2 weeks after the start of chemotherapy revealed to be the most accurate cut-off value for prediction of clinical and histopathological response after a full-course of preoperative chemotherapy lasting for 12 weeks. We have further noticed that the metabolic response to induction chemotherapy is an independent and important prognostic factor in cases of locally advanced adenocarcinoma of the oesophago-gastric junction. This suggests that PET can be used to tailor treatment according to the chemosensitivity of tumours located at the oesophago-gastric junction. This concept has been realised in the MUNICON-1 trial [Lordick F et al. Lancet Oncol 2007]: In metabolic non-responders, chemotherapy could be discontinued at an early stage, thereby saving time, and reducing side-effects and costs. Compared to previous studies one can deduce that the outcome of metabolic non-responders was at least not compromised by the early discontinuation of chemotherapy.
Recommendations and Conclusions: Based on these results, integration of FDG-PET can be recommended for further clinical studies in oesophago-gastric cancer like the planned EORTC IMAGE trial.

SP169
Gap & priorities: Biomarker integration in drug development

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Substantial improvements in genomics, proteomics and the way that human tumors are characterized, are allowing clinical exploration of new targeted strategies. As a consequence, cancer treatment is shifting from a "one size fits all" therapeutic approach to a more personalized approach, in which specific cancer subpopulations are treated based on genetic defects. To be successful, such an approach requires the discovery and development of biomarkers to (a) select which patients to treat (Prognostic Biomarker); (b) determine whether the drug interacts with the target (Target Biomarker); (c) assess whether the drug elicits a biological effect (Mechanism Biomarker) and (d) determine whether the drug produces a positive clinical outcome following treatment (Outcome Biomarker). Although there have been clinical successes in targeting molecularly defined subsets of several tumor types using molecular targeted agents, the ability to apply such successes in a broader context is limited by the lack of a strategy to evaluate targeted agents in patients. The solution requires biomarkers integrated into the drug development process and the ability to reliably select patients with molecularly defined cancers. In this tutorial I will highlight key approaches for the use of such biomarkers, focusing on gaps and priorities.

SP172
Getting the most from the least tissue

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The field of clinical oncology is poised to undergo a paradigm shift where personalized therapies based on tumor and host molecular profiles supplant the current practice of empirical clinical decision-making based on tumor stage, age and performance status. Considering the heterogeneous and varied nature of most solid tumors, molecularly-targeted agents designed to inhibit abnormal signaling events will likely be of benefit only to a subset of patients whose tumors are uniquely dependent on the target(s) of such agents. Tumor profiling will also prove valuable for selection of optimal cytotoxic chemotherapies. However, individually tailored regimens administered in rational therapeutic combinations can only be accomplished if high quality tumor specimens are available for rigorous collection and analysis. Recently, tumor diagnosis and staging has become more reliant on fine needle aspirates or core biopsies, sufficient for pathological evaluation, but inadequate for much additional molecular characterization. Furthermore, DNA artifacts, produced by the formalin fixation process, interfere with PCR amplification and may lead to erroneous data if the starting material is too limited. Tumor heterogeneity and admixed normal cells (stroma, vascular, immune etc) also may contribute to ambiguous data. Multiple approaches are being explored to improve the predictive capacity of biomarkers from limited tissue sources. For instance, highly sensitive and precise methodologies are currently undergoing validation to improve quality of individual high-utility markers, including mutation detection, gene copy number and tumor RNA levels. Additionally, platforms designed to produce multiplex or even genome-wide molecular signatures are demonstrating notable promise for tumor prognostics and prediction of treatment sensitivity/resistance. Targets of measurement include DNA mutations, methylation and copy number; RNA levels and proteomics, among others. In the absence of sufficient archival tissue for these analyses, alternative sources of tumor material may be exploited for molecular diagnostics, including shed tumor DNA in peripheral circulation, circulating tumor cells and plasma "omic" profiles. For personalized therapy strategies to be introduced into mainstream practice, the infrastructure for specimen acquisition, processing, storage, pathological oversight and standardized analysis must be established.

SP163
BMP4 and the inhibitors of differentiation, Id-1 and Id-3, play an essential role in the maintenance of colon cancer-initiating cells

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Cancer-Initiating cells have been identified in numerous solid tumors, including colon. Markers utilized to identify Colon C-IC (CC-IC) include CD133 and CD44. The aim of this study was to examine the role of bone morphogenic protein-4 (BMP4) and its major target genes, inhibitor of differentiation-1 and -3 (Id-1 and Id-3), in colon cancer and the CC-IC subset.
To study the effect of BMP4 on colon cancer 2×10^5 human colon cancer cells were injected subcutaneously (SQ) into NOD/SCID mice. A total of four groups were studied (n = 5 per group): (1) no treatment, (2) heparin-coated acrylic beads, (3) BMP4 (100 ng) and (4) Noggin (100 ng) (BMP4 inhibitor), both conjugated to heparin-coated acrylic beads. The experiment was repeated with 4 colon cancers (all smad 4+). Once tumor volume reached 0.5 cm^3 intra-tumoral injections were administered weekly until xenografts reached 1 cm^3, at which time the mice were sacrificed.
The administration of Noggin resulted in tumor regression in 11/20 mice, with a mean tumor weight of 92.4 ± 37.2 mg. In contrast, the mean tumor weights (mg) for the BMP4, acrylic bead, and untreated mice were: 673.8 ± 65, 734.6 ± 94, and 684.5 ± 100.8. The CD133+ fraction was significantly elevated in the BMP4 treated tumors, 27.15% vs. 0.36% in control tumors. To better understand the mechanism of action of BMP4 we looked at two of its major target genes, Id-1 and Id-3. Short hairpin RNA (shRNA) mediated knockdown of Id-1 and Id-3 was carried out in primary colon cancer cells. Five groups were included: (1) untransduced, (2) transduced control, (3) Id-1 shRNA, (4) Id-3 shRNA, (5) Id-1/3 shRNA. A total of 1×10^5 cells were injected SQ into NOD/SCID mice (n = 32/group) to assess tumor formation. The combined inhibition of Id1/3 resulted in decreased tumor formation, the mean tumor weight (mg) being 588.1 ± 89 in transduced controls (n = 32) vs. 56 ± 19.1 in Id1/3 knockdown (n = 32) ($p < 0.05$). The tumors in the Id1/3 knockdown group demonstrated decreased self-renewal and decreased chemoresistance to oxaliplatin.
These experiments indicate that BMP4 plays a central role in colon cancer and the maintenance of CC-ICs. Furthermore, the knockdown of two of the major target genes of BMP4, Id-1/3, also resulted in a decrease in xenograft formation. We have identified a multifunctional role for Id1/3 in CC-ICs that includes maintenance of self-renewal and chemoresistance. Current studies are underway to further investigate how Id-1 and Id-3 affect self-renewal in colon cancer-initiating cells.

SP154
The role of pharmacogenetics and pharmacogenomics in cancer therapy

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Introduction and Purpose: Both pharmacogenetics and pharmacogenomics can affect the efficacy of cancer therapy with cytotoxic drugs targeted against DNA as well as drugs targeted against signalling. Pharmacogenetics is the impact of one or some genes on the effect of a drug, which includes both gene expression and genetic polymorphisms. Pharmacogenomics is the impact of a cluster of genes, e.g. by gains or losses. Next to non-genetic factors both can affect the pharmacokinetics and the pharmacodynamics of a drug, influencing either drug toxicity or the antitumor effect.
Main Message and Recommendations: The pharmacogenetics of a drug is usually the result of a genetic polymorphism, which is classified by a genetic variation in the DNA in more than 1% of the patients. Many candidate genetic polymorphisms have a rational preclinical basis and have subsequently been identified in retrospective studies; several of them have been validated in prospectively sampled studies, but few were sufficiently robust to be used for selection of patients and have been identified by the FDA as a potential risk factor. For most of these genetic polymorphisms data were not strong enough or too heterogeneous to predict an antitumor effect. Although there is a general concordance for most pharmacogenetic markers between germline and e.g. colorectal cancer, this does not seem to be sufficient to predict efficacy, also because in tumors gene regulation is often deregulated. Furthermore in combination therapy more genetic factors in the tumor play a role, so that risk of toxicity to one drug in a combination can be predicted more reliably then the chance to respond. Since combination therapy (cytotoxic drugs and/or targeted drugs) is common, it seems more appropriate to use a set of genes to test the tumor. A wide application also requires a robust source for RNA or DNA.