# Personalized Immunotherapy for Non-small Cell Lung Cancer

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Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

SMILOW CANCER HOSPITAL AT YALE-NEW HAVEN

# Plan for this Presentation

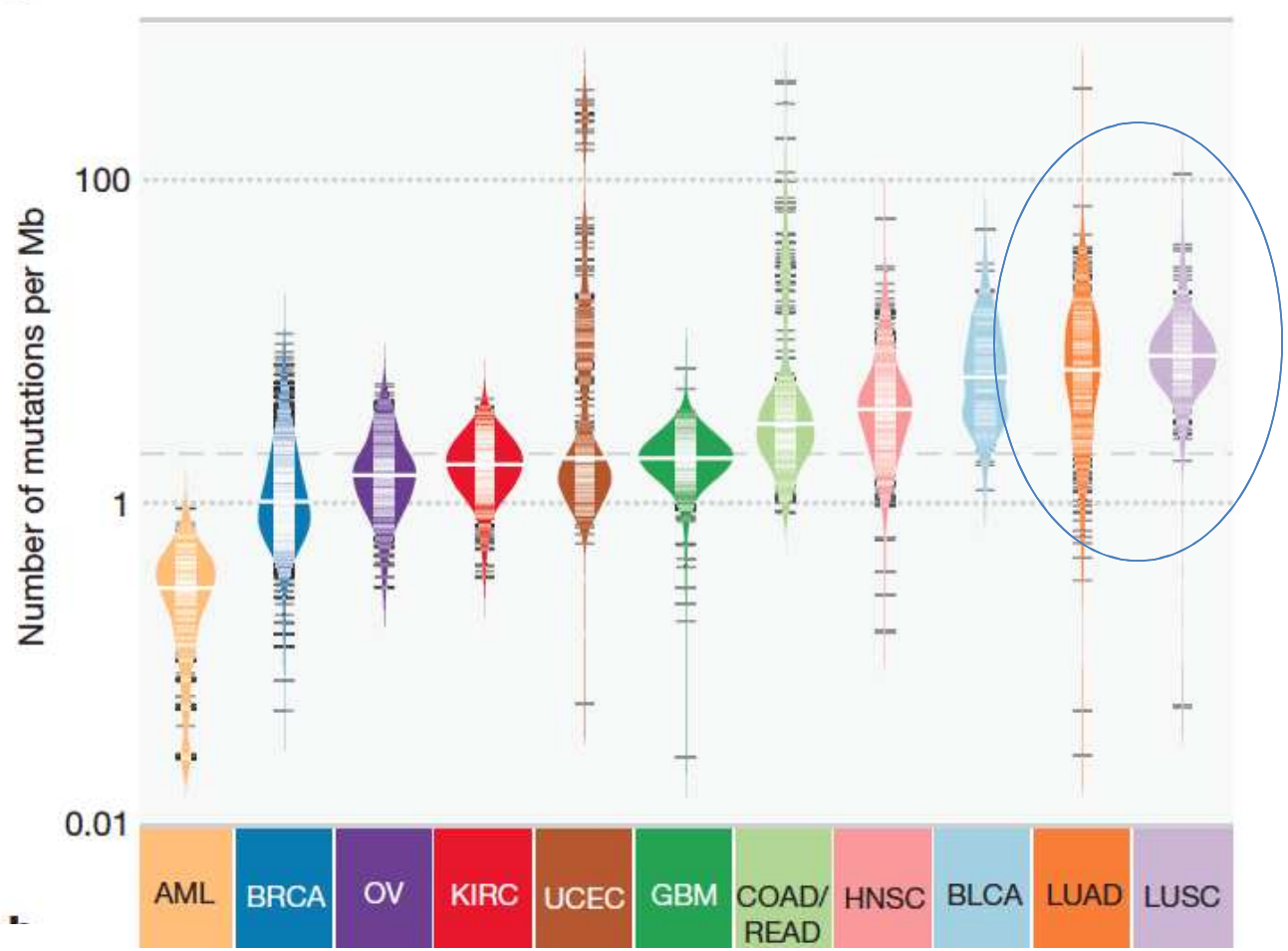
- Immunotherapy has already been much discussed at this meeting
- Experience in Melanoma is guiding lung cancer combination therapy
- I will provide my version of the top ten lessons learned so far in NSCLC

# Top Ten Lessons Learned about Immunotherapy for NSCLC

# Top Ten Lessons Learned about Immunotherapy for NSCLC

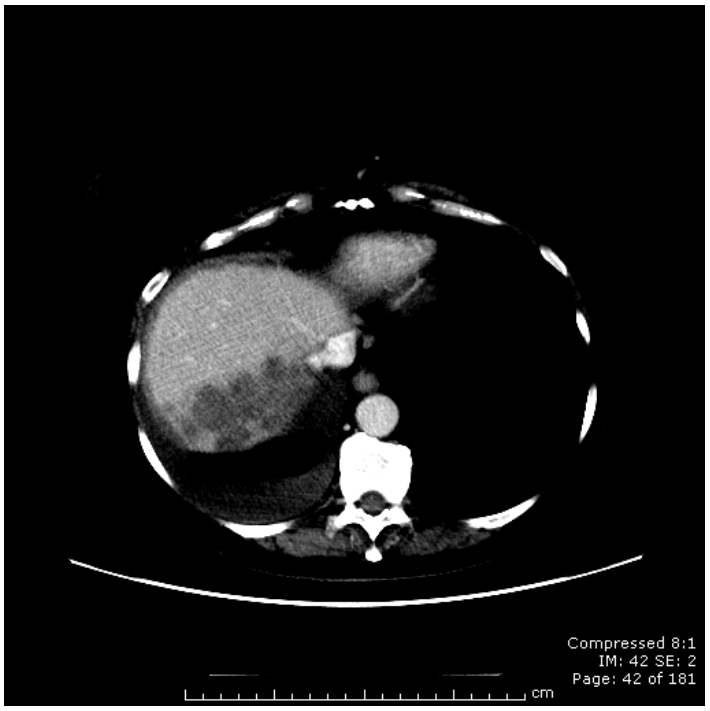
10. These agents really work- it is clearly a breakthrough for patients!

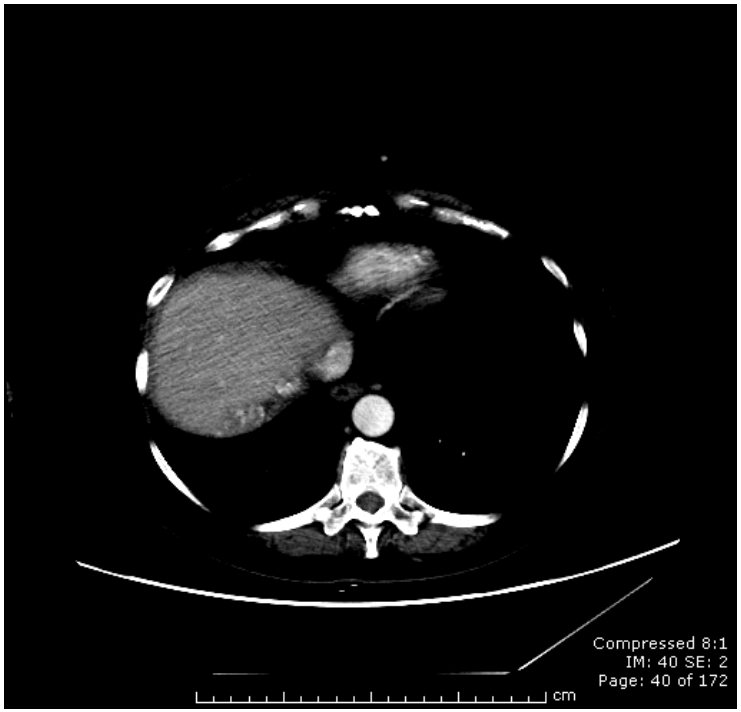
# Mutational Burden



# Anti-PD-1 Therapy

## Pre/Post MDX 1106 (Dec / Feb ’10)




- 66 y/o ex smoker with KRAS mutant adenocarcinoma of the lung
- 5 prior treatments for Stage IV disease
- RUQ abdominal pain, anorexia and fatigue resolved within 2 months
- Duration of response: 10 months

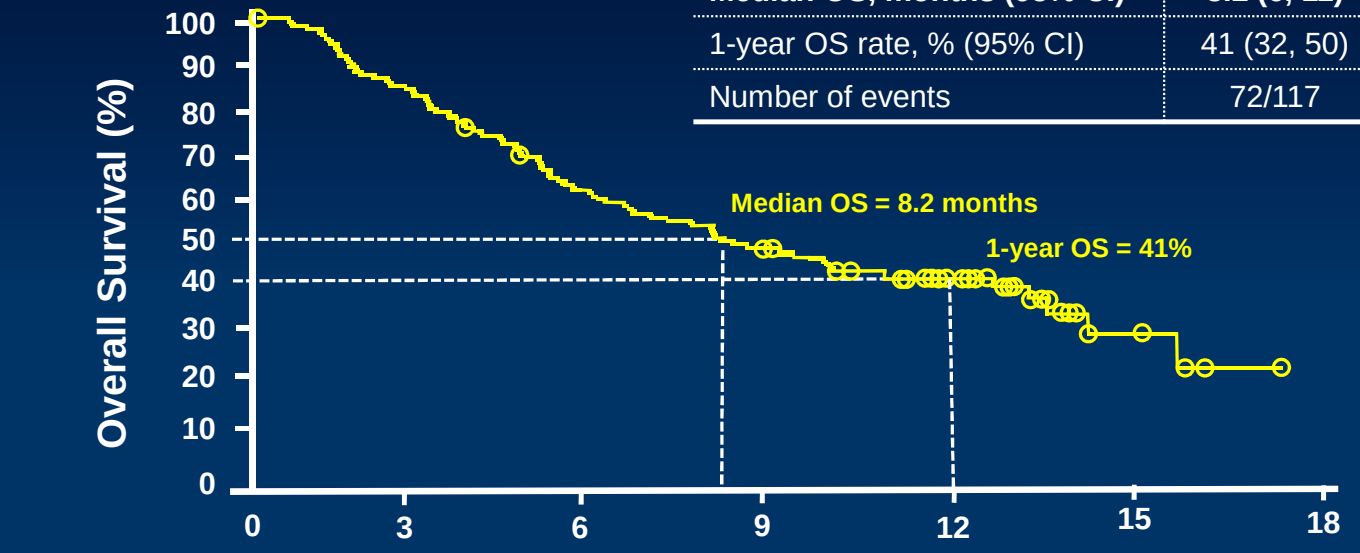
**Courtesy of S. Gettinger**

# Activity of anti-PD1 and anti-PD-L1 in NSCLC

| Agent | Dose mg/kg | N= | ORR[a,b] % (n/N) | Estimated Median DOR Weeks (Range) | PFS rate at 24 weeks | Median PFS Months (95% CI) | Median OS Months (95% CI) | 1 yr/2yr survival rate |
|---|---|---|---|---|---|---|---|---|
| Nivolumab | 1-10 mg/kg q2w | 129 | 17.1% | 74.0 | ND | 2.3 | 9.9 | 42%/24% |
| MK-3475 | 2-10 mg/kg q2-3w | 146 | 19% | ND | ND | Approx 2.5 | Approx 8 | ND |
| MPDL3280A | .01-20 mg/kg q3w | 53 | 23% | ND | 46% | ND | ND | ND |
| BMS-936559 | 1-10 mg/kg q2w | 49 | 10% | ND | 31% | ND | ND | ND |
| Medi-4736 | 0.1 -10 mg/kg q2w | 84 | ~16% | ND | ND | ND | ND | ND |

# CHECKMATE 063: OS in All Treated Patients

| | |
|---|---|
| **Median OS, months (95% CI)** | **8.2 (6, 11)** |
| 1-year OS rate, % (95% CI) | 41 (32, 50) |
| Number of events | 72/117 |




**Number of Patients at Risk**

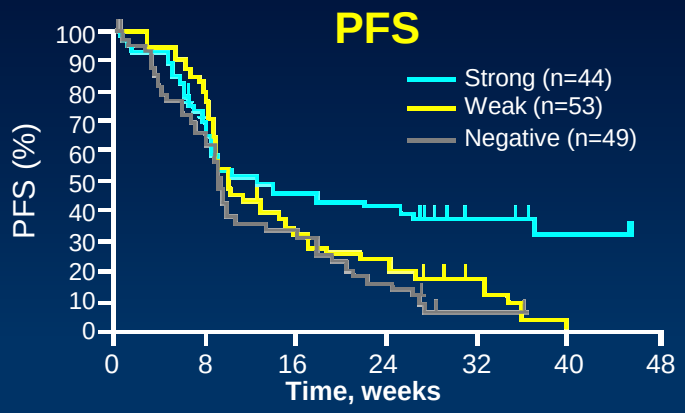
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Nivolumab 3mg/kg** | **117** | **93** | **68** | **51** | **28** | **5** | **0** |

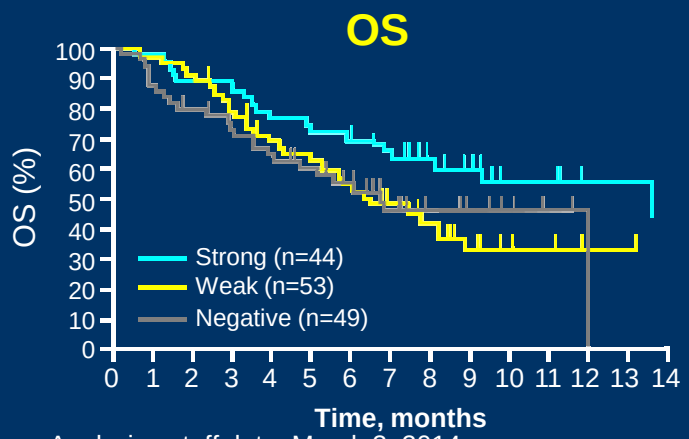
**Median follow-up for survival: 8 months (range, 0-17 months)**

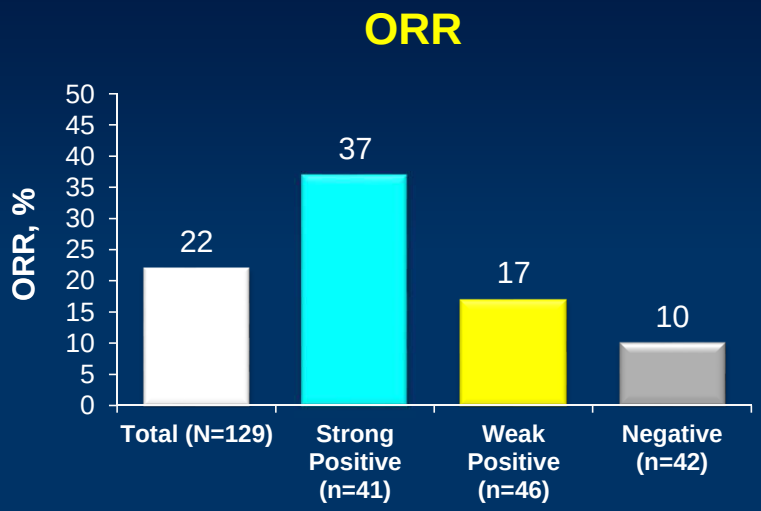
Based on July 2014 DBL; Symbols represented censored observations

Ramalingam, et al. Presented at: CMSTO. 2014 (abstr LB2).

# KEYNOTE-001: PFS, OS, and ORR by PD-L1 Expression



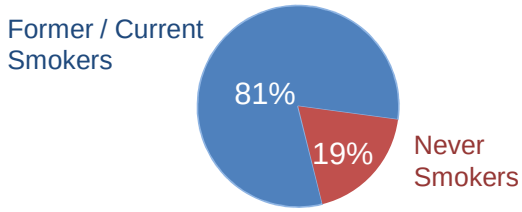

Analysis cutoff date: March 3, 2014.

Garon, et al. Presented at: ESMO. 2014 (abstr LBA43).

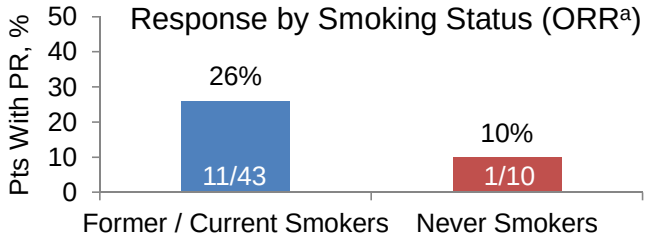
International Association for the Study of Lung Cancer
IASLC
IASLC 15th World Conference on Lung Cancer
October 27 – October 30, 2013
*Sydney, Australia*
WCLC.IASLC.ORG

# MPDL3280A Phase Ia: Response by Smoking and Mutational Status

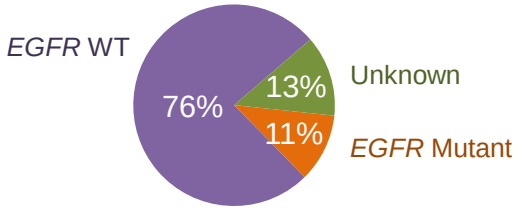
## Smoking Status (NSCLC; n = 53)



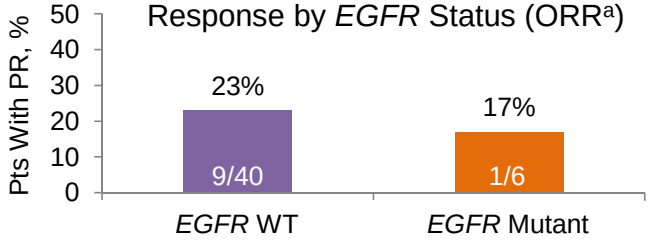

## Response by Smoking Status (ORR[a])



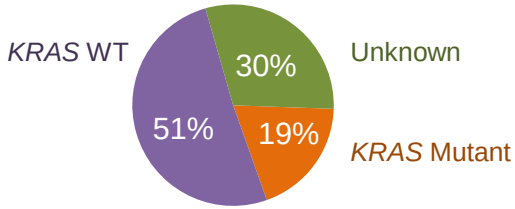

## *EGFR* Status (NSCLC; n = 53)



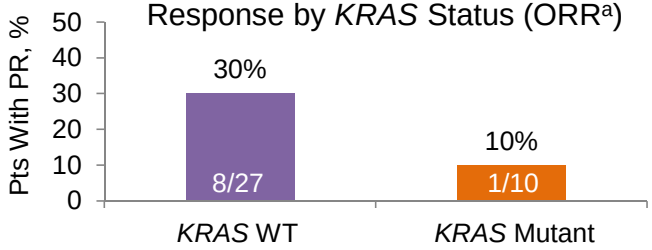

## Response by *EGFR* Status (ORR[a])




## *KRAS* Status (NSCLC; n = 53)




## Response by *KRAS* Status (ORR[a])

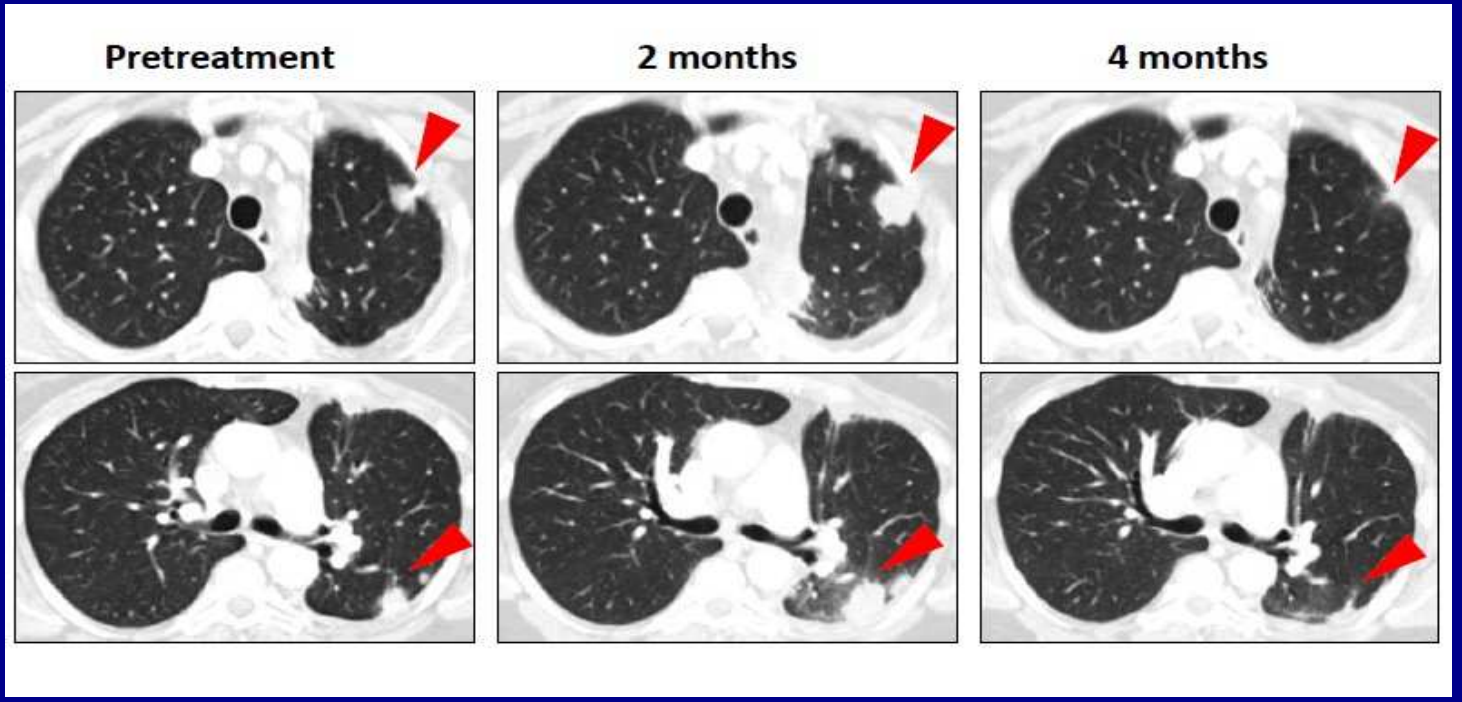



[a] ORR includes investigator-assessed u/c PR by RECIST 1.1. Patients first dosed at 1-20 mg/kg by Oct 1, 2012. Data cutoff: Apr 30, 2013.

## Top Ten Lessons Learned about Immunotherapy for NSCLC

9. It is still unclear what is the most appropriate endpoint

# Delayed Response of Metastatic NSCLC (Nivolumab, 10mg/kg) Pseudoprogression



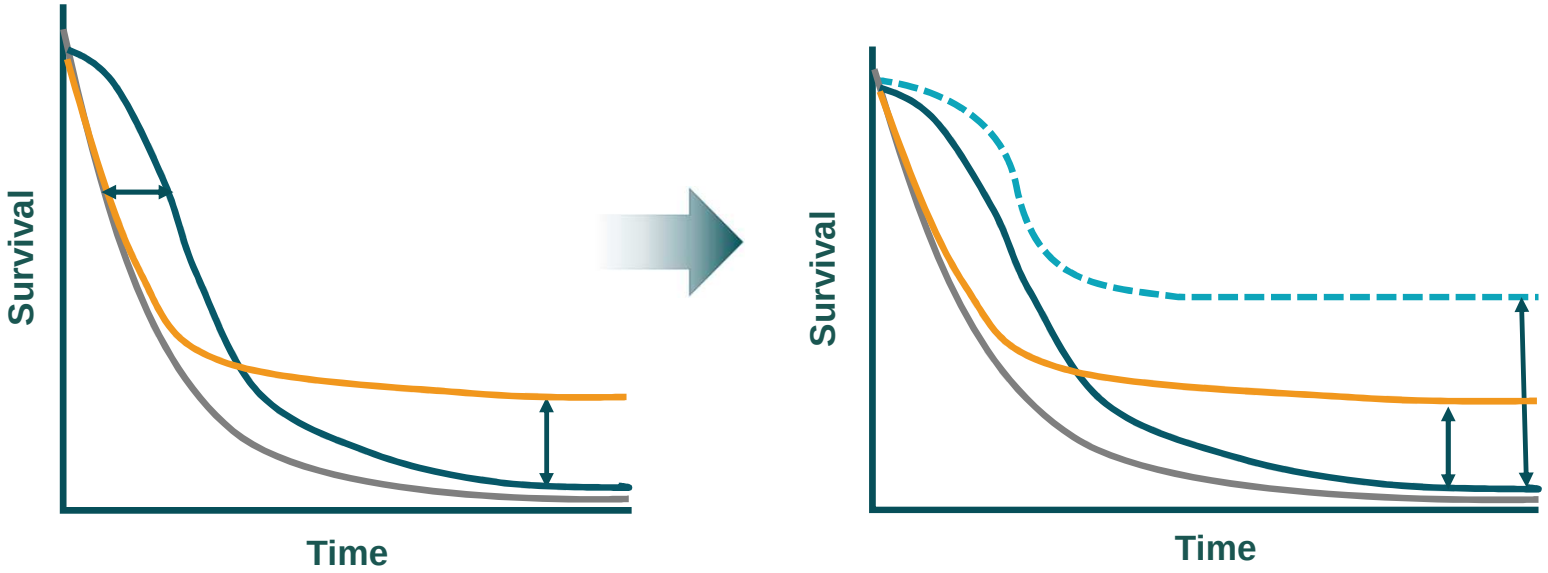

- Initial progression of pulmonary lesions in a patient with EGFR mutant (del19, T790M) NSCLC, followed by regression
- Prior treatment with gemcitabine/ carboplatin, erlotinib, erlotinib + LBH589, and pemetrexed

# Endpoints for Combinations with CTLA-4 or PD-1 pathway blockade

- ORR
- iRC RR -
- CR –
- CBR/DCR –
- **Aggregate clinical activity -**
- 'Deep' (> 80% regression) responses -
- Median duration of response –
- Median PFS -
- 1-year and 2 year PFS –
- 3 year PFS
- Median Survival –
- 1- year and 2-year survival

## Where we are now

## Where we want to be




Salvati M, 3rd Intl Symp in Lung Ca, 2014; Ribas A, WCM, 2013; Ribas A, et al. Clin Cancer Res 2012; Drake CG. Ann Oncol 2012

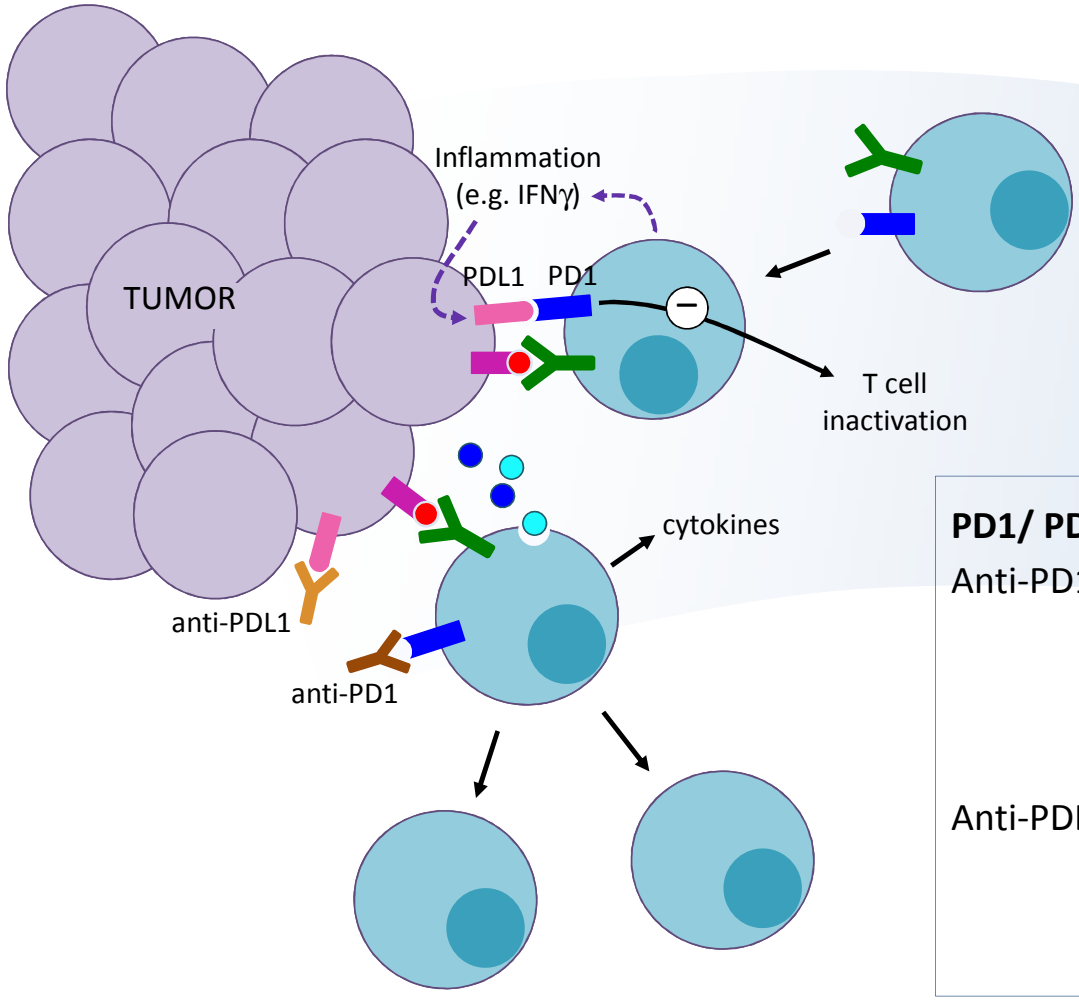
# Top Ten Lessons Learned about Immunotherapy for NSCLC

8 .  All checkpoint antibodies are not the same?  Or are they?

# Are there differences in Activity/Toxicity among agents

- **Binding Affinity**
- **Different targets**
- **Antibody Isotype  (IgG4 vs IgG1 vs engineered)**
- **ADCC**
- **Anti PD1 vs anti PDl1**

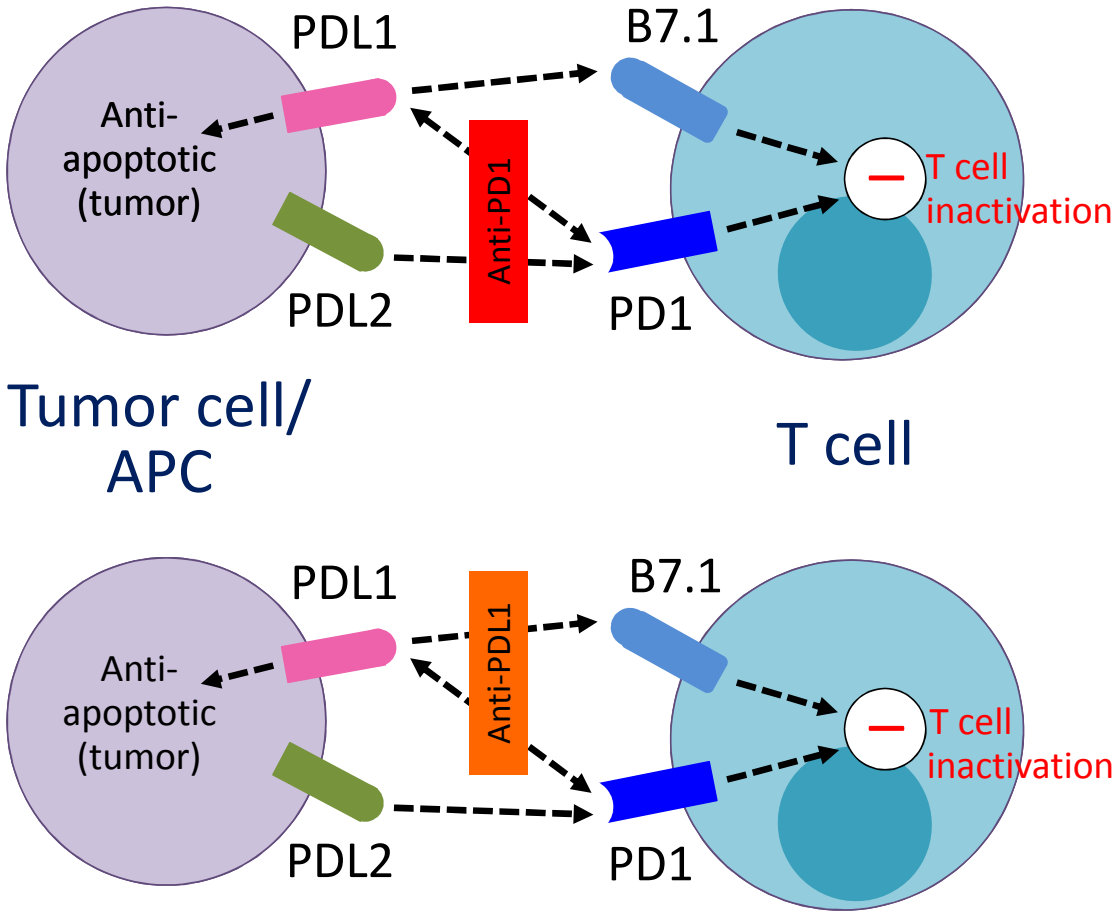
# Programmed Death Receptor 1 (PD1)/ B7-H1 Pathway

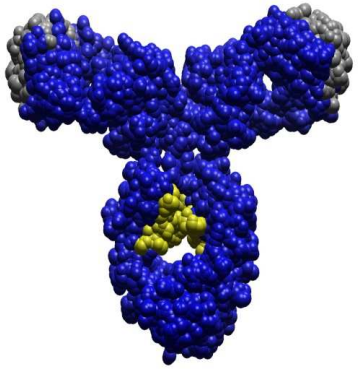



**PD1/ PDL1 Blockade in Clinical Trials**

| | |
|---|---|
| Anti-PD1 | Nivolumab |
| | Pembrolizumab |
| | CT-011 |
| | AMP-514 |
| | AMP-224 |
| Anti-PDL1 | MPDL3280A |
| | MEDI4736 |
| | BMS-936559 |
| | MSB0010718C |

# PD1 vs. PDL1 Blockade



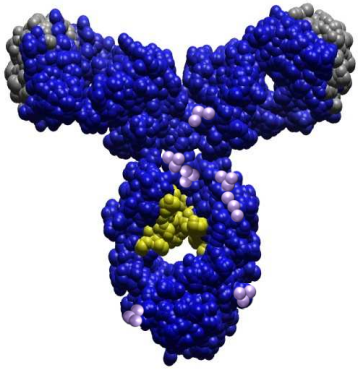


**IgG1 wt**

Examples: Anti-PD-1

**ADCC intact ➔**
**Potential to deplete activated T cells and TILs and diminish activity**

**Blocks PD-1/PD-L2 interaction in lungs ➔**
***Potential for autoimmune pneumonitis***

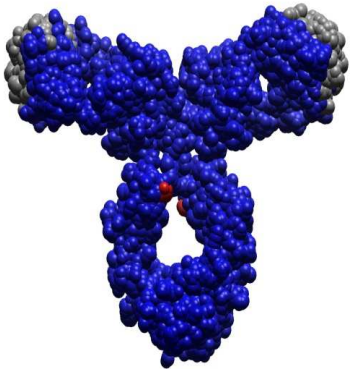


**IgG4 hinge mutant**

Anti-PD-1
Anti-PD-1

**40% reduced ADCC† ➔**
**Potential to deplete activated T cells and TILs and diminish activity**

**Blocks PD-1/PD-L2 interaction in lungs ➔**
***Potential for autoimmune pneumonitis***



***IgG1 Engineered***

**Anti-PD-L1**

***MPDL3280A***

**No ADCC† ➔**
**Decreased potential to deplete activated T cells and TILs**

**Leaves PD-1/PD-L2 interaction intact in lungs ➔**
***Decreased potential for autoimmune pneumonitis***

**Blocks PD-L1/B7.1 interaction ➔**
***Potential for enhanced priming***

**†at clinically relevant doses**

## Top Ten Lessons Learned about Immunotherapy for NSCLC

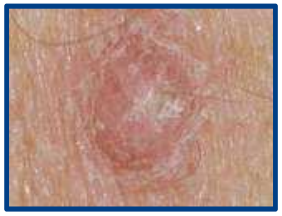
7. These agents, while different from chemotherapy, do have unique toxicities

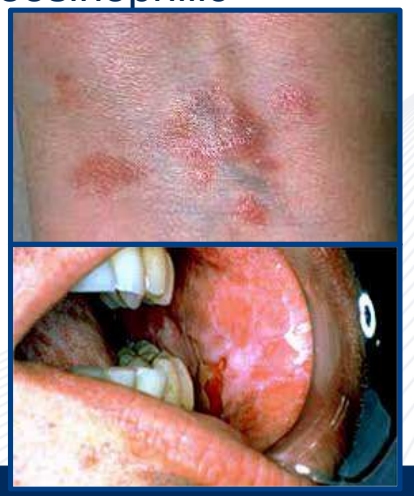
# Immune related Adverse Events (IRAEs)

| System | Adverse Events |
|---|---|
| Gastrointestinal | diarrhea, colitis, perforation |
| Renal | acute interstitial nephritis |
| Pulmonary | Pneumonitis |
| Dermatologic | Lichenoid/ spongiotic dermatitis, rash, vitaligo |
| Hepatic | Hepatitis |
| Neurologic | Central and peripheral (aseptic meningitis, Guillan-Barre syndrome, myasthenia gravis, |
| Endocrine | hypophysitis, hypopituitarism, thyroiditis, adrenal insufficiency |
| Ocular | uveitis, iritis, or episcleritis. |

# Dermatitis

- Symptoms:
  - Maculopapular rash (may be pruritic)
  - Distribution on trunk, hands and feet
    - May be intense and widespread
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, blistering/peeling skin; epidermal spongiosis, eosinophilic infiltrates, hair depigmentation
  - Mucositis and oral lesions



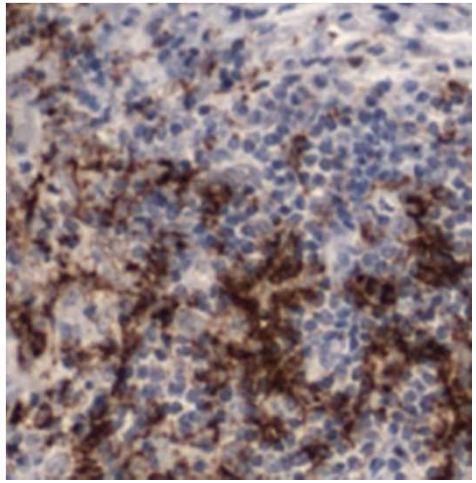


- Initial work-up:
  - Dermatology referral
  - Rule out allergic causes, contact dermatitis

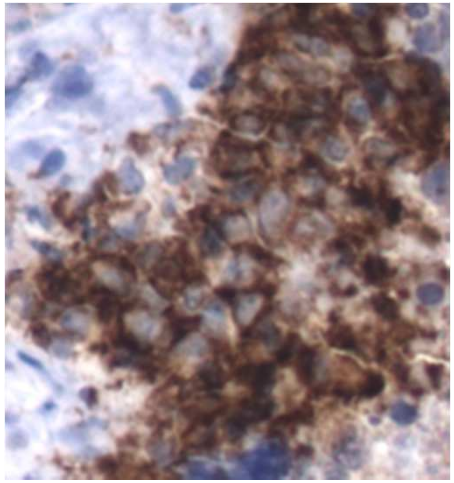
## Top Ten Lessons Learned about Immunotherapy for NSCLC

6. The PDL1 Biomarker(s) has some flaws

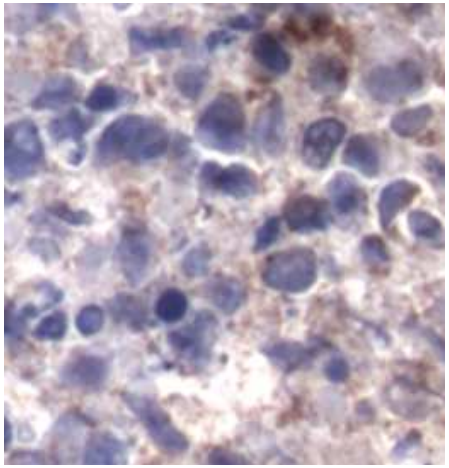
# PD-L1 Immunohistochemistry (5H1): Role as a Biomarker



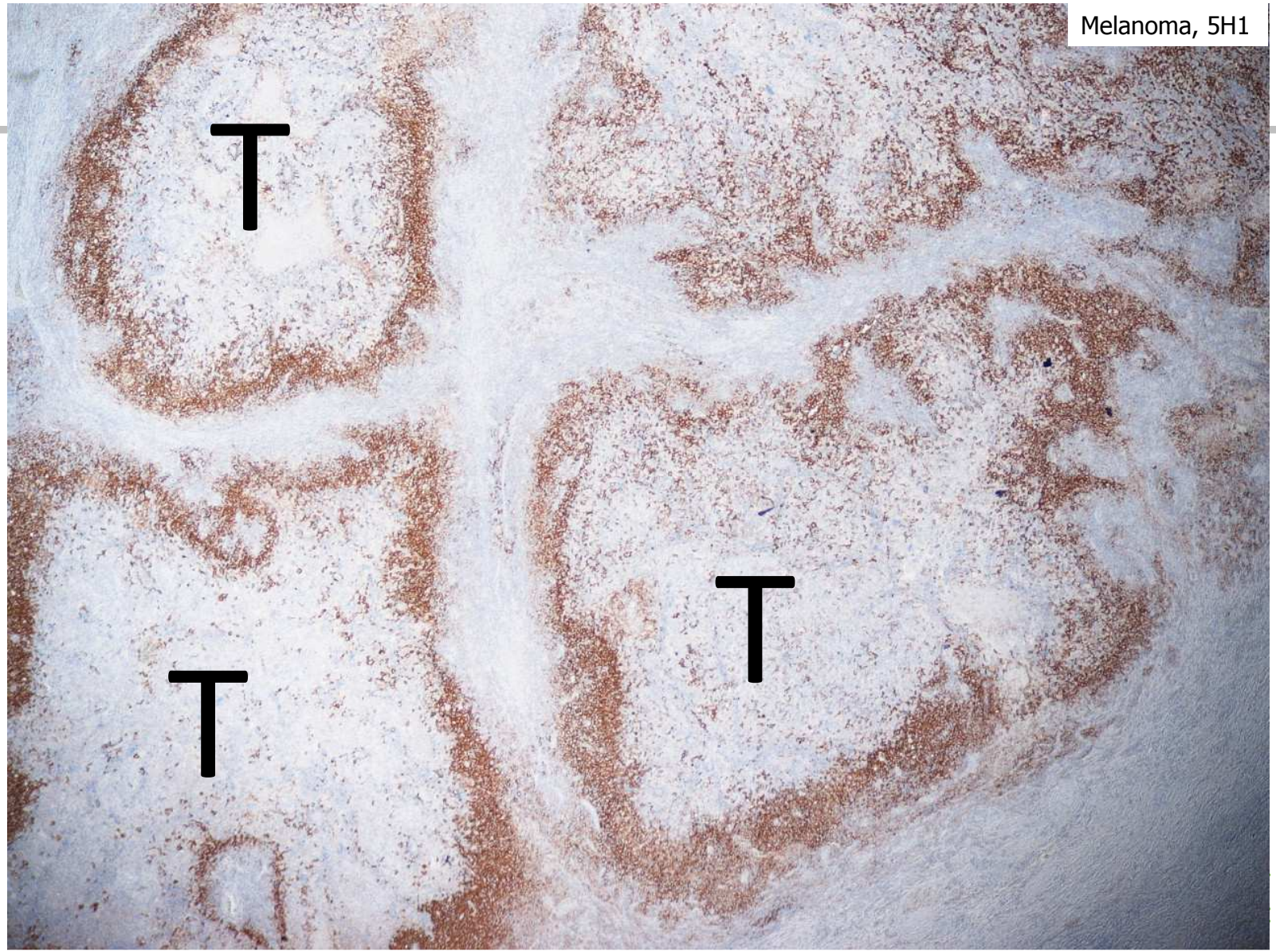
A. PDL1 + tumor with TILS



B. PDL1 + tumor



C. Control antibody


Melanoma, 5H1
T
T
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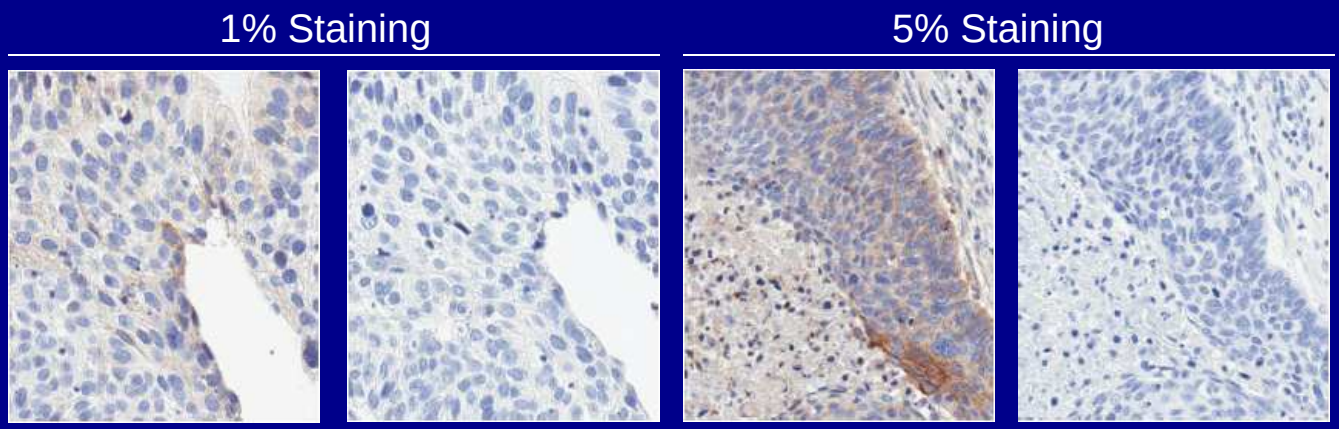
# Assay Methodology

- Bx type - Excisional versus core versus FNA
- **Addressing heterogeneity** – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment – effect of other therapies
- Primary versus metastatic disease
- Antibody and staining conditions
- Frozen versus FFPE tissue
- Automated versus 'manual' read
- **Defining a positive result (cut-offs):**
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Presence or absence of T-cells near PD-L1 expression
  - Location of expression – cell surface versus intracellular
  - intensity
  - Distribution - patchy versus diffuse, intratumoral versus peripheral
  - percent of cells 'positive'

# PD-L1 Expression in NSCLC Samples Stained With Anti-PD-L1 Antibody (clone 28.8)




[a]Figure from Antonia SJ, et al. WCLC 2013. Poster P2.11-035. PD-L1 staining is shown in archival tumor tissue

- PD-L1 expression was measured in archival pretreatment tumor tissue (including >1 year old)
- Responses were seen in both PD-L1$^{+}$ and PD-L1$^{-}$ patients; ORRs were 15% (5/33) and 14% (5/35), respectively
- In the subset of patients for whom tissue was available, PD-L1 expression appeared to have no clear association with OS; median OS was 7.8 and 10.5 mo in PD-L1$^{+}$ and PD-L1$^{-}$ patients, respectively

PD-L1 expression was measured using the automated IHC assay based on the anti-PD-L1 monoclonal antibody (clone 28-8). Positive staining with this assay is defined as tumor cell membrane staining at any intensity, analyzed with cut-off values of 1% and 5% in a minimum number of 100 evaluable cells

# CHECKMATE 063: Exploratory Analysis of ORR by PD-L1 Expression

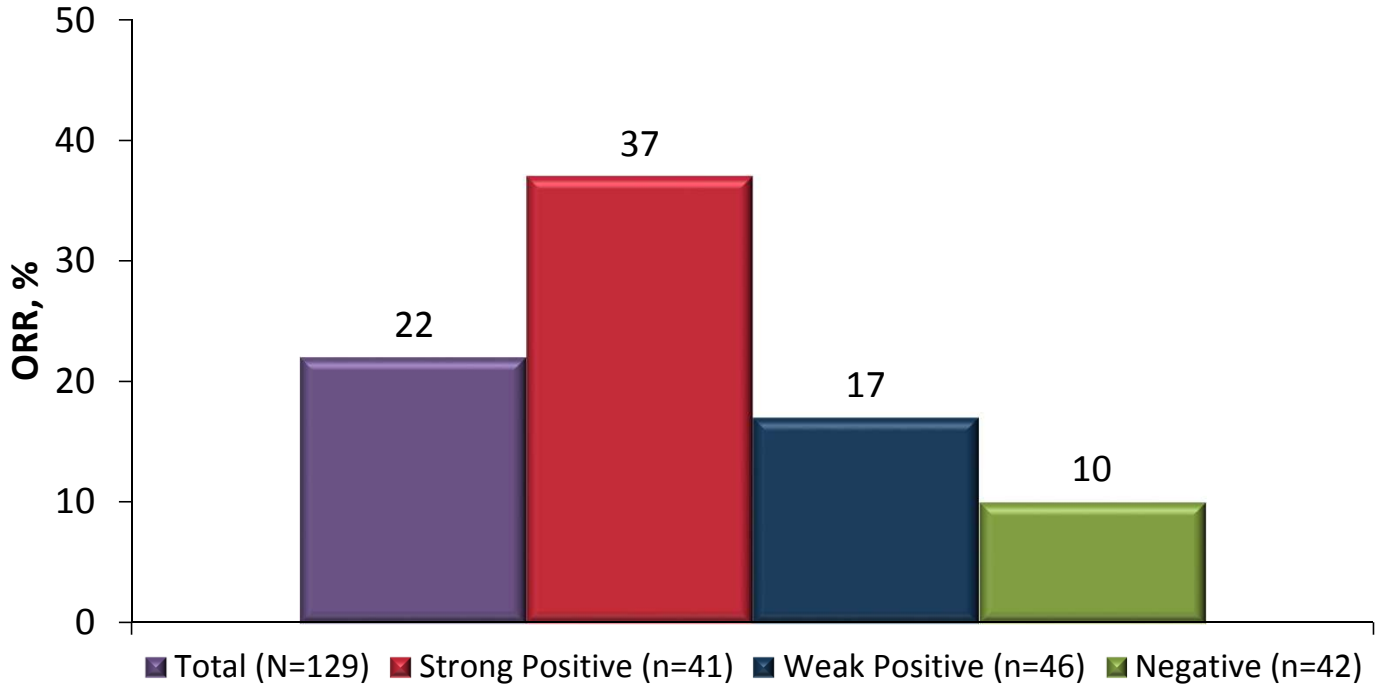
| Subgroups | | ORR, % (n/N) |
|---|---|---|
| **Overall** | | **15 (17/117)** |
| PD-L1 | ≥1% | 20 (9/45) |
| | <1% | 13 (4/31) |
| | ≥5% | 24 (6/25) |
| | <5% | 14 (7/51) |
| | Non-evaluable | 30 (3/10) |

- 86 available sample
- 76 evaluable samples[#]

*July 2014 DBL; [#] One responder did not have tumor tissue available

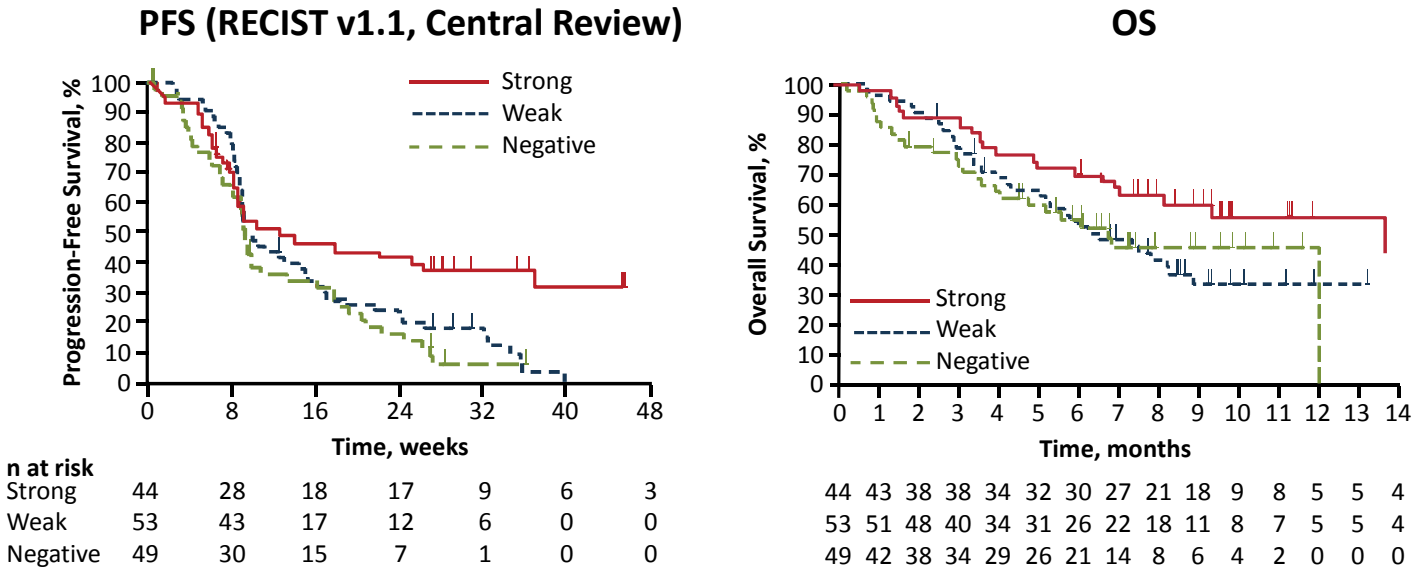
Ramalingam, et al. Presented at: CMSTO. 2014 (abstr LB2).

# Response Rate by Level of PD-L1 Expression
## (RECIST 1.1, Central Review)




[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.
Analysis cut-off date: March 3, 2014.

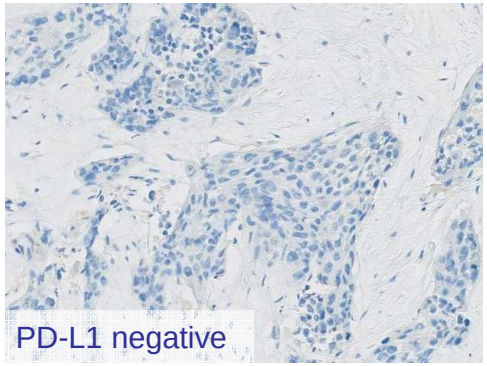
# Kaplan-Meier Estimates of Survival

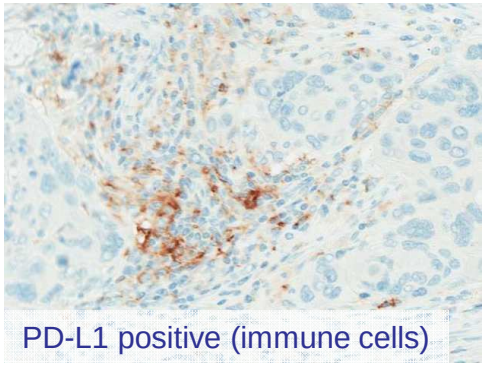


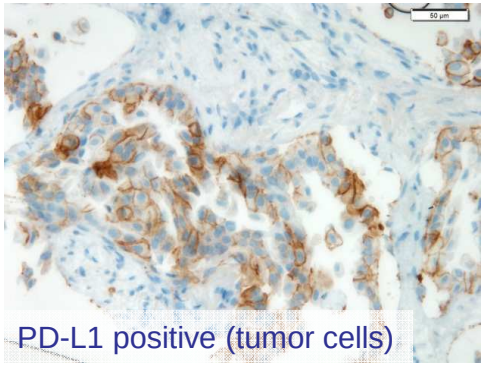

- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression.
Strong PD-L1 positivity defined as staining in ≥50% of tumor cells, and weak PD-L1 positivity as staining in 1-49% of tumor cells. Negative staining is no PD-L1 staining in tumor cells.
Data cut-off: March 3, 2014.

# MPDL-3280 Dx PD-L1 IHC Reagent – a Robust Assay to Measure PD-L1 in Human Tissues


PD-L1 negative

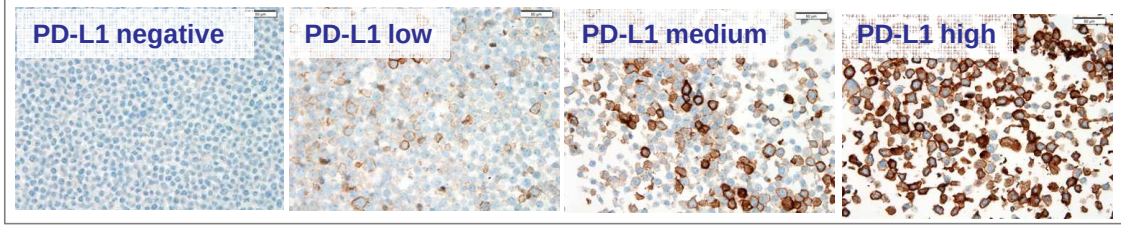

PD-L1 positive (immune cells)


PD-L1 positive (tumor cells)

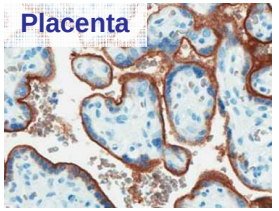
**PD-L1 IHC (**MPDL-3280 **Dx):**

- 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 Status and Predictive Biomarkers in NSCLC Patients Treated With MPDL3280A: Efficacy

Elevated baseline PD-L1 expression is associated with response to MPDL3280A

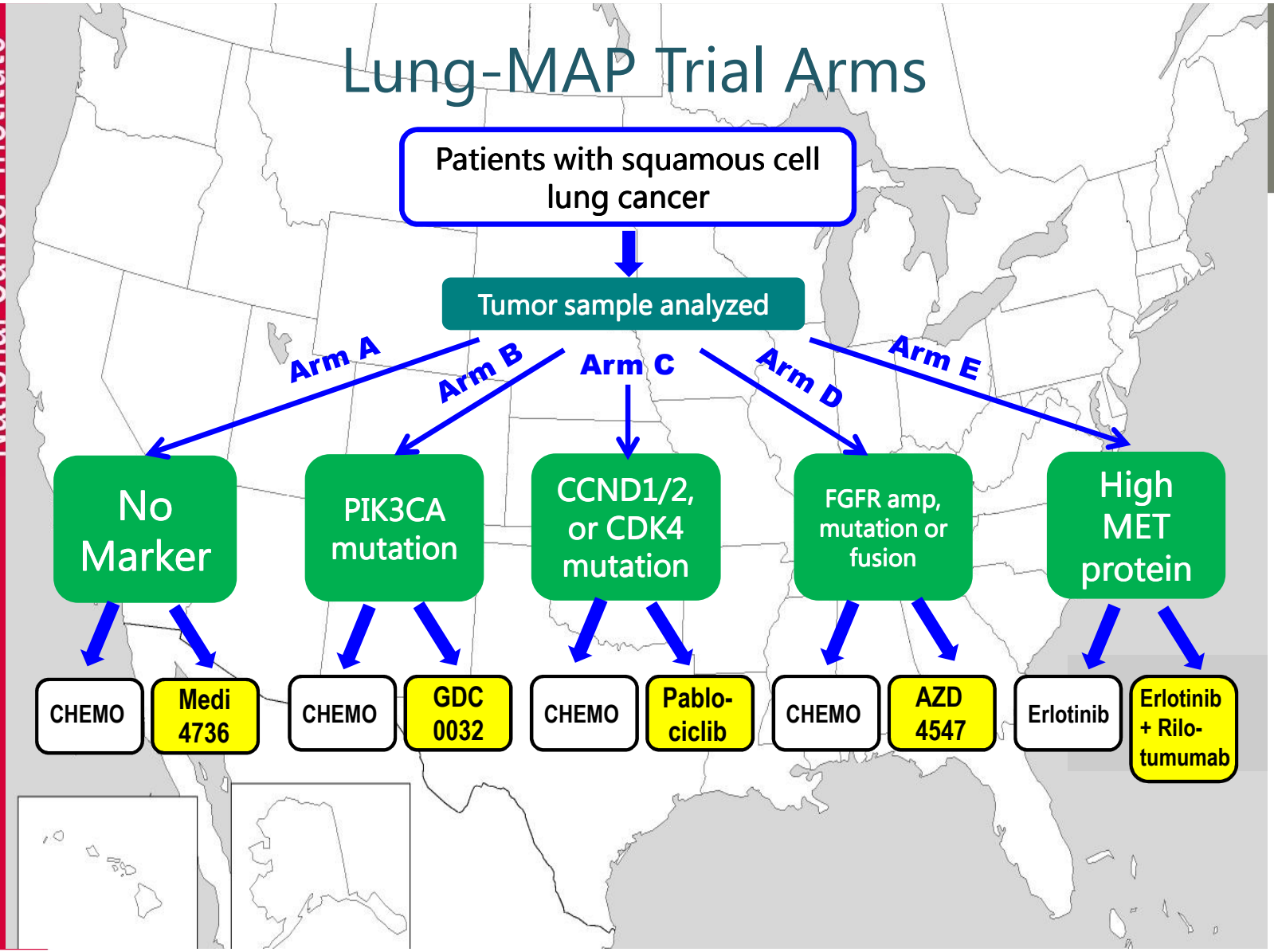
| PD-L1 Status | N = 53 | |
|---|---|---|
| | ORR[a] | PD Rate[b] |
| IHC 3 (n = 6) | 83% (5/6) | 17% (1/6) |
| IHC 2 and 3 (n = 13) | 46% (6/13) | 23% (3/13) |
| IHC 1/2/3 (n = 26) | 31% (8/26) | 38% (10/26) |
| All patients [c] (N = 53) | 23% (12/53) | 40% (21/53) |

[a] ORR includes investigator-assessed unconfirmed and confirmed PR by RECIST v1.1.
[b] PD rate indicates patient with best response with progressive disease.
[c] Includes patients with IHC 0/1/2/3 and 7 patients with unknown diagnosis.

Gettinger et al. IASLC WLCL 2013. Herbst et al, Manuscript in Preparation.

National Cancer Institute

# Lung-MAP Trial Arms

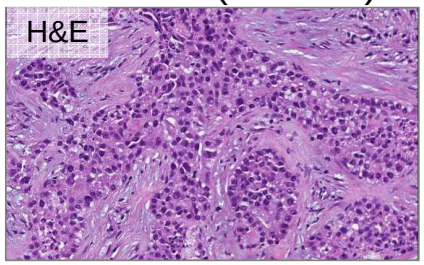


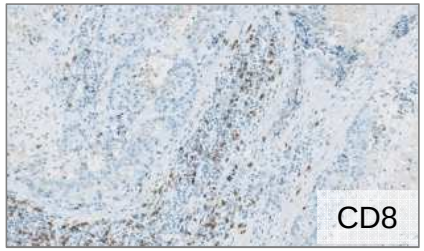
# Top Ten Lessons Learned about Immunotherapy for NSCLC

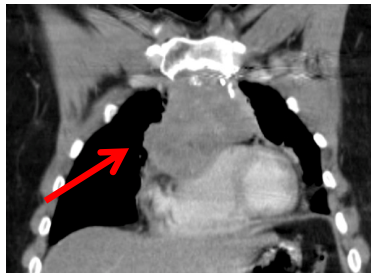
5. Science can help drive the Show: Biopsies and Immune monitoring should be done when possible

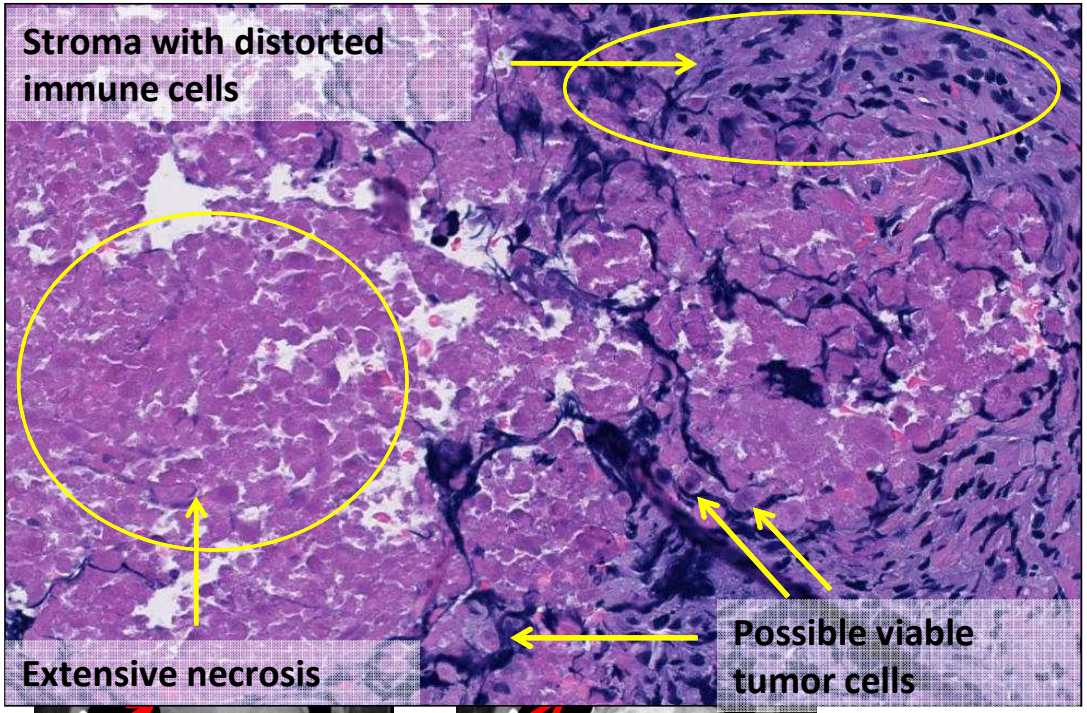
# Correlation of Radiographic and Pathologic Response to MPDL3280A

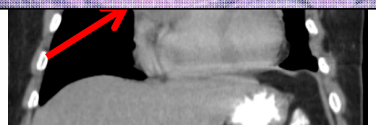
Baseline (5-21-12)

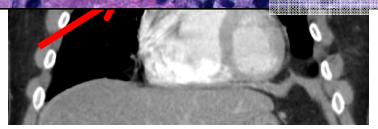


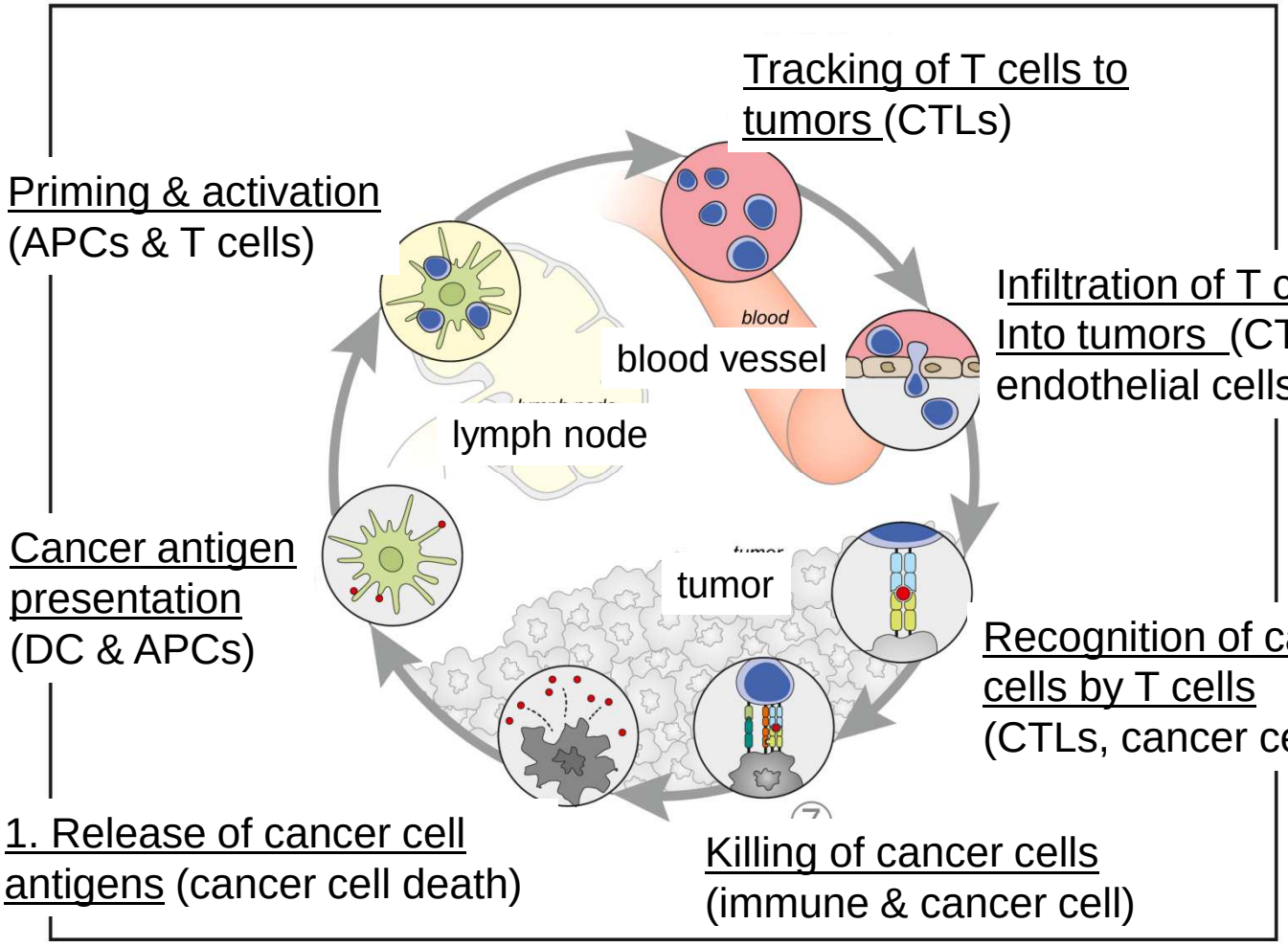




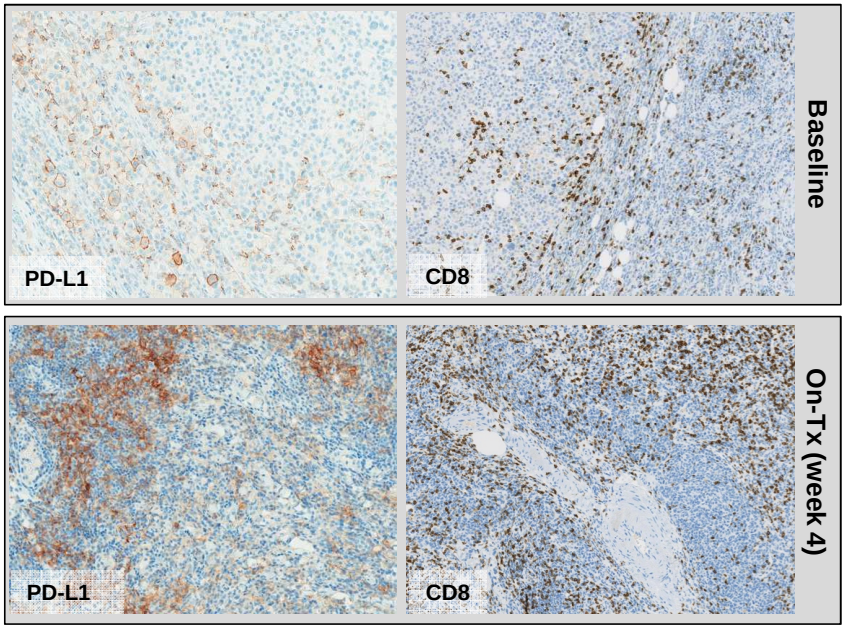
46 y.o. male, former smoker (20 PYH); *EGFR*–, *ALK*– and *RAS*–negative; PD-L1 IHC 1; 6 prior regimens

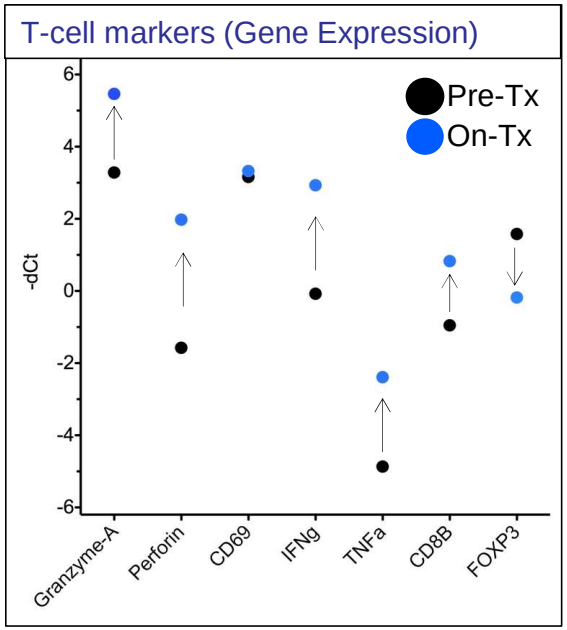
# The cancer-immunity cycle




**[Chen & Mellman Immunity 39, July 25, 2013]**

# MPDL3280A Leads to Increased T-cell Activation in PD-L1–Positive Patient Responding to Treatment

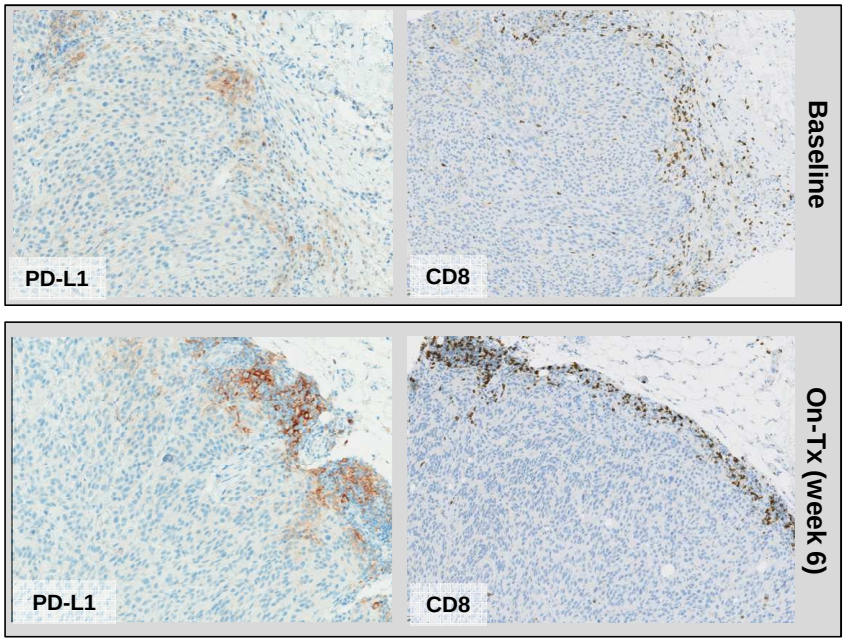


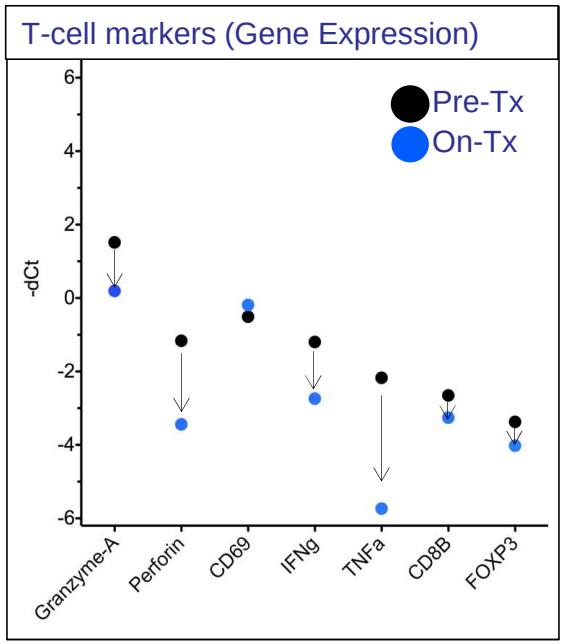




**Possible MoA of response to MPDL3280A:**

- Pre-existing intra-tumoral CD8+ T cells
- Increased trafficking or proliferation of intra-tumoral CD8+ cells
- Increased T-cell activation and cytotoxicity (e.g., Granzymes and Perforin production)

# PD-L1–Negative Patient Not Responding to MPDL3280A Exhibits Low Frequency of Intratumoral T cells



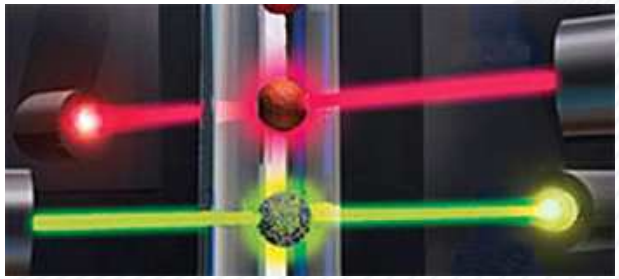

## Possible MoA of resistance:

- CD8+ T cells remain at the edge of the tumor (possible impaired trafficking)
- No increase in T-cell cytotoxicity
- No T-cell recognition of cancer antigens in this patient

# Multiplex Cytokine Analysis

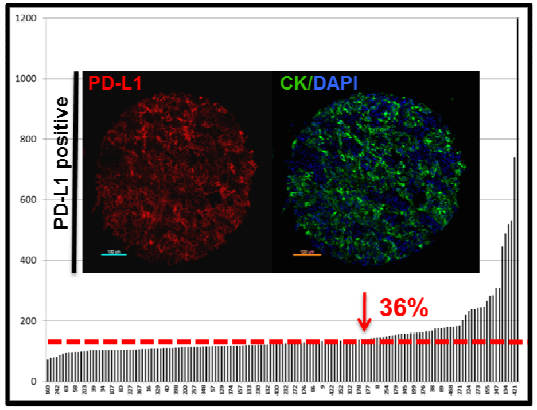
Cytokine analysis

- Multiplex cytokine analysis
- Detection of up to 100 analytes
  - Dual laser
  - Flow based
  - Sorting and detection

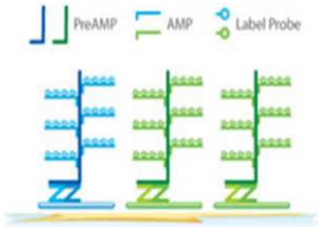


# Tissue Profiling – in situ protein and mRNA

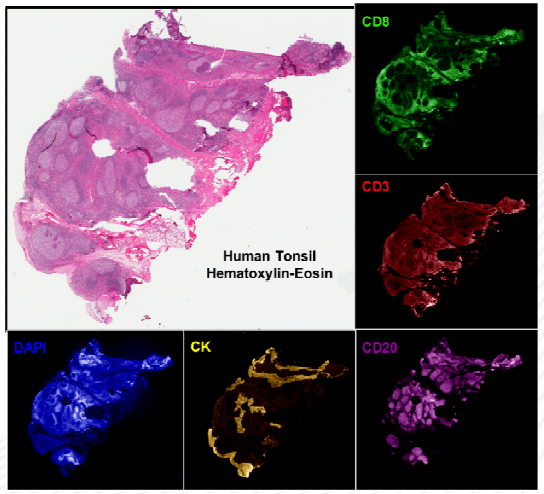
Tissue analysis




Quantitative Measurement of PD-L1 protein or mRNA in situ




Quantitative Multiplexed Objective TIL assay

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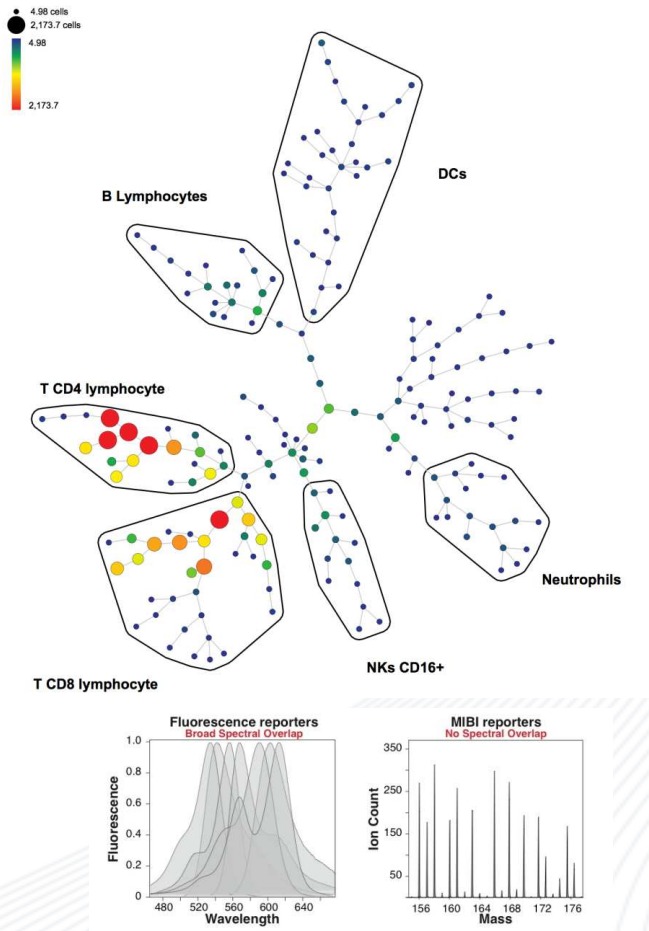
# CyTOF analysis

CyTOF analysis

- Single cell data
- Deep profiling
- 34 simultaneous parameters (100 theoretically)
- Detection of 10k cells
- Liquid or solid tumors

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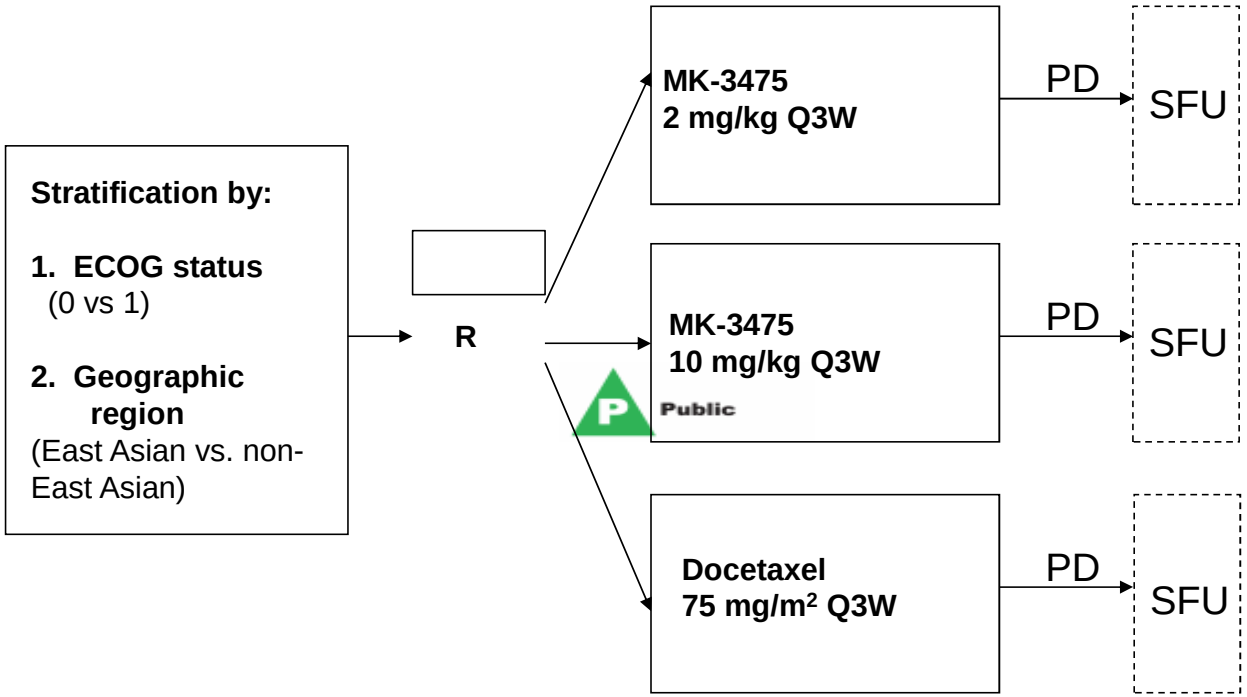
# Top Ten Lessons Learned about Immunotherapy for NSCLC

4. Questions remain regarding dose and duration of therapy

# MK-3475 PN010-06: Previously-Treated NSCLC




R = Randomization PD = Progressive Disease SFU = Survival Follow-up

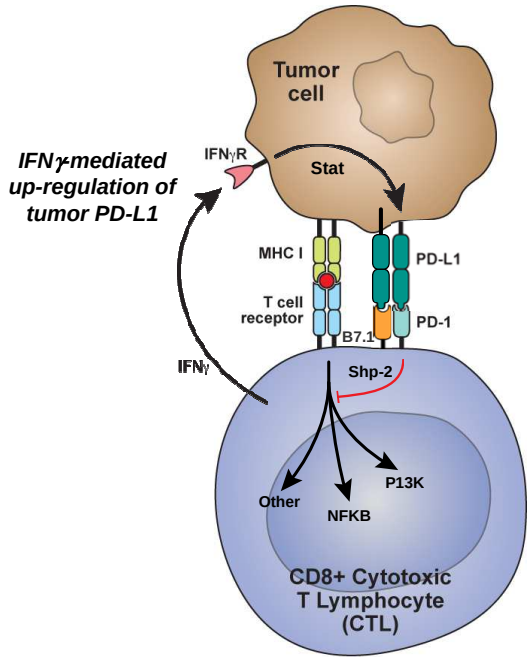
# Top Ten Lessons Learned about Immunotherapy for NSCLC

3. Combination therapy is a must: the search for other checkpoints should continue

# Combinations

- Chemotherapy
- Targeted Therapy
- Immune Therapy
- Other checkpoints- B7-H4

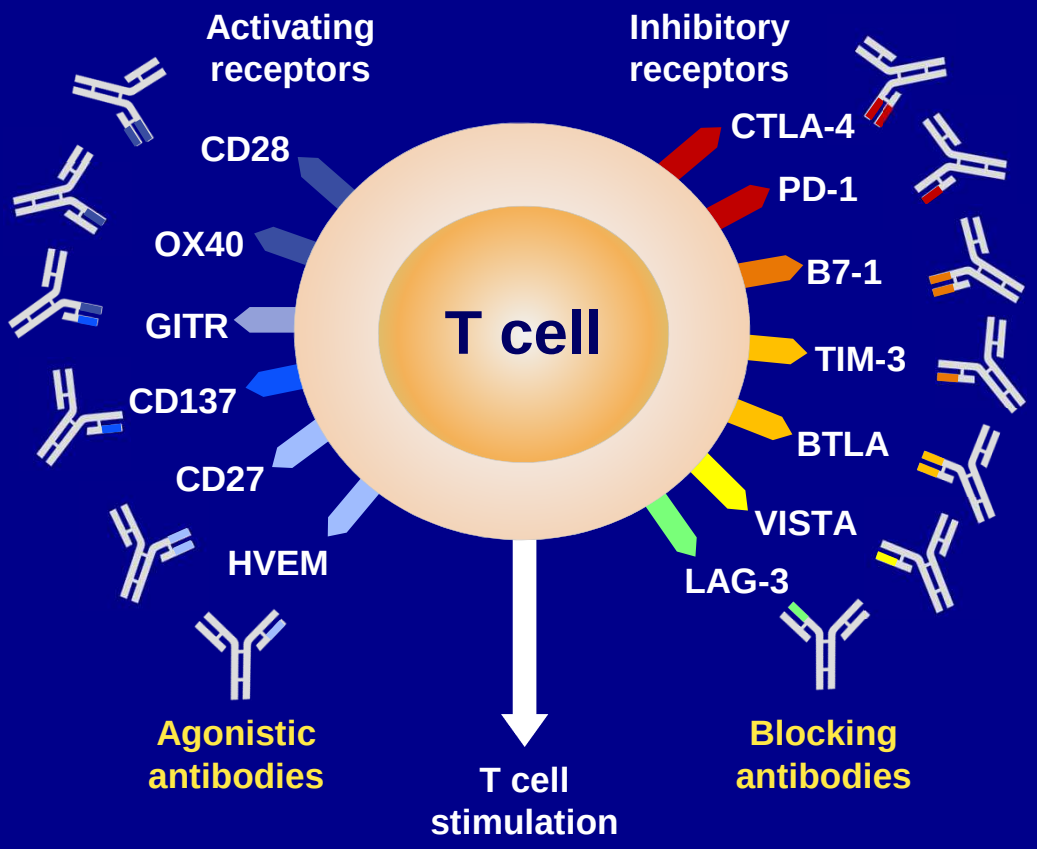
- Cancer cells can evade immune attack by expressing PD-L1




This will require some serious scientific analysis- The clinic must become the lab

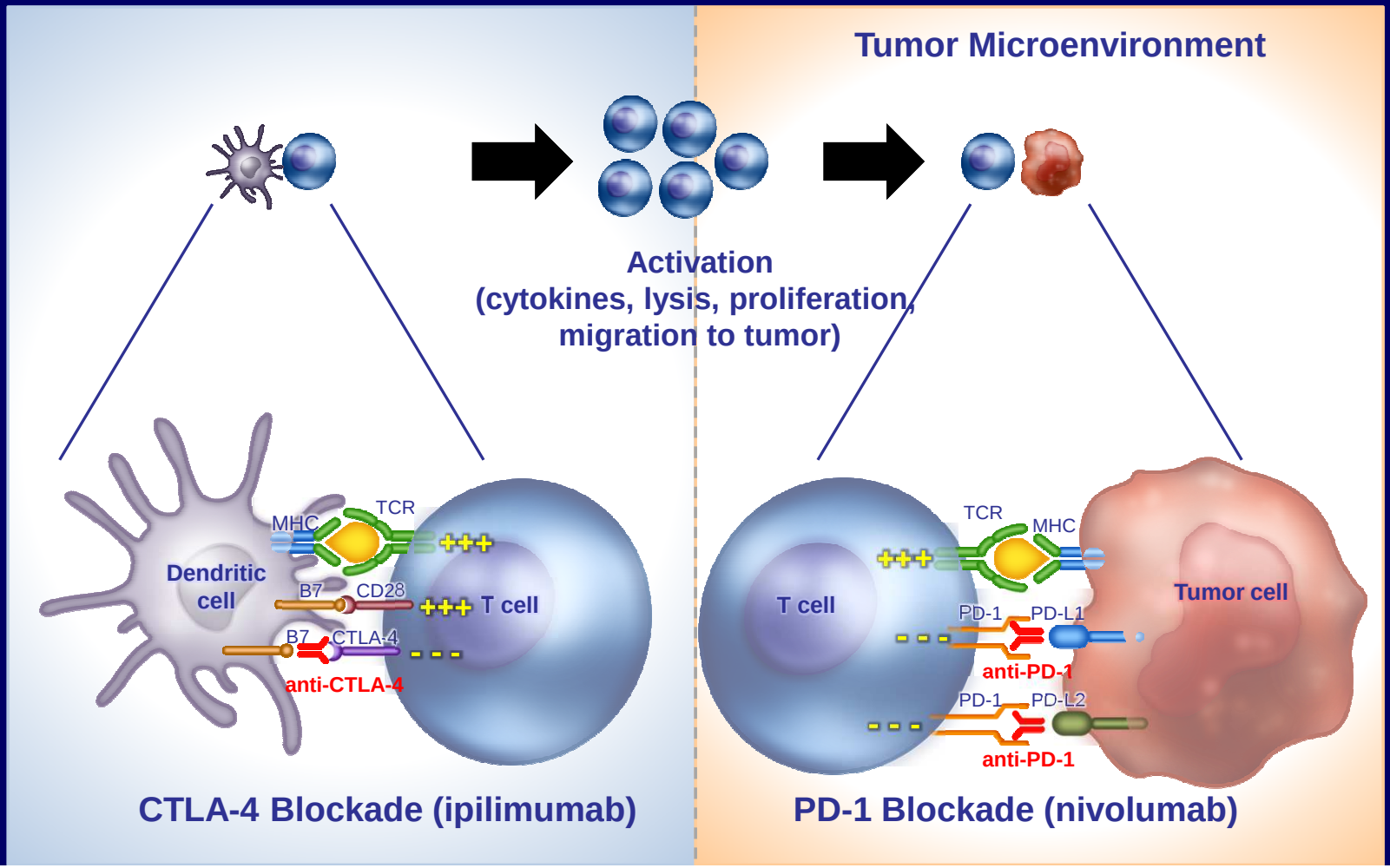
Chen DS, Irving BA, Hodi FS.
*Clin Cancer Res.* 2012;18:6580.

# T-Cell Immune Checkpoints as Targets for Immunotherapy

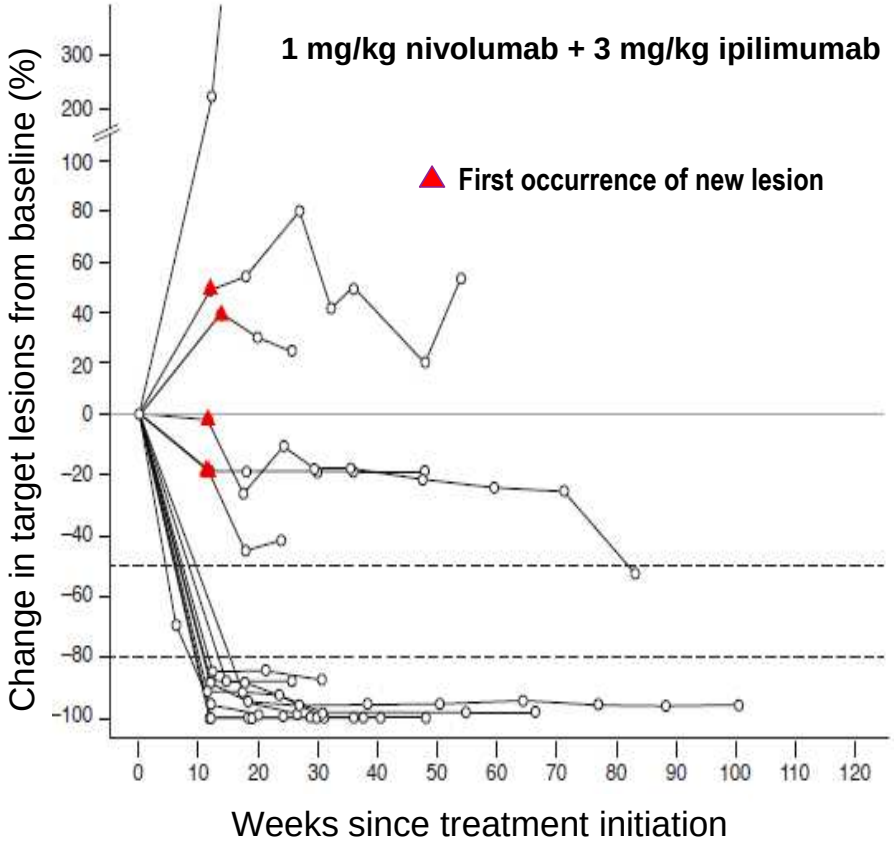


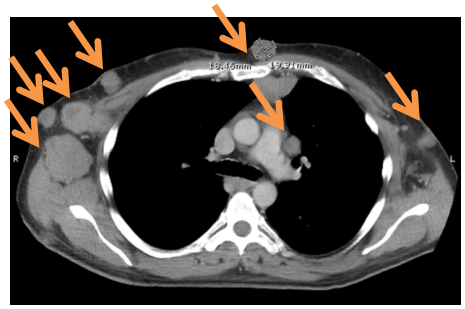

Mellman I et al. *Nature*. 2011;480:481–489.

# Blocking CTLA-4 and PD-1

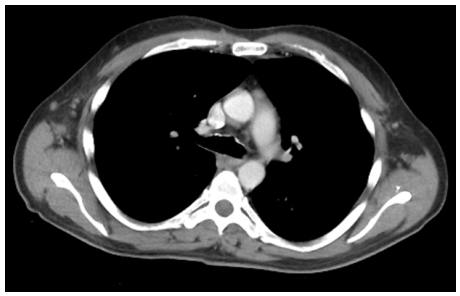


# Rapid and Durable Changes in Target Lesions (melanoma)



Pre-treatment



12 weeks

- A 52-year-old patient presented with extensive nodal and visceral disease
- Baseline LDH was elevated (2.3 x ULN); symptoms included nausea and vomiting
- Within 4 wk, LDH normalized and symptoms resolved
- At 12 wk, there was marked reduction in all areas of disease as shown

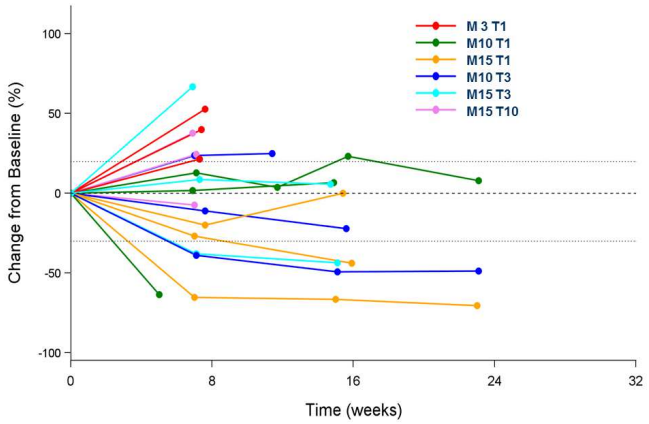
# Clinical activity: MEDI4736 + tremelimumab

- **Overall response rate (ORR) and percentage for patient with best response of stable disease by PD-L1 status**

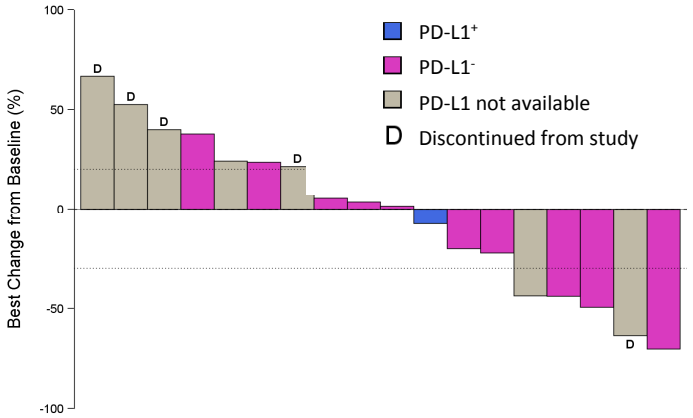
| | MEDI4736 + tremelimumab combination | | |
|---|---|---|---|
| | All patients[a] | PD-L1$^-$ | PD-L1$^+$ |
| **RECIST response (ORR), % (n/N)** | 28 (5/18) | 30 (3/10) | 0 (0/1) |
| **Stable disease, % (n/N)** | 28 (5/18) | 40 (4/10) | 100 (1/1) |

[a]Response evaluable (N) = patients with measurable disease at baseline + ≥1 on-treatment scan (includes discontinuations due to disease progression or death prior to first follow-up scan); RECIST response includes confirmed/unconfirmed CR or PR; Not all patients were assessed for PD-L1 status (defined by VENTANA assay)

- **Tumour shrinkage (n=18)**



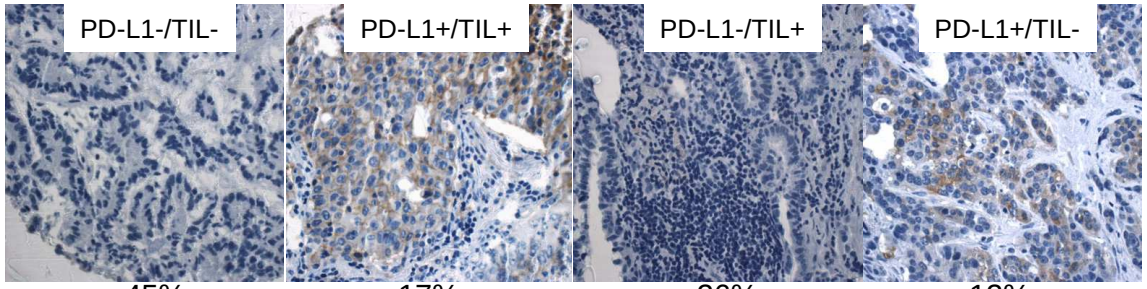

- **Best change in tumour size based on PD-L1 status (n=18)**




Patients with baseline and ≥1 on-treatment scan
Data cut-off: August 25, 2014

Antonia S, et al. Poster presented at ESMO 2014 [1327P]

# Four Categories of Tumors Based on Presence of PD-L1 and TILS

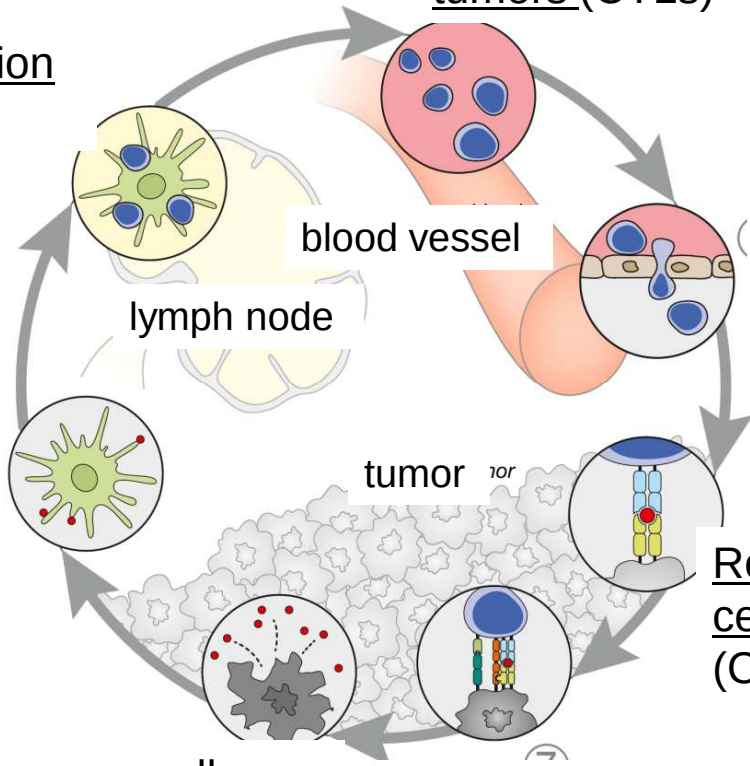



45% Type I | 17% Type II | 26% Type III | 12% Type IV

**Table 3. Proposed mechanisms associated with NSCLC resistance to anti-PD-1/B7-H1 therapy**

| Subgroup | | Type | Tumor Distribution | Possible Resistance Mechanism(s) | Analysis |
|---|---|---|---|---|---|
| **B7-H1** | TIL | | | | |
| - | - | I | 45% | Poor priming of general T cell responses | Peripheral CD4+ and CD8+ T cell responses to autologous tumor cells |
| | | | | Lack of inflammatory cell recruitment | Chemokine expression in biopsy or FFPE samples |
| + | + | II | 17% | Incomplete PD-1/B7-H1 pathway blockade and activation of alternate immune suppressive pathways | CD80 expression on TILs, expression of alternate suppressive pathways in TME |
| - | + | III | 26% | Alternate immune suppressive pathways | Expression of select molecules in pathways with roles in evasion of NSCLC immunity |
| + | - | IV | 12% | Intrinsic induction of B7-H1 by oncogenes | Expression of molecules triggering aberrant signaling events |

# The cancer-immunity cycle




Tracking of T cells to tumors (CTLs)

Priming & activation (APCs & T cells)

Infiltration of T cells Into tumors (CTLs, endothelial cells)

Cancer antigen presentation (DC & APCs)

Recognition of cancer cells by T cells (CTLs, cancer cells)

1. Release of cancer cell antigens (cancer cell death)

Killing of cancer cells (immune & cancer cell)

**[Chen & Mellman Immunity 39, July 25, 2013]**

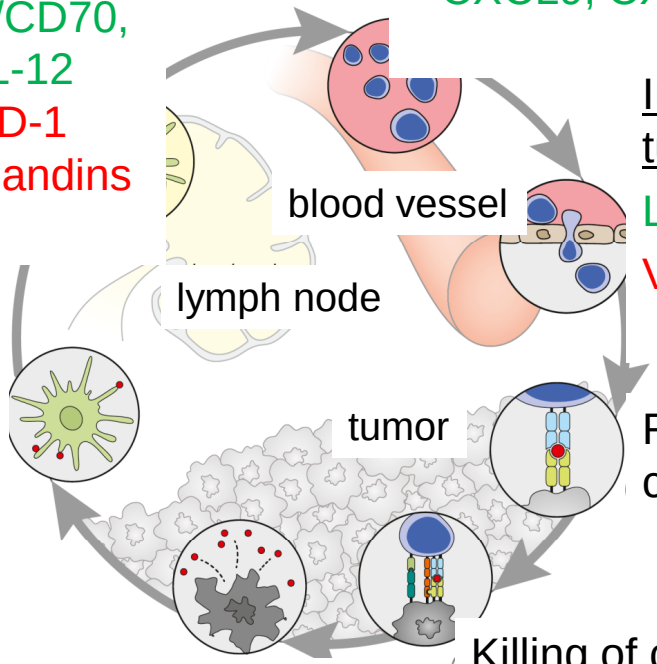
# Stimulatory & Inhibitory Factors

**Priming & activation**

CD28/B7.1, CD137/CD137L
OX40/OX40L, CD27/CD70,
HVEM, GITR, IL-2, IL-12
CTA4/B7.1, PD-L1/PD-1
PD-L1/B7.1, prostaglandins

**Tracking of T cells to tumors**

Chemokines; CX3CL1,
CXCL9, CXCL10, CCL5




**Infiltration of T cells into tumors**

LFA1/ICAM1 Selections
VEGF, Endothelin B-R
Hyaluronin

**Recognition of cancer cells by T cells**

TCR
Reduced HLA

**Killing of cancer cells**

INF-γ T cell granule content
PD-L1/PD-1, PD-L1/B7.1
IDO, TGF-β, BTLA, VISTA
LAG-3, Arginase, MICA/MICB
B7-H4, TIM-3/phospholipids

**Release of cancer cell antigens**

Immunogenic cell death
Tolerogenic cell death

**Cancer antigen presentation**

TNF-α, IL-1, INF-α
CD40L/CD40
CDN, ATP
HMGB1, TLR
IL-10, IL-4, IL-13

# Top Ten Lessons Learned about Immunotherapy for NSCLC

2. Immunotherapy will be Used in all Lines of Therapy

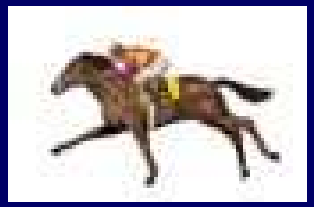
# Ongoing Phase II/III Trials for Advanced NSCLC

- Salvage Docetaxel vs. PD1/PDL1 monotherapy
  - Nivolumab, Squamous/ Non-squamous trials accrual
- Maintenance
- Adjuvant
- Neoadjuvant
- Combinations

- ? Accelerated approval if high RR in Phase II Setting

# Top Ten Lessons Learned about Immunotherapy for NSCLC

1. It's a Horse Race !!



I predict the first checkpoint drug approved for NSCLC will be:

I don't know

:

- The winning group will be the one with the best drug, best biomarker, best strategy and a little bit of luck!!!

- The winners are the patients! Thank You!!!