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

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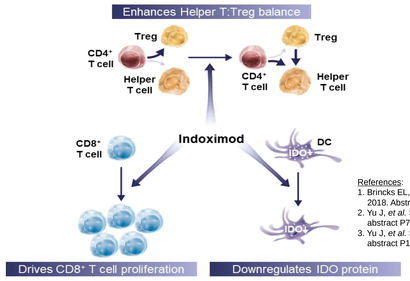
Background

- 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 hypothesize 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 effector T cells
  - Drives differentiation into T helper cells vs Tregs
  - Downregulates 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

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**

INDUCTION CYCLE (with Conformal Radiation Therapy)
Indoximod (at RP2D, 38.4 mg/kg/day divided BID)
Conformal Radiation (typically 54 Gy)

MAINTENANCE (12 planned cycles)
CORE REGIMEN
Indoximod (at RP2D, 38.4 mg/kg/day divided BID, days 1-28)
Temozolomide (200 mg/m^2/dose daily, days 1-5)

Major Eligibility Criteria

- Age 3 to 21 years
- Pediatric patient with newly-diagnosed treatment-naïve diffuse intrinsic pontine glioma (DIPG).
- Patients must be able to swallow capsules

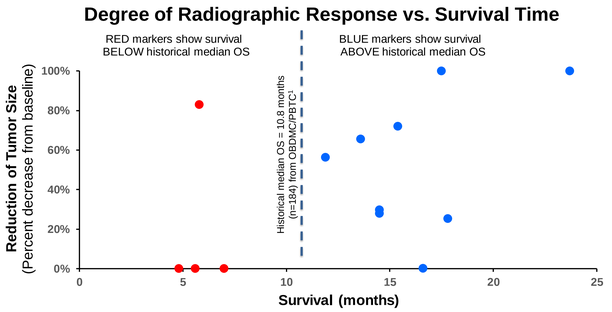
Primary Objective

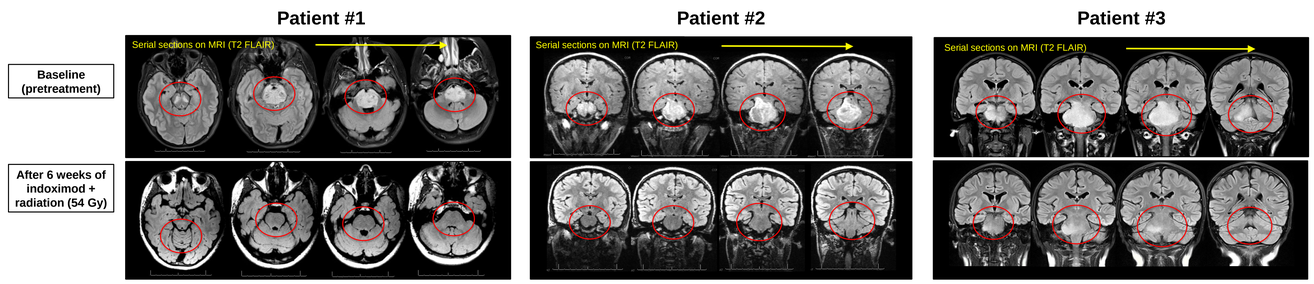
- Identify preliminary evidence of efficacy of indoximod combined with conformal radiation therapy, followed by indoximod combined with cyclic temozolomide for treatment of newly diagnosed DIPG

Outcome Results and Representative MRI Results for DIPG Patients with Good Responses

Estimated Overall Survival (OS)	**NLG2105 (n=13)**	St. Err.	Historical Data OBDMC/PBTC[1] (n=184)	St. Err.
Median OS (months)	**14.5**	--	10.8	--
12-month OS (%)	**61.5%**	+/- 1.3%	45.3%	+/- 3.7%
18-month OS (%)	**30.8%**	+/- 1.3%	16.2%	+/- 2.8%

[1] 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.





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
VIth nerve disorder	3 (23)	0
Insomnia	3 (23)	0
Ataxia	3 (23)	0

AST=Aspartate aminotransferase

Serious adverse events by patient (N=9)
Fatal where noted (N=1); possibly related where noted (5 events)

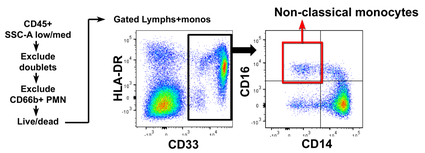
Subject	SAE Preferred Term(s)
115-043	Constipation
115-047	Respiratory failure (fatal)
115-048	Pyrexia, somnolence
115-055	Depressed level of consciousness
153-042	Adrenal insufficiency, dizziness (2) (1 possibly related), hydrocephalus (possibly related)
153-062	Dermatitis (possibly related)
153-066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

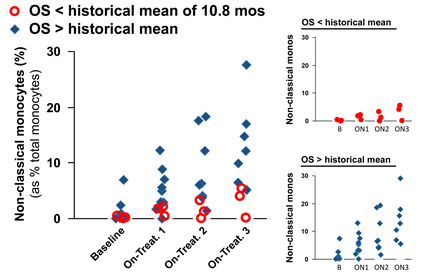
Most severe AEs by SOC/PT/Grade N = 13 (%)

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)	-	-
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (8)	-	-
	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

Circulating Non-classical Monocytes in Responding Patients





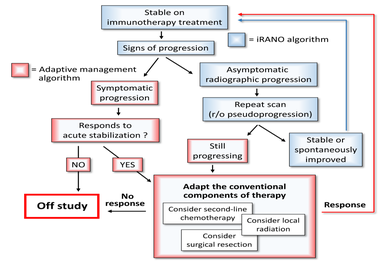
Increase in circulating non-classical monocytes (CD16+ CD14(-)) during treatment.
Peripheral monocytes that are CD14-low/negative and CD16+ are termed "non-classical" monocytes, and are thought to represent activated, inflammatory cells. Peripheral whole blood was stained for the markers below, and non-classical monocytes defined as CD33+ HLADR+ cells that were CD14-low/negative and CD16+. Scatter-plots show the percentage of total monocytes displaying the non-classical phenotype, in samples at baseline; at the end of radiation ("On-treatment #1"); and from the two subsequent samples on chemotherapy (On-treatment #2 and On-treatment #3). One patient did not have blood samples available and is not included. Results are graphed separately for the 3 patients whose overall survival (OS) was less than the historical median of 10.8 months (red), versus the 9 patients whose survival was greater than the historical median (blue).

Conclusions

- We show data supporting the hypothesis that some DIPG patients may benefit from indoximod-based multi-modal immuno-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:



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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 *et al.* Pediatr Blood Cancer. 2018;65:e26832.

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