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Adding Capivasertib to Fulvestrant Improves Progression-free Survival in Patients With Advanced Hormone Receptor-positive Breast Cancer

SAN ANTONIO – In patients with hormone receptor (HR)-positive, HER2-negative tumors resistant to aromatase inhibitors, addition of the investigational AKT inhibitor capivasertib to fulvestrant (Faslodex) doubled the median progression-free survival compared with placebo plus fulvestrant in the phase III CAPItello-291 clinical trial, according to results presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

Patients with HR-positive, HER2-negative breast cancer are commonly treated in the first line with an endocrine therapy—such as an aromatase inhibitor, which blocks the production of estrogen—alongside a CDK4/6 inhibitor, which stalls the cell cycle. Eventually, however, most tumors develop resistance to these therapies, and options for further treatment are limited.

“After progression on CDK4/6 inhibitors, further endocrine therapies given alone have relatively low efficacy,” said Nicholas Turner, MD, PhD, a professor of molecular oncology at The Institute of Cancer Research, London, and a consultant medical oncologist at The Royal Marsden NHS Foundation Trust, who presented the study. “We need new treatment options for these patients.”

Many HR-positive, HER2-negative breast cancers also harbor genetic alterations in AKT pathway genes, such as AKT, PIK3CA, and PTEN, which promote tumor growth and have been implicated in the development of endocrine resistance. While the PI3K inhibitor alpelisib (Piqray) was approved by the U.S. Food and Drug Administration (FDA) in 2019 to treat patients with PI3K-mutated breast cancer, more treatments targeting this pathway are needed, said Turner.

Turner and colleagues conducted the phase III CAPItello-291 trial to determine whether the addition of the potential first-in-class AKT inhibitor capivasertib to fulvestrant would improve outcomes in patients with HR-positive breast cancer whose tumors had developed resistance to an aromatase inhibitor. The researchers randomly assigned 355 patients to receive capivasertib plus fulvestrant and 353 patients to receive a placebo plus fulvestrant.

Patients treated with capivasertib plus fulvestrant had a median progression-free survival of 7.2 months, compared to 3.6 months in patients treated with placebo plus fulvestrant. This amounted to a 40 percent lower risk of progression among patients who received capivasertib plus fulvestrant. The objective response rate was 22.9 percent among patients treated with capivasertib plus fulvestrant, compared with 12.2 percent for patients treated with placebo plus fulvestrant.

Overall, 41 percent of patients assigned to treatment had tumors with AKT pathway mutations. Among patients with AKT pathway mutations treated with capivasertib plus fulvestrant, the median progression-

free survival was 7.3 months, and the objective response rate was 28.8 percent. Among patients with AKT pathway mutations treated with placebo plus fulvestrant, the median progression-free survival was 3.1 months, and the objective response rate was 9.7 percent.

The most common adverse events of grade 3 or higher among patients treated with capivasertib plus fulvestrant were rash (12.1 percent), diarrhea (9.3 percent), and hyperglycemia (2.3 percent). The rate of discontinuation due to adverse events was 13 percent among patients who received capivasertib plus fulvestrant and 2.3 percent among patients who received placebo plus fulvestrant. The adverse events profile, Turner said, was manageable and consistent with data from previous studies.

“The improvement in progression-free survival with relatively well-tolerated side effects is extremely encouraging,” Turner said. “We are hopeful that capivasertib will become a new treatment option for patients whose cancer has progressed on a regimen containing an endocrine therapy.”

Limitations of this study include immature overall survival data.

This study was funded by AstraZeneca. Turner has served on the advisory board for AstraZeneca, and his institution has received research funding from AstraZeneca.

Abstract

GS3-04

Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial

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Background: AKT pathway activation has been implicated in the development of endocrine therapy resistance in hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2–) advanced breast cancer (ABC). In the Phase II, placebo (PBO)-controlled FAKTION trial, the addition of the pan-AKT inhibitor capivasertib to fulvestrant significantly improved progression-free survival (PFS) and overall survival in postmenopausal women with aromatase inhibitor (AI)-resistant HR+/HER2– ABC. The Phase III, randomized, double-blind, PBO-controlled CAPItello-291 trial (NCT04305496) investigated the efficacy and safety of capivasertib + fulvestrant in patients with AI-resistant HR+/HER2– ABC.

Methods: Eligible pre/peri or postmenopausal women or men with HR+/HER2– ABC that had recurred or progressed on or after AI therapy with or without a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor were randomized 1:1 to receive fulvestrant (per standard dosing schedule) with either PBO or capivasertib (400 mg twice daily; 4 days on, 3 days off). Randomization was stratified by the presence of liver metastases, prior use of CDK4/6 inhibitors, and geographic location. AKT pathway alteration status (at least one qualifying PIK3CA, AKT1, or PTEN alteration) was determined using next-generation sequencing in tumor tissue. The dual primary endpoint was investigator-assessed PFS in the overall population and in patients with AKT pathway-altered tumors.

Results: A total of 708 patients were randomized: 355 to capivasertib + fulvestrant and 353 to PBO + fulvestrant. Overall, 41% of patients had AKT pathway-altered tumors (48% [n=289/602] of patients with tumor sequencing results), 22% were pre/perimenopausal and 77% postmenopausal, with 1% male. Prior therapy for advanced disease included: 87% of patients with ≥1 line of prior treatment, 69% with a prior CDK4/6 inhibitor, and 18% with prior chemotherapy. Demographic and baseline characteristics were broadly balanced between the overall and altered populations and by treatment groups. At primary analysis (data cut-off Aug 15, 2022), 551 and 236 PFS events had occurred in the overall and pathway-altered populations, respectively. Overall, the median PFS was 7.2 months with capivasertib + fulvestrant

and 3.6 months with PBO + fulvestrant (hazard ratio [HR] 0.60; 95% confidence interval [CI] 0.51–0.71; p<0.001). In patients with AKT pathway-altered tumors, median PFS was 7.3 months with capivasertib + fulvestrant and 3.1 months with PBO + fulvestrant (HR 0.50; 95% CI 0.38–0.65; p<0.001). The objective response rate in patients with measurable disease was 22.9% for capivasertib + fulvestrant vs 12.2% for PBO + fulvestrant overall and 28.8% vs 9.7% in the AKT pathway-altered population. The most frequent all-grade adverse events (AEs) with capivasertib + fulvestrant were diarrhea (72.4% vs 20.0% PBO + fulvestrant arm), rash (group term of rash, rash macular, rash maculo-papular, rash papular, rash pruritic; 38.0% vs 7.1%) and nausea (34.6% vs 15.4%). The most frequently reported grade ≥3 AEs were rash (group term; 12.1% vs 0.3%), diarrhea (9.3% vs 0.3%), and hyperglycemia (2.3% vs 0.3%); grade ≥3 stomatitis was 2.0% vs 0%. AEs leading to discontinuation of capivasertib/placebo were reported in 13.0% and 2.3% of patients, respectively.

Conclusions: Capivasertib + fulvestrant significantly improved PFS compared to fulvestrant alone in the overall population, and in patients with AKT pathway-altered tumors, and may become a future treatment option in this setting. The safety profile of capivasertib + fulvestrant was generally manageable and consistent with prior data.

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