Combination Immunotherapies Designed to Target the Tumor Microenvironment

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A special thanks to all of the patients and families who participated in these studies

Sunrise, Mt. Kilimanjaro Tanzania

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Acknowledgments

- Joy Levi
- James Leatherman
- Xiaobu Ye, MD MS
- Steve Piantadosi, MD PhD
- Silvia Petrik, RN
- Richa Gupta
- Katrina Purtell, RN
- Tianna Dauses, RN
- Maureen Berg, RN
- Maithili Daphtary, PhD
- Marina Laiko, MD
- Irwin Freed
- John Ullman
- Elizabeth Manning, PhD
- Justin Asquith
- Melek Sunay
- Lanquing Huang, PhD
- Nora Disis MD
- Elizabeth Jaffee MD

CLIMB FOR HOPE

STEPPING UP TO BEAT BREAST CANCER

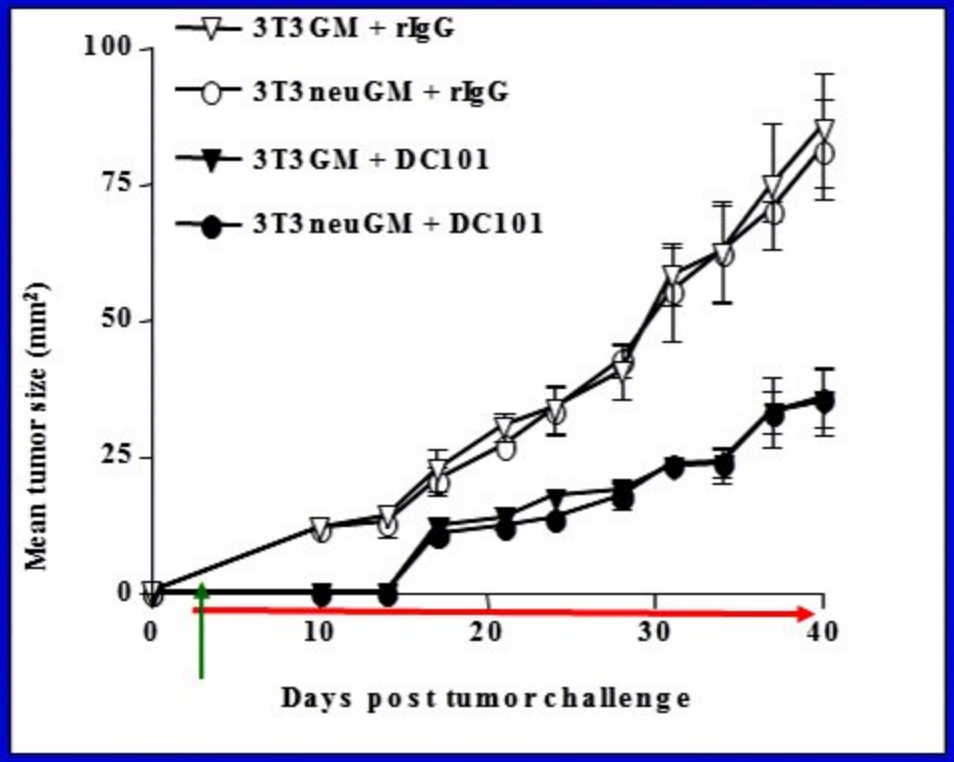
Sunrise, Mt. Cotopaxi Ecuador

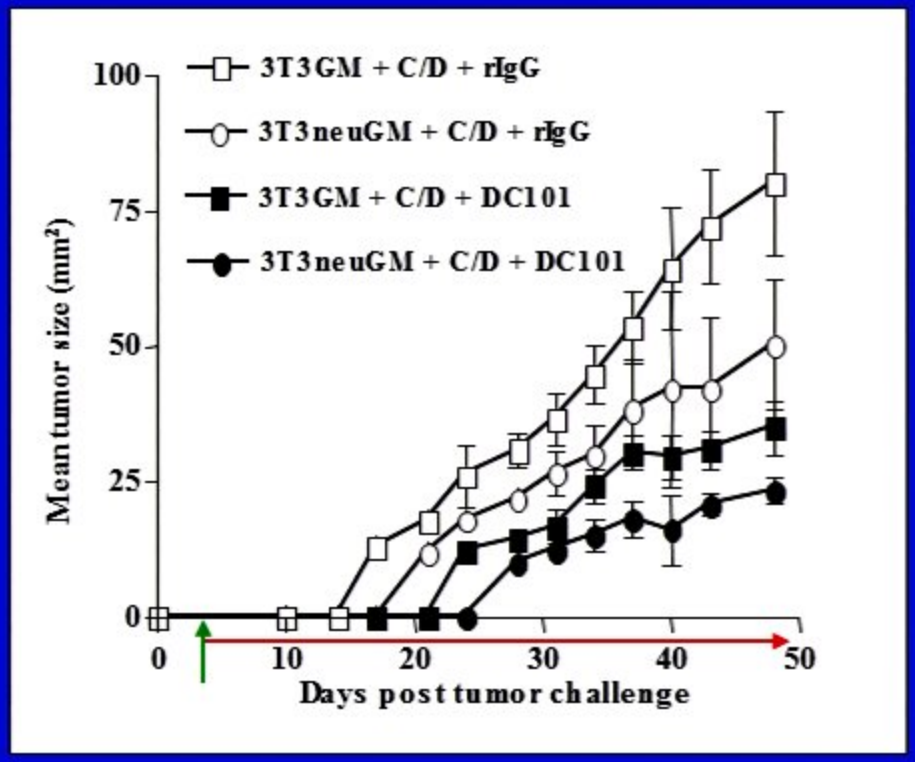
Conclusions

- Cancer therapeutics can have immune effects even in the absence of active vaccination
- Abrogating the influence of tolerance can release the immune-activating potential of vaccines and distinctly targeted cancer therapeutics
    - Targeted immunotherapy: checkpoint modulators, TLR modulators
- Strongly argues for the scientifically-based integration of tumor vaccines/immunotherapies into standard therapies for early and late stage cancer to maximally harness the therapeutic host immune response

"Hope is not a strategy—you have to follow the science"

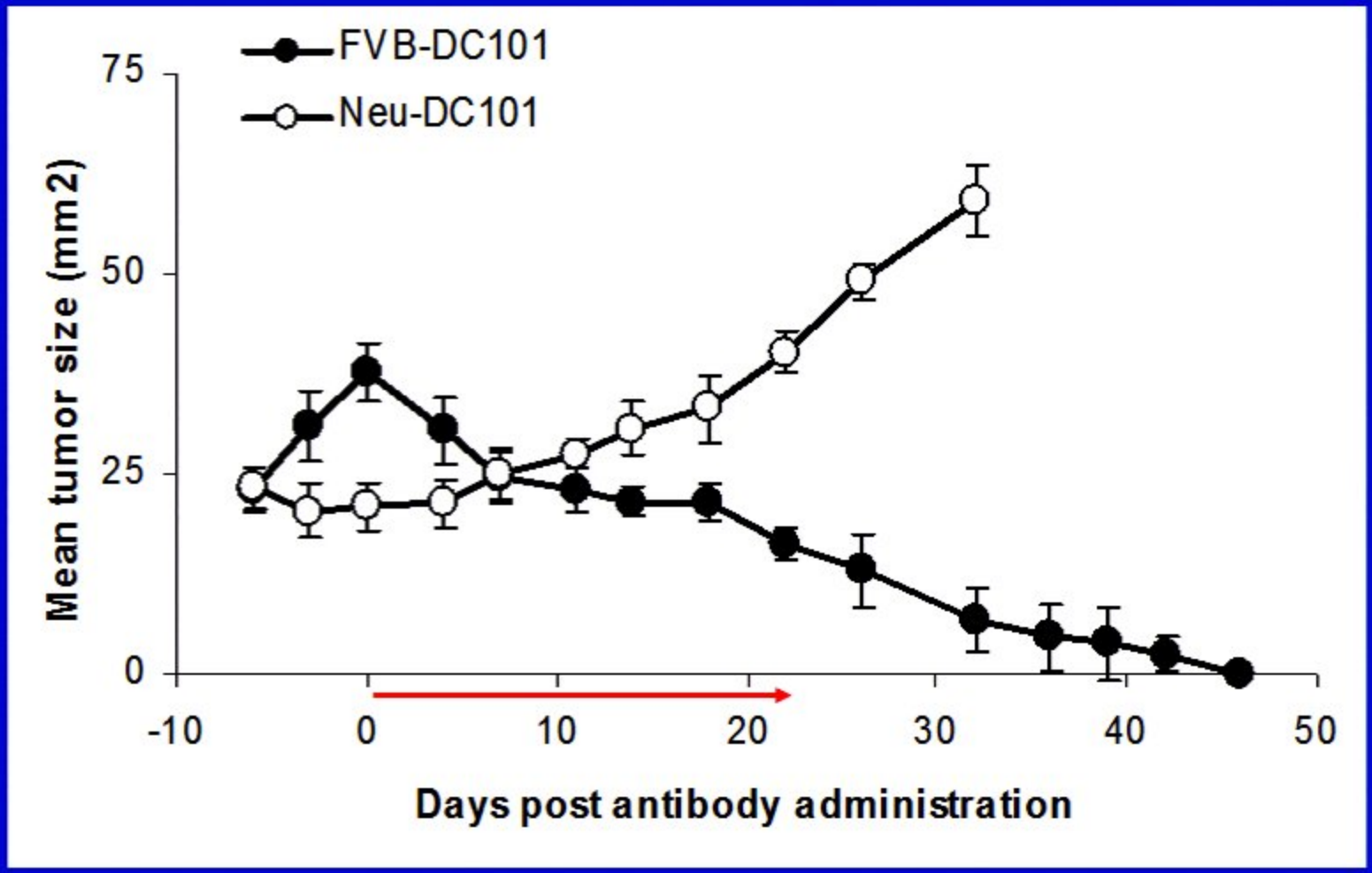
Immune-Modulating Chemotherapy Unmasks Synergy Between Anti-VEGF-R2 MAb and Vaccine in *Neu* Mice





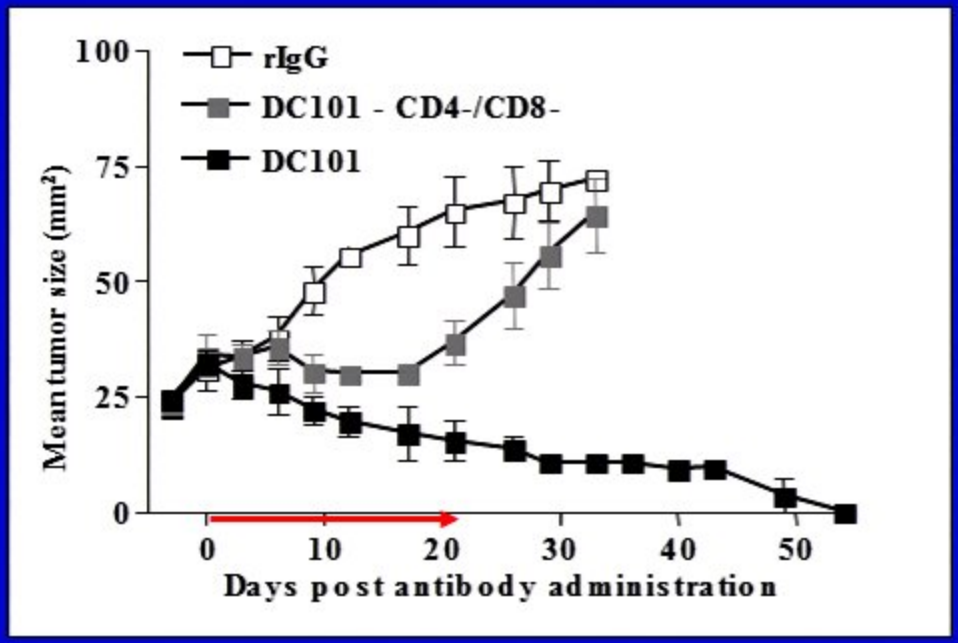
Manning et al, 2007, Clin Cancer Res

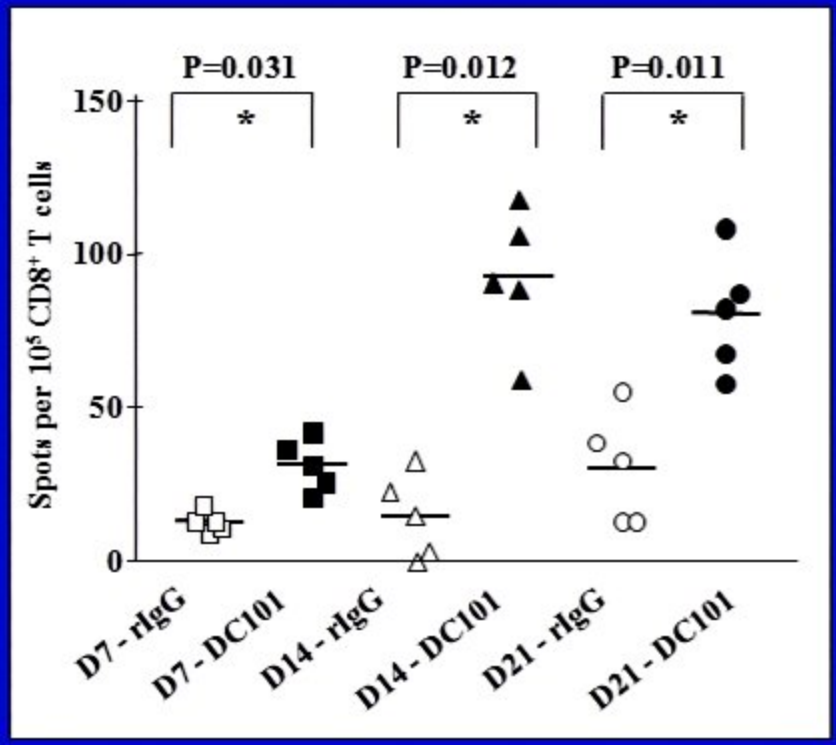
Anti-VEGF-R2 MAb: FVB vs. *Neu* Mice



Manning et al, 2007, Clin Cancer Res

Anti-VEGF-R2 MAb Alone Induces T Cell-Dependent Tumor Immunity





Manning et al, 2007, Clin Cancer Res

Tumor Immunity and Monoclonal Antibodies Targeting the Tumor Microenvironment: VEGFR2

Conclusions

- Vaccination sequenced with CY in the setting of standard Trastuzumab therapy is:
  - Safe
  - Well-tolerated
  - Can induce new or augmented HER-2-specific DTH in HER-2^{+} metastatic breast cancer patients
- The CBR at 6 months was 50%

Emens et al, 2011, Proc Am Soc Clin Oncol, abstr 2535

Clinical Outcomes

Clinical Outcome	*Trastuzumab + CY-modulated vaccination	Trastuzumab alone 1st line (Vogel 2002)	Trastuzumab alone 2nd/3rd line (Cobleigh 1999)
CBR at 6 months	50%	48%	56%
Median survival	39.9 months	24.4 months	13 months

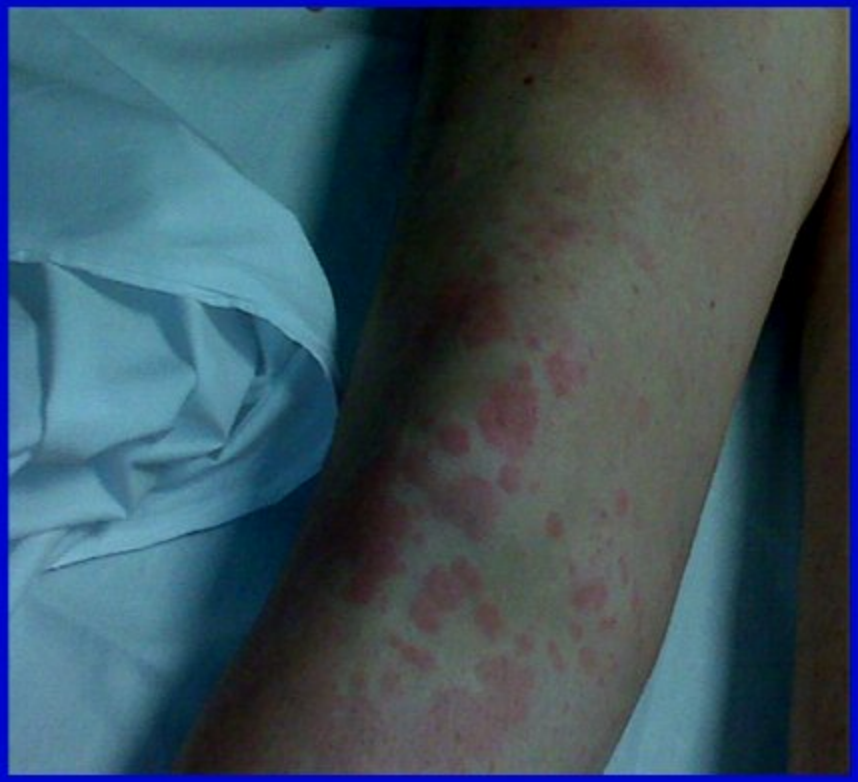
***CBR at 1 year was 35%**

***HER-2-specific DTH developed in 7 out of 20 subjects (35%)**

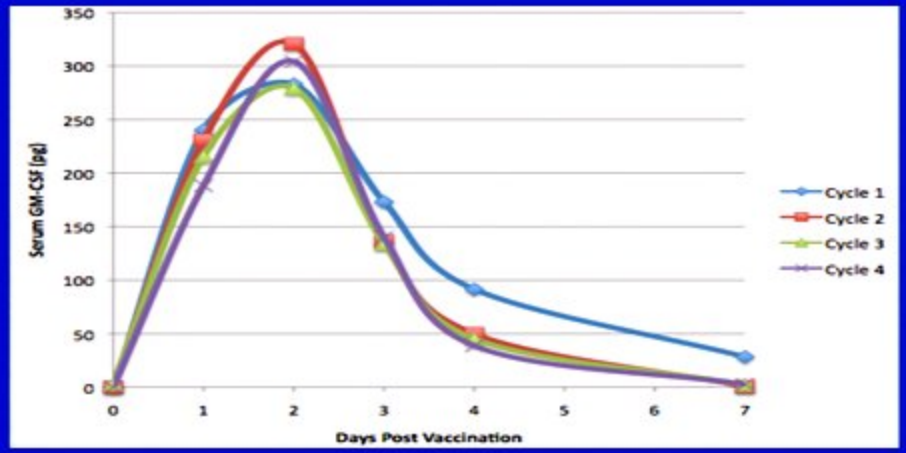
Emens et al, 2011, Proc Am Soc Clin Oncol, abstr 2535

Systemic Effects of Trastuzumab-Modulated Vaccination

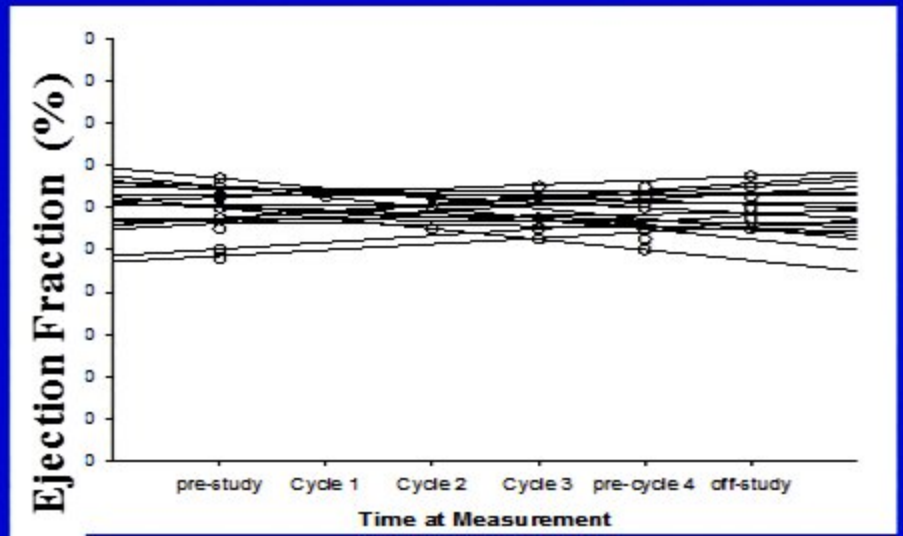
Urticaria



GM-CSF Pharmacokinetics

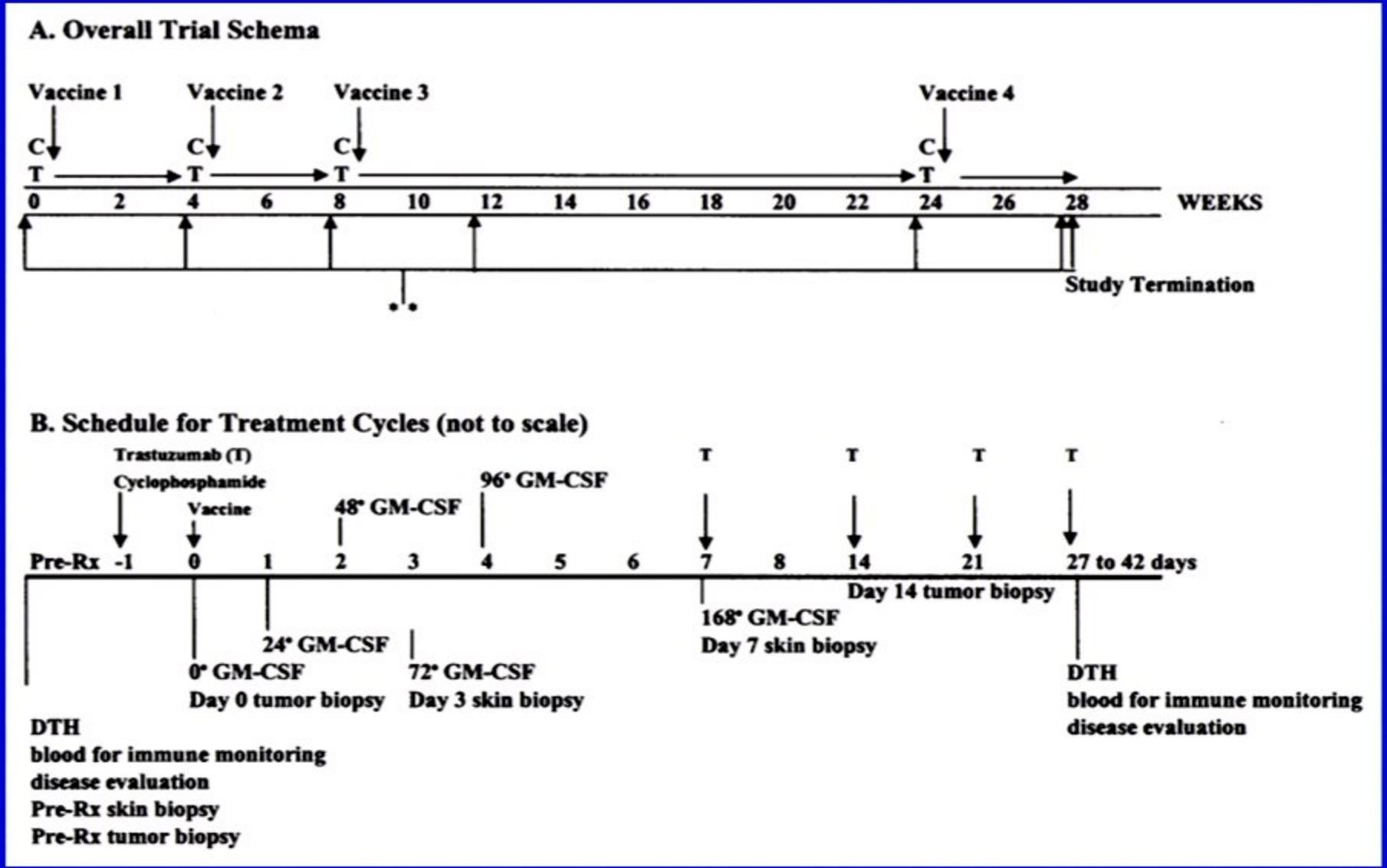


No Cardiac Toxicity



Emens et al, 2011, Proc Am Soc Clin Oncol, abstr 2535

Treatment Schema



Emens et al, 2011, Proc Am Soc Clin Oncol, abstr 2535

Therapeutic HER-2 MAb Augments Fc-Dependent Immune Priming

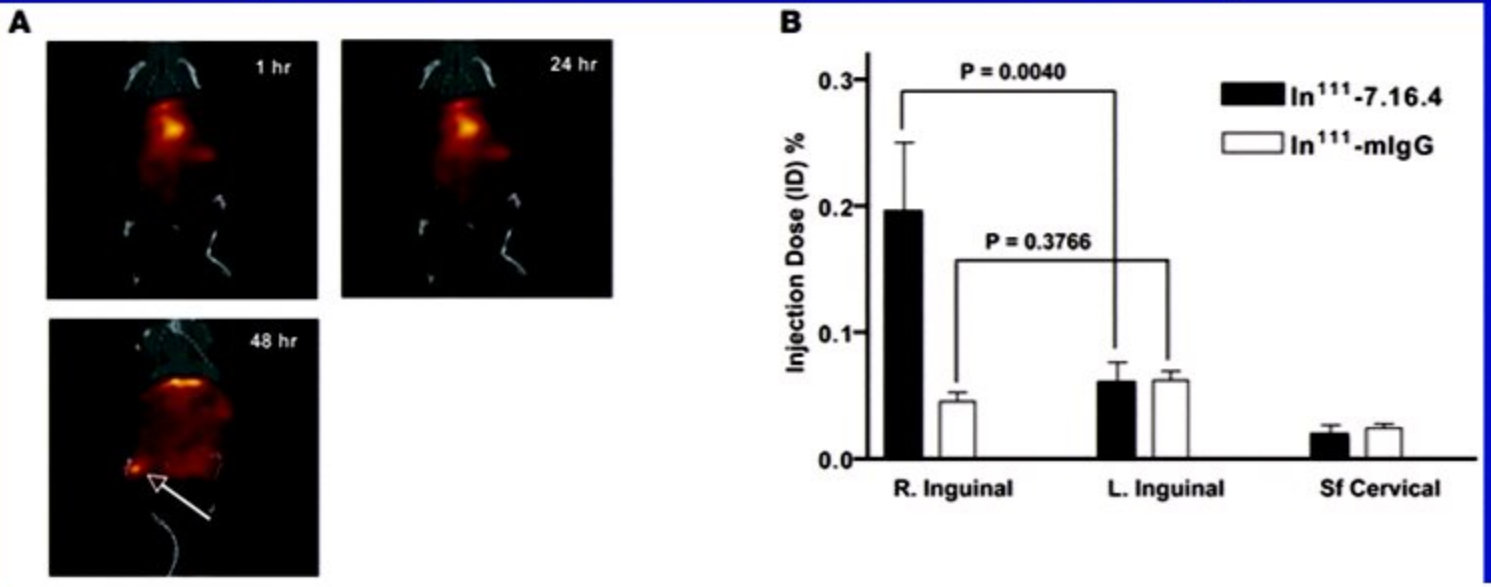


Table 1

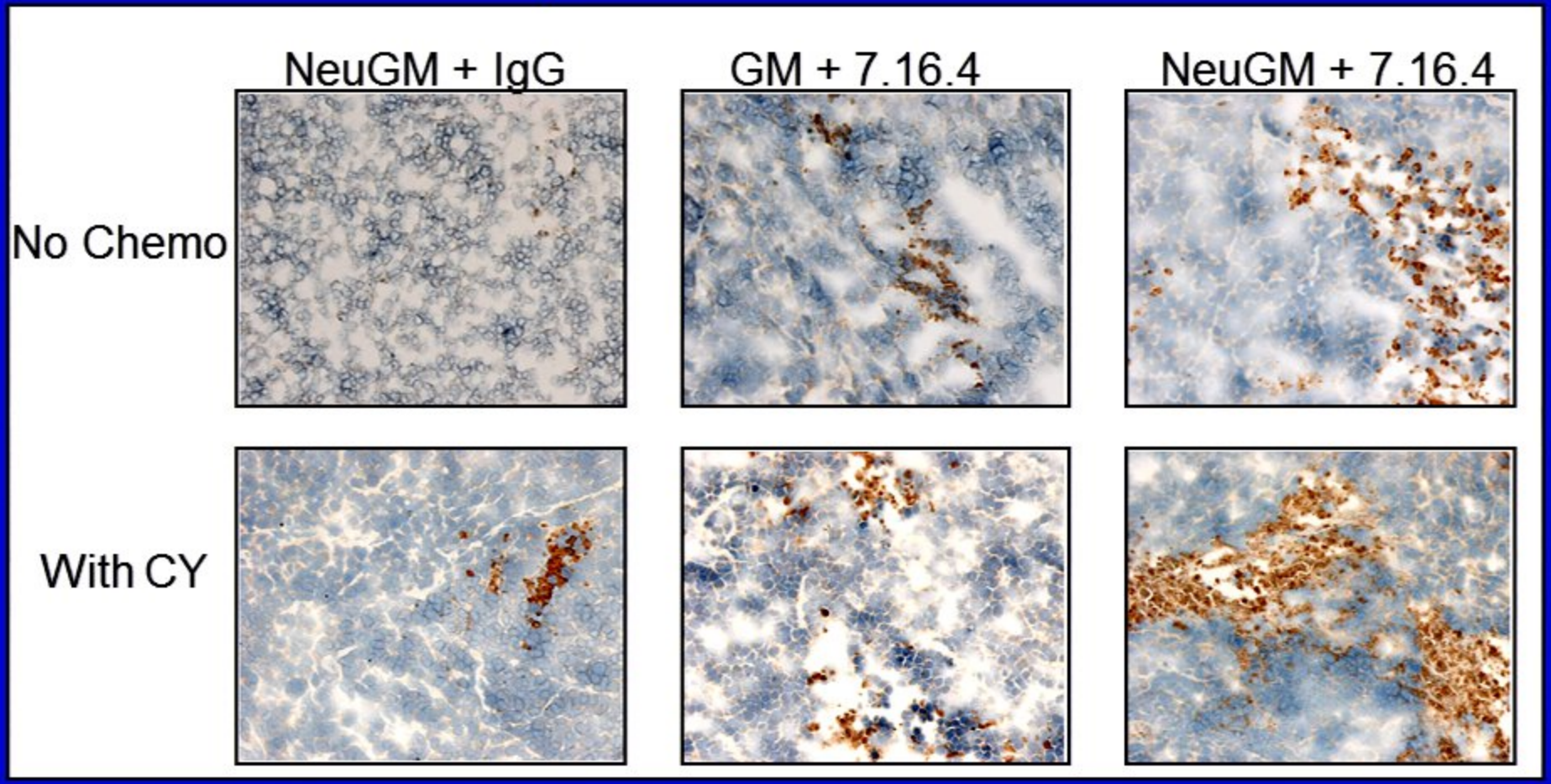
Percentage PKH67⁺CD11c⁺ DCs on days 1–5 after in vivo administration of vaccine + mAb

	% PKH67⁺CD11c⁺ DCs in VDLNs				
Treatment	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
3T3 neu/GM + intact 7.16.4 mAb	4.78 ± 0.52	3.02 ± 0.80	2.02 ± 0.40	5.08 ± 0.60	5.36 ± 0.76
3T3 neu/GM + 7.16.4 F(ab′)$_2$	2.13 ± 0.3[A]	1.98 ± 0.23	2.00 ± 0.28	2.61 ± 0.38[A]	3.06 ± 0.44[A]
3T3 neu/GM + mIgG	2.43 ± 0.57[A]	2.15 ± 0.38	1.9 ± 0.36	2.90 ± 0.54[A]	3.32 ± 0.23[A]
3T3/GM + mIgG	1.53 ± 0.43[A]	1.66 ± 0.26[A]	2.25 ± 0.22	2.54 ± 0.36[A]	2.88 ± 0.62[A]
Naive	0.59 ± 0.12[A]	0.51 ± 0.14[A]	0.69 ± 0.06[A]	0.55 ± 0.18[A]	0.54 ± 0.16[A]

Data represent mean ± SD of at least triplicate samples. [A]$P < 0.05$ versus 3T3 neu/GM + intact 7.16.4 mAb, Mann-Whitney *U* test.

Kim et al, 2008, J Clin Invest

Chemotherapy-Modulated Vaccination Induces Maximal Tumor Apoptosis When Combined with Therapeutic HER-2 MAb

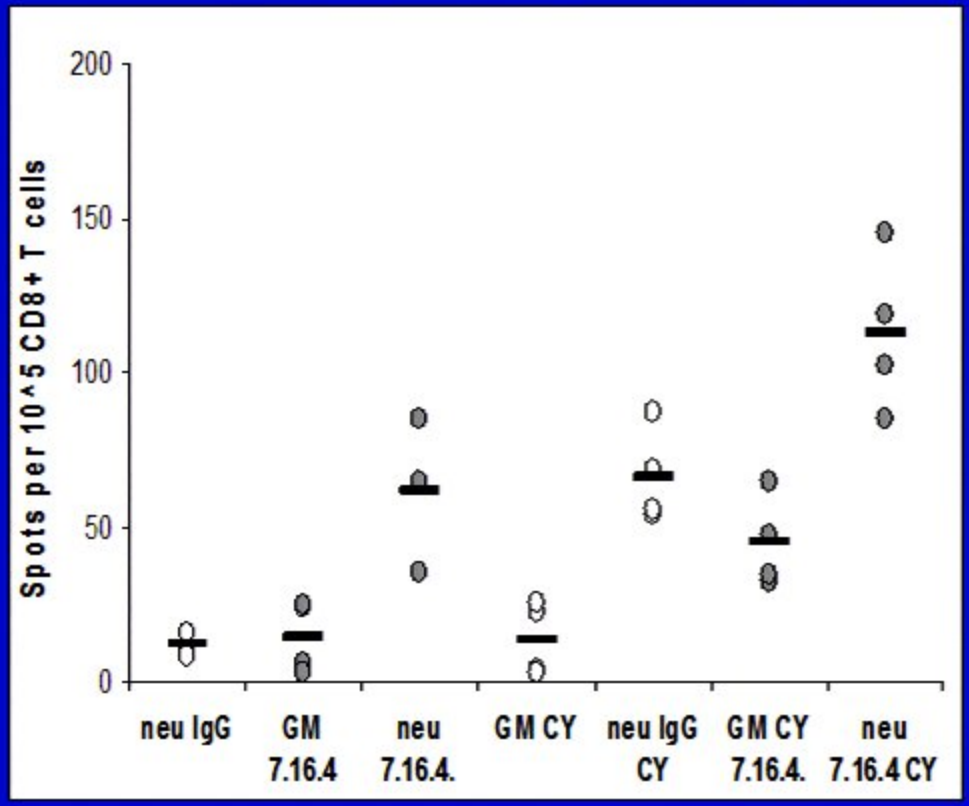


Tumors were harvested and snap frozen. 5 um sections were cut onto slides and immunohistochemistry was performed using antibodies specific for cleaved caspase 3.

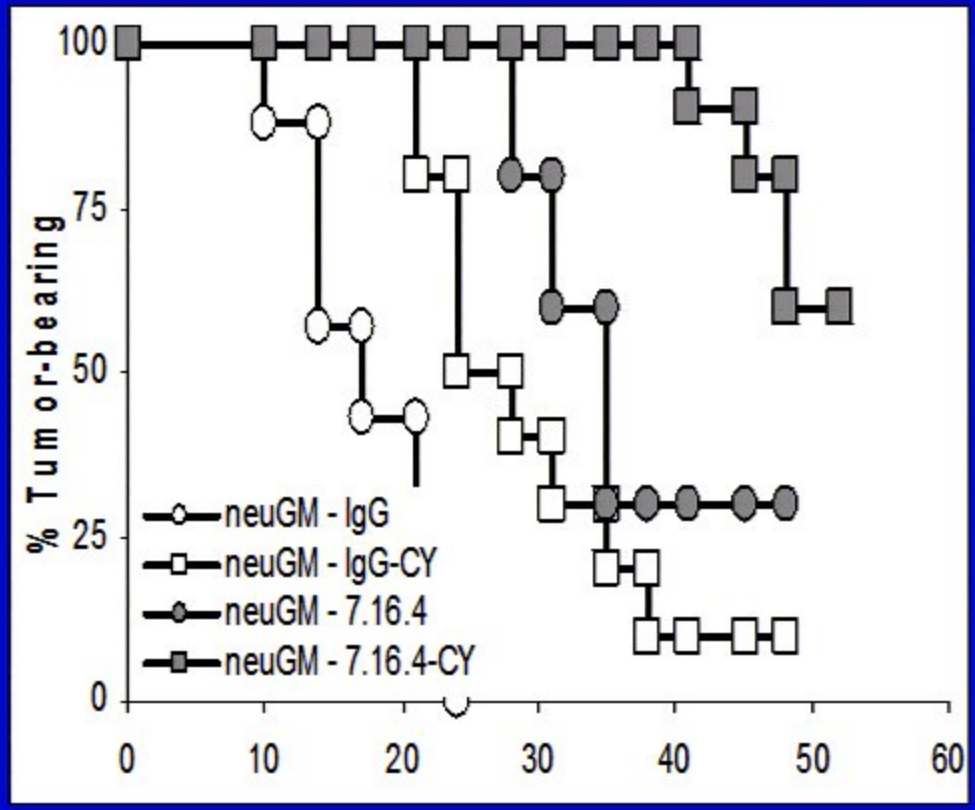
Emens, unpublished data

Therapeutic HER-2 MAb Augments Vaccine-Induced HER-2-specific CD8$^+$ T Cells and Tumor-Free Survival

CD8$^+$ T Cells



Tumor-Free Survival



Emens, unpublished data

Rationale for Combining Active Vaccination with Trastuzumab Therapy

- Minimal antibody responses in vaccinated *neu* mice
- Cell cycle arrest (PI3K/Akt pathways)
- Inhibits pro-growth signals/angiogenesis (VEGF)
- Promotes apoptosis
- Trastuzumab+chemotherapy induces T cells
- Inhibits DNA damage repair
- Promotes ADCC
- Augments $CD8^+$ CTL activity/antigen processing
- Enhances immune priming, immune memory

Mohsin et al, 2005, J Clin Oncol; Taylor et al, 2007, Clin Cancer Res
zum Buschenfelde et al, 2002, Cancer Res; Wolpoe et al, 2003, J Immunol; Kono et al, 2004, Clin Cancer Res; Kim et al, 2008, J Clin Invest

HER-2-specific Monoclonal Antibodies and Vaccination

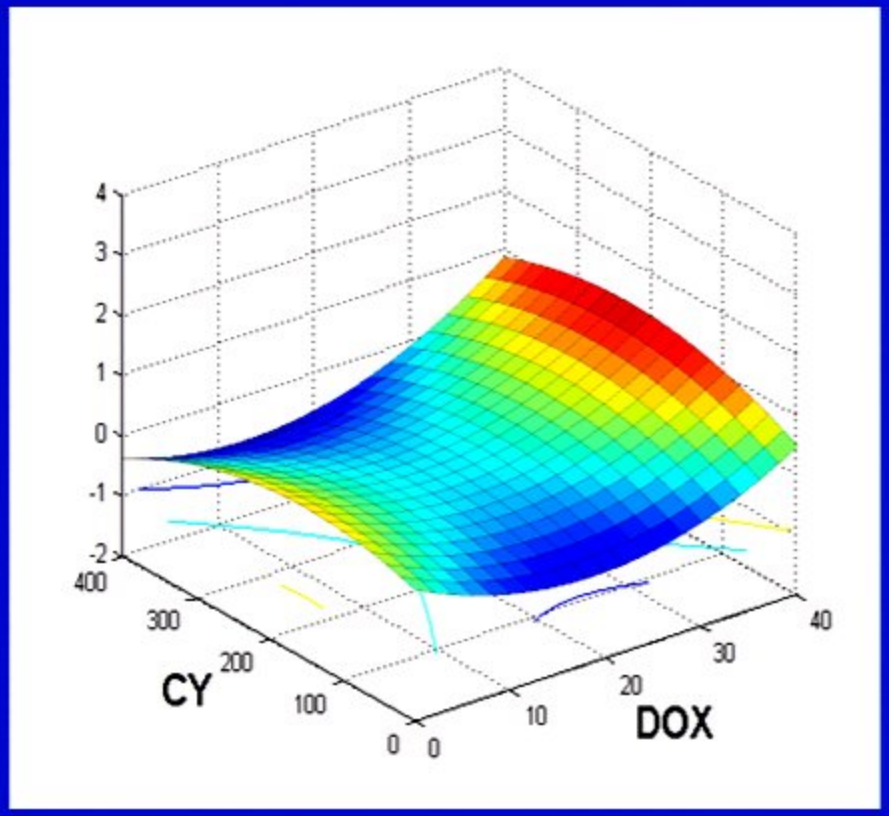
Conclusions

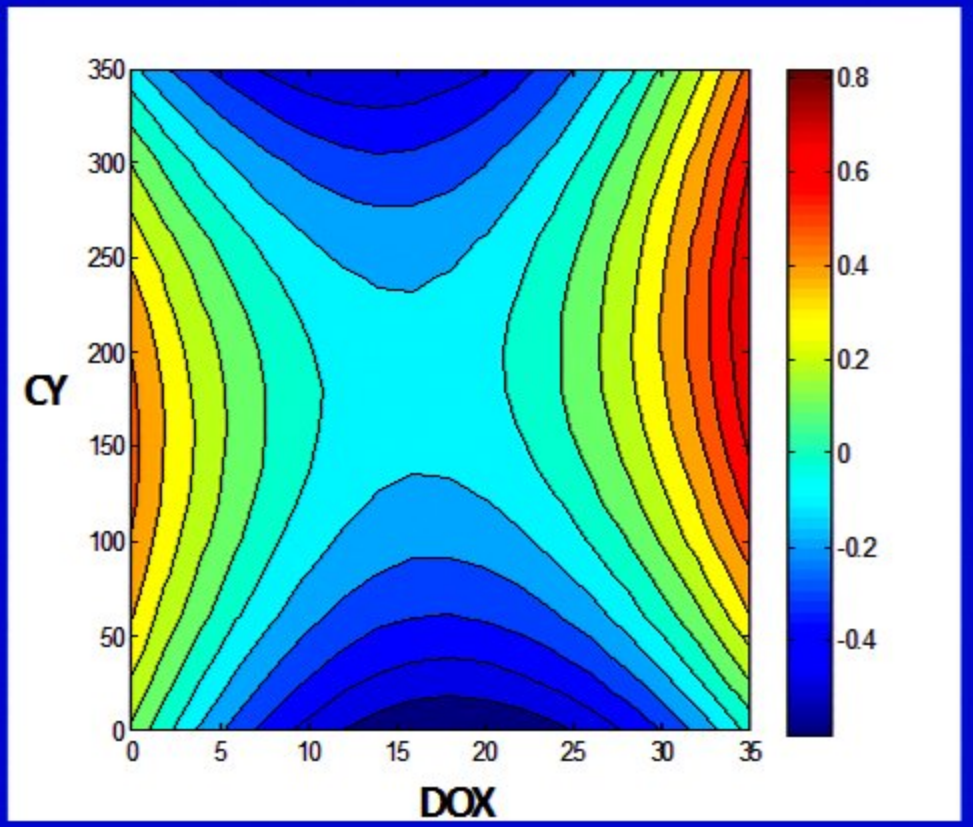
- CY 200 mg/m^2 augments HER-2-specific humoral immunity
- Doses of CY >200 mg/m^2 suppress both DTH and antibody responses
- The optimal chemotherapy dose combination:

  CY 200 mg/m^2 with DOX 35 mg/m^2

Three-Dimensional and Contour Plots of the Predicted Responses Surfaces Using a Second Order Polynomial Regression Model

$$y_u = \beta_0 + \beta_1 x_{1u} + \beta_2 x_{2u} + \beta_{11} x_{1u}^2 + \beta_{22} x_{2u}^2 + \beta_{12} x_{1u} x_{2u} + e_u$$



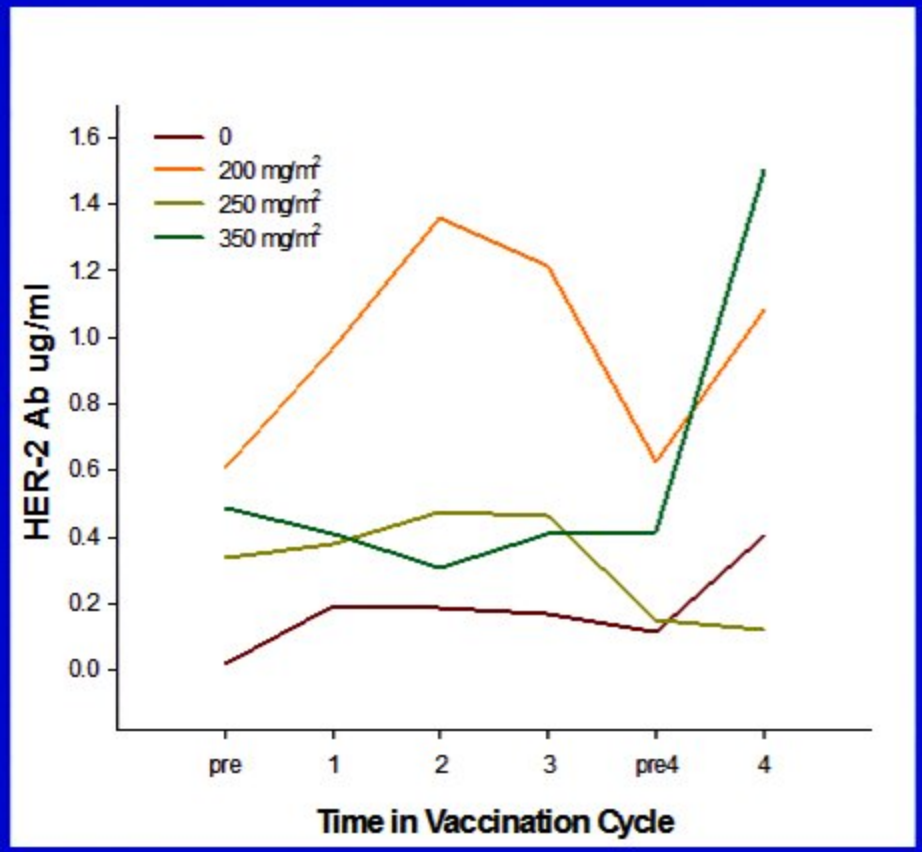


Predicted Max Peak Increase is 0.739 µg/ml, at CY= 193 mg/m², DOX=35 mg/m²

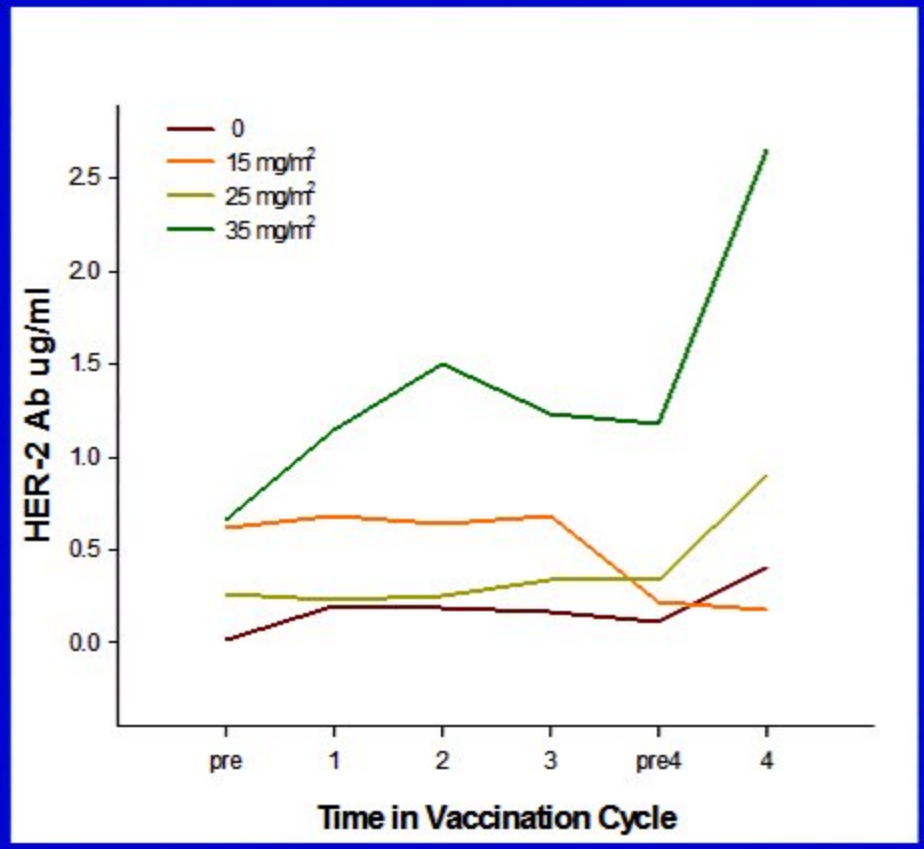
Emens et al, 2009, J Clin Oncol

Impact of Increasing Chemotherapy Dose on Vaccine-Induced Immunity—Serum HER-2 Ab

CY



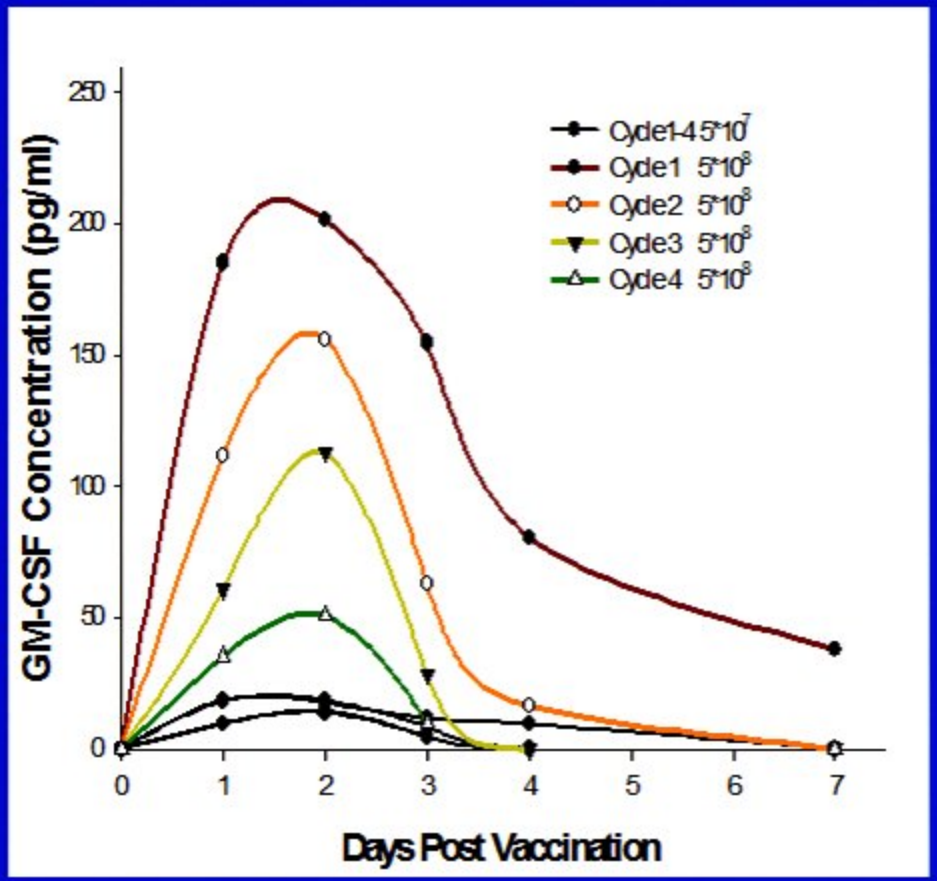
DOX



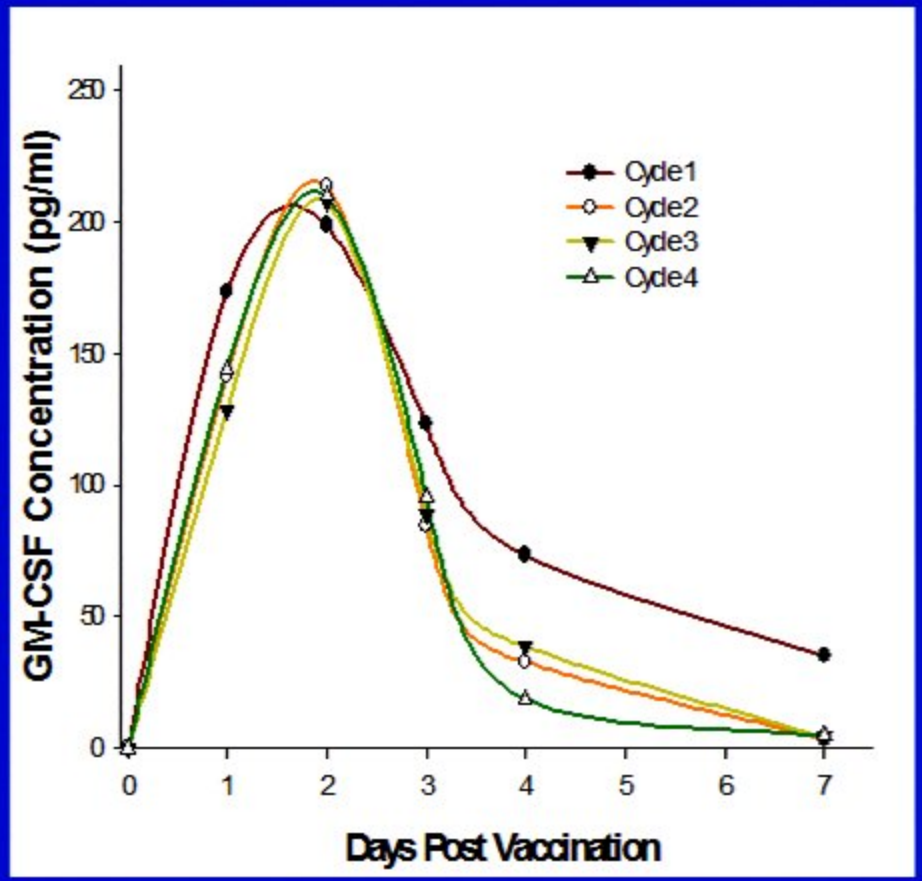
Emens et al, 2009, J Clin Oncol

GM-CSF Pharmacokinetics

Vaccine Alone



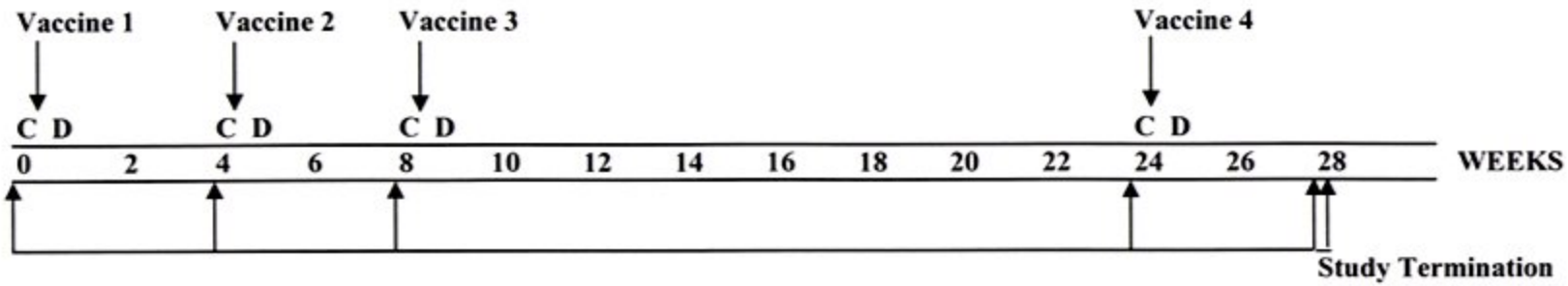
Vaccine + Chemo



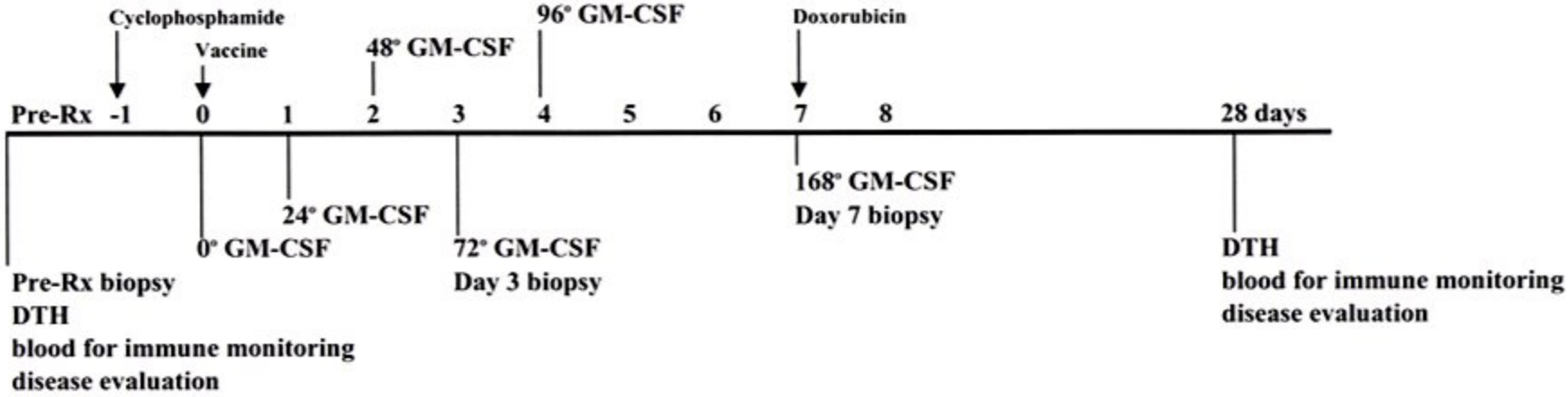
Emens et al, 2009, J Clin Oncol

Treatment Schema

B. Overall Trial Schema

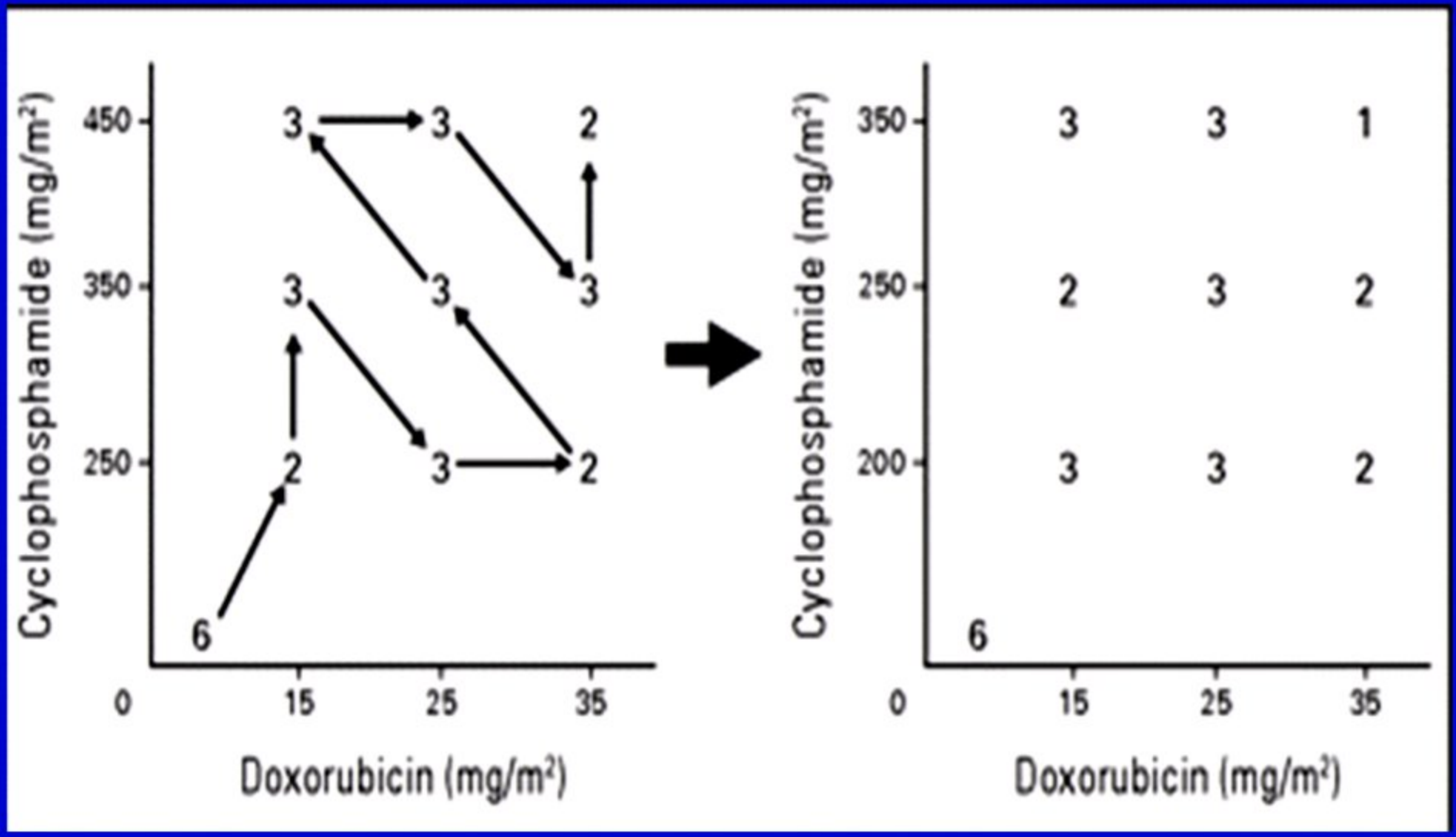


C. Schedule for Treatment Cycles (not to scale)



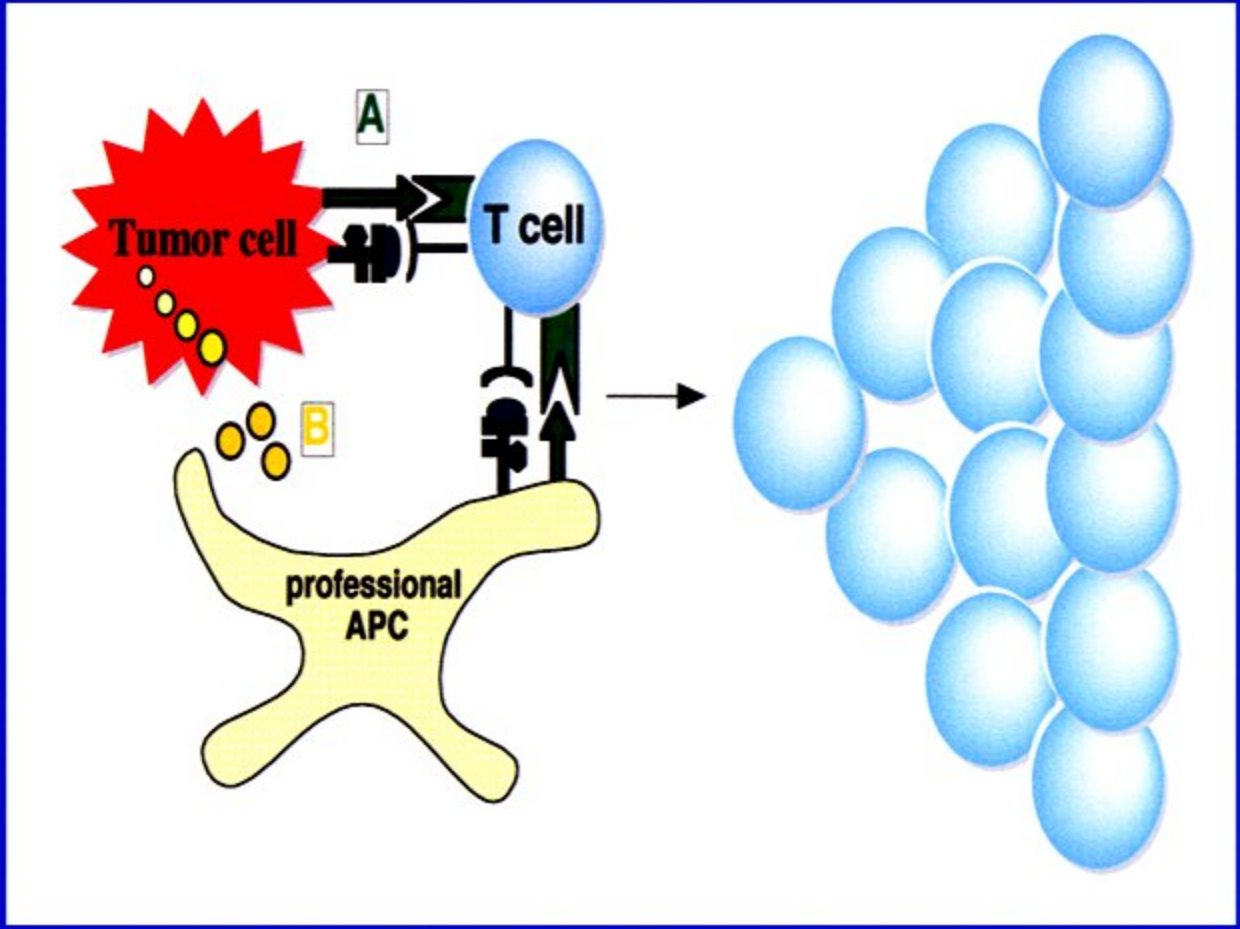
Emens et al, 2009, J Clin Oncol

Study Design Matrix



Emens et al, 2009, J Clin Oncol

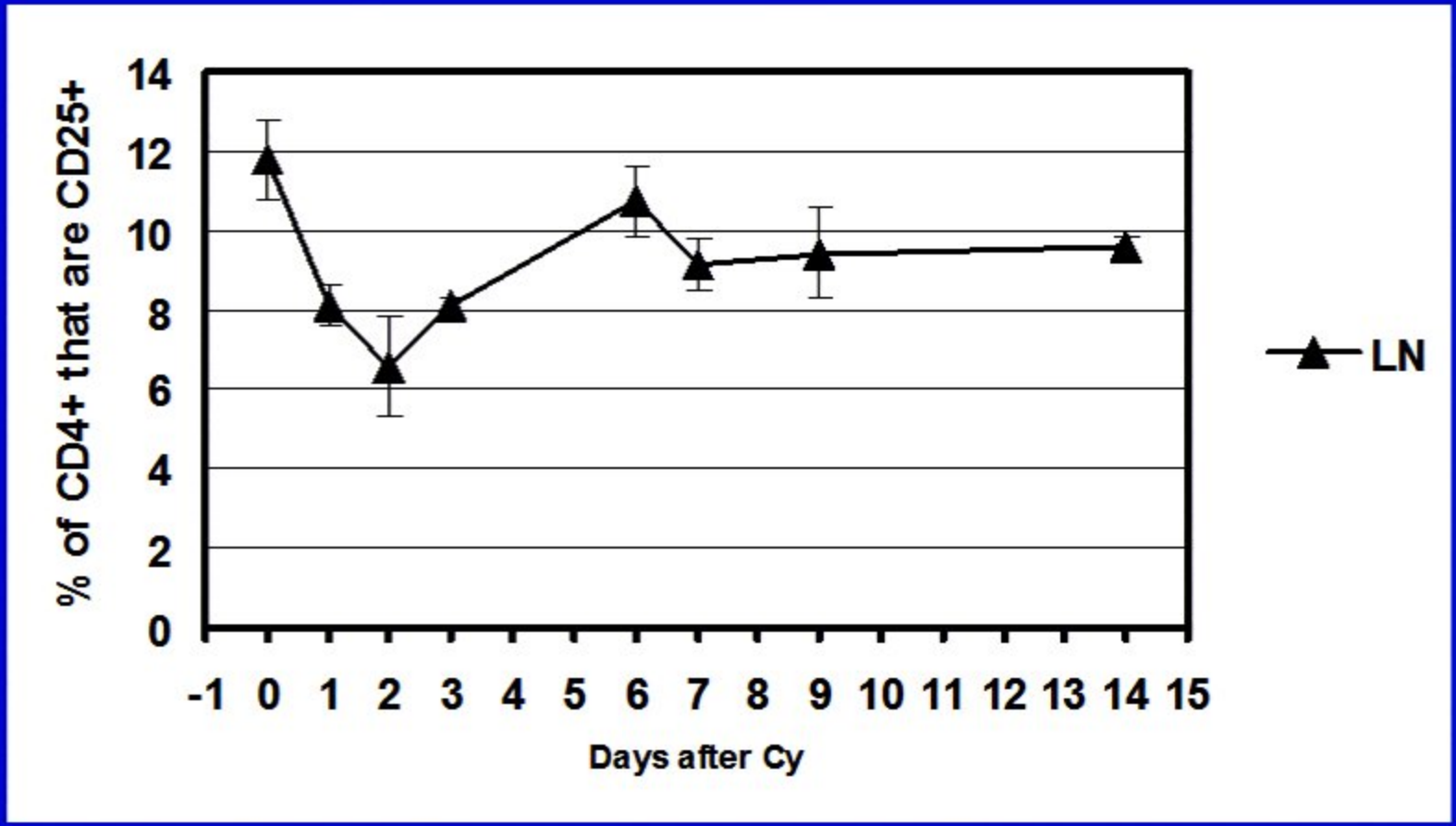
A Human GM-CSF-secreting Breast Cancer Vaccine



- Allogeneic breast tumor cells
  - SKBR3: HER-2+, ER-
  - T47D: HER-2-, ER+
- Generalizable
- Allows unbiased antigen delivery
- Secretes human GM-CSF 324 ng/10^6 cells/24 hrs

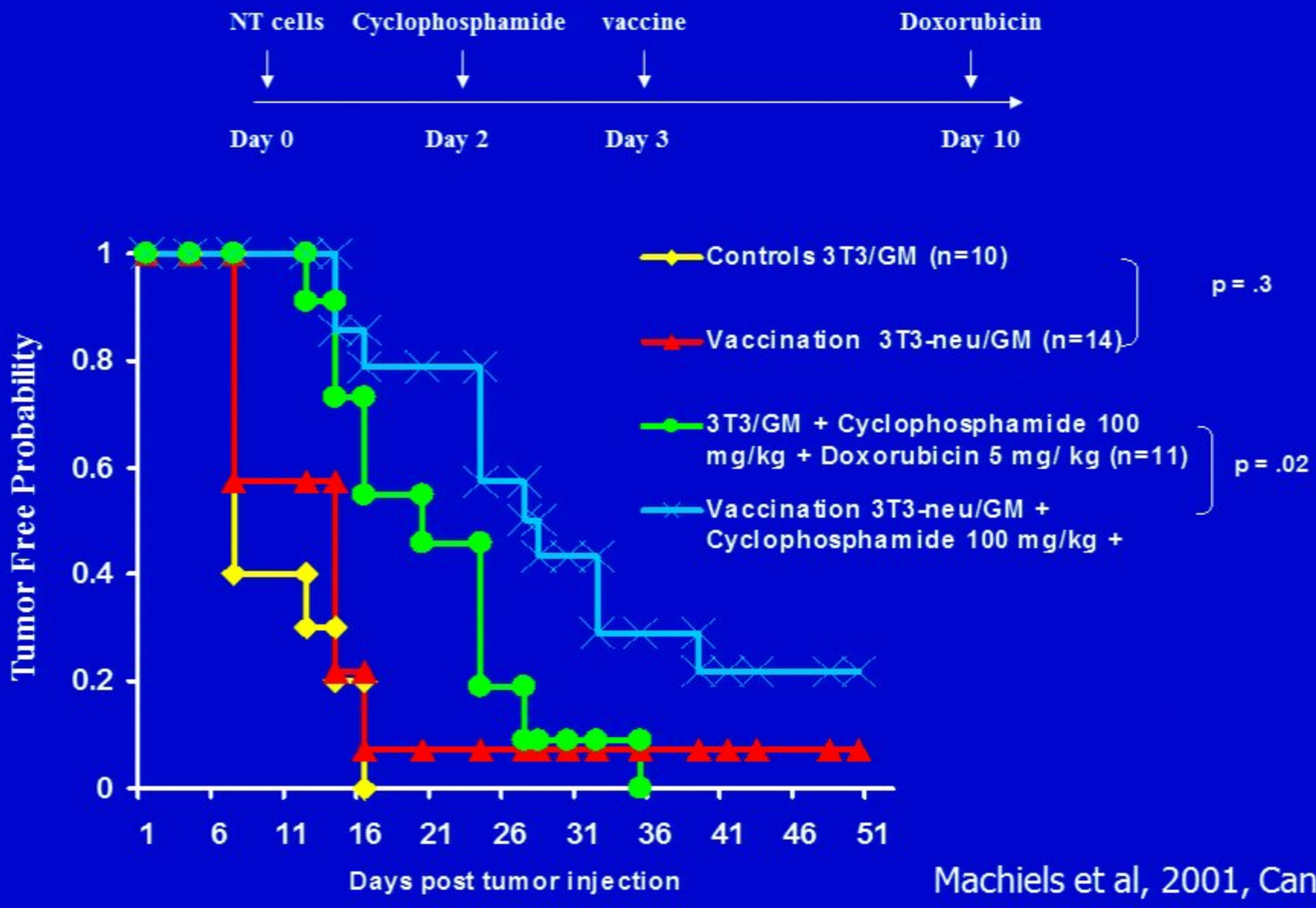
Davis-Sproul et al, 2003, Cytotherapy

Cyclophosphamide Treatment Temporarily Suppresses Peripheral Regulatory T Cell Numbers



Ercolini et al, 2005, J Exp Med

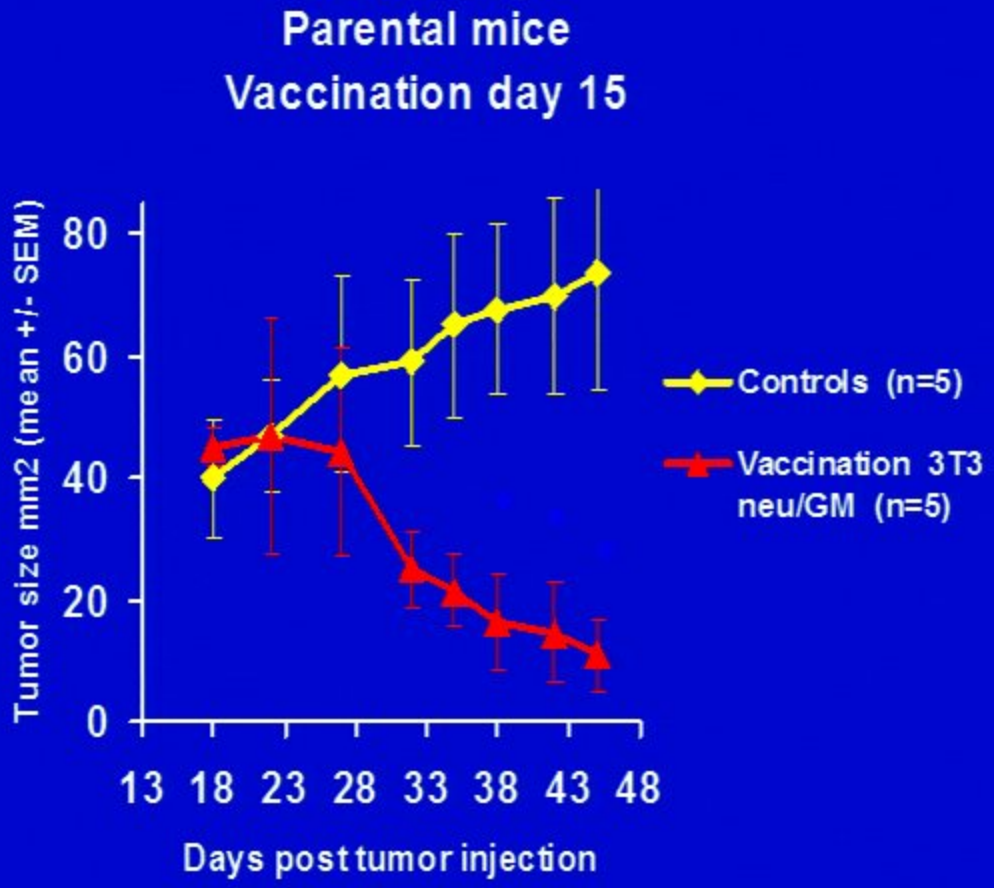
Polychemotherapy Maximizes HER-2/*neu*-Targeted Vaccination in *Neu* Mice

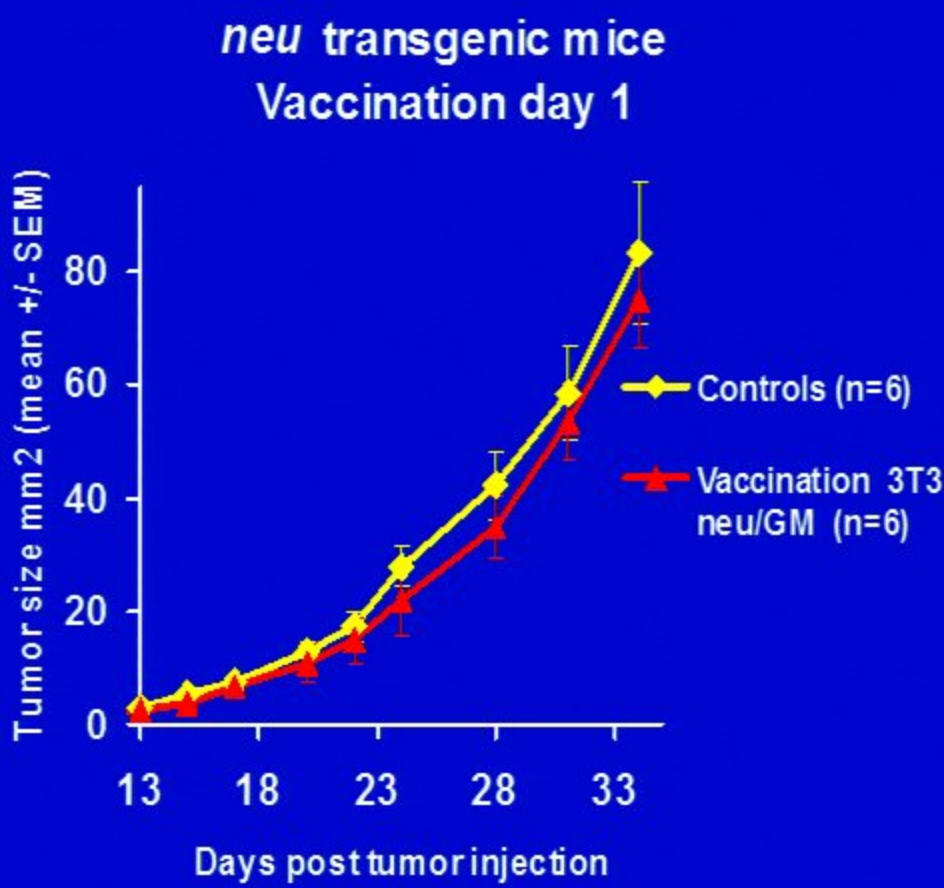


Machiels et al, 2001, Cancer Res

Chemotherapy and Vaccination

Immune Tolerance to HER-2/*neu* in *Neu* Transgenic Mice





* $p < .05$

Machiels et al, 2001, Cancer Res

Approaches

- Integrate with established breast cancer therapeutics
  - Chemotherapy
  - Ttumor-specific monoclonal antibodies (HER-2)
- Target distinct components of the tumor microenvironment
  - VEGFR2
  - Multi-kinase inhibitors

Conflict of Interest Statement

Biosante: Under a licensing agreement between Biosante and the Johns Hopkins University, the University is entitled to milestone payments and royalty on sales of the vaccine product described in the presentation. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Genentech/Roche: Breast Cancer Advisory Board, Research Funding

Bristol Myers Squibb: PD-1/PD-L1 Breast Advisory Board