Radio-chemo-immunotherapy using the IDO-inhibitor indoximod for children with progressive brain tumors in the phase 1 setting (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

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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 (dose-escalation) with temozolomide

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

Group 2: Expansion cohorts using the "Core Regimen" - **Open**

- Indoximod (RP2D = 19.2 mg/kg/dose, PO, twice daily on days 1-28)
- Temozolomide (200 mg/m^2/day, PO, daily on days 1-5)

Group 3: Up-front cycle of indoximod (dose-escalation) plus radiation therapy

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

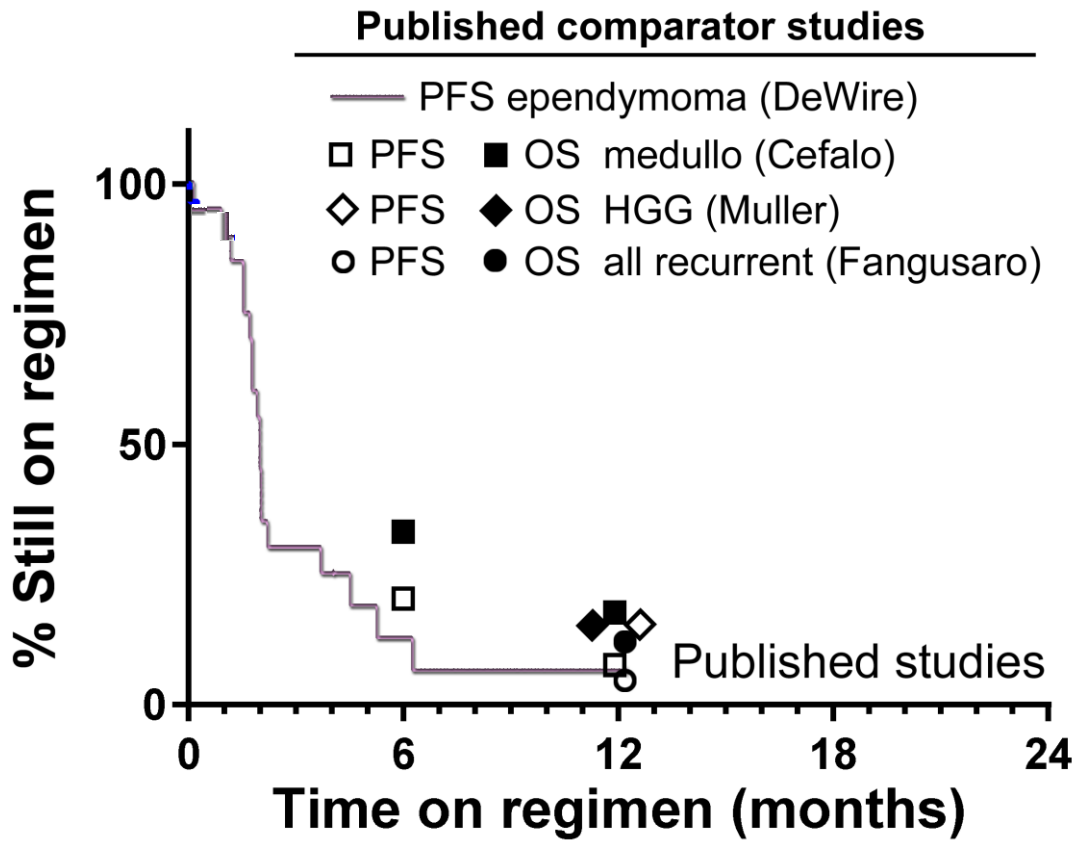
Radiographic evidence of progression (escape lesions) can be managed with continued indoximod and:

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

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

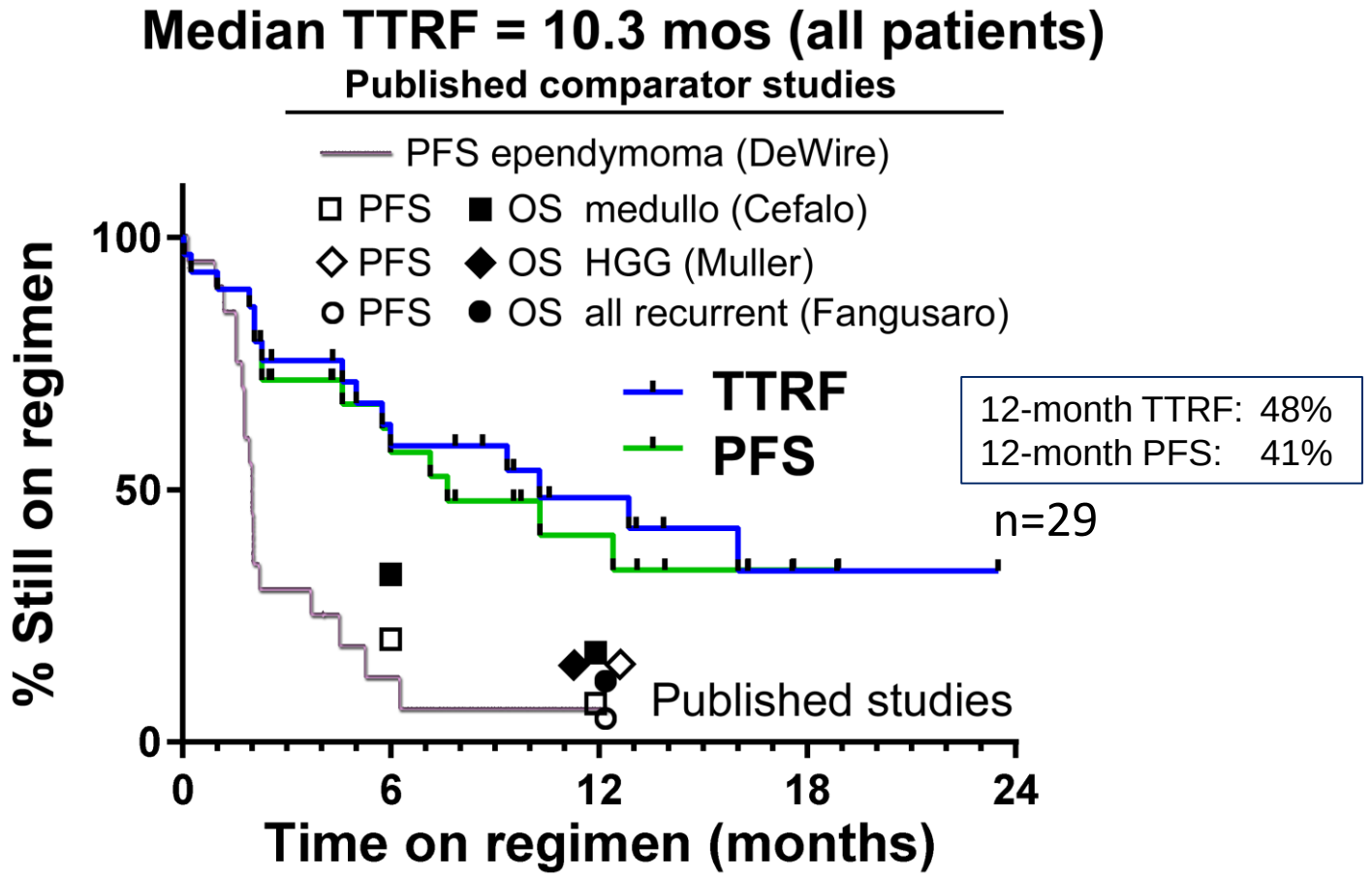
Historical control data for relapsed brain tumors



Historical controls adapted from:

DeWire M, *et al*. 2015. *J Neurooncology*. 123:85.
Cefalo G, *et al*. 2014. *Neuro-oncology*. 16:748.
Muller K, *et al*. 2014. *Radiation Oncology*. 9:177.
Fangusaro JR, et al. 2017. J Clin Oncol. 35(suppl): abstract 10543.

Favorable outcome with indoximod-based therapy



Historical controls adapted from:

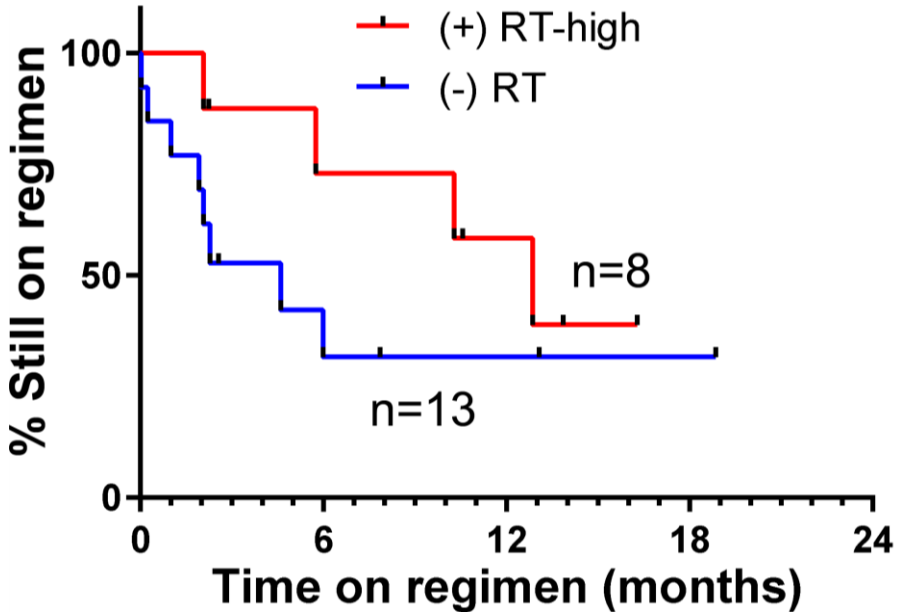
DeWire M, *et al*. 2015. *J Neurooncology*. 123:85.
Cefalo G, *et al*. 2014. *Neuro-oncology*. 16:748.
Muller K, *et al*. 2014. *Radiation Oncology*. 9:177.
Fangusaro JR, et al. 2017. J Clin Oncol. 35(suppl): abstract 10543.

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

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Radio-immunotherapy improves time to regimen failure (TTRF)

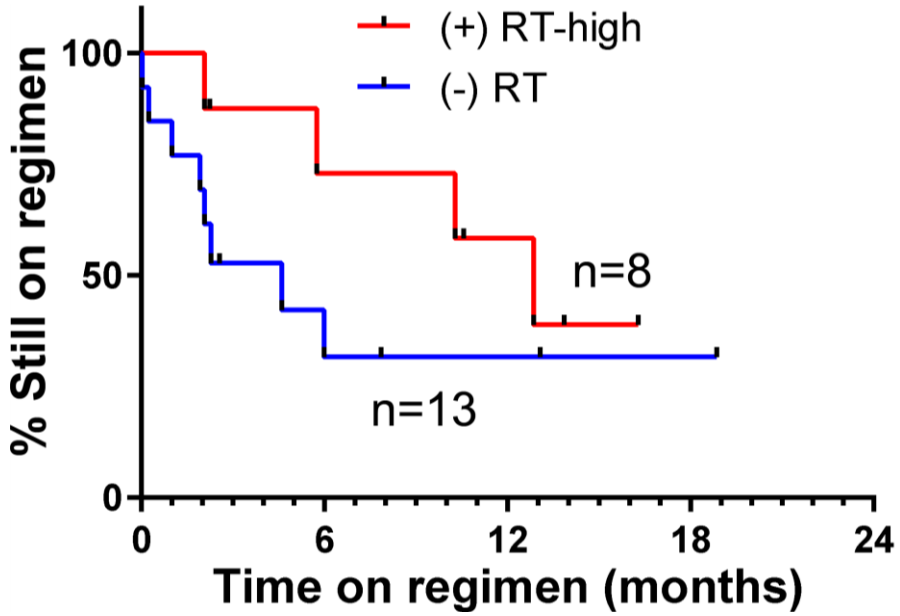
	High-dose RT (n=8)	vs. No RT (n=13)
Median TTRF	**13 months**	4.6 months
RT dose	≥ 50 Gy	
Median target vol.	165 cm3	
RT to all tumors	6/8 (75%)	



Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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%)	



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***.

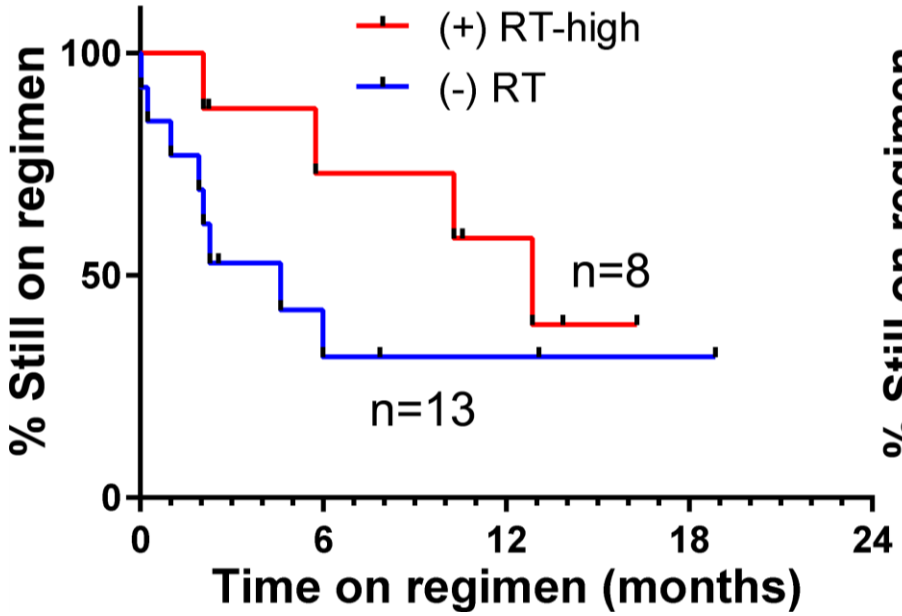
GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

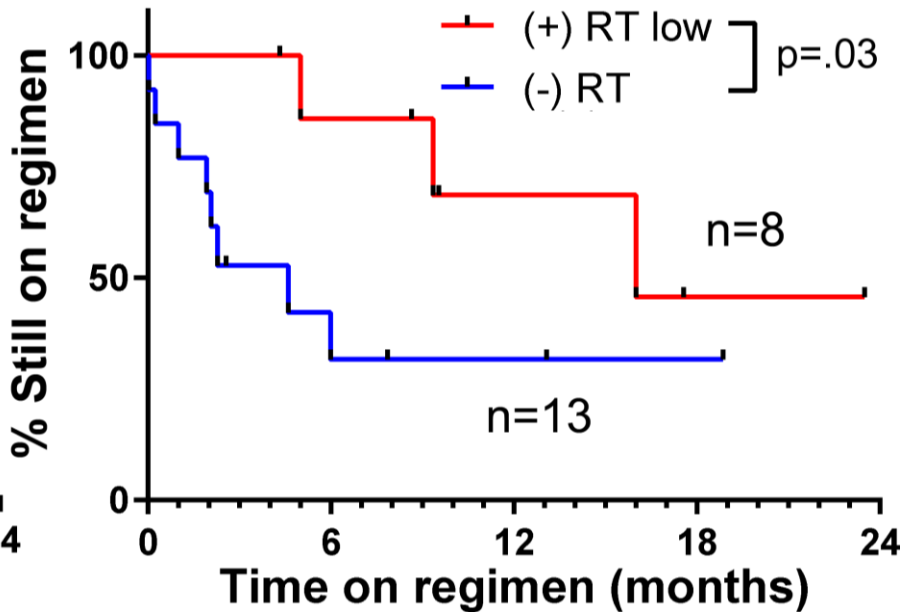
Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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%)	

	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%)	





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***.

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

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 Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

Conclusion and future directions

- **First empiric evidence that adding immunotherapy may have a significant dose-sparing effect on highly toxic conventional therapy**
- Continue to enroll expansion cohorts (3-4 per month)
- Move to front-line therapy for DIPG (2 patients 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 ($\leq$ 30 Gy) will be efficacious when combined with IDO-blockade
    - Currently only 20%-25% would qualify for re-irradiation, and at much higher doses

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.

Acknowledgements

Augusta University

- David H. Munn
- Ahmad Al-Basheer
- Diana Fridlyand
- Cole A. Giller
- Ian M. Heger
- Ravindra B. Kolhe
- William Martin
- Waleed F. Mourad
- Rafal Pacholczyk
- Rebecca Parker
- Amyn M. Rojiani
- Ramses F. Sadek

Emory University

- Tobey J. MacDonald
- Dolly Aguilera
- Bree R. Eaton
- Natia Esiashvili

NewLink Genetics Corp.

- Gene Kennedy
- Nick Vahanian
- Amy Bell
- Chris Smith
- Lucy Tenant

Grant Support

- Alex's Lemonade Stand Foundation
- Cannonball Kids' cancer Foundation
- Hyundai Hope on Wheels Foundation
- Press On Foundation / CAM Fund

Collaborators

MD Anderson Cancer Center
- David Grosshans

Univ. of Alabama at Birmingham
- Gregory K. Friedman
- John B. Fiveash

Akron Children's Hospital
- Michael Kelly

Medical College of Wisconsin
- Selim Firat
- Jeffrey Knipstein

Children's Hospital Colorado
- Nicholas Foreman
- Arthur Liu

Child's Hosp. King's Daughters
- Raven M. Cooksey

Hampton Univ. Proton Therapy Inst.
- Allan Thornton

GEORGIA CANCER CENTER
AUGUSTA UNIVERSITY

Presented at the Society for NeuroOncology, 22nd Annual Meeting, San Francisco, CA, Nov. 19, 2017.