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

Clinical effectiveness

Committee A

Lead team: Mohit Sharma and Pam Rees

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

NICE technical team: Marcela Haasova and Joanna Richardson

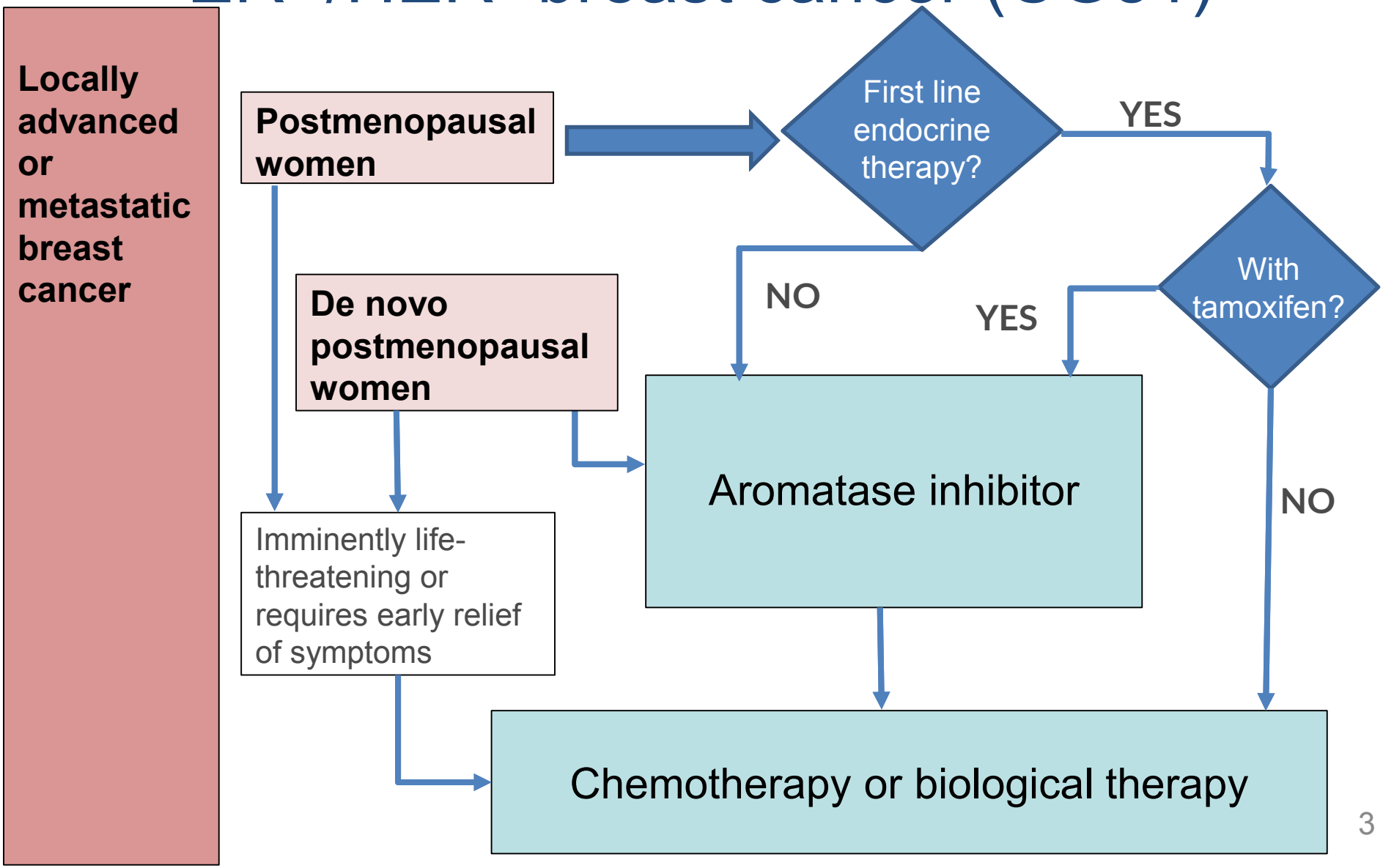
5th July 2017

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)

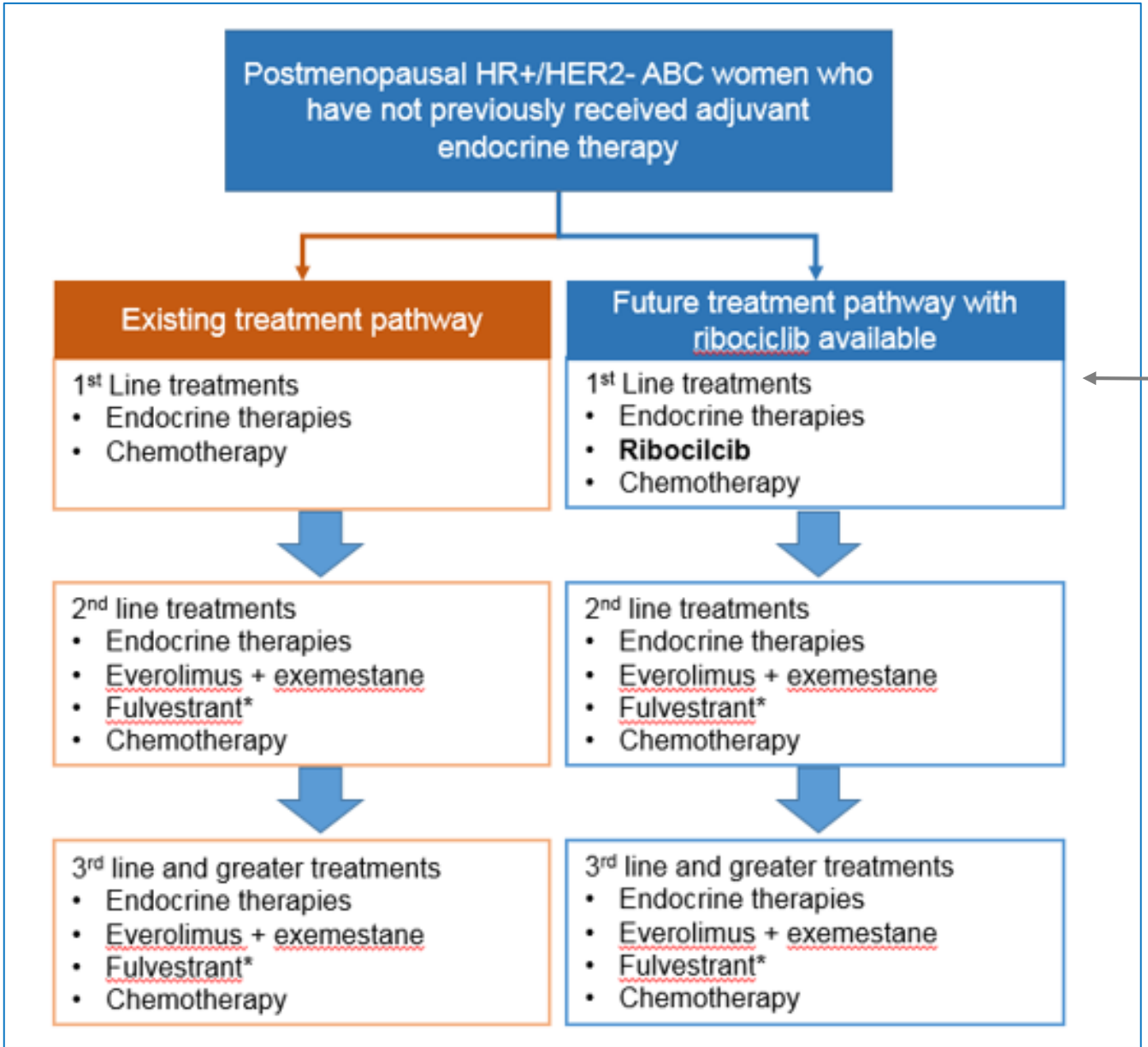


Ribociclib (Kisqali, Novartis)

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	[redacted]
Cost of a course of treatment	[redacted] anticipated number of repeat courses of treatments: [redacted] Simple PAS discount approved

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.

Impact on Patients (Breast Cancer Care)

- *“I have gone from being the person that was there to help other people, to being an ill, disabled person; a condition, a diagnosis."*
- Fear; Uncertainty; Living from “scan to scan”; Unable to plan long-term.
- Pain, fatigue, nausea, poor appetite and sleep difficulties.
- People with metastatic breast cancer face limited treatment options.
- Patients want treatments that will halt progression, extend life for as long as possible and have few or manageable side effects and
- To be able to continue with their day-to-day activities as much as possible, be that going to work, parenting and social responsibilities and activities.

Patient views on Ribociclib (Breast Cancer Care)

- Significant step forward in effective treatment options for a large proportion of the advanced breast cancer population.
- The key benefit of Ribociclib is a prolonged period of PFS
- It can allow people to delay chemotherapy for a substantial amount of time
- It allows people a good quality of life, with limited side effects.
- Simple to take oral medication means reduced trips to and time in hospital.
- There are some increased side effects from this treatment.
- 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.

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.

Clinical evidence: MONALEESA-2

Design	Double blind placebo-controlled phase 3 RCT
Location	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 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; 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)

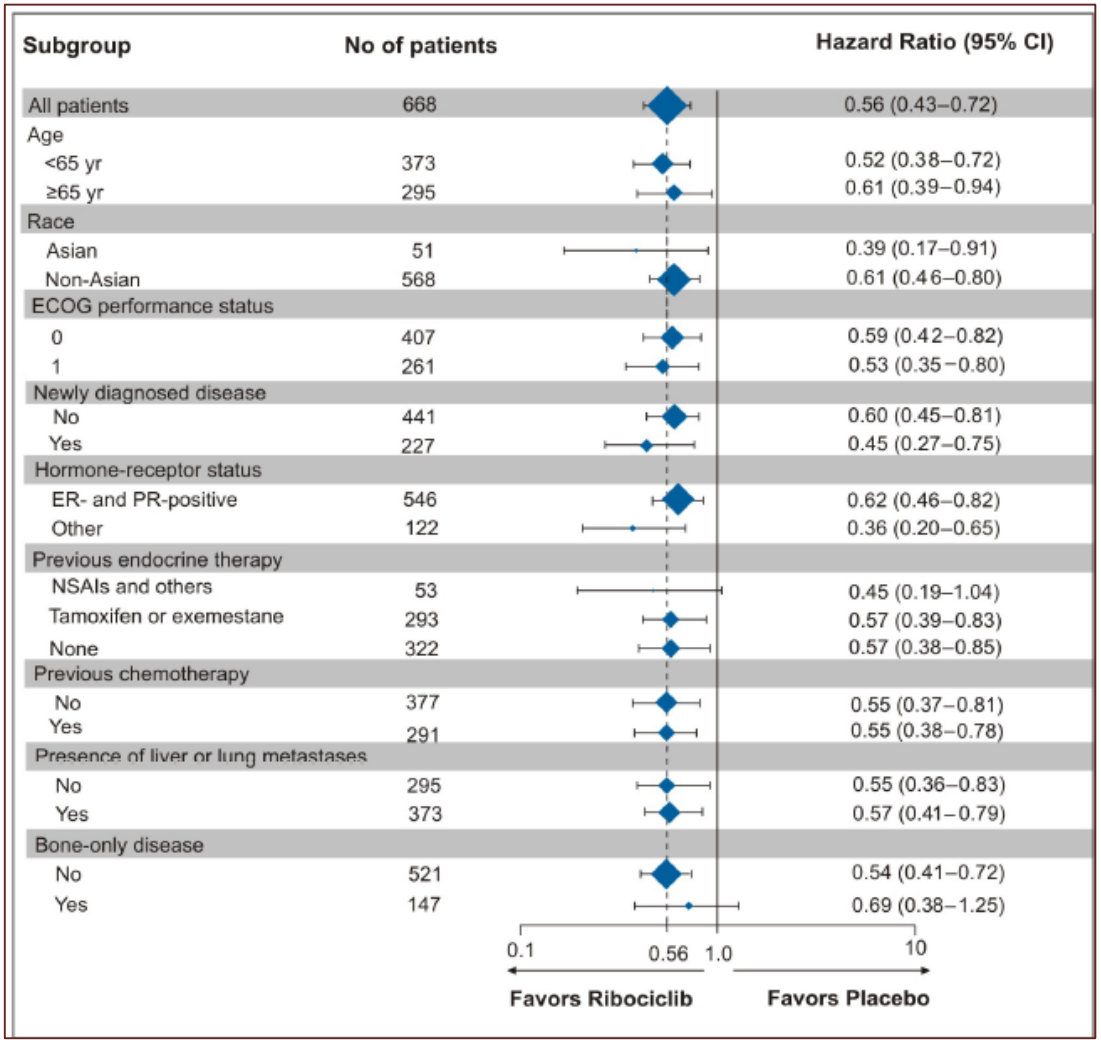
MONALEESA-2 PFS (I)

(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: PFS difference of 7.1 months for local assessment				
Median (95 CI)	22.4 (20.8, NE)	15.3 (13.4, 16.7)	NE (22.9, NE)	NE (NE, NE)
HR	0.559 (0.443, 0.706) p<0.001		0.597 (0.430, 0.830) p<0.001	
KM 18 months (95%CI)	[redacted]	[redacted]	[redacted]	[redacted]
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)	[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

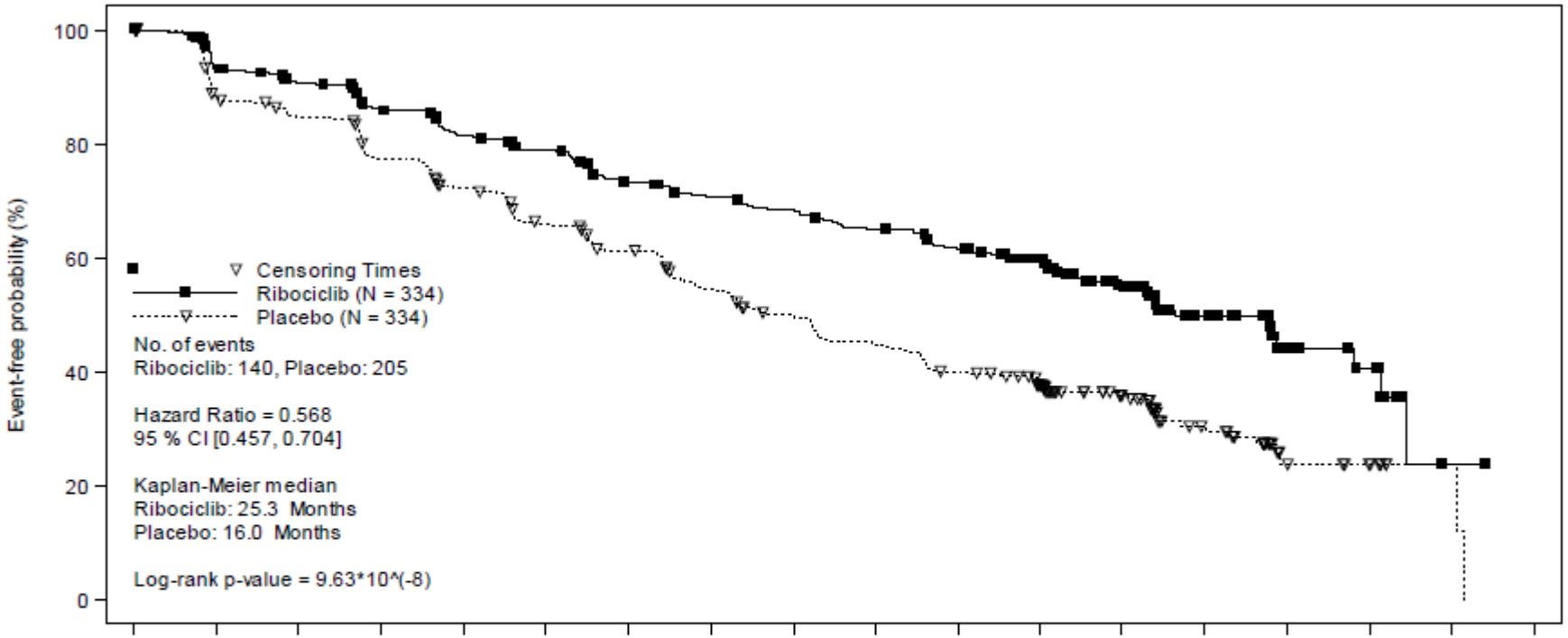
Key: ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; NSAI, non-steroidal aromatase inhibitor; PR, progesterone receptor; yr, years .

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)

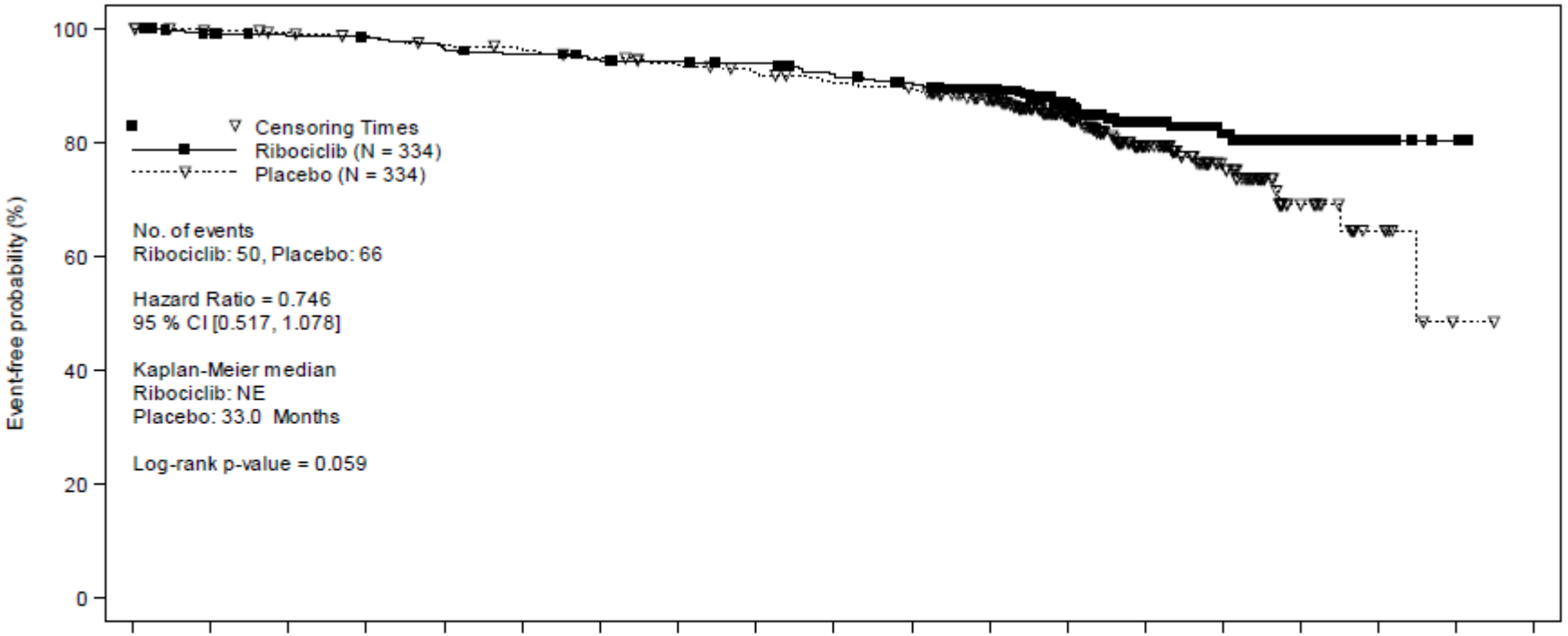
	Ribo & Let n=334	Pbo & Let n=334
January 2016 data cut-off		
Median (95 CI) months	NR	NR
HR	1.128 (0.619–2.055) p=0.653	
KM 12 months (95%CI)	[redacted]	[redacted]
Deaths n (%)	23/334 (6.9)	20/330 (6.1)
January 2017 data cut off		
Median (95 CI) months	NE (NE, NE)	33.0 (33.0, NE)
HR	0.746 (0.517, 1.078)	
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 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).
- [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

- [redacted]
- [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
- proportion of de novo patients (34%) higher than in general population (10%)
- 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]
- The original 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), however 2017 local assessment used in the ERG base-case as 2017 central assessment not available

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.