STATE OF THE ART 4: Combination Immune Therapy-Chemotherapy

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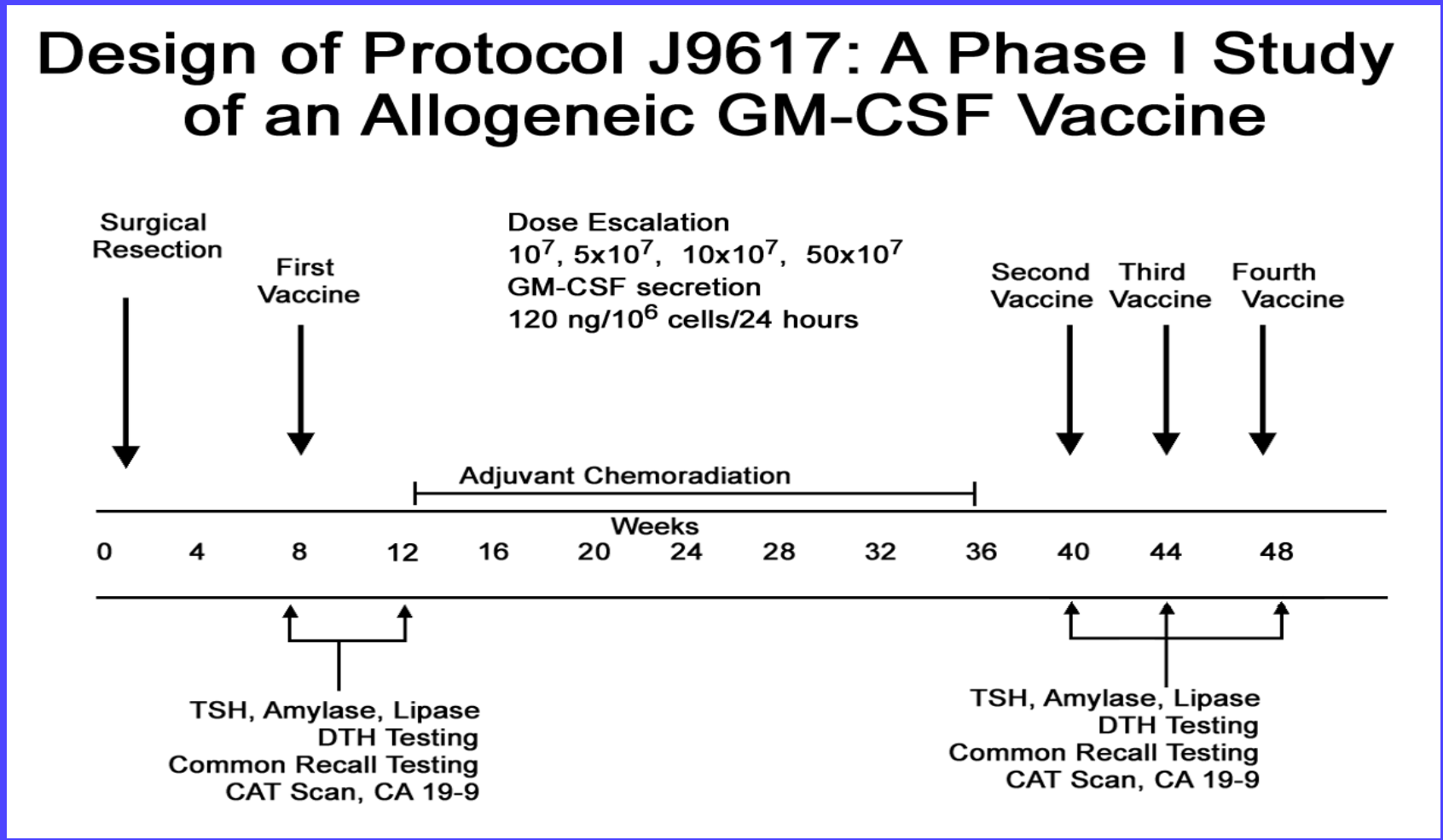
Topics for Consideration

- What are the rules for integrating chemotherapy with immune therapy?
- What mechanisms should be targeted when using chemotherapy to modulate host:immune interactions?
- What is the science driving the integration of chemotherapy with immune based therapies?

Can traditional chemotherapy be integrated with immune-based therapy?

- Should pre-clinical models be used to evaluate this question?
- Published data suggests that the timing and dosing of each agent is critical to uncovering potential synergies.
- Traditional chemotherapies have immune potentiating mechanisms of action when delivered in the proper sequence and with the right dosing

Example of integrating chemoradiation with a pancreatic tumor vaccine

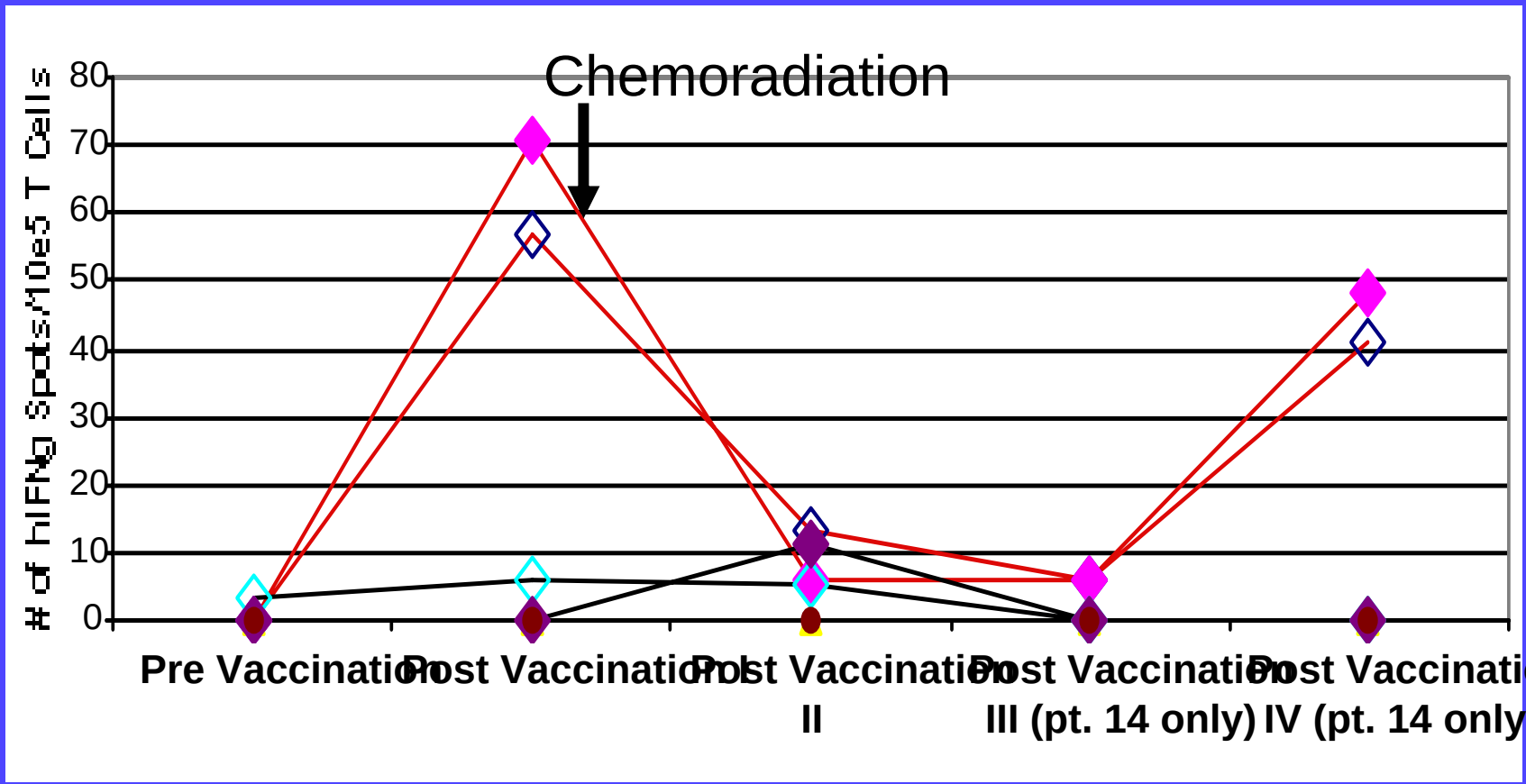


Jaffee et al. JCO, 2001.

Results

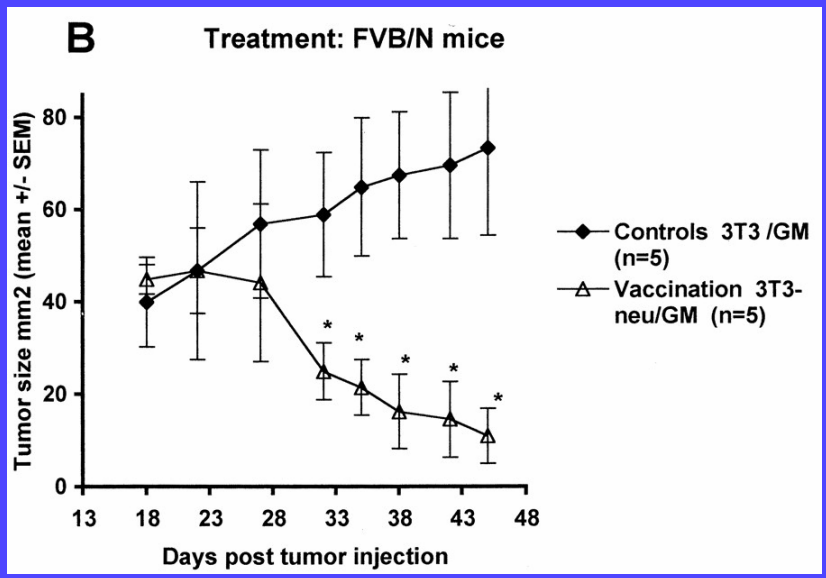
- 8 patients treated on highest 2 dose levels
- 3/8 patients with induction of mesothelin CD8+ T cell responses 4 weeks after 1st vaccine
- These 3 patients (stage IIb/III pancreatic cancer) remain disease free >8 years

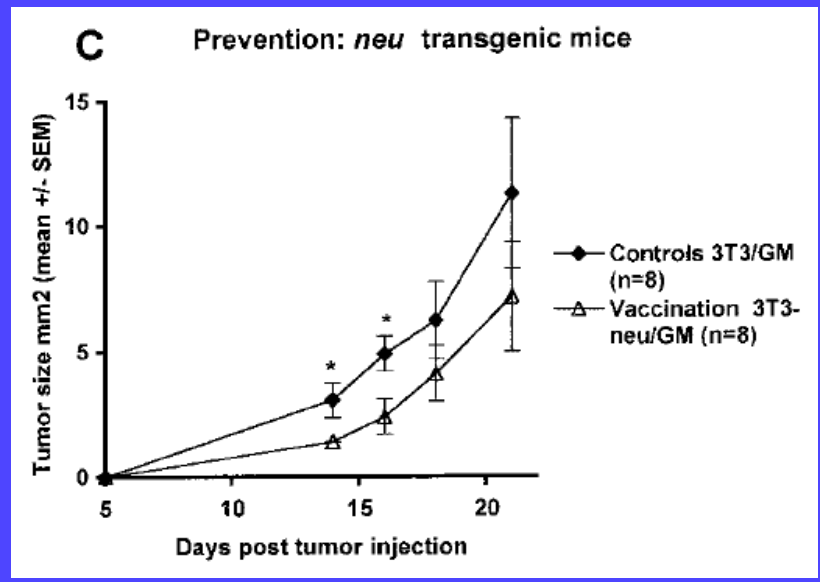
Mesothelin T cell responses declined during chemoradiation and recurred following 3 additional vaccinations



Her-2/*neu* Transgenic Mouse Model Provides Insight into Combinations

- **HER-2/*neu* as a therapeutic target:**
  - 185 kDa transmembrane tyrosine kinase (EGFR superfamily)
  - Natural tumor antigen, overexpressed in ~30% of breast cancers
- ***neu* transgenic mice are a clinically relevant model:**
  - Derived from FVB/N mice (H-2^q), *neu* transgenic mice express rat *neu* cDNA under MMTV promoter
  - Spontaneously develop mammary carcinomas at 4-6 months of age
  - Results in immune tolerance to Her-2/*neu* not seen in FVB/N mice





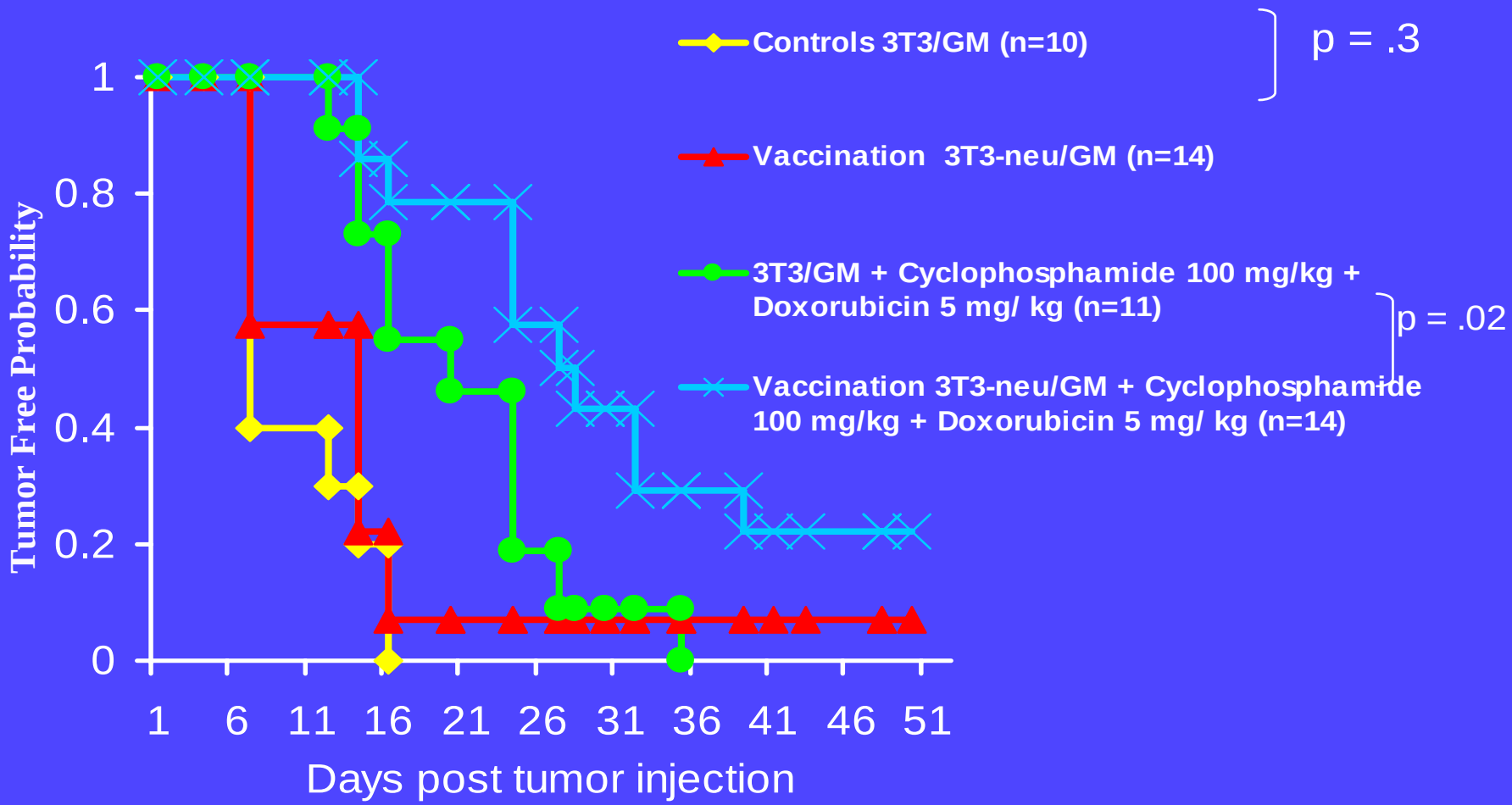
(Machiels, JP, et al, Cancer Research, 2001)

Chemotherapy Dose and Schedule Correlate with Vaccine Efficacy

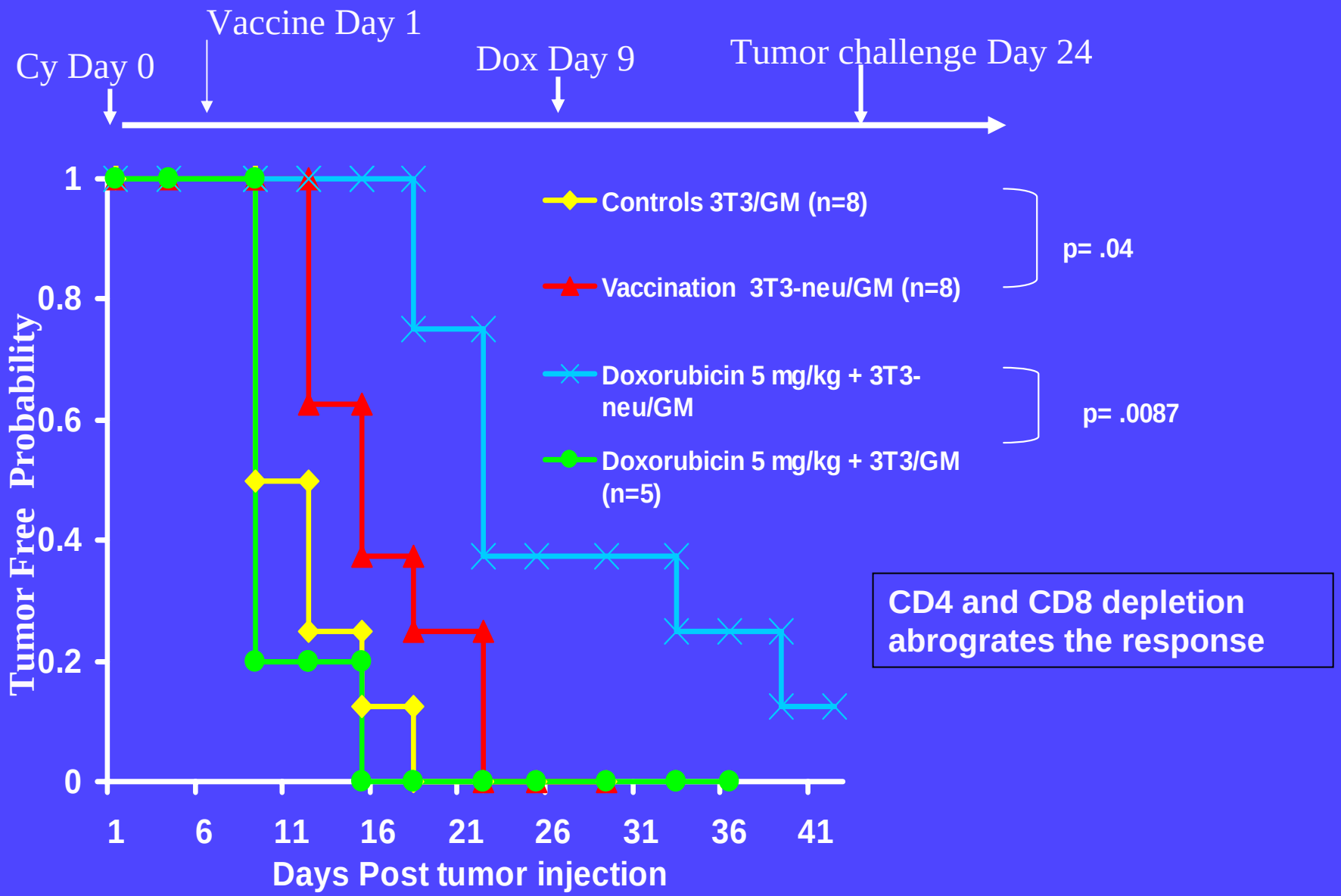
		T cells count (nadir) number/μl (normal range: 4000-9000)	1 day before vaccine	7 days after vaccine
CTX	50 mg/kg	6128	+	-
	100 mg/kg	5120	+	-
	150 mg/kg	1559	+	NT
	200 mg/kg	1100	+/-	NT
	250 mg/kg	989	+/-	NT
PTX	20 mg/kg	4365	+	-
	30 mg/kg	4200	+	NT
	35 mg/kg	3600	+/-	NT
	40 mg/kg	3451	+/-	NT
DOX	4 mg/kg	6265	+/-	+
	8 mg/kg	5586	+/-	+
	15 mg/kg	4180	-	-

Machiels, et al., Cancer Research 2001

CY Plus Dox Given In Proper Sequence Best Enhance The Anti-Tumor Effect Of The Vaccine

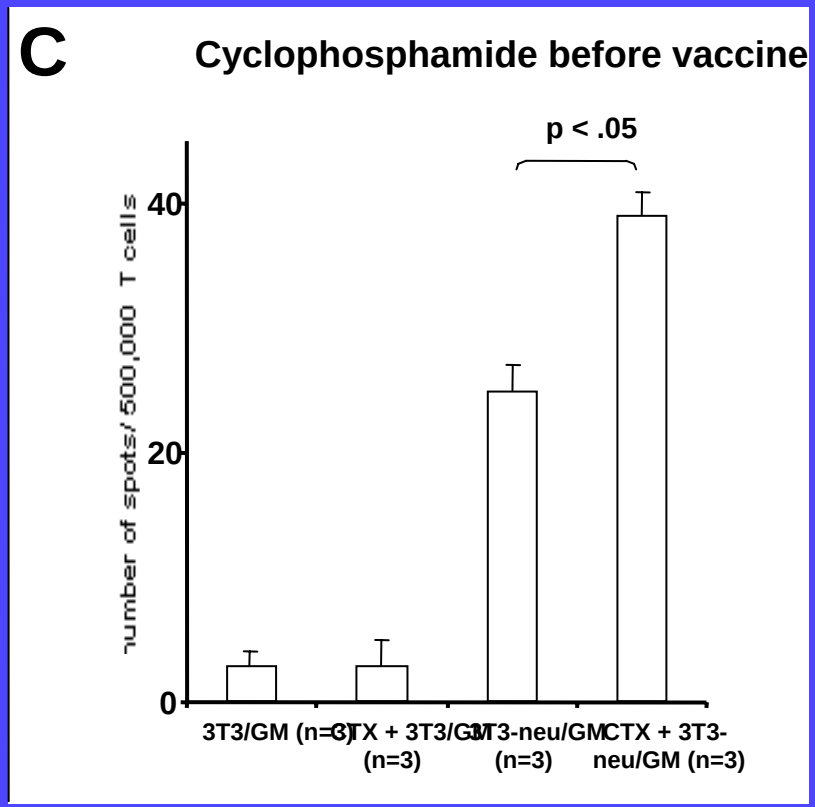


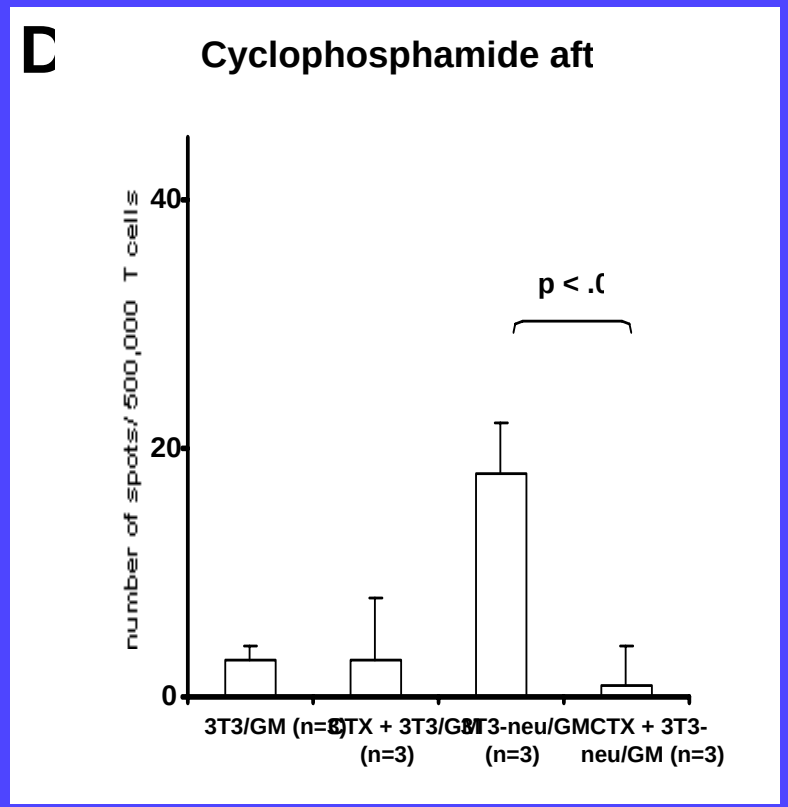
Chemotherapy Enhances The Potency Of The Vaccine Through A Mechanism Distinct From Direct Tumor Lysis



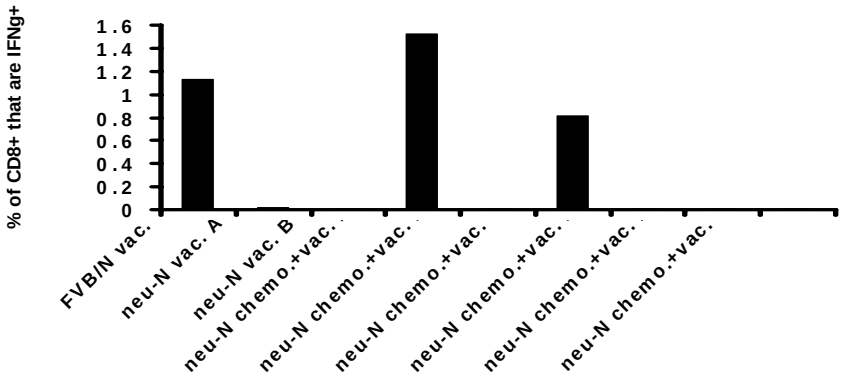
CD4 and CD8 depletion abrogrates the response

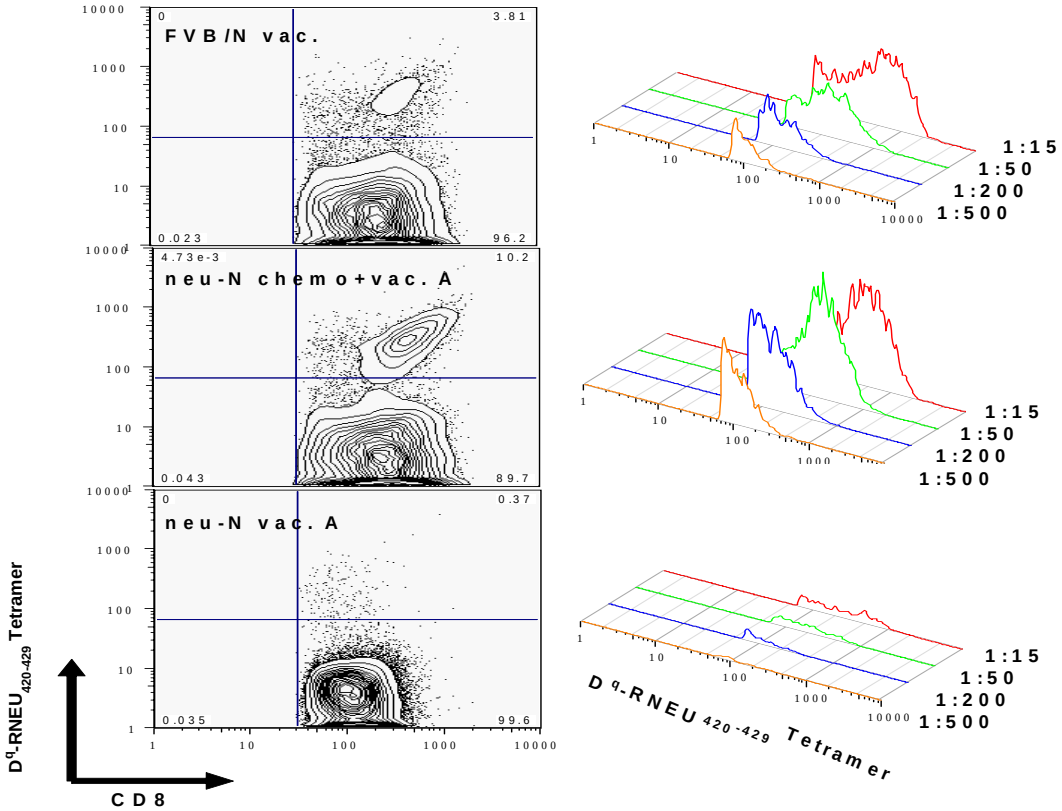
Cy Increases The Number Of Vaccine Induced *neu* T cells In *neu* Mice By ELISPOT





Cyclophosphamide (Cy) = 100 mg/Kg


% of CD8+ that are IFNg+
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
FVB/N vac.
neu-N vac. A
neu-N vac. B
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.
neu-N chemo.+vac.


FVB/N vac.
0
3.81
0.023
96.2
neu-N chemo+vac. A
4.73e-3
10.2
0.043
89.7
neu-N vac. A
0
0.37
0.035
99.6
10000
1000
100
10
1
1
10
100
1000
10000
D q-RNEU 420-429 Tetramer
CD8
1:15
1:50
1:200
1:500
1:15
1:50
1:200
1:500
1:15
1:50
1:200
1:500
D q-RNEU 420-429 Tetramer

Have combinations of immune based therapy with chemotherapy at standard doses shown clinical efficacy?

- Studies comparing IL-2, IFN and 5-FU versus IL-2 alone in RCC show no consistent benefit in response rates and inferior survival in the adjuvant setting (Cytokine Working Group, Cancer J 1997; Atzpodien et al, Br J Cancer 2005)

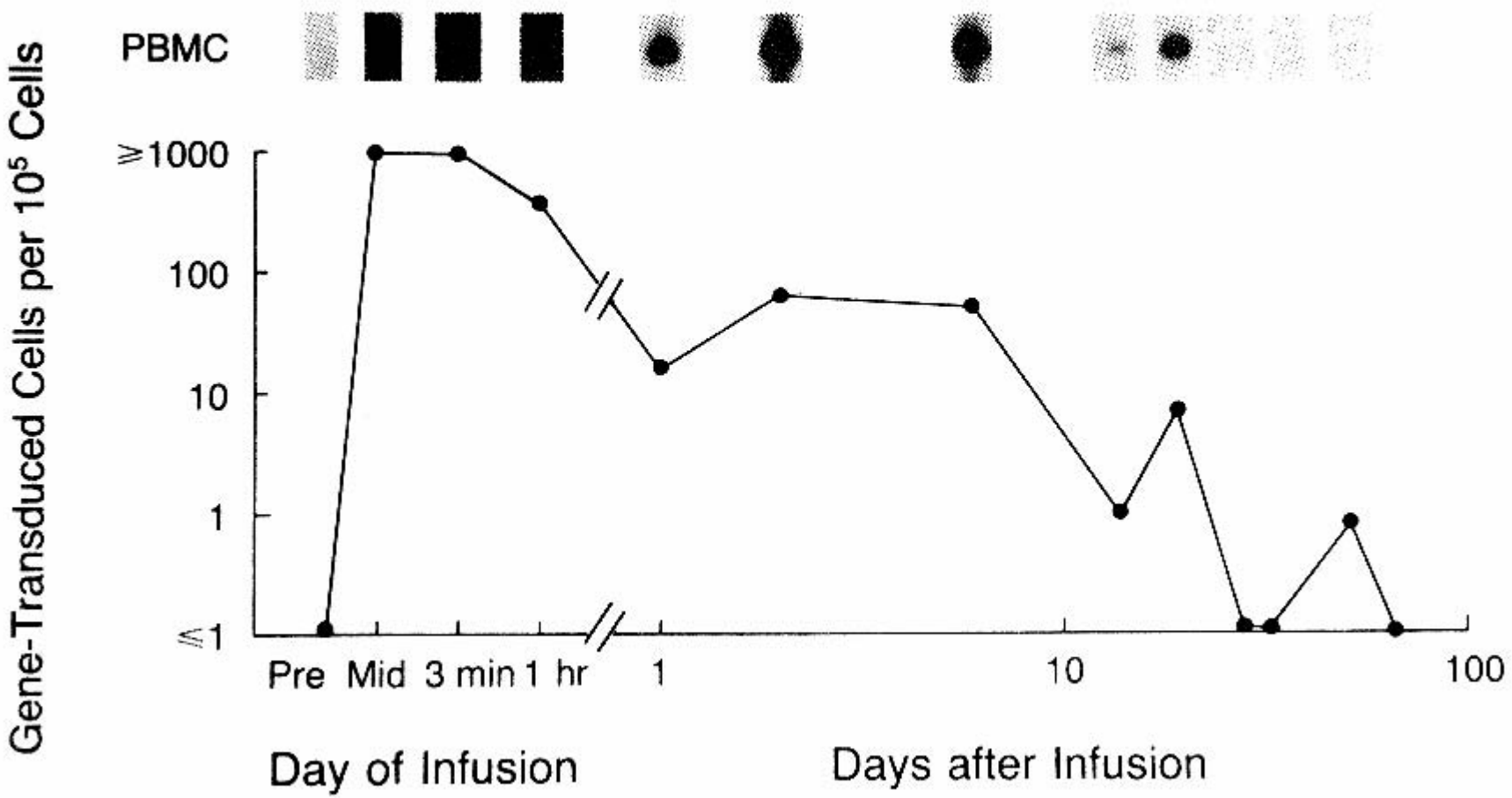
- Despite encouraging Phase II data, randomized study of chemo-immunotherapy vs. chemotherapy alone in patients with melanoma shows no survival benefit and a possible decrease in durable responses compared to historical results with IL-2 alone (Rosenberg et al, JCO 1999)

High dose chemotherapy can modulate the host:immune environment

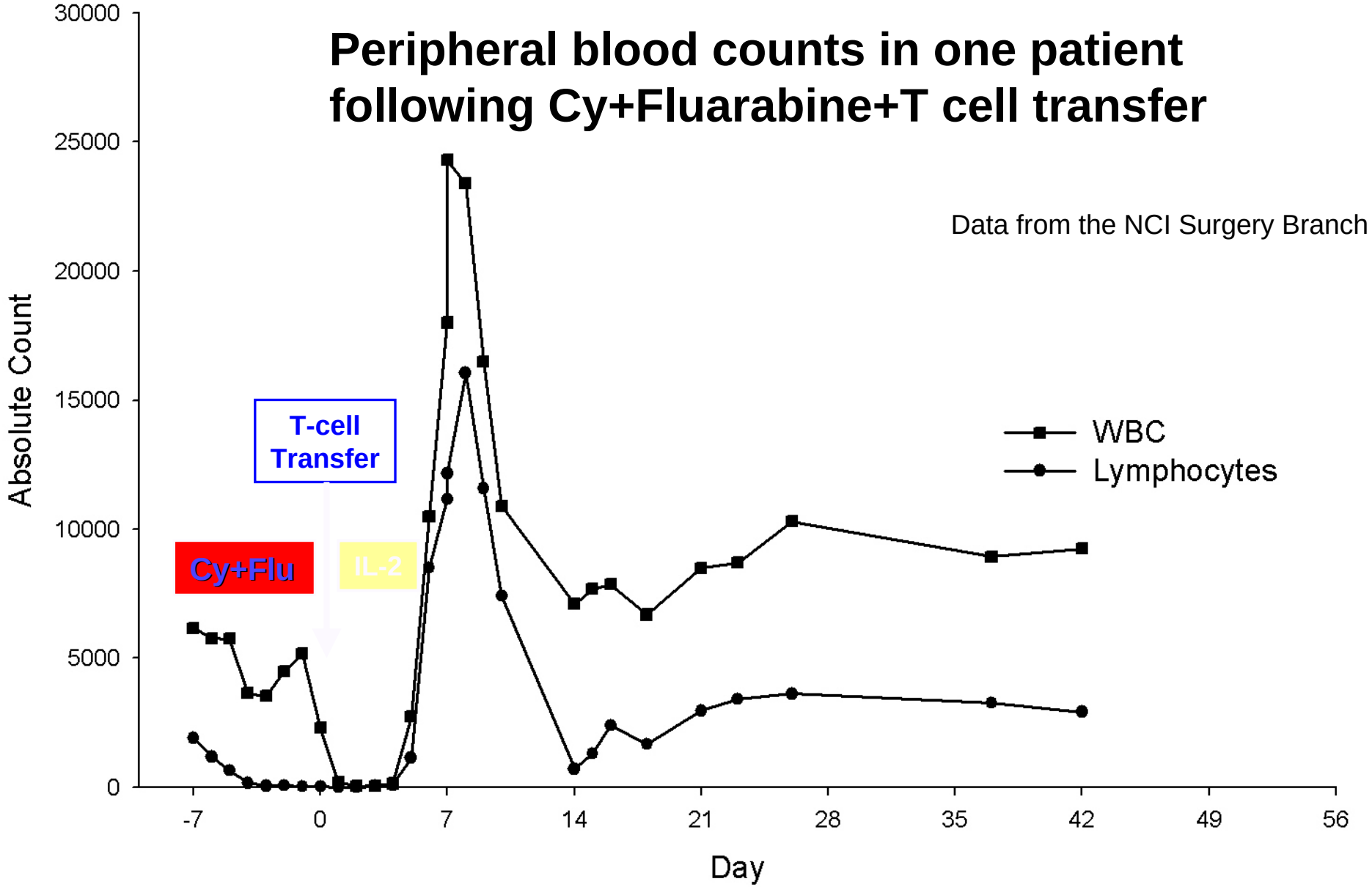
- Chemotherapy-induced lymphopenia can lead to brisk homeostatic proliferation (Rocha, Surh and others)
- Preparative lymphodepletion can deplete host regulatory T-cells and augment tumor rejection by adoptively transferred T-cells (Antony 2005)
- Lymphodepletion with Cyclophosphamide and Fludarabine prolongs survival of transferred lymphocytes and augments adoptive transfer therapy of melanoma in patients (Dudley et al 2002)

Survival of Cultured Lymphocytes without Host Lymphodepletion

(Gene-marked cells given and tracked by quantitative PCR)



Data from the NCI Surgery Branch


Peripheral blood counts in one patient following Cy+Fluarabine+T cell transfer
Data from the NCI Surgery Branch
Absolute Count
30000
25000
20000
15000
10000
5000
0
T-cell Transfer
Cy+Flu
IL-2
WBC
Lymphocytes
-7
0
7
14
21
28
35
42
49
56
Day

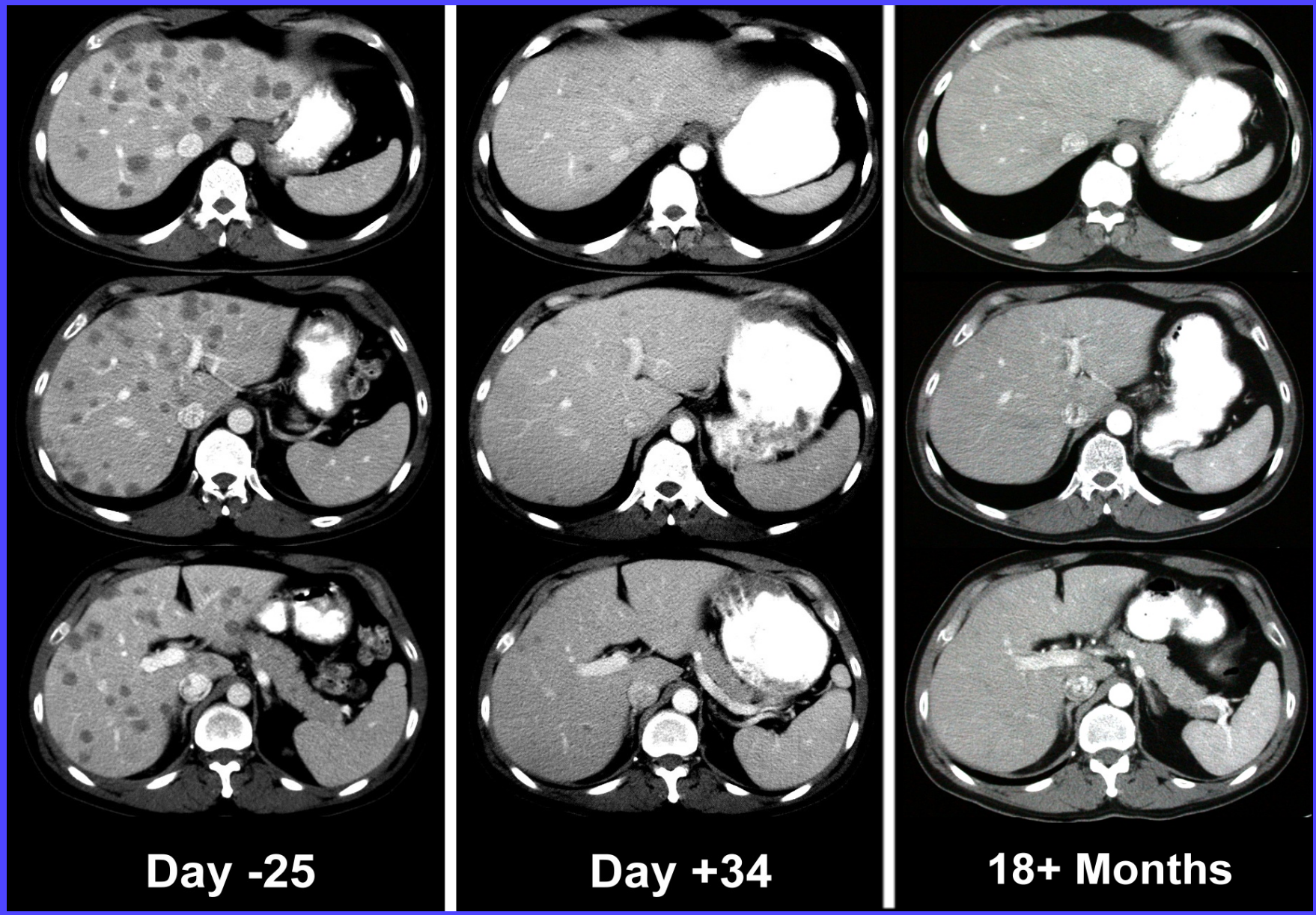
Phase II Studies of T-Cell Adoptive Transfer with and without Preparative Chemotherapy: Patients with Metastatic Melanoma

Regimen	# Pts	RR
TIL/IL-2	31	31%
Cy + TIL/IL2	57	35%
Cy + Flu* + TIL/IL-2	35	51%

* Fully lymphodepleting regimen

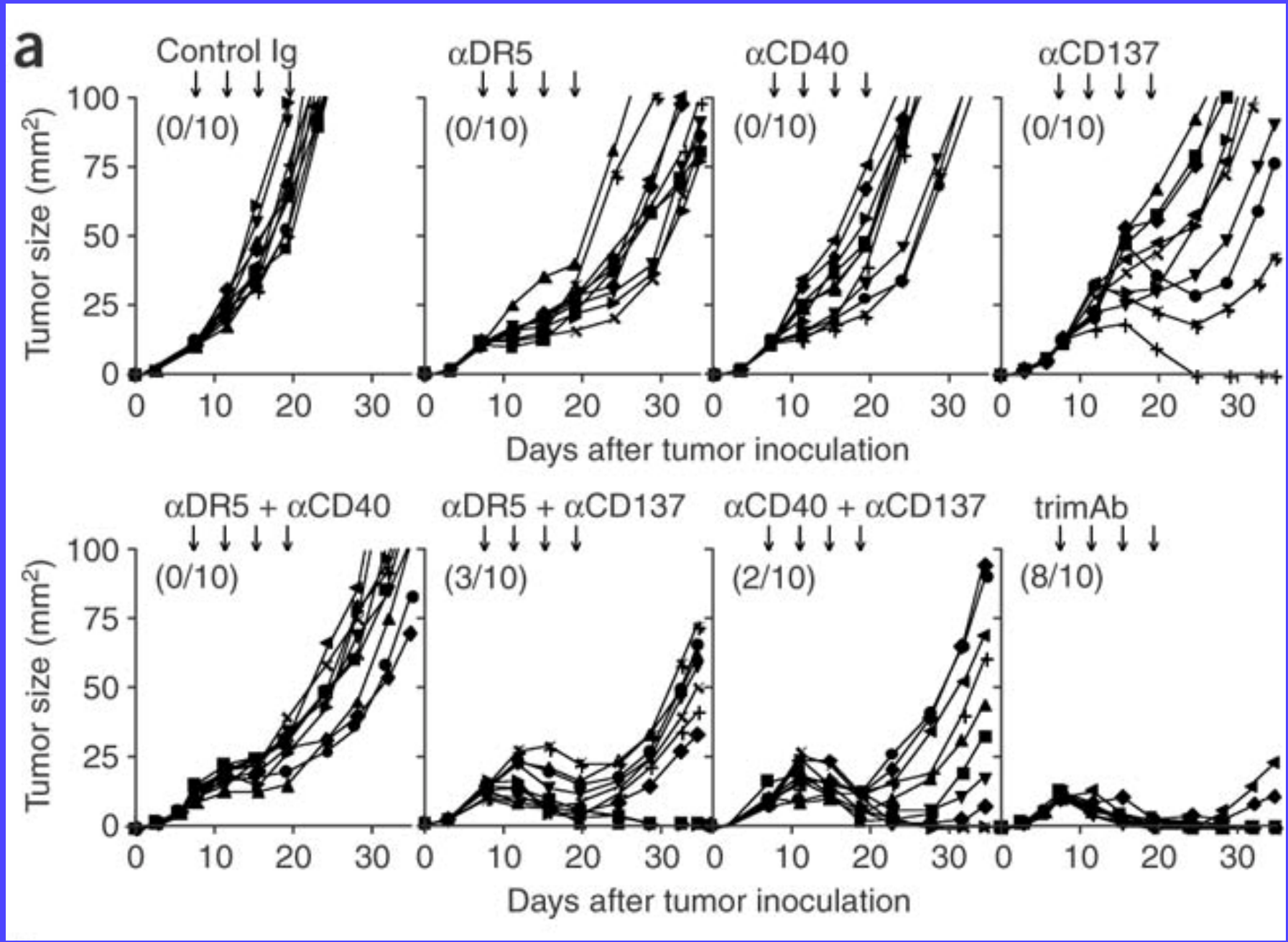
Data from the NCI Surgery Branch

Metastatic Melanoma: Host Lymphodepletion with TIL Transfer and IL-2



Targeted agents have a synergistic effect on the presentation of tumor antigens

- Uno et al (Nat Med 2006) showed that DR5-mediated tumor apoptosis allowed agonist antibodies against CD40 and CD137 to cause the regression of large established tumors in mice via a CTL-dependant mechanism
- This was interpreted as improved presentation of endogenous tumor antigens by apoptotic tumors facilitating an anti-tumor immune response
- Another apoptosis-inducing agent, Gemcitabine had similar but less-pronounced effects
- Other targeting antibodies such as anti-HER-2/neu have been shown to enhance antigen uptake, processing and presentation in the tumor micro-environment (Reilly et al, JI 2004).



Uno et al, Nat Med 2006

Rationale for use of Cytokines + Hypomethylating Agents

- Re-expression of silenced tumor antigens
  - Permits greater target recognition by activated lymphocytes, improved antigen presentation by activated APCs
- Re-expression of genes mediates direct antiproliferative/proapoptotic effects of interferons
  - Rendering tumor target more susceptible to direct antitumor effects of type I and type II interferons
- Re-expression of immunostimulatory genes in lymphocytes, monocytes, and dendritic cells
  - Augments ability of cytokines to stimulate cellular and humoral immune responses against tumor targets

Data Supporting Combinations Cytokines + Hypomethylating Agents

- **Preclinical data**
  - Direct antimelanoma effect of IFN-g requires distinct changes in gene expression by activation of various MAP kinase signaling components (Gollob JA *et al*., Cancer Res 2005;65:8869-77)
  - Decitabine (5-Aza-2′-deoxycytidine) treatment can re-express genes in melanoma and RCC cells necessary for the direct antimelanoma effect of type I interferons (Rue FJ *et al.,* Cancer Res 2006)

- **Clinical Data**
  - Phase I trial of sequential low-dose decitabine plus high-dose IV bolus IL-2 showed objective responses associated with autoimmunity in 30% of patients (Gollob JA *et al.,* Clin Cancer Res 2006)

Rationale for Combining IFN-alpha + Multiple-Kinase Inhibitors

- IFN-alpha has been shown to block VEGF and bFGF gene expression in vitro and in animal models
- Phase II trials of sorafenib + IFN-alpha in RCC show promise
  - Duke/UNC: RR ~40% with 2 CRs
  - SWOG: RR 19% (28% if include unconfirmed PRs)
- Could IFN-alpha be suppressing induction of VEGF thereby contributing to the synergy in terms of tumor response as well as to the decrease in hand-foot reaction?
- Phase II trial of IFN-alpha + sorafenib followed by maintenance sorafenib in development (Duke/UNC/Baylor Sammons) will test hypothesis that IFN-alpha is suppressing sorafenib-induced VEGF/bFGF/PDGF-β

Rationale for integrating a "Chemo-Switch" Strategy with Immunotherapy

- Murine solid tumor model demonstrating superior responses and survival when initial responses to "MTD" chemotherapy followed by antiangiogenic regimen of metronomic low-dose chemotherapy plus VEGFR/PDGFR-β inhibition (so-called "chemo-switch")
  - Pietras K and Hanahan D, J Clin Oncol 2005;23:939-52

- In melanoma, best response rates seen with biochemotherapy, but quality of responses is poor (short duration, no impact on survival, frequent CNS progression)

- Proof of principle Phase II "chemo-switch" trial scheduled to open at Duke this summer:
  - Concurrent biochemotherapy x 2 cycles, followed by 8-week cycles of continuous sorafenib (VEGFR/PDGFR-β inhibition) + metronomic low-dose temozolomide in responders and patients with SD

Topics for Consideration

- What mechanisms should be targeted when using chemotherapy to modulate host:immune interactions?
- What preclinical studies should be done and what models should be used to drive the integration of chemotherapy with immune based therapies?
- What are the rules for effectively integrating chemotherapy with immune therapy?
  - Agents, dosing, schedule
- Are innovative study designs needed to identify synergies when evaluating multi-targeted therapy?
  - To maximize dosing, scheduling and ultimately synergy?