Recommendations and Conclusions: A better understanding of the molecular/histopathological features of breast cancer subgroups is of paramount importance, to unravel the heterogeneous nature of tumor subgroups and for the identification of prognostic/predictive biomarkers (both at the genome and proteome level), for ideal systemic therapy regimens and novel therapeutic targets.

SP173

Predictive markers for EGFR targeting therapies

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A first hurdle in developing good predictive biomarkers for anti-EGFR drugs, is the complexity of the EGFR pathway itself. EGFR forms a transmembrane receptor after homo or heterodimerization with 3 related proteins, after stimulation with at least ten different ligands, each with their own receptor selectivity. The activated receptor signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity. Autophosphorylation triggers a series of complex intracellular pathways that may result in cancer-cell proliferation, blocking apoptosis, activating invasion and metastasis, and stimulating tumor-induced neovascularization. Many components of the downstream signalling cascade are insufficiently understood. The impact of EGFR targetting therapies will largely depend on the usage of the pathway by the different tumors, as well as the mechanism of oncogenic addiction to the pathway. Activating EGFR mutations found in a subset of NSCLC are strong biomarkers of efficacy in this disease, but only for EGFR tyrosine kinase inhibitors. Biomarkers may differ according to the mechansims of action of the drug, adding another layer of complexity. We will revieuw the latest knowledge on EGFR signalling in NSCLC and colorectal cancer, describe the validated biomarkers and their clinical use, and discuss the areas of future investigations.

SP146

Coordinating biological material collection in the context of multinational clinical trials

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Despite recent efforts, access to human biospecimens is still fraught with difficulties. Whilst, in principle, most patients would agree for their material to be used for the best quality research, wherever that may be, being carried out, the transport of human material across borders is subject to a plethora of country-specific Ethics policies. The most highly prized material for research is highly annotated material from patients entered into clinical trials. The ability to be able to collate material from a number of different countries depends largely on the process of informed consent and the support provided locally for tissue collection. Generic or enduring consent is increasingly accepted by a number of different countries. This approach allows patients to provide a one-off consent for their material to be used in research projects. In addition, patients should be made aware that their material may be sent outside the country in which it is collected, whilst being assured that their identity will be protected at all times.

In addition, clinical trialists need to be aware of differences in specimen collection. In the majority of cases, operative material is placed in fixative prior to leaving the operating theatre. Clinical trials that require frozen material therefore need to liaise closely with pathology departments to obtain the samples that they need without prejudicing the diagnostic need. Processes in pathology labs are far from standardised even within countries, and both the type and duration of fixation, and the further processing to paraffin wax, varies considerably even within one country. All of these so-called pre-analytical variables can have effects on downstream biomarker studies. In addition, the storage of archive blocks from the diagnostic record is increasingly carried out by commercial companies. Where clinical trials obtain material from the diagnostic archive, detailed information therefore of processing of tissue and appropriate remuneration for block retrieval needs to be considered.

Appropriate targeting of new molecular agents to patients who will benefit most can only be carried out with an understanding of the expression of the targets of these agents in tissue from patients in clinical trials. In the longer term, this should limit use of potentially toxic agents in the absence of efficacy, and also enable restricted national health budgets to be used to best effect.

SP161

NNBC3 Europe – Evaluation of the ASCO recommended prognostic factors uPA/PAI-1 in node negative breast cancer patients

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Introduction: The invasion factor uPA (urokinase-type plasminogen activator) and its inhibitor PAI-1 are prognostic markers, recommended by ASCO for risk assessment in N0 breast cancer patients (Harris et al. JCO 2007; 25: 5287). Ten-years follow-up data on the prognostic value were recently presented (Harbeck et al. ASCO 2009). In the prospective NNBC 3-Europe trial the following additional questions were addressed:

1. Evaluation of risk-assessment by uPA/PAI-1 and clinico-pathological factors.
2. Comparison of adjuvant FEC*3-Doc*3 vs. standard FE100C*6 in N0 high-risk patients.
3. Feasibility of fresh tissue sampling for biomarker determination.

Methods: Risk assessment was based on grade, and in G2 tumors, either by uPA/PAI-1 status (UP) or by a St. Gallen adapted algorithm (CP). Type of assessment was chosen by each centre prior to start of accrual. High-risk patients received adjuvant chemotherapy as randomized. Endocrine therapy was given in line with guidelines. HER2 overexpression was confirmed centrally. Use of fresh tissue sampling was necessary for determination of uPA/PAI-1 by ELISA. All laboratories (n = 9) took part on the central quality assurance program (QA).

Results: From Dec 2002 to Jan 2009, by 153 centres 4,150 pts were recruited. Risk assessment was based on grade and, in G2 tumors, either by UP (2,500 pts) or by CP algorithm (1,644 pts). Median follow-up is 12.6 months. By UP, 39% were assigned to the low-risk group, whilst 61% of the patients still had to receive adjuvant chemotherapy. By CP, 31% were assigned to the low-risk group. In G2-tumors, 42% were assessed as low risk by UP and 43% by CP. As to all low-risk pts, 1,483 pts had endocrine therapy, only. Concerning the high-risk pts, 1,334 were in the FEC-Doc and 1,328 in the FEC arm. Median uPA level were at 2.40 ng/mg protein (below cut-off), median PAI-1 at 15.9 (above cut-off). In the QA, mean coefficients of variations are 12% for uPA and PAI-1 determination.

Conclusion: NNBC-3 Europe is the first completed prospective and biggest biomarker trial focussed on node-negative breast cancer patients. Routine uPA/PAI-1 determination has shown to be feasible and using UP for additional prognostic information may prevent chemotherapy from many patients. Survival data will not available before 2010.

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