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Background:

In the Phase 3 randomized, double-blind CAPItello-291 trial, the addition of capivasertib (a potent, selective pan-AKT inhibitor) to fulvestrant in patients with aromatase inhibitor-resistant, hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative (HER2- defined as immunohistochemistry [IHC] 0, or 1-positive or IHC2-positive/in situ hybridization-negative) advanced breast cancer (ABC) significantly improved progression-free survival (PFS) versus placebo + fulvestrant (hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.51–0.71; $p < 0.001$). PFS benefit was observed in patients with detectable AKT pathway alterations (HR 0.50, 95% CI 0.38–0.65; $p < 0.001$) and without (0.70; 95% CI; 0.56–0.88). Here, we report PFS by gene within the AKT pathway-altered population.

Methods:

Patients were randomized 1:1 to receive fulvestrant (500 mg intramuscularly on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either placebo or capivasertib (400 mg twice daily; 4 days on, 3 days off). AKT pathway-alteration status (at least one qualifying alteration in the genes PIK3CA, AKT1, or PTEN) was determined post-randomization, using next-generation sequencing in tumor tissue. HRs were calculated using Cox proportional hazards models. Data cut-off Aug 15, 2022.

Results:

Of the 708 patients randomized to treatment, 289 (41%) had AKT pathway-altered tumors (capivasertib-fulvestrant $n=155$; placebo-fulvestrant $n=134$). In the AKT pathway-altered population, 43% had liver metastases and 40% primary endocrine therapy resistance. Prior therapy for advanced disease included: 89% of patients with ≥ 1 line of prior treatment, 71% with a prior cyclin-dependent kinase 4 and 6 inhibitor, and 18% with prior chemotherapy. Baseline characteristics were broadly balanced between treatment groups.

Most patients with an AKT pathway-altered tumor had only one detectable alteration (272/289, 94%). Thirteen patients (capivasertib-fulvestrant $n=4$; placebo-fulvestrant $n=9$) had co-occurring PIK3CA and PTEN alterations, and four patients (capivasertib-fulvestrant $n=2$; placebo-fulvestrant $n=2$) had co-occurring PIK3CA and AKT1 alterations.

Consistent PFS benefit of capivasertib-fulvestrant over placebo-fulvestrant was observed across all alterations (Table).

The safety profile of capivasertib-fulvestrant in the AKT pathway-altered population was consistent with the overall population.

Conclusions:

Compared with fulvestrant alone, the addition of capivasertib to fulvestrant provided a consistent PFS benefit across alterations in all three key genes within the AKT pathway in patients with HR-positive/HER2-negative ABC.

<https://clinicaltrials.gov/>: NCT04305496

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Table.

Alteration	N (%)	HR* for PFS (95% CI)
Any AKT pathway alteration	289 (100)	0.50 (0.38–0.65)
<i>PIK3CA</i> only	202 (69.9)	0.51 (0.37–0.70)
<i>PTEN</i> only	37 (12.8)	0.43 (0.21–0.88)
<i>AKT1</i> only	33 (11.4)	0.51 (0.22–1.12)
<i>PIK3CA</i> with/without <i>AKT1/PTEN</i> alterations	219 (75.8)	0.51 (0.37–0.69)
*HR<1 favors capivasertib-fulvestrant over placebo-fulvestrant.		

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Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer: exploratory analysis of PFS by *PIK3CA*/*AKT1*/*PTEN* alteration from the Phase 3 CAPItello-291 trial

Sacha J. Howell,¹ Hope S. Rugo,² Mafalda Oliveira,³ Florence Dalenc,⁴ Javier Cortes,⁵ Henry L. Gomez,⁶ Xichun Hu,⁷ Komal Jhaveri,⁸ Petr Krivorotko,⁹ Sibylle Loibl,¹⁰ Serafin Morales Murillo,¹¹ Meena Okeru,¹² Yeon Hee Park,¹³ Joo-Hyuk Sohn,¹⁴ Masakazu Toi,¹⁵ Eriko Tokunaga,¹⁶ Lyudmila Zhukova,¹⁷ Andrew Lloyd,¹⁸ Elza C de Bruin,¹⁸ Coumaran Egile,¹⁸ Celina D'Cruz,¹⁹ Nicholas C. Turner²⁰

¹The Christie NHS Foundation Trust, Manchester, UK; ²University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; ³Medical Oncology Department, Vall d'Hebron University Hospital and Breast Cancer Unit, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; ⁴Institut Claudius Regaud, Institut Universitaire du Cancer – Oncopole Toulouse, Toulouse, France; ⁵Oncology Department, International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group and Medica Scientia Innovation Research (MedSIR), Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; ⁶Instituto Nacional de Enfermedades Neoplásicas (INEN), Departamento de Oncología Médica and Universidad Ricardo Palma, Lima, Peru; ⁷Shanghai Cancer Center, Fudan University, Shanghai, China; ⁸Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; ⁹Petrov Research Institute of Oncology, St. Petersburg, Russia; ¹⁰GBG Forschungs GmbH, Neu-Isenburg, Germany and Centre for Haematology and Oncology, Bethanien, Frankfurt, Germany; ¹¹Institut de Recerca Biomèdica, Barcelona, Spain; ¹²ICON Cancer Centre, Adelaide, SA, Australia; ¹³Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea; ¹⁴Yonsei University College of Medicine – Yonsei Cancer Center, Seoul, Republic of Korea; ¹⁵Affiliation at the time the work was conducted; Kyoto University Hospital, Kyoto, Japan; ¹⁶National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; ¹⁷Logvinov Moscow Clinical Scientific Center, Moscow, Russia; ¹⁸Oncology R&D, AstraZeneca, Cambridge, UK; ¹⁹Oncology R&D, AstraZeneca, Waltham, MA, USA; ²⁰Royal Marsden Hospital, Institute of Cancer Research, London, UK

Objective

- To report the findings of an exploratory analysis of PFS by altered gene within the population of patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors from the CAPItello-291 study, including a pooled analysis with the inclusion of data from the Chinese extension cohort

Conclusions

- In patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors, the addition of capivasertib to fulvestrant provided a clinically meaningful PFS benefit compared to fulvestrant alone, with consistent benefit regardless of gene alteration detected, including:
 - PIK3CA* altered tumors
 - AKT1* altered tumors
 - PTEN* altered tumors
- Consistent clinical benefit was maintained in an exploratory analysis of the larger pooled population of patients enrolled in the global population and Chinese extension cohort
- The safety profile of capivasertib plus fulvestrant in the *PIK3CA*/*AKT1*/*PTEN*-altered population was consistent with the overall population
- Capivasertib plus fulvestrant has the potential to be a future treatment option for patients with HR-positive/HER2-negative advanced breast cancer who have progressed on, or after, an endocrine-based regimen, regardless of *PIK3CA*, *AKT1*, or *PTEN* tumor alteration detected

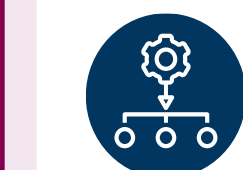
Plain language summary



- Why did we perform this research?**
- In the CAPItello-291 clinical study, researchers investigated whether combining a drug called capivasertib with another drug called fulvestrant could increase the length of time that it takes for a tumor to grow, spread, or get worse (known as progression-free survival)
 - Researchers found that participants taking capivasertib (a new drug that blocks the activity of a protein called AKT, reducing the growth of cancer cells) plus fulvestrant (a standard treatment for breast cancer) had (on average) longer progression-free survival compared with those taking placebo (an inactive substance that looked the same and was given the same way as capivasertib) plus fulvestrant
 - The AKT protein is part of the PI3K/AKT signaling pathway, a biological pathway made up of various proteins (including PI3K, AKT and PTEN) that regulate cell growth and survival. Participants in the CAPItello-291 study had their tumor tissue tested to see if it had alterations in any of the *PIK3CA*, *AKT1* or *PTEN* genes that make these proteins
 - In this analysis, researchers investigated whether the benefits of adding capivasertib to fulvestrant depended on the type of gene alterations that participants had in their tumors



- How did we perform this research?**
- In this analysis, researchers investigated whether the benefits of adding capivasertib to fulvestrant depended on the type of gene alterations that participants had in their tumors. Analysis was done in all participants in the global study, as well as an additional analysis that included data from participants from a Chinese extension study
 - Participants were grouped according to the genetic alterations they had in their tumor tissue: *PIK3CA*, *AKT1*, or *PTEN*



- What were the findings of this research, and what are the implications?**
- Participants who took capivasertib plus fulvestrant lived for longer without their disease getting worse compared with those that were treated with fulvestrant and placebo, no matter which of the three genes were altered in their tumor
 - Based on the results of this study, capivasertib in combination with fulvestrant, could potentially be a new option to add to the range of treatments available to people with HR-positive advanced breast cancer whose cancer has grown or spread despite endocrine therapy (with/without a CDK4/6 inhibitor)



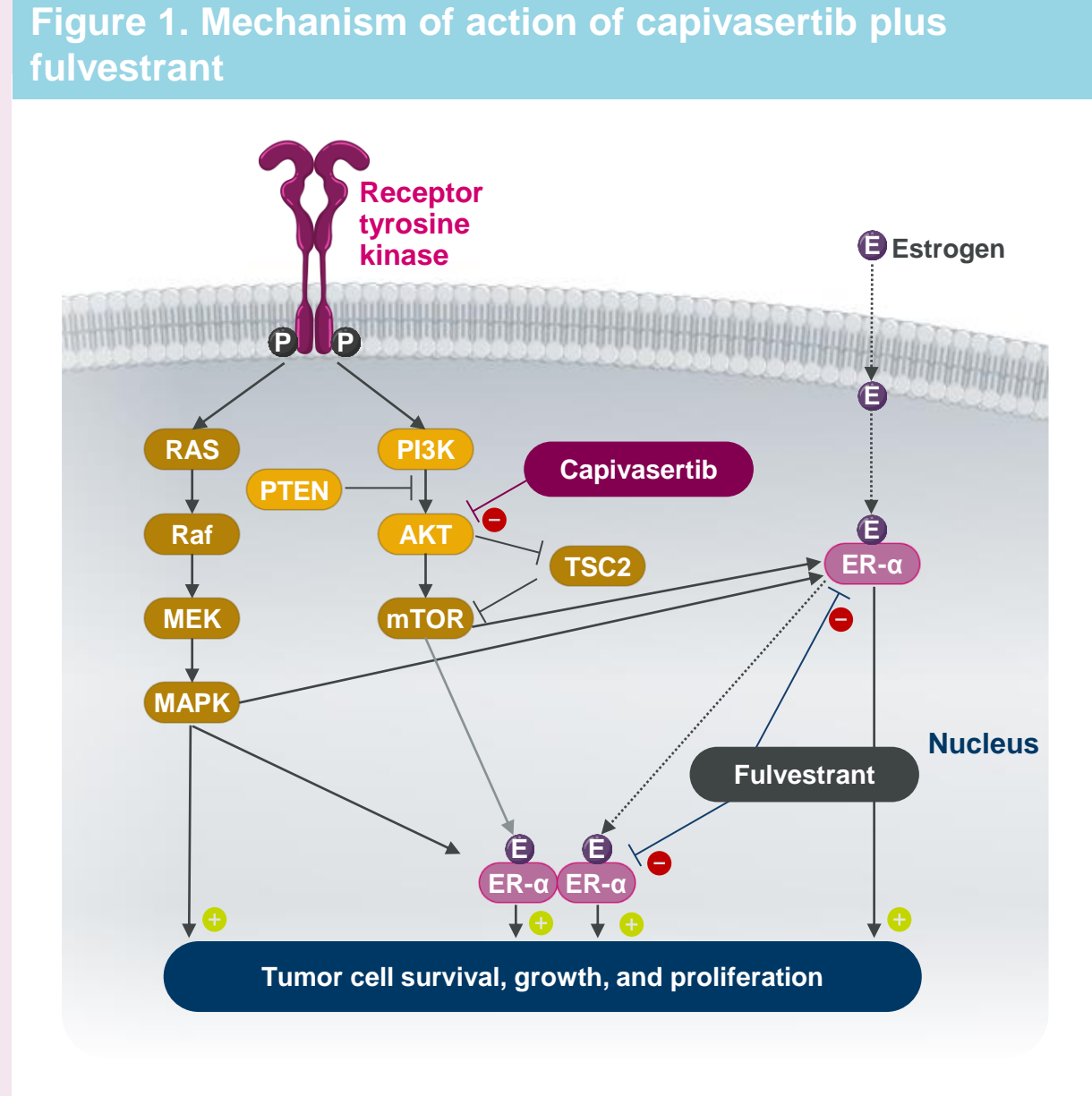
- Where can I access more information?**
- CAPItello-291 study identifier: NCT04305496



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Corresponding author email address: sacha.howell@nhs.net

Introduction

- PI3K/AKT pathway activation frequently occurs in HR-positive/HER2-negative advanced breast cancer through alterations in *PIK3CA*, *AKT1*, and *PTEN* genes, but may also occur in cancers without those genetic alterations^{1,2}
 - PI3K/AKT/PTEN signaling is also implicated in the development of resistance to endocrine therapy²
- Capivasertib is a potent, selective inhibitor of all three AKT isoforms (AKT1/2/3) (Figure 1)³
- In the global Phase 3 CAPItello-291 trial in patients with HR-positive/HER2-negative advanced breast cancer who had relapse or disease progression during or after aromatase inhibitor treatment with or without prior CDK4/6 inhibitor therapy, the addition of capivasertib to fulvestrant significantly improved the dual primary endpoints of PFS in the overall (hazard ratio: 0.60; 95% CI 0.51–0.71; p<0.001) and *PIK3CA*/*AKT1*/*PTEN*-altered (hazard ratio: 0.50; 95% CI 0.38–0.65; p<0.001) populations compared with placebo plus fulvestrant.⁴ PFS benefit was also observed in patients without detectable *PIK3CA*/*AKT1*/*PTEN*-alterations (hazard ratio 0.70; 95% CI: 0.56–0.88, including patients with unknown status)
- Here, we report PFS by *PIK3CA*, *AKT1* and/or *PTEN* alteration for the original global study population and a pooled analysis with the inclusion of data from the Chinese extension cohort⁵



Results

Patient characteristics of the global population

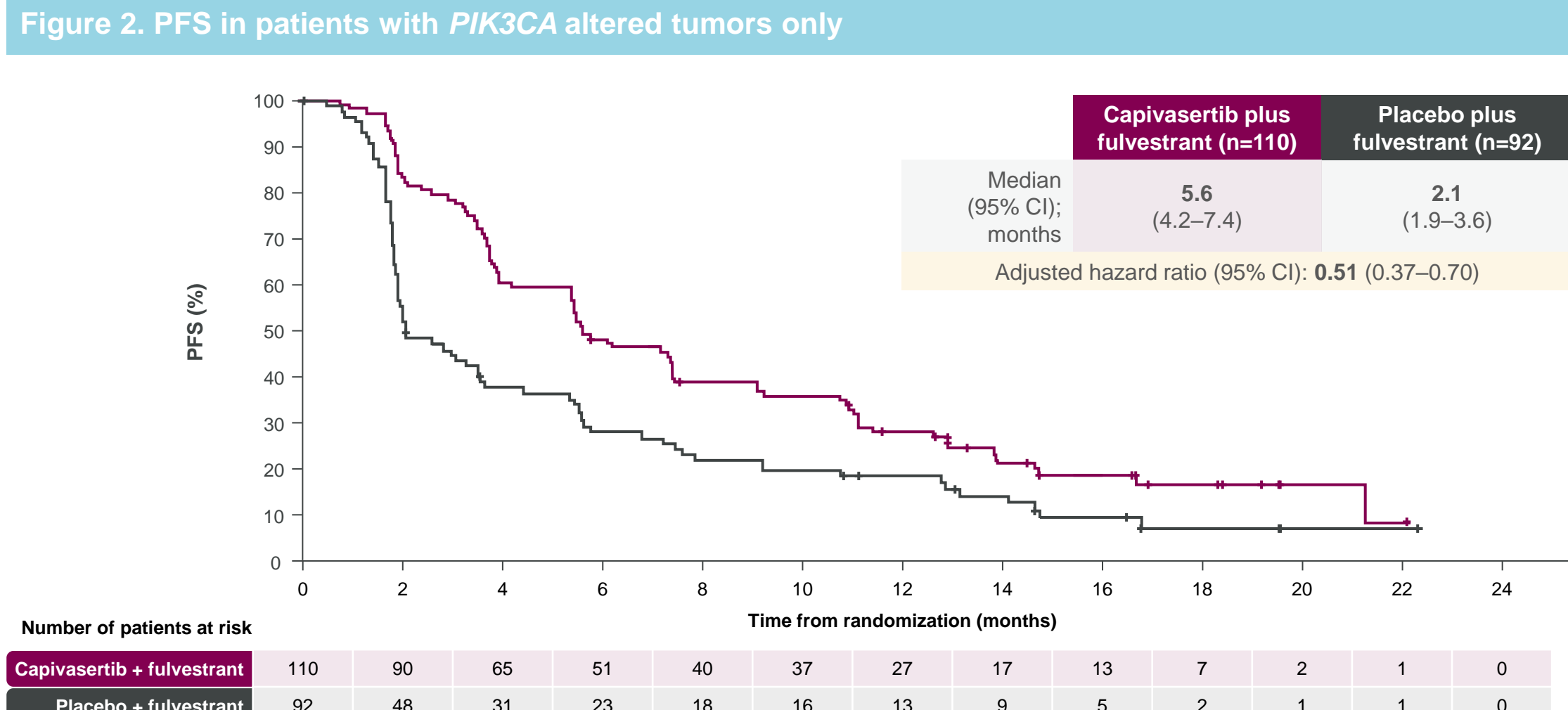
- Of the 708 patients randomized to treatment (capivasertib plus fulvestrant, n=355; placebo plus fulvestrant, n=353), 289 (41%) had *PIK3CA*/*AKT1*/*PTEN*-altered tumors (capivasertib plus fulvestrant, n=155; placebo plus fulvestrant, n=134)
- Baseline characteristics were broadly balanced between treatment groups (Table 2). Most patients had only one detectable tumor alteration (272/289, 94%)

Table 2. Baseline characteristics of patients with <i>PIK3CA</i> / <i>AKT1</i> / <i>PTEN</i> -altered tumors			
Characteristic		Capivasertib plus fulvestrant (n=155)	Placebo plus fulvestrant (n=134)
Median age; years (range)		58 (36–84)	60 (34–90)
Female; n (%)		153 (98.7)	134 (100)
Post menopausal; n (%)		130 (83.9)	105 (78.4)
Metastatic sites; n (%)	Bone only	25 (16.1)	16 (11.9)
	Liver	70 (45.2)	53 (39.6)
	Visceral	103 (66.5)	98 (73.1)
Hormone receptor status; n (%)	ER+/PR+	116 (74.8)	101 (75.4)
	ER+/PR–	35 (22.6)	31 (23.1)
	ER+/PR unknown	4 (2.6)	2 (1.5)
Endocrine resistance; n (%)**	Primary	60 (38.7)	55 (41.0)
	Secondary	95 (61.3)	79 (59.0)
Prior endocrine therapy for ABC; n (%)	0	13 (8.4)	20 (14.9)
	1	131 (84.5)	96 (71.6)
	2	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant ABC	79 (51.0)	67 (50.0)
		30 (19.4)	23 (17.2)
Alteration; n (%)	<i>PIK3CA</i> only	110 (71.0)	92 (70.9)
	<i>AKT1</i> only	18 (11.6)	15 (11.2)
	<i>PTEN</i> only	21 (13.5)	16 (11.9)

*Baseline stratification factors. **Primary and secondary resistance were defined using the 4th ESO-ESMO International Consensus Guidelines for ABC.

PFS in the global population

- Consistent clinically meaningful benefit with capivasertib plus fulvestrant compared to placebo plus fulvestrant was observed in patients with *PIK3CA* tumor alteration alone (Figure 2)
- Consistent clinically meaningful benefit with capivasertib plus fulvestrant compared to placebo plus fulvestrant was also observed in patients with *AKT1* or *PTEN* tumor alterations only, despite the small patient numbers (Figures 3 and 4)
- Benefit was similar when including those with combined alterations (Figure 5)



* Indicates a censored observation. The hazard ratio was estimated using the Cox proportional hazard model stratified by the presence of liver metastases (yes vs no) and prior use of CDK4/6 inhibitors (yes vs no).

Methods

- The CAPItello-291 study is a global Phase 3, randomized, double-blind, placebo-controlled study in patients (n=708) with aromatase inhibitor-resistant, HR-positive/HER2-negative* advanced breast cancer (NCT04305496)
 - The study also enrolled an extended Chinese cohort (n=134; 24 of whom were also included in the global study population) from mainland China (n=118) and NMPA-certified sites in Taiwan (n=16).⁵ The Chinese cohort continued to enroll patients after global enrollment had closed
- Patients were randomized (regardless of their tumour alteration status) 1:1 to receive fulvestrant (500 mg intramuscularly on days 1 and 15 of cycle 1, and day 1 of each subsequent 28-day cycle) with either placebo or capivasertib (400 mg twice daily; 4 days on, 3 days off)
- PIK3CA*/*AKT1*/*PTEN*-alteration status (at least one qualifying alteration in *PIK3CA*, *AKT1*, or *PTEN* genes) was determined centrally, post-randomization, using next-generation sequencing of tumor tissue with the FoundationOne®CDx assay in the Global cohort (Table 1) and using the OncoScreen Plus assay from Burning Rock Biotech for patients from mainland China
- Analysis of PFS by gene alteration was an exploratory post-hoc analysis; hazard ratios were calculated using Cox proportional hazard models
- Additional exploratory, *post-hoc* analysis of PFS was also conducted for the pooled population of patients enrolled under either the Global population or Chinese extension cohort. Modelling was stratified according to the Statistical Analysis Plan defined pooling strategy
- Data cut-off for analysis: Aug 15, 2022 (May 8, 2023 for the Chinese extension cohort)

*HER2-negative defined as IHC 0, or 1-positive or IHC2-positive/ISH-negative.

Table 1. Eligible <i>PIK3CA</i> , <i>AKT1</i> , and <i>PTEN</i> alterations		
Gene (transcript)	Variant class	Biomarker rules defining biomarker positive status
<i>AKT1</i> (NM_001014431)	Short variant	Any short variant with protein effect E17K
<i>PIK3CA</i> (NM_006218)	Short variant	Any of 19 short variants: R88Q, N345K, C420R, E542K, E545A, E545D, E545Q, E545K, E545G, Q546E, Q546K, Q546R, Q546P, M1043V, M1043I, H1047Y, H1047R, H1047L, and G1049R
	Short variant	Any of 13 short variants: C124R, C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R and R173C
<i>PTEN</i> (NM_000314)	Copy number alteration	Any nonsense, frameshift, or splice site alteration
	Rearrangement	Any homozygous deletion of one or more exons, regardless of transcript Any rearrangement that disrupts protein function, regardless of transcript • Intragenic events including duplications of only part of the gene, deletions, or inversions • Translocations, deletions, or inversions where one breakpoint is in <i>PTEN</i> and the other breakpoint is in another gene or intergenic region

*OncoScreen Plus assay does not call *PTEN* rearrangements

Pooled analysis

- PFS benefit with capivasertib plus fulvestrant compared to placebo plus fulvestrant was also consistent across alterations in an exploratory *post-hoc* analysis in the larger pooled population of patients enrolled in the global population and Chinese extension cohort of the CAPItello-291 study (Figure 5)
- The safety profile of capivasertib plus fulvestrant in the overall pooled analysis population was broadly consistent with that of the global population (Supplemental Table 2)



*excludes patients with unknown alteration status. Hazard ratios were estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region (overall population), the presence of liver metastases and prior use of CDK4/6 inhibitor (any alteration, *PIK3CA*, and non-altered subgroups) and prior use of CDK4/6 inhibitor only (unknown subgroup and any *PTEN*). Hazard ratio for subgroups with <50 patients were estimated using an unstratified Cox proportional hazard model.

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- Capivasertib was discovered by AstraZeneca subsequent to a collaboration with Astex Therapeutics (and its collaboration with the Institute of Cancer Research and Cancer Research Technology Limited)
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Disclosures

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Abbreviations

ABC, advanced breast cancer; AE, adverse event; AKT, AKT serine/threonine kinase; AST, aspartate aminotransferase; CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ER, estrogen receptor; ESMO, European Society for Medical Oncology; ESO, European School of Oncology; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; NC, not calculable; NMPA, National Medical Products Administration; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, progesterone receptor; PTEN, phosphatase and tensin homologue; Raf, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; TSC2, tuberous sclerosis complex 2.

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