

Highlights from the 37th Annual San Antonio Breast Cancer Symposium



The 37th Annual San Antonio Breast Cancer Symposium (SABCS) was held December 9-13, 2014. For thirty-seven years, the Symposium's mission has been to provide state-of-the-art information on breast cancer research. From a one-day regional conference, the Symposium has grown to a five-day program attended by a broad international audience of academic and private researchers and physicians from over 90 countries.

The Symposium aims to achieve a balance of clinical, translational, and basic research, providing a forum for interaction, communication, and education for a broad spectrum of researchers, health professionals, and those with a special interest in breast cancer.

On the IBC specific front, there was no new breaking news presented. However, we were excited to hear that an immune checkpoint inhibitor may have possible clinical activity with breast cancer. This immune checkpoint inhibitor has been very promising in melanoma, renal cell carcinoma, non-small cell lung cancer, etc. This year, the Morgan Welch IBC Program will have a clinical trial that will allow us to provide immune checkpoint inhibitors to those patients with metastatic IBC who responded to chemotherapy. This is a novel approach that will provide a new option for our patients.

The Morgan Welch Inflammatory Breast Cancer Research Program and Clinic had a great turn out at SABCS. As a program, a total of nine abstracts were presented. Please join us in congratulating each program member on their recent presentations.



37th Annual San Antonio Breast Cancer Symposium Abstracts

Nab-paclitaxel, doxorubicin, cyclophosphamide, and pegfilgrastim with or without bevacizumab in treating women with inflammatory or locally advanced breast cancer

Zeina A Nahleh, William E Barlow, Daniel F Hayes, Anne F Schott, Julie R Gralow, Edith A Perez, William M Sikov, Sudhathi Chennuru, Hamid Mirshahidi, Sarah Vidito, Danika L Lew, Lajos Pusztai, Robert B Livingston and Gabriel N Hortobagyi

Drugs used in chemotherapy, such as paclitaxel albumin-stabilized nanoparticle formulation, doxorubicin, and cyclophosphamide, work in different ways to stop the growth of tumor cells, either by killing the cells or by stopping them from dividing. Colony-stimulating factors, such as pegfilgrastim, may increase the number of immune cells found in bone marrow or peripheral blood and may help the immune system recover from the side effects of chemotherapy. Monoclonal antibodies, such as bevacizumab, can block tumor growth in different ways. Some find tumor cells and kill them or carry tumor-killing substances to them. Others interfere with the ability of tumor cells to grow and spread. Bevacizumab may also may stop the growth of tumor cells by blocking blood flow to the tumor. Giving these treatments before surgery may make the tumor smaller and reduce the amount of normal tissue that needs to be removed. It is not yet known which treatment regimen is more effective in treating women with breast cancer. This randomized phase II trial is studying paclitaxel albumin-stabilized nanoparticle formulation, doxorubicin, cyclophosphamide, and pegfilgrastim to compare how well they work when given with or without bevacizumab in treating women with inflammatory or locally advanced breast cancer.

A Phase II Study of TKI258 (Dovitinib Lactate) as Salvage Therapy in Patients with Stage IV HER2-negative IBC and Local or Distant Relapse

Ricardo H Alvarez, Mariana Chavez-MacGregor, Joe Ensor, James L Murray, Kimberly Koenig, Savitri Krishnamurty, Antony Lucci, Gildy V Babiera, Wendy Woodward, Gary J Whitman, Summer A Jackson, Michael Shi, Kenneth Culver, James L Reuben, Naoto T Ueno and Vicente Valero.

Dovitinib has antitumor activity in patients with HER2-negative advanced IBC. The primary objective of this study is to to determine the disease control rate (CR, PR, and SD). Secondary objective: to evaluate safety profile. Exploratory biomarkers: circulating tumor cells (CTC), CTC undergoing EMT, and cancer stem cells.

Circulating tumor cells (CTC) are associated with defects in innate and adaptive immunity in inflammatory breast cancer (IBC) patients

Michal Mego, Hui Gao, Evan N Cohen, Simone Anfossi, Antonio Giordano, Sanda Tin, Tamer M Fouad, Wendy A Woodward, Ricardo H Alvarez, Vicente Valero, Naoto T Ueno, Gabriel N Hortobagyi, Massimo Cristofanilli and James M Reuben.

CTCs play a crucial role in tumor dissemination and are prognostic factor in primary and metastatic breast cancer patients. Immune cells in peripheral blood (PB) contribute to an unfavorable microenvironment for the CTCs survival. As such, effective host innate and adaptive immune surveillance systems could adversely influence tumor dissemination whereas dysfunctional immune systems could provide a favorable microenvironment for the dissemination of CTCs and cancer progression. This study aimed to correlate CTCs with the functions of innate [natural killer (NK) cells] and adaptive (T-cells) immune effector cells in PB of IBC patients.



Issue 3: January 2015

Mesenchymal stem cells and macrophage interactions promote inflammatory breast cancer cell invasion and self renewal

Adam R Wolfe, Rachel Atkinson, Bisrat G Debeb, Yan Zhang, Brian Ruffel, James M Reuben, Naoto T Ueno and Wendy A Woodward. Inflammatory breast cancer (IBC) is responsible for 10% of breast cancer deaths. The hallmarks of IBC are skin involvement and a high propensity to metastasize. Our lab has shown previously, "normal" breast tissue from women with an IBC diagnosis had significantly greater macrophage infiltration and increased cells with stem cell markers compared to non IBC "normal" breast tissue. These changes were present prior to diagnosis in two patients where pre-IBC biopsies were available. Therefore, we hypothesized changes in the normal breast microenvironment prior to tumor formation contributes to the IBC phenotype.

Dr. Wolfe was selected to receive an AACR Scholar-in-Training Award in the amount of \$700 to support his attendance at the 2014 San Antonio Breast Cancer Symposium (SABCS), December 9-13, 2014 in San Antonio, Texas. He was chosen for this honor because his abstract "Mesenchymal Stem Cells and Macrophage Interactions Promote Inflammatory Breast Cancer Cell Invasion and Self Renewal" was highly rated by the Abstract Selection Committee. Congratulations!

Co-stimulation through 4-1BB/CD137 improves expansion and function of tumor-infiltrating T lymphocytes from primary and metastatic triple-negative breast cancer and inflammatory breast cancer

Michiko Harao, Hui Gao, Jie Qing Chen, Elizabeth A Mittendorf, Gildy V Babiera, Sarah M DeSnyder, Korrene F Rockwood, Savitri Krishnamurthy, Huiming Sun, Jie S Willey, Naoto T Ueno, James M Reuben and Laszlo G Radvanyi.

Increased CD8+ tumor-infiltrating lymphocytes (TIL) is associated with improved prognosis in triple-negative breast cancer (TNBC) suggesting that T-cell responses at the tumor site can be harnessed for autologous T-cell therapy using TIL expanded ex vivo. Although TIL therapy has been developed for solid tumors such as melanoma, cervical, and ovarian cancer. Moreover, methods facilitating CD8+ TIL expansion from TNBC are desirable given their cytotoxic potential against tumor cells. One approach to address this need is to provide agonist signals through the 4-1BB/CD137 pathway during TIL expansion selectively costimulating CD8+ T-cell activation. In this study, we established a method of expanding TIL from surgical specimens and core biopsies from primary TNBC patients and compared the phenotype and function of these TIL to lymphocytes from peripheral blood.

High MELK expression levels correlate with shorter overall survival in breast cancer

Takahiro Kogawa, Diane D Liu, Gaurav B Chauhan, Juliana M Taliaferro, Hiroko Masuda, Steven J Van Laere, François Bertucci, Yu Shen, Naoto T Ueno, Kevin N Dalvy and Chandra Bartholomeusz.

Triple-negative breast cancer (TNBC) is thought to relapse and metastasize because cancer stem cells (CSCs) resist conventional chemotherapy and radiotherapy and later give rise to secondary tumors. MELK (maternal embryonic leucine zipper kinase), a protein kinase of the Snf1/AMPK kinase family, is known to play a critical role in promoting cell proliferation, CSC maintenance, apoptosis, and transformation. MELK is frequently upregulated in basal-like breast cancers but is not expressed in normal vital organs (Lin et al, Breast Cancer Res 2007;9:R17; Wang et al, eLife 14;10.7554/eLife.01763). We hypothesized that MELK is upregulated in TNBC and that high expression correlates with poor progression-free survival (PFS), distant metastasis-free survival (DMFS), and overall survival (OS) in breast cancer.



Issue 3: January 2015

A class I histone deacetylase inhibitor, entinostat, enhances lapatinib efficacy in both HER2-overexpressing inflammatory and non-inflammatory breast cancer cells through FOXO3-mediated Bim1 expression

Jangsoon Lee, Chandra Bartholomeusz, Gabriel N Hortobagyi, Peter Ordentlich and Naoto T Ueno.

Dr. Lee and colleagues investigated the combinational effect of entinostat (an oral isoform-selective histone deacetylase type I inhibitor) and lapatinib (a HER2/epidermal growth factor receptor dual tyrosine kinase inhibitor) in HER2+ breast cancer cells including inflammatory breast cancer (IBC). He found that compared with entinostat or lapatinib alone, combinational treatment synergistically inhibited HER2+ breast cancer cell growth both in vitro and in vivo xenograft model. Furthermore, entinostat sensitized trastuzumab/lapatinib-resistant HER2+ cells to the trastuzumab-lapatinib combination and enhanced the anti-proliferation effect compared with single-agent with lapatinib or combination treatment with lapatinib and trastuzumab. Taken together, his findings lead to conducting a clinical trial (clinicaltrials.gov, NCT01434303, PI: Naoto T. Ueno) of combinational treatment with entinostat, lapatinib, and trastuzumab in patients with HER2+ IBC or non-IBC that is resistant to trastuzumab-based treatment.

High miR-19a serum levels correlate with favorable prognosis in patients with metastatic HER2+ inflammatory breast cancer and may result from an effective antibody-dependent cell-mediated cytotoxicity induced by trastuzumab

Simone Anfossi, Antonio Giordano, Lei Huo, Ricardo H Alvarez, Vicente Valero, Gabriel N Hortobagyi, Wendy A Woodward, Naoto T Ueno, George A Calin and James M Reuben.

IBC is a rare but highly aggressive form of locally advanced breast cancer (5-year OS rate: 40.5% IBC vs 85% non-IBC patients) accounting for 10% of all breast cancer deaths. To date, no unique molecular diagnostic or prognostic biomarker has been identified for IBC. Increasing evidence supports the potential value of miRNA as prognostic and predictive serum biomarker in cancer. We found that IBC cells expressed high levels of miR-19a and patients with metastatic IBC HER2+ (MIBC HER2+) and high miR-19a serum levels had better prognosis than patients with MIBC HER2+ and low miR-19a serum levels. As one of the mechanisms of action of trastuzumab is the induction of antibody-dependent cell-mediated cytotoxicity (ADCC), we hypothesized that the increased miR-19a serum levels in MIBC HER2+ patients with favorable clinical outcome could result from an effective ADCC and be used as biomarker to monitor the response to trastuzumab.

The microRNA miR-141 is a key regulator of brain metastasis from breast cancer

Bisrat G Debeb, Lara Lacerda, Simone Anfossi, Parmeswaran Diagaradjane, Khoi Chu, Lei Huo, Caimiao Wei, Richard A Larson, Adam R Wolfe, Wei Xu, Daniel L Smith, Li Li, Cristina Ivan, Pamela K Allen, Xiang H Zhang, George A Calin, Savitri Krishnamurthy, Naoto T Ueno, Thomas A Buchholz, James M Reuben and Wendy A Woodward.

Brain metastasis poses a major treatment challenge and remains an unmet clinical need. Finding novel therapies to prevent and treat brain metastases requires an understanding of the biology and molecular basis of the process, which currently is constrained by a dearth of experimental models and specific therapeutic targets. The purpose of this study was to develop preclinical models and identify molecular mediators of brain metastasis from breast cancer.



Quarterly Oral Presentations

Exploring IBC Specific Targeted Therapies

Xiaoping Wang, PhD
Breast Medical Oncology

Role of MEK inhibitor, AS703026 for modulating EMT in basal-like phenotype and inflammatory breast cancer

Jangsoon Lee, PhD
Breast Medical Oncology

Current IBC Projects: Overview and Update

Bedrich Eckhardt, PhD
Breast Medical Oncology

IBC Research Update

Naoto Ueno, MD, PhD
Breast Medical Oncology

Targeting Cell Cycle/Mitotic Regulators in IBC

Angela Alexander, PhD
Experimental Radiation Oncology

Exploring Novel Therapeutics in Inflammatory Breast Cancer

Bora Lim, MD
Breast Medical Oncology

Grant Workshop

Wendy Woodward, MD, PhD
Radiation Oncology

Current Clinical Trials

2008-0372	Phase II Panitumumab, Nab-paclitaxel, and carboplatin HER2- IBC
2010-0842	A phase I Entinostat and Lapatinib + Herceptin HER2+ MBC failed Herceptin
2006-1072	IBC Registry
2011-0930	Randomized phase II double blind study of VPA vs. placebo to shorten time of indwelling pleural catheter
2013-0007	Phase II study of denosumab to define the role of bone related biomarkers in patients with breast cancer and bone metastasis

Current Lab Studies

PA12-0453	EpCAM-CTC-EMT
PA12-0728	TIL for TNBC and IBC
PA12-0860	Assessing feasibility of sentinel lymph node increase dissection in IBC
PA12-0097	Prognostic Utility of CTCs Assessed by Adnagen Technology and Clinical Outcome of Patients with Stage III Breast Cancer

If you are interested in learning more about our clinical trials, or lab studies, please email the

Morgan Welch Inflammatory Breast Cancer Research Program and Clinic directly at ibcp@mdanderson.org.

We are happy to provide general information and eligibility guidelines for our clinical trials and lab studies.

Upcoming Events

Houston Area IBC Meet Up

February 18, 2015
6:00-9:00pm
Amazon Grille
Kirby Drive, Houston

Website - theibcnetwork.org

Hunt for Hope Houston

February 22, 2015
2:00-4:30pm
Southside Place Park Clubhouse
Houston, Texas

Website - Huntforhopehouston.com

Impact Award Luncheon

March 2, 2015
11:30am
The Junior League of Houston
Houston, Texas

Website - eraseibc.com

