MONALEESA-7 trial

First-line ribociclib vs placebo 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

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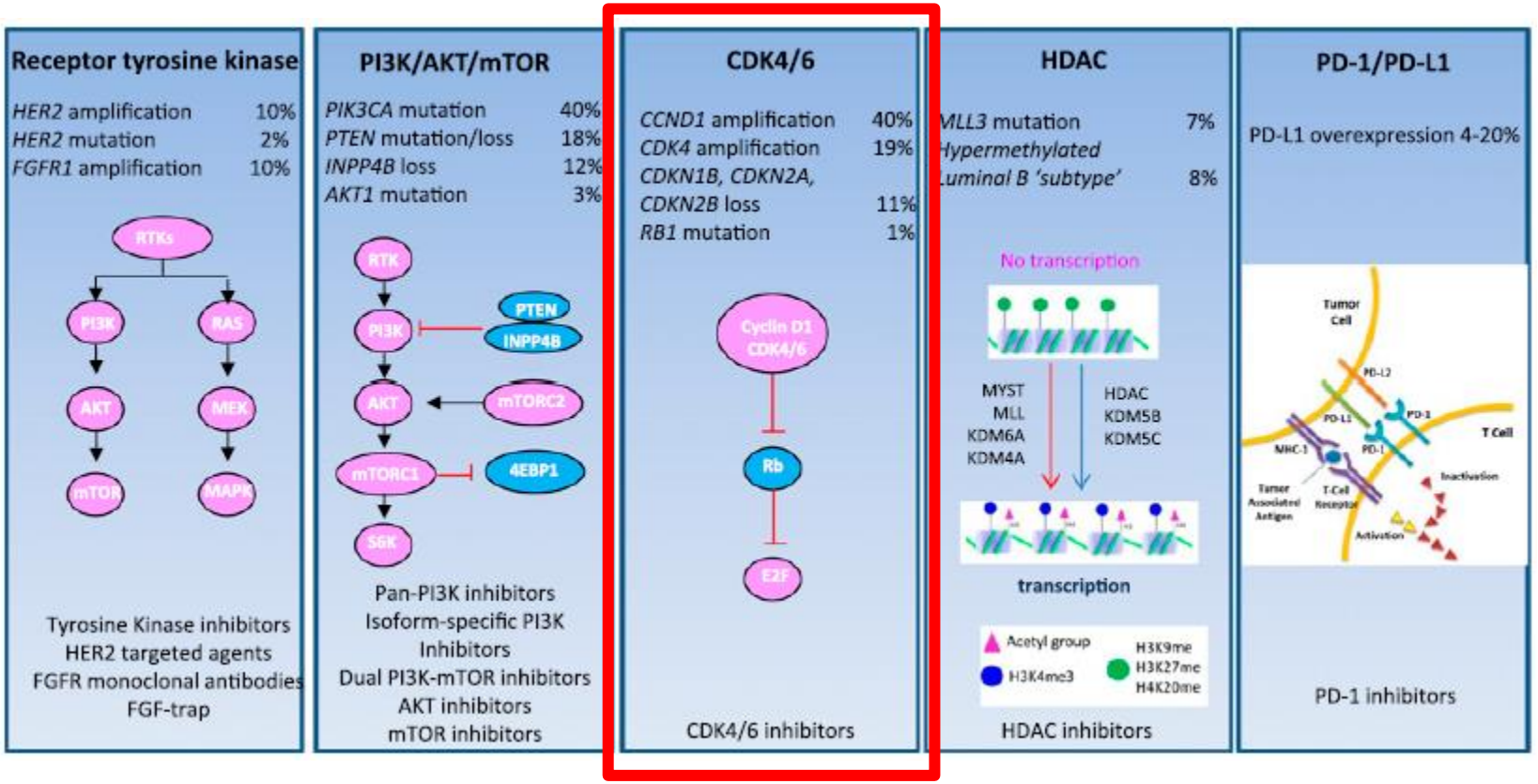
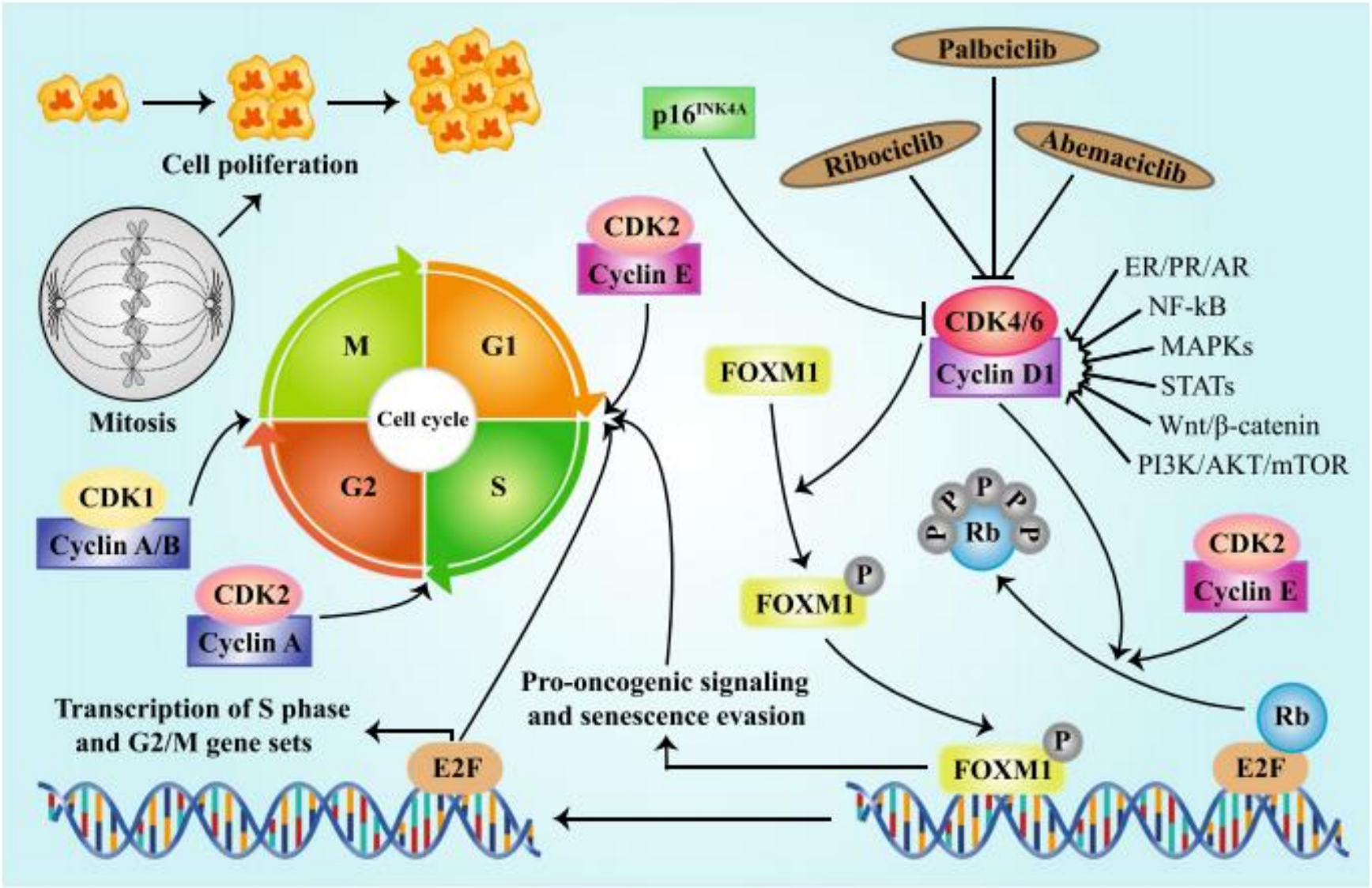
Introducción: RE



ASCO Ed book 2016

Introducción: CDK 4/6



Xu et al. J Hematology & Oncology 2017

Inh CDK 4/6: Primera Línea

PALOMA 2

The NEW ENGLAND JOURNAL of MEDICINE

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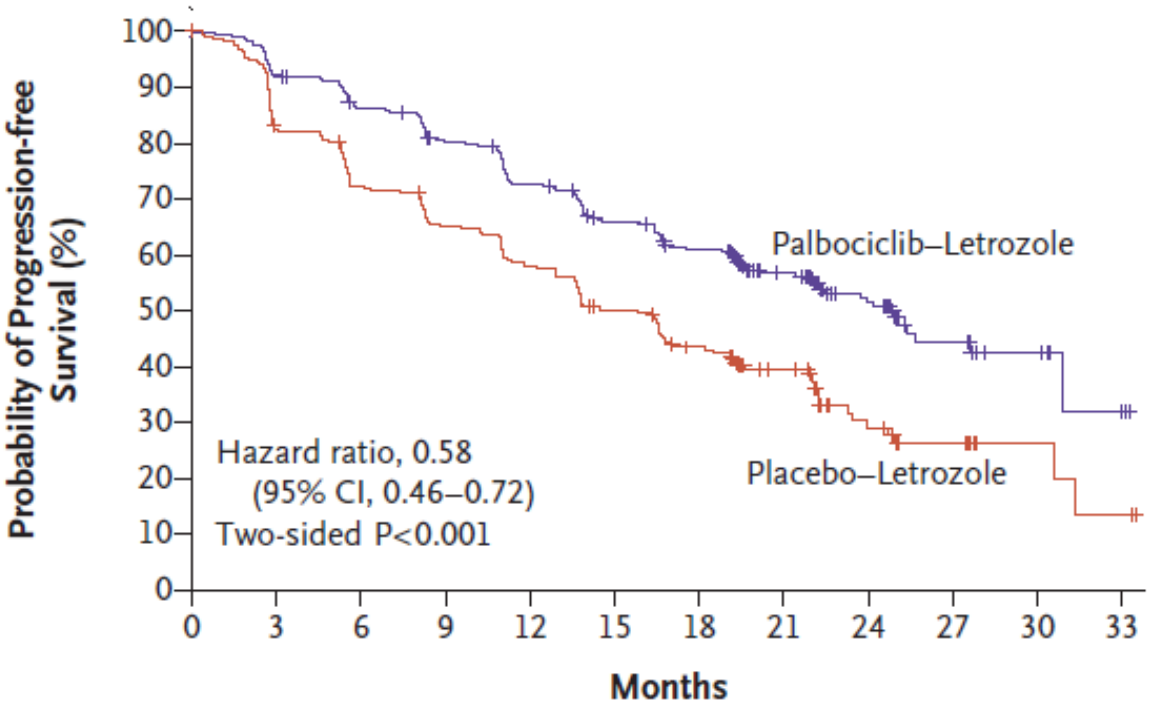
Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.



24.8 m

14.5 m

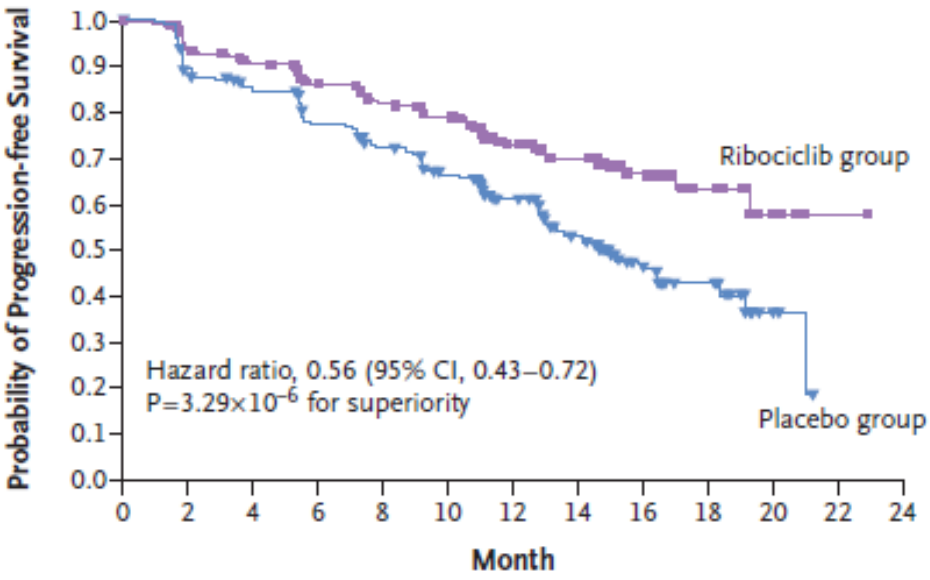
Inh CDK 4/6: Primera Línea

MONALEESA-2

ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy



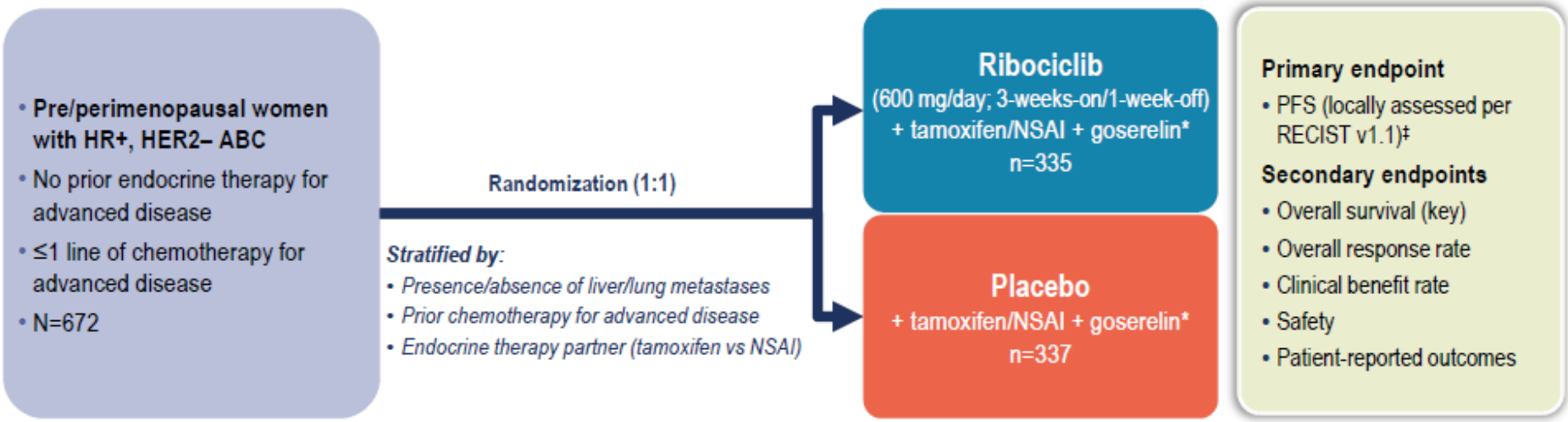
NR

14.7 m

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

Debu Tripathy,[1] Joohyuk Sohn,[2] Seock-Ah Im,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Sara Hurvitz,[8] Louis Chow,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Gary Carlson,[14] Gareth Hughes,[15] Ivan Diaz-Padilla,[15] Caroline Germa,[14] Samit Hirawat,[14] Yen-Shen Lu[16]

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.

MONALEESA-7

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

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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)

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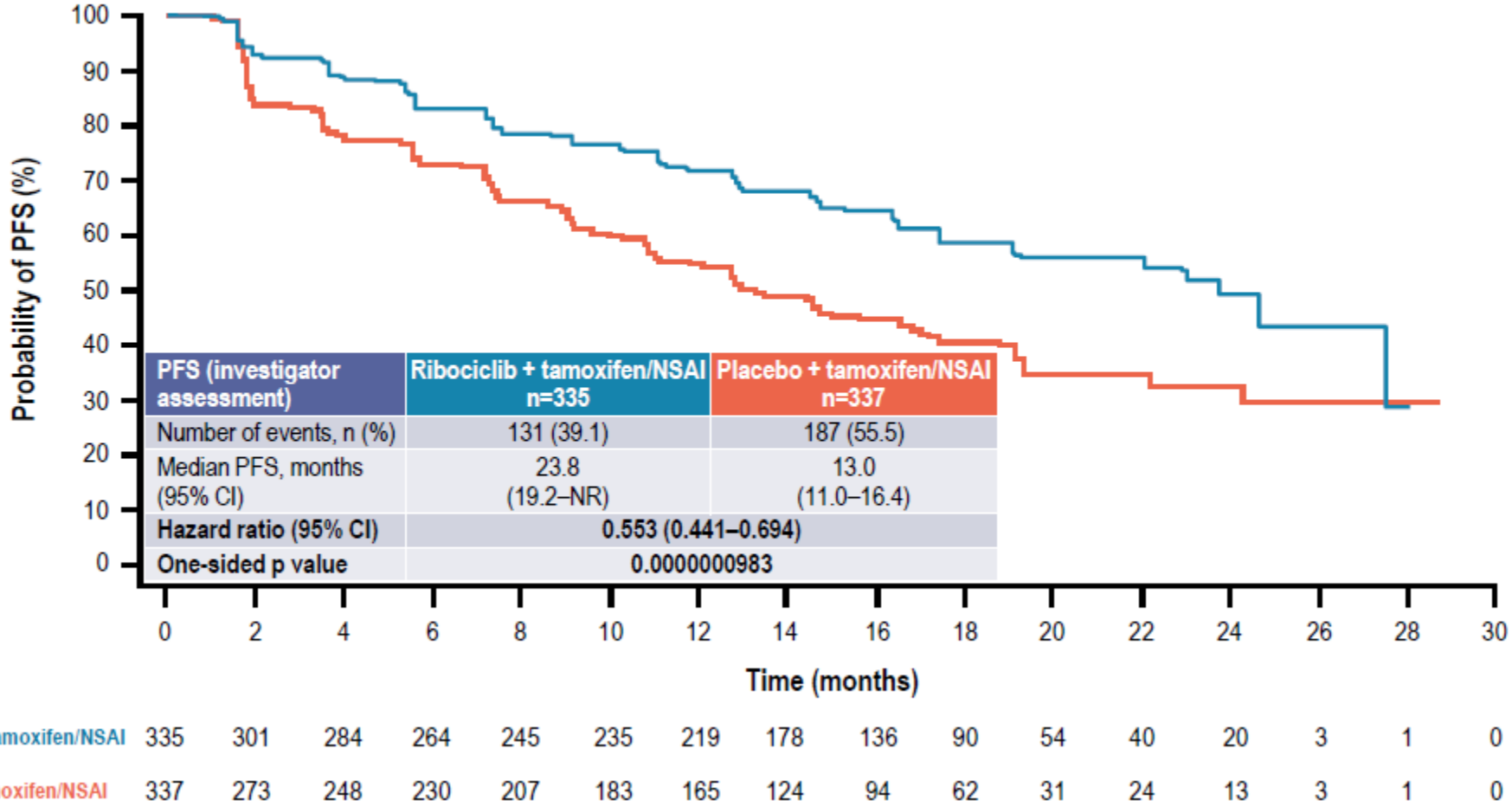
Primary endpoint: PFS (investigator-assessed)



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

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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)**	

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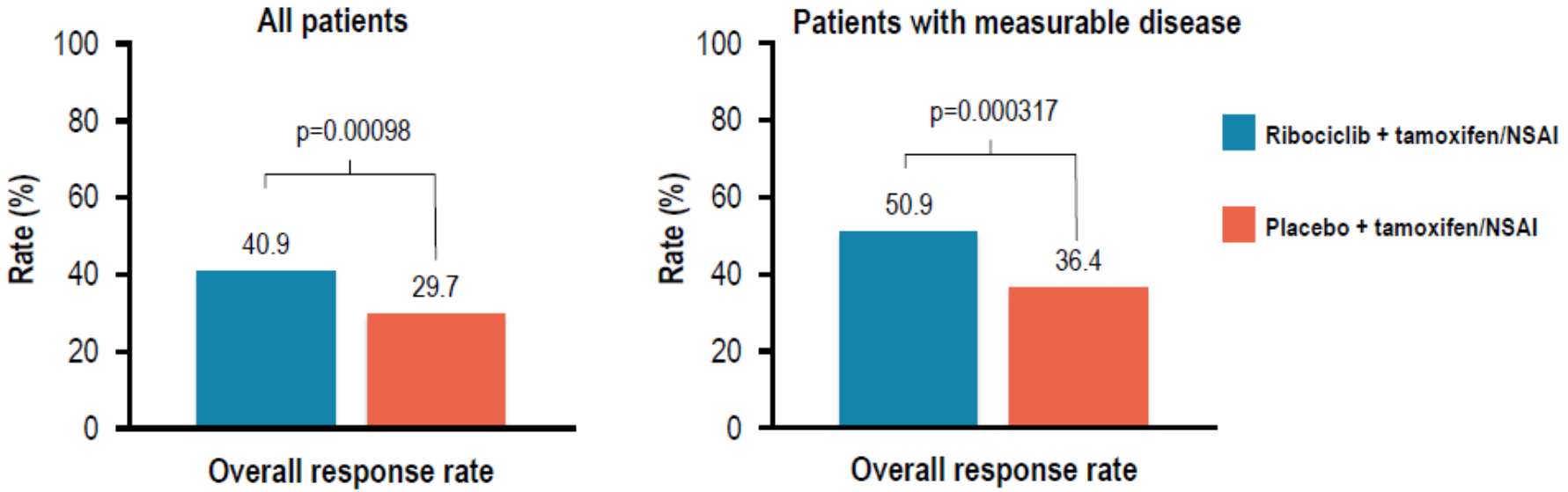
Secondary endpoints



- 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

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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

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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

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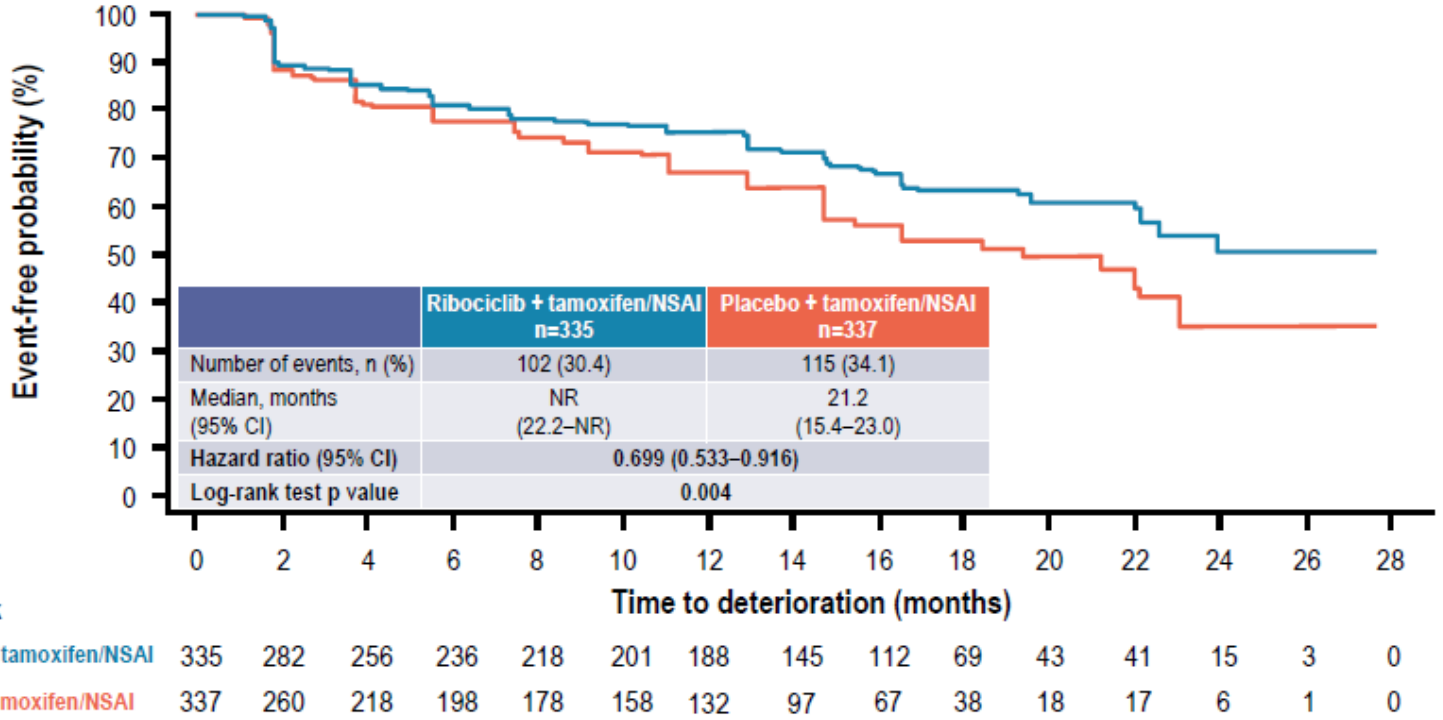
Patient-reported outcomes (EORTC QLQ-C30 – global health status)



	Ribociclib + tamoxifen/NSAI n=335	Placebo + tamoxifen/NSAI n=337
Number of events, n (%)	102 (30.4)	115 (34.1)
Median, months (95% CI)	NR (22.2–NR)	21.2 (15.4–23.0)
Hazard ratio (95% CI)	0.699 (0.533–0.916)	
Log-rank test p value	0.004	

No. at risk

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

CONCLUSIONES

- Ribociclib en primera línea demuestra beneficio en mujeres pre MP con cancer mama avanzado.
- Beneficio en PFS y QoL
  - mPFS 23.8 vs 13 m HR 0.5 p<0.05
  - Independiente de subgrupos y TAM/IA.
  - Data inmadura OS
- Perfil efectos adversos predecibles y manejables
- ¿Nueva alternativa vs nuevo estándar?
  - Acceso

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