

A randomized Phase III trial of Brentuximab vedotin (Bv) for de novo High-Risk Classical Hodgkin Lymphoma (cHL) in children and adolescents - Study Design and Incorporation of secondary endpoints in Children's Oncology Group (COG) AHOD1331.

S. M. Castellino¹, S. K. Parsons², Q. Pei³, K. McCarten⁴, S. Kessel⁴, A. Punnett⁵, T. M. Horton⁶, T. O. Henderson⁷, D. Hodgson⁸, H. Dave⁹, A. - M. Charpentier¹⁰, F. G. Keller¹, K. M. Kelly¹¹

¹ Emory University/Children's Healthcare of Atlanta, Pediatrics/Aflac Cancer and Blood Disorders Center, Atlanta, Georgia, United States of America

² Tufts University School of Medicine, Tufts University Medical Center, Boston, Massachusetts, United States of America

³ University of Florida, Biostatistics; COG Statistics and Data Center, Gainesville, Florida, United States of America

⁴ IROC Rhode Island, Providence, Rhode Island, United States of America

⁵ University of Toronto/SickKids, Toronto, Ontario, Canada

⁶ Baylor College of Medicine, Texas Children's Cancer Center, Houston, Texas, United States of America

⁷ University of Chicago, Chicago, Illinois, United States of America

⁸ University of Toronto, Princess Margaret Hospital/ University Health Network, Toronto, Ontario, Canada

⁹ Children's National Medical Center, Washington DC, United States of America

¹⁰ University of Montreal, Radiation Oncology, Montreal, Québec, Canada

¹¹ University of Buffalo, Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States of America

Children's Oncology Group

Introduction

Among patients with high-risk cHL initial cure rates are suboptimal and rely on high cumulative doses of alkylating agents, anthracyclines and radiation therapy (RT). Our overarching goal is to improve disease control and minimize treatment burden by incorporating the targeted antibody drug conjugate Bv into the COG legacy chemotherapy backbone, thus facilitating omission of bleomycin and reduction of RT fields.

Methods

Patients 2 to 21 years with newly diagnosed cHL of Stages IIB with bulk, IIIB, IV and adequate organ function were eligible for enrollment. Patients were randomized (1:1) to 5 cycles of either adriamycin, bleomycin, vincristine, etoposide, prednisone, cyclophosphamide (ABVE-PC) or Bv-AVEPC given on a 21-day interval compression schedule (NCT02166463). Response by FDG-PET after 2 cycles directed involved site RT (ISRT) based on central imaging review. Patients received GCSF support to neutrophil count recovery with each cycle. Protocol-prescribed dose reduction was designed to preserve Bv dose, based on mandatory clinical grading of peripheral neuropathy (PN) at each treatment cycle with the Balis Scale. The study has approximately 86% power to detect an 8% improvement in 3-year event-free survival (EFS) in

the Bv arm with log-rank test. Secondary and exploratory endpoints include: characterization of pharmacokinetics of Bv in children < 13 years, expression of tumor-specific antigens and changes in immunogenicity, evaluation of reduction in normal tissue irradiation, patient-reported outcomes (PRO) of PN and health-related quality of life (HRQL), and assessment of resource use and cost.

Results

600 patients were enrolled across 192 COG institutions between March 2015 and August 2019. The PRO and cost effectiveness sub-studies met accrual of 310 in September 2017. PRO completion rates exceeded 90% throughout treatment and remain high through 36 months. Peripheral blood samples for immune function studies were received in 75% of patients. The majority of adverse events were as expected, associated with the known myelosuppression of the chemotherapy backbone. Stopping rules based on PN rates were never met.

Conclusion

This trial will inform on the efficacy of Bv with a chemotherapy backbone other than AVD in pediatric patients with high-risk cHL, and on the impact of this targeted agent on important secondary outcomes including immune function, normal tissue volume reduction with ISRT, HRQL and cost-effectiveness.