Front-line Therapy of DIPG Using the IDO Pathway Inhibitor Indoximod in Combination With Radiation and Chemotherapy

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Disclosures

• Theodore S. Johnson, M.D., Ph.D.
  • NewLink Genetics Corporation is partially funding a pediatric clinical trial, which will be discussed
    • The presenter receives no direct financial support from NewLink Genetics Corporation
  • No other relevant financial relationships exist with respect to this presentation
  • Off-label use of chemotherapy drugs will be discussed for pediatric patients
IDO Pathway and Cancer: Key Immuno-oncology Target

•IDO (indoleamine 2,3-dioxygenase): intracellular enzyme that regulates immune response by degrading tryptophan to kynurenine

•IDO pathway activity results in a shift of the ratio of tryptophan (↓) to kynurenine (↑)

•This shift in ratio signals a suppressive phenotype rather than an activated antitumor phenotype

•Tumors hijack the IDO pathway, a normal part of the immune system, to facilitate immune escape


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IDO Pathway and Cancer: Key Immuno-oncology Target (cont)

Key points:

• IDO is a natural mechanism of immunosuppression and tolerance in the immune system involved in
  • Acquired peripheral tolerance (pregnancy, mucosal tolerance)
  • Maintenance of tolerance to apoptotic cells (including apoptotic tumor cells)
• We hypothesize that the effect on tolerance to apoptotic cells may be critical for synergy with chemotherapy and radiation
IDO1 Expression in Various Tumor Types is Associated With Poor Patient Outcomes

- IDO1 is highly expressed in multiple tumor types
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - Colorectal cancer
  - Glioblastoma
  - Squamous cell carcinoma
  - Endometrial carcinoma
  - DLBCL
  - RCC
  - TCC
  - TNBC
Indoximod Differentiated Mechanism of Action

- Orally administered, small-molecule IDO pathway inhibitor that reverses the immunosuppressive effects of low tryptophan and high kynurenine that result from IDO activity

- Immunostimulatory effects involving 3 main cell types: CD8+ T cells, T regulatory cells, and dendritic cells
  - Reverses effects of low tryptophan by increasing proliferation of effector T cells
  - Directly reprograms T regulatory cells to helper T cells
  - Downregulates IDO expression in dendritic cells

- Potential synergy has been shown with checkpoint blockade, chemotherapy, radiation and vaccines

IDO, indoleamine 2,3-dioxygenase; Treg, T regulatory cell; DC, dendritic cell.


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Indoximod vs Epacadostat Mechanism of Action

Indoximod Directly Reprograms T Regulatory Cells to Helper T cells

Indoximod has a differentiated mechanism within the IDO pathway

Indoximod

Epacadostat

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Designing Multimodal Chemo-radio-immunotherapy

• Hypothesis:
  • Immune activation (immunotherapy) can allow responsiveness to chemotherapy and radiation in patients who would otherwise be refractory

• However, this synergy with chemotherapy/radiation requires targeting the antigen-presenting step and creating a pro-inflammatory (immunogenic) tumor milieu
  • Essentially, it must break tolerance to the dying/apoptotic tumor cells
  • This antigen cross-presentation step lies upstream of the conventional T-cell checkpoints

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Recurrent/Refractory Pediatric Brain Tumors

- Recurrent/refractory brain tumors represent the greatest single cause of mortality in pediatric cancer
  - Cannot be cured by current standard treatments (treatment-refractory)
  - Standard of care is largely palliative

**Historical control data for relapsed brain tumors**

- PFS, progression-free survival; OS, overall survival; HGG, high grade glioma.

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First-in-children Phase 1 Trial of Indoximod-based Multimodal Chemo-radio-immunotherapy

- Relapsed or refractory primary brain tumor patients

- Primary endpoints:
  - Regimen-limiting toxicities of indoximod + temozolomide
  - Objective response rate
  - Regimen-limiting toxicities of indoximod + radiation
  - Safety

- Key eligibility criteria
  - 3-21 years of age
  - Histologically proven initial diagnosis of primary malignant brain tumor, with no known curative treatment options
  - MRI confirmation of tumor progression

- Multimodal management is a key feature of the regimen

- Radiographic evidence of progression (escape lesions) can be managed with continued indoximod and:
  - Surgical resection (regain local control)
  - Targeted radiation (regain local control)
  - Crossover to 2nd-line chemotherapy (cyclophosphamide/etoposide)

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First-in-children Phase 1 Trial of Indoximod-based Multimodal Chemo-radio-immunotherapy (cont)

Group 1
- Indoximod dose escalation (study dose, PO, twice daily on days 1-28)
- Temozolomide (200 mg/m²/day, PO, once daily on days 1-5 of 28-day cycles)

Group 2 (expansion cohort of Group 1)
- RP2D of indoximod
- Temozolomide (200 mg/m²/day, PO, once daily on days 1-5 of 28-day cycles)

Group 3
- Indoximod dose escalation (study dose, PO, twice daily on days 1-28)
- Individualized radiation plan
- Followed by indoximod combined with cyclic temozolomide

Group 4 (progressive disease on indoximod + temozolomide)
- Indoximod (32 mg/kg/dose PO, twice daily on days 1-28)
- Cyclophosphamide (2.5 mg/kg/dose PO, once daily)
- Etoposide (50 mg/m²/dose PO, once daily)

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# Patient Demographics (Mixed Population)

<table>
<thead>
<tr>
<th>Total patients enrolled</th>
<th>N = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>14 (48)</td>
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<tr>
<td>Malignant glioma*</td>
<td>9 (31)</td>
</tr>
<tr>
<td>Medulloblastoma**</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
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</tr>
<tr>
<td>Female</td>
<td>10 (34)</td>
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<tr>
<td>Male</td>
<td>19 (66)</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
<td>African American</td>
<td>3 (10)</td>
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<tr>
<td>Caucasian</td>
<td>23 (79)</td>
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<tr>
<td>Hispanic</td>
<td>0</td>
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<tr>
<td>Other</td>
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<tr>
<td>Declined to provide</td>
<td>1 (3)</td>
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<tr>
<td>Age, years</td>
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</tr>
<tr>
<td>Median</td>
<td>12.5</td>
</tr>
<tr>
<td>Range</td>
<td>3–20</td>
</tr>
</tbody>
</table>

*Includes one each gliosarcoma, bithalamic glioma, and ganglioglioma.

**Includes one previously classified as primitive neuroectodermal tumor.
Patient 001: Example of Multimodal Management Chemo-radio-immunotherapy

- **Low-dose outpatient chemo**
  - 7-year-old with ependymoma: prolonged disease responsiveness
  - Indoximod-based multimodal regimen is well tolerated

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Patient 001: Continued Responsiveness Using Indoximod-based Multimodal Management

indoximod + radiation tumor (20 Gy)

NOT TARGETED WITH NEW RADIATION

indoximod + 3rd-line chemo

indoximod + 3rd-line chemo

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Radio-immunotherapy Improves Time to Regimen Failure (TTRF)

Median TTRF without RT = 3.2 mos
with any RT = 12 mos

% Still on regimen

Time on regimen (months)

Published studies

(+) RT (n=17) [p=0.04]

(-) RT (n=12)
New Metastatic Tumor Arising While on Therapy that Later Regresses

14 yo with CSF relapse of medulloblastoma

Begin indoximod + temozolomide

Pretreatment  2 cycles  4 cycles

Potential for late responses makes TTRF an important outcome metric

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Indoximod-based Multimodal Regimen Is Well Tolerated

• In the 29 patients included in the study, SAEs possibly related to indoximod included 1 case each of:
  • Febrile neutropenia
  • Hemiparesis
  • Hydrocephalus
  • Spinal cord compression
  • Status epilepticus
  • Urinary tract infection

• Overall, indoximod did not worsen the toxicity of the base treatment
Pilot Cohort in Diffuse Intrinsic Pontine Glioma (DIPG)

**Group 1**
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Pilot cohort
- Patients with radiographic diagnosis or histologically proven DIPG

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DIPG Is Rapidly Fatal

• DIPG has the worst prognosis of any pediatric cancer
• Median time to progression after radiation is ~6 months\(^1\)
• At progression, patients follow a rapidly declining course
  • Median OS is 10-12 months\(^2\)
  • Uniformly fatal

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Effective Treatments for DIPG are Lacking

- Standard-of-care treatment is palliative radiation (usually 54 Gy)
- Chemotherapy has no proven benefit
- Thus far, trials have not shown clinical benefit from currently available chemotherapy, radiosensitizing drugs, or biologics
- Due to their location in the brainstem, DIPGs cannot be surgically removed
Multimodal Chemo-radio-immunotherapy for DIPG Pilot Cohort

• First question: could DIPG patients tolerate the indoximod immunotherapy regimen?
  • DIPG patients are often highly symptomatic

• Pilot cohort of 6 newly diagnosed DIPG patients
  • All 6 patients have finished upfront radiation combined with indoximod
  • All 6 patients showed initial improvement in symptoms
  • 3/6 later developed inflammatory symptoms (eg, waxing/waning, migratory)
    • 2 of these occurred during first cycle of temozolomide with indoximod

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NLG2105-037: 9.4-Year-Old Male With Newly Diagnosed DIPG

Baseline (pretreatment)

DIPG scans reviewed by Tina Young-Poussaint, M.D., Boston Children’s Hospital

Patient 037 classified as: “Significant response”

After 6 weeks of indoximod + radiation (54 Gy)

This patient is neurologically normal at 6 months

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NLG2105-035: 9.3-Year-Old Male With Newly Diagnosed DIPG

Baseline (pretreatment)

This patient has sustained neurological improvement at 6 months

After 6 weeks of indoximod + radiation (54 Gy)

Serial sections on MRI (T2 Flair)

Baseline (pretreatment) Serial sections on MRI (T2 Flair) This patient has sustained neurological improvement at 6 months

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Baseline (pretreatment) 

After 6 weeks of indoximod + radiation (54 Gy) 

Additional Newly Diagnosed DIPG Patients 

NLG2105-042 12 yo male 

NLG2105-043 15 yo female 

NLG2105-047 5 yo female 

NLG2105-048 6 yo female 

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Conclusions and Future Directions

- Phase 1 data suggest that indoximod-based immunotherapy can allow disease responsiveness to conventional therapy (radiation, chemotherapy)
- Pilot cohort is under way applying this approach to newly diagnosed DIPG patients
- Phase 2 trial is planned
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