discovered 26 years ago in melanoma, and are found in 20% of melanoma cases. However, targeting mutant RAS with drugs remains an elusive goal. The identification of *BRAF* mutations in 2002 was the watershed event that turned the attention of the melanoma field to this concept. Seven years passed between the identification of BRAF mutations and the validation of this target in melanoma patients with a potent and specific BRAF inhibitor, PLX4032. As phase II and phase III single-agent trials have been completed with the aim of establishing single-agent BRAF inhibition as a new standard of care for the BRAF mutated subpopulation, attention now turns to understanding mechanisms of resistance and rational combination approaches. Current efforts are focused on combining other targeted therapies with BRAF inhibitors in the subgroup of patient who have BRAF mutations.
Subsequent to the discovery of BRAF mutations, KIT mutations have been described in a small subset of melanomas; a significant finding since KIT inhibitors are already clinically available based on their efficacy in gastrointestinal stromal tumour, where KIT mutations are more commonly found. In ocular melanoma, three genetic discoveries in the past two years point to the way to new therapeutic approaches in that historically treatment-refractory subset of patients as well. For the first time, there is a clear strategy for how to build toward increasingly efficacious therapies for advanced melanoma, with the hope that even greater advances lie ahead in the next few years.

129 INVITED

Combining TKI's in Melanoma: Which Rationale, How and When

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The field of melanoma treatment has been dramatically changed with the clinical development of highly specific driver oncogene inhibition of mutated BRAF or c-kit. In both cases, the presence of a driver mutation in the oncogenic kinase is the pre-requisite for a tumour response, and tumour responses are frequent when treating patients with metastatic melanoma bearing the mutant kinase.
The type I BRAF inhibitors vemurafenib (PLX4032/RG7204) and GSK2118436 provide a very high rate of initial response rates in patients with $BRAF^{V600E}$ mutant melanoma. However, the sustained clinical activity is limited primarily by the development of acquired resistance leading to tumour progression.
Mechanisms of acquired resistance fall into two broad groups that predict for secondary responses when adding agents that block the resistance mechanisms. One is the reactivation of the mitogen-activated protein kinase (MAPK) pathway, either through secondary mutations in NRAS or upregulation of COT, or mutations in MEK. These escape mechanisms may be targeted by the addition of a MEK or an ERK inhibitor. Another broad mechanism of acquired resistance is mediated by alternative survival pathways downstream of receptor tyrosine kinases (RTK) like PDGFRb or IGF1R, which may be targeted by the addition of inhibitors to PI3K or AKT. Such combination studies could treat and/or prevent acquired resistance to single agent BRAF inhibitors.
Another possibility to increase the duration of responses combination of targeted oncogenic inhibitors and immunotherapy. The ability of BRAF inhibitors to induce regression of melanoma in a high proportion of patients with $BRAF^{V600E}$ positive melanoma could provide several benefits with the potential to synergize with tumour immunotherapy: i) Increased expression of melanosomal tumour associated antigens upon MAPK pathway inhibition. ii) Release of tumour antigens by dying melanoma tumour cells resulting in increased antigen cross-presentation to CTLs. iii) Modulation of the anti-apoptotic environment in cancer cells upon BRAF inhibition to become more sensitive to the pro-apoptotic effects of CTLs. These immune sensitizing effects, together with the intratumoral infiltration by lymphocytes upon treatment with anti-CTLA4 antibodies, would increase the pool of TILs able to respond to released tumour antigens inside tumours. The clinical testing of combinations of BRAF inhibitors and anti-CTLA4 antibodies or other immune modulators is underway.
In conclusion, the understanding of molecular mechanisms of oncogene signaling in melanoma have opened the door to a new generation of highly active therapies for this disease, and understanding the mechanisms of resistance and the interaction with the immune system can expand the benefits of these therapies.

130 INVITED

TKI's, BRAF Inhibitors and the Problem of New Toxicities Such as Keratoacanthoma and Induction of Invasive SCC

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New targeted therapies of cancer induce multiple and various skin side effects. One particularly intriguing and concerning of these cutaneous adverse events is the emergence of skin tumours during therapy with drugs targeting RAF proteins. Indeed, all drugs targeting RAF proteins can induce benign, borderline (keratoacanthomas) or malignant tumours originating from keratinocytes (Squamous Cell Carcinomas, SCC).
The mechanism underlying this phenomenon is probably linked to the paradoxical activation of the MAPkinase pathway by this drugs in the cells that are not mutated for BRAF. Additional somatic event like EGFR activation in the hair follicles, UV-induced RAS or TP53 mutations or viral proteins might be necessary to lead to a fully transformed cell.
Until now, we did not observe any metastatic evolution of these skin tumours and the treatment consists in surgical resection of the skin lesions. However, when observing the effects of RAF inhibitors on the skin and on keratinocytes *in vitro*, one can address the question of the potential risk of developing such neoplasms also in other organs elsewhere in the body. Caution has to be taken and the physiological bases of these induced cancers should be deeply explored before RAF inhibitors are used in the adjuvant setting.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Molecular Genetics in Lymphoma − Current Knowledge and New Insights From High-Throughput Technologies

131 INVITED

Chronic Lymphocytic Leukaemia (CLL)

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Copy number alterations and mutations of key tumour suppressors as *ATM* or *TP53* have been described in chronic lymphocytic leukemia (CLL). Nonetheless, recurrent mutations are relatively rare in CLL and ongoing whole genome sequencing approaches are expected to yield novel mutations contributing to the pathogenesis of CLL. Ideally, our improved understanding of molecular lesions in CLL could be used to develop genotype specific approaches and to exploit the disease specific mutations by directly targeting these or consecutive pathway dependencies.
Currently genotype specific treatments in CLL are considered in ultra-high risk patients with 17p (*TP53*) deletion. In the future, patients with *TP53* mutations (in the absence of 17p deletion) may be considered in a similar risk category.
In order to advance the field further, it will be crucial to build stronger models of CLL subgroups. In these models it will be important to consider genetic risk groups (e.g. *TP53* mutation and 17p deletion, unmutated *IGHV*) alongside clearer clinical subgroups. CLL may be an ideal disease where pretreatment (genomic aberrations, *TP53* mutation, *IGHV* status) and post treatment factors (MRD level, response depth and duration) could be integrated into novel models. While most current approaches consider pretreatment factors, it should be possible to design combinatorial models. Our understanding of the genetic make-up of CLL is likely to increase as more whole genome sequencing data becomes available. This will undoubtedly lead to new insights and questions with regard to biological basis as well as clinical treatment approaches.

132 INVITED

Mantle Cell Lymphoma (MCL)

Abstract not received

133 INVITED

Diffuse Large Cell Lymphoma (DLCL)

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Diffuse large B-cell lymphoma (DLBCL) is heterogeneous biologically and clinically. Over the last decade, high-throughput technologies have helped to define two major subtypes of DLBCL based on their gene expression