Scientific Meeting Report

Christos Sotiriou, Executive Committee Chair · Angelo di Leo, Scientific Committee Chair

The 2nd IMPAKT Breast Cancer Conference: **IMP**rove c**A**re and **K**nowledge through **T**ranslational research

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IMPAKT
BREAST CANCER CONFERENCE
improving care and knowledge through translational research

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The 2nd IMPAKT Breast Cancer Conference: IMProve cAre and Knowledge through Translational research

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 multi-disciplinary 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 St. Gallen Primary Therapy of Early Breast Cancer Conference, 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 2nd IMPAKT Breast Cancer Conference took place in Brussels in a new and strikingly modern environment. SQUARE Brussels Meeting Centre is housed in the extensive former Palais des Congrés, an elegant, architecturally significant building originally constructed for the 1958 World Expo. Many of the original features, including expansive murals by Paul Delvaux, René Magritte and Louis van Lint, have been carefully restored and are now juxtaposed with contemporary design conceived by a team of leading European designers.

The 2nd IMPAKT Conference was a resounding success, with 737 participants from 56 countries. By evaluating the novel scientific discoveries, delegates could better understand their relevance and future directions in the research and treatment of breast cancer. New molecular and functional diagnostic, prognostic, and predictive tools are being developed and participants could learn about methodologies, and where we stand in the practical implementation of these novel techniques.

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 80 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 Educational program was composed of lectures on DNA sequencing, Comparative genomic hybridization array, Epigenetics, RNA expression profiles, Emerging technologies on mi-RNA and metabolomics, and Circulating markers. Within the Pathology session, renowned experts spoke about standard biomarkers and systems pathology.

Following this were lectures focused on the methodology in biomarkers research, the challenge of statistical validation of biomarkers, and ins and outs of the careful markers assessment.

An impressive list of invited speakers covered the part of the Conference program on recent scientific discoveries. The fact that all of the topics were presented by scientists who have been involved in the discoveries testifies to the quality of the program. The program comprised keynote lectures on Interrogating the architecture of cancer genomes and Cancer metabolism as a potential treatment target.

During the lecture, Peter Campbell of the Cancer Genome Project, Wellcome Trust Sanger Institute, Cambridge, UK spoke about the findings from the first handful of genomes which illustrate the potential for next-generation sequencing to provide unprecedented insights into mutational processes, cellular repair pathways and gene networks associated with cancer development. He also reviewed possible applications of these technologies in a diagnostic and clinical setting, and the potential routes for translation.

Grahame Hardie of the College of Life Sciences, University of Dundee, UK presented a truly interesting lecture on a key cellular inhibitor of target-of-rapamycin complex-1 (TORC1) - the AMP-activated protein kinase (AMPK), a sensor of cellular energy status. AMPK is activated by the biguanide drug metformin and, intriguingly, retrospective studies have shown that diabetics treated with metformin have a lower incidence of cancer. Whether AMPK activators will be useful for treating existing cancer remains unclear at present, although clinical trials are underway.

Eric Winer of the Department of Medicine, Dana Farber Cancer Institute, Boston, USA spoke about neoadjuvant trials that can be used to identify the most active treatment schedule/regimen, to estimate an effective size, and to narrow the population included in a definitive study by correlating clinical and biologic parameters with response. While early phase trials will generally not lead directly to a change in clinical practice, they can speed the conduct of the definitive phase III trial. At present, studies must show an improvement in disease-free and overall survival to result in a change in clinical practice, but ultimately oncologists hope to use response in the breast and/or regional lymph nodes to define new standards of care. Before adopting such an approach, there is a need for additional studies that demonstrate a strong association between improvement in breast response and long-term outcomes.

During the session on practice-changing discoveries in translational research, speakers covered topics on cytotoxics as targeted agents, resistance to anti-HER2 agents, and how to overcome resistance to hormonal therapy. John Bartlett of the Edinburgh Cancer Research Centre, UK debated the potential value of biomarkers to aid selection of patient groups most likely to benefit from cytotoxic treatments. Recent advances in biomarkers of anthracycline response may indicate fresh directions for future research and potential clinical utility. Biologically targeted agents, such as PARP inhibitors, when combined with appropriately selected cytotoxic agents, are being used to target pathways to increase the therapeutic efficacy of both the biological and cytotoxic treatments. Such combinations of targeted delivery of cytotoxic agents with biological agents represent a significant potential for future progress in treating early breast cancer.

The 2nd IMPAKT Conference also covered multiple molecular pathways in breast cancer development and progression, with topics presented from the point of view of basic scientists and also from the perspective of clinicians, who provided further insight into the drugs in development for those particular pathways. Presentations were followed by discussion, mixed with questions from the floor. Imaging specialists added to the discussion by identifying early signs of drug response, and patient entities who will most likely respond to targeted therapies that interfere with those pathways.

From abstracts submitted to different categories (Detection and diagnosis, Loco-regional therapy, Adjuvant medical therapy, Imaging, Molecular biology (preclinical), and New drug development), the Scientific Committee selected 126 abstracts for oral and poster presentations. The IMPAKT Abstract Book, published in a supplement of Annals of Oncology, is a compilation of basic, translational, and clinical research in breast cancer, and includes a range of abstracts from molecular biology and biomarkers to imaging and drug development. Here we present some of the scientific results presented during IMPAKT and attempt to put challenging translational research questions into perspective:

1. To shed a new light on the issue of different breast cancer subtypes and the reliability of groupings, Dr Benjamin Haibe-Kains and colleagues of the Computational Biology and Functional Genomics Laboratory, Dana-Farber Cancer Institute, Boston, USA, the Functional Genomics and Translational Research Unit, Institut Jules Bordet, Brussels, Belgium, and the Machine Learning Group, Universite Libre de Bruxelles, Brussels, Belgium, performed the largest comparative study to date, analyzing 32 publicly available gene expression datasets which included 4607 breast cancer patients and six different classification models. Furthermore, they studied their concordance with respect to molecular subtypes and their clinical relevance through survival analysis of 1471 untreated node-negative pa-

tients. Two main classes of classification models, the Single Sample Predictor (SSP) and the Sub-type Classification Model (SCM), were analyzed in terms of concordance and prognostic value and, for the first time, investigators estimated their robustness - capacity to assign the same tumors to the same molecular sub-types whatever the gene expression data used to fit this model. They found that SCM models were significantly more robust than SSPs in identification of molecular subtypes. Although all models were concordant, SCM models yielded stronger concordance than SSPs models. Importantly, survival analysis of SCM yielded better discrimination of low-risk patients (low-proliferative ER+/HER2- tumors).

Practice point and future research opportunities

In this study investigators observed that sub-type classification models, including a simple model that uses only three genes (ESR1, ERBB2 and AURKA) were significantly more robust than single sample predictors. By demonstrating the robustness and concordance of the three-gene model, this study is a significant step towards bringing this classification model into the clinic. The technology is quite challenging and may take a few years for validation and feasibility studies, followed by development into an inexpensive commercial assay.

2. Belgian and USA researchers led by Dr Sherene Loi from the Institute Jules Bordet in Brussels, Belgium have discovered molecular evidence that may explain why some women with HER2 over-expressing breast cancer do not respond to trastuzumab. They used 11 datasets with gene expression and clinical outcome data (1100 patients among whom 17% HER2+), array comparative genomic hybridization (309 patients among whom 27% HER2+), 74 HER2+ treated by neoadjuvant trastuzumab, and HER2+ breast cancer cell lines treated with anti-HER2 agents to determine if estrogen receptor (ER) status plays a significant part in the biology of HER2+ breast cancer and response to anti-HER2 therapies. Their results show that patients with ER+/HER2+ compared with ER-/HER2+ breast cancers have different outcome. Investigators noted that in HER2+ breast cancer, ESR1 gene expression was significantly inversely correlated with ERBB2, EGFR, and gene sets of RAS, RAF, MAPK and MEK pathway activation. However, there were positive correlations between ESR1 and ERBB3 and AKT1. A gene set of PI3K/AKT pathway activation could predict pCR in trastuzumab-chemotherapy patients in ER+/HER2+ but not in the ER-/HER2+ group. These data explain why ER+/HER2+ patients may actually benefit more from drugs that inhibit the PI3K/AKT molecular pathway, as this could be the dominant biological pathway for tumor growth and progression.

Practice point and future research opportunities

In HER2+ breast cancer patients, ER status defines distinct molecular and clinical phenotypes. ER signaling may antagonize EGFR/RAS/MAPK signaling, leading to increased PI3K/AKT output in ER+/HER+ breast cancers. Future clinical trials in HER2+ breast cancers should be stratified for ER status. Furthermore, each HER2+ sample could have a different profile of kinase activation and it can have implication for combination trials (mTOR inhibitors, MEK inhibitors, ERBB3 inhibitors,…).

3. Genomic analysis by microarray and, more recently, DNA sequencing has provided important insights into the role of copy number variation in human cancer. However, these methods can yield only approximate results when applied to mixed populations of rapidly evolving cells. In such cases our understanding would be improved by dissecting genetic events at the single cell level. James Hicks, PhD, of the Cold Spring Harbor Laboratory in New York, USA and colleagues have developed a method of single nucleus sequencing (SNS) to quantify the genomic copy number of individual tumor cells. They have used SNS along with other methods for genomic profiling to analyze tumor segments and more than 100 single cells isolated from macrodissected primary tumors and metastases. From two heterogeneous basal-like breast carcinomas they constructed a detailed phylogenetic lineage, showing that the majority of cells belong to one of several major subpopulations that have clonally expanded to form the mass of the tumor. In both cases the earliest detectable evolutionary stage was a hypodiploid clone with a characteristic sawtooth pattern. A geographically adjacent segment contained cells carrying the identical genomic markers that had apparently undergone endoreduplication to generate a pseudo-triploid genome that in subsequent steps had acquired many additional focal amplifications and deletions of cancer genes including in one case, KRAS, EFNA5 and COL4A5.

Practice point and future research opportunities

Single cell copy number profiling confirmed that the vast majority of genomic events characteristic of the clones were present in each individual cell and that complex aneuploid patterns are not the result of mixed populations of tumor cells, but rather represent single tumor cells that have clonally expanded. These simple findings open up enormous research possibilities. Still, single-cell analysis is too time consuming, expensive, and experimental for use in clinical practice but if further validated and developed, it could assist genetic researchers who are looking into biomarkers. While the researchers studied only breast tumor cells, the results may apply to other tumor types, and investigators see a possible role for the single nucleus sequencing method in fine needle aspiration of prostate cancer.

4. Dr Antonio Giordano of the MD Anderson Cancer Center, Houston, USA reported results of the study in which an artificial neural network (ANN), a sophisticated computer model, has been used to investigate the relationship between increasing numbers of circulating tumor cells (CTCs) and survival for different, immunohistochemically defined, molecular subtypes of primary breast cancers. Since 2004, it has been known that patients with 5 or more of CTCs in 7.5 ml of blood survive on average for less time than those with fewer than 5 cells. Dr Giordano and colleagues used a training dataset from 310 (60%) of 516 consecutive metastatic breast cancer patients to develop the artificial neural network and predict the probability of death. Overall survival was calculated from the date of baseline CTC measurement. The following covariates were evaluated by ANN: age, estrogen and progesterone receptors, HER2, visceral metastasis, metastatic disease sites, type and line of therapy, CTC continuous value. Predictions obtained in the training dataset were validated in a test set comprising the other 40% (206) of patients. At the median follow-up (12.5 months), risk of death estimated by ANN linearly increased with increasing number of CTCs (0-250) in all molecular subtypes of tumor. Patients with >100 CTCs had the highest Log-Hazard at one year compared with all other quintiles' of CTC number. Most importantly, the risk of death after 1 year for patients with 40 circulating tumor cells in 7.5 ml of blood was about twice that for patients with none.

Practice point and future research opportunities

These results show that the simple cutoff number of 5 circulating tumor cells probably does not adequately represent the complexity of this prognostic variable. Translated to clinical practice, results of this study suggest that monitoring of circulating tumor cell numbers should now be considered for patients with metastatic breast cancer. While the treatment of this condition remains palliative, monitoring of circulating tumor cells could help determine when to modify regimens or discontinue therapy.

5. The study of Lorenza Mittempergher of The Netherlands Cancer Institute, Amsterdam, The Netherlands, evaluated if the DASL gene expression assay, specifically designed to generate reproducible data from degraded RNAs, is a reliable method to apply on RNA from fixed in formalin, paraffin embedded (FFPE) tissue samples. Investigators analyzed 50 breast cancer samples (44 FFPE tissues from 1977-1999 and 2007; 6 fresh frozen (FF) tissues from 1985-1993) and 20 liposarcoma samples (12 FFPE tissues from 1986-2007; 8 FF tissues 1996-2007) on the 502 cancer-related genes DASL platform. They found a similar level of sensitivity in gene detection between matched FF and FFPE samples.

The fluorescence signal intensity between FFPE and FF tissues was comparable. The 502-DASL assay yielded high self-self correlation with FFPE RNA inputs. Because of the promising results with the 502 genes-DASL assay investigators increased the number of matched FFPE and FF samples (additional 20 breast cancer pairs FFPE-FF 2008) for analysis on the Whole Genome DASL platform (WG-DASL assay). All the samples showed a good RNA quality and the authors performed biological and technical replicates.

Practice point and future research opportunities

In light of what is reported above, emerges that the DASL assay could be a valid approach to identify/validate gene expression signatures using fixed in formalin, paraffin embedded material. Tissue samples collected during surgery and biopsies are often fixed in formalin, paraffin embedded blocks. Unfortunately, such archival material may lead to partial RNA transcript degradation, limiting the amount of information that can be derived from such samples. Results of this work could have implications to long-recruiting studies, however it remains to answer if variation in fixation affects some transcripts more than others and whether DASL assay is of more value than multiplex qRT-PCR.

6. Catherine Oakman of the Hospital of Prato, Istituto Toscano Tumori, Prato, Italy used serum metabolomic profiles in the pilot study to identify early stage breast cancer patients with residual micrometastases. Serum metabolomic assessment was performed in 44 early breast cancer patients with pre- and post-operative samples; 51 metastatic patients as control; and 45 post-operative early patients for validation. Differential metabolomic clustering was identified between early and advanced patients. This difference was used to calculate early patient 'metabolomic risk' of relapse. Metabolomic risk was compared with Adjuvant! Online 10-year mortality assessment. For most early pre-operative patients, surgery reduced the metabolomic risk. Comparison of metabolomic risk with Adjuvant! Online revealed discordance and the post-operative pattern of discordance was confirmed in the validation cohort.

Practice point and future research opportunities

In early breast cancer, current prognostic tools are inadequate. Metabolomics may be an alternative or complementary approach for identification of early stage patients with residual micrometastases. Compared with traditional risk factors, metabolomics may identify more patients with lower relapse risk. Validation of this model in the study cohort of patients with long term follow-up is underway.

Twenty-one travel grants have been awarded by the IMPAKT 2010 Breast Cancer Conference Scientific Committee on a competitive basis from among the accepted abstracts. In addition, 19 travel grants have been 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 2010 Scientific Committee.

The 2nd IMPAKT Breast Cancer Conference with its scientific backbone served as an ideal platform for social networking among delegates. New to the 2nd IMPAKT Conference program was a Poster walking session – 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, as well as a very warm reception by renowned breast cancer experts.

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.

During the 2nd IMPAKT Breast Cancer Conference, the world renowned harmonica player Toots Thielemans gave a charity concert at the Uccle Cultural Centre in Brussels to raise funds for international breast cancer research. The event was organized by the non-profit association Fonds Jean-Claude Heuson.

The foundation of IMPAKT left us a serious task for the future and the 2nd edition of IMPAKT Breast Cancer Conference successfully addressed some of 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 2nd IMPAKT Conference and we look forward to seeing all of our colleagues around the world again next year.

To watch webcast sessions from the 2nd IMPAKT Breast Cancer Conference, please visit:
http://esmo.onsite.tv/impakt2010/

Abstracts from the 2nd IMPAKT Conference are available at:
http://annonc.oxfordjournals.org/content/21/suppl_4

Save the date:
IMPAKT Breast Cancer Conference 5-7 May 2011, with the pre-conference Early-career oncologist training course 4 and 5 May 2011.

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