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

at Children's Hospital Los Angeles between October 2013 and May 2018. Blinded assessment of left ventricular function by fractional shortening (FS) and ejection fraction (EF) was performed on all available echocardiograms obtained before, during, and following therapy, as well as after re-initiation of therapy. RESULTS: Twenty-six patients underwent MEKi therapy with echo follow-up during the study period. Twenty-four of these had complete echo data. Median follow-up was 12 months. Borderline EF (EF 53-57.9%) occurred in 12 (50%) patients; and 3 (12.5%) progressed to abnormal EF (EF <53%). Cardiac dysfunction, when it occurred, was mild (lowest documented EF was 45%, and lowest FS was 24.4%). EF abnormalities typically fluctuated during therapy, resolved off therapy, and recurred with MEKi re-initiation. No clinical or demographic differences were detected between those who maintained normal cardiac function and those who developed borderline or overt cardiac dysfunction. Symptomatic heart failure did not occur. CONCLUSION: In this cohort of children and young adults, MEKi use was associated with a relatively high incidence of borderline decrease in left ventricular function, often of uncertain clinical significance. There was no evidence of permanent cardiac dysfunction. Further evaluation in larger prospective trials is needed.

LGG-24. NEUROCOGNITIVE IMPAIRMENT AND FUNCTIONAL INDEPENDENCE IN ADULT SURVIVORS OF CHILDHOOD GLIOMA: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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PURPOSE: Survivors of pediatric glioma are at risk of developing physical and neurocognitive sequelae secondary to their tumor and its treatment. The contribution of these conditions to attainment of functional independence has not previously been examined. METHODS: 1,284 adult survivors of pediatric glioma (48% male, median [range] 30 [18-51] years at assessment, 22 [15-34] years since diagnosis) completed the CCSS Neurocognitive Questionnaire with impairment defined as scores > 90th %ile of sibling norms. Treatment exposures were categorized as surgery only, chemotherapy (± surgery), or cranial radiation (± chemotherapy/surgery). Self-reported chronic health conditions (CHCs) were graded by organ system using NCI's CTCAE v4.3. Latent class analysis utilized six factors (employment, marital status, independent living, driver's license, assistance with routine needs, assistance with personal care needs) to identify classes of functional independence. Multivariable modified Poisson regression evaluated relative risk (RR) of neurocognitive impairment between the classes, adjusting for sex, race, age at assessment, and age at diagnosis. Path analysis explored the impact of treatment exposures on functional independence, mediated by Grade 2-4 CHCs and neurocognitive impairment. RESULTS: Three latent classes of functional independence were identified: independent (58%), moderately independent (20%), and non-independent (22%). Compared to the independent class, non-independent survivors were at elevated risk for impaired task efficiency (RR=3.86, 95% CI, 2.97-5.01), memory (RR=2.39, 95% CI, 1.91-2.98), organization (RR=2.04, 95% CI, 1.64-2.54), and emotional regulation (RR=1.67, 95% CI, 1.30-2.15). Path analysis revealed significant direct paths from cranial radiation (β=0.14), impaired task efficiency (β=0.42), and sensorimotor (β=0.22) and endocrine conditions (β=0.24) to non-independence. Cranial radiation also was indirectly associated with non-independence through impaired task efficiency (β=0.06), and sensorimotor (β=0.06) and endocrine conditions (β=0.10). CONCLUSIONS: Neurocognitive impairment and chronic health conditions partially mediate the association between treatment exposures and attainment of independence in adulthood, identifying potential intervention targets to promote independence in long-term survivors.

LGG-25. THE FIRST-IN-CLASS ERK INHIBITOR ULIXERTINIB (BVD-523) SHOWS ACTIVITY IN MAPK-DRIVEN PEDIATRIC LOW-GRADE GLIOMA MODELS AS SINGLE AGENT AND IN COMBINATION WITH MEK INHIBITORS OR SENOLYTICS

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Ulixertinib (BVD-523) is a catalytic ERK1/2 inhibitor that showed promising responses in adult patients with mitogen-activated protein kinase (MAPK)-driven solid tumors. Pediatric low-grade gliomas (pLGG) are the most common pediatric brain tumors, with the most frequent driving alterations in the MAPK pathway. The anti-tumor activity of ulixertinib in pLGG and its potential synergism in combination with MEK inhibitors, senolytics, and chemotherapy were investigated in vitro using metabolic activity, MAPK reporter assay and high-content microscopy in pLGG-derived cell lines (DKFZ-BT66 - KIAA:BRAF fusion; BT40 - BRAF V600E mutation and CDKN2A/B deletion). The most clinically relevant combinations were further validated in vivo: 1) in zebrafish embryo models (BT40 and DKFZ-BT66 yolk sac injection) and 2) in NSG mice (BT40 orthotopic PDX) including in vivo pharmacokinetic and -dynamic analyses. Ulixertinib inhibited MAPK pathway activity in all models and reduced cell viability in the BRAF V600E mutated cell line at concentrations in the nanomolar range. In vivo pharmacokinetic and -dynamic analyses showed penetrance of the drug into mouse brain tissue and on-target activity, with concentrations above the in vitro IC50 and reduction of MAPK activity. Ulixertinib treatment slowed tumor growth and significantly increased survival in NSG mice with BT40 xenografts. Ulixertinib showed indications for anti-proliferative synergy in vitro in combination with MEK inhibitors (trametinib, binimetinib) or BH3 mimetics (navitoclax, A-1331852). Combinations with chemotherapy (carboplatin, vinblastine) were at most additive. Indications for synergy with binimetinib and navitoclax were confirmed in the zebrafish embryo models. In the NSG mouse model, the combination of ulixertinib with senolytics induced effects on tumor growth and survival comparable to ulixertinib monotherapy. Ulixertinib shows promising potential as a clinically relevant therapeutic option for the treatment of pLGG to be further investigated in upcoming clinical trials. Potential synergism with MEK inhibitors and BH3 mimetics was noted and warrants further investigation.

LGG-26. PREDICTING MAPK INHIBITOR SENSITIVITY IN PEDIATRIC LOW-GRADE GLIOMAS WITH NOVEL GENE EXPRESSION-DERIVED SIGNATURES

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