evaluation of MAPK signaling inhibitors, VEGF signaling inhibitors, survival kinase inhibitors, and cyclin-dependent kinase inhibitors in melanoma. An overview of melanoma biology and established targets, followed by a summary of completed and ongoing early phase clinical trials will highlight the failure of the first generation of targeted therapies to improve outcomes as single agents. In contrast, early hints of improved outcomes have been generated by clinical trials testing the combination of sorafenib and chemotherapy. The potential of targeted therapies in combination with chemotherapy or regimens consisting of multiple targeted therapies will be explored as increasing evidence suggests that combination therapeutics could finally impact the outcome of metastatic melanoma.

175 INVITED

Target discovery in melanoma

L. Cueni, M. Nikolic, M. Detmar. *Swiss Federal Institute of Technology ETH Zurich, Institute of Pharmaceutical Sciences, Zurich, Switzerland*

Tumor metastasis to regional (sentinel) lymph nodes represents the first step of tumor dissemination in most melanomas and serves as a major prognostic indicator for disease progression. However, little is known about the mechanisms how tumor cells gain entry into the lymphatic system. In this respect, we have previously shown that tumors can actively induce the formation of lymphatic vessels (leading to the new concept of tumor lymphangiogenesis) and that tumor lymphangiogenesis was correlated with lymph node metastasis in an orthotopic breast cancer model. Our studies in human cutaneous malignant melanomas demonstrated the presence of both intratumoral and peritumoral lymphangiogenesis in cutaneous melanoma. They also showed that primary melanomas that later metastasized were characterized by increased lymphangiogenesis – as compared to non-metastatic tumors – and that the degree of tumor lymphangiogenesis can serve as a novel predictor of lymph node metastasis and overall patient survival, independently of tumor thickness. Moreover, we found that the extent of lymphatic vessel growth in primary human cutaneous melanomas was the most sensitive parameter for predicting whether these tumors had already metastasized to the sentinel (draining) lymph node at the time of surgery. Importantly, we have recently found - for the first time - that metastastic tumor cells can induce lymphatic vessel growth within lymph nodes, furthering their metastatic spread. This has led to the new concept of lymph node lymphangiogenesis. Surprisingly, we found that tumor cells can induce lymph node lymphangiogenesis already before they metastasize, giving a new twist to the seed-and-soil hypothesis and suggesting that tumors can prepare lymph nodes for their future arrival. We have characterized the transcriptional profile of normal and of tumor-associated lymphatic and blood vessels by laser capture microdissection. This has enabled us to identify a number of new targets for anti-(lymph)angiogenic cancer therapy. Taken together, tumor lymphangiogenesis has emerged as a novel prognostic parameter for the metastatic risk of human melanomas, and inhibition of tumor-associated lymphangiogenesis appears to represent an exciting new strategy to inhibit cancer progression.

Symposium (Wed, 26 Sep, 14:45−16:45)
New drugs and new tools in the treatment of patients with myeloma

176 INVITED

New insights in the biology of multiple myeloma: basis for novel therapies

J. San Miguel Izquierdo. *Hospital Universitario de Salamanca, Servicio de Hematologia, Salamanca, Spain*

Multiple myeloma (MM) remains as an incurable disease; therefore, new treatment strategies are needed in order to improve the outcome of these MM patients. The increase knowledge in MM biology is already contributing to a more specific drug design, and we have recently learned that in the pathogenesis of MM, as important as the malignant cells themselves, is their interaction with the microenvironment.
Multiple myeloma requires a multistep transformation process that implies the sequential generation of primary Ig translocations, chromosomal instability (including mutations – RAS s– and deletions − RB), as well as secondary translocations. Most Primary immunoglobulin gene translocations occur early in the pathogenesis of MM. These translocations, which are mediated by errors in immunoglobulin heavy-chain switch recombination, result in the juxtaposing of an oncogene and an immunoglobulin enhancer. On the basis of Ig H translocations MM patients can be divided into 5 subgroups: (1) D-type cyclins: Cyclin D1 on 11q23, Cyclin D3 on 6p21 and Cyclin D2 on 12p13 (25% of cases); (2) MMSET/FGFR3 proteins (4p16.3) (15% of cases); (3) B-zip transcription factors: c-maf on 16q23 and maf B on 20q11 (15% of cases); (4) other Ig H translocations (20% of cases); and (5) No Ig H translocations (25% of cases). Secondary oncogenic events may involve both genes different from Ig locus, as well as the 14q32 region, as occur in the c-myc translocations.
Some of these molecular events represent potential therapeutic targets. Thus t(4;14) translocation generate a constitutive activation of the oncogenic receptor tyrosine kinase FGFR3 with subsequent phosphorylation of the antiapoptotic STAT3 signaling pathway. Therefore, the use of Kinase inhibitors of FGFR3 tyrosine kinase as well as Kinase inhibitors of cyclin dependent kinases would be attractive therapeutic targets. Similarly C-maf, that is over expressed in MM patients with t(14;16) as well as in some MM cases lacking this translocation, also represent a potential target.
The second area of MM pathogenesis that may have important implications for treatment intervention is the interaction between the malignant cell and the bone marrow microenvironment. MM cells adhere to the extra cellular matrix (ECM) proteins and bone marrow stromal cells (BMSC) through a series of adhesion molecules, such as the β1-integrin family (VLA-4, VLA-5 and VLA-6 or CD49d, e and f, respectively) as well as ICAM-1 and VCAM-1. Adhesion of myeloma cells to BM microenvironment induces a CAM-DR phenotype (cell-adhesion-mediated drug resistance). Interruption by downregulating the interactions between the tumor cell and its microenvironment can potentially halt cell growth and proliferation, and be of benefit to patients with MM. The binding of MM cell to BM microenvironment it also induces the transcription and secretion of cytokines (TNFa, IL-6, IGF-1, IL-21, SDF1a, VEGF), by both the PC and BMSC, which triggers signalling pathways (such as the RAF/MEK/MAPK, PI3K/AKT, and JAK/STAT pathways), that promote cell proliferation and prevent apoptosis. These pathways are also potential targets for therapeutic intervention.

177 INVITED

New drugs

M. Boccadoro. *Italy*

Abstract not received.

178 INVITED

Autologous and allogeneic transplantation in multiple myeloma

J. Blade. *University of Barcelona, IDIBAPS Institute of Hematology and Oncology, Barcelona, Spain*

In patients with multiple myeloma (MM) high-dose therapy/stem cell transplant (HDT/SCT) can be applied in different clinical settings and by using different approaches. In patients with relapsed/refractory disease, HDT/SCT is of no benefit. In contrast, patients with sensitive relapse are the most likely to benefit. Concerning newly diagnosed patients, two randomized trials showed that autologous transplant resulted in higher response rate as well as in longer progression-free and overall survival when compared with standard chemotherapy; however, other three randomized trials failed to show a significant survival advantage in favour of high-dose therapy. In any event, autologous transplantation in currently considered as part of the up-front therapy in younger myeloma patients. Double autologous (tandem) seems to be of benefit for patients not achieving complete remission or very good partial response with a single procedure. Allogeneic transplant with conventional conditioning results in a high response rate and cure in about 20% of patients. However, the transplant-related mortality (TRM) is between 30 and 50%. For this reason, the so-called “mini-allogeneic” or reduced-intensity conditioning allogeneic transplant (allo-RIC) is currently used in most institutions. The TRM with allo-RIC is about 20%; however, the relapse rate is higher than with conventional conditioning, this resulting in a similar long-term outcome with the two allogeneic approaches. In patients with advanced disease the allo-RIC seems to be of no benefit. In MM, HDT/SCT constitutes an important tool for tumour mass decrease. In the current era of novel agents and more effective treatment combinations, the additional tumour mass reduction achieved with HDT/SCT will hopefully result in an improved long-term outcome for patients with multiple myeloma.

179 INVITED

Waldenström macroglobulinaemia

M. Dimopoulos, E. Kastritis, A. Anagnostopoulos. *Medical School Athens University, Department of Clinical Therpeutics, Arhens, Greece*

Waldenström’s macroglobulinemia (WM) results from the clonal proliferation of lymphocytes that produce monoclonal immunoglobulin M (IgM) and always involves the bone marrow. The normal counterpart of WM malignant cell is believed to be a post-germinal center B cell. WM cells do not bare