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

SAN ANTONIO BREAST CANCER SYMPOSIUM®

2015

UT Medicine CTRC Health Science Center San Antonio

AACR American Association for Cancer Research

Baylor College of Medicine

ISSUE 3

Plenary Lecture #3: Systemic Therapy of HER2 Positive Breast Cancer

Friday, December 11, 9:00 am, Hall D

Mothaffar Rimawi, MD; Baylor College of Medicine; Houston, TX

As a major driver for cell proliferation, invasion, and metastasis, and overexpressed in 20 to 25 percent of breast cancers, the human epidermal growth factor receptor 2 (HER2) is an attractive therapeutic target for cancer treatment. At the forefront of HER2 positive breast cancer research, Dr. Mothaffar Rimawi will discuss the current challenges of treatment resistance as well as the work performed by the scientific community in furthering the understanding of tumors.

Dual inhibition utilizes more than one anti-HER2 agent to target the same pathway, resulting in enhanced efficacy. The concept first achieved major success after a 2005 adjuvant trastuzumab trial reported remarkable improvement in outcomes of patients who received treatment for one year in the curative stages of HER2 positive breast cancer. However, an adjuvant trial comparing treatment of both lapatinib and trastuzumab and treatment of just trastuzumab later showed no meaningful survival advantage. As the results of the APHINITY trial are yet to be reported, the benefits in outcome of dual inhibition are uncertain. In his presentation, Dr. Rimawi will discuss whether or not dual inhibition with chemotherapy will improve outcomes.

Stemmed from the possibility of omitting non-discriminatory treatment such as chemotherapy, the concept of de-escalation has been garnering support and advancement in recent years. Clinical trials have shown meaningful responses–although in just a minority of patients– to anti-HER2 treatment alone without chemotherapy. A regimen of a single agent chemotherapy along with trastuzumab for patients with smaller lower-risk tumors was proven successful; this demonstrates that in carefully-selected patients, omitting a part of treatment can spare patients the toxicity and cost without compromising outcomes. The challenge now is to identify other groups of patients who will benefit from de-escalation. In order to do so, Dr. Rimawi believes it is essential to understand the biology of the tumor. Correlative studies from recent clinical trials have noted potential mechanisms of resistance to anti-HER2 treatment to include the reliance on the estrogen receptor and the activation of the phosphoinositide 3-kinase pathway.

The growing knowledge and clinical information about the tumor is vital in designing more intelligent treatments for HER2 positive breast cancer, particularly in decreasing toxic treatments for patients.

Issue at a GLANCE

Symposium UPDATES*

FRIDAY, DECEMBER 11*

POSTERS WITHDRAWN:

- P5-07-14
- P5-08-11
- P5-08-32
- P5-11-06

PRESENTER UPDATE:

- Mini Symposium 2: Defining the actionable genome – *Gordon Mills*

* All updates will be noted in the Abstracts2View online program after the Symposium and on the SABCS Website.

* At Press Time

Product Theatre SCHEDULE

HALL C

FRIDAY, DECEMBER 11

12:15 PM
The Extended Endocrine Dilemma & Decision Making: Case Review and Panel Discussion
Presented by bioTheranostics

2:00 PM - *CORRECTED TIME*
The Science of Biosimilars
Presented by Hospira

Award

AACR OUTSTANDING INVESTIGATOR AWARD FOR BREAST CANCER RESEARCH
Friday, December 11, 11:30 am, Hall D

Breast Tumor Heterogeneity: Act Locally, Think Globally
Dr. Mohamed Bentires-Alj
Friedrich Miescher Institute for Biomedical Research (FMI), Basel, Switzerland

The AACR Outstanding Investigator Award for Breast Cancer Research, funded by Susan G. Komen®, recognizes an investigator of no more than 50 years of age whose novel and significant work has had or may have a far-reaching impact on the etiology, detection, diagnosis, treatment, or prevention of breast cancer. Such work may involve any discipline across the continuum of biomedical research, including basic, translational, clinical and epidemiological studies.

Dr. Mohamed Bentires-Alj is honored for his seminal work on normal and neoplastic breast cell plasticity which found that mutant PI3K induces multipotency and multi-lineage mammary tumors, and that SHP2 promotes breast cancer progression and maintains tumor-initiating cells. Notably, his research has revealed that co-targeting PI3K/mTOR and JAK2 in triple-negative breast cancer models decreases tumor volume, seeding and metastasis and increases overall survival. He also discovered that discontinuation of CCL2 inhibition accelerates breast cancer metastasis by promoting angiogenesis.

Dr. Bentires-Alj's dedication to discovering new and more effective cancer treatments and for training the next generation of scientists is also noteworthy, and so are his relentless efforts in building bridges between basic research and the clinic. Dr. Bentires-Alj explores complementary and interdisciplinary approaches to understand the mechanisms of cancer, and has proven himself to be exceptionally community minded and open to collaboration.

The Bentires-Alj lab aims to understand the cellular and molecular mechanisms regulating normal and neoplastic breast stem cells, progression to metastasis, and resistance to targeted therapy.

Dr. Bentires-Alj studied Pharmaceutical Sciences at the University of Liège, Belgium from 1991 to 1996, followed by a PhD in Pharmaceutical Sciences at the same university in 2001. Then he did his postdoctoral work at Beacon Israel Deaconess Medical Center at Harvard Medical School in Boston from 2001 to 2006 where he studied the effects of Gab2 and PTP1B in breast cancer.

Dr. Bentires-Alj is the founder and president of the European Network for Breast Development and Cancer that fosters global interactions between labs in these areas, and co-founder of the Basel Breast Consortium committed to promoting local basic, clinical, and translational interdisciplinary research projects, and is the FMI representative at the EU-Life translational working group.

A Novel Agent, and Mastectomy vs. Breast-Conserving Therapy

Since endocrine therapy-resistant tumors maintain estrogen receptor 1 (ESR1) signaling, there is a need to target the interactions between ESR1 and its coregulators. Dr. Ratna Vadlamudi and his group therefore designed and evaluated a family of ESR1 coregulator binding inhibitors (ECBIs), which mimic the coregulator nuclear receptor box motif and block formation of the receptor/coactivator complex.

Dr. Vadlamudi showed that in cell proliferation assays, ECBI-11 inhibited growth of ESR1+ ZR-75 cells in a dose-dependent manner, but did not affect growth of triple-negative breast cancer (BC). ECBI expectedly reduced estrogen signaling, but also upregulated pathways in apoptosis and death receptor signaling. ECBI was also shown to interact with mutant forms of ESR1 with high affinity.

Further, ECBI treatment of both MCF-7 model cells with acquired resistance to tamoxifen and letrozole-resistant cells resulted in dose-dependent reduction in growth. For clinical relevance, the group tried doses of ECBI up to 100 mg/kg in immune-competent mouse models and found that ECBI is orally bioavailable with minimal toxicity.

Next, Dr. Marissa van Maaren discussed findings of a study comparing the 10-yr overall survival (OS) and disease-free survival after breast-conserving therapy (BCT) vs. mastectomy (MAST) in early BC.

In a cohort of 37,207 patients, patients receiving BCT had ~20% better 10-yr OS than MAST in every T and N stage. In a subcohort of 7,552 patients, 61.5% received BCT of which 11% experienced distant metastasis, and 38.5% underwent MAST of which 14.7% experienced distant metastasis.

Although Dr. van Maaren concluded that BCT is a more successful option than MAST, she acknowledged that this observational study is limited by confounding—in particular, although results were adjusted for tumor size and nodal staging, surgeons and patients tended to elect MAST for cases perceived to have greater risk, so that patients undergoing BCT were also generally younger and with more favorable prognosis compared to those undergoing MAST.

Clonal Progression in LCIS, and HER2 Status as Predictive Marker for Aromatase Inhibitor Benefit

On Thursday afternoon, Dr. Jorge Reis-Filho presented findings on a study aiming to determine the genomic landscape of lobular carcinoma in situ (LCIS) and the mutational processes involved in the clonal evolution and progression from LCIS to invasive lobular carcinoma (ILC).

This prospective study collected classic LCIS and associated lesions from 15 patients undergoing prophylactic or therapeutic mastectomy. All samples were subjected to whole exome sequencing analysis in order to ascertain the clonal relatedness of LCIS and other lesions in the same patient.

Results showed that LCIS is often clonally related to more advanced lesions. They have CDH1 pathogenic mutations, which affect genes often mutated in luminal A and lobular invasive breast cancers. In the study, ILCs were clonally related to at least one LCIS in 7/10 patients, and ductal carcinoma in situ (DCIS) was clonally related to at least one LCIS in 3/6 patients. Results concluded that LCIS is a non-obligate precursor of DCIS and ILC. Furthermore, the progression from LCIS to ILC may result in the selection of subclones.

Later, Dr. John Bartlett presented data from a TRANS-AIOG meta-analysis that looked at 12,129 patients from the ATAC, BIG 1-98, and TEAM trials with centrally determined HER2. They concluded that HER2 is a predictive marker for greater benefit from aromatase inhibitor therapy—specifically in ER+/HER2- patients (during first 2-3 yr of treatment)—compared to patients with HER2+ disease.

Caveats that Dr. Bartlett pointed out were that there was evidence of heterogeneity in the HER2+ subgroup that did not reach statistical significance, that most of the HER2+ cancers were not eligible for chemotherapy and did not receive HER2-directed therapies (eg, trastuzumab), and that there was a small number of HER2+ cancers and events. "Observed heterogeneity coupled with minimal treatment using HER2-directed therapies precludes us from recommending any changes to practice," he concluded.

Updated Abstract

S6-07: COMPARISON OF 12 WEEKS NEOADJUVANT NAB-PACLITAXEL COMBINED WITH CARBOPLATINUM VS. GEMCITABINE IN TRIPLE- NEGATIVE BREAST CANCER: WSG-ADAPT TN RANDOMIZED PHASE II TRIAL

Gluz O, Nitz U, Liedtke C, Christgen M, Sotlar K, Grischke EM, Forstbauer H, Braun M, Warm M, Hackmann J, Uleer C, Aktas B, Schumacher C, Bangemann N, Lindner C, Kuemmel S, Clemens M, Potenberg J, Staib P, Kohls A, Pelz E, Kates RE, Wuerstlein R, Kreipe HH, Harbeck N

Westdeutsche Studiengruppe GmbH, Moenchengladabach, Germany; Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany; University Clinics Schleswig-Holstein/Campus Luebeck, Women's Clinic; Medical School Hannover, Institute of Pathology; University of Munich (LMU), Institue of Pathology; University Clinics Tuebingen, Women's Clinic; Practice Network Troisdorf; Rotkreuz Clinics Munich; Clinics of Cologne - Hospital Holweide; Marien-Hospital Witten; Gynecologic Oncologic Practice Hildesheim; University Clinics Essen, Women's Clinic; St. Elisabeth Hospital Cologne; Charité Berlin, Clinic of Gynecology; Agaplesion Diakonie Clinic; Clinics Essen-Mitte, Breast Center; Mutterhaus der Borromäerinnen Trier; Ev. Waldkrankenhaus; St. Antonius Hospital, Clinicsof Hematology and Oncology; Ev. Hospital Ludwigsfelde; Pathology Viersen; Palleos Healthcare Services, Statitistics; Breast Center, University of Munich and CCCLMU

Background: Pathological complete response (pCR) is associated with improved prognosis in TNBC, but optimal chemotherapy remains unclear. Use of weekly nab- paclitaxel (Nab-Pac) vs. conventional paclitaxel and also addition of carboplatinum(Carbo) to anthracycline-taxane(A/T) containing chemotherapy results in significantly higher pCR rates in TNBC with unclear impact on survival and increased toxicity.

The ADAPT study seeks to compare Carbo vs. gemcitabine(Gem) added to nab- paclitaxel as a short 12-week A-free regimen. It also assesses efficacy in early responders vs. non-responders by 3-week proliferation and/or imaging response.

Methods: ADAPT TN compares 12-week neoadjuvant regimens: Carbo vs. Gem combined with Nab-Pac and aims to identify early-response markers for pCR (yPN0 and ypT0/is). TNBC patients (centrally confirmed ER/PR <1%, HER2 neg.), cT1c- cT4c, cN0/+ were randomized to arm A (Nab-Pac 125/ Gem 1000 d1,8 q3w) vs. B (Nab-Pac 125/Carbo AUC2 d1,8 q3w). Randomization was stratified by center and nodal status. The trial is powered for pCR comparison by therapy arm and by presence vs. absence of early response markers. Pre-planned interim analysis aimed to identify a dynamic biomarker, e.g. drop of 3-week Ki-67, and to validate trial assumptions.

Results: 336 patients were enrolled from 47 centers between 06/13-02/15 (n=182 ArmA: Nab-Pac/Gem and n=154 ArmB: Nab-Pac/Carbo). 90% and 95% completed therapy according to protocol respectively (n.s.). Median age was 50y. At baseline: A/B: 73% and 74%% had G3 tumors, median Ki-67 of 70% and 75%; 62.6% and 62.9%% had cT2-4c tumors, pN0 status prior to chemotherapy was confirmed in 50.5% and 50%, respectively.

pCR (ypT0/is/ypN0) was A: 28.7% and B: 45.9% (p<0.001). Total pCR (ypT0/ypN0) was A: 25.8% and B: 45.2% respectively (p <0.001).

Nab/Gem arm was associated with significantly higher frequency of dose reductions (20.6% vs. 11.9% (p=0.03), treatment related SAE's (13% vs. 5%, p=0.02), grade 3-4 infections (6.1% vs. 1.3%, p=0.04) and ALAT elevations (11.7 vs. 3.3%, p=0.01) compared to the Nab-Carbo arm.

Within the planned interim analysis (n=130: A/B: 69/61), baseline Ki-67 (Nab- Pac/Carbo arm), age>50 years, and low cellularity (<500 tumor cells and/or Ki-67≤10% in the 3-week biopsy) (Nab-Pac/Gem arm) were positively associated with pCR by logistic regression analysis (separately by therapy arm). In all patients, therapy arm itself was significant for pCR.

Validation of responder definitions for the whole study will be presented at the meeting.

Conclusion: This is the first large randomized study comparing two short 12-week anthracycline- free regimens in unselected TNBC. Our results suggest superior efficacy and excellent toxicity of Nab-Pac/Carbo vs. Gem. Longer A/T-Carbo containing regimens render quite comparable pCR rates, thus overtreatment by 4xEC in unselected TNBC may be present in some patients. Early response criteria seem to differ according to regimen; their assessment may be impaired by substantial tumor necrosis already after the first therapy cycle.

Please note all revisions will be noted on the Abstracts2View™ online program after the Symposium.

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