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Correlative biomarker analysis of intrinsic subtypes and efficacy across the MONALEESA Phase III studies

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Background

- The Phase III MONALEESA-2, -3, and -7 trials assessed the combination of RIB and ET in patients with HR+/HER2− ABC and showed a significant benefit in PFS with RIB over PBO[1-3]
- The prognostic and predictive value of the 4 main intrinsic subtypes of breast cancer (ie, luminal A, luminal B, HER2 enriched, and basal like) in HR+/HER2− ABC treated with ET and RIB is currently unknown
- Pooling samples across the MONALEESA trials (n = 1160) increases the sample size and statistical power for analysis of intrinsic subtype in patients treated with a CDK4/6 inhibitor
- In this retrospective, exploratory analysis, we evaluated the association of intrinsic subtypes with PFS and ORR to assess whether a prognostic and/or predictive relationship exists in tumor samples from the MONALEESA trials

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

1. Hortobagyi G, et al. *N Eng J Med*. 2016;375:1738-1748. 2. Slamon DJ, et al. *J Clin Oncol*. 2018;24:2465-2472;
3. Tripathy D, et al. *Lancet Oncol*. 2018;7:904-915.

Patients and methods

- Gene expression profiling of formalin-fixed, paraffin-embedded tumor samples was performed using a customized NanoString nCounter GX 800-gene panel (primary and metastatic samples)
- From the MONALEESA trials, 1303 tumor samples underwent gene expression and PAM50-based subtype profiling; 1160 samples passed quality control measures and were evaluated in this analysis

Study	RIB + ET, n	PBO + ET, n
MONALEESA-2	180	178
MONALEESA-3	329	160
MONALEESA-7	163	150

- The prognostic relationship of PAM50-based subtypes with PFS and risk of tumor progression by subtype and treatment were evaluated using univariate and multivariable Cox proportional hazard models
- Multivariable models were adjusted for known clinical prognostic factors, including age, prior CT, prior ET, ECOG performance status, presence of visceral disease (liver/lung metastases), presence of bone-only metastases, histological grade, number of metastatic sites, and presence of de novo metastatic disease

CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

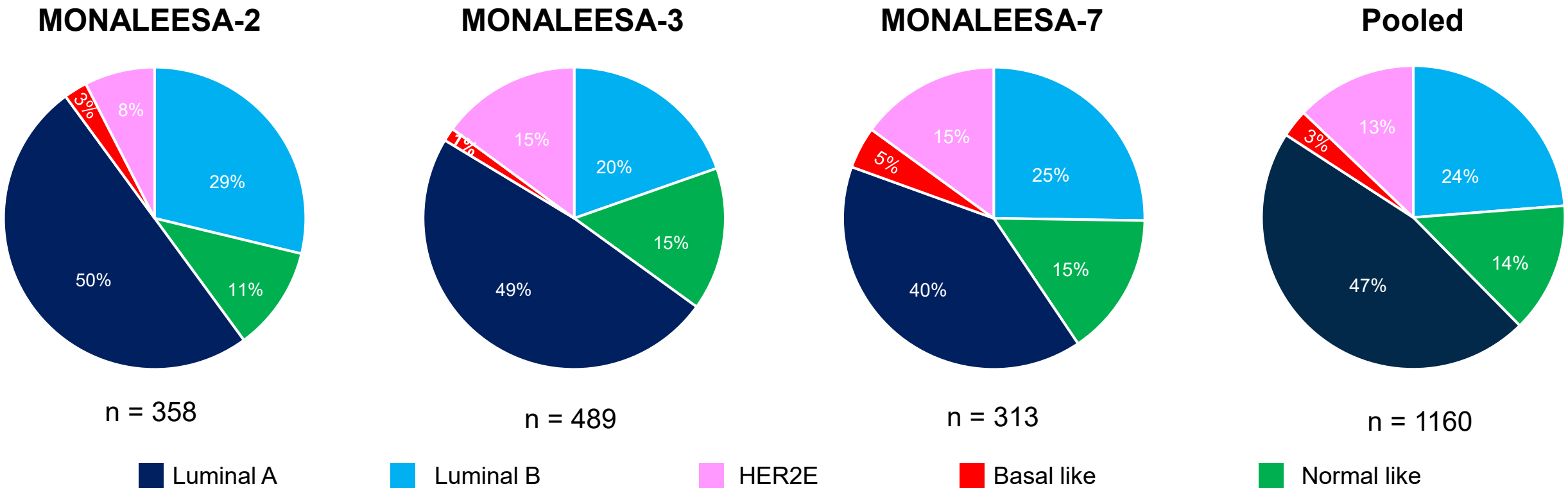
Selected patient characteristics

	Category	ITT Population		Biomarker Population	
		PBO (n = 913)	RIB (n = 1153)	PBO (n = 488)	RIB (n = 672)
		n (%)	n (%)	n (%)	n (%)
Histological grade	Well differentiated	91 (10.0)	103 (8.9)	52 (10.7)	58 (8.6)
	Moderately differentiated	396 (43.4)	533 (46.2)	213 (43.6)	323 (48.1)
	Undifferentiated/poorly differentiated	233 (25.5)	270 (23.4)	131 (26.8)	166 (24.7)
	Missing/unknown	193 (21.1)	247 (21.4)	92 (18.9)	125(18.6)
ECOG performance status	0	615 (67.4)	760 (65.9)	332 (68.0)	445 (66.2)
	1+	294 (32.2)	389 (33.7)	155 (31.8)	225 (33.5)
	Missing	4 (0.4)	4 (0.3)	1 (0.2)	2 (0.3)
De novo metastatic disease	Yes	289 (31.7)	347 (30.1)	156 (32.0)	212 (31.5)
	No	623 (68.2)	806 (69.9)	332 (68.0)	460 (68.5)
	Missing	1 (0.1)	NA	NA	NA
Visceral metastases (liver/lung)	Yes	482 (52.8)	597 (51.8)	259 (53.1)	364 (54.2)
	No	430 (47.1)	556 (48.2)	229 (46.9)	308 (45.8)
	Missing	1 (0.1)	NA	NA	NA

- Clinical-pathological characteristics of patients in the biomarker population were well balanced compared with the ITT population

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2E, HER2 enriched; ITT, intention to treat; NA, not applicable; PBO, placebo; RIB, ribociclib.

Intrinsic subtype distribution across the MONALEESA trials



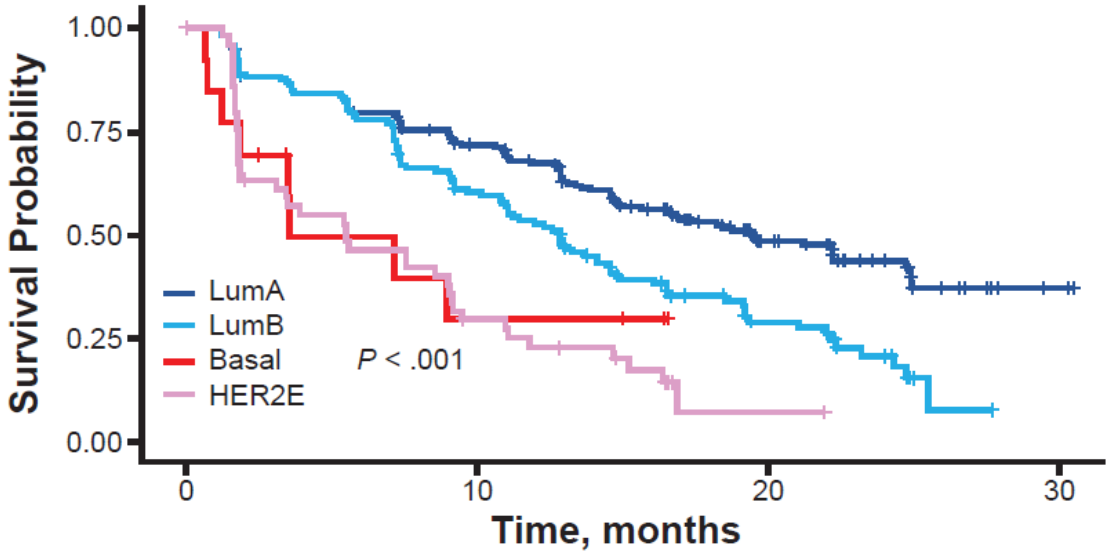
- The distribution of subtypes within each trial showed statistically significant differences, but when comparing the studies, the distribution of each subtype was similar, with luminal A being the most prevalent subtype and basal like being the least

HER2E, HER2 enriched.

Prognosis based on intrinsic subtype

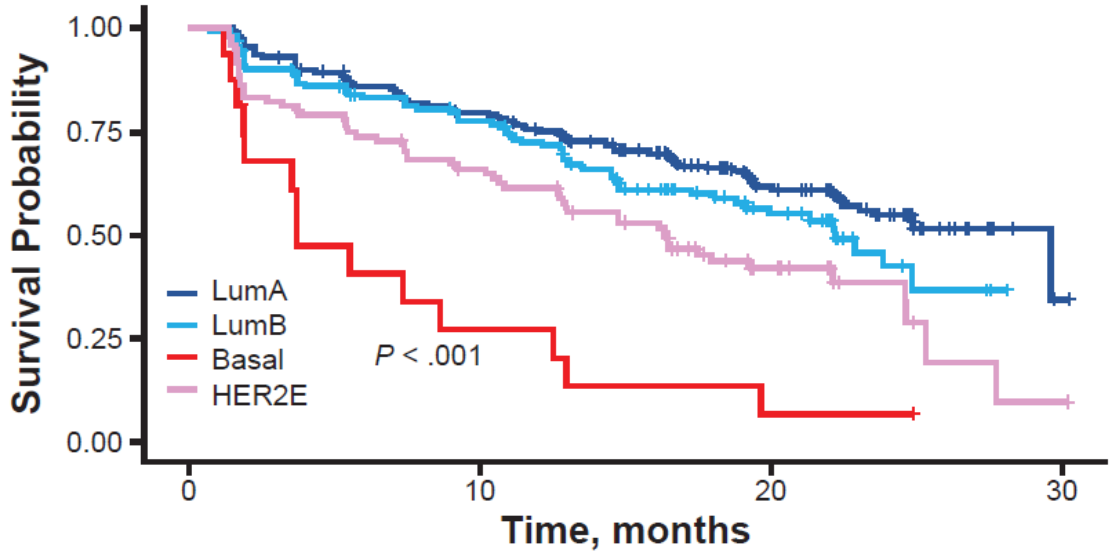
PBO

	n	Events, n	Median PFS	95% CI
LumA	222	110	19.48	15.61-24.80
LumB	124	89	12.85	10.84-14.82
Basal	14	8	3.58	1.87-NA
HER2E	52	41	5.52	3.12-9.17



RIB

	n	Events, n	Median PFS	95% CI
LumA	320	114	29.60	23.03-NA
LumB	154	66	22.21	18.79-NA
Basal	16	14	3.71	1.91-13.0
HER2E	95	56	16.39	12.71-24.6



- Basal-like subtype had the worst prognosis in both treatment arms
- Intrinsic subtype was significantly associated with PFS in both the PBO ($P < .0001$) and RIB ($P < .0001$) arms

HER2E, HER2 enriched; LumA, luminal A; LumB, luminal B; Basal, basal like; NA, not applicable; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Subtype remains prognostic after adjusting for clinical factors

Variable	RIB Arm		PBO Arm		All Patients	
	Adjusted PFS Hazard Ratio[a]	*P* Value	Adjusted PFS Hazard Ratio[a]	*P* Value	Adjusted PFS Hazard Ratio[a]	*P* Value
Luminal A	1.00	–	1.00	–	1.00	–
Luminal B	1.17	0.35	1.68	.00055	1.41	.0015
HER2E	1.76	.00082	3.47	< .0001	2.30	< .0001
Basal like	5.1	< .0001	3.05	.0040	3.97	< .0001
Normal like	0.98	.93	1.69	.0028	1.31	.039
RIB vs PBO	–	–	–	–	0.50	< .0001

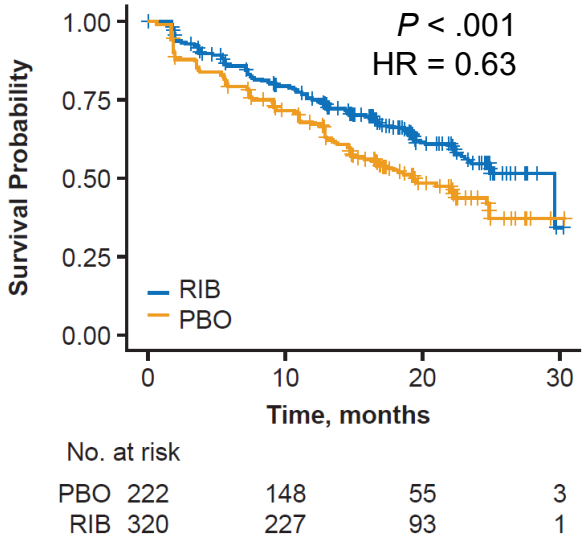
- Compared with luminal A, luminal B, HER2E, basal like, and normal like subtypes showed higher risk of tumor progression in all patients
- Compared with luminal A, HER2E and basal like subtypes showed higher risk of tumor progression in the RIB arm
- Intrinsic subtype was independently associated with PFS (*P* < .0001), after adjusting for ECOG PS, presence of de novo disease, presence of visceral disease, extent of histological grade differentiation, prior ET, and treatment arm

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HER2E, HER2 enriched; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

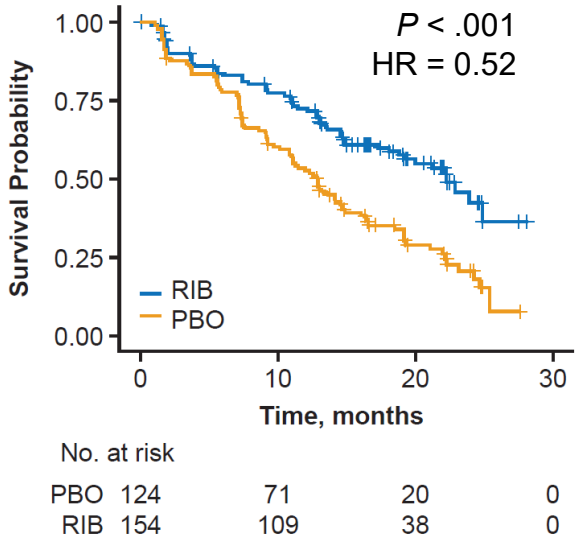
[a] Obtained from multivariable Cox model including age, prior chemotherapy, ECOG performance status, presence of visceral disease (liver/lung metastases), presence of bone-only metastases, histological grade, number of metastatic sites, prior ET, and presence of de novo metastatic disease as covariates.

PFS analysis by subtype

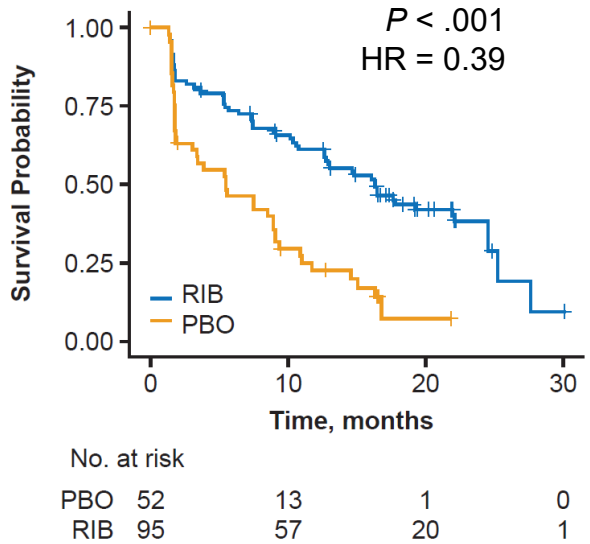
Luminal A



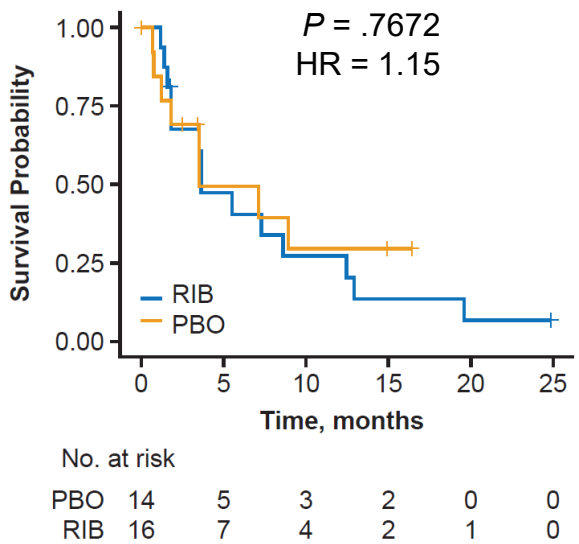
Luminal B



HER2E



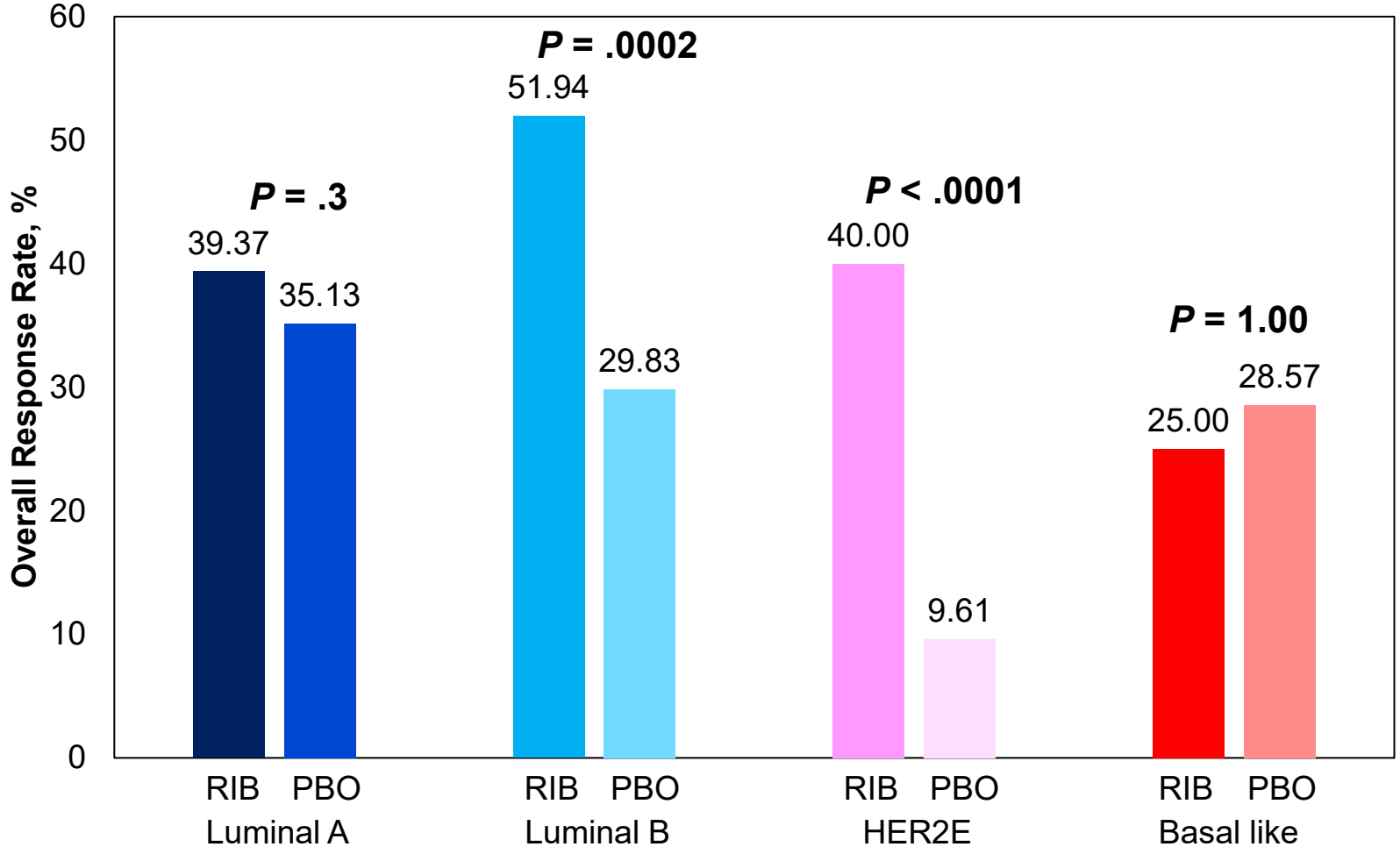
Basal like



- A PFS benefit of RIB vs PBO was observed in all subtypes except for basal like
- The interaction test between subtype and treatment arm was statistically significant (*P* = .045)

HER2E, HER2 enriched; PBO, placebo; PFS, progression-free survival; RIB, ribociclib.

Overall response rates by molecular subtype



- The HER2E and LumB subtypes demonstrated a significant increase in ORR with RIB treatment, while the other subtypes did not

HER2E, HER2 enriched; ORR, overall response rate; PBO, placebo; RIB, ribociclib.

Conclusions

- This is the largest analysis evaluating the correlation of intrinsic subtype with efficacy outcomes in patients treated with CDK4/6 inhibitors
- These results confirm the independent prognostic value of the intrinsic subtypes in patients treated with ET alone
- The prognostic value of intrinsic subtype is maintained in the context of ET in combination with RIB
- Patients with HER2E, luminal A, and luminal B subtypes all exhibited a consistent PFS benefit with RIB treatment, while patients with basal-like subtype did not
- The HER2E subtype exhibited the greatest relative reduction in risk of progression or death with RIB plus ET
- Further validation studies will be required to firmly establish the clinical utility of intrinsic subtype as a biomarker in HR+/HER2− ABC

ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinase 4/6; ET, endocrine therapy; HER2E, HER2 enriched; RIB, ribociclib.

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