ONCOLOGY PRO
Educational Portal for Oncologists

# The 3rd IMPAKT Breast Cancer Conference: IMProve cAre and Knowledge through Translational research

5-7 May, 2011
Brussels, Belgium

## SUMMARY

IMPAKT, IMProving cAre and Knowledge in Translational research, is more than just a breast cancer meeting. It represents a strong commitment by a growing and united multidisciplinary alliance between many of Europe's leading professional medical societies, breast cancer research groups and cancer patient organizations, and a unique forum for discussion among basic, translational, and clinical researchers. It is organized by the Breast International Group (BIG) and European Society for Medical Oncology (ESMO), in collaboration with the Foundation "St. Gallen Oncology Conferences", the European Organisation for Research and Treatment of Cancer (EORTC) Breast Cancer Group, the European Society of Breast Cancer Specialists (EUSOMA), and Europa Donna - the European Breast Cancer Coalition.

## INTRODUCTION

The 3rd IMPAKT Breast Cancer Conference took place in a strikingly modern environment. The SQUARE Brussels Meeting Centre is housed in an elegant, architecturally significant building originally constructed for the 1958 World Expo. The Conference was a resounding success, with 563 participants from 51 countries. The program provided information on scientific discoveries that already have or will have impact on breast cancer research and treatment in the near future. The presentations put in perspective advances on a molecular level exploited for clinical purposes. Delegates could thus better understand the relevance and directions for a wide range of diagnostic, prognostic and predictive tools in breast cancer. Furthermore, the program addressed specific methodologies, and where we stand in the practical implementation of novel discoveries. It was designed to help participants stay in tune with scientific progress in breast cancer research as the therapeutic road from the laboratory to the clinic shortens.

The pre-IMPAKT training course offered a unique teaching program of the fundamentals in new disciplines and techniques in translational research, through exposure and a hands-on approach. The attendance was limited to 50 early-career oncologists, selected through application on a competitive basis, to ensure an ideal learning environment. The training course faculty welcomed the participants with a social lunch prior to the presentation of fellowship opportunities. The course enabled close exchange between faculty and participants, new contacts and stressed a need for professional development of newer generation specialists and collaborative initiatives in breast cancer research. The Educational program was composed of lectures on: biomarkers development, system biology as a roadmap to smart targeted drug development, new technologies for tailored oncology treatment, investigating the potential of an immunotherapy and immune signatures in breast cancer, and circulating markers.

IMPAKT Breast Cancer Conference: A detail from the IMPAKT Training course

An impressive list of invited speakers covered the part of the main IMPAKT Conference program on recent scientific discoveries. The fact that all of the topics were presented by scientists who have been actively involved in the research presented testifies to the quality of the program. The program comprised keynote lectures on breast cancer genome, how to use genomic data, and integration of risk from new breast cancer genes. Topics were presented by world renowned scientists and then discussed from the clinical perspective.

Presentations on clinically challenging subtypes of breast cancer, mechanistic understanding and

clinical solutions in poor prognosis estrogen receptor (ER)-positive disease, as well as about medullary, inflammatory and metaplastic breast cancers were very attractive to the participating clinical community. The sessions further covered topics on combined pathways inhibition and provided in-depth insight into the drugs in development for those particular pathways. The combinations discussed were PI3K and MEK, IGF1R and mTOR, and Hedgehog plus Notch inhibitors.

The program provided new views on possibilities for targeting the tumor microenvironment and discussed from several aspects the blood marker perspectives. Special educational sessions on pre-operative therapy as a faster route to the clinic for new therapeutics consisted of presentations on ongoing clinical studies.

Sessions additionally covered topics on pharmacogenetics, and presented several examples and current practices in tumor genotyping in two European and USA cancer centers. A need for molecular enrichment in phase I/II trials was stressed, as there is a risk for false conclusions that a new targeted agent does not work if the trial did not include a minimal number of patients with a specific molecular alteration.


Anita Dunbier, from the Breakthrough Breast Cancer Research Centre at The Institute of Cancer Research (ICR) in London, presenting Mechanisms underlining poor prognosis ER-positive breast cancer

From abstracts submitted under different categories (Molecular biology - preclinical, Detection and diagnosis, Circulating tumor cells, Imaging, Adjuvant medical therapy, Loco-regional therapy, Triple negative breast cancer, New drug development, and Collaborative initiatives in translational research), the Scientific Committee selected 123 abstracts for oral and poster presentations. The IMPAKT Abstract Book, published in a supplement of Annals of Oncology, is a compilation of results in basic, translational, and early clinical research of breast cancer. Here, we present some of the scientific results presented during IMPAKTand aim to put challenging translational research questions into perspective.

## CIRCULATING TUMOR CELLS AND CYFRA 21-1 AS PROGNOSTIC BIOMARKERS IN FIRST-LINE METASTATIC BREAST CANCER

French researchers conducted a prospective study in 267 patients who received first-line chemotherapy for metastatic breast cancer in 5 cancer centers. For each patient, they performed a count of circulating tumor cells (CTCs), plus an analysis of other blood markers. Measurements were taken at the beginning of treatment, before cycle 2, at clinical and/or radiological evaluation, and at tumor progression. Median follow-up was 16 months.

Of the 260 patients who were evaluable for CTC levels at baseline, 170 (65%) had at least one CTC per 7.5 mL blood sample, and 115 (44%) had five or more. The researchers also correlated CTCs and CYFRA 21-1 with other tumor markers, tumor burden, performance status, and number of metastatic sites, whereas they were independent of the tumor subtype. A multivariate analysis showed that several factors, including CTC counts, were correlated with progression-free survival and overall survival (Fig.1). Furthermore, a persistence of a high level of CTCs before the second cycle of chemotherapy was shown as a strong and early predictive marker for poor progression-free survival, before radiological evaluation.

The authors reported that the relative-risk of the high-risk group vs. low-risk group did not significantly change whether a threshold was defined as 1 CTC or 5 CTC. The researchers concluded that their data suggest that using the lower threshold of 1 CTC is feasible and is not affected by any major loss of specificity of CTC detection.

Practice point and future research opportunities

This is the first study that has been prospectively designed for reporting CTC-associated outcome as the primary endpoint in a homogenous population of metastatic breast cancer patients treated with first-line chemotherapy. The study confirms data provided by earlier small studies that CTCs are prognostic at baseline, and that CTC changes under treatment may be an early indicator of

chemotherapy efficiency. The findings represent the strongest evidence so far that presence of CTCs in samples of a patient's blood is linked to poor outcome such as a shorter progression-free survival. However, head to head comparison of CTC vs serum markers for progression-free survival prediction showed no significant difference. Yet, the study was not statistically powered for this particular analysis. The number of CTCs was not disclosed to the treating physicians, therefore making it impossible for them to adapt the treatment strategy. The study findings now set the scene for ongoing interventional trials designed to see if improved outcomes can be achieved by modifying treatment based on CTC counts. The study results also add evidence to an ongoing discussion about how many CTCs per blood sample should be used to define patients at high-risk for poor outcome.

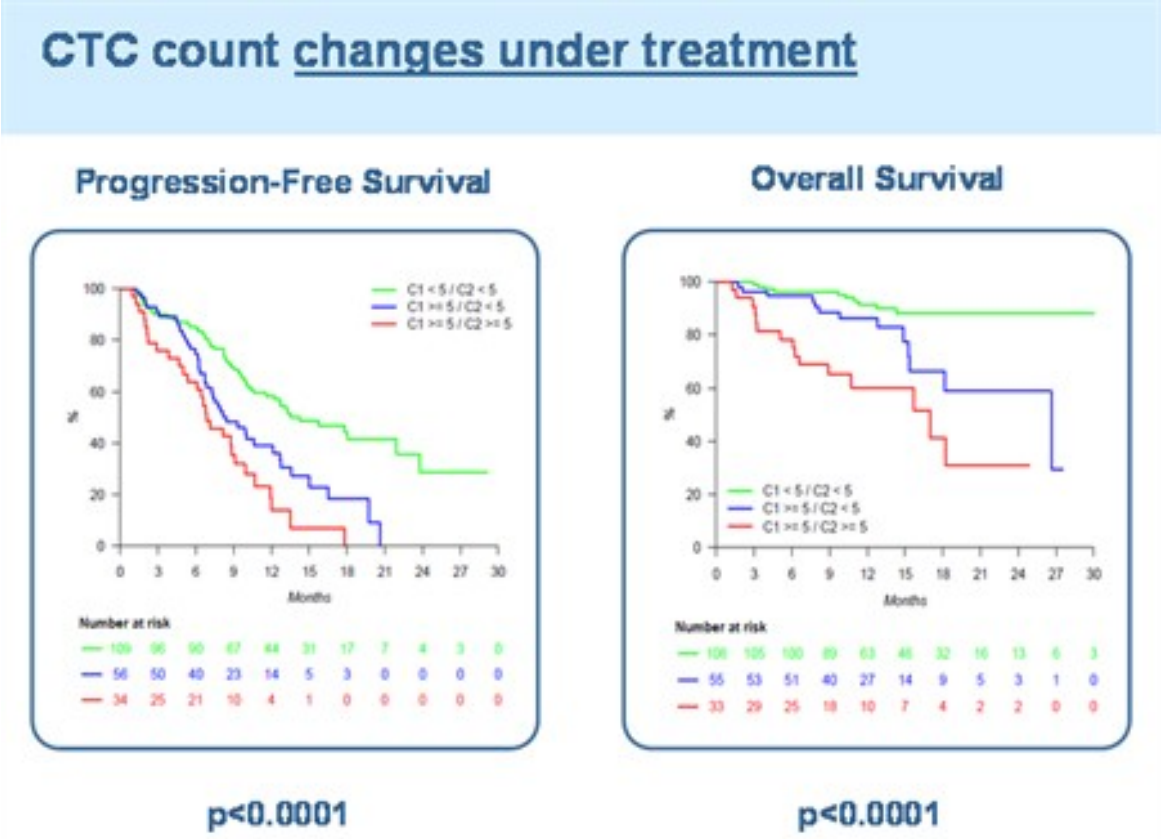



Fig.1. Changes in number of circulating tumor cells and correlation with progression-free survival and overall survival (courtesy of Francois-Clement Bidard)

## LARGE EPIGENETIC STUDY REVEALS NEW INSIGHTS INTO BREAST CANCER

A goal of the study performed by Belgian researchers was to assess the epigenetic differences between frozen breast tissue samples, normal tissue and primary tumor samples, compare diversities, and extract biologically and clinically meaningful information. They performed a comprehensive DNA methylation profile on a main set of 123 samples, and a validation set of 125

samples. They used the recently developed assay to assess methylation status in over 14,000 genes.

When they performed a clustering analysis of samples based on their DNA methylation profiles, tumors segregated into two distinct groups. The first group was mainly composed of estrogen receptor (ER)-negative tumors, and the second one of ER-positive tumors. This finding indicates that ER-negative and ER-positive tumors have very different methylation profiles.

Furthermore, when they looked at more than 400 genes whose expression is positively or negatively correlated to expression of the ER gene, they found a reverse correlation between methylation and expression status of the majority of these genes. This suggests that epigenetics is probably involved in the regulation of expression of genes playing an important role in the establishment of the two major phenotypes of breast cancer determined by ER status.

The analysis also revealed information about new subtypes of breast cancer. The researchers showed that DNA methylation profiles enabled breast tumors to be classified in more groups than those currently defined. Some of these tumor groups coincide with already known subtypes, but some new entities have also been discovered.

The researchers also found a strong epigenetic component in the regulation of key immune pathways, revealing a set of immune genes having high prognostic value in specific tumor categories.

Several patients displaying the same known subtype of breast cancer can respond differently to a given drug. An epigenetic difference between the tumors might explain the difference observed in terms of treatment response. Therefore, DNA methylation profiling could help to refine the current breast cancer classification and thus may help to stratify patients within a particular subtype both in terms of prognosis and prediction to treatment response (Fig.2).

## Practice point and future research opportunities

This is the most comprehensive analysis to date of epigenetic modifications in breast cancer. Although it was known that epigenetics are important in cancer, information about its exact contribution to breast carcinogenesis was missing. Data from this study suggest that epigenetic dysregulation occurs early during carcinogenesis. DNA methylation profiling could help to refine the current breast cancer taxonomy. DNA methylation markers might help to better stratify patients in terms of prognosis and prediction of response to a given drug. An epigenetic therapy, alone or in combination with conventional therapies, is conceivable. Indeed, several drugs have been developed and some clinical trials have already shown promising results in some other cancer types, particularly leukemia. By laying the ground for better understanding of breast cancer biological diversity and improved tumor classification, the precise epigenetic data obtained in this study could contribute in

the future to better treatment of breast cancer patients.

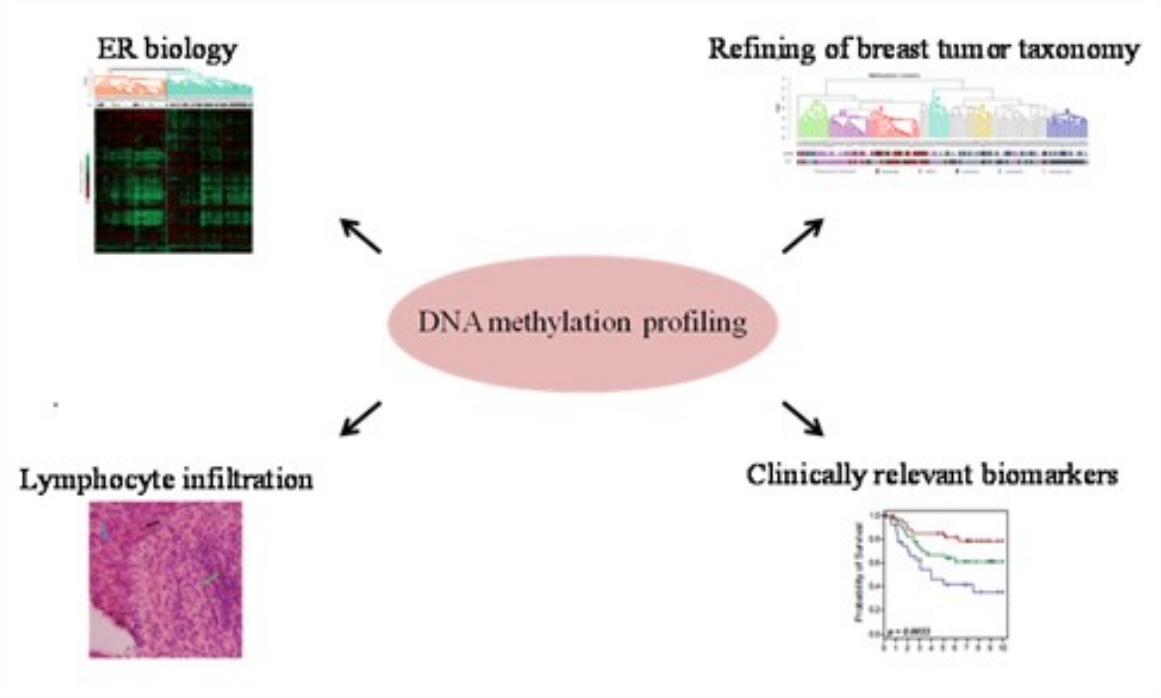



Fig.2. Novel findings emerged from the epigenetic study of breast cancer (courtesy of Sarah Dedeuwaerder)

## CONCORDANCE BETWEEN THE 21-GENE AND THE PAM50 INTRINSIC CLASSIFIER FOR PROGNOSIS IN EARLY STAGE ER-POSITIVE BREAST CANCER

Currently, there are at least four different breast cancer subtypes with clinical relevance (luminal A, luminal B, basal-like and HER2-enriched) and several commercial assays are being introduced to assign clinical subtype or predict risk of recurrence for breast cancer. An imminent clinical challenge for practicing oncologists is to understand how these different assays relate to each other and what to expect when more than one assay is performed on the same cancer.

Irish researchers and colleagues in the USA examined the agreement in prediction results between two multi-gene assays, the widely used 21-multigene assay (OncotypeDX®) and a newer PAM50 breast cancer intrinsic classifier. They presented the first results of comparing these two conceptually different prognostic risk predictors.

They extracted RNA from 119 formalin-fixed, paraffin-embedded tissue blocks from breast cancer patients who had been classified as being at clinically intermediate risk for recurrence based on several criteria: median tumor size (1.5cm), all ER-positive, HER2 negative, lymph-node negative and most of them grade II. These patients would likely be a challenge in terms of whether they would

benefit from adjuvant chemotherapy or not. In these situations, multi-gene assays can provide additional independent prognostic information. The researchers then performed the PAM50 assay and semi-quantitative Ki67 analysis and compared the results to the OncotypeDX® recurrence score.

The results showed that all patients with high RS according to the OncotypeDX® were classified as luminal B or basal-like by the PAM50 classifier, whereas the majority of low RS cases (83%) were luminal A type. Half (51%) of the intermediate RS cancers were re-categorized as low risk luminal A cancers by PAM50 (Fig.3). All luminal A cancers were either low (70%) or intermediate (30%) risk by RS, whereas luminal B cancers were comprised of a mixed risk group by RS including 33% assessed as high risk by OncotypeDX®.

Practice point and future research opportunities

Two multi-gene assays designed to predict the risk of disease progression and response to chemotherapy in breast cancer produce broadly similar results for high and low risk patients, but do not always agree in their predictions for patients at intermediate risk. At the present time, it is uncertain whether patients with an intermediate OncotypeDx® recurrence score benefit from chemotherapy and it is interesting that PAM50 re-categorized about half of these patients to the low risk luminal A category which suggests that these patients may not benefit much from adjuvant chemotherapy due to their already very good prognosis and limited chemotherapy sensitivity. This is the first study that compared these two conceptually different prognostic risk predictors. PAM50 is currently undergoing validation and researchers will have to wait for outcome data to see which test is most accurate in predicting outcome.

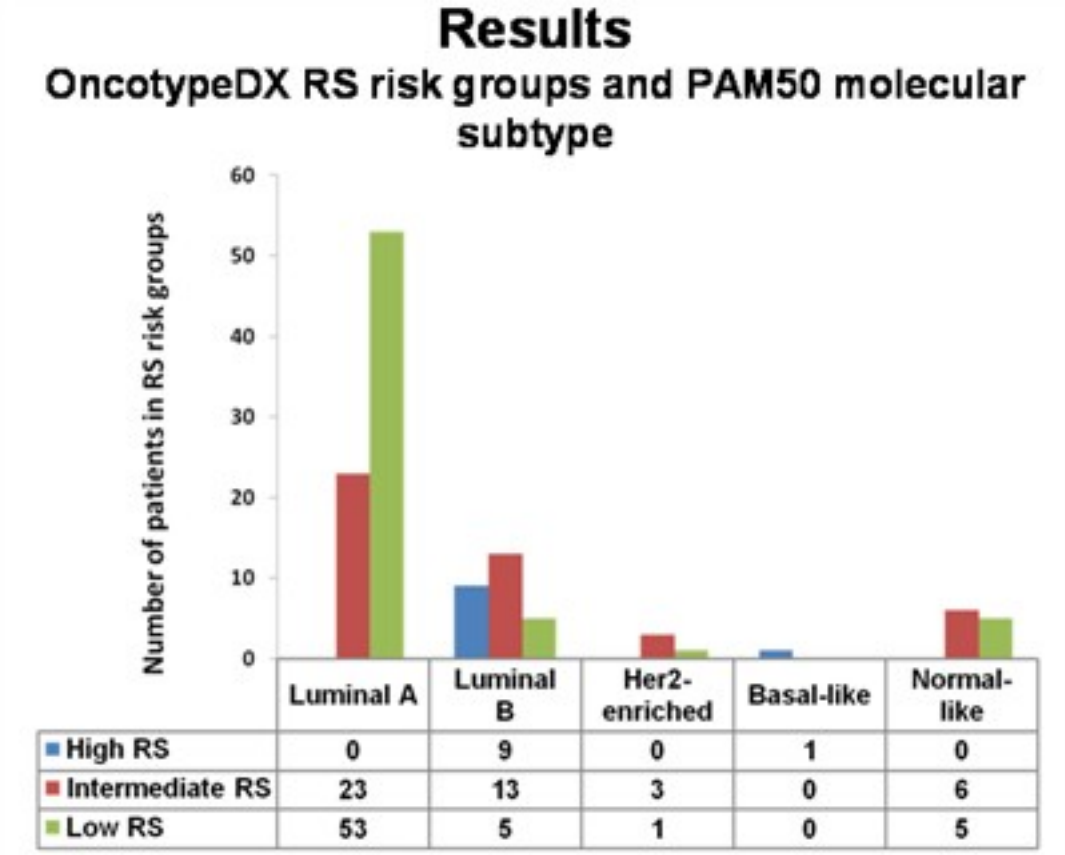



Fig. 3. OncotypeDX recurrence score risk groups and PAM50 molecular subtype (courtesy of Catherine Kelly)

## PREOPERATIVE CELECOXIB TREATMENT REVEALS ANTITUMOR RESPONSE AT MOLECULAR LEVEL IN PRIMARY BREAST CANCER TISSUES

Dutch researchers reported results of a randomized trial, conducted in 45 patients with primary invasive breast cancer. Patients were randomized to receive either 400mg celecoxib twice daily for two to three weeks, or control treatment, which was either placebo or no treatment. The researchers analyzed the expression of particular genes in samples from the tumors before and after the treatment. Immunohistochemical Ki67 and caspase-3 staining were performed on all tissue sections to determine changes in proliferation and apoptosis.

After treatment, 1,109 genes were significantly up-regulated and 556 genes were significantly down-regulated in celecoxib-treated breast cancer tissues, when compared to control treatment. Pathway analysis of deregulated genes revealed overrepresentation of genes involved in cell proliferation, cell cycle, apoptosis, extracellular matrix biology, and inflammatory immune response corresponding to an antitumor activity (Fig.4).

The number of patients enrolled in the study was too small to adequately highlight the benefit of using celecoxib. The treatment period was not long enough to see a significant change of tumor size or histological grade, and it can be only speculated whether a longer treatment with celecoxib would have resulted in measurable tumor shrinkage as well. However, the researchers concluded that even short preoperative treatment with celecoxib sets up transcriptional programs supporting antitumor activity in primary breast cancer tissues.

Practice point and future research opportunities

The results of this initial study show that neoadjuvant celecoxib can induce an antitumor response at molecular level, and confirm the existing data from several preclinical studies by showing that COX-2 inhibition leads to changes in cell proliferation, apoptosis, and extracellular matrix biology in primary breast cancer tissues. Until now, most clinical results suggested that COX inhibitors may be useful for cancer prevention, and these novel findings might provide evidence that COX-2 inhibition could also be efficient as cancer treatment, at least in breast cancer. Currently, COX inhibitors are well established medications for some other, non-cancerous, diseases and have relatively low toxicity. There are close links between COX-2 expression, HER-2 status, and aromatase levels in breast cancer, and therefore it could be rational to investigate COX2 inhibitors in such combinations. However, sufficiently powered studies, longer treatment, and follow-up are needed to validate initial observations from this study.

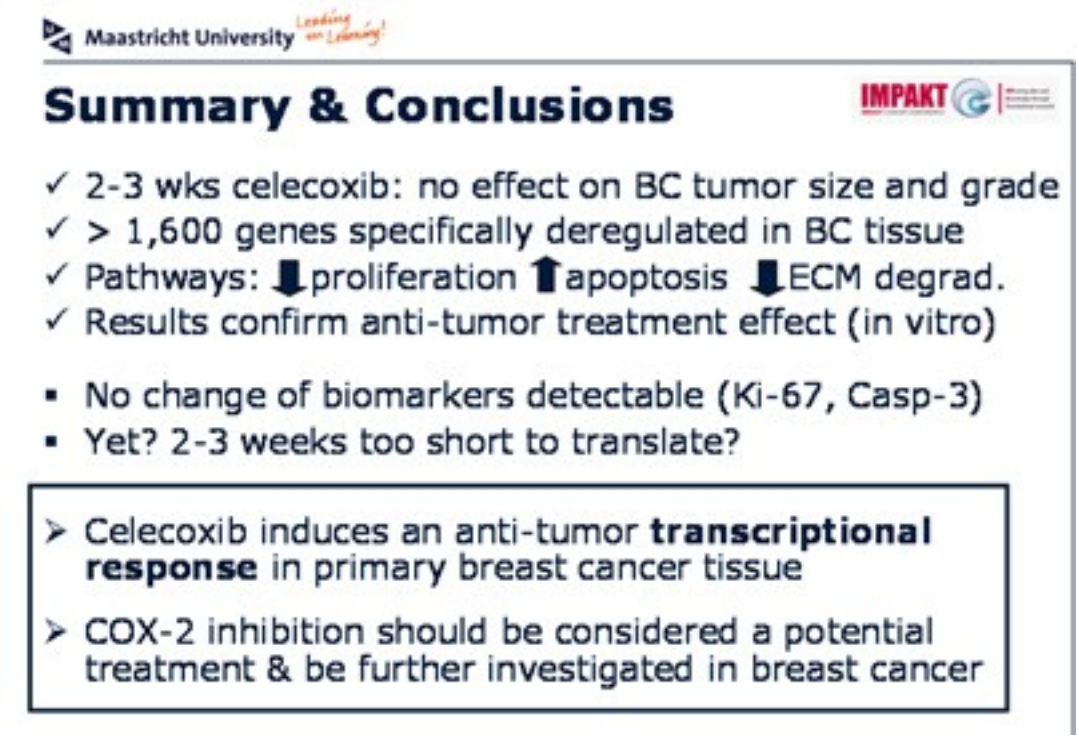



Fig.4. Celecoxib sets up transcriptional response in primary breast cancer tissues (courtesy of Jürgen

Veeck)

## THE WNT SIGNALLING CASCADE AS A POTENTIAL NOVEL BIOMARKER OF TRIPLE NEGATIVE BREAST CANCER

German researchers undertook a three-step study in examining a role of wnt signaling cascade in triple negative breast cancers. First, they conducted a gene expression analysis in breast cancer tissue samples, looking specifically for genes whose expression level differed between triple negative cancers and non-triple negative cancers. That analysis revealed that sFRP1 was the most highly overexpressed gene in triple negative breast cancer relative to others. The degree of difference was up to 4.7-fold in triple negative vs. non-triple negative breast cancers. The results were a surprise to researchers, as sFRP1 has so far been understood as an antagonist within the wnt signaling cascade.

The researchers then tested genes for an association with relapse-free survival and response to neoadjuvant chemotherapy, finding that while sFRP1 expression was not associated with recurrence-free survival, it was significantly correlated with an increased sensitivity to neoadjuvant chemotherapy. No correlation between expression of Ki67 and sFRP1 could be demonstrated.

Finally, the researchers conducted knockdown experiments in cell culture, using the triple negative breast cancer cell line MDA-MB 468. These experiments involved the use of siRNA, designed to block the expression of sFRP1. In breast cancer cells where sFRP1 expression was knocked down, there was significantly decreased sensitivity to paclitaxel, doxorubicin, and platinum-containing chemotherapy (Fig.5).

Practice point and future research opportunities

A level of the molecule sFRP1, which is much more highly expressed in triple negative breast cancer, correlates in an individual tumor with its sensitivity to chemotherapy. It is needed to further validate sFRP1 signaling as a biomarker tailored to the triple negative breast cancer. Although, the approach used in this study provides more insights into the wnt pathway and represents a proof-of-principle, the results are not yet ready to be transferred to the clinic. The researchers are currently in the process of examining the effect of knockdown of other members of the wnt pathway and of transfection of sFRP1 naive cell lines with a sFRP1 containing vector on in-vitro behavior of triple-negative breast cancer cell lines.

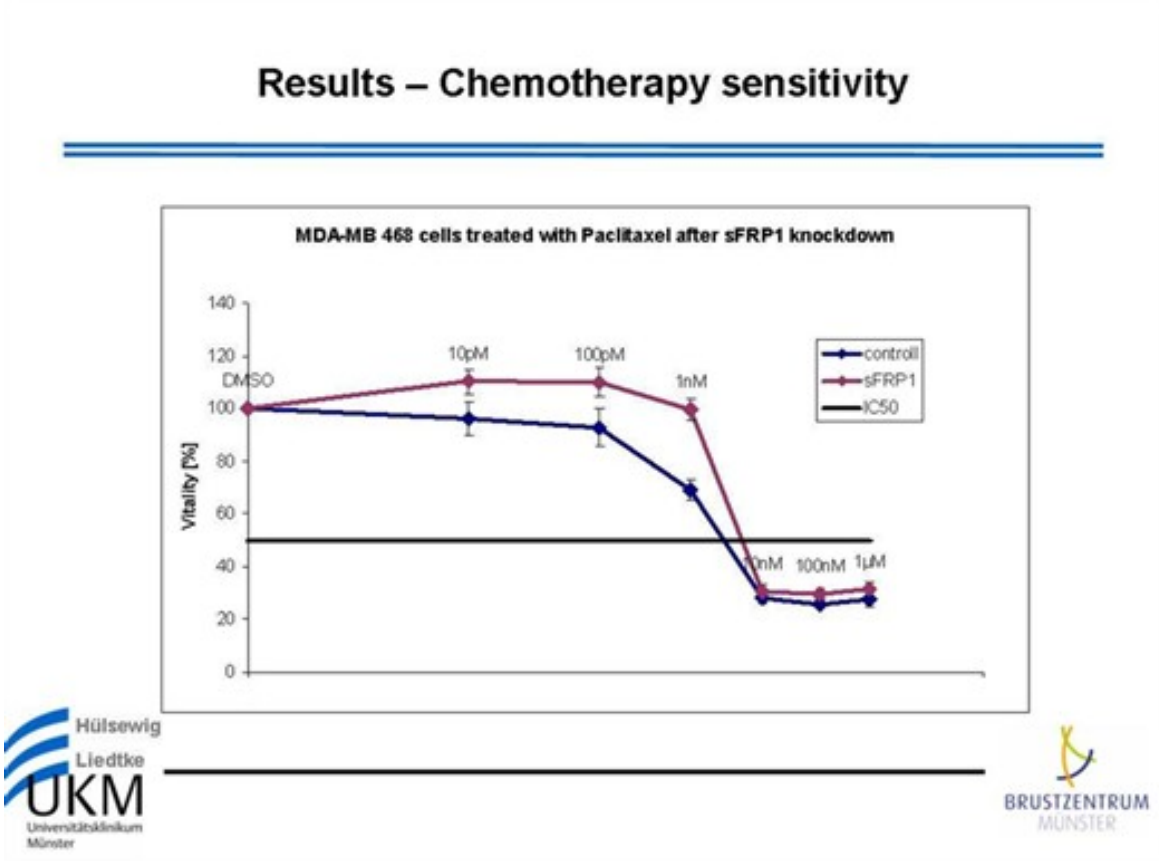



Fig.5. In vitro analysis: sFRP1 knockdown results in a chemo-resistance (courtesy of Carolin Huelsewig)

## COMBINING PROTEIN INTERACTION AND GENE PROFILING METHODS FOR PREDICTING LAPATINIB RESPONSE

UK scientists presented cutting-edge research on molecular interactions that could help predict how breast cancer patients will respond to lapatinib. They used a microscope technique known as Foerster Resonance Energy Transfer (FRET) imaging, which allows measuring the interactions between proteins.

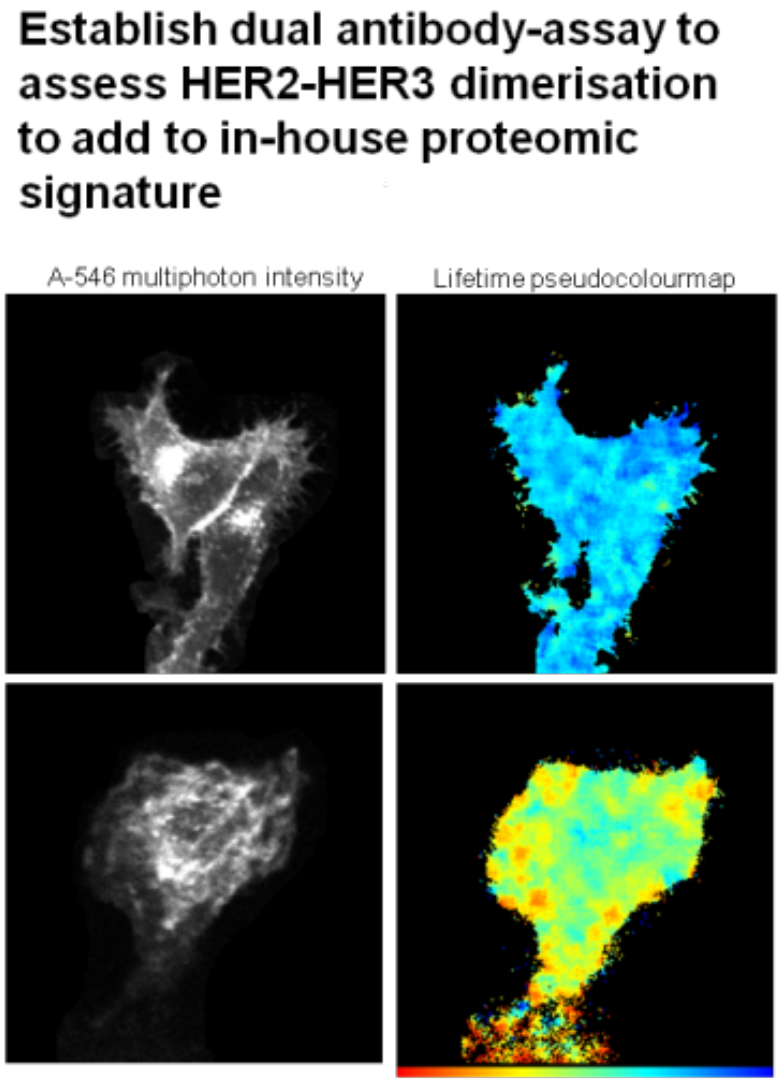
In an earlier work, the group used this molecular imaging technique in a breast cancer cell line to characterize molecular determinants for the lapatinib-responsive formation of the HER2/HER3 complex (Fig.6). Researchers now aim to establish a signature representing functional molecular biology, by examining protein-protein interactions, and to correlate this signature with established prognostic gene transcription signatures and clinical and radiological data to predict patient outcome in terms of response to lapatinib. The results presented at IMPAKT are the start of their work.

The technology captures images of the molecular state of HER2/HER3 dimer. Researchers have also

identified a specific mutation in HER2, which reduces dimerization and the lapatinib effect. It is possible to test tumor samples for this HER2 mutation, which would confer resistance to treatment.

Practice point and future research opportunities

Currently, more than 60% of patients with breast cancer exhibit primary resistance to lapatinib. With this work, researchers aim to add to the tools available a signature that reflects the functional state of cancer cells, by assessing protein-protein interactions. Their goal is to integrate this information with genomic and clinical data to more accurately identify a population of patients most likely to benefit from treatment.




Upper panel: HER3-X546 IgG alone
Lower panel: HER2-Cy5 IgG +HER3-X546 IgG

Fig.6. HER2-3 dimers imaged for the first time using an antibody based assay (courtesy of Gargi Patel)

The 3rd IMPAKT Breast Cancer Conference with its scientific backbone served as an ideal platform for social networking among delegates. A Poster walking session was a chance to truly engage with the presenters and dedicated expert faculty members assigned to a specific poster category. The session drew a huge interest among IMPAKT participants and served as a good opportunity to interact closely with the faculty of renowned breast cancer experts.

Poster walking session: A detail from the poster area on abstracts in the Circulating Tumor Cells category

Nineteen travel grants were awarded by the IMPAKT 2011 Breast Cancer Conference Scientific Committee on a competitive basis from among the accepted abstracts. From those, 8 travel grants were awarded by the Susan G. Komen for the Cure® to early-career oncologists actively working in the field of breast cancer translational research. Grants were awarded on the merits of individual applications based on the recommendation of the IMPAKT 2011 Scientific Committee.


The IMPAKT exhibition space is an important component of the Conference, providing participants with an ideal platform to network with pharmaceutical and bioresearch organizations and a dedicated opportunity to gain further insights into tangible advances in the research and treatment of breast cancer. In addition, it was the place to meet colleagues and exchange news and ideas beyond the program sessions during the lunch and coffee breaks.


The foundation of IMPAKT left us a serious task for the future and the 3rd edition of IMPAKT Breast Cancer Conference successfully addressed some of the challenging aspects. We wish to thank all members of the Scientific Committee, invited speakers, the Conference organizers, collaborators, and sponsors for their commitment and dedication to making IMPAKT a must-attend meeting in translational research in breast cancer. We thank all participants of the 3rd IMPAKT Conference and we look forward to seeing all of our colleagues from around the world again next year.

## RELATED INFORMATION

Click here to access the meeting abstract page.

Click here to access the meeting webcast page.

Save the date: IMPAKT Breast Cancer Conference 3-5 May 2012, with the pre-conference Early-career oncologist training course, 2-3 May 2012.

## AFFILIATIONS

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