Chair's presentation

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

3rd Appraisal Committee meeting

Committee A

Lead team: Mohit Sharma, Pam Rees and 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

4th October 2017

Slides for Committee – CIC redacted

Ribociclib

MA received on 22nd August	Treatment of postmenopausal women with hormone receptor (HR)-positive, (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy in combination with an aromatase inhibitor.
Mechanism of action	Selective CDK4/6 inhibitor. When either of these two proteins are activated they can cause the cancer cells to proliferate
Administration	600 mg (3 x 200 mg tablets) orally once daily for 21 days of 28-day cycle 400 - 200 mg/day dose reductions to manage treatment-related AEs Treatment continued as long as the patient has clinical benefit or until unacceptable toxicity
Acquisition cost	List price: £2,950 per 21 days of 600 mg dose (3 x £983.33).*

Key: AE, adverse events; CDK4/6, cyclin-dependent kinase 4 and 6 HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive
Note: *, company submission.

History of appraisal

- Committee meeting July 5th - the decision was deferred.

  DSU was asked to support the committee:

  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?

- Committee meeting September 5th – ACD not released
  - Company submitted new PAS and updated time to treatment discontinuation data

Key: ACD, appraisal consultation document; DSU, decision support unit; PAS, participant access scheme.

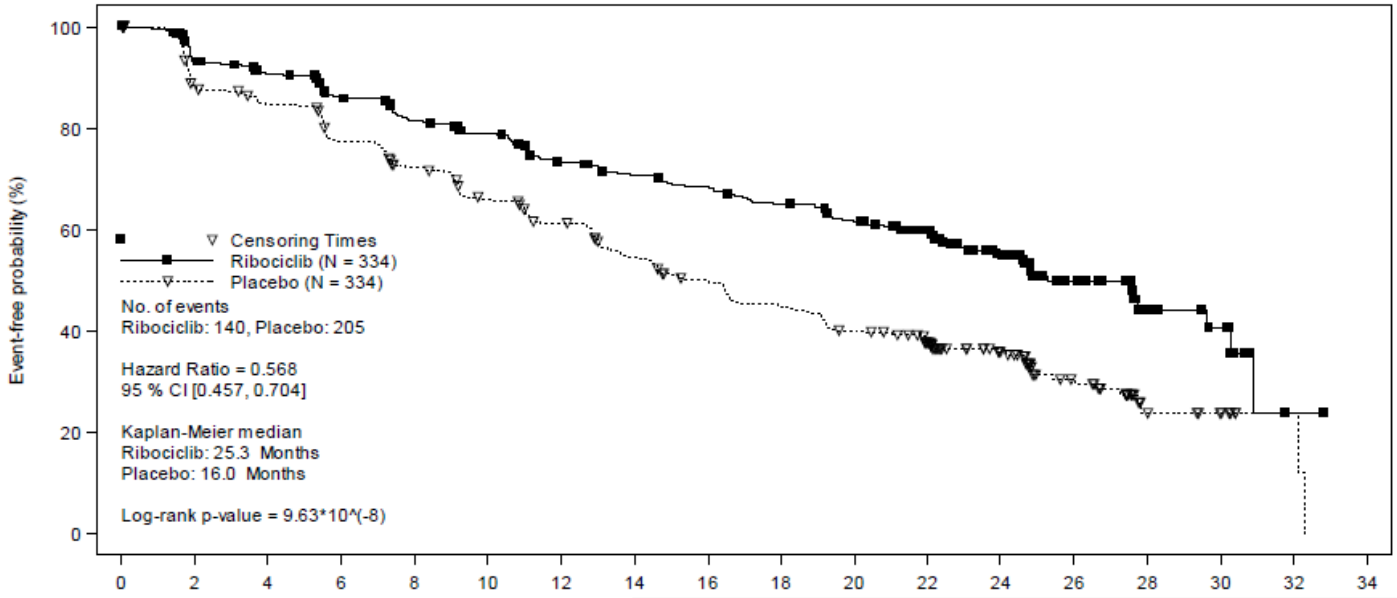
Clinical evidence: MONALEESA-2

Design	Double blind placebo-controlled phase 3 RCT, 223 sites, 29 countries
Intervention and comparator	Ribociclib with letrozole (n=334) Matched placebo with letrozole (n=334):
Primary outcome	*Primary:* PFS based on local assessment Secondary: OS, ORR, CBR, safety, QoL

	Ribo & let	Placebo & let	Diff.	HR (95%CI)
PFS 2017 data cut-off: median, months				
Local	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)	**9.3**	0.568 (0.457, 0.704) p<0.001
Central	Not assessed			
OS 2016 data cut-off: median, months				
Median	NE (NE, NE)	33.0 (33.0, NE)	-	0.746 (0.517, 1.078)
Deaths	50 (15%)	65 (19.7%)	-	-

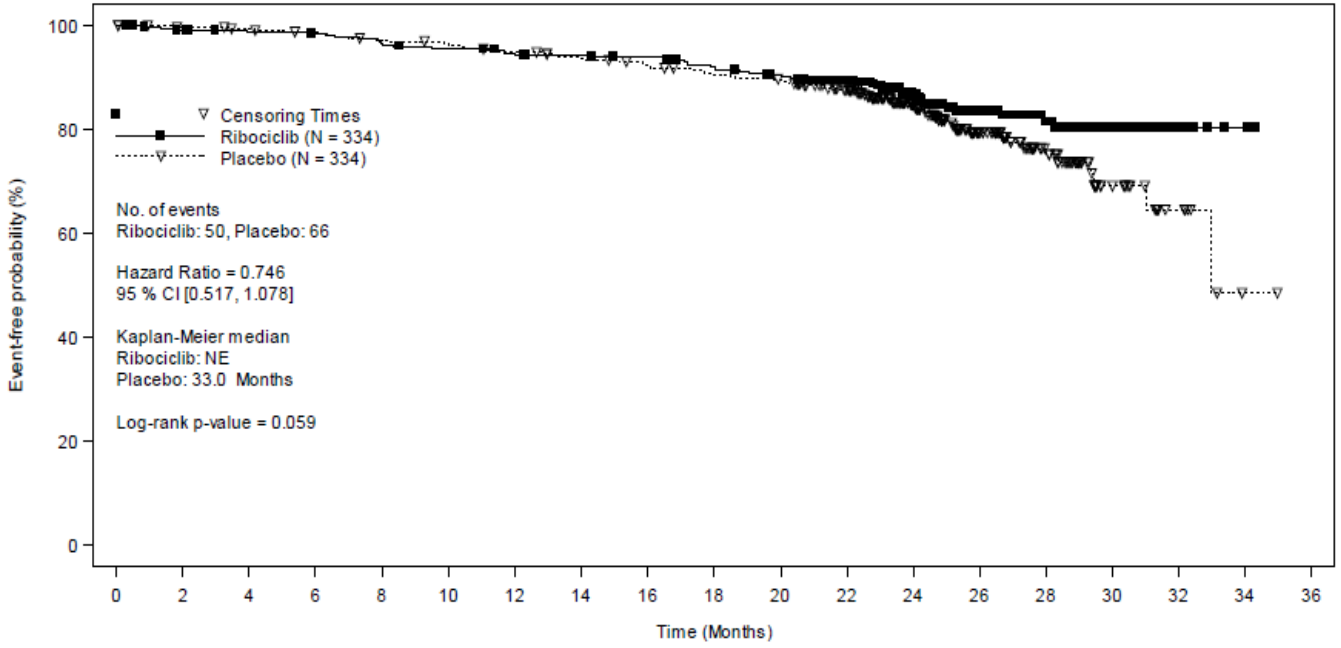
Key: CBR, clinical benefit rate; Diff., difference, let, letrozole; NE, not estimable; OS, overall survival; ORR, objective response rate; PFS, progression free survival; QoL, Quality of Life; RCT, randomised controlled trial; Ribo, ribociclib.

MONALEESA-2 PFS and OS



PFS KM:
January 2017 cut-off

OS KM:
January 2016 cut-off



Key: KM, Kaplan-Mayer curve; OS, overall survival; PFS, progression free survival;

Company's model and original inputs

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

PFS1

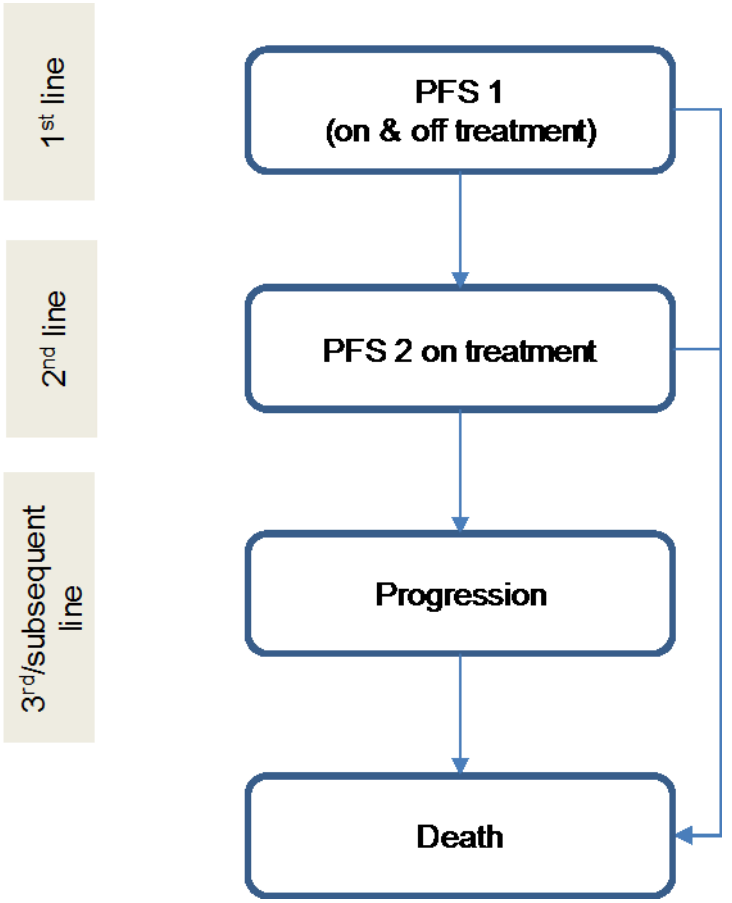
- IPD from MONALEESA-2
- **TTD and PFS are modelled independently using exponential curves***
- **PFS gain = OS gain ***
- **PFS1 Utility from trial using EQ5D- 5L***
- patients cannot move to *Progression* directly

PFS2

- everolimus & exemestane, exemestane monotherapy, or capecitabine therapy
- IPD from BOLERO-2: RCT of everolimus & exemestane vs placebo
- **Utility lower than PFS1***

Progression

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



- **Inputs in model further discussed**

Company's base case (at 2nd meeting)

- Company's assumptions in the base-case:
  - PFS & TTD separate exponential extrapolations (using latest 2017 data for PFS, 2016 for TTD)
  - £2,000 3rd line cost
  - PFS1=[redacted](EQ5D-5L), PFS2=0.774 (Lloyd et al. 2006 BOLERO-2 adjusted)
  - Full OS surrogacy i.e. all PFS gain translates to OS gain

Full surrogacy	Total QALYs		Total Costs		ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib	
Company's base case*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,140 3rd line cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
£1,140 and 3-L PFS1=[redacted] & PFS2=0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ5D-5L, European quality of life-5 dimensions-5 levels; ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.
Note: *, same as at ACM1; all results are with ribociclib PAS.

2nd meeting: DSU scenario analyses

- DSU's preferred assumptions:
  - PFS and TTD Weibull extrapolation (2017 PFS, 2016 TTD data)
    - Weibull curve allows the rate of events to vary: more progression/deaths would be expected over time, and there also would be more AE-related discontinuations early on in the trial
    - exponential model results in mean TTD and PFS of [redacted] months respectively, the difference is smaller for Weibull ([redacted] months for TTD and PFS respectively)
  - £1,140 3rd line cost
  - PFS1=[redacted](EQ5D-3L), PFS2=0.69 (Mitra et al. 2016)
  - Reduced dose ribociclib as preferred by committee

	PFS: Exponential	PFS: exponential	PFS: Weibull	PFS: Weibull
	TTD: Exponential	TTD: Weibull	TTD: Exponential	TTD: Weibull
		Full OS surrogacy		
ICER	[redacted]	[redacted]	[redacted]	[redacted]
		Partial OS surrogacy		
ICER	[redacted]	[redacted]	[redacted]	[redacted]

Key: EQ5D-3L, European quality of life-5 dimensions-3 levels; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

Committee's preferred assumptions

- committee accepted company's approach to modelling
- committee accepted that BOLERO represents 2nd line therapies
- Weibull curve for progression free survival and time to treatment discontinuation preferred because reduced the difference between TTD and PFS
- the estimated cost of progression (3rd-line) of 1,140
- 3-level updated utility values
- Ribociclib dose reduction based on the MONLEESA-2 individual participant data
- both the full and partial OS surrogacy assumption results will be considered in its decision making

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

Company's new submission

- Introduced new PAS, updated TTD data to latest 2017 cut
- Company's assumptions in new base-case:
  - PFS and TTD exponential extrapolation (using 2017 data for both)
  - £1,500 3rd line cost
  - PFS1=[redacted](EQ5D-3L), PFS2=0.69 (as per DSU)
  - partial OS surrogacy (38.5%)
- Further discusses the following assumptions:
  - **Utilities, cost of 3rd line, OS surrogacy and PFS & TTD extrapolation**
- The company's new results have not yet been verified.

Key: EQ5D-3L, European quality of life-5 dimensions-3 levels; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; TTD, time to treatment discontinuation.

Utilities

- **Company's new base case used committee preferred utilities:**
  - **PFS1:** in [redacted] MONALEESA-2 EQ5D-5L mapped to 3L
  - **PFS2:** 0.69 EQ-5D scores from Mitra et al. 2016
- Company:
  - inconsistent with previous appraisals where the Lloyd values were used, e.g. appraisal of everolimus plus exemestane [TA241] which is the 2nd line therapy represented by PFS2
  - Using the 3L and 0.69 values increased the original ICER
- DSU:
  - NICE recommends to map 5L valuation set to 3L
  - EQ-5D scores preferable for PFS2

Key: EQ5D, European quality of life-5 dimensions; 3L, 3-levels; 5L, 5-levels; ICER, incremental cost-effectiveness ration; OS, overall survival; PFS, progression-free survival

3rd line costs

- **Company's new base case:** £1,500
- **Committee preferred cost:** £1,140
- Company: £1,140 was generated 8 years ago and underestimates the cost, original base case value was £2,000, limitations to DSU calculations of cost
- DSU: £1,140 probably overestimates cost, but is closer than £2,000
- CDF clinical lead: estimated 3rd line cost to be [redacted] to [redacted]/ per month treatment costs (including PAS) plus disease related costs

3rd line cost	Inc. QALY's	Total cost		ICER (ICER with TTD 2016)
		Ribociclib	Letrozole	
New base case* £1,500	[redacted]	[redacted]	[redacted]	[redacted]
£2,000	[redacted]	[redacted]	[redacted]	[redacted]
£1,140	[redacted]	[redacted]	[redacted]	[redacted]

Note: *New base case assumptions: PFS & TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted], PFS2 = 0.69 (Mitra et al.), partial OS surrogacy and 2017 TTD data..

OS surrogacy

- **Company's new base case:** partial OS surrogacy
- **Committee preferred cost:** major area of uncertainty, both full and partial OS surrogacy results will be considered
- Company:
  - ID 915: the level of benefit PFS/OS relationship is likely to lie somewhere between the manufacturer's assumption of a 1:1 relationship and the ERG's assumption of 38.5%
  - adopted partial surrogacy but present range scenarios
- DSU: it is not clear if a full OS surrogacy approach is valid

OS surrogacy	Inc. QALY's	Total cost		ICER (ICER with TTD 2016)
		Ribociclib	Letrozole	
New base case* Partial (38.5%)	[redacted]	[redacted]	[redacted]	[redacted]
60%	[redacted]	[redacted]	[redacted]	[redacted]
Full	[redacted]	[redacted]	[redacted]	[redacted]

Note: *New base case assumptions: PFS & TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted], PFS2 = 0.69 (Mitra et al.), partial OS surrogacy and 2017 TTD data..

PFS and TTD extrapolation (i)

- **Company's new base case:** PFS & TTD exponential extrapolation
- **Committee preferred case:** PFS & TTD Weibull extrapolation
- Company:
  - exponential for PFS and TTD in ERG's preferred base-case
  - exponential extrapolation for PFS and TTD preferred in ID915
  - [redacted] difference between the Kaplan Meier curves for median TTD and median PFS
  - Weibull curves for PFS and TTD converge and crossover at the tail

PFS and TTD extrapolation (ii)

- DSU:
  - PFS: exponential 2nd best according to statistical goodness of fit,
  - TTD: exponential worst according to statistical goodness of fit

	Mean TTD	Mean PFS	difference
Exponential	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]

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- ERG
  - Weibull and exponential equally plausible for PFS

[redacted]

Note: *, [redacted] of ribociclib patients discontinued due to adverse events

PFS and TTD extrapolation (iii)

NHS England:

- KM plots indicates approx. 6 month difference between TTD and PFS in MONALEESA and PALOMA trials:
  - Partly due to: additional toxicity, trial protocol and to clinician unfamiliarity with ribociclib/palbociclib and the substantial neutropenia they cause. Also letrozole continued after ribociclib/ palbociclib discontinuation without evidence of disease progression.
- Model: [redacted] difference between the mean PFS and TTD using exponential extrapolating is not clinically realistic, [redacted] difference using Weibull extrapolation is more clinically realistic.
- PFS: exponential extrapolation is clinically reasonable.
- TTD: is not only determined by the rate of developing resistance but also other factors: toxicities, management of toxicities, clinician familiarity with the management and treatment protocols. There is some justification to use Weibull extrapolation.

ACM3: Company's new base case and scenario analyses

PFS & TTD: exponential	Total QALYs		Total Costs		ICER (ICER with TTD 2016)
	Let.	Ribo.	Let.	Ribo.	
Company's NEW base case partial surrogacy, £1,500 3rd line, PFS1/2= /0.69	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company's original base case full surrogacy, £2,000 3rd line, PFS1/2= /0.774	[redacted]	[redacted]	[redacted]	[redacted]	NA [redacted]

Scenarios:

Curves	PFS: Exponential TTD: Exponential	PFS: exponential TTD: Weibull	PFS: Weibull TTD: Exponential	PFS: Weibull TTD: Weibull
Full OS surrogacy				
£1,500	[redacted]	[redacted]	Not provided	Not provided
£1,140	[redacted]	[redacted]	[redacted]	Not provided
Partial OS surrogacy				
£1,500	[redacted]	[redacted]	Not provided	Not provided
£1,140	[redacted]	[redacted]	[redacted]	Not provided

Key: *, using 2016 TTD data CS; **Note:** New base case assumptions: PFS & TTD = Exponential, 3rd Line + treatment costs = £1,500, EQ-5D-3L for PFS1 = [redacted], PFS2 = 0.69 (Mitra et al.), partial OS surrogacy and 2017 TTD data.

Questions for committee

- What does the committee consider to be appropriate utilities for PFS 1 and PFS2?
- What does the committee consider is a reasonable cost to model for 3rd line treatment?
- TTD (for costs) and PFS (for outcome) are modelled using exponential curves; the DSU has suggested Weibull may be more appropriate; what is the committee's view?
- OS data is immature. The ICER is different if PFS gain is assumed to translate to an equal OS gain, compared with 38% of the PFS gain which is assumed in 'partial surrogacy' derived from PALOMA 1, an open label study for palbociclib. What is the committee's view on this area of uncertainty?

Key: DSU, decision support unit; EQ5D-5L, European quality of life-5 dimensions-5 levels; ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.