MB-32. FEASIBILITY OF VORINOSTAT COMBINED WITH ISOTRETINOIN AND CHEMOTHERAPY FOR YOUNG CHILDREN WITH NEWLY DIAGNOSED EMBRYONAL BRAIN TUMORS: A PEDIATRIC BRAIN TUMOR CONSORTIUM STUDY
Sarah Leary1,4, Lindsay Kilburn2, J. Russell Geyer1,4, James M. Olson1,4, Tobey MacDonald8, David Ellison3, Mehmet Kocak3, Arzu Onar3, Ralph Ermoian6, Tina Young Poussaint7, James M. Boyett3, Larry Kun3, and Maryam Fouladi3; 1Seattle Children’s, Seattle, WA, USA; 2Children’s National Medical Center, Washington, DC, USA; 3St. Jude Children’s Research Hospital, Memphis, TN, USA; 4Fred Hutchinson Cancer Research Center, Seattle, WA, USA; 5Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA; 6University of Washington, Seattle, WA, USA; 7Dana Farber Cancer Institute, Boston, MA, USA; 8Children’s Healthcare of Atlanta, Atlanta, GA, USA

BACKGROUND: Pre-clinical evaluation of vorinostat and isotretinoin demonstrated cytotoxicity in medulloblastoma (MB) and synergistic activity when combined with cisplatin. This study sought to evaluate the feasibility of combining vorinostat and isotretinoin with cytotoxic chemotherapy in young children with newly diagnosed brain tumors. METHODS: Eligible patients were less than 4 years of age with newly diagnosed medulloblastoma (MB) or supratentorial primitive neuroectodermal tumor (CNS-PNET). Localized desmoplastic MB was excluded. Treatment consisted of 3 induction cycles given every 21 days with vorinostat and isotretinoin(days 1-4), cisplatin(day 4), vincristine(days 4, 11, 18), cyclophosphamide(days 5-6), and etoposide(days 4-6); 3 consolidation cycles with carboplatin and thiopeta(days 1-2) with stem cell rescue(day 4); and 12 cycles of monthly maintenance therapy with vorinostat and isotretinoin. Patients with M0 MB received focal radiation therapy following consolidation therapy; others received radiation at the discretion of the treating physician. Craniospinal radiation was not allowed on protocol. RESULTS: 31 patients received treatment on study; 19 (61.3%) were male; 7 (22.6%) had spinal cord or cerebrospinal fluid metastasis at diagnosis. Diagnosis was MB for 20, other CNS-PNET for 11. 24/31 patients completed 3 cycles of induction therapy within the pre-specified feasibility endpoint of 98 days. Eight experienced disease progression on therapy. Twelve completed therapy, five continue on therapy, five discontinued study treatment without progression, and one died of pulmonary toxicity following second cycle of consolidation. Two-year Progression Free Survival and Overall Survival for the entire cohort were 64.4% (SE ± 11.1%) and 75.6% (SE ± 10.0%), respectively; 68.2% (SE ± 12.8%) and 77.0% (SE ± 11.1%) for MB. Frozen tumor was collected from 30/31 tumors. CONCLUSION: It is feasible to administer vorinostat with isotretinoin and chemotherapy to young children with newly diagnosed MB or CNS-PNET. This multimodality therapy regimen resulted in encouraging progression-free survival without craniospinal radiation in a high-risk group of young children. Genomic studies are planned.