

First-line ribociclib + endocrine therapy vs combination chemotherapy in aggressive HR+/HER2- advanced breast cancer: a subgroup analysis of patients with or without visceral crisis from the phase II RIGHT Choice study

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KEY FINDINGS & CONCLUSIONS

- This subgroup analysis of patients with clinically aggressive HR+/HER2- ABC from the RIGHT Choice trial shows a similar PFS with RIB + ET vs combo CT (hazard ratio, 0.95; 95% CI, 0.57-1.58) in patients with investigator-assessed visceral crisis

- In patients with visceral crisis, a similar TTR was observed in those treated with RIB + ET vs combo CT

- In patients with clinically aggressive disease who presented without visceral crisis, a clinically meaningful PFS benefit was observed with RIB + ET (hazard ratio, 0.42; 95% CI, 0.25-0.70), along with similar ORR but longer TTR than with combo CT

- In both subgroups, patients receiving RIB + ET experienced lower rates of symptomatic AEs than those receiving combo CT

- This exploratory analysis supports that RIB + ET could be considered as a valid first-line treatment option in premenopausal patients with clinically aggressive HR+/HER2- ABC, including those with visceral crisis

This study is sponsored by Novartis Pharma AG.

Poster presented at: 2024 NCODA Spring Forum; April 3-5, 2024; Dallas, TX.

INTRODUCTION

- Combination chemotherapy (combo CT) is the recommended first-line treatment for patients with aggressive, hormone-receptor positive, human epidermal growth factor receptor 2 negative (HR+/HER2-) advanced breast cancer (ABC), including visceral crisis^{1,2}

- Visceral crisis, defined subjectively as severe organ dysfunction, as assessed by signs and symptoms, laboratory studies, and rapid progression of the disease, in patients with ABC often requires a treatment with rapid efficacy¹⁻³

- The phase II RIGHT Choice trial in patients with clinically aggressive HR+/HER2- ABC reported a statistically significant median progression-free survival (mPFS) benefit of ≈1 year with ribociclib (RIB) + endocrine therapy (ET) over combo CT (hazard ratio, 0.54; 95% CI, 0.36-0.79; P=.0007)⁴

- Here we present an exploratory subgroup analysis of key efficacy endpoints from the RIGHT Choice trial in patients with investigator-assessed visceral crisis and in those without visceral crisis

RESULTS

- The data reported here are from the final database lock (cut-off date 10 May 2023)
 - The data presented in Lu et al., SABCS 2022 (oral GS1-10) were from an interim analysis (cut-off date 12 April 2022)⁴
- The updated median PFS for the intention-to-treat population in the RIGHT Choice trial (final database lock, cut-off date 10 May 2023) was 21.8 months vs 12.8 months with RIB + ET vs combo CT (hazard ratio, 0.61; 95% CI, 0.43-0.87; P=0.003)

Baseline Characteristics and Disease History

- As determined by the investigators, 106 patients presented with visceral crisis and 116 patients presented without visceral crisis

- In both subgroups, the demographics and baseline clinical characteristics were generally well-balanced across RIB + ET and combo CT arms (Table 1)

Table 1. Demographics and Baseline Clinical Characteristics of Patients

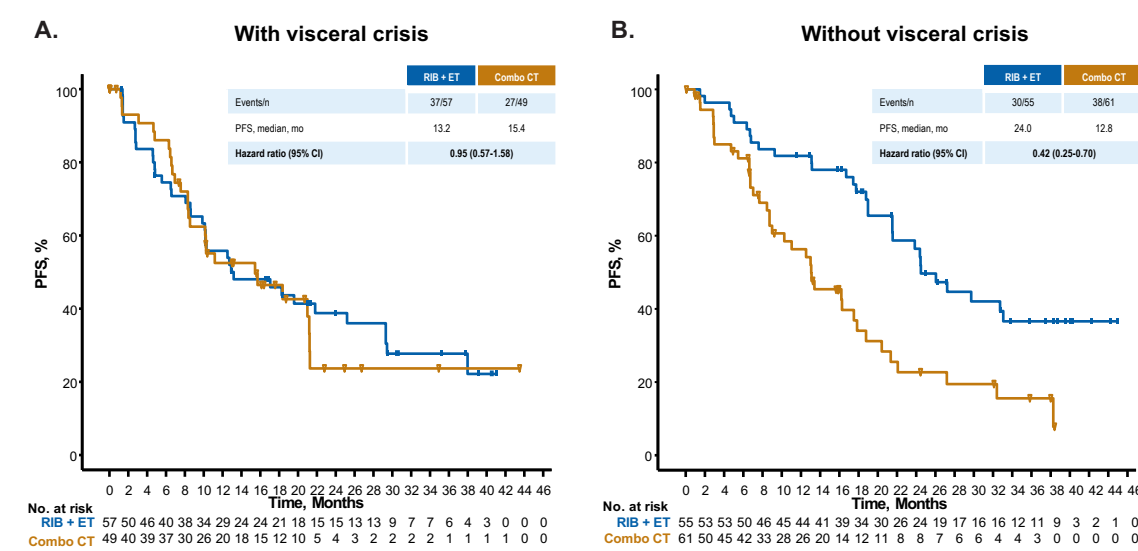
Parameter	With Visceral Crisis		Without Visceral Crisis	
	RIB + ET n=57	Combo CT n=49	RIB + ET n=55	Combo CT n=61
Age, median, years	43.0	43.0	45.0	43.0
Race, n (%) ^a				
Asian	40 (70.2)	36 (73.5)	35 (63.6)	39 (63.9)
White	16 (28.1)	13 (26.5)	20 (36.4)	22 (36.1)
ECOG PS, n (%)				
0	19 (33.3)	15 (30.6)	27 (49.1)	27 (44.3)
1	36 (63.2)	32 (65.3)	27 (49.1)	30 (49.2)
2	2 (3.5)	2 (4.1)	1 (1.8)	4 (6.6)
Histological grade, n (%)				
1	5 (8.8)	6 (12.2)	5 (9.1)	10 (16.4)
2	33 (57.9)	30 (61.2)	33 (60.0)	31 (50.8)
3	18 (31.6)	11 (22.4)	17 (30.9)	18 (29.5)
Disease status, n (%)				
De novo	35 (61.4)	28 (57.1)	35 (63.6)	45 (73.8)
≥50% ER+, n (%)	45 (78.9)	43 (87.8)	50 (90.9)	53 (86.9)
Aggressive disease characteristics, n (%) ^b				
Rapid progression	9 (15.8)	3 (6.1)	14 (25.5)	15 (24.6)
Symptomatic nonvisceral disease	0	0	15 (27.3)	16 (26.2)
Symptomatic visceral metastasis	48 (84.2)	46 (93.9)	26 (47.3)	30 (49.2)
Visceral metastatic sites, n (%) ^c				
Liver	38 (66.7)	31 (63.3)	16 (29.1)	22 (36.1)
Lung	36 (63.2)	27 (55.1)	26 (47.3)	28 (45.9)
Liver or lung	54 (94.7)	45 (91.8)	33 (60.0)	37 (60.7)

^a 1 patient in the patients with visceral crisis subgroup in the RIB arm was African American; ^b Based on investigator's judgment; ^c The same patient may have multiple visceral metastatic sites.

PFS in Patients With and Without Visceral Crisis

- In patients with visceral crisis, the mPFS was similar in both treatment arms (Figure 2A)
 - In patients with visceral crisis, RIB + ET showed a 58% relative reduction in risk of disease progression or death vs combo CT (Figure 2B)
- In patients without visceral crisis, RIB + ET showed a 58% relative reduction in risk of disease progression or death vs combo CT (Figure 2B)

Figure 2. PFS in Both Arms by Subgroups



Acknowledgments

The authors thank the patients enrolled in this study and their families as well as the study investigators. Medical editorial assistance was provided by MediTech Media, Ltd, and was funded by Novartis Pharmaceuticals Corporation. The authors had final responsibility for the poster.

Disclosures

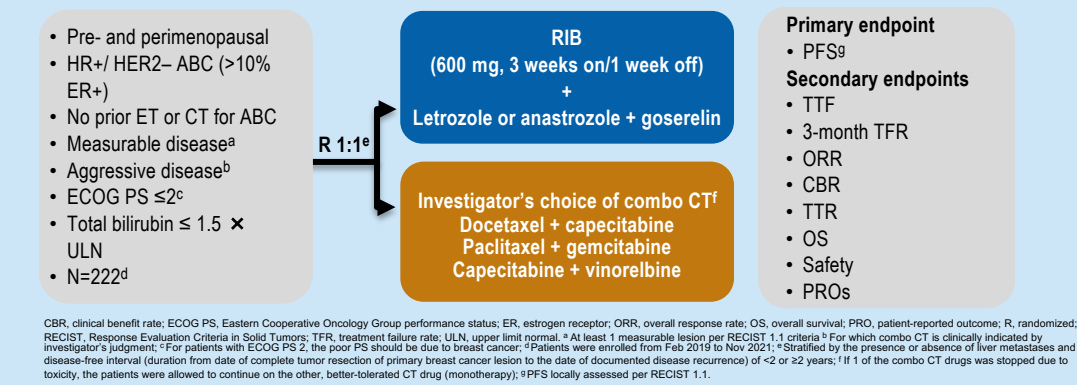
Dr. Azim reports personal fees and non-financial support from Novartis, Roche, MSD, ASZ; personal fees from BMS, Lilly; grants from Pfizer. Dr. El Saghir reports personal fees from AstraZeneca, Lilly, MSD, Novartis, Pfizer, Pierre Fabre, Roche. Dr. Yap reports personal fees and travel support from Lilly/DKSH, AstraZeneca; personal fees from Novartis, Pfizer, Eisai, MSD, Inivata, Specialised Therapeutics, Roche; grants from MSD. Dr. Eralp reports personal fees from Novartis, Gilead, MSD, Glaxo Smith Kline, Roche; grants from Roche; non-financial support from Roche, Novartis, Boston Scientific. Dr. Im reports personal fees from AstraZeneca, Novartis, Hanmi, Pfizer, Eisai, Roche, Lilly, GSK, MSD, Daiichi-Sankyo, Idience, Bertis; research grants from AstraZeneca, Pfizer, Eisai, Roche, Daewoong Pharm, Boryung Pharm, Daiichi-Sankyo. Dr. Malwinder has nothing to disclose. Dr. Abdel-Razeq has nothing to disclose. Dr. Gupta has nothing to disclose. Julie Rihani has nothing to disclose. Teresa Delgar Alfaro, Jiwen Wu, Huilin Hu, and Melissa Gao report employment and stock ownership from Novartis. Dr. Lu reports grants and personal fees from Novartis, Merck Sharp & Dohme, Pfizer, AstraZeneca; personal fees from Novartis, Roche, MSD, Pfizer, AstraZeneca, Eisai, Eli Lilly, Daiichi Sankyo.

Previously presented at the 2023 ESMO; Hamdy, et al. October 20-24, 2023; Madrid, Spain. Poster 402P - Reused with permission.

METHODS

- In the RIGHT Choice trial, patients with clinically aggressive HR+/HER2- ABC were randomized 1:1 to receive RIB + ET or investigator's choice of combo CT (Figure 1)
 - Patients were eligible if combo CT was clinically indicated per investigator's judgment for aggressive disease, namely, symptomatic visceral metastases, rapid disease progression or impending visceral compromise, or markedly symptomatic non-visceral disease
- The presence or absence of visceral crisis was determined by the investigators, principally based on ABC3 guidelines available at the time of trial design³
- Hazard ratios for PFS, time to treatment failure (TTF), and time to response (TTR) in the 2 subgroups were obtained from a Cox proportional hazards model stratified by randomization stratification factors per interactive response technology

Figure 1. Study Design

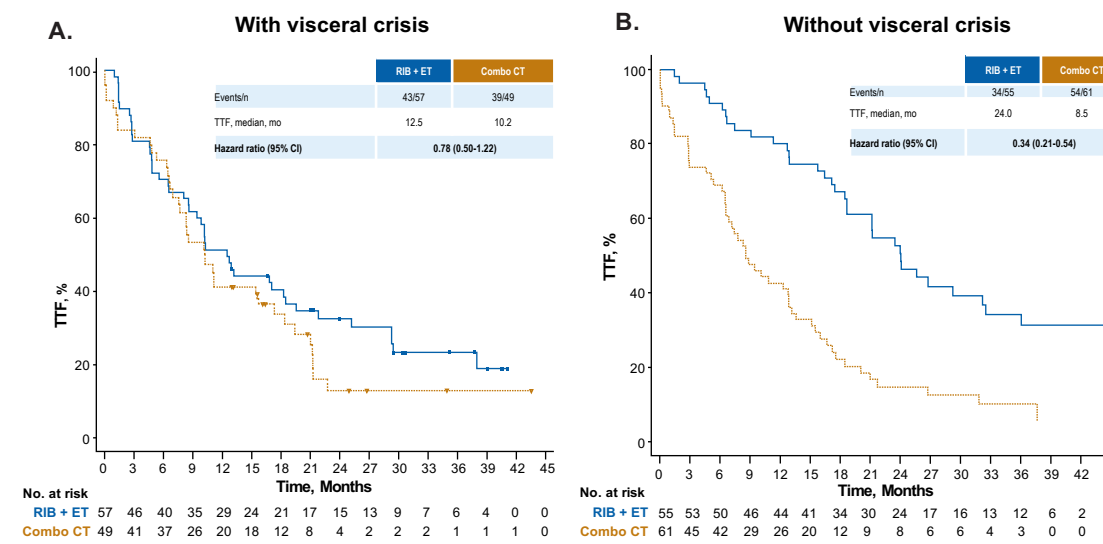


CR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ORR, overall response rate; OS, overall survival; PRO, patient-reported outcome; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; TFR, treatment failure rate; ULN, upper limit of normal; *At least 1 measurable lesion per RECIST 1.1 criteria; †For which combo CT is clinically indicated by investigator's judgment; ††For patients with ECOG PS 2, the poor PS should be due to breast cancer; †††Patients were enrolled from Feb 2019 to Nov 2021; ††††Stratified by the presence or absence of liver metastases and by elevated liver transaminase (duration from date of complete tumor resection of primary breast cancer lesion to the date of documented disease recurrence) of <2 or ≥2 years; ††††† If 1 of the combo CT drugs was stopped due to toxicity, the patients were allowed to continue on the other, better-tolerated CT drug (monotherapy); †††††† PFS locally assessed per RECIST 1.1.

TTF and TFR in Patients With and Without Visceral Crisis

- In patients with visceral crisis, the median TTF was similar in both arms, with a 22% relative reduction in risk of treatment failure with RIB + ET vs combo CT (Figure 3A)
 - The 3-month TFR was similar in the RIB + ET (n=11; 19.3%; 95% CI, 9.1%-29.5%) and combo CT (n=8; 16.3%; 95% CI, 6.0%-26.7%) arms
- In patients without visceral crisis, TTF was longer with RIB + ET than with combo CT, with a 66% relative reduction in risk of treatment failure (Figure 3B)
 - The 3-month TFR with RIB + ET (n=2; 3.6%; 95% CI, 0.0%-8.6%) was lower than with combo CT (n=16; 26.2%; 95% CI, 15.2%-37.3%)

Figure 3. TTF in Both Arms by Subgroups



TTR, ORR, and CBR in Patients With and Without Visceral Crisis

- In patients with visceral crisis, TTR was similar in both arms, while for patients without visceral crisis, TTR was longer with RIB + ET than combo CT (Figure 4)
- In patients with visceral crisis, the ORR was numerically higher with RIB + ET than combo CT while the CBR was similar in both treatment arms (Figures 5A)
- In patients without visceral crisis, the ORR was similar in both treatment arms while the CBR was higher with RIB + ET than combo CT (Figure 5B)

Figure 4. TTR in Both Arms by Subgroups

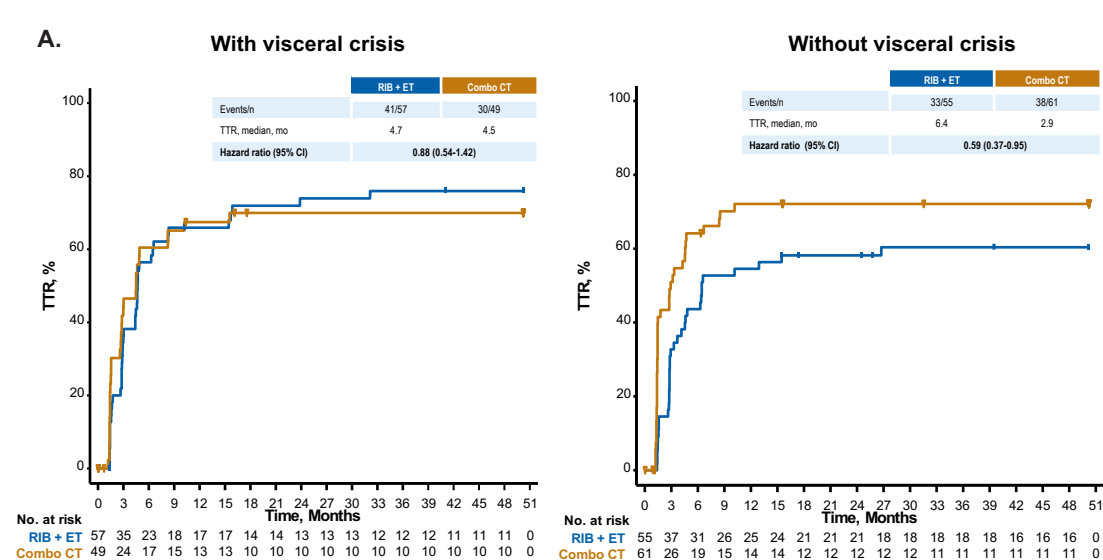
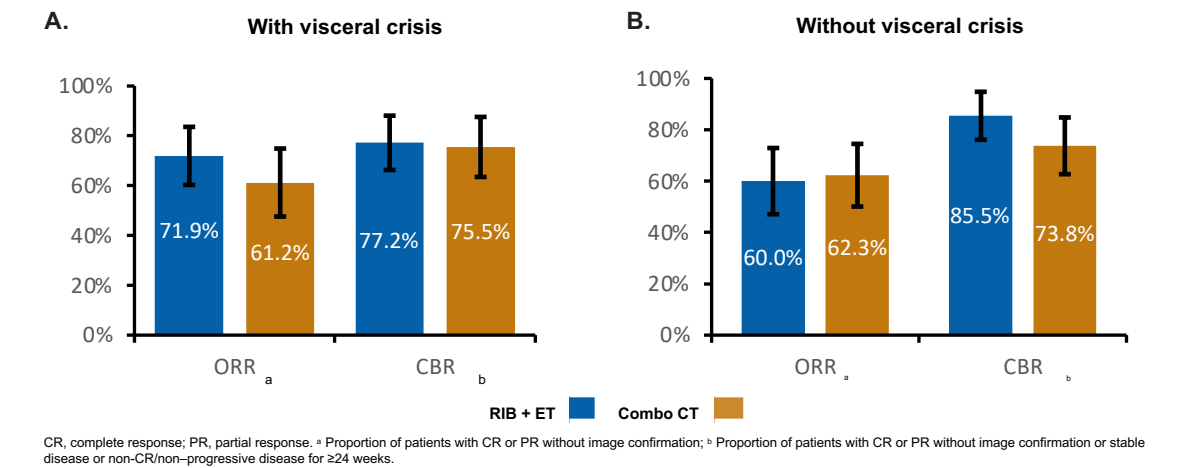


Figure 5. ORR and CBR in Both Arms by Subgroups



CR, complete response; PR, partial response; ^a Proportion of patients with CR or PR without image confirmation; ^b Proportion of patients with CR or PR without image confirmation or stable disease or non-CR/non-progressive disease for ≥24 weeks.

Duration of Treatment Exposure in Patients With and Without Visceral Crisis

- In patients with visceral crisis, the median duration of exposure was similar in both arms (12.9 months with RIB + ET vs 11.0 months with combo CT)
- In patients without visceral crisis, the median duration of exposure was longer in the RIB + ET arm (22.1 months) compared to the combo CT arm (10.6 months)

Safety in Patients With and Without Visceral Crisis

- Regardless of the presence or absence of visceral crisis, no new safety signals were observed for patients in the RIB + ET arm compared with results previously reported⁵ (Table 2)
 - Adverse events (AEs) observed with combo CT in both subgroups were also consistent with the historical AE profile of combo CT^{5,6}
- In both subgroups, higher rates of symptomatic AEs (including nausea, vomiting, palmar-plantar erythrodysesthesia, fatigue, and diarrhea) were observed in patients receiving combo CT vs RIB + ET

Table 2: AEs in ≥20% of Patients Regardless of Causality in Either Treatment Arm in Both Subgroups

AE Grouping, n (%)	With Visceral Crisis*		Without Visceral Crisis*	
	RIB + ET n=57	Combo CT n=45	RIB + ET n=55	Combo CT n=55
Hematologic AEs				
Neutropenia ^a	46 (80.7)	34 (59.6)	21 (46.7)	14 (31.1)
Leukopenia ^a	25 (43.9)	11 (19.3)	9 (20.0)	4 (8.9)
Anemia	21 (36.8)	4 (7.0)	19 (42.2)	6 (13.3)
Nonhematologic AEs				
Elevated aspartate aminotransferase	17 (29.8)	6 (10.5)	12 (26.7)	2 (4.4)
Elevated alanine aminotransferase	13 (22.8)	5 (8.8)	10 (22.2)	2 (4.4)
Elevated gamma-glutamyl transferase	12 (21.1)	8 (14.0)	3 (6.7)	1 (2.2)
Electrocardiogram QT prolonged	11 (19.3)	0	6 (13.3)	0
Nausea	7 (12.3)	0	11 (24.4)	0
Vomiting	5 (8.8)	1 (1.8)	14 (31.1)	0
Palmar-plantar erythrodysesthesia	2 (3.5)	0	17 (37.8)	3 (6.7)
Fatigue	4 (7.0)	0	9 (20.0)	0
Diarrhea	0	0	13 (28.9)	0
Arthralgia	4 (7.0)	0	1 (2.2)	13 (23.6)
Covid-19	8 (14.0)	1 (1.8)	3 (6.7)	0
Alopecia	4 (7.0)	0	8 (17.8)	0

G, grade; ^a 4 patients in the patients with visceral crisis subgroup and 6 in the patients without visceral crisis subgroup randomized to the combo CT arm were not included in the safety set as they did not receive any study treatment after withdrawal of consent following knowledge of randomization to the CT arm (n=9) and withdrawal based on investigator's decision (n=1). ^b Neutropenia includes 'neutropenia' and 'neutrophil count decreased'; ^c Leukopenia includes 'leukopenia' and 'white blood cell count decreased'; ^d 1 patient in the patients with visceral crisis subgroup and 1 in the patients without visceral crisis subgroup were not included in the safety set as they did not receive any study treatment after withdrawal of consent following knowledge of randomization to the CT arm (n=9) and withdrawal based on investigator's decision (n=1).

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