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