TITLE: First-in-children phase 1 trial of indoximod-based chemo-immunotherapy for patients with pediatric brain tumors: analysis of safety, tolerability, and 5-year outcome

BACKGROUND: Recurrent brain tumors are the leading cause of cancer death in children. We conducted a first-in-children, two-institution, Phase 1 open-label dose-confirmation study using a 3+3 design, with expansion cohorts, to determine the recommended pediatric dose of the IDO pathway-inhibitor indoximod (NCT02502708). DESIGN/METHODS: Eligible patients were 3-22 years old with either recurrent malignant brain tumor or newly-diagnosed diffuse intrinsic pontine glioma (DIPG). Palliative radiation, surgery or dexamethasone were allowed as needed for patient management. Separate dose-finding arms were performed for indoximod plus temozolomide (200 mg/m2/day orally for 5 days of each 28-day cycle) and for indoximod plus conformal radiation (in patients for whom re-irradiation was planned as standard-of-care). At progression, patients who were otherwise clinically stable were offered crossover to indoximod plus a second-line chemotherapy regimen (cyclophosphamide 2.5 mg/kg/day orally and etoposide 50 mg/m2/day orally for 21 days of each 28-day cycle). RESULTS: Between December 2015 and January 2019, the study enrolled 81 brain tumor patients, including newly-diagnosed DIPG (n= 13) or recurrent ependymoma (n= 27), glioblastoma/high-grade glioma (n= 19), medulloblastoma (n= 13), or other CNS tumors (n= 9). Median follow-up was 52 months (range 39-77 months). No dose-limiting toxicities were observed, and the pediatric indoximod dose was determined (19.2 mg/kg/dose, given twice daily). Indoximod was well tolerated and did not affect the ability to deliver chemotherapy or radiation as planned. Median overall survival was 13.6 months (n= 81). Median overall survival was 34.7 months for the subset of patients who continued indoximod with second-line chemotherapy after progression on indoximod plus temozolomide (n= 18). CONCLUSIONS: Indoximod was well tolerated and could be combined with a variety of standard treatments for pediatric brain tumors. Preliminary anti-tumor activity and overall survival suggest that indoximod with standard therapy should be further evaluated in pediatric brain tumors, and potentially other pediatric solid tumors.

Authors:
Theodore S. Johnson1,2, Rafal Pacholczyk1, Dolly Aguilerá8, Ahmad Al-Basheer1,3, Manish Bajaj4,9, Prattiti Bandopadhayay20, Zuzana Berro2,9, Eric Bouffet19, Robert C. Castellino8, Kathleen Dorris12, Bree R. Eaton10, Natia Esiashvili10, Nicholas Foreman12, Diana Fridlyand2,8, Cole Giller5, Ian M. Heger5,13, Nadja Kadom11, Eugene P. Kennedy14, Neevika Manoharan20, William Martin3, Colleen McDonough12,17, Rebecca Parker2,15, Vijay Ramaswamy19, Eric Ring1,2, Amy Rojani1,6,16, Ramses F. Sadek1,7, Amy Smith17, Chris Smith14, Rachel Vaizer18, Kee Kiat Ye©20, Tobey J. MacDonald3, David H. Munn1,2

1 Georgia Cancer Center, Augusta University, Augusta, GA
2 Department of Pediatrics, Augusta University, Augusta, GA
3 Department of Radiation Oncology, Augusta University, Augusta, GA
4 Department of Radiology, Augusta University, Augusta, GA
5 Department of Neurosurgery, Augusta University, Augusta, GA
6 Department of Pathology, Augusta University, Augusta, GA
7 Department of Population Health Sciences, Augusta University, Augusta, GA
8 Aflac Cancer & Blood Disorders Center at Children’s Healthcare of Atlanta and Department of Pediatrics, Emory University, Atlanta, GA
9 (current address: Children’s Healthcare of Atlanta and Department of Radiology, Emory University, Atlanta, GA)
10 Department of Radiation Oncology and Winship Cancer Institute of Emory University, Atlanta, GA
11 Department of Radiology and Winship Cancer Institute of Emory University, Atlanta, GA
12 Department of Pediatrics, Children’s Hospital Colorado, Aurora, CO
13 (current address: Pediatric Neurosurgery Program, Medical City Children’s Hospital, Dallas, TX)
14 Lumos Pharma (formerly NewLink Genetics Corporation), Ames, IA
15 (current address: Cancer and Blood Diseases Institute, Children’s Hospital Los Angeles, Los Angeles, CA)
16 (current address: Department of Pathology, Penn State Health/College of Medicine, Hershey, PA)
17 Department of Pediatrics, Arnold Palmer Hospital for Children, Orlando, FL
18 (current address: Department of Pediatrics, UPMC Children’s Hospital of Pittsburgh, Pittsburgh, PA)
19 Department of Paediatrics, The Hospital for Sick Children, Toronto, Canada
20 Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston MA
21 (current address: Kids Cancer Centre, Sydney Children's Hospital, Randwick, Australia)