Wednesday, 17 November 2010 08:00–09:45

WORKSHOP 1

Characterising the target for improved drug tailoring

7 INVITED

Assessing target functionality for drug and patient tailoring: a clinical perspective

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The ultimate aim of the treatment of cancer is to find the best possible drug or treatment, in the most optimal condition, for the individual cancer patient. This does not mean that treatment can only be based on an individual basis, but that we should try to identify the characteristics of patient (sub-) populations that fit best to the characteristics of the drug or treatment.
Molecular biology achievements have enabled us over the last decade to more precisely identify these characteristics and develop better tailored drugs. On the other hand we should also acknowledge that the success rate of biomarker driven development is relatively limited. In that sense it is fascinating to see the number of definitions one can find in the literature on "biomarker". Evidently, we need to better define the topic of our discussion on biomarkers.
From the perspective of drug development, assuming that a molecular change leads to the occurrence of cancer, there may be 3 milestones with key questions: (1) does the drug affect the target (molecular change), which identifies proof of mechanism, (2) does the effect on the target lead to a change in tumor biology, which identifies proof of principle, and (3) does the signal of change in tumor biology lead to a clinical evidence of absence of tumor growth, or even of tumor size regression and ultimately improve (progression free- or overall-) survival, which would be the proof of concept. To each of these one could link a biomarker that signals the effect.
Since either form of survival is a long term endpoint, and therewith unattractive for drug development evaluation, a lot of resources have been spend in finding so called surrogate markers for ultimate clinical outcome. Particularly in this scenario we have not been very successful. The examples of successful use of biomarkers are in the selection of patient populations based on proof of mechanism and proof of principle. If these can be ensured, apparently there is a high likelihood that proof of concept will follow. This is exemplified in the development of agents such as imatinib, herceptin, and more recently GDC-0449, PF-02341066 (Crizotinib) and some others.
A case will be made that drug development should be focussing on these selection-biomarkers, predictive for effect, rather than the late prognostic ones that have been used for a while now.

8 INVITED

Pharmacodynamic markers of targeted agents

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Abstract not received

9 INVITED

Pharmacoepigenetics and epigenetic drugs

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Recent years have seen the mapping of increasing numbers of genes in which promoter CpG islands are hypermethylated in cancer. Such DNA-methylation mapping has revealed unique profiles of hypermethylated CpG islands that define each neoplasia. For the various cancers for which DNA-methylation profiles are available, CpG-island hypermethylation has been used as a tool to detect cancer cells in all types of biological fluid and biopsy. Another interesting aspect correspond to to pharmacoepigenetics: DNA methylation as a predictor of response to chemotherapy. The most compelling evidence that epigenomic profiles can predict responses of cancer to therapy is provided by the methylation-associated silencing of the DNA-repair protein MGMT in human brain tumours. MGMT is directly responsible for reversing the addition of alkyl groups to the guanine base of DNA and this base is the preferred point of attack in the DNA of several alkylating chemotherapeutic drugs, including BCNU (carmustine), ACNU (nimustine), procarbazine, streptozotocin and temozolamide. MGMT hypermethylation is the best independent predictor of response to BCNU and temozolomide in gliomas. The potential of MGMT to predict the chemoresponse of human tumours to alkylating agents can also be extended to other drugs with similar modes of action, such as cyclophosphamide. Most importantly, one of the essential differences between human cancer genetics and epigenetics is that DNA methylation and histone modification changes are reversible under the right circumstances. Thus, epigenetic alterations are one of the weakest points in the defences of the cancer cell, because those hypermethylated tumour-suppressor genes in their long "sleep" can be awoken and reactivated with the right drug regimens and exert their normal growth-inhibitory functions. Two families of epigenetic drugs, DNA-demethylating agents and inhibitors of histone deacetylase, have emerged as the most promising compounds in this area, and several pharmaceutical compounds have received approval for the treatment of hematological malignancies.

10 INVITED

Biosample collection in clinical trials

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Access to biological materials (BM) in both sufficient quantity and quality is considered one of the key bottlenecks hindering successful bench to bedside translation. However, this does not need to be the case. Clinical trials offer a unique opportunity in which to collect biological materials; large, multi-centred studies often containing randomized treatment and control arms, administration of novel drugs and drug combinations, combined with high quality clinical data and patient follow up. Biological materials collected in this context provide a valuable opportunity to address study designs for biomarker discovery and validation that would be difficult to fulfill from community or population based BM collections alone.
Due to the multidisciplinary nature, integration of biological materials collection into clinical trials warrants careful upfront planning and input from a range of expertises. Currently, the EORTC is building on its existing experiences and expertise gained from specific initiatives, the EORTC Virtual Tumour Bank and also EORTC Group activities and is further developing new mechanisms to support investigators with the practical aspects of collection, storage and access to biological materials.
As much as possible the BM collection should be integrated into standard clinical practices and must be made as simple as possible to facilitate the collection. To aid this integration of BM collection in EORTC clinical trials, a checklist has been developed involving the key areas of up front statistical planning and clear biomarker research objectives, biosample quality requirements and ethical and practical restrictions, which are increasingly important to successful translational research, and combines these into a simple tool for practical use. Identifying and managing key risk areas early in clinical study set up can lead to maximizing the BM collection success and efficient trial set up.

Wednesday, 17 November 2010 08:00–09:45

WORKSHOP 2

Pharmacogenetics and pharmacogenomics in cancer

11 INVITED

To genotype or to phenotype: that's the question

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In our goal to personalize anti-cancer treatment, many different dosing strategies have been suggested over the years. Earlier, for most anti-cancer drugs, dosing based on body-surface area solely has been proven ineffective to lower the inter-individual pharmacokinetic variability (IIV). A more tailored therapy should lead to a clinically relevant decrease in IIV and should ultimately create a minimum amount of serious side effects and a maximal therapeutic effect in individual patients.
Extremes in patients' capacity to metabolise the drug of interest may be the result of pharmacogenetic variability, as undeniably shown for the enzyme thiopurine S-methyltransferase (TPMT) in the metabolism of azathioprine. But also in the metabolism of irinotecan and tamoxifen, the