Correlative Analysis of Overall Survival by Intrinsic Subtype Across the MONALEESA-2, -3, and -7 Studies of Ribociclib + Endocrine Therapy in Patients With HR+/HER2− Advanced Breast Cancer

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Disclosure Information

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- Institutional research funding from Syndax, Novartis, NanoString Technologies, AbbVie, Seattle Genetics, and Veracyte
- An immediate family member has a royalty-sharing agreement and investorship interest in licensed IP to start-up company Falcon Therapeutics
- Uncompensated relationships with Sanofi, Novartis, G1 Therapeutics, Genentech/Roche, GlaxoSmithKline, AstraZeneca/Daiichi Sankyo, Aptitude Health, Exact Sciences, and Eisai

Introduction

- Ribociclib + ET demonstrated statistically significant PFS and OS benefit in 3 phase 3 clinical trials (MONALEESA-2, -3, and -7) in patients with HR+/HER2− advanced breast cancer[1-6]
- A prior pooled analysis of patients in the MONALEESA trials demonstrated a significant PFS benefit with ribociclib + ET vs placebo + ET in the luminal A (HR, 0.63; *P* = .0007), luminal B (HR, 0.52; *P* < .0001), and HER2E (HR, 0.39; *P* < .0001) subtypes[7]
  - Note the meta-analysis of PFS by intrinsic subtype in HR+ MBC (Schettini F, et al. SABCS 2021. Poster P4-07-08.)
- This retrospective exploratory analysis evaluated the association of intrinsic subtype with OS using tumor samples pooled from the MONALEESA-2, -3, and -7 trials

ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HER2E, human epidermal growth factor receptor 2 enriched; HR, hazard ratio; HR+, hormone receptor positive; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival.

1. Hortobagyi G, et al. *N Eng J Med*. 2016;375(18):1738-1748. 2. Hortobagyi G, et al. ESMO 2021. Oral; abstract LBA17. 3. Slamon DJ, et al. *J Clin Oncol*. 2018;36(24):2465-2472. 4. Slamon DJ, el al. *N Engl J Med*. 2020;382(6):514-524. 5. Tripathy D, et al. *Lancet Oncol*. 2018;19(7):904-915. 6. Im S-A, et al. *N Engl J Med*. 2020; 382(6):514-524. 7. Prat A, et al. *J Clin Oncol*. 2021;39(13):1458-1467.

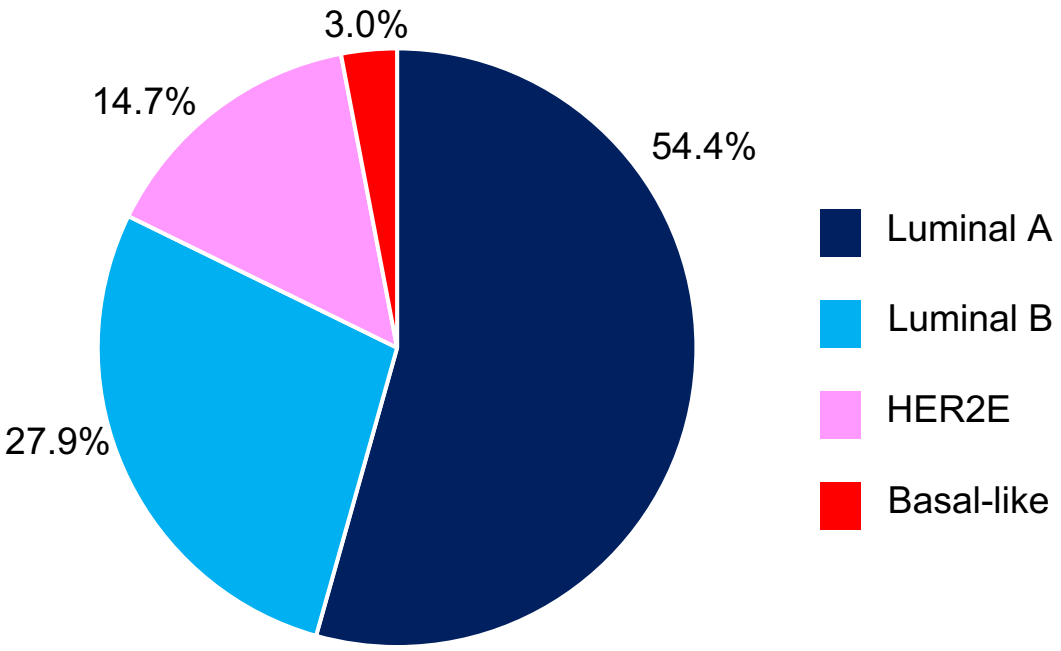
Methods

- Gene expression profiling was performed on tumor samples (primary and metastatic) by using a customized NanoString nCounter GX 800-gene panel, including 36/50 PAM50 genes
  - Intrinsic subtyping was performed using a 152-gene set that was selected based on the ability to identify PAM50 subtype in 48 independent tumors and the original PAM50 microarray training data set
- The relationships between PAM50-based subtypes with OS were evaluated using univariable and multivariable Cox proportional hazard models
  - Kaplan-Meier curves were generated, and median OS (95% CI) was estimated by subtype and treatment arm
  - Multivariable models were adjusted for known clinical prognostic factors
- The *P* values generated are descriptive and were not adjusted for multiplicity or false discovery

OS, overall survival; PAM50, Prediction Analysis of Microarray 50.

Tumor samples and subtype distribution

Subtype distribution in the pooled MONALEESA data set



Samples in this analysis (N = 997)[a]

- Ribociclib + ET (n = 585) and placebo + ET (n = 412)
  - MONALEESA-2: 318 samples
  - MONALEESA-3: 414 samples
  - MONALEESA-7: 265 samples
- 71% were from primary tumors in the pooled data set
  - MONALEESA-2: 73% primary
  - MONALEESA-3: 68% primary
  - MONALEESA-7: 74% primary

ET, endocrine therapy; HER2E, human epidermal growth factor receptor 2 enriched.
[a] Samples with normal-like subtype (n = 163) were excluded from this analysis because this subtype has a high proportion of normal tissue.

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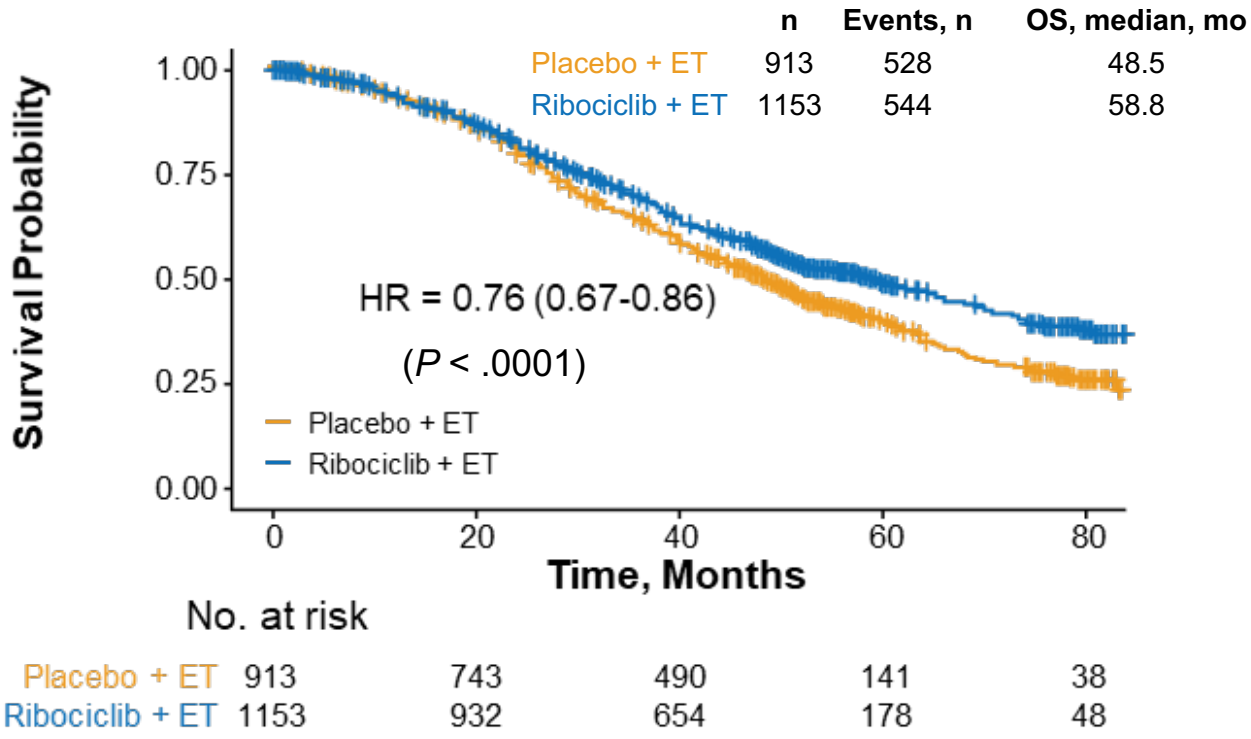
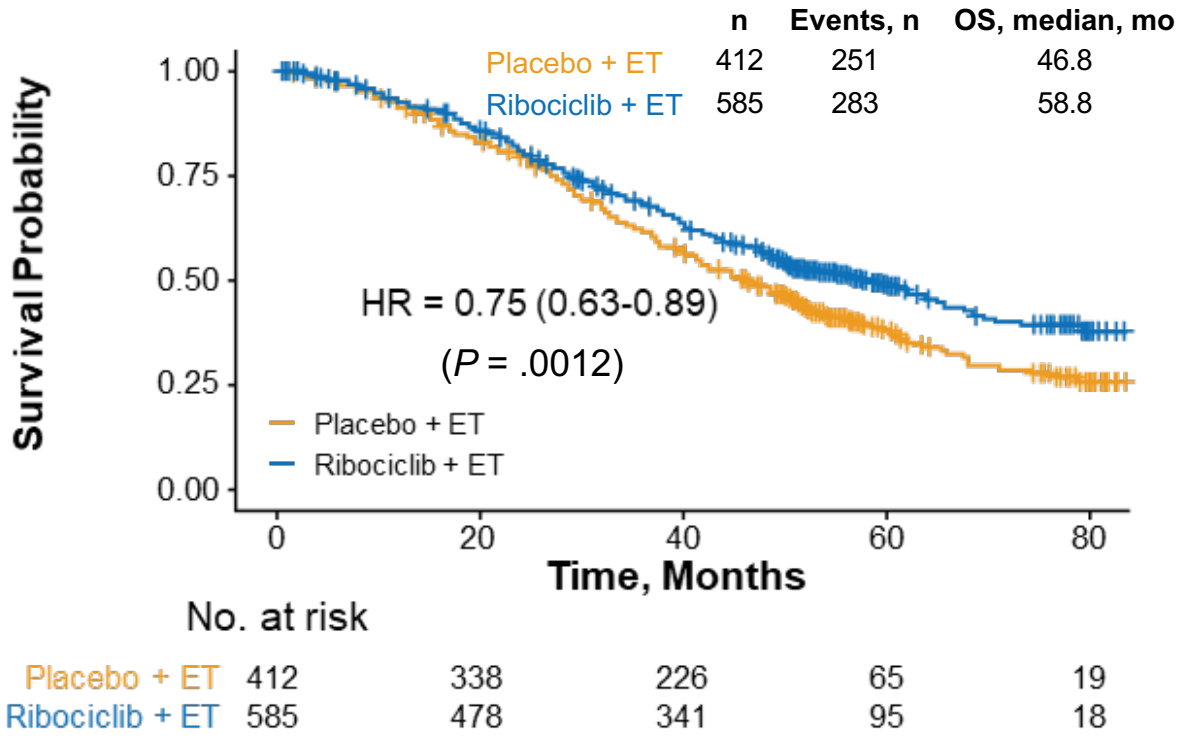
Consistent OS benefit in the ITT and biomarker populations

ITT (N = 2066)



Biomarker (n = 997)



- Similar OS benefit with ribociclib + ET vs placebo + ET in both ITT and biomarker populations

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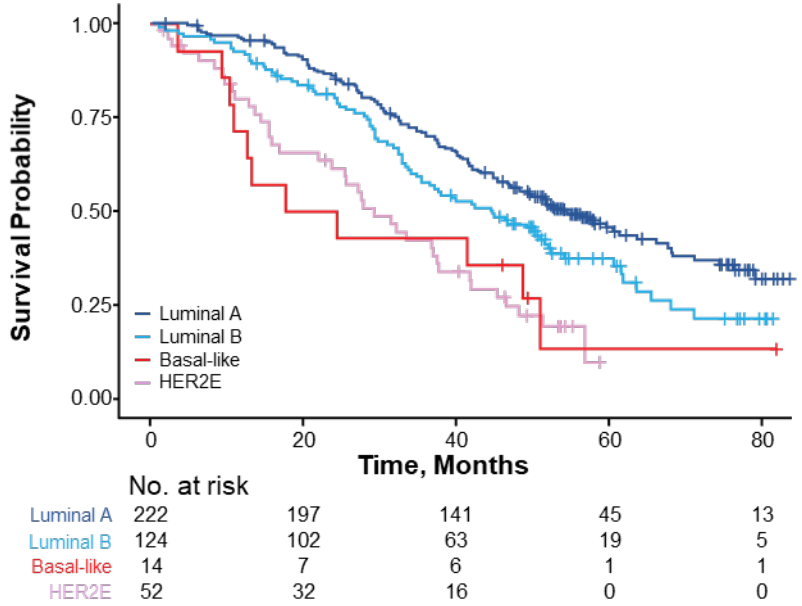
ET, endocrine therapy; ITT, intent to treat; OS, overall survival.

Intrinsic subtype was prognostic for OS

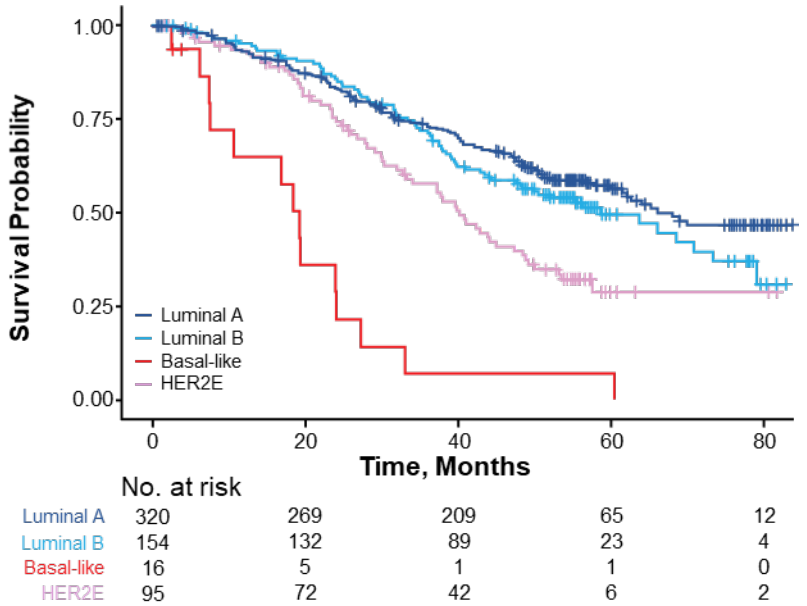
Placebo + ET

	n (%)	Events, n	OS, median, mo	95% CI
Luminal A	222 (54)	122	54.6	48.3-66.2
Luminal B	124 (30)	79	44.9	35.5-52.6
HER2E	52 (13)	39	29.4	23.9-42.0
Basal-like	14 (3)	11	21.2	12.8-NR



Ribociclib + ET

	n (%)	Events, n	OS, median, mo	95% CI
Luminal A	320 (55)	135	68.0	61.5-NR
Luminal B	154 (26)	75	58.8	48.3-79.2
HER2E	95 (16)	59	40.3	33.4-49.0
Basal-like	16 (3)	14	19.4	10.7-33.2



- OS was associated with subtype in both the ribociclib + ET and placebo + ET arms ($P < .0001$ for both)
- Median OS was longest in patients with luminal A tumors and shortest in those with basal-like tumors

ET, endocrine therapy; NR, not reached; OS, overall survival.

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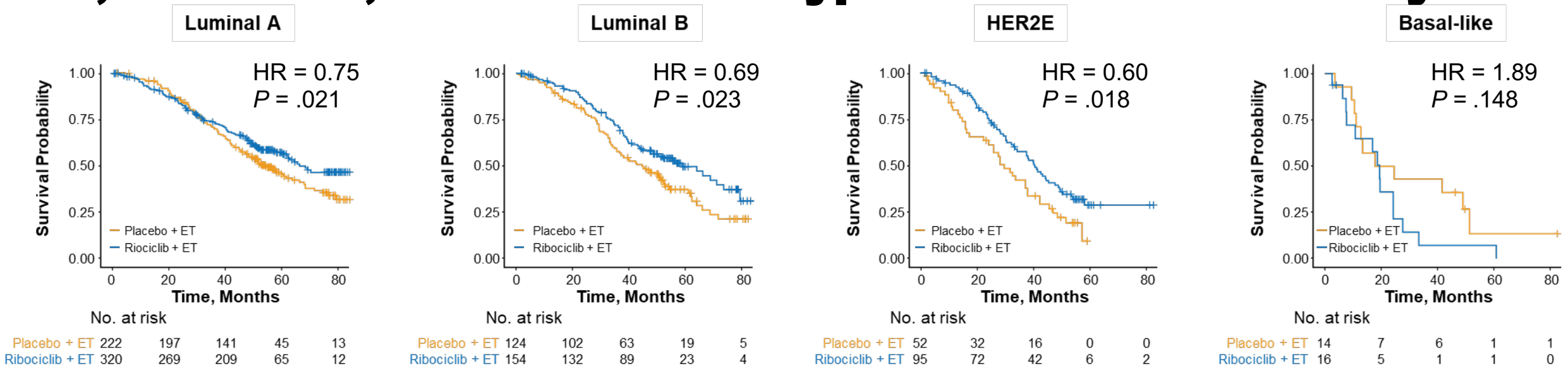
Intrinsic subtype was prognostic for OS in multivariable models

	Ribociclib + ET			Placebo + ET		
	Adjusted HR[a]	95% CI	*P* Value	Adjusted HR[a]	95% CI	*P* Value
Luminal A	1.00	–	–	1.00	–	–
Luminal B	1.16	0.86-1.57	.32	1.47	1.08-2.00	.013
HER2E	1.83	1.33-2.52	.00023	2.87	1.93-4.26	< .0001
Basal-like	7.06	3.73-13.40	< .0001	2.35	1.20-4.58	.012

- Subtype remained prognostic for OS in both arms (*P* < .001 for both) after adjusting for clinical covariates

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; HR, hazard ratio; OS, overall survival.
[a] Obtained from multivariable Cox model, including age, prior chemotherapy, prior ET, ECOG performance status, visceral disease (presence of liver/lung metastases), bone-only metastases, histological grade, number of metastatic sites, tumor type, and de novo metastatic disease.

Consistent OS benefit observed with ribociclib in luminal A, luminal B, and HER2E subtypes in univariable analysis



- In univariable analysis, OS benefit with ribociclib + ET was observed in patients with luminal A, luminal B, and HER2E subtypes
  - Patients with basal-like subtype did not demonstrate OS benefit with ribociclib + ET, but the sample size was small (n = 30 total; 3% in each arm)
- Interaction test result between subtype and treatment arm was statistically significant (*P* = .016)
  - With basal-like subtype removed, the interaction test result was no longer statistically significant (*P* = .47)

ET, endocrine therapy; HER2E, human epidermal growth factor receptor 2 enriched; HR, hazard ratio; OS, overall survival.

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OS benefit observed with ribociclib in luminal A, luminal B, and HER2E subtypes in multivariable models

Subtype	Adjusted HR[a]	95% CI
Luminal A	0.77	0.60-0.99
Luminal B	0.63	0.46-0.88
HER2E	0.53	0.35-0.80
Basal-like	2.71	1.18-6.24

- Interaction test result between subtype and treatment arm remained statistically significant after adjusting for clinical covariates (*P* = .0065)
  - After removing basal-like subtype from this analysis, the interaction test result was no longer statistically significant (*P* = .32)

HER2E, human epidermal growth factor receptor 2 enriched; HR, hazard ratio; OS, overall survival.
[a] Obtained from multivariable Cox model, including age, prior chemotherapy, prior ET, ECOG performance status, visceral disease (presence of liver/lung metastases), bone-only metastases, histological grade, number of metastatic sites, tumor type, and de novo metastatic disease.

Conclusions

- In this pooled analysis of the MONALEESA-2, -3, and -7 trials, consistent OS benefit was observed with ribociclib + ET in the luminal A, luminal B, and HER2E subtypes
  - Patients with basal-like subtype (3% in each arm) did not derive benefit from ribociclib; however, these results should be interpreted with caution due to the small sample sizes in this subgroup
- The prognostic value of PAM50-based intrinsic subtype for OS in patients treated with ribociclib + ET and those treated with ET alone was confirmed
- The results of this analysis are consistent with those of the prior analysis of PFS using the pooled MONALEESA data set
- The activity of ribociclib + ET in the HER2E subtype, which has poor outcomes compared with luminal subtypes, is being further investigated in the phase 3 HARMONIA[a] trial
  - HARMONIA will examine if ribociclib has a particular impact in HER2E tumors based on these clinical data and preclinical data generated in patient-derived xenograft models
- A genomic profiling analysis by intrinsic subtype across the MONALEESA trials is also being presented at SABCS 2021 (Prat A, et al. SABCS 2021. Spotlight Poster Discussion PD2-05)

ET, endocrine therapy; HER2E, human epidermal growth factor receptor 2 enriched; OS, overall survival.
[a] The phase 3 HARMONIA trial will evaluate patients with HER2E HR+/HER2– advanced breast cancer treated with ribociclib plus ET or palbociclib plus ET.

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