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)

Dennis J. Slamon,[1] Patrick Neven,[2] Stephen Chia,[3] Guy Jerusalem,[4] Michelino De Laurentiis,[5] Seock-Ah Im,[6] Katarina Petrakova,[7] Giulia Valeria Bianchi,[8] Miguel Martín,[9] Arnd Nusch,[10] Gabe S. Sonke,[11] Luis De la Cruz-Merino,[12] J. Thaddeus Beck,[13] Craig Wang,[14] Uday Deore,[15] Arunava Chakravartty,[15] Juan Pablo Zarate,[15] Tetiana Taran,[14] Peter A. Fasching[16]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Multidisciplinary Breast Centre, Universitair Ziekenhuis Leuven, Leuven, Belgium; [3]British Columbia Cancer Agency, Vancouver, BC, Canada; [4]CHU Liege and Liège University, Liège, Belgium; [5]Istituto Nazionale Tumori IRCCS "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]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; [10]Practice for Hematology and Internal Oncology, Velbert, Germany; [11]Netherlands Cancer Institute/Borstkanker Onderzoek Groep Study Center, Amsterdam, the Netherlands; [12]Hospital Universitario Virgen Macarena, Seville, Spain; [13]Highlands Oncology Group, Fayetteville, AR; [14]Novartis Pharma AG, Basel, Switzerland; [15]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [16]University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany.

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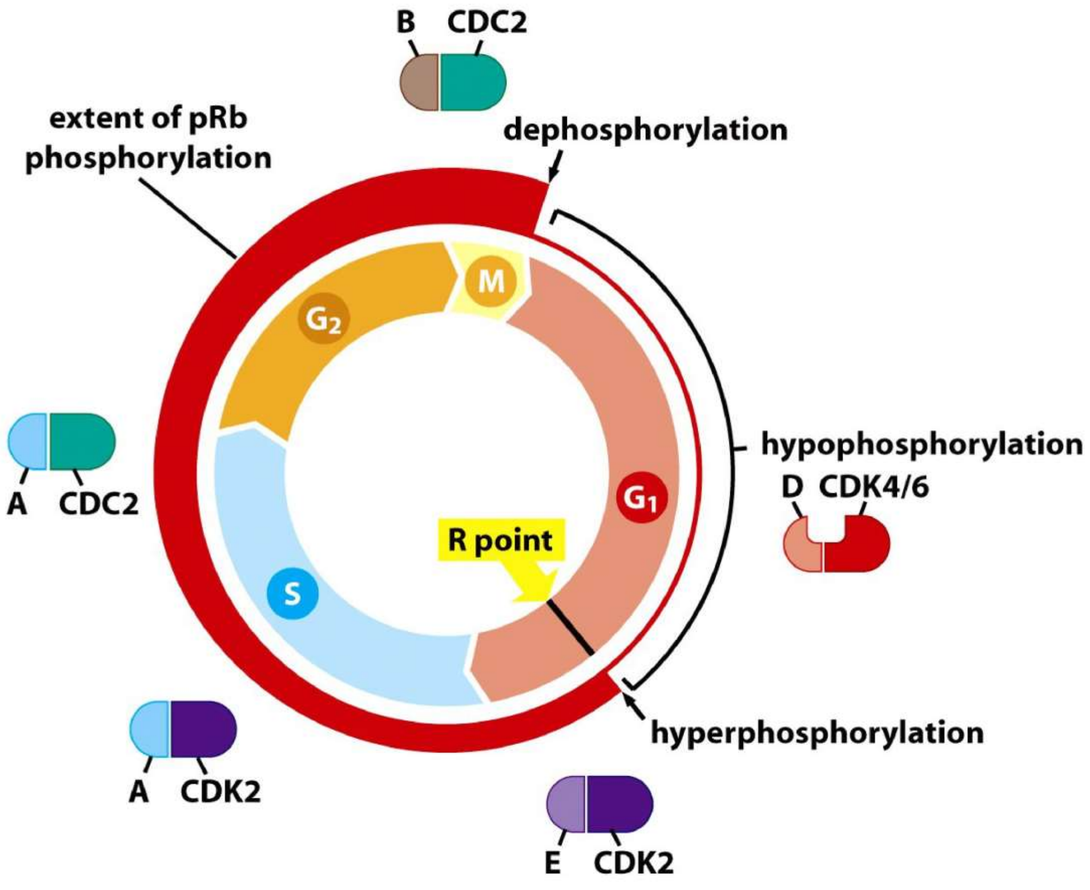
Disclosure

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

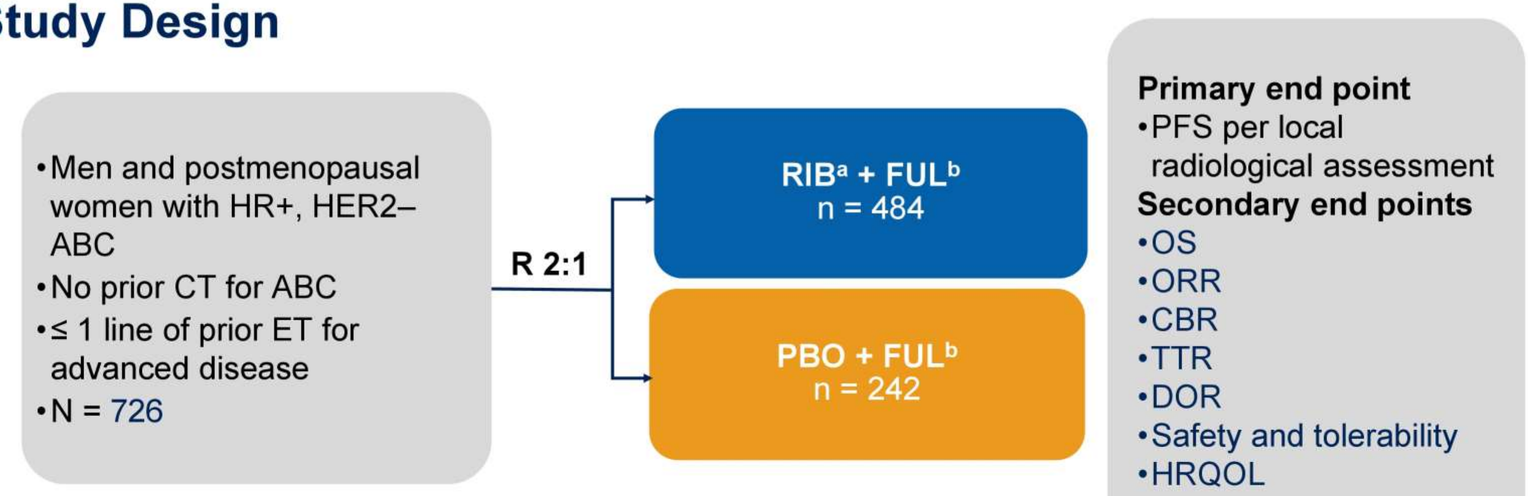
Can inhibiting CDK4/6-cyclin D prevent hyperphosphorylation of Rb and thereby prevent cell cycle progression?

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

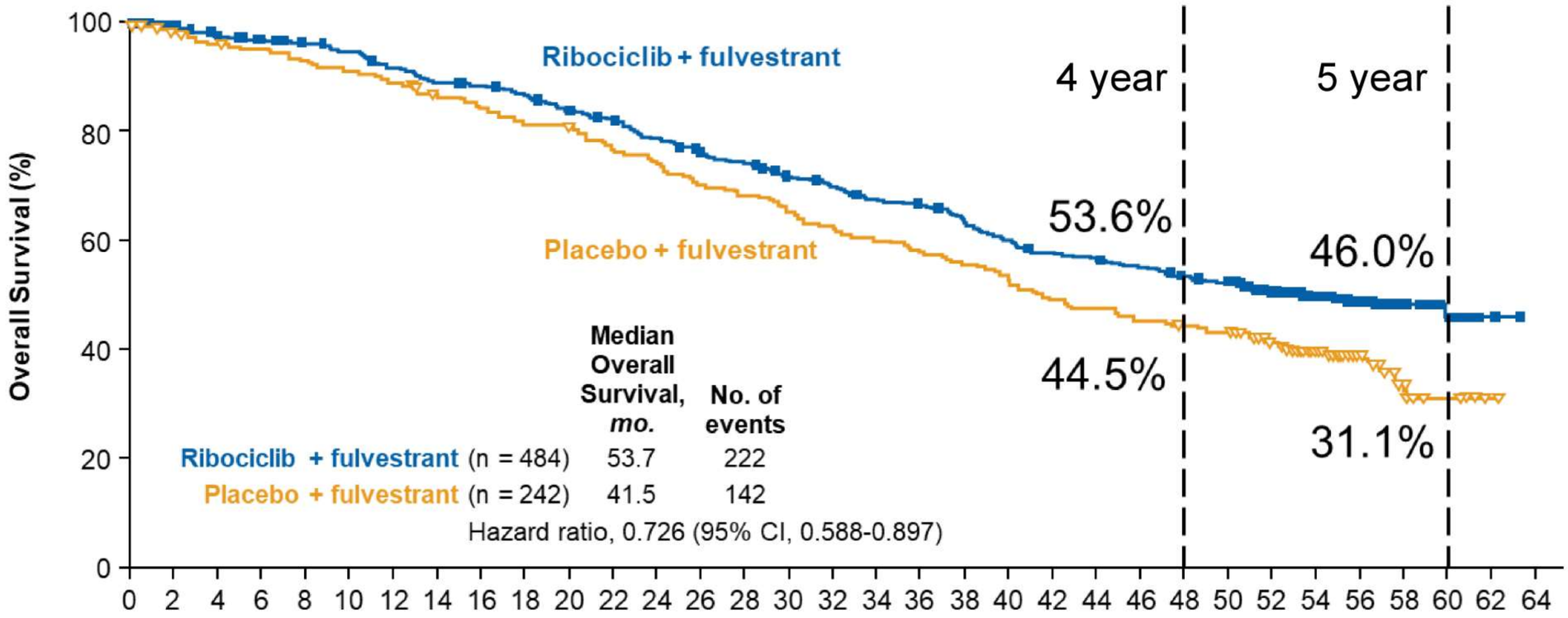
Parameter, n (%)	Ribociclib + Fulvestrant (n = 484)	Placebo + Fulvestrant (n = 242)	All Patients (N = 726)
Patients randomized			
Untreated	1 (0.2)	1 (0.4)	2 (0.3)
Treated	483 (99.8)	241 (99.6)	724 (99.7)
Patients treated			
Treatment ongoing[a]	68 (14.0)	21 (8.7)	89 (12.3)
End of treatment	415 (85.7)	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



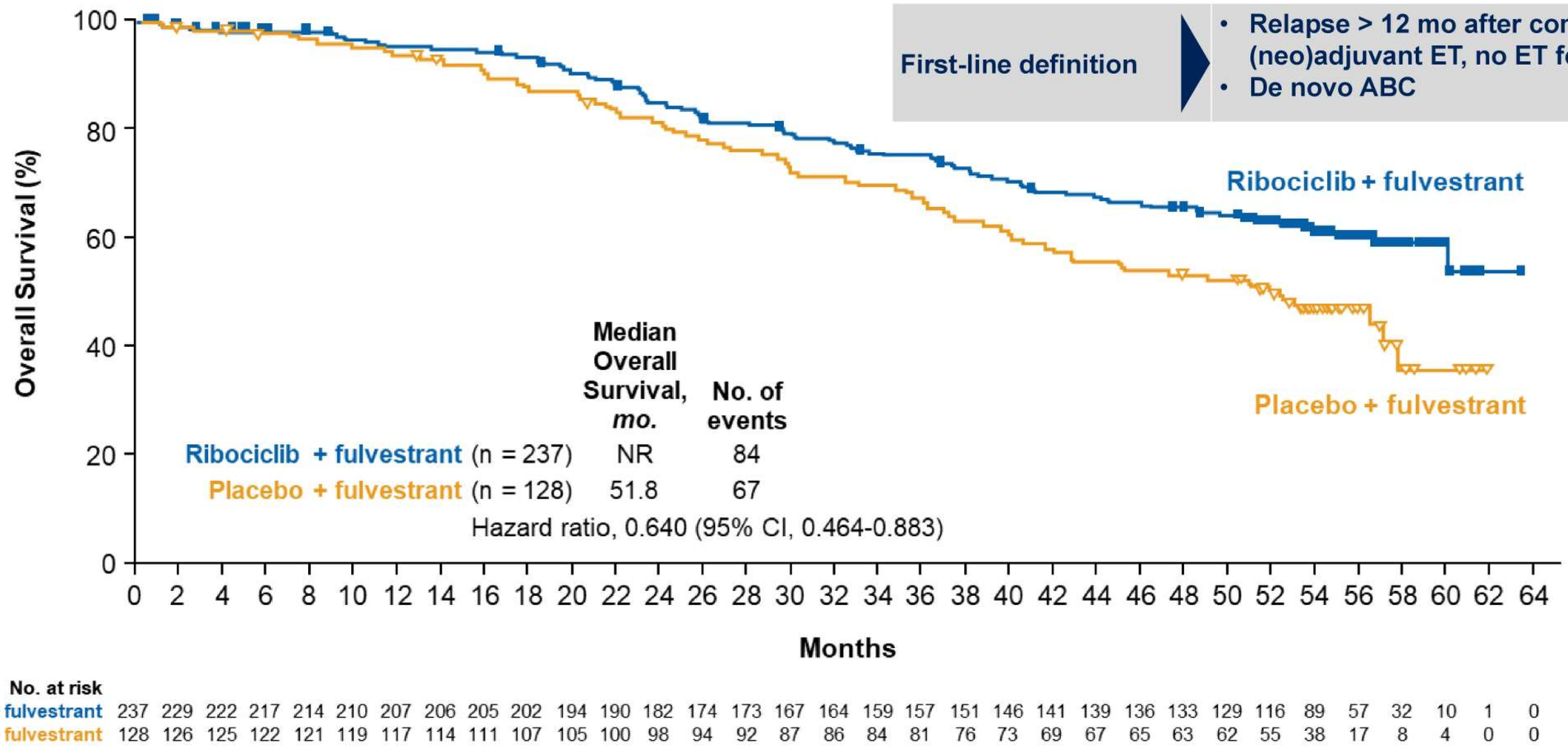
- With an extended follow-up of > 4 years, ribociclib + fulvestrant continued to demonstrate a clinically relevant > 1 year OS benefit compared with placebo + fulvestrant

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

Overall Survival in Patients Treated in the First-line Setting

First-line definition

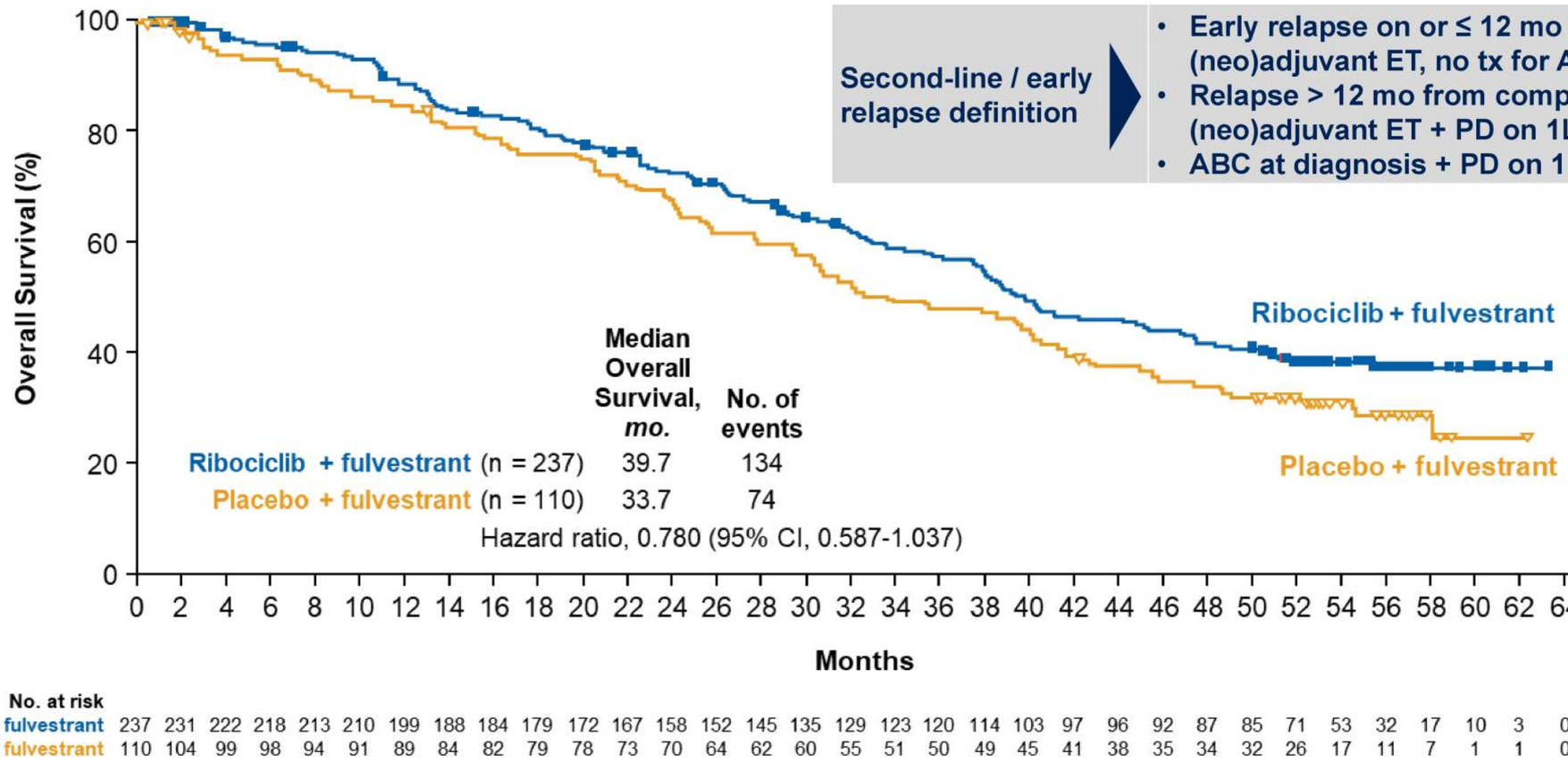
- Relapse > 12 mo after completion of (neo)adjuvant ET, no ET for ABC
- De novo ABC



- 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

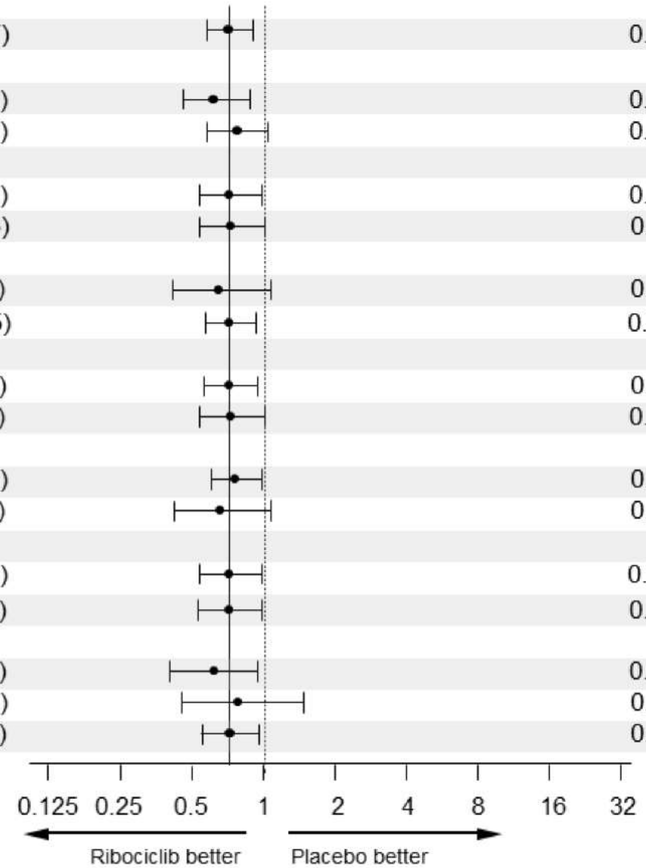


- Ribociclib + fulvestrant demonstrated a 6-month longer median OS over placebo + fulvestrant in the second-line setting

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 *No. of deaths/total no. (%)*	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)

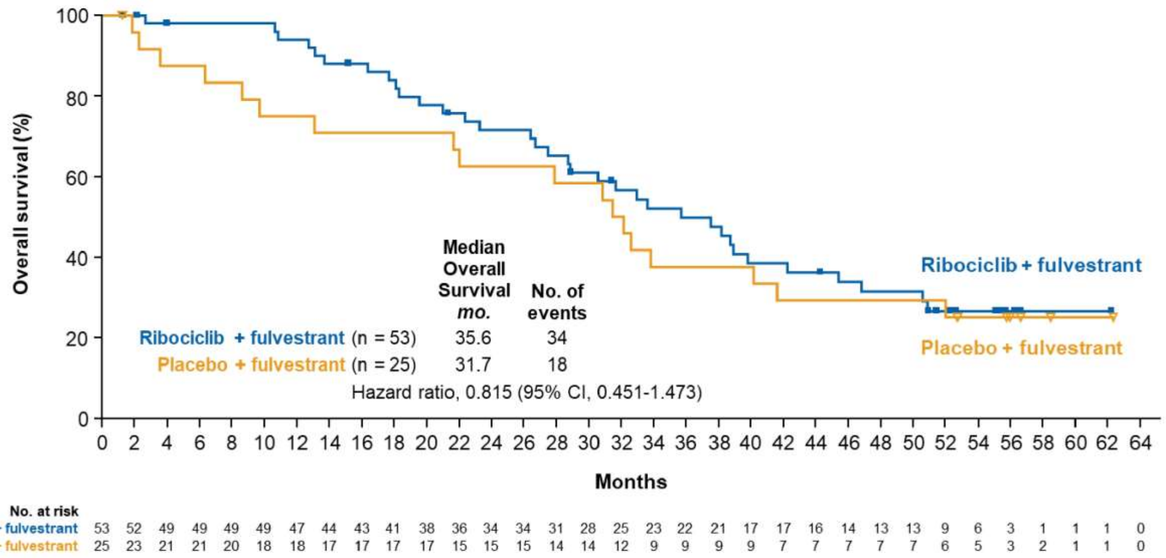


- A consistent OS benefit was observed across most subgroups, including harder-to-treat patients, eg, patients with liver/lung metastases, ≥ 3 metastatic sites, and endocrine resistance

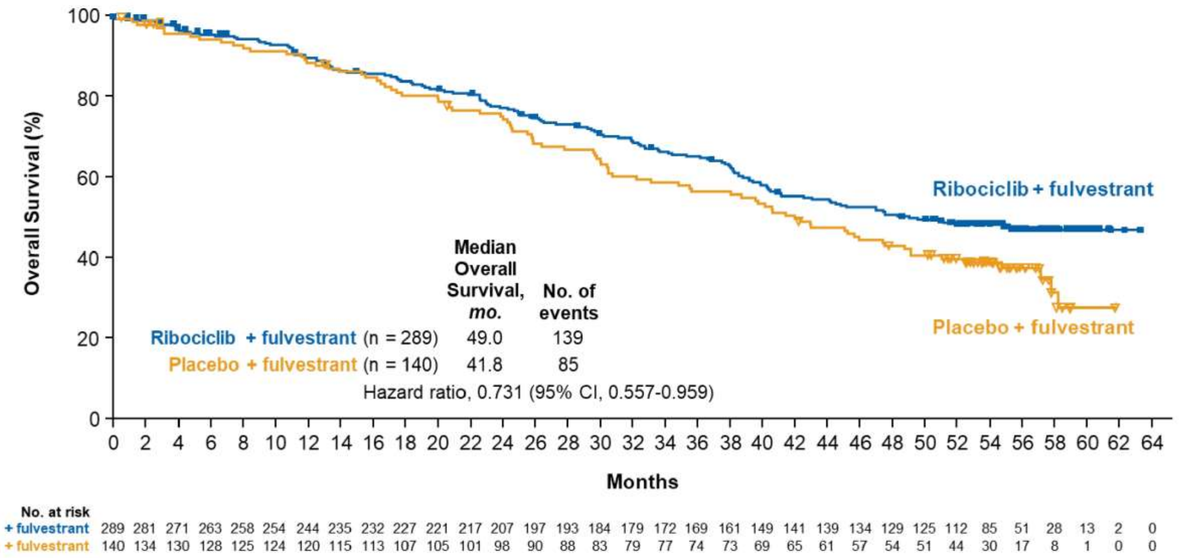
Data cutoff: October 30, 2020.
ET, endocrine therapy; OS, overall survival.

Overall Survival by Endocrine Sensitivity

Endocrine-resistant[a] population



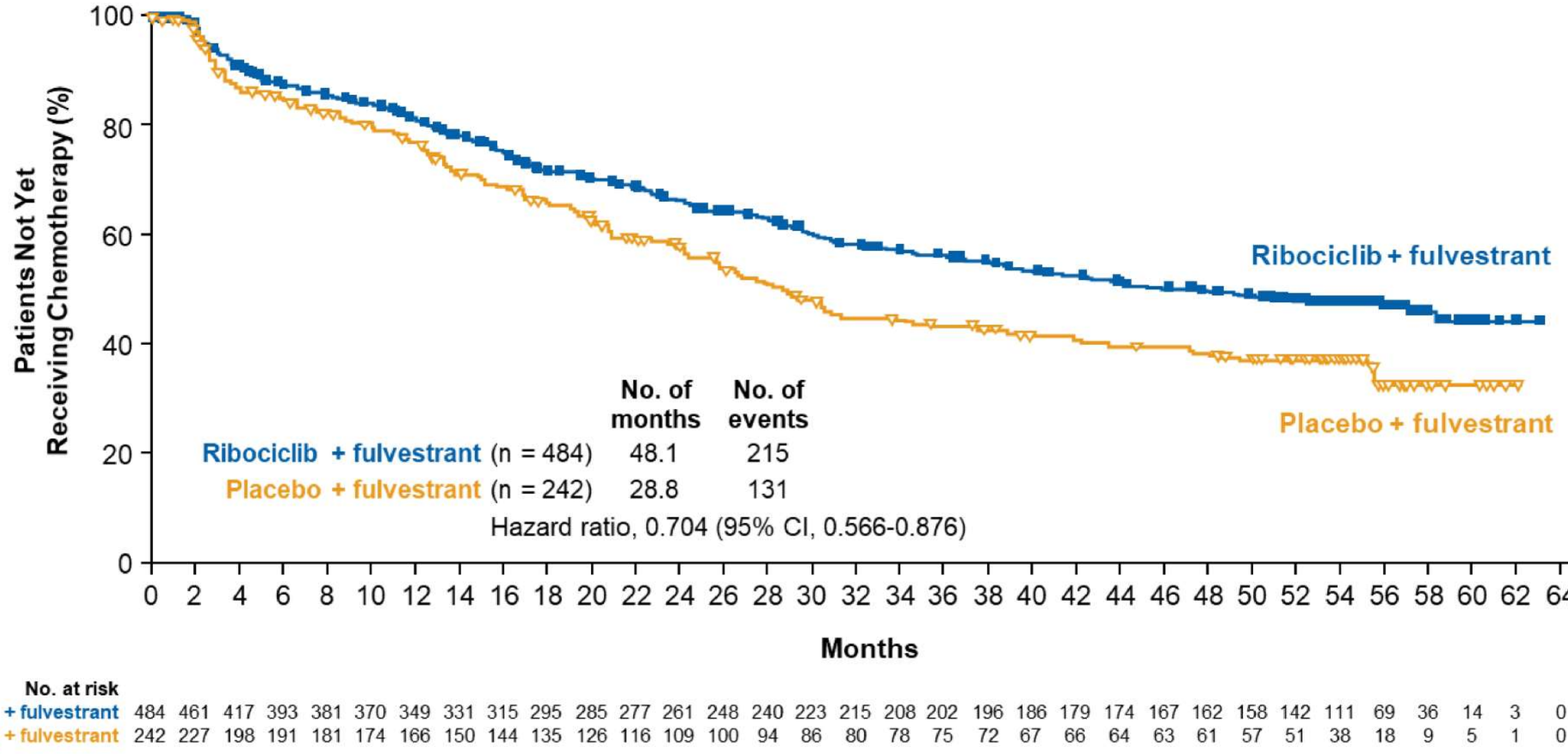
Endocrine-sensitive[b] population



- 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]

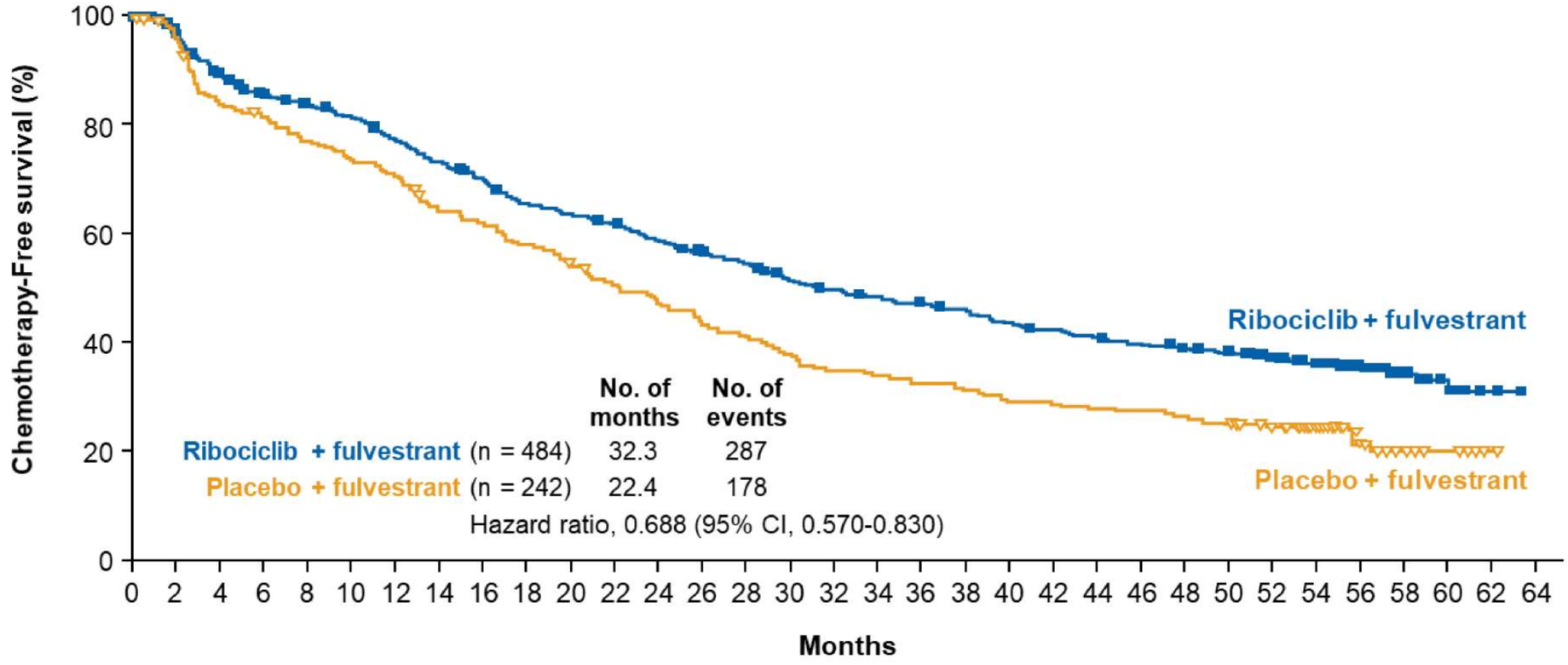


- Ribociclib + fulvestrant was associated with a nearly 20-month delay in first subsequent chemotherapy use over placebo + fulvestrant

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]

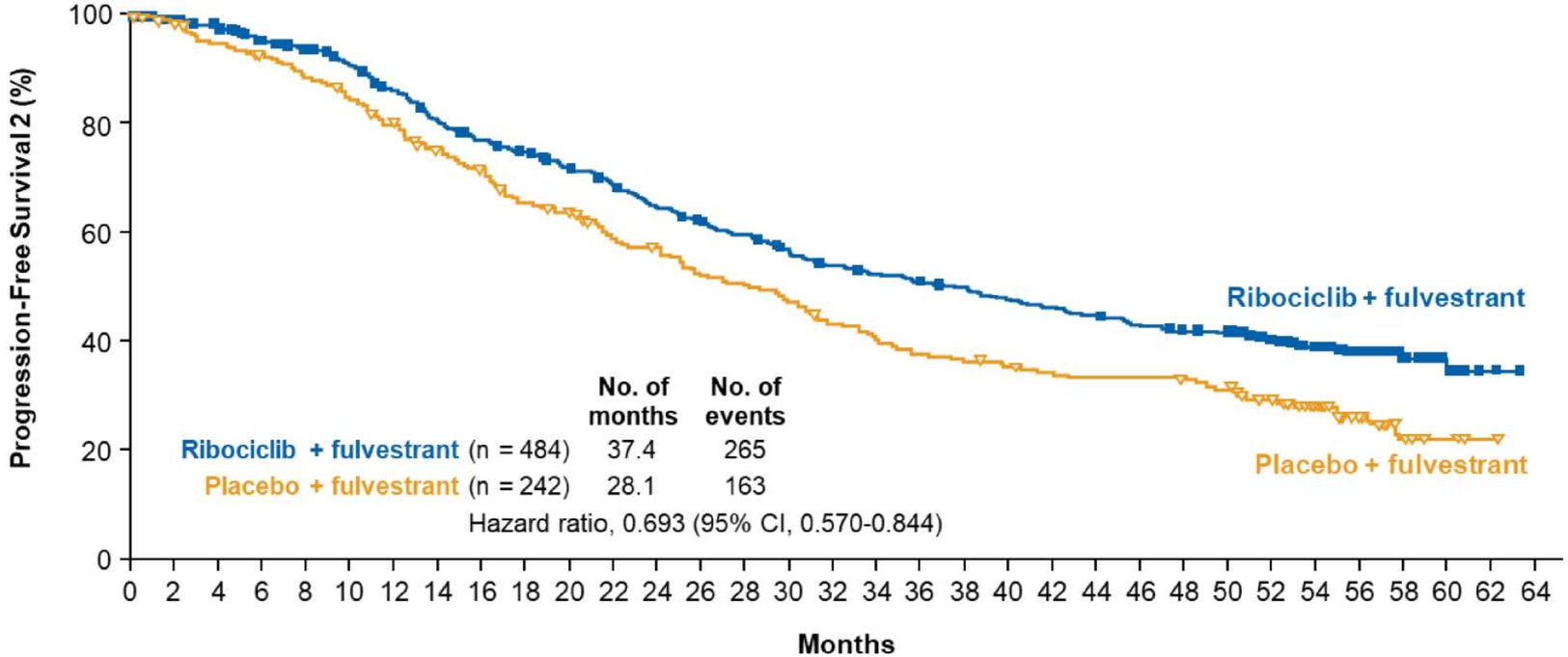


- Chemotherapy-free survival was approximately 10 months longer with ribociclib + fulvestrant over placebo + fulvestrant

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

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