Phase Ib Study of Ribociclib plus Fulvestrant and Ribociclib plus Fulvestrant plus PI3K Inhibitor (Alpelisib or Buparlisib) for HR$^+$ Advanced Breast Cancer

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ABSTRACT

Purpose: Resistance to treatment with endocrine therapy in patients with HR$^+$, HER2$^-$ advanced breast cancer (ABC) is common and dual inhibition of CDK4/6 and PI3K pathways may delay the development of resistance. This phase Ib trial evaluates the safety and tolerability of triple and double regimens containing the CDK4/6 inhibitor ribociclib.

Patients and Methods: In this open-label, multicenter, phase Ib study, 70 postmenopausal women with HR$^+$, HER2$^-$ ABC were enrolled into one of four treatment combinations: ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant; ribociclib (continuous dosing) plus fulvestrant; ribociclib plus alpelisib plus fulvestrant; or ribociclib plus buparlisib plus fulvestrant.

Results: The recommended phase II dose (RP2D) of ribociclib was confirmed to be 600 mg (3 weeks on, 1 week off) and 400 mg (continuous dosing) plus fulvestrant 500 mg. For the triple combination with buparlisib, the RP2D was ribociclib 400 mg plus buparlisib 30 mg plus fulvestrant 500 mg. Enrollment for the triple combinations was stopped due to unexpected toxicity. No RP2D was determined for the alpelisib combination. The safety profiles of the ribociclib plus fulvestrant combinations were consistent with those in previous studies. There was no marked difference in ribociclib exposure in the presence of triple-combination partners. The highest overall response rate was seen in the buparlisib triple combination (25.0%; 95% confidence interval, 9.8–46.7).

Conclusions: Ribociclib plus fulvestrant demonstrated safety in the treatment of patients with HR$^+$, HER2$^-$ ABC. Triple combinations with alpelisib or buparlisib plus fulvestrant are not recommended for phase II investigation.

See related commentary by Clark et al., p. 371

Introduction

Endocrine therapy (ET) is the preferred treatment option for hormone receptor–positive (HR$^+$) advanced breast cancer (ABC; ref. 1). First-line ET has demonstrated a clinical benefit: for example, in the phase III FALCON study (NCT01602380), fulvestrant versus anastrozole showed a significant prolongation of progression-free survival (PFS) by a median of 2.8 months [HR, 0.80; 95% confidence interval (CI), 0.64–1.00; $P = 0.0486$; ref. 2]. Objective response rate was 46.1% in the fulvestrant arm and 44.9% in the anastrozole arm (2). The combination of fulvestrant plus anastrozole significantly prolonged overall survival (OS) compared with anastrozole alone in the first-line setting (3). However, with continued treatment, patients' tumors typically develop resistance to ET and subsequent treatment is not well defined (4). Preclinical and clinical data suggest that inhibiting cyclin-dependent kinases 4 and 6 (CDK4/6) activity or the PI3K signaling pathway may delay the development of endocrine resistance (5–7).

The combination of CDK4/6 inhibitors and ET is associated with significant improvements in PFS and OS (8–11). The CDK4/6 inhibitors palbociclib and ribociclib are approved in the United States and European Union for use in combination with ET for HR$^+$, human epidermal growth factor receptor-2–negative (HER2$^-$) ABC (12–17). Abemaciclib, another CDK4/6 inhibitor, is approved in the United States in combination with ET or as monotherapy for HR$^+$, HER2$^-$ ABC (18). Both ribociclib and abemaciclib in combination with ET have shown significant improvements in OS (8–11). However, despite positive outcomes with these CDK4/6 inhibitors in combination with ET, hormone resistance remains an unmet clinical need.

PI3K pathway–targeting agents for the treatment of breast cancer include alpelisib (an α isoform-selective PI3K inhibitor; ref. 19),

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Trial registration number: NCT02088684.

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Clin Cancer Res 2021;27:418–28

doi: 10.1158/1078-0432.CCR-20-0645

Translational Relevance

Endocrine therapy is the preferred treatment option for HR$^+$, HER2$^-$ ABC; however, the development of endocrine resistance is common. Preclinical and clinical data suggest that inhibiting CDK4/6 activity or the PI3K signaling pathway may delay the development of endocrine resistance. This phase Ib trial evaluates the safety and tolerability of triple and double regimens containing the CDK4/6 inhibitor ribociclib for the treatment of HR$^+$, HER2$^-$ ABC. These data show that the safety profile of ribociclib plus fulvestrant in the patient population was consistent with those of previous studies, and that the safety profiles of the combinations generally reflected the adverse events of the individual agents. Triple combinations of ribociclib and fulvestrant plus either alpelisib or buparlisib are not recommended for phase II investigation because of the safety profile of these combinations.

buparlisib (a pan-class PI3K inhibitor; ref. 20), taselisib (21), and pictilisib (22). As single agents, alpelisib and buparlisib have demonstrated activity in heavily pretreated breast cancer populations (19, 20). In the phase III SOLAR-1 study (NCT02437318), in which patients had disease progression on or after aromatase inhibitor (AI) therapy, alpelisib demonstrated strong clinical efficacy in patients with *PIK3CA*-mutated cancer: prolongation of PFS by a median of 5.3 months [HR, 0.65; 95% confidence interval (CI), 0.5–0.85; $P < 0.001$] was observed in patients treated with alpelisib plus fulvestrant (19). Overall response was greater with alpelisib plus fulvestrant than with placebo plus fulvestrant (26.6% vs. 12.8%), and clinical benefit was also greater with alpelisib plus fulvestrant (61.5% vs. 45.3%; ref. 19). Permanent discontinuation due to adverse events (AEs) occurred in 71 (25.0%) patients receiving alpelisib plus fulvestrant and 12 (4.2%) patients receiving placebo plus fulvestrant. The most frequent AEs leading to discontinuation of alpelisib were hyperglycemia and rash (19). Alpelisib is approved in the United States in combination with fulvestrant for the treatment of men and postmenopausal women with HR$^+$, HER2$^-$ *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen (19). In the phase III BELLE-2 study (NCT01610284), in which patients also had disease progression on or after aromatase inhibitor (AI) therapy, buparlisib plus fulvestrant showed a clinically meaningful improvement in PFS in patients with *PIK3CA* mutations in circulating tumor DNA (20). Overall response was greater in the buparlisib plus fulvestrant arm than in the placebo plus fulvestrant arm (11.8% vs. 7.7%; ref. 20).

In studies using breast cancer cell lines, it has been shown that CDK4/6 inhibitors and PI3K inhibitors act synergistically to inhibit cell growth; this offers strong justification for combining PI3K and CDK4/6 inhibitors for the treatment of HR$^+$, ET-resistant breast cancer (23–25). Combining agents that target the CDK4/6 and PI3K pathways simultaneously may lead to a more complete and sustained sensitivity to estrogen withdrawal in postmenopausal patients with HR$^+$, HER2$^-$ ABC.

This phase Ib study (NCT02088684) evaluated the triple treatment combination of ribociclib plus fulvestrant plus either alpelisib or buparlisib in postmenopausal women with HR$^+$, HER2$^-$ ABC; dose regimen confirmation of double treatment of ribociclib plus fulvestrant (3 weeks on/1 week off or continuous dosing) was also undertaken. The primary objective of this study was to estimate the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) of the two triple treatment combinations and the two double treatment combinations. The secondary objectives were to characterize the safety and tolerability of all four treatment combinations; to characterize the pharmacokinetic (PK) properties of ribociclib, alpelisib, and buparlisib within each combination; and to assess preliminary clinical antitumor activity of all four treatment combinations. Exploratory analysis included the assessment of *PIK3CA* and *PTEN* mutational status in the context of clinical efficacy of all treatment combinations using next-generation sequencing (NGS) of tumor tissue samples.

Patients and Methods

Study design

This was an open-label, multicenter, four-arm, phase Ib study. This study consisted of two dose confirmation arms to verify the safety of the following double treatment combinations (**Fig. 1**): ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant, and ribociclib (continuous dosing) plus fulvestrant. The study also included two dose escalation arms to estimate the MTD/RP2D of the following triple

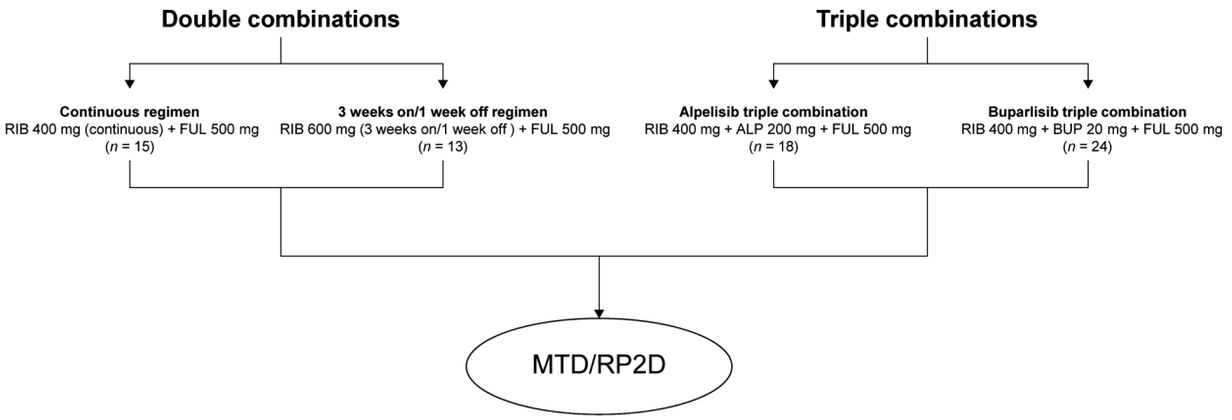

Figure 1.

Study design of diagram of treatment combinations and patient allocations. Dose escalations in the triple combinations: ribociclib (400 and 600 mg) plus alpelisib (200, 300, and 400 mg) plus fulvestrant 500 mg; or ribociclib (400 and 600 mg) plus buparlisib (20, 30, 40, 80, and 100 mg) plus fulvestrant 500 mg. ALP, alpelisib; BUP, buparlisib; FUL, fulvestrant; RIB, ribociclib.

treatment combinations: ribociclib plus alpelisib plus fulvestrant, and ribociclib plus buparlisib plus fulvestrant.

This study was to be followed by a randomized phase II study to assess the clinical efficacy, safety, and tolerability of the MTD/RP2D of the two triple combinations, plus one of the double combinations.

Patient population

This study was conducted in adult women with locally advanced or metastatic HR^+, $HER2^-$ breast cancer, who had progressed on aromatase inhibitor (AI) treatment.

Eligible women were ≥18 years of age, postmenopausal at the time of trial entry, and had histologically or cytologically confirmed estrogen-receptor positive and/or progesterone receptor–positive breast cancer. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and have received ≤2 prior lines of chemotherapy for metastatic or recurrent breast cancer. Patients had to be refractory to AI: had experienced progression during or within 12 months of completing adjuvant treatment with an AI, or during or within 1 month of completing AI treatment for locally advanced or metastatic breast cancer. Patients could receive any number of endocrine/hormonal lines of therapy before or after meeting the definition of "refractory to AI," which does not need to occur within any specified time period prior to randomization. Patients receiving fulvestrant prior to screening did not have to discontinue fulvestrant but should have delayed their next dose, if necessary, to coincide with the on-study dosing. Patients were required to have one or more measurable lesions (per RECIST v1.1). If a patient presented with central nervous system metastases, lesions had to be clinically stable and the patients needed to be fully recovered from local treatment such as radiation and/or surgery and be receiving stable doses of steroids for ≥2 weeks. Patients who had HER2 overexpression, per local laboratory testing, and prior CDK or PI3K inhibitor treatment were not permitted to enroll. Patients with uncontrolled hypertension (systolic blood pressure ≥140 mm Hg) and clinically significant cardiac disease or impaired cardiac function, including Fridericia corrected QT >450 msec, were also not permitted to enroll. Patients who had received hormone therapy (HT) were permitted to enroll if HT was discontinued prior to starting the study treatment. Eligibility was not based on PI3K pathway mutational status.

Study oversight

The study was conducted in accordance with the ICH E6 Guideline for Good Clinical Practice that has its origin in the Declaration of Helsinki. The study protocol and all amendments were reviewed by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for each center. Written informed consent was obtained from all patients before conducting any study-specific procedures including an optional biomarker component. Representatives of the trial sponsor, Novartis Pharmaceuticals, analyzed the data.

Dose and regimen selections

Patients were allocated into each treatment arm of the study dependent upon slot availability. Dose-limiting toxicity (DLT) was defined as an AE or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first 28 days of treatment and met any of the criteria described in Supplementary Table S1. Investigators may elect to treat patients receiving any dose of alpelisib with an oral antihistamine during the first cycle to prevent rash. Guidelines for the treatment of study drug combination induced rash can be found in Supplementary Table S2.

Double treatment arms

The doses for the double treatment combination under the 3 weeks on, 1 week off regimen were ribociclib 600 mg and fulvestrant 500 mg (dosed on days 1 and 15 in cycle 1, and day 1 of each subsequent cycle). The selected ribociclib dose was the recommended dose determined from the first-in-human study, CLEE011X2101 [Study X2101 (NCT01237236); ref. 26], whereas the dose chosen for fulvestrant was that recommended for treating metastatic breast cancer (2). The doses for the continuous regimen were ribociclib 400 mg daily and fulvestrant 500 mg (dosed on days 1 and 15 in cycle 1, and day 1 of each subsequent cycle); this regimen delivers a lower total dose of ribociclib when dosed daily over a 4-week period (11,200 mg) compared with that delivered over a 4-week period when ribociclib is dosed for 3 weeks followed by a 1-week break (12,600 mg). Taking into consideration all information currently available about the DLT relationships of ribociclib and fulvestrant as single agents, and the uncertainty about the toxicity of the combinations, the prior distribution of DLT rates derived from a Bayesian logistic regression model (BLRM) indicated that the proposed starting dose combinations met the escalation with overdose control (EWOC) criterion (less than 25% chance that true DLT rate ≥35%; ref. 27). No drug–drug interactions were expected between ribociclib and fulvestrant.

Triple-treatment arms

The triple drug combination consisted of ribociclib (once daily, 3 weeks on, 1 week off), fulvestrant (dosed on days 1 and 15 in cycle 1, and day 1 of each subsequent cycle), plus alpelisib daily or buparlisib daily.

Starting doses in each of the treatment arms were based on the recommended dose for treatment of metastatic breast cancer and a review of the safety, tolerability, and PK profiles observed at the different dose levels tested in studies CLEE011X2101 (NCT01237236; ref. 26), BYL719X2101 (NCT01219699; ref. 28), CBKM120X2101 (NCT01068483; ref. 29), CBKM120F2302 (NCT01610284; ref. 20), and CBKM120F2303 (NCT01633060; ref. 30). All information currently available about the DLT relationships of ribociclib, fulvestrant, alpelisib, and buparlisib as single agents, the uncertainty about the toxicity of the combinations, and the prior distribution of DLT rates derived from a BLRM, indicating that the proposed starting dose combinations met the EWOC criterion, were all considered in determining the starting dose.

Triple dose regimens were as follows: ribociclib 400 mg (escalating to 600 mg) once daily on days 1 to 21 of each 28-day cycle plus alpelisib 200 mg (escalating to 400 mg) plus fulvestrant 500 mg; or ribociclib 400 mg (escalating to 600 mg) once daily on days 1 to 21 of each 28-day cycle plus buparlisib 20 mg (escalating to 30, 40, 80, up to 100 mg) plus fulvestrant 500 mg.

Dose escalations

To be considered evaluable for dose escalation decisions, patients were required to have completed a minimum of one cycle of treatment with the minimum safety evaluation and drug exposure, or to have had a DLT within the first cycle of treatment. For each of the combination treatments, decisions were based on a synthesis of all relevant data available from all dose levels of the combination treatment in the ongoing study: data included safety information [including AEs and laboratory abnormalities that were not DLTs), DLTs, all Common Terminology Criteria for Adverse Events (CTCAE)] of grade ≥2 toxicity during cycle 1, and PK and pharmacodynamic data from evaluable patients. At each dose-escalation decision, the adaptive BLRM provided the next recommended dose for the combinations

that met the EWOC criteria, to control the risk of DLT in future patients on study. Dose escalations for each arm were to continue until the MTD or the RP2D for each treatment arm was identified. The MTD was defined as the highest dose combination drug usage that had less than 25% chance of causing a DLT in >35% of patients in the first cycle of treatment. When several combinations corresponded to this definition, more than one MTD could be identified with different doses of the combination partners. One of these MTDs, or a lower dose combination, was then selected as the RP2D.

The MTD(s) or RP2D(s) were to be determined when the following conditions were met: at least six patients had been treated with the dose, and that the dose satisfied one of the following conditions: the posterior probability of targeted toxicity at this dose exceeded 50% and was highest among potential doses, or a minimum of 15 patients had already been treated in the triple-treatment arms, or a minimum of six patients had already begun treatment in the double treatment arms.

Study assessments

Safety

The primary objective was to calculate the MTD and/or RP2D of all treatment combinations assessed through the incidence of DLTs in cycle 1.

The secondary objective was to evaluate the safety and tolerability of all treatment combinations. This was assessed through reported AEs, serious AEs, changes in hematology and chemistry values, vital signs, electrocardiograms, dose interruptions, dose reductions, and dose intensity.

Pharmacokinetics

Plasma concentrations of ribociclib, alpelisib, buparlisib, and fulvestrant were measured using a validated LC/MS-MS assay. The lower limit of quantitation (LLOQ) was 1.00 ng/mL for all four analytes. For all treatment arms, blood was collected for PK profiling on days 1, 2, 8, 15, 21, and 22 of cycle 1 for enrolled patients. Additional predose samples were collected on day 1 of cycles 2–6. Predose samples were collected for fulvestrant PK analysis on day 1 and day 15 of cycle 1, and day 1 of each subsequent cycle for cycles 2–6.

PK parameters were determined for all PK-evaluable patients through noncompartmental analysis using Phoenix WinNonlin V6.4 (Pharsight). PK parameters reported are maximum plasma concentration, time to reach maximum plasma concentration, and AUC 0–24 hours postdose (AUC_{24h}; ref. 31). All concentrations below the LLOQ and missing data were reported as zero.

Efficacy

Preliminary clinical antitumor activity was investigated by evaluation of the overall response rate (ORR) and PFS based on RECIST v1.1 (by local investigator assessment) for each treatment combination. All efficacy assessments were given a 7-day window; if the last prior tumor evaluation was within 28 days of end of treatment or if objective evidence of progressive disease had already been documented, then the tumor evaluations were not repeated at end of treatment. Any potentially measurable lesion that had been previously treated with radiotherapy was considered a nonmeasurable lesion. However, if a lesion previously treated with radiotherapy had clearly progressed since radiotherapy, it was considered a measurable lesion. For patients with nonmeasurable lytic or mixed (lytic + blastic) bone lesions and absence of measurable disease at baseline, if bone lesions had been previously irradiated, at least one lesion must have clearly progressed since the radiotherapy (assessed by computed tomography, magnetic resonance imaging, or X-ray) for trial entry. For the purposes of the safety and efficacy evaluations, the results from the triple-treatment combinations were combined. Different doses were evaluated in the triple-combination arms as part of the dose escalation. Instead of presenting these different doses separately, all patients who received the alpelisib triple regimen were grouped together, as were those who received any dose of the buparlisib triple regimen.

Biomarkers

Genetic alterations (e.g., mutations, amplifications, deletions) that are involved in the D-cyclin–CDK4/6–INK4a–Rb and PI3K signaling pathways, such as mutations of *PIK3CA* and *PTEN* as well as other cancer-associated genes, were determined by NGS. This was conducted for all patients, with the intention of identifying potential predictive markers related to therapeutic responses. The results from these exploratory analyses were correlated with the clinical outcome to identify potential predictive biomarkers for ribociclib, alpelisib, and buparlisib.

Results

Patient disposition and characteristics

Between May 19, 2014, and April 17, 2018, a total of 70 women, 49 of whom were aged <65 years, received one of the four treatment combinations (**Fig. 1**; **Table 1**). Out of 70 patients, 46 (65.7%), 19 (27.1%), and seven (10%) had received hormonal therapy, chemotherapy, or treatment with PI3K/AKT/mTOR inhibitors at the last treatment, respectively (Supplementary Table S3). The primary reason for end of treatment was disease progression (70.0%), followed by AEs (12.9%), and patients who completed the study that were transferred to a new study protocol to continue with their treatment (8.6%).

Median exposure to study treatment for all patients was 6.9 months (range, 1.8–33.3; **Table 1**).

For ribociclib (3 weeks on, 1 week off) plus fulvestrant, nine (69.2%) patients had ≥1 dose interruption (Supplementary Table S4), and most dose interruptions were due to AEs (53.9%). Three (23.1%) patients had ≥1 dose reduction due to AEs. For ribociclib (continuous daily dosing) plus fulvestrant, 11 (73.3%) patients had ≥1 dose interruption, with 46.7% due to dosing error and 40.0% due to AEs. Four (26.7%) patients had ≥1 dose reduction due to AEs.

In the alpelisib triple combination, 15 (83.3%) patients had ≥1 dose interruption, mostly due to AEs (66.7%) and as per protocol (55.6%). Ten (55.6%) patients experienced ≥1 dose reduction, mostly due to AEs (44.4%). In the buparlisib triple combination, 23 (95.8%) patients had ≥1 dose interruption, mostly due to AEs (n = 19, 79.2%), and sixteen (66.7%) patients experienced ≥1 dose reduction.

Safety

RP2D/MTD

The RP2D of ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant (dosed on days 1 and 15 in cycle 1, and day 1 of each subsequent cycle) was confirmed to be 600 and 500 mg, respectively, with pulmonary embolism in one patient (7.7%) being the only DLT reported in this treatment arm. For the continuous-dosing treatment arm, the RP2D for ribociclib plus fulvestrant was confirmed to be ribociclib 400 mg daily plus fulvestrant 500 mg. Increased aspartate aminotransferase (AST) in one patient (6.7%) was the only DLT reported in this treatment arm.

Patient enrollment in the dose-escalation triple-combination arms was stopped early due to elevated rates of rash that were clinically incompatible with long-term dosing; as a result, the MTDs were not identified for the triple combinations and no RP2D was determined for

Table 1. Baseline demographics and treatment exposure by treatment combination.

	Ribociclib 600 mg + fulvestrant ($n = 13$)	Ribociclib 400 mg (continuous) + fulvestrant ($n = 15$)	Triple-combination ribociclib + alpelisib + fulvestrant ($n = 18$)	Triple-combination ribociclib + buparlisib + fulvestrant ($n = 24$)
Age, years				
Mean	59.5	57.5	60.3	56.5
SD	8.0	8.8	11.7	10.2
Median	59.0	58.0	57.5	57.5
Minimum	47.0	42.0	44.0	34.0
Age category, *n* (%)				
<65 years	8 (61.5)	11 (73.3)	11 (61.1)	19 (79.2)
≥65 years	5 (38.5)	4 (26.7)	7 (38.9)	5 (20.8)
Sex, *n* (%)				
Female	13 (100.0)	15 (100.0)	18 (100.0)	24 (100.0)
Race, *n* (%)				
Asian	2 (15.4)	3 (20.0)	5 (27.8)	10 (41.7)
Black or African	0	1 (6.7)	0	0
Unknown	2 (15.4)	0	0	3 (12.5)
White	9 (69.2)	11 (73.3)	13 (72.2)	11 (45.8)
Ethnicity, *n* (%)				
Not Hispanic or Latino	6 (46.2)	10 (66.7)	16 (88.9)	14 (58.3)
Not reported	7 (53.8)	3 (20.0)	2 (11.1)	8 (33.3)
Unknown	0	2 (13.3)	0	2 (8.3)
ECOG PS (WHO), *n* (%)				
0	9 (69.2)	12 (80.0)	16 (88.9)	16 (66.7)
1	4 (30.8)	3 (20.0)	2 (11.1)	8 (33.3)
Duration of exposure to study treatment, months				
Median	7.4	5.7	4.1	8.3
Minimum	1.8	1.8	1.8	1.8
Maximum	13.8	32.7	29.5	33.3

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation; WHO, World Health Organization.

the alpelisib triple combination. DLTs for the triple combinations with alpelisib were diarrhea [$n = 1$ (33.3%)] and vomiting [$n = 1$ (33.3%)] for ribociclib 200 mg plus alpelisib 200 mg plus fulvestrant; increased AST [$n = 1$ (16.7%)], and hyperglycemia [$n = 1$ (16.7%)] for ribociclib 400 mg plus alpelisib 150 mg plus fulvestrant; and rash [$n = 3$ (50.0%)] for ribociclib 400 mg plus alpelisib 200 mg plus fulvestrant. For the triple combination with buparlisib, RP2D was determined to be ribociclib 400 mg (once daily, 3 weeks on, 1 week off) plus buparlisib 30 mg (daily) plus fulvestrant 500 mg. DLTs for the triple combinations with buparlisib were diarrhea [$n = 1$ (10.0%)], increased AST [$n = 1$ (10.0%)], and increased alanine aminotransferase [ALT; $n = 1$ (10.0%)] for ribociclib 400 mg plus buparlisib 30 mg plus fulvestrant; increased AST [$n = 1$ (16.7%)] and increased ALT [$n = 1$ (16.7%)] for ribociclib 400 mg plus buparlisib 40 mg plus fulvestrant; and electrocardiogram QT prolonged [$n = 1$ (20.0%)] and rash [$n = 1$ (20.0%)] for ribociclib 600 mg plus buparlisib 30 mg plus fulvestrant.

AEs

All grade serious AEs were reported in 26 (37.1%) patients, of which 23 (32.9%) patients experienced grade ≥3 events, with neutropenia, pneumonia, and syncope being the most frequent [$n = 3$ (4.3%)]. Eleven patients (15.7%) discontinued due to AEs, including two (15.4%) patients in the ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant treatment arm, 2 (13.3%) patients in the ribociclib continuous-dosing treatment arm, 5 (27.8%) patients in the alpelisib triple treatment arm and two patients (8.3%) in the buparlisib triple-treatment arm. There were no on-treatment deaths.

AEs of special interest that were most commonly seen in all treatment combinations were hepatobiliary toxicity, infections, and neutropenia. In the double combination of ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant, hepatobiliary toxicity was seen in six (46.2%) patients (15.4% grade ≥3), and seven (53.8%) patients experienced at least one infection (7.7% grade ≥3). For the continuous-dosing treatment arm, six (40.0%) patients experienced hepatobiliary toxicity (20.0% grade ≥3) and five (33.3%) patients had at least one infection (6.7% grade ≥3). In the alpelisib triple combination, nine (50.0%) patients experienced hepatobiliary toxicity (38.9% grade ≥3) and six (33.3%) patients experienced at least one infection (16.7% grade ≥3). In the buparlisib triple combination, 18 (75.0%) patients and nine (37.5%) patients experienced hepatobiliary toxicity and at least one infection, respectively (29.2% and 12.5% grade ≥3, respectively). Hepatobiliary toxicity is an important identified risk for ribociclib.

In this study, five (7.1%) patients experienced blood bilirubin increase, while 30 (42.9%) patients and 27 (38.6%) patients experienced AST and/or ALT increase, respectively (**Table 2**). The majority of increases of AST or ALT were grade 1–2 in severity. No patients in the study met the Hy's law criteria for hepatobiliary toxicities.

Grade ≥3 rash was only observed in patients treated with alpelisib and buparlisib triple combination (22.2% and 4.2%, respectively); similarly, maculopapular rash (all grades) was only reported in the alpelisib and buparlisib triple-combination arms (5.6% and 12.5%, respectively).

Table 2. Treatment-related all-grade and grade 3/4 AEs (≥10% of patients in any treatment group).

	Ribociclib 600 mg + fulvestrant (*n* = 13)		Ribociclib 400 mg (continuous) + fulvestrant (*n* = 15)		Triple-combination ribociclib + alpelisib + fulvestrant (*n* = 18)		Triple-combination ribociclib + buparlisib + fulvestrant (*n* = 24)	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total, *n* (%)	13 (100)	11 (84.6)	14 (93.3)	8 (53.3)	18 (100)	15 (83.3)	24 (100)	20 (83.3)
Neutropenia	10 (76.9)	8 (61.5)	10 (66.7)	7 (46.7)	8 (44.4)	7 (38.9)	17 (70.8)	10 (41.7)
Nausea	6 (46.2)	0	6 (40.0)	0	10 (55.6)	0	16 (66.7)	0
Fatigue	9 (69.2)	2 (15.4)	3 (20.0)	0	8 (44.4)	0	12 (50.0)	2 (8.3)
AST increased	3 (23.1)	1 (7.7)	4 (26.7)	2 (13.3)	7 (38.9)	4 (22.2)	10 (41.7)	5 (20.8)
ALT increased	3 (23.1)	1 (7.7)	4 (26.7)	2 (13.3)	8 (44.4)	6 (33.3)	9 (37.5)	6 (25.0)
Diarrhea	4 (30.8)	0	2 (13.3)	0	8 (44.4)	1 (5.6)	9 (37.5)	1 (4.2)
Hyperglycemia	1 (7.7)	0	0	0	12 (66.7)	3 (16.7)	8 (33.3)	1 (4.2)
Decreased appetite	5 (38.5)	0	1 (6.7)	0	4 (22.2)	0	9 (37.5)	1 (4.2)
Rash	1 (7.7)	0	1 (6.7)	0	7 (38.9)	4 (22.2)	10 (41.7)	1 (4.2)
Vomiting	4 (30.8)	0	3 (20.0)	0	4 (22.2)	0	8 (33.3)	0
Pruritus	2 (15.4)	0	2 (13.3)	0	2 (11.1)	0	7 (29.2)	0
Thrombocytopenia	3 (23.1)	0	0	0	4 (22.2)	0	6 (25.0)	1 (4.2)
White blood cell count decreased	4 (30.8)	2 (15.4)	2 (13.3)	1 (6.7)	2 (11.1)	1 (5.6)	4 (16.7)	2 (8.3)
Stomatitis	0	0	2 (13.3)	0	5 (27.8)	0	4 (16.7)	0
Anemia	6 (46.2)	0	0	0	2 (11.1)	1 (5.6)	2 (8.3)	0
Headache	1 (7.7)	0	2 (13.3)	0	4 (22.2)	0	2 (8.3)	0
Neutrophil count decreased	2 (15.4)	2 (15.4)	1 (6.7)	1 (6.7)	1 (5.6)	1 (5.6)	4 (16.7)	3 (12.5)
Dysgeusia	2 (15.4)	0	0	0	0	0	5 (20.8)	0
Platelet count decreased	3 (23.1)	0	0	0	1 (5.6)	0	3 (12.5)	1 (4.2)
Blood creatinine increased	2 (15.4)	0	0	0	1 (5.6)	0	3 (12.5)	1 (4.2)
Dizziness	1 (7.7)	0	1 (6.7)	0	2 (11.1)	0	2 (8.3)	0
Dry skin	0	0	0	0	0	0	6 (25.0)	0
Dyspepsia	0	0	0	0	4 (22.2)	0	2 (8.3)	0
ECG QT prolonged	2 (15.4)	0	1 (6.7)	0	1 (5.6)	0	2 (8.3)	1 (4.2)
Leukopenia	1 (7.7)	1 (7.7)	2 (13.3)	0	1 (5.6)	0	2 (8.3)	1 (4.2)
Arthralgia	1 (7.7)	0	2 (13.3)	0	1 (5.6)	0	1 (4.2)	0
GERD	0	0	0	0	1 (5.6)	0	4 (16.7)	0
Lymphocyte count decreased	2 (15.4)	0	0	0	0	0	3 (12.5)	1 (4.2)
Alopecia	0	0	0	0	3 (16.7)	0	1 (4.2)	0
Amylase increased	2 (15.4)	0	0	0	0	0	2 (8.3)	0
Asthenia	0	0	2 (13.3)	0	1 (5.6)	0	1 (4.2)	1 (4.2)
Blood bilirubin increased	1 (7.7)	0	0	0	2 (11.1)	1 (5.6)	1 (4.2)	0
Muscle spasms	1 (7.7)	0	0	0	0	0	3 (12.5)	0
Oral pain	2 (15.4)	0	0	0	1 (5.6)	0	1 (4.2)	0
Rash maculopapular	0	0	0	0	1 (5.6)	0	3 (12.5)	1 (4.2)
Transaminases increased	0	0	0	0	0	0	3 (12.5)	0
Musculoskeletal pain	0	0	2 (13.3)	0	0	0	0	0

Note: A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. A patient with multiple AEs is counted only once in the total row.
Abbreviations: AE, adverse event; ECG, electrocardiogram; GERD, gastroesophageal reflux disease.

Pharmacokinetics

Ribociclib PK in combination with fulvestrant, alpelisib, and buparlisib were consistent with historical PK for ribociclib as monotherapy and in combination with fulvestrant in patients with cancer (26). The data suggested no marked difference in ribociclib PK in the presence of any of the combination partners. Alpelisib exposure was not affected after administration of alpelisib 200 mg plus ribociclib 200 mg or alpelisib 400 mg plus fulvestrant. Varying doses of ribociclib plus fulvestrant had no impact on buparlisib exposure following administration of 30 mg. Regardless of the combination partner, the exposure of ribociclib metabolite LEQ803, measured by AUC, ranged from 870 ng/h/mL to 3,510 ng/h/mL for all treatment combinations and doses. This is within overlapping ranges compared with observed historical data following administration of corresponding doses of ribociclib as single agent to patients with cancer (Study X2101; ref. 26).

Efficacy

The ORRs for the four treatment arms are presented in **Table 3**. ORRs of 23.1% and 13.3% were observed in the ribociclib (once daily, 3 weeks on, 1 week off) plus fulvestrant and ribociclib (continuous) plus fulvestrant treatment arms, whereas in the alpelisib and buparlisib triple combinations ORRs were 16.7% and 25.0%, respectively. One patient who received the alpelisib triple combination (ribociclib 400 mg + alpelisib 200 mg + fulvestrant 500 mg) had a complete response.

Median PFS data for the treatment arms are presented in **Table 3** and ranged from 7.2 to 11.0 months.

Table 3. Summary: PFS and best overall response by treatment.

	Ribociclib 600 mg + fulvestrant (*n* = 13)	Ribociclib 400 mg (continuous) + fulvestrant (*n* = 15)	Triple-combination ribociclib + alpelisib + fulvestrant (*n* = 18)	Triple-combination ribociclib + buparlisib + fulvestrant (*n* = 24)
PFS				
Median PFS, months	7.2	11.0	7.2	11.0
95% CI	5.5–10.8	3.8–32.2	3.7–16.9	7.4–13.9
Best overall response				
CR, *n* (%)	0	0	1 (5.6)	0
PR, *n* (%)	3 (23.1)	2 (13.3)	2 (11.1)	6 (25.0)
SD, *n* (%)[a]	9 (69.2)	7 (46.7)	8 (44.4)	12 (50.0)
ORR, *n* (%)[b]	3 (23.1)	2 (13.3)	3 (16.7)	6 (25.0)
95% CI	5.0–53.8	1.7–40.5	3.6–41.4	9.8–46.7
CBR, *n* (%)[c]	12 (92.3)	9 (60.0)	11 (61.0)	18 (75.0)

Note: Best overall response is based on investigator's assessment of disease status using RECIST 1.1. *N*: The total number of patients in the treatment group is the denominator for percentage calculation. *n*: Number of patients who were at the corresponding category.
Abbreviations: CBR, clinical benefit rate; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
[a]SD: non-CR/non-PD.
[b]ORR: CR + PR.
[c]CBR: CR + PR + SD ≥24 weeks.

Biomarkers

Tumor specimens were successfully sequenced (by NGS) in 65 (92.9%) patients enrolled, allowing evaluation of *PIK3CA* and *PTEN* mutational status. A total of 21 (32.3%) patients had a *PIK3CA* mutation, four (6.2%) had a *PTEN* mutation, and two (3.1%) had both a *PIK3CA* and *PTEN* mutation. No marked difference was observed in ORR between wild-type patients and patients with *PIK3CA* and *PTEN* mutation, in any of the treatment combinations (**Fig. 2**). Furthermore, we did not detect any marked associations between functional alterations in other sequenced genes (this assessment was performed for genes with functional alterations in at least two patients) and ORR (all unadjusted $P > 0.05$) as a preliminary analysis suggested.

Discussion

Ribociclib in combination with fulvestrant demonstrated clinical activity, based on PFS and OS, in patients with HR^+, $HER2^-$ ABC whose disease had progressed on or after AI treatment as seen in the MONALEESA-3 study (NCT02422615; refs. 10, 16). Because there were no expected interactions between ribociclib and fulvestrant, ribociclib was given in combination with fulvestrant at a dose of 600 mg daily for 21 days of a 28-day cycle (16). Given the established efficacy of fulvestrant in this patient population, all patients in all arms started at the standard dose of fulvestrant (500 mg dosed monthly with one additional dose of 500 mg given on day 15 of cycle 1). On the basis of the potential for drug–drug interactions impacting alpelisib and buparlisib in the triple combinations, low starting doses were selected.

Hepatobiliary toxicity is an important identified risk for ribociclib, however, the majority of hepatotoxicities observed in this study were asymptomatic and reversible transaminase increases. The etiology has been explored in clinical trials and no apparent relationship has been observed between ribociclib exposure and transaminase increases. Diarrhea and rash are AEs observed with various PI3K inhibitors, including buparlisib (a pan-class PI3K inhibitor), taselisib (a beta-sparing PI3K inhibitor), and alpelisib (an α isoform-selective PI3K inhibitor; refs. 19, 20, 32). Rates of grade ≥3 diarrhea in previous PI3K inhibitor phase II and III studies ranged from 3.7% to 11.7% (19, 20, 32). In this study, the rates of grade ≥3 diarrhea in the alpelisib and buparlisib triple combinations were 5.6% and 4.2%, respectively. In previous PI3K inhibitor phase II and III studies, grade ≥3 rash was seen in 1.7% to 9.9% of patients treated with a PI3K inhibitor (19, 20, 32). However, in this study, the rate of grade ≥3 rash in the alpelisib triple combination was 22.2% and rash was reported as a DLT in three (20.0%) patients treated with the alpelisib triple combination. Rate of grade ≥3 rash in the buparlisib triple combination was 4.2% and rash was reported as a DLT in one (4.8%) patient in the buparlisib triple combination. Although psychiatric disorders are commonly reported adverse events with buparlisib (20, 33), we did not observe significant neurologic side effects in patients receiving the combination therapy in this study.

Because of the unexpected toxicities seen in the alpelisib triple combination, no RP2D was determined in this study. However, the RP2D was determined for the buparlisib triple combination and both double combinations. No MTDs were determined for either of the triple combinations. The phase II study for the triple combinations is no longer deemed a desirable option due to the observed combination safety profile. In addition, the physician observations of rash were deemed clinically incompatible with long-term dosing in patients treated with the alpelisib triple combination.

Regardless of the PI3K inhibitor used, there was no significant drug–drug interaction demonstrated because the exposure of the ribociclib and its metabolite LEQ803 were within overlapping ranges (compared with historical data) after administration of corresponding doses of ribociclib as single-agent therapy to patients with cancer (26). Varying doses of ribociclib did not impact the exposure of either alpelisib or buparlisib.

Correlation of genetic alterations of PI3K pathway (i.e., *PIK3CA* and *PTEN*) with response in the combination groups was explored; however, sample size was too small to draw any conclusion.

The safety profile of ribociclib plus fulvestrant in the intended target patient population was consistent with those of previous studies; safety profiles of the combinations generally reflected the AEs of the individual agents, and these results are encouraging. The continuous dosing regimen of ribociclib (400 mg), as part of more complex

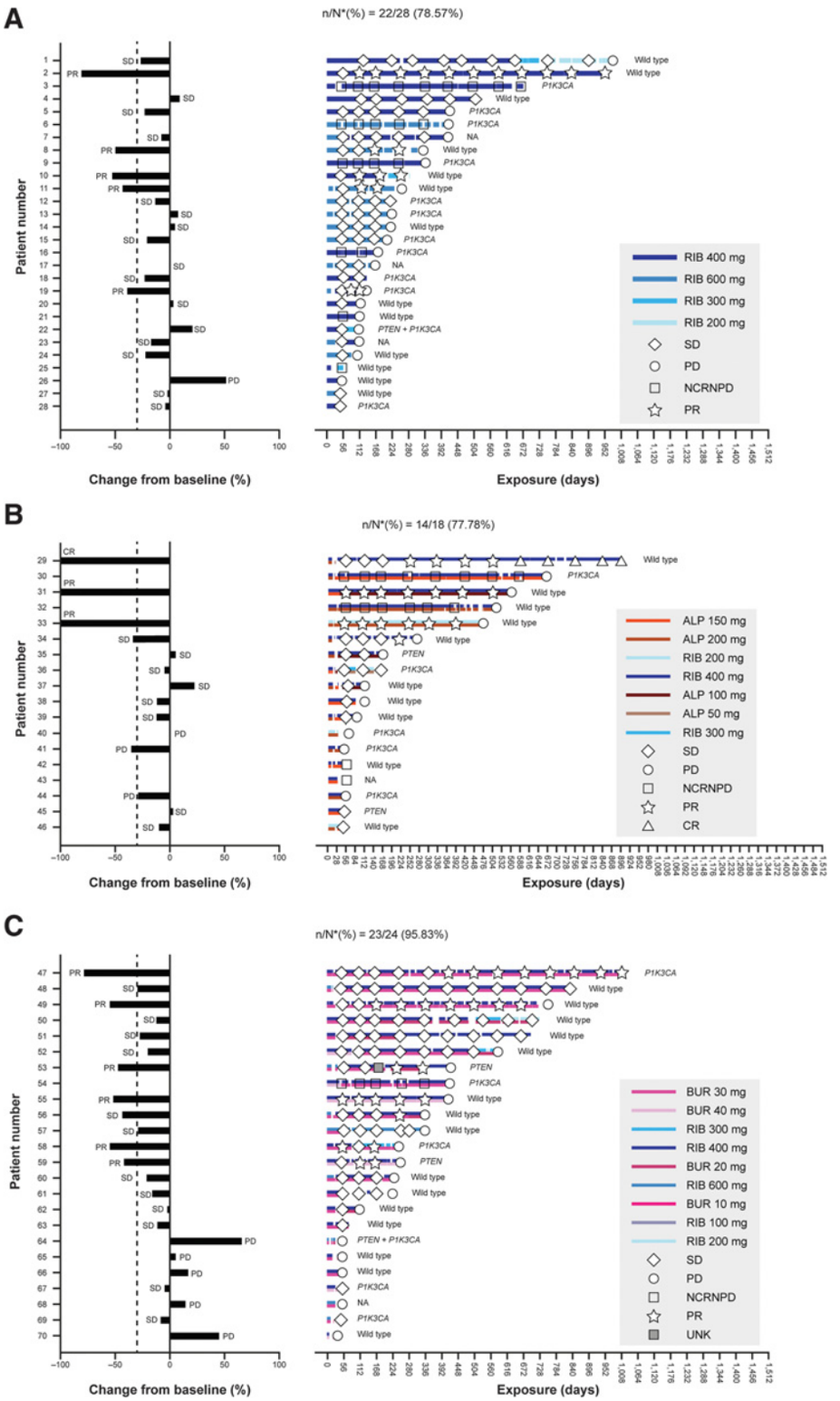

Figure 2.

Best percentage change from baseline in sum of longest diameters of target lesions and best overall response by treatment (left); duration of exposure and overall response by treatment, with *PIK3CA* gain-of-function (activating single amino acid substitutions, one case of gene amplification) and *PTEN* loss-of-function alterations (deep deletions, truncating mutations, one case of catalytic-dead single amino acid substitution) indicated (right). **A,** Ribociclib 400 mg (continuous dosing) + fulvestrant 500 mg and ribociclib 600 mg + fulvestrant 500 mg. **B,** Ribociclib 200 mg + alpelisib 200 mg + fulvestrant 500 mg; ribociclib 400 mg + alpelisib 150 mg + fulvestrant 500 mg; and ribociclib 400 mg + alpelisib 200 mg + fulvestrant 500 mg. **C,** Ribociclib 400 mg + buparlisib 30 mg + fulvestrant 500 mg; ribociclib 400 mg + buparlisib 40 mg + fulvestrant 500 mg; and ribociclib 600 mg + buparlisib 30 mg + fulvestrant 500 mg. ALP, alpelisib; BUR, buparlisib; NCRNPD, neither complete response nor progressive disease; RIB, ribociclib; UNK, unknown; NA, no genetic data available; wild-type, no alterations in *PIK3CA* or *PTEN*.

regimen options for ribociclib therapy (double, triple combinations), was explored in this study in combination with fulvestrant, and demonstrated that utilization is feasible and promising. Triple combinations of ribociclib plus alpelisib or buparlisib plus fulvestrant are not recommended for phase II investigation because of the toxicities experienced by patients.

Authors' Disclosures

S.M. Tolaney reports grants from Novartis (research funding to institution) during the conduct of the study; grants and personal fees from AstraZeneca (research funding to institution; honorarium for advisory board/consulting), Eli Lilly (research funding to institution; honorarium for advisory board/consulting), Merck (research funding to institution; honorarium for advisory board/consulting), Nektar (research funding to institution; honorarium for advisory board/consulting), Novartis (research funding to institution outside this work; honorarium for advisory board/consulting), Pfizer (research funding to institution; honorarium for advisory board/consulting), Immunomedics (research funding to institution; honorarium for advisory board/consulting), Genentech/Roche (research funding to institution; honorarium for advisory board/consulting), Bristol-Myers Squibb (research funding to institution; honorarium for advisory board/consulting), Eisai (research funding to institution; honorarium for advisory board/consulting), NanoString (research funding to institution; honorarium for advisory board/consulting), Sanofi (research funding to institution; honorarium for advisory board/consulting), Odonate (research funding to institution; honorarium for advisory board/consulting), and Seattle Genetics (research funding to institution; honorarium for advisory board/consulting), grants from Exelixis (research funding to institution) and Cyclacel (research funding to institution), personal fees from Abbvie (honorarium for advisory board/consulting), Athenex (honorarium for advisory board/consulting), G1 Therapeutics (honorarium for advisory board/consulting), Silverback Therapeutics (honorarium for advisory board/consulting), Puma (honorarium for advisory board/consulting), OncoPep (honorarium for advisory board/consulting), Daiichi-Sankyo (honorarium for advisory board/consulting), Kyowa Kirin Pharmaceuticals (honorarium for advisory board/consulting), Samsung Bioepsis Inc. (honorarium for advisory board/consulting), and CytomX (honorarium for advisory board/consulting) outside the submitted work. E. Calvo reports personal fees and other from Abbvie (institutional), Bristol-Myers Squibb (institutional), Janssen Oncology (institutional), Merck (institutional), Merus (institutional), Nanobiotix (institutional), Novartis (institutional), Pfizer (institutional), PharmaMar (institutional), Roche-Genentech (institutional), Amcure (institutional), Seattle Genetics (institutional), and Astellas (institutional), other from Amgen (institutional), Bayer (institutional), Boehringer Ingelheim (institutional), Lilly (institutional), Nektar (institutional), PsiOxus (institutional), Puma (institutional), Regeneron (institutional), Sanofi (institutional) ACEA Bio (institutional), Cytomx (institutional), Incyte (institutional), Kura (institutional), LOXO (institutional), Macrogenics (institutional), Menarini (institutional), Principia (institutional), Tahio (institutional), Tesaro (institutional), Transgene (institutional), Takeda (institutional), MSD (institutional), Mersana (institutional), GSK (institutional), Daiichi (institutional), ORCA (institutional), Boston Therapeutics (institutional), Dynavax (institutional), DebioPharma (institutional), Synthon (institutional), Rigontec (institutional), and Adaptaimmune (institutional), grants, personal fees, and other from AstraZeneca (institutional), grants and other from BeiGene (institutional), and personal fees from Servier outside the submitted work; and is the President of Foundation INTHEOS (Investigational Therapeutics in Oncological Sciences) Methods in Clinical Cancer Research (MCCR) Workshop in Zeist, Netherlands, the Joint ECCO-AACR-EORTC-ESMO Workshop on Methods in Clinical Cancer Research codirector, a member of SEOM, ESMO, ASCO, and EORTC, and a scientific board member at PsiOxus; and reports ownership in START Madrid, Oncoart Associated, International Cancer Consultants and employment in HM Hospitals Group. Y.-S. Lu reports grants and personal fees from Novartis (clinical trial, and speaker fee, advisory board) during the conduct of the study; Merck (clinical trial, speaker fee), personal fees from AstraZeneca (speaker fee), Eisai (speaker fee), Roche (speaker fee), Pfizer (speaker fee), and Eli Lilly (speaker fee) outside the submitted work. E. Hamilton reports grants from Novartis (Institutional financial support for clinic trials only, no personal conflicts) during the conduct of the study and other from Puma Biotechnology [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)], Daiichi Sankyo [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)], Mersana Therapeutics [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)], NanoString [consulting fees paid to institution (no personal fees)], AstraZeneca [consulting fees paid to institution (no personal fees), research/clinical trial support paid to institution], Novartis [consulting fees paid to institution (no personal fees)], Silverback Therapeutics [consulting fees paid to institution (no personal fees), research/clinical trial support paid to institution], Black Diamond [consulting fees paid to institution (no personal fees)], Hutchinson MediPharma [research/clinical trial support paid to institution (no personal fees)], OncoMed [research/clinical trial support paid to institution (no personal fees)], MedImmume [research/clinical trial support paid to institution (no personal fees)], StemCentrx [research/clinical trial support paid to institution (no personal fees)], Curis [research/clinical trial support paid to institution (no personal fees)], Verastem [research/clinical trial support paid to institution (no personal fees)], Zymeworks [research/clinical trial support paid to institution (no personal fees)], Syndax [research/clinical trial support paid to institution (no personal fees)], Lycera [research/clinical trial support paid to institution (no personal fees)], Rgenix [research/clinical trial support paid to institution (no personal fees)], Novartis [research/clinical trial support paid to institution (no personal fees)], Mersana [research/clinical trial support paid to institution (no personal fees)], Millenium [research/clinical trial support paid to institution (no personal fees)], TapImmune [research/clinical trial support paid to institution (no personal fees)], Lilly [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)], BerGenBio [research/clinical trial support paid to institution (no personal fees)], Medivation [research/clinical trial support paid to institution (no personal fees)], Pfizer [research/clinical trial support paid to institution (no personal fees)], Tesaro [research/clinical trial support paid to institution (no personal fees)], Boehringer Ingelheim [research/clinical trial support paid to institution (no personal fees)], Eisai [research/clinical trial support paid to institution (no personal fees)], H3 Biomedicine [research/clinical trial support paid to institution (no personal fees)], Radius Health [research/clinical trial support paid to institution (no personal fees)], Acerta [research/clinical trial support paid to institution (no personal fees)], Takeda [research/clinical trial support paid to institution (no personal fees)], Macrogenics [research/clinical trial support paid to institution (no personal fees)], Abbvie [research/clinical trial support paid to institution (no personal fees)], Immunomedics [research/clinical trial support paid to institution (no personal fees)], FujiFilm [research/clinical trial support paid to institution (no personal fees)], Effector [research/clinical trial support paid to institution (no personal fees)], Merus [research/clinical trial support paid to institution (no personal fees)], Nucana [research/clinical trial support paid to institution (no personal fees)], Regeneron [research/clinical trial support paid to institution (no personal fees)], Leap Therapeutics [research/clinical trial support paid to institution (no personal fees)], Taiho Pharmaceuticals [research/clinical trial support paid to institution (no personal fees)], EMD Serono [research/clinical trial support paid to institution (no personal fees)], Daiichi Sankyo [research/clinical trial support paid to institution (no personal fees)], ArQule [research/clinical trial support paid to institution (no personal fees)], Syros [research/clinical trial support paid to institution (no personal fees)], Clovis [research/clinical trial support paid to institution (no personal fees)], CytomX [research/clinical trial support paid to institution (no personal fees)], InventisBio [research/clinical trial support paid to institution (no personal fees)], Deciphera [research/clinical trial support paid to institution (no personal fees)], Unum Therapeutics [research/clinical trial support paid to institution (no personal fees)], Sermonix Pharmaceuticals [research/clinical trial support paid to institution (no personal fees)], Sutro [research/clinical trial support paid to institution (no personal fees)], Aravive [research/clinical trial support paid to institution (no personal fees)], Zenith Epigenetics [research/clinical trial support paid to institution (no personal fees)], Arvinas [research/clinical trial support paid to institution (no personal fees)], Torque [research/clinical trial support paid to institution (no personal fees)], Harpoon [research/clinical trial support paid to institution (no personal fees)], Fochon [research/clinical trial support paid to institution (no personal fees)], Black Diamond [research/clinical trial support paid to institution (no personal fees)], Orinove [research/clinical trial support paid to institution (no personal fees)], Molecular Templates [research/clinical trial support paid to institution (no personal fees)], Compugen [research/clinical trial support paid to institution (no personal fees)], G1 Therapeutics [research/clinical trial support paid to institution (no personal fees)], Karyopharm Therapeutics [research/clinical trial support paid to institution (no personal fees)], Torque Therapeutics [research/clinical trial support paid to institution (no personal fees)], Pfizer [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)], and Genentech/Roche [research/clinical trial support paid to institution (no personal fees), consulting fees paid to institution (no personal fees)] outside the submitted work. A. Forero-Torres reports other from Seattle Genetics (employment with Seattle Genetics since November 2018) outside the submitted work. T. Bachelot reports grants, personal fees, and nonfinancial support from

Novartis, Roche, Pfizer, and AstraZeneca and personal fees from Seattle Genetics outside the submitted work. R. Tiedt reports he is a full-time employee and shareholder of Novartis. U. Stammberger reports other from Novartis Institutes for BioMedical Research (employee of NIBR) and other from Novartis Institutes for BioMedical Research (owns Novartis stocks) during the conduct of the study. A.M. Abdelhady reports other from Novartis Pharmaceuticals (employment and own stocks) outside the submitted work. S.C. Lee reports grants and other from Pfizer (advisory board, invited speaker) and other from Eli Lilly (advisory board) and Novartis (advisory board, invited speaker) during the conduct of the study, other from Roche (advisory Board, invited speaker), grants and other from Taiho (grant), grants and other from Eisai (advisory board, invited speaker) and ACT Genomics (invited speaker), other from AstraZeneca (advisory board, invited speaker), MSD (advisory board), and Amgen (travel support to conference), and grants from Bayer (grant) outside the submitted work. No disclosures were reported by the other authors.

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Acknowledgments

We thank the patients who took part in this trial and their families, as well as staff members at each study site. Financial support was provided by Novartis Pharmaceuticals. We thank Lauren Halliwell, Healthcare Consultancy Group LLC, for her medical editorial assistance with this manuscript that was funded by Novartis Pharmaceuticals Corporation.

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Received March 5, 2020; revised June 29, 2020; accepted September 1, 2020; published first September 4, 2020.

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