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Addition of Bevacizumab to Conventional Therapy Improved Progression-Free Survival in HER2-Positive Breast Cancer

- Bevacizumab demonstrated benefit as first-line therapy in treating HER2-positive disease.
- AVEREL study is the first randomized trial of bevacizumab in HER2-positive breast cancer.
- Biomarkers are being studied to determine the best use of bevacizumab.

SAN ANTONIO — Data evaluated by an independent review committee revealed that the addition of bevacizumab to trastuzumab and docetaxel significantly improved progression-free survival in HER2-positive breast cancer, despite findings from an investigator assessment that the improvement was present but statistically non-significant.

Luca Gianni, M.D., director of medical oncology at the San Raffaele Cancer Center in Milano, Italy, presented results from AVEREL, a randomized, phase 3 trial, at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011. The trial is designed to evaluate bevacizumab combined with trastuzumab and docetaxel as first-line therapy for HER2-positive, locally recurrent/metastatic breast cancer. The study is the first randomized trial of bevacizumab in this type of breast cancer, according to the researchers.

Patients had measurable or evaluable HER2-positive, locally recurrent/metastatic breast cancer and Eastern Cooperative Oncology Group performance status 0/1 and had not received prior chemotherapy for advanced disease. Patients with central nervous system metastases were excluded.

Researchers enrolled 424 patients from 60 centers during September 2006 to February 2010, with 421 patients receiving treatment. They randomly assigned patients to receive

trastuzumab and docetaxel (n=208) or to receive trastuzumab and docetaxel plus bevacizumab (n=216).

At a median follow-up of 26 months, investigator assessment revealed an 18 percent reduction in risk of progression or death with the addition of bevacizumab compared with that of patients who received only trastuzumab and docetaxel. However, an independent review committee analysis found a 28 percent reduction in risk for progression or death with the addition of bevacizumab. Overall, median progression-free survival increased by 2.8 and 2.9 months with bevacizumab according to investigator analysis and independent review committee analysis, respectively.

Gianni said that because there are effective treatments for women with HER2-positive breast cancer, researchers are now examining the precise role of an anti-angiogenic drug in combination with existing therapy.

“The concept of this trial was a test for the benefit observed in early phase 1 and phase 2,” Gianni said. “In a way, we confirmed that combining an anti-angiogenic and [other treatment] is a good idea. But now, we have to search the subset of women who have the characteristics associated with benefit from addition of an anti-angiogenic. The key element is looking for a restricted indication that might have a longer-lasting effect than we can observe in AVEREL.”

Biomarkers will be important in helping determine the best role for bevacizumab in treating HER2-positive cases, he said.

“The limit in anti-angiogenic therapy is that we treat all participants and we have no hint of what are the tumor characteristics or the patient characteristics that deserve intervention with anti-angiogenic therapy,” Gianni said. “We have started some study investigation of biomarkers, and we hope that the AVEREL results, together with other studies, can help in finding ways of restricting indication of bevacizumab to those who could have the right benefit.”

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 34th annual symposium is expected to draw nearly 8,000 participants from more than 90 countries.

Presenter: Luca Gianni, M.D.

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Title: First results of AVEREL, a randomized phase III trial to evaluate bevacizumab (BEV) in combination with trastuzumab (H) + docetaxel (DOC) as first-line therapy for HER2-positive locally recurrent/metastatic breast cancer (LR/mBC)

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Background: H + taxane is an established and effective first-line treatment for HER2-positive LR/mBC. Preclinical data provide the rationale for combining BEV and H in HER2-positive LR/mBC but clinical data in this setting are limited to single-arm phase II studies. AVEREL is the first randomized trial of BEV in HER2-positive LR/mBC.

Methods: Eligible patients had measurable or evaluable HER2-positive LR/mBC (centrally confirmed IHC 3+ or FISH/CISH +), ECOG performance status 0/1, and had received no prior chemotherapy for advanced disease. Prior adjuvant H/taxanes were permitted unless disease had recurred <6/<12 months after the last dose, respectively. Patients with CNS metastases were excluded. Patients were stratified according to adjuvant H, prior (neo)adjuvant taxane (further stratified by time to relapse since last dose of [neo]adjuvant chemotherapy/no chemotherapy), hormone receptor status, and measurable disease, and were randomized to receive either H (8 mg/kg → 6 mg/kg q3w) + DOC (100 mg/m² q3w) or H + DOC + BEV (15 mg/kg q3w). H and BEV were given until disease progression; DOC was given for a planned minimum of 6 cycles unless progression or unacceptable toxicity mandated earlier discontinuation. The primary endpoint was progression-free survival (PFS). Additional endpoints included overall survival (OS), overall response rate (ORR; assessed by RECIST 1.0), duration of response, time to treatment failure, safety (NCI CTCAE v3.0 adverse events [AEs] and AEs of special interest for BEV), quality of life (FACT-B), and translational research. The primary analysis of PFS was prespecified after 310 investigator-assessed PFS events. The statistical design provided 90% power to detect a PFS hazard ratio (HR) of 0.69 (median PFS 11→16 months) with $\alpha=0.05$.

Results: Between Sep 2006 and Feb 2010, 424 patients were enrolled from 60 centers; 421

received treatment. Baseline characteristics were generally well balanced in the H + DOC and H + DOC + BEV arms: median age 55 and 53 years, respectively; visceral metastases 71% and 77%; prior adjuvant H 12% and 13%; disease-free interval <12 months 43% in both arms; measurable disease 85% in both arms. Median follow-up was 26 months in both arms. Efficacy results are summarized in the table.

Endpoint	H + DOC	H + DOC + BEV
PFS	(n=208)	(n=216)
Investigator assessed		
Events, n (%)	154 (74)	153 (71)
HR, unstratified analysis (95% CI)	0.82 (0.65-1.02)	
p-value ^a	0.0775	
Median, months (95% CI)	13.7 (11.4-16.3)	16.5 (14.1-19.1)
HR, stratified analysis (95% CI)	0.76 (0.60-0.96)	
IRC assessed (stratified, censored for non-protocol therapy)		
Events, n (%)	114 (55)	111 (51)
HR (95% CI)	0.72 (0.54-0.94)	
p-value	0.0162	
Median, months (95% CI)	13.9 (11.2-16.7)	16.8 (14.1-19.5)
ORR	(n=176)	(n=183)
Investigator assessed, %	69.9	74.3
p-value	0.3492	
IRC assessed, %	65.9	76.5
p-value	0.0265	

^aBoundary for significance p=0.0445; IRC = Independent Review Committee

No new safety signals were observed. The following grade ≥ 3 AEs were more common in the BEV-containing arm than the H + DOC arm: congestive heart failure (5.1% vs 2.9%, respectively); febrile neutropenia (11.6% vs 8.7%); hypertension (11.6% vs 0.5%). Grade 5 AEs occurred in 1.4% of the H + DOC + BEV arm vs 1.9% of the H + DOC arm.

Conclusions: The addition of BEV to H + DOC improved PFS without reaching statistical significance according to investigator assessment (unstratified HR 0.82; 95% CI 0.65-1.02). The

improvement as assessed by Independent Review Committee was statistically significant. Evaluation of biomarkers is ongoing to try to identify those patients who may benefit from first-line BEV-containing therapy for HER2-positive LR/mBC.