First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial

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Unmet need in premenopausal patients with HR+, HER2– ABC

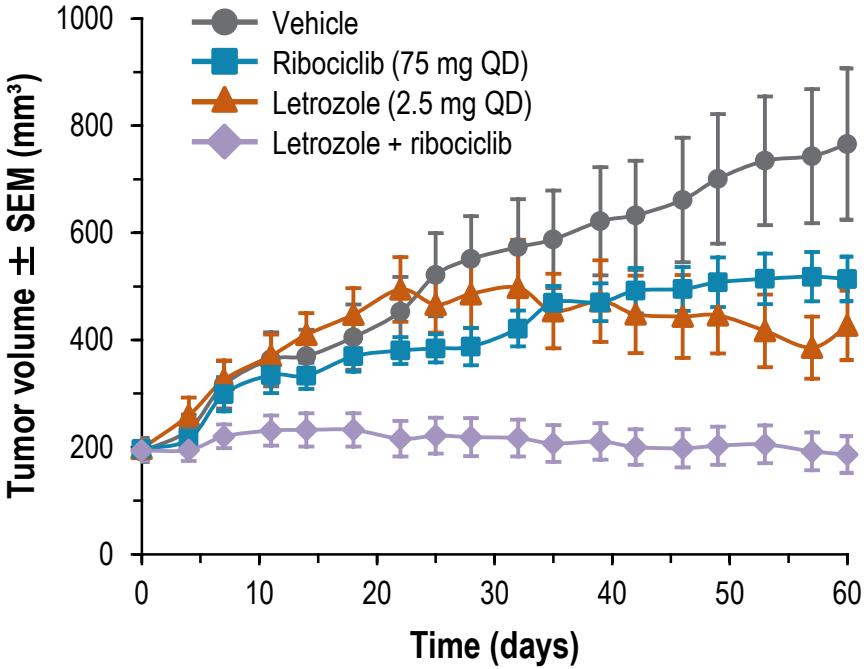
- Estimates suggest that in 2017 in the US, ~19% of invasive breast cancers will be diagnosed in women aged ≤49 years[1]
  - The proportion of patients aged <50 years may be up to 42% in the Asia-Pacific region[2]
- The last randomized trial focusing solely on premenopausal women with ABC was published in 2000[3]
- Young women with ABC have a distinct tumor biology,[4] experience more aggressive disease, and are more likely to die from their cancer than older women[5]
- Endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– ABC;[6–8] 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[9]
- MONALEESA-7 is the first Phase III trial investigating CDK4/6 inhibitor-based regimens as a front-line treatment specifically for premenopausal 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.

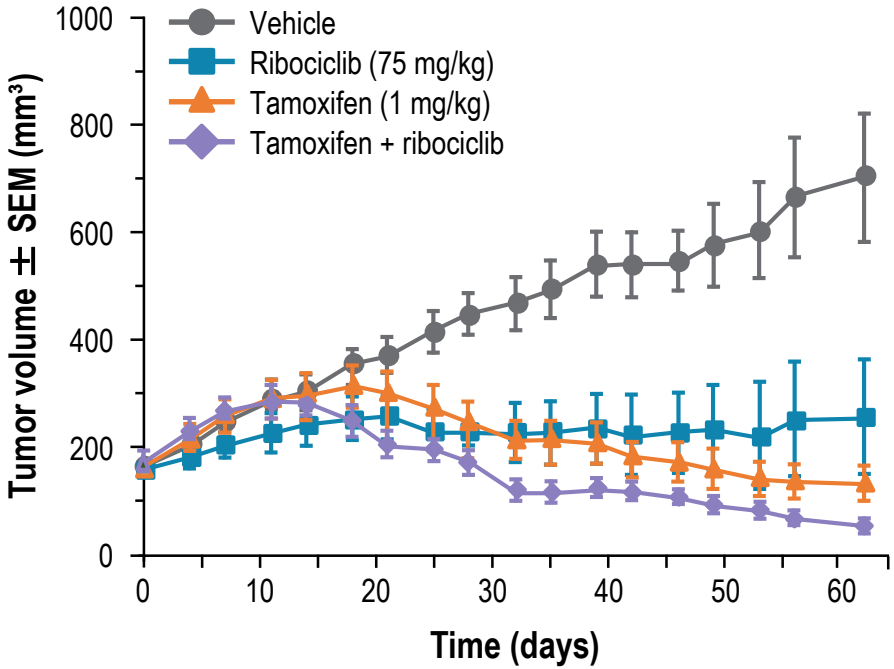
1. Desantis CE, *et al. CA Cancer J Clin* 2017;ePub ahead of print; 2. Youlden DR, *et al. Cancer Biol Med* 2014;11:101–115; 3. Klijn JGM, *et al. J Natl Cancer Inst* 2000;92:903–911; 4. Zaidi S, *et al. SABCS* 2017 (abstract P2-05-10); 5. Anders CK, *et al. Semin Oncol* 2009;36:237–249; 6. NCCN Clinical 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.

Preclinical activity of ribociclib-based combinations*

Ribociclib + letrozole[1]



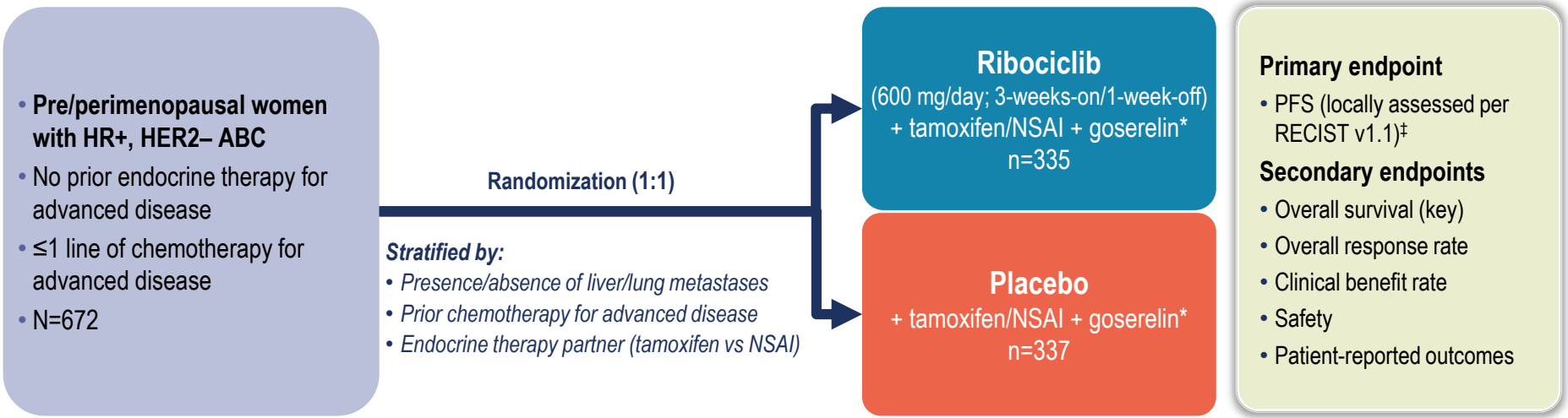
Ribociclib + tamoxifen[2]



QD, once daily; SEM, standard error of the mean.
*Patient-derived ER+ breast cancer xenograft model (HBX34) used for both analyses.

1. O'Brien NA, *et al. Cancer Res* 2014;74(suppl 19):abst 4756;
2. Caponigro G, *et al. Keystone Symposia – Kinases: Next-Generation Insights and Approaches* 2017:oral.

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



- Tumor assessments were performed every 8 weeks for 18 months, then every 12 weeks thereafter
- Primary analysis planned after ~329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm[1,2]), 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;
‡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. Mourisden H, *et al. J Clin Oncol* 2001;19:2596–2606.

Key enrollment criteria

Key inclusion criteria

- Pre/perimenopausal women (per NCCN guidelines)
- ≥1 measurable lesion (RECIST 1.1) or ≥1 predominantly lytic bone lesion
- ECOG performance status of ≤1
- ≤1 line of chemotherapy for ABC
- Prior (neo)adjuvant therapy was allowed:
  - If no prior endocrine therapy OR if ≥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

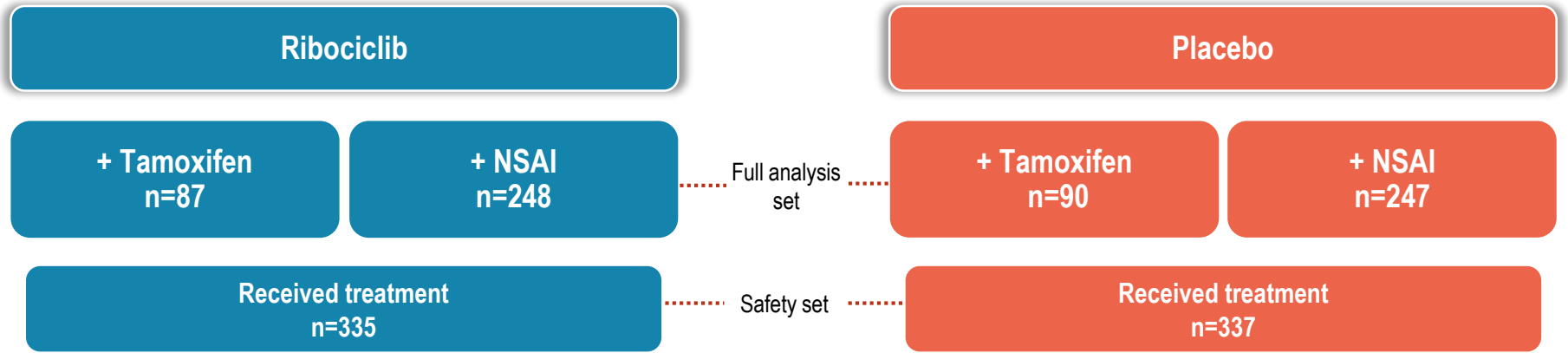
Key exclusion criteria

- 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



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Patient demographics and baseline characteristics

Characteristic*	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Median age, years (range)	43 (25–58)	45 (29–58)
Race		
Caucasian	187 (55.8)	201 (59.6)
Asian	99 (29.6)	99 (29.4)
Other‡	29 (8.7)	19 (5.6)
Unknown	20 (6.0)	18 (5.3)
ECOG performance status§		
0	245 (73.1)	255 (75.7)
1	87 (26.0)	78 (23.1)
Missing	3 (0.9)	3 (0.9)
Metastatic sites		
Visceral disease	193 (57.6)	188 (55.8)
Bone-only disease	81 (24.2)	78 (23.1)
***De novo* metastatic disease**	136 (40.6)	134 (39.8)
Non-*de novo* metastatic disease	199 (59.4)	203 (60.2)
Disease-free interval		
≤12 months	23 (6.9)	13 (3.9)
>12 months	176 (52.5)	190 (56.4)
Prior (neo)adjuvant endocrine therapy	127 (37.9)	141 (41.8)
Prior chemotherapy		
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; ‡'Other' includes Black, Native American, and other;
§ One patient in the placebo arm had an ECOG performance status of 2.
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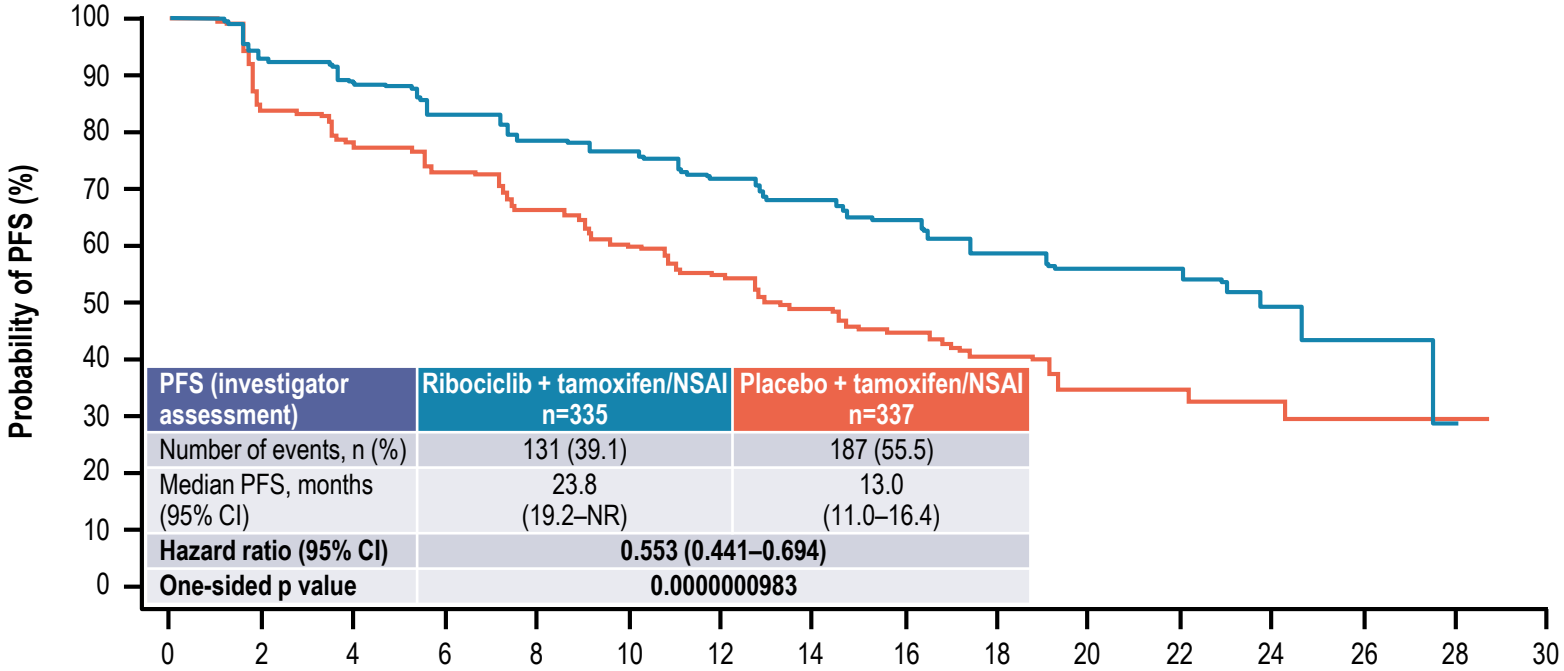
Primary endpoint: PFS (investigator-assessed)



PFS (investigator assessment)	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	131 (39.1)	187 (55.5)
Median PFS, months (95% CI)	23.8 (19.2–NR)	13.0 (11.0–16.4)
Hazard ratio (95% CI)	**0.553 (0.441–0.694)**	
One-sided p value	**0.0000000983**	

No. at risk

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.

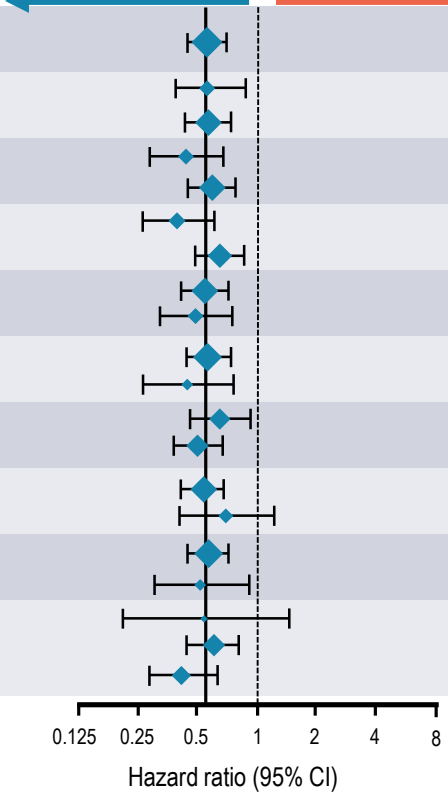
PFS by endocrine therapy partner (investigator-assessed)

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

Goserelin included in all combinations.

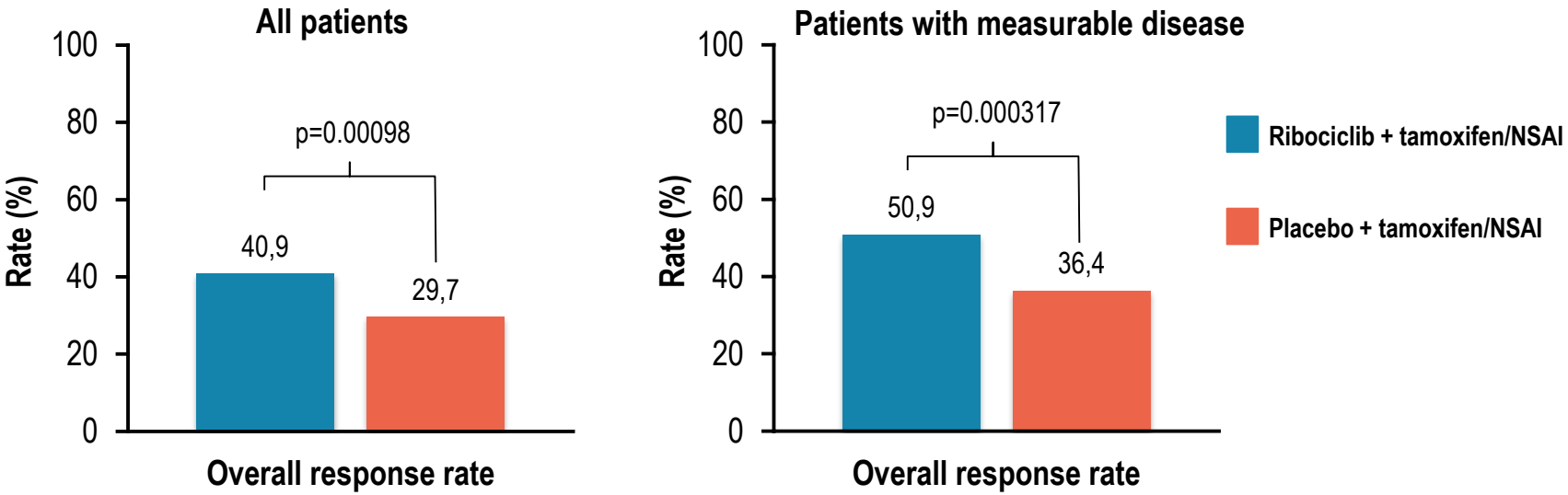
PFS subgroup analysis*

Subgroup		n (%)	Hazard ratio	95% CI
All patients		672 (100)	0.553	0.441–0.694
Endocrine therapy partner	Tamoxifen	177 (26)	0.585	0.387–0.884
	NSAI	495 (74)	0.569	0.436–0.743
Age	<40 years	186 (28)	0.443	0.293–0.671
	≥40 years	486 (72)	0.590	0.449–0.777
Race‡	Asian	198 (29)	0.401	0.258–0.625
	Non-Asian	413 (61)	0.657	0.492–0.877
ECOG performance status§	0	500 (74)	0.549	0.417–0.721
	≥1	166 (25)	0.495	0.320–0.765
ER/PgR status	ER+ and PgR+	572 (85)	0.574	0.446–0.739
	Other	100 (15)	0.444	0.258–0.765
Liver and/or lung involvement	No	329 (49)	0.642	0.454–0.907
	Yes	343 (51)	0.503	0.375–0.677
Bone-only disease	No	513 (76)	0.533	0.415–0.686
	Yes	159 (24)	0.703	0.414–1.194
Prior chemotherapy for advanced disease	No	578 (86)	0.566	0.443–0.724
	Yes	94 (14)	0.547	0.314–0.954
Disease-free interval	≤12 months	36 (5)	0.560	0.210–1.490
	>12 months	366 (54)	0.615	0.455–0.832
	De novo	270 (40)	0.428	0.287–0.640



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.

Secondary endpoints



- 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

CBR, clinical benefit rate.
CBR = complete response + partial response + (stable disease + non-complete response/non-progressive disease ≥24 weeks).
Goserelin included in all combinations.

Hematologic adverse events

Regardless of study treatment relationship

AEs ≥5% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Neutropenia	75.8	50.7	9.9	7.7	3.0	0.6
Leukopenia	31.3	13.1	1.2	5.6	1.2	0
Anemia	20.9	3.0	0	10.1	2.1	0
Thrombocytopenia	8.7	0.6	0.3	2.1	0.3	0.3

- Febrile neutropenia occurred in 2.1% of patients in the ribociclib arm vs 0.6% of patients in the placebo arm

Goserelin included in all combinations.

Non-hematologic adverse events

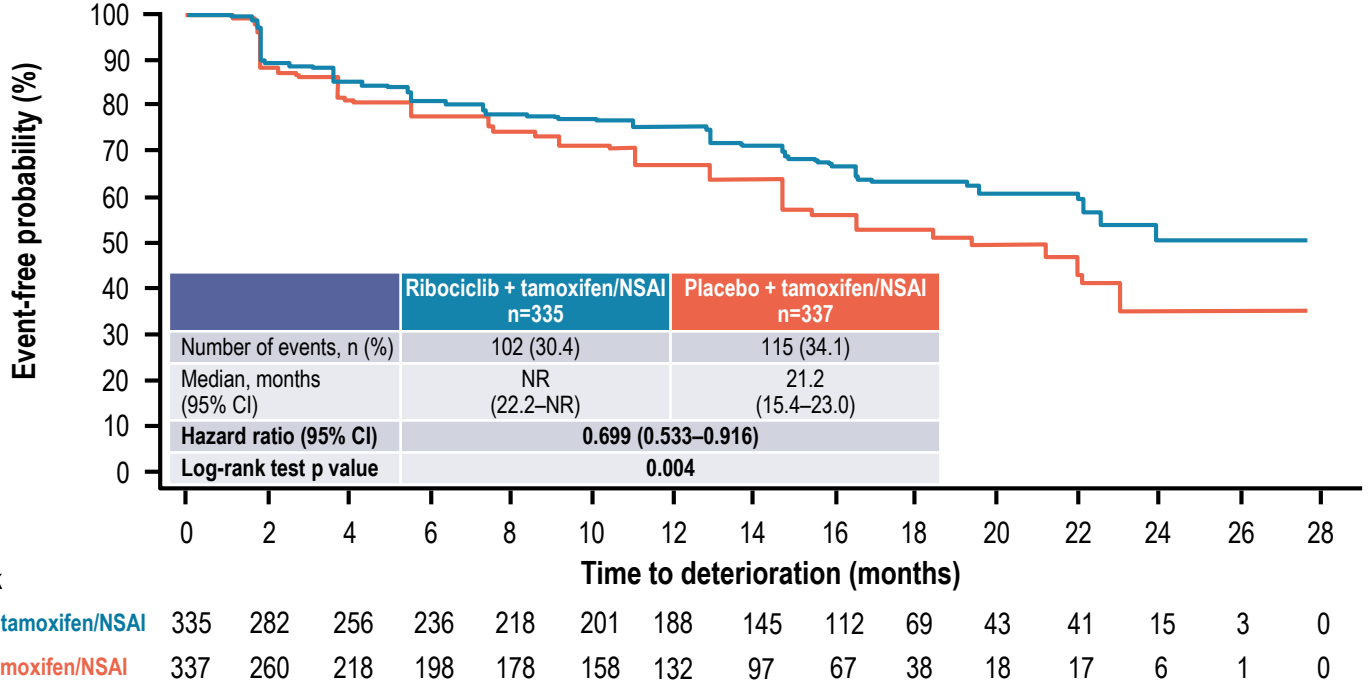
Regardless of study treatment relationship

AEs ≥20% in either arm, %	Ribociclib + tamoxifen/NSAI n=335			Placebo + tamoxifen/NSAI n=337		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Hot flush	34.0	0.3	0	33.5	0	0
Nausea	31.6	0.6	0	19.6	0.3	0
Arthralgia	29.9	0.9	0	27.3	0.9	0
Fatigue	23.6	1.2	0	24.6	0	0
Headache	23.0	0	0	24.3	0.9	0
Diarrhea	20.3	1.5	0	18.7	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

ECG, electrocardiogram.
Goserelin included in all combinations.

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



- 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

QoL, quality of life.
Goserelin included in all combinations.

Conclusions

- MONALEESA-7 represents 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 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 tamoxifen/NSAI + goserelin is a potential new treatment option for premenopausal women with HR+, HER2– advanced breast cancer, regardless of disease-free interval or endocrine partner