Type-1 Dendritic Cell Vaccines in Combination with Poly-ICLC

Association Between Positive Tetramer Response and 6-Month Progression-Free Survival

Hideho Okada, Frank S. Lieberman, Ryo Ueda, Aki Hoji,
Pawel Kalinski, Arlan H. Mintz, Johnathan A. Engh, Deric M. Park,
David L. Bartlett, Herbert Zeh, Teresa E. Donegan,
Theresa L. Whiteside, Lisa H. Butterfield,
Walter J. Storkus, Douglas M. Potter,
Ronald L. Hamilton, Andres M. Salazar
and Ian F. Pollack

University of Pittsburgh Cancer Institute

Acknowledgement

Funding Sources

NIH/NCI and NIH/NINDS

Musella Foundation

Pittsburgh Foundation

The Brain Tumor Society

Brain Tumor Program

Clinical Research Services

IMCPL

Of the UPCI

Drs. Ronald Herberman Michael T Lot
and Robert L. Ferris

Participants and their families

Cathedral of Learning
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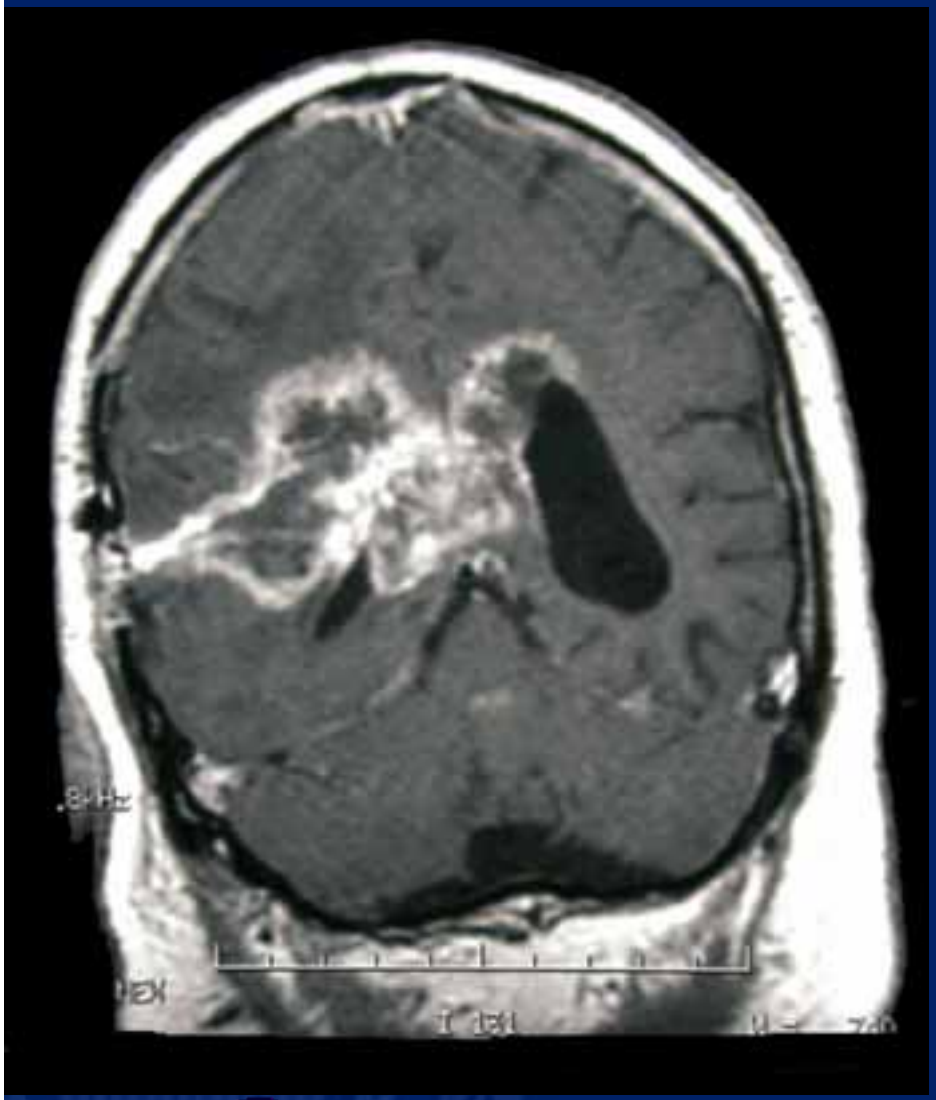
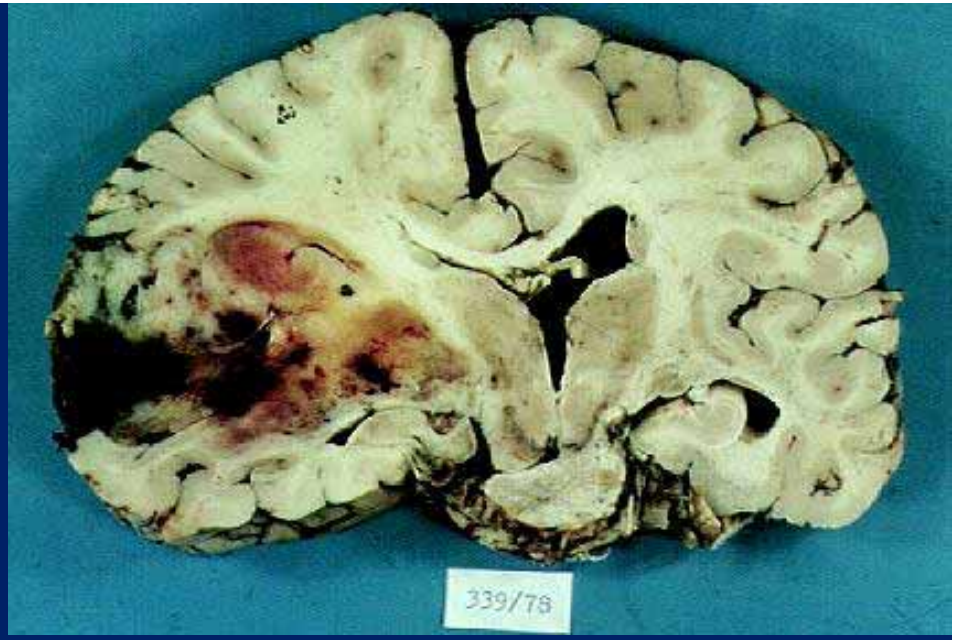
Conflicts of Interests (COI)

Hideho Okada and Walter J. Storkus are inventors of the IL-13Rα2 (345-353:1A9V) peptide, for which an exclusive licensing agreement has been executed with Stemline, Inc.

Per the University of Pittsburgh COI policy, interpretation of presented data was not performed solely by Hideho Okada, but by the investigator team.

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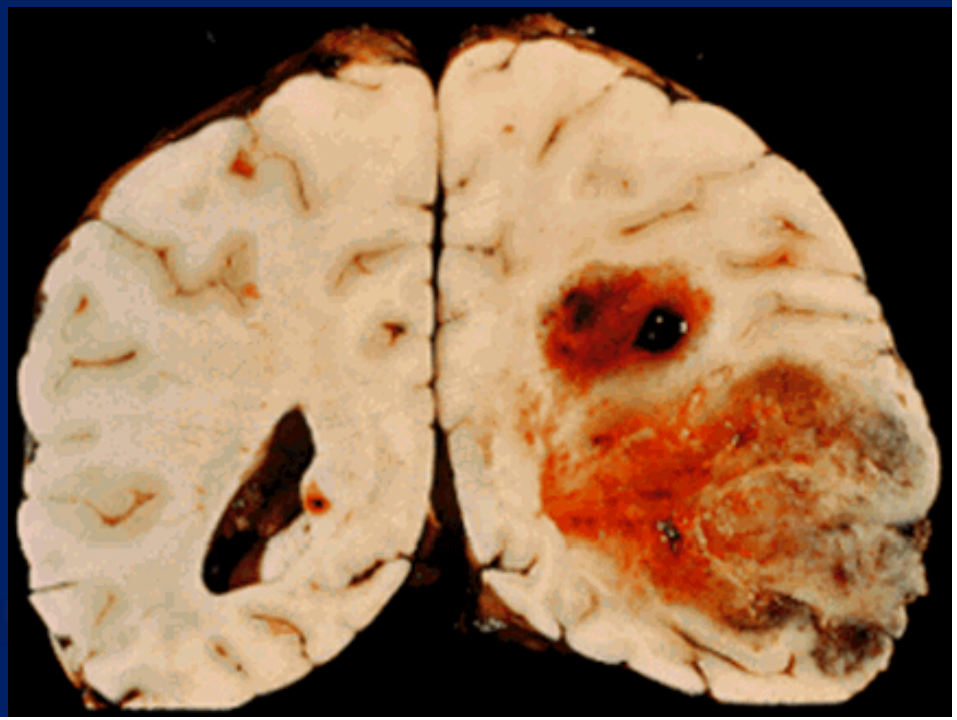


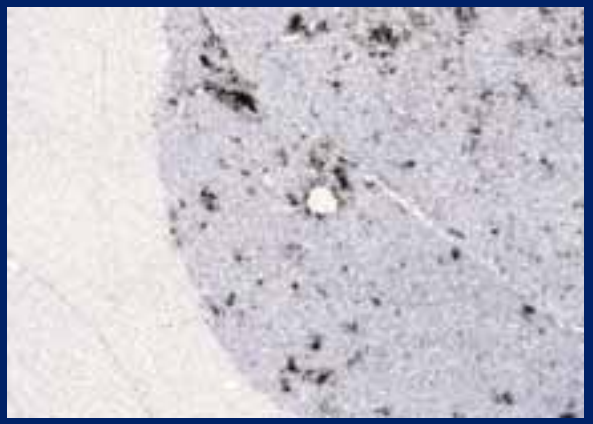
Critical Aspects/Factors for Potent Dendritic Cell Vaccines

- Type of DCs
  - Type-1 DCs (alphaDC1)
- Target Antigens
  - Multiple CTL epitopes from 4 GAAs
- Administration Route
  - Intranodal administration (superior to s.c)
- Adjuvant
  - Poly-ICLC as a ligand for intracellular dsRNA receptors

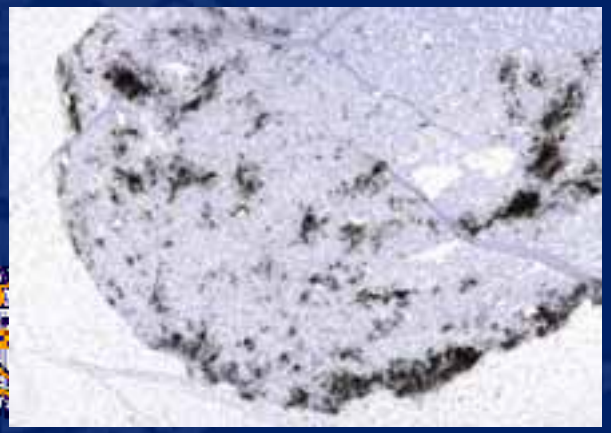
Upregulated expression of CXCL10 mRNA in murine GL261 glioma treated with GAA-vaccines and i.m. poly-ICLC (*In situ* hybridization)

A Vaccine Plus Poly-ICLC

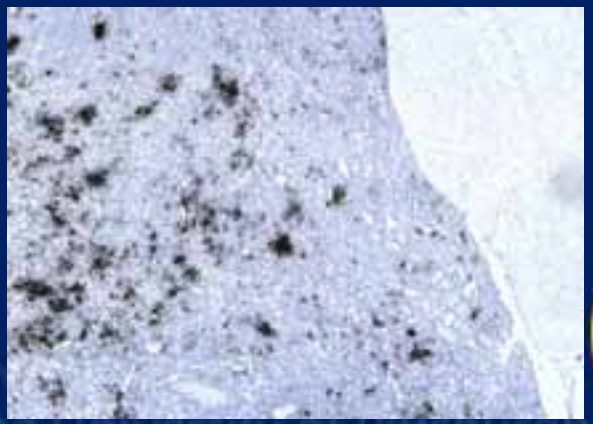
B Vaccine Alone



C Poly-ICLC Alone



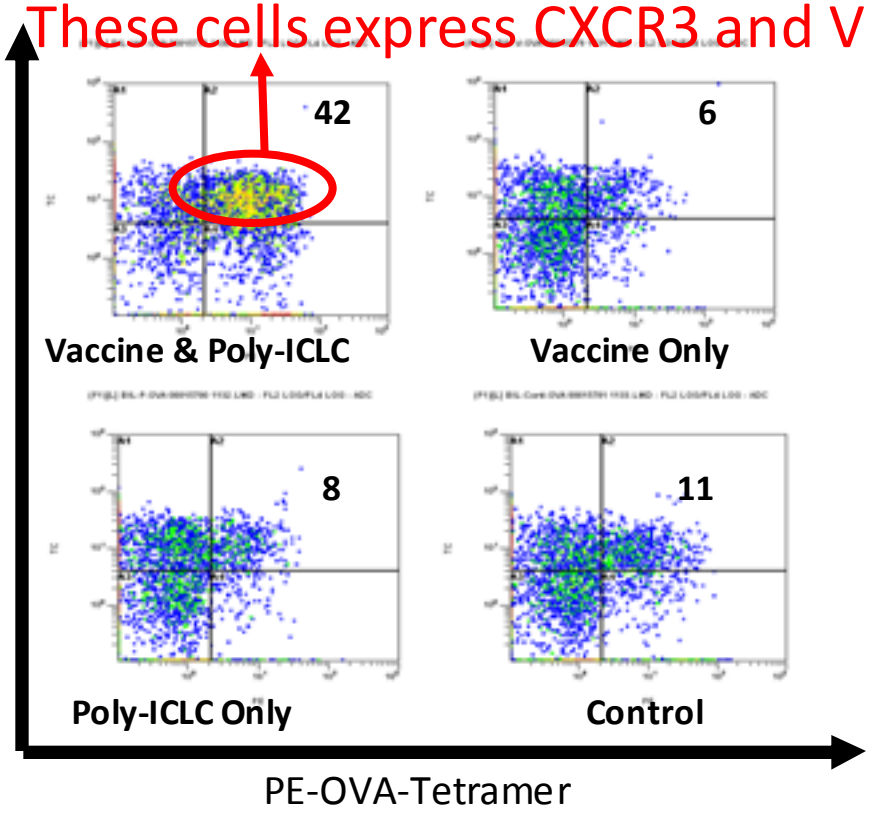
D Mock-Treatment



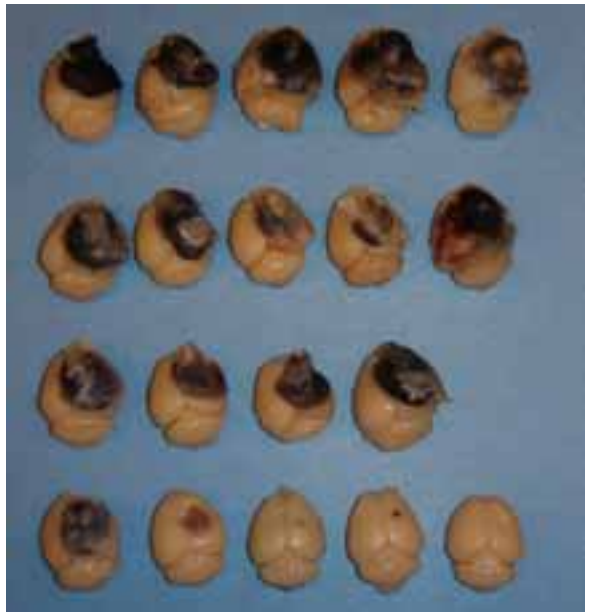
Poly-ICLC administration enhances the infiltration of OVA-Specific T cells and therapeutic efficacy

Brain-Infiltrating T cells

These cells express CXCR3 and VLA-4



Anti-Tumor Effect



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Objectives (UPCI 05-115)

- Primary Objective
  - Safety - to determine the maximal tolerated dose of DC1 and evaluation of toxicities
- Secondary Objectives
  - Assess immunological response against GAAs using ELISPOT and tetramer assays
  - Assess the preliminary anti-tumor clinical activity of the vaccines as measured by radiological response (MRI), overall survival as well as 6 month-progression free survival (PFS).

Eligibility

- Adult patients with recurrent GBM or WHO grade 3 AG
- HLA-A2+ based on flow-cytometry
- Minimum corticosteroid (4 mg/day or less for Dexamethasone)
- Maximum 2 previous recurrences

Treatment

- Ultrasound-guided intranodal injections of type-1 DC1 (1 or 3 x 10^7 /injection with dose escalation) loaded with 4 glioma-associated antigen (GAA)-derived HLA-A2-restricted CTL epitopes

  (IL-13Ra2$_{345\text{-}353:1A9V}$, gp100$_{209\text{-}217:2M}$, EphA2$_{883\text{-}891}$ and YKL-40$_{201\text{-}210}$)

- Intramuscular injections of poly-ICLC (20 mg/kg; Twice/week)

Demographics for All Patients Enrolled (N=22)

Parameter	No.	%
Received at least one vaccine	22	
Completed at least 4 vaccines	19	86
	(10 and 9 for dose levels 1 and 2)	
Median age, years	48.6	
Range	28-71	
Tumor Histology		
AA	6	27
AO	3	14
GBM	13	59
No. of Previous Recurrences		
0	5	23
1	11	50
2	6	27

The regimen was well-tolerated

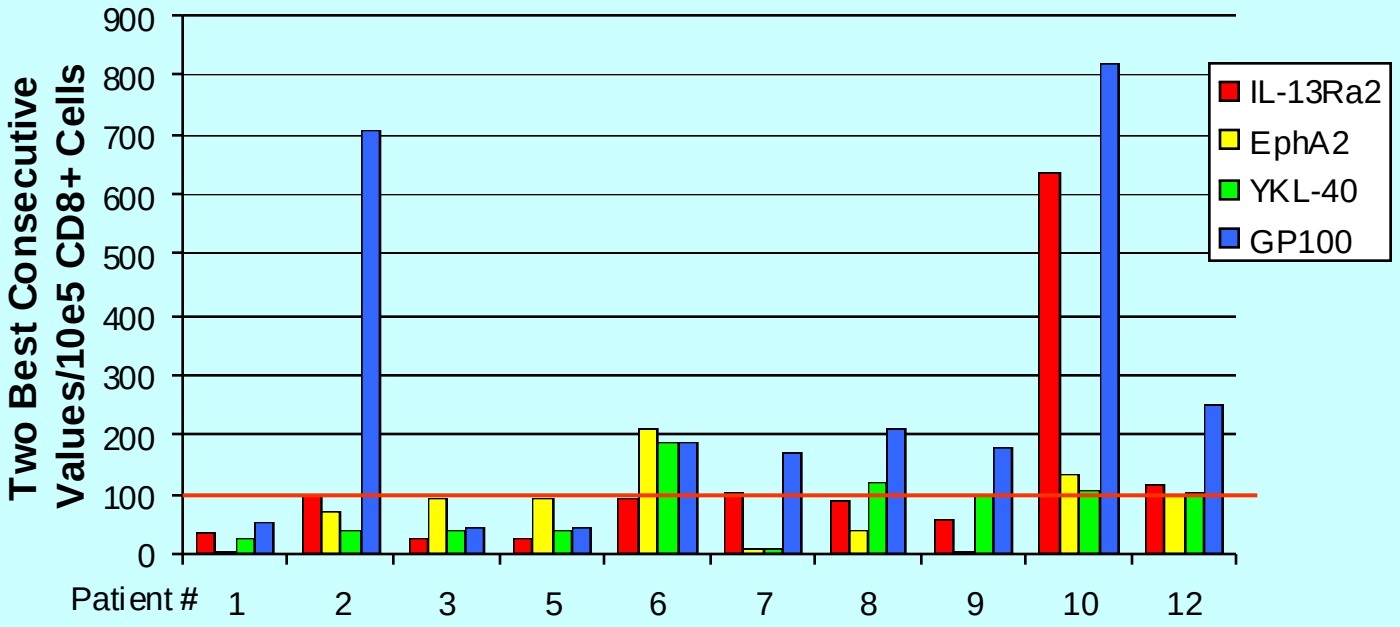
No CTCAE grade 3 or grade 4 events observed related to treatment.

All adverse events listed above were believed to be possibly, probably, or definitely related to the vaccine and/or poly ICLC regimen.

The numbers represent the No. of patients (of 22) experiencing a particular event at any point during the treatment period, with the highest grade reported for any single individual.

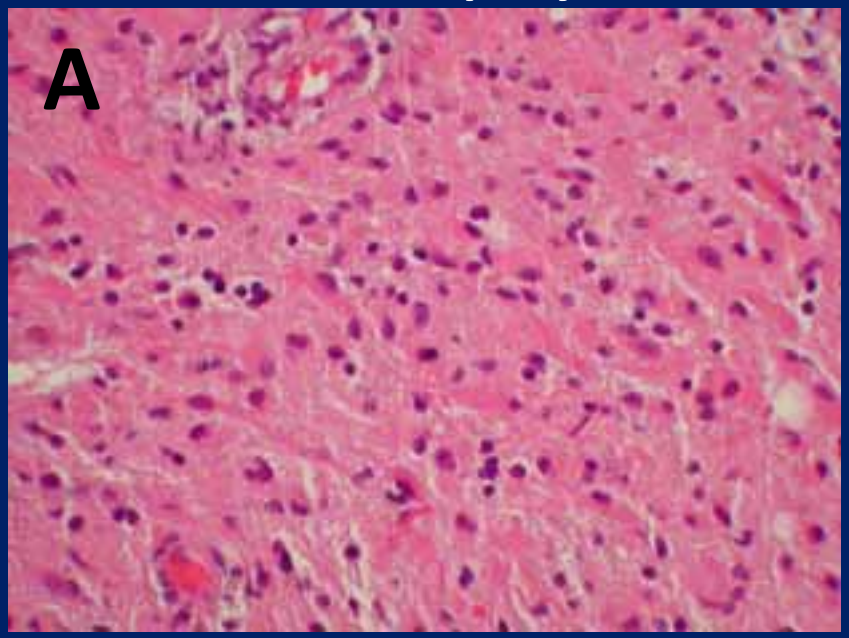
	Grade 1		Grade 2	
Adverse Event	No.	%	No.	%
Injection site reactions				
Redness, induration, pruritis, pain	15	68	3	13.6
Constitutional symptoms				
Fatigue	13	59	2	9
Fever	4			
		18.1		
Chills/Rigors	5	22.7		
Nausea	6	27.3		
Vomiting	1	4.5		
Headache	4	18.1	1	4.5
Insomnia	1	4.5		
Dyspnea				
Light headed/dizziness	1	4.5		
Dermatological				
Skin rash	3	13.6		
Dry skin	1	4.5		
Bruising	1	4.5		
Musculoskeletal				
Pain, back spasm				
Arthralgias				
Myalgias	4	18.1		
Muscle weakness/pain	6	27.3	2	9
GI				
Constipation				
Diarrhea				
Cardiovascular				
Tachycardia				
Edema				
Pain				
Throat/pharynx/larynx	2	9		
Pulmonary/Upper Respiratory				
Rhinitis/Runny nose	1	4.5		

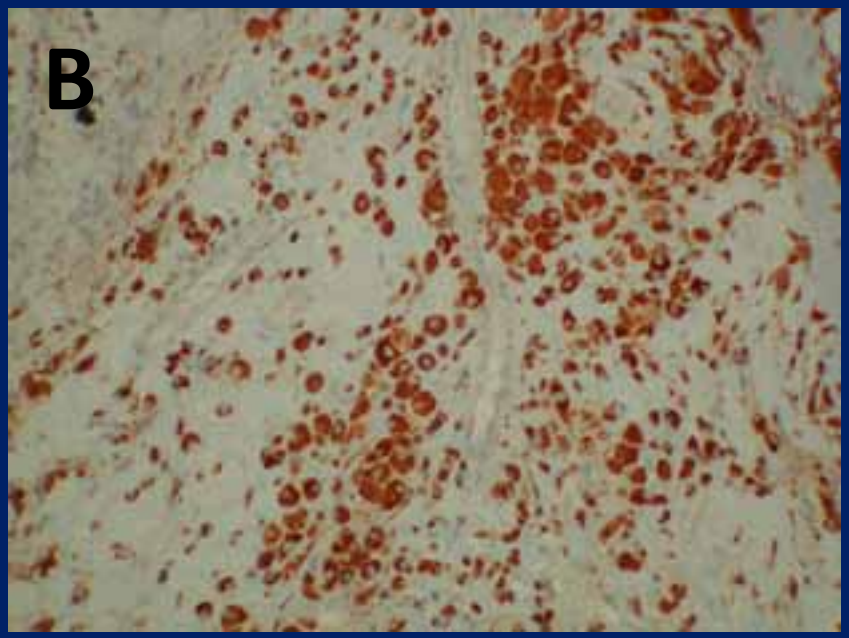
ELISPOT Response and Clinical Outcomes

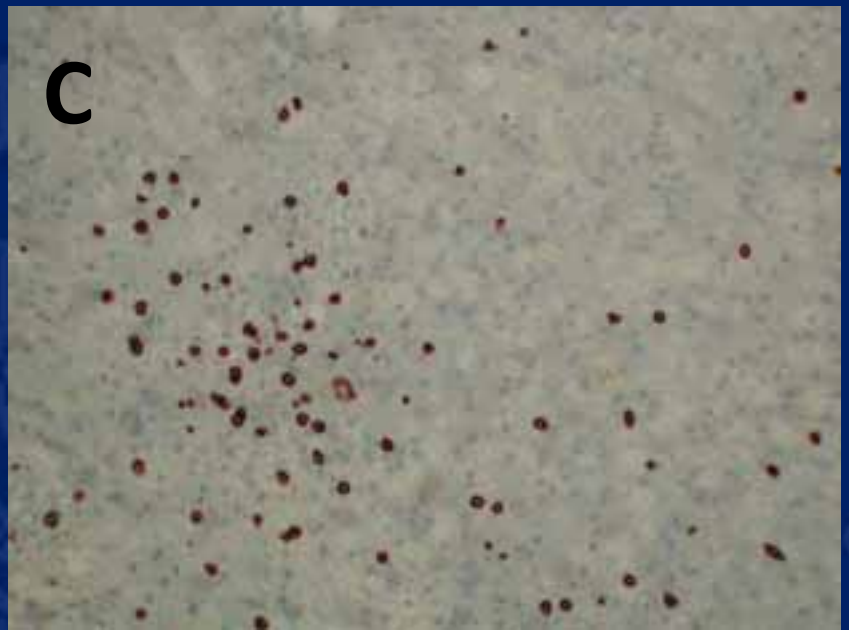


Path	GBM	GBM	AA	GBM	AA	AA	GBM	AO	GBM	AO
Tet	+	+	+	-	+	+	+	-	-	+
9W	PR	PD	SD	PD	SD	SD	SD	PD	SD	SD
6M-PFS	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes
TTP (M)	7	<2	4	<2	20+	23+	16	<2	4	13
DC# x10e7	1	1	1	1	1	1	1	1	1	3

Biopsy of the Residual Tumor





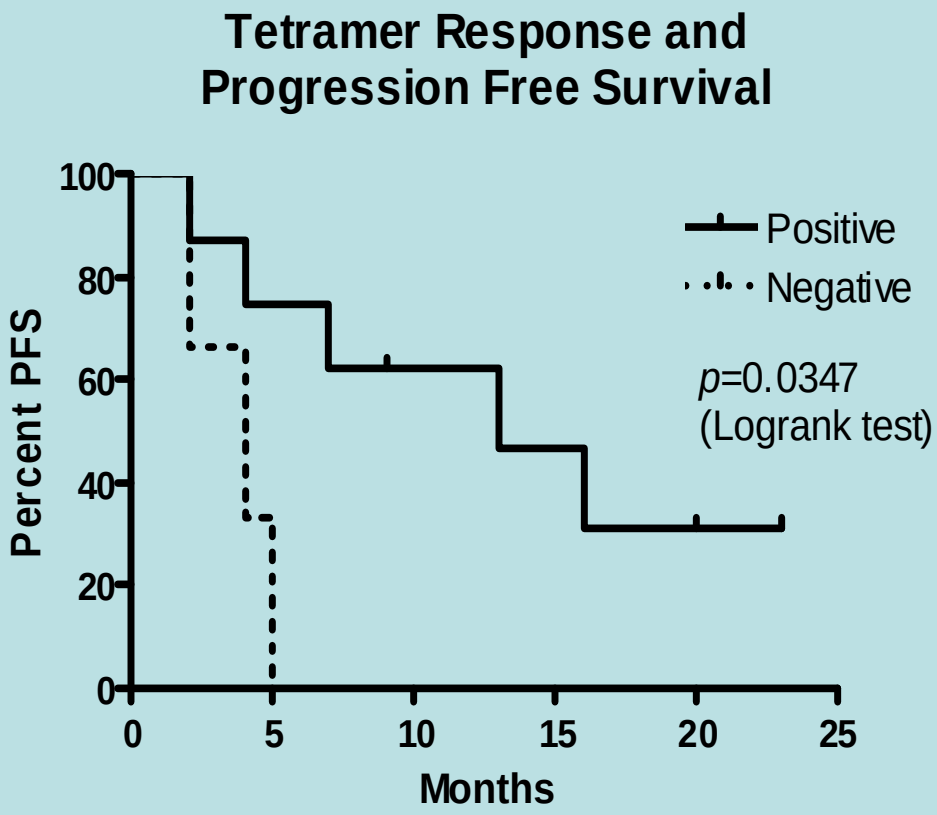


A: H&E; cellular area with reactive gliosis and possible residual glioma with no evidence of mitosis (400x)

B: CD68 – numerous macrophages (200x)

C: most of the T cells are CD8+ (200x)

Association between Positive Tetramer Response and 6M-PFS



An association between positive tetramer response (against any of the GAAs) and progression-free survival by Logrank test.

Fisher's exact test also indicated a positive association for 6M-PFS (p= 0.040 [one-sided]; 0.048 [two-sided])

Summary

1. These interim data demonstrate the safety of the regimen and, for the first time, induction of specific reactivity against novel IL-13Rα2- and EphA2-derived epitopes in vaccine recipients.
2. Although we treated mixed tumor types, our preliminary data also indicated an association between positive tetramer response and progression free survival.

Ongoing Vaccine Trials using glioma-associated antigen (GAA)-peptides and poly-ICLC as the common platform

- Type-1 DCs loaded with GAA-peptides in recurrent high grade gliomas (UPCI 05-115)

Novel trials using GAA in Montanide ISA-51 VG (Seppic, Inc) and poly-ICLC

- GAA-peptide vaccines plus poly-ICLC in patients with newly diagnosed WHO G2 gliomas with high risk factors (UPCI 07-057)
- The same vaccine as above for recurrent LGG (UPCI08-135)
- GAA-peptide vaccines plus poly-ICLC in pediatric patients with gliomas (CHP)

Clinical Immunology Society

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- Key inter-disciplinary organization for the field of clinical immunology and is devoted to fostering developments in the science and practice of clinical immunology;
- International professional organization which includes clinicians, investigators, and trainees;
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  - New Therapeutics in Autoimmunity
- Will provide education for clinician scientists in immunology.
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I am stopping my talk

– though our work will never stop at any time!

THANK YOU!