First-in-children phase 1 trial of indoximod-based chemo-immunotherapy for patients with pediatric brain tumors: analysis of safety, tolerability, and 5-year outcome

NLG2105, NCT02502708

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Pediatric Immunotherapy Program

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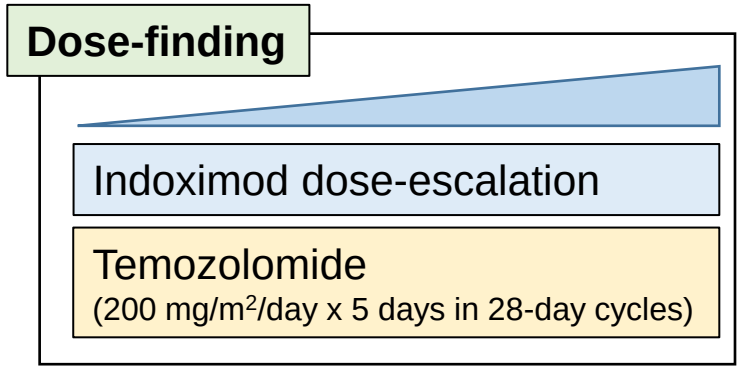
Disclosures

- Augusta University (AU) holds patents on IDO-inhibitor drugs (indoximod)
- Lumos Pharma, Inc. (formerly NewLink Genetics Corp.) licensed the indoximod IP from AU, partially funded the NLG2105 clinical trial, and provides indoximod for GCC1949 and GCC2020 trials.
  - The presenter receives no direct financial support from Lumos Pharma
- Off-label use of chemotherapy drugs for pediatric patients will be discussed

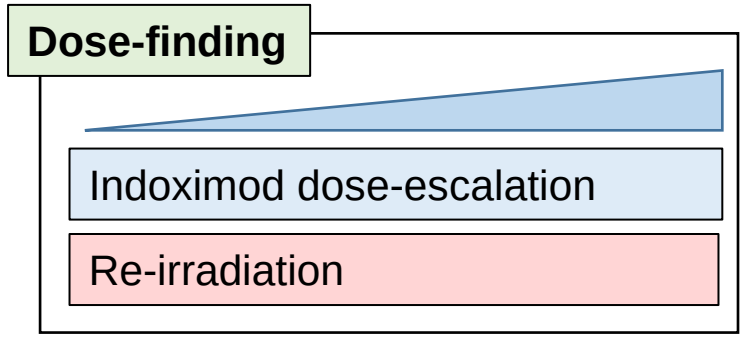
NLG2105 phase 1 study (NCT02502708)

First-in-children trial using the IDO pathway inhibitor indoximod plus temozolomide (+/- radiation) for patients aged 3-22 years with relapsed or refractory primary brain cancer

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



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



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Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.

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

Dose-finding

- Indoximod dose-escalation
- Temozolomide
  (200 mg/m^2/day x 5 days in 28-day cycles)

Group 2: expansion cohorts – progressive CNS tumors

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

Indoximod RP2D
(38.4 mg/kg/day divided BID)

- Temozolomide
- +/- Re-irradiation

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

Dose-finding

- Indoximod dose-escalation
- Re-irradiation

Group 3b: newly-diagnosed DIPG

- DIPG

- Indoximod RP2D
- Up-front Radiation (54 Gy)
- Indoximod RP2D
- Temozolomide

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Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.

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IDO-inhibitors are inherently team players

- IDO is a fundamental molecular mechanism of immune suppression and tolerance to apoptotic cells (normal cell turnover in the body)
- Blocking the IDO pathway with indoximod helps **change the tumor microenvironment** so that tumor antigens are now presented in an immunogenic fashion
- IDO-inhibitors do not work alone – you have to kill some tumor cells to trigger immune activation ... e.g., combination with:
  - Chemotherapy
  - Radiation/proton therapy
  - Targeted therapy (TKI's, etc.)

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%)

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.

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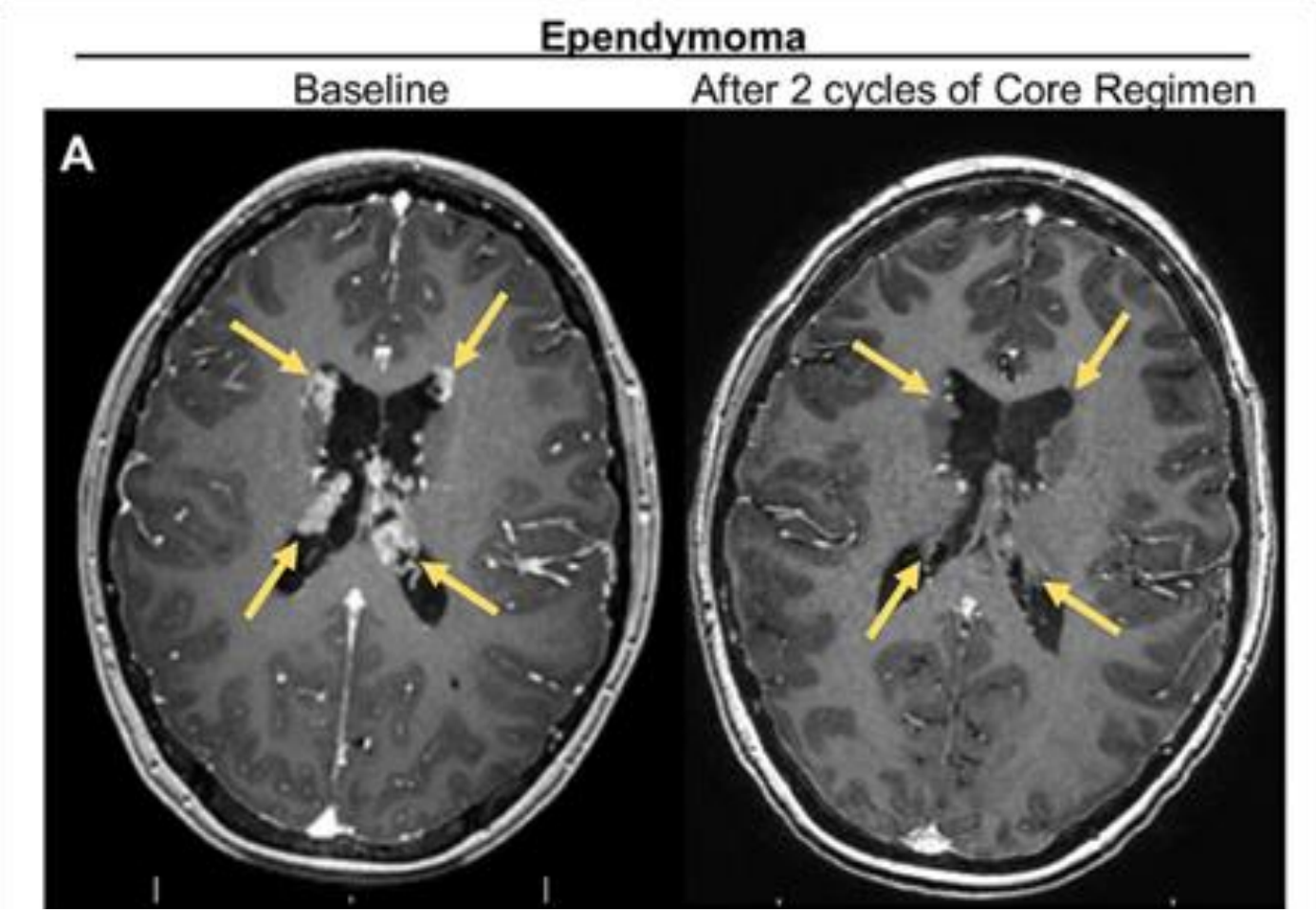
Disease status and prior therapy at study entry

	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%)

Ependymoma after 2 cycles of indoximod + temozolomide



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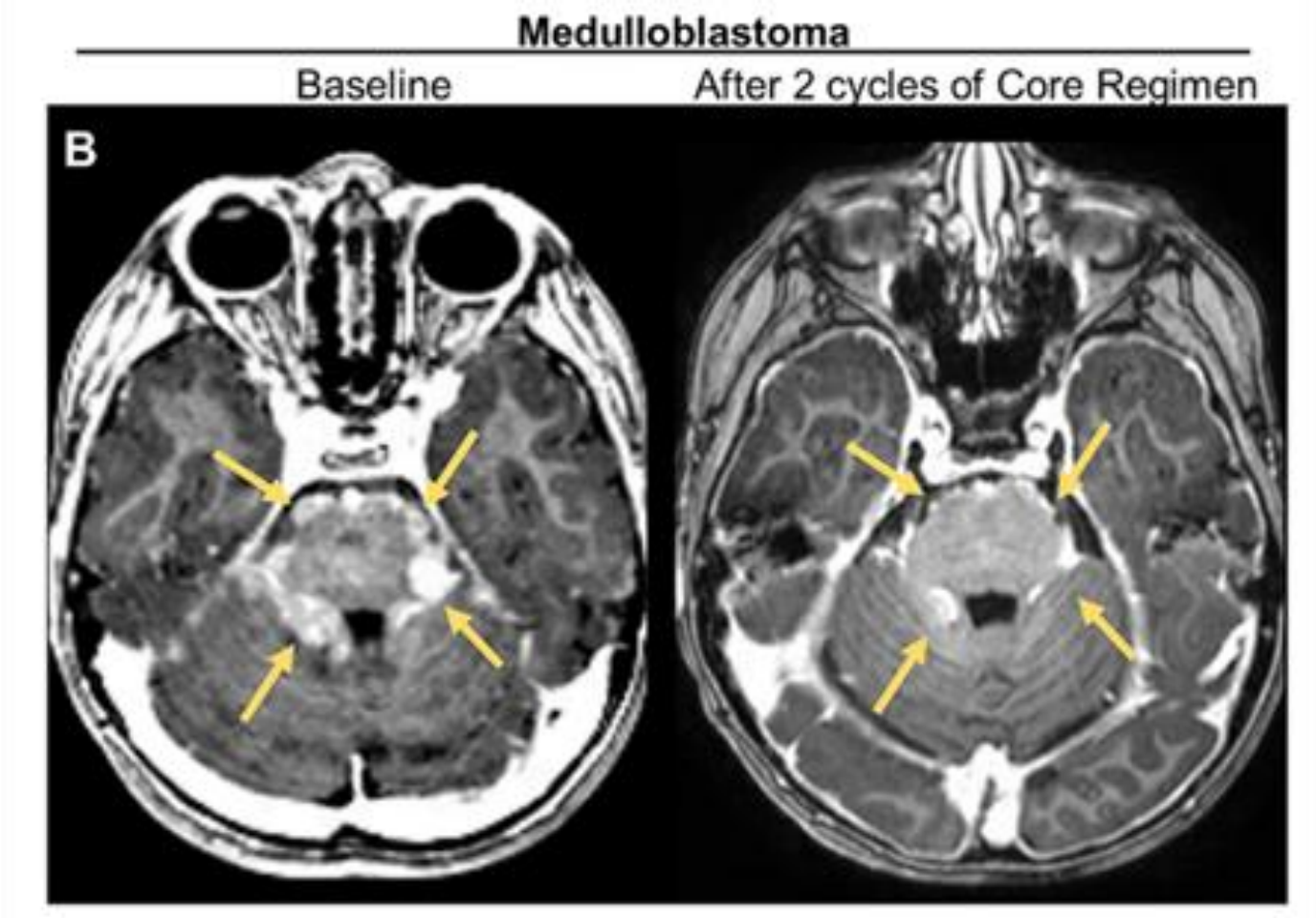
Medulloblastoma after 2 cycles of indoximod + temozolomide



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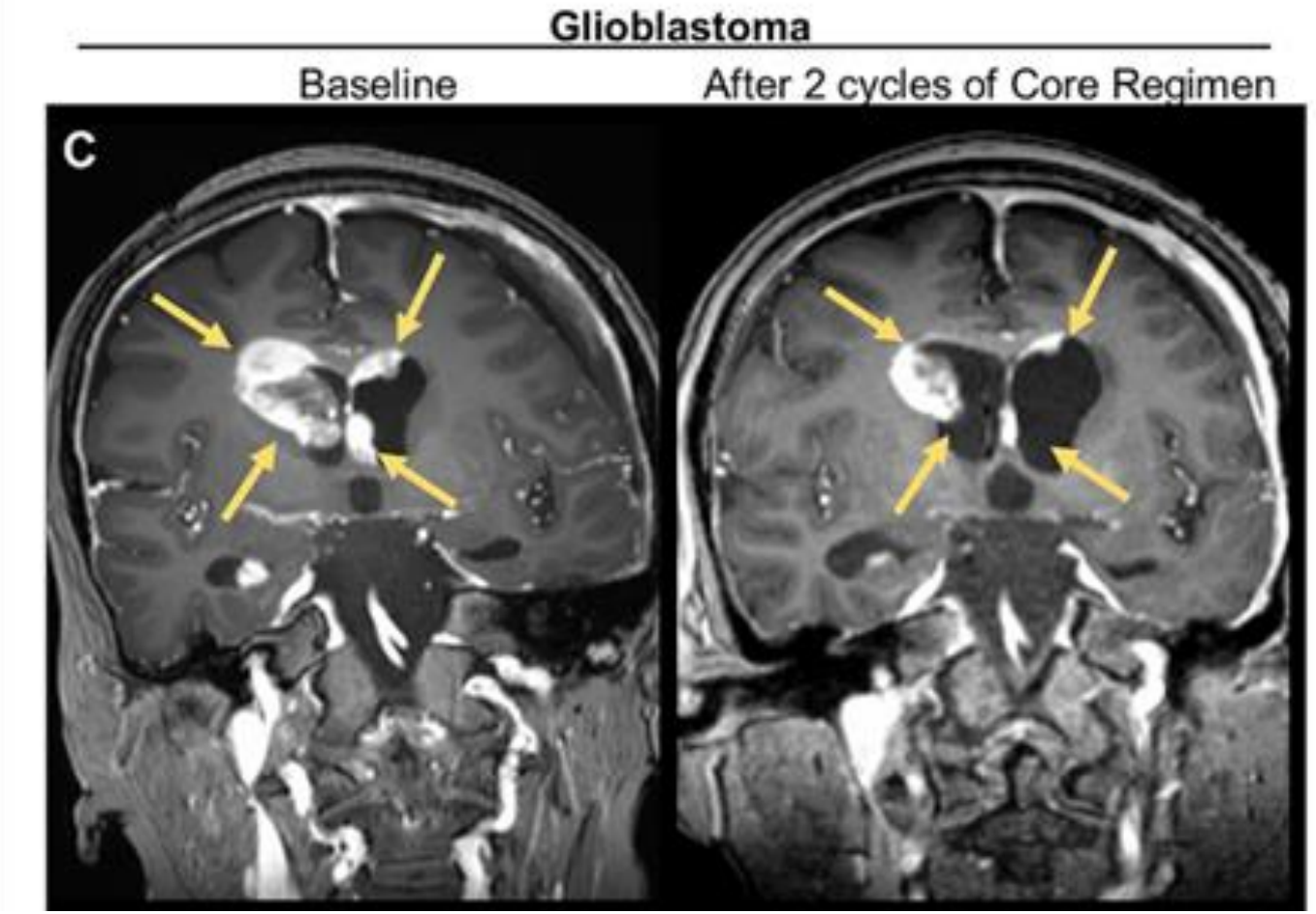
Glioblastoma after 2 cycles of indoximod + temozolomide



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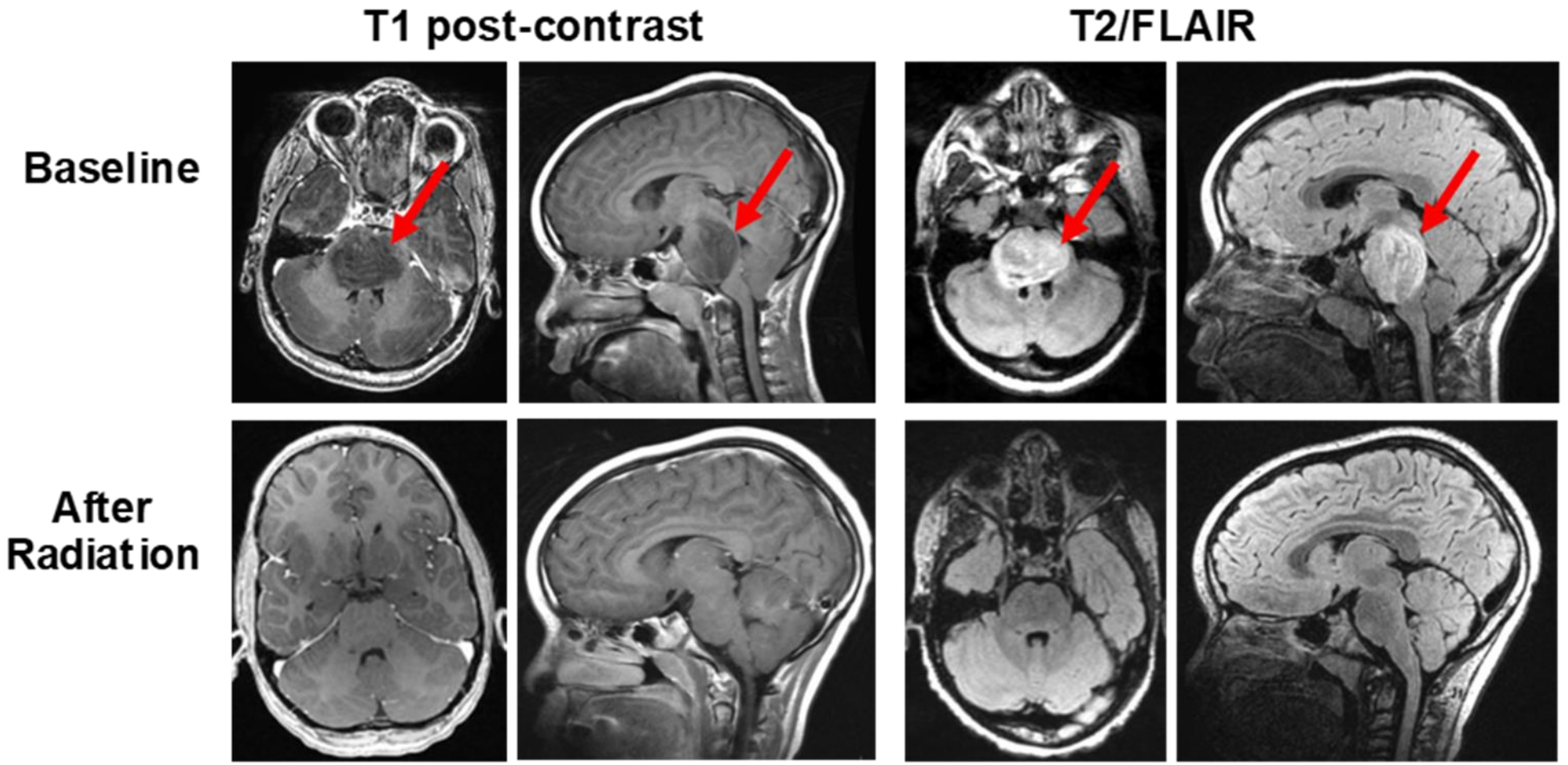
DIPG after indoximod + radiation



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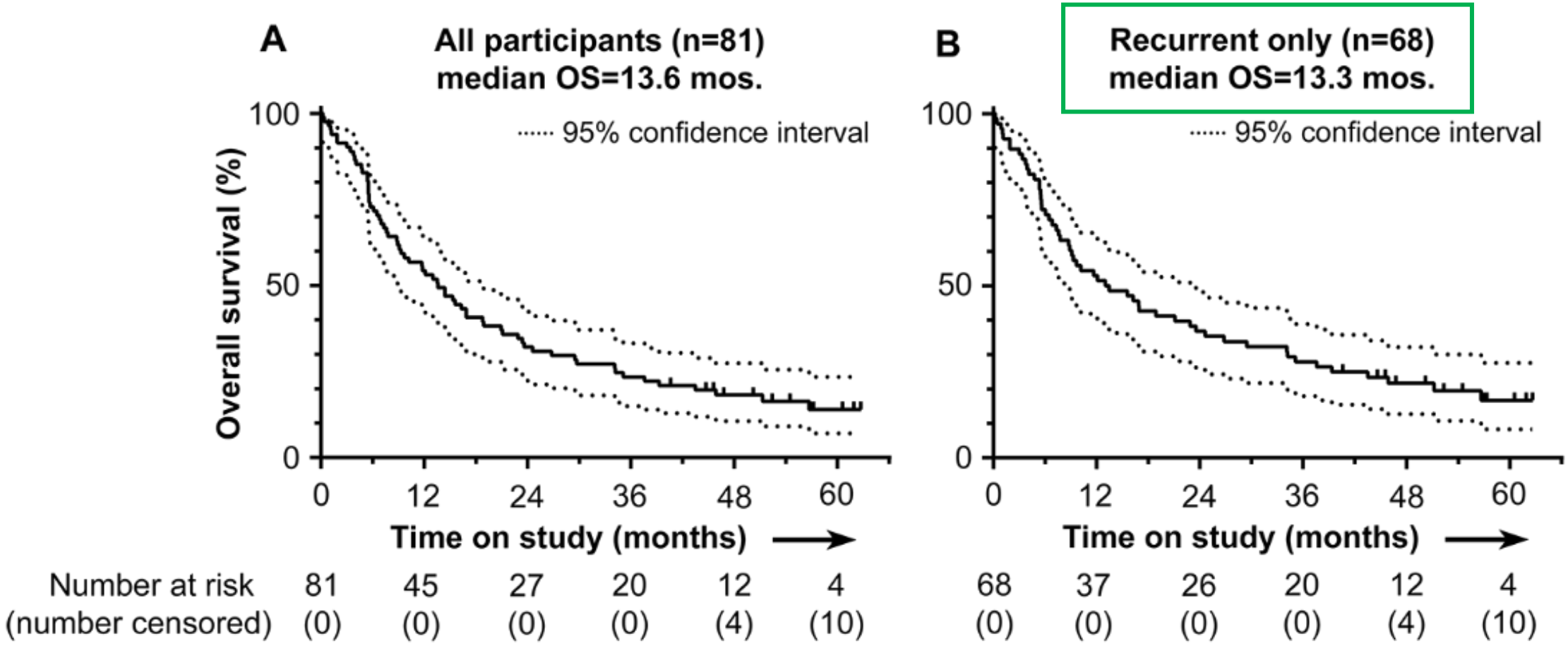
Favorable outcome with indoximod-based therapy



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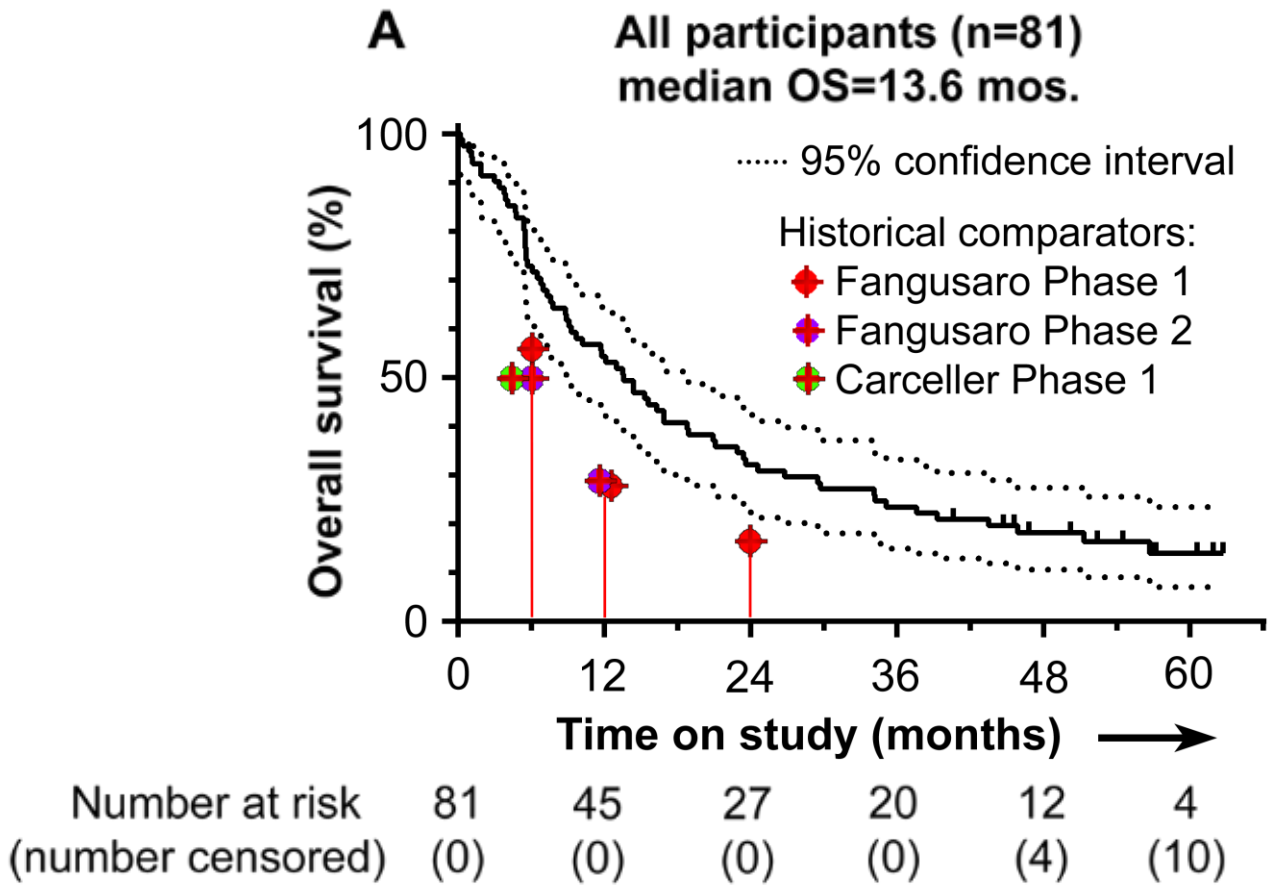
Favorable outcome with indoximod-based therapy



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Historical comparators 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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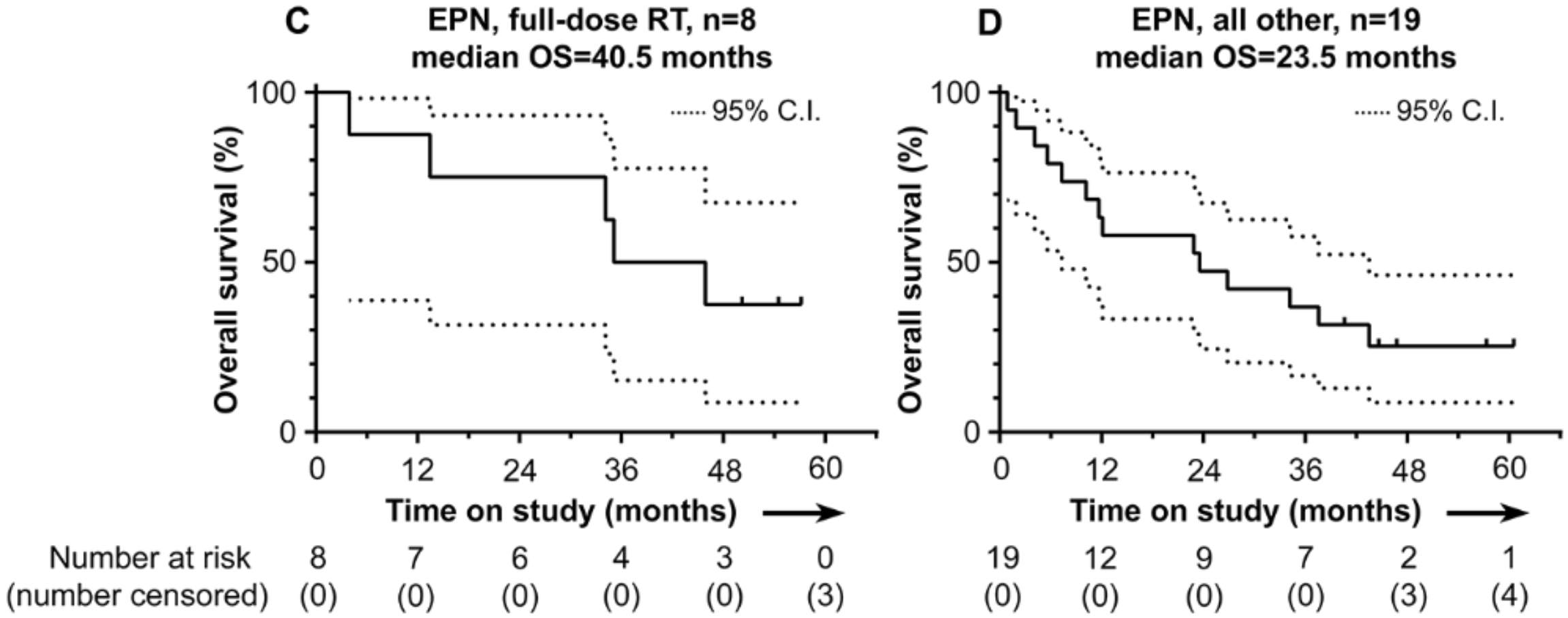
Ependymoma cohort (relapsed)



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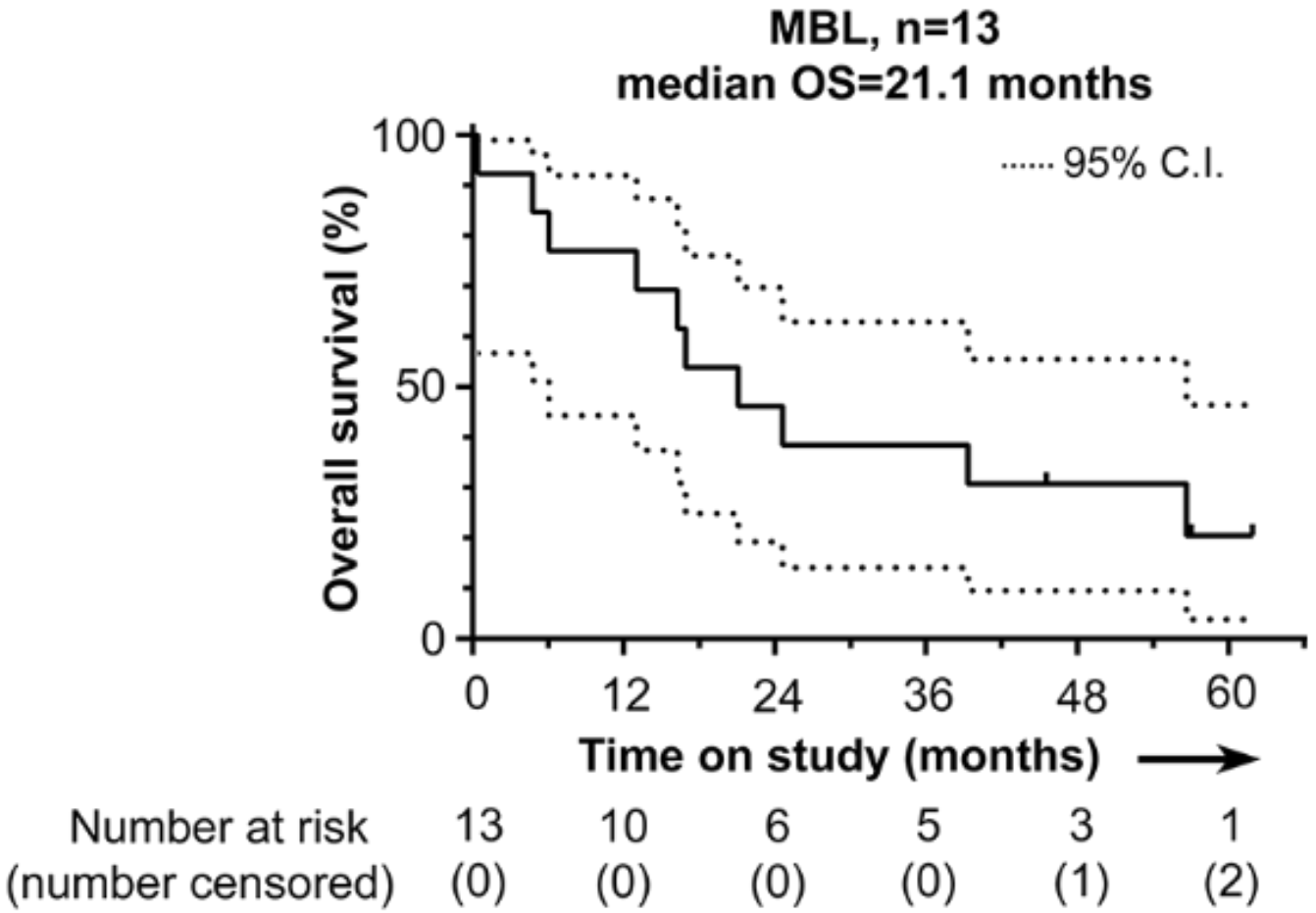
Medulloblastoma cohort (relapsed)



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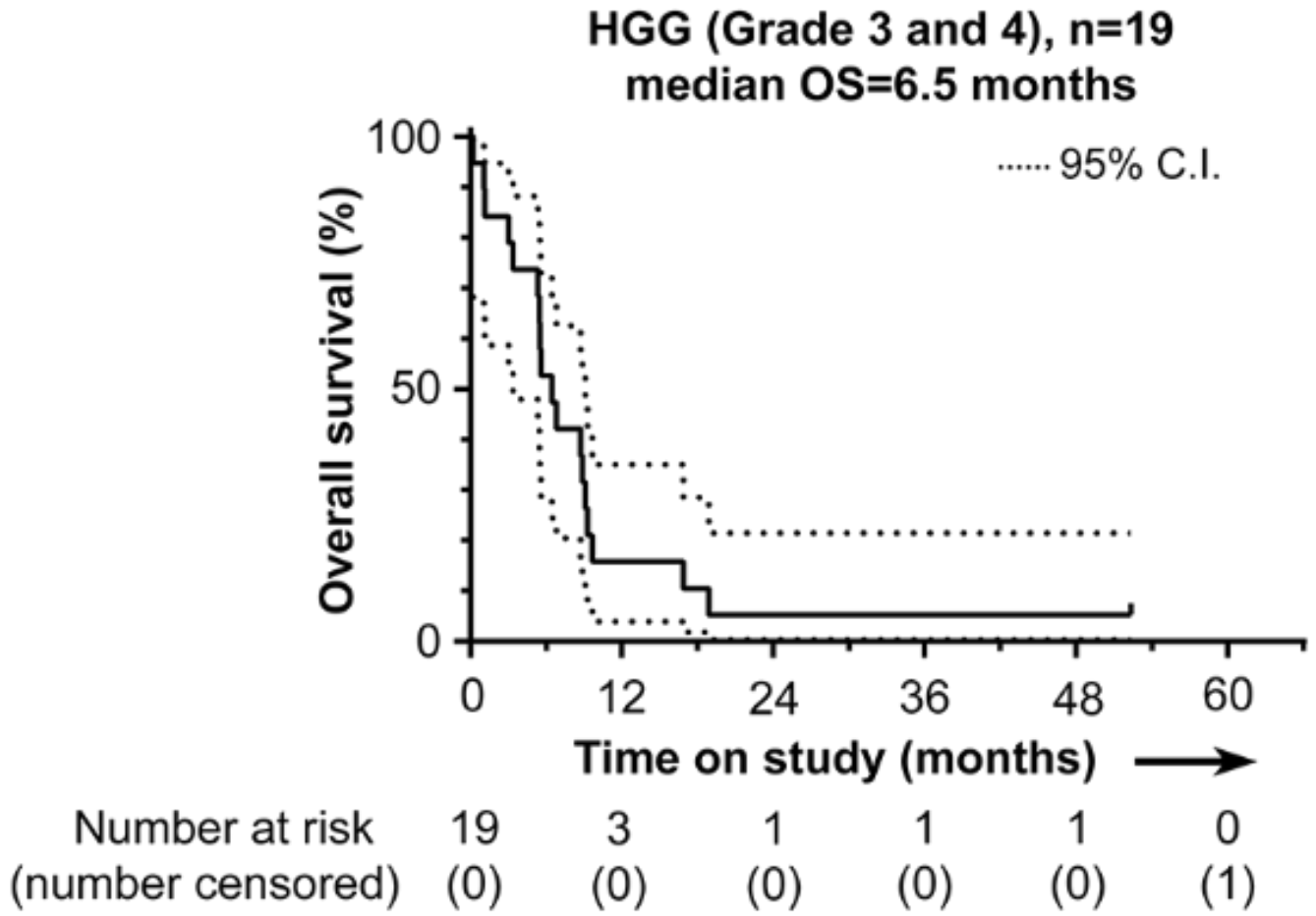
Glioblastoma cohort (relapsed)



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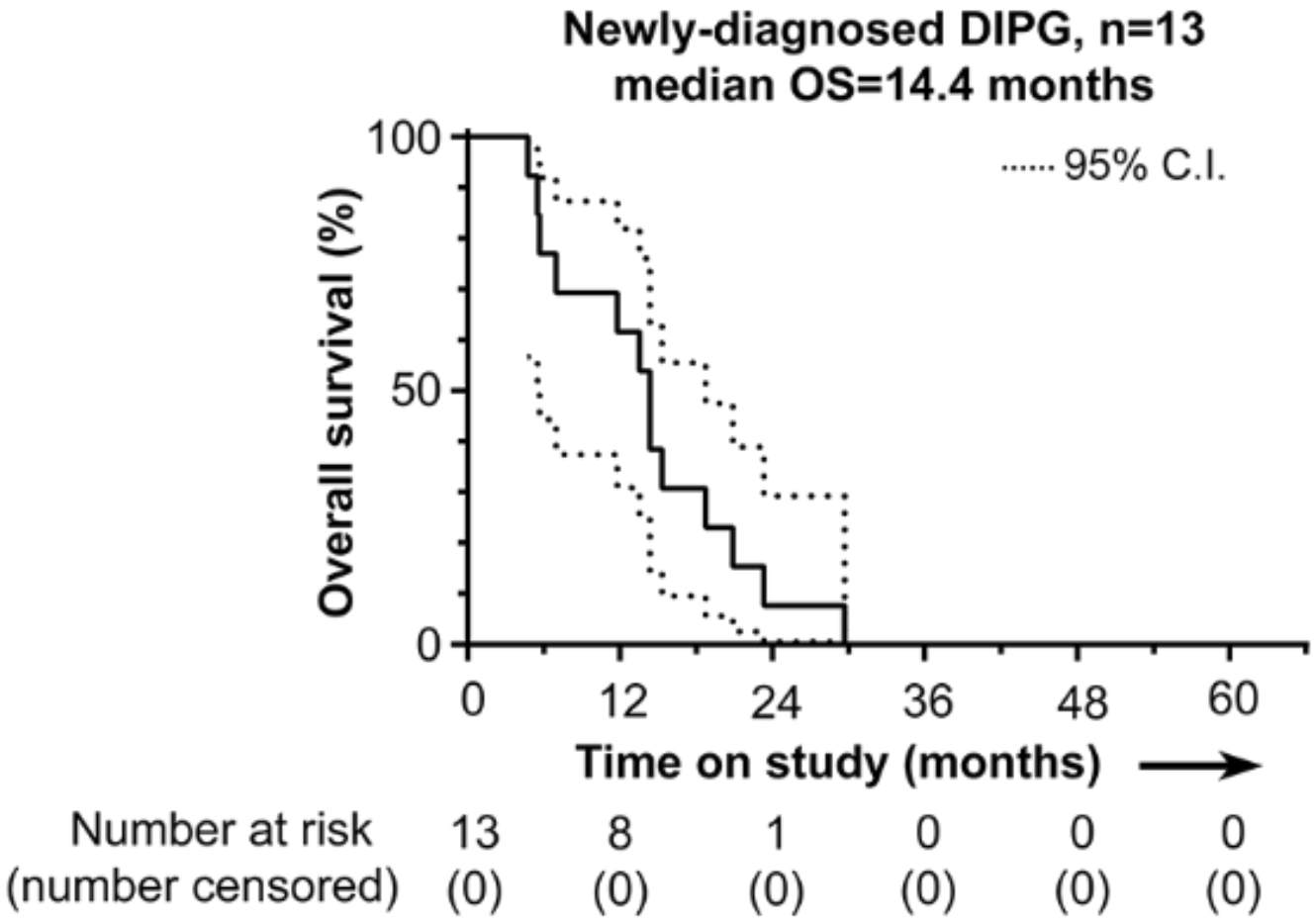
Newly diagnosed DIPG cohort



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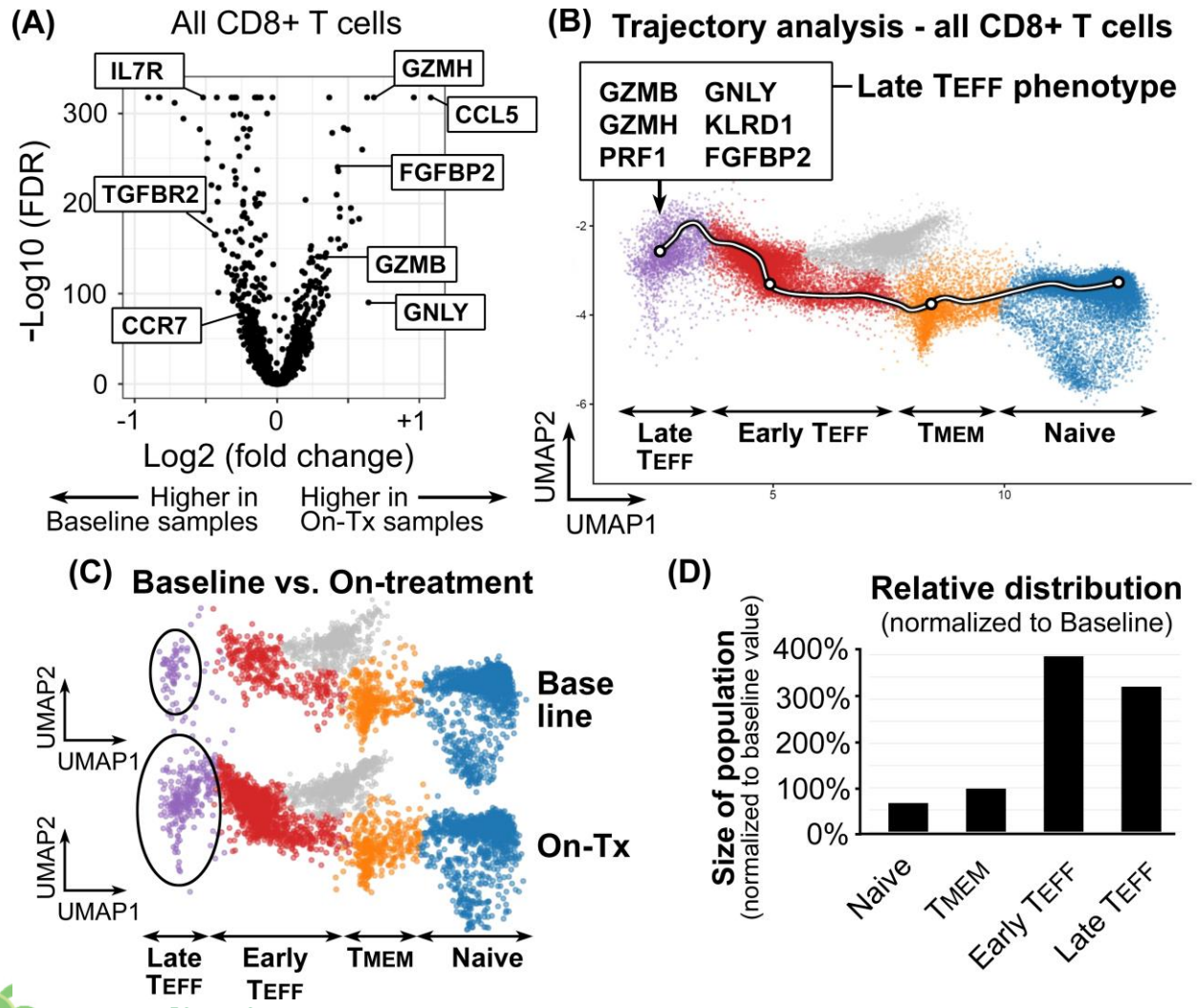
Emergence of CD8+ effector T cells in peripheral blood during study therapy



- Single-cell RNA-sequencing analysis of PBMCs (peripheral blood mononuclear cells)
- Hypothesis: Treatment with IDO blockade allows dendritic cells to mature and cross-present tumor antigen, leading to T cell activation and upregulation of anti-tumor effector pathways

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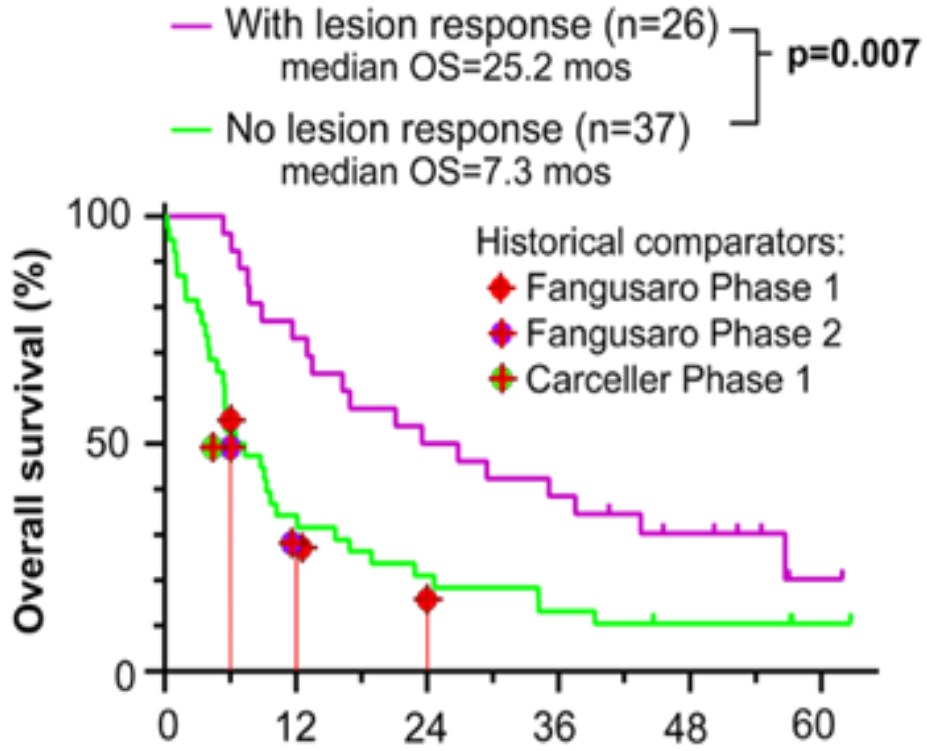
Response in any lesion correlates with survival



Number at risk (number censored)						
With lesion response	26 (0)	20 (0)	14 (0)	11 (0)	7 (2)	2 (6)
No lesion response	37 (0)	14 (0)	9 (0)	6 (0)	4 (1)	2 (3)

- Mixed responses are very common in patients treated with immunotherapy
- Hypothesis: Response in any single lesion is a proxy for immune response and therefore correlates with survival
  - Stratified patients according to whether any lesion achieved PR/CR by RAPNO criteria
- n=63 patients with relapsed/refractory disease at study entry
  - (5 patients with no active disease excluded)
- 26/63 (41%) showed at least one responsive lesion, by RAPNO criteria

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“Adaptive Management” – cross-over salvage algorithm

Can patients with progression on immunotherapy be salvaged?

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

"Adaptive Management" – cross-over salvage algorithm

Dose-finding

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

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

Expansion Cohorts

Group 2: expansion cohorts – progressive CNS tumors

Group 3b: newly-diagnosed DIPG

Cross-over at progression

Patients allowed to cross over to a compassionate-access salvage regimen at progression

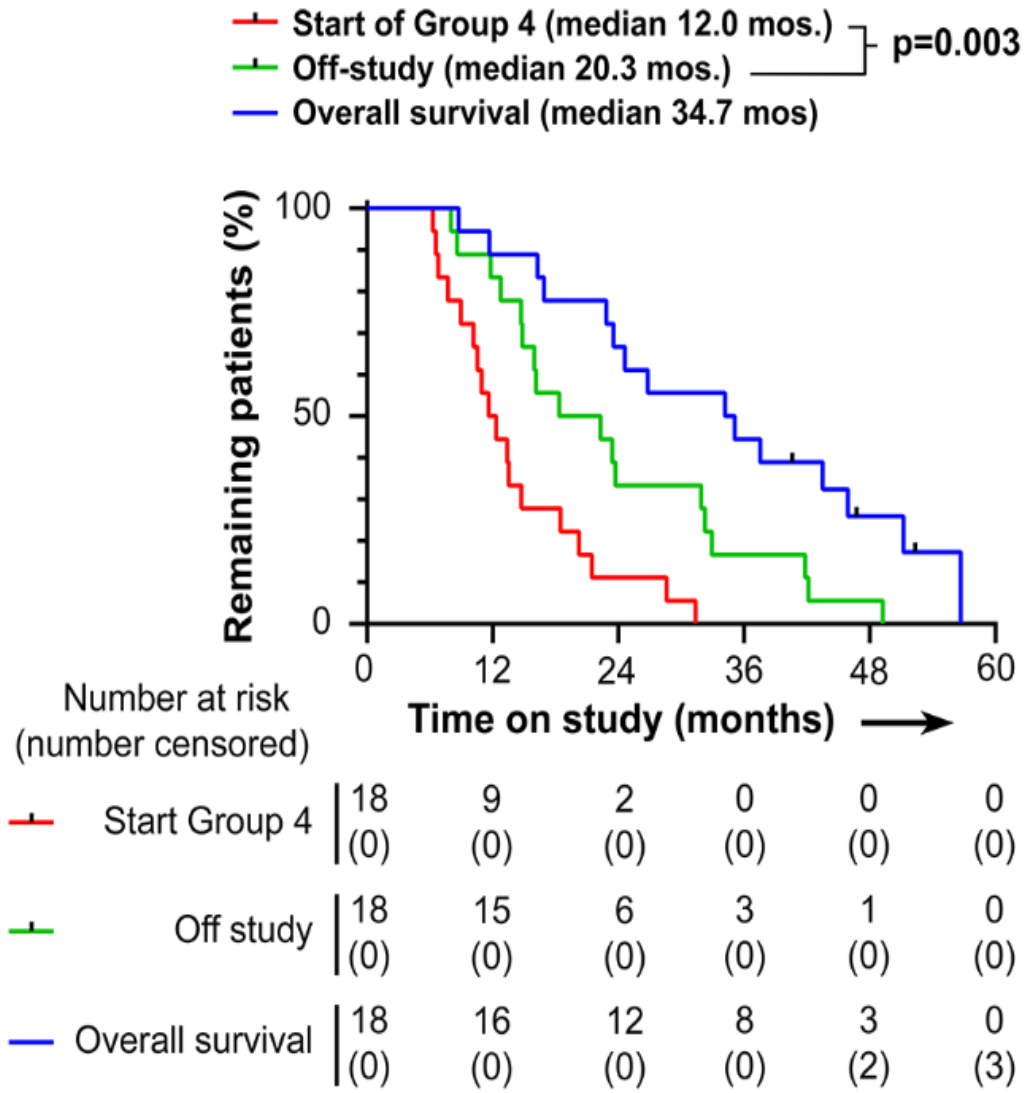
Group 4: Salvage regimen

Indoximod RP2D

Oral metronomic chemotherapy (in 28-day cycles):
Cyclophosphamide (2.5 mg/kg/day x 21 days, max 100mg/day)
Etoposide (50 mg/m^2/day x 21 days)

Palliative radiation, surgery or dexamethasone were allowed as needed for patient management.

“Adaptive Management” – cross-over salvage algorithm



- ***Can patients with progression on immunotherapy be salvaged?***

  Salvage regimen (28-day cycles):
  - Indoximod at RP2D
  - Cyclophosphamide (2.5 mg/kg/day x 21 days, max 100mg/day)
  - Etoposide (50 mg/m^2/day x 21 days)
- n=18 patients treated on Group 4 salvage therapy
- 12/18 (67%) were able to restabilize progressing disease (SD or better)
- 6/18 (33%) were treated longer than 12 months on Group 4 salvage therapy

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Favorable outcome with indoximod-based therapy (summary)

- 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)
- 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)

Performance status for patients treated on indoximod longer than 30 months

	Diagnosis	Time on indoximod (months)	Overall survival (months)	Received Group 4 therapy (Yes/No)	Performance score (Lansky/Karnofsky)			
					Baseline	6 months on therapy	Best score on therapy	1 month prior to off-therapy
1.	Medulloblastoma	31.8	61.9 LDOC†	No	80	90	100	100
2.	Ependymoma	31.9	35.1	Yes	100	90	100	80
3.	Ependymoma	32.3	46.8 LDOC†	Yes	100	100	100	100
4.	Ependymoma	32.9	37.5	Yes	50‡	70	90	90
5.	PNET	41.9	51.2	Yes	90	100	100	90
6.	High grade glioma	42.1	52.3 LDOC†	Yes	80	90	100	90
7.	Ependymoma	44.6	44.6 LDOC†	No	100	100	100	100**
8.	Medulloblastoma	49.2	56.7	Yes	80	90	90	80

LDOC=last date of contact. †These patients are still alive. ‡This patient experienced dramatic improvements in baseline symptoms (severe ataxia, right-side weakness, dysarthria, nausea, headaches). **This patient continues therapy.

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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Currently enrolling IDO-inhibitor trials for children

Indoximod plus chemotherapy +/- radiation

- GCC1949 (NCT04049669) – Phase 2 (enrolling)
  - (NIH-funded R01; multi-center; IND-holder T. Johnson)

Ibrutinib and Indoximod plus chemotherapy

- GCC2020 (NCT05106296) – Phase 1 (enrolling)
  - (First-in-human trial using this combination; IND-holder T. Johnson)

Referrals:
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