From the 2011 San Antonio Breast Cancer Symposium

# New therapies, genetic assays translate into early detection of recurrence, encouraging outcomes

*The following reports are based on presentations at the San Antonio Breast Cancer Symposium, held December 6–10, 2011.*

## Bevacizumab improves survival in HER2-positive metastatic disease

KERRI WACHTER

Bevacizumab (Avastin) improved progression-free survival (PFS) when added to standard treatment in a study of more than 400 women with human epidermal growth factor receptor 2 (HER2)–positive locally recurrent or metastatic breast cancer.

That finding, which emerged from the AVEREL trial, adds another wrinkle in the ongoing controversy regarding use of bevacizumab in breast cancer treatment.

For the primary endpoint of investigator-assessed PFS, conducted at a median follow-up of 26 months, the addition of bevacizumab resulted in a hazard ratio (HR) of 0.82 ($P$ = 0.0775), compared with treatment with trastuzumab (Herceptin) and docetaxel alone. This difference was not statistically significant. Median investigator-assessed PFS was 16.5 months with bevacizumab versus 13.7 months without it.

In an assessment by an independent review committee (IRC), however, a significant improvement in PFS was seen with the addition of bevacizumab (hazard ratio, 0.72; P = 0.0162). Median IRC-assessed PFS was 16.8 months with bevacizumab, compared with 13.9 months without the drug.

Lead investigator Dr. Luca Gianni reported the results at the 2011 San Antonio Breast Cancer Symposium. AVEREL is a randomized, placebo-controlled phase III trial designed to evaluate bevacizumab combined with trastuzumab and docetaxel as first-line therapy for HER2-positive, locally recurrent or metastatic breast cancer.

The findings add more data to support the effectiveness of the drug in particular subpopulations of patients with metastatic breast cancer.

In November, the US Food and Drug Administration (FDA) announced it was revoking its approval of the metastatic breast cancer indication for bevacizumab after concluding the drug had not been shown safe and effective for that use (see page 567).

Many in the breast cancer community consider the agency's decision unwarranted. "Bevacizumab improves the response rate—about doubles it—which for my symptomatic patients is a clear benefit," said press conference moderator Dr. Lisa Carey, professor of medicine at the University of North Carolina at Chapel Hill. "It improves the progression-free survival to a greater or lesser degree in every trial in which it's ever been studied."

She conceded that the drug "doesn't do anything to overall survival." The FDA cited the lack of improvement in overall survival for metastatic breast cancer patients in its decision. Dr. Gianni noted, however, that "survival is a very important endpoint, but it's not the only endpoint in metastatic breast cancer."

Patients were eligible for the AVEREL trial if they had measurable or evaluable HER2-positive locally recurrent or metastatic breast cancer with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. They could not have received previous chemotherapy for advanced disease. Patients with central nervous system metastases were excluded.

The researchers enrolled 424 women with previously untreated disease. The women were randomized to receive either trastuzumab plus docetaxel (208 patients) or the same regimen plus bevacizumab (216

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patients). Trastuzumab was given IV with an 8-mg/kg loading dose followed by 6 mg/kg given every 3 weeks. Docetaxel was given IV at a dose of 100 mg/m$^2$ every 3 weeks. Bevacizumab was given IV at a dose of 15 mg/kg every 3 weeks.

Trastuzumab and bevacizumab were given until disease progression. Docetaxel was given for a planned minimum of six cycles or until disease progression or unacceptable toxicity occurred. The primary endpoint was investigator-assessed PFS. Secondary endpoints included overall survival, overall response rate, duration of response, time to treatment failure, safety (including adverse events of special interest for bevacizumab), and quality of life. Exploratory analyses included PFS evaluated by an IRC (to comply with FDA recommendations) and biomarker assessment.

In terms of safety, "there were no new safety signals observed in this patient population with respect to what we really know from other patient populations exposed to Avastin," said Dr. Gianni, director of medical oncology at the San Raffaele Cancer Center in Milan, Italy.

The researchers also conducted an exploratory analyses of plasma vascular endothelial growth factor-alpha (VEGF-A). Their results suggest a potentially predictive effect—greater benefit with high VEGF-A levels—that is consistent with observations in HER2-negative locally recurrent or metastatic breast cancer.

The AVEREL trial was sponsored by Hoffman-La Roche. Dr. Gianni has disclosed that he is a consultant to Roche, Genentech, GlaxoSmith-Kline, Wyeth, Novartis, Eisai, Pfizer, Millennium Takeda, sanofi-aventis, Boehringer Ingelheim, Biogen Idec, AstraZeneca, Genomic Health, and Celgene. Dr. Carey reported that she has no relevant financial relationships to disclose.

# Brachytherapy doubles the risk of breast loss

BRUCE JANCIN

In a large study, accelerated partial-breast brachytherapy, delivered as part of breast-conserving therapy for early-stage breast cancer, was associated with twice the mastectomy rate following standard whole-breast irradiation. Moreover, accelerated partial-breast brachytherapy entailed substantially higher rates of acute and late complications, Dr. Benjamin D. Smith said in a presentation at the symposium.

Dr. Smith and his colleagues reviewed the Medicare claims data for all 130,535 beneficiaries whose early-stage breast cancer was treated with lumpectomy followed by adjuvant irradiation during 2000–2007. The use of accelerated partial-breast brachytherapy in this population increased from less than 1% in 2000 to 13% in 2007.

The incidence of mastectomy during 5 years of follow-up was 4% in 7,291 brachytherapy recipients, compared with 2% after whole-breast irradiation ($P < 0.001$). After adjusting for the brachytherapy recipients' older average age, more comorbid conditions, and lower rate of positive axillary lymph nodes, brachytherapy was associated with a 2.2-fold increased risk of losing the treated breast within 5 years, reported Dr. Smith, a radiation oncologist at The University of Texas MD Anderson Cancer Center, Houston. "After we had adjusted for various clinical and sociodemographic factors, we found that brachytherapy was the variable that had the strongest correlation with the risk of subsequent mastectomy," he noted.

Partial-breast brachytherapy was also associated with significantly higher rates of postoperative wound infection and acute noninfectious complications, as well as increased 5-year rates of fat necrosis and breast pain. Fat necrosis is considered a marker of tissue injury caused by surgery and/or radiotherapy.

Within a year of breast cancer diagnosis, infectious complications involving the breast or surrounding skin or soft tissues occurred in 16% of women treated with brachytherapy, compared with 10% of those who received standard whole-breast irradiation.

Noninfectious complications, including surgical wound breakdown, postoperative bleeding, or seroma formation, were twice as common with brachytherapy than without, 16% and 8%, respectively. The 5-year rate of fat necrosis was also higher with brachytherapy than without it (9% vs 4%, respectively) as was the rate of breast pain (15% vs 12%).

Accelerated partial-breast brachytherapy was developed to address the shortcomings of whole-breast irradiation, the historic standard of care, which entails up to 7 weeks of daily Monday-through-Friday treatment. Whole-breast irradiation is inconvenient. Indeed, it is such a hardship, especially for patients in areas distant from a radiotherapy center, that some women opt for mastectomy as a matter of convenience. Moreover, 15%–30% of women who undergo lumpectomy forgo prescribed radiation therapy, placing themselves at increased risk of local recurrence.

Accelerated partial-breast brachytherapy may improve patient compliance with radiotherapy. It shortens the treatment course to 1 week. It entails temporary placement of radioactive

beads within the breast via a catheter system. This method delivers radiation only to breast tissue immediately adjacent to the lumpectomy. This technique is but one of several forms of partial breast irradiation; however; the new findings do not apply to 3-D external-beam radiation therapy, for example.

Accelerated partial breast brachytherapy has boomed in popularity in recent years, especially in community practice. But these new data may put the brakes on that trend. "This study has changed the way I think about these two different treatment options, and it's changed the way I practice," Dr. Smith said in an interview.

Dr. Jennifer A. Ligibel, who chaired a press conference at which Dr. Smith presented his findings, said the study carries an important message. "Although observational data using a claims database are no substitute for a randomized trial with long-term follow-up, what we see in this study is that this technique was not as effective, and it was also associated with a lot more complications. So if your argument in using this is that it's sparing patients from additional problems, we're not seeing that in this study."

"This study really does give pause to the incorporation of accelerated partial-breast brachytherapy into routine clinical practice. These results should make people wait for the results of the ongoing randomized trials before they offer this as a standard procedure for their patients," added Dr. Ligibel of Dana-Farber Cancer Center, Boston.

The major randomized trial under way is the National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413 study. This trial has enrolled 4,000 of a planned 4,500 patients with early-stage breast cancer. The emphasis is on patients under age 50, because they have a higher local recurrence risk than older women. Participants are randomized to whole-breast irradiation or various forms of partial breast irradiation after lumpectomy. Mature results aren't expected until mid-decade.

Dr. Smith and Dr. Ligibel reported that they had no relevant financial interests to disclose.

# Gene profile identifies early recurrence in ER-positive breast cancer

KERRI WACHTER

An investigational genetic test to identify women who are likely to have early recurrence of estrogen receptor (ER)-positive breast cancer because of treatment failure could also guide physicians in deciding which patients might require agents beyond endocrine therapy to prevent the early onset of distant metastases. "We hope to exploit these molecular differences of early and later recurrences to help us guide novel drug combinations in ER-positive early-stage disease," Dr. Minetta C. Liu said at a press briefing at the symposium.

The 91-gene classifier essentially distinguishes patients who are destined to recur early (within 3 years of diagnosis) from those who will likely recur late (beyond 10 years of diagnosis). "Our work is very much hypothesis-generating," Dr. Lui said. "To be able to identify early and late recurrences at the time of diagnosis would be useful, but we actually need to be able to know what to do about it once we identify it."

Session moderator Dr. Jennifer Ligibel said that being able to do such an analysis would mean that patients who do not have tumors consistent with early relapse would not receive chemotherapy unnecessarily, and that patients whose tumors are consistent with early relapse will receive endocrine therapy beyond the initial 5 years of treatment.

Dr. Liu and his colleagues acquired snap-frozen, pretreatment tumor biopsies collected at the Edinburgh Breakthrough Breast Cancer Research Unit between 1982 and 1990. The samples were from patients with stage I, II, or III ER-positive breast cancer who were starting tamoxifen-alone adjuvant treatment. These patients had to have at least a 10-year follow-up in the absence of distant release.

The researchers performed a histologic review of the samples, and those that contained at least 50% tumor were cleared for RNA extraction for gene-expression profiling. This training dataset included 111 samples, with 57 relapses. Tumors from patients with relapse were subdivided into early recurrence (25 patients) and late recurrence (22 patients). Median follow-up was 13 years.

The researchers then selected a validation dataset from the literature that met certain criteria, such as quality of data and follow-up *(Loi S et al. BMC Genomics 2008;9:239)*. This previously published data set included 255 samples from patients with stage I or II ER-positive breast cancer with tamoxifen-alone adjuvant treatment. Of those, 67 had distant relapse—25 patients had early recurrences and 7 had late recurrences. The median follow-up was 9 years. The researchers

used this training data set to develop a 91-gene classifier that separated those patients who were going to recur early from those who were going to recur late. They optimized the classifier and applied it to a validation data set.

"We had very high accuracy, sensitivity, specificity, positive predictive value, and negative predictive value, but we didn't stop at developing a classifier. We wanted to understand what the genes were trying to tell us within the classifier…a novel computational method allowed us to look at ER network topology and to create a map basically."

The researchers identified several genes that were overexpressed in patients with early recurrences: *CALM1, CALM2, CALM3, SRC, CDK1,* and *MAPK1*. They also identified genes that had increased expression in patients with late recurrences: *ESR1, ESR2, EGFR, BCL2,* and *AR*. "Clearly, there are robust molecular differences between tumors that recur early and those that recur much later, despite adjuvant tamoxifen. Most of the genes in our classifier relate to apoptosis and proliferation," said Dr. Liu, who is associate professor of medicine and oncology and director of translational breast cancer research at Georgetown Lombardi Comprehensive Cancer Center in Washington, DC.

Dr. Liu reported that she has no relevant financial relationships to disclose.

# Zoledronic acid's survival benefit lasts in premenopausal patients

DIANA MAHONEY

Adding zoledronic acid to adjuvant endocrine therapy significantly improves disease-free and overall survival in premenopausal women with endocrine receptor (ER)–positive early-stage breast cancer at 7 years' follow-up, Dr. Michael Gnant reported.

Women in the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-12 trial who were randomized to receive zoledronic acid in addition to ovarian function suppression and endocrine therapy had a 28% reduction in risk of recurrence and 37% reduction in mortality risk at 84 months, compared with women randomized to adjuvant endocrine therapy alone, said Dr. Gnant, professor of surgery at the Medical University of Vienna, Austria.

The findings confirm data previously reported by the ABCSG-12 investigators, which demonstrated disease-free and overall survival benefits associated with the treatment regimen at 48 and 62 months of follow-up *(Gnant M et al. Lancet Oncol 2011;12:631–641)*. "The continued success of this treatment means we can intervene early and still observe persistence of the benefit of treatment," said Dr. Gnant, president of the ABCSG.

The four-arm open-label trial randomly assigned 1,803 women to ovarian suppression and endocrine therapy with or without zoledronic acid for 3 years. Investigators used log-rank tests and Cox models to evaluate disease-free survival and overall survival, Dr. Gnant explained.

All of the patients (mean age, 44.5 years) were premenopausal and had undergone surgery for stage I or II hormone receptor–positive breast cancer. They were treated for 3 years with 3.6 mg of goserelin SC every 28 days and randomized to treatment with 20 mg/d of oral tamoxifen plus placebo, 1 mg/d of oral anastrozole plus placebo, or either of the latter with 4 mg IV zoledronic acid every 6 months.

At a median 84 months' follow-up, the hazard ratios for breast cancer recurrence and death for women receiving adjuvant zoledronic acid were 0.72 and 0.63, respectively, Dr. Gnant reported, noting that the reductions remained significant in univariate and multivariate analyses. Further, in multivariate analysis, "there was no interaction between zoledronic acid and tumor parameters or endocrine therapy," he said. "The hazard ratios were identical for small and large tumors, node-positive and node-negative tumors, and for patients receiving anastrozole and tamoxifen."

There was a strong interaction between zoledronic acid and age in terms of survival benefit, however, with patients older than 40 years experiencing a 34% reduction in recurrence risk and a 44% reduction in mortality, according to Dr. Gnant. No similarly significant survival benefits were observed among patients younger than 40 years, he said.

As expected, patients receiving zoledronic acid experienced more arthralgia, Dr. Gnant stated, "but, importantly, there were no cases of osteonecrosis of the jaw and no renal failure in the treatment population."

The findings, which are consistent with those seen in the postmenopausal cohort of the Adjuvant Zoledronic Acid to Reduce Recurrence (AZURE) trial, "suggest that estrogen deprivation and reduction of bone turnover-derived growth factors

in the bone marrow microenvironment are needed to sufficiently suppress dormant micrometastases," Dr. Gnant explained. Together with the known bone-protective benefits of zoledronic acid, the new data provide sufficient support for adding the bisphosphonate to adjuvant endocrine therapy in premenopausal women with early-stage ER-positive breast cancer, he said.

Dr. James N. Ingle of the Mayo Clinic in Rochester, Minnesota, the discussant for the session, concluded that the ABCSG-12 findings provide level-one evidence for the value of adding zoledronic acid to goserelin and tamoxifen or anastrozole in this patient population. "Zoledronic acid as standard of care [in these patients] will be more widely accepted when the results of the ongoing SOFT [Suppression of Ovarian Function trial] are reported," which will clarify the value of tamoxifen compared with exemestane in conjunction with ovarian suppression, he said.

Dr. Gnant and Dr. Ingle reported that they had no relevant financial disclosures.

# DCIS gene assay predicts recurrence risk after breast surgery

DIANA MAHONEY

A risk score based on a 12-gene assay is expected to help physicians determine whether postsurgical radiation for ductal carcinoma in situ (DCIS) would improve an individual patient's outcome, Dr. Lawrence J. Solin reported at the symposium.

In a biomarker validation study, investigators demonstrated that a prespecified score on the Onco*type* DX DCIS measure developed by Genomic Health can predict the risk of an ipsilateral breast event—either the development of a new invasive breast cancer or the recurrence of DCIS in the same breast—in women who have undergone breast-conservation surgery.

The 12-gene assay is a subset of the Onco*type* DX 21-gene assay for invasive breast cancer. Dr. Solin, chair of radiation oncology at Albert Einstein Medical Center in Philadelphia, and his colleagues in the Eastern Cooperative Oncology Group (ECOG) evaluated the assay's predictive value in 327 patients drawn from the prospective multicenter ECOG E5194 study in which the more extensive assay had been performed, he explained. All of the patients had low- or intermediate-grade DCIS, defined as ≤ 2.5 cm; or high-grade DCIS, defined as ≤ 1 cm, he said *(Hughes LL et al. J Clin Oncol 2009;27:5319–5324)*.

Based on the 21-gene assay, central pathology review, and a recurrence algorithm, the investigators calculated a DCIS score from 0 to 100, with scores < 39, 39–54, and ≥ 55 classified as low, intermediate, and high risk, respectively, for recurrence, Dr. Solin said. During nearly 9 years of follow-up, recurrent DCIS developed in 20 patients and invasive cancer in the ipsilateral breast in 26 patients, he reported. Among patients with low- or intermediate-grade DCIS and high-grade DCIS, the 10-year breast event rates were 15.4% and 15.1%, respectively, and the invasive breast event rates were 5.6% and 9.8%, he reported.

By DCIS score, "75% of the patients were in the low-risk category, compared with 14% classified as intermediate risk and 11% as high risk," said Dr. Solin. The rates of any ipsilateral breast event and invasive breast cancer were directly related to DCIS risk score, with 12.0% of patients in the low-grade DCIS risk score group, 24.5% in the intermediate-grade group, and 27.3% in the high-grade group experiencing any ipsilateral breast event and 5.1%, 8.9%, and 19.1%, respectively, developing invasive breast cancer, he said. In multivariate analysis, DCIS score, menopausal status, and tumor size were all significantly associated with recurrence.

The DCIS score is "groundbreaking," according to Dr. Solin, because it is the first validated molecular marker that clearly differentiates low-risk disease from high-risk disease in DCIS, Dr. Solin stressed. The tool "will help physicians understand the underlying biology of [DCIS] for the individual patient, accurately gauging the risk for that patient and helping guide treatment," he said. Clinical and pathologic factors are not reliable enough on their own to determine whether radiation therapy following breast-conservation surgery will confer any survival benefit, he explained.

In response to questions about the price of the test and insurance coverage, Dr. Solin noted that, in aggregate, the savings associated with avoiding unnecessary additional treatment in patients with a low-risk DCIS score would more than compensate for the price of the test in individual patients.

Dr. Solin reported having no relevant financial disclosures. The study team included employees of Genomic Health.

# Immediate zoledronic acid beats delayed therapy in early-stage breast cancer

DIANA MAHONEY

Immediate treatment with zoledronic acid (Zometa) in postmenopausal women with hormone receptor–positive breast cancer initiating letrozole therapy was associated with a 34% reduction in recurrence risk and 31% improvement in overall survival, compared with women of similar status who received the bisphosphonate later, according to new data from the Zometa-Femara Adjuvant Synergy Trial (ZO-FAST), which assessed the impact of zoledronic acid on aromatase inhibitor–associated bone loss after surgery for early-stage breast cancer.

Additional disease-free and overall survival benefits were observed among the subgroup of patients who had been postmenopausal for at least 5 years, according to Dr. Richard de Boer. The findings update those previously reported by Dr. de Boer of the Royal Melbourne Hospital, Australia, and his colleagues in the ZO-FAST trial, demonstrating that early treatment with zoledronic acid significantly improved bone mineral density and improved breast cancer disease-free survival.

The new, long-term data confirm the overall survival benefits, and the results of an exploratory subgroup analysis based on menopausal status indicates that the addition of zoledronic acid confers the most benefit to women who are truly menopausal at diagnosis, Dr. de Boer reported.

The study involved 1,065 postmenopausal women with hormone receptor–positive early-stage breast cancer with a bone mineral density T score of –2. In addition to receiving adjuvant endocrine therapy with 2.5 mg of letrozole four times daily for 5 years, the women were randomized to receive 4 mg of zoledronic acid every 6 months either immediately or when their post-baseline T score dipped below –2 or they suffered a nontraumatic or asymptomatic fracture. Patients were included in the analysis if they had established menopause at the time of diagnosis or if they became menopausal as a consequence of chemotherapy or ovarian suppression, Dr. de Boer explained.

At 60 months' follow-up, the hazard ratios for recurrence and mortality in the immediate-treatment group were 0.66 and 0.69, respectively, with only the former representing a statistically significant improvement over the delayed-treatment patients, Dr. de Boer reported. Exploratory analyses of the 670 women who were postmenopausal for more than 5 years or older than 60 years at study entry showed that immediate zoledronic acid treatment significantly improved disease-free survival, with a hazard ratio of 0.63, and significantly prolonged overall survival, with a hazard ratio of 0.50, compared with the delayed treatment group.

With respect to bone mineral density in the lumbar spine, "the benefits observed in the immediate therapy group early on, when bone loss is at its greatest, continued out over 5 years, with a net difference of 10% favoring the immediate zoledronic acid [treatment] group," Dr. de Boer said, noting that similar results were observed in total hip bone mineral density, "with an overall change of close to 6% in the immediate group at the 5-year time point."

In a subset analysis comparing the immediate-treatment group with the 27% of patients who initiated zoledronic acid, "we observed a hazard ratio 0.62 for recurrence in favor of the upfront zoledronic acid group," Dr. de Boer said. "Bone was the most common site of recurrence, and this favored the immediate-treatment group, with 14 events, compared with 24 in the delayed-treatment group."

In a comparison of patients who did and did not initiate therapy, "the hazard ratio for disease-free survival was in favor of those who did initiate treatment, suggesting a delay in bisphosphonate initiation could still have an impact on disease outcomes," Dr. de Boer said.

In terms of safety, there were three confirmed cases of osteonecrosis of the jaw in the trial, all in the immediate-treatment group. "This compares favorably with published results of studies in which zoledronic acid was administered on a 6-month schedule," said Dr. de Boer. "The AZURE study had a more intensive administration schedule, and thus had more cases of jaw osteonecrosis."

The findings of this study, together with those of other recent studies including the AZURE trial, "support the hypothesis that the anticancer benefits of zoledronic acid may best be realized in a low-estrogen environment," Dr. de Boer concluded.

The additional anticancer benefit observed in the truly postmenopausal women compared with the recently postmenopausal women in this study warrants additional investigation, according to Dr. James Ingle of the Mayo Clinic in Rochester, Minnesota, the discussant for the session. "The study met its primary analysis endpoint, which was bone mineral density improvement, but it was not powered nor designed to detect a difference in breast events. Although the findings demonstrate the value of zoledronic acid, they are based on an unplanned analysis and thus insufficient on their own to support zoledronic acid as [a] standard of care in postmenopausal women."

Dr. de Boer is on the speakers' bureau for Novartis. Dr. Ingle said he had no financial conflicts to disclose.