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PD2-04

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)

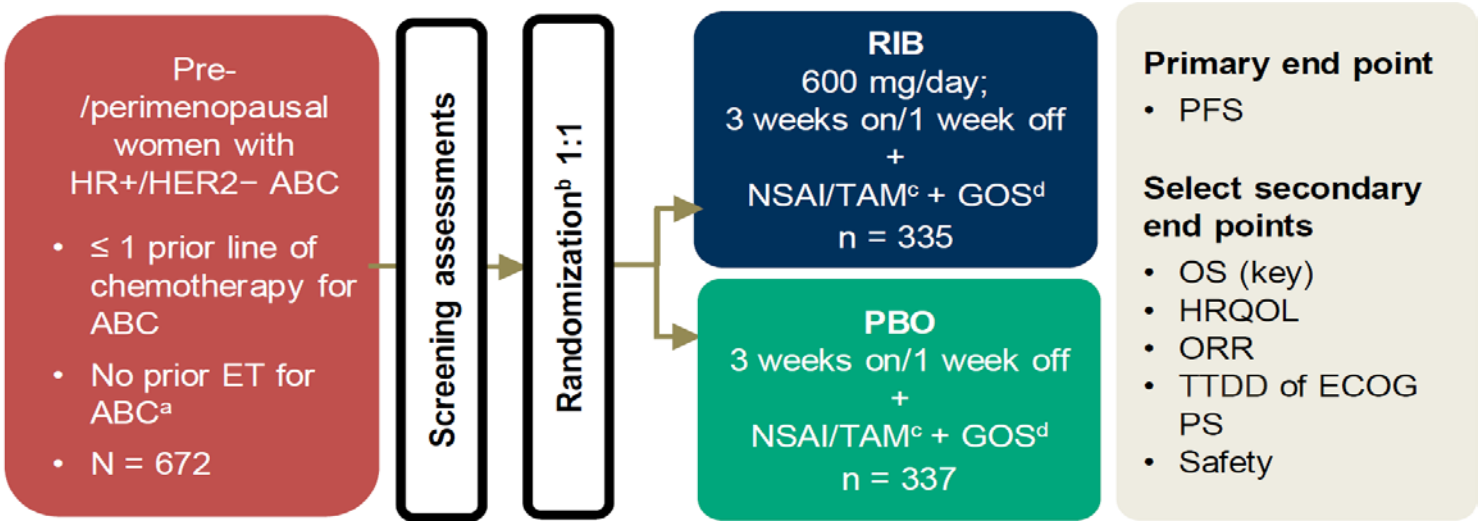
Patients and Study Design

- 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)

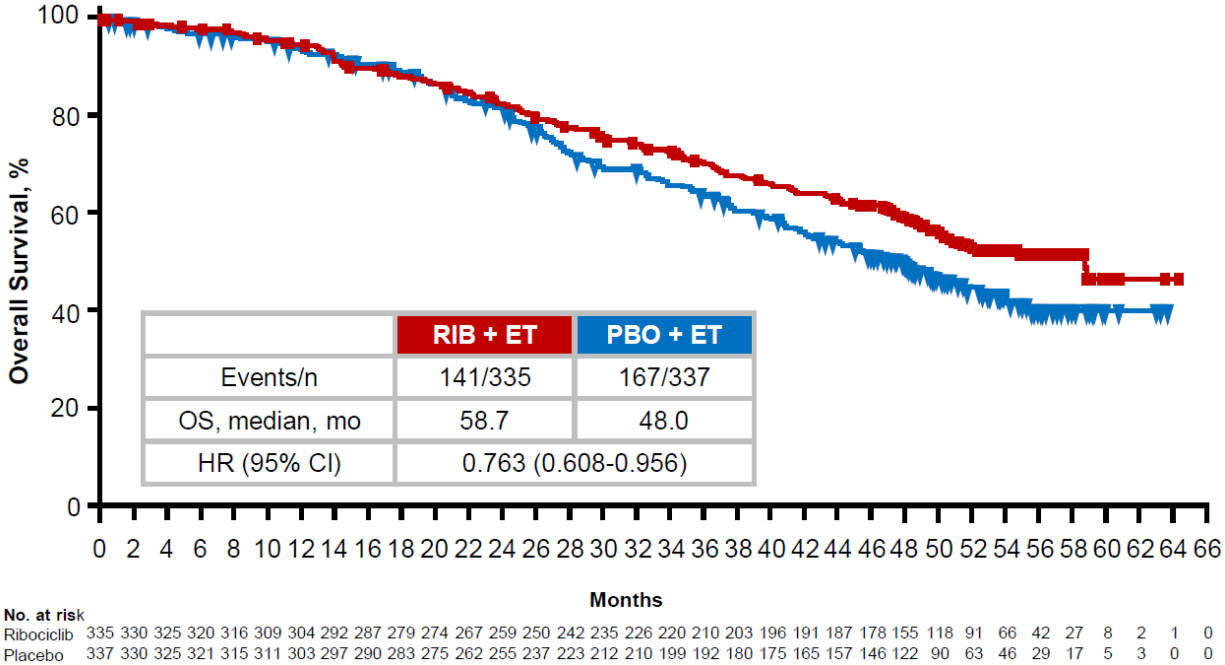
Overall Survival

- 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)

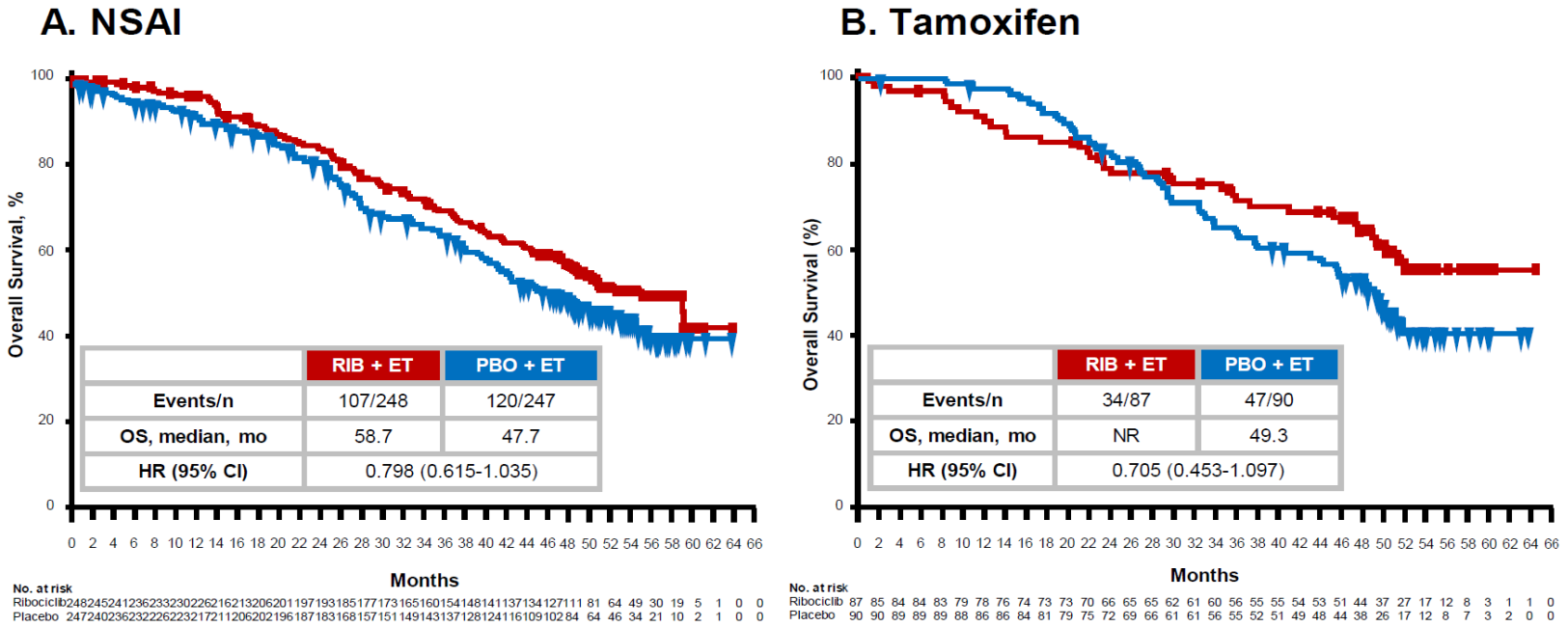
Figure 2. OS in the Intent-to-Treat Population



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

Results (5 of 11)

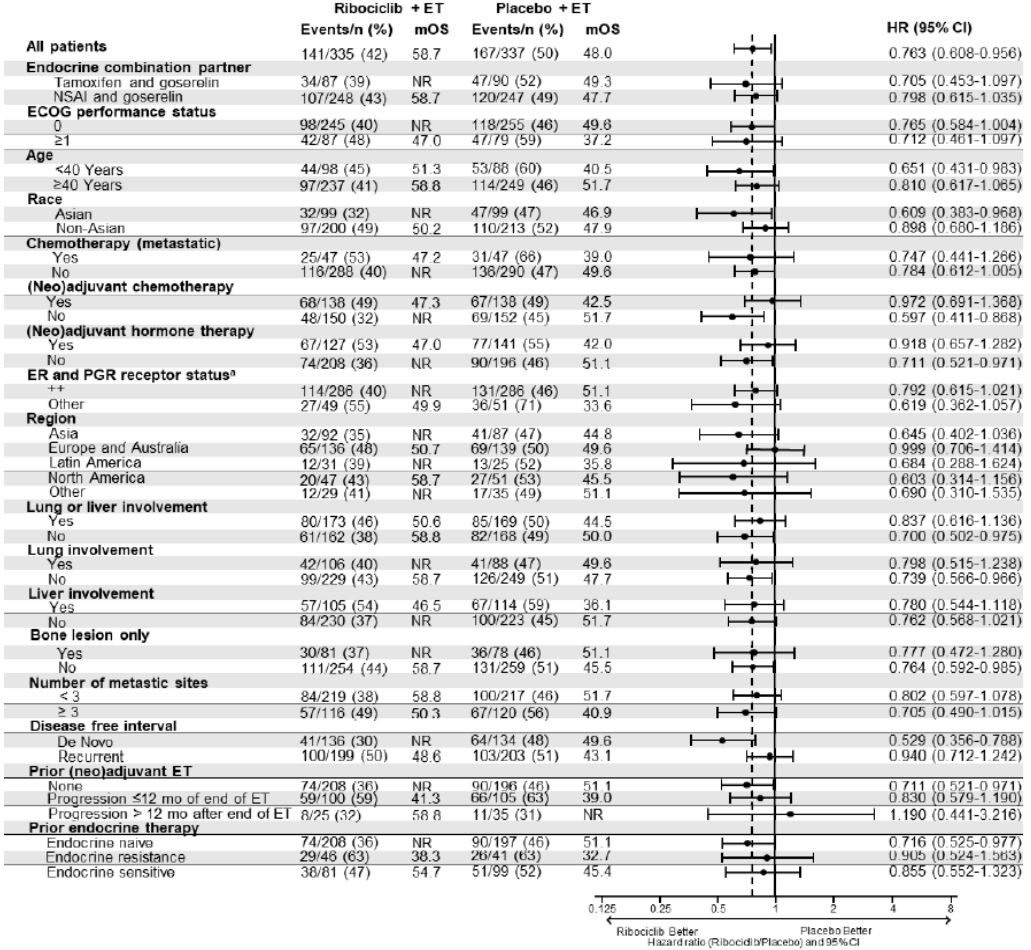
Figure 3. OS Subgroup Analyses by Endocrine Partner



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



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)

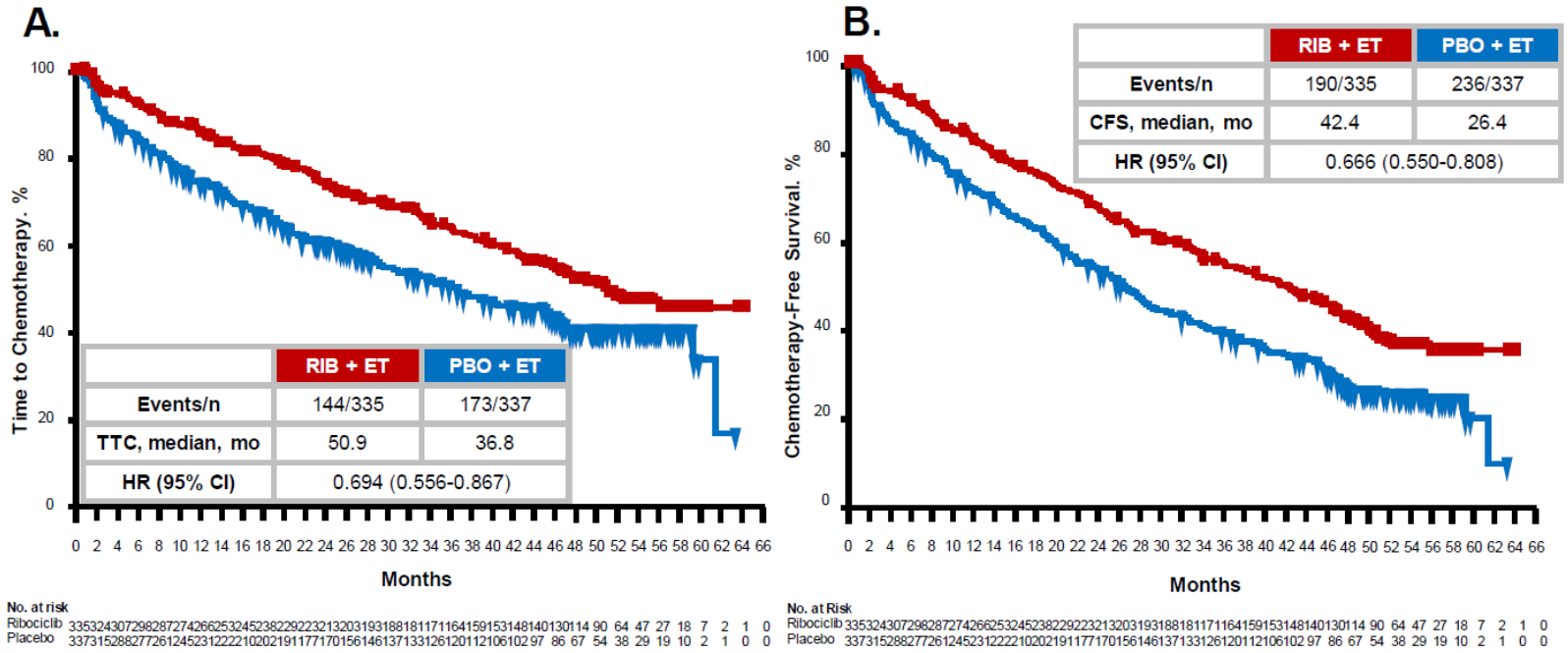
Subsequent Therapies and PFS2

- 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)

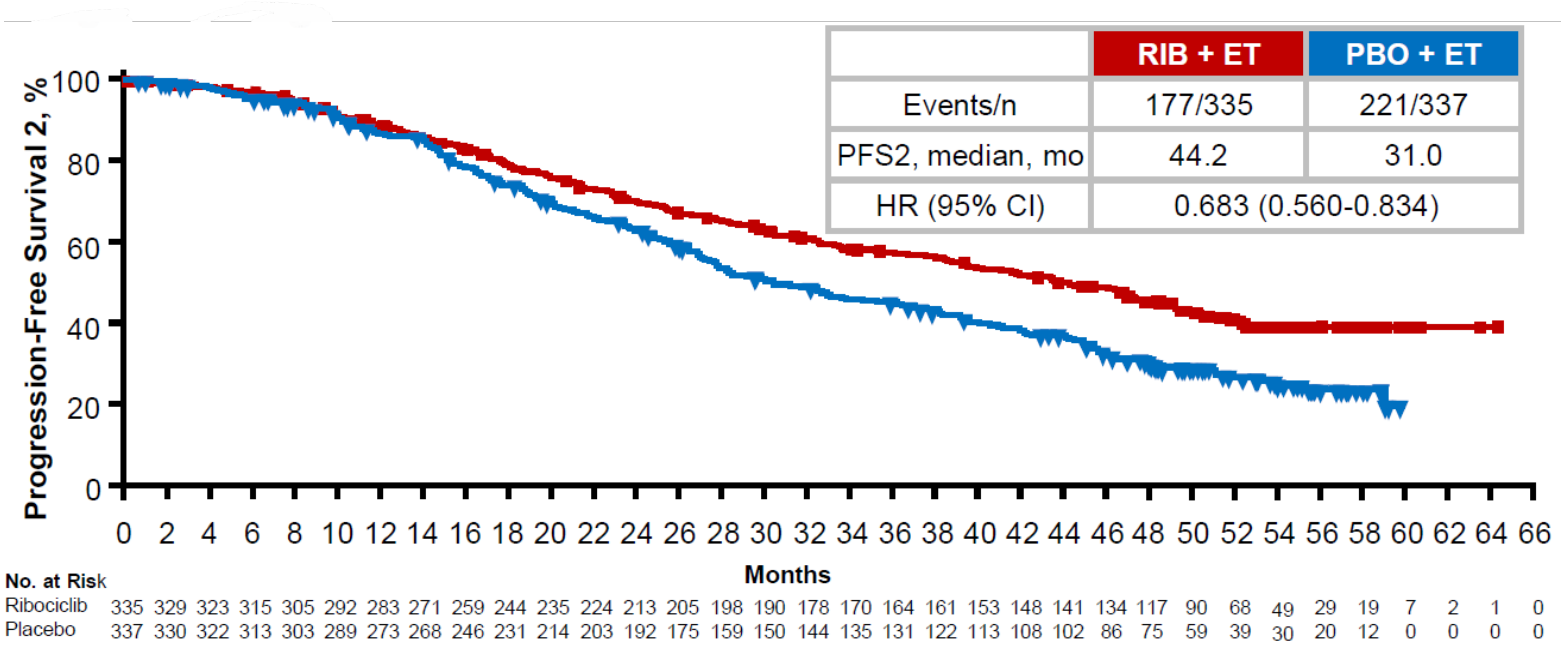
Figure 5. Time to Chemotherapy (A) and Chemotherapy-Free Survival (B)



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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