cleavage levels in normoxia and hypoxia, suggesting that this therapy would be as effective in treatment of tumors with potentially resistant hypoxic necrotic cores. The effect of sunitinib on EPN cellular proliferation was tracked visually using Incucyte cell imaging technology, demonstrating consistent dose-dependent inhibition of proliferation. Sunitinib achieved more acute upregulation of apoptosis than axitinib, an EPN-selective RTKI currently being studied in preclinical models. A prior phase II trial of sunitinib in pediatric EPN and high-grade glioma showed that treatment was well tolerated but with no clinical benefit as a monotherapy. However, given encouraging clinical results of combining sunitinib with radiation, our ongoing preclinical studies of sunitinib in EPN are being conducted in the context of radiation which is standard treatment for EPN. Sunitinib presents a promising treatment to an intractable pediatric brain tumor that exhibits high rates of relapse and morbidity in affected individuals.

EPEN-13. CLINICALLY RELEVANT MOLECULAR HALLMARKS OF PFA EPENDYMOMAS DISPLAY INTRATUMORAL HETEROGENEITY AND CORRELATE WITH TUMOR MORPHOLOGY

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PFA ependymomas are aggressive posterior fossa tumors that mainly effect children and have a poor prognosis despite intensive therapy. Histopathology reveals glial neoplasms that usually show perivascular pseudorosettes throughout the tumor. Tumor cell density may vary within a tumor and sometimes shows well demarcated nodules of extremely densely packed tumor cells within surrounding loose glial tissue harboring diffusely distributed tumor cells. To determine potential molecular differences in such areas and to understand the clinical meaning, we analysed 70 clinically well-annotated PFA samples and 9 corresponding relapse samples. Areas of low and high cell density were digitally identified with a cut-off of 8,500 cells/mm². Global DNA methylation and copy-number profiling was performed in 52/79 cases for the entire tumor area of the sample and in 15/79 cases for the cell-dense and less cell-dense regions, separately. Fluorescence-in-situ-hybridization was performed for 20 cases, and scRNA-Seq data were analysed for 12 cases. The proportion of cell-dense areas proved to be highly variable on a continuum ranging from 0 % to 100 % of the tumor area. It was significantly higher in relapses in comparison to the respective primary tumors (p=0.036). Also, cell-dense areas displayed a significantly higher proportion of proliferating tumor cells (p<0.01). Global DNA methylation was similar, but not identical in different tumor areas. In 6/15 cases, the PFA subtype changed as determined by the current version of the brain tumor classfier (v12, www.molecularneuropathology.org). Chromosomal changes at 1q and 6q were only detectable in cell-dense areas in 5/12 and in 3/12 cases, respectively. Finally, scRNA-Seq data confirmed a widespread heterogeneity regarding 1q and 6q changes in PFA ependymoma cells. These data suggest that PFA ependymoma habor a previously unrecognized heterogeneity that has to be accounted for when selecting material for the analysis of clinically relevant DNA methylation profiles or copy number changes.

EPEN-14. A PHASE 1, SAFETY AND DOSE ESCALATION STUDY OF BXQ-350 IN PATIENTS WITH ADVANCED SOLID MALIGNANCIES DEMONSTRATES THAT BXQ-350 IS WELL TOLERATED AND SHOWS SIGNS OF POTENTIAL CLINICAL ACTIVITY IN EPENDYMOMA PATIENTS

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The significance of a dysregulated sphingolipid metabolism in cancer, including brain tumors, has been demonstrated and several enzymes involved in sphingolipid metabolism are being investigated as novel therapeutic targets for adult and pediatric brain cancers. Saposin C (Sphingolipid Activator PrO[S]etIN) is a human protein encoded by the Psap gene and is an allosteric activator of several enzymes involved in sphingolipid/ceramide metabolism. BXQ-350 is a nanovesicle of Saposin C that has broad anticancer activity, selectively inducing apoptosis of cancer cells by lowering Sphingosine-1-Phosphate and increasing ceramides concentrations and inducing an anti-tumoral immune response. BXQ-350 was investigated in a Phase 1 dose-escalation safety study in cancer patients with advanced solid malignancies including brain tumors (NCT02859857). The primary objective of this single agent study was to describe the safety profile and to determine the maximum tolerated dose, or the biological effective dose, of BXQ-350 administered intravenously at escalating doses from 0.7 mg/kg up to 2.4 mg/kg. Multiple secondary parameters were included to characterize BXQ-350's pharmacokinetic parameters, efficacy profile and potential biomarkers. This trial was performed at four US sites. Results indicate that BXQ-350 was safe and well-tolerated as no DLT was observed and an MTD was not reached. RANO or RECIST 1.1 criteria were used to evaluate tumor response. Analysis of plasma samples suggests that BXQ-350 modulates sphingolipid metabolism and impacts the immune system positively. Furthermore, potential signs of single agent activity were observed across tumor types, including in two ependymomas for which results will be presented.

EPEN-15. RADIOTHERAPY WITH HELIUM IONS HAS THE POTENTIAL TO IMPROVE BOTH ENDOCRINE AND NEUROCOGNITIVE OUTCOME IN PEDIATRIC PATIENTS WITH EPENDYMOMA

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BACKGROUND: Ependymoma are the third most frequent pediatric brain tumors. To prevent local recurrence, the resection site should be irradiated. Especially the treatment of pediatric patients requires precise dose application and optimal protection of organs at risk. Compared to photon radiation treatment, proton therapy often achieves better results regarding target coverage and organ-sparing. Due to their physical properties, helium ions can further reduce side effects, providing better protection of healthy tissue despite similar target coverage. PATIENTS AND METHODS: In our in-silico study, 15 pediatric patients (median age six years) with ependymoma located in the posterior cranial fossa were considered. All patients underwent adjuvant radiotherapeutic treatment with active scanned protons at Heidelberg Ion-Beam Therapy Center (HIT). Both helium ion and highly conformal IMRT plans were calculated to evaluate the potential dosimetric (and clinical) benefit of ion beam therapy compared to the current state of the art photon-based treatments. RESULTS: Target coverage was comparable in all three modalities (He, H^+, Ph): homogeneity indices (HI) and inhomogeneity coefficients (IC) of HI_{He}=5.8±3.8, HI_{H^+}=7.5±4.0, HI_{Ph}=6.4±4.3, IC_{He}=0.2±0.1, IC_{H+}=0.2±0.1, IC_{Ph}=0.2±0.1. As expected, the integral dose absorbed by the healthy brain tissue could be reduced significantly using helium ions versus IMRT (-45.3%±15.1%). Based on our preliminary results, even compared to active scanned protons – currently the most precise radiation technique worldwide – the relative dose reduction for critical neuronal structures using helium ions on average amounts to -27.2%±14.4%. CONCLUSION: Previous studies could clearly demonstrate that the dosimetric advantage of protons translates into a measurable clinical benefit for pediatric patients with brain tumors. Given the dose response relationship of critical organs at risk, the results of our in-silico study provide a strong rationale that the use of helium ions has the potential to even further reduce the risk for treatment related sequelae.

EPEN-16. EPITHELIAL PROGENITOR CELL ABUNDANCE AND COPY NUMBER VARIANT GAINS AND LOSSES IMPACT THE BIOLOGY OF RECURRENT EPENDYMOMA

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Ependymoma (EPN) is a common pediatric brain tumor that is fatal in approximately 50% of cases. Posterior fossa A (PFA) EPN has the highest rate of recurrence and the worst prognosis of all EPN subtypes. At relapse, it is typically incurable even with re-resection and re-irradiation. The biology of recurrent ependymoma remains largely unknown, which hinders clinical advances. In this study, we use paired samples of primary and recurrent disease from the same patient to investigate the drivers of recurrence. DNA methylation studies reveal frequent copy number variants at recurrence that were not present at primary presentation. We report a frequent gain of chromosome 1q and loss of 6p at recurrence, which has not been previously reported and may be a driver of recurrent disease. We have previously shown that PFA EPN is comprised of 4 main neoplastic cell populations, two well-differentiated populations termed ciliated and transportive ependymal cells, a mesenchymal cell population, and an undifferentiated population. Using spatial transcriptomics (Visium) integrated with single-nuclei RNA-seq (Chromium), we discovered that a highly proliferative EPN progenitor population of epithelial lineage is significantly upregulated at recurrence which we hypothesize drives refractory disease. Accordingly, we found higher expression of EPN progenitor gene signatures in bulk RNA transcriptomes of primary tumors that later recurred compared to tumors that never recurred. Together, these findings highlight the biologic differences between primary and recurrent disease and add to our understanding of treatment resistance in childhood ependymoma.