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

2nd Appraisal Committee meeting

Committee A

<u>Lead team</u>: Mohit Sharma, Pam Rees and Brian Shine

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

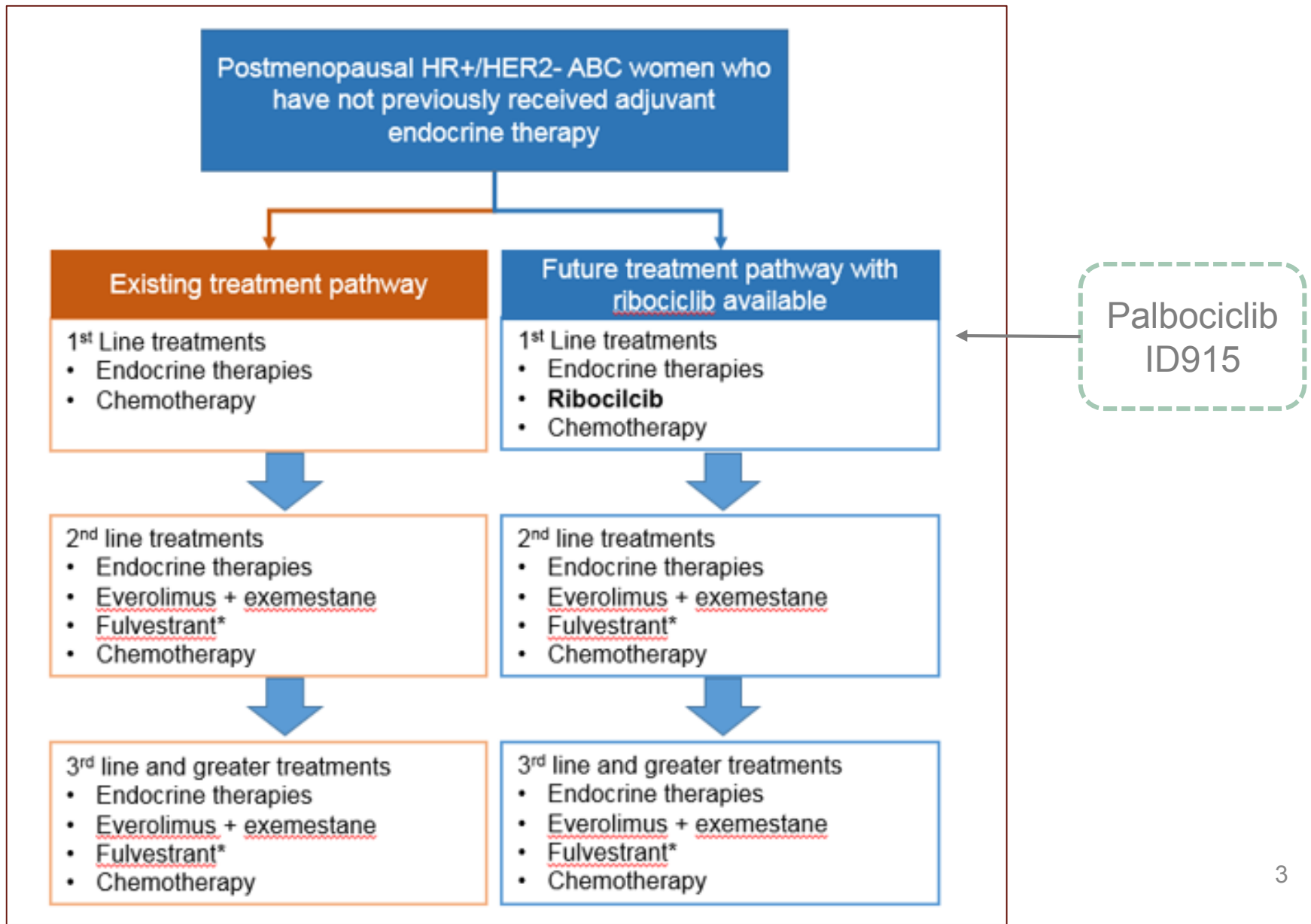<u>NICE technical team</u>: Marcela Haasova and Joanna Richardson

5th September 2017

Ribociclib, Novartis

MA received on 22nd August	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	£2,950 per 21 days of the recommended 600 mg dose (3 x £983.33)
Cost of a course of treatment	▬▬▬▬ anticipated number of repeat courses of treatments: 14 Simple PAS discount approved.

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

Company – proposed treatment pathway

Postmenopausal HR+/HER2- ABC women who have not previously received adjuvant endocrine therapy

Existing treatment pathway

1st Line treatments
- Endocrine therapies
- Chemotherapy

2nd line treatments
- Endocrine therapies
- Everolimus + exemestane
- Fulvestrant*
- Chemotherapy

3rd line and greater treatments
- Endocrine therapies
- Everolimus + exemestane
- Fulvestrant*
- Chemotherapy

Future treatment pathway with ribociclib available

1st Line treatments
- Endocrine therapies
- **Ribocilcib**
- Chemotherapy

2nd line treatments
- Endocrine therapies
- Everolimus + exemestane
- Fulvestrant*
- Chemotherapy

3rd line and greater treatments
- Endocrine therapies
- Everolimus + exemestane
- Fulvestrant*
- Chemotherapy

Palbociclib ID915

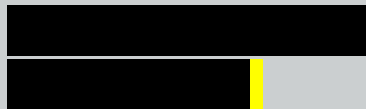# Appraisal committee meeting on 5th July 2017

- The decision was deferred.
  - ID1026 model has a fixed post progression state (PFS2) which is a new approach in this disease area;
  - The company's comparison with ID915 model which used similar clinical data showed different cost-effectiveness results;
  - ID1026 model gave some counterintuitive results: a decrease in survival gains resulted in ribociclib becoming more cost-effective;
  - some of the model assumptions and inputs were questioned.

- 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?

Key: DSU, decision support unit; PFS 2, second-line progression-free survival.

Clinical evidence: MONALEESA-2

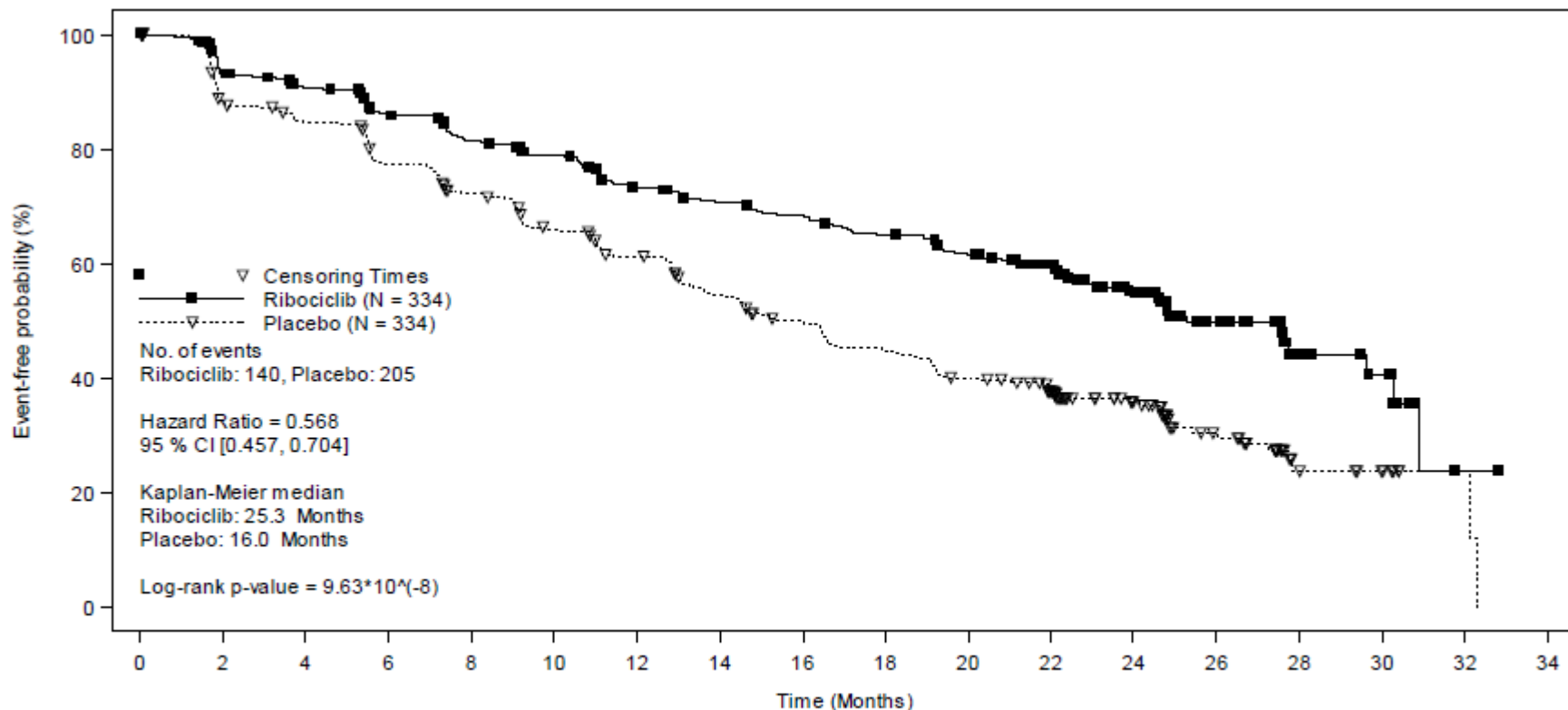|	
Design	Double blind placebo-controlled phase 3 RCT
Location	223 sites in 29 countries: ▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮
Population	Post-menopausal women with ER+ and/or PR+, HER2- recurrent or metastatic breast cancer who had not received systemic therapy for advanced breast cancer
Intervention and comparator	Ribociclib with letrozole (n=334) Matched placebo with letrozole (n=334):
Primary outcome	*Primary:* PFS based on local assessment Secondary: OS, ORR, CBR, safety, EORTC QLQ-C30, EQ5D, safety & breast cancer module EORTC QLQ-BR23 Supportive analysis: Central PFS (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; EQ5D-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 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)	22.9	NR
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)	███████	███████
January 2017 data cut-off: PFS difference of 9.3 months for local assessment				
Median (95 CI)	25.3 (23.0, 30.3)	16.0 (13.4, 18.2)	Not assessed	
HR	0.568 (0.457, 0.704) p<0.001			
KM 18/ 30 months (95%CI)	███████	███████		

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

MONALEESA-2 PFS (II)

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

Kaplan-Meier plot details:

- Censoring Times
- Ribociclib (N = 334)
- Placebo (N = 334)

No. of events
Ribociclib: 140, Placebo: 205

Hazard Ratio = 0.568
95 % CI [0.457, 0.704]

Kaplan-Meier median
Ribociclib: 25.3 Months
Placebo: 16.0 Months

Log-rank p-value = 9.63×10^{-8}

Y-axis: Event-free probability (%)
X-axis: Time (Months)

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 ▮▮▮▮ in ribociclib and ▮▮▮▮ in letrozole group.
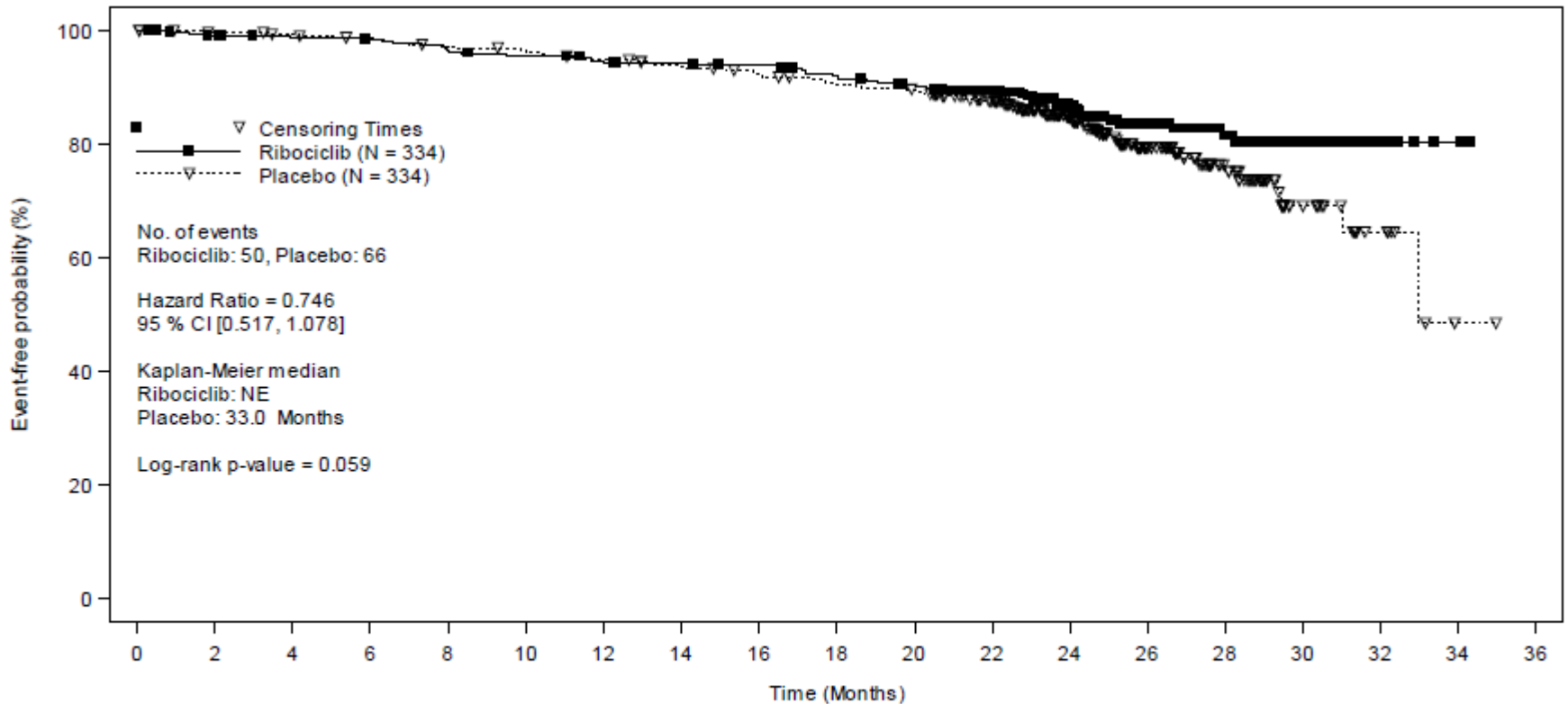
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MONALEESA-2 OS (I)

	Ribo & Let n=334	Pbo & Let n=334
January 2016 data cut-off		
Median (95 CI) months	NR	NR
HR	1.128 (0.619–2.055) p=0.653	
KM 12 months (95%CI)	███████████	███████████
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)	███████████	███████████
Deaths n (%)	50 (15)	65 (19.7)

- January 2016 interim analysis: ████████ deaths were expected. Further analyses: ███████████ deaths (expected ███████████ from the date of the first patient to be randomised). ▮

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

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MONALEESA-2 OS (II)

- **Kaplan-Meier plot:** January 2017 cut-off

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
-

June 2016 data available
-

January 2017 data not available

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Company's model

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
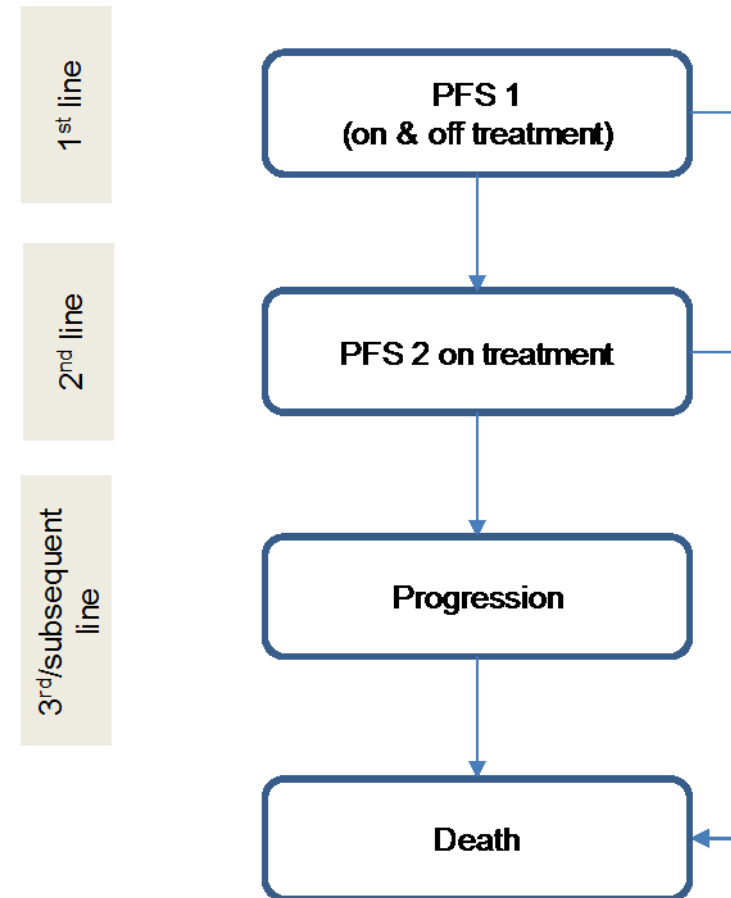- patients cannot move to *Progression* directly

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

1st line

2nd line

3rd/subsequent line

PFS 1
(on & off treatment)

PFS 2 on treatment

Progression

Death

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.

ACM1: company's base case with PAS

Deterministic results: January 2017 cut-off

- **Company incorporated 3 ERG's changes & enhanced PAS**
  1. fixing programming errors and using 2017 data
  2. incorporating wastage costs
  3. ERG modelling of post-treatment discontinuation survival after 2nd-line chemotherapy

	Total costs	Total LYG	Total QALYs	Inc. costs	Inc. LYG	Inc. QALYs	ICER
Letrozole	■■■■	■■■■	■■■■	-	-	-	-
Ribociclib	■■■■	■■■■	■■■■	■■■■	■■■■	0.89	■■■■
Probabilistic results: January 2016 cut-off				■■■■	■■■■	0.88	■■■■

- **Company did not incorporate 2 of the ERG's changes in the base case but did so in scenario analyses:**
  1. OS surrogacy based on PALOMA-1 (ratio of 38.5%)
  2. using 3rd-line inflation adjusted costs from TA239 (£1,140)

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

ACM1: scenario analyses with PAS

	Ribociclib		Letrozole alone		Incr. QALYs	ICER
	Total costs	Total QALYs	Total costs	Total QALYs		
Company's scenario analyses (changes to company's base-case)[a]						
Company's base-case (CBS)	■	■	■	■	**0.89**	■
a) 3rd-line cost = £1,500	■	■	■	■	0.89	■
b) 3rd-line cost = £1,140 (TA421)	■	■	■	■	0.89	■
c) PALOMA-1 OS surrogacy	■	■	■	■	0.53	■
CBS + b & c = ERG base-case[b]	■	■	■	■	**0.53**	■
ERG's scenario analyses (changes to ERG's base-case)[b]						
1: Weibull for PFS1 and TTD	■	■	■	■	0.41	■
2a: 3rd-line cost = £0	■	■	■	■	0.53	■
2b: 3rd-line cost = £2,000	■	■	■	■	0.53	■
3: 1 & 4	■	■	■	■	0.74	■
4: PFS1 utility = 0.72	■	■	■	■	0.44	■

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; QALYs, Quality-Adjusted Life Year.
Notes: a, company submission; b, ERG addendum 1 and 2.

Issues for consideration

1. Model structure

   - validation

   - full versus partial OS surrogacy

   - is BOLERO-2 representative of patients progressing on 1st- line?

2. Model inputs

   - cost of ribociclib

   - cost of 3rd-line treatments

   - OS modelling after letrozole and ribociclib

   - utilities: PFS1 and PFS2

   - Weibull versus exponential curve for PFS/TTD

   - treatment duration versus PFS

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

DSU: Model structure

- Many breast cancer economic models in NICE technology appraisals used a partitioned survival approach, extrapolating PFS and OS from clinical trials.

- Company state that the immaturity of OS data in MONALEESA-2 makes direct estimation challenging and external data were used to estimate OS in a patient-level state-transition model.

- PFS data from MONALEESA-2 are extrapolated, and OS for 2nd-line, estimated by extrapolating time to discontinuation and post-discontinuation survival data from BOLERO-2 (and applying hazard ratios to model different treatments), is added. With the following 2 assumptions:

  1. **BOLERO-2 is representative of patients progressing on first line therapy**
  2. **100% OS surrogacy: PFS gain translates into OS gain**

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

DSU: BOLERO-2

| 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

- The median ages in the two studies are similar, whereas we may expect the patients in BOLERO-2 to be slightly older

- ECOG status, the proportion with previous neoadjuvant or adjuvant chemotherapy, and number of metastatic sites are similar between the studies.

- 100% BOLERO-2 patients had previous treatment with letrozole/ anastrazole.

- **BOLERO-2 seems to be representative of patients progressing in MONALEESA-2.**

Key: HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; OS, overall survival; RCT, randomised controlled trial; TTD, time to disease discontinuation.

DSU: 100% OS surrogacy assumption

- **Relationship between PFS and OS gains:** studies included in company submission, ID915 company's submissions, and in Davies at al. 2012 DSU and Fisher at al. 2016 OHE reports were reviewed by DSU:
  - while PFS gain is likely to result in OS gain, there is no clear relationship.
- **Validation of the company approach:** OS for 1st (PALOMA-1), 2nd (BOLERO-2), & 3rd-line (TA423), therapy was estimated by adding OS of the next line onto the PFS for that line for the proportion of patients still alive and compared to actual values from the trials:
  - The results suggest an overestimate of OS in 1st-line, an underestimate in 2nd-line, and estimates closer to trial values (with no clear relationship) in 3rd-line.
- **Company's long-term validation** with LEA and ALLIANCE
  - letrozole OS based on MONALEESA-2 PFS and BOLERO-2 OS, is consistent with the average OS of LEA and ALLIANCE
  - but other studies (Paridaens et al. 2008, Bergh et al. 2012 and Moridsen et al. 2003) reported much lower median OS. With the large variation in OS estimates, it is difficult to know which estimate is relevant for validation, and whether the predicted results are valid.
- **It is unclear whether 100% OS surrogacy is a valid approach**

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

DSU: Model and OS surrogacy

- Company's base-case with *full OS surrogacy* gives ICER of ▮▮▮▮▮
  - time spent in PFS2 & 3rd line is the same for ribociclib and letrozole, so these treatments do not influence the cost-effectiveness results

- ERG: *partial surrogacy* more plausible; 38.5% PALOMA-1 ratio (PFS/OS scaling factor) decreases company's base-case to ▮▮▮▮
  - OS for ribociclib is reduced and so is the difference in OS for ribociclib vs. letrozole: OS difference < PFS1 difference.
  - **increased ICER** would be expected **BUT** in order to reduce ribociclib OS, ribociclib patients spend less time in PFS2 & 3rd line than letrozole patients, so the cost-effectiveness of these treatments influence ICERs
  - if PFS2 & 3rd line are less cost-effective (company's 3rd line cost estimate is £2,000 per month with utility of 0.505), than ribociclib vs. letrozole under full surrogacy (e.g. when ribociclib PAS price is used), then ribociclib patients are spending less time in a less cost-effective states, so the ICER under partial surrogacy decreases.
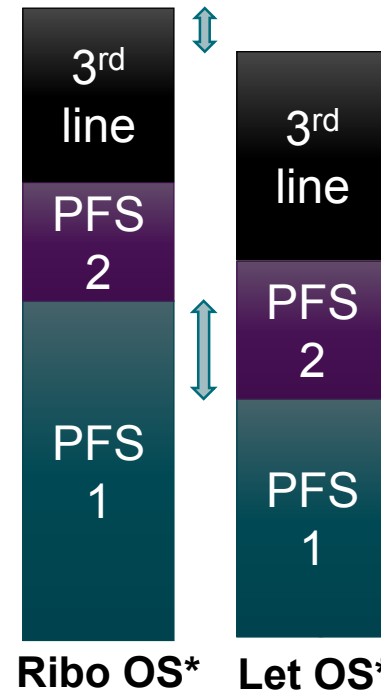
Key: ICER, Incremental Cost-Effectiveness Ratio; let, letrozole; OS, overall survival; Ribo, ribociclib; PFS, progression free survival; QALYs, Quality-Adjusted Life Year.
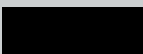**Note:** All results are with ribociclib PAS;*, all data are illustrative.

Ribo OS*   Let OS*

DSU: Model validation

- Black-box testing was used to asses the model's external validity. Inputs from the ID915 were used within the model. In addition, key inputs were altered to be consistent with ID915.

  - **These two tests of quality assurance provided reassurance that the model structure is externally valid and does not contain hidden errors.** However, it should be noted that the DSU did not attempt to exhaustively validate the model.

- The black-box analysis also explored the impact on the ICER of varying different inputs under the assumption of both full and partial surrogacy. The following inputs had the greatest impact on the ICER:

  - **The drug costs of ribociclib**

  - **Progression-free survival**

  - **Overall survival**

  - **Costs beyond second line**

  - **Utilities**

Key: ICER, Incremental Cost-Effectiveness Ratio.

DSU: Ribociclib cost and dose

- Licenced dose:
  - 600 mg (3 x 200 mg tablets) once daily for 21 days of 28-day cycle with 400 - 200 mg/day reductions to manage treatment-related AEs
  - each 200mg tablet has the same price regardless of the pack size
- Company used IPD to calculate the total number of days patients received each dose for per cycle to cost the drug per cycle (cycle 10 is used for cycle 10 onwards due small numbers) assuming that patients who reduce their dose do not waste tablets.
- The ERG included wastage at discontinuation, which increased the ICER by less than £1,000 per QALY.
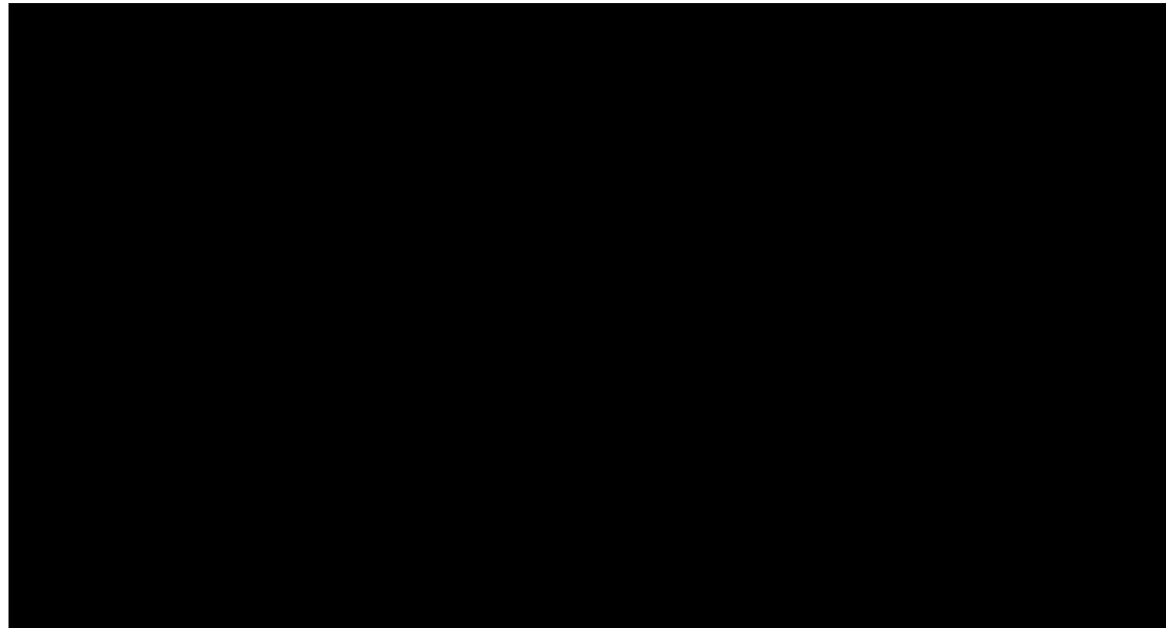- **Assuming that all patients received full dose increases the ICER:**

Ribociclib dose	ICER
Company's base case: dose reduction	██████
Full dose	██████

DSU: Ribociclib cost and TTD

- Duration of treatment: TTD

  – Company fitted exponential curve as it was also used for PFS

TTD curve	ICER
Company's base case: exponential	■■■■■
Weibull	■■■■■

  – ICER sensitive to the choice of curve

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.
Note: All results are with ribociclib PAS.
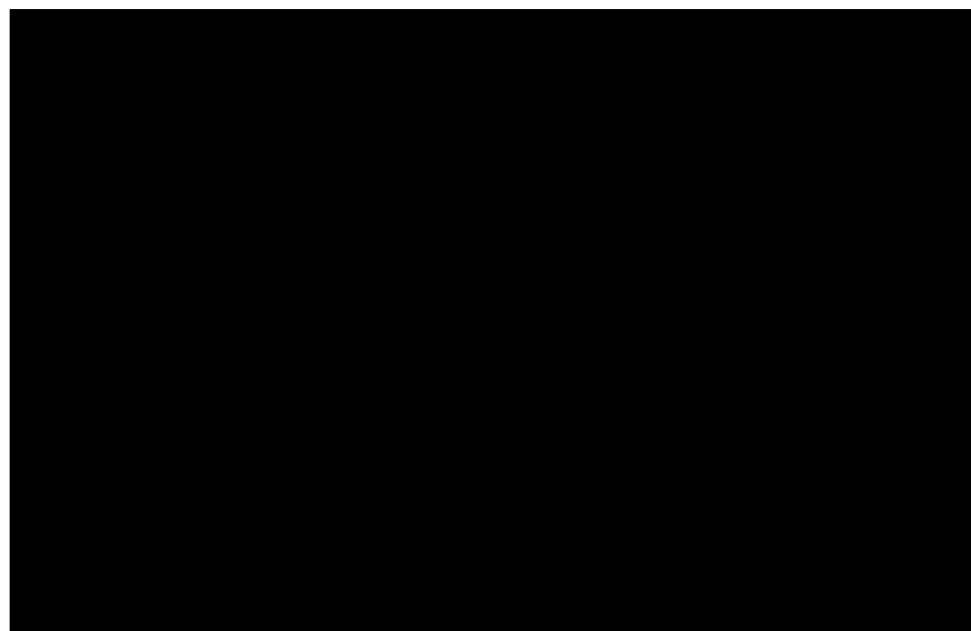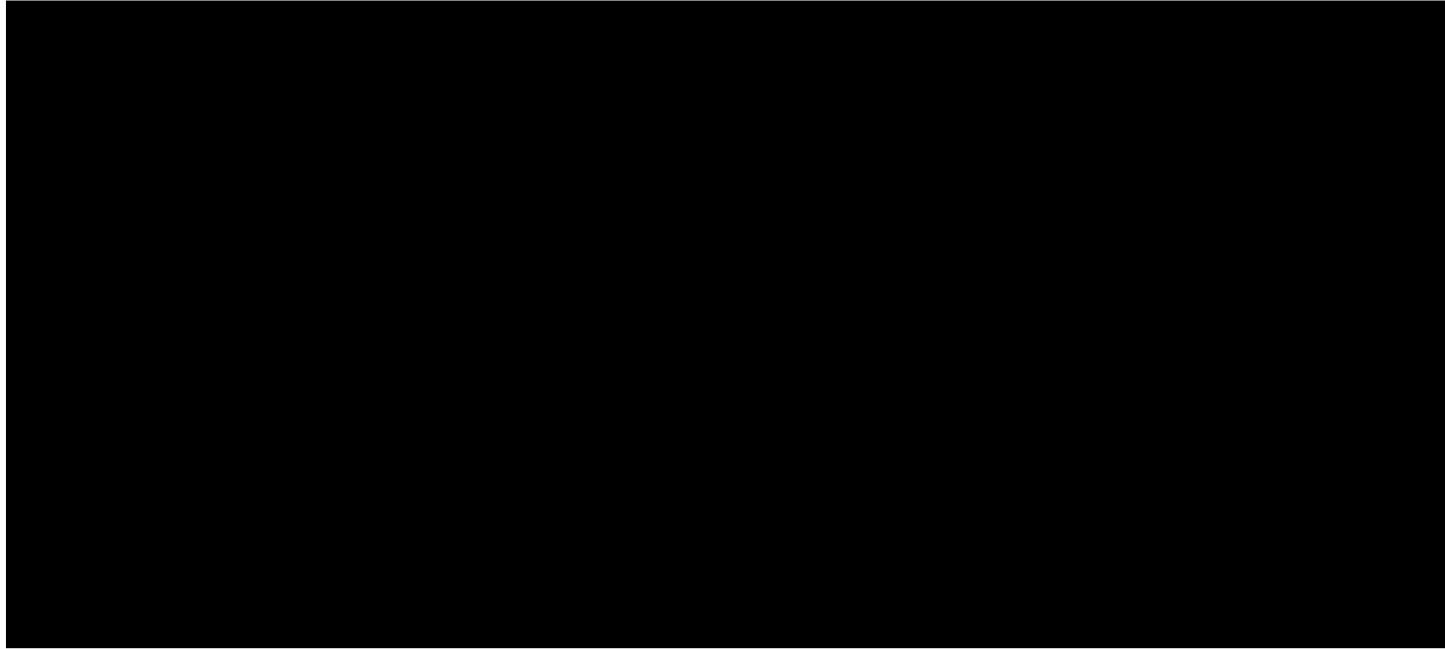
DSU: PFS extrapolation

- Company used exponential distribution: it had the second-lowest AIC and BIC scores, was close to LEA and ALLIANCE, validated with clinical experts, was used in ID915

- The ERG commented that ███████████████████ curves were ████████ to PALOMA-2 and MONALEESA-2, whereas ███████████ was ████████ to LEA and ALLIANCE

PFS curve	ICER
Company's base case: exponential	███████
Weibull	███████

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.
Note: all results are with ribociclib PAS.

DSU: PFS and TTD extrapolation (I)

- Exponential curve assumes a constant rate of events over time:
  - so patients at the beginning of the PFS/TTD curve are the same as those at the end
- Weibull curve allows the rate of events to vary:
  - for PFS assumes that rate of progression increases over time
  - for TTD assumes that rate of discontinuation decreases over time
  - therefore Weibull (blue) PFS and TTD curves converge more quickly than the exponential (purple) PFS and TTD curves

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

DSU: PFS and TTD extrapolation (II)

- ▮▮▮▮ of ribociclib patients discontinued due to adverse events

	Mean TTD	Mean PFS	(100% – ▮▮▮ Mean PFS
Exponential	▮▮▮▮	▮▮▮▮	▮▮▮▮
Weibull	▮▮▮▮	▮▮▮▮	▮▮▮▮

- ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

- ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮

- Company used exponential curve to extrapolate PFS and TTD

  - For PFS, exponential was second-best according to statistical goodness of fit

  - For TTD, exponential was worst according to statistical goodness of fit

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

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DSU: 3rd-line cost (progression state)

- Company: monthly cost of £2,000 based on clinical opinion assumed

- ERG: TA239 inflation adjusted estimate of £1,140 is more plausible

- DSU: in the model ribociclib and letrozole patients spend ████████ years in progression, respectively. For example this would equate to:

  - ███ months of capecitabine or ███ months of eribulin (longer with eribulin's PAS) ribociclib patients when using £2,000

  - ███ months of capecitabine or ███ months of eribulin (longer with eribulin's PAS) ribociclib patients when using £1,140

  - BUT the mean time on 3rd-line is 6.1 months (Kurosky et al. 2015) AND capecitabine & paclitaxel times are longer than patients are alive in model.

- **£1,140 probably overestimates 3rd-line cost, but is closer than £2,000**

3rd-line cost	Company (full surrogacy) ICER	ERG (partial surrogacy) ICER
£2,000 per month	████████	████████
£1,140 per month	████████	████████
£0 per month	NR	████████

- **In partial OS surrogacy, 3rd-line cost has a big impact on the ICER**

Key: ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival.
Note: all results are with ribociclib PAS.

DSU: utilities

- **NICE reference case**:
    - EQ-5D is the preferred measure of health-related quality of life in adults
    - 5L valuation set is not recommended and should be mapped to 3L
- **PFS1:** company used MONALEESA-2 EQ-5D-5L of ██████
    - MONALEESA-2 mapped to 3L results in ██████.
- **PFS2:** company used Lloyd et al. 2006 (vignettes valued by the general population using standard gamble) BOLERO-2 adjusted value of 0.774 (used in TA421), which does not meet NICE's reference case.
    - EQ-5D scores of 0.69 for 2nd-line available in Mitra et al. 2016
- **Beyond PFS2** (progressed disease): company used 0.505 (Lloyd et al. 2006)
- **Using NICE reference case utilities increased the ICER:**

Utilities	ICER
Company's base case: PFS1= 5L (████), PFS2 =0.774	████
PFS1= 3L(████), PFS2 = PFS1	████
PFS1= 3L(████), PFS2: 0.69 (Mitra et al. 2016)	████

Key: EQ5D-5L, European quality of life-5 dimensions-5 levels; 5L, 5 levels EQ5D; 3L, 3 levels EQ5D; ICER, Incremental Cost-Effectiveness Ratio; PFS 1, first-line progression-free survival; PFS 2, second-line progression-free survival. **Note:** all results are with ribociclib PAS.

DSU: combined scenario analyses

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

- **Scenarios with £1,140 3rd-line cost, 3L PFS1 (■) & PFS2 of 0.69:**

ICERs	PFS: Exponential TTD: Exponential	PFS: exponential TTD: Weibull	PFS: Weibull TTD: Exponential	PFS: Weibull TTD: Weibull
Full OS surrogacy				
Reduced	■	■	■	■
Full dose	■	■	■	■
Partial OS surrogacy				
Reduced	■	■	■	■
Full dose	■	■	■	■

Key: Exp, exponential; ICER, Incremental Cost-Effectiveness Ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; QALYs, Quality-Adjusted Life Year; Wei, Weibull; 3L, 3 levels EQ5D.
Note: all results are with ribociclib PAS.

Company: response to DSU report and new base-case

- Questions the DSU choice of utility for PFS2 (0.69; Mitra et al. 2016)

- Noted limitations of Kurosky et al. 2015 to inform cost of 3rd line and proposed value of £1,500 (as used in company's scenario analyses) instead

- Considers PFS/TTD exponential extrapolations to be appropriate:

  – clinical expert validation, use in ID915, and external long term validation: LEA & ALLIANCE more relevant than Paridaens 2008, Bergh 2012 & Mourisden 2003. Treatment pathway changed since the 3 studies were conducted, this can also explain some of the reduced OS in the 3 studies.

- Dose reductions appropriate as full dose does not reflect MONALEESA-2 data

- **Company's new base-case**: ▮▮▮▮▮▮▮▮, dose reductions, exponential PFS & TTD extrapolation, 3rd line cost of £1,500, PFS1= ▮▮▮▮ and PFS2=0.69:

	Total QALYs		Total Costs			ICER
	Letrozole	Ribociclib	Letrozole	Ribociclib		
New company's base-case		▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮
1: ▮▮▮▮		▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮
2: with PFS2= ▮▮▮▮ *		▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮
3: combined 1 & 2		▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮	▮▮▮▮

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

Note: all results are with ribociclib PAS;*, mapped 3 levels EQ5D value for progressed disease in MONALEESA-2.

Questions for committee

- Is the committee minded to accept company's approach to modelling?

- Is the use of BOLERO to represent 2nd line therapy acceptable?

- Utility values for PFS1 were from EQ5D-5L (not currently recommended), what utility values are appropriate?

- Does the committee accept that some patients will take a reduced dose (fewer tablets) which will lead to lower costs than the full dose?

- 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.