

L'immunologie : les bases pour comprendre les traitements actuels et à venir

Les groupes de travail de la SPLF

Groupe d'oncologie de langue française

Groupe GOLF



Pr Maha Ayyoub

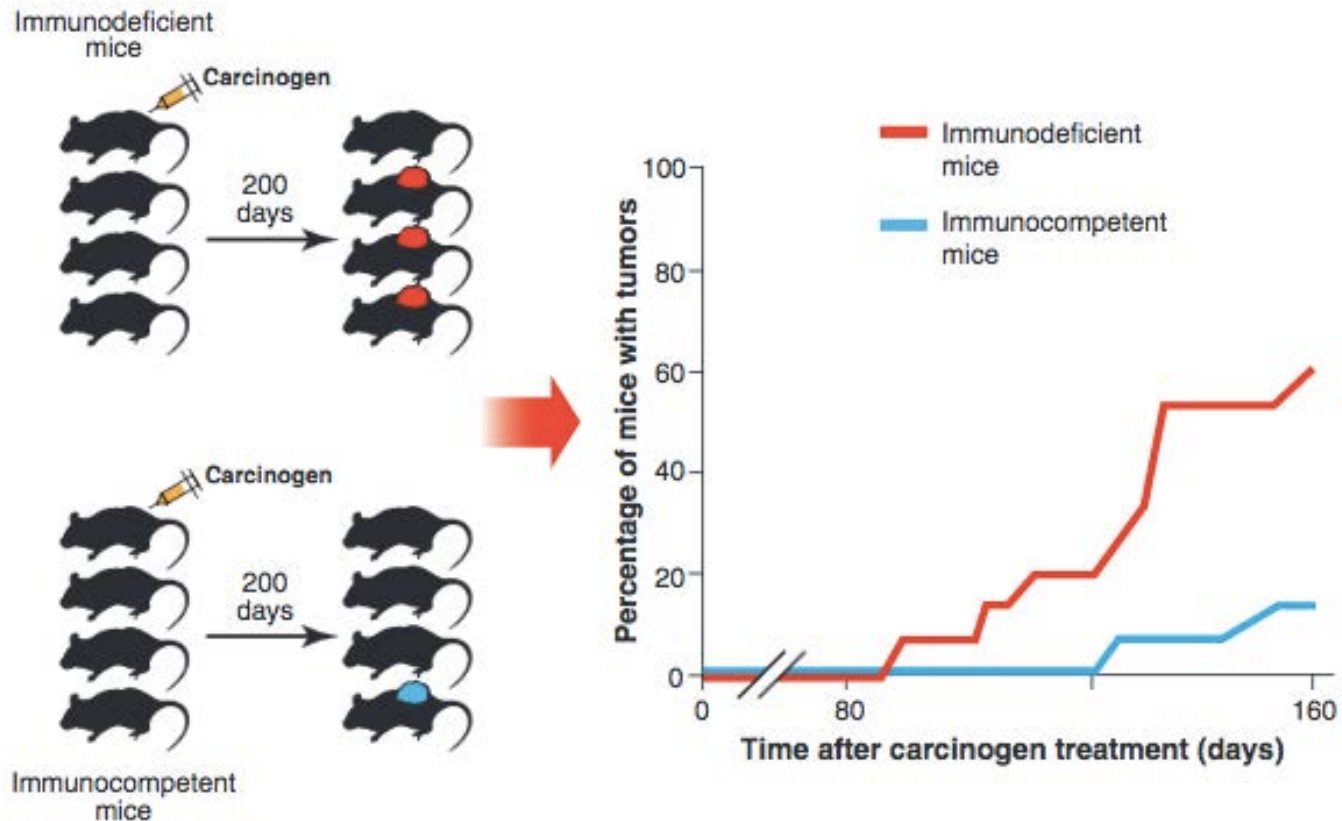
Centre de Recherches en Cancérologie de Toulouse – Inserm UMR 1037

Institut Universitaire du Cancer de Toulouse – Oncopole

Université Paul Sabatier Toulouse III

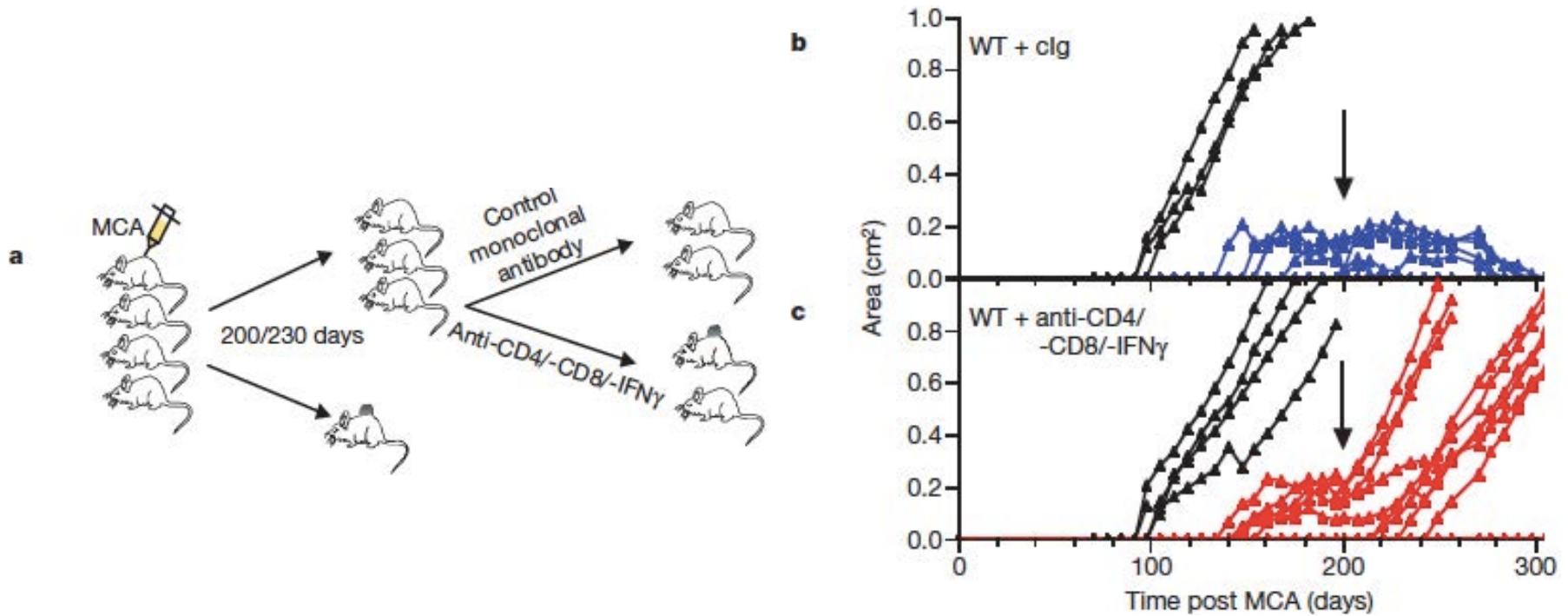
Cours du GOLF, Toulouse, 7 oct. 2019

Cancer immunoediting



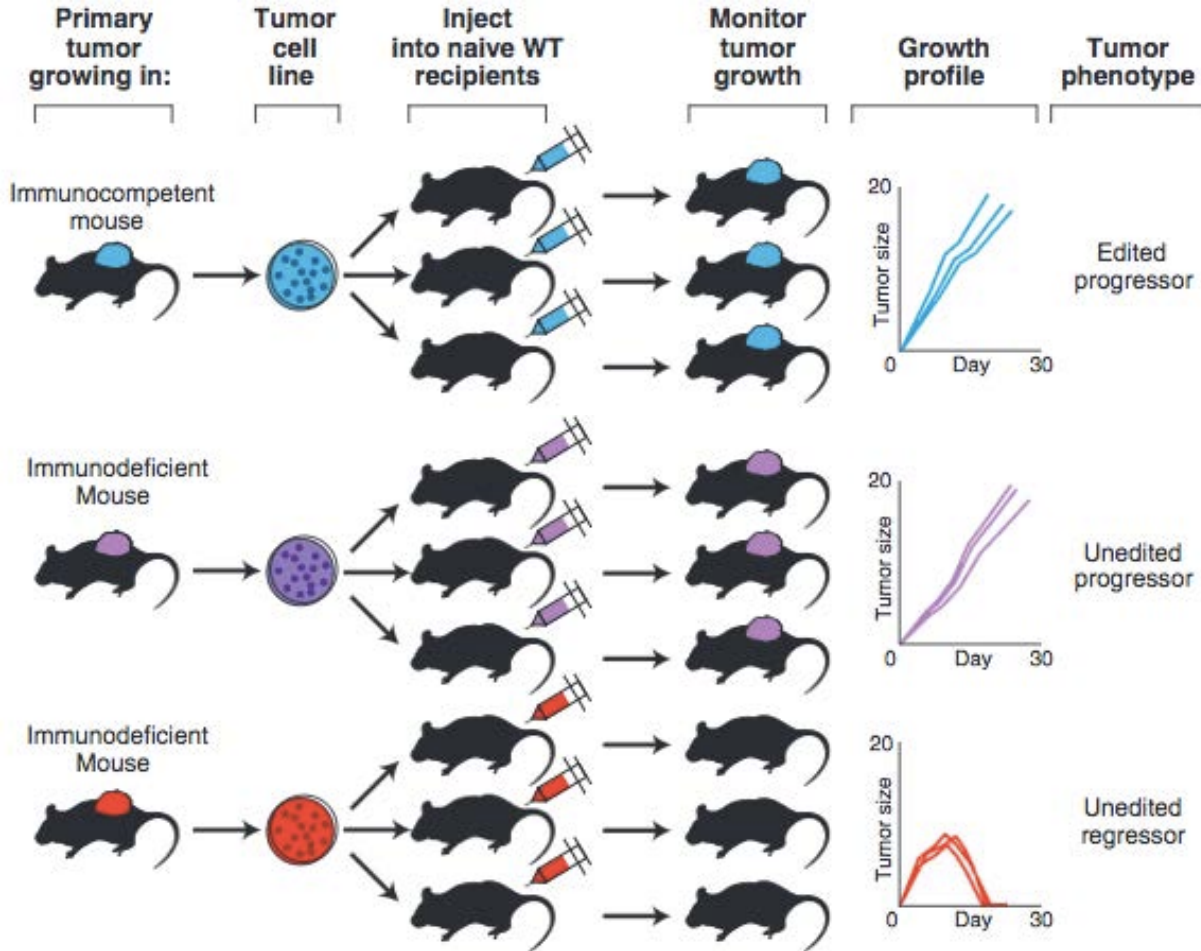
☑ Adaptive immunity can control transformation

Cancer immunoediting



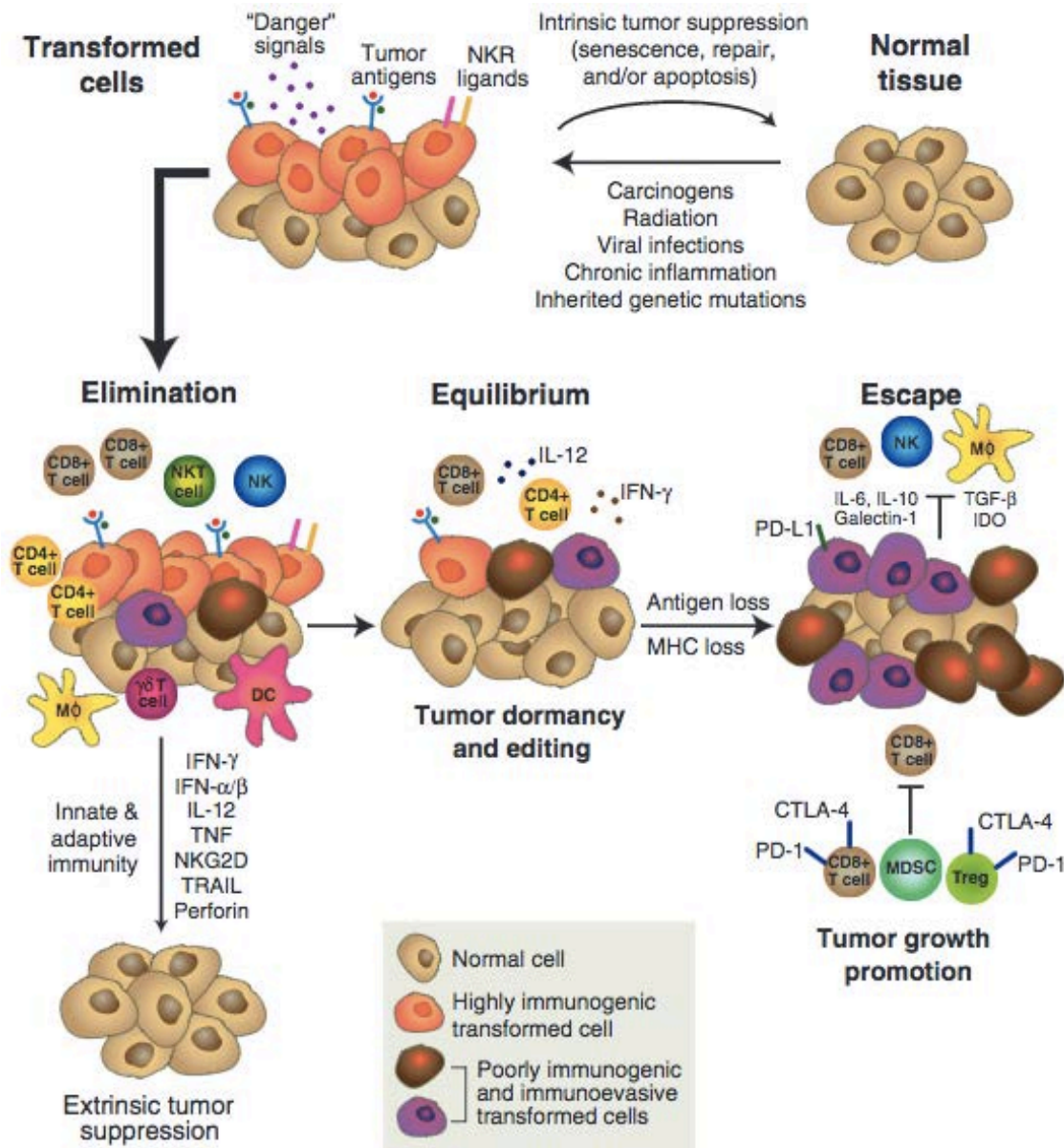
☑ Adaptive immunity can maintain tumors under check

Cancer immunoediting



☑ Pressure of adaptive immunity can select less immunogenic / more resistant tumor variants

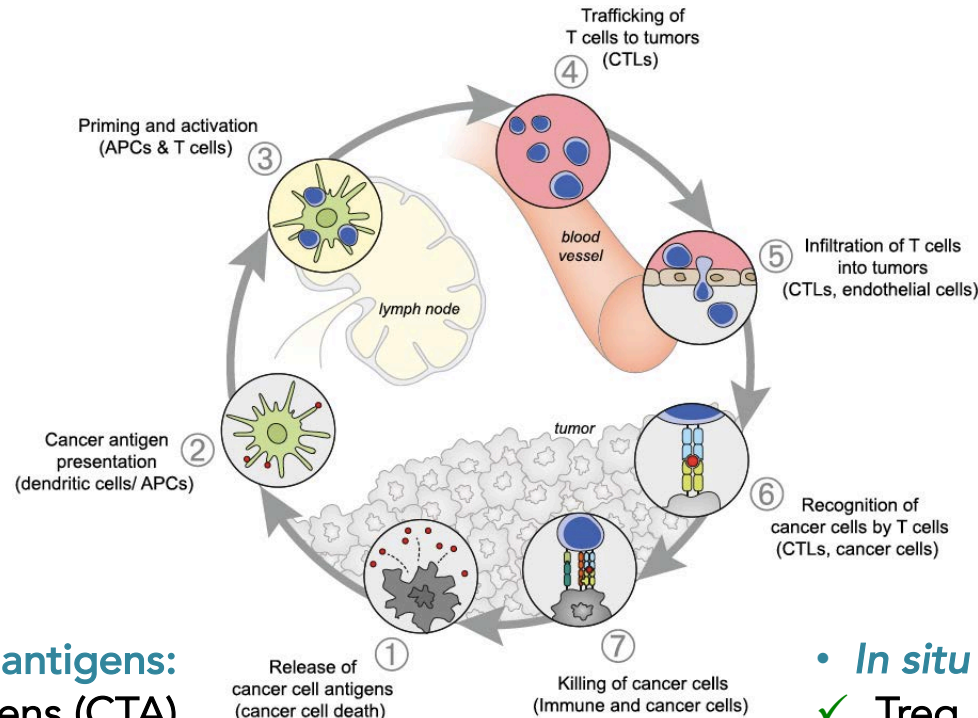
Cancer immunoeediting



Antigen-specific T cells in the cancer immune cycle

- Circulating specific CD4 and CD8 T cells

- T-cell trafficking to the tumor



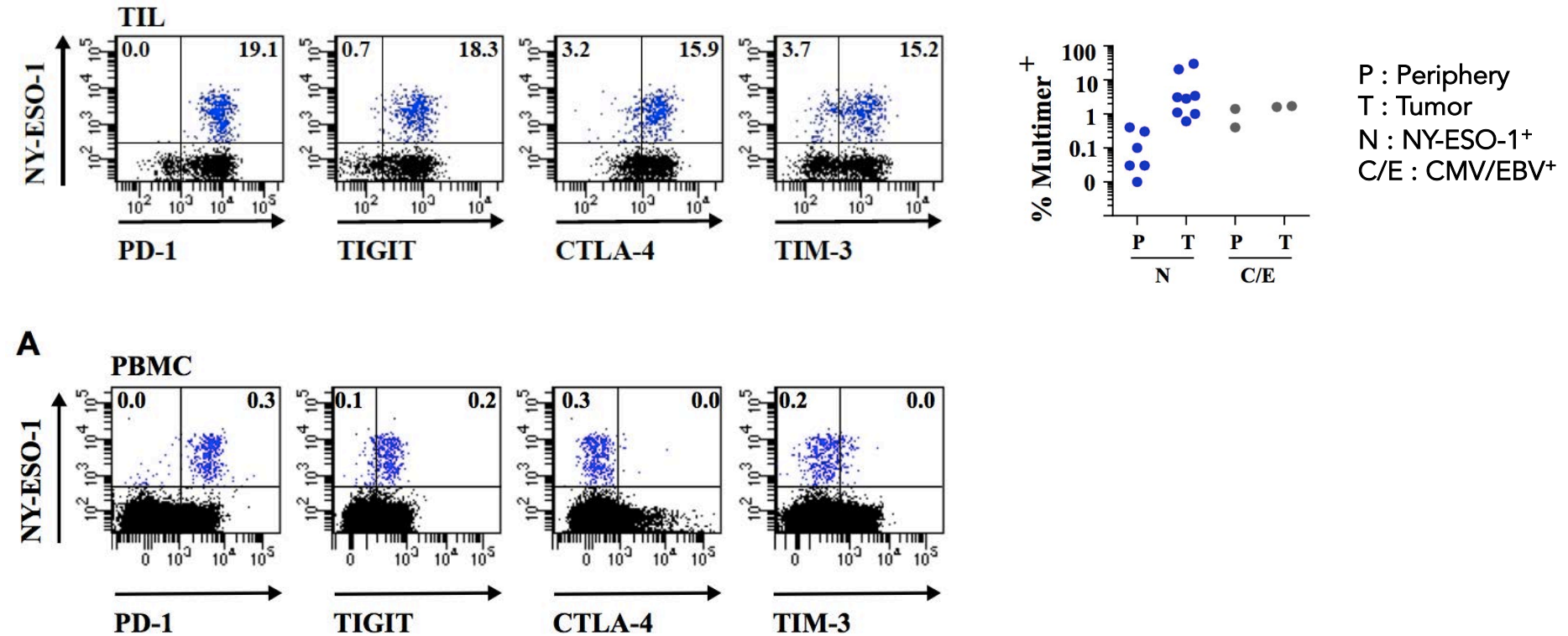
- **Tumor antigens:**

- ✓ Cancer testis antigens (CTA)
- ✓ Oncoviral antigens
- ✓ Neo-antigens

- **In situ immune regulation**

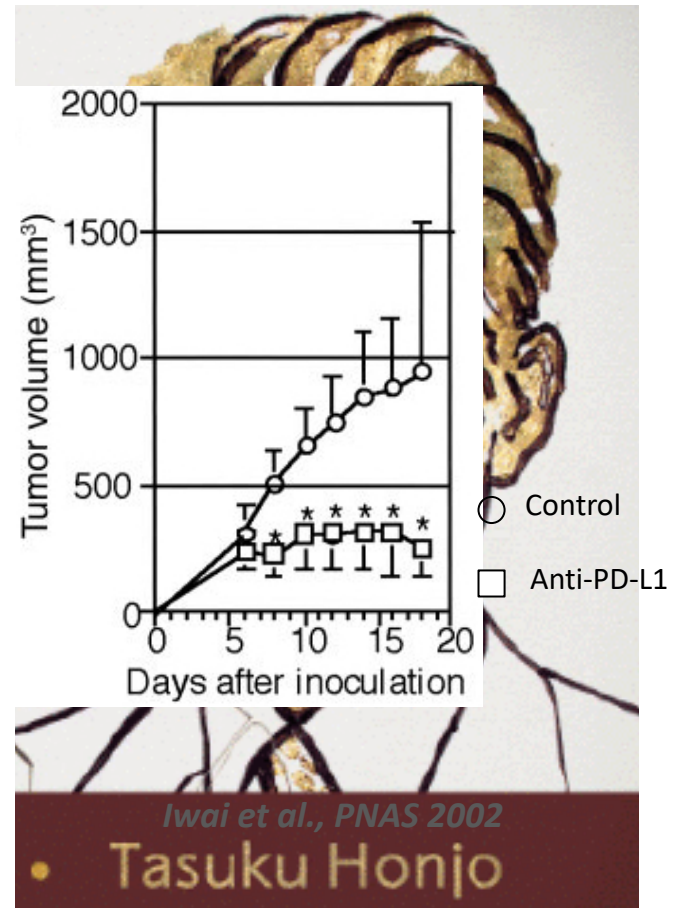
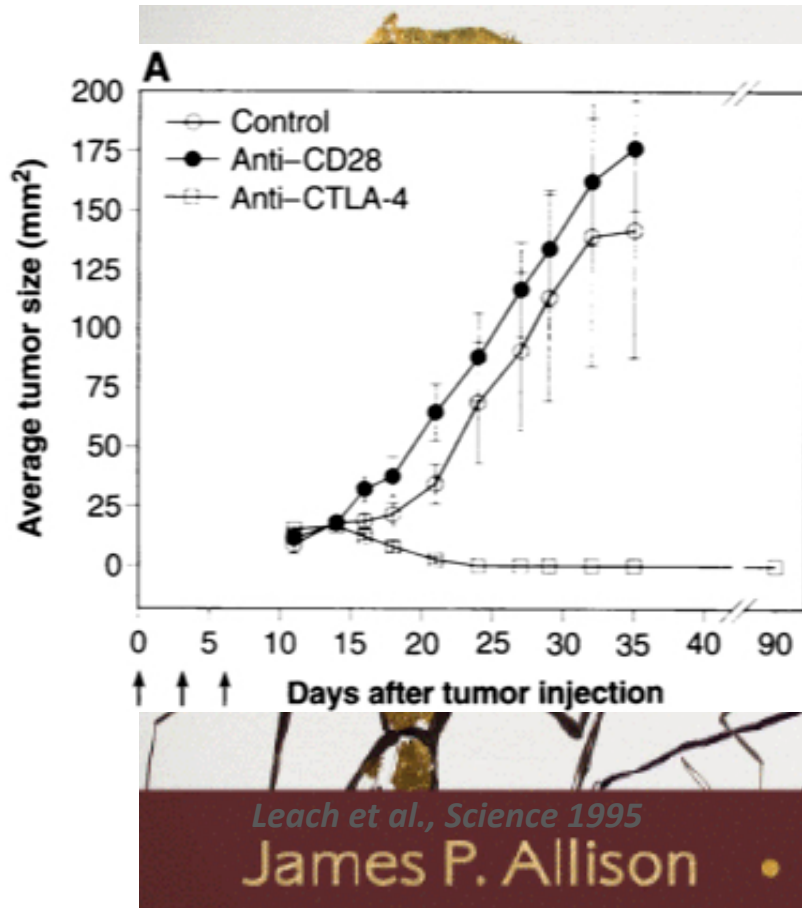
- ✓ Treg, MDSC, M2 macs...
- ✓ Immune checkpoints

Antigen-specific T cells in the cancer immune cycle



Tumor-specific CD8 T cells accumulate at the tumor site but they express immune checkpoints

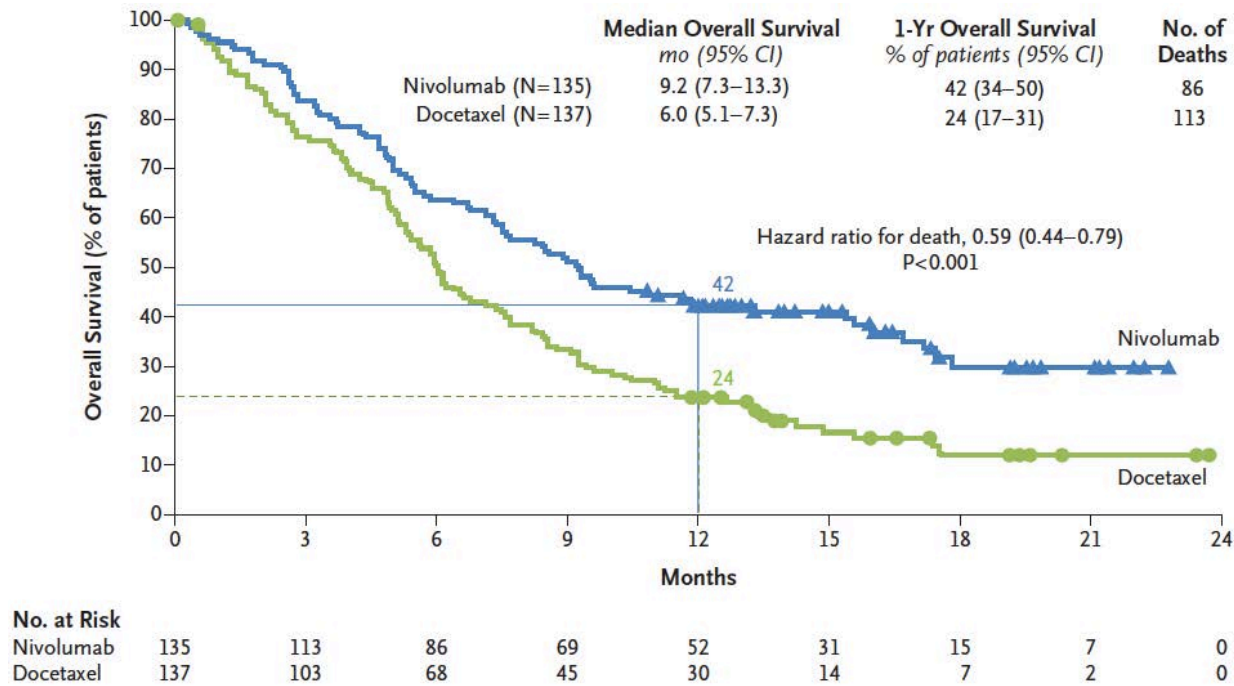
T cell control by immune checkpoints



☑ Immune checkpoint blockade leads to tumor regression

Immune checkpoint blockade in NSCLC

Nivolumab versus Docetaxel in Advanced Squamous-Cell NSCLC



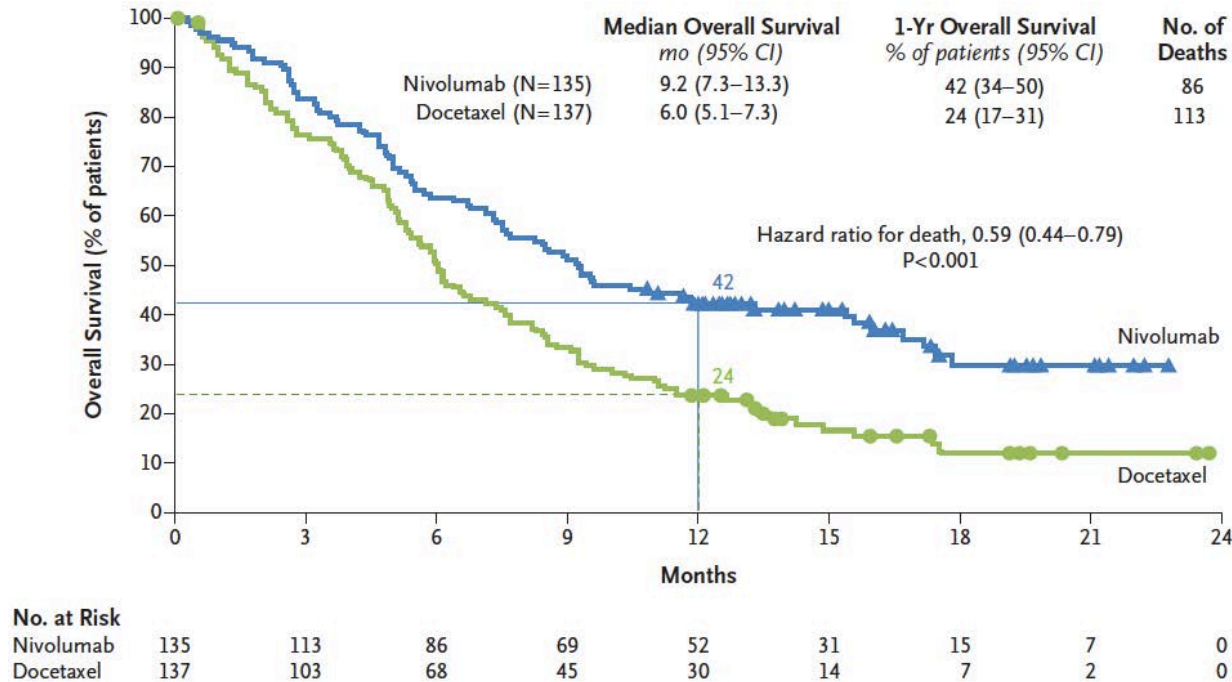
Brahmer J, NEJM 2015

Immune checkpoint blockade in NSCLC



Immune checkpoint blockade in NSCLC

Nivolumab versus Docetaxel in Advanced Squamous-Cell NSCLC



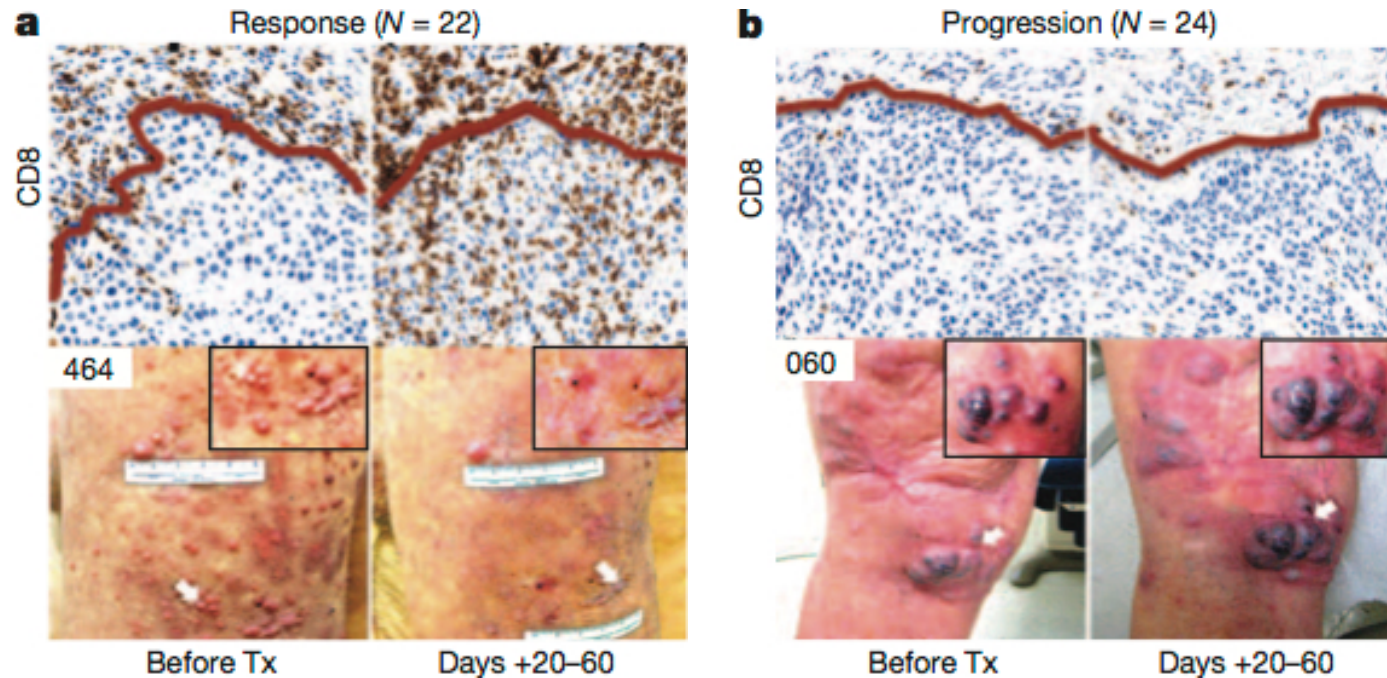
Brahmer J, NEJM 2015

☑ How can we capitalize on success?

- ✓ High throughput research: biomarkers of response...
- ✓ Hypothesis-driven research: mechanisms of action...

Biomarkers of response to ICB

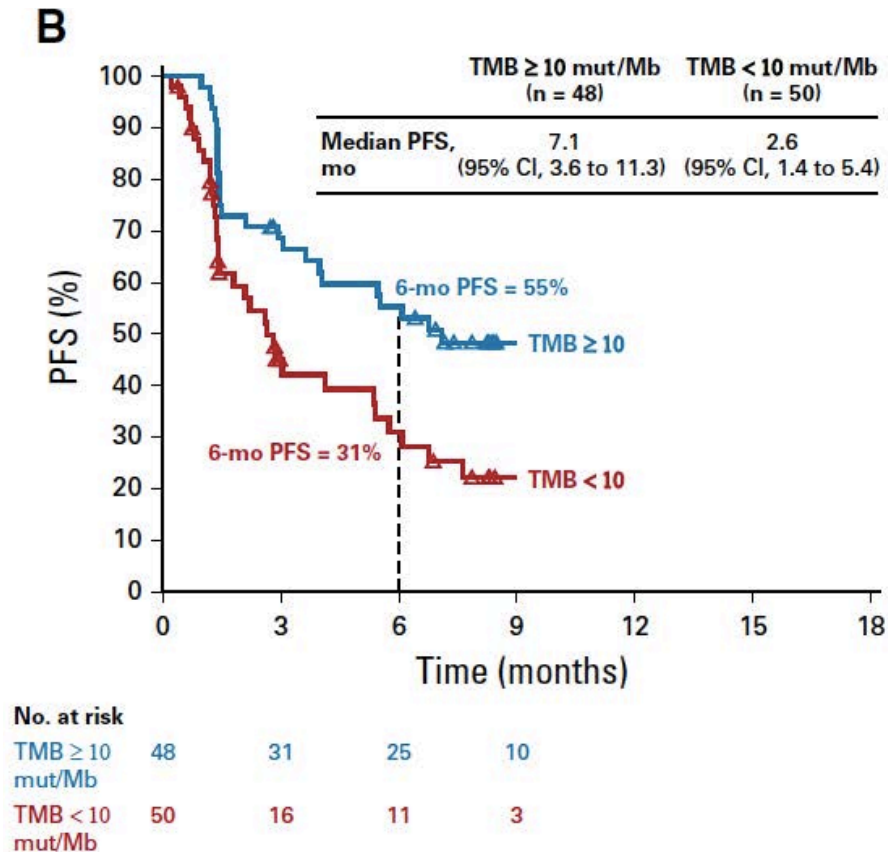
Pembrolizumab in melanoma



- ☑ CD8 infiltrate pre-therapy + increase of the infiltrate on therapy

Biomarkers of response to ICB

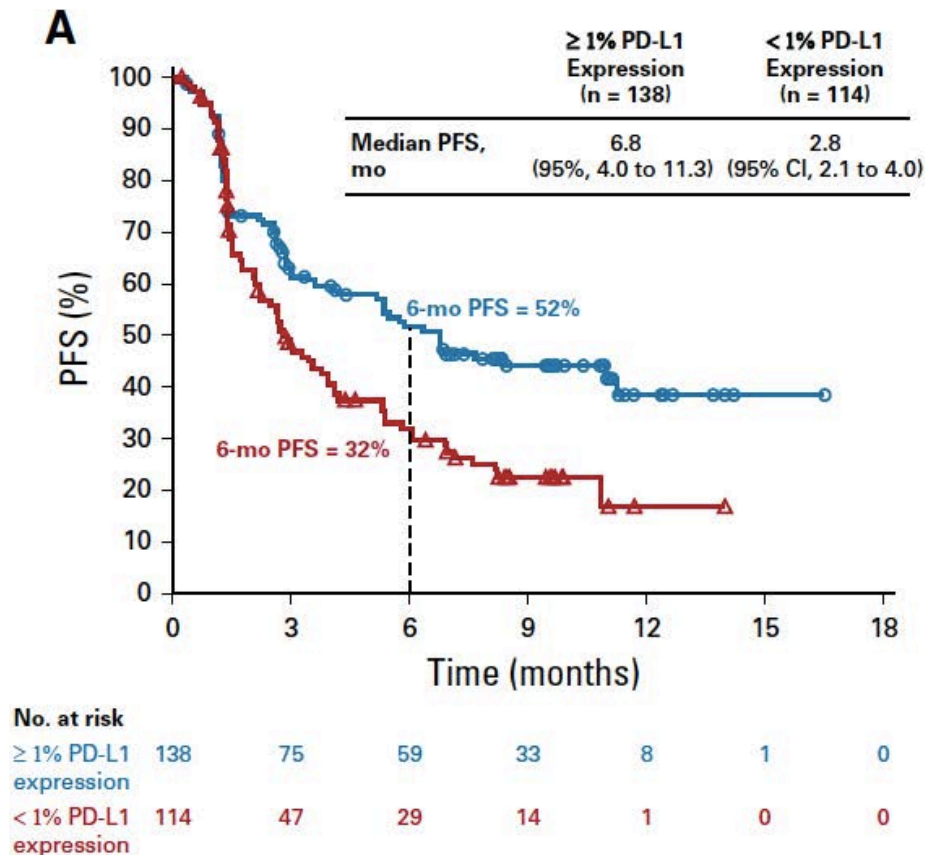
CheckMate 568: phase II, nivolumab plus low-dose ipilimumab as first-line treatment of advanced/metastatic NSCLC



☑ TMB = antigens recognized by T cells?

Biomarkers of response to ICB

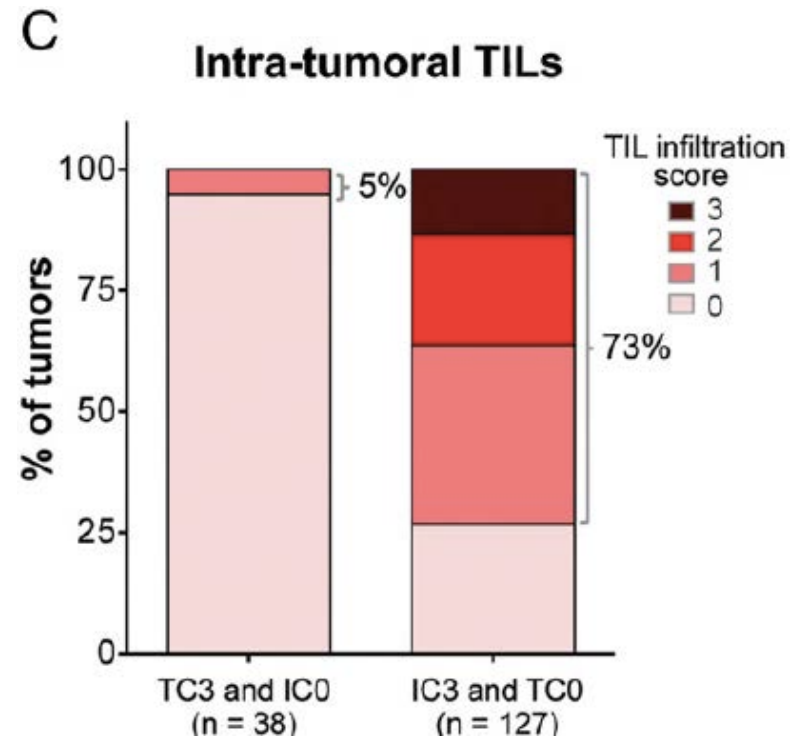
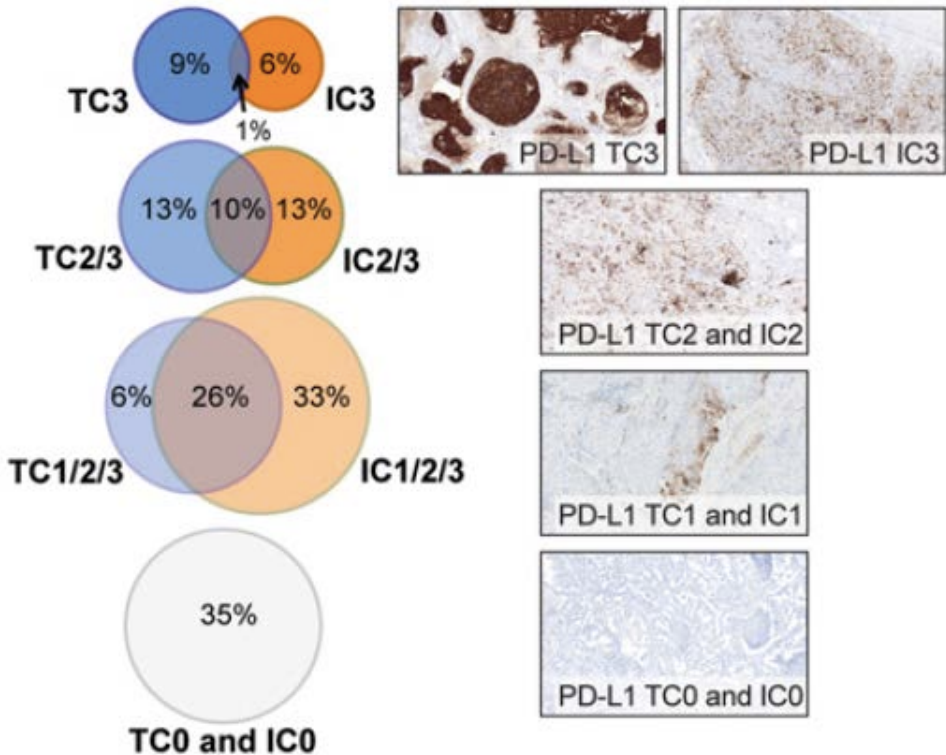
CheckMate 568: phase II, nivolumab plus low-dose ipilimumab as first-line treatment of advanced/metastatic NSCLC



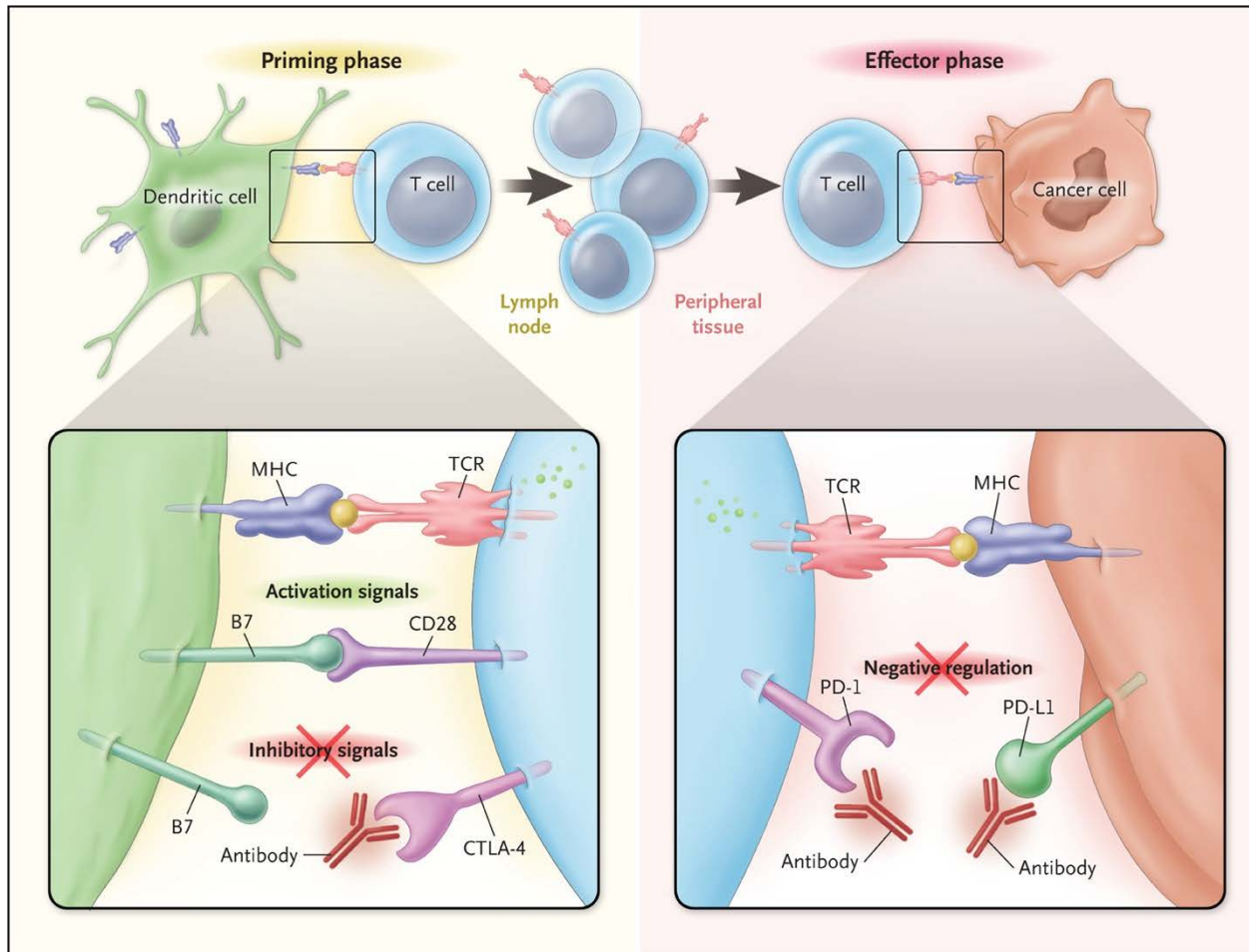
☑ PD-L1 as biomarker of response to anti-PD-1: contrasted data

Biomarkers of response to ICB

PD-L1 in tumor cells and immune cells: which one matters?



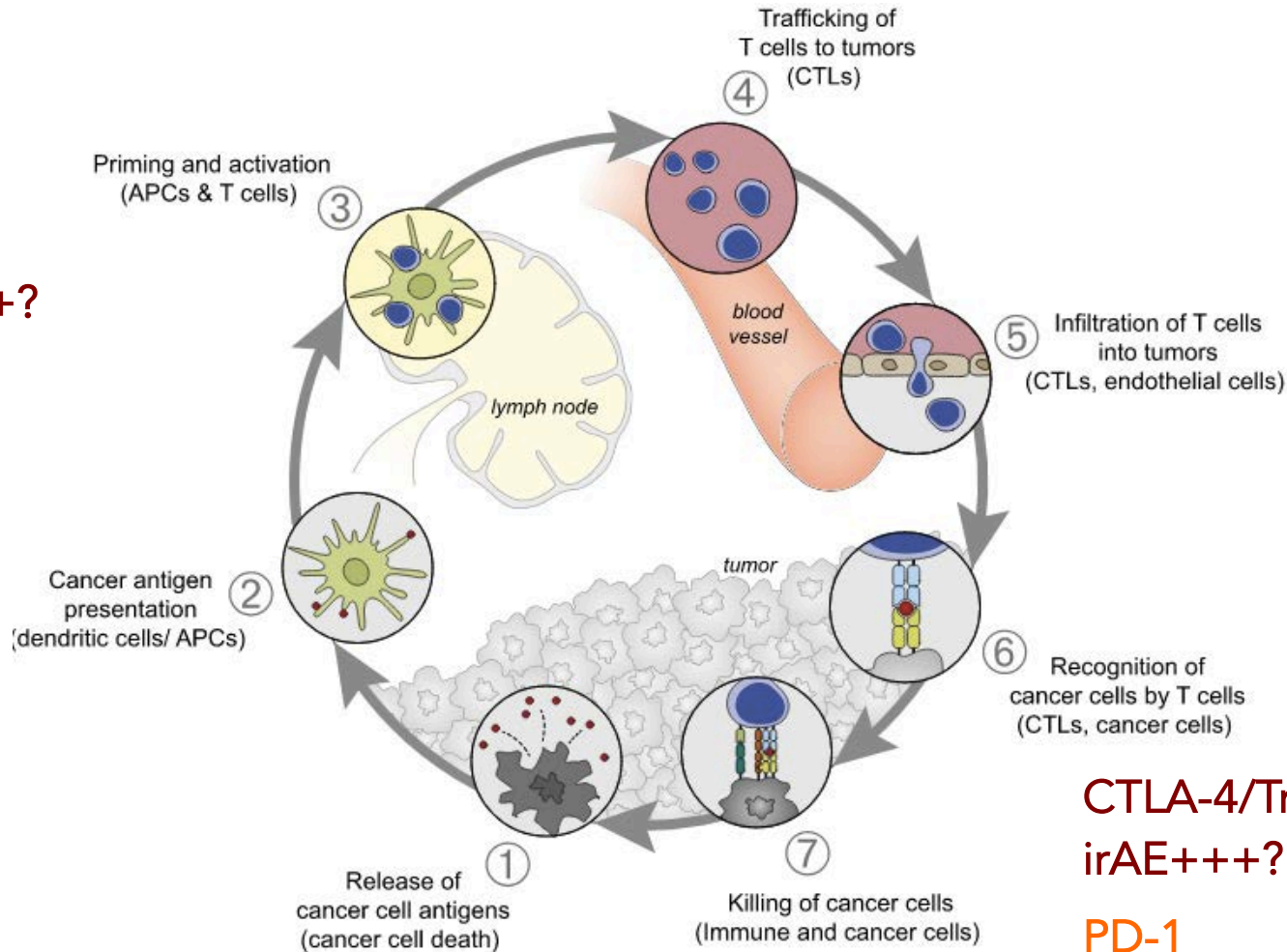
T cell control by immune checkpoints



- ☑ Immune checkpoints can control priming/amplification and effector functions of T cells

T cell control by immune checkpoints

CTLA-4
irAE+++?



CTLA-4/Treg function
irAE+++?

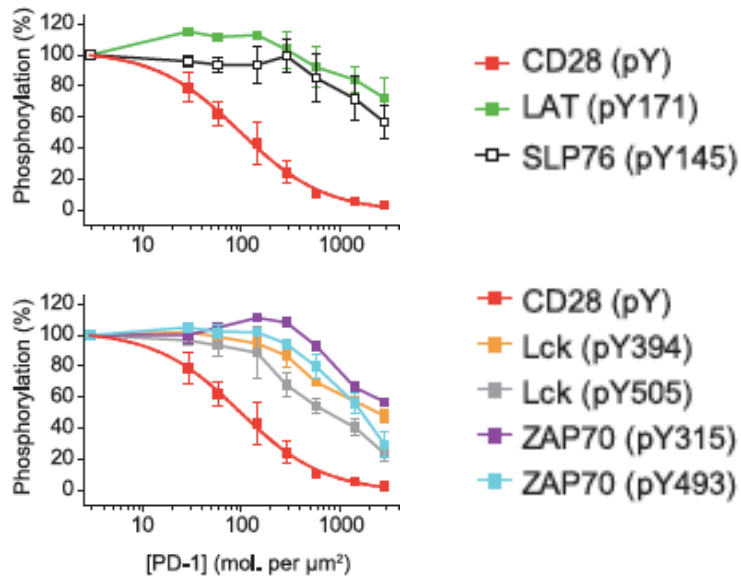
PD-1

PD-L1=response?

Exhausted T cells and their reinvigoration

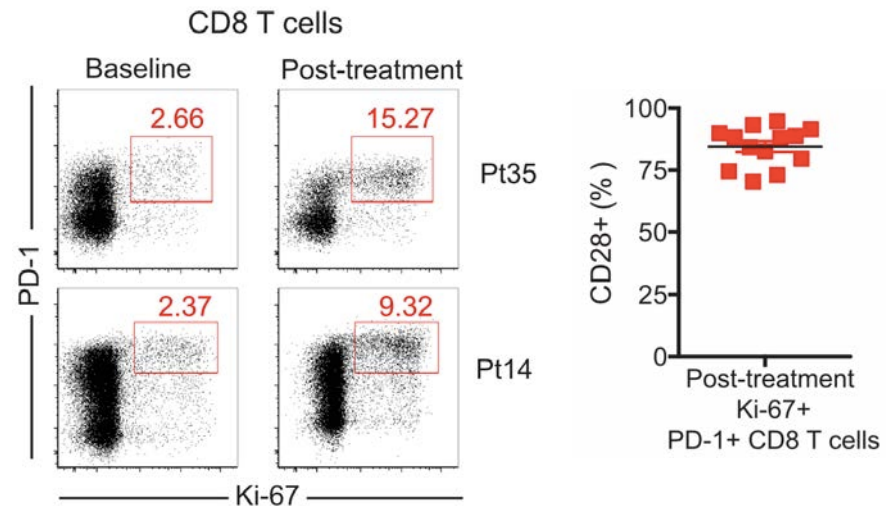
T cell costimulatory receptor CD28 is a primary target for PD-1-mediated inhibition

Enfu Hui,^{1*} Jeanne Cheung,² Jing Zhu,² Xiaolei Su,¹ Marcus J. Taylor,¹ Heidi A. Wallweber,² Dibyendu K. Sasmal,³ Jun Huang,³ Jeong M. Kim,² Ira Mellman,^{2†} Ronald D. Vale^{1†} *Science, 2017*



Rescue of exhausted CD8 T cells by PD-1-targeted therapies is CD28-dependent

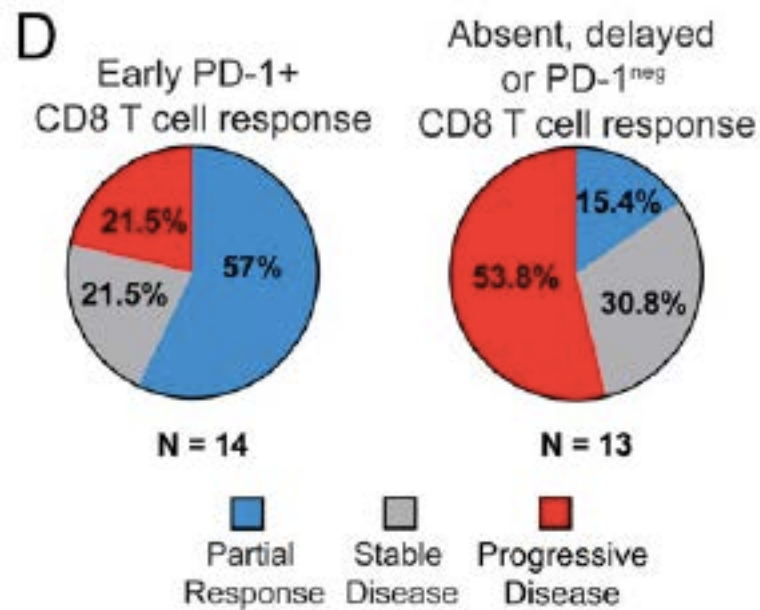
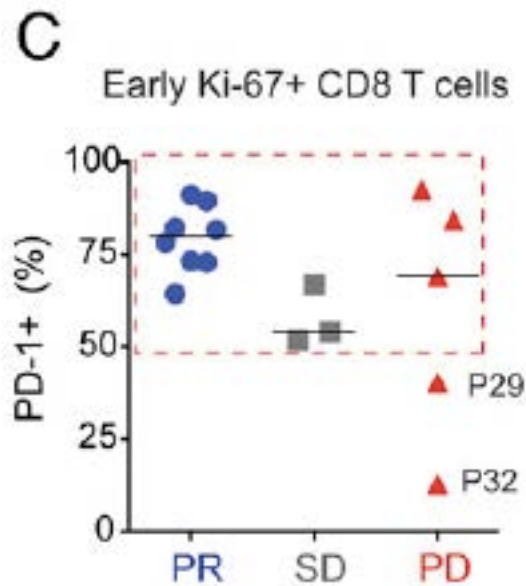
Alice O. Kamphorst,¹ Andreas Wieland,¹ Tahseen Nasti,¹ Shu Yang,^{1,2*} Ruan Zhang,³ Daniel L. Barber,^{1,4} Bogumila T. Konieczny,¹ Candace Z. Daugherty,¹ Lydia Koenig,⁵ Ke Yu,⁵ Gabriel L. Sica,⁶ Arlene H. Sharpe,⁷ Gordon J. Freeman,⁸ Bruce R. Blazar,⁹ Laurence A. Turka,³ Taofeek K. Owonikoko,⁵ Rathi N. Pillai,⁵ Suresh S. Ramalingam,⁵ Koichi Araki,¹ Rafi Ahmed^{1†} *Science, 2017*



Exhausted T cells and their reinvigoration

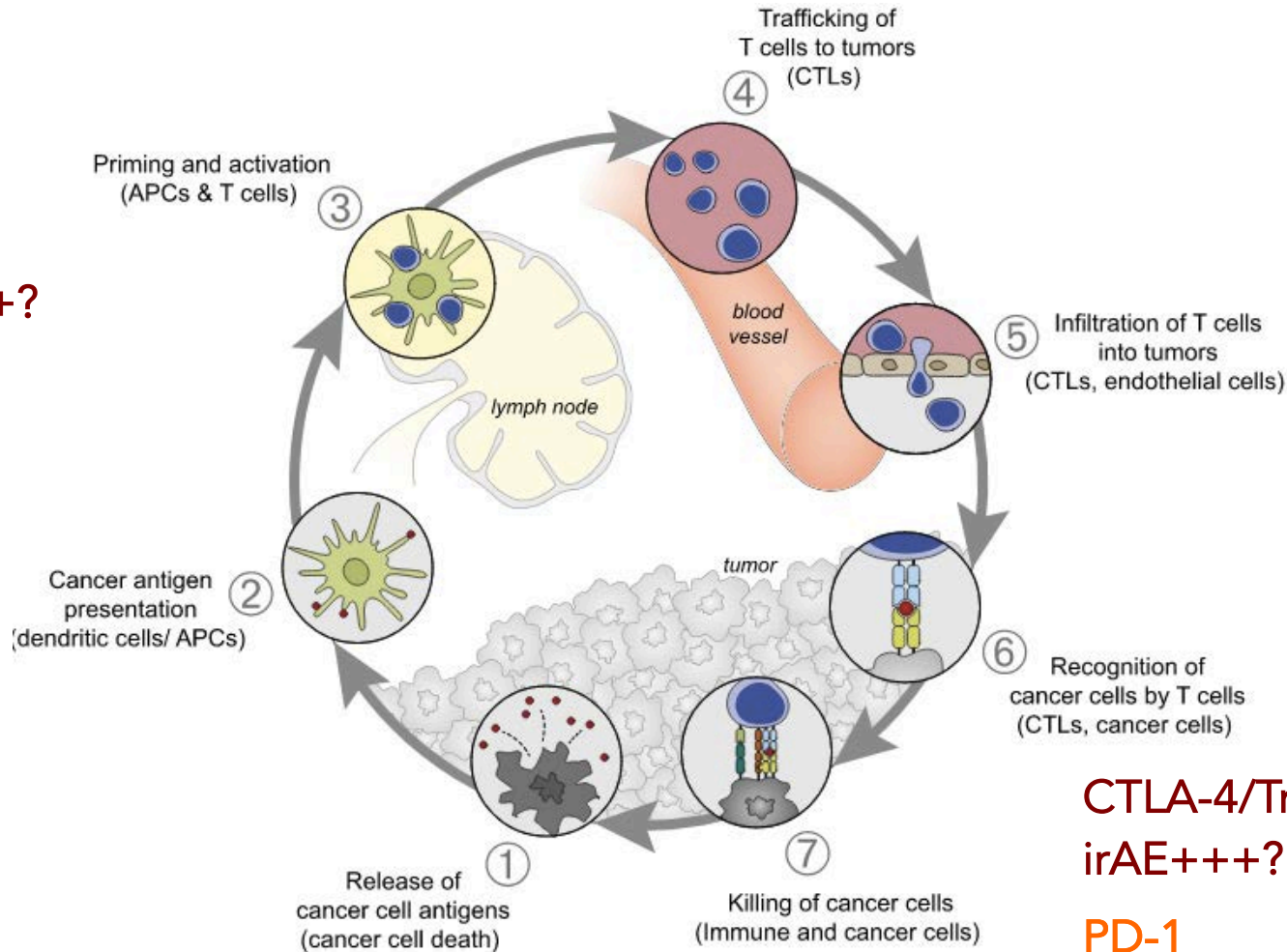
Proliferation of PD-1+ CD8 T cells in peripheral blood after PD-1-targeted therapy in lung cancer patients

Alice O. Kamphorst^{a,1}, Rathi N. Pillai^{b,1}, Shu Yang^{a,2}, Tahseen H. Nasti^a, Rama S. Akondy^a, Andreas Wieland^a, Gabriel L. Sica^c, Ke Yu^b, Lydia Koenig^b, Nikita T. Patel^b, Madhusmita Behera^b, Hong Wu^a, Megan McCausland^a, Zhengjia Chen^d, Chao Zhang^d, Fadlo R. Khuri^{b,3}, Taofeek K. Owonikoko^b, Rafi Ahmed^{a,4}, and Suresh S. Ramalingam^{b,4}



T cell control by immune checkpoints

CTLA-4
irAE+++?

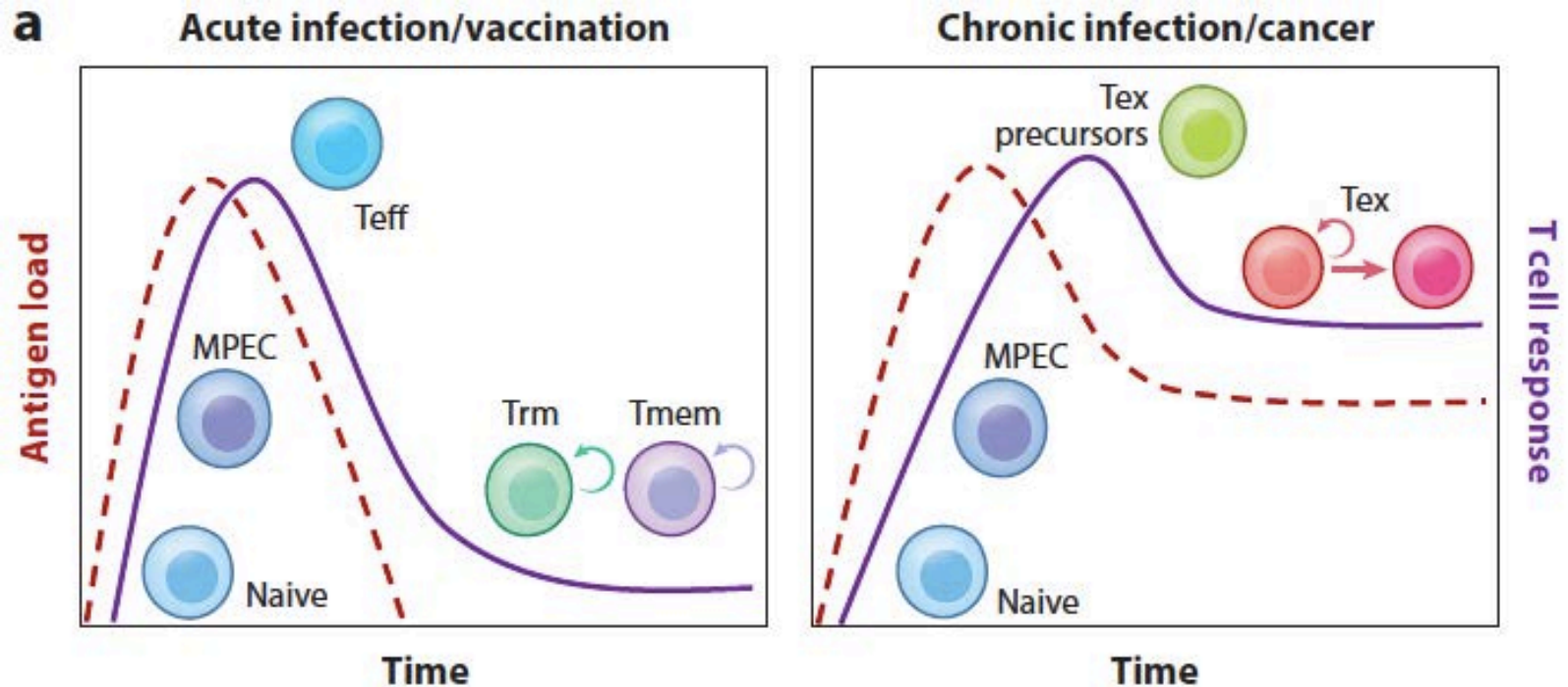


CTLA-4/Treg function
irAE+++?

PD-1

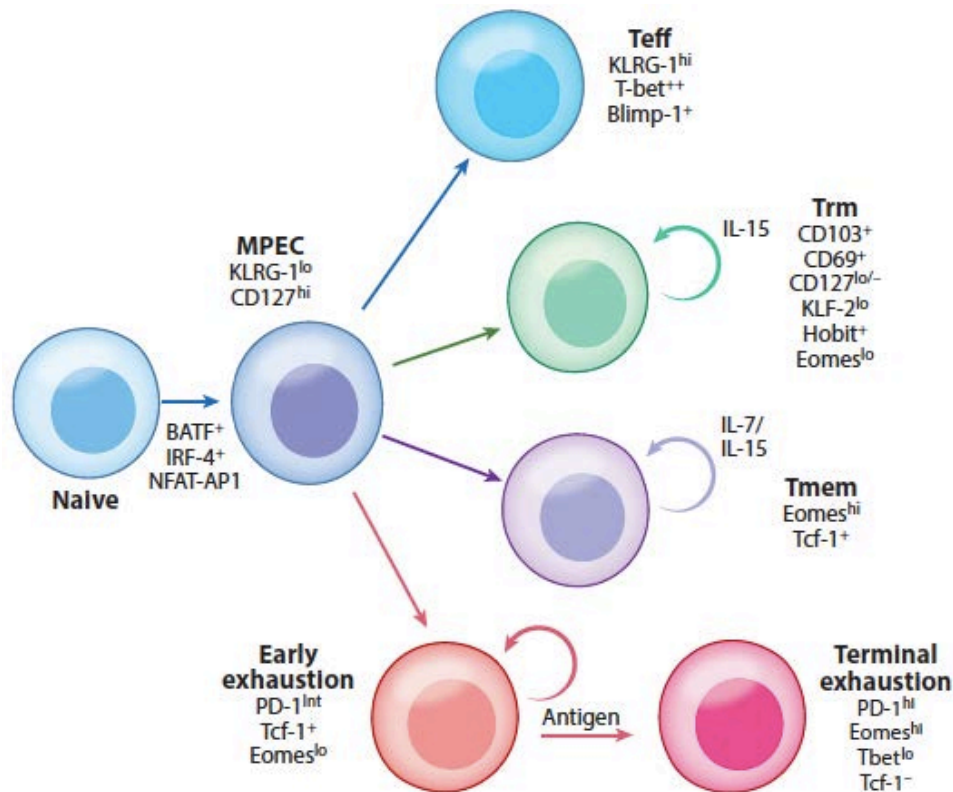
PD-L1=response?

Exhausted T cells and their reinvigoration



- ☑ Exhausted T cells could represent a CD8 T cell lineage, distinct from memory cells, resulting from chronic infection & cancer

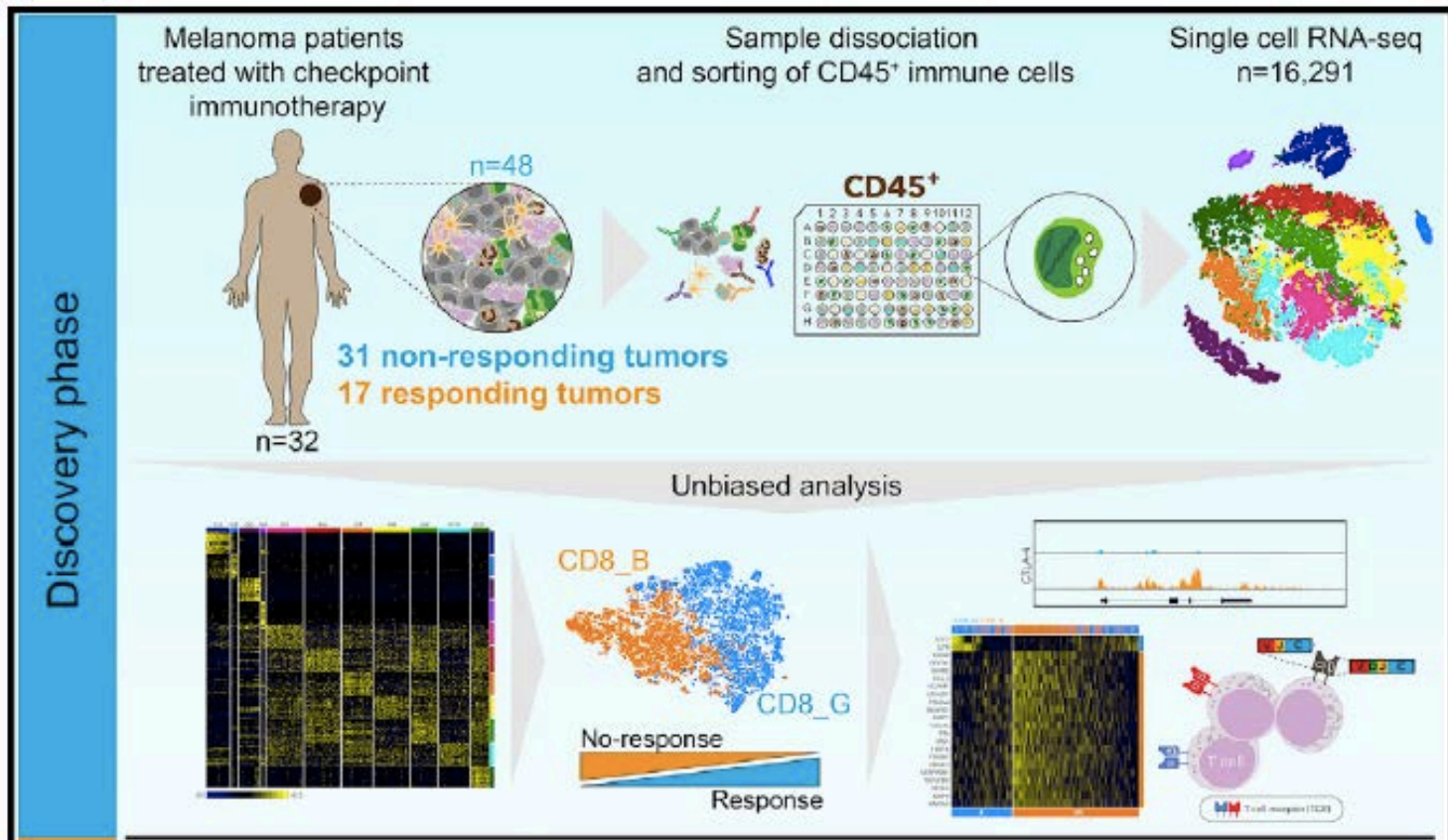
Exhausted T cells and their reinvigoration



- ✓ **Early exhausted:** PD-1^{int}, TCF-1⁺, TIM-3⁻
- ✓ **Terminally exhausted:** PD-1^{hi}, TCF-1⁻, TIM-3⁺

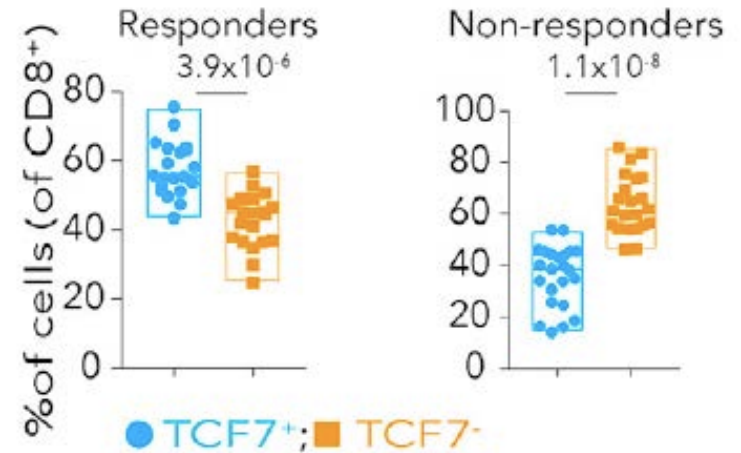
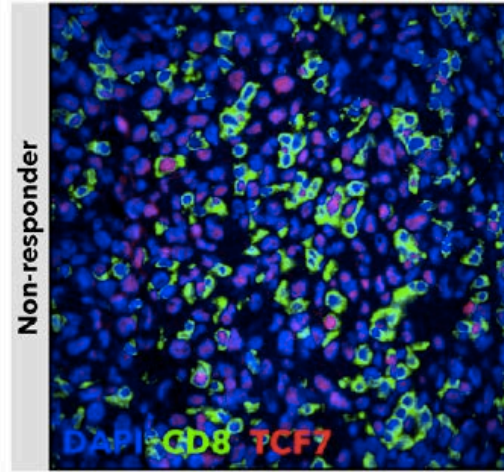
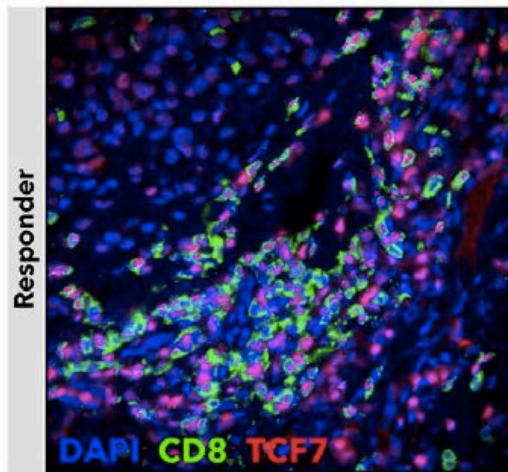
- ☑ Exhausted T cells could represent a CD8 T cell lineage, distinct from memory cells, resulting from chronic infection & cancer

Exhausted T cells in response to ICB



- ✓ Early exhausted = ?
- ✓ Terminally exhausted = ?

Exhausted T cells in response to ICB



- ✓ **Early exhausted** = response to ICB
- ✓ **Terminally exhausted** = unrelated to response

Exhausted T cells in response to ICB

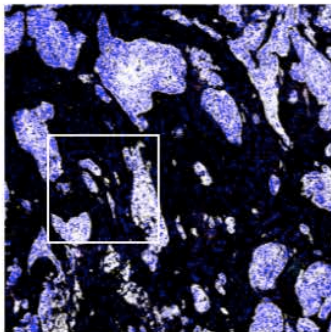
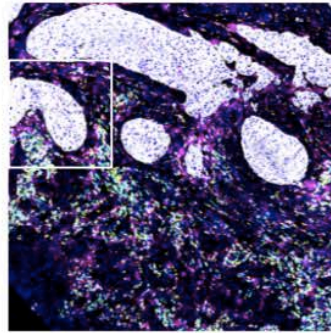
Nuclei

MNF116

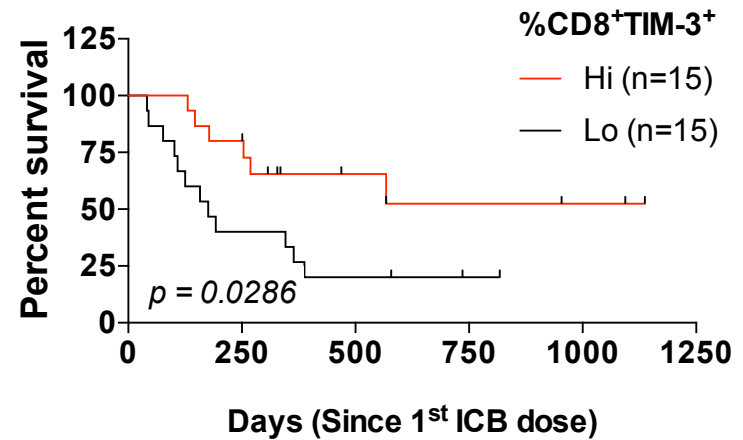
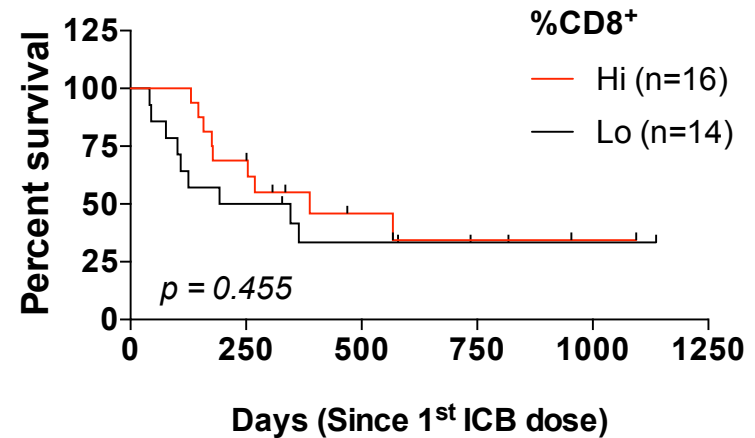
CD3

CD8

TIM-3



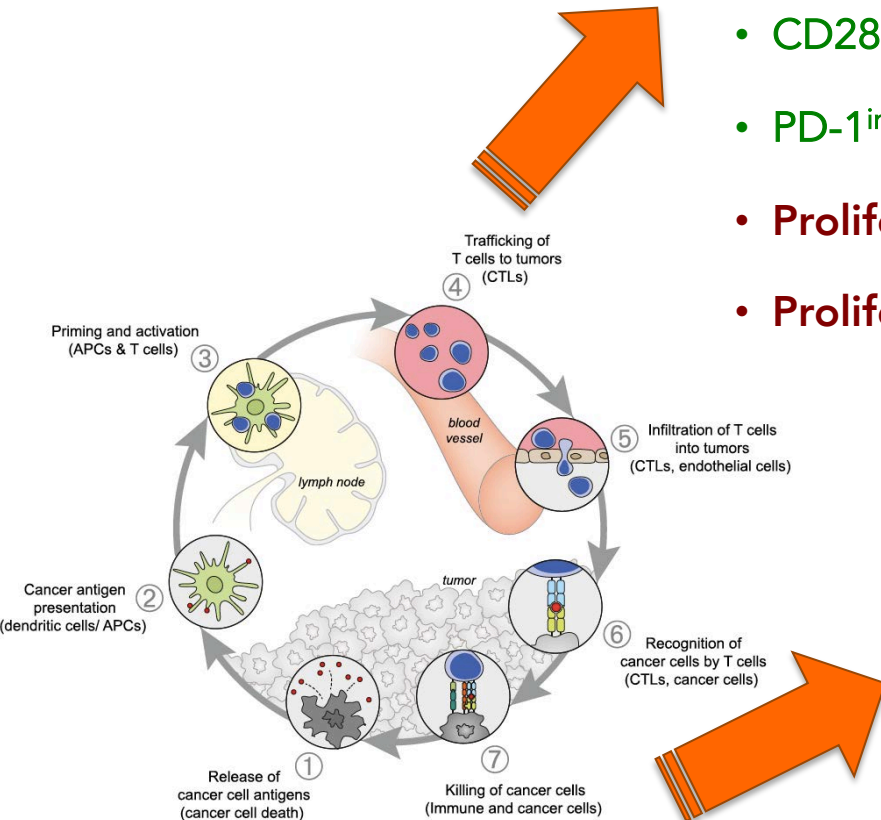
✓ **Terminally exhausted** = biomarker of response in head and neck cancer



Exhausted T cells in response to ICB

Circulating tumor-specific CD8 T cells

- CD28⁺
- PD-1^{int}TIGIT^{int}
- Proliferation enhanced *in vitro* by PD-1 inhibition
- Proliferate *in vivo* in response to PD-1/PD-L1 blockade?



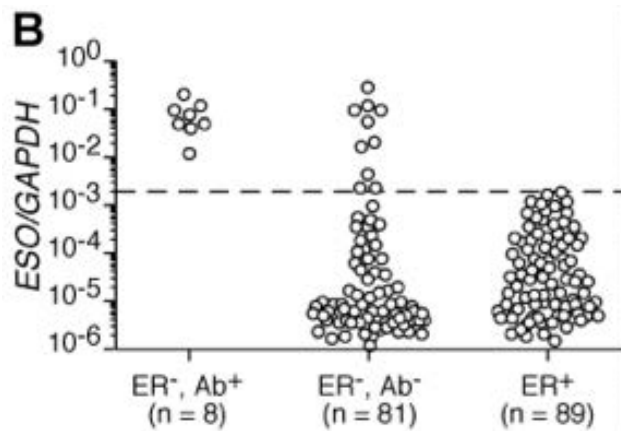
In situ tumor-specific CD8 T cells

- CD28^{+/-}
- PD-1^{hi}TIGIT^{hi}CTLA-4⁺TIM-3⁺CD39⁺ + T_{RM} markers
- Function restored *in vitro* by PD-1 inhibition
- Predictors of response to ICB

Where do we go from here?

☑ TMB = antigens recognized by T cells = response

✓ All patients with antigen⁺ tumors do not develop T-cell responses



Hamai A et al., Plos One 2011

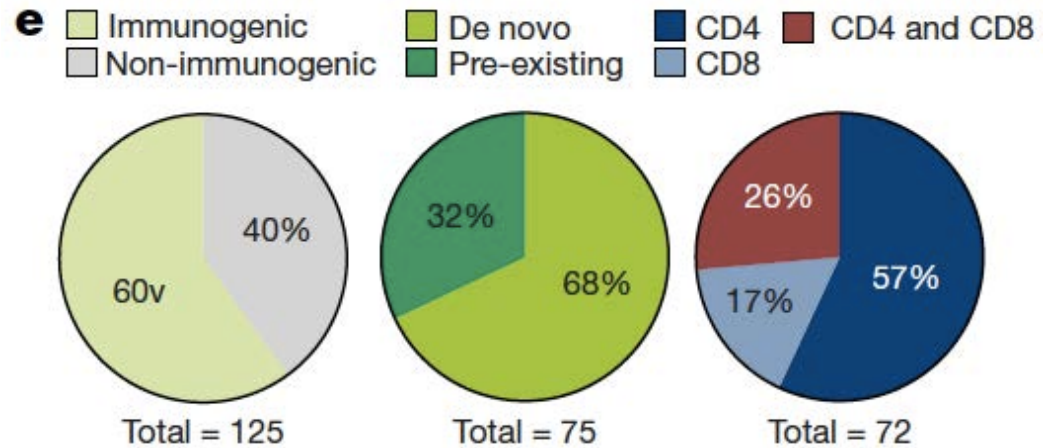
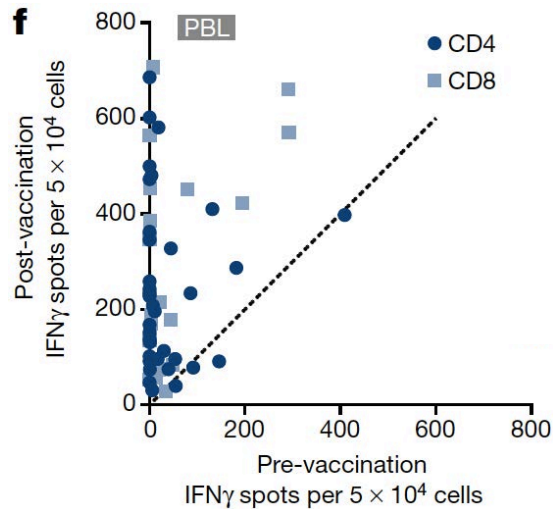
✓ = *a priori* targetable tumors but not directly with ICB

✓ How can we bring in an antigen-specific response = which combinations?

Stimulate a T-cell response & combine to ICB

☑ Vaccines

- ✓ Neoantigen-based personalized approach...but feasible



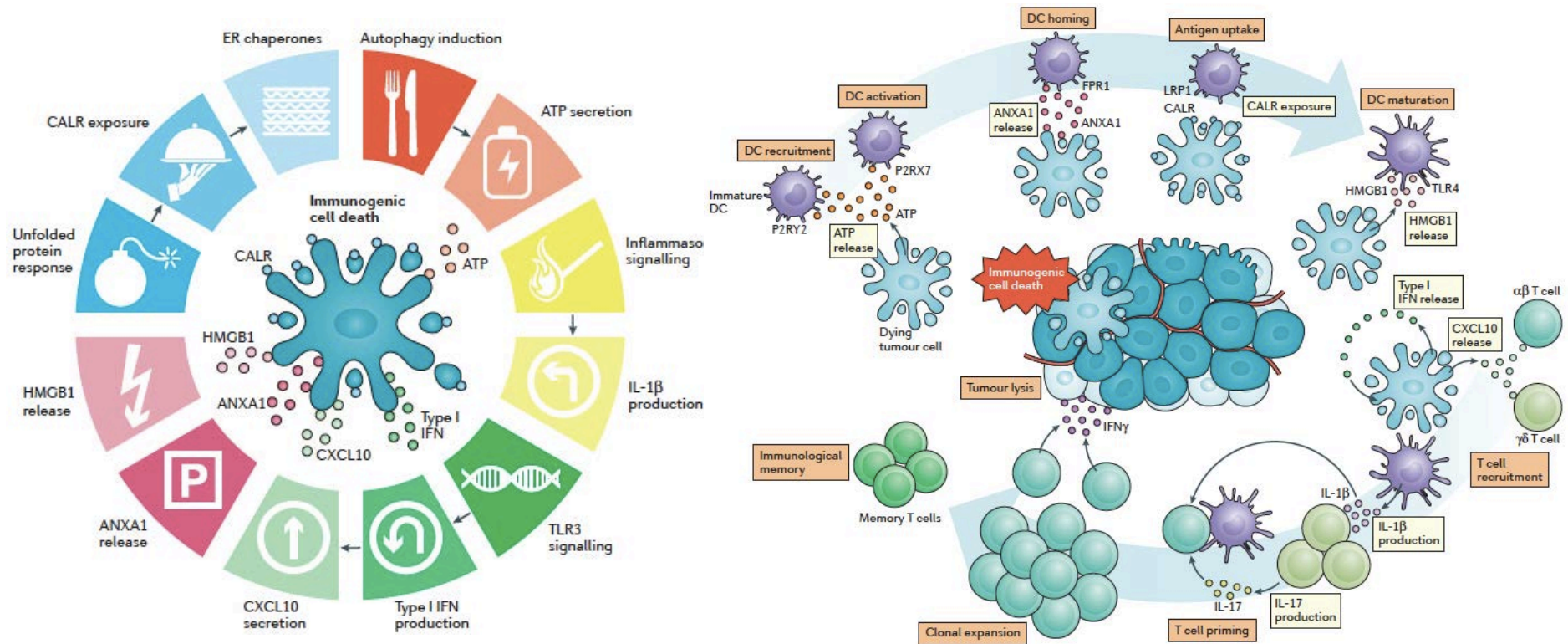
Sahin U et al., Nature 2017

- ✓ Shared antigens-based vaccines: CTA, HPV...

Stimulate a T-cell response & combine to ICB

☑ Chemo, radio, targeted therapies?

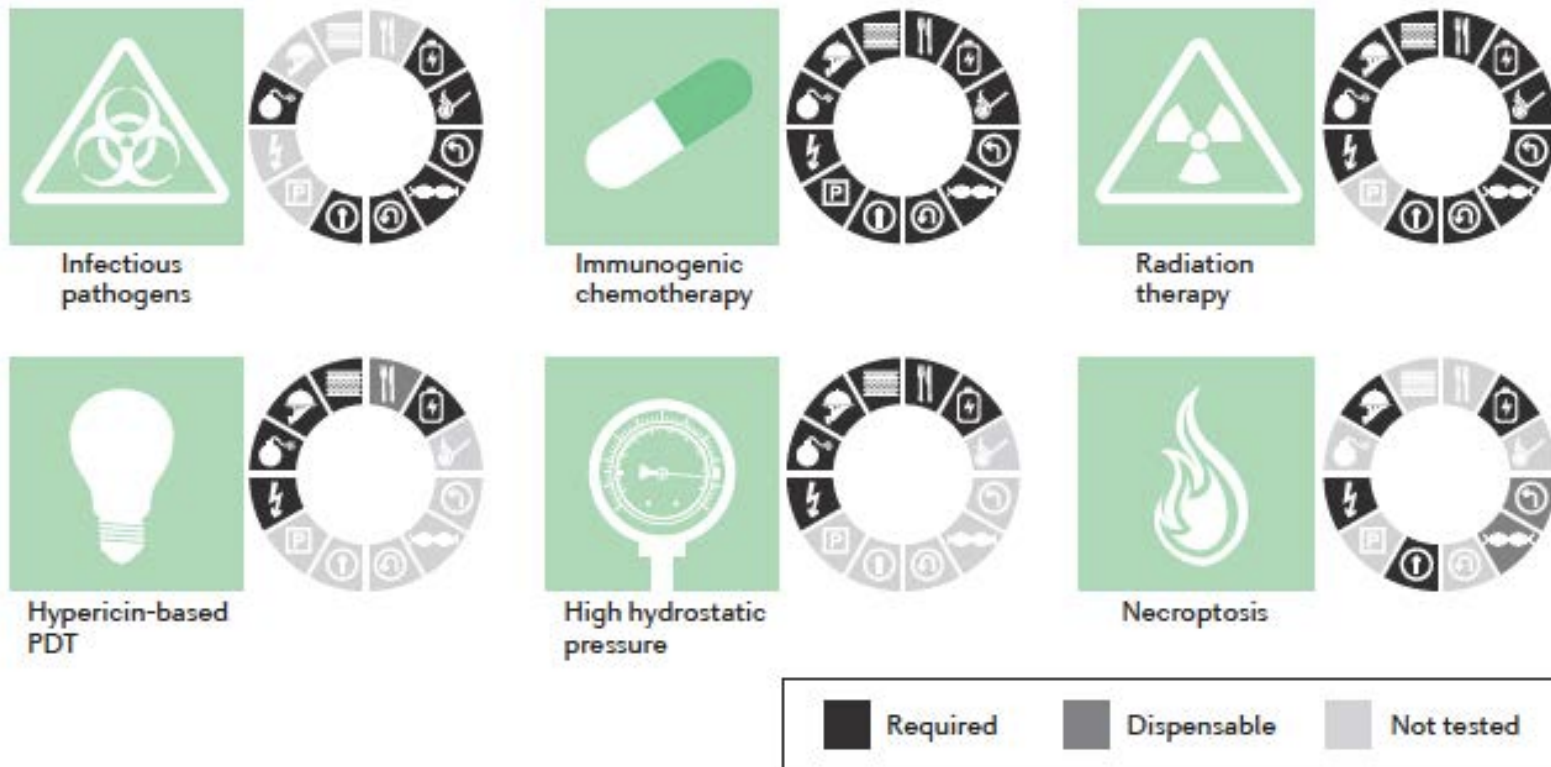
✓ Rational: immunogenic cell death



Stimulate a T-cell response & combine to ICB

☑ Chemo, radio, targeted therapies?

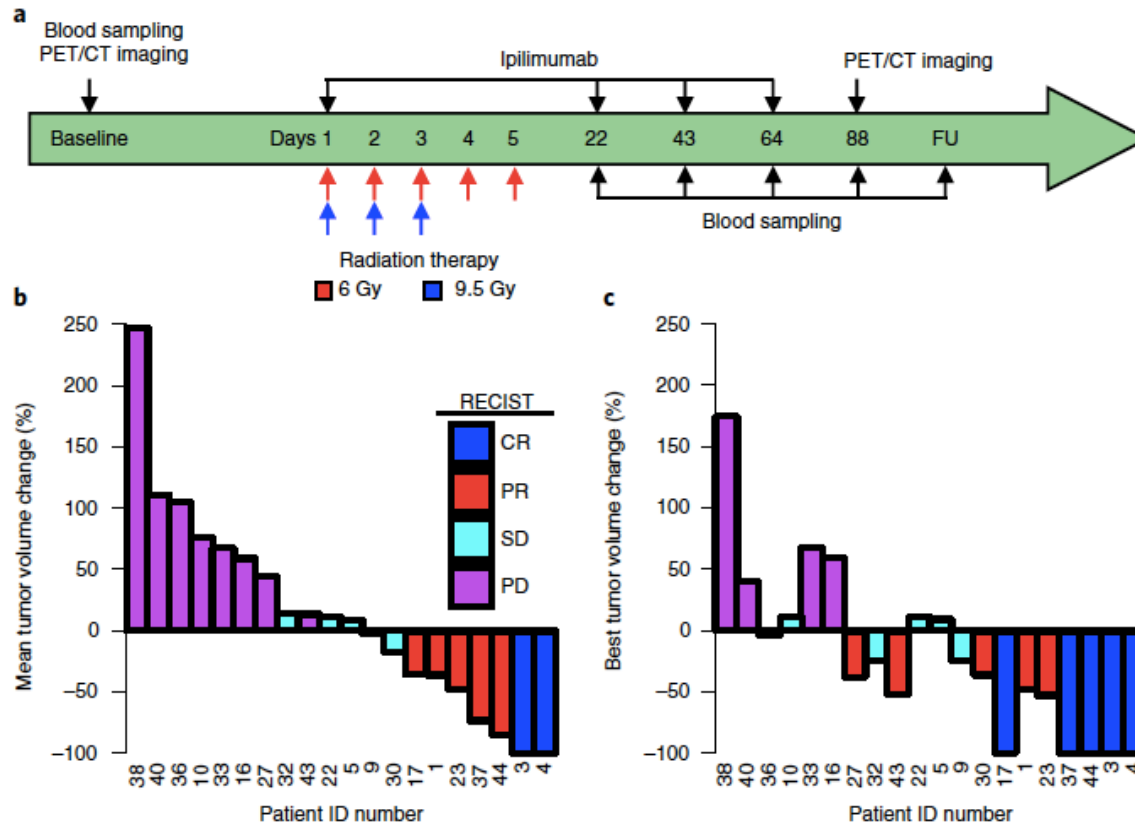
✓ Rational: immunogenic cell death



Stimulate a T-cell response & combine to ICB

☑ Chemo, radio, targeted therapies?

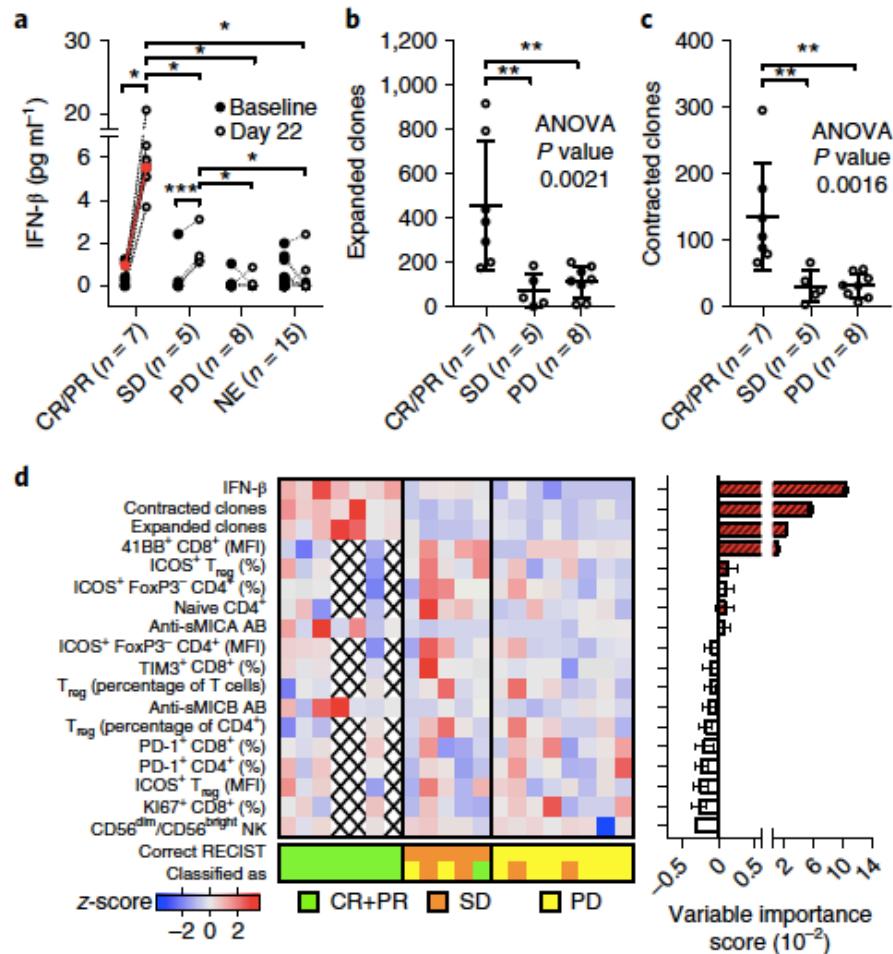
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Stimulate a T-cell response & combine to ICB

☑ Chemo, radio, targeted therapies?

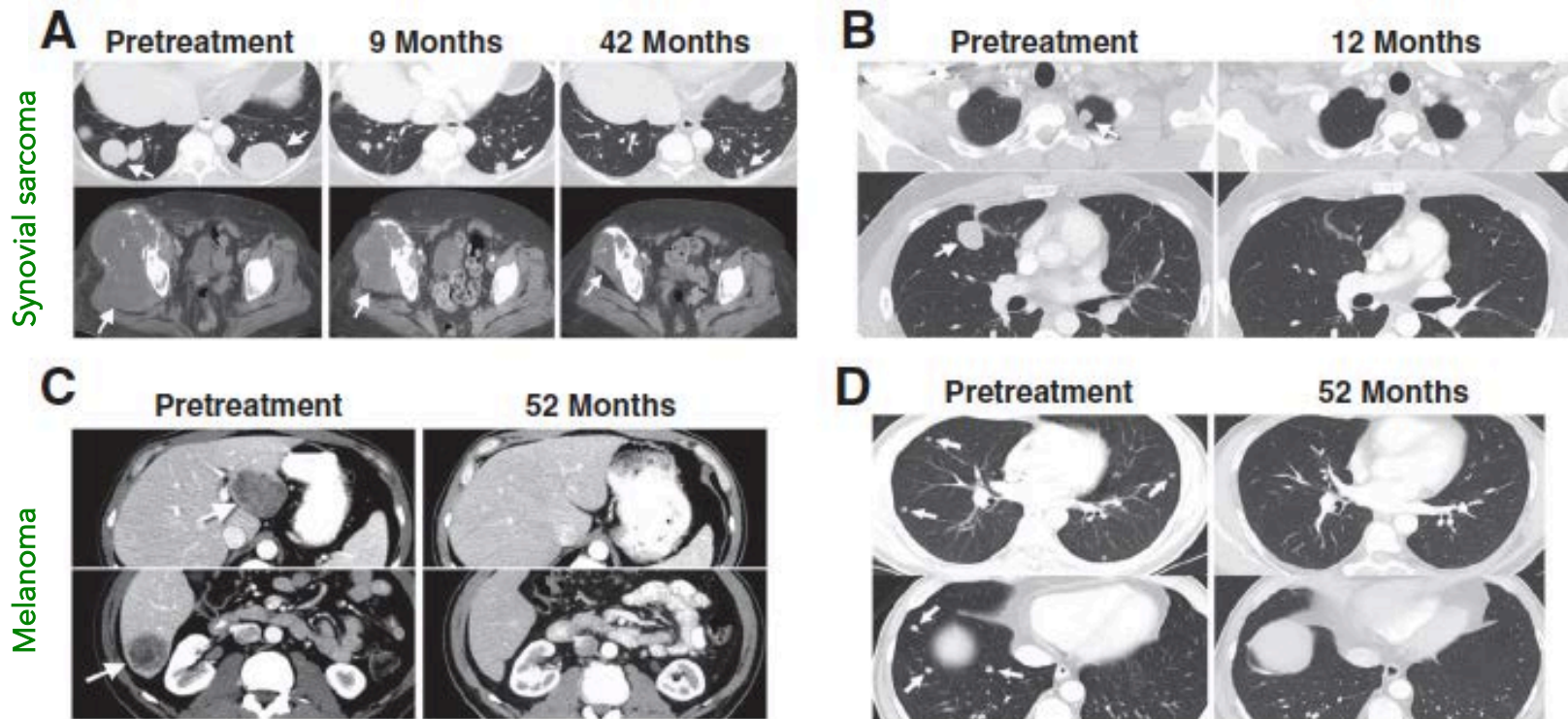
- ✓ Rational: immunogenic cell death



T-cell adoptive transfer, + ICB?

☑ TIL, transgenic TCR or CAR T

✓ Can be efficient



NY-ESO-1-specific ICR engineered T cells

Robbins PF et al., Clin Cancer Res, 2015

✓ Transferred T cells acquire exhaustion -> need to combine to ICB?

Where do we go from here?

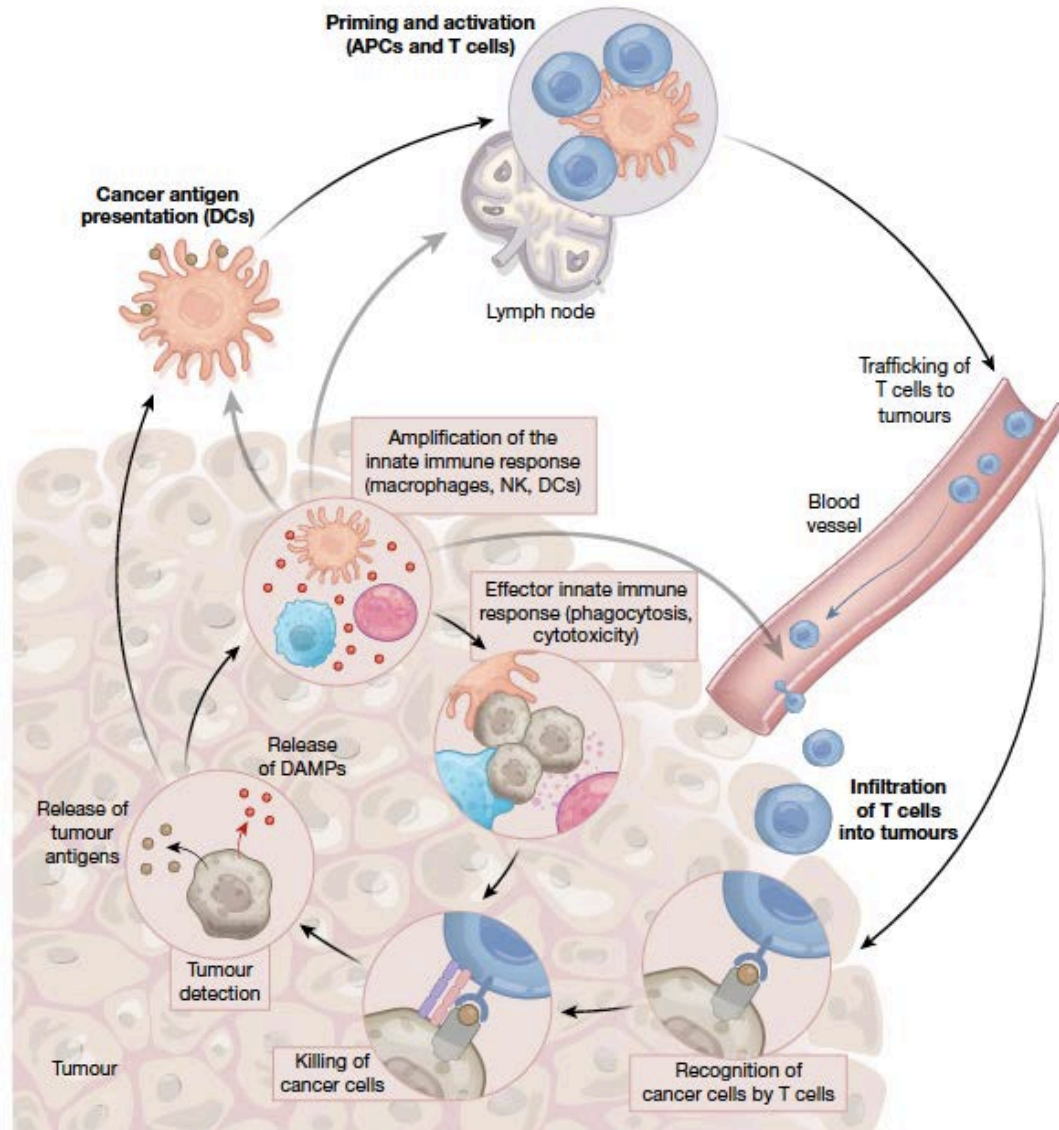
☑ Target more T-cell checkpoints?

- ✓ Anti-PD-1 + anti-CTLA-4 > anti-PD-1 alone
- ✓ Ongoing & future trials: anti-PD-1 + targeting TIM-3, TIGIT, VISTA, CD39...
- ✓ Study exhaustion to design the most rational combinations

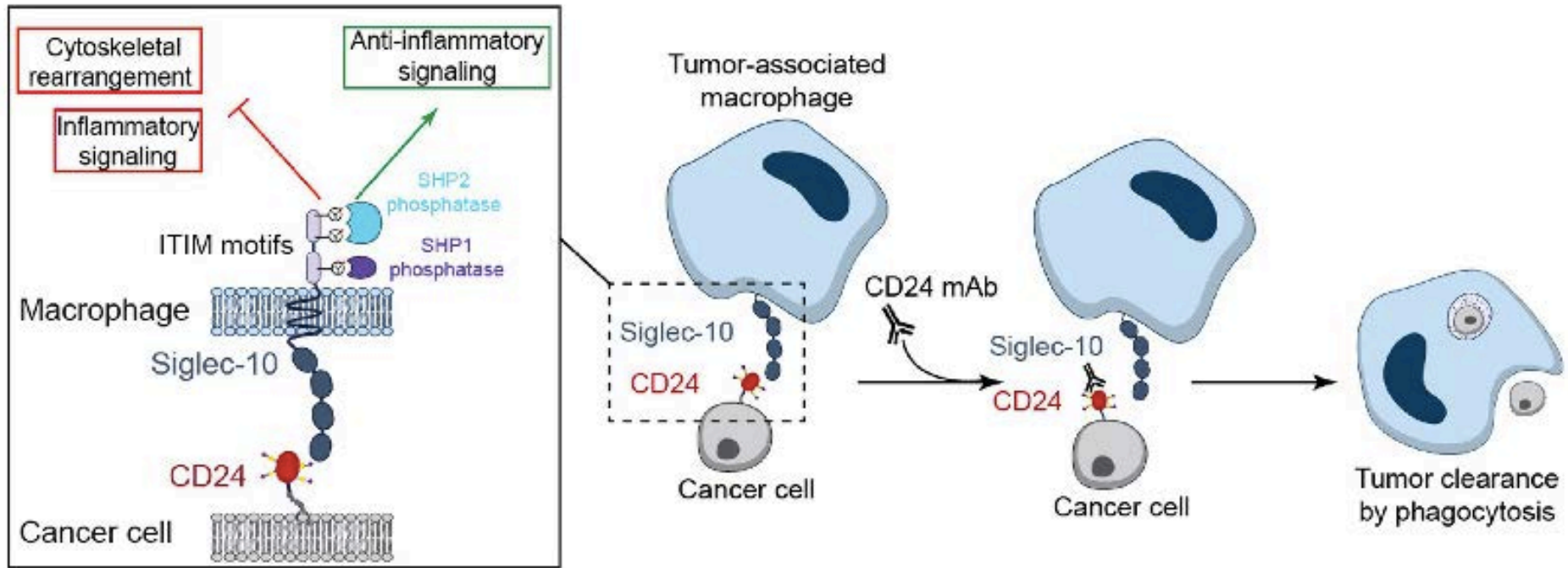
☑ Innate checkpoints?

- ✓ For better T-cell priming
- ✓ For direct innate anti-tumor effector functions (inhibit "don't eat me" signals, CD24, CD47...)

Innate immune checkpoints: the newcomers?

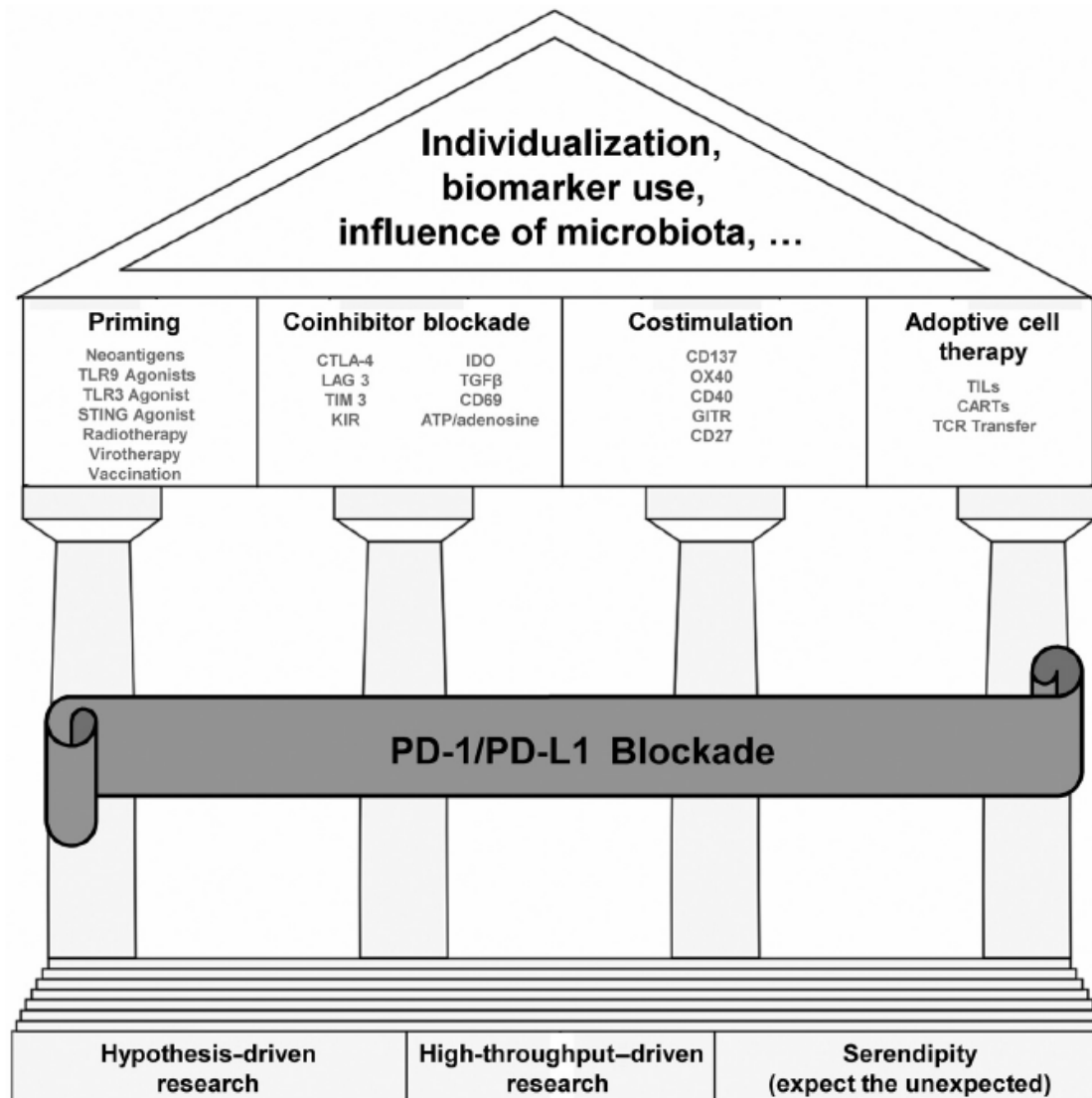


Innate immune checkpoints: the newcomers?



✓ Don't eat me signals: CD24 (Siglec-10), CD47 (SIRP α),

Where do we go from here?



Where do we go from here?

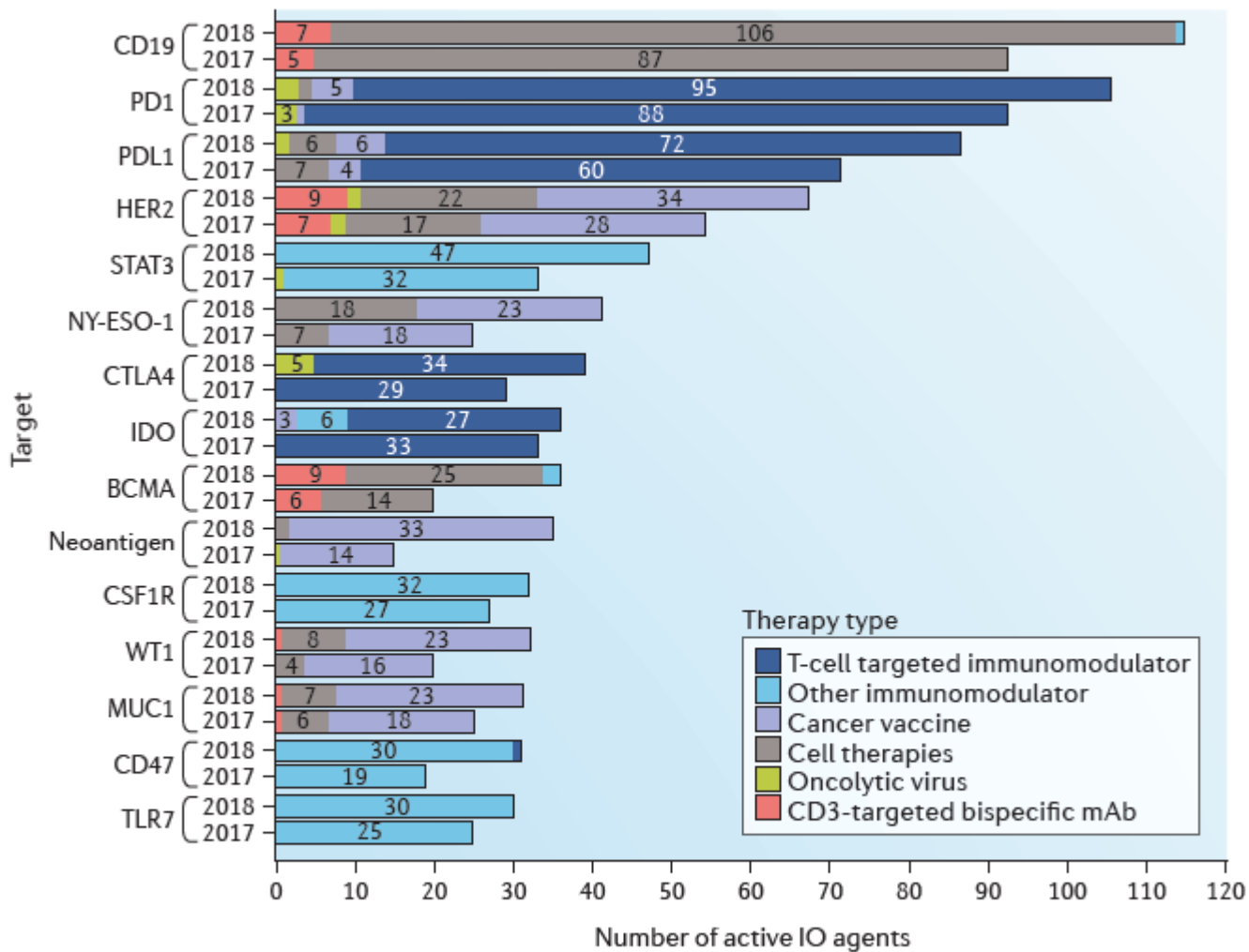


Figure 2 | **Trends in IO targets.** The top 15 of a total of 417 immuno-oncology targets in the current pipeline, a 50% increase since the previous survey. IO, immuno-oncology; mAb, monoclonal antibody.



"There's nothing I can do for you,
Ms. Brown - Your optimism is
incurable!"

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