Phase 2 trial using indoximod-based chemo-immunotherapy for patients with childhood brain cancer: Interim analysis of the GCC1949 study

(NCT04049669)

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Disclosures

- Off-label use of chemotherapy drugs for pediatric patients will be discussed

Lumos Pharma	Provides indoximod drug for these trials: • GCC1949 (phase 2) • GCC1953 (expanded access) • GCC2020 (phase 1)
Janssen Scientific Affairs, LLC	Provides ibrutinib drug for the trial: • GCC2020 (phase 1)

IDO-inhibitors are inherently team players

- IDO is a fundamental molecular mechanism of immune suppression and tolerance to apoptotic cells (including apoptotic cells after chemotherapy)
- The relevant site of IDO activity is within antigen presenting cells (APCs) in the tumor microenvironment
- Blocking the IDO pathway with indoximod helps **activate the antigen-presenting cells (APCs) in tumor and tumor-draining lymph nodes** 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.)
- NLG2105 phase 1 trial completed (n=81 patients)*

*Johnson TS, *et al.* 2023. *Neuro-Oncology.* 26(2):348–361.

GCC1949 phase 2 study (NCT04049669)

NIH-funded phase 2 trial using the IDO pathway inhibitor indoximod plus temozolomide (+/- radiation) for patients aged 3-21 years with relapsed or refractory primary brain cancer

Relapsed or refractory CNS tumors*

- High-grade glioma[1]
- Medulloblastoma
- Ependymoma

[1] Includes WHO grade 4 glioma and extrapontine diffuse midline glioma.

- Indoximod (38.4 mg/kg/day PO, divided BID, 28-day cycles)
- Temozolomide (200 mg/m^2/day PO for 5 days)

OR

- Indoximod
- Re-irradiation (or Proton)
- Indoximod
- Temozolomide

Newly-diagnosed DIPG (diffuse intrinsic pontine glioma)*

- DIPG[2]

[2] No previous radiation or systemic therapy.

- Indoximod
- Up-front Radiation (54 Gy in 30 fractions)
- Indoximod
- Temozolomide

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

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Patient demographics

All participants	(n = 80)
Age, years	
Median (range)	11.6 (3-21)
Sex	
Female	34 (43%)
Male	46 (58%)
Race	
American Indian or Alaska Native	1 (1%)
Asian	6 (8%)
Black or African American	6 (8%)
White	58 (73%)
More than one race	1 (1%)
Not reported or unknown	8 (10%)
Ethnicity	
Hispanic	6 (8%)
Non-Hispanic	65 (81%)
Not reported or unknown	9 (11%)
Tumor diagnosis	
Ependymoma, relapsed	31 (39%)
Medulloblastoma, relapsed	22 (28%)
High-grade glioma, relapsed[1]	18 (23%)
DIPG, newly diagnosed[2]	9 (11%)

Data are median (range) or n (%).

[1] The original trial inclusion criterion of “glioblastoma” now includes WHO grade 4 glioma and extrapontine diffuse midline glioma.

[2] No previous radiation or systemic therapy.
DIPG = diffuse intrinsic pontine “glioma.”

Indoximod + temozolomide: Patients experiencing high-grade adverse events (regardless of attribution)

	Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)
Any event	**49**	**61%**	**22**	**28%**	**1**	**1.3%**
Tumor Hemorrhage	..		..		1	1.3%
Platelet count decreased	6	8%	11	14%	..	
Neutrophil count decreased	5	6%	7	9%	..	
Respiratory failure	..		5	6%	..	
Edema cerebral	2	3%	2	3%	..	
Hydrocephalus	4	5%	2	3%	..	
Somnolence	4	5%	2	3%	..	
Vision decreased	..		2	3%	..	
White blood cell decreased	4	5%	2	3%	..	
Apnea	..		1	1%	..	
Acites	..		1	1%	..	
Dysphagia	1	1%	1	1%	..	
Dyspnea	1	1%	1	1%	..	
Hypokalemia	..		1	1%	..	
Lung infection	..		1	1%	..	
Lymphocyte count decreased	4	5%	1	1%	..	
Neck Pain	2	3%	1	1%	..	
Seizure	4	5%	1	1%	..	
Headache	9	11%	..		..	

	Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)
Muscle weakness, localized	8	10%	..		..	
Ataxia	5	6%	..		..	
Anemia	4	5%	..		..	
Muscle weakness, generalized	4	5%	..		..	
Agitation	3	4%	..		..	
Anorexia	3	4%	..		..	
Blurred vision	3	4%	..		..	
Dysarthria	3	4%	..		..	
Hypertension	3	4%	..		..	
Paresthesia	3	4%	..		..	
Vomiting	3	4%	..		..	
Back pain	2	3%	..		..	
Dehydration	2	3%	..		..	
Fatigue	2	3%	..		..	
Febrile neutropenia	2	3%	..		..	
Hearing impaired	2	3%	..		..	
Hypotension	2	3%	..		..	
Hypoxia	2	3%	..		..	
Memory impairment	2	3%	..		..	
Nausea	2	3%	..		..	
Pain in extremity	2	3%	..		..	

Data are n (%), with each participant reported once at the highest grade experienced.

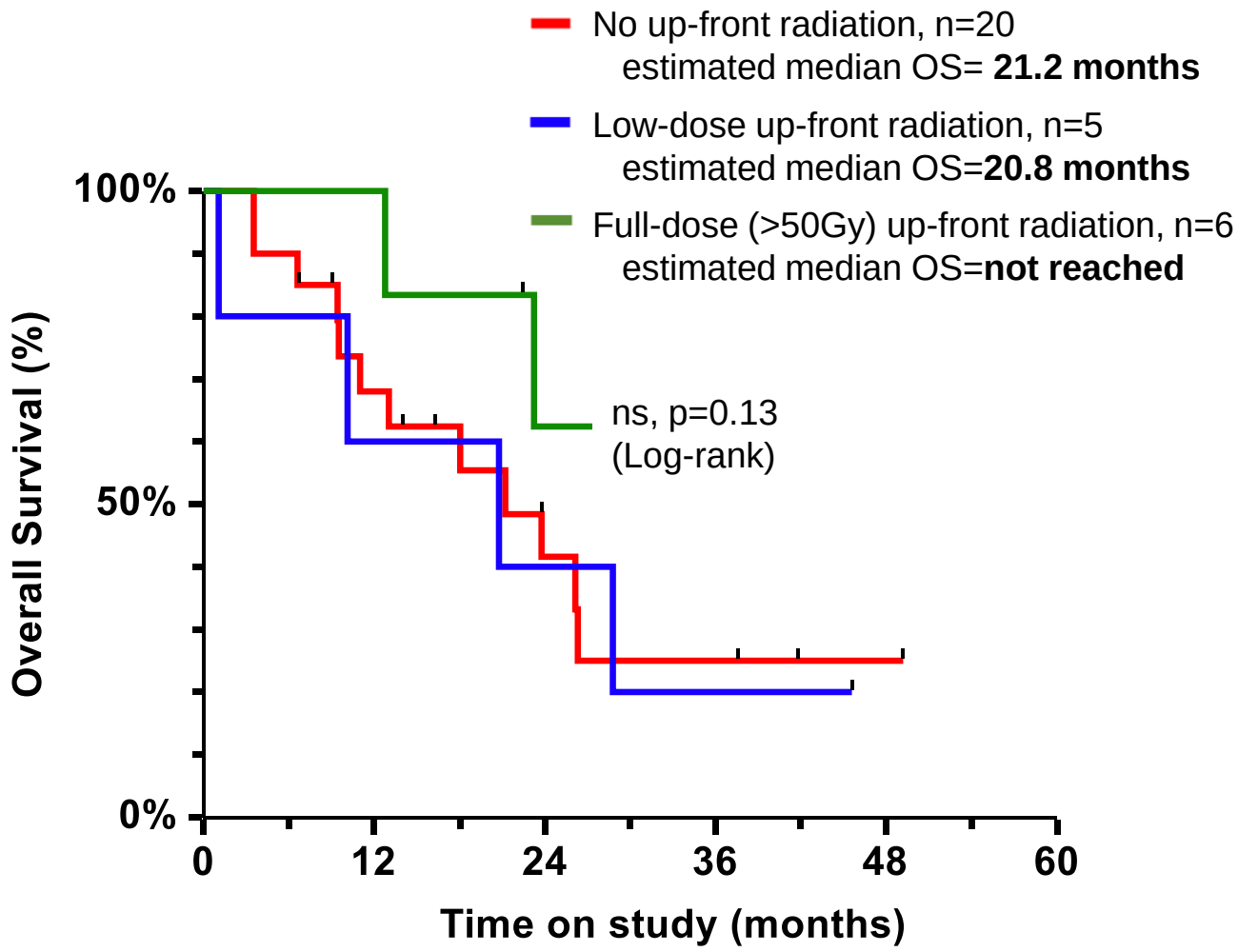
Shown are treatment-emergent adverse events occurring in at least 2 patients for Grade 3 or 4; and all grade 5 events.

Interim outcome with indoximod-based therapy
(GCC1949 interim analysis)

- Estimated median follow-up time (n=80): 31.9 months (range: 1.1 – 49.2)
- Estimated median OS by diagnosis:
  - Ependymoma (recurrent): 23.8 months (n= 31)
  - Medulloblastoma (recurrent): 13.1 months (n= 22)
  - High-grade glioma (recurrent): 5.6 months (n= 18)
  - DIPG (treatment-naïve): 15.0 months (n= 9)

Interim outcome with indoximod-based therapy (GCC1949 interim analysis)

Ependymoma (relapsed)



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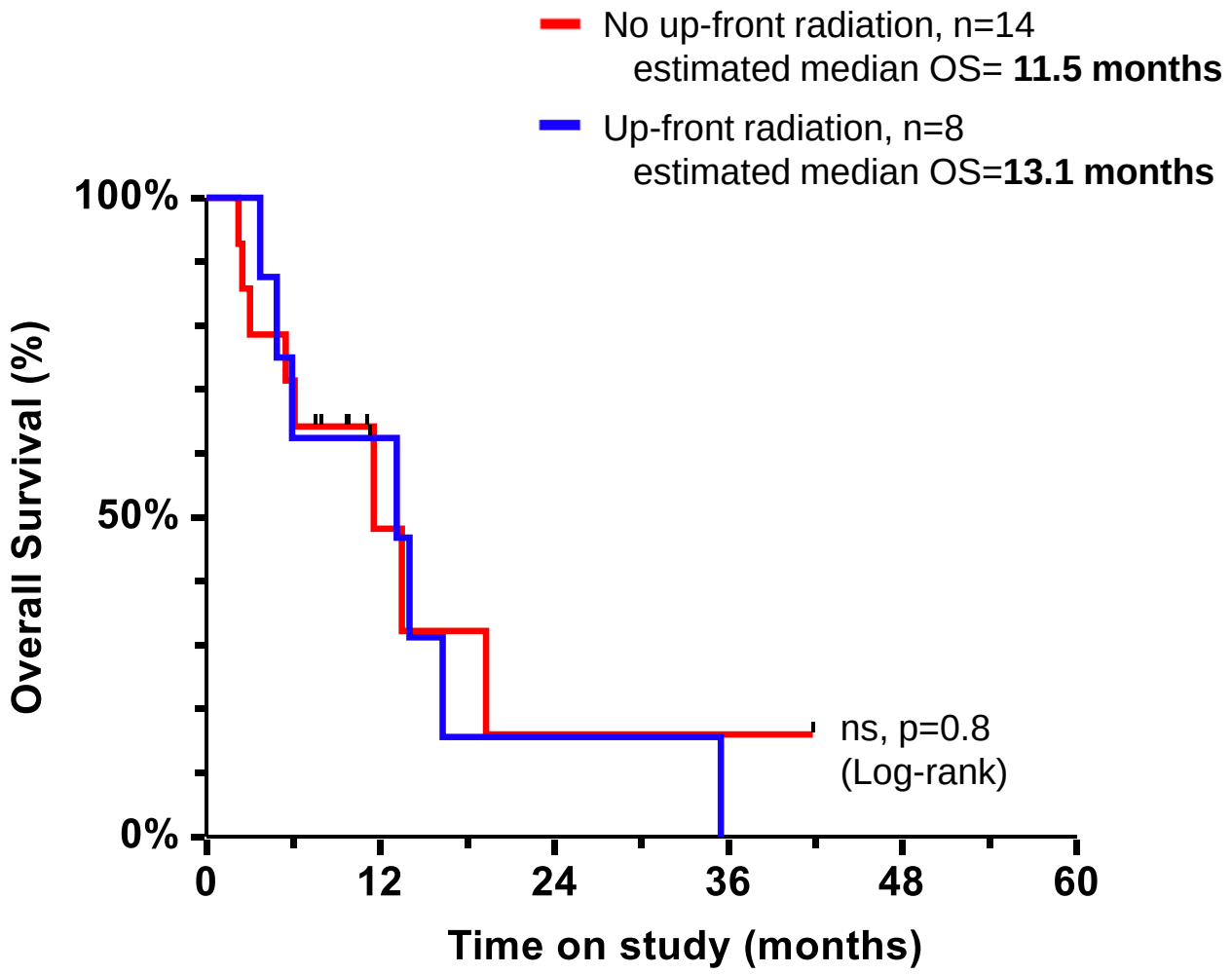
Interim outcome with indoximod-based therapy (GCC1949 interim analysis)

Medulloblastoma (relapsed)



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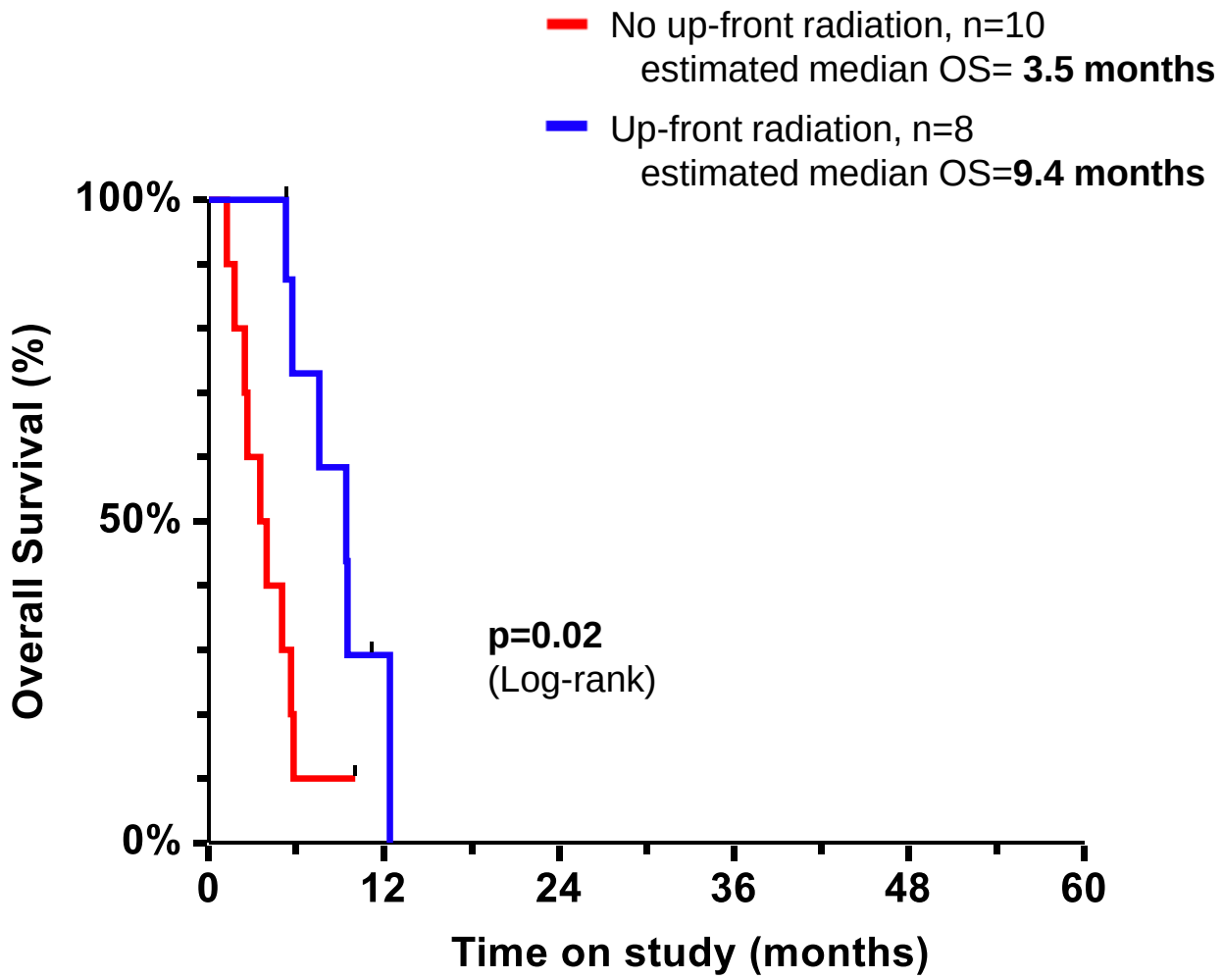
Interim outcome with indoximod-based therapy (GCC1949 interim analysis)

High Grade Glioma (relapsed)



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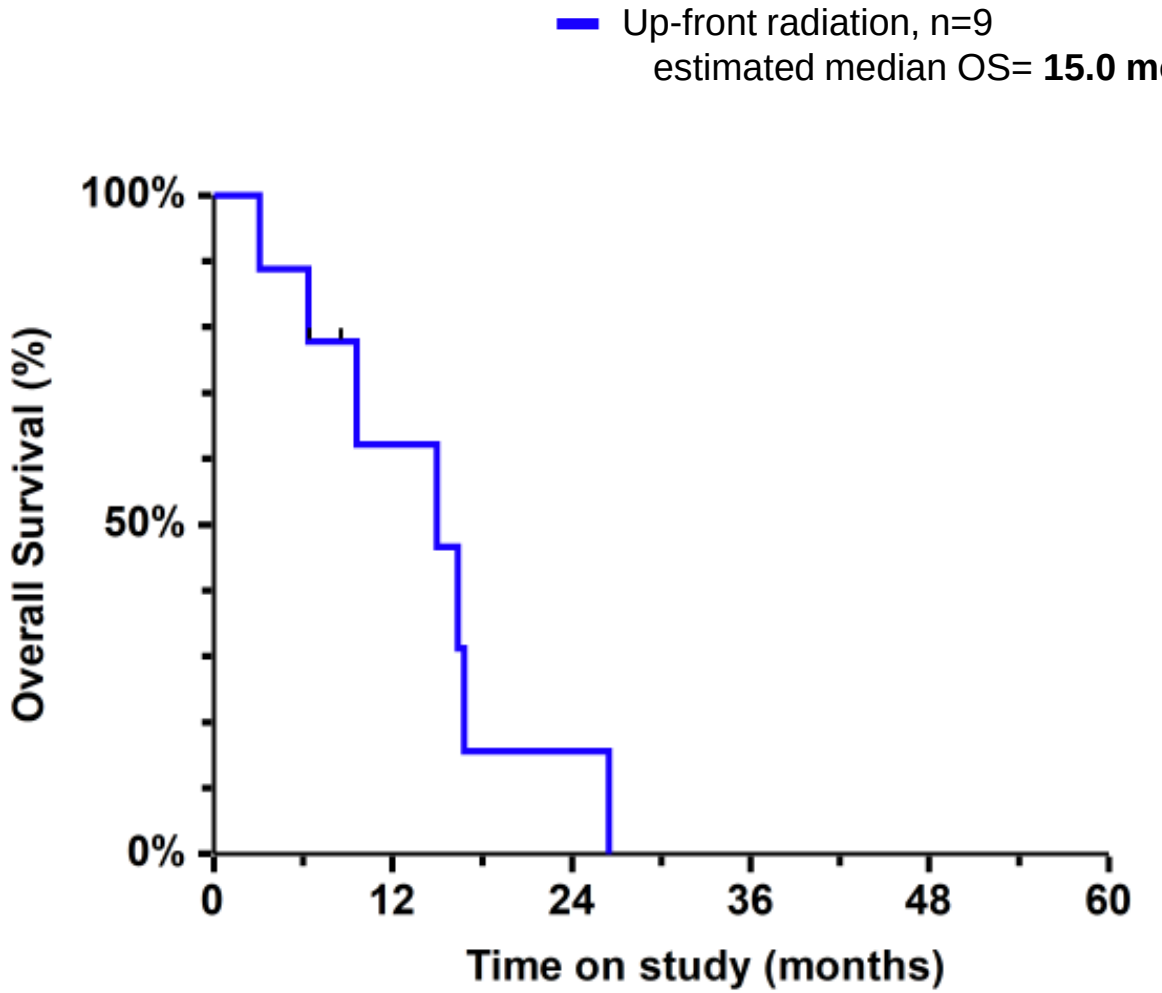
Interim outcome with indoximod-based therapy (GCC1949 interim analysis)

DIPG (treatment naive)



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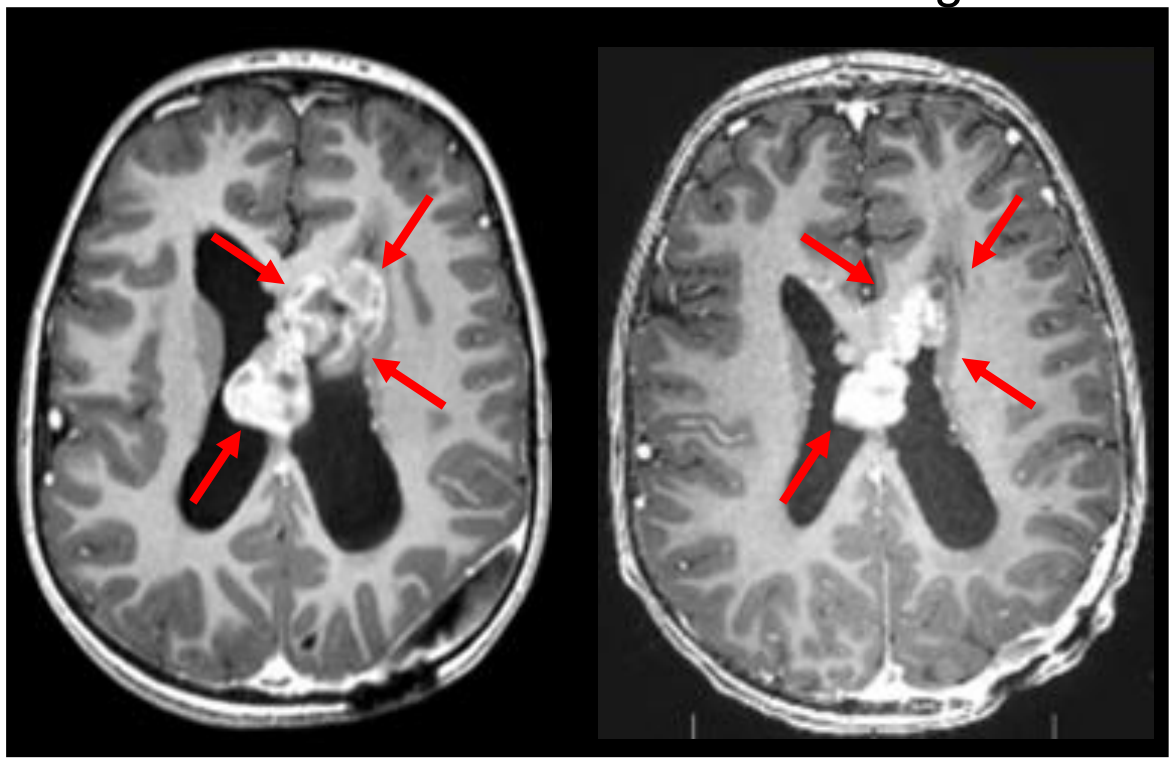
Early responses after 2 cycles of indoximod + temozolomide

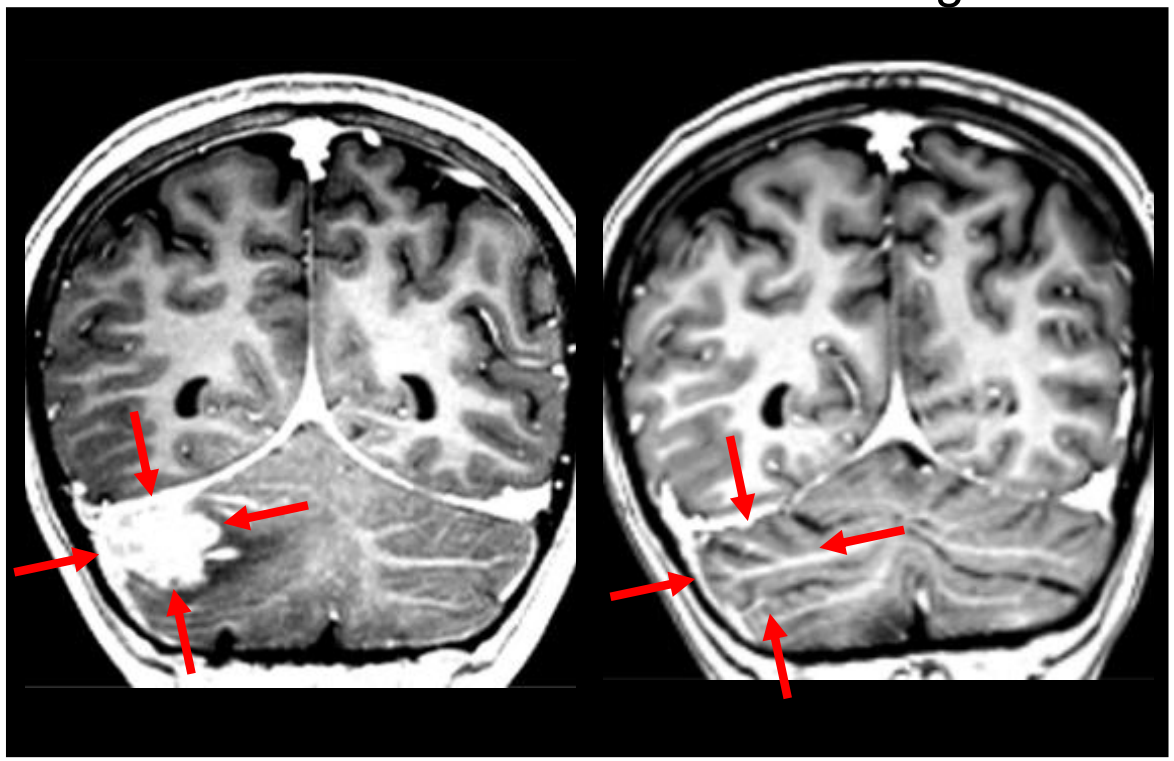
Ependymoma

Baseline | After 2 cycles of Core Regimen



Medulloblastoma

Baseline | After 2 cycles of Core Regimen



Shown are post-contrast T1-weighted images

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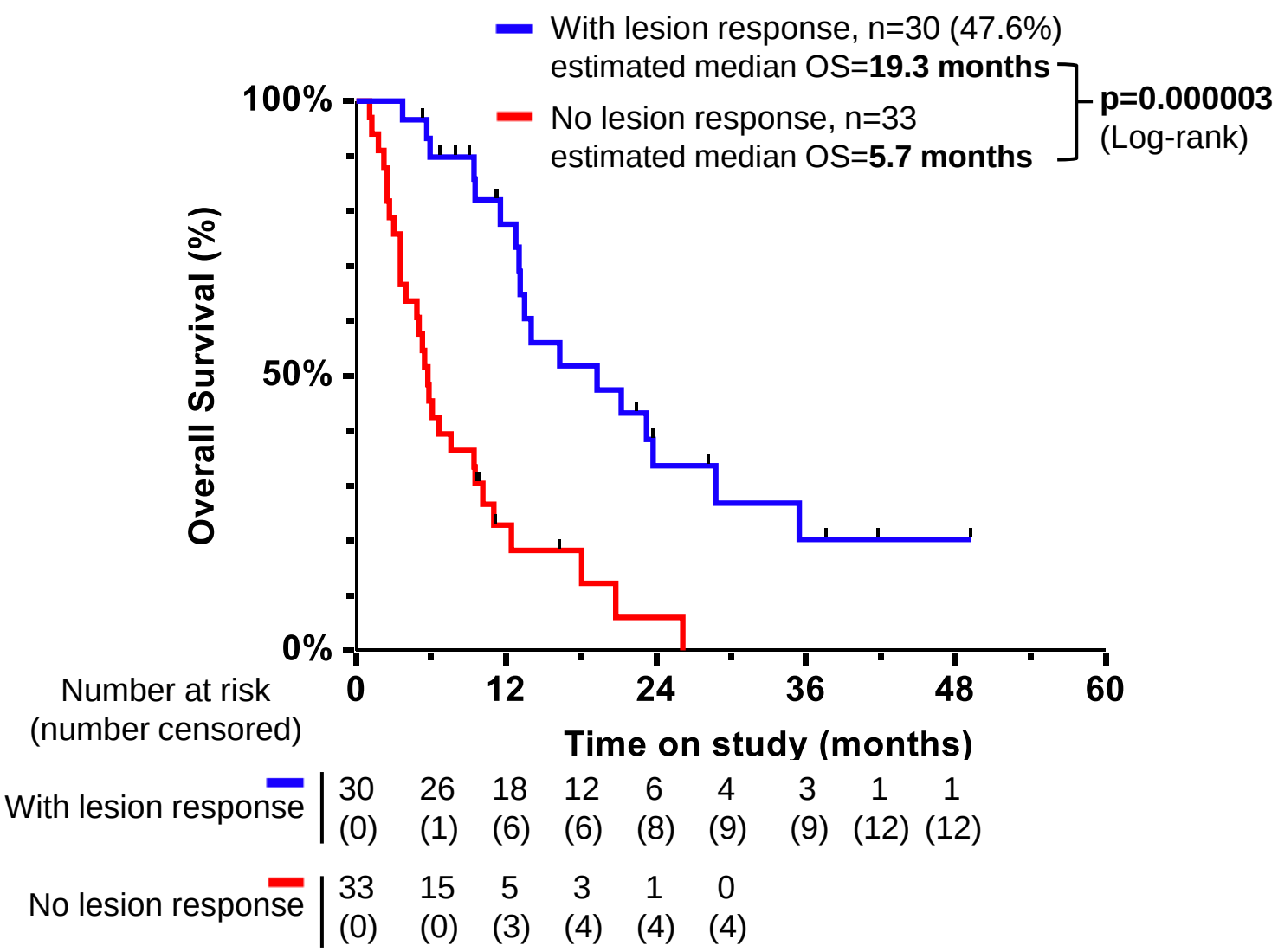
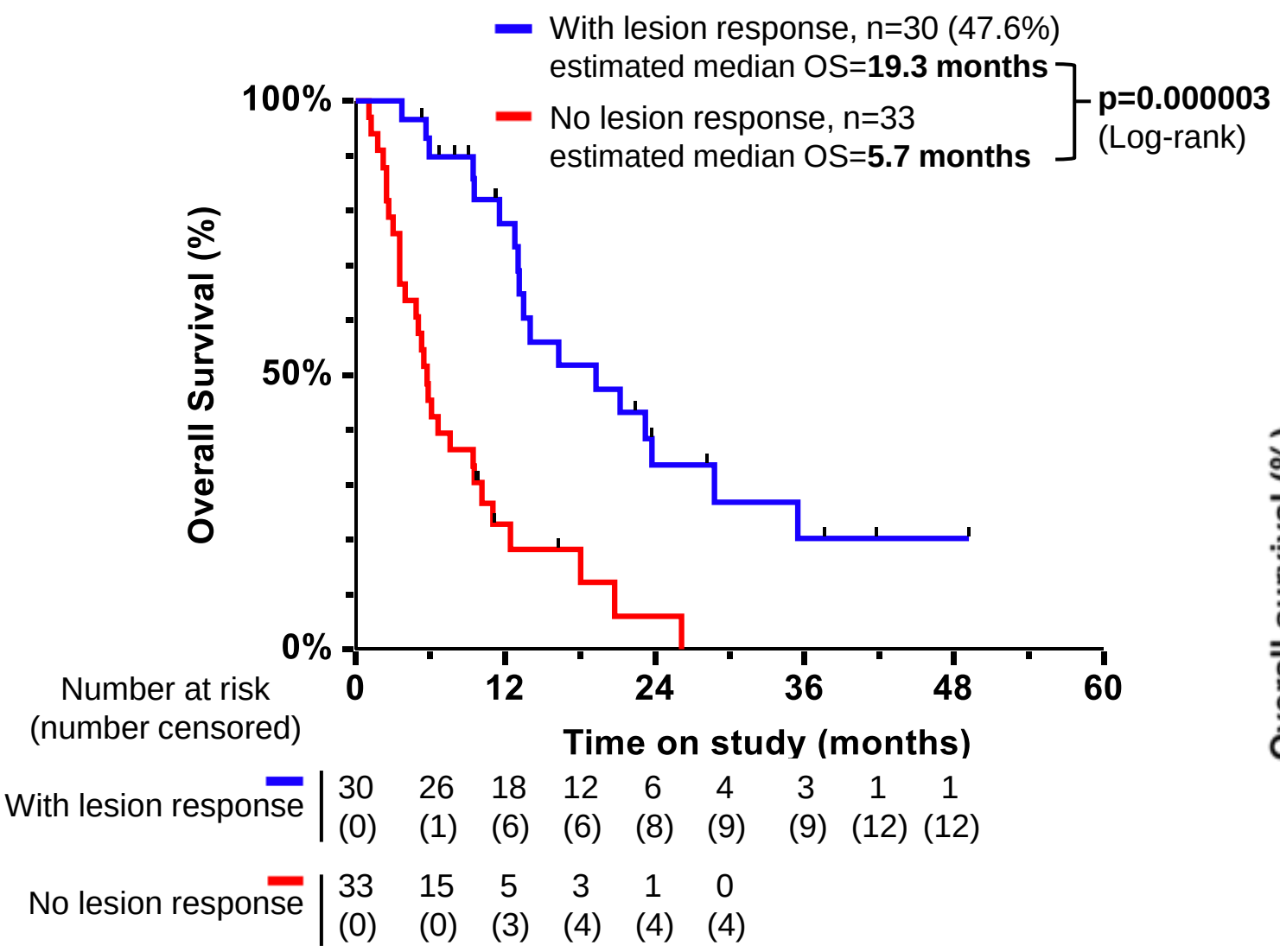
Response in any lesion correlates with survival



- 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 response-evaluable *recurrent disease* at interim analysis

  Not included:
  - (9 patients – newly diagnosed DIPG)
  - (3 patients – no active disease at entry)
  - (2 patients – GTR before first MRI)
  - (3 patients – too early to assess)
- **30/63 (47.6%)** showed at least one responsive lesion, by RAPNO criteria

Response in any lesion correlates with survival

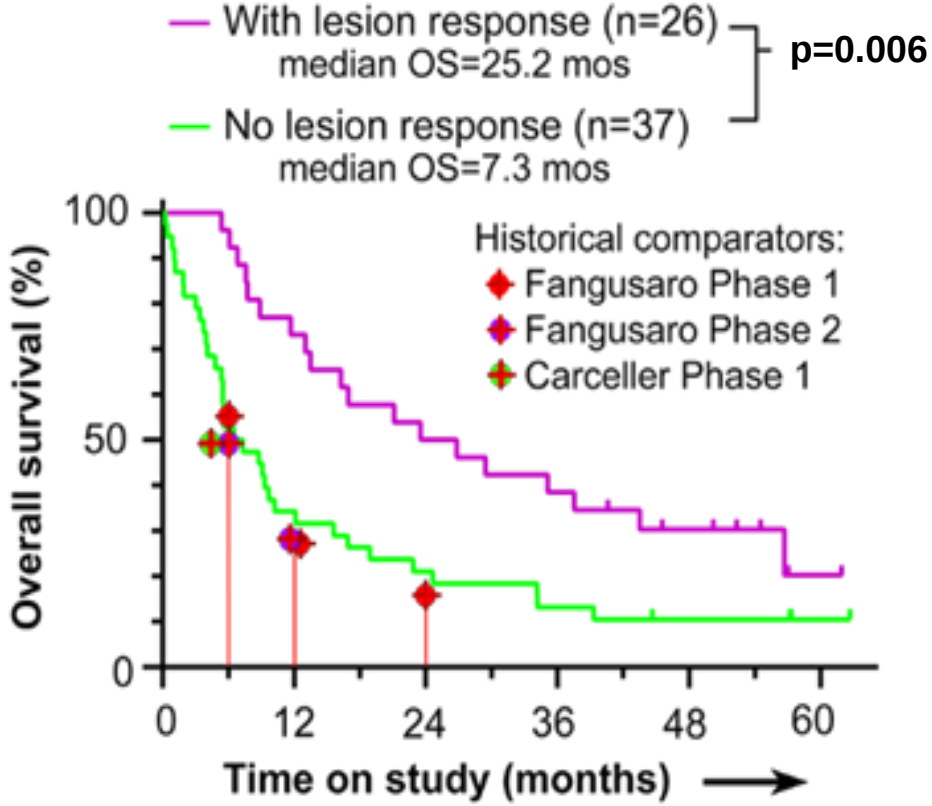


*Johnson TS, *et al.* 2023. *Neuro-Oncology.* 26(2):348–361.

Replicating data from the

NLG2105 phase 1 trial*

26/63 (41%) showed at least one responsive lesion, by RAPNO criteria



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.

“Adaptive Management” – cross-over salvage algorithm

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

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

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

Core regimen

Cohort 1 – Ependymoma

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

Cohort 2 – medulloblastoma

Cohort 3 – HGG

Cross-over at progression

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

Salvage regimen-1

- Indoximod at 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)

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Indoximod + cyclophos/etoposide: Patients experiencing high-grade adverse events (regardless of attribution)

	Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)
Any event	**14**	**74%**	**7**	**37%**	**1**	**5%**
Lung infection	2	11%	..		1	5%
Lymphocyte count decreased	1	5%	4	21%	..	
Neutrophil count decreased	3	16%	3	16%	..	
Platelet count decreased	1	5%	2	11%	..	
Anemia	2	11%	1	5%	..	
Dyspnea	1	5%	1	5%	..	
Hyponatremia	1	5%	1	5%	..	
Hypotension	..		1	5%	..	
Hypoxia	1	5%	1	5%	..	
Pneumothorax	..		1	5%	..	
White blood cell decreased	3	16%	1	5%	..	
Vomiting	4	21%	..		..	
Seizure	3	16%	..		..	
Ataxia	2	11%	..		..	
Dysarthria	2	11%	..		..	
Dysphagia	2	11%	..		..	
Headache	2	11%	..		..	
Muscle weakness, localized	2	11%	..		..	
Nausea	2	11%	..		..	

Data are n (%), with each participant reported once at the highest grade experienced.

Shown are treatment-emergent adverse events occurring in at least 2 patients for Grade 3 or 4; and all grade 5 events.

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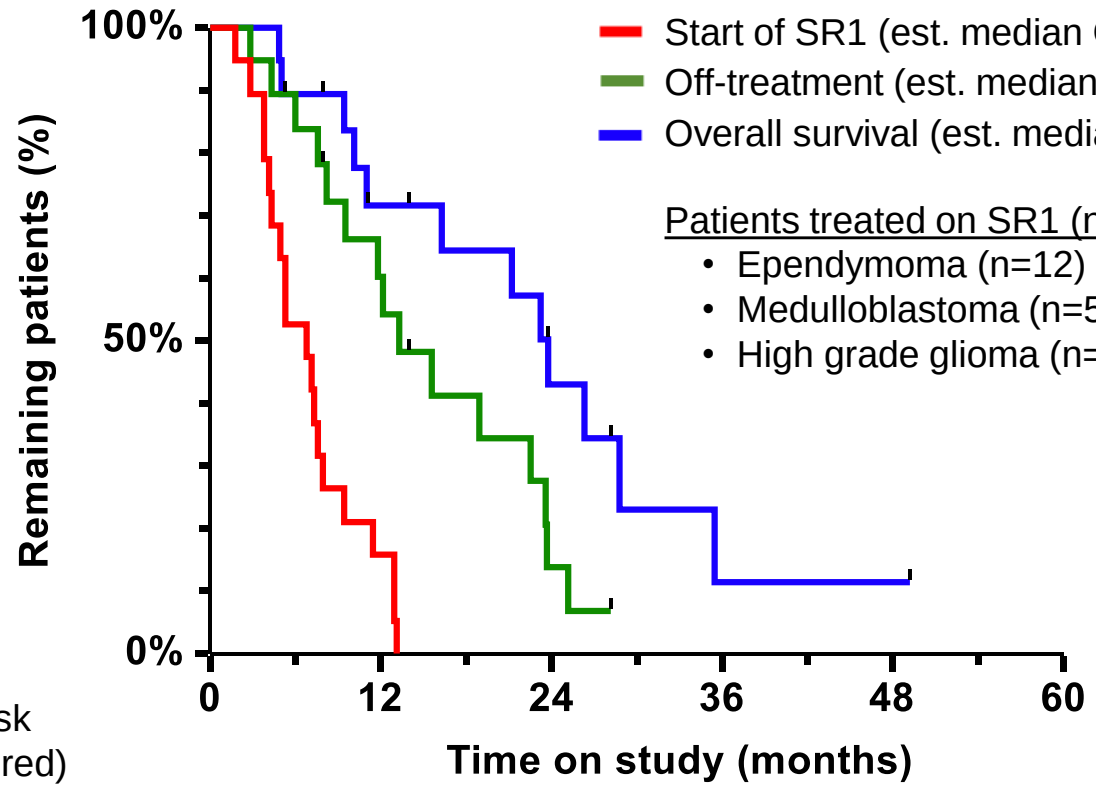
Cross-over to Salvage Regimen-1 (SR1) at progression



Start of SR1 (est. median OS= **6.8 months)**
Off-treatment (est. median OS= **13.3 months)**
Overall survival (est. median OS= **23.8 months)**

p=0.0001

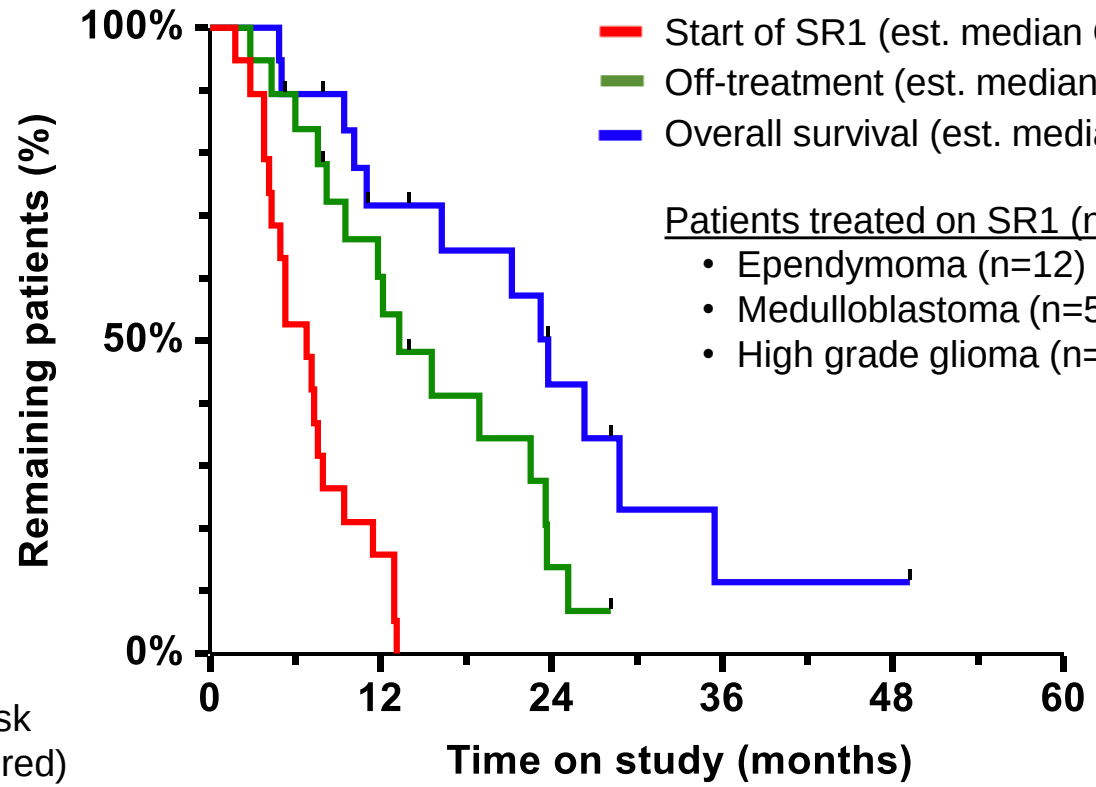
Patients treated on SR1 (n=19)

- Ependymoma (n=12)
- Medulloblastoma (n=5)
- High grade glioma (n=2)

Number at risk
(number censored)

Start of SR1	19 (0)	10 (0)	3 (0)	0 (0)					
Off-treatment	19 (0)	16 (0)	10 (3)	6 (4)	2 (4)	0 (4)			
Overall Survival	19 (0)	16 (1)	11 (3)	9 (4)	5 (5)	2 (6)	1 (6)	1 (6)	1 (6)

Cross-over to Salvage Regimen-1 (SR1) at progression



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Patients treated on SR1 (n=19)
- Ependymoma (n=12)
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- High grade glioma (n=2)

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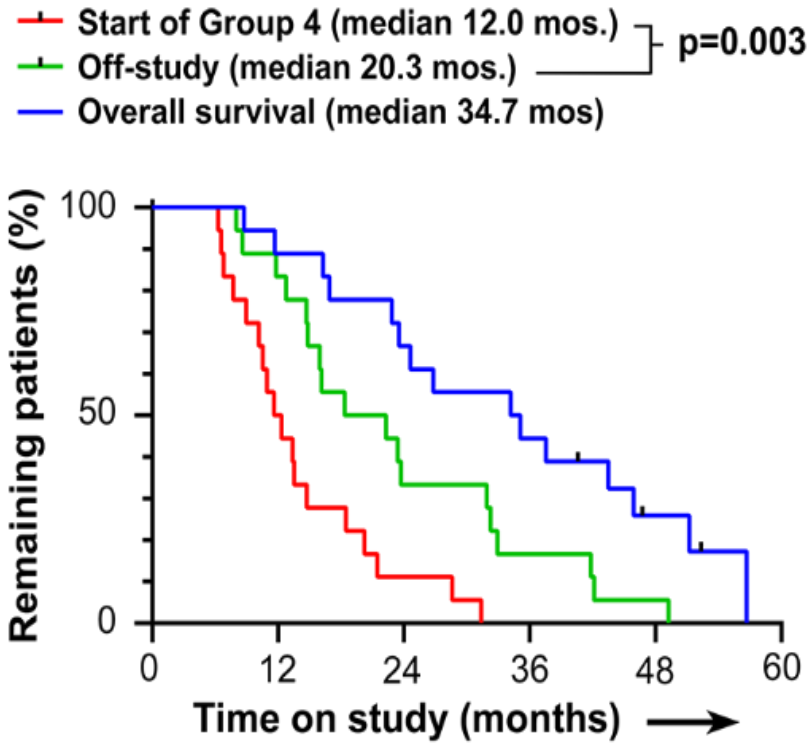
Replicating data from the

NLG2105 phase 1 trial*



*Johnson TS, *et al.* 2023. *Neuro-Oncology.* 26(2):348–361.

Children with long-term control of recurrent brain cancer (at least 48 months free of disease)

NLG2105 (phase 1) trial*:

Patient #	Age (years)	Diagnosis	Metastatic (Y/N)	Time Treated (months)	Received Radiation (Y/N)	SLR? (Y/N)	Time Off Therapy (months)	Received Additional Therapy
027	18	Ependymoma	Y	26	N	N	57	N
065	5	Ependymoma	N	60**	N	N	13	N
023	14	Medulloblastoma	Y	32	N	Y	56	N
069*	15	Medulloblastoma	Y	5	Y	Y	66	Y*

*This patient stopped indoximod-based therapy due to a new diagnosis of myelodysplastic syndrome (MDS), which was treated with 6 cycles of azacytidine monotherapy.

MDS was in remission after azacytidine cycle #4, and azacytidine was stopped after cycle #6 at the patient's request; 6 months later an MRI showed resolution of the brain cancer.

Both remissions are sustained to current day.

**This patient continued therapy on a SP-IND protocol after the NLG2105 ended.

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*Johnson TS, *et al.* 2023. *Neuro-Oncology.* 26(2):348–361.

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Children with long-term control of recurrent brain cancer

GCC1949 (phase 2) trial:

Patient #	Age (years)	Diagnosis	Metastatic (Y/N)	Time Treated (months)	Received Radiation (Y/N)	SLR? (Y/N)	Time Off Therapy (months)	Received Additional Therapy
007*	17	Ependymoma	N	24	N	Y	25	Y*
010	13	Ependymoma	N	26	Y	**	21	N
016	4	Ependymoma	N	14	N	***	27	N
022	9	Ependymoma	Y	26	N	Y	13	N
031	7	Ependymoma	Y	14	Y	***	19	N
017	6	Medulloblastoma	Y	24	N	Y	18	N

*This patient had local relapse, stopped GCC1949, had a GTR followed by brachytherapy, and remains in remission.

**This patient had GTR before after cycle #1 of GCC1949 therapy.

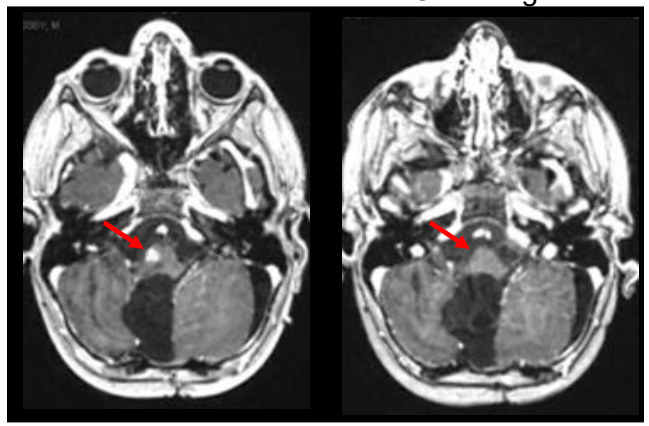
**These patients had GTR (NED) before starting GCC1949 therapy.

Treatment-emergent CD8+ effector T cells in peripheral blood

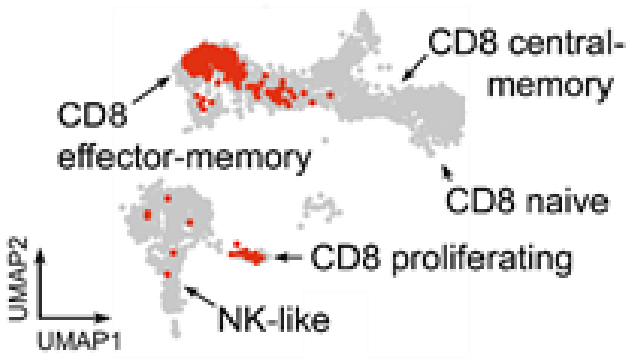
- Paired Single-cell RNA-sequencing and single-cell TCR-sequencing of PBMCs (peripheral blood mononuclear cells)
- Hypothesis: Treatment with IDO blockade allows dendritic cells to mature and cross-present tumor antigen in tumor-draining lymph nodes (TDLNs), leading to activation and clonal expansion of circulating CD8 T cells.

Medulloblastoma

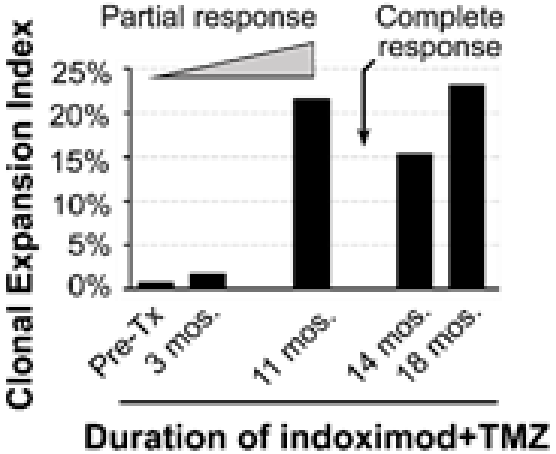
Baseline | After 2 cycles of Core Regimen



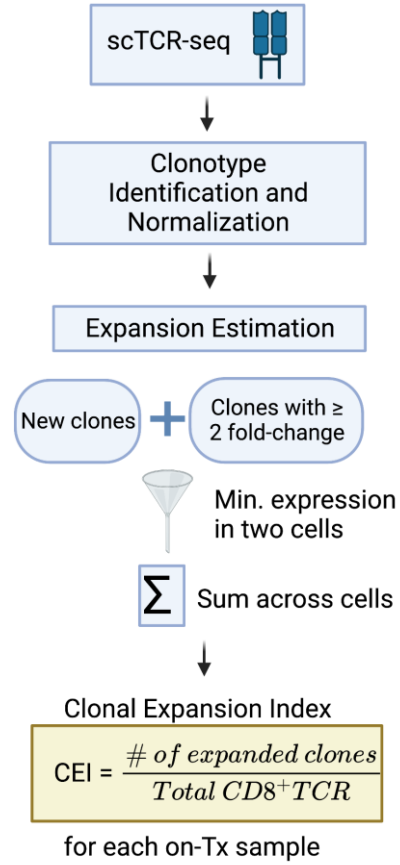
Patient #17 (Indoximod + TMZ x 11 mos)
Azimuth reference clusters (CD8 / NK)



Patient #17 - Clonal Expansion Index



Quantitation of clonal expansion using the Clonal Expansion Index (CEI)



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Figures adapted from a poster (Johnson TS, *et al*.) presented at the 2023 Annual Meeting of the American Association for Cancer Research (AACR). April 18, 2023. Orlando, Florida.

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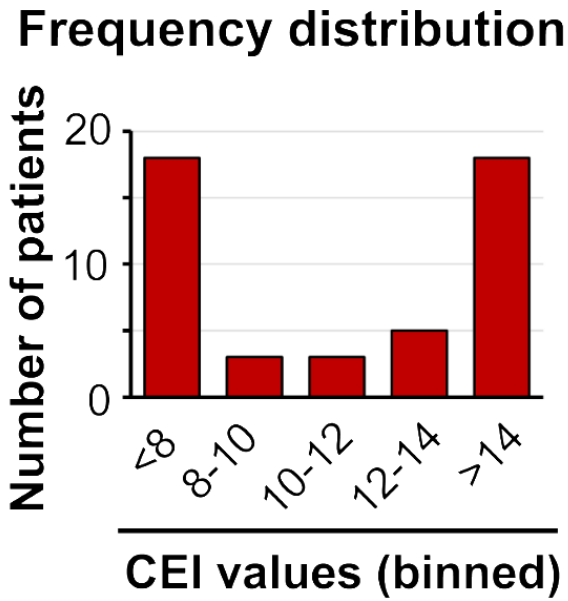
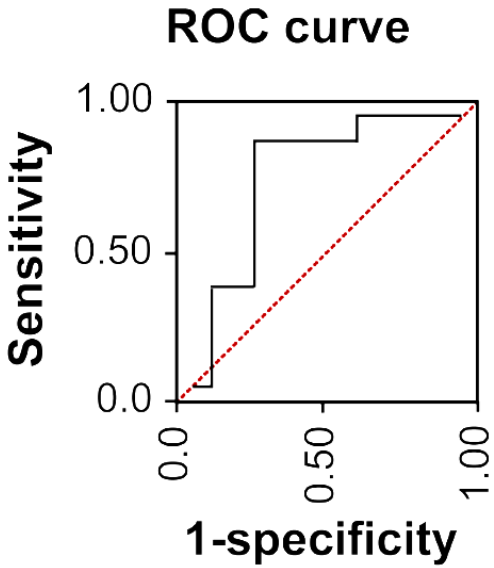
Assay Development: an on-treatment pharmacodynamic measurement of immune activation (Clonal Expansion Index)

- The Training Set for the analytic pipeline comprised n=44 patients selected across multiple indoximod-based studies (**NLG2015, GCC1949, and GCC2020**)
    - Including patients with recurrent medulloblastoma, ependymoma and high-grade glioma; and newly-diagnosed DIPG





Optimal cut-point
CEI=8.6%

Sensitivity = 91%

Specificity = 77%

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Figures adapted from a poster (Pacholczyk R, *et al*.) presented at the 2024 Annual Meeting of the Annual Meeting of the American Society of Clinical Oncology (ASCO). June 1, 2024. Chicago, Illinois.

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Peak CEI cutoff threshold stratifies subjects into "Immune Responders" vs "Non-responders"

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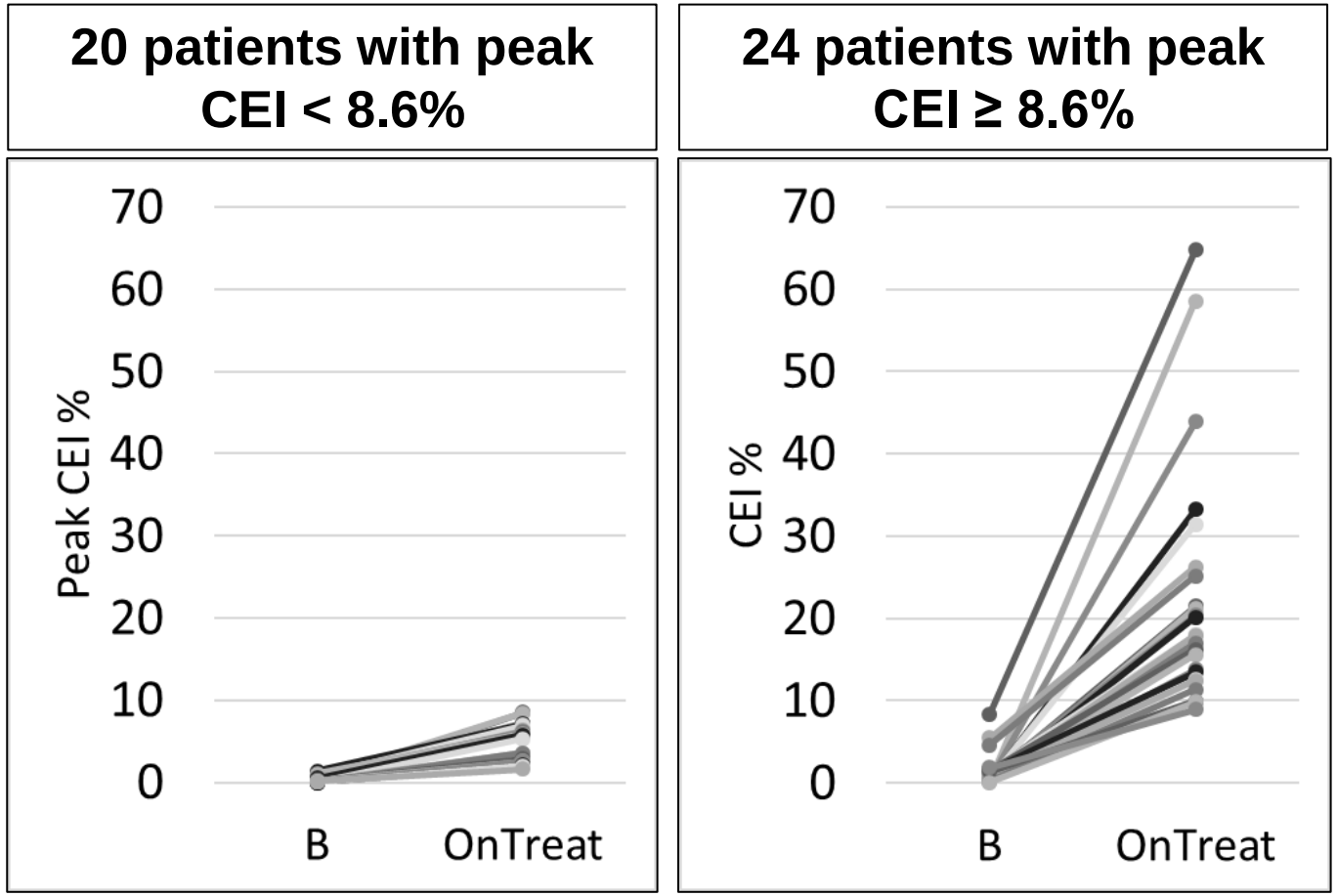

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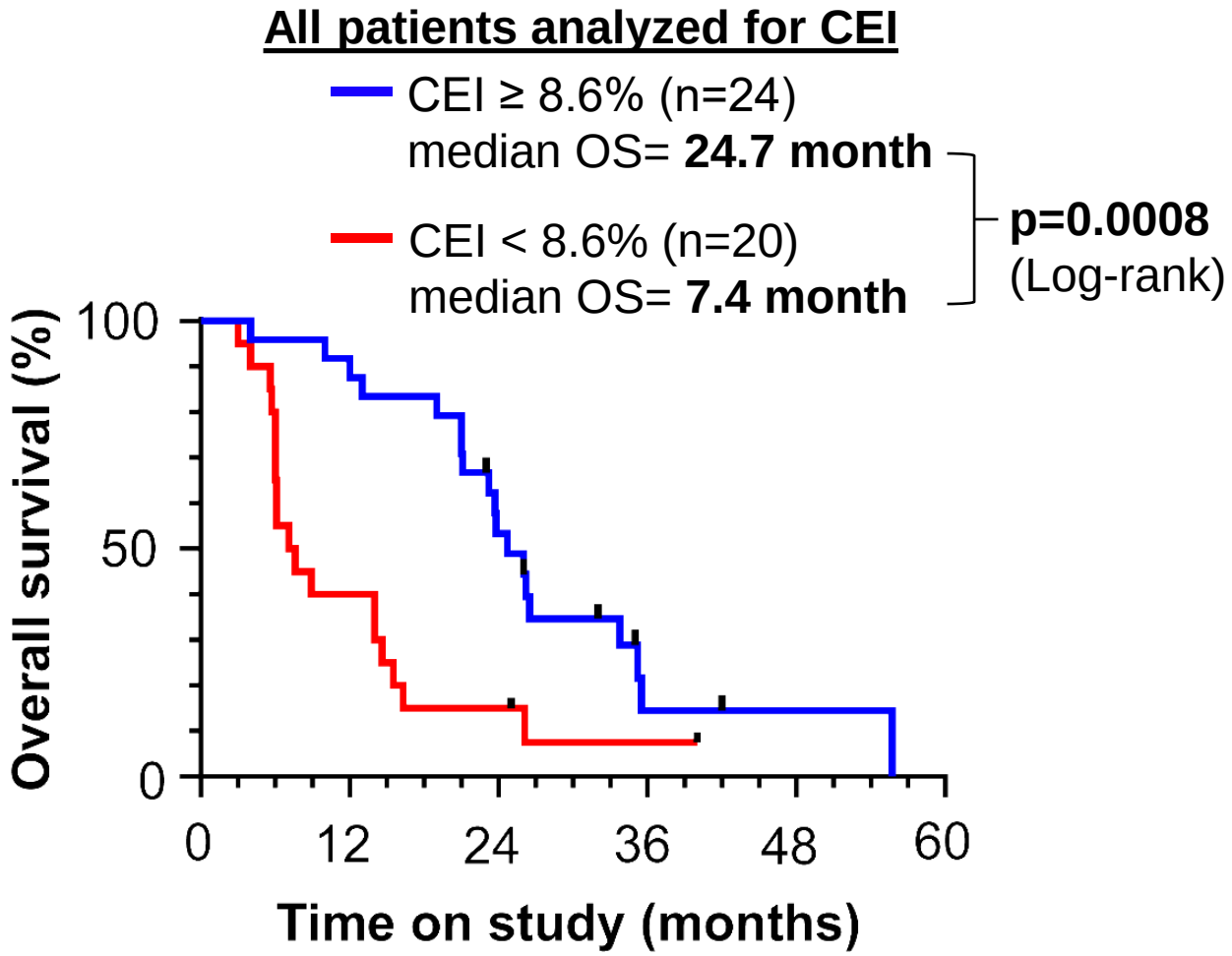
- The Training Set for the analytic pipeline comprised n=44 patients selected across multiple indoximod-based studies (**NLG2015, GCC1949, and GCC2020**)
  - Including patients with recurrent medulloblastoma, ependymoma and high-grade glioma; and newly-diagnosed DIPG
  - Patients were stratified by whether their CEI was above (blue line) or below (red line) 8.6% of total CD8+ T cells



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High concordance between the expanded CEI clonotypes in peripheral blood and TCR sequences in tumor biopsy.

Fraction of circulating T cells matching a clonotype found in tumor		
Patient	Treatment-expanded clonotypes (CEI)	Other T cells
Patient A	36%	4%
Patient B	39%	2%
Patient C	66%	3%
Patient D	65%	2%
Patient E	70%	1%

Five of the patients in the training-set had on-treatment biopsies available for bulk RNA-sequencing of TCR beta-chain.

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 6yo and older)
  - (First-in-human trial using this combination; IND-holder T. Johnson)

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