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ORIGINAL ARTICLE

BEECH: a dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a *PIK3CA* mutant sub-population

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Background: BEECH investigated the efficacy of capivasertib (AZD5363), an oral inhibitor of AKT isoforms 1–3, in combination with the first-line weekly paclitaxel for advanced or metastatic estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer, and in a phosphoinositide 3-kinase, catalytic, alpha polypeptide mutation sub-population (*PIK3CA*+).

Patients and methods: BEECH consisted of an open-label, phase Ib safety run-in (part A) in 38 patients with advanced breast cancer, and a randomised, placebo-controlled, double-blind, phase II expansion (part B) in 110 women with ER+/HER2− metastatic breast cancer. In part A, patients received paclitaxel 90 mg/m^2 (days 1, 8 and 15 of a 28-day cycle) with capivasertib taken twice daily (b.i.d.) at two intermittent ascending dosing schedules. In part B, patients were randomly assigned, stratified by *PIK3CA* mutation status, to receive paclitaxel with either capivasertib or placebo. The primary end point for part A was safety to recommend a dose and schedule for part B; primary end points for part B were progression-free survival (PFS) in the overall and *PIK3CA*+ sub-population.

Results: Capivasertib was well tolerated, with a 400 mg b.i.d. 4 days on/3 days off treatment schedule selected in part A. In part B, median PFS in the overall population was 10.9 months with capivasertib versus 8.4 months with placebo [hazard ratio (HR) 0.80; $P = 0.308$]. In the *PIK3CA*+ sub-population, median PFS was 10.9 months with capivasertib versus 10.8 months with placebo (HR 1.11; $P = 0.760$). Based on the Common Terminology Criteria for Adverse Event v4.0, the most common grade ≥3

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adverse events in the capivasertib group were diarrhoea, hyperglycaemia, neutropoenia and maculopapular rash. Dose intensity of paclitaxel was similar in both groups.

Conclusions: Capivasertib had no apparent impact on the tolerability and dose intensity of paclitaxel. Adding capivasertib to weekly paclitaxel did not prolong PFS in the overall population or *PIK3CA*+ sub-population of ER+/HER2− advanced/metastatic breast cancer patients.
ClinicalTrials.gov: NCT01625286.

Key words: ER+, HER2–, metastatic breast cancer, AKT inhibitor, *PIK3CA*, capivasertib

Introduction

The PI3K/AKT/mTOR (phosphoinositide 3-kinase/AKT/mechanistic target of rapamycin) signalling pathway is critical for controlling cell metabolism, proliferation and survival and is the most frequently dysregulated pathway in cancer [1]. Activating phosphoinositide 3-kinase, catalytic, alpha polypeptide (*PIK3CA*) mutations are the most common genetic alterations in estrogen receptor-positive (ER+) breast cancers [2–4] and have been implicated in cancer therapy resistance [5]. Taxanes are among the most active agents against metastatic breast cancer [6] and have significantly improved response rate and progression-free survival (PFS) [7]. However, in some disease settings, exposure to cytotoxic agents, including taxanes, activates AKT signalling [8–10], which may initiate survival pathways that limit chemotherapy effectiveness [11].

Capivasertib (AZD5363), a potent, selective oral inhibitor of AKT isoforms 1–3, is under investigation for a range of therapeutic indications [12, 13]. Capivasertib inhibits the growth of various breast cancer cell lines [including ER+ and human epidermal growth factor receptor 2 (HER2)-amplified cell lines] and HER2+ breast xenograft models, and sensitises breast cancer xenografts to docetaxel [14]. Cancer models with a *PIK3CA* mutation, phosphatase and tension homolog (PTEN) loss or inactivating mutation have increased sensitivity to capivasertib [14].

In breast cancer xenograft models, capivasertib intermittent and continuous dosing schedules were both active, although higher intermittent schedules induced apoptosis while a lower continuous schedule only inhibited proliferation [14, 15]. The preclinical models suggested the importance of sequence: docetaxel administered before capivasertib improved efficacy, while docetaxel administered after capivasertib was antagonistic [15]. This collective evidence provided the rationale to conduct the phase I/II randomised BEECH study evaluating capivasertib in combination with the first-line weekly paclitaxel in patients with advanced or metastatic ER+/HER2– breast cancer. Weekly paclitaxel was chosen as the combination therapy because of superior tolerability to docetaxel [16, 17].

Patients and methods

Study design and participants

BEECH was an international, multicentre study comprising two parts: part A was an open-label, safety run-in of capivasertib in combination with paclitaxel, in patients with advanced/metastatic breast cancer, to identify the recommended dosing schedule for part B. Part B was a double-blind, randomised expansion phase of capivasertib in combination with paclitaxel versus placebo plus paclitaxel, in patients with ER+ advanced breast cancer with or without a *PIK3CA* mutation receiving chemotherapy for the first time in the advanced setting.

The study protocol was approved by an institutional review board or independent ethics committee at each site. Signed informed consent was obtained from each patient (ClinicalTrials.gov identifier: NCT01625286). The study was carried out in accordance with the principles of the International Conference on Harmonisation Guidelines for Good Clinical Practice, the Declaration of Helsinki, and all applicable national and local laws.

Procedures

In part A, multiple ascending doses of two intermittent dosing schedules of capivasertib were combined with weekly paclitaxel. Paclitaxel was given at 90 mg/m^2 in 4-weekly cycles (3 weeks on and 1 week off treatment), while capivasertib was taken orally as capsules or dose-equivalent tablets (40–200 mg) twice daily (b.i.d.), each week paclitaxel was received. Two intermittent dosing schedules of schedule 1 (2 days on then 5 days off treatment, starting at a dose of 560 mg b.i.d.) and schedule 2 (4 days on then 3 days off treatment, starting at a dose of 360 mg b.i.d.) were investigated. For both schedules, three to six assessable patients were enrolled into each dose cohort. The decision to escalate dose was determined by safety evaluation and, if available, pharmacokinetic (PK) data. If two or more of the six patients experienced a dose-limiting toxicity (DLT), this was considered the non-tolerated dose (NTD), and dosing escalation ceased. The maximum tolerated dose (MTD) was defined as the highest last dose assessed below the NTD.

In part B, patients were randomly assigned double-blind (1 : 1), stratified by *PIK3CA* mutation status, to receive paclitaxel with either capivasertib or placebo, at a dosing schedule identified from part A. Enrolment was capped to ensure that 50 patients each with *PIK3CA*+ and *PIK3CA*– disease were included. *PIK3CA* mutation status was determined from the most recent archival tumour tissue (derived from the diagnostic tumour or a metastatic site) and/or circulating tumour DNA (ctDNA) using the validated cobas® PIK3CA Mutation Test RUO (Roche Diagnostics, Mannheim, Germany) [18]. Patients were allocated to the *PIK3CA*+ stratum if a mutation was identified in tissue or ctDNA.

In both parts, capivasertib dosing continued until disease progression (Response Evaluation Criteria In Solid Tumors [RECIST] v1.1), unacceptable toxicity, death or patient withdrawal. Adverse events (AEs) were assessed and graded according to Common Terminology Criteria for Adverse Events (CTCAE) 4.0. For patients experiencing hyperglycaemia [post-dose plasma glucose level ≥8.9 mmol/L (≥160 mg/dL)], metformin was recommended on the days of capivasertib administration.

End points

In part A, the primary objective was to assess safety and tolerability, to recommend a dose and schedule for part B. In part B, the primary objective was to assess the efficacy of capivasertib when combined with paclitaxel by assessment of PFS in the overall population and in the *PIK3CA*+ sub-population. PFS was defined as the time from randomisation until objective disease progression. Secondary end points are described in supplementary material, available at *Annals of Oncology* online.

Statistical analysis

For part B, the planned sample size was 100 patients with 76 PFS events for primary analysis of the overall population. This was required to detect a hazard ratio (HR) of 0.61 with 80% power at the one-sided 10% level, which corresponded to an increase in median PFS from 5.0 to 8.2 months for the overall population. This sample size would also enable detection of an improvement in PFS from 9.0 to 14.8 months (in case of superior performance of the control arm). In the *PIK3CA*+ sub-population, 38 events were required to detect an HR of 0.5, using the same power and significance levels.

For part A, the efficacy analysis set included all patients who received at least one dose of study treatment, and for part B, this was defined as all randomised patients on an intention-to-treat basis. PFS for part B was analysed using Cox proportional hazards models. The model for the overall study effect was stratified by *PIK3CA* mutation status, along with 80% confidence intervals (CI) and two-sided *P* values. The safety analysis set for both parts of the study was defined as all patients who received at least one dose of study treatment.

More details on patients and methods are found in supplementary material, available at *Annals of Oncology* online.

Results

Part A: safety run-in phase

Between 3 October 2012 and 1 December 2014, 44 patients were assessed for eligibility, of whom 20 received dosing schedule 1 and 18 received dosing schedule 2 (Figure 1A). The data cut-off was 23 February 2015. Baseline characteristics of part A patients are shown in supplementary Table S1, available at *Annals of Oncology* online.

In part A, the most common AEs, irrespective of causality, were diarrhoea, nausea and asthenia (supplementary Table S2, available at *Annals of Oncology* online). Diarrhoea and neutropoenia were DLTs in schedule 1 (occurring in the 640 mg b.i.d. dose cohort), and allergic reaction and skin rash were DLTs in schedule 2 (occurring in the 480 mg b.i.d. dose cohort; supplementary Figure S3, available at *Annals of Oncology* online).

The capivasertib MTD for schedule 1 was 560 mg b.i.d. in combination with 90 mg/m^2 paclitaxel; for schedule 2 was 400 mg b.i.d. in combination with 90 mg/m^2 paclitaxel. Schedule 2 (4 days on/3 days off) at capivasertib 400 mg b.i.d. was selected as the recommended dosing schedule for part B. This dose was also supported by safety data from the phase I monotherapy study [13] and preclinical PK–pharmacodynamic-efficacy mathematical modelling [15], which predicted that the capivasertib MTD of schedule 1 was not sufficiently high enough to compensate for the shorter treatment duration. The efficacy data for part A are summarised in supplementary Table S4, available at *Annals of Oncology* online.

Part B: randomised phase

For part B, patients were enrolled from 6 February 2014 to 1 March 2016, with a data cut-off of 28 January 2017. Of the 194 patients screened, 110 were randomised: 54 to the paclitaxel plus capivasertib arm and 56 to the paclitaxel plus placebo arm (Figure 1B).

Baseline characteristics for part B were well balanced between treatment groups and within each *PI3KCA*+/– stratum, with respect to demographic and other clinical characteristics. There was no evidence of a baseline characteristic sub-group effect (supplementary Table S5 and Figure S6, available at *Annals of Oncology* online). Fifty-one (46%) patients were *PIK3CA*+ and 59 (54%) were *PIK3CA*– (supplementary Tables S1 and S8 and Figure S7, available at *Annals of Oncology* online). Further details on baseline characteristics and *PIK3CA* mutation data are described in supplementary Results, available at *Annals of Oncology* online.

In the overall population, median PFS was 10.9 months (95% CI 8.3–12.4) on capivasertib plus paclitaxel and 8.4 months (95% CI 8.2–10.8) on placebo plus paclitaxel (HR 0.80; 80% CI 0.60–1.06; $P = 0.308$; Figure 2A). In the *PIK3CA*+ sub-population, the median PFS was 10.9 months (95% CI 8.7–11.5) on capivasertib plus paclitaxel compared with 10.8 months (95% CI 8.3–14.3) on placebo plus paclitaxel (HR 1.11; 80% CI 0.73–1.68; $P = 0.760$; Figure 2B). Exploratory analysis including efficacy in the *PIK3CA*– sub-population and secondary efficacy end points are described in supplementary Results, available at *Annals of Oncology* online (supplementary Table S12 and Figures S9–S11, available at *Annals of Oncology* online).

The most common AEs of any grade in patients who received capivasertib plus paclitaxel were diarrhoea ($n = 41$; 76%), alopecia ($n = 28$; 52%) and nausea ($n = 21$; 39%). Thirty-two (59%) patients in the capivasertib arm, and 17 (31%) patients in the placebo arm had an AE of grade ≥3 (supplementary Table S13, available at *Annals of Oncology* online). Per investigator opinion, causally related AEs of grade ≥3 occurred in 28 (52%) patients receiving capivasertib and 11 (20%) receiving placebo. The most common grade ≥3 AEs causally related to either treatment group (capivasertib versus placebo) were diarrhoea (22% versus 2%), hyperglycaemia (13% versus 0%), neutropoenia (11% versus 9%) and maculopapular rash (9% versus 0%; supplementary Table S13, available at *Annals of Oncology* online). Overall, 96 (87.3%) patients discontinued study treatment: 47 (87.0%) in the capivasertib group and 49 (87.5%) in the placebo group. Capivasertib/placebo discontinuations were mostly due to disease progression (35/47 patients in the capivasertib group and 35/49 in the placebo group), with only 2 (3.7%) patients discontinuing treatment due to AEs causally related to capivasertib/placebo only. The relative dose intensity (RDI) of capivasertib/placebo was lower in the capivasertib group (86.1%) than in the placebo group (95.4%). The mean paclitaxel RDI was similar in the capivasertib group (91.5%) and in the placebo group (92.5%; supplementary Table S14, available at *Annals of Oncology* online). Further safety assessments are described in supplementary safety data.

In line with previous clinical data [13], significant decreases of GSK3β phosphorylation (a biomarker for capivasertib activity [19]) in platelet-rich plasma (PRP) were observed in the capivasertib plus paclitaxel arm compared with the placebo plus paclitaxel arm, with a nadir of –50% at 4 hours after the first dose (supplementary Table S15 and S16, available at *Annals of Oncology* online). The median pGSK3β values decreased with increasing capivasertib plasma concentration, but the maximum reduction in pGSK3β was observed approximately 2 hours after the peak plasma concentration. On cycle 1, week 3, day 2 (3 days after the latest dose), pre-dose pGSK3β had returned to baseline,

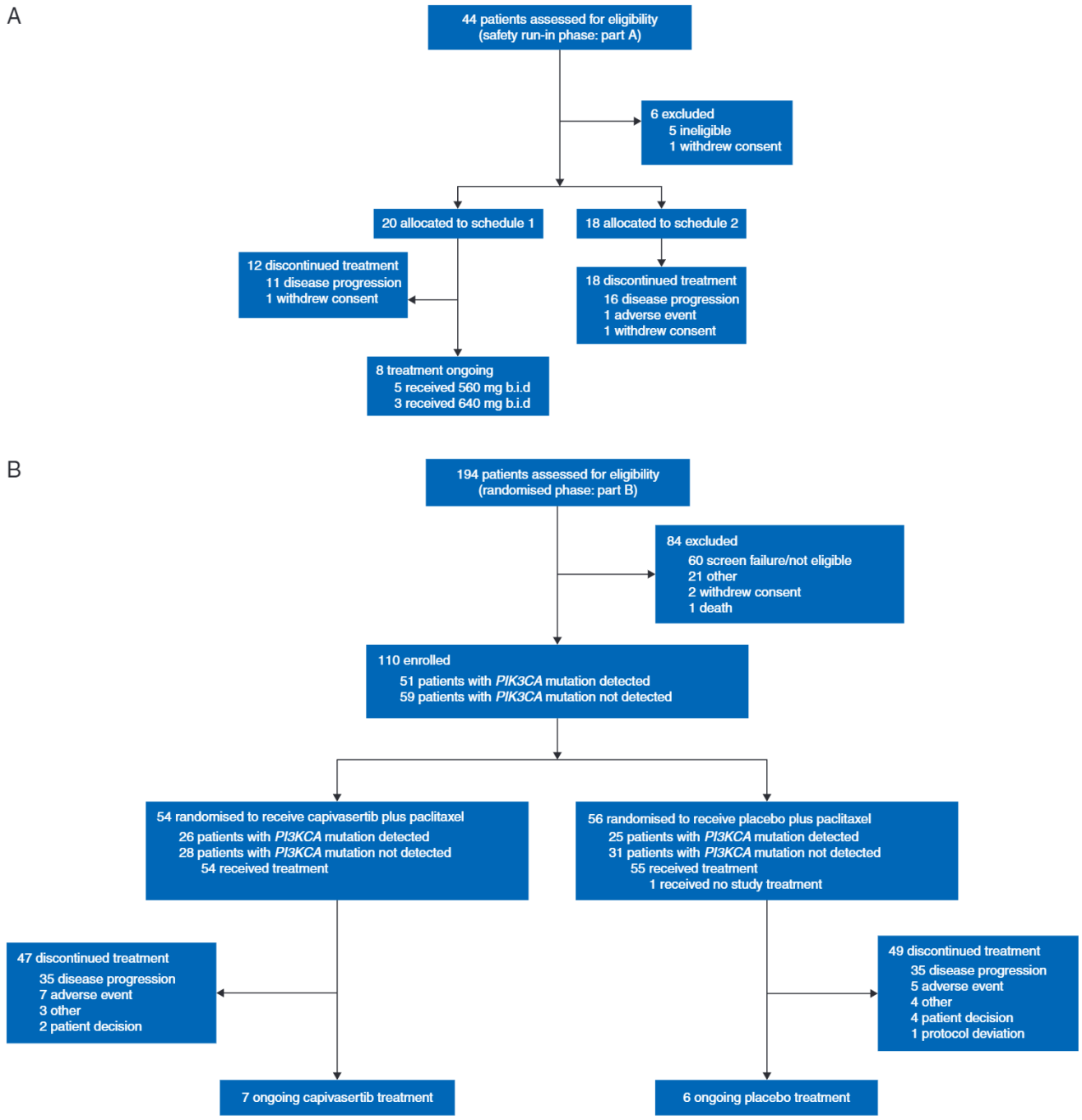

Figure 1. Trial profile. (A) Part A and (B) part B. Screen failure was largely attributable to patients with no *PIK3CA* mutations identified after 25 September 2015 when enrolment of *PIK3CA*– patients had ceased because the target number of *PIK3CA*– patients had been reached. All randomised patients received paclitaxel and all but one, randomised to the placebo group, received either capivasertib or matching placebo as assigned per the randomisation schema. b.i.d., twice daily; *PIK3CA*, phosphoinositide-3-kinase, catalytic, alpha polypeptide.

and at 4 hours post dose the reduction was similar to that after the first dose.

Discussion

In this phase I/II trial, capivasertib was well tolerated, with a low discontinuation rate and no apparent marked impact on tolerability and dose intensity of paclitaxel. Toxicity appeared to be well managed with dose modifications and supportive care.

No statistically significant differences in primary or secondary end points between capivasertib and placebo were demonstrated in the overall population or in the *PIK3CA*+ sub-population. This is despite strong preclinical data [14] and a phase I study [13] showing *PIK3CA*+ cancers are associated with a response to capivasertib monotherapy. Similarly, other studies have demonstrated a lack of preclinical translation into a clinical setting, with

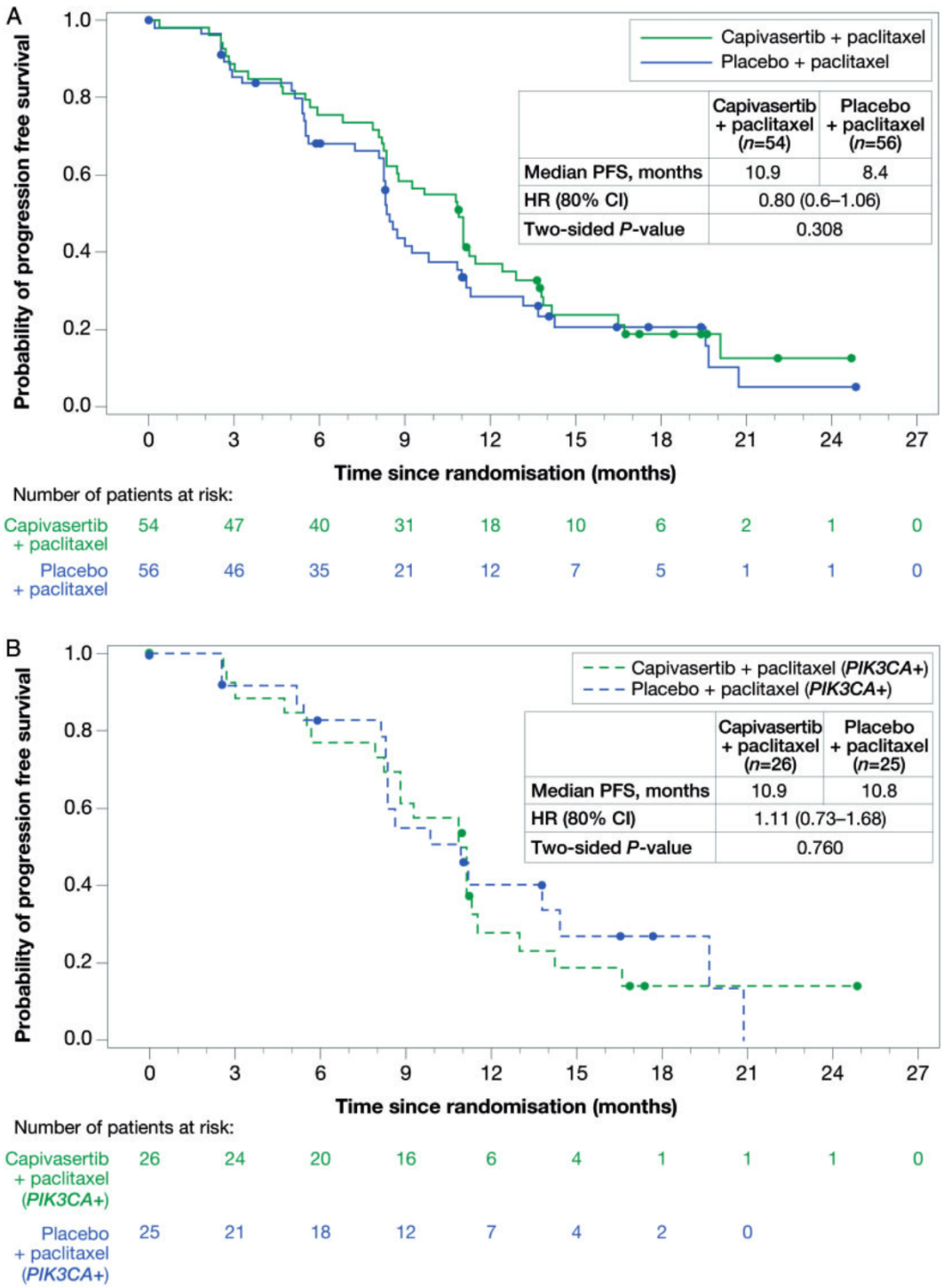

Figure 2. Progression-free survival (PFS) in part B. (A) PFS in the overall population of part B. (B) PFS in the *PIK3CA*+ sub-population of part B. ●, a censored observation, assessed using RECIST v1.1 criteria. HR, hazard ratio; PFS, progression-free survival; *PIK3CA*, phosphoinositide-3-kinase, catalytic, alpha polypeptide; RECIST, Response Evaluation Criteria In Solid Tumours Version 1.1.

PIK3CA+ tumours failing to show a significant benefit from PI3K-targeted therapies when combined with paclitaxel in the ER+ breast cancer setting [20–22]. It is unclear whether this is a failure of the pre-clinical hypothesis or an inability to sufficiently inhibit PI3K/AKT signalling while maintaining paclitaxel exposure in ER+ breast cancer patients. Two AKT inhibitors (capivasertib and ipatasertib) in combination with paclitaxel have now independently shown improved PFS and overall survival compared with placebo plus paclitaxel in unselected triple-negative breast cancers (PAKT and LOTUS trials, respectively),

with more pronounced benefit in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumours [23, 24]. In LOTUS, an even larger improvement in PFS was shown in the *PIK3CA*/*AKT1*-mutant subpopulation, although efficacy in this sub-group should be interpreted with caution because of limited sample size [25]. This demonstrates efficacy of AKT inhibition in combination with paclitaxel in triple-negative breast cancers. Of note, approximately half of triple-negative breast cancers have deficient expression of the tumour suppressor PTEN, which is associated with a higher degree of AKT pathway activation [26, 27], as well as frequent loss of expression of the pathway phosphatase INPP4B [28]. BEECH was conducted in ER+ breast cancer patients, and no concomitant endocrine therapy was allowed during the study. Inhibition of the PI3K pathway results in enhanced ER function and dependence in ER+ breast cancer, suggesting that combinations of PI3K pathway and ER inhibitors may be required [29]. Several mechanisms could drive ER expression following PI3K/AKT inhibition, including FOXO3a-driven transcription and the epigenetic regulator histone-lysine N-methyltransferase 2D [30]. This is also supported by the complex nature of the cross talk between ER and AKT, where increased AKT signalling may lead to ligand-independent ER activity. Alternatively, AKT signalling can suppress ER expression, circumventing the need for ER-driven transcription. In this setting, perturbation/suppression of PI3K/AKT signalling induces ER-dependent transcriptional activity, which may be reversed with ER-targeted therapies [28]. Of note, inhibition of AKT with monotherapy capivasertib in the HBCx22OvaR xenograft model modestly increased ER expression and activated ER-dependent genes, which was ameliorated by combination with fulvestrant [31]. Therefore, although BEECH was not designed to address the question, the lack of ER blockade may have played a role in the inability of capivasertib to improve outcome in combination with paclitaxel.

Limitations to this study include the relatively small number of patients in each sub-group. BEECH investigated a specific schedule of capivasertib administration. The current study did not consider other molecular aberrations of the PI3K/AKT/mTOR pathway as part of patient selection. Further analyses of ctDNA are underway that may reveal other potential biomarkers that could be evaluated in future trials. In a previous phase I study of capivasertib in patients with advanced, solid tumours [11], retrospective analysis of archival tumour tissue from the two patients who achieved partial responses revealed *AKT1* (*E17K*) mutation. The predictive role of *AKT1* (*E17K*) mutation in the present study cannot be assessed due to the rarity of this aberration and, therefore, the expected small numbers of mutant cases. This remains a question of interest, also in view of the activity of capivasertib in patients whose tumours harbour this aberration [12, 32, 33].

Capivasertib is being investigated further in combination with paclitaxel in triple-negative breast cancer patients, and in combination with fulvestrant in ER+/HER– breast cancer patients either unselected and resistant to aromatase inhibitors, or in AKT1/PTEN-mutant segments.

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Disclosure

AF, BRD, CR, CS, ECdB, GS, JPOL, JR, MC, MM, MP, PR and RM are employees of AstraZeneca UK, and AF, BRD, CC, ECdB, GS, PR and RM are also shareholders. SYAC was an AstraZeneca employee at the time of this research, and is currently an employee of Centara. AA holds ownership interest (including patents) in AstraZeneca. EO is an employee of Anchora Consultancy Ltd UK, contracted by AstraZeneca UK when the study was conducted via a freelance contract with Aptus Clinical. JAPF received speakers bureau for AstraZeneca, Bayer, Ipsen MSD, Pfizer, PharmaMar and Roche; travel expenses funded by AstraZeneca, Celgene, Pfizer, Roche and Sandoz; and Advisory Board participation expenses for AstraZeneca, Clinigen, Clovis Oncology, Eli Lilly, PharmaMar and Teva Pharmaceuticals. MPS received lecture fees from Eisai and consulting fees from AstraZeneca. NT received advisory board honoraria and research funding from AstraZeneca. MO received grant/research support (to the institution) from AstraZeneca, Boehringer-Ingelheim, Cascadian Therapeutics, Celldex, Genentech, GlaxoSmithKline, Immunomedics, Novartis, Seattle Genetics, Philips Healthcare, Piqur, PUMA Biotechnology, Roche and Sanofi; consultant fees from GSK, PUMA Biotechnology and Roche; honoraria from Roche; and travel grants from GP Pharma, Grünenthal, Novartis, Pierre-Fabre and Roche. All remaining authors have declared no conflicts of interest.

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