

The 4th IMPAKT Breast Cancer Conference: IMProve cAre and Knowledge through Translational research

3-5 May, 2012

Brussels, Belgium

SUMMARY

IMPAKT is an international conference dedicated to translational research and drug development in breast cancer. IMPAKT focused this year on PI3K and metabolism, next generation sequencing and tumor heterogeneity, triple negative breast cancers and implementation of gene expression arrays in daily practice. Several key messages were delivered during the conference. Firstly, PI3K has very strong interactions with DNA repair, and some strategies combining PI3K and PARP inhibitors could lead to antitumor effects. Secondly, a tumor should no longer be considered as a single population of cells, but rather as a population of heterogeneous cells. Thirdly, data have been presented that suggest that targeting DNA repair could impact outcome in triple negative breast cancers. Finally, although the technology is ready for implementation, the genomic signatures have not yet shown that they change patient outcome in the context of prospective trials.

INTRODUCTION

IMPAKT is a unique breast cancer conference that bridges the gap between research and the clinic while also providing the right environment for young professionals to network with and access the knowledge of their senior counterparts. IMPAKT 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.



The 4th IMPAKT conference has attracted 555 attendees from 57 countries. The Conference was a resounding success. As usual, IMPAKT was divided into the training course and main conference. A particular effort was made this year to attract colleagues from Asia. Also, several partnerships were developed to broaden the attendance. This includes a new partnership with the European Society of Pathology (ESP). The main conference focused on four topics: metabolism, next generation sequencing, triple negative breast cancer and gene expression arrays for daily practice.

TRAINING COURSE

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 approximately 80 early-career oncologists, researchers and pathologists, selected through application on a competitive basis, to ensure an ideal learning environment. The training course faculty welcomed the participants with a networking 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.

This year the training course focused on PI3K biology and new technologies. All aspects of cancer research were discussed during the part dedicated to PI3K. L. Cantley introduced the biology followed by B. Hennessy who introduced the genomic alterations observed in breast cancer. Finally, presentations were given on clinical development. Interestingly, some speakers from pharmaceutical companies were present to give an industry perspective to this topic. The part dedicated to new technologies discussed all possible perspectives introduced by the development of high throughput molecular approaches. J. Reis Filho gave a very elegant presentation on next generation sequencing (NGS) and summarized what we can expect from NGS in breast cancer research. One of the messages from the training course was the fact that NGS will not solve all research issues in breast cancer, and new, complementary approaches, are needed including assessment of protein activation, assessment of non coding RNA, splicing, and other techniques in order to have a more

comprehensive picture of altered pathway in each breast cancer patient.

SCIENTIFIC HIGHLIGHTS OF THE 4th IMPAKT BREAST CANCER CONFERENCE

The main meeting was divided into four scientific topics (PI3K-metabolism, tumor heterogeneity and next generation sequencing, triple negative breast cancer and gene expression arrays) and the presentation of original research.

Selected presentations of original research

Ten abstracts were selected for presentation during the two oral sessions. These abstracts were then discussed by experts, who aimed to put the presented data into perspective. We summarize below the main presentations.

A significant number of the presented abstracts were related to gene expression array.

Igniatiadis et al. presented a meta-analysis of studies testing gene expression array in the neoadjuvant setting. The main goal of the analysis was to identify associations between pathological complete response (pCR) and gene modules describing biologically relevant processes and "druggable" oncogenic pathways in breast cancer subtypes. They reported that immune signatures could provide additional information on clinical and pathological characteristics, regarding chemosensitivity. Their analysis shows that high expression of immune modules is independently associated with increased pCR in HER2-positive and ER-negative/HER2-negative subtypes, suggesting that novel immune strategies may be tested in these subtypes.

Azim et al. evaluated which genomic pathways were enriched in breast cancers from young women. For example, a gene signature of the PI3K molecular pathway is highly associated with young age. PI3K is an important targetable signalling pathway in breast cancer and these results could encourage investigating its role in breast cancer arising in young women. This study looked at genomic data from 3,000 patients and showed that young age is associated also with high expression of RANKL. RANKL is known to play a vital role in the spread of cancer to the bones, and emerging preclinical data have shown that RANKL appears to have an antitumor effect aside from its role in bone metastasis. Putting all the information in context, the researchers hypothesized that perhaps targeting RANKL could be particularly interesting in young breast cancer patients. They are in fact planning a clinical trial in which premenopausal breast cancer patients will receive two injections of denosumab, which is a RANKL-inhibitor, one week before surgery. The aim of the study is to evaluate the effect of RANKL-targeting on the tumor biology. The study is expected to start before the end of 2012.

Still in the field of genomic data, Sinn et al. reported that a high level of MUC1 is associated with resistance to chemotherapy. This finding is interesting considering that cancer vaccines targeting MUC1 are currently tested in clinical trials. The aim of their study was to evaluate the frequency of MUC1 expression and its predictive value for response and survival after neoadjuvant anthracycline/taxane-based chemotherapy. They observed that MUC1 is frequently expressed in a large cohort of breast cancers, especially in hormone receptor positive tumors. Evaluation of this gene is feasible by immunohistochemistry and QRT PCR. Low levels of expression were predictive for pathological complete response following neoadjuvant chemotherapy in this study.

Several presentations related to targeted therapies.

Bachelot et al. evaluated predictive biomarkers for the efficacy of everolimus in patients presenting an estrogen receptor positive breast cancer resistant to endocrine therapy. Based on a small number of patients, they could identify that activation of the pathway (pS6K) was associated with an increased sensitivity to everolimus. More interestingly, they reported that a subset of breast cancer is lacking LKB1, a key molecular event for the mTOR activation. This LKB1 loss was associated with higher sensitivity to mTOR inhibitor everolimus.

Finally, in the field of drug development, Finn et al. reported results of a phase II randomized trial showing that a CDK4 inhibitor could reverse resistance to endocrine therapy. PD0332991, a selective inhibitor of CDK4/6, prevents cellular DNA synthesis by blocking cell cycle progression. Preclinical studies in a breast cancer cell line panel identified the luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16 expression as being associated with sensitivity to PD0332991. Synergistic activity was also observed in vitro when combined with tamoxifen. Based on these observations, a phase I/II study in combination with letrozole was initiated and the researchers presented at IMPAKT results from the randomized phase II portion on 66 randomized patients. Their findings show that the combination of PD0332991 and letrozole is well tolerated with encouraging clinical benefit, confirming the sensitivity of ER-positive breast cancer observed in preclinical models.

The 4th 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. Twenty travel grants were awarded by the IMPAKT 2012 Breast Cancer Conference Scientific Committee on a competitive basis from among the accepted abstracts.



Report from scientific sessions

An impressive list of invited speakers covered the part of the main IMPAKT Conference program dedicated to 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 two keynote lectures focussed on targeting PI3K/Akt/mTOR pathways in breast cancer and intratumor heterogeneity as a challenge for personalized medicine. All topics were presented by world renowned scientists and then discussed from the clinical perspective. The first keynote lecture was also followed by a discussion on the implications for development of biomarkers.

The first half day presentations were dedicated to PI3K and metabolism. During a keynote lecture, L. Cantley presented new data about the interaction between PI3K and DNA repair. He showed that PTEN loss and PI3K activation are associated with a deficiency in DNA repair pathway in triple negative breast cancer. Interestingly, he showed that combining PI3K inhibitors and PARP inhibitors induced synthetic lethality and had major antitumor effects in triple negative breast cancers. It is planned to investigate this strategy in clinical trials. A full session was dedicated to metabolism and emphasized the potential of AMPK inhibitors (metformin) in the breast cancer treatment and prevention. Finally, in the session dedicated to FGFR inhibitors, the rationale for developing such drug family in combination with endocrine therapy was discussed. A presentation on clinical development emphasized the challenges in terms of clinical operation.

The second day was dedicated to tumor heterogeneity and next generation sequencing. C. Swanton reported data on next generation sequencing and showed that cancers present a high level of molecular heterogeneity. Interestingly, this heterogeneity does not affect the initial oncogenic events, and expert opinion is becoming more and more consensual that cancers behave like a tree where key oncogenic events could be the trunk and acquired genomic events could be the branches. This new way of looking at the cancer genome was made possible thanks to next generation sequencing.

During the afternoon, a full session was dedicated to new therapeutic strategies in patients with triple negative breast cancers.

Finally, half a day was dedicated to the application of new technologies to practice. A joint ESP-ESMO-BIG session emphasized the need for central assessment of molecular markers for patient stratification. This session also emphasized the role of pathologist in the development of personalized medicine. Finally, the meeting ended with the first consensus conference on breast cancer biomarkers. This consensus conference evaluated the medical usefulness of genomic tests for chemotherapeutic decision-making, and which tools could optimally define breast cancer subtypes. The working group concluded that the prognostic value of Oncotype Dx and MammaPrint tests has been validated. Nevertheless, their clinical utility still needs to be proven. Finally, the second working group concluded that neither genomic, nor immunohistochemistry (IHC)-based classifications presented clinical utility.

RELATED INFORMATION

Click [here](#) to access the Conference abstracts.

Click [here](#) to access the meeting webcast page.

Save the date: IMPAKT Breast Cancer Conference 2-4 May 2013, with the pre-conference training course, 1-2 May 2013.

AFFILIATIONS AND DISCLOSURE

Affiliations

Fabrice Andre, 4th IMPAKT Scientific Committee Chair

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Disclosure

Fabrice Andre: Advisory board, speaker board Novartis.

Sherene Loi: Reported no conflicts of interest..

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