to chromatin, where it is also phosphorylated. RNF8/UBC13 complexes go to sites of DNA damage through their forkhead domain and initiate the synthesis of K63 polyubiquitin chains on chromatin that recruit the BRCA1 complex through the ubiquitin-interacting motif domains (UIM) of RAP80. In addition, the SUMO pathways components (UBC9-protein inhibitor of activated STAT (PIAS) and UBC9-PIAS1) also accumulate at DSBs, where they catalyze the SUMOylation of BRCA1. SUMOylation stimulates BRCA1 E3 ubiquitin ligase activity, leading to ubiquitylation of target proteins at DSBs, including the H2AX. Depletion of PIAS1 and PIAS4 impaired recruitment of BRCA1 to DSBs, significantly impaired ubiquitylation at DSBs, and reduced ubiquitylation of H2AX. PIAS SUMO ligases are required for homologous recombination and non-homologous end-joining. PIAS1 and PIAS4 depletion resulted in ionizing radiation hypersensitivity. Therefore, these could be essential components − together with BRCA1 − for predicting response to radiotherapy and cisplatin-based chemotherapy. Based on the plethora of evidence for the central role of BRCA1 in conferring differential sensitivity to irradiation and DNA-damaging drugs (cisplatin, carboplatin) and to antimicrotubule drugs (paclitaxel, docetaxel, vinorelbine), we performed a study of customized treatment, mainly in adenocarcinoma, where stage IV NSCLC patients with EGFR mutations received erlotinib and those without EGFR mutations were assigned to chemotherapy based on BRCA1 mRNA levels. The multivariate analysis also showed that levels of RAP80 were an independent prognostic marker. We have examined multiple genes involved in DNA repair and outcome in EGFR mutant NSCLCs treated with erlotinib. Only BRCA1 was significantly relevant. The model shows that BRCA1 can independently repair the damage caused by EGFR TKI inhibitors in tumours with EGFR mutations. It could be cardinal for customizing PARP inhibitors to examine 53BP1 in conjunction with BRCA1. In wild-type cells, BRCA1 displaces 53BP1 from double strand breaks, enabling resection at the break site by factors such as CtIP, which promotes RPA loading onto single stranded regions of DNA. In contrast, in BRCA1 depleted cells, 53BP1 is not displaced and prevents resection. In the absence of resection the DNA breaks persist and are not repaired. However, in cells depleted by both BRCA1 and 53BP1, double strand breaks are repaired. It could be essential to interpret the benefit of PARP inhibitors according to the levels of BRCA1 and 53BP1.
Recently important advances in squamous cell lung cancer have been found that constitute important new therapeutic targets which could be clinically exploited.

269 INVITED

Biomarkers: Differences Between Medical Oncology Versus Radiotherapy

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With the development of specific molecular targeted treatments and the establishment of new molecular methods, research into biomarkers that are able to predict treatment outcome is of increasing importance in oncology. It is perspicuous, that predictors for local tumour control after curatively intended radiotherapy will not be the same as those for chemotherapy alone. However, there may also be overlaps, like in the use of putative cancer stem cell markers. There are data showing a correlation of expression of the surface marker CD44 alone or in combination with other markers with tumour regression after chemotherapy. For radiotherapy, a recent publication has shown that expression of CD44 correlates with long-term local tumour control after primary radiotherapy in patients with early squamous cell carcinoma of the larynx. This correlation is in line with the observation of a preferential expression of CD44 in cancer stem cells, the knowledge that all cancer stem cells have to be inactivated to achieve permanent local tumour control and that a higher number if cancer stem cells needs a higher irradiation dose for local tumour control.
However, in most cases biomarkers for Medical Oncology and Radiation Oncology will be different, not only because different treatments and different settings are used. Even for treatment effects of the same drug, used either as sole therapy or in combination with other systemic treatments versus in combination with radiotherapy, we have to expect different values of potential biomarkers. First, it is important which endpoint has to be predicted: In palliative schedules for patients with advanced tumours, biomarkers will be adequate that predict antiproliferative effects. For combination of different drugs, treatment interactions may be a relevant parameter. When combination schedules of drugs with radiotherapy are used in curative setting, a relevant biomarker has to predict cytotoxic effects that are either independent or due to radiosensitisation. A good example is the application of epidermal growth factor receptor (EGFR) inhibitors, where specific mutations of the EGFR-tyrosine kinase (TK) correlate with response to EGFR-TK inhibitors, whereas KRAS mutations appear to correlate with non-response to TK inhibitors or cetuximab. In contrast, preclinical data suggest that KRAS mutated tumours may be radiosensitised by cetuximab and that for local tumour control after combined irradiation and cetuximab treatment the protein and gene expression of the recetor may be relevant.
The talk will give an overview on potential biomarkers for radiotherapy and combined treatments.

Scientific Symposium (Mon, 26 Sep, 09:00−11:00)
Optimizing Treatment in Gliomas

270 INVITED

Molecular Biomarkers

Abstract not received

271 INVITED

Optimizing Treatment for Gliomas − Radiotherapy

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Optimal treatment of gliomas includes a judicious combination of observation, surgery, radiotherapy and chemotherapy, but because of the considerable biological heterogeneity of gliomas, the appropriate therapeutic combination can vary considerably. Key radiotherapy issues to be addressed from clinical trial results in this session will focus on the following questions:

1. For adult low grade glioma, does immediate post-operative radiotherapy alter survival for either the entire cohort, or for selected high-risk subsets of patients? Prior randomized trials have shown no dose-effect, and although a progression-free survival benefit is identified, there is no impact on overall survival. To these data, we will add a recent analysis from the US SEER database, showing a decrement in survival in low-risk patients, but possible improvement in high-risk cohorts.
2. For adult low grade glioma, does chemotherapy provide a survival benefit when combined with radiotherapy? Although the overall study results do not support, a subset analysis of RTOG 9802 is suggestive of a possible positive effect which needs to be explored further and will be presented.
3. For anaplastic oligodendroglioma, the addition of chemotherapy to radiotherapy provides an advantage in progression-free survival, and longer-term analysis of RTOG 9402 suggests an improving hazard ratio in terms of survival, and these data will be presented.
4. For anaplastic astrocytoma, the role of combining temozolomide with radiotherapy remains inadequately defined; results of RTOG 9813 suggest a superior toxicity profile with the use of temozolomide rather than procarbazine, lomustine and vincristine with radiotherapy.
5. For glioblastoma, the combination of 60 Gy radiotherapy with temozolomide has become "standard-of-care", and attempts at improving this through temozolomide dose-intensification were carried out in RTOG 0525, results of which will be presented. This trial also allowed two different radiotherapy techniques to be utilized, without a significant survival advantage from either. Earlier, non-temozolomide RTOG trials focusing on dose escalation with radiosurgery or 3D dose-escalation or fractionated stereotactic radiotherapy boost did not provide convincing evidence for a survival advantage.

These trials, and their results will be discussed.

272 INVITED

Optimising Treatment in Gliomas − Translational

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Numerous animal models have during the past 60 years been developed, to study brain tumour development. Although such models have made significant contributions to our understanding of the mechanisms related to tumour initiation and progression, it is now clear that this knowledge only to a limited extent has been translated into more effective treatment principles. Therapeutic efficacy has been demonstrated in different animal models, yet the same treatment modalities fail in Phase II/III clinical trials. We have developed human glioblastoma (GBM) animal xenograft models that display the clonal heterogeneity and the genotypic and phenotypic traits of the corresponding human GBMs. Since GBMs are highly hypoxic and angiogenic, they are considered as good candidates for anti-angiogenic therapy. Preclinical experiments targeting the Vascular Endothelial Growth Factor (VEGF) by the monoclonal antibody bevacizumab have shown anti-tumour effects that have led to clinical trials either as monotherapy or

in combination with cytotoxic agents. Unfortunately, in the clinic, anti-angiogenic therapy has not yet met initial expectations despite high radiological response rates. The direct anti-tumour effect of anti-angiogenic drugs is not clear and eventually all GBMs recur, indicating that the tumours develop escape mechanisms towards treatment.
In a series of preclinical studies using intracranial patient-derived xenografts, we have shown that such escape mechanisms are associated with a metabolic switch in the tumours towards glycolysis, as indicated by an up-regulation of the transcription factor HIF-1 (hypoxia inducible factor-1) and several metabolites associated with the glycolytic pathway (e.g. lactate). In conclusion, we have identified in a robust preclinical model system, specific biological escape mechanisms towards anti-angiogenic therapy, and based on this information novel therapeutic principles will be discussed.

273 INVITED

Targeting Angiogenesis in Glioma − Challenges and Pitfalls

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Malignant gliomas, notably glioblastoma are among the most vascularized and angiogenic cancers, and microvascular proliferation is one of the hallmarks for the diagnosis of glioblastoma. Angiogenesis is regulated by a balance of pro- and antiangiogenic signals; overexpression of VEGF and activation of its receptors, most notable VEGFR-2 and -3, results in endothelial cell proliferation and leaky vasculature. Heterogeneous perfusion and oxygenation, peritumoral edema and increased interstitial pressure are the consequence. Both endothelial and tumour cells are strongly dependent on integrin-mediated adhesion for cell proliferation, survival, migration and invasion.
Strategies aiming at inhibition of cell signaling and angiogenesis, including integrin inhibitors, have been clinically investigated in gliomas over the last 5 years. Radiological responses, a decreased requirement of corticosteroids and temporary improvement in performance status have repeatedly been observed. Toxicity was mild-moderate and manageable, notably there was no evidence for a substantially increased incidence of intracranial bleeding. However definitive comparative (randomized !) investigation has failed to demonstrate improved outcome with single agent inhibition of EGFR, or PDGFR or VEGF/VEGFRs pathways in recurrent glioblastoma. Definitive phase III trials combining the anti-VEGF monoclonal antibody bevacizumab, or cilengitide, a peptidic integrin-inhibitor, together with temozolomide and radiotherapy are ongoing (accrual completed).
The integration of anti-angiogenic strategies in the management of malignant glioma also poses entirely new challenges in patient management: 1) Many agents are known for increasing the risk of thrombosis, embolism and intracranial bleeding. 2) Evaluation of treatment efficacy is difficult and new biomarkers of activity, including functional, metabolic or molecular imaging techniques are urgently needed. Normalization of vasculature leads to decrease in contrast enhancement without necessarily reflecting tumour shrinkage. Tumour heterogeneity, putative prognostic or predictive factors require early controlled trials, novel trial designs and endpoints. 3) Activation of alternate pathways and tumour escape mechanisms may require combination of multiple agents, which is often not feasible due to regulatory restrictions and potential complex toxicities. Emerging clinical and experimental evidence suggests that anti-angiogenic drugs might need to be combined with drugs targeting tumour adaptive mechanisms in addition to cytotoxic chemotherapy and irradiation for a maximal antitumour effect.

274 INVITED

Clinical

Abstract not received

Scientific Symposium (Mon, 26 Sep, 09:00−11:00) **The Role of IGFs/IGF-1R Pathway in Paediatric Malignancies**

275 INVITED

Biology of IGF/IGFR Pathway in Sarcomas

Abstract not received

276 INVITED

IGF1R Inhibitors in the Treatment of Ewing Sarcomas

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IGF signaling has been shown to play a role in a variety of pediatric sarcomas, including Ewing's sarcomas. While no genetic alterations in IGFIR have been identified, epigenetic changes in the form of loss of imprinting of the ligand, IGF-2, have been found in Ewing's sarcomas. These findings led to clinical studies testing a variety of IGFIR humanized antibodies in patients with recurrent Ewing's sarcomas. The Sarcoma Alliance for Research through Collaboration (SARC) initiated an international study utilizing the fully human IGFIR antibody R1507, in collaboration with Roche. We entered 132 unselected patients with recurrent Ewing's sarcoma from December 18, 2007 through April 4, 2010, and 115 patients were eligible for evaluation. Most patients were treated at a dose of 9 mg/kg as a weekly IV infusion, and five patients were treated with a dose of 27 mg/kg given every three weeks as an IV infusion when an amendment was included to test this dose at the end of the study. Overall, objective responses were seen in 19 patients for a RR of 16.5% including two CRs. Eight of the 19 responses lasted greater than 18 weeks, and 11 responses lasted less than 18 weeks. Most responses developed rapidly after initiating therapy, although there was at least one patient who developed a PR after more than 20 weeks of treatment. Patients tolerated therapy extremely well. The common Grade 3/4 toxicities observed included thrombocytopenia 7%, anemia 7% and hyperglycemia of 3%. We have created models to study the effects of IGFIR antibody treatment in mice and have identified factors that likely influence response. First, IGFIR density is quite variable in the surface of tumours, and tumours with very low density IGFIR do not respond to IGFIR Ab treatment. Second, similar to patients treated on this study, responding tumours eventually re-grow and this tumour re-growth corresponds with re-activation of pAKT, in the setting of continued IGFIR suppression. Thus we hypothesize that activation of "by pass" pathways leads to recurrence in responding patients. We still need to identify positive predictors of response and are engaged in analyzing patient samples treated on this study do so. Finally, we are using our preclinical models to identify combination therapy that might mitigate activation of "by pass pathways and these will be discussed.

277 INVITED

IGF1R Targeting in Non-sarcoma Pediatric Malignancies

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Insulin-like growth factors and their receptor insulin-like growth factor type 1 receptor (IGF-1R) are implicated in tumour growth, metastatic dissemination and drug resistance, and thus represent a promising therapeutic target in cancer. Physiological cell growth is widely regulated by growth factors such as IGF1 and IGF2, and normally down-regulated after growth. In multiple cancer cells, particularly pediatric cancers, this growth factor pathway is activated. Whereas *IGF-1R* gene mutations or gene amplification appear rarely, loss of imprinting of IGF2 (11p15) have been reported occurring in rhabdomyosarcoma, neuroblastoma, hepatoblastoma, nephroblastoma; elevated IGFBP-3 levels are found associated with EWS-FLI transfusion products in Ewing sarcoma. *MYCN* overexpression modulates IGF action through increased IGF-1R expression and decreased IGF-BP3 expression, resulting in increased tumorigenicity in neuroblastoma. In Wilms' tumours, mutations/deletions in WT1 result in overexpression of IGF-1R and IGF-II; the prior was found associated with relapsed disease. IGF-1R targeting using IGF1R antisense, different monoclonal antibodies or small molecule tyrosine kinase inhibitors has been explored preclinically in osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, and neuroblastoma mostly showing anti-proliferative effects *in vitro* and growth inhibition in xenografts *in vivo*, Enhanced effects were observed when IGF1R targeting was combined with classical anticancer agents or other growth factor receptor or downstream pathway inhibitors such as PI3K, AKT or mTOR. The clinical evaluation