Cancer Immunotherapy by PD1& PDL1 Self Tolerance Blockade

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CANCER THERAPY & RESEARCH CENTER

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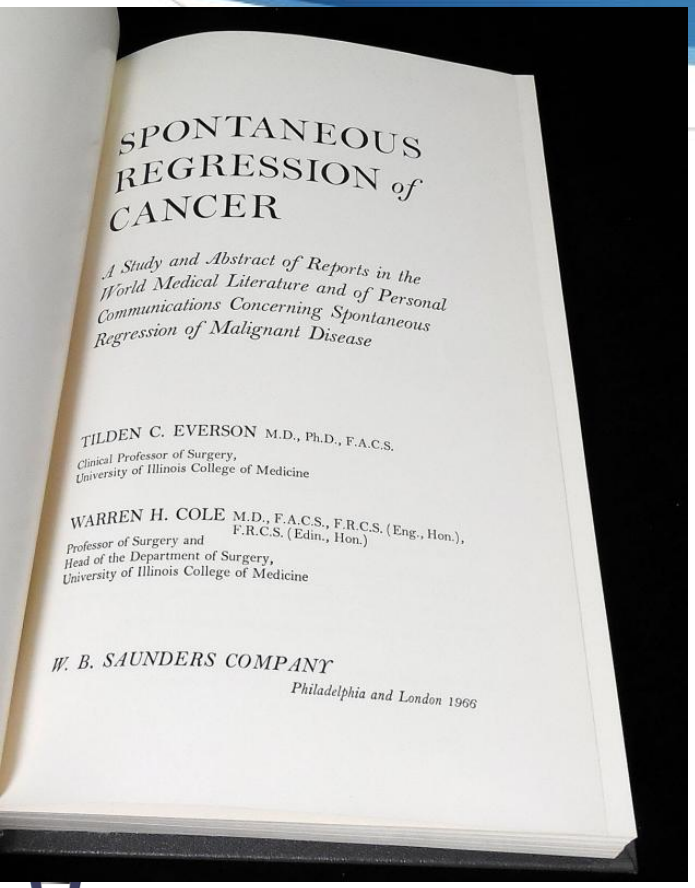
Overview

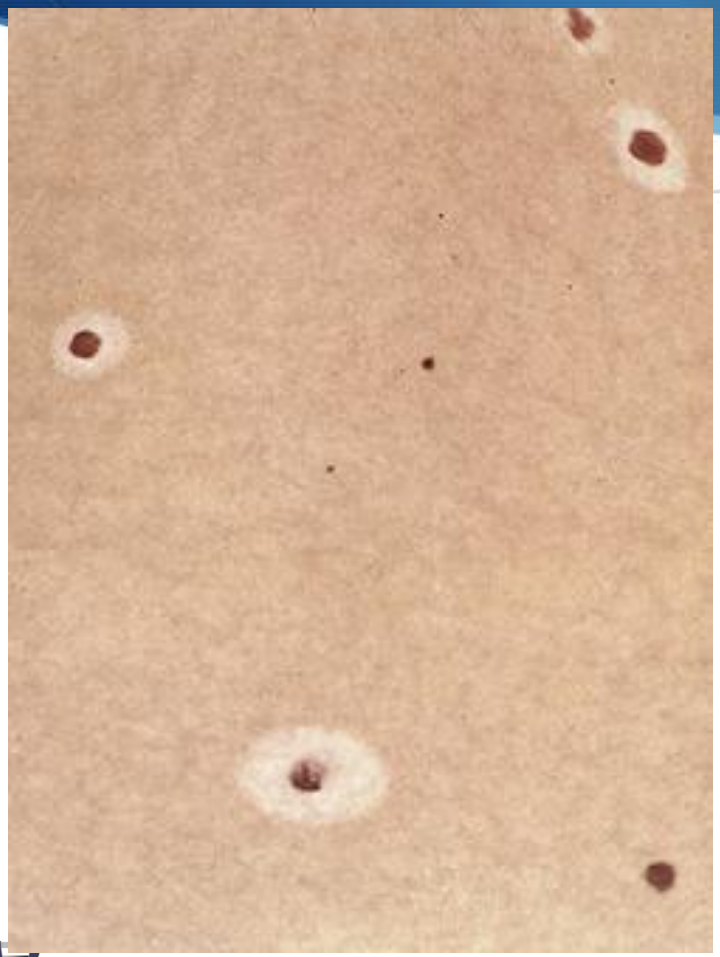
- Background & History Immunotherapy
  - Immune self tolerance
  - Melanoma, vitiligo, animal models
- Immune Correlates of Cancer Survival
  - Auto-immunity
  - Tumor infiltrating lymphocytes (TIL)
- Pharmacologic Self Tolerance Blockade
  - Central (priming phase) vrs Peripheral (effector phase)
  - PD1 & case presentation
  - PDL1 & case presentation
  - Biomarkers

Historical Cases of Spontaneous Regression of Cancer



- Rohdenburg summarized 185 spontaneous regressions, 1918
- Fauvet reported 202 cases between 1960–1964
- Boyd reported 98 cases in 1966
- Everson and Cole described 176 cases between 1900–1960
- Challis summarized 489 cases between 1900–1987
- Hobohm, in a meta-analysis, investigated about 1000 cases
  - Frequency was estimated to be about 1 in 100,000 cancers

Why Study Malignant Melanoma in Tumor Immunology? Can See It

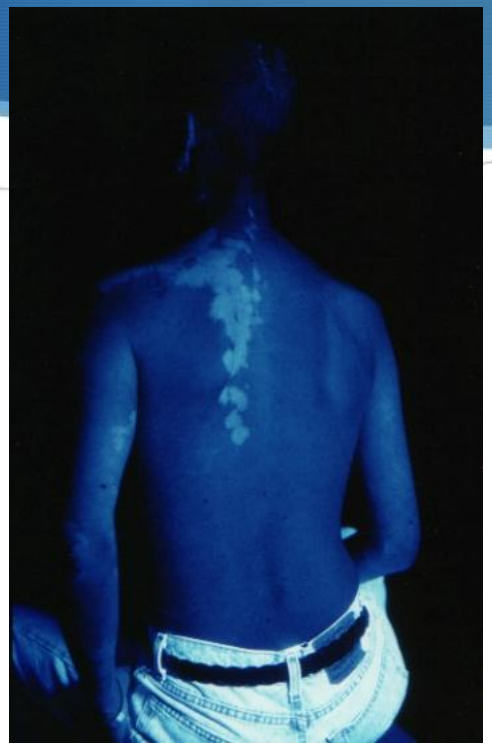
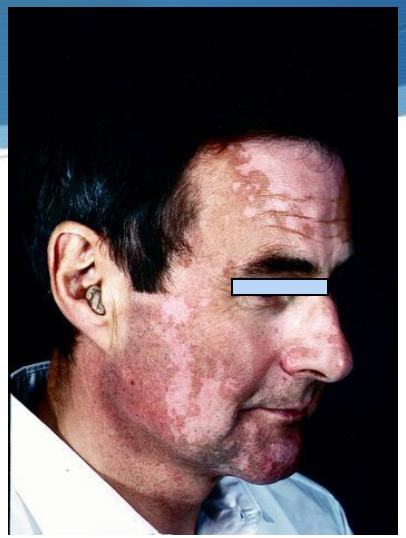
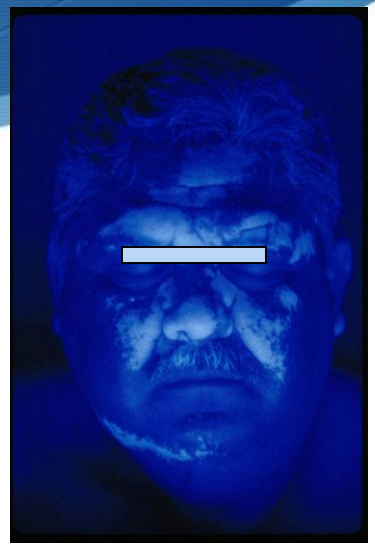


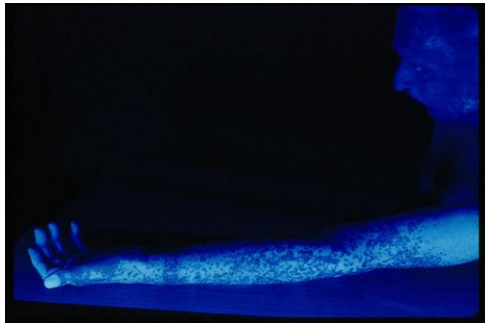
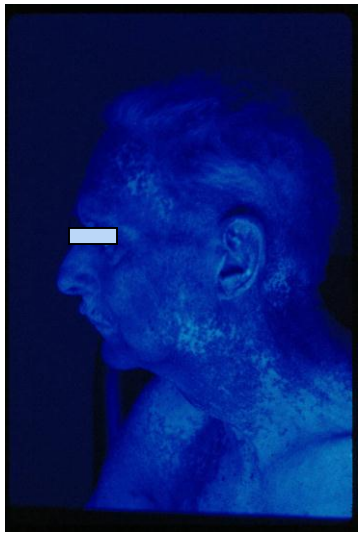
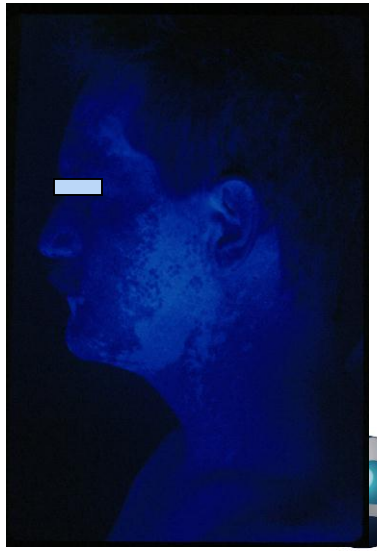
Halo Nevi

- Model for Melanoma regression
  - Human and animal models
  - Occurs with auto-immunity to melanocyte self-antigens (vitiligo) easily seen
  - Specific T-cell and humoral responses occur
  - Break self-tolerance
- Vitiligo patterns may be a template of antigen repertoire
- Immune system can recognize any tumor (not just melanoma)

IL-2 Melanoma Immunotherapy

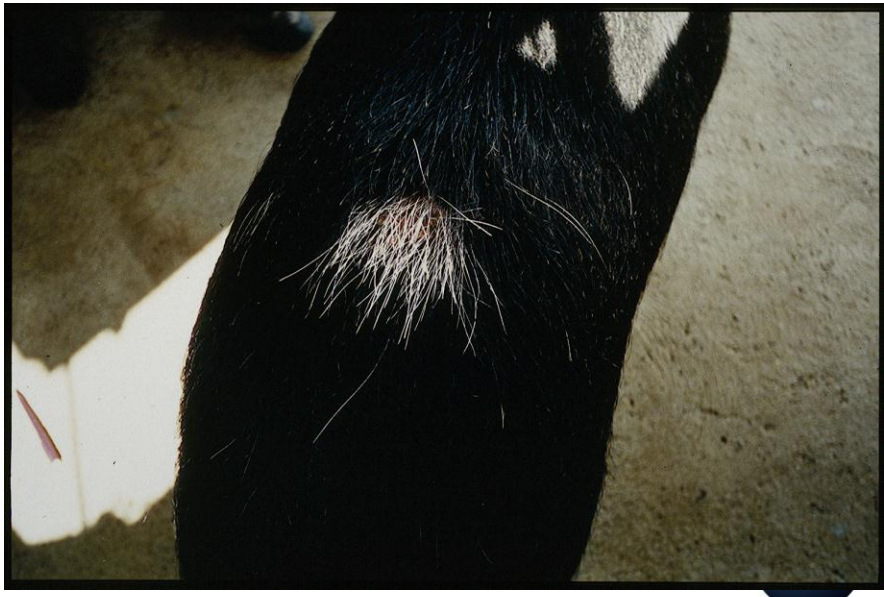
Breaking self tolerance with vitiligo, Strongest clinical marker of melanoma regression

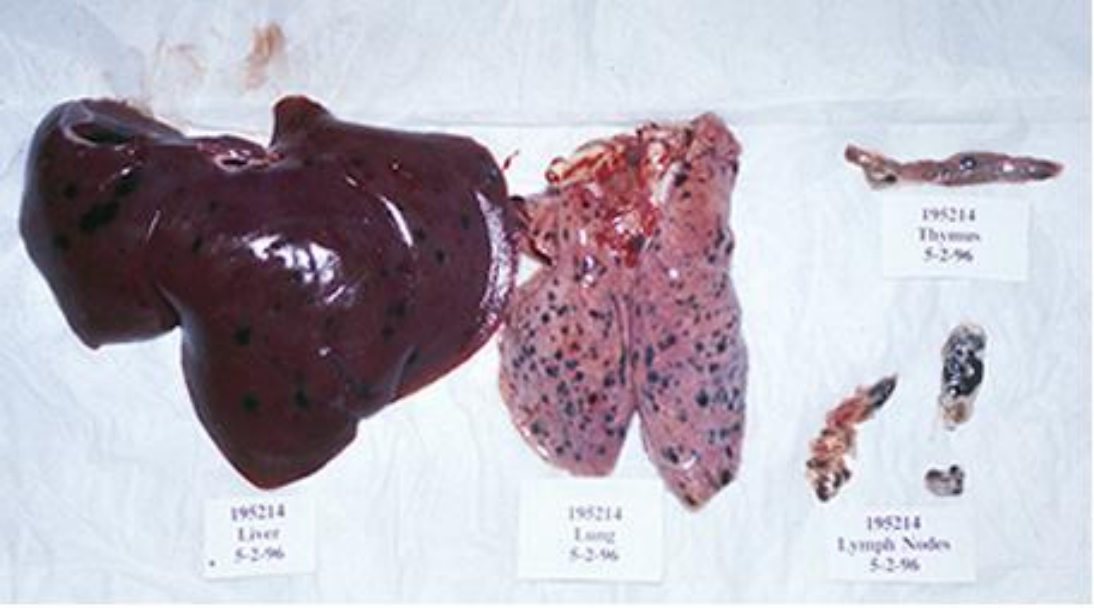





Animal Models of Immunotherapy

Sinclair Swine Melanoma




195214
Liver
5-2-96
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Lung
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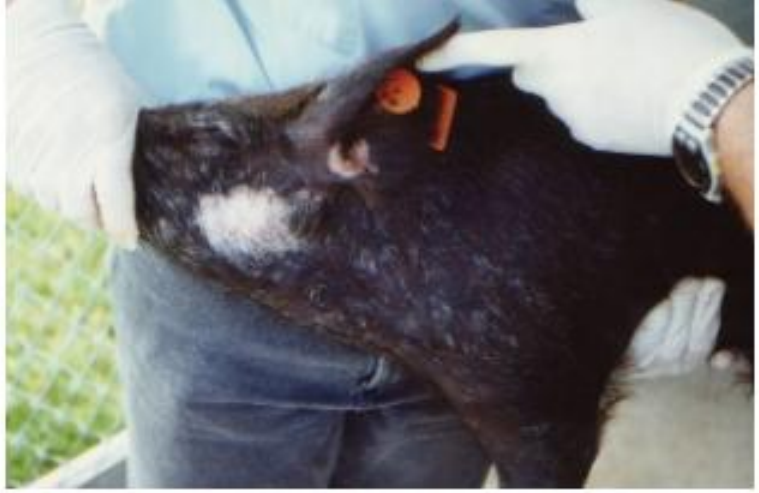
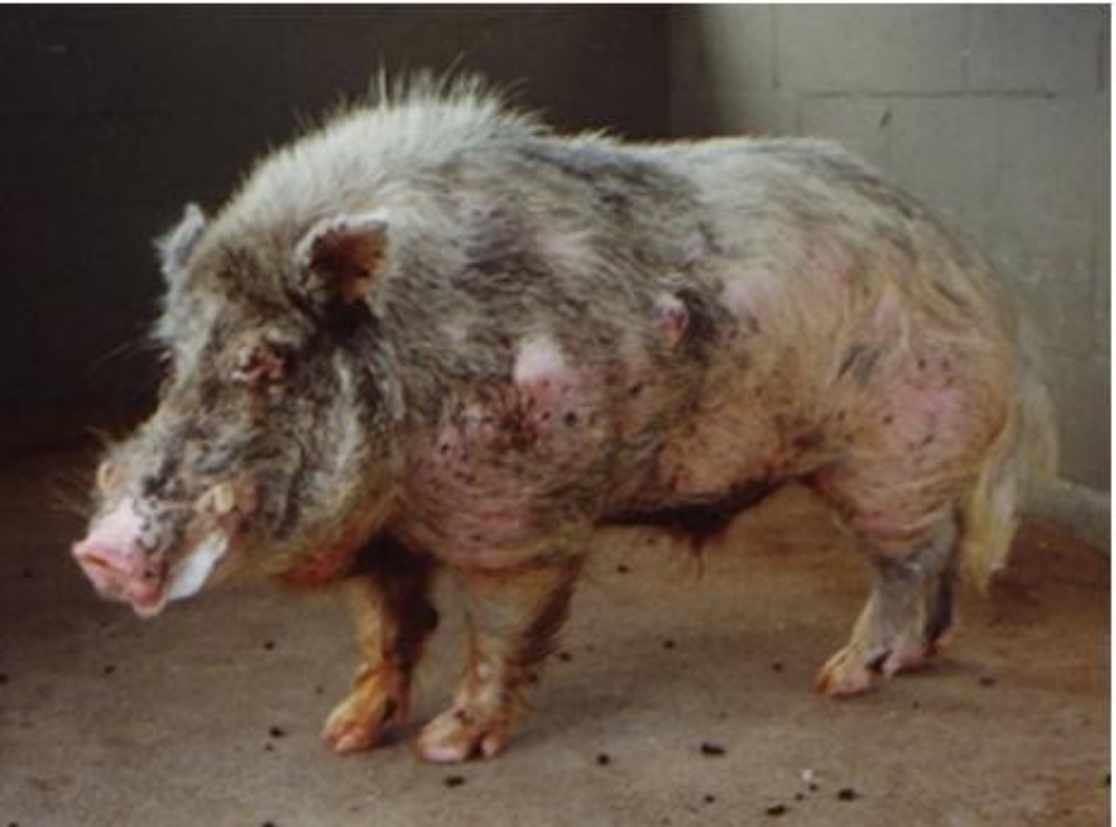
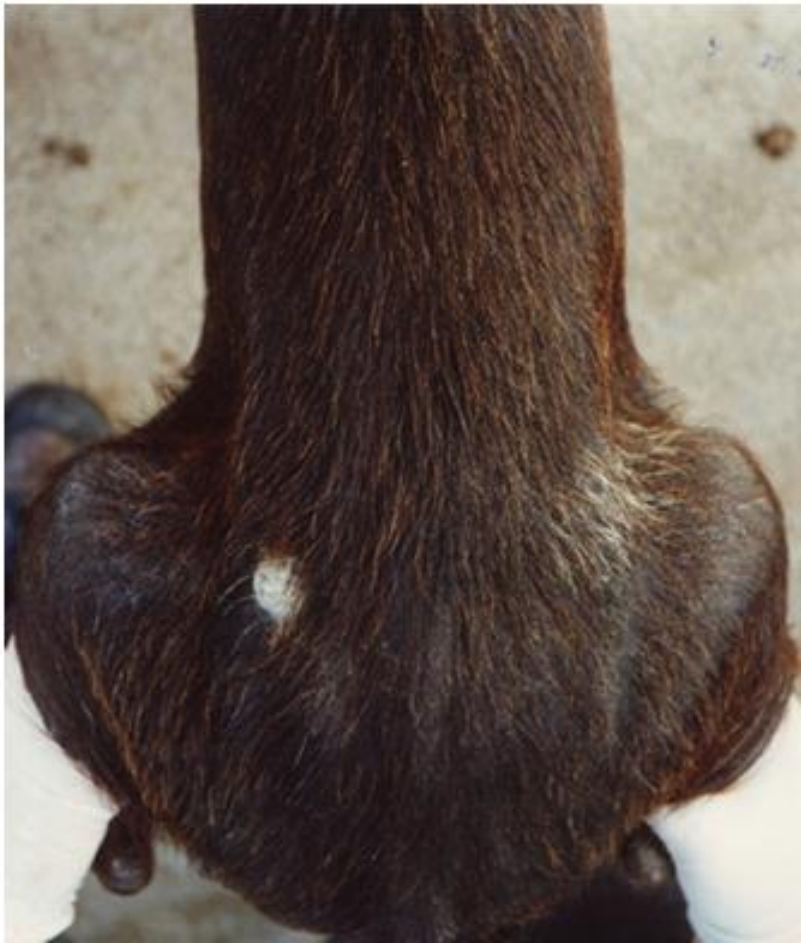
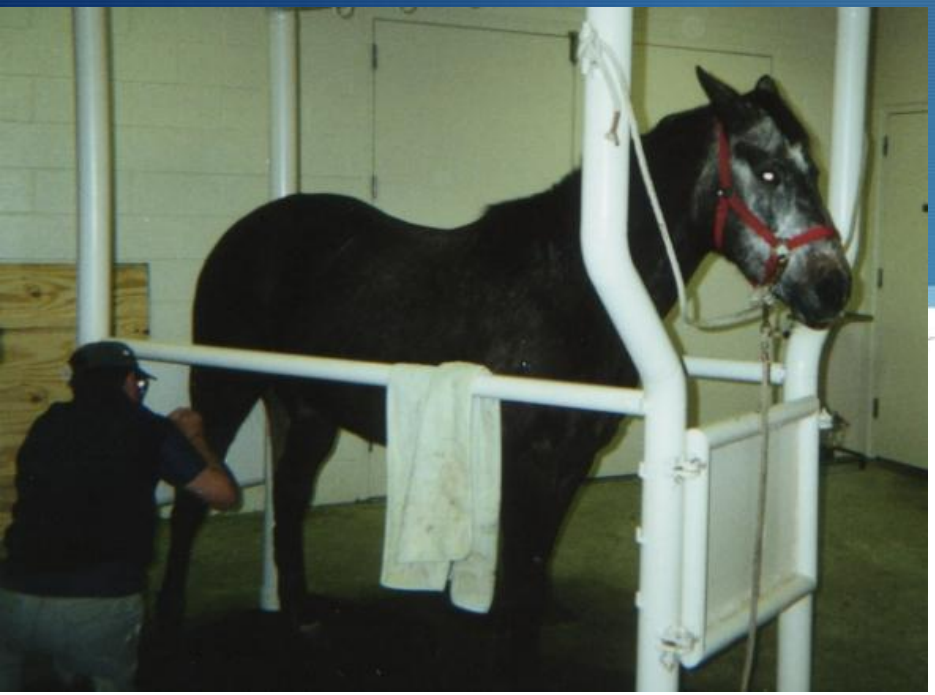
Thymus
5-2-96
195214
Lymph Nodes
5-2-96

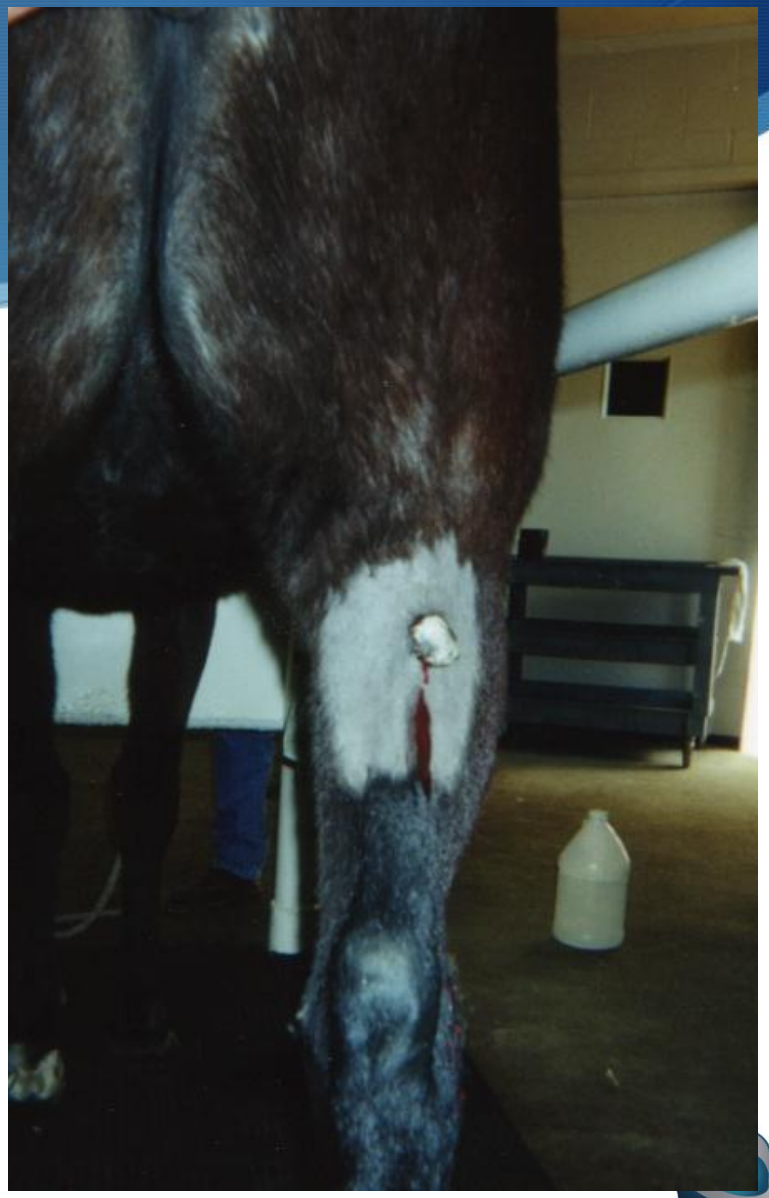






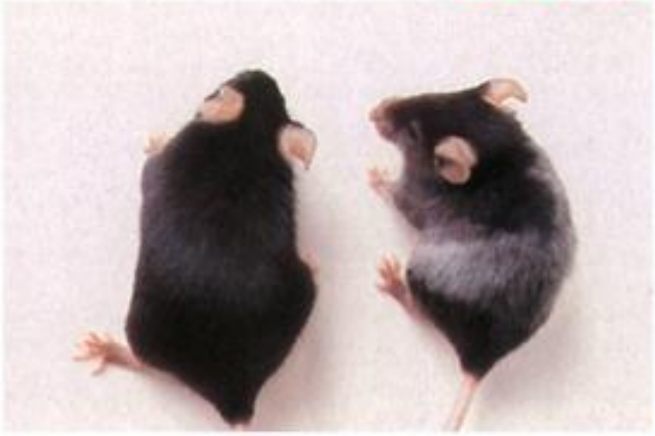
Grey Horse Melanoma



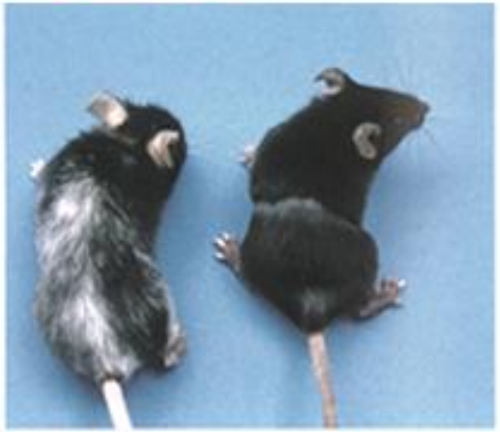


Mouse Melanoma Immunotherapy

Break vrs *Block* Self-Tolerance

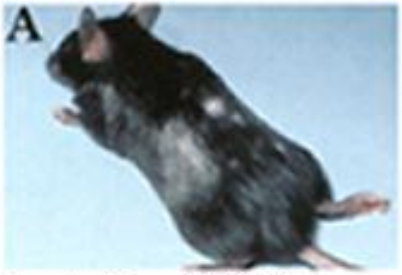


Anti-TRP1 murine Ab
Hara, Takechi, Houghton 1995
Passive

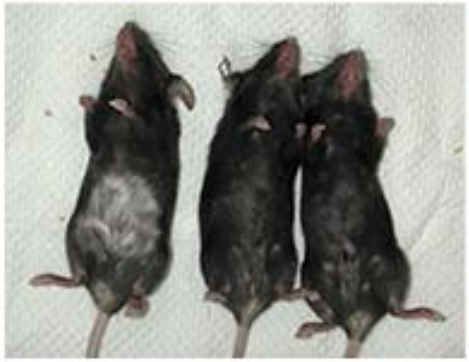


Insect Expressed TRP1 vaccination
Naftzger, Hara, Houghton 1996
Active, Mono-Valent, Non-Self

Vaccinia virus encoding TRP1
Overwijk, Restifo, Rosenberg 1998
Active, Mono-Valent, Altered-Self



Vaccination GM-CSF expressing
irradiated murine melanomas
CTLA-4 mAb blockade
Van Ela, Hurwitz, Allison 1999
Active, Poly-Valent, Self
Block Self-Tolerance



Alphavirus encoding TRP1
Lietner, Restifo 2003
Active, Mono-Valent,
Altered-Self

Chemokine knockout mice
CCR5-/- and MIP1α -/-
Melanoma lysate pulsed DCs
Ng-Cashin, Powderly,
Serody 2003
Active, Poly-Valent, Self

Adoptive T-Cell Transfer
Vaccinia, Fowlpox Virus
Encoding mutated gp100
Overwijk, Restifo 2004
Active, Adoptive, Mono-Valent
Altered Self, Mutated Peptide

Immune Correlates of Cancer Survival

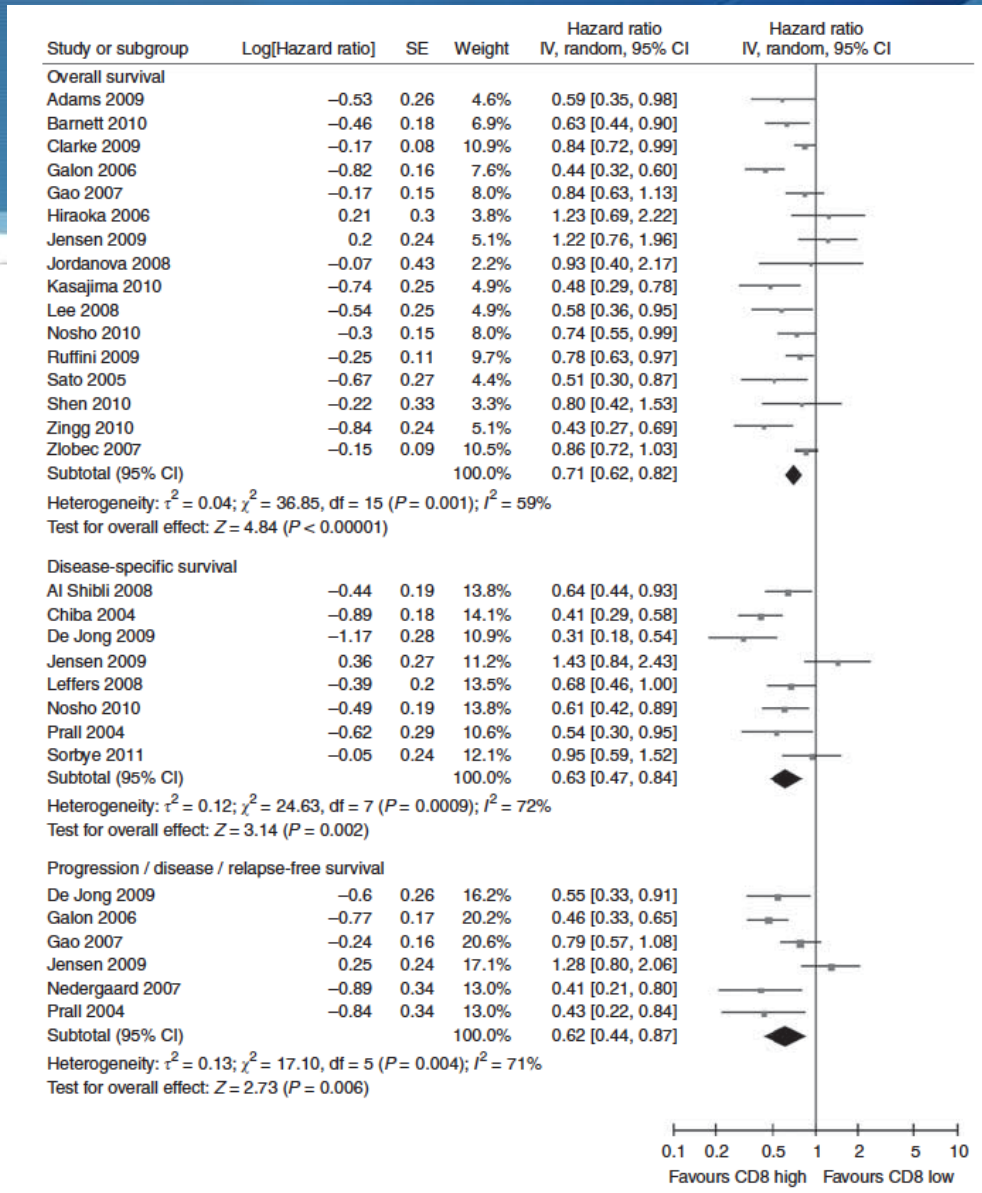
Presence of Tumor Infiltrating Lymphocytes Correlate with Survival

Prognostic Influence of TIL in Cancer: A Systematic Review with Meta-Analysis

Gooden et al; British Journal Cancer 2011; 105: 93-103

52 studies that included
>100 patients each study,
Total 12,445 patients.
Median f/u 4 years,
ratios CD3:CD4:CD8:FoxP3

Results: CD3, CD8 TIL favorable effect on survival.
High CD8:FoxP3 ratio most predictive survival.



Autoimmunity Associated With Clinical Response to Immune Therapy

M. Dsis 2011 JCO

- Prospective observational study of 3,000 patients evaluated clinical factors associated with favorable outcome
  - Vitiligo predictive in multivariate analysis (p = .006 for OS)
- Study evaluating the laboratory and clinical characteristics of 374 patients treated with IL-2 to determine biomarkers of response (NCI)
  - Thyroid dysfunction (p = .01) and vitiligo (p < .01) were predictors of increased survival
- Trial of 198 MM or RCC patients treated with ipilimumab suggested a higher response rate in patients who developed enterocolitis compared to those that did not (p = .0065) (NCI)
- Evaluation of 200 stage II/III melanoma patients treated with interferon; development of autoimmunity correlated with longer relapse-free survival (p < .001) as well as OS (p < .001)
  - Some immunity was sub-clinical (serologic only) and still demonstrated effect

Disis, 2011.

Tumor Immune Evasion

Immune system is exponentially more adaptable then tumor

Vaccines Are *The* greatest success story of modern medicine by eradicating infectious diseases.

So why don't cancer vaccines work?

- Infections
  - Discriminate self from *non*-self
- Tumors
  - Discriminate self from *altered*-self
    - Every tumor cell potentially unique
  - Discriminate ***absence*** of self
    - Tumor cells lose HLA and antigens

Self Tolerance = Self Preservation

- 98% anti-self lymphocytes undergo apoptosis
- Remaining T-cells >90% tolerizing surveillance

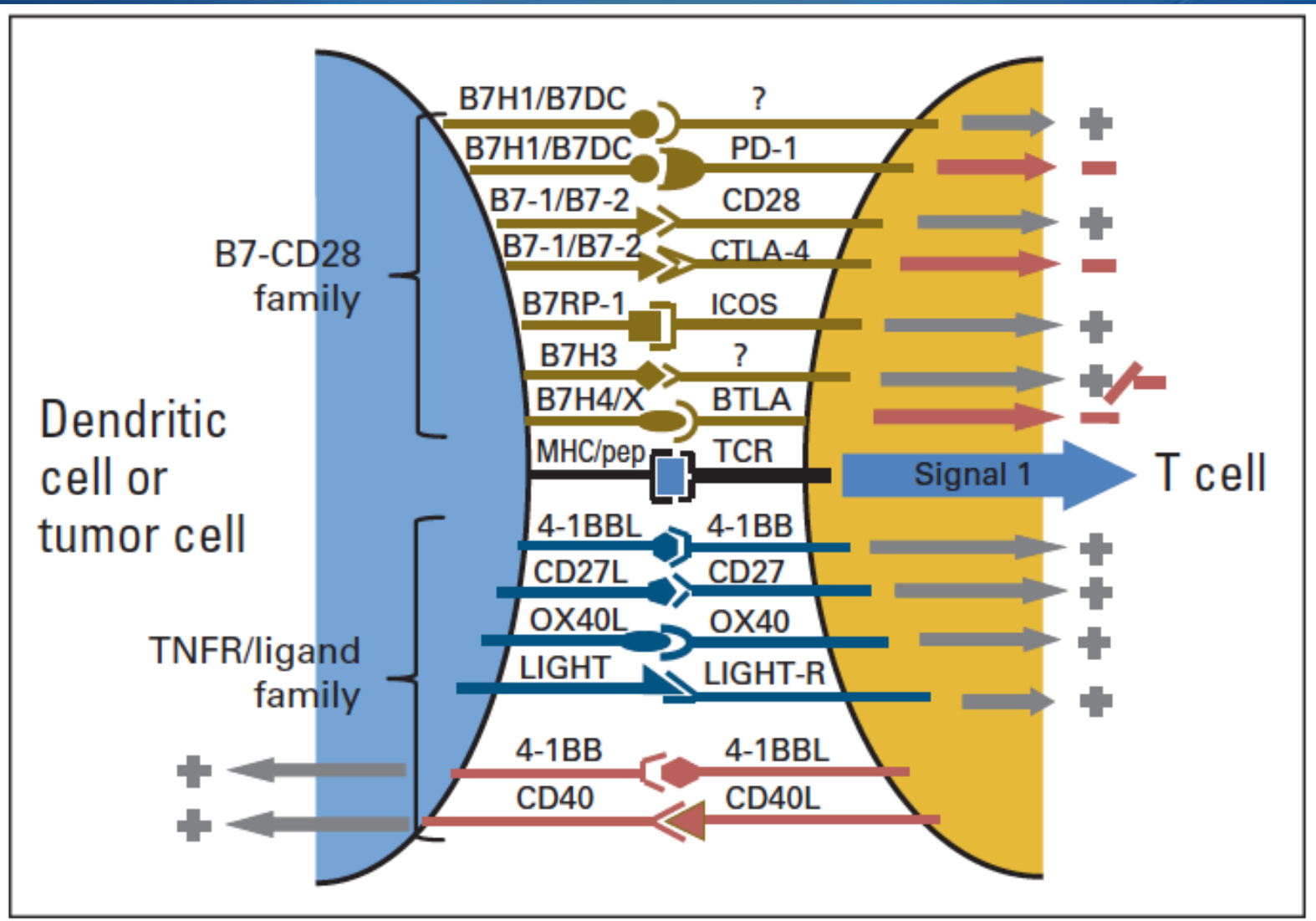
Pharmacologic Self-Tolerance Blockade (CTLA-4, PD1/PDL1) Induces Durable Tumor Regression

Cancer Self-Tolerance Blockade

- Self Tolerance: cancer is viewed as self & tolerated
- Self-tolerance blockade: cancer is viewed as foreign & rejected
- Tumors exploit mechanisms to suppress the host immune response
  - Immune checkpoints (CTLA-4, PD1/PDL1) abort immune responses
    - Co-opted by tumors to evade immune destruction
  - Immune checkpoint inhibitors can block self-tolerance of cancer, and enable anti-tumor immune destruction
    - Risk: auto-immunity
    - *Central* (*priming phase*) self tolerance blockade: CTLA4 in lymph node compartment during antigen presentation
    - *Peripheral* (*effector phase*) self tolerance blockade: PD1/PDL1 at site of tumor inflammation during lymphocyte infiltration

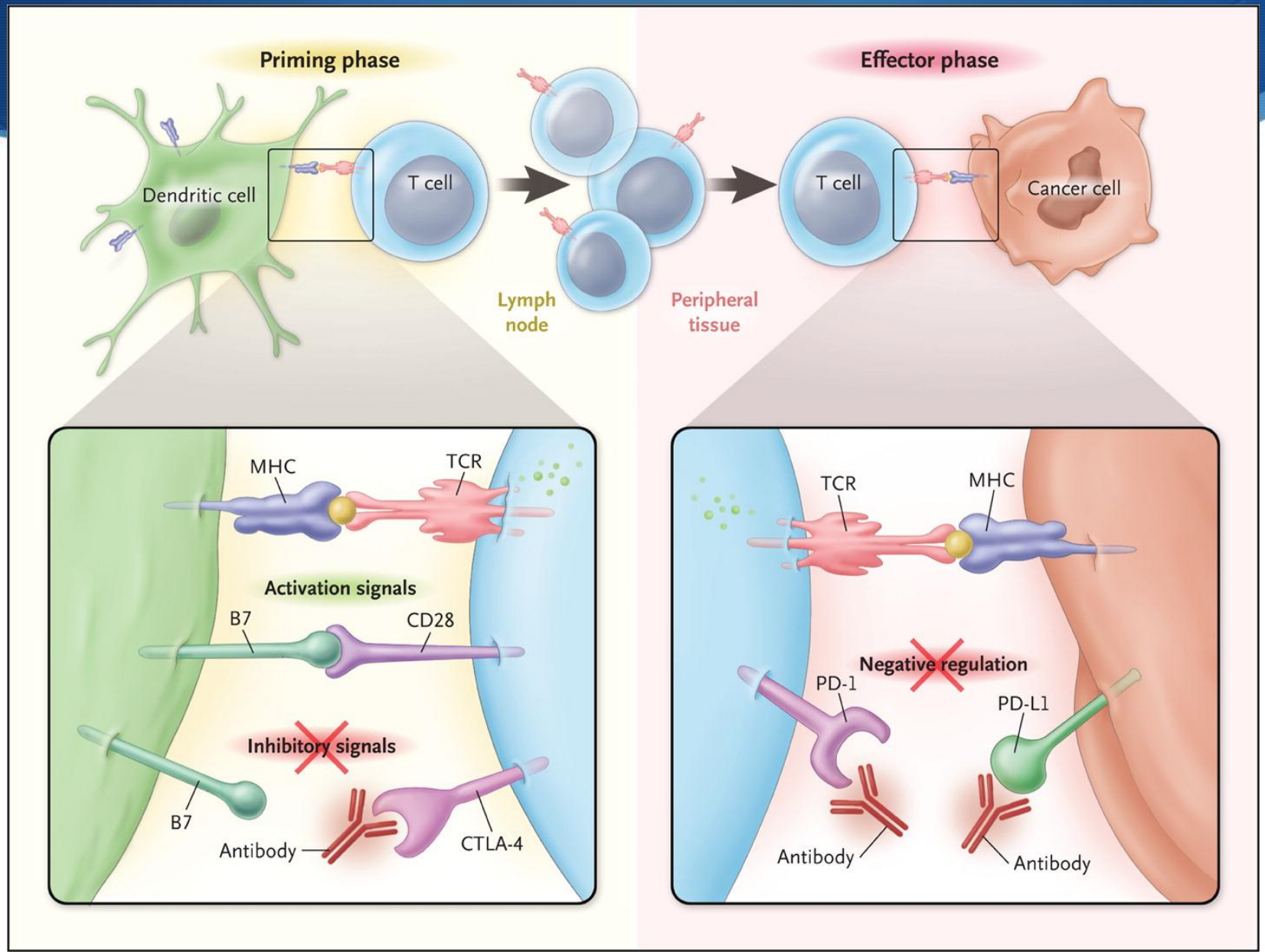
Immune Recognition & Tolerance

Adapted from “Cancer Immunotherapy Comes of Age” Topalian, Weiner, Pardoll, JCO 2011



Tumor Immunotherapy CTLA4 vrs PD1/PDL1

Antoni Ribas, NEJM epub June 2012



Self-Tolerance Blockade Drugs in Development

- Anti-CTLA-4
  - Ipilimumab (Fully human IgG1) FDA Approved 2011
  - Tremelimumab (Fully human IgG2) Phase III
- Anti-PD-1
  - MDX-1106, Nivolumab, (Fully human IgG4) Phase III
  - CT-011 Pidilizumab (Humanized IgG1) Phase II
  - MK3475 Pembrolizumab (formerly Lambrolizumab) (Humanized IgG4) FDA Approved 2014
  - AMP-224 (B7-DC/IgG1fusion protein) Phase I-II
  - MEDI0680, AMP514 Phase I
- Anti-PD-L1
  - MDX-1105, (Fully human IgG4) Phase I
  - MPDL3280A, RG7446 Phase II
  - MEDI4736 Phase III
  - MSB0010718C Phase I

PD1 Blockade

MDX-1106 001: Phase I Study of Single-Agent anti PD1 (MDX-1106, Nivolumab) in Refractory Solid Tumors: Safety, Clinical Activity, Pharmacodynamics, and Immunologic Correlates;

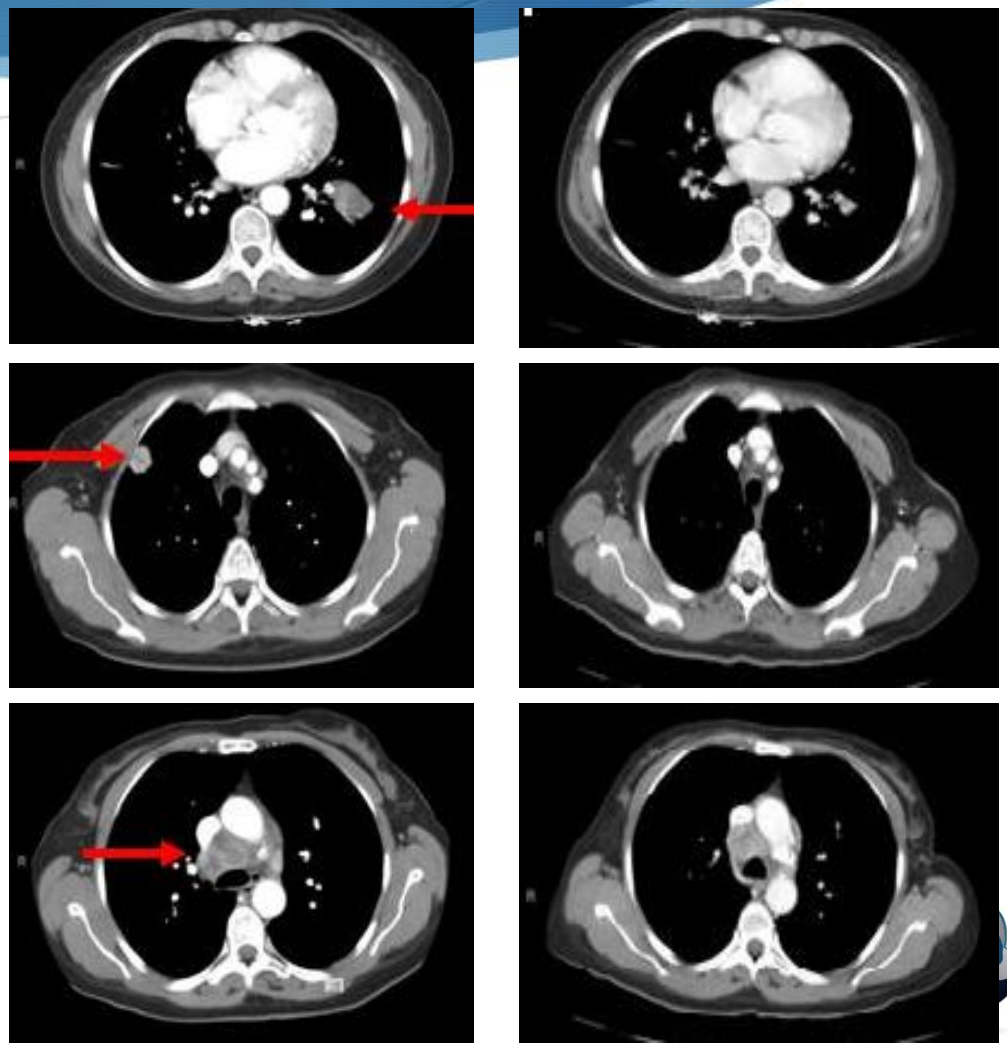
Brahmer, Drake, Wollner, Powderly, Topalian et al, JCO 2010 28:3167

61yo BF Stage IV NSCLung CA (squamous) bilateral lung metastasis, bone mets. Prior treatment carboplatin/vinorelbine/bevacizumab

May 2007, Rx single dose of MDX-1106, anti-PD1mAb (1mg/kg IV)

8 week 41% RECIST partial response, but 12 week scans showed new spine mets (mixed response).

Rechallenged MDX-1106, progressed

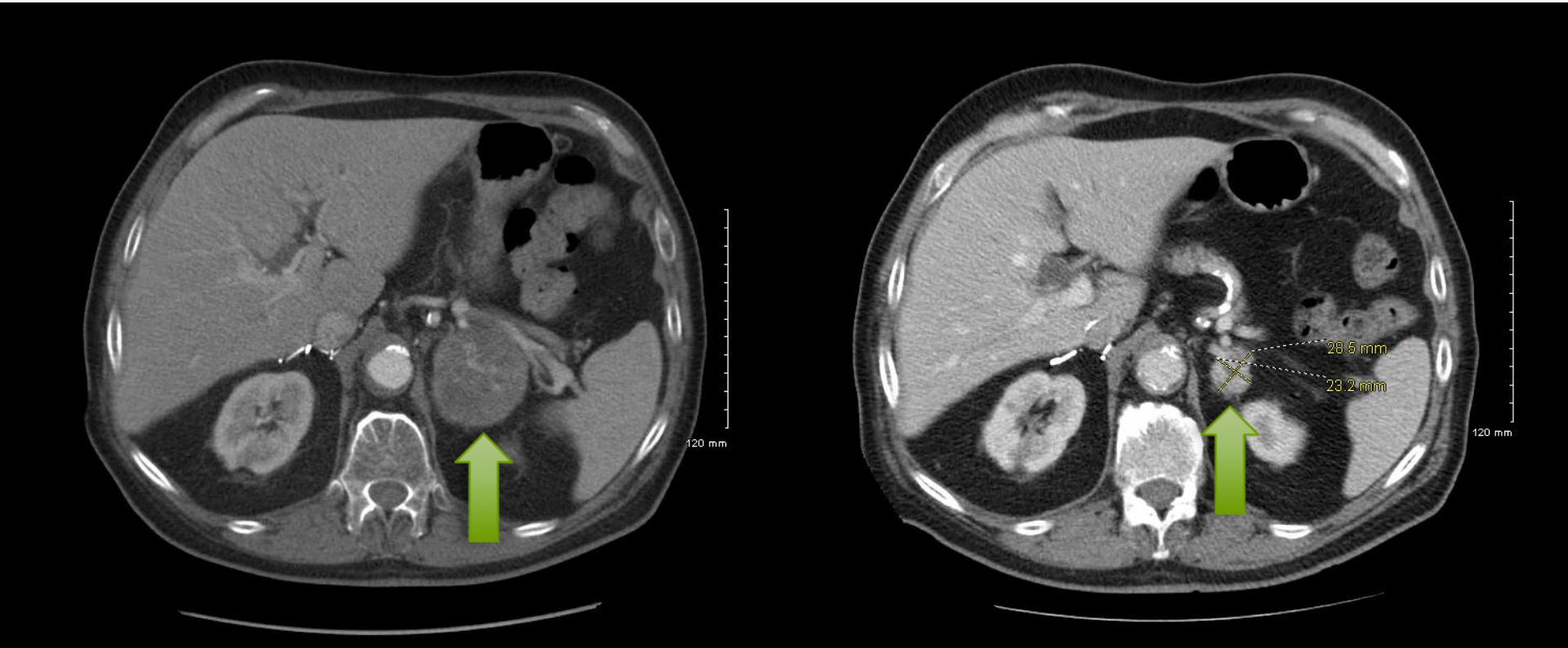


Durable Response Anti-PD1 mAb blockade Still Alive in Near Remission 2014 (5 years)

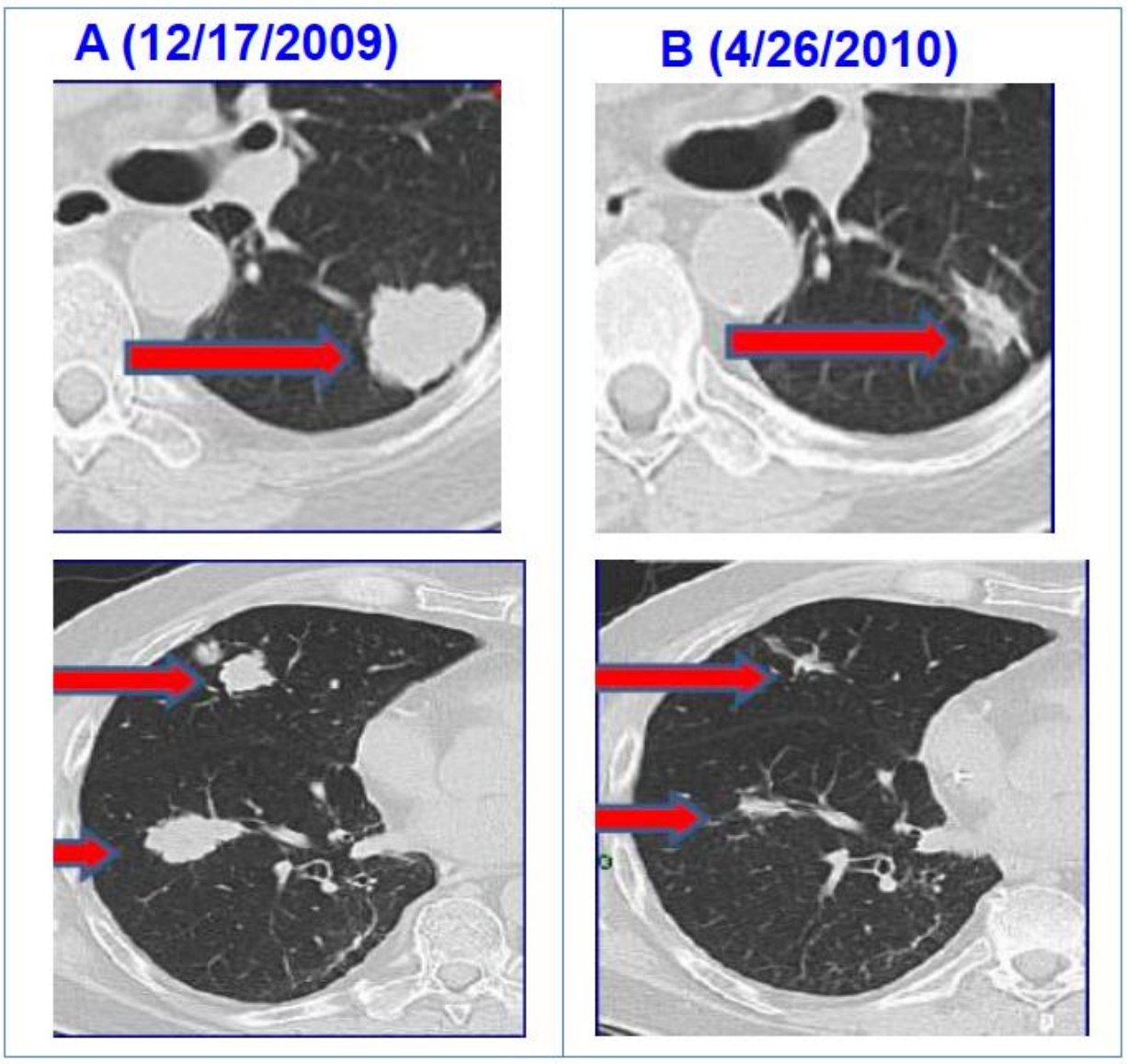
69yo WM Metastatic Squamous Cell Lung Cancer
Failed prior carboplatin/paclitaxel/bevacizumab 2008

February 2009

September 2009



Anti-PD1 mAb Lung Cancer Response



60 yr/male patient
•diagnosed in 2002

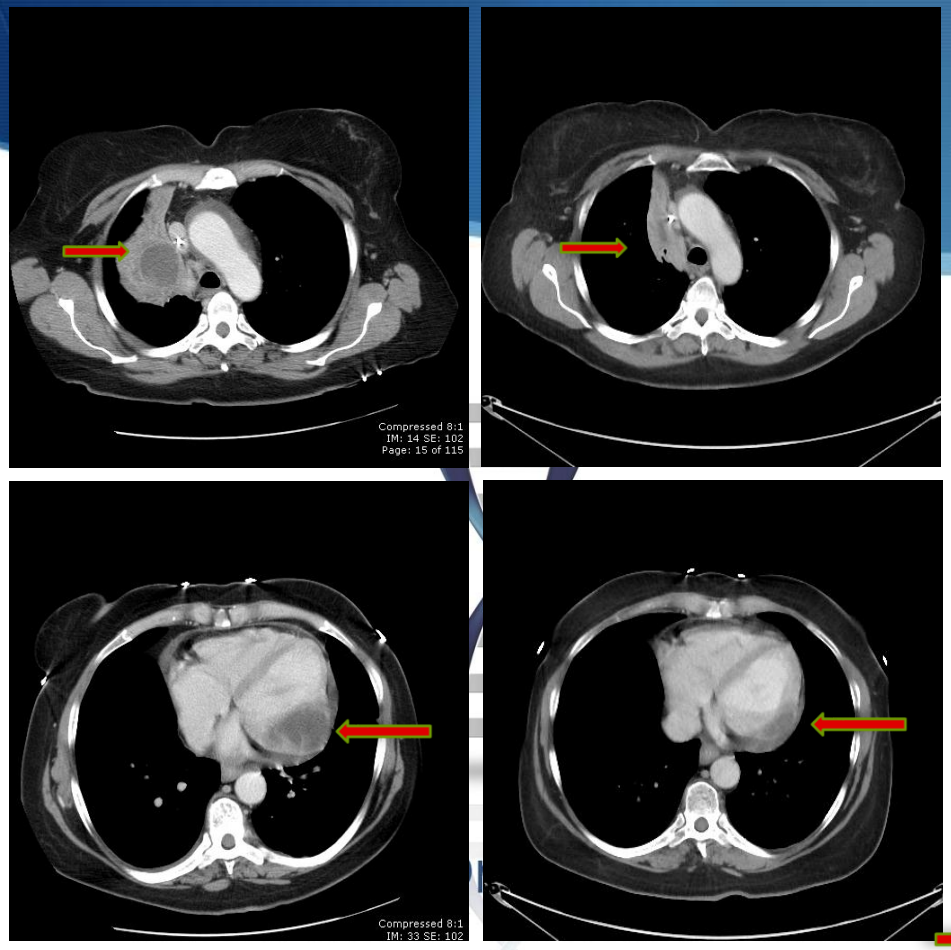
• Intermittent responses but eventual progression on multiple prior combination chemotherapies and radiation therapy.

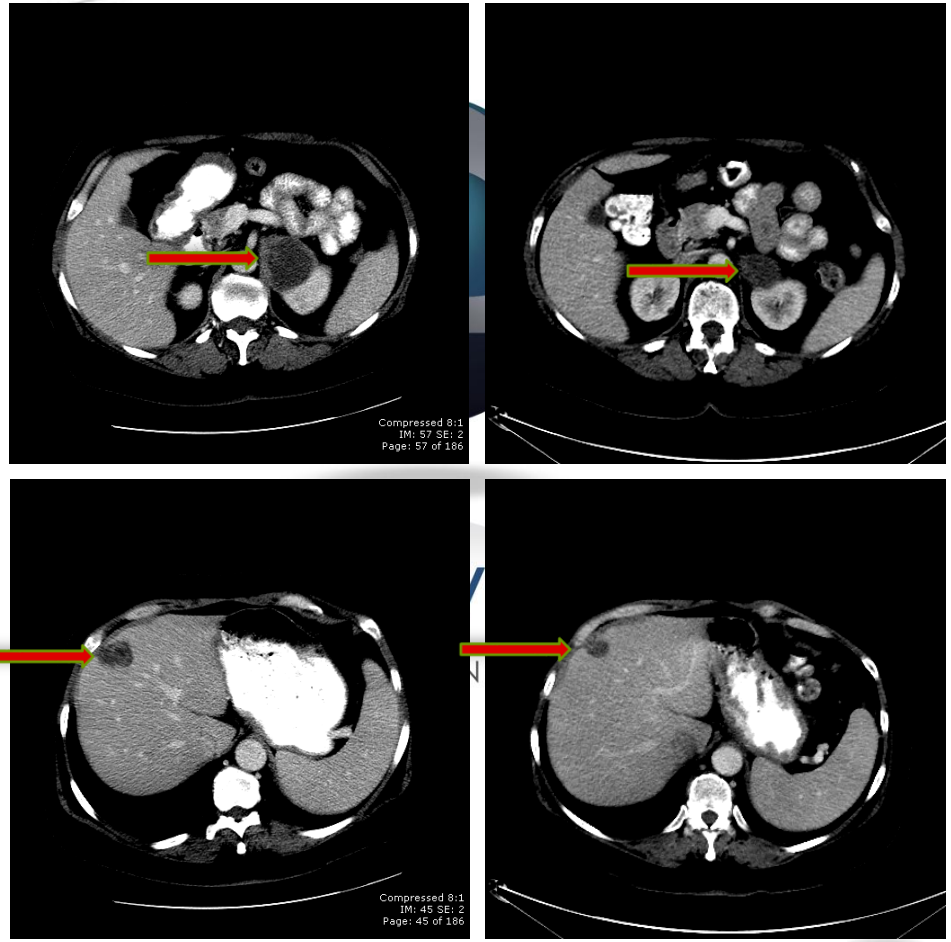
Rx MDX-1106 10mg/kg

A: Baseline
B: Cycle 2 assessment

Courtesy of Dr. Julie Brahmer and Dr. Suzanne Topalian, John Hopkins

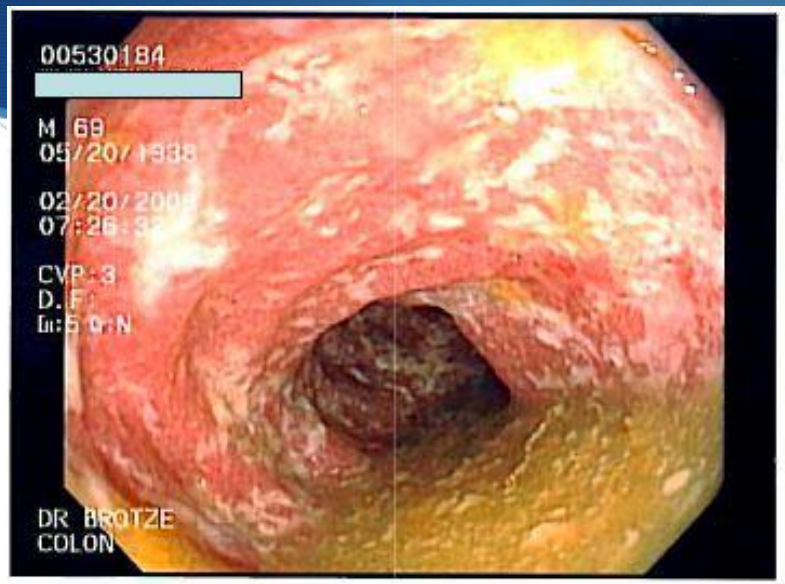
Pre/ Post Anti-PD1 mAb (Jun / Oct ’11)

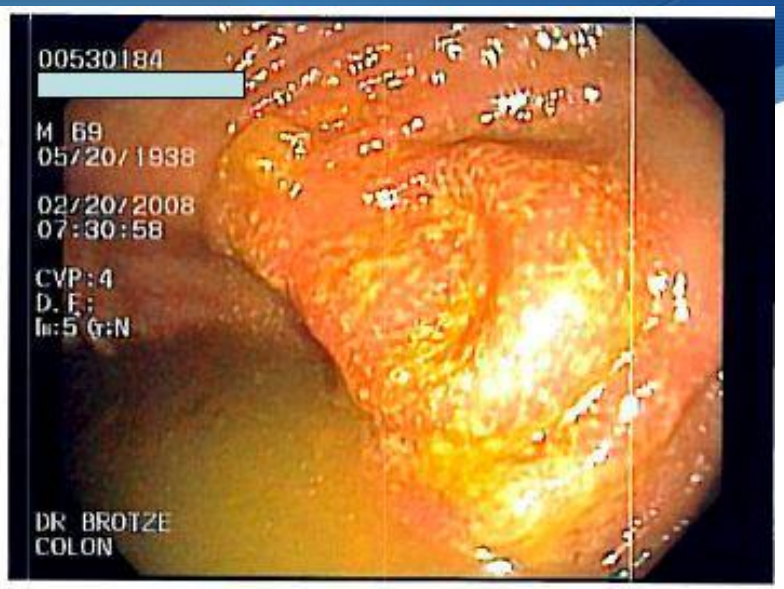


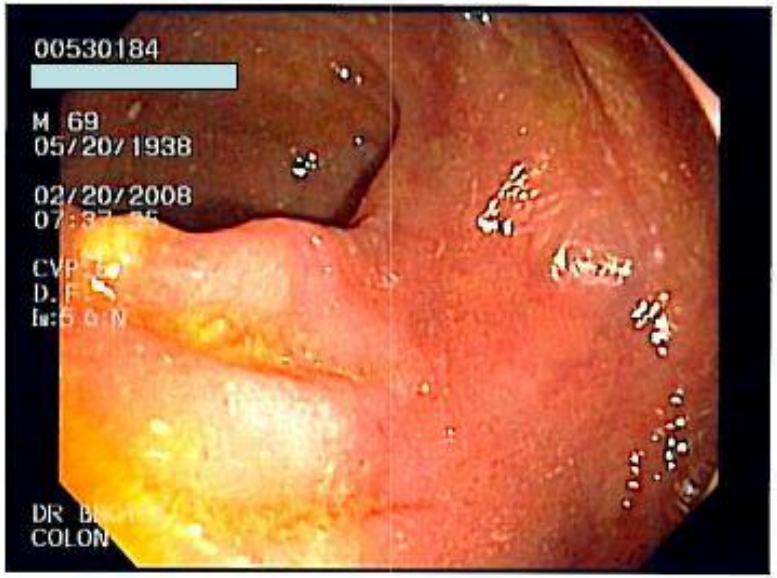


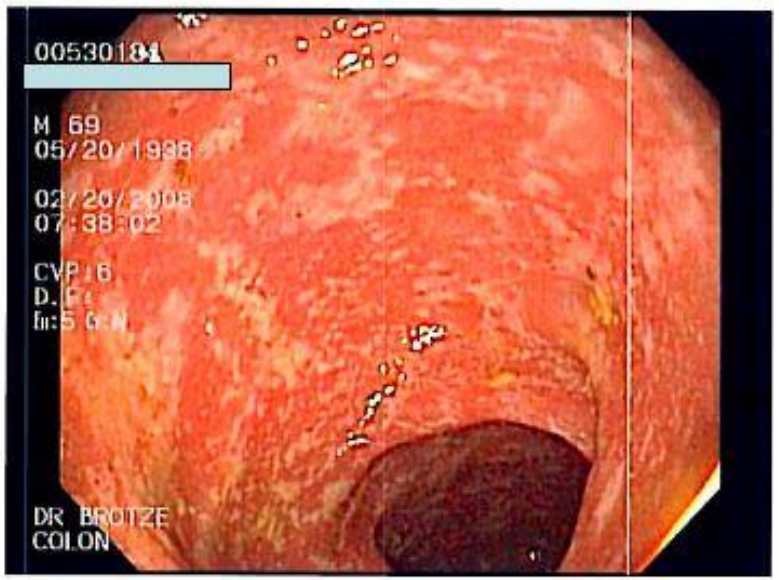
- 58 y/o ex smoker with squam NSCLC
- 4 prior tx for Stage IV disease
- Left flank pain resolved within 2 mos
-Slides Dr. Gettinger, Yale

Anti-PD1 mAb Ocular Melanoma, Grade 3 Colitis









Nivolumab Phase I

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D. , F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

June 2012

ABSTRACT

Safety, Activity and Immune Correlates of Anti-PD1Antibody (Nivolumab) in Cancer Topalian, Hodi, Brahmer, Gettinger, Smith, McDermott, Powderly, Drake, Sznol, et al NEJM epub June 2012, & ASCO 2012

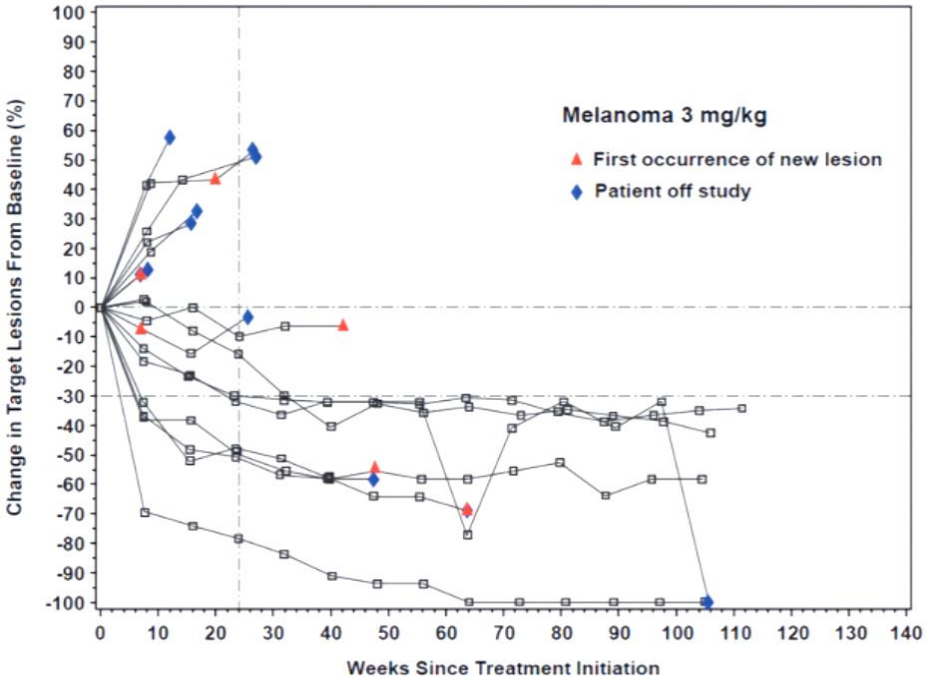
- Phase Ib, 296 patients solid tumors stage IV
  - Rx monotherapy mAb Q2 weeks (4 doses over a 8 week cycle) upto 12 cycles until PD or CR
  - Cumulative objective response (RECIST)
    - Melanoma 28%
    - Renal Cell Cancer 27%
    - NonSmall Cell Lung 18%
  - 65% of Responders were durable > 1 year
  - Drug related AEs 14% (fatigue, cough, fever, rash, diarrhea, nausea)
    - Drug related Grade 3-4 toxicity 11%,
    - Grade 3-4 pneumonitis 1%, including 3 deaths from pneumonitis (2 NSCL, 1 renal)
    - MTD not reached; 5% of patients stopped therapy due to AEs.
  - Among 42 archived tumors, response correlated with PDL1 tumor expression (p=0.006)

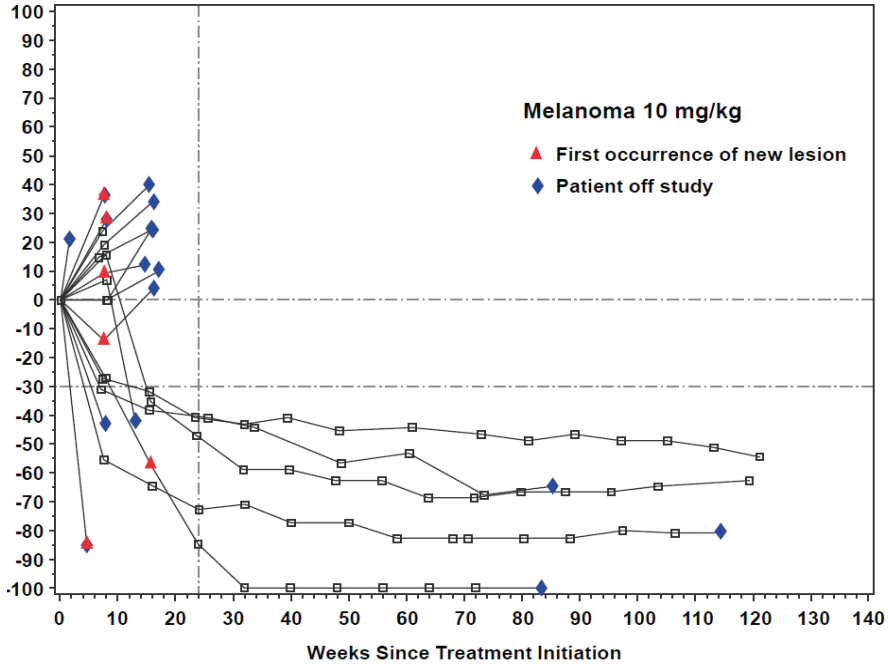
Safety, Activity and Immune Correlates of Anti-PD1 mAb (Nivolumab) in Cancer Topalian, Hodi, Brahmer, Gettinger, Smith, McDermott, Powderly, Drake, Sznol, et al NEJM epub June 2012, & ASCO 2012

- Among the 122 NSCLC, all failed prior chemo (94%) or TKI (34%)
  - 55% failed > 3 regimens
- NSCLung objective responders, cumulative 18% response (CR+PR)
  - By dose: 1mg/kg (6%); 3mg/kg (32%); 10mg/kg (18%)
  - By histology: 33% in squamous; 12% nonsquamous;
- NSCLung Stable disease $\geq$ 24 weeks = 7%
- NSCLung Clinical Benefit (CR+PR+SD) = 25%

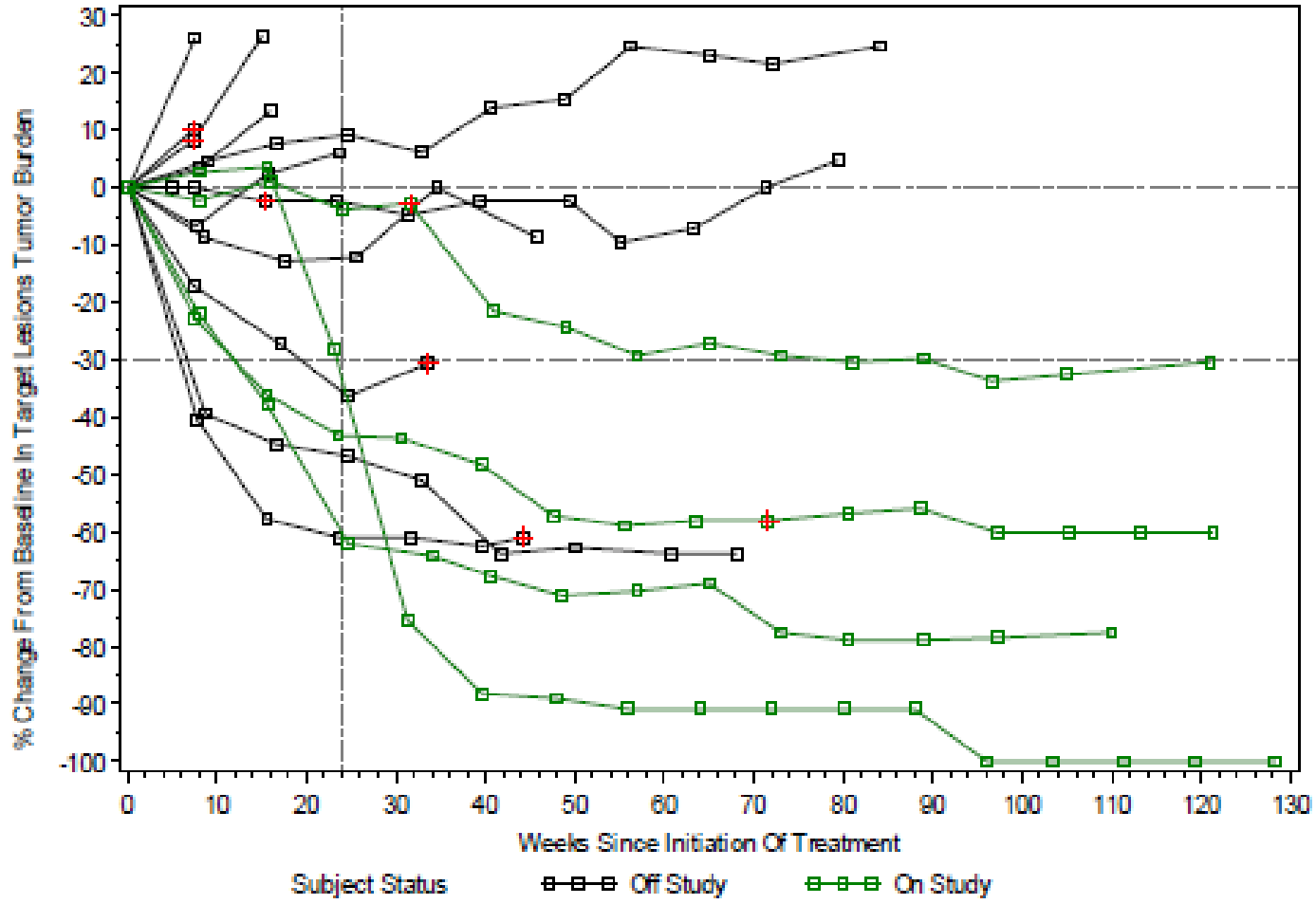
Anti-PD1 mAb Change in Melanoma Tumor Burden Topalian, NEJM 2012

- Among 296 patients with advanced solid tumors, included104 melanoma patients
  - 26 objective responses observed at doses ranging from 0.1–10.0 mg/kg
  - 3.0 mg per kilogram: Objective responses noted in 41%
  - SD lasting 24 wks or more was observed in 6 patients (6%)



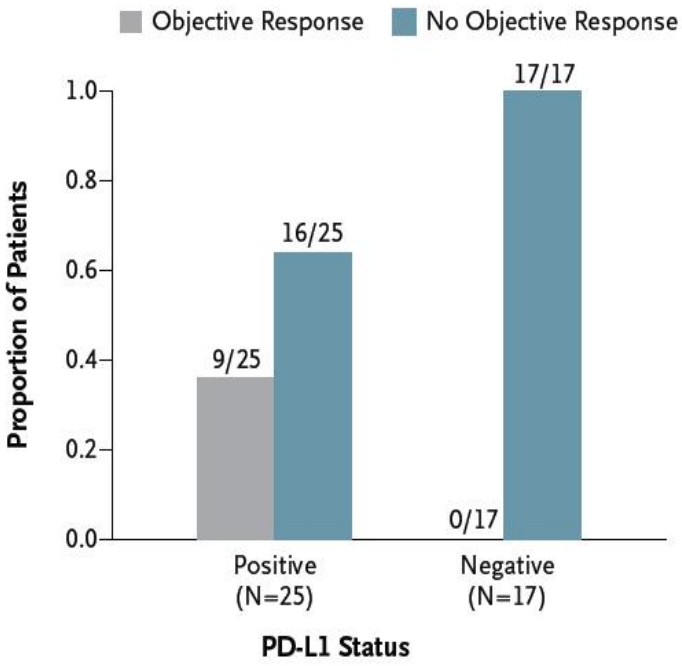


Renal Cell Cancer anti-PD1 mAb 10mg/kg cohort



PDL1 Expression on Tumor Correlates with anti-PD1 mAb Response

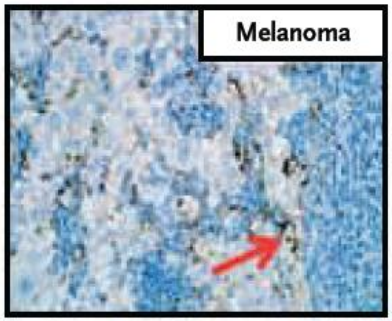
B

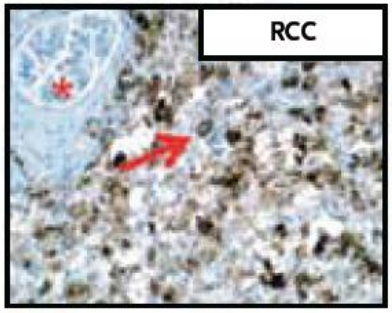


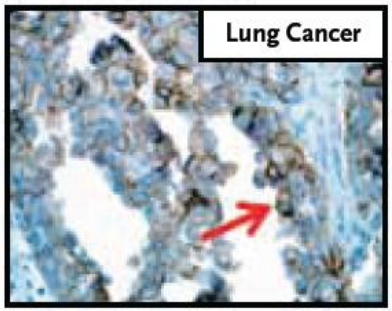
Association between Pretreatment Tumor PD-L1 Expression and Clinical Response

Response Status	PD-L1–Positive	PD-L1–Negative	Total
		number (percent)	
Objective response	9 (36)	0	9 (21)
No objective response	16 (64)	17 (100)	33 (79)
All	25	17	42

P=0.006 for association by Fisher's exact test







Pembrolizumab (Formally Lambrolizumab)

The NEW ENGLAND JOURNAL of MEDICINE 2013

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.

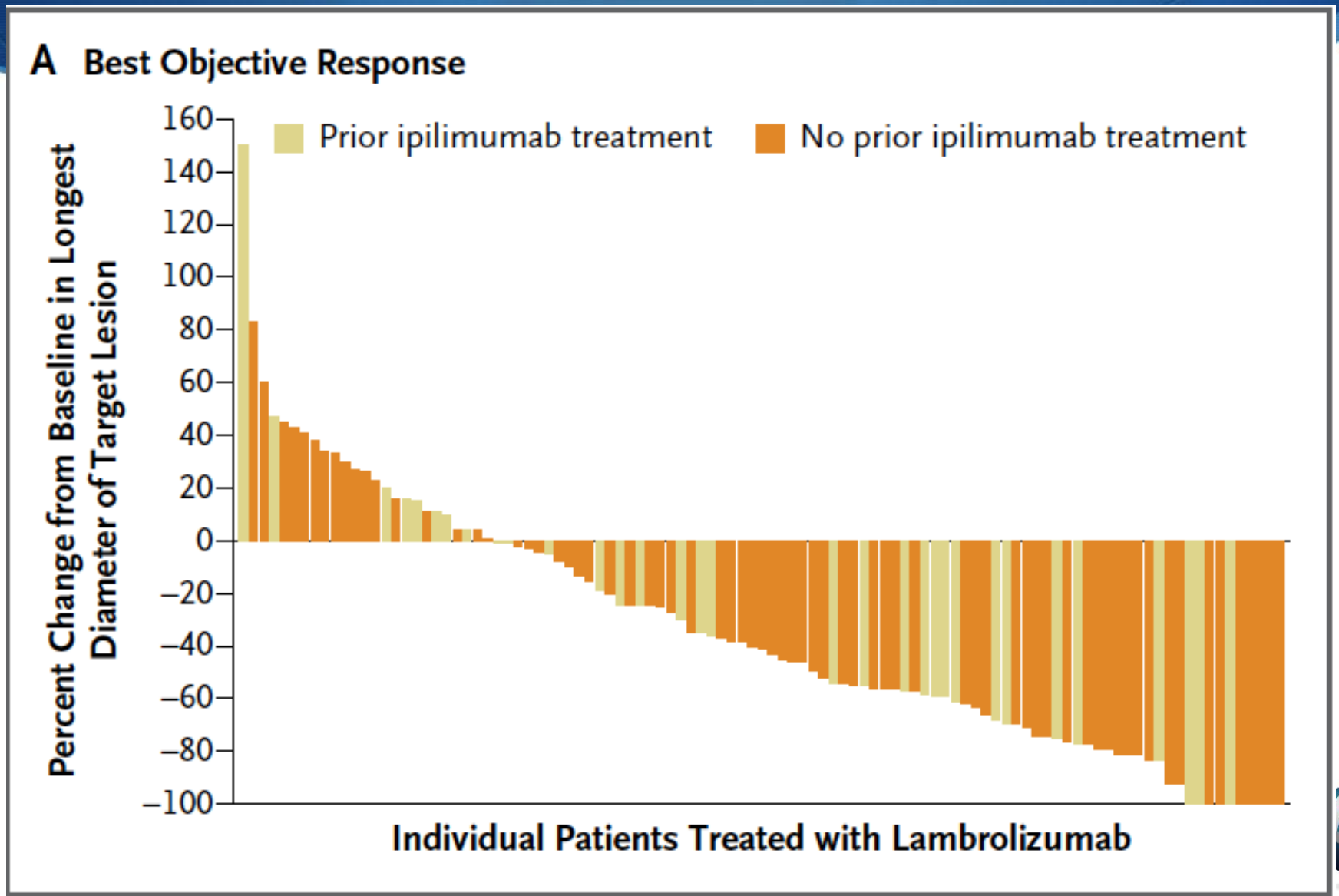
Safety and Tumor Responses with Lambrolizumab (Pembrolizumab, Anti-PD1) in Melanoma

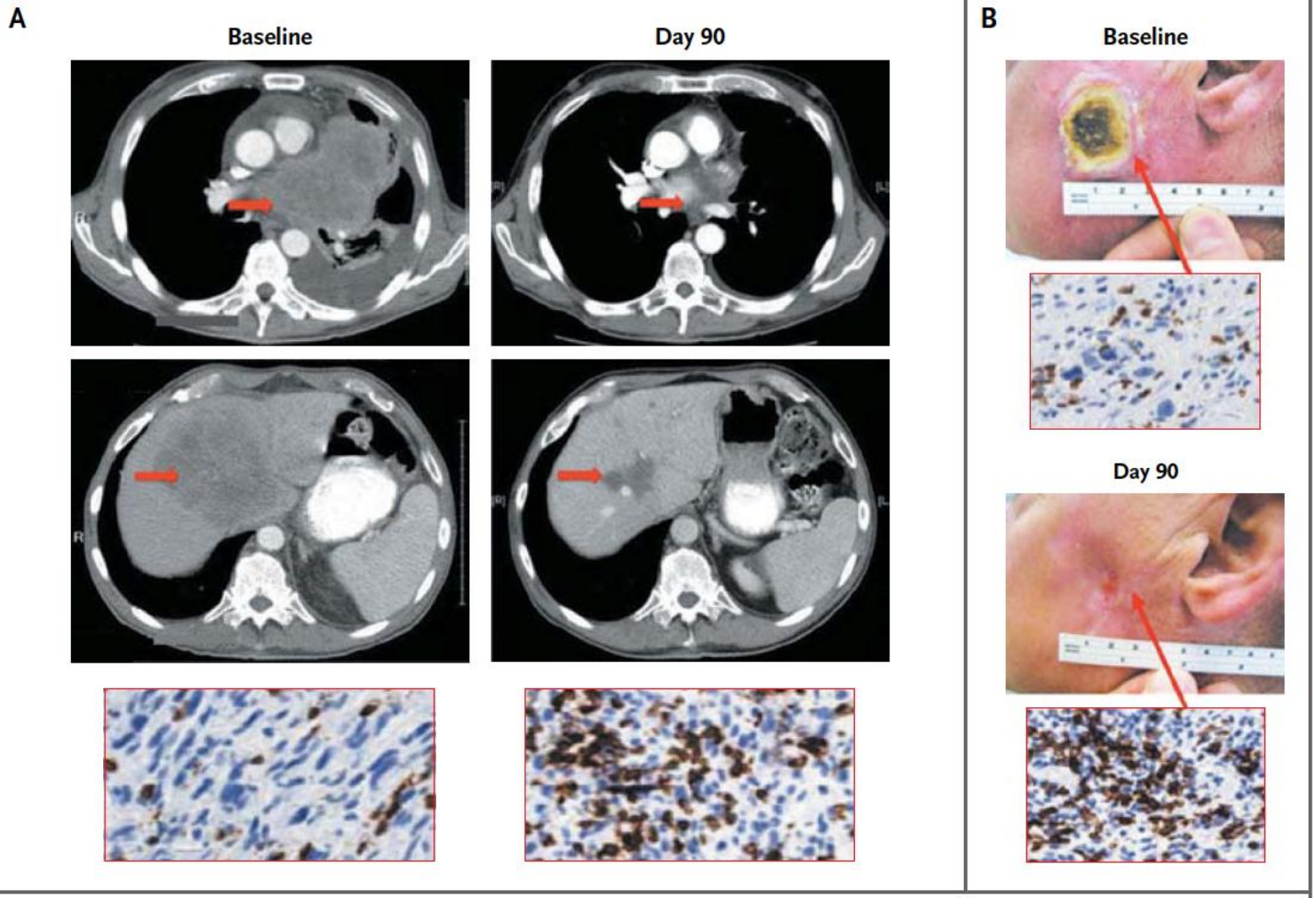
Hamid NEJM 2013

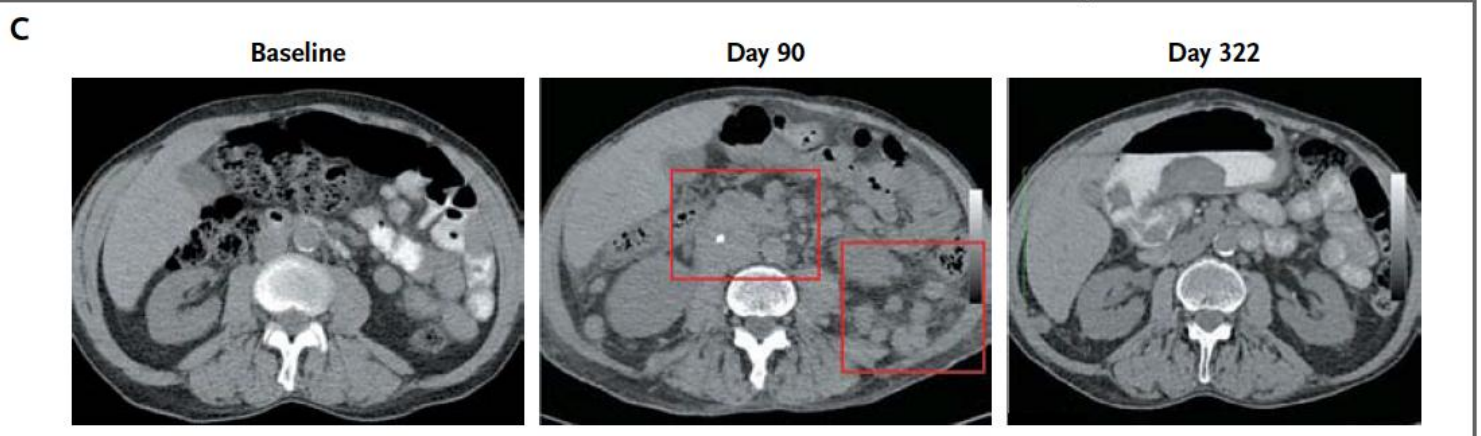
- 135 Stage IV melanoma patients (both Ipi naïve and Ipi failures)
  - 38% RECIST response rate in all dose cohorts
    - 52% RECIST highest in cohort of 10mg/kg Q2 weeks.
    - No statistical significant difference in response rate with prior Ipi exposure (but trend favored prior Ipi exposure)
    - Median progression free survival > 7 months
    - 79% any grade drug related adverse events (fatigue, asthenia, fever, chills, myalgias, HA). 21% had rash & pruritis, 20% diarrhea, 8% hypothyroidism, 9% vitiligo.
    - 13% grade 3-4 drug related adverse events
    - Auto-immune adverse events: 4% pneumonitis

Pembrolizumab Melanoma

Hamid NEJM 2013







Pembrolizumab Responders

NEJM 2013

Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial

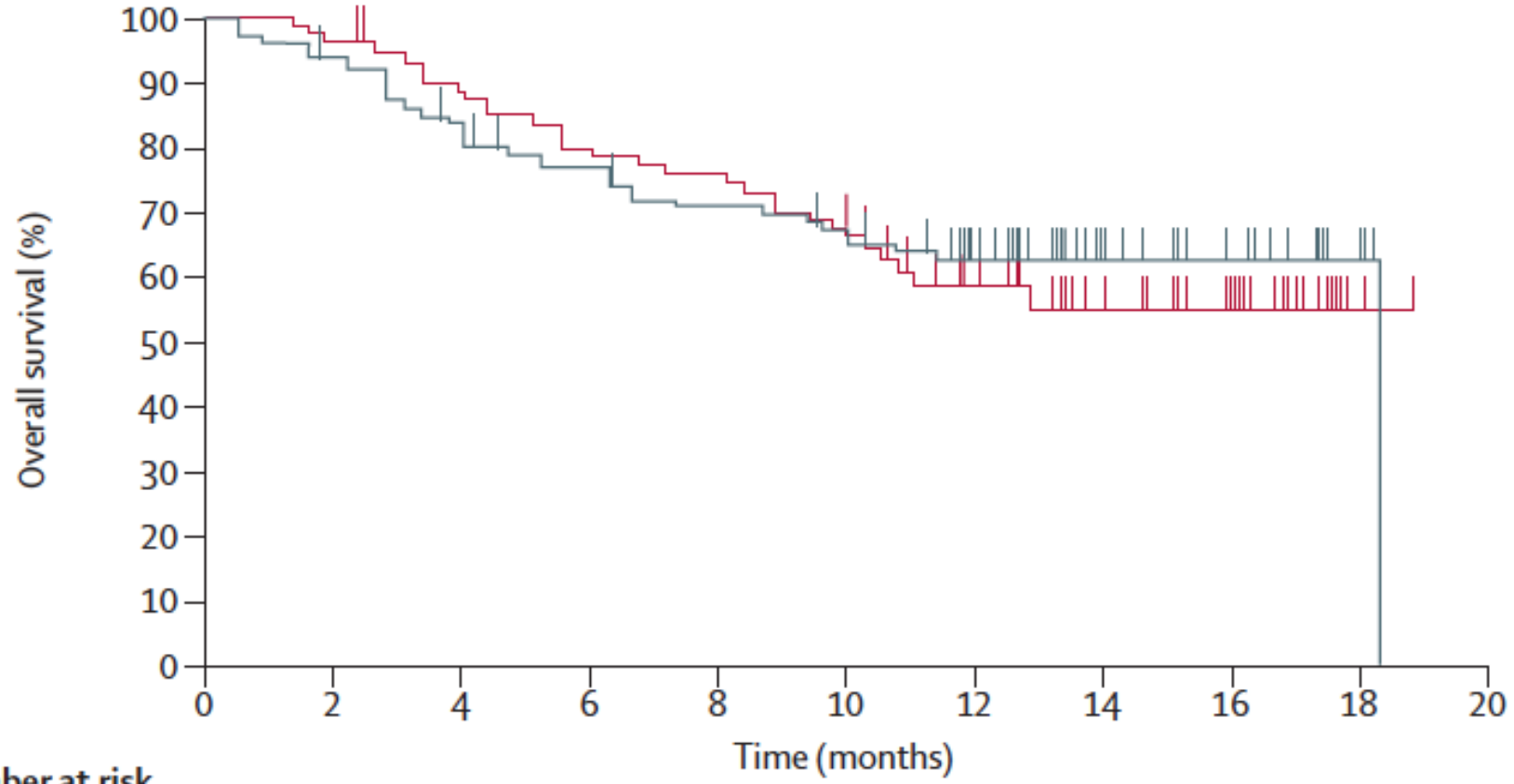
Lancet July 2014

Caroline Robert, Antoni Ribas, Jedd D Wolchok, F Stephen Hodi, Omid Hamid, Richard Kefford, Jeffrey S Weber, Anthony M Joshua, Wen-Jen Hwu, Tara C Gangadhar, Amita Patnaik, Roxana Dronca, Hassane Zarour, Richard W Joseph, Peter Boasberg, Bartosz Chmielowski, Christine Mateus, Michael A Postow, Kevin Gergich, Jeroen Elassaiss-Schaap, Xiaoyun Nicole Li, Robert Iannone, Scot W Ebbinghaus, S Peter Kang, Adil Daud

- Randomized Expansion cohort of original Phase I, additional 173 patients
- Dedicated to Ipilimumab “refractory” patients (received at least 2 doses Ipi). Excluded prior Ipi grade 3,4 toxicities. Allowed prior grade 2 toxicity, if resolved to grade 0-1, and off steroids. Stable brain mets allowed.
- 2mg/kg IV Q3 weeks vrs 10mg/kg IV Q3 weeks
- Results: ORR 26% in both doses, similar safety profiles, no drug related deaths, fatigue (33%), pruritus (26%), rash (18%). Only grade 3 drug AE was fatigue (3%).

Pembrolizumab Survival

Robert Lancet 2014



Number at risk											
Pembrolizumab 2 mg/kg	89	86	76	69	66	57	42	29	16	1	0
Pembrolizumab 10 mg/kg	84	78	65	61	55	50	37	18	12	1	0

Pembrolizumab FDA Approved September 2014

- Pembrolizumab is a human programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.
- This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials
- 2mg/kg IV over 30 minutes, Q3 weeks “until disease progression or unacceptable toxicity”
- **Warnings & Precautions: Immune mediated adverse reactions:** pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hypo- or hyper-thyroiditis.
  - Withhold for grade 2, Rx prednisone >40mg/day, taper over 1 month
  - Resume pembrolizumab if recovers to grade 0-1.
  - Permanently discontinue for grade 3 or 4, or inability to reduce prednisone < 10mg/day within 12 weeks.

Ipilimumab + Nivolumab Melanoma

Wolchok NEJM 2013

- Metastatic Melanoma, n = 88
  - Concurrent cohort: n = 53, ORR 40%,
  - Clinical Benefit SD+PR+CR = 65%
  - Grade 3-4 drug related AEs 53% (lipase, transaminitis, colitis)

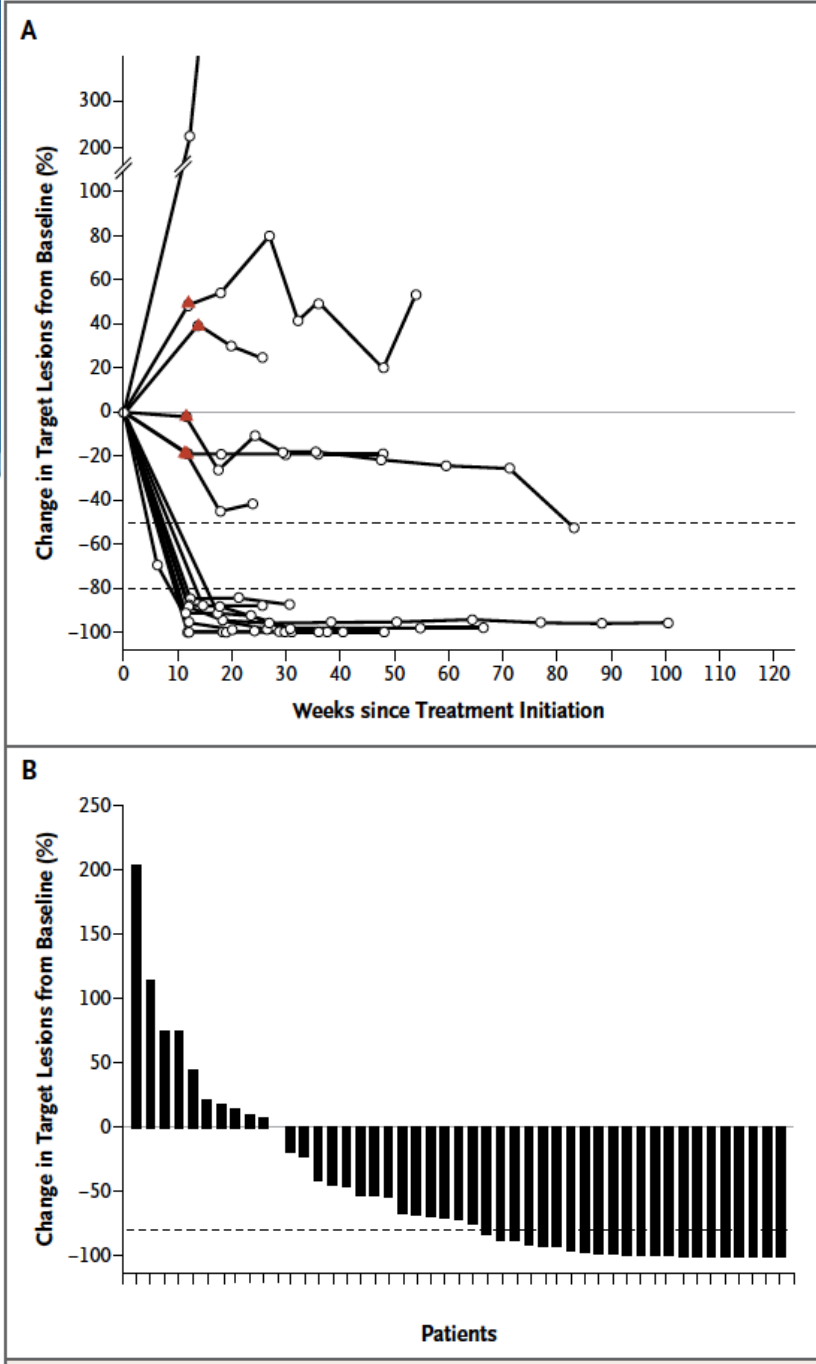


Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Ipilimumab Nivolumab Melanoma Wolchok NEJM 2013

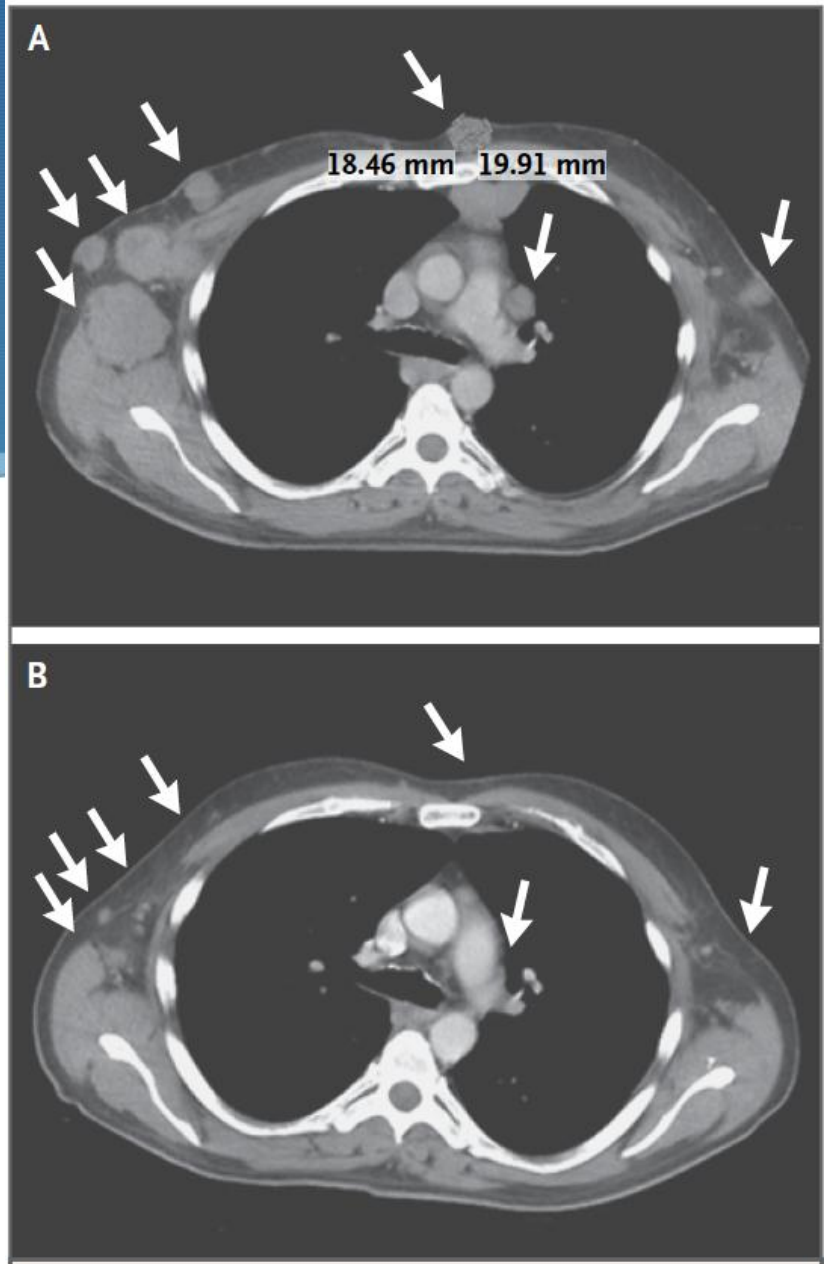


Figure 2. Computed Tomographic (CT) Scans of the Chest Showing Tumor Regression in a Patient Who Received the Concurrent Regimen of Nivolumab and Ipilimumab.

Nivolumab 1rst Line NSCLung

Gettinger ASCO 2014

- 1rst line lung monotherapy Nivolumab, n = 20
  - ORR 30% (50% PDL1+), Clinical Benefit SD+PR+CR = 65%
  - Grade 3-4 drug related AEs = 20%

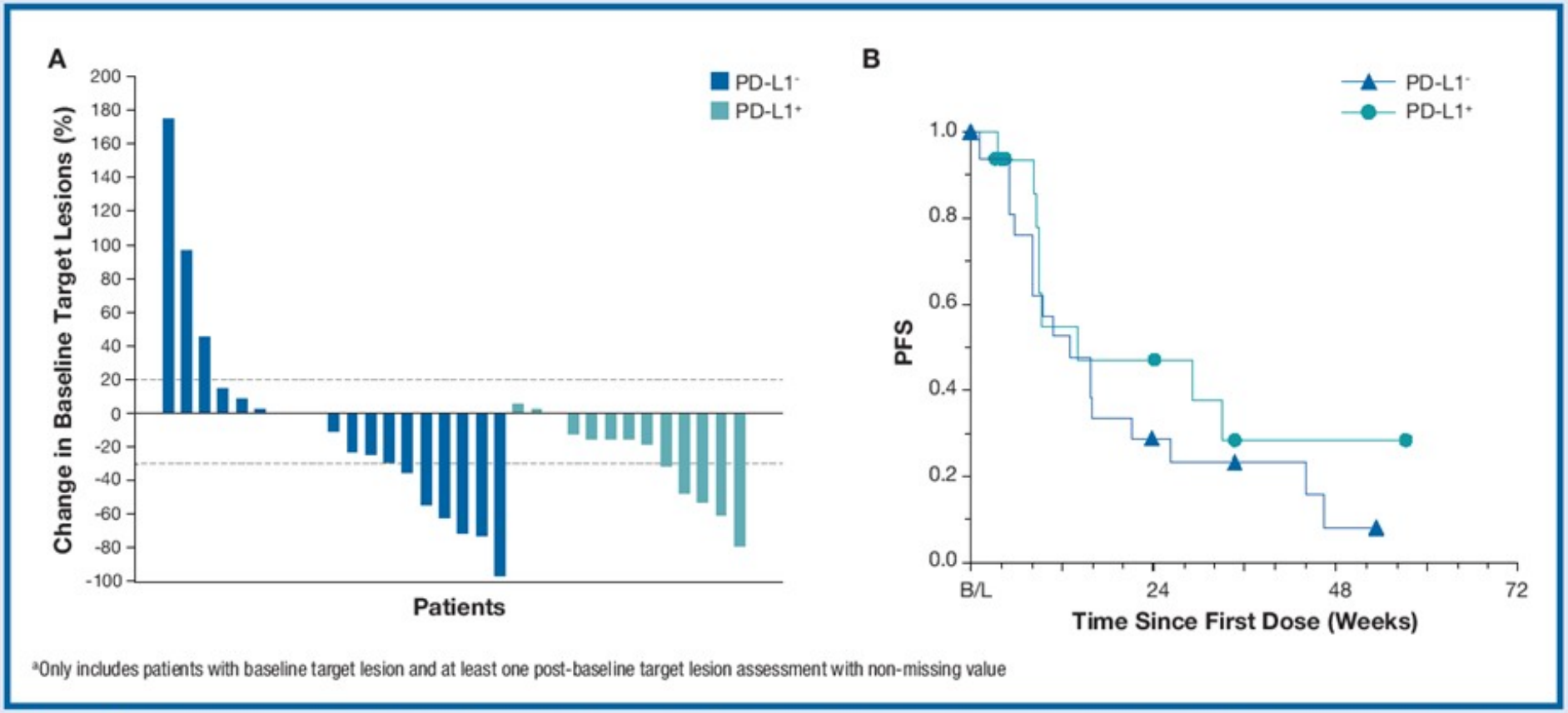


Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline[a] and B) PFS

Ipilimumab + Nivolumab 1rst Line Lung

SJ Antonio, ASCO 2014

- Phase IB, Front line lung cancer, n = 49
  - ORR 19% (PDL1+), 14% (PDL1-)
  - PFS 24 weeks 47% (PDL1+), 29% (PDL1-)
  - Drug related grade 3-4% AEs = 49%

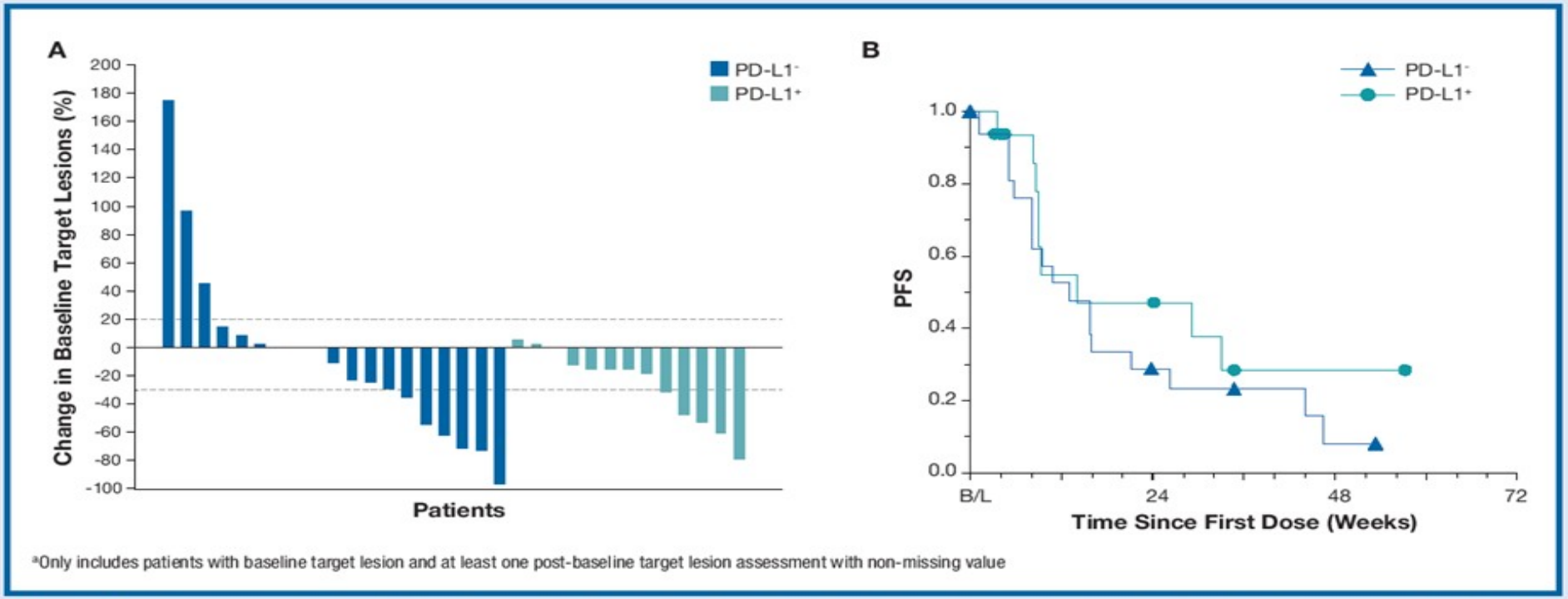


Figure 7. Response by PD-L1 status in NSCLC patients treated with nivolumab plus ipilimumab: A) best percent change in target lesion tumor burden from baseline[a] and B) PFS

PDL1 Blockade

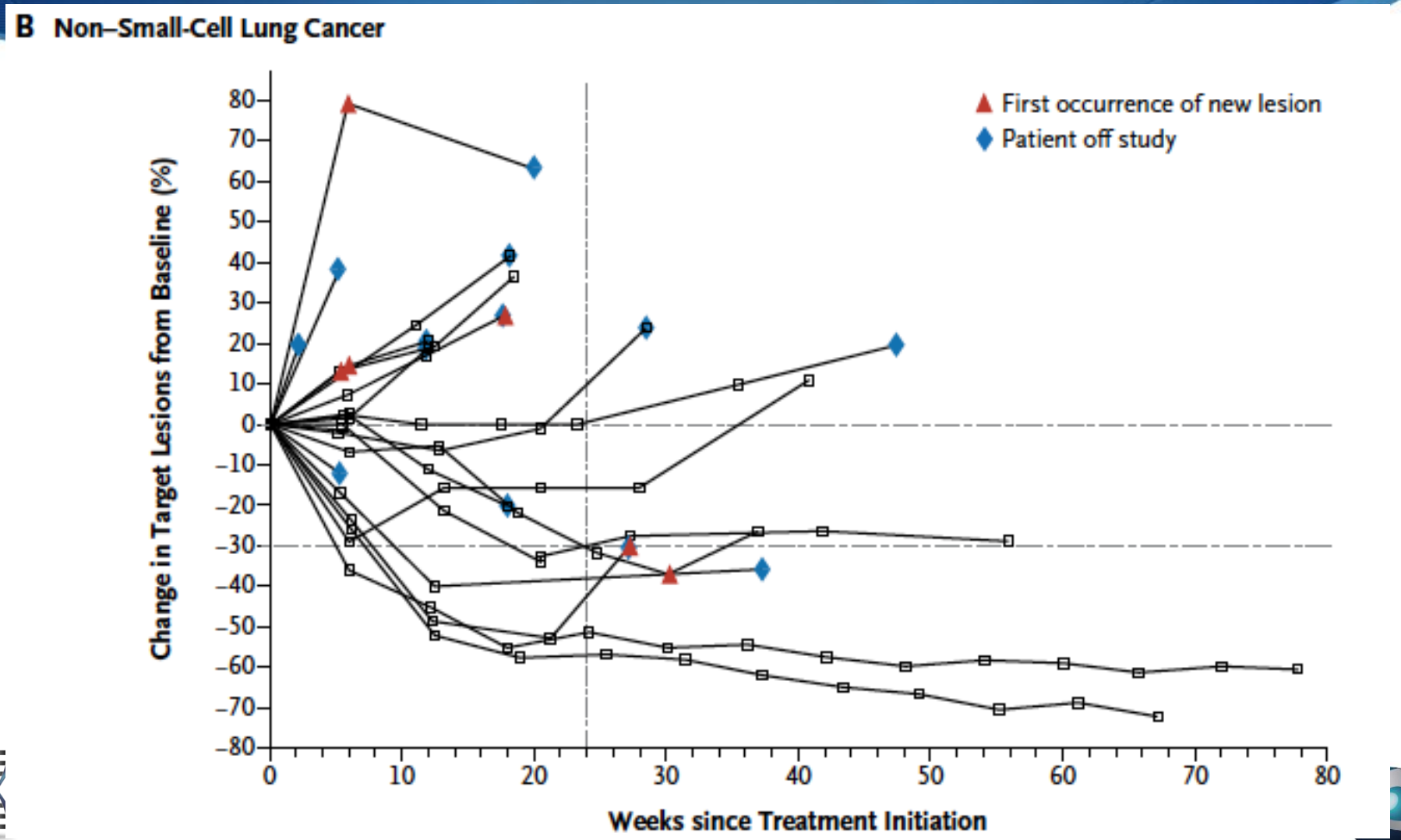
Safety and Activity of Anti-PDL1(MDX-1105) Antibody in Patients with Advanced Cancer

Brahmer, Tykodi, Topalian, Hwu, Wigginton et al; NEJM epub June 2012 and ASCO 2012

- Phase Ia, 207 patients solid tumors Stage IV
  - Rx monotherapy mAb Q2 weeks (3 doses over 6 week cycles) upto 16 cycles until PD or CR
  - Cumulative objective response:
    - Melanoma 17%
    - Renal Cell 12%
    - NSCL 10% (75 patients with NSCL)
  - 50% of responders durable > 1 year
  - Immune related events 39% (rash, hypothyroidism, hepatitis, myasthenia gravis)
  - Drug related grade 3-4 AEs 9%
  - NSCL 12% stable disease; Clinical benefit (CR+PR+SD) = 22%

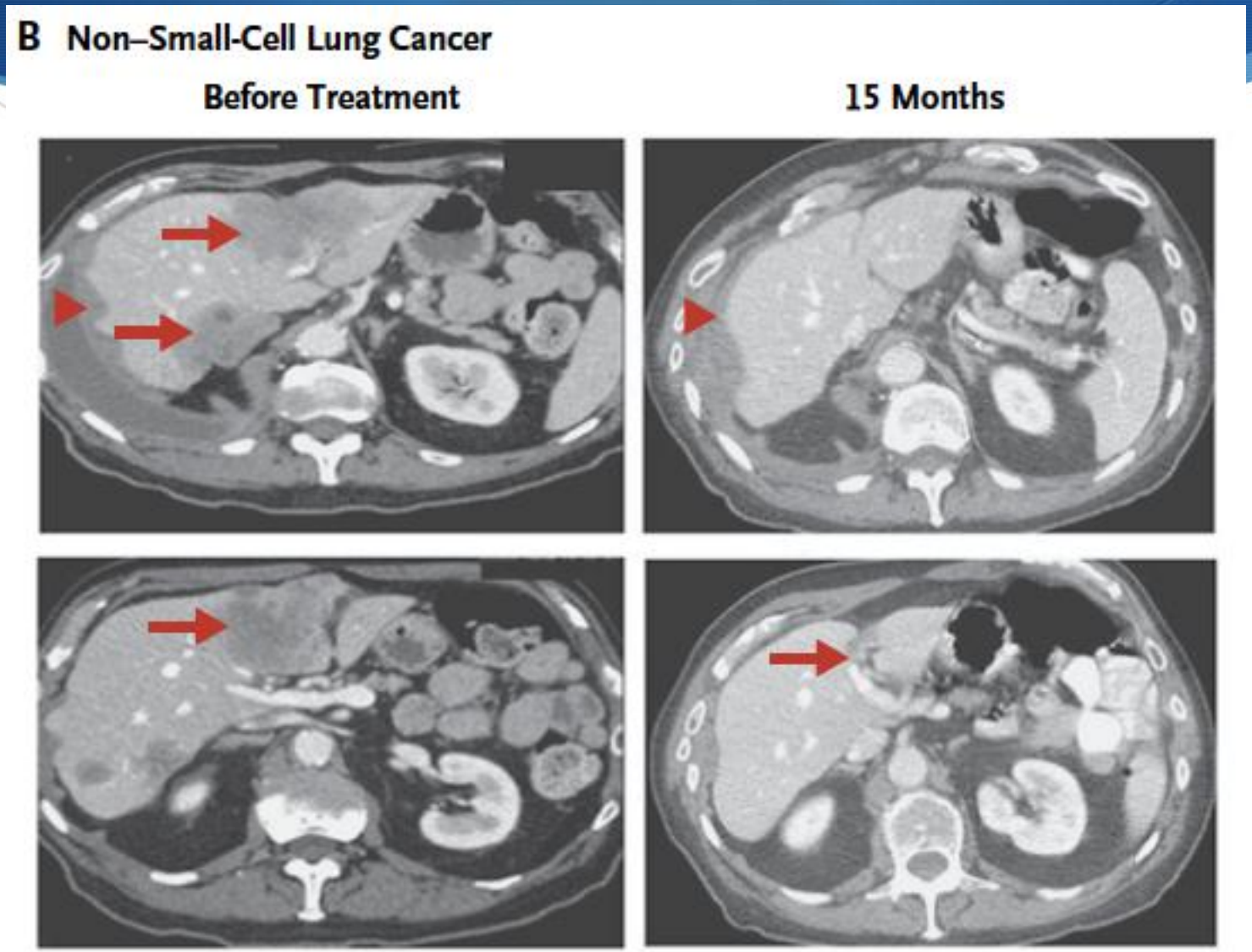
Safety and Activity of Anti-PDL1 Antibody in Patients with Advanced Cancer

Brahmer, Tykodi, Topalian, Hwu, Wigginton et al; NEJM epub June 2012 and ASCO 2012



Safety and Activity of Anti-PDL1 Antibody in Patients with Advanced Cancer

Brahmer, Tykodi, Topalian, Hwu, Wigginton et al; NEJM epub June 2012 and ASCO 2012



PDL1 Phase I Response Rates

PDL1 Drug (Author, year)	Tumor	Patient #	ORR	Grade 3-4 Drug AEs	Comments
MPDL3280A (Herbst, Tabernero 2013)	Solid tumors	140	21%	2%	PDL1+, ORR 39%
MPDL3280A (Powles 2014)	Bladder	31	50%	4%	
MPDL3280A (Rizvi 2014)	NSCLung	53	23%	11%	PDL1 IHC 3+, ORR 83% (smokers respond better, Soria ECC 2013)
MEDI4736 (Segal 2014)	Solid tumor	346	11%	7%	PDL1+, ORR 22%
MEDI4736 (Brahmer 2014)	NSCLung	13	16%	4%	PDL1+, ORR 39%
MSB0010718C (Heery 2014)	Solid tumor	28		14%	

MEDI4736 PDL1 mAb

Segal ASCO 2014

Response in Patient with Head and Neck Cancer

Baseline

Day 28

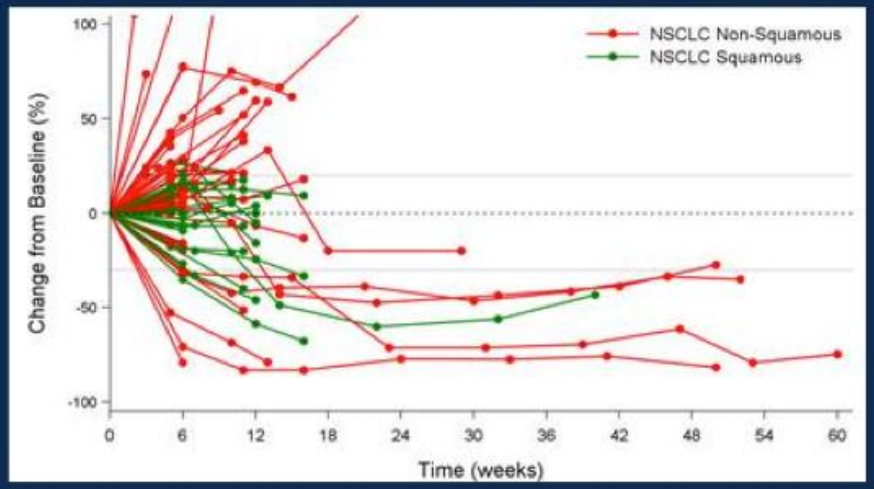
- 96 y.o. female
  - Progressed on previous cetuximab
  - HPV negative, PD-L1 positive
  - Treatment ongoing at 8 weeks

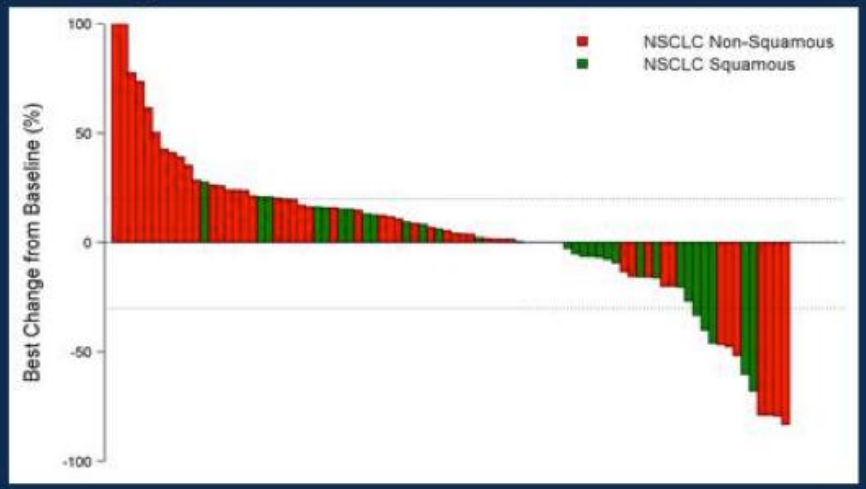
MEDI4736 PDL1 mAb

Segal ASCO 2014

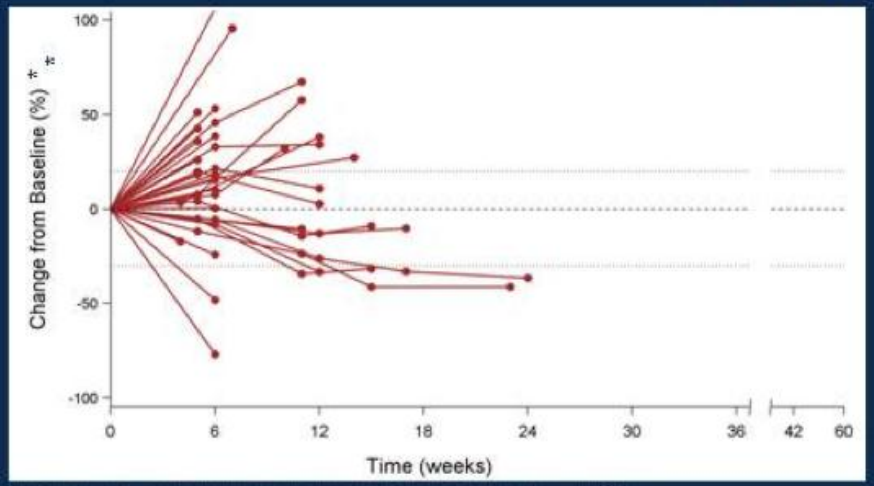
Emerging Clinical Activity in Multiple Tumors

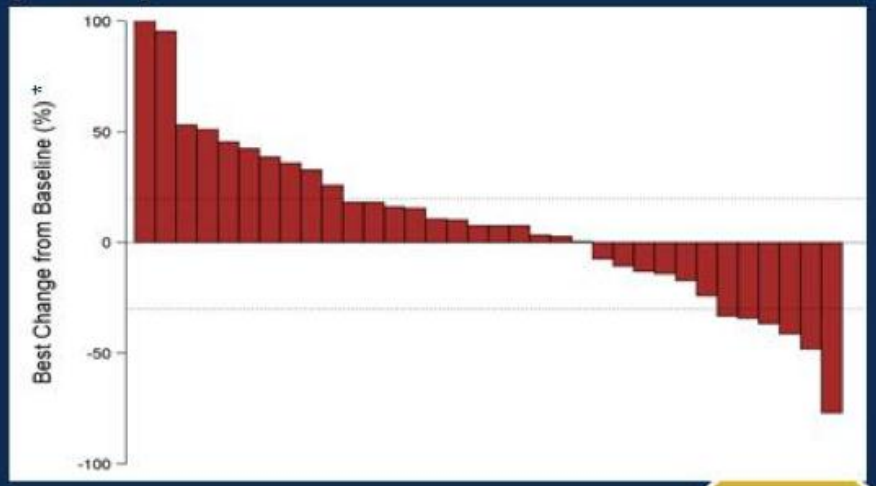
NSCLC (n = 84)





SCCHN (n=34)



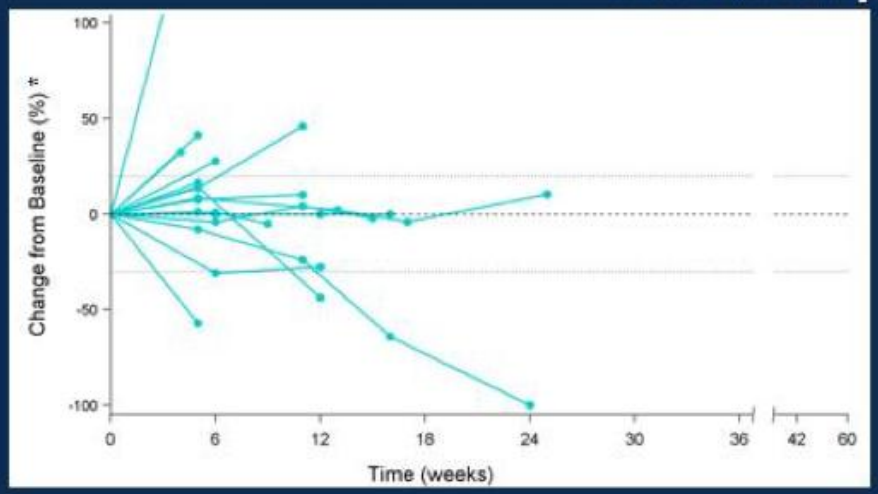


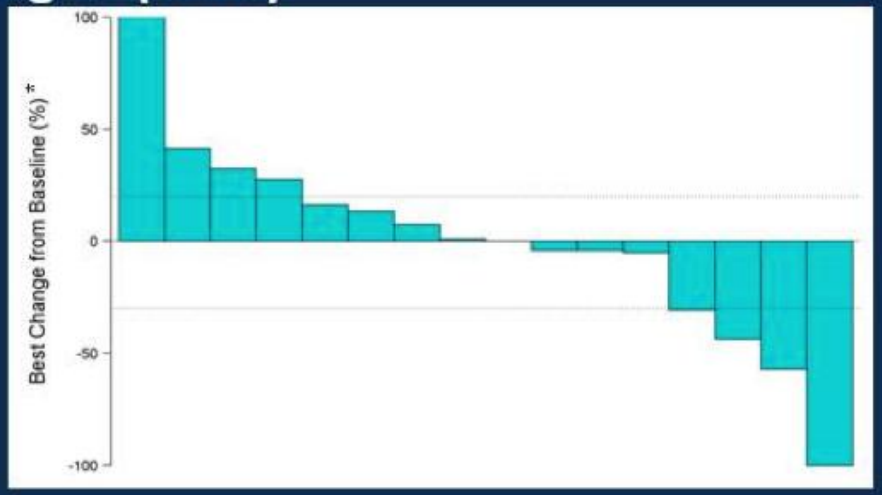
MEDI4736 PDL1 mAb

Segal ASCO 2014

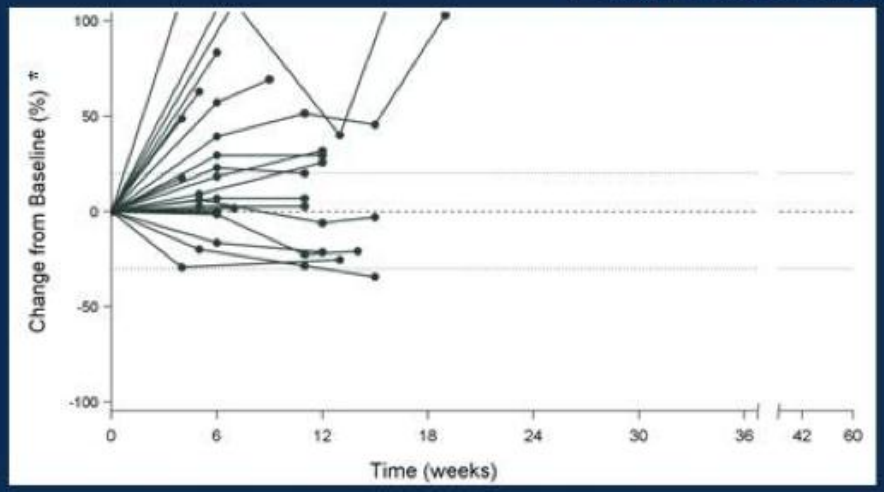
Emerging Clinical Activity in Multiple Tumors

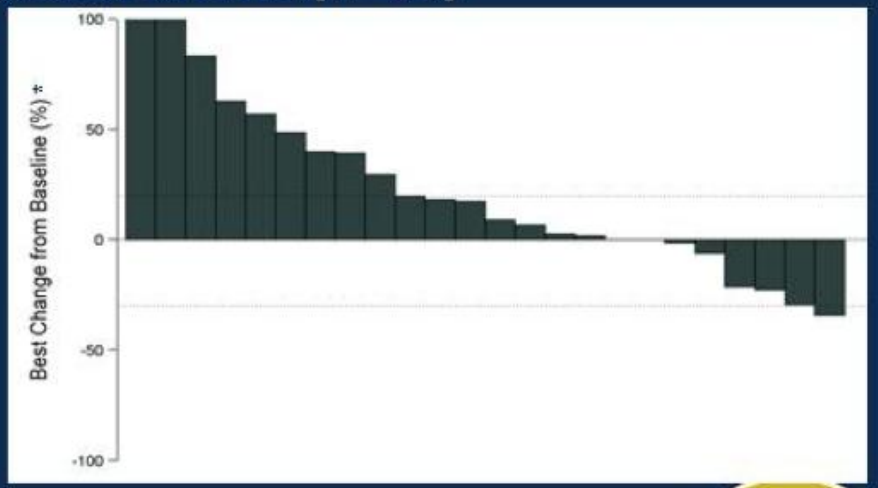
Gastroesophageal (n=16)





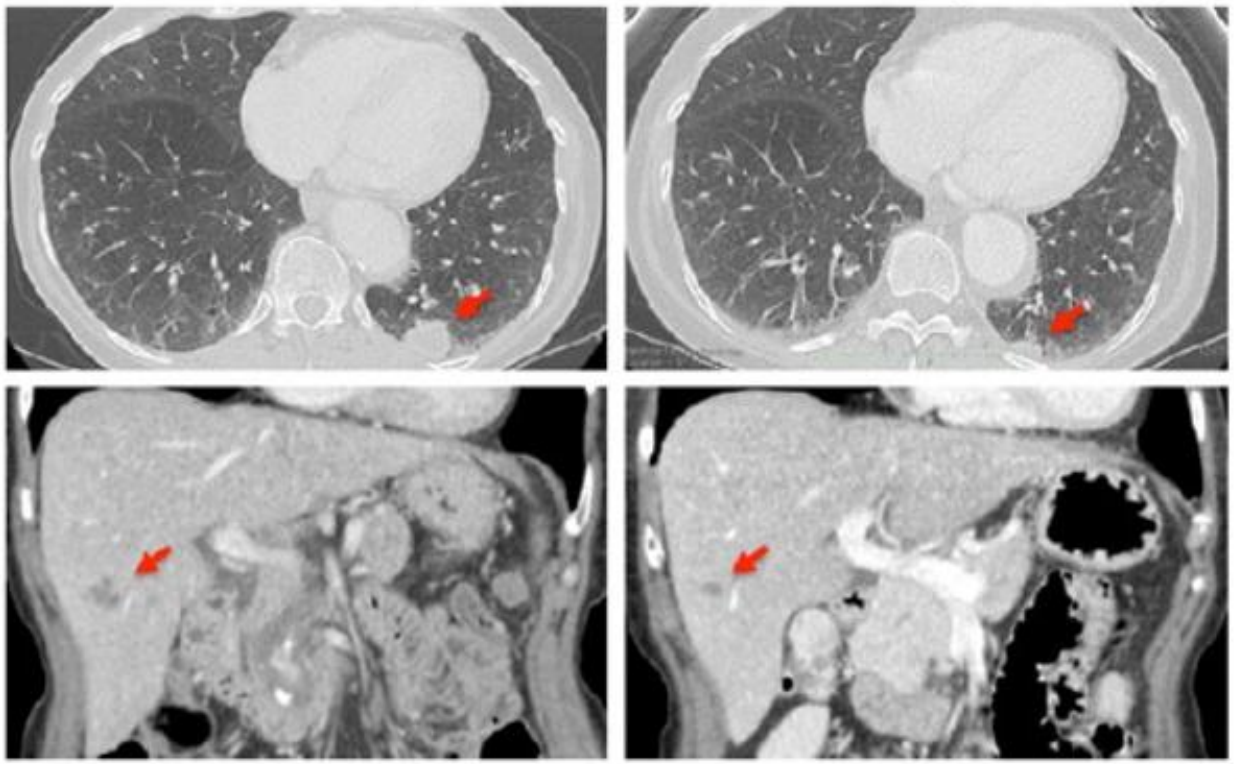
Pancreatic adenocarcinoma (n=24)





MPDL3280A PDL1 mAb

Tabenero ASCO 2013



Carolina BioOncology Institute (Powderly).

- 73-year-old female with CRC s/p partial colectomy, FOLFOX/bevacizumab, capecitabine, PD-L1 positive

BioMarkers

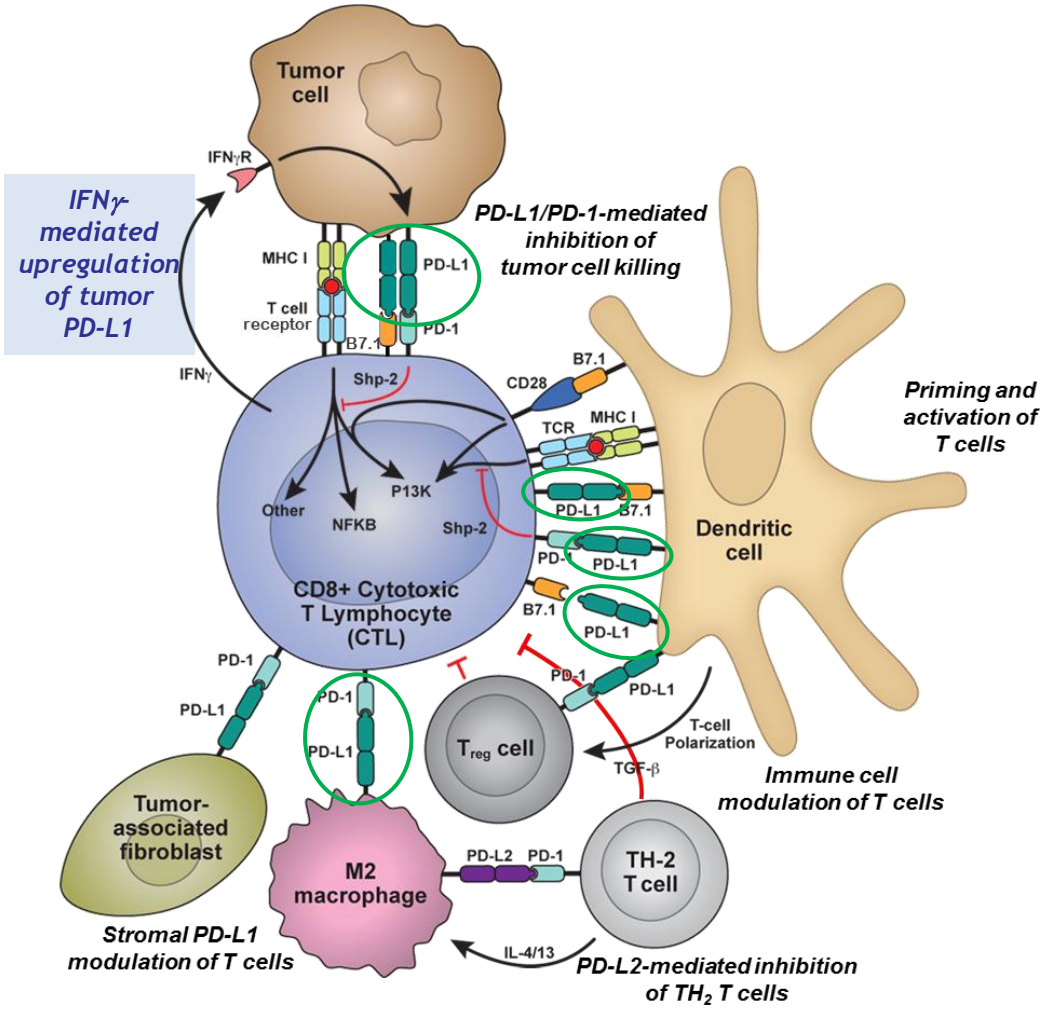
PDL1 Tumor Expression

- Distinct mechanisms of PDL1 expression:
  - Interferon gamma induced dynamic upregulation in the inflammatory tumor microenvironment (“adaptive resistance”)
  - Oncogenic driver mutations that constitutively express PDL1
  - Epithelial to Mesenchymal transformation of the carcinoma phenotype

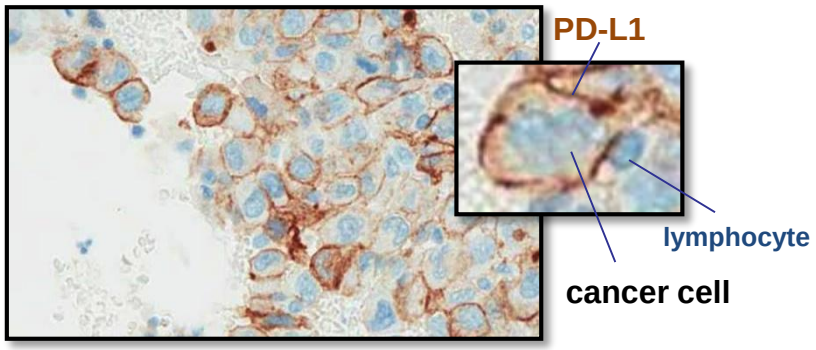
Biomarkers and Associations With the Clinical Activity of PD-L1 Blockade in a MPDL3280A Study

Powderly J[1], Koeppen H[2], Hodi FS[3], Sosman J[4], Gettinger S[5], Desai R[2], Tabernero J[6], Soria JC[7], Hamid O[8], Fine G[2], Xiao Y[2], Mokatrin A[2], Wu J[2], Anderson M[2], Irving B[2], Chen DS[2], Kowanetz M[2]

PD-L1 plays an important role in dampening the anti-tumor immune response



Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.

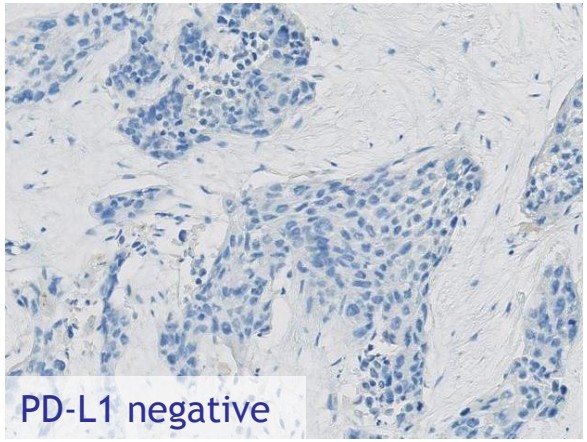


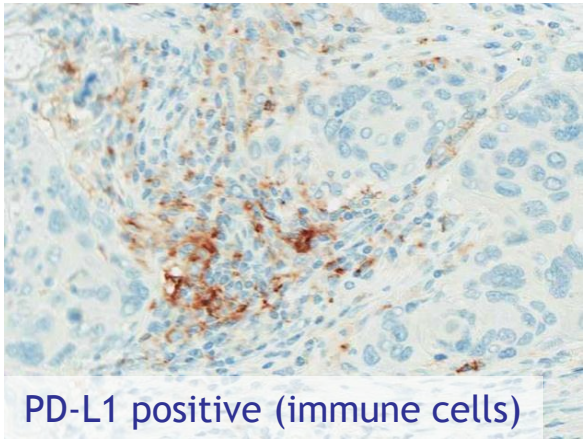
Presence of intratumoral T cells may lead to adaptive immune resistance

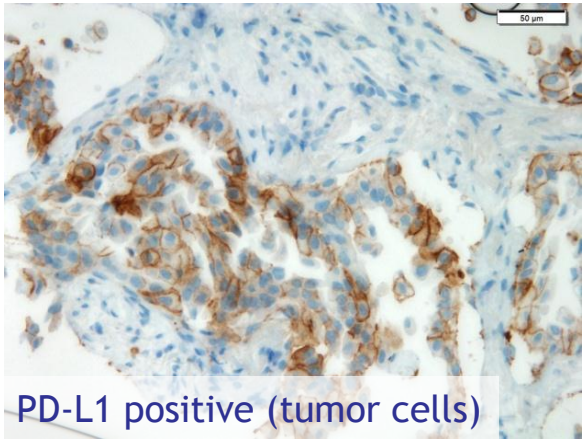
PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T-cell activity:

1. PD-L1 expression by tumor infiltrating ***immune cells***
2. PD-L1 expression by ***cancer cells***

Proprietary Dx PD-L1 IHC Reagent – Assay to Measure PD-L1 in Human Tissues



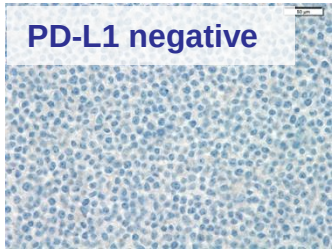


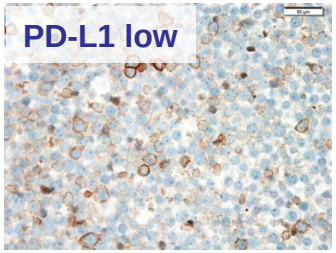


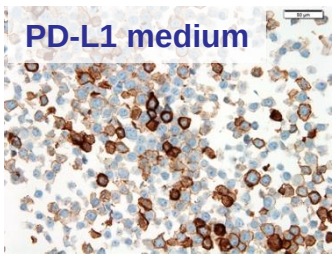
PD-L1 IHC:

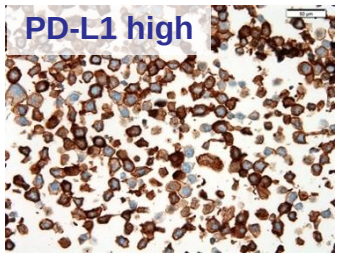
- Monoclonal Ab against human PD-L1
- High sensitivity and specificity
- No background
- Recognizes PD-L1 in tumor cells and tumor infiltrating immune cells

PD-L1 expression in control cell lines

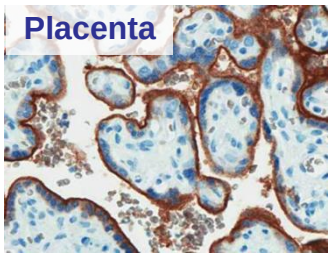






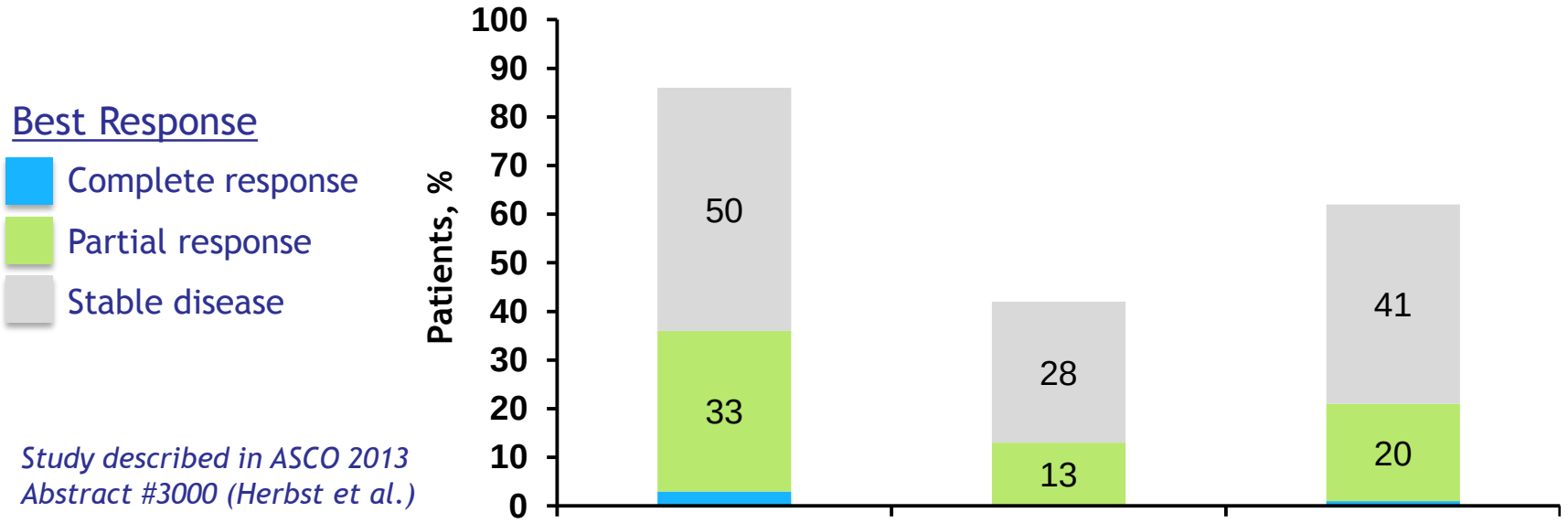


Positive tissue control



PD-L1 Expression by IHC is Associated With Anti-tumor Response to MPDL3280A

Investigator-Assessed Overall Response Rate (ORR*); % (n/n)			
	PD-L1 Positive	PD-L1 Negative	All†
Overall population (N = 140)	36% (13/36)	13% (9/67)	21% (29/140)



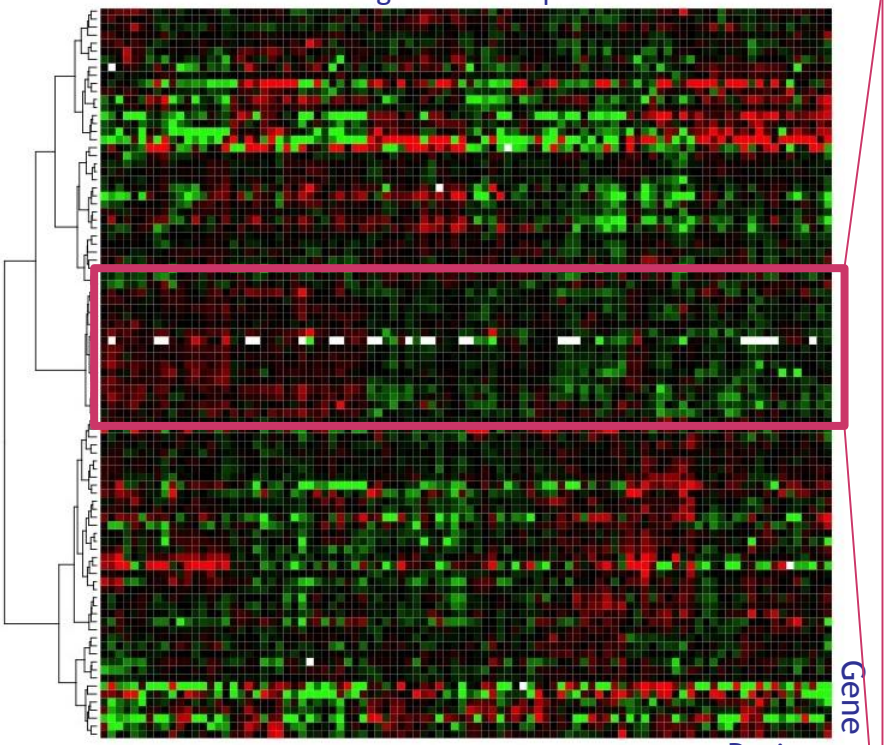
Study described in ASCO 2013 Abstract #3000 (Herbst et al.)

- ***PD-L1 positive*** **defined as tumors with infiltrating immune cells that stain for PD-L1 Dx IHC**
- **Further assessment of PD-L1 Dx ongoing**

* ORR includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1
† All patients include PD-L1–positive, PD-L1–negative and patients with unknown tumor PD-L1 status. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013.

Anti-tumor Response to MPDL3280A is Associated With Th1-type T-cell Markers

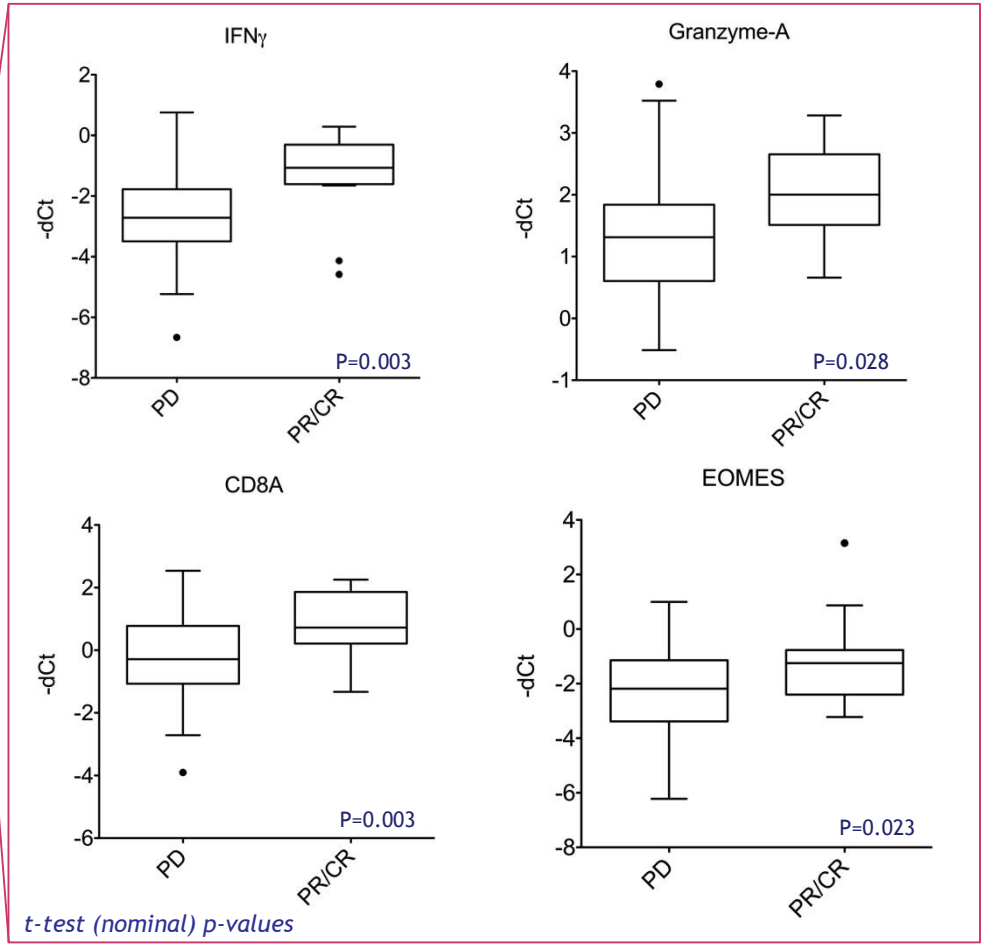
Hierarchical clustering of Ph1 samples



Up-regulation

Down-regulation

Baseline tumor samples, n = 96 (MPDL3280A, Phase 1a). Data for samples available as of Dec 1, 2012. Patients first dosed at 1-20 mg/kg prior to Aug 1, 2012; data cutoff Feb 1, 2013. Includes investigator-assessed unconfirmed and confirmed PR/CR by RECIST 1.1

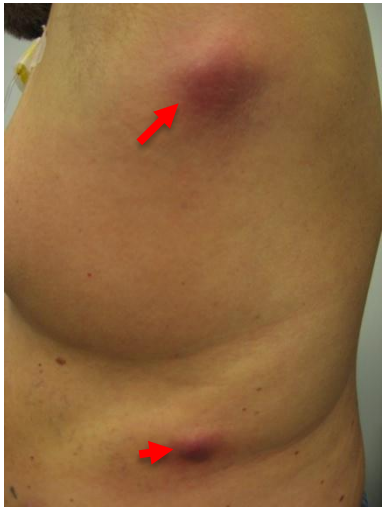


t-test (nominal) p-values

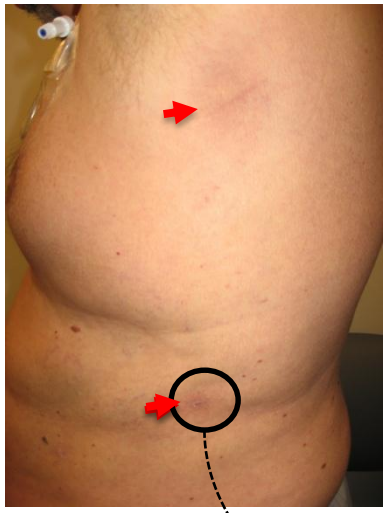
Higher expression of cytotoxic Th1 T-cell markers in tumor tissue is associated with MPDL3280A activity

Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A

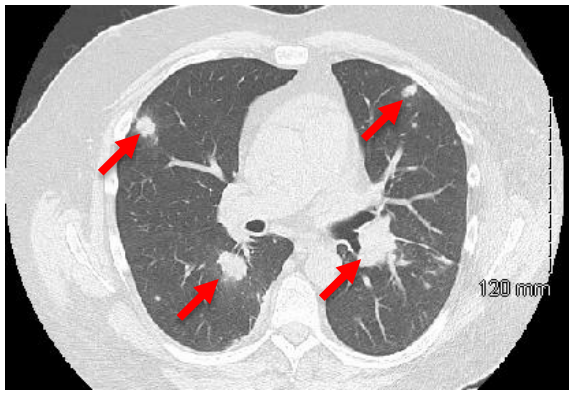
1 week tumor Flare



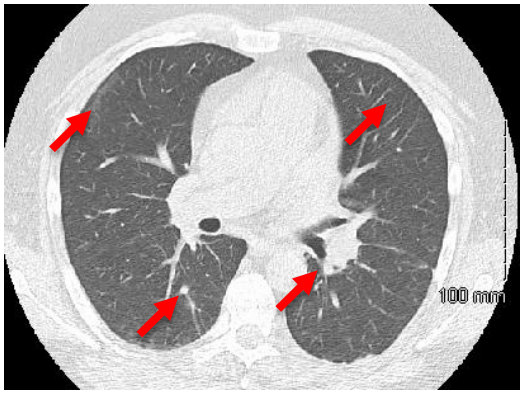
After 4 weeks



Baseline



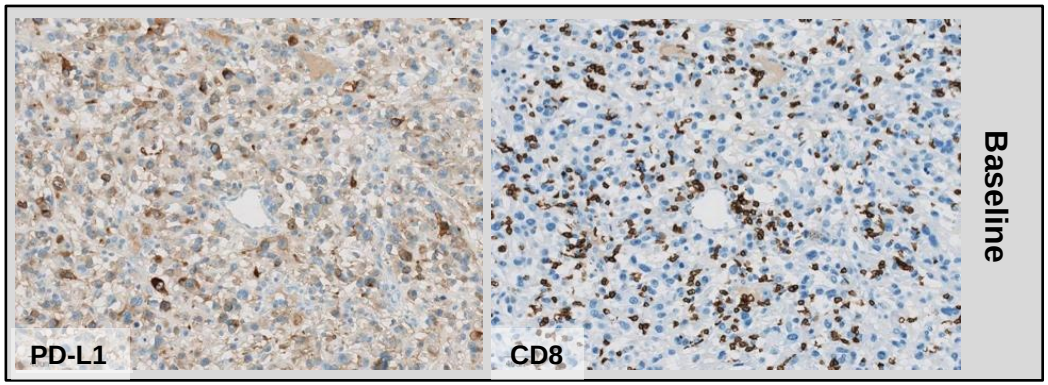
After 6 weeks

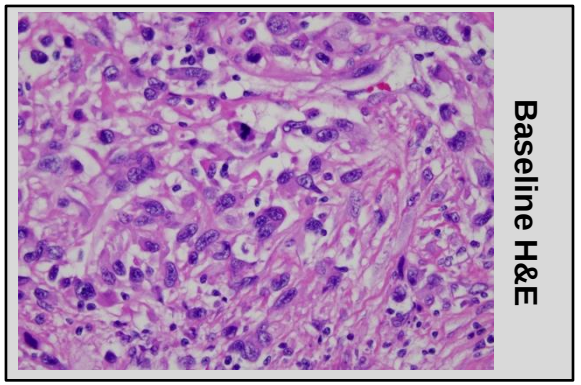


Surgical resection of responding mass, 0.75 x 0.75 cm at time of resection

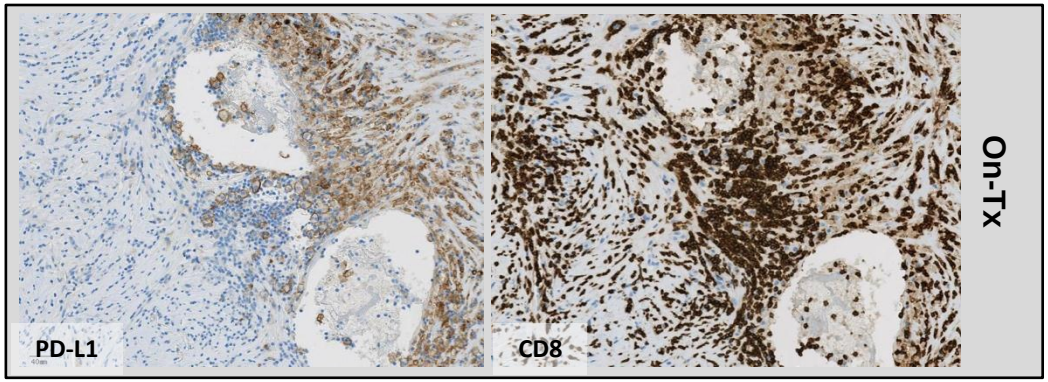
51-year-old male with Sarcomatoid RCC s/p L nephrectomy, sunitinib, XRT T9, temsirolimus, PD-L1 positive

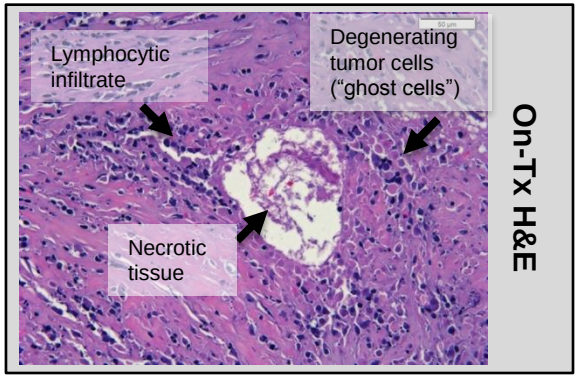
Serial Biopsy in a PD-L1–Positive RCC Patient With a Rapid Response to MPDL3280A





Biomarkers at baseline:
PD-L1 positive
CD8+ T cells present

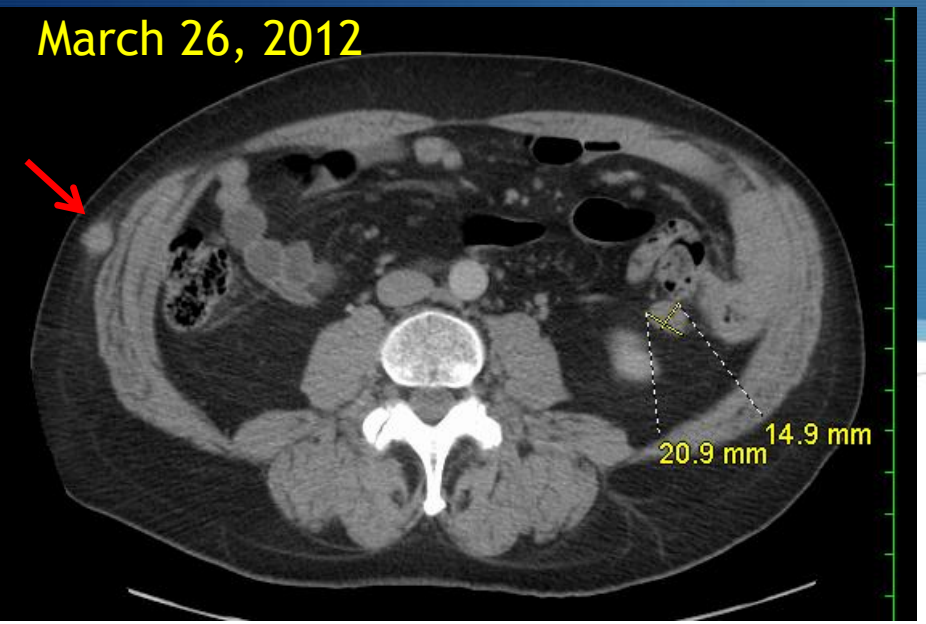


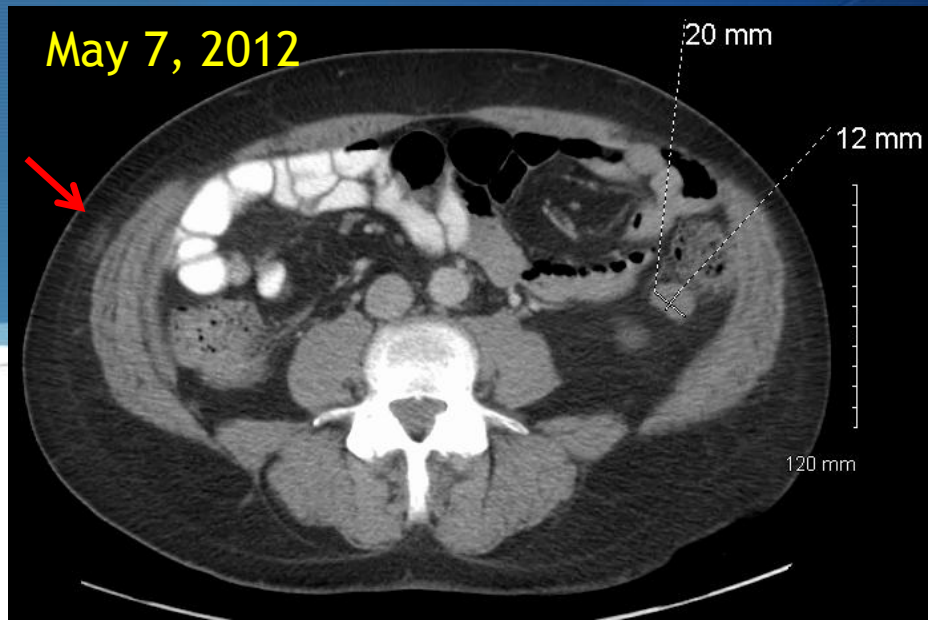


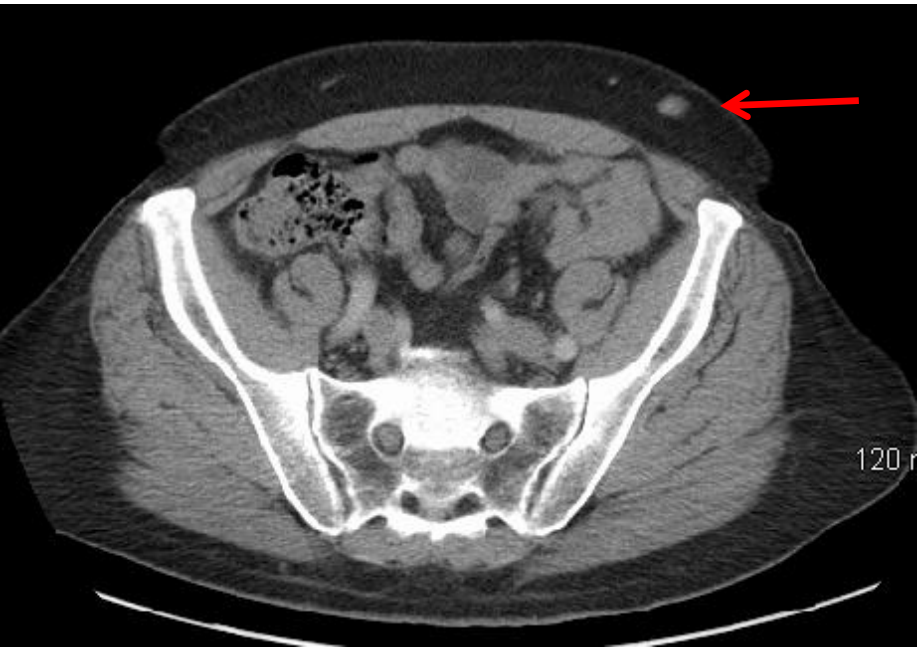
Biomarkers at week 4 post C1D1:
PD-L1 positive
Increased CD8+ T-cell infiltrate

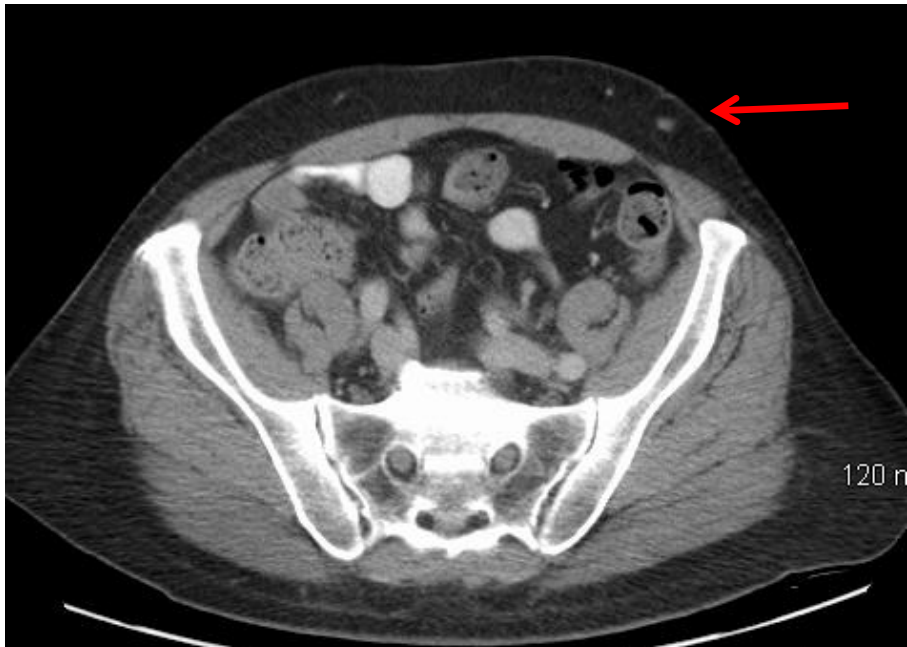
On-treatment H&E:
dense lymphocytic infiltrate
and *no viable* tumor cells seen

Melanoma Anti-PDL1 mAb

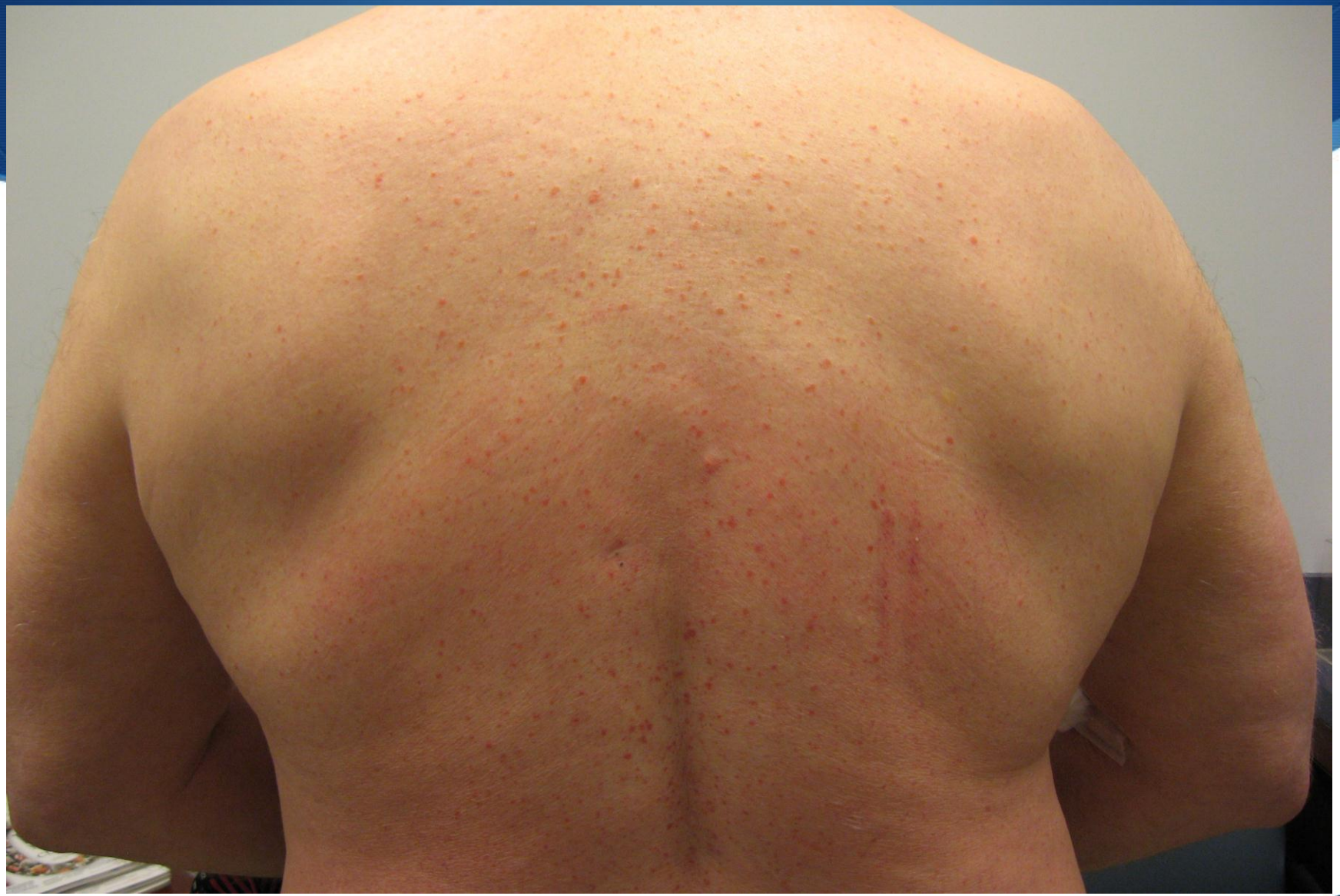








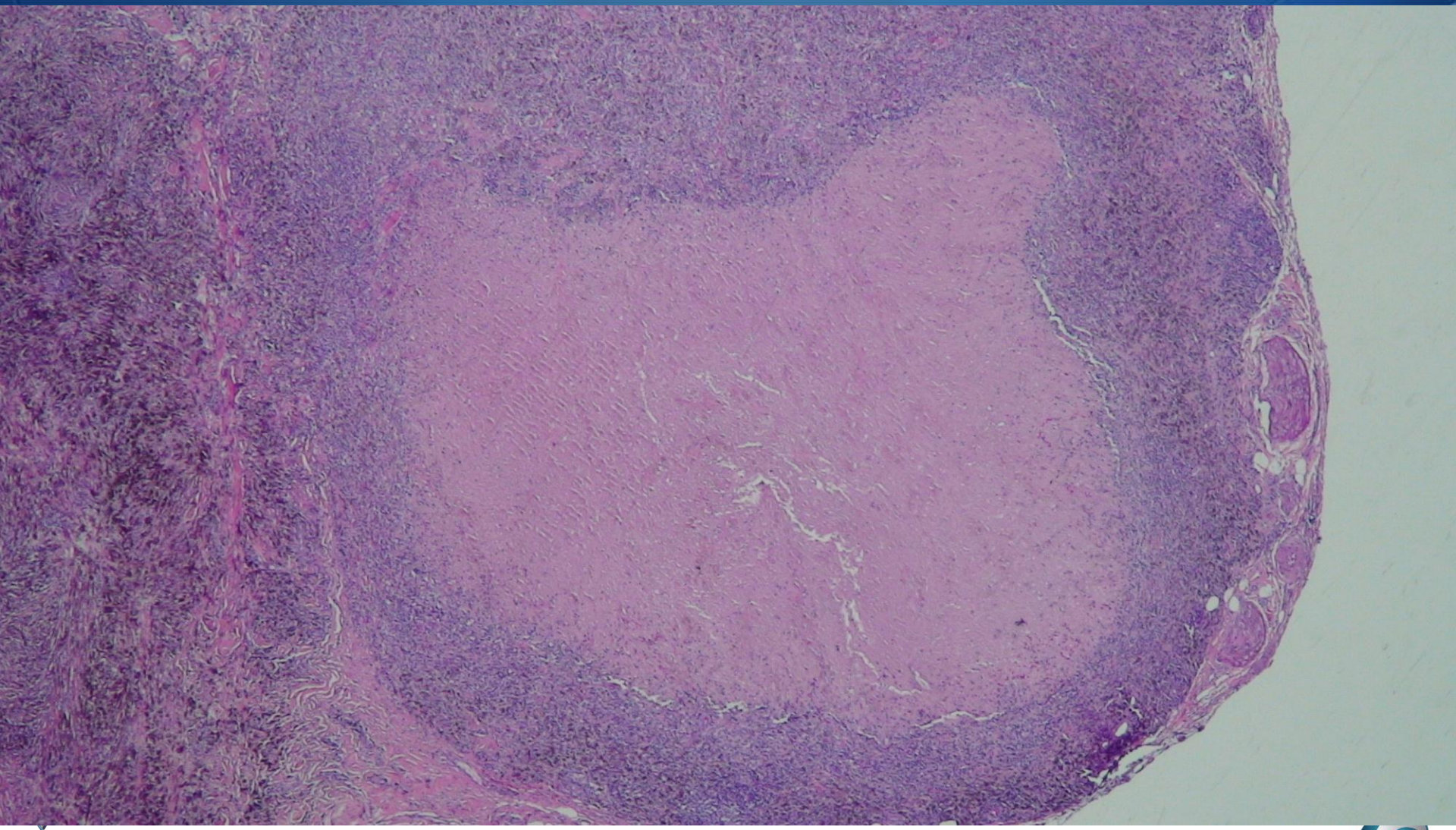
Melanoma



April 9, 2012 (cycle 1, week 1) Mild pruritic rash, then diffuse vitiligo

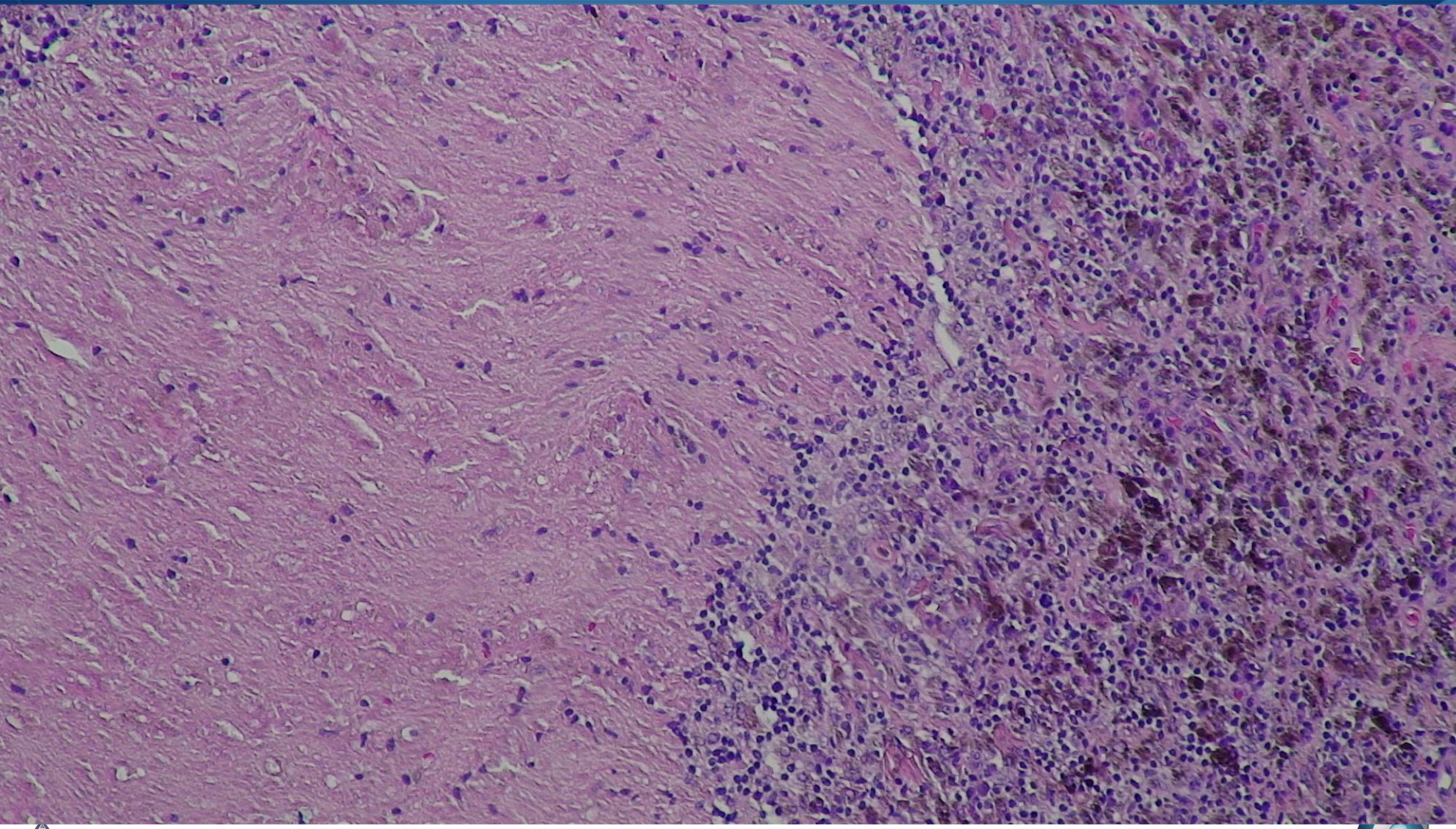
Path Excised R flank Regressing Melanoma

April 30, 2012

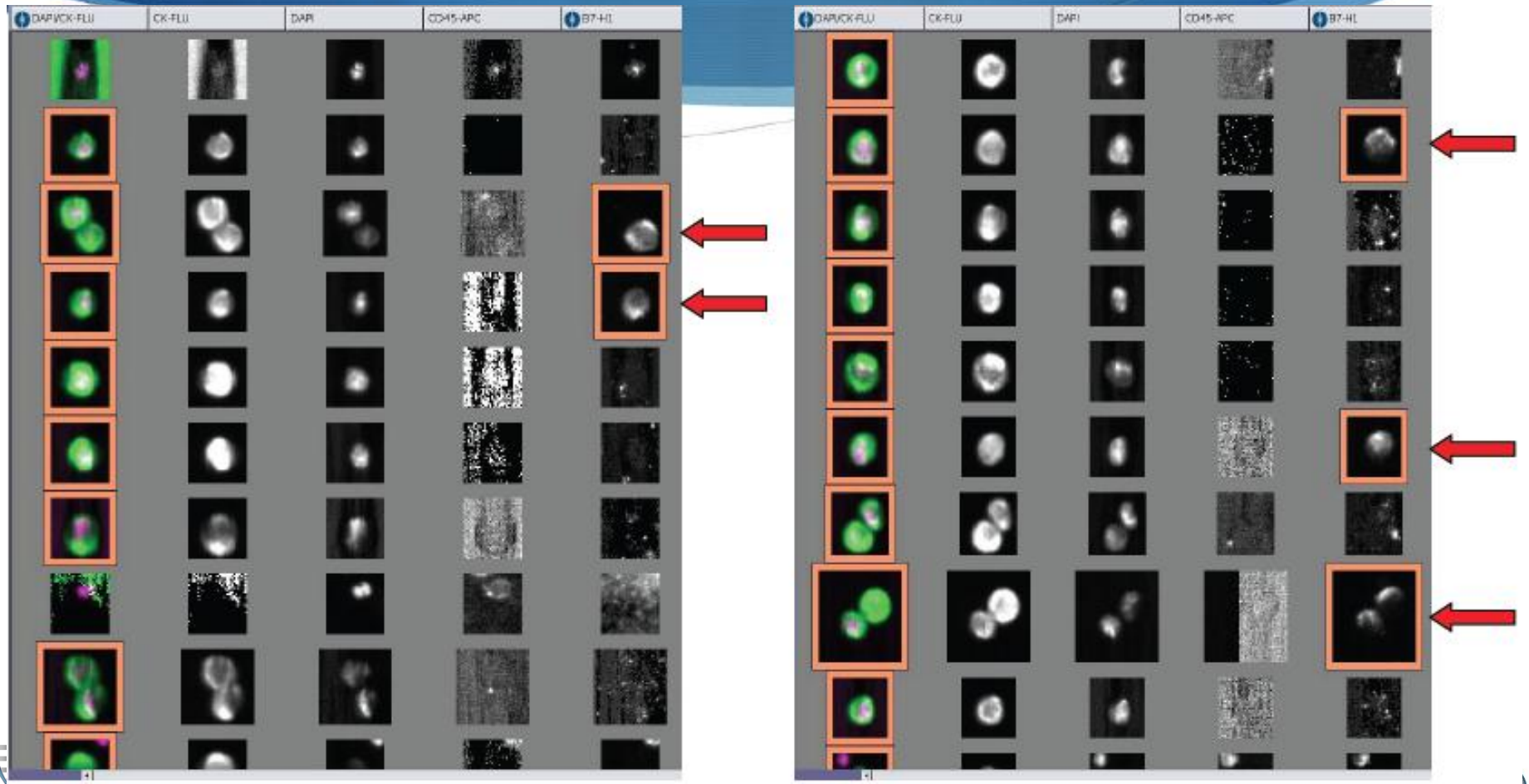


Path Excised R flank Regressing Melanoma

April 30, 2012



B7-H1 (PDL1) Profiling of Circulating Tumor Cells



Immune Principles

- More mutations = more tumor antigens to be recognized by T cells
- Highly mutated tumors (melanoma & lung) may respond to immunotherapy via self tolerance blockade
  - Explains why smokers may respond better than nonsmokers
  - Explains early evidence that “hyper-mutators” respond (BRCA mutants, Lynch syndrome, micro-satellite instability tumors)
  - Explains why tumors associated with carcinogens (lung, bladder, pancreatic) may respond
- Virally induced tumors (HPV cervical cancer, HPV Head & Neck) respond because viral tumor antigens recognized by T cells

Questions:

- PDL1 may be expressed on tumors by which distinct mechanisms:
  - A. Interferon gamma induced dynamic upregulation in the inflammatory tumor microenvironment.
  - B. Oncogenic driver mutations that constitutively express PDL1
  - C. Epithelial to Mesenchymal transformation of the carcinoma phenotype
  - D. all of the above.
- Answer is D (remarkable that so many biological circuits can cause PDL1 expression. Major take home point (the target is on any/all tumors potentially, not just melanoma).

Questions:

- PD1/PDL1 axis inhibitors are self tolerance blockade of which "compartment & phase" of the immune system:
  - A: Central immune self tolerance blockade in the lymph node during the priming phase.
  - B: Peripheral immune self tolerance blockade at the site of tumor inflammation during the effector phase.
  - C: Myeloid growth phase in the bone marrow compartment
  - D: all of the above
- Answer: B