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

NLG2105, NCT02502708

Theodore S. Johnson, M.D., Ph.D.
Co-Director, Pediatric Immunotherapy Program

Children’s Hospital of Georgia
Medical College of Georgia (MCG)
Georgia Cancer Center
Augusta University
Disclosures

• Augusta University (AU) holds patents on IDO-inhibitor drugs (indoximod)

• Lumos Pharma, Inc. (formerly NewLink Genetics Corp.) licensed the indoximod IP from AU, partially funded the NLG2105 clinical trial, and provides indoximod for GCC1949 and GCC2020 trials.
  • The presenter receives no direct financial support from Lumos Pharma

• Off-label use of chemotherapy drugs for pediatric patients will be discussed
NLG2105 phase 1 study (NCT02502708)
First-in-children trial using the IDO pathway inhibitor indoximod plus temozolomide (+/- radiation) for patients aged 3-22 years with relapsed or refractory primary brain cancer.

**Group 1:** phase 1 (plus chemo) – 3+3 design

- **Dose-finding**
  - Indoximod dose-escalation
  - Temozolomide (200 mg/m²/day x 5 days in 28-day cycles)

**Group 3:** phase 1 (plus radiation) – 3+3 design

- **Dose-finding**
  - Indoximod dose-escalation
  - Re-irradiation

Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.
**NLG2105 phase 1 study (NCT02502708)**

First-in-children trial using the IDO pathway inhibitor indoximod plus temozolomide (+/- radiation) for patients aged 3-22 years with relapsed or refractory primary brain cancer

**Group 1:** phase 1 (plus chemo) – 3+3 design

- **Dose-finding**
  - Indoximod dose-escalation
  - Temozolomide (200 mg/m²/day x 5 days in 28-day cycles)

**Group 2:** expansion cohorts – progressive CNS tumors

<table>
<thead>
<tr>
<th>CNS Tumor</th>
<th>Indoximod RP2D</th>
<th>Temozolomide</th>
<th>+/- Re-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma (relapsed)</td>
<td>(38.4 mg/kg/day divided BID)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma (relapsed)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other CNS tumor (relapsed)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Group 3:** phase 1 (plus radiation) – 3+3 design

- **Dose-finding**
  - Indoximod dose-escalation
  - Re-irradiation

**Group 3b:** newly-diagnosed DIPG

- **DIPG**
  - Indoximod RP2D
  - Up-front Radiation (54 Gy)
  - Indoximod RP2D
  - Temozolomide

Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.
IDO is a fundamental molecular mechanism of immune suppression and tolerance to apoptotic cells (normal cell turnover in the body).

Blocking the IDO pathway with indoximod helps **change the tumor microenvironment** so that tumor antigens are now presented in an immunogenic fashion.

IDO-inhibitors do not work alone – you have to kill some tumor cells to trigger immune activation ... e.g., combination with:

- Chemotherapy
- Radiation/proton therapy
- Targeted therapy (TKI’s, etc.)
## Patient demographics

<table>
<thead>
<tr>
<th></th>
<th>All participants (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>11 (3-21)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>39 (48%)</td>
</tr>
<tr>
<td>Male</td>
<td>42 (52%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>White</td>
<td>60 (74%)</td>
</tr>
<tr>
<td>More than one race</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Not reported or unknown</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>61 (75%)</td>
</tr>
<tr>
<td>Not reported or unknown</td>
<td>15 (19%)</td>
</tr>
</tbody>
</table>
Patient demographics

<table>
<thead>
<tr>
<th>Lansky or Karnofsky performance score</th>
<th>All participants (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-100</td>
<td>37 (46%)</td>
</tr>
<tr>
<td>70-80</td>
<td>29 (36%)</td>
</tr>
<tr>
<td>50-60</td>
<td>15 (19%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ependymoma, relapsed</td>
<td>27 (33%)</td>
</tr>
<tr>
<td>Medulloblastoma, relapsed</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Glioblastoma, relapsed</td>
<td>16 (20%)</td>
</tr>
<tr>
<td>Other high grade glioma, relapsed*</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Other CNS malignancy, relapsed†</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>DIPG, newly diagnosed‡</td>
<td>13 (16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Steroid treatment while on study</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with any corticosteroid</td>
<td>54 (67%)</td>
</tr>
<tr>
<td>Dexamethasone at any time</td>
<td>50 (62%)</td>
</tr>
</tbody>
</table>

*Includes:
- grade 3 glioma NOS (n=2),
- anaplastic astrocytoma (n=1).

†Includes:
- relapsed DIPG (n=1),
- embryonal tumor with astrocytic differentiation (n=1),
- ganglioglioma (n=1),
- gliosarcoma (n=1),
- high-grade neuroepithelial tumor (n=2),
- pineoblastoma (n=1),
- primitive neuro-ectodermal tumor (n=1),
- thalamic astrocytoma (n=1).

‡No previous radiation or systemic therapy.
## Disease status and prior therapy at study entry

<table>
<thead>
<tr>
<th></th>
<th>All relapsed participants (n=68)</th>
<th>Ependymoma (n=27)</th>
<th>Medulloblastoma (n=13)</th>
<th>GBM/HGG (n=19)</th>
<th>Other CNS tumor (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic disease at study entry</td>
<td>44 (65%)</td>
<td>18 (67%)</td>
<td>11 (85%)</td>
<td>10 (53%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>No evidence of disease at study entry</td>
<td>5 (7%)</td>
<td>3 (11%)</td>
<td>..</td>
<td>1 (5%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

**Prior treatment**

- Any surgical resection or debulking: 60 (88%) 27 (100%) 12 (92%) 15 (79%) 6 (67%)
- Any radiation or proton therapy: 65 (96%) 27 (100%) 12 (92%) 19 (100%) 7 (78%)
- Any systemic therapy: 56 (82%) 17 (63%) 13 (100%) 18 (95%) 8 (89%)
  - Prior temozolomide therapy: 24 (35%) 3 (11%) 5 (38%) 13 (68%) 3 (33%)
Ependymoma after 2 cycles of indoximod + temozolomide
Medulloblastoma after 2 cycles of indoximod + temozolomide
Glioblastoma after 2 cycles of indoximod + temozolomide
DIPG after indoximod + radiation
Favorable outcome with indoximod-based therapy

A. All participants (n=81)
   median OS=13.6 mos.

   - 95% confidence interval

B. Recurrent only (n=68)
   median OS=13.3 mos.

   - 95% confidence interval

Number at risk
(n=81)

Time on study (months)

Overall survival (%)
Favorable outcome with indoximod-based therapy

Historical comparators adapted from:
Ependymoma cohort (relapsed)

**Graph C**
EPN, full-dose RT, n=8
median OS=40.5 months

<table>
<thead>
<tr>
<th>Time on study (months)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>100</td>
</tr>
<tr>
<td>12-24</td>
<td>50</td>
</tr>
<tr>
<td>24-36</td>
<td>25</td>
</tr>
<tr>
<td>36-48</td>
<td>10</td>
</tr>
<tr>
<td>48-60</td>
<td>0</td>
</tr>
</tbody>
</table>

Number at risk: 8
(number censored): 0

**Graph D**
EPN, all other, n=19
median OS=23.5 months

<table>
<thead>
<tr>
<th>Time on study (months)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>100</td>
</tr>
<tr>
<td>12-24</td>
<td>95</td>
</tr>
<tr>
<td>24-36</td>
<td>80</td>
</tr>
<tr>
<td>36-48</td>
<td>60</td>
</tr>
<tr>
<td>48-60</td>
<td>40</td>
</tr>
</tbody>
</table>

Number at risk: 19
(number censored): 3

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Pediatric Immunotherapy Program

Georgia Cancer Center
Medulloblastoma cohort (relapsed)

MBL, n=13
median OS=21.1 months

Overall survival (%)

Time on study (months)

Number at risk (number censored)
13 (0)
10 (0)
6 (0)
5 (0)
3 (1)
1 (2)

95% C.I.
Glioblastoma cohort (relapsed)

HGG (Grade 3 and 4), n=19
median OS=6.5 months

Overall survival (%)

Time on study (months)

Number at risk
(number censored)

19 3 1 1 1 1 0
(0) (0) (0) (0) (0) (0) (1)

95% C.I.
Newly diagnosed DIPG cohort

Newly-diagnosed DIPG, n=13
median OS=14.4 months

Overall survival (%)

Time on study (months)

Number at risk (number censored)
13 (0)
12 (0)
24 (0)
36 (0)
48 (0)
60 (0)

95% C.I.
Emergence of CD8+ effector T cells in peripheral blood during study therapy

- Single-cell RNA-sequencing analysis of PBMCs (peripheral blood mononuclear cells)

- **Hypothesis:** Treatment with IDO blockade allows dendritic cells to mature and cross-present tumor antigen, leading to T cell activation and upregulation of anti-tumor effector pathways
Response in any lesion correlates with survival

- Mixed responses are very common in patients treated with immunotherapy.

- **Hypothesis:** Response in any single lesion is a proxy for immune response and therefore correlates with survival.
  - Stratified patients according to whether any lesion achieved PR/CR by RAPNO criteria.
  - n=63 patients with relapsed/refractory disease at study entry.
  - (5 patients with no active disease excluded)
  - 26/63 (41%) showed at least one responsive lesion, by RAPNO criteria.
“Adaptive Management” – cross-over salvage algorithm

*Can patients with progression on immunotherapy be salvaged?*

**Fundamental hypothesis:**

The *tumor* can mutate ...

... to become resistant to the specific chemotherapy agent

... or to develop stronger immunosuppression (immune selection pressure)

However, the *immune system* does not mutate, and it still expresses IDO – it may be even more activated and responsive

Therefore, when patients progress on combined chemo-immunotherapy, our strategy is to change the chemotherapy agent, but don’t stop the immunotherapy
“Adaptive Management” – cross-over salvage algorithm

**Dose-finding**

**Group 1:** phase 1 (plus chemo) – 3+3 design

**Group 3:** phase 1 (plus radiation) – 3+3 design

**Expansion Cohorts**

**Group 2:** expansion cohorts – progressive CNS tumors

**Group 3b:** newly-diagnosed DIPG

**Cross-over at progression**

Patients allowed to cross over to a compassionate-access salvage regimen at progression

**Group 4: Salvage regimen**

- Indoximod RP2D
- Oral metronomic chemotherapy (in 28-day cycles):
  - Cyclophosphamide (2.5 mg/kg/day x 21 days, max 100mg/day)
  - Etoposide (50 mg/m²/day x 21 days)

Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.
Can patients with progression on immunotherapy be salvaged?

Salvage regimen (28-day cycles):
- Indoximod at RP2D
- Cyclophosphamide (2.5 mg/kg/day x 21 days, max 100mg/day)
- Etoposide (50 mg/m²/day x 21 days)

- n=18 patients treated on Group 4 salvage therapy
- 12/18 (67%) were able to restabilize progressing disease (SD or better)
- 6/18 (33%) were treated longer than 12 months on Group 4 salvage therapy
Favorable outcome with indoximod-based therapy (summary)

- Median overall survival, all patients – 13.6 months (n=81)
- Median overall survival (OS) by diagnosis:
  - **Ependymoma** (relapsed) – 34.1 months (n=27)
    - Indoximod plus **full-dose** re-RT – 40.5 months (n=8)
    - All other ependymoma cases – 23.5 months (n=19)
  - **Medulloblastoma** (relapsed) – 21.1 months (n=13)
  - **High-grade glioma** (relapsed) – 6.5 months (n=19)
  - **DIPG** (treatment-naïve) – 14.4 months (n=13)
- Patients who crossed-over to Group 4 after progression
  Indoximod + oral metronomic cyclophosphamide and etoposide
  Median OS since study entry – 34.7 months (n=18)
## Performance status for patients treated on indoximod longer than 30 months

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Time on indoximod (months)</th>
<th>Overall survival (months)</th>
<th>Received Group 4 therapy (Yes/No)</th>
<th>Performance score (Lansky/Karnofsky)</th>
<th>LDOC=last date of contact. †These patients are still alive. ‡This patient experienced dramatic improvements in baseline symptoms (severe ataxia, right-side weakness, dysarthria, nausea, headaches). **This patient continues therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Medulloblastoma</td>
<td>31.8</td>
<td>61.9 LDOC†</td>
<td>No</td>
<td>80 90 100 100</td>
<td></td>
</tr>
<tr>
<td>2. Ependymoma</td>
<td>31.9</td>
<td>35.1</td>
<td>Yes</td>
<td>100 90 100 80</td>
<td></td>
</tr>
<tr>
<td>3. Ependymoma</td>
<td>32.3</td>
<td>46.8 LDOC†</td>
<td>Yes</td>
<td>100 100 100 100</td>
<td></td>
</tr>
<tr>
<td>4. Ependymoma</td>
<td>32.9</td>
<td>37.5</td>
<td>Yes</td>
<td>50‡ 70 90 90</td>
<td></td>
</tr>
<tr>
<td>5. PNET</td>
<td>41.9</td>
<td>51.2</td>
<td>Yes</td>
<td>90 100 100 90</td>
<td></td>
</tr>
<tr>
<td>6. High grade glioma</td>
<td>42.1</td>
<td>52.3 LDOC†</td>
<td>Yes</td>
<td>80 90 100 90</td>
<td></td>
</tr>
<tr>
<td>7. Ependymoma</td>
<td>44.6</td>
<td>44.6 LDOC†</td>
<td>No</td>
<td>100 100 100 100**</td>
<td></td>
</tr>
<tr>
<td>8. Medulloblastoma</td>
<td>49.2</td>
<td>56.7</td>
<td>Yes</td>
<td>80 90 90 80</td>
<td></td>
</tr>
</tbody>
</table>
Patients experiencing high-grade adverse events regardless of attribution to study therapy

<table>
<thead>
<tr>
<th>Event</th>
<th>Indoximod with temozolomide, Groups 1 and 2 (n=54)</th>
<th>Indoximod with up-front radiation then indoximod with temozolomide, Groups 3a and 3b (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>Grade 3: 41 (76%)</td>
<td>Grade 3: 23 (85%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (15%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (13%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>6 (11%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>6 (11%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>5 (9%)</td>
<td>14 (26%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>4 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (6%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>3 (6%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Muscle weakness, generalized</td>
<td>3 (6%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>3 (6%)</td>
<td>5 (9%)</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>3 (6%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>2 (4%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Muscle weakness, localized</td>
<td>2 (4%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2 (4%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>3 (6%)</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>3 (11%)</td>
<td>3 (11%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

Data are n (%), with each participant reported once at the highest grade experienced. Shown are treatment-emergent adverse events occurring in at least 5% patients for Grade 3 or 4.

**Grade 5 events** occurred in three patients (cardiac arrest, respiratory failure, and stroke), and all were attributable to tumor progression. No cases of radiation-related central nervous system necrosis were documented.
Currently enrolling IDO-inhibitor trials for children

**Indoximod plus chemotherapy +/- radiation**
- GCC1949 (NCT04049669) – Phase 2 (enrolling)
  - (NIH-funded R01; multi-center; IND-holder T. Johnson)

**Ibrutinib and Indoximod plus chemotherapy**
- GCC2020 (NCT05106296) – Phase 1 (enrolling)
  - (First-in-human trial using this combination; IND-holder T. Johnson)

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(706) 825-0979  
thjohnson@augusta.edu
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(706) 825-0979
thjohnson@augusta.edu