and, induced mitotic catastrophe in the most sensitive cell lines U87MGLuc and E2. These events were apoptosis-independent. Combination with IR increased GSC cell death in the two GSC models tested to date. Accumulation of cells in mitosis following ME-344 treatment was recapitulated in orthotopic GBM xenografts *in vivo*, although few mitotic catastrophe events were observed 24 h after treatment. ME-344 demonstrated therapeutic efficacy as a single agent in U87MGLuc2 orthotopic xenografts by extending mouse survival compared to vehicle (p=0.043). CONCLUSION: Two agents that induce mitosis through different mechanisms have promising single agent activity against all GBM cell lines tested *in vitro* and *in vivo*. Further preclinical evaluation in combination with IR and/or temozolomide is underway. Results indicate that this therapeutic strategy for GBM has clinical potential.

OS1.5 HARNESSING SOLUBLE LRIG1 FOR PAN-RTK TARGETING IN GLIOBLASTOMA

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INTRODUCTION: The role of receptor tyrosine kinases (RTKs) in glioblastoma is widely acknowledged. However, therapies based on RTK targeting have been continuously unsuccessful in GBM patients, highlighting the complexity of RTK signaling and biology. LRIG1 (Leucine-rich Repeats and ImmunoGlobulin domains protein 1) was identified as an endogenous inhibitor of epidermal growth factor receptor (EGFR) and other RTKs, and was confirmed as a tumor suppressor in various cancer types. We previously identified the soluble form of LRIG1 as a potent inhibitor of GBM growth *in vivo*, irrespective of EGFR status. Here, we aim to shed light on the molecular mechanisms underlying its anti-cancer activity. MATERIAL AND METHODS: We used GBM cells overexpressing EGFRvIII, with or without soluble LRIG1 overexpression. In parallel, we generated a recombinant human soluble LRIG1 protein (rh-sLRIG1) by expressing LRIG1 ectodomain in insect cells via baculovirus infection and subsequent His-tag purification. rh-sLRIG1 was applied in the medium of classical GBM cell lines and patient-derived GBM stem-like cells. Applying a variety of cell-based assays, cell proliferation, migration, cell morphology, as well as protein expression and protein-protein interactions were investigated. RESULTS: We confirmed that sLRIG1 efficiently reduced proliferation and invasion capacities of GBM cells, and modulated cytoskeleton proteins and cell shape. Inhibition of cell proliferation by sLRIG1 was independent of EGFR expression levels in GBM cells and interestingly, rh-sLRIG1 treatment was associated with downregulation of AXL, which constitutes a newly-identified regulatory function of LRIG1. We are currently addressing the impact of the LRIG1-AXL signaling axis on GBM invasion and resistance to EGFR inhibition. CONCLUSION: We identified AXL as a novel LRIG1 target and provide evidence for the potential therapeutic application of recombinant sLRIG1 in the inhibition of growth factor signaling in GBM.

OS1.6 CHARACTERIZING THE OVER-EXPRESSION OF YKI/YAP/TAZ TRANSCRIPTION FACTORS IN GLIOMAGENESIS AND RESULTS OF A PHASE 0 CLINICAL TRIAL FOR A PROPOSED NOVEL TREATMENT OF GLIOBLASTOMAS

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BACKGROUND: Glioblastomas (GBMs) harbor frequent genetic lesions that include amplification, mutation, and/or over expression of receptor tyrosine kinases (RTKs). Using a novel kinome wide RNAi screen we identified the Hippo kinase pathway and it downstream targets, Yki-YAP/TAZ transcription factors, as tumor enhancers in gliomagenesis. YAP/TAZ promote the initiation and progression of other tumor types and several published studies show that pharmacologic inhibition of YAP and TAZ with the drug verteporfin (VP) blocks tumor cell growth. Thus, we hypothesize that, because of RTK mutations, YAP/TAZ become overexpressed and activated to constitutively drive a TEAD-dependent gene expression program that provokes an uncontrolled expansion of RTK-PI3K mutant neural stem/progenitor cells to create malignant glial tumors. MATERIAL AND METHODS: We tested VP in vitro on genotyped neurosphere cultures which were assessed for self-renewal, proliferation, and survival using neurosphere formation and WST-1 assays. To confirm that VP inhibits expression of YAP/TAZ-TEAD transcriptional targets, we performed experiments and harvested RNA for RNAseq, qPCR, and completed western blots and ChIP analysis. In-vivo experiments were carried out in murine xenografts bearing YAP/TAZ-expressing GBM that were used to make organotypic slice cultures which were treated with VP and assayed for tumor growth and cell survival. A Phase 0 clinical trial was designed to determine VP bioavailability. Because VP has virtually the same excitation and emission spectra as protoporphyrin IX, we administered VP to patients prior to surgery and used fluorescence-assisted microscopy to determine if VP is visible in tumors. On encountering tumor intraoperatively, the operative microscopy system was used to illuminate the tumor bed with blue light (400–410 nm), and photographs were taken through the microscope using a camera adapted for imaging in the red (620–700 nm) emissions spectrum. Resected tumor tissue remaining after satisfying clinical goals was sent for ex vivo research analysis. RESULTS: Our data reveal that YAP and TAZ become overexpressed in tumor cells with RTK mutations, and that YAP/TAZ drive brain tumor cell growth and progression by up-regulation of novel RTK genes including EGFR. VP treatment knocks down target gene transcription, protein levels, leads to cell death and halts tumor progression. VP extraction from tumor tissue and fluoroscopic examination show successful drug uptake from all patients in a Phase 0 clinical trial. CONCLUSION: We believe that as a consequence of RTK mutations, YAP/TAZ becomes over-expressed in gliomas and constitutively drive a TEAD-dependent gene expression program that provokes an uncontrolled expansion of RTK -PI3K mutant neural stem/progenitor cells to create malignant glial tumors that can be treated with VP which shows bioavailability in glioblastomas.

OS1.7 GENOMIC ATTRIBUTES OF TUMOR EVOLUTION AND TREATMENT RESPONSE IN DIFFUSE GLIOMA

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BACKGROUND: Though the genomic landscape of primary gliomas has been well characterized by The Cancer Genome Atlas, the genetic determinants of malignant transformation and response to therapy remains poorly understood. MATERIAL AND METHODS: Prospective clinical sequencing was performed on 1,004 gliomas from 923 patients. This dataset includes primary and recurrent tumors and contains detailed clinical annotation, including review of the patients' imaging. RESULTS: We investigated the germline and somatic attributes of IDH1/2-wildtype and IDH1/2-mutant tumors at the time of diagnosis and recurrence. 13% of patients harbored either a pathogenic or likely pathogenic germline mutation, whereof 29% arose in genes mediating DNA repair. In astrocytomas, agnostic of IDH status, cell cycle alterations were depleted in low-grade tumors. Moreover, mutations in effectors of the cell cycle were associated with the development of enhancing disease in IDH-mutant astrocytomas but not oligodendrogliomas. IDH-mutant astrocytomas with a cell-cycle alteration have a significantly shorter progression-free survival from recurrence compared to tumors without a cell cycle alteration (median 2. 5 vs. 35. 3 months, HR 3. 25, log-rank p-value 0. 00061). Based on our data, hypermutation appears to occur exclusively in the context of pre-existing cell cycle alterations in astrocytic tumors, regardless of IDH status. We next correlated molecular findings with clinical behavior and treatment response and defined subsets of gliomas that are uniquely susceptible to targeted treatment and have a differential prognosis. CONCLUSION: Cell-cycle alterations are lineage-specific alterations associated with aggressive disease in glioma. Targeted genomic sequencing can identify subsets of tumors with a greater sensitivity to treatment and a better prognosis.

OS2 NON-SURGICAL TREATMENT

OS2.1 OBJECTIVE RESPONSES TO CHEMOTHERAPY IN RECURRENT GLIOMA DO NOT PREDICT BETTER SURVIVAL: A PROSPECTIVE ANALYSIS FROM THE GERMAN GLIOMA NETWORK

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BACKGROUND: Outside of clinical trials, the occurrence of objective responses (OR) to chemotherapy in patients with recurrent gliomas is poorly characterized. Further, the predictive value of OR for progression-free survival (PFS) and overall survival (OS) in glioma patients is unclear. MATERIAL AND METHODS: We screened the German Glioma Network Database for patients who had received any chemotherapy for recurrent glioma from 2004–2008. Patients with a prior gross total resection of the recurrent tumor, patients receiving additional radiotherapy for the recurrent