For public - ACiC information redacted

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

1st Appraisal Committee meeting

Cost effectiveness

Committee A

Lead team: Brian Shine

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

NICE technical team: Marcela Haasova and Joanna Richardson

5th July 2017

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

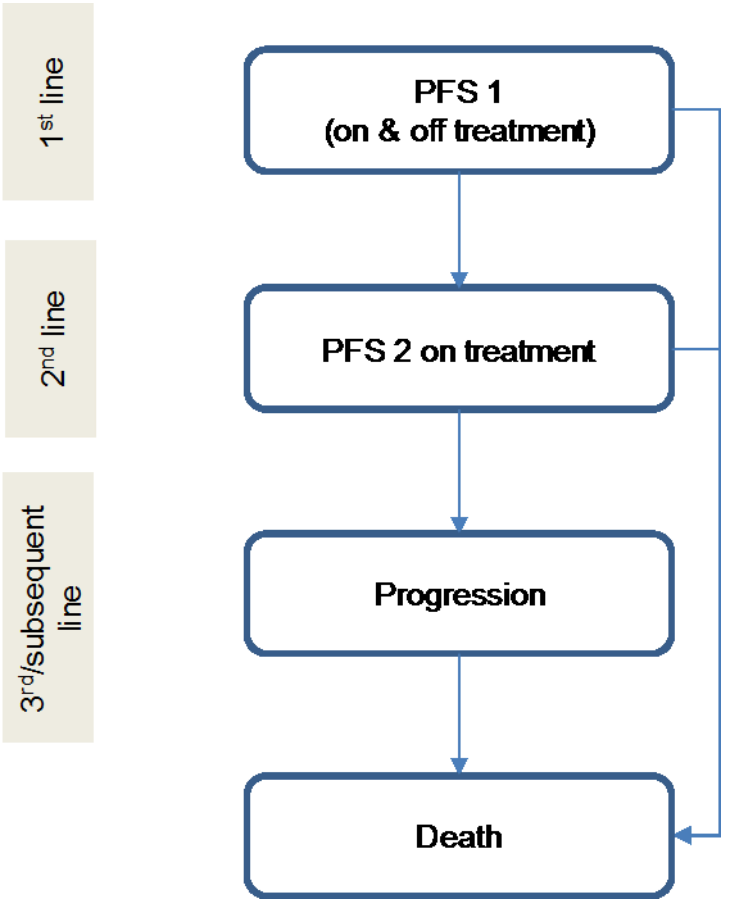
PFS2

- everolimus & exemestane, exemestane monotherapy, or capecitabine 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
- second-line treatments based on clinical opinion & differ by treatment arm
  - scenario with same treatments modelled in both arms explored
- 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 modelling: **January 2016 cut-off**

- Letrozole: [redacted] = best and second best statistical fit
- Ribociclib: [redacted] 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 [redacted] was chosen for PFS extrapolation
- The same distribution chosen when PFS updated to **January 2017 data**

TTD modelling: **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:

- Pooled data from MONALEESA-2 and PALOMA-2 used.
- Result were updated using **January 2017 data:**
  - Letrozole: [redacted]
  - CDK4/6 inhibitors (ribociclib & palbociclib): [redacted]

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

PFS Modelling

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

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.

Clinical evidence *PFS2* state: BOLERO-2

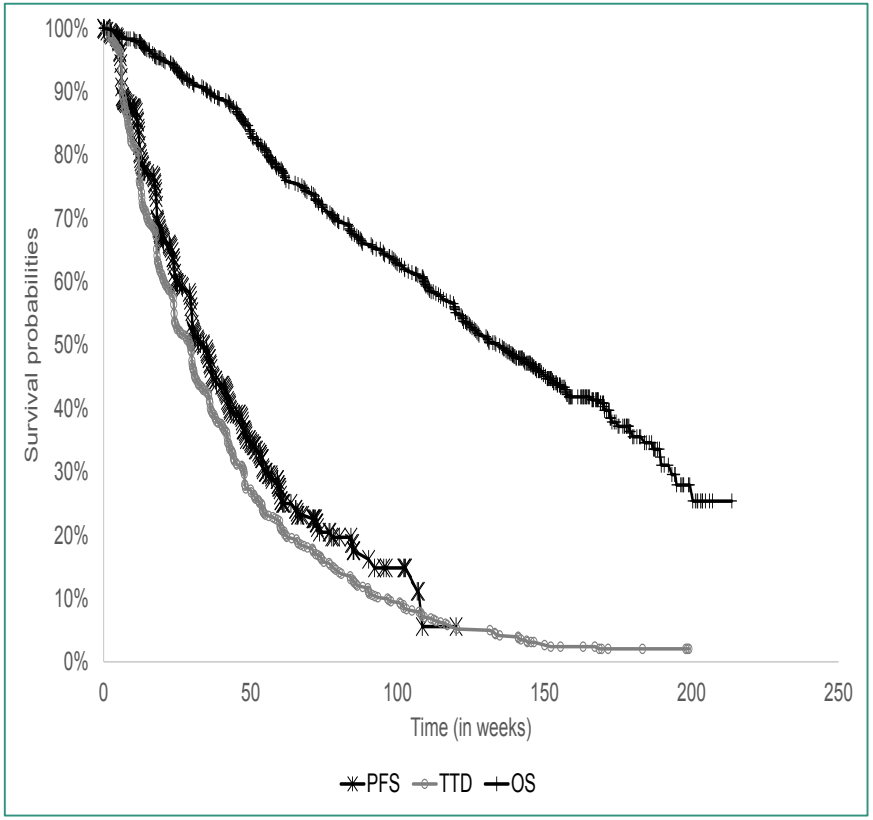
BOLERO-2	
Design	Placebo-controlled phase 3 RCT (randomised on visceral metastasis and sensitivity to endocrine therapy)
Location	Multinational
Population	N=724; postmenopausal women with HR+/HER2- advanced breast cancer refractory to letrozole or anastrozole
Intervention and comparator	• Everolimus 10 mg/day with exemestane 25 mg/day • Placebo with exemestane 25 mg/day
Outcomes:	• Primary: PFS based on local assessment: data cut-off December 2011 (no data for PFS collected after this date). • TTD and OS (latest data cut-off is October 2013)

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.

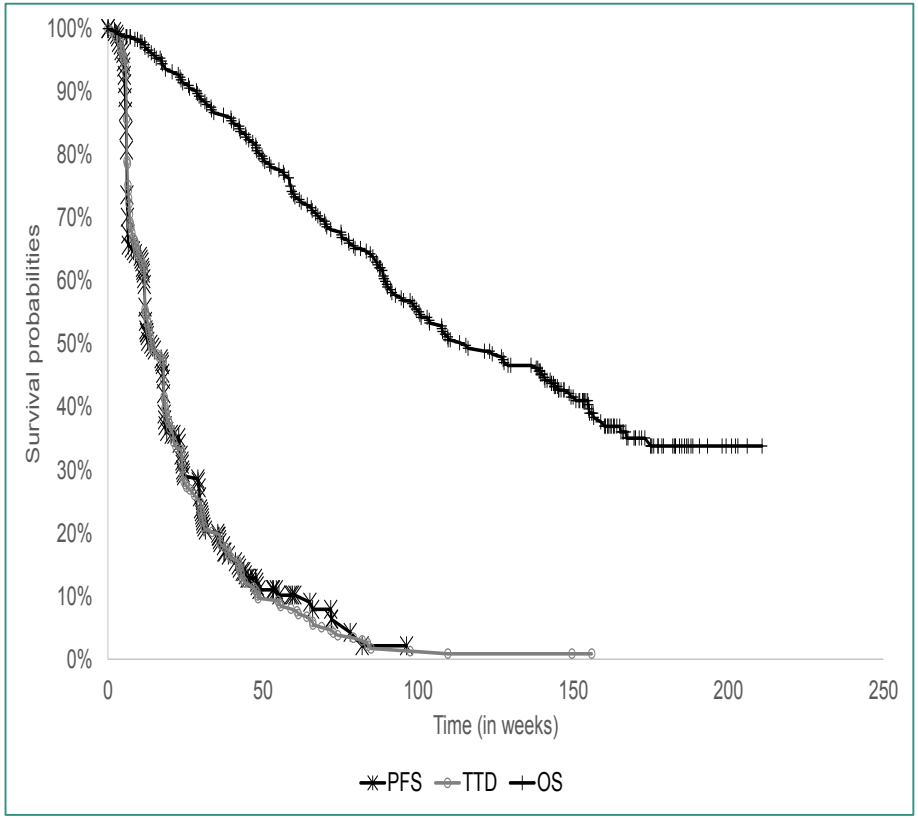
BOLERO-2: PFS, OS and TDD

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

Time to treatment discontinuation is a proxy for disease progression:

- Everolimus:
  - 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

Time to death from treatment discontinuation (post-discontinuation survival curve) estimates the time patients spend in progressive disease (including both *PFS2* off treatment and *Progression*).

- Everolimus and exemestane pooled: 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; KM, Kaplan–Meier; PFS, progression free survival.

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 have used follow-up treatments from 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

TTD modelling: proportional hazard assumption violated, but survival of:

- exemestane monotherapy is modelled by applying HR from BOLERO-2 to everolimus arm TTD and
- chemotherapy by adjusted HR of chemotherapy versus "everolimus-based therapy" form Li et al. 2015 (the adjustments & comparator 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
PFS1 on treatment	[redacted]	[redacted]	[redacted]	[redacted]
PFS1 off treatment	[redacted]	[redacted]	[redacted]	
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 [redacted]

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

ERG: utilities

PFS1: [redacted] from MONALEESA-2 EQ5D-5L

- 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.
- ID915 palbociclib: pre-progression state utility was 0.72 (PALOMA 2 EQ-5D data), and post-progression value of 0.51 (Lloyds 2006).
- The 5L instrument shifts mean utility scores towards full health.

Utilities in *PFS2*: 0.774

- 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

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

AE

- Company: neutropenia (grade 3/4) was reported in approximately [redacted] of patients. It was not included in the economic model because:
  - [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.

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 of £1,140 to be a more plausible

ERG: Sensitivity analysis of company's original base case with initial PAS

ERG changes

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

Scenario analyses	Ribociclib		letrozole alone		Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs		
Company base-case January 2017 PFS	[redacted]	[redacted]	[redacted]	[redacted]	0.90	[redacted]
ERG preferred base-case	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
1: ERG + Weibull function for PFS1 and TTD	[redacted]	[redacted]	[redacted]	[redacted]	0.41	[redacted]
2a: ERG + 3rd-line costs = £0	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
2b: ERG +3rd-line costs = £2,000 per month	[redacted]	[redacted]	[redacted]	[redacted]	0.53	[redacted]
4: ERG + company Full OS surrogacy	[redacted]	[redacted]	[redacted]	[redacted]	0.89	[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 PFS data

January 2017	Clinical trial result		Model result	
	Median	Mean	Median	Mean
Ribociclib				
First-line progression-free survival (PFS1)	[redacted]	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)	[redacted]	Not reached, not reported	[redacted]	[redacted]
Overall survival	[redacted]	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 (change 1 in ERG analyses):
  - enhanced PAS
  - including the costs of wastage (change 2 in ERG analyses)
  - changing the modelling of the post-treatment discontinuation survival after chemotherapy (change 4 in ERG analyses)

- The following ERG changes were not accepted:
  - Cost of 3rd line therapy based on TA239 (£1,140; change 3 in ERG analyses)
  - PFS-OS surrogacy based on PALOMA-1 (ratio of 38.5%; change 5 in ERG analyses)
  - scenario analyses with the above changes suggested by ERG presented

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]

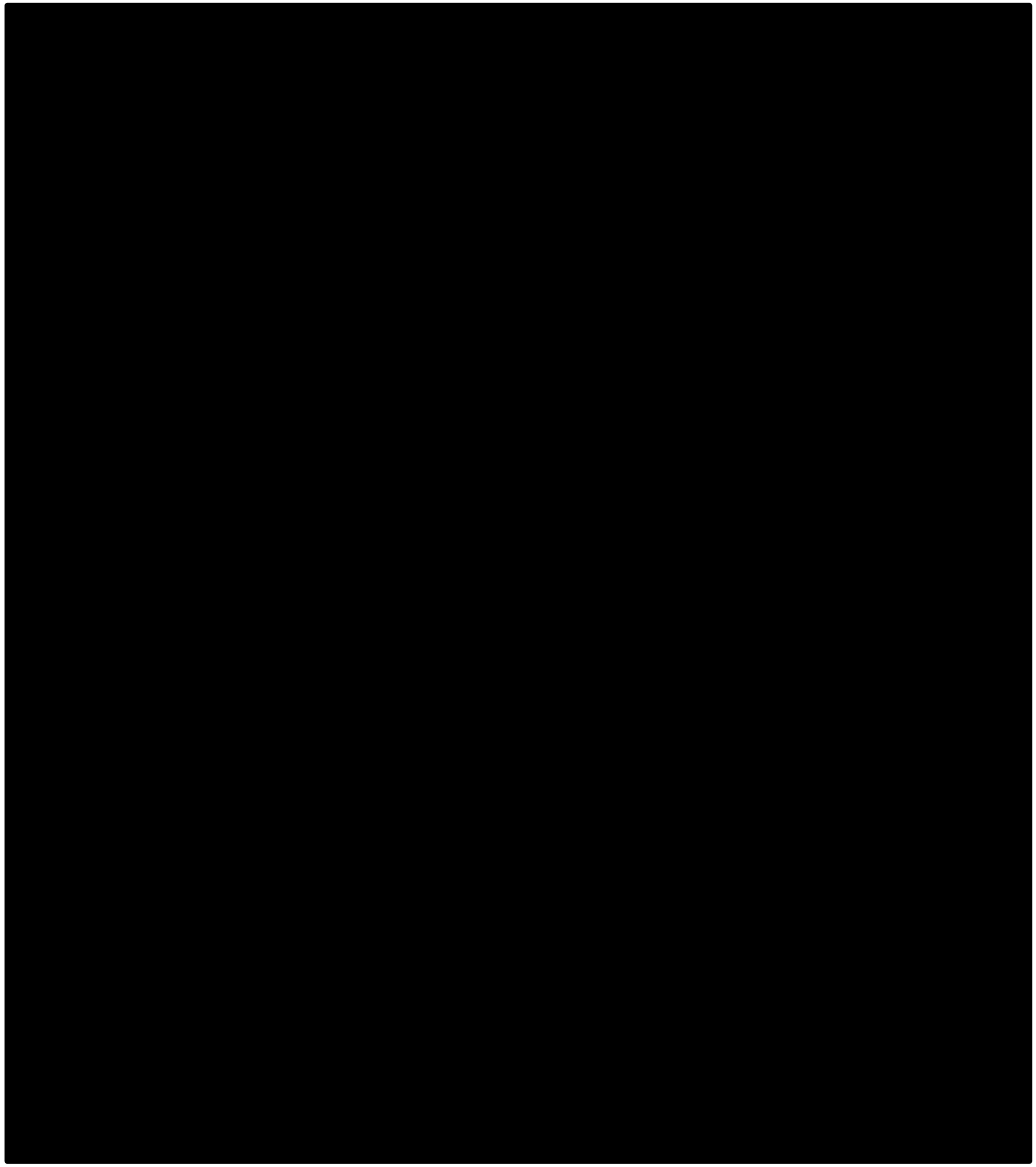
Probabilistic analyses

	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 Is the same as ERG's base-case	[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.

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Company: differences between ribociclib and palbociclib NICE appraisals

(Pre-consultation models 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	*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 AEs from MONALEESA-2	Only neutropenia
LYG	[redacted]	3.79 palbo & 3.02 let: **difference: 0.77**
QALYs	[redacted] **difference: 0.96**	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?
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