

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 ( $\pm$  surgery), or cranial radiation ( $\pm$  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: (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 ( $\beta$ =0.14), impaired task efficiency ( $\beta$ =0.42), and sensorimotor ( $\beta$ =0.22) and endocrine conditions ( $\beta$ =0.24) to non-independence. Cranial radiation also was indirectly associated with non-independence through impaired task efficiency ( $\beta$ =0.06), and sensorimotor ( $\beta$ =0.06) and endocrine conditions ( $\beta$ =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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