



## 33rd Annual San Antonio Breast Cancer Symposium

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### Aromatase Inhibitors as Upfront Endocrine Therapy in Early Breast Cancer

**San Antonio** - Clinical studies have shown that aromatase inhibitors (AIs) have more benefits and fewer serious side effects than tamoxifen for treating early-stage, hormone receptor-positive breast cancer. In the large-scale MA.27 study, the irreversible steroidal AI exemestane and the nonsteroidal AI anastrozole were compared with event-free survival (EFS) as the primary end point. Although the trial fell short of meeting the primary end point of EFS superiority, the results demonstrated the noninferiority of exemestane to anastrozole, suggesting the steroidal AI offers physicians and patients a valuable option for endocrine therapy in breast cancer. Subgroup analyses showed similar results with the 2 agents across a wide range of characteristics. The secondary end points of overall survival, distant disease-free survival and disease-specific survival also did not differ between treatment groups. The size of MA.27 resulted in a large tissue repository and permitted multiple substudies, which should prove useful in moving toward the goal of personalized therapy.

Aromatase inhibitors (AIs) have an established role in adjuvant endocrine therapy for early breast cancer. However, according to Dr. Paul Goss, Massachusetts General Hospital, Harvard Medical School, Boston, structural and molecular differences offer theoretical advantages for the steroidal AI exemestane over the nonsteroidal AI anastrozole. For example, exemestane binds irreversibly to the estrogen receptor, whereas anastrozole is a reversible inhibitor. Moreover, Dr. Goss told SABCS delegates, the steroidal AI “has certain androgenic properties not seen with the nonsteroidal AIs. Together, those 2 factors suggest exemestane might have more potent inhibition of aromatase.”

Preclinical studies have supported this hypothesis. Unlike anastrozole, exemestane inhibits both breast and intra-tumoural aromatase. The mild androgenic activity suggests possible secondary antitumour mechanisms. Additionally, it has more favourable bone and lipid metabolism compared with the nonsteroidal agents, noted Dr. Goss.

#### MA.27 Rationale

The theoretical advantages of exemestane provided a strong rationale for a randomized comparison with anastrozole, culminating in the MA.27 trial co-ordinated by the National Cancer Institute of Canada. Investigators in Canada, the US and Europe enrolled 7576 postmenopausal women with hormone receptor-positive, localized breast cancer. Women with locally advanced or metastatic breast cancer were not eligible. Designed to test the superiority of exemestane over anastrozole, the trial was powered to detect an improvement in 5-year event-free survival (EFS) estimated at 87.5% with anastrozole to 89.9% with exemestane.

Following definitive surgery, patients were randomized to 5 years of adjuvant anastrozole 1 mg/day or exemestane 25 mg/day. The study population had a median age of 64

and 95% were Caucasian. About 70% of patients had breast-conserving surgery and 72% had T1 disease. About a third of the patients had received adjuvant chemotherapy and 4% had received trastuzumab.

#### Consistent Results

After a median follow-up of 4.1 years, patients treated with exemestane had an EFS of 90.8%, compared with 90.9% for patients treated with anastrozole. Subgroup analyses showed similar results regardless of nodal status at enrolment or chemotherapy history. “The survival curves were virtually superimposable,” reported Dr. Goss.

At study end, the comparison between the 2 patient groups yielded an EFS hazard ratio (HR) of 1.02. Node-positive patients, who accounted for 71% of the study population, had an HR of 1.04 compared with 0.99 for node-negative patients. Patients who received adjuvant chemotherapy had an EFS HR of 1.02 compared to 1.01 for those who did not. Overall survival was about 94% in both groups, distant disease-free survival (DFS) was about 96% and disease-specific survival was about 97%.

Both hormonal therapies were well tolerated, but several statistically significant differences emerged from the safety analysis, due in part to the large size of the study. Liver enzyme elevation, acne and androgenic changes occurred in about 1% to 2% of patients in the exemestane arm and were significantly increased compared with anastrozole ( $P=0.04$  to  $P<0.0001$ ).

Hypertriglyceridemia occurred in 2% of exemestane patients vs. 3% of the anastrozole group ( $P=0.002$ ), hypercholesterolemia in 15% vs. 18% of patients, respectively ( $P=0.01$ ) and osteoporosis in 31% vs. 35% ( $P=0.001$ ). As expected, vaginal bleeding and self-reported cases of new osteoporosis diagnosis were less common with the steroidal AI. Cardiovascular events were similar between the 2 arms,

although atrial fibrillation was less common with anastrozole. Treatment adherence was problematic in both treatment groups. At 4 years, 30% to 40% of the patients had discontinued treatment.

“Although the primary end point was not met, we do not see this as a negative trial,” stated Dr. Goss. “We believe the results clearly demonstrated that exemestane is comparable to anastrozole and provides a new option for 5 years of upfront adjuvant therapy for patients with hormone receptor-positive early breast cancer.”

The size of MA.27 resulted in a large tissue repository and permitted multiple substudies, which should prove useful in moving toward the goal of personalized therapy. “I expect that clinicians and scientists will be reading about the MA.27 study for years to come,” concluded Dr. Goss. “The first publications should be coming out soon.”

### Overcoming Resistance to Hormonal Therapy

Another presentation in San Antonio provided details of a randomized clinical trial of the investigational agent AMG 479 (ganitumab), an antagonist of insulin-like growth factor type 1 receptor (IGF-1R). The rationale for clinical development of the agent came from experimental evidence that resistance to hormonal therapy may involve increased or aberrant signalling through the IGF-1R pathway, explained Dr. Peter Kaufman, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

In a preclinical model of estrogen receptor-positive breast cancer, simultaneous inhibition of the estrogen receptor and IGF-1R increased suppression of cell proliferation compared with blocking either pathway alone (Cohen et al. *Clin Cancer Res* 2005;11:2063-73). “Inhibition of the IGF-1R signalling pathway may enhance the activity of second-line hormonal therapy in breast cancer patients,” stated Dr. Kaufman.

To test the theoretical advantages of IGF-1R inhibition, investigators enrolled 156 postmenopausal patients with hormone receptor-positive locally advanced or metastatic breast cancer. The patients were randomized 2:1 to AMG 479 or placebo plus an endocrine therapy of the investigator’s choice (exemestane or fulvestrant). The primary end point was progression-free survival (PFS).

When the trial ended, AMG 479 had failed to demonstrate superiority over placebo. In fact, patients randomized to placebo plus endocrine therapy had a 2-month greater PFS compared with

the AMG 479 group (5.7 vs. 3.9 months, HR 1.17;  $P=0.435$ ). Analysis of the results by type of endocrine therapy showed that exemestane led to a longer duration of PFS when paired with AMG 479 or placebo, 4.8 and 7.3 months, respectively, compared with 3.7 and 5.4 months with fulvestrant.

Patients randomized to AMG 479 had a slightly better clinical benefit rate (complete and partial response plus stable disease), 35% vs. 31% in the placebo arm.

Rates and severity of adverse events were similar between treatment groups. “AMG 479 in combination with fulvestrant or exemestane did not appear to delay or reverse resistance to hormonal therapy in this population of patients with prior endocrine therapy-resistant, hormone receptor-positive metastatic breast cancer,” stated Dr. Kaufman. “PFS was no different for patients receiving AMG 479 vs. placebo. There were no meaningful differences in overall response rate, clinical benefit rate or rate of durable stable disease.”

Patients who progressed on placebo could cross over to AMG 479, he added. Data from the crossover phase have not been analyzed.

### Bone Effects of Endocrine Therapy

Differences in metabolic effects of options for endocrine therapy remain a consideration in choosing an agent. A multinational research group examined the differences in a meta-analysis of 3 randomized substudies of the Tamoxifen Exemestane Adjuvant Multicenter (TEAM) study, the largest phase III trial to compare an AI and tamoxifen in postmenopausal breast cancer patients. The substudies evaluated the effects of the 2 endocrine therapies on bone mineral density (BMD) and markers of bone turnover.

Patients treated with tamoxifen had a 0.2% increase in lumbar BMD from baseline to 24 months compared with a 3.5% decrease in exemestane-treated patients, reported Dr. Payman Hadji, Philipps University, Marburg, Germany, here at the SABCS. The difference was statistically significant ( $P<0.0001$ ). Total hip BMD decreased by 0.4% at 24 months in the tamoxifen group compared with a decrease of 3.3% in the exemestane arm ( $P<0.05$ ).

Markers of bone turnover decreased in the tamoxifen group and increased in the exemestane group. Dr. Hadji noted BMD and markers of bone turnover appeared to undergo adverse changes at the onset of treatment and then stabilize thereafter. □

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