RADIO-IMMUNOTHERAPY USING THE IDO PATHWAY INHIBITOR INDOXIMOD FOR CHILDREN WITH NEWLY-DIAGNOSED DIPG

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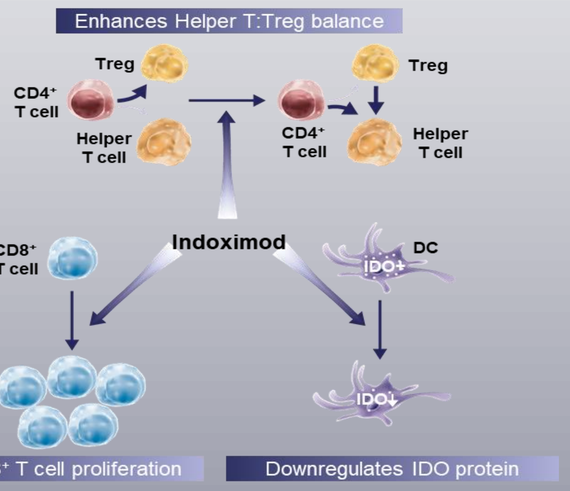
Background

- The indoleamine 2,3-dioxygenase (IDO) pathway is a natural mechanism of immune suppression that growing tumors exploit to evade
- **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
- Immuno-stimulatory effects of indoximod impact 4 main cell types: CD8+ T cells, CD4+ T helper cells, T regulatory cells, and dendritic cells
  - Reverses the effects of low tryptophan by increasing proliferation of effector T cells
  - Drives differentiation into T helper cells vs regulatory T cells
  - Downregulates IDO expression in dendritic cells



Phase 1 Study Schema

- Indoximod, in combination with up-front conformal 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)

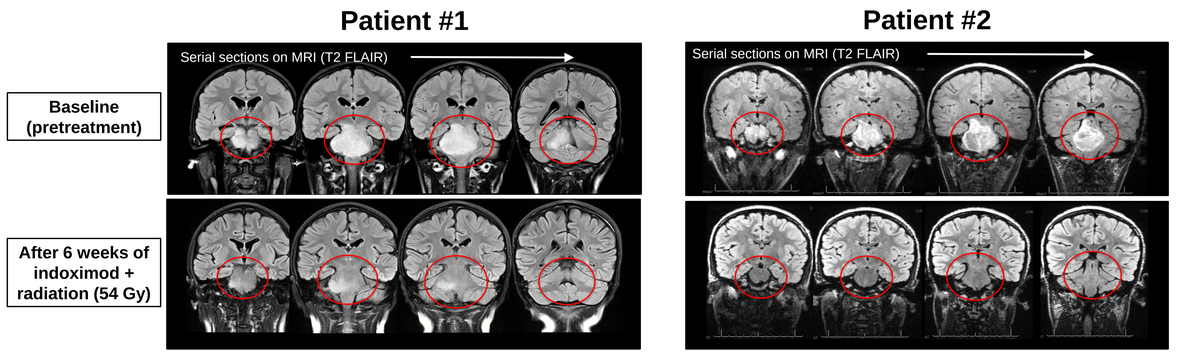
Major Eligibility Criteria

- Age 3 to 21 years
- Corticosteroid therapy is allowed
- Patients must be able to swallow capsules until bio-equivalence study is complete

Primary Objective

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

Representative Imaging from the Initial MRI Results at Completion of Radiation for the First Two DIPG Patients



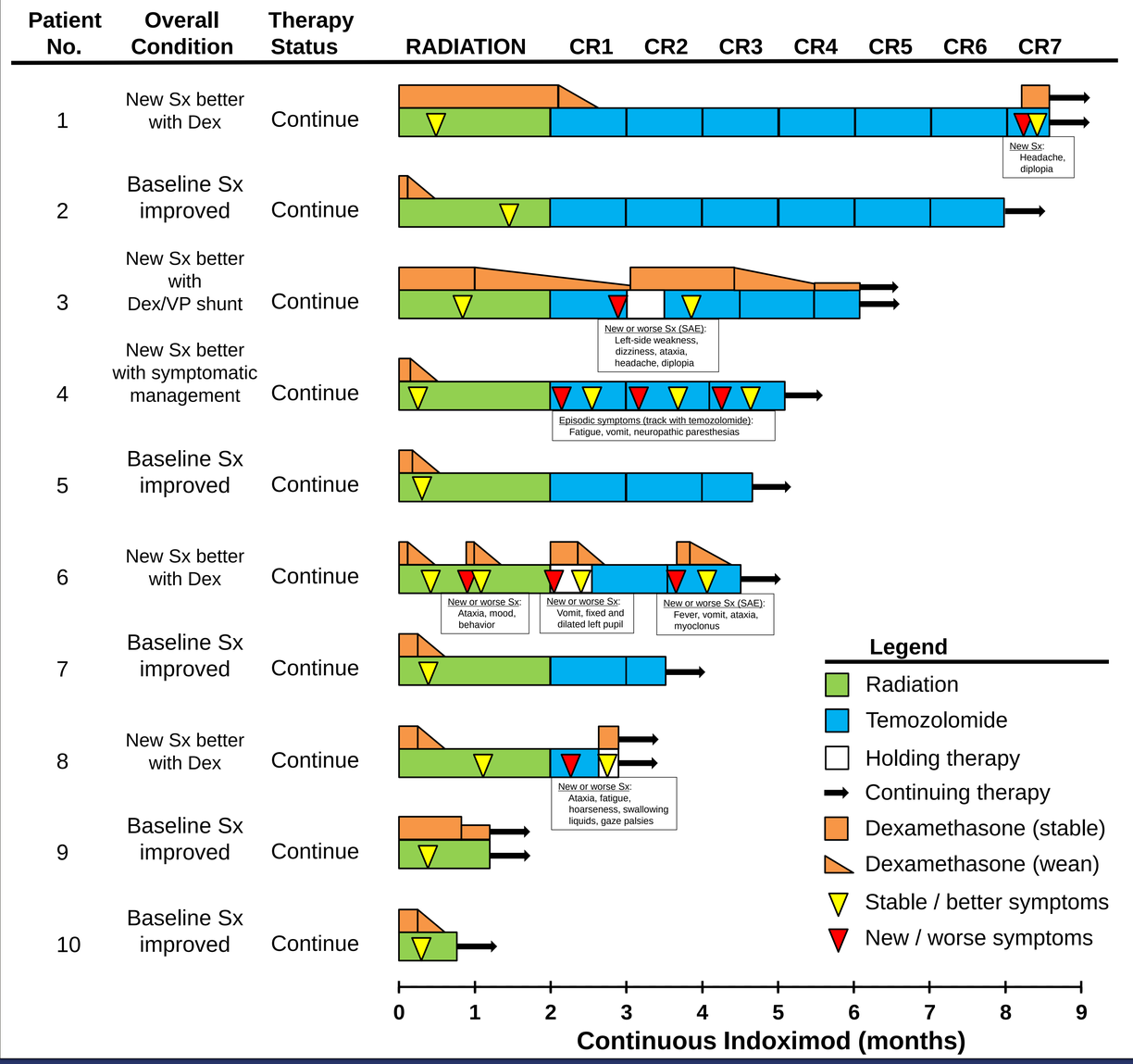
Synopsis of DIPG Patient Data (n=10)

10/10 remain on study
- Longest treated, 8.5 months
- 10/10 had initially improved Sx
- 8/10 have completed radiation
- 2 are continuing radiation

5/10 developed inflammatory Sx
- 1 during radiation, 5 during chemo
- 3 held indoximod briefly
- 4 improved with steroids
- 1 required CSF diversion

3/10 had SAE's
- Pt#3: Left-sided weakness, ataxia, headache, dizziness, diplopia
- Pt#4: Constipation
- Pt#6: Fever, vomit, ataxia

Clinical Course of the DIPG patients to date (n=10)

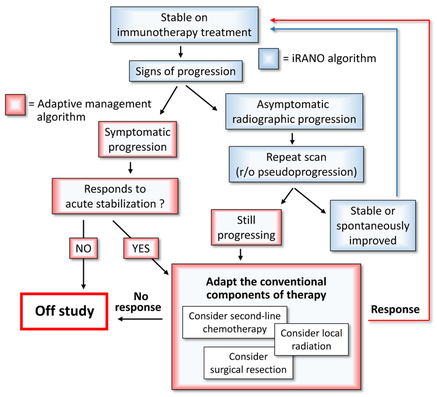


Conclusions

- We hypothesize that multi-modal immuno-radio-chemotherapy may allow responsiveness in DIPG tumors
- Adding indoximod to radiation for DIPG patients is well-tolerated to date
- All patients have had initial improvements in symptoms to date
- Inflammatory symptoms, defined as non-progressive or steroid-responsive symptoms, are common (50% to date)
  - Such symptoms require active management, and do not mandate removal from the study
  - Hydrocephalus should be managed via CSF diversion when appropriate
- Inflammatory MRI changes may complicate interpretation, making Overall Survival the best overall measure of efficacy
- The trial is currently enrolling with a target of 30 DIPG patients

Future Directions

- Ongoing enrollment and maturation of Overall Survival (OS) data
- 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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