# The immunotherapy of cancer: past, present & the next frontier

Ira Mellman

Genentech

South San Francisco, California

CancerImmunology

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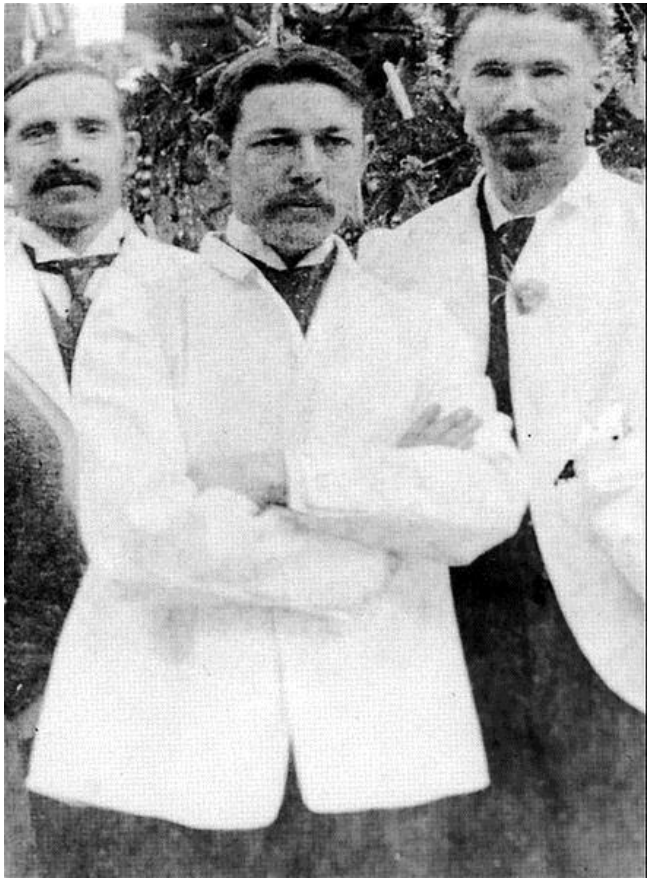
# William Coley and the birth of cancer immunotherapy



New York Times - July 29, 1906

## ERYSIPELAS GERMS AS CURE FOR CANCER

**Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.**

**MANY CASES CURED HERE**

**Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.**

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York. It came out yester-

*Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later*

# Past activities focused on vaccines & cytokines

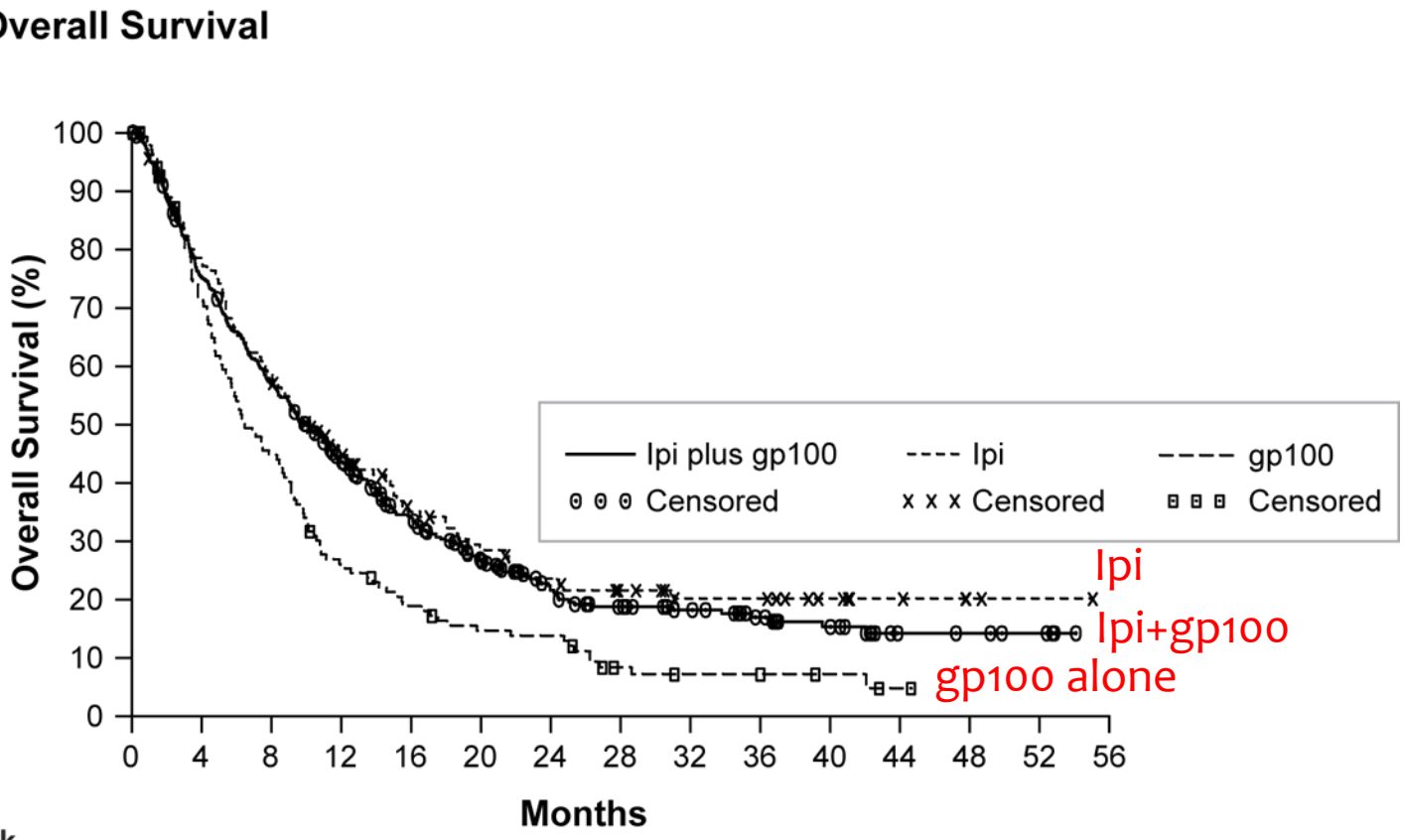
- Discovery that T cells in cancer patients detected tumor-associated epitopes (Thierry Boon, Brussels)

- Attempts to boost T cell responses with (peptide) vaccines
  - Thousands treated, few clinical responses
  - Poor mechanistic understanding of immunization

- Attempts to boost T cell responses with cytokines (IL-2, interferon)
  - Promising but limited clinical activity in various settings
  - On target toxicity an additional limit to broad use
  - Limited mechanistic understanding

- **Cancer immunology & immunotherapy fails to find a home in either immunology or cancer biology**

# Dawn of the present: Ipilumumab (anti-CTLA4) elicits low frequency but durable responses in metastatic melanoma

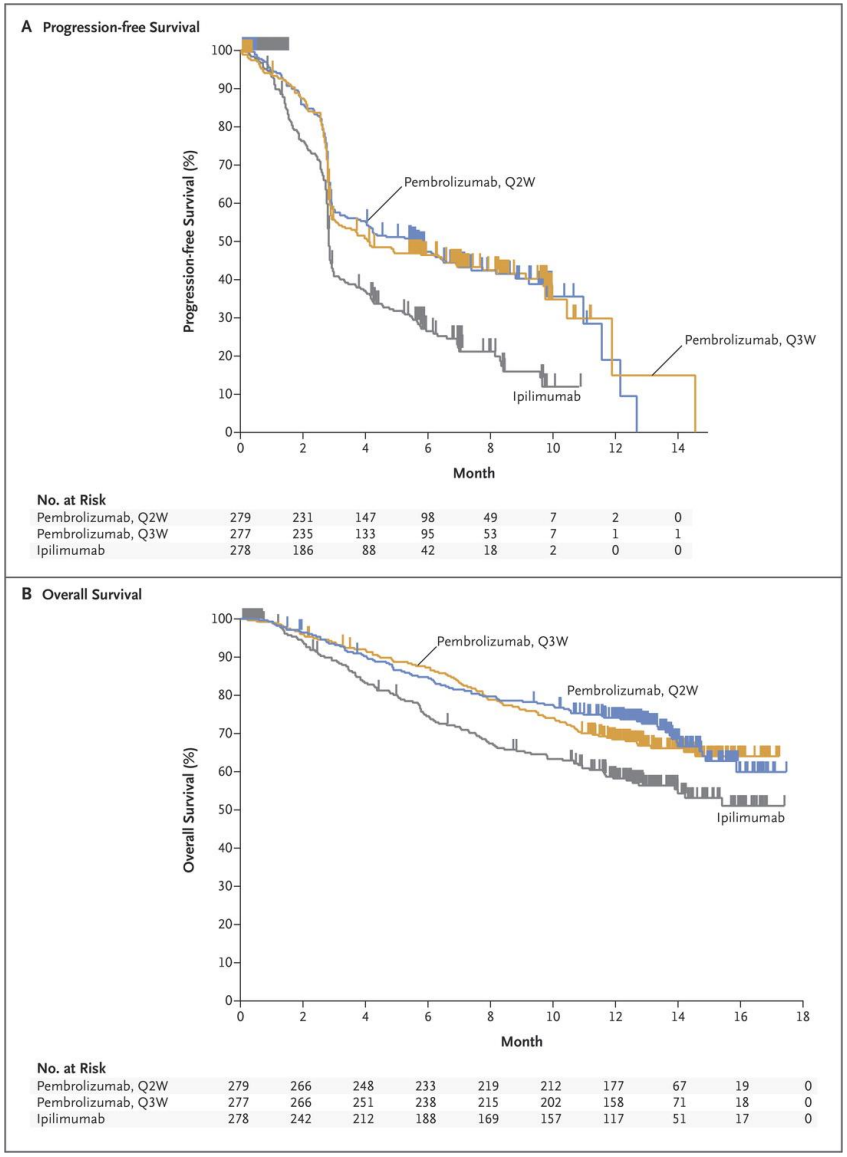



No. at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ipi plus gp100 | 403 | 297 | 223 | 163 | 115 | 81 | 54 | 42 | 33 | 24 | 17 | 7 | 6 | 4 | 0 |
| Ipi | 137 | 106 | 79 | 56 | 38 | 30 | 24 | 18 | 13 | 13 | 8 | 5 | 2 | 1 | 0 |
| gp100 | 136 | 93 | 58 | 32 | 23 | 17 | 16 | 7 | 5 | 5 | 3 | 1 | 0 | 0 | 0 |

Hodi et al (2010) NEJM

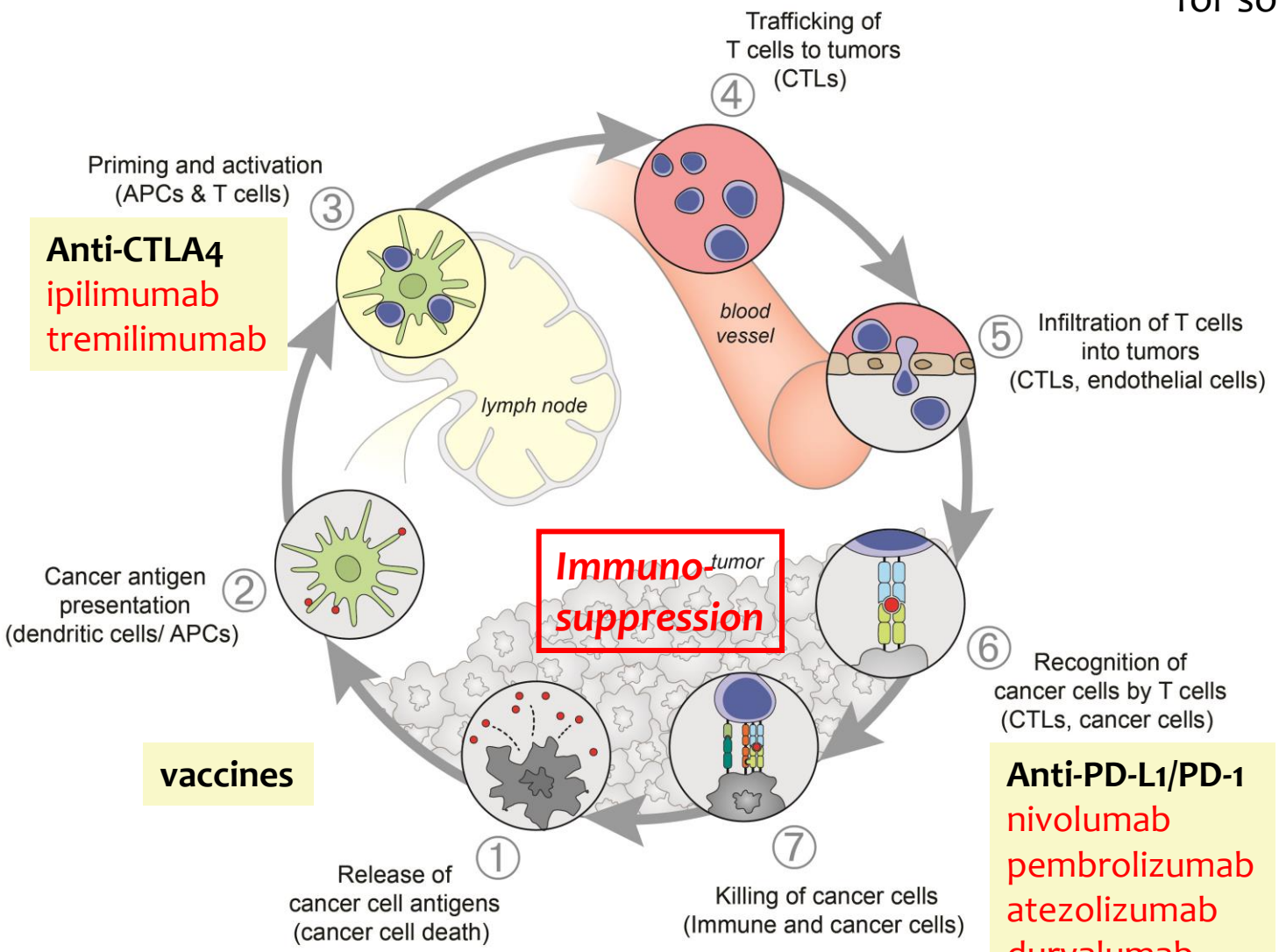
# The sun continues to rise: anti-PD-1 is superior to and better tolerated than anti-CTLA4 (melanoma)




Robert C et al. N Engl J Med 2015;372:2521-2532.

# What we have learned: immunosuppression is a rate limiting step to effective anti-tumor immunity*

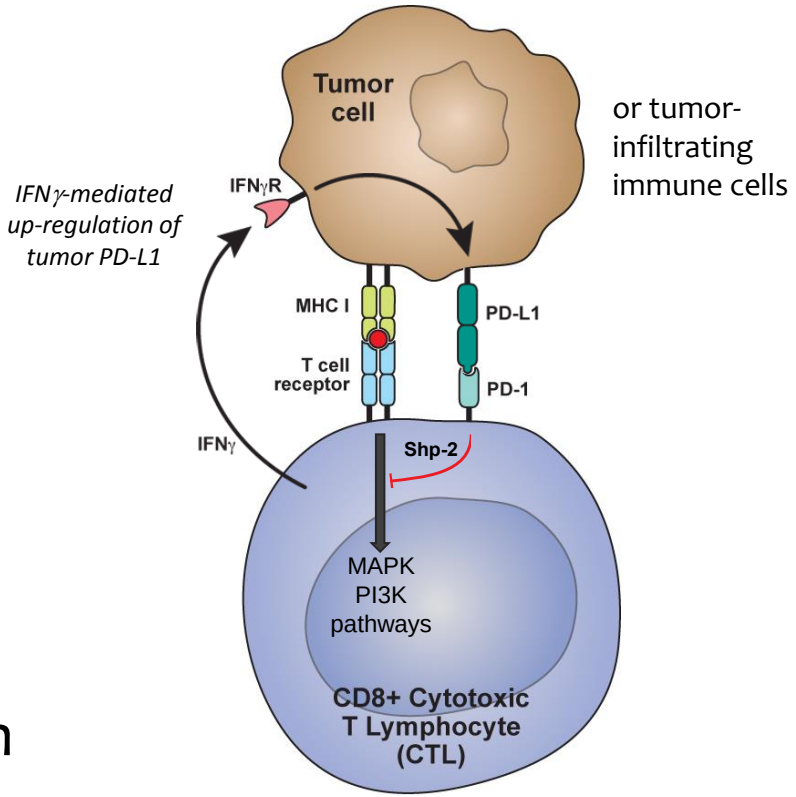
*for some patients




Chen & Mellman (2013) Immunity

# Blocking the PD-L1/PD-1 axis restores, or prevents loss of, T cell activity

- PD-L1/PD-1 interaction inhibits T cell activation, attenuates effector function, maintains immune homeostasis
- Tumors & surrounding cells up-regulate PD-L1 in response to T cell activity
- Blocking PD-L1/PD-1 restores or prevents loss of T effector function

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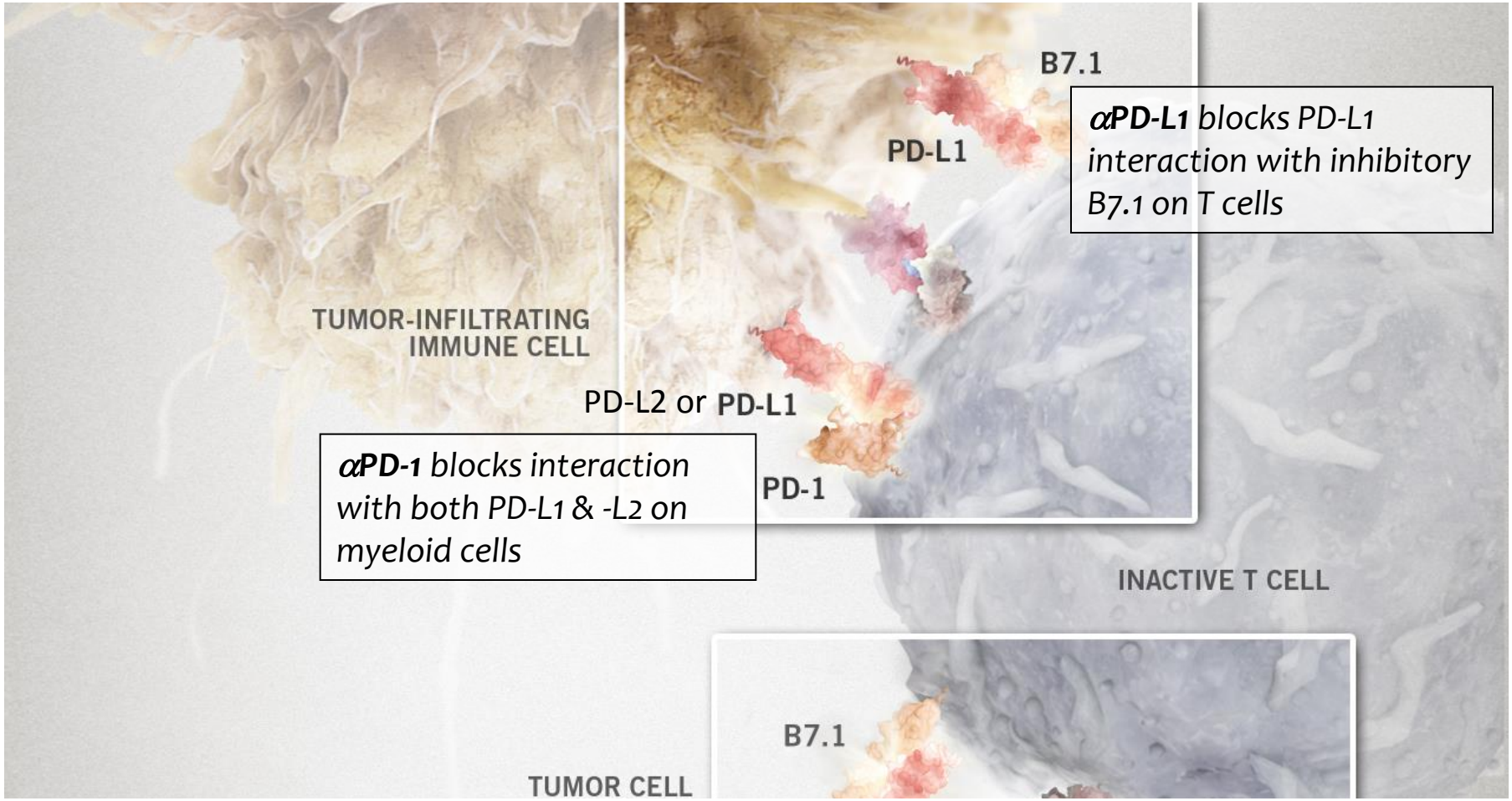
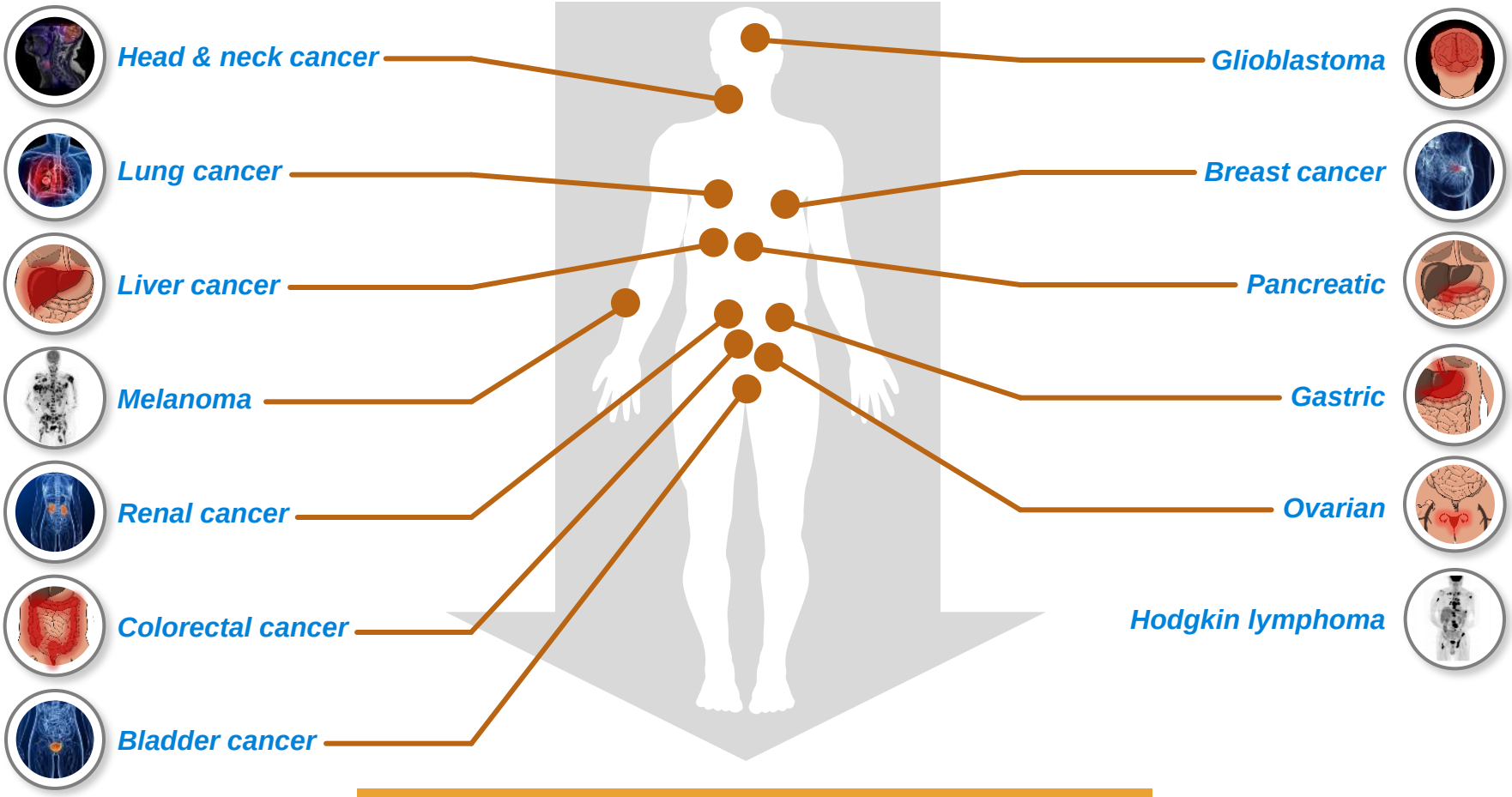
# αPD-L1 and αPD-1 exhibit similar early activities despite blocking different secondary interactions



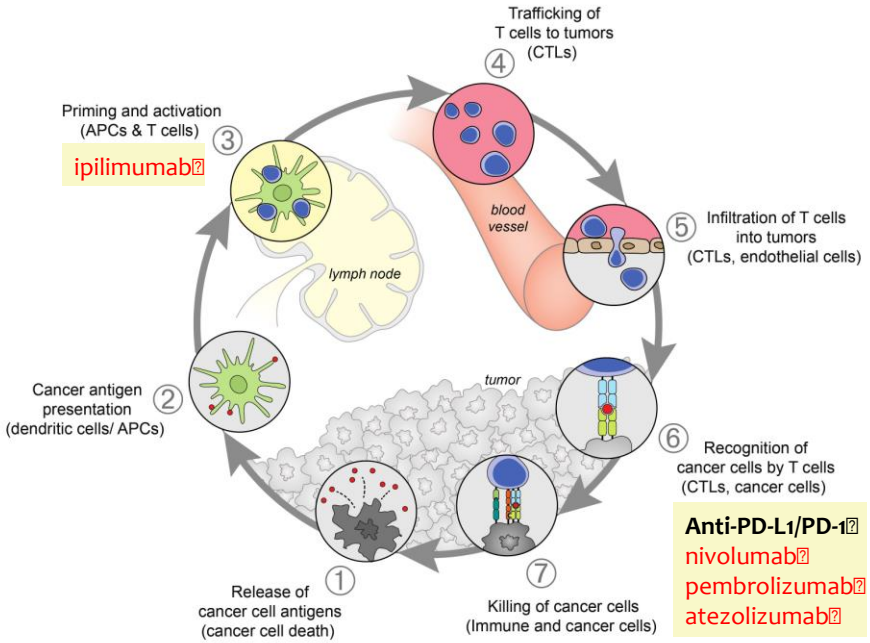
# Broad activity for anti-PD-L1/PD-1 in human cancer




**Broad activity, but only subset of patients benefit: ~10-30%**

# Cancer Immunotherapy: present focus I

## Diagnostic biomarkers to enrich responders to PD-L1/PD-1




- Identify patients most likely to respond to αPD-L1/PD-1
- Identify combinations that extend the depth and breadth of response to PD-L1/PD-1
- Investigate new targets to overcome immunosuppression, enhance T cell expansion

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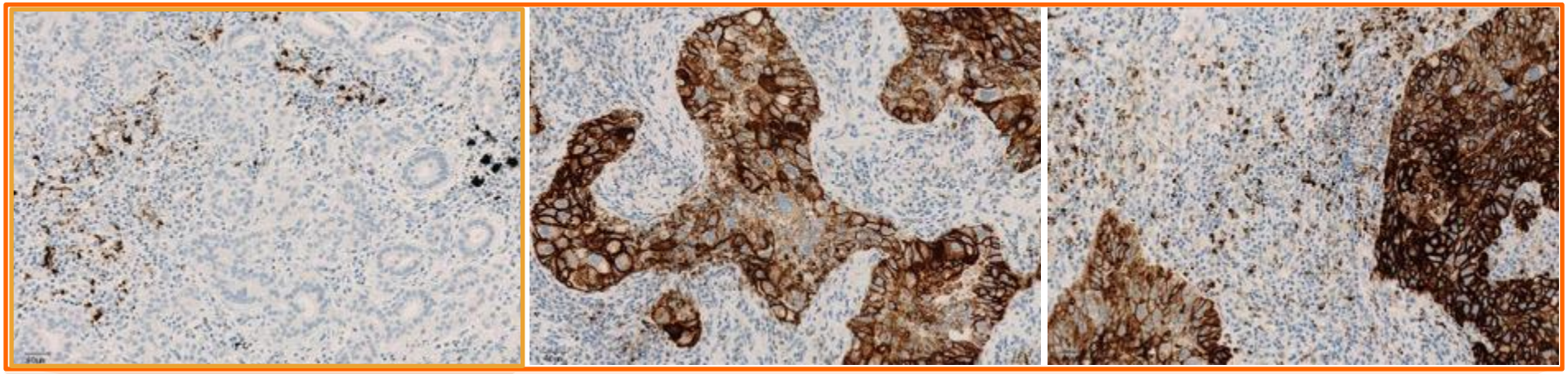
# PD-L1 expression predicts clinical response: *an imperfect but useful Dx biomarker*

***Immune cells (ICs)***

***Tumor cells (TCs)***

***Tumor and immune cells (TCs and ICs)***



**Predictive of benefit in bladder cancer (ORR/OS)[1]**

**Predictive of benefit in lung cancer (ORR/PFS/OS)[2]**

WCLC 2015

[1]IMvigor 210 (ECC 2015), [2]POPLAR (ECC 2015)

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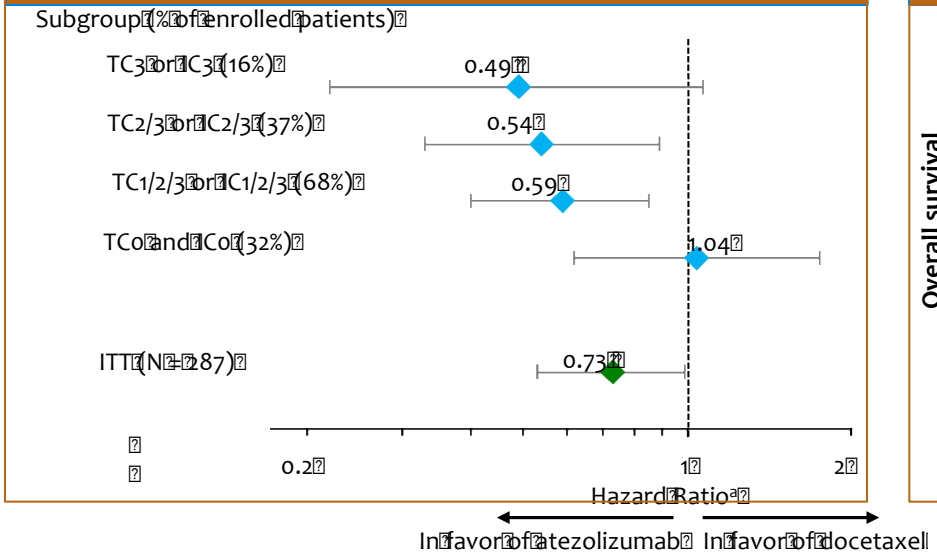
# PD-L1 expression by tumors can enrich for responses to atezolizumab (anti-PD-L1) in NSCLC and bladder cancer

## *Lung cancer (TC + IC)*

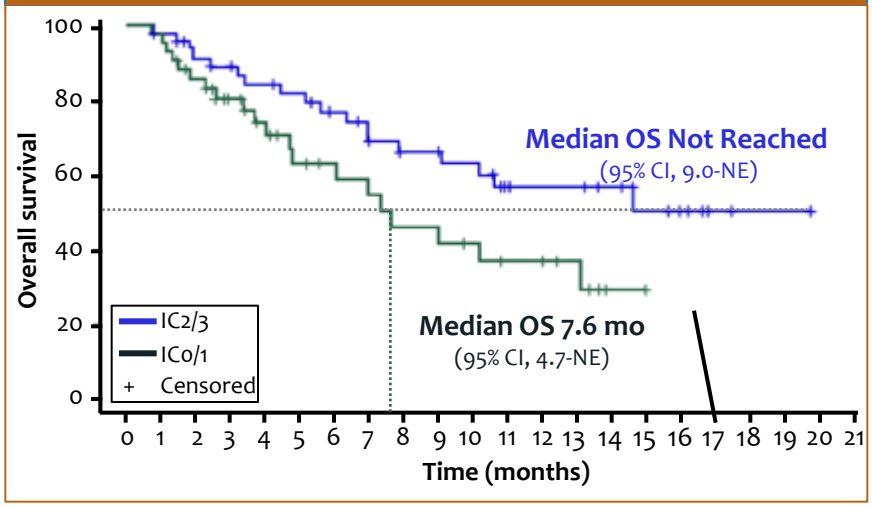
### Survival hazard ratio*




Vansteenkiste et al (2015) ECC

## *Bladder cancer (IC only)*

### Overall survival*




Rosenberg et al (2015) ECC

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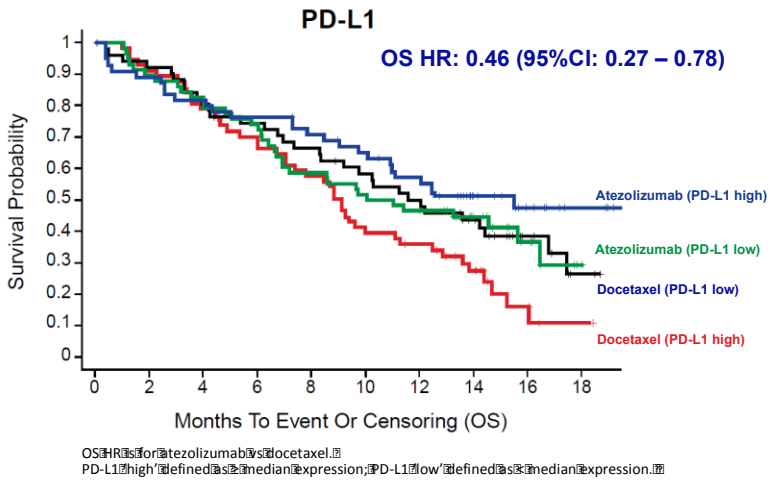
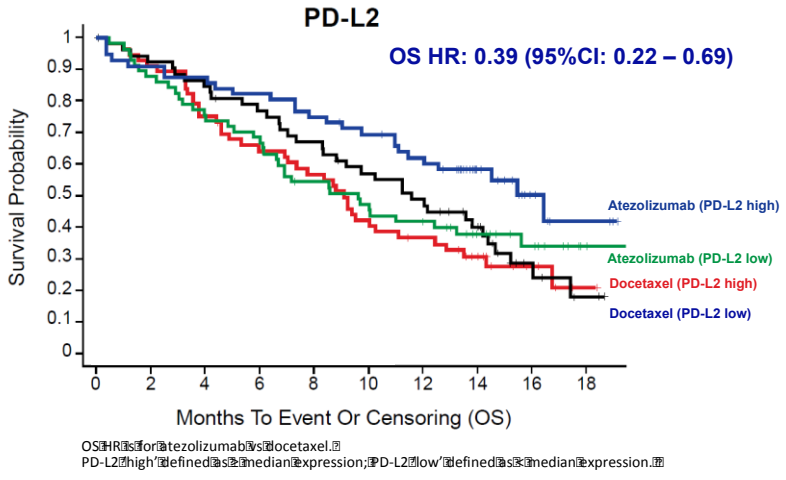
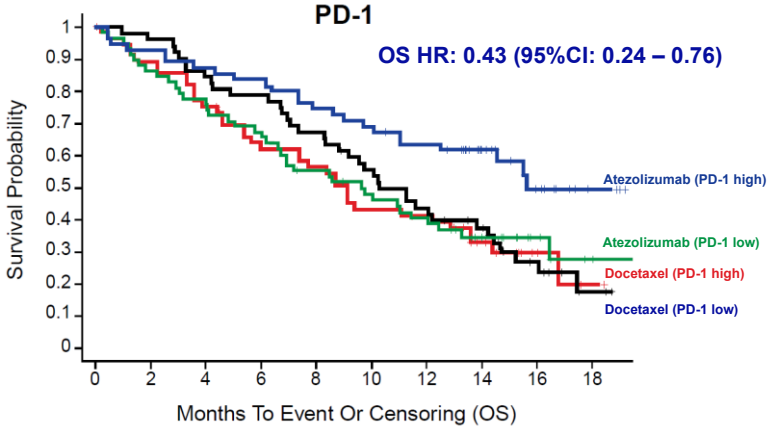
# PD-L2 also correlates with clinical benefit to atezoluzumab (n=238 patients)



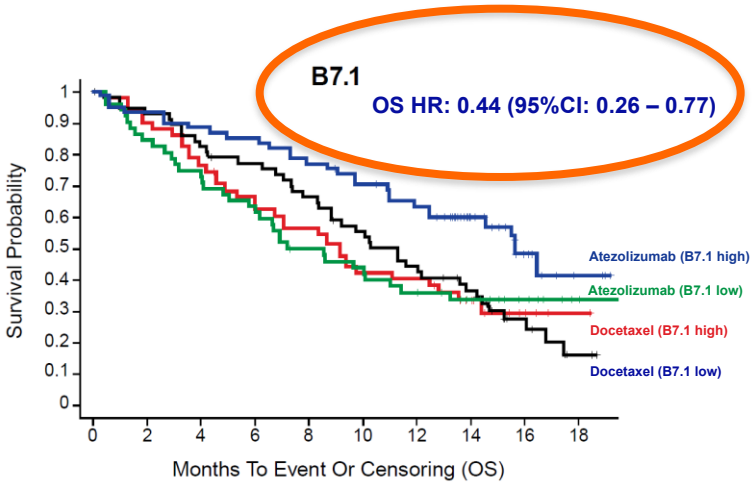

OS HR is for atezolizumab vs docetaxel.
PD-L1 'high' defined as ≥ median expression; PD-L1 'low' defined as < median expression.




OS HR is for atezolizumab vs docetaxel.
PD-L2 'high' defined as ≥ median expression; PD-L2 'low' defined as < median expression.




OS HR is for atezolizumab vs docetaxel.
PD-1 'high' defined as ≥ median expression; PD-1 'low' defined as < median expression.

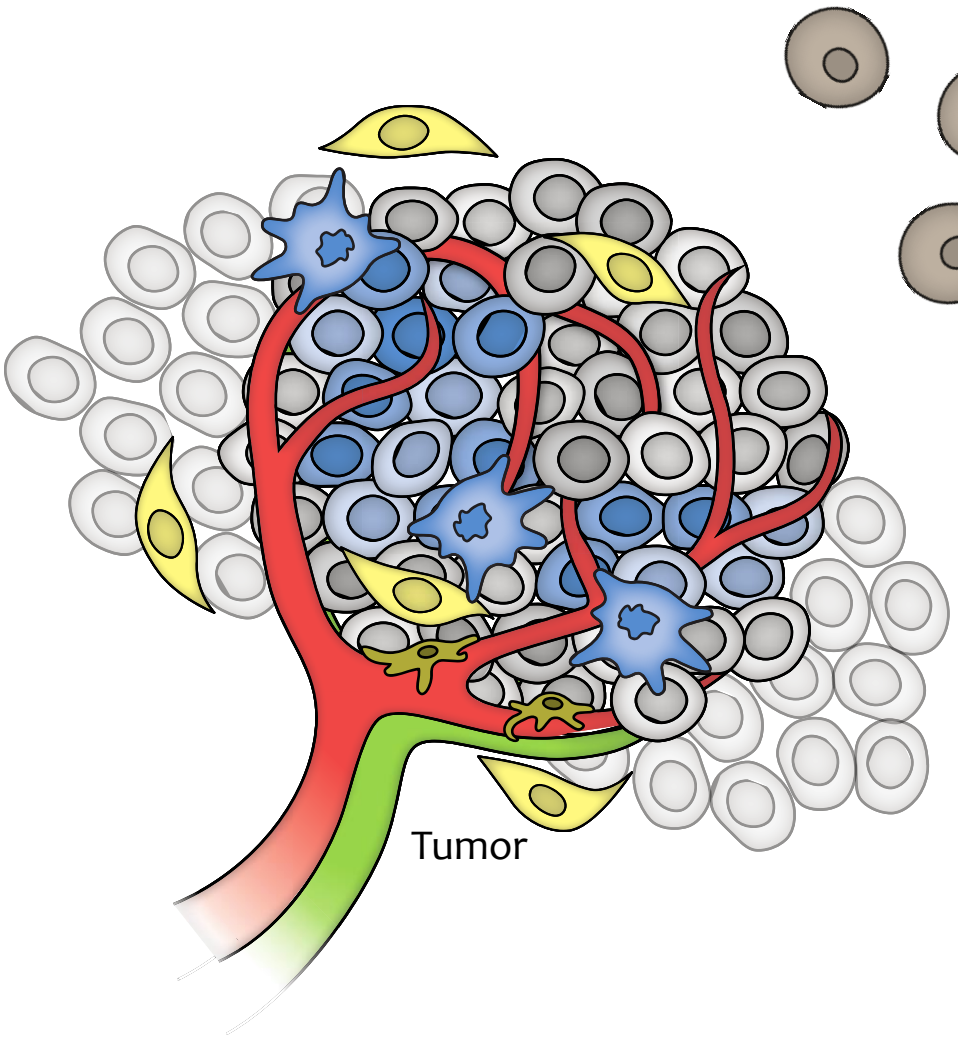



OS HR is for atezolizumab vs docetaxel.
B7.1 'high' defined as ≥ median expression; B7.1 'low' defined as < median expression.

Schmid et al (2015) ECC; data from Fluidigm panel

# The predictive power of PD-L1+ IC's suggests a special role for infiltrating immune cells in anti-tumor T cell function

* Taube et al (2012) Science Transl. Med.




IFNγ+ T cell effectors

- Why can PD-L1 expression by immune infiltrating cells more predictive than PD-L1+ tumor cells?
- Do PD-L1+ myeloid cells, not tumor cells, regulate T cell function at baseline?
- What is the actual mechanism of PD-1-mediated suppression?

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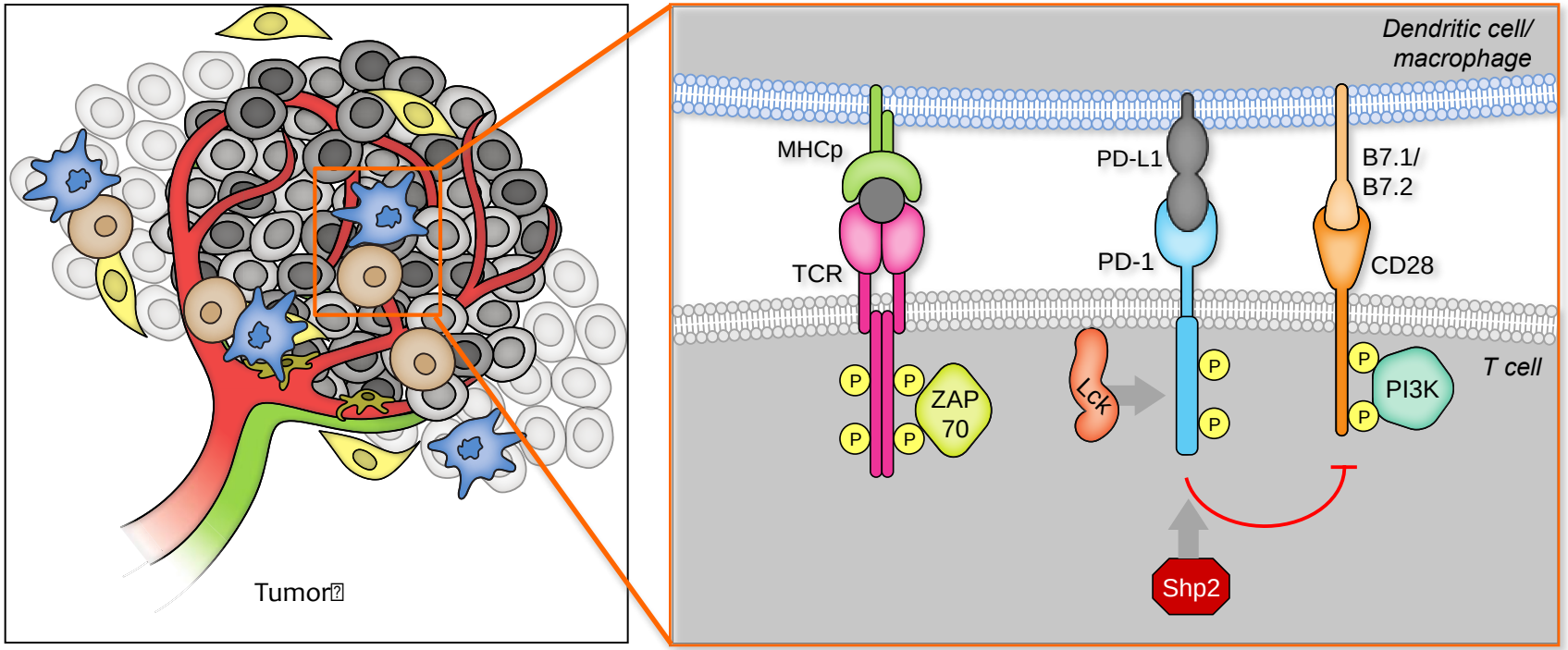
# PD-1 acts by down-regulating T cell costimulation via CD28, not TCR signaling

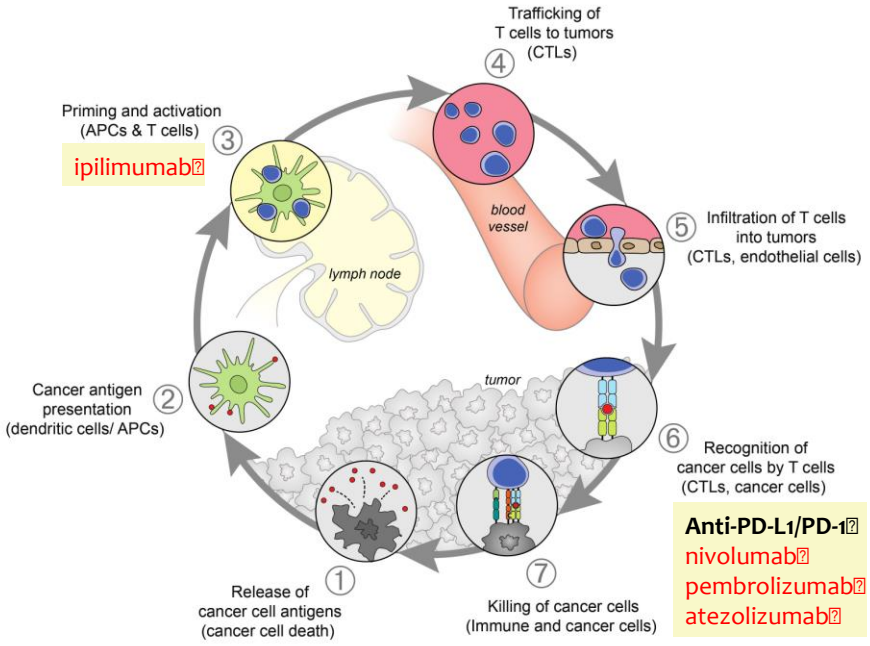



- Infiltrating immune cells may provide costimulation to help activate TILs, and then homestatically turn them off
- Importance of B7.1 and its interaction with PD-L1?

Hui et al and Kamphorst et al (2016) Submitted

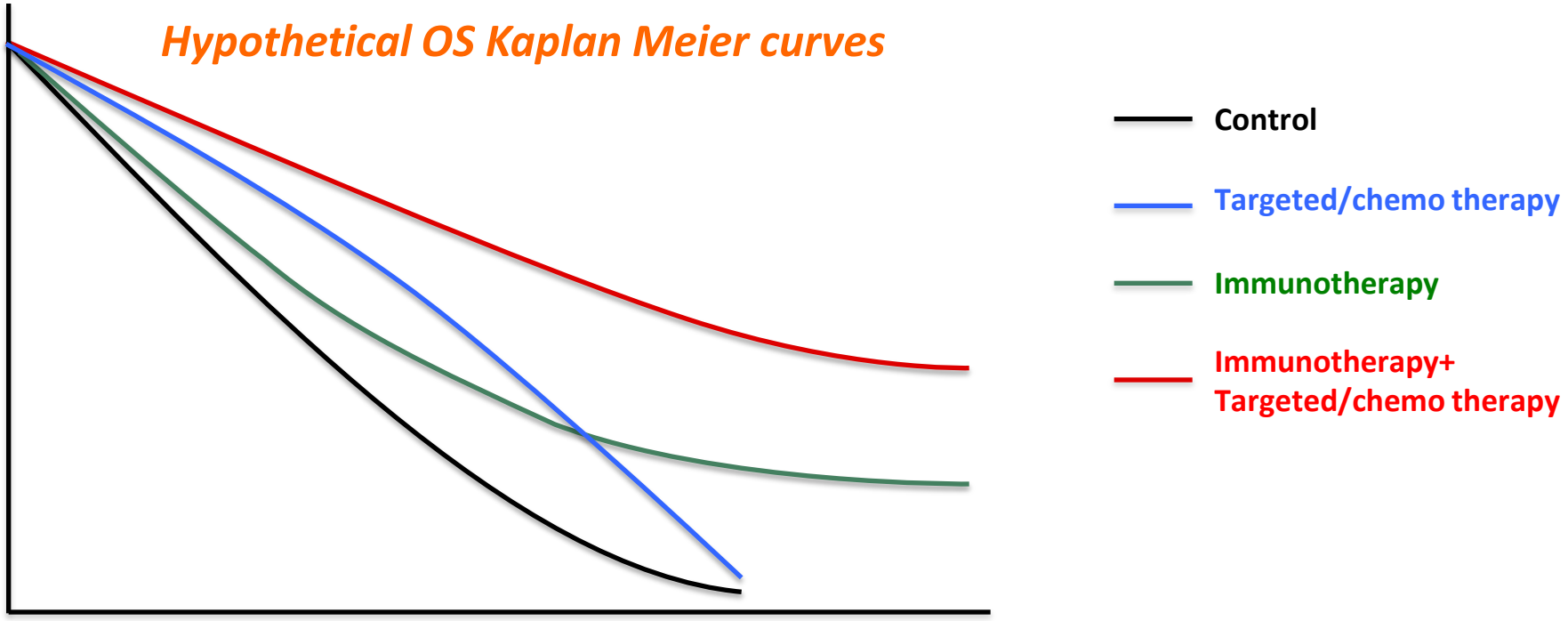
# Cancer Immunotherapy: present focus II

## Combinations



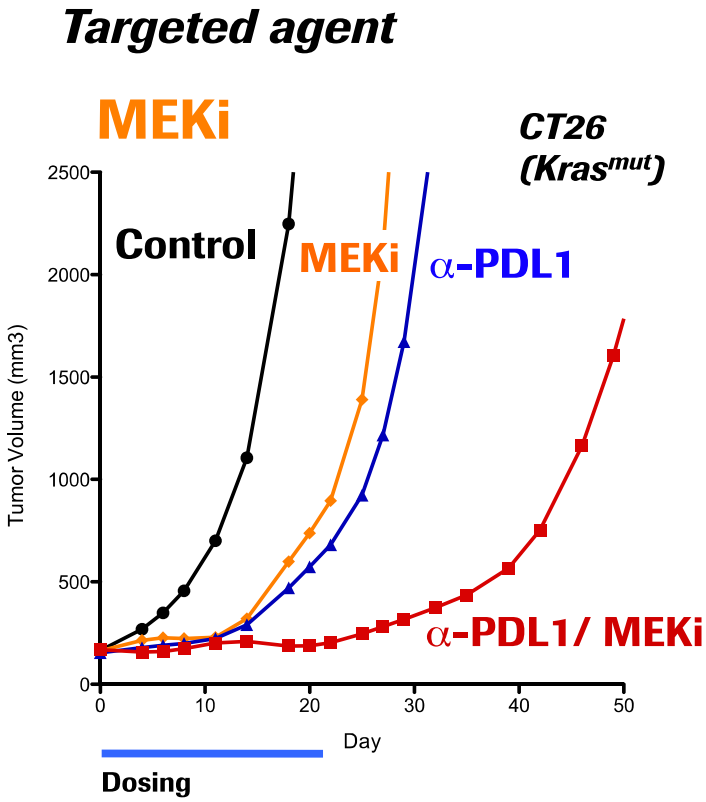

- Identify patients most likely to respond to αPD-L1/PD-1
- Identify combinations that extend the depth and breadth of response to PD-L1/PD-1
- Investigate new targets to overcome immunosuppression, enhance T cell expansion

# Combinations of immunotherapeutics or immunotherapeutics with SOC/targeted therapies



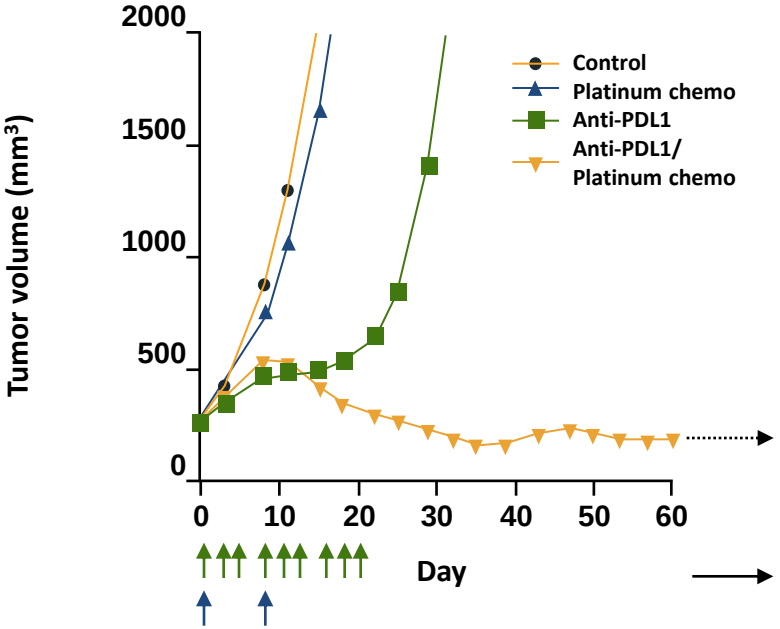

- Agents must be safe in combination with anti-PD-L1
- Targeted/chemo therapy should not interfere with immune response or immunotherapeutic mechanism of action

# Combinations may extend the benefit of anti-PDL1
## *Chemo and targeted therapies*

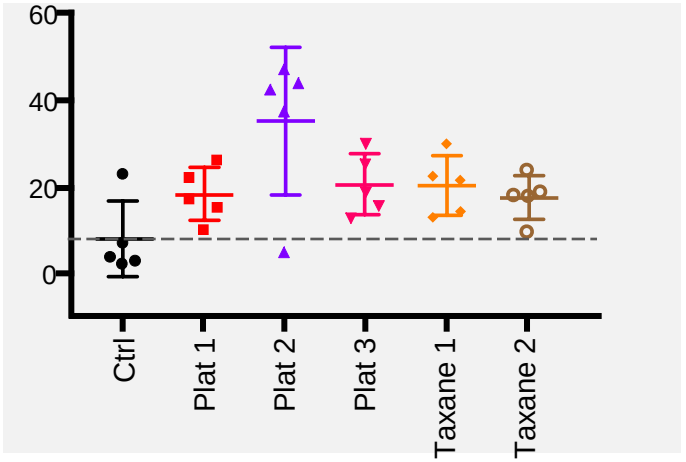



- MEK is not required for T cell killing
- MEK inhibition slows T cell apoptosis in tumors

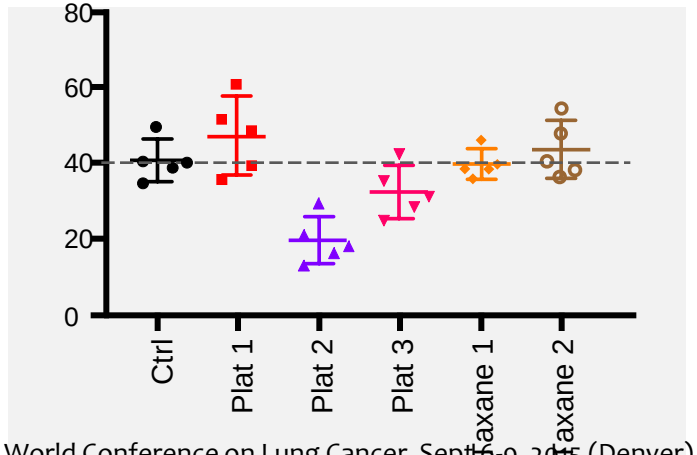
# Chemotherapy as immunotherapy: *effect of platins on preclinical efficacy and immunobiology*



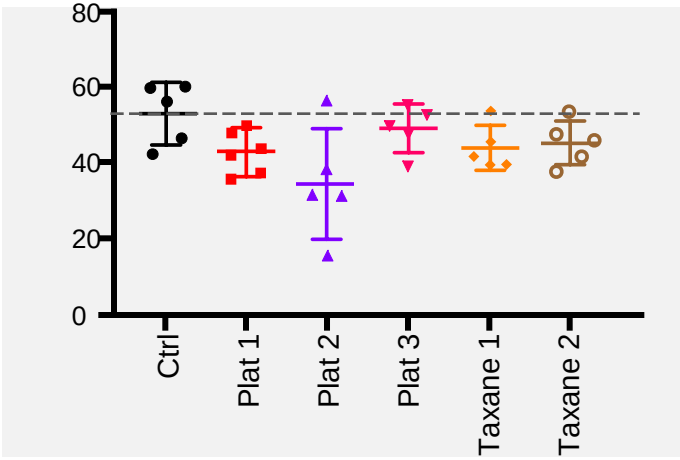

***Tumor CD8+ (cell type)***




***Tumor CD11b⁺Ly6C⁺ (cell type)***



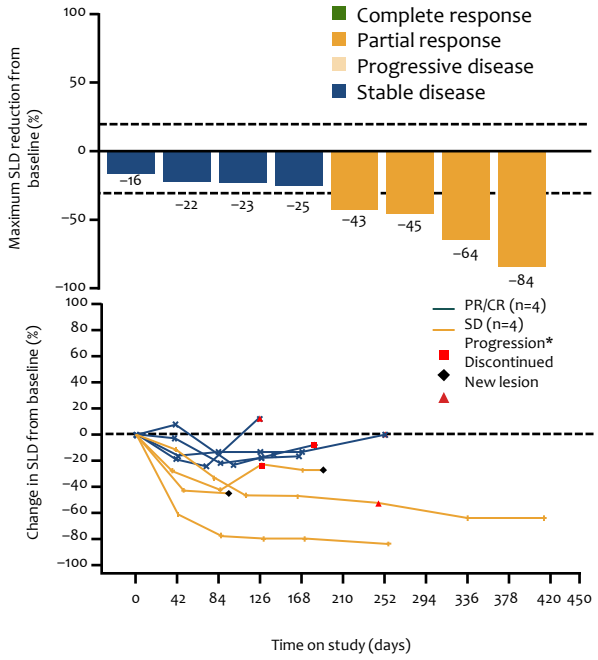

***Tumor CD4⁺FoxP3⁺ (cell type)***



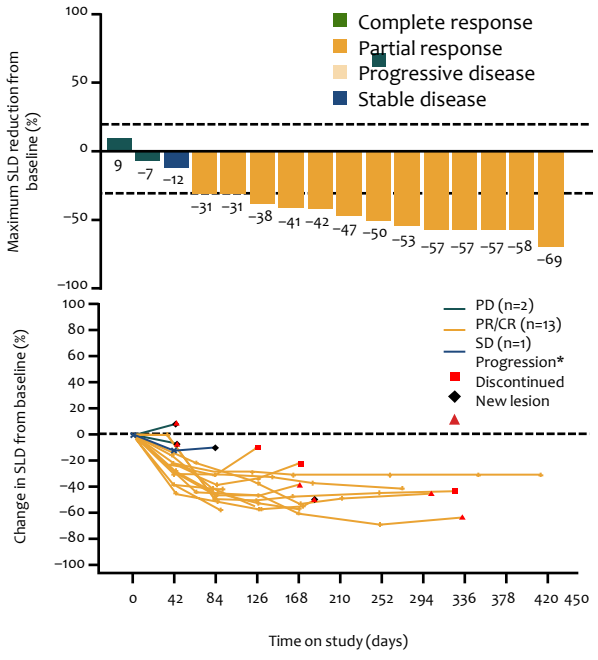

Camidge et al., 16th World Conference on Lung Cancer, Sept 6-9, 2015 (Denver)

# Early data suggests that anti-PD-L1 may combine with chemotherapy in NSCLC (& TNBC)

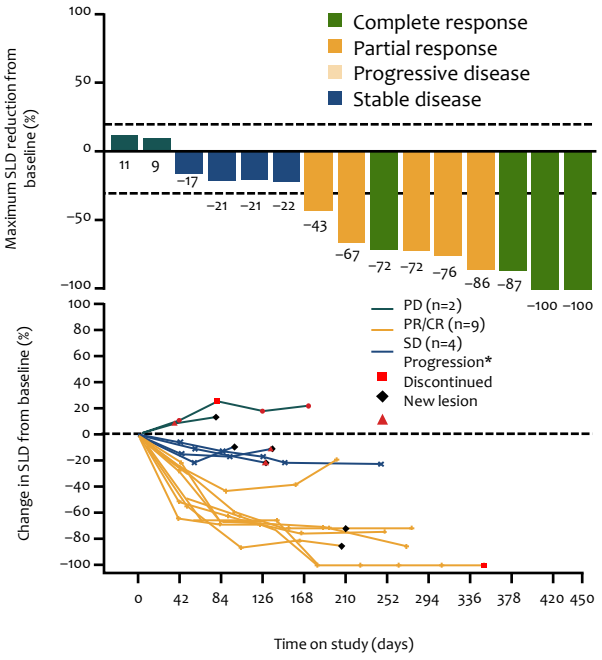
Arm C – cb/pac (n=8)




Arm D – cb/pem (n=17)



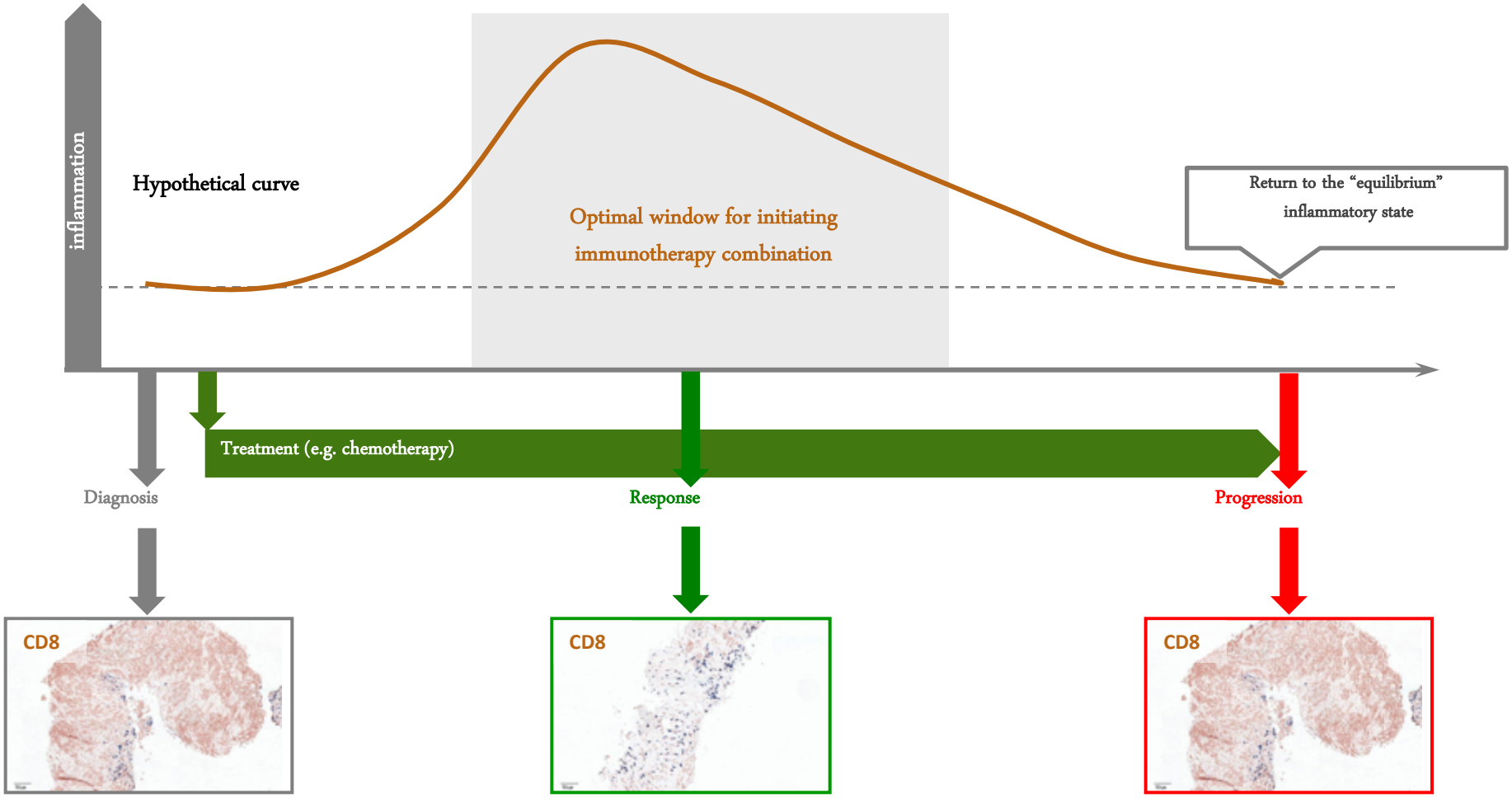

Arm E – cb/nab (n=16)




Includes all patients dosed by 10 Nov 2014; data cut-off: 10 Feb 2015; SLD, sum of longest diameters; ASCO 2015

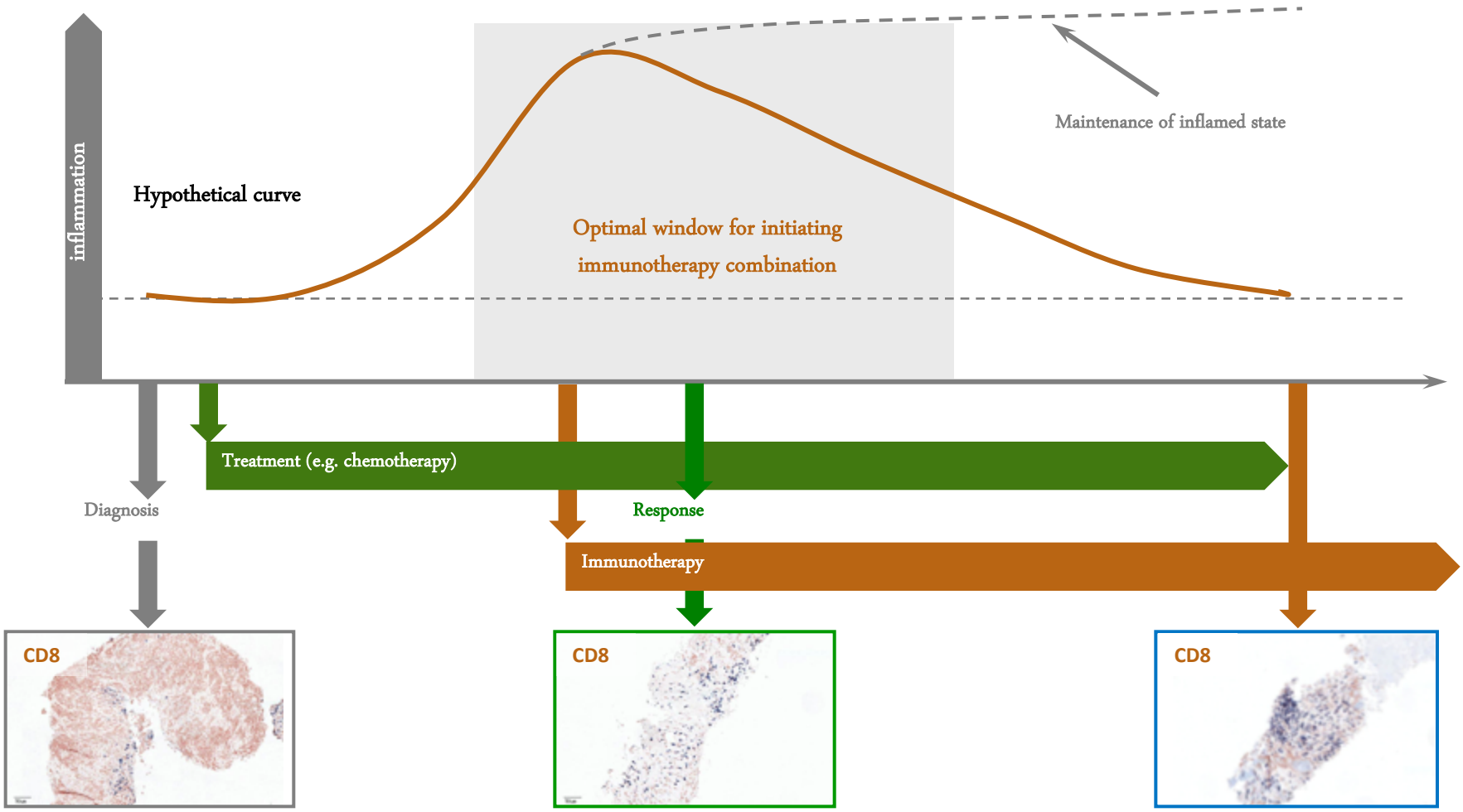
*PD for reasons other than new lesions

# Modulation of tumor immune status by chemotherapy may be transient



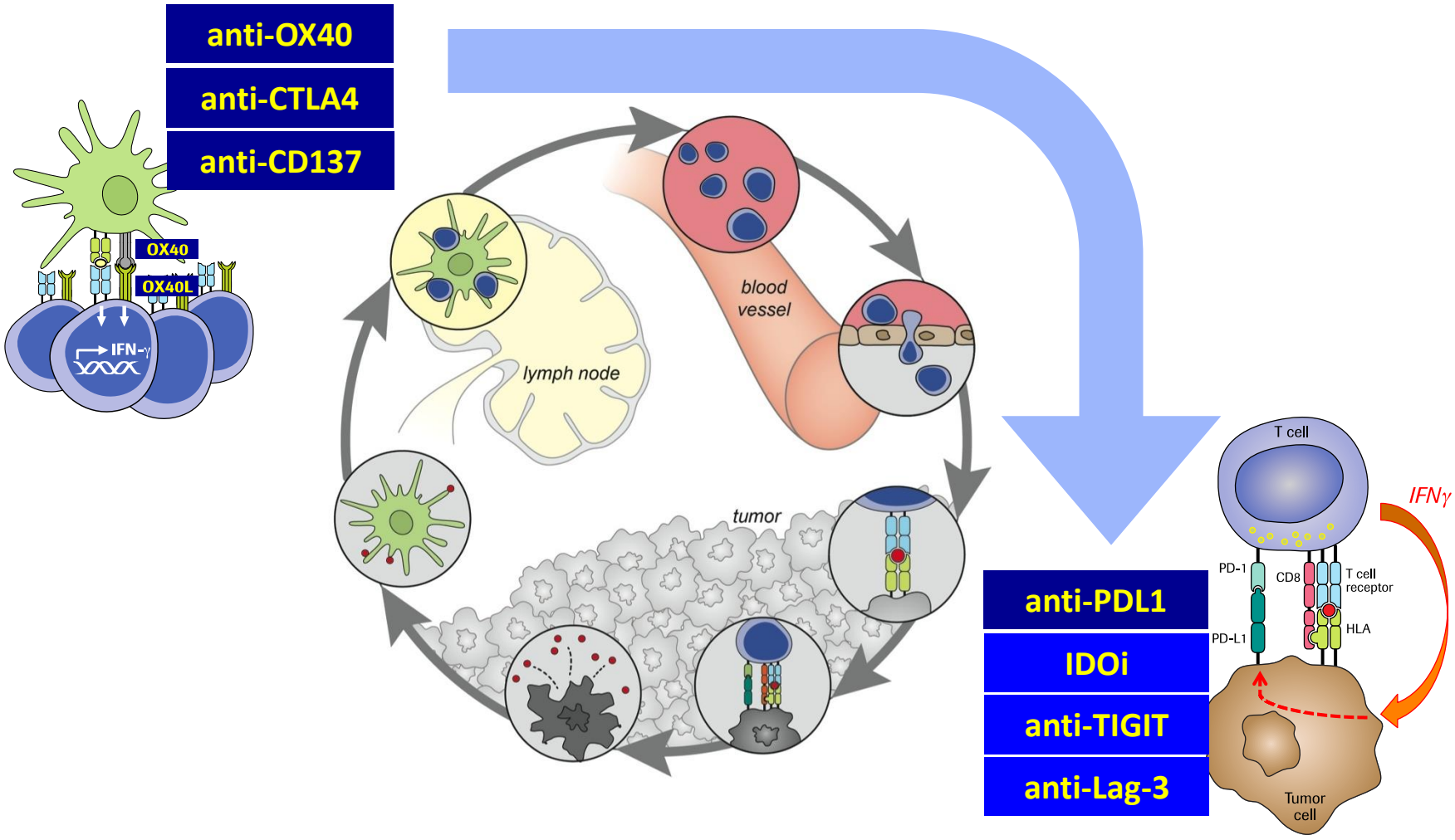

CD8 staining images are illustrative

# Simultaneous combinations may help to maintain and extend tumor inflamed state



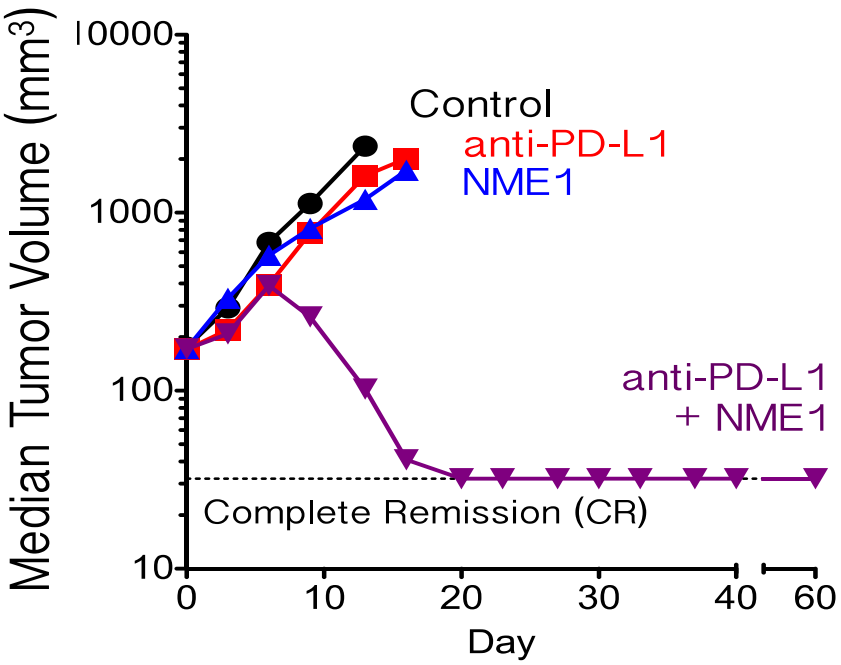

CD8 staining images are illustrative

# Immune doublets: (1) agonist + PD-L1/PD-1
# (2) second negative regulator + PD-L1/PD-1




PD-L1/PD-1 as a foundational therapy

# Negative regulator anti-TIGIT combines with PD-L1 to produce complete tumor regression in mice




R. Johnson et al (2014) Cancer Cell

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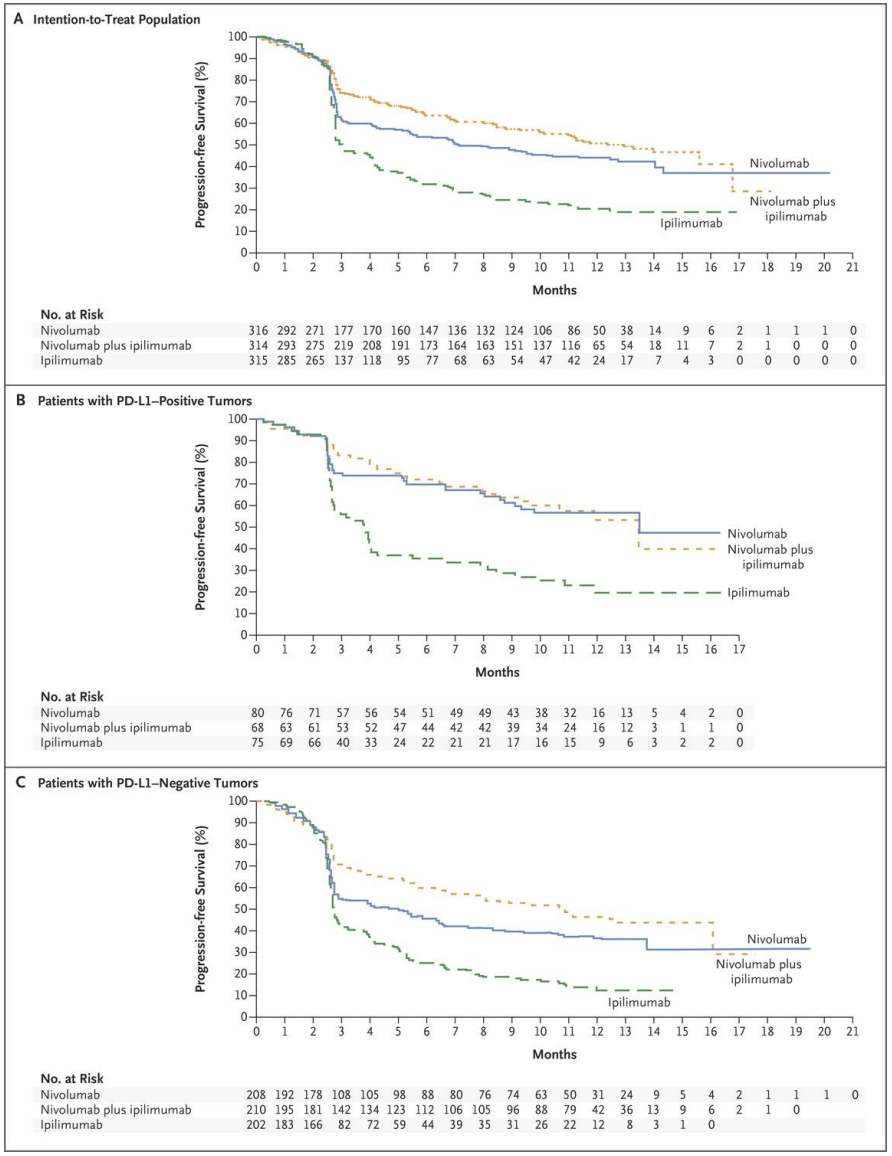
# Ipi+nivo combination in melanoma: difficulty in assessing combos where one agent is more active

**Marginal PFS benefit in all comers?**

**No PFS benefit in PD-L1-positive patients?**

**PFS benefit restricted to PD-L1-negative patients?**




Larkin J et al. N Engl J Med 2015;373:23-34

# Challenges with endpoints in combination trials

- Difficulty in assessing the success of a given combination when one agent is significantly more active than the other

- The utility of traditional radiographic response criteria for cancer immunotherapy (CIT) may be limited by the non-classical tumor kinetics ("pseudoprogression") observed in some patients with clinical benefit

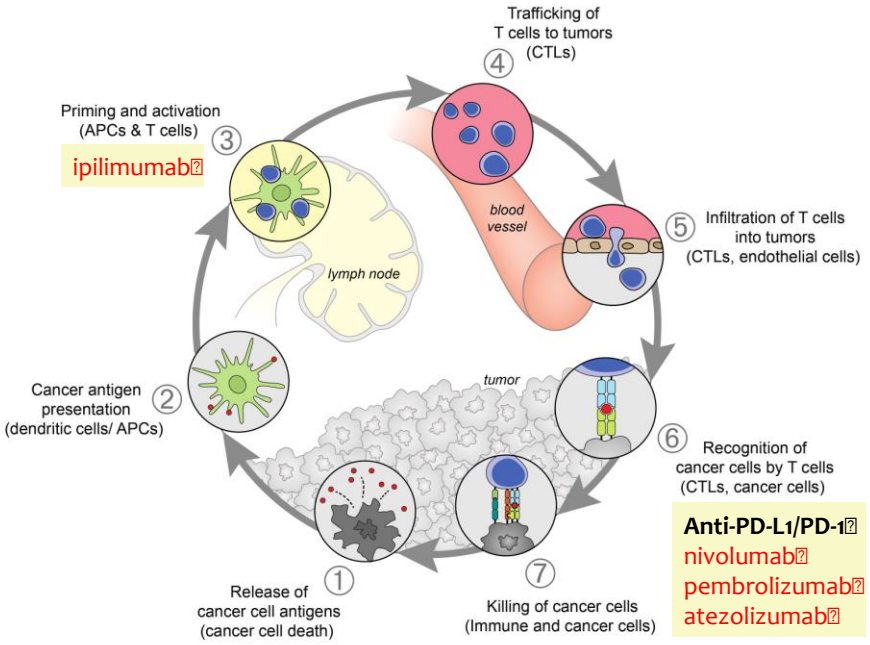
- **ORR and PFS have underestimated the overall survival (OS) benefit in monotherapy studies with PD1/PDL-1 inhibitors: how do we keep later line cross-over from confounding and prolonging studies?**

- Immune modified RECIST may capture of benefit of atypical responses otherwise missed with RECIST 1.1
  - All atezolizumab trials include RECIST 1.1 and imRECIST

# Cancer Immunotherapy present focus III: looking for next generation targets in the same space

Agonists to costimulators

αOX40
αCD27
αCD137
αCD40
αGITR




Antagonists of negative regulators, Treg depletors

αLag-1 (MHCII blocker)
αKIR (NK cell activator)
αTim-3 (PS? Galectin? CEACAM?)
αTIGIT (PVR blocker, CD226 activator)
NKG2a,
IDOi

# Current approaches largely address patients with pre-existing immunity

| Pre-existing Immunity (20-30%?) | Non-functional immune response | Excluded infiltrate | Immune desert |
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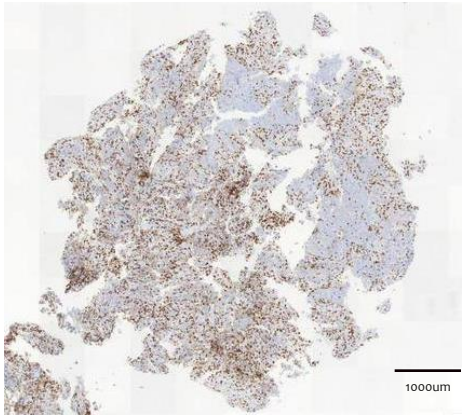
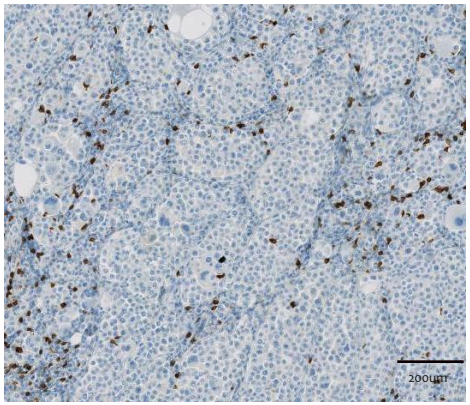
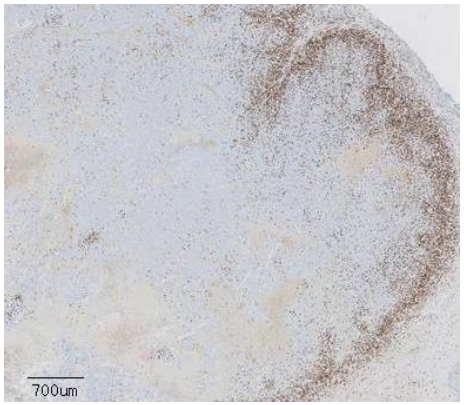
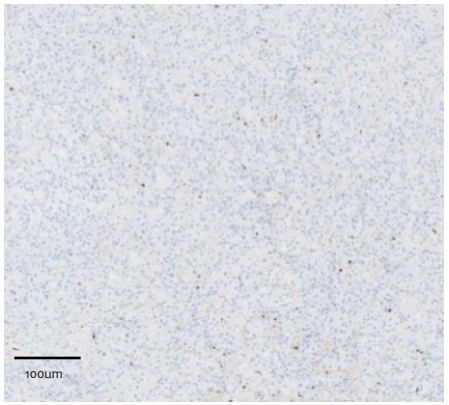
|  |  |  |  |

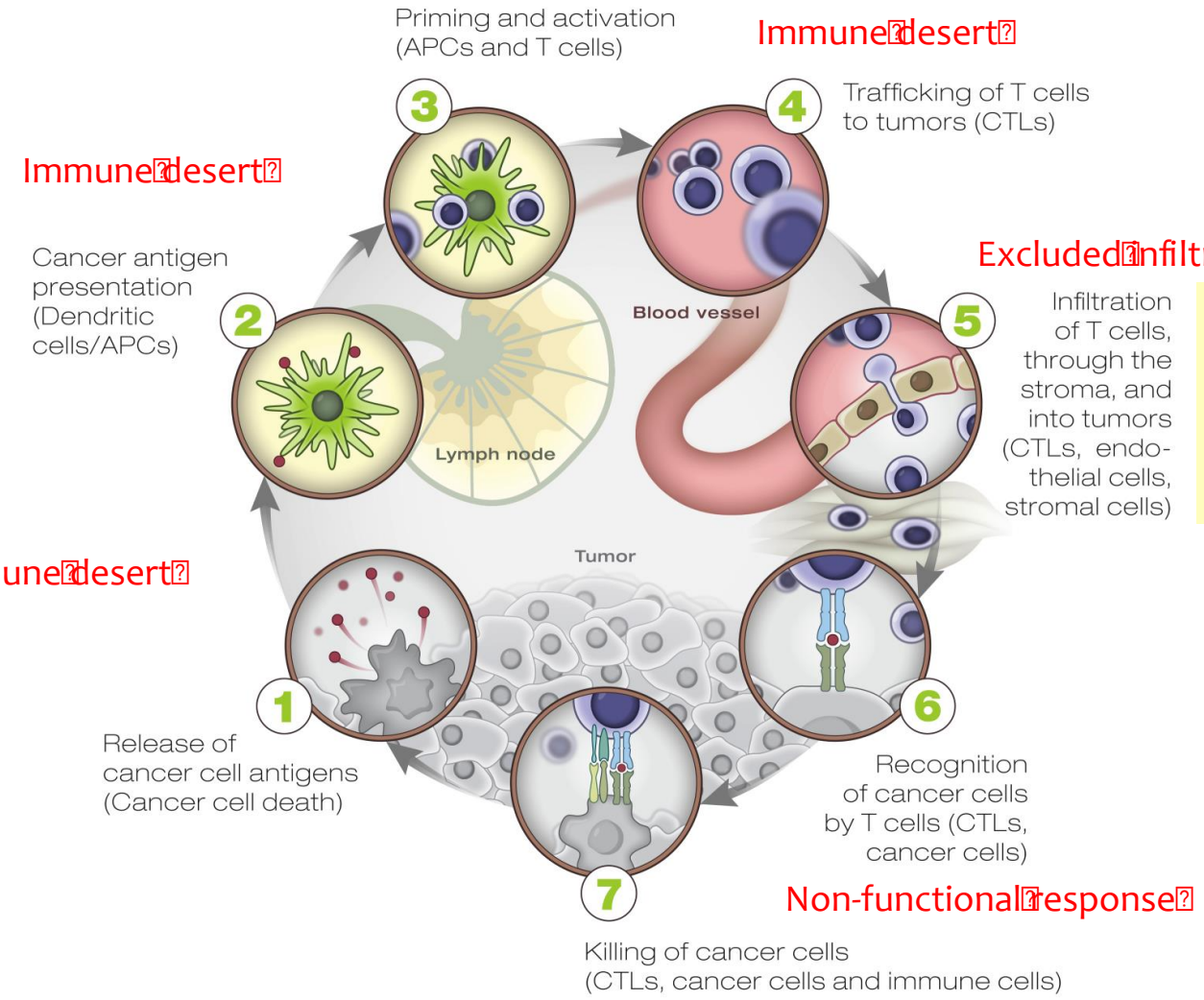


**CD8/IFNγ signature**

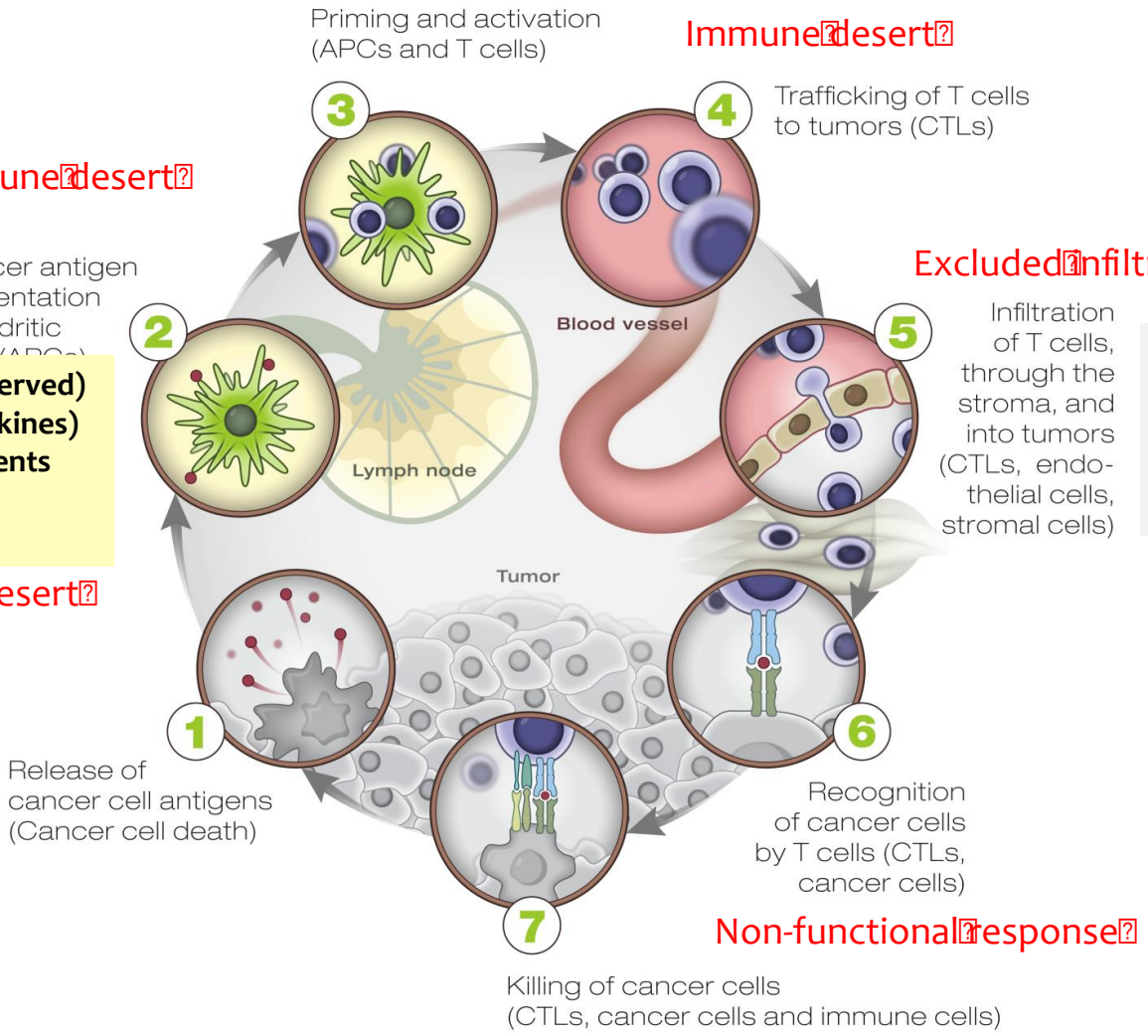
**Response to immunotherapy**

**Many or most patients may lack pre-existing immunity**

# Cancer immunotherapy: the next frontier
# Exploring the entirety of the cancer immunity cycle



# Cancer immunotherapy: the next frontier
# Capturing patients without pre-existing immunity

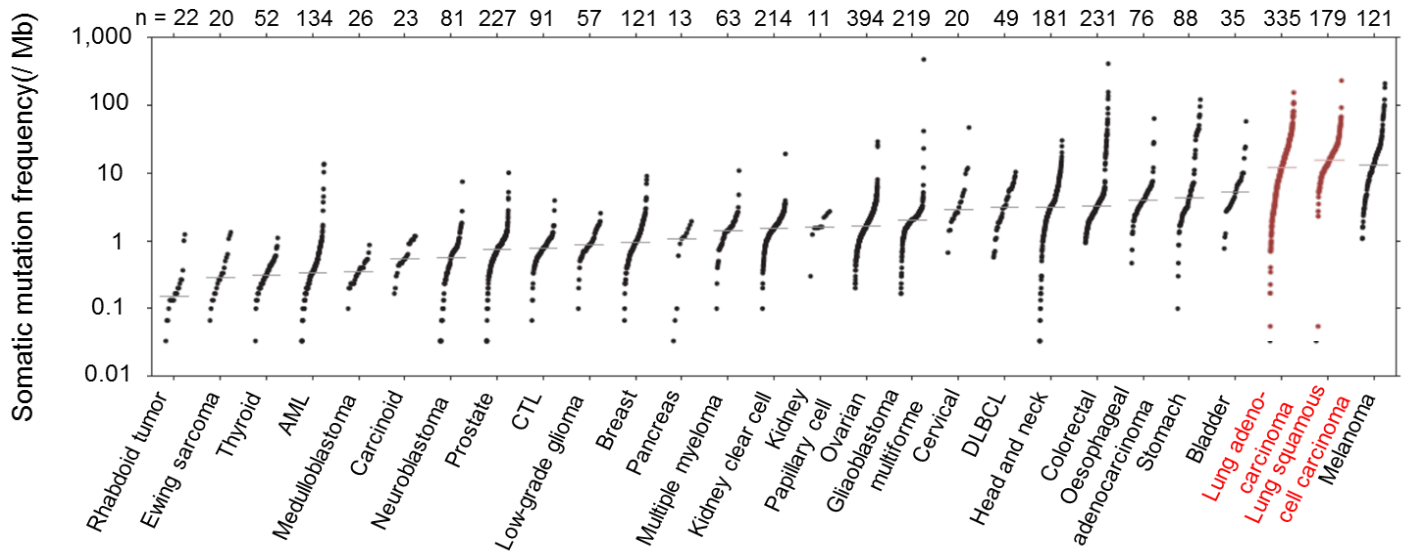



**Vaccines (neo-epitope, conserved)**
**Induced inflammation (cytokines)**
**Chemotherapy, targeted agents**
**Oncolytic viruses**
**T cell-directed bispecific antibodies**

Extracellular matrix
MDSCs, B cells
Chemokines
Protease processing
Angiogenesis

# Indication response rates correlate with mutation frequency

Somatic mutation frequencies observed in exomes from 3083 tumor-normal pairs




- Patients with lung cancer have a high rate of somatic mutations

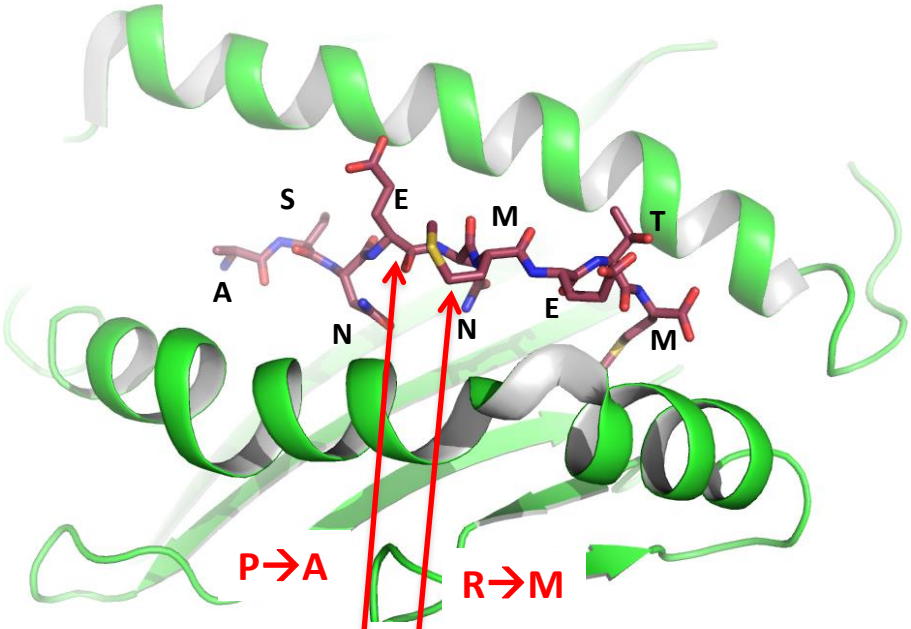
Reprinted by permission from Macmillan Publishers Ltd: *Nature*, Lawrence MS, et al. Jul 11;499(7457):214-8, 2013.

- Higher mutation rates have been observed in lung cancer tumors from smokers vs nonsmokers[a]
- High mutational rates likely contribute to increased immunogenicity[b]

[a] Imielinski M, et al. *Cell*. 2012; [b] Chen DS, et al. *CCR*. 2012.

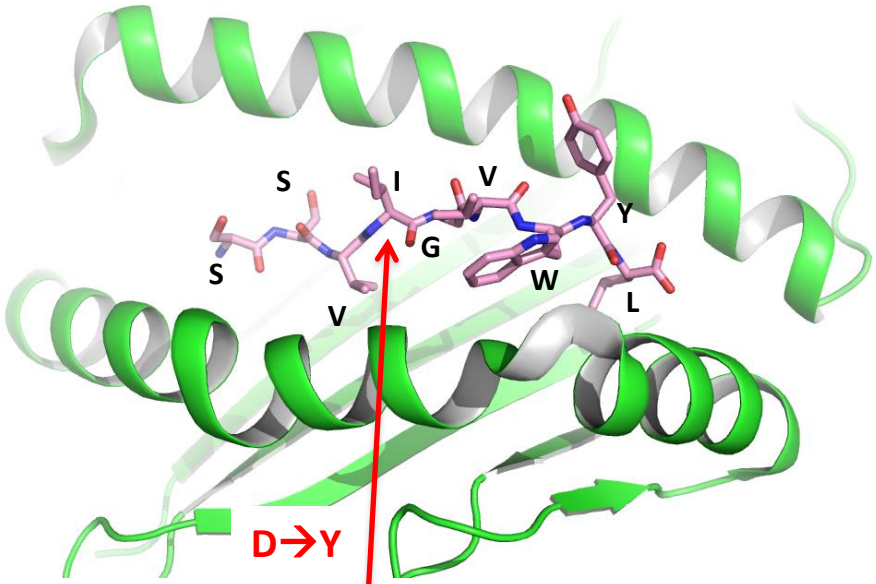
# Structural analysis suggests that only some mutations will be accessible to T cell receptors

## Immunogenic?
*solvent-exposed mutation*




| | |
|---|---|
| REPS1 | AQLPNDVVL |
| ADPGK | ASMTNRELM |
| FLU-NP | ASNENMETM |

## Non-immunogenic?
*mutation in MHC groove*



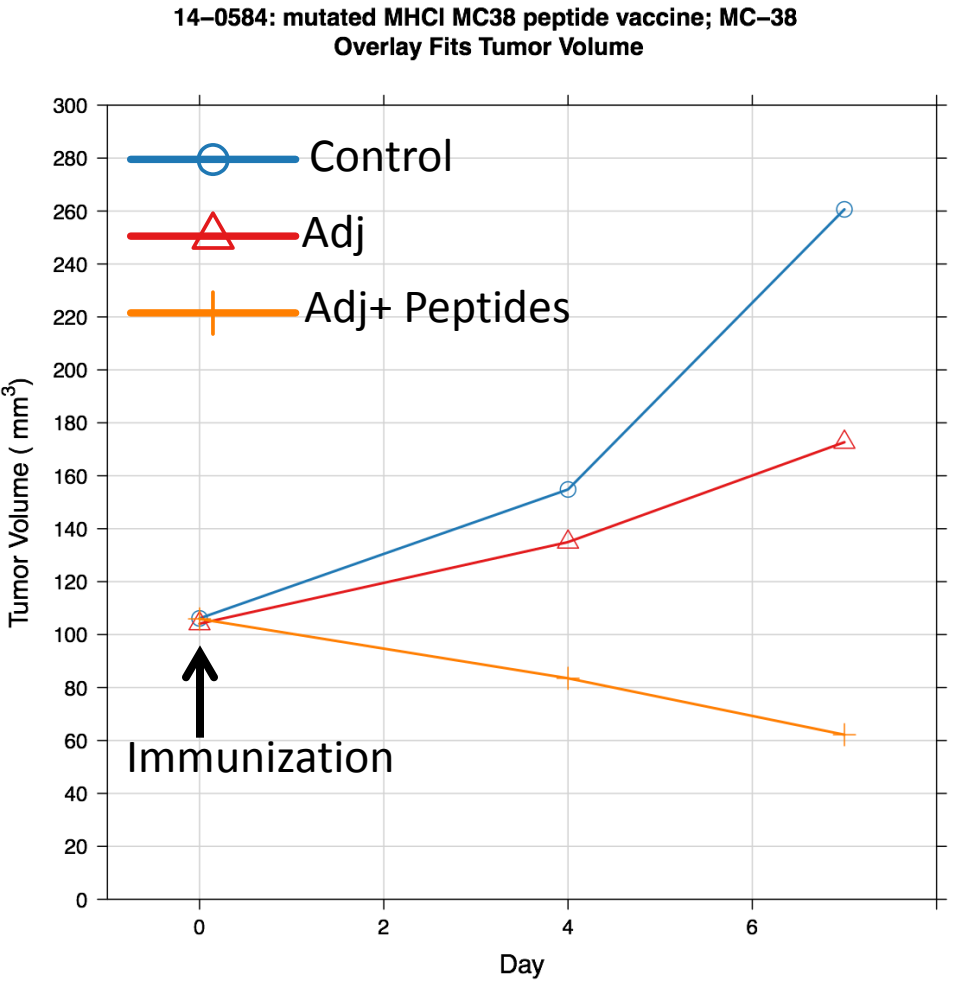

| | |
|---|---|
| Copine-1 | SSPDSLHYL |
| H60 | SSVIGVWYL |

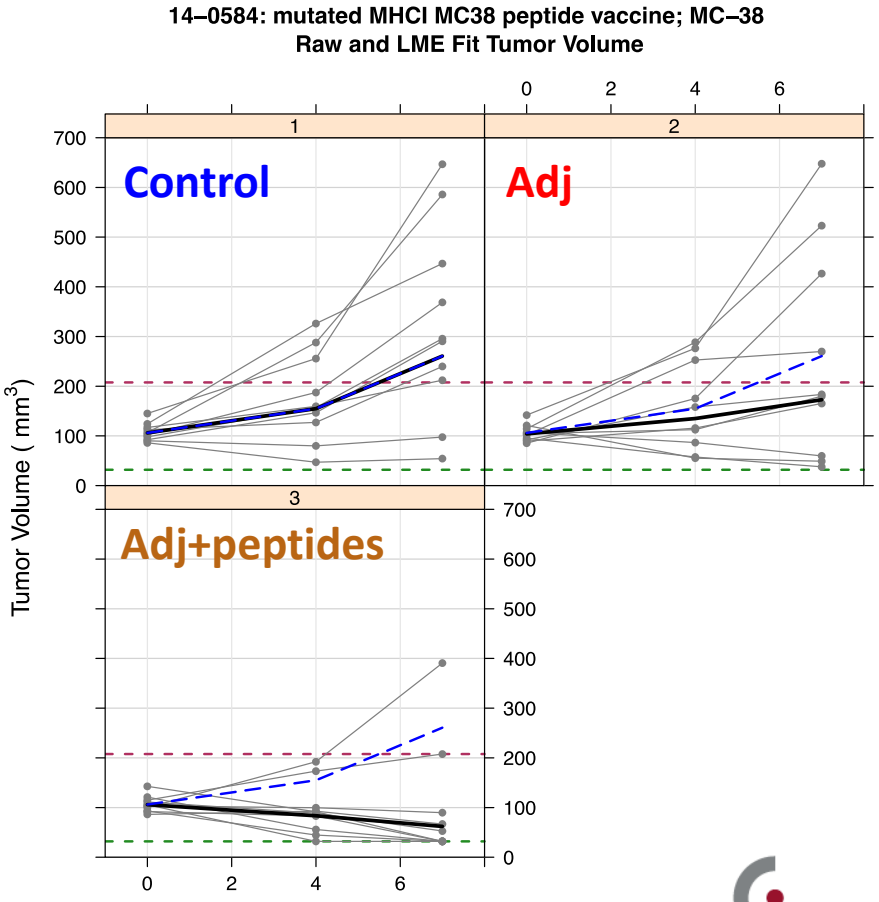
Yadav et al (2014) Nature

CancerImmunology

Genentech

# Promise for an indivdualized vaccine?: *immunization with antigenic peptides regresses MC-38 tumor growth*



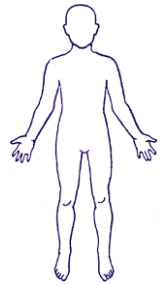

Yadav et al. (2014) Nature

CancerImmunology

Genentech

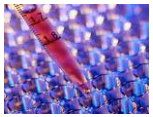
# Cancer immunotherapy: the frontier
# Environment, microbiome, and patient genetics

Milieu Intérieur
Vers une médecine personnalisée



Clinical data


Serology

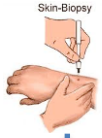


Whole blood 20ml

Whole blood 50ml

Nasal swabs /Stool

Skin Biopsy




Microbes

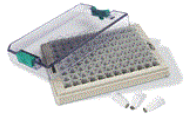
Adjuvants

Cytokines

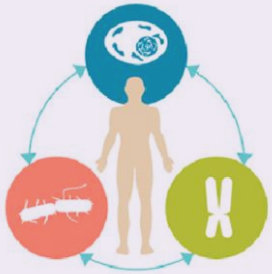
TCR stim

Supernatant

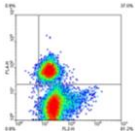
Cell pellets



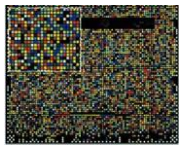
√ Fully recruited
1000 donors
5 decades of life
2 timepoints



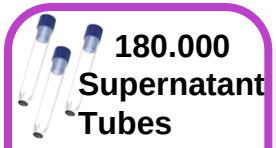
**1000 eCRF**
**≥ 300 var / p**



**10 Panels**
**15000 FCS files**
**≥ 500 var / p**



**1000 Genotypes**
**750K var / p**

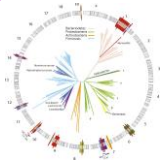


**180.000 Supernatant Tubes**

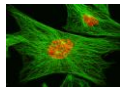
**≈ 50 var / tube**
**≈ 2000 var / p**

**60.000 RNA profiles**

**≥ 600 var / tube**
**≥ 24000 var / d**



**1000 Enterotypes**
**16S rRNA NGS**



**300 fibroblast lines**

**→ iPS**

# Summary

**The past:**

- Hampered by a poor understanding of human immunology

**The present:**

- Realization that normal immune homeostatic mechanisms restrict anti-cancer immunity
- Predominant focus on targets relevant to patients with pre-existing immunity

**The frontier:**

- Need to expand focus to include targeting stroma and to understand host genetics, the microbiome, and the environment
- Return to our origins to induce immunity in patients who have none

# Perspectives

- We are at the beginning of an exciting journey for patients and for scientific investigation
- Excitement has been driven by clinical data, outpacing the basic science foundation of cancer immunology
- Investigating cancer immunology by "reverse translating" to the lab from clinical studies is needed to bring benefit to an ever greater number of patients
- Rapid clinical progress and new response patterns have created a critical need for new approaches to regulatory assessment
- Although the journey is just beginning, we can see the destination, justifying courageous action to accelerate our arrival time