decade enabling the delivery of high radiation doses, reducing side-effects in tumour-adjacent normal tissues. While increasing local tumour control, current and future efforts ought to deal with microscopic disease at a distance of the primary tumour, ultimately responsible for disease-progression. This talk will explores the possibility of bimodal treatment combining radiotherapy with immunotherapy. L19 targets the extra domain B (ED-B) of fibronectin, a marker for tumor neoangiogenesis, and can be used as immunocytokine when coupled to IL2. We hypothesize that radiotherapy in combination with L19-IL2 provides an enhanced antitumor effect, which is dependent on ED-B expression.
EXPERIMENTAL DESIGN: Mice were injected with syngeneic C51 colon carcinoma, Lewis lung carcinoma (LLC), or 4T1 mammary carcinoma cells. Tumor growth delay, underlying immunologic parameters, and treatment toxicity were evaluated after single-dose local tumor irradiation and systemic administration of L19-IL2 or equimolar controls.
RESULTS: ED-B expression was high, intermediate, and low for C51, LLC, and 4T1, respectively. The combination therapy showed (i) a long-lasting synergistic effect for the C51 model with 75% of tumors being cured, (ii) an additive effect for the LLC model, and (iii) no effect for the 4T1 model. The combination treatment resulted in a significantly increased cytotoxic (CD8(+)) T-cell population for both C51 and LLC. Depletion of CD8(+) T cells abolished the benefit of the combination therapy.
CONCLUSIONS: These data provide the first evidence for an increased therapeutic potential by combining radiotherapy with L19-IL2 in ED-B-positive tumors. This new opportunity in cancer treatment will be investigated in a phase I clinical study for patients with an oligometastatic solid tumor (NCT02086721). An animation summarizing our results is available at https://www.youtube.com/watch?v=xHbwQuCTkRc .
REFERENCE:. Zegers CM1, Rekers NH2, Quaden DH3, Lieuwes NG2, Yaromina A2, Germeraad WT4, Wieten L5, Biessen EA6, Boon L7, Neri D8, Troost EG2, Dubois LJ2, Lambin P2. Radiotherapy combined with the immunocytokine L19-IL2 provides long-lasting antitumor effects. Clin Cancer Res. 2015 Mar 1;21(5):1151-60.

SP-0576
The contribution of cancer stem cells to tumour radioresistance
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For a number of tumour types there is increasing acceptance that cancer stem cells play an important role in tumour initiation and recurrence after treatment. In line with this model, increasing evidence indicates that cancer stem cells exhibit resistance to conventional cytotoxic agents. In the case of glioblastoma, an incurable primary brain tumour associated with dismal prognosis and devastating effects on quality of life, a series of influential publications have demonstrated that the radiation resistance of glioblastoma stem-like cells (GSC) is associated with constitutive upregulation of the DNA damage response (DDR).
In this presentation I will outline the evidence supporting this model, and present new data that elucidates the relative contributions of DNA repair and cell cycle checkpoints to this phenotype. Subsequently I will investigate the effects of inhibiting various components of the DDR, alone and in combination, and discuss the potential clinical application of a number of promising new small molecule inhibitors.

SP-0577
Novel insights in radioresistance of head and neck cancer
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Recent technological advances in DNA sequencing with greater speed and resolution at lower costs has provided new insights in cancer genetics. The next-generation sequencing (NGS) technology is tremendously facilitating the in-depth genome-wide search for genetic alterations which might significantly contribute to aggressive and/or treatment-resistant phenotypes of cancers, thereby establishing the basis for improvement of cancer treatment. We hypothesized that NGS should also be useful for dissecting the molecular mechanisms of radioresistance in squamous cell carcinoma of the head and neck (HNSCC).
We therefore applied the technology of targeted NGS to clinical samples from two multicenter studies of definitive and adjuvant cisplatin-based chemoradiation of locally advanced HNSCC. We evaluated whether by molecular profiling using targeted NGS it is possible to prospectively discriminate between patients who clearly benefit from chemoradiation and those with poor locoregional control and reduced overall survival after such treatment. Our studies could confirm previous reports of poor efficacy of radiotherapy in HNSCC tumors harboring *TP53* mutations. For the first time, we identified additional mutations in other genes as predictive biomarkers of outcome after chemoradiation.
The talk will summarize the results of NGS studies in HNSCC and other carcinoma models, thereby focusing on studies in which molecular mechanisms involved in radio-/chemoresistance have been addressed. It will present unpublished results from functional studies in preclinical models in which we are evaluating the mode of interaction of distinct genetic variants with radio-/chemoresistance. Concepts of how to integrate the results from NGS into novel personalized treatment strategies for HNSCC will be discussed.

Symposium with Proffered Papers: Towards Personalised Radiation Oncology (PRO)

SP-0578
New technologies for genomic tumour profiling
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Massive parallel sequencing technologies (also: next generation sequencing) have revolutionized our understanding of the genomic and transcriptional makeup of malignomas. Aided by equally impressive developments in sequencing- and chip-based epigenetic tumor profiling and developments in mass spectrometry which allow for a comprehensive proteomic and metabolomic profiling we are now able to draw fairly comprehensive multi –omics landscapes of individual tumors both from tissue but increasingly also from blood or circulating tumor cells. However, many issues remain still challenging when it comes to a translation of these findings into a potential clinical outreach. This includes matters of tumor heterogeneity specifically with respect to tumor evolution in the metastatic setting as well as under therapeutic pressure. Other widely unresolved issues include the usefulness of identified drivers as novel targets for therapy or as predictive biomarkers and strategies to implement broad high throughput genomic testing into individualized patient care. Specifically the latter issue will decide which of these multi-omics technologies will take the step from tools merely for biological research profiling to advanced and modern routine clinical care.

SP-0579
Gene expression profiles in tumours for PRO
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Gene expression profiles hold great promises for PRO (Personalized Radiation Oncology), yet very few - if any - are implemented in routine clinical practice and used as predictive biomarkers for treatment decisions in radiation oncology.