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## Combating Breast Cancer 2014: Molecular understanding of breast cancer: digging deeper

On November 21-22, 2014, the seventh Conference on Molecular Basics and Therapeutic Implications in Breast Cancer (COMBAT) was held in Düsseldorf, Germany. This year's conference followed the motto "Molecular Understanding of Breast Cancer: Digging Deeper". Under the chairmanship of Nadia Harbeck (University Hospital Munich), Achim Rody (University Hospital Schleswig-Holstein Campus Lübeck) and Michael Gnant (AKH Vienna), the conference was again an outstanding success. Mostly young clinicians and researchers from Germany, Austria and Switzerland participated to share and further their insight into molecular biology and the scientific background of modern individualized breast cancer therapy. Moreover, national and international guests presented the latest discoveries and insights of breast cancer research in over 20 lectures covering a broad scientific spectrum ranging from conventional and targeted therapeutic agents to risk prediction and therapy selection based on multigene assays to practical and logistical aspects of breast cancer care.

The winner of the annual Combating Award was Frederik Marmé of Heidelberg University Hospital and the German National Center for Tumor Diseases (NCT Heidelberg) for his excellent continuous work in translational research in breast cancer. For his professorial thesis, he researched genetic polymorphisms and their establishment as prognostic and predictive markers in gynecological malignancies.

### AGO TraFo Meets COMBAT

Continuing the successful partnership established in 2011, the AGO TraFo Meeting (AGO TraFo = Arbeitsgemeinschaft Gynäkologische Onkologie, Kommission Translationale Forschung) was again held in conjunction with the COMBAT Meeting. Translational research refers to the continuous exchange between clinicians, clinical researchers, and lab-based scientists and the back-and-forth of questions and answers to provide explanations for observed clinical phenomena and to evaluate scientific discoveries regarding their clinical use. Chaired by Tanja Fehm (University Hospital Düsseldorf), Peter Fasching (University Hospital Erlangen) and Dieter Niederacher (University Hospital Düsseldorf), the symposium started with the session on "Predictive Markers and Individualized Tumor Therapy". Peter Fasching emphasized the potential of Germany as a leader in the conduction of clinical trials and within them the asservation of biomaterials along with clinical patient data. As it has become tradition, the symposium gave young researchers the opportunity to present their innovative translational research strategies and models. Out of numerous abstracts, the best four were selected for oral presentation. As a new component in the educational package offered by the TraFo symposium, tutorials by experienced scientists and statisticians covering themes such as statistics, study design, publishing, presentation and molecular analysis and lab work served to equip aspiring researchers with the tools for success.

### COMBATing 2014

Following the TraFo Meeting, COMBAT started off with a warm welcome from Nadia Harbeck. The first session covered the most recent developments since the previous conference. Jürgen Dittmer (University Hospital Halle) introduced the audience to new insights into the importance of interaction between tumor cells and surrounding tissue, demonstrating the effect of stroma-rich tumor histomorphology on prognosis and detailing current hypotheses on the effects of fibroblast activation and stromal glycolysis activity. An overview over current clinical trials evaluating and comparing classic chemotherapy, endocrine, and HER2-targeted therapeutic concepts to avoid over- and undertreatment in primary breast cancer was given by Oleg Gluz (Bethesda Hospital Mönchengladbach) for the West German Study Group (WSG). The wealth of markers used to categorize and stratify tumors necessitates innovative concepts to keep clinical trials feasible, such as the evaluation and establishment of surrogate parameters including disease-free survival and complete histopathological remission rate. Apart from the introduction of new substances, trials seek to optimize choice, sequence, density, and intensity of therapy and to custom tailor it for each patient, using, identifying, and validating new biomarkers. Current estimations suggest that about 35 mutations separate a cancer cell from a healthy cell, and each of these may be a potential prognostic and predictive factor or even a therapeutic target. As a prominent example, Peter Fasching's lecture described the PI3K pathway, from PI3K's physiological functions to pathological alterations in oncogenesis to its modulation as a therapeutic concept and associated challenges concerning patient selection and toxicity management. It is representative of the process of "digging deeper" into the complex mechanisms regulating mitotic activation and inhibition and cell cycle processes within the cell and in the context of its microenvironment. As a later step in pro-mitotic signaling, Cycline Dependent Kinases were

discussed by Cornelia Liedtke (University Hospital Schleswig-Holstein Campus Lübeck), who demonstrated the potential of their inhibition and upcoming targeted agents, with the most advanced in clinical trials being palbociclib. In the last lecture of this session, Günter Steger (Medical University Vienna) outlined new additions to the breast cancer drug arsenal, with a focus on trastuzumab emtansine as one of the few truly new agents, and underlined the international heterogeneity in handling of drug approval.

For the first time, the COMBATing agenda included a separate session on eHealth. Timo Schinköthe (University Hospital Munich), representing Germany, and Andreas Trojan (OncoCenter Zurich), representing Switzerland, provided an exciting and informative look into this innovative field of medical science apart from traditional patient care. In Switzerland and Germany, the assistance of oncologic patient care via internet or mobile device was shown to be well accepted across various patient demographic groups including elderly patients, with programs such as Cankado (www.cankado.de) or Consilium showing great developmental maturity and promising to facilitate therapy monitoring and patient guidance. Both presentations showed that the concepts currently employed in routine care are just the tip of the iceberg, with major companies currently investing massively in advancing this branch of medical care.

The third session provided an opportunity for the conference's industry sponsors to demonstrate the latest and most advanced products in their respective pipelines. Eugen Rückhäberle (University Hospital Düsseldorf) showed the history of the development of Astra Zeneca's olaparib as the best known representative of PARP inhibitors. He outlined the promises of early trials focusing on the treatment of breast and ovarian cancer and the setbacks suffered before this substance reemerged in the more narrow setting of BRCA-mutated breast cancer. Maik Pruess of NanoString presented the standardized version of the PAM50 test called Prosigna, and its applications and potential in clinical decision-making, providing evidence-based guidance in formerly unclear situations, and as a new research tool in multigenetic testing. Lastly, Gernot Guderian of Novartis explained the design of the BELLE and MONALEESA trials investigating the previously introduced PI3K and CDK4/6 inhibitors in the setting of metastatic breast cancer and the networks needed to condutct these new trials.

A highlight of the conference was the Award Lecture (Henner-Graeff Award 2012) held by Georg Pfeiler, a young professor of Medical University Vienna, on the difficulties and pitfalls of development of targeted therapies and selection and validation of markers predictive of therapeutic efficacy. Recent results of his research suggest an impact of BMI and body fat on the effectiveness of endocrine therapy with different agents.

The day concluded with the laudation for Frederik Marmé and the announcement of the winners of the COMBAT travel scholarship, Eva-Beatrice Kohls and Kim Chi Katharina Ho (University Hospital Schleswig-Holstein Campus Kiel), Florian Schindler (Hospital Starnberg), and Lennard Schröder and Julian Koch (University Hospital Munich).

The second day started off with the Key Note Lecture held by Bruce A. Littlefield of Eisai on drug development using Eribulin as an example, both as a molecule and a therapeutic agent. He reminded the audience that "there is no history of success in medicine, but a history of mistakes made and lessons learnt", as Eribulin's complex chemical structure made its synthesis an unusual challenge. Its remarkable effect on overall survival in the metastatic breast cancer setting encourages detailed exploration of its mechanisms of action. Hypotheses concerning effects apart from traditional antimitotic activity include tumor vasculature remodeling, reversal of epithelial-mesenchymal transition and decreased capacity for migration and invasion.

The session on signaling pathways commenced with a lecture by Christian Singer (Medical University Vienna) focused on the role of RANK signaling both in bone metastasis and in breast tumorigenesis, thereby providing a possible explanation for the increase in breast cancer risk associated with progesterone-containing hormone replacement therapy. Further away from generating an effective clinical treatment approach but nevertheless highly intriguing, the Src pathway was explained by Beyhan Ataseven (Hospital Essen-Mitte). We currently lack sufficiently predictive biomarkers to identify a patient population that may benefit from the use of Src inhibitors (such as dasatinib) in breast cancer in order to offset their toxicity profile, as well as an ideal combination partner substance. The session was concluded by Volkmar Müller's (University Hospital Hamburg-Eppendorf) comparison of circulating tumor cells and circulating tumor DNA. The data quality concerning prognostic value favors CTCs, but opportunities for both methods' application in the clinical setting are continuously refined as clinical trials (such as the ambitious DETECT trial series) aim to clarify their predictive potential and establish them as biomarkers to guide therapeutic choices.

The next topic was dedicated to hereditary and triple negative breast cancer. Kerstin Rhiem (University Hospital

Cologne) provided an outlook on intermediate-risk and low-risk mutations apart from the well-established BRCA defects. Given the vast spectrum of mutations and their respective clinical relevance, she illustrated the need for effective tools for individual risk assessment and for clear guidance to aid clinical decision-making regarding the use of prophylactic diagnostics and procedures. She also presented the new guidelines by AGO and the German Consortium on Hereditary Breast and Ovarian Cancer. Preventive strategies and their application in high-risk and intermediate-risk mutation carriers were discussed by Nina Ditsch (University Hospital Munich), separated into primary (before onset of disease), secondary (early detection), and tertiary (in diagnosed patients) forms of prevention. She summarized that risk-adapted screening should be applied to affected women. Furthermore, she underlined the effectiveness of prophylactic adnectomy and mastectomy in both BRCA1 and BRCA2 mutation carriers while warning of a too liberal use of these invasive procedures in women with a low or unclear risk profile. Apart from hereditary factors, other carcinogenic influences such as radiation exposure may warrant the use of intensified preventive measures. New guidelines for BRCA mutation carriers are under development and will be presented in early 2015.

Cornelia Liedke offered a detailed look into the data regarding the use of platinum-based agents in BRCA-positive and in any triple negative breast cancer. She concluded that platinum-based chemotherapy may offer improved survival in triple-negative breast cancer at the cost of significant toxicity, though currently available data from trials such as GeparSixto (carboplatin vs. control, combined with paclitaxel and NPLD) and CALBG40603 (carboplatin vs. control, combined with paclitaxel) is limited to pCR rates with survival analysis event thresholds still on the horizon. In a different approach, the ADAPT TN sub-study randomizes carboplatin + nab-paclitaxel vs. gemcitabine + nab-paclitaxel, thereby deescalating instead of intensifying the therapy. While the AGO guidelines offer to recommend platinum therapy for any TNBC, trial participation is still preferred since more mature data as well as better validated predictive tools are required to guide patient selection for these therapies. Candidates for predictors include gene signatures, individually or summarized as a homologous recombination deficiency score (HRD), as well as microenvironment-oriented features such as tumor infiltrating lymphocytes.

The final session centered on multigene assays. Their prognostic potential was laid out by Marcus Schmidt (University Hospital Mainz), who also presented the current AGO guidelines regarding their use for patient selection for adjuvant therapy and emphasized the increasing wealth of supporting data. He also provided background information to adjudicate their reliability compared to basic immunohistochemistry for ER/PR/HER2/Ki67 evaluation. Michael Knauer (Hospital of the St. Gallen Canton) elaborated on predictive applications of the assays. The more established tests—OncotypeDX, EndoPredict, and PAM50—are recognized by guidelines as useful tools in the subset of clinical situations where indication based on traditional criteria remains unclear. In trials, about 30 % of clinical decisions were altered based on test results. Apart from systemic therapy, Eugen Rückhäberle explained how also loco-regional treatment issues ranging from surgical margins to radiotherapy may receive guidance from such tests using tools such as the genomic nodal index predicting nodal status, which may help reduce or entirely avoid nodal surgery in low-risk patients.

In summary, COMBAT was again extraordinarily successful in furthering the exchange of information between lab-based research and clinical practice as well as in teaching doctors and scientists about breast cancer and its treatment. The annual meeting tradition is scheduled to continue in fall of 2015.

Further information on COMBAT is available at www.combating.de alongside many original presentations and materials.