About half of all pediatric high-grade gliomas (HGG) harbor mutations in histone 3 or IDH genes. The remaining HGG are currently broadly classified as H3-/IDH-wild-type. Since the introduction of a uniform approach to DNA methylation-based classification of CNS tumors in 2018, DNA methylation data from over 45,000 CNS tumor samples have been generated. From this large cohort, a number of smaller yet distinct subgroups start to emerge within H3-/IDH-wild-type HGG. Three such subgroups are enriched for EGFR amplifications and H3K27M mutations and defined as pedGBM_MYCN, pedGBM_RTK1 and pedGBM_RTK2. Since a significant subset of samples in each subgroup is lacking characteristic alterations, we further investigated the molecular and transcriptional composition of H3-/ IDH-wild-type HGG. We evaluated DNA methylation and copy-number profiles in >1000 tumors classified as H3-/IDH-wild-type HGG. Tumors classified pedGBM_MYCN showed a focal MYCN amplification in 25%, with a similar fraction showing amplification of EGRF (8% of samples harbored both alterations, compared to 4% and 4% in pedGBM_RTK1 and pedGBM_RTK2, respectively). Deletions of CDKN2A/B, however, were more prevalent in the pedGBM_RTK2 subgroup (>50% compared to 27% in pedGBM_RTK1 and <10% in the pedGBM_MYCN group). We defined a pedGBM_MYCN transcriptional signature, which will be helpful in identifying subgroup-defining mechanisms and fortracing. Initial results suggest an involvement of the sonic hedgehog pathway and genes controlling stem-cell pluripotency. Patient-derived xenograft models and murine neural stem cells are now being used for functional characterization and pre-clinical testing of potential drug targets in these molecularly defined subgroups.

BACKGROUND: Pediatric treatment-induced high-grade glioma (TIHGG) is among the most severe late effects observed in childhood cancer survivors and is uniformly fatal. We previously showed that TIHGG are divergent from de novo pediatric high-grade glioma (pHGG) and cluster into two gene expression subgroups, one stemlike and the other inflammatory.
morphic xanthoastrocytoma were high, but the Ki-67 labeling index was 1%. In the ganglioglioma, the T/N ratio of FLT was high, but the T/N ratio of MET was low. CONCLUSION: Specialized multiple PET accumulation patterns for tumors are useful for discriminating each tumor.

**IMG-03. RESPONSE ASSESSMENT IN PEDIATRIC LOW-GRADE GLIOMA (pLGG): RECOMMENDATIONS FROM THE RESPONSE ASSESSMENT IN PEDIATRIC NEURO-ONCOLOGY (RAPNO) WORKING GROUP**

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**INTRODUCTION:** Pediatric low-grade gliomas (pLGG) show clinical and biological features that are distinct from their adult counterparts. Consequently, additional considerations are needed for response assessment in children compared to the established adult Response Assessment in Neuro-Oncology (RANO) criteria. Standardized response criteria in pediatric clinical trials are lacking, complicated by the diversity of treatment regimens across studies. We therefore established an international committee of the Radiologic Assessment in Pediatric Neuro-Oncology (RAPNO) working group to develop consensus recommendations for response assessment in pLGG. METHODOLOGY: The committee consisted of 25 international experts working in the areas of Pediatric Neuro-Oncology, Neuroimaging, and Neurosurgery. The committee first developed a set of agreed upon topics they deemed necessary to understand the controversies of imaging utilization and assessment in pLGG. These topics were divided up among the committee members who presented all available literature to the entire RAPNO committee via teleconference. Once presented, the group discussed these data and developed consensus statements and recommendations based on available literature, committee expertise and clinical experience. Each topic was discussed until a consensus was reached. RESULTS: Consensus recommendations and response definitions have been established in an international and interdisciplinary consensus paper to standardize the evaluation of response to treatment in pediatric low-grade gliomas. INTRODUCTION: Response criteria for pediatric high-grade gliomas (pHGG) have varied historically and across clinical trials, with adult HGG, pHGG response assessment has unique challenges. An international Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group was established to develop pHGG response assessment criteria. Previous pHGG response assessment criteria were developed with a lack of data from randomized controlled trials and in the absence of a standardized, universally accepted definition of response. This was achieved by identifying major challenges, reviewing existing literature, and finally developing recommendations through an iterative process. RESULTS: Categories for response assessment include complete response, partial response, minor response, stable disease, and progressive disease. Refractory disease is excluded. Criteria used to determine response assessment are quantitative assessment of measurable disease, qualitative assessment of diffusion imaging, presence or absence of new lesions, clinical status using performance score, and vascular endothelial growth factor inhibitor and/or corticosteroid use. Response is determined over 2-time points ≥ 8 weeks apart, and when progressive disease is unclear, guidance for repeat MRI imaging and/or utility of repeat biopsy is described. A number of recommendations are also given to standardize response assessment across clinical trials including MRI protocol sequence recommendations for brain and spine, definitions for measurable and non-measurable disease, and imaging time points with post-operative considerations. In addition, guidance is given for differentiating vasogenic edema versus tumor invasion in non-enhancing disease. CONCLUSION: Consensus recommendations and response definitions have been established and, similar to other RAPNO recommendations, prospective validation in clinical trials is warranted.

**IMG-05. INITIAL RADIOGRAPHIC ASSESSMENT OF DWI AND ADC VALUES IN CHILDREN AND YOUNG ADULTS TREATED WITH DAY101 (TAK-580) FOR RECURRENT LOW-GRADE GLIOMAS (LGG) HARBORING MAPK ALTERATIONS**

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**BACKGROUND:** Apparent diffusion coefficient (ADC) is a quantitative measure reflecting observed net movement of water calculated from a diffusion-weighted image (DWI), correlating with tumor cellularity. The higher cellularity of high-grade gliomas results in decreased ADC values, whereas the lower cellularity of low-grade gliomas (LGGs) gives higher ADC values. Here we examine changes in ADC values in patients with LGGs treated with the type 2 RAF inhibitor DAY101 (formerly TAK-580). METHODS: A retrospective clinical trial was conducted to evaluate the safety, tolerability, and efficacy of DAY101 in patients with recurrent LGGs harboring MAPK pathway alterations. Tumor MRIs for 9 patients enrolled on a phase 1 study of DAY101 in children and young adults with radiographically recurrent or progressive LGG harboring MAPK pathway alterations were obtained, de-identified and independently evaluated for ADC changes. Imaging endpoints included baseline, first follow-up, and best response. Data processing of ADC estimates was performed using pmdt molecular image software package. ADC changes were displayed as a histogram with mean values. Results were based upon a single read paradigm in 1MRIs. RESULTS: There was a shift to lower ADC values for the solid component of tumors, reflecting changes in cellularity and tissue organization, while necrosis correlated with a shift toward higher ADC values. DWI