

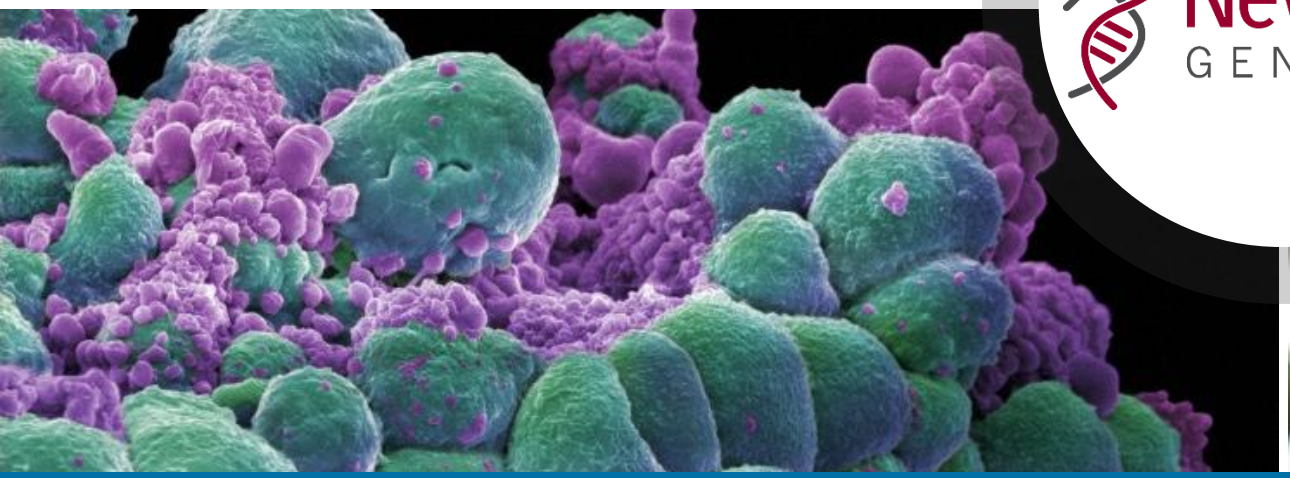


NewLink GENETICS

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

## American Association of Cancer Research (AACR) 2018

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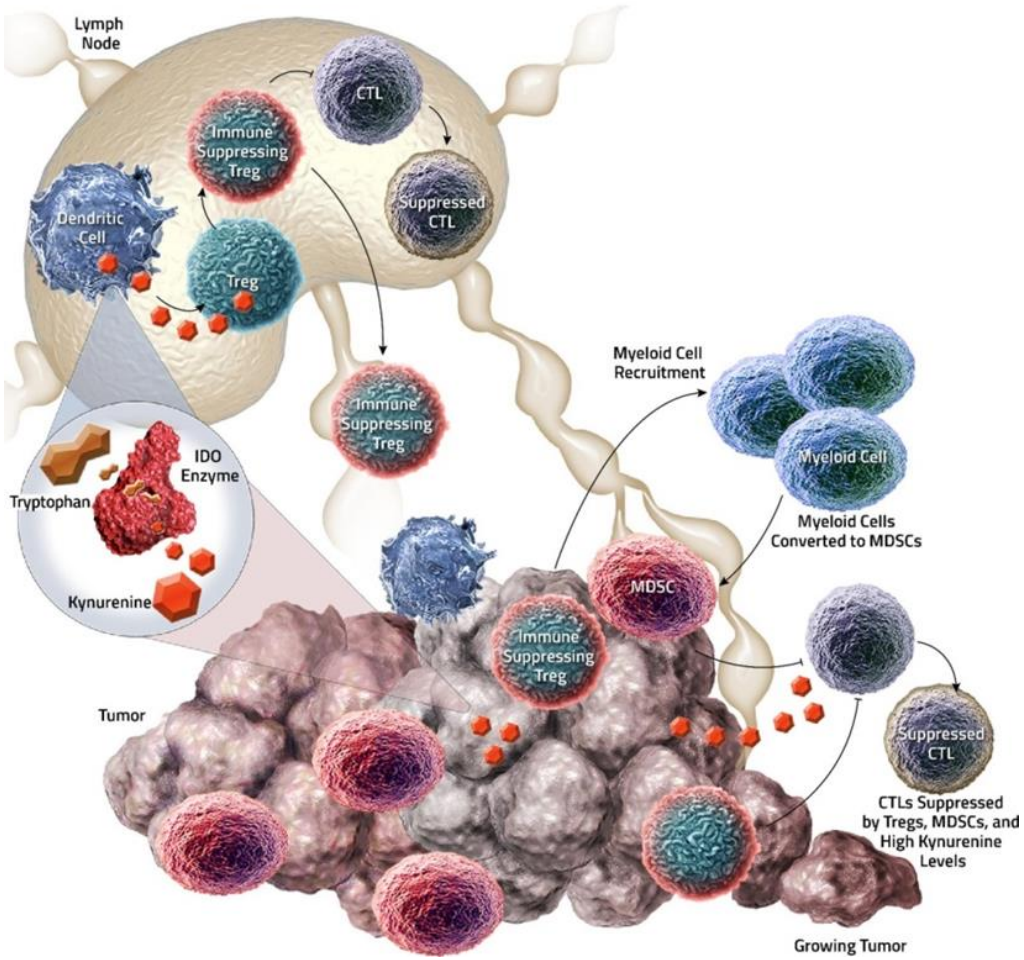
# IDO Pathway a Key Immuno-oncology Target

- IDO (indoleamine 2,3-dioxygenase): intracellular enzyme that regulates immune response by degrading tryptophan to kynurenine[1]
- IDO pathway activity results in a shift of the ratio of tryptophan (↓) to kynurenine (↑)[1]
- This shift in ratio signals a suppressive phenotype rather than an activated antitumor phenotype[1]
- Tumors hijack the IDO pathway, a normal part of the immune system, to facilitate immune escape[2]



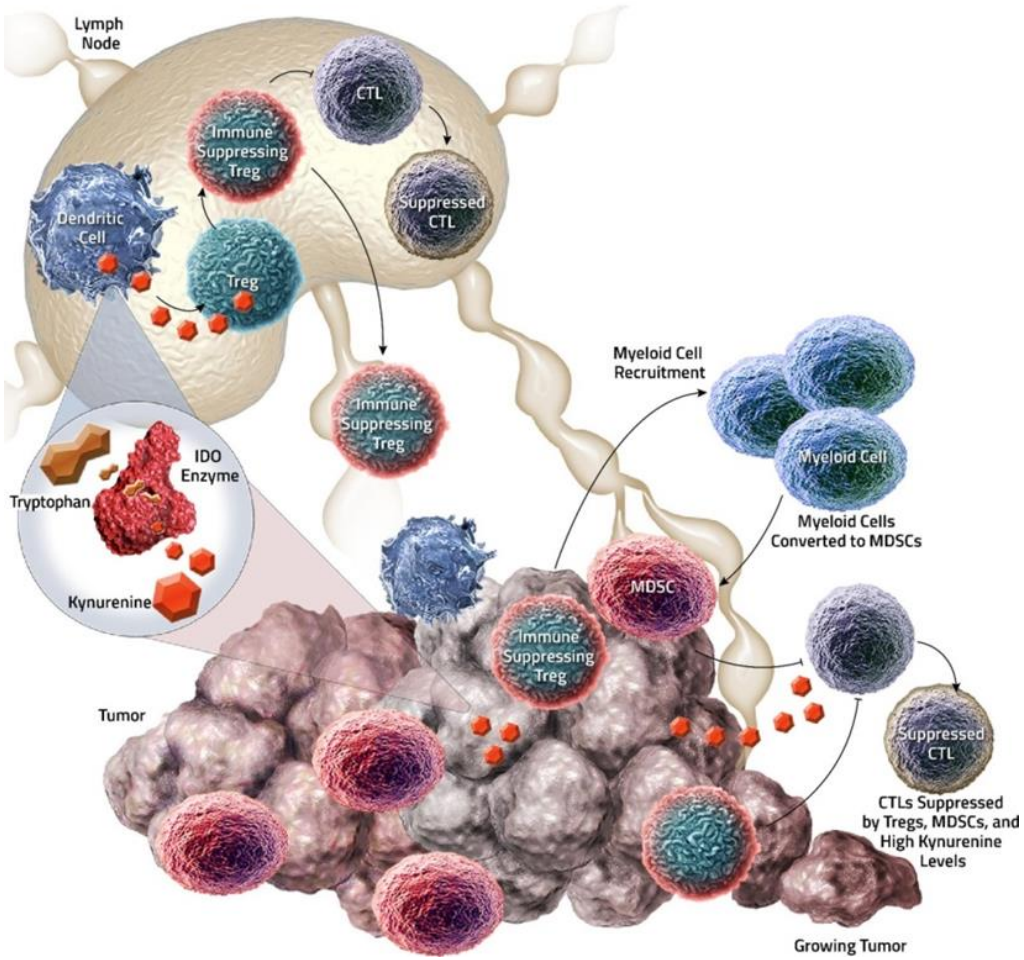

Treg, regulatory T cell; IDO, indoleamine 2,3-dioxygenase; MDSC, myeloid-derived suppressor cell; CTL, cytotoxic T lymphocyte.

1. Metz R. *Oncoimmunology*. 2012;1(9):1460-1468. 2. Johnson TS. *Immunol Invest*. 2012;41(6-7):765-797.

# IDO Pathway a Key Immuno-oncology Target

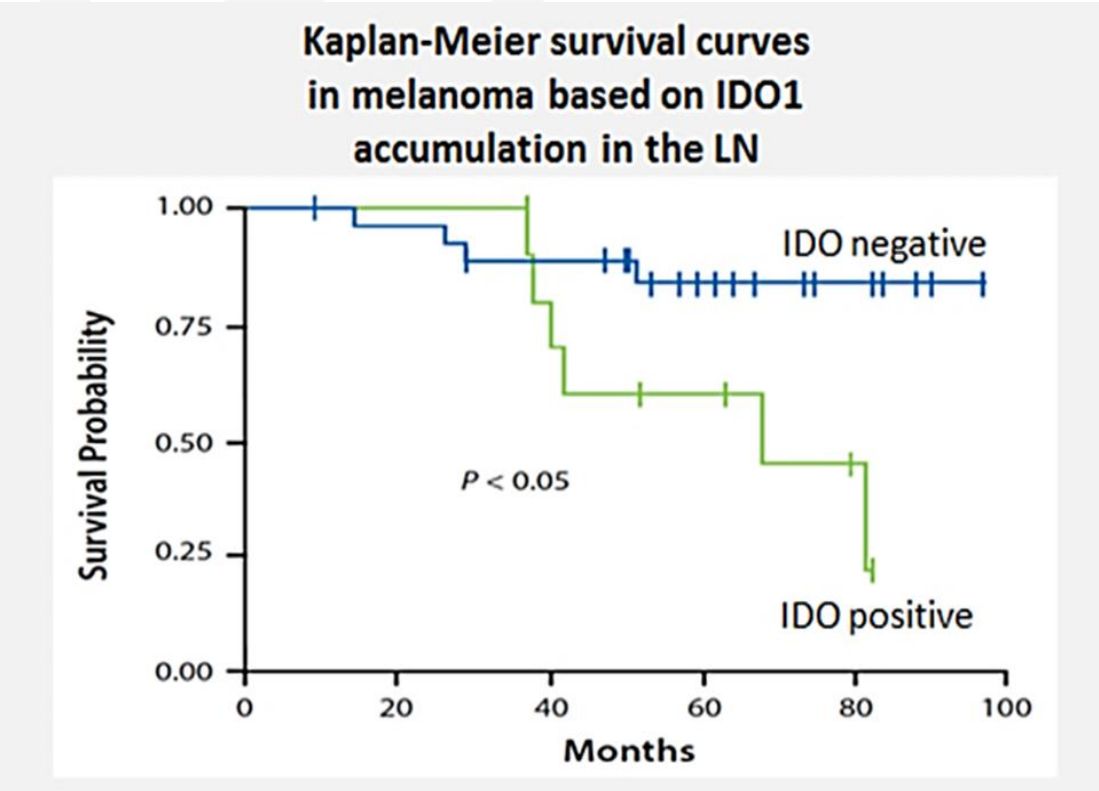
Key points:

- 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




Treg, regulatory T cell; IDO, indoleamine 2,3-dioxygenase; MDSC, myeloid-derived suppressor cell; CTL, cytotoxic T lymphocyte.

# IDO Expression in Certain Tumors is Associated with Poor Patient Outcomes

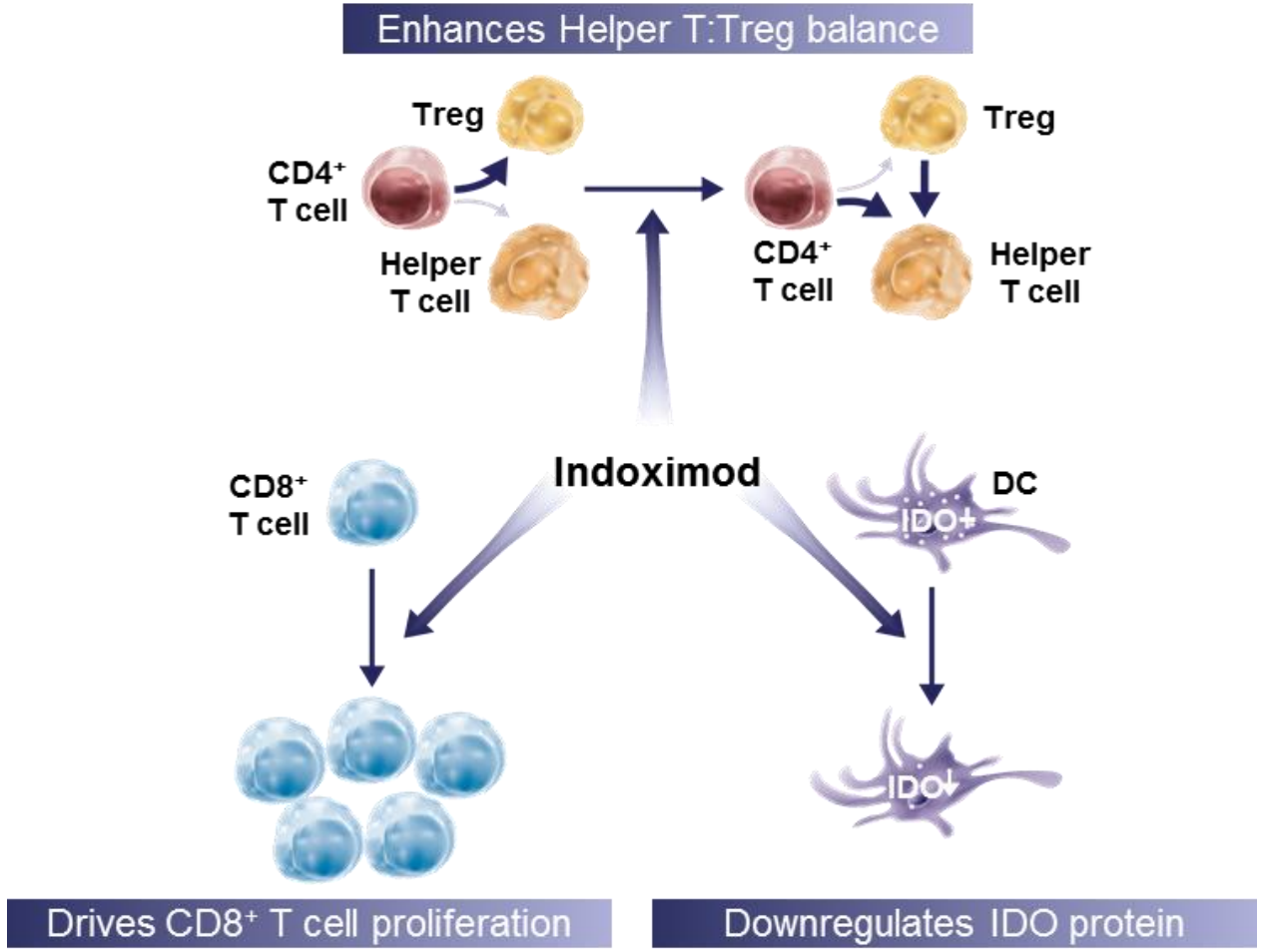



- IDO1 is highly expressed in multiple tumor types
  - Melanoma
  - NSCLC
  - Ovarian cancer
  - Pancreatic cancer
  - Colorectal cancer
  - Glioblastoma
  - Squamous cell carcinoma
  - Endometrial carcinoma
  - DLBCL
  - RCC
  - TCC
  - TNBC

IDO, indoleamine 2,3-dioxygenase; LN, lymph node; NSCLC, non-small cell lung cancer; DLBCL, diffuse large B-cell lymphoma; RCC, renal cell carcinoma; TCC, transitional cell carcinoma; TNBC, triple-negative breast cancer. Munn DH, et al. *J Clin Invest*. 2004;114(2):280-290.

# 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[1]
  - 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

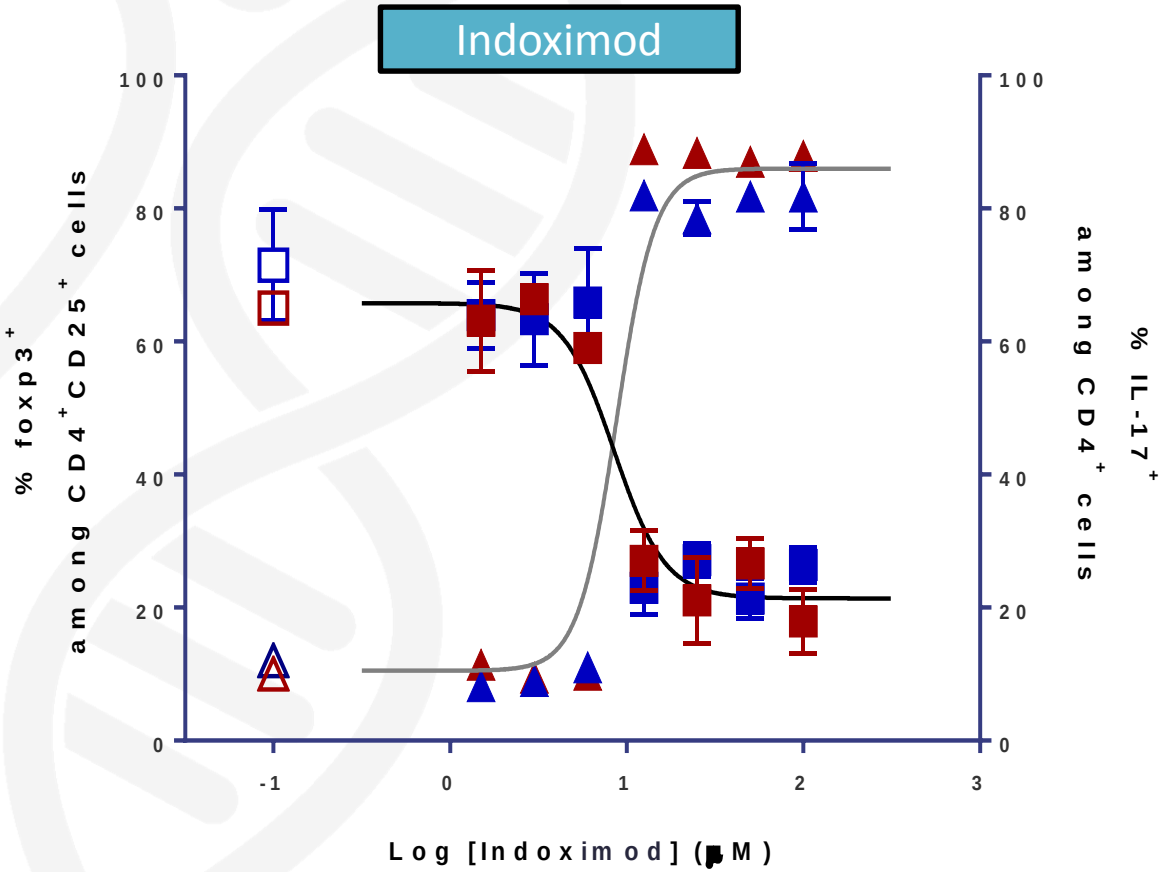


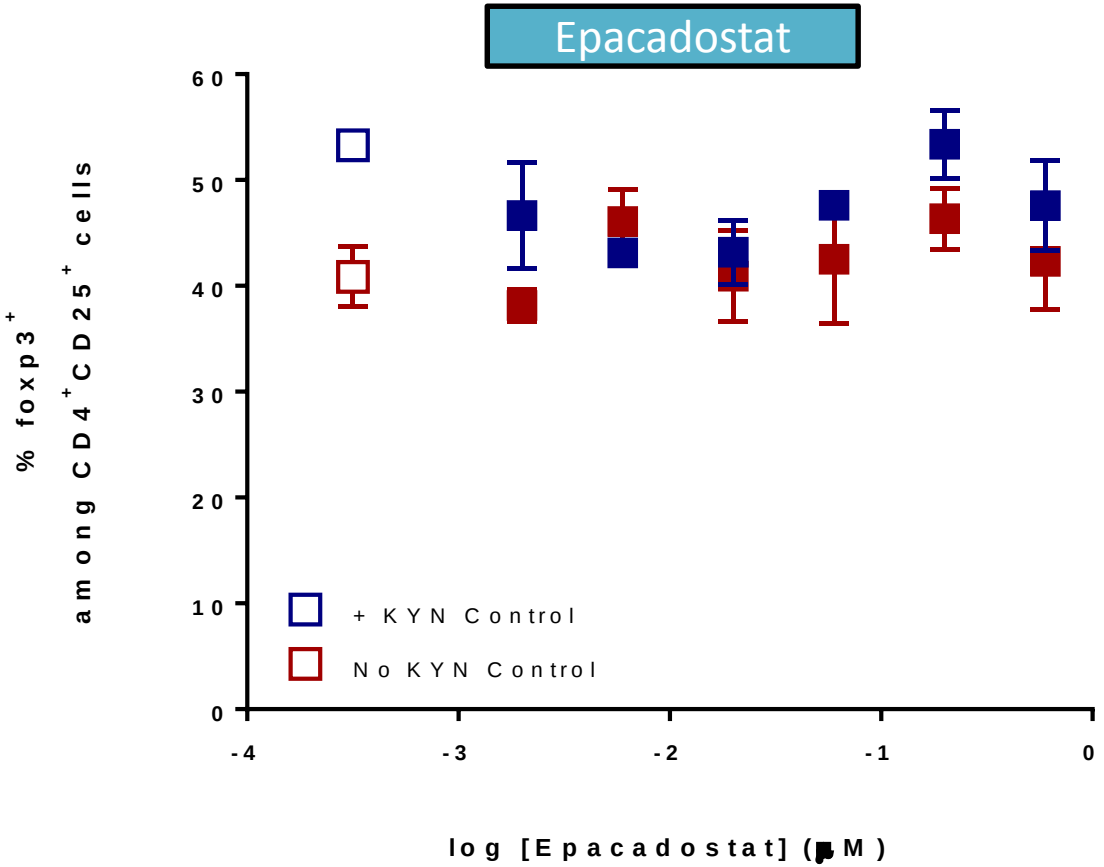

IDO, indoleamine 2,3-dioxygenase; Treg, T regulatory cell; DC, dendritic cell.

1. Brincks EL, et al. Poster presented at the AACR Annual Meeting. April 14-18, 2018. Abstract 3753.

# Indoximod vs Epacadostat: A Differentiated Mechanism of Action

## Indoximod Directly Reprograms T Regulatory Cells Helper T Cells




AACR Poster #3753 (Brincks, EL, *et al*, 2018)

# Designing Multimodal Chemo-radio-immunotherapy

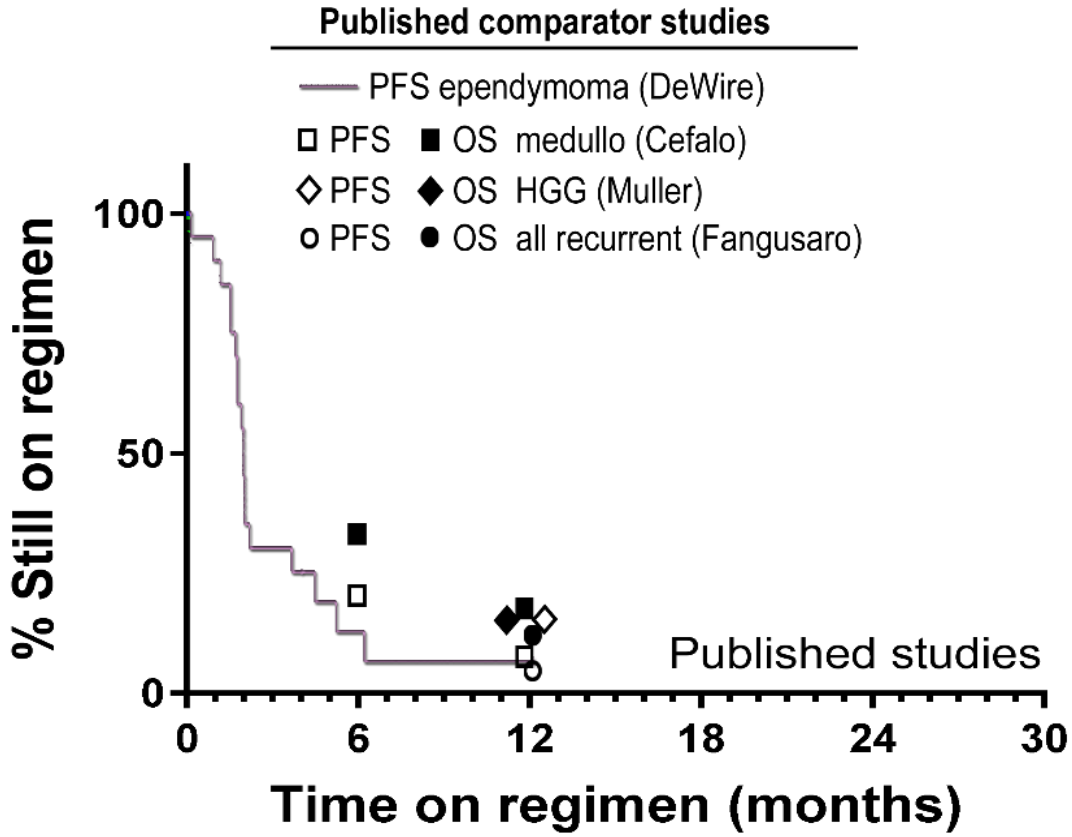
- Hypothesis
  - Immune activation (immunotherapy) can allow responsiveness to chemotherapy and radiation in patients who would otherwise be refractory
- However, this synergy with chemotherapy/radiation requires targeting the antigen-presenting step and creating a pro-inflammatory (immunogenic) tumor 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

# 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. Historical controls adapted from: DeWire M, et al. *J Neurooncol*. 2015;123:85; Cefalo G, et al. *Neuro Oncol*. 2014;16:748; Muller K, et al. *Radiat Oncol*. 2014;9:177; Fangusaro JR, et al. *J Clin Oncol*. 2017;35(suppl): abstract 10543

# 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)

MRI, magnetic resonance imaging.
Clinicaltrials.gov (NCT02502708).

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

**Group 1**
- **Indoximod dose escalation (study dose, PO, twice daily on days 1-28)**
- **Temozolomide (200 mg/m$^2$/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/m$^2$/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/m$^2$/dose PO, once daily)

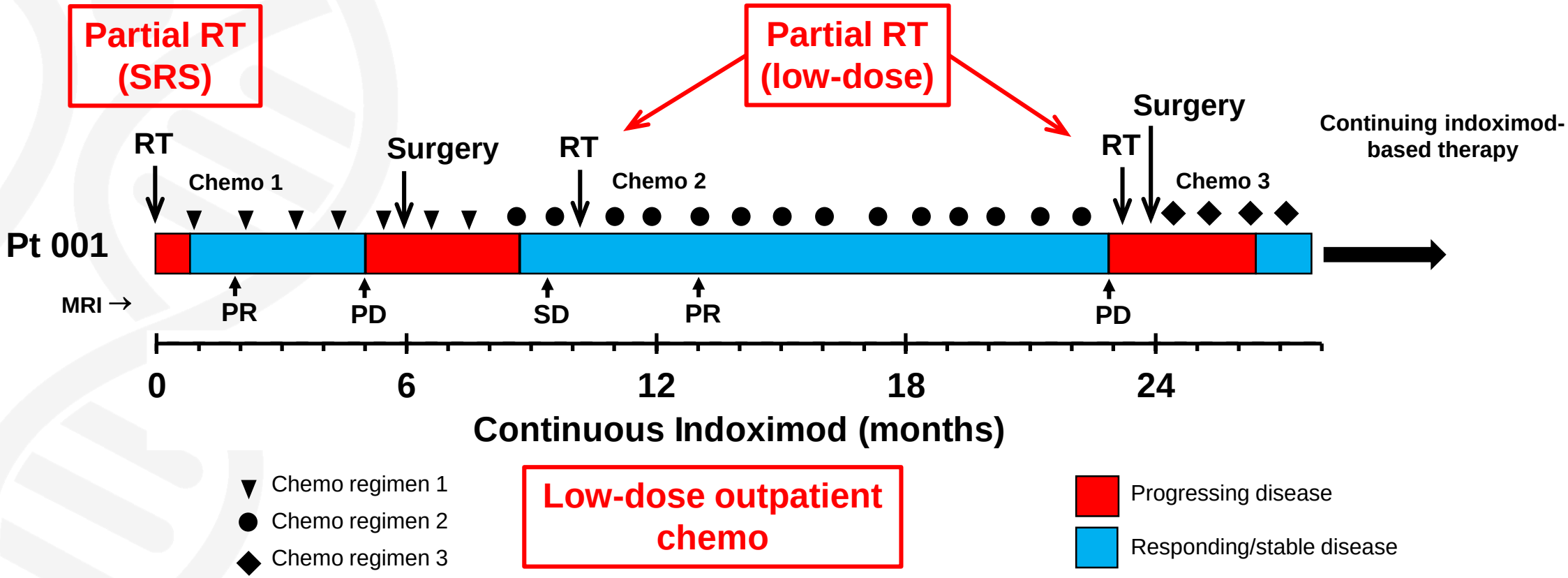
PO, orally; RP2D, recommended phase 2 dose.
Clinicaltrials.gov (NCT02502708

# Patient Demographics (Mixed Population)

| Total patients enrolled | N = 29 |
|---|---|
| Diagnosis, n (%) | |
| Ependymoma | 14 (48) |
| Malignant glioma* | 9 (31) |
| Medulloblastoma** | 6 (21) |
| Gender, n (%) | |
| Female | 10 (34) |
| Male | 19 (66) |
| Race, n (%) | |
| African American | 3 (10) |
| Caucasian | 23 (79) |
| Hispanic | 0 |
| Other | 2 (7) |
| Declined to provide | 1 (3) |
| Age, years | |
| Median | 12.5 |
| Range | 3–20 |

*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

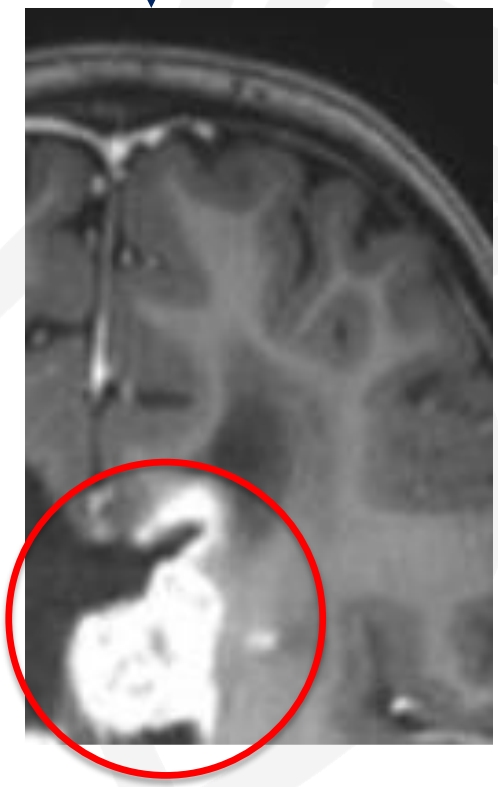



- 7-year-old with ependymoma: prolonged disease responsiveness
- Indoximod-based multimodal regimen is well tolerated

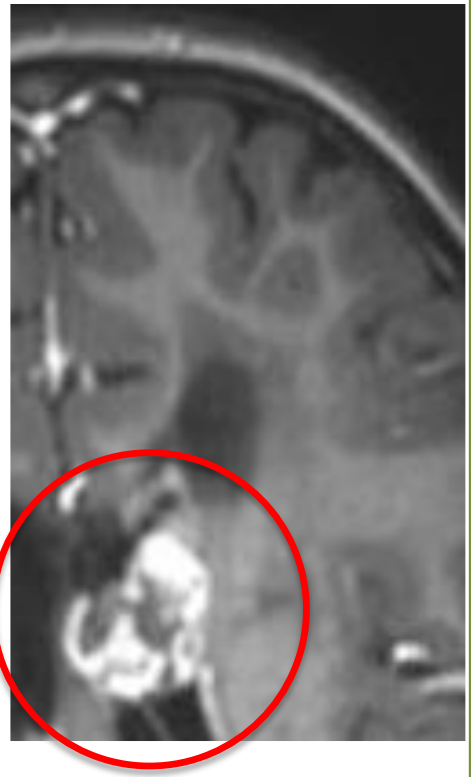
SRS, stereotactic radiosurgery; RT, radiation therapy; PR, partial response; PD, progressive disease; SD, stable disease.

# Patient 001: Continued Responsiveness Using Indoximod-based Multimodal Management

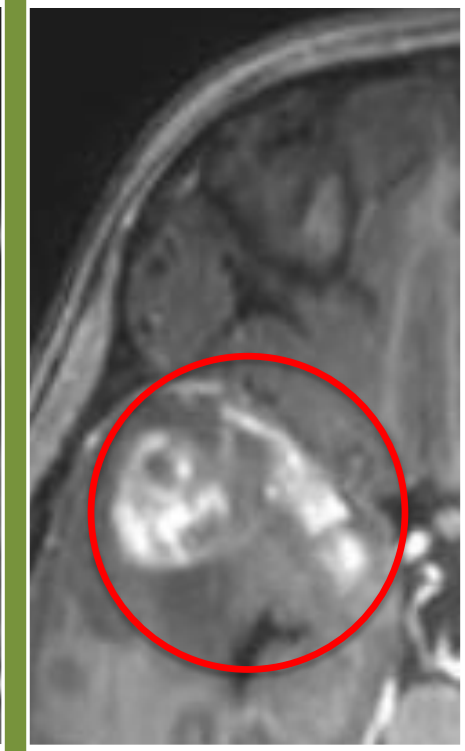
indoximod + radiation tumor (20 Gy)



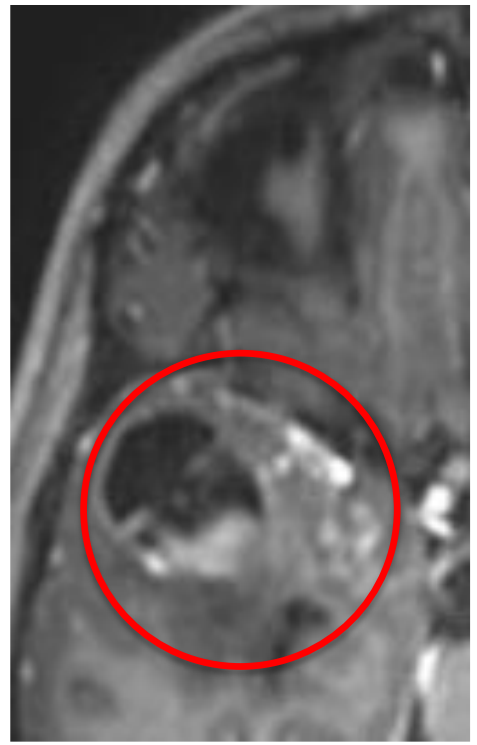
indoximod + 3rd-line chemo



**NOT TARGETED WITH NEW RADIATION**

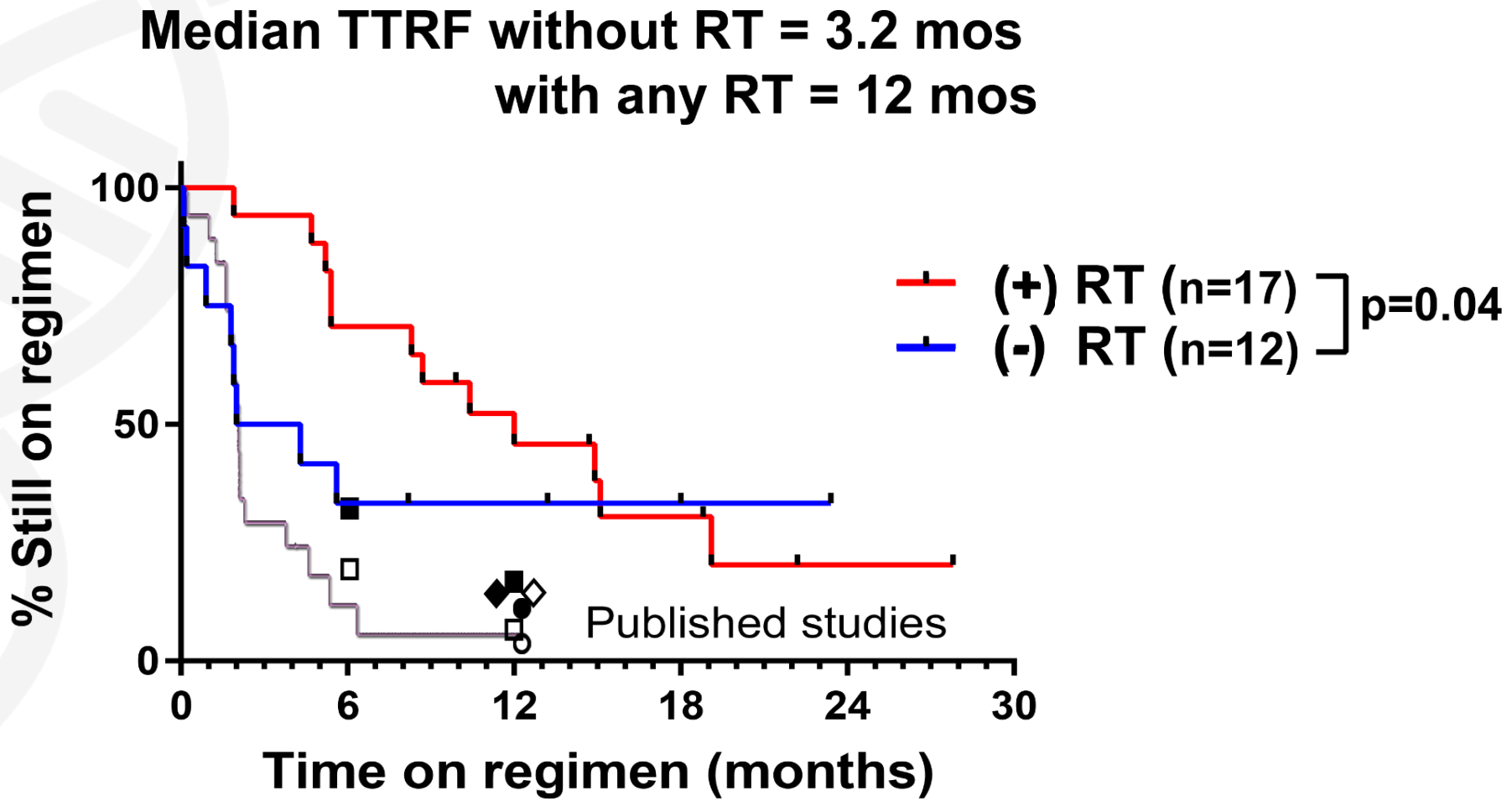


indoximod + 3rd-line chemo



Johnson, T, *et al*, AACR 2018

# Radio-Immunotherapy Improves Time to Regimen Failure (TTRF)

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Cefalo G, *et al*. *Neuro Oncol* 2014;16:748.
Muller K, *et al*. *Radiat Oncol* 2014;9:177.

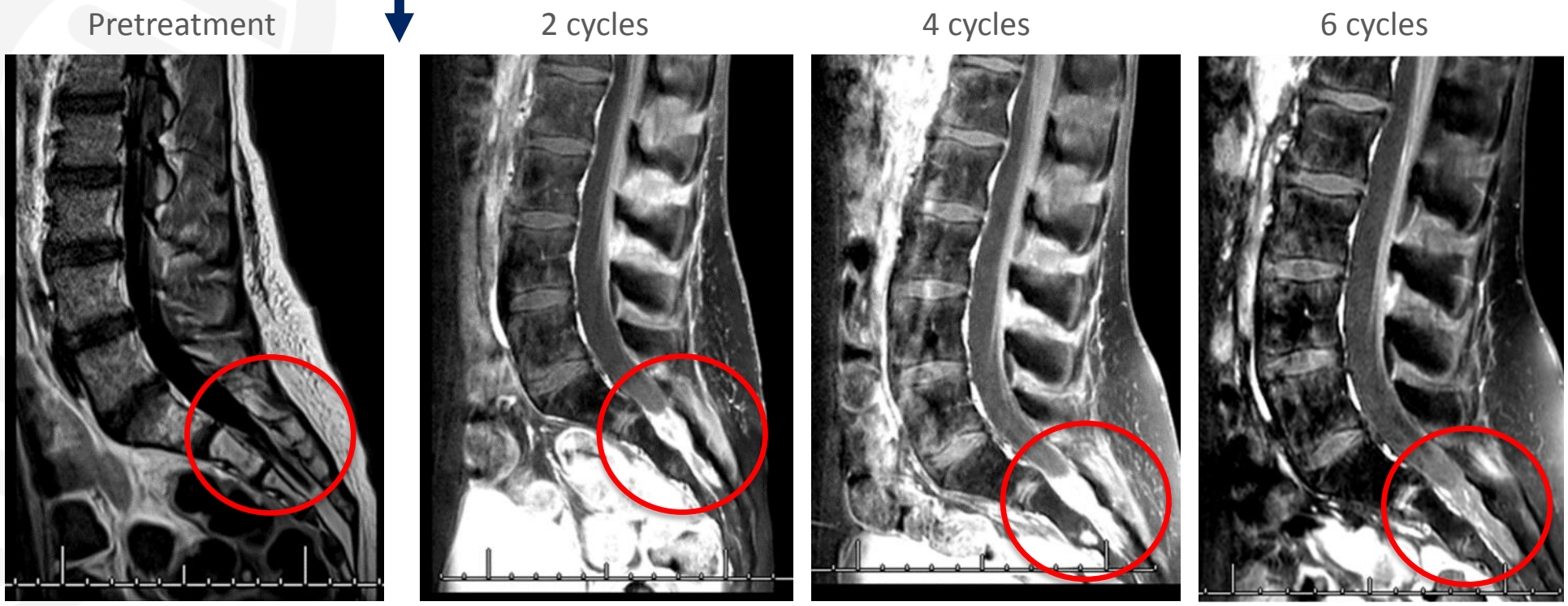
RT, radiation therapy

Fangusaro JR, et al. J Clin Oncol, 2017;35(suppl): abstract 10543.

# New Metastatic Tumor Arising While on Therapy Later Regresses

14 yo with CSF relapse of medulloblastoma

Begin indoximod + temozolomide




***Potential for late responses makes TTRF an important outcome metric***

CSF, cerebrospinal fluid; TTRF, time to regimen failure.

# 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**
- **Indoximod dose escalation (study dose, PO, twice daily on days 1-28)**
- **Temozolomide (200 mg/m$^2$/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/m$^2$/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**

→

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

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/m$^2$/dose PO, once daily)

# 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

DIPG, diffuse intrinsic pontine glioma; OS, overall survival.

1. Wolff JE, et al. *J Neurooncol*. 2012;106(2):391-397. 2. Cohen KJ, et al. *Neuro Oncol*. 2011;13(4):410-416.

# 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

DIPG, diffuse intrinsic pontine glioma.

# 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

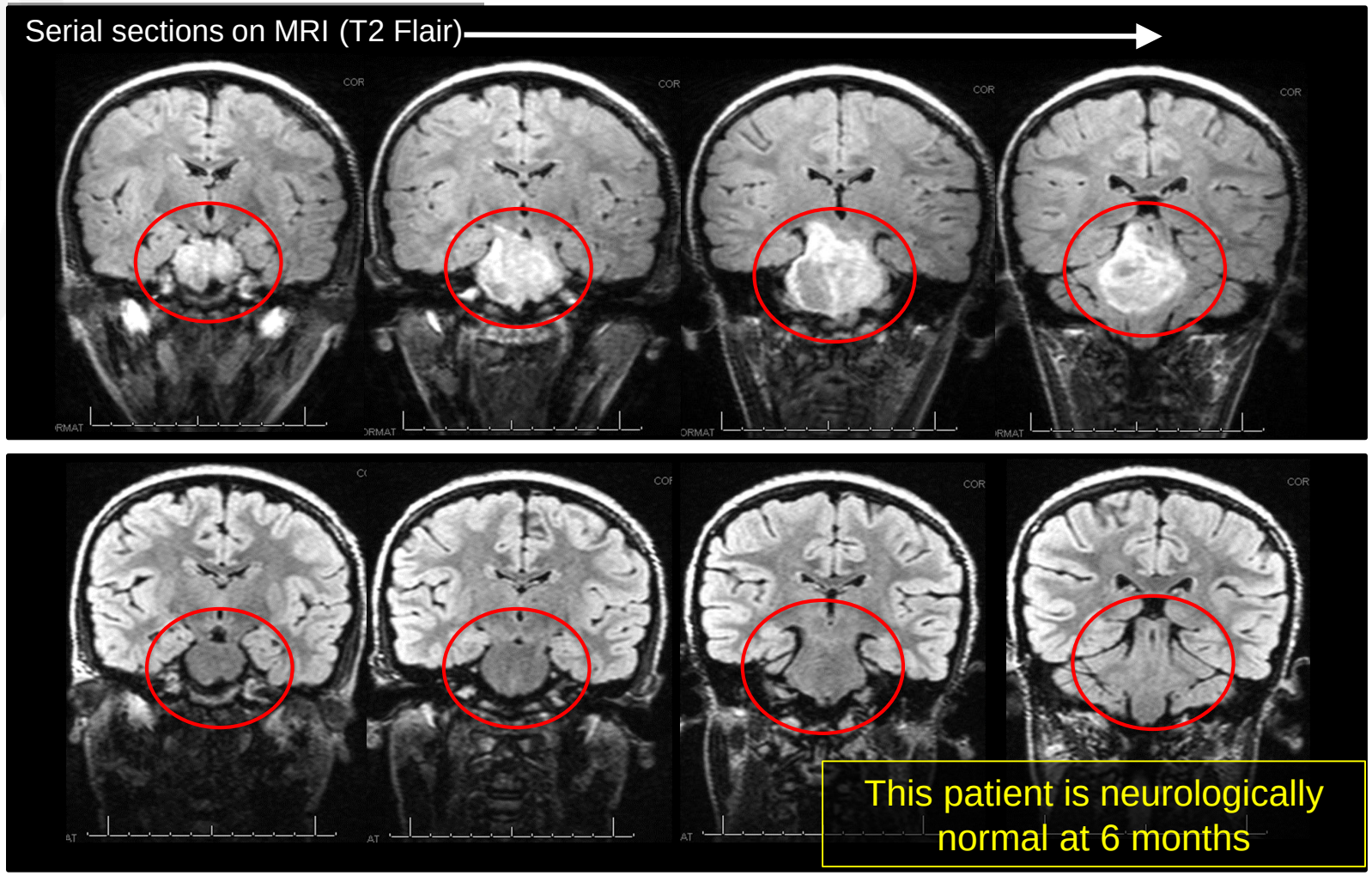
# NLG2105-037: 9.4-Year-Old Male with Newly Diagnosed DIPG

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)

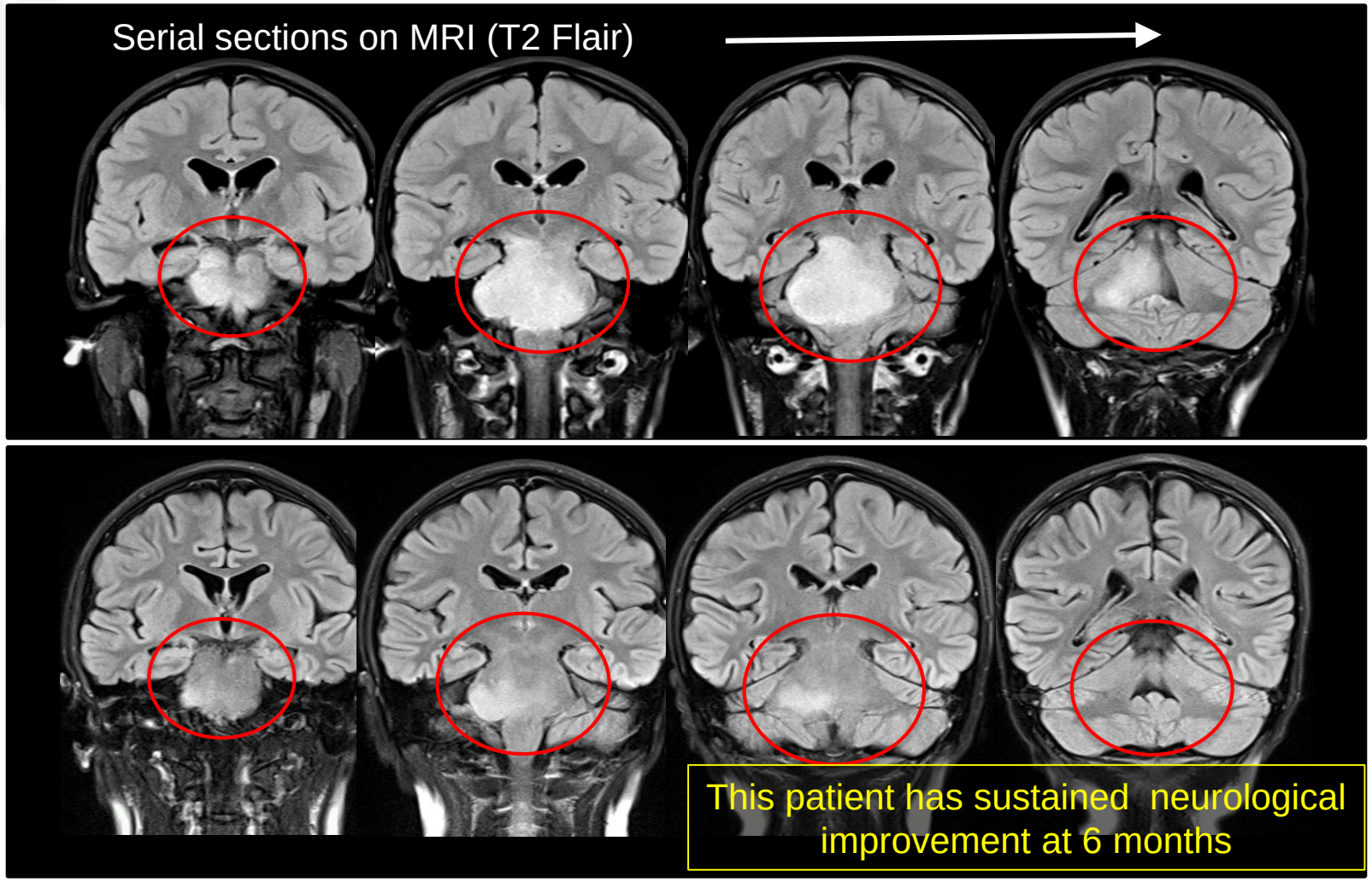



· DIPG, diffuse intrinsic pontine glioma; MRI, magnetic resonance imaging..

# NLG2105-035: 9.3-Year-Old Male with Newly Diagnosed DIPG

Baseline (pretreatment)

After 6 weeks of indoximod + radiation (54 Gy)

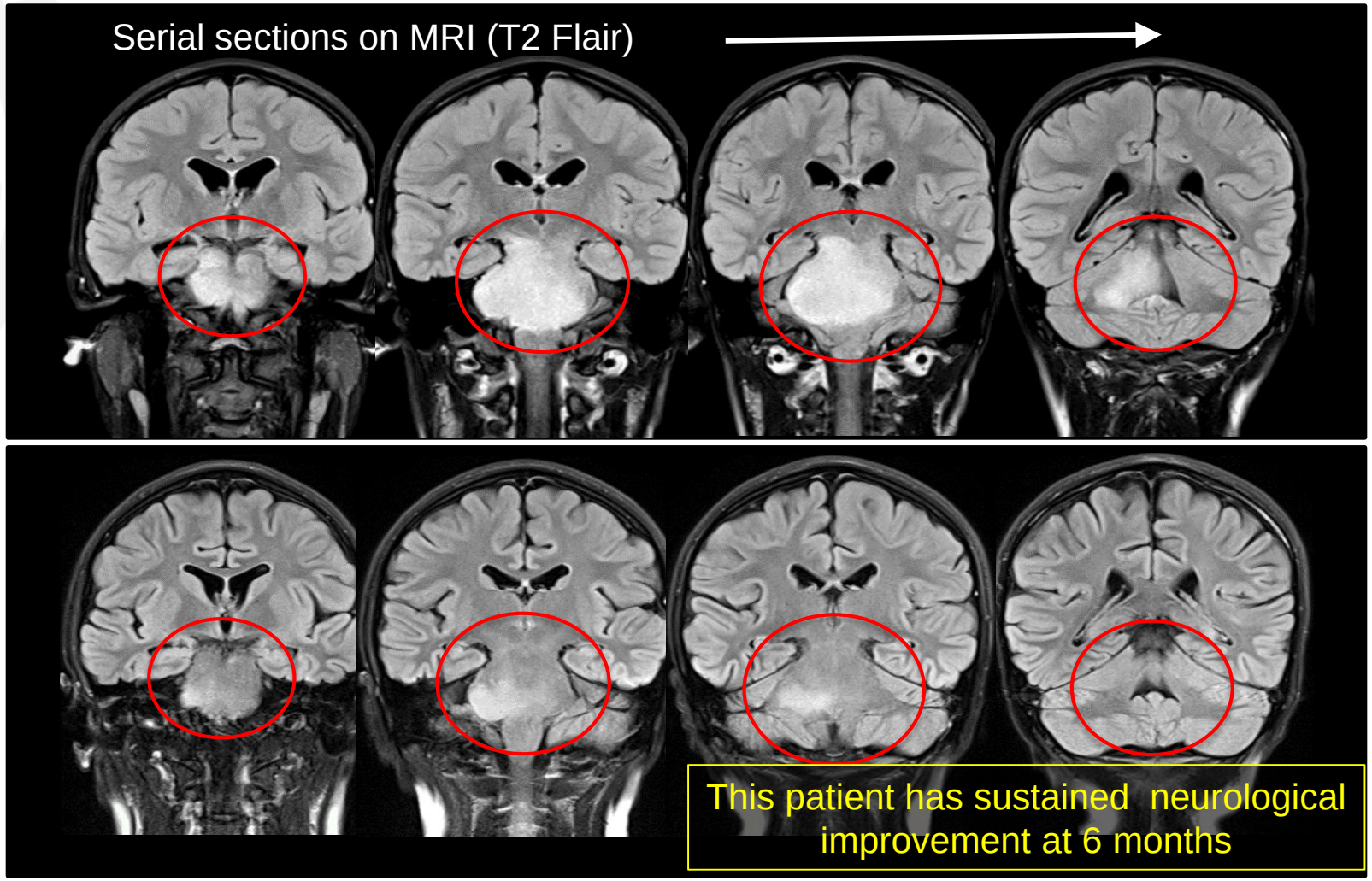



· DIPG, diffuse intrinsic pontine glioma; MRI, magnetic resonance imaging..

# Additional Newly Diagnosed DIPG Patients

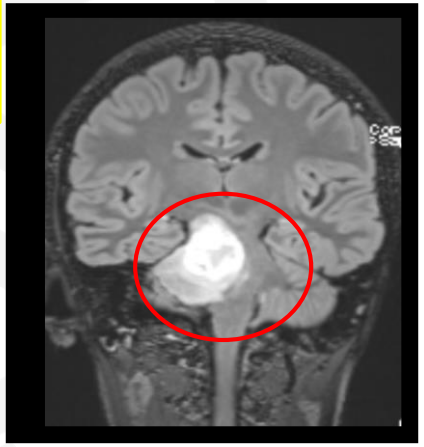
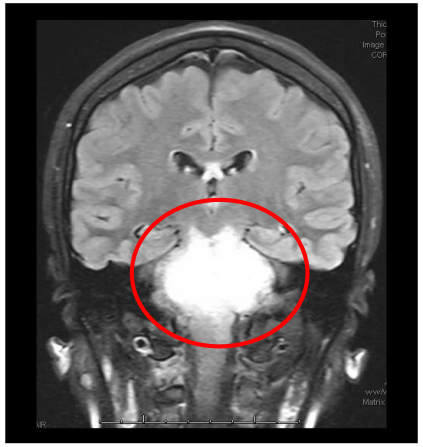
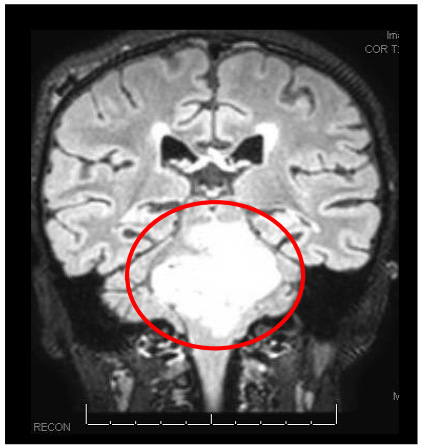
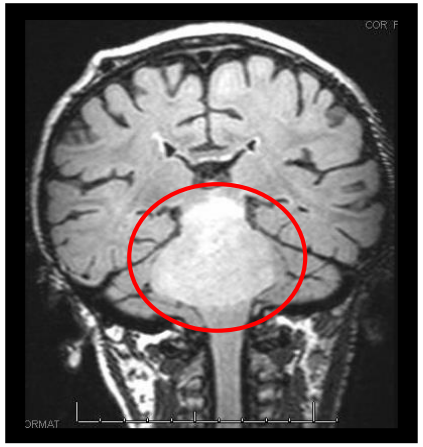
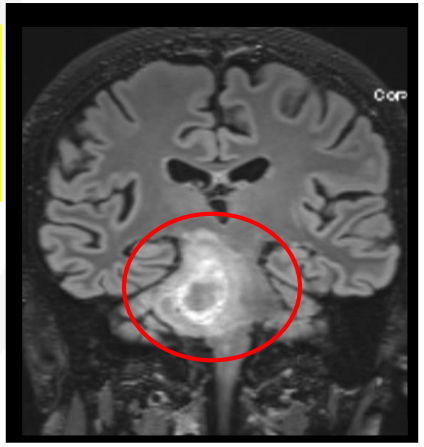
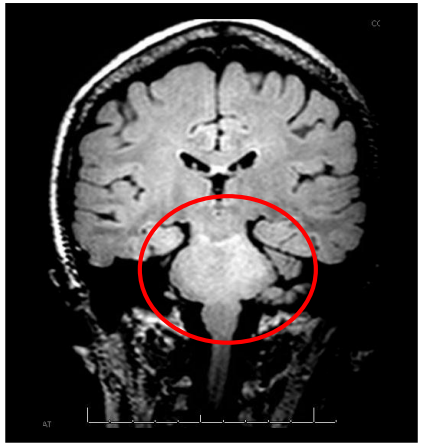
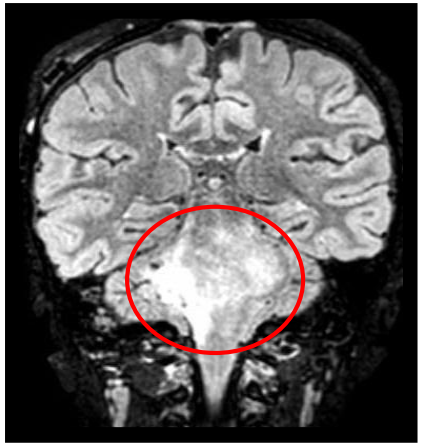
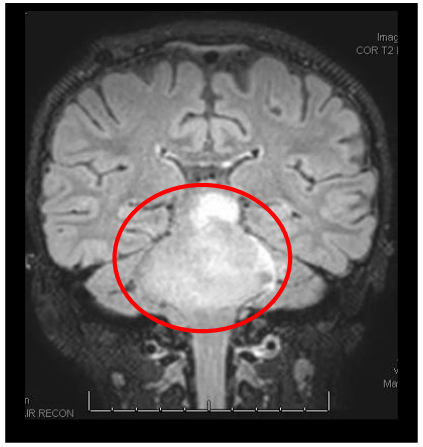
Baseline (pretreatment)

After 6 weeks of indoximod + radiation (54 Gy)




DIPG, diffuse intrinsic pontine glioma

# Additional Newly Diagnosed DIPG Patients

| | NLG2105-042<br>12 yo male | NLG2105-043<br>15 yo female | NLG2105-047<br>5 yo female | NLG2105-048<br>6 yo female |
|---|---|---|---|---|
| Baseline (pretreatment) |  |  |  |  |
| After 6 weeks of indoximod + radiation (54 Gy) |  |  |  |  |

DIPG, diffuse intrinsic pontine glioma

# 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