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

SAN ANTONIO BREAST CANCER SYMPOSIUM®

UT Medicine CTRC Health Science Center San Antonio | AACR American Association for Cancer Research | Baylor College of Medicine

Newsletter 2014

ISSUE 5

Advances in Basic Research

There was a tremendous amount of new developments in basic breast cancer research during the past year. On Saturday morning, Dr. Charlotte Kuperwasser focused on research contributions from 2014 in three important areas: stem cell biology, clonal analysis, and novel therapeutic agents.

She began with an important finding from Jane Visvader's group that used a novel technique to show the existence of multipotent and bipotent stem cells in the adult mammary gland. By examining mouse tissues in situ with high-resolution microscopy in combination with lineage tracing, they were able to confirm that basal cells contain clones that are able to give rise to both myoepithelial and luminal epithelial lineages in the physiologic condition of aging. She pointed out that work from other labs "suggests that unipotent stem cells probably are the ones that contribute the most to tissue homeostasis but that bipotent stem cells exist and can contribute to both lineages."

She also presented information from Martin Hirst and his group that used cellular barcoding to clonally identify cells and examine progeny of those cells with high throughput sequencing, and showed data that suggests Slug is required for unlocking the activities of stem cells required for tissue homeostasis, transplantation, and tumor initiation.

Switching gears to clonal heterogeneity, Dr. Kuperwasser presented an interesting paper by Kornelia Polyak's group, which provided compelling evidence about the idea that different clones in a tumor provide non-cell-autonomous driving mechanisms to support tumor clonality and tumor growth. "The data really highlights the idea that you have multiple clones in a tumor, and that these clones actually cooperate and talk with one another to promote micro environmental changes that are sustained for tumor growth and progression," Dr. Kuperwasser said. These studies suggest that there might not be one dominant clone taking over a tumor, though dominant clones could interfere with tumor expansion and lead to tumor collapse.

These concepts in tumor invasion were further explored. Dr. Kuperwasser presented data from other studies suggesting that heterotypic interactions between different cancer cell clones and different cancer cell populations in the primary tumor play an important role in tumor invasion. Tumor invasion "requires this phenotypic conversion of single cells at the leading edge of tumors such that there's a collective migration of cells into the tumor stromal border as opposed to a single-cell migration," Dr. Kuperwasser said.

In the past year, researchers have focused on alternative vulnerabilities in cancer cells that could be exploited for therapeutic targets, such as endoplasmic reticulum (ER) stress induction and ER membrane kinase PERK inhibition. Dr. Kuperwasser discussed investigations by Piyush Gupta's group that could lead to a novel therapeutic target. They showed that epithelial-to-mesenchymal transition (EMT)

Issue at a GLANCE

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sensitizes cells to ER stress, which is likely due to increased extracellular matrix synthesis. Further, they showed that EMT constitutively activates the PERK branch of ER stress signaling. The finding that PERK causes multidrug resistance through Nrf2 suggests that, PERK inhibition may be a new, targeted route to therapy.

Update on Translational Research

Dr. Jorge Reis-Filho began his Year in Review of translational research with new findings in genomics and genetics.

He first discussed research conducted by Antonis Antoniou on the PALB2 gene, a gene which interacts with BRCA2. Heterozygous germline mutations of PALB2 are associated with increased risk for breast cancer (BC), male BC, ovarian cancer, and pancreatic cancer. PALB2 mutations may even confer similar risk to that from BRCA2 mutations, and account for approximately 2.4% of BC familial aggregation. They are also associated with sensitivity to platinum salts and PARP inhibitors.

Because of these findings, it has been suggested that PALB2 should be added to genetic testing for BRCA1 and BRCA2 on a multigene panel. Dr. Reis-Filho pointed out there are some issues to address, such as risk for other cancers, such as male BC, and identifying prevalence of PALB2 loss-of-function mutations in different populations.

"Intra-tumor genetic heterogeneity is a common phenomenon," Dr. Reis-Filho said. Mutational heterogeneity in terms of point mutations is a gradual process that occurs as cancer cells evolve. He acknowledged that copy number alterations usually occur in "punctuated bursts" of evolution. Therefore, minor subclones within a tumor may have functional significance, but it may be very difficult to identify them.

The talk was finalized by touching on tumor-infiltrating lymphocytes (TILs). Dr. Reis-Filho presented data (Adams et al) that demonstrated stromal TILs may be a prognostic indicator of outcomes of patients with triple-negative BC who were treated with chemotherapy. He concluded by pointing out the challenges of the need for standardizing the methodology used for evaluating TILs, and the need for further validation of TILs as a prognostic or predictive marker in HER2-positive disease.

Adjuvant and Neoadjuvant Therapy in Early-Stage Breast Cancer

High-quality, multidisciplinary care including the widespread use of adjuvant therapy for BC has lowered risk for recurrence. Dr. Harold Burstein opened his Year in Review talk with data (Cossetti RJj et al) showing that risk for recurrence for all major types of BC tumors has improved by more than 50% in the past 20 years.

"In addition, we are seeing extraordinary outcomes in select subgroups of patients," he said. A study of women with HER2+ disease who received paclitaxel and trastuzumab showed disease-free survival of greater than 98% (Tolaney S et al).

Dr. Burstein proposed that treatment of women at lower-risk is often surrounded by management-type challenges, such as careful use of radiology and pathology to guide treatment selection, minimizing side effects, and using less toxic therapy. But in the treatment of higher-risk women, the challenges lie around innovation, such as advances in understanding tumor biology better, understanding patient subsets, and therapeutic innovations.

One such innovation that surfaced in the past year included the definition of adequate surgical margins. A new guideline was established, and according to the Society of Surgical Oncology, the use of no ink on a tumor should be the standard as an adequate margin for invasive cancer in the era of multidisciplinary therapy because of the low rates of in-breast tumor recurrence and the potential to reduce the rates of re-excision, improve cosmetic outcomes, and decrease health care costs. Dr. Burstein pointed out that this may not apply to all women with BC diagnoses, such as women with ductal carcinoma in situ or extensive intraductal component.

"We've done a fantastic job of simplifying what our adjuvant chemotherapy regimen should be," he said. He summarized recent studies that concluded there is no role for 5-FU or capecitabine, and that there is no data that show 6 cycles of any regimen are more effective than 4. He added, "It looks to me that dose-dense AC followed by T is the winner."

Moving on, Dr. Burstein said, "I think you should absolutely be thinking about ovarian suppression." Drawing on findings from the SOFT and TEXT trials, Dr. Burstein said ovarian suppression should be considered for women with stage II or III cancer at higher risk for recurrence, with intermediate- to high-grade tumors, especially if they are younger than 35 years of age. But for slightly older women, where the role of chemotherapy is more marginal or where the women might become menopausal on chemotherapy, ovarian suppression should be carefully discussed. Women with lower risk tumors (typically stage I), who are older, would likely not benefit from chemotherapy or ovarian suppression.

Then Dr. Burstein raised the question of whether improving pathologic complete response (pCR) improves breast cancer outcomes. A meta-analysis from Patricia Cortazar showed no specific relationship between the odds ratio for pCR and the hazard ratio for event-free survival. Dr. Burstein commented that the model may work for "rather extraordinary drugs" or drugs with remarkable activity as targeted therapy, but it appears difficult to use this model for drug discovery with "ordinary drugs."

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Update in Metastatic Disease

Dr. William Gradishar discussed highlights and new developments in bevacizumab use, trastuzumab resistance, endocrine therapy, and platinum activity in triple-negative breast cancer.

Despite findings of recent bevacizumab trials, such as IMELDA and TANIA, Dr. Gradishar expressed that use of the agent was unlikely to change in the near future. In IMELDA, patients who received bevacizumab and capecitabine were shown to have a significant improvement in progression-free survival (PFS), or about a 7-month advantage, compared to bevacizumab alone. The study also suggested that there was an enhancement in overall survival. But Dr. Gradishar cautioned that before strategies using bevacizumab change, important questions about survival advantage, costs, and potential adverse events remain to be answered.

Dr. Gradishar also expressed that drugs aimed to overcome trastuzumab resistance, such as mTOR inhibitors, are likely to offer only an incremental improvement at this time, “unless we can tease out specific subsets.”

Among new endocrine agents, palbociclib appears promising for treating patients with estrogen receptor-positive (ER+) BC. Palbociclib is an oral, highly selective inhibitor of CDK4/6 kinase activity, which was shown to double PFS, compared to single-agent endocrine therapy — palbociclib plus the endocrine agent letrozole was shown to result in PFS of about 20 months, vs 10 months for letrozole alone. However, Dr. Gradishar pointed out, “There’s no evidence that translates into improvement in overall survival.”

PI3K mutations appear more common in ER+ BC, compared to other types, such as those in HER2+ and triple-negative disease. Dr. Gradishar noted that since PI3K inhibition is such an active area of investigation, a variety of drugs such as pictilisib have emerged and, in preliminary studies, appear to have a role in the setting of PI3K mutations.

Dr. Gradishar concluded by commenting that at present, platinum salts appear mostly active in BRCA1 or BRCA2 mutations, but should not be viewed as the standard of care for triple-negative BC. Also, although data about immune modulation and immune checkpoint inhibitors are highly preliminary at this point, they are likely to be hot topics in upcoming SABCS meetings.

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AUDIO

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Wednesday, December 10th:

Genome-Directed Therapeutics for Endocrine Therapy Resistant ER+ Breast Cancer
Presenter: Matthew J. Ellis, MD, PhD
Baylor College of Medicine
Houston, TX
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_11.mp3

Survival Advantage of Anastrozol Compared to Tamoxifen for Lobular Breast Cancer in the ABCSG-8 Study
Presenter: Michael Knauer, MD, PhD
Breast Center
St. Gallen, Switzerland
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_01.mp3

Comprehensive Molecular Characterization of Invasive Lobular Breast Tumors
Presenter: Giovanni Ciriello, PhD
Memorial Sloan Kettering Cancer Center
New York, NY
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_12.mp3

Thursday - December 11th

Patient Derived Xenografts - Pre-Clinical Models for Prevention and Treatment of Metastasis
Presenter: Alana L. Welm, PhD
Oklahoma Medical Research Foundation
Oklahoma City, OK
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_13.mp3

Patient-Reported Endocrine Symptoms, Sexual Functioning and Quality of Life in the IBCSG SOFT Trial
Presenter: Karin Ribi
Head, Quality of Life Office, International Breast Cancer Study Group
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_14.mp3

NSABP B-36: FEC-100 vs Standard Adjuvant Chemotherapy
Presenter: Charles E. Geyer, Jr., MD
Massey Cancer Center at Virginia Commonwealth University
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_02.mp3

Principles Governing A-to-I RNA Editing in Breast Cancer Transcriptome
Presenter: Christos Sotiriou, MD
Jules Bordet Institute
Brussels, Belgium
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_15.mp3

Analysis of the SOFT Trial: Ovarian Suppression Reduces Recurrence for Some Young Breast Cancer Patients
Presenter: Prudence A. Francis, MD
Head of Breast Medical Oncology, Peter MacCallum Cancer Centre, Australia
International Breast Cancer Study Group
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_03.mp3

Identification of a Notch-Driven Breast Cancer Stem Cell Gene Signature for Anti-Notch Therapy in an ER+ Presurgical Window Model
Presenter: Kathy S. Albain, MD with Clodia Osipo, PhD
Loyola University Chicago, Stritch School of Medicine
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_04.mp3

Audio Files...*continued*

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Macrophage-Specific Deletion of STAT5 Disrupts Normal Mammary Gland Development and Accelerates Mammary Tumorigenesis
Presenter: Nicholas J. Brady
University of Minnesota
Minneapolis, MN
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Ten-Year Update of E1199: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer
Presenter: Joseph A. Sparano, MD
Montefiore Medical Center, Albert Einstein College of Medicine
Bronx, NY
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_19.mp3

Friday - December 12th

Final Survival Analysis from the Randomized Women's Intervention Nutrition Study (WINS)
Presenter: Rowan T. Chlebowski, MD, PhD
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Cent
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_05.mp3

Changing Paradigms of Screening for Breast Cancer
Presenter: Jean M. Weigert, MD
Hospitals of Central Connecticut, New Britain, CT
in conversation with Jafi Lipson, MD
Stanford University School of Medicine
Palo Alto, CA
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_06.mp3

BOLERO-1: Daily Everolimus Plus Weekly Trastuzumab and Paclitaxel as First-Line Therapy in HER2+ Advanced Breast Cancer
Presenter: Sarah A. Hurvitz, MD
University of California
Los Angeles
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_07.mp3

TBCRC023: A randomized multicenter phase II neoadjuvant trial of lapatinib plus trastuzumab, with endocrine therapy and without chemotherapy, for 12 vs. 24 weeks in patients with HER2 overexpressing breast cancer
Presenter: Mothaffar F. Rimawi, MD
Baylor College of Medicine
Houston, TX
https://s3.amazonaws.com/sabcs/data/sabcs14/sabcs14_17.mp3

Randomized phase II trial of fulvestrant alone of in combination with bortezomib in hormone receptor-positive metastatic breast cancer resistant to aromatase inhibitors: A New York Cancer Consortium trial
Presenter: Kerin B. Adelson, MD
Yale Cancer Institute, Yale University School of Medicine
New Haven, CT and Doris Germain, PhD
Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai New York, NY
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