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?

A. Awada[1], P. Aftimos[1]. [1]*Institut Jules Bordet, Head of the Medical Oncology Clinic, Bruxelles, Belgium*

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

J. Allison[1], P. Sharma[2]. [1]*Memorial Sloan Kettering Cancer Center, Department of Immunology, New York,* [2]*MD Anderson Cancer Center, Genitourinary Cancer, Houston, USA*

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

J.D. Wolchok[1]. [1]*Memorial Sloan-Kettering Cancer Center, Medicine, New York, USA*

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

gp100 peptide vaccine or gp100 vaccine alone. The results demonstrated a significant overall survival benefit for the ipilimumab-containing arms and established ipilimumab as the first drug to improve overall survival in patients with metastatic melanoma. Side effects in this study were managed and generally responsive to the use of corticosteroids and other immunosuppressants, according to treatment algorithms. Data from this trial served as the basis for approval of ipilimumab by the US Food and Drug Administration for treatment of patients with metastatic melanoma in March, 2011. The second phase 3 trial randomized 502 treatment-naïve patients to ipilimumab with dacarbazine or dacarbazine with placebo. The primary data from this trial is still under embargo at the time of this abstract submission; however, it is now known that the ipilimumab plus dacarbazine group had a statistically significant improvement in overall survival compared with dacarbazine alone. These two studies each with mature follow up of more than 4 years respectively, and enrolled regardless of b-raf mutation status, demonstrate that C TLA-4 blockade with ipilimumab prolongs survival in patients with metastatic melanoma, regardless of prior therapy.

92 INVITED

Combination Strategies for Ipilimumab

J. Weber[1]. [1]*Moffitt Cancer Center, Cutaneous Oncology, Tampa, USA*

Background: The aim of this analysis was to describe the experience with ipilimumab combination therapies, and determine, based on current scientific and clinical data, what drugs should be added to ipilimumab, a treatment that has recently been approved by the US FDA for the treatment of unresectable metastatic melanoma.
Materials and Methods: Published and publicly presented results from combination and single agent clinical trials of ipilimumab in different histologies were analyzed, and an assessment of which trials were most promising and would have the greatest likelihood, in a large randomized phase III study, of augmenting the clinical benefit, while minimizing the side effects of ipilimumab was performed.
Results: Small single arm and randomized phase II studies, as well as phase I studies have examined the addition of chemotherapeutic agents to ipilimumab, without evidence of altering the benefit of ipilimumab monotherapy, but suggesting that they alter the side effect profile. In one small phase II study, the response rate and median OS of ipilimumab plus DTIC were superior to that of ipilimumab alone. However, none of the current phase II or phase III data suggest that additional of a vaccine, or chemotherapeutic agent will improve outcome compared to ipilimumab alone. GM-CSF and IL-2 have also been added to ipilimumab, without data to suggest synergy for either agent, but long-term responders were noted in the IL-2 plus ipilimumab group. Preclinical data support the addition of anti-CD137 antibody to ipilimumab, and indicated that toxicity might be reduced. Recent data suggest that changes in expression of ICOS and Ki-67 on CD8+ T cells was associated with development of immune related toxic events, and that increased EOMES expresson on CD8+ T cells was associated with reduced RFS, both $p = 0.03$. Baseline EOMES CD8+ T cell expression was predictive of lower likelihood of relapse in a recent pilot adjuvant trial of ipilimumab with $p = 0.02$, and a high double positive EOMES+/Ki67+ population was predictive of favorable RFS. These markers may be useful for guiding the choice of future ipilimumab regimens.
Conclusions: Chemotherapeutic combinations may not be optimal at high doses of ipilimumab; high dose IL-2, and anti CD37 antibody merit further analysis. Alterations in activation markers ICOS and EOMES were significantly associated with adverse events and favorable outcome, respectively, and may constitute novel markers which would facilitate the decision to choose optimal combination therapies with ipilimumab for further testing.

Scientific Symposium (Sat, 24 Sep, 16:00−18:00) **Molecular Cancer Epidemiology − The Next Generation**

93 INVITED

Cancer Incidence and Mortality in Europe − GLOBOCAN 2008

D. Forman[1]. [1]*IARC, Cancer Epidemiology, Lyon, France*

This presentation will review the latest information on the overall burden of cancer in Europe as estimated from current results in the GLOBOCAN database, maintained by the International Agency for Research on Cancer. In the EURO region, as defined by the World Health Organisation, there were an estimated 3.4m new cancer diagnoses and 1.9 deaths from cancer in 2008. In general, half of the burden in men is constituted by prostate, lung and colorectal cancers while half the burden in women comprises breast, lung and colorectal cancers. There are, however, important variations in the risk of different cancers within Europe which it is necessary to understand if national cancer control programmes are to be developed successfully. For example standardised rates of cervical cancer vary from less than 5 per 100,000 (in Finland) to over 20 per 100,000 (in Lithuania). This variation cannot be explained by differences in the quality of cancer recording. Further examples of the pattern of cancer within Europe will be provided and the implications of these for both cancer service planning and research will be discussed.

94 INVITED

Genetic Susceptibility − Are We Surfing or Diving Genome?

P. Pharoah[1]. [1]*University of Cambridge, Oncology, Cambridge, United Kingdom*

There is ample evidence from twin and family based epidemiological studies that a substantial proportion of the inter-individual variation in risk of the common cancer is the result of inherited genetic variation. In the 1990's, when our understanding of the architecture of genetic variation in human genomes was limited, the molecular basis of several family cancer syndromes was identified through the identification of high penetrance alleles of genes such as BRCA1, BRCA2 and the mis-match repair genes. However, these alleles are rare in most human populations and they account for less than 20 percent of the genetic component of cancer susceptibility. Ten year later, the advent of the human genome project, the international HapMap project and the availability of new high throughput genotyping methods heralded the genome wide association study. These have been very successful at identifying loci with common alleles (>10 percent) that have modest effects on cancer risk. To date, over 20 such alleles have been identified for breast cancer, more than 30 for prostate cancer, more than 10 for colorectal cancer, and a handful of loci for each of most of the other common cancers. Until now we have only been surfing the genome. Large, multi-centre consortia are now carrying out genetic association studies on an unprecendented scale, for example, the COGS project is genotyping over 200 k markers in nearly 200 k subjects from breast, ovarian and prostate cancer case-control studies. These experiments are likely to increase the number of common susceptibility loci substantially. However, once these study are complete, the known loci, common and rare, will account for less than a half of the genetic component of disease susceptibility. The characteristics of alleles that account for the rest are not known, but it is likely that uncommon or rare variants play an important role. Studies such as the 1000 Genomes Project are now beginning to yield information about the range of rare variation in human populations. New sequencing technologies are becoming more affordable at the same time, finally it will be possible to comprehensively evaluate the role of germline genetic variation in susceptibility to the common cancers.

95 INVITED

Are "Environmental Wide Association Studies" (EWAS) the Missing Piece?

P. Vineis[1]. [1]*Imperial College London, MRC/HPA Centre for Environement and Health School for Public Health St Mary's Campus, London, United Kingdom*

The Achilles heel of current epidemiologic studies is the poor characterization and quantification of environmental exposures. Inaccuracy in exposure assessment leads to blurring of potentially causal associations. The term "exposome" refers to the totality of environmental exposures from conception onwards, and has been proposed to be a critical entity for disease etiology. Although fully characterizing human exposomes throughout life is daunting, strategies can be developed for getting "snapshots" of critical portions of a person's exposome during critical stages of life. We propose a "top-down" strategy which would measure all chemicals (or products of their downstream processing or effects, so-called read-outs or signatures) in a subject's blood. To make the top-down approach feasible, the exposome would comprise a profile of the most prominent classes of toxicants that are known to cause disease, namely, reactive electrophiles, endocrine (hormone) disruptors, modulators of immune responses, agents that bind to cellular receptors, and metals. Characterizing the exposome represents a technological challenge like that of the Human Genome project, which began when DNA sequencing was in its infancy. Analytical systems are needed to process small amounts of blood from thousands of subjects. Assays should be multiplexed for measuring many chemicals in each class of interest. Platforms for high-throughput assays should lead to economies of scale, again like those experienced by the human genome project. Pilot studies around the concept of "exposome" have been launched in order to validate the methodologies.