## Wednesday 8 November 08:00–09:45

**WORKSHOP 1**

# Biomarkers in cancer drug discovery and target evaluation

**7** INVITED

**Rational drug development in oncology: setting the scene for use of biomarkers**

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A "biomarker" is a measurement (usually protein, RNA, or DNA-based) in blood or tissue that is indicative of a particular effect, state or outcome. Biomarkers may be used in early detection of cancer, to follow tumour burden, to assess the impact of a drug on its target and to sort patients with similar histology into groups of differing prognosis (prognostic factors) or different likelihood of benefit from a specific therapy (predictive factors). In the clinical development of targeted therapeutics, use biomarkers may add value by (a) confirming that a new agent has its intended molecular effect in normal or tumour tissue (pharmacodynamic studies) and (b) defining subpopulations most likely to benefit from a specific targeted therapy.

*In phase I trials*, assessment of biomarkers in serial samples of blood, normal or tumour tissue can evaluate the effect of drug on its intended target. The assessment of downstream markers of EGFR signalling in skin and tumour in early trials of EGFR inhibitors is an example. Aside from challenges in repeated sampling of tissue or serum, the major hurdles in the execution of these type of studies are i) the need for a validated assay that reliably measures the effect of drug on target and ii) sufficient prior knowledge about the magnitude of target change needed for activity.

Reliable biomarkers to identify which patient subset is most likely to benefit (or least likely to fail) therapy are most helpful in *Phase II and III trials*. Restricting enrolment on the basis of an appropriate biomarker (i.e. population enrichment) may reduce both the risk of false negative results in phase II and the sample size needed to detect meaningful differences in phase III. Unfortunately, it is not possible to know *with certainly* the best enrichment biomarker(s) prior to clinical study. Large data sets may be required to understand which marker best parses the population into those likely to fail/succeed with therapy. The recent experience of EGFR inhibitors in NSCLC is a good example; there is still not clarity on which biomarker should be used to determine who to treat. Potential predictors for efficacy may be those intuited by the target of treatment or based on preclinical data of efficacy in molecularly characterized models. Hypothetical biomarkers must be tested in prospective clinical studies which are designed not only to assess activity, but also to evaluate the differential impact of the new drug in different biomarker subsets.

**8** INVITED

**Guidance or misdirection, the challenge of implementing biomarker assays in clinical trials – a case study from EGFR inhibitors**

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The successful development of targeted therapies, such as trastuzumab, imatinib and cetuximab, in selected subsets of patients has led to the expectation of a paradigm shift in the way new targeted therapies are evaluated in clinical trials. It has been suggested that only patients whose tumors express the target of interest should be included in future studies. Unfortunately, this new paradigm has not been successful in the development of the EGFR tyrosine kinase inhibitors, gefitinib and erlotinib. Since no correlations were observed between EGFR status and clinical outcomes in initial studies, most subsequent clinical trials had no eligibility requirements regarding EGFR status. Four large clinical trials of these agents in combination with chemotherapy as 1st-line treatment of unselected patients with NSCLC were disappointingly negative. A randomized, placebo-controlled study of single-agent erlotinib as 2nd/3rd-line treatment of patients with NSCLC demonstrated a modest, but statistically significant survival benefit. A similar, but non-significant trend was observed for gefitinib. Erlotinib in combination with gemcitabine also resulted in a small but statistically significant survival benefit for patients with advanced pancreatic cancer. The relatively small magnitude of benefit in these studies strongly suggests that selected subsets of patients, probably based on biomarkers in the EGFR pathway, might derive considerable benefit from these agents. Tumor samples were optional in each of these studies. This strategy confirmed the well-known difficulty in obtaining adequate tissue samples for the assessment of biomarkers, a significant barrier for the development of molecularly targeted agents. Rates of tissue collection were 22−44% in these large clinical trials. To date, none of the biomarkers that have been evaluated definitely identifies subsets of patients who will or will not benefit from treatment with these agents. So, what went wrong in the development of these EGFR inhibitors? The most obvious answer is that we still do not know how to determine if a tumor is truly dependent on the EGFR pathway for survival and progression. In addition, tissue collection and current assay techniques are far from optimal. Another possibility is that these agents have some off-target activity that may be important for individual tumors. These studies also demonstrated the importance of identifying the most appropriate clinical endpoint for correlative studies.

**9** INVITED

**Proper biochemical target evaluation – which types of clinical trials are needed for validation?**

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Biomarkers characterize biological properties of tumor cells and can be determined on DNA, RNA, and protein level. They may serve as *prognostic* (further course of disease) or *predictive* (therapy response) and *targets for tumor biological therapies*. Similarly to marker development for prognostic or predictive biomarkers that uses a hierachical system of levels of evidence, therapy targets may also be validated by a sequence of well-designed clinical trials. In general, hypothesis generating pre-clinical trials using retrospectively collected patient material need to show relevant correlations between target and tumor aggressiveness. The method for target determination in clinical material needs to be standardized and quality-controlled. Once clinical relevance of a potential target has been validated at high level of evidence, ideally by a meta-analysis or a prospective clinical trial (e.g. as a secondary endpoint of a therapy trial), targeted therapy approaches may be warranted. After preclinical (effectiveness) and early phase (tolerability, dosing) testing of suitable agents, proof of principle for their clinical effectiveness can be obtained in the advanced metastatic or preoperative neoadjuvant setting. In breast cancer, preoperative therapy is an ideal setting to study both effectiveness of novel drugs using pathological response rate in the easily accessible primary tumor as a surrogate endpoint as well as their target specificity by tissue analysis at various times. Administration of novel agents in phase II clinical trials in the advanced setting is certainly necessary for moving such agents further into early potentially curable stages of the disease. Yet, if the proper target cannot be reproducibly determined and thus patient selection is not specific enough, low response rates may preclude potentially effective agents from further development. Moreover, choice of appropriate endpoints taking into account tumor biological action of novel agents is crucial. Time-to-progression or clinical benefit rate including disease stabilization may be a more suitable endpoint than response rate. Surrogate markers such as soluable proteins in blood or disseminated tumor cells in blood or bone marrow may also help in target validation. Development of anti-HER2 or anti-uPA agents in breast cancer may serve as examples of how to validate suitable targets from preclinical prognostic and predictive markers to therapy targets using clinical trials.

## Wednesday 8 November 08:00–09:45

**WORKSHOP 2**

# Endpoints in oncology clinical trials – are we making any progress?

**10** INVITED

**RECIST version 2.0**

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The new Response Evaluation Criteria In Solid Tumors (RECIST) were launched in February 2000 and were rapidly implemented across academic and industry driven trials. In 2006, a review of the literature published about RECIST revealed that in general, RECIST has been well received by the scientific community and most validation studies fully support the implementation of the new criteria. As expected, however, some issues have been identified. In keeping with the mathematical differences in definition of progression, RECIST delays the identification of progression as compared to WHO criteria in some instances. RECIST criteria are not easily applicable in some types of trials such as those in pediatric