

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



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Newsletter 5

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Sunday Morning Year in Review

On Sunday morning, SABCS Director C. Kent Osborne, MD, of Baylor College of Medicine, Houston, Texas, moderated the final session, featuring a report and synthesis of major developments in breast cancer research during 2010. Four speakers presented expert analysis in the areas of basic research, translational research, treatment of early breast cancer, and progress in advanced breast cancer. The following are highlights from this thought-provoking session.

Suzanne A.W. Fuqua, PhD, of Baylor College of Medicine in Houston, presented the review of basic breast cancer research. Dr Fuqua divided the year's highlights into 5 subject areas:

Metastasis. Several avenues of research in this area were of note. Circos plot analysis comparing primary tumors with their metastases and xenografts shows that, (a) there is considerable heterogeneity in the primary tumor; (b) new mutations occur in metastasis; and (c) the xenograft shares a mutation spectrum with the metastasis, rather than the primary tumor. This suggests that cellular selection during xenograft formation is similar to that during metastasis, and that xenografts may be valuable in vivo models for studying metastasis. Seeding experiments have shown that tumor self-seeding occurs via aggressive circulating tumor cells (CTCs). Tumor-derived cytokines (IL-6 and -8) act as CTC attractants, and self-seeding can affect tumor size, vascularization, prognosis, and local recurrence.

Genomics. The good news from genomic studies is that different tumor types (HER2-positive, estrogen receptor [ER]-positive, triple negative) share some hot spots for mutations and that these mutations are relatively common and susceptible to drug therapy. The bad news is that many additional mutations appear to be specific to tumor type, and are much less common. An unexpected discovery was that *BRCA1*, basal-like tumors originate from luminal progenitors, rather than from basal stem cells. This suggests plasticity in stem and progenitor cells, so that tumor phenotype may not always equal cell of origin.

Breast cancer stem cells. As discussed this year at SABCS, breast cancer stem cells appear to be ER-negative, even when the primary tumor is ER-positive. The working hypothesis is that mature hormone receptor (HR)-positive ductal cells generate paracrine signals in response to hormone exposure that affect replicative ability in breast stem cells.

Early events in transformation. The RANK ligand (RANKL) is drawing increasing attention for its role in breast tumorigenesis. Several papers published this year have highlighted the role of RANKL in progesterin-induced mammary proliferation and carcinogenesis. The clinical implication of this work is that inhibitors of RANKL may function as cancer preventive agents.

Treatment resistance. Akt (protein kinase B), a serine/threonine kinase, is a critical enzyme in several signal transduction pathways involved in cell proliferation, apoptosis, and angiogenesis. Recent studies have now demonstrated that Akt inhibitors can sensitize cells to radiotherapy, so that pretreatment with these agents can increase treatment efficacy.

Mitchell Dowsett, MD, PhD, of the Royal Marsden Hospital, London, synthesized the current picture in translational breast cancer research:

The cutting edge: (pharmaco)genetics. Next-generation sequencing is poised to offer total genomic sequencing for \$1000, but because of the volume of data generated and difficulties in analysis and storage, this remains a discovery tool, rather than an option for patient management. In genome-wide association studies, new breast cancer susceptibility genes continue to be identified, but we are only beginning to understand how these genes interrelate. For example, it has recently been discovered that the expression of the 3 genes immediately upstream of *ESR1* on chromosome 6 correlate very highly with *ESR1* expression. At present, the inclusion of these high-risk susceptibility genes into existing breast cancer risk models has resulted in only modest improvements in predictive ability.

Improving standards and understanding impact of heterogeneity. There is keen interest in finding new biomarkers for prognosis and prediction of treatment efficacy. Intratumoral and primary-metastasis heterogeneity of marker expression makes this a challenge, especially if biomarkers are to be used to understand and predict response in metastatic disease or benefit from adjuvant treatment. Changes in biomarker measurement between primary tumor and metastasis may result from limited assay accuracy and reproducibility, from sampling error, or from a genuine switch in biology.

Molecular profiling. The original molecular subtyping, published in 2000, divided breast cancer into subtypes using DNA microarrays containing over 8000 genes. Researchers continue to seek ways to subdivide breast cancer into clinically meaningful subgroups based on smaller numbers of genes. The PAM 50 assay can reproduce the intrinsic subtypes from the original assay based on only 50 genes, and has been shown to provide more prognostic information than clinical factors. An assay based on 167 genes associated with ER status has been shown to predict sensitivity to tamoxifen therapy. One group has attempted with some success to replicate the original molecular subtyping using ER, progesterone receptor, and HER2 identified immunohistochemically. Immune/inflammatory signatures are also being explored for their potential in prognosis and prediction, but these signatures are extremely complex, and likely to be different in different contexts.

Circulating tumor cells. CTCs continue to be of great interest because of their potential as prognostic indicators, as tools to monitor treatment response, and as a medium for assessing biomarkers in patients with metastatic breast cancer. At this meeting, CTCs were also shown to be of potential use in assessing prognosis in patients with primary breast cancer.

Body mass index. The role of BMI in breast cancer risk, prognosis, and treatment efficacy continues to be a subject of much debate. Several papers presented at SABCs provided new information about this issue. For example, BMI does not appear to be predictive of benefit from taxane or anthracycline-based therapy. This area remains somewhat of a puzzle, but an important one. It will be disappointing if the increasing incidence of obesity dilutes improvements in breast cancer outcome from new treatments and better targeting.

Alan Coates, MD, of the University of Sydney, Australia, spoke about the year's progress in understanding and managing early breast cancer.

Epidemiology and screening. Some years ago, the report of increased incidence of breast cancer among women taking combined estrogen-progestin hormone therapy (HT) caused considerable concern and a major reduction in its use. Some later reports, however, suggested that the excess cancers were less aggressive. In the trial of estrogen alone after hysterectomy, no major effects were observed: indeed, the incidence of breast cancer was numerically reduced. For combined estrogen and progestin, however, new data from the Women's Health Initiative trial may raise the level of concern—it confirms that the incidence of breast cancer was significantly, if modestly, increased by combined HT use, but mortality was nearly doubled. Regarding screening, a large study out of Norway revealed that among women who were not screened for breast cancer, there was an 18% reduction in the rate of death from breast cancer, compared with the preceding 10-year period. This improvement reflects better care, but not better screening. Among women who were screened, there was a 28% reduction in mortality from breast cancer during the same period. Thus, the reduction in mortality that was related to actual screening program was 10%, or about one-third of the total mortality reduction.

Surgery. Results from the NSABP B-32 trial showed no clinical benefit in proceeding with a complete axillary lymph node dissection in patients who were sentinel node-negative. Standard of care in most countries now suggests that axillary dissection is not indicated after negative sentinel node biopsy.

Radiation therapy. The TARGIT-A trial demonstrated that intraoperative radiotherapy appeared safe and effective with no evidence of inferiority to conventional external beam therapy. A poster shown at SABCS by Dr Roland Reitsamer and colleagues from Salzburg, Austria, reported that intraoperative electron therapy as a boost was superior to conventional external boost.

Adjuvant systemic therapies. Updated results from the NSABP B-30 trial showed a superior outcome for sequential use of docetaxel after doxorubicin + cyclophosphamide. In addition, results indicated that chemotherapy-induced amenorrhea was associated with improved survival, regardless of treatment and ER status. This finding was of special interest because the benefit was seen in both ER-positive and ER-negative subgroups. Ovarian suppression has value in the treatment of breast cancer, but the effect was thought to be restricted to ER-positive disease. Two trials reported at SABCS examined the addition of capecitabine to standard chemotherapy. Neither trial provided definitive evidence of a benefit from capecitabine, but both noted a greater benefit with capecitabine in high-risk subsets: for example, those with 4 or more involved nodes, high Ki67, or (in FinXX) triple-negative disease. Results from the NCIC-CTG MA.27 trial showed no event-free survival difference in exemestane versus anastrozole for up-front adjuvant endocrine therapy.

Update from the Early Breast Cancer Trialists' Collaborative Group. At a September 2010 meeting, the group reported that there was a clear relationship between measured ER level and the efficacy of adjuvant tamoxifen. This is important not because it is surprising, but because it reassures us that whatever noise is present in the ER levels, there is also a biological signal. Another interesting finding from this meeting was that the benefit of adding an anthracycline to CMF (cyclophosphamide, methotrexate, fluorouracil) chemotherapy was confined to the early part of follow-up. There is no benefit in years 2 through 9, and by year 10 the benefit appears to be for CMF alone (although the patient numbers are much smaller for this subgroup).

Lisa A. Carey, MD, University of North Carolina, Chapel Hill, provided a synthesis of progress in advanced breast cancer.

Does cancer change with time? This question has many implications for breast cancer treatment. In 4 important studies published this year examining changes in ER and HER2, there was a small but real change in the frequency of markers. Re-biopsying at the time of relapse is important to confirm the presence of metastatic disease, while re-phenotyping at that time may also provide important information to guide treatment. The number of identified breast cancer subtypes is growing all the time, and the number of potential treatments has increased exponentially.

The nature of metastatic disease. An important concept in metastatic disease is that all treatment is palliative. Although survival rates have increased significantly over the last 30 years, the main goals of treatment are to retain control of the disease and its symptoms, while maintaining quality of life.

Metastatic sites. Breast cancer tropisms differ by subtype; bone metastases are more dominant in HR-positive disease, while visceral and central nervous system metastases are more common in HR-negative disease. Bone metastases are the most common, with several agents now available for treatment. Bisphosphonates have multiple actions: they lessen bone degradation through osteoclast inhibition, and also appear to have anti-VEGF and antiproliferative activities. Denosumab is a novel RANKL-targeted monoclonal antibody that provides osteoclast inhibition and may also be associated with decreased migration. In a head-to-head comparison of denosumab versus zoledronic acid in patients with advanced breast cancer, bone metastases, and no prior bisphosphonate treatment, denosumab resulted in a significantly increased time until first on-study skeletal-related event. There was no difference between treatment groups in progression-free or overall survival (PFS, OS). Of special note, the incidence of adverse events with denosumab was substantially lower than with zoledronic acid.

Targeting HER2. Trastuzumab-DM1 is essentially a Trojan horse molecule, designed to carry a toxic anti-microtubule agent directly into HER2-positive cancer cells before releasing the toxic activity. This extremely localized therapy would be anticipated to have few systemic side effects because of the degree of specificity, but is it as efficacious as systemic therapy delivered by a standard route? A clinical trial to address this question compared trastuzumab-DM1 with trastuzumab-docetaxel for the treatment of patients with HER2-positive, recurrent, locally advanced or metastatic breast cancer. There was no difference between the 2 treatment arms in objective response or clinical benefit, but there were many more grade 3/4 adverse events in the trastuzumab-docetaxel arm compared with the trastuzumab-DM1 arm (75% vs 37.3%, respectively), chiefly involving alopecia, neutropenia, and diarrhea.

Anti-angiogenic therapies. Sunitinib is a small molecule tyrosine kinase inhibitor that targets VEGFRs, PDGFRs, c-Kit, RET, and Flt3. It has shown efficacy in renal cell carcinoma, gastrointestinal stromal tumors, and in phase 2 studies in breast cancer. Several phase 3 trials were reported in 2010 in which sunitinib was added to capecitabine (SUN 1099) or docetaxel (SUN 1064). There was no significant difference in PFS between treatment arms in either trial. In comparison, summary results from 3 trials using bevacizumab for first-line therapy showed significantly improved PFS in all studies. However, a pooled analysis of the same trials showed no difference in OS as a function of bevacizumab treatment.

Targeting microtubules. Some of the oldest drugs in the cancer armamentarium, the vinca alkaloids, produce their anticancer effect by targeting microtubules within the cells. The taxanes, epothilone B analogues (eg, ixabepilone), and maytansine analogues (eg, trastuzumab-DM1) also belong to this class of drugs. The newest anti-microtubule drug to be tested in breast cancer is eribulin, a halichondrin analogue derived from sea sponges. In a phase 3 trial involving patients with heavily pretreated locally recurrent or metastatic breast cancer, eribulin was compared with a treatment of the physician's choice (TPC; any cancer-approved monotherapy or supportive care). There was a significant benefit in overall survival in the eribulin arm compared with the TPC (13.7 months vs 10.7 months, $P=.041$), but it should be noted that this was an unusual trial design, and it is not clear whether eribulin would have performed as well compared with a protocol-designated treatment regimen.

PARP inhibitors. PARP inhibitors alone appear to work in *BRCA1/2*-associated cancer. A phase 2 study using the PARP inhibitor iniparib added to chemotherapy for the treatment of patients with triple-negative breast cancer showed increased PFS and OS, with exceptionally low toxicity. Results from a phase 3 trial of this drug are expected in early 2011. Other PARP inhibitors have not yet shown similar effects in triple-negative breast cancer.


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