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Report of the EORTC Laboratory Research Division (LDR) Meeting

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Despite advances over the last decades in diagnosing and treating breast cancer (using local-regional modalities, adjuvant cytotoxic and/or hormonal treatments and, more recently, targeted therapies) that resulted – since the early nineties – in decreased mortality, it remains a major public health problem, with an increasing incidence in Western countries. Major unresolved clinical and scientific problems (in addition to causes for increasing incidence, strategies of prevention, specific, sensitive and possibly non-invasive approaches for early diagnosis) are related to i) disease progression (impact of tumor biology, role of microenvironment and identification of solid and reliable predictive biomolecular tools); ii) treatment (who needs it and what is the best/optimal for subsets or individual patients); iii) resistance and toxicity to clinical treatments (how to predict, prevent and overcome them). Recently, top-notch quality technical approaches for comprehensive molecular analyses offered a new way to classify human breast cancer and now offer a paradigm shift for reducing disease complexity, unraveling biologic heterogeneity (that represents one of the major constraints to the resolution of clinico-biologic problems) and thus better identifying those patients that will present with new disease manifestations for a rational planning of therapeutic strategies.

In March 2009, the European Organization for Research and Treatment of Cancer (EORTC) organized in concomitance with its General Annual Meeting the first Laboratory Research Division (LDR) Meeting, focused on an updated contribution of investigators from the two EORTC preclinical groups (the Pharmacology

Breast Care

and Molecular Mechanism (PAMM) Group and the PathoBiology Group (PBG), already used to organize joint meetings) to improve diagnosis and treatment of cancer patients. The LRD Meeting included 15 presentations, a 4-topic young LDR investigator session and a panel discussion in which in addition to the participation of EORTC Headquarters representatives also Disease-Oriented Groups Chairs have been invited.

Ann Jackman (Institute of Cancer Research, Sutton, Surrey, UK) opened the Meeting with a keynote address on rational drug discovery programs for folate-based thymidylate synthase inhibitors and discussed the current issues for a successful development, in terms of biomarkers, combination treatments and reduction of toxicity, within this broad class of drugs. Another non ‘disease-oriented presentation’ was given by Terry Jones (Manchester, UK), and dealt with the potential for supporting drug development in phase 1 studies by position emission tomography (PET). However, notwithstanding that PET could provide measurements of regional tissue pharmacokinetics and pharmacodynamics, lack of tumor specific imaging biomarkers and methodology availability made this approach significantly under-developed.

The results of prognosis- and treatment-addressed studies on breast cancer have been reported by 7 investigators from 5 Institutions. Specifically, Bauke Ylstra (VU University Medical Center, Amsterdam, the Netherlands) discussed tumor molecular heterogeneity and provided convincing data on the utility of chromosomal copy number aberrations (as detected by array CGH, feasible and reliable also on formalin-fixed paraffin embedded material) as a marker for better cancer classification and prediction of prognosis and treatment response in several neoplasms, including breast cancer.

A better prognostic classification could be provided in DCIS by complementing the Van Nuys prognostic index with a genomic grade index based on the expression of 4 genes detected by RT-PCR, as the preliminary data provided by S. Altintas (University Hospital of Antwerp, Belgium) suggest. However, such findings should be biologically and clinically validated on larger case series.

The role of molecular markers and genomic signature on breast cancer prognosis and response to specific treatments has been investigated by several research groups, the most active being investigators from Rotterdam. In fact, John Martens (Erasmus MC Rotterdam, Josephine Nefkens Institute, Rotterdam, the Netherlands) identified microRNAs distinctly associated with prognosis in lymph-node negative cases and response to tamoxifen

treatment in metastatic cases. He further demonstrated that clinically relevant signatures are different for ER positive and negative tumors for microRNA as already proven for RNA. A multinational study carried out by the Rotterdam group and presented by A. Umar identified by proteomic analysis EMMPRIN (extracellular matrix metalloprotease inducer), an additional biomarker associated with early progression following tamoxifen treatment in ER-positive tumors. Taken into consideration the availability of well annotated breast cancer specimens and top-notch quality technical approaches for comprehensive molecular analyses, it is conceivable that the Rotterdam group in a relatively short time will provide us with much valuable information to integrate into the clinico-pathologic stage of breast cancer treatment decision-making.

Nils Brunner (University of Copenhagen, Denmark) showed that the expression of tissue-inhibitor of metalloproteinases (TIMP-1) proven by immunohistochemistry is predictive of failure from anthracycline treatment in breast cancer, and this finding is unrelated to TOP2A status. Such data are in keeping with previous clinically-relevant information provided by TIMP-1 also in other tumor types and shown by this research group.

Anieta Sieuwerts (Erasmus MC Rotterdam, Josephine Nefkens Institute, Rotterdam, the Netherlands)

made an elegant investigation correlating the presence of circulating tumor cells with the intrinsic subtype classification of breast cancer. Interestingly, normal-like breast cancer cells, which exhibit an aggressive behavior, were not recognized by the commercially available method to detect breast cancer stem cells. Such a finding is highly disturbing in consideration of the wide distribution of the CellSearch™ isolation method and its clinical use for monitoring disease outcome.

Finally, Christoph Thomssen (University Medical Center, Halle, Germany) updated the information on the invasion markers uPA/PAI-1, that proved to be not only prognostic but also predictive of treatment response, and on the large prospective clinical trials on node-negative breast cancers (NNBC3, NNBC4) that actually represent an added value of the collaboration within the PBG group (as well as within the former Receptor and Biomarker Group, as was named the PBG before merging with the EORTC-Pathology Group).

Taking into consideration this last finding, we believe that initiatives like the LRD Meeting will foster the collaboration even within EORTC groups with partially different aims, such as the PAMM and the PBG. Merging pharmacogenetics and pharmacogenomics will provide useful information to help clinicians in patient management, for sure.