Journées Enseignement et Recherche du GETUG

Quels arguments biologiques pour associer des anti-PD1/L1 entre eux et avec les traitements conventionnels ?

Paris, 30 mars 2018

Francesco Ricci
MD PhD

Unité d'Investigation Clinique
Département d'Oncologie Médicale
Institut Curie, Paris

francesco.ricci@curie.fr

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Quelle immunothérapie? Les Anti-PD1/L1

Association -> Synergie (1+1=3) vs Somme (1+1=2) vs Séquence (2+0=1+1)

Cancer urologiques et Anti-PD1/L1: est-ce qu'on pouvait faire mieux?

Kidney Cancer

NCCN Evidence Blocks™

Version 3.2018 — February 6, 2018

NCCN.org

FIRST-LINE THERAPY
(alphabetical by category and preference)

- Clinical trial
- Pazopanib (category 1, preferred)
- Sunitinib (category 1, preferred)
- Bevacizumab + interferon alfa-2b (category 1)
- Temsirolimus (category 1 for poor-prognosis patients,[h] category 2B for selected patients of other risk groups)
- Axitinib
- Cabozantinib (for poor- and intermediate-risk groups)[i]
- High-dose IL-2 for selected patients[j]
- Active surveillance for select, asymptomatic patients[k]

Bladder Cancer

NCCN Evidence Blocks™

Version 3.2018 — March 14, 2018

NCCN.org

	First-line systemic therapy for locally advanced or metastatic disease (Stage IV)
Cisplatin eligible	Preferred regimens • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	Preferred regimens • Gemcitabine and carboplatin[11] • Atezolizumab[12] • Pembrolizumab[13] Other recommended regimens • Gemcitabine[14] • Gemcitabine and paclitaxel[15]

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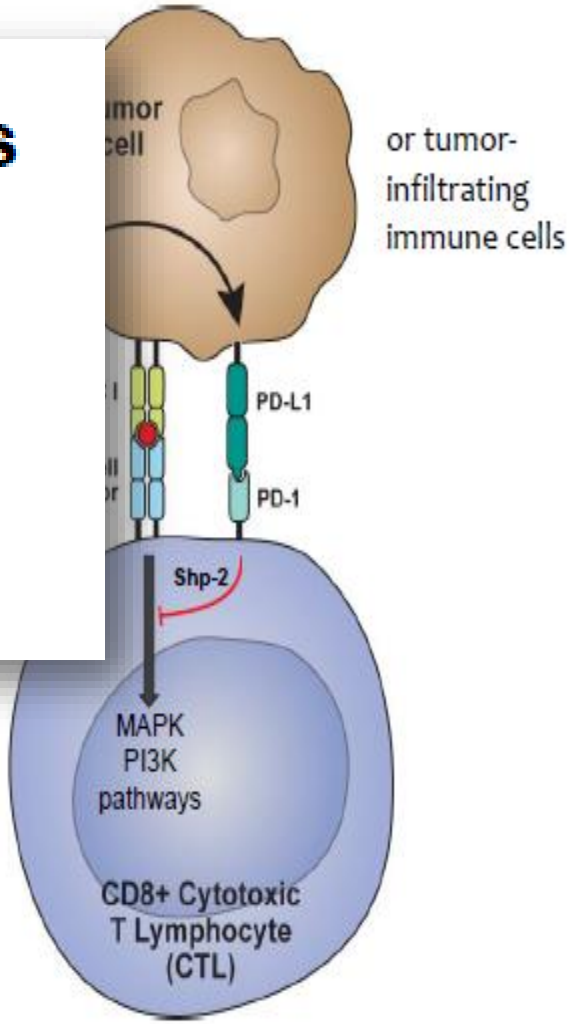
Cancer urologiques et Anti-PD1/L1

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

- PD-L1/PD-1 interaction inhibits T cell activation, effector functi immune home
- Tumors & surr regulate PD-L1 cell activity
- Blocking PD-L1/PD-1 restores or prevents loss of T effector function

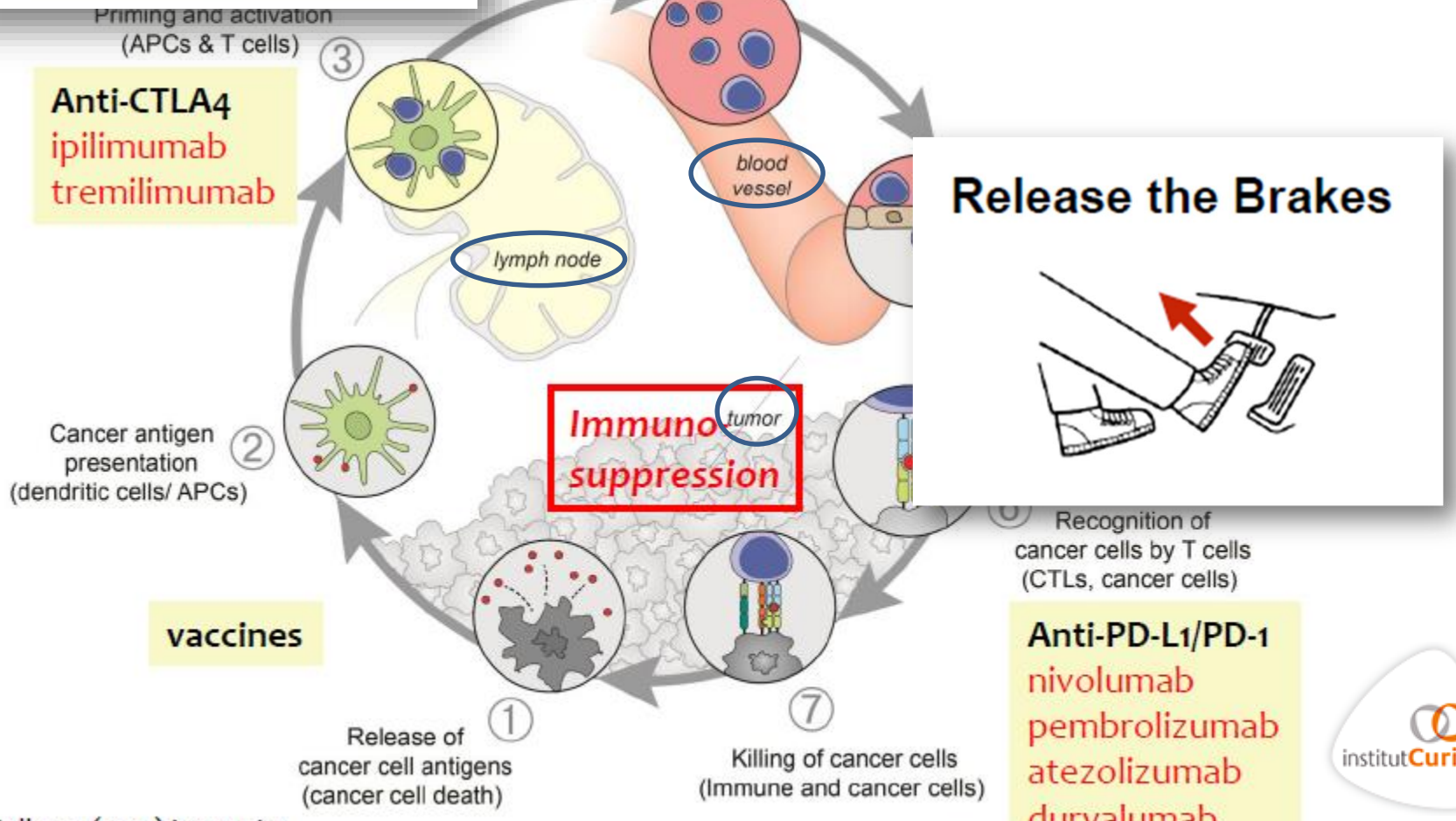


Mellman I, Cancer Immunology

W[illegible]: immunosuppression is a rate limiting st[illegible]umor immunity*

*for some patients

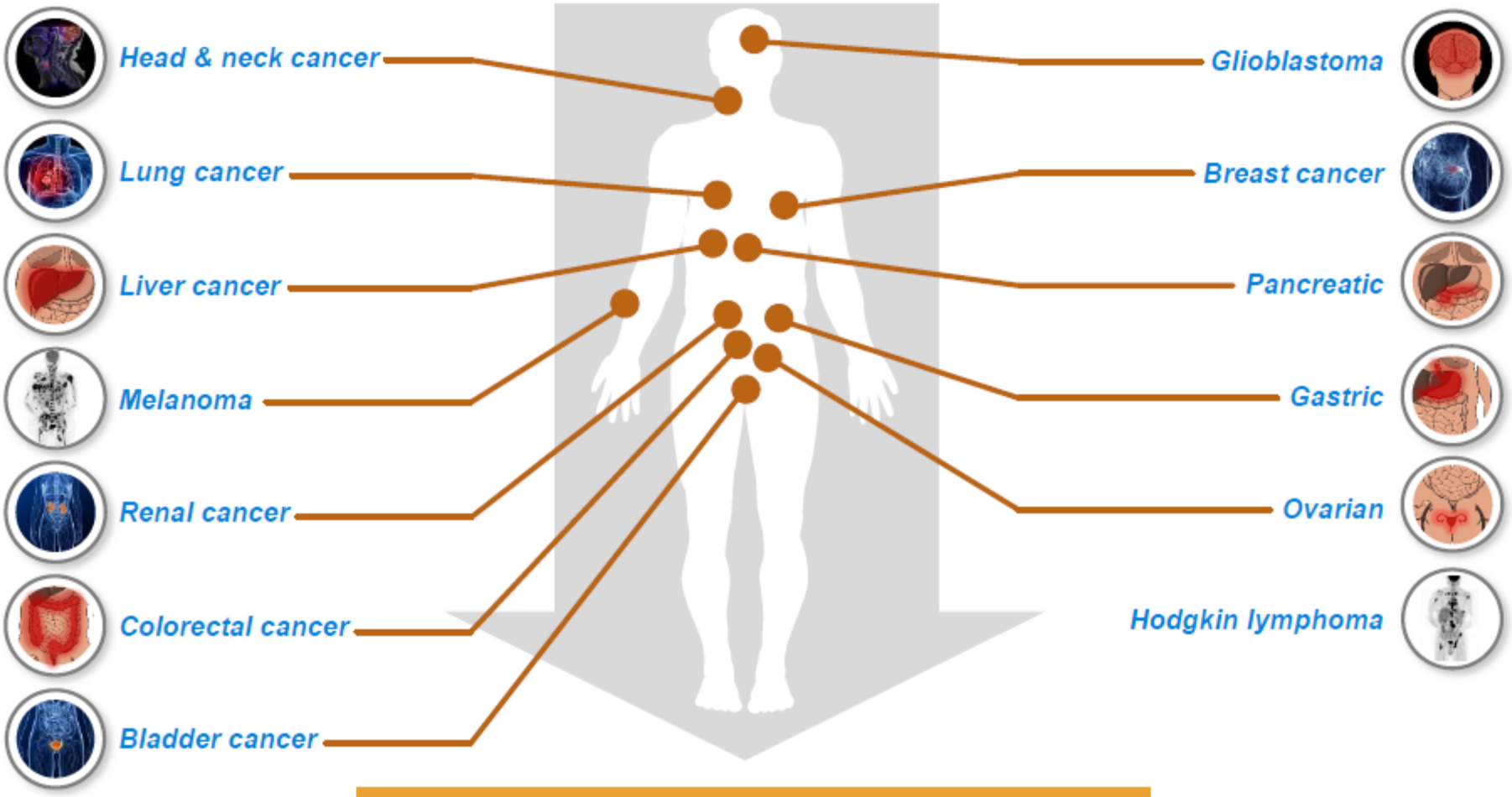
Step on the Gas



Release the Brakes

Chen & Mellman (2013) Immunity

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



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

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How to do it better?

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

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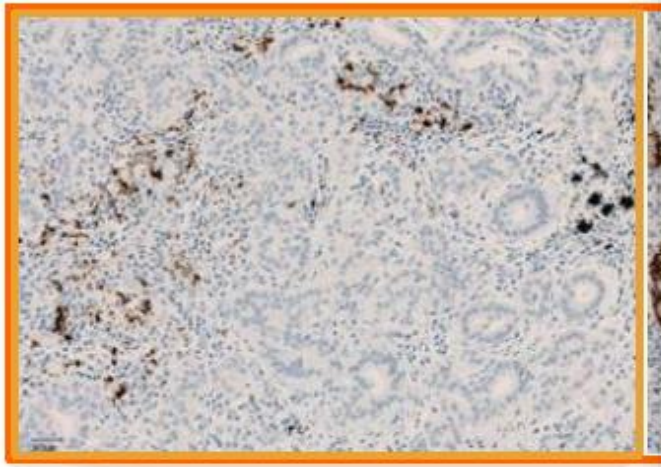
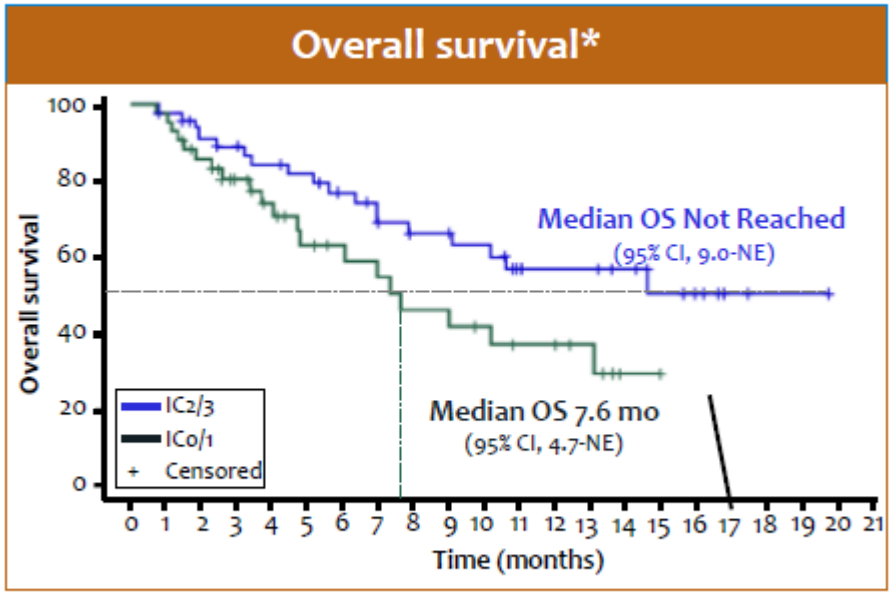
1) PD-L1 expression predicts clinical response: an imperfect but interesting biomarker

Immune cells (ICs)



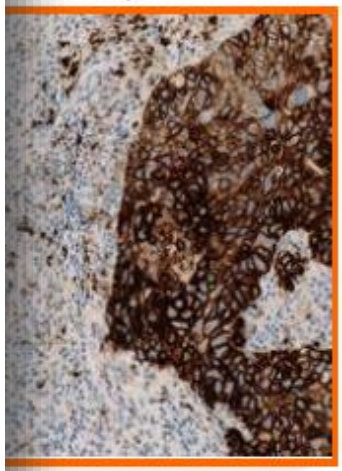
Predictive of benefit in bladder cancer (ORR/OS)[1]

Bladder cancer (IC only)



Rosenberg et al (2015) ECC

mmune cells nd ICs)



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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Challenges

- Pronostique vs prédictive?
- Homogénéité Inter-labs?
- Tumeurs ≠ -> Expression ≠
- Cut-offs?
- ICs vs TCs?

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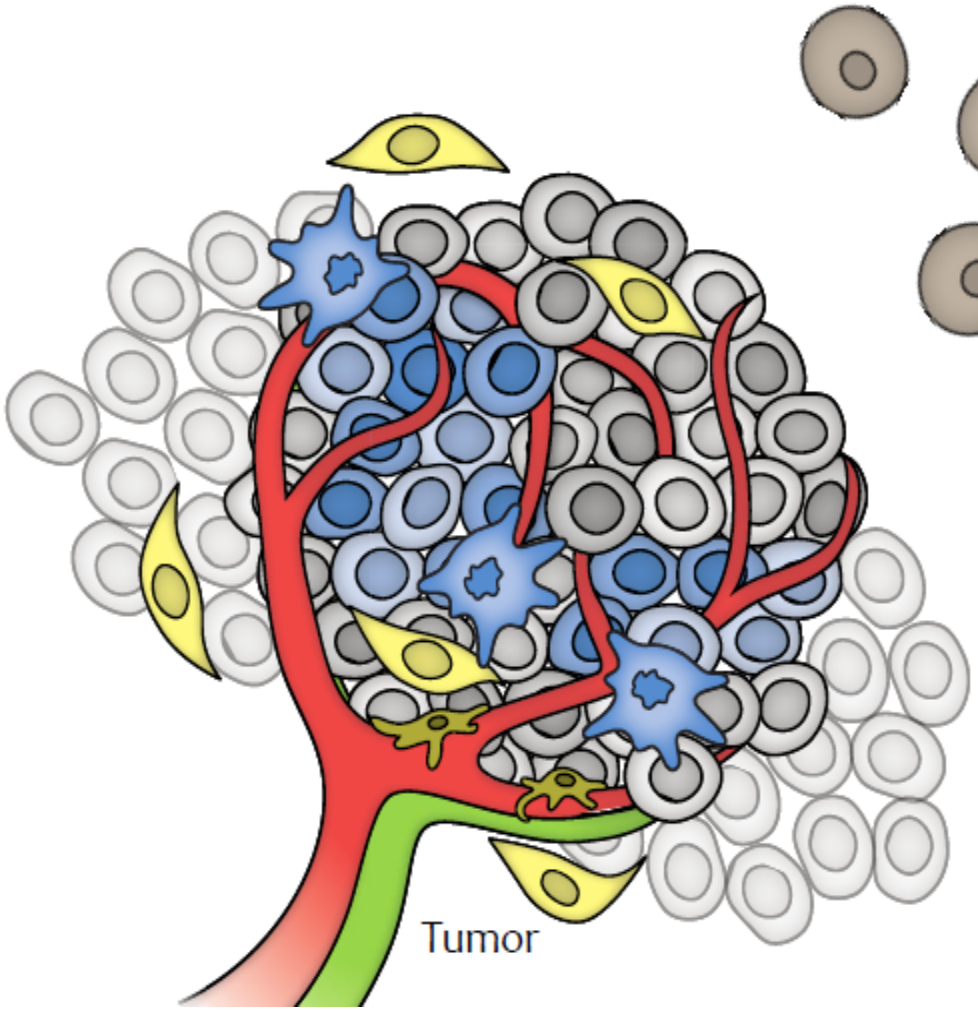
The predictive power of PD-L1+ IC's suggests a special role for infiltrating immune cells in anti-tumor T cell function

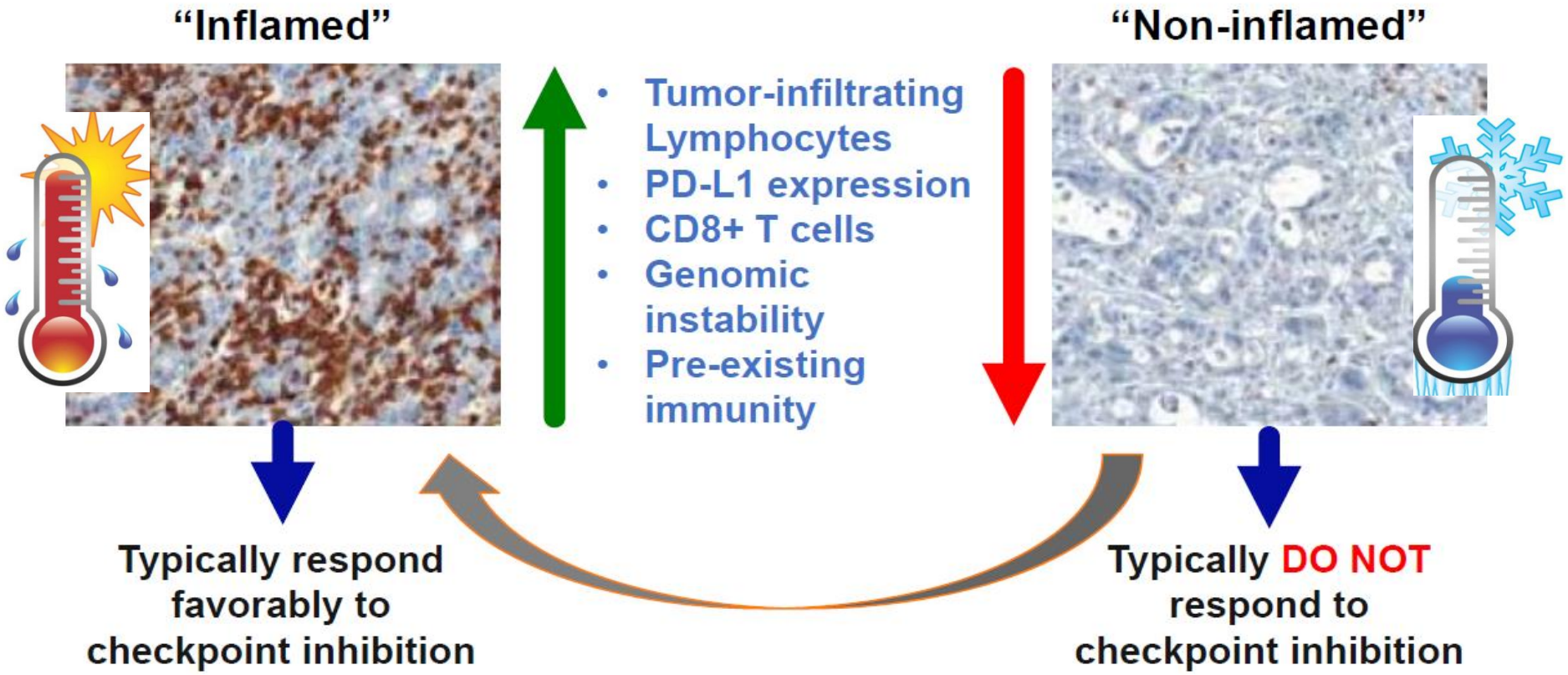
* Taube et al (2012) Science Transl. Med.



- 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?

Mellman I, Cancer Immunology

PD-L1/PD-1 targeted therapies work best in inflamed tumors vs. non-inflamed tumors



Converting from 'non-inflamed' to 'inflamed' is likely to be only 1 piece of the puzzle….

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2 and 3) To identify combinations that extend the depth and breadth of response to αPD-L1/PD-1 -> How Can we interact with the Immune System? New targets?

≠ TOXICITY

Release the Brakes

Block Checkpoint Inhibitors

PD-1 or PD-L1 antibodies
OX40 antibodies
Soluble LAG-3
…

Step on the Gas

Expand or Bring T cells into tumour

+ anti-CTLA-4
+ others immune activating Ab
+ cytokines
+ TLR agonists
+ IDO inhibitors
+ Targeted therapies
+ …

Fill the Tank

Generate Effectors

Vaccines
Oncolytic virus
Adoptive Transfer
CAR
Radiotherapy
…

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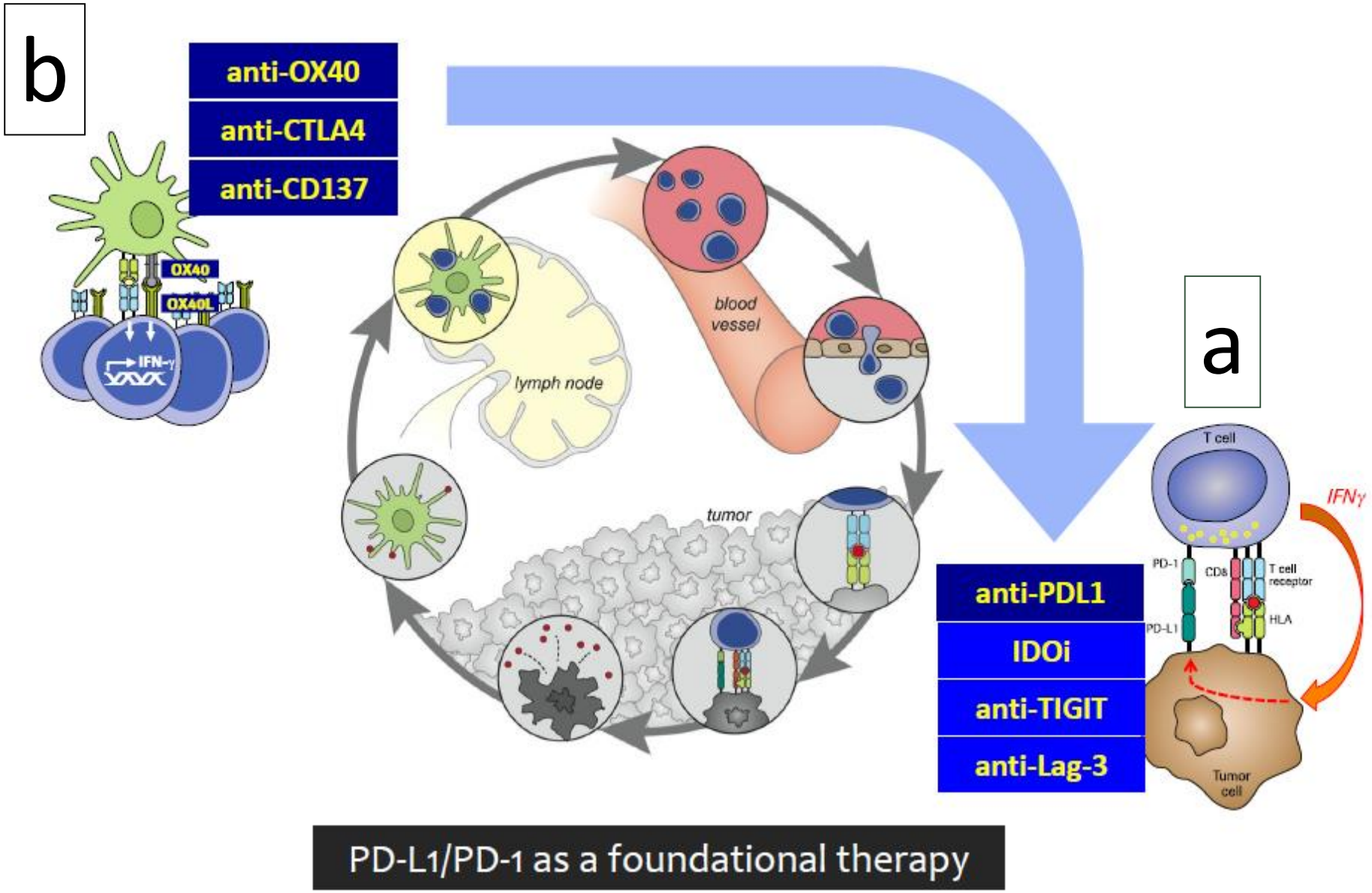
Immune doublets: αPD-L1/PD-1 + agonist (a+b) vs αPD-L1/PD-1 + second negative regulator (a+a)

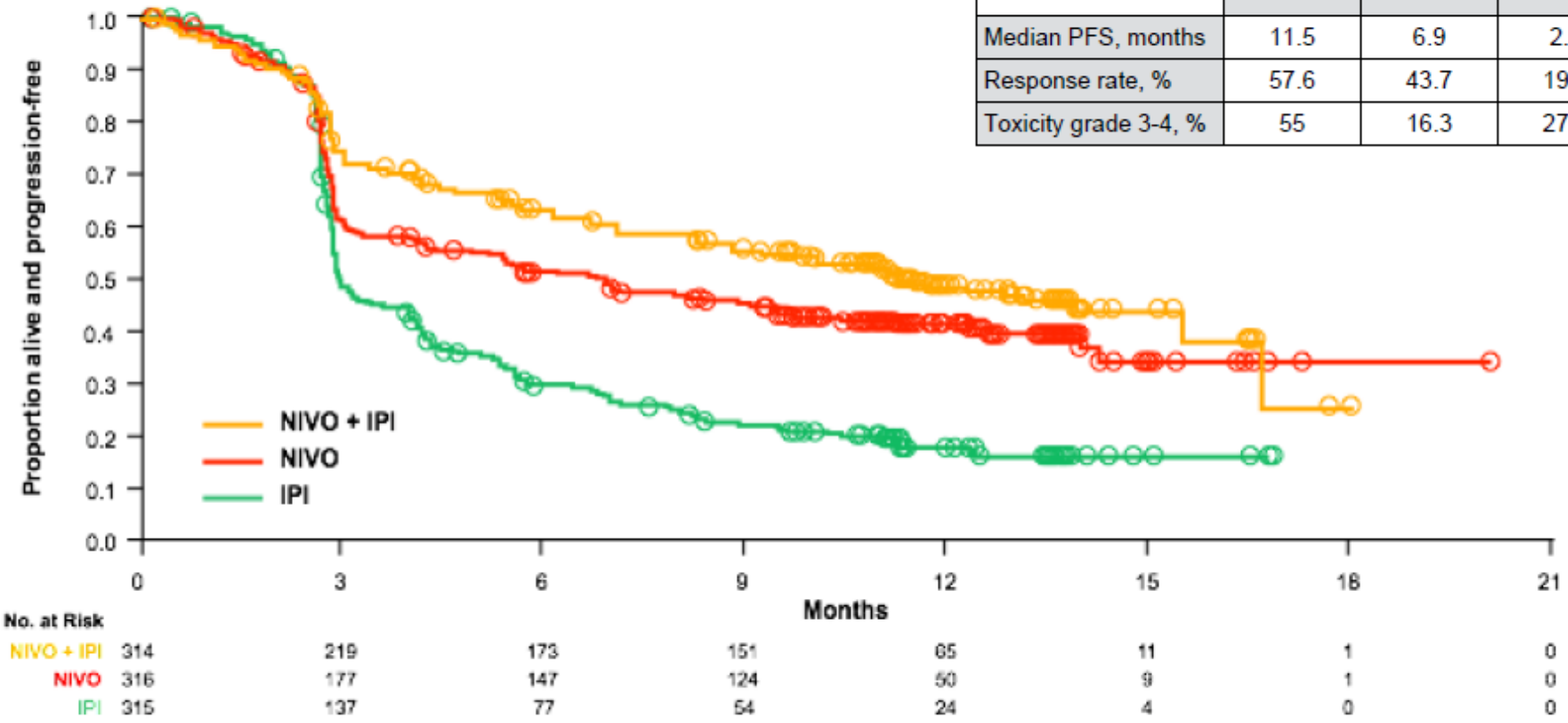


PD-L1/PD-1 as a foundational therapy

CA209-067 : Combination better than monotherapy ?

a+b

	IPI + NIVO (n=314)	NIVO (n=316)	IPI (n=315)
Median PFS, months	11.5	6.9	2.9
Response rate, %	57.6	43.7	19.0
Toxicity grade 3-4, %	55	16.3	27.3

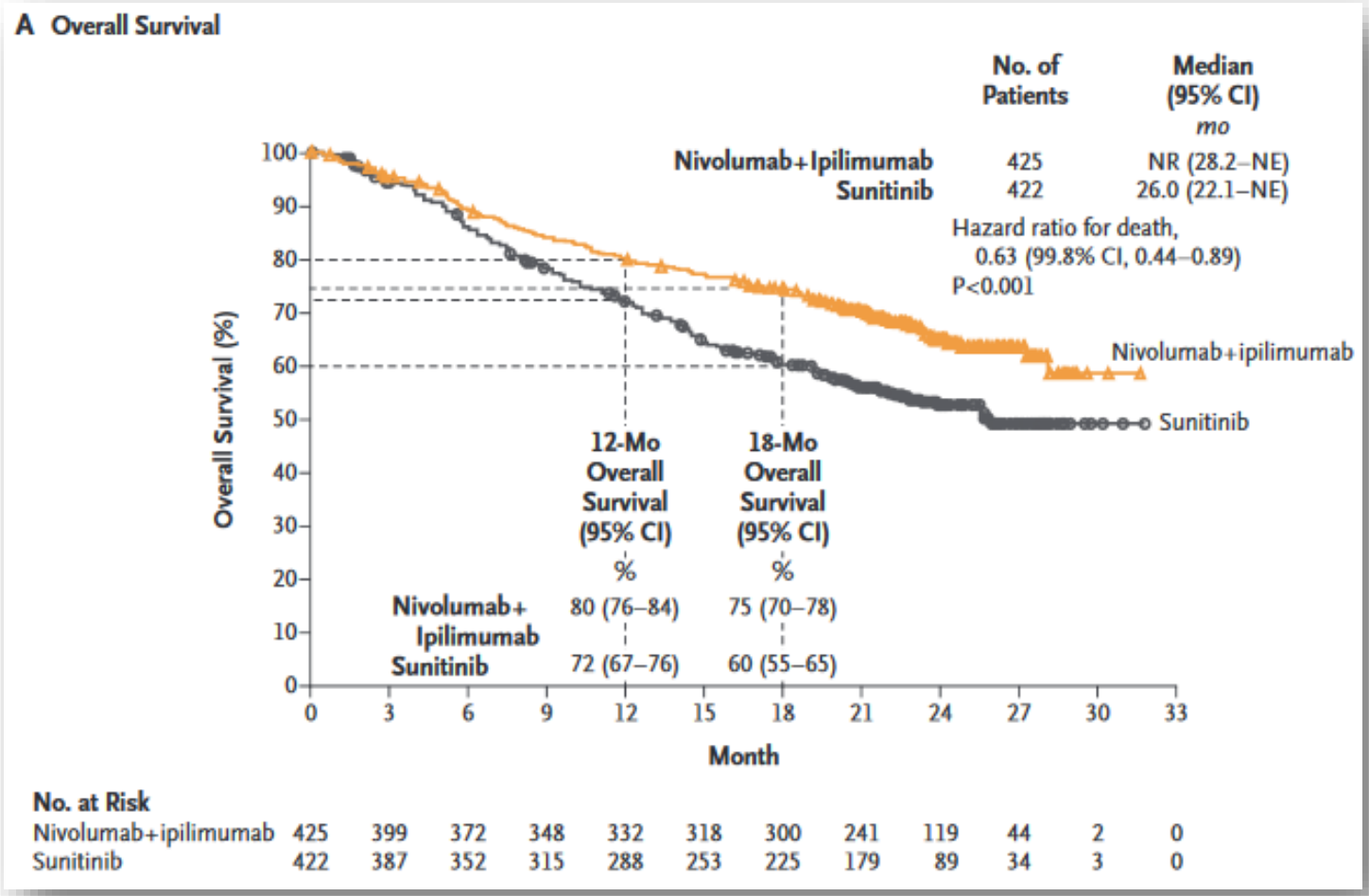


Larkin NEJM 2015

The NEW ENGLAND JOURNAL of MEDICINE

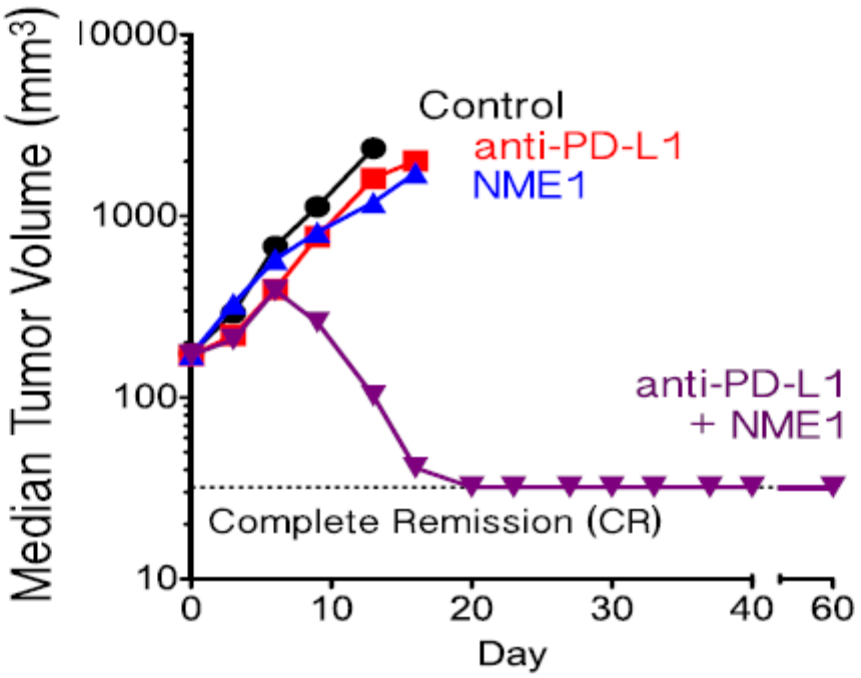
ORIGINAL ARTICLE

Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma



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

a+a



R. Johnson et al (2014) Cancer Cell

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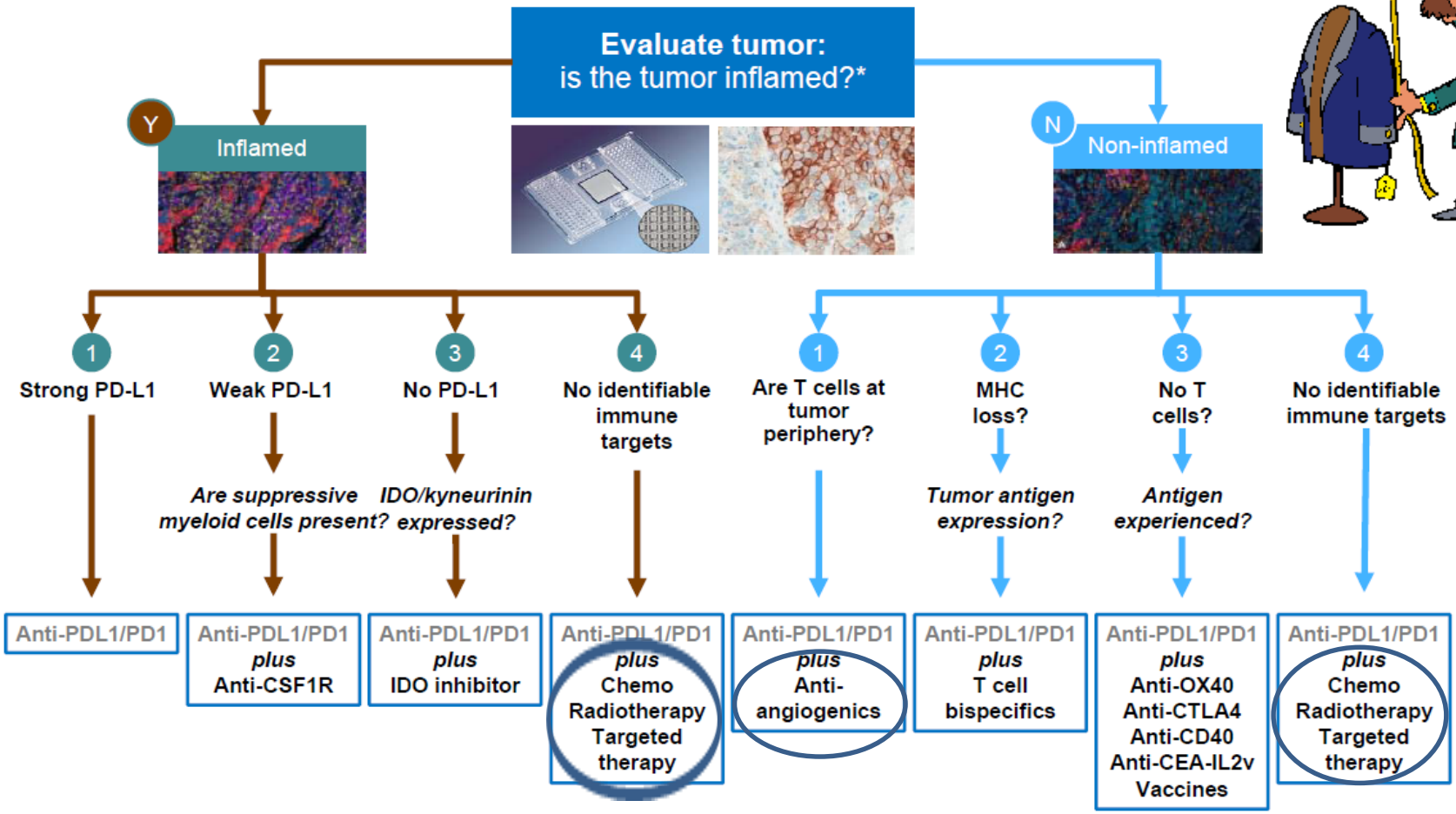
Tailoring immunotherapies

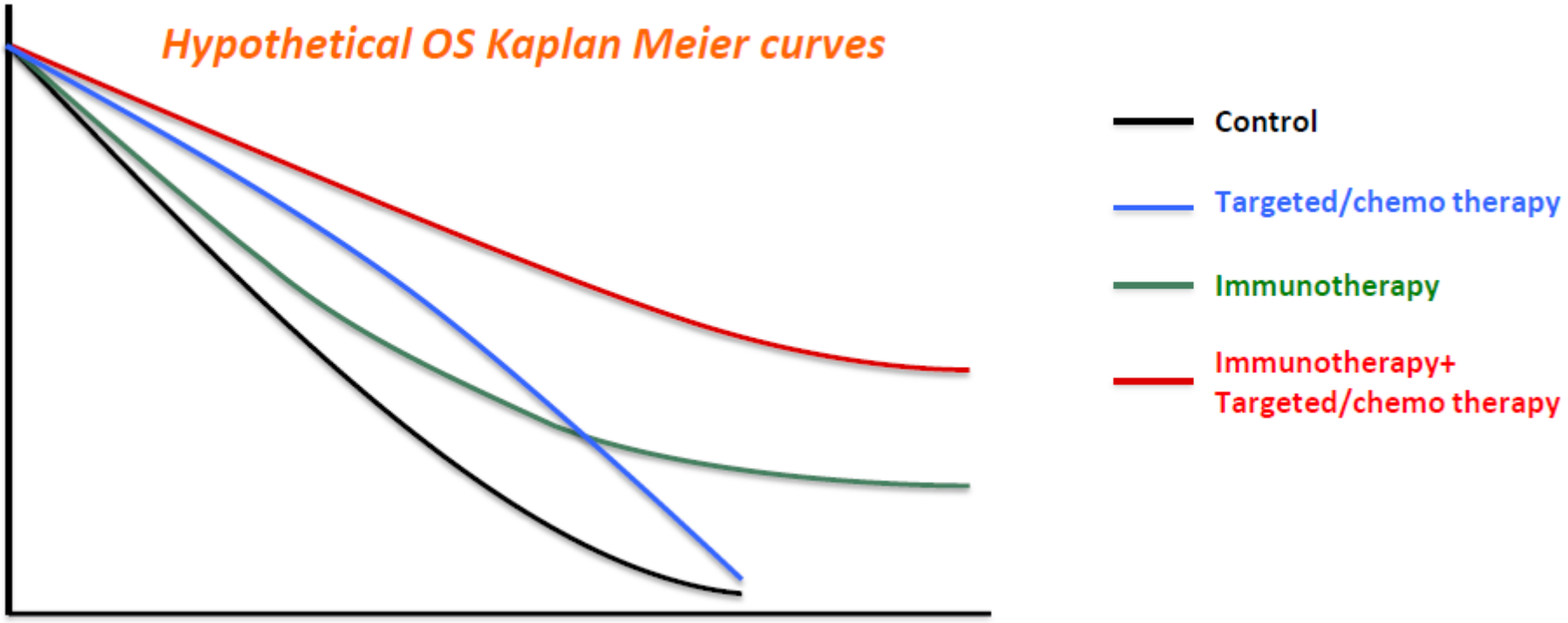
Vision: personalized cancer immunotherapy algorithms

*Possible hypothetical algorithm:



Chen CRI EATI CIMT AACR 2015

Combinations of immunotherapeutics with Chemo/targeted therapies



- **Agents must be safe in combination with anti PD1-L1**
- **Targeted/chemo therapy should not interfere with immune response or immunotherapeutic mechanism of action**

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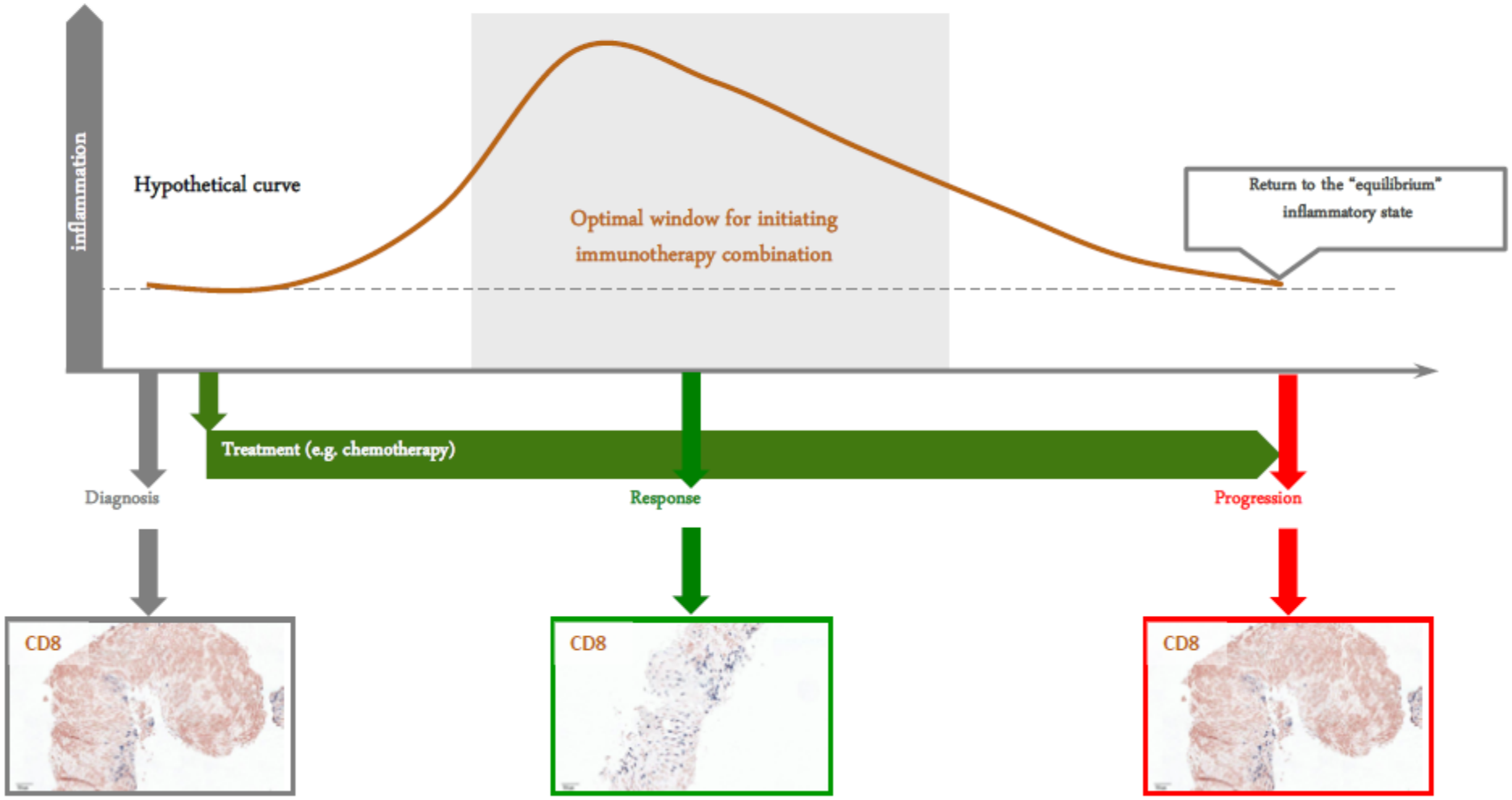
Modulation of tumor immune status by chemotherapy may be transient



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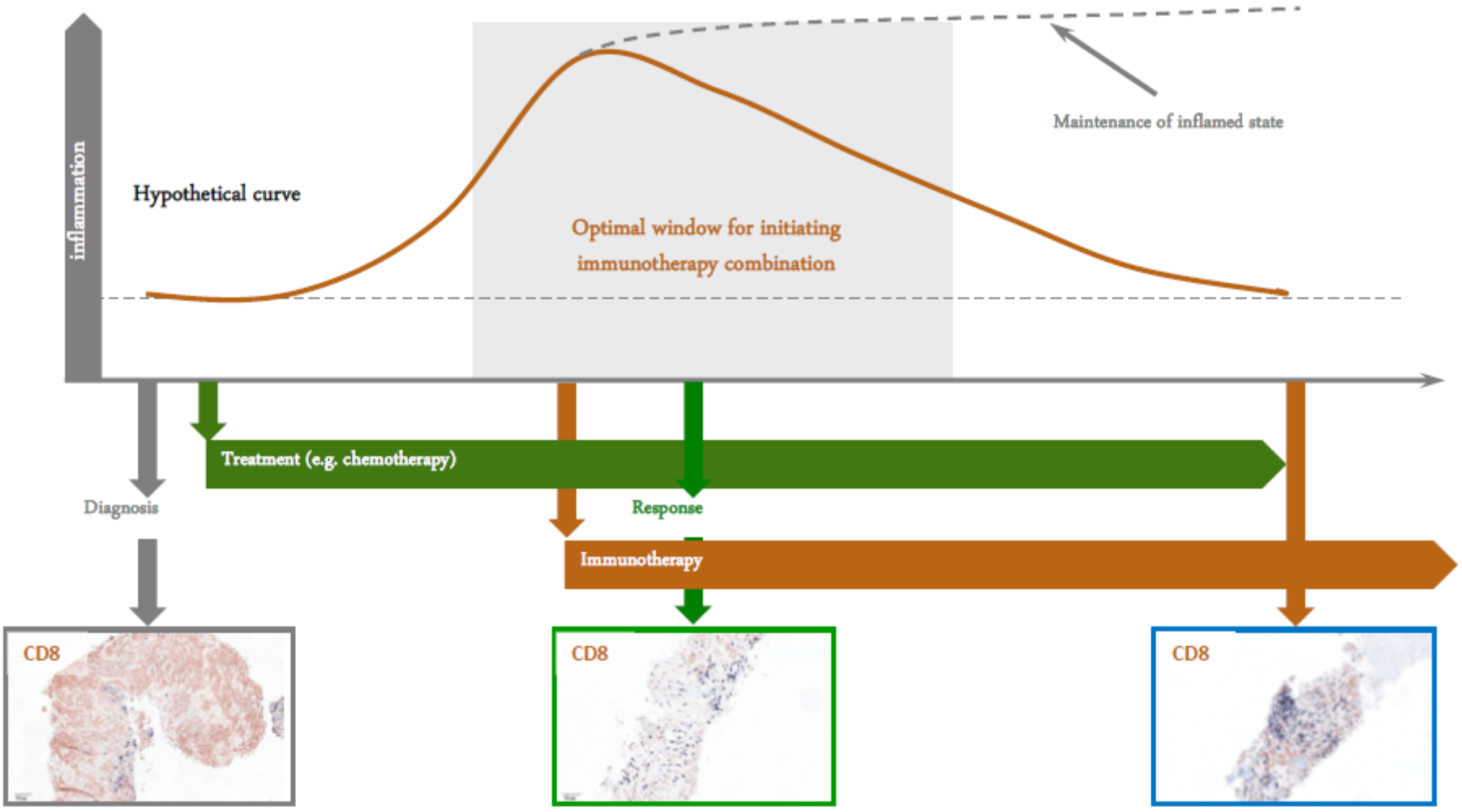
Simultaneous combinations may help to maintain and extend tumor inflamed state



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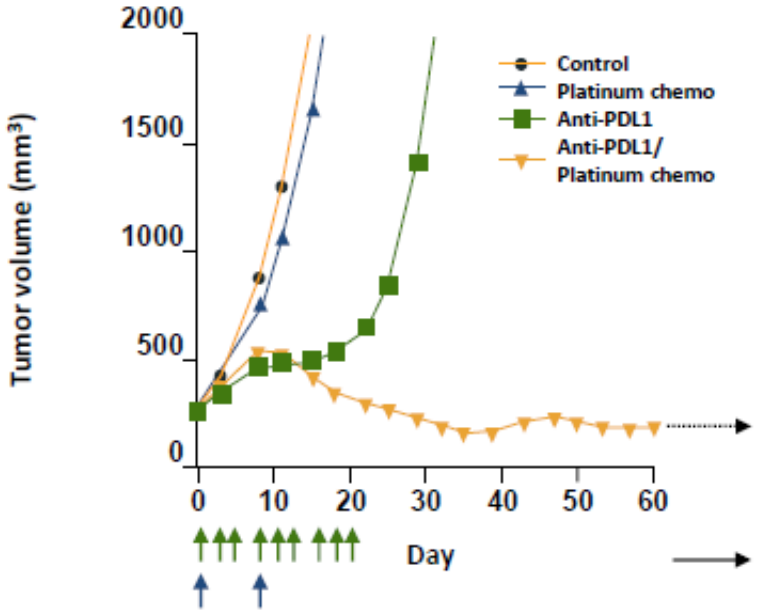
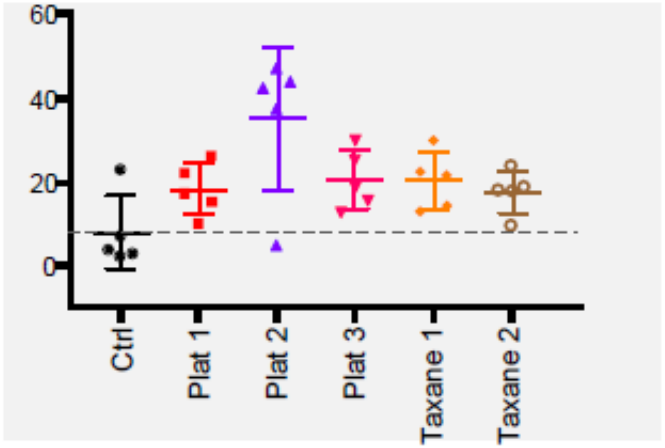
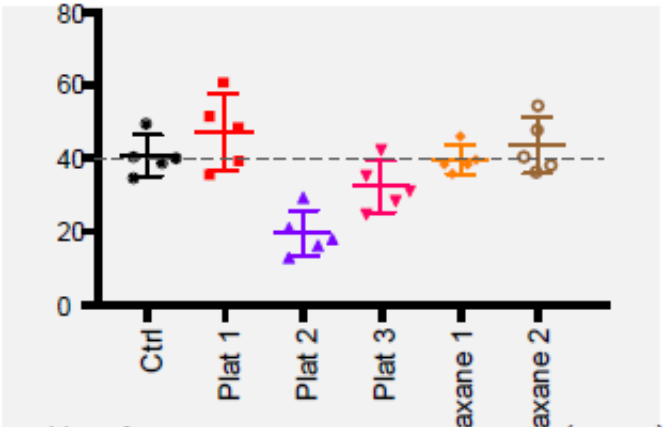
Chemotherapy as immunotherapy: *effect of platins on preclinical efficacy and immunobiology*



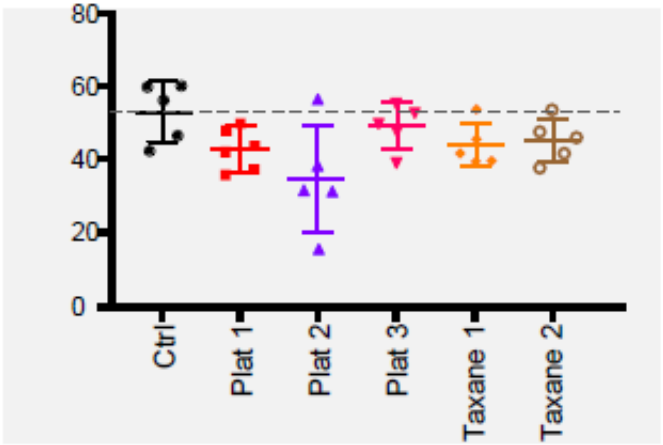
Tumor CD8+ (cell type)



Tumor CD11b⁺Ly6C⁺ (cell type)



Tumor CD4⁺FoxP3⁺ (cell type)



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

The FASEB Journal • Research Communication

Anti-angiogenesis therapy can overcome endothelial cell anergy and promote leukocyte-endothelium interactions and infiltration in tumors

Anita E. M. Dirkx,* Mirjam G. A. oude Egbrink,‡ Karolien Castermans,* Daisy W. J. van der Schaft,*,† Victor L. J. L. Thijssen,* Ruud P. M. Dings,§ Lucy Kwee,* Kevin H. Mayo,§ John Wagstaff,* Jessica C. A. Bouma-ter Steege,* and Arjan W. Griffioen*,†,1

Angiogenesis Laboratory, Research Institute for Growth and Development (GROW), Departments of *Internal Medicine and †Pathology, Maastricht University & University Hospital, Maastricht, the Netherlands; ‡Laboratory for Microcirculation, Cardiovascular Research Institute Maastricht, Department of Physiology, Maastricht University, Maastricht, the Netherlands; and §Department of Biochemistry, University of Minnesota, Minneapolis, Minnesota, USA

ABSTRACT **Tumor escape from immunity, as well as the failure of several anti-cancer vaccination and cellular immunotherapy approaches, is suggested to be due to the angiogenesis-mediated suppression of endothelial cell (EC) adhesion molecules involved in leukocyte-vessel wall interactions. We hypothesized that inhibition of angiogenesis would overcome this escape from immunity. We investigated this in vivo by means of intravital microscopy and ex vivo by immunohistochemistry in two mouse tumor models. Angiogenesis inhibitors anginex, endostatin, and angiostatin, and the chemotherapeutic agent paclitaxel were found to significantly stimulate leukocyte-vessel wall interactions by circumvention of EC anergy in vivo,**

OVER THE LAST DECADES, immuno-directed anti-tumor strategies, based on adoptive or vaccination approaches, have been developed (1, 2). This approach has not been as effective as had been anticipated. Several explanations for this have been put forward. First, most vaccines have been directed toward stimulating cytotoxic T lymphocyte (CD8) responses; the continuous stimulation of these cells without T cell help (CD4) eventually leads to anergy and tumor escape. Second, regulatory host T cell responses may counteract induced immunity. Third, the antigens toward which the immunity is directed are not tumor specific enough. An alternative explanation might be that although immune effector cells are being gener-

nature COMMUNICATIONS

ARTICLE

Received 1 Feb 2016 | Accepted 18 Jul 2016 | Published 30 Aug 2016

DOI: 10.1038/ncomms12624 OPEN

Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma

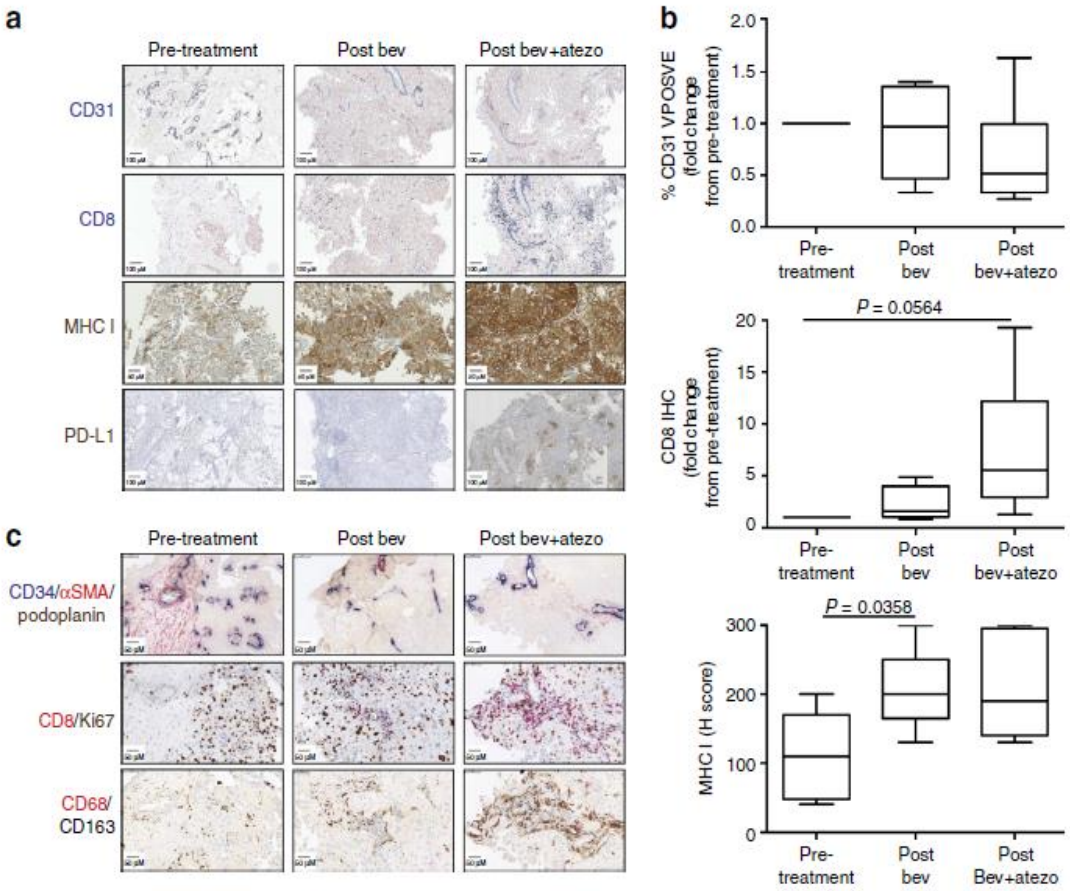


Figure 3 | Protein expression of immune and vasculature markers in baseline and on-treatment tumour samples. (**a**) Representative images of CD8 (blue), CD31 (blue), PD-L1 (brown) and MHC-I (brown) by IHC from patient 3 tumours. (**b**) Quantitation of CD31, CD8 and MHC-I IHC. *P* values were determined by paired *t*-test. The line in the middle of the box is plotted at the median. Lines above and below the boxes represent variability outside the upper and lower quartiles. (**c**) IHC images for the indicated triple and double stains of serial sections from patient 3 tumours. A scale bar for each image representing 50 or 100 μm is shown. atezo, atezolizumab; bev, bevacizumab.

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/cei.12069

Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect *in vivo*

S. Yasuda,* M. Sho,* I. Yamato,
H. Yoshiji,† K. Wakatsuki,*
S. Nishiwada,* H. Yagita‡ and
Y. Nakajima*
*Department of Surgery, †Third Departm
Internal Medicine, Nara Medical Univer
Nara, and ‡Department of Immunology,
University School of Medicine, Tokyo, Ja

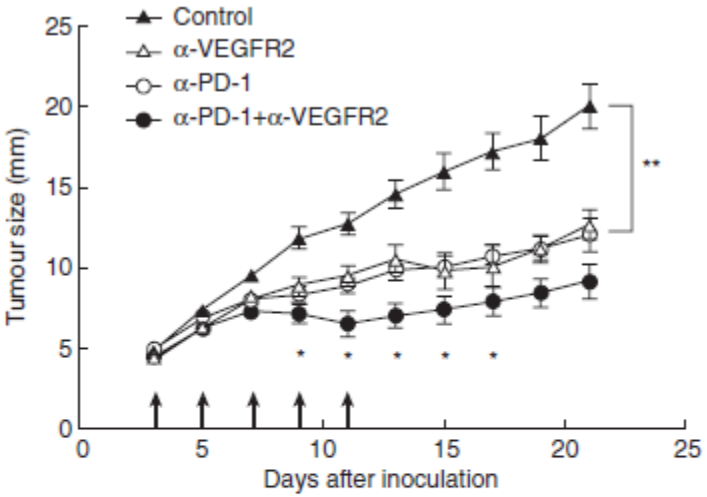


Fig. 1. Simultaneous blockade of programmed death (PD)-1 and vascular endothelial growth factor receptor 2 (VEGFR2) induced synergistic anti-tumour effect *in vivo*. BALB/c mice were inoculated subcutaneously with Colon-26 cells and were given with control rat immunoglobulin (Ig)G, anti-PD-1 monoclonal antibody (mAb), anti-VEGFR2 mAb or both mAbs five times (arrow). Data are presented as mean ±standard error of seven to 10 mice of each group. $^*P < 0.05$; $^{**}P < 0.01$.

that the programmed death
ole in tumour immunity, and
t several human cancers. We
night augment the efficacy of
bining the blockade of PD-1
or 2 (VEGFR2) in a murine
. Interestingly, simultaneous
onoclonal antibodies (mAbs)
without overt toxicity. Block-
tion significantly, as demon-
while PD-1 blockade had no
e might promote T cell infil-
d local immune activation, as
flammatory cytokine expres-
interfere with T cell infiltra-
PD-1 blockade. In conclusion,
induced a synergistic *in-vivo* anti-tumour effect, possibly through different mechanisms that might not be mutually exclusive. This unique therapeutic strategy may hold significant promise for future clinical application.

Keywords: anti-angiogenesis, anti-tumour immunity, immune checkpoint, PD-1, VEGFR2

Accepted for publication 10 January 2013
Correspondence: M. Sho, Department of Surgery, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan.
E-mail: m-sho@naramed-u.ac.jp

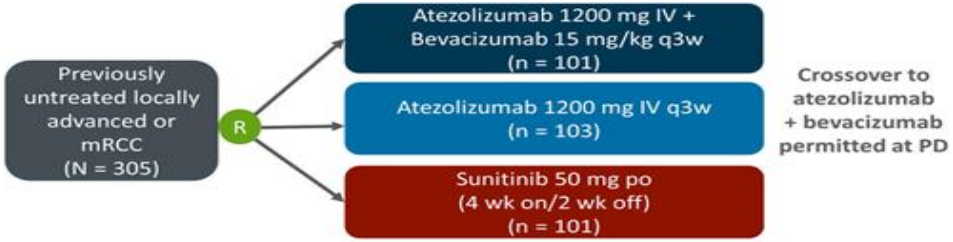
Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial

Michael B Atkins, Elizabeth R Plimack, Igor Puzanov, Mayer N Fishman, David F McDermott, Daniel C Cho, Ulka Vaishampayan, Saby George, Thomas E Olencki, Jamal C Tarazi, Brad Rosbrook, Kathrine C Fernandez, Mariajose Lechuga, Toni K Choueiri

Lancet Oncol 2018; 19: 405–15
Published Online
February 10, 2018

Phase 2 Study of Atezolizumab + Bevacizumab: IMmotion150

Atkins MB, et al. *J Clin Oncol*. 2017;35(suppl). Abstract 4505.



Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial

Toni K Choueiri, James Larkin, Mototsugu Oya, Fiona Thistlethwaite, Marcella Martignoni, Paul Nathan, Thomas Powles, David McDermott, Paul B Robbins, David D Chism, Daniel Cho, Michael B Atkins, Michael S Gordon, Sumati Gupta, Hirotsugu Uemura, Yoshihiko Tomita, Anna Compagnoni, Camilla Fowst, Alessandra di Pietro, Brian I Rini

Lancet Oncol 2018
Published Online
March 9, 2018

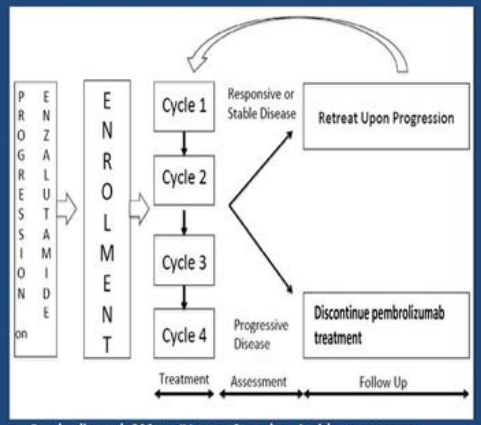
PD-L1 is highly expressed in Enzalutamide resistant prostate cancer

Jennifer L. Bishop[1], Alexander Sio[1], Arkhjamil Angeles[1], Morgan E. Roberts[2], Arun A. Azad[3], Kim N. Chi[3] and Amina Zoubeidi[1,4]

[1] Vancouver Prostate Centre, Vancouver, BC, Canada

First Evidence of Significant Clinical Activity of PD-1 Inhibitors in Metastatic, Castration Resistant Prostate Cancer (mCRPC)

Addition of Pembrolizumab Upon Progression on Enzalutamide in Men with mCRPC



Pembrolizumab 200 mg IV every 3 weeks x 4 with retreatment
Continued Enzalutamide therapy

Activity

- 5 of 27 (19%) patients had a confirmed PSA response
- 4 of 19 (21%) patients had stable disease > 6 months (range 34-64 weeks) without a PSA response
- Median follow up 19 weeks (range 3-67 weeks)

2016 ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

of monitoring circulating cell PD-L1 pathway activity in CRPC patients to predict responsiveness to checkpoint immunotherapy, is warranted.

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KN365 – Study Design I
Prostate Umbrella Trial to Study Combinations with Pembrolizumab

3 Open label single arm combination studies

Metastatic castrate resistant prostate cancer
RECIST measurable and non-measurable disease

PDL -1 positive and negative subjects
70 PTS/ COHORT

10 patient safety run in for each arm
Dose modification if > 5 pts require dose reductions

- **A** Pembro + Olaparib post docetaxel
- **B** Pembro + Docetaxel/Prednisone post Abi or Enza
- **C** Pembro + Enzalutamide post Abi
- **D** Pembro +
- **E** Pembro +
- **F** Pembro +

If 1 drug DC other drug continued (except for maximum 10 cycles of docetaxel)
Treatment continued until PD, unacceptable toxicity, withdrawal of consent.;
OS Follow up
Primary objective: safety/tolerability of combination, estimate PSA response rate
Interim analysis (ORR): only Cohort A after 40th patient complete 8 cycles or have discontinued therapy

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GEP 15 - MOVIE

Essai N° : UC-0101/1709

EudraCT N° : 2017-001857-14

UNE ÉTUDE DE BASKET PHASE I/II ÉVALUANT LA COMBINAISON DE LA VINORELBINE MÉTRONOMIQUE ORALE ET D'UNE ASSOCIATION D'IMMUNOTHÉRAPIE ANTI-PD-L1/ANTI-CTLA4 CHEZ DES PATIENTS ATTEINTS DE TUMEURS SOLIDES AVANCÉES.

Coordonnateur

Dr Anthony GONCALVES **– Institut Paoli Calmettes Marseille**

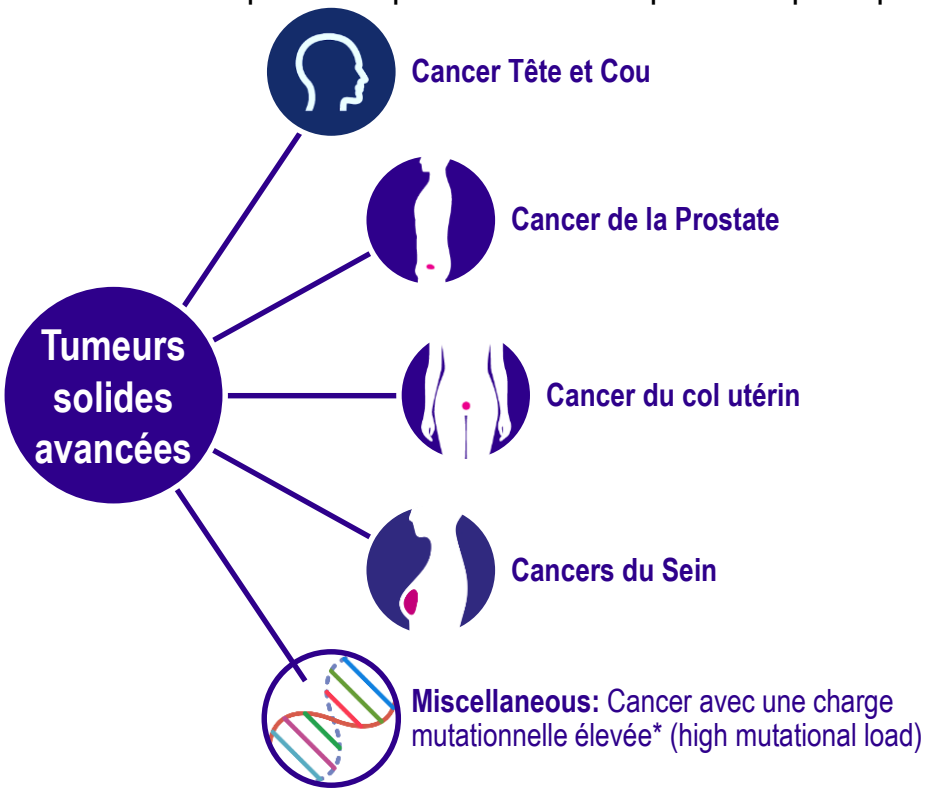
PHASE II : RECHERCHE D'ACTIVITÉ

Objectif Principal : **Activité de la combinaison**

- Déterminer l'activité anti-tumorale de la combinaison en évaluant le taux de bénéfice Clinique (CBR) dans 5 cohortes selon RECIST v1.1
- **CBR = CR + PR + SD (≥ 24 semaines)**

Méthodologie : **Multicohorte et Bayésien**

- De 10 à 30 patients inclus dans 5 cohortes,
- Evaluation au 10 premiers patients/cohorte puis chaque 5 patients/cohorte (si poursuite)



UNICANCER R&D

** Discuté durant un précédent RCP pour patients métastatique/Tumor Board local*

Combination therapy: Challenges

- Difficulty in assessing the success of a given combination when one agent is significantly more active than the other
- Immune modified RECIST may capture of benefit of atypical responses otherwise missed with RECIST 1.1
- ORR and PFS have underestimated the overall survival (OS) benefit in monotherapy studies with PD1/PDL-1 inhibitors: what about combination studies?
- Association vs sequence?

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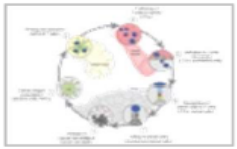
Conclusions

INCREASING CURE RATE

Personalized CIT (2025+)
Multiple combos targeted at Dx sub-groups

Expand Beyond Checkpoint Inhibitors (2020-2025)
Competition + (Immuno 1, Immuno 2, …)
Atezolizumab + (Immuno 1, Immuno 2)



Combine with Existing Tx (2015-2020)
Nivo + Ipi (2015)
Pembrolizumab + (chemo or …)
Nivolumab + (chemo or …)
Atezolizumab + (chemo, bev, K, cotellic)

Where we are at today

Checkpoint Inhibitors Monotherapy (2011-2016)
Ipilimumab (2011)
Pembrolizumab (2014)
Nivolumab (2014)
Atezolizumab (2016)

Grazie