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HGG-42. COMBINED PRECLINICAL AND CLINICAL INVESTIGATION OF WHICH PEDIATRIC HIGH-GRADE GLIOMA SUBTYPES BENEFIT FROM CCNU/TEMOZOLOMIDE
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BACKGROUND: The only chemotherapy regimen that has shown a clear survival benefit in pediatric high-grade glioma (pHGG) is combining temozolomide (TMZ) and lomustine (CCNU) with RT per COG ACNS0423. However, which pHGG subgroups benefit from this treatment is unknown. METHODS: Through the Children’s Brain Tumor Network (CBTN) database, we found 20 pHGG patients treated with RT-TMZ-CCNU, along with 95 control patients who received other treatment. We compared overall (OS) and event-free survival (EFS) using the Log-rank test for the respective pHGG subtype. We used a patient-derived xenograft (PDX) model, representing newly diagnosed hemispheric pHGG (diffuse hemispheric glioma, G34R-mutant (DHG), to test the effects of combining TMZ-CCNU. RESULTS: From our clinical (CBTN) data, we found that median OS for the RT-TMZ-CCNU group was significantly greater compared to the control cohort (990 days (d) vs. 427d, p=0.011), as was EFS (510 vs. 215d, p=0.0041). For patients with hemispheric tumors, median OS and EFS were significantly increased for the RT-TMZ-CCNU group (n=8) vs. controls (n=47) (OS 5,274 vs. 496d, p=0.018; EFS 903 vs. 271d, p=0.018). For patients with midline pHGG, median OS and EFS were not significantly different between the RT-TMZ-CCNU group (n=11) and controls (n=43). In our PDX model, we found that TMZ-CCNU led to long-term survival compared to vehicle control and single-agent treatment (p=0.001).

DISCUSSION: Patients with hemispheric pHGG had a significant survival benefit from RT-TMZ-CCNU treatment, while those with midline pHGG did not. Hemispheric pHGG, which are enriched for H3G34 and IDH mutations, may be more likely to respond to RT-TMZ-CCNU. These findings are supported by preclinical data showing that mice with DHG, G34R-mutant were cured after TMZ-CCNU treatment. Given our results and those from ACNS0423, RT-TMZ-CCNU should be strongly considered for treatment of patients with hemispheric pHGG and as a backbone for future clinical trials in this population.