Radio-chemo-immunotherapy using the IDO-inhibitor indoximod for childhood brain cancer (NCT02502708)

Theodore S. Johnson, M.D., Ph.D.

Pediatric Immunotherapy Program
Medical College of Georgia (MCG)
Georgia Cancer Center
Augusta University

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

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Disclosures

- Theodore S. Johnson, M.D., Ph.D.
  - NewLink Genetics Corporation is partially funding a pediatric clinical trial which will be discussed
    - The presenter receives no direct financial support from NewLink Genetics Corporation
  - No other relevant financial relationships exist with respect to this presentation
  - Off-label use of chemotherapy drugs will be discussed for pediatric patients

Can combined radio-chemo-immunotherapy improve efficacy with lower toxicity?

- Pediatric brain tumors are ~70% curable
- In the relapse setting, conventional therapy is either not effective, or works for some cases but is too toxic
  - Relapsed glioblastoma
    - Radiation - unclear benefit
    - Chemotherapy - does not work
  - Relapsed medulloblastoma
    - Many patients have already failed tandem autologous transplant
  - Relapsed ependymoma
    - Full dose radiation - works but too toxic for 80% of cases
    - Lower dose radiation - doesn't work
    - Chemotherapy – doesn't work

Hypothesis

Radio-immunotherapy using IDO-blockade may act as a one-time endogenous vaccine to activate native immunity

… but must be followed by

Cyclic chemo-immunotherapy to achieve sustained responses and late responses.

Resulting anti-tumor immunity may allow ***less intense conventional therapy to be effective.***

Phase I trial schema (NCT02502708)

Relapsed or refractory brain tumor patients age 3-21 years of age

Group 1: "Core Regimen"

- Indoximod (study dose, PO, twice daily on days 1-28)
  - Dose-escalation
  - PK analysis
- Temozolomide (200 mg/m^2/day, PO, daily on days 1-5)
- 28-day cycles

Indoximod dose-levels:

- 80% of adult RP2D (25.6 mg/kg/day divided BID)
- 100% of adult RP2D (32 mg/kg/day divided BID)
- 120% of adult RP2D (38.4 mg/kg/day divided BID)

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Group 3: Up-front Radiation therapy with indoximod

- Indoximod (study dose, PO, twice daily)
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- Individualized radiation plan
- Followed by the "Core Regimen" as maintenance therapy

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Radiographic evidence of progression (escape lesions) can be managed with continued indoximod and:

- Surgical resection (regain local control)
- Targeted radiation (regain local control)
- Cross-over to 2nd-line chemo (cyclophosphamide/etoposide)

Phase I trial of indoximod in combination with temozolomide-based therapy for children with progressive primary brain tumors (NCT02502708 / NLG2105)

Relapsed or refractory brain tumor patients age 3-21 years of age

Group 2: Indoximod (RP2D) plus temozolomide "Core Regimen" (expansion cohorts) (**Open**, using indoximod at DL3)

- Group 2a: High-grade glioma
- Group 2b: Ependymoma
- Group 2c: Medulloblastoma
- Group 2d: Other histology
- *Group 2e: Newly diagnosed DIPG (upfront radiation/indoximod)
  - Opens after a 6-patient pilot cohort enrolls in Group 3

Group 4: Cross-over Arm (**Open**)

- Indoximod (PO, twice daily on days 1-28)
- Cyclophosphamide (2.5 mg/kg/dose, PO, daily on days 1-21)
- Etoposide (PO, daily on days 1-21)
- 28-day cycles

Patient demographics (dose-escalations)

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

* includes one each gliosarcoma, bithalamic glioma, ganglioglioma

** includes one previously classifies as PNET

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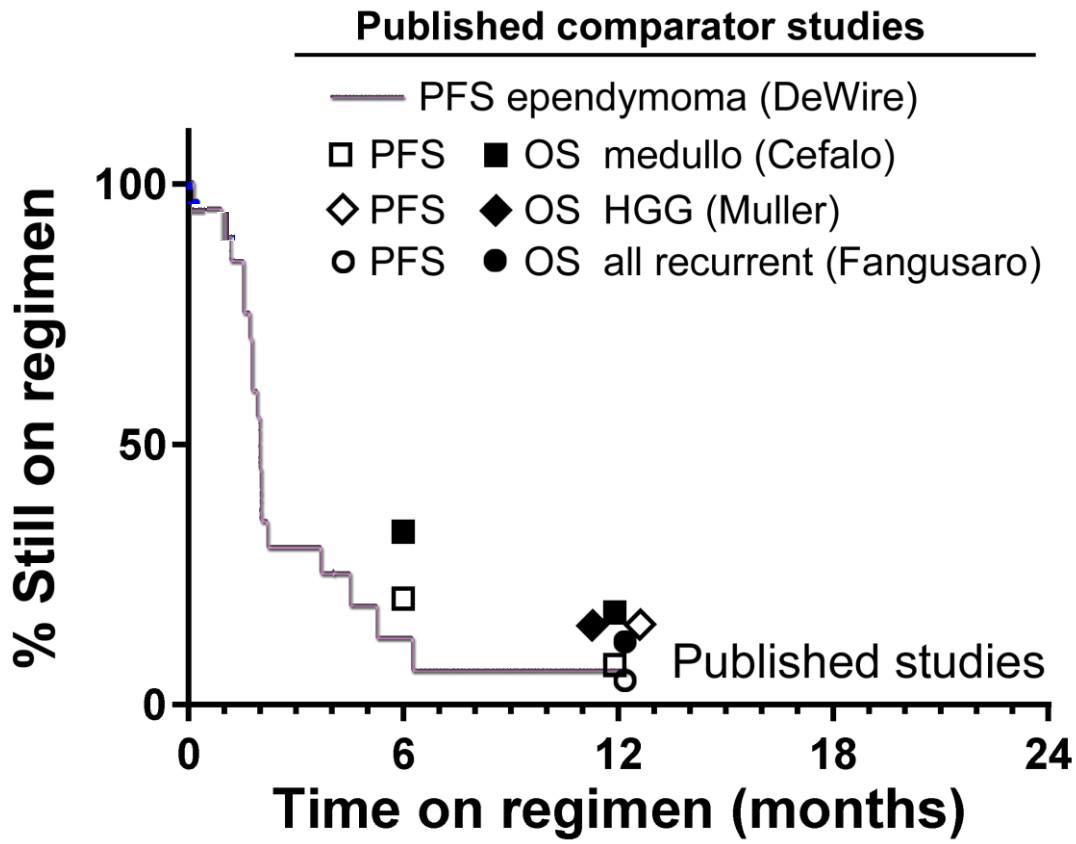
Historical control data for relapsed brain tumors



Historical controls adapted from:

DeWire M, *et al*. 2015. *J Neurooncology*. 123:85.
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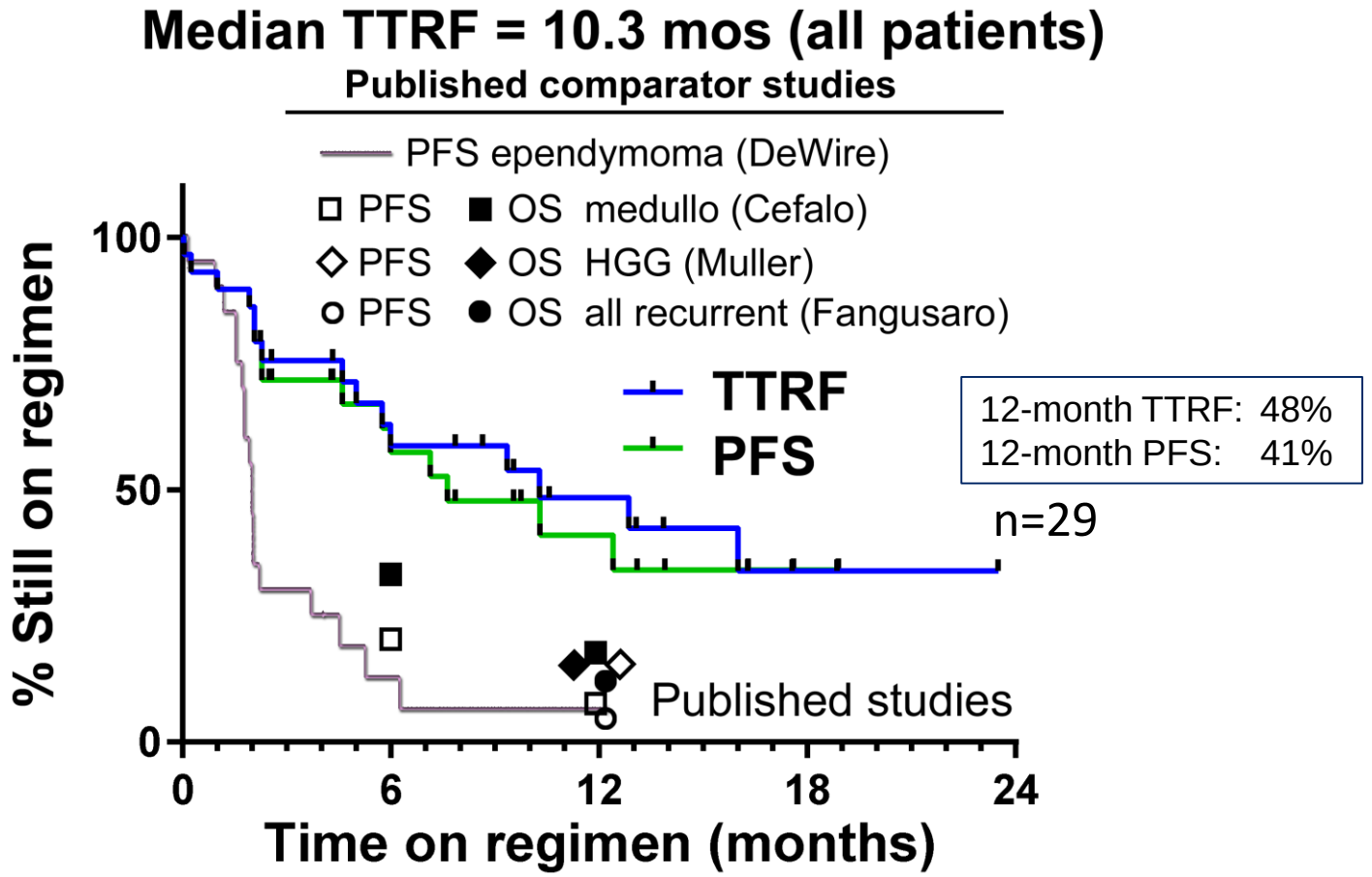
Favorable outcome with indoximod-based therapy



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TTRF, Time To Regimen Failure;
PFS is not yet centrally reviewed

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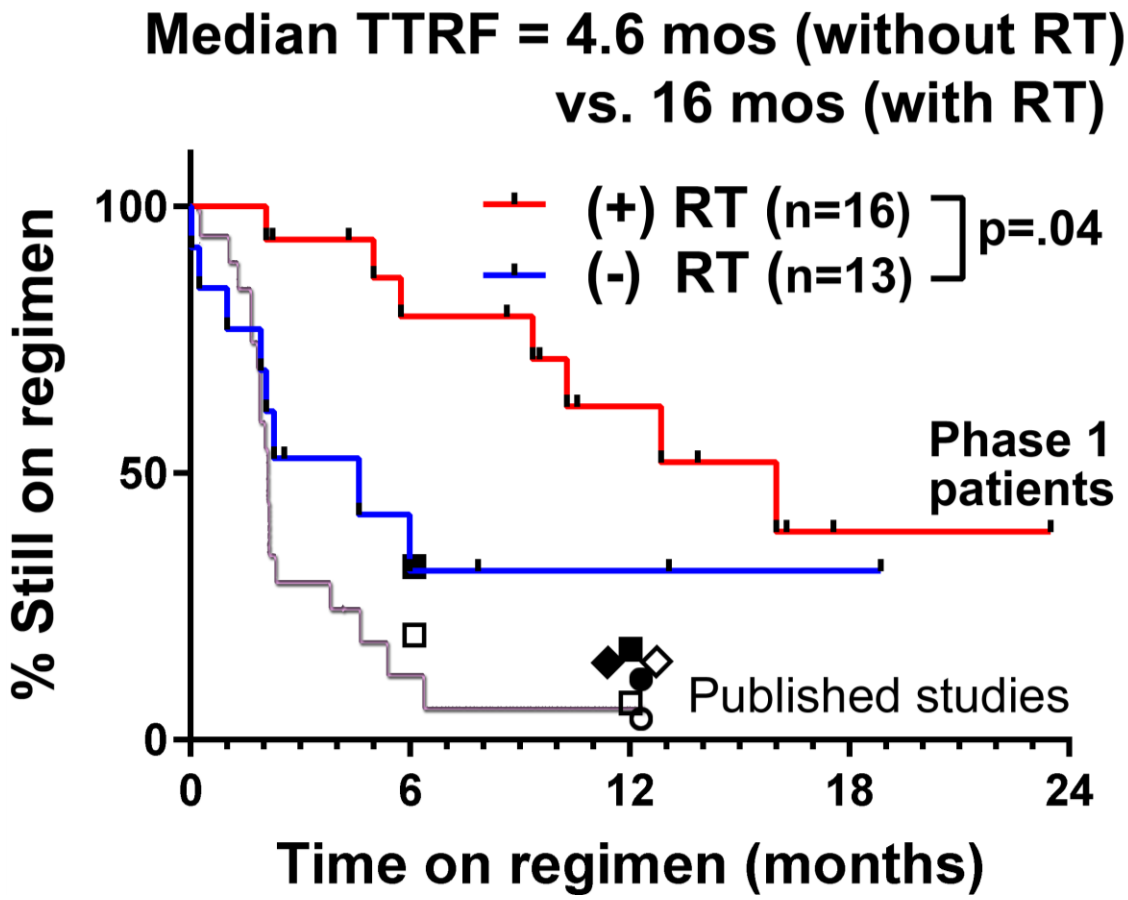
Radio-immunotherapy improves time to regimen failure (TTRF)



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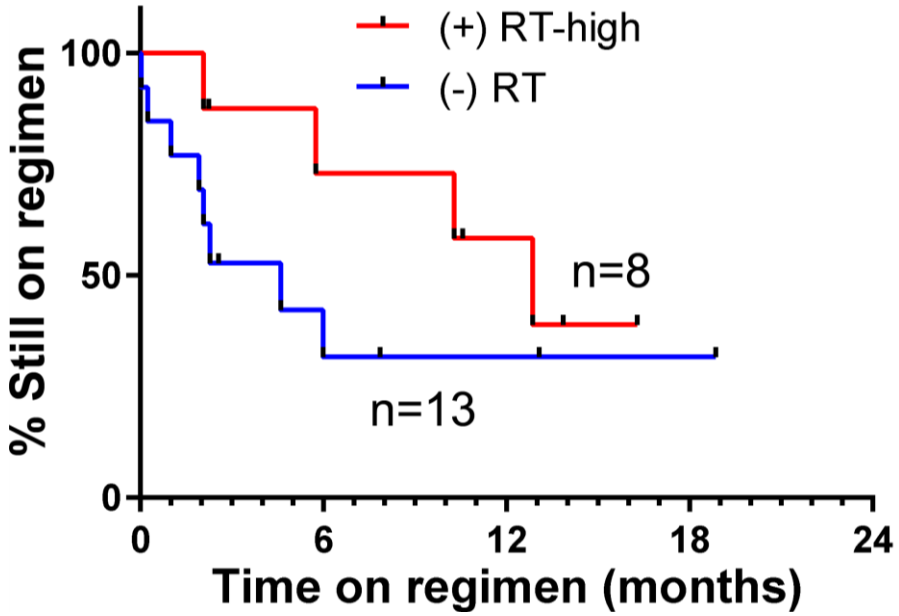
Radio-immunotherapy improves time to regimen failure (TTRF)

	High-dose RT (n=8)	vs. No RT (n=13)
Median TTRF	**13 months**	4.6 months
RT dose	≥ 50 Gy	
Median target vol.	165 cm3	
RT to all tumors	6/8 (75%)	



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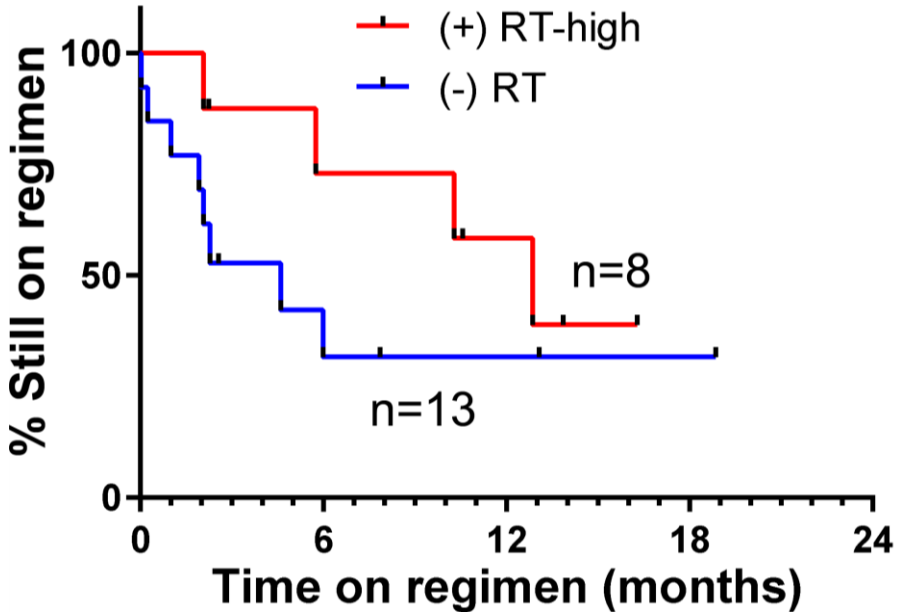

Hypothesis: *Radio-immunotherapy* followed by *cyclic chemo-immunotherapy* may act as an endogenous vaccine to achieve anti-tumor immunity and ***allow less intense conventional therapy to be effective***.

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RT dose	≥ 50 Gy	
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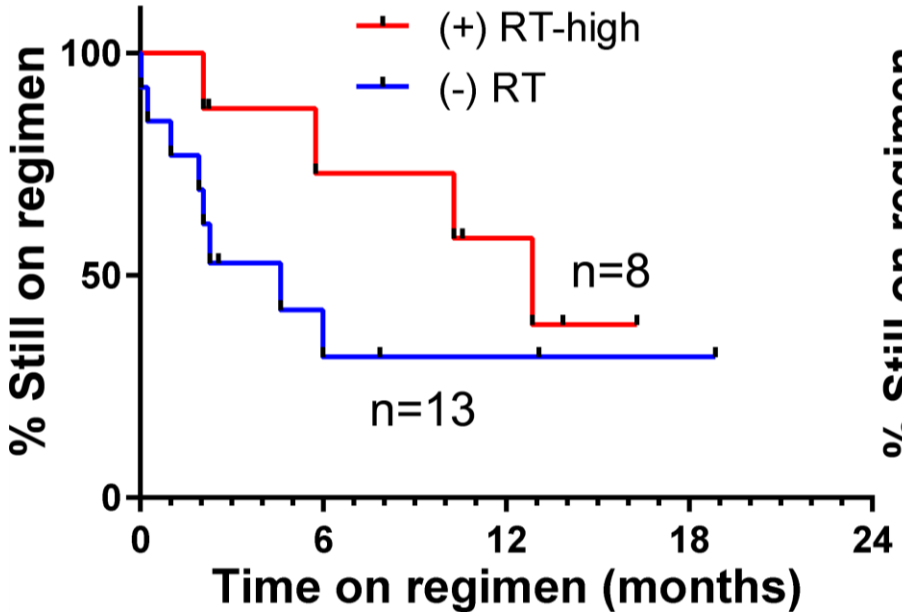
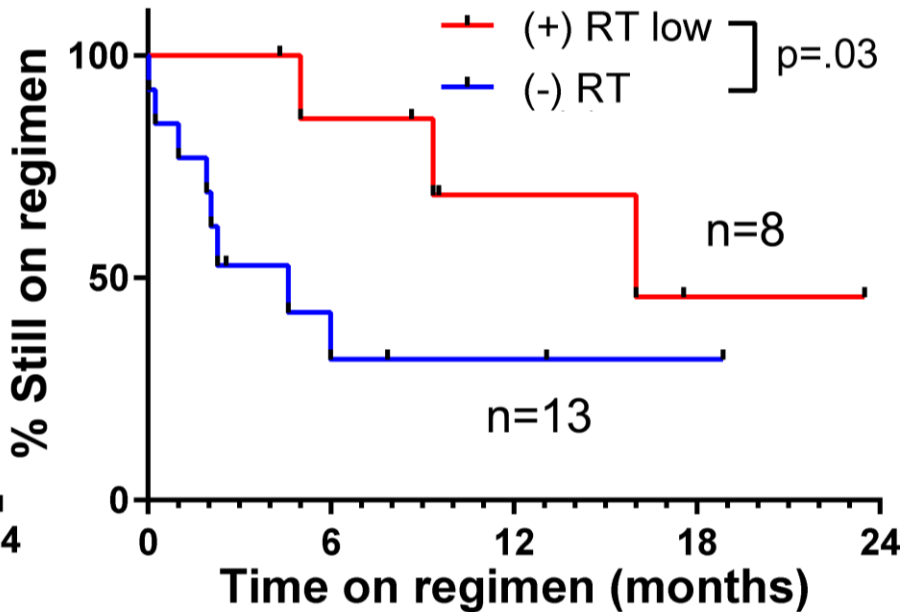
RT to all tumors	6/8 (75%)	

	Low-dose RT (n=8)	vs. No RT (n=13)
Median TTRF	**16 months**	4.6 months
RT dose	≤ 30 Gy	
Median target vol.	108 cm3	
RT to all tumors	2/8 (25%)	





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Conclusion

- **First empiric evidence that adding immunotherapy may have a significant dose-sparing effect on highly toxic conventional therapy**

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Patterns of response to immunotherapy

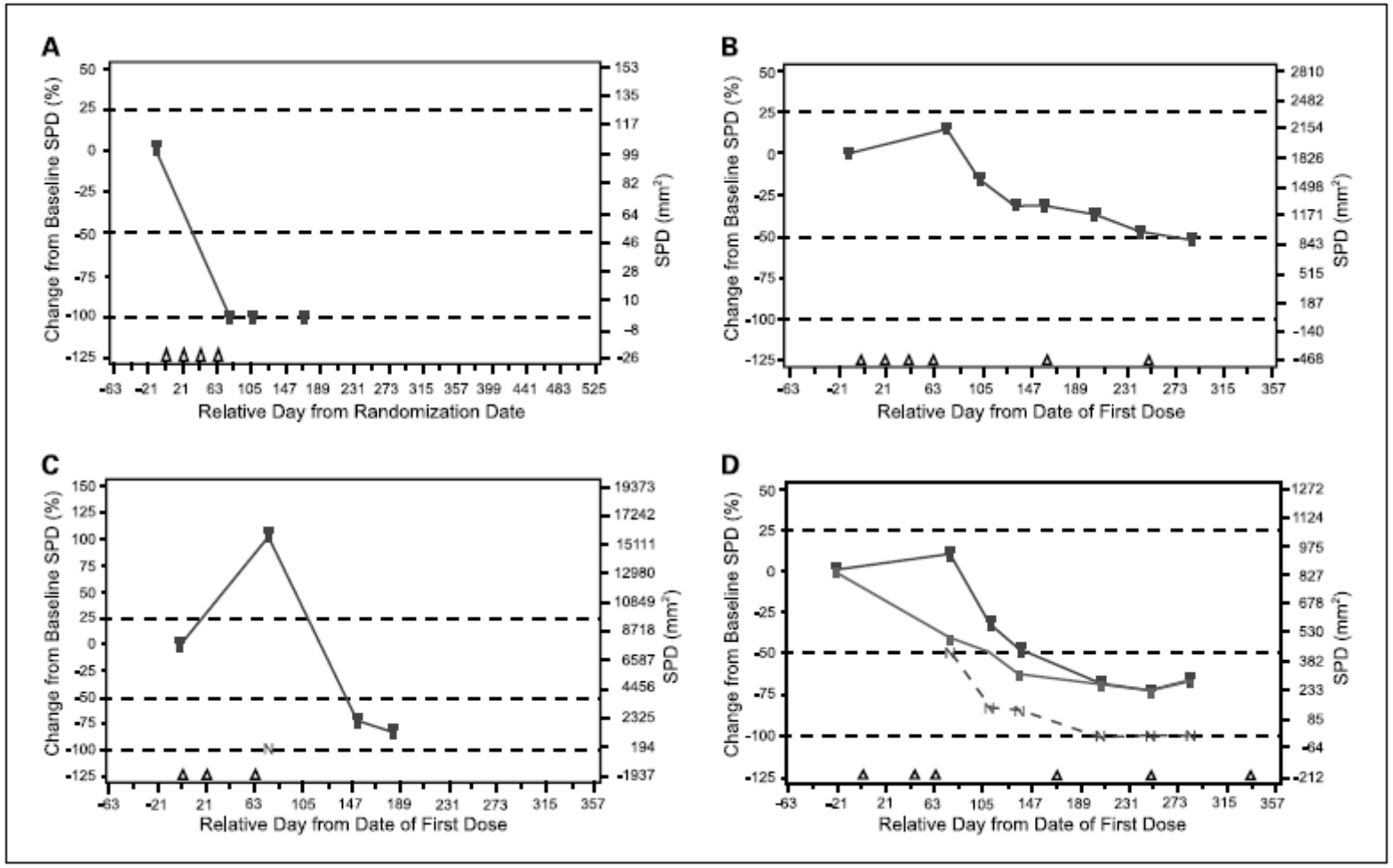

Fig. 1. Patterns of response to ipilimumab observed in advanced melanoma. Shown are the four response patterns observed in advanced melanoma

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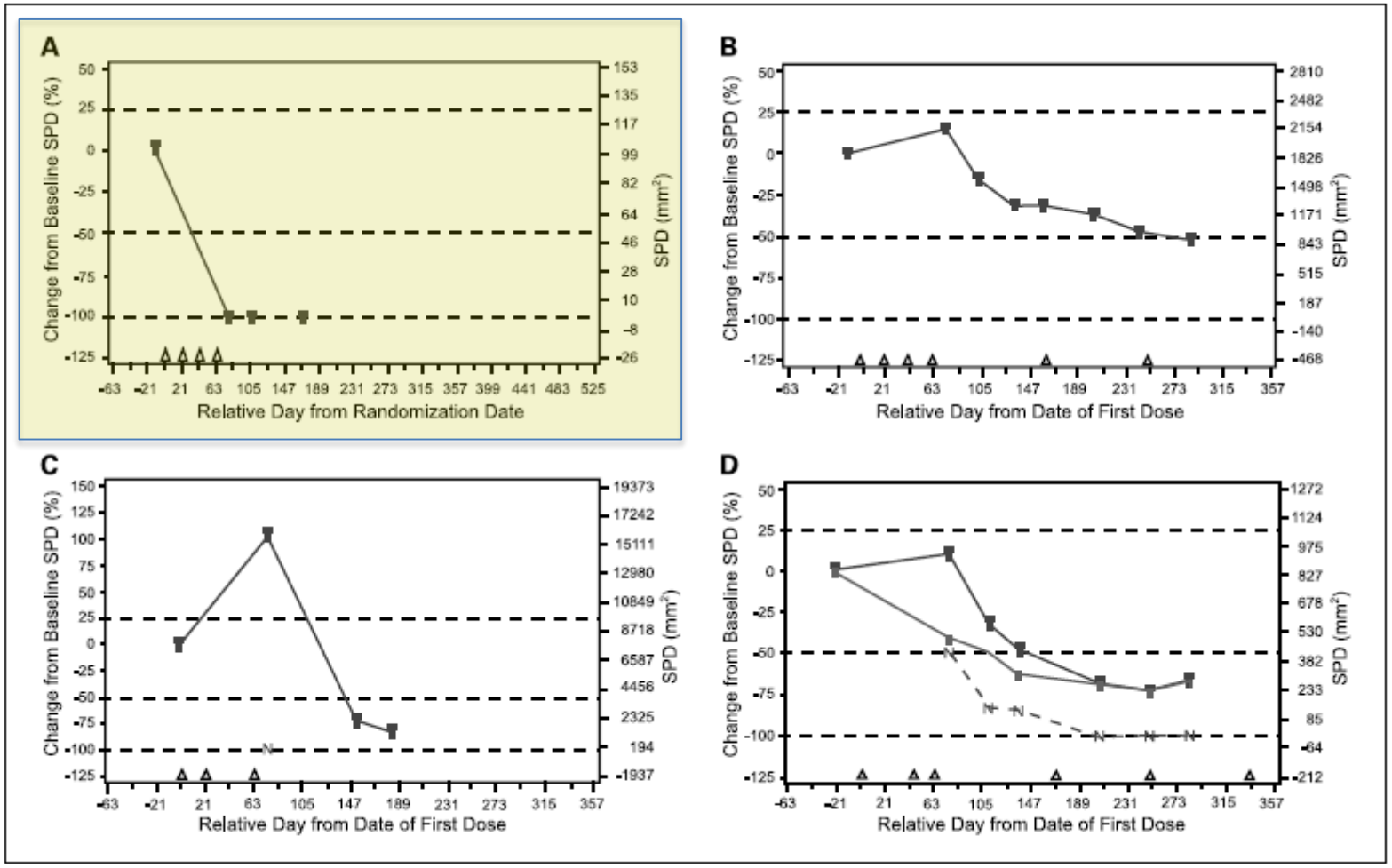
Figure adapted from: J. Wolchok, *et al*. 2009, *Clin Cancer Res*. 15:7412.

Standard pattern of response



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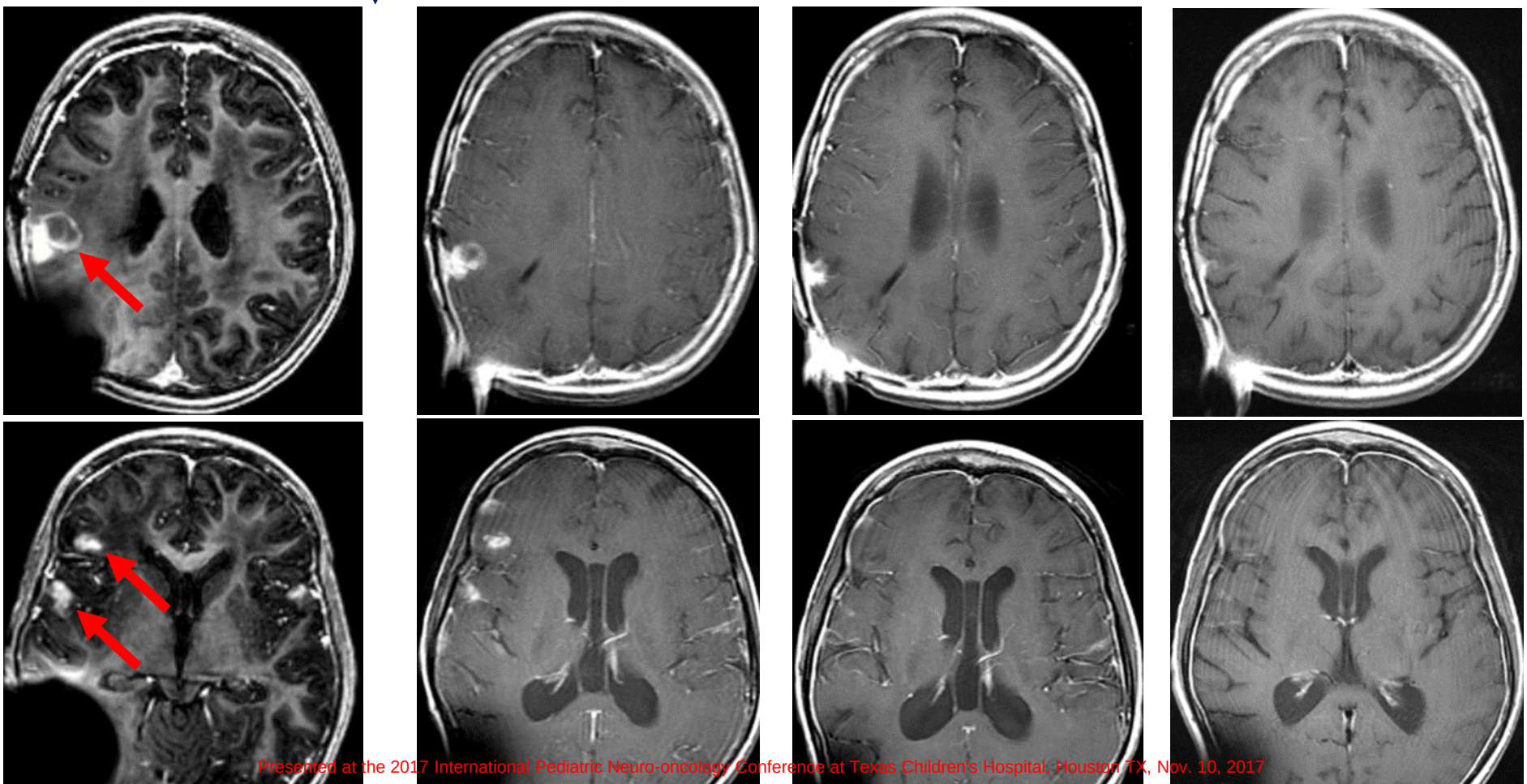
Standard pattern of response

Begin Indoximod +
Radiation (30 Gy in 20 fractions)

11 yo with metastatic medulloblastoma

followed by Indoximod + Temozolomide

Pre-treatment | After radiation | 2 cycles | 4 cycles



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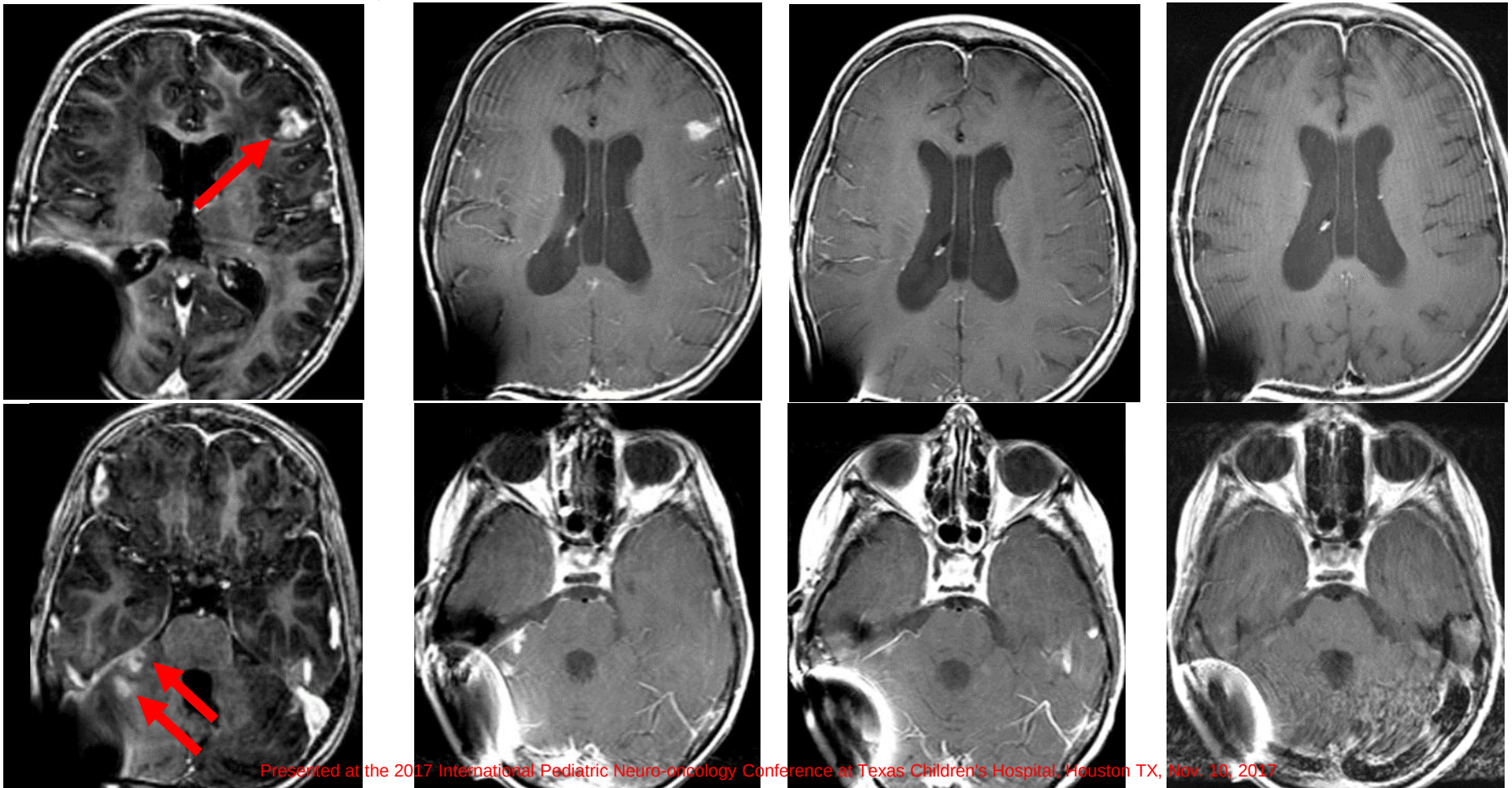
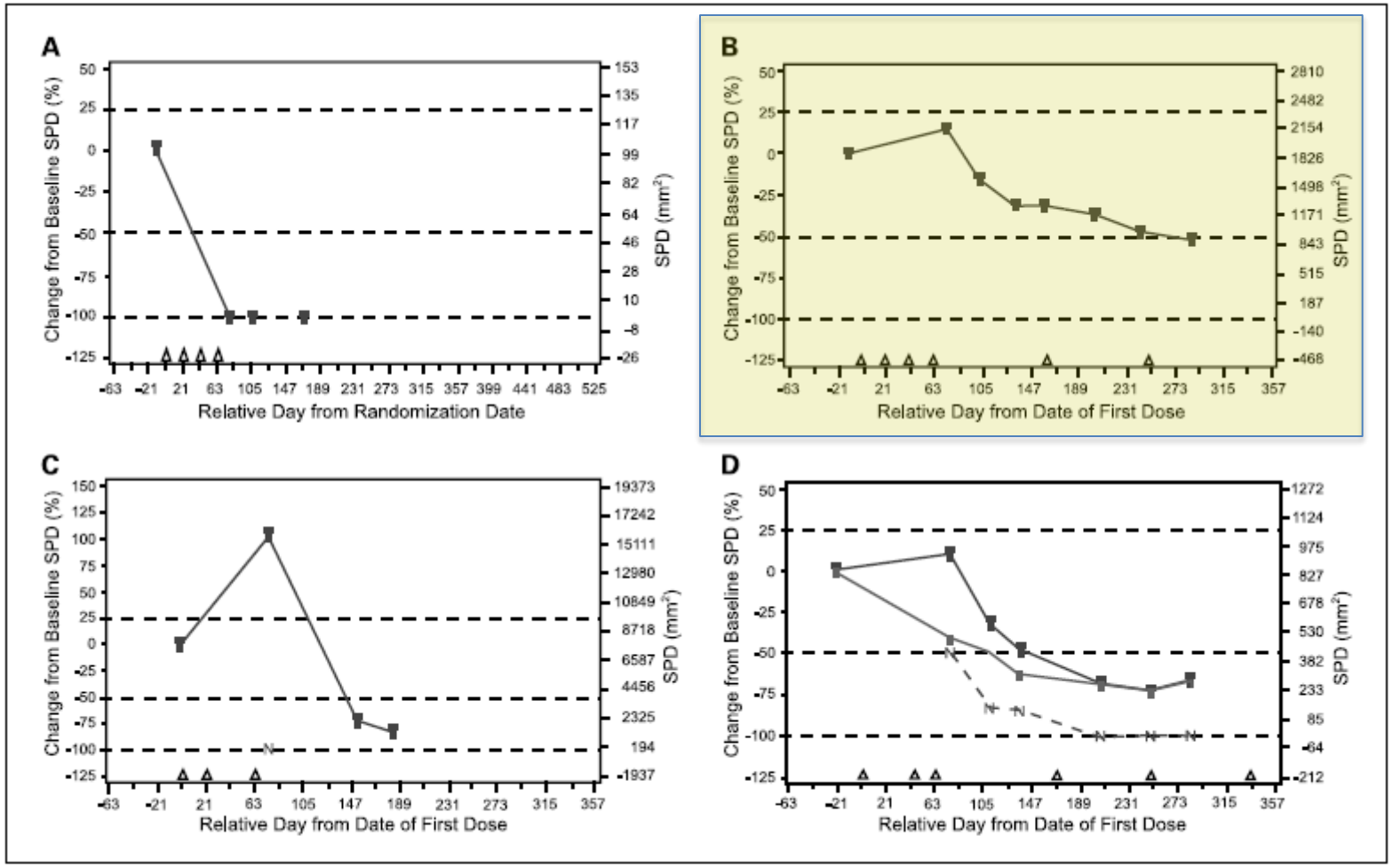


Sustained stabilization of growing disease



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Begin
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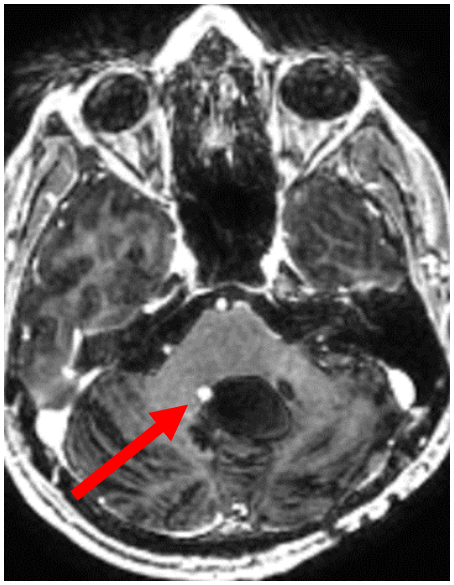
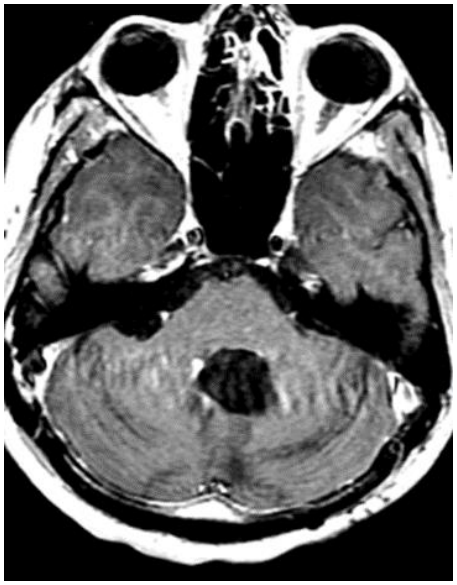
19 yo with metastatic ependymoma

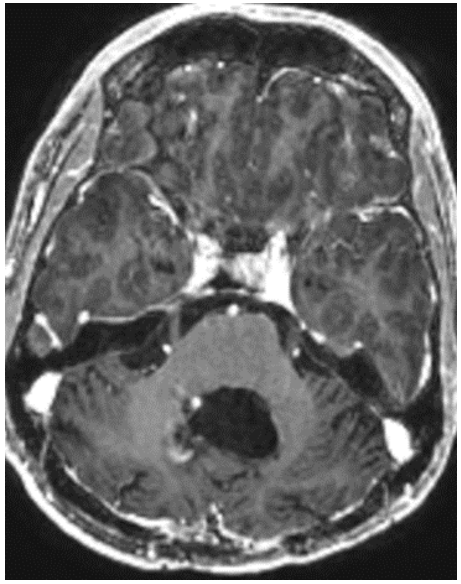
Pre-treatment



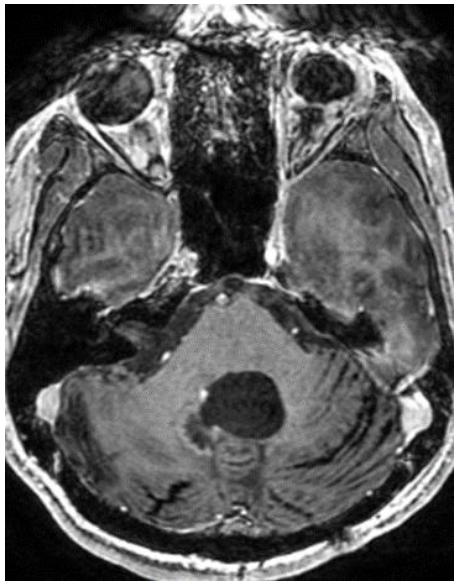
2 cycles



4 cycles



6 cycles



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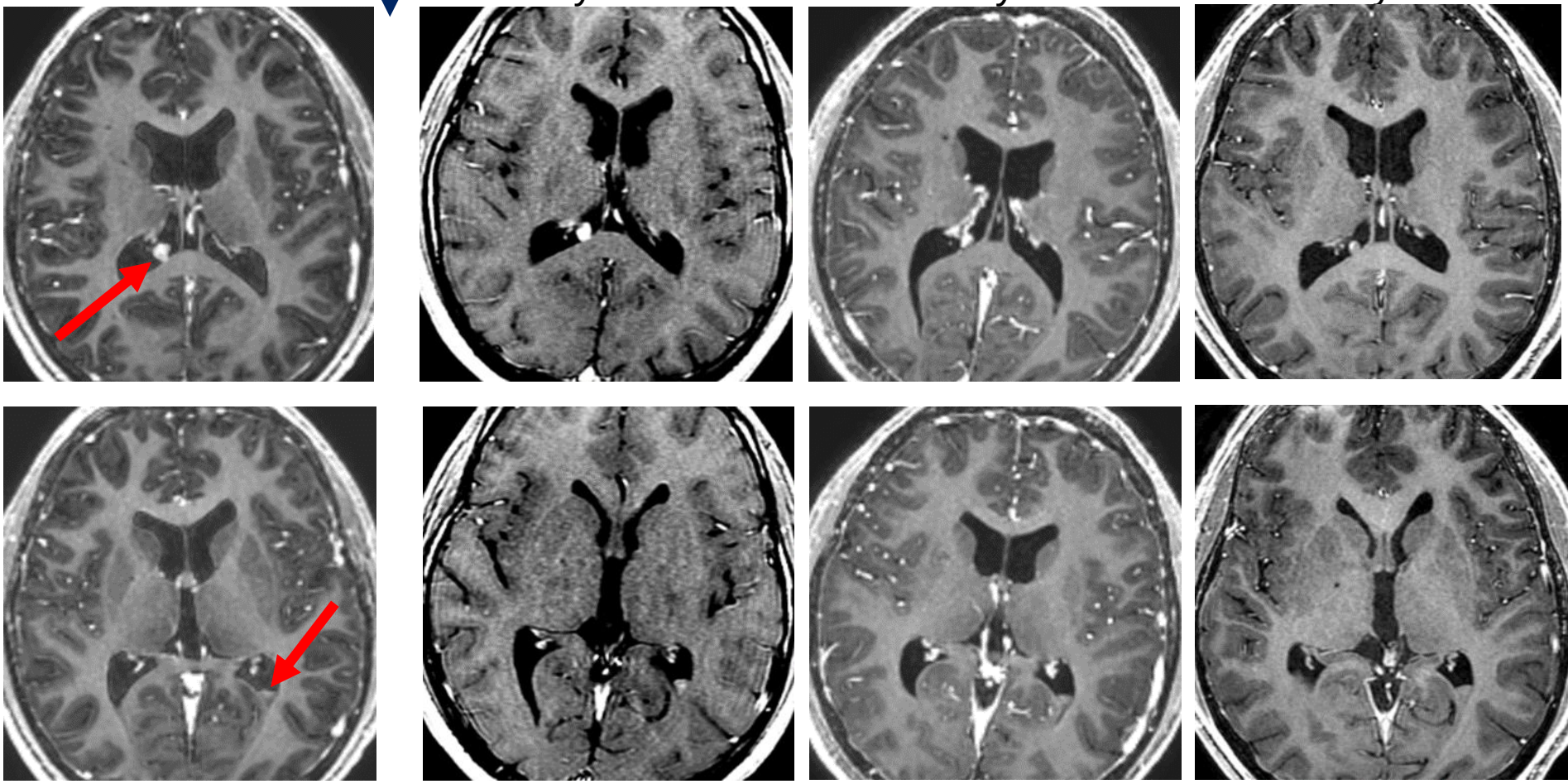

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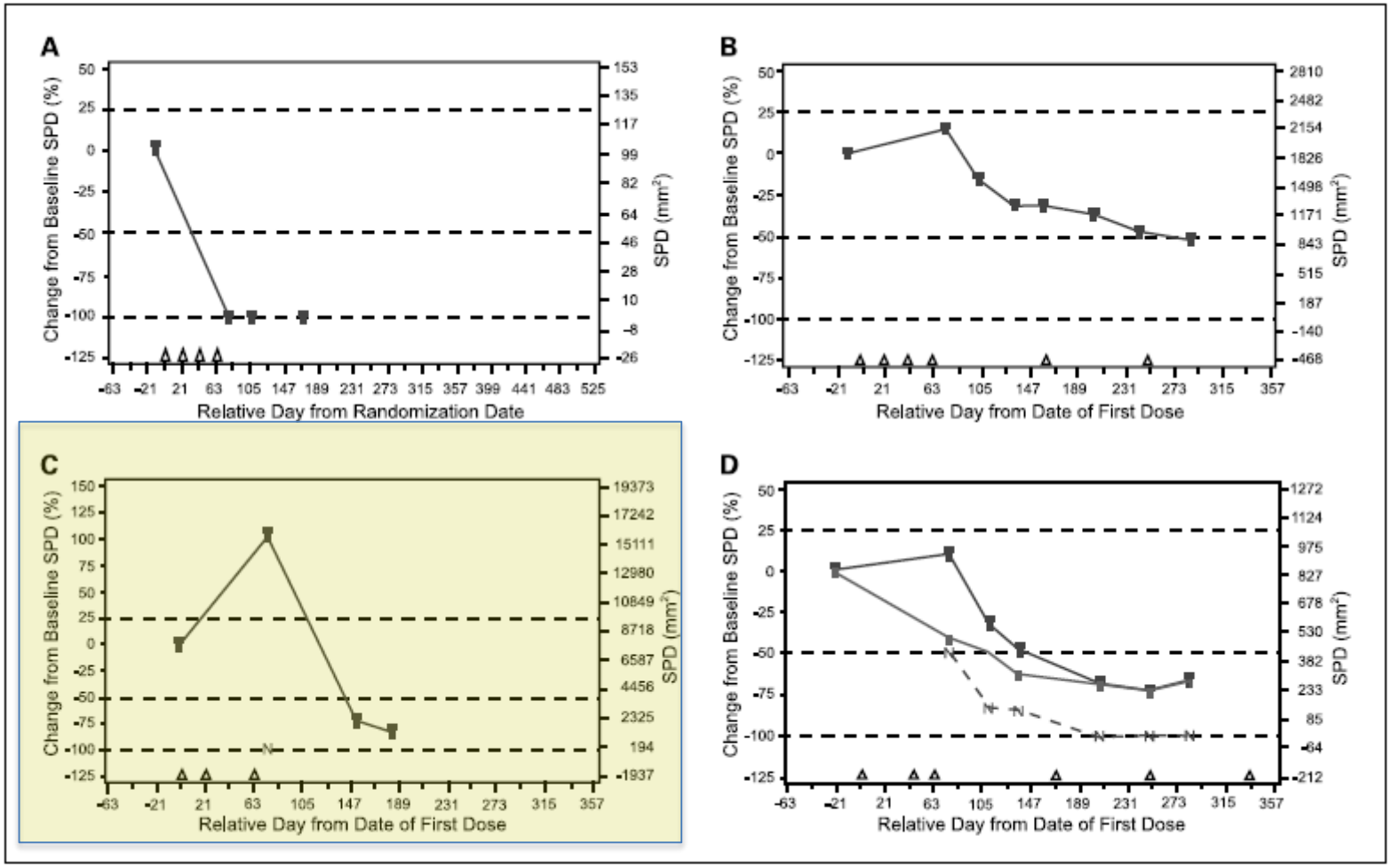
Initial tumor enlargement followed by regression



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Initial tumor enlargement followed by regression

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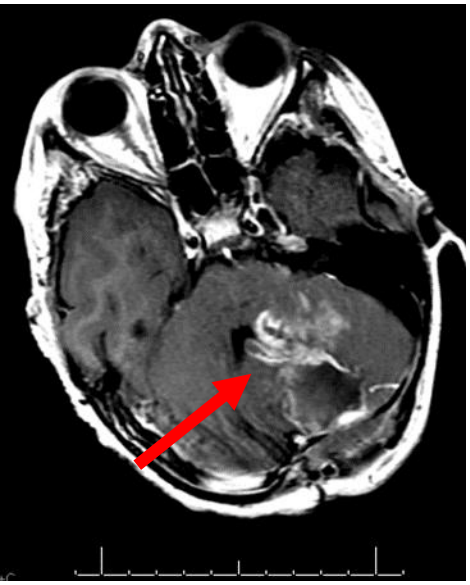
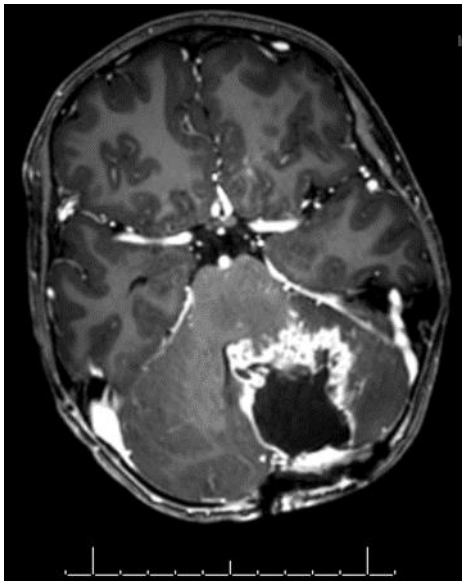
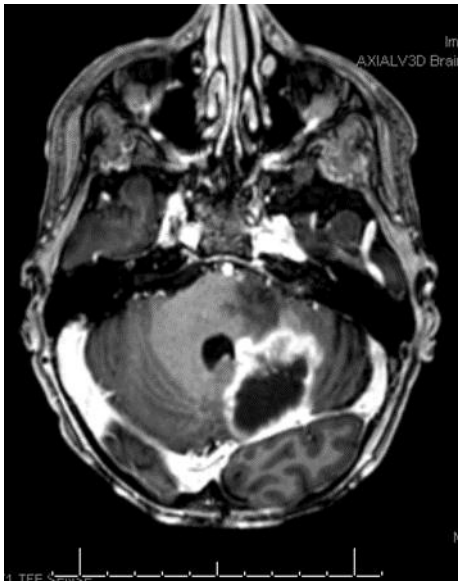
12 yo Li Fraumeni patient with glioblastoma

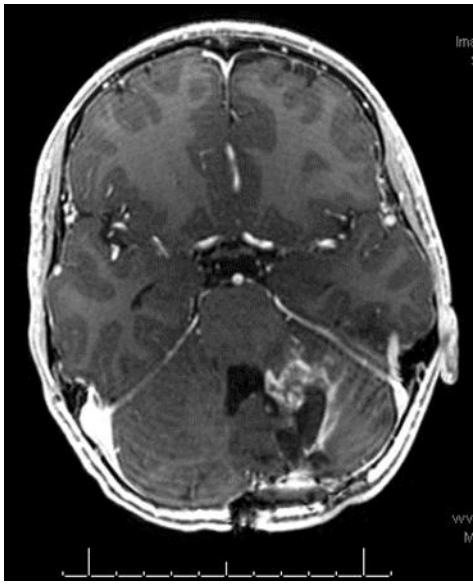
followed by Indoximod + Temozolomide

Pre-treatment | After radiation | 2 cycles | 4 cycles









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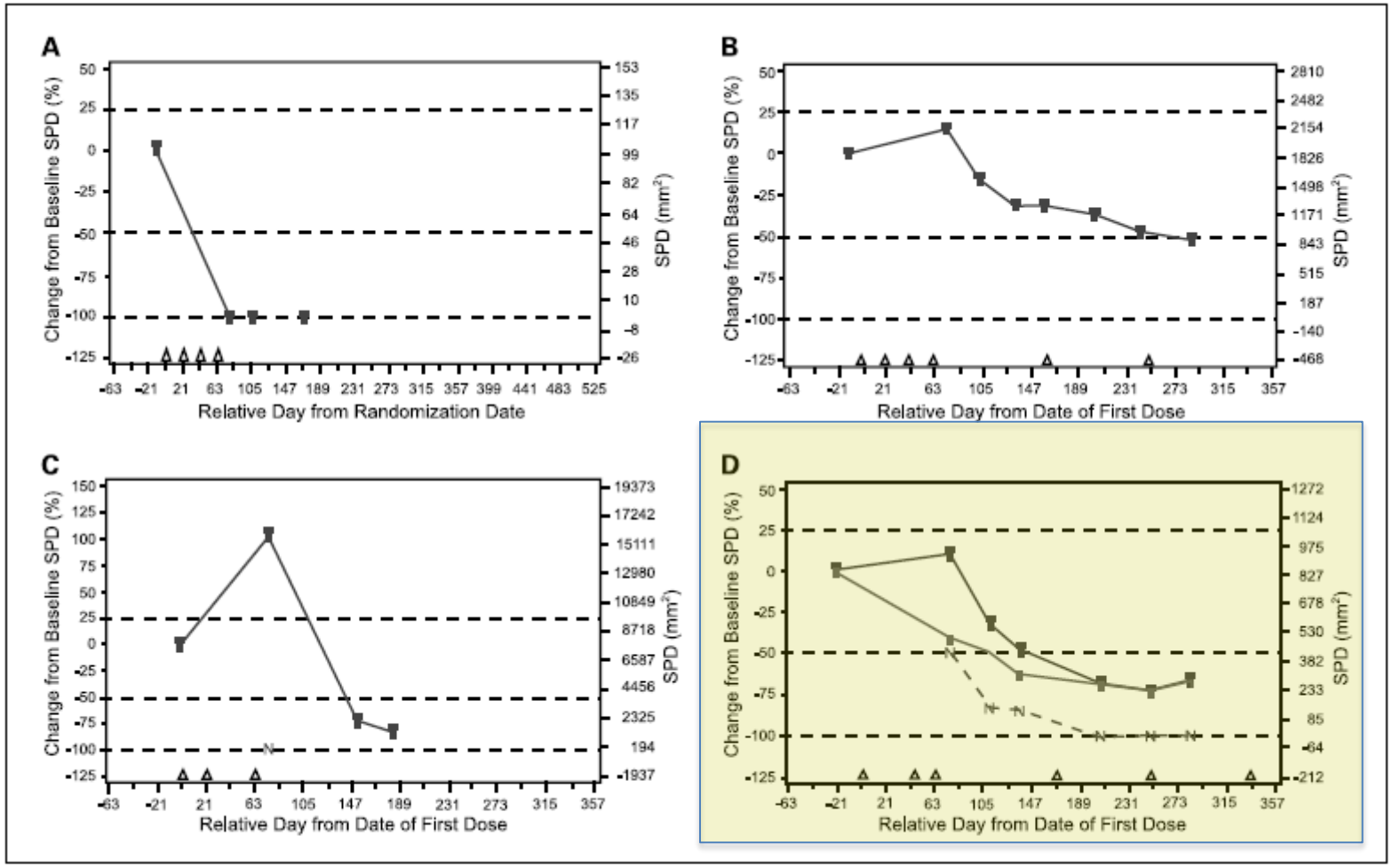
New metastatic tumor on therapy that later regresses



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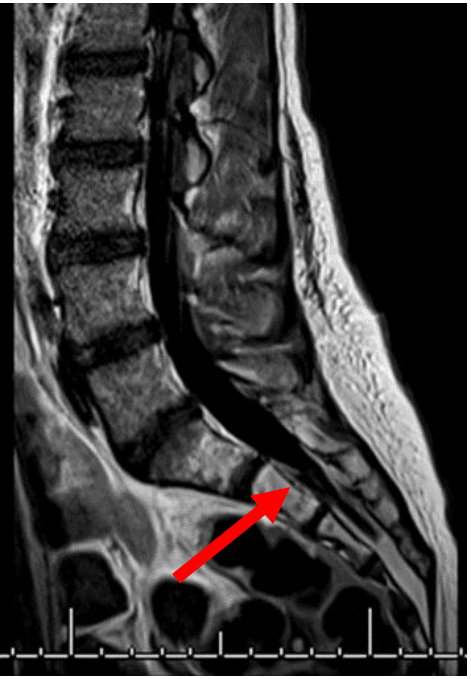
New metastatic tumor on therapy that later regresses

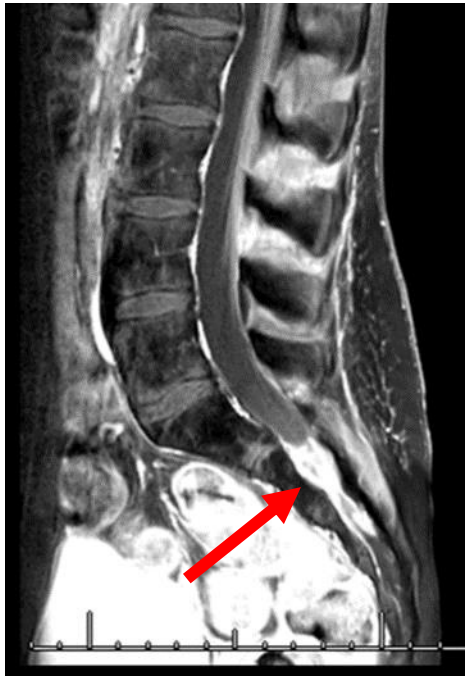
Begin
Indoximod + Temozolomide

14 yo with CSF relapse of medulloblastoma

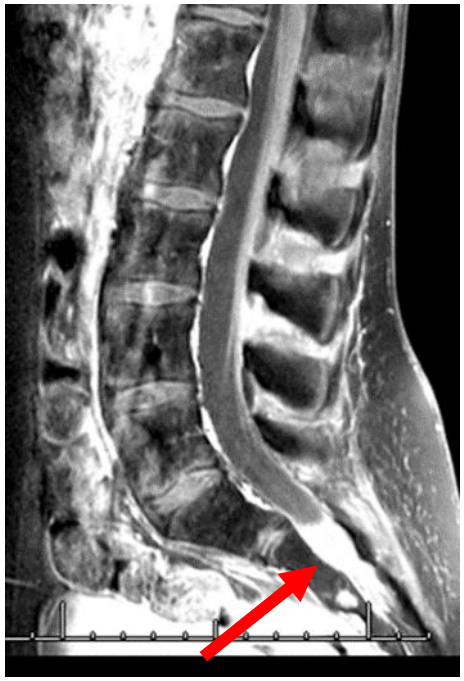
Pre-treatment



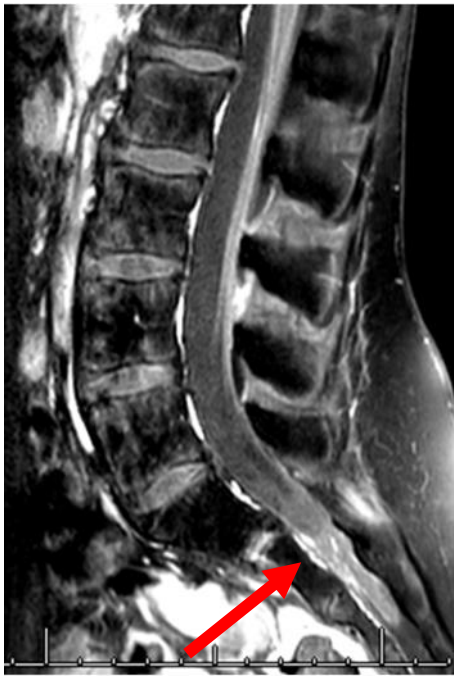
2 cycles



4 cycles



6 cycles



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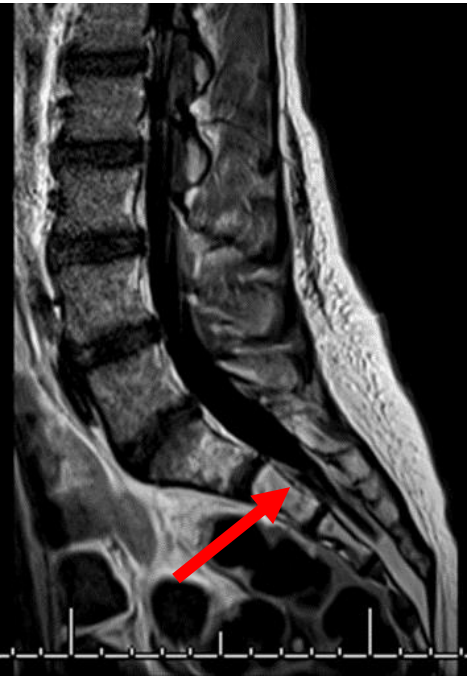

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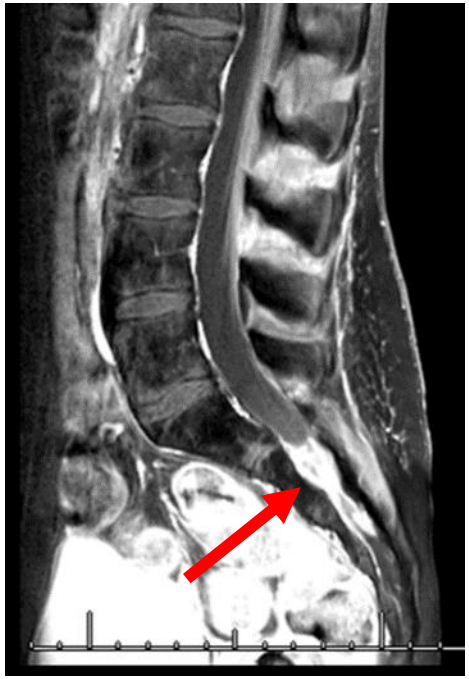

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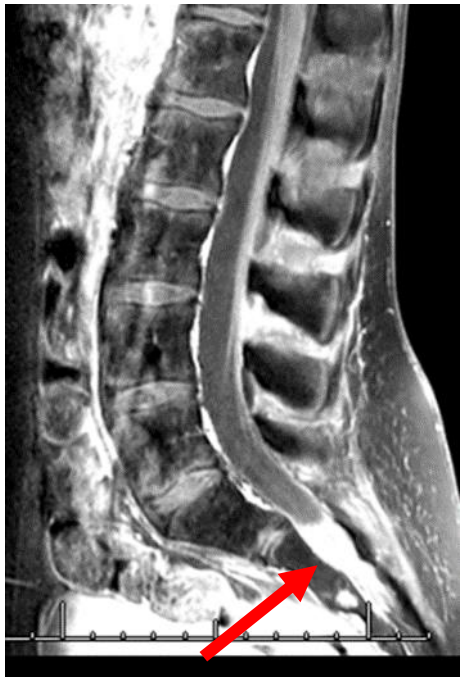

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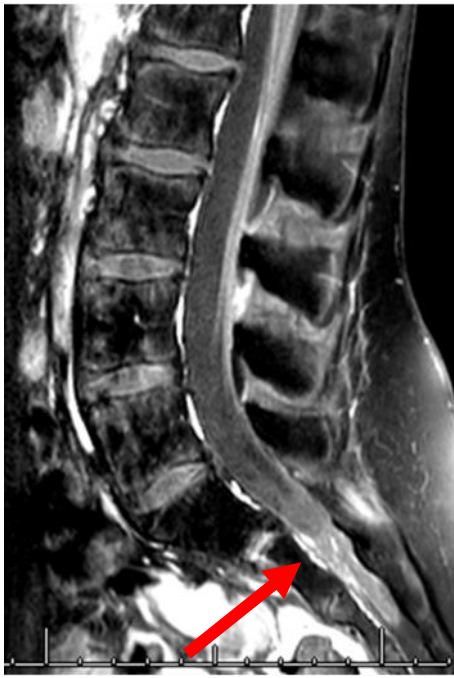

Time To Regimen Failure (TTRF) as an important metric

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Delayed cycles and dose-reductions

- Indoximod + radiation:
  - 16 patients received a total of 20 radiation plans
  - All patients completed their radiation plans
  - 3 patients (15%) had delays in starting maintenance Rx:
    - Wound infection (n=1)
    - Urinary tract infection (n=1)
    - Transaminitis (n=1)

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    - Wound infection (n=1)
    - Urinary tract infection (n=1)
    - Transaminitis (n=1)
- Indoximod + temozolomide:
  - 26 patients completed 158 temozolomide cycles
  - 17 cycles (11%) were delayed:
    - Thrombocytopenia (n=10)
    - Neutropenia (n=4)
    - Thrombocytopenia with neutropenia (n=1)
    - Hemiparesis (resolved) (n=1)
    - Noncompliance (n=1)
  - 11 patients (38%) had dose-reductions in temozolomide

Serious adverse events

15 patients (52%) experienced 21 SAE's

Event	Grade (n)				Relationship to Indoximod				
	1	2	3	4	Unrelated	Unlikely	Possible	Likely	Related
Fever	1	1			1	1			
Febrile neutropenia			1			1			
Lung infection			1			1			
Urinary tract infection		1					1		
Wound infection			1		1				
Anaphylaxis (blood product)			1		1				
Hydrocephalus			1	1	1	1			
Muscle weakness		1	2		2	1			
Seizure		1			1				
Hemiparesis*			1				1		
Spinal cord compression*			1				1		
Encephalopathy*				1	1				
Vomiting		1	2		1	2			
Hyponatremia				1		1			
Adrenal insufficiency				1		1			

*resolved

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Presented at the 2017 International Pediatric Neuro-oncology Conference at Texas Children's Hospital, Houston TX, Nov. 10, 2017

Quality of Life

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Conclusions

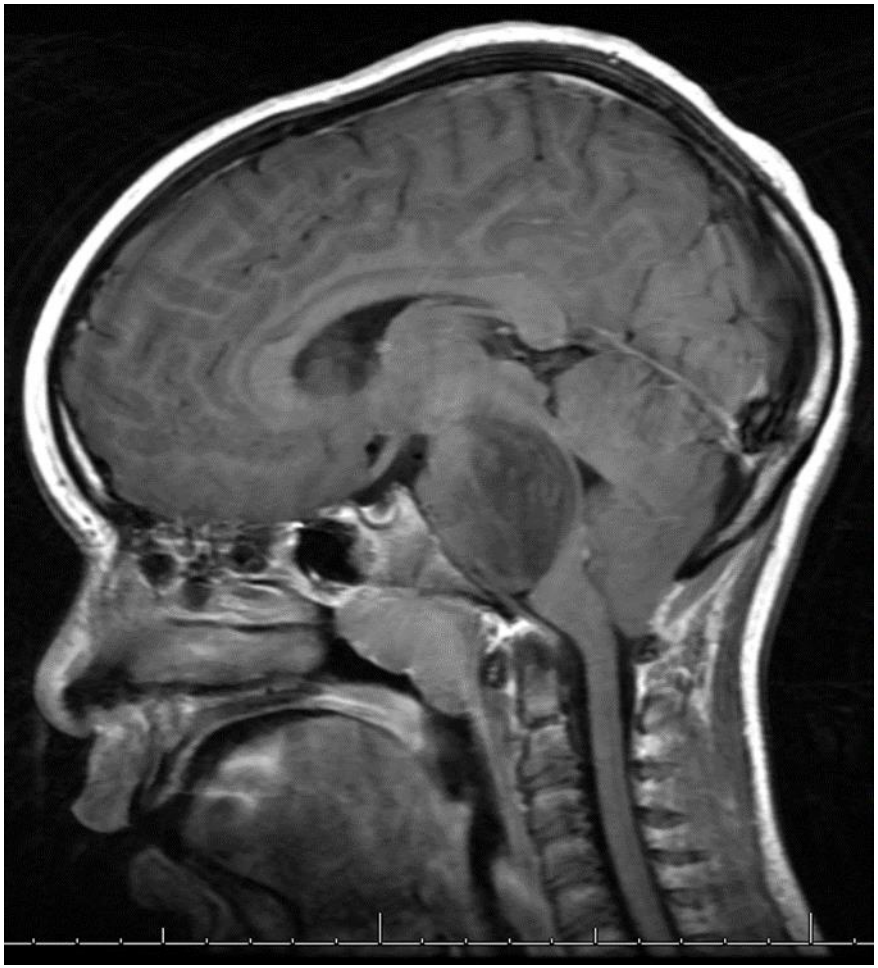
- **First empiric evidence that adding immunotherapy may have a significant dose-sparing effect on highly toxic conventional therapy**
- **Indoximod is well tolerated at the highest dose-level studied**

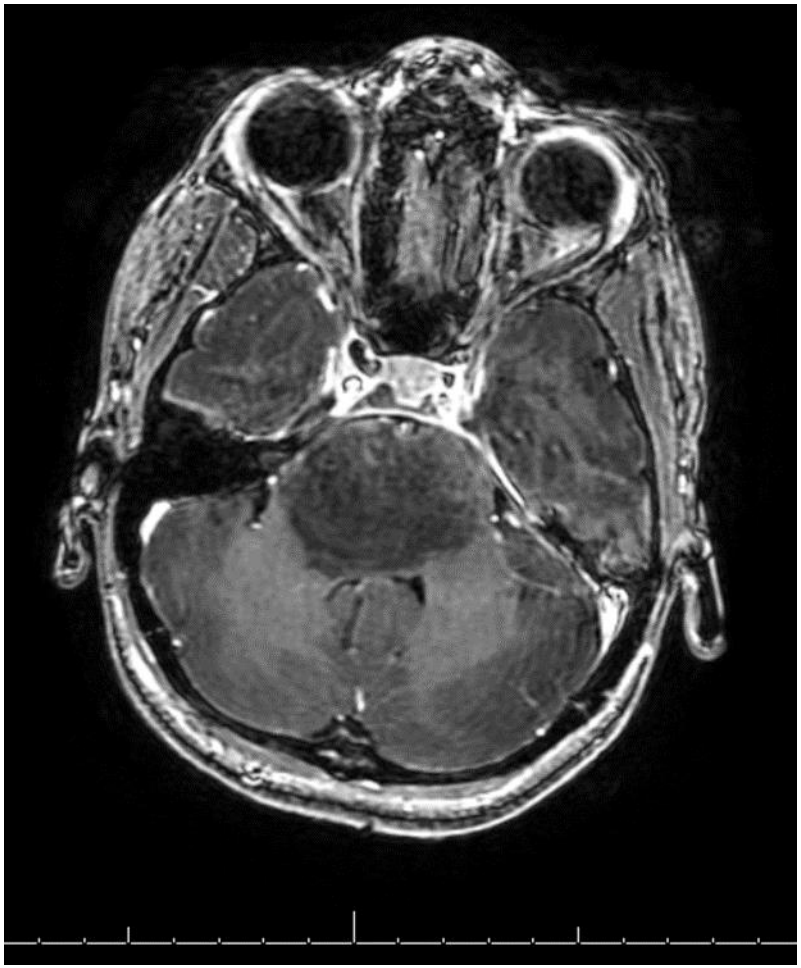
  … And does not compromise the ability to deliver the backbone therapy (radiation / temozolomide)

Future Directions

- Continue to enroll expansion cohorts
  - Group 2 – open for enrollment using indoximod at DL3
  - 3-4 patients per month
- Move to front-line therapy for DIPG
  - First 2 patients have enrolled
- Phase 2 trial to formally test the radiation dose-sparing hypothesis (planned for 2018 / 2019)
  - Plan radio-immunotherapy using IDO-blockade for all enrolled patients (unless contraindicated)
  - Test the hypothesis that low-dose radiation plans (≤ 30 Gy) will be efficacious when combined with IDO-blockade
    - Currently only 20%-25% would qualify for re-irradiation, and at much higher doses

Future Directions
9 yo with newly diagnosed DIPG





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