disappears with no pleasure on mealtime. The interference with family life seems to be of greater importance than PEG related problems of discomfort, leakage or blockage *(Rogers, 2007)*.
Since the insertion of the PEG is a minor surgical procedure, there is a common belief that it is harmless with a low impact on daily life. However, it transfers the treatment responsibility and activity to patients and their spouse to a large extent. Moreover, it moves treatment from inpatient settings to home with a need for care of by district nurses and general practitioners. Preliminary results from a study conducted in our group confirms that a majority of patients handle the PEG feeding by them selves, but those in need for assistance were mainly supported by their spouse and more seldom from district nurses. This might reflect that the patients' wants to live as normal a life as possible, and according to previous research, the nurses find this as a burdensome responsibility to fulfil *(Strandberg, 2003, Scott, 2005, Jordan 2006, Madigan 2007, Millard 2006, From, 2009, Bjuresäter, 2010)*. Studies on patients' experience of living with a PEG, is mostly qualitative with small sample sizes, but they all addresses the same problems of dependency, responsibility, time and skills shortages. Even though PEG is part of established practice there are obviously some flaws regarding the use of it. This highlights the need of an improved care chain for patients living with a PEG.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Head and Neck: What Next in Biologically Targeted Therapy?**

81 INVITED

Stem Cells in Head and Neck Cancer

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Despite improved management of patients with head and neck cancer, locoregional failure or distant metastases after high-dose radiotherapy or combined treatments occur in a substantial proportion of patients. Recent preclinical and clinical evidence suggests that among other radiobiological mechanisms the number of cancer stem cells (CSC) and their radiation sensitivity might contribute to treatment failures. Of particular interest and subject of intense research are putative CSC markers such as CD44 for prediction of response and CSC-related pathways of radiation response for novel approaches of molecular targeted drugs. It has been shown for breast cancer and glioma cells that radiation sensitivity in CSC-marker positive cells is governed by molecular pathways which might be distinct from CSC-marker negative cells. Such a differential response or direct targeting of CSC-marker molecules may offer new opportunities in molecular targeting. The CSC concept and recent data with relevance for radiation oncology will be discussed.

82 INVITED

New Targeted Drugs − Biological Agents

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For head and neck cancers, the outcome of treatment is largely dominated by the success or failure of attempts to control the primary lesion and its locoregional extent. Radiotherapy (RT) is a key component of this treatment, but frequently fails to achieve locoregional control. By combining cisplatin chemotherapy with RT, we can improve tumour control probability (TCP) but this comes at the cost of increased toxicity from non-specific sensitisation of normal tissues. Indeed, it is widely accepted that most combination chemoradiation regimens are already delivered at or close to the limits of normal tissue tolerance and this limits further development of this strategy. The greatest opportunity for using RT more effectively in the future lies with the development of targeted drugs to achieve tumour-selective radiosensitisation. Promising strategies based on monoclonal antibodies or small molecules that act as inhibitors of EGFR, HSP90 or Chk1 will be discussed. In addition, the potential for rational patient selection (based on HPV status) for treatment intensification and de-intensification strategies will be discussed. These agents may also play an important role in palliative treatment of relapsed disease. In addition to these conventional agents, a range of novel biological therapies based on replication competent oncolytic viruses are now in phase I-III clinical trials. Data on our programme of work with oncolytic reovirus (Reolysin) and oncolytic herpes simplex virus (OncoVEX-GMCSF) will be also be presented.

83 INVITED

Management Based on Results of Functional Imaging

Abstract not received

84 INVITED

Targeted Agents in Salivary Gland Tumours

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The efficacy of molecularly targeted agents in recurrent or metastatic malignant salivary gland tumours (MSGT) has been modest but the momentum to mount clinical trials in these rare tumours warrants continued support. Typically, due to the histological heterogeneity of this diagnosis, most MSGT studies divide patients into adenoid cystic carcinoma (ACC) versus non-ACC cohorts. Molecularly targeted agents such as the epidermal growth factor receptor (EGFR) inhibitors, HER-2 targeting agents and multi-kinase antiangiogenic inhibitors have been evaluated in single-arm phase II trials of advanced MSGT, with limited evidence of tumour shrinkage and variable degrees of disease stabilization. As agents with novel mechanisms of action (e.g. agents modulating cancer stem cells, apoptosis, DNA repair, cellular adhesion, etc) enter preclinical and clinical development, there needs to be an efficient approach to determine their activity in MSGT. Clinical trials of combinations of molecularly targeted agents to overcome resistance via compensatory pathways are also emerging in the field of experimental therapeutics. Preclinical models that can reliably predict efficacy of new agents alone, in combination with other agents or with radiation, are lacking. The design of early phase clinical trials in MSGT needs to be reinvigorated to proficiently screen out inactive agents while selecting the precious few that justify late phase assessment. Through targeted and next-generation sequencing of the cancer genome, specific somatic mutations and other genetic aberrations that drive many human malignancies are increasingly being identified. This rapidly growing knowledge and technology in cancer genomics has brought promise to a new era of personalized medicine that may ultimately benefit the selection of therapies in MSGT.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Clinical Trial Methodology**

85 INVITED

How to Optimise the Preclinical to Phase I Transition?

Abstract not received

86 INVITED

Novel Designs and Alternate Endpoints for New Drug Studies

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The rate of novel antitumour agents failing at phase III is high in comparison to other therapeutic areas, resulting in registration of less than 10% only. In the era of targeted therapies, the proof of mechanism of action (MoA) on the base of a qualified assay became part of the phase I and may even be anticipated by so-called phase 0 trials, assessing pharmacodynamic responses up-front. Phase I cohorts should be enriched for the target population to allow the detection of the underlying MoA, but should not be limited to it. Biomarker studies have to be integrated into the phase I process for patient selection and assessment of the MoA. Once, the recommended dose for phase II has been reached, enriched expansion cohorts are to be set up to assess antitumour activity already early in the development as demonstrated for hedgehog inhibitors in basal cell carcinoma (Von Hoff et al, NEJM 2009). The optimal time point and methods of patient enrichment are debatable. The ultimate goal of the phase I trial procedure is to guarantee that the number of patients treated at sub- and/or supra-therapeutic doses is minimized. Whereas the accelerated titration design, which successfully avoids unnecessary toxicity, is widely used, the more individualizing continual reassessment method has not found wide acceptance so far due to its immanent complexity necessitating biomathematical support on-site. Whereas the goal of classical non-randomized phase II trials was to gain an estimate of response and safety, new phase II trial methodology aims at the evaluation of the therapeutic activity and toxicity in the context of the target modulation. Examples are the development of vandetanib in *RET*-mutated medullary thyroid carcinoma (Wells et al, JCO 2010) and that of crizotinib in *EML4-ALK* gene fusion positive NSCLC (Bang et al, Proc ASCO 2010). Adaptive trial designs in the phase II as exemplified by the BATTLE trial, coupling real-time molecular interrogation of cancer specimens with an adaptive Bayesian clinical trial design, merit systematic integration(Kim et al, Cancer Discovery 2010). For cytostatic antineoplastic compounds with PFS as endpoint, the use of the randomized discontinuation design during phase II

has proven to be useful (Hunsberger et al, CCR 2009). Of special interest is the single-arm trial approach to compare PFS while using patients as their own control in a so-called N = 1 design. The treatment selection is based on molecular profiling, therewith representing an individual patient tailored approach (Von Hoff et al, JCO 2010). Under certain conditions, the multi-arm multi-stage design can result in faster and more efficient treatment evaluation by combining phase II and III (Parmar et al, JNCI 2008). Last but not least, using more demanding end points in phase III, such as a larger value of δ, representing the difference in the primary end points between experimental and control groups, will yield clinically more relevant results at a lower tribute of patients and money (Ocana & Tannock, JNCI 2011).

87 INVITED

How to Optimise Strategies for Clinical Development of Combinations Based on Targeted Agents?

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Anti-cancer treatment relied on three modalities: surgery, radiation and chemotherapy.
An understanding of the biology of cancer has led to the development of "molecular-targeted therapies". Cancer can be envisioned as a "signaling disease", in which alterations in the cellular genome affect the expression and/or function of several proteins. Targeted therapy refers to drug designed to interfere with a molecular target, playing a critical role in carcinogenesis. These drugs includes monoclonal antibodies, small molecule, targeted agents coupled with cytotoxics or radioactive elements. However, the activity of these agents administered alone or in combination with standard treatments, although was clinically relevant, is overall modest except in circumstances in which tumour pathogenesis is dominated by a key molecular abnormality. These include a select group of diseases (CML, GIST) or subgroups of common diseases (neu in breast, EGFR mutations in NSCLC, BRAF mutations in melanoma,. . .) or some orphan tumours (e.g. hedgehog pathway in basal cell carcinoma). Identification of biomarkers (K-Ras, Her 2, EGFR mutations) has led to a shy improvement but limitations appear to be linked to the escape of tumours by the development of secondary mutations, targets alteration and the development of redundant pathways. Trying to overcome the resistance has led to the development of targeted therapy-based combinations. However, some combination clinical trials were a success while others have failed as in colorectal cancer where by combining anti-VEGF agents with anti-EGFR therapy and chemotherapy has resulted in a lower outcome.
Clues to the success of combination therapies are first to avoid an empirical selection of the agents, the evaluation of targeted agents combinations in tumours which dispose greater knowledge of the molecular biology and mechanisms of sensitivity/resistance and finally the knowledge of drugs side effects. In fact, selecting the best combinations should be based on two elements: 1) solid preclinical data. This implies the choice of agents which lead to tumour shrinkage and cure. The optimal sequence administration in a combination should also be predefined from the preclinical setting. 2) the choice of the tumours needs also to be made on the basis of knowledge of the relevance of the targets in these tumours and their role in tumour carcinogenesis and escape.
Finally, it is important to stress that an alternative to developing combinations of targeted agents-based therapies could be by using agents that hit multiple targets at the same time. Nevertheless this approach has its own limitation. Example of these agents are the multitargeted kinase inhibitors.
In conclusion, it is clear that preclinical studies provide valuable information for designing appropriate clinical trials to test combinations. However, designing innovative clinical trials and selecting the best patients and tumours as well as the most active drugs are key to the success of targeted therapy combinations.

88 INVITED

Are Big Phase III Realistic in the Era of Personalised Medicine? Non-Traditional Approaches for Registration

Abstract not received

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Melanoma − Realising the Potential in Immunotherapy**

89 INVITED

New Insights in Mechanism of Action of Anti-CTLA4

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Over the past several years it has become apparent that cell intrinsic and extrinsic regulatory pathways that act in concert to minimize harm to normal tissues have limited the effectiveness of active immunologic strategies for cancer therapy. We conducted extensive pre-clinical studies in mouse models which showed that blockade of the inhibitory signals mediated by CTLA-4 in T cells, either alone or in combination with a variety of immunologic and conventional therapies, led to tumour eradication and long-lived immunity. This work led to the generation of antibodies to human CTLA-4 and the conduct of an extensive series of clinical trials in human cancer. Over 6,000 patients have been treated with the CTLA-4 antibody Ipilimumab (Bristol-Meyers Squibb). Objective responses have been observed in metastatic melanoma, castrate resistant prostate cancer, as well as renal, lung, and ovarian cancer. In a recent Phase III trial, Ipilimumab was shown to prolong survival of stage IV metastatic melanoma patients, with 25% alive and ongoing at 4 years. This is the first drug of any type to show a survival benefit in metastatic melanoma in a placebo controlled randomized trial. In March 2011 Ipilimumab was approved by the FDA for both first and second line therapy of metastatic melanoma. A Phase III registration trial in castrate resistant prostate cancer is now underway.
In order to enhance the efficacy of anti-CTLA-4, we have been exploring combinations other modalities of treatment. to identify those that might enhance efficacy of checkpoint blockade. These include combinations with other immunotherapies as well as with conventional (radiation, chemotherapy) and genetically targeted therapies.
We have previously noted that in both humans and mice the frequency of expression of ICOS on CD4 cells is increased following CTLA-4 blockade. In metastatic melanoma patient's sustained elevation of the increase for 12 weeks after initiation of treatment is associated with clinical benefit. This led us to determine whether engagement of ICOS during treatment would enhance the efficacy of CTLA-4 blockade. We developed a tumour cell vaccine expressing ICOS ligand (Ivax) and found that it strongly enhanced the ability of anti-CTLA-4 to induce rejection of B16 melanoma.
Recent studies have shown that the genetic instability inherent in cancer results in an extraordinary number of coding mutations in cancer. Many of these give rise to neoantigens which can provide multiple avenues for attack of tumour cells. It seems logical to begin to combine conventional therapies, or the new "targeted" therapies, that can cause tumour cell destruction with immune checkpoint blockade in order to obtain effective immune responses to these neoantigens, thereby effectively increasing the valency of therapy and minimizing the chances of acquistion of tumour resistance and escape. We have begun to explore the effects of targeted therapies on immune responses and whether the combination of anti-CTLA-4 and targeted therapy in pre-clinical models. The ultimate goal is to determine whether we can take advantage of the high response rate to genetically targeted agents with the durability of immunotherapy.

90 INVITED

Can Chemotherapeutics Synergize With Anti-CTLA4?

Abstract not received

91 INVITED

Update CTLA-4 Blockade Using Ipilimumab as First Line and Second Line Therapy for Advanced Melanoma

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Ipilimumab is a human IgG1 monoclonal antibody which blocks CTLA-4, a critical immune checkpoint which constrains T cell activation and proliferation. Phase 1 and 2 trials revealed clinical activity of ipilimumab in advanced melanoma, along with a unique set of tissue-specific inflammatory side effects, termed immune mediated adverse events. Based on the observation of durable clinical benefit in patients with metastatic melanoma, two randomized, placebo-controlled phase 3 trials were conducted to further establish the activity of ipilimumab in the first-line and refractory treatment settings. The initial study, MDX010–020, randomized 646 patients to ipilimumab alone, ipilimumab with a