Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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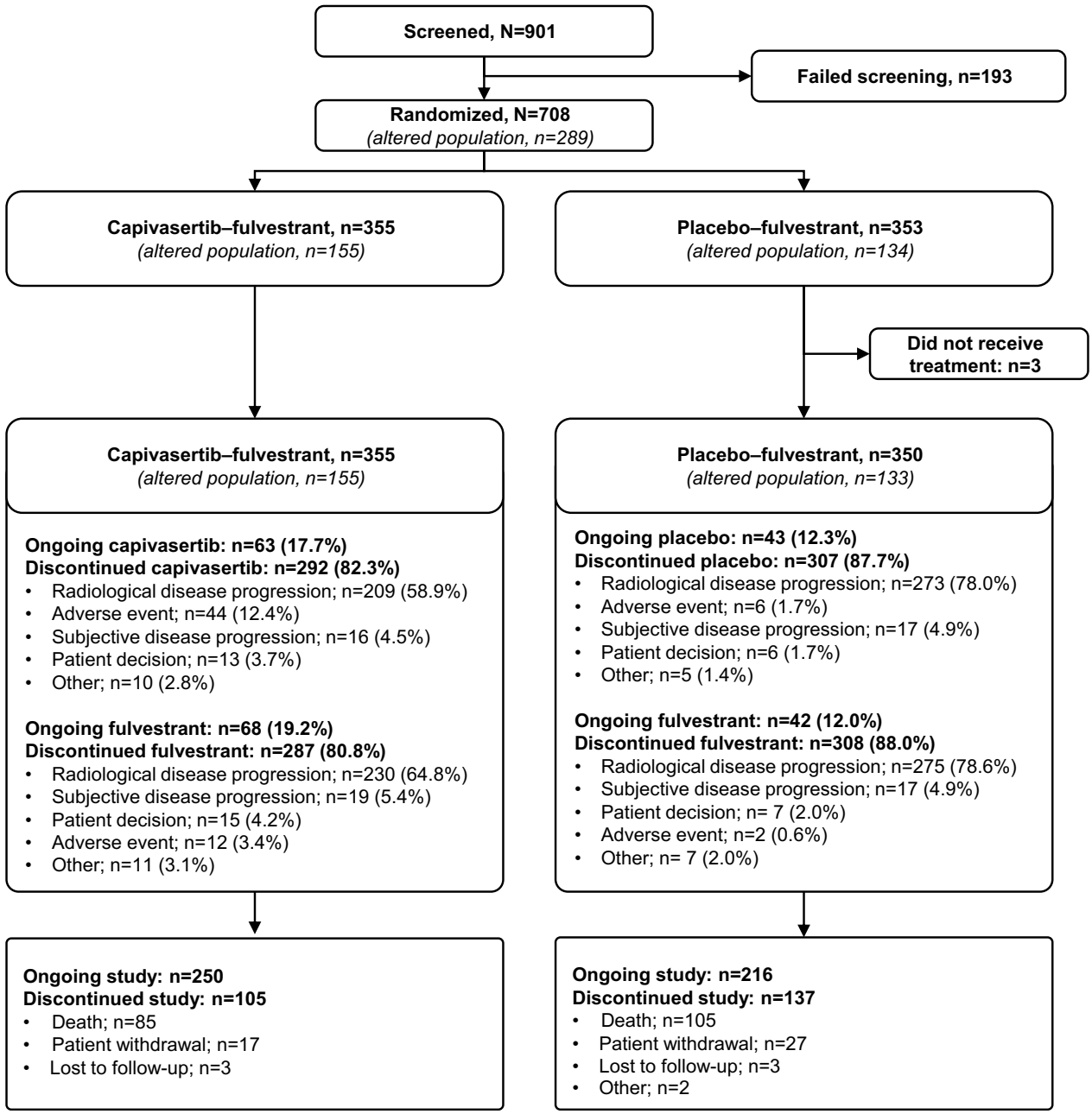
Capivasertib was discovered by AstraZeneca after a collaboration with Astex Therapeutics (and its partnership with the Institute of Cancer Research and Cancer Research Technology Limited).

SUPPLEMENTAL FIGURES

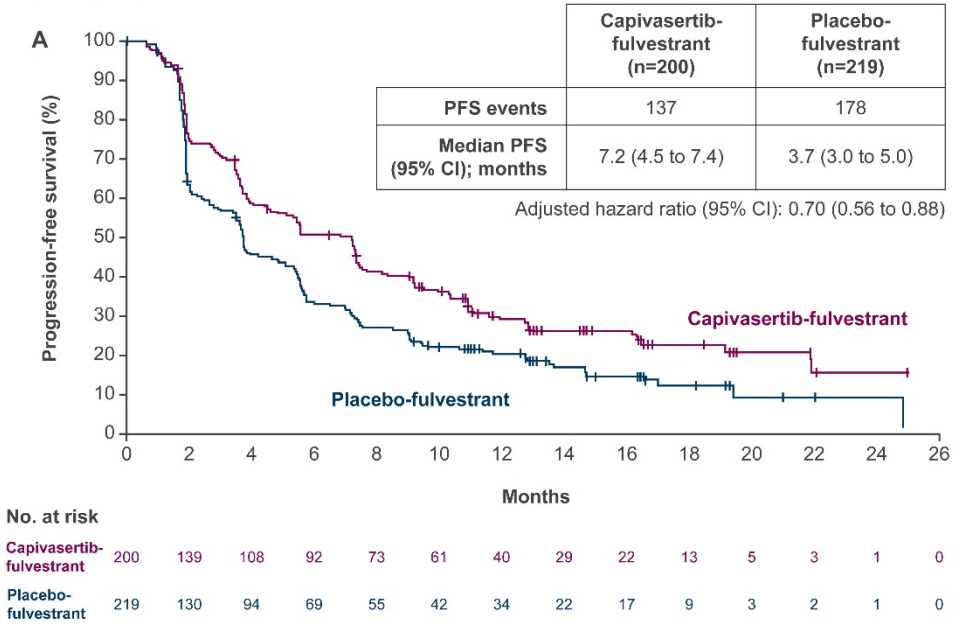
Figure S1. Study overview (consort diagram).

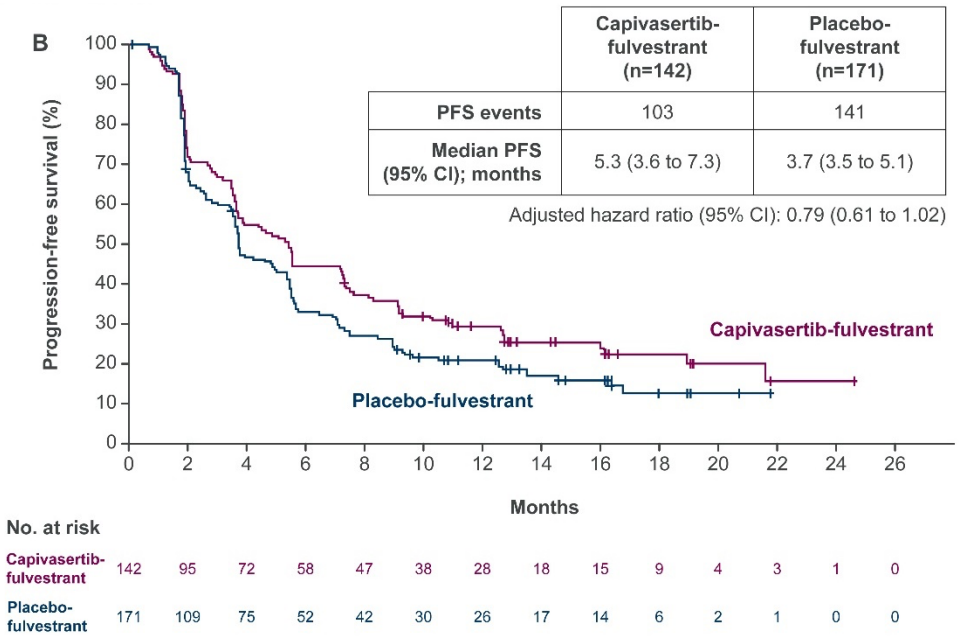


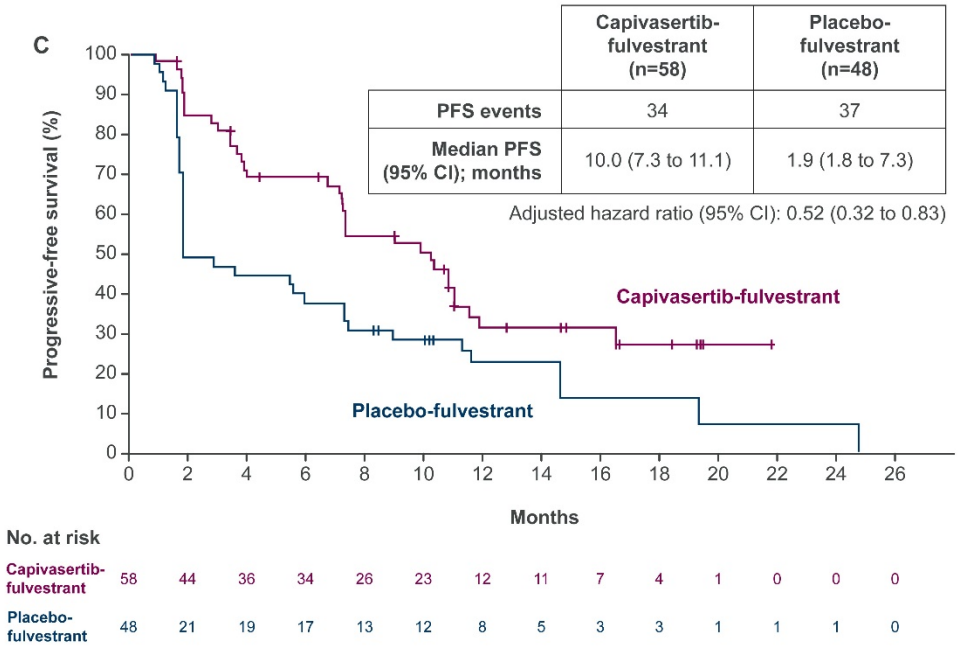
The altered population was defined as patients with AKT pathway (*PIK3CA*, *AKT1*, or *PTEN*) altered tumors determined by next-generation sequencing.

Deaths obtained from public records or survival follow-up.

Figure S2. Investigator-assessed progression-free survival in A) patients with AKT pathway non-altered tumors including unknown NGS result (per protocol) and B) patients with AKT pathway non-altered tumors excluding unknown NGS result (exploratory analysis), and C) only patients with unknown NGS result (*post-hoc* exploratory analysis).



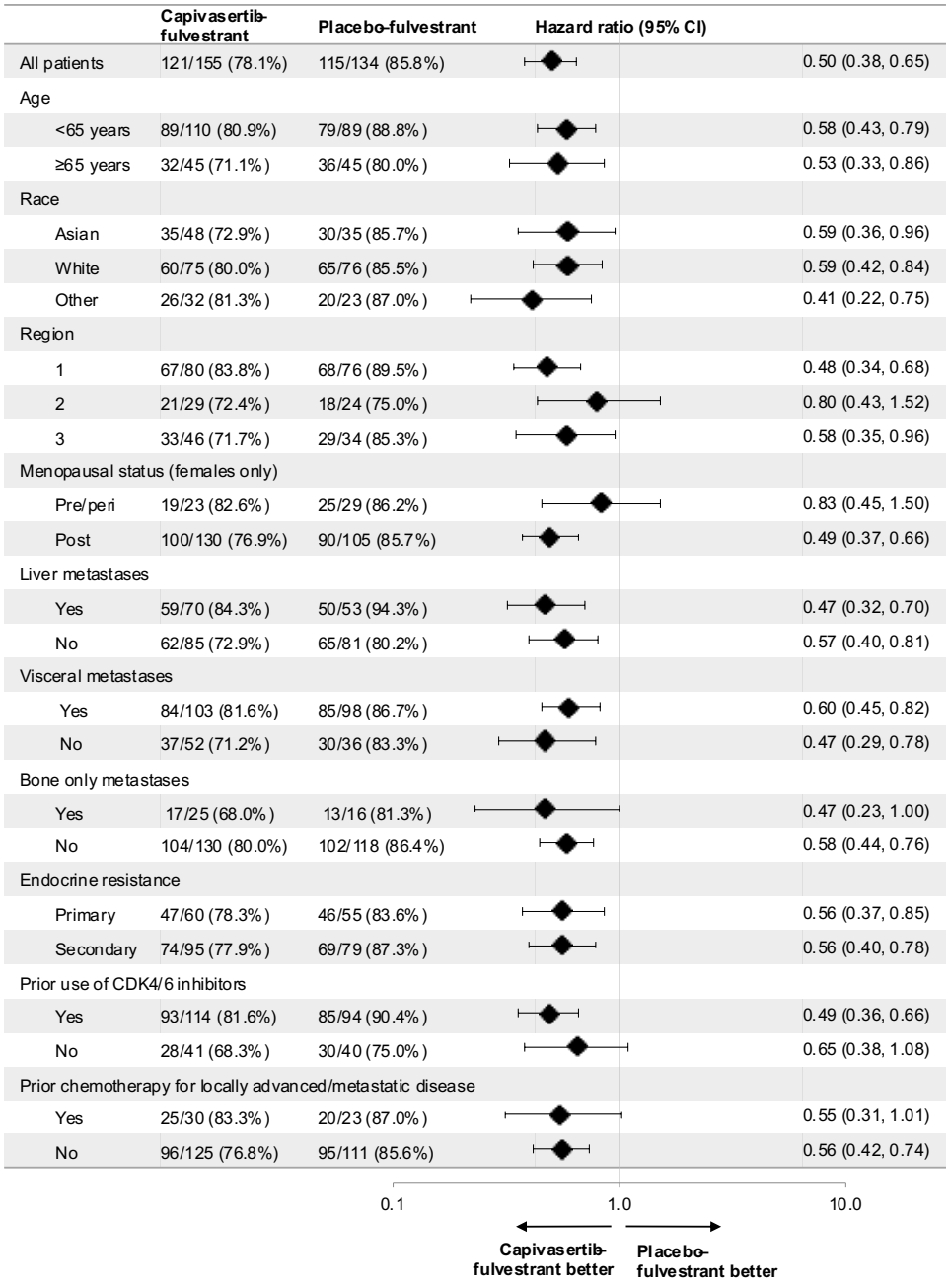




Symbols indicate censored data. Baseline characteristics were broadly comparable between treatment arms in all three populations, however, exploratory/*post-hoc* subgroup analyses should be interpreted with caution.

CI, confidence interval; NGS, next-generation sequencing; PFS, progression-free survival.

Figure S3. Investigator-assessed progression-free survival by subgroup in patients with AKT pathway-altered tumors.

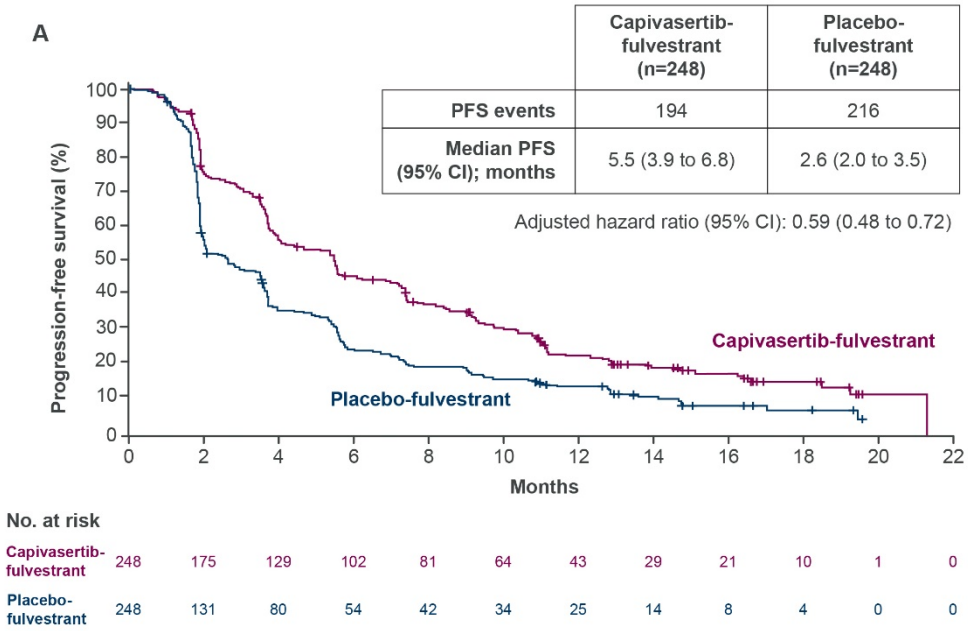


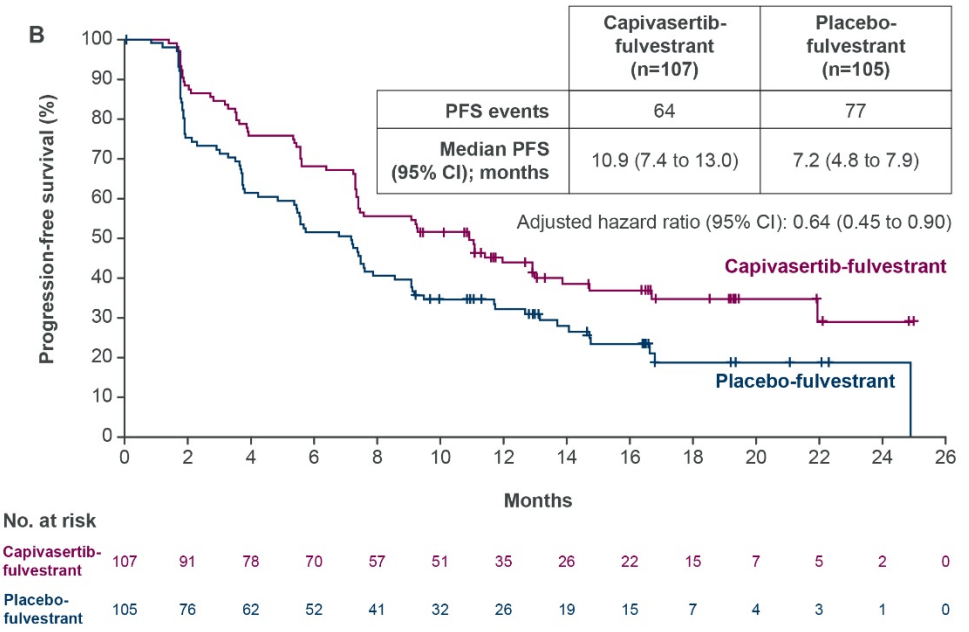
Region 1: United States, Canada, Western Europe, Australia, and Israel; Region 2: Latin America, Eastern Europe, and Russia; Region 3: Asia.

Subgroup analyses within the AKT pathway-altered population were performed at each subgroup level using a Cox proportional hazards model, including treatment term only. Selected subgroups of interest are shown.

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval.

Figure S4. Investigator-assessed progression-free survival in the overall population in A) patients with prior CDK4/6 inhibitor exposure and B) patients without prior CDK4/6 inhibitor exposure

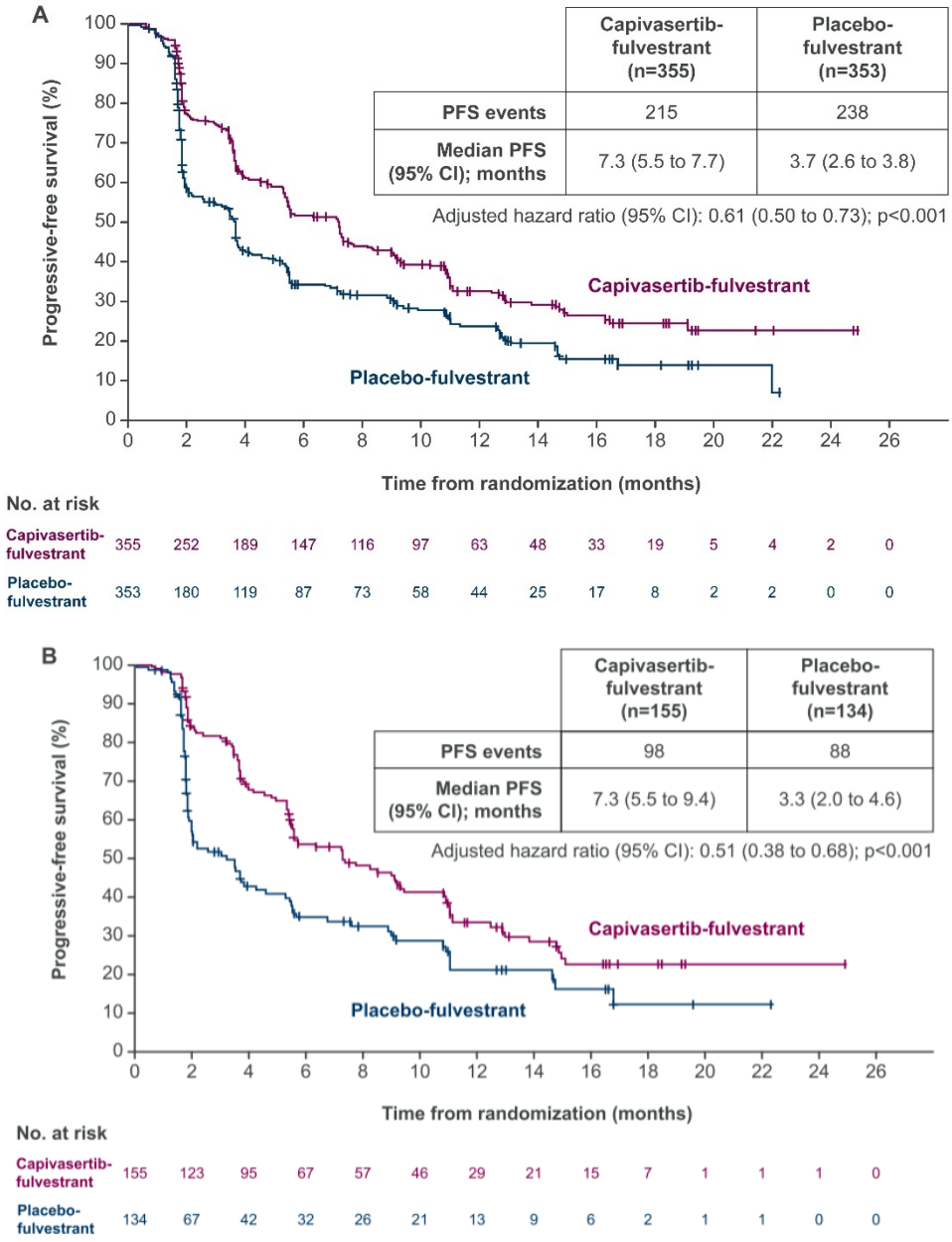




Symbols indicate censored data.

CDK4/6, cyclin-dependent kinase 4/6; CI, confidence interval; PFS, progression-free survival.

Figure S5. Progression-free survival by blinded independent central review in A) the overall population and B) patients with AKT pathway-altered tumors.



Symbols indicate censored data. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region in the overall population and by the presence of liver metastases and prior use of CDK4/6 inhibitor in patients with AKT pathway altered tumors.

CI, confidence interval; PFS, progression-free survival.

SUPPLEMENTAL TABLES

Table S1. AKT pathway alteration status by next-generation sequencing.

Alteration; n (%)		Capivasertib-fulvestrant (n=355)	Placebo-fulvestrant (n=353)
Any AKT pathway alteration		155 (43.7)	134 (38.0)
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
AKT pathway non-altered		200 (56.3)	219 (62.0)
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Pre-analytical failure		39 (11.0)	34 (9.6)
Post-analytical failure		9 (2.5)	10 (2.8)

AKT2, AKT serine/threonine kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog.

Preanalytical failure = sample did not meet sample quality metrics at pathology review or did not meet wet lab processing quality metrics. Postanalytical failure = sample did not meet bioinformatic quality metrics.

Table S2. Representativeness of Study Participants.

Category	Example
Disease, problem, or condition under investigation	Hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-negative) advanced breast cancer.
Special considerations related to:	
Sex and gender	Breast cancer is more common in women than men, with approximately 99% of all breast cancer cases occurring in women.[1]
Age	Globally, the rate of all breast cancers are generally higher in women aged ≥70 years and lowest in women aged <50 years.[2] In the United States, the median age of diagnosis for invasive breast cancer, of any subtype, is 62 years.[3] Patients with HR+/HER2-negative breast cancer are most commonly diagnosed with invasive breast cancer between 50–64 years of age in the United States.[4]
Race or ethnic group	In the United States, breast cancer is most commonly diagnosed in Black women and White women, with similar incidence rates of 127.8 and 133.7 cases per 100,000, respectively.[3] Overall, women with HR+/HER2-negative breast cancers comprise the highest proportion of women with breast cancer across all racial/ethnic groups in the United States.[3] In women with HR+/HER2-negative breast cancer aged 20 years and older, the age-adjusted incidence rate of breast cancer is highest in White women (141 cases per 100,000), Black women, and American Indian/Alaskan Native women (112 cases per 100,000 each), and lowest in Asian/Pacific Islander women (102 cases per 100,000) and Hispanic women (99 cases per 100,000).[2]
Geography	Breast cancer incidence and mortality rates differ by country and region.[5]
Other considerations	It is important to note that epidemiologic data for advanced HR+/HER2-negative breast cancer is currently limited, hence there is no solid reference point for drawing comparisons between this specific study population and the real-world population.

	Overall representativeness of this trial	The study cohort sex distribution was representative of the global population of individuals with breast cancer, whereby 99.2% and 98.9% of participants in the capivasertib and placebo arms, respectively, were female. The median age of participants was 58 years (range 26 to 90), which is similar to the median age of onset of invasive breast cancer in the United States (62 years) and aligned with the age in which patients with HR+/HER2-negative breast cancer are most commonly diagnosed (50–64 years). White individuals comprised the majority of study participants, with Black or African American individuals being under-represented. This study had global representation: 56% from Region 1 (United States, Canada, Western Europe, Australia, and Israel), 19% from Region 2 (Latin America, Eastern Europe and Russia), and 25% from Region 3 (Asia)

Table S3. Summary of tumor response by investigator assessment and blinded independent central review.

	Overall population		Patients with AKT pathway-altered tumors	
	Capivasertib-fulvestrant (n=355)	Placebo-fulvestrant (n=353)	Capivasertib-fulvestrant (n=155)	Placebo-fulvestrant (n=134)
Investigator assessment				
No. of patients with measurable disease at baseline	310	320	132	124
Objective response rate — n (%)	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)
Odds ratio (95% CI)*	2.19 (1.42 to 3.36)		3.93 (1.93 to 8.04)	
Median (95% CI) duration of response — months	9.8 (7.6 to 19.5)	8.4 (5.3 to 17.6)	9.4 (7.4 to 19.5)	8.6 (3.8 to 9.2)
Best overall response in all patients — n (%)	355	353	155	134
Complete response	4 (1.1)	1 (0.3)	3 (1.9)	0
Partial response	68 (19.2)	38 (10.8)	35 (22.6)	12 (9.0)
Stable disease (≥8 weeks)	187 (52.7)	152 (43.1)	84 (54.2)	55 (41.0)
Progressive disease	83 (23.4)	149 (42.2)	31 (20.0)	62 (46.3)
Non-evaluable	13 (3.7)	13 (3.7)	2 (1.3)	5 (3.7)
Clinical benefit rate† — n (%)	182 (51.3)	111 (31.4)	87 (56.1)	37 (27.6)
Blinded independent central review				
Objective response rate — n (%)	69 (19.4)	30 (8.5)	38 (24.5)	10 (7.5)
Best overall response in all patients — n (%)				
Complete response	2 (0.6)	0	1 (0.6)	0
Partial response	67 (18.9)	30 (8.5)	37 (23.9)	10 (7.5)
Stable disease (≥8 weeks)	182 (51.3)	157 (44.5)	82 (52.9)	54 (40.3)
Progressive disease	86 (24.2)	145 (41.1)	31 (20.0)	60 (44.8)
Non-evaluable	17 (4.8)	19 (5.4)	3 (1.9)	9 (6.7)

*Analysis was performed using logistic regression adjusted for liver metastases (yes vs. no), prior use of CDK4/6 inhibitors (yes vs. no) in patients with measurable disease in the overall population, and prior use of CDK4/6 inhibitors (yes vs. no) in patients with measurable disease in the altered population.

†Clinical benefit rate, a secondary objective, was defined the percentage of patients who have a complete or partial response, stable disease per RECIST v1.1 (without subsequent cancer therapy) maintained ≥24 weeks after randomization.

CI, confidence interval.

Table S4. Serious adverse events in the overall population.*

Serious adverse events — no. (%)	Capivasertib-fulvestrant (n=355)	Placebo-fulvestrant (n=350)
Patients with any SAE	57 (16.1)	28 (8.0)
Diarrhea	6 (1.7)	1 (0.3)
Rash maculo-papular	5 (1.4)	0
Vomiting	4 (1.1)	2 (0.6)
Acute kidney injury	3 (0.8)	0
Hyperglycemia	3 (0.8)	0
Platelet count decreased	0	3 (0.9)
Sepsis	2 (0.6)	1 (0.3)
Asthenia	2 (0.6)	0
Pneumonia aspiration	2 (0.6)	0
Hypercalcemia	1 (0.3)	2 (0.6)
Nausea	1 (0.3)	2 (0.6)
COVID-19	1 (0.3)	1 (0.3)
Drug-induced liver injury	1 (0.3)	1 (0.3)
Herpes zoster	1 (0.3)	1 (0.3)
Pain in extremity	1 (0.3)	1 (0.3)
Pleural effusion	1 (0.3)	1 (0.3)
Pneumonia	1 (0.3)	1 (0.3)
Pyrexia	1 (0.3)	1 (0.3)
Acute myocardial infarction	1 (0.3)	0
Acute respiratory failure	1 (0.3)	0
Adenocarcinoma of colon	1 (0.3)	0
Anaphylactic reaction	1 (0.3)	0
Arthralgia	1 (0.3)	0
Atrial fibrillation	1 (0.3)	0
Back pain	1 (0.3)	0
Bacterial colitis	1 (0.3)	0
Bladder transitional cell carcinoma	1 (0.3)	0
Body temperature increased	1 (0.3)	0
Cerebral hemorrhage	1 (0.3)	0
Cerebral infarction	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	0
Deep vein thrombosis	1 (0.3)	0
Dehydration	1 (0.3)	0
Dermatitis exfoliative generalized	1 (0.3)	0
Diabetic ketoacidosis	1 (0.3)	0
Diabetic metabolic decompensation	1 (0.3)	0
Drug eruption	1 (0.3)	0
Drug hypersensitivity	1 (0.3)	0
Drug reaction with eosinophilia and systemic symptoms	1 (0.3)	0
Endometrial cancer	1 (0.3)	0
Erythema multiforme	1 (0.3)	0

Fatigue	1 (0.3)	0
Femur fracture	1 (0.3)	0
Hepatitis B reactivation	1 (0.3)	0
Hordeolum	1 (0.3)	0
Infectious pleural effusion	1 (0.3)	0
Injection site abscess	1 (0.3)	0
Nephrolithiasis	1 (0.3)	0
Osteonecrosis of jaw	1 (0.3)	0
Peritonitis	1 (0.3)	0
Pneumonia bacterial	1 (0.3)	0
Pneumonia pneumococcal	1 (0.3)	0
Pyelonephritis	1 (0.3)	0
Rash	1 (0.3)	0
Rash erythematous	1 (0.3)	0
Rash papular	1 (0.3)	0
Renal failure	1 (0.3)	0
Retroperitoneal fibrosis	1 (0.3)	0
Skin infection	1 (0.3)	0
Stomatitis	1 (0.3)	0
Supraventricular extrasystoles	1 (0.3)	0
Syncope	1 (0.3)	0
Toxicity to various agents	1 (0.3)	0
Tumor associated fever	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Visceral pain	1 (0.3)	0
Abdominal pain	0	1 (0.3)
Anemia	0	1 (0.3)
Aspartate aminotransferase increased	0	1 (0.3)
Confusional state	0	1 (0.3)
Cytomegalovirus infection	0	1 (0.3)
Device intolerance	0	1 (0.3)
Dizziness	0	1 (0.3)
Femoral neck fracture	0	1 (0.3)
Forearm fracture	0	1 (0.3)
Humerus fracture	0	1 (0.3)
Ileus	0	1 (0.3)
Non-small cell lung cancer	0	1 (0.3)
Pathological fracture	0	1 (0.3)
Pneumothorax	0	1 (0.3)
Respiratory failure	0	1 (0.3)
Small cell lung cancer	0	1 (0.3)

*Adverse events are reported regardless of the relationship to the study drugs.

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