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To interview Mafalda Oliveira, please contact Julia Gunther at julia.gunther@aacr.org or 770-403-7690. For a photo of Oliveira, click here.

Camizestrant May Be Superior to Fulvestrant in Patients With Hormone Receptor-positive, HER2-negative Breast Cancer

SAN ANTONIO – The next-generation selective estrogen receptor degrader (SERD) camizestrant improved progression-free survival, compared with fulvestrant (Faslodex), in patients with hormone receptor-positive, HER2-negative breast cancer in the phase II SERENA-2 trial, according to results presented at the San Antonio Breast Cancer Symposium, held December 6-10, 2022.

Hormone receptor-positive, HER2-negative breast cancer is often treated with drugs that inhibit the activity of the estrogen receptor (ER), which drives the growth of these tumors. Common forms of treatment include selective ER modulators (SERMs), which inhibit ER in breast tissue; aromatase inhibitors, which prevent the production of estrogen; and SERDs, which antagonize and destabilize the ER, leading to its inhibition and degradation.

However, most tumors eventually develop resistance to available endocrine therapies and commonly acquire a mutation in the ER gene, ESR1. SERDs, such as fulvestrant, can block ER activity in such cases.

“These ESR1-mutated tumors have constitutive activation of the ER and worse prognosis, and they are in need of novel therapeutic options,” said Mafalda Oliveira, MD, PhD, an attending physician in the Medical Oncology Department at the Vall d’Hebron University Hospital and in the Breast Cancer Group at the Vall d’Hebron Institute of Oncology in Barcelona, Spain, who presented the study. “Next generation oral SERDs have the potential to shut down the growth signaling derived from a constitutively activated ER, which is especially important in the setting of tumors with ESR1 mutations.”

As fulvestrant is currently the only SERD approved by the U.S. Food and Drug Administration for breast cancer treatment, and it must be given via injection in a physician’s office, researchers are working to develop newer, more accessible, and more effective SERDs. Camizestrant, for example, is taken as a daily pill.

Oliveira and colleagues conducted the phase II SERENA-2 trial to determine whether patients with ER-positive breast cancer would benefit more from camizestrant or fulvestrant. Patients who were previously treated with no more than one prior endocrine therapy regimen and no more than one prior chemotherapy regimen were randomly assigned to receive fulvestrant or one of three dose levels of daily camizestrant: 75 mg, 150 mg, or 300 mg. The 300 mg arm was discontinued early due to strategic reasons, in the absence of toxicity concerns.

The 75 mg camizestrant arm, the 150 mg camizestrant arm, and the fulvestrant arms included 74, 73, and 73 patients, respectively. In the overall population, camizestrant significantly reduced the risk of disease progression or death by 42 percent at 75 mg and 33 percent at 150 mg, compared to fulvestrant. Patients treated with 75 mg of camizestrant and 150 mg of camizestrant had a median progression-free

survival (PFS) of 7.2 months and 7.7 months, respectively, compared with 3.7 months for patients treated with fulvestrant.

Among patients with an ESR1 mutation, camizestrant reduced the risk of disease progression or death by 67 percent at the 75 mg dose (median PFS of 6.3 vs. 2.2 months) and by 45 percent at 150 mg (median PFS of 9.2 vs. 2.2 months). A reduction in the risk of disease progression or death was also observed in patients without a detectable ESR1 mutation, with a 22 percent reduction in risk at the 75 mg dose and a 24 percent reduction in risk at the 150 mg dose.

Camizestrant also demonstrated improved efficacy compared to fulvestrant in other high-risk patient subgroups; those with lung and/or liver metastases experienced a reduction in the risk of disease progression or death of 57 percent for the 75 mg dose and 45 percent for the 150 mg dose, compared to fulvestrant. Patients who had been previously treated with CDK4/6 inhibitor therapy experienced a reduction in the risk of disease progression or death of 51 percent at the 75 mg dose and 32 percent at the 150 mg dose.

Adverse events of grade 3 or higher in the 75 mg/day, 150 mg/day, and fulvestrant arms occurred in 12.2 percent, 21.9 percent, and 13.7 percent of patients, respectively.

Oliveira and colleagues are following up on these data with two phase III clinical trials, both in combination with a CDK4/6 inhibitor—one evaluating the efficacy of camizestrant versus an aromatase inhibitor in first-line therapy, and the other examining the benefit of treatment acceleration to camizestrant when ESR1 mutations are detected in circulating tumor DNA.

“The results of this study support further development of camizestrant in hormone receptor-positive breast cancer,” Oliveira said. “These results are noteworthy and may relaunch the enthusiasm for the development of oral SERDs in breast cancer.”

Limitations of this study include a relatively small sample size characteristic of phase II studies.

This study was funded by AstraZeneca. Oliveira has received personal funding from AstraZeneca, Guardant Health, Roche, Merck Sharp & Dohme, Pfizer, Seagen, iTeos Therapeutics, Eisai, Novartis, Relay Therapeutics, and Gilead.

Abstract

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Camizestrant, a next-generation oral SERD vs fulvestrant in post-menopausal women with advanced ER-positive HER2-negative breast cancer: Results of the randomized, multi-dose Phase 2 SERENA-2 trial

Presenting Author: Mafalda Oliveira, MD, PhD – Vall d’Hebron University Hospital, Vall d’Hebron Institute of Oncology

Background
Camizestrant (C), a next-generation oral selective estrogen receptor (ER) antagonist and degrader (ngSERD) has shown promising clinical activity in ER+ breast cancer (BC) in the Phase 1 SERENA-1 study[1,2] with a dose-dependent safety profile. The Phase 2 randomized SERENA-2 study (NCT04214288) initially assessed three doses of C vs fulvestrant (F) in post-menopausal women with ER+ HER2- BC with disease recurrence or progression after ≤1 endocrine therapy (ET) in the advanced setting.

Methods

SERENA-2 evaluated efficacy and safety of C 75, 150 or 300 mg monotherapy QD vs F (per label). Eligible patients were randomized 1:1:1:1. The Primary objective was to determine clinical efficacy of C vs F by investigator-assessed progression-free survival (PFS). Secondary endpoints included objective

response rate, response duration, clinical benefit rate at 24 weeks, overall survival and safety. Patients had no prior F or oral SERD and ≤1 ET and ≤1 chemotherapy (CTX) in the advanced setting. To assess the impact of prior CDK4/6 inhibitor (CDK4/6i) treatment, randomization was stratified so that 50% of patients had prior CDK4/6i. Planned enrolment of 288 patients began in April 2020. The C 300 arm was closed after 20 patients were enrolled, changing target enrolment to 236. By August 2021, 240 patients had been randomized. Primary analysis was triggered when 108 progression events (75% maturity) had occurred in the best performing pair (C vs F) in August 2022. Efficacy analyses compared C 75 and 150 mg doses with F, with no formal analyses of C 300 vs F. 108 events for pairwise comparison vs F gave 86% power at the 2-sided 10% significance level. Primary analyses used a Cox proportional hazards model to compare PFS, adjusting for prior CDK4/6i and lung/liver metastases. *ESR1* mutations (*ESR1*m*)* were detected in plasma samples using next-generation sequencing.

Results
119/240 (49.6%) patients had had prior CDK4/6i therapy. At baseline, 88 (36.7%) patients had detectable *ESR1*m and 140 (58.3%) had lung/liver metastases. Prior CTX or ET rates in the advanced setting were 19.2 and 65.4%.

	Camizestrant 75 mg	Camizestrant 150 mg	Fulvestrant 500 mg
Overall population (N)	74	73	73
PFS events, n (%)	50 (67.6)	51 (69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7–10.9)	7.7 (5.5–12.9)	3.7 (2.0–6.0)
PFS adjusted HR (90% CI) vs F	0.58 (0.41–0.81)	0.67 (0.48–0.92)	–
2-sided p value vs F	0.0124*	0.0161*	–
*ESR1*m detected subgroup (n) (36.7%)	22	26	35
PFS events, n (%)	15 (68.2)	22 (84.6)	31 (88.6)
Median PFS, months (90% CI)	6.3 (3.4–12.9)	9.2 (3.7–12.9)	2.2 (1.9–3.8)
PFS adjusted HR (90% CI) vs F	0.33 (0.18–0.58)	0.55 (0.33–0.89)	–
*ESR1*m not detected subgroup (n) (63.3%)	51	46	37
PFS events, n (%)	34 (66.7)	28 (60.9)	26 (70.3)
Median PFS, months (90% CI)	7.2 (3.7–10.9)	5.8 (3.8–14.9)	7.2 (2.0–10.7)
PFS adjusted HR (90% CI) vs F	0.78 (0.50–1.22)	0.76 (0.48–1.20)	–
*Statistically significant			

Treatment-emergent adverse events (AEs) (grade ≥3) occurred in 77.0 (12.2), 90.4 (21.9) and 68.5 (13.7) % of patients in the C 75, C 150 and F arms. AEs leading to treatment discontinuation occurred in 2.7, 0 and 0% of patients in the C 75, C 150 and F arms.

The most common AEs considered by the investigator to be causally related to study drug were photopsia (18.4%) and (sinus) bradycardia (13.6%) – all were grade 1 or 2. Hot flush (2.7%) and myalgia (2.7%) were the most common AEs related to F.

Conclusions
SERENA-2 is the first Phase 2 trial investigating multiple dose levels of an ngSERD vs F in post-menopausal women with advanced ER+ HER2- BC with disease recurrence or progression after ≤1 ET in the advanced setting. C at both 75 and 150 mg dose levels showed a statistically significant and clinically

meaningful benefit in PFS vs F in the overall study population, and was well tolerated. The results of SERENA-2 support the further development of C in ER+ HER2- BC.

Acknowledgements
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