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Final results of RIGHT Choice: Ribociclib plus endocrine therapy vs combination chemotherapy in premenopausal women with clinically aggressive HR+/HER2− advanced breast cancer

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Context Summary

Key Objective

Can a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) plus endocrine therapy (ET) be used instead of combination chemotherapy (CT) for treating patients with clinically aggressive hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC), in which combination CT is typically used to achieve a rapid response?

Knowledge Generated

This first ever prospective head-to-head comparison between a CDK4/6i (ribociclib) plus ET, and combination CT showed improved progression-free survival, similar response rates, and lower symptomatic adverse event rates with ribociclib plus ET versus combination CT in patients with clinically aggressive HR+/HER2− ABC.

Relevance (written by Kathy Miller): The 'conventional wisdom' that patients with visceral disease need chemotherapy even if ER+ should be retired.

Abstract

Purpose

A head-to-head comparison of efficacy between a cyclin-dependent kinase 4/6 inhibitor plus endocrine therapy (ET) versus combination chemotherapy (CT) has never been reported in patients with clinically aggressive hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC).

Patients and methods

In this open-label, multi-center, randomized phase 2 trial, pre/perimenopausal women with clinically aggressive HR+/HER2− ABC were randomized 1:1 to first-line ribociclib (600 mg daily; 3-weeks-on, 1-week-off) plus letrozole/anastrozole and goserelin or investigator's choice of combination CT (docetaxel plus capecitabine, paclitaxel plus gemcitabine, or capecitabine plus vinorelbine). The primary endpoint was progression-free survival (PFS).

Results

Among 222 patients randomized to ribociclib plus ET (n=112) or combination CT (n=110), 150 (67.6%) had symptomatic visceral metastases, 41 (18.5%) had rapid disease progression per investigator's judgment, and 31 (14.0%) had symptomatic non-visceral disease. Overall, 106 (47.7%) patients had investigator-assessed visceral crisis. Median follow-up time was 37.0 months. At data cutoff, 31.3% (ribociclib arm) and 15.5% (CT arm) of patients had completed study treatment and transitioned to post-trial access. The median PFS was 21.8 months (ribociclib plus ET; 95% CI, 17.4-26.7

months) and 12.8 months (combination CT; 95% CI, 10.1-18.4 months); hazard ratio [HR], 0.61; 95% CI, 0.43-0.87; *P*=.003. The overall response rates and the median time to response in the ribociclib versus CT arms, respectively, were 66.1% and 61.8% and 4.9 months and 3.2 months (HR, 0.76; 95% CI, 0.55-1.06). Lower rates of symptomatic adverse events were observed in the ribociclib versus CT arm

Conclusions

First-line ribociclib plus ET showed a significant PFS benefit, similar response rates, and better tolerability over combination CT in patients with clinically aggressive HR+/HER2− ABC.

Keywords: ribociclib, cyclin-dependent kinases 4 and 6 inhibitors, combination chemotherapy, advanced breast cancer, endocrine therapy

Introduction

Approximately one-third of newly diagnosed breast cancer (BC) cases are in premenopausal women, in whom the disease is often aggressive.[1-4] For hormone receptor–positive, human epidermal growth factor receptor 2–negative (HR+/HER2−) advanced breast cancer (ABC) with aggressive disease features, including symptomatic, rapidly progressing disease or life-threatening visceral crisis requiring rapid disease control, combination chemotherapy (CT) remains a recommended first-line treatment.[5, 6] Several regimens (eg, docetaxel plus capecitabine, paclitaxel plus gemcitabine, or capecitabine plus vinorelbine) have demonstrated superior efficacy to that of single-agent CT but are associated with higher incidences of adverse events (AEs).[7-13] Combination CT continues to be preferred in patients with critical disease features due to the need for a more rapid response and higher response rate in these patients.[7-13] However, unlike the clear preference for CT for HR− ABC treatment, CT is generally less effective in HR+ ABC.[14] Thus, an unmet medical need exists in the HR+/HER2− ABC patient population for therapy options that provide a rapid response and durable efficacy while sparing patients the toxicities associated with combination CT.

Cyclin-dependent kinase 4 and 6 inhibitors (CDK4/6i, eg, ribociclib, palbociclib, and abemaciclib) plus endocrine therapy (ET) have shown significant progression-free survival (PFS) benefit over ET alone and are now standard first-line treatment for patients with HR+/HER2− ABC.[6, 15-19] A significant PFS and overall survival (OS) benefit with a higher response rate was observed for first-line ribociclib plus ET over ET alone in the phase 3 MONALEESA-7 trial in premenopausal patients with HR+/HER2−

ABC.[18, 20, 21] However, although phase 3 CDK4/6i studies included patients with visceral disease, those with high burden of disease, extensive symptomatic visceral disease, or visceral crisis were excluded from these trials.[15-19, 22]

To date, no published randomized controlled trial (RCT) data have reported a comparison between a first-line CDK4/6i plus ET and combination CT in patients with clinically aggressive, high disease burden HR+/HER2− ABC. Here we report the final analysis of the RIGHT Choice trial, the first prospective comparison of a first-line CDK4/6i (ribociclib) plus ET versus combination CT in premenopausal women with HR+/HER2− ABC with symptomatic visceral metastases, rapid disease progression or impending visceral compromise, or markedly symptomatic non-visceral disease; these patients were defined as having clinically aggressive ABC.

Methods

Study Design

This open label phase 2 trial was conducted in 13 countries. Patients were randomized (1:1) to oral ribociclib (600 mg per day on a 3-weeks-on, 1-week-off schedule) plus ET (letrozole 2.5 mg or anastrozole 1 mg orally; continuous daily schedule) with goserelin (3.6 mg subcutaneous implant; day 1 of each 28-day cycle) or combination CT of investigator's choice among one of three regimens (docetaxel plus capecitabine, paclitaxel plus gemcitabine, or capecitabine plus vinorelbine; **Table S1**). If one CT agent was discontinued because of AEs, patients could continue the other agent as monotherapy.

Randomization was stratified by presence of liver metastases (present or absent) and a disease-free interval (the time between complete tumor resection for primary BC lesion to disease recurrence) <2 years (yes or no; patients with de novo stage 4 disease were included in the disease-free interval ≥2 years group for the purpose of stratification only). The statistician was blinded to treatment until database lock. Patients received treatment until disease progression, unacceptable toxicity, death, or discontinuation for any other reason.

Participants

Eligible patients were pre/perimenopausal (hereby referred to as premenopausal) women aged 18- 59 years, with histologically or cytologically confirmed progesterone or estrogen (>10%) receptor positive (ER+ or PR+), HER2− ABC (locoregionally recurrent or metastatic, not amenable to curative therapy) and an ECOG performance status of 0 to 2. Measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 was required.[23] Patients were eligible if combination 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. Patients who received (neo)adjuvant therapy for BC were eligible; adjuvant therapy with aromatase inhibitors was permitted if the subsequent treatment-free interval was >12 months.

Patients were ineligible if they received prior systemic anti-cancer therapy for ABC. Patients with liver metastases were ineligible if bilirubin levels were >1.5x the upper limit of normal (ULN), or if the aspartate transaminase (AST) or alanine transaminase (ALT) levels were >5x the ULN.

Endpoints

The primary endpoint was locally assessed PFS (time from the date of randomization to the date of the first documented progression or death due to any cause). Secondary endpoints were time to treatment failure (TTF), 3-month treatment failure rate (TFR), overall response rate (ORR), clinical benefit rate (CBR), time to response (TTR), OS, health-related quality of life, and safety (**Table S2**). The 3-month TFR analysis was planned to assess the early efficacy of the treatments. The ORR, CBR, and TTR outcomes were without confirmation; confirmation imaging was not mandatory according to the study protocol as this was a phase 2, non-registrational study.[23]

Assessments

Tumor assessments were performed every 6 weeks (first 12 weeks), every 8 (next 32 weeks), and then every 12 weeks (**Table S3**). AEs were characterized and graded according to the NCI CTCAE, v4.03. After discontinuation of study treatment, all patients were followed up for safety for 30 days (except in case of death, follow-up loss or consent withdrawal). Exploratory endpoints were biomarker analyses and medical resource utilization. An exploratory PFS analysis of select subgroups is reported here; quality-of-life endpoints will be reported separately. Visceral crisis determination was according to investigator's judgment at start of the study, largely based on ABC 3 guidelines.[5]

The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and any amendments were approved by an independent ethics committee or institutional review board at each site and the Health

Authority of participating countries. A steering committee comprising of participating investigators, Novartis representatives, and one patient with BC who did not participate in this trial, supervised the study. All patients provided written informed consent. RIGHT Choice is registered with ClinicalTrials.gov (NCT03839823).

Statistical Analysis

All efficacy analyses were performed using the full analysis set, comprising all randomized patients, per the intent-to-treat principle. Safety analyses were performed in patients who received ≥1 dose of any study treatment component (safety set).

For the primary efficacy analysis, PFS was compared between treatment arms using a log rank test stratified according to randomization stratification criteria. For the prespecified primary analysis, a determination that ~110 patients had disease progression or died was required to detect a hazard ratio (HR) of 0.67 with a power of 80% at a one-sided alpha level of 10%. The PFS was censored at the last adequate tumor assessment if no event was documented. Additionally, any event documented following two or more missing tumor assessments or initiation of a new anti-neoplastic therapy was censored at the adequate tumor assessment prior to the event. For TTF, discontinuation reasons that counted as events included AEs, death, loss to follow-up, pregnancy, progressive disease, physician or patient decision, or receipt of new antineoplastic therapy. Kaplan-Meier method was used to estimate time-to-event analyses. A stratified Cox proportional-hazards model was used to estimate the HR and 95% confidence intervals (CI). This study was not powered to demonstrate a treatment difference in secondary endpoints. The PFS and secondary endpoints analysis presented here is from the final database lock (May 10, 2023).

Results

Patients

From March 4, 2019 to November 16, 2021, a total of 222 patients were randomized to receive ribociclib plus ET (n=112) or combination CT (n=110; CONSORT diagram [**Fig. 1**]). Demographics and baseline characteristics were well balanced between the treatment arms (**Table 1**). While 143 patients (64.4%) had de novo advanced or metastatic disease, 79 (35.6%) patients had relapsed from early disease. In total, 150 patients (67.6%) had symptomatic visceral metastases, 41 (18.5%) experienced rapid disease progression, and 31 (14.0%) had symptomatic non-visceral metastases. Overall, 106 patients (47.7%) had investigator-assessed visceral crisis. Also, most patients (n=191; 86.0%) had ≥50% ER+ tumors. The majority of patients (n=124, 55.9%) had ≥3 metastatic sites. Specifically, liver-only, lung-only, and liver or lung metastases were present in 107 (48.2%), 117 (52.7%), and 169 (76.1%) patients, respectively.

In the CT arm, 10 patients did not receive any study treatment due to consent withdrawal (n=9) and physician's decision to withdraw (n=1); all patients in the ribociclib arm received study treatment. Among the 100 patients who received combination CT, 24 (24.0%) received docetaxel plus capecitabine, 34 (34.0%) received paclitaxel plus gemcitabine, and 42 (42.0%) received capecitabine plus vinorelbine. At the second and final database lock data cutoff, the median follow-up time (the time from randomization to data cutoff date) was 37.01 months. Overall, 35 (31.3%) and 17 (15.5%) patients in the ribociclib and CT arms, respectively, completed study treatment and were transitioned to the post-trial access program. Treatment was discontinued in 77 (68.8%)

and 83 (75.5%) patients in the ribociclib and CT arms, mostly due to disease progression (65 [58.0%] and 65 [59.1%] patients in the ribociclib and CT arms, respectively [**Table S4**]). The median duration of treatment exposure was 17.6 months (interquartile range [IQR], 7.9-29.5 months) in the ribociclib arm and 10.9 months (IQR, 6.3-17.7 months) among the three combination CT regimens. The median relative dose intensity in the ribociclib arm was 97.35% (IQR, 73.02%-100.0%). In the ribociclib arm, 24.1% and 5.4% of patients required 1 or 2 ribociclib dose reductions, respectively; >2 ribociclib dose reductions were not allowed. In the CT arm, 13.0%, 16.0%, and 20.0% of patients required 1, 2, or 3 or more dose reductions, respectively.

Primary Endpoint

At data cutoff for final PFS analysis, at which 132 events had occurred, the median PFS was 21.8 months (95% CI, 17.4-26.7 months) with ribociclib plus ET versus 12.8 months (95% CI, 10.1-18.4 months) with combination CT (HR, 0.61; 95% CI, 0.43-0.87; one-sided *P*=.003; **Fig. 2A**). At 12 and 24 months, the PFS rates were 68.9% (95% CI, 59.3%-76.7%) and 46.5% (95% CI, 36.4%-56.0%) in the ribociclib versus 54.5% (95% CI, 43.7%-64.0%) and 23.6% (95% CI, 14.2%-34.4%) in the CT arm, respectively. The PFS benefit in the subgroups was generally consistent with the overall population; however, the degree of benefit was less in patients in visceral crisis and in those with recurrent disease (**Fig. 3**).

Secondary Endpoints

The median TTF was 18.6 months versus 9.1 months with ribociclib plus ET and combination CT (HR, 0.50; 95% CI, 0.36-0.68; **Fig. 2B**), respectively. The three-month

TFRs were 11.6% (95% CI, 6.3%-19.0%) with ribociclib plus ET versus 21.8% (95% CI, 14.5%-30.7%) with combination CT. Most three-month treatment failure events were due to disease progression with similar rates in both arms (ribociclib plus ET, 9.8%; combination CT, 10.0%; **Table S5**).

The median TTR was 4.9 months versus 3.2 months with ribociclib plus ET and combination CT (HR, 0.76; 95% CI, 0.55-1.06; **Fig. 2C**), respectively. Waterfall plots showed comparable tumor size changes from baseline to weeks 6 and 12 between the treatment arms (**Fig. S1**). The ORR was 66.1% in the ribociclib arm and 61.8% in the CT arm, while the CBR was 81.3% in the ribociclib arm and 74.5% in the CT arm (**Table 2**). Sensitivity analyses in the safety set, which excluded the ten patients in the CT arm that did not receive any study treatment, confirmed these findings (**Table S6**, **Fig. S2**).

The OS data were immature at database cutoff date, with 34 (30.4%) and 29 (26.4%) deaths in the ribociclib and CT arms, respectively. The median OS was not reached (NR) in the ribociclib arm (95% CI, 38.6 months-NR) or the CT arm (95% CI, 30.8 months-NR; HR, 0.92, 95% CI, 0.56-1.52). The 12-, 18-, 24- and 30- month OS rates were 87.9%, 85.1%, 77.3%, and 66.6% and 92.5%, 86.5%, 73.7%, and 64.6% in the ribociclib and CT arm, respectively (**Fig. 2D**).

Safety

The safety set included 112 and 100 patients in the ribociclib and CT arms, respectively. All patients experienced at least one all-grade AE (**Tables 3 and S7**). Higher rates of hematologic events including neutropenia and leukopenia were observed with ribociclib

plus ET while higher rates of non-hematologic events including nausea, vomiting, diarrhea, and fatigue were observed with combination CT.

Overall, 79.5% and 73.0% of patients in the ribociclib and CT arms, respectively, experienced an all-cause grade 3 or 4 AE. The most common grade 3 or 4 AEs were neutropenia (59.8% and 36.0%) and leukopenia (25.0% and 8.0%) in the ribociclib and CT arm, respectively. The most common grade 3 or 4 biochemical abnormality was an increased ALT level (ribociclib arm, 6.3%; CT arm, 12.0%; **Table S8**). Two patients (1.8%) in the ribociclib arm experienced ≥ grade 3 QTc prolongation without evidence of arrythmia. ≥Grade 3 febrile neutropenia was reported in 3 patients (3.0%) in the CT arm only. All-grade and grade 3/4 infections occurred in 39.3% and 5.4% versus 44.0% and 12.0% of patients in the ribociclib and CT arms, respectively. The colony stimulating factors were used in 4.5% of patients in the ribociclib arm (not recommended per protocol for patients receiving ribociclib with neutropenia without infection) versus 25.0% in the CT arm. Overall, treatment-related AEs led to discontinuation of any study component in 6.3% versus 27.0% of patients in the ribociclib and CT arms, respectively. In the ribociclib arm, patients discontinued due to increased AST (4 patients) or bilirubin (2 patients); in the CT arm, patients discontinued due to neutropenia (6 patients), palmar-plantar erythrodysesthesia (5 patients), peripheral sensory neuropathy (3 patients), or pulmonary embolism (2 patients). Treatment-related serious AEs were reported in 2 (1.8%) and 8 (8.0%) patients in the ribociclib and CT arms, respectively.

Five deaths (4.5%) occurred in the ribociclib arm during the 30 days after the end of study treatment; these deaths were attributed to BC progression. These five patients had a ribociclib treatment duration of 1.0 month, 8.6 months, 9.9 months, 18.2 months,

and 23.4 months. No on-treatment deaths occurred in the combination CT arm. The patient in the ribociclib arm who died during the first 6 months of treatment experienced a serious AE of sepsis, which was not considered treatment related according to the principal investigator's judgment, with death on study day 38 attributed to ABC.

Discussion

This final analysis of the RIGHT Choice trial showed a clinically meaningful, statistically significant PFS benefit with first-line ribociclib plus ET over combination CT in premenopausal women with clinically aggressive HR+/HER2− ABC in which combination CT is typically is used to achieve a rapid tumor response. This PFS benefit was observed in most subgroups. In this trial, PFS with combination CT was longer than the historical data in advanced disease.[7-13] Ribociclib plus ET showed a longer TTF as well as a similar ORR as combination CT, matching historical combination CT tumor response rates.[7-9] Although the median TTR slightly favored combination CT over ribociclib plus ET by 1.7 months in this premenopausal patient population (**Fig. 2C**), the similar ORR along with the similar changes in tumor size from baseline to weeks 6 and 12 with ribociclib plus ET and combination CT (**Fig. S1**), indicated comparable activity at those time points. The OS data, although immature at final database lock, showed a similar survival trend for both arms, suggesting there is likely no meaningful difference in survival benefit with combination CT versus ribociclib plus ET.

AEs with ribociclib plus ET were in line with the known safety profile, with no new safety signals observed.[17-19] AEs with combination CT were also consistent with previously

published data, with higher rates of symptomatic AEs including nausea, vomiting, fatigue, and diarrhea, compared with ribociclib plus ET.[7-9, 24] Additionally, treatment-related AEs that led to discontinuation of any study component were seen in a higher percentage of patients receiving combination CT versus those receiving ribociclib plus ET, thus supporting a favorable tolerability of ribociclib plus ET. As determining the choice of treatment includes taking into account the relative toxicity of each treatment, these efficacy and safety data collectively show that ribociclib plus ET may be a better alternative to combination CT in this patient population.

In RIGHT Choice, 47.7% of patients were determined to have visceral crisis by investigators' assessment (principally based on ABC 3 guidelines available at the time of study design), reflecting the considerable disease burden of the trial patients.[5] The visceral crisis definition remains imprecise, and determination largely depends on clinical judgment; thus, some subjectivity was involved when characterizing patients in this regard. The ABC 5 guidelines, published in 2020, further clarified the visceral crisis definition by adding laboratory evaluation of liver function based on elevated bilirubin levels.[6] However, patients with liver metastases and bilirubin levels >1.5 times the ULN were ineligible for this trial, as such patients require immediate individualized treatment, which clearly impedes their inclusion in a RCT. Exploratory subgroup analysis of patients with investigator-assessed visceral crisis in this trial showed similar PFS and TTR durations in the two arms, however, the symptomatic AE rates were lower in those in the ribociclib versus the CT arm.[25]

A few specificities of this trial must be considered. The sample size was smaller in this phase 2 proof of concept study, as performing large-scale phase 3 studies for this

specific patient population was not possible. As treatment blinding could not be implemented in the open-label design of this trial, investigators and patients were aware of treatment assignment information that may have led to detection and performance bias. Ten patients in the CT arm did not receive any study treatment; however, this fact likely did not affect the efficacy results for the intent-to-treat population, as confirmed by sensitivity analyses in the safety set that excluded these patients (**Fig. S2, Table S6**). The CT regimens used here are commonly used CT regimens in the ABC clinical setting. Not all combination CT regimens used in the ABC setting in clinics could be included in the comparator arm. Anthracycline-based combination CT regimens, which have been shown to have efficacy as first-line treatments in patients with ABC, were not included because of potential of increased cardiotoxicities associated with them; notably, 32 (14.4%) patients had received anthracycline in (neo)adjuvant setting and relapsed.[26-29] Also, most patients had >50% ER+ tumors as well as PR+ tumors; therefore, these findings may not apply to patients with low ER+ or PR− tumors. The 50% ER cutoff to split patients with lower versus higher endocrine sensitivity was used based on significant differences in ET benefit between these tumor ER expression levels.[30] Finally, the majority of patients in this trial have de novo ABC disease, and thus the validity of these findings in patients with recurrent disease warrants further investigation.

The results of the RIGHT Choice trial are aligned with those from the MONALEESA-7 trial, which showed PFS benefit (median PFS: 23.8 months) with first-line ribociclib plus ET in premenopausal patients with HR+/HER2− ABC.[18] However, MONALEESA-7

excluded patients with extensive symptomatic disease or visceral crisis and included patients with prior CT in the advanced setting.[18] The Young-PEARL and PEARL trials are the only published examples comparing a CDK4/6i plus ET with single-agent CT in patients with HR+/HER2− ABC.[31, 32] In Young-PEARL, which excluded patients with symptomatic serious visceral metastases, second-line palbociclib plus exemestane demonstrated longer PFS over capecitabine by 5.7 months in premenopausal patients.[32] In PEARL, second-line palbociclib plus ET did not meet the superiority threshold versus single-agent CT in postmenopausal women with less aggressive disease.[31] Conversely, RIGHT Choice investigated first-line treatment of patients with a significant disease burden using combination CT as the comparator.

In conclusion, we report the final analysis of the phase 2 RIGHT Choice trial of first-line ribociclib plus ET versus combination CT in premenopausal women with clinically aggressive HR+/HER2− ABC, including investigator-assessed visceral crisis. The data show PFS superiority with ribociclib plus ET over combination CT, with similar response rates, lower symptomatic AE rates, and fewer discontinuations due to treatment-related AEs. Thus, ribociclib plus ET could be considered a first-line treatment option in this patient population.

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Tables and Figures

Table 1. Patient Characteristics at Baseline

Characteristics	**Ribociclib + ET (n=112)**	**Combination CT (n=110)**
Age, median (range) — years	44.0 (26-58)	43.0 (26-55)
Female sex, n(%)	112 (100.0)	110 (100.0)
Race — n (%)		
Asian	60 (53.6)	58 (52.7)
White	51 (45.5)	52 (47.3)
Black or African American	1 (0.9)	0
Histological tumor grade, n (%)		
I	10 (8.9)	16 (14.5)
II	66 (58.9)	61 (55.5)
III	35 (31.3)	29 (26.4)
Missing	1 (0.9)	4 (3.6)
ECOG performance status, n (%)		
0	46 (41.1)	42 (38.2)
1	63 (56.3)	62 (56.4)
2	3 (2.7)	6 (5.5)
Disease free interval*, n (%)		
De novo disease	70 (62.5)	73 (66.4)
Relapsed from early breast cancer	42 (37.5)	37 (33.6)
≤12 months	6 (5.4)	2 (1.8)
>12 and ≤24 months	8 (7.1)	7 (6.4)
>24 months	28 (25.0)	28 (25.5)
HER2 receptor negative, n (%)	112 (100.0)	110 (100.0)
Estrogen receptor positive**, n (%)	112 (100.0)	110 (100.0)
≥50%	95 (84.8)	96 (87.3)
<50%	8 (7.1)	4 (3.6)
Progesterone receptor positive†, n (%)	99 (88.4)	102 (92.7)
Disease history, n (%)		
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 status, n (%)		
Yes	57 (50.9)	49 (44.5)
Metastatic sites‡, n (%)		
Bone	60 (53.6)	68 (61.8)
Bone only	5 (4.5)	4 (3.6)
CNS	1 (0.9)	3 (2.7)
Liver	54 (48.2)	53 (48.2)
Liver or lung	87 (77.7)	82 (74.5)

Lung	62 (55.4)	55 (50.0)
Lymph node	74 (66.1)	75 (68.2)
Other	46 (41.1)	38 (34.5)
Skin	9 (8.0)	2 (1.8)
Soft tissue	3 (2.7)	5 (4.5)
Number of metastatic sites, n (%)		
1	19 (17.0)	11 (10.0)
2	29 (25.9)	39 (35.5)
≥3	64 (57.1)	60 (54.5)

CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2. *Defined as the duration between the date patient received complete tumor resection for primary breast cancer lesion to the date of disease recurrence. **Among the 9 patients in the ribociclib plus ET arm with missing estrogen receptor percentage, 1 patient had an Allred score of 5, 2 patients had an Allred score of 6, 5 patients had an Allred score of 8, and 1 patient did not have estrogen receptor percentage or Allred score. †Two patients in the ribociclib plus ET arm had an unknown progesterone receptor status. ‡The same patient may have multiple visceral metastatic sites.

Table 2. Overall Response Rate and Clinical Benefit Rate (full analysis set)

	Ribociclib + ET (n=112)*	Combination CT (n=110)*
Best overall response		
Complete response	7 (6.3)	3 (2.7)
Partial response	67 (59.8)	65 (59.1)
Stable disease	27 (24.1)	20 (18.2)
Progressive disease	9 (8.0)	6 (5.5)
Unknown	2 (1.8)	16 (14.5)
Overall response rate** (%) [95% CI]	74 (66.1) [56.5-74.7]	68 (61.8) [52.1-70.9]
Clinical benefit rate† (%; 95% CI)	91 (81.3) [72.8-88.0]	82 (74.5) [65.4-82.4]

Data are n (%) or n (%) [95% CI]. The 95% CIs for the frequency distribution of each variable were computed using a normal approximation method. *Patients with measurable disease at baseline were included in these analyses. **Patients with complete or partial response without confirmation. †Patients with complete or partial response without confirmation (or stable disease lasting 24 weeks or more or noncomplete response without progressive disease lasting 24 weeks or more). Confirmation imaging was not mandatory according to the study protocol as this was a phase 2, non-registrational study.[23]

Table 3. Adverse Events

Events, n (%)	Ribociclib + ET (n=112)			Combination CT (n=100)*		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any event**	112 (100.0)	71 (63.4)	18 (16.1)	100 (100.0)	62 (62.0)	11 (11.0)
Hematologic events						
Neutropenia	94 (83.9)	57 (50.9)	10 (8.9)	50 (50.0)	29 (29.0)	7 (7.0)
Leukopenia	55 (49.1)	28 (25.0)	0	26 (26.0)	7 (7.0)	1 (1.0)
Anemia	40 (35.7)	6 (5.4)	0	43 (43.0)	11 (11.0)	0
Non-hematologic events						
Alanine aminotransferase increased	23 (20.5)	6 (5.4)	0	30 (30.0)	6 (6.0)	0
Aspartate aminotransferase increased	23 (20.5)	8 (7.1)	0	29 (29.0)	5 (5.0)	0
Nausea	14 (12.5)	0	0	27 (27.0)	1 (1.0)	0
Alopecia	12 (10.7)	0	0	20 (20.0)	0	0
Vomiting	8 (7.1)	1 (0.9)	0	30 (30.0)	0	0
Diarrhea	3 (2.7)	0	0	26 (26.0)	1 (1.0)	0
Fatigue	9 (8.0)	0	0	25 (25.0)	2 (2.0)	0
Palmar-plantar erythrodysesthesia	3 (2.7)	0	0	32 (32.0)	5 (5.0)	0

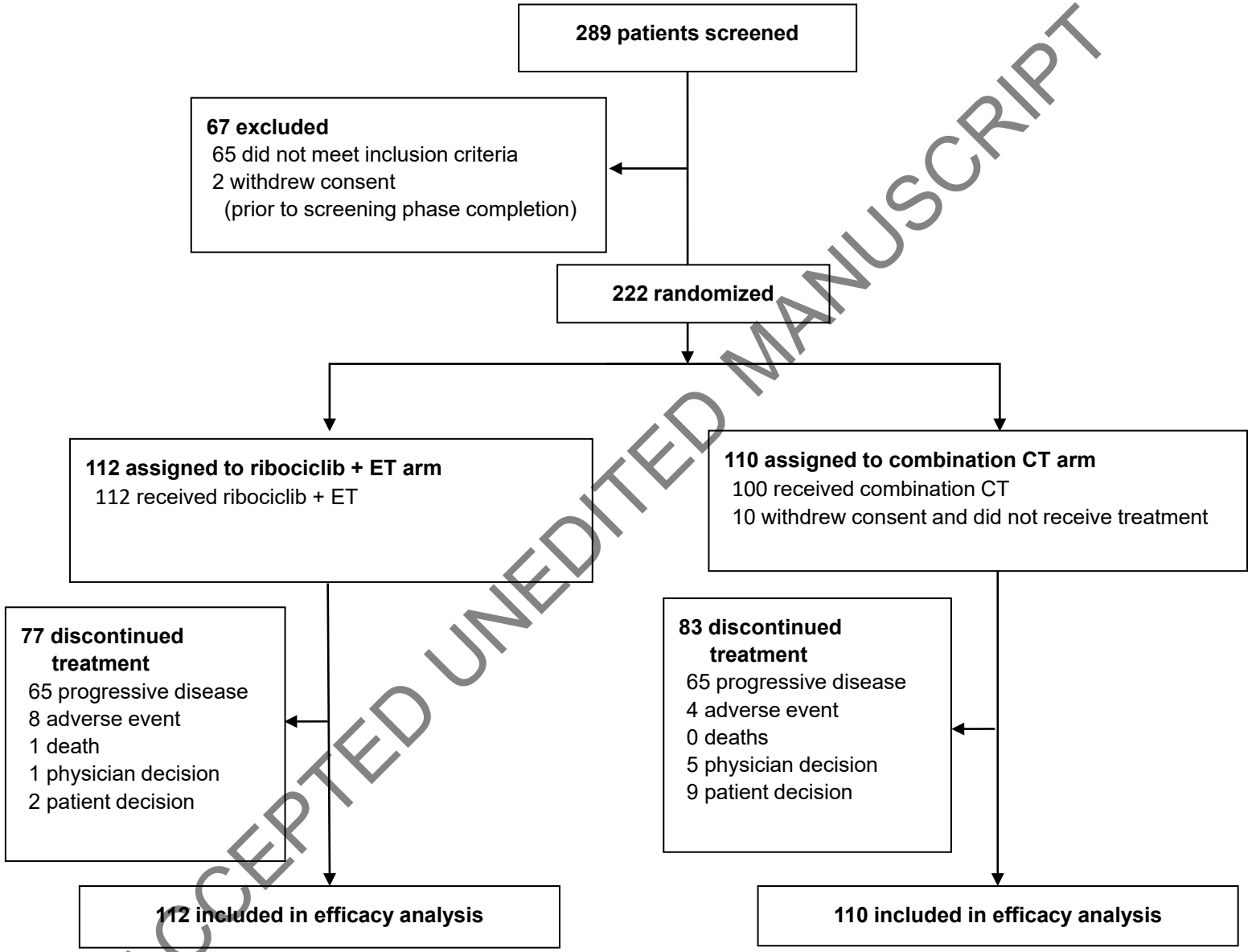
*The 10 patients in the combination CT arm who were randomized to CT but did not receive any treatment were not included in the safety set. **Listed are events that were reported in at least 20% of the patients in either arm irrespective of causality.

Figure 1. CONSORT Diagram

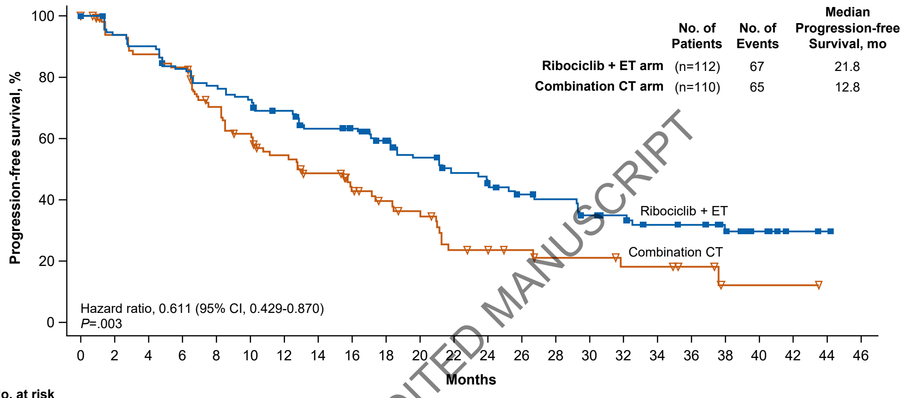
Figure 2. Kaplan-Meier Analysis of (A) Progression-free Survival, (B) Time to Treatment Failure, (C) Time to Response, and (D) Overall Survival

Figure 3. Subgroup Analysis of Progression-free Survival

The results from subgroups with small patient numbers (disease-free interval less than 2 years and low [<50] estrogen receptor–positive status) need to be interpreted with caution.



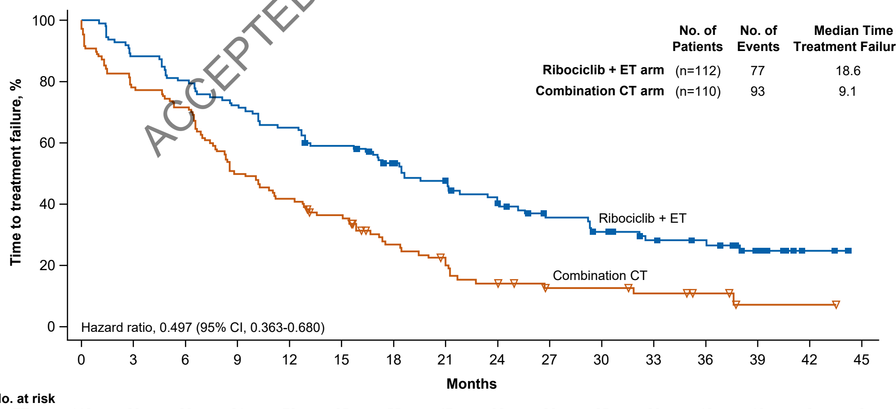
A.



No. at risk

Ribociclib + ET arm	112	103	99	90	84	79	73	65	63	56	48	41	39	32	30	25	23	19	17	13	6	2	1	0
Combination CT arm	110	90	84	79	63	54	46	38	29	24	21	13	12	10	8	8	6	6	4	1	1	1	0	0

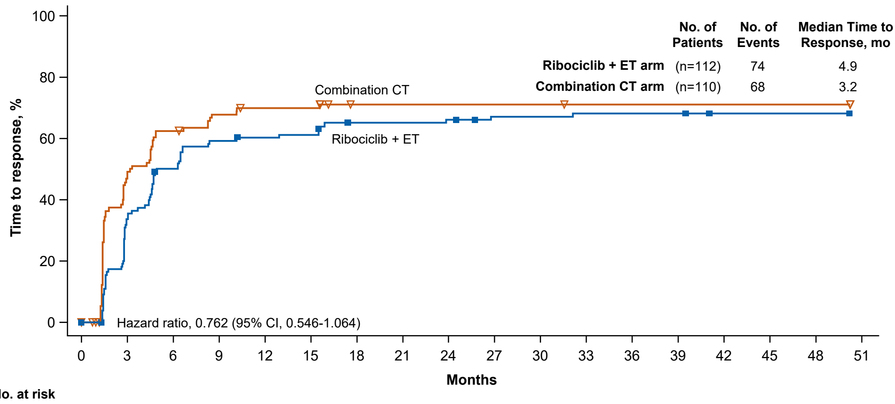
B.



No. at risk

Ribociclib + ET arm	112	99	90	81	73	65	55	47	39	30	25	20	18	10	2	0
Combination CT arm	110	86	79	55	46	38	24	17	12	8	8	6	4	1	1	0

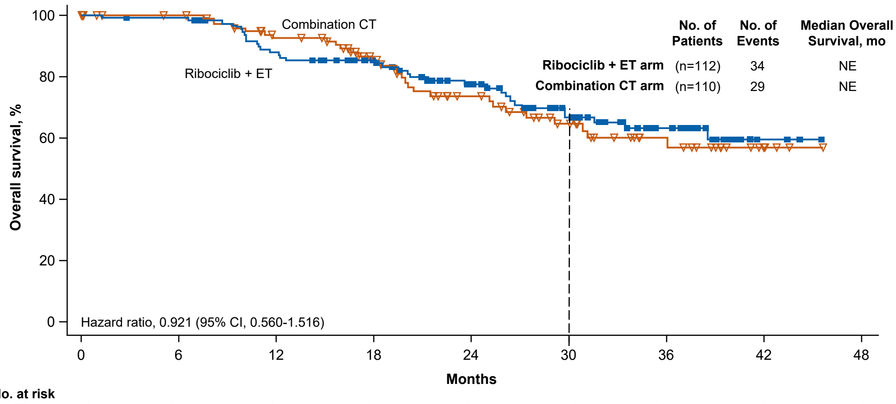
C.



No. at risk

Ribociclib + ET arm	112	72	54	44	42	41	35	35	34	31	31	30	30	30	27	27	27	0
Combination CT arm	110	50	36	30	27	27	22	22	22	22	22	21	21	21	21	21	21	0

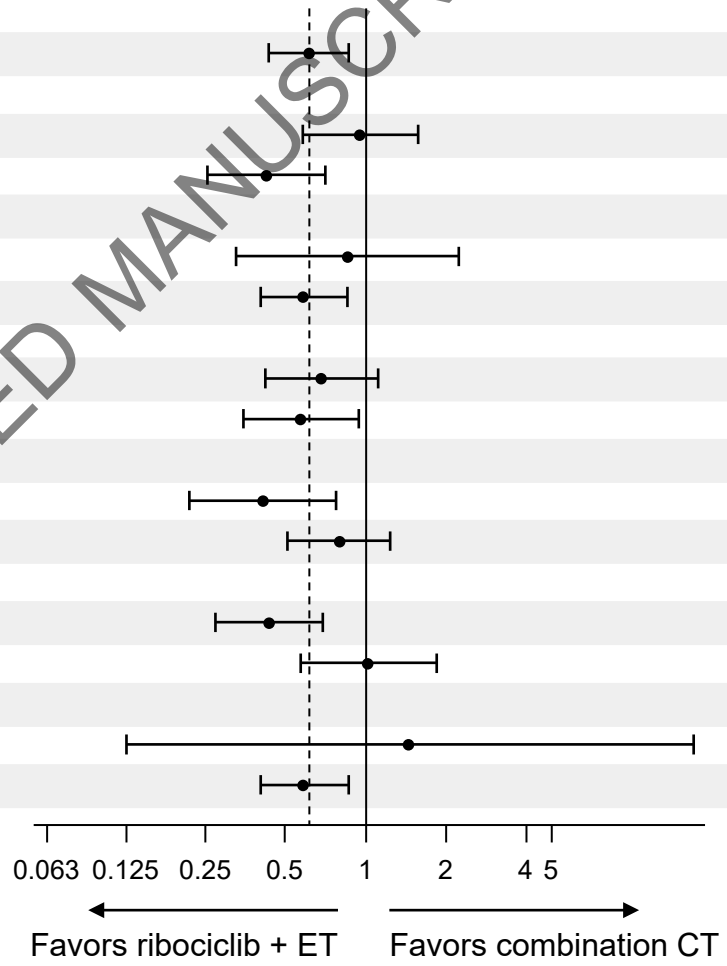
D.



No. at risk

Ribociclib + ET arm	112	110	94	80	63	45	25	3	0
Combination CT arm	110	97	83	65	44	31	19	5	0

Subgroup	Ribociclib + ET arm n/N	Combination CT arm n/N	Hazard Ratio (95% CI)
All patients	67/112	65/110	0.611 (0.429, 0.870)
Visceral crisis status (yes vs no)			
Yes	37/57	27/49	0.953 (0.574, 1.582)
No	30/55	38/61	0.423 (0.254, 0.704)
Disease free interval			
< 2 years	11/14	8/9	0.851 (0.325, 2.231)
≥ 2 years	56/98	57/101	0.581 (0.398, 0.847)
Presence of liver metastasis (yes vs no)			
Yes	35/54	32/53	0.681 (0.420, 1.106)
No	32/58	33/57	0.565 (0.343, 0.933)
Age			
< 40 years	19/32	28/38	0.410 (0.217, 0.776)
≥ 40 years	48/80	37/72	0.789 (0.505, 1.232)
De novo (yes vs no)			
Yes	36/70	45/73	0.432 (0.270, 0.689)
No	31/42	20/37	1.016 (0.562, 1.836)
Estrogen receptor status			
< 50	4/8	3/4	1.457 (0.124, 17.079)
≥ 50	57/95	56/96	0.585 (0.398, 0.860)



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