TR-08. TARGETED COMBINATORIAL APPROACH FOR TREATMENT OF PEDIATRIC LOW GRADE GLIOMAS IN THE CONTEXT OF BRAF<sup>V600E</sup> AND KIAA1549:BRAF MUTATIONS

Aleksandra K. Olow1, Sabine Mueller1, Xiaodong Yang1, Rintaro Hashizume2, Justin Meyerowitz1, William Weiss1, Adam C. Resnick3, Angela J. Waanders3, Mitchell S. Berger1, Nalin Gupta1, C. David James2, and Daphne A. Haas-Kogan3;

1University of California, San Francisco, CA, USA; 2Northwestern University Feinberg School of Medicine, Chicago, IL, USA; 3The Children’s Hospital of Philadelphia, Philadelphia, PA, USA

Pediatric low-grade gliomas (PLGG) constitute the most common group of central nervous system tumors in children. Viewed as a chronic disease, ideal therapy for PLGG should carry limited side effects that can be best achieved through selective, personalized therapy. Despite the known heterogeneity of PLGGs and characterized driver mutations most children are still treated with standard chemotherapy protocols as first line therapy. Alteration of the BRAF/MEK/MAPK pathway is the hallmark of PLGG and mTOR activation has been documented in the majority of these tumors. This study investigates combinations of MEK1/2, BRAF<sup>V600E</sup> and mTOR inhibitors in PLGGs carrying specific genetic alterations of the MAPK pathway. We used human glioma cell lines containing BRAF<sup>V600E</sup> (AM38, DBTRG, BT40), or wild-type BRAF (SF188, SF9427, SF9402) and isogenic systems of KIAA1549:BRAF-expressing NIH3T3 cells and BRAF<sup>V600E</sup>-expressing murine brain tumors. Signaling inhibitors included everolimus (mTOR), PLX4720 (BRAF<sup>V600E</sup>), and AZD6244 (MEK1/2). Cell cycle distribution and apoptosis were assessed using flow cytometry; proliferation was determined using an ATP-based assay (CellTiter-Glo). In vivo activity of these inhibitors was assessed in the BT40 PLGG xenograft mouse model. In BRAF<sup>V600E</sup> tumors, the combination of MEK inhibitor with either mTOR or BRAF<sup>V600E</sup>-specific inhibitor is superior to monotherapy and to combination of BRAF and mTOR inhibitors in reducing cell viability reduction and arresting cell cycle progression. In BRAF<sup>WT</sup> pediatric gliomas, everolimus + AZD6244 is superior to either agent alone. KIAA1549:BRAF-expressing tumors display marked sensitivity to MEK1/2 inhibition alone. In vivo studies in the PLGG xenograft model BT40 showed the greatest survival advantage in mice treated with combination of AZD6244 + PLX4720 or AZD6244 + everolimus compared with respective monotherapies (p < 0.01).