and their links to cancer, together with relevant examples of regulation of their functions, will be presented.

Scientific Symposium (Tue, 22 Sep, 14:45–16:45)
Investigating novel targets and anti-angiogenic agents in brain tumours

158 INVITED

Anti-EGFR and anti-angiogenic therapy – from mice to men

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The development and clinical evaluation of therapeutic agents directed against the epidermal growth factor receptor (EGFR) or against tumor angiogenesis are two major strategies in targeting malignant gliomas. EGFR is overexpressed in approximately 60% of primary glioblastomas, frequently associated with *EGFR* gene amplification, and the constitutively active EGFRvIII variant is expressed in about half of the amplified cases. Specific EGFR targeting has been achieved using small molecule tyrosine kinase inhibitors (TKIs), such as erlotinib (Tarceva®) and gefitinib (Iressa®), as well as monoclonal antibodies (mAbs), such as cetuximab (Erbitux®). Erlotinib and gefitinib are the most well studied anti-EGFR agents. Xenograft studies in mice suggested that glioblastoma sensitivity to erlotinib is associated with the expresson of amplified and aberrant EGFR combined with wild-type PTEN. However, while two clinical studies found some evidence that a subset of patients with coexpression of EGFRvIII and wild-type PTEN or with high expression of wild-type EGFR and low levels of p-Akt respond to TKIs, a larger randomized EORTC trial detected no clinical benefit for erlotinib and no association with molecular markers. Using a highly invasive orthotopic mouse model with patient-derived xenografts, we found that response to local treatment with cetuximab depended on the presence of amplified and/or mutated EGFR, whereas the PTEN or p-Akt status was irrelevant. A recent phase II study showed that a small subgroup of patients with recurrent malignant glioma may benefit from cetuximab (administered i.v.), but response did not correlate with EGFR copy number. Promising results were recently reported for a vaccination approach, using a peptide that spans the EGFRvIII fusion junction. Phase I and II trials showed that this treatment led to T- and B-cell immunity in patients, eliminated tumor cells expressiong EGFRvIII, and caused an unexpectedly long patient survival.
Most anti-angiogenic strategies target the vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) system, which is crucial to angiogenesis and edema formation in malignant gliomas. Xenograft studies showed that anti-VEGF and anti-VEGFR mAbs could strongly inhibit glioblastoma growth and prolong survival, however, treatment led to increased tumor invasion along the host vasculature. The most well studied anti-angiogenic compound is bevacizumab (Avastin®), a neutralizing mAb against VEGF. Bevacizumab has shown encouraging antitumor activity in combination with irinotecan, however this effect may be restricted to radiographic response and prolongation of progression-free survival, without prolongation of overall survival. Contrast-enhanced MRI can easily overestimate the effect of anti-angiogenic treatment, since it relies on extravasation of the contrast agent, which is impeded by the vascular permeabilty-reducing, anti-edematous effect of Bevacizumab. Nevertheless, strong subjective patient improvement and a steroid-sparing effect are clear benefits. Interestingly, tumor recurrence patterns after Bevacizumab treatment appear to confirm studies in rodents, since glioblastoma recurrences in humans are also more infiltrative. Ongoing larger randomized trials will show whether this represents a true increase in tumor cell invasiveness or a relative suppression of enhancing tumor growth, and they will further show whether Bevacizumab alone or in combination can prolong overall survival.

159 INVITED

PTEN and growth factor receptor targeting in glioblastoma

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There is compelling evidence in a variety of human cancers that activating mutations in signal transduction pathways can result in tumor cell "dependence" on the mutant pathway and predict clinical response to pathway inhibition. In some of these diseases, clinical responses have been so consistent that the main challenge is no longer to achieve an initial treatment response, but to understand, overcome, and delay the emergence of acquired resistance to these agents. Progress with targeted cancer therapeutics has been slow in glioblastoma. When used as single therapy in molecularly unselected patient populations, most signal transduction inhibitors have produced radiographic responses in only a small fraction of patients. Mechanisms of resistance to specific signal transduction inhibitors in glioblastoma are largely unknown. My presentation will discuss molecular mechanisms of resistance to signal transduction inhibitors in glioblastoma, in particular PTEN-associated resistance to EGFR kinase inhibitors.

161 INVITED

Combining the adhesion pathway inhibition with radiotherapy – from the bench to the clinic

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Background: Tumor response to radiotherapy is controlled by many intracellular tumoral factors whose deregulation leads to the modulation of the tumoral radiosensitivity, but also by micro-environmental factors such as hypoxia. These factors such as growth factors and their receptors and their downstream pathways can be intrinsically activated in some tumor cells leading to radioresistance, in particular via the inhibition of radiation-induced cellular deaths. These pathways are activated by irradiation, amplifying the phenomena of resistance by the activation of the radiation-induced DNA beaks repair, by the induction of tumoral repopulation, or stimulation of the migration pathways. Thus, irradiation activates receptors such as EGFR, FGFR, or avb3 and avb5 integrins involved in adhesion and angiogenesis, known to control tumor radioresistance via the induction of hypoxia, the control of tumor radiosensitivity via that of the endothelial cells, and its importance in the radioresistant tumor stem cells survival.
Methods and Results: We and other have shown that irradiation activates avb3/avb5 integrins, which are highly expressed in glioblastoma (GBM). Our lab has recently demonstrated that irradiation activates these integrins, which in turn control radioresistance in GBM cells via the integrin linked kinase (ILK) and RhoB under its farnesylated form, leading to the inhibition of the radiation induced mitotic death. These factors are moreover implicated in the control of the tumor micro-environment, particularly in angiogenesis and hypoxia. We have shown that the avb3/avb5 integrins, control intracellular radioresistance but also hypoxia *in vivo* and the regulation of HIF-1a via the focal adhesion kinase and RhoB, HIF-1a being a factor of radioresistance which is also activated by irradiation. Inhibition of this pathway leads to radiosensitization, normalization of hypoxia and angiogenesis. Moreover, we have shown in an other tumor that the co-expression of b3 integrin and FGF-2 was associated with a worse local control after radiochemotherapy, demonstrating the clinical relevance of this pathway in the control of the radiosensitivity.
Thus, one of the strategies to improve the radiosensitivity of radioresistant and hypoxic tumors as GBM consists in the association with the radiotherapy of inhibitors of these pathways. We and others have shown that the integrin inhibitor cilengitide induced a radiosensitization of GBM cells and xenografts. We have shown that inhibiting the farnesylation of RhoB led to radiosensitization, reoxygenation and normalization of the vasculature in GBM models. These results led us to design and conduce clinical phase I and II trials in GBM associating the farnesyltransferase inhibitor tipifarnib to radiotherapy showing good tolerance and encouraging results. An early phase trial associating cilengitide to radio-chemotherapy has shown promising results, in patients presenting the MGMT promoter methylation, probably due to a normalization of the vascularization obtained by cilengitide.
Conclusions: The optimal sequences of association between these targeted drugs and the radiotherapy remain incompletely elucidated and need to be studied. The precise study of the mechanisms of action of these therapies and of their interaction with radiotherapy, as well as the follow-up by metabolic imaging, of the patients accrued in such trials, will allow the determination of the optimal schedule of these promising combined treatments.

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Clinical management of the elderly

162 INVITED

Geriatric assessment in oncology: a tool to provide better cancer care in the elderly

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The aging population is characterized by an extreme diversity in terms of clinical, functional and social status. As a consequence, life expectancy in