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Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

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Disclosure Information

Dr. Lu reports:

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Background

- Chemotherapy (CT) is the standard of care in ABC with clinically aggressive disease features that include rapidly progressing or highly symptomatic disease and life-threatening visceral crisis, which requires rapid disease control[1]
- Combination CT is associated with a higher ORR and longer PFS than single-agent CT and may be preferred for those who have a critical disease condition and may tolerate potentially toxic treatment[2]
- Ribociclib (RIB) + endocrine therapy (ET) demonstrated statistically significant PFS and OS benefits over ET alone in 3 Phase III clinical trials (MONALEESA-2, -3, and -7) in patients with HR+/HER2− ABC, including patients with visceral metastases and a high tumor burden[3-11]
- No data on a head-to-head comparison of CDK4/6 inhibitor + ET vs combination CT in the patient population with aggressive HR+/HER2− disease have been published
- Here we report the prespecified primary analysis of PFS and key secondary endpoints from the randomized, open-label, multinational, Phase II RIGHT Choice trial

ABC, advanced breast cancer; CDK4/6, cyclin-dependent kinases 4 and 6; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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RIGHT Choice study design

- Pre-/perimenopausal women
- HR+/ HER2– ABC (>10% ER+)
- No prior systemic therapy for ABC
- Measurable disease per RECIST 1.1
- Aggressive disease[a]
  - Symptomatic visceral metastases
  - Rapid disease progression or impending visceral compromise
  - Markedly symptomatic non-visceral disease
- ECOG PS ≤ 2[b]
- Total bilirubin ≤ 1.5 ULN
- N = 222[c]

Stratified by (1) the presence or absence of liver metastases and by (2) DFI[d] < or ≥2 years

R 1:1

Ribociclib
(600 mg, 3 weeks on/1 week off)
+
Letrozole or anastrozole + goserelin

Investigators' choice of combination CT[e]

Docetaxel + capecitabine
Paclitaxel + gemcitabine
Capecitabine + vinorelbine

Tumor imaging evaluation
Q6W for 1st 12 weeks, Q8W for next 32 weeks, then Q12W[f]

Primary endpoint
- PFS (locally assessed per RECIST 1.1)

Secondary endpoints
- TTF
- 3-month TFR
- ORR
- CBR
- TTR
- OS
- Safety
- QOL

Exploratory endpoints
- Biomarker analyses
- Healthcare resource utilization

ABC, advanced breast cancer; CBR, clinical benefit rate; CT, chemotherapy; DFI, disease-free interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen receptor positive; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q6W, every 6 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; QOL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response; ULN, upper limit of normal.
[a] Where combination CT is clinically indicated by physician's judgment; [b] For patients with ECOG 2, the poor performance status should be due to breast cancer; [c] Patients were enrolled from Feb 2019 to Nov 2021; [d] Disease-free interval is defined as the duration from date of complete tumor resection for primary breast cancer lesion to the date of documented disease recurrence; [e] If one of the combination CT drugs had to be stopped because of toxicity, the patient was allowed to continue on the other, better-tolerated CT drug (monotherapy); [f] Until disease progression, death, withdrawal of consent, loss to follow-up, or patient/guardian decision, and at end of treatment.

Statistical methods

- The prespecified PFS analysis was planned after disease progression or death in approximately 110 patients
  - The study had a power of 80% to detect a HR of 0.67 at a one-sided α level of 10%
- Stratified Cox regression was used to estimate the HR for PFS, TTF, and TTR
- The efficacy analyses were performed on all randomized patients, while the safety analysis was performed on all patients who received at least one treatment dose
  - Ten patients randomized to the combination CT arm were not included in the safety set as they did not receive any study treatment after 9 of these patients withdrew consent following knowledge of randomization to the CT arm, and 1 was withdrawn based on physician's decision
- OS data were immature at data cutoff (12 April 2022)

CT, chemotherapy; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TTF, time to treatment failure; TTR, time to response.

Baseline characteristics were well balanced

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Median age, years	44.0	43.0
≥40 years	80 (71.4)	72 (65.5)
Race[a]		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Histological grade		
Grade 1	10 (8.9)	16 (14.5)
Grade 2	66 (58.9)	61 (55.5)
Grade 3	35 (31.3)	29 (26.4)
≥50% ER+	95 (84.8)	95 (86.4)
PR+	99 (88.4)	102 (92.7)

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 110
Disease status		
De novo	71 (63.4)	73 (66.4)
Visceral metastatic sites[b]		
Liver	56 (50.0)	57 (51.8)
Lung	63 (56.3)	58 (52.7)
Liver or lung	89 (79.5)	85 (77.3)
Aggressive disease characteristic		
Rapid progression	23 (20.5)	18 (16.4)
Symptomatic non-visceral disease	15 (13.4)	16 (14.5)
Symptomatic visceral metastases	74 (66.1)	76 (69.1)
Visceral crisis[c]	61 (54.5)	55 (50.0)

Combo CT, combination chemotherapy; ER+, estrogen receptor positive; ET, endocrine therapy; RIB, ribociclib.
[a] One patient (0.9%) in the RIB arm was African American; [b] The same patient may have multiple visceral metastatic sites. [c] Based on PI's judgment, which followed ABC3 and NCCN guidelines, which were available at the time of study design.

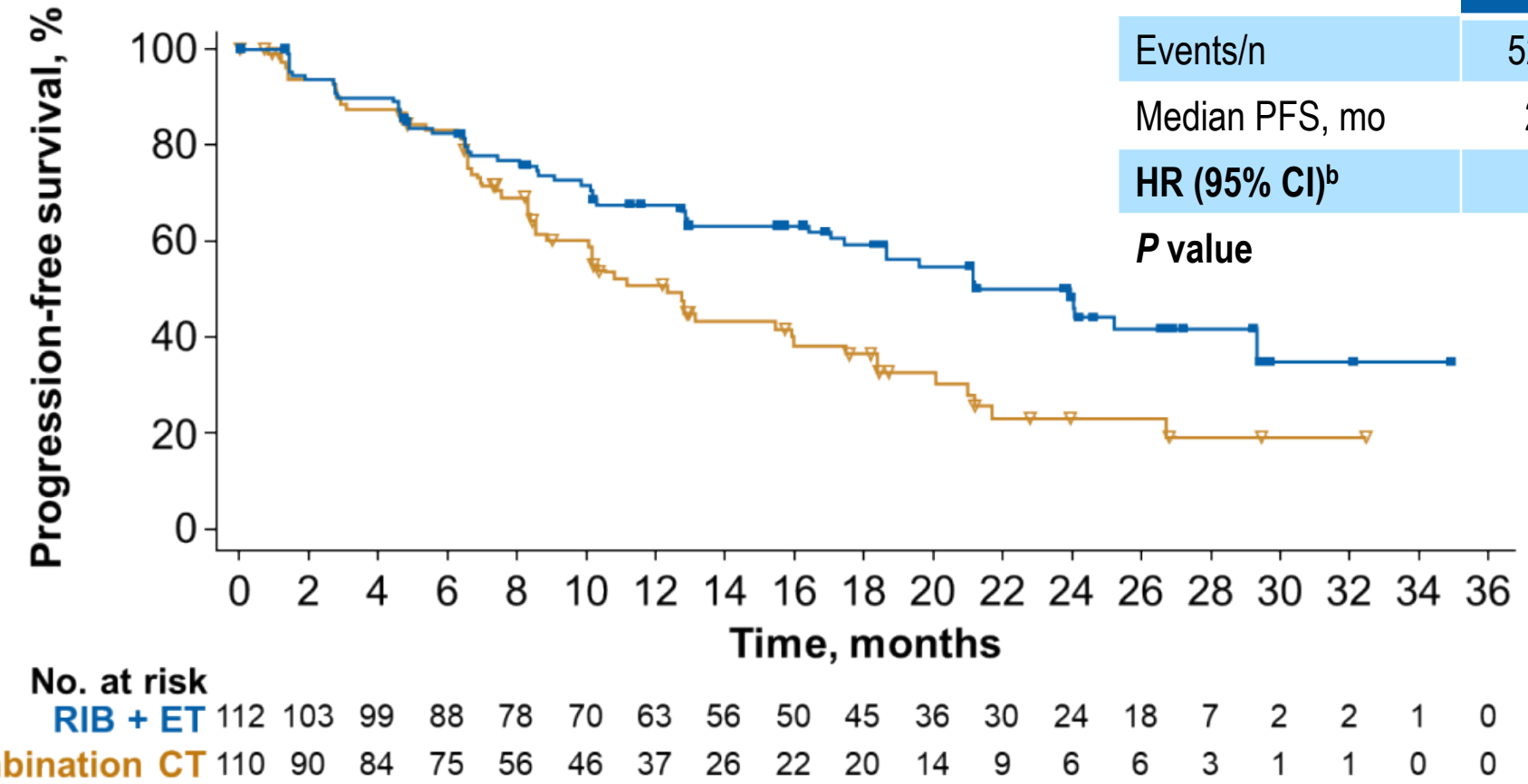
Treatment ongoing in 46% of patients in the RIB + ET arm

	RIB + ET n = 112	Combination CT n = 110[a]	All Patients N = 222
Patients treated			
Treatment ongoing[b]	51 (45.5)	26 (23.6)	77 (34.7)
Reason for end of treatment[c]			
Progressive disease	50 (44.6)	58 (52.7)	108 (48.6)
Adverse event	8 (7.1)	3 (2.7)	11 (5.0)
Death	1 (0.9)	0	1 (0.5)
Physician decision	1 (0.9)	5 (4.5)	6 (2.7)
Subject decision	1 (0.9)	8 (7.3)	9 (4.1)

- Median duration of follow-up was 24.1 months[d] (data cutoff: 12 April 2022)

CT, chemotherapy; ET, endocrine therapy; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] Patients continued study treatment at the time of the cutoff (12 April 2022); [c] In patients who received study treatment (RIB + ET, n = 112; combination CT, n = 100); [d] Time from randomization to data cutoff date.

First-line RIB + ET achieved a statistically significant PFS benefit of ≈ 1 year over combination CT in aggressive HR+/HER2− ABC



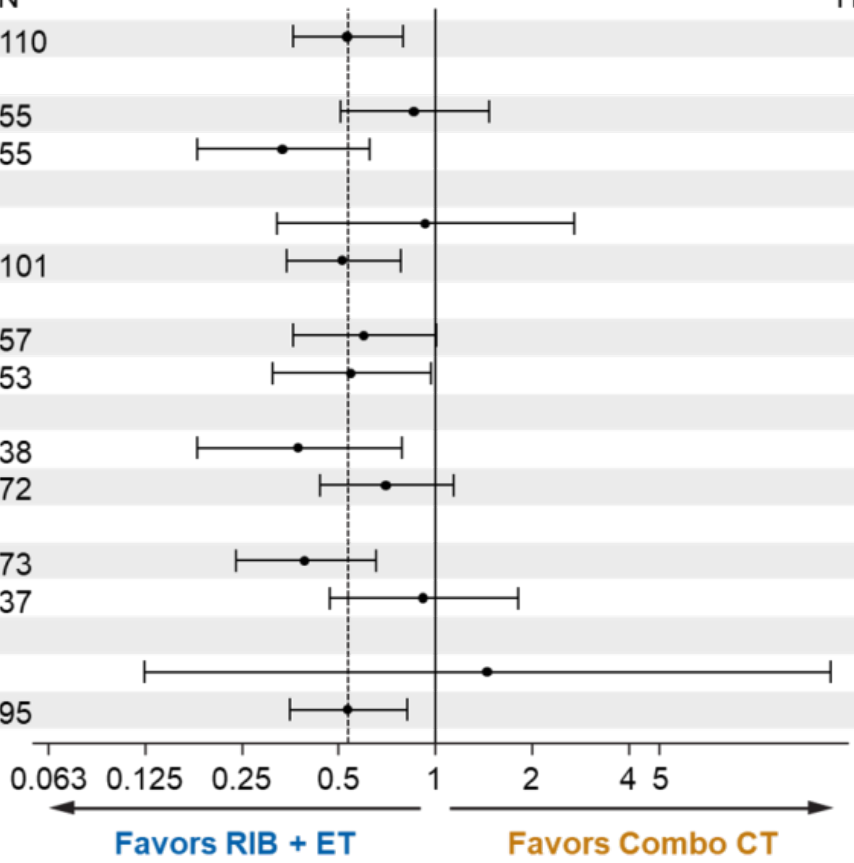
	RIB + ET	Combo CT
Events/n	52/112	58/110[a]
Median PFS, mo	24.0	12.3
HR (95% CI)[b]	**0.54 (0.36-0.79)**	
***P* value**	**.0007**	

ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; IRT, interactive response technology; PFS, progression-free survival; RIB, ribociclib.

[a] Ten patients in CT arm did not receive any treatment; [b] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT.

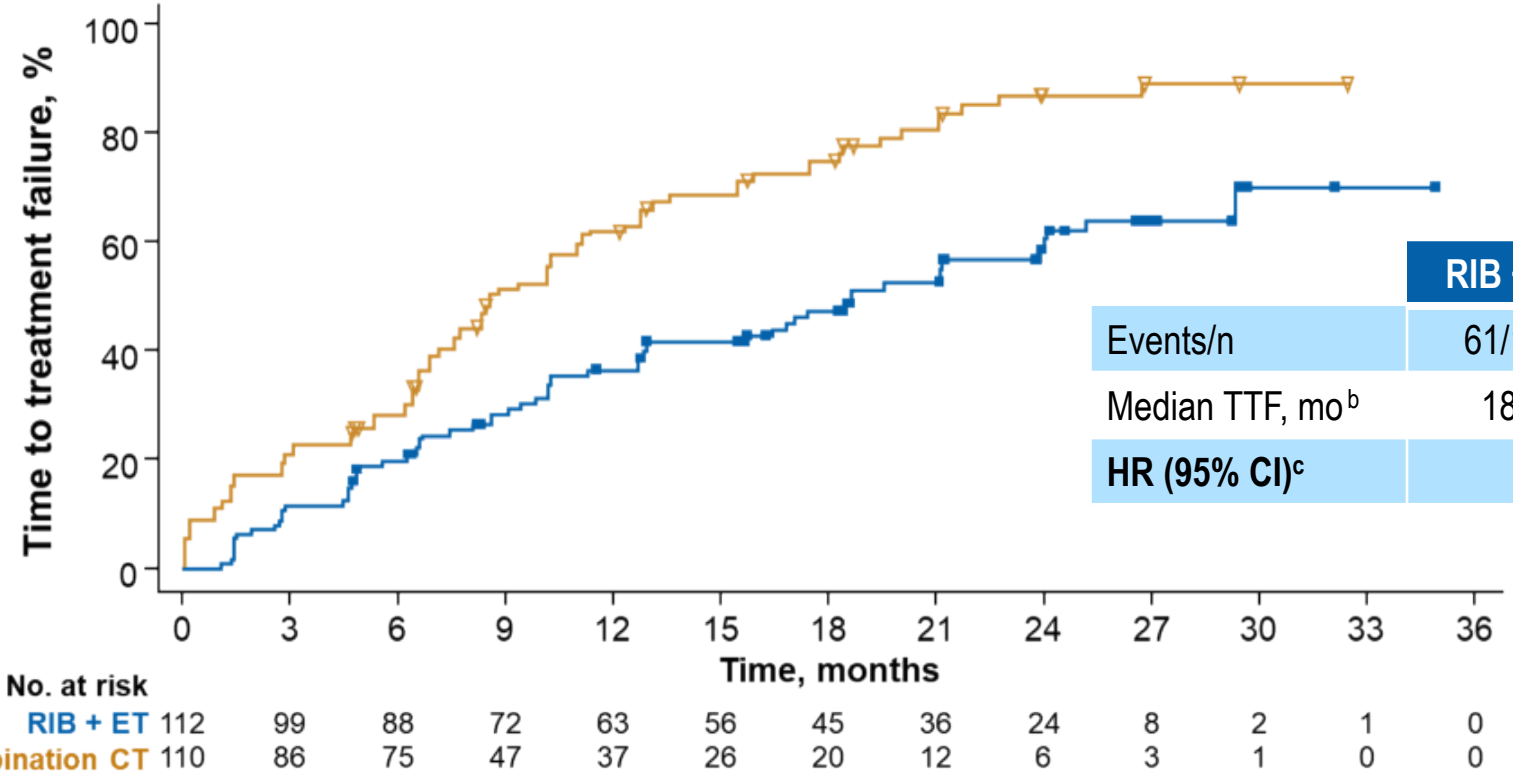
PFS benefit with RIB + ET over combination CT was consistent across most subgroups of patients with aggressive HR+/HER2− ABC

Subgroup	RIB + ET n/N	Combo CT n/N	Hazard Ratio (95% CI)
All patients	52/112	58/110	0.54 (0.36-0.79)
Visceral crisis status			
Yes	33/61	26/55	0.87 (0.51-1.47)
No	19/51	32/55	0.34 (0.18-0.63)
Disease free interval			
<2 years	9/13	6/9	0.94 (0.32-2.73)
≥2 years	43/99	52/101	0.52 (0.34-0.78)
Presence of liver metastasis			
Yes	29/56	31/57	0.60 (0.36-1.01)
No	23/56	27/53	0.55 (0.31-0.97)
Age			
<40 years	12/32	25/38	0.38 (0.18-0.79)
≥40 years	40/80	33/72	0.71 (0.44-1.15)
De novo			
Yes	29/71	42/73	0.40 (0.24-0.66)
No	23/41	16/37	0.92 (0.47-1.82)
Estrogen receptor status			
<50	2/8	3/5	1.46 (0.12-17.08)
≥50	47/95	50/95	0.54 (0.35-0.82)



ABC, advanced breast cancer; Combo CT, combination chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; PFS, progression-free survival; RIB, ribociclib.

Median time to treatment failure (TTF) was longer with RIB + ET vs combination CT

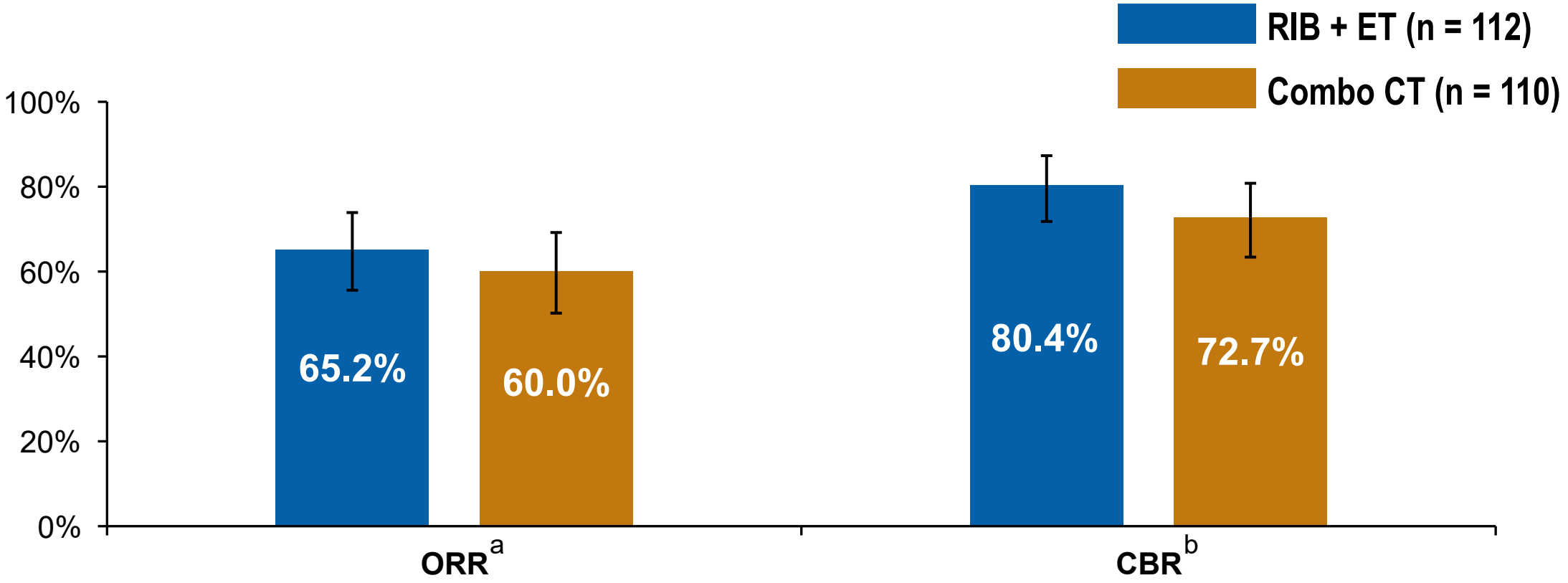


	RIB + ET	Combo CT
Events/n	61/112	84/110[a]
Median TTF, mo[b]	18.6	8.5
HR (95% CI)[c]	**0.45 (0.32-0.63)**	

- A sensitivity analysis[d] confirmed the TTF findings in the safety set
- The 3-month treatment failure rate[e] in the RIB arm was approximately half (n = 13; 11.6%; 95% CI, 6.3%-19.0%) that in the combination CT arm (n = 24; 21.8%; 95% CI, 14.5%-30.7%)

Combo CT, combination chemotherapy; ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] Defined as the time from randomization to progression, death, change to other anticancer therapy, or discontinuation; [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment; [e] The proportion of patients who discontinued study treatment due to progressive disease, death, change to other anticancer therapy, or discontinuation due to reasons other than protocol violation.

ORR and CBR were similar between RIB + ET and combination CT

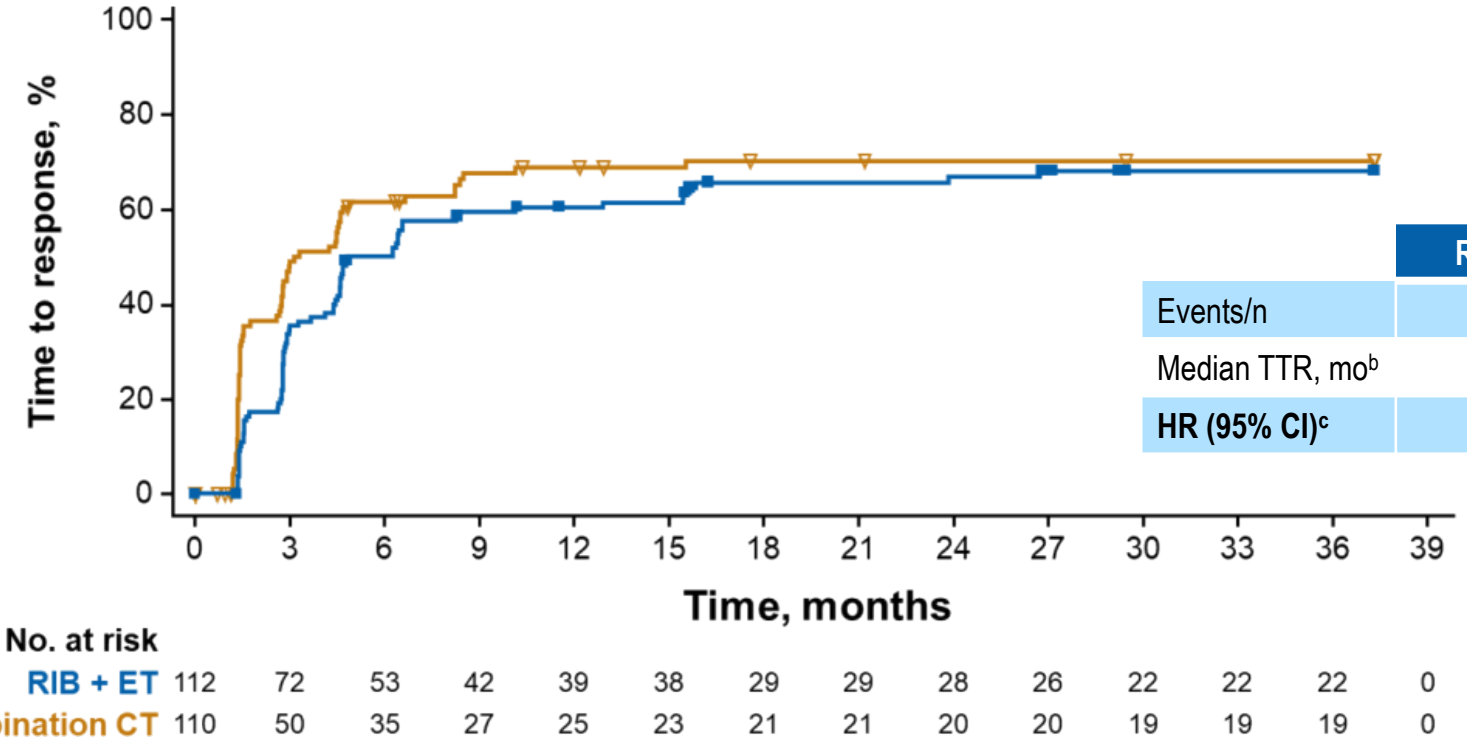


- A sensitivity analysis[c] confirmed the ORR and CBR findings in the safety set

CBR, clinical benefit rate; Combo CT, combination chemotherapy; CR, complete response; ET, endocrine therapy; ORR, overall response rate; PD, progressive disease; PR, partial response, RIB, ribociclib; SD, stable disease.

[a] Proportion of patients with CR or PR without confirmation (confirmation imaging was not mandatory according to study protocol); [b] Proportion of patients with CR or PR without confirmation or SD or non-CR/non-PD ≥24 weeks; [c] This analysis included all patients who received ≥1 dose of any component of the study treatment (safety set).

Time to onset of response (TTR) for RIB + ET was similar to combination CT



	RIB + ET	Combo CT
Events/n	73/112	66/110[a]
Median TTR, mo[b]	4.9	3.2
HR (95% CI)[c]	**0.78 (0.56-1.09)**	

- A sensitivity analysis[d] confirmed the TTR findings in the safety set

Combo CT, combination chemotherapy; CR, complete response, ET, endocrine therapy; HR, hazard ratio; IRT, interactive response technology; PR, partial response; RIB, ribociclib.
[a] Ten patients in CT arm did not receive any treatment; [b] TTR is defined as the time from the date of randomization to the first documented response of either CR or PR without confirmation (confirmation imaging was not required according to study protocol); [c] HR is obtained from Cox Proportional-Hazards model stratified by liver metastasis and disease-free interval per IRT; [d] The sensitivity analysis excluded the 10 patients in the CT arm who did not receive any treatment and were removed from the denominator for the CT arm.

Fewer dose reductions were observed with RIB + ET vs combination CT

Parameter, n (%)	RIB + ET n = 112	Combo CT n = 100[a]
Number of dose reductions		
0	81 (72.3)	54 (54.0)
1	27 (24.1)	12 (12.0)
2	4 (3.6)	14 (14.0)
≥3	0	20 (20.0)

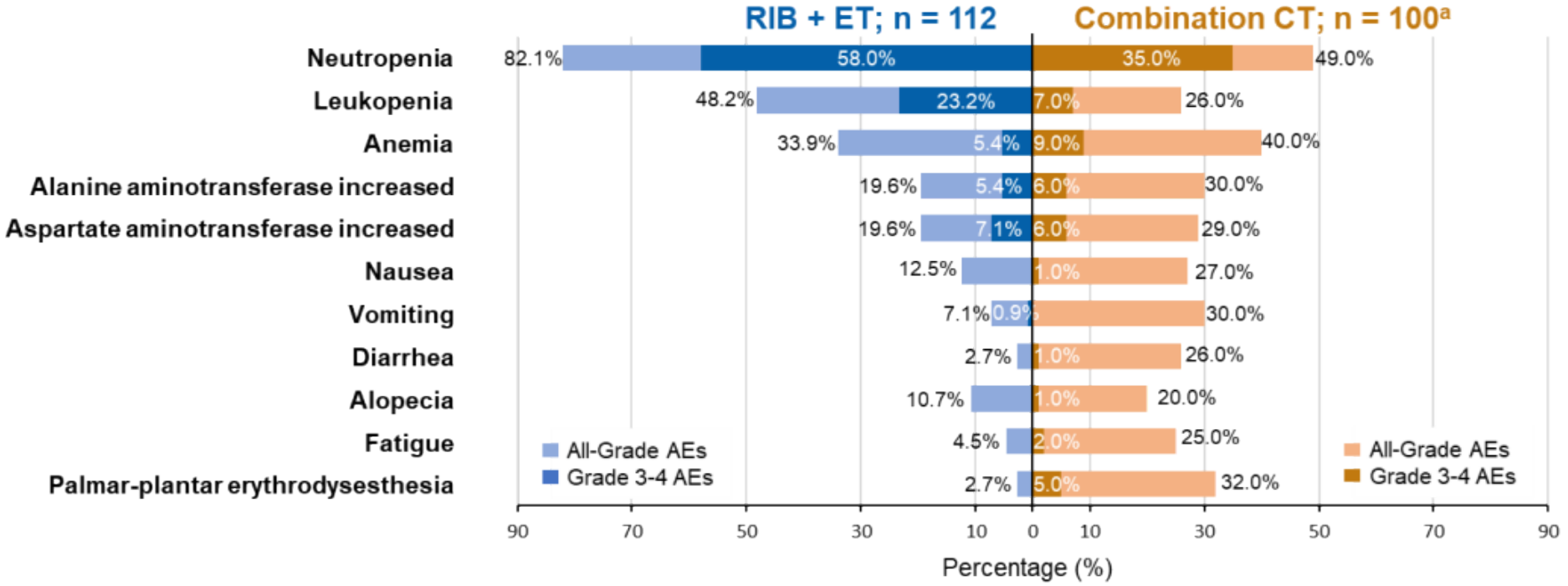
- The median duration of exposure to study treatment was 15.0 months (Q1-Q3, 7.4-24.5 months) in the RIB arm and 8.6 months (Q1-Q3, 6.1-15.0 months) in the combination CT arm[b]

Combo CT, combination chemotherapy; ET, endocrine therapy; RIB, ribociclib; Q1, quartile 1; Q3, quartile 3.
[a] Ten patients in CT arm that did not receive any treatment were not included in the safety set; [b] Duration from start of treatment to last treatment as per data cutoff date.

Fewer TRAEs with RIB + ET vs combination CT

n (%)	RIB + ET; n = 112		Combination CT; n = 100[a]	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Total AEs	112 (100.0)	84 (75.0)	100 (100.0)	71 (71.0)
Treatment-related serious AEs	2 (1.8)	1 (0.9)	8 (8.0)	7 (7.0)
Treatment-related AEs leading to discontinuation[b]	8 (7.1)	7 (6.3)	23 (23.0)	7 (7.0)

AEs irrespective of causality (≥20% incidence in either RIB or combination CT arms)



- Two patients (1.8%) in RIB arm[c] and none in CT arm showed grade ≥3 QT prolongation

AE, adverse event; CT, chemotherapy; ET, endocrine therapy; RIB; ribociclib; TRAE, treatment-related adverse event. [a] Ten patients in CT arm that did not receive any treatment were not included in the safety set; [b] AEs leading to discontinuation of any component of the study treatment are included. [c] Without evidence of arrythmia.

Conclusions

- RIGHT Choice is the first prospective study comparing a CDK4/6 inhibitor + ET with combination CT and demonstrating the PFS superiority of RIB + ET over combination CT in patients with HR+/HER2− ABC with aggressive clinical features of rapidly progressing or highly symptomatic disease, including visceral crisis
  - First-line RIB + ET demonstrated a statistically significant PFS benefit (≈1 year longer) vs combination CT (24.0 vs 12.3 months; HR, 0.54) in pre/perimenopausal patients with aggressive HR+/HER2− ABC
- RIB + ET also showed longer TTF than combination CT with similar TTR and ORR between the two treatment groups, matching the high tumor response rate seen with combination CT
- No new safety signals were observed with RIB + ET
  - Compared with RIB +ET, combination CT was associated with higher rates of treatment-related AEs, many that impact QOL
- First-line RIB + ET offers an efficacious, clinically meaningful treatment option for patients with aggressive HR+/HER2− ABC, obviating the need for combination CT and related toxicities

ABC, advanced breast cancer; AE, adverse event; CDK4/6, cyclin-dependent kinases 4 and 6; CT, chemotherapy; ET, endocrine therapy; HER2–, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; RIB, ribociclib; TFR, treatment failure rate; TTF, time to treatment failure; TTR, time to response.

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