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.

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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

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Molecular Biomarkers

Abstract not received

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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.

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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