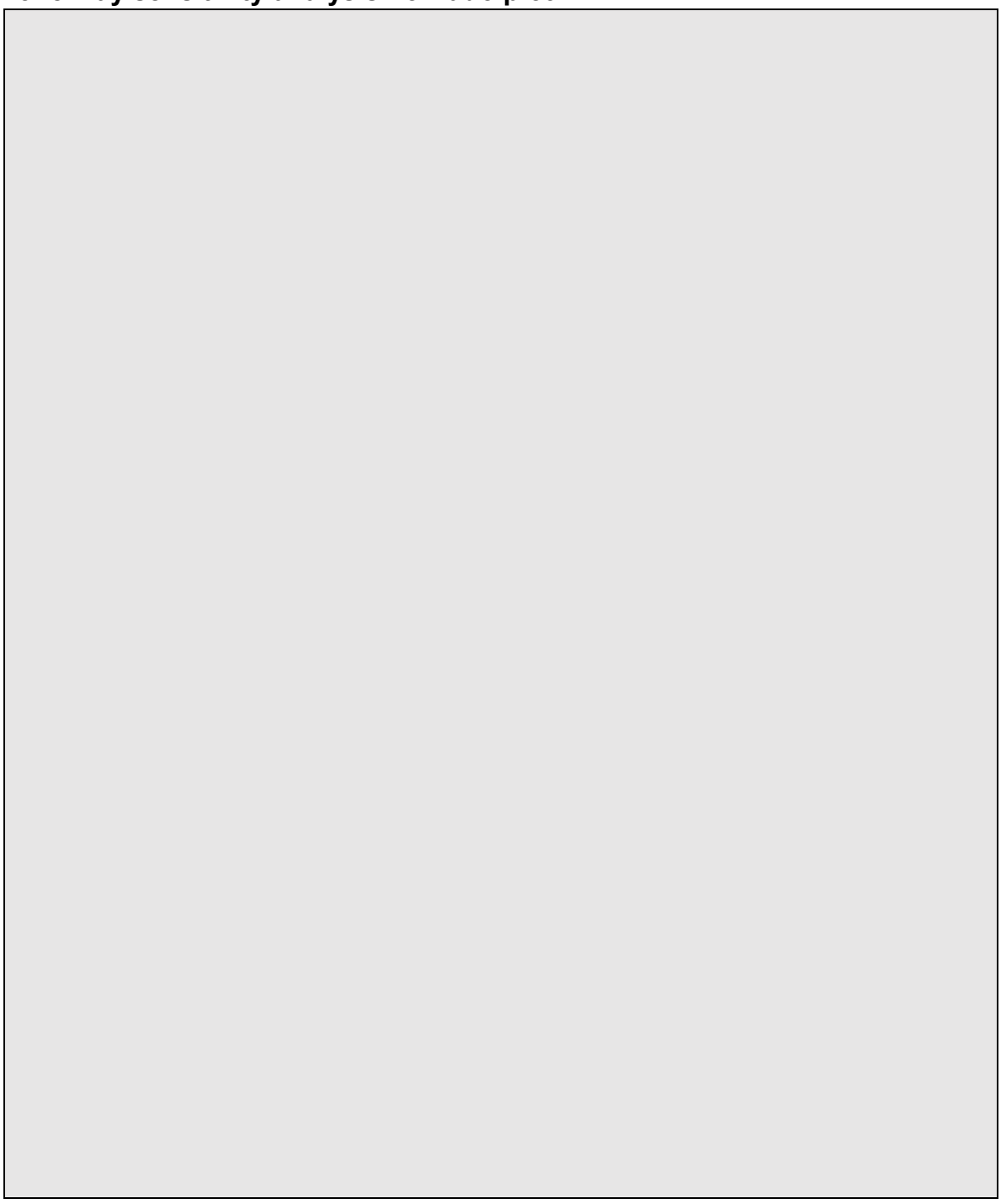
[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analysis was conducted as described in section 5.8.2. in the main submission document. The sensitivity analysis results, including the PAS are presented in Figure 1 below:

Figure 1 Ribociclib [redacted] + letrozole versus letrozole monotherapy one-way sensitivity analysis Tornado plot



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

PSA was conducted as described in Section 5.8 in the main submission document. The mean ICER, including the PAS, is presented in Table 6.

Table 6 Mean PSA result including PAS

	Ribociclib in combination with letrozole	**Letrozole monotherapy**
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.97
ICER (£)	N/A	[redacted]

Figure 2 Cost-effectiveness plane including PAS

Figure 3 Cost-effectiveness acceptability curve including PAS

In this analysis, the probability of ribociclib's cost-effectiveness at £30,000/QALY are:

- Versus letrozole monotherapy: [redacted]

4.11 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the technology appraisal.

As described in Section 5.8.3. of the main submission, a number of scenario analyses were undertaken. Table 7, below, presents the results of these scenario analyses including the Patient Access Scheme.

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure,

level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

A simple scheme/discount is used; no criteria or clinical variables are required.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 7 Results showing the impact of Patient Access Scheme on ICERs

	ICER for ribociclib + letrozole versus:	
	letrozole monotherapy	
	Without PAS	**With PAS**
Base-case analysis	[redacted]	[redacted]
Time horizon = 5 years	[redacted]	[redacted]
Time horizon = 10 years	[redacted]	[redacted]
Time horizon = 15 years	[redacted]	[redacted]
Time horizon = 20 years	[redacted]	[redacted]
Time horizon = 25 years	[redacted]	[redacted]
Time horizon = 30 years	[redacted]	[redacted]
PFS (parametric function)		
Weibull	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]
Use of HR for PFS	[redacted]	[redacted]
KM plus parametric PFS	[redacted]	[redacted]
Overall survival: Surrogacy assumption		
Threshold PFS to have OS gain = 4 months	[redacted]	[redacted]
Threshold PFS to have OS gain = 8 months	[redacted]	[redacted]

Threshold PFS to have OS gain = 10 months	[redacted]	[redacted]
Threshold PFS to have OS gain = 12 months	[redacted]	[redacted]
Threshold PFS to have OS gain = 28 months	[redacted]	[redacted]
Threshold OS gain = 4 months	[redacted]	[redacted]
Threshold OS gain = 8 months	[redacted]	[redacted]
Threshold OS gain = 10 months	[redacted]	[redacted]
Threshold OS gain = 12 months	[redacted]	[redacted]
Threshold OS gain = 28 months	[redacted]	[redacted]
Chemotherapy used in second-line	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Doxorubicin	[redacted]	[redacted]
Treatment pathway – second-line treatment used		
Same treatment pathway: Eve + exe = 25% Single agent endocrine therapy = 25% Chemotherapy = 50%	[redacted]	[redacted]
Same pathway: Eve + exe = 100%	[redacted]	[redacted]
Same pathway: Single agent endocrine therapy = 100%	[redacted]	[redacted]
Same pathway: Chemotherapy = 100%	[redacted]	[redacted]
Parametric functions used in 2nd line		
TTD Eve = Exp	[redacted]	[redacted]
TTD Eve = Gomp	[redacted]	[redacted]
TTD Eve = Log-Normal	[redacted]	[redacted]
TTD Eve = Log-logistic	[redacted]	[redacted]
PFS Eve = Exp	[redacted]	[redacted]
PFS Eve = Gomp	[redacted]	[redacted]
PFS Eve = Log-Normal	[redacted]	[redacted]
PFS Eve = Log-logistic	[redacted]	[redacted]
PPS Eve = Exp	[redacted]	[redacted]
PPS Eve = Gomp	[redacted]	[redacted]
PPS Eve = Log-Normal	[redacted]	[redacted]
PPS Eve = Log-logistic	[redacted]	[redacted]
OS Eve = Exp	[redacted]	[redacted]
OS Eve = Gomp	[redacted]	[redacted]
OS Eve = Log-Normal	[redacted]	[redacted]
OS Eve = Log-logistic	[redacted]	[redacted]
Third line (progression HS) costs		
£1000 per month	[redacted]	[redacted]

£425 per month	[redacted]	[redacted]
£0 per month	[redacted]	[redacted]
Death upon first line progression		
Pooled 1st line progression %	[redacted]	[redacted]

PAS: patient access scheme.

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study
- outcomes of the new study
- expected duration of data collection

- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.4 Please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable

Key Considerations Pertaining to the Cost-effectiveness of Ribociclib [1026]

The original Novartis base case (March 2017) was underpinned by the following key assumptions:

- PFS (Progression-Free Survival) Exponential extrapolation;
- TTD (Time to Treatment Discontinuation) Exponential extrapolation;
- cost of third and subsequent lines of treatment of £2,000;
- EQ-5D-5L utility values for 1st line (ribociclib) PFS and adapted Lloyd utility values for 2nd line PFS;
- full PFS to OS (Overall Survival) surrogacy.

This resulted in an ICER of [redacted] with the level of PAS offered at the time of submission. Following further consideration by the Committee, ERG and DSU and our desire to make ribociclib routinely available to patients at the earliest opportunity, Novartis are now offering an improved PAS increasing the level of discount from the original [redacted] This subsequent improved PAS would have further decreased Novartis' original base case ICER to [redacted] (as per the original base case assumptions).

The ERG proposed an alternative preferred base case (ERG Report dated 7.6.17) which was largely driven by changing two key assumptions; partial rather than full PFS to OS surrogacy and a lower cost associated with 3rd and subsequent lines of treatment i.e. £1,140 rather than £2,000. Taking account of the ERG's preferred base case assumptions and the improved PAS [redacted], the resulting ICER would be [redacted]. The ERG's preferred base case ICERs are summarised in Table 1 below.

Table 1 - Key ERG ICERs

	Total QALYs		**Total Costs**		**ICER**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
ERG					
Original Base case* [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original Base case* [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,140, EQ-5D-5L for PFS1 = [redacted], EQ-5D-3L for PFS2 = 0.774 (adapted Lloyd et al.), PFS to OS partial surrogacy 38.5%.

After the 1st Appraisal Committee the DSU were commissioned to validate the structure of, and inputs to, Novartis' economic model. The DSU did not raise any concerns regarding the structure of the model or the way that it performed. In August 2017 (after the 1st Appraisal Committee meeting), NICE's new position statement on the use of utility values generated from the EQ-5D-5L was issued. This necessitated Novartis to map the utility values from the EQ-5D-5L, collected directly from the clinical trial, to EQ-5D-3L values. In addition, utilities from a previously accepted NICE appraisal TA421 for PFS associated with 2nd line treatment had to be downgraded from 0.774 to 0.69. We would ask that consideration be given to the impact of using EQ-5D-5L utility values and utilities from TA421 to represent 2nd line treatments (as accepted in previous appraisals). However, to be consistent with the new NICE position statement on the use of EQ-5D-5L, we have adopted the mapped EQ-5D-3L and 0.69 for PFS1 and PFS2 health states respectively in our updated base case.

Following receipt of the DSU Report, and as suggested, Novartis incorporated the mapped EQ-5D-3L utility values and adopted PFS to OS partial surrogacy. In addition, we reduced the costs associated with third and subsequent lines of treatment from £2,000 to £1,500. This resulted in an ICER of [redacted] based on a PAS of [redacted]. However, we acknowledge that, as is the case with all appraisals, there may be some

uncertainty and therefore to expedite approval we are offering an improved PAS of [redacted] which reduces the ICER further to [redacted] when using the 2016 TTD data and [redacted] using the most up to date 2017 TTD data.

Justification is provided below for the key assumptions underpinning the updated base case. We have also provided several scenarios exploring the impact on the ICER of varying these assumptions.

The key Novartis ICERs are summarised in Table 2 below.

Table 2 - Key Novartis ICERs

	Total QALYs		**Total Costs**		**ICER**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Company ICERs					
Original Base case [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Original base case [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case* [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.
**ICER when using TTD 2016 data cut off

A justification for the adoption of the key assumptions and relevant scenario analyses are provided below.

Progression–Free Survival (PFS)

In the Novartis base case, PFS data were extrapolated using an Exponential distribution. This approach was selected over the other parametric distributions based on consideration of the following:

- statistical goodness of fit;
- clinical expert validation of model predictions at various time-points in the curve;
- validation of the curves using long term data from letrozole studies (LEA and ALLIANCE) and;
- precedents set by previous NICE appraisals in advanced breast cancer.

Both clinical expert input and validation of the curves, and the long term letrozole data from both the LEA and ALLIANCE studies (see

Figure ***1***) favour an Exponential extrapolation over the Weibull approach. Hence the weight of available evidence supports the use of an Exponential extrapolation over any of the other distributions. In the ERG Report the ERG concurred with an Exponential extrapolation of PFS and adopted this approach in their preferred base case.

In the palbociclib submission [ID915] the ERG argued that it would be more appropriate to extrapolate PFS data using the Exponential distribution rather than the Weibull distribution which was originally employed by the manufacturer. The ERG's justification for this choice, as referenced in the ACD is "…*The logic here is that patients who have done well following treatment, either because of the treatment itself or because of some underlying characteristic, and who have lived for many years after beginning treatment are actually at greater risk of progression (or death) than patients who were sicker or less responsive and died earlier…*"

(palbociclib ERG report page 94). The ERG considered the Weibull extrapolation to be an implausible assumption over the life time horizon of the model. This was discussed and accepted at the first Appraisal Committee meeting and is documented in the Appraisal Committee Document for palbociclib [ID915].

In summary, the weight of evidence and views of 2 ERGs have deemed the Exponential extrapolation of PFS to be the most appropriate approach. Given that ribociclib and palbociclib are both CDK4/6 inhibitors, with similar trial designs and clinical data, we would like to understand from the Appraisal Committee what data would justify a different approach to the extrapolation of PFS for ribociclib as opposed to the already accepted approach for palbociclib [ID915].

Figure 1 - External Validation of PFS Letrozole Arm

Various scenarios are presented in the Table 3, below to explore the impact on the ICER of adopting different extrapolation approaches for PFS.

Table 3 PFS - Scenario ICERs (with PAS)

	Total QALYs		**Total Costs**		**ICER (TTD 2016)**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy (38.5%)					
PFS Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy					
PFS Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5%, and most up to date 2017 TTD data.

Time to Treatment Discontinuation (TTD)

As previously discussed TTD data was only available for the January 2016 data cut off at the point of the ERG report. Subsequently the TTD data based on the January 2017 cut off has become available. The TTD January 2017 data (see Figure 3 and Figure 3) has been used to derive the updated ICERs presented in this document. The same analyses using the earlier January 2016 data are presented in the Appendix for ease of reference.

As can be seen in Figure 2, the difference between the PFS and TTD Kaplan Meier 2017 curves persists.

Figure 2 - Ribociclib PFS and TTD K-M data

NB: The tails of the 2 TTD and PFS Kaplan Meier curves should be disregarded as they represent very few patients at risk at the time of the analyses.

Difference between TTD and PFS

There has been discussion regarding the difference between TTD and PFS. It should be noted that a substantial difference, of approximately [redacted], exists between the Kaplan Meier curves for median TTD and median PFS before any extrapolation is applied, see

Figure **3**. This clinical data confirms that the difference is a real and substantial effect and not an artefact of extrapolation. When the Weibull extrapolation is applied to both the TTD and PFS curves the difference between the mean PFS and mean TTD is approximately [redacted] which is [redacted] based on the observed difference from the clinical trial. Furthermore, as seen in

Figure **3**, the Weibull curves for PFS and TTD converge and crossover at the tail. This is not a plausible scenario as patients were not allowed to continue on ribociclib post-progression which means that a crossover of the curves is implausible.

In the MONALEESA-2 trial, [redacted] patients discontinued ribociclib treatment prior to progression due to adverse events ([redacted]) or the clinician/patient/guardian's decision (6.6%). These patients were allowed to continue on letrozole monotherapy until progression. As letrozole is a proven, effective monotherapy that confers PFS benefits, a difference between TTD and PFS is not unexpected. Clinical data from the MONALEESA-2 trial demonstrates that PFS for letrozole monotherapy is 16 months. Therefore the mean difference that is generated when using the Exponential extrapolation for both PFS and TTD is not implausible.

Figure 3 - Ribociclib PFS and TTD

NB: The tails of the 2 TTD and PFS Kaplan Meier curves should be disregarded as they represent very few patients at risk at the time of the analyses.

Various scenarios are presented in the Table 4, below to explore the impact on the ICER of adopting different extrapolation approaches for TTD.

Table 4 - TTD Scenario ICERs (with PAS)

	Total QALYs		**Total Costs**		**ICER (TTD 2016)**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy					

TTD Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy					
TTD Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Long Term Validation

In the DSU Report reference is made to Paridaens 2008, Bergh 2012 and Mouridsen 2003, "…which reported much lower median OS than LEA and ALLIANCE." However these studies were conducted prior to the availability of newer targeted therapies such as everolimus plus exemestane and erubilin that have had a significant impact on the survival of breast cancer patients. The selection of survival data from the LEA and ALLIANCE studies to validate the predicted survival curves was ratified by clinical expert opinion and at the second Appraisal Committee Meeting the DSU confirmed that studies, such as LEA and ALLIANCE, which were conducted more recently, were preferred.

Utilities

In the Novartis base case, utility values collected from the MONALEESA-2 trial using EQ-5D-5L were used for PFS1 (PFS conferred by ribociclib) and utility values adapted from Lloyd et al. 2006 and used in TA421 were used for PFS2 (PFS conferred by 2nd line treatment). At the time of our submission use of EQ-5D-5L data was consistent with the documented reference case. Following the first Appraisal Committee meeting a new position statement on the use of EQ-5D-5L data was issued. Consequently we were asked to map the EQ-5D-5L data collected from MONALEESA-2 to EQ-5D-3L values. This reduced the utility value for PFS1 from [redacted] to [redacted]. We were also asked to use a utility value of 0.69 from the literature for our second line treatment progression free health state rather than the adapted utility value from the Lloyd *et al*. paper. The latter is inconsistent with many previous breast cancer appraisals where the Lloyd value has been used, including the appraisal of everolimus plus exemestane [TA241] which is the 2nd line therapy represented by PFS2.

The EQ-5D-5L was developed to increase sensitivity of the instrument and remove the ceiling effect, recognised limitations of EQ-5D-3L. Therefore by mapping the EQ-5D-5L, data collected in the trial back to the EQ-5D-3L we are likely to lose some of the value captured by the newer, improved version of the instrument. In addition the process of mapping is known to be associated with limitations.

The net impact of making adjustments to these utility values increases the ICER. Bearing in mind the timing of the introduction of the new position on EQ-5D-5L, the fact that data were collected in good faith directly from the MONALEESA-2 study and the requested departure from the previously accepted Lloyd utility values (representing inconsistency with previous Committee decisions) we would ask the Committee to consider our original utility values as plausible options.

Various scenarios are presented in the Table 5, below to explore the impact on the ICER of adopting different utility values. In general, adopting the original EQ-5D-5L and previously accepted Lloyd utilities the ICER is [redacted] in the order of over [redacted].

Table 5 - Utility Value Scenarios ICERs (with PAS)

	Total QALYs		Total Costs		ICER (TTD 2016)
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L & 0.774	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L & 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Cost of 3rd and Subsequent Lines of Treatment

A figure of £1,500 has been employed in the Novartis base case to reflect the cost of 3rd and subsequent lines of therapy including any administration costs. The ERG suggested that the figure of £1,140 taken from the appraisal of TA239 should be used. However as highlighted previously, this figure has been taken from data that was generated over 8 years ago, before the newer targeted therapies such as everolimus and eribulin were available. Furthermore this figure does not include the cost of radiotherapy or administration costs nor does it include further lines of therapy post 3rd line. Therefore a figure of £1,140 is likely to be too low.

The DSU discusses the treatment pathway and associated costs beyond second line, which is represented in the economic model progression health state. The two sources of evidence used by the DSU in trying to understand the treatment costs beyond second line are the poster by Kurosky et al. and data from the Systemic Anti-Cancer Therapy (SACT) chemotherapy dataset. There are a number of limitations with the approach taken by the DSU in estimating the treatment costs beyond second line.

Firstly, it appears that the DSU limits the estimated cost to third line treatments only based on the Kurosky et al poster. This approach would not result in a value reflective of the input required for the economic model and further has the potential to underestimate the true cost patients would experience. It might be expected that patients will go on to receive a number of treatments post second and third line treatments and thus, lead to increased treatment costs.

Secondly, the DSU have limited the treatments to only capecitabine, paclitaxel and eribulin, while ignoring other potential treatments that patients may receive, including everolimus + exemestane and fulvestrant, although it acknowledged that fulvestrant does not have NICE approval, there is evidence to suggest that fulvestrant is widely used in England and Wales. The DSU reference the SACT Chemotherapy Top Regimens report for palliative regimens in breast cancer, however as highlighted by the DSU this does not provide any further information as to particular indications for each treatment. It is worth noting there are an additional 265 treatment regimens recorded in SACT as palliative regimens for breast cancer, although they are not listed by name. This would further support that high costing treatments are potentially used and not being captured by the DSU. Additional evidence highlights that eribulin may account for up to 23% of third line and 19% of fourth line treatments in the UK based on CancerMpact Kantar Health.

Thirdly, there are a number of limitations associated with the Kurosky *et al.* poster. These limitations include:

- Records were obtained from physicians who were willing and available to participate in the study, resulting in a convenience sample. Therefore, generalizability of the study results may be limited

- The third line treatment population is relatively small, only 116 patients, of which only 30.2% had progressed and treatment was ongoing at the time of abstraction for n (%) = 75 (64.7%) of third line patients. Thus, time on treatment for third line therapies in the poster would underestimate the true expected length of treatment patients would likely experience

- The poster does not present any information regarding treatments patients experience post third line

In light of the available evidence, and for the reasons given, we believe that the cost of 3rd, and subsequent lines of therapy, is likely to be substantially more than £1,140. Furthermore it can be seen from Table 6 that a difference in costs of just a few hundred pounds could make the difference between being cost-effective or not. In the absence of definitive data we would ask the Committee to consider the possibility that the cost of 3rd and subsequent lines of therapy may be somewhat higher than that suggested by data that is more than 8 years old.

Various scenarios are presented in the Table 6, below to explore the impact on the ICER of adopting different costs for third and subsequent lines of treatment.

Table 6 - Third Line Plus Cost Scenarios ICERs (with PAS)

Third Line and greater costs	Total QALYs		Total Costs		ICER (TTD 2016)
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£2,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,900	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,800	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,600	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,500 base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,400	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Full or Partial Surrogacy

In the Novartis base case and in the absence of mature OS data we had assumed full surrogacy of PFS to OS in the original base case analysis. The Appraisal Consultation Document (ACD) for palbociclib [ID915] acknowledges that PFS is likely to translate into a survival benefit and that the PFS to OS relationship is "*complex and difficult to predict because of the number of further lines of treatment that the person would have, and the precise relationship is unclear*", however the level of benefit is likely to lie somewhere between the manufacturer's assumption of a 1:1 relationship and the ERG's assumption of 38.5%. Consequently we have adopted the partial surrogacy as the base case, however as shown in Table 6 below, the ICER ranges from [redacted] depending on the level of surrogacy.

Various scenarios are presented in the Table 7, below to explore the impact on the ICER of adopting different PFS to OS surrogacy levels.

Table 7 - PFS to OS Surrogacy Scenarios ICERs (with PAS)

	Total QALYs		**Total Costs**		**ICER (TTD 2016)**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Updated base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data..

Summary

The updated base case ICER of [redacted] relies on assumptions that are supported by the available evidence base, clinical expert opinion and precedents set by previous NICE decisions. Although, as with all other appraisals, there are some areas of uncertainty it can be seen from the scenarios that on balance it is likely that ribociclib is cost-effective, especially considering that when the EQ-5D-5L utilities are adopted the ICERs are [redacted] in the order of [redacted].

A full range of scenarios are provided in the Appendix including tables showing the impact of using the earlier TTD data cut from 2016, as utilised in the original base case.

Appendix

The scenario analyses presented in Table 8 show the impact of varying a number of model inputs. All ICERs presented are based on TTD 2017 data cut off.

Table 8 Scenario Analyses (with PAS and TTD 2017)

Surrogacy	PFS	TTD	Utility Values	Third Line and greater costs	Total QALYs		Total Costs		ICER
					Ribociclib	Letrozole	Ribociclib	Letrozole	
Partial	Exp	Exp	5L & 0.774	£2,000	[redacted]				
				£1,500					
				£1,140					
			5L & 0.69	£2,000					
				£1,500					
				£1,140					
			3L & 0.69	£2,000					
				£1,500*					
				£1,140					
		Wei	5L & 0.774	£2,000					
				£1,500					
				£1,140					
			5L & 0.69	£2,000					
				£1,500					
				£1,140					
			3L & 0.69	£2,000					
				£1,500					
				£1,140					
Full	Exp	Exp	5L & 0.774	£2,000					
				£1,500					
				£1,140					
			5L & 0.69	£2,000					
				£1,500					
				£1,140					
			3L & 0.69	£2,000					
				£1,500					
				£1,140					
		Wei	5L & 0.774	£2,000					
				£1,500					
				£1,140					
			5L & 0.69	£2,000					
				£1,500					
				£1,140					
			3L & 0.69	£2,000					
				£1,500					
				£1,140					

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Exp: Exponential, Wei: Weibull

The following tables present the equivalent analyses as per above when using the Time to Treatment Discontinuation 2016 data cut off.

Table 9 PFS - Scenario ICERs (with PAS and TTD 2016)

	Total QALYs		Total Costs		ICER
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole
Equivalent base case TTD 2016*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy (38.5%)					
PFS Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy					
PFS Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Table 10 - TTD Scenario ICERs (with PAS and TTD 2016)

	Total QALYs		Total Costs		ICER
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole
Equivalent base case TTD 2016*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy					
TTD Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy					
TTD Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTD Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Table 11 - Utility Value Scenarios ICERs (with PAS and TTD 2016)

	Total QALYs		Total Costs		ICER
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole
Equivalent base case TTD 2016*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-5L & 0.774	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EQ-5D-3L & 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Table 12 - Third Line Plus Cost Scenarios ICERs (with PAS and TTD 2016)

Third Line and greater costs	Total QALYs		Total Costs		ICER
	Ribociclib	Letrozole	Ribociclib	Letrozole	Ribociclib vs. letrozole

Equivalent base case TTD 2016*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£2,000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,900	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,800	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,700	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,600	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,500	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,400	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,300	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,200	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,140	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

Table 13 - PFS to OS Surrogacy Scenarios ICERs (with PAS and TTD 2016)

	Total QALYs		**Total Costs**		**ICER**
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Equivalent base case TTD 2016*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 40%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 50%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 60%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 70%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 80%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial 90%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*base case: PFS = Exponential, TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L), EQ-5D-3L for PFS2 = 0.69 (Mitra et al.), PFS to OS partial surrogacy 38.5% and most up to date 2017 TTD data.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisals

Patient access scheme submission template

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

June 2017

File name	Version	Contains confidential information	Date
		Yes	**27/10/2017**

1 Introduction

The 2014 Pharmaceutical Price Regulation Scheme (PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the PPRS (2104) is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the functions of the PPRS (2014) is to improve patients' access to medicines at prices that better reflect their value through Patient Access Schemes.

Patient Access Schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient Access Schemes propose a discount, rebate or other variation from the list price of a medicine that may be linked to the number of patients estimated to receive the medicine, the clinical response of patients to the medicine or the collection of new evidence (outcomes) relating to the medicine. Proposed schemes should aim to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Care Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the PPRS (2014).

Patient Access Schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

The PPRS recognises the need to ensure that the cumulative burden on the NHS arising from Patient Access Schemes is manageable, and notes that these schemes should be the exception rather than the rule. Simple discount Patient Access Schemes are preferred to complex schemes because they create no significant implementation burden for the NHS. Where a more complex scheme is proposed, applicants should use the complex scheme proposal template rather than this simple discount scheme template, and will need to explain and justify their choice of scheme.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If companies and sponsors want the National Institute for Health and Care Excellence (NICE) to consider a Patient Access Scheme as part of a technology appraisal, they should use this template. NICE can only consider a Patient Access Scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal'
- 'Specification for company/ of evidence' and
- Pharmaceutical Price Regulation Scheme 2014.

For further details on the technology appraisal process, please see NICE's 'Guide to the processes of technology appraisal. The 'Specification for company submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically via NICE docs: https://appraisals.nice.org.uk.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal'

If you are submitting the Patient Access Scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the Patient Access Scheme

3.1 Please give the name of the technology and the disease area to which the Patient Access Scheme applies.

Name of technology: Kisqali® (ribociclib)

The anticipated marketing authorisation: Kisqali (ribociclib) in combination with an aromatase inhibitor for the treatment of postmenopausal women with HR+/human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer as initial endocrine-based therapy.

Following a positive recommendation by NICE for ribociclib for the treatment of postmenopausal women with HR+/HER2- advanced or metastatic breast cancer as initial endocrine-based therapy, the patient access scheme (PAS) will be applied to all supplies and preparations of ribociclib and is applicable to all current and future indications.

3.2 Please outline the rationale for developing the Patient Access Scheme.

The simple discount PAS is a mechanism through which the NHS will be able to procure ribociclib at net prices lower than the current list prices. The discount result in a price that is cost-effective versus current treatment alternatives.

The proposed patient access scheme is a simple discount to the ribociclib list price. The discount will apply at the point of invoicing for ribociclib. The scheme for ribociclib will only be implemented upon publication of positive NICE guidance.

Should the list prices of ribociclib change, the percentage discount will change accordingly to maintain a fixed net price.

3.3 Please describe the type of Patient Access Scheme, as defined by the PPRS (2014). If it is a Simple Discount scheme, please include details of the list price and the proposed percentage discount/fixed price.

Financially-based scheme: simple discount to list price. The amount of discount and net price will remain commercial in confidence.

Table 1 Ribociclib list price per pack

Formulation	Pack size (# tablets)	Price per pack
200mg tablets	63	£2,950.00

200mg tablets	42	£1,966.67
200mg tablets	21	£983.33

Table 2 Ribociclib net price [redacted]

Formulation	Pack size (# tablets)	Price per pack
200mg tablets	63	[redacted]
200mg tablets	42	[redacted]
200mg tablets	21	[redacted]

3.4 Please provide specific details of the patient population to which the Patient Access Scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The scheme applies to the entire anticipated licensed population for ribociclib, namely postmenopausal women with HR+/HER2- locally advanced or metastatic breast cancer as initial endocrine-based therapy.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

Following positive NICE guidance for ribocilcib the PAS will apply to all supplies and preparations of ribociclib and is applicable to all current and future indications. No additional criteria will need to be met.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme is applicable to 100% of the population treated with ribociclib in the NHS in England and Wales.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

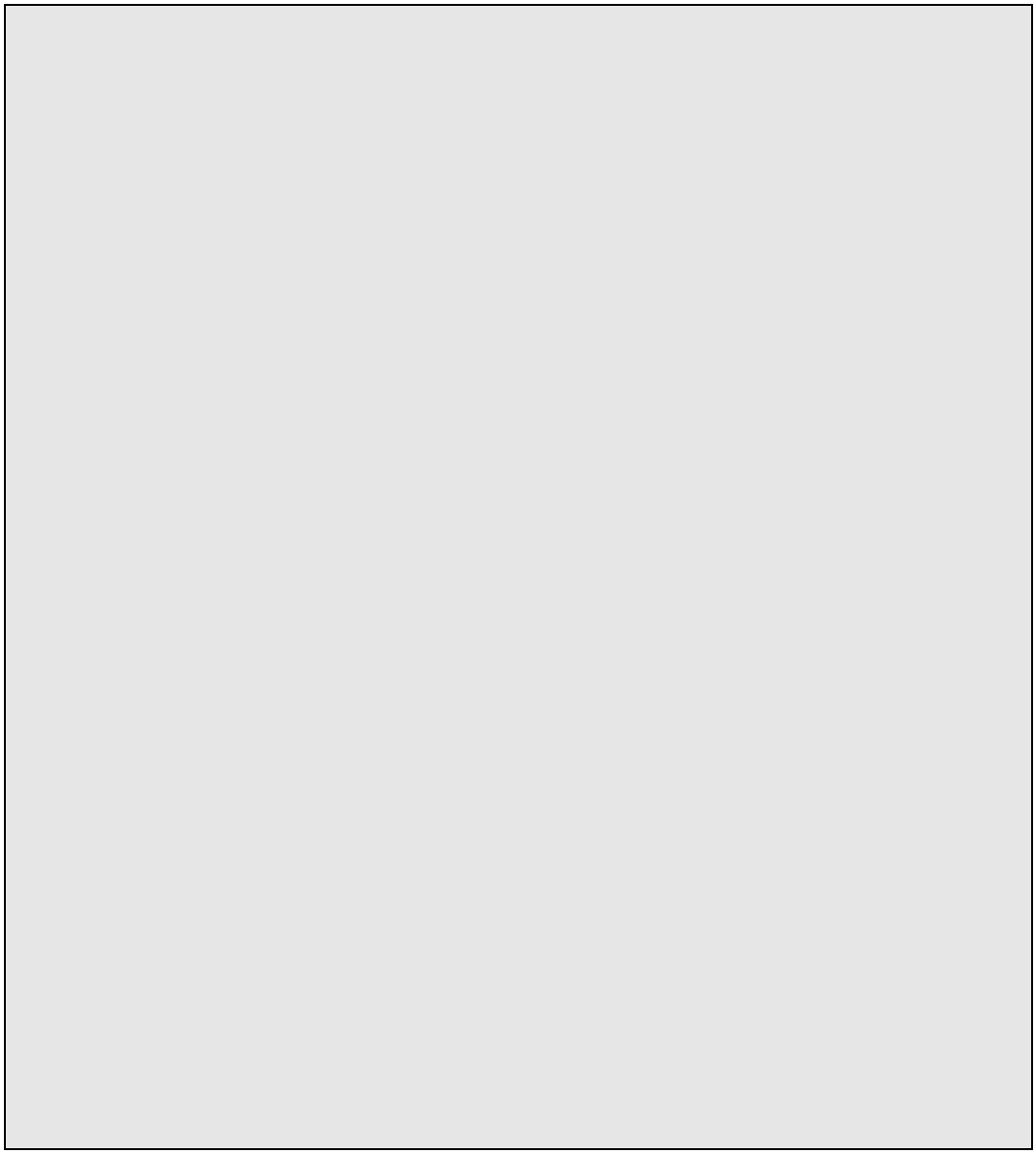
[redacted] The amount of discount and net price will remain commercial in confidence.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

There will be no need to collect any additional information.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

The scheme will not require any additional NHS resource to access the PAS net price [redacted]



3.10 Please provide details of the duration of the scheme.

Subject to positive NICE guidance for ribociclib, the proposed scheme will be in place until NICE review of the guidance, subject to the usual NICE review process.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to this scheme.

3.12 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix A.

Not applicable

4 Cost effectiveness

4.1 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main company/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for company/sponsor submission of evidence'. You should complete those sections both with and without the Patient Access Scheme. You must also complete the rest of this template.

The population to whom the scheme applies has been presented in the main submission of evidence and subsequent ERG report.

4.2 If you are submitting the Patient Access Scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

N/A – this patient access scheme is being submitted for consideration alongside the main submission and subsequent ERG report in this technology appraisal.

4.3 Please provide details of how the Patient Access Scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

In the main submission document, list prices are used for ribocilcib.

[redacted]

4.4 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the Patient Access Scheme.

A simple scheme/discount is used; only drug acqusition cost for ribociclib is changed by the patient access scheme.

The clinical effectiveness data presented in the main submission of evidence and subsequent ERG report is used in the economic model including the Patient Access Scheme.

Following receipt of the ERG report, [redacted] alongside incorporating the ERG adaptations (Table 6.1 in ERG report) and are presented in Table 3 below, to ensure cost-effectiveness.

Table 3 ERG adaptations used in the economic analysis

ERG report location	ERG adaptations incorporated	Classification of ERG adaptations
Section 5.3.1, page 110	Fixing errors	Fixing errors
Section 5.3.1, page 111	Using the results from PFS data cut-off January 2017	Fixing violations
Section 5.3.1, page 111	including the costs of wastage (i.e. unused tablets)	Fixing violations
Section 5.3.1, page 111/112	changing the modelling of the post-treatment discontinuation survival after chemotherapy	Matters of judgement

The ERG also presented two preferred amendments, which the ERG classified as 'Matters of judgement'. These amendments are as follows:

1) Post-progression (progression health state) third line or greater treatment costs. The value the ERG preferred was £1,140 per month and based upon the fulvestrant NICE appraisal (TA239) published in 2011. However, there are limitations to this value, specifically this value was derived prior to 2011 and thus fails to capture the significant change in treatments available for HR+/HER2- advanced breast cancer patients. Two treatments of note are everolimus (TA421), which has a list price of £2,673 per month and a PAS price of [redacted], and eribulin (TA423), which would cost approximately £2,202.88 per month including administration (not including PAS).

   Given the significant change of the treatment pathway in this setting, it can be considered that the 2016 inflation adjusted value of £1,140 is likely to represent the lower bound of 3rd line treatment costs. The company therefore has used the value of

£2,000 per month (as per CS) for the new base-case analysis, while also proposed an alternative value of £1,500 in the scenario analyses presented in section 4.11.

2) The ERG preferred to utilise a PFS-OS surrogacy based upon the PALOMA-1 study (gain in median OS/gain in median PFS), however it should be recognised that the PALOMA-1 study has a number of limitations, such as: the study being an open-label phase I/II RCT with a small sample size, which is not powered to show a statistical difference, the two distinct patient cohorts may mean that the PALOMA-1 population is not sufficiently similar to the MONALEESA-2 population. Although palbociclib and ribociclib are both CDK 4/6 inhibitors it does not necessarily mean that the association between PFS and OS will be the same.

   Given the complex nature of the relationship between PFS and OS in advanced breast cancer and associated uncertainty, the company has maintained the 1:1 ratio in the new base-case analysis, while incorporating the ERG's preferred ratio in the scenario analyses presented in section 4.11.

4.5 Please list any costs associated with the implementation and operation of the Patient Access Scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 5.5 of the 'Specification for manufacturer/sponsor submission of evidence'.

The proposed scheme consists of simple discounts, and therefore there will be no additional costs associated with its implementation and operation in NHS England and Wales.

4.6 Please provide details of any additional treatment-related costs incurred by implementing the Patient Access Scheme. A suggested format is presented in table 3. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Table 3 Additional treatment-related costs for the intervention both with and without the patient access scheme (PAS)

	Ribociclib without PAS		Ribociclib with PAS		Reference source
	Unit cost (£)	**Total cost e.g. per cycle, per patient (£)**	**Unit cost (£)**	**Total cost e.g. per cycle, per patient (£)**	
Treatment acquisition – PFS1 health state	£2,950* [redacted]	[redacted]	[redacted]	[redacted]	Economic model
Treatment acquisition – PFS2 health state	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Health state resource use costs (PFS1)	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Health state resource use costs (PFS2)	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Progression health state related costs	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Terminal care	[redacted]	[redacted]	[redacted]	[redacted]	Economic model
Total treatment-related costs	N/A	[redacted]	N/A	[redacted]	Economic model

Note: *Ribociclib 600mg - £2,950, ribociclib 400mg - £1,966.67, ribociclib 200mg - £983.33

** [redacted]

Treatment acquisition – PFS1 health state includes the total combination cost of ribociclib in combination with letrozole

Summary results

Base-case analysis

4.7 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

A suggested format is shown below (table 4).

The base case results for ribociclib in combination with letrozole versus letrozole monotherapy with and without the patient access scheme are presented below

Table 4 Base-case cost-effectiveness results without Patient Access Scheme

	Ribociclib in combination with letrozole	**Letrozole monotherapy**
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.89
ICER (£)	N/A	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 5 Base-case cost-effectiveness results with the Patient Access Scheme

	Ribociclib in combination with letrozole	Letrozole monotherapy
Intervention cost (£)	[redacted]	[redacted]
Other costs (£)	[redacted]	[redacted]
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.89
ICER (£)	N/A	[redacted]

4.8 Please present in separate tables the incremental results as follows. [2]

- the results for the intervention without the Patient Access Scheme
- the results for the intervention with the Patient Access Scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

The table above contains the only results, as the comparison is ribociclib in combination with letrozole versus letrozole monotherapy only and therefore no incremental analysis is required.

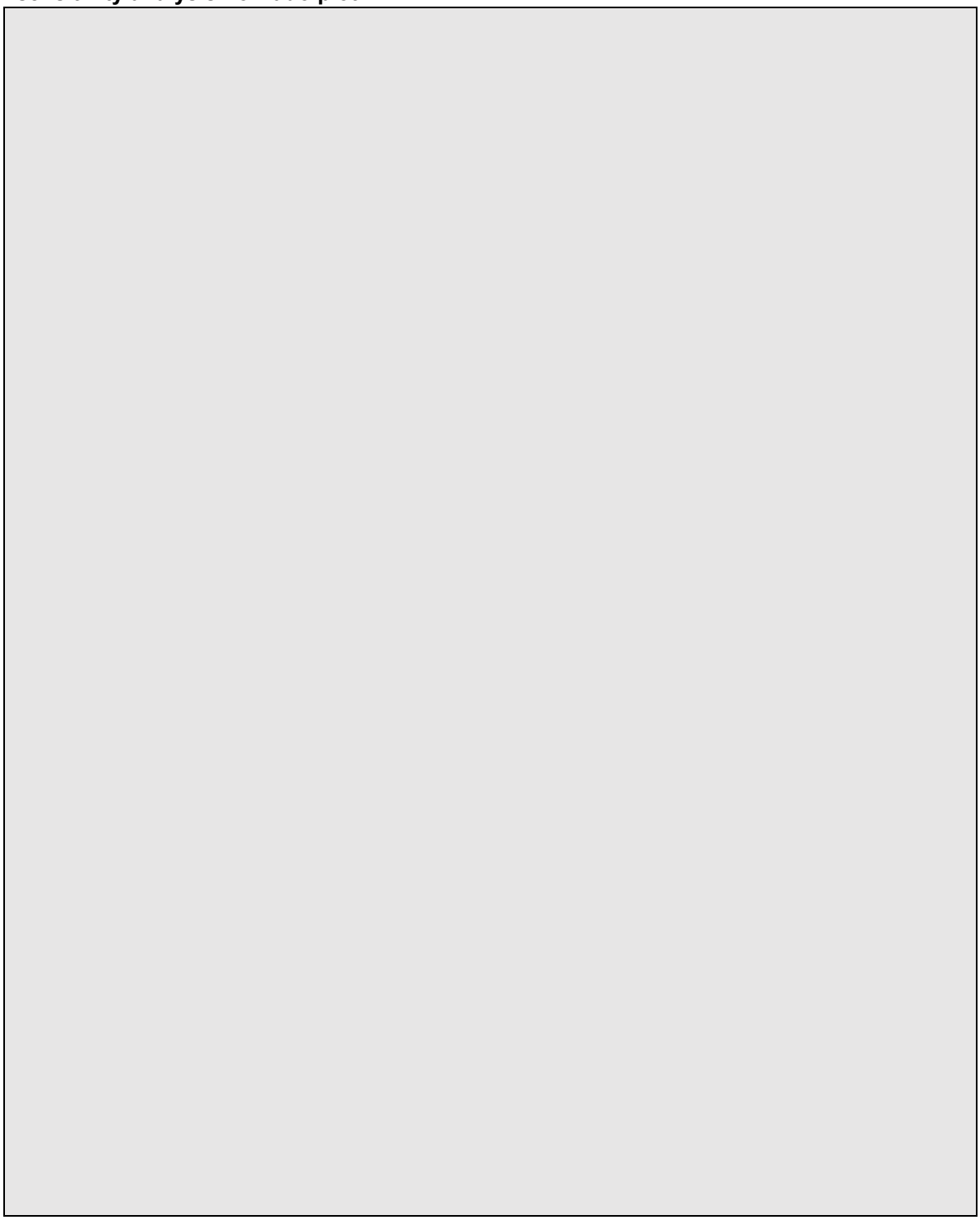
[2] For outcome-based schemes, please see section 5.2.9 in appendix B.

Sensitivity analyses

4.9 Please present deterministic sensitivity analysis results as described for the main company/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

Deterministic sensitivity analysis was conducted as described in section 5.8.2. in the main submission document. The sensitivity analysis results, including the PAS are presented in Figure 1 below:

Figure 1 Ribociclib [redacted] + letrozole versus letrozole monotherapy one-way sensitivity analysis Tornado plot



4.10 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

PSA was conducted as described in Section 5.8 in the main submission document. The mean ICER, including the PAS, is presented in Table 6.

Table 6 Mean PSA result including PAS

	Ribociclib in combination with letrozole	**Letrozole monotherapy**
Total costs (£)	[redacted]	[redacted]
Difference in total costs (£)	N/A	[redacted]
LYG	[redacted]	[redacted]
LYG difference	N/A	[redacted]
QALYs	[redacted]	[redacted]
QALY difference	N/A	0.88
ICER (£)	N/A	[redacted]

Figure 2 Cost-effectiveness plane including PAS

Figure 3 Cost-effectiveness acceptability curve including PAS

In this analysis, the probability of ribociclib's cost-effectiveness at £30,000/QALY are:

- Versus letrozole monotherapy: [redacted]

4.11 Please present scenario analysis results as described for the main company/sponsor submission of evidence for the technology appraisal.

As described in Section 5.3.1. of the ERG report, a number of scenario analyses are presented. Table 7, below, presents the results of these scenario analyses including the Patient Access Scheme.

4.12 If any of the criteria on which the Patient Access Scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the

Appraisal Committee can determine which criteria are the most appropriate to use.

A simple scheme/discount is used; no criteria or clinical variables are required.

Impact of Patient Access Scheme on ICERs

4.13 For financially based schemes, please present the results showing the impact of the Patient Access Scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the Patient Access Scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

Table 7: Revised base-case cost effectiveness analysis, incorporating ERG and company amendments with PAS

Scenarios	Ribociclib plus letrozole		Letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. PAS addendum Base-case analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 1) Base-case* and (ERG) post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 2) Base-case* and (ERG) PFS-OS ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 3) Base-case* and (company alternative**) post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 to 2) Base-case and (ERG) post-progression costs and PFS-OS ratio# **NB: Incorporates all ERG's modifications**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 2 + 3) Base-case and (company alternative**) post-progression costs and PFS-OS ratio **NB: Incorporates all of the ERG's amendments except 3rd line treatment costs**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

PAS: patient access scheme.
*New base-case analysis including ERG's adaptations as presented in section 4.4
**Company alternative post-progression cost value £1,500 as presented in section 4.4
#PFS-OS ratio incorporated based on the ERG's calculated PALOMA-1 gain in median OS/gain in median PFS

Table 8: Revised base-case cost effectiveness analysis, incorporating ERG and company amendments without PAS

Scenarios	Ribociclib plus letrozole		Letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. PAS addendum Base-case analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 1) Base-case* and (ERG) post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 + 2) Base-case* and (ERG) PFS-OS ratio	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 3) Base-case* and (company alternative **) post-progression costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(0 to 2) Base-case* and (ERG) post-progression costs and PFS-OS ratio# **NB: Incorporates all ERG's modifications**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(0 + 2 + 3) Base-case* and (company alternative **) post-progression costs and PFS-OS ratio **NB: Incorporates all of the ERG's amendments except 3rd line treatment costs**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

PAS: patient access scheme.
*New base-case analysis including ERG's adaptations as presented in section 4.4
**Company alternative post-progression cost value £1,500 as presented in section 4.4
#PFS-OS ratio incorporated based on the ERG's calculated PALOMA-1 gain in median OS/gain in median PFS

5 Appendix A: Details for outcome-based schemes only

5.1 If you are submitting an outcome based scheme which is expected to result in a price increase, please provide the following information:

- the current price of the intervention
- the proposed higher price of the intervention, which will be supported by the collection of new evidence
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.2 If you are submitting an outcome based scheme which is expected to result in a price reduction or rebate, please provide the following details:

- the current price of the intervention (the price that will be supported by the collection of new evidence)
- the planned lower price of the intervention in the event that the additional evidence does not support the current price
- a suggested date for when NICE should consider the additional evidence.

Not applicable

5.3 Provide the full details of the new information (evidence) planned to be collected, who will collect it and who will carry the cost associated with this planned data collection. Details of the new information (evidence) may include:

- design of the new study
- patient population of the new study

- outcomes of the new study
- expected duration of data collection
- planned statistical analysis, definition of study groups and reporting (including uncertainty)
- expected results of the new study
- planned evidence synthesis/pooling of data (if applicable)
- expected results of the evidence synthesis/pooling of data (if applicable).

Not applicable

5.4 Please specify the period between the time points when the additional evidence will be considered.

Not applicable

5.5 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered.

Not applicable

5.6 Please provide the other data used in the economic modelling of the scheme at the different time points when the additional evidence is to be considered. These data could include cost/resource use, health-related quality of life and utilities.

Not applicable

5.7 Please present the cost-effectiveness results as follows.

- For a scheme that is expected to result in a price increase, please summarise in separate tables:
  - the results based on current evidence and current price
  - the anticipated results based on the expected new evidence and the proposed higher price.
- For a scheme that is expected to result in a price reduction or rebate, please summarise in separate tables:

- the results based on the expected new evidence and the current price (which will be supported by the additional evidence collection)
- the results based on the current evidence and the lower price (if the new evidence is not forthcoming).

A suggested format is shown in table 3, section 4.7.

5.8 Please present in separate tables the incremental results for the different scenarios as described above in section 5.2 for the type of outcome-based scheme being submitted.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4, section 4.8.

Not applicable

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Single technology appraisal

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

Dear Adam,

The Evidence Review Group, Kleijnen Systematic Reviews, and the technical team at NICE have looked at the submission received on 23 March 2017 from Novartis. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **2pm** on **Friday 5 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals https://appraisals.nice.org.uk/request/27560

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as [redacted] in turquoise, and all information submitted as [redacted] in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact XXXXXXX XXXXXXXX, Technical Lead XXXXXXXXXXXXXXXXXXX . Any procedural questions should be addressed to the Project Team (TACommA@nice.org.uk)

Yours sincerely

Joanna Richardson

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Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question**: a. Please could the company provide evidence that letrozole and anastrazole are equally effective as comparators for this population; i.e. is it possible that anastrazole is more effective than letrozole and that a comparison of ribociclib plus letrozole versus anastrazole would have resulted in less favourable results for ribociclib?

b. If the company cannot demonstrate equivalence, then all comparators should be included. Therefore, the ERG would request a comparison of aromatase inhibitors, including a review of all trials that make this comparison.

c. Please provide the correct reference for the following study mentioned on page 31 of CS and remove the confidential marking as appropriate:

> *Similar results from aromatase inhibitors in HR+ advanced breast cancer have been shown in different clinical studies. Efficacy of anastrozole and letrozole was compared in a phase IIIb/IV study in first-line or second-line therapy for advanced breast cancer (patients who had progressed on first-line antiestrogen or were clinically resistant to adjuvant tamoxifen). The primary end point, time to progression (TTP), was 5.7 months in both arm and the overall response rate (ORR) was was significantly higher in the letrozole arm (19.1% vs. 12.3%; p=0.013).* [57]

A2. **Priority question**: Please provide the full CSR for the MONALEESA-2 trial (including chapters 14, etc. with tables, figures, patient listings and statistical analysis plan).

A3. **Priority question**: a. The cut-off date for the interim analysis of MONALEESA-2 is 29 January 2016. Are there any more up to date data available? This would be particularly helpful as overall survival data were not mature at the time of interim analysis. The CS notes that 3 further analyses of OS are planned. Have sufficient events occurred to enable analysis? Please could the company provide any more up-to-date survival data? If not, when do the company anticipate that these data will be available? Please provide both centrally (BICR) and locally assessed results.

b. According to a FDA review document[3] of ribociclib, "In a 90-day safety update provided to FDA, the Applicant provided updated efficacy data on PFS and OS with a data cut-off date of June 22, 2016. An additional PFS analysis was conducted at the second interim analysis of OS, with a data cut-off date of January 2, 2017." Please provide all available data from June 2016 and from the second interim analysis in January 2017. Please provide both centrally (BICR) and locally assessed results.

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A4. Please provide information about the number of patients from England and Wales in each arm of the MONALEESA-2 trial, and results for these patients only.

A5. Please could the company comment on how well the patient characteristics in the MONALEESA-2 trial reflect the population to be treated in England and Wales?

A6. Please could the company provide further breakdown of the number of participants in each age decade in MONALEESA-2, i.e. 20 to 29, 30 to 39, 40 to 49, 50 to 59 etc? What were the relative proportions of patients with a surgical menopause and a natural menopause?

A7. In Table 13 at various time points in the MONALEESA-2 trial the centrally ascertained progression-free survival and the locally assessed progression-free survival seem quite different. As both types of assessor conducted a blinded assessment, what do you consider accounts for the differences in the results?

A8. The company states that results for central assessment in the MONALEESA-2 study were generally in good agreement with local evaluation (p. 52 CS). However, [redacted]. Please could the company please provide the Kaplan-Meier plot of PFS according to central assessment?

A9. **Priority question**: Subgroup analyses (progression-free survival):

a. For the MONALEESA-2 trial, please provide the median progression-free survival (and 95% confidence intervals) in each treatment arm and hazard ratio (and 95% confidence intervals) between arms for:

i. Patients with de novo disease.

ii. Patients who have received previous adjuvant/neoadjuvant therapy.

A10. Is the company aware of any trials of ribociclib that were excluded or missed; e.g. due to being published before the search start date of 2007 or not being published in English? Please explain why the clinical effectiveness searches have not been updated since June 6, 2016.

A11. Please could the company provide a list of excluded studies with bibliographic details and reasons for exclusion?

A12. **Priority question**: a. How were the non-randomised trials selected for inclusion in the submission as the search strategy for the review of clinical effectiveness was restricted to RCTs only? Is there other non-randomised evidence that might provide relevant information for the submission particularly in terms of adverse events?

b. Please clarify why searches were not conducted for non-randomised and non-controlled evidence (non-RCTs) including searches for searches for indirect and

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mixed treatment comparisons (MTC). Also please explain why searches for adverse reactions (AEs) were not conducted. If separate searches for non-RCTs/AE/MTC were conducted, please report full search methods and provide full search strategies for each resource searched.

A13. The references for two of the non-randomised studies listed in Table 15 (CLEE011X2107 and CLEE011X2108) are to poster presentations. Are any fuller publications available?

A14. Please could the company confirm that no relevant interim data are available from any of the three ongoing trials listed in Table 20 (MONALEESA-3, MONALEESA-7 and COMPLEEMENT-1)?

A15. The FDA recommended two trials as a post-marketing requirement. One of these was to 'assess the efficacy and safety of an alternative dosing regimen after evaluation of ECG, PK and efficacy data from on-going MONALEESA-3 and MONALEESA-7 studies'. This was to mitigate the risks for QT prolongation without compromising efficacy. The second was to complete an on-going pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment. However these trials do not appear to be listed under ongoing studies. Please could the company provide information on these trials and their current status?

A16. Please could the company clarify how many reviewers were involved in the selection of studies, data extraction and quality assessment for the review of clinical effectiveness. How were discrepancies resolved?

A17. According to the CS (CS, Table 7, page 39) included studies should have "Ribociclib as monotherapy or as part of a combination therapy". Does this mean all studies comparing different types of comparators (such as letrozole versus anastrazole) were excluded?

A18. According to the CS, QoL was not a relevant outcome (CS, Table 7, page 39). Were any studies excluded that had QoL as an outcome, but not any other relevant outcome? If so, please provide the reference and the pdf.

A19. Please provide a table comparing the baseline characteristics of LEA, PALOMA-2, ALLIANCE and MONALEESA-2 trials. The company uses the results from these studies to assess the plausibility of their long-term extrapolation of PFS and OS (of the letrozole arm). We would like to see if the baseline characteristics of the patients within these trials are comparable.

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Section B: Clarification on cost-effectiveness data

Literature review on cost effectiveness

B1. Please provide the rationale for limiting the cost-effectiveness search to English language, to 2000-2016, and why it have not been updated since August 5, 2016?

B2. Please explain why TA 263 (bevacizumab in combination with capecitabine), TA 214 (bevacizumab in combination with a taxane) and TA 116 (gemcitabine) were not included as relevant STAs in section 5.1.3, even though they were mentioned in the NICE scope.

B3. In section 5.1.3, the choice of the technology appraisals that were discussed in detail for comparing model structure and simulation (e.g. Table 24 for TA 239 and TA 295, respectively), cost and resource utilization (e.g. Table 25 and 26 for TA 239 and TA 421, respectively) and valuation of health benefits (e.g. Table 27 for TA 239 and TA 421, respectively) seemed to be arbitrary. Please provide tables comparing values/assumptions from all relevant appraisals, including ID915 (Palbociclib), as well.

Model structure

B4. **Priority request:** Please incorporate the anastrazole monotherapy as a comparator in the economic model, in case the equivalence between two comparators could not be demonstrated in question A1.

B5. Please provide the number of progressed patients who did not receive any further active treatments after 1st line and immediately received best supportive care in the MONALEESA-2 trial or any other relevant sources (e.g. another clinical trial for first line breast cancer treatment in the same population or patient registries). Based on the findings, update the model in such a way that a proportion of patients might move to the "progression" state without receiving 2nd line treatment.

B6. **Priority request:** Please provide all details of the communication between the company and the clinical experts. The details include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or TC, list of expert recommendations and justifications for clinical assumptions used in the model (e.g. the distribution of 2nd line treatments and difference between ribociclib and placebo arms in terms of treatments received in the 2nd line), etc.

B7. Please add a scenario analysis in which the percentage of 2nd line treatments received in the model was based on the treatments received in MONALEESA-2 study after progression.

B8. **Priority request:** Please provide a more detailed, clear and transparent explanation of each function in each VBA macro module (compared to the existing comment lines).

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Please provide a figure that explains the overview code structure of the economic model, explaining the role of each function.

Treatment effect in cost effectiveness model

B9. **Priority request:** The current OS surrogacy approaches assume that the gain in PFS is 100% translated into OS gain in the base case (in some scenarios only if PFS/TTP is above a threshold)

a. Some studies have indicated that duration of PFS gain will translate into an OS gain that is shorter, especially in HER2-negative patients.[4-6] In light of this, please justify the model assumption that any PFS gain translates 100% into an OS gain. Was this assumption checked with clinical experts?

b. Add a scenario where the gain of PFS is translated into OS with a factor less than 1 (e.g. using the proportion of median OS gain to median PFS gain from BOLERO-2 or another relevant trial)

B10. Please provide average patient characteristics (age, time from diagnosis etc.) from the economic model after patients progress from first line treatment under both ribociclib and placebo arms.

B11. **Priority request:** Please confirm that all the PFS, OS and TTD parametric extrapolations conducted in the economic model were based on the ITT patient level data from MONALEESA-2 and BOLERO-2 trials. Otherwise, please update the economic model and its results, in which all PFS extrapolations were based on ITT data in all the scenarios.

B12. **Priority request:**

a. Please incorporate the scenario analyses to the economic model, where the MONALEESA-2 PFS extrapolations were based on central assessment review PFS data instead of local assessment review PFS data, in line with the Kaplan Meier plots provided in question A8.

b. Please incorporate the scenario analyses to the economic model where the PFS extrapolations were based on the PFS data from the most recent data cut-off point and based on central assessment review, in line with question A3.

B13. In the model, after progression, the same treatment effectiveness was assumed for everolimus in the second line no matter which treatment was received in the first line (i.e. ribociclib or placebo as an add-on to letrozole). Please justify the plausibility of this assumption from clinical trial, literature and experts' opinion.

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B14. The log-cumulative hazard plots provided in Figure 24 [redacted]. It seems there is [redacted]. Please provide a piecewise model for PFS of ribociclib and placebo arms, in line with the NICE DSU recommendations provided in Figure 22. Please incorporate this flexible piecewise model into the cost effectiveness model, as well.

Costs

B15. If choosing the Gompertz distribution for the time to treatment discontinuation in the first-line, the health economic model in Excel gives an error when computing 5,000 patients. Please confirm this error and repair this option.

B16. In the model, 3rd line therapies are not explicitly modelled and a separate cost is added in the base case in the progressed disease health state to reflect the drug acquisition for subsequent lines of therapies. Please provide a table with the details of these costs (i.e. assumptions regarding the type of treatments provided, treatment duration, drug costs per treatment (including administration costs), type of adverse events per treatment (including costs). Please also provide sources for each of these values.

Utility

B17. Since the adverse events seem not to occur constantly over time, the health-related quality of life measurements in the MONALEESA-2 might have missed the temporary disutility impact of adverse events. In the trial, patients in the ribociclib arm seem to have more adverse events compared to the placebo arm, and incorporating only the cost implications of adverse events might create a bias. Please incorporate the disutilities due to adverse events for both treatment arms, using disutility results from the published literature/ previous appraisals.

B18. In the company submission, it is stated that the health state utility value for PFS in the second-line is taken directly from the EQ-5D estimated from BOLERO-2, which was used in the previous submission for everolimus + exemestane (TA421).

a. Please provide the details on how this utility value for PFS2 state is derived (e.g. was it generated from a disease specific instrument and mapped or was it derived from EQ-5D questionnaire? When were the questionnaires filled in, by whom? Etc…)

b. Please justify why the mean utility value in Table 38 for progressive disease health state ([redacted]) was not used for the PFS2 state, but the utility value estimated from BOLERO-2 trial was used instead.

B19. In the company submission, it is stated that, for simplicity, the same utility value was assumed for everolimus + exemestane and for exemestane monotherapy

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used in the second line. Please provide utility values separately for each treatment arm.

B20. Please clarify why the health-related quality-of-life studies (5.4.3) searches have not been updated since August 5, 2016 (except the NICE website search [March 2017]).

B21. Please provide details of the search date and search terms used for the NICE website search. In the PRISMA flowchart there is a box "Bibliographic searching: 3 publications": please clarify what 'bibliographic searching' is.

B22. Please clarify how resource identification, measurement and valuation studies were identified. Section 5.5.1 states that details of the searches are described in 'section 0'. It is not clear if resource use data were identified through the health-related quality-of-life studies searches, the cost-effectiveness searches, or elsewhere.

Other – Validation

B23. The total QALYs estimate for letrozole monotherapy with the company's model ([redacted]) is [redacted] than the estimate from ID915 (1.77). The company argues this is due to the modelling differences. Please run the model with the clinical effectiveness inputs and baseline characteristics identical to those from ID915 and report the total QALYs and total LYs under letrozole monotherapy.

B24. In Section 5.3.1 from the company submission, it is stated that the company conducted internal and external validation efforts. Please provide more details on these efforts, including the details of the quality control check of the model (list of questions in the quality control check, number of people involved and their roles in the quality control check, and the results), results of the internal validation efforts on costs, health state utilisation and utility inputs, and detailed minutes of the external validation meetings with clinical and health economic experts.

Section C: Textual clarifications and additional points

C1. An incorrect reference is cited in the main CS. (Ferlay J. Int J Cancer 2015;136:E359-86).[2] Please could the company provide the correct reference.

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References:

[1] Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med* 2007;131(1):18-43.

[2] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136(5):E359-86.

[3] US Food and Drug Administration. *KISQALI (ribociclib) tablets. NDA 209092. Multi-discipline review/summary, clinical, non-clinical [Internet]*: US Food and Drug Administration, 2016 [accessed 4.4.17] Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/209092Orig1s000MultidisciplineR.pdf

[4] Petrelli F, Barni S. Surrogate endpoints in metastatic breast cancer treated with targeted therapies: an analysis of the first-line phase III trials. *Med Oncol* 2014;31(1):776.

[5] Michiels S, Pugliano L, Marguet S, Grun D, Barinoff J, Cameron D, et al. Progression-free survival as surrogate end point for overall survival in clinical trials of HER2-targeted agents in HER2-positive metastatic breast cancer. *Ann Oncol* 2016;27 (6):1029-1034.

[6] Liu L, Chen F, Zhao J, Yu H. Correlation between overall survival and other endpoints in metastatic breast cancer with second- or third-line chemotherapy: Literature-based analysis of 24 randomized trials. *Bull Cancer* 2016 103(4):336-44.

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5th May 2017

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Dear Joanna,

Thank you for the opportunity to respond to the clarification questions posed by the Evidence Review Group, Kleijnen Systematic Reviews Ltd, regarding the Novartis submission for Kisqali® (ribociclib) [ID1026]. Please find below responses to the clarification questions which I hope will be helpful. In summary Novartis has provided a response to all 44 questions posed, however Novartis would like to highlight the following:

- Novartis has agreed to provide the full CSR as requested by the ERG, however this is shared under condition that this is in a controlled environment and the CSR is treated as commercial in confidence. Novartis requests that should NICE or the ERG wish to perform additional exploratory analysis, they request permission from Novartis

- Novartis has provided communication with clinical experts for the validation, however these are shared under the condition they remain commercial in confidence. Should the ERG and/or NICE wish to discuss or present this information outside of agreement for commercial in confidence a request will need to be made to Novartis

- Novartis would like further clarification from the ERG regarding question C1 as it is unclear why the ERG considerers the cited reference incorrect

If you require any further information, please let me know,

Kind regards,

Adam Lee
Health Economics & Outcomes Research Manager
Novartis Oncology UK Ltd.

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question**: a. Please could the company provide evidence that letrozole and anastrazole are equally effective as comparators for this population; i.e. is it possible that anastrazole is more effective than letrozole and that a comparison of ribociclib plus letrozole versus anastrazole would have resulted in less favourable results for ribociclib?

There have been no substantive head to head randomised controlled studies of letrozole compared with anastrozole (third generation aromatase inhibitors) for the first line treatment of patients with HR+, HER2 –ve advanced breast cancer.

There has been one phase IIIb/IV study which directly compared the clinical outcomes of letrozole and anastrozole in postmenopausal women with advanced breast cancer. [11] The study showed no significant difference in time to progression, time to treatment failure or overall survival between the two drugs. It should be noted that this study was performed in patients who had all received prior anti-oestrogen therapy and that 51% of the population had unknown hormone receptor status, so it is not entirely reflective of the situation for this appraisal.

The evidence review performed for NICE Clinical Guideline [CG81] [7], considered the available evidence for the hormonal treatments used to treat metastatic breast cancer. This review was performed in 2009 and gathered an evidence base which included a guideline, five systematic reviews, five RCTs and a pooled analysis of RCT data. The majority of the evidence involved the use of aromatase inhibitors. When the focus was refined to the third generation aromatase inhibitors, the available evidence did not show a significant difference in time to progression, progression free survival or overall survival between the third generation aromatase inhibitos.

This is presumably why NICE clinical guideline [CG81] makes no distinction between aromatase inhibitors for the first line treatment of HR+/HER2- advanced breast cancer patients, and simply refers to Aromatase inhibitors. [8]

From CG81:
“Recommendations

- Offer an aromatase inhibitor (either non-steroidal or steroidal) to:
    - postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
    - postmenopausal women with ER-positive breast cancer previously treated with tamoxifen.

Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival)." [8]

It should also be noted that in the NICE appraisal of Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915], a comparison with letrozole alone was considered appropriate. [9]

b. If the company cannot demonstrate equivalence, then all comparators should be included. Therefore, the ERG would request a comparison of aromatase inhibitors, including a review of all trials that make this comparison.

Justification for equivalent efficacy between aromatase inhibitors is provided in the response to question A1 part a. It is felt that this justification supports the comparison of ribociclib + letrozole with letrozole monotherapy as the most relevant comparison and there is no requirement to include further treatment comparisons.

c. Please provide the correct reference for the following study mentioned on page 31 of CS and remove the confidential marking as appropriate:

> *Similar results from aromatase inhibitors in HR+ advanced breast cancer have been shown in different clinical studies. Efficacy of anastrozole and letrozole was compared in a phase IIIb/IV study in first-line or second-line therapy for advanced breast cancer (patients who had progressed on first-line antiestrogen or were clinically resistant to adjuvant tamoxifen). The primary end point, time to progression (TTP), was 5.7 months in both arm and the overall response rate (ORR) was was significantly higher in the letrozole arm (19.1% vs. 12.3%; p=0.013).* [57]

The above statement comes directly from an ESMO publication: *Review of hormone-based treatments in postmenopausal patients with advanced breast cancer focusing on aromatase inhibitors and fulvestrant.[10]*

The correct reference in the CS is reference number 47 (as shown below) and has been updated.

The reference for the original study is provided here:

[11] Rose C, Vtoraya O, Pluzanska A, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer Comparison of the aromatase inhibitors letrozole and anastrozole. Eur J Cancer 2003;39:2318–27.

A2. **Priority question**: Please provide the full CSR for the MONALEESA-2 trial (including chapters 14, etc. with tables, figures, patient listings and statistical analysis plan).

The full CSR, as requested, is provided commercial in confidence as an attachment to this response titles "[redacted]"

A3. **Priority question**: a. The cut-off date for the interim analysis of MONALEESA-2 is 29 January 2016. Are there any more up to date data available? This would be particularly helpful as overall survival data were not mature at the time of interim analysis. The CS notes that 3 further analyses of OS are planned. Have sufficient events occurred to enable analysis? Please could the company provide any more up-to-date survival data? If not, when do the company anticipate that these data will be available? Please provide both centrally (BICR) and locally assessed results.

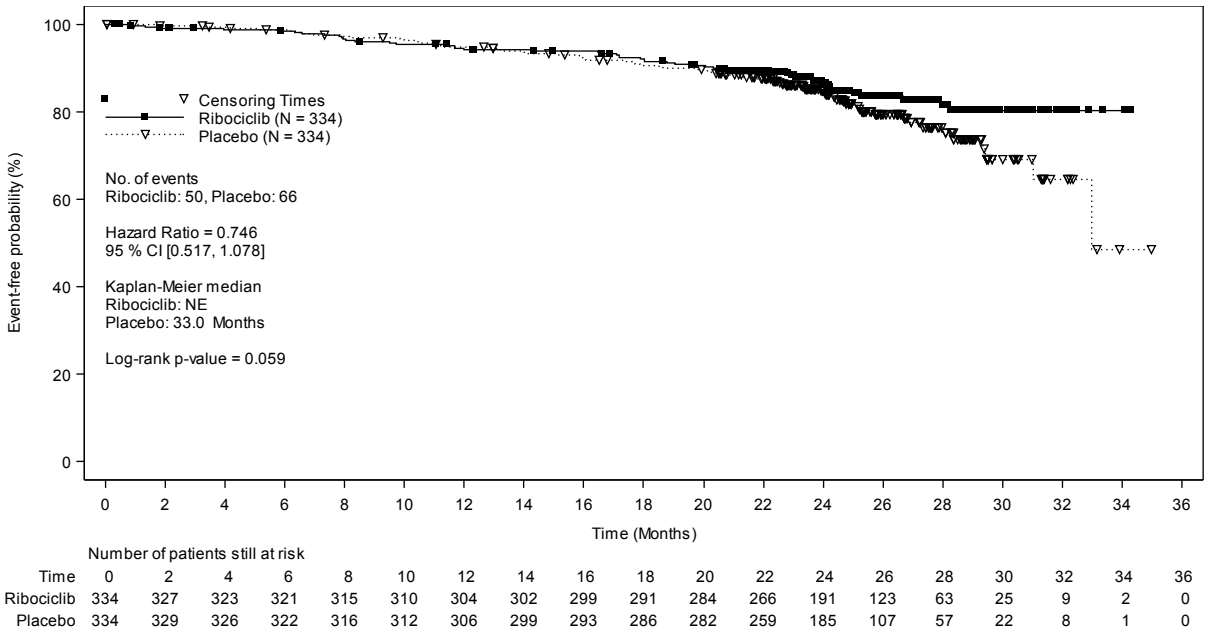
The CS was based upon the primary analysis of MONALEESA-2 in January 2016. Subsequently two additional analyses have been performed, please see further explanation below:

- An additional 90-day safety analysis update, as per a request from the FDA with a data cut-off of June 22, 2016. This analysis provides an updated data of PFS for the primary efficacy assessment, local assessment and supportive central (BICR) assessment. This data is provided in commercial in confidence as an attachment to this response, titled "[redacted]"

- A second interim OS analysis with a data cut off of January 2, 2017. This analysis provides updated data for OS (second interim analysis) and PFS for the primary efficacy assessment, local assessment. This data is provided in commercial in confidence as an attachment to this response, titled "[redacted]"

At the point of the second OS interim analysis, a total number of 116 deaths [redacted] had occurred and the estimated hazard ratio (and the associated 95% C.I.) are 0.746 (0.517, 1.078), representing an estimated 25.4% risk reduction in the ribociclib arm compared to the placebo arm. The results did not exceed the O'brien-Fleming stopping boundary criteria for this interim analysis (one-sided p=0.059 vs. the 3.15×10-5 threshold to claim significance). The OS data remain immature at the second interim analysis. Although the median OS duration (95% C.I.) was not reached for the ribociclib arm and the median OS duration (95% C.I.) was 33.0 months (33.0, NE) for the placebo arm. The median OS for the placebo arm should be interpreted with caution, as it was primarily driven by a single death. The second interim analysis OS K-M curve is presented in Figure 1.

Figure 1 Kaplan-Meier plot of OS (Full Analysis Set) data cut-off January 2017



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
Ribociclib	334	327	323	321	315	310	304	302	299	291	284	266	191	123	63	25	9	2	0
Placebo	334	329	326	322	316	312	306	299	293	286	282	259	185	107	57	22	8	1	0

b. According to a FDA review document[3] of ribociclib, "In a 90-day safety update provided to FDA, the Applicant provided updated efficacy data on PFS and OS with a data cut-off date of June 22, 2016. An additional PFS analysis was conducted at the second interim analysis of OS, with a data cut-off date of January 2, 2017." Please provide all available data from June 2016 and from the second interim analysis in January 2017. Please provide both centrally (BICR) and locally assessed results.

The information requested has been provided within the response to question A3 part a.

A4. Please provide information about the number of patients from England and Wales in each arm of the MONALEESA-2 trial, and results for these patients only.

There were a total of [redacted] across the UK included in MONALEESA-2 study: [redacted]

In the MONALEESA-2 study a total [redacted] were recruited in the study. The [redacted] MONALEESA-2 study were assigned to [redacted] and at the latest data cut-off [redacted]

Further information on patient enrolment by country is provided in the full Interim CSR [redacted]

A5. Please could the company comment on how well the patient characteristics in the MONALEESA-2 trial reflect the population to be treated in England and Wales?

Advisory Boards were conducted in the UK in 2016 and 2017 in order to [redacted]

Clinical experts considered that the patients enrolled in MONALEESA-2 are in general representative of the aBC population in England and Wales. [redacted].

[redacted]

[redacted]

[redacted]

As per the ERGs request in question B6, reports from the Advisory Boards have been provided in confidence to NICE with the identity of the advisors involved anonymised.

Attachments

[redacted]

A6. Please could the company provide further breakdown of the number of participants in each age decade in MONALEESA-2, i.e. 20 to 29, 30 to 39, 40 to 49, 50 to 59 etc? What were the relative proportions of patients with a surgical menopause and a natural menopause?

Age group

[redacted]

Surgical vs natural menopause

[redacted]

Source: [redacted]

A7. In Table 13 [redacted] the MONALEESA-2 trial the centrally ascertained progression-free survival and the locally assessed progression-free survival [redacted]. As both types of assessor conducted a blinded assessment, [redacted]?

In clinical practice PFS is a combined end point that may include symptomatic progression (eg. pain due to bone metastasis) in addition to radiologic progression. Symptomatic deterioration may be a reason to discontinue or alter therapy. Blinded independent central review (BICR) of progression in randomised clinical trials has been advocated to control bias; however it may introduce bias because censoring unconfirmed locally determined progressions. Therefore, BIRC should probably be used as an audit tool to confirm the results of the local assessment. [12-14]

In MONALEESA-2 the primary efficacy endpoint was based on radiological assessment (RECIST v1.1) of disease progression by local investigators and central review (BIRC) was conducted as supportive assessment.

[redacted]

[redacted]

As discussed in the CS (page 52), the hazard ratios between local and central assessments were quite similar showing overall robustness of the treatment effect through both local and central radiology assessments. [redacted]

[redacted]

A8. The company states that results for central assessment in the MONALEESA-2 study were generally in good agreement with local evaluation (p. 52 CS). However, [redacted]. Please could the company please provide the Kaplan-Meier plot of PFS according to central assessment?

The Kaplan-Meier plot for PFS according to central assessment from the primary analysis (data cut off: January 2016) is shown in Figure 2. [redacted]

Figure 2 Kaplan-Meier plot of PFS based on central BIRC review (Full analysis set) data cut-off January 2016

The results and Kaplan-Meier plot for PFS according to central assessment from the additional 90-day safety analysis update (data cut off: June 2016) are shown in Table 1 and Figure 3.

[redacted]

Table 1 Analysis of PFS per BIRC's assessment (Full Analysis Set) data cut-off June 2016

Category	Ribociclib+ letrozole N=334	Placebo + letrozole N=334
[redacted]		

Figure 3 Kaplan-Meier plot of PFS based on BIRC's assessment (Full Analysis Set) data cut-off June 2016

A9. **Priority question**: Subgroup analyses (progression-free survival):

a. For the MONALEESA-2 trial, please provide the median progression-free survival (and 95% confidence intervals) in each treatment arm and hazard ratio (and 95% confidence intervals) between arms for:

i. Patients with de novo disease.

ii. Patients who have received previous adjuvant/neoadjuvant therapy.

Median PFS and hazard ratio (and 95% confidence intervals) by treatment arm and stratified by prior neo/adjuvant treatment and de novo are presented in Table 2 and shown in [redacted]. These figures are presented in the MONALEESA-2 publication (Hortobagyi G et al N Engl J Med 2016 375 (18) 1738-48).

Table 2 Subgroup analyses (progression-free survival) data cut-off January 2016

[redacted]

A10. Is the company aware of any trials of ribociclib that were excluded or missed; e.g. due to being published before the search start date of 2007 or not being published in English? Please explain why the clinical effectiveness searches have not been updated since June 6, 2016.

There were no trials of ribociclib published before 2007 or published in languages other than English. On Pubmed, the earliest publication of ribociclib or LEE011 was in 2013.

According to the Cochrane Handbook for Systematic Reviews of Interventions, the potential impact of studies published in languages other than English in a meta-analysis may be minimal because of the shift towards publication of studies in English [15]. This is further supported by a comprehensive study by Morrison et al., which found no evidence of a systematic bias from the use of language restrictions in systematic review-based meta-analyses in conventional medicine [16]. Further, the handbook states that review authors may want to search without language restrictions but if they do so then decisions about including reports from languages other than English may need to be taken on a case-by-case basis. Finally, systematic literature reviews for clinical and cost-effectiveness evidence that have been performed for previous NICE appraisals have frequently excluded non-English language publications from their search terms of eligibility criteria. As such, given that clinical and cost-effectiveness evidence had been identified by the searches when restricting to the English language, a pragmatic decision to not expand the search to non-English language articles was made. A search of PubMed for ribociclib NOT English[language] on 4th May 2017 found only 2 publications not

in English, neither of which were RCTs, so we are confident that no relevant studies have been excluded or missed in this review due to not being published in English.

In response to the clarification for why the clinical effectiveness searches have not been updated since June 6th 2016, an update to the clinical systematic literature review has since been performed. This update adhered to the same methodology (where possible, owing to time constraints) as described for the original search of clinical effectiveness studies in Section 4.1 of our submission.

Searches were conducted in MEDLINE, MEDLINE In-Process and Embase simultaneously using Ovid SP, using the same search terms as the original review. CDSR, CENTRAL and DARE were searched simultaneously via the Cochrane Library Wiley Online platform. Access to CDSR, CENTRAL and DARE databases via Ovid SP was not available for the update review; as such, the search terms from the original review were translated as appropriate for use in the Cochrane Library Wiley Online platform (see Table 3).

Table 3 Search terms for CDSR, CENTRAL and DARE (searched simultaneously via the Cochrane Library Wiley Online platform, 3rd May 2017)

No.	Search String	Hits
#1	[mh "breast neoplasms"] or [mh "breast cancer"]	10162
#2	(breast* near/3 (cancer* or neoplas* or oncolog* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or sarcoma*)):ti,ab	22004
#3	(mammar* near/3 (cancer* or neoplas* or oncolog* or tumor* or tumour* or malignanc* or carcinoma* or adenocarcinoma* or sarcoma*)):ti,ab	181
#4	(metasta* or advance* or second* or recurren* or inoperab* or disseminat* or incur*):ti,ab,kw	203266
#5	(1 or 2 or 3) and 4	11247
#6	exp Breast/ and exp Neoplasm Metastasis/	17
#7	(breast* near/3 (metasta* or advance* or second* or recurren* or inoperab* or disseminat* or incur*)):ti,ab	6418
#8	(mammar* near/3 (metasta* or advance* or second* or recurren* or inoperab* or disseminat* or incur*)):ti,ab	48
#9	(breast* or mammar*):ti,ab,kw	31657
#10	((stage or grade or type) near/2 ("3" or III or "c" or "4" or "IV" or d)):ti,ab	21884
#11	(N1 or N2* or N3* or pN1* or pN2* or pN3*):ti,ab,kw	3342
#12	#9 and (#10 or #11)	2063
#13	{or #5-#8,#12}	12075
#14	(letrozole or Femara or "CGS 20267" or "CGS-20267" or "112809-51-5"):ti,ab,kw	985
#15	(anastrozole or Arimidex or ZD1033 or "ZD-1033" or "ICI D1033" or "120511-73-1"):ti,ab,kw	797
#16	(exemestane or examestane or Aromasin or Aromasine or Aromasil or "FCE 24304" or "FCE-24304" or "107868-30-4"):ti,ab,kw	531
#17	(tamoxifen or Nolvadex or Novaldex or Soltamox or Tomaxithen or Zitazonium or "ICI 46474" or "ICI-46474" or "ICI 47699" or "ICI-47699" or "10540-29-1"):ti,ab,kw	3979

No.	Search String	Hits
#18	(fulvestrant or Faslodex or "ICI 182780" or "ICI-182780" or "ZM 182780" or "ZM-182780" or "129453-61-8"):ti,ab,kw	255
#19	(palbociclib or Ibrance or "PD 0332991" or "PD-0332991" or "571190-30-2"):ti,ab,kw	64
#20	(everolimus or Afinitor or Certican or RAD001 or "RAD 001" or "SDZ RAD" or "SDZ-RAD" or "159351-69-6"):ti,ab,kw	1978
#21	(LEE011 or "LEE-011" or Ribociclib or "1211441-98-3"):ti,ab,kw	18
#22	(abemaciclib or LY2835219 or LY2835210 or "1231929-97-7"):ti,ab,kw	11
#23	(capecitabine or Xeloda or "154361-50-9"):ti,ab,kw	1844
#24	(doxorubicin or Adriamycin or Doxil or Adriablastin or Adriablastine or Adriblastin or Adriblastina or Adriblastine or Adrimedac or Doxolem or Doxorubicin or Doxotec or Farmiblastina or Myocet or Onkodox or Ribodoxo or "Rubex 23214-92-8"):ti,ab,kw	6472
#25	(paclitaxel or Abraxane or Paxene or NSC-125973 or NSC125973 or Anzatax or Onxol or Praxel or Taxol or "33069-62-4"):ti,ab,kw	5310
#26	(docetaxel or Taxotere or Docefrez or "RP 56976" or "RP-56976" or "114977-28-5"):ti,ab,kw	3712
#27	(cyclophosphamide or cytophosphane or Cytoxan or Endoxan or "NSC 26271" or "B 518" or "B-518" or Cyclophosphane or Cytophosphan or Neosar or Procytox or "NSC-26271" or "50-18-0"):ti,ab,kw	8897
#28	(eribulin or Halaven or "NSC 707389" or "NSC-707389" or "B 1793" or "B 1939" or "B-1793" or "B-1939" or "E 7389" or "E-7389" or "ER 086526" or "ER-086526" or "ER-86526" or "ER086526" or eribulin or Halaven or "253128-41-5"):ti,ab,kw	114
#29	{or #14-#28}	25935
#30	#13 and #29	5718
#31	(lapatinib or tykerb or tyverb or GW572016 or "GW-572016" or GW282974X or "388082-78-8"):ti	301
#32	(trastuzumab or herceptin or “180288-69-1”):ti	786
#33	((trastuzumab near/1 emtansine) or “trastuzumab-DM1” or (“ado-trastuzumab” near/1 emtansine) or kadcyla or “T-DM1” or TDM1 or “trastuzumab-MCC-DM1” or “1018448-65-1”):ti	48
#34	(perjeta or pertuzumab or “380610-27-5” or D05446):ti	107
#35	{or #31-#34}	1043
#36	#30 not #35	5304
#37	#36 Publication Year from 2016 to 2017, in Cochrane Reviews (Reviews Only), Other Reviews and Trials	375

Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2017
Database of Abstracts of Reviews of Effect : Issue 2 of 4, April 2015
Cochrane Central Register of Controlled Trials : Issue 4 of 12, April 2017

The database searches were conducted on the 3rd May 2017 for the period of 1st June 2016 to 1st May 2017. Due to time constraints, all records identified were reviewed for relevance according to the title/abstract only based on the eligibility criteria used in the original review. The review was undertaken by one systematic reviewer only, with the input of a second reviewer in cases of uncertainty.

In alignment with the original review, an update to the searches of relevant conferences was also performed, for conferences occurring between 1st June 2016 and 1st May 2017 (note ASCO 2016 occurred in June 2016 and was searched for the original review; therefore, it was not searched again for this update). A list of the conferences searched in this update is provided in Table 4. Due to time constraints, the conference proceedings were searched for the term "ribociclib" only.

Table 4 List of conferences searched

Conference	Link	Number of hits
AACR (American Association for Cancer Research)	Conference website: http://aacr.posterview.com/nosl/?searchterm=ribociclib&searchtype=Keyword for "ribociclib" in keywords Abstract book: http://www.aacr.org/Documents/AACR2017_Proceedings.pdf for "ribociclib"	2 6
San Antonio Breast Cancer Symposium 2016	Abstract book: https://www.sabcs.org/Portals/SABCS2016/Documents/SABCS-2016-Abstracts.pdf?v=1 for "ribociclib"	1
European CanCer Organisation (ECCO 2017)	Conference website: http://www.eccocongress.org/Scientific-Programme/Abstract-search for "ribociclib"	1

The database searches retrieved a total of 804 hits, of which 6 records met the eligibility criteria of the review as described in Section 4.1 of our original submission, based on review of the title and abstract. A further 1 conference abstract of relevance to the review criteria was identified from the conference proceedings of the European CanCer Organisation (ECCO 2017). The PRISMA flow diagram highlighting the reasons for exclusion for the excluded studies is presented in Figure 4.

A list of the 7 records included in the update to this SLR is provided in Table 5. Six of these records are further publications of data for the MONALEESA-2 trial. One publication is the protocol for MONALEESA-3, but no results have yet been published for this trial. As such, no further trials for the clinical effectiveness of ribociclib in women with HR+ /HER2- ABC who have received no prior systematic cancer treatment for advanced disease was identified. Therefore, we hope that the ERG can be satisfied that no relevant data has been omitted from our submission.

Figure 4 PRISMA flow diagram for clinical SLR update

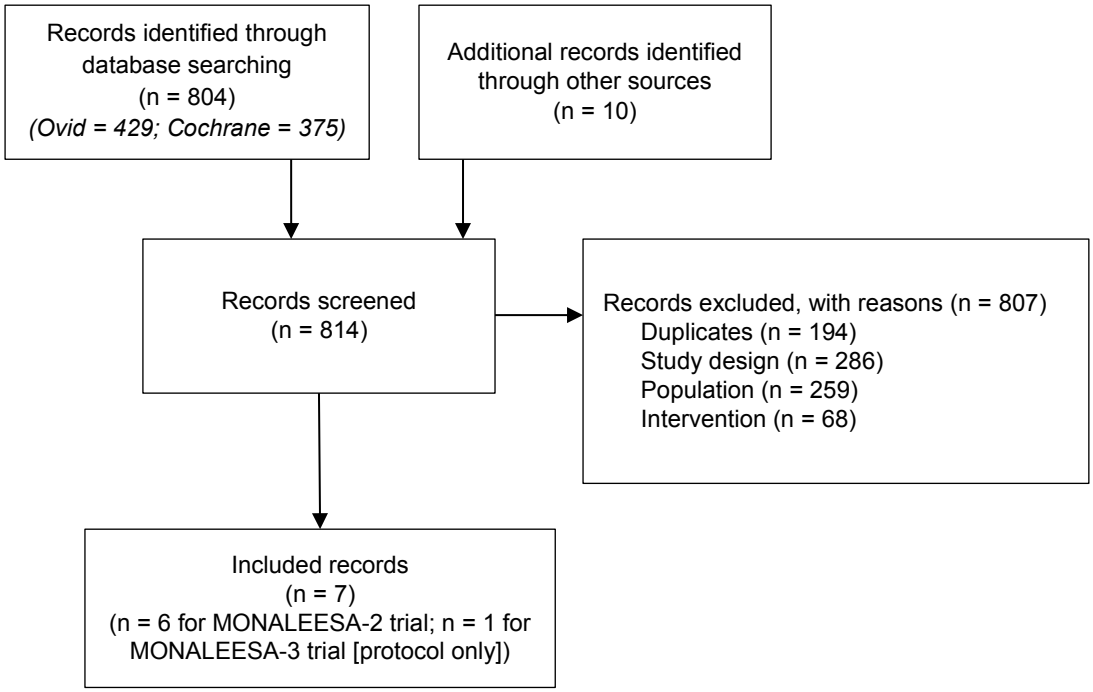


Table 5 Relevant references identified in SLR update

Study	Reference
MONALEESA-2	Andre F, Stemmer SM, Hortobagyi GN, et al. Ribociclib + letrozole for first-line treatment of HR+, HER2-ABC: Efficacy, safety, and pharmacokinetics. European Journal of Cancer 2016;69:S7.
	Holt RE, Topps A, Lim YY, et al. Tomosynthesis as an alternative to magnetic resonance imaging (MRI) in assessing invasive lobular carcinoma (ILC) multifocality. Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States 2017;77.
	Hortobagyi GN, Stemmer SM, Burris HA, et al. PR First-line ribociclib + letrozole for postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-), advanced breast cancer (ABC). Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO 2016;27.
	Janni W, Nusch A, Grischke EM, et al. Ribociclib + letrozole for postmenopausal women with hormone receptor-positive (HR+), HER2-negative, advanced breast cancer (ABC) who received no prior therapy for advanced disease. Oncology Research and Treatment 2016;39:214-215.
	Takeshita T, Yamamoto Y, Yamamoto-Ibusuki M, et al. Clinical significance of sequential measurements of ESR1 mutations in plasma cell-free DNA in estrogen receptor positive recurrent metastatic breast cancer patients. Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States 2017;77.

Study	Reference
	Sonke GS, Hart LL, Campone M, et al. LATE-BREAKING ABSTRACT: Efficacy and safety of ribociclib (LEE011) + letrozole in elderly patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC) in MONALEESA-2. ECCO2017 European Cancer Congress.
MONALEESA-3	Fasching PA, Jerusalem GHM, Pivot X, et al. Phase III study of ribociclib (LEE011) plus fulvestrant for the treatment of postmenopausal patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (aBC) who have received no or only one line of prior endocrine treatment (ET): MONALEESA-3. Journal of Clinical Oncology. Conference 2016;34.

A11. Please could the company provide a list of excluded studies with bibliographic details and reasons for exclusion?

The list of excluded studies with bibliographic details have been provided as an attached to this response titled “Novartis Clinical efficacy SLR aBC SLR screening and PRISMA - NICE clarification responses 050517“

A12. **Priority question**: a. How were the non-randomised trials selected for inclusion in the submission as the search strategy for the review of clinical effectiveness was restricted to RCTs only? Is there other non-randomised evidence that might provide relevant information for the submission particularly in terms of adverse events?

The clinical efficacy and safety assessment of the intervention treatment, ribociclib + letrozole, and the comparator treatment, letrozole monotherapy, considered in this appraisal were informed on the single pivotal RCT, MONALEESA-2. The following justification for limiting the search strategy to RCT data only were:

- The NICE Guide to the methods of technology appraisal recommend that RCTs are considered to be the most appropriate source for measures of relative treatment effect due to minimising potential external influences when assessing an effect on 1 or more interventions on outcomes.

- NICE consider Non-randomised and non-controlled evidence have the potential to contain multiple biases and may lead to difficulty in interpreting the true treatment effect and providing valid conclusions.

- Currently there are no non-randomised trial outccomes available for the intervention treatment, ribociclib, which would provide more robust clinical information over and above the pivotal phase III MONALEESA-2 trial.

- The non-randomised trials listed in table 15 (page 64 and 65) are included based on internal knowledge and as context and confirmation for the RCT MONALEESA-2 trial. The non-RCTs were not used to drive the submission.

- The availability of patient level data for the pivotal trial data, MONALEESA-2, enables the most robust analysis of the trial data, strengthening the conclusions that can be made of the treatment effect.

- Clinical expert validation supported MONALEESA-2 as being a clinically relevant study that provides robust data on the effect of ribociclib + letrozole in patients with aBC.

Considering the NICE guide to the methods of technology appraisal, availability of non-RCT data for ribociclib and external clinical validation, it is felt that the key pivotal (RCT) trial, MONALEESA-2, should be considered the most robust trial data available when considering the comparison of ribociclib + letrozole versus letrozole monotherapy, and was the only trial data used to inform the submission.

b. Please clarify why searches were not conducted for non-randomised and non-controlled evidence (non-RCTs) including searches for searches for indirect and mixed treatment comparisons (MTC). Also please explain why searches for adverse reactions (AEs) were not conducted. If separate searches for non-RCTs/AE/MTC were conducted, please report full search methods and provide full search strategies for each resource searched.

As clarified in question A12 part a, clinical data for adverse reactions (AEs) for this appraisal are informed based upon the pivotal randomised-controlled trial MONALEESA-2. It is felt that the MONALEESA-2 trial should be considered the most robust source of clinical efficacy and safety data for the comparison of ribociclib + letrozole versus letrozole monotherapy for the same reasons presented in A12 part a.

There were no indirect (ITC) and/or mixed treatment comparisons (MTC) performed, since these were not deemed applicable to this submission. The decision problem for this appraisal listed aromatase inhibitors as the treatment comparator, however as previously discussed in the CS and question A1 part a and b, aromatase inhibitors are considered equivalent in efficacy. Given this justification, the comparison with letrozole is deemed most appropriate based on the pivotal RCT, MONALEESA-2 study, providing a direct head-to-head treatment comparison of ribociclib + letrozole versus letrozole monotherapy. The efficacy and safety analysis derived directly from the individual patient data from MONALEESA-2 study should be considered the most robust source of evidence for this appraisal.

A13. The references for two of the non-randomised studies listed in Table 15 (CLEE011X2107 and CLEE011X2108) are to poster presentations. Are any fuller publications available?

There are only poster presentations for CLEE011X2107 and CLEE011X2108 available at this current time.

A14. Please could the company confirm that no relevant interim data are available from any of the three ongoing trials listed in Table 20 (MONALEESA-3, MONALEESA-7 and COMPLEEMENT-1)?

There are no interim data available yet. The timing of the interim analyses for MONALEESA 3 and MONALEESA-7 are based on the number of progression events. Neither study has reached the required number of events to trigger interim analysis, [redacted]

[redacted]

A15. The FDA recommended two trials as a post-marketing requirement. One of these was to 'assess the efficacy and safety of an alternative dosing regimen after evaluation of ECG, PK and efficacy data from on-going MONALEESA-3 and MONALEESA-7 studies'. This was to mitigate the risks for QT prolongation without compromising efficacy. The second was to complete an on-going pharmacokinetic trial CLEE011A2116 (part 1) to determine an appropriate dose of ribociclib in patients with severe renal impairment. However these trials do not appear to be listed under ongoing studies. Please could the company provide information on these trials and their current status?

[redacted]

A16. Please could the company clarify how many reviewers were involved in the selection of studies, data extraction and quality assessment for the review of clinical effectiveness. How were discrepancies resolved?

Two reviewers screened, extracted, and assessed the quality of each record in parallel. If there was a discrepancy, a third reviewer reviewed and resolved the discrepancy.

A17. According to the CS (CS, Table 7, page 39) included studies should have "Ribociclib as monotherapy or as part of a combination therapy". Does this mean all studies comparing different types of comparators (such as letrozole versus anastrazole) were excluded?

The criteria in this table were only applied to identify trials for the intervention of interest, ribociclib. Trials of other comparators were identified using a separate set of criteria.

A18. According to the CS, QoL was not a relevant outcome (CS, Table 7, page 39). Were any studies excluded that had QoL as an outcome, but not any other relevant outcome? If so, please provide the reference and the pdf.

No trials were excluded in their entirety for this reason. In some cases, where a publication was found to report QoL outcomes only, there were other publications for the same trial reporting other outcomes of interest. For such trials, publications reporting only QoL outcomes were retained.

A19. Please provide a table comparing the baseline characteristics of LEA, PALOMA-2, ALLIANCE and MONALEESA-2 trials. The company uses the results from these studies to assess the plausibility of their long-term extrapolation of PFS and OS (of the letrozole arm). We would like to see if the baseline characteristics of the patients within these trials are comparable.

In response to the clarification request, Table 6 presents the baseline characteristics for MONALEESA-2, PALOMA-2, LEA and ALLIANCE trials. An attachment titled "[redacted]" has also been provided which contains Table 6 below.

Table 6 Baseline characteristics of MONALEESA-2, PALOMA-2, LEA and ALLIANCE trials

	MONALEESA-2		PALOMA-2		LEA		ALLIANCE	
	Let+Ribo N = 334	Placebo+Let N = 334	Let+Palbo N = 444	Placebo+Let N = 222	ET* N = 184	ET+Beva N = 190	Letrozole N = 170	Let+Beva N = 173
Median Age, years	62	63	62	61	66	64	59	56
ECOG Status, n (%)								
0	205 (61.4)	202 (60.5)	257 (57.9)	102 (45.9)	131 (71.2)	139 (73.2)	101 (59)	105 (61)
1	129 (38.6)	132 (39.5)	178 (40.1)	117 (52.7)	53 (28.8)	51 (26.8)	64 (38)	64 (37)
2	—	—	9 (2.0)	3 (1.4)	—	—	2 (1)	1 (1)
Race, n (%)								
White	269 (80.5)	280 (83.8)	344 (77.5)	172 (77.5)	—	—	155 (91)	154 (89)
Asian	28 (8.4)	23 (6.9)	65 (14.6)	30 (13.5)	—	—	12 (7)	9 (5)
Black	10 (3.0)	7 (2.1)	8 (1.8)	3 (1.4)	—	—	3 (2)	2 (1)
De novo metastatic disease, n (%)	114 (34.1)	113 (33.8)	167 (37.6)	81 (36.5)	–	–	81 (48)	74 (43)
Median disease free interval (years)	—	—	—	—	4.3	4.3	—	—
Disease free interval (%)								
DFI ≤12 months	4 (1.2)	10 (3.0)	99 (22.3)	48 (21.6)	—	—	2 (1)	11 (6)
DFI >12 months	216 (65)	210 (62.9)	178 (40.1)	93 (41.9)	—	—	84 (49)	85 (49)
Visceral disease, n (%)	197 (59.0)	196 (58.7)	214 (48.2)	110 (49.5)	88 (47.8)	90(47.4)	—	—
Visceral-only, n (%)	—	—	—	—	—	—	41 (24%)	41 (24%)
Bone and visceral, n (%)	—	—	—	—	—	—	83 (49%)	88 (51%)
Bone-only disease, n (%)	69 (20.7)	78 (23.4)	103 (23)	48 (21.6)	118 (64.1)	124 (65.3)	43 (25)	41 (24)
Prior (neo)adjuvant ET, n (%)	175 (52.4)	171 (51.2)	249 (56)	126 (56.8)	95 (51.6)	100 (52.6)	83 (49)	82 (47)
Prior chemotherapy, n (%)	146 (43.7)	145 (43.4)	213 (48.0)	109 (49.1)	88(47.8)	83 (43.7)	65 (38)	72 (42)

* ET (letrozole or fulvestran): 21 patients in the ET arm received fulvestrant and 16 patients in the ET + Bevazizumab arm. All other patients received letrozole.

Section B: Clarification on cost-effectiveness data

Literature review on cost effectiveness

B1. Please provide the rationale for limiting the cost-effectiveness search to English language, to 2000-2016, and why it have not been updated since August 5, 2016?

The original cost-effectiveness search was limited to studies published between 2000 and 2016 to selectively identify economic evaluations that assess current treatment modalities for the target population (i.e. subjects with previously untreated advanced or metastatic hormone receptor-positive HER2-negative breast cancer). Studies that were published prior to 2000 (e.g. great than 17 years prior to the decision problem) are unlikely to provide additional relevant information that would support decision-making for ribociclib.

The original economic evaluation review was conducted during the model development phase. We have updated the searches from August 5, 2016 to April 26, 2017. The search results are presented in Table 7 below.

Table 7 Updated search results in EMBASE

No.	Query	Results
#1	'breast tumor'/exp OR 'breast tumour' OR 'breast tumor'	449,377
#2	'breast'/exp OR 'breast'	649,243
#3	'breast neoplasms'/exp OR 'breast neoplasm' OR breast NEAR/5 carcinoma OR breast NEAR/5 cancer OR breast NEAR/5 malignan*	504,510
#4	#1 OR #2 OR #3	651,110
#5	advanced OR metastat* OR 'late' NEXT/2 'stage' OR 'stage iii' OR (stage AND iii*) OR 'stage iv' OR 'stage 3' OR 'stage 4' OR 'breast metastasis'/exp OR 'metastasis'/exp	1,332,672
#6	#4 AND #5	153,722
#7	'economics'/de OR 'economic aspect'/de OR 'cost'/de OR 'health care cost'/de OR 'drug cost'/de OR 'hospital cost'/de OR 'socioeconomics'/de OR 'health economics'/de OR 'pharmacoeconomics'/de OR 'fee'/exp OR 'budget'/exp OR 'economic evaluation'/exp OR 'hospital finance'/de OR 'financial management'/de OR 'health care financing'/de OR 'low cost' OR 'high cost' OR health*care NEXT/1 cost* OR 'health care' NEXT/1 cost* OR fiscal OR funding OR financial OR finance OR cost NEXT/1 estimate* OR 'cost variable' OR unit NEXT/1 cost* OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR price*:ab,ti OR pricing:ab,ti OR (cost* NEAR/3 (treat* OR therap*)):ab,ti OR health*care NEXT/1 (utilisation OR utilization) OR 'health care' NEXT/1 (utilisation OR utilization) OR resource NEXT/1 (utilisation OR utilization OR use)	1,869,301
#8	#6 AND #7	8,179
#9	#8 AND [animals]/lim	222
#10	#8 AND ([conference abstract]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim)	4,701
#11	#9 OR #10	4,776
#12	#8 NOT #11	3,403
#13	#12 AND [english]/lim	3,209
#14	#13 AND [2000-2017]/py AND[5-8-2016]/sd NOT [26-4-2017]/sd	269

A total of 269 new studies were published since the last literature search. The search results are presented in the attached file titled “Novartis Economic SLR NICE clarification response 050517”.

Due to time constraints, screening of the new studies was carried out by reviewing titles only (single reviewer). Of the 269 studies published since August 2016, only three presented

results of cost-effectiveness analysis in subjects with HR+/HER2- advanced breast cancer. The three published results are presented in Table 8.

Table 8 Key characteristics of the new studies reporting economic evaluations identified in EMBASE

Study author	Study title	Study description
Walstra 2017	Cost-effectiveness of palbociclib plus letrozole versus letrozole alone as a first-line treatment in women with oestrogen receptor-positive, HER2-negative, advanced breast cancer. Revised results for the Swiss health care setting	Analysis type: Cost-effectiveness analysis Country: Switzerland Perspective: Healthcare Population: Women with oestrogen receptor positive, HER2- advanced breast cancer Intervention: Palbociclib plus letrozole Comparator: Letrozole alone Outcome: ICER (Incremental costs per QALY)
Tremblay 2016	Economic evaluation of eribulin as second line treatment for metastatic breast cancer in South Korea	Analysis type: Cost-effectiveness analysis Country: South Korea Perspective: Healthcare Population: Women with HER2- tumor who have progressed on prior chemotherapeutic regimen for advanced disease Intervention: Eribulin Comparator: Capecitabine, Vinorelbine Outcome: ICER (Incremental costs per QALY)
van-Kampen 2017	Real-world and trial-based cost-effectiveness analysis of bevacizumab in HER2-negative metastatic breast cancer patients: a study of the Southeast Netherlands Breast Cancer Consortium.	Analysis type: Cost-effectiveness analysis Country: Netherlands Perspective: Healthcare Population: Women with HER2- advanced breast cancer Intervention: Bevacizumab plus taxane Comparator: Taxane monotherapy Outcome: ICER (Incremental costs per QALY)

None of these studies were UK specific and were therefore, not deemed relevant to the decision problem.

As with the EMBASE database search, a total of 61 studies were identified in the PubMED database. The search results are presented in Table 9 and in the more detailed in the attached file titled Novartis Economic SLR 2 NICE clarification response 050517.

As previously, screening of the 61 studies was carried out by reviewing the title of the study only. None of the studies are relevant and provide any information about cost-effectiveness, healthcare-resource utilization or quality of life in the UK.

Table 9 Updated search queries performed in PubMED [27 April 2017]

No	Query	Results
#1	Search "breast neoplasms"	285,749
#2	Search ("breast cancer" or ‘‘breast tumor’‘ OR ‘‘breast tumour’‘ OR ‘‘breast neoplasms’‘ OR ‘‘breast neoplasm’‘ OR “breast carcinoma” OR "breast malignan*")	344,959
#3	Search Breast cancers[tiab]	19,122
#4	Search Breast neoplasm[tiab]	497
#5	Search Breast neoplasms[tiab]	8,028
#6	Search Breast tumour[tiab]	1,387

No	Query	Results
#7	Search Breast tumor[tiab]	8,024
#8	Search Breast tumors[tiab]	9,697
#9	Search Mammary carcinoma[tiab]	6,116
#10	Search Mammary carcinomas[tiab]	2,081
#11	Search Mammary neoplasm[tiab]	40
#12	“Search Mammary neoplasms[tiab]	603
#13	Search Breast tumours[tiab]	2,094
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	349,229
#15	Search Advanced	431,804
#16	Search Metastatic	865,436
#17	Search "Stage 3"	262,427
#18	Search "Stage 4"	220,944
#19	Search "Stage III"	56,764
#20	Search "Stage IIIB"	5,634
#21	Search "Stage IIIC"	1,408
#22	Search "Stage IV"	42,942
#23	Search Metastasis	302,055
#24	Search Metastases	299,455
#25	Search Unresectable	15,024
#26	Search Inoperable	11,325
#27	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,743,773
#28	#14 AND #27	104,690
#29	Search economics OR “economic aspect” OR cost OR “health care cost” OR “drug cost” OR “hospital cost” OR socioeconomics OR “health economics” OR “pharmacoeconomics” OR “fee” OR “budget” OR “economic evaluation” OR “hospital finance” OR “financial management” OR “health care financing”	1,259,371
30	Search “low cost” OR “high cost” OR “healthcare costs” OR (healthcare AND cost) OR fiscal OR funding OR financial OR finance	885,372
31	Search (cost AND estimate*) OR “cost estimate” OR “cost variable” OR (unit AND cost)	91,999
32	Search economic* OR pharmacoeconomic* OR price* OR pricing	692,757
33	Search (healthcare OR “health care”) AND (utilization OR utilisation)	135,684
34	Search cost* AND (treat* OR therap*)	157,192
35	Search (direct OR indirect) AND cost*	28,050
36	Search “cost effectiveness analysis” OR “cost benefit analysis” OR “cost utility analysis” OR “cost minimization analysis” OR “economic evaluation”	241,134
37	Search (economic OR “cost-benefit” OR “cost-effectiveness” OR “cost-utility”) AND (evaluation* OR analys* OR model* OR intervention*)	330,355
38	Search (“cost minimization” OR “cost minimisation”) AND (analys* OR model*)	2,091
39	Search “resource use” OR “resource utilization" OR “resource utilisation”	236,807
40	Search (“treatment costs” OR “costs of treatment” OR “cost of treatment” OR “costs of therapy” OR “cost of therapy” OR “cost of treating”)	363,025
41	Search economic AND (evaluation* OR model)	117,844
42	Search #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	1,683,695
43	Search #28 AND #42	5,293
44	Search #43 Filters: Publication date from 2016/08/05 to 2017/04/26; Humans)	61

B2. Please explain why TA 263 (bevacizumab in combination with capecitabine), TA 214 (bevacizumab in combination with a taxane) and TA 116 (gemcitabine) were not included as relevant STAs in section 5.1.3, even though they were mentioned in the NICE scope.

The literature review on cost-effectiveness studies was conducted prior to publication of the NICE scoping document for ribociclib. TA 263, TA 214 and TA 116 was not deemed relevant as the populations considered in these appraisals do not match the decision problem for ribociclib i.e. the above mentioned HTA did not specifically consider patients with HR+/HER2- advanced breast cancer.

B3. In section 5.1.3, the choice of the technology appraisals that were discussed in detail for comparing model structure and simulation (e.g. Table 24 for TA 239 and TA 295, respectively), cost and resource utilization (e.g. Table 25 and 26 for TA 239 and TA 421, respectively) and valuation of health benefits (e.g. Table 27 for TA 239 and TA 421, respectively) seemed to be arbitrary. Please provide tables comparing values/assumptions from all relevant appraisals, including ID915 (Palbociclib), as well.

For informing the cost-effectiveness modelling process, only two technology appraisals were used (TA 239 and TA 295). TA295 has recently been updated (Dec 2016) with more evidence, and now forms the basis of TA421. ID915 is an ongoing appraisal, which was not published at the time of model development, however an ACD was published shortly before the NICE submission of ribociclib. Table 10 provides a comparison of the key model characteristics between the three mentioned appraisals.

The choice of technology appraisals TA239 (fulvestrant) and TA295 (now superseded by TA421, everolimus + exemestane) should not be considered arbitrary given the patient populations of focus in those appraisals, HR+/HER2- advanced breast cancer patients following treatment progression, which align closely with the TA for ribociclib. The main difference between TA239 and TA421 and this appraisals is in respect to the treatment line, first line (this appraisal) compared with second line (TA239 and TA421). Given that the patient population is effectively the same, HR+/HER2- advanced breast cancer, and that the model structure, patient pathway followed and this appraisal incorporates everolimus + exemestane as a second line treatment option in the model, these appraisals should be considered directly relevant.

Table 10 Comparison of key model characteristics as reported in TA 239, TA 295 and TA421

Characteristics	TA 239	TA 295	ID915
Model structure and simulation	Three state partitioned survival model comprising of pre-progression, post-progression and Death state.	Three state partitioned survival model comprising of PFS, PD and Death state.	Three state partitioned survival Markov model comprising of PFS, PD and Death state. The PD includes three tunnel states.

Characteristics	TA 239	TA 295	ID915
Healthcare costs	Resource data for pre-progression state were based on expert opinion, as no studies were identified in the literature review • Resource data for post-progression states was treatment dependent and based on feedback from clinical experts. The post-progression treatment pathway options included :Third line hormonal therapy, supportive palliative care • Chemotherapy, supportive palliative care • Third line hormonal therapy , chemotherapy, supportive palliative care • Supportive palliative care Resource use for third line hormonal therapy was assumed to be the same as that during second line hormonal therapy.	Monthly resource use in stable disease health state comprised of :1community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, and 1 social worker visit lasting 1 hour Monthly resource use in stable disease health state comprised of :community nurse home contact lasting 40 minutes, 1 GP home visit, clinical nurse specialist contact lasting 4.5 hrs, and social worker contact lasting 2.5 hrs Terminal care costs was considered in the analysis, but subsequent therapy costs was not considered	**Pre-progression state resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, and 1 consultant visit (oncologist) once every 6 moths lasting 1 hour **2nd line post progression (subsequent treatment 1) resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins and 1 CT scan **3rd line post progression (subsequent treatment 2) resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, 1 CT scan, Therapist lasting 30 mins and Physiotherapist lasting 30 mins **4th line post progression (subsequent treatment 3) resource use**: 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 consultant visit (oncologist) once every 6 moths lasting 1 hour, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, 1 CT scan, Therapist lasting 30 mins and Physiotherapist lasting 30 mins **BSC resource use:** 1 community nurse home visit lasting 20 minutes, 1 GP visit, 1 clinical nurse specialist lasting 1 hr, 1 social worker visit lasting 1 hour, 1 palliative care (outpatient) lasting 20 mins, Therapist lasting 30 mins, Physiotherapist lasting 30 mins and lymphoedema nurse lasting 20 mins
Health benefits	Health benefits using quality adjusted life years (QALYs), assessed viaEQ-5D was incorporated in the cost-effectiveness analysis.	Health benefits using quality adjusted life years (QALYs), assessed using EORTC QLQ-C30 at 7 12 and 18 months was incorporated in the cost-effectiveness analysis.	Health benefits using quality adjusted life years (QALYs), assessed via EQ-5D was incorporated in the cost-effectiveness analysis.

Model structure

B4. **Priority request:** Please incorporate the anastrazole monotherapy as a comparator in the economic model, in case the equivalence between two comparators could not be demonstrated in question A1.

The justification for not including anastrozole monotherapy as a comparator in the economic model is provided in question A1.

B5. Please provide the number of progressed patients who did not receive any further active treatments after 1st line and immediately received best supportive care in the MONALEESA-2 trial or any other relevant sources (e.g. another clinical trial for first

line breast cancer treatment in the same population or patient registries). Based on the findings, update the model in such a way that a proportion of patients might move to the "progression" state without receiving 2nd line treatment.

[redacted] went on to receive a non-therapeutic product, [redacted] of the total population who received antineoplastic therapy since discontinuation of study treatment. [redacted] Applying the MONALEESA-2 proportion in the economic model, as per requested in question B5, [redacted]

Alternative sources of evidence which provide a detailed understanding of which therapies patients would receive post first line treatment discontinuation, particularly post first line CDK 4/6 inhibitor treatment, are limited. In the UK, there are no specific patient registries which can be used. It should also be noted that there is currently no CDK 4/6 inhibitor with national reimbursement in the UK, and thus, clinical practice has so far been limited to trial settings.

As presented in the CS and discussed in question B6, it is felt that the clinical expert validation should be considered the best available evidence for modelling the post progression treatment pathway i.e. 2nd line therapies.

B6. **Priority request:** Please provide all details of the communication between the company and the clinical experts. The details include anonymised information about the clinical experts, detailed minutes of the face-to-face meeting and/or TC, list of expert recommendations and justifications for clinical assumptions used in the model (e.g. the distribution of 2nd line treatments and difference between ribociclib and placebo arms in terms of treatments received in the 2nd line), etc.

All communications and outputs from validations undertaken with clinical experts have been anonymised and provided as attachment to this request. This information should be treated with strict confidence. If the ERG and NICE wish to discuss or present this information outside of agreement for commercial in confidence a request will need to be made to Novartis.

The attached response is titled [redacted]

B7. Please add a scenario analysis in which the percentage of 2nd line treatments received in the model was based on the treatments received in MONALEESA-2 study after progression.

[redacted]

However, if the ERG or NICE believe this analysis is necessary, it is possible to perform, although additional time would be required to ensure the data can be analysed.

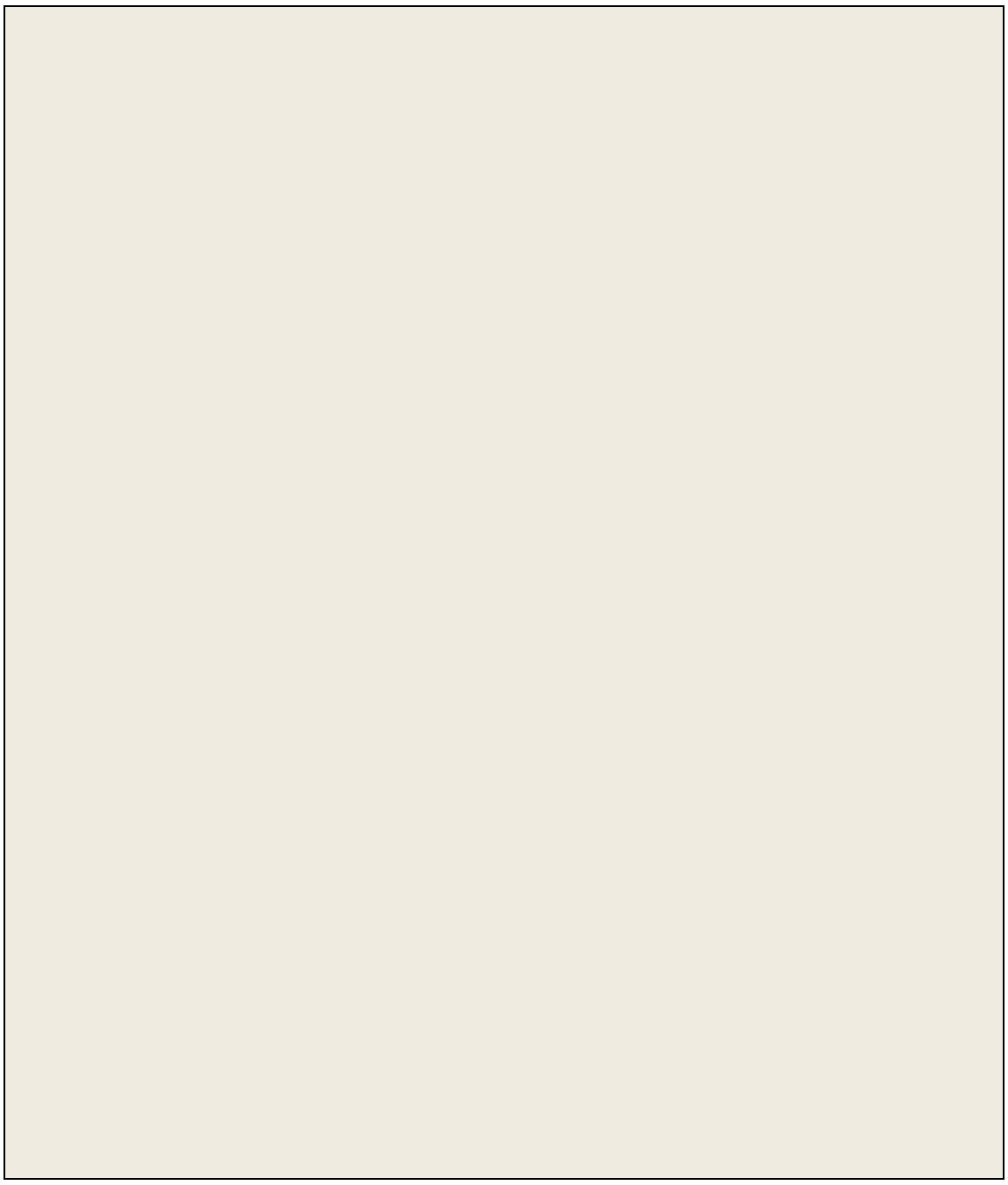
The economic model applied proportions for 2nd line treatments based upon clinical expert validation (as per attachments listed above) and it is felt that this provides the most robust source of evidence for consideration of the UK.

B8. **Priority request:** Please provide a more detailed, clear and transparent explanation of each function in each VBA macro module (compared to the existing comment lines). Please provide a figure that explains the overview code structure of the economic model, explaining the role of each function.

[redacted]

[redacted]

[redacted]



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Treatment effect in cost effectiveness model

B9. **Priority request:** The current OS surrogacy approaches assume that the gain in PFS is 100% translated into OS gain in the base case (in some scenarios only if PFS/TTP is above a threshold)

a. Some studies have indicated that duration of PFS gain will translate into an OS gain that is shorter, especially in HER2-negative patients.[4-6] In light of this, please justify the model assumption that any PFS gain translates 100% into an OS gain. Was this assumption checked with clinical experts?

It is widely accepted that in advanced breast cancer the relationship between PFS and OS is complex and difficult to predict, especially for the population being appraised, first line HR+/HER2- advanced breast cancer patients. This is because of a number of reasons, which are explored below:

Post-progression Treatment

It would be expected that patients would go on to receive multiple therapies post-progression and subsequently patients would experience a number of treatment lines between first line therapy and death.

Future Treatment Options

There are a number of therapies licensed for second line advanced breast cancer. However, as shown in B5 and B6, the therapies used depends on a number of factors including national reimbursement and patient characteristics. This is recognised by Petrelli et al (2014) [4] in which is mentioned that *"Because of the availability of multiple treatment choices, the standard of care in advanced stage cancer settings is to deliver sequential agents; however, this approach has substantially reduced the achievement of survival benefit in first-line trials."*

New Molecular Class of Therapies

Ribociclib is a CDK 4/6 inhibitor which is a new class of therapy in advanced breast cancer. While the relationship between PFS and OS in breast cancer has been investigated to varying degrees, as per the referenced publications by the ERG, it should also be noted that a limitation of these publications are that they do not consider modern molecular agents such as CDK 4/6 inhibitors. A further limitation of the Michiels et al (2016) [5] publication is that this is limited to HER2-positive metastatic breast cancer and does not truly represent the population of interest in this appraisal, which is HR+/HER2- advanced or metastatic breast cancer.

The ERG refers to other studies which suggest that the duration of PFS gain may translate into a shorter OS gain. Whilst there are a number of studies available in breast cancer, these studies appear to show different ratios for PFS gain to OS gain, suggesting that it is not possible to generalise results from one study to another without conducting a proper synthesis and assessment of the evidence. Perhaps more importantly, there are also a number of problems with using data from these studies. In particular, it is unclear whether data from second-line are generalizable to first line. It is also unclear whether evidence for agents with

a different mechanism of action is appropriate. CDK4/6 inhibitors have a different mechanism of action compared with the mTOR inhibitor everolimus for example. There are also a number of issues with the using the median to estimate this ratio, as the median only provides a snapshot at a single time point for PFS and OS. This could lead to biases (either ways) as the curve for OS could separate prior to the median and join at the median and separate again later on. In this case, no OS gain would be estimated using the median which may not be true when considering the full area under the curve.

However, even when considering the complexities associated to assessing the relationship between PFS and OS in advanced breast cancer, the model assumption of 100% PFS gain into OS gain was based upon the following reasons:

1. The OS data from the pivotal clinical study, at the point of submission, was immature and there is no ability to confirm that a 100% PFS gain to OS gain relationship would not be achieved.

2. Clinical expert validation supported the belief that the significant PFS benefit achieved in MONALEESA-2 would likely lead to a translation in OS gain, however it was unclear as to the level of OS benefit.

3. NICE accepted that the PFS benefit for palbociclib, a CDK 4/6 inhibitor, (ID915) [9] would translate into an OS gain.

Further to the above points, two scenarios exploring the relationship between OS and PFS were presented in the original submission to NICE, whereby a proportion of patients where assumed to have a surrogacy (i.e a shift in PFS translate into a shift in OS) based on either the time to progression or PFS gain. As discussed within our original submission, these scenarios were considered to be exploratory given the number of assumptions required.

Whilst we believe that in the absence of robust or alternative evidence, the full surrogacy should be assumed, as discussed during the palbociclib appraisal committee, an additional scenario has been included whereby a gain in PFS is translated into a reduced gain in OS (by various factors) in response to the ERG, and for transparency.

b. Add a scenario where the gain of PFS is translated into OS with a factor less than 1 (e.g. using the proportion of median OS gain to median PFS gain from BOLERO-2 or another relevant trial)

Given the uncertainty in the ratio between PFS gain to OS gain, scenario analyses were conducted assuming the factor to [redacted]

[redacted]

[redacted]

[redacted]

Ratio applied	Gain in PFS	Gain in OS	Ratio calculated	ICER (list price)	ICER PAS price)
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

B10. Please provide average patient characteristics (age, time from diagnosis etc.) from the economic model after patients progress from first line treatment under both ribociclib and placebo arms.

While the economic model did not explicitly apply a starting age, the population being modelled was based upon the MONALEESA-2 study, and thus, the median age for the all patient population of the MONALEESA-2 study is would be considered most appropriate in the economic model. Table 11 provides detailed information as requested.

Table 11 MONALEESA-2 baseline characteristics (age) and the economic model

	Ribociclib + letrozole treatment arm	Placebo + letrozole treatment arm	All patients
MONALEESA-2 median age – years	62	63	62
Economic model median age at start	62	62	62
Economic model median age at first line progression*	[redacted]	[redacted]	–

*The economic model median age at first line progression is calculated based on the modelled median PFS from the January 2016 data cut

B11. **Priority request:** Please confirm that all the PFS, OS and TTD parametric extrapolations conducted in the economic model were based on the ITT patient level data from MONALEESA-2 and BOLERO-2 trials. Otherwise, please update the economic model and its results, in which all PFS extrapolations were based on ITT data in all the scenarios.

All PFS, OS and TTD parametric extrapolations conducted in the economic model were based upon the ITT patient level data for both the MONALEESA-2 and BOLERO-2 trials.

B12. **Priority request:**

a. Please incorporate the scenario analyses to the economic model, where the MONALEESA-2 PFS extrapolations were based on central assessment review PFS data instead of local assessment review PFS data, in line with the Kaplan Meier plots provided in question A8.

As discussed in question A3, the supportive central assessment was not performed at the January 2017 data cut off, this was due to the additional length of time to perform central assessment and consequently full efficacy assessment by BIRC was not available at time of data lock. However, the supportive central assessment review (BIRC) was conducted at the additional 90-day safety analysis (data cut-off June 2016), and remained consistent in supporting the primary endpoint by local assessment review.

Should the ERG or NICE consider modelling the supportive central assessment essential, this could be performed on the June 2016 data cut-off analysis. However, that data analysis would be based on an a set of data six months earlier compared to the January 2017 analysis modelled in response to this clarification question.

Given that the second interim OS analysis (data cut-off January 2017) provides an additional 12 months follow up, the local assessment review is the primary endpoint of the MONALEESA-2 trial and local assessment reflects clinical practice, the economic model has been updated to include the second interim OS analysis (data cut-off January 2017) local assessment PFS data. The economic model PFS extrapolations for the updated data is presented in Figure 5 below.

Figure 5 Modelled PFS extrapolation against the observed KM (data cut-off January 2017)

[redacted]

[redacted]

b. Please incorporate the scenario analyses to the economic model where the PFS extrapolations were based on the PFS data from the most recent data cut-off point and based on central assessment review, in line with question A3.

[redacted]

[redacted]

B13. In the model, after progression, the same treatment effectiveness was assumed for everolimus in the second line no matter which treatment was received in the first line (i.e. ribociclib or placebo as an add-on to letrozole). Please justify the plausibility of this assumption from clinical trial, literature and experts' opinion.

Given the absence of long-term RCT data demonstrating the treatment effect of everolimus + exemestane post ribociclib + aromatase inhibitor, clinical expert validation was sought. Through clinical expert validation it was considered appropriate to model the same treatment effectiveness for everolimus (BOLERO-2 trial effectiveness) for patients progressing on ribociclib + aromatase inhibitor. Clinical experts considered that the use of ribociclib should not change the mechanism of action of everolimus and they would expect everolimus to be as efficacious.

[redacted]

B14. The log-cumulative hazard plots provided in Figure 24 do not seem to be straight lines. It seems there is a change of hazard after approximately [redacted]. Please provide a piecewise model for PFS of ribociclib and placebo arms, in line with the NICE DSU recommendations provided in Figure 22. Please incorporate this flexible piecewise model into the cost effectiveness model, as well.

[redacted]

[redacted]

[redacted]

Figure 6 shows the model prediction against the observed KM when applying a piecewise extrapolation approach.

Figure 6 Piecewise modelled PFS extrapolation against the observed KM (data cut-off January 2017)

Costs

B15. If choosing the Gompertz distribution for the time to treatment discontinuation in the first-line, the health economic model in Excel gives an error when computing 5,000 patients. Please confirm this error and repair this option.

This is not an error, but rather an artefact of the model. The time to discontinuation is estimated from the parametric function, by looking up the value of time, which is associated with the survival probability defined by the random number generated.

The random number (or survival probability) can in theory take any value between 0 to 1 and therefore, the parametric function used to estimate the time to event need to be complete in order to generate the time to event for any given random number between 0 to 1.

[redacted]

[redacted]

[redacted]

B16. In the model, 3rd line therapies are not explicitly modelled and a separate cost is added in the base case in the progressed disease health state to reflect the drug acquisition for subsequent lines of therapies. Please provide a table with the details of these costs (i.e. assumptions regarding the type of treatments provided, treatment duration, drug costs per treatment (including administration costs), type of adverse events per treatment (including costs). Please also provide sources for each of these values.

The cost associated with 3rd line or greater therapies, which are implemented in the economic model in the progression health state, were not explicitly modelled based on the following reasons:

- The complex treatment pathway in advanced breast cancer
- Additional number of assumptions required to derive a treatment matrix for estimating the cost
- The cost occurs late on in the economic model, progression health state, and thus could be considered to have a lower impact on the ICER
- Clinical expert validation was sought, due to limited robust evidence and in particular real world evidence for England and Wales that could be considered a stronger source of evidence for this treatment line and patient population

However, when considering previous NICE appraisals and costs utilised for what are considered 3rd line or greater therapies, evidence from the appraisal of fulvestrant (TA239) [17] support the value used in the CS.

Fulvestrant (TA239)

In TA239 [17] a complex treatment schematic and matrix of assumptions was developed as presented in Figure 7. The resulting monthly cost per patient was £1,084 (in 2011 values) for post-progression treatment in NICE appraisal. It should also be noted that this cost only accounts for treatment related costs and does not include AE's associated costs. Inclusion if AE associated costs would result in a higher monthly cost. This can be considered representative of the 3rd line or greater therapy costs being discussed for the ribociclib appraisal. However, as mentioned, this relies on a number of assumptions.

Figure 7 Fulvestrant TA239 post-progression treatment cost matrix

Figure 34 Overview of treatment pathways during post-progression

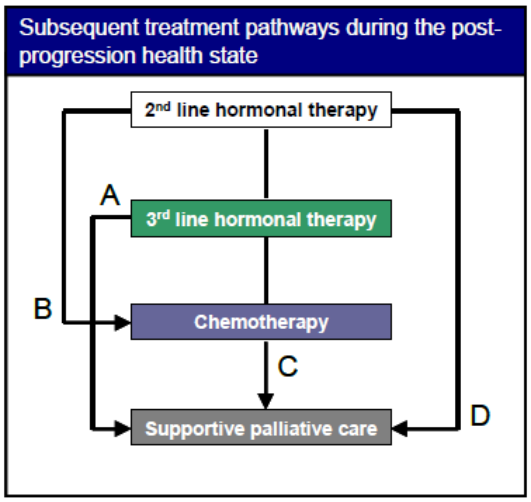

Table B68 Average costs, durations, and proportions of patients per treatment sequence

Post-progression sequences	% patients receiving sequence	Average total time (months)	Average total cost per treatment sequence
A) Third line hormonal therapy + supportive palliative care	7%	7.8 (=2.8 + 5.0)	£5,622 (=£1,580 + £4,042)
B) Chemotherapy + Supportive palliative care	30%	15.8	£18,449
C) Third line hormonal therapy + Chemotherapy + Supportive palliative care	51%	18.6 (=2.8 + 15.8)	£20,029 (=£1,580 +18,449)
D) Supportive palliative care	12%	5.0	£4,042
Total (weighted averages)	**100%**	**15.13**	**£16,628**
Average cost post-progression per month			**£1,084**

Given the additional assumptions required to derive a complex treatment matrix as previously done in TA239, it is worth considering the uncertainty this may add.

[redacted]

It is still felt that the clinical expert validation provides the strongest source for estimating the 3rd line or greater therapy costs. However, given the number of assumptions and no clear published cost for 3rd line or greater therapy treatment, a range of costs for 3rd line or greater treatment cost were explored in scenario analyses in the CS.

Utility

B17. Since the adverse events seem not to occur constantly over time, the health-related quality of life measurements in the MONALEESA-2 might have missed the temporary disutility impact of adverse events. In the trial, patients in the ribociclib arm seem to have more adverse events compared to the placebo arm, and incorporating only the cost implications of adverse events might create a bias. Please incorporate the disutilities due to adverse events for both treatment arms, using disutility results from the published literature/ previous appraisals.

[redacted], it has been widely accepted by NICE that disutilities are not appropriate to include in the economic modelling. This is because:

- Trial date captures the HRQoL impact for patients in the study, including any potential negative impact AEs would have, i.e. QoL inherently captures overall impact
- The potential for double counting when modelling disutilities
- While a concern is that disutilites might not be captured in certain patients, it could also be that utilities are being captured while patients are experiencing AEs

It should be noted that the utility values presented in the NICE appraisal of palbociclib (ID915) [9] did not model disutilities for the base case analysis and this was accepted by NICE.

We believe the impact of measurement of QoL would impact both arms. Whilst patients on ribociclib experienced more adverse events, these were temporary and unlikely to significantly impact quality of life as shown by the absence of difference in QoL between arms.

For transparency, in response to the ERG, we have applied utility decrement for AEs as per Table 12:

- The decrement in utility reported by Hudgens et al (2016) [18] associated with main adverse events (assumed to last a month) weighted by the prevalence of adverse events from the MONALEESA-2 trial

Table 12 Utility decrement associated with AE's

Adverse events	Mean
Diarrhoea	-0.006
Fatigue	-0.029
Infection	-0.050
Nausea	-0.021
Febrile neutropenia	-0.012
Pulmonary embolism	-0.050
Vomiting	-0.050

[redacted]

[redacted]

B18. In the company submission, it is stated that the health state utility value for PFS in the second-line is taken directly from the EQ-5D estimated from BOLERO-2, which was used in the previous submission for everolimus + exemestane (TA421).

a. Please provide the details on how this utility value for PFS2 state is derived (e.g. was it generated from a disease specific instrument and mapped or was it derived from EQ-5D questionnaire? When were the questionnaires filled in, by whom? Etc…)

Factual accuracy clarification: In the CS on page 150, Table 41 and on page 151 it is stated that the EQ-5D utility values were sourced directly from the BOLERO-2 study for Health State Utility values in second line (PFS2 health state). However it is the case that the utility values were not directly sourced from BOLERO-2 and were sourced from Lloyd et al. (2006) [19] and then adjusted based on BOLERO-2. The CS has been updated to reflect the answer to this clarification question as per below.

The utilities applied for PFS in second-line, represented in the CS and economic model as PFS2 health state, were sourced based on the everolimus + exemestane NICE appraisal TA421. Further details on how the utility values were derived are described below:

The Lloyd et al. (2006) [19] publication, a UK Health State Utility study in metastatic breast cancer, was used to define the utility values and then these published utilities were adjusted for:

- age (to be consistent with the average age of patients used to estimate UK EQ-5D tariffs)

  and

- the degree of response to treatment, based on the clinical benefit rate observed in the BOLERO-2 trial (this adjustment was only made for the 'stable disease' health state).

This approach was taken as per the ERG request during the original NICE appraisal TA295. The same utility values were subsequently used in the appraisal TA421 [20], as they had previously been accepted by NICE.

b. Please justify why the mean utility value in Table 38 for progressive disease health state ([redacted]) was not used for the PFS2 state, but the utility value estimated from BOLERO-2 trial was used instead.

The utility value applied for the PFS2 health state was 0.774 and sourced from the TA421 based on the following considerations:

- The utility value used was derived based upon a publication specifically in metastatic breast cancer patients in the UK, as discussed in question B18 part a
- The utility value used was age adjusted (UK) and adjusted for treatment response of everolimus + exemestane based BOLERO-2, as discussed in question B18 part a
- Previously accepted use of the utility value (0.774) in NICE technology appraisal (TA421)
- Everolimus + exemestane is included in the economic model as a second line treatment option (PFS2 health state) and, thus, the utility value is directly relevant

[redacted]

[redacted]

[redacted]

[redacted]

B19. In the company submission, it is stated that, for simplicity, the same utility value was assumed for everolimus + exemestane and for exemestane monotherapy used in the second line. Please provide utility values separately for each treatment arm.

The utility values used in the everolimus submission were as follows:

- Everolimus + exemestane 0.774

[redacted]Exemestane alone [redacted]

No distinction was made in our original submission for simplicity because the values were relatively close and the relative impact would be expected to be the same in both arms.

As per the ERGs request and for transparency, a scenario analysis was conducted assuming different utility values for everolimus + exemestane (0.774) and single agent hormonal therapy (exemestane alone) [redacted]

[redacted]

[redacted]

B20. Please clarify why the health-related quality-of-life studies (5.4.3) searches have not been updated since August 5, 2016 (except the NICE website search [March 2017]).

As with the literature review on cost-effectiveness studies, the review on health-related quality of life studies was conducted during the model development phase.

We have updated the searches from August 5, 2016 until April 26, 2017. The search results are presented in Table 13 below. Due to time constraints the searches were carried out in PubMED only.

Table 13 Updated search queries performed in PubMED [27 April 2017]

No	Query	Results
#1	Search "breast neoplasms"	285,749
#2	Search ("breast cancer" or ‘‘breast tumor‘‘ OR ‘‘breast tumour‘‘ OR ‘‘breast neoplasms‘‘ OR ‘‘breast neoplasm‘‘ OR “breast carcinoma” OR "breast malignan*")	344,959
#3	Search Breast cancers[tiab]	19,122
#4	Search Breast neoplasm[tiab]	497
#5	Search Breast neoplasms[tiab]	8,028
#6	Search Breast tumour[tiab]	1,387
#7	Search Breast tumor[tiab]	8,024
#8	Search Breast tumors[tiab]	9,697
#9	Search Mammary carcinoma[tiab]	6,116
#10	Search Mammary carcinomas[tiab]	2,081
#11	Search Mammary neoplasm[tiab]	40
#12	Search Mammary neoplasms[tiab]	603
#13	Search Breast tumours[tiab]	2,094
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	349,229
#15	Search Advanced	431,804
#16	Search Metastatic	865,436
#17	Search "Stage 3"	262,427
#18	Search "Stage 4"	220,944
#19	Search "Stage III"	56,764
#20	Search "Stage IIIB"	5,634
#21	Search "Stage IIIC"	1,408
#22	Search "Stage IV"	42,942
#23	Search Metastasis	302,055
#24	Search Metastases	299,455
#25	Search Unresectable	15,024
#26	Search Inoperable	11,325

No	Query	Results
#27	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26	1,743,773
#28	#14 AND #27	104,690
#29	Search ((“utility score” OR “utility scores” OR “utility-based outcomes” OR “utility-based measures” OR “Health Utilities” OR “Health utility” OR “health state” OR “health utility state” OR “health utility states” OR “utility-weights” OR “utility-weight” OR “Weighted health utility” OR “health status utilities” OR “health status utility” OR “utility measure” OR “Utility preference scores” OR “Health Utilities Index score” OR “Utility outcomes” OR “Utility analysis” OR “health state utility” OR “health state utilities”))	17,973
#30	Search ((“health utility index” OR hui OR hrqol OR hqol OR “quality of life” OR “quality-of-life” OR qol OR hui))	266,657
#31	Search (“utility values” OR “utility evaluations” OR “utility value” OR “utility evaluation”)	1,128
#32	Search (“health state preference” OR “stated preference” OR “preference scores” OR “health state preferences”)	720
#33	Search (“quality adjusted life year” OR “quality adjusted life”)	13,442
#34	Search “Quality-adjusted survival”	4040
#35	Search (qaly* OR qald* OR qale* OR qtime* OR “disability adjusted life” OR daly* OR “health survey” OR hye* OR health*year*equivalent)	44,751
#36	Search (wellbeing OR qwb)	12,179
#37	Search (quality AND well*being)	514,411
#38	Search (“willingness to pay” OR “standard gamble”)	4,323
#39	Search (“probability-time tradeoff” OR “time-value tradeoff” OR “time tradeoff” OR “time trade-off”)	1,180
#40	Search (“discrete choice experiments” OR “discrete choice experiment”)	948
#41	Search (disutili* OR tto OR “short form 36”OR sf36 OR “sf-36” OR “sf 36” OR “short form 12” OR sf12 OR “sf-12” OR “sf 12” OR “short form 6” OR sf6 OR “sf-6” OR “sf 6” OR euroqol OR euro*qol OR “eq5d” OR “eq-5d” OR “eq 5d” OR rosser)	34,732
#42	Search (“visual analog scale” OR “visual analog scales”)	20,632
#43	Search (#29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42)	705,960
#44	Search (#28 AND #43)	5,142
#45	Search #44 AND Filters: Publication date from 2016/08/05 to 2017/04/26; Humans)	66

The search identified 66 unique studies that were published since the date of the last search. Of these studies, only one study was identified, shown in Table 14, that is likely to provide information relevant to the ribociclib cost-effectiveness analysis. This study reported the findings of a systematic review of health state utility values in patients with late stage breast cancer.

Table 14 Key characteristics of the new studies reporting health related quality of life data identified in PubMED

Study author	Study title	Study description
Paracha 2016	Health state utility values in locally advanced and metastatic breast cancer by treatment line: a systematic review	Analysis type: Systematic review of studies reporting health state utility values in locally advanced or metastatic advanced breast cancer

The results of the searches are provided as a further attachment to this response. The attachment is titled “Novartis Economic SLR 3 NICE clarification response 050517“

B21. Please provide details of the search date and search terms used for the NICE website search. In the PRISMA flowchart there is a box “Bibliographic searching: 3 publications”: please clarify what ‘bibliographic searching’ is.

The search term was used for identifying relevant HTA appraisals on August 5 2016 and March 2 2017 is presented in Table 15.

Table 15 Search terms used for identifying studies in the NICE website

Search terms	No. of hits
Breast cancer	256

Bibliographic searching refers to the reviewing of secondary studies cited in primary studies identified through literature searches using search terms in biomedical databases.

B22. Please clarify how resource identification, measurement and valuation studies were identified. Section 5.5.1 states that details of the searches are described in 'section 0'. It is not clear if resource use data were identified through the health-related quality-of-life studies searches, the cost-effectiveness searches, or elsewhere.

Resource utilization studies were identified as part of the economic evaluation review (i.e. cost-effectiveness searches). Of the 30 economic studies identified, 13 reported cost and resource use data. Of these 13, only four reported costs relevant to the UK healthcare system.

Other – Validation

B23. The total QALYs estimate for letrozole monotherapy with the company's model ([redacted]) is [redacted] than the estimate from ID915 (1.77). The company argues this is due to the modelling differences. Please run the model with the clinical effectiveness inputs and baseline characteristics identical to those from ID915 and report the total QALYs and total LYs under letrozole monotherapy.

Given the different modelling approaches, it is not possible to rerun our model using the exact same assumptions as in ID915. [9] In ID915, OS is estimated directly by fitting a parametric function to PALOMA-1. In our model, OS is estimated as a function of the time spent in PFS1, PFS2 and progressed disease. Furthermore, as recognised by the ERG in ID915, there are several issues with using data from PALOMA-1 to estimate OS, in particular with respect to the population included.

Whilst we cannot rerun easily our model using assumption from ID915, two key aspects explain the differences in QALYs between models, namely:

- the estimate of OS, and
- the utility value used

These are described in turn below

a. Differences in the estimate of OS and post-progression survival

[redacted]

[redacted]

[redacted]

[redacted]

As highlighted on page 188 of the CS, the total LY in previous NICE appraisals for HR+/HER2- advanced breast cancer in second-line was [redacted] for everolimus (TA421) and 2.62 years for fulvestrant (TA239) respectively.

[redacted]

[redacted]

[redacted]

b. Differences in utility values used

In addition to the differences in OS, the differences in QALYs can also be explained by the differences in utility values used. Utility values in first-line in ID915 are not publicly available (marked confidential). However, in the model submitted for ID915, following first-line treatment, a utility value of 0.50 based on Lloyd et al. (2006) [19] was used for the remaining of the model following first line treatment.

In our model, we assumed that patients in second-line had a utility value of 0.77 until second progression (as accepted in TA421), after which a utility value of approximately 0.5 was used thereafter until death.

[redacted]

B24. In Section 5.3.1 from the company submission, it is stated that the company conducted internal and external validation efforts. Please provide more details on these efforts, including the details of the quality control check of the model (list of questions in the quality control check, number of people involved and their roles in the quality control check, and the results), results of the internal validation efforts on costs, health state utilisation and utility inputs, and detailed minutes of the external validation meetings with clinical and health economic experts.

The economic model was quality control checked through a two stage process, as follows:

- The model developer performed a series of validation exercises, as described further below.
- Two Health Economists (modellers) who were independent to the development of the economic model provided a review and quality control check on the model at two time points. The first review took place once the model had initially been developed and considered as draft final version, to identify calculation errors, correct functionality and assess in detail against a QC checklist. The QC checklist is presented in Table 16. A second follow up review was performed on the economic model once all recommendations had been implemented in the model, identified in the first QC.

As per the below table:

Table 16 Independent economic review checklist

Action	Expected Outcome
Set all costs to 0.0.	Did the costs sum up to 0.0?
Double all costs	Did the total costs double?
Set Treatment costs to 0	Is the total costs of treatment=0?
Double treatment costs	Did the treatment costs doubled?
Set Administration costs to 0	Is the total costs of Administration=0?
Double Administration costs	Did the administration costs doubled?
Set all Utilities to zero.	Did the QALYs sum up to 0.0?
Set all Utilities to 1.0.	Are the QALYs equal to the life expectancy?

Set health state utilities same for all states	Same QALYs for surviving patients (life years and QALYs should have same ratio in both arms)
Increase the cost of the treatment.	Did the ICER also increase?
Sum up the state probabilities in each simulation step.	Did the probability mass sum up to reach 1.0 in each simulation step.
Set the discount rate for the costs to 0.0	Is the discounted total cost equal to the undiscounted total cost?
Set the discount rate of costs to 100%	Costs should be significantly reduced
Set the discount rate of the benefit measure (QALYs LE) to 0.0	Is the discounted total effectiveness measure equal to the undiscounted effectiveness measure (LE, QALYs).
Set the discount rate of benefits to 100%	LE, QALYs should be significantly reduced
Perform a life time simulation.	Did the sum of the state probabilities, which are interpreted as "dead", converge asymptotically to 1.0.
Match the trajectories of the model-generated state probabilities to the observations from clinical trials?	Is the deviation of both trajectories acceptable with respect to a predefined rule?
Set 'treatment' to comparator and 'comparator' to treatment	Costs and QALYs should be the same but inverted
Make all the parameters for the comparator arm and the treatment arm equal.	Are the costs and outcomes equal for both the treatment and the comparator arm?
Use Spell Check function in Excel	No spelling mistakes or grammatical error
Check for consistency in units. Applies for both graphs and cells.	Check if the appropriate currency is used for Costs, ICERs, etc.
Set mortality rate to 0% at all ages	No deaths in model
Set mortality rate to 100% at all ages	All patients dead at cycle 1but still generate expected costs and QALYs
Set mortality rate to 100% at age 70	All patients dead after x years (starting age 70 - x) but still generate expected costs and QALYs.
Increase mortality rate	Reduced costs.
If different cycles have different transition probabilities (TPs), are the TPs applied correctly?	TPs applied correctly
Are transition probability of treatment arm & comparator arm applied at appropriate places? There is possibility of error if treatment transition probability is applied to comparator arm and vice versa	TPs applied correctly
In calculations, have the drug costs been adjusted for cycle length? For e.g. if model has annual drug costs and cycle length is 3 months, then drug costs should be divided by 4 while applying in cycles.	Adjustments to drug costs made correctly
Wherever functions (e.g. Vlookup,Hlookup,name ranges etc.) the arguments of those functions are used correctly?	Function is applied correctly
In presenting ICER results, are negative ICERs (if any) labeled appropriately as 'Dominant' and 'Less effective'?	Negative ICERs are reported appropriately
Have all VBA macros been checked to ensure they do not overwrite any of the existing cells?	The macros are working fine

Enter nonsensical values for input parameters (e.g., "A" in place of a numerical value; negative value for costs; percentages greater than 100%, etc.)	Alert in place to show that the values are not within the correct range.
Check for calculations or results that are giving errors (#REF,DIV#0, #N/A etc.)	The model should not have any of the errors.

Additionally, clinical expert validation was performed to assess the modelled outputs for both PFS and OS and provide validation to the model prediction. The clinical expert validation has been provided in confidence in response to clarification questions B6, B13, B16 and B24.

As mentioned above, the model developer conducted the following three key validation exercises:

- Face validity and clinical validity: This was done by comparing the model predictions against the observed data. Whilst this type of validation is typically done to check the clinical plausibility, this validation was used to ensure that there are no "major" errors in the coding when estimating the time to events. It should be noted that whilst useful, minor errors could still have occurred. This type of validation is important given the complexity of the model.

- Checking the VB code: The original developer of the model checked each line of code to ensure that the model is doing what it is supposed to do. Whilst this phase is necessary, it should be noted that this process could be biased as the original developer may not be able to identify his own errors. Therefore, whilst this process was conducted by the original developer, the process was repeated by an independent economic modeller separately.

- Rebuilding components of the model in Excel: The model is constructed in VB, mostly to estimate the time to events and to add flexibility to the model. Therefore, once we estimated the trace (similar to a partitioned survival approach), it is possible to calculate the costs and QALYs directly in Excel using an approach similar to a standard cohort model. As raised by the ERG, the model includes a large number of functions and lines of code. Therefore, we felt that rebuilding part of the model in Excel (for validation) was necessary. This validation exercise is presented in the "Validation" sheet in the economic model. Within this sheet, costs and QALYs are calculated directly in Excel based on the trace estimated from VB and compared with the results where calculations are undertaken in VB. [redacted]

[redacted]

[redacted]

Section C: Textual clarifications and additional points

C1. An incorrect reference is cited in the main CS. (Ferlay J. Int J Cancer 2015;136:E359-86).[2] Please could the company provide the correct reference.

Please could the ERG or NICE provide further clarification on this question, as when checking the CS and the mentioned reference it was not clear why the reference is considered incorrect. If the ERG or NICE could please provide further clarity, any necessary update can be addressed.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name:

Name of your organisation: Breast Cancer Care

Your position in the organisation: Policy Manager

Brief description of the organisation:

Breast Cancer Care is the only specialist UK-wide charity providing support for women, men, families and friends affected by breast cancer.

Our free services include support over the phone with a nurse or someone who's been there, our welcoming online forums, reliable information and local group support.

Every day, our care, support and information help thousands of people to find a way to live with, through and beyond breast cancer.

(For example: who funds the organisation? How many members does the organisation have?)

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None to declare

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Breast Cancer Care offers supports people living with or affected by metastatic breast cancer. We hear from many people about their experiences of living with the condition, as well as their hopes for new treatments.

Uncertainty is a key element of living with metastatic breast cancer. On average, people live with the disease for two to three years after diagnosis. However, this can vary considerably from person to person, with some only living for months after their diagnosis, while others live for many years longer.

As a result, many people tell us that they live from "scan to scan", and feel unable to plan their lives in any long-term way. Many are keen to reach a personal milestone, such as seeing their child go to secondary school, or attending a family wedding.

The physical impact of metastatic breast cancer differs greatly, depending on where a person's breast cancer has spread (for example, the lungs or brain), the extent of this progression, and treatment received. Broadly, physical effects include but aren't limited to: pain, fatigue, nausea, poor appetite, and sleep difficulties.

However, if symptoms and side effects can be managed successfully, metastatic breast cancer can become more like a chronic condition, with people experiencing a good quality of life for some time.

One person living with metastatic (also known as secondary) breast cancer told us:

"My diagnosis of secondary breast cancer has changed my life in so many ways. I live in pain despite being on morphine constantly. I live with the fear of my death. I live knowing that I will not be able to see my son grow to adulthood. I live knowing he will have no parent to help him in his life. I live knowing that my life is a series of treatments, scans, appointments.

"I know that in the near future my career will be taken from me as the pain and treatments, fatigue and side effects take a grip. Cancer frightens other people: they don't know what to say; they don't know how they can help. My friends disappeared. My family also disappeared. I have had to keep my fears to myself: how can I tell anyone the truth and reality of living with incurable breast cancer? I have gone from being the person that was there to help other people, to being an ill, disabled person; a condition, a diagnosis."

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment outcomes and expectations will vary for each individual according to their own personal circumstances, goals and priorities.

However, in general, we know what people living with metastatic breast cancer place a high value on treatments which provide them with valuable additional months or years. One person living with metastatic breast cancer told us that they value:

"… maximum life expectancy and time with loved ones. Some people I know, have young children, and are desperate to extend their time, even if it only gives 6 months extra."

We also know from speaking with people living with the disease that living well is often preferable to treatments which are effective but have significant side effects that impact on everyday quality of life. A good quality of life is important. Treatments which have few or manageable side effects allow people to continue with their day-to-day activities as much as possible, be that going to work, parenting and social responsibilities and activities.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

People with metastatic breast cancer face limited treatment options. Current treatment options for this patient group include aromatase inhibitors, such as letrozole, and chemotherapy.

Like ribociclib, letrozole provides an alternative or additional option to chemotherapy. This may be preferable for many people, helping to defer the use of chemotherapy and its side effects which often impact heavily on quality of life.

Chemotherapy may be used in cases where the use of an aromatase inhibitor or other hormone therapies are unsuitable, or after these have become ineffective, but has increased side effects and requires frequent trips to hospital to receive treatment.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

The key benefit of ribociclib is a prolonged period of progression-free survival (PFS), compared with letrozole alone.

The MONALEESA-2 trial has shown a median PFS of 25.3 months for ribociclib plus letrozole, compared with 16.0 months for letrozole alone, a significant difference of almost 10 months.

This extension in PFS means that other treatments such as chemotherapy, which have greater side effects, can potentially be delayed for longer.

Ribociclib can allow people to live with a good quality of life for longer, meaning that they may be able to continue with their day-to-day activities as much as possible.

For people living with metastatic breast cancer, this additional time is unquestionably invaluable.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

As mentioned above, the potential for an extended period of PFS with a good quality of life means that ribociclib is preferable to letrozole alone. Postponing or avoiding the need for chemotherapy is also a significant benefit.

Ribociclib is taken in tablet form, every day for 3 weeks, with a 1 week break. This method of administration may be preferable for some patients over other treatments which require more time in a hospital setting, such as chemotherapy.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None that we are aware of

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might

be willing to accept or tolerate and which would be difficult to accept or tolerate)

- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

People living with metastatic breast cancer have limited treatment options, and have concerns about the future availability of new treatments for their disease on the NHS.

The current uncertainty around the future availability of CDF funded drugs, plus the planned changes to NICE technology appraisal system in England (such as the proposed £20 million Budget Impact Test), add to the feeling of uncertainty felt by people living with metastatic breast cancer.

Please list any concerns patients or carers have about the treatment being appraised.

Ribociclib can cause liver problems and a heart problem called QT prolongation. Healthcare professionals should monitor patients to ensure these adverse effects are identified swiftly and managed appropriately.

Other side effects for ribociclib include nausea, fatigue, diarrhoea and hair thinning.

The administration method of ribociclib (tablet) is convenient, but some people may find remembering to take tablets problematic.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

None that we are aware of

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Not that we are aware

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Not that we are aware

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

X Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Not applicable

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

MONALEESA-2 captured outcomes for progression-free survival, which is highly valued by people with a diagnosis of metastatic breast cancer.

We are not aware of any limitations.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Not applicable

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes X No

If yes, please provide references to the relevant studies.

8. *Equality*

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None that we are aware of

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of

9. *Other issues*

Do you consider the treatment to be innovative?

X Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Ribociclib has the potential to give people with metastatic breast cancer a significant period of progression-free survival, with a relatively good quality of life. This additional time means that people can continue with their day-to-day activities as much as possible, such as going to work or caring for their family.

We know from talking to people living with metastatic breast cancer that this additional time is so valuable.

Are there any other issues that you would like the Appraisal Committee

to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Ribociclib presents a significant leap forward in treatment options for people with untreated advanced or metastatic breast cancer
- The key benefit of ribociclib is a prolonged period of PFS, compared with letrozole alone. The median PFS of 25.3 months shown in MONALEESA-2 would provide people with metastatic disease with invaluable additional and quality time with those closest to them
- Ribociclib can allow people to delay having chemotherapy for a substantial amount of time
- Ribociclib allows people to live with a good quality of life, with limited side effects, meaning they can continue with their day-to-day activities as much as possible.
- The tablet format of ribociclib means reduced trips to and time in hospital, which can be a significant benefit for some patients

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Breast Cancer Now

Your position in the organisation: Policy Assistant

Brief description of the organisation: Breast Cancer Now is the UK's largest breast cancer charity, dedicated to funding ground-breaking research into the disease. Our ambition is that by 2050, everyone who develops breast cancer will live. We're bringing together all those affected by the disease to improve the way we prevent, detect, treat and stop breast cancer. We're committed to working with the NHS and governments across the UK to ensure that breast cancer services are as good as they can be, and that breast cancer patients benefit from advances in research as quickly as possible.

This submission reflects the views of Breast Cancer Now, based on our experience of working with people who are affected by breast cancer. We know that access to effective drugs is hugely important to our supporters and that quality of life is valued just as much as length of life.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Metastatic breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones and liver. There is no cure for metastatic breast cancer, so most medicines aim to extend the length of life and to improve quality of life for patients. A patient can be diagnosed with metastatic (stage 4) cancer initially, or they can develop the condition years after treatment for their primary breast cancer has ended.

Living with metastatic breast cancer is difficult to come to terms with for both patients and family. Patients' time is limited and the treatments usually have some side effects. Patients therefore tell us that quality of life is just as

important to take into account as length of life, as this means that they would be able to spend quality time with their loved ones.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

A recent diagnosis of metastatic breast cancer will come as a shock to most patients and their families, as it is a terminal condition with a short life expectancy. Patients are keen to find treatments that will halt progression and extend life for as long as possible. The vast majority of recently-diagnosed patients would feel it is important to start treatment quickly to get their disease under control. The type and severity of side effects experienced is also important for patients as these could impact negatively on their quality of life. Quality time with their loved ones will be a key objective in their treatment.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

Patients with previously untreated advanced or metastatic hormone receptor-positive, HER2 negative breast cancer are usually offered aromatase inhibitors to control a new diagnosis of advanced disease. Aromatase inhibitors are generally tolerated well by patients, but some patients will experience strong menopausal side effects such as night sweats. Patients will continue on aromatase inhibitors until their disease progresses, indicating that their cancer has become resistant to the treatment. There are three aromatase inhibitors currently offered to this group of patients in England – anastrozole, letrozole and exemestane. Whether patients will be able to move from one aromatase inhibitor to another, once they progress, will depend on their particular cancer and also on how well they tolerate the side effects of a particular drug. Once patients progress on an aromatase inhibitor, the next step after progression would be systemic (non-targeted) chemotherapies, which are associated with serious side effects.

Palbociclib, in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor positive HER2 negative

breast cancer or is currently being appraised by NICE for routine funding on the NHS.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

At the time of the interim analysis of the MONALEESA-2 trial, the median duration of progression free survival had not been reached. However, the trial has shown that ribociclib plus letrozole, compared to letrozole alone, saw a progression free survival benefit across all subgroups of patients that received ribociclib. After 12 months, 72.8% of patients in the ribociclib group and 60.9% in the placebo group showed no disease progression. After 18 months 63.0% of patients in the ribociclib group and 42.2% in the placebo group showed no disease progression.

The combination of ribociclib and letrozole compared to letrozole alone, reduced the risk of disease progression or death by 44%. Overall survival data was not mature at the time of interim analysis.

This class of drug is a significant step forward in effective treatment options for the hormone positive, HER2-negative group of metastatic patients.

Please explain any advantages that patients or carers think this

treatment has over other NHS treatments in England.

Delaying progression means more quality time with family and loved ones as well as a delay to other therapies and, ultimately, starting on systemic (non-targeted) chemotherapies, which are traditionally associated with more severe side effects and a poorer quality of life for patients.

Delay to progression of disease can also have benefits for the mental health of patients, as lack of progression indicates that the medicine is working. A longer time to progression may mean that the patient is able to lead a more or less normal daily life throughout this time. Lack of progression of a metastatic cancer is also likely to bring some comfort to relatives and friends of the patient, as this is the best possible outcome for a terminal illness.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

There are some increased side effects associated with ribociclib plus letrozole, compared with letrozole alone. Each patient's situation will be different and this will impact on their willingness and ability to take ribociclib. 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.

There is some extra monitoring for patients taking ribociclib, but this is mostly in the form of regular blood tests rather than lengthy trips to the hospital to administer their treatment, so is unlikely to be too burdensome for patients and their families.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)

- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

The current first-line treatments available on the NHS for this group of patients are aromatase inhibitors. These are quite effective in controlling advanced hormone positive, HER2-negative disease. However, all patients will eventually progress on this treatment, and will eventually only have the option of taking traditional chemotherapies to control their disease. Since traditional chemotherapies are generally associated with severe side effects and usually have a negative impact on quality of life for patients, patients generally prefer to delay this stage of treatment for as long as possible.

Please list any concerns patients or carers have about the treatment being appraised.

Ribociclib plus letrozole is associated with some increased side effects, compared to letrozole alone. These include low white blood cell count (neutropenia) fatigue and diarrhoea. The most common adverse (grade 3 or 4) side effects included neutropenia and leukopenia . These side effects will affect some patients more than others and the severity of side effects will determine whether patients will be able to continue on this treatment or whether they will need to switch to an aromatase inhibitor as a mono-therapy.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

We are not aware of any particular differences of opinion between patients for this treatment but we do know that patients will have different

approaches and attitudes to the levels of risk they are happy to undertake. It is therefore important that the side effects of this drug are clearly discussed with the patient so that they can make an informed decision about whether this treatment is suitable for them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

This treatment has been tested in post-menopausal women with advanced hormone positive, HER2-negative breast cancer. This treatment is likely to benefit a significant number of metastatic breast cancer patients.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients who are not hormone positive, HER2-negative will not benefit. Certain patients were excluded from the MONALEESA-2 trial such as those that had received prior treatment for their advanced cancer, or previous neoadjuvant or adjuvant therapy with an aromatase inhibitor, those with heart disease, brain metastases, gastrointestinal problems and inflammatory breast cancers.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☒ Yes ☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Ribociclib is not currently recommended for use in routine NHS care.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the

treatment has been assessed in clinical trials?

Yes and no respectively, to the best of our knowledge.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Ribociclib is not currently recommended for use in routine NHS care.

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☒ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

Not that we are aware of.

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Not that we are aware of.

9. Other issues

Do you consider the treatment to be innovative?

☒ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Ribociclib is a small molecule inhibitor of cyclin-dependent kinases uses CDK4 and CDK6. This class of drug is an innovative treatment in terms of both its mechanism and the progression free survival results, which show that this mechanism seems to be effective at controlling disease.

Are there any other issues that you would like the Appraisal Committee to consider?

Not that we are aware of.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- This class of drug is innovative with potentially strong progression free survival data, based on the initial analysis of the MONLEESA-2 trial.
- As a first line treatment for advanced breast cancer, it has an important role in extending the time that hormone treatments work at controlling patients' disease progression. This is an important delay before patients will eventually be offered generic chemotherapies which are known to have severe side effects.
- Ribociclib could benefit a large proportion of the advanced breast cancer population, as the largest proportion of breast cancers are hormone positive, HER2 negative.
- This drug is given in oral form, which makes it simple for patients to take. Apart from short-stay, regular blood tests, patients are not required to spend long lengths of time at the hospital, so it is unlikely that this will place a significant additional burden on patients and their families.
- There are some increased side effects from ribociclib plus letrozole, compared to letrozole alone, however not all patients will experience side

effects. The benefits and risks of a treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them.

NHS England submission for the appraisals of palbociclib and ribociclib in the treatment of ER positive her-2 negative locally advanced or metastatic breast cancer

[redacted]

NHS England wishes to make the following observations on the appraisals of palbociclib and ribociclib.

Marketing authorisations and patients on which the evidence is based

Palbociclib is indicated for the treatment of hormone receptor positive her-2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor in patients who are or have been rendered postmenopausal. The PALOMA-2 phase III trial combined palbociclib with letrozole and allowed entry to patients with an ECOG performance score of 0, 1 or 2. All patients were previously **untreated** with systemic **endocrine-based** anti-cancer therapy for their **advanced** ER pos her-2 neg disease. Patients had to have completed any prior adjuvant therapy with anastrazole or letrozole with a disease-free interval of at least 12 months achieved off treatment before relapse. Less than 2% of patients in PALOMA-2 were of performance status 2.

Ribociclib is indicated for the treatment of hormone receptor positive her-2 negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor as **initial endocrine based therapy**. The MONALEESA-2 phase III trial combined ribociclib with letrozole and allowed entry to patients with an ECOG performance score of 0 or 1. All patients were previously **untreated** with systemic **endocrine-based** anti-cancer therapy for their **advanced** ER pos her-2 neg disease. Patients had to have completed any prior adjuvant therapy with anastrazole or letrozole with a disease-free interval of at least 12 months achieved off treatment before relapse.

Although the marketing authorisation is worded as being wider for palbociclib, NHS England regards the two drugs to have identical places in the advanced breast cancer treatment pathway: for initial endocrine-based systemic therapy of ER pos her-2 neg locally advanced or metastatic breast cancer in patients who have either de novo presentations of such disease or have relapsed disease and completed any previous adjuvant therapy with anastrazole/letrozole such that a disease-free interval without such treatment of at least 12 months has been achieved.

Extrapolation of progression-free survival (PFS) and time to treatment discontinuation (TTD)

NHS England is fully aware of the unusual, significant and consistent difference observed between TTD and PFS in these trials. NHS England notes that treatment with letrozole was continued after palbociclib/ribociclib had been discontinued without there being evidence of disease progression and examination of the KM plots for both drugs indicates that there is about a 6 month difference between TTD for these two agents and PFS. This will have been partly due to the additional toxicity of the drugs, partly due to trial protocol and partly due to clinician unfamiliarity with the 2 drugs and the substantial neutropenia they cause.

NHS England does not regard there being a good reason (on the basis of present knowledge) for the rate of patients developing progressive disease to increase with time whilst on palbociclib/ribociclib and hence exponential extrapolation of PFS for both drugs seems reasonable. However, whilst the rate of developing progressive disease whilst on palbociclib/ribociclib plus anastrazole/letrozole is determined by the rate at which tumours become resistance to these combinations, the rate of discontinuing palbociclib is not only determined by the rate of developing resistance to such endocrine-based therapy but also other factors: toxicities, the management of such toxicities, clinician familiarity with the management of such toxicities and treatment protocols. There is therefore some justification for considering that the rate of TTD would increase with time and thus preferring the Weibull extrapolation. [redacted]

Drug costs of subsequent 2nd and 3rd line therapies

As has been discussed above, the appropriate group of patients to be treated with an aromatase inhibitor (anastrazole or letrozole) and either palbociclib or ribociclib is those with incurable locally advanced or metastatic ER positive her-2 negative breast cancer who are previously untreated with endocrine-based therapy for their locally advanced or metastatic disease. Patients must be postmenopausal either by having undergone the menopause or by medical imposition of the menopause (usually with LHRH agonists).

When treating women with ER positive advanced breast cancer, oncologists wish to maximise the opportunities of benefitting from hormone therapies before then needing to switch to cytotoxic chemotherapy because of either the development of hormone refractoriness or the development of visceral spread which requires a rapid response to treatment. Oncologists therefore wish to work endocrine-based treatment as hard as

possible before resorting to chemotherapy and there are several lines of hormone treatment for ER pos patients. In determining the likely treatments received by patients failing palbocicblb/ribociclib with nastrazole/letrozole, it must be remembered that patients starting and continuing on palbociclib/ribociclib will be fit (performance status 0 or 1) and will also be closely monitored on therapy. Thus there will be few patients not proceeding to 2nd line therapies. It is however reasonable to assume that later lines of therapy (3rd line and beyond) are associated with significant numbers of patients not proceeding to a further line of treatment and figures of a drop off rate of 20-25% are reasonable.

The response rate data for palbociclib and ribociclib are strikingly similar. The overall response rates for both drugs was 42%; the overall response rate for patients with measurable disease was 55%; and the clinical benefit response rate was 85-90% (this means the percentage of patients having a complete response, a partial response and those that achieved stable disease, the latter having to last at least 24 weeks). Thus the overwhelming majority of patients benefitted from hormone treatment plus palbociclib/ribociclib and thus most of these would proceed to 2nd line hormone therapy and many would still receive hormone treatment as 3rd line treatment. However, as treatment lines proceed for this ER pos group, there is increasing use of chemotherapy.

NHS England in consultation with its experts in the Chemotherapy Clinical Reference Group has estimated the proportions of patients proceeding to various therapies in the 2nd and 3rd line settings. Such estimations are complex as some patients present de novo with locally advanced/metastatic ER pos breast cancer, some will have been treated with previous adjuvant aromatase inhibitors, some with previous adjuvant tamoxifen and many will have had adjuvant chemotherapy with anthracyclines only and some with both anthracyclines and taxanes. In addition, the time since completion of adjuvant chemotherapy and adjuvant hormone therapy are additional considerations in determining the likely next treatment. The routes are therefore very diverse by which patients arrive at the point in the treatment pathway at which palbociclib/ribociclib are indicated.

To further complicate the situation, the commissioning and thus use of fulvestrant is variable across the country (this is commissioned by CCGs). Nevertheless use is widespread, despite the current negative NICE recommendation for relapsed metastatic breast cancer.

<u>2nd line treatment following palbociclib/ribociclib</u>

1. 100% of patients should be assumed to proceed to 2nd line therapy. A cohort of 100 patients will be used to determine 2nd line treatment costs.
2. Approximately 67 will have further hormone therapy
3. Approximately 33 will switch to chemotherapy at least in the first instance
4. Of the 67 patients having further hormone treatment, 27 will have the combination of everolimus and exemestane, 17 will have tamoxifen, 17 will have fulvestrant and 6

will have exemestane. No patients will receive anastrazole or letrozole as they have just progressed on it

5. Of the 33 patients having chemotherapy, 17 will have single agent capecitabine, 8 a taxane and usually weekly paclitaxel and 8 anthracyclines/other treatments
6. Only everolimus as a 2nd line treatment option has a confidential Patient Access Scheme and both the outcomes with its list and PAS prices will be presented
7. Fulvestrant has a loading dose schedule and this has been incorporated into its cost. It is sometimes administered by hospitals and a worst case scenario is assumed which has 100% hospital administration
8. Tamoxifen and single agent exemestane are prescribed by GPs and thus have no HRG administration costs
9. Relevant chemotherapy HRG administration costs (2017/18) are as follows: £120 for oral administration (everolimus plus exemestane [monthly] and also for 3-weekly capecitabine but calculated monthly); £150 for simple parenteral administration (fulvestrant and given monthly); and £301 for complex parenteral administration per visit but calculated monthly (weekly paclitaxel for 3 weeks out of 4, 3-weekly anthracyclines/other regimens)
10. It should be noted that the only high cost agents in this 2nd line setting are everolimus and fulvestrant. All the rest are generic and therefore inexpensive. NHS England does therefore not recognise the large proportion of patients having expensive chemotherapy regimens under the category of 'other' as outlined in the LRIG commentary.

Drug	Drug cost £	Admin cost £	No. patients	Total cost £
Evero +exem	2673 (LP) + 4	120	27	75519
Tamoxifen	1	0	17	17
Fulvestrant	603	150	17	12801
Exemestane	4	0	6	24
Capecitabine	27	156	17	3111
Paclitaxel	36	903	8	7512
Anthra/other	45	391	8	3488

This gives an average drug cost per patient of £1025 for 2nd line therapy. However if the PAS for everolimus is incorporated into the calculation, the average cost per patient for 2nd line treatment drops to [redacted]. These figures are illustrative but informative as to the likely approximate drug costs of 2nd line treatment, it being known that different case mixes of patients will cause costs to increase/decrease.

<u>3rd line treatment following palbociclib/ribociclib</u>

1. 75% of patients should be assumed to proceed to 3rd line therapy. Of those proceeding, a cohort of 100 patients will be used to determine 3rd line treatment costs.
2. Approximately 50 will have further hormone therapy
3. Approximately 50 will have chemotherapy at least in the first instance
4. Of the 50 patients having further hormone treatment, 13 will have the combination of everolimus and exemestane, 15 will have tamoxifen, 18 will have fulvestrant and 4 will have exemestane. No patients will receive anastrazole or letrozole as they have already progressed on it
5. Of the 50 patients having chemotherapy, 20 will have single agent capecitabine, 13 a taxane and usually weekly paclitaxel, 13 eribulin and 4 anthracyclines/other treatments
6. Everolimus and eribulin have confidential Patient Access Schemes and both the outcomes with their list and PAS prices will be presented
7. Fulvestrant has a loading dose schedule and this has been incorporated into its cost. It is sometimes administered by hospitals and a worst case scenario is assumed which has 100% hospital administration
8. Tamoxifen and single agent exemestane are prescribed by GPs and thus have no HRG administration costs
9. Relevant chemotherapy administration costs (2017/18) are as follows: £120 for oral administration (everolimus plus exemestane [monthly] and also for 3-weekly capecitabine but calculated monthly); £150 for simple parenteral administration (fulvestrant and given monthly); and £301 for complex parenteral administration per visit and calculated monthly (weekly paclitaxel for 3 weeks out of 4, 3-weekly anthracyclines/other regimens, eribulin given twice every 3 weeks)
11. It should be noted that the only high cost agents in these settings are everolimus, fulvestrant and eribulin. All the rest are generic and therefore inexpensive. NHS England does therefore not recognise the large proportion of patients having expensive chemotherapy regimens in the category 'other' as outlined in the LRIG commentary.

Drug	Drug cost £	Admin cost £	No. patients	Total cost £
Evero +exem	2673 (LP) + 4	120	13	36361
Tamoxifen	1	0	15	15
Fulvestrant	603	150	18	13553
Exemestane	4	0	4	16
Capecitabine	27	156	20	3660
Paclitaxel	36	903	13	12207
Eribulin	2347	783	13	40690
Anthra/other	45	391	4	1744

This gives an average cost per patient of £1082 for 3rd line therapy. However if the PAS prices for everolimus and eribulin are incorporated into the calculation, the average cost per patient for 3rd line treatment drops to [redacted]. These figures are illustrative but informative as to the likely approximate drug costs of 3rd line treatment, it being known that different case mixes of patients will cause costs to increase/decrease.

4th line treatment following palbociclib/ribociclib

In such a line of therapy, there will be much less hormone therapy and little use of everolimus and exemestane, this combination being the main cost driver of hormone therapy. There would be more use of eribulin, the main cost driver of chemotherapy in the 3rd line setting and also some use of oral vinorelbine. The end result is likely to be a modest increase on 3rd line treatments costs but unlikely to be in excess of [redacted] once the PAS price of eribulin has been taken into consideration.

Post progression health state costs

NHS England agrees with the assumption that health state costs of progressed disease (other than the drug costs associated with active treatment) will progressively increase with each line of therapy as there is escalating need for diagnostic tests, blood tests, palliative radiotherapy, palliative care, out patients visits etc.

Prof Peter Clark

NHS England National Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

30 September 2017

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer [ID1026]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: Nicholas Turner

Name of your organisation
Royal Marsden NHS Foundation Trust and Institute of Cancer Research

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology
- a specialist in the clinical evidence base that is to support the technology.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

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Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

Hormone receptor positive and HER negative breast cancer (hereafter referred to as HR positive) is the most common form of breast cancer, representing approximately 70% of all breast cancers. Patients with metastatic HR positive have incurable disease, but may live normal or near normal lives for many years with treatment (Turner et al Lancet 2016). The mainstay of treatment for HR positive breast cancer is endocrine therapy, therapies that target oestrogen receptor expression in the tumour. Many patients who present with metastatic HR positive breast cancer have either not had endocrine therapy before, or if they had endocrine therapy before they stopped it over a year prior to relapse. For these women endocrine therapy is the standard treatment, and for women with post-menopausal breast cancer an aromatase inhibitor such as letrozole or anastrazole (hereafter referred to as AI) is the current standard. For women with pre-menopausal metastatic HR positive breast cancer, standard treatment is to render the patient biochemically post-menopausal (with gonadotropin-releasing hormone analogue injections or by oophorectomy) and mange the patient as for post-menopausal women.

All metastatic HR positive tumours will eventually become resistant to AI and progress. Identifying therapies that enhance the effects of AI is of critical importance for the treatment of these women. Progression on therapy results in morbidity, worsening quality of life, and the need to change to more toxic treatments such as chemotherapy. Highly effective therapies are also likely to translate to improve overall survival.

There are no significant geographical variations in the first line management of metastatic HR positive breast cancer. This appraisal is not relevant to patients with visceral crisis, impending organ failure from metastatic cancer, who should be managed with chemotherapy first, before switching over to maintenance with an AI. In addition this appraisal is not relevant to patients who relapse on an AI, or within one year of stopping adjuvant AI, who are managed differently. There are no differences in opinion between professionals on the management of metastatic HR positive breast cancer, and all guidelines UK and international are consistent. There are no standard clinical variables that can be used to predict benefit from AIs, with the exception of patients with visceral crisis who are considered for chemotherapy prior to maintenance AI.

Ribociclib in combination with letrozole substantially improves progression free survival in patients with metastatic HR positive breast cancer. The benefits are highly clinically meaningful (Hazard ratio, 0.56 (95% CI, 0.43–0.72), p<0.0001, Hortobagyi et al NEJM 2017), with PFS improved from 16.0 months on letrozole and placebo to 25.3 months on letrozole and ribocicib (updated analysis after 26.4 months median following up Hortobagyi et al SABCS 2016).

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Ribociclib was well tolerated. Although there were frequent blood test abnormalities reflecting bone marrow suppression, with high rates of neutropenia being the most common adverse effect seen in 74.3% of patients, these blood test abnormalities rarely translated into clinical sequelae. Febrile neutropenia was observed in only 1.5% of patients on ribociclib and letrozole.

Ribociclib for symptomatic side effects was largely well tolerated. There was an increase in nausea, and small increases in fatigue, alopecia, diarrhoea, and stomatitis. Infrequent abnormalities in liver function tests and lengthening of the QTc interval were also noted.

Ribociclib should be administered in secondary care by an oncologist who specialises in the management of breast cancer, who is experienced in the correct management of the drug, and managing effects of bone marrow suppression with dose delays, interruptions or reductions as required. Ribocicilb is not currently used in the NHS.

The management of HR positive breast cancer with AIs is supported by NICE guidance (CG81, Published date: February 2009 Last updated: July 2014). The guidance has not been updated since CDK4/6 inhibitors became licensed. CDK4/6 inhibitors in combination with letrozole are recommended as first line therapy in the current American Society of Clinical Oncology Guideline (Rugo et al JCO 2016) and US National comprehensive cancer network (NCCN) Clinical Practice Guidelines in Oncology, Breast Cancer 2016 (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site)

The advantages and disadvantages of the technology

Aromatase inhibition for the management of metastatic HR positive breast cancer has been the standard therapy for over two decades. No drugs have been proven to improve over AIs during this time. Identification of a substantial benefit from the addition of ribociclib is therefore a highly important advance in advancing the treatment of this form of breast cancer. Ribociclib is strongly based on our understanding of the biology of HR positive breast cancer, with CDK4/6 identified as the key protein that allow HR positive breast cancer cells to grow. In many ways, CDK4/6 can be seen as being as critical to the biology of HR positive breast cancer as the oestrogen receptor itself.

Multiple other phase III studies have demonstrated very substantial benefit from adding a CDK4/6 inhibitor to endocrine therapies, in the phase III PALOMA3 study (fulvestrant plus palbocicilb, Turner et al NEJM 2015) and in the phase III PALOMA-2 study (letrozole plus palbociclib, Finn et al NEJM 2016), demonstrating class effect of CDK4/6 inhibitors). CDK4/6 inhibition is therefore the most important advance in the management of HR positive breast cancer in two decades.

The advantages and disadvantages of ribociclib and AI should be viewed with respect to therapy with AI alone.

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The advantages of ribociclib and AI are substantially improved progression free survival. Ribociclib causes relatively few symptomatic side effects, and is well tolerated by the majority of patients who take it. I have treated patients with ribociclib in combination with letrozole. Patients may have no discernable increase in side effects compared to endocrine therapy alone.

The effect of ribociclib on overall survival is unknown at this time. Precisely assessing the effects of a therapy on overall survival in HR positive breast cancer is highly challenging, as median overall survival extends to a median of 3-4 years, with multiple post-progression therapies available.

The disadvantages of therapy with ribociclib plus AI is the need for more close monitoring of the patient with blood tests than current standard practive on AI alone, and the small/modest increase in symptomatic adverse effects listed earlier. Although neutropenia is frequent, the sequela of febrile neutropenia is very rare only 1.5% patients on therapy. Although neutropenia requires monitoring, and potential dose modification or delays to manage, the CDK4/6 induced neutropenia does not lead to frequent febrile neutropenia, in stark contrast to chemotherapy induced neutropenia. The development of neutropenia is an early adverse effect, and patients on long-term treatment require less frequent monitoring. Patients on ribociclib also need monitoring in the first four weeks with ECG to assess QT interval, and monitoring of liver function tests.

The use of ribociclib and letrozole in the MONALEESA2 study closely reflects how the drug would be used in standard clinical practice in the NHS.

Equality and Diversity

This appraisal has no impact on equality and diversity.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

There are no major implementation issues for ribociclib and letrozole. The therapies are oral, and monitoring of therapy is with standard blood tests.

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Single Technology Appraisal (STA)

Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast [ID1026]

Please sign and return via NICE Docs/Appraisals.

I confirm that:

- I agree with the content of the statement submitted by Breast Cancer Now and consequently I will not be submitting a personal statement.

Name: .....

Signed: .....

Date: 27/06/2017

Decision Support Unit Project Specification Form	
Project Number	ID1026
Appraisal title	Ribociclib in combination with an aromatase inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer
Synopsis of the technical issue	Single technology appraisals for ribociclib (ID1026) and palbociclib (ID915) in the same indication have used different economic models and report different cost-effectiveness results, whereas the trials report similar findings. With such large differences, and the ribociclib model using a fixed post progression state (PFS2) which the appraisal committee had not seen in this disease area before, the appraisal committee want to have confidence in the approach and data used in the ribociclib analysis. The committee also had questions around why the ribociclib model gave some counterintuitive results: in the absence of a PAS increasing survival gains resulted in ribociclib becoming less cost effective. The committee also questioned some of the assumptions used in the modelling.
Question(s) to be answered by DSU	1. How does the ribociclib model structure compare with other approaches to modelling early breast cancer? Is the structure valid? 2. For the issues that are the main source of uncertainty for the appraisal committee, what is the quality of the evidence to support the assumptions?
How will the DSU address these questions	1. Review the model assumptions, inputs, and structure: a) Compare the EQ-5D-5L utilities (from MONALEESA-2) with the EQ-5D-3L utilities (from PALOMA-2) and the utility values in BOLERO-2 and Lloyd et al. b) Time to first line discontinuation in the model relative to PFS in the trial c) First line drug costs d) Duration and cost of second line treatments e) Duration and cost of treatments beyond second line f) Progression free survival g) Overall survival h) Other inputs

	2. Research the key assumptions and data in the ribociclib model to explore the quality of the evidence underpinning them, and alternative values which could be used
Exact analyses required	1. The following analyses are required: a) Comment on the use of a fixed PFS2 state and whether there appears to be justification in using this approach to modelling in advanced breast cancer? b) Can it be explained why: • when using list prices the ICERs decrease with a decrease in OS, while the opposite is true when PAS prices are used? • that ribociclib increases time spent in PFS1, but then limits the time spent in PFS2 and progression? c) Compare the ordering of health states using 5L, 3L (5L mapped to 3L in combination with Lloyd et al) and utilities used in ID915 and discuss the validity of these values. d) Describe the approach to modelling time to first line discontinuation • is the anticipated number of cycles of ribociclib treatment plausible, given the median PFS in MONALEESA-2? e) Report first line drug costs (dosing and pack costs) f) Describe the approach to modelling second line treatment, including description of the treatments, duration and cost g) Describe the approach to modelling treatment beyond second line, including description of the treatments, duration and cost h) Report distribution and parameters for progression free survival i) Describe the approach and sources used in modelling survival j) Report other inputs k) Adapt the structure, inputs and assumptions in the ribociclib model, individually and cumulatively to consider the above changes to assumptions (these may be further prioritised based on time and resource constraints) • Total and incremental life years, quality-adjusted life years (QALYs) and costs for treatment and comparator will be reported

	at each stage without the PAS. After all changes have been made, final analyses will be reported with and without the PAS. 2. Describe the assumptions or data that cause the greatest uncertainties. a) Where appropriate, validate existing values or suggest alternatives from published literature, expert opinion, and NICE/NHS datasets. b) Perform scenario analyses for ribociclib using suggested estimates, reporting results with the PAS.
DSU deliverables/outcomes (eg report, statement, etc)	Please provide a written report for committee.

RIBOCICLIB IN COMBINATION WITH AN AROMATOSE INHIBITOR FOR PREVIOUSLY UNTREATED ADVANCED OR METASTATIC HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE BREAST CANCER: A REVIEW OF THE MODEL STRUCTURE, INPUTS AND ASSUMPTIONS

REPORT BY THE DECISION SUPPORT UNIT

August 2017

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

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1. EXECUTIVE SUMMARY

The National Institute for Health and Care Excellence (NICE) is appraising ribociclib in combination with an aromatose inhibitor for previously untreated advanced or metastatic hormone receptor-positive, HER2-negative breast cancer. The model submitted by the company (Novartis) uses an approach that the Committee have not seen in advanced breast cancer before and so NICE have requested the Decision Support Unit (DSU) to explore the validity of the structure, data and assumptions.

Novartis' model assumes that after progression on ribociclib or comparator, patients who are still alive follow the progression-free survival (PFS) and overall survival (OS) of the subsequent treatment. Novartis estimate subsequent PFS and OS from a trial of everolimus plus exemestane in patients with hormone receptor-positive, HER2-negative breast cancer who have previously received an aromatose inhibitor. This approach assumes full surrogacy: that survival after progression is identical for ribociclib and the comparator, and therefore any gain in PFS translates into the same gain in OS. The DSU conducted a non-systematic review to establish whether the assumption of full surrogacy is valid in this population and found that the evidence was inconclusive. An alternative to assuming full surrogacy is to conduct analyses assuming partial surrogacy: where OS gain is smaller than PFS gain. Partial surrogacy is implemented by decreasing the time spent in states after first line PFS in the ribociclib arm of the model.

Regardless of whether full or partial surrogacy is assumed, the cost-effectiveness of ribociclib is influenced by the costs of ribociclib treatment, time to discontinuation (TTD), PFS and the utility values in PFS.

Novartis assume the observed dose reduction on ribociclib in the trial decreases drug costs as patients can take fewer than the recommended 3 tablets daily.

The extrapolation of TTD and PFS beyond the trial period relies on parametric distributions fitted in survival analysis – in the base case Novartis use the exponential distribution for both TTD and PFS, but the ERG consider that the Weibull may be equally plausible, which increases the incremental cost-effectiveness ratio (ICER). When the exponential distributions are used for TTD and PFS, the mean TTD for ribociclib is much lower than the mean PFS for ribociclib. When using the Weibull distribution for TTD and PFS, the difference between

mean PFS and mean TTD for ribociclib is less than when using the exponential, and it appears more consistent with rate of discontinuations due to AEs for ribociclib.

Novartis used EQ-5D-5L utilities in the PFS1 state, valued using the 5L value set. The 5L value set is not recommended by NICE, so Novartis have now mapped the scores to 3L, which produces a lower utility. The value Novartis used for PFS2 was not EQ-5D, and [redacted]. An EQ-5D score for second line treatment in this population is available from another source.

Under the assumption of full surrogacy, the treatment pathway, survival, costs and utilities beyond progression on first line treatment are the same for ribociclib and comparator, and therefore do not influence cost-effectiveness results. Under the assumption of partial surrogacy, the costs, life years and quality-adjusted life years (QALYs) accrued beyond first-line progression differ for ribociclib and comparator, and therefore do influence cost-effectiveness results. If later-line treatments are more cost-effective, this favors the comparator as patients in the comparator arm receive them for longer – and so the ICER for ribociclib increases. If later-line treatments are less cost-effective, this favors ribociclib as patients in the ribociclib arm receive them for less time – and so the ICER for ribociclib decreases.

Novartis' model assumes that patients receive that patients receive treatment for all lines post progression on second line therapy with a fixed drug cost of £2,000 after progression on second line treatment. Novartis' assumption that these treatments cost £2,000 per month until death likely overestimates the cost of treatments beyond second line. The ERG provided an alternative cost of £1,140 which appears more reasonable.

Novartis' base case ICER was [redacted]/QALY without the patient access scheme (PAS), and [redacted]/QALY with the PAS. Using the ERG's cost for treatment after progression and EQ-5D-3L utilities for PFS1 (EQ-5D-5L mapped to 3L from the trial) and PFS2 (EQ-5D-3L in second line therapy from Mitra *et al* 2016) [redacted] the ICERs to [redacted](without PAS) and [redacted](with PAS). Varying the assumptions around TTD, PFS, dosing and surrogacy [redacted] the ICERs to a [redacted] of [redacted](without PAS) and [redacted](with PAS).

CONTENTS

TABLES

FIGURES

ABBREVIATIONS AND DEFINITIONS

3L	Three level (EuroQol Five Dimension)
5L	Five level (EuroQol Five Dimension)
BNF	British National Formulary
BOLERO-2	Breast Cancer Trials of Oral Everolimus-2
CG	Clinical Guideline
DSU	Decision Support Unit
eMIT	Electronic Marketing Information Tool
EQ-5D	EuroQol Five Dimension
ER	(O)estrogen receptor
ERG	Evidence Review Group
HR	Hormone receptor
HER2	Human epidermal growth factor
ICER	Incremental cost-effectiveness ratio
MONALEESA-2	Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety-2
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PALOMA-1	Palbociclib: Ongoing Trials in the Management of Breast Cancer-1
PALOMA-2	Palbociclib: Ongoing Trials in the Management of Breast Cancer-2
PAS	Patient access scheme
PDS	Post-discontinuation survival
PFS	Progression-free survival
QALY	Quality-adjusted life-year
SACT	Systemic Anti-Cancer Therapy
TA	Technology Appraisal
TPC	Treatment of physician's choice
TTD	Time to discontinuation

2. INTRODUCTION

2.1. Background

The National Institute for Health and Care Excellence (NICE) is appraising ribociclib (Novartis) in combination with an aromatose inhibitor for previously untreated advanced or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer (ID1026)[1]. NICE is also appraising palbociclib (Pfizer) in the same indication (ID915)[2]. The companies for the two technologies used different economic models and reported different cost-effectiveness results, whereas the clinical trials report similar findings. Pfizer developed a partitioned survival analysis model for palbociclib, whereas Novartis used a patient level simulation model to model later-line treatments after patients have progressed on ribociclib or comparator. The committee have not seen the approach used by Novartis in this disease area before, and want to have confidence in the approach and data used. The committee questioned some of the assumptions and results in Novartis' model for ribociclib.

The Decision Support Unit (DSU) has been commissioned to help the committee understand Novartis' model, and whether it is a valid approach. The DSU have been asked to:

- review the model assumptions, inputs and structure, and explore the quality of the evidence underpinning these
- describe the assumptions or data that cause the greatest uncertainties and:
    - critique the values used by the company
    - identify plausible alternatives if those used by the company lack validity
    - perform scenario analyses to explore the impact of using plausible alternative values

2.2. Treatment pathway in HER2-negative, Hormone-receptor positive advanced breast cancer

NICE Clinical Guideline (CG)81 on advanced breast cancer recommends endocrine therapy as first-line treatment for the majority of patients with oestrogen receptor (ER)-positive advanced breast cancer[3]. This endocrine therapy should be an aromatose inhibitor for postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy, and for postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. The comparator for ribociclib in the scope for ID1026 is aromatose inhibitors[4], and this will is the positioning for ribociclib in combination with an aromatose inhibitor in the company submission[5]

CG81 recommends that on disease progression, systemic sequential chemotherapy is offered to the majority of patients who have decided to be treated with chemotherapy.

Technology Appraisal (TA)421 recommends everolimus, in combination with exemestane, within its marketing authorisation, as an option for treating advanced HER2-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor[6].

TA423 recommends eribulin for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)[7].

CG81 recommends that for patients not suitable for anthracyclines, the sequence of chemotherapy should be single-agent docetaxel followed by single-agent vinorelbine or capecitabine and then single-agent capecitabine or vinorelbine.

3. MODELLING APPROACH

3.1. Partitioned survival analysis

Many economic models for previous NICE technology appraisals in breast cancer have used a partitioned survival approach, extrapolating PFS and OS curves from the clinical trials (TA214[8], TA263[9], TA116[10], TA257[11], TA458[12], TA421[6], TA423[7], TA239[13]). Partitioned survival models use the "area under the curve" to calculate the proportion of patients in the pre-progression, post-progression and death states at each time point. Typically, survival analysis is performed to fit curves to the Kaplan-Meier data, and extrapolate data beyond the trial period until all patients have died. Time to discontinuation (TTD) may be modelled in the same way as PFS and OS. This approach is shown in **Error! Reference source not found.**. The DSU has published a technical support document (TSD) on partitioned survival analysis, including an explanation, review and critique[14]. This is the approach that Pfizer have taken for palbociclib – although they have adjusted the parametric curve for OS for palbociclib such that the difference between the median OS for palbociclib and median OS for placebo is equal to the difference between median PFS for palbociclib and median PFS for placebo.

3.2. Modelling approach in ID1026

Novartis do not use partitioned survival analysis, and instead use a patient-level state-transition model. Novartis stated that the immaturity of OS data in MONALEESA-2 would make direct estimation of OS challenging and for this reason external data is used to estimate

OS[5]. In this approach, Novartis extrapolate the PFS data from their trial, and then add on survival from the next line of therapy to patients who are still alive. Survival for the next line of therapy is estimated by extrapolating time to discontinuation (TTD) and post-discontinuation survival (PDS) data from the BOLERO-2 study and applying hazard ratios to model different treatments. TTD and PDS on any given second line therapy is the same for patients who received letrozole plus placebo and ribociclib plus letrozole in first line. This broad approach is shown in Figure 2. More detail around second line treatment is presented in Figure 3 – three second line treatments are modelled, and a different proportion of patients on ribociclib and placebo receive each second line treatment.

The approach used by Novartis assumes that PFS gain translates into OS gain (100% surrogacy) and that patients entering the second line BOLERO-2 study are representative of patients progressing on first line therapy. We have reviewed the evidence to support the assumption that PFS gain is a surrogate for OS gain, and tested the validity of this approach in advanced breast cancer.

Figure 1: Partitioned Survival Analysis (all data illustrative)

OS: Overall survival, PFS: progression free survival, TTD: time to discontinuation

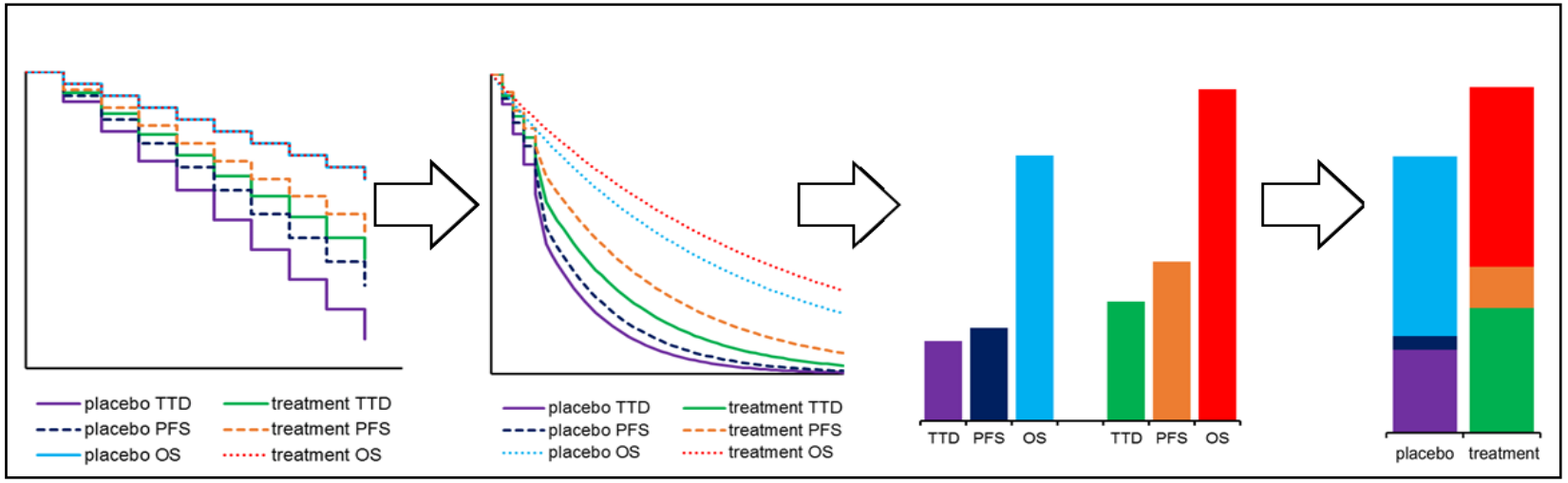


Figure 1: Modelling approach in ID1026 (all data illustrative)

OS: overall survival, PDS: post discontinuation survival, PFS: progression-free survival, TTD: time to discontinuation

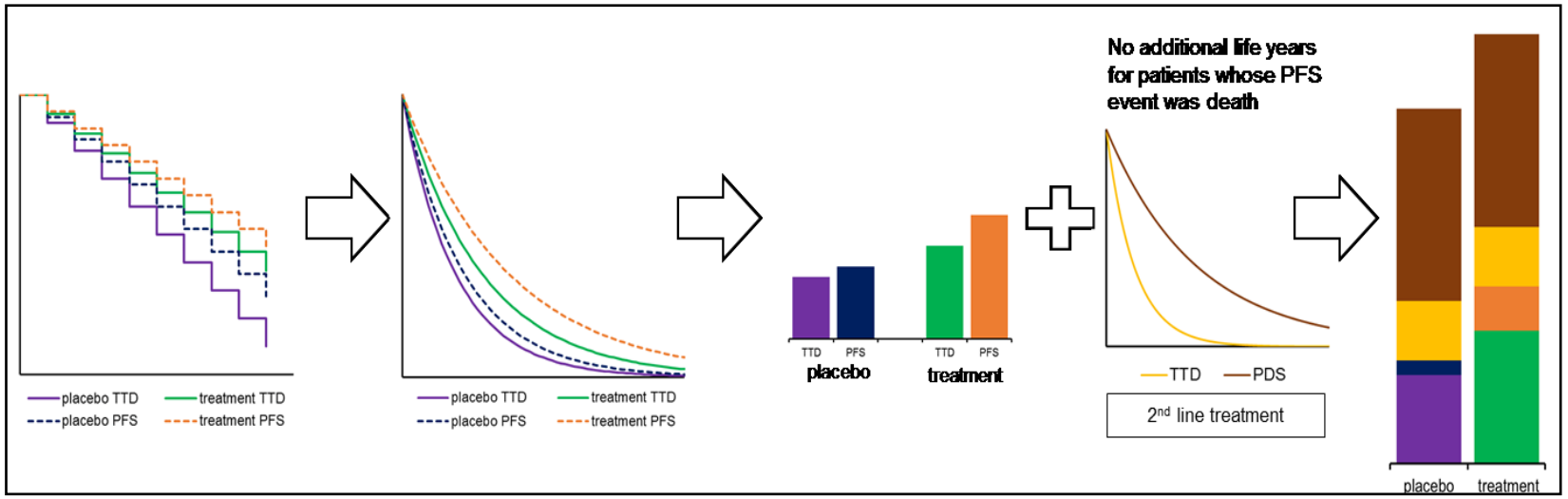
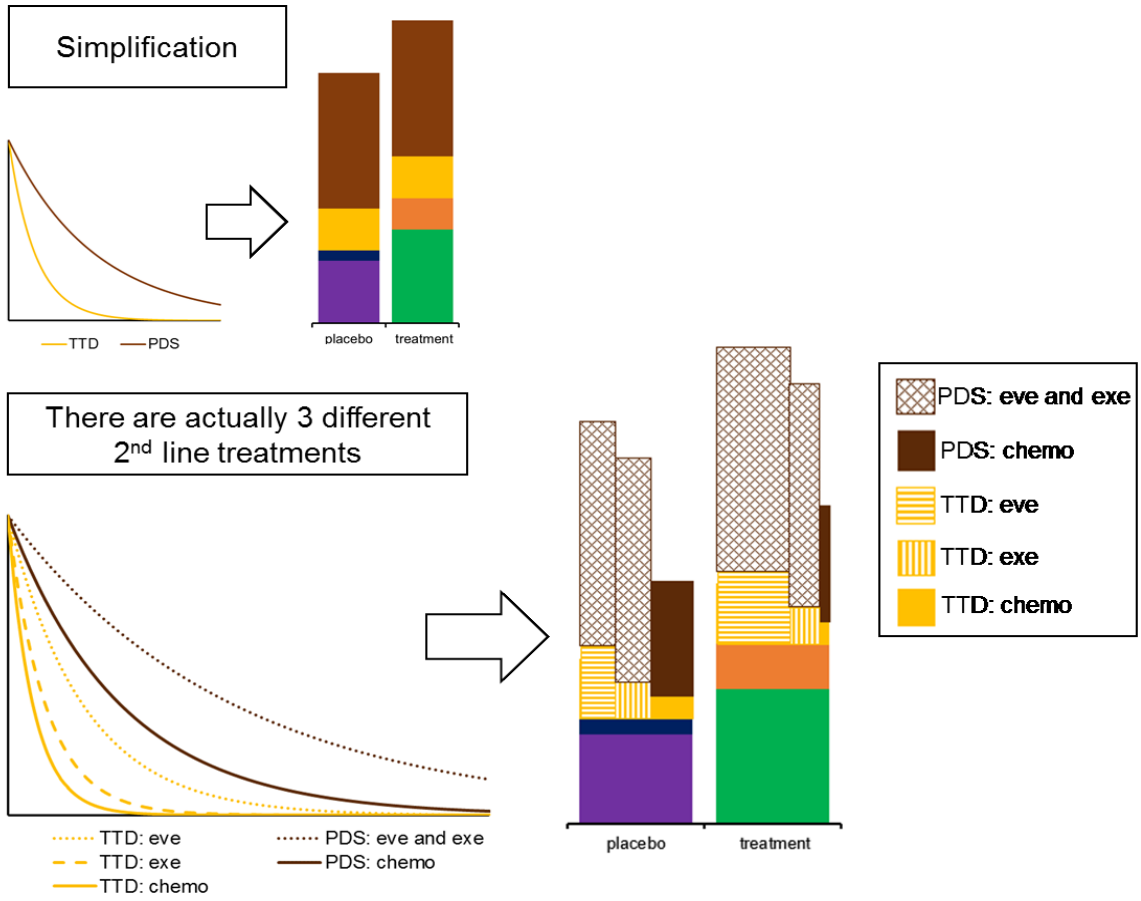


Figure 2: Modelling approach in ID1026: continued

Chemo: chemotherapy, eve: everolimus plus exemestane, exe: exemestane only, PDS: post discontinuation survival, TTD: time to discontinuation



3.2.1. PFS gain as a surrogate for OS gain

We reviewed the relationship between PFS and OS gains in several studies – these studies were identified as those included in the company submissions for ribociclib[5] and palbociclib[15], and those included in the DSU report[16] (and update[17]) reviewing the relationship between PFS and OS. The results, shown in Table 1, suggest that while a PFS gain is likely to result in an OS gain, there is no clear relationship between the size of PFS gain and OS gain.

Table 1: Relationship between PFS gain and OS gain

Study	Line of therapy	Intervention	Comparator	Δ median PFS	Δ median OS	PFS gain greater or less than OS gain?	Difference between Δ median PFS and Δ median OS
PALOMA-1[15]	First line	Palbociclib + letrozole	Letrozole	10.0	4.2	Greater	5.8
Parideans[18]	First line	Exemestane	Tamoxifen	4.2	6.1	Less	-2.0
Martin[19]	First line	Bevacizumab + letrozole/ fulvestrant	Letrozole/ fulvestrant	4.9	0.3	Greater	4.6
Dickler [20]	First line	Bevacizumab + letrozole	Letrozole	4.6	3.3	Greater	1.3
BOLERO-2[21]	Second line	Everolimus + exemestane	Exemestane	4.6	4.4	Greater	0.2
Study301[22]	Third line	Eribulin	Capecitabine	0.2	2.6	Less	-2.4
Study305[22]	Fourth line	Eribulin	TPC	1.5	2.9	Less	-1.4
Beauchemin[23]	Mixed	Various	Various	ΔOS = -0.088 + 1.753 x ΔPFS		Less	Varies
Burzykowski [24]	First line	Anthracycline (alone or in combination)	Taxane (alone in or combination with anthracycline)	A weak and imprecise positive association between treatment effects for PFS and OS			
Miksad[25]	Mixed	Anthracycline or taxane based	Any	Statistically significant association between both direction and magnitude of trial-level treatment effect on PFS and OS			
Petrelli and Barni[26]	First line	Various	Various	Highly significant correlation between HR for PFS and OS in a linear regression			
Michiels[27]	Mixed	Various – but all HER2+	Various – but all HER2+	Treatment effects on PFS correlated moderately with treatment effects on OS			
Sherrill[28]	Mixed	Various	Various	Treatment effect on progression is concordant but not as large for the OS outcome			

HER2+: human epidermal growth factor positive, HR: hazard ratio, PFS: progression-free survival, OS: overall survival

3.2.2. Testing the validity of this approach

To test the validity of the approach used by Novartis, we performed similar analysis using median and mean estimates for PFS and OS in varying lines of treatment. We estimated OS for first, second and third line therapy by adding the OS of the next line of therapy onto the PFS for that line for the proportion of patients still alive. We compared these cumulative estimates of survival to the actual values from the trial. We did this for median values (reported in the literature) and mean values (reported in the literature or calculated from the

parametric distributions in the economic models). The first line estimates are from the PALOMA-1 study[15], the second line estimates are from BOLERO-2[21], and the third line and fourth estimates are from study 301 and study 305 in TA423[22]. The proportion of patients who have died by the median or mean PFS was calculated by reading off the Kaplan-Meier graphs for overall survival from each source.

In each case, we do not know which treatment patients in the trial actually received as their subsequent therapy, so we present estimates using the treatment and comparator arm of the next line trial.

The results, shown in Table 2, demonstrate that this approach appears to overestimate survival in first line, and underestimate survival in second line. In third line, the estimates from the cumulative approach appear closer to the actual values, with the cumulative approach overestimating survival for some treatment sequences and underestimating survival in others. It is unclear whether this approach is valid – and which direction it may be biasing results. We explored this further by considering the proportion of patients receiving subsequent lines of therapy, baseline characteristics, and longer-term validation.

Table 2: Validating the cumulative survival approach

OS: overall survival, PFS: progression-free survival, TPC: treatment of physician's choice

	Line	Treatment	Assumed next line treatment	PFS	% dead by PFS	OS of next line	Cumulative OS	Trial OS	Cumulative greater or smaller than trial?	Difference between cumulative and trial
Median	1L	Palbociclib	Everolimus plus Exemestane	20.2	0.15	31	46.6	37.5	Greater	9.1
		Palbociclib	Exemestane			26.6	42.8		Greater	5.3
		Letrozole	Everolimus plus Exemestane	10.2	0.1	31	38.1	33.3	Greater	4.8
		Letrozole	Exemestane			26.6	34.1		Greater	0.8
	2L	Exemestane	Eribulin	7.8	0.08	16.1	22.6	31	Smaller	-8.4
		Exemestane	Capecitabine			13.5	20.2		Smaller	-10.8
		Everolimus plus Exemestane	Eribulin	3.2	0.03	16.1	18.8	26.6	Smaller	-7.8
		Everolimus plus Exemestane	Capecitabine			13.5	16.3		Smaller	-10.3
	3L	Eribulin	TPC	4.0	0.11	13	13.7	13.5	Smaller	-2.4
		Eribulin	Eribulin			10.1	16.4		Greater	0.3
		Capecitabine	TPC			13	13.0		Smaller	-0.5
		Capecitabine	Eribulin			10.1	15.6		Greater	2.1
Mean	1L	Palbociclib	Everolimus plus Exemestane	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		Palbociclib	Exemestane							
		Letrozole	Everolimus plus Exemestane							
		Letrozole	Exemestane							
	2L	Exemestane	Eribulin							
		Exemestane	Capecitabine							
		Everolimus plus Exemestane	Eribulin							
		Everolimus plus Exemestane	Capecitabine							
	3L	Eribulin	TPC	4.56	0.07	16.07	16.68	21.75	Smaller	-5.1
		Eribulin	Eribulin			13.03	19.51		Smaller	-2.2
		Capecitabine	TPC	3.99	0.11	16.07	15.59	17.13	Smaller	-1.5
		Capecitabine	Eribulin			13.03	18.29		Greater	1.2

3.2.2.1. Proportion of patients receiving subsequent therapies

We note that not all patients may receive the next line of therapy when they progress. However, in the clarification questions, Novartis stated that [redacted] went on to receive a non-therapeutic therapy after progression in the MONALEESA-2 study[5].

3.2.2.2. Patient characteristics

The baseline characteristics of the MONALEESA-2 study[5] and the BOLERO-2 study[29] are reproduced in Table 3 and Table 4.

Table 3: MONALEESA-2 baseline characteristics

Baseline characteristics	**Ribociclib group (n=334)**	**Placebo group (n=334)**
Median age (years)	62	63
Age range (years)	23-91	29-88
Race, (%)		
White	80.5	60.5
Asian	8.4	6.9
Black	3.0	2.1
Other	8.1	7.2
ECOG performance status, (%)		
0	61.4	60.5
1	38.6	39.5
2	0	0
No. of metastatic sites, (%)		
0	0.6	0.3
1	29.9	35.0
2	35.5	30.8
≥3	34.1	33.8
Previous neoadjuvant or adjuvant chemotherapy (%)	43.7	43.4

Table 4: BOLERO-2 baseline characteristics

Baseline characteristics	**Everolimus and exemestane group (n=334)**	**Placebo and exemestane group (n=334)**
Median age (years)	62	61
Age range (years)	34-93	28-90
Race, (%)		
White	74	78
Asian	3	1
Black	20	19
Other	3	2
ECOG performance status, (%)		
0	60	59
1	36	35
2	2	3
No. of metastatic sites, (%)		
0	0	0
1	32	29
2	31	34
≥3	36	37
Previous neoadjuvant or adjuvant chemotherapy (%)	44	40

The median ages in the two studies are similar, whereas we may expect the patients in BOLERO-2 to be slightly older as it is a later line of therapy– but we would not expect this to make a large difference. The distribution of ECOG status and number of metastatic sites are similar between the studies. The proportion with previous neoadjuvant or adjuvant chemotherapy is similar between the studies. 100% of patients in BOLERO-2 had received previous treatment with letrozole or anastrazole. There does not appear to be anything

obvious to indicate that BOLERO-2 could not represent patients progressing in MONALEESA-2.

3.2.2.1. Long term validation

Novartis compared the predicted OS for letrozole from their model with two more mature studies of first line endocrine therapy in advanced breast cancer: LEA[19] and ALLIANCE[20]. The median OS estimates for endocrine therapy in LEA and ALLIANCE are 51.8 and 43.9 months. Although the LEA and ALLIANCE studies provide slightly different Kaplan-Meier estimates for the OS on endocrine therapy, the modelled OS prediction for letrozole from the Novartis model, which is based on PFS data from the MONALEESA-2 study and OS from BOLERO-2, seems to be [redacted] with the average OS of these two longer-term studies (Figure 3).

Figure 3: Novartis' validation of overall survival (reproduced)

Original figure 45 on page 185 of Novartis' company submission. Reproduced from Novartis' economic model using progression-free survival data from January 2017. Ribociclib data removed for clarity.

[redacted]

In ID915, Pfizer compared their predicted OS for letrozole to Paridaens 2008[18], Bergh 2012[30] and Mouridsen 2003[31] which reported much lower median OS than LEA or ALLIANCE: 37.2, 37.8 and 34.0 months respectively. There is such a large variation in OS estimates for

endocrine therapy that it is difficult to know which estimate is most relevant for validation, and therefore whether Novartis' predicted results are valid.

3.3. Other modelling approaches in (breast) cancer

There are a few NICE technology appraisals in breast cancer that did not use partitioned survival analysis: TA424 used response as a surrogate for survival[32], TA112 used disease-free survival data and relapse to model progression to metastatic disease and modelled survival from metastatic disease using other sources[32], and TA108 used a similar approach to TA112 using recurrence-free progression[33].

Although the approach of "adding on" overall survival from a later line has not been used previously in NICE appraisals for breast cancer, it has been used in the evaluation of bosutinib for chronic myeloid leukaemia in TA401[34]. In this appraisal, the clinical effectiveness data for bosutinib came from a single arm trial and overall survival data was immature. The committee accepted a cumulative approach in which the overall survival from standard care was added on after time on treatment for bosutinib.

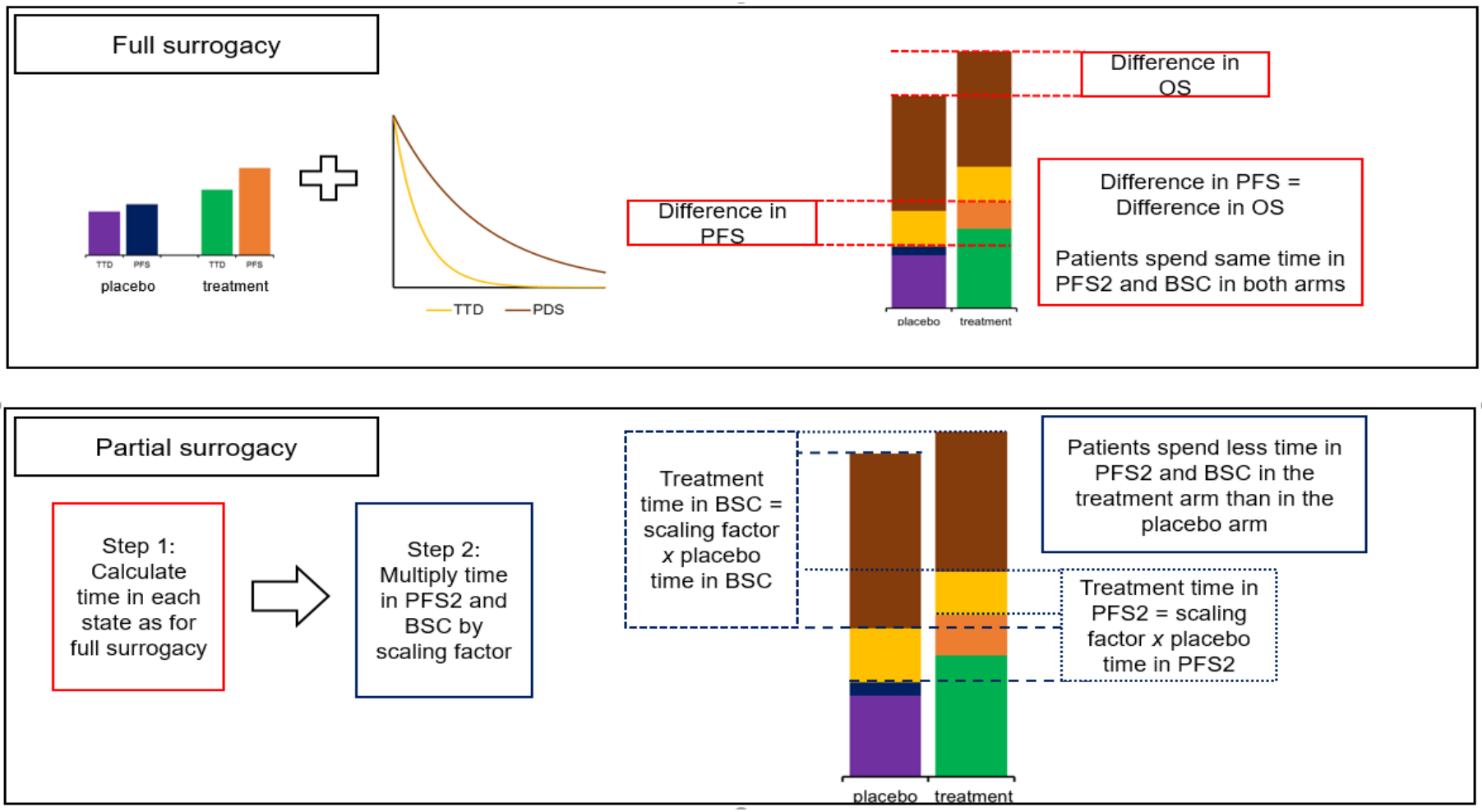
4. FULL OR PARTIAL SURROGACY

4.1. Time in health states

As discussed in Section 3.2, Novartis assumed 100% surrogacy. The evidence review group (ERG) considered this assumption speculative, and referred to the PALOMA-1 trial where the ratio of gain in median OS to gain in median PFS was 38.5% (37.5-33.3)/(25.7-14.8)[5]. (We note an updated analysis indicates that the ratio of median OS gain to median PFS gain may be smaller at 27.5% (37.5-34.5)[35]/(25.7-14.8)[15]). The ERG assumed partial surrogacy using the ratio of 38.5% in their base case analysis. For all analyses in this document using partial surrogacy, we use the ratio of 38.5%. To implement this in the economic model for ribociclib, a scaling factor is applied to reduce the time spend in the health states beyond PFS to adjust the total life years such that the difference in OS between treatment and comparator is reduced. This means that the time in PFS2 and BSC is lower for ribociclib than for placebo. The scaling factor was incorporated by Novartis in response to a request from the ERG. A comparison of full and partial surrogacy is shown in Figure 5.

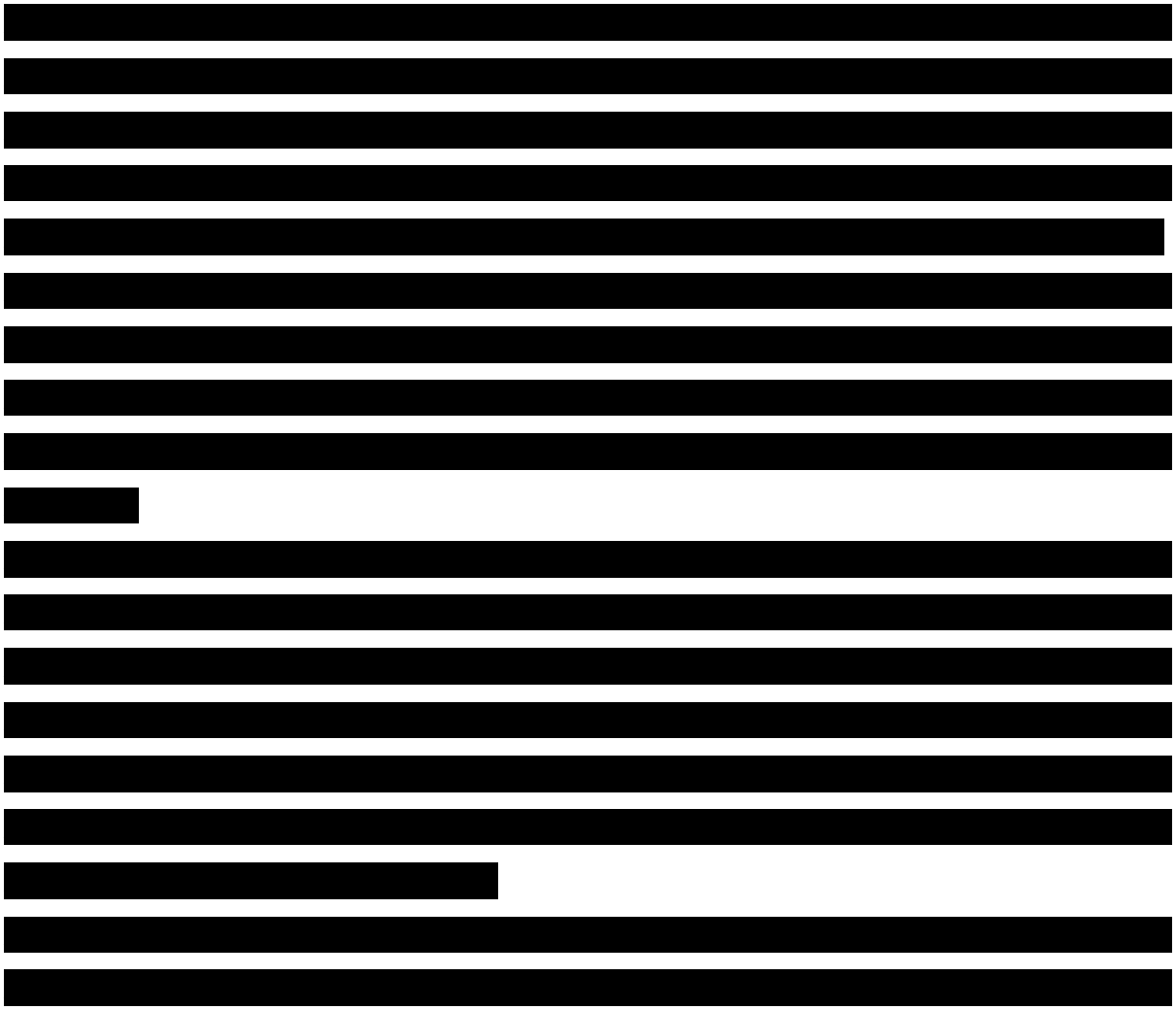
Figure 4: Full and partial surrogacy

BSC: best supportive care, Chemo: chemotherapy, eve: everolimus plus exemestane, exe: exemestane only, PDS: post discontinuation survival, PFS: progression-free survival, TTD: time to discontinuation



4.2. Effect of full or partial surrogacy on cost-effectiveness

The different health states have different costs and different utility values. The cost per quality-adjusted life year (QALY) for each health state therefore differs, shown in Table 5. The overall incremental cost-effectiveness ratio (ICER) for treatment versus comparator depends on the difference in costs and QALYs for PFS1, PFS2 and BSC. The costs and QALYs in PFS1 are the same when full or partial surrogacy are assumed as the time in PFS1 does not change. The costs and QALYS in PFS2 and BSC are similar for treatment and comparator when full surrogacy is assumed, but they differ substantially when partial surrogacy is assumed because patients on treatment spend less time PFS2 and BSC than patients on placebo. Patients spend longer in BSC than PFS2 so the cost effectiveness of the BSC state makes a bigger difference than the PFS2 state. Two costs are available for the BSC state: £2,000 per month used by Novartis, or £1,140 per month preferred by the ERG[5].



[redacted]

Table 5: Health state costs, utilities and cost per QALY

Health state	Health state cost /week	Treatment cost /week	AE cost /week	Monitoring cost /week	Total cost /week	Utility value	Cost per QALY
BSC: CS	£45	£462			£507	0.51	[redacted]
BSC: ERG	£45	£263			£308	0.51	[redacted]
PFS2: eve	£36	[redacted]			[redacted]	0.77	[redacted]
PFS2: exe	£36	£1.39			£37	0.77	[redacted]
PFS2: chemo	£36	£109			£145	0.66	[redacted]
PFS1: off treatment	£36	£0			£36	[redacted]	[redacted]
PFS1: on letrozole	£36	£0.38	£0.65		£37	[redacted]	[redacted]
PFS1: on ribociclib (list price)	£36	[redacted]			[redacted]	[redacted]	[redacted]
PFS1: on ribociclib (PAS)	£36	[redacted]	£2.07	0-4: £44 6-20: £4 24+ £0	[redacted]	[redacted]	[redacted]

AE: adverse event, BSC: best supportive care, Chemo: chemotherapy, CS: company submission, ERG: evidence review group, eve: everolimus plus exemestane, exe: exemestane only, PAS: patient access scheme, PDS: post discontinuation survival, PFS: progression-free survival, QALY: quality-adjusted life-years

5. MODEL VERIFICATION

To determine whether the Novartis model is structurally sound and does not contain hidden errors we used black-box testing and assessed the external validity of the Novartis model using inputs from the palbociclib appraisal, as the decision problems for these two appraisals are similar. Black-box testing is a form of model validation that involves changing the model

inputs and observing whether the model outputs move in the manner expected. In this case, we used the model inputs from the palbociclib appraisal within the ribociclib model. From this we confirmed that the model outputs behaved in the manner expected when alternative values were inputted one at a time. We also assessed the external validity of the Novartis model structure by making several of the key inputs consistent with those used in the palbociclib model. We found that the Novartis model was able to produce outputs reasonably consistent with those reported for palbociclib when using inputs from the palbociclib model, which confirms the external validity of the ribociclib model. These two tests of quality assurance provide some reassurance that the model structure used by Novartis is externally valid and does not contain any hidden errors. However, it should be noted that the DSU did not attempt to exhaustively validate the Novartis model.

The black-box analysis was also useful in exploring the impact on the ICER of varying different inputs under the assumption of both full and partial surrogacy. We identified that the inputs that cause the greatest impact on the ICER are:

1. The drug costs of ribociclib
2. Costs beyond second line, if partial surrogacy is used
3. Utilities
4. Progression-free survival
5. Overall survival

Each of these inputs is discussed in more detail in later sections. Sections 6 - 10 report scenario analyses to demonstrate the impact of using alternative inputs for each of the key model drivers listed above, using Novartis' base case as a starting point. Scenarios for the costs and survival beyond second line are conducted for both full and partial surrogacy as the impact of second line costs varies depending on this assumption, but in the other sections full surrogacy is used as per Novartis' base case. Section 11 reports results of scenario analyses using the inputs we consider most plausible.

6. DRUG COSTS OF RIBOCICLIB

The total drug cost for ribociclib is influenced by the duration of ribociclib treatment and the cost per dose. Both of these are discussed further.

6.1. Duration of ribociclib treatment

Novartis fitted parametric curves to the TTD data from MONALEESA-2 (Figure 5). They chose the exponential curve on the basis that it was also used for PFS, visual inspection and

clinical validation. The exponential had the highest Akaike Information Criterion (AIC) score and Bayesian Information Criterion (BIC) score for ribociclib, indicating the least good statistical fit. The ERG for ID915 also used the exponential distribution for TTD, but used Kaplan-Meier data at the beginning of the curve. Neither Novartis nor the ERG for ID1026 report scenario analysis varying the TTD curve in isolation, and instead vary both the TTD and PFS curves simultaneously. We note that the [redacted] curves in Figure 5 [redacted] the PFS curve, suggesting that patients [redacted]. The economic model contains a constraint in the coding that sets time on treatment to be the minimum of the sampled time on treatment and sampled progression free survival, to ensure that simulated patients do not continue treatment beyond progression.

Figure 5: Novartis' time to discontinuation parametric curves (reproduced)

PFS: progression-free survival. Reproduced from Novartis' company submission, figure 29 page 120.

In their company submission, Novartis state that the expected number of courses of treatment is [redacted] courses ([redacted] months), from the CSR[5]. The mean of the fitted exponential TTD distribution is [redacted] months. The mean of the fitted exponential PFS distribution is [redacted] months. It is unclear why TTD is so much shorter than PFS. We note that in modelling second line treatment, TTD is used as a proxy for PFS, implying the two are similar if not the same. The company submission states that [redacted] of patients had adverse events leading to discontinuation. If [redacted] of patients had discontinued due to adverse events at the beginning of the study, and the remaining [redacted] had discontinued upon progression or death, then the mean TTD using the

[redacted]_distribution for PFS would be [redacted] months ([redacted] * [redacted] months). This is notably higher than the mean of the fitted [redacted] distribution for TTD.

Using the exponential distribution for TTD assumes that the rate of discontinuing is constant over time (patients are equally likely to discontinue at the beginning, middle or end of the study). We may expect that there is a higher rate of discontinuing early in the study if there is a proportion of patients who experience intolerable adverse events, or later in the study if patients are then more likely to progress or die.

Unlike the exponential, the Weibull distribution allows the rate of discontinuation to vary over time. The Weibull curve fitted to the TTD data assumes that the rate of discontinuation decreases over time. The Weibull curve that fitted to the PFS data assumes that the rate of progression or death increase over time. This means that the Weibull PFS and TTD curves converge more quickly than the exponential PFS and TTD curves (Figure 7), and the difference between the mean Weibull PFS and mean Weibull TTD is less than the difference between the mean exponential PFS and mean exponential TTD.

The mean of the fitted [redacted] TTD distribution is [redacted] months. The mean of the fitted PFS [redacted] distribution is [redacted] months. If [redacted] of patients had discontinued due to adverse events at the beginning of the study, and the remaining [redacted] had discontinued upon progression or death, then the mean TTD using the [redacted] distribution for PFS would be [redacted] months ([redacted] * [redacted] months). This is close to the mean of the fitted [redacted] distribution for TTD. This may suggest that the Weibull distribution is a more appropriate extrapolation of TTD and PFS than the exponential distribution.

Additionally, we note that the data for PFS uses analysis from a cut-off in January 2017. The data for TTD uses analysis from a cut-off in January 2016 and is therefore less mature and there is more uncertainty around the extrapolation beyond the cut-off.

Figure 6: Ribociclib PFS and TTD

PFS: progression-free survival, TTD: time to discontinuation

When we used the Weibull curve for TTD (for both ribociclib and letrozole), the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. We also considered a scenario using the log-normal curve as an example with a much longer TTD. We chose the log-normal on the basis that the Gompertz does not look like a good visual fit, and the AIC and BIC are lower (better) for the log-normal than the log-logistic. When we used the log-normal curve, the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. This demonstrates that the ICER is sensitive to the choice of curve. Full results are provided in Table 6.

Table 6: Scenario analysis varying TTD curves

	Total QALYs		Total Costs		ICER
	Ribociclib	**Letrozole**	**Ribociclib**	**Letrozole**	**Ribociclib vs. letrozole**
Without PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull					
log-normal					
With PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull					
log-normal					

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

6.2. Ribociclib cost

The licensed dose for ribociclib is 600mg once daily for 21 days of a 28 day cycle[5]. This dose consists of three 200mg tablets. Ribociclib 200mg is available in packs of 63, 42, and 21 tablets, with a pricing structure such that each 200mg tablet has the same price regardless of the pack size.

A proportion of patients in MONALEESA-2 had their dose reduced to 400mg and 200mg daily. Novartis assumed that patients who reduce their dose do not waste tablets as they can simply take fewer tablets daily, and so a pack lasts longer. Novartis used individual patient data to calculate the total number of days patients received each dose for per cycle to cost the drug per cycle (cycle 10 data is used for cycle 10 onwards due to decreasing patient numbers). Drug acquisition costs per cycle are reproduced from Novartis' submission in Table 7 (without the PAS). Without considering dose reduction, one cycle of ribociclib costs [redacted] (without the PAS).

Table 7: Novartis' ribociclib drug costs (reproduced)

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Reproduced from Novartis' company submission, table 43 page 153.

The ERG noted that wastage at discontinuation should be included, which increased the ICER by less than [redacted] per QALY.

When we assumed that all patients received the full dose of ribociclib each cycle, the ICER increased by around [redacted] without the PAS, and by around [redacted] with the PAS. Full results are provided in Table 8.

Table 8: Scenario analysis varying dose reduction

	Total QALYs		**Total Costs**		**ICER**
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case: dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Full dose	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

7. TREATMENTS BEYOND SECOND LINE

Novartis did not explicitly model treatments beyond second line, but instead applied a monthly drug cost of £2,000 to the progressed health state. Novartis stated this cost was based upon "expert clinical validation and consideration of previous NICE appraisals…in advanced breast cancer"[5]. In their scenario analysis, Novartis found that reducing this cost to £0 increased the ICER by less than [redacted] (without PAS). This is because under the

assumption of full surrogacy, the time in the progressed health state is similar between arms (see Section 4.2). The ERG preferred to use a monthly drug cost of £1,140 in the progressed health state, based on third-line treatment costs in TA239[13]. When the ERG varied this cost under the assumption of partial surrogacy, they found that this cost had a big impact on the ICER: using a cost of £0 [redacted] the ICER by around [redacted] with the PAS, and by around [redacted] without the PAS. Using a cost of [redacted] decreased the ICER by around [redacted] with the PAS and by around [redacted] without the PAS[5]. When we applied the partial surrogacy assumption used by the ERG (38.5% of full surrogacy) to Novartis' base case, we found that using the ERG's 3rd line cost instead of Novartis' [redacted] the ICER by around [redacted] without the PAS, and by around [redacted] with the PAS. Full results are presented in Table 9.

Table 9: Scenario analysis varying 3rd line costs: partial surrogacy

	Total QALYs		Total Costs		ICER
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case: Full surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with ERG 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: Full surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with Novartis' 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Partial surrogacy with ERG 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG: evidence review group, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

7.1. Treatment pathway beyond second line

In Novartis' model, patients in the progressed health state remain there until death, and thus are assumed to receive the treatments included in the monthly drug cost until death.

The NICE guidance does not appear to specify a number of lines of treatments, and the pathway is not clear. A poster by Kurosky *et al.*[36] reports that the most popular regimens in third line are capecitabine, fulvestrant, tamoxifen, eribulin and anastrazole. Fulvestrant is not recommended by NICE[13], tamoxifen is recommended only for premenopausal and perimenopausal women in CG81[3], and patients in Novartis' model have already received an aromatose inhibitor (letrozole) so it seems unlikely that they would receive another (anastrazole). The Systemic Anti-Cancer Therapy (SACT) chemotherapy dataset Top Regimens reports that the most common palliative regimens in breast cancer include capecitabine, paclitaxel and eribulin, although we note that this dataset is not specific to this particular indication[37].

7.1.1. Costs of treatments beyond second line

7.1.1.1. Capecitabine

Novartis included the cost of capecitabine in their model as a second-line treatment. Novartis costed treatment using the British National Formulary (BNF), giving a drug cost per cycle of £146. We note that a cost for capecitabine is available from the NHS Electronic Marketing Information Tool (eMIT) (£19.55 for 120 500mg tablets and £3.13 for 60 150mg tablets)[38] which reduces the drug costs to £19.71 per cycle. Novartis considered an administration cost of £181 to deliver oral chemotherapy from NHS reference costs. Using Novartis' administration costs and drug costs from eMIT, the cost per 21-day cycle is therefore £201.

7.1.1.1. Paclitaxel

Novartis included the cost of paclitaxel in their model as a potential second-line treatment. Novartis costed treatment using the BNF, giving a drug cost per cycle of £668. We note that a cost for paclitaxel is available from eMIT (£34.33 for 300mg/50ml and £61.92 for 30mg/5ml)[38] which reduces the drug costs to £96 per cycle. Novartis considered an administration cost of £239 in the first cycle and £326 in subsequent cycles, from NHS reference costs[39]. Using Novartis' administration costs and drug costs from eMIT, the cost per 21-day cycle is therefore £347 for the first cycle and £435 for subsequent cycles.

7.1.1.1. Eribulin

TA423 reports that the per cycle drug cost for eribulin is £1,805[22]. There is a confidential PAS scheme in place for eribulin, so we know that the true cost to the NHS is less than this[22], although we do not know what this is. Eribulin is administered intravenously, and there are two doses, so there are two sets of administration costs each cycle. Using the administration costs from Novartis' model, the administration cost is £566 (£239 + £326) in the first cycle

and £653 (£326 + £326) in subsequent cycles. Without a PAS, the cost per 21-day cycle of eribulin is therefore £2,371 in the first cycle and £2,458 in subsequent cycles.

7.1.2. Duration of treatments beyond second line

The poster by Kurosky *et al.*[36] reports mean time on third-line treatments as 6.1 months for chemotherapy only. TA423 reports that the anticipated number of 21-day cycles for eribulin is 6, and the mean PFS for eribulin after one prior chemotherapy is 4.06 months[22]. The mean PFS for capecitabine after one prior chemotherapy in TA423 was 3.99 months[22].

7.1.3. Total costs of treatment beyond second line

7.1.3.1. Total costs of treatment using Novartis's monthly cost

In Novartis' model, patients in the ribociclib arm spend [redacted] years in progression, and patients in the letrozole arm spend [redacted] years in progression.

Using Novartis's cost of £2,000 per month, the total discounted third line drug cost is [redacted] for letrozole, and [redacted] for ribociclib.

Following letrozole, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without eribulin's PAS (longer with eribulin's PAS). Following ribociclib, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without the PAS (longer with eribulin's PAS). These durations of treatment are much longer than those reported in Section 7.1.2, and for capecitabine and paclitaxel are longer than patients are alive in the model for. Applying the monthly cost of £2,000 for the duration of progressed disease therefore clearly overestimates drug costs beyond second line.

7.1.3.2. Total costs of treatment using the ERG's monthly cost

Using the ERG's cost of £1,140 per month, the total discounted third line drug cost is [redacted] for letrozole and [redacted] for ribociclib.

Following letrozole, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without eribulin's PAS (longer with eribulin's PAS). Following ribociclib, this would equate to [redacted] months of capecitabine or [redacted] months of paclitaxel or [redacted] months of eribulin without the PAS (longer with eribulin's PAS). These durations of treatment are still longer than those reported in Section 7.1.2, and for capecitabine and paclitaxel are longer than patients are alive in the model for. Applying the monthly cost of £1,140 for the duration of progressed disease therefore also likely overestimates costs beyond second line, but is closer than the cost of £2,000 per month.

8. UTILITIES

The NICE reference case for measuring and valuing health effects states that the EQ-5D is the preferred measure of health-related quality of life in adults[40]. If not available from trials, EQ-5D values can be obtained from the literature or mapped from other health-related measures in the relevant clinical trials. The methods guide states that the EQ-5D-5L may be used for reference-case analysis, and that the validated mapping function from EQ-5D-5L to EQ-5D(-3L)[41] should be used until an acceptable valuation set is available for EQ-5D-5L. NICE's position statement on the EQ-5D-5L value set states that the 5L valuation set is not recommended for use and that data gathered using EQ-5D-5L should be mapped onto the 3L valuation set using the function developed by van Hout et al (2012)[41,42]

8.1. PFS1

EQ-5D-5L estimates for patients with progression free disease ([redacted]) were based on data collected in the MONALEESA-2 trial. The mean estimate for PFS1 was derived from a mixed effects model in order to reflect the fact that patients contribute repeated observations throughout the trial. Scores were calculated using the value set by Devlin et al 2016[43]. The estimate was [redacted] (standard error = [redacted]). These data were combined for both arms of the trial. There was [redacted].

Upon NICE's request, Novartis mapped their EQ-5D-5L scores to 3L, which produced a score of [redacted] for the PFS1 state.

8.2. PFS2

The utility value for PFS2 was taken from Lloyd et al (2006)[44], with adjustments made for age and the numbers of degree of response to treatment based on rates observed in the BOLERO-2 trial. Lloyd is based on vignettes valued by the general population using standard gamble[44]. The mean estimate was 0.774. This utility value was used in TA421 for the appraisal of everolimus with exemestane after endocrine therapy[6]. For patients receiving chemotherapy, a decrement of 0.113 is applied, which Novartis state is based on a study by Peasgood et al (2010)[45], although the ERG was unable to verify this disutility.

Previous technology appraisals in later-line therapies for advance breast cancer have differentiated utility between pre and post progression (TA421[6], TA423[7]), so it would appear appropriate use a different utility for PFS2 than that used for progressed disease. However, the value used by Novartis (0.774) does not meet NICE's reference case, [redacted]

Additionally, we note that the FAD for TA421 states that the committee concluded it would have been appropriate for Novartis to present estimates for 'stable disease' from BOLERO-2, which included a disease-specific measure of health-related quality of life which could theoretically be mapped to EQ-5D[6].

8.1. Beyond PFS2

For progressed disease, the utility estimate was also taken from Lloyd et al (2006) and was a mean of 0.5052, as has been used in previous technology appraisals in HER2-negative, HR-positive advanced breast cancer[22].

In scenario analysis we consider that the utility value for PFS2 could be the same as for PFS1, or could be 0.69 in line with EQ-5D scores for second line therapy in the same population from a conference poster by Mitra *et al*. (2016)[46]. We also consider a scenario using the same utilities as in ID915: [redacted] for PFS1 and the same as BSC for PFS2 (0.5052).
In scenario analysis, we found that when we used the PFS1 mapped 3L utility value for PFS1 and PFS2, the ICER [redacted] by around [redacted] without the PAS, and by around [redacted] with the PAS. When we used the PFS1 mapped 3L value for PFS1 and 0.69 for PFS2, the ICER [redacted] by around [redacted] without the PAS, and by around [redacted] with the PAS. In a scenario using the PFS1 utility from ID915 and the BSC utility for PFS2 (the same value is used in ID915 and the ribociclib BSC health states), the ICER [redacted] by around [redacted] without the PAS and by around [redacted] with the PAS. Full results are shown in Table 10.

Table 10: Scenario analysis varying PFS1 and PFS2 utility values

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: PFS1: 5L, PFS2: TA421	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L, PFS2: PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L PFS2: 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: ID915, PFS2: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: PFS1: 5L, PFS2: TA421	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L, PFS2: PFS1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: 3L PFS2: 0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS1: ID915, PFS2: BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3L: EQ-5D 3Level, 5L: EQ-5D 5L, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality-adjusted life years, TA: technology appraisal

9. PROGRESSION-FREE SURVIVAL

Novartis fitted parametric curves to the PFS data from MONALEESA-2. Extrapolating beyond the trial period introduces uncertainty. Novartis selected the exponential distribution for PFS, on the basis that it had the second-lowest (second-best) AIC and BIC scores, comparison to long-term studies (LEA[19] and ALLIANCE[20]), "validation with clinical experts", and the ERG for ID915 suggesting that the exponential is more appropriate than the Weibull[5].

[redacted]

The ERG considered that the exponential and Weibull curves are equally plausible. We have discussed the exponential and Weibull curves in Section 6.1.

Figure 7: Novartis' time to discontinuation parametric curves (reproduced)

KM: Kaplan-Meier, ML-2: MONALEESA-2. Reproduced from Evidence Review Group report, figure 5.9 on page 80.

With Novartis' base case settings, when we used the Weibull for PFS (but not for TTD), the ICER increased by around [redacted] with the PAS, and by around [redacted] without the PAS. Full results are shown in Table 11.

Table 11: Scenario analysis varying progression-free survival

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, QALYs: quality-adjusted life years

10. OVERALL SURVIVAL

Extrapolating overall survival beyond the trial period introduces uncertainty. As discussed in Section 3.2, overall survival data in MONALEESA-2 is immature and so Novartis did not fit

parametric curves. As an alternative to the approach taken by Novartis, we explored a scenario in which overall survival followed an exponential distribution, with median survival for letrozole and ribociclib assumed to be the same as the median survival for letrozole and palbociclib respectively in the PALOMA-1 trial[15]. In this scenario, we estimated overall survival in the same way that a partitioned survival approach estimates survival. This does not use the assumption of full surrogacy, but nor does it use the scaling factor. However, the difference in median OS estimates is less than the difference in PFS, so in effect it assumes partial surrogacy. The time in the PFS1 and PFS2 states does not change unless the overall survival is less than the time in these states. The time in BSC is the difference between the overall survival and the sum of the time in PFS1 and PFS2. The time in BSC therefore changes when overall survival changes.

Using Novartis' base case assumptions, this [redacted] the ICER by around [redacted] without the PAS and [redacted] the ICER by around [redacted] with the PAS (Table 12). [redacted] Using the ERG's third line drug cost, using median survival from PALOMA-1 [redacted] the ICER by around [redacted] without the PAS and decreased the ICER by less than [redacted] with the PAS.

Table 12: Scenario analysis varying overall survival using partitioned survival approach

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: using second-line OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1 with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case: using second-line OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS from PALOMA-1 with ERG's 3rd line costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, QALYs: quality-adjusted life years

The difference in survival between ribociclib and letrozole has a substantial impact on the ICER – this is already discussed in the context of full and partial surrogacy (Section 4). Under the assumption of full surrogacy, the survival after ribociclib and letrozole does not impact results since it is the same between both arms – this is why Novartis found that varying the post-discontinuation survival curve did not impact their ICER[5]. However, under the assumption of partial surrogacy, the relative survival benefit of ribociclib depends on the absolute survival for letrozole. As discussed in Section 4.2, under the assumption of partial surrogacy, ICERs are influenced by the cost-effectiveness of later line treatments. Using Novartis' base case assumptions, under the assumption of partial surrogacy, without the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using Novartis' base case assumptions, under the assumption of partial surrogacy, with the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using the ERG's third line drug cost, under the assumption of partial surrogacy, without the PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by around [redacted]. Using the ERG's third line drug cost, under the assumption of partial surrogacy, with the

PAS, using the exponential instead of the Weibull for second-line post discontinuation survival [redacted] the ICER by [redacted], and using the log-normal [redacted] the ICER by [redacted]. Full results are shown in Table 13. We note that the log-normal has the highest AIC and BIC, does not appear to be a good visual fit to the data, and reports survival estimates that do not appear valid compared to long-term studies. The log-normal is presented here as a hypothetical example and is not considered further.

Table 13: Scenario analysis varying overall survival: partial surrogacy

	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	Ribociclib vs. letrozole
Without PAS					
Base case: Full surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS	[redacted]				
Base case: Full surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
With PAS					
Base case: Full surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS	[redacted]				
Base case: Full surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy with Weibull for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with exponential for everolimus PDS+OS with ERG 3rd line cost	[redacted]				
Partial surrogacy, with log-normal for everolimus PDS+OS with ERG 3rd line cost	[redacted]				

ICER: incremental cost-effectiveness ratio, OS: overall survival, PAS: patient access scheme, PDS: post-discontinuation survival, QALYs: quality-adjusted life years

11. SCENARIO ANALYSES VARYING THE KEY INPUTS

We have performed scenario analyses varying the key inputs, as identified in Section 5. For the utilities and costs beyond second line, we have identified alternative values that the DSU

considers to be more plausible than the values used in the Novartis base case. Here we present analyses demonstrating the impact that changing these have on Novartis' base case ICER. For TTD and PFS, we present all analyses with the Weibull and Exponential curves as the ERG considered them equally plausible. We present all analyses assuming dose reduction for ribociclib in line with the trial data, and assuming full dosing in line with the licence. To address the uncertainty associated with overall survival, we present all analyses under the assumption of both full and partial surrogacy. We do not vary the extrapolation of survival as previous scenario analysis (Section 10) indicated that using the exponential instead of Weibull has minimal impact, and the log-normal does not appear to be a valid choice.

Table 14 presents results with Novartis' base case assumptions and changes made using the DSU's preferred inputs: first using the ERG 3rd line drug cost, and then additionally using EQ-5D 3L utilities for PFS1 (using the MONALEESA-2 5L scores mapped to 3L) and for PFS (using the value of 0.69 for second line treatment from Mitra *et al*[46]). Scenario analyses for the Novartis base case updated with the DSU's preferred values are summarised using ICERs alone in Table 15 without the PAS, and Table 16 with the PAS. Total costs and QALYs and ICERs for each scenario are shown in Table 17 without the PAS and Table 18 with the PAS.

Table 14: Impact of applying the DSU's preferred values for utilities and 3rd line drug costs

	Total QALYs		**Total Costs**		**ICER**
	Letrozole	**Ribociclib**	**Letrozole**	**Ribociclib**	**Ribociclib vs. letrozole**
Without PAS					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: ERG 3rd line cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 plus PFS: EQ-5D 3L utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
With PAS					
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1: ERG 3rd line cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1 plus PFS: EQ-5D 3L utilities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ERG 3rd line cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

ERG: evidence review group, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality-adjusted life years

Table 15: Summary of scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): without PAS

		PFS: Exponential		PFS: Weibull	
		TTD: Exponential	TTD: Weibull	TTD: Exponential	TTD: Weibull
Full surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				
Partial surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

PAS: patient access scheme, PFS: progression-free survival, TTD: time to discontinuation

Table 16: Summary of scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): with PAS

		PFS: Exponential		PFS: Weibull	
		TTD: Exponential	TTD: Weibull	TTD: Exponential	TTD: Weibull
Full surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				
Partial surrogacy	Dose reduction	[redacted]	[redacted]	[redacted]	[redacted]
	Full dose				

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

PAS: patient access scheme, PFS: progression-free survival, TTD: time to discontinuation

Table 17: Scenario analyses (using DSU preferred values for utilities and 3rd line drug costs): without PAS

Full/ Partial	Dosage	PFS curve	TTD curve	Total QALYs		Total Costs		ICER
				Ribociclib	Letrozole	Ribociclib	Letrozole	
Full	Reduced	Exp	Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
Partial	Reduced	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

Exp: exponential, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality adjusted life years, TTD: time to discontinuation, Wei: Weibull

Table 18: Scenario analyses: with PAS

Full/ Partial	Dosage	PFS curve	TTD curve	Total QALYs		Total Costs		ICER
				Ribociclib	Letrozole	Ribociclib	Letrozole	
Full	Reduced	Exp	Exp	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
Partial	Reduced	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					
	Full	Exp	Exp					
			Wei					
		Wei	Exp					
			Wei					

3rd line drug cost=£1,140. EQ-5D 3L for PFS1 = [redacted] (MONALEESA-2 5L mapped to 3L). EQ-5D-3L for PFS2 = 0.69 (Mitra et al).

Exp: exponential, ICER: incremental cost-effectiveness ratio, PAS: patient access scheme, PFS: progression-free survival, QALYs: quality adjusted life years, TTD: time to discontinuation, Wei: Weibull

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Dear Meindert,

Thank you for sharing the Decision Support Unit (DSU) report with Novartis on 24th August 2017. We are very pleased to see that the DSU and the ERG have now confirmed that the model structure we have used is sound and behaves appropriately when various assumptions are explored.

We acknowledge that NICE did not expect a formal response; however, we felt it was important to highlight a number of pertinent points discussed within the DSU report to support the Committees ability to make a decision. Therefore, we hope, as previously agreed, that our formal response would be shared with committee prior to the meeting so as to make an informed decision.

We have now accommodated NICE's recent position on EQ-5D-5L utility values, despite our submission being prior to the publication of positioning statement. We are confident that with this [redacted] enables us to provide a cost-effective treatment for locally advanced or metastatic breast cancer patients based on the most plausible ICER.

Notwithstanding the points we have already raised in relation to the ERG's Report we feel that there is nothing in the DSU Report that would undermine the findings of the ERG regarding the most appropriate assumptions as it was presented in the first appraisal committee meeting on July 5th 2017.

If you require any further information, please let me know.

Kind regards,

Adam Lee
Health Economics & Outcomes Research Manager
Novartis Oncology UK Ltd.

1. Summary

We welcome the Decision Support Unit (DSU) report, shared with Novartis on 24th August 2017 and are pleased that the DSU confirms that the model structure is sound and behaves appropriately when various assumptions are explored and further supports the ERG report.

We now feel that there is nothing in the DSU Report that would undermine the findings of the ERG regarding the most appropriate assumptions as presented in the first appraisal committee meeting on July 5th 2017 and can be used to support the Committees ability to make a decision.

In light of NICE's position on EQ-5D-5L utility values, we have accommodated these in the analyses below. [redacted] results in a cost-effective base-case ICER of [redacted] as presented in Table 2.

Our comments are provided in response to pertinent points discussed in the DSU report below.

Utilities

NICE issued a position statement regarding the use of EQ-5D-5L Health Related Quality of Life (HRQoL) utility values in in August 2017, after the company submission and first appraisal committee meeting for ribociclib, in which NICE states that EQ-5D-5L should not be used. The submission for ribociclib incorporated the EQ-5D-5L utility values collected in the MONALEESA-2 clinical trial. Subsequent to the NICE position statement a mapping from EQ-5D-5L to EQ-5D-3L was performed and resulted in utility values of [redacted] for Progression-free and [redacted] for progressed disease.

The position statement from NICE and requirement to use EQ-5D-3L utility values for the base-case analysis means the utility value is a [redacted].

The DSU present the case that the utility value for second line treatment of 0.774 is not considered to meet NICE's reference case, although it is pertinent to remember that this utility value was accepted by NICE for TA421. However, the DSU present an alternative utility value of 0.69 from a poster by Meitra et al. 2016. Although, there are number of limitations with the Meitra et al (2016) poster, these include:

- The sample of patients are not considered to be truly random and were likely to have recruited patients who consulted with their clinician more frequently, this may likely bias towards patients with a more severe disease
- The utility value for second line treatment was based on a population of 202 patients, which could be considered a small sample size

To provide further context, previous NICE Technology Appraisals for advanced breast cancer have considered the following utility values for either second line or third line treatments as appropriate utility values.

TA423 in which eribulin was assessed for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens, used the utility values of 0.715 (stable) and 0.790 (responsive) in the PFS health state. This would be representative of third-line treatments or greater, i.e. progression health state, and these were based on Lloyd et al (2006).

TA239 in which fulvestrant was appraised the treatment of locally advanced or metastatic breast cancer, applied the value of 0.72 for the pre-progression treatment state, which is representative

of second-line treatment, i.e. PFS2 health state, in the ribociclib economic model. Based on Lloyd et al. (2006).

TA421 in which everolimus with exemestane was appraised for treating advanced breast cancer after endocrine therapy, i.e. second line, used the utility value of 0.774 for the pre-progression treatment state, which was based on the Lloyd et al. (2006) publication and adjusted for BOLERO-2 study baseline characteristics.

The Meitra et al (2016) poster presents the lowest utility value when compared to previous NICE accepted utility values for second or third line treatments; however, we have considered this value in deriving the new base-case analysis presented in Table 2.

Thus the DSU's conclusions that the second line utility value, 0.774, used in the ribociclib model lacks face validity is contrary to the fact that NICE have accepted the Lloyd et al values in numerous breast cancer appraisals.

Treatments beyond second line

The DSU discusses the treatment pathway beyond second line and subsequently the costs associated with treatments beyond second line, which is represented in the economic model progression health state. The two sources of evidence used by the DSU in trying to understand the treatment costs beyond second line are the poster by Kurosky et al. and data from the Systemic Anti-Cancer Therapy (SACT) chemotherapy dataset. There are a number of limitations with the approach taken by the DSU in estimating the treatment costs beyond second line.

Firstly, it appears that the DSU limits the estimated cost to third line treatments only based on the Kurosky et al poster. This approach would not result in a value reflective of the input required for the economic model and further has the potential to underestimate the true cost patients would experience. It might be expected that patients will go on to receive a number of treatments post second and third line treatments and thus, lead to increased treatment costs for patients.

Secondly, the DSU have limited the treatments to only Capecitabine, Paclitaxel and Eribulin, while ignoring other potential treatments that patients may receive, including everolimus + exemestane and fulvestrant, although it acknowledged that fulvestrant does not have NICE approval, there is evidence to suggest that fulvestrant is widely used in England and Wales. The DSU reference the SACT chemotherapy Top Regimens report for palliative regimens in breast cancer, however as highlighted by the DSU this does not provide any further information as to particular indications for each treatment. It is worth noting there are an additional 265 treatment regimens recorded in SACT as palliative regimens for breast cancer, although they are not listed by name. This would further support that high costing treatments are potentially used and not being captured by the DSU. Additional evidence highlights that eribulin may account for up to 23% of third line and 19% of fourth line treatments in the UK based on CancerMpact Kantar Health.

Thirdly, there are a number of limitations associated with the Kurosky et al poster. These limitations include:

- Records were obtained from physicians who were willing and available to participate in the study, resulting in a convenience sample. Therefore, generalizability of the study results may be limited
- The third line treatment population is relatively small, only 116 patients, of which only 30.2% had progressed and treatment was ongoing at the time of abstraction for n (%) = 75 (64.7%) of third line patients. Thus, time on treatment for third line therapies in

the poster would underestimate the true expected length of treatment patients would likely experience
- The poster does not present any information regarding treatments patients experience post third line

As discussed previously in the ID1026 PAS addendum, we still believe that the £1,140 per month cost underestimates the likely treatment costs patients treated beyond second line would experience. It should be noted that the £1,140 figure comes TA239, which uses data from over 8 years previous, and since then the treatment path for breast cancer has significantly altered with the introduction of newer and costlier targeted therapies. However, we appreciate the analysis performed by the DSU and in consideration of that; we believe the alternative value of £1,500 per month, as presented in the previous PAS addendum, can be considered justifiable and reasonable in light of the uncertainty associated with this cost. The DSU nor the ERG were able to provide any robust sources of evidence to confirm the true cost. Therefore, to account for the uncertainty of this cost, we have used a cost between the original base case value of £2,000 and the ERG value of £1,140.

Long term extrapolation of TTD and PFS

The DSU discuss the plausibility of both the Exponential and Weibull extrapolations for PFS and TTD, however as previously presented in the company submission, the ERG report and discussed at the committee meeting for ribociclib, the Exponential extrapolations for PFS and TTD were considered appropriate. The justification for using the Exponential extrapolation was based on the external long term validation, clinical expert validation and the published ACD for the appraisal of palbociclib (ID915) in which the ICERs were based on the Exponential extrapolation for both TTD and PFS.

Drug costs of ribociclib

As further clarification to the discussion presented in the DSU report, the incorporation of dose reduction for ribociclib is appropriately modelled based upon the MONALEESA-2 study Individual Patient Data (IPD). Since ribociclib has a linear pricing structure, as patients reduce the dosage size, the price associated with treatment on ribociclib will also reduce. Incorporating dose reduction is consistent with NICE reference case and previous oncology appraisals. More importantly, the reduced dose observed in the MONALEESA-2 trial resulted in the efficacy outcomes that afforded ribociclib its regulatory licence. It seems unreasonable to assume a full dose that does not reflect the actual dose patients received from the pivotal trial.

Long term validation

The DSU discuss the various studies used to provide external validation for the modelled OS predictions for letrozole in both the ribociclib and palbociclib (ID915) appraisals. In the ribociclib appraisal both the LEA and ALLIANCE studies were used, however in ID915 three alternative studies were presented, Paridaens 2008, Bergh 2012 and Mourisden 2003.

As further clarification, the rational for using the LEA and ALLIANCE studies are based on both studies evaluating letrozole monotherapy as a treatment arm, the recent date of the studies being conducted and the both studies having patient populations that are considered reasonably similar to the MONALEESA-2 study. The suitability of using both the LEA and ALLIANCE studies to provide validation for the modelled estimates was further confirm through expert clinical validation.

The other studies discussed are Paridaens 2008, Bergh 2012 and Mourisden 2003. While the patient populations of these studies could be considered reasonably similar to the MONALEESA-2 study, all three studies should be considered less appropriate for long term,

OS, survival validation because all three studies were conducted prior to a number of newer targeted therapies receiving marketing authorisation and being available for usage, specifically everolimus plus exemestane and eribulin. The advanced breast cancer treatment pathway has changed substantially since these three studies were conducted and would have a significant impact on the resulting OS estimates from the studies. This could in part explain why the Paridaens 2008, Bergh 2012 and Mourisden 2003 studies would all appear to have lower median OS estimates than the LEA and ALLIANCE studies.

1. Economic analysis and results

The economic model has been updated to incorporate the assumptions presented in Table 1 and results in an ICER per QALY gained of [redacted] (with PAS), presented in Table 2.

Table 1 Assumptions used in the new economic analysis

	Inputs
PAS	[redacted]
PFS extrapolation	Exponential
TTD extrapolation	Exponential
PFS to OS surrogacy	[redacted]
Dosage	Dose reduction allowed
Treatment costs beyond Second line	£1,500
Utility value PFS1	[redacted] (EQ-5D-3L)
Utility value PFS2	0.69 (Mitra et al)

Table 2 Revised base-case cost effectiveness analysis, incorporating DSU and company amendments with PAS

Scenarios	Ribociclib plus letrozole		Letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. New Base-case analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]
Scenario analyses							
Scenario 1: New Base-case analysis with [redacted]#	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81	[redacted]
Scenario 2: New Base-case analysis with PFS2 utility [redacted]##	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]
Scenario 3: New Base-case analysis with [redacted] and PFS2 utility [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81	[redacted]

PAS: patient access scheme.
*New base-case analysis as presented in Table 1

[#] [redacted] incorporated with all other assumptions as per Table 1
[##]PFS utility value [redacted] incorporated with all other assumptions as per Table 1

Table 3 Revised base-case cost effectiveness analysis, incorporating DSU and company amendments without PAS

Scenarios	Ribociclib plus letrozole		Letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. New Base-case analysis*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]
Scenario analyses							
Scenario 1: New Base-case analysis with [redacted] [#]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81	[redacted]
Scenario 2: New Base-case analysis with PFS2 utility [redacted] [##]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.46	[redacted]
Scenario 3: New Base-case analysis with [redacted] and PFS2 utility [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.81	[redacted]

PAS: patient access scheme.
*New base-case analysis as presented in Table 1
[#] [redacted] incorporated with all other assumptions as per Table 1
[##]PFS utility value [redacted] incorporated with all other assumptions as per Table 1

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15th August 2017

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Dear Jo,

As per the email from NICE on Thursday 10th August, in which NICE requested further clarification on why the Time to Treatment Discontinuation (TTD) in the model is shorter than the PFS in the trial.

In the MONALEESA-2 study patients who experienced disease progression or death were captured as an "event" in the Progression-Free Survival (PFS) Kaplan-Maier (K-M) curve. Patients who stopped treatment for reasons other than progression or death were captured as an "event" in the TTD K-M curve, and were permanently censored in the PFS K-M curve.

As the economic model uses both the PFS and TTD K-M curves to perform the analyses, the difference between both the median and modelled PFS and TTD results is due to patients discontinuing study treatment for reasons other than disease progression or death. The difference in PFS and TTD can be explaining in most part due to patients discontinuing ribociclib due to adverse events ([redacted]).

Further, it would be expected that TTD is lower than PFS in this trial, as the MONALEESA-2 study did not allow for treatment beyond disease progression for the combination of ribociclib plus letrozole.

This remains consistent with what has been seen in previous NICE appraisals of oncology medicines and in particular ID915 in which the ERG discussed the difference between TTD and PFS for the CDK 4/6 inhibitor Palbociclib.

If you require any further information, please let me know.

Kind regards,

Adam Lee
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Dear Jo,

As per the email from NICE on Thursday 27th July, in which NICE requested Novartis to provide revised estimates for health state utilities from the MONALEESA-2 study by using the Van Hout et al. (2012) methodology for mapping between EQ-5D-5L to EQ-5D-3L. Please find below the revised 3L mapped utility values, in order to allow the decision support unit to carry out the required sensitivity analyses. However, Novartis would like to highlight the following:

- Novartis maintain that the utility values directly elicited from the MONALEESA-2 study (EQ-5D-5L) should be considered the most relevant and robust utility values for the base case analysis
- The revised mapped EQ-5D-3L utility value for First Line treatment PFS are [redacted]
- There are several limitations when applying the Van Hout et al (2012) mapping, for example:
    - A key limitation of using the values generated using the cross-walk is the restricted range of values. When converting values from 5L scale to 3L scale, an artificial floor effect on 5L values is observed that opposes research findings that suggests 5L scales broadens the measurement continuum; and therefore generate lower values compared to 3L scales
    - The mapping of EQ-5D-3L from EQ-5D-5L is based on pooled data (of domain scores for the EQ-5D-5L and EQ-5D-3L) for respondents from different countries. The domain scores were collected using interpretation of different 5L translations. Respondents in different cultures interpret the 5L translations differently, causing an inherent difference in the generated values.

If you require any further information, please let me know.

Kind regards,

Adam Lee
Health Economics & Outcomes Research Manager
Novartis Oncology UK Ltd.

Progression-Free Survival

As presented in Table 1, the revised mapped 3L utility mean value for Progression-Free Survival (PFS) is [redacted]. It should be noted, that the revised 3L utility value is presented in Table 1 [redacted]

Novartis believe that the EQ-5D-5L health state utility values (HSUVs) obtained from the MONALEESA-2 study are the most relevant source of utility values for the population being considered in this appraisal, that is, HR+/HER2- locally advanced or metastatic breast cancer who are being treated with ribociclib as initial endocrine-based therapy. This study produced utility values of [redacted] for the progression-free (PF) state and [redacted] for the progressed disease (PD) state. It should be noted, that the utility value for the PD state represents disease progression in the MONALEESA-2 study, and that applying this value within the economic model would be relevant to the PFS2 health state and not the Progression health state. This is because PD represents patients experiencing disease progression from First Line treatment and progressing onto Second Line treatment.

Table 1 Health Statue Utility by Status (Progression Free/Progressed Disease)

	PD	PF
Overall		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Missing	[redacted]	[redacted]
PBO+LET2.5		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Missing	[redacted]	[redacted]
RIBO600+LET2.5		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (IQR)	[redacted]	[redacted]
Range	[redacted]	[redacted]
Missing	[redacted]	[redacted]

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

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

Produced by	Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University
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Declared competing interests of the authors

None.

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None.

[redacted]

[redacted]

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors

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

Abbreviations

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

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

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1. SUMMARY

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

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

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

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

1.2 Summary of clinical effectiveness evidence submitted by the company

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results are available for three time points:

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

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

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

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

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

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

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

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

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

[redacted]

[redacted]

1.4 Summary of cost effectiveness evidence submitted by the company

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1.6.1 Strengths

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

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

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

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

1.6.2 Weaknesses and areas of uncertainty

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

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

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

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

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

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

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

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

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

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

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

Table 1.2: Key finding from company and ERG analyses

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

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

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

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

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

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

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

2. BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

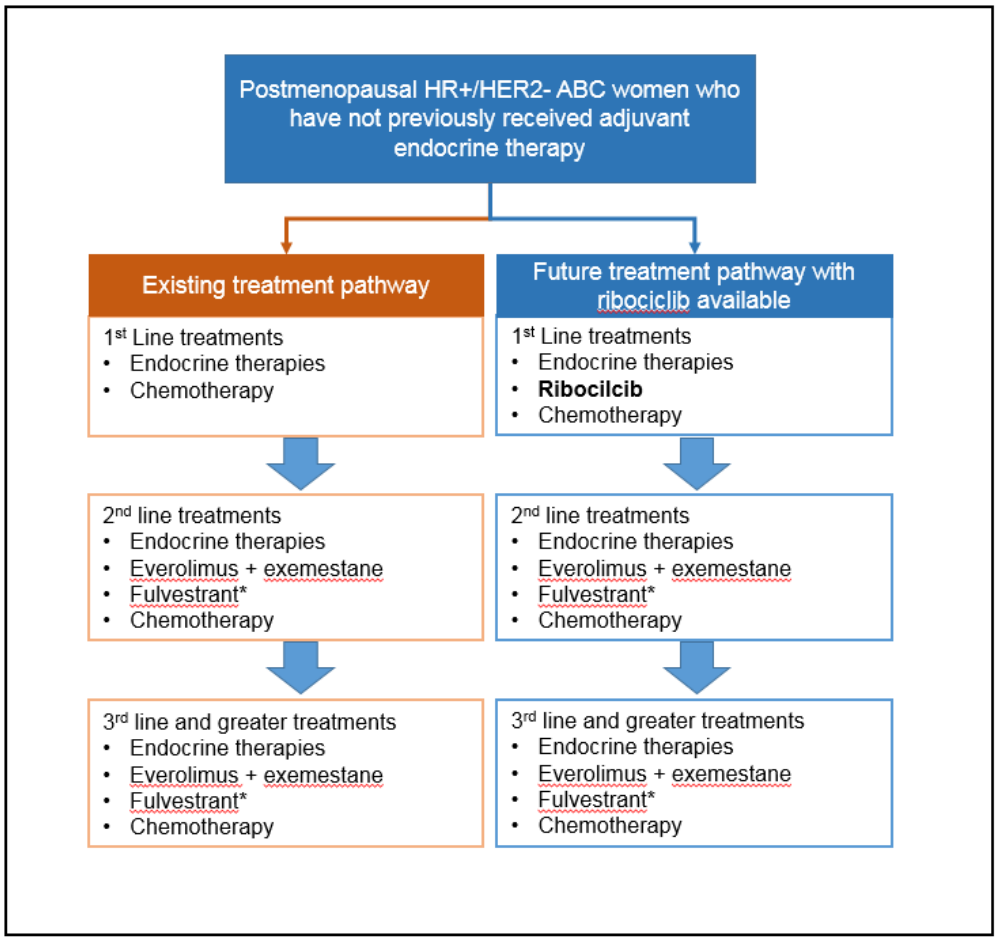
We identified some discrepancies which we investigated further.

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

2.2 Critique of company's overview of current service provision

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

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



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

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

Everolimus + exemestane TA421[20]

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

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

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

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

In terms of endocrine therapy NICE guidance states:

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

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

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

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

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

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

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

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

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

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

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

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

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

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

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

3.1 Population

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

3.2 Intervention

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

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

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

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

3.3 Comparators

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

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

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

3.4 Outcomes

The NICE final scope lists the following outcome measures:

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

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

3.5 Other relevant factors

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

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

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

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

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

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

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

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

ERG comment:

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

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

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

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

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

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

4.1.2 Inclusion criteria

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

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

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

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

ERG comment:

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

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

4.1.3 Critique of data extraction

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

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

4.1.4 Quality assessment

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

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

4.1.5 Evidence synthesis

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

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

4.2.1 Overview of the evidence in the submission

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

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

4.2.2 The MONALEESA-2 trial

4.2.2.1 Methodology of the MONALEESA-2 trial

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

Table 4.2: Methodology of the MONALEESA-2 trial

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

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

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

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

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

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

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

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

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

4.2.2.2 Statistical analysis of the MONALEESA-2 trial

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

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

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

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

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

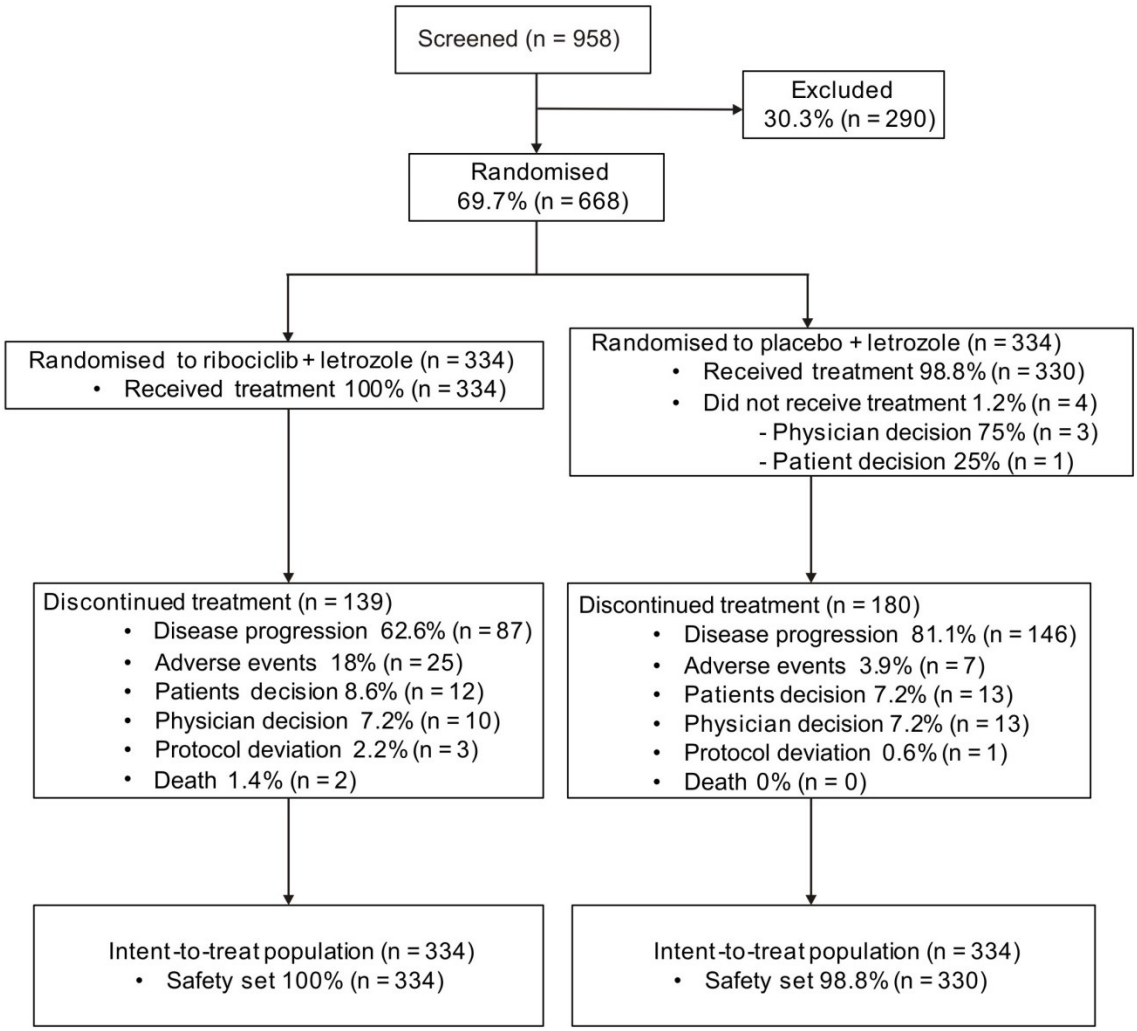
Efficacy analyses were performed in the ITT population which was all randomised patients who were analysed according to the treatment and stratum assigned at randomisation. Safety analyses were performed in the safety population which was defined as all patients who received at least one dose of study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

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

4.2.2.3 Participants in the MONALEESA-2 trial

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

Figure 4.1: CONSORT diagram for MONALEESA-2



Source: CS, Figure 6, page 47

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

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

Table 4.3: Participant characteristics of the MONALEESA-2 TRIAL

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

Baseline characteristics	Ribociclib group (n = 334)	Placebo group (n = 334)
Prior therapy, n (%)[c]		
Radiotherapy	178 (53.3)	167 (50.0)
Neoadjuvant or adjuvant chemotherapy	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	175 (52.4)	171 (51.2)
Tamoxifen	140 (41.9)	145 (43.4)
Anastrozole	47 (14.1)	42 (12.6)
Letrozole	34 (10.2)	25 (7.5)
Exemestane	19 (5.7)	25 (7.5)
Goserelin	6 (1.8)	3 (0.9)
Other	2 (0.6)	4 (1.2)

Source: CSR, Table 11, pages 48-49
a. Race was self-reported; b. Visceral involvement included liver, lung and other visceral metastases;
c. Some patients received both chemotherapy and endocrine therapy as neoadjuvant or adjuvant treatment.
ECOG PS = Eastern Cooperative Oncology Group performance status; HER2 = human epidermal growth factor receptor 2.

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

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

Table 4.4: Age breakdown in the MONALEESA-2 TRIAL

Age group	Ribociclib group (n = 334)	Placebo group (n = 334)	All patients (n = 668)
20 - < 30	[redacted]	[redacted]	[redacted]
30 - < 40	[redacted]	[redacted]	[redacted]
40 - < 50	[redacted]	[redacted]	[redacted]
50 - < 60	[redacted]	[redacted]	[redacted]
60 - < 70	[redacted]	[redacted]	[redacted]
70 - < 80	[redacted]	[redacted]	[redacted]
80 - < 90	[redacted]	[redacted]	[redacted]
90 - < 100	[redacted]	[redacted]	[redacted]

Source: CLEE011A2301 - Additional analyses (Cut-off date: 04JAN2017) – provided by the company

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

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

[redacted]'[26]

ERG comment:

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

4.2.2.4 Quality assessment of the MONALEESA-2 trial

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

Table 4.5: Quality of the MONALEESA-2 TRIAL

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

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

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

4.2.2.5 Efficacy results of the MONALEESA-2 trial

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

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

Table 4.6 summarises the key efficacy data for this study.

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

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

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

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

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

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

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

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

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

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

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

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

NA = not assessed, NE = not estimable, NR = Not reached

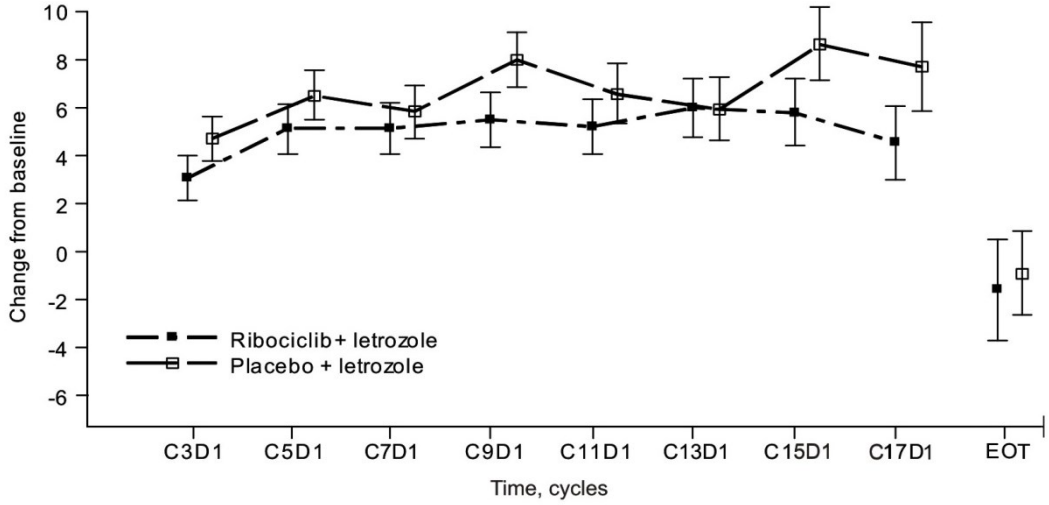
4.2.2.6 HRQoL results of the MONALEESA-2 trial

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

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

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

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



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

Source: MONALEESA-2 CSR 2016.[41]

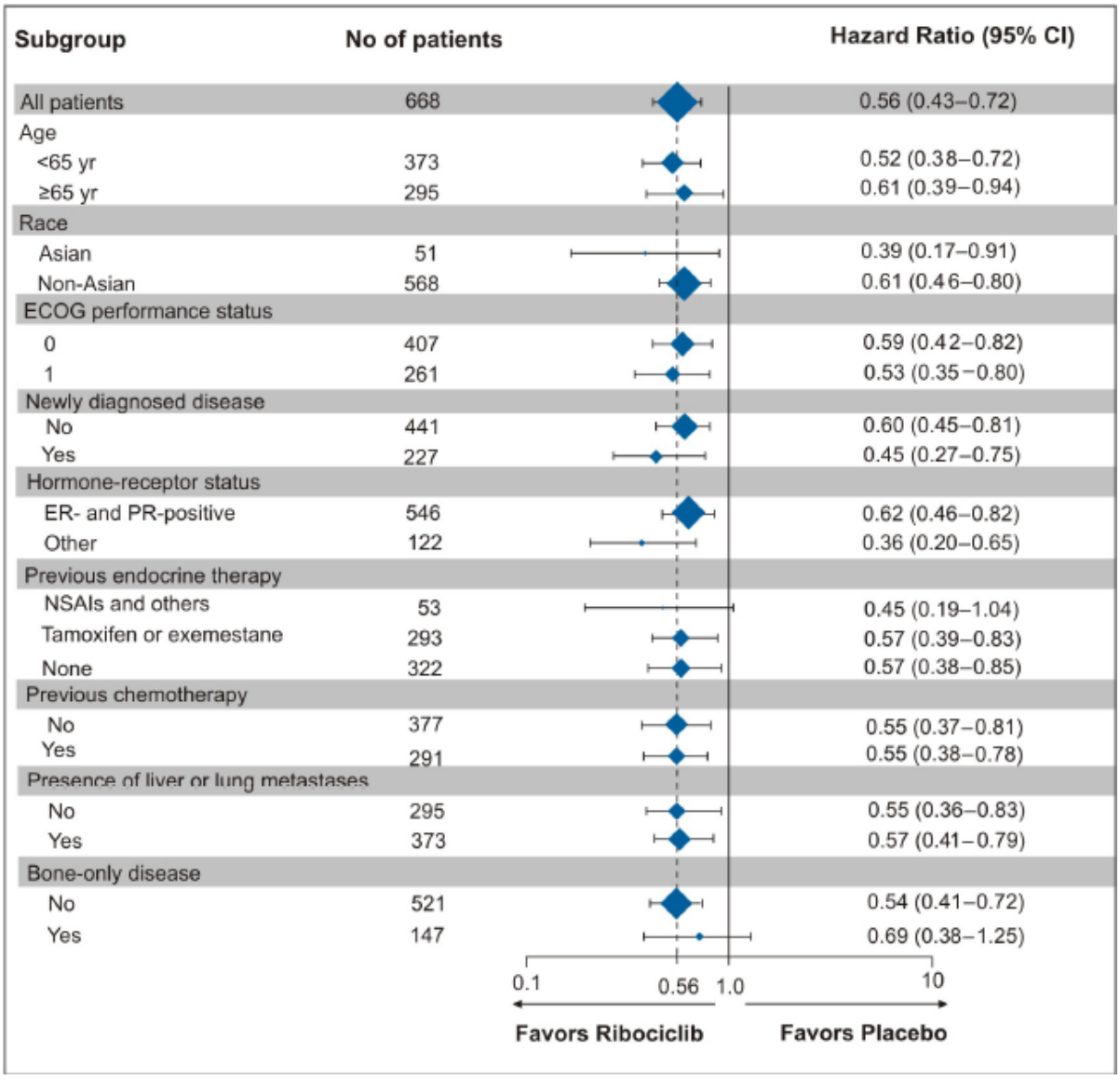
C3D1 = cycle 3 day 1; EORTC QLQ-C30 GHS/QOL = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Global Health Status/Quality of Life; EOT = end of therapy, LS = least squares; SEM = standard error of the mean.

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

4.2.2.7 Subgroup analyses of the MONALEESA-2 trial

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

Figure 4.3: PFS across various selected subgroups



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

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

ERG comment:

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

4.2.2.8 Safety results of the MONALEESA-2 trial

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

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

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

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

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

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

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

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

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

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

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

Source: Hortobagyi et al. 2016[23]

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

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

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

‡ Neutropenia includes a decreased neutrophil count and granulocytopenia.

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

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

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

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

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

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

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

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

[redacted]

[redacted]

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

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

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

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

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

[redacted].

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

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

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

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

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

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

Table 4.12: Methodology of the non-randomised evidence

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

Source: Table 15 of CS

MTD = maximum tolerated dose; PFS = progression-free survival

a. 3 weeks/1 week off

b. every 28 days with 1 additional dose on day 15 of cycle 1

Table 4.13: Results of the non-randomised evidence

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

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

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

4.2.4 Ongoing trials

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

Table 4.14: Ongoing trials

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

ERG comment:

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

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

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

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

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

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

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

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

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

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

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

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

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

Results are available for three time points:

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

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

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

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

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

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

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

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

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

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

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

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

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

5. COST EFFECTIVENESS

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

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

5.1.1 Searches performed for cost effectiveness section

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

Searches for cost effectiveness analysis review

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

ERG comment:

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

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

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

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

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

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

Measurement and valuation of health effects

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

ERG comment:

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

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

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

Cost and healthcare resource identification, measurement and valuation

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

ERG comment:

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

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

5.1.2 Inclusion/exclusion criteria used in the study selection

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

Table 5.1: Inclusion criteria for the study selection

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

ERG comment:

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

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

5.1.3 Included/excluded studies in the cost effectiveness review

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 5.3: Summary of the company submission economic evaluation

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

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

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

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

5.2.1 NICE reference case checklist (TABLE ONLY)

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

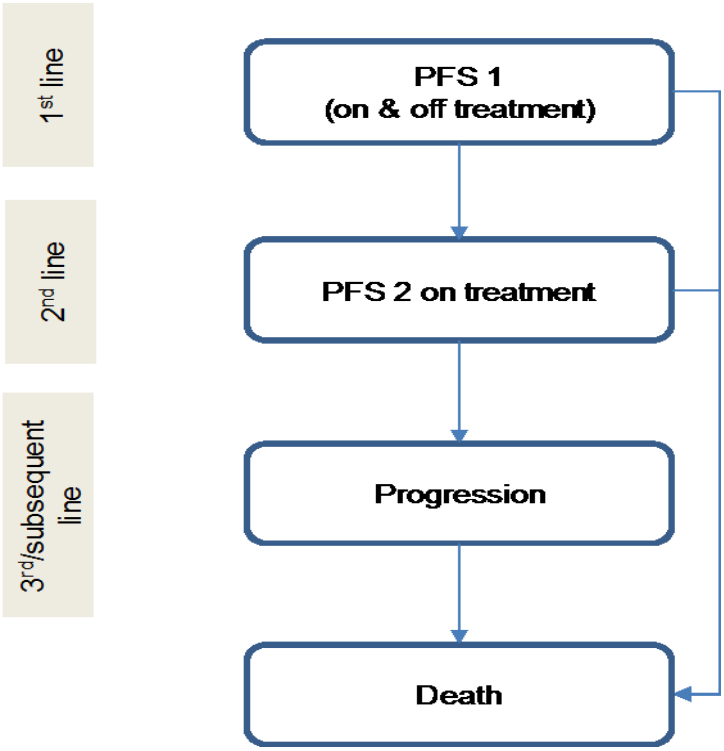
Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether de novo evaluation meets requirements of NICE reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Partly	Only letrozole was considered as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

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

5.2.2 Model structure

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

Figure 5.1: De novo model structure



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

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

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

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

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

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

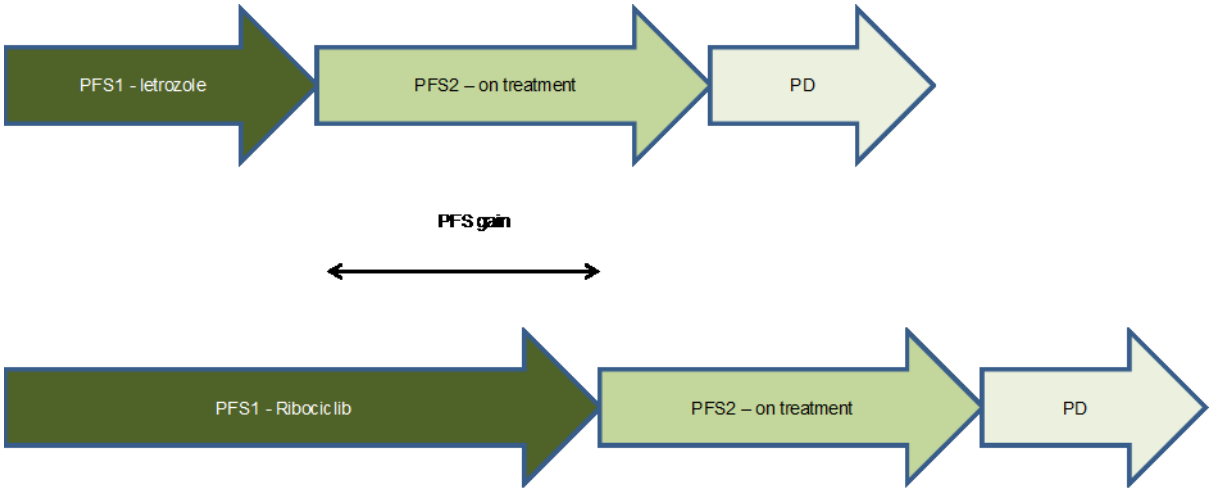
For the patients who received exemestane monotherapy or everolimus in combination with exemestane in the second-line, relevant model clinical inputs like TTD and the probability of death before treatment discontinuation in the second-line, and time to death after TTD are derived from the analysis of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

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

5.2.2.1 Modelling of the OS

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

Figure 5.2: Illustration of the perfect OS surrogacy approach

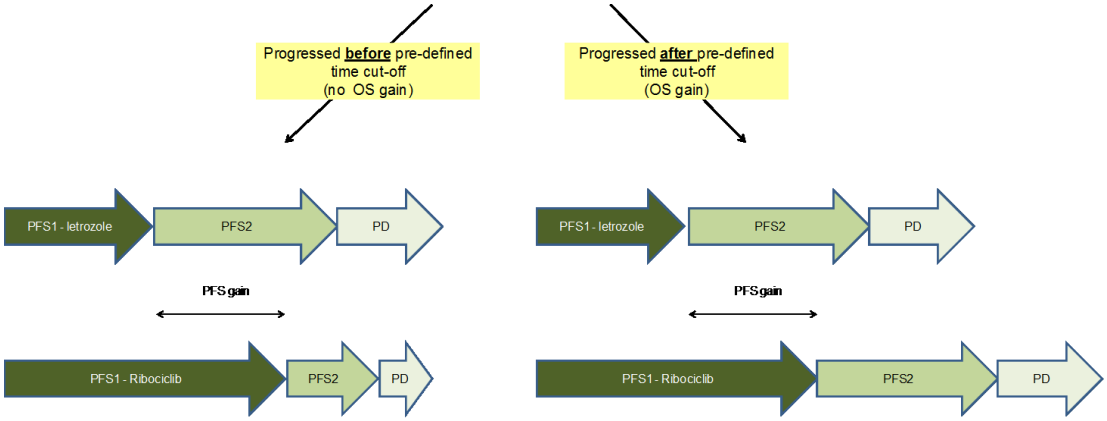


Source: CS, Figure 20, page 102
PFS = progression-free survival; PD = progressive disease.

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

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

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



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

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

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

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

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

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

5.2.3 Population

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

ERG comment:

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

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

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

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

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

5.2.4 Interventions and comparators

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

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

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

ERG comment:

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

5.2.5 Perspective, time horizon and discounting

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

ERG comment:

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

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

5.2.6 Treatment effectiveness and extrapolation

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

5.2.6.1 PFS in the first-line therapy

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

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

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

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

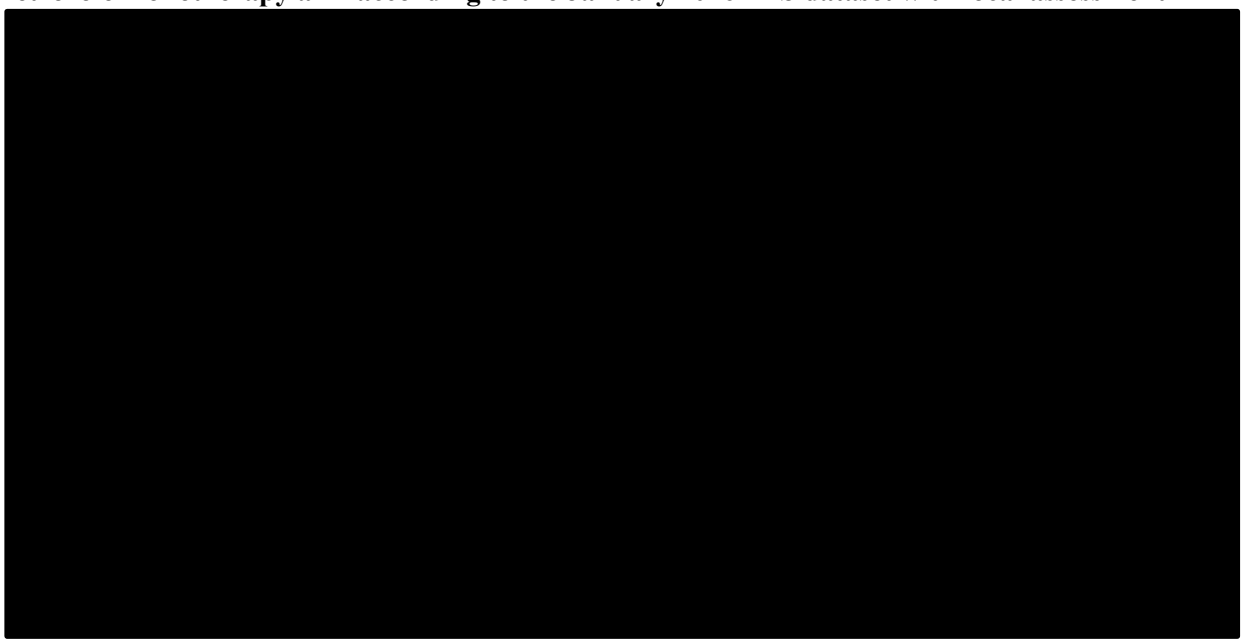
The visual assessment of fit for the parametric survival models to the observed PFS data was conducted by plotting the overlaid estimated survival curves for each distribution on top of the corresponding Kaplan-Meier curve, for both ribociclib plus letrozole and letrozole monotherapy, as presented in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

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

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

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

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



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

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

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

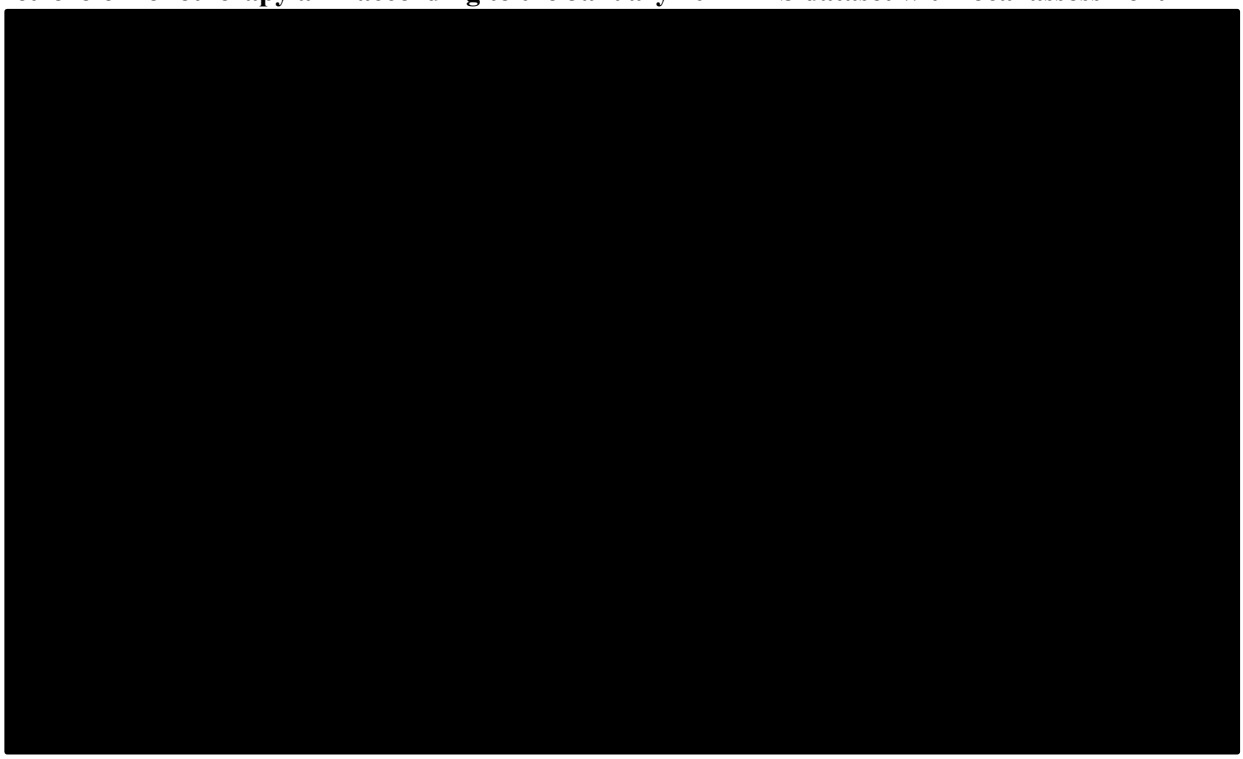
In line with the DSU guidance,[70] which recommends that the same distribution parametric models should be selected for all treatment arms, the exponential distribution was also chosen for ribociclib plus letrozole arm in the base-case. The impact of choosing other parametric functions for the survival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

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

ERG comment:

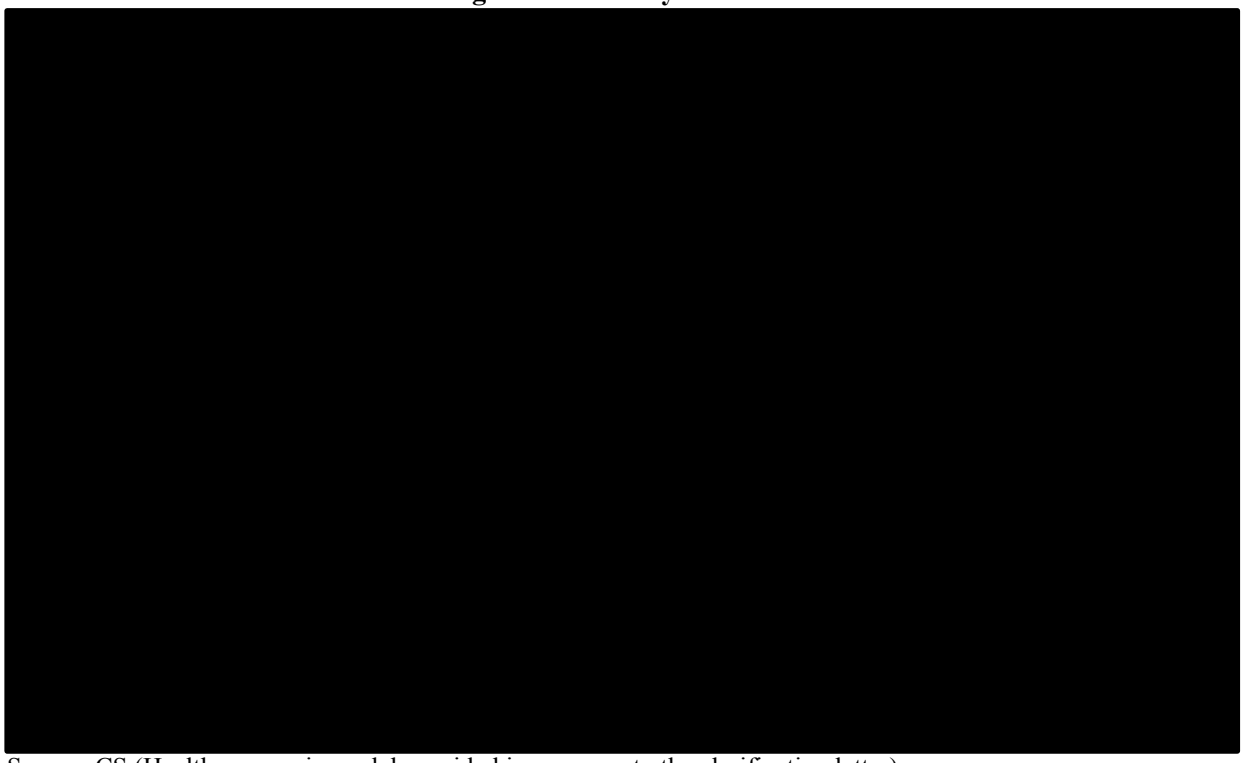
The survival analyses conducted in the CS were based on the PFS dataset from the first interim analysis (January 2016) and the local assessment of the PFS events. As discussed previously in section 4.2, the ERG considers PFS results from central assessment to be more plausible compared to the local assessment.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

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



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

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



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

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

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

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

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

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

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

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

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

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

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

ERG comment:

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

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

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

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

5.2.6.3 TTD in the first-line therapy

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

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

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

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

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

ERG comment:

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

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

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

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

5.2.6.4 Distribution of treatments received in the second-line

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

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

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

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

ERG comments:

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

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

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

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

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

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

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

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

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

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

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

ERG comment:

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

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

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

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

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

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

5.2.7 Adverse events

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

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

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

ERG comment:

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

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

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

5.2.8 Health-related quality of life

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

ERG comment:

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

5.2.8.1 Pre-progression utility values

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

5.2.8.2 Post-progression (including PFS2) utility values

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

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

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

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

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

ERG comments:

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

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

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

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

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

5.2.9 Resources and costs

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

5.2.9.1 Drug acquisition costs

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

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

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

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

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

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

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

ERG comment:

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

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

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

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

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

5.2.9.2 Administration costs

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

5.2.9.3 Monitoring costs

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

5.2.9.4 Health state costs

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

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

Table 5.10: Health state costs

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

5.2.9.5 Costs of adverse events

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

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

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

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

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

ERG comments:

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

5.2.10 Cost effectiveness results

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

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

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

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

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

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

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

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

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

Table 5.14: Disaggregated QALYs by health state

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

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

Table 5.15: Disaggregated costs by health state

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

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

ERG comments:

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

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

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

5.2.11 Sensitivity analyses

Probabilistic sensitivity analyses (PSA)

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

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

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

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

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

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

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.98	[redacted]
Source: CS, Table 62 ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.							

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

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Letrozole monotherapy	[redacted]	[redacted]	[redacted]				
Ribociclib plus letrozole	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.97	[redacted]
Source: Company PAS submission, Table 6 ICER = incremental cost effectiveness ratio; LYG = life years gained; QALYs = quality-adjusted life years.							

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

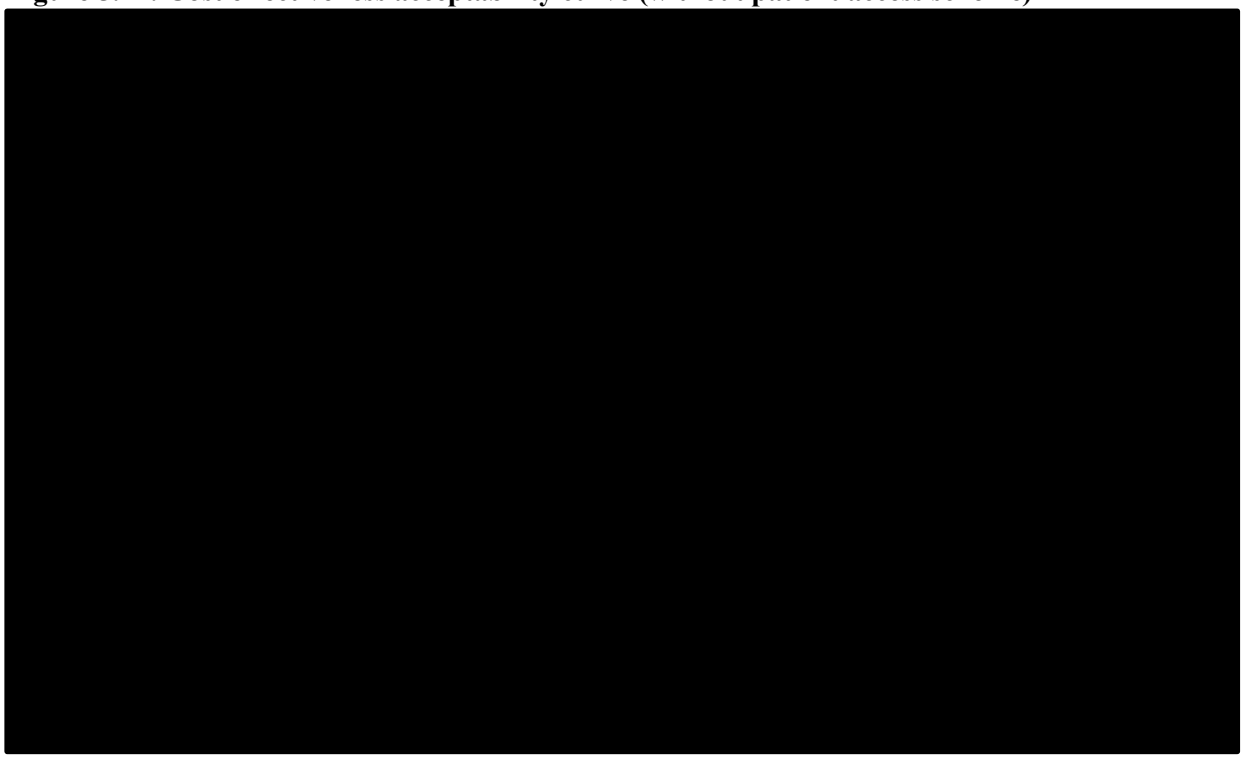
Figure 5.10: Cost effectiveness plane (without patient access scheme)

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

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

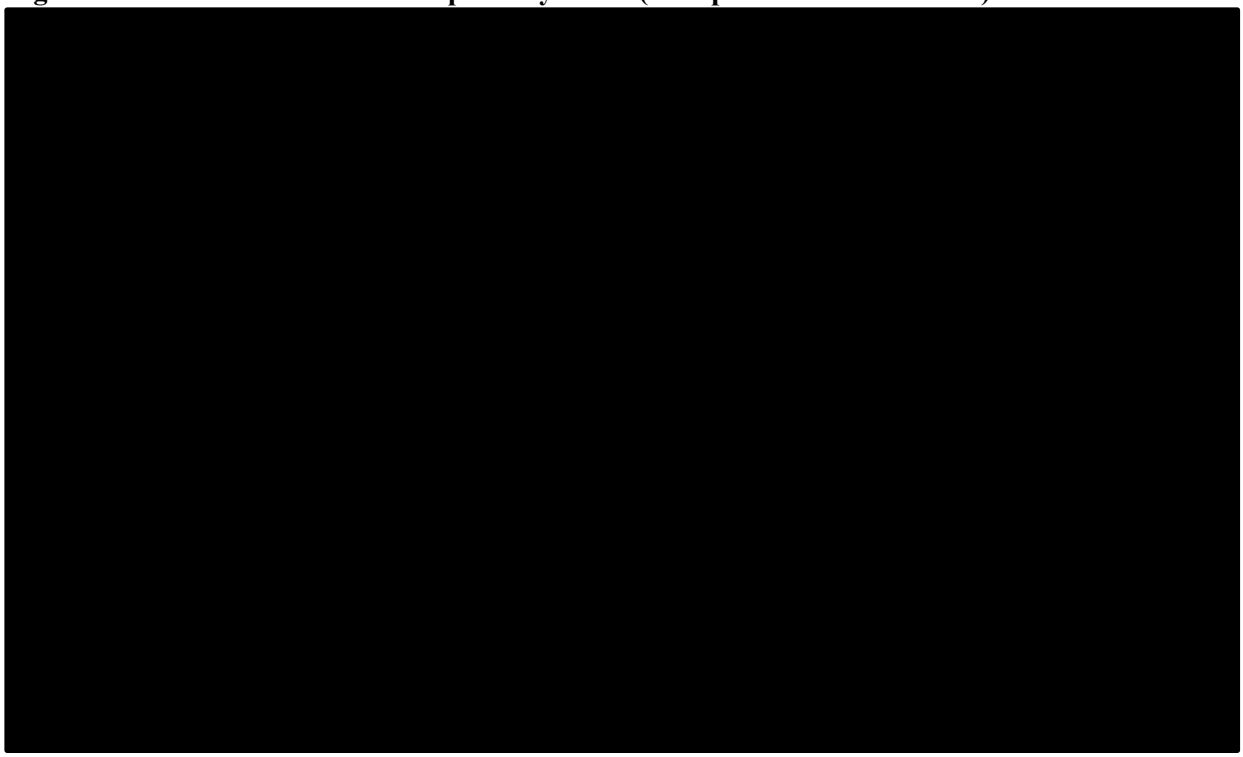
Source: Company PAS submission, Figure 2
QALYs = quality-adjusted life years.

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



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

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



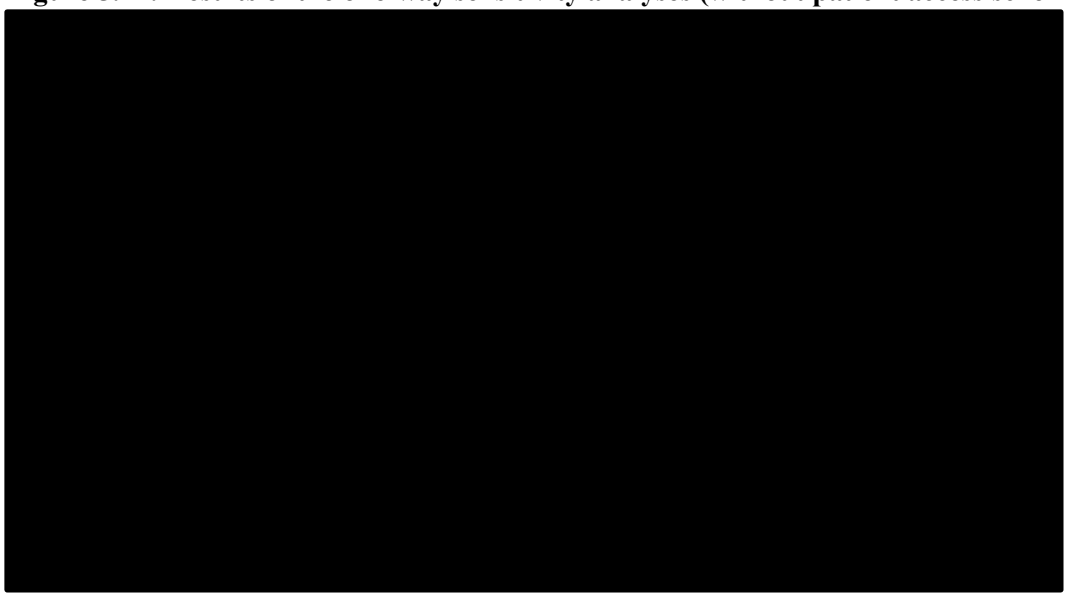
Source: Company PAS submission, Figure 3
QALYs = quality-adjusted life years.

Deterministic sensitivity analyses

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

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

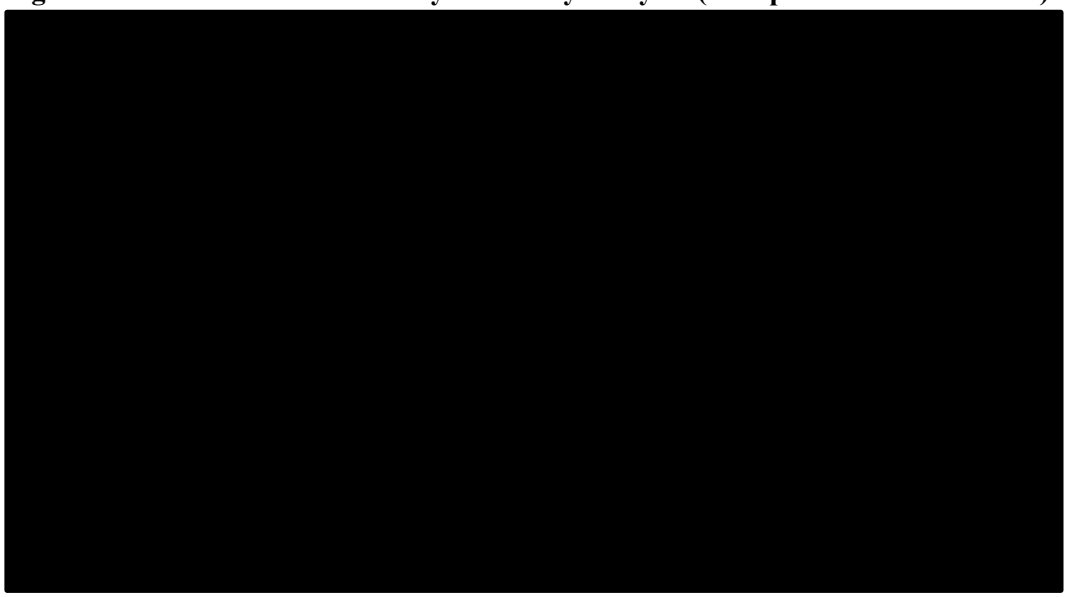
Figure 5.14: Results of the one-way sensitivity analyses (without patient access scheme)



Source: CS, Figure 42

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

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



Source: Company PAS submission, Figure 1

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

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

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

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

Scenario analyses

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ERG comment:

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

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

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

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

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

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

5.2.12 Model validation and face validity check

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

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

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

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

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

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

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

ERG comment:

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

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

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

5.3 Exploratory and sensitivity analyses undertaken by the ERG

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

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

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

5.3.1 Explanation of the ERG adjustments

Fixing errors

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

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

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

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

Fixing violations

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

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

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

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

Matters of judgement

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

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

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

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

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

6. Assuming partial OS surrogacy

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

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

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

Additional scenarios

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

Scenario 1. Weibull distribution for PFS1 and TTD

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 5.24: Disaggregated QALYs by health state

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

Table 5.25: Disaggregated costs by health state

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

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

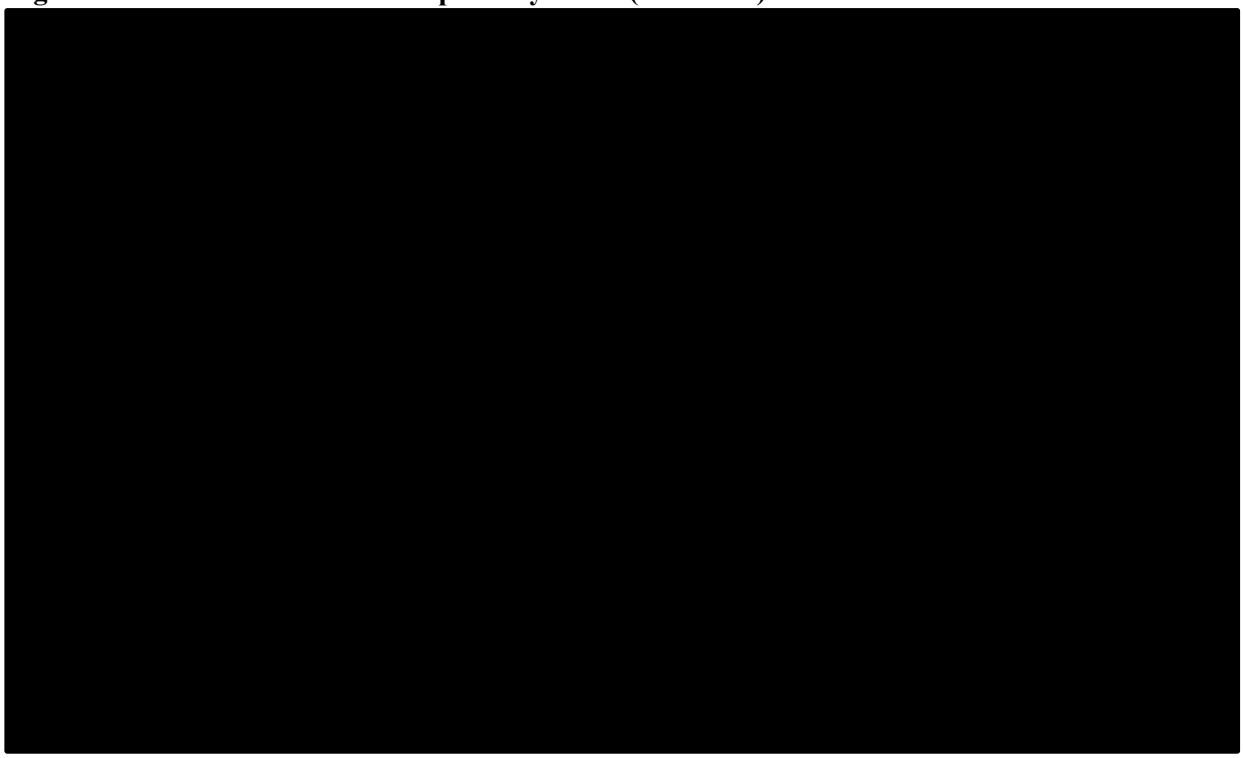
The results of 1,000 PSA iterations are shown in the figures below. The cost effectiveness planes show the incremental QALYs and costs of ribociclib plus letrozole relative to the letrozole monotherapy (Figure 5.16 [with PAS]). Additionally, the cost effectiveness acceptability curves (CEAC) are presented,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

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

Figure 5.16: Cost effectiveness plane (with PAS)

[redacted]

Figure 5.17 Cost effectiveness acceptability curve (with PAS)



5.3.3 Results from the ERG additional exploratory scenario analyses

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

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

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

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

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

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

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

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

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

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

5.4 Conclusions of the cost effectiveness section

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

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

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

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

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

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

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

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

Several other issues were addressed through exploratory scenario analyses.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7. OVERALL CONCLUSIONS

7.1 Statement of principal findings

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

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

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

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

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

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

Results are available for three time points:

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

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

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

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

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

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

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

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

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

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

Quality of life scores showed [redacted]

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

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

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

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

[redacted]

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

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

7.2 Strengths and limitations of the assessment

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

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

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

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

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

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

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

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

7.3 Suggested research priorities

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

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
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Maastricht University

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

1st ADDENDUM

ERG base-case and scenario analysis results with the new PAS

Produced by

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

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YO19 6FD

1 Exploratory and sensitivity analyses undertaken by the ERG with the new PAS

The company provided a new PAS, which offers a [redacted] discount on the list price of the ribociclib. In their new PAS submission, the company applied this new PAS price to a different base-case from the ERG preferred base-case explained in the ERG report (all changes in the ERG base case were implemented except for the third-line treatment costs and PFS gain/OS gain relationship. Third-line treatment costs were assumed to be £2,000 per month and OS gain was assumed to be the same as the PFS gain). Therefore, in this addendum, we reconstructed the ERG preferred base-case and the scenario analyses from Section 5.3 of the ERG report with the new PAS price.

1.1 Results from the ERG preferred base-case with the new PAS

The results from the ERG preferred base-case are presented in Table 1.1. After the new PAS, the incremental QALYs gained did not change and remained 0.53, whereas the incremental costs with the new PAS is [redacted], and the corresponding ICER is [redacted] per QALY gained.

Table 1.1: ERG base-case cost effectiveness results (with patient access scheme)

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

The results of 1,000 PSA iterations are shown in Table 1.2 and the figures below. The cost effectiveness planes show the incremental QALYs and costs of ribociclib plus letrozole relative to letrozole monotherapy (Figure 1.1). In addition, the cost effectiveness acceptability curves (CEAC) are presented, showing the likelihood of ribociclib plus letrozole being cost effective at different willingness-to-pay thresholds (Figure 1.2). For the £30,000 per QALY gained threshold, the probability that ribociclib is cost-effective compared to the letrozole alone is [redacted]

Mean incremental QALYs from ribociclib plus letrozole were around 0.53. When taking into account the new patient access scheme, the incremental costs decreased to [redacted], and the corresponding probabilistic ICER was [redacted] (comparable to the deterministic, base-case ICER of [redacted]). The mean (incremental) results from the 1000 iterations are provided below:

Table 1.2: ERG PSA base-case cost effectiveness results (with the new patient access scheme)

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

Figure 1.1: Cost effectiveness plane (with the new PAS price)

Figure 1.2 Cost effectiveness acceptability curve (with PAS)

1.2 Results from the ERG additional exploratory scenario analyses

The results of the additional scenarios described in section 5.3.1 of the ERG report, which are now performed on the ERG preferred base-case with the new PAS prices, are provided in Table 1.3 below.

Table 1.3: Results from the additional scenario analyses conducted on the ERG preferred base-case (with the new PAS price)

Scenarios	Ribociclib in combination with letrozole		Letrozole monotherapy		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
New CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 1 (Weibull function for PFS1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
Scenario 2a (Third-line treatment costs = £0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 2b (Third-line treatment costs = £2,000 per month)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 3 (Drug acquisition costs from cycle 11 onwards based on mean costs of cycle 11 to 26)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
Scenario 4 (Full OS surrogacy)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
Scenario 5 (Full OS surrogacy and Weibull function for PFS 1 and TTD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.74	[redacted]
Scenario 6 (similar second-line treatments)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.50	[redacted]

QALYs = quality adjusted life years; ICER = incremental cost effectiveness ratio; CS = company submission; PFS = progression-free survival; TTD = time to treatment discontinuation.

Among the scenarios above, with the new PAS price, the largest impact on the ERG base-case ICER occurred in scenario 1, i.e. when the base-case PFS/TTD distributions for the first-line were changed from exponential to Weibull, which led to a substantial increase in the ICER. Since in section 5.2.6.1 of the ERG report, it was previously discussed that the Weibull distribution can be as plausible as the

company's preferred exponential distribution, the ERG stresses that this scenario might be reflective of the uncertainty of the cost effectiveness of ribociclib.

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

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

Table 0.4: Revised base-case cost effectiveness analysis, incorporating corrections and amendments identified by the ERG (with the new PAS)

Scenarios	Ribociclib plus letrozole		letrozole alone		Incr. costs	Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs			
0. New CS base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(1). Using post-progression costs from TA239 (fulvestrant)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[redacted]
(2). Changing PFS gain / OS gain = 1 assumption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
(1 to 2 all): ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]

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

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from Kleijnen Systematic Reviews Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm, Tuesday 20 June 2017** using the below proforma 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 Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Subgroup analysis: data interpretation

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 11, 45, 58, 125 Subgroup analyses showed that results for PFS favour ribociclib for all subgroups including both those with newly diagnosed disease and those with existing disease and those who have received prior therapy and patients who have not. Nevertheless, there are differences in effectiveness. Most noticeably, results for ribociclib are more favourable for younger patients (<65 yr), newly diagnosed patients (vs not newly diagnosed), not ER- and PR-positive (vs other hormone-receptor status), and not bone-only disease (vs. bone-only disease).	We suggest amending the text to state: "Subgroup analyses showed that results for PFS favour ribociclib for all subgroups."	As presented in the CSR, treatment effects were consistent across subgroups without any interaction as supported by higher treatment-by-subgroup interaction p-value (CSR Table 14.2-1.9) and overlapping 95% confidence intervals of the HRs (CSR Table 14.2-1.19).	Not a factual error.

Issue 2 [redacted]

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12, 51, 58, 126 [redacted]	We would suggest amending the text to state: [redacted]	Factual inaccuracy. [redacted]	Not a factual error. The company have clarified this now and this is fully reported in our report on page 49 and in Table 4.11. No change

[redacted]	[redacted]	[redacted]	necessary.

Issue 3 PFS and OS data preferences

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 12	It is not accurate to state that the OS HR [redacted] is the company's preference. We based our analysis on the only data available at the time of our submission rather than selecting a particular data set. Suggested wording in table 1.1 would be to change	Factual inaccuracy and clarification. The OS HR was not used in the economic model, due to the modelling approach and immaturity of OS data. PFS HR is based upon the statistically significant primary efficacy analysis (local assessment).	Not a factual error. The company could choose between local and central assessment and between 2016 and 2017 data. By choosing local results and 2016 data we concluded that is

 "As can be seen from the results presented in Table 1.1 PFS results are more favourable for ribociclib in the company preferred results; while OS results are more favourable for ribociclib in the ERG preferred results. It should be kept in mind that the economic model is informed by the PFS results from the MONALEESA-2 trial, but not by the OS results from the MONALEESA-2 trial."	Company preference to Company inputs Suggested wording: "As can be seen from the results presented in Table 1.1 PFS results are more favourable for ribociclib in the company base case results; while OS results are more favourable for ribociclib in the ERG preferred results. It should be kept in mind that the economic model is informed by the PFS results from the MONALEESA-2 trial, but not by the OS results from the MONALEESA-2 trial."	It should be noted that at the time of the submission only data from the January 2016 data cut of MONALEESA 2 were available. At the point of company submission no other data cuts, June 2016 or January 2017, were available.	their preferred base-case.

Issue 4 PALOMA-1 PFS to OS ratio

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 14, 16, 74, 112, 119, 127	We would suggest adding the following wording where PALOMA-1 is discussed as providing a PFS to OS ratio.	The current text is misleading. The amendment provides additional clarification.	Not a factual error. In its response to the clarification letter, the company provided

On several pages throughout the report, the ERG refer to the use of the PALOMA-1 study to provide a PFS to OS ratio, as below. "This trend can be also observed in the PALOMA-1 trial (comparing palbociclib plus letrozole vs letrozole) where a "gain in median OS/gain in median PFS" ratio close to 38.5% was observed. The ERG considered the observed ratio of 38.5% more evidence-based than the completely arbitrary 100% that the company assumed." "Although the data from the PALOMA-1 trial have their limitations, that trial is the only one currently available for providing insight in the association between PFS and OS of patients treated with a CDK 4/6 inhibitor." "Even though the ERG is aware of the limitations of the PALOMA-1 trial, which were elaborately discussed in ID914"	"it should be recognised that the PALOMA-1 study has a number of limitations, such as: the study being an open-label phase I/II RCT with a small sample size, which is not powered to show a statistical difference, the two distinct patient cohorts may mean that the PALOMA-1 population is not sufficiently similar to the MONALEESA-2 population. Although palbociclib and ribociclib are both CDK 4/6 inhibitors it does not necessarily mean that the association between PFS and OS will be the same. Further caution should be applied when interpreting the PFS to OS ratio derived for PALOMA-1 as this is based upon the median figures, which are less reliable than mean figures. Additionally, it is widely accepted that in advanced breast cancer the relationship between PFS and OS is complex and difficult to predict, especially for the population being appraised, first line HR+/HER2- advanced breast cancer patients. In consideration of all the limitations of deriving a gain in median OS/gain in median PFS ratio based on the PALOMA-1 study, as per the preferred ERG approach, the resulting ratio could represent the lowest ratio likely to be experienced." "Even though the ERG is aware of the limitations of the PALOMA-1 trial, which were	The additional wording will aid understanding and clarity. Without presenting the limitations of using PALOMA-1 in deriving a PFS to OS ratio, it may lead to false understanding and a misrepresentation of the strength of PALOMA-1 data, and ability to accurately predict the expected OS for ribociclib. The ERG requested further clarification regarding the use of a full PFS to OS surrogacy. The company provided a rationale and discussed in detail the challenges of applying a robust ratio. However, the ERG do not discuss the clarification response in the report. In the appraisal of palbociclib, ID915, it was accepted by the committee that relationship between progression-free and overall survival was complex and difficult to predict.	some studies indicating the complexity of the PFS/OS relationship. However, no evidence or convincing rationale was provided for a full PFS to OS surrogacy. Therefore, the ERG has used the only evidence available regarding the PFS/OS relationship in patients with hormone receptor-positive, HER2-negative, advanced breast cancer treated with a CDK 4/6 inhibitor. The ERG has indicated that the data from the PALOMA-1 have their own limitations, and refers to ID915.

	elaborately discussed in ID915”		

Issue 5 Progression health state treatment costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 92 “Nevertheless, the company found support in the NICE appraisal of fulvestrant (TA239) in which an overview of treatment pathways was provided during post-progression, as well as average cost post-progression per month amounting to £1,084 (excluding costs associated to adverse events). Although the ERG realises that TA239 was published in 2011, and the treatment pathway will have changed” **Page 111** “In the CS, a monthly third-line treatment related cost estimate of £2,000 was used, which was based on clinical expert opinion. The details on how this cost estimate had been derived were not provided. Therefore, the ERG believes the inflation adjusted cost	We would suggest adding the following wording where the progression/third line plus treatment costs are discussed. “However, it should be noted that the treatment pathway for HR-positive/HER2-negative advanced breast cancer has changed significantly since the publication of TA239 with the additional availability of eribulin (TA423) and everolimus (TA421)” “However, it should be noted that the treatment pathway for HR-positive/HER2-negative advanced breast cancer has changed significantly since the publication of TA239 with the subsequent availability and usage of eribulin (TA423) and everolimus (TA421) increasing the cost per month to a level higher than that accepted in the 2011 fulvestrant guidance and the ERG estimated value. Thus, the 2016	Additional text provides further clarification. The ERG requested further information regarding the costing of third line or greater treatment costs at the clarification stage. The company provided further justification and rational, which the ERG has not considered in the report. While the ERG intimate that the treatment pathway has changed since the fulvestrant (TA239) appraisal, they do not provide any clear details. This additional wording will help provide further needed context.	Not a factual error. In the CS and in the clarification letter, the details on how this cost estimate of £2,000 had been derived were not provided transparently. Although, the ERG acknowledges that the treatment pathway might have been changed since the publication of TA239 (as mentioned in the ERG report), the ERG considers the estimate as used in TA239 to be a more transparent and reliable estimate. Costs of everolimus are (partly) taken into account, since costs and effects of second-line therapies are modelled separately.

estimate from TA239, £1,140 to be a more plausible and a more transparent estimate. The details on how this estimate was derived can be traced in the TA2392 as well as in the company's response to the clarification letter document26 (question B16)." **Page 119** "Consequently, in the ERG base-case post-progression costs (of third-line and subsequent lines of treatment) were based on TA239, the NICE appraisal of fulvestrant (2011)21 which included as average costs post-progression per month £1,084 (excluding costs associated to adverse events). Although the ERG realises that TA239 was published in 2011, and the treatment pathway will have changed"	inflation adjusted value of £1,140 is likely to represent the lower bound of 3rd line treatment costs." "However, it should be noted that the treatment pathway for HR-positive/HER2-negative advanced breast cancer has changed significantly since the publication of TA239 with the subsequent availability and usage of eribulin (TA423) and everolimus (TA421)"		

Issue 6 Time to Treatment Discontinuation (TTD) modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 16, 84, 120, 127 "Although for the PFS the results	We suggest the wording to be updated as per the following:	Factual inaccuracy. TTD data is based on the primary analysis data cut January 2016.	This is a reporting error and the ERG agrees that data from "June 2016" cut-off was never

from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the June 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER." "Finally, as discussed in Section 5.2.6.1 of this report, the results from the latest PFS data cut-off (January 2017) were provided, however the TTD used in the model is still based on the June 2016 cut-off PFS dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date, despite the fact that it was clearly requested in the clarification letter." "the TTD used in that model was still based on the June 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off	"Although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG is unsure how applying TTD for the latest data cut, January 2017, might impact the ICER." "Finally, as discussed in Section 5.2.6.1 of this report, the results from the latest PFS data cut-off (January 2017) were provided, however the TTD used in the model is still based on the January 2016 cut-off PFS dataset." ""the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG is unsure how applying TTD for the latest data cut, January 2017, might impact the ICER."	The ERG have commented in the report that the omission of using TTD data based on the updated data cut (January 2017) is an important omission. The ERG state that they clearly requested the updated TTD data to be applied in the economic analyses at the clarification stage, however, as per below, the clarifications and requests made by the ERG at the clarification stage do not request TTD data. The ERG requested updated PFS data only. **ERG clarification questions:** B11. Priority request: Please confirm that all the PFS, OS and TTD parametric extrapolations conducted in the economic model were based on the ITT patient level data from MONALEESA-2 and BOLERO-2 trials. Otherwise, please update the economic model and its results, in which all PFS extrapolations were based on ITT data in all the scenarios. B12. a. Please incorporate the scenario analyses to the economic model, where the MONALEESA-2 PFS extrapolations were based on central assessment	used. It is corrected throughout the report in the Erratum. The remark on treatment after progression was in the real clinical practice context, not in the trial protocol.

date and is unsure how this might impact the ICER." "Although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the June 2016 cut-off dataset. The ERG considers it as an important omission from the company to not to provide the data from the most recent cut-off date and is unsure how this might impact the ICER." **<u>Page 84</u>** "Furthermore, some clinicians might choose the continuation of the same treatment even after the disease progression"	"Although for the PFS the results from the latest data cut-off (January 2017) were included in the revised model that the company provided, the TTD used in that model was still based on the January 2016 cut-off dataset. The ERG is unsure how applying TTD for the latest data cut, January 2017, might impact the ICER." This statement is misleading, as treatment beyond disease progression was not allowed in the study protocol. This statement should be removed.	review PFS data instead of local assessment review PFS data, in line with the Kaplan Meier plots provided in question A8. b. Please incorporate the scenario analyses to the economic model where the PFS extrapolations were based on the PFS data from the most recent data cut-off point and based on central assessment review, in line with question A3. Misleading statement. Treatment beyond disease progression was not allowed in MONALEESA-2 study.	

Issue 7 Consistency

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 15, 16, 84, 120, 127 The ERG mention throughout the report that the ribociclib TTD data is based upon June 2016 data cut off. **Page 76, 77, 78** The ERG have mentioned in several pages that PFS for ribociclib plus letrozole and letrozole monotherapy (first-line) is modelled based on June 2016 data cut. "The PFS for ribociclib in combination with letrozole and letrozole monotherapy in the first-line were based on IPD from the MONALEESA-2 trial from the dataset of June 2016 cut-off" **Page 82** "Proportion of deaths among PFS events in the first line therapy (June 2016 cut-off PFS dataset)"	Wording updates to ensure consistency: The ribociclib TTD data is modelled based upon the IPD from the January 2016 data cut off. The company modelled PFS based on IPD for January 2016 data cut off in the company submission. "The PFS for ribociclib in combination with letrozole and letrozole monotherapy in the first-line were based on IPD from the MONALEESA-2 trial from the dataset of January 2016 cut-off" Figures 5.4, 5.5, 5.6 title update "Proportion of deaths among PFS events in the first line therapy (January 2016 cut-off PFS dataset)" Table 5.5 title update	Factual inaccuracy and consistency throughout report. It should be noted that at the time of the submission only data from the January 2016 data cut of MONALEESA 2 were available.	This is a reporting error and the ERG agrees that data from "June 2016" cut-off was never used. It is corrected throughout the report.

Issue 8 CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 75 "In response to the clarification letter, the company explained that within the economic model the median age at first line progression was 64.3 and 63.3" **Page 82** Table 5.6 [redacted]	CIC marking "In response to the clarification letter, the company explained that within the economic model the median age at first line progression was [redacted] and [redacted]" Mark the following values CIC in table 5.6 [redacted] (letrozole - PFS events - MONALEESA-2) [redacted] (letrozole in combination with a CDK 4/6 inhibitor – PFS events - MONALEESA-2) Remove CIC marking for 137 and 194, PFS events, n for PALOMA-2.	CIC marking	The current CIC marking will be corrected.

(please cut and paste further tables as necessary)