

# RIBOCICLIB PLUS GOSERELIN AND TAMOXIFEN OR A NON-STEROIDAL AROMATASE INHIBITOR FOR PREMENOPAUSAL WOMEN WITH HR+, HER2– ADVANCED BREAST CANCER IN THE RANDOMIZED PHASE III MONALEESA-7 TRIAL

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# Disclosures

Seock-Ah Im	Advisory board/consultant (Hanmi Corp, Novartis, Pfizer, Roche); research funding (AstraZeneca)
Joohyuk Sohn	Nothing to declare
Debu Tripathy	Consultant (Novartis, Pfizer); research funding (Pfizer)
Louis Chow	Nothing to declare
Marco Colleoni	Advisory board/consultant (AstraZeneca, Celldex, OBI Pharma, Pierre Fabre, Pfizer, PUMA); honoraria (Novartis)
Fabio Franke	Nothing to declare
Aditya Bardia	Consultant (Genentech, Novartis, Pfizer); steering committee (Novartis)
Nadia Harbeck	Honoraria (Eli-Lilly, Novartis, Pfizer)
Sara Hurvitz	Grants (Amgen, Bayer, BI Pharma, Biomarin, Cascadian, Dignitana, Eli-Lilly, Genentech, GlaxoSmithKline, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, PUMA, Roche, Seattle Genetics); travel support (Bayer, Eli-Lilly, Novartis, OBI Pharma)
Keun Seok Lee Kyung Hae Jung Young-Hyuck Im	Nothing to declare
Nagi El Saghir	Advisory board (Eli-Lilly, Novartis, Pfizer); honoraria (Eli-Lilly, Novartis, Pfizer)
Mei-Ching Liu	Advisory board (Novartis, Pfizer, Roche); travel support (Pfizer)
Melissa Tripodi	Employment (Novartis); stock/share ownership (Novartis)
Rahul Tyagi	Employment (Novartis); stock/share ownership (Novartis)
Gareth Hughes	Employment (Novartis Pharma AG)
Michelle Miller	Employment (Novartis); stock/share ownership (Novartis)
Yen-Shen Lu	Nothing to declare

Study sponsored by Novartis Pharmaceuticals Corporation

# Introduction

- Premenopausal women represents a very important subgroup of the overall population with breast cancer
- Estimates suggest that in 2017 in the US, ~19% of invasive breast cancers would be diagnosed in women aged ≤49 years<sup>1</sup>
  - The proportion of patients aged <50 years may be up to 42% in the Asia-Pacific region<sup>2</sup>
- The last randomized trial focusing solely on premenopausal women with ABC was published in 2000<sup>3</sup>
- Young women with ABC have a distinct tumor biology,<sup>4</sup> experience more aggressive disease, and are more likely to die from their cancer than older women<sup>5</sup>
- Endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– ABC;<sup>6–8</sup> however, resistance and disease progression ultimately occur
- Adding ribociclib to letrozole significantly prolonged PFS compared with letrozole alone in postmenopausal women with *de novo* and/or recurrent HR+, HER2– ABC<sup>9</sup>
- **MONALEESA-7 is the first Phase III trial investigating ribociclib-based regimens as a front-line treatment specifically for pre and perimenopausal women with ABC**

ABC, advanced breast cancer; CDK, cyclin-dependent kinase; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; PFS, progression-free survival.

Advanced breast cancer refers to locoregionally recurrent or metastatic disease.

1. Desantis CE, et al. CA Cancer J Clin 2017; ePub ahead of print; 2. Youlden DR, et al. Cancer Biol Med 2014;11:101–115; 3. Klijn JGM, et al. J Natl Cancer Inst 2000;92:903–911; 4. Liao S, et al. Breast Cancer Res 2015;17:104; 5. Anders CK, et al. Semin Oncol 2009;36:237–249;
6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2017; 7. Rugo HS, et al. J Clin Oncol 2016;34:3069–3103;
8. Cardoso F, et al. Ann Oncol 2017;28:16–33; 9. Hortobagyi GN, et al. N Engl J Med 2016;375:1738–1748.

# MONALEESA-7: Phase III placebo-controlled study of ribociclib and tamoxifen/NSAI + goserelin

- Pre/perimenopausal women with HR+, HER2– ABC
- No prior endocrine therapy for advanced disease
- ≤1 line of chemotherapy for advanced disease
- N=672

Randomization (1:1)

Stratified by:

- Presence/absence of liver/lung metastases
- Prior chemotherapy for advanced disease
- Endocrine therapy partner (tamoxifen vs NSAI)

## Ribociclib

(600 mg/day; 3-weeks-on/1-week-off)  
+ tamoxifen/NSAI + goserelin\*  
n=335

## Placebo

+ tamoxifen/NSAI + goserelin\*  
n=337

## Primary endpoint

- PFS (locally assessed per RECIST v1.1)<sup>‡</sup>

## Secondary endpoints

- Overall survival (key)
- Overall response rate
- Clinical benefit rate
- Safety
- Patient-reported outcomes

- Tumor assessments were performed every 8 weeks for the first 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events had occurred
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided  $\alpha=2.5\%$ , corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm<sup>1,2</sup>), and a sample size of 660 patients

NSAI, non-steroidal aromatase inhibitor; RECIST, Response Evaluation Criteria In Solid Tumors.

\*Tamoxifen = 20 mg/day; NSAI: anastrozole = 1 mg/day or letrozole = 2.5 mg/day; goserelin = 3.6 mg every 28 days;

<sup>‡</sup>PFS by Blinded Independent Review Committee conducted to support the primary endpoint.

1. Klijn JG, et al. J Clin Oncol 2001;19:343–353; 2. Mouridsen H, et al. J Clin Oncol 2001;19:2596–2606.

# Key enrolment criteria

## Key inclusion criteria

- Pre/perimenopausal women (per NCCN guidelines)
- $\geq 1$  measurable lesion (RECIST 1.1) or  $\geq 1$  predominantly lytic bone lesion
- ECOG performance status of  $\leq 1$
- $\leq 1$  line of chemotherapy for ABC
- Prior (neo)adjuvant therapy was allowed:
  - If no prior endocrine therapy OR if  $\geq 12$  months since the last dose, patient was eligible for tamoxifen or an NSAI, per investigator/patient choice
  - If last dose of tamoxifen was  $< 12$  months prior to randomization, patient was eligible for an NSAI
  - If last dose of AI/NSAI was  $< 12$  months prior to randomization, patient was eligible for tamoxifen

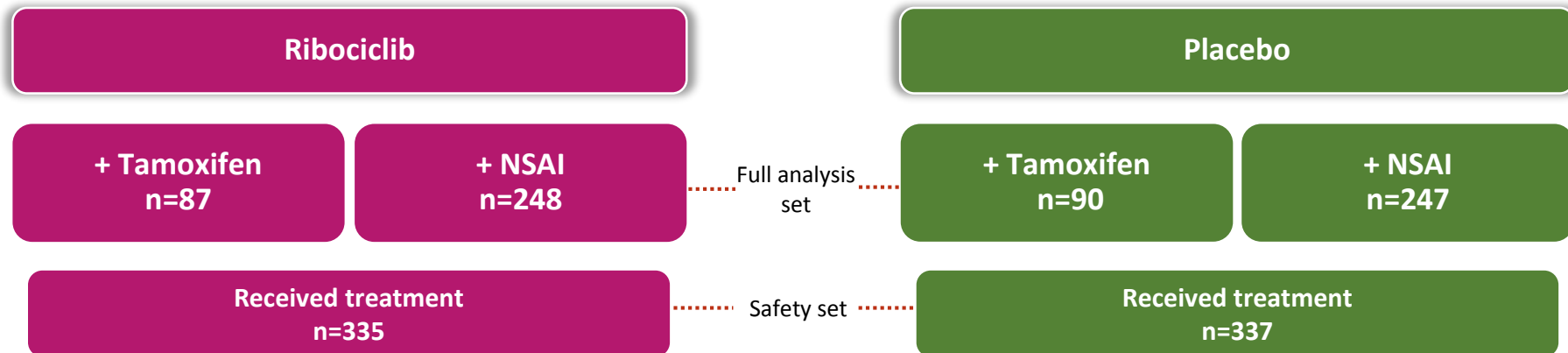
## Key exclusion criteria

- Any prior endocrine therapy for ABC
- Inflammatory breast cancer
- Active cardiac disease or history of cardiac dysfunction, including QTcF  $> 450$  msec
- CNS metastases
- Symptomatic visceral disease

AI, aromatase inhibitor; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; NCCN, National Comprehensive Cancer Network; QTcF, Fridericia's corrected QT interval. Perimenopausal defined as neither premenopausal nor postmenopausal per NCCN guidelines. Goserelin included in all combinations.

# Accrual and analysis details

**672 patients randomized** between December 2014 and August 2016  
**Data cut-off date:** August 20, 2017 (318 events)  
**Median time from randomization to data cut-off date:** 19.2 months



# Patient demographics and baseline characteristics

Characteristic*	Ribociclib + tamoxifen/NSAI (n=335)	Placebo + tamoxifen/NSAI (n=337)
<b>Median age, years (range)</b>	43 (25–58)	45 (29–58)
<b>Race, n (%)</b>		
Caucasian	187 (55.8)	201 (59.6)
Asian	99 (29.6)	99 (29.4)
Other <sup>†</sup>	29 (8.7)	19 (5.6)
Unknown	20 (6.0)	18 (5.3)
<b>ECOG performance status, n (%)<sup>§</sup></b>		
0	245 (73.1)	255 (75.7)
1	87 (26.0)	78 (23.1)
Missing	3 (0.9)	3 (0.9)
<b>Metastatic sites, n (%)</b>		
Visceral disease	193 (57.6)	188 (55.8)
Bone-only disease	81 (24.2)	78 (23.1)
<b>De novo metastatic disease, n (%)</b>	136 (40.6)	134 (39.8)
<b>Non-de novo metastatic disease, n (%)</b>	199 (59.4)	203 (60.2)
<b>Disease-free interval, n (%)</b>		
≤12 months	23 (6.9)	13 (3.9)
>12 months	176 (52.5)	190 (56.4)
<b>Prior (neo)adjuvant endocrine therapy, n (%)</b>	127 (37.9)	141 (41.8)
<b>Prior chemotherapy, n (%)</b>		
For advanced disease	47 (14.0)	47 (13.9)
(Neo)adjuvant only	138 (41.2)	138 (40.9)
None	150 (44.8)	152 (45.1)

\*All values are n (%), unless stated otherwise; <sup>†</sup>'Other' includes Black, Native American, and other;

<sup>§</sup>One patient in the placebo arm had an ECOG performance status of 2.  
Goserelin included in all combinations.

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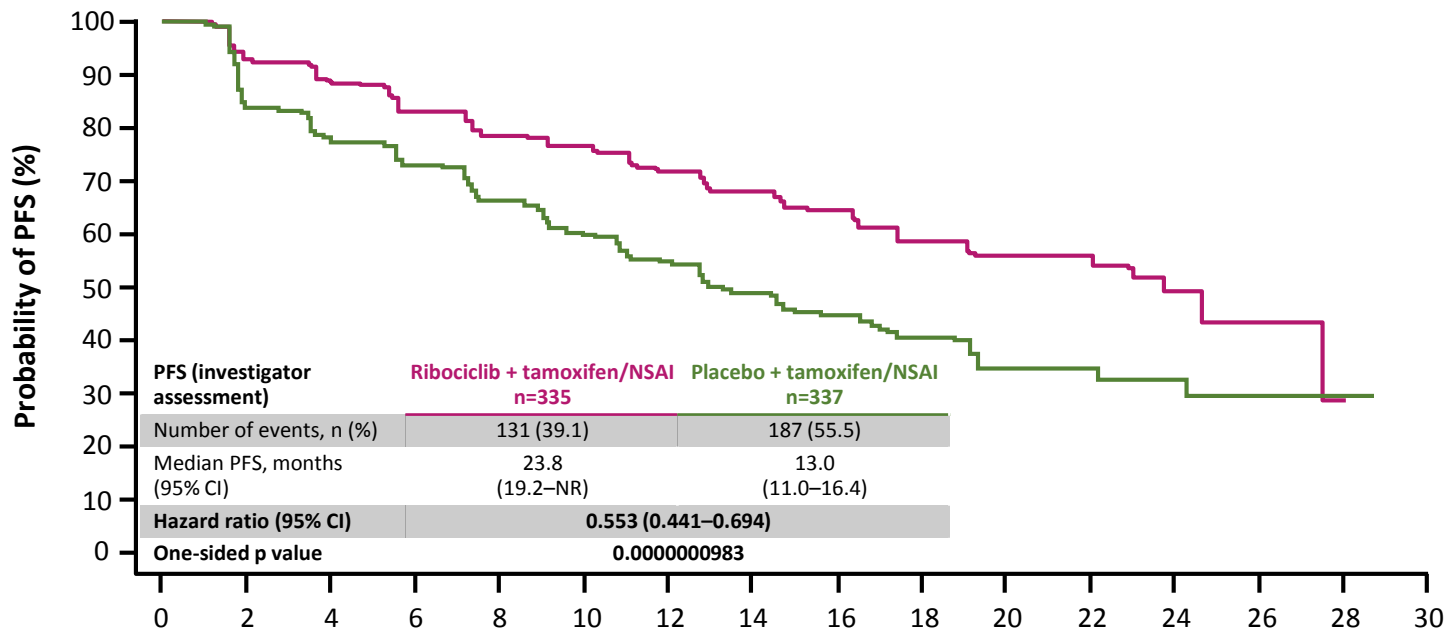
Goserelin included in all combinations.



# Patient disposition

Disposition, n (%)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Treatment ongoing	174 (51.9)	121 (35.9)
Treatment discontinued	161 (48.1)	216 (64.1)
<b>Primary reason for treatment discontinuation</b>		
Disease progression	122 (36.4)	174 (51.6)
Physician decision	8 (2.4)	19 (5.6)
AEs	12 (3.6)	10 (3.0)
Patient/guardian decision	14 (4.2)	8 (2.4)
Death	3 (0.9)	3 (0.9)
Protocol deviation	0	2 (0.6)
Lost to follow-up	2 (0.6)	0

# Primary endpoint: PFS (investigator-assessed)



## No. at risk

	Time (months)															
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Ribociclib + tamoxifen/NSAI	335	301	284	264	245	235	219	178	136	90	54	40	20	3	1	0
Placebo + tamoxifen/NSAI	337	273	248	230	207	183	165	124	94	62	31	24	13	3	1	0

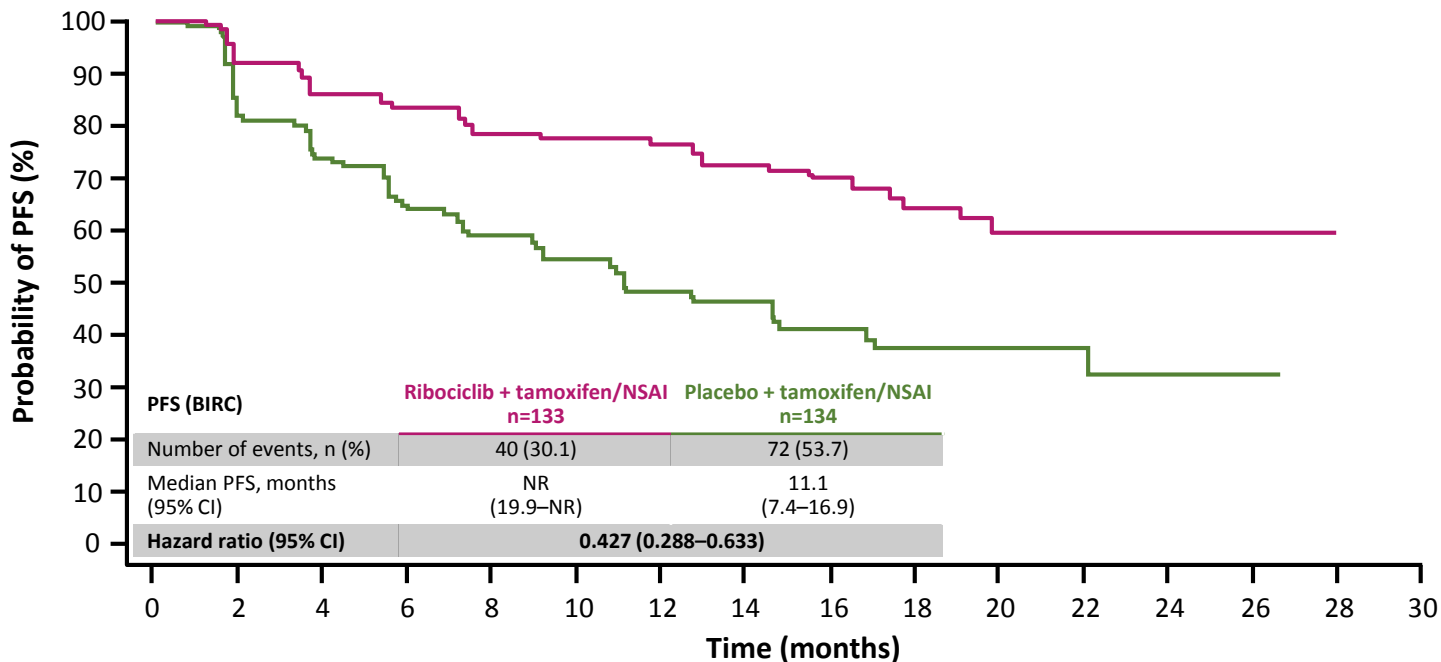
CI, confidence interval; NR, not reached.  
Goserelin included in all combinations.

# PFS by endocrine therapy partner (investigator-assessed)

PFS (investigator assessment)	NSAI		Tamoxifen	
	Ribociclib arm n=248	Placebo arm n=247	Ribociclib arm n=87	Placebo arm n=90
Number of events, n	92	132	39	55
Median PFS, months (95% CI)	27.5 (19.1–NR)	13.8 (12.6–17.4)	22.1 (16.6–24.7)	11.0 (9.1–16.4)
Hazard ratio (95% CI)	<b>0.569 (0.436–0.743)</b>		<b>0.585 (0.387–0.884)</b>	

The PFS benefit with ribociclib vs placebo was observed irrespective of endocrine therapy partner.

# Supportive analysis: PFS (blinded independent review committee\*)



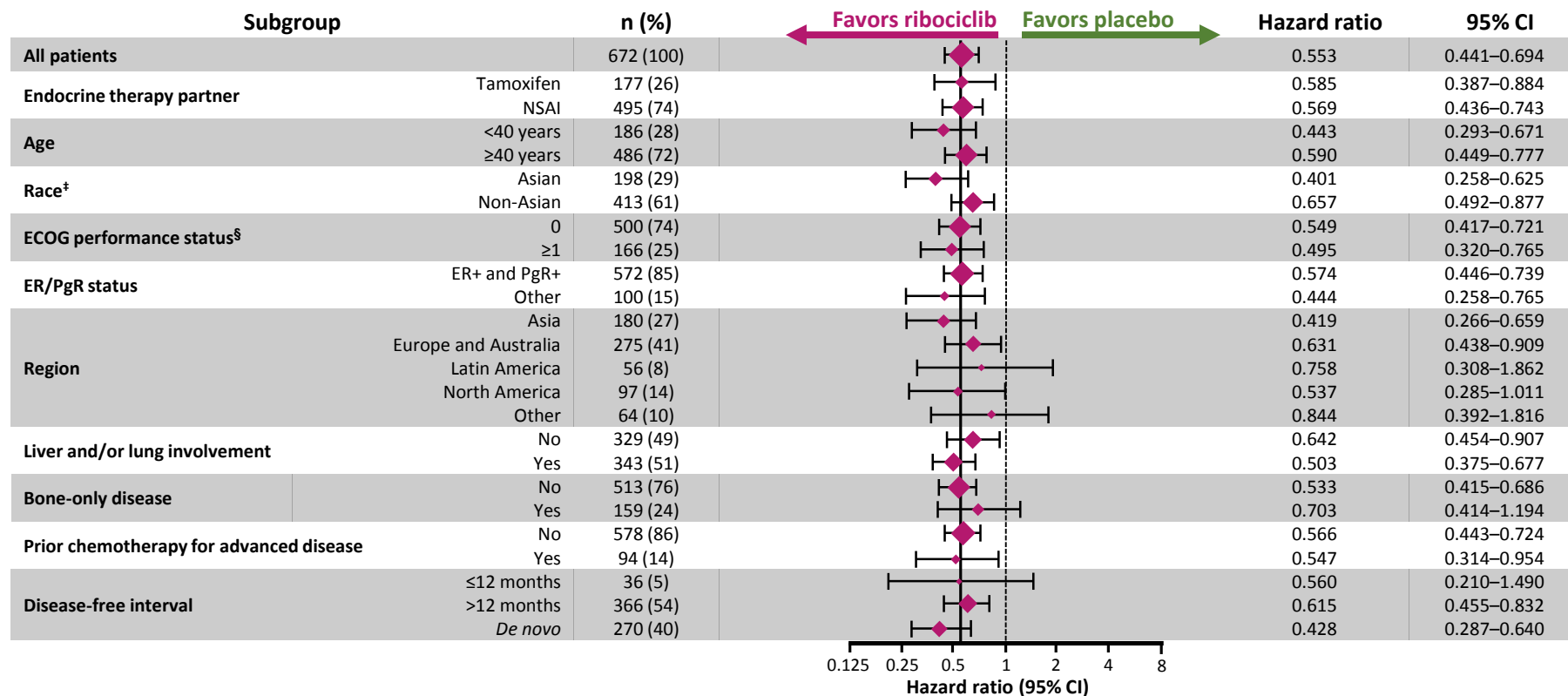
No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
Ribociclib + tamoxifen/NSAI	133	115	105	100	90	87	85	64	46	32	23	16	9	2	1	0
Placebo + tamoxifen/NSAI	134	103	91	76	69	61	52	38	29	21	11	7	5	1	0	0

BIRC, Blinded Independent Review Committee.  
\*Audit-based review of 40% of randomized patients.  
Goserelin included in all combinations.



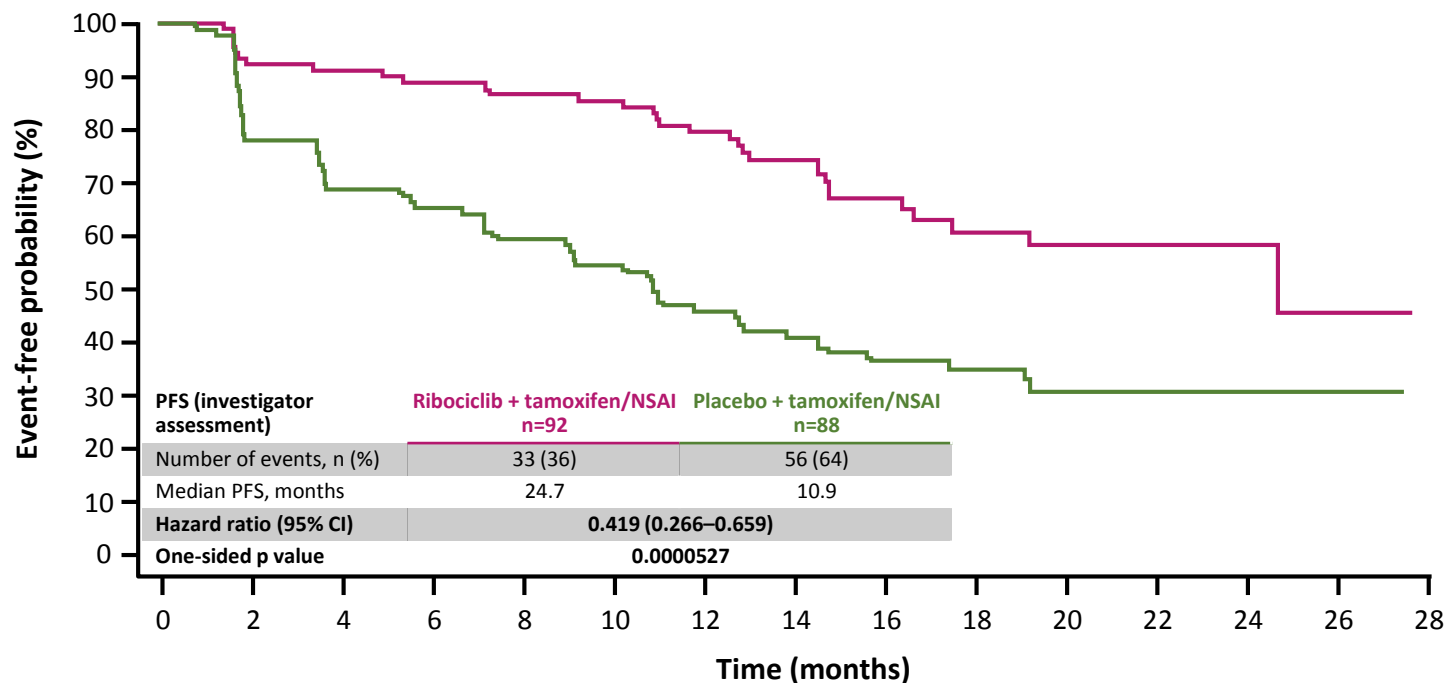
# PFS subgroup analysis\*



ER, estrogen receptor; PgR, progesterone receptor.

\*Locally assessed PFS; ‡Non-Asian race includes Caucasian, Black, and Native American; §ECOG performance status missing for n=6; 1 patient had an ECOG performance status of 2.

# PFS: Asian subgroup analysis\*

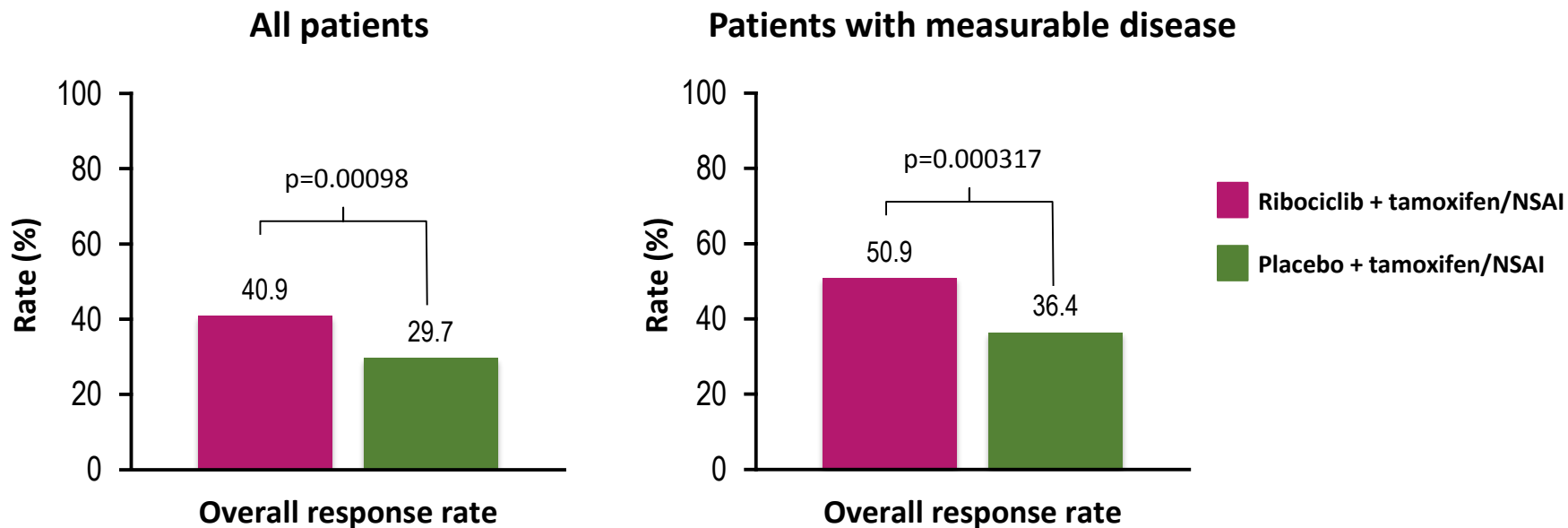


No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib + tamoxifen/NSAI	92	83	81	78	74	71	66	55	40	27	20	15	10	1	0
Placebo + tamoxifen/NSAI	88	67	59	55	50	44	37	31	25	20	9	9	3	1	0

\*Locally assessed PFS in Asian patients (by region).  
Goserelin included in all combinations.

# Secondary endpoints: ORR and CBR



- The CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI ( $p=0.000340$ )
- Overall survival data were immature at the cut-off date

# Treatment exposure and dose adjustments

	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
<b>Treatment exposure</b>		
Median duration of exposure to ribociclib/placebo, months	15.1	11.4
Median ribociclib/placebo dose intensity, mg/day	563.9	600.0
Median relative ribociclib/placebo dose intensity, %	94.0	100
<b>Ribociclib/placebo dose adjustments*, n (%)</b>		
Dose interruptions	255 (76.6)	126 (37.6)
Dose interruptions due to AEs	229 (68.8)	55 (16.4)
Dose reductions	117 (35.1)	21 (6.3)
Dose reductions due to AEs	104 (31.2)	17 (5.1)

\*2 patients in each arm did not receive ribociclib or placebo component.  
Goserelin included in all combinations.



# Hematologic adverse events

Regardless of study treatment relationship

AEs ≥5% in either arm, n (%)	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	254 (75.8)	170 (50.7)	33 (9.9)	26 (7.7)	10 (3.0)	2 (0.6)
Leukopenia	105 (31.3)	44 (13.1)	4 (1.2)	19 (5.6)	4 (1.2)	0
Anemia	70 (20.9)	10 (3.0)	0	34 (10.1)	7 (2.1)	0
Thrombocytopenia	29 (8.7)	2 (0.6)	1 (0.3)	7 (2.1)	1 (0.3)	1 (0.3)

- Febrile neutropenia occurred in 7 patients (2.1%) in the ribociclib arm vs 2 patients (0.6%) in the placebo arm

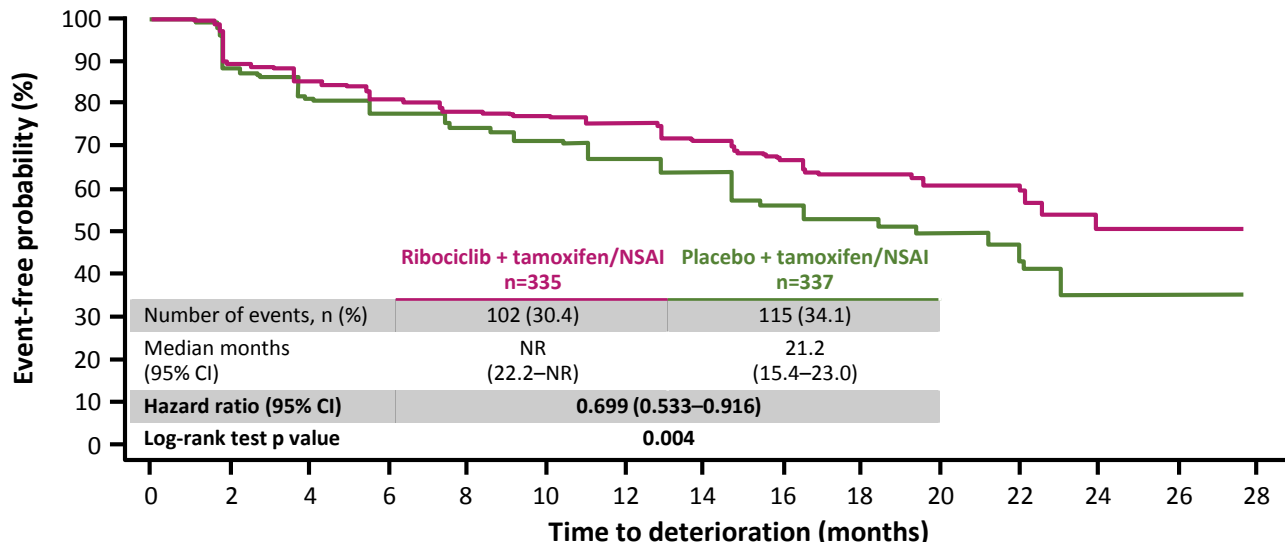
# Non-hematologic adverse events

Regardless of study treatment relationship

AEs ≥20% in either arm, n (%)	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hot flush	114 (34.0)	1 (0.3)	0	113 (33.5)	0	0
Nausea	106 (31.6)	2 (0.6)	0	66 (19.6)	1 (0.3)	0
Arthralgia	100 (29.9)	3 (0.9)	0	92 (27.3)	3 (0.9)	0
Fatigue	79 (23.6)	4 (1.2)	0	83 (24.6)	0	0
Headache	77 (23.0)	0	0	82 (24.3)	3 (0.9)	0
Diarrhea	68 (20.3)	5 (1.5)	0	63 (18.7)	1 (0.3)	0

- Post-baseline QTcF >480 msec, based on ECG data, occurred in 23 patients (6.9%) in the ribociclib arm vs 4 patients (1.2%) in the placebo arm
  - Post-baseline QTcF >500 msec occurred in 5 patients (1.5%) vs 1 patient (0.3%)
- Treatment discontinuation due to QT prolongation AEs occurred in 1 patient (0.3%) in the ribociclib arm vs 2 patients (0.6%) in the placebo arm
- QT prolongation events were not associated with clinical symptoms or arrhythmia

# Patient-reported outcomes (EORTC QLQ-C30 – global health status)



## No. at risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
Ribociclib + tamoxifen/NSAI	335	282	256	236	218	201	188	145	112	69	43	41	15	3	0
Placebo + tamoxifen/NSAI	337	260	218	198	178	158	132	97	67	38	18	17	6	1	0

- There was a sustained improvement in time to definitive deterioration of at least 10% for the global health status/QoL scale in the ribociclib arm vs the placebo arm
- A clinically meaningful (>5 points) improvement from baseline in pain score was observed as early as 8 weeks in the ribociclib arm, and was sustained

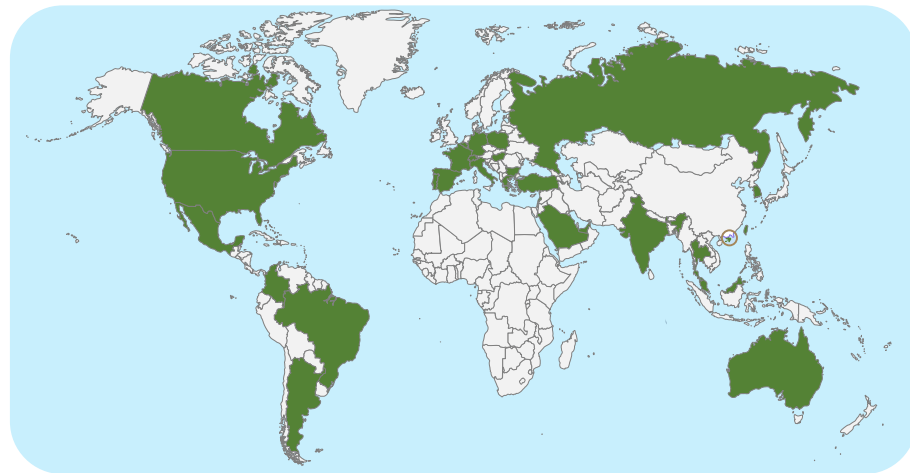
# Conclusions

- MONALEESA-7 is the first Phase III trial dedicated to the evaluation of a CDK4/6 inhibitor-based regimen as front-line treatment for premenopausal women with HR+, HER2– advanced breast cancer
- PFS was significantly prolonged with the addition of ribociclib to tamoxifen/NSAI + goserelin vs placebo + tamoxifen/NSAI + goserelin
  - Median PFS = 23.8 months vs 13.0 months; hazard ratio = 0.553; p=0.0000000983
- Treatment benefit was consistent across patient subgroups, including in patients treated in Asia, and regardless of endocrine partner
- Ribociclib-based combinations demonstrated a predictable and manageable safety profile
- A clinically meaningful improvement in time to deterioration of QoL and improvement in pain score were observed for patients in the ribociclib arm
- Ribociclib combined with endocrine therapy is a potential new treatment option for premenopausal women with HR+, HER2– advanced breast cancer, regardless of disease-free interval or endocrine partner

# Acknowledgments

- Patients who participated in MONALEESA-7 and their families
- Members of the Study Steering Committee, all investigators, research coordinators, and site staff
- Members of the Data Monitoring Committee
- This study was sponsored by Novartis Pharmaceuticals Corporation, who provided financial support for medical editorial assistance from ArticulateScience Ltd.

Ribociclib was discovered by Novartis Institutes for BioMedical Research in collaboration with Astex Pharmaceuticals



■ Countries with active centers

Argentina	Hong Kong	Russia
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Belgium	India	Singapore
Brazil	Italy	Spain
Bulgaria	Korea	Switzerland
Canada	Lebanon	Taiwan
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