Indoximod-based Chemo-immunotherapy for Pediatric Patients with Brain Cancer

Presentation to POETIC

June 30, 2022 (Orlando, FL)

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Medical College of Georgia (MCG)
Georgia Cancer Center
Augusta University

Pediatric Immunotherapy Program

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Tumor-induced immune suppression

- By the time a tumor is large enough to be discovered and diagnosed
  - … it has already found a way to suppress anti-tumor immune responses

- This immune suppression is active, specific and acquired
  - … but this creates a vulnerability of the tumor
  - … if we can reverse the immune suppression using immunotherapy

Immunotherapy strategies
(not mutually exclusive)

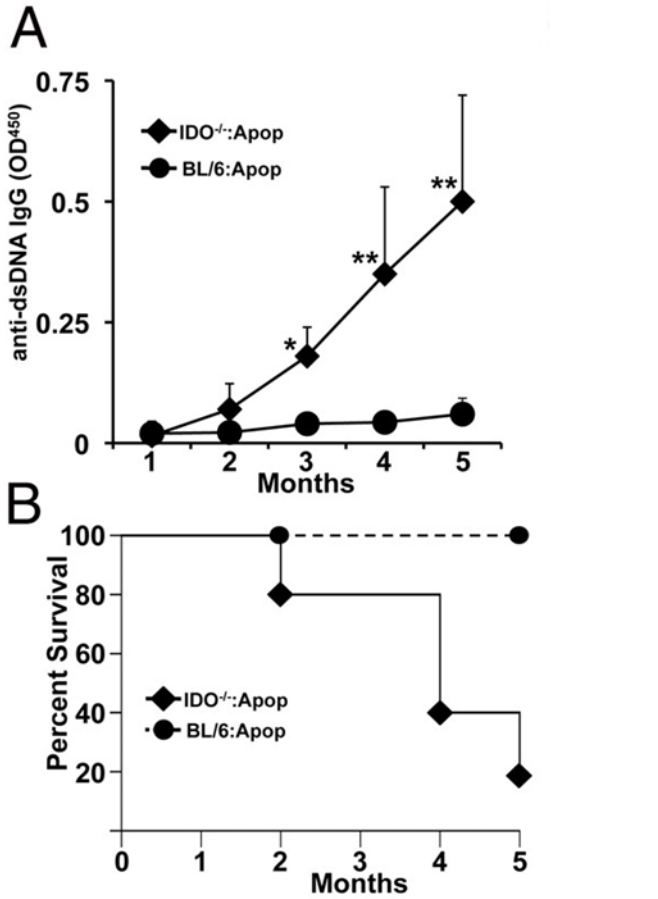
- Take the brakes off the **T cells**
  - Conventional checkpoint blockade (PD-1, CTLA-4)
  - T cells activated *ex vivo*
  - Chimeric Antigen Receptor (CAR) T cells

- Change the **tumor microenvironment** so that endogenous tumor antigens are presented in an immunogenic fashion
  - inhibit the IDO pathway (indoleamine 2,3-dioxygenase)
  - Inhibit other myeloid checkpoint pathways
  - block the activated Tregs
  - immunogenic chemotherapy and radiation

IDO suppresses the immune response to dying cells

- IDO is a natural mechanism of acquired immune tolerance
  - operates during normal pregnancy, mucosal tolerance, organ transplant, chronic infection (HIV, etc)
- IDO also plays a fundamental role in enforcing normal self-tolerance to dying cells
  - This is a natural role of IDO in the immune system (IDO expressed in APCs)
  - blocking IDO can break tolerance to even normal "self" proteins
  - fortunately normal tissues can compensate for the loss of IDO (no spontaneous autoimmunity with indoximod), but tumors cannot compensate
- We hypothesize that tumors are heavily dependent on IDO to maintain immune tolerance to the wave of dying tumor cells after chemotherapy
  - the role of IDO in driving immune tolerance to dying cells is highly relevant to the tolerance to tumor proteins after chemotherapy
  - this role of IDO is tumor agnostic (*i.e.*, any dying tumor cells can elicit IDO)
    … and chemotherapy agnostic (*i.e.*, many chemo drugs can damage the tumor)

IDO-KO mice develop lupus autoimmunity when challenged with large doses of apoptotic self cells



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Figures adapted from: Ravishankar B, *et al*. 2012. *PNAS*. **109**:3909.

Development of IDO-inhibitor drugs as immunotherapy for children

- IDO is a hard-wired mechanism of immune suppression in the immune system
- The first IDO-inhibitor drug (indoximod) was invented at the Medical College of Georgia (Augusta University)

  ... now there are multiple drugs in clinical trials
- In pediatrics, **we are conducting the only trials of IDO-inhibitor drugs in children**

Pediatric Immunotherapy Program at Augusta University

Theodore S. Johnson, MD, PhD

Director, Clinical Trials Program
Pediatric Immunotherapy

David H. Munn, MD

Director, Basic Research Program
Pediatric Immunotherapy

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Clinical Trials Program

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- Kimberly Gray, CCRP
- Dana Cook, RN
- Taylor King, RN
- Brittany Chubb, MPH
- Amy Pizio-Moore, CPHT

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IDO-inhibitor trials for children

Indoximod plus chemotherapy +/- radiation

- NLG2105 – Phase 1 first-in-pediatrics (completed)
- GCC1949 – Phase 2 (NIH-funded R01; multi-center; IND-holder T. Johnson)
  - Enrolled 40 patients, target enrollment 121 patients
- GCC1953 – compassionate-use protocol (IND-holder- T. Johnson)

Ibrutinib and Indoximod plus chemotherapy

- GCC2020 – first patient enrolled Feb. 2022 (IND-holder T. Johnson)

NLG2105
(first-in-children clinical trial)

"Phase 1 trial of indoximod in combination with temozolomide-based therapy for children with progressive primary brain tumors" (NCT02502708)

Principal Investigator: Theodore Johnson, M.D., Ph.D.

Industry Sponsored (IND# 120813) (Lumos Pharma, Inc.)

Foundation Funding: ALSF (BTIG), CKc, Press On, NNCCF, *etc*.

Clinicaltrials.gov #: NCT02502708

Investigational Agent: Indoximod

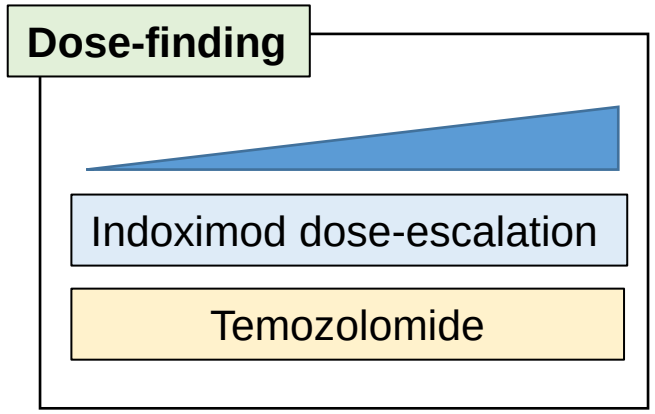
Enrollment Target: 54-66 patients

Actual Enrollment: 81 patients

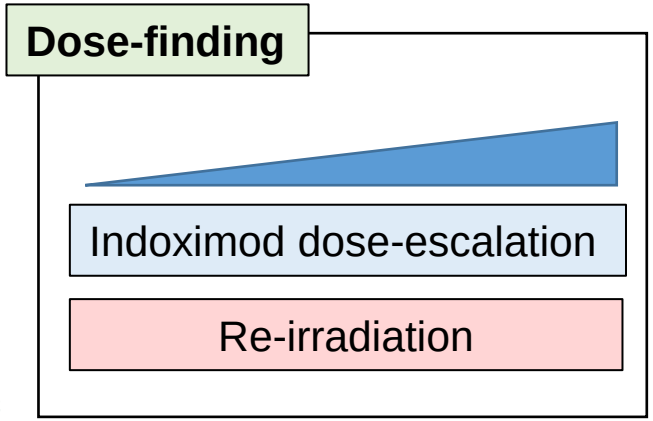
NLG2105 pediatric phase 1 study (completed)

Indoximod plus Temozolomide in recurrent pediatric brain tumors

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



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



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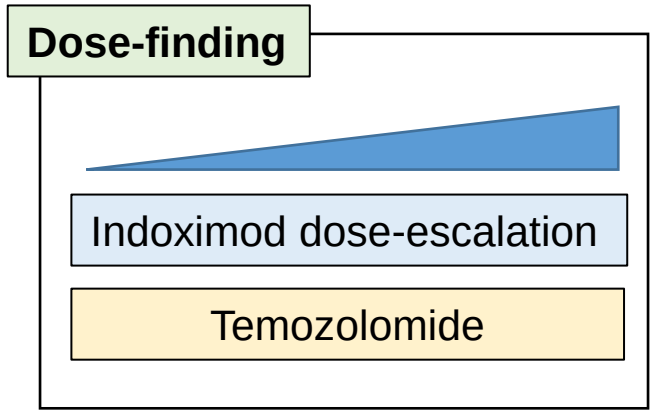
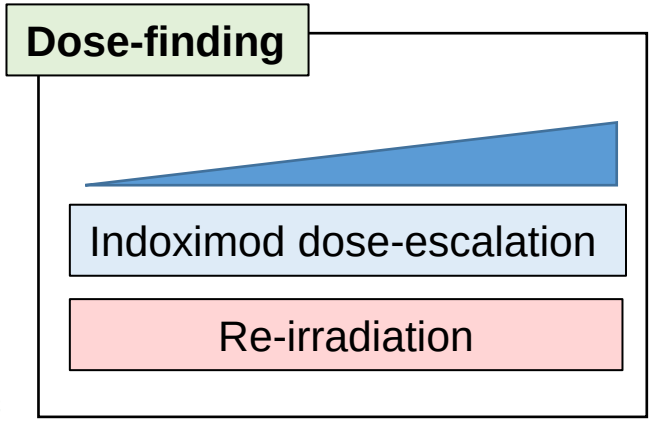
NLG2105 pediatric phase 1 study (completed)

Indoximod plus Temozolomide in recurrent pediatric brain tumors

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



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



Group 2: expansion cohorts – progressive CNS tumors

- Ependymoma (relapsed)
- Medulloblastoma (relapsed)
- Glioblastoma (relapsed)
- Other CNS tumor (relapsed)

Indoximod RP2D

Temozolomide

+/- Re-irradiation

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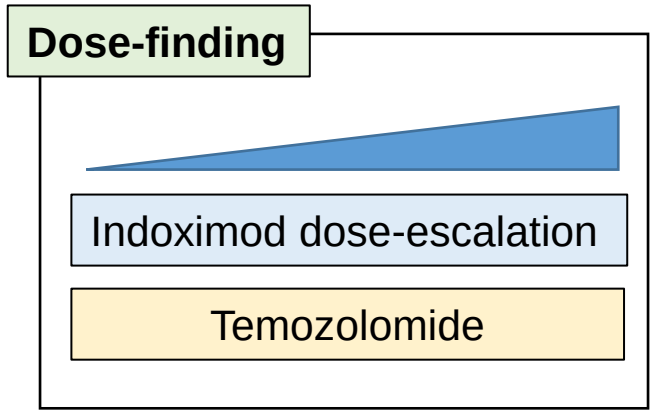
NLG2105 pediatric phase 1 study (completed)

Indoximod plus Temozolomide in recurrent pediatric brain tumors

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

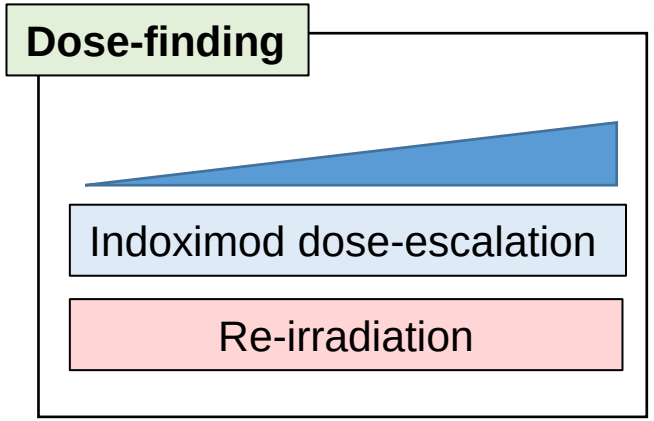


Group 2: expansion cohorts – progressive CNS tumors

- Ependymoma (relapsed)
- Medulloblastoma (relapsed)
- Glioblastoma (relapsed)
- Other CNS tumor (relapsed)

→ Indoximod RP2D + Temozolomide + +/- Re-irradiation

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



Group 3b: newly-diagnosed DIPG

- DIPG

→ Indoximod RP2D + Up-front Radiation → Indoximod RP2D + Temozolomide

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NLG2105 patient demographics

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

NLG2105 patient demographics

	All participants (n=81)
Lansky or Karnofsky performance score	
90-100	37 (46%)
70-80	29 (36%)
50-60	15 (19%)
Tumor diagnosis	
Ependymoma, relapsed	27 (33%)
Medulloblastoma, relapsed	13 (16%)
Glioblastoma, relapsed	16 (20%)
Other high grade glioma, relapsed*	3 (4%)
Other CNS malignancy, relapsed†	9 (11%)
DIPG, newly diagnosed‡	13 (16%)
Steroid treatment while on study	
Treated with any corticosteroid	54 (67%)
Dexamethasone at any time	50 (62%)

*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.

NLG2105 patient demographics

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

Patients experiencing high-grade adverse events regardless of attribution to study therapy

	Indoximod with temozolomide, Groups 1 and 2 (n=54)		Indoximod with up-front radiation then indoximod with temozolomide, Groups 3a and 3b (n=27)	
	Grade 3	Grade 4	Grade 3	Grade 4
Any event	41 (76%)	23 (43%)	23 (85%)	13 (48%)
Vomiting	8 (15%)	..	1 (4%)	..
Anemia	7 (13%)	2 (4%)	4 (15%)	1 (4%)
Ataxia	6 (11%)	..	2 (7%)	..
Hydrocephalus	6 (11%)	1 (2%)	1 (4%)	1 (4%)
Platelet count decreased	5 (9%)	14 (26%)	4 (15%)	8 (30%)
Dehydration	4 (7%)	..	1 (4%)	..
Headache	4 (7%)	..	1 (4%)	..
Lymphocyte count decreased	4 (7%)	1 (2%)	3 (11%)	2 (7%)
Seizure	4 (7%)	1 (2%)	..	..
Fatigue	3 (6%)	..	..	..
Gait disturbance	3 (6%)	..	3 (11%)	..
Muscle weakness, generalized	3 (6%)	..	3 (11%)	..
Neutrophil count decreased	3 (6%)	5 (9%)	3 (11%)	5 (19%)
White blood cell decreased	3 (6%)	..	4 (15%)	2 (7%)
Weight gain	2 (4%)	..	2 (7%)	..
Febrile neutropenia	2 (4%)	2 (4%)	1 (4%)	1 (4%)
Muscle weakness, localized	2 (4%)	..	5 (19%)	..
Paresthesia	2 (4%)	..	2 (7%)	..
Respiratory failure	..	3 (6%)	..	..
Suicidal ideation	..	..	3 (11%)	..
Hypotension	..	..	2 (7%)	..

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.

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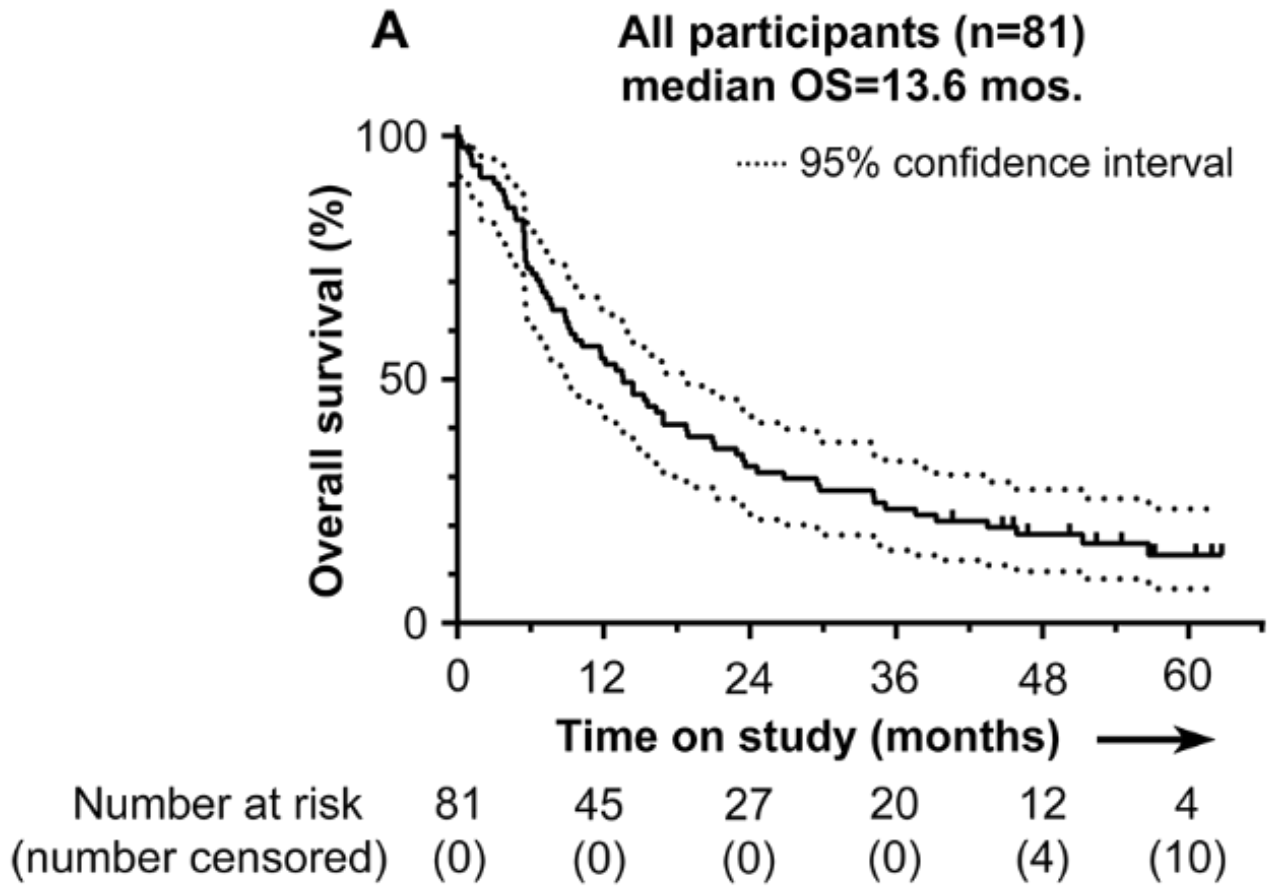
Favorable outcome with indoximod-based therapy



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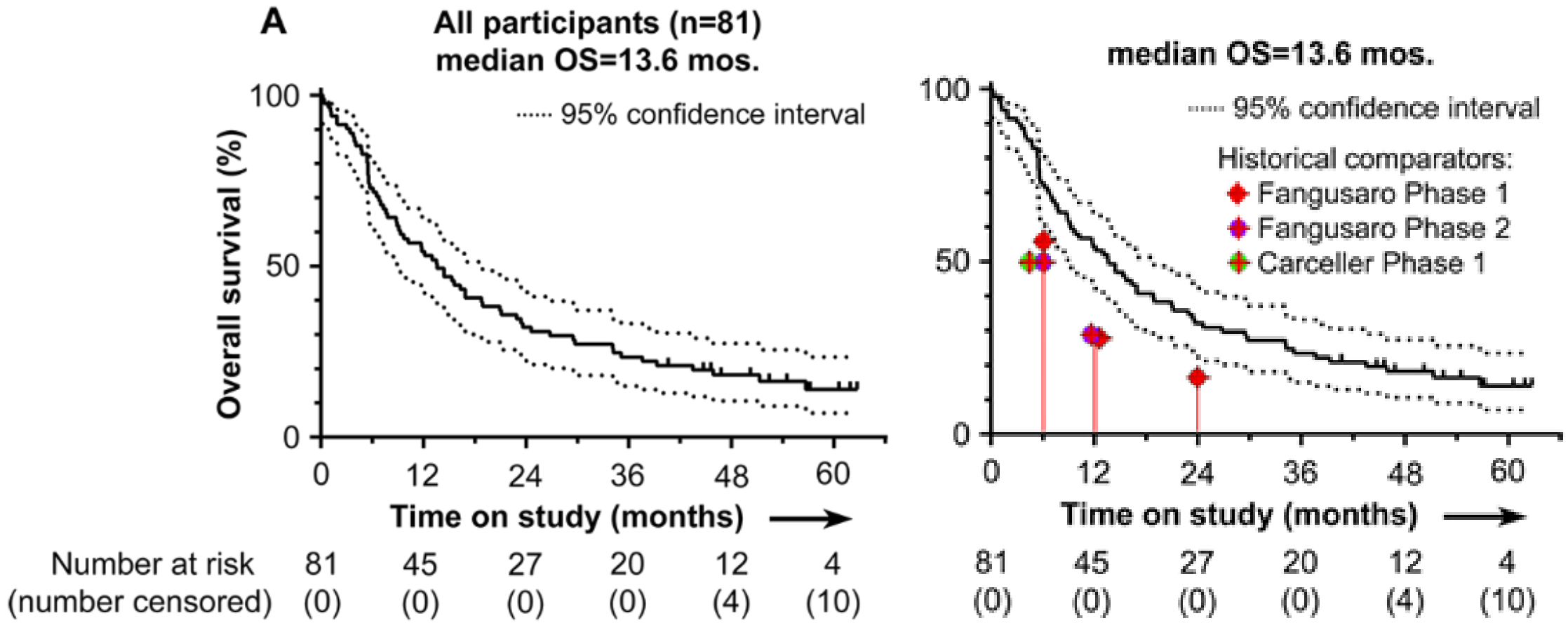
Favorable outcome with indoximod-based therapy



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Historical controls adapted from:
Fangusaro J, *et al.* 2021. *Pediatr Blood Cancer*. 68:e28756.
Fangusaro J, *et al.* 2021. *Front. Oncol.* 11:660892.
Carceller, F, *et al*. 2018. *Journal of Neuro-Oncology.* 137:83.

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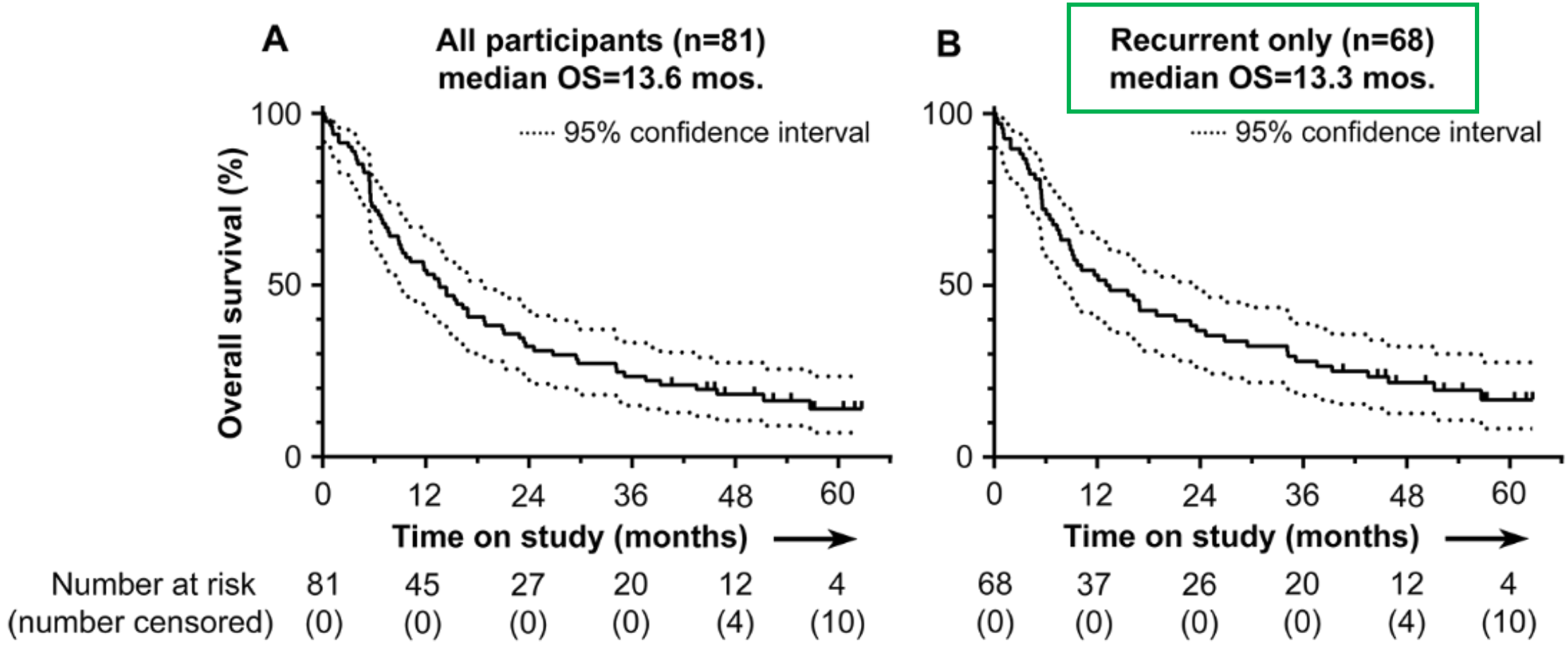
Favorable outcome with indoximod-based therapy



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Favorable outcome with indoximod-based therapy

- 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)

Favorable outcome with indoximod-based therapy

- Median overall survival, all patients – 13.6 months (n=81)
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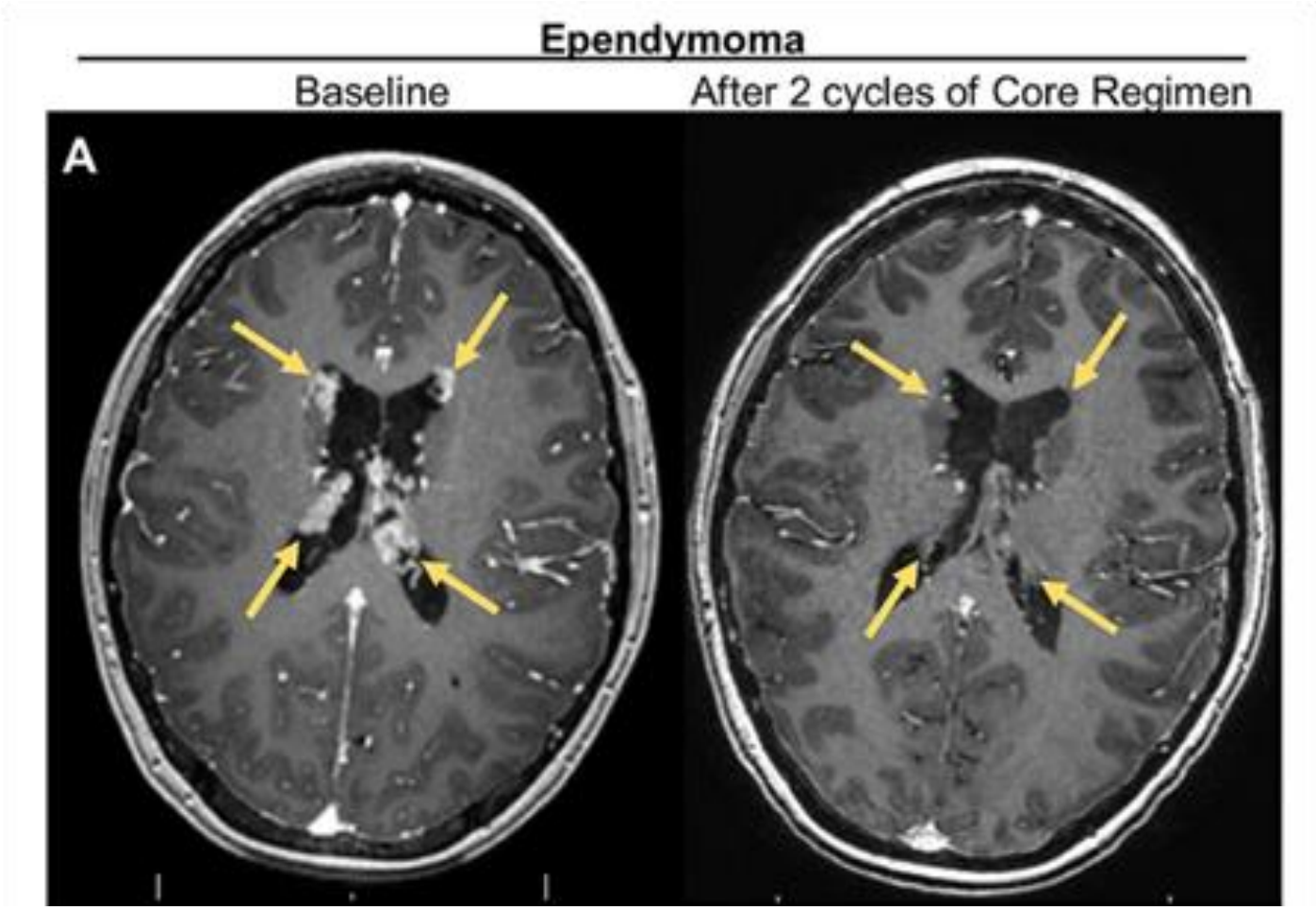
  - **Medulloblastoma** (relapsed) – 21.1 months (n=13)
  - **High-grade glioma** (relapsed) – 6.5 months (n=19)
  - **DIPG** (treatment-naïve) – 14.4 months (n=13)
- Patients who crossed-over to Group 4 after progression

  Indoximod + oral metronomic cyclophosphamide and etoposide

  Median OS since study entry – 34.7 months (n=18)

Responses with indoximod plus temozolomide



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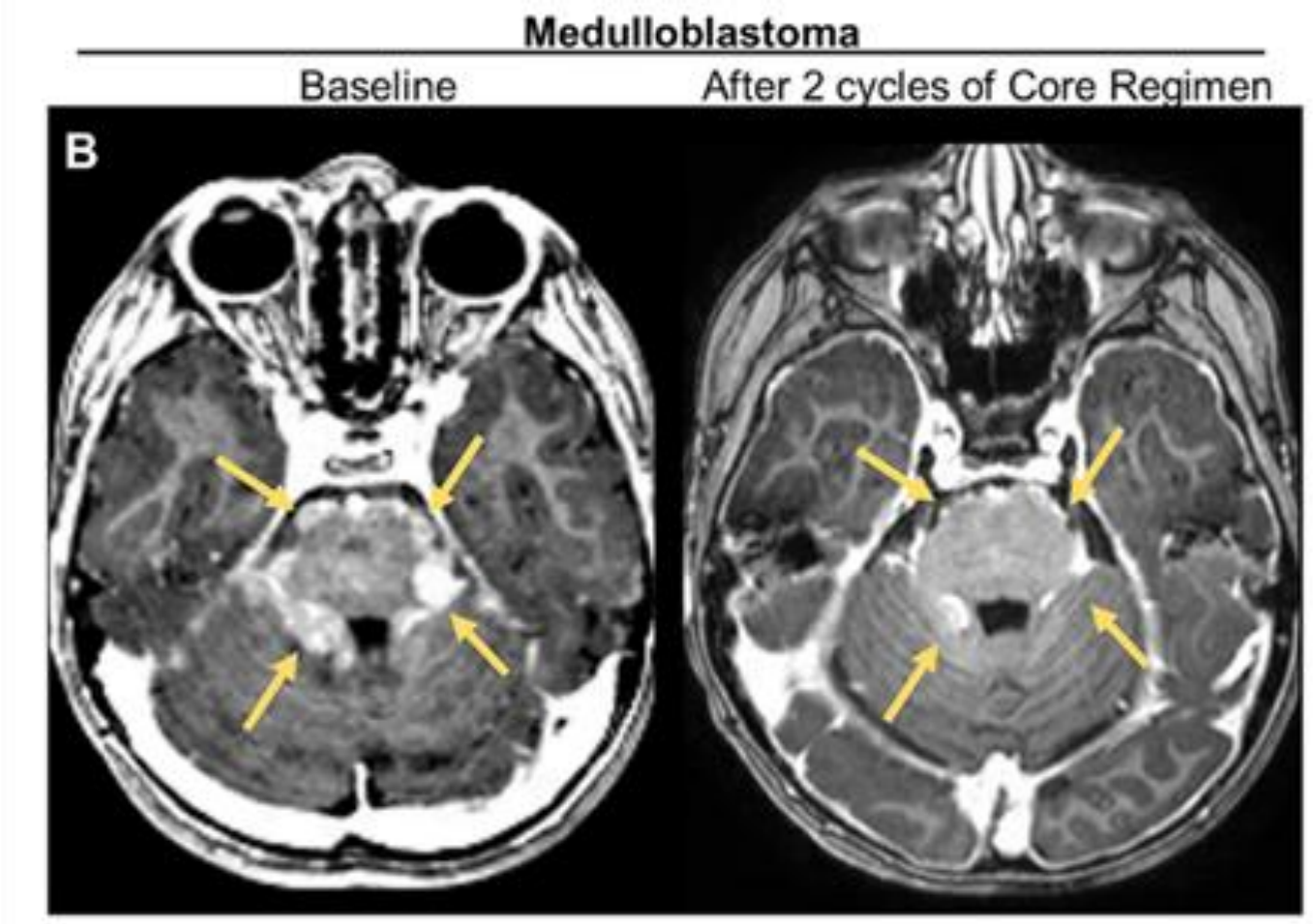
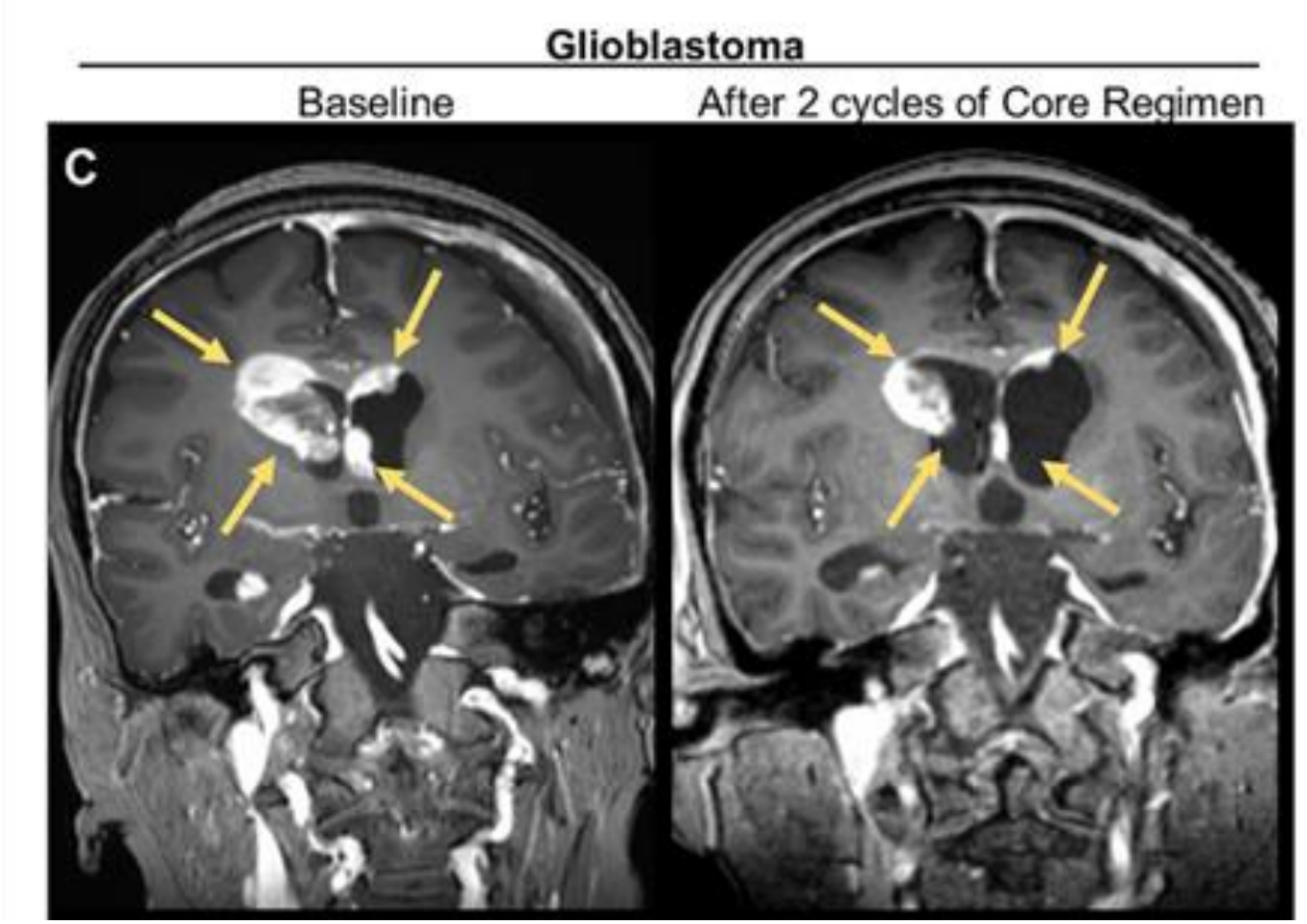
Responses with indoximod plus temozolomide



Responses with indoximod plus temozolomide



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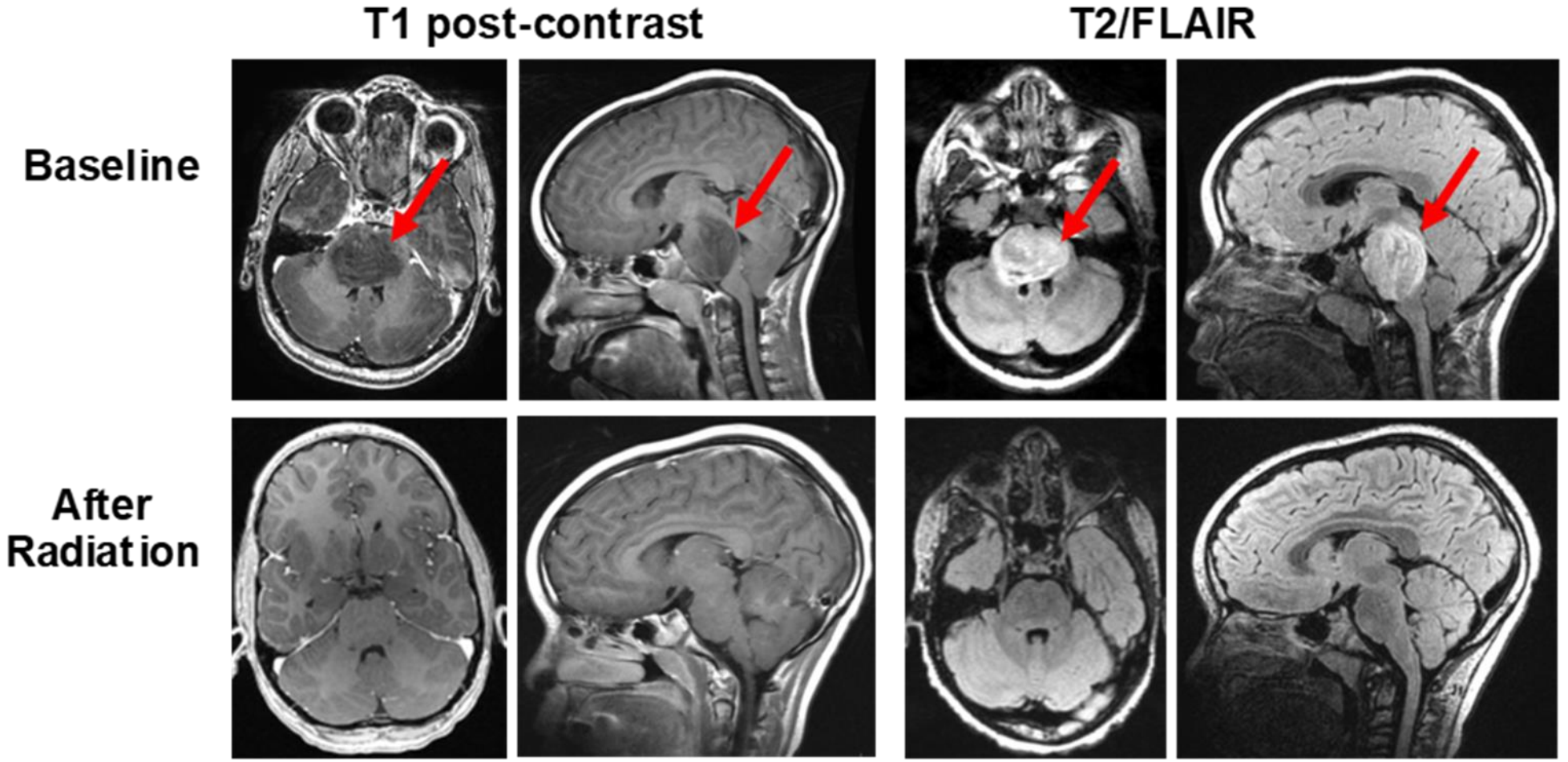
Responses after indoximod plus radiation (DIPG patient #12)



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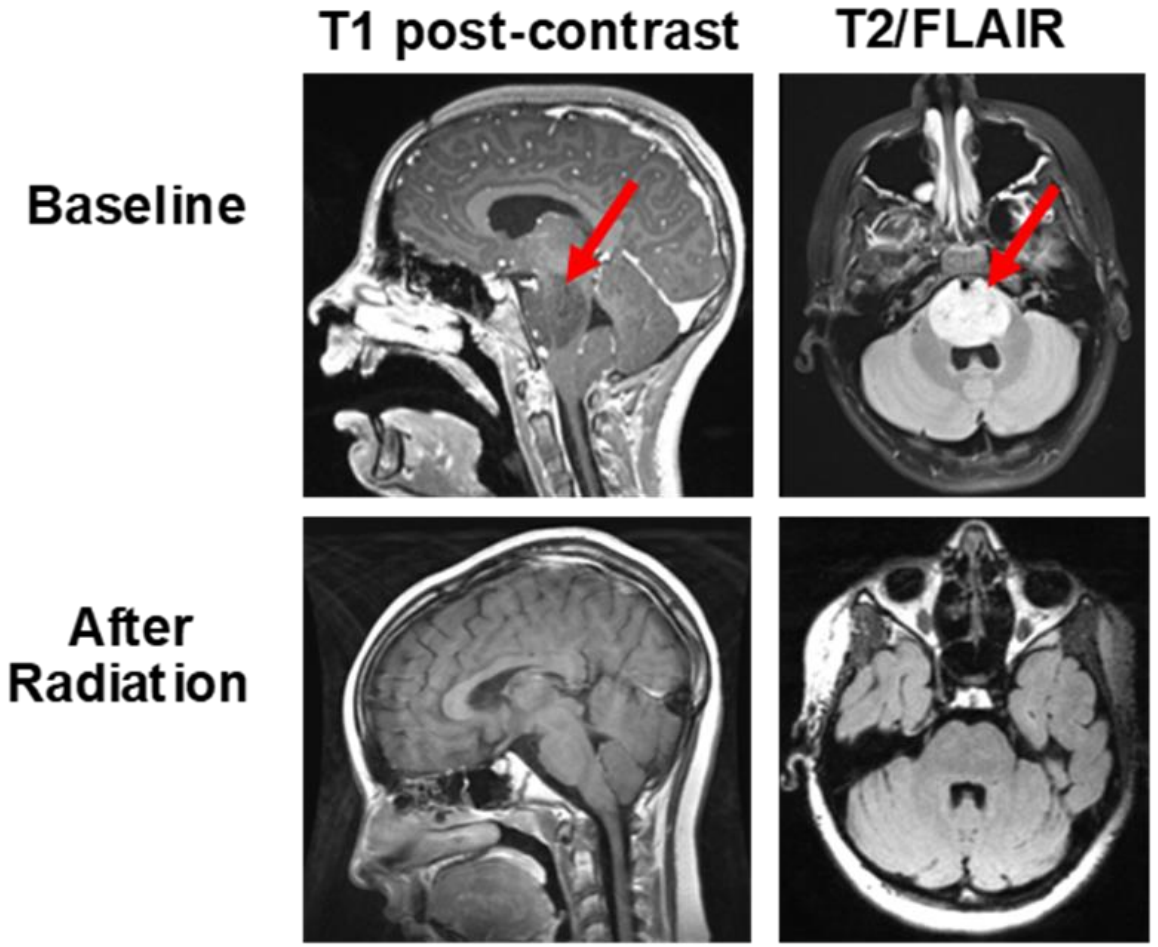
Responses after indoximod plus radiation (DIPG patient #13)



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GCC1949 Clinical Trial

"Phase 2 trial of indoximod with chemotherapy and radiation for children with progressive brain tumors or newly diagnosed DIPG" (NCT04049669)

Sponsor-Investigator: Theodore Johnson, M.D., Ph.D.

Investigator-initiated IND issued (Dr. Johnson)

NIH Funding: NCI R01CA229646 (MPI: Johnson and Munn)

Foundation Funding: CKc, ALSF (AMM), Press On, NNCCF, Halsey, etc

Clinicaltrials.gov #: NCT04049669

Investigational Agent: Indoximod

Enrollment Target: 121 evaluable patients (140 total patients)

GCC1949 phase 2 trial - experimental design

BASIC DESIGN AND ENTRY CRITERIA:

Phase 2 trial using indoximod-based chemo-radio immunotherapy for patients age 3 to 21 years with the follow diagnoses:

Cohort 1 (A,B):	progressive glioblastoma	(2x13 = 26 patients)
Cohort 2 (A,B):	progressive medulloblastoma	(2x13 = 26 patients)
Cohort 3 (A,B,C):	progressive ependymoma	(3x13 = 39 patients)
Cohort 4:	newly-diagnosed DIPG	(30 patients)
	Total evaluable patient accrual	121 patients

Sub-cohorts B and C are treated with up-front radiation/indoximod

“Adaptive Management” – cross-over salvage algorithm

as used in NLG2105 Phase 1, and now on-going pediatric brain-tumor Phase 2 (GCC1949)

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

The **problem** with this, however, is that it does not deal with the additional mechanisms of immunosuppression ...

... hence the search that led us to search for synergistic checkpoints

Taking it to the next level ...

- Indoximod-based chemo-immunotherapy is very encouraging

  ... significantly better than other available Phase 1 treatments in these patients

- however, some patients are resistant from the start

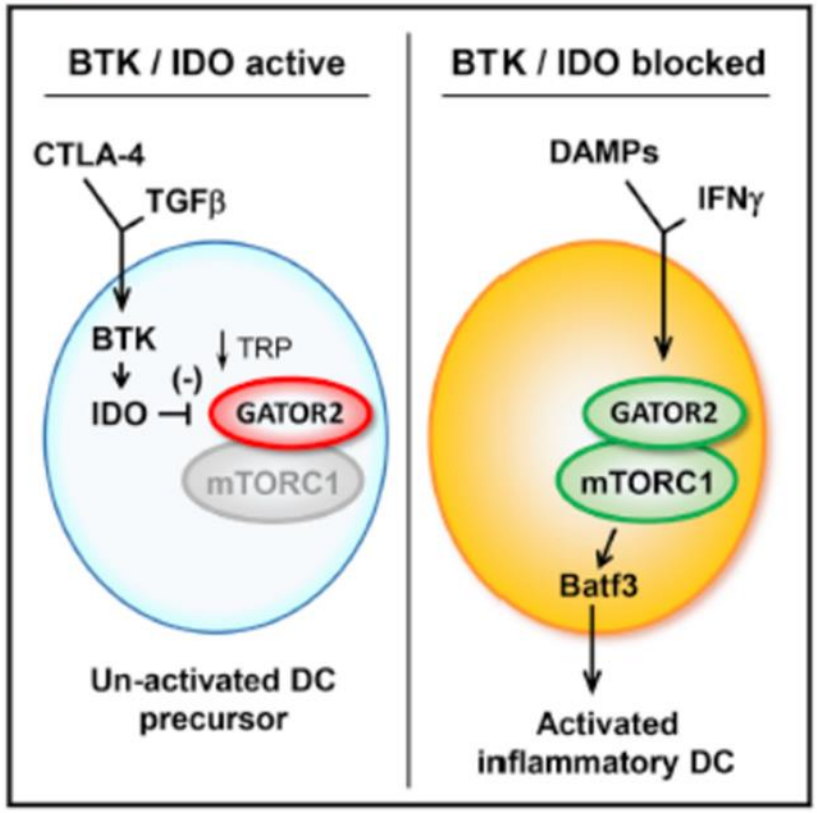
  ... and even patients who respond dramatically will eventually escape and begin to progress

- Hypothesis: there must be additional immuno-suppressive pathways that allow “escape” (acquired resistance) to IDO-inhibitor drugs

Immunity

Inhibition of the BTK-IDO-mTOR axis promotes differentiation of monocyte-lineage dendritic cells and enhances anti-tumor T cell immunity

Graphical abstract



Authors

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dmunn@augusta.edu

In brief

Dendritic cells (DCs) in tumors are often dysfunctional, failing to effectively cross-present tumor antigens following chemotherapy. Sharma et al. reveal a pathway consisting of the kinase BTK and the tryptophan-depleting enzyme IDO that suppresses the activation of monocyte-lineage DCs by inhibiting amino acid-sensitive mTORC1 signaling. Pharmacological blockade of this pathway promotes the differentiation of inflammatory DCs and enhances antitumor T cells responses.

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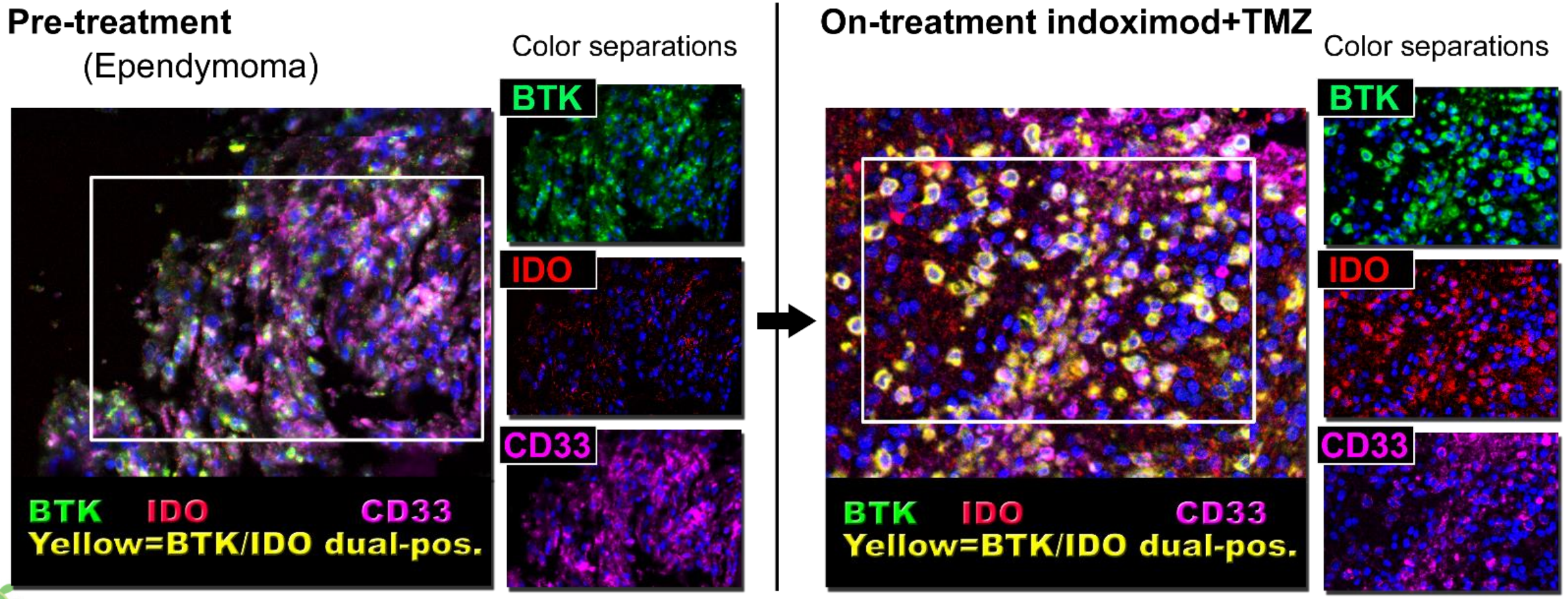
Figures adapted from: Sharma, M., *et al.* 2021. *Immunity*. 54:2354–2371.

On-treatment biopsy – ependymoma after 2 cycles of indoximod + temozolomide

Upregulation of BTK and IDO expression in infiltrating myeloid cells after 2 cycles of therapy



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Translation to the clinic

- Hypothesis: Following chemotherapy, IDO and BTK act together to form a linked checkpoint, which must be blocked in order to allow immune activation

- In preclinical models, blocking both pathways together is highly synergistic

- The IDO and BTK target genes are co-expressed in many DCs in human tumors

GCC2020 Clinical Trial

"Repurposing ibrutinib for chemo-immunotherapy in a phase 1b study of ibrutinib with indoximod plus metronomic cyclophosphamide and etoposide for pediatric patients with brain cancer"

(NCT05106296)

Sponsor-Investigator: Theodore Johnson, M.D., Ph.D.

Investigator-initiated IND issued (Dr. Johnson)

Funding: Philanthropic (CKc, Press On, Halsey Foundation, etc.)

NIH grant applied for

Clinicaltrials.gov #: NCT05106296

Investigational Agent: Ibrutinib, Indoximod

Enrollment Target: 28-37 patients

First patient enrolled: February, 2022

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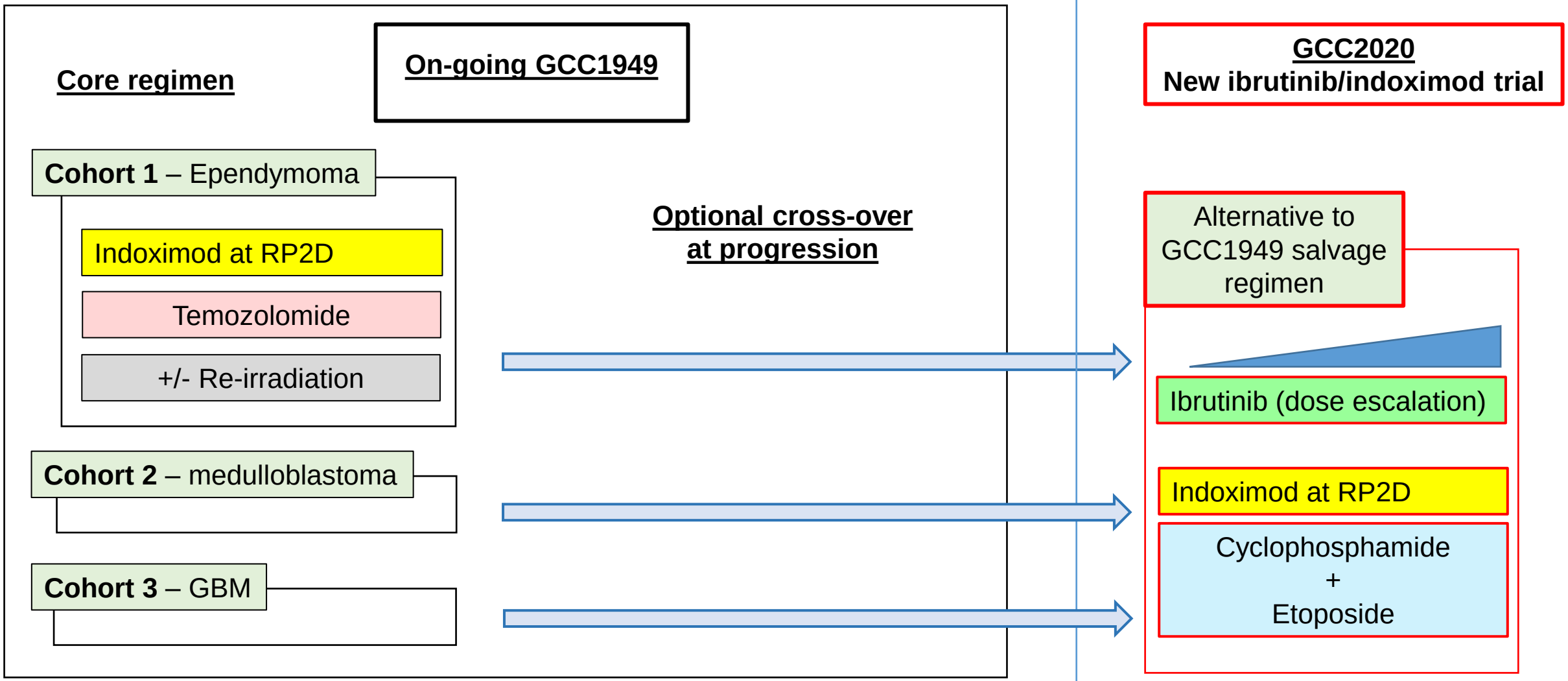
GCC2020: Phase 1b trial using ibrutinib plus indoximod



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GCC2020: Phase 1b trial using ibrutinib plus indoximod

ENTRY CRITERIA: Patients age 12 to 25 years with relapsed or refractory pediatric brain cancer that progressed after previous treatment with indoximod-based therapy.

STUDY TREATMENT REGIMEN (28-day cycles)
Ibrutinib (Study Dose, once per day, PO, days 1-21)
Indoximod (RP2D, 38.4 mg/kg/day, divided twice daily, PO, days 1-28
Cyclophosphamide (2.5 mg/kg/dose, once per day, PO, days 1-21)
Etoposide (50 mg/m^2/dose, once per day, PO, days 1-21)

Duration of Therapy: Patients may continue Study Therapy, up to a maximum of 12 cycles, as long as there is stable disease or response using iRANO criteria, and no limiting toxicity.

Referrals: Ted Johnson
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(706) 825-0979

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- Eric Ring, MD
- Carlee Leopard, CPNP
- Robin Dobbins, RN
- Dana Cook, RN
- Kimberly Gray, BBA, CCRP
- Brittney Chubb, MPH
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- Kendra Jones, BS

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- Cannonball Kids' cancer Foundation
- Halsey Foundation
- Hyundai Hope on Wheels Foundation
- Northern Nevada Children's Cancer Research Foundation
- Press On Foundation / CAM Fund

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- Julianne Creager
- Chris Smith
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- Corey Neal
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Emory University

- Tobey J. MacDonald
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