Title

Phase I/II Trial of Exemestane, Ribociclib, and Everolimus in Women with HR+/HER2− Advanced Breast Cancer after Progression on CDK4/6 Inhibitors (TRINITI-1)

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Phase I/II trial of triplet therapy (exemestane, ribociclib, and everolimus) after progression on a CDK4/6 inhibitor in HR+/HER2– advanced breast cancer (TRINITI-1)

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Abstract

PURPOSE—Standard-of-care treatment for metastatic hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) breast cancer includes endocrine therapy (ET) combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). Optimal treatment after progression on CDK4/6i is unknown. The TRINITI-1 trial investigated ribociclib, a CDK4/6i which has recently demonstrated significant OS benefit in 2 phase III trials, in combination with everolimus and exemestane in patients with HR+, HER2– advanced breast cancer (ABC) after progression on a CDK4/6i.

METHODS—This multicenter, open-label, single-arm, phase I/II study included patients with locally advanced/metastatic HR+/HER2– BC. The primary endpoint was clinical benefit rate (CBR) at week 24 among patients with ET-refractory disease with progression on a CDK4/6i. Other endpoints included safety and biomarker analysis.

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RESULTS—Of 104 patients enrolled (phases I and II), 96 had prior CDK4/6i. Recommended phase II doses (all once daily days 1–28 of 28-day cycle) were ribociclib 300 mg, everolimus 2.5 mg, and exemestane 25 mg (group 1) and ribociclib 200 mg, everolimus 5 mg, and exemestane 25 mg (group 2). CBR among 95 efficacy-evaluable patients (phases I and II) at week 24 was 41.1% (95% CI, 31.1%–51.6%), which met the primary endpoint (predetermined threshold: 10%). Common adverse events included neutropenia (69.2%) and stomatitis (40.4%). No new safety signals were observed; no grade 3/4 QTc prolongation was reported.

CONCLUSION—Preliminary TRINITI-1 safety and efficacy results support further investigation of CDK4/6 blockade and targeting of the PI3K/AKT/mTOR signaling pathway in patients with ET-refractory HR+/HER2– ABC after progression on a CDK4/6i.

Introduction

Although hormone receptor–positive (HR+) breast cancers are primarily driven by estrogen receptor signaling, additional signaling pathways may serve as an escape from treatment with endocrine therapy (ET).[1,2] Aberrant activation of the cyclin D–cyclin-dependent kinase (CDK) 4/6–inhibitor of CDK4 (INK4)–retinoblastoma (RB) pathway (Supplemental Figure 1) can lead to unrestricted cell cycle progression as well as resistance to ET.[1,3] The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway has also been widely implicated in breast cancer tumorigenesis and ET resistance.[4–6]

A standard of care for postmenopausal women with HR+/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC) includes ET combined with a CDK4/6 inhibitor (CDK4/6i), usually given in the first-line setting.[7,8] Although the addition of a CDK4/6i to ET has improved outcomes in patients with HR+/HER2– ABC, most patients will eventually experience disease progression due to de novo or acquired resistance.[1,9–11] Optimal treatment after progression on a CDK4/6i remains unclear. Use of an mTOR inhibitor, or more recently, a PI3K inhibitor (for those whose tumors harbor mutated *PIK3CA)* may be considered.[8,12–14] Numerous levels of crosstalk exist between the estrogen receptor (ER), CDK4/6, and PI3K/AKT/mTOR signaling pathways, suggesting a potential benefit in combining inhibitors of these pathways.[1,4] However, a paucity of clinical data exists on the benefit of continued CDK4/6 blockade following disease progression on CDK4/6i therapy.[8]

In preclinical cell line and mouse xenograft studies, inhibition of the PI3K/AKT/mTOR signaling pathway blocked progression of ET/CDK4/6i-resistant tumors, although no benefit was observed with continuation of CDK4/6i.[15–17] The phase III BOLERO-2 trial demonstrated that everolimus (EVE) + exemestane (EXE) resulted in significantly longer progression-free survival (PFS) than placebo + EXE among CDK4/6i-naive patients with ABC who were refractory to an aromatase inhibitor (AI).[13,14] Subsequently, the potential benefit of EVE + ET in this patient population was also observed in phase II trials using other ET combinations: EVE + fulvestrant (PrECOG 0102) and EVE + tamoxifen (TAMRAD).[18,19] However, none of these trials included patients who were previously

treated with a CDK4/6i; thus, the activity of mTOR inhibition in CDK4/6i-resistant disease has not been well explored.

Ribociclib (RIB) is a selective, orally available CDK4/6i. Among patients with HR+/HER2– ABC, RIB in combination with ET has demonstrated a significant benefit (including a significant overall survival [OS] benefit in pre- and postmenopausal women) and an acceptable toxicity profile.[20–24] Preliminary results from a phase Ib trial of RIB + EVE + EXE in postmenopausal women with ER+/HER2– ABC refractory to nonsteroidal AIs showed an acceptable toxicity profile and early signals of clinical activity.[25,26]

Triplet therapy with Ribociclib, AfINitor® and AI posT CDK 4/6 Inhibitor (TRINITI-1) is a phase I/II trial of RIB, EVE, and EXE in patients with ET-refractory HR+/HER2– ABC (NCT02732119). Here we present interim efficacy and exploratory biomarker results among patients with progression on a CDK4/6i as well as overall safety results from TRINITI-1.

Methods

Patients

Men and postmenopausal women aged 18 years with HR+/HER2– locally advanced/metastatic breast cancer not amenable to curative treatment by surgery or radiotherapy were eligible. Additional key inclusion criteria were disease progression on up to 3 lines of prior therapy for ABC including 1 to 3 lines of ET and 1 line of chemotherapy, measurable disease or lytic/mixed bone lesions, adequate bone marrow and organ function, and Eastern Cooperative Oncology Group performance status (ECOG PS) of 1. In phase II, patients were required to have progressed on a CDK4/6i after 4 months of therapy as the last prior treatment regimen. The selection of 4 months for secondary resistance was reflective of the inclusion of patients with multiple lines of prior treatment for ABC and the trend toward quicker progression on later lines of therapy. Patients with visceral crisis, central nervous system involvement < 4 weeks from completion of prior therapy, or clinically significant, uncontrolled heart disease or cardiac repolarization abnormalities were excluded.

Study Design

TRINITI-1 was a multicenter, open-label, phase I/II study (Supplemental Table 1). Phase I evaluated the maximum tolerated dose (MTD) of RIB, EVE, and EXE; phase II evaluated antitumor activity. All treatments were administered orally and were continuous, with no rest days (once daily on days 1–28 of a 28-day cycle). After optimal doses were determined in phase I, phase II was initiated (Figure 1). Treatment continued until disease progression, unacceptable toxicity, withdrawal of consent, loss to follow-up, or study termination.

In group 1 of phase I, patients were enrolled to treatment in cohort A (RIB 250 mg + EVE 2.5 mg + EXE 25 mg daily). If 33% of patients experienced a dose-limiting toxicity (DLT) in cohort A, enrollment proceeded to cohort B (RIB 300 mg + EVE 2.5 mg + EXE 25 mg daily). DLTs were defined as adverse events (AEs) or abnormal laboratory values unrelated to disease or disease progression with a reasonably possible relationship to the study medication(s) that occurred within the first 28 days of cycle 1 and met predefined criteria per the National Cancer Institute Common Terminology Criteria for Adverse Events

(NCI CTCAE) v4.03. In group 2, dose de-escalation (cohort C; RIB 200 mg + EVE 5 mg + EXE 25 mg daily) was explored. If DLTs were experienced, the treatment dose was reduced. In phase II, efficacy and safety were evaluated at the recommended phase II doses (RP2Ds) determined for groups 1 and 2 (RP2D1 and RP2D2).

Endpoints

The primary endpoint was clinical benefit rate (CBR), defined as the proportion of patients with complete response (CR), partial response, stable disease, or non-CR/nonprogressive disease, at week 24 (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1). The predefined primary endpoint threshold was > 10%, which was chosen as a conservative estimate of the percentage of patients post-CDK4/6i who might benefit from triplet therapy. Key secondary endpoints included PFS, OS, overall response rate, and safety outcomes. Safety outcome measures included percentages of patients with AEs, serious AEs, changes in hematology and chemistry values, vital signs, and electrocardiograms (ECGs). Exploratory endpoints included analysis of circulating tumor DNA (ctDNA) for gene mutations, including those relevant to the CDK4/RB pathway, *ESR1*, and other breast cancer resistance patterns.

Assessments

Efficacy—All patients enrolled in phase I or II whose disease progressed on prior CDK4/6i therapy and received 1 dose of the assigned combination of study drugs were included in efficacy analyses. Tumor response assessments were performed locally per RECIST 1.1 at screening, every 8 weeks starting from day 1 of study treatment for the first 12 months, and then every 12 weeks thereafter until disease progression.

Safety—The safety-evaluable population included all patients who enrolled in phase I or II, received 1 dose of any of the investigational treatment components, and had 1 valid postbaseline safety assessment. Safety was assessed at screening, continuously during treatment, and for 30 days after the last dose of study drug. AEs were assessed according to NCI CTCAE v4.03. A 12-lead standard ECG was performed at baseline, cycle (C) 1 day (D) 15, C2 D1 and D15, C3–6 D1, at every third cycle thereafter for patients with a QT interval corrected using Fridericia's formula 481 ms at any time prior to cycle 7, and at the end of treatment. ECGs could also be performed at any time as clinically indicated.

Pharmacokinetics—Blood samples for pharmacokinetic (PK) analysis from all patients in phases I and II were collected on C1 D15, C2 D1 and D15, and C3 D1. Patients with prior CDK4/6i treatment within 30 days of starting study drug also provided samples on C1 D1.

Biomarkers—Patients enrolled in phase I or II whose disease progressed on prior CDK4/6i therapy and received 1 dose of the assigned combination of study drugs were included in the exploratory biomarker analyses. Blood for ctDNA analysis was collected (EDTA collection tube) at baseline, on D1 of C1, 3, 5, and 7, and at the end of study treatment. DNA was extracted from patient plasma (plasma extracted by double spin processing) using the QIAamp Circulating Nucleic Acid Kit (QIAGEN, Wetzlar, Germany). DNA libraries were constructed using the TruSeq Nano DNA Library Prep kit (Illumina, San Diego,

CA). Coding regions were enriched by hybridization capture to a customized SureSelectXT (Agilent, Santa Clara, CA) 566-gene panel (Supplemental Table 2). Samples were sequenced on the HiSeq 2500 System (Illumina, San Diego, CA), aiming for an average target coverage depth of 1000×.

Statistical Analysis

The data cutoff for this interim analysis was October 24, 2018. For the primary endpoint, it was estimated (taking into account a dropout rate of 10%) that 66 patients would provide 80% power to test the null hypothesis that the CBR rate at 24 weeks was 10%, with an alternative hypothesis that this rate was > 10%. The CBR was calculated with an exact 95% Clopper-Pearson confidence interval (CI). The null hypothesis was to be rejected and a successful clinical benefit will be demonstrated if the lower limit of the 95% CI was greater than at least 0.10.

PFS and OS were analyzed using the Kaplan-Meier product-limit method. Similar analyses were performed for biomarkers identifying groups of patients by mutation type to evaluate their association with clinical outcomes (PFS, CBR). Clinical, safety, and biomarker data were also summarized. Summary statistics were provided and 95% CIs were also reported as appropriate. Inferential confirmatory statistics were not provided because of inadequate sizes of subgroups.

The study was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial protocol and all amendments were approved by an institutional review board, independent ethics committee, or research ethics board. All patients provided written informed consent before enrollment. Safety, efficacy, and available PK data were monitored by an independent data monitoring committee.

Results

Patients

A total of 104 patients (all women) with ET-refractory disease were enrolled; 25 in phase I and 79 in phase II. Of those patients, 96 had prior CDK4/6i treatment. Among the patients with prior CDK4/6i treatment (n = 96), the median age at baseline was 58 years; the majority of patients were white (81.3%), with an ECOG PS of 0 (57.3%), and had a median of 1 prior line of ET (range, 1–4) (Table 1). At data cutoff, study treatment was ongoing in 14 of 96 patients (14.6%; Supplemental Table 3). The most frequent reason for discontinuation was progressive disease (PD) (56.3%). Median duration of exposure was 16.5 weeks.

Dose Determination

In phase I, 18 and 7 patients were treated in groups 1 and 2, respectively, and the MTD was not reached in either group. RP2D1 was RIB 300 mg/day + EVE 2.5 mg/day + EXE 25 mg/day and RP2D2 was RIB 200 mg/day + EVE 5 mg/day + EXE 25 mg/day.

In a preliminary PK analysis (phase I; cohort A, n = 8; cohort B, n =10), a continuous combination regimen of RIB 250 to 300 mg/day, EVE 2.5 mg/day, and EXE 25 mg/day resulted in exposure that was consistent with that observed in a previous study of single-agent RIB 280 mg.[27] The concentrations of RIB and its metabolite LEQ803 were not affected by EVE (Supplemental Figure 2A, B). A dose-dependent drug-drug interaction was observed between RIB and EVE during concurrent continuous dosing, resulting in an EVE plasma trough concentration that was 2- to 3-fold and 4- to 5-fold higher than expected in cohorts A and B, respectively, which allowed the use of a lower EVE dose to reach therapeutic range (Supplemental Figure 2C).[28,29]

Efficacy

A total of 95 patients progressed on prior CDK4/6i and were evaluable for efficacy (phase I, n = 17; phase II, n = 78; 1 patient in phase II group 2 did not meet criterion of prior CDK4/6i progression). At week 24, the CBR was 41.1% (95% CI, 31.1%−51.6%; Table 2). This exceeded the predetermined boundary of 10% and therefore met the primary endpoint. CBRs at week 24 among patients treated in phase II with RP2D1 vs RP2D2 were similar (44.2% [95% CI, 27.0%−56.8%] vs 37.9% [95% CI, 18.6%−53.2%]). The CBR among all patients in the study (n = 104) was comparable (Supplemental Table 4).

In the efficacy-evaluable population, the median follow-up was 3.1 months (mean, 5.4 months). The median PFS was 5.7 months (95% CI, 3.6–9.1 months) and the 1-year PFS rate was 33.4% (95% CI, 22.8%−44.4%; Figure 2). The median OS had not been reached at the time of this analysis. Nine patients remained on treatment for > 6 months, with 5 remaining on all 3 agents (Supplemental Figure 3).

Biomarkers

Of 95 efficacy-evaluable patients, 89 had a baseline ctDNA biomarker assessment. *PIK3CA* and *ESR1* were the most common mutations at baseline, both occurring in 33.7% of patients (Supplemental Table 5). Baseline characteristics of patients with *PIK3CA* and *ESR1* mutations were comparable to those of the overall population (Table 1). Concomitant *PIK3CA* and *ESR1* mutations were found in 14 patients (15.7%; Supplemental Table 6). CBR at week 24 was 36.7% among patients with *PIK3CA* mutations and also 36.7% among those with *ESR1* mutations (Supplemental Table 7). A trend of longer median PFS was found in patients with either wild-type (WT) *PIK3CA* or WT *ESR1* at baseline compared with those who had a mutation in the respective gene (Figure 3A, B). Patients with both WT *PIK3CA* and WT *ESR1* at baseline had a numerically longer median PFS than patients who had mutated *PIK3CA* and *ESR1* or 1 mutated and 1 WT gene ($PIK3CA^{WT}/ESR1^{MUT}$ or $PIK3CA^{MUT}/ESR1^{WT}$) (Figure 3C). Interestingly, patients with early PD (2 months) had a median of 3 ctDNA mutations, while those who did not (> 2 months) had a median of 4 (Supplemental Figure 4); further analysis is needed to understand the exact mutations in each group. The distributions between the 2 groups were similar, with the exception of 2 patients in the early PD group who had 10 mutations (all massively parallel sequencing results available as supplement file).

Safety

The safety analysis included 104 patients. Among 5 patients who discontinued from only 1 agent of the triplet, 3 discontinued from EVE, 1 from RIB, and 1 from EXE. Ten deaths occurred (breast cancer, 7; AE, 1; infections/infestation, 1; pneumonia, 1). The most common hematologic (also most common overall) AE was neutropenia (all grades, 69.2%; grade 3/4, 51.0%) (Table 3). Additional common hematologic AEs or laboratory abnormalities included anemia (all grades, 28.8%; grade 3/4, 9.6%) and thrombocytopenia (all grades, 27.9%; grade 3/4, 1.0%). Grade 3/4 hypophosphatemia and hyperglycemia were observed in 5.8% and 6.7% of patients, respectively. Grade 3/4 gamma-glutamyltransferase, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) increases were observed in 1.9%, 1.0%, and 0% of patients, respectively.

The most common nonhematologic AE was stomatitis (all grades, 40.4%; grade 3/4, 2.9%). Patients were instructed to use dexamethasone alcohol-free mouthwash 3 times daily for 2 consecutive treatment cycles (56 days) as a prophylaxis for EVE-associated stomatitis; the median duration of patient adherence was 27.6 weeks. Nausea and diarrhea of all grades occurred in 33.7% (grade 3/4, 1.9%) and 27.9% (grade 3/4, 1.9%) of patients, respectively. No grade 3/4 QTc prolongation was reported. AEs were consistent with the individual safety profiles of RIB, EVE, and EXE.

Discussion

TRINITI-1 is the first trial to demonstrate the feasibility and tolerability of continuous triplet therapy with CDK4/6i + mTOR inhibitor + ET in patients with ET-refractory HR+/HER2– ABC after CDK4/6i progression. The CBR of 41.1% at week 24 exceeded the predefined threshold, meeting the primary endpoint of the study. The safety profile was acceptable; the most common AE was neutropenia, and there was no grade 3/4 QTc prolongation. Biomarker analyses demonstrated worsened outcomes in patients with mutations in *PI3KCA* or *ESR1*.

EVE may have counteracted compensatory aberrant activation of the PI3K/AKT/mTOR signaling pathway in patients resistant to ET. However, patients with mutations in *PIK3CA* and/or *ESR1* at baseline had worse outcomes than those without. *PIK3CA* mutations are among the most common genetic alterations in HR+/HER2– breast cancer (≈ 40%) and may contribute to PI3K signaling pathway hyperactivation and resistance to ET.[30–32] Blocking aberrant PI3K may shut down the PI3K signaling pathway in these patients.[12] *ESR1* mutations are also frequently observed in patients with ABC with prior ET and are known to confer resistance to aromatase inhibitor therapy.[33,34] Additional data also suggest that alterations to *ESR1* may contribute to tumor invasion and metastasis.[35] Since TRINITI-1 was initiated, ctDNA analyses in other clinical trials studying fulvestrant in patients with ABC have been reported. In these analyses, treatment with fulvestrant (including in combination with a CDK4/6i) showed potential efficacy benefit in patients with *ESR1*-mutated tumors.[36–38] Fulvestrant, rather than EXE (which was used in TRINITI-1), may be a more suitable option for these patients; however, it is unknown whether continuation of a CDK4/6i in combination with fulvestrant and EVE would be the optimal treatment. Consistent with the results of TRINITI-1, *PIK3CA* was the most common mutation in

BOLERO-2 and the median PFS was shorter in patients with mutated *PIK3CA*.[39] *ESR1* mutations were also found to be associated with shorter median PFS.[40] Together, these data suggest that tumor molecular alterations may potentially confer therapeutic resistance and that their presence at baseline may be associated with worsened outcomes. However, in TRINITI-1, no formal testing addressed interactions between biomarkers and outcomes, and treatment effect vs prognostic effect could not be separated. Additional biomarker-driven studies are needed to confirm these observations.

No new safety signals were observed in TRINITI-1. Overall, AEs were consistent with the known safety profiles of the individual components of the triplet therapy, although some differences should be noted. Incidences of both all-grade and grade 3/4 stomatitis were lower in TRINITI-1 than in the EVE arm of BOLERO-2 (all grade, 56%; grade 3/4, 8%), which is likely due to use of prophylactic dexamethasone mouthwash in the current study.[14] In addition, the incidences of grade 3/4 AST and ALT increases were lower in TRINITI-1 than in the RIB arms of MONALEESA-2 or –3.[21,22]

TRINITI-1 also showed the potential for continuous and lower doses of RIB and EVE. The preliminary PK analysis demonstrated that continuous dosing of RIB resulted in exposure levels consistent with those in single-agent studies. Concurrent dosing of RIB with EVE increased dose-dependent exposure of EVE, allowing lower doses of EVE to be used. Results of TRINITI-1 showed that this dosing regimen used in triplet combination had acceptable safety and clinical benefit.

The single-arm study design of TRINITI-1 does not allow a definitive understanding of whether continuing CDK4/6 blockade is beneficial; it remains unclear whether continuing with a CDK4/6i in addition to EVE + endocrine therapy or EVE + endocrine therapy alone is the optimal treatment for these patients. However, an acceptable safety profile and preliminary efficacy results in TRINITI-1 provide support for further investigation in larger randomized, controlled trials. Additionally, targeting mTOR, a downstream component of the PI3K signaling pathway seems to be a reasonable treatment approach for progression on CDK4/6i, suggesting that other targets in the pathway may be promising as well. Additional studies are ongoing to evaluate treatment sequencing post-CDK4/6i + ET in HR+/HER2– ABC with or without continued CDK4/6 blockade, including the MAINTAIN trial of fulvestrant ± RIB (NCT02632045), the PACE trial of fulvestrant + palbociclib ± avelumab (NCT03147287), the PALMIRA trial of palbociclib + fulvestrant or letrozole (NCT03809988), and the BYLieve trial of alpelisib + fulvestrant or letrozole in *PIK3CA*-mutant HR+/HER2– ABC (NCT03056755).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Translational relevance

Standard of care for patients with hormone receptor positive/ human epidermal growth factor receptor 2 negative (HR+/HER2−) advanced breast cancer includes endocrine therapy combined with a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i). However, most patients will eventually experience disease progression, and optimal post-CDK4/6i treatment remains unclear. TRINITI-1 was a single-arm, open-label, multicenter, phase I/II study that tested ribociclib in combination with everolimus and exemestane in patients with HR+/HER2- advanced breast cancer and prior progression on a CDK4/6i. The study met its primary endpoint for efficacy and had an acceptable safety profile. These results suggest that continued CDK4/6 blockade with ribociclib and targeting of the PI3K/AKT/mTOR signaling pathway may be a promising approach in patients with HR+/HER2− advanced breast cancer who have progressed on a CDK4/6i. Additional studies of these combinations are warranted.
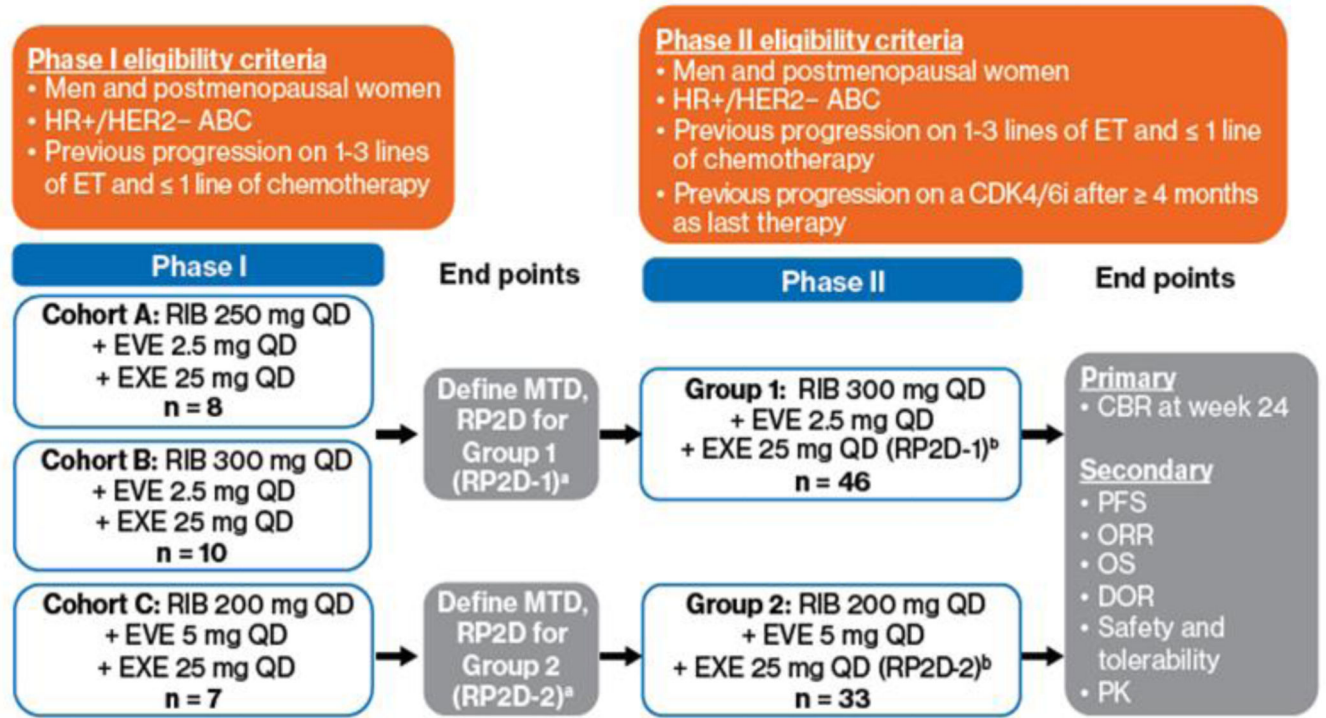
Figure 1.
TRINITI-1 study design. [a] The MTD was defined as the highest combination drug dose not causing DLTs in > 33% of treated patients in the first treatment cycle. ABC, advanced breast cancer; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DLT, dose-limiting toxicity; DOR, duration of response; ET, endocrine therapy; EVE, everolimus; EXE, exemestane; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QD, once daily; RIB, ribociclib; RP2D; recommended phase II dose.
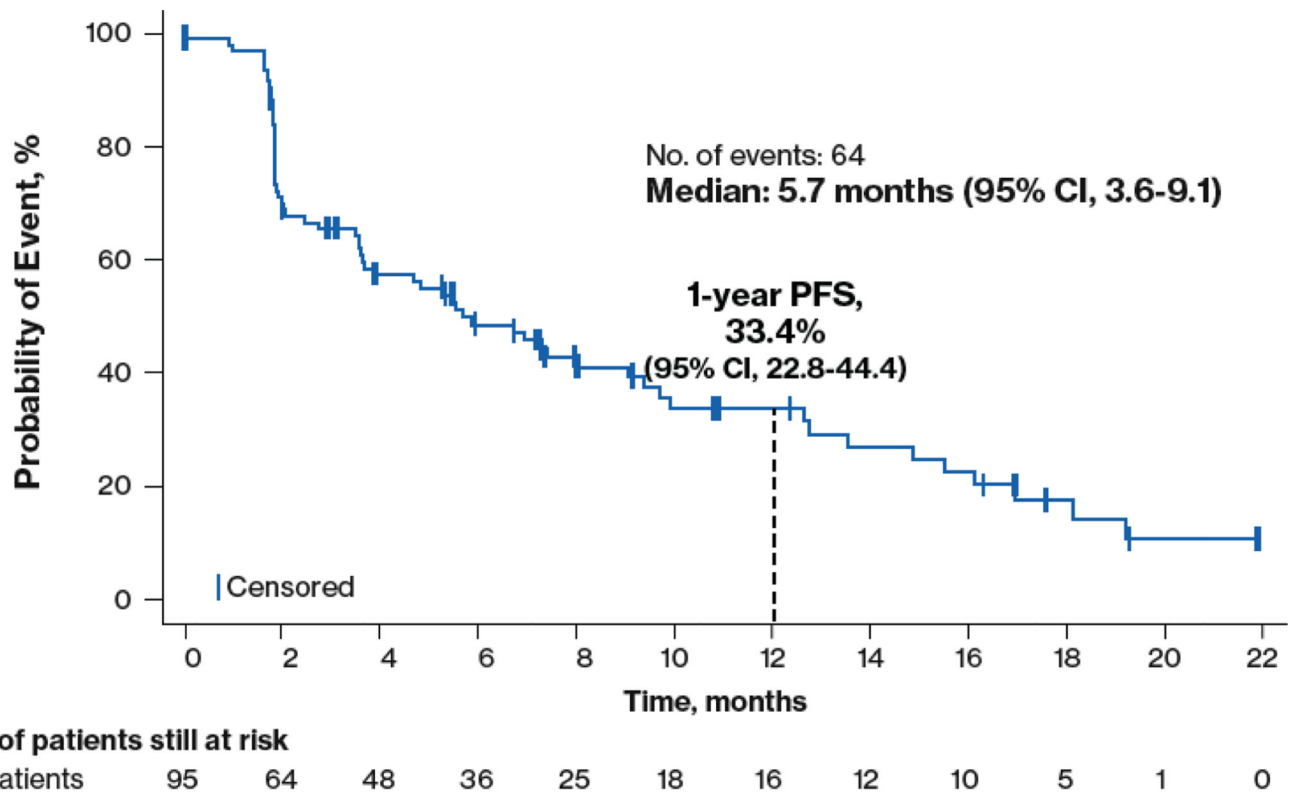
Figure 2.
Progression-free survival among n = 95 efficacy-evaluable patients. PFS, progression-free
survival.
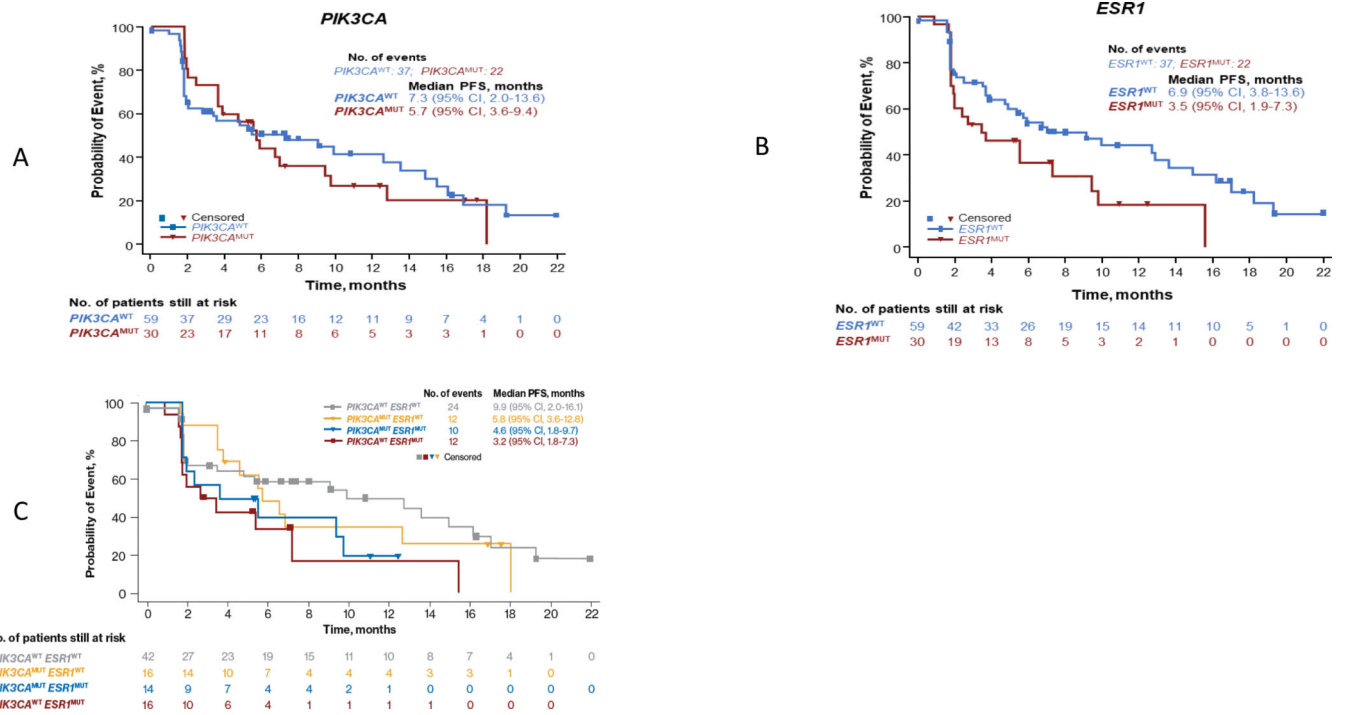
Figure 3.
Progression-free survival by baseline mutation of (A) *PIK3CA*, (B) *ESR1*, and (C) *PIK3CA* and/or *ESR1*. MUT, mutated; PFS, progression-free survival; WT, wild type.

Table 1.

Baseline Characteristics

	Total[a] (n = 96)	*PIK3CA* WT (n = 59)	*PIK3CA* Altered (n = 30)	*ESR1* WT (n = 59)	*ESR1* Altered (n = 30)
Median age (range), years	58 (32–83)	59 (33–83)	59 (32–83)	59 (33–83)	56 (32–70)
Sex, n (%)					
Female	96 (100)	59 (100)	30 (100)	59 (100)	30 (100)
Race, n (%)					
White	78 (81.3)	51 (86.4)	26 (86.7)	51 (86.4)	25 (83.3)
Asian	2 (2.1)	1 (1.7)	0	1 (1.7)	0
Black	4 (4.2)	2 (3.4)	1 (3.3)	2 (3.4)	2 (6.7)
Other or unknown	12 (12.5)	5 (8.5)	3 (10.0)	5 (8.5)	3 (10.0)
ECOG PS, n (%)					
0	55 (57.3)	37 (62.7)	16 (53.3)	37 (62.7)	17 (56.7)
1	41 (42.7)	22 (37.3)	14 (46.7)	22 (37.3)	13 (43.3)
Sites of metastases, n (%) [b]					
Bone	74 (77.1)	48 (81.4)	22 (73.3)	45 (76.3)	26 (86.7)
Liver	63 (65.6)	40 (67.8)	18 (60.0)	37 (62.7)	20 (66.7)
Lung	33 (34.4)	19 (32.2)	11 (36.7)	20 (33.9)	9 (30.0)
Lymph nodes	28 (29.2)	19 (32.2)	9 (30.0)	18 (30.5)	10 (33.3)
Previous treatment [c]					
Lines of treatment overall, median (range)	1 (1–8)	1 (1–8)	1 (1–5)	1 (1–5)	1 (1–8)
CDK4/6i, n (%)	96 (100)	59 (100)	30 (100)	59 (100)	30 (100)
Lines of treatment, median (range)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)	1 (1–2)
1 prior line	92 (95.8)	56 (94.9)	29 (96.7)	57 (96.6)	28 (93.3)
2 prior lines	4 (4.2)	13 (5.1)	1 (3.3)	2 (3.4)	2 (6.7)
Median duration of CDK4/6i (range), mo	18.0 (6.0–141.0)	14.0 (4.0–29.4)	10.0 (3.5–34.0)	11.5 (3.5–34.0)	14.0 (4.6–26.7)
Prior CDK4/6i, n [d]					
Ribociclib	12	6	4	9	1

	Total[a] (n = 96)	PIK3CA WT (n = 59)	PIK3CA Altered (n = 30)	ESR1 WT (n = 59)	ESR1 Altered (n = 30)
Palbociclib	96	61	31	58	34
ET, n (%)	96 (100)	59 (100)	30 (100)	59 (100)	30 (100)
Lines of treatment, median (range)	1 (1–4)	1 (1–4)	1 (1–3)	1 (1–4)	1 (1–3)
1 prior line	75 (78.1)	46 (78.0)	24 (80.0)	48 (81.4)	22 (73.3)
2 prior lines	17 (17.7)	11 (18.6)	4 (13.3)	8 (13.6)	7 (23.3)
3 prior lines	4 (4.1)	2 (3.4)	2 (6.7)	3 (5.1)	1 (3.3)
Prior ET, n (%)[d]					
Anastrozole	17 (17.7)	9 (15.3)	7 (23.3)	10 (16.9)	5 (16.7)
Letrozole	69 (71.9)	41 (69.5)	23 (76.7)	41 (69.5)	23 (76.7)
Exemestane	3 (3.1)	1 (1.7)	2 (6.7)	1 (1.7)	2 (6.7)
Fulvestrant	37 (38.5)	25 (42.4)	8 (26.7)	23 (39.0)	10 (33.3)
Chemotherapy, n (%)	12 (12.5)	6 (10.2)	2 (6.7)	6 (10.2)	1 (3.3)
1 prior line	12 (12.5)	6 (10.2)	2 (6.7)	6 (10.2)	1 (3.3)

CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; ESR1, estrogen receptor 1; ET, endocrine therapy; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; WT, wild type.

[a] Intent-to-treat population.

[b] Select sites of metastases.

[c] In advanced/metastatic setting.

[d] Patients can be counted in multiple rows.

Table 2.

Best Overall Response[a]

	Total Patients (n = 95)
CBR at week 24, n (%) [95% CI] [b]	39 (41.1) [31.1–51.6]
ORR, n (%) [95% CI] [c]	8 (8.4) [3.7–15.9]
Best overall response, n (%)	
CR	1 (1.1)
PR	7 (7.4)
SD	47 (49.5)
PD	32 (33.7)
Non-CR/non-PD, n (%)	3 (3.2)
DCR, n (%) [95% CI] [d]	58 (61.1) [50.5–70.9]

CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; NCRNPD, non-CR, non-PD; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Local investigator assessment per Response Evaluation Criteria in Solid Tumors version 1.1. Patients with measurable disease at baseline: n = 75; patients with only nonmeasurable disease at baseline: n = 20. Five patients discontinued without postbaseline tumor evaluation.

[b] CBR: patients with CR, PR, SD, or NCRNPD at week 24.

[c] ORR: patients with CR or PR.

[d] DCR: patients with CR, PR, SD, or NCRNPD at any time during the study.

Table 3.

Adverse Events Regardless of Study Drug Relationship

Preferred Term, n (%)	All Grade	Grade 3/4
Total	104 (100)	77 (74.0)
Hematologic AEs or laboratory abnormalities occurring at > 10% incidence		
Neutropenia[a]	72 (69.2)	53 (51.0)
Anemia	30 (28.8)	10 (9.6)
Thrombocytopenia	29 (27.9)	1 (1.0)
AST increased	20 (19.2)	1 (1.0)
Hypophosphatemia	20 (19.2)	6 (5.8)
Hyperglycemia	19 (18.3)	7 (6.7)
Hypokalemia	16 (15.4)	1 (1.0)
ALT increased	15 (14.4)	0
GGT increased	11 (10.6)	2 (1.9)
Platelet count decreased	11 (10.6)	0
Nonhematologic AEs occurring at > 10% incidence and grade 3/4 incidence of 1.5%		
Stomatitis	42 (40.4)	3 (2.9)
Nausea	35 (33.7)	2 (1.9)
Diarrhea	29 (27.9)	2 (1.9)
Pyrexia	19 (18.3)	3 (2.9)
Pneumonitis	15 (14.4)	5 (4.8)
Dyspnea	13 (12.5)	4 (3.8)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

[a]Neutropenia or decreased neutrophil count.