Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer

Turner NC, Oliveira M, Howell SJ, Dalenc F, Cortes J, Gomez Moreno HL, et al.

NEJM. 2023;388(22):2058-2070.

Background

Clinical Context

- ~70% of cases of ABC are HR+ without overexpression of HER2
- First-line treatment for HR+, HER2- ABC typically includes ET (often an AI) + CDK4/6 inhibitor
- Most patients eventually progress after first-line treatment, and subsequent therapy is a clinical challenge
- Alteration/overactivation of the PI3K-AKT-PTEN pathway occurs in ~50% of HR+, HER2- breast cancers and is implicated in resistance to ET

Potential Benefit for Patients

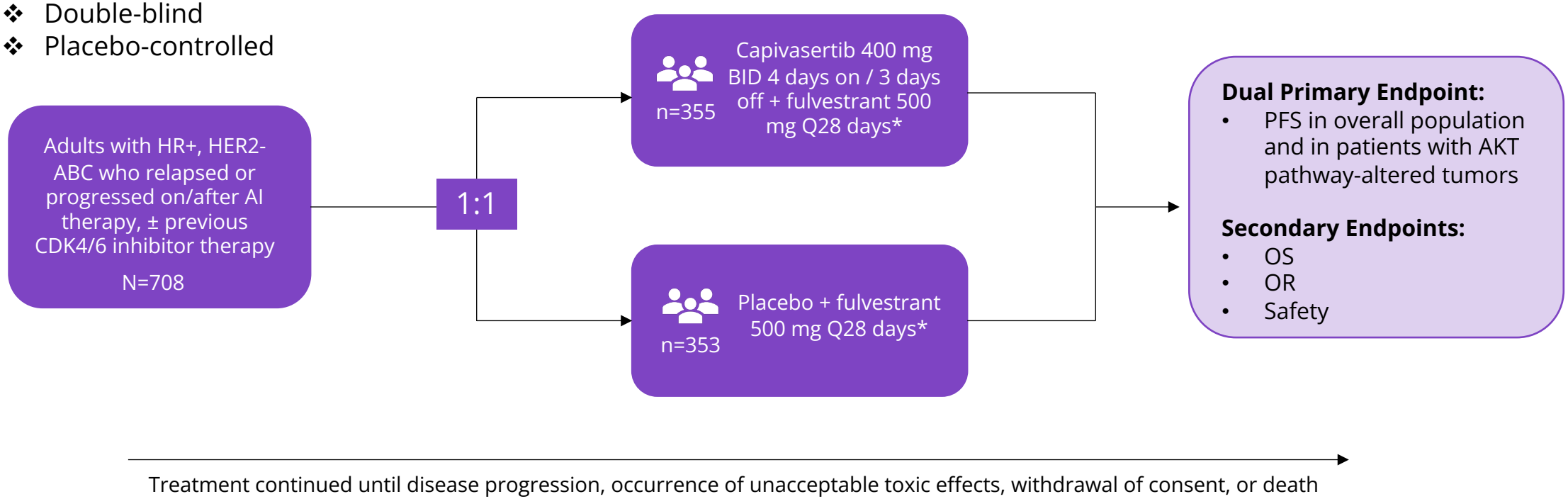
- Previous agents that inhibit the AKT pathway (eg, alpelisib and everolimus) have shown efficacy in combination with ET (e.g., fulvestrant and exemestane) in previously treated HR+ breast cancer vs ET alone
- Data is limited on the efficacy of AKT pathway inhibition combined with ET ± CDK4/6 inhibitor in this population
- Capivasertib is an oral, small-molecule inhibitor of the AKT pathway that showed significant improvement in PFS and OS in combination with fulvestrant vs fulvestrant alone in a Phase 2 study of postmenopausal women with HR+ ABC previously treated with ET

ABC, advanced breast cancer; **AI**, aromatase inhibitor; **AKT**, protein kinase B; **CDK4/6**, cyclin-dependent kinase 4 and 6; **ET**, endocrine therapy; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **OS**, overall survival; **PFS**, progression-free survival; **PI3K**, phosphatidylinositol 3-kinase; **PTEN**, phosphatase and tensin homolog.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

CAPItello-291 Study Design

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled



*Fulvestrant was administered every 14 days for the first three injections and every 28 days thereafter

ABC, advanced breast cancer; **AKT**, protein kinase B; **AI**, aromatase inhibitor; **BID**, twice daily; **CDK4/6**, cyclin-dependent kinase 4 and 6; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **OR**, objective response; **OS**, overall survival; **PFS**, progression-free survival; **Q**, every.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

SP MEDICAL WRITING

CAPItello-291 Eligibility Criteria

Inclusion Criteria

- Premenopausal, perimenopausal, or postmenopausal women or men age ≥18 years (≥20 years in Japan)
- HR+, HER2- locally advanced or metastatic breast cancer
- Disease progression with previous treatment with an aromatase inhibitor, with or without a CDK4/6 inhibitor
- Up to two prior lines of endocrine therapy and one prior line of chemotherapy for advanced disease allowed
- Measurable disease per RECIST v1.1, or at least one lytic or mixed lytic-blastic bone lesion with an identifiable soft-tissue component assessable by CT or MRI
- ECOG performance status 0 or 1 (no deterioration in prior 2 weeks)
- Tumor tissue available for molecular analysis
- Tumors with at least one qualifying alteration in *PIK3CA*, *AKT1*, or *PTEN* genes were included in AKT pathway-altered population

Exclusion Criteria

- Prior treatment with fulvestrant or another selective estrogen-receptor degrader
- Prior treatment with AKT, PI3K, or mTOR inhibitors
- Diabetes mellitus requiring insulin, or baseline HbA1c ≥8.0% (63.9 mmol/mol)

AKT, protein kinase B; **CDK4/6**, cyclin-dependent kinase 4 and 6; **CT**, computed tomography; **ECOG**, Eastern Cooperative Oncology Group; **HbA1c**, hemoglobin A1c; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **MRI**, magnetic resonance imaging; **mTOR**, mammalian target of rapamycin; **PI3K**, phosphatidylinositol-3 kinase; **RECIST**, response evaluation criteria in solid tumors.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

CAPItello-291 Baseline Characteristics

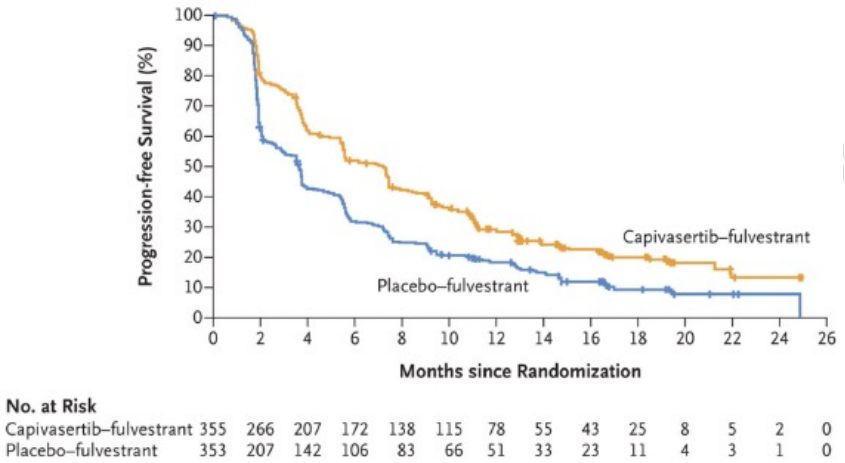
	Overall Population		Patients with AKT Pathway-Altered Tumors	
	Capivasertib + Fulvestrant (n=355)	**Placebo + Fulvestrant (n=353)**	**Capivasertib + Fulvestrant (n=155)**	**Placebo + Fulvestrant (n=134)**
Median Age (range), years	59 (26–84)	58 (26–90)	58 (36–84)	60 (34–90)
Female Sex, n (%)	352 (99.2)	349 (98.9)	153 (98.7)	134 (100)
White Race, n (%)	201 (56.6)	206 (58.4)	75 (48.4)	76 (56.7)
Postmenopausal or Menopausal, n (%)	287 (80.8)	260 (73.7)	130 (83.9)	105 (78.4)
ECOG Performance-Status Score, n (%)				
0	224 (63.1)	241 (68.3)	93 (60.0)	97 (72.4)
1	131 (36.9)	111 (31.4)	62 (40.0)	36 (26.9)
Liver Metastases, n (%)	156 (43.9)	150 (42.5)	70 (45.2)	53 (39.6)
Number Previous Therapies for ABC, n (%)				
0	37 (10.4)	52 (14.7)	12 (7.7)	20 (14.9)
1	235 (66.2)	208 (58.9)	107 (69.0)	79 (59.0)
2	73 (20.6)	77 (21.8)	31 (20.0)	29 (21.6)
3	10 (2.8)	16 (4.5)	5 (3.2)	6 (4.5)
Previous CDK4/6 Inhibitor, n (%)				
As Neoadjuvant or Adjuvant Therapy	2 (0.6)	5 (1.4)	0	2 (1.5)
As Therapy for ABC	245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)

ABC, advanced breast cancer; **AKT**, protein kinase B; **CDK4/6**, cyclin-dependent kinase 4 and 6; **ECOG**, Eastern Cooperative Oncology Group.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

CAPItello-291 Efficacy Results

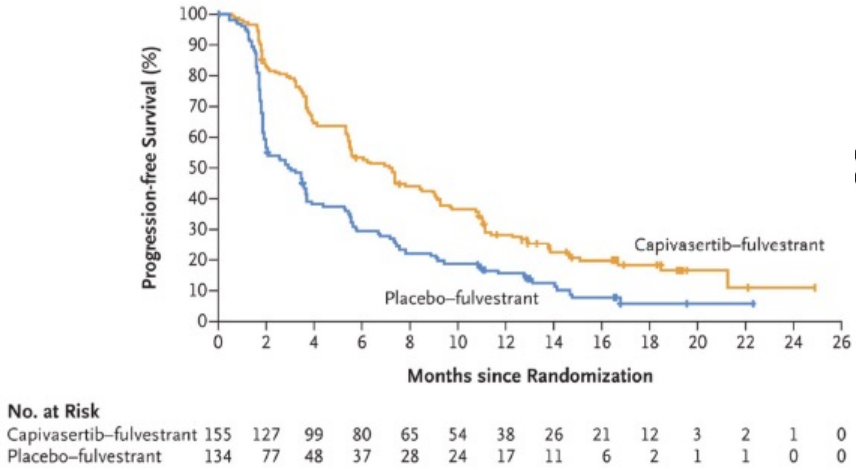
PFS: Overall Population



	# Patients	# Events	Median PFS, months (95% CI)
Capivasertib + Fulvestrant	335	258	7.2 (5.5–7.4)
Placebo + Fulvestrant	353	293	3.6 (2.8–3.7)

Adjusted HR for Disease Progression or Death: 0.60 (95% CI, 0.51–0.71)
P<0.001

PFS: Patients with AKT Pathway-Altered Tumors



	# Patients	# Events	Median PFS, months (95% CI)
Capivasertib + Fulvestrant	155	121	7.3 (5.5–9.0)
Placebo + Fulvestrant	134	115	3.1 (2.0–3.7)

Adjusted HR for Disease Progression or Death: 0.50 (95% CI, 0.38–0.65)
P<0.001

CI, confidence interval; **HR**, hazard ratio; **PFS**, progression-free survival.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

SP MEDICAL WRITING

CAPItello-291 Safety Results (Overall Population)

Most Common AEs of Any Grade

n (%)	Capivasertib + Fulvestrant (n=355)	Placebo + Fulvestrant (n=350)
Diarrhea	257 (72.4)	70 (20.0)
Rash	135 (38.0)	25 (7.1)
Nausea	123 (34.6)	54 (15.4)

Most Common AEs of Grade ≥3

n (%)	Capivasertib + Fulvestrant (n=355)	Placebo + Fulvestrant (n=350)
Rash	43 (12.1)	1 (0.3)
Diarrhea	33 (9.3)	1 (0.3)
Hyperglycemia	7 (2.0)	1 (0.3)
Stomatitis	7 (2.0)	0
Anemia	7 (2.0)	4 (1.1)

Additional AE Data

n (%)	Capivasertib + Fulvestrant (n=355)	Placebo + Fulvestrant (n=350)
Serious AEs	57 (16.1%)	28 (8.0%)
Death due to AEs*	4 (1.1%)	1 (0.003%)
AEs Causing Dose Interruption	124 (34.9%)	36 (10.3%)
AEs Causing Dose Reduction	70 (19.7%)	6 (1.7%)
Discontinuation due to AEs	46 (13.0%)	8 (2.3%)

The safety profile of capivasertib + fulvestrant in the AKT pathway-altered population was similar to that of the overall population.

*None of the deaths were related to capivasertib or fulvestrant, per local investigators.
AE, adverse event; **AKT**, protein kinase B
1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.

Conclusions

- Capivasertib + fulvestrant provided a clinically meaningful and statistically significant improvement in PFS vs fulvestrant alone in the overall and AKT pathway-altered populations
- AEs were consistent with the known safety profile of AKT inhibitors
- The most common AEs in the study were diarrhea and rash, and the rate of discontinuation due to AEs was relatively low (13%)
- The trial included a majority of patients previously treated with CDK4/6 inhibitors (69.1%), addressing a gap in evidence for previous treatment with a CDK4/6 inhibitor
- Randomization was not stratified according to AKT pathway alteration, potentially allowing for the inclusion of patients with more aggressive disease
  - Suggests the trial population was more reflective of a real-world population with clinical heterogeneity
- These results support the consideration of AKT inhibition + ET in patients with HR+, HER2- ABC with disease progression after receiving AI therapy ± CDK4/6 inhibitor

ABC, advanced breast cancer; **AE**, adverse event; **AI**, aromatase inhibitor; **AKT**, protein kinase B; **CDK4/6**, cyclin-dependent kinase 4 and 6; **ET**, endocrine therapy; **HER2**, human epidermal growth factor receptor 2; **HR**, hormone receptor; **PFS**, progression-free survival.

1. Turner NC, et al. *NEJM*. 2023;388(22):2058-2070.