Immune Checkpoint Blockade in Cancer Therapy: New Insights and Opportunities

Jim Allison
Ludwig Center for Cancer Immunotherapy
Howard Hughes Medical Institute
Department of Immunology
Memorial Sloan-Kettering Cancer Center

2010 Smalley Lecture
iSBTc

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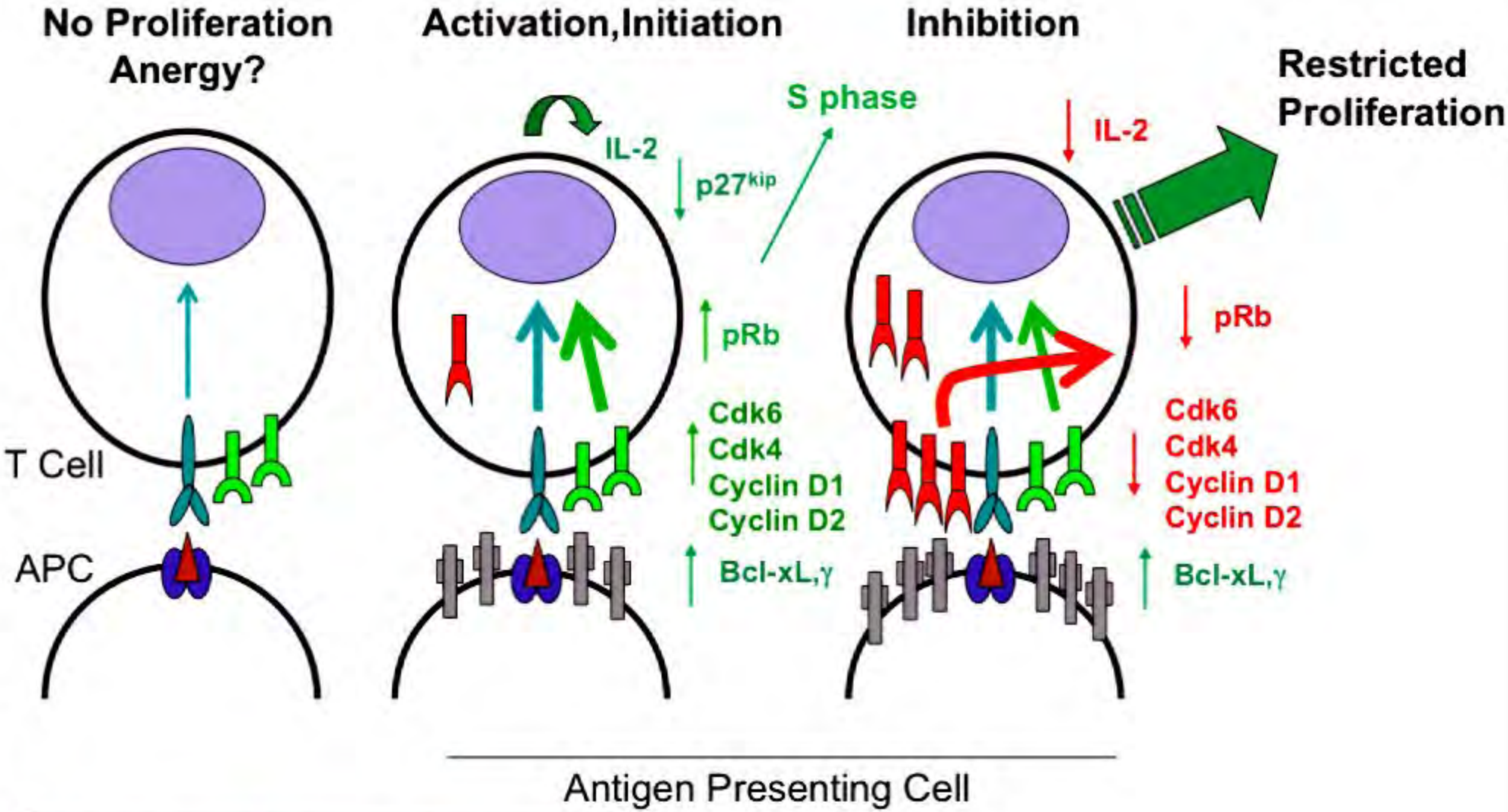
Consultant for Bristol Meyers-Squibb

Dynamic Integration of TCR and Costimulatory Signals



Gross, Harding,
Krummel, Chambers, Brunner, Egen, Kuhns

Localization of CD28 and CTLA-4 to the T Cell-APC Interface

CD28

CTLA-4

~ 5 minutes

Egen

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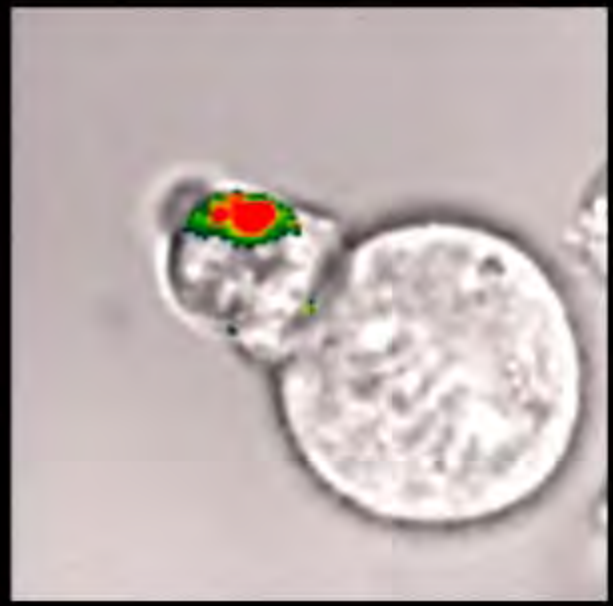

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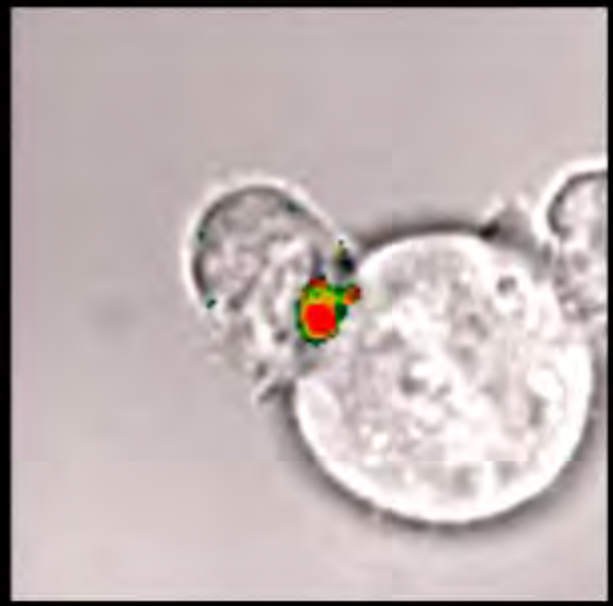

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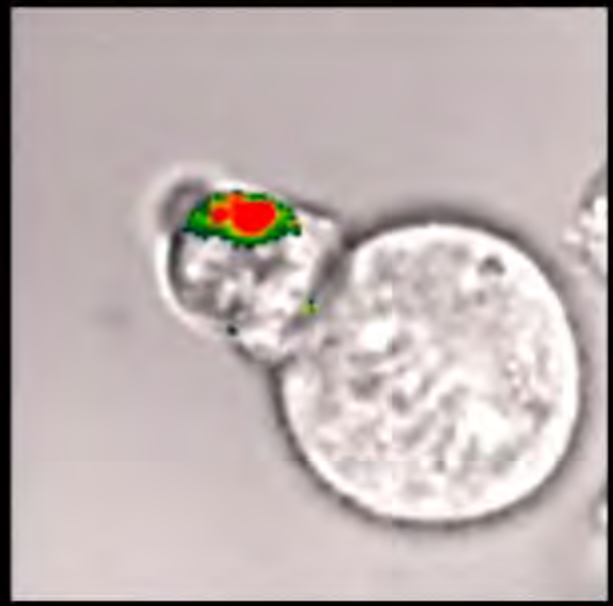

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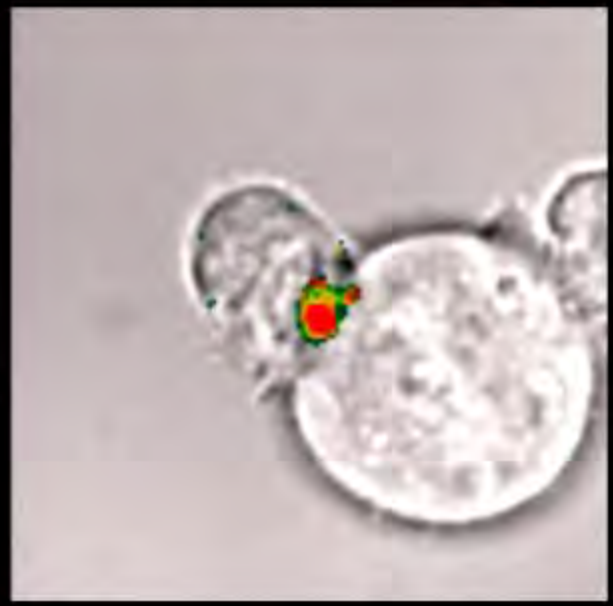

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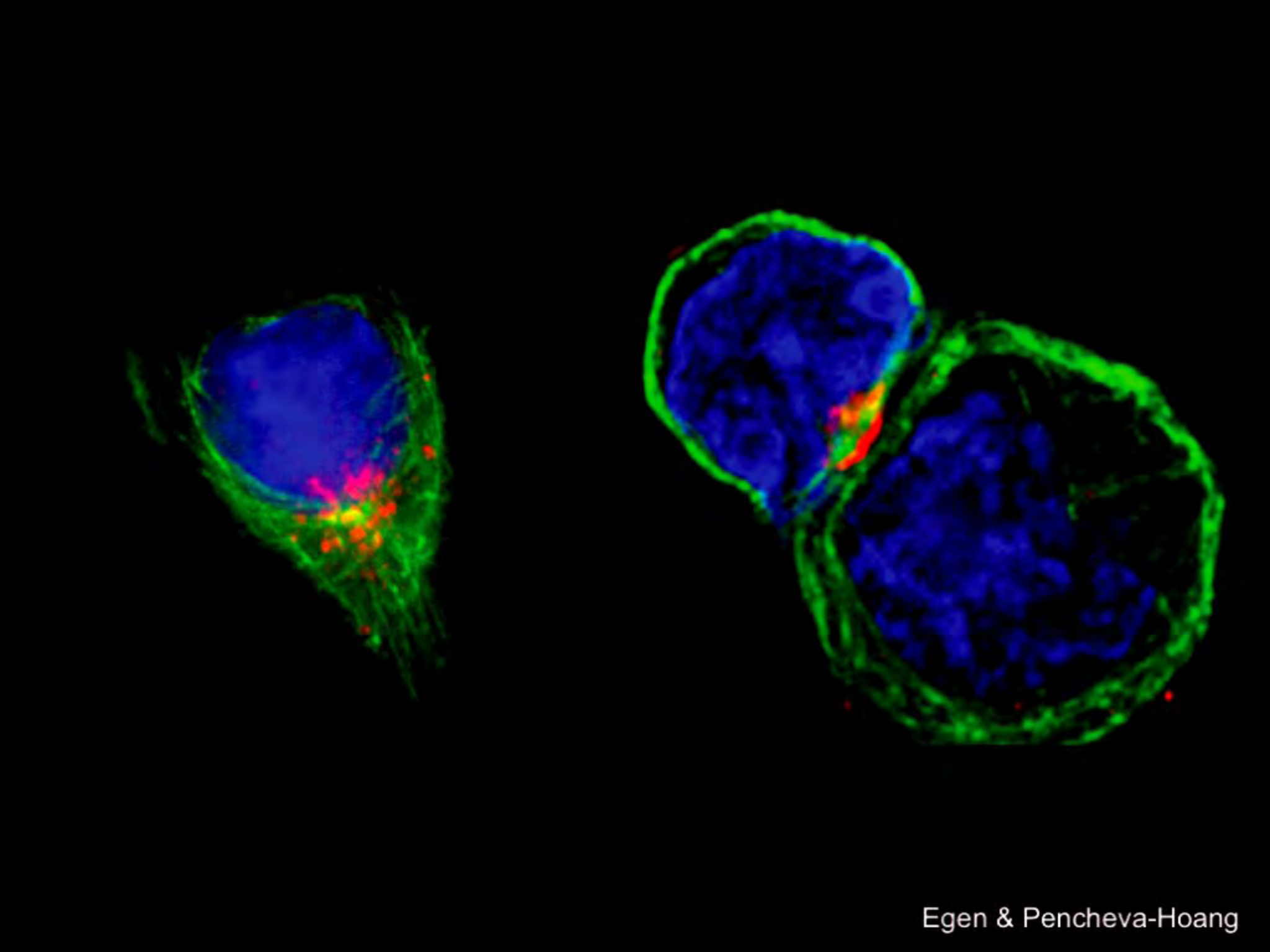
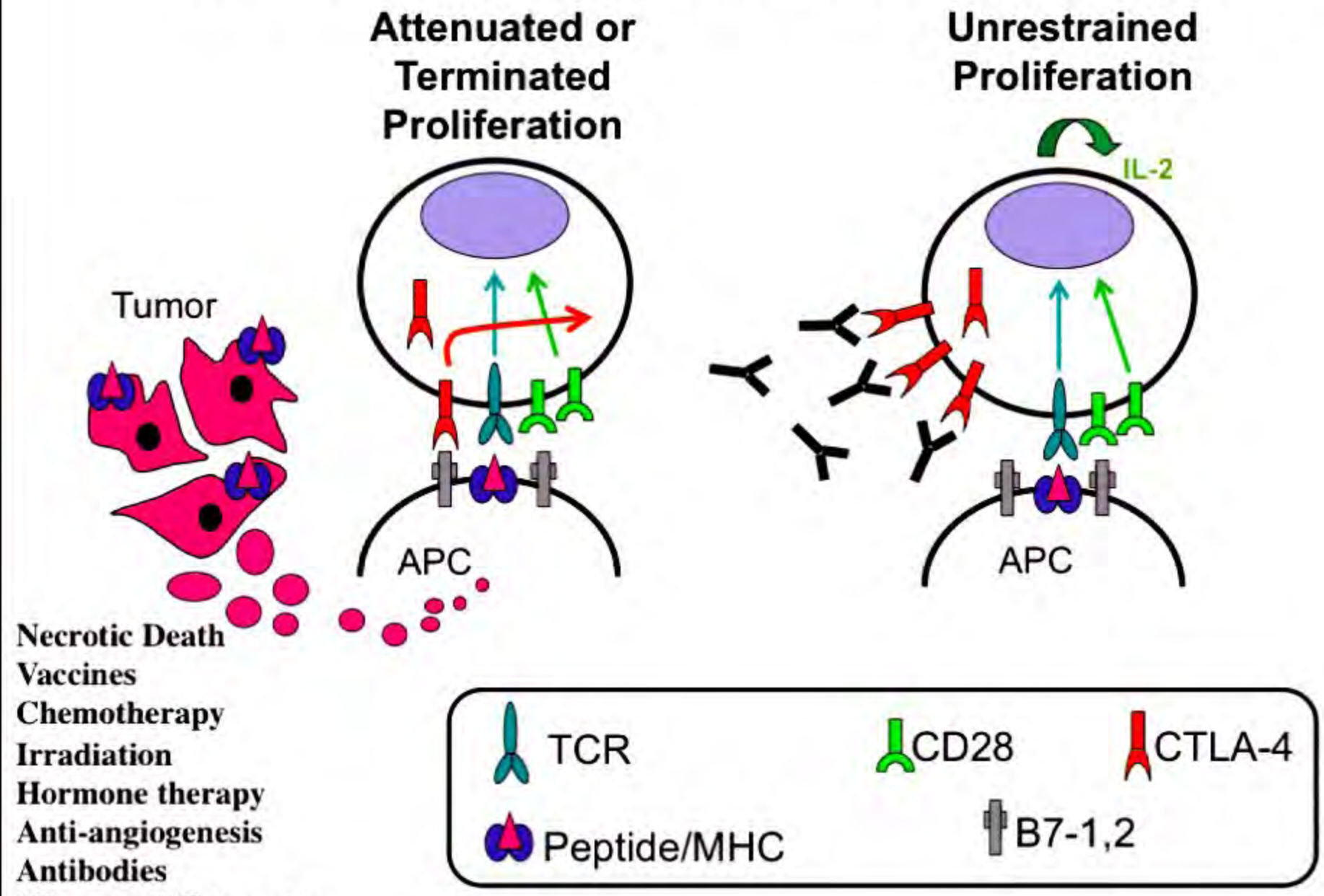
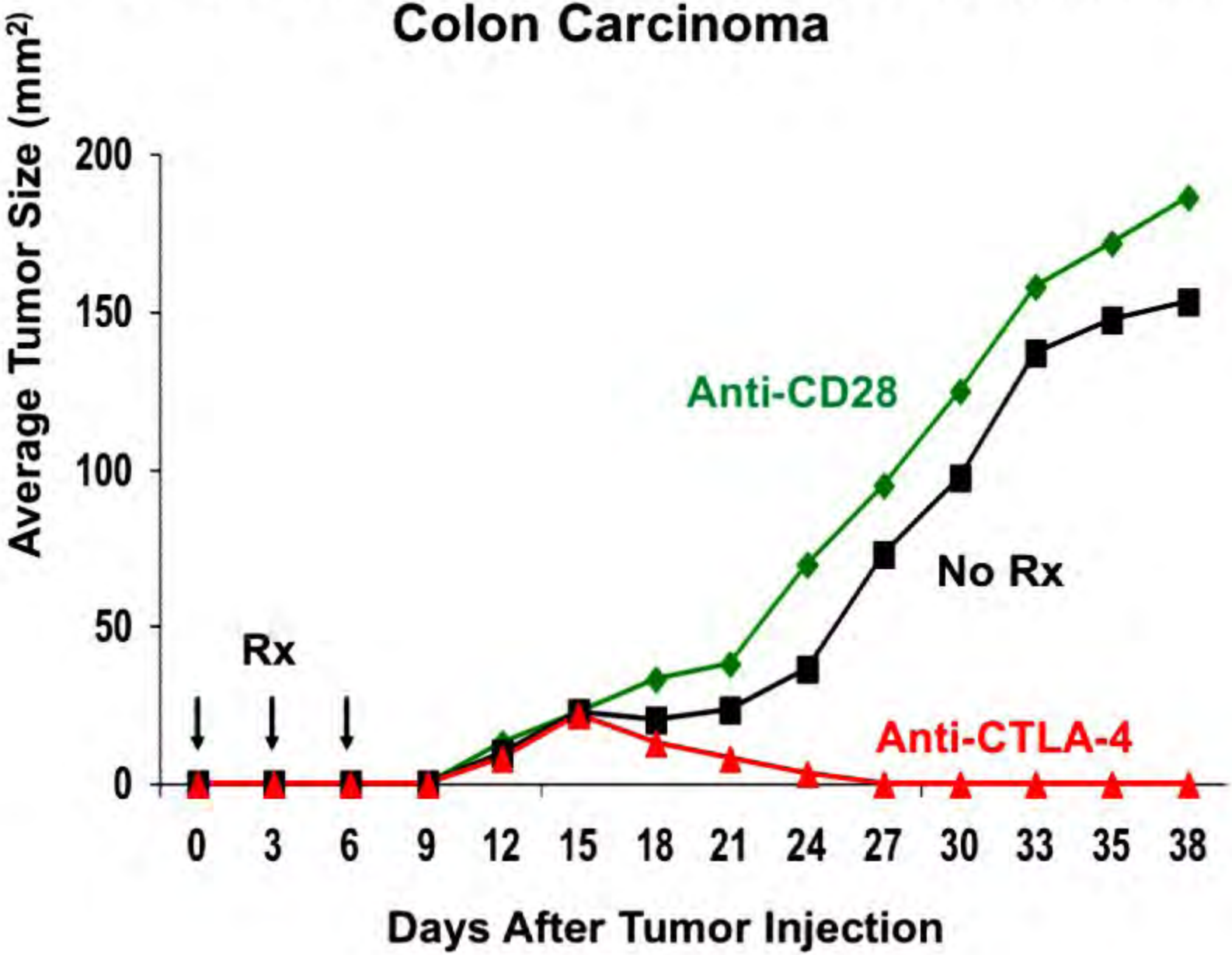

Egen & Pencheva-Hoang

CTLA-4 Blockade
Enhances Tumor-Specific Immune Responses

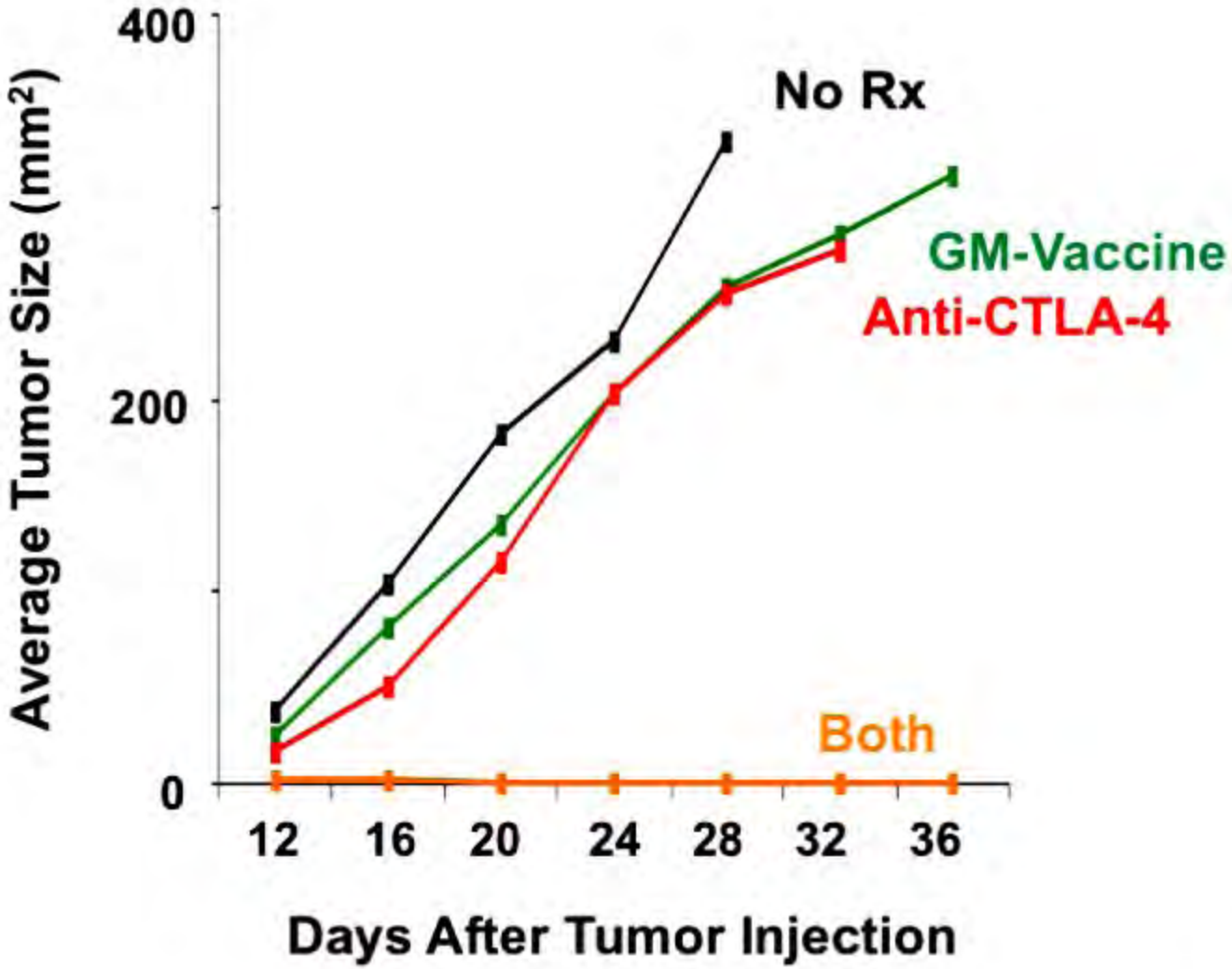


Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma



Leach

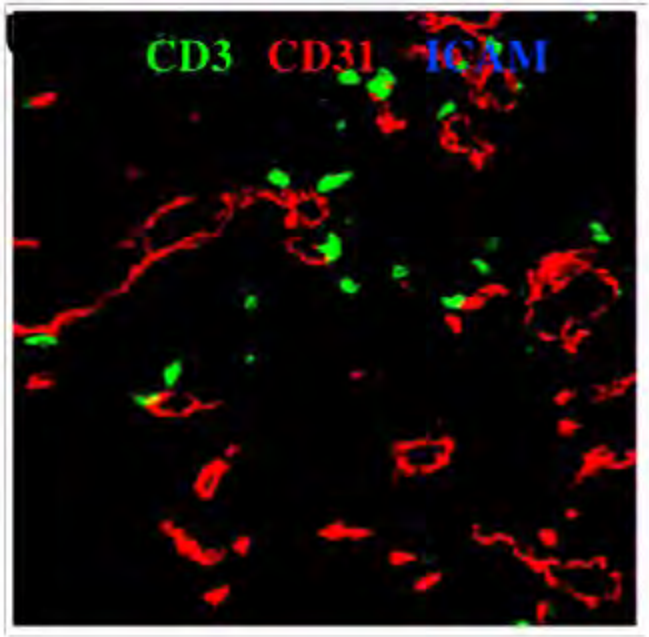
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

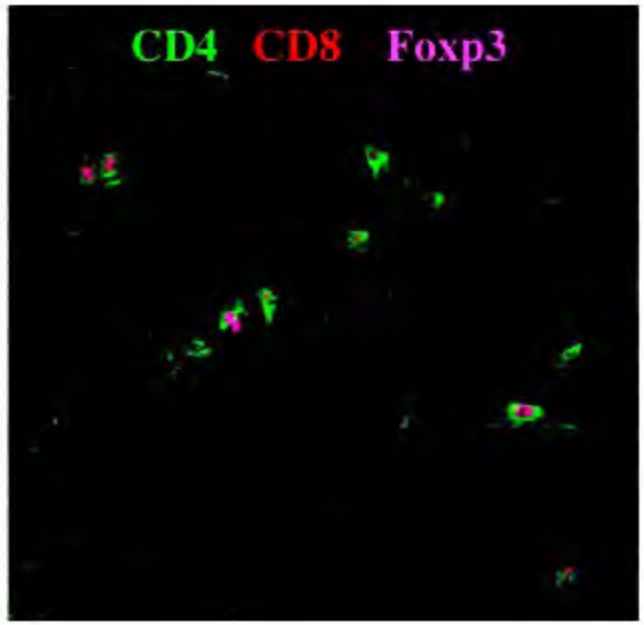


van Elsas,Hurwitz

anti-CTLA-4/GVAX therapy activates the tumor vasculature and increases infiltration of tumors by CD4 and CD8 effector cells

Untreated





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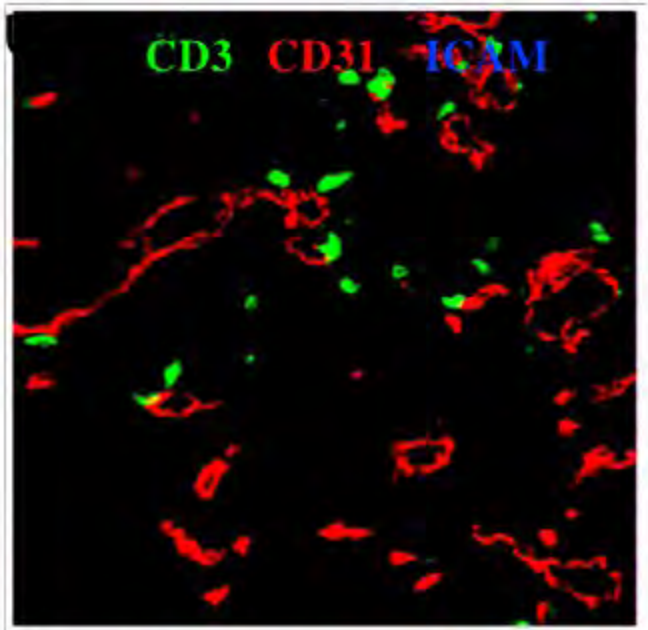
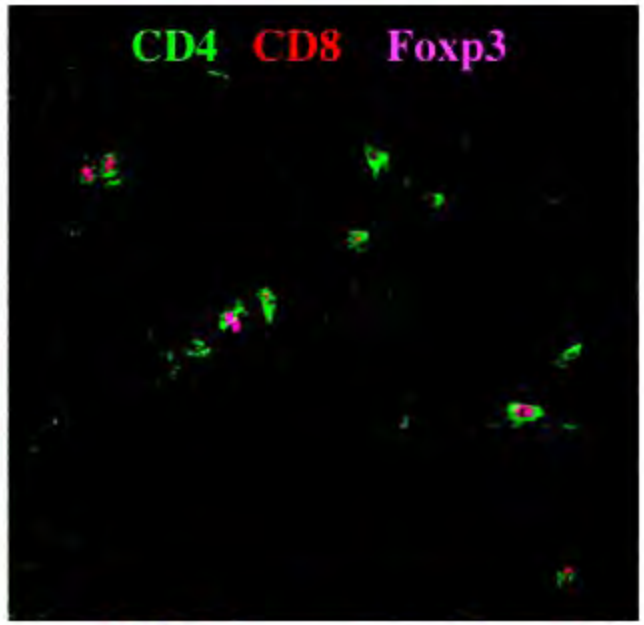
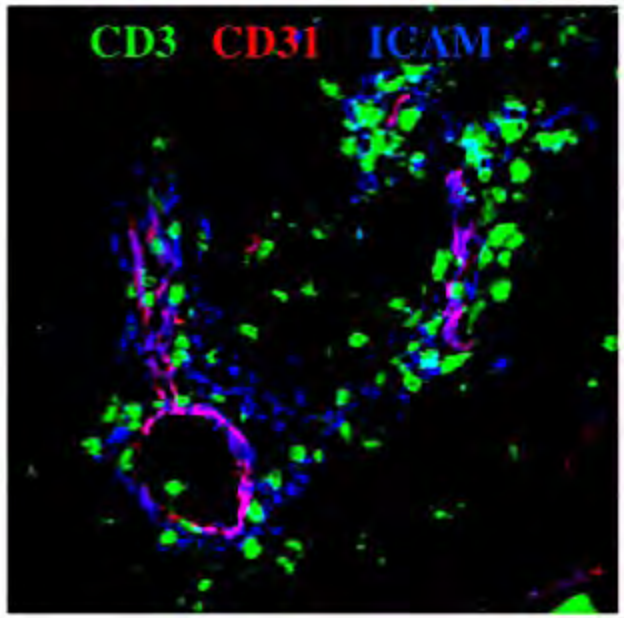
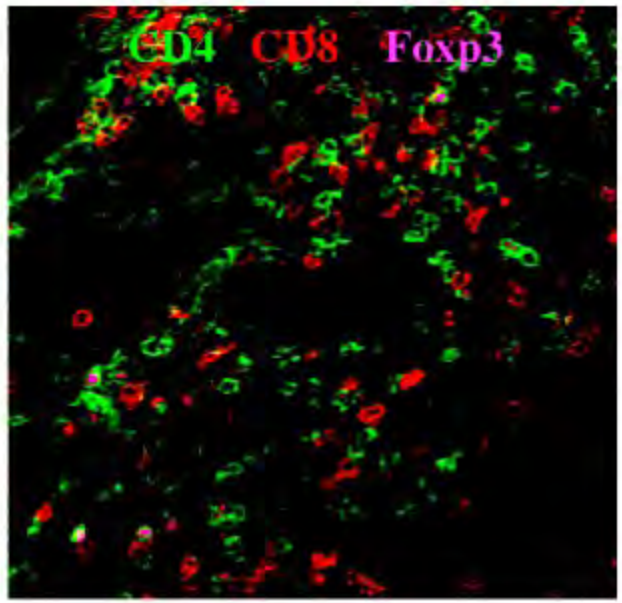


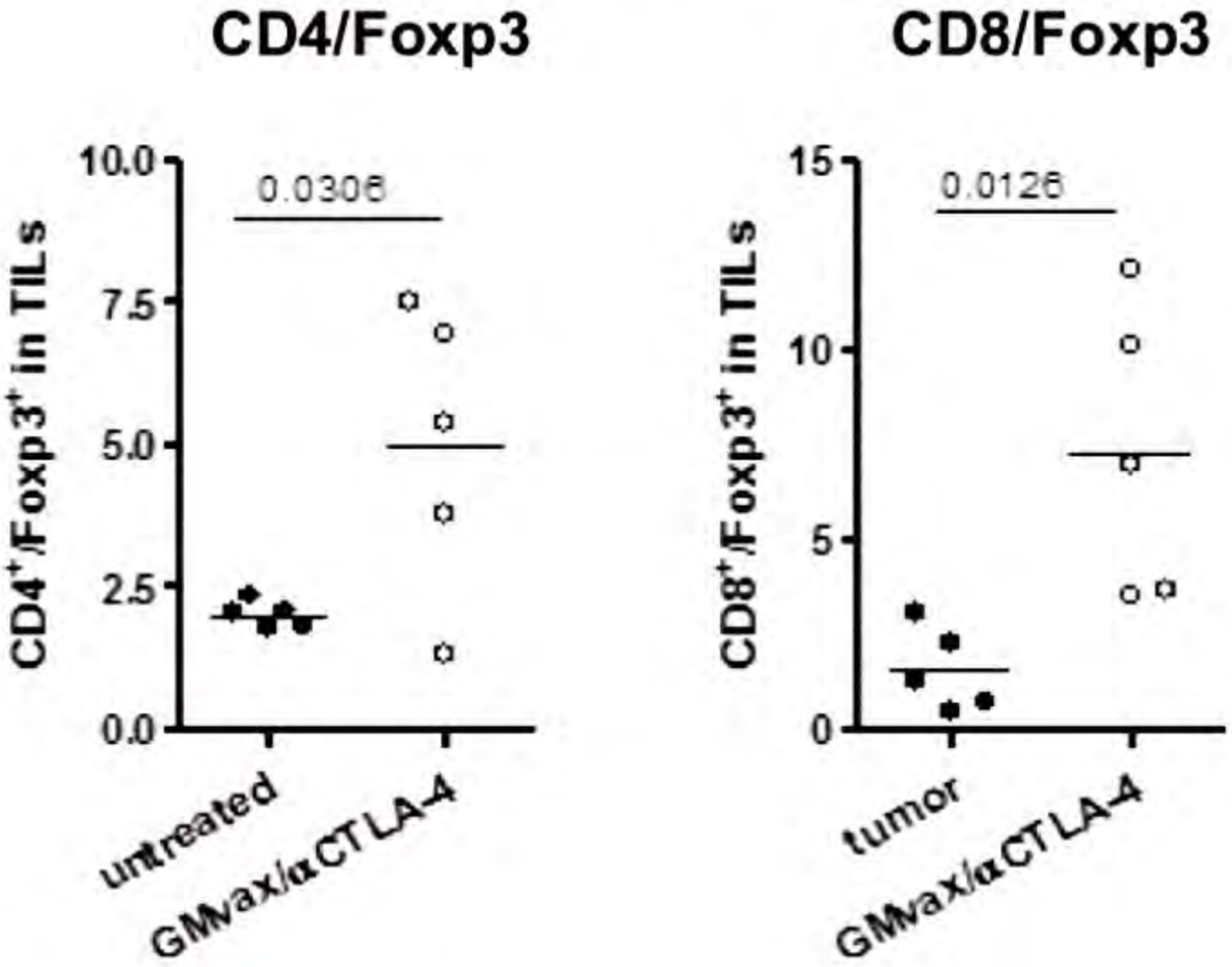


αCTLA-4/GVAX





αCTLA-4/GVax Increases Teff/Treg Ratio In Tumor



Quezada

Effective Combinations using anti-CTLA-4 Against Poorly Immunogenic Tumors

Immunotherapies

- Gvax: B16 melanoma, TRAMP CaP
- Peptide-pulsed (mugp100) DCs: B16 melanoma
- DNA Vaccine (huTRP2): B16 Melanoma
- Prior depletion of $CD25^+$ cells + vaccine: B16 melanoma
- Adoptive T cell Transfer: B16 melanoma

Conventional therapies

- Chemotherapy (cisplatin): Mammary carcinoma
- Local Irradiation: Mammary carcinoma
- Androgen deprivation: TRAMP CaP
- Surgical reduction: TRAMP CaP
- Cryoablation: TRAMP CaP
- Targeted Therapies (17AAG): TRAMP CaP

Most Anything that kills tumor cells or primes T cells

Ipilimumab

(Bristol-Myers Squibb)

>4,000 patients treated to date:

- **Metastatic Melanoma: Data from second line phase III trial is at FDA, first line Phase III completed, awaiting data analysis.**
- **Castrate-resistant Prostate Cancer: Phase II trials completed, randomized Phase III open**
- **Objective responses in ovarian, lung, kidney cancer**

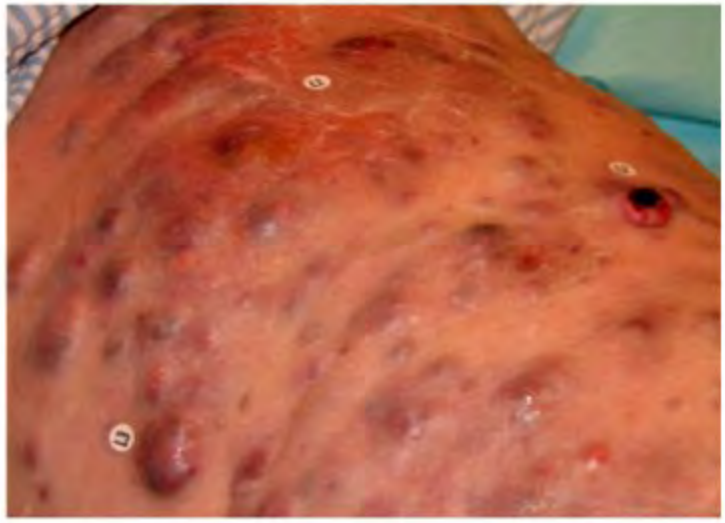
Ipilimumab: Summary of Clinical Experience

- ~15% (RECIST, mWHO) in melanoma as monotherapy, some are complete responses

- Survival benefit in ~35-40% of patients

- Responses are durable:
  - Months to years without retreatment, although maintenance treatment is possible

Baseline 11/28/06



Wolchok (MSKCC)

1/9/07

6 Weeks

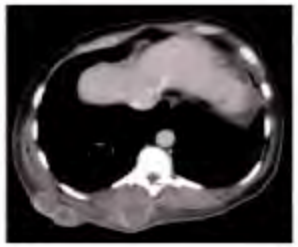
2/12/07

10 Weeks

Wolchok (MSKCC)

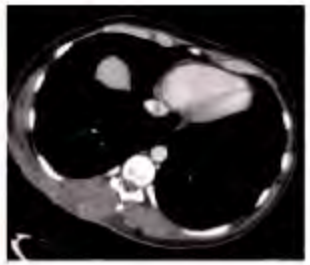
Evolution of Response: Patient Example

Screening

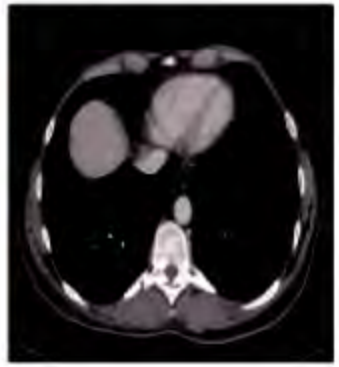


Week 12
Initial increase in total tumor burden (mWHO PD)

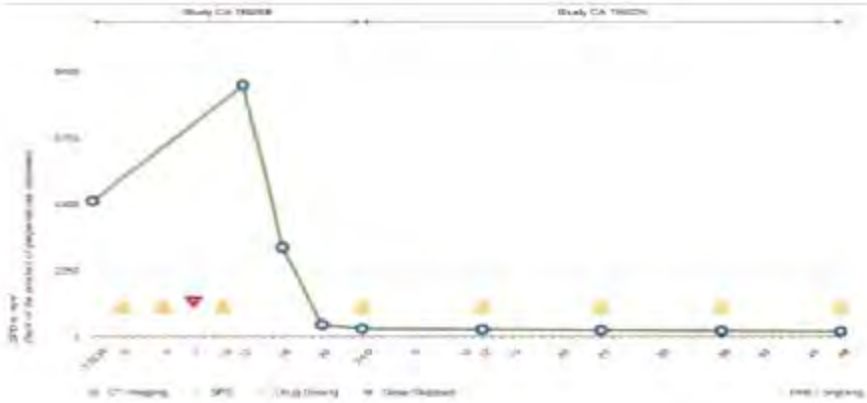
Week 16
Responding



Week 72
Durable & ongoing response without signs of IRAEs



20006



Harmankaya

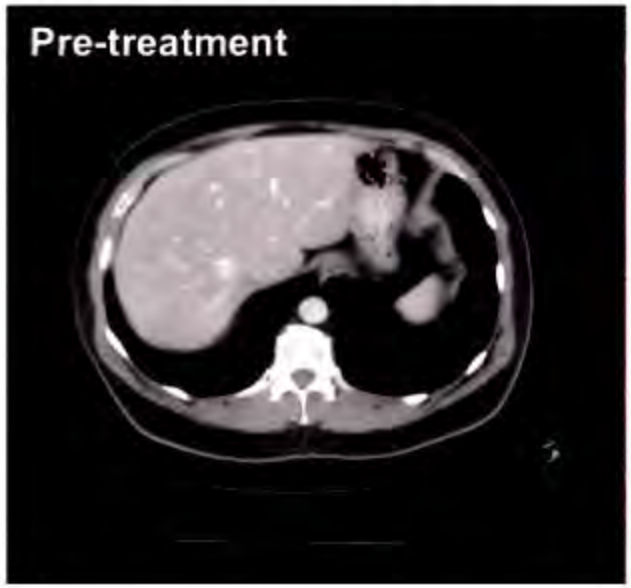
Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

May, 2007

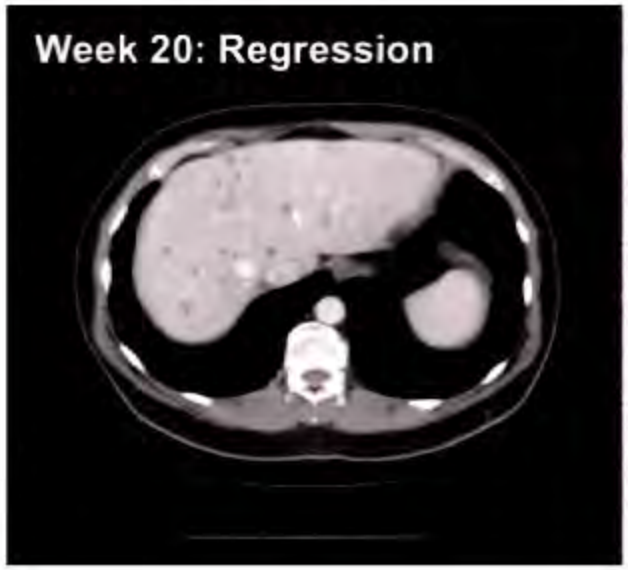
Source: 2008 ASCO
Abstract #3020 Wolchok.

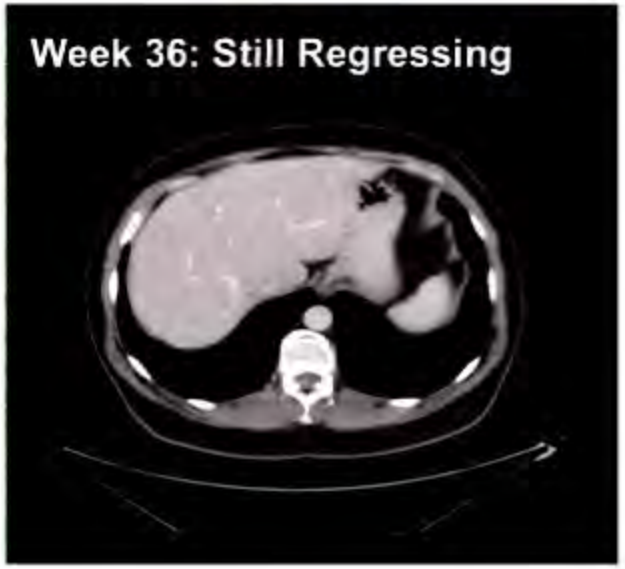
Wolchok
(MSKCC)

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



10 mg/kg ipilimumab Q3W X 4





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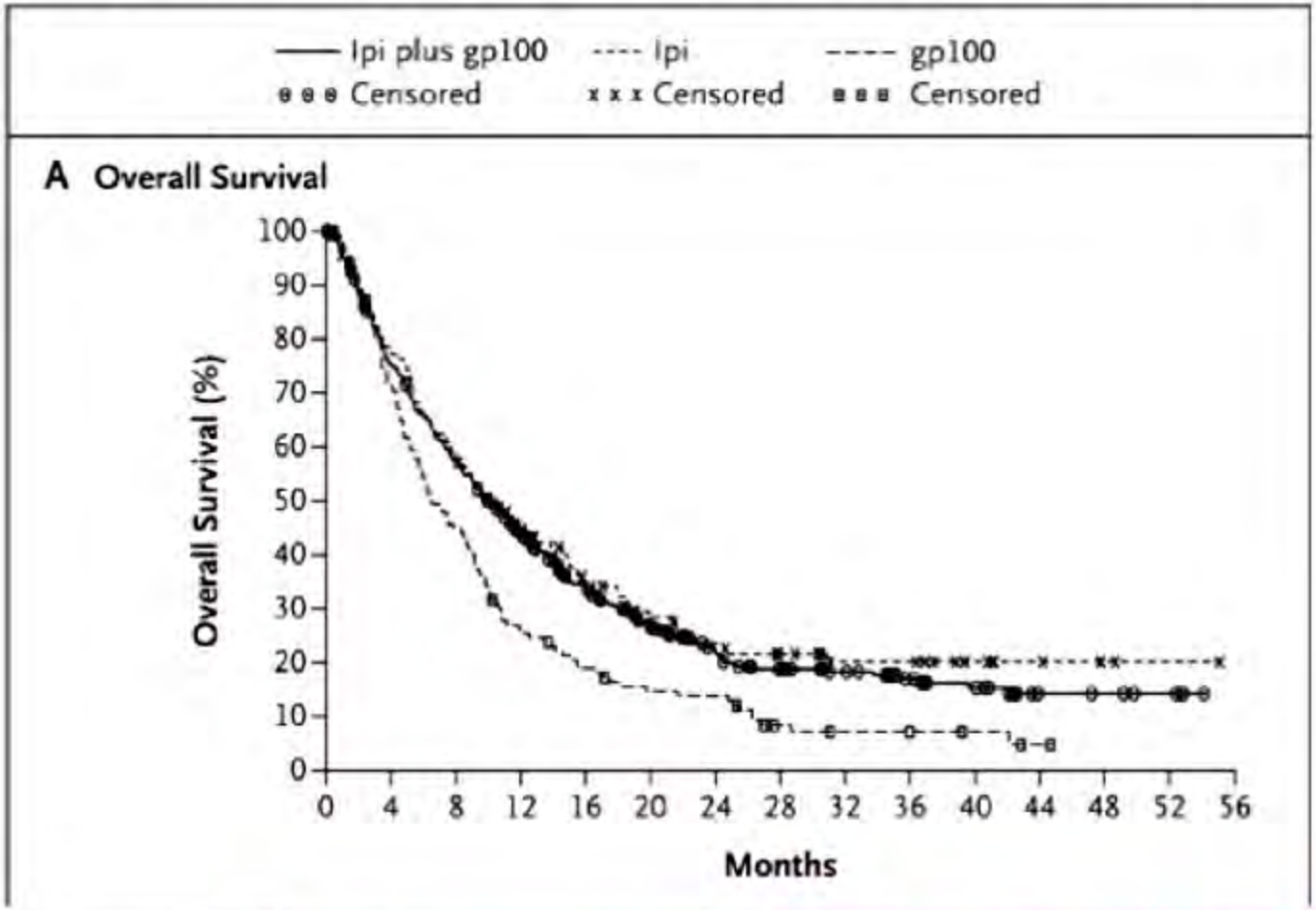
Wolchok (MSKCC)

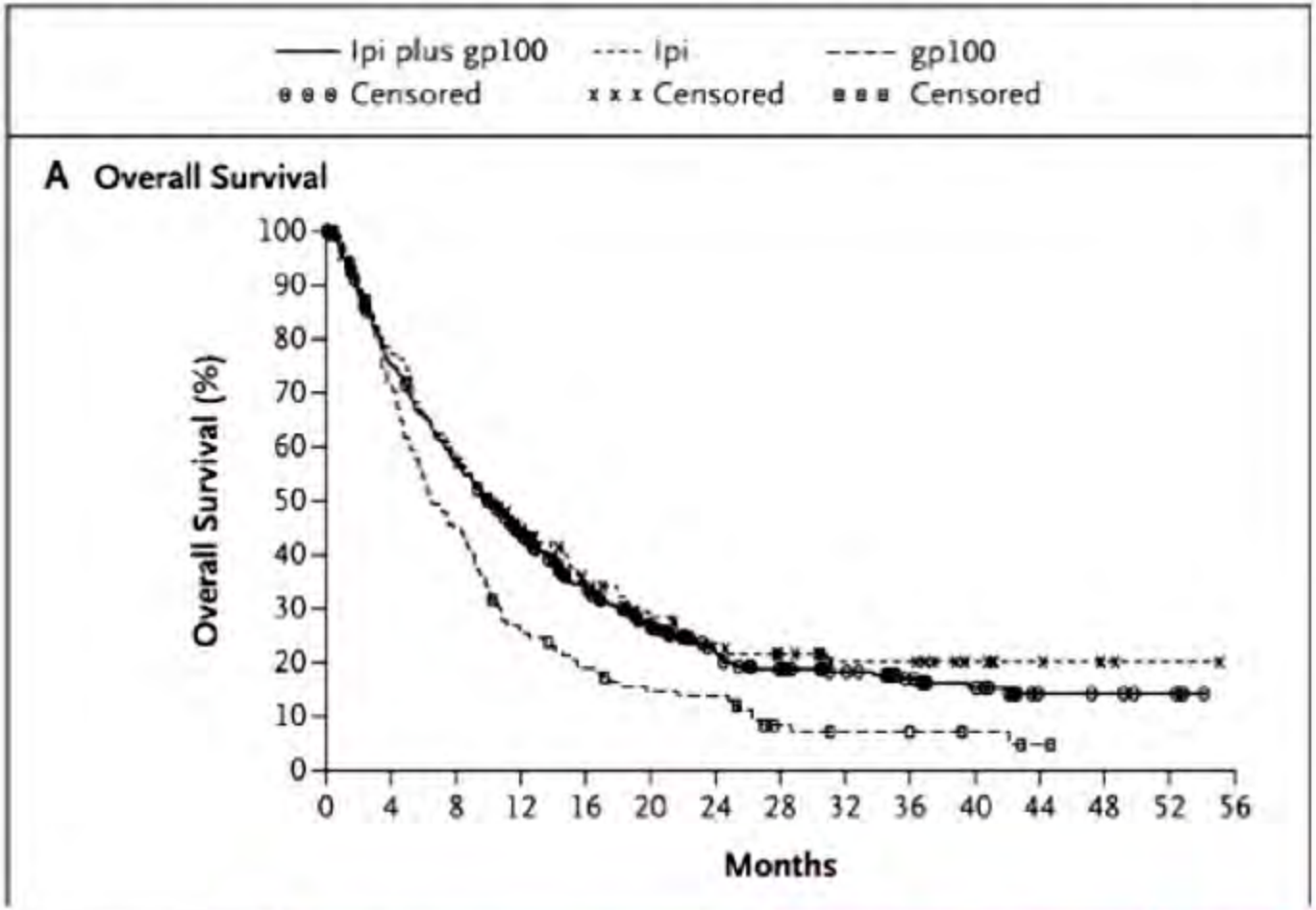
Kaplan-Meier Analysis of Survival



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

ASCO 2010, Hodi et al. NEJM 2010

Kaplan-Meier Analysis of Survival



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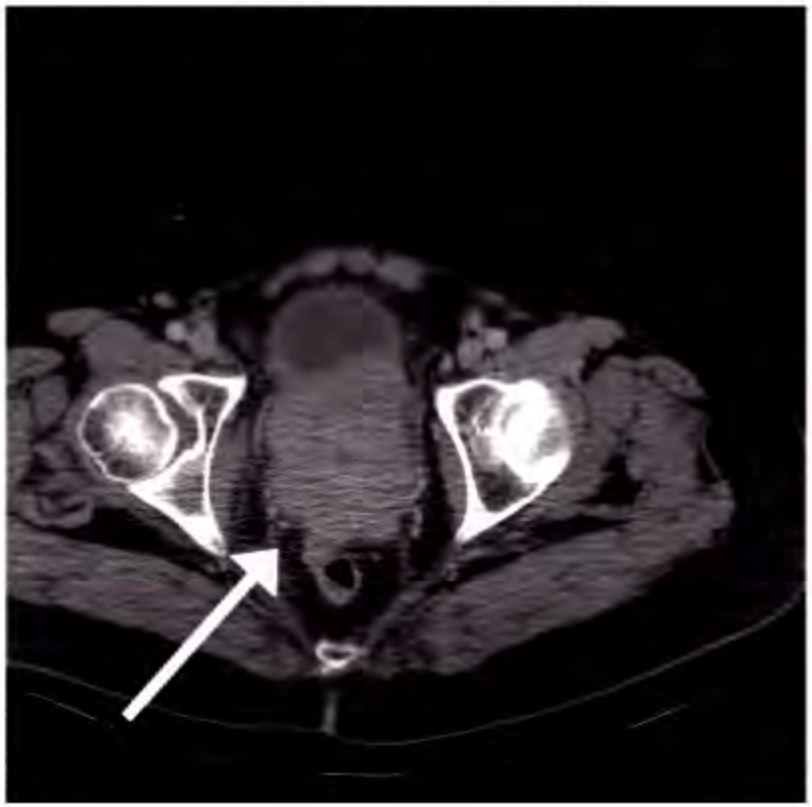
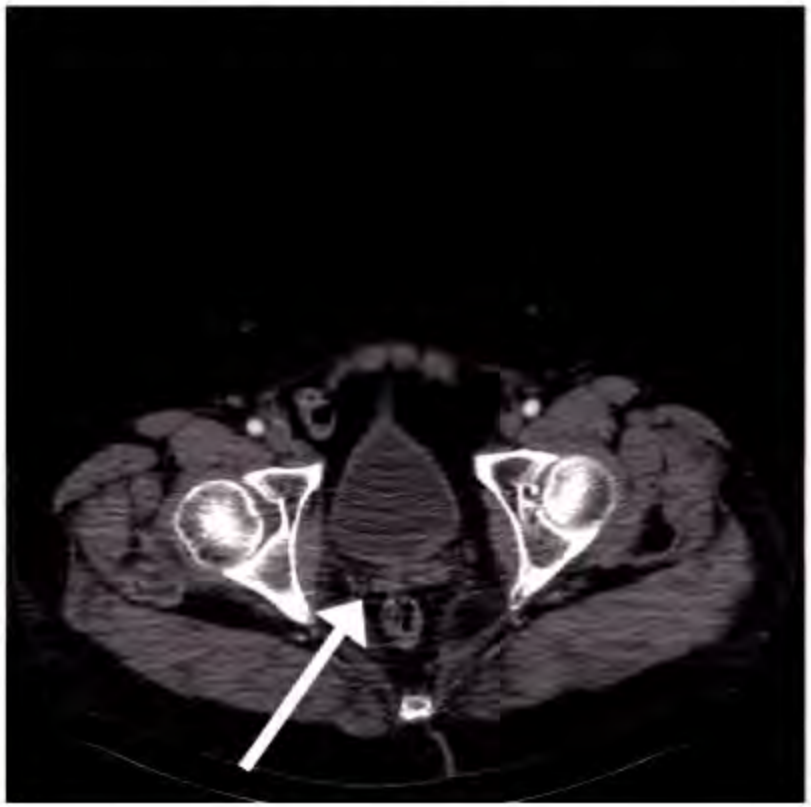
Subject 3020:
Resolution of Prostate Mass

Screening



14 months



Medarex and BMS

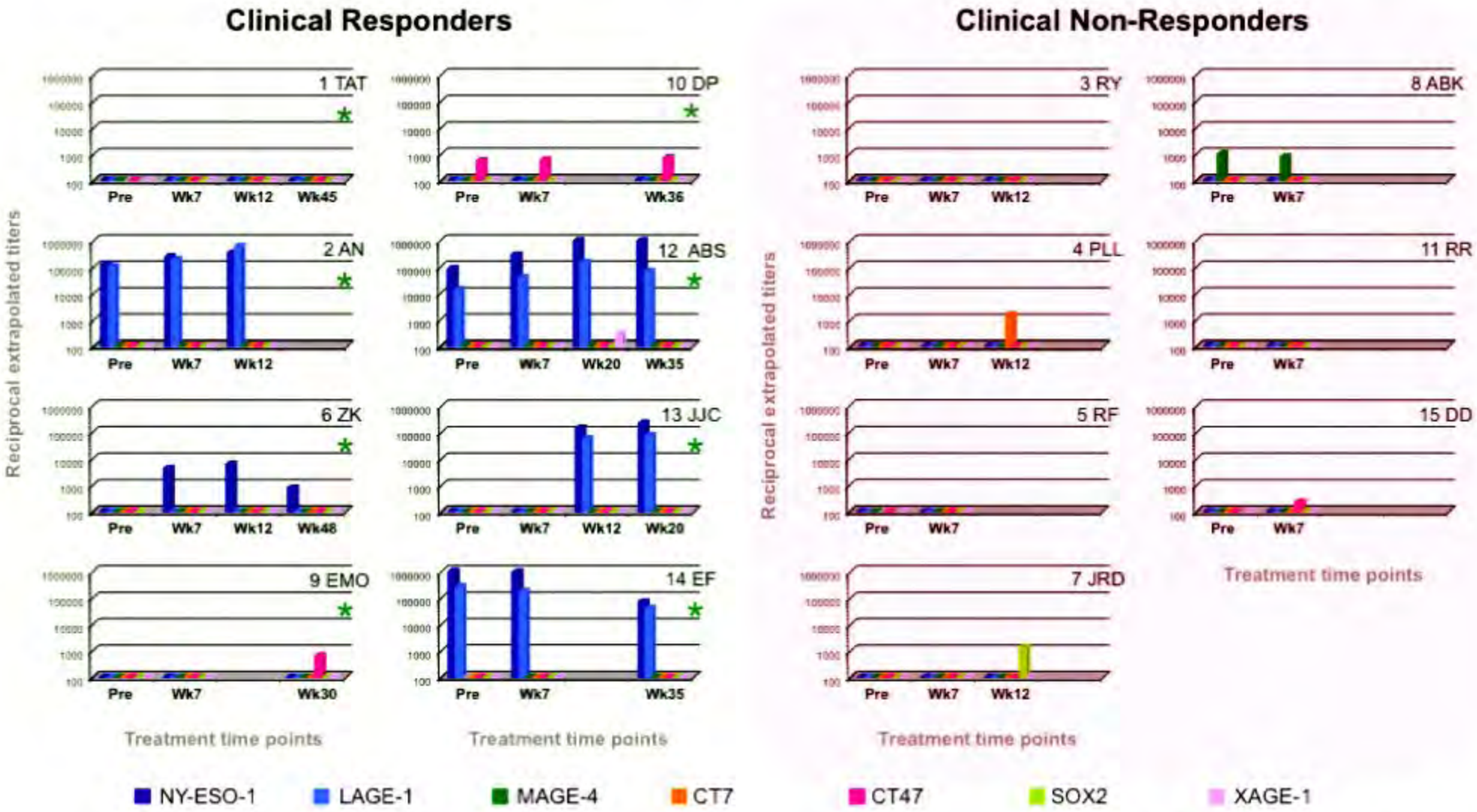
Critical Questions for Further Clinical Development of anti-CTLA-4

- What are the cellular and molecular mechanisms involved in the anti-tumor effect?
- What distinguishes responders from non-responders?
- What are the best conventional therapies or vaccines to be used combinatorially?

Cancer Testes (CT) Antigens

- ~100 known family members
- Expressed during germ cell development in immune privileged sites, but not in other normal tissues
- Expressed in many cancer types
- Spontaneous immune responses against these antigens can be detected in some cancer patients

NY-ESO-1 Antibody May Correlate with Clinical Responses In Metastatic Melanoma patients



Gnjatic & Wolchok

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

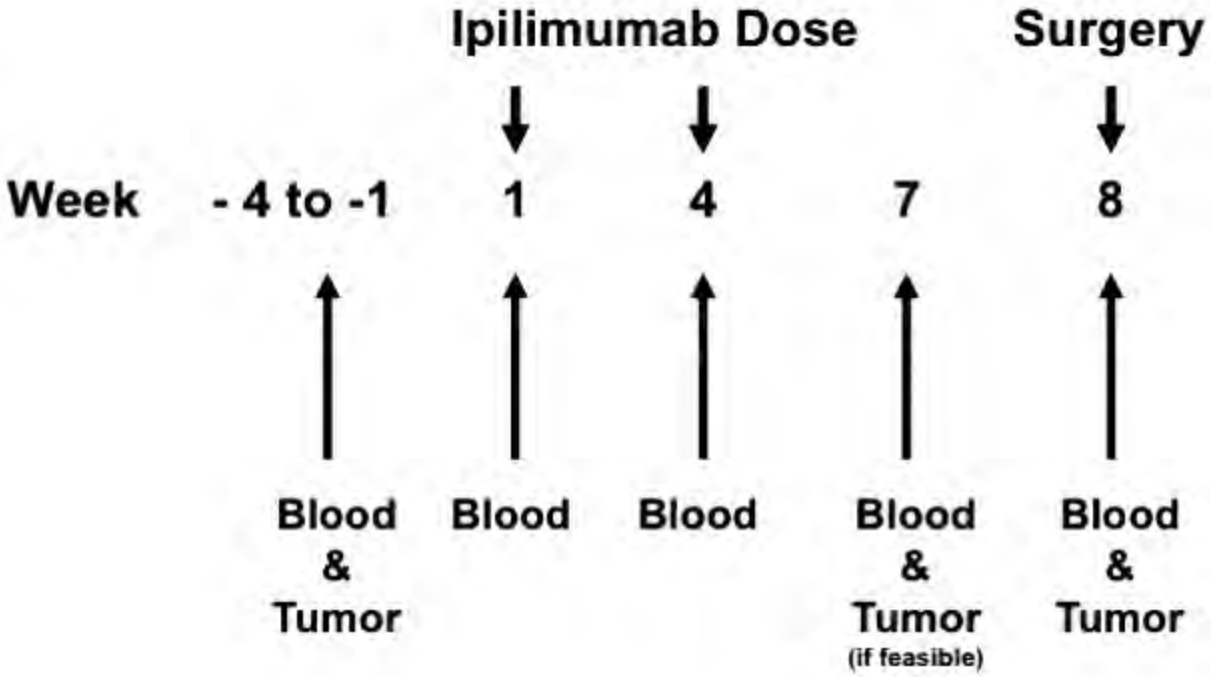
According to Immune-related response criteria:

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

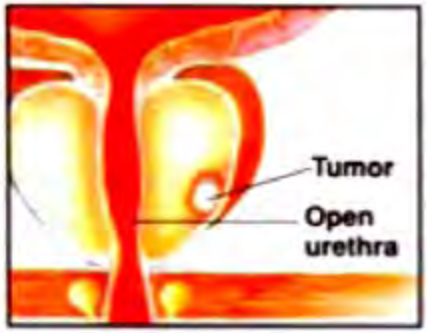
Gnjatic & Wolchok, Ludwig Center/MSKCC
Halaban and Sznol, Yale

Neoadjuvant anti-CTLA-4 trial in Bladder Cancer



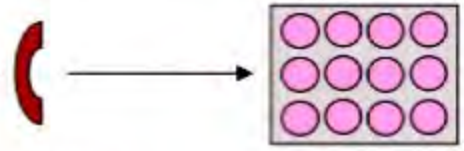
Padmanee Sharma, MDACC

Tissue Analysis



RNA later

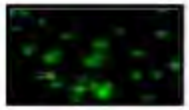
Core biopsy (~ 1 cm x 1mm x 1mm)



Core biopsy

TIL expansion

Fine needle aspiration and chunks



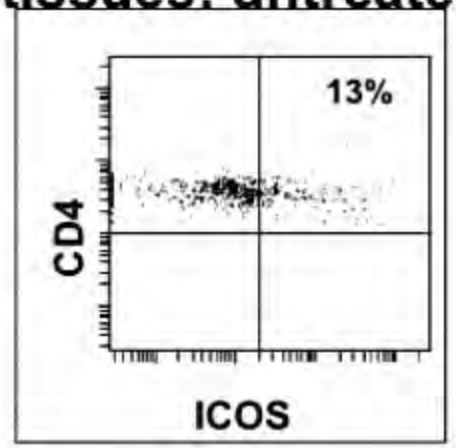
IF in frozen sections

Histology sections

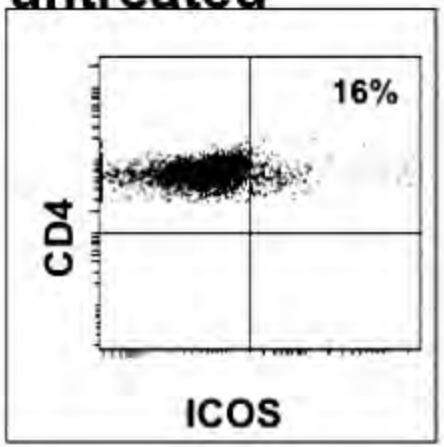
IHC in paraffin sections

Bladder:
ICOS expression is higher in tumor tissues from anti-CTLA-4 treated patients

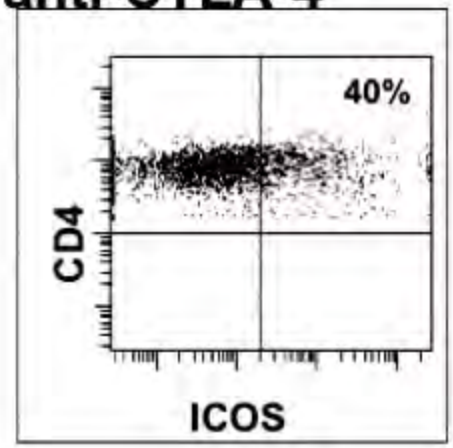
Non-malignant tissues: untreated



Tumor tissues: untreated

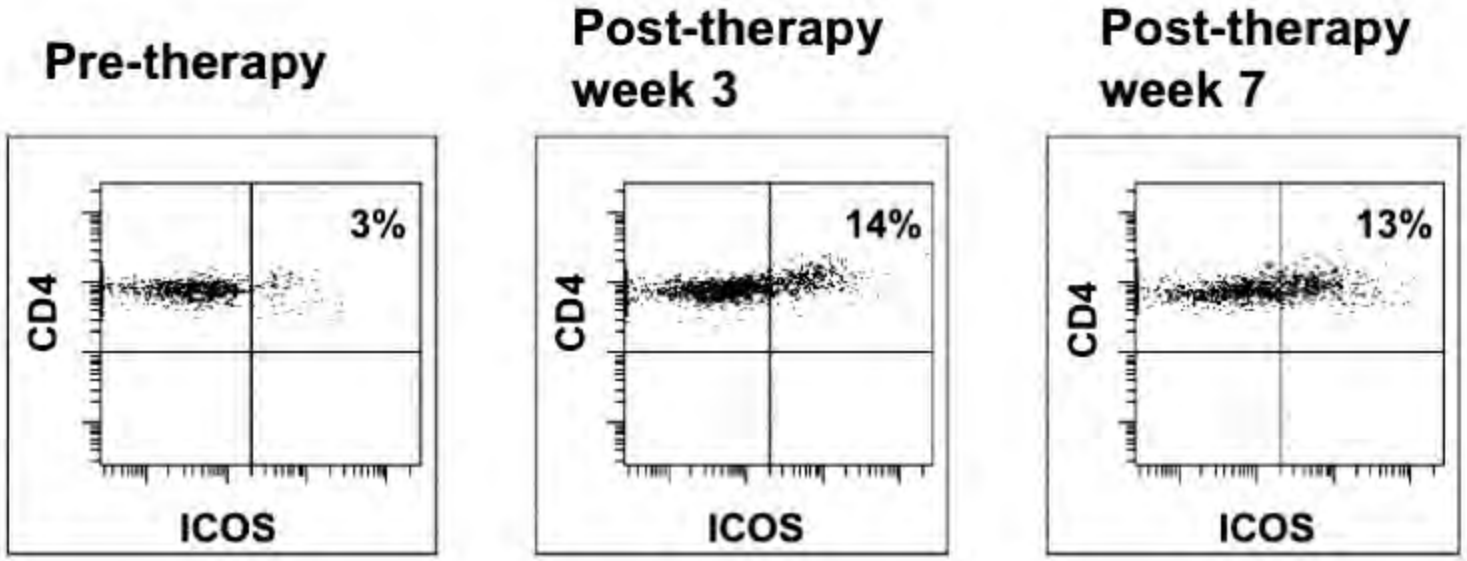


Tumor tissues: anti-CTLA-4



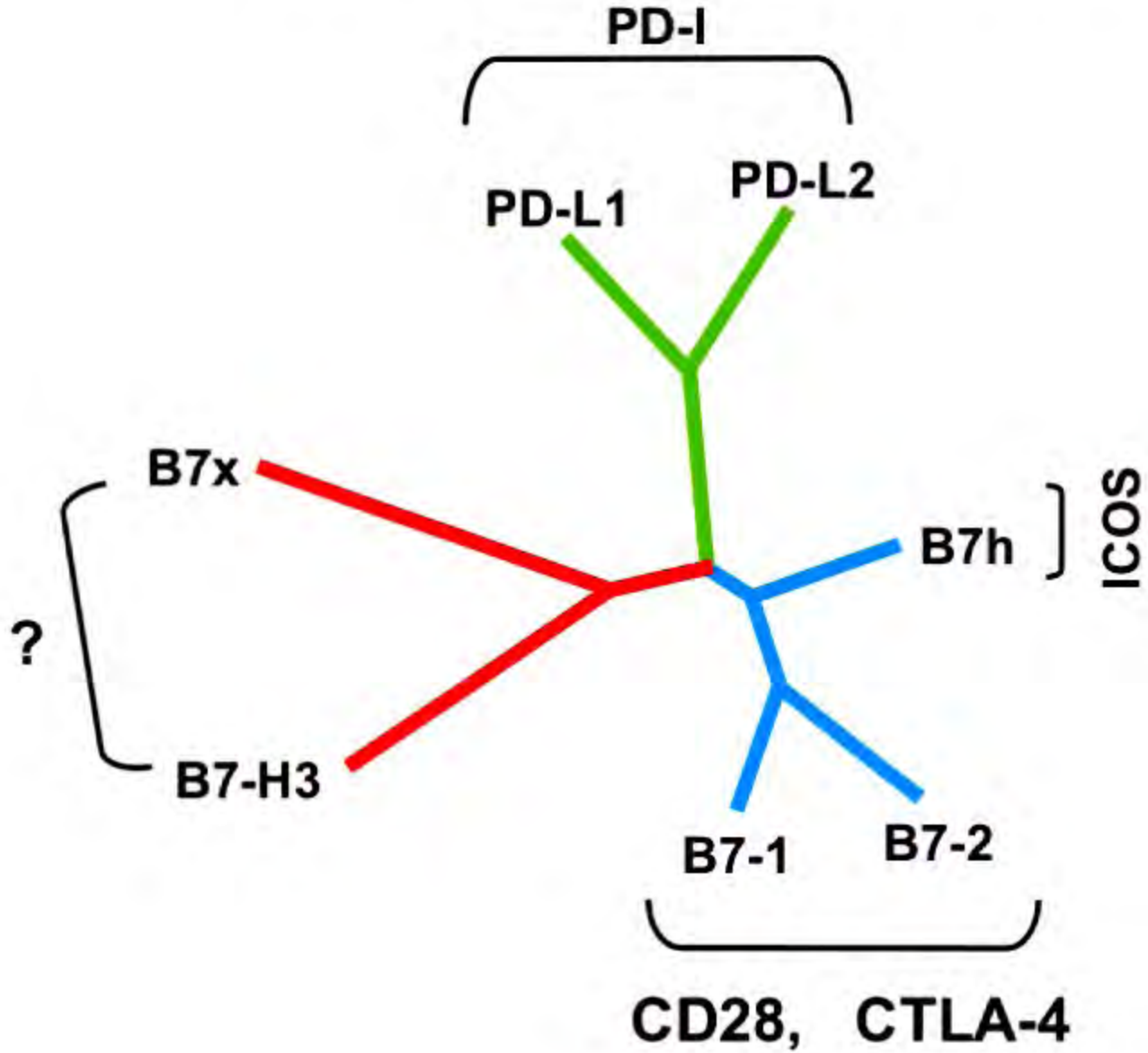
Liakou et al., *Proc Natl Acad Sci*, 2008

Blood:
$ICOS^{high}$ CD4 T cells in Blood of Bladder Cancer Patients after anti-CTLA-4 Treatment

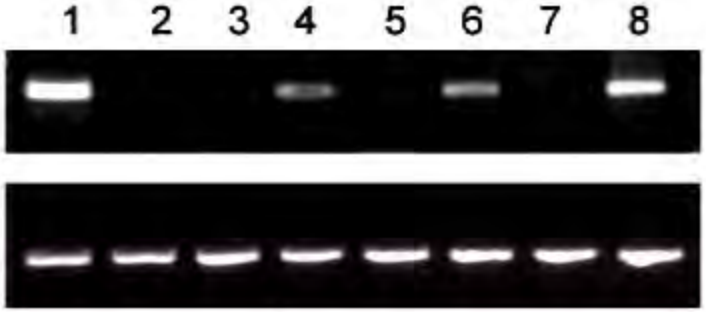


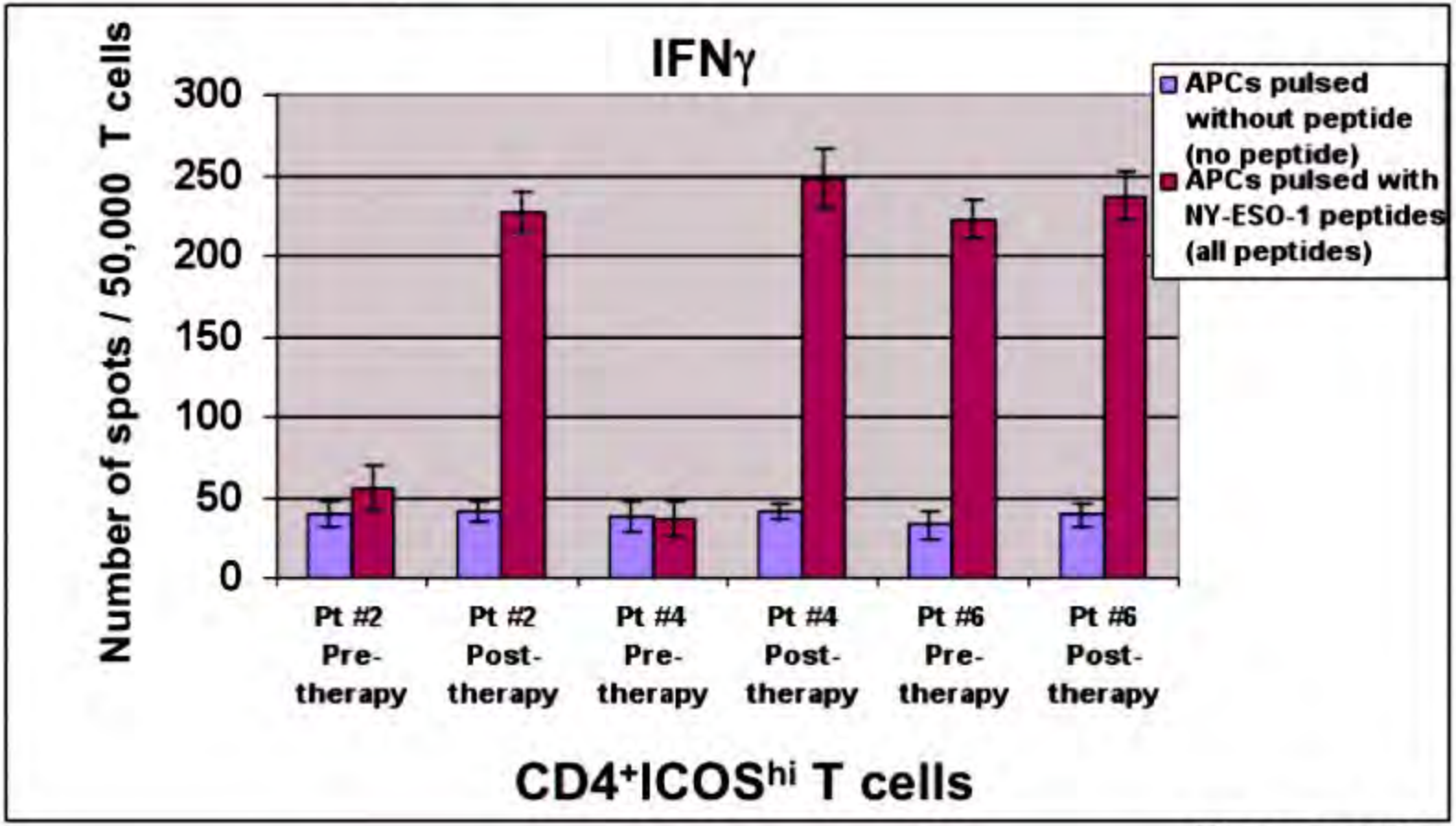
Sharma, MDACC

Extended B7-CD28 Family



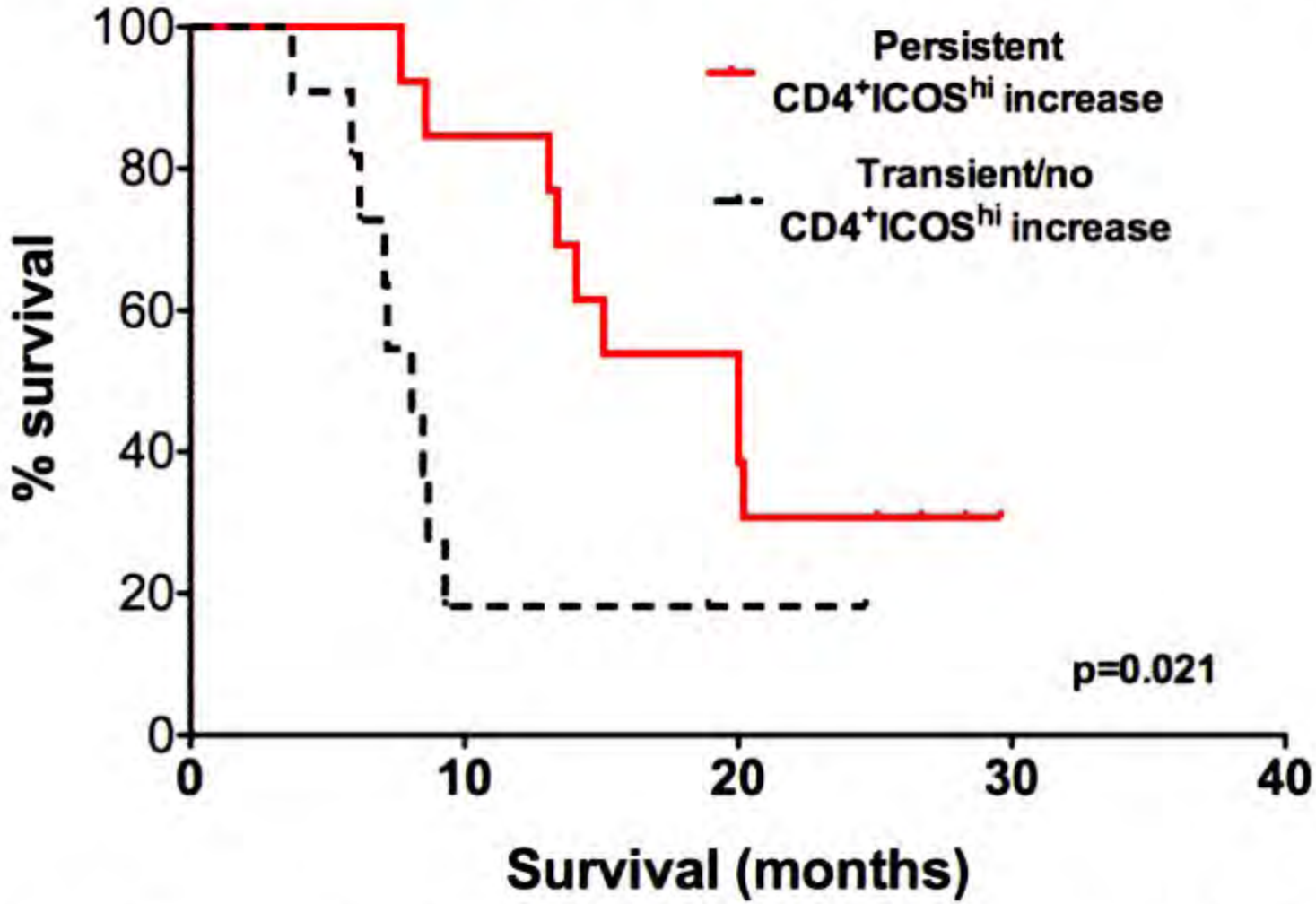
ICOS^{hi} T cells from peripheral blood recognize NY-ESO-1 tumor antigen and produce IFNγ





Sharma, MDACC

Kaplan-Meier curve of overall survival (OS) for melanoma patients receiving ipilimumab therapy.

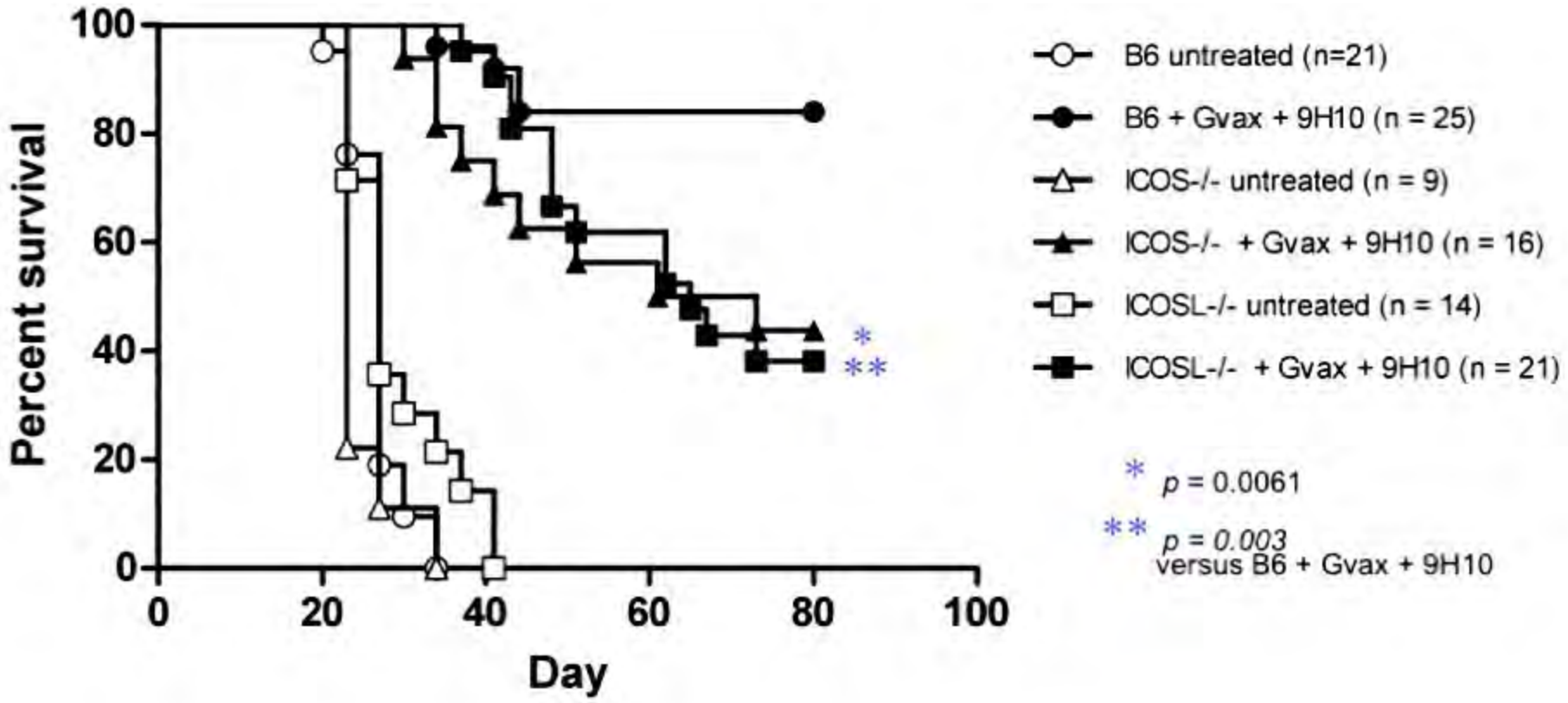


Median survival for $ICOS^{hi}$ and $ICOS^{lo}$ is 20 months & 8.1 months.

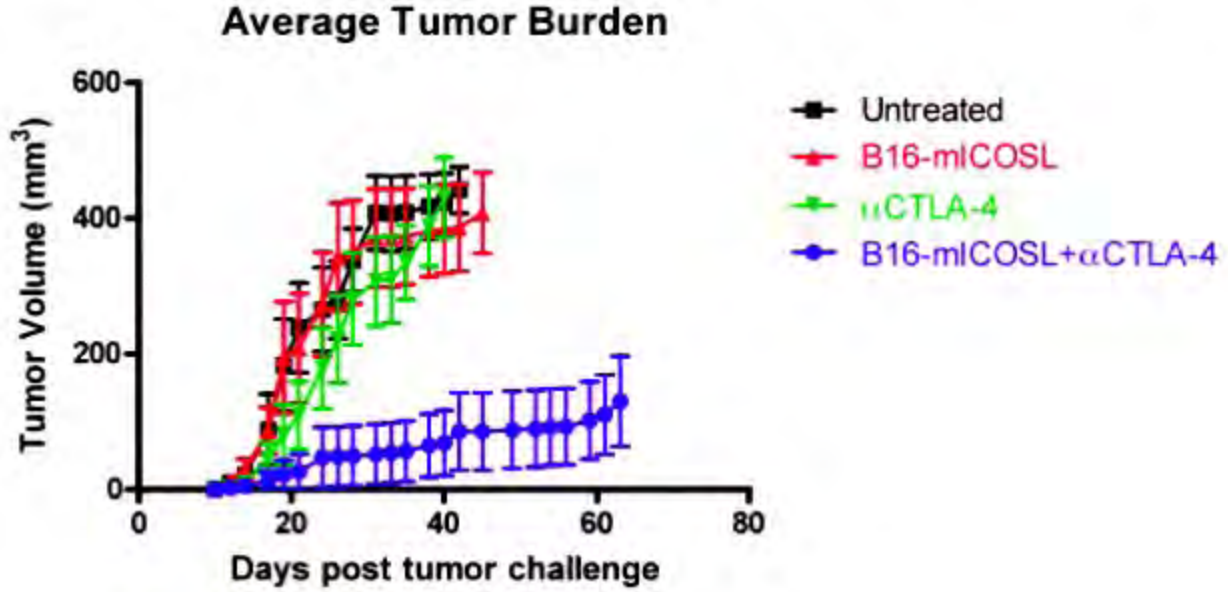
Updated from Carthon et al. *Clin Cancer Res* 2010

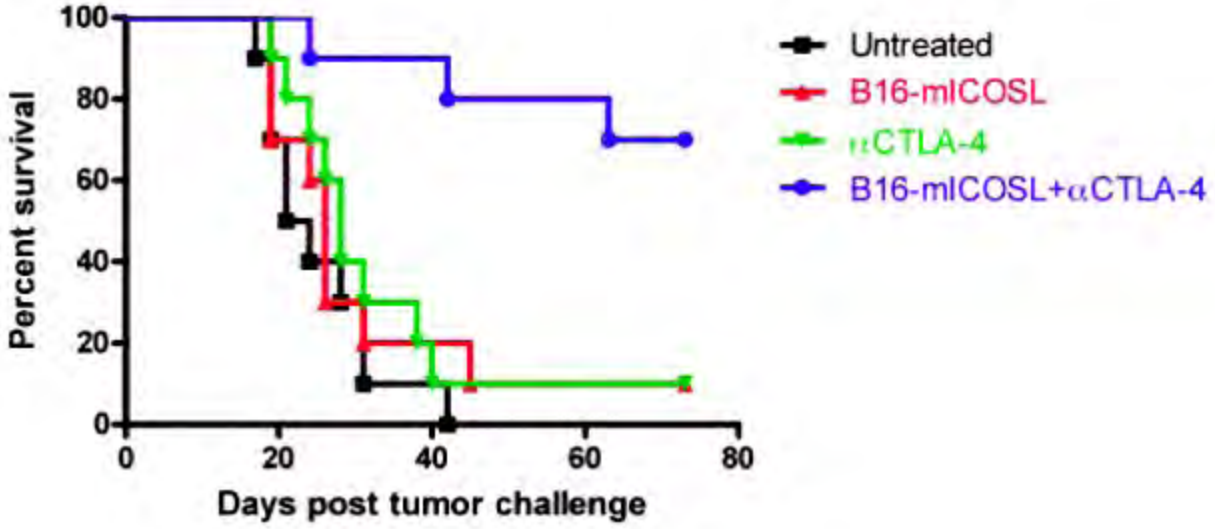
What is the functional significance of ICOS expression after CTLA-4 blockade?

ICOS and ICOS-ligand knockout mice have impaired tumor rejection after anti-CTLA-4 therapy

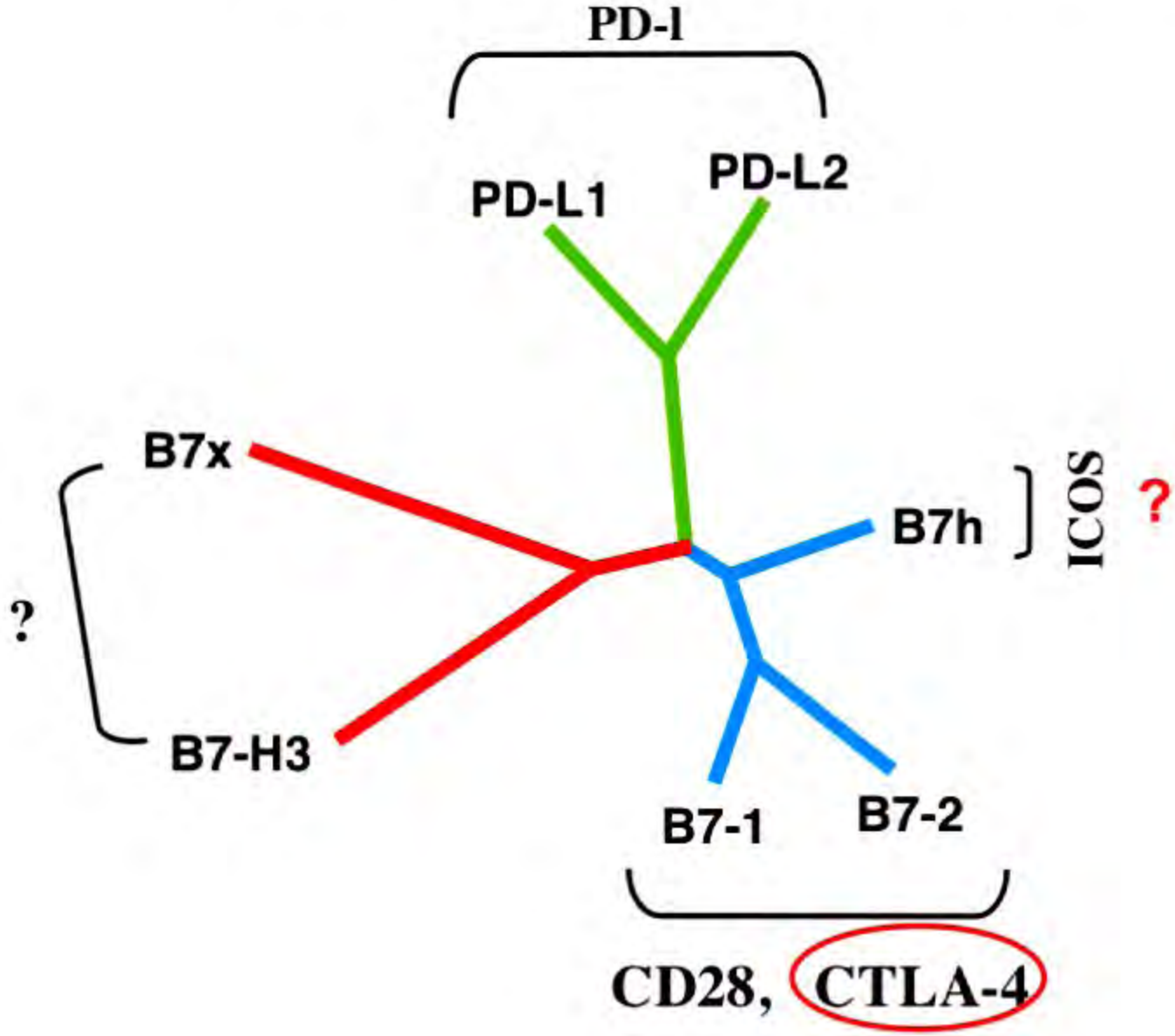


Ivax: A novel way of enhancing the effectiveness of CTLA-4 Blockade





Extended B7-CD28 Family



Phase II Trial of anti-PD-1 (MDX-1106)

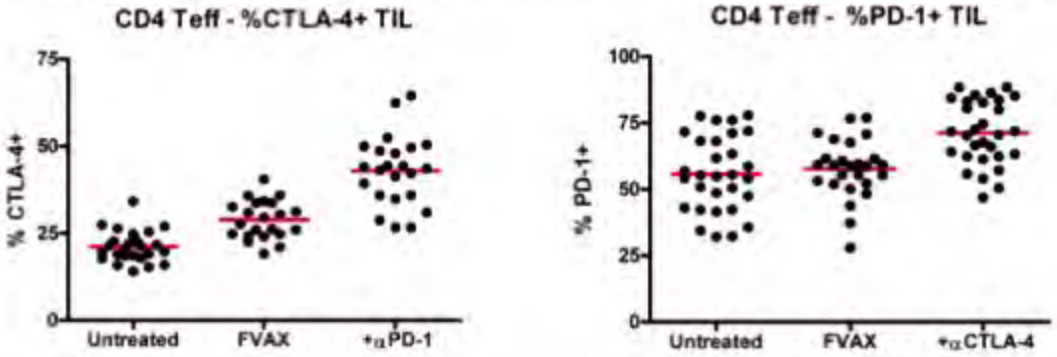
21 patients, diverse cancer types
(5 CC, 2NSCLC, 8 MEL, 5 HRPC, 1RCC)

1 complete response, 5 partial responses

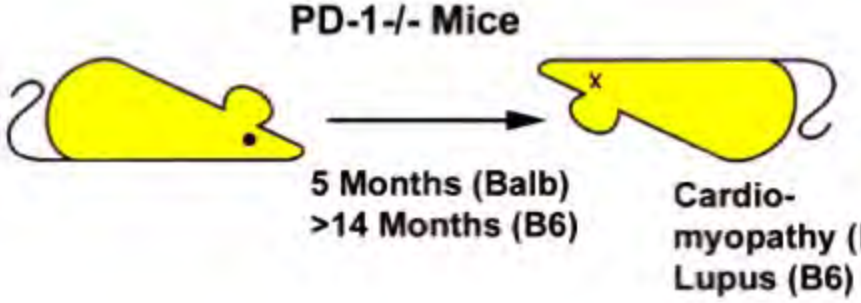
Limited toxicity

Why study combination blockade of CTLA-4 and PD-1?

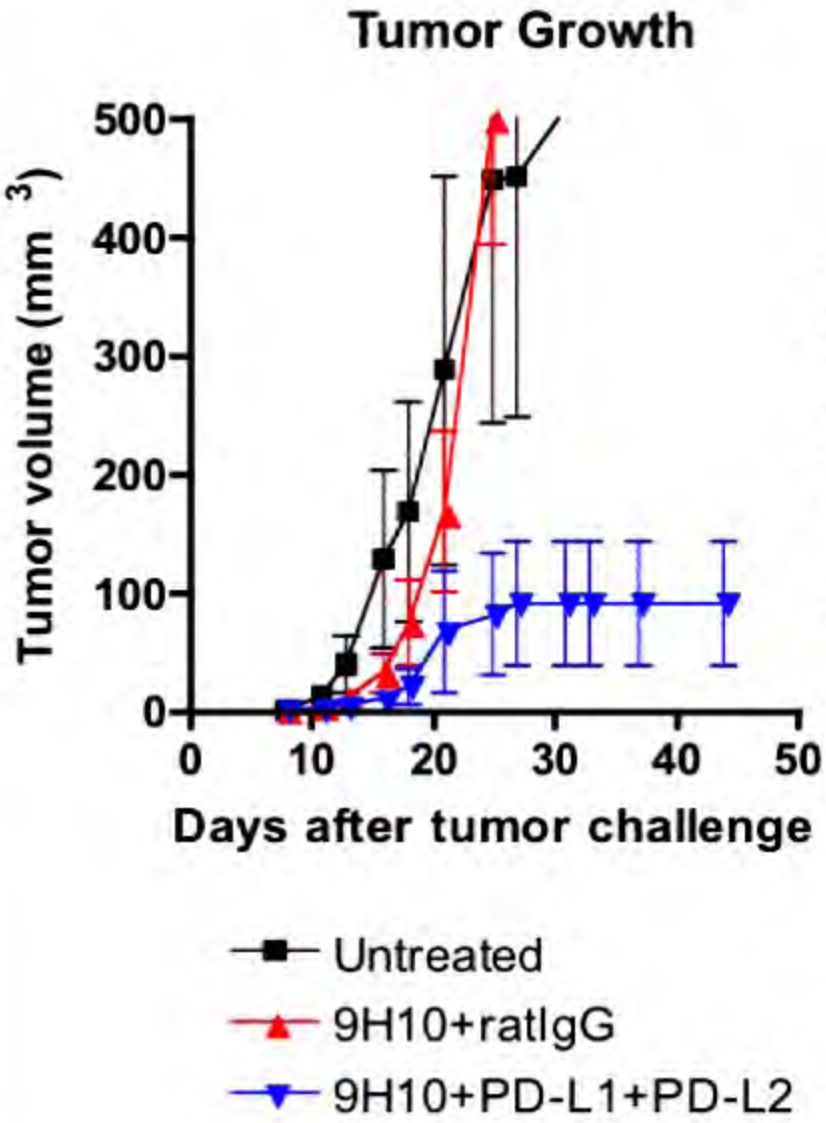
Blocking one co-inhibitory receptor leads to upregulation of the other

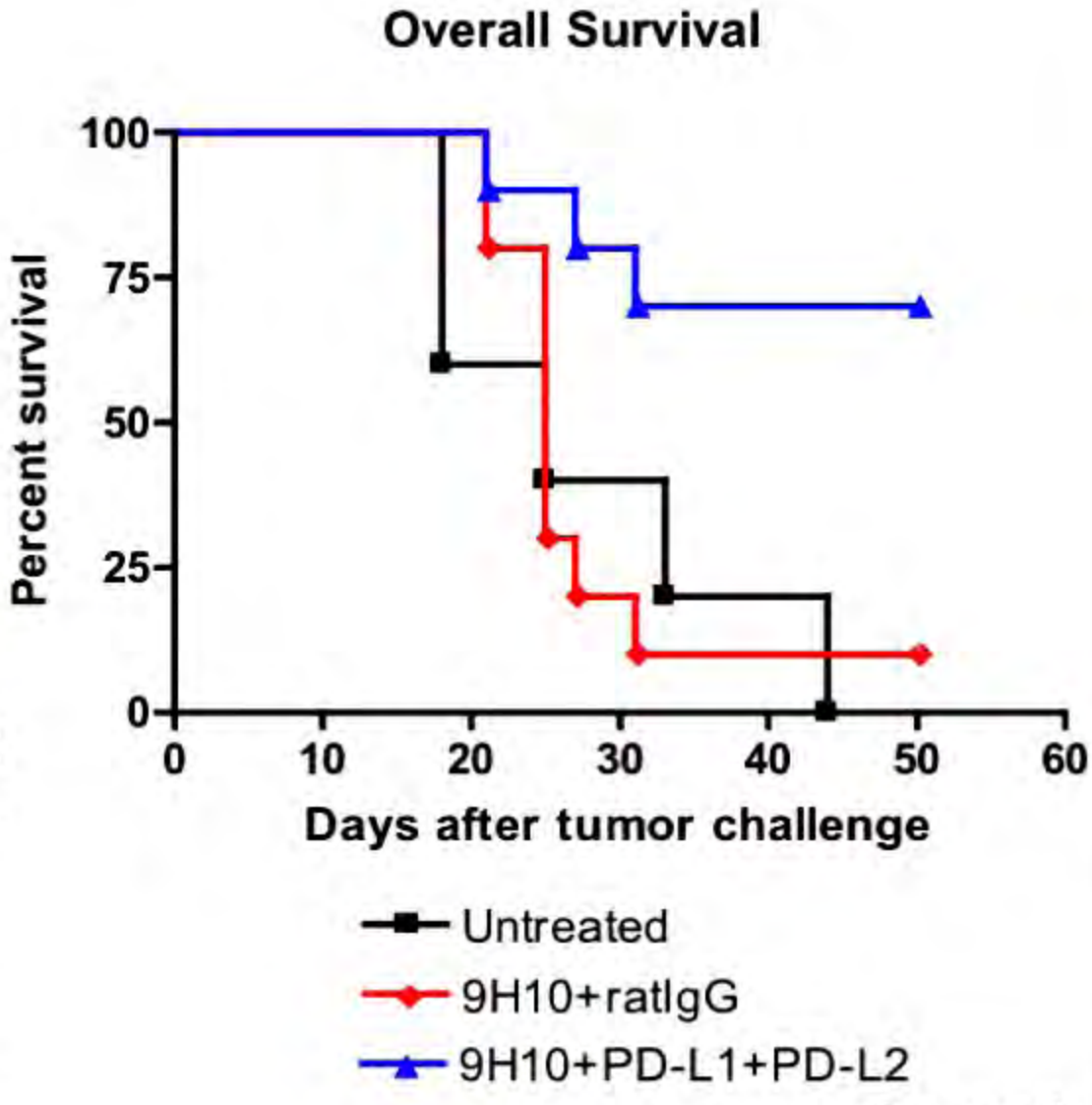


CTLA-4 and PD-1 inhibitory signals are non-redundant



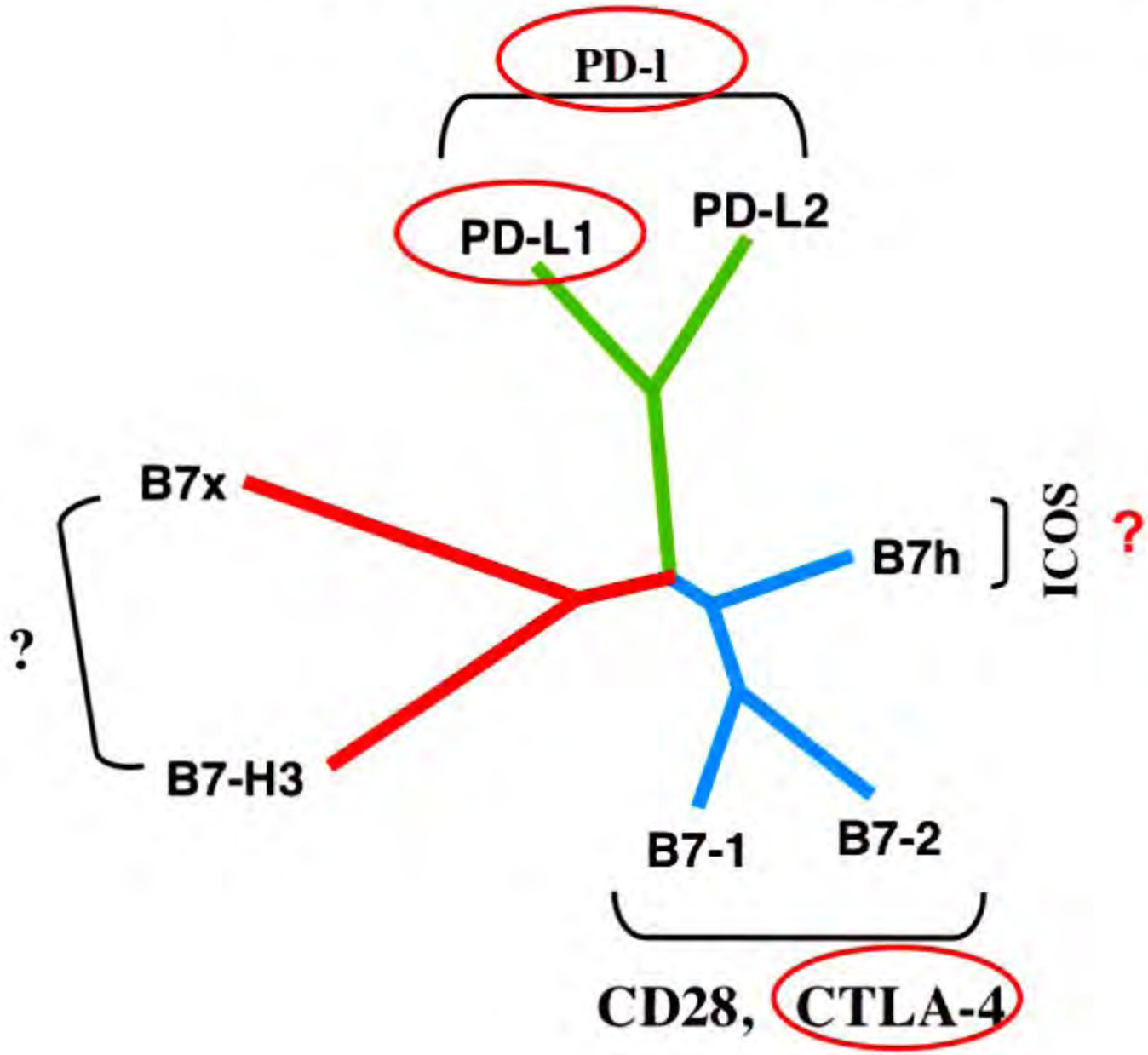
Blockade of PD-1 Pathway Synergizes with CTLA-4 Blockade





Quezada

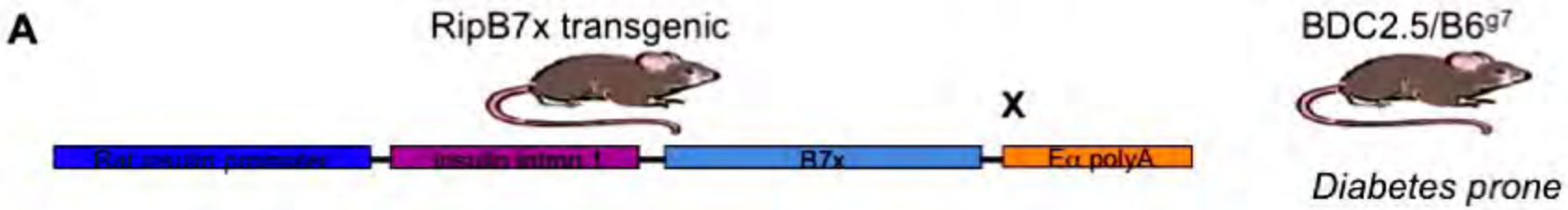
Extended B7-CD28 Family

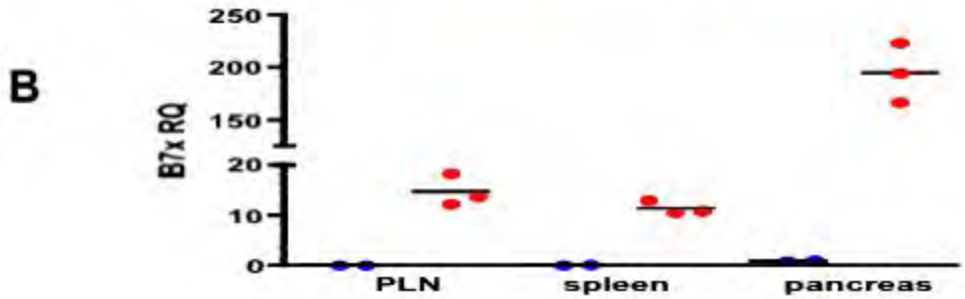


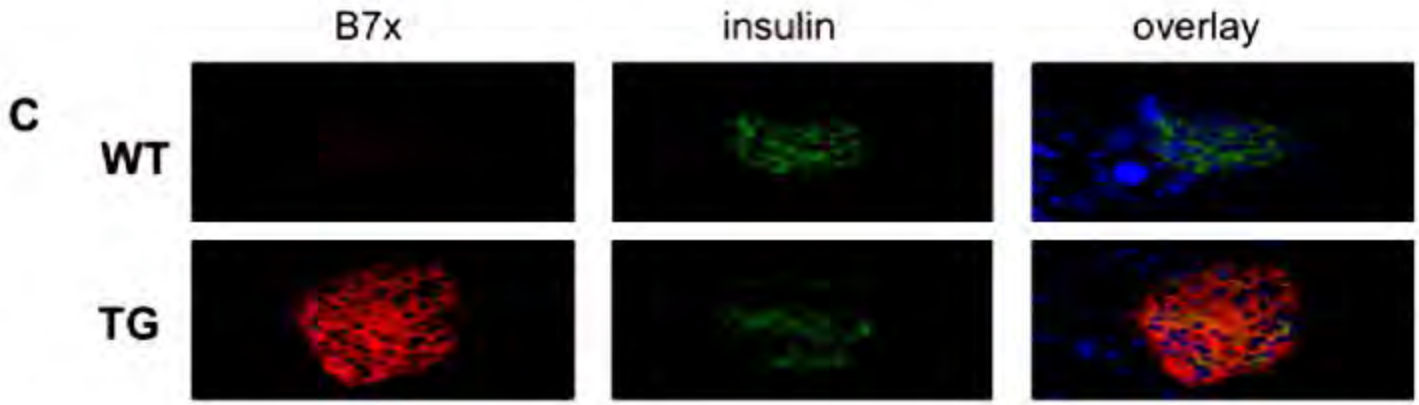
B7-H4 (B7x) and B7H3

- Co-inhibitory *in vitro*
- Expressed at low levels in many tissues
- Not expressed by antigen-presenting cells
- May play a role in tissue defense against autoimmune attack
- Expressed by many tumor cell types
- Soluble form in serum of prostate and renal cancer patients

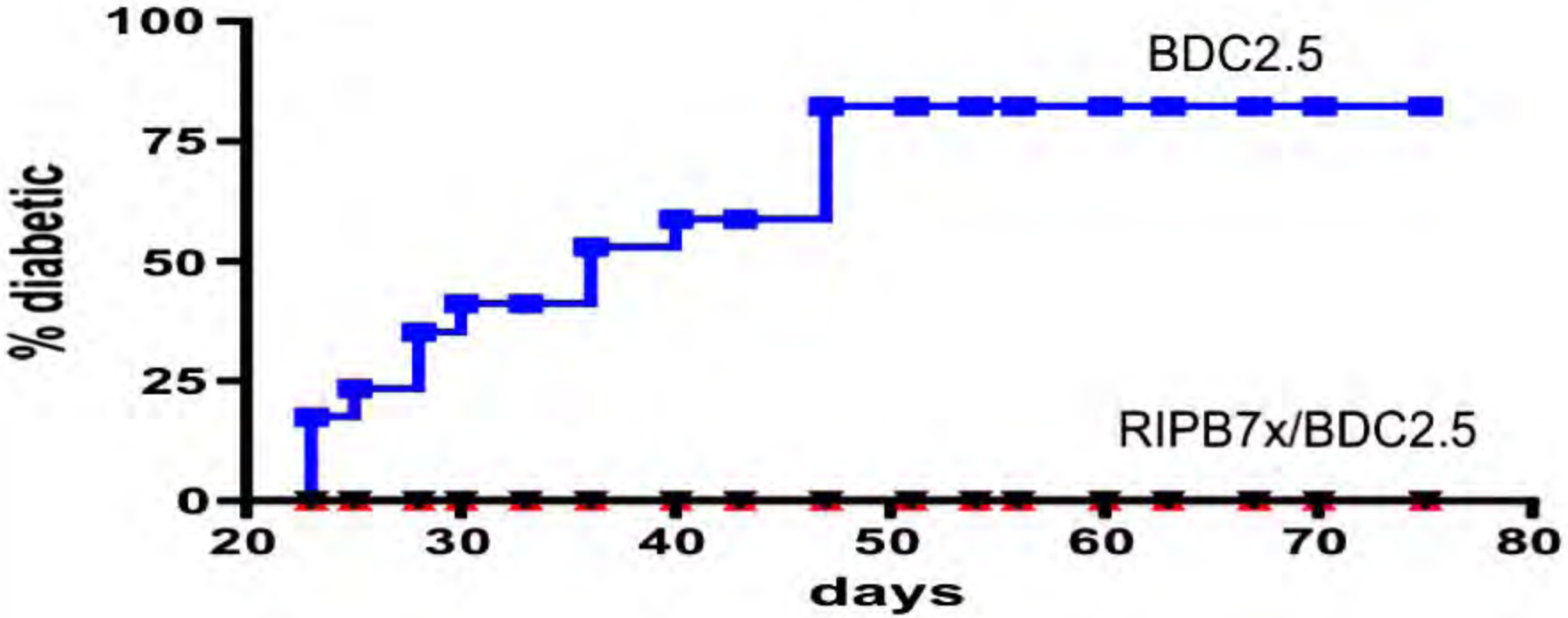
Increased Expression of B7x in Pancreatic Islets of RIPB7x Transgenic Mice





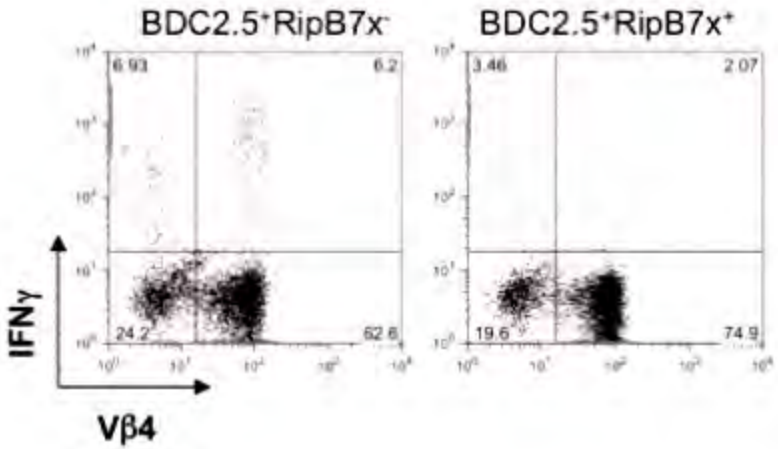


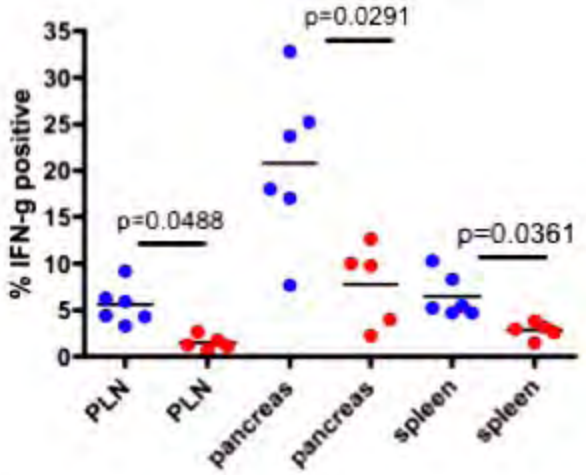
Overexpression of B7x in Pancreas in BDC2.5 Mice Prevents Diabetes

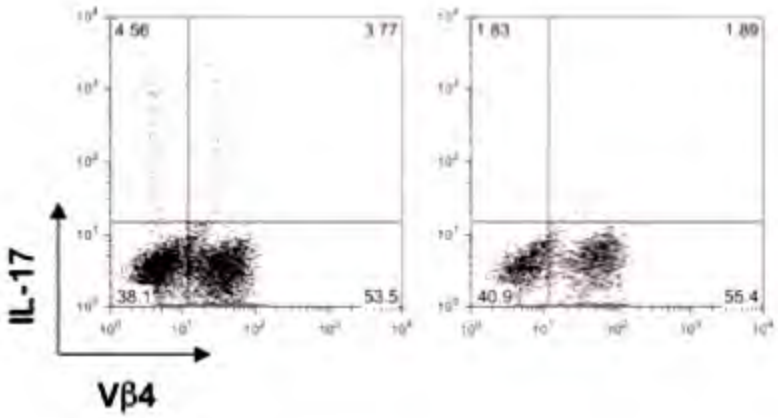


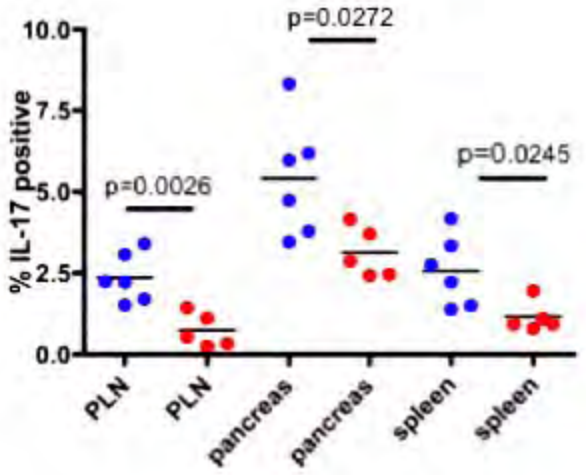
Overexpression of B7x in pancreatic islets inhibits IFN-γ and IL-17 production by BDC2.5 T cells

Intracellular cytokine staining of pancreatic islets



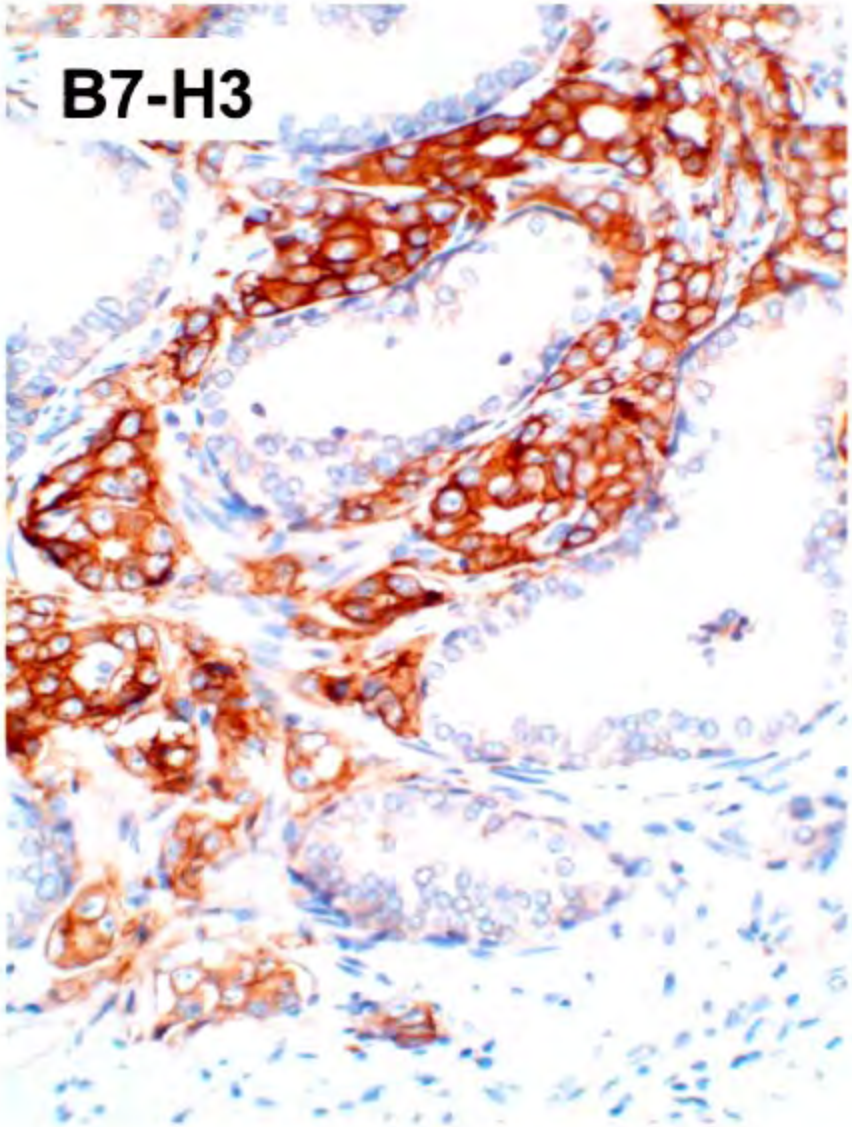


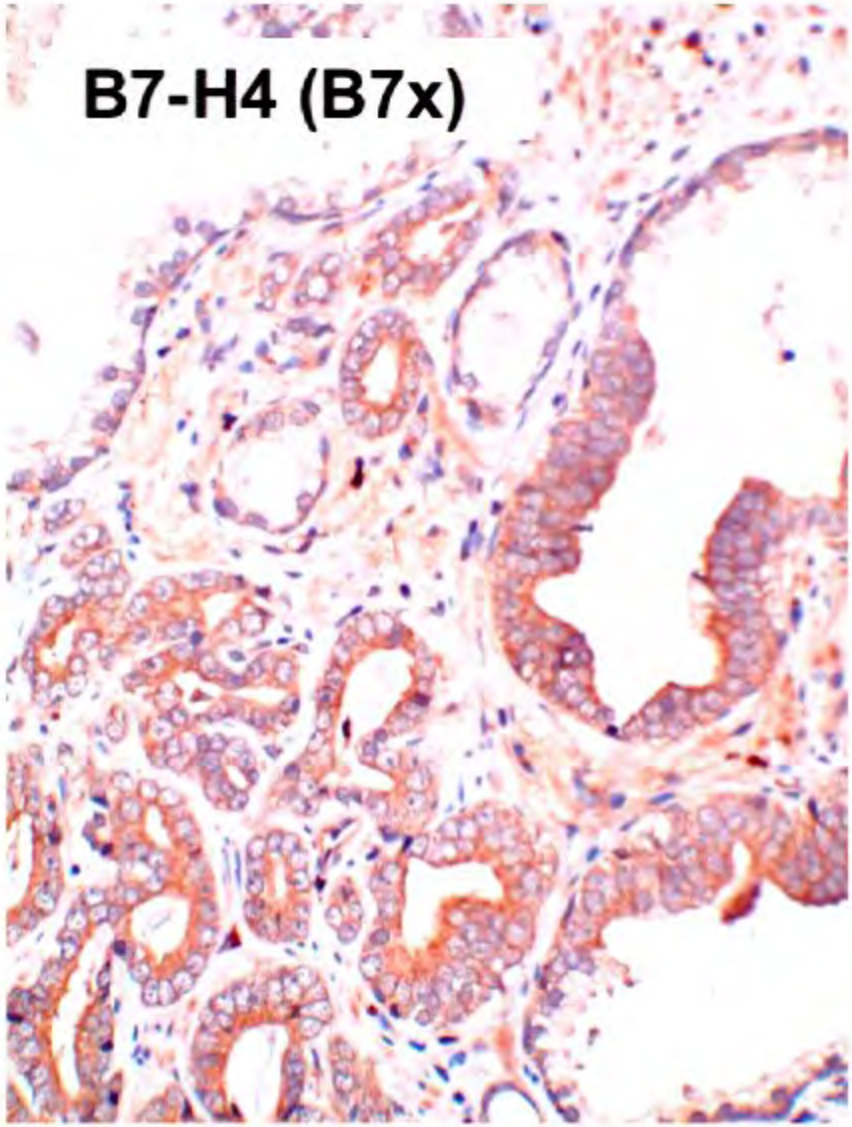




• BDC2.5+RipB7x-
• BDC2.5+RipB7x+

Human prostate cancer





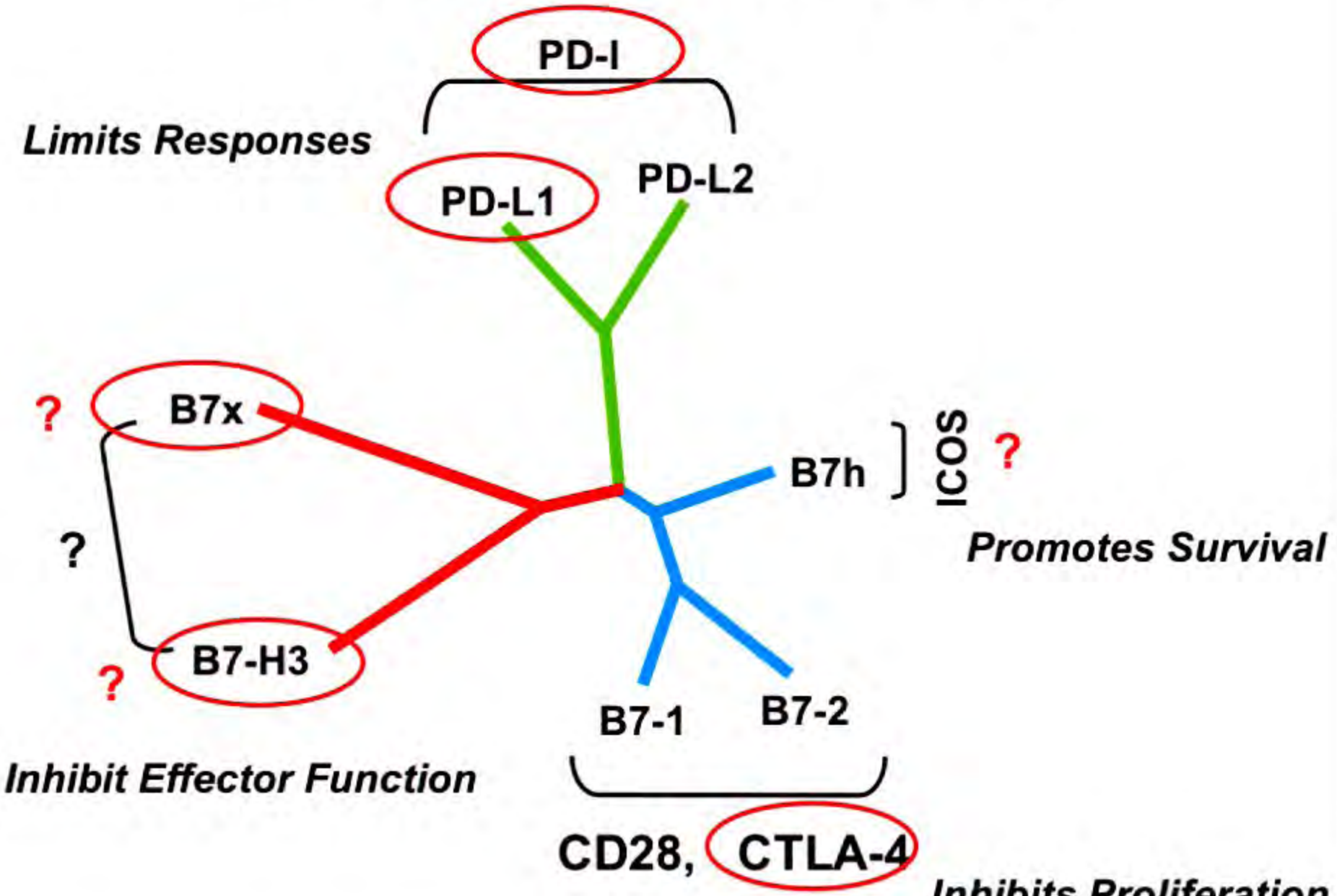
Reuter

Hi level expression of B7x/H3 in prostatectomy samples (n=803) correlates with:

- Extracapsular extension and non-organ confined disease at time of prostatectomy
- Higher risk of clinical failure (metastasis)
- Higher risk of death within 7 years of surgery

Zang et al. *PNAS 2007*

Extended B7-CD28 Family



Implications for Cancer Vaccines

Don't worry about:

- **Variegated expression of antigens that are targeted by vaccines**
- **Whether vaccine targets are essential to the tumor survival**
- **Clonality of transferred T cells**

Because death of cells should lead to cross-priming with a battery of other antigens which should be enhanced by checkpoint blockade

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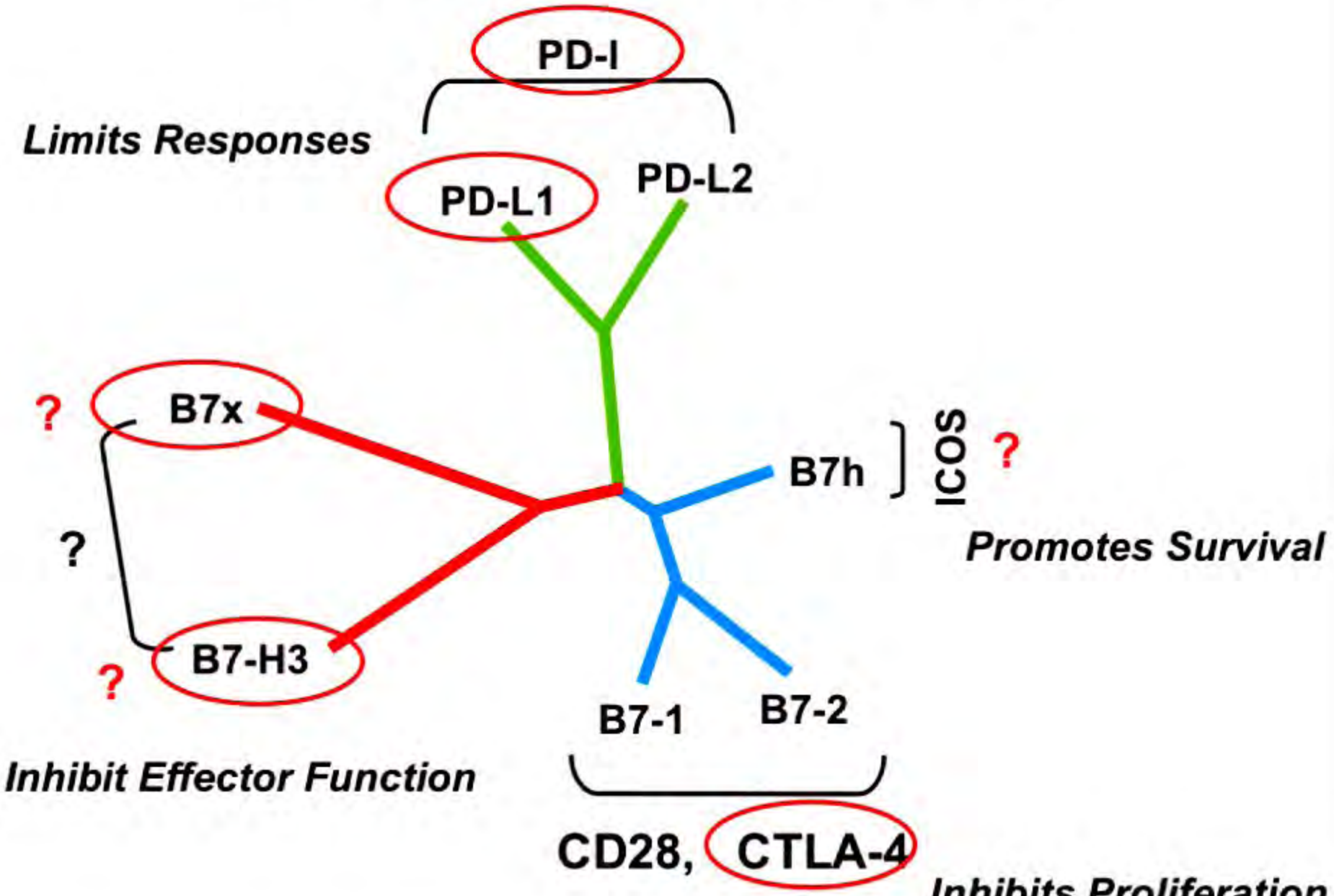

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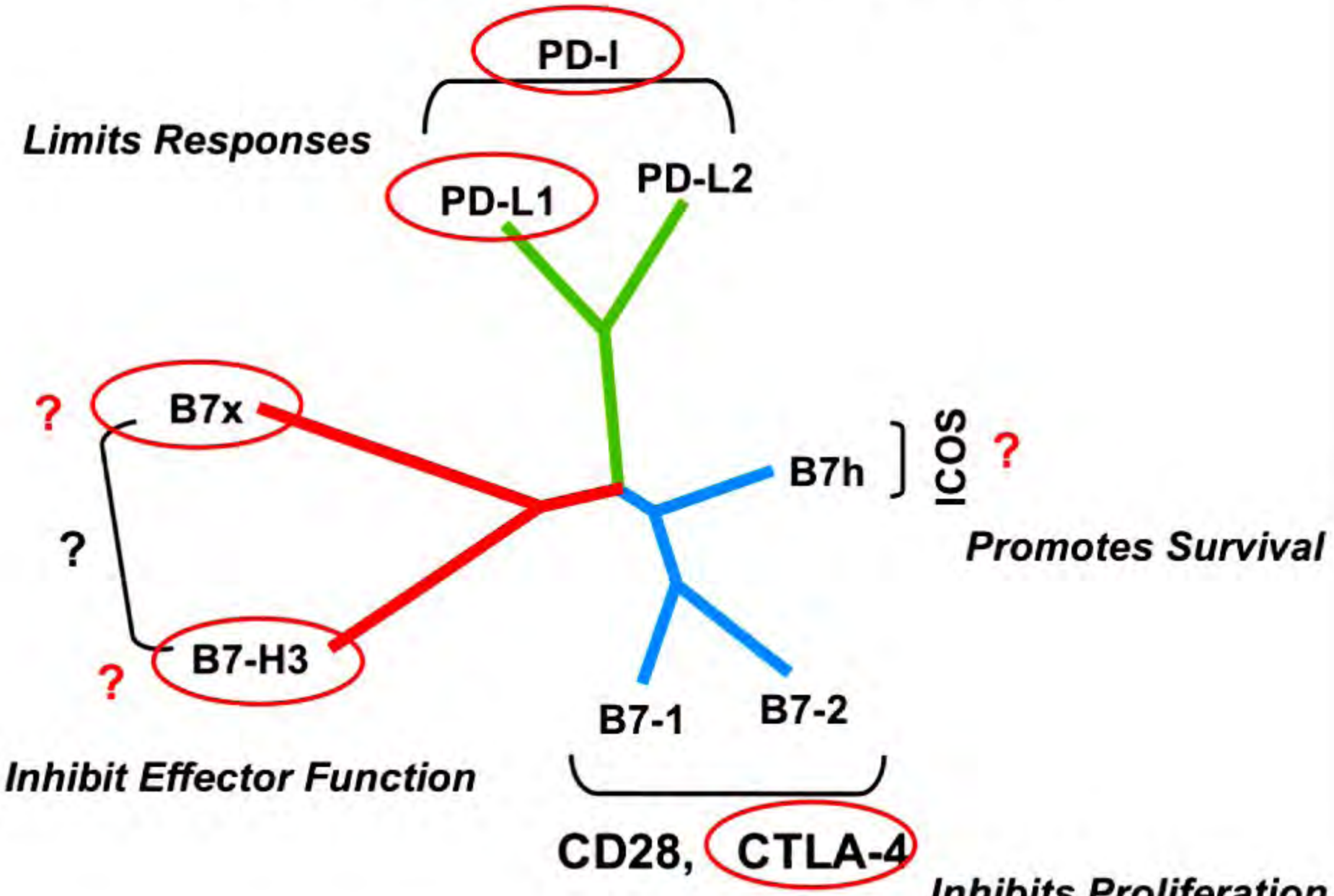

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Implications for "Immunosupportive" Therapies

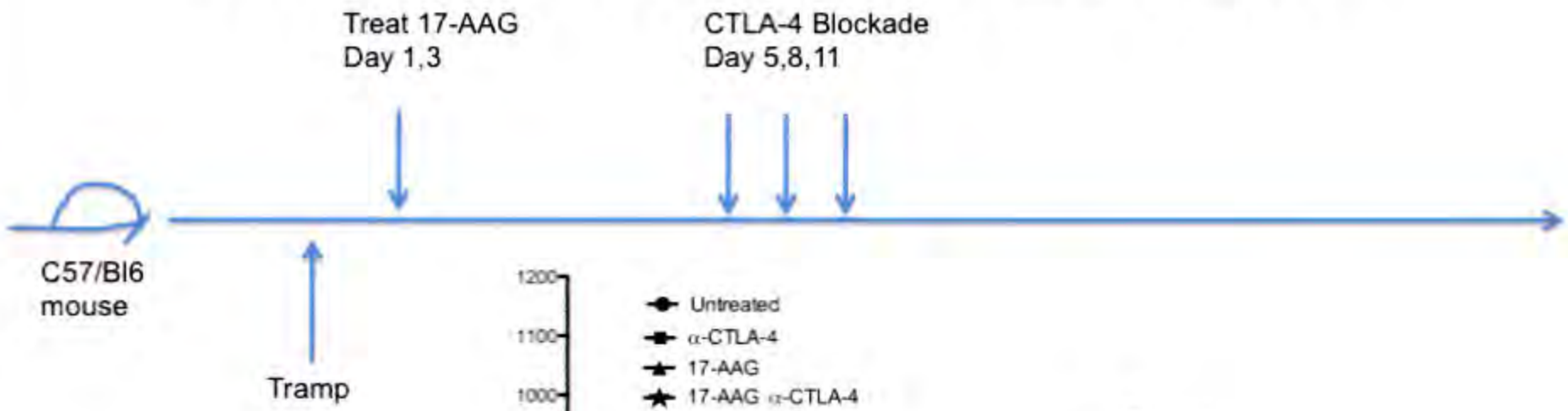
Genomic instability is the bane of targeted therapies,

but a goldmine for the immune system

Agents that kill tumor cells (chemotherapy, radiation, hormone therapy, "targeted" therapies) can be considered *vaccines*

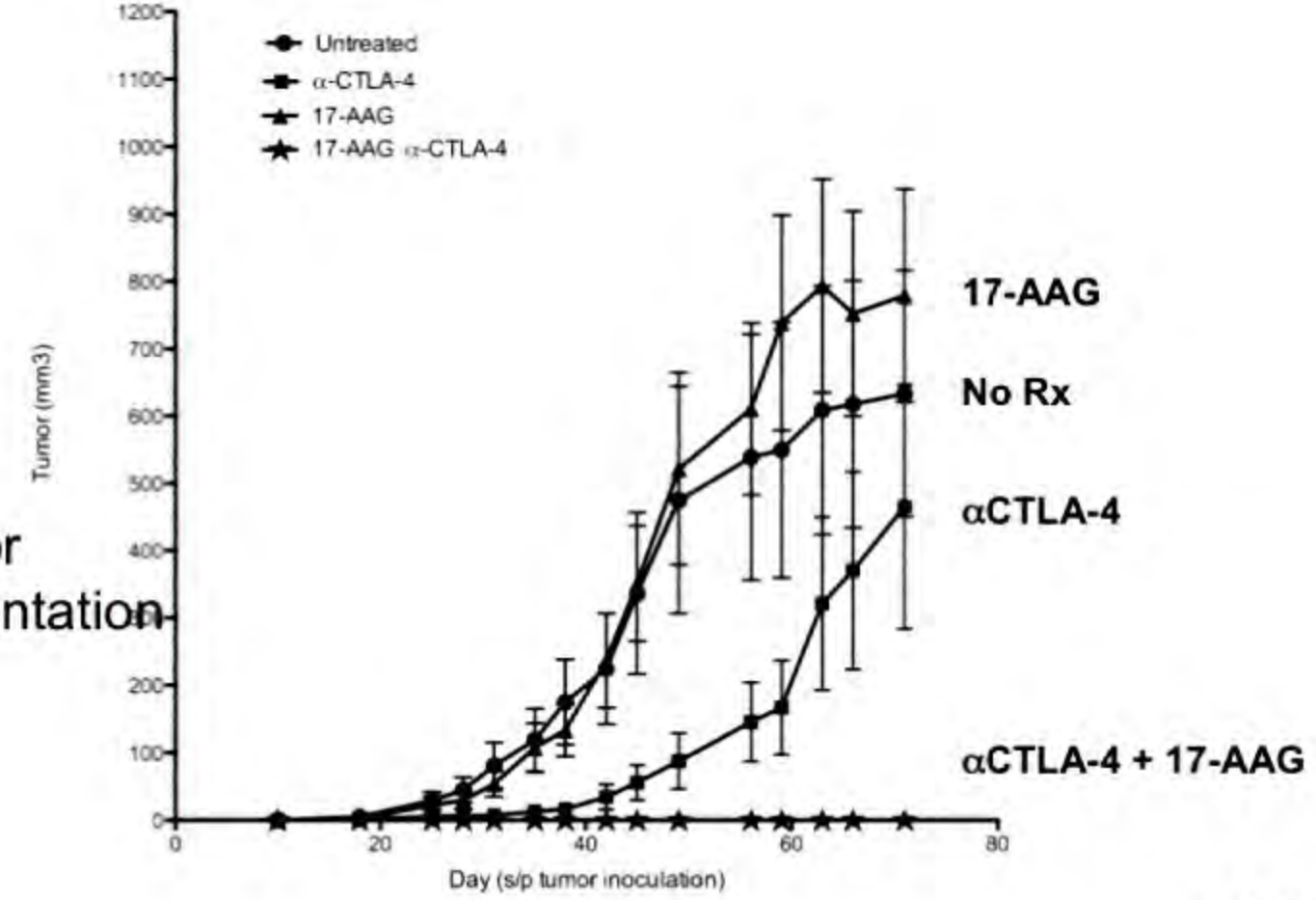
Use with checkpoint blockade to unleash the immune system to maximize T cell responses to multiple targets (turn 1 target into 6)

17-AAG plus CTLA-4 blockade is Effective In Treatment of TRAMP-C2 Prostate Tumors



17-AAG

- HSP 90 inhibitor
- Blocks antigen presentation



Ariyan

Allison Lab

Alejandro Sepulveda
Anne Trumble
Charlotte Ariyan
Emily Corse
Jenna Geddes
Jocelyn Lu
Joyce Wei
Michael Curran
Preston Sprenkle
Rachel Gottschalk
Rebecca Waitz
Sergio Quezada
Tsvetelina Hoang
Tyler Simpson
Virginia Pedicord
Welby Montalvo
Xiaozhou Fan

Ludwig Center for Cancer Immunotherapy

Jedd Wolchok

Lloyd Old

Pam Sharma

Sacha Gnjatic

Jianda Yuan & the IMF Crew