TOCA 511 & TOCA FC: EVALUATION OF DURABLE RESPONSE RATE IN THE POST-RESECTION SETTING AND ASSOCIATION WITH SURVIVAL IN PATIENTS WITH RECURRENT HIGH GRADE GLIOMA

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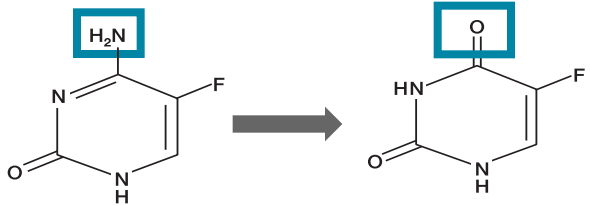
Disclosure:

- I have been compensated for consultation with: Celgene, Tocagen, VBL, Puma, AbbVie, BMS, Merck, Genocea, Cortice, GW Pharma, Wellcome Trust, Cancer Panels
- I am Chairman for DSMB for VBI-1901
- I am on the Steering Committee for BBI-DSP7888
- I have stock option with: Notable Labs
- I am a board member and CMO for Global Coalition for Adaptive Research

Toca 511 (vocimagene amiretrorepvec)
Retroviral replicating vector that carries a prodrug activator enzyme

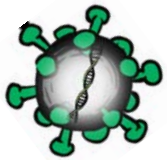
Regulatory genes — Structural RRV genes — CD gene — Regulatory genes

Optimized CD (cytosine deaminase)



5-FC (Toca FC) Antifungal Prodrug → **5-FU Anticancer Drug**

5-FU has a very short half-life with direct cell killing localized to cancer microenvironment



Tumor selectivity and replication in cancers cells is driven by:

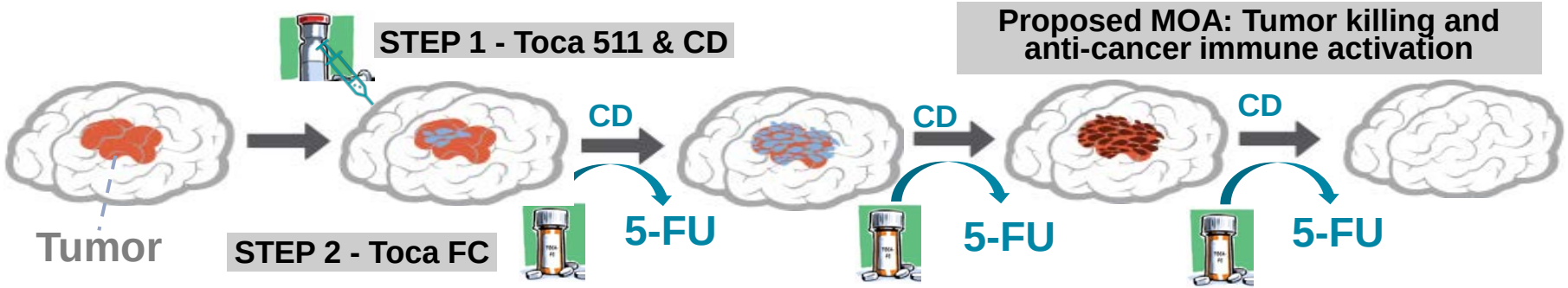
- Defects in the innate immune system of cancer cells
- Virus enters some normal cells, but is rapidly eliminated by innate and acquired immunity
- Virus spreads through tumor without triggering immune system
- Virus only infects dividing cells

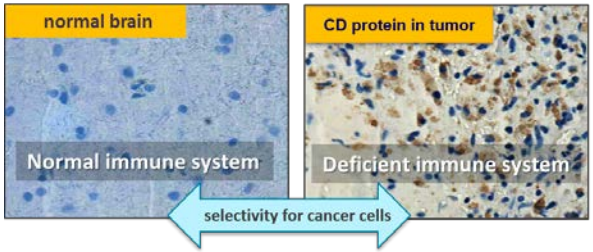
RRV= Retroviral replicating vector

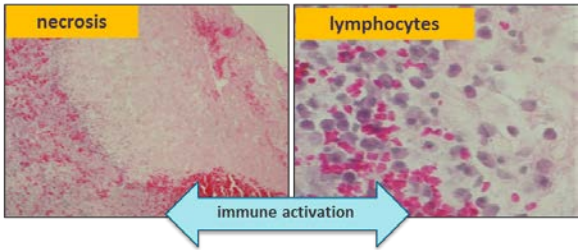
Toca 511 & Toca FC:

Toca 511 spreads then converts Toca FC to 5-FU for tumor killing and immune activation

Novel 5-FU delivery kills tumor cells and activates immune system







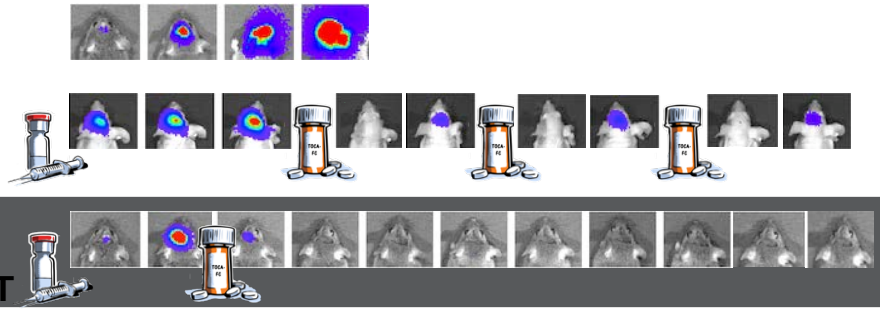
Brain and tumor samples from Tocagen clinical trial patients

CD = cytosine deaminase (yeast)
Toca FC = extended release 5-FC

Toca 511 & 5-FC

Activates a Durable Anti-Cancer Immune Response

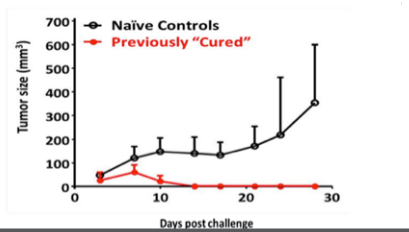
Pre-Clinical Evidence of Durable Immune Activation



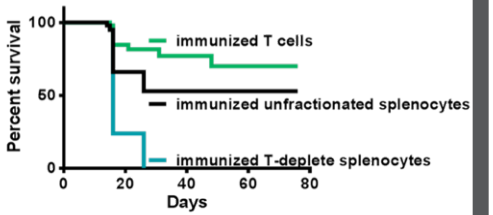
Images modified for illustrative purposes

Multiple cycles of tumor-associated antigen (TAA) release during FC treatment cycles, coupled with simultaneous depletion of immune suppressive cells in the tumor microenvironment, leads to immune activation, effective TAA presentation, and lymphocytic infiltration, resulting in gradual killing and shrinkage of the tumor, sometimes completely, over a long period of time.

"Cured" Mice Reject Re-Challenge of Same Tumor in Flank



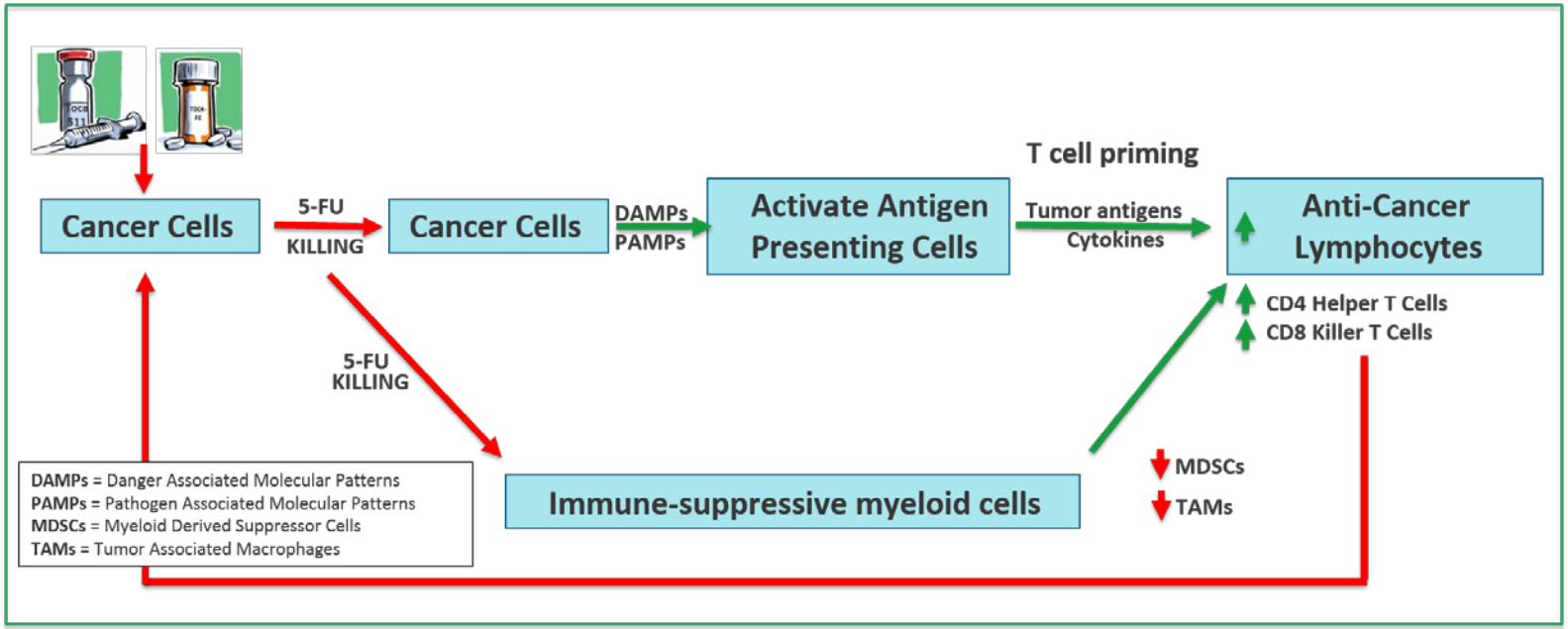
T Cells From "Cured" Mice Increase Survival in Adoptive Transfer Model



Adapted from Mitchell et al., Neuro-Oncol. 2017 and Hiraoka et al., Neuro-Oncol. 2017 .

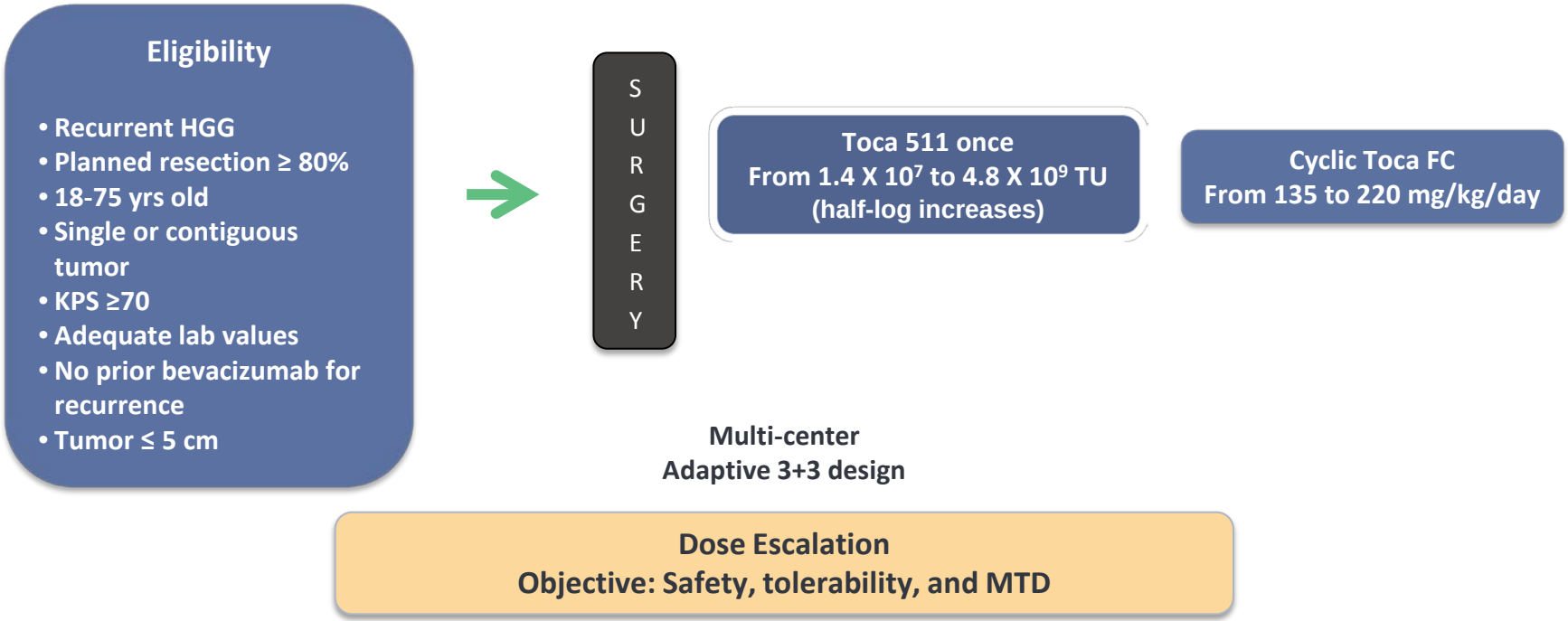
Toca 511 & Toca FC
A cancer-selective immunotherapeutic

Directly kills tumor cells and immune-suppressive myeloid cells leading to immune activation and long-term durable responses



Ph1 ascending dose trial of safety and tolerability of Toca 511 & Toca FC in rHGG

Toca 511 administered into the resection cavity wall



Adapted from M.A. Vogelbaum, MD PhD, SNO, Nov. 21st, 2015

Basic demographics show predominantly GBM patients

Population	All Patients N = 56	Higher Doses and Ph3 Entry Criteria Subset[2] N=23
Median Age (range)	56 (24-75)	54.8 (24-70)
	n (%)	**n (%)**
Male	43 (77)	20 (87)
Karnofsky Performance Score		
70-80	17 (30)	5 (22)
90-100	39 (70)	18 (78)
Initial Tumor Histology		
GBM[1]	46 (82)	19 (83)
Anaplastic Astrocytoma	6 (11)	4 (17)
Anaplastic Oligodendroglioma	1 (2)	0
Other gliomas	3 (5)	0
Number of Recurrences Including Current		
1	28 (50)	19 (83)
2	13 (23)	4 (17)
≥ 3 or greater	15 (27)	0

[1]includes gliosarcoma

[2]Higher doses (cohorts 4-7a) and meet Ph3 entry criteria of 1st and 2nd recurrence, no prior Avastin in rAA or rGBM , tumor not > 5cm

Data cutoff date August 15th, 2017

All responders are now in complete response and alive

All responses are in higher dose cohort and durable

Response Category[1]	All Patients N=53[2] n (%)	Higher Doses and Ph3 Entry Criteria Subset[3] N=23 n (%)
Durable response rate (CR or PR ≥24 weeks)	6 (11.3); All CR[4]	**5 (21.7); All CR[5]**
Median duration of durable response	Not reached (median follow-up: 36.5mos)	**Not reached (median follow-up: 37.4mos)**
Stable disease	12 (22.6)	5 (21.7)
Progressive disease	35 (66.0)	13 (56.6)
Clinical Benefit Rate (CR, PR, and SD at 8 weeks)	16 (30.2)	10 (43.5)

Compares favorably with lomustine*:

- Overall response - 4.3%
- Duration of response - 2.8-9.6 months

*Wick, JCO 2010

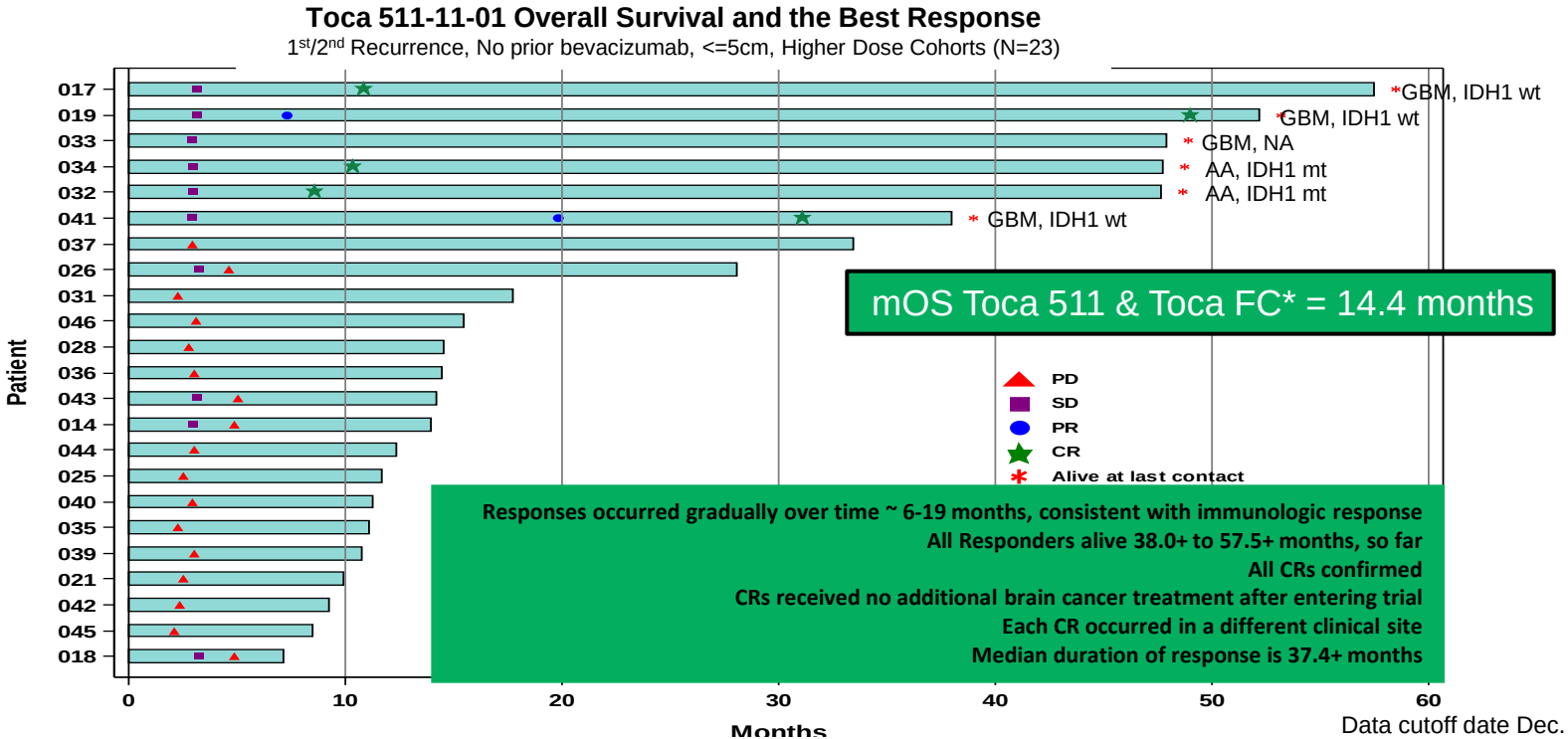
[1]Includes MRI by independent radiology review and clinical data
[2]of 56 safety evaluable patients, 53 patients who received Toca 511 & Toca FC are efficacy evaluable and of these 2 were not evaluable for response
[3]Higher doses (cohorts 4-7a) and meet Ph3 entry criteria of 1st and 2nd recurrence, no prior Avastin in rAA or rGBM, tumor not > 5cm
[4]Includes 4 IDH1 wildtype and 2 IDH1 mutant patients
[5]Two patients converted from PR to CR status since last data cutoff

Data cutoff date Dec. 20th, 2017

A positive association of durable response with overall survival

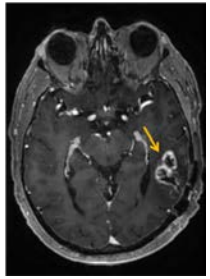
Best response & survival post progression

All Responses are Durable Complete Responses & Associated with Long Term Survival



Data cutoff date Dec. 20th, 2017

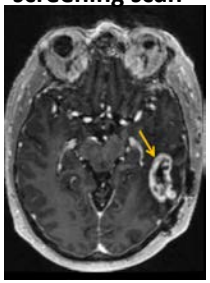
Complete Response in a Patient with Progressive GBM, IDH1 wt



8/13/14

tumor progression

screening scan



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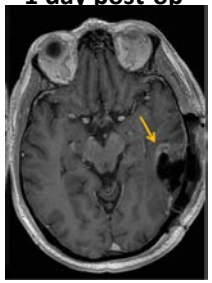
resection of enhancing tumor then Toca 511 injection

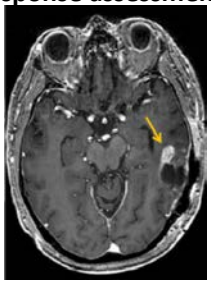
1 day post-op



10/10/14

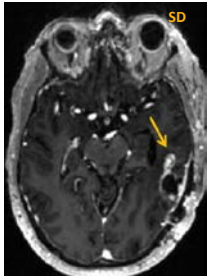
tumor progression

baseline scan for response assessment



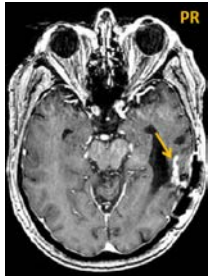
11/12/14

stable disease



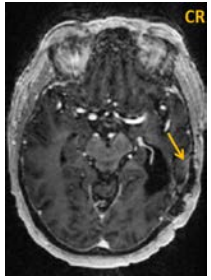
1/7/15

partial response



6/2/16

complete response



5/11/17

Alive and with ongoing complete response

> 36 months

Toca FC cycles (1 week per 6 weeks)

PR and CR by independent Radiology Review, Macdonald criteria.
Modified based on Cloughesy et al. SNO Conference, 2017.

Toca 511 associated with a very low % of treatment-related AEs, across all Grades

Adverse events related to Toca 511 – pooled across three phase 1 studies

Treatment-Related Adverse Events	Toca 511 n = 127	
	Grade 1/2	Grade ≥ 3*
	n (%)	n (%)
Any treatment-related event	**32 (25.2)**	**9 (7.1)**
Treatment-related event in ≥ 3 patients		
Fatigue	14 (11.0)	1 (0.8)
Headache	6 (4.7)	1 (0.8)
Convulsion	6 (4.7)	0
Confusional state	5 (3.9)	0
Pyrexia	5 (3.9)	0
Nausea	4 (3.1)	0
Hemiparesis	3 (2.4)	0
Vasogenic cerebral edema	1 (0.8)	2 (1.6)
Any treatment-related SAE	1 (0.8)	7 (5.5)

Data cutoff 17 Apr 2017; excludes data from continuation study

Absence of vector insertion site clonality supports safety

*No deaths considered related to Toca 511

Toca FC has very limited Grade ≥ 3 treatment-related toxicities

Adverse events related to Toca FC– pooled across three phase 1 studies

Treatment-Related Adverse Events	Toca FC n = 122	
	Grade 1/2	Grade ≥ 3*
	n (%)	n (%)
Patients with any treatment-related event	50 (41.0)	4 (3.3)
Treatment-related event in ≥ 3 patients		
Fatigue	27 (22.1)	0
Diarrhea	16 (13.1)	1 (0.8)
Nausea	12 (9.8)	0
Decreased appetite	6 (4.9)	0
Vomiting	4 (3.3)	0
Rash	3 (2.5)	0
Patient with any treatment-related serious adverse event	0	2 (1.6)
Adverse Events Leading to Discontinuation	1 (0.8)	2 (1.6)

*No deaths considered related to Toca FC

Data cutoff 17 Apr 2017; excludes data from continuation study

Conclusions

- Toca 511 & 5-FC activates durable T-cell mediated immune responses pre-clinically
- Treatment was well tolerated – limited Grade ≥ 3 drug-related toxicities in three Ph1 studies (127 patients)
- Ph1 resection/injection study indicates:
  - Prolonged survival relative to historical benchmarks
  - In a subset (n=23) that mirrors Phase 3 study (Toca 5) population
    - 5 complete responses (3 rGBM with IDH1 wt, 2 rAA with IDH1 mt) are ongoing
    - Median duration of response has not been reached after a median follow-up of 37.4 months
    - Durable response rate may be a valuable endpoint for immunotherapeutics
    - A positive association between durable response and overall survival
  - Clinical activity and MOA data supported Breakthrough Therapy and PRIME designations
- Findings support ongoing Phase 3 randomized study (Toca 5) in patients with rHGG
  - Currently enrolling patients with rAA or rGBM, at 1st or 2nd recurrence, no prior Avastin in rHGG, tumor not > 5cm

Thanks to all the patients, their families and caregivers who have supported this work.

Study sponsor: Tocagen™

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accelerate brain cancer cure

National Brain Tumor Society

American Brain Tumor Association®

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VOICES AGAINST BRAIN CANCER

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