

Long-term Follow-up of ACT III: A Phase II Trial of Rindopepimut (CDX-110) in Newly Diagnosed Glioblastoma

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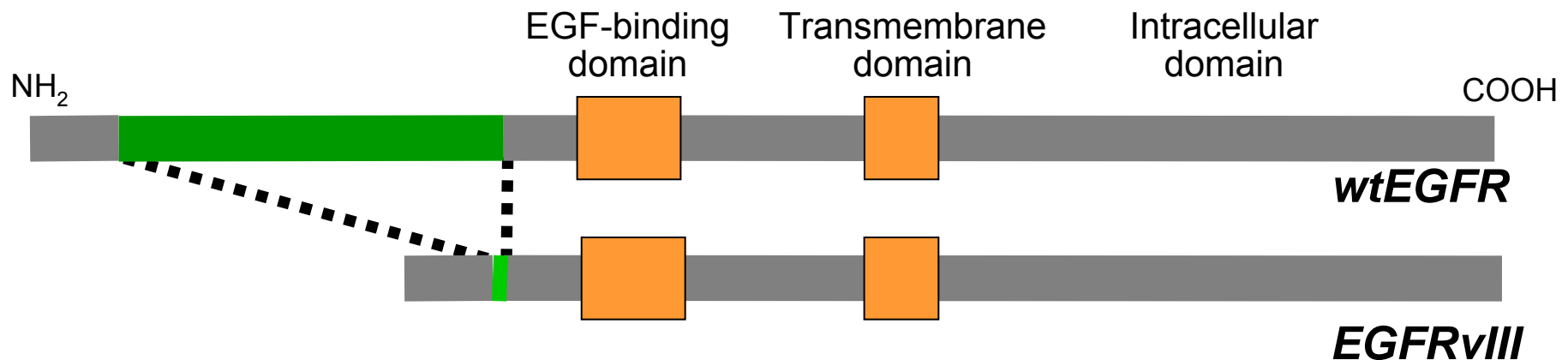
Presented on behalf of the entire ACT III Study Group

Presented at the 2011 SNO Annual Scientific Meeting, Orange County, CA

Disclosures

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- The ACT III study was sponsored by Celldex Therapeutics, Inc.

EGFR Mutation Variant III (EGFRvIII)

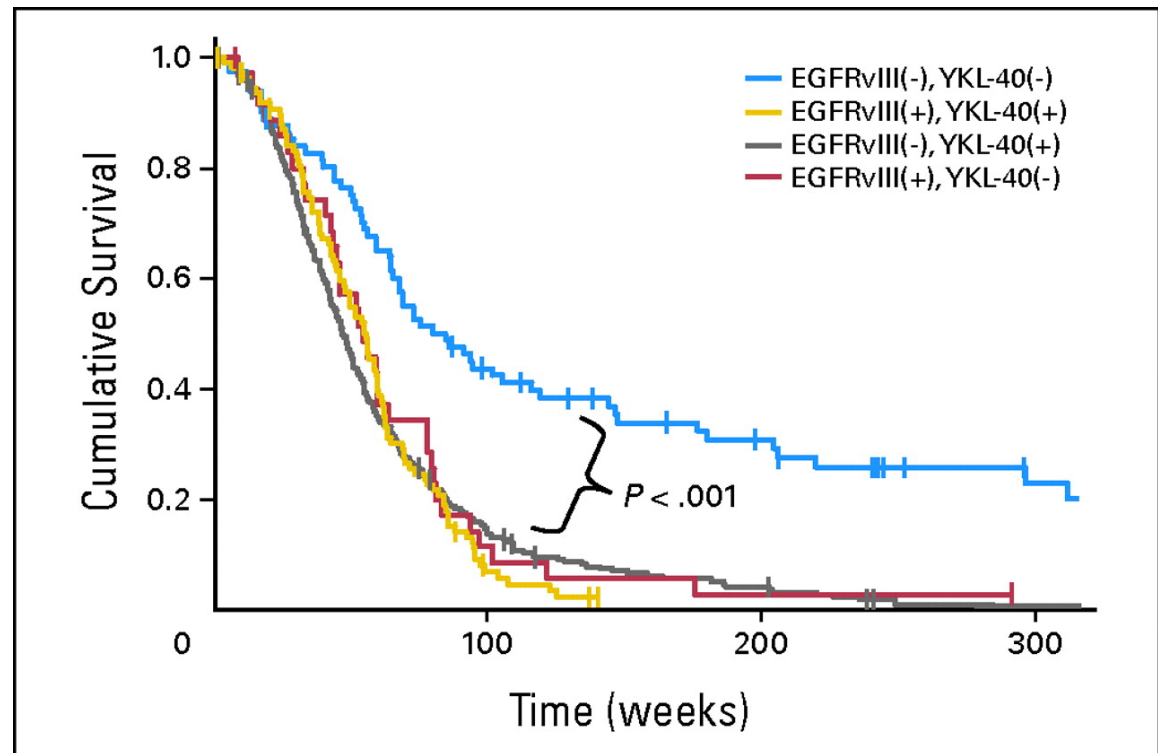


- Tumor-specific oncogene ideally suited for immune targeting
- Expressed in 31% of primary glioblastoma, but not in normal tissue
- In-frame deletion of exons 2-7 results in constitutively active protein with unique amino acid sequence at the fusion junction
- Epitope is in the extracellular domain; accessible to antibodies and highly immunogenic

Epidermal Growth Factor Receptor Variant III (EGFRvIII)

- Constitutively active and tumorigenic
- EGFRvIII(+) cells may induce growth in EGFRvIII(-) cells
 - Paracrine signaling via EGFRvIII-mediated production of IL-6 family cytokines¹
 - Intracellular transfer of the EGFRvIII phenotype via membrane-derived microvesicles²
 - Frequently expressed in GBM tumor stem cells³

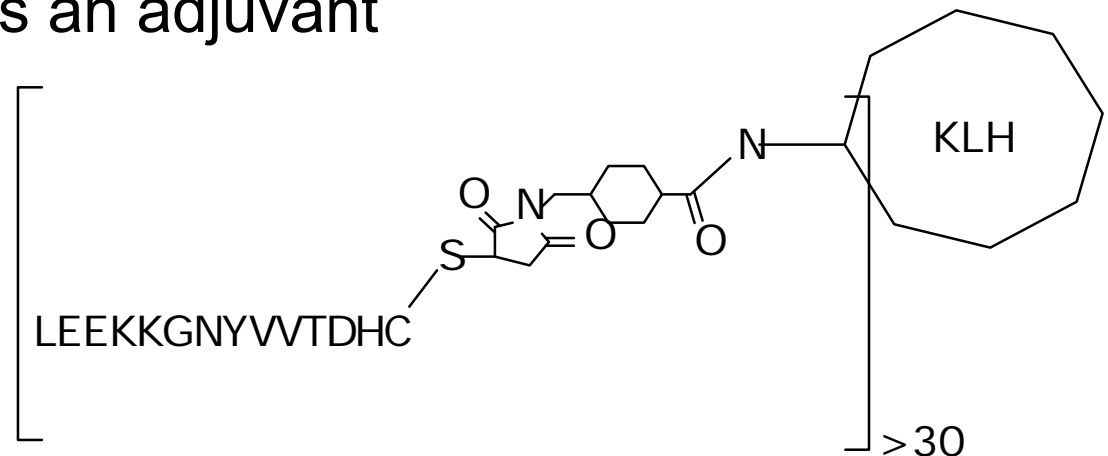
EGFRvIII linked to poor long term survival⁴



1. Inda, et al. Genes Dev. 2010
2. Al-Nedawi, et al. Nat Cell Biol. 2008
3. Wong, et al. JCO. 2008
4. Pelloski, et al. JCO. 2007

Rindopepimut (CDX-110)

- Vaccine designed to generate a specific immune response against EGFRvIII-expressing tumors
 - “Off the shelf” vaccine recognized across HLA types
 - Consists of the EGFRvIII antigen (unique 13 amino acid peptide sequence) chemically conjugated to Keyhole Limpet Hemocyanin
 - Delivered as intradermal injection of 500ug rindopepimut with 150ug GM-CSF as an adjuvant
 - Stable, lyophilized formulation



Previous Clinical Experience (ACTIVATE and ACT II)

- Single-arm Phase II clinical studies (MDACC, Duke) ^{1,2}
- Newly diagnosed, resected, EGFRvIII-expressing glioblastoma; completed chemoradiation without progression
 - ACTIVATE (n = 18; enrolled June 2004 - Aug 2005)
 - › rindopepimut/GM-CSF biweekly x3, then monthly until intolerance or progression
 - ACT II (n = 22; enrolled Aug 2005 - Feb 2008)
 - › rindopepimut/GM-CSF concurrent with either standard or dose-intensive adjuvant TMZ

1. Sampson, et al. JCO. 2010
2. Sampson, et al. Neuro Oncol. 2010

ACT III Study Design

- Phase II, single-arm, multicenter study (31 centers)
- Endpoints:
 - Progression-free rate (PFR) at 5.5 months from vaccination
 - Safety and tolerability, OS and PFS, immune responses
- Patient Population (n=65, enrolled Aug 2007 - Nov 2009)
 - Newly diagnosed, de novo glioblastoma
 - Tumoral EGFRvIII expression ($\geq 10\%$ of cells positive by IHC, as assessed at a central laboratory)
 - No progression during TMZ/radiation; KPS $\geq 70\%$
 - No diffuse leptomeningeal disease, gliomatosis cerebri, multifocal disease, active infections
 - No supraphysiologic corticosteroid therapy (>2 mg dexamethasone or equivalent)
 - All HLA sub-types

ACT III: Patient Characteristics

		N = 65
Age, years (median [range])		56 (30-83)
≥ 50 years		52 (80%)
Male (n [%])		33 (51%)
KPS (median [range])		90 (70 - 100)
Duration from diagnosis to Day 0, in months (median [range])		3.0 (2.3 - 4.4)
MGMT methylation status	Unmethylated	40 (62%)

Long-term Safety

- In ACT III, ten patients have received treatment \approx 1.5 - 3.3 years
 - Treatment-related adverse events:
 - Grade 1-2 injection site reaction (including erythema, pruritus, swelling, rash) in nearly all patients; one grade 3 urticarial rash
 - > Reactions experienced throughout long-term treatment
 - Fatigue (26%), rash (22%), nausea (12%) and pruritus (11%).
 - Two cases of treatment discontinuation due to toxicity:
 - Grade 3 toxic epidermal necrolysis (possible dapsona hypersensitivity syndrome); resolved within 12 days of admission.
 - Grade 2 hypersensitivity reaction (pruritus, erythema, flushing and mild shortness of breath); onset within 10 minutes of dosing and resolved within one hour of antihistamine/corticosteroid treatment.
- In ACTIVATE/ACT II, seven patients have received treatment for \approx 3 - 7.3 years with no evidence of cumulative toxicity over time.

ACT III: Therapies Received Post-Progression

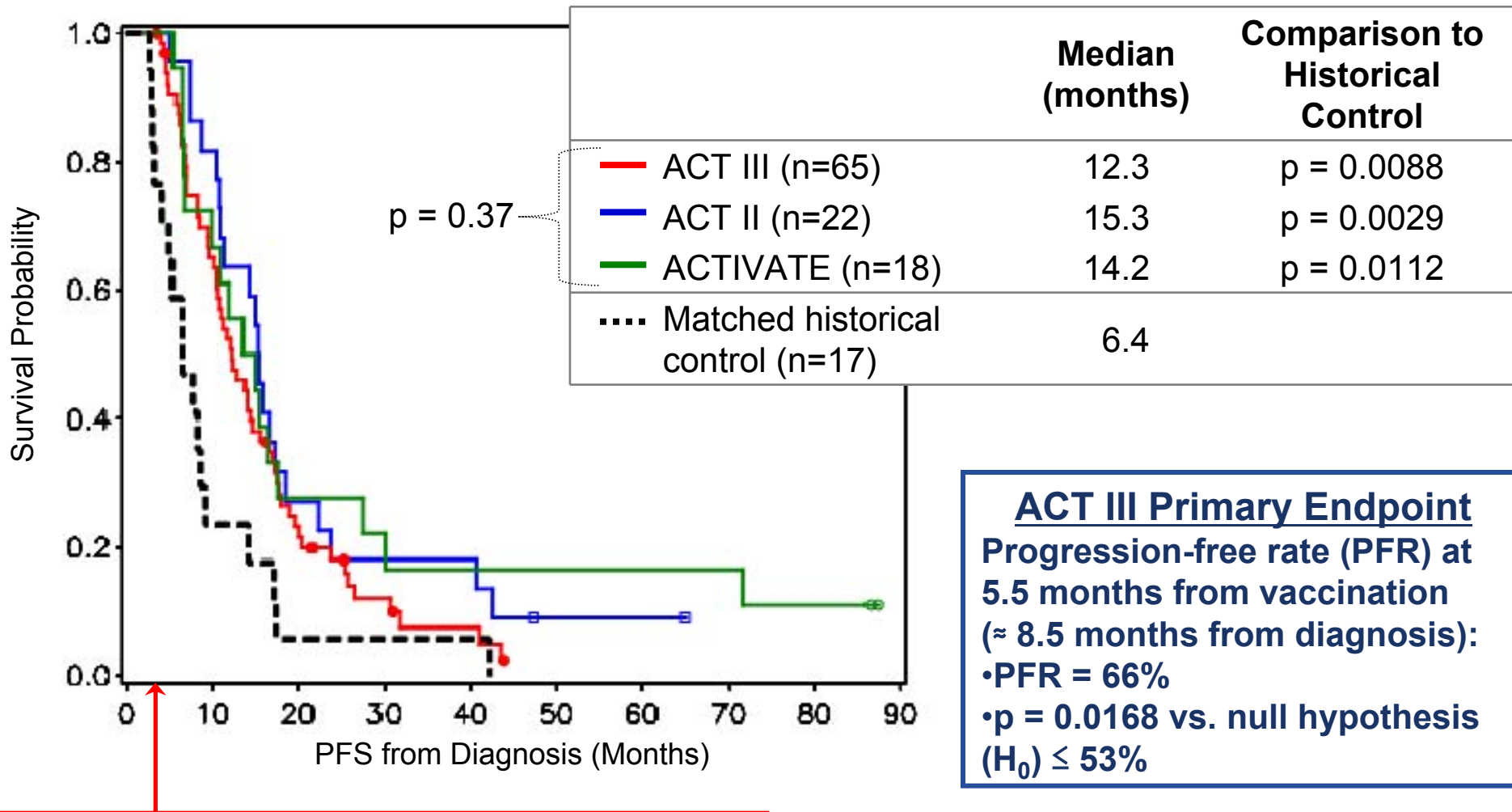
No additional treatment	17 (26%)
Additional Treatment	43 (66%)
Bevacizumab	31 (48%)
Chemotherapy (other than TMZ)	28 (43%)
Repeat resection	14 (22%)
Temozolomide (TMZ)	11 (17%)
Investigational agents	11 (17%)
Radiation	4 (6%)
Progression not yet documented	5 (8%)

Comparative Historical Control Cohort EGFRvIII-expressing Glioblastoma

	ACT III (n=65)	Historical Control (n=17)
Age, years (median [range])	56 (30-83)	59 (37-71)
≥ 50 years	52 (80%)	15 (88%)
Male (n [%])	33 (51%)	8 (47%)
KPS (median [range])	90 (70 - 100)	90 (80 -100)

Historical controls were treated at M.D. Anderson contemporaneously to the ACTIVATE trial and matched for eligibility (EGFRvIII-positive, gross-total resection, radiation/TMZ, no progression through ~3 months post-diagnosis)

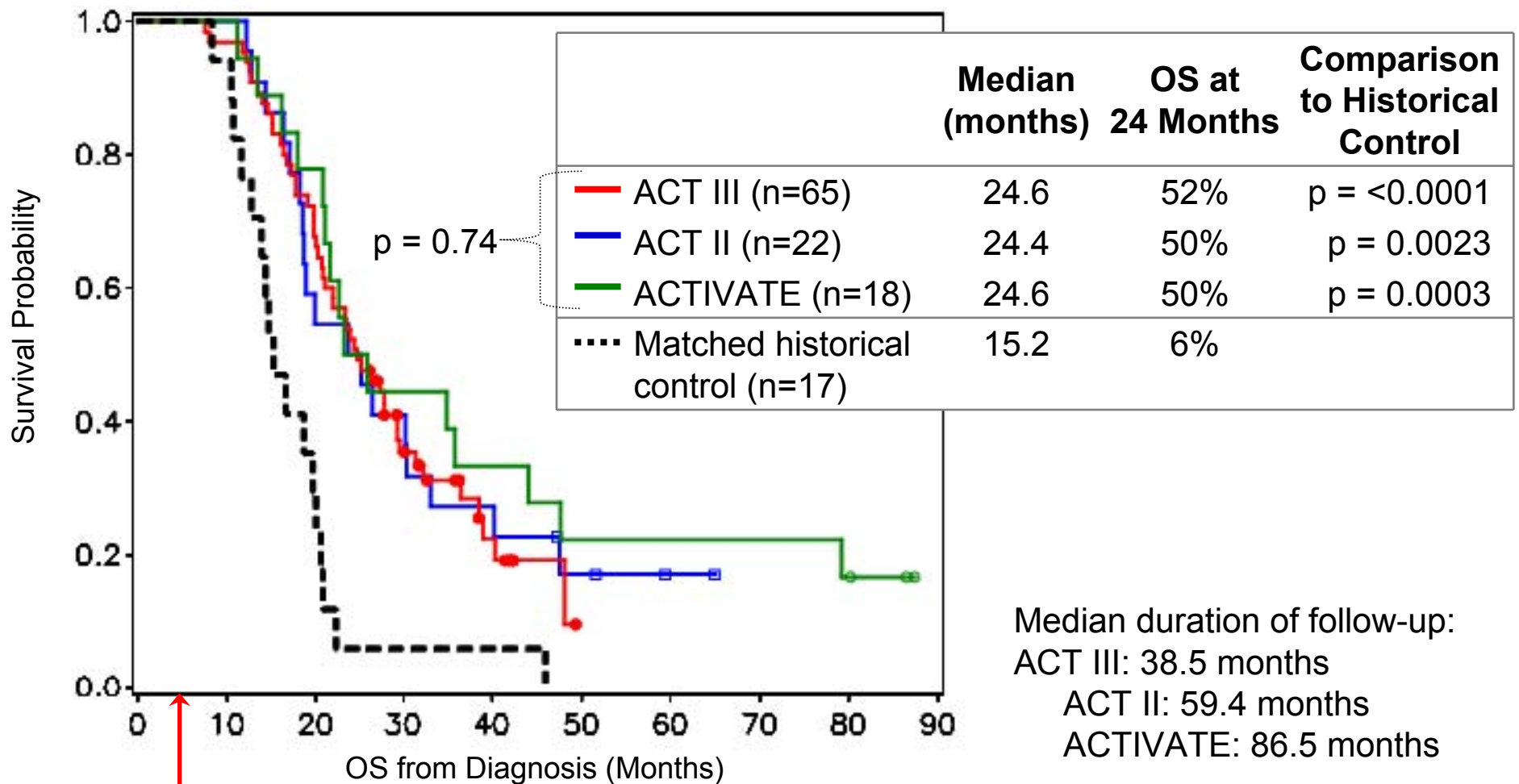
PFS from Diagnosis



Vaccinations begin approximately 3 months after diagnosis

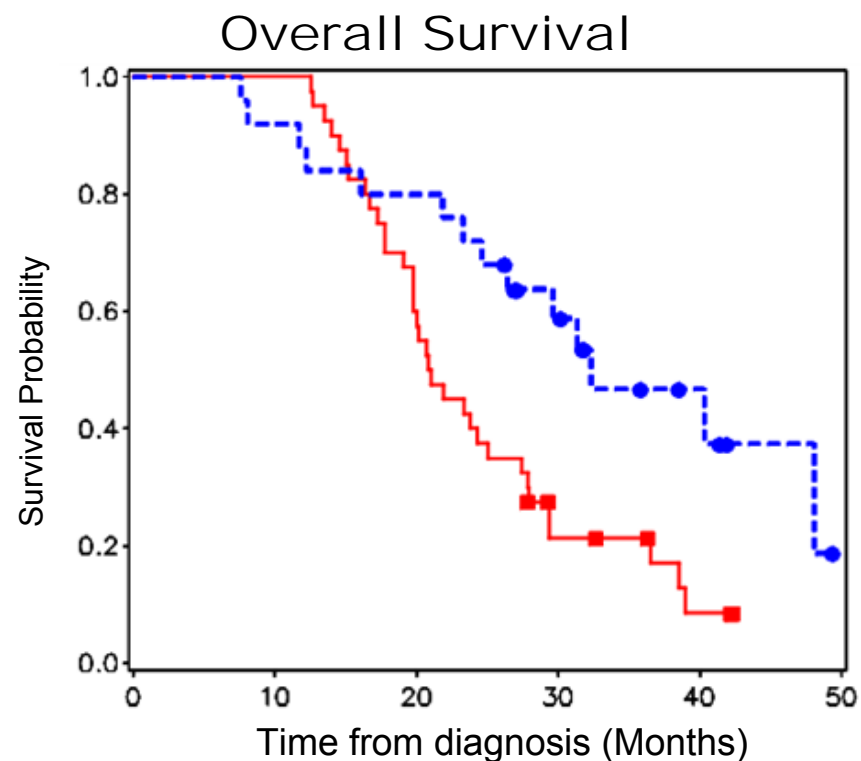
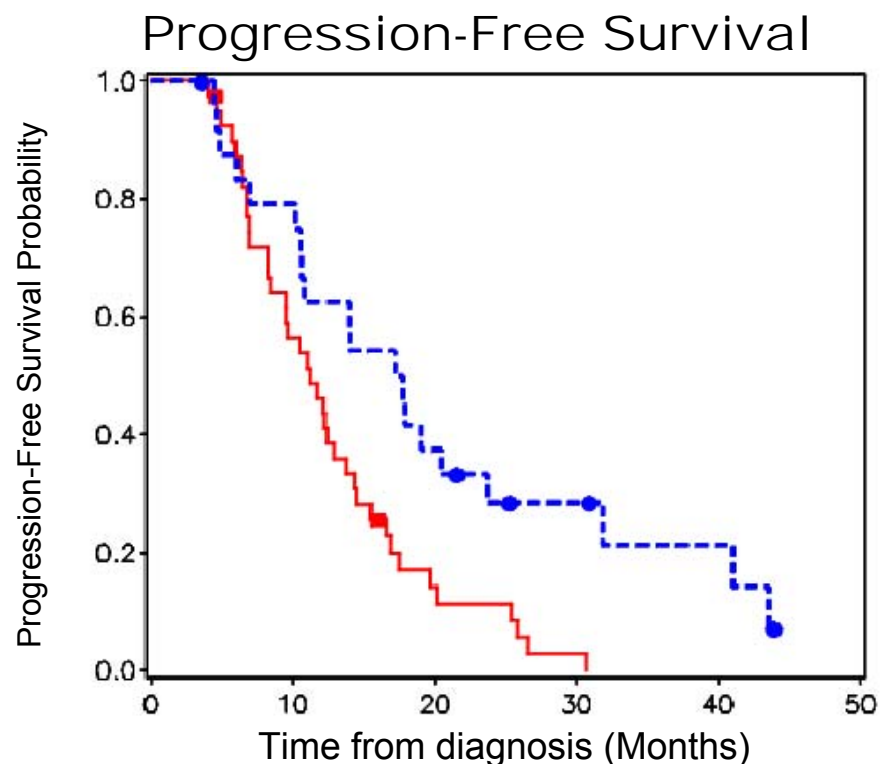
ACT III Primary Endpoint
Progression-free rate (PFR) at 5.5 months from vaccination (≈ 8.5 months from diagnosis):
 • PFR = 66%
 • p = 0.0168 vs. null hypothesis (H_0) ≤ 53%

OS from Diagnosis



Vaccinations begin approximately 3 months after diagnosis

ACT III: PFS and OS from Diagnosis, by MGMT Methylation Status



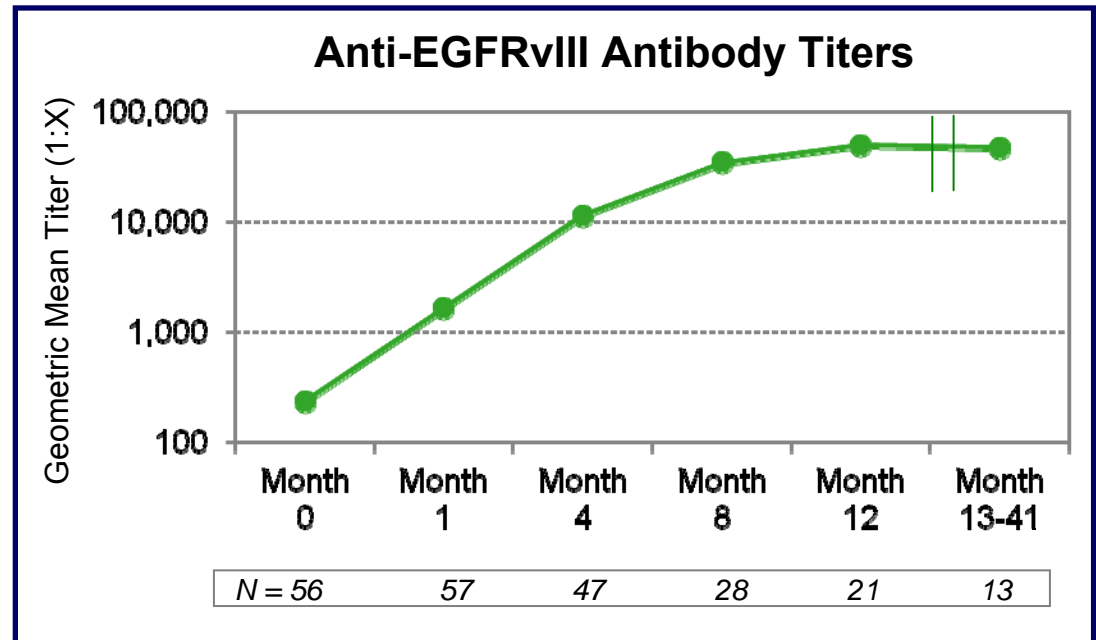
MGMT Methylation Status	Median PFS (months)	Median OS (months)
.... Methylated (n=25)	17.5	32.3 *
— Unmethylated (n=40)	11.2	20.9

$p = 0.0057$ (for PFS) and $p = 0.0067$ (for OS)

* Not yet final

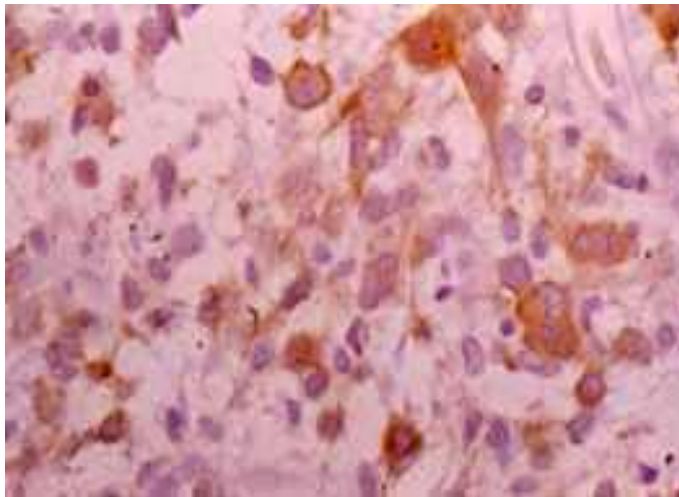
ACT III: Anti-EGFRvIII-Specific Immune Response

- 85% of patients developed significant anti-EGFRvIII antibody titers
- Majority (67%) developed titers above 1:12,800
- Anti-EGFRvIII antibody titers increased with time on study
- Cellular responses were detected in some patients but the analysis was compromised by TMZ-induced lymphopenia
- No correlations with HLA type identified

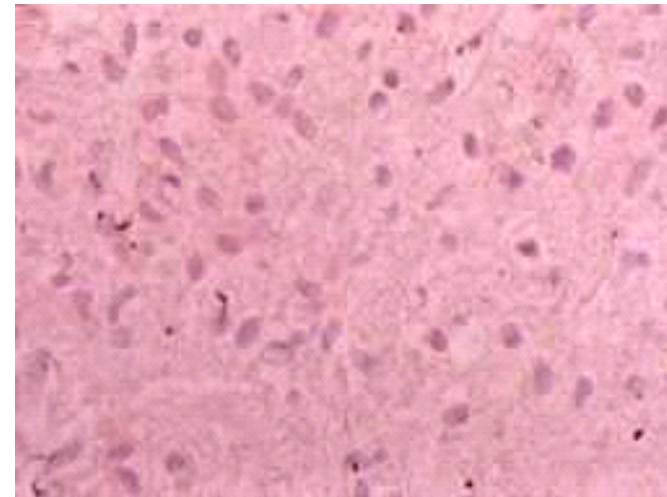


Elimination of EGFRvIII

Pre-Vaccine Primary Tumor



Post Vaccine Recurrent Tumor



- EGFRvIII was selectively eliminated in recurrent tumors for 26/32 (81%) patients across all three studies
 - 15/15 control patients treated with TMZ/radiation (+/- CPT-11, bevacizumab or erlotinib) were EGFRvIII(+) at recurrence ¹
- Robust anti-EGFRvIII titers in most patients; titers maintained for > 6 months following cessation of treatment

1. Mehta, et. al. JCO 2011

Conclusions

- Primary endpoint analysis for ACT III was positive, with a 66% progression-free survival rate at ~ 8.5 months from diagnosis.
- Results are consistent across the ACT III trial (31 centers) and the two previous phase II trials in the same population (ACTIVATE & ACT II):
 - Promising benefits in PFS and OS
 - › Median OS of 24.6 months vs. 15.2 months for matched EGFRvIII-positive controls
 - › Notable long-term survival
 - › Apparent benefit in patients with both methylated and unmethylated MGMT promoter
 - EGFRvIII eliminated in post-treatment, recurrent tumor samples
 - Well tolerated with generation of robust, specific and durable immune responses.

Future Directions

- **Phase III trial being initiated**
 - Front-line glioblastoma
 - 374 patients with gross total resection
 - Randomized, double-blind design (KLH control)
 - Endpoints: OS (primary), PFS, QOL
 - International trial conducted at over 150 centers
 - Site recruitment is ongoing
- **Phase II trial in recurrent glioblastoma (“ReACT”)**
 - Rindopepimut in combination with bevacizumab
 - Up to 95 bevacizumab naïve and refractory pts in 1st or 2nd relapse
 - Expected to initiate by year-end 2011
- **Pediatric pontine glioma pilot study**
 - Open; led by Paul Fisher and Albert Wong, Stanford Univ.

