targeting the senescent part of PA. IC_{50}s of the clinically available drug navitoclax were >20-fold below achievable plasma concentration indicating translatability. Genes from the gene set HALLMARK_XENOBIOTICS_METABOLISM could represent a predictive biomarker.

LGG-20. DEFINING SUBGROUPS IN LOW GRADE GLIOMAS BY THEIR IMMUNE AND STROMAL MICROENVIRONMENT

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Immunologic treatment options are still uncommon in low grade gliomas, although such therapies might be beneficial for inoperable and aggressive cases. Knowledge on immune and stromal cells in low grade gliomas, which is a mandatory prerequisite for such approaches, is still scarce. We therefore gathered published gene-expression data from 400 low grade gliomas as well as 302 high grade gliomas in order to quantify 10 microenvironment cell populations. First, we investigated general differences in the microenvironment of low- and high-grade gliomas. Lower-grade and high-grade tumors cluster together, respectively, and show a general similarity within and distinct differences between these groups, the main difference being a higher infiltration of fibroblasts and T-cells in high-grade gliomas. Among the analysed entities, gangliogliomas and pleomorphic xanthoastrocytomas presented the highest overall immune cell infiltration. Further analyses of the low-grade gliomas presented three distinct microenvironmental signatures of immune cell infiltration, which can be divided into T-cell/dendritic/natural killer cell-, neutrophilic/B lineage/natural killer cell-, and monocytic/vascular/stromal-dominated immune clusters. These clusters correlated with tumor location, age, and histological diagnosis, but not with sex or progression-free survival. Our work shows that low- and high-grade gliomas can be characterized and differentiated by their immune cell infiltration. Low grade gliomas cluster into three distinct immunologic tumor microenvironments, which may be of further interest for upcoming immunotherapeutic research.

LGG-21. DURABILITY OF RESPONSE TO TARGETED THERAPIES IN PEDIATRIC LOW-GRADE GLIOMAS: A MULTI-INSTITUTION RETROSPECTIVE REVIEW

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BACKGROUND: The discovery of the driving oncogenic alterations in pediatric low-grade gliomas (pLGGs) has shifted our focus towards management with targeted therapies, especially in relapsing or progressive disease. Limited data is available on the durability of response to targeted therapy in pLGGs once the therapy has ceased. METHODS: Multi-institutional retrospective chart review of patients with pLGGs younger than 25 years, between 2010-2021, was undertaken to evaluate the durability of response to targeted therapy and determine risk factors associated with disease progression after cessation of therapy. RESULTS: Current analysis included 18 patients from two centers. Seven (39%) had neurofibromatosis type-1 (NF-1). DIAGNOSES INCLUDED: optic pathway glioma (OPG) (6/18, 33%), pilocytic astrocytoma (8/18, 44%), diffuse fibrillary astrocytoma (1/18), ganglioglioma (1/18), glioneural neoplasm (2/18). Sixteen patients received at least one prior line of chemotherapy (range 1-5). Targeted agents included trametinib (50%), selumetinib (5%), binimetinib (22%), vemurafenib (11%) and everolimus (11%). Median time on therapy was 351 days (range 29-979 days). All, but one patient had residual intracranial findings at the end of therapy: eight patients (44%) had stable disease, while ten required additional therapy; 50% were NF-1 patients with OPG. Median time to progression was 203 days (range 29-615 days). Of those who did not require any additional therapies, 50% had suprasellar tumors. Genomic data was available for twelve patients; BRAF-KIAA1549 fusion was the most common genomic alteration. Others included mutations in KRAS, BRAF (V600E), PTPN11, SOX6-RAF1 fusion, NF-1, and a patient with FGFR1, KMT2C, and PTPN11 alterations. CONCLUSION: Preliminary analysis demonstrates that despite initial response, the majority of patients required additional line of therapy. Patients with NF-1 and OPGs tend to progress after discontinuing therapy, while suprasellar non-NF1 pLGGs tend to develop sustained response to targeted therapies. Additional multi-institutional analysis is underway and will be presented at the meeting.

LGG-22. SJ901: PHASE I/II EVALUATION OF SINGLE AGENT MIRDAMETINIB (PD-0325901), A BRAIN-PENETRANT MEK1/2 INHIBITOR, FOR THE TREATMENT OF CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH LOW-GRADE GLIOMA (LGG)

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BACKGROUND: MEK inhibitor trials in pediatric low-grade glioma (pLGG) have yielded promising results, but there remains room for improvement since objective responses are rarely complete and disease recurrence after completion of therapy is common. Mirdametinib (PD-0325901) is a highly selective MEK1/MEK2 inhibitor that, in preclinical studies, has been reported to have superior blood-brain-barrier penetration compared to other MEK inhibitors. As such, we recently launched the SJ901 clinical trial (NCT04923126) to determine the safety, recommended phase 2 dose, pharmacokinetics, and preliminary efficacy of mirdametinib in patients with pLGG when administered continuously. Here, we present preliminary phase 1 data. METHODS: SJ901 is a multi-arm phase I/II trial of mirdametinib in patients >2 and <25 years with LGG. Phase I requires participants to have no prior exposure to MEK inhibitors and recurrent/progressive disease with biopsy-proven evidence of MAPK pathway activation. Three escalating dose levels (2 mg/m2/dose BID, 2.5mg/m2/dose BID and 3mg/m2/dose BID) are planned using a rolling 6 design. RESULTS: Accrual began in June 2021. As of Jan 13, 2022, eleven patients enrolled: 5 on dose level 1 (DL1) and 6 on dose level 2 (DL2). Median age is 10 (3-21) years. Ten patients have somatic gene rearrangements (7 BRAF, 1 MYB, 1 RAF1, 1 FGFR1) and one has an NF1 germline mutation. Four have metastatic disease. No dose-limiting toxicities occurred for DL1 (whereas data are pending for DL2) and only grade 1/2 treatment-related adverse events have been observed. No MEK-related retinopathy or cardiopathy has been observed. Four of the six patients with at least one follow-up disease evaluation have a minor response (>25%-<50% decrease). Median time on therapy is 6.6 (2.2-7) months. No disease progressions have occurred. **CONCLUSION:** Thus far, mirdametinib is well-tolerated and clinically promising when dosed continuously in patients with recurrent/progressive pLGG. More information will be forthcoming.

LGG-23. CARDIAC FUNCTION IN CHILDREN AND YOUNG ADULTS TREATED WITH MEK INHIBITORS: A SINGLE INSTITUTION RETROSPECIVE COHORT STUDY

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INTRODUCTION: MEK inhibitors (MEKi) have shown efficacy in pediatric low-grade glioma, among other tumors, but have been associated with acute cardiac dysfunction in adults. Cardiac consequences in children are unknown. MATERIAL AND METHODS: We performed a single center retrospective cohort study evaluating cardiac function by echocardiography (echo) in children and young adults <21 years old receiving MEKi