Tumor-Specific Peptide Vaccination in Newly Diagnosed Patients with GBM

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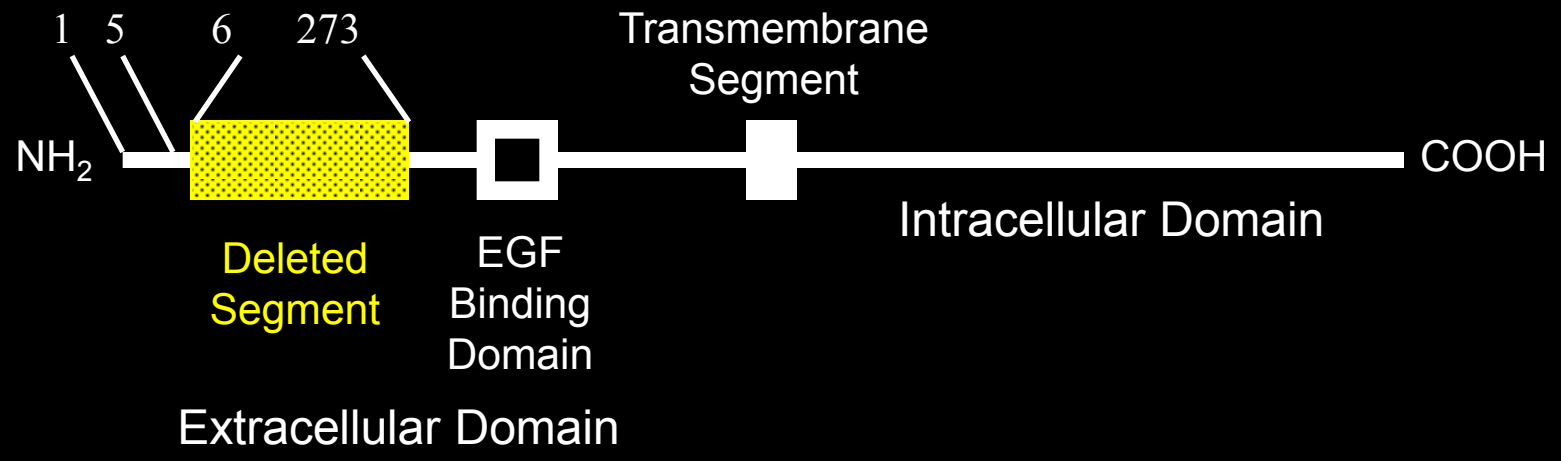
Epidermal Growth Factor Receptor Mutation

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 1               5   6              273
   LEU-GLU-GLU-LYS-LYS-VAL-CYS-...-PRO-ARG-ASN-TYR-VAL-VAL-THR-ASP-HIS
Wild Type Amino Acid Sequence

   CTG-GAG-GAA-AAG-AAA-GTT-TGC-...-CCC-CGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC
Wild Type cDNA Sequence

   CTG-GAG-GAA-AAG-AAA-GGT-AAT-TAT-GTG-GTG-ACA-GAT-CAC
Variant III cDNA Sequence

   LEU-GLU-GLU-LYS-LYS-GLY-ASN-TYR-VAL-VAL-THR-ASP-HIS   ← PEP-3
Variant III Amino Acid Sequence
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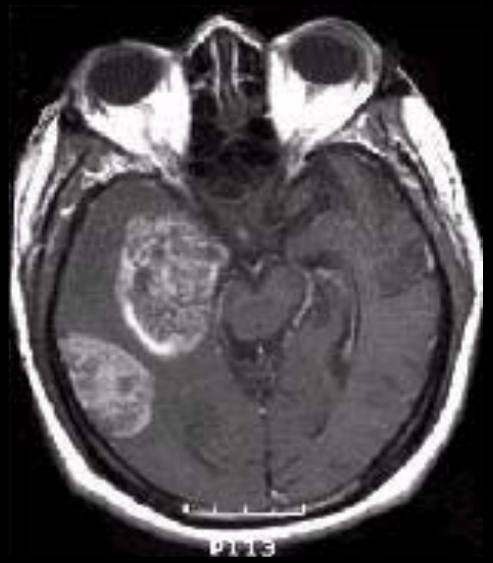
Glioblastoma Multiforme (GBM)

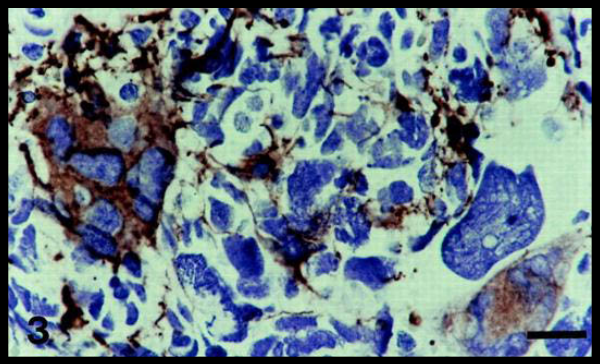
- **GBM is the most aggressive and common primary malignant brain tumor in adults characterized by diffuse infiltration of the brain parenchyma**

- **Newly diagnosed GBM patients treated with radiation and temozolomide have a time to progression and median survival of 6.9 and 14 months respectively[1]**

- **The expression of epidermal growth factor receptor variant III (EGFRvIII) does not impact median survival (12.8 months)[2]**

- **EGFRvIII is expressed on 30-50% of GBM[2,3]**





[1] Stupp et al., New England Journal of Medicine, 352(10):987-996, 2005.
[2]Heimberger et al., Clinical Cancer Research, 22(5):1462-1466, 2005.
[3]Liu et al., Journal of Molecular Medicine, 83(11):917-926, 2005.

Patient Selection

Inclusions

Newly Diagnosed Glioblastoma Multiforme

Karnofsky $\geq$ 80

s/p gross total resection (95% volumetric)

s/p XRT $\pm$ temozolomide

No evidence of progression on MRI post XRT

EGFRvIII expression

Exclusions

Hepatitis B serology positive

Pregnancy

Corticosteroids (above physiologic levels)

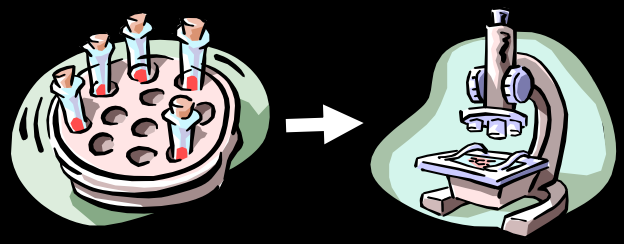
Leptomeningeal Disease

Autoimmune Disorder

Immunosuppressive Disease

Severe Intercurrent medical conditions

ACTIVATE Trial



Immunologic Monitoring

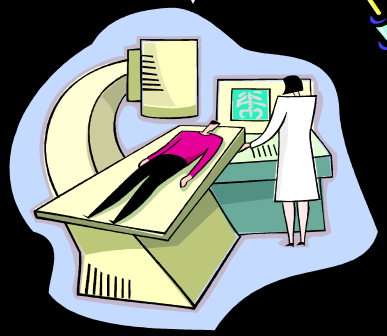
Leukapheresis

Saline + GM-CSF
(Every 2 weeks i.d.)

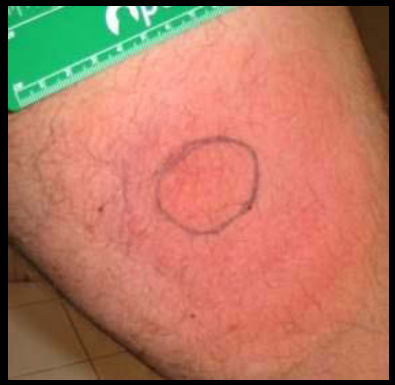
Randomize

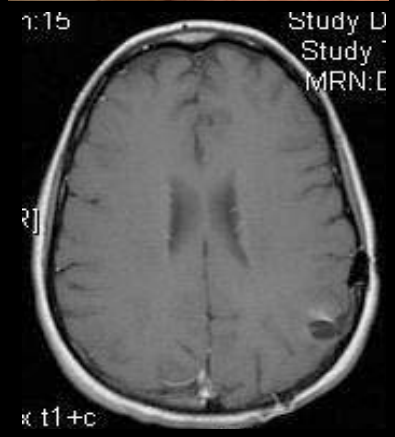
PEPvIII-KLH + GM-CSF
(Every 2 weeks i.d.)

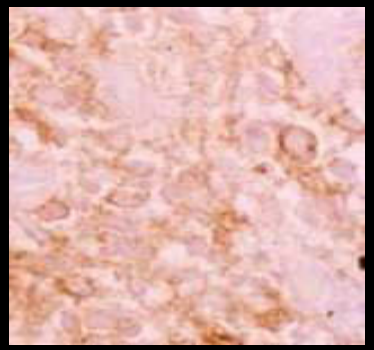
PEPvIII-KLH + GM-CSF
(Every 1 month i.d.)



6000 cGy

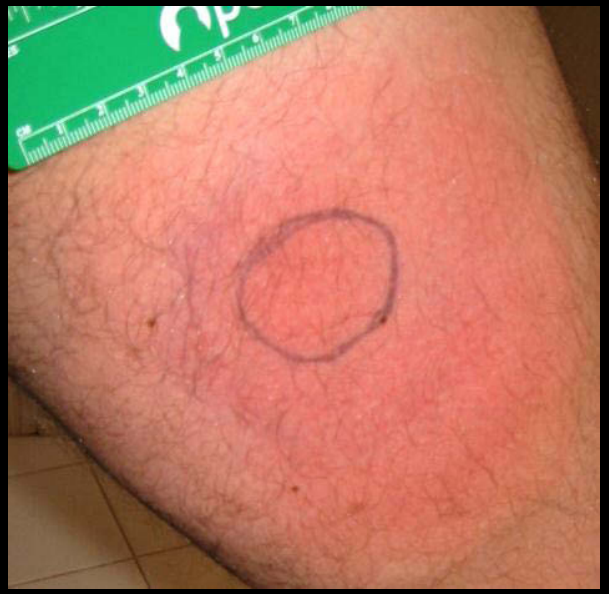


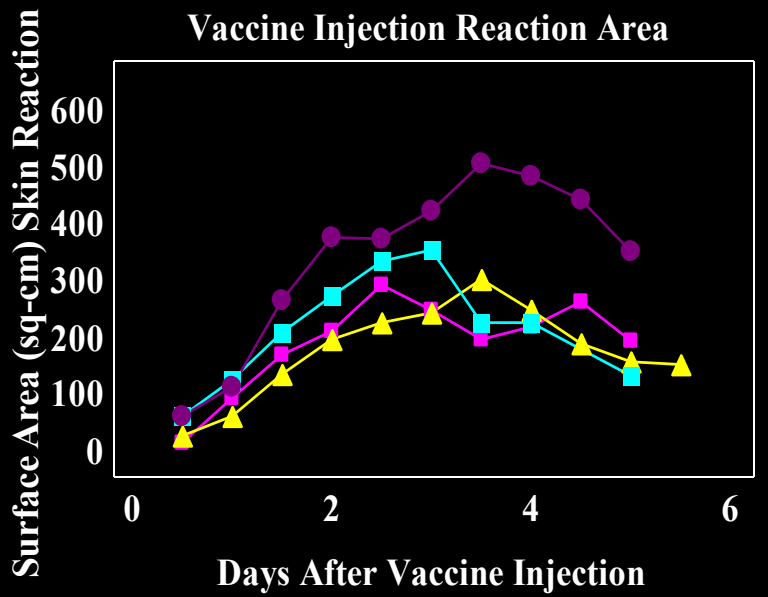




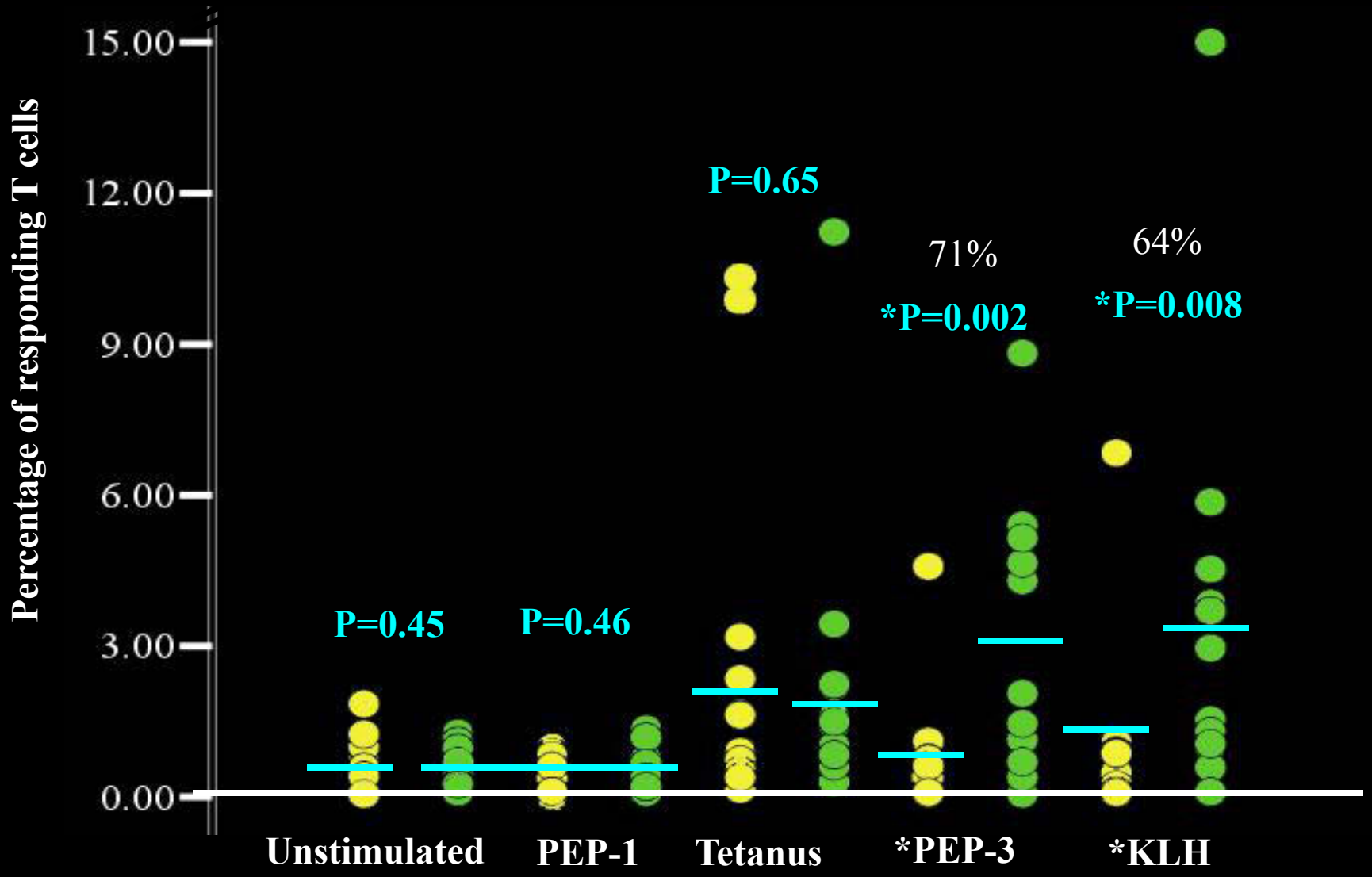
Toxicity

Event	Grade	N
Injection site reaction/Urticaria	1	23
Leukoencephalopathy with radiographic changes	1	1
Allergic reaction	1	1

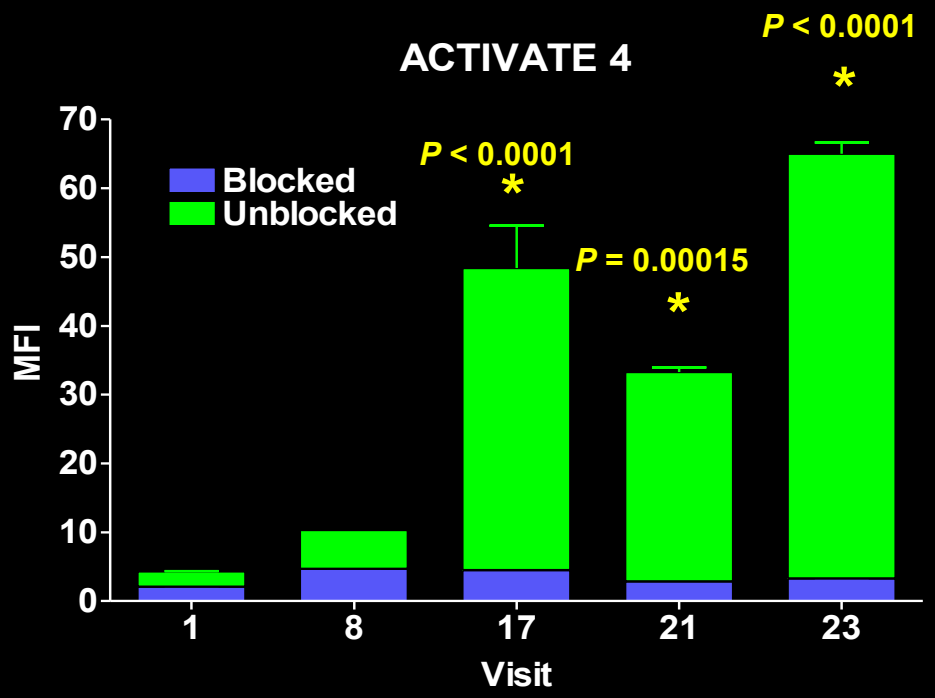


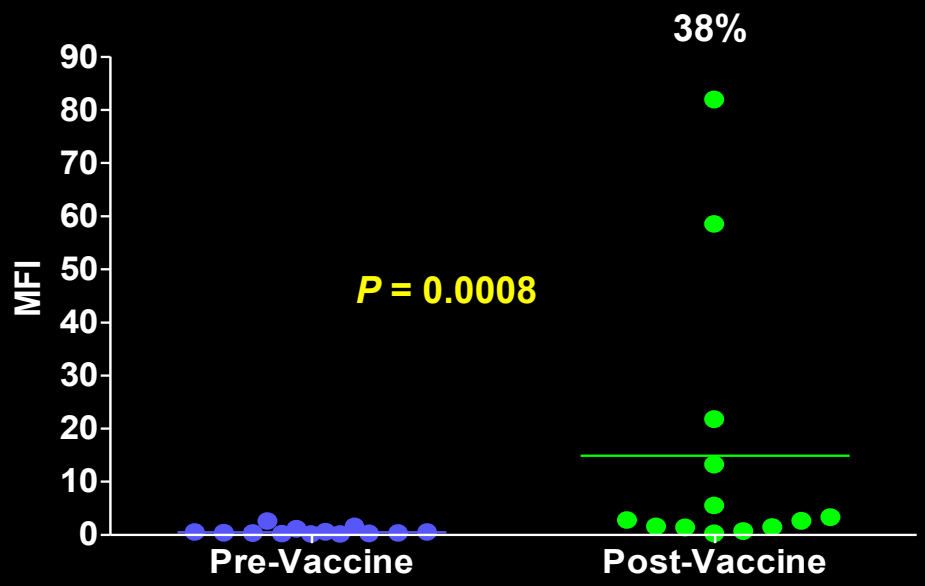


Immunological responses: Vaccination results in the induction of CD8+γ-IFN EGFRvIII T cells

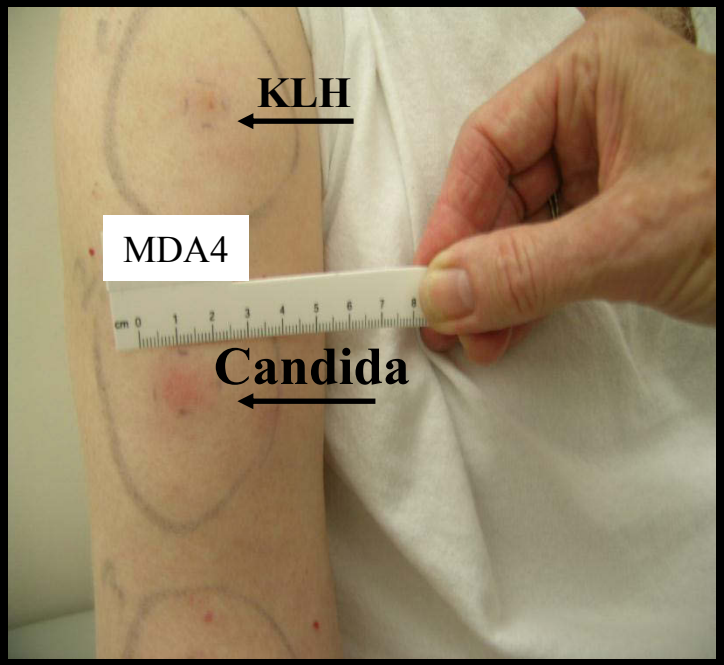


Immunological Responses: Vaccination results in the induction of EGFRvIII-specific humoral responses





Immunological Responses: Delayed-type hypersensitivity reactions



	Pre-Vaccination	Post-Vaccination	3-Months	6-Months
Candida	25%	50%	64%	75%
Trichophyton	10%	25%	29%	17%
Tetanus	25%	70%	100%	58%
PEP-3	0%	0%	7%	15%
KLH	0%	35%	47%	62%

Demographic characteristics of patients with glioblastoma multiforme treated with the EGFRvIII peptide vaccination and the historical cohort

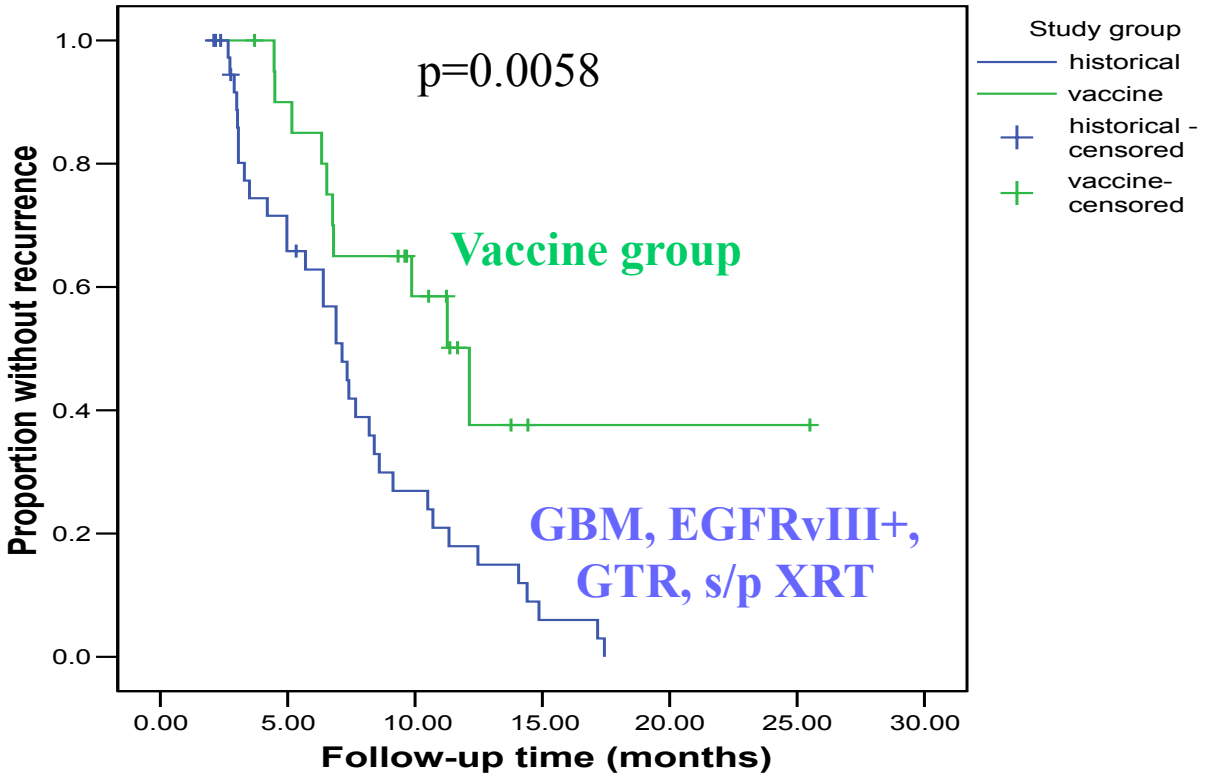
Parameter		EGFRvIII vaccine group	Historical cohort
Total, N		23	39
Sex, N (%)	M	16 (70)	21 (54)
	F	7 (30)	18 (46)
Age, years, Median (range)		52 (29-73)	59 (31-82)
KPS score, Median (range)		91 (80-100)	90 (70-100)
EGFRvIII expression, N (%)		23 (100)	39 (100)
Radiation, N (%)		23 (100)	39 (100)
Extent of surgical resection, Median (range)		>95 (95-100)	100 (95-100)
Temozolomide delivered concurrently with radiation, N (%)		22 (96)	17 (44)

[a]EGFR, epidermal growth factor receptor; vIII, vIII mutant; KPS, Karnofsky Performance Scale

Time to progression of GBM patients receiving the EGFRvIII vaccine compared to a historical cohort

TTP in the vaccine group is **12.8 months**

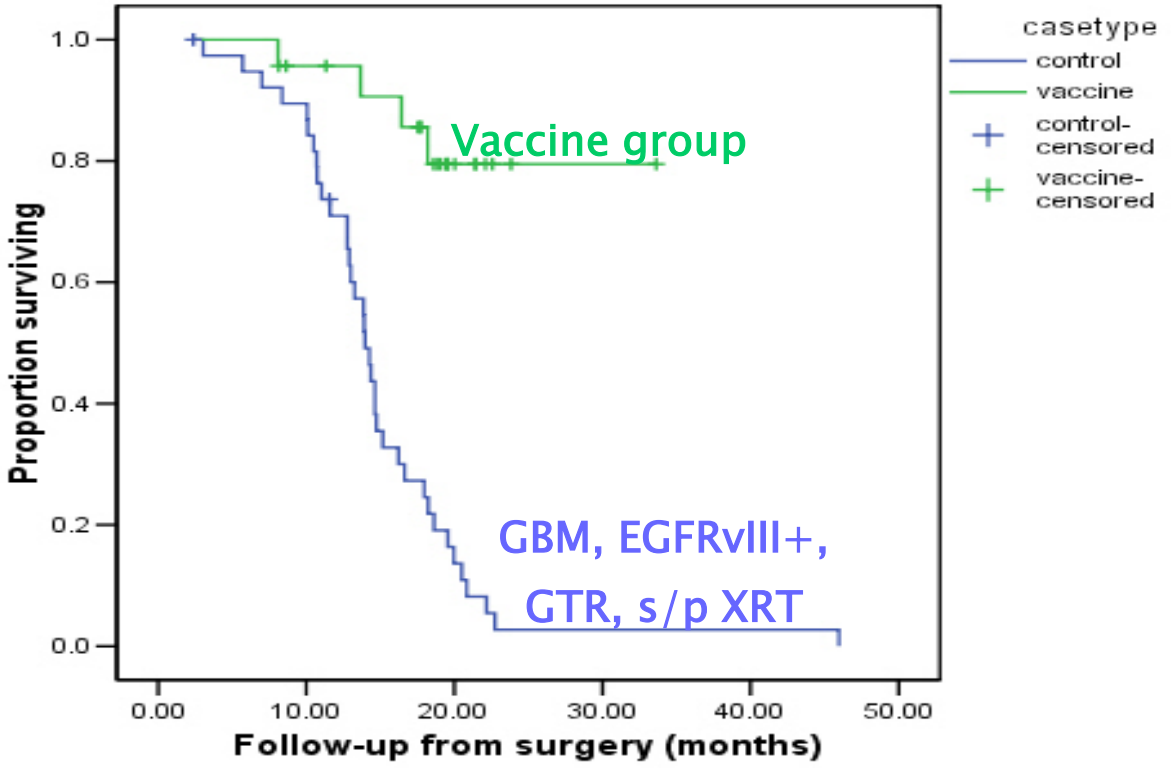
TTP in the historical cohort is 7.1 months



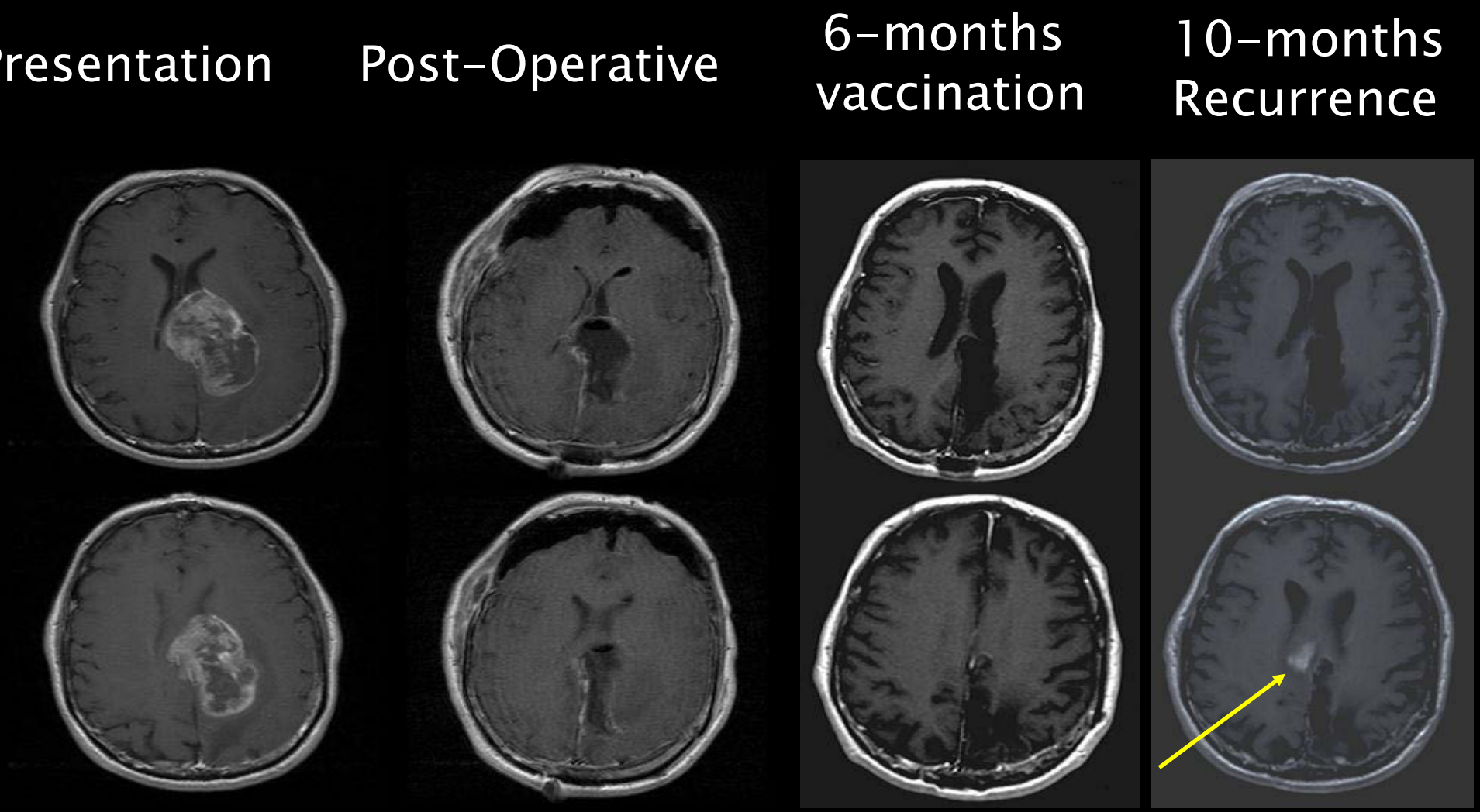
Median Survival of GBM patients receiving the EGFRvIII vaccine compared to a historical cohort

MS in the vaccine group is **>18 months**

MS in the historical cohort is 13 months



EGFRvIII Vaccinated GBM Patient MRI

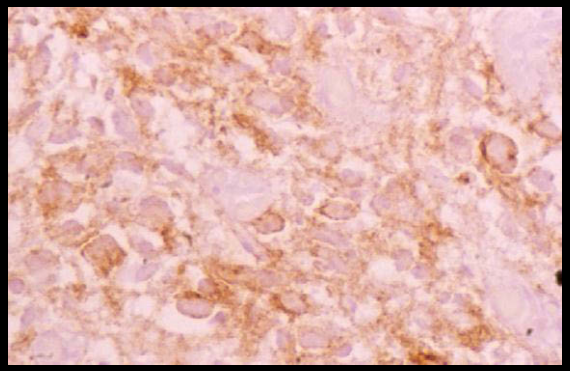


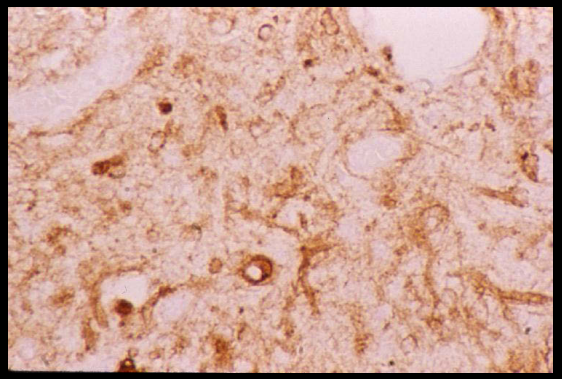
EGFRvIII is not expressed at tumor recurrence n=6

Pre Vaccination

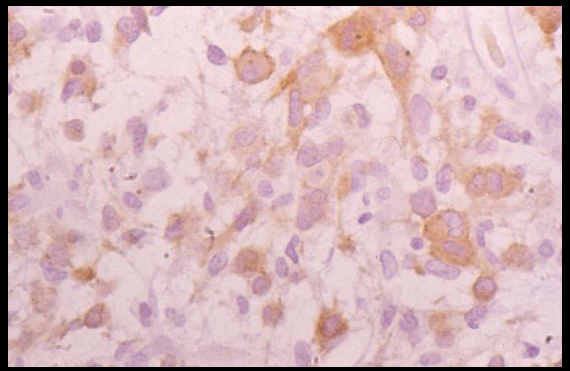
Post Vaccination Recurrence

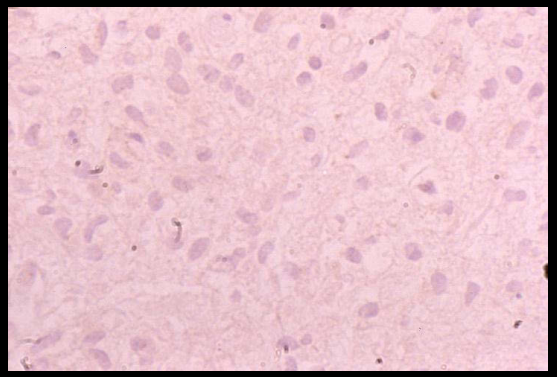
EGFR





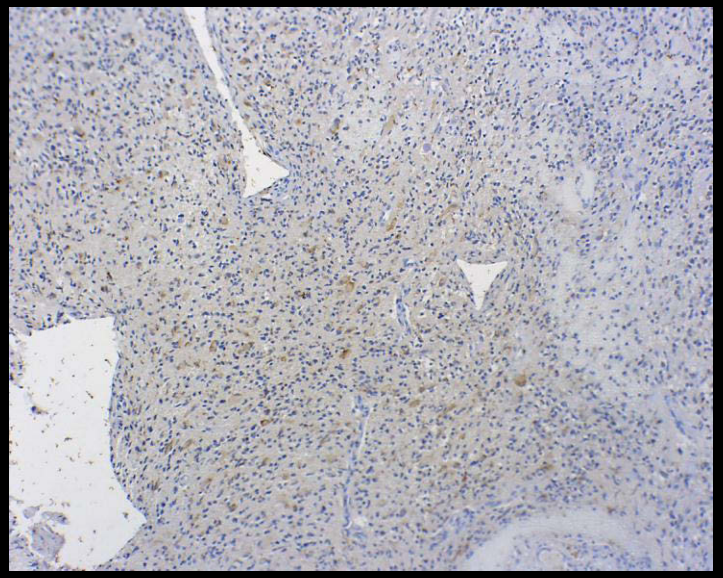
EGFRvIII

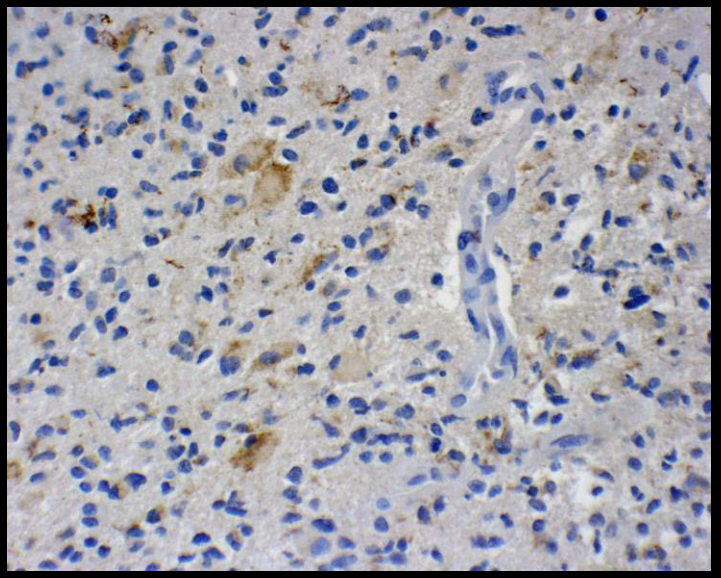




Magnification is 250X

EGFRvIII expression is maintained in a patient that was randomized to saline and recurred





CONCLUSIONS

- Toxicity is minimal
- CD8+ γ-IFN EGFRvIII-specific cytotoxic T cell responses are induced
- EGFRvIII humoral responses are induced
- Time to tumor progression is 12.1 months
- Median survival has not yet been reached but will exceed at least 18 months
- Treatment failure presumably is secondary to the loss of epidermal growth factor receptor variant III antigen

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