La certeza de ofrecer más vida[1,2,3]

KISQALI OVERALL SURVIVAL – MONALEESA-2

ESMO 2021 (final analysis)

▼ KISQALI® ribociclib

NOVARTIS

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021. **2.** Slamon D, Neven P, Chia S, et al. Updated overall survival (OS) results from the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2− advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). ASCO Annual Meeting 2021 **3.** Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. San Antonio Breast Cancer Virtual Symposium; December; San Antonio, Texas 2020. p. PD2-04.

ES2201245179

ES2109159379

2021 ESMO congress

Overall Survival Results From the Phase III MONALEESA-2 Trial of Postmenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib[1]

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1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Declaration of interests

Gabriel N. Hortobagyi has served as a paid consultant for Novartis Pharmaceuticals. His institution has also received research funds from Novartis Pharmaceuticals in support of the MONALEESA trials.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Background

- The Phase III MONALEESA-2 trial investigated ribociclib plus letrozole in the first-line setting in postmenopausal patients with HR+/HER2− advanced breast cancer
  - A statistically significant PFS benefit was reported with ribociclib plus letrozole vs placebo plus letrozole (median, 25.3 vs 16.0 months; HR, 0.568; $P = 9.63 \times 10^{-8}$)[1,2]
- The Phase III trials MONALEESA-7 and MONALEESA-3 both demonstrated a statistically significant OS benefit with the addition of ribociclib to endocrine therapy compared with endocrine therapy alone in pre- and postmenopausal patients with HR+/HER2− advanced breast cancer[3,4,a]
- Here we report the final OS analysis from MONALEESA-2

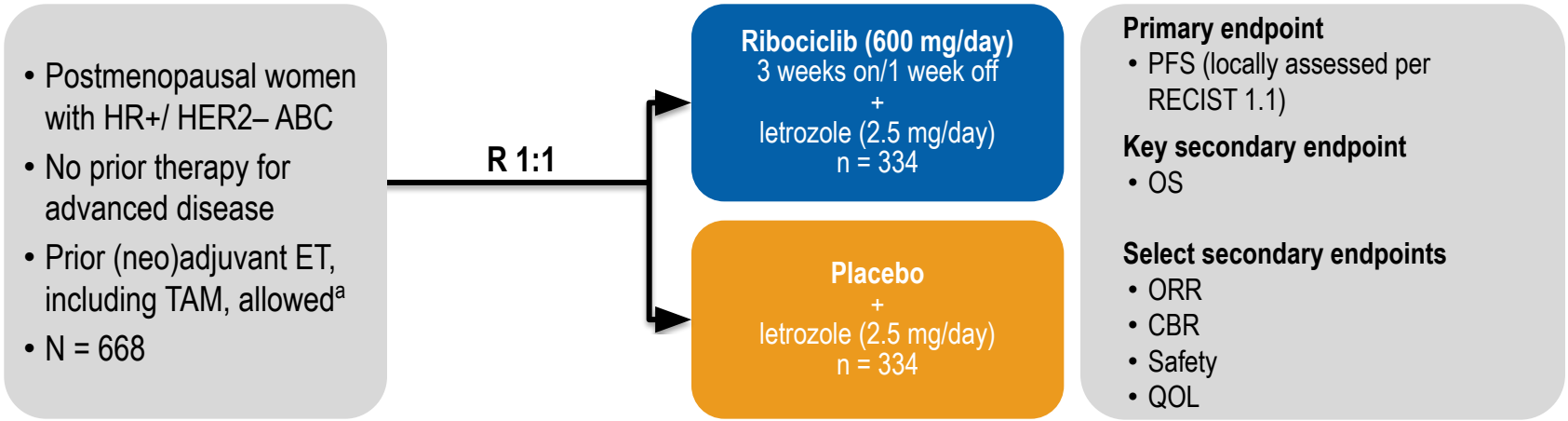
HER2−, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; OS, overall survival; PFS, progression-free survival.

[a] MONALEESA-7 investigated ribociclib plus endocrine therapy in pre- and perimenopausal patients, while MONALEESA-3 investigated ribociclib plus fulvestrant in postmenopausal patients.

1. Hortobagyi GN, et al. *N Engl J Med*. 2016;375(18):1738-1748. 2. Hortobagyi GN, et al. *Ann Oncol*. 2018;29(7):1541-1547. 3. Im S-A, et al. *N Engl J Med*. 2019;381(4):307-316. 4. Slamon DJ, et al. *N Engl J Med*. 2020;382(6):514-524.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

MONALEESA-2 study design



Stratified by the presence/absence of liver and/or lung metastases

ABC, advanced breast cancer; CBR, clinical benefit rate; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QOL, quality of life; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TAM, tamoxifen.

[a] Treatment-free interval > 12 months from completion of treatment until randomization required for prior NSAI use.

Hortobagyi GN, et al. *N Engl J Med*. 2016;375(18):1738-1748.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Statistical methods

- This is the final protocol-specified OS analysis (planned after approximately 400 deaths)
- A hierarchical testing strategy was used; OS was to be tested under a 5-look group sequential design only if PFS results were positive
- Prespecified Lan-DeMets (O'Brien-Fleming) stopping boundary for claiming superior efficacy was defined as 1-sided *P* value ≤ .0219
    - Study had approximately 90% power to detect a difference in OS
- An exploratory analysis on time to first subsequent chemotherapy was also performed

OS, overall survival; PFS, progression-free survival.
Hortobagyi GN, et al. *N Engl J Med*. 2016;375(18):1738-1748.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Patient disposition (data cutoff: 10 June 2021)

Median duration of follow-up[a] was 80 months (minimum, 75 months)

Parameter, n %	RIB + LET n = 334	PBO + LET n = 334	All Patients N = 668
Patients treated			
Treatment ongoing[b]	30 (9.0)	17 (5.1)[c]	47 (7.0)
End of treatment	304 (91.0)	313 (93.7)	617 (92.4)
Reason for end of treatment			
Progressive disease	204 (61.1)	263 (78.7)	467 (69.9)
Patient/guardian decision	29 (8.7)	23 (6.9)	52 (7.8)
Adverse event	37 (11.1)	9 (2.7)	46 (6.9)
Physician decision	25 (7.5)	20 (6.0)	45 (6.7)
Death	6 (1.8)	1 (0.3)	7 (1.0)
Protocol deviation	3 (0.9)	1 (0.3)	4 (0.6)

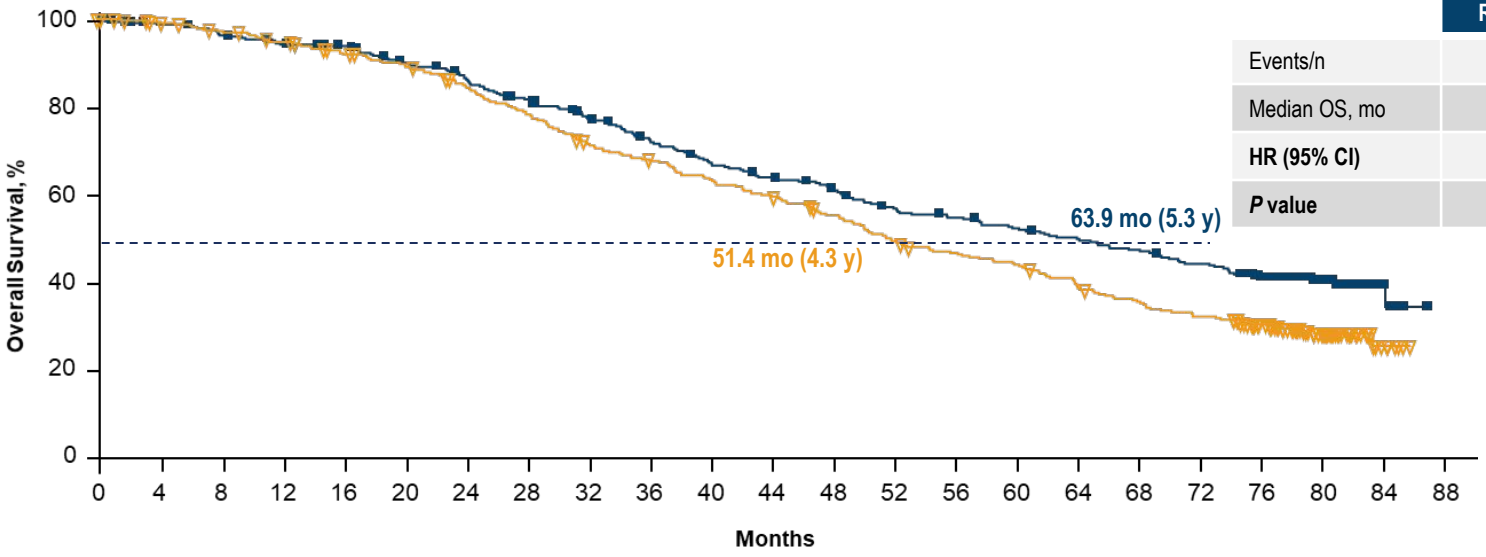
LET, letrozole; PBO, placebo; RIB, ribociclib.

[a] Follow-up from randomization to data cutoff. [b] At the time of data cutoff (10 June 2021). [c] Four patients in the PBO arm did not receive study treatment.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole



	RIB + LET	PBO + LET
Events/n	181/334	219/334
Median OS, mo	63.9	51.4
HR (95% CI)	**0.76 (0.63-0.93)**	
***P* value**	**.004**	

No. at risk																						
RIB + LET	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
PBO + LET	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

The P value of .004 crossed the prespecified boundary to claim superior efficacy

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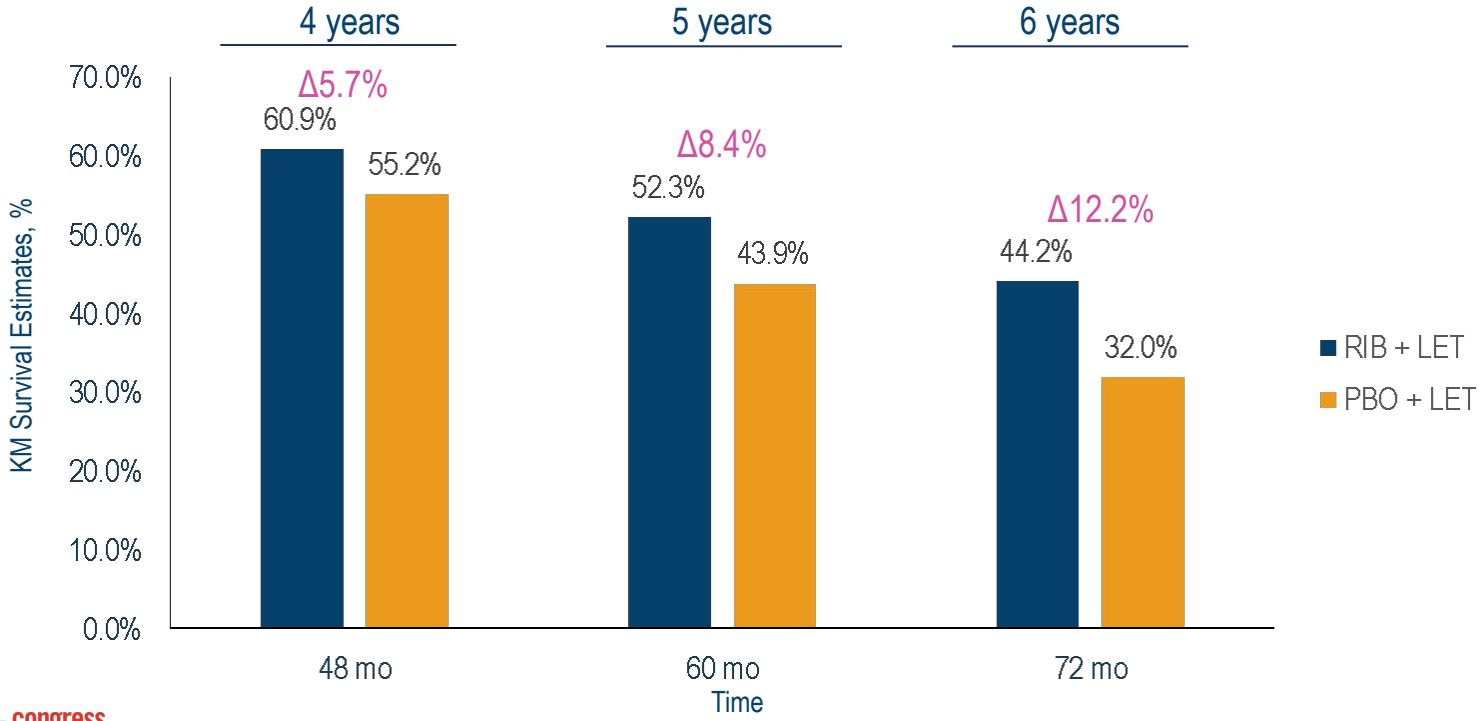
1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

The OS benefit with ribociclib increased over time

At 6 years, the survival rate of patients receiving ribociclib was 44.2%



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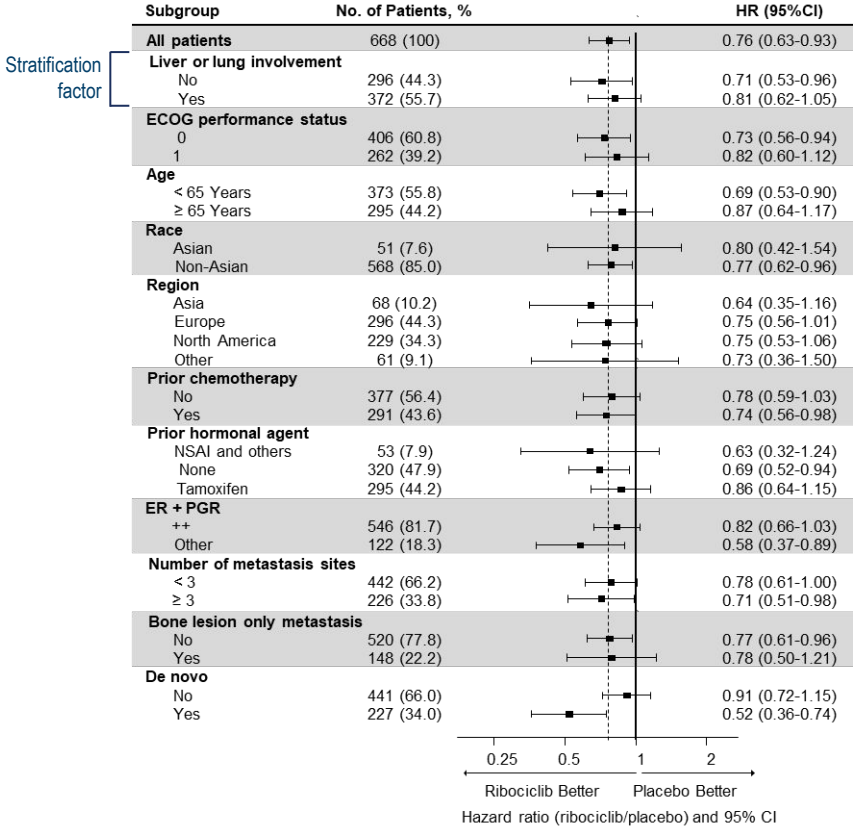
LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

Consistent OS benefit was seen across key subgroups



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ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PGR, progesterone receptor.

Subsequent therapy after discontinuation

CDK4/6i use was higher in the placebo arm (34.4%) than the ribociclib arm (21.7%)

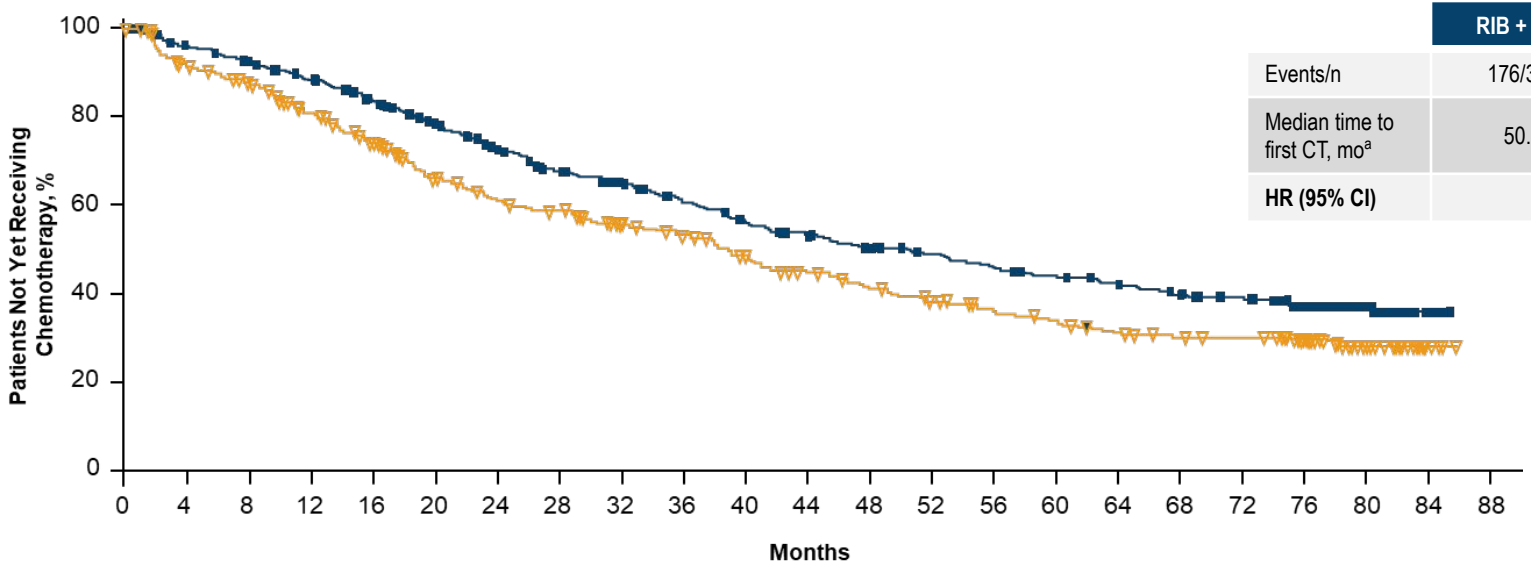
Parameter, n (%)	RIB + LET n = 334	PBO + LET n = 334
Patients who discontinued study treatment	304 (91.0)	317 (94.9)
Patients who received first subsequent therapy[a,b]	267 (87.8)	286 (90.2)
Hormone therapy alone	100 (32.9)	92 (29.0)
Hormone therapy + other therapy	74 (24.3)	94 (29.7)
Chemotherapy alone	53 (17.4)	61 (19.2)
Chemotherapy + hormone or other therapy	32 (10.5)	33 (10.4)
Patients who received a CDK4/6i in any subsequent line of therapy[a,c]	66 (21.7)	109 (34.4)
Palbociclib	49 (16.1)	100 (31.5)
Ribociclib	14 (4.6)	6 (1.9)
Abemaciclib	8 (2.6)	12 (3.8)

CDK4/6i, cyclin-dependent kinases 4 and 6 inhibitor; LET, letrozole; PBO, placebo; RIB, ribociclib.

[a] Percentages reported are based on the number of patients who discontinued study treatment. [b] Two patients (0.6%) in the ribociclib arm and 4 patients (1.2%) in the placebo arm received other therapies as the first subsequent antineoplastic therapy. [c] A patient with multiple occurrences of receiving a subsequent CDK4/6i is only counted once for the total row.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

Ribociclib delayed time to first chemotherapy by ≈ 1 year



	RIB + LET	PBO + LET
Events/n	176/334	200/334
Median time to first CT, mo[a]	50.6	38.9
HR (95% CI)	**0.74 (0.61-0.91)**	

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CT, chemotherapy; HR, hazard ratio; LET, letrozole; PBO, placebo; RIB, ribociclib.

[a] Time to first chemotherapy was defined as the time from randomization to the start of the first chemotherapy following discontinuation of the study treatment.

Safety

- The median treatment duration was approximately 2 years and 1 year in the ribociclib and placebo arms, respectively
- After 80 months (> 6.5 years) of follow-up, no new safety signals were identified
  - The majority of events occurred in the first 12 months of treatment
- The rates of grade 3/4 adverse events[a] of special interest in the ribociclib and placebo arms, respectively, were
  - Neutropenia, 63.8% and 1.2%
  - Hepatobiliary toxicity, 14.4% and 4.8%
  - Prolonged QT interval, 4.5% and 2.1%
  - Interstitial lung disease/pneumonitis, 0.6% and 0%

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

[a] Adverse event reporting was based on group terms.

Conclusions

- First-line ribociclib + letrozole demonstrated a statistically significant and clinically meaningful OS benefit compared with placebo + letrozole in postmenopausal patients with HR+/HER2− advanced breast cancer
  - Median OS was prolonged by more than 12 mo (63.9 mo with ribociclib plus letrozole vs 51.4 mo with placebo plus letrozole)
  - HR was 0.76 (95% CI, 0.63-0.93); *P* = .004
  - Six-year survival rates were 44.2% and 32.0% for ribociclib and placebo, respectively
- No new safety signals were seen with ribociclib after > 6.5 years of follow-up
- Ribociclib combined with endocrine therapy is the only first-line treatment with OS benefit and should therefore be considered as the preferred treatment option for HR+/HER2− advanced breast cancer
- The MONALEESA trials with ribociclib demonstrate a consistent overall survival benefit regardless of endocrine therapy partner, line of therapy, or menopausal status

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

HER2−, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; OS, overall survival.

Acknowledgements

We thank the patients who participated in this trial, their families and caregivers, data monitoring committee members, study steering committee members, and staff who assisted with the trial at each site.

We also thank the 1889 investigators in 29 countries who contributed to this trial.

Additionally, we thank the team that supported this trial, including Michelle Miller, Deepak Lokhande, Omprakash Patil, Keerthi Arji, Hameed Sadiq Mothali, Emile Fournier, Claudia Gasch, Tim Cartwright, Eva Vagnon, Rajani Masineni, Laureen Mansencal Strittmatter, Shanu Rana, and Balachander Chellamuthu.

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

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021.

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La certeza de ofrecer más vida[1,2,3]

KISQALI OVERALL SURVIVAL – MONALEESA-3

ESMO 2019 (final analysis)
ASCO 2021 (updated analysis)

▼ KISQALI® ribociclib

NOVARTIS

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

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BARCELONA 2019 ESMO congress

Overall Survival Results From the Phase III MONALEESA-3 Study of Fulvestrant ± Ribociclib in Postmenopausal Patients With HR+/HER2– Advanced Breast Cancer

Dennis J. Slamon,[1] Patrick Neven,[2] Stephen Chia,[3] Peter A. Fasching,[4] Michelino De Laurentiis,[5] Seock-Ah Im,[6] Katarina Petrakova,[7] Giulia Val Bianchi,[8] Francisco J. Esteva,[9] Miguel Martín,[10] Arnd Nusch,[11] Gabe S. Sonke,[12] Luis De la Cruz-Merino,[13] J. Thaddeus Beck,[14] Xavier Pivot,[15] Manu Sondhi,[16] Yingbo Wang,[17] Arunava Chakravartty,[16] Karen Rodriguez-Lorenc,[16] Guy Jerusalem[18]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [3]British Columbia Cancer Agency, Vancouver, British Columbia, Canada; [4]University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [5]Istituto Nazionale Tumori "Fondazione G. Pascale," Naples, Italy; [6]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [7]Masaryk Memorial Cancer Institute, Brno, Czech Republic; [8]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy; [9]New York University Langone Health, New York, NY, USA; [10]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [11]Practice for Hematology and Internal Oncology, Velbert, Germany; [12]Netherlands Cancer Institute/Borstkanker Onderzoek Groep Study Center, Amsterdam, the Netherlands; [13]Hospital Universitario Virgen Macarena, Seville, Spain; [14]Highlands Oncology Group, Fayetteville, AR, USA; [15]Institut Régional du Cancer, Strasbourg, France; [16]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [17]Novartis Pharma AG, Basel, Switzerland; [18]Centre Hospitalier Universitaire de Liège and Liège University, Liège, Belgium

Disclosure

Dennis J. Slamon

- Leadership: Biomarin
- Stock and Other Ownership Interests: Pfizer, Merck, Amgen
- Honoraria: Novartis
- Consulting or Advisory Role: Lilly; Novartis
- Research Funding: Novartis; Pfizer
- Travel, Accommodations, Expenses: Biomarin; Novartis; Pfizer

Background

- In the Phase III MONALEESA-7 trial of premenopausal patients, the addition of ribociclib (RIB) to ET demonstrated a statistically significant improvement in overall survival (HR, 0.71; *P* = 0.00973) compared with ET alone[1,2]
- The Phase III MONALEESA-3 study investigated RIB, a CDK4/6 inhibitor, plus fulvestrant (FUL) in postmenopausal patients with HR+/HER2− ABC
  - The primary report revealed a statistically significant longer PFS (primary end point) with RIB + FUL vs PBO + FUL (median, 20.5 vs 12.8 months; HR, 0.593; *P* < 0.0001)[3,4]
  - OS data were not mature[3]
  - Median PFS was not reached in patients receiving 1L RIB[3]
- Here we report OS data from MONALEESA-3 and provide an update on the primary and other secondary end points

1L, first line; ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival ;PBO, placebo; PFS, progression-free survival.

1. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915. 2. Im S-A, et al. *N Engl J Med*. 2019;381:307-316. 3. Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472. 4. Slamon DJ, et al. ASCO 2018 [Abstract 1000].

Rb as the master regulator of the G1/S cell cycle checkpoint

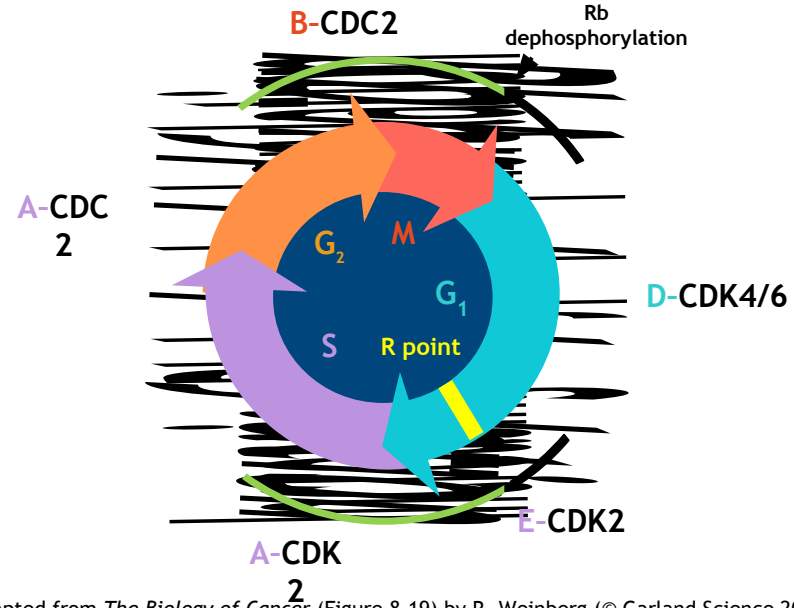


Figure adapted from *The Biology of Cancer* (Figure 8.19) by R. Weinberg (© Garland Science 2007).

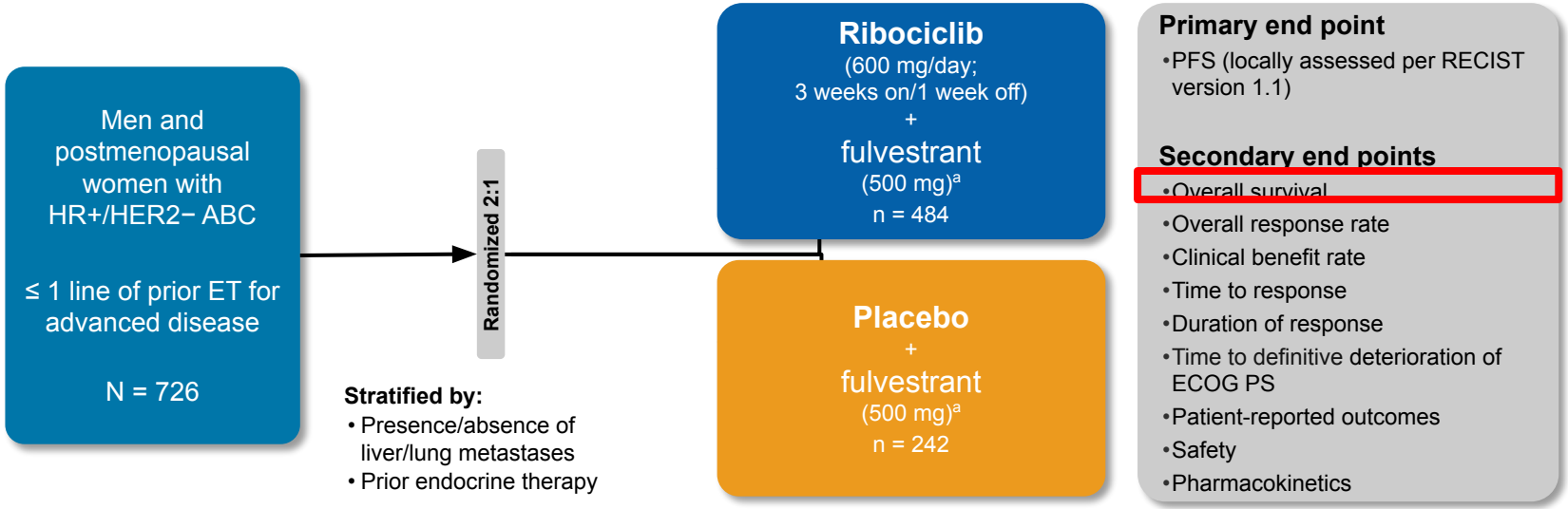
- CDK protein kinases control cell cycle progression by binding to specific regulatory subunits, known as cyclins[1]
- CDKs 4 and 6 (CDK4/6) function in complex with D-type cyclins[1]
  - p16 is a negative regulator of the cyclin-D-CDK4/6 complex
- The resulting active cyclin-D-CDK4/6 complexes initiate hyperphosphorylation of Rb[1]
- Hyperphosphorylation of Rb results in its inactivation, which allows the cell to progress from G1 to S-phase[1]

Can inhibiting cyclin D-CDK4/6 prevent Rb hyperphosphorylation and cell cycle progression?

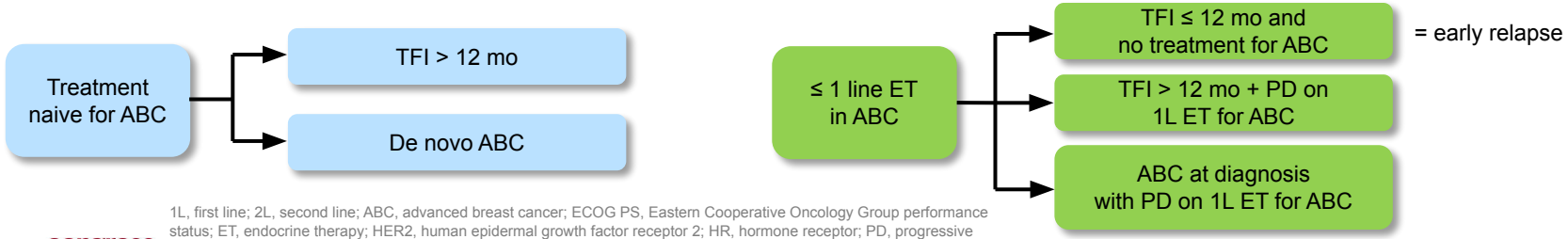
CDK, cyclin-dependent kinase; G, gap phase; M, mitotic phase; Rb, retinoblastoma; S, synthesis phase.

1. Hosford S and Miller T. *Pharmgenomics Pers Med.* 2014;7:203–215.

MONALEESA-3 Study Design



Patient population definitions



1L, first line; 2L, second line; ABC, advanced breast cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TFI, treatment-free interval.

[a] Fulvestrant 500 mg intramuscularly every 28 days plus an additional dose on Cycle 1, Day 15.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-247.

Statistical Methods

- This is the second of 3 protocol-specified OS analyses (planned after ≈ 263 deaths)
  - Data cutoff for this prespecified interim analysis was 3 June 2019 (275 deaths)
- A hierarchical testing strategy was used; OS was to be tested under a 3-look group sequential design only if PFS results were positive
  - PFS improvement was statistically significant during the primary analysis
- Prespecified Lan DeMets (O'Brien-Fleming) stopping boundary for claiming superior efficacy was defined as $P \leq 0.01129$ from 1-sided log-rank test
  - Study had 85% power to detect a difference in OS
- During survival follow-up, descriptive, exploratory analyses were performed on PFS (including by line of therapy), time to first subsequent chemotherapy, and PFS2

CTCAE, Common Terminology Criteria for Adverse Events; OS, overall survival; PFS, progression-free survival; PFS2, time to progression on next-line therapy.

Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472.

Patient Disposition

Median follow-up time was 39.4 months

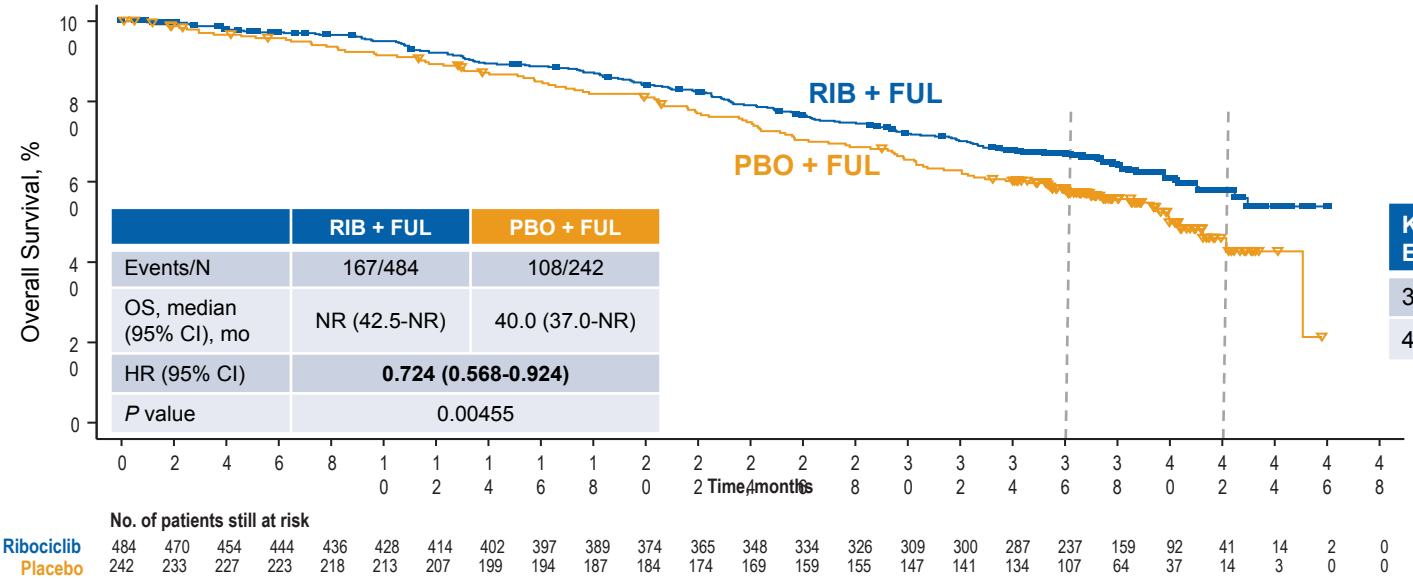
Parameter, n (%)	RIB + FUL n = 484	PBO + FUL n = 242	All Patients N = 726
Patients treated	483 (99.8)	241 (99.6)	724 (99.7)
Treatment ongoing[a]	121 (25.0)	32 (13.2)	153 (21.1)
End of treatment	362 (74.8)	209 (86.4)	571 (78.7)
Reason for end of treatment			
Progressive disease	263 (54.3)	184 (76.0)	447 (61.6)
Adverse event	43 (8.9)	9 (3.7)	52 (7.2)
Physician decision	28 (5.8)	8 (3.3)	36 (5.0)
Patient/guardian decision	26 (5.4)	6 (2.5)	32 (4.4)
Death	2 (0.4)	1 (0.4)	3 (0.4)
Protocol deviation	1 (0.2)	1 (0.4)	2 (0.3)
Technical issue	0	1 (0.4)	1 (0.1)

FUL, fulvestrant; PBO, placebo; RIB, ribociclib.

[a] At the time of data cutoff: 03 June 2019.

Overall Survival

The reduction in relative risk of death with RIB was 28%



	RIB + FUL	PBO + FUL
Events/N	167/484	108/242
OS, median (95% CI), mo	NR (42.5-NR)	40.0 (37.0-NR)
HR (95% CI)	**0.724 (0.568-0.924)**	
P value	0.00455	

Landmark Analysis

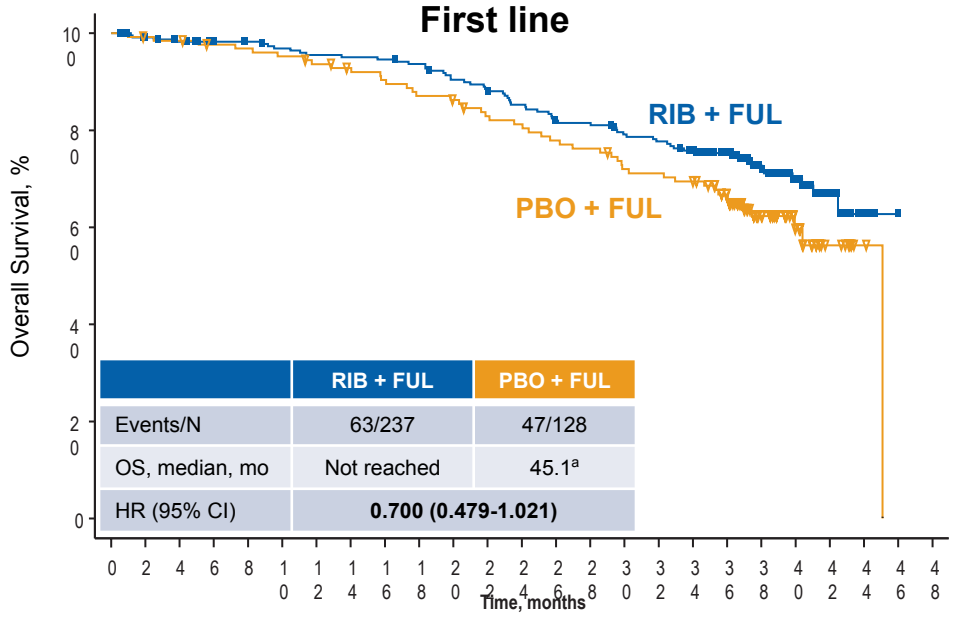
KM Estimate	RIB + FUL	PBO + FUL
36 months	67.0%	58.2%
42 months	57.8%	45.9%

- The *P* value of 0.00455 crossed the prespecified boundary to claim superior efficacy ($P < 0.01129$)

FUL, fulvestrant; HR, hazard ratio; KM, Kaplan-Meier; NR, not reached; OS, overall survival; PBO, placebo; RIB, ribociclib.

Overall Survival by Line of Therapy

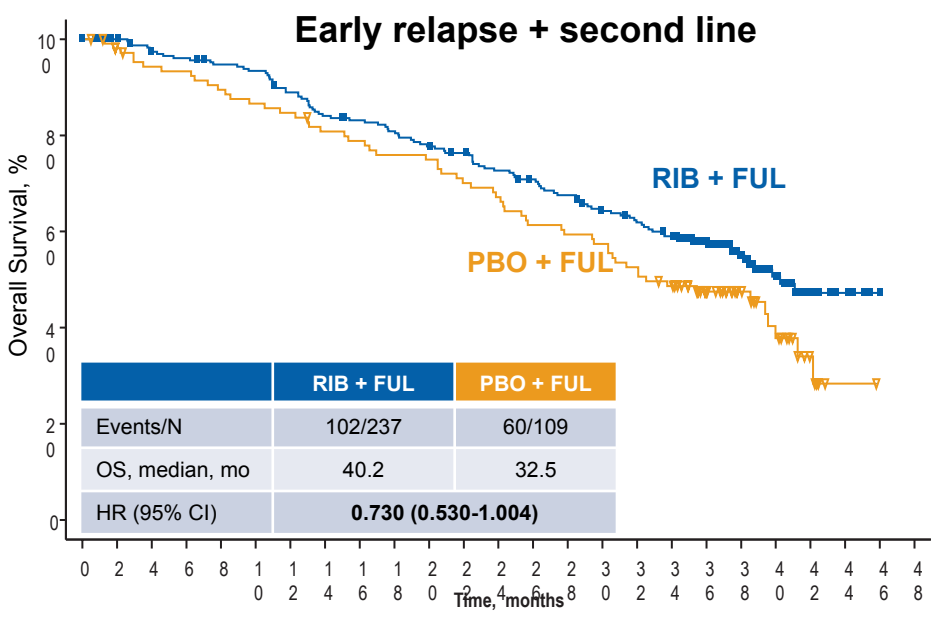
OS by line of therapy was consistent with overall population



	RIB + FUL	PBO + FUL
Events/N	63/237	47/128
OS, median, mo	Not reached	45.1[a]
HR (95% CI)	**0.700 (0.479-1.021)**	

No. of patients still at risk

Ribociclib	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	166	163	157	138	92	54	22	6	1	0
Placebo	128	126	125	122	121	119	116	113	110	106	104	99	97	93	91	85	84	82	70	40	21	8	2	0	0



	RIB + FUL	PBO + FUL
Events/N	102/237	60/109
OS, median, mo	40.2	32.5
HR (95% CI)	**0.730 (0.530-1.004)**	

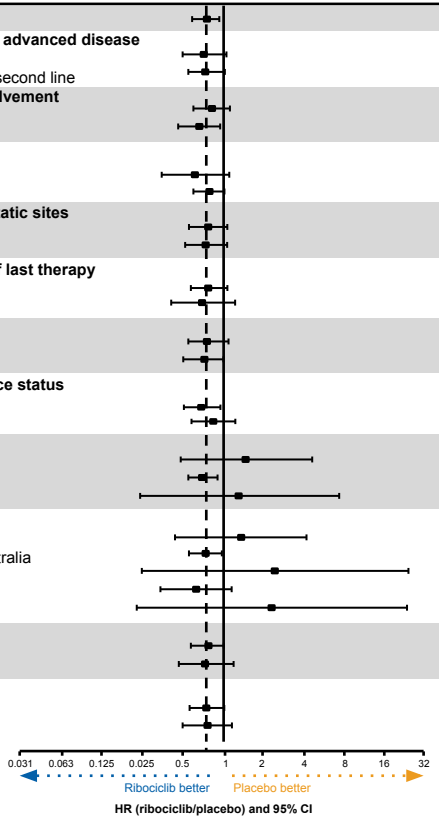
No. of patients still at risk

Ribociclib	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

FUL, fulvestrant; HR, hazard ratio; OS, overall survival; PBO, placebo; RIB, ribociclib.

[a] This median value may not be estimated reliably due to the last patient on follow-up, who had an event at 45.1 months.

Overall Survival Subgroup Analysis

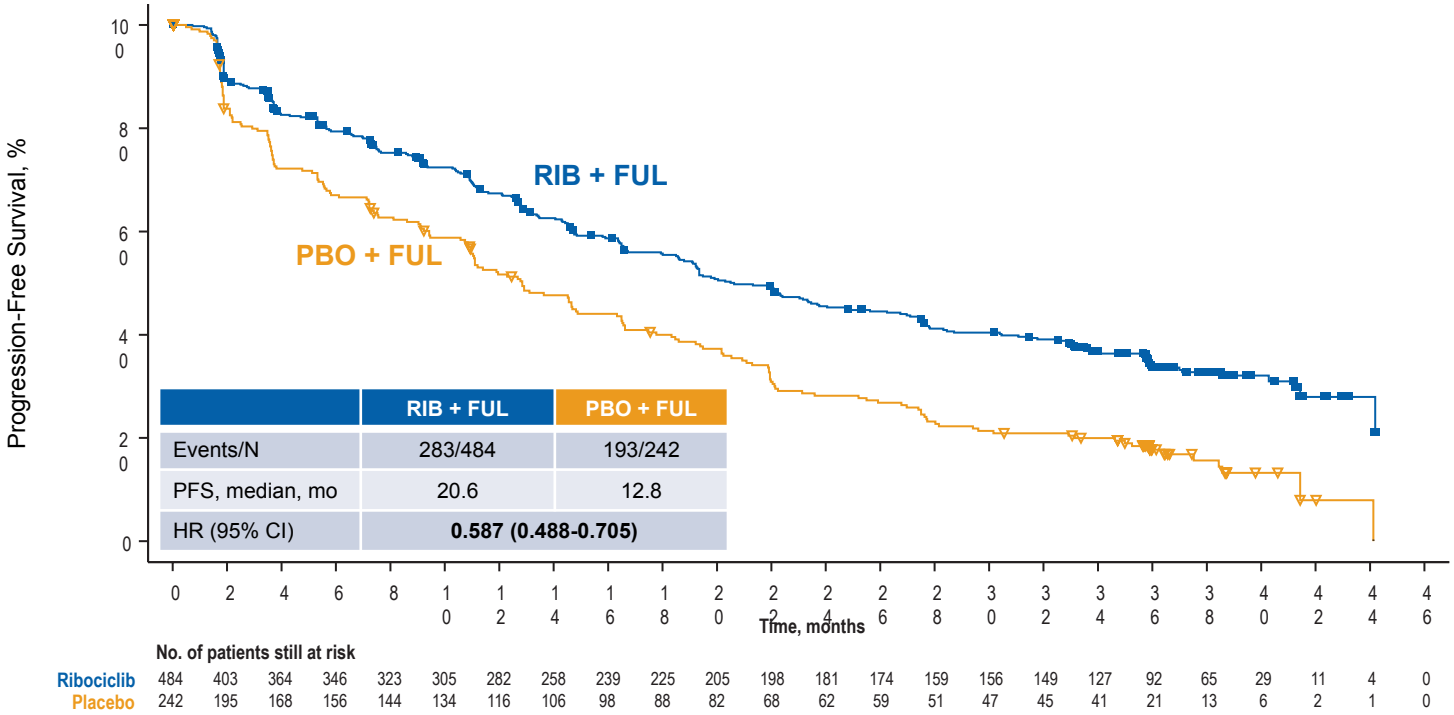


	HR (95% CI)	Ribociclib Events, n/N (%)	Placebo Events, n/N (%)
All patients	0.72 (0.57-0.92)	167/484 (34.5)	108/242 (44.6)
Treatment line for advanced disease			
First line	0.70 (0.48-1.02)	63/237 (26.6)	47/128 (36.7)
Early relapse + second line	0.73 (0.53-1.00)	102/237 (43)	60/109 (55)
Liver or lung involvement			
Yes	0.81 (0.58-1.12)	97/242 (40.1)	57/122 (46.7)
No	0.65 (0.45-0.93)	70/242 (28.9)	51/119 (42.9)
Bone lesion only			
Yes	0.60 (0.33-1.07)	27/102 (26.5)	22/51 (43.1)
No	0.76 (0.58-1.00)	140/382 (36.6)	86/190 (45.3)
Number of metastatic sites			
<3	0.75 (0.54-1.04)	93/308 (30.2)	60/147 (40.8)
≥3	0.73 (0.50-1.05)	74/176 (42)	48/94 (51.1)
Disease setting of last therapy			
(Neo-)adjuvant	0.77 (0.57-1.04)	99/264 (37.5)	72/151 (47.7)
Metastatic	0.69 (0.40-1.20)	45/112 (40.2)	19/42 (45.2)
Age, years			
<65	0.76 (0.54-1.07)	85/258 (32.9)	54/129 (41.9)
≥65	0.7 (0.49-1.00)	82/226 (36.3)	54/113 (47.8)
ECOG performance status			
0	0.67 (0.48-0.92)	92/311 (29.6)	64/158 (40.5)
1	0.81 (0.56-1.19)	74/172 (43)	44/83 (53)
Race			
Asian	1.42 (0.46-4.33)	15/45 (33.3)	4/18 (22.2)
White	0.68 (0.52-0.88)	137/407 (33.7)	99/214 (46.3)
Other	1.26 (0.23-6.83)	9/17 (52.9)	2/5 (40)
Region			
Asia	1.31 (0.42-4.06)	13/40 (32.5)	4/16 (25)
Europe and Australia	0.72 (0.54-0.96)	123/347 (35.4)	79/173 (45.7)
Latin America	2.33 (0.24-22.8)	4/6 (66.7)	1/3 (33.3)
North America	0.60 (0.33-1.12)	22/69 (31.9)	23/43 (53.5)
Other	2.22 (0.22-22.7)	5/22 (22.7)	1/7 (14.2)
PgR			
+	0.74 (0.55-1.00)	118/353 (33.4)	72/167 (43.1)
–	0.72 (0.45-1.15)	40/113 (35.4)	32/69 (46.4)
ER/PR			
Double positive	0.73 (0.54-0.98)	115/350 (32.9)	72/167 (43.1)
Other	0.74 (0.48-1.13)	52/134 (38.8)	36/74 (48.6)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy; HR, hazard ratio; PgR, progesterone receptor.
Solid line shows no effect point, and dotted line shows overall treatment effect point. HR (95% CI) is based on Cox proportional hazards model stratified by lung and/or liver metastasis and previous ET per IRT. Exception: For subgroup analyses related to stratification factors, unstratified models are used. Subgroups are based on CRF.

Progression-Free Survival: Overall Population

Descriptive analysis of PFS consistent with primary report

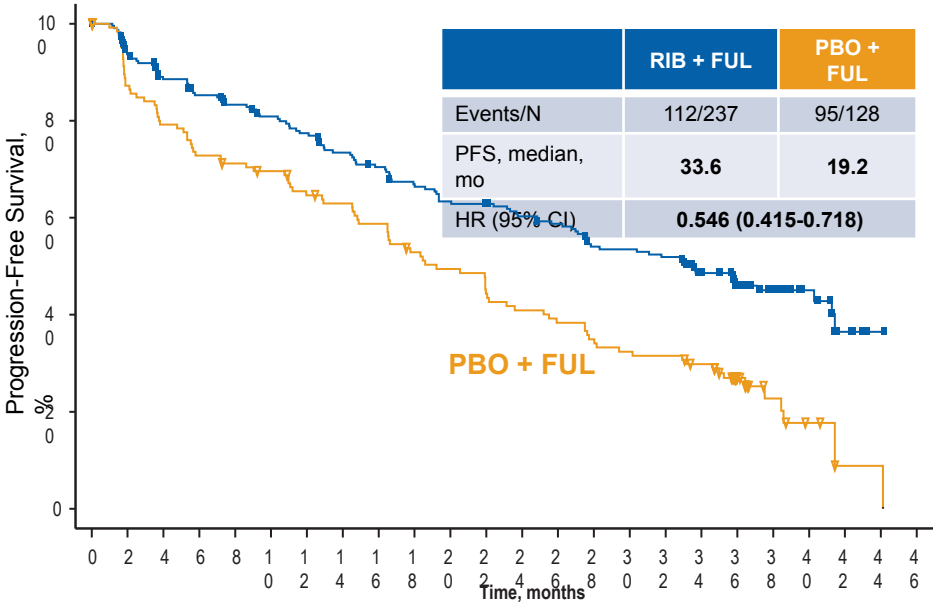


FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Progression-Free Survival by Line of Therapy

Median PFS for RIB + FUL is now reached in first line (33.6 months)

First line

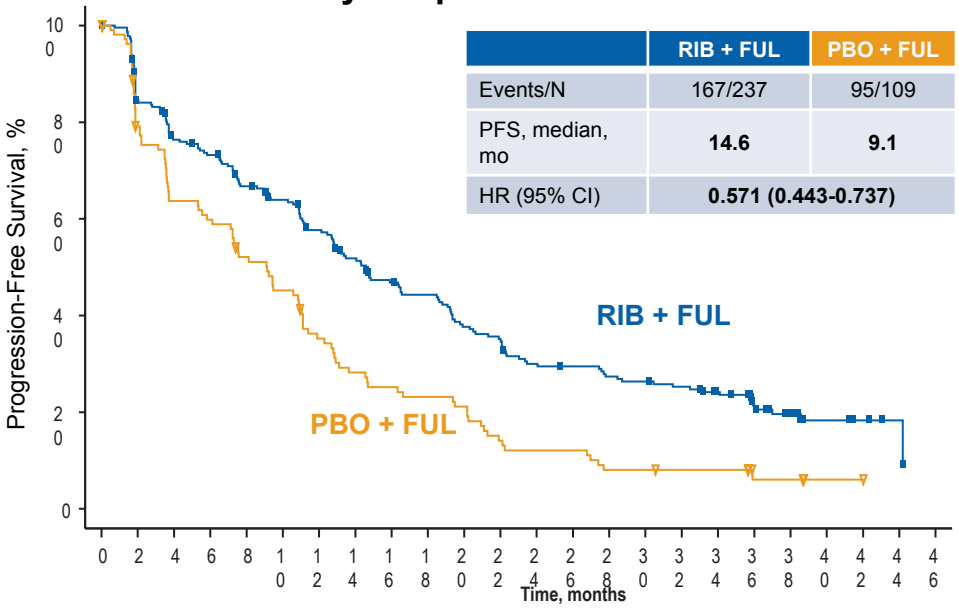


	RIB + FUL	PBO + FUL
Events/N	112/237	95/128
PFS, median, mo	**33.6**	**19.2**
HR (95% CI)	**0.546 (0.415-0.718)**	

No. of patients still at risk

Ribociclib	237	204	187	178	171	164	157	147	140	132	125	123	117	113	102	101	98	84	63	44	20	7	2	0
Placebo	128	109	99	91	88	85	78	75	70	62	58	52	48	45	41	38	37	33	17	9	5	1	1	0

Early relapse + second line



	RIB + FUL	PBO + FUL
Events/N	167/237	95/109
PFS, median, mo	**14.6**	**9.1**
HR (95% CI)	**0.571 (0.443-0.737)**	

No. of patients still at risk

Ribociclib	237	189	168	160	144	134	119	105	93	87	74	69	58	56	52	50	47	41	27	19	9	4	2	0
Placebo	109	82	66	62	53	46	35	28	25	23	21	14	12	12	8	8	7	7	3	3	1	1	0	0

FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Subsequent Therapy After Discontinuation

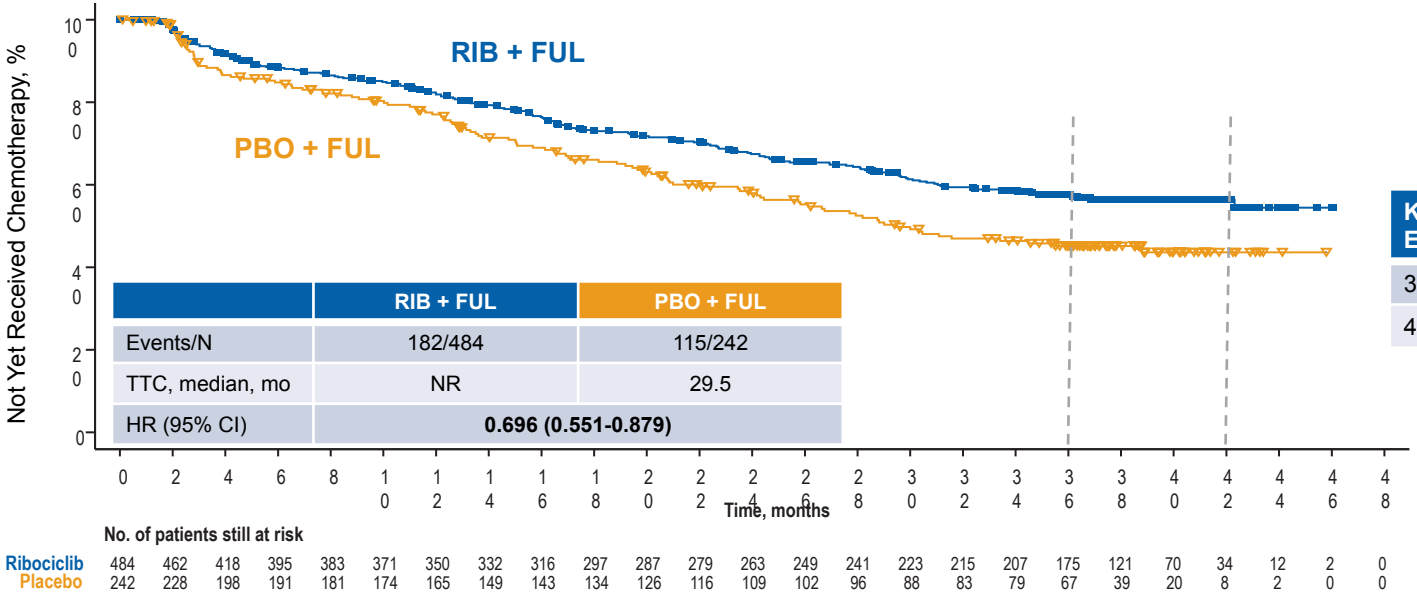
First Subsequent Therapy After Discontinuation by Type, n (%)[a]	RIB + FUL n = 484 n discontinued = 362	PBO + FUL n = 242 n discontinued = 209
Any medication	295 (81.5)	177 (84.7)
Chemotherapy alone	84 (23.2)	42 (20.1)
Chemotherapy + hormone therapy/other[b]	46 (12.7)	33 (15.8)
Hormone therapy alone	94 (26.0)	38 (18.2)
Hormone therapy + other[c]	66 (18.2)	61 (29.2)
Targeted therapy alone	5 (1.4)	3 (1.4)

- CDK4/6 inhibitors as any line of subsequent therapy after discontinuation were received by 11% of patients in the RIB arm and 25% of patients in the PBO arm

CDK4/6i, cyclin-dependent kinase inhibitor; FUL, fulvestrant; PBO, placebo; RIB, ribociclib.
[a] For all rows, patients counted only once in each medication type, and categories are mutually exclusive except for CDK4/6 inhibitors; percentages are based on the number of patients who discontinued. [b] Includes patients who received chemotherapy + any nonchemotherapy. [c] Includes patients who received hormonal therapy + other without chemotherapy.

Time to First Chemotherapy

Time to first chemotherapy was longer with RIB + FUL



	RIB + FUL	PBO + FUL
Events/N	182/484	115/242
TTC, median, mo	NR	29.5
HR (95% CI)	**0.696 (0.551-0.879)**	

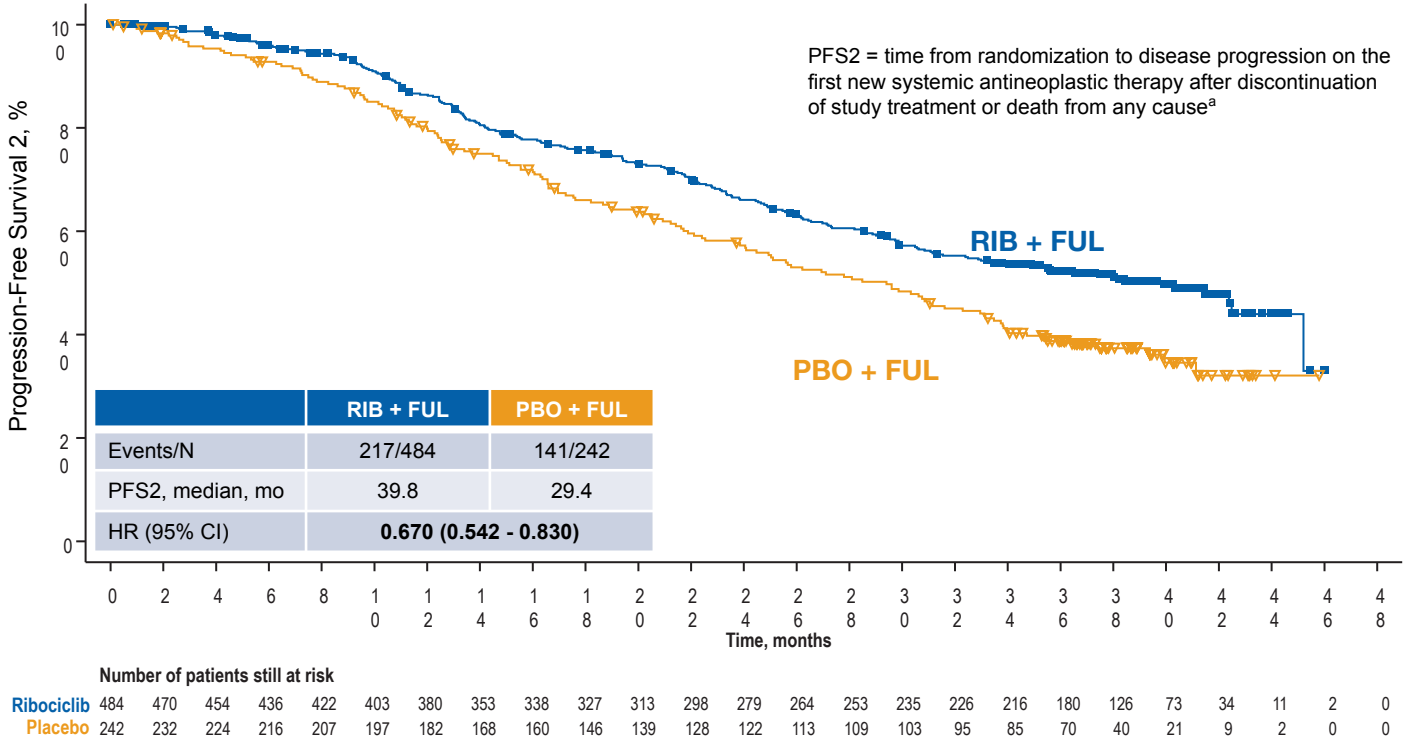
Landmark analysis

KM Estimate	RIB + FUL	PBO + FUL
36 months	57.4%	45.2%
42 months	56.4%	43.7%

FUL, fulvestrant; HR, hazard ratio; NR, not reached; PBO, placebo; RIB, ribociclib; TTC, time to first chemotherapy.

Progression-Free Survival 2

RIB + FUL demonstrated a 10-month improvement in PFS2



	RIB + FUL	PBO + FUL
Events/N	217/484	141/242
PFS2, median, mo	39.8	29.4
HR (95% CI)	**0.670 (0.542 - 0.830)**	

FUL, fulvestrant; HR, hazard ratio; PBO, placebo; PFS2, time to first progression on next-line therapy or death; RIB, ribociclib.

[a] The first documented progression on next-line treatment was based on investigator assessment of progressive disease.

Safety Summary

- After approximately 40 months of follow-up, no new safety signals were observed
- For this analysis, the rates of key grade 3/4 adverse events of special interest in the RIB and PBO arms, respectively, were:
  - Neutropenia, 57.1% and 0.8%
  - Hepatobiliary toxicity, 13.7% and 5.8%
  - Respiratory disorders, 2.3% and 3.3%
    - Interstitial lung disease, 0.2% and 0%
  - QTc prolongation, 3.1% and 1.2%
    - No episodes of Torsades de Pointes were observed

PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Conclusions

- MONALEESA-3 demonstrated a statistically significant OS benefit with ribociclib + fulvestrant vs placebo + fulvestrant, with a 28% reduction in the relative risk of death (hazard ratio: 0.724; 95% CI, 0.568-0.924; *P* = 0.00455)
  - OS benefit was consistent across patient subgroups
- Improvements in PFS2 and time to chemotherapy suggest that the benefit of ribociclib may extend beyond the study treatment
- Safety profile remains consistent with longer exposure; no new signals were identified
- The combined data set of MONALEESA-3 and -7 (approximately 1400 patients) represents the largest body of evidence of OS benefit for any CDK4/6 inhibitor
  - These data demonstrate a consistent, meaningful prolongation of survival with ribociclib with multiple ET partners, regardless of menopausal status and line of therapy

1L, first line; ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; FUL, fulvestrant; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not reached; OS, overall survival; PBO, placebo; PFS, progression-free survival; PFS2, time to first progression on next-line therapy; RIB, ribociclib.

Acknowledgments

We thank the patients who participated in this trial, their families and caregivers, data monitoring committee members, study steering committee members, and staff who assisted with the trial at each site.

We also thank the team that supported this trial, including Tim Cartwright, Xunwei Dong, Kamisha Dowling, Annie Hilliard, Rajani Masineni, Yogesh Mugutrao, Eva Vagnon, Rahul Tyagi, Li Wang, and Balachander Chellamuthu.

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

2021 ASCO ANNUAL MEETING

UPDATED OVERALL SURVIVAL (OS) RESULTS FROM THE PHASE III MONALEESA-3 TRIAL OF POSTMENOPAUSAL PATIENTS (PTS) WITH HR+/HER2− ADVANCED BREAST CANCER (ABC) TREATED WITH FULVESTRANT (FUL) ± RIBOCICLIB (RIB)

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June 5, 2021

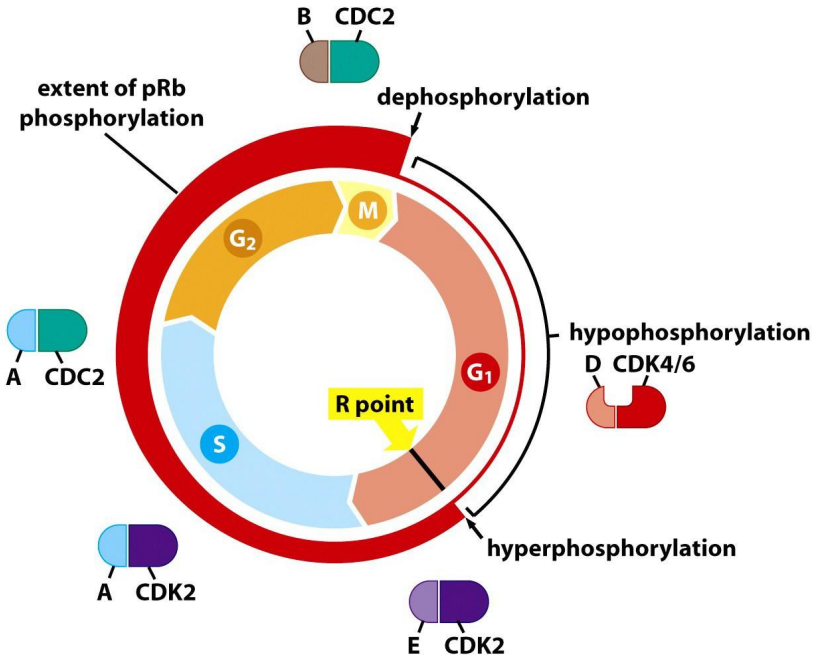
ES2105314043

Disclosure

Dennis J. Slamon

- Leadership: BioMarin
- Stock and Other Ownership Interests: Pfizer, Merck, Amgen, Vertex, BioMarin
- Honoraria: Novartis
- Consulting or Advisory Role: Lilly, Novartis
- Research Funding: Novartis, Pfizer
- Travel, Accommodations, Expenses: BioMarin, Novartis, Pfizer

Rb as a Master Regulator of the G1/S Checkpoint[1]



- Protein kinases control cell cycle progression and rely on associations with regulatory subunits called cyclins
- Cyclin-dependent kinases (CDK) 4/6 associate with cyclin D and hyperphosphorylate Rb
- Hyperphosphorylation of Rb inactivates Rb and allows the cell to progress from G1 to S phase
- P16 inhibits the CDK4/6-cyclin D complex

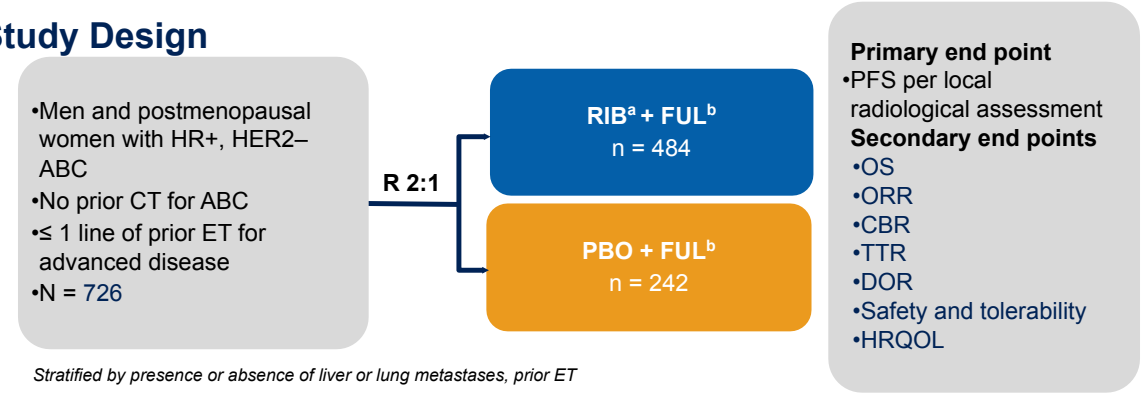
Can inhibiting CDK4/6-cyclin D prevent hyperphosphorylation of Rb and thereby prevent cell cycle progression?

1. Weinberg RA. The Biology of Cancer, First Edition. W.W. Norton; 2006. Reprinted with permission of W. W. Norton & Company, Inc.

Background

- The MONALEESA-3 trial evaluating ribociclib + fulvestrant in postmenopausal patients with HR+/HER2– ABC previously demonstrated a significant PFS and OS benefit over fulvestrant alone[1,2]
  - Median OS in the final protocol-specified OS analysis was not reached in the ribociclib arm and was 40.0 months in the placebo arm (hazard ratio, 0.72; 95% CI, 0.57-0.92; *P* = 0.00455)[2]
- **Here we report an exploratory update of OS with longer follow-up (median follow-up, 56.3 months)**

MONALEESA-3 Study Design



Stratified by presence or absence of liver or lung metastases, prior ET

ABC, advanced breast cancer; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.
[a] 600 mg/day (3 weeks on, 1 week off).
[b] 500 mg/28 days (1 additional dose on cycle 1 day 15).
1. Slamon DJ, et al. *J Clin Oncol*. 2018;24:2465-2472. 2. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524.

Patient Disposition

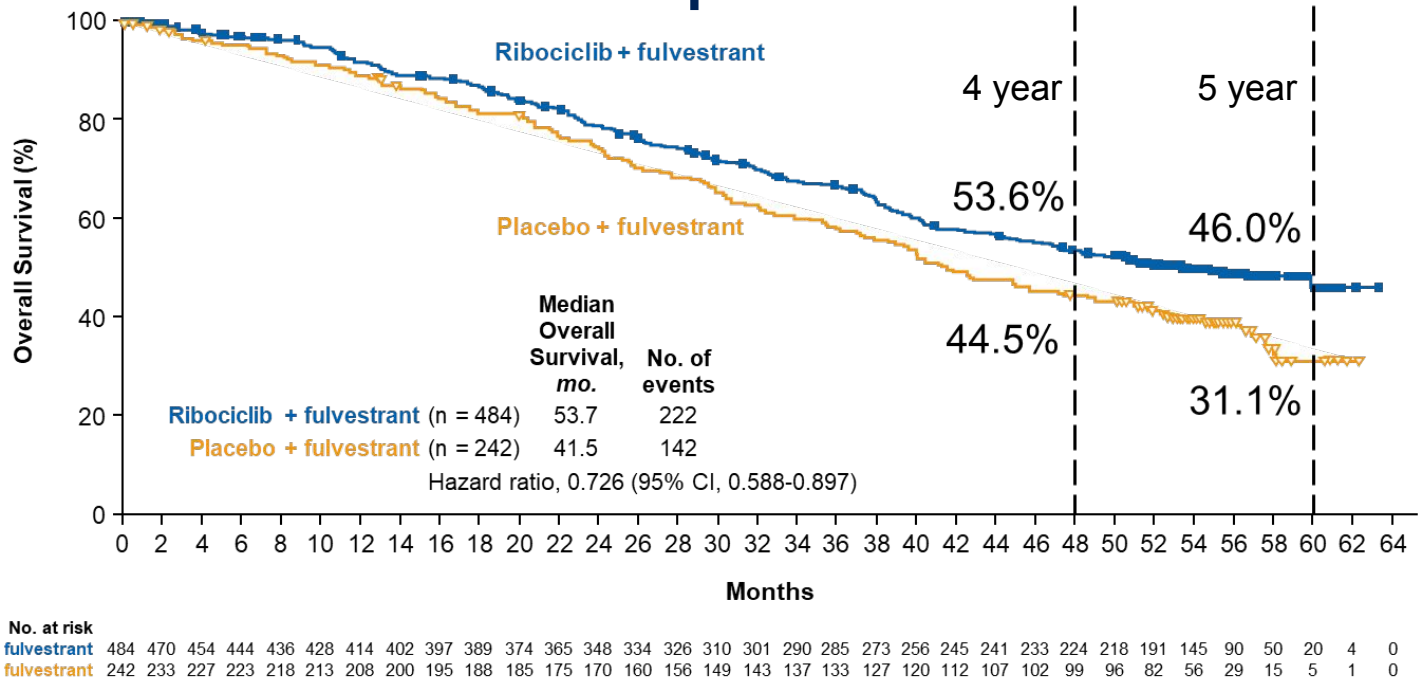
Parameter, n (%)	Ribociclib + Fulvestrant (n = 484)	Placebo + Fulvestrant (n = 242)	All Patients (N = 726)
Patients randomized			
Untreated	1 (0.2)	1 (0.4)	2 (0.3)
Treated	483 (99.8)	241 (99.6)	724 (99.7)
Patients treated			
Treatment ongoing[a]	68 (14.0)	21 (8.7)	89 (12.3)
End of treatment	415 (85.7)	220 (90.9)	635 (87.5)
Reason for end of treatment			
Progressive disease	299 (61.8)	193 (79.8)	492 (67.8)
Adverse event	49 (10.1)	9 (3.7)	58 (8.0)
Patient/guardian decision	33 (6.8)	7 (2.9)	40 (5.5)
Physician decision	32 (6.6)	9 (3.7)	41 (5.6)
Death	2 (0.4)	1 (0.4)	3 (0.4)
Protocol deviation	1 (0.2)	1 (0.4)	2 (0.3)
Technical problems	0	1 (0.4)	1 (0.1)
Entered survival follow-up[b]	352 (84.8)	203 (92.3)	555 (87.4)

Data cutoff: October 30, 2020.

[a] Patients continuing study treatment at cutoff.

[b] The percentages of patients who entered survival follow-up use the number of patients with end of treatment as the denominator.

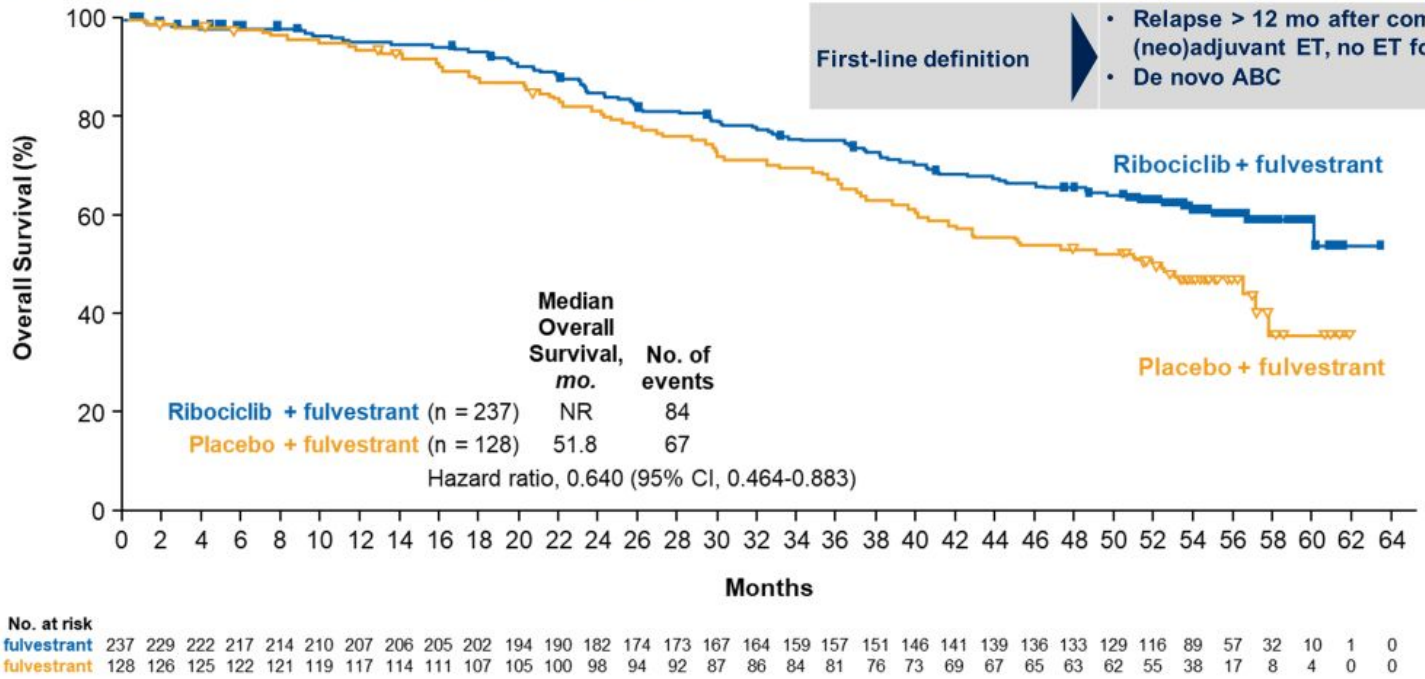
Overall Survival in the Overall Population



- With an extended follow-up of > 4 years, ribociclib + fulvestrant continued to demonstrate a clinically relevant > 1 year OS benefit compared with placebo + fulvestrant

Data cutoff: October 30, 2020.
OS, overall survival.

Overall Survival in Patients Treated in the First-line Setting

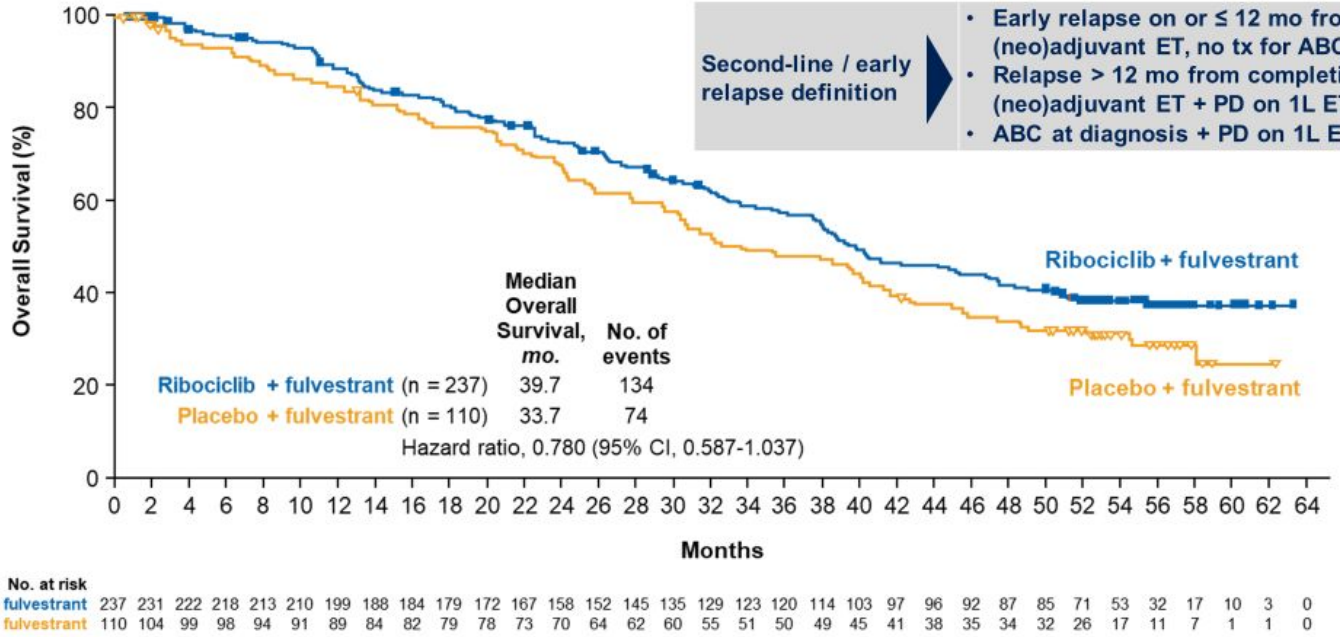


- A larger magnitude of benefit of ribociclib + fulvestrant over placebo + fulvestrant in the first-line setting was observed compared with the prior reported data cutoff for OS (HR, 0.70; 95% CI, 0.48-1.02)[1]

Data cutoff: October 30, 2020.
ET, endocrine therapy; OS, overall survival.

1. Slamon DJ, et al. *N Engl J Med*. 2020;382:514-524.

Overall Survival in Patients Treated in the Second-line Setting or who had Early Relapse

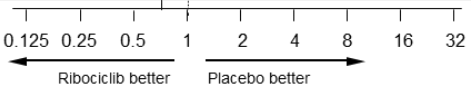


- Ribociclib + fulvestrant demonstrated a 6-month longer median OS over placebo + fulvestrant in the second-line setting

Data cutoff: October 30, 2020.
ET, endocrine therapy; OS, overall survival.

Overall Survival in Relevant Patient Subgroups

Subgroup	Ribociclib + Fulvestrant *No. of deaths/total no. (%)*	Placebo + Fulvestrant	Hazard Ratio (95% CI)
All patients	222/484 (45.9)	142/242 (58.7)	0.73 (0.59-0.90)
Treatment line of ET for advanced disease			
First line	84/237 (35.4)	67/128 (52.3)	0.64 (0.46-0.88)
Early relapse or second line	134/237 (56.5)	74/110 (67.3)	0.78 (0.59-1.04)
Liver or lung involvement			
Yes	118/242 (48.8)	77/122 (63.1)	0.73 (0.55-0.98)
No	104/242 (43.0)	65/119 (54.6)	0.74 (0.54-1.01)
Bone lesion only			
Yes	45/102 (44.1)	29/51 (56.9)	0.67 (0.42-1.08)
No	177/382 (46.3)	113/190 (59.5)	0.74 (0.58-0.93)
No.of metastasis sites			
< 3	132/308 (42.9)	84/147 (57.1)	0.73 (0.55-0.96)
≥ 3	90/176 (51.1)	58/94 (61.7)	0.74 (0.53-1.04)
Most recent therapy			
(Neo)adjuvant	130/264 (49.2)	94/152 (61.8)	0.78 (0.60-1.01)
Metastatic	57/112 (50.9)	25/41 (61.0)	0.67 (0.42-1.09)
Age			
< 65 Years	116/258 (45.0)	75/129 (58.1)	0.73 (0.54-0.97)
≥ 65 Years	106/226 (46.9)	67/113 (59.3)	0.72 (0.53-0.99)
Prior endocrine therapy			
Endocrine naive	48/139 (34.5)	39/74 (52.7)	0.62 (0.41-0.95)
Endocrine resistance	34/53 (64.2)	18/25 (72.0)	0.82 (0.45-1.47)
Endocrine sensitive	139/289 (48.1)	85/140 60.7)	0.73 (0.56-0.96)

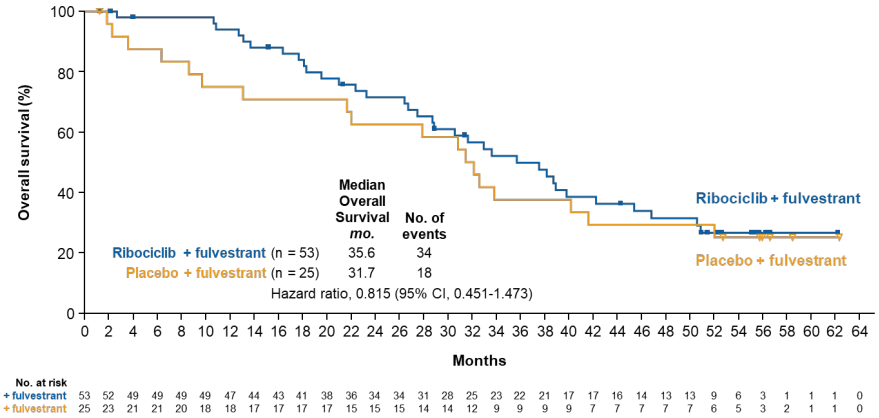


- A consistent OS benefit was observed across most subgroups, including harder-to-treat patients, eg, patients with liver/lung metastases, ≥ 3 metastatic sites, and endocrine resistance

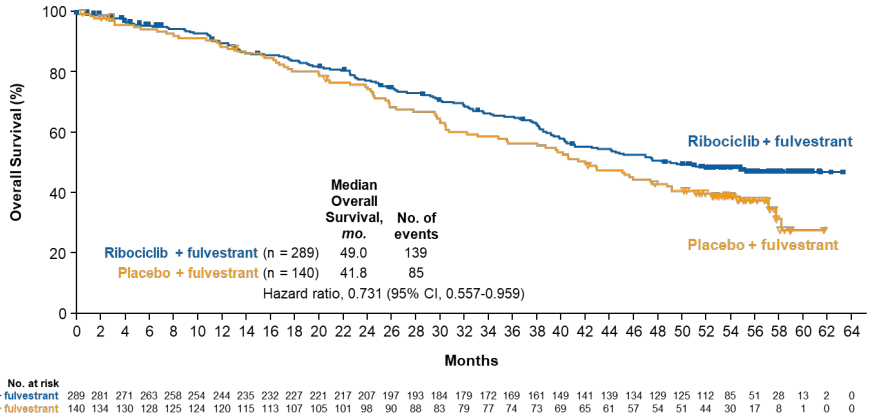
Data cutoff: October 30, 2020.
ET, endocrine therapy; OS, overall survival.

Overall Survival by Endocrine Sensitivity

Endocrine-resistant[a] population



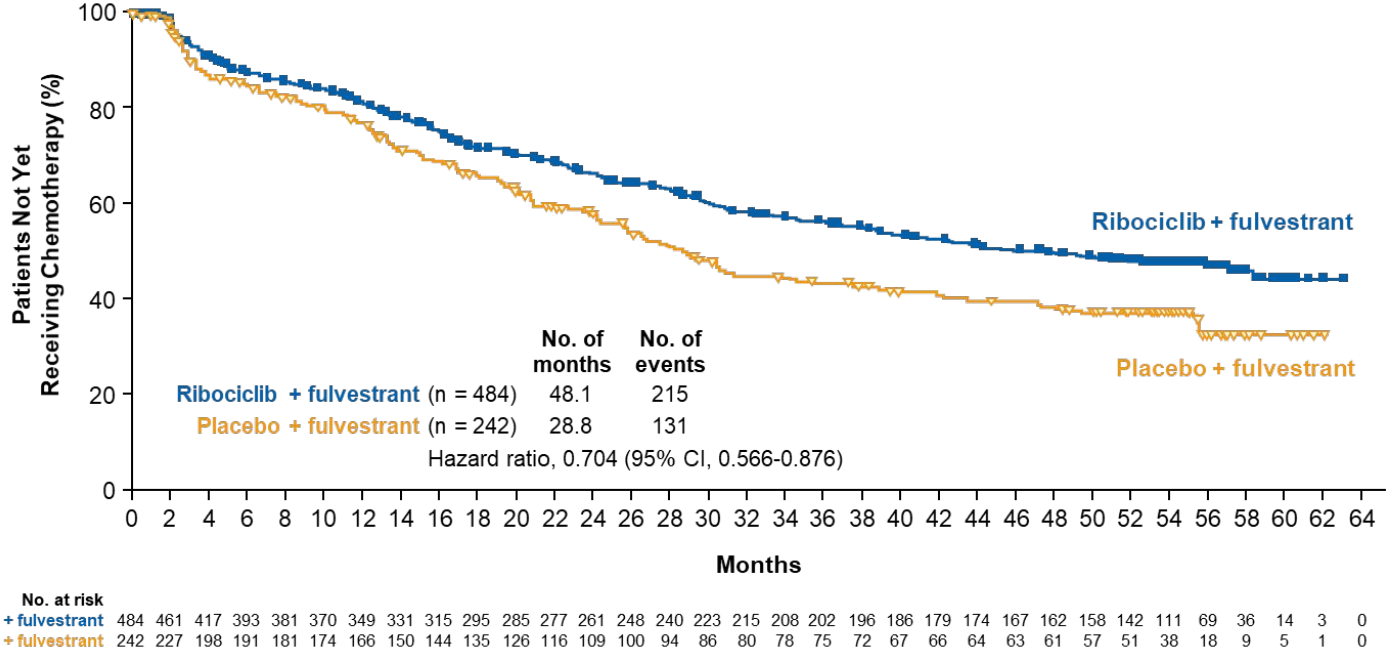
Endocrine-sensitive[b] population



- Ribociclib + fulvestrant prolonged median OS over placebo + fulvestrant in patients who were sensitive to ET as well as those who were resistant to ET

Data cutoff: October 30, 2020.
ET, endocrine therapy; OS, overall survival.
[a] Patients with progressive disease within the first 6 months of first-line ET for ABC while on ET or patients with relapse within the first 2 years of (neo)adjuvant therapy.
[b] Patients who received prior ET for ABC who did not have progressive disease within the first 6 months of first-line ET for ABC while on ET and did not relapse within the first 2 years of (neo)adjuvant therapy.

Time to First Chemotherapy[a]

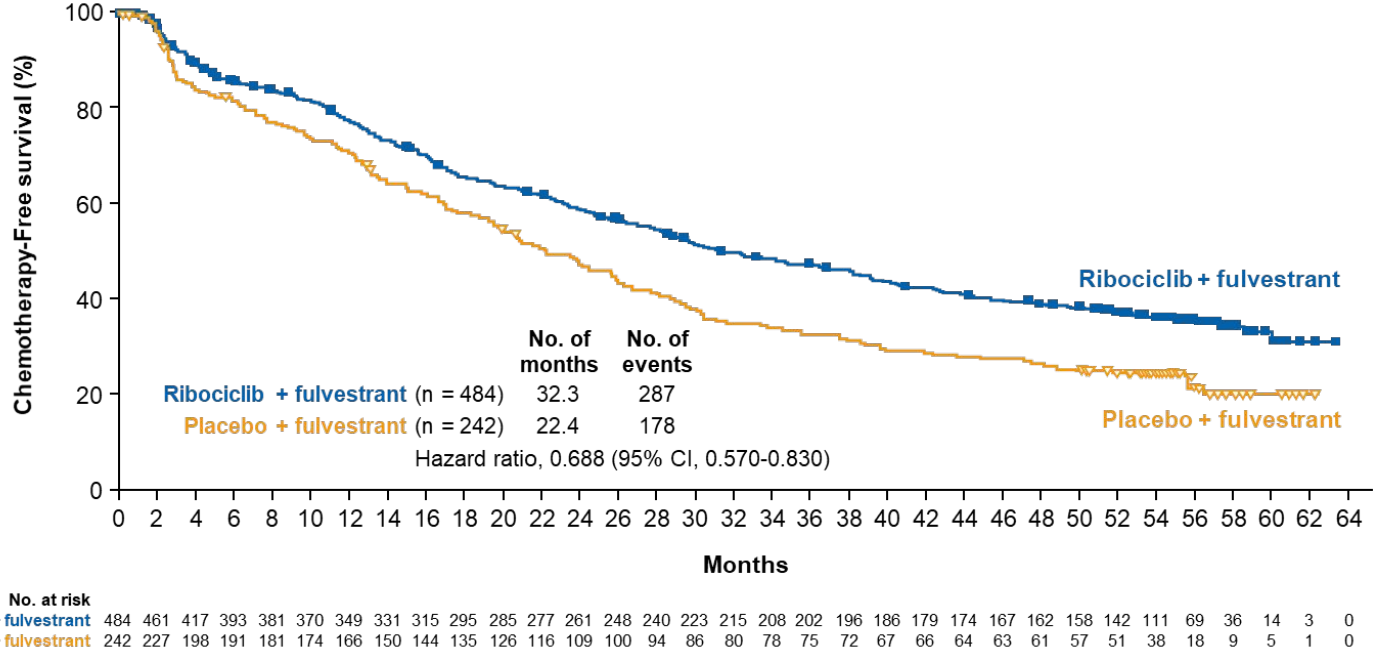


- Ribociclib + fulvestrant was associated with a nearly 20-month delay in first subsequent chemotherapy use over placebo + fulvestrant

Data cutoff: October 30, 2020.

[a] Time to first chemotherapy was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen, with death being censored.

Chemotherapy-Free Survival[a]

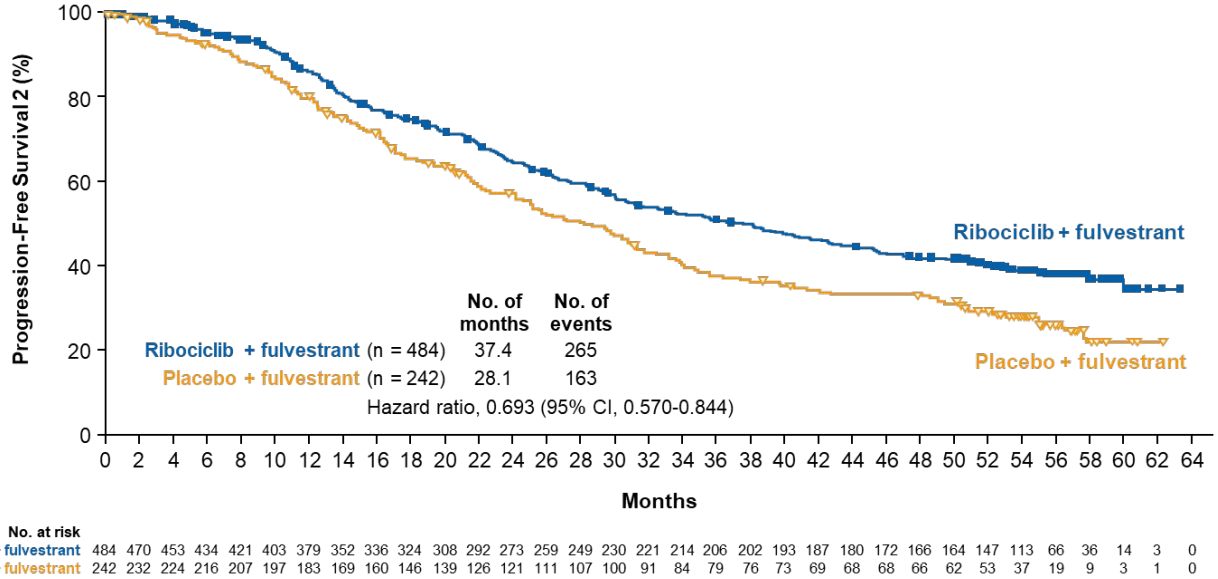


- Chemotherapy-free survival was approximately 10 months longer with ribociclib + fulvestrant over placebo + fulvestrant

Data cutoff: October 30, 2020.

[a] Chemotherapy-free survival was defined as the time from randomization to the beginning of the first chemotherapy or death after discontinuation of the trial regimen.

PFS2[a] in All Patients



- A longer PFS2 was observed for patients receiving ribociclib + fulvestrant vs placebo + fulvestrant, demonstrating that patients had improved benefit beyond disease progression
- This benefit was observed regardless of treatment setting, but was especially notable in the first-line setting (HR, 0.63; 95% CI, 0.47-0.84)

Data cutoff: October 30, 2020.
PFS2, progression-free survival 2.
[a] PFS2 was defined as the time from randomization to the first documented disease progression (physician reported) while the patient was receiving subsequent antineoplastic therapy or death from any cause, whichever occurred first.

Subsequent Antineoplastic Therapies

Variable	Ribociclib + Fulvestrant n = 484	Placebo + Fulvestrant n = 242
No. of patients who discontinued the trial regimen	415	220
Patients who received any subsequent therapy, n (%)	340 (81.9)	190 (86.4)
First subsequent antineoplastic therapy		
Chemotherapy alone	96 (23.1)	44 (20.0)
Chemotherapy plus hormone therapy or other therapy[a]	36 (8.7)	29 (13.2)
Hormone therapy alone	115 (27.7)	47 (21.4)
Hormone therapy plus other therapy[b]	88 (21.2)	69 (31.4)
Targeted therapy alone	5 (1.2)	1 (0.5)
Patients who received any subsequent CDK4/6 inhibitor, n (%)	58 (14.0)	66 (30.0)
Palbociclib	36 (8.7)	52 (23.6)
Ribociclib	14 (3.4)	11 (5.0)
Abemaciclib	10 (2.4)	5 (2.3)

- Among patients who discontinued study treatment, 81.9% and 86.4% received a next-line subsequent antineoplastic therapy, with 14.0% and 30.0% receiving a CDK4/6 inhibitor as ***any*** subsequent line in the ribociclib vs placebo arms, respectively

Data cutoff: October 30, 2020.
CDK4/6, cyclin-dependent kinase 4/6.
[a] This category includes patients who received chemotherapy in combination with any non-chemotherapy.
[b] This category includes patients who received hormone therapy plus another medication without chemotherapy.

Adverse Events of Special Interest

	Ribociclib + Fulvestrant n = 483			Placebo + Fulvestrant n = 241		
AESI grouping[a]	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hematologic AESIs, n (%)						
Neutropenia	348 (72.0)	245 (50.7)	36 (7.5)	9 (3.7)	2 (0.8)	0
Leukopenia	157 (32.5)	79 (16.4)	3 (0.6)	4 (1.7)	0	0
Anemia	97 (20.1)	19 (3.9)	0	21 (8.7)	7 (2.9)	0
Thrombocytopenia	45 (9.3)	5 (1.0)	1 (0.2)	6 (2.5)	0	0
Other	2 (0.4)	1 (0.2)	0	0	0	0
Nonhematologic AESIs, n (%)						
Infections	283 (58.6)	39 (8.1)	0	108 (44.8)	10 (4.1)	0
Pulmonary toxicity[a]	184 (38.1)	10 (2.1)	2 (0.4)	77 (32.0)	7 (2.9)	1 (0.4)
Interstitial lung disease/ pneumonitis	10 (2.1)	2 (0.4)	0	2 (0.8)	0	0
Hepatobiliary toxicity	117 (24.2)	51 (10.6)	16 (3.3)	43 (17.8)	13 (5.4)	2 (0.8)
Renal toxicity	64 (13.3)	7 (1.4)	1 (0.2)	13 (5.4)	0	0
QT interval prolongation	41 (8.5)	14 (2.9)	1 (0.2)	5 (2.1)	3 (1.2)	0
Pulmonary embolism	27 (5.6)	13 (2.7)	1 (0.2)	15 (6.2)	8 (3.3)	1 (0.4)
Reproductive toxicity	2 (0.4)	0	0	1 (0.4)	0	0

- Adverse events were consistent with those in previous analyses of MONALEESA-3

Data cutoff: October 30, 2020.
AESI, adverse event of special interest.
[a] This category includes respiratory disorders.

Conclusions

- In this exploratory analysis with an extended median follow-up of 56.3 months, ribociclib + fulvestrant maintained the OS benefit in postmenopausal patients with HR+/HER2– ABC, and this benefit was consistent across most patient subgroups and settings
  - With ribociclib + fulvestrant vs fulvestrant alone, median OS was 53.7 vs 41.5 months (hazard ratio, 0.73; 95% CI, 0.59-0.90)
- MONALEESA-3 remains the only randomized trial evaluating a CDK4/6i to demonstrate an OS benefit in postmenopausal patients with HR+/HER2– ABC treated in the first-line[a] setting
- Ribociclib + fulvestrant delayed the use of subsequent chemotherapy and prolonged the chemotherapy-free survival compared with fulvestrant alone
- An improvement in PFS2 was observed with ribociclib + fulvestrant compared with fulvestrant alone; this effect was observed regardless of line of treatment
- In general, rates and choice of immediate subsequent therapy were similar in both arms
  - Subsequent CDK4/6i at any time was lower in patients treated with ribociclib + fulvestrant vs fulvestrant alone; despite this, the OS benefit of ribociclib + fulvestrant vs fulvestrant alone was still evident
- No new safety signals were detected at a follow-up of ≈ 4.5 years

ABC, advanced breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS2, progression-free survival 2.

[a] The first-line category in MONALEESA-3 included patients with newly diagnosed ABC and patients that relapsed >12 months from completion of (neo)adjuvant ET with no treatment for advanced or metastatic disease.

Acknowledgments

We thank the patients who participated in these trials, their families and caregivers, data monitoring committee members, study steering committee members, investigators, and staff who assisted with the trials at each site.

We also thank the team that supported this analysis. Writing assistance was provided by MediTech Media, funded by Novartis.

2021 ASCO ANNUAL MEETING

ANNALS OF ONCOLOGY
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Full Publication Available in Annals of Oncology

La certeza de ofrecer más vida[1,2,3]

KISQALI OVERALL SURVIVAL – MONALEESA-7

ASCO 2019 (final analysis)
SABCS 2020 (updated analysis)

▼ KISQALI® ribociclib

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ES2201245179

▼ Este medicamento está sujeto a seguimiento adicional, es prioritaria la notificación de sospechas de reacciones adversas asociadas a este medicamento.

1. Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival results from the phase III MONALEESA-2 trial of postmenopausal patients with HR+/HER2− advanced breast cancer treated with endocrine therapy ± ribociclib. Presented at: 2021 European Society for Medical Oncology; September 16-21, 2021. **2.** Slamon D, Neven P, Chia S, et al. Updated overall survival (OS) results from the Phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2− advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). ASCO Annual Meeting 2021 **3.** Tripathy D, Im S-A, Colleoni M, et al. Updated overall survival (OS) results from the phase III MONALEESA-7 trial of pre- or perimenopausal patients with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib. San Antonio Breast Cancer Virtual Symposium; December; San Antonio, Texas 2020. p. PD2-04.

Phase III MONALEESA-7 Trial of Premenopausal Patients With HR+/HER2− Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib: Overall Survival Results

Sara Hurvitz,[1] Seock-Ah Im,[2] Yen-Shen Lu,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Louis Chow,[8] Joohyuk Sohn,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Arunava Chakravartty,[14] Gareth Hughes,[15] Ioannis Gounaris,[15] Karen Rodriguez Lorenc,[14] Tetiana Taran,[14] Debu Tripathy[16]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Division of Medical Senology, Istituto Europeo di Oncologia, Milan, Italy; [5]Hospital de Caridade de Ijuí, CACON, Ijuí, Brazil; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA, [7]Department of Obstetrics and Gynecology, Breast Center, Ludwig-Maximilians-University Munich, Munich, Germany; [8]Organisation for Oncology and Translational Research, Hong Kong; [9]Severance Hospital, Yonsei University Health System, Seoul, Korea; [10]Center for Breast Cancer, National Cancer Center, Gyeunggi-do, Korea; [11]Centro Oncológico Estatal, Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Mexico; [12]Institut Català d'Oncologia, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [15]Novartis Pharmaceuticals Corporation, Basel, Switzerland; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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Unmet Needs in Premenopausal Patients With Advanced Breast Cancer

- Young women with breast cancer tend to have poorer prognoses and more aggressive cancer compared with older women, yet premenopausal patients are underrepresented in clinical trials[1-3]
- Ribociclib, a CDK4/6 inhibitor, plus ET with ovarian suppression demonstrated a significantly longer PFS vs ET alone as initial ET in premenopausal patients with HR+/HER2– ABC in the MONALEESA-7 trial[4]
- **To date, there have been no reports of a statistically significant improvement in OS with the addition of a CDK4/6 inhibitor to ET**

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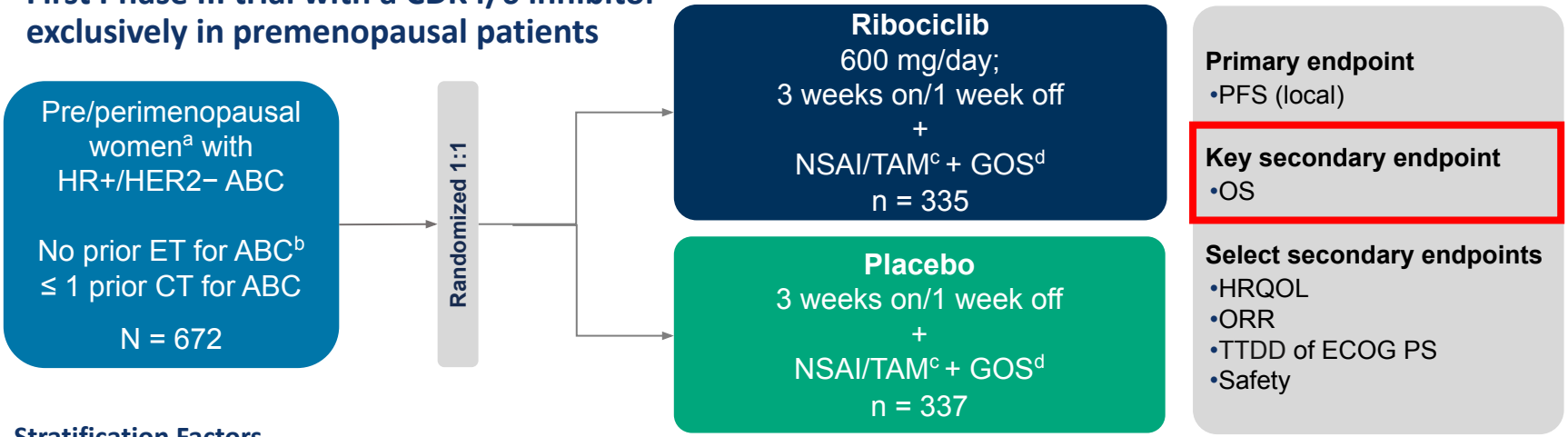
ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival; PFS, progression-free survival.

References: 1. Azim HA Jr, Partridge AH. *Breast Cancer Res*. 2014;16:427. 2. Bardia A, Hurvitz S. *Clin Cancer Res*. 2018;24:5206-5218. 3. Klijn JG, et al. *J Natl Cancer Inst*. 2000;92:903-911. 4. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

MONALEESA-7 Study Design

First Phase III trial with a CDK4/6 inhibitor exclusively in premenopausal patients



Stratification Factors

- Liver/lung metastasis (yes/no)
- Prior chemotherapy (yes/no)
- Combination partner (NSAI/TAM)"

"Combination with Tamoxifen is not approved and reimboursed in Spain.

ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxifen; TTDD, time to definitive deterioration.

[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must be in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg. and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.

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Statistical Methods

- A hierarchical testing strategy was used; OS to be tested under a 3-look group sequential design only if PFS results were positive
- PFS improvement was statistically significant during the primary analysis
  - Median PFS was 23.8 months in ribociclib + ET arm and 13.0 months in ET only arm (HR, 0.55 [95% CI, 0.44-0.69]; $P < .0001$)
- OS was the key secondary endpoint; this prespecified interim analysis took place after 192 deaths
- Prespecified Lan DeMets (O'Brien-Fleming) stopping boundary for claiming superior efficacy was defined as $P \leq .01018$
- Study had 80% power to detect a difference in OS

Reference: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

Key Patient Baseline Characteristics

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)
Age (range), years	43 (25-58)	45 (29-58)
Race, n (%)		
White	187 (56)	201 (60)
Asian	99 (30)	99 (29)
Black	10 (3)	9 (3)
Other/unknown	39 (12)	28 (8)
ECOG PS, n (%)[a]		
0	245 (73)	255 (76)
1	87 (26)	78 (23)
2	0	1 (< 1)
Previous neoadjuvant or adjuvant ET, n (%)		
No	208 (62)	196 (58)
Yes	127 (38)	141 (42)
Previous chemotherapy for advanced disease, n (%)	47 (14)	47 (14)

[a] Data were missing for 3 patients in each arm.

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Patient Disposition at Interim Analysis Data Cutoff

Median follow-up of 34.6 months

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)	All Patients (N = 672)
Patients treated, n (%)	335 (100)	337 (100)	672 (100)
Treatment ongoing	**116 (35)**	**57 (17)**	**173 (26)**
End of treatment	219 (65)	280 (83)	499 (74)
Reason for end of treatment, n(%)			
Adverse event	11(3)	13 (4)	24 (4)
Lost to follow-up	2(< 1)	0	2 (< 1)
Physician decision	10 (3)	22 (7)	32 (5)
Disease progression	173 (52)	230 (68)	403 (60)
Protocol deviation	0	2 (< 1)	2 (< 1)
Patient/guardian decision	20 (6)	10 (3)	30 (4)
Death	3 (< 1)	3 (< 1)	6 (< 1)

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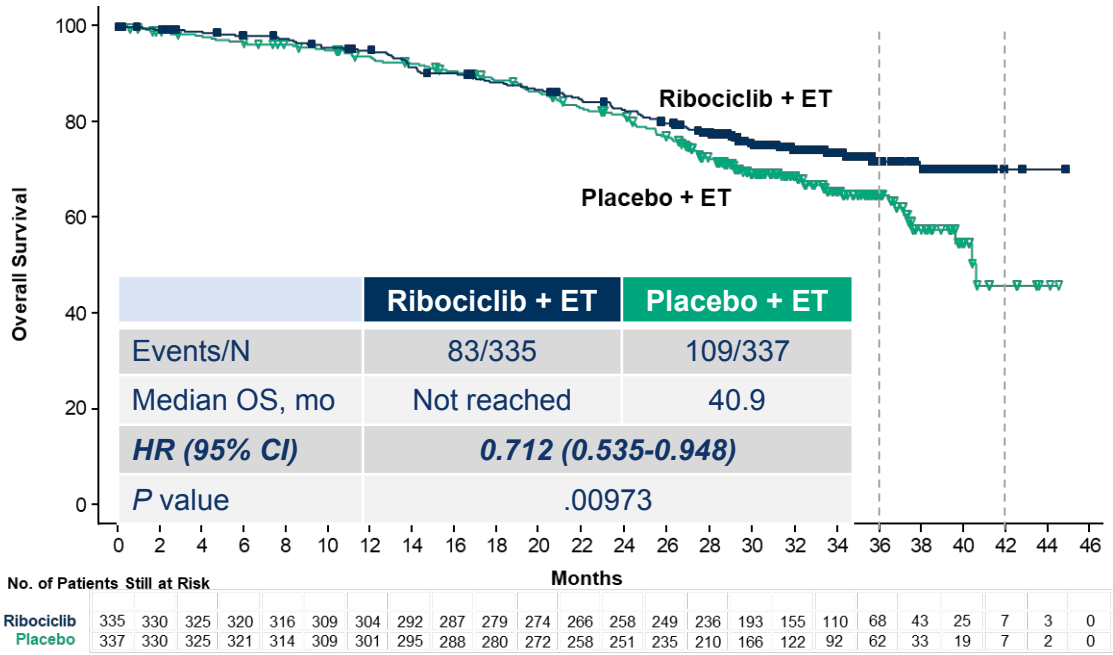
Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

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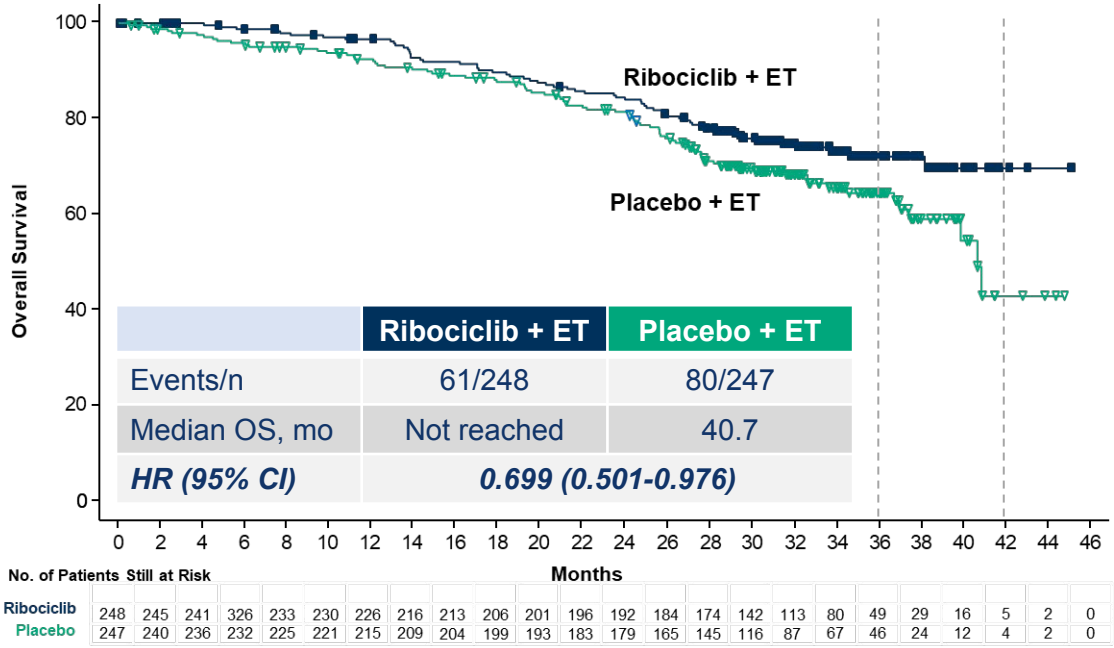
Overall Survival in the NSAI Subgroup



	Ribociclib + ET	Placebo + ET
Events/n	61/248	80/247
Median OS, mo	Not reached	40.7
HR (95% CI)	***0.699 (0.501-0.976)***	

- ≈ 30% relative reduction in risk of death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

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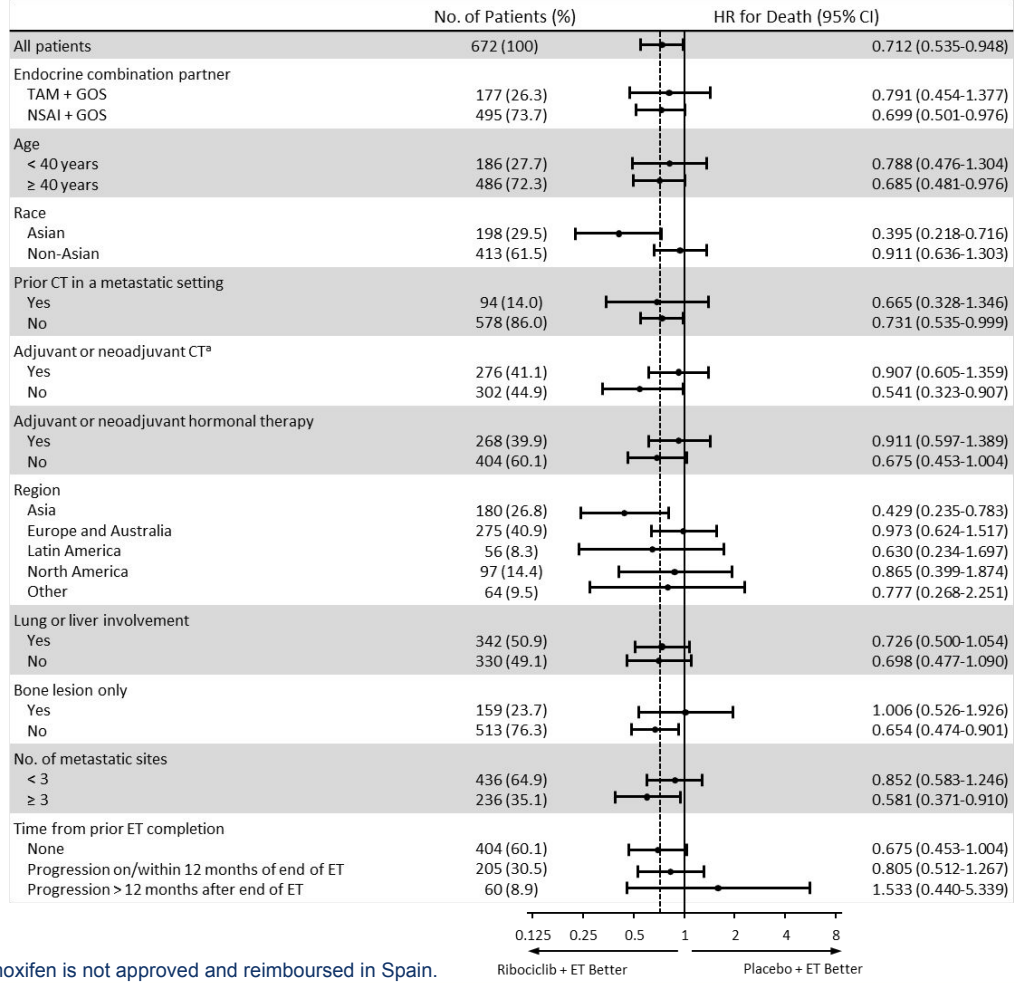
Overall Survival Subgroup Analysis

- Consistent OS benefit seen within subgroups



[a] In patients with no prior chemotherapy in the metastatic setting.

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Subsequent Therapies After Treatment Discontinuation

First Subsequent Therapy

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)
Patients who discontinued study treatment, n	219	280
Any medication, n (%)[a]	151 (69)	205 (73)
Chemotherapy alone	49 (22)	80 (29)
Chemotherapy + hormone therapy/other	18 (8)	22 (8)
Hormone therapy alone	49 (22)	57 (20)
Hormone therapy + other	31 (14)	41 (15)
Other	4 (2)	5 (2)

- Receipt of any subsequent CDK4/6 inhibitors in patients who discontinued study treatment
  - Ribociclib arm: 22/219 patients (10%)
  - Placebo arm: 52/280 (19%)

[a] Percentages are based on the number of patients who discontinued treatment.

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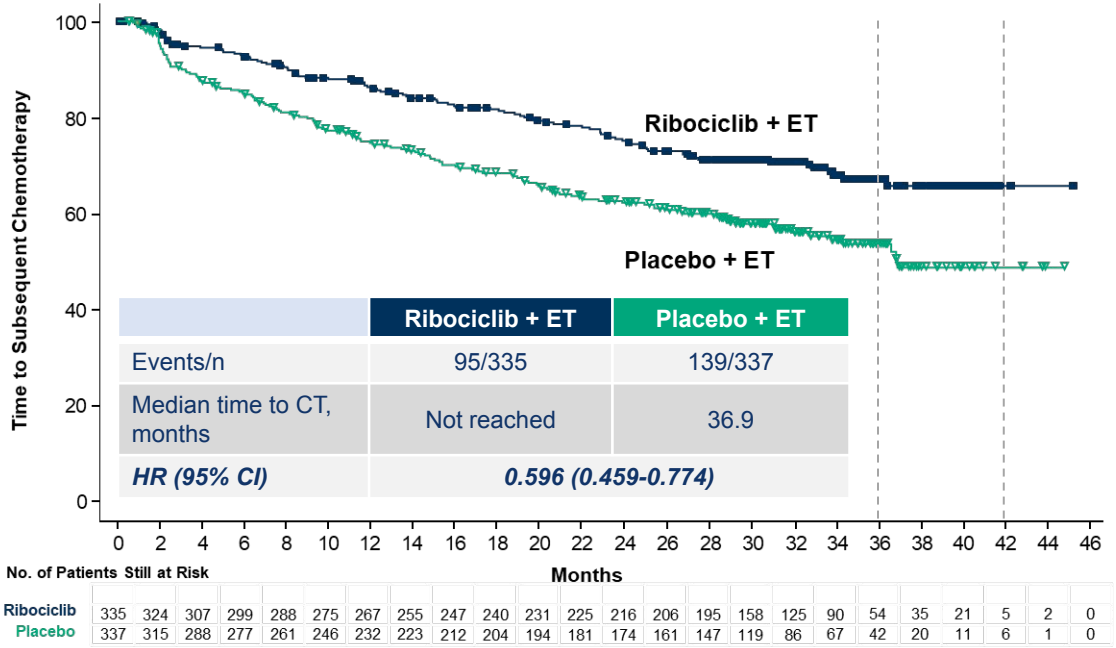
Time to First Subsequent Chemotherapy



	Ribociclib + ET	Placebo + ET
Events/n	95/335	139/337
Median time to CT, months	Not reached	36.9
HR (95% CI)	***0.596 (0.459-0.774)***	

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

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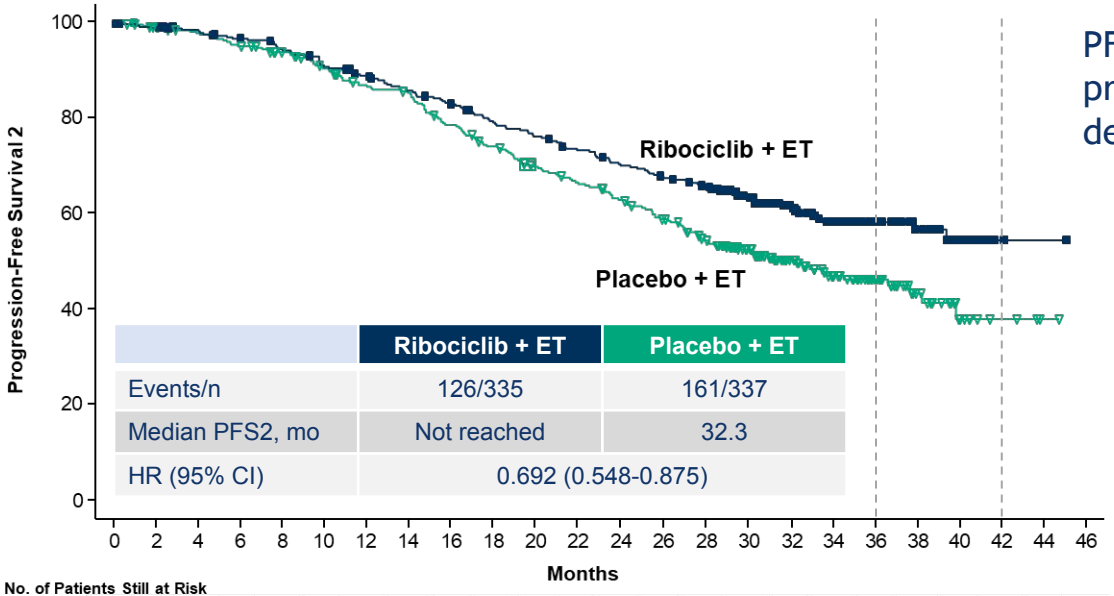
Progression-Free Survival 2



	Ribociclib + ET	Placebo + ET
Events/n	126/335	161/337
Median PFS2, mo	Not reached	32.3
HR (95% CI)	0.692 (0.548-0.875)	

No. of Patients Still at Risk

Ribociclib	335	329	323	315	305	293	284	272	261	247	238	227	216	208	199	162	125	90	57	35	20	5	2	0
Placebo	337	330	322	313	302	287	271	266	244	228	212	200	188	173	154	125	88	67	45	23	11	4	1	0

PFS 2: time from randomization to progression on the next line of therapy or death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	58.4%	46.2%
42 months	54.6%	37.8%

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Safety

- The median treatment duration was approximately 2 years in the ribociclib arm and approximately 1 year in the placebo arm
- After 15 months of additional follow-up, the adverse event profile for the ribociclib arm remained consistent with the known safety profile
- The rates of grade 3 or 4 adverse events of special interest in the ribociclib and placebo arms, respectively, were:
  - Neutropenia, 63.5% and 4.5%
  - Hepatobiliary toxicity, 11% and 6.8%
  - Prolonged QT interval, 1.8% and 1.2%

Reference: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

Conclusions

- MONALEESA-7 is the only study to date to evaluate CDK4/6 inhibitors exclusively in premenopausal women
- Ribociclib plus ET resulted in a statistically significant longer OS compared with ET alone
  - Approximate 29% relative reduction in risk of death
  - Approximate 30% relative reduction in risk of death in the NSAI cohort
  - Treatment ongoing in 35% of patients in the ribociclib arm
- The benefit of ribociclib extends beyond initial treatment based on time to subsequent chemotherapy and PFS 2
- **This is the first time a statistically significant improvement in OS has been observed with a CDK4/6 inhibitor in combination with ET in patients with HR+/HER2– ABC**

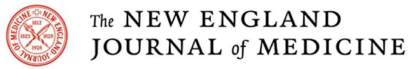
Acknowledgements

We thank the patients who participated in this trial, their families and caregivers, data monitoring committee members, study steering committee members, and staff who assisted with the trial at each site.

We also thank the team that supported this trial, including Melissa Tripodi, Delphine Kerzerho, Jay Harshadbhai Shah, Rahul Tyagi, Tiffany Yuen, Vijay Muthineni, Maria Ruiz, and Tim Cartwright.

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

Simultaneous Publication in *The New England Journal of Medicine*



ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

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Novartis Oncology

Updated Overall Survival (OS) Results From the Phase III MONALEESA-7 Trial of Pre- or Perimenopausal Patients With HR+/HER2− Advanced Breast Cancer (ABC) Treated With Endocrine Therapy (ET) ± Ribociclib

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Introduction (1 of 2)

- In the Phase III MONALEESA (ML)-7 (NCT02278120) trial, ribociclib (RIB) + ET demonstrated a significant progression-free survival (PFS) and OS benefit over placebo (PBO) + ET in pre- and perimenopausal patients with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) ABC[1,2]
  - With RIB + ET vs PBO + ET, median PFS was 23.8 vs 13.0 mo (hazard ratio [HR], 0.55; 95% CI, 0.44-0.69; *P* < .0001)
  - Median OS in the final protocol-specified OS analysis was not reached (NR) in the RIB arm and was 40.9 mo in the PBO arm (HR, 0.71; 95% CI, 0.54-0.95; *P* = .00973), with a median follow-up of 34.6 mo (minimum, 28.0 mo)
- To date, ML-7 is the only trial to examine a cyclin-dependent kinase (CDK) 4/6 inhibitor (CDK4/6i) specifically in pre- and perimenopausal patients, who tend to have poor prognoses and aggressive cancer compared with postmenopausal patients[3-5]

ABC, advanced breast cancer; ET, endocrine therapy; vs, versus.

Introduction (2 of 2)

- Following the significantly improved OS previously reported in ML-7, it is important to understand the efficacy of RIB + ET in young women with a longer follow-up[2]
- Here, we report an exploratory analysis of OS in ML-7 with a median follow-up of 53.5 mo

ET, endocrine therapy; ML, MONALEESA; mo, month; pt, patient; OS, overall survival; RIB, ribociclib.

Objective

- To provide an exploratory update of OS associated with RIB + ET in pre- and perimenopausal patients in the ML-7 trial after a median follow-up of 53.5 mo

ET, endocrine therapy; ML, MONALEESA; mo, month; OS, overall survival; RIB, ribociclib.

Methods (1 of 3)

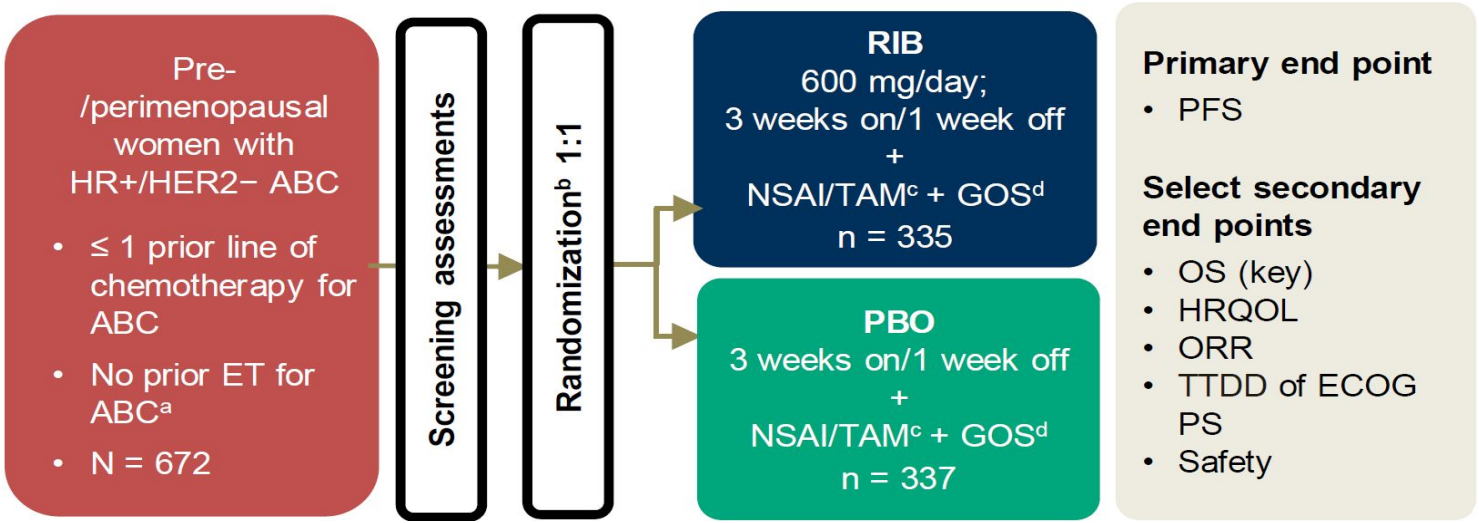
Patients and Study Design

- Pre-perimenopausal women with HR+/HER2− ABC were randomized 1:1 to receive either RIB or PBO + a nonsteroidal aromatase inhibitor (NSAI) or tamoxifen + goserelin (**Figure 1**)
- One prior line of chemotherapy in the advanced setting was permitted and was received by 14% of patients in each arm

ET, endocrine therapy; HER2−, human epidermal growth factor receptor 2−negative; HR+, hormone receptor−positive; ML, MONALEESA; mo, month; OS, overall survival; PBO, placebo; RIB, ribociclib.

Methods (2 of 3)

Figure 1. Study Design



[a] Prior use of NSAI/TAM ± GOS for ≤ 14 days was allowed. [b] Stratified by liver/lung metastasis (yes/no), prior chemotherapy for advanced disease (yes/no), and combination partner (NSAI/TAM). [c] Oral TAM or NSAI was administered daily. TAM dose was 20 mg, letrozole dose was 2.5 mg, and anastrozole dose was 1 mg. d GOS 3.6 mg was administered by subcutaneous injection.

ABC, advanced breast cancer; ET, endocrine therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GOS, goserelin; HER2−, human epidermal growth factor receptor 2−negative; HR+, hormone receptor−positive; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib; TAM, tamoxifen; TTDD, time to definitive deterioration.

Methods (3 of 3)

Study End Points

- OS was defined as the time from randomization to death from any cause
- Time to subsequent chemotherapy was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen, with death being censored
- Chemotherapy-free survival had the same definition as time to subsequent chemotherapy but without censoring for death
- PFS2 was defined as the time from randomization to the first documented disease progression (physician reported) while the patient was receiving subsequent antineoplastic therapy or death from any cause, whichever occurred first
- Adverse events (AEs) were monitored throughout the trial and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03

OS, overall survival; PFS, progression-free survival.

Results (1 of 11)

Patient Disposition and Duration of Follow-Up

- Baseline characteristics have been previously reported[1]
- As of the data cutoff (June 29, 2020), 21.2% of patients in the RIB arm and 9.2% of patients in the PBO were still on treatment (**Table 1**)
  - 15 patients in the PBO arm crossed over to RIB following unblinding at the final analysis
- The median duration of follow up was 53.5 mo (min-max, 46.9-66.4 mo)

Mo, month; PBO, placebo; RIB, ribociclib.

Results (2 of 11)

Table 1. Patient Disposition

	RIB + ET (n = 335)	PBO + ET (n = 337)	All Patients (N = 672)
Patients treated, n (%)	335 (100)	337 (100)	672 (100)
Treatment ongoing[a]	71 (21.2)	31 (9.2)	102 (15.2)
Ended treatment	264 (78.8)	306 (90.8)	570 (84.8)
Reason for end of treatment, n (%)			
Progressive disease	210 (62.7)	248 (73.6)	458 (68.2)
Patient/guardian decision	21 (6.3)	16 (4.7)	37 (5.5)
Physician decision	12 (3.6)	25 (7.4)	37 (5.5)
Adverse event	16 (4.8)	12 (3.6)	28 (4.2)
Death	3 (0.9)	3 (0.9)	6 (0.9)
Lost to follow-up	2 (0.6)	0	2 (0.3)
Protocol deviation	0	2 (0.6)	2 (0.3)
Entered survival follow-up, n (%)[b]	232 (87.9)	279 (91.2)	511 (89.6)

[a] Patients continuing study treatment at the time of the cutoff (June 29, 2020). [b] The percentage of patients who entered survival follow-up uses the number of patients with who ended treatment as the denominator.
ET, endocrine therapy; PBO, placebo; RIB, ribociclib.

Results (3 of 11)

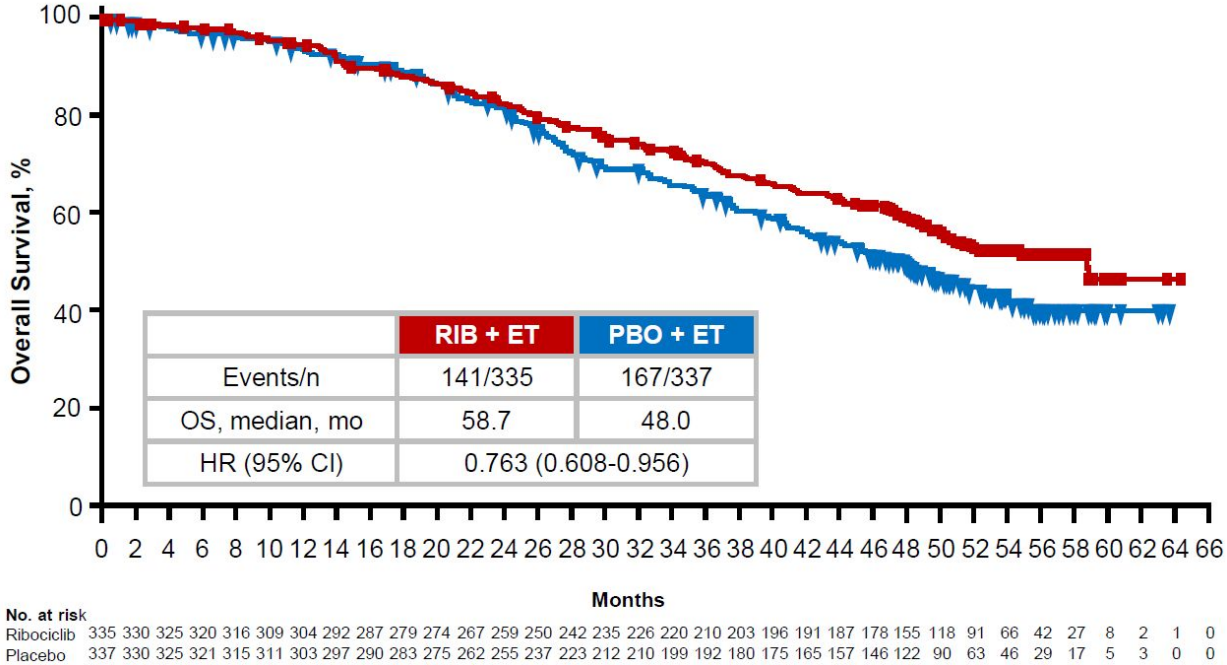
Overall Survival

- The median OS was 58.7 mo with RIB + ET and 48.0 mo with PBO + ET (HR, 0.76; 95% CI, 0.61-0.96), with a 24% relative reduction in the risk of death with RIB (**Figure 2**)
- In a subgroup analysis by endocrine partner, patients receiving an NSAI had a median OS of 58.7 mo in the RIB + ET arm and 47.7 mo in the PBO + ET arm (HR, 0.80; 95% CI, 0.62-1.04), while patients receiving tamoxifen did not reach the median OS in the RIB + ET arm and had a median OS of 49.3 mo in the PBO + ET arm (HR, 0.71; 95% CI, 0.45-1.10) (**Figure 3**)
- Exploratory subgroup analysis results were generally consistent with the OS results in the overall population but should be interpreted with caution due to small numbers of patients, relatively wide confidence intervals, and lack of statistical power (**Figure 4**)

CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; RIB, ribociclib.

Results (4 of 11)

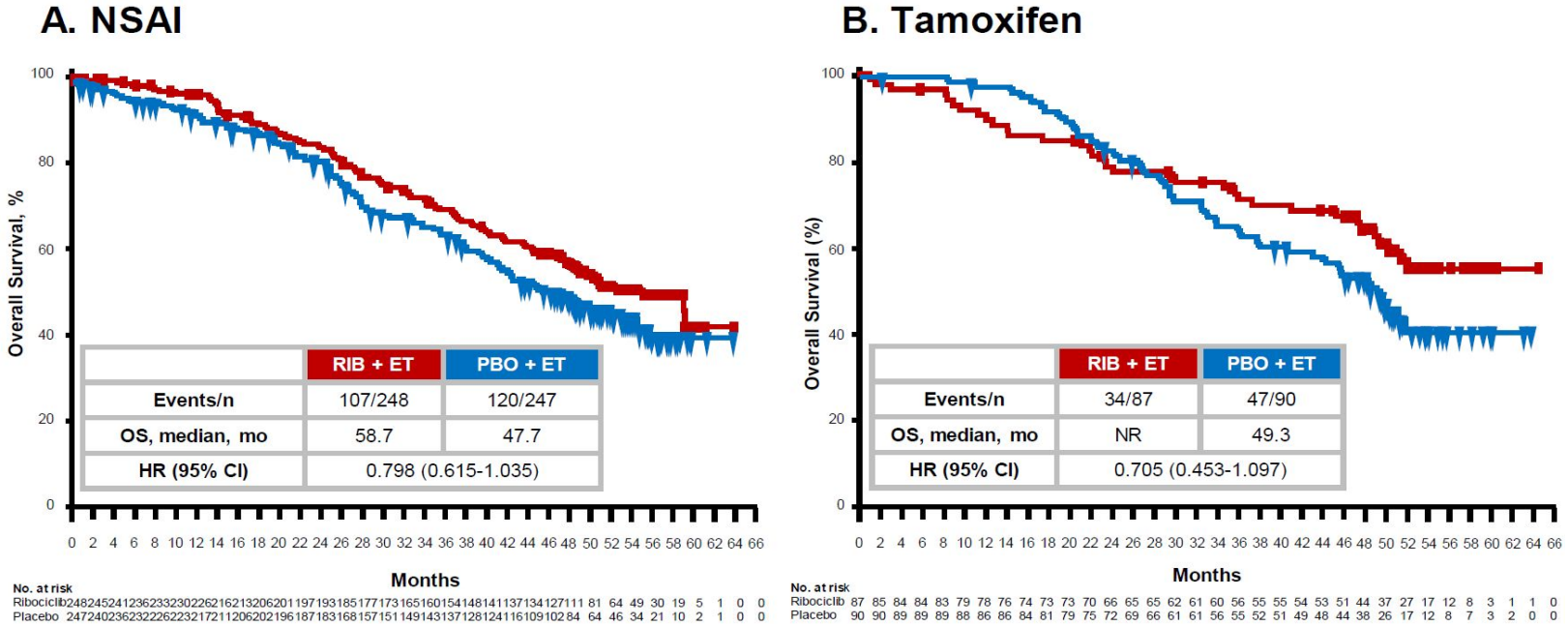
Figure 2. OS in the Intent-to-Treat Population



CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; RIB, ribociclib.

Results (5 of 11)

Figure 3. OS Subgroup Analyses by Endocrine Partner

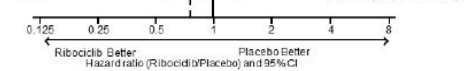


CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; mo, month; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PBO, placebo; RIB, ribociclib.

Results (6 of 11)

Figure 4. OS Subgroup Analyses

	Ribociclib + ET		Placebo + ET		HR (95% CI)
	Events/n (%)	mOS	Events/n (%)	mOS	
All patients	141/335 (42)	58.7	167/337 (50)	48.0	0.763 (0.608-0.956)
Endocrine combination partner					
Tamoxifen and goserelin	34/87 (39)	NR	47/90 (52)	49.3	0.705 (0.453-1.097)
NSAI and goserelin	107/248 (43)	58.7	120/247 (49)	47.7	0.798 (0.615-1.035)
ECOG performance status					
0	98/245 (40)	NR	118/255 (46)	49.8	0.765 (0.584-1.004)
≥1	42/87 (48)	47.0	47/79 (59)	37.2	0.712 (0.461-1.097)
Age					
<40 Years	44/98 (45)	51.3	53/86 (60)	40.5	0.651 (0.431-0.983)
≥40 Years	97/237 (41)	58.8	114/249 (46)	51.7	0.810 (0.617-1.065)
Race					
Asian	32/99 (32)	NR	47/99 (47)	46.9	0.609 (0.383-0.968)
Non-Asian	97/200 (49)	50.2	110/213 (52)	47.9	0.898 (0.680-1.186)
Chemotherapy (metastatic)					
Yes	25/47 (53)	47.2	31/47 (66)	39.0	0.747 (0.441-1.266)
No	116/288 (40)	NR	136/290 (47)	49.8	0.784 (0.612-1.005)
(Neo)adjuvant chemotherapy					
Yes	68/138 (49)	47.3	67/138 (49)	42.5	0.972 (0.691-1.368)
No	48/150 (32)	NR	69/152 (45)	51.7	0.597 (0.411-0.868)
(Neo)adjuvant hormone therapy					
Yes	67/127 (53)	47.0	77/141 (55)	42.0	0.918 (0.657-1.282)
No	74/208 (36)	NR	90/196 (46)	51.1	0.711 (0.521-0.971)
ER and PGR receptor status[a]					
++	114/286 (40)	NR	131/286 (46)	51.1	0.792 (0.615-1.021)
Other	27/49 (55)	49.9	36/51 (71)	33.6	0.619 (0.362-1.057)
Region					
Asia	32/92 (35)	NR	41/87 (47)	44.8	0.645 (0.402-1.036)
Europe and Australia	65/136 (48)	50.7	69/139 (50)	49.6	0.999 (0.706-1.414)
Latin America	12/31 (39)	NR	13/25 (52)	35.8	0.684 (0.288-1.624)
North America	20/47 (43)	58.7	27/51 (53)	45.5	0.603 (0.314-1.156)
Other	12/29 (41)	NR	17/35 (49)	51.1	0.690 (0.310-1.535)
Lung or liver involvement					
Yes	80/173 (46)	50.6	85/169 (50)	44.5	0.837 (0.616-1.136)
No	61/162 (38)	58.8	82/168 (49)	50.0	0.700 (0.502-0.975)
Lung involvement					
Yes	42/106 (40)	NR	41/88 (47)	49.6	0.798 (0.515-1.238)
No	99/229 (43)	58.7	126/249 (51)	47.7	0.739 (0.566-0.966)
Liver involvement					
Yes	57/105 (54)	46.5	67/114 (59)	36.1	0.780 (0.544-1.118)
No	84/230 (37)	NR	100/223 (45)	51.7	0.762 (0.568-1.021)
Bone lesion only					
Yes	30/81 (37)	NR	36/78 (46)	51.1	0.777 (0.472-1.280)
No	111/254 (44)	58.7	131/259 (51)	45.5	0.764 (0.592-0.985)
Number of metastic sites					
< 3	84/219 (38)	58.8	100/217 (46)	51.7	0.802 (0.597-1.078)
≥ 3	57/116 (49)	50.3	67/120 (56)	40.9	0.705 (0.490-1.015)
Disease free interval					
De Novo	41/136 (30)	NR	64/134 (48)	49.6	0.529 (0.356-0.788)
Recurrent	100/199 (50)	48.6	103/203 (51)	43.1	0.940 (0.712-1.242)
Prior (neo)adjuvant ET					
None	74/208 (36)	NR	90/196 (46)	51.1	0.711 (0.521-0.971)
Progression ≤12 mo of end of ET	59/100 (59)	41.3	66/105 (63)	39.0	0.830 (0.579-1.190)
Progression > 12 mo after end of ET	8/25 (32)	58.8	11/35 (31)	NR	1.190 (0.441-3.216)
Prior endocrine therapy					
Endocrine naive	74/208 (36)	NR	90/197 (46)	51.1	0.716 (0.525-0.977)
Endocrine resistance	29/46 (63)	38.3	26/41 (63)	32.7	0.905 (0.524-1.563)
Endocrine sensitive	38/81 (47)	54.7	51/99 (52)	45.4	0.855 (0.552-1.323)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ER, endocrine receptor; ET, endocrine therapy; HR, hazard ratio; mo, month; mOS, median overall survival; NR, not reached; OS, overall survival; PGR, progesterone receptor.

Results (7 of 11)

Table 2. Subsequent Antineoplastic Therapies

	RIB + ET (n = 335)	PBO + ET (n = 337)
Patients who discontinued, n (%)	264 (78.8)	306 (90.8)
Patients who received any subsequent therapy, n (%)[a]		
Chemotherapy alone	204 (77.3)	239 (78.1)
Chemotherapy plus hormone therapy or other therapy[b]	59 (22.3)	87 (28.4)
Hormone therapy alone	27 (10.2)	31 (10.1)
Hormone therapy plus other therapy[c]	73 (27.7)	56 (18.3)
Other	40 (15.2)	55 (18.0)
Patients who received any subsequent CDK4/6i, n (%)[a]	34 (12.9)	80 (26.1)
Palbociclib	25 (9.5)	67 (21.9)
Ribociclib	6 (2.3)	12 (3.9)
Abemaciclib	4 (1.5)	2 (0.7)

[a] The percentage of patients who received a subsequent therapy uses the number of patients who discontinued treatment as the denominator. [b] This category includes patients who received chemotherapy in combination with any non chemotherapy. [c] This category includes patients who received hormone therapy plus another medication without chemotherapy.

CDK4/6i, cyclin dependent kinase 4 or 6 inhibitor; ET, endocrine therapy; PBO, placebo; RIB, ribociclib.

Results (8 of 11)

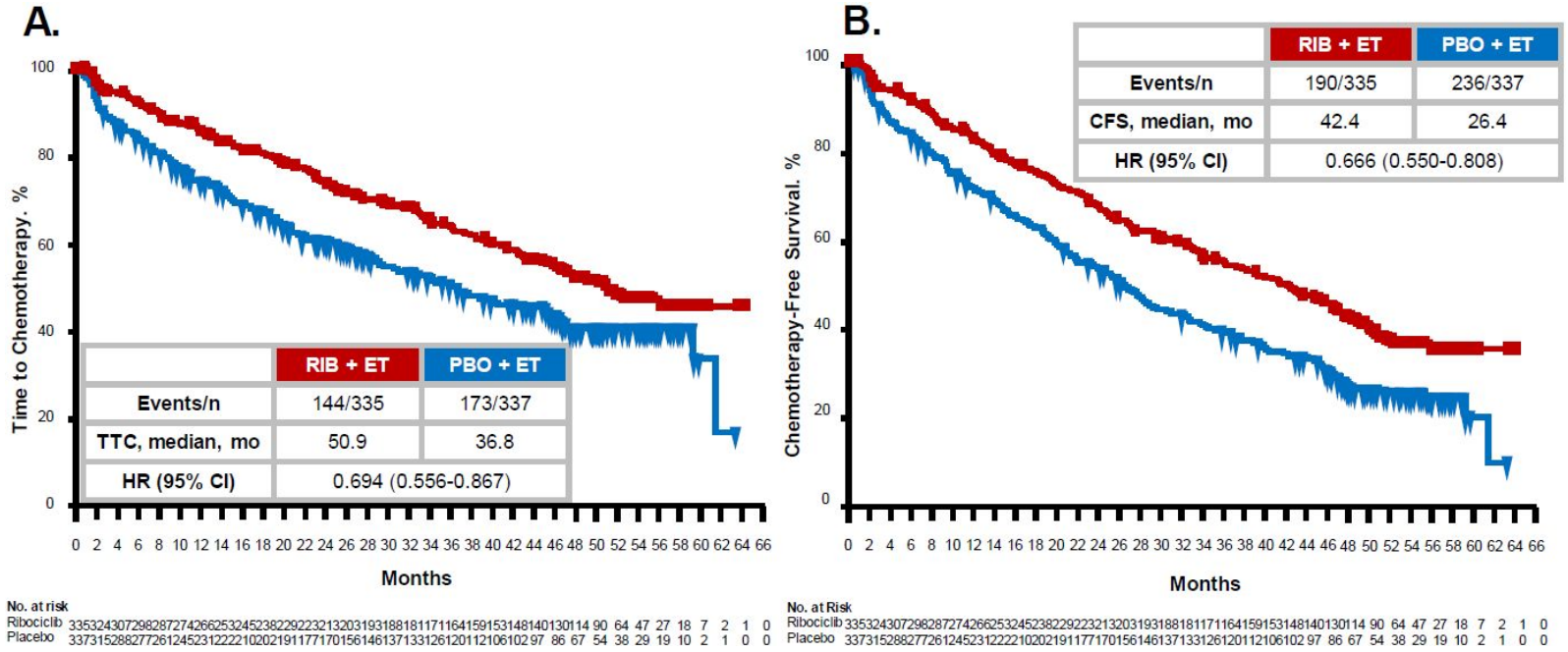
Subsequent Therapies and PFS2

- Discontinuations of RIB and PBO occurred in 79% and 91% of patients, respectively
- The most common first subsequent therapies were chemotherapy alone and hormone therapy alone, similar to the final OS analysis (**Table 2**)
- The use of subsequent CDK4/6i following discontinuation was higher in the PBO group (RIB, 13%; PBO, 26%); in the PBO arm, 15 patients crossed over to RIB following unblinding
- The median time to first subsequent chemotherapy (TTC) was 50.9 mo with RIB + ET vs 36.8 mo with PBO + ET (HR, 0.69; 95% CI, 0.56-0.87) (**Figure 5A**), while median chemotherapy-free survival (CFS) was 42.4 mo vs 26.4 mo, respectively (HR, 0.67; 95% CI, 0.55-0.81) (**Figure 5B**)
- The median PFS2 was 44.2 mo in the RIB arm and 31.0 mo in the PBO arm (HR, 0.68; 95% CI, 0.56-0.83) (**Figure 6**)

CDK4/6i, cyclin dependent kinase 4 or 6 inhibitor; CI, confidence interval; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Results (9 of 11)

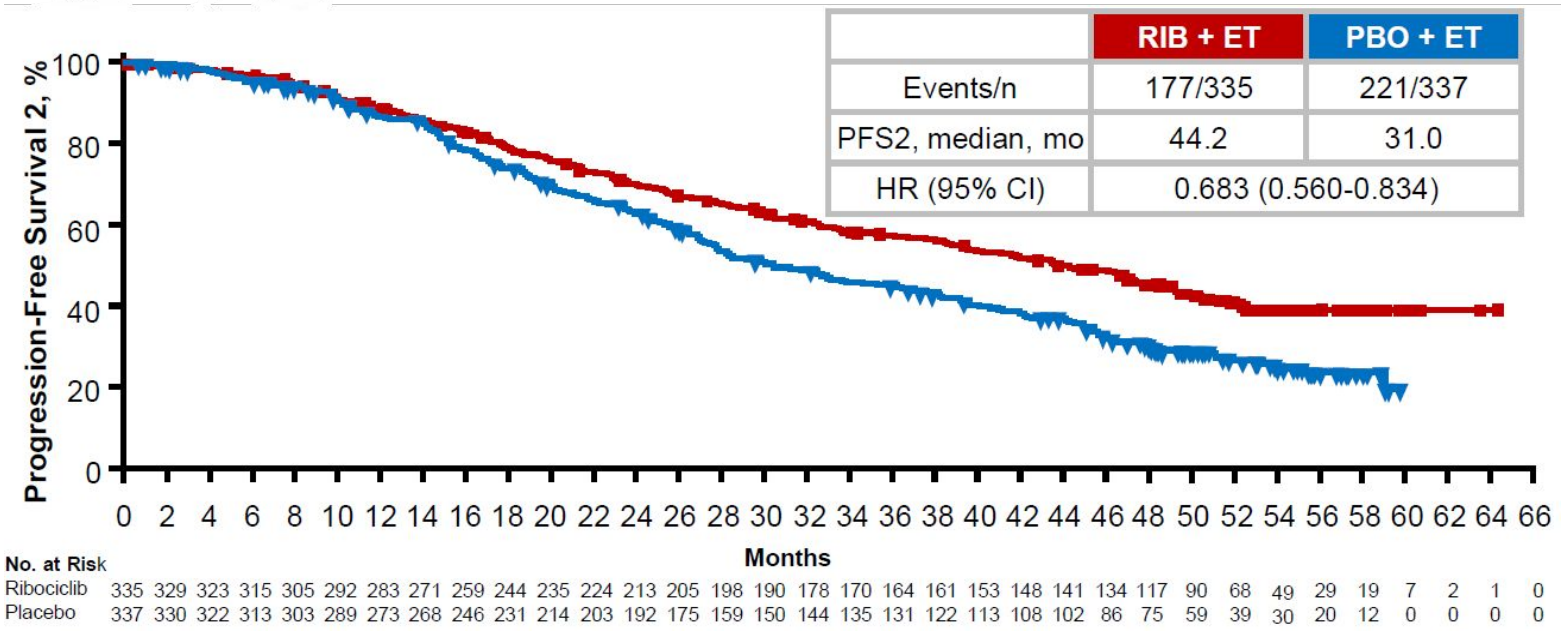
Figure 5. Time to Chemotherapy (A) and Chemotherapy-Free Survival (B)



CI, confidence interval; CFS, chemotherapy-free survival; ET, endocrine therapy; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; RIB, ribociclib; TTC, time to first subsequent chemotherapy.

Results (10 of 11)

Figure 6. Progression-Free Survival 2



	RIB + ET	PBO + ET
Events/n	177/335	221/337
PFS2, median, mo	44.2	31.0
HR (95% CI)	0.683 (0.560-0.834)	

CI, confidence interval; ET, endocrine therapy; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; PFS2, progression-free survival; RIB, ribociclib.

Results (11 of 11)

- AEs in the safety population were consistent with those reported in the primary and final OS analyses (**Table 3**)

Table 3. Adverse Events of Special Interest (AESIs)

	RIB + ET (n = 335)			PBO + ET (n = 337)		
AESIs, n (%)	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Neutropenia	261 (77.9)	178 (53.1)	39 (11.6)	36 (10.7)	16 (4.7)	3 (0.9)
Leukopenia	119 (35.5)	52 (15.5)	4 (1.2)	20 (5.9)	5 (1.5)	1 (0.3)
Anemia	76 (22.7)	13 (3.9)	0	39 (11.6)	9 (2.7)	0
Hepatobiliary toxicity	98 (29.3)	38 (11.3)	3 (0.9)	80 (23.7)	23 (6.8)	2 (0.6)
QTc prologation	43 (12.8)	6 (1.8)	0	22 (6.5)	3 (0.9)	1 (0.3)
ILD/pneumonitis	2 (0.6)	0	0	0	0	0

AE, adverse event; ET, endocrine therapy; ILD, interstitial lung disease; OS, overall survival; PBO, placebo; QTc; corrected QT interval; RIB, ribociclib.

Conclusions (1 of 2)

- This analysis demonstrated a consistent significant OS benefit with ribociclib after a median follow-up of 53.5 months, despite crossover and use of subsequent CDK4/6i in the placebo arm
- Subgroup analyses, including by endocrine partner, were generally consistent with the intent-to-treat population
- Subsequent antineoplastic therapies were relatively similar between treatment arms; however, more patients in the placebo arm received a CDK4/6i following discontinuation of study treatment
- Ribociclib significantly delayed subsequent chemotherapy compared with placebo and showed a significant improvement in PFS2
- The safety profile was consistent with previously published analyses

CDK4/6i, cyclin dependent kinase 4 or 6 inhibitor; mo, month; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Conclusions (2 of 2)

- This analysis demonstrates a median OS of 58.7 months, the longest reported in HR+/HER2− ABC and among all Phase III trials in ABC
- This exploratory analysis confirms the benefit and continued use of ribociclib in the first-line setting for pre- or perimenopausal patients with HR+/HER2− ABC

ABC, advanced breast cancer; HER2−, human epidermal growth factor receptor 2−negative; HR+, hormone receptor−positive; mo, month; OS, overall survival; RIB, ribociclib.

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