(110P) Phase II: Pediatric Trial of Indoximod with Chemotherapy and Radiation for Relapsed Brain Tumors or Newly Diagnosed DIPG (NCT04049669)

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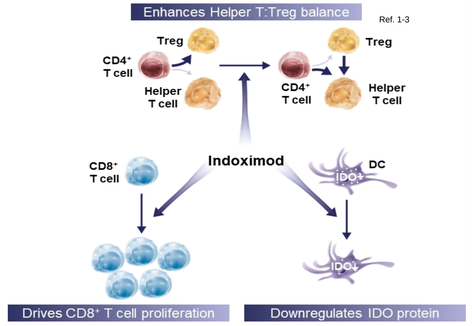
Background

- The IDO (indoleamine 2,3-dioxygenase) pathway is a natural immunosuppressive mechanism, which is coopted by tumors to evade anti-tumor immune responses.
- Indoximod is a small-molecule inhibitor of the IDO pathway, which is capable of reversing immune suppression imposed by IDO.
- We hypothesize that Inhibiting the pivotal IDO pathway by adding indoximod immunotherapy during chemotherapy and/or radiation is a potent approach for breaking immune tolerance to pediatric tumors that will improve outcomes, relative to standard therapy alone.
- A Phase I Pediatric indoximod trial has been completed, enrolling 81 children, and confirming the recommended phase-II dose of indoximod.
- The Phase II trial will evaluate the efficacy of indoximod combined with temozolomide and/or radiation therapy, in comparison to historical control data.
  - This trial focuses on clinical outcomes, including survival and quality of life, and offers a well-tolerated oral therapy option.
- Indoximod exerts effects on CD8+ T cells, CD4+ T helper cells, Tregs, and dendritic cells
  - Increases proliferation of effector T cells
  - Drives differentiation of CD4 T cells into helper T cells rather than 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

Study Design and Patient Population

Major Inclusion Criteria

- Age 3 to 21 years.
- Patients must be able to swallow pills.
- Diagnosis:
  - Progressive glioblastoma, medulloblastoma, or ependymoma; With confirmation of progression by either MRI or CSF analysis; Measureable disease is not required for study entry.
    - Patients with progressive disease must have been previously treated with therapeutic radiation.
  - Newly diagnosed DIPG (diffuse intrinsic pontine glioma) with no prior therapy (including no prior radiation); Biopsy is not required for DIPG.
  - Central review of tissue diagnosis is required, except non-biopsied DIPG; Archival tumor tissue must be located and available prior to study entry.
  - Patients with metastatic disease are eligible.
- Lansky or Karnofsky performance status score must be ≥ 50%.
- Adequate organ function, including bone marrow, renal, and hepatic.
  - Seizure disorders must be well controlled on antiepileptic medication.

Major Exclusion Criteria

- Patients previously treated with indoximod
- Patients with DIPG who have been treated with any prior radiation or medical therapy
- Midline glioma that does not include significant brain stem involvement
- Patients with active systemic infection requiring treatment
- Patients with active autoimmune disease that requires systemic therapy
- Pregnant women

Primary Endpoint for patients with relapsed brain tumors

- 8-month iRANO-PFS (Progression-Free Survival, defined by immune-adapted iRANO criteria[4]), compared to historical data[5]

Primary Endpoint for patients with newly diagnosed DIPG

- 12-month Overall Survival (OS), compared to historical data[6]

Selected Secondary Endpoints

- Overall Survival (OS)
- iRANO-PFS
- Time to Regimen Failure (TTRF)

References:
4. Okada H, *et al.* 2015. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol 16: e534-e542.
5. Nicholson HS, *et al.* 2007. Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer 110: 1542-1550.
6. Kilburn LB, *et al.* 2018. A pediatric brain tumor consortium phase II trial of capecitabine rapidly disintegrating tablets with concomitant radiation therapy in children with newly diagnosed diffuse intrinsic pontine gliomas. Pediatr Blood Cancer 65(2).

Study Design

Disease-specific Cohorts (non-randomized, open-label):

Cohort 1 (A,B):	progressive glioblastoma	(2 x 13 = 26 patients)
Cohort 2 (A,B):	progressive medulloblastoma	(2 x 13 = 26 patients)
Cohort 3 (A,B,C):	progressive ependymoma	(3 x 13 = 39 patients)
Cohort 4:	newly-diagnosed DIPG	(30 patients)

Total evaluable patient accrual: 121 patients

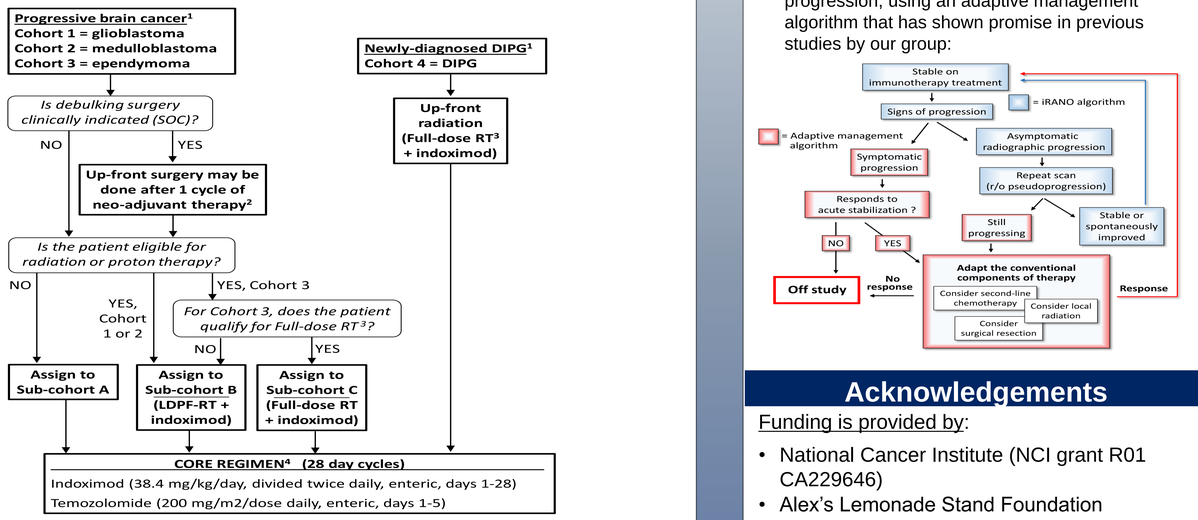
Radiation (or proton) plan sub-cohorts (non-randomized, open-label):

Sub-cohort A: for patients not eligible for re-irradiation

Sub-cohort B: for patients who are eligible for partial re-irradiation

Sub-cohort C: for patients who are eligible for full-dose radiation (All newly diagnosed DIPG patients and some relapsed ependymoma patients)

Treatment Plan Flow Diagram



Footnotes
1. Cohort assignment is contingent upon central review of the tissue diagnosis using archival tumor tissue, except non-biopsied DIPG.
2. For patients who consent to a neo-adjuvant therapy cycle prior to debulking surgery and who are deemed clinically stable; otherwise, the patient may have up-front surgery prior to protocol therapy.
3. Full-dose RT is a radiation plan that delivers ≥50 Gy to brain and/or ≥45 Gy to spine, and irradiates all known sites of disease; Proton therapy is excluded for newly-diagnosed DIPG patients.
4. For patients who receive radiation or proton therapy, the first cycle of Core Regimen therapy should begin at least 10 days after the radiation or proton therapy plan is complete.

DIPG, Diffuse intrinsic pontine glioma; LDPF, Low-dose partial-field; RT, radiation therapy; SOC, Standard of care.

Trial Status

- This clinical trial is currently open and actively enrolling patients.
- This NCI-funded study is being conducted under an investigator-sponsored IND (Dr. Theodore Johnson, IND-holder), with two performance sites (Augusta University and Emory University).
- This clinical trial will enroll and treat up to 140 children with brain cancer over the next 4-5 years (including some patients who may fail central review of pathological diagnosis).
- Associated biology studies include innovative, hypothesis-driven immune biomarkers, performed in the Georgia Cancer Center Human Immune Monitoring Core Facility.

Future Directions

Some patients could possibly benefit from continued indoximod-based therapy after progression, using an adaptive management algorithm that has shown promise in previous studies by our group:

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ClinicalTrials.gov Identifier

NCT04049669

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