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

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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

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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?

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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?

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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.