



2015

ISSUE 2

Plenary Lecture #2: Genomic Heterogeneity of Breast Cancer

Thursday, December 10, 9:00 am, Hall D
Samuel Aparicio, BM, BCh, PhD, FRCPath;
The University of British Columbia; Vancouver, Canada

Recent studies have presented evidence of extensive genetic variability between breast cancer patients and diversity within their tumors. Though molecular definition of subgroups of breast cancer patients and their tumors has increased the understanding of primary cancer subtypes, the heterogeneity that affects key cancer pathways and mutations continues to pose a challenge in the development of targeted medicine.

By understanding the mechanisms that contribute to this variation and the notion that cancers have been described as "ecosystems of evolving cellular clones," future clinical research can be directed to the selective pressures that drive clonal evolution. This is particularly of interest when evolution of clonal genotypes or epigenotypes can be associated with positive or negative selection.

On Thursday morning, Dr. Samuel Aparicio will discuss the work he has been doing with sequencing of tumors and methods for single-cell analysis, and how they have led to newer approaches to solid epithelial malignancies. He will also touch on the implications of clonal evolution for cancer medicine and research.

Dr. Aparicio and his team have developed a system of informatics approaches to population-level clonal analysis, and the application of these methodologies to single-cell measurements of genotypes will be discussed as well.

Data from recently conducted single-cell sequencing and clonal analysis applied to clonal evolution of patient-derived tumor xenografts will also be presented.

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THURSDAY, DECEMBER 10*

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PRESENTER UPDATE:

- S4-03- Simon N. Powel

Award

AACR DISTINGUISHED LECTURESHIP IN BREAST CANCER RESEARCH
Thursday, December 10, 11:30 am, Hall D

Molecular Evolution Under Neoadjuvant Chemotherapy

Dr. Anne-Lise Børresen-Dale
Oslo University Hospital, Oslo, Norway

The AACR Distinguished Lectureship in Breast Cancer Research has been established to recognize outstanding science that has inspired or has the potential to inspire new perspectives on the etiology, diagnosis, treatment, or prevention of breast cancer.

Dr. Anne-Lise Børresen-Dale is Professor at University of Oslo and head of the Department of Genetics, Oslo University Hospital Radiumhospitalet. She is among the leading geneticists in research on molecular biology of breast cancer, and her group was among the pioneers in expression profiling of breast carcinomas in collaboration with groups at Stanford, demonstrating that breast cancer can be divided into distinct sub-groups with differences in molecular profiles and in overall and relapse-free survival. Her achievements are seminal for understanding breast cancer evolution, and have had an enormous impact on our view of the complexity of breast cancer. She has authored more than 450 published scientific papers, books chapters, and invited reviews.

Dr. Børresen-Dale has received several prizes and awards, the most recent being the Swiss Bridge Award for Outstanding Cancer Research in 2004, the Möbius prize for Outstanding Research from the Research Council of Norway in 2008, the Helmholtz International Fellow Award, Germany in 2014, and the Fridtjof Nansen's Award for Outstanding Research in 2015. Dr. Børresen-Dale has been a Member of the Board of Directors of both AACR and ECCO, is the past president of EACR, and is an Elected Member of The Royal Academy of Science, Norway, The Norwegian Academy of Science and Letters, and the European Academy of Cancer Sciences.

Dr. Børresen-Dale's current research projects focus on exploring the systems biology of breast cancer using high dimensional data in integrated approaches. These studies aim to identify the genotypes and gene expression profiles that contribute to elevated cancer risk, radiation sensitivity, tumor aggressiveness and therapy resistance. The goal of this work is to follow the linear time course of tumor progression to dissect the molecular mechanisms triggered at each stage of disease. Using a systems biology approach, the Børresen-Dale lab follows the multidimensional interactions at various levels to improve risk estimation, prognostication, and prediction.

Antibody Therapies: Javelin and Manticore Trials

On Wednesday, Dr. Luc Dirix presented findings from the JAVELIN trial, which looked at the use of avelumab, a human anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer (BC).

Of the 168 enrolled patients, 58 had triple-negative BC (TNBC), 72 had ER+/HER2- or PR+ disease, and 26 had HER2+ disease. End-points of the study included safety and tolerability.

Avelumab was found to have an acceptable safety profile. Potentially immune-related side effects occurred in 17 patients, and were associated with decreased thyroid function, thrombocytopenia, and/or autoimmune hepatitis.

Dr. Dirix acknowledged that the overall response rate of avelumab was low (4.8%), but that there were more signs of activity in TNBC. Of the 8 responders, 5 had TNBC.

The group also found that response to avelumab was higher in patients with positive PD-L1 expression by immune cells within the tumor, compared to those with negative expression (33.3% vs 2.4%). Among 5 TNBC responders, 4 had PD-L1+ immune cells.

Adjuvant Endocrine Therapy on Disease-Free Survival and Estrogen Receptor Mutations and Outcomes

Dr. Michael Gnant presented additional data of the ABCSG-18 (Austrian Breast & Colorectal Cancer Study Group) trial on the impact of adjuvant therapy with the osteoporosis-inhibiting monoclonal antibody denosumab (DSM) on disease-free survival (DFS). Prior to this study, there was a clear benefit of adjuvant bisphosphonates in reducing recurrence and improving survival in postmenopausal breast cancer (BC) patients with early-stage hormone receptor-positive BC.

This randomized, double-blind trial compared subcutaneous DSM (60 mg every 6 mo) to placebo in 3,425 postmenopausal patients. Safety was excellent, with no measurable difference between DSM and placebo in terms of adverse events. An 18% relative DFS improvement by DSM was also indicated. The observed DFS benefit in this trial is similar to the bisphosphonate meta-analysis.

As a clinical conclusion, the adjuvant DSM dose reduces the risk of disease recurrence or death in postmenopausal BC patients. Additionally, clinical and vertebral fractures are significantly reduced and bone mineral density improved. "Personally, I believe that adjuvant DSM should be offered to postmenopausal BC patients on adjuvant aromatase inhibitors," Dr. Gnant closed.

Following the presentation on the JAVELIN trial, Dr. Edith Pituskin discussed the findings of MANTICORE, a Canadian study developed to determine if ACE inhibitors and β -blockers prevent cardiac issues and LV remodeling in HER2+ early BC patients receiving trastuzumab (TRZ)-based chemotherapy. TRZ-related cardiac toxicity is common, leading to LV dysfunction in 20% and heart failure (with 50% 5-year mortality) in 1%-5%.

In this randomized trial, 99 patients received placebo, the ACE inhibitor perindopril, or the β -blocker bisoprolol. Patient demographics were homogeneous, the treatment was safe, and a vast majority of patients tolerated the standard dosing.

The study concluded that the prophylactic use of bisoprolol therapy protects against declines in LVEF, reduces TRZ interruptions, and is safe. However, the study did not prove that ACE inhibitors or β -blockers prevent TRZ-associated LV remodeling. Because the primary end-point of preventing LV remodeling was negative, Dr. Pituskin believes it is "an important area of research in order to identify the earliest changes in cardiac geometry and function, and results hint that TRZ exposure potentially is not reversible."

Later in the afternoon, Sarat Chandralapaty discussed how he and his group turned to the BOLERO-2 trial to answer questions about prevalence and clinical outcomes of estrogen receptor (ER) mutations in metastatic BC.

They performed droplet digital PCR analysis on DNA extracted from 541 archival plasma samples from BOLERO-2, and saw a high (29%) rate of D538G and/or Y537S mutation. These mutations were correlated with a decrease in median overall survival, compared to wild-type samples.

While wild type and D538G mutation were also correlated with short median progression-free survival (PFS; \approx 4 mo and 2.7 mo, respectively), the Y537S mutant was not, suggesting "maybe that there are differences between different mutations." Similarly, patients with wild type and D538G mutation both had benefits in PFS from the addition of everolimus to exemestane therapy, but those with Y537S mutation did not see an increase in median PFS.

Understanding these types of differences between variations of mutations may help predict the efficacy of therapies in certain populations of patients.

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

* At Press Time

Updated Abstracts

P2-05-19: BREAST CANCER DORMANCY, RE-EMERGENCE, AND TREATMENT

Sarah E. Wheeler¹, Amanda M. Clark¹, Venkateswaran C. Pillai¹, Carissa L. Young², Colin Beckwitt¹, Donna B. Stolz¹, Douglas A. Lauffenburger², Raman Venkataraman¹, Linda G. Griffith², Alan Wells¹

¹Departments of Pathology, Cell Biology, Surgery, Pharmaceutical Sciences, McGowan Institute for Regenerative Medicine, University of Pittsburgh School of Medicine and University of Pittsburgh Medical Center and the Center for Innovative Regenerative Therapies;

²Biological Engineering Department, Massachusetts Institute of Technology, Cambridge, MA

Breast cancer (BrCa) mortality continues to result predominately from distant metastases that can emerge years after successful treatment of the primary disease. Metastatic resistance to agents that eradicate the primary mass is likely due to protection from the metastatic microenvironment and the quiescent state of dormant BrCa cells. Advancements for the treatment of metastatic tumors have been made, but significant progress has been hampered by the lack of relevant model systems, particularly for dormancy. We address this gap with an innovative all-human 3D liver microphysiological system (MPS). The liver is both a major site for BrCa metastasis (and other solid tumors) and the primary site of drug metabolism and limiting toxicities, an important consideration in evaluating cancer therapy efficacy and availability.

Primary hepatocytes and non-parenchymal cells (NPC) from human liver resections were seeded into the MPS. Following tissue formation on day 3, tagged BrCa cells were seeded and allowed a minimum of 4 days to integrate into the tissue before interventions were initiated. On day 7, chemotherapy treatment of micrometastases was initiated for 72h. Cultures were allowed 3 days to recover before the MPS was challenged with inflammatory factors (LPS/EGF) for 48h. BrCa cells were then re-treated with chemotherapy (either the same or alternate therapy) on day 21 for 72h. Hepatocyte function and injury were measured by urea, AST, ALT, A1AT, fibrinogen and CYP P450 assays. BC proliferation was monitored by quantification, Ki67 staining, and EdU incorporation. Communication networks within the metastatic microenvironment during different stages of metastatic BrCa progression were identified using Luminex assays (55 analytes).

The metastatically aggressive MDA-MB-231 BrCa cells demonstrated growth attenuation after 12d of culture in a subpopulation of cells (Ki67-/EdU-). Treatment of BrCa cells with doxorubicin for 72h eradicates the cycling cells, leaving behind a dormant cell population (Ki67-/EdU-) that can be subsequently stimulated to cycle by addition of inflammatory stimuli. A second dose of doxorubicin or cisplatin reduced the BrCa load but did not eradicate the BrCa. Luminex analysis of culture supernatants identified signaling molecules potentially involved in metastatic progression. In addition, we present the use of adjuvant therapy in the MPS to prevent this outgrowth of the dormant tumor cells.

In parallel, we have piloted hydrogel scaffolds that better support tissue formation and produce signals consistent with a healthier liver physiology. Hydrogels enhanced MDA-MB-231 cell entry into dormancy, resulting in reduced efficacy of doxorubicin treatment with greater persistence of tumor load.

The MPS provides a mechanism to close the gap in understanding metastatic dormancy. We demonstrate spontaneous dormancy for the first time in an all-human system and mimicked the dormancy and outgrowth observed in patients. Namely, that dormant BrCa are resistant to chemotherapy and can be stimulated to reemerge following an inflammatory insult. The completion of these studies will provide insights into the tumor biology of metastatic seeding, dormancy, and re-emergence and provide an accessible tool for testing therapeutics against metastatic BrCa in a metabolically competent system capable of evaluating dose-limiting toxicity.

P2-13-08: BREAST LIPOFILLING: A SYSTEMATIC REVIEW OF CURRENT PRACTICE AND ONCOLOGICAL SAFETY

Umar Wazir, MBBS MRCS MSc¹, Abdul Kasem, MD FRCS¹, Hannah Headon¹, Kefah Mokbel, MS FRCS¹

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Background: Lipofilling is a reconstructive and aesthetic technique that has recently grown in popularity and is increasingly being used in breast surgery. Concerns had been raised regarding its safety when used for remodelling and reconstruction of the breast.

Methods: We reviewed the current literature by systematically searching PubMed and Google Scholar databases regarding the current evidence regarding the oncological safety of the procedure in patients seeking aesthetic breast enhancement and in patients requiring oncoplastic reconstruction.

Results: Among the 864 patients included in the currently available studies on breast cancer patients who underwent lipofilling, only 14 (1.6%) recurrences were identified. However, evidence has emerged suggestive that the use of lipofilling in the background of ductal carcinoma in situ (DCIS) may be associated with an increased risk of neoplasia.

Conclusions: Over the subsequent two decades, little evidence has been found to support these early theoretical concerns, and growing numbers of proponents of the procedure are confident in its safety. Further study is required to better delineate the effect of lipofilling on DCIS.