Is There a Role for Combining Chemotherapy and Immunotherapy?

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Conflict of Interest

- Aduro: Under a licensing agreement between Aduro 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: Research Funding

- Bristol Myers Squibb, Roche, Aveo, Celgene, Vaccinex: Advisory Board or Consultant

Key Concept #1

Chemotherapy Has Pleiotropic Effects on Tumor Immunity

Pleiotropic Effects of Chemotherapy on Immunity

Chemotherapy Drug	Immunologic Process	Mechanism
Doxorubicin, Daunorubicin, Mitoxantrone	Antigen uptake/processing	Calreticulin, HMGB1/TLR4
High dose chemotherapy (cyclophoshamide/fludarabine)	Homeostatic proliferation	IL-7, IL-15, IL-21, inhibition Treg
Cyclophosphamide, Cisplatin, Paclitaxel, Temozolamide, Fludarabine	Regulatory cell function	Inhibition of Treg
Gemcitabine, 5-Fluorouracil	Regulatory cell function	Inhibition of MDSC
Cyclophosphamide, Paclitaxel, Bleomycin, Melphalan	Reversal of immunologic skew	Promotes T helper type 1 immunity
Cyclophosphamide, Vincristine, Vinblastine, Paclitaxel, Methotrexate, Mitomycin-C, Doxorubicin, 5-Aza-2'-deoxycytidine	Antigen presentation	Augment DC function --Cyclophosphamide: decr $CD8^+$ DC --Paclitaxel: thru TLR-4/Myd-88
5-Aza-2'-deoxycytidine	Antigen processing	Increased MHC Class I and/or tumor antigen expression
Melphalan, Mitomycin-C, Cytosine arabinoside	Co-stimulation	Upregulates B7-1, B7-2 expression
Cytosine arabinoside	Counter-stimulation	Downregulates B7-H1 expression
Cyclophosphamide, Dacarbazine	T cell repertoire	Increases diversity, avidity
Cyclophosphamide, Paclitaxel, Cisplatin, Doxorubicin	Target cell lysis	Upregulation of lytic sensitivity to TRAIL, fas, granzyme B

Chemotherapy and Regulatory T Cells

Preclinical Models

- Low dose cyclophosphamide
- Cisplatinum
- Paclitaxel
- Metronomic cyclophosphamide, paclitaxel, temozolamide

Clinical Setting

- Low dose and metronomic cyclophosphamide
- Standard dose fludarabine
- Standard dose dacarbazine
- Standard Gemcitabine/FOLFOX4 + sq GM-CSF + IL-2

Chemotherapy and Myeloid-Derived Suppressor Cells

Preclinical Models

- Gemcitabine
- 5-fluorouracil
- Docetaxel
- Low dose paclitaxel
- Cyclophosphamide (expansion)
- Doxorubicin (reduction and expansion)
- Melphalan (expansion)

Clinical Setting

- Standard cyclophosphamide/doxorubicin (expansion)

Key Concept #2

Chemotherapy is a Double-Edged Sword for Tumor Immunity

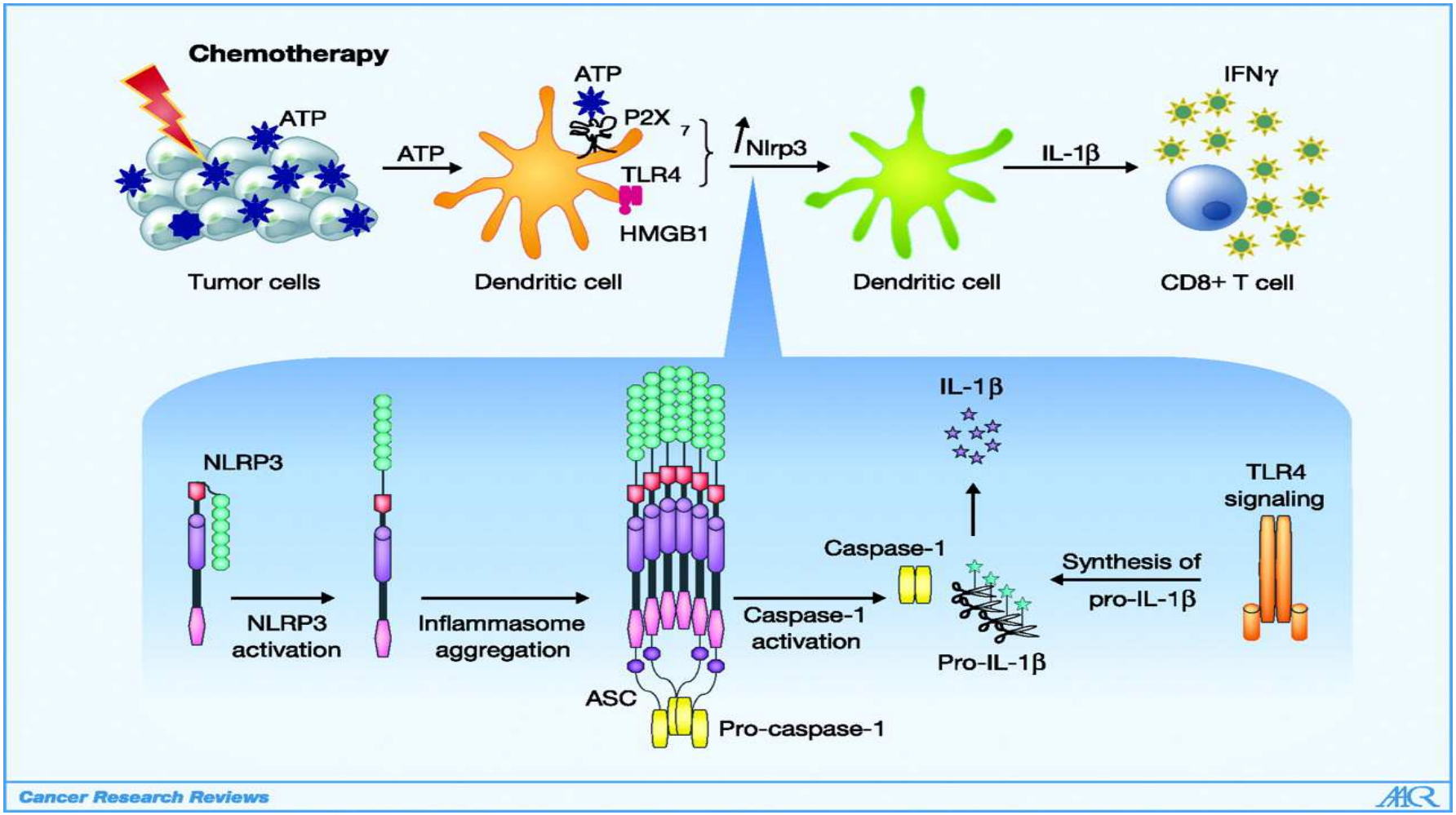
Chemotherapy and Tumor Immunity: The Bad

- Chemotherapy is immunosuppressive, causing lymphopenia and neutropenia
- Co-administration of glucocorticoids compounds treatment-related immune suppression
- Chemotherapy is frequently used to suppress autoimmune disease: cyclophosphamide and methotrexate
- Chemotherapy can induce immune tolerance
- Chemotherapy sometimes induces non-immunogenic cell death

Chemotherapy and Tumor Immunity: The Good

- Chemotherapy sometimes induces immunogenic cell death
- Chemotherapy can make space, allowing homeostatic T cell proliferation
- Chemotherapy can abrogate mechanisms of immune tolerance
    - Tregs
    - MDSCs
- Chemotherapy can modulate the tumor microenvironment to favor immunity
    - Upregulates tumor antigens
    - Upregulates molecules involved in antigen processing/presentation
    - Modulates accessory molecules of T cell activation/inhibition

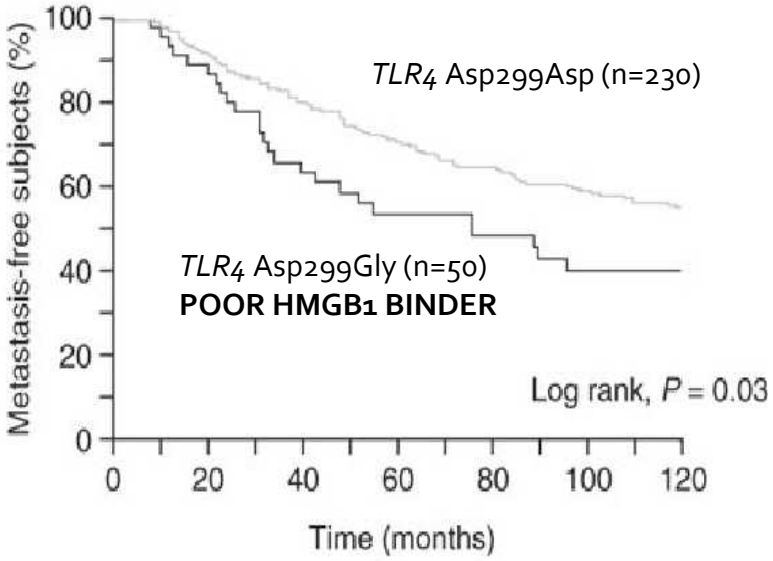
The NRLP3 Inflammasome Mediates Immunogenic Cell Death



Aymeric L et al: Cancer Res 2010; 70: 855-858.

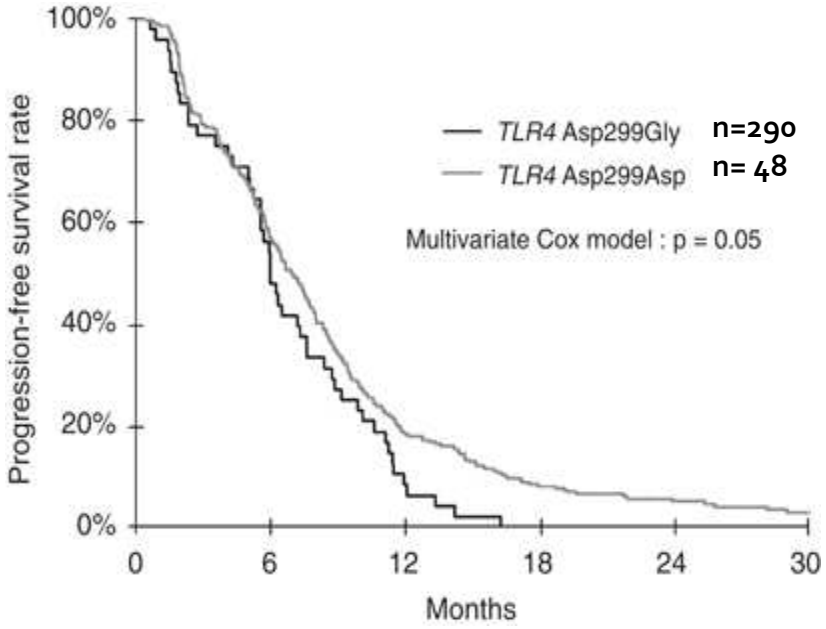
HMGB1-TLR4 Axis: Impact on Efficacy of Chemotherapy for Breast and Colon Cancer

Adjuvant Anthracyline Therapy for Breast Cancer



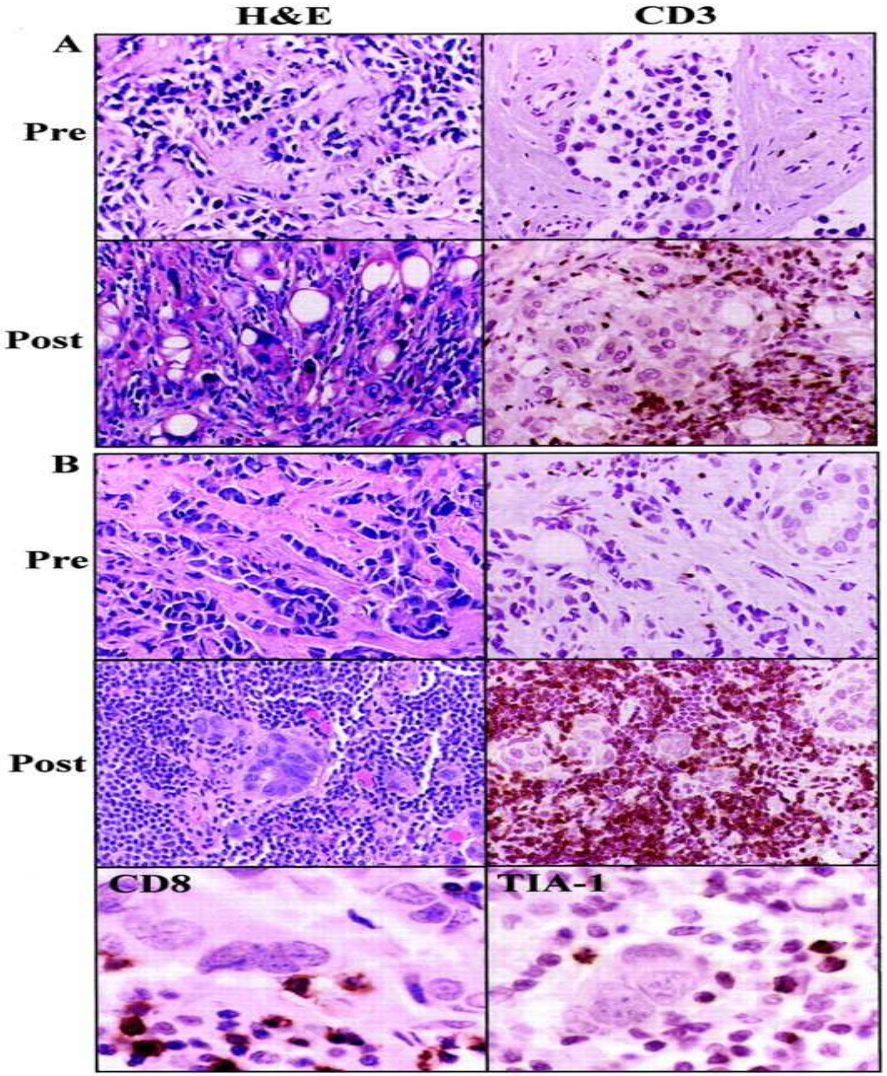
Apetoh, L et al: Nature Med 2007; 13: 1050

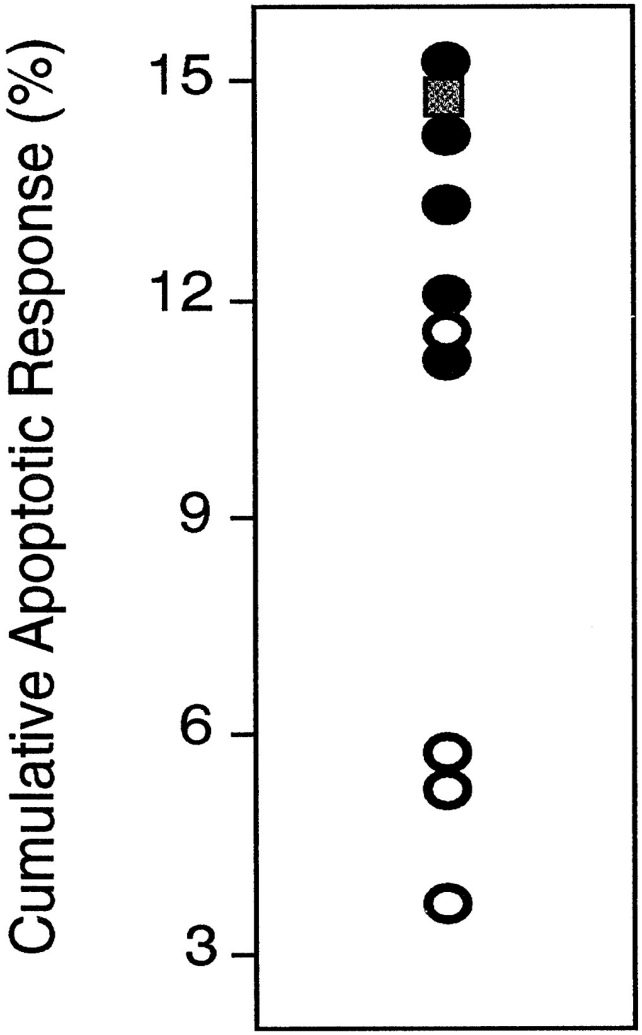
Oxaliplatin Therapy for Metastatic Colon Cancer



Tesniere A et al: Oncogene 2010; 29: 482

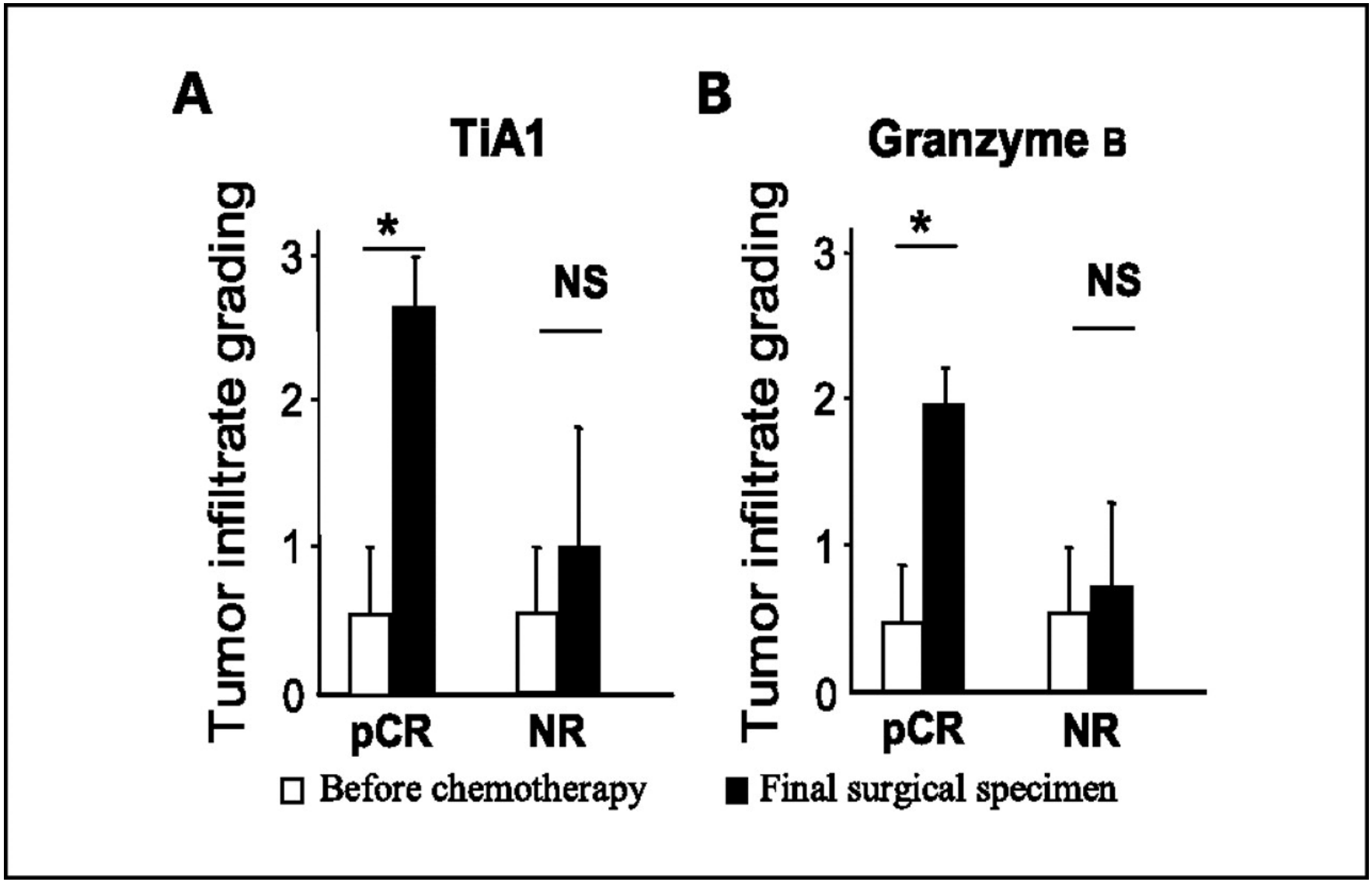
Neoadjuvant Paclitaxel Therapy for Breast Cancer Results in TIL Accumulation





Demaria S et al Clin Cancer Res 2001 7: 3025

Neoadjuvant pCR is Associated with Increased $CD8^+$ T Cell Activation in Early Breast Cancer

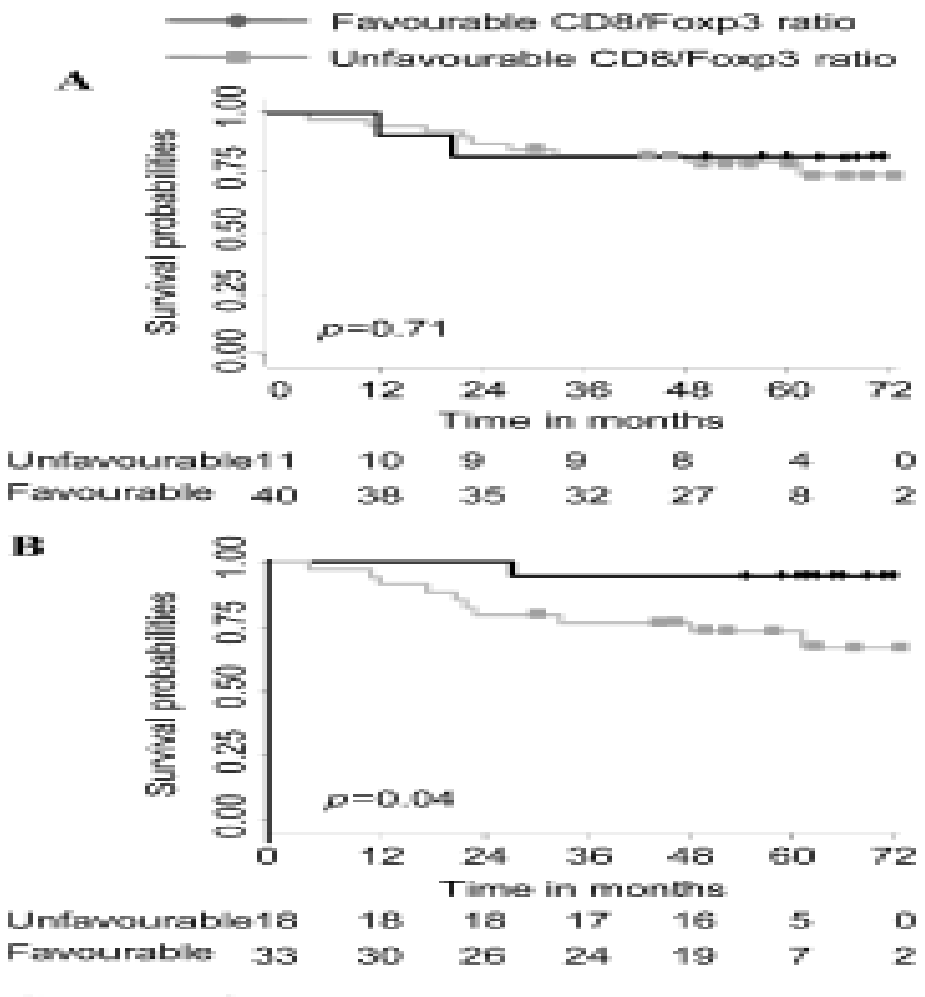


Ladoire S et al. Clin Cancer Res 2008;14:2413-2420

$CD8^+/FoxP3^+$ T cell Ratio after Neoadjuvant Chemotherapy for Breast Cancer Predicts Survival

Before Treatment

After Treatment



The Journal of Pathology
Volume 224, Issue 3, pages 389-400, 25 MAR 2011 DOI: 10.1002/path.2866
http://onlinelibrary.wiley.com/doi/10.1002/path.2866/full#fig4

Key Concept #3

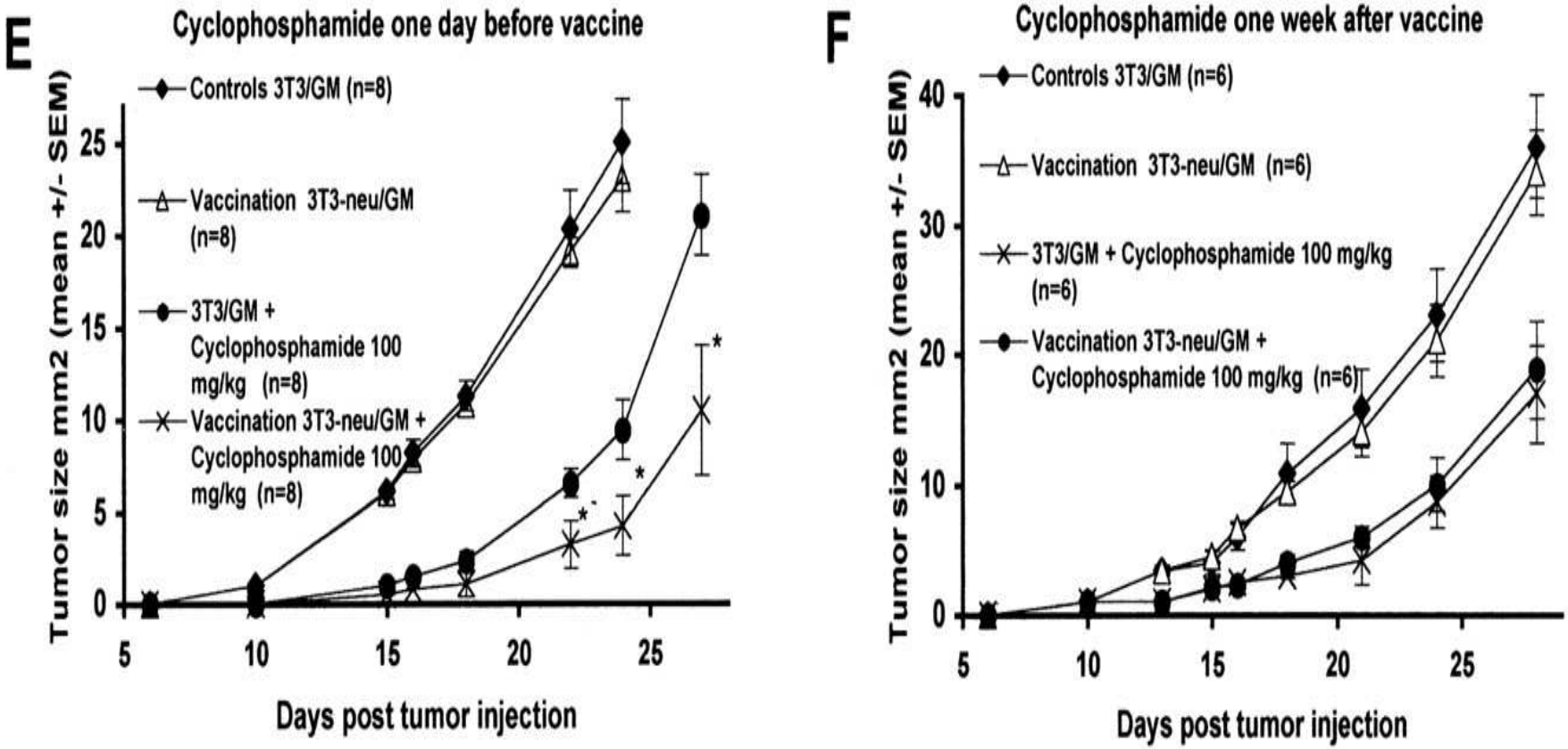
The impact of chemotherapy on tumor immunity depends on the drug, its dose, and the timing of drug exposure relative to tumor antigen delivery or release/T cell priming.

Chemotherapy-Induced Immunomodulation is Drug, Dose, and Schedule Dependent

	T cell count (nadir) number/ μl ± SD (normal range, 4000–9000)[b]	Chemotherapy 1 day before vaccine	Chemotherapy 7 days after vaccine
CTX			
50 mg/kg	6128 ± 847	+[c]	–
100 mg/kg	5120 ± 1033	+	–
150 mg/kg	1559 ± 356	+	NT
200 mg/kg	1100 ± 478	+/–	NT
250 mg/kg	989 ± 122	+/–	NT
PTX			
20 mg/kg	4363 ± 301	+	–
30 mg/kg	4200 ± 675	+	NT
35 mg/kg	3600 ± 543	+/–	NT
40 mg/kg	3451 ± 345	+/–	NT
DOX			
4 mg/kg	6263 ± 1298	+/–	+/–
8 mg/kg	5586 ± 945	+/–	+/–
15 mg/kg	4180 ± 301	–	–
CIS			
2 mg/kg	6320 ± 903	+/–	+/–
3 mg/kg	6200 ± 674	+/–	+/–
5 mg/kg	3679 ± 455	–	–
10 mg/kg	3400 ± 697	–	–

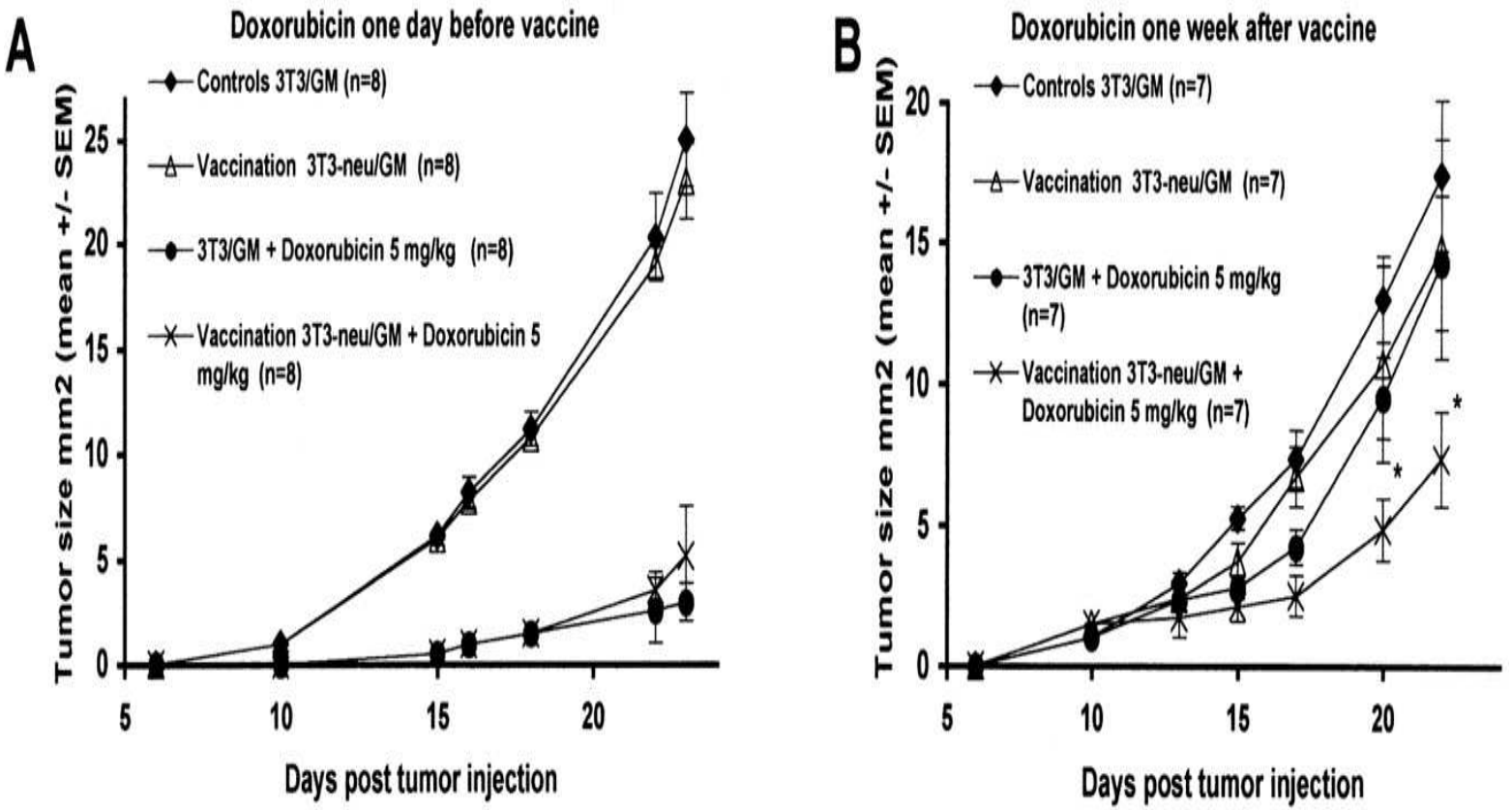
Machiels JP et al Cancer Res 2001 61: 3689

Low Dose Cyclophosphamide Enhances HER-2-targeted Vaccination in *Neu* Transgenic Mice



Machiels JP et al Cancer Res 2001 61: 3689

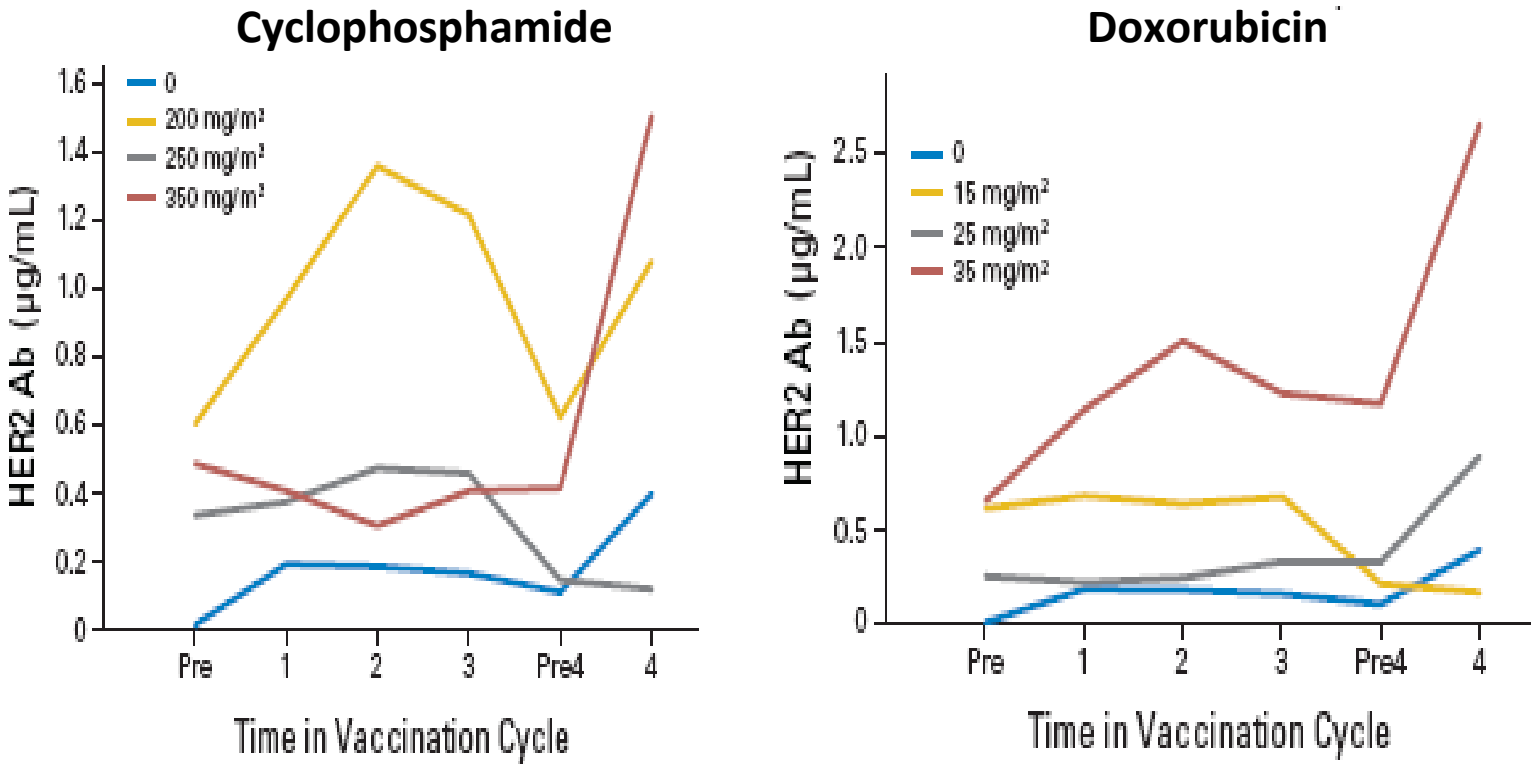
Low Dose Doxorubicin Enhances HER-2-targeted Vaccination in *Neu* Transgenic Mice



Machiels JP et al Cancer Res 2001 61: 3689

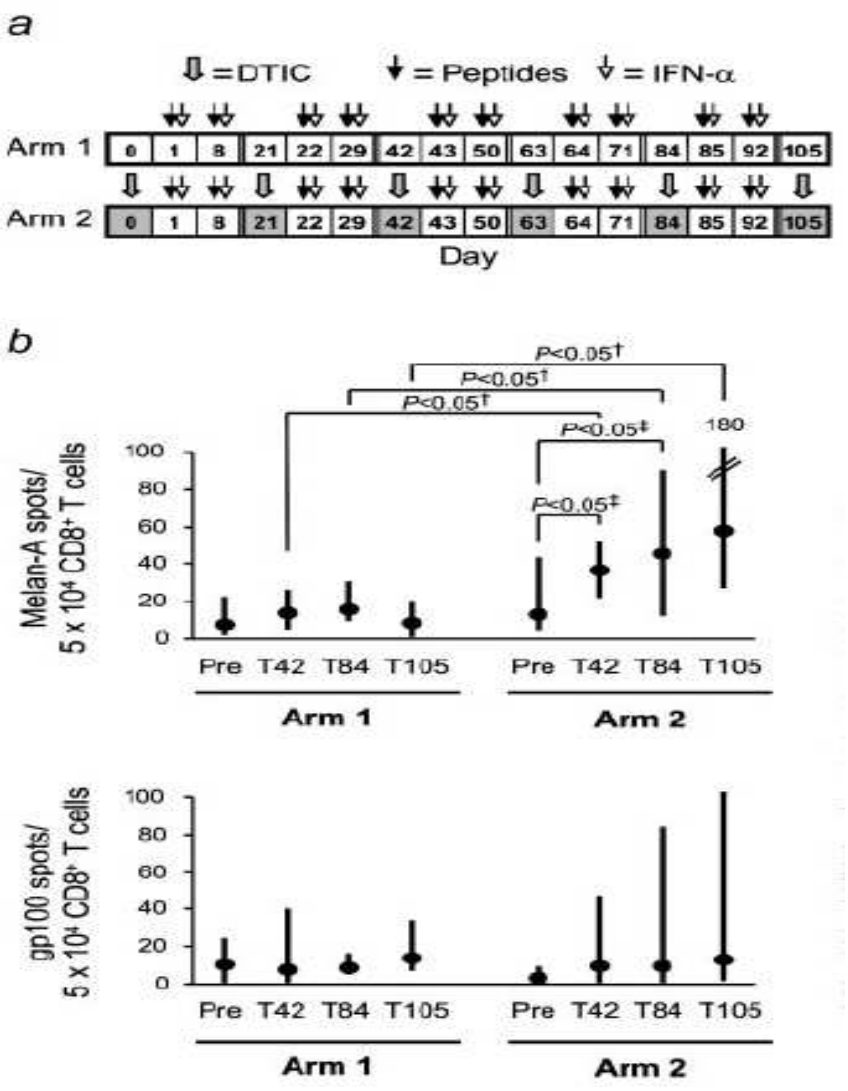
What About Cancer Vaccines in Patients?

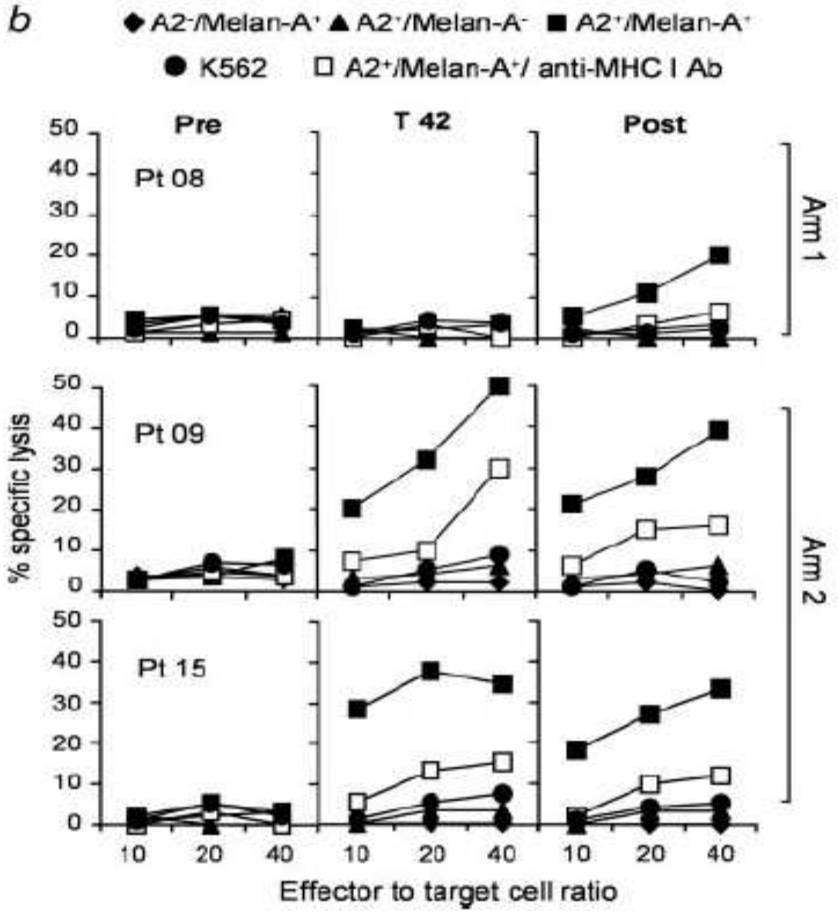
Chemotherapy-Modulated Vaccination Enhances Vaccine-Induced Immunity in Metastatic Breast Cancer Patients



Emens LA et al J Clin Oncol 2009 37: 5912

Dacarbazine Pre-Treatment Enhances gp100 Peptide Vaccination in Metastatic Melanoma Patients

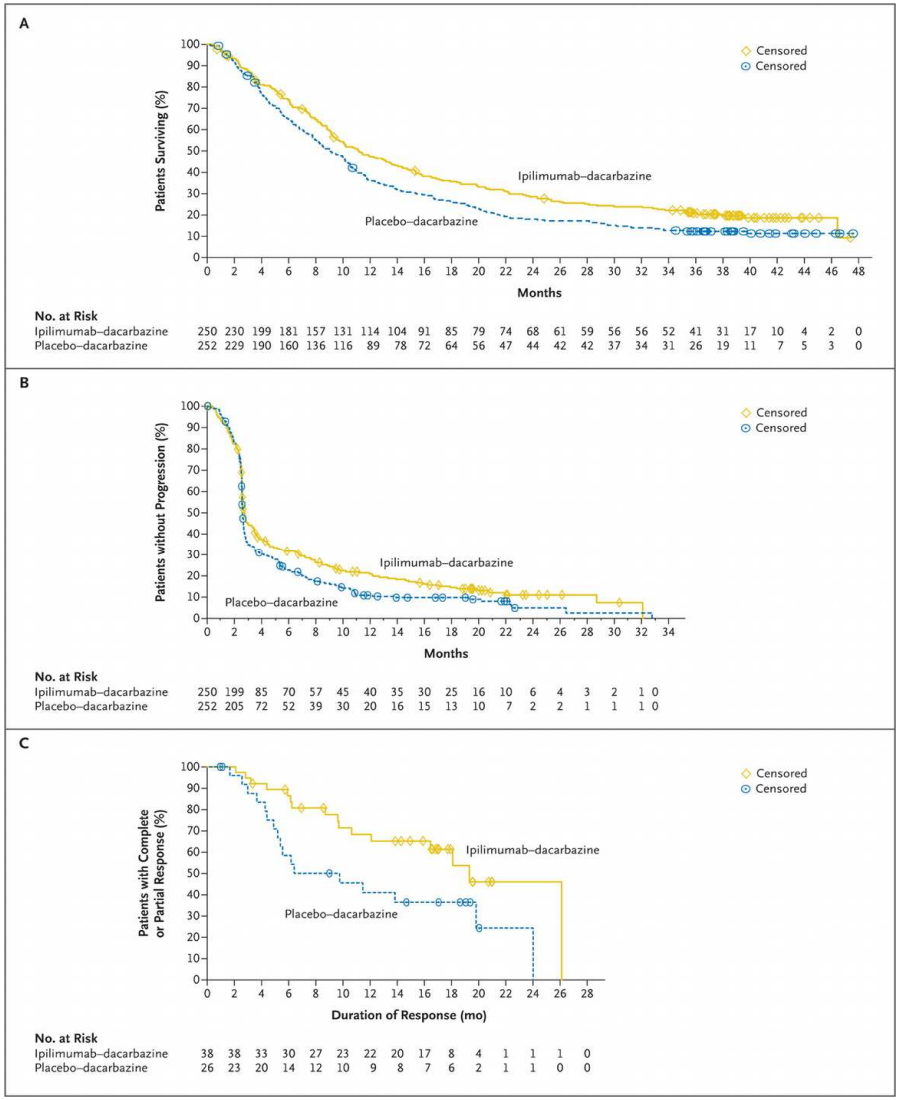




Nistico P et al Int J Oncol 2009 124:130

What About Immune Checkpoint Blockade in Patients?

First Line Dacarbazine + Ipilimumab for Metastatic Melanoma



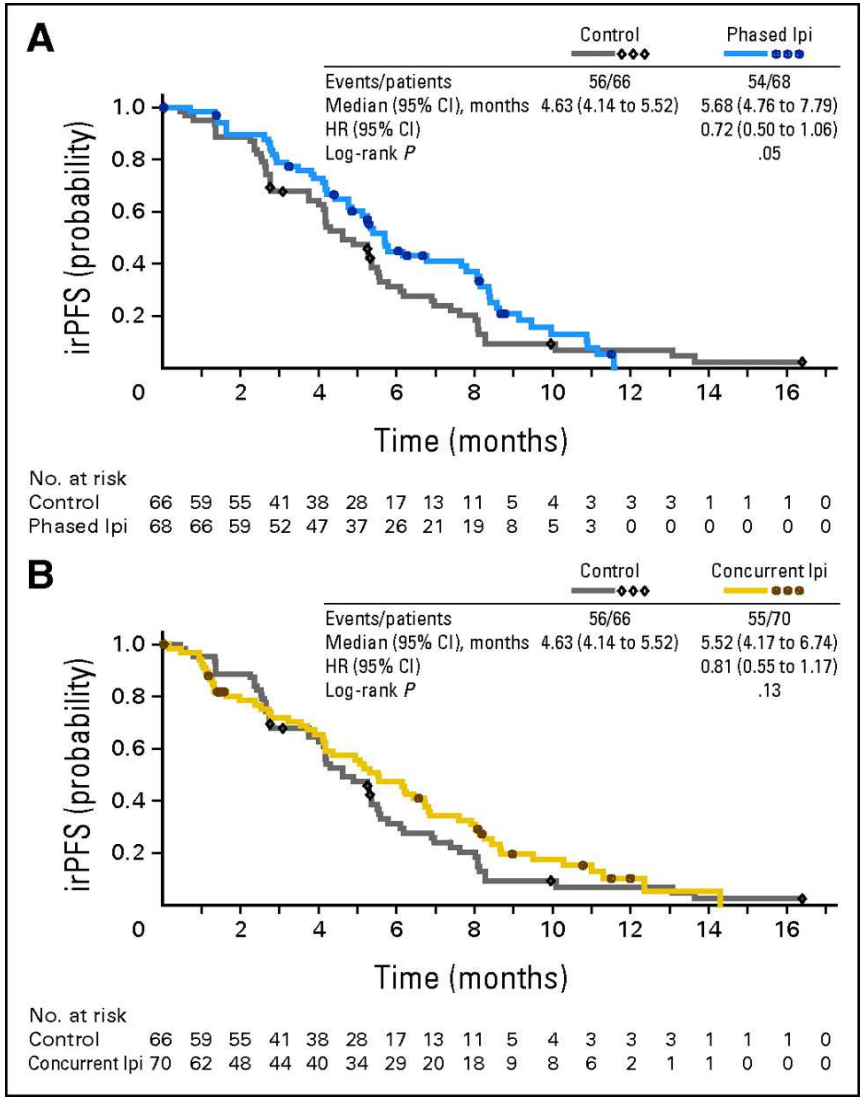
n=502, randomized 1:1

Ipi or placebo+D (850 mg/m^2 weeks 1, 4, 7, 10, then D alone every 3 weeks thru week 22, then ipi or placebo every 12 weeks as maintenance)

	D + placebo	D + Ipilimumab
OS	9.1 months	11.2 months
1 year survival	36.3%	47.3%
2 year survival	17.9%	28.5%
3 year survival	12.2%	20.8%
Grade 3-4 AEs	27.5%	56.3%

Robert C et al. N Engl J Med 2011;364:2517-2526.

First Line Ipilimumab with Carboplatinum/Paclitaxel for Stage IIIB/IV NSCLC



N=204, randomized 1:1:1

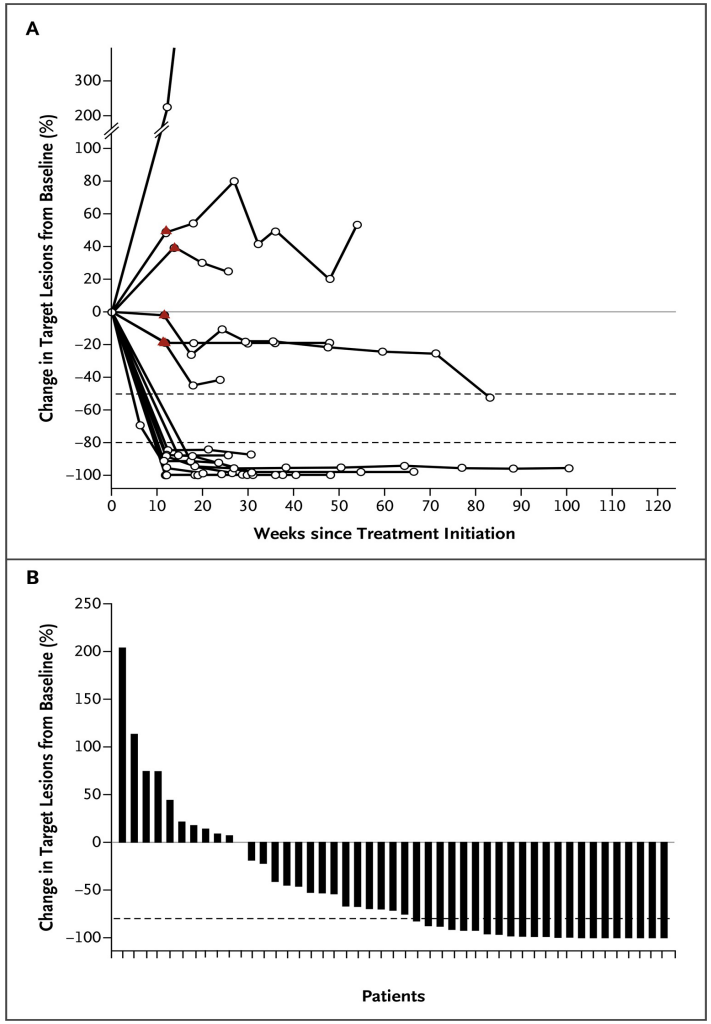
Control: Paclitaxel 175 mg/mg^2 + Carboplatinum AUC 6 + placebo
Concurrent: chemo+ ipilimumab x 4 then chemo + placebo x 2
Phased: chemo + placebo x 2 then ipilimimab + chemo x 4

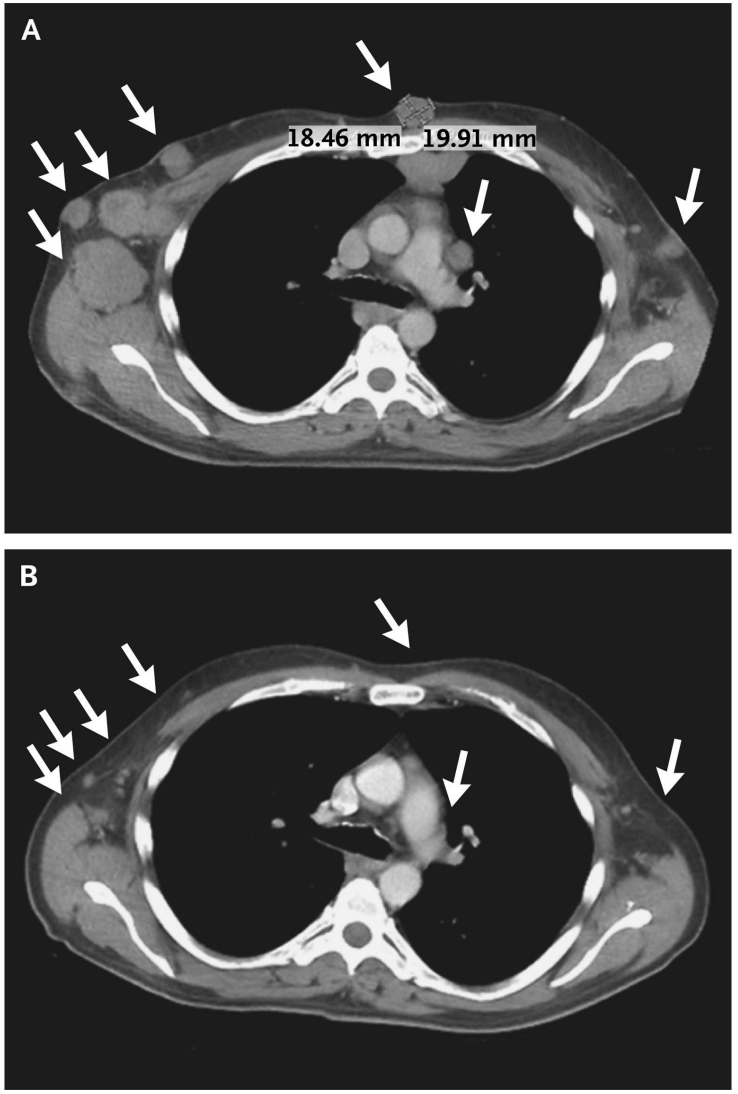
	Control	Concurrent	Phased
irPFS	4.6 mo	5.5 mo	5.7 mo
irBORR	18%	21%	32%
OS	8.3 mo	9.7 mo	12.2 mo
Grade 3-4 AEs	6%	20%	15%

Lynch T J et al. JCO 2012;30:2046-2054

Could Immunotherapy Without Chemotherapy Be Enough?

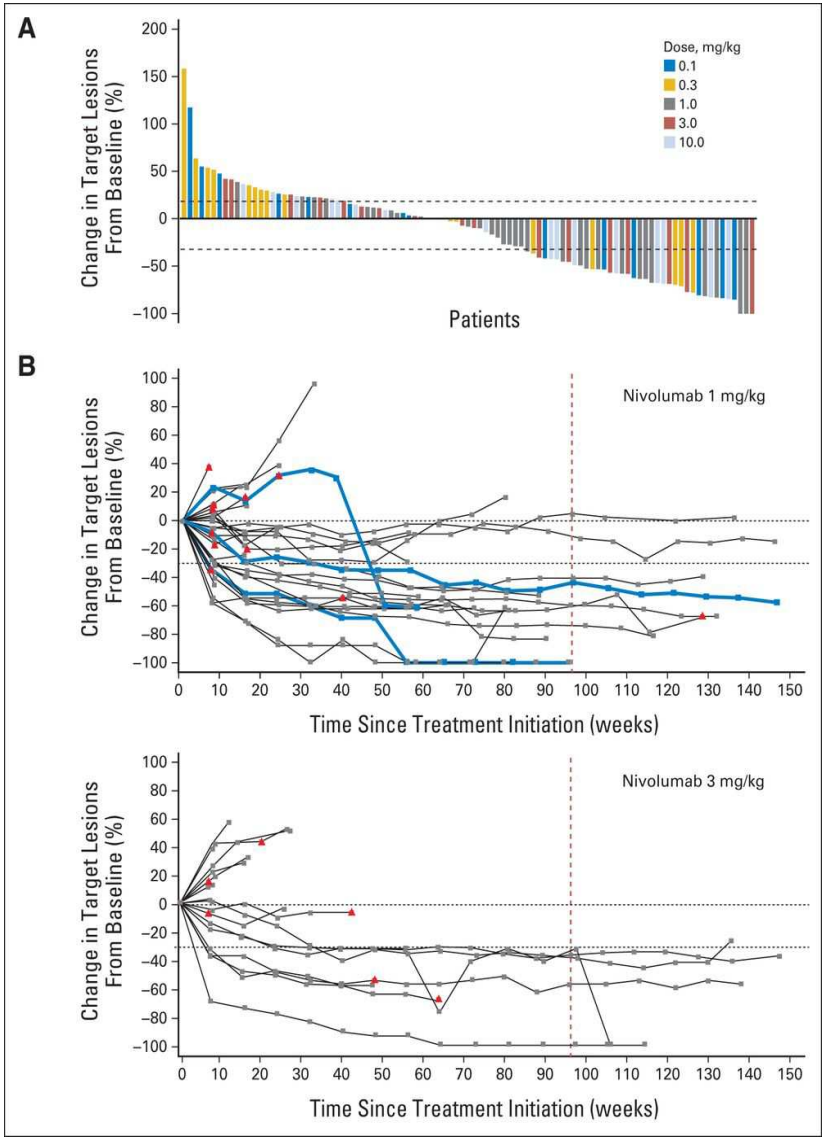
Concurrent Ipilimumab and Nivolumab Induces Rapid, Deep, and Durable Responses in Melanoma Patients

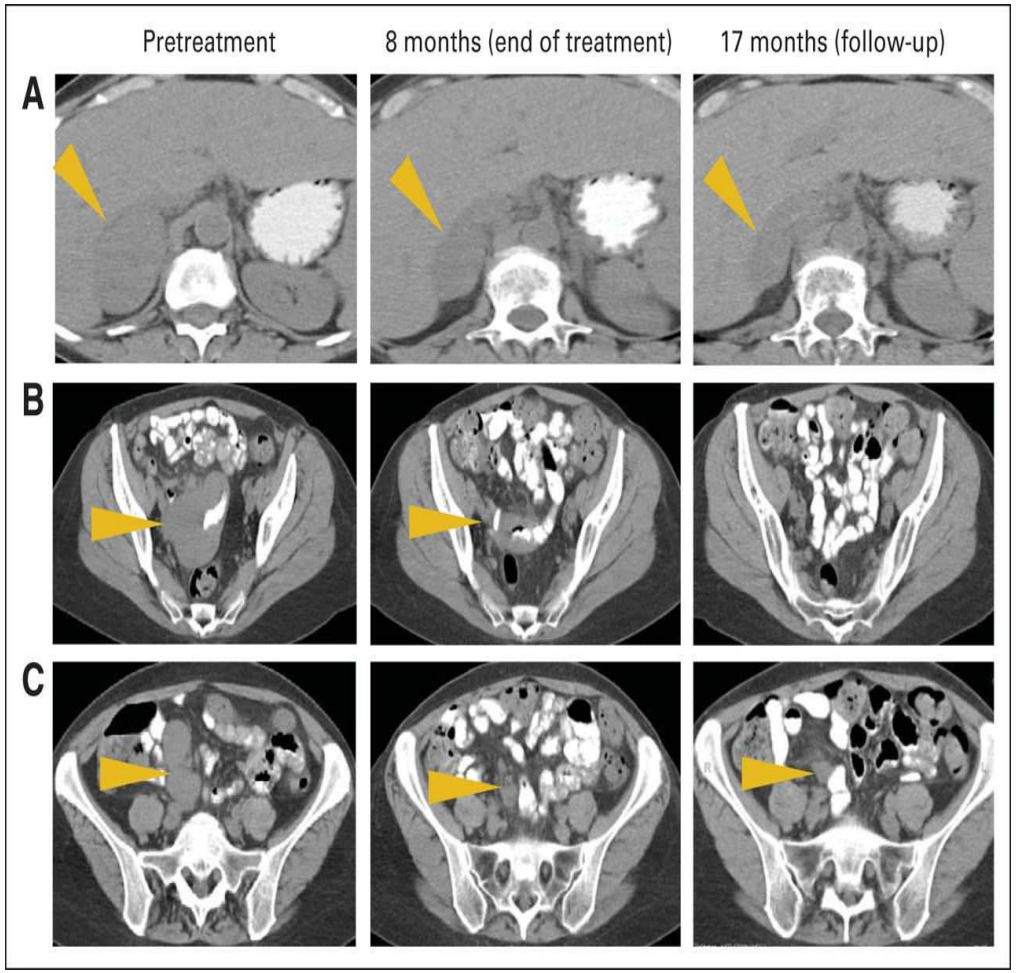




Wolchok JD et al. N Engl J Med 2012;369: 122-133.

Single Agent Nivolumab Induces Durable Responses in Melanoma Patients





Topalian S L et al. JCO 2014;32:1020-1030

Take Home Message

The ultimate goal is to support T cells in controlling tumor growth, promoting tumor rejection and cure.

For successful chemoimmunotherapy, it is critical to understand how to harness the immune activities of chemotherapy and immunotherapy so that they are additive--preferably synergistic--and not inhibitory to tumor immunity.

Summary

- Chemotherapy has pleiotropic effects on the immune system, impacting multiple pathways and cellular regulators of the immune response.
- Chemotherapy can impact the immune response in both positive and negative ways depending on the active context during exposure.
- The positive or negative impact of chemotherapy on tumor immunity depends on the drug, its dose, and the timing of drug exposure relative to tumor antigen delivery or release/T cell priming.

Bottom Line: Combining chemotherapy and immunotherapy may result in greater clinical activity if the scientific rationale underlying the dose and schedule is sound. Combination therapy may be necessary for some tumors, but not for others.