205P

Novartis Oncology

Pooled Exploratory Analysis of Survival in Patients with HR+/HER2− Advanced Breast Cancer and Visceral Metastases Treated With Ribociclib + Endocrine Therapy in the MONALEESA Trials

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Introduction

- Visceral metastases in patients with hormone receptor–positive/human epidermal growth factor–negative (HR+/HER2–) advanced breast cancer (ABC) indicate a more aggressive cancer that shows less treatment benefit and shorter time to disease progression, with particularly poor survival in those with liver metastases or multiple metastatic sites[1,2]
- The three Phase III MONALEESA (ML) trials have demonstrated statistically significant progression-free survival (PFS) and overall survival (OS) benefits of ribociclib (RIB) + endocrine therapy (ET) in patients with HR+/HER2− ABC[3-11]
- The median PFS (mPFS) and median OS (mOS) benefit of RIB + ET over placebo (PBO) + ET in patients with visceral metastases (and in those with liver metastases) was previously demonstrated in both the ML-3 and ML-7 trials[12]
- Here we present a large pooled PFS and OS analysis in patients with visceral metastases, with a focus on those with liver metastases or multiple metastatic sites, in the overall and first-line (1L) populations of the ML-2, -3, and -7 trials

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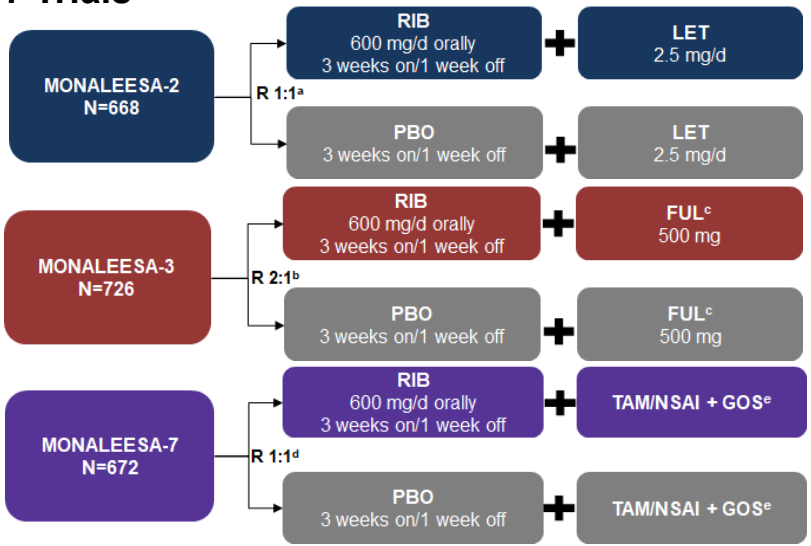
Methods (1 of 2)

- ML-2 and ML-3 included postmenopausal women while ML-7 included premenopausal women; the study designs for the three trials are shown in **Figure 1** (from ML-7**,** the current analysis only included patients in the non-steroidal aromatase inhibitor [NSAI] cohort)

Figure 1. Study Designs of the ML-2, ML-3, and ML-7 Trials



[a] Stratified by presence/absence of liver/lung metastases; [b] Stratified by presence/absence of liver/lung metastases and prior ET; [c] FUL administered intramuscularly on cycle 1 day 1, cycle 1 day 15, and day 1 of every 28-day cycle thereafter; [d] Stratified by presence/absence of liver/lung metastases, prior chemotherapy for advanced disease, and ET partner (TAM vs NSAI); [e] TAM: 20 mg/d, NSAI: anastrozole 1 mg/d or letrozole 2.5 mg/d, GOS: 3.6 mg every 28 days.
FUL, fulvestrant; GOS, goserelin; LET, letrozole; ML, MONALEESA; NSAI, non-steroidal aromatase inhibitor; PBO, placebo; R, randomized; RIB, ribociclib; TAM, tamoxifen.

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Methods (2 of 2)

- In this exploratory analysis, mPFS and mOS were evaluated using Kaplan-Meier methods in a pooled dataset of patients with (1) visceral metastases, (2) liver metastases, and (3) visceral metastases with ≥3 metastatic sites (of any type) from the three trials; the same analyses were conducted in the 1L population separately
- For this analysis, 1L patients were defined as those with de novo disease (no prior exposure to ET) and those with relapse >12 months from the end of (neo)adjuvant ET (late relapse); patients with relapse ≤12 months from the end of (neo)adjuvant ET (early relapse) were excluded from this subgroup definition as they behave more like second-line (2L) patients; data from the 2L patient population were not analyzed separately

1L, first-line; 2L, second-line; ET, endocrine therapy; mOS, median overall survival; mPFS, median progression-free survival.

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Results (1 of 8)

Characteristics and Disposition of Patients With Visceral Metastases

- Of the 1889 patients included from the ML trials, the majority (n=1124; 59.5%) had visceral metastases **(Table 1)**; of the 1229 patients receiving 1L therapy, 57.7% (n=709) had visceral metastases
- The median time between randomization and cutoff date for patients in the RIB and PBO arm of the visceral metastases group was 71.26 and 72.23 months, respectively
- At the data cutoff for this analysis, 12.5% of patients with visceral metastases in the RIB arm and 6.8% in the PBO arm were still receiving treatment; treatment was discontinued in others primarily due to progressive disease (RIB arm, 65.9%; PBO arm, 78.5%)

Table 1. Baseline Characteristics of Patients With Visceral Metastases

	RIB + ET	PBO + ET
Visceral metastases, n	**640**	**484**
Age, median, y	58.0	57.0
ECOG PS, n (%)		
0	408 (63.8)	319 (65.9)
1	230 (35.9)	164 (33.9)
No. of metastatic sites, n (%)		
1	76 (11.9)	68 (14.0)
2	230 (35.9)	153 (31.6)
3	196 (30.6)	146 (30.2)
4	95 (14.8)	77 (15.9)
≥5	43 (6.7)	40 (8.3)
Site of visceral metastasis, n (%)		
Lung	382 (59.7)	289 (59.7)
Liver	276 (43.1)	222 (45.9)
Liver or lung	560 (87.5)	441 (91.1)
CNS	6 (0.9)	2 (0.4)
Other[a]	161 (25.2)	102 (21.1)
Treatment-free interval (defined as time from end of [neo]adjuvant treatment to disease recurrence)		
De novo[b]	139 (21.7)	111 (22.9)
≤12 mo[c]	199 (31.1)	157 (32.4)

[a] Other visceral includes any metastatic sites other than soft tissue, breast, bone, lung, liver, CNS, skin and lymph nodes; [b] de novo refers to (1) no date of first recurrence/progression or (2) first recurrence/progression within 90 days of initial diagnosis with no prior antineoplastic therapy received, including medication or medication/radiation (for ML-2); [c] Percentage of patients with treatment-free interval ≤12 months for the RIB and PBO arms in the intent-to-treat (ML-2, ML-3) and NSAI (ML-7) populations: ML-2, 17.7% and 19.2%; ML-3, 28.5% and 29.3%; ML-7: 39.1% and 40.9%, respectively.
CNS, central nervous system; ECOG PS; Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; ML, MONALEESA; NSAI, non-steroidal aromatase inhibitor; PBO, placebo; RIB, ribociclib.

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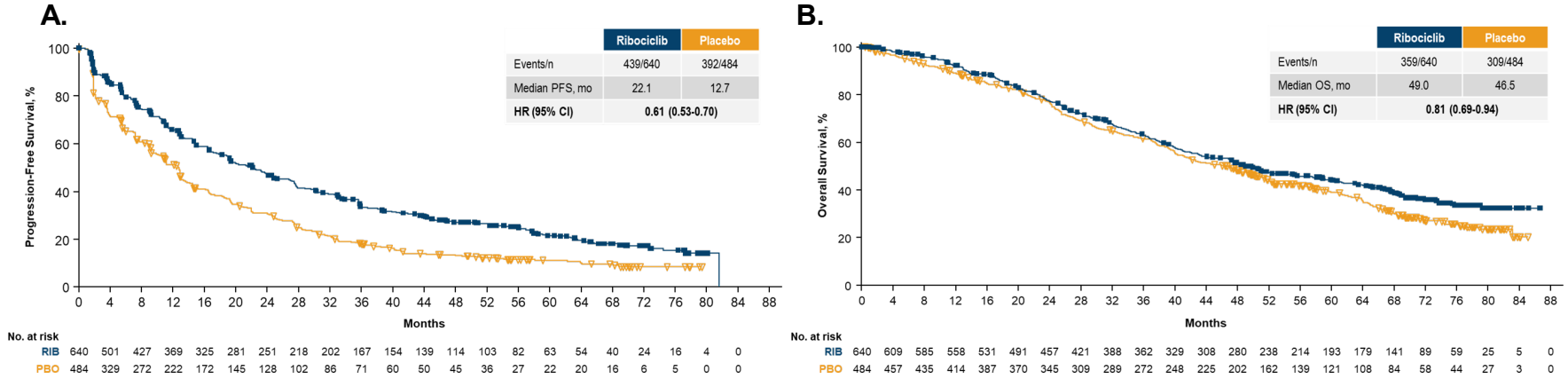
Results (2 of 8)

Survival in Patients With Visceral Metastasis

- In the overall population of patients with visceral metastases, RIB was associated with a 39% relative reduction in risk of disease progression or death (mPFS, 22.1 vs 12.7 months; HR, 0.61; 95% CI, 0.53-0.70) and a 19% relative reduction in risk of death (mOS, 49.0 vs 46.5 months; HR, 0.81; 95% CI, 0.69-0.94) vs PBO, respectively (**Figure 2A and B**)

Figure 2A and B. PFS and OS in All Patients With Visceral Metastases



CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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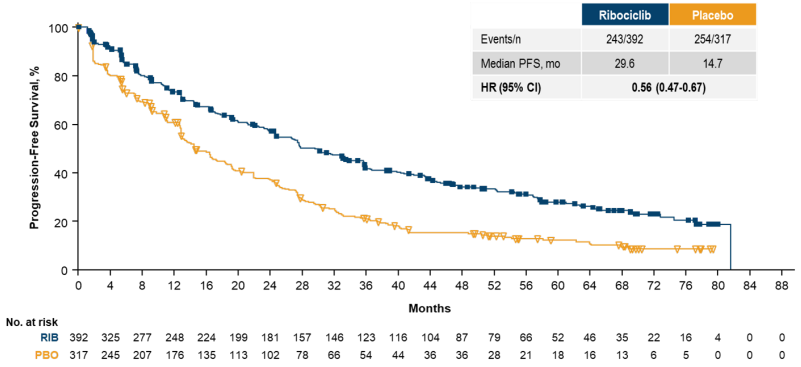
Results (3 of 8)

Survival in Patients With Visceral Metastasis

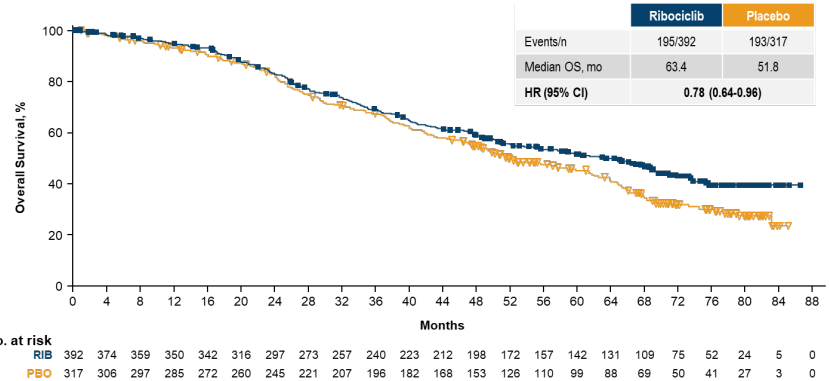
- Likewise, in the 1L population of patients with visceral metastases, RIB was associated with a nearly 15-month longer mPFS (29.6 vs 14.7 months; HR, 0.56; 95% CI, 0.47-0.67) and a nearly 12-month-longer mOS (63.4 vs 51.8 months; HR, 0.78; 95% CI, 0.64-0.96) vs PBO (**Figure 2C and D**)

Figure 2C and D. PFS and OS in 1L Patients With Visceral Metastases

C.



D.



1L, first-line; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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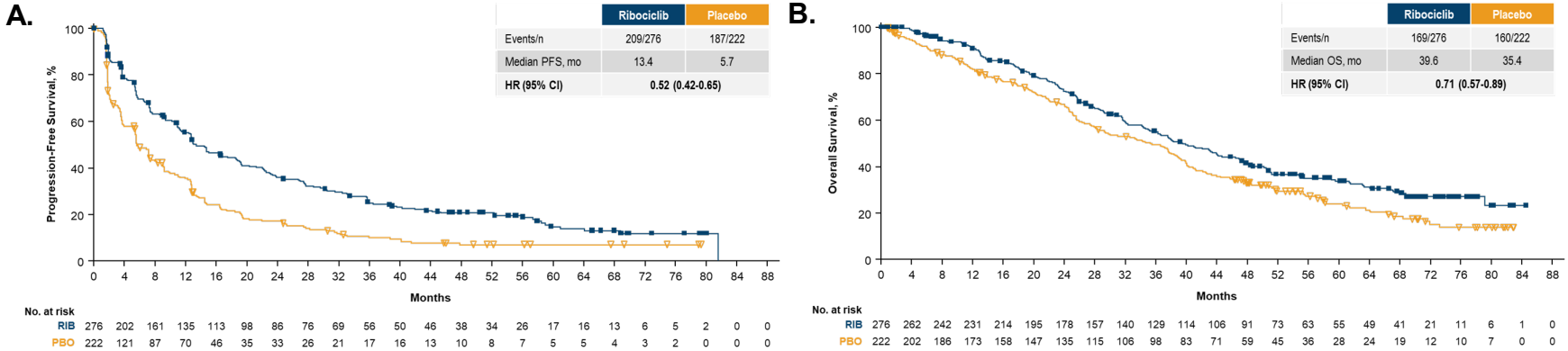
Results (4 of 8)

Survival in Patients With Visceral Metastasis

- Overall, 498 of 1889 patients (26.4%) had liver metastases; 247 (89.5%) and 212 (95.5%) of these patients in the RIB and PBO arms had discontinued treatment at the data cutoff; 256 of the 1229 patients (20.8%) receiving 1L therapy had liver metastases
- In the overall population of patients with liver metastases, RIB was associated with a 48% relative reduction in the risk of disease progression or death (mPFS, 13.4 vs 5.7 months; HR, 0.52; 95% CI, 0.42-0.65) and a 29% relative reduction in the risk of death (mOS, 39.6 vs 35.4 months; HR, 0.71; 95% CI, 0.57-0.89) vs PBO (**Figure 3A and B**)

Figure 3A and B. PFS and OS in All Patients With Liver Metastases



CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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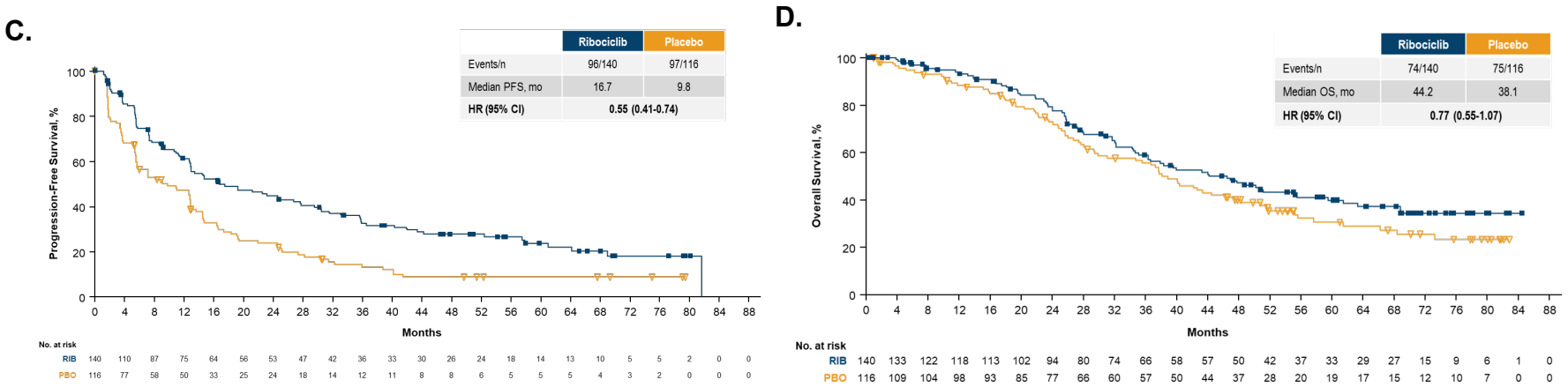
Results (5 of 8)

Survival in Patients With Visceral Metastasis

- Similarly, in the 1L population of patients with liver metastases, RIB was associated with a significantly longer mPFS (16.7 vs 9.8 months; HR, 0.55; 95% CI, 0.41-0.74) and a numerically longer mOS (44.2 vs 38.1 months; HR, 0.77; 95% CI, 0.55-1.07) vs PBO (**Figure 3C and D**)

Figure 3C and D. PFS and OS in 1L Patients With Liver Metastases



1L, first-line; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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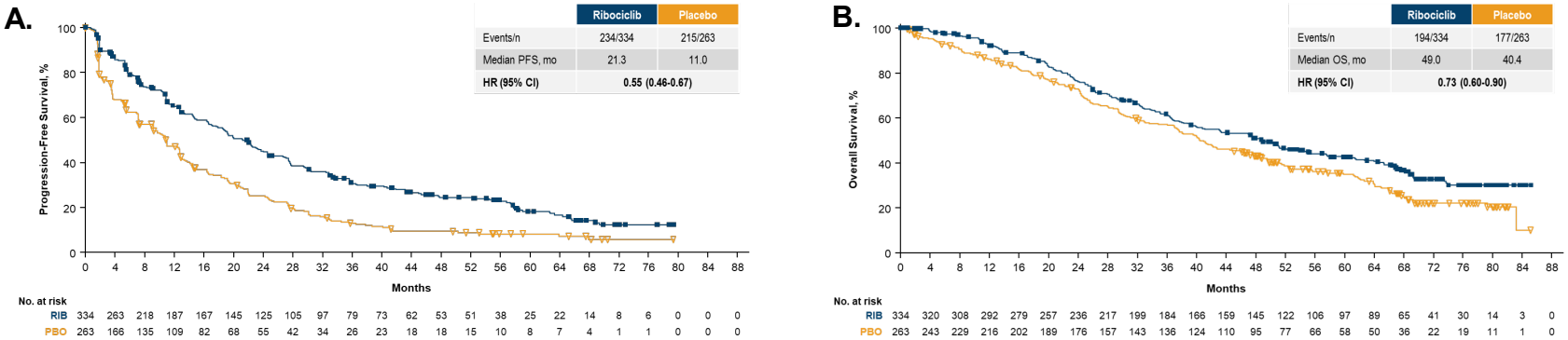
Results (6 of 8)

Survival in Patients With Visceral Metastasis and ≥3 Metastatic Disease Sites

- In total, 597 of 1889 patients (31.6%) had visceral metastasis and ≥3 metastatic sites (of any type); 299 (89.5%) and 249 (94.7%) patients on RIB and PBO had discontinued treatment at the data cutoff; 447 of the 1229 patients (36.4%) receiving 1L therapy had ≥3 metastatic sites
- RIB treatment was associated with a survival benefit in patients with ≥3 metastatic sites, with a significantly longer mPFS (21.3 vs 11.0 months; HR, 0.55; 95% CI, 0.46-0.67) and mOS (49.0 vs 40.4 months; HR, 0.73; 95% CI, 0.60-0.90) vs PBO (**Figure 4A and B**)

Figure 4A and B. PFS and OS in All Patients With ≥3 Metastatic Sites



CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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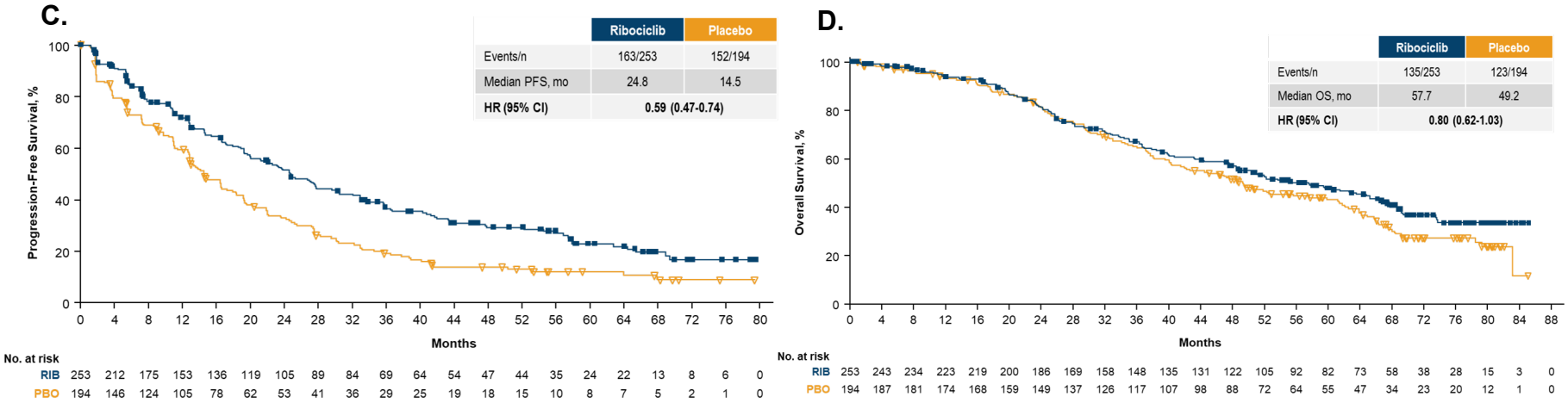
Results (7 of 8)

Survival in Patients With Visceral Metastasis and ≥3 Metastatic Disease Sites

- The 1L population with ≥3 metastatic sites also benefited with RIB, with a significantly longer mPFS (24.8 vs 14.5 months; HR, 0.59; 95% CI, 0.47-0.74) and a numerically longer mOS (57.7 vs 49.2 months; HR, 0.80; 95% CI, 0.62-1.03) vs PBO (**Figure 4C and D**)

Figure 4C and D. PFS and OS in 1L Patients With ≥3 Metastatic Sites



1L, first-line; CI, confidence interval; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

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Results (8 of 8)

Adverse Events in Patients With Visceral and Liver Metastases

- Adverse events (AEs) in patients with visceral metastases receiving RIB were consistent with AEs in those without visceral metastases (**Table 2**)
  - Likewise, rates of AEs of special interest (AESIs) in the RIB arms were similar in patients with vs without visceral metastasis, respectively - AESI ≥20% (all grade) in RIB arm: neutropenia (77.2% vs 73.5%), infections (56.8% vs 61.3%), leukopenia (35.2% vs 34.5%), hepatobiliary toxicity (27.2% vs 27.9%), and anemia (21.4% vs 21.4%)
- The rates of AEs were similar between patients with and without liver metastases
  - Rates of all-grade neutropenia (59.3% vs 64.3%), nausea (45.1% vs 49.2%), diarrhea (33.8% vs 32.4%), fatigue (30.5% vs 35.4%), and arthralgia (30.2% vs 42.0%) were similar in patients with vs without liver metastases in the RIB arm, respectively
  - Rates of grade 3/4 alanine aminotransferase (7.3% vs 9.9%) and aspartate aminotransferase (7.6% vs 5.5%) elevations were similar in patients with vs without liver metastases in the RIB arm, respectively

Table 2. AEs in Patients With or Without Visceral Metastases in the RIB Arm

AEs ≥30% in RIB Arm, n (%)	With Visceral Metastasis (n = 639)		Without Visceral Metastasis (n = 426)	
	All grade	Grade 3/4	All grade	Grade 3/4
Neutropenia	397 (62.1)	320 (50.1)	249 (58.5)	200 (46.9)
Nausea	303 (47.4)	15 (2.3)	194 (45.5)	3 (0.7)
Arthralgia	236 (36.9)	7 (1.1)	162 (38.0)	5 (1.2)
Fatigue	213 (33.3)	11 (1.7)	162 (38.0)	12 (2.8)
Diarrhea	211 (33.0)	13 (2.0)	146 (34.3)	7 (1.6)

AE, adverse event; AESI, AE of special interest; RIB, ribociclib.

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Key Findings and Conclusions

- This large, pooled, exploratory analysis of the ML trials confirms the consistent survival benefit with RIB + ET over ET alone across the 1L and 2L population of patients with HR+/HER2– ABC with aggressive disease, which frequently indicates a worse prognosis and resistance to treatment
- This analysis found that patients receiving 1L RIB + ET who had:
  - visceral metastases had a 44% relative reduction in risk of disease progression and a 22% reduction in the risk of death
  - liver metastases had a 45% relative reduction in risk of disease progression and a 23% reduction in the risk of death
  - visceral metastases and a high tumor burden had a 41% relative reduction in risk of disease progression and 20% reduction in the risk of death
- This trend of RIB benefit was consistent when the overall population of patients (1L and 2L) with visceral metastases, liver metastases, and a high tumor burden was analyzed
- No new safety signals were observed in this patient population with a high disease burden and aggressive disease, with no difference in rates of liver enzyme elevations in patients with liver metastases
- Patients with visceral metastases experienced a clinically meaningful survival benefit with RIB + ET over ET alone, with a 1-year improvement in mOS in patients receiving 1L therapy, making it an effective therapeutic option in this patient population

1L, first-line; 2L, second-line; ABC, advanced breast cancer; ET, endocrine therapy, HR+/HER2–, hormone receptor–positive/human epidermal growth factor–negative; ML, MONALEESA; mOS, median overall survival; RIB, ribociclib.

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References

1. Wang R, et al. *BMC Cancer*. 2019;19:1091.
2. Harb WA. *Cancer Manag Res*. 2015;7:37-46.
3. Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.
4. Slamon DJ, et al. *J Clin Oncol*. 2018;36:2465-2472.
5. Hortobagyi GN, et al. *N Engl J Med*. 2016;375:1738-1748.
6. Im SA, et al. *N Engl J Med*. 2019;381:307-316.
7. Slamon DJ, et al. *N Engl J Med.* 2020;382:514-524.
8. Hortobagyi GN, et al. *N Engl J Med*. 2022;386:942-950.
9. Hortobagyi GN, et al. ESMO 2021. Oral LBA17_PR.
10. Tripathy D, et al. SABCS 2020. Poster PD2-04.
11. Slamon DJ, et al. ASCO 2021. Oral 1001.
12. Yardley DA, et al. ASCO 2020. Poster P1054.

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