Results of the NLG2105 phase 1 trial using the IDO pathway inhibitor indoximod, in combination with radiation and chemotherapy, for children with newly diagnosed DIPG

Theodore S. Johnson1,2, Dolly Aguilera5, Ahmad Al-Basheer1,3, Zuzana Berrong1, Robert C. Castellino5, Bree R. Eaton6, Natia Esiashvili6, Nicholas Foreman7, Ian M. Heger8, Eugene P. Kennedy9, Nicholas Vahanian9, William Martin3, Rafal Pacholczyk1, Eric Ring1,2, Ramses F. Sadek1,4, Michiko Shimoda1, Amy Smith10, Chris Smith9, Tobey J. MacDonald5, David H. Munn1,2

1Georgia Cancer Center and Departments of 3Pediatrics, 5Radiation Oncology, and 4Population Health Sciences, Augusta University, Augusta, GA. 2Aflac Cancer & Blood Disorders Center at Children’s Healthcare of Atlanta and Department of Pediatrics, Emory University, Atlanta, GA. 3Department of Radiation Oncology and Winship Cancer Institute of Emory University, Atlanta, GA. 4Department of Pediatrics, Children’s Hospital Colorado, Aurora, CO. 5Pediatric Neurosurgery Program, Medical City Children’s Hospital, Dallas, TX. 6NewLink Genetics Corporation, Ames, IA. 10Department of Pediatrics, Arnold Palmer Hospital for Children, Orlando, FL.

Background

• The indoleamine 2,3-dioxygenase (IDO) pathway is a natural mechanism of immune suppression that tumors exploit to evade immune responses.

• Indoximod is an orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of the IDO pathway.

• We hypothesized that immune activation using indoximod immunotherapy can allow responsiveness to chemotherapy and radiation in patients who would otherwise be refractory.

• Indoximod impacts CD8+ T cells, CD4+ T helper cells, Tregs, and dendritic cells.

• Reverses the effects of low tryptophan by increasing proliferation of effecter T cells.

• Drives differentiation into T helper cells vs Tregs.

• Downregulates IDO expression in dendritic cells.

Phase 1 Study Schema

• Indoximod, in combination with up-front radiation therapy, followed by maintenance indoximod plus chemotherapy for pediatric patients with newly-diagnosed treatment-naive DIPG.

Major Eligibility Criteria

• Age 3 to 21 years.

• Pediatric patient with newly-diagnosed treatment-naive diffuse intrinsic pontine glioma (DIPG).

• Patients must be able to swallow capsules.

Primary Objective

• Identify preliminary evidence of efficacy of indoximod combined with conformal radiation therapy, followed by indoximod combined with cyclophosphamide for treatment of newly diagnosed DIPG.

Safety Data for DIPG Patients Treated on NLG2105

• There were 13 patients enrolled in the phase 1 trial.

• The median OS was 10.8 months.

• The 12-month OS was 61.5%.

• The 18-month OS was 30.8%.

Circulating Non-classical Monocytes in Responding Patients

Conclusions

• We show data supporting the hypothesis that some DIPG patients may benefit from indoximod-based multi-modal immune-radio-chemotherapy.

• Adding indoximod to radiation for DIPG patients has been well-tolerated to date.

• Most patients have had initial improvements in symptoms.

• Inflammatory MRI changes may complicate interpretation, making Overall Survival the best overall measure of efficacy.

• Increased non-classical monocyte populations in peripheral blood may represent a biomarker of on-target immune responses in these patients.

Future Directions

• We have recently opened a phase 2 trial, which includes newly-diagnosed DIPG patients (NCT04049669).

• This trial will enroll 30 DIPG patients.

• Some patients could possibly benefit from continued indoximod-based therapy after progression, using an adaptive management algorithm that has shown promise in non-DIPG patients with relapsed brain cancer.