

Endogenous and Exogenous Vaccination in the Context of Immunologic Checkpoint Blockade

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Memorial Sloan-Kettering Cancer Center**



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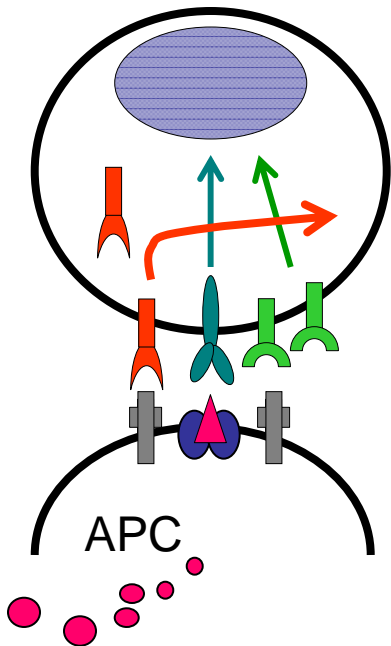
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Disclosure

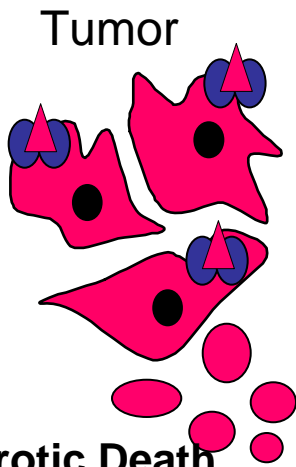
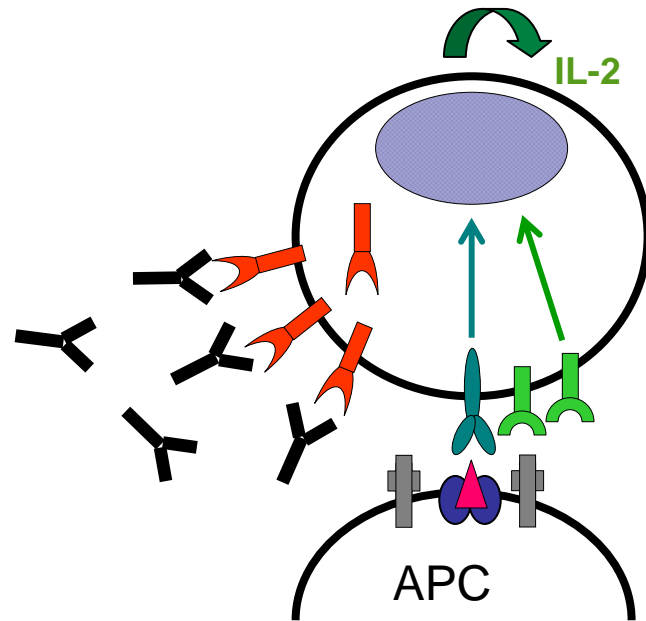
- Consultant: Bristol-Myers Squibb

CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

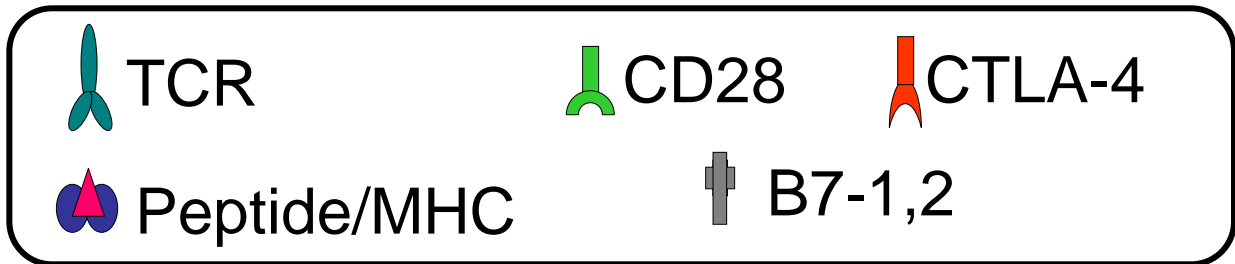
Attenuated or Terminated Proliferation



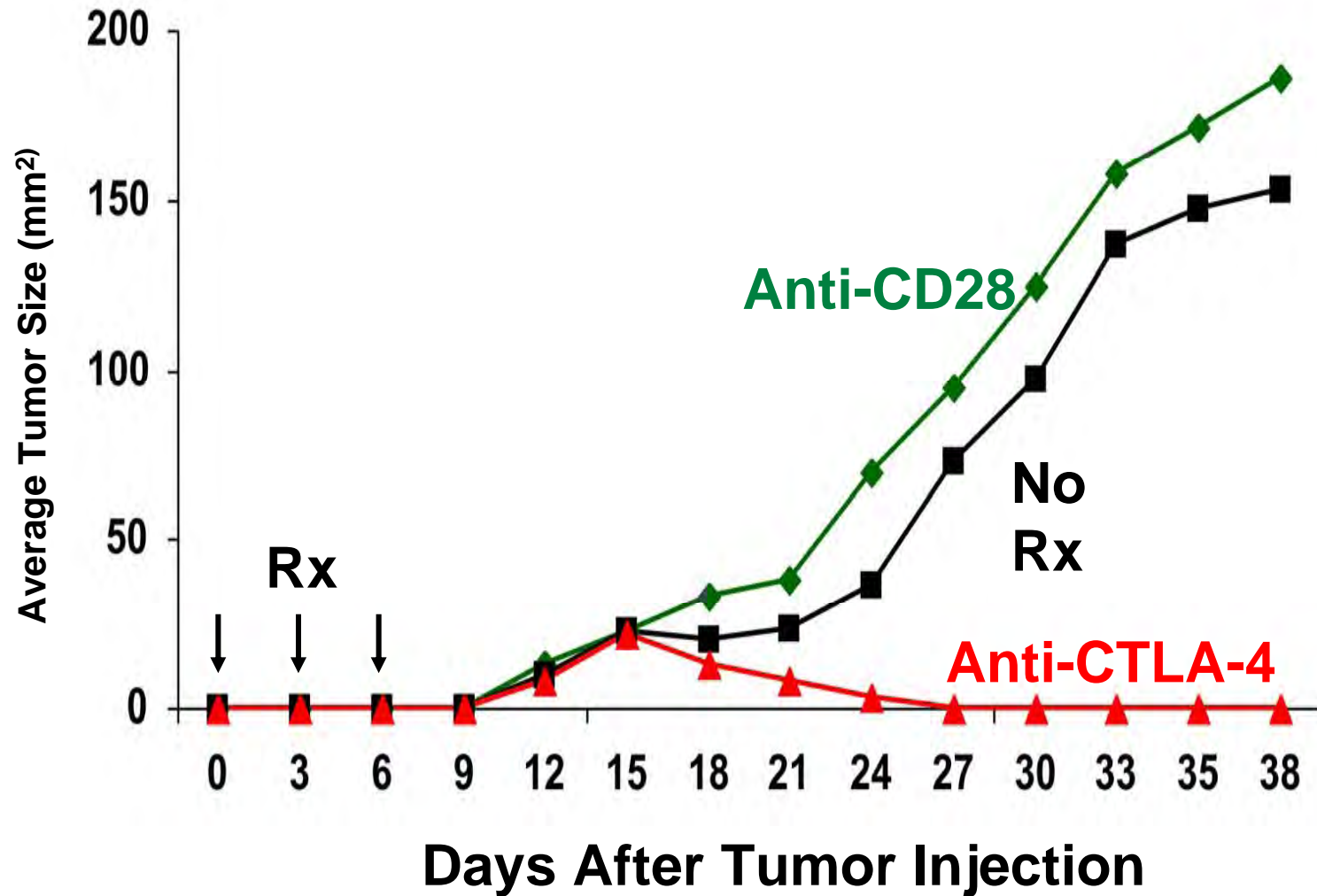
Unrestrained Proliferation



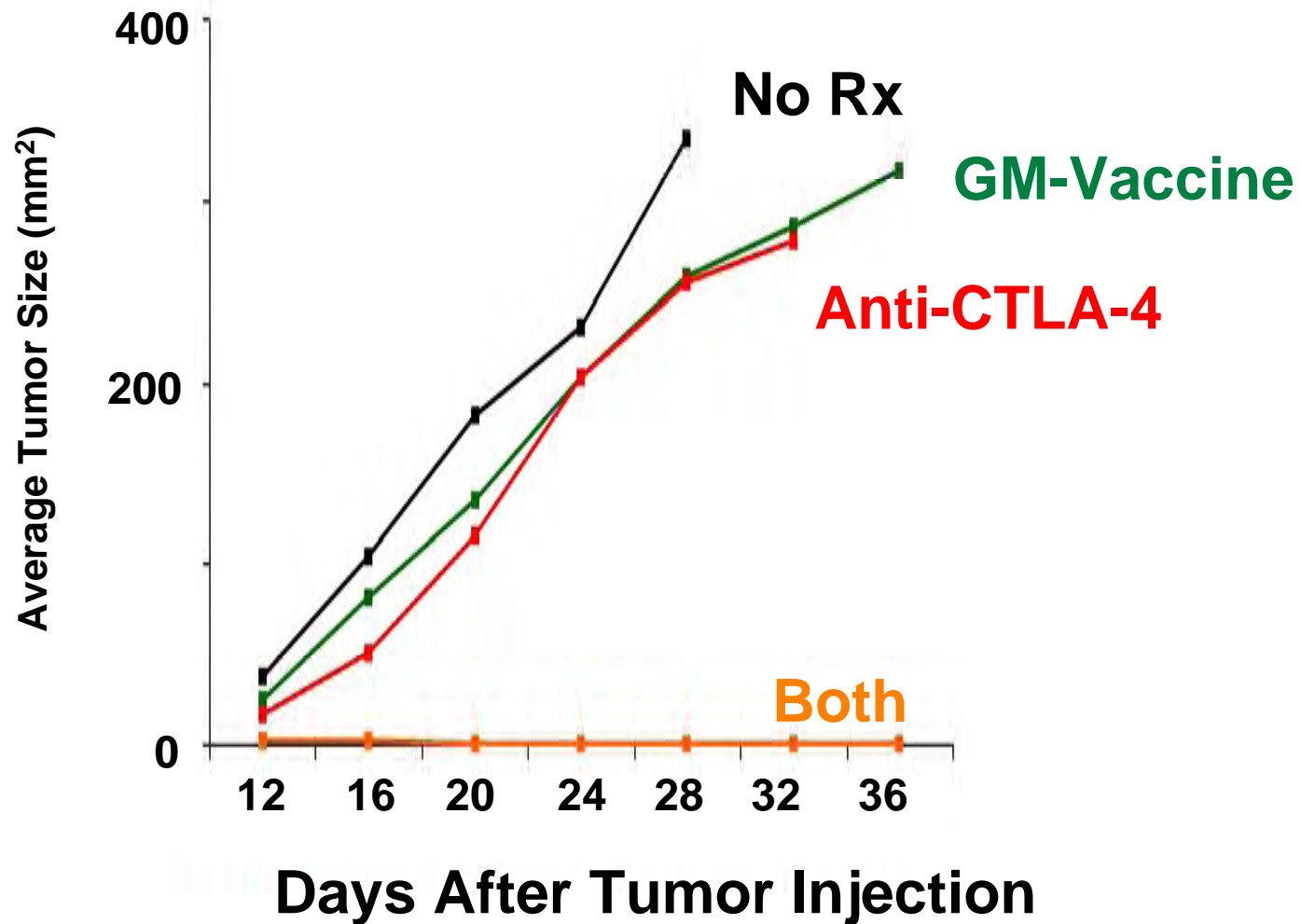
- Necrotic Death
- Vaccines
- Chemotherapy
- Irradiation
- Hormone therapy
- Anti-angiogenesis
- Antibodies
- “Targeted” Therapies



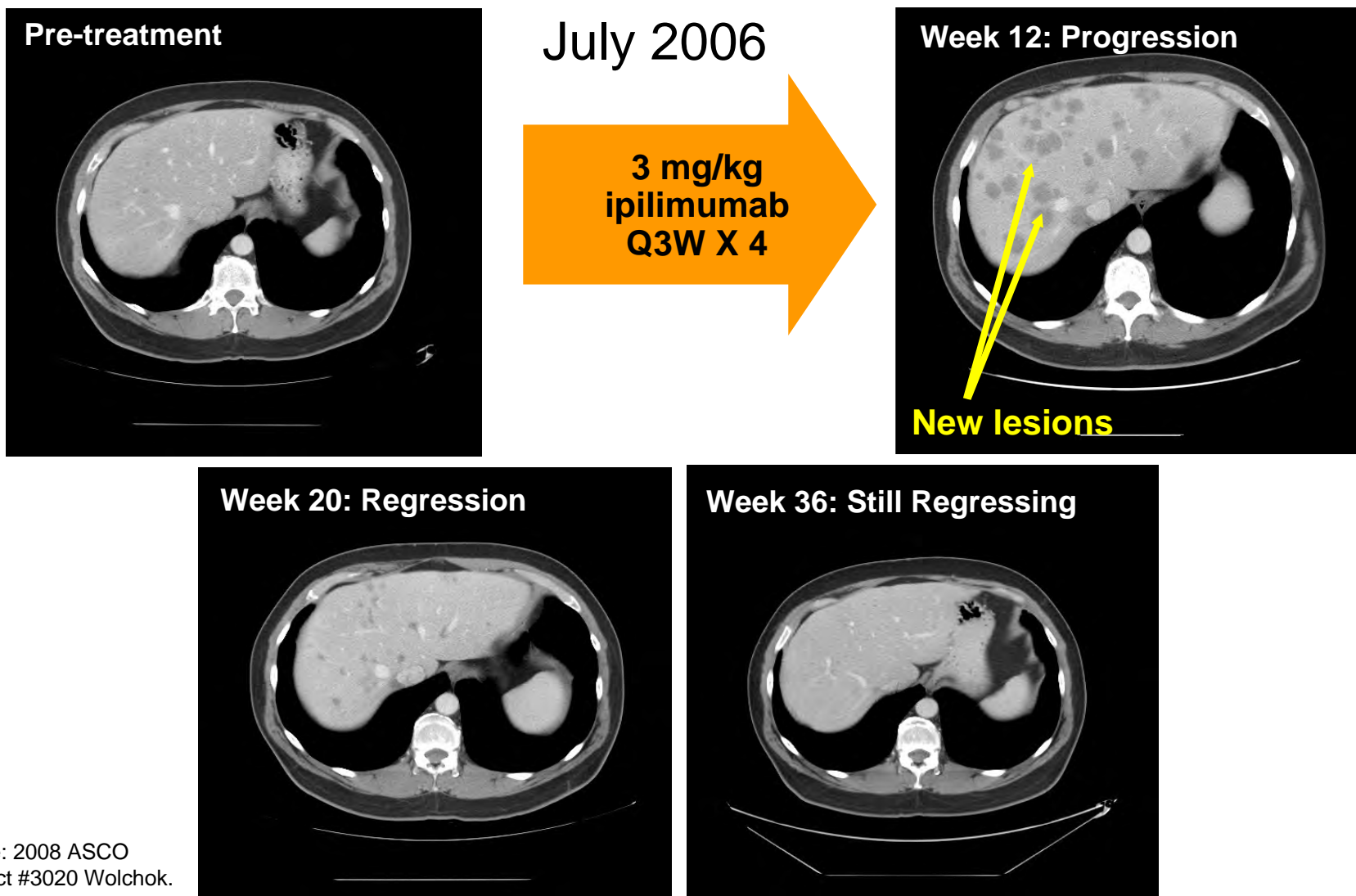
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma



Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma



Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

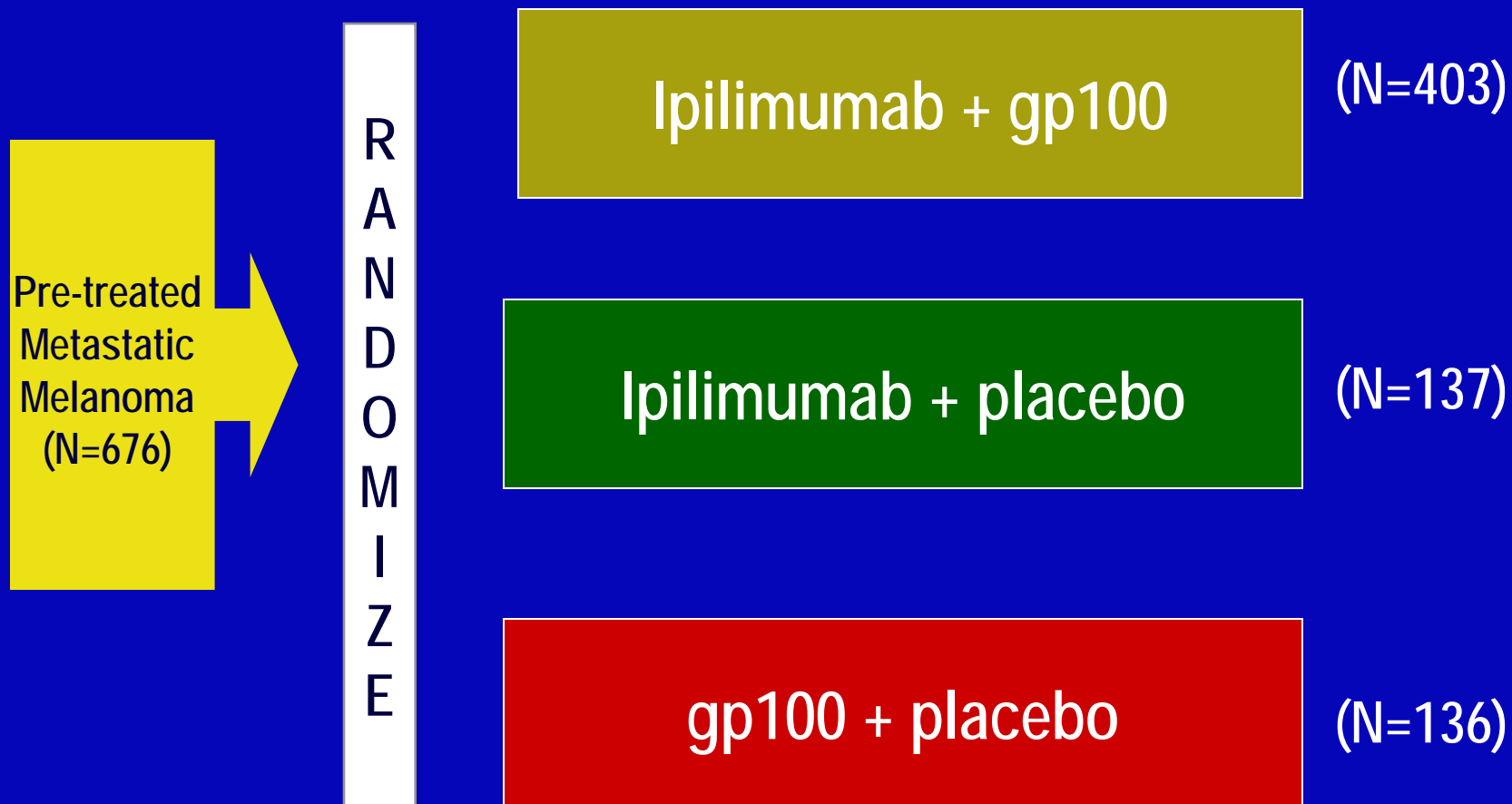


Source: 2008 ASCO
Abstract #3020 Wolchok.

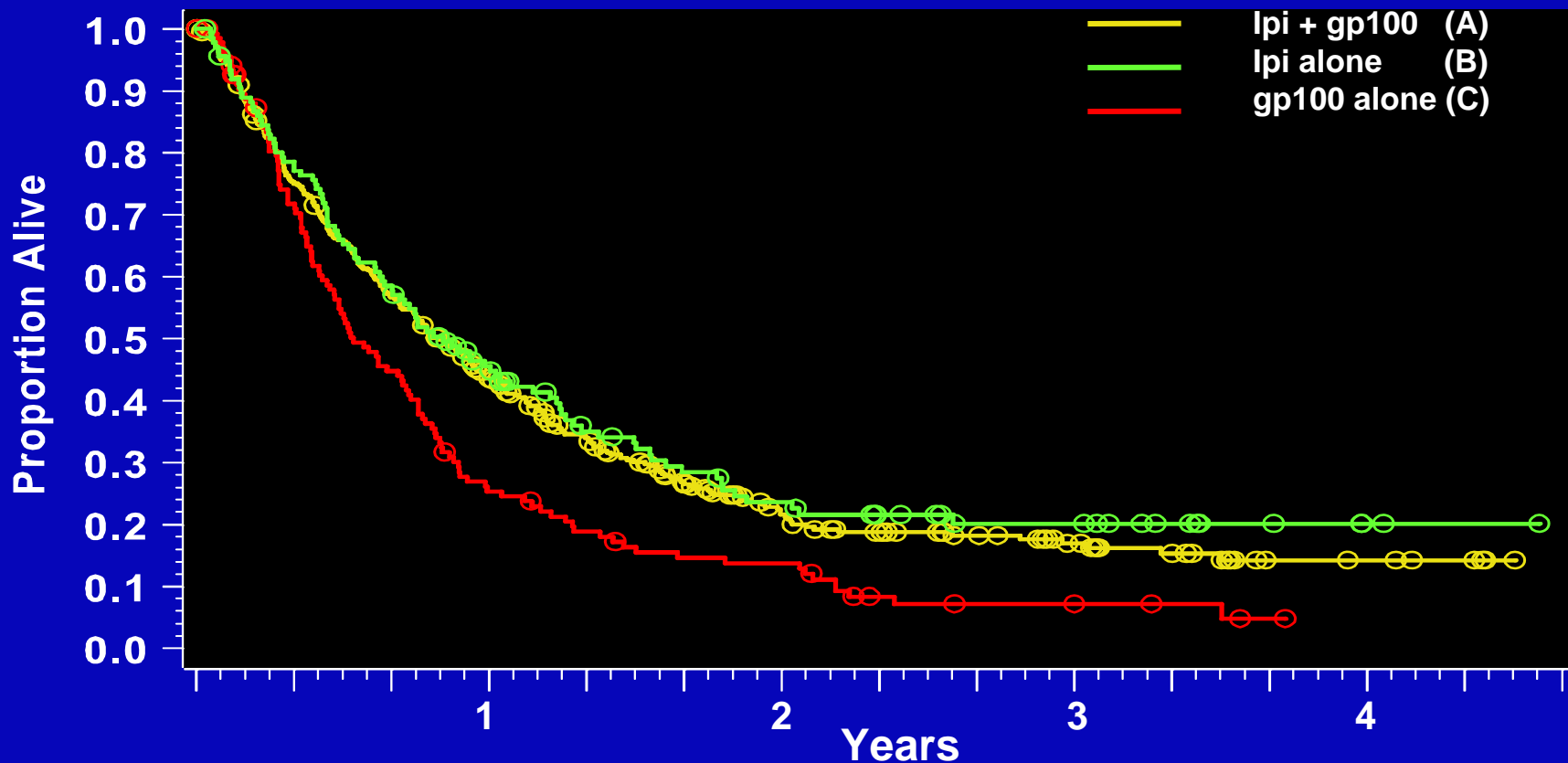
Hypopigmentation



MDX010-20: Study Design

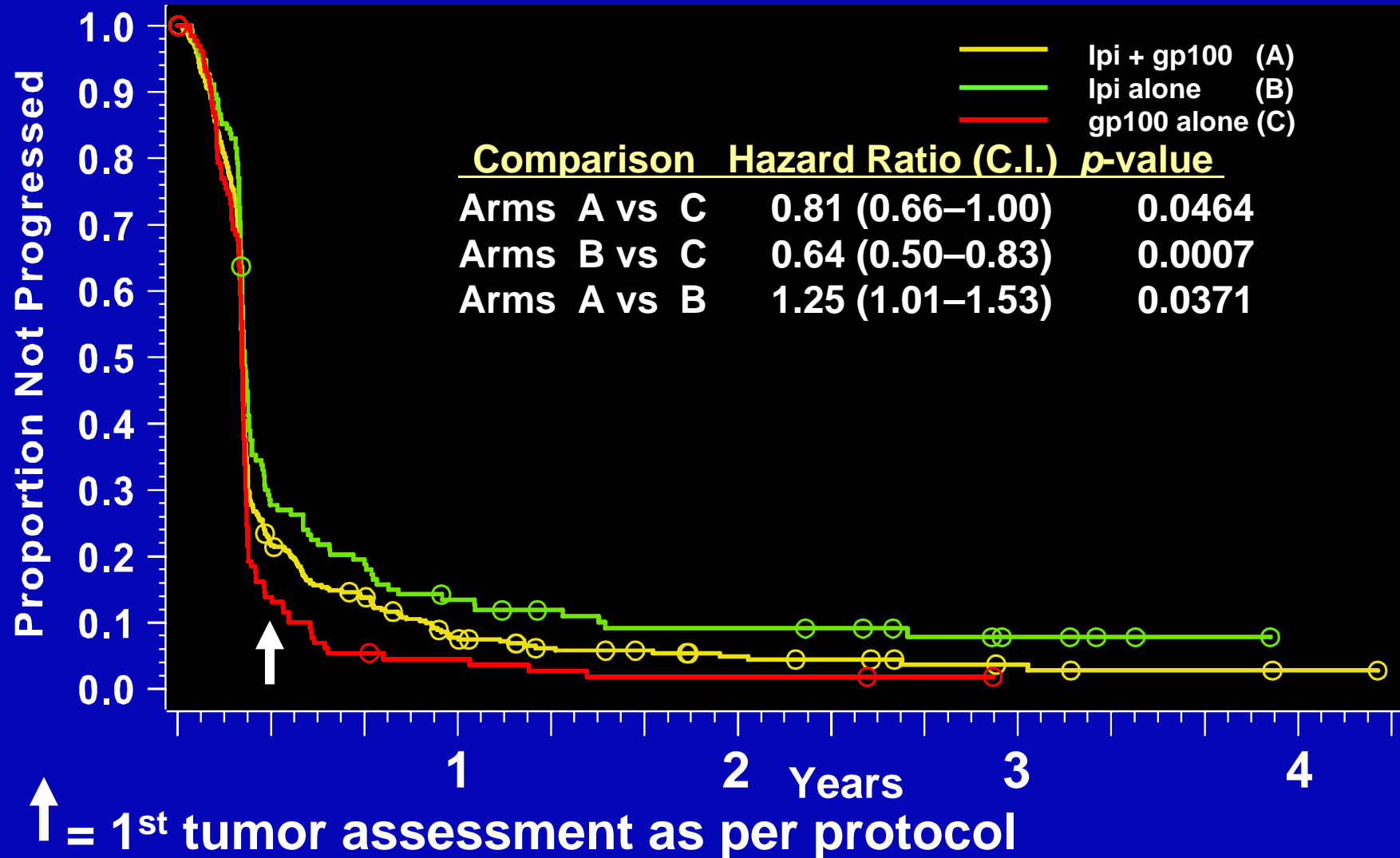


Kaplan-Meier Analysis of Survival



Survival Rate	Ipi + gp100 N=403	Ipi + pbo N=137	gp100 + pbo N=136
1 year	44%	46%	25%
2 year	22%	24%	14%

PFS: Impact of Both Ipilimumab Regimens vs gp100



Ipilimumab Improves Best Objective Response Rate (BORR)

	Arm A Ipi + gp100 N=403	Arm B Ipi + pbo N=137	Arm C gp100 + pbo N=136
BORR, %	5.7	10.9	1.5
P-value: A vs C	0.0433		
P-value: B vs C	0.0012		
DCR[‡], %	20.1	28.5	11.0
P-value: A vs C	0.0179		
P-value: B vs C	0.0002		

[‡]Disease control rate: percentage of patients with CR, PR, or SD

Vaccines and CTLA-4 Blockade

- Pre-clinical models in melanoma support synergy
- Clinical trial shows equivalent overall survival but inferior response and disease control rates
 - Correct vaccine?
 - Antigen escape?
 - Polarization of response?
 - Antigen sink?

CTLA-4 Blockade: A Case Study for Immunotherapy in Need of Biomarkers

Knowns

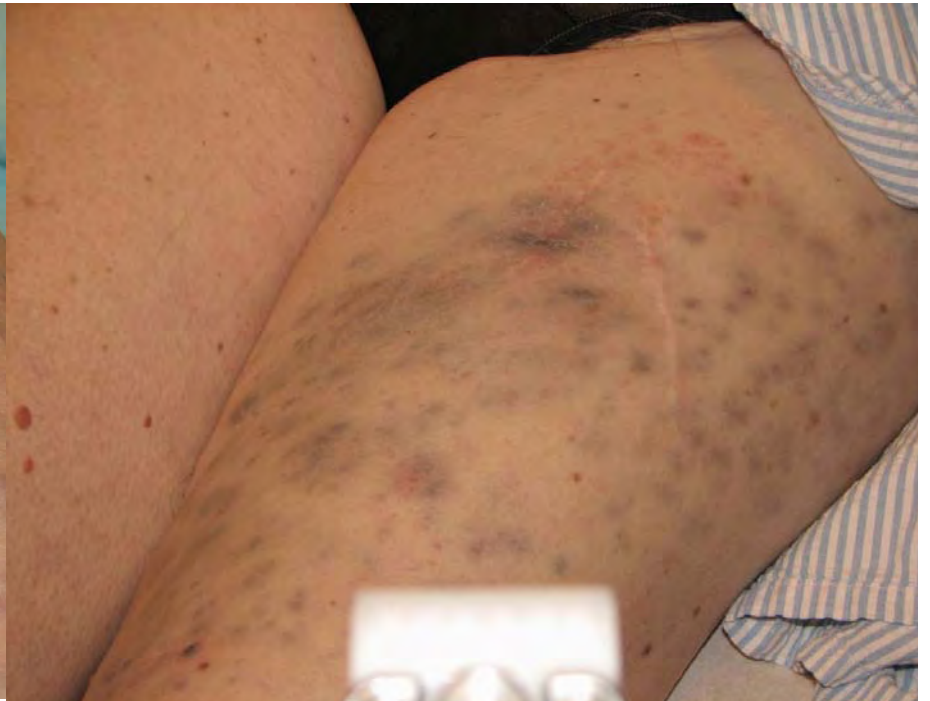
- Clinical benefit for a subset of patients with refractory melanoma
- Reversible mechanism-based side effects
- Tumor responses tend to be durable
- Kinetics of response unlike cytotoxics

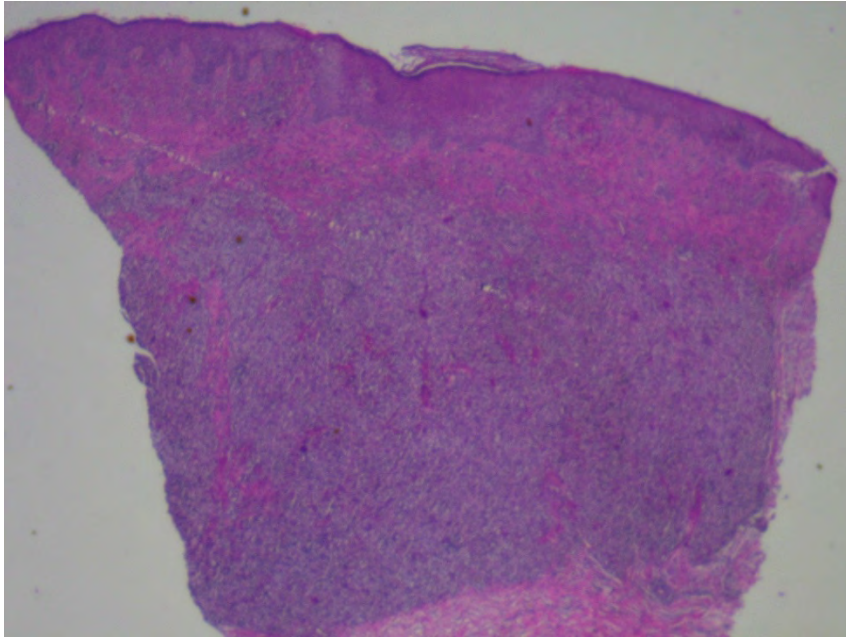
Unknowns

- Biomarkers for response
- Biomarkers for toxicities
- Effect on effector vs regulatory T cells in humans
- Antigens recognized after infusion
- Importance of vaccination before treatment
- Relevance of PBMC vs tumor site findings

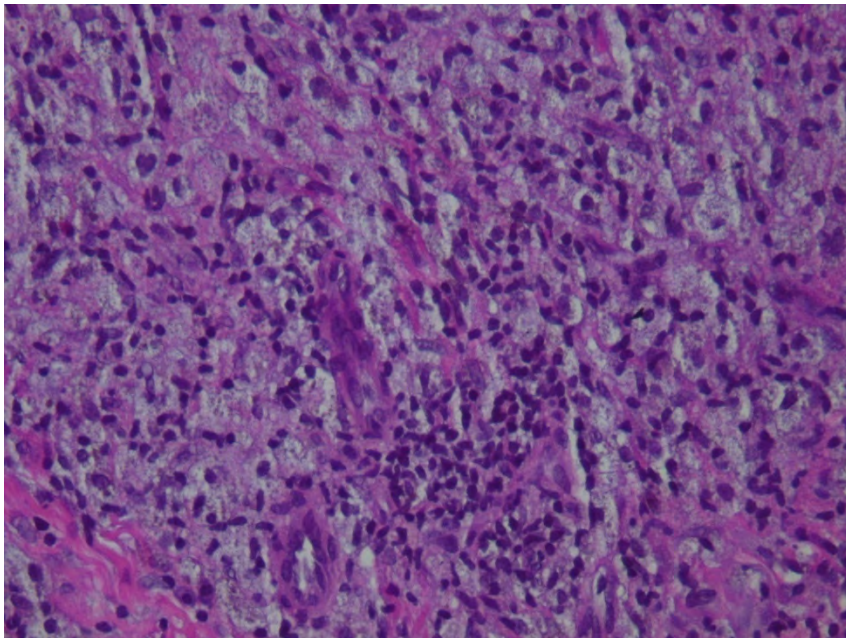
11/28/06

2/12/07

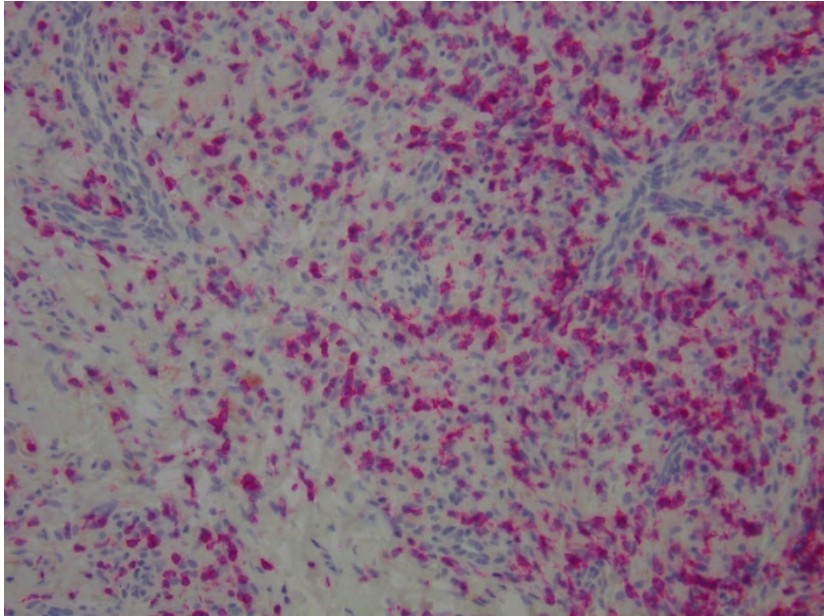




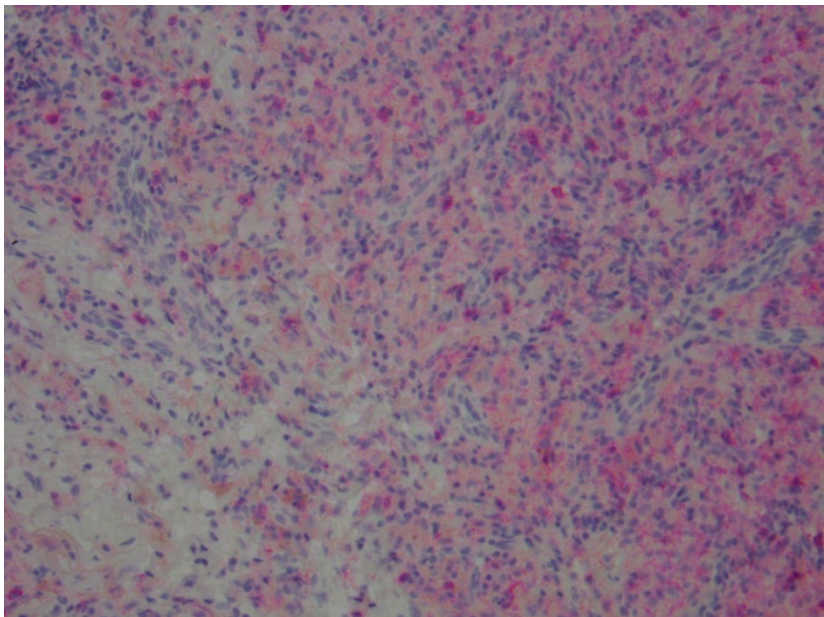
Tumorous nodule
with melanin pigment
(macrophages and
lymphocytes;
no melanocytes)



Macrophages and
lymphocytes are present,
but no tumor cells

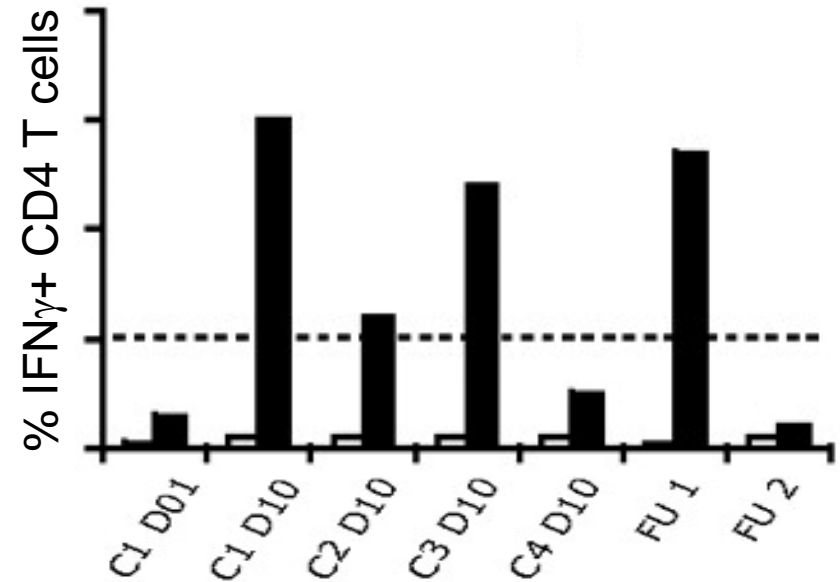
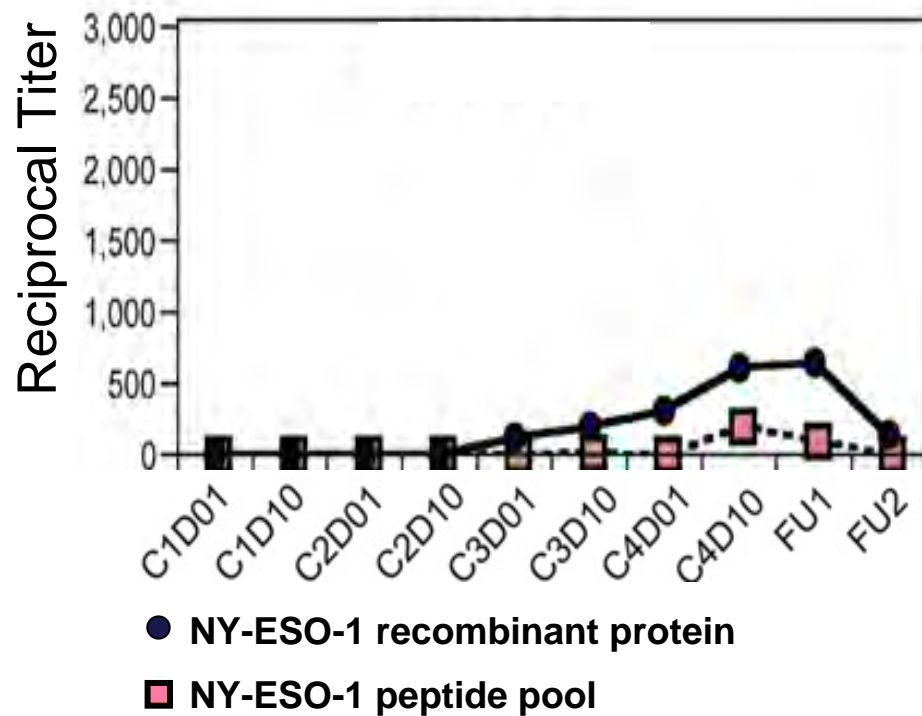


CD8-positive T-cells



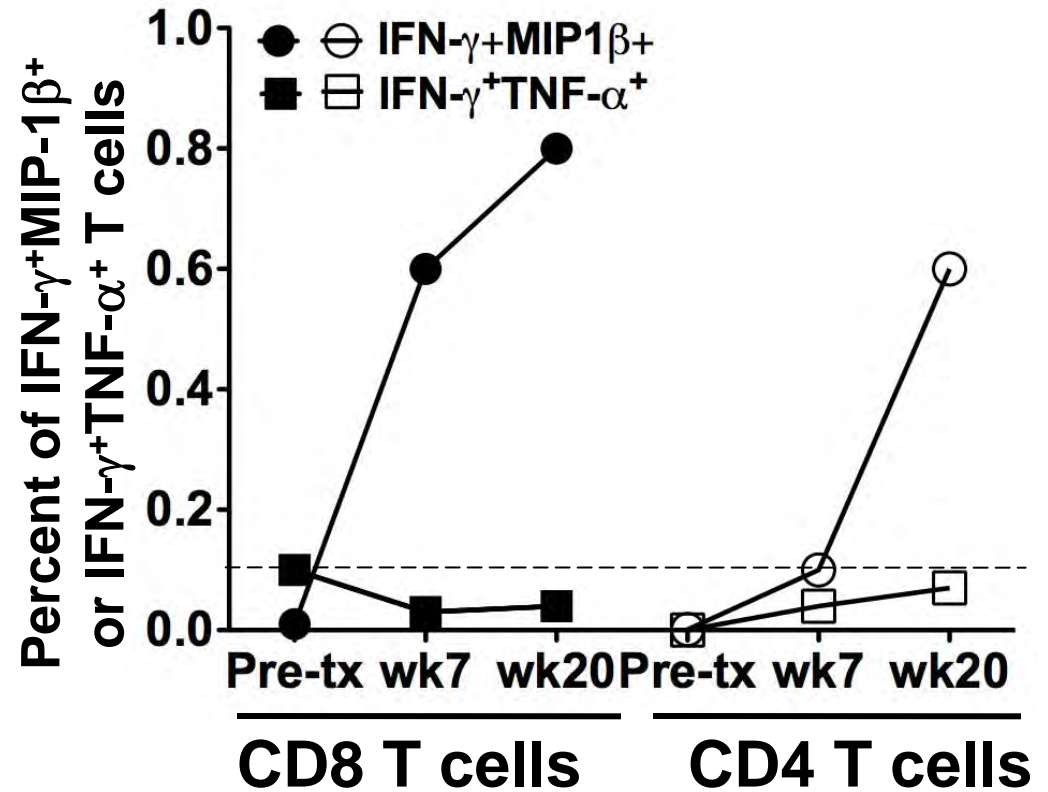
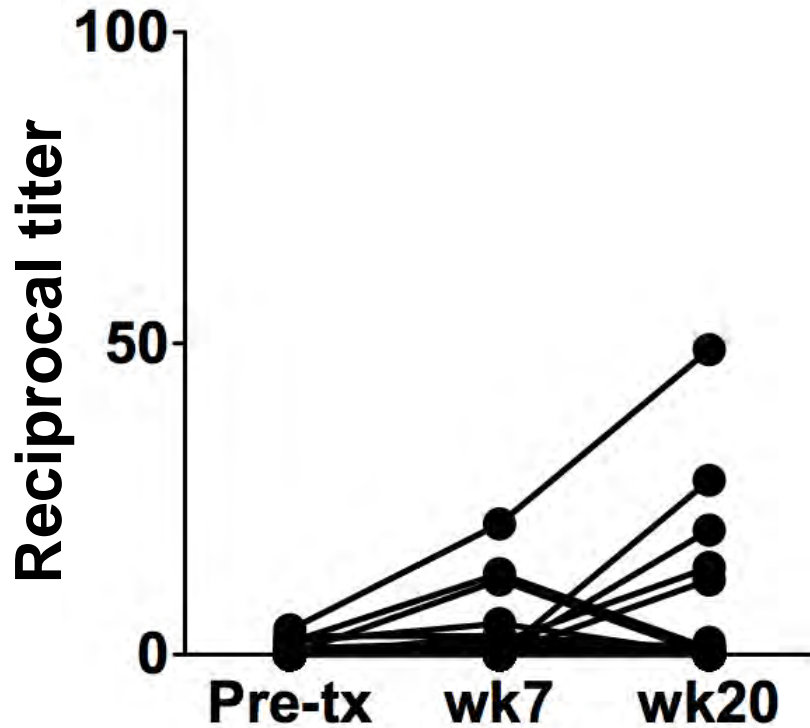
CD4-positive T-cells
(macrophages are also
weakly pos for CD4)

NY-ESO-1 antibody and CD4 T-cell response were detected after full-length NY-ESO-1 protein vaccination

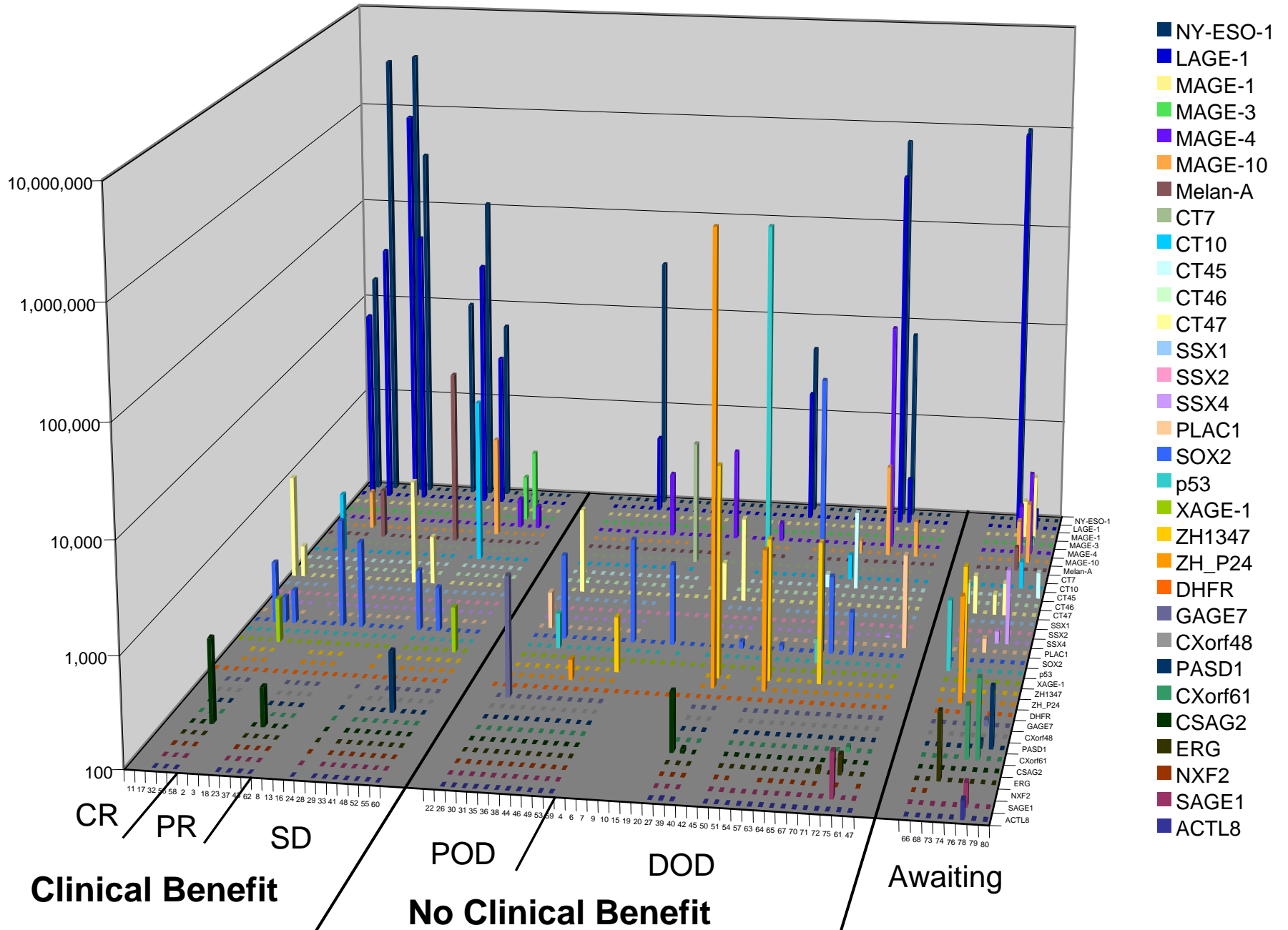


Modified from Adams S et al. *J Immunology* 2008, 181:776

NY-ESO-1 CD4 and CD8 T-cell specific response after CTLA-4 blockade (Patient IMF-11)




Grand Serology in CTLA-4 treated patients (peak response): Correlation with clinical benefit



Correlation of NY-ESO-1 antibody with clinical course following anti-CTLA-4 treatment

Patients with NY-ESO-1 antibodies at any time point during study



Response	# patients Status at wk24 (%)	# NY-ESO-1 SERONEGATIVE Status wk24 (%)	# NY-ESO-1 SEROPOSITIVE Status wk24 (%)
CR	6 (5.1%)	4	2
PR	14 (12.0%)	9	5
SD	25 (21.4%)	19	6
Clinical Benefit	45 (38.5%)	32 (33.7%)	13 (59.1%)
No Clinical Benefit	72 (61.5%)	63 (66.3%)	9 (40.9%)
Total	117 (100%)	95	22

According to Immune-related response criteria:

Fisher's exact test:
P value 0.0498

CR: Complete Response

PR: Partial Response

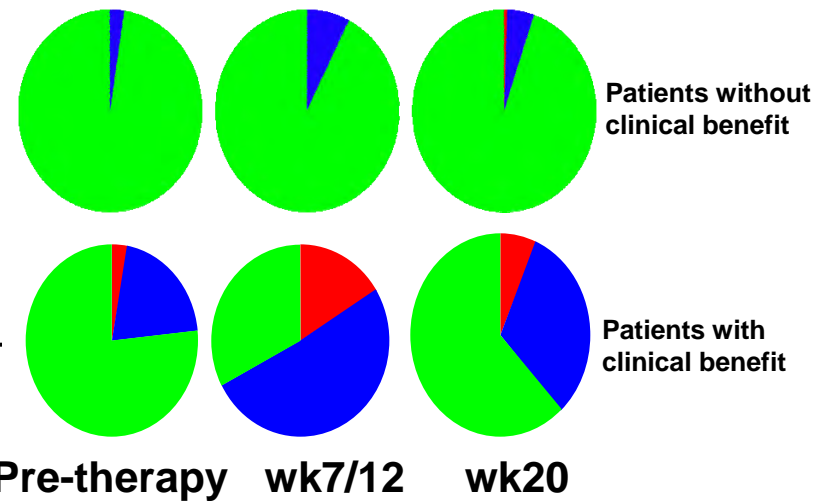
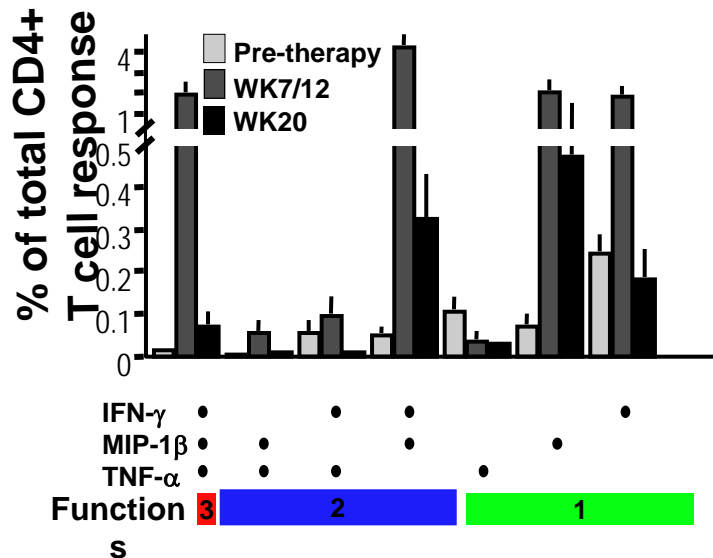
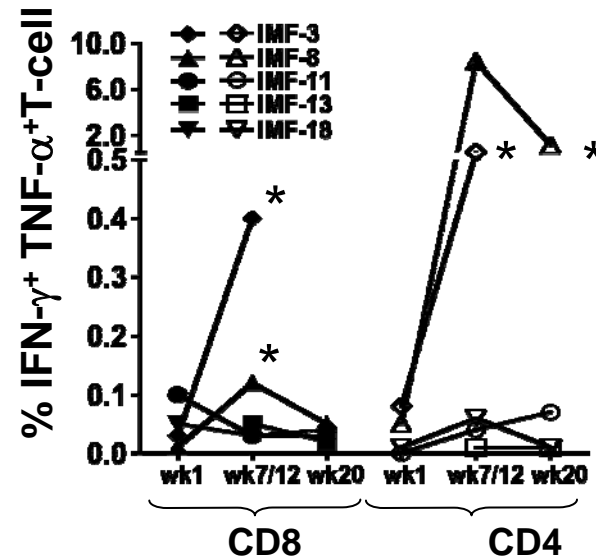
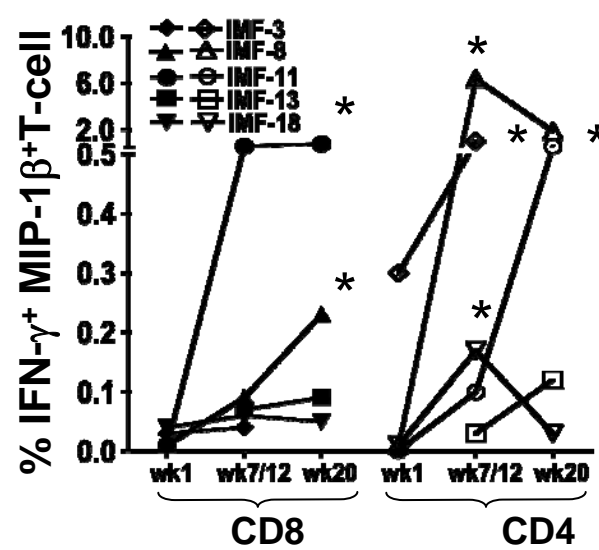
SD: Stable Disease

POD: Progression of Disease (includes MR: mixed response)

DOD: Dead of Disease

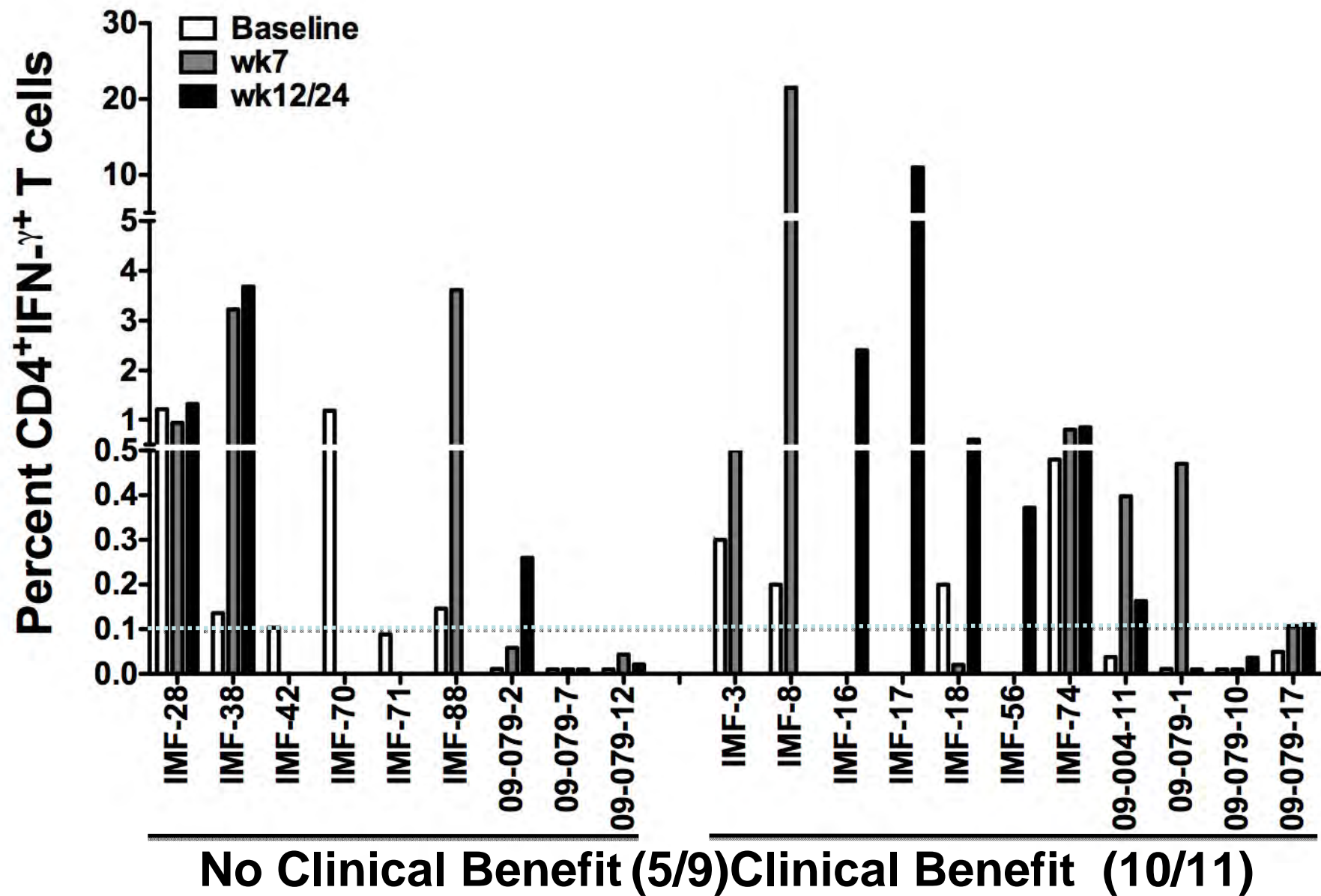
Gnjatic & Wolchok, Ludwig Center/MSKCC
Halaban and Sznol, Yale

Polyfunctional NY-ESO-1 Specific T cells in Blood Of Melanoma Patients Treated with aCTLA-4



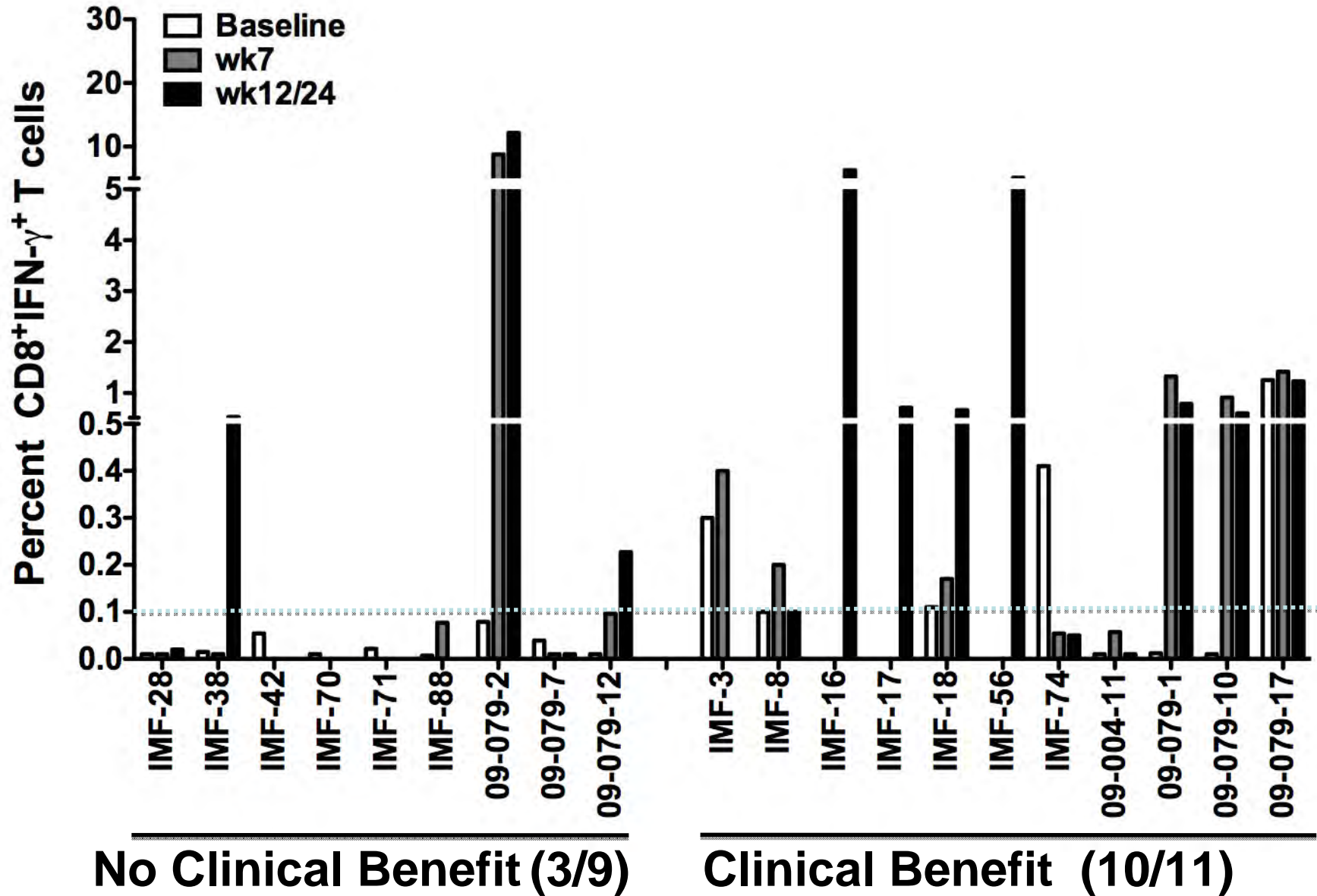
Yuan, Gnjatic, Wolchok

NY-ESO-1 antigen-specific CD4 T cell response



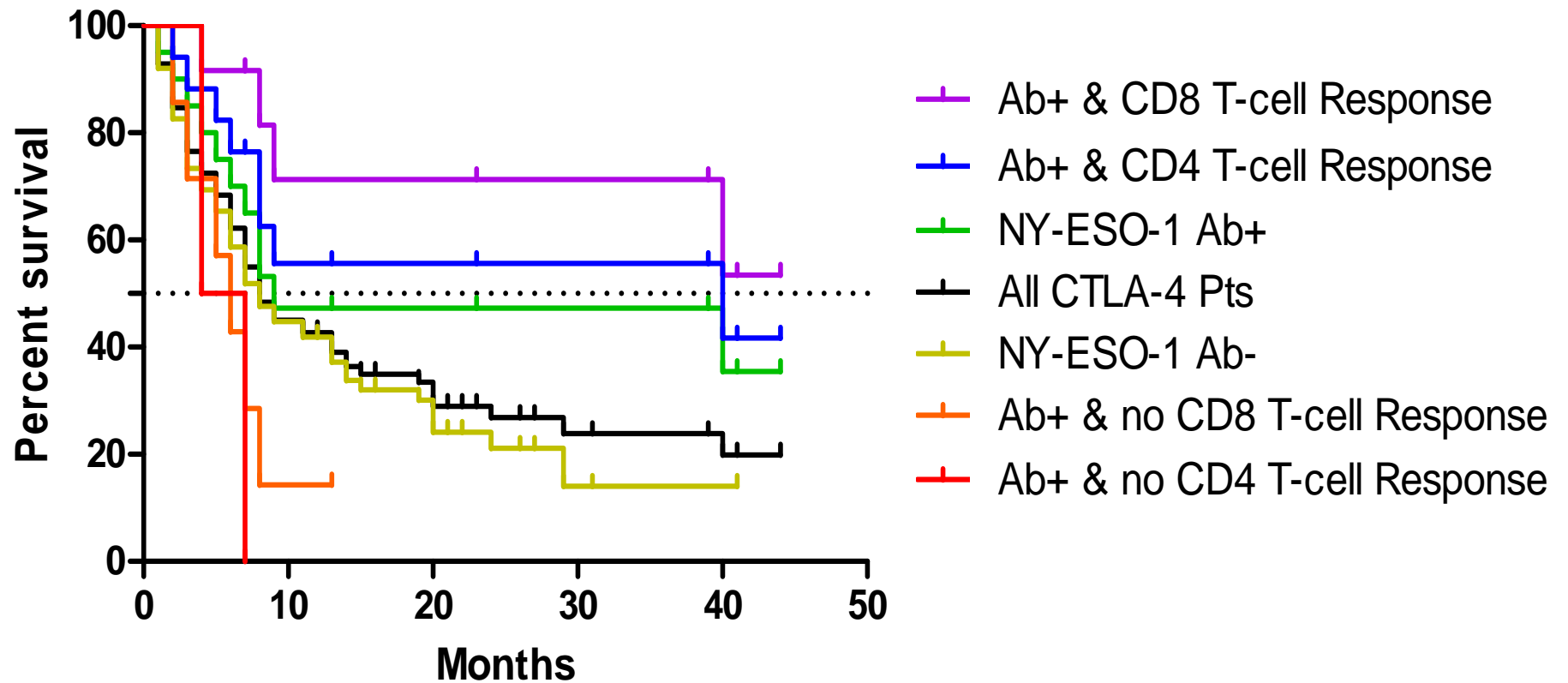
P=0.127 by Fisher's Exact Test

NY-ESO-1 antigen-specific CD8 T cell response

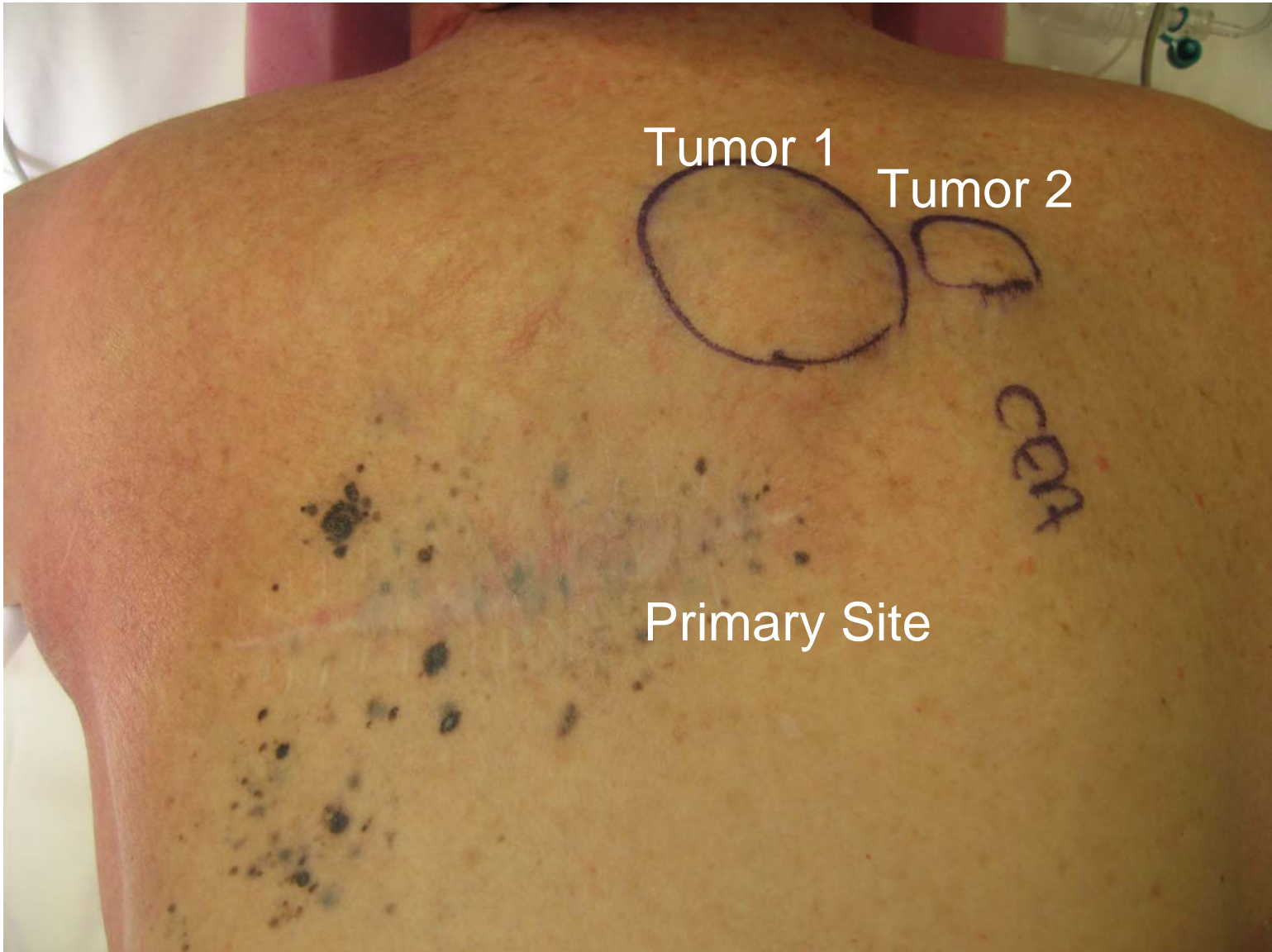


P=0.016 by Fisher's Exact Test

Kaplan-Meier Overall Survival Curve



NY-ESO-1 seropositivity with a CD8+ T-cell response correlates with survival (median survival not reached vs. 8 months, $p=0.0158$).



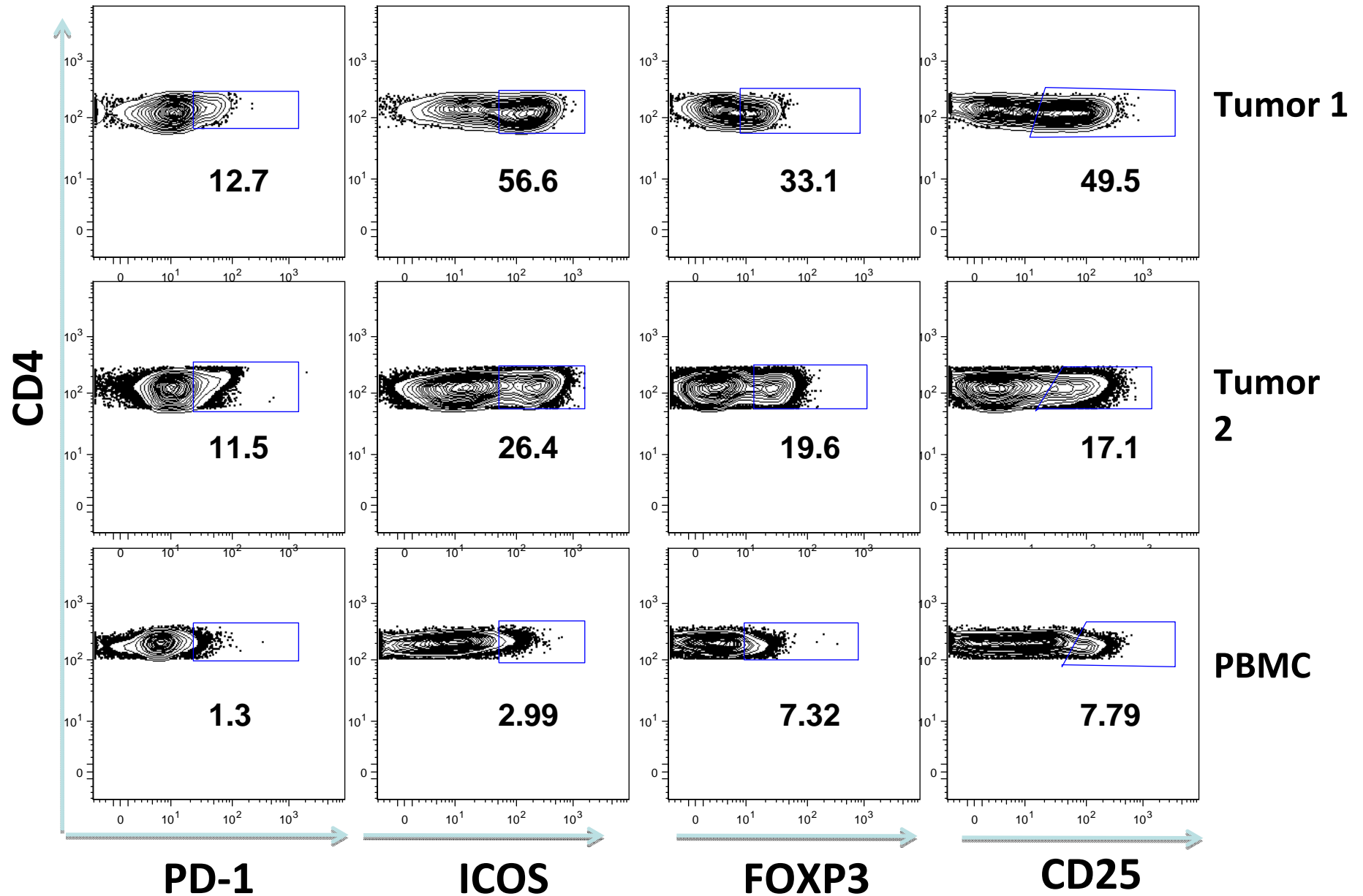
Tumor 1

Tumor 2

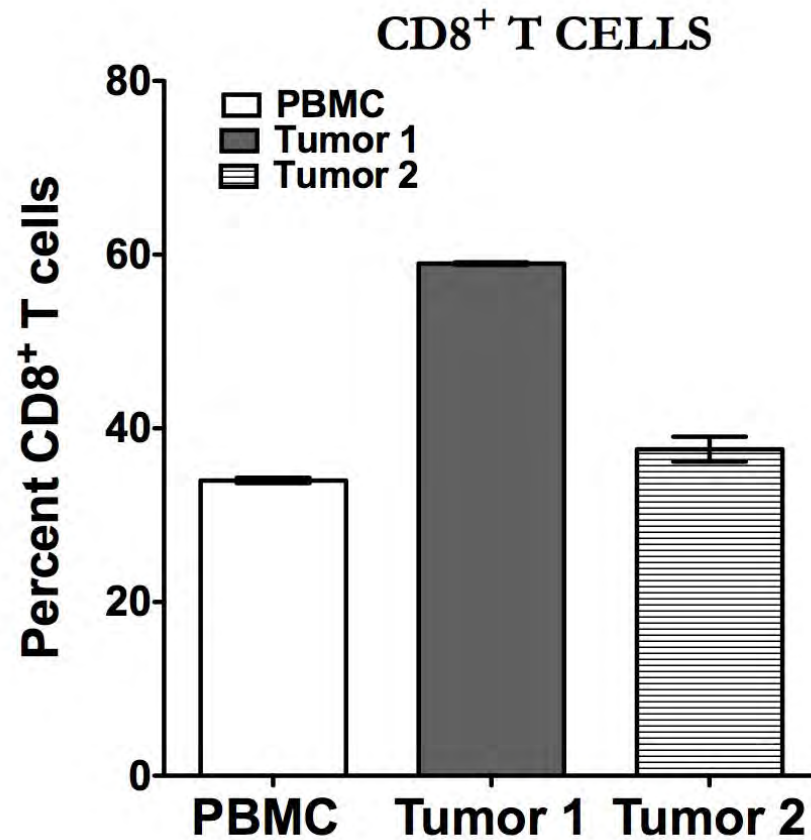
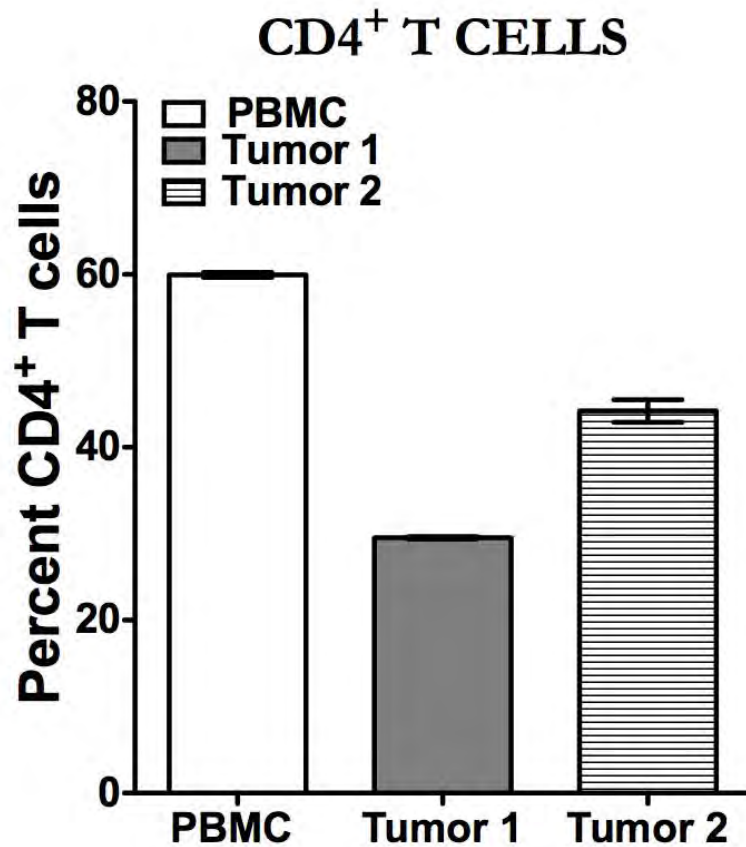
Primary Site

CER

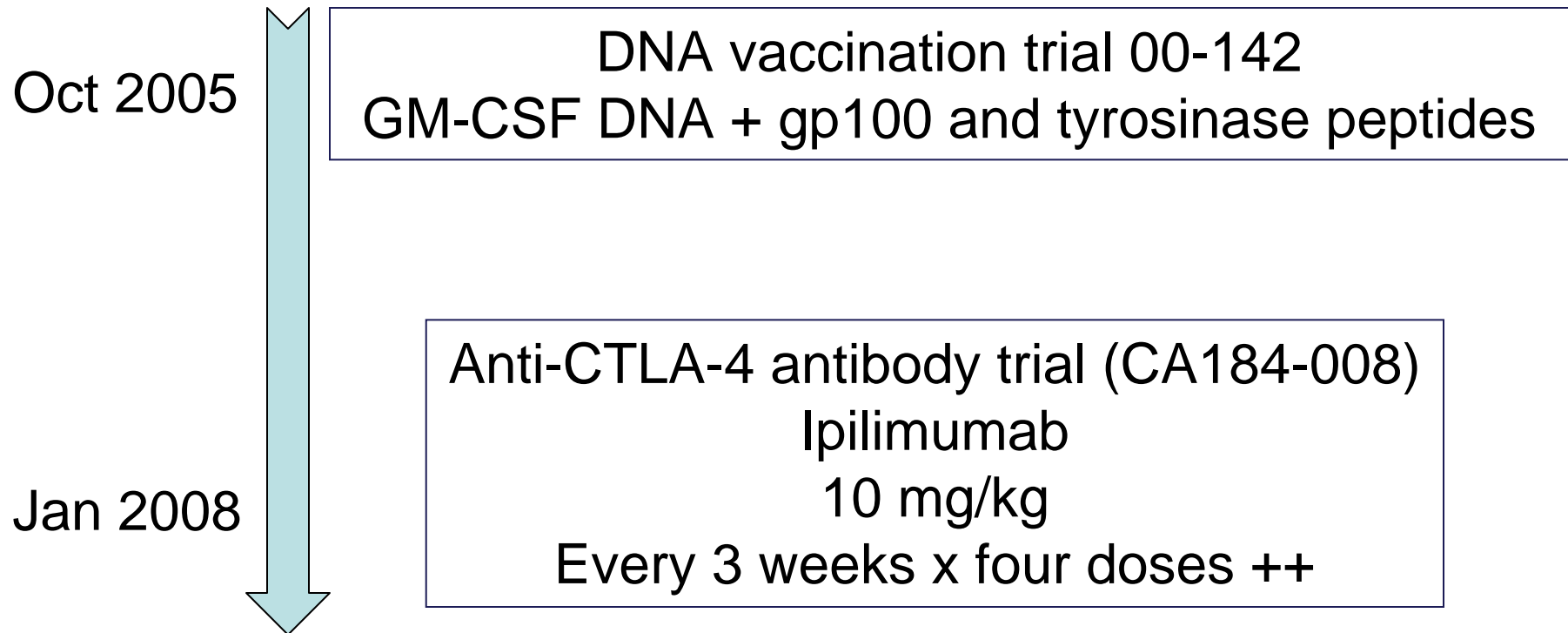
PHENOTYPE OF PBMCS (PT. IMF-91E) & TUMORS (00-144-413)



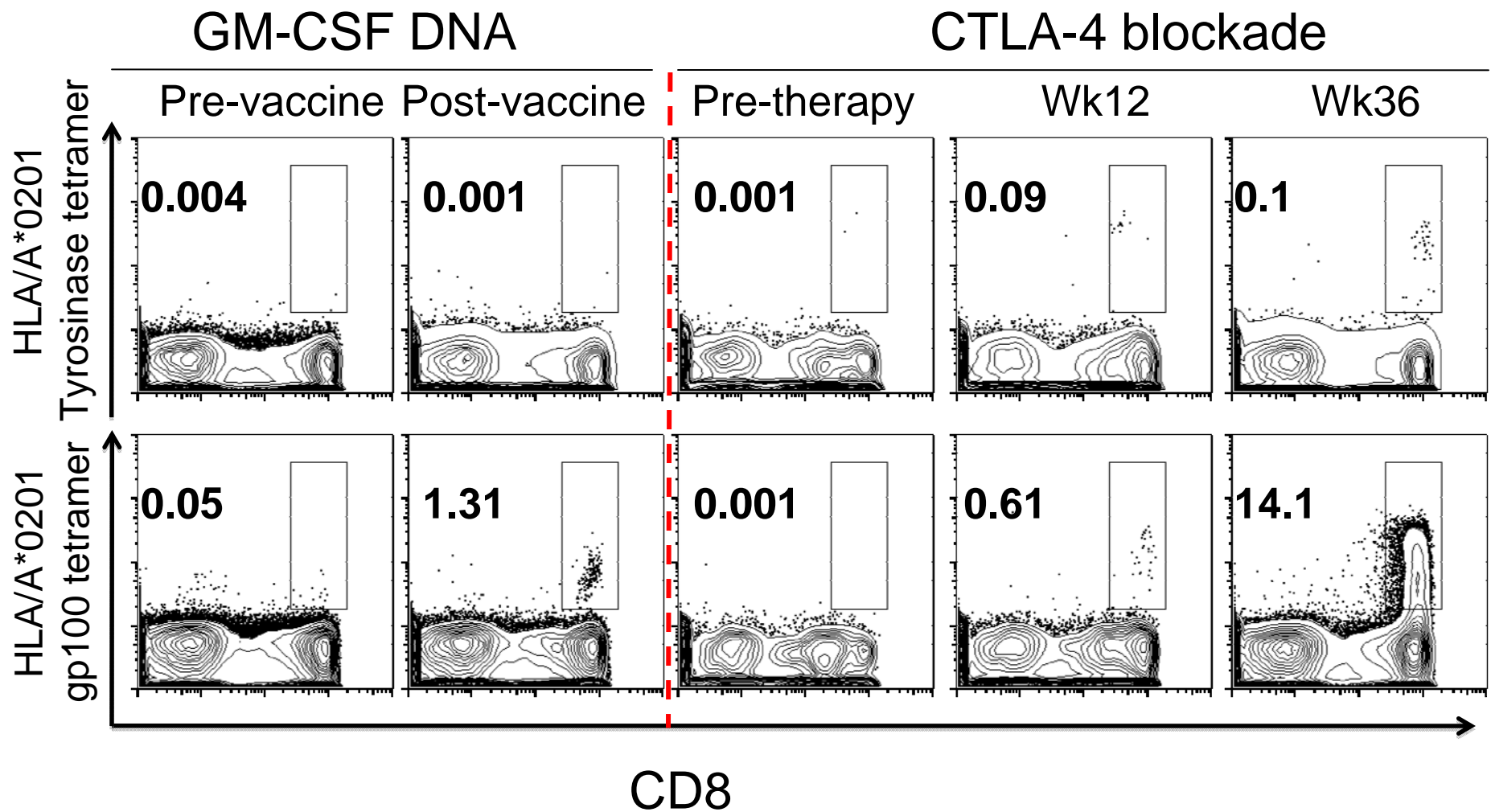
PHENOTYPE OF PBMCs (PT. IMF-91E) & TUMORS (00-144-413)



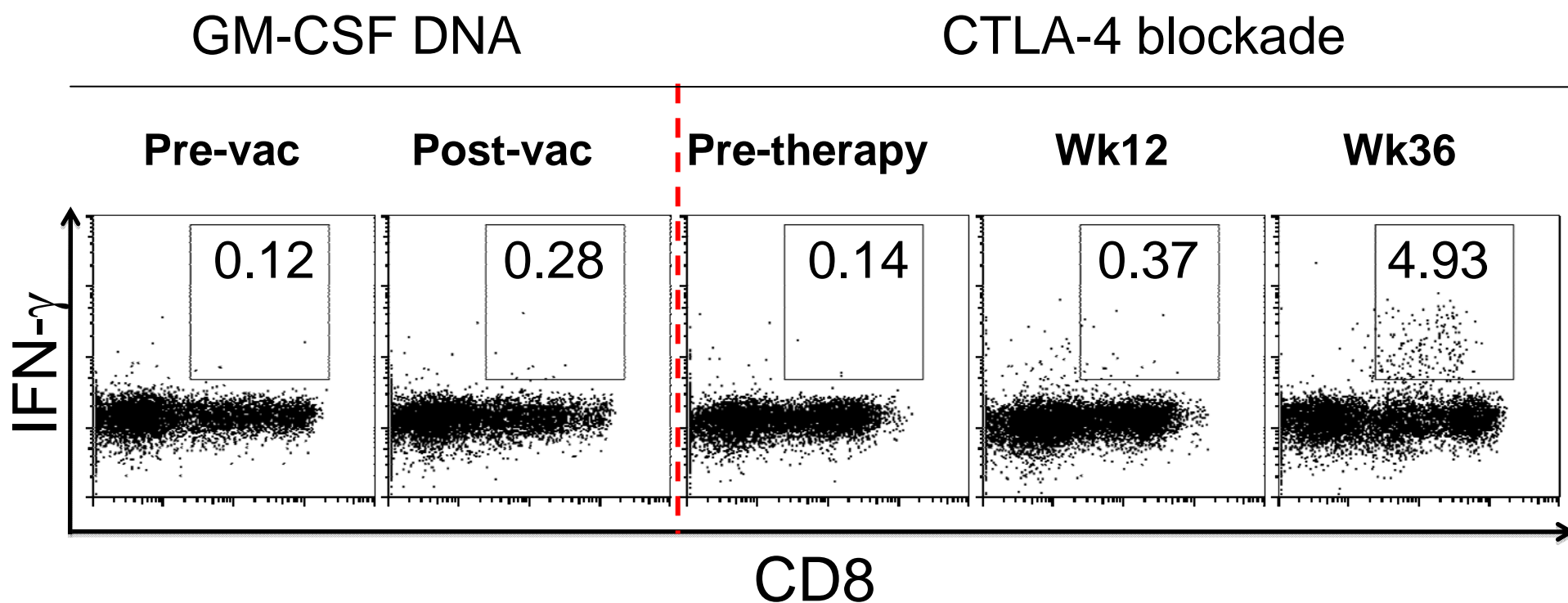
Tyrosinase and gp100 specific immunity in patient IMF-32



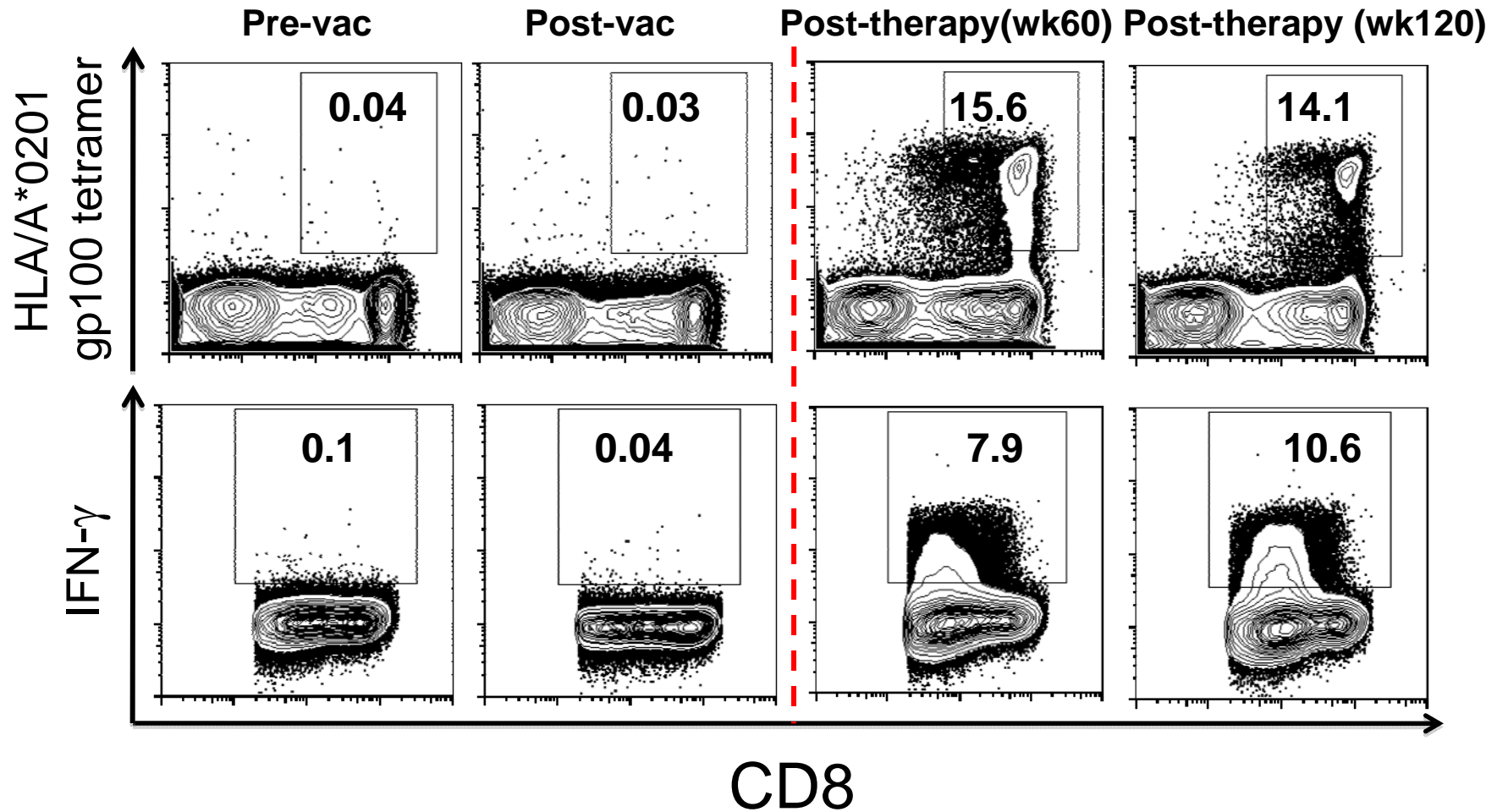
Tyrosinase and gp100 antigen-specific response during GM-CSF DNA and CTLA-4 blockade



Gp100 specific CD8 T-cell response during GM-CSF DNA and CTLA-4 blockade



CD8 gp100²⁰⁹ specific T-cell response during gp100 DNA vaccine and CTLA-4 blockade (patient IMF-24)

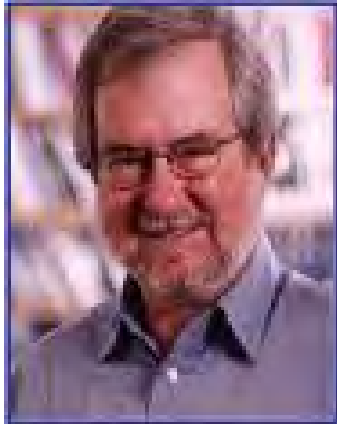


Summary

- CTLA-4 blockade with ipilimumab results in prolonged survival of patients with refractory melanoma.
- Clinical response has been associated with: changes in ALC, NY-ESO-1 immunity and induction of ICOS expression on CD4+ T cells. These require prospective evaluation in ongoing clinical trials.
- De novo immune responses to self antigens has been manifest by autoimmune hypopigmentation.
- Tumor microenvironment is fertile ground to study the mechanism underlying immunologic checkpoint blockade.

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Jim Allison



Lloyd Old



Alan Houghton



Sacha Gnjatc



Charlotte Ariyan



Jianda Yuan & the IMF Crew



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