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

profiles that reflect different stages of B-cell development. Specifically, the germinal center B cell-like (GCB) DLBCL shows some features of physiological germinal center B-cells such as expression of BCL6 and the process of ongoing somatic hypermutation of the immunoglobulin genes. Conversely, the activated B cell-like (ABC) DLBCL shows features of post-germinal center B-cells such as the expression of IRF4 and activation of the NFkB pathway. In the CHOP treatment era, patients with ABC DLBCL had inferior survival times compared to patients with GCB DLBCL, and this survival difference appears to be still evident in the R-CHOP treatment era. The definition of the GCB and ABC DLBCL subgroups based on their transcriptional profiles is supported by underlying genetic alterations, many of which cluster within each subgroup. BCL2 translocations and 2p amplifications (c-rel locus) are almost exclusively discovered in GCB DLBCL, whereas amplification of the BCL2 locus, mutations/deletions of PRDM1 and deletions of the CDKN2 tumour suppressor locus frequently occur in ABC DLBCL. More recently, deep sequencing strategies have identified an ever growing number of additional genetic mutations that occur predominantly in GCB or ABC DLBCL. Mutations of the polycomb-group oncogene EZH2 and alterations of the acetyltransferase genes CREBBP and EP300 are predominantly associated with the GCB DLBCL subgroup. On the other hand, mutations/deletions in key genes of the NFkB pathway including A20, CARD11, TRAF2 and TRAF5 are a feature of ABC DLBCL, in which chronic active B-cell receptor signaling can be observed as a consequence of frequent mutations in the B-cell receptor signaling molecules CD79B and CD79A. Approximately 30% of ABC DLBCL carry MYD88 mutations that lead to activation of the NFkB signaling cascade, but also to activation of the JAK/STAT pathway. Ongoing sequencing efforts in DLBCL are likely to identify additional key mutations that might help to explain the heterogeneity of DLBCL and that may lead to the development of novel therapeutic concepts.

134 INVITED

A Molecular Portrait of Follicular Lymphoma

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The clinical diversity of follicular lymphoma (FL) is manifest by a wide range in patient survival and unpredictable risk of aggressive transformation. This variability is reflected in a heterogeneous group of secondary (epi-)genetic changes that typically accompany the hallmark t(14;18) and over-expression of BCL2. As profiling tools have become more sophisticated, we are starting to deliver the 'first draft' of an exceedingly complex portrait of the disease which includes fundamental roles for epigenetic reprogramming and cross-talk between the tumour and its microenvironment.
High throughput genetic profiling has developed many aspects of FL research. *Genome Wide Association Studies* have detected novel susceptibility loci, rs10484561 and rs6457327, on chromosome 6p in the immune gene-rich human leukocyte antigen region and follow the demonstration that immune response in FL can predict outcome. This had been established using *gene expression profiling* that characterised Immune Response I and II signatures that reflect the composition of non-malignant infiltrating immune cells in the tumour. Within the malignant cells, the identification of recurring regions of chromosomal aberrations and the corresponding gene targets is set to accelerate with the introduction of *high throughput sequencing* strategies. *TP53* mutations are linked with poor outcome in the disease, although at 6% these are relatively infrequent and a more important target will be *TNFRSF14*/*HVEM* on 1p36, mutated in 20% of FL, and which functions as a potential inhibitory modulator of BCR signalling. The demonstration of mutations in key histone methyltransferases, *EZH2* and *MLL2*, and the acetyltransferase genes, *CREBBP* and *EP300,* suggest that a shift from gene activation to gene repression may be a pre-requisite for onset of FL. This is consistent with *methylation profiling* studies, which show repressive hypermethylation at 7% of gene promoter regions in these tumours.
These advances come at a time when the assumption that each episode of FL reflects the emergence of a more aggressive sub-clone of cells from an existing FL population is under review. By tracing the genetic changes in sequential FL biopsy samples it transpires that recurrent episodes of disease may originate from a more undifferentiated B-cell population. It is a real possibility, therefore, that FL arises from this pool of progenitor B cells and that many of the (epi-)genetic events described can directly influence these cells and are responsible for the clinical features of the disease. That said, we are still some way off from understanding how such diverse changes complement each other to give rise to FL and influence patient outcome.

Scientific Symposium (Sun, 25 Sep, 09:00−11:00)
Multidisciplinary Quality Assurance

135 INVITED

Quality Assurance of Oral Compliance

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Cytotoxic agents block the growth of cancer cells by influencing cell metabolism during the cell cycle so that cell division and reproduction is inhibited. The mechanisms of cytotoxic action are likely to lead to carcinogenic, mutagenic and teratogenic effects. It is suspected that even the smallest doses of cytotoxic agents have an irreversible and cumulative effect and, although they do not have a threshold value, they represent a low but nevertheless clearly defined risk as a consequence.
Over the last few years, impressive progress has been made in the treatment of cancer, not only in research and clinical application but also in clinical and pharmaceutical practice. There has been a massive increase in the number of cytotoxic and supportive drugs for cancer and with the ongoing development of novel therapeutic agents, many of which can be taken orally, it has become increasingly vital that drugs that can be toxic to healthcare workers are prepared, transported and delivered as safely as possible. The role of the hospital pharmacy is paramount in this process.
The quality standard for oncology pharmacy service, developed in Germany, has become the working standard throughout Europe. Rules and guidelines, which may help to ensure uniform safety and quality, need to be defined for all areas involved in handling cytotoxic agents. However, there is still a long way to go before uniformly high standards of safe preparation are achieved across Europe.
The quality assurance and documentation in the diagnosis and treatment of tumours become increasingly important. As the interdisciplinary approaches are standardized in terms of treatment protocols and clinical pathways adequate quality assured multi-professional care of patients with oral cancer chemotherapy is therefore urgently required.
Nationwide training started in Germany already in May 2010, in order to improve the knowledge of pharmacy staff on selected oncological and pharmaceutical topics (e.g drug interactions in oncology, specifically pharmaceutical oncology case studies, side effects of cancer).
Nearly 20.000 Pharmacists and Technicians in community and hospital, which contribute to increase drug treatment safety in oral cytostatic therapy and provide information and counseling services for people with cancer in pharmacies will be targeted in Germany by ESOP speakers from September 2011 in three main topics in the following month.
Based on the knowledge about tumour, the pharmacology of prescribed oral cytotoxic drugs and the relevant supportive care, patient-specific recommendations can be given and documented.
Physicians and pharmacies together with patients will be able to afford on this basis, an active contribution to improving the pharmaceutical care of cancer patients locally and for the oncology outcomes research as well as to improve the adherence for increasing quality of life while the continuously treatment.

136 INVITED

Quality Assurance Through Outcome Registration in Colorectal Cancer − an ECCO Initiative for Europe

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In recent years there have been significant improvements in cancer treatment. Besides effective (neo)adjuvant treatment regimes, new surgical techniques made a big contribution to these improvements. Standardised and quality controlled surgical trials seem to have a positive effect that reaches further then the patients and doctors that participated in the study. Good examples are the Dutch TME trial and the Dutch D1-D2 Gastric Cancer Trial. In both trials standardisation and quality of surgical treatments was continuously emphasised by means of masterclasses, supervision and visitation with lasting positive effects.
However, most patients are treated without being enrolled in clinical trials. Furthermore, elderly patients or those with multiple comorbidities are often excluded from trials, leaving little evidence for the treatment of these categories of patients. Therefore, to improve quality of care for the entire patient population, a comprehensive audit could be a more effective instrument. In Europe, several national rectal cancer audit registries have been established of which all showed positive and very economic effects on outcome of surgical care. Despite these laudable efforts there is still a wide variation in treatment outcome between countries, regions and institutions, which calls for a European audit on cancer treatment outcome.
Urged by these arguments, the European Society of Surgical Oncology (ESSO) initiated an international, multidisciplinary, outcome-based quality