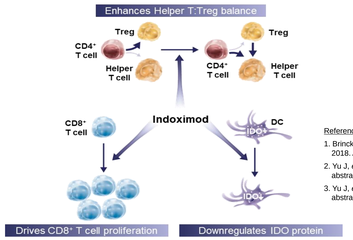
First-in-children phase 1b study using the IDO pathway inhibitor indoximod in combination with radiation and chemotherapy for children with newly diagnosed DIPG (NCT02502708, NLG2105)

Theodore S. Johnson[1,2], Rafal Pacholczyk[1], Dolly Aguilera[6], Ahmad Al-Basheer[1,3], Manish Bajaj[1,4], Zuzana Berrong[1], Robert C. Castellino[6], Bree R. Eaton[7], Natia Esiashvili[7], Nicholas Foreman[8], Ian M. Heger[9], Eugene P. Kennedy[10], William Martin[3], Eric Ring[1,2], Ramses F. Sadek[1,5], Amy Smith[11], Chris Smith[10], Rachel Vaizer[1,2], Tobey J. MacDonald[6], David H. Munn[1,2]

[1]Georgia Cancer Center and Departments of [2]Pediatrics, [3]Radiation Oncology, [4]Radiology, and [5]Population Health Sciences, Augusta University, Augusta, GA. [6]Aflac Cancer & Blood Disorders Center at Children's Healthcare of Atlanta and Department of Pediatrics, Emory University, Atlanta, GA. [7]Department of Radiation Oncology and Winship Cancer Institute of Emory University, Atlanta, GA. [8]Department of Pediatrics, Children's Hospital Colorado, Aurora, CO. [9]Pediatric Neurosurgery Program, Medical City Children's Hospital, Dallas, TX. [10]Lumos Pharma (formerly NewLink Genetics Corporation), Ames, IA. [11]Department of Pediatrics, Arnold Palmer Hospital for Children, Orlando, FL.

Background

- The indoleamine 2,3-dioxygenase (IDO) pathway is an innate immunoregulatory mechanism that tumors exploit to evade immune responses
- **Indoximod** is an orally administered, small-molecule IDO pathway-inhibitor which reverses immunosuppressive effects of the IDO pathway
- We hypothesize that immune activation using indoximod immunotherapy can allow responsiveness to radiation and chemotherapy in patients who would otherwise be refractory
- Indoximod has effects on CD8+ T cells, CD4+ T helper cells, Tregs, and dendritic cells, and acts by:
  - Reversing the effects of low tryptophan by increasing proliferation of effector T cells
  - Driving differentiation into T helper cells vs Tregs
  - Downregulating IDO expression in dendritic cells

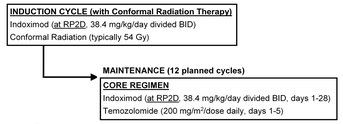


References:

1. Brincks EL, *et al.* AACR 2018. Abstract 3753.
2. Yu J, *et al.* SITC 2018; abstract P706.
3. Yu J, *et al.* SITC 2018; abstract P142

Study Schema

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



Major Eligibility Criteria

- Pediatric glioma (DIPG).
- Age patient with newly-diagnosed treatment-naïve diffuse intrinsic pontine 3 to 21 years.
- 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 cyclic temozolomide for treatment of newly diagnosed DIPG

Enrollment

- 13 patients with newly-diagnosed DIPG

Summary of Study Participant Outcomes

	NLG2105 (n=13)	St. Err.	Historical Data OBDMC/PBTC[(a)] (n=184)	St. Err.
Median OS (months)	**14.5**	--	10.8	--
12-month OS (%)	**61.5%**	+/- 13%	45.3%	+/- 3.7%
18-month OS (%)	**30.8%**	+/- 13%	16.2%	+/- 2.8%

Abbreviations: OS, Overall Survival; St.Err., Standard Error. Footenote: (a) Historical data (n=184) was obtained from OBDMC/PBTC (Operations, Biostatistics and Data Management Core/ Pediatric Brain Tumor Consortium), and was previously published in aggregate by Kilburn LB, Kocak M, Baxter P, et al. Pediatr Blood Cancer. 2018;65:e26832.

Patient Index Number	Age at Study Entry (years)	Number of Treatment Cycles[(a)]	Time on Therapy (months)	Survival Time (months)
1	11	3	3.9	4.8
2	6	3[(b)]	5.5	5.6
3	5	5	5.5	5.8
4	11	5	6.1	7.0
5	5	5	6.6	11.9
6	9	8	8.6	13.6
7	13	6	7.1	14.5
8	15	9[(c)]	10.8	14.5
9	6	15[(d)]	15.3	15.4
10	15	10	12.4	19.0
11	20	6	7.3	21.2
12	9	19	20.4	23.7
13	9	29[(e)]	29.3	29.3[(e)]

Abbreviations: nc-Monos, "non-classical" monocytes; n.d., not determined. Footnotes: (a) Number of cycles includes the up-front cycle of indoximod with radiation therapy in cycle #1. (b) After the 3rd cycle, this patient started re-irradiation (receiving 7.2 Gy in 4 fractions), but was unable to complete the radiation plan due to symptomatic disease progression. (c) After the 9th cycle, this patient abortively attempted cross-over to the salvage chemotherapy plus indoximod arm for symptomatic disease progression, but only received 2 days of oral cyclophosphamide and etoposide. (d) After the 12th cycle, this patient crossed-over to the salvage chemotherapy plus indoximod arm for symptomatic disease progression, and had 3 additional cycles using oral cyclophosphamide and etoposide. (e) After the 15th cycle, this patient crossed-over to the salvage arm, and received indoximod plus radiation therapy (20 Gy in 10 fractions) and 13 additional cycles of indoximod plus oral cyclophosphamide and etoposide. This patient was alive as of the data cutoff.

Safety Data for DIPG Patients Treated on NLG2105

Most common AEs in descending order of frequency occurring in > 2 subjects

Adverse Event Preferred Term	N=13 (%)	Indoximod related N (%)
Headache	8 (62)	1 (8)
Vomiting	7 (54)	2 (15)
Platelet count decreased	6 (46)	3 (23)
Constipation	5 (38)	1 (8)
Ataxia	5 (38)	1 (8)
Hemiparesis	5 (38)	0
Vision blurred	4 (31)	1 (8)
Dysphagia	4 (31)	0
Fatigue	4 (31)	2 (15)
Gait disturbance	4 (31)	0
Weight increased	4 (31)	1 (8)
Muscular weakness	4 (31)	0
Dizziness	4 (31)	2 (15)
Dysarthria	4 (31)	0
Depression	4 (31)	0
Dermatitis acneiform	4 (31)	0
Abdominal pain	3 (23)	0
Nausea	3 (23)	2 (15)
Pyrexia	3 (23)	1 (8)
AST increased	3 (23)	0
Back pain	3 (23)	0
VI nerve disorder	3 (23)	0
Insomnia	3 (23)	0
Irritability	3 (23)	0

Serious adverse events by patient (N=9)

Fatal where noted (N=1), possibly related where noted (5 events)

Subject	SAE Preferred Term(s)
115-043	Constipation
115-047	Respiratory failure (fatal)
115-048	Pyrexia, somnolence
115-055	Depressed level of consciousness
153-042	Adrenal insufficiency, dizziness (2) (1 possibly related), hydrocephalus (possibly related)
153-062	Dermatitis (possibly related)
153-066	Anxiety, Troponin increased
153-067	Febrile neutropenia (2) (possibly related)
153-068	Abdominal pain

Most severe AEs by SOC/PT/Grade N = 13 (%)

SOC	PT	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders	Anemia	1 (8)	-	-
	Febrile neutropenia	-	1 (8)	-
	Neutropenia	-	1 (8)	-
Endocrine disorders	Adrenal insufficiency	1 (8)	-	-
Gastrointestinal disorders	Abdominal pain	1 (8)	-	-
	Constipation	1 (8)	-	-
	Vomiting	1 (8)	-	-
General disorders and administration site conditions	Gait disturbance	2 (15)	-	-
Investigations	Neutrophil count decreased	-	2 (15)	-
	Platelet count decreased	2 (15) 1 (8)	4 (31) 2 (15)	-
	Weight increased	2 (15) 1 (8)	-	-
Metabolism and nutrition disorders	Dehydration	1 (8)	-	-
Musculoskeletal and connective tissue disorders	Muscular weakness	2 (15)	-	-
Nervous system disorders	Ataxia	1 (8)	-	-
	Dizziness	1 (8)	-	-
	Hemiparesis	2 (15)	-	-
	Hydrocephalus	1 (8)	-	-
	Myoclonus	1 (8)	-	-
	Paresthesia	1 (8)	-	-
	Somnolence	-	1 (8)	-
Psychiatric disorders	Anxiety	1 (8)	-	-
	Depression	1 (8)	-	-
	Suicidal ideation	1 (8)	-	-
	Dysgeusia	1 (8)	-	-
Respiratory, thoracic and mediastinal disorders	Respiratory failure	-	1 (8)	

SOC, System organ class; PT, Preferred term. Red text indicates attribution of possible, probable, or definite related to indoximod by principal investigator

Examples of Patients with Responsive DIPG Tumors

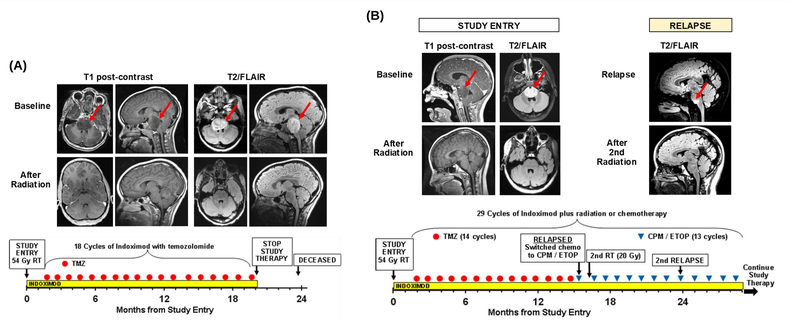
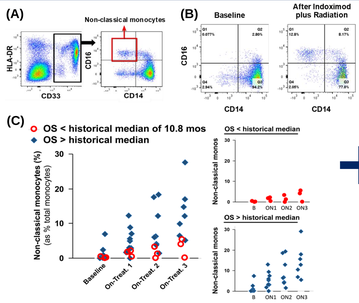


Figure 1. ***(A)*** Treatment summary/timeline and MRI results for patient #12, who had a near-complete response after indoximod plus radiation. Representative T1 post-contrast images and T2/FLAIR images are shown for MRI studies at baseline (study entry) and after radiation was completed prior to starting maintenance cycle #1. ***(B)*** Treatment summary/timeline and MRI results for patient #13, who had a near-complete response after indoximod plus up-front radiation and a 2nd near-complete response after indoximod plus re-irradiation for relapse. Representative T1 post-contrast images and T2/FLAIR images are shown for MRI studies at baseline (study entry) and after radiation was completed prior to starting maintenance cycle #1, and representative T2/FLAIR images are shown for MRI studies at relapse and after 2nd radiation was completed. Abbreviations: CPM, cyclophosphamide; ETOP, etoposide; FLAIR, fluid-attenuated inversion recovery; Gy, Gray; RT, radiation therapy; TMZ, temozolomide. The red arrows show the location of the pontine tumors. On the treatment timeline, the yellow stripe indicates duration of continuous indoximod therapy, the red markers show the start of each cycle of temozolomide, and the blue markers show the start of each cycle of oral metronomic cyclophosphamide and etoposide.

Circulating Non-classical Monocytes Correlates with Response



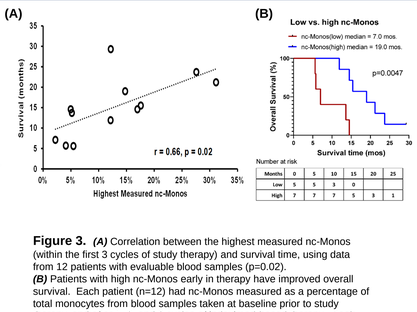


Figure 2. ***(A)*** nc-Monos were gated on CD33 and HLA-DR as shown, and defined as cells expressing CD16 but low or negative for CD14, in peripheral whole blood samples stained for flow cytometric analyses. All nc-Monos were HLA-DR+. ***(B)*** Increment in nc-Monos in a study patient after indoximod plus radiation. Representative dot-plots showing quantitation of non-classical monocytes (upper left quadrant) in a patient at baseline and after receiving indoximod plus radiation therapy. ***(C)*** Results graphed separately for the 3 patients whose overall survival (OS) was less than the historical median of 10.8 months (red markers), versus the 9 patients whose survival was greater than the historical median (blue markers). Scatter-plots show the percentage of total monocytes displaying the non-classical phenotype in samples at baseline ("B"), at the end of radiation ("On-treat. 1" or "ON1"); and after the two subsequent samples of chemotherapy ("On-treat. 2" or "ON2", and "On-treat. 3" or "ON3"). One patient did not have blood samples available and is not included.

Figure 3. ***(A)*** Correlation between the highest measured nc-Monos (within the first 3 cycles of study therapy) and survival time, using data from 12 patients with evaluable blood samples (p=0.02). ***(B)*** Patients with high nc-Monos early in therapy have improved overall survival. Each patient (n=12) had nc-Monos measured as a percentage of total monocytes from blood samples taken at baseline prior to study therapy, and after 1, 2, and 3 cycles of indoximod-based therapy. Peak nc-Monos were used to stratify patients, defined as the highest measured nc-Monos within the first 3 cycles of indoximod-based therapy. Shown is a Kaplan-Meier analysis of patients treated with indoximod-based therapy, stratified on the basis of whether their nc-Monos were above (blue line) or below (red line) 10% of total monocytes (p=0.0047). Elevated circulating nc-Monos was predictive of subsequent OS. Patients with nc-Monos >10% (n=7) had median OS of 19 months, whereas patients with nc-Monos below 10% (n=5) had median OS of 7 months (p=0.0047).

Abbreviations: nc-Monos, non-classical monocytes; OS, Overall Survival; PBTC, Pediatric Brain Tumor Consortium).

Results

- 13 patients with DIPG were treated
  - Median age 9 years, range 5 to 20 years
- Median OS was 14.5 months vs. expected median OS of 10.8 months, from published historical data from the Pediatric Brain Tumor Consortium[1].
- Two patients showed near-complete responses lasting until relapsing after 7.6 months and 13.3 months of study therapy, respectively.
- Elevated circulating nc-Monos was predictive of subsequent OS. Patients with nc-Monos >10% (n=7) had median OS of 19 months, whereas patients with nc-Monos below 10% (n=5) had median OS of 7 months (p=0.0047).
- The most common indoximod-attributed adverse events were thrombocytopenia, neutropenia, nausea, vomiting, dizziness, and fatigue. No patients stopped therapy for toxicity.

Conclusions

- Adding indoximod immunotherapy to conventional radiation and chemotherapy for front-line treatment of pediatric patients with DIPG was well-tolerated.
- Improved outcomes were observed in patients having evidence of pharmacodynamic response.

Future Directions

- We have recently opened a phase 2 trial, which includes newly-diagnosed DIPG patients (NCT04049669)
- Enrolling 30 additional patients with DIPG and 91 patients with relapsed or refractory ependymoma, medulloblastoma, or glioblastoma.
- Contact: thjohnson@augusta,edu; tayking@augusta.edu

Acknowledgements

Funding was provided by:

- Alex's Lemonade Stand Foundation
- Cannonball Kids' cancer Foundation
- Eli's Block Party Foundation
- Gracie's Hope
- Hyundai Hope on Wheels Foundation
- Northern Nevada Children's Cancer Foundation
- Press On Foundation/CAM Fund
- NewLink Genetics Corporation, as Sponsor of the trial

[1]Historical data (n=184) were obtained from OBDMC/PBTC (Operations, Biostatistics and Data Management Core/ Pediatric Brain Tumor Consortium), and was previously published in aggregate by Kilburn *et al.* Pediatr Blood Cancer. 2018;65:e26832.

Presented at the 6th Biennial Pediatric Neuro-Oncology Research Conference (sponsored by the Society of Neuro-Oncology). June 10-12, 2021. (virtual format).