"An international scientific symposium for interaction and exchange among basic scientists and clinicians in breast cancer."

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Sunday Morning Year-End Review

This year, SABCS broke with tradition by devoting the Sunday morning session to a report and synthesis of major developments in breast cancer during the past year. Chaired by Kent Osborne, MD, 4 speakers presented expert analysis in the areas of basic science research, translational research, early breast cancer, and metastatic breast cancer. Following are some of the highlights from this exciting session.

Adrian Lee, PhD, from Baylor College of Medicine, presented the review of basic science research, with major advances in 2009 divided into 5 categories:

1. *Hormones and receptors.* The crystal structure of aromatase cytochrome P450 was elucidated, revealing that, unlike the active sites of many microsomal P450s that metabolize drugs and xenobiotics, aromatase has an androgen-specific cleft that snugly binds the substrate, androstenedione. This has implications for monitoring amino acids important to the binding site and for the development of fourth-generation aromatase inhibitors. Estrogen receptor (ER) binding to sites anchored at gene promoters has been found to generate long-range chromatin interactions, suggesting that ER functions by extensive chromatin looping to bring genes together for coordinated transcriptional regulation. This finding should contribute to our understanding of the mechanism of aromatase inhibitor resistance. Progesterone receptor remains understudied, but mechanisms of ligand-independent action are being elucidated.

2. *Genetics and genomics.* How we study genetics will undergo major changes over the next few years because of the availability of next-generation sequencing techniques that are now able to sequence an entire genome in a month. Complete sequencing of a metastatic ER-positive lobular breast cancer has revealed that, of the 32 coding mutations found in the metastatic lesion, 6 were present at lower frequencies in the primary tumor and 19 were not detected. Focal amplification of the insulin receptor is higher in metastatic disease compared with primary tumors, and RNA sequencing detects the appearance of a form normally found only in embryos. MCF-7 cells, which are widely used to study ER in vitro, have been found to contain more than 10,000 genetic aberrations, including promoter translocations, gene truncations, and gene-gene fusions.

3. *The PI3K/PTEN pathway.* This pathway, which appears to be essential for the growth of many cancers, continues to draw attention, with 4 new pathway activators and inhibitors discovered just this year. Understanding redundancy, alternative pathways, and feedback control is critical for successful targeting of the pathway.

4. *Extracellular matrix (ECM).* Increasing evidence underlines the importance of the microenvironment of the ECM in tumor cell development. As a cell differentiates from normal to premalignant to malignant, the ECM stiffens, activating integrin/PI3K. This is associated with cytoskeletal changes contributing to proliferation and invasion. Tumor cell detachment from the ECM alters metabolism and the formation of reactive oxygen species; tumor cells use numerous mechanisms to overcome the loss of ECM attachment.

5. *Cancer stem cells.* This remains one of the most controversial areas in breast cancer biology. There is increasing evidence that the "cell of origin" is critical to breast cancer subtype and progression, and new treatment approaches that target cancer stem cells may be warranted.

Carlos Arteaga, MD, from Vanderbilt University School of Medicine, offered his synthesis of important developments in translational research:

1. *Trastuzumab-DM1.* This conjugate of trastuzumab with a derivative of the anti-microtubule agent maytansine is nontoxic, because the DM1 cannot be cleaved extracellularly. Trastuzumab-DM1, but not trastuzumab, induces apoptosis and cell lysis, and works even in trastuzumab-resistant tumors. A first-line phase 3 trial is planned to start next year that will evaluate trastuzumab-DM1 alone and with paclitaxel compared with trastuzumab plus taxane in HER2-positive metastatic and relapsing locally advanced breast cancer.

2. *Combined antibody strategy in HER2-positive breast cancer.* HER2 is present on the cell surface as heterodimers and homodimers. The homodimers do not activate the PI3K pathway necessary for HER2-induced transformation; high levels of these homodimers correlate with increased clinical benefit from trastuzumab. Heterodimers can be inhibited by pertuzumab and the combination of the 2 antibodies shows enhanced antitumor activity compared with either alone.

3. *Role of PI3K and MEK in basal cell–like triple negative (TN) breast cancer.* PI3K and Ras/MEK/ERK activation are both implicated in TN breast cancer. The combined inhibition of PI3K and MEK has been shown to be effective in all basal-like preclinical breast cancer models. TN represents the best subgroup for initial testing of this combined treatment.

4. *Innovative presurgical and neoadjuvant clinical trials.* Medium-sized neoadjuvant trials with novel drugs are feasible in breast cancer; these can provide decision-making information before proceeding to a phase 3 trial. High-quality biopsies are relatively easy to obtain in close to 100% of patients in this setting. The molecular profiling of tumors in this setting allows for the discovery of biomarkers associated with response that can later be used prospectively for patient selection. Correlative data (eg, Ki67, TUNEL) generated from an intervening biopsy shortly after treatment initiation may correlate with clinical outcome.

5. *Profiling post-neoadjuvant residual cancer.* Not all residual tumors after neoadjuvant chemotherapy are the same with respect to growth markers. In less than pathological complete response tumors, the percentage of Ki67-positive cells may vary from 5% up to 98%. This may reflect the need for 'supra-adjuvant' placebo-controlled trials with targeted therapies in patients with high Ki67 after neoadjuvant chemotherapy.

Ian Smith, MD, from the Royal Marsden Hospital in London, summarized recent results from clinical trials in early breast cancer management:

1. *BIG-198 update.* At a median follow-up of 67 months, this comparison of letrozole and tamoxifen continues to favor letrozole as monotherapy. An important observation about this finding, however, is that 25% of tamoxifen patients crossed over to letrozole in 2005 when the study was unblinded. This presents a statistical problem: analyzing by intent to treat (ITT) will bias in favor of letrozole, while censoring at crossover will be biased in favor of tamoxifen. Dr Smith presented the possibility of using inverse probability of censoring weighted analysis, in which the follow-up for the women who stay on tamoxifen is weighted so that they account not only for themselves but also for the censored follow-up of matched patients who cross over. There is some indication that this would give a better estimate of the true results than using ITT in the presence of selective crossover. In general, current results from the BIG-198 trial show that first-line letrozole is superior to tamoxifen and show a very strong trend towards a survival benefit. There is now strong evidence against any efficacy benefit with a switch policy starting with tamoxifen, compared with an aromatase inhibitor up front.

2. *MA17 update.* A disease-free survival (DFS) benefit of 10% to 11% with extended letrozole therapy was seen in both node-positive and node-negative women who were premenopausal at initial diagnosis. This is a larger effect than that seen in postmenopausal women, but there may be serious quality of life issues in this younger population.

3. *Cognitive function associated with letrozole versus tamoxifen.* The notion that letrozole caused a reduction in cognitive function greater than that seen with tamoxifen was not supported by substudy data from the BIG-198 trial, which showed a trend towards improved cognitive function in patients treated with letrozole compared with tamoxifen.

4. *ABCSG-12.* At 48-month follow-up, this trial of tamoxifen plus goserelin versus anastrozole plus goserelin in patients with premenopausal breast cancer showed no difference in DFS. Patients receiving zoledronic acid to prevent bone loss showed improved DFS.

5. *ZO-FAST.* This trial demonstrated that zoledronic acid improved DFS in postmenopausal breast cancer.

6. *HERA trial 4-year update.* The HERA trial continues to show a benefit in DFS and overall survival (OS) in patients who received 1 year of trastuzumab. However, analysis of results from this trial also suffers from the crossover issue seen in the BIG-198 trial. The crossover effect in these trials is increasingly likely to confound OS analyses in large randomised trials where small but statistically (although not necessarily clinically) significant differences emerge early. New statistical approaches are needed to deal with this.

7. *BCIRG 006.* Results from this trial indicate that a non-anthracycline regimen of docetaxel, carboplatin, and trastuzumab is a reasonable option if cardiotoxicity is an issue.

8. *NCCTG N9831.* A key finding in these late-breaking results is that trastuzumab concurrently with a taxane, rather than sequentially, is not an inferior treatment strategy.

9. *Taxane trials.* Taxanes in addition to anthracyclines are probably not of universal benefit. Evidence suggests little benefit in ER-positive/HER2-negative tumors that also have low Ki67 or are luminal A (which account for a large number of cancers). There is evidence from 1 trial (USO 9375) that short-duration taxanes instead of anthracyclines are more effective, and from another trial (BCIRG 006) that they are not significantly inferior.

10. *CYP2D6.* The CYP2D6 story remains controversial and unproven, both with regards to genotype and SSRI inhibitors. It is preferable to avoid strong CYP2D6 inhibitors (eg, fluoxetine or paroxetine) where alternatives exist. Instead, it is recommended to use another agent (eg, citalopram [weak inhibitor] or venlafaxine [does not inhibit CYP2D6]) when necessary.

11. *Micrometastases and isolated tumor cells.* Evidence from the MIRROR trials indicates a worse prognosis in patients with micrometastases or isolated tumor cells who receive no adjuvant therapy. Such patients should probably be considered for chemotherapy, but not for axillary dissection.

The final presentation of the symposium was given by Clifford Hudis, MD, from Memorial Sloan Kettering, who summarized the year's developments in metastatic breast cancer management. The 3 areas Dr Hudis chose to emphasize all involve targeted therapies:

1. *Anti-HER2 therapy.* There is still no consensus on exactly how trastuzumab works. It is known to be active as a single agent, show a treatment benefit when added to first-line chemotherapy or hormonal therapy, and to be effective after progression on chemotherapy. Lapatinib, also active as a single agent, provides additional benefit when added to trastuzumab. There are multiple new agents in development, including new tyrosine kinase inhibitors, monoclonal antibodies, and Hsp90 inhibitors. In normal cells, Hsp90 is present in a latent state, associated with low-affinity binding. Under stress conditions, it is present in an activated, high-affinity state, in which it helps to hold HER2 at the cell surface. The Hsp90 inhibitor 17-AAG has shown response rates equivalent to pertuzumab, neratinib, and trastuzumab-DM1 after progression on trastuzumab. The growing availability of these targeted agents increases the likelihood that the overall direction of breast cancer treatment will soon be shifted away from chemotherapy.

2. *Bevacizumab.* Bevacizumab added to paclitaxel or docetaxel improves progression-free survival (PFS) in patients with metastatic breast cancer compared with either taxane alone. Several recent trials pairing bevacizumab with different drugs demonstrate that it does not have a specific affinity for certain drugs, but can be effective across multiple drug families. A problematic issue in some of these studies is that, while certain drug combinations may result in a significant improvement in PFS, they do not have an effect on OS. PFS was originally accepted as a surrogate end point for OS in clinical trials so that trial length and cost could be reduced. Over the intervening years, it has come to be accepted as a legitimate end point in its own right, and we are perhaps overdue for a discussion about whether this is appropriate.

3. *Tyrosine kinase inhibitors: Sorafenib.* Several papers were presented at the symposium with results from the phase 2 trials of the Trials to Investigate the Efficacy of Sorafenib in breast cancer (TIES) program (see next article), showing that this multikinase inhibitor is effective when used in combination with a variety of drugs. The main disadvantage of sorafenib is that it is associated with a high incidence of high-grade hand-foot skin reaction (HFSR), which has become a main cause of treatment discontinuation. In order to pursue use of this promising agent, clinicians will need to formulate a good strategy for preventing or managing this adverse event.

4. *PARP inhibitors.* Poly(ADP ribose) polymerase (PARP) is critical for DNA repair in patients with BRCA1-positive breast cancer. For these patients, the normal homologous recombination pathway is not available, and other repair processes, which require PARP, become critical for survival. Olaparib, a PARP inhibitor, has shown a remarkable response rate in patients with BRCA-deficient metastatic breast cancer (22% at 100 mg BID, and 41% at 400 mg BID). Prior therapy did not affect the response. Now in question is whether PARP inhibitors will be effective in other types of breast cancer, or even in other cancers.

Nearly 3000 meeting attendees remained until the end of this exciting and informative session. Dr Osborne remarked that, given a favorable response from attendees, this review session might become a regular feature at SABCS.

New Advances in Targeted Therapy

Targeted therapies for breast cancer are aimed at specific molecules related to cancer cell growth and proliferation. They hold the enticing promise of combining a high degree of efficacy with potentially less toxicity. Four papers presented on Friday afternoon described ongoing studies in the development of 3 targeted therapies: sorafenib, sunitinib, and a gamma-secretase inhibitor (GSI) targeting the Notch pathway.

Sorafenib inhibits multiple kinases involved in tumor growth and angiogenesis. It is currently approved for the treatment of advanced renal cell carcinoma and hepatocellular carcinoma, and has shown modest activity in heavily pretreated metastatic breast cancer. The TIES program consists of 4 phase 2b screening trials in advanced breast cancer using sorafenib in combination with other therapeutic agents. William Gradishar, MD, from Northwestern University in Chicago, presented results from 1 of these trials on Friday afternoon. The study enrolled 220 patients with untreated HER2-negative locally recurrent or metastatic breast cancer, who were randomized to receive sorafenib or placebo in addition to paclitaxel as first-line treatment. For the primary endpoint, PFS, there was a 21% reduction in the risk of disease progression or death associated with the sorafenib arm, although this difference was not significant (HR=0.788, *P*=.0857). In subgroup analysis, the benefit favoring sorafenib was seen regardless of hormone receptor status, presence of visceral disease, country of origin (India vs other), prior chemotherapy, or ITT status. The median time to progression was 8.1 months in the sorafenib arm compared with 5.6 months in the placebo arm, and this difference was significant (HR=0.674, *P*=.017). Both overall response rate and mean duration of response were also significantly higher in the sorafenib arm. Adverse event rates were similar in the 2 treatment arms, except for a higher incidence of HFSR in the sorafenib arm (55% overall, 30% grade 3) compared with the placebo arm (7% overall, 3% grade 3). A higher number of deaths in the sorafenib arm was partially attributable to unusual causes (eg, tuberculosis, meningitis); most were considered to be unrelated to treatment.

A second paper investigating sorafenib, the SOLTI-0701 trial, was presented by José Baselga, MD, from Vall d'Hebron University Hospital in Barcelona. This phase 2b study evaluated the efficacy and safety of sorafenib or placebo plus capecitabine in patients with locally advanced or metastatic breast cancer who had been treated with either 0 or 1 previous chemotherapy regimens. As in the prior study, the primary adverse event was HFSR, which showed a higher incidence in the sorafenib arm (89% overall, 45% grade 3) compared with the capecitabine arm (63% overall, 13% grade 3). This was the most common adverse event related to treatment discontinuation in both study arms. Patients in the sorafenib arm showed a 42% improvement in time to disease progression or death compared with the placebo arm (6.4 versus 4.1 months, respectively; HR=0.576, *P*=.0006). There was no significant difference in overall response rate between the 2 study arms. A pre-specified subgroup analysis demonstrated that the PFS advantage seen in the sorafenib arm was not affected by age, hormone receptor status, visceral disease, measurable disease, or ITT status. A sorafenib benefit was also seen across different treatment variables (line of treatment, prior use of taxanes, prior use of anthracyclines), although there was a slightly reduced benefit associated with second-line versus first-line treatment (50% vs 35% reduction, respectively). The benefit in the sorafenib arm was also seen in exploratory subgroup analyses. These pre-specified and exploratory subgroup analyses confirm the robustness of the PFS benefit associated with sorafenib. In response to an audience question, Dr Baselga noted that the majority of patients (90%) required sorafenib dose reduction.

Sunitinib is similar to sorafenib in inhibiting multiple kinases associated with cell growth and proliferation, and has shown single-agent activity in heavily pretreated patients with metastatic breast cancer. Carlos Barrios, MD, from the PUCRS School of Medicine in Brazil, presented results of a phase 3, open-label study comparing sunitinib to capecitabine in patients with previously treated HER2-negative advanced breast cancer. The PFS seen in the sunitinib arm was significantly inferior to that observed with capecitabine (2.8 months vs 4.2 months, HR=1.47, *P*=.002). The clinical benefit rate was significantly lower with sunitinib compared with capecitabine (19.3% vs 27%, OR=0.65, *P*=.05). There was no difference in OS between the 2 treatment arms at 25 months. All-cause grade 3/4 adverse events occurring in ≥5% of patients in the sunitinib arm were (in order of frequency) neutropenia, HFSR, thrombocytopenia, fatigue, and diarrhea. In the capecitabine arm, the only grade 3/4 adverse events occurring in ≥5% of patients were HFSR and diarrhea. Dr Barrios noted that HER2 negativity may not be the ideal marker to select patients for antiangiogenic therapy.

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Contributing Faculty Editor:
Gary C. Chamness, PhD

The 2009 San Antonio Breast Cancer Symposium (SABCS) *is presented by the CTRC, AACR, and the Baylor College of Medicine. The driving force behind this collaboration is the shared mission of the organizations to advance progress against breast cancer. By combining their respective strengths, the San Antonio Breast Cancer Symposium encompasses the full spectrum of breast cancer research and facilitates the rapid transition of new knowledge into improved care for breast cancer patients.*

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The cancer stem cell (CSC) hypothesis suggests that standard therapies may eliminate the majority of the cells in a tumor, but leave more resistant CSCs that can re-grow. On the other hand, CSC-specific treatments may not cause a significant reduction in tumor volume. Thus, combination therapies are most likely needed to completely eradicate a malignancy. CSCs may also be intrinsically resistant to conventional chemotherapy, requiring novel drugs to selectively target them. Jenny Chang, MD, from Baylor College of Medicine, presented the results of preclinical and clinical studies from her group examining the effectiveness of a GSI targeting the Notch pathway in eliminating this unique population of tumorigenic cells. The study used a population of $CD44^+/CD24^-$ cells derived from a malignant pleural effusion; these cells were found to generate new tumors when transplanted into immunocompromised mice. When grown in suspension in non-adherent conditions, the cells are able to generate primary mammospheres that can self-renew. An analysis of 35 patients showed that the frequency of $CD44^+/CD24^-$ cells increased after chemotherapy, and that the ability of these cells to form tumors in immunocompromised mice also increased. Because Notch pathway molecules were found to be upregulated in these cells, a GSI targeting this pathway was chosen as a candidate drug. In vitro tests showed that the GSI was able to significantly reduce the ability of the cells to form primary mammospheres, and to eliminate their ability to form secondary mammospheres. In vivo tests with a xenograft model showed that the GSI did not alter tumor volume, but was able to inhibit mammosphere formation when the cells were removed and tested in vitro. In a clinical trial with the GSI and docetaxel, biopsy samples taken before, during, and after treatment showed that the number of CSCs had been significantly reduced by the end of treatment. The ability of the cells to form primary mammospheres had also been reduced. These preclinical and clinical data provide evidence for a subpopulation of chemotherapy-resistant cells that can be effectively targeted with a GSI.

Created by:
M2 Communications, Inc.
10524 Moss Park Road
Suite 204-310
Orlando, FL 32832