Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Non-Small Cell Lung Carcinoma

Bernard A. Fox, PhD
Earle A. Chiles Research Institute,
Providence Cancer Center

Advances in Cancer Immunotherapy™ - Detroit
July 31, 2015

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I have Consultant/Advisory Roles or Research support/Grant to disclose

Bristol-Myers Squibb, Aduro, Immunophotonics, Dendreon, 3M, Ventana/Roche, Nodality, Definiens, Janssen/Johnson & Johnson, PerkinElmer, MedImmune/AstraZeneca, Viralytics, Argos, *Peregrine*

I have a Leadership Position / Stock Ownership to disclose.

UbiVac, UbiVac-CMV, Insys Ther

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Earle A. Chiles Research Institute

Objectives

- Review current understanding of the mechanism of action for anti-PD-1 therapy
- Have an appreciation for the types of adverse events associated with nivolumab (anti-PD-1)
- Review what might be done to improve response rates in patients with NSCLC.

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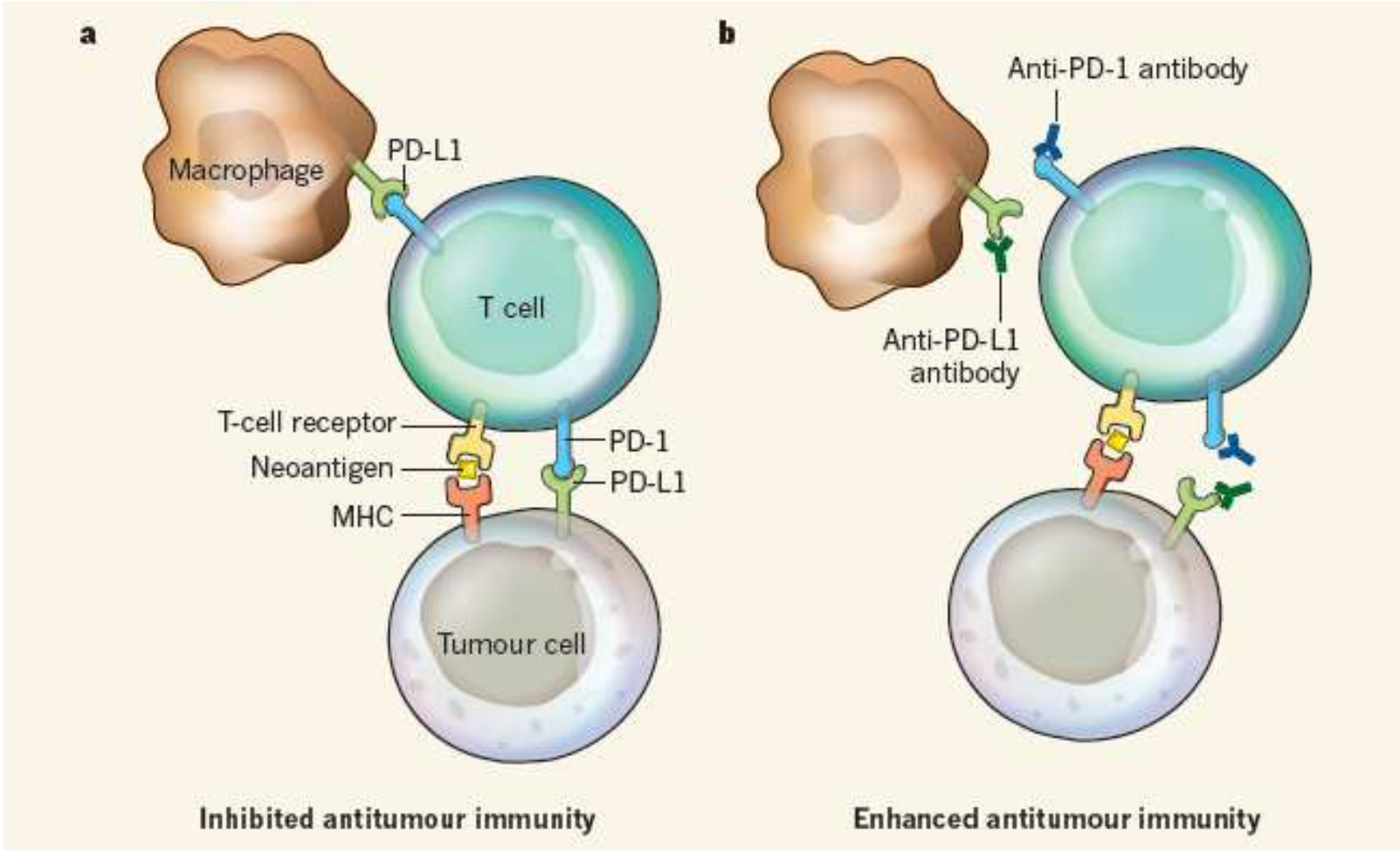
CANCER

Antitumour immunity gets a boost

JEDD D. WOLCHOK & TIMOTHY A. CHAN

496 | NATURE | VOL 515 | 27 NOVEMBER 2014

Five papers extend the list of cancers that respond to therapies that restore antitumour immunity by blocking the PD-1 pathway, and characterize those patients who respond best. SEE LETTERS P.558, P.563, P.568, P.572 & P.577



ORIGINAL ARTICLE

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

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Overall Survival

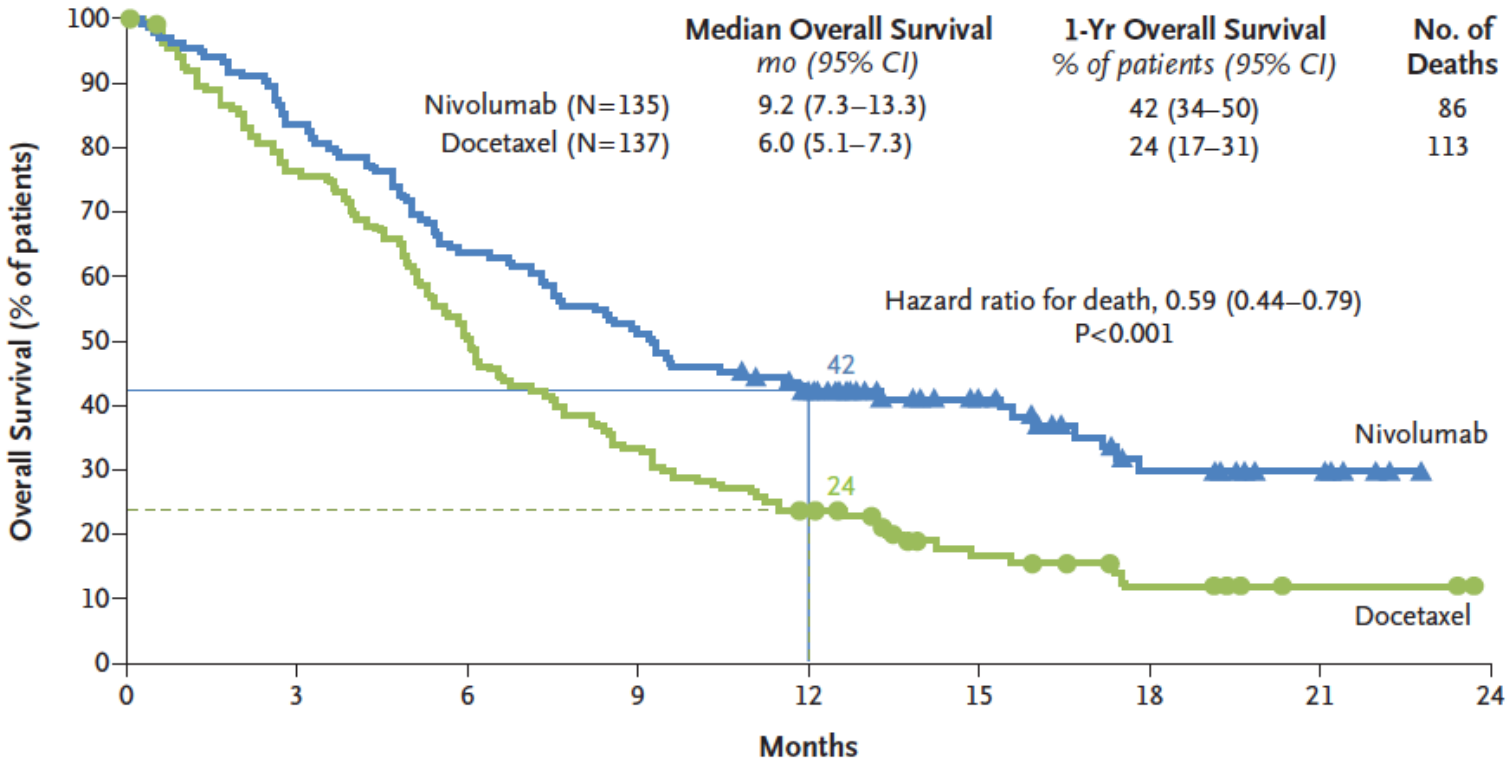
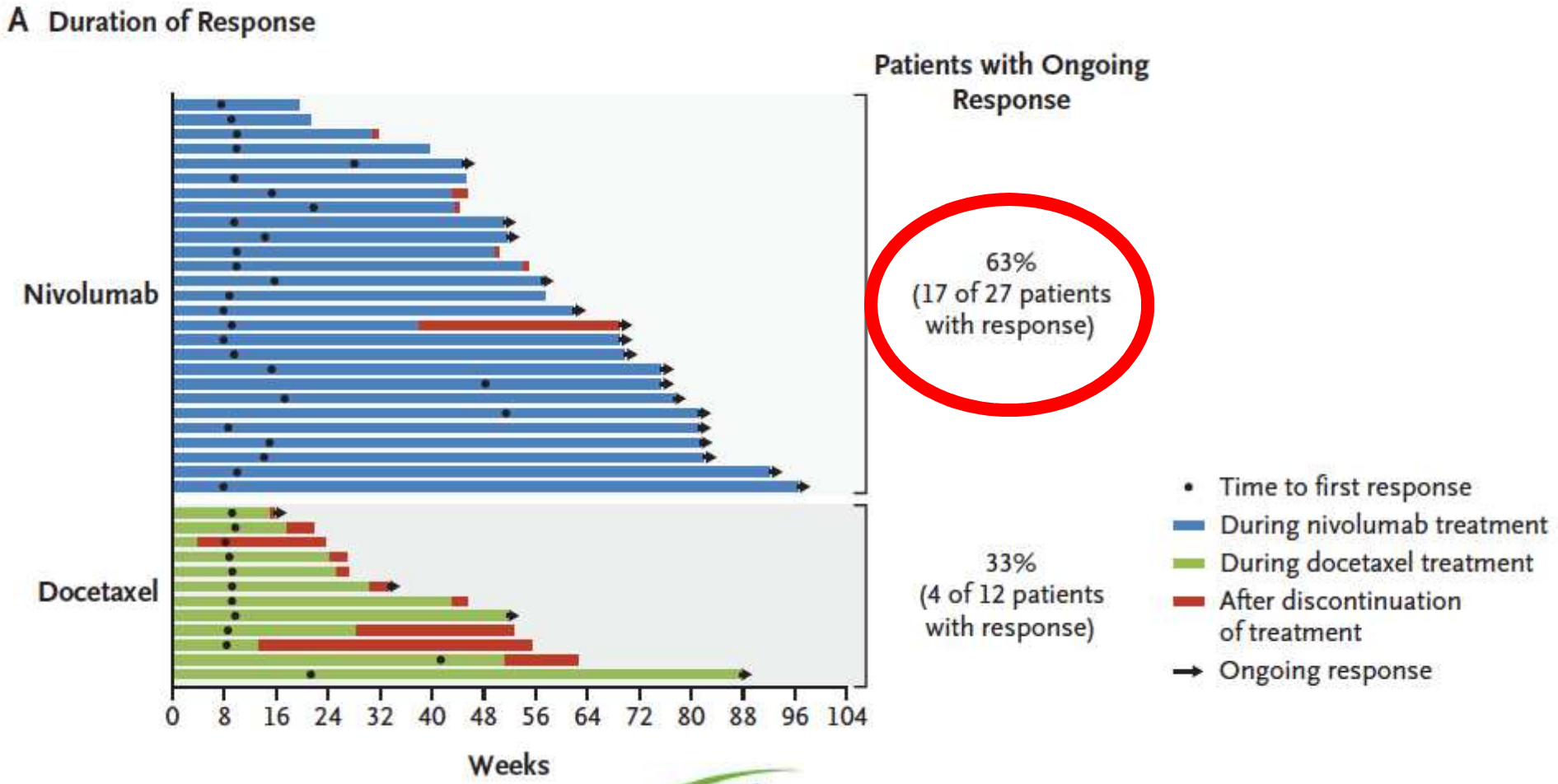


Figure 1. Kaplan–Meier Curves for Overall Survival.

The analysis included all the patients who underwent randomization. Symbols indicate censored observations, and horizontal lines the rates of overall survival at 1 year.

Duration of Response



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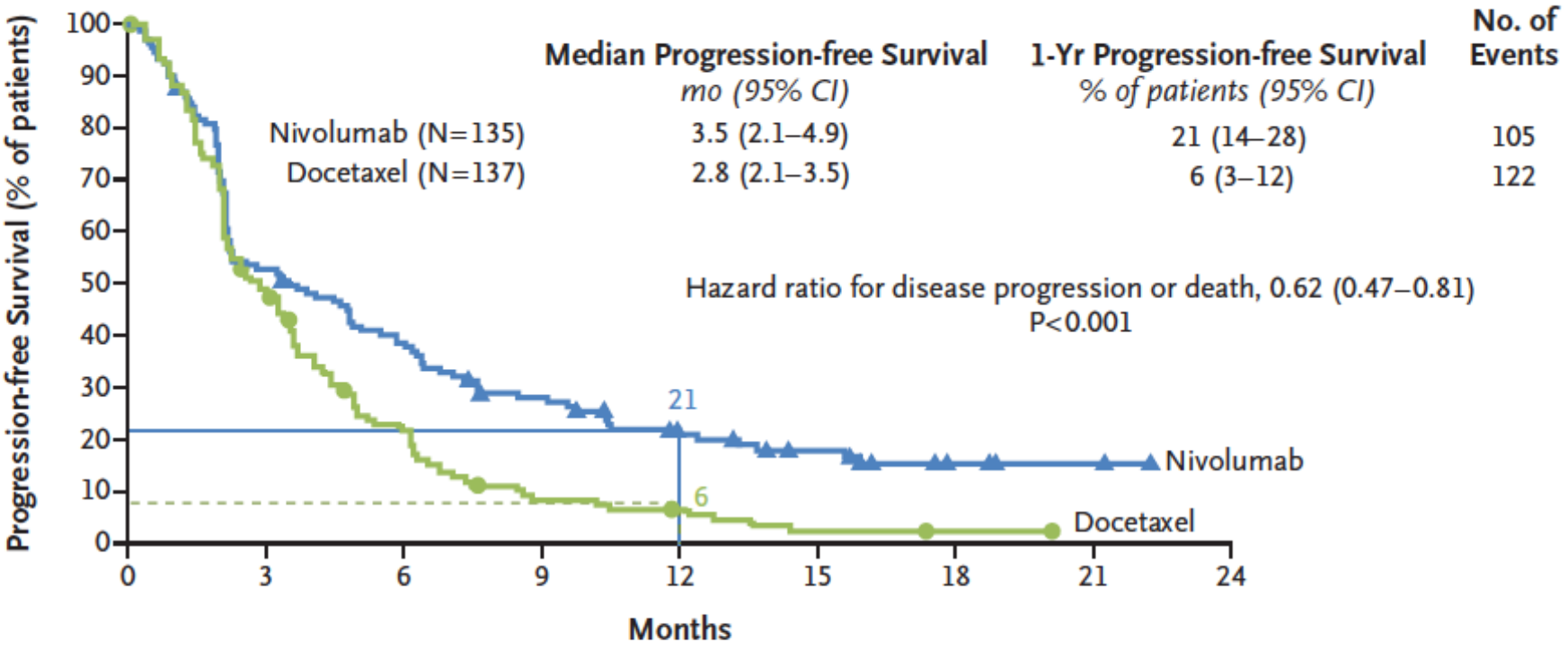
Progression-Free Survival

B Progression-free Survival



	Median Progression-free Survival *mo (95% CI)*	1-Yr Progression-free Survival *% of patients (95% CI)*	No. of Events
Nivolumab (N=135)	3.5 (2.1–4.9)	21 (14–28)	105
Docetaxel (N=137)	2.8 (2.1–3.5)	6 (3–12)	122

Hazard ratio for disease progression or death, 0.62 (0.47–0.81)
P<0.001

No. at Risk

Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

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Table 3. Treatment-Related Adverse Events Reported in at Least 5% of Patients.*

Event	Nivolumab (N = 131)		Docetaxel (N = 129)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with an event (percent)			
Any event	76 (58)	9 (7)	111 (86)	71 (55)
Fatigue	21 (16)	1 (1)	42 (33)	10 (8)
Decreased appetite	14 (11)	1 (1)	25 (19)	1 (1)
Asthenia	13 (10)	0	18 (14)	5 (4)
Nausea	12 (9)	0	30 (23)	2 (2)
Diarrhea	10 (8)	0	26 (20)	3 (2)
Arthralgia	7 (5)	0	9 (7)	0
Pyrexia	6 (5)	0	10 (8)	1 (1)
Pneumonitis	6 (5)	0	0	0
Rash	5 (4)	0	8 (6)	2 (2)
Mucosal inflammation	3 (2)	0	12 (9)	0
Myalgia	2 (2)	0	13 (10)	0
Anemia	2 (2)	0	28 (22)	4 (3)
Peripheral neuropathy	1 (1)	0	15 (12)	3 (2)
Leukopenia	1 (1)	1 (1)	8 (6)	5 (4)
Neutropenia	1 (1)	0	42 (33)	38 (30)
Febrile neutropenia	0	0	14 (11)	13 (10)
Alopecia	0	0	29 (22)	1 (1)

* Safety analyses included all the patients who received at least one dose of study drug. No treatment-related deaths occurred in patients treated with nivolumab. Treatment-related deaths were reported in three patients treated with docetaxel (one death each from interstitial lung disease, pulmonary hemorrhage, and sepsis).

CANCER

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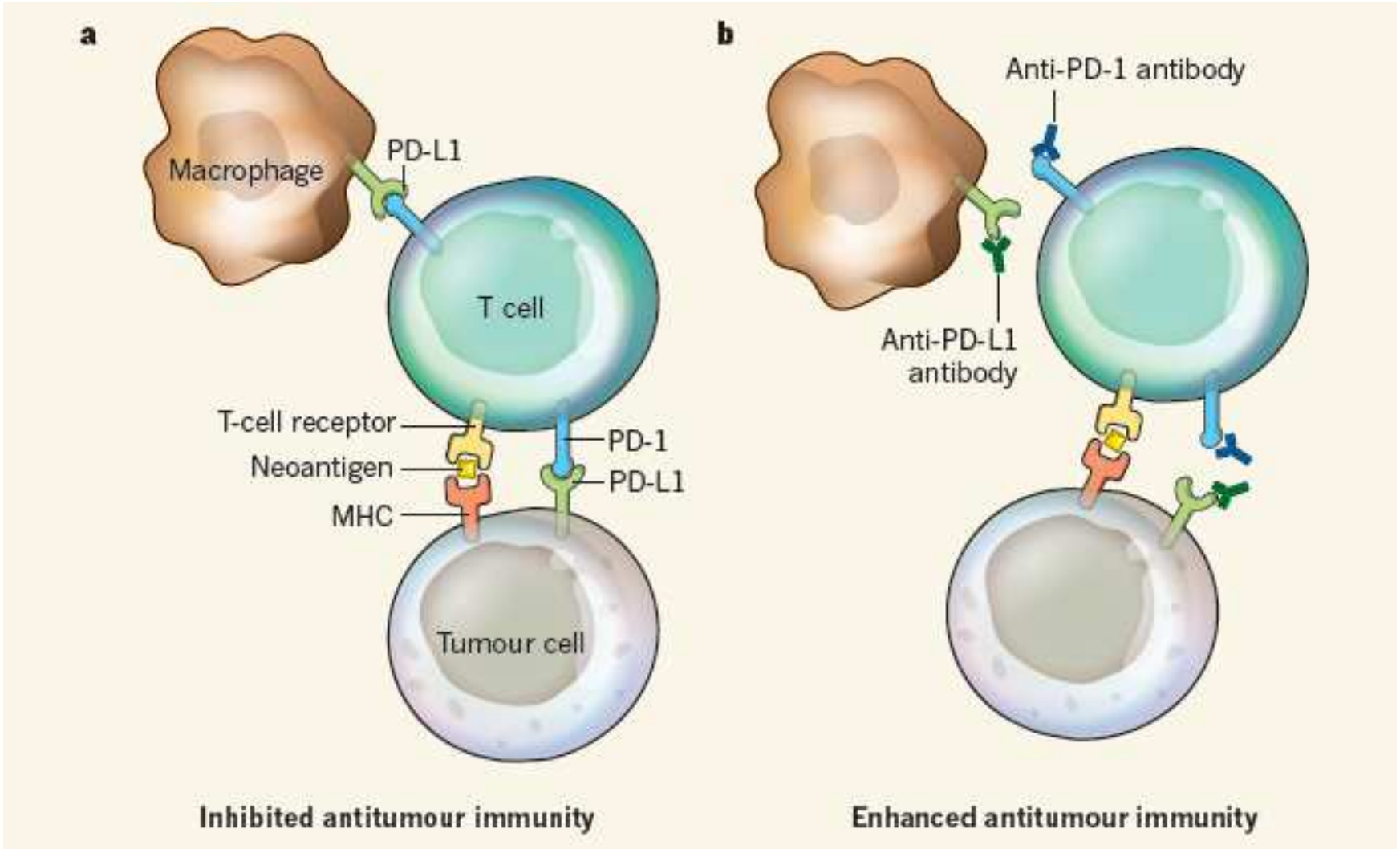
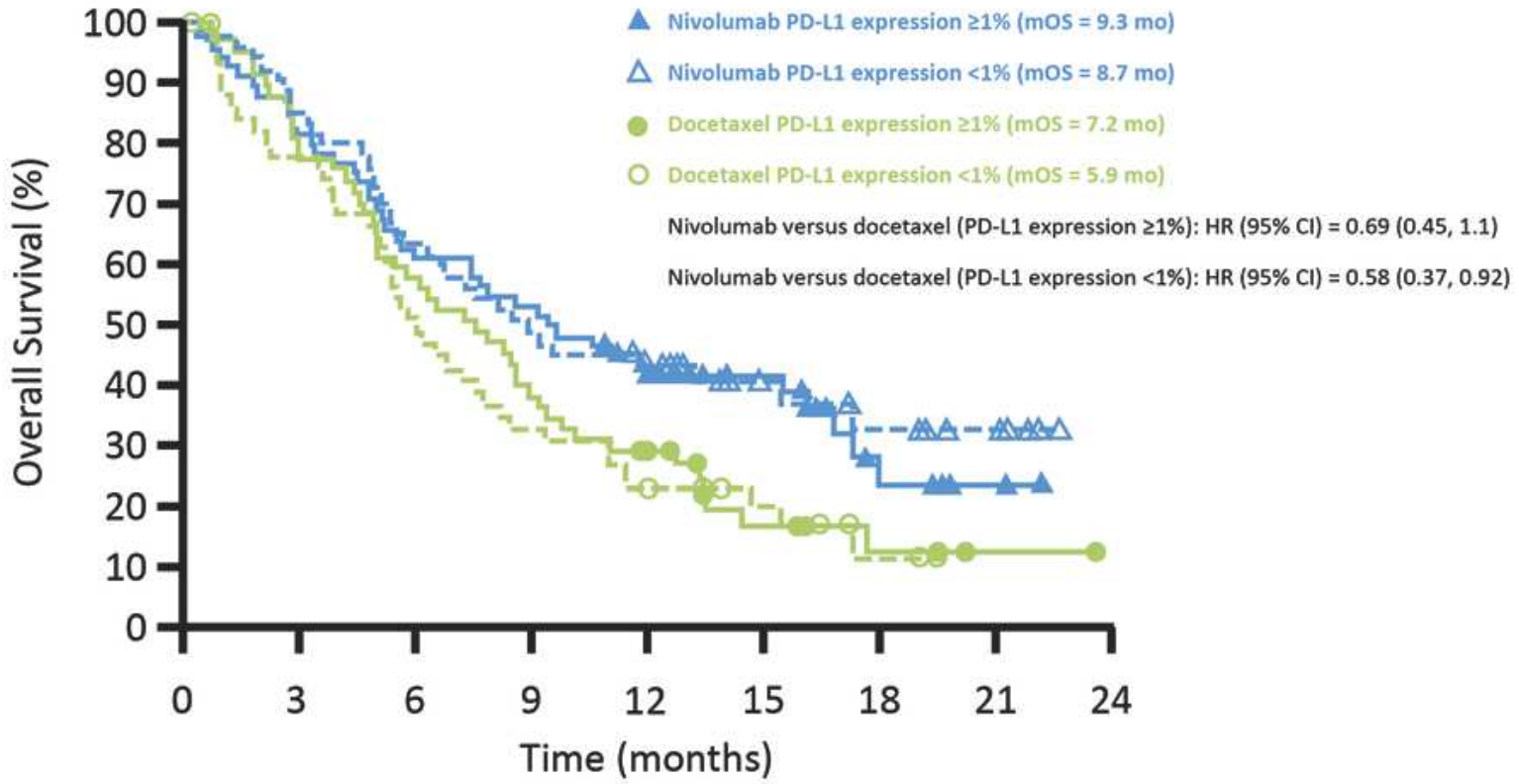


Controversy: PD-L1 Expression

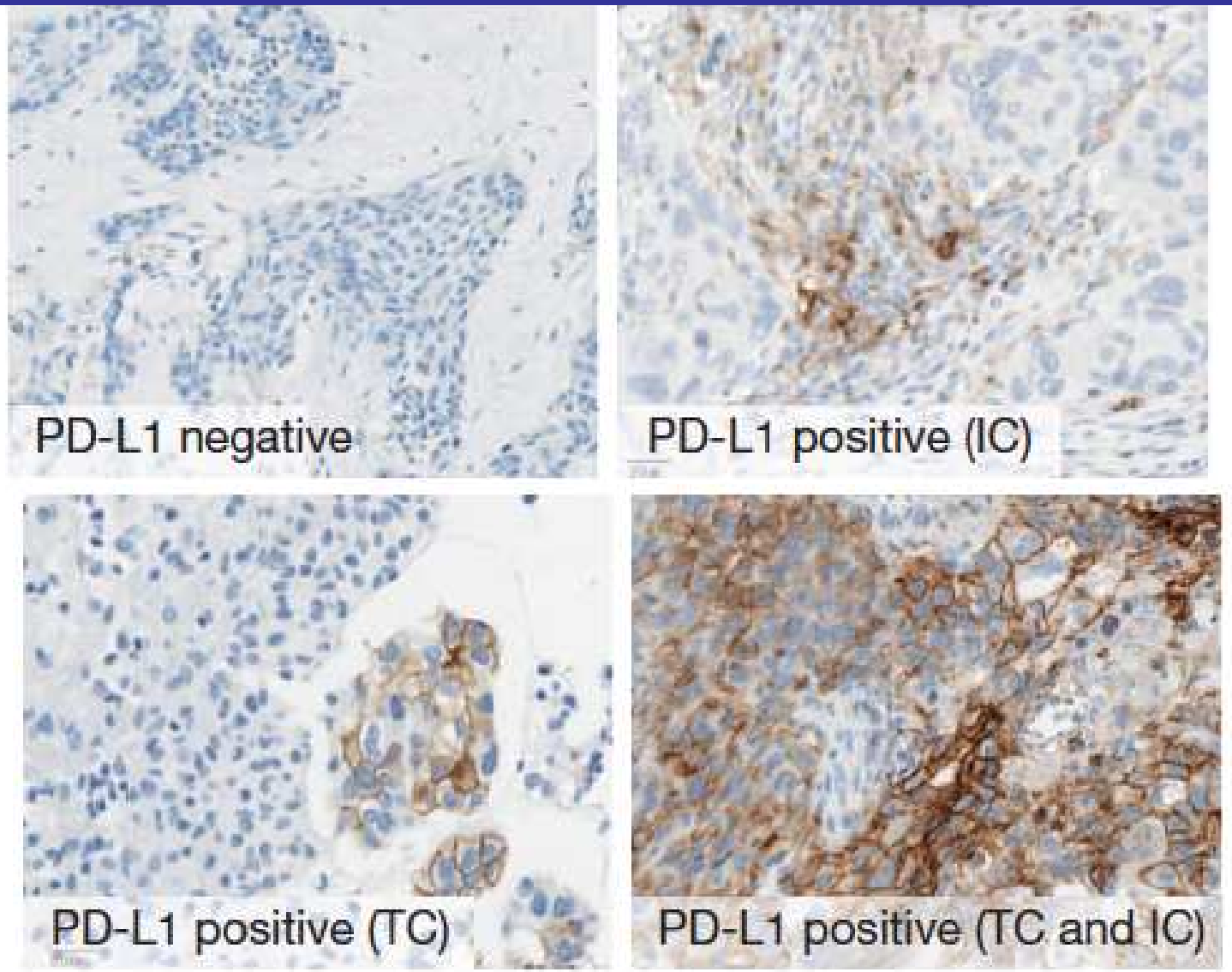
Overall Survival: 1% PD-L1 Expression



Number of patients at risk

Nivolumab PD-L1 expression ≥1%	63	51	38	32	23	15	5	2	0
Nivolumab PD-L1 expression <1%	54	46	34	26	21	11	8	5	0
Docetaxel PD-L1 expression ≥1%	56	43	31	21	14	6	3	1	0
Docetaxel PD-L1 expression <1%	52	39	25	16	11	6	2	0	0

Controversy: PD-L1 Expression



Controversy: PD-L1 Expression

Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients

Roy S. Herbst[1], Jean-Charles Soria[2], Marcin Kowanetz[3], Gregg D. Fine[3], Omid Hamid[4], Michael S. Gordon[5], Jeffery A. Sosman[6], David F. McDermott[7], John D. Powderly[8], Scott N. Gettinger[1], Holbrook E. K. Kohrt[9], Leora Horn[10], Donald P. Lawrence[11], Sandra Rost[3], Maya Leabman[3], Yuanyuan Xiao[3], Ahmad Mokatrin[3], Hartmut Koeppen[3], Priti S. Hegde[3], Ira Mellman[3], Daniel S. Chen[3] & F. Stephen Hodi[12]

Problems:

Different methods used to detect PD-L1

Patients without detectable PD-L1 Can still respond

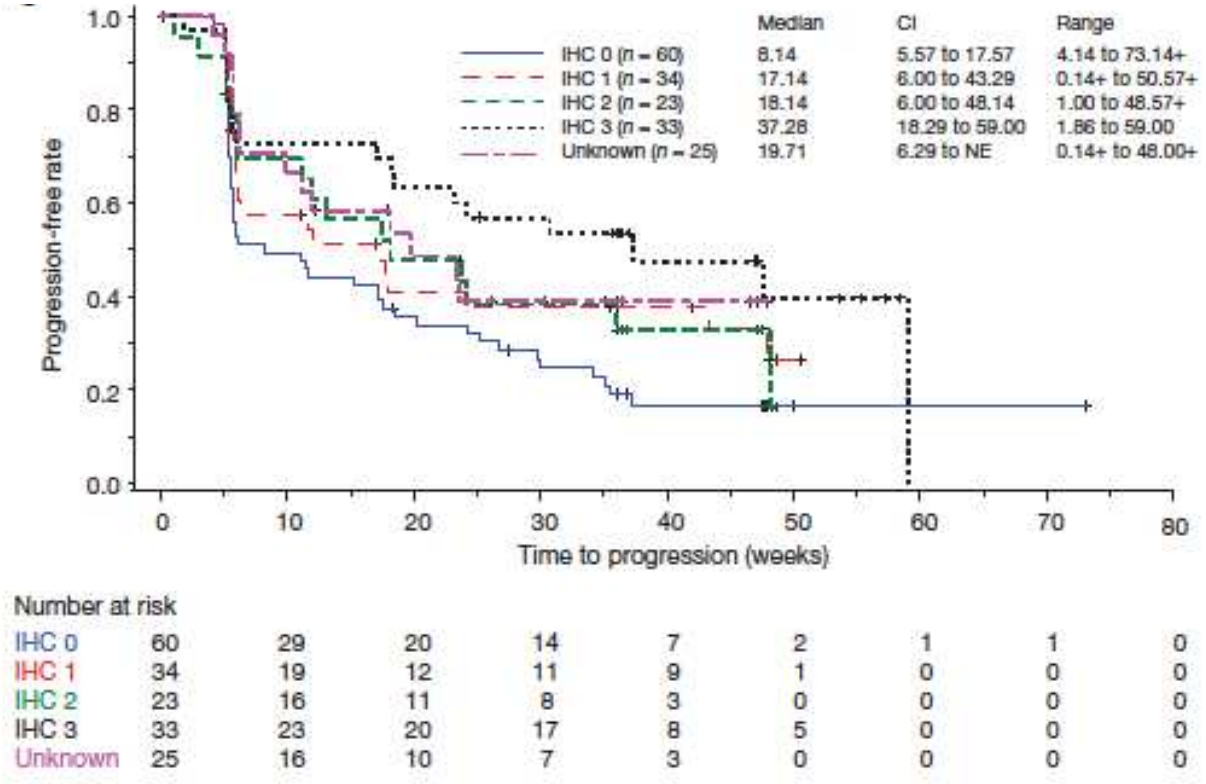
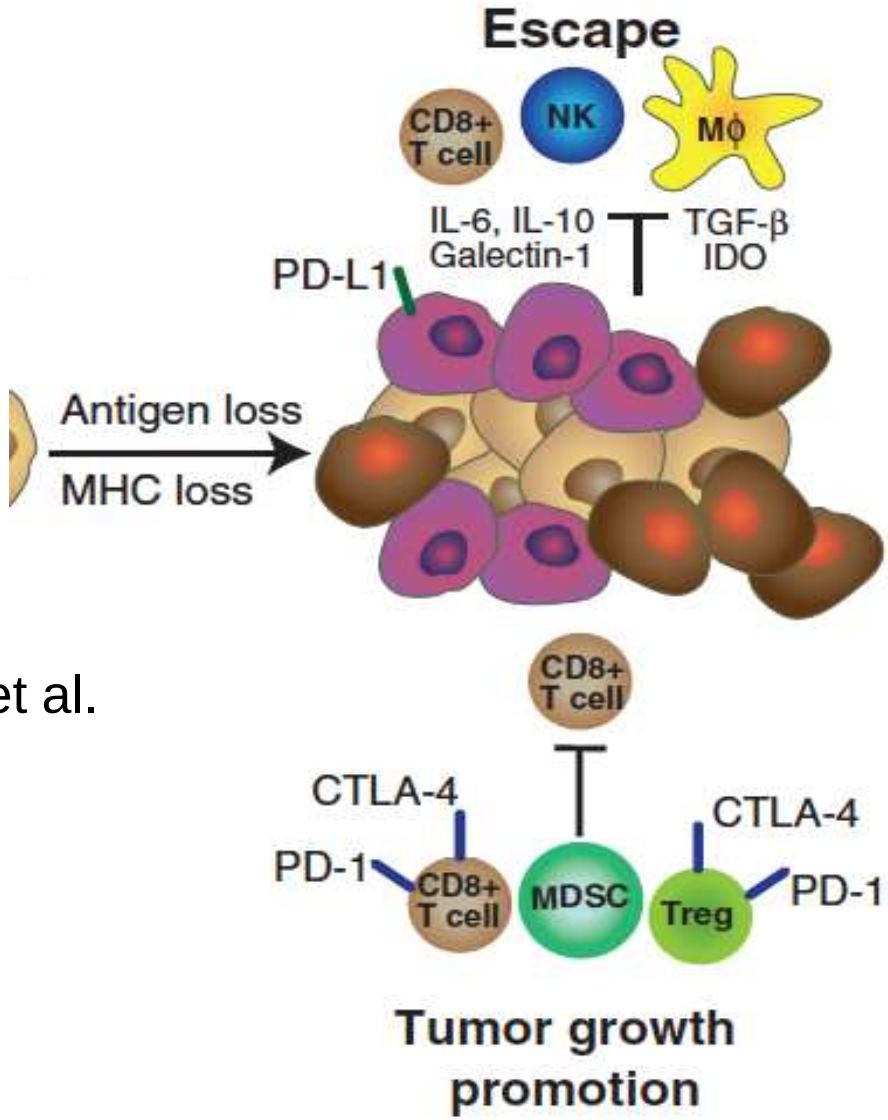


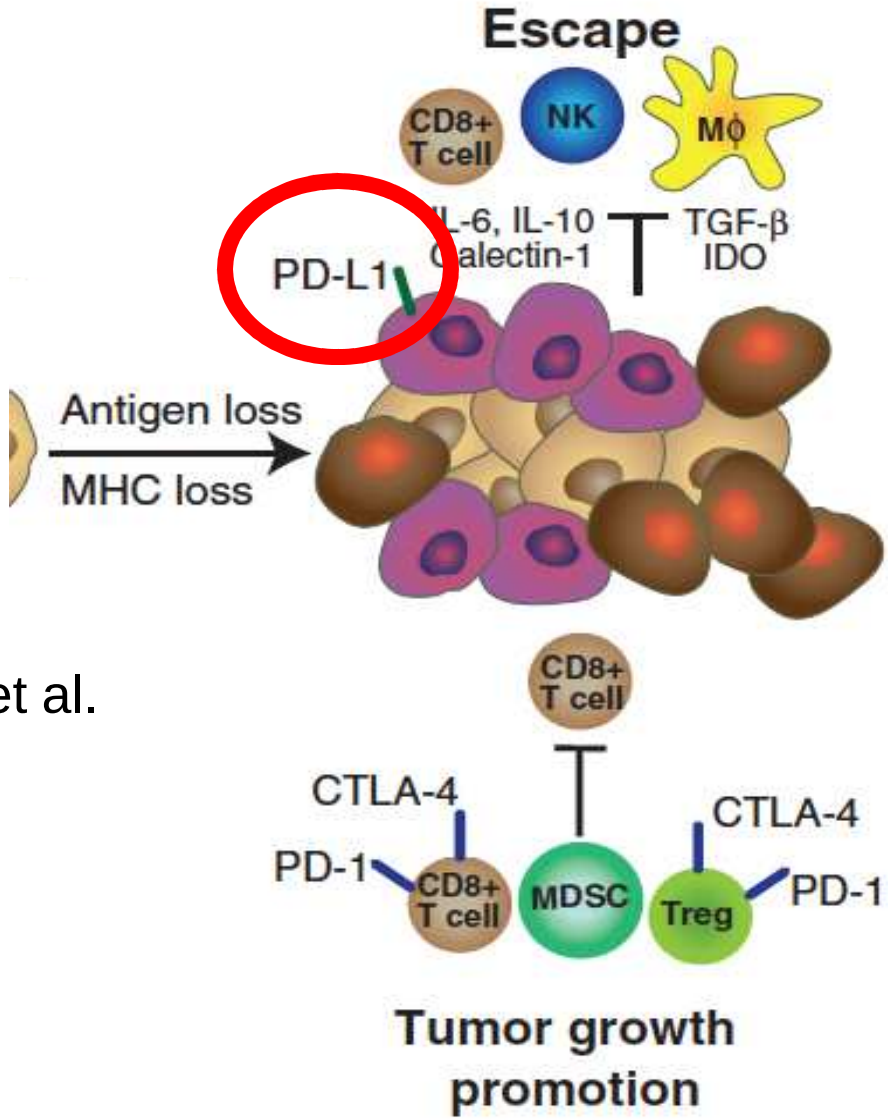
Figure 3 | Antitumour activity of MPDL3280A by immunohistochemistry (IHC) tumour-infiltrating immune cell (IC) and biomarker status. a, Table of antitumour activity in patients with NSCLC by PD-L1 IHC (IC) status.

What did they “look” at?



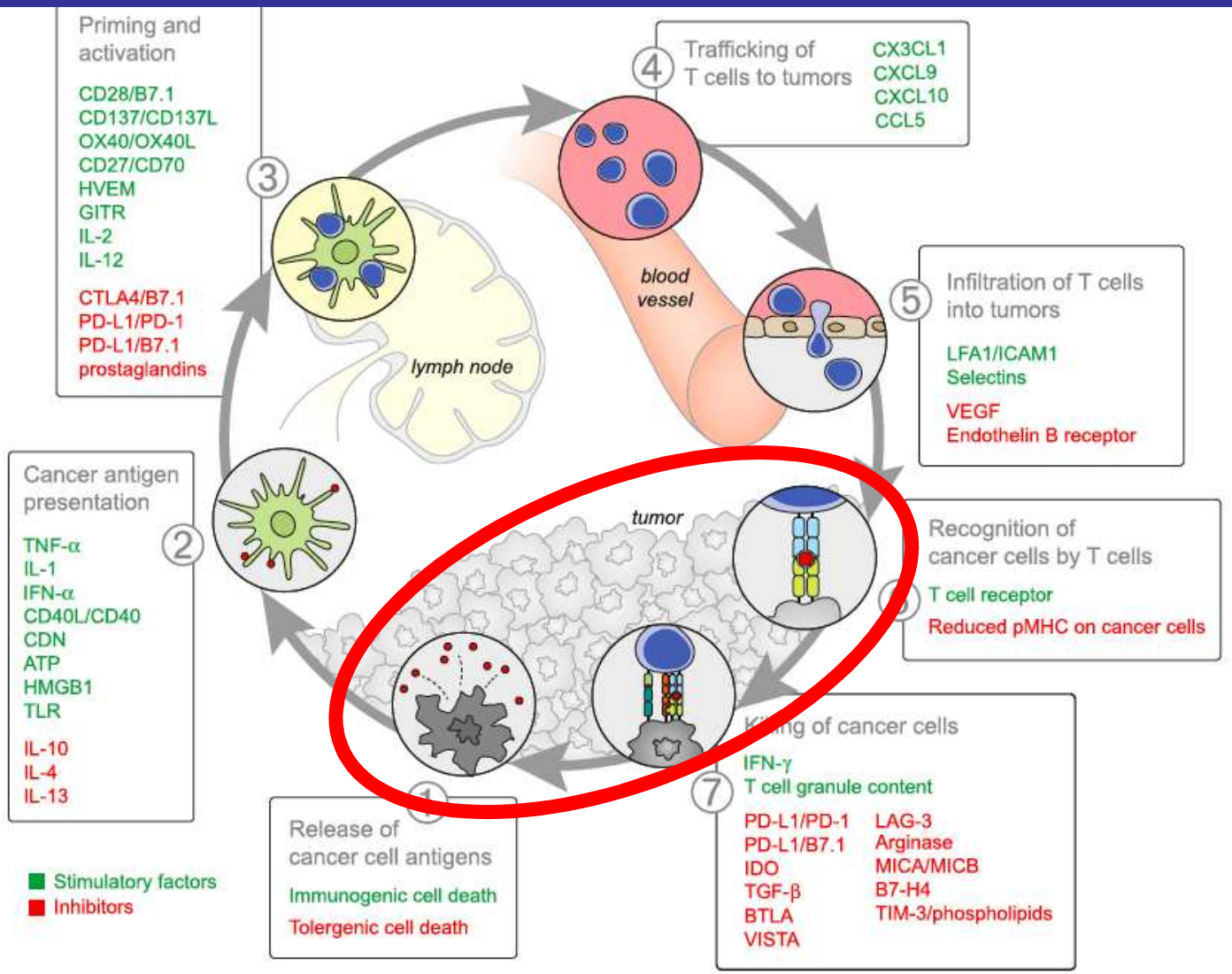
R D Schreiber et al.
Science 2011,
331:1565-1570

What did they “look” at?



R D Schreiber et al.
Science 2011,
331:1565-1570

What else can we “look” at?



Immunity
Review

Chen and Mellman Immunity 39, July 25, 2013

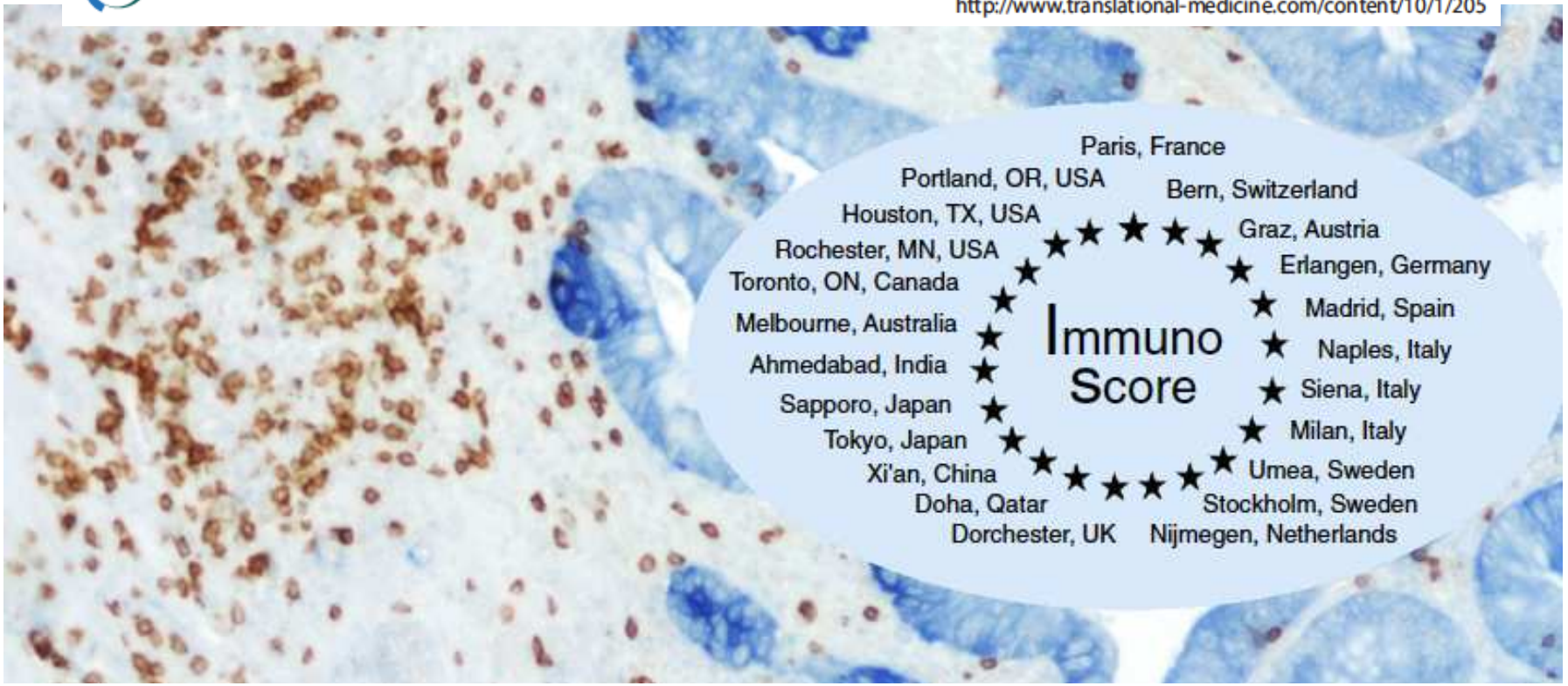
SITC Immunoscore Taskforce

Cancer classification using the Immunoscore: a worldwide task force

Galon *et al.*

BioMed Central

Galon *et al. Journal of Translational Medicine* 2012, **10**:205
http://www.translational-medicine.com/content/10/1/205



SITC Immunoscore Taskforce

EDITORIAL Open Access

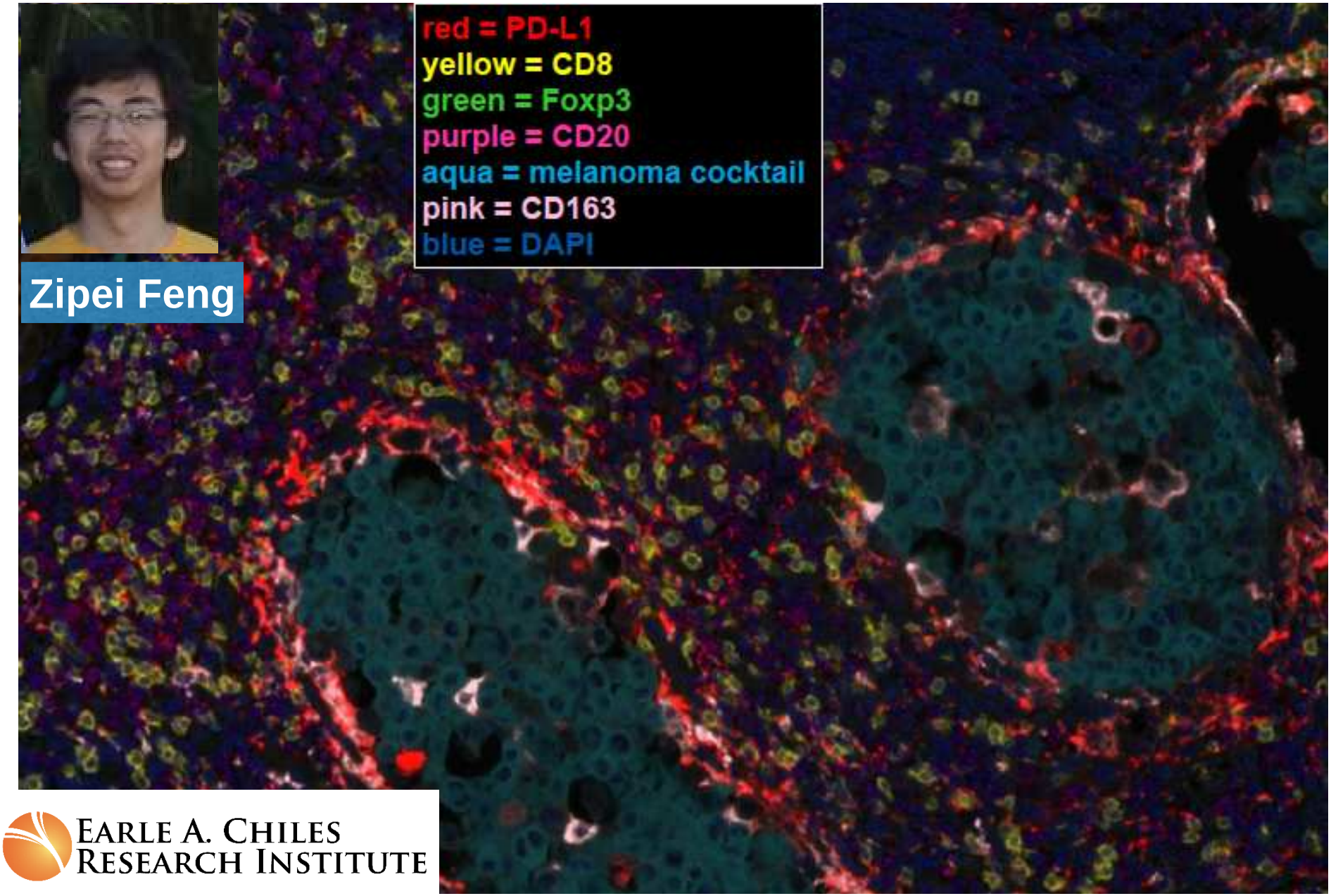
The additional facet of immunoscore: immunoprofiling as a possible predictive tool for cancer treatment

Paolo A Ascierto[1*], Mariaelena Capone[1], Walter J Urba[2], Carlo B Bifulco[2], Gerardo Botti[1], Alessandro Lugli[3], Francesco M Marincola[4], Gennaro Ciliberto[1], Jérôme Galon[5,6,7] and Bernard A Fox[2,8]

J. Transl Med. 11: 54 2013

B Fox CFDA

Melanoma section showing PD-L1+ macrophages surrounding PD-L1- tumor cells



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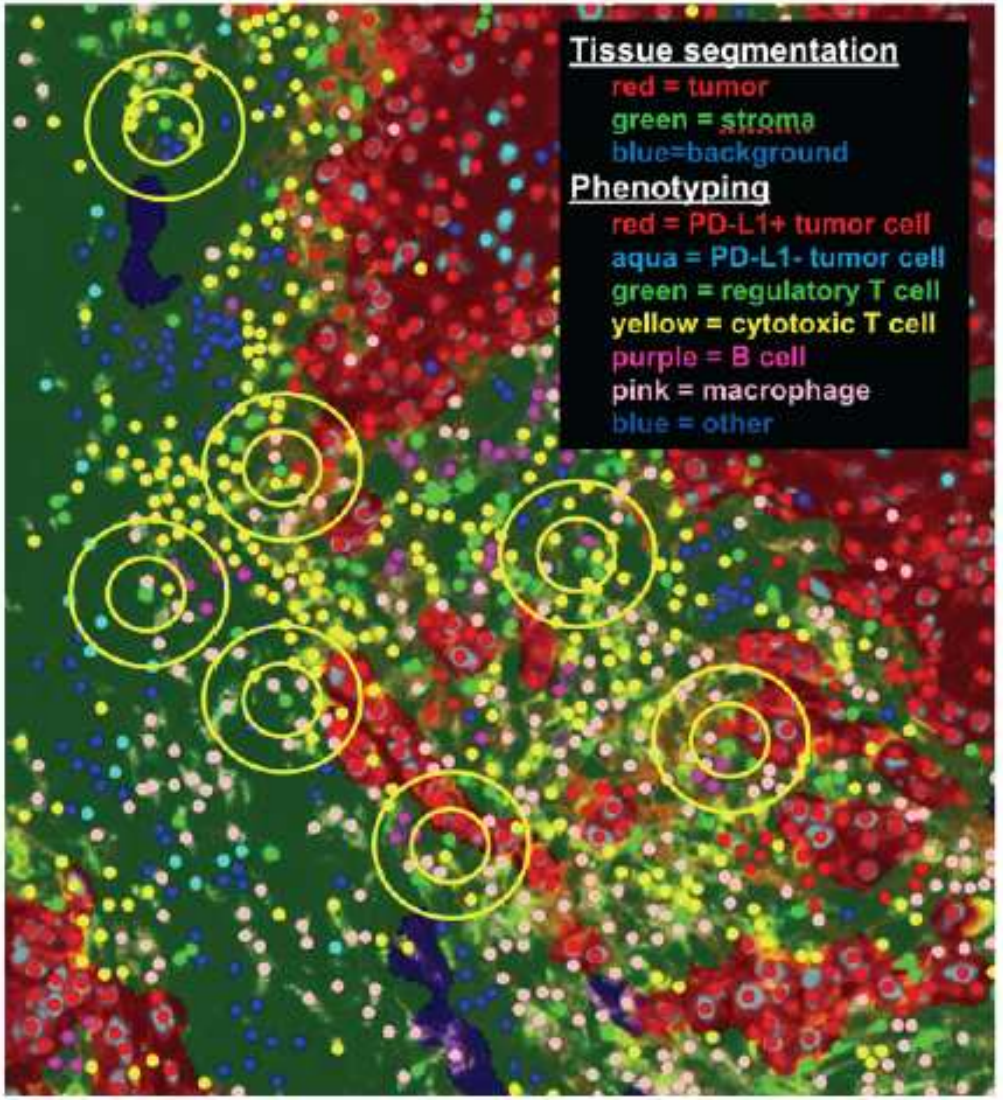
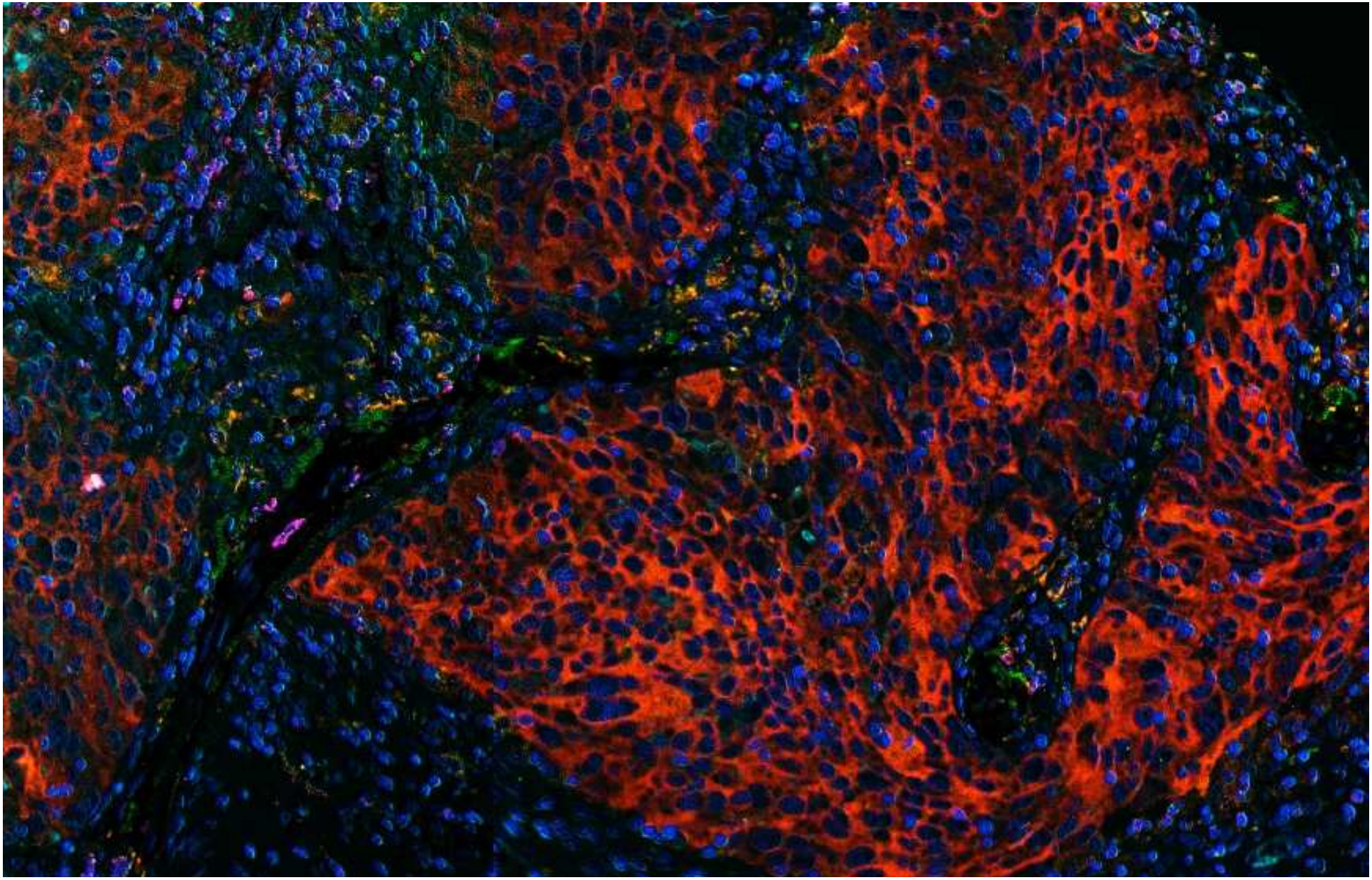
Relationships, e.g. T-regs

Example interaction distance measurement:

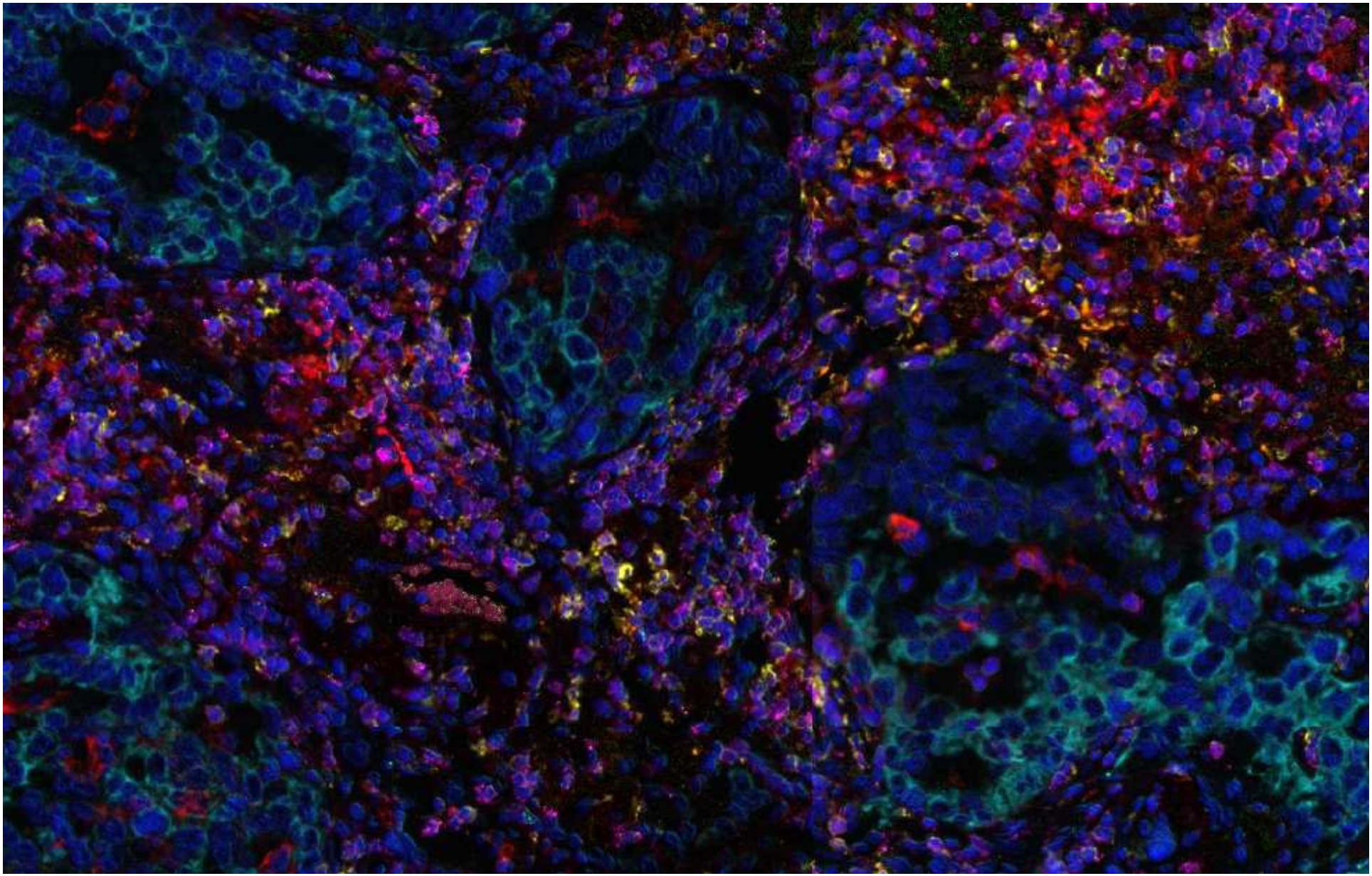
What are the average numbers of PD-L1+ tumor cells and cytotoxic T cells within 10 and 25 microns of regulatory T cells?

Calculations performed with R scripts. operating on inForm cell phenotype output files





PDL-1 – Cy5 / CD8 – Cy3 / FoxP3 – FITC / CD3 – Alexa 594
CD163(Mcphg) – Alexa 514 / Cytokeratin – coumarin / DAPI



PDL-1 – Cy5 / CD8 – Cy3 / FoxP3 – FITC / CD3 – Alexa 594
CD163(Mcphg) – Alexa 514 / Cytokeratin – coumarin / DAPI

Most Important Question in Immuno-Oncology Today?

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Most Important Question in Immuno-Oncology Today?

Why do people
not respond
to immunotherapy?

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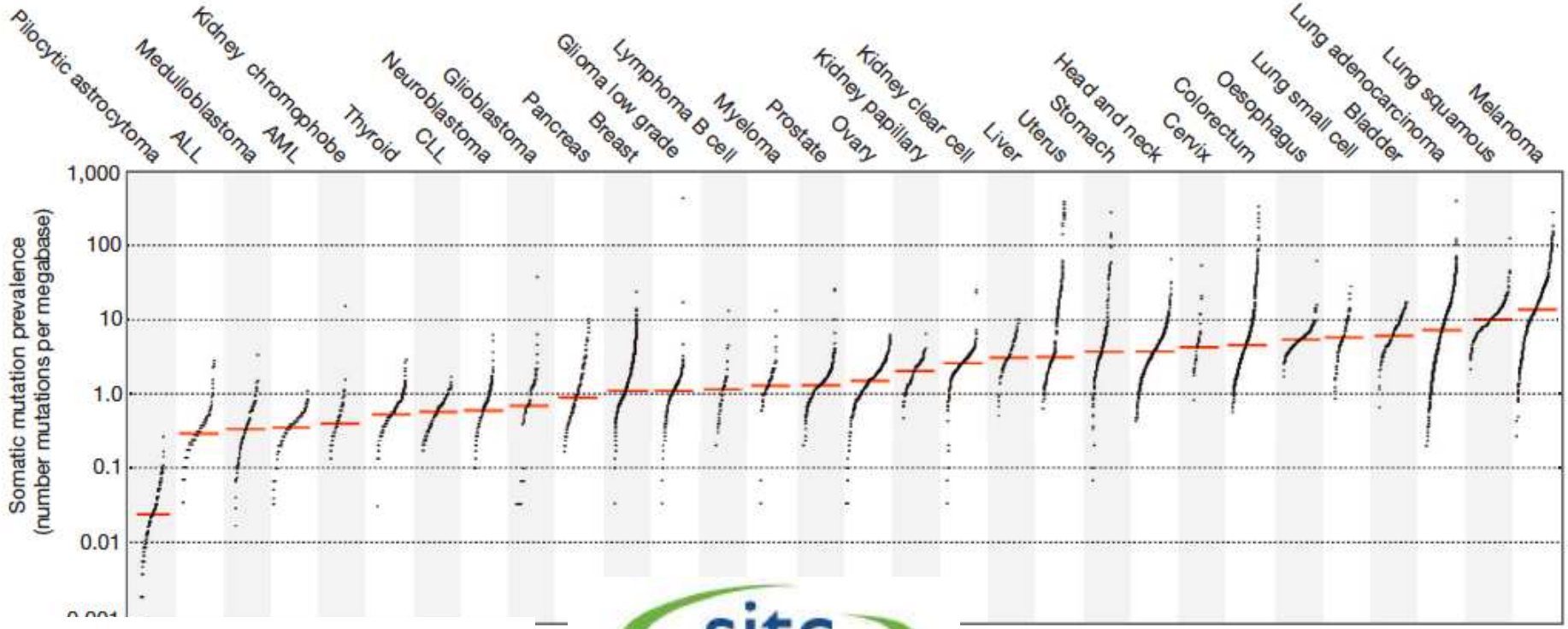
ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

Alexandrov L et al. Nature 2013



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ARTICLE

doi:10.1038/nature12477

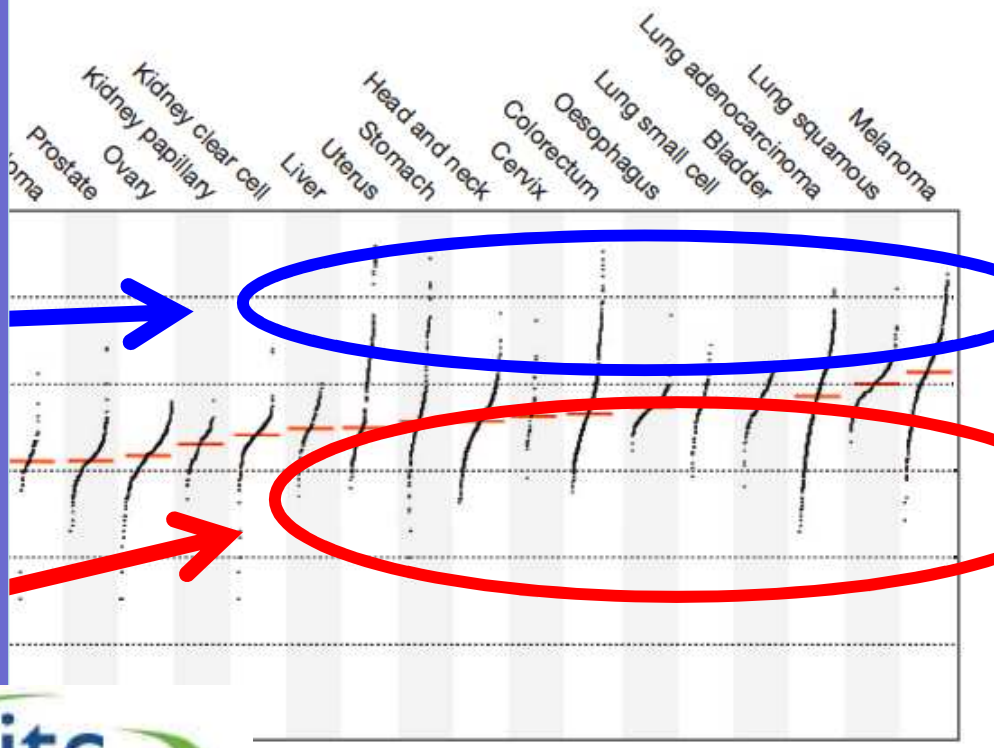
Signatures of mutational processes in human cancer

Alexandrov L et al. Nature 2013

Hypothesis

Immune Resp +

Immune Resp -



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ARTICLE

doi:10.1038/nature12477

Signatures of mutational processes in human cancer

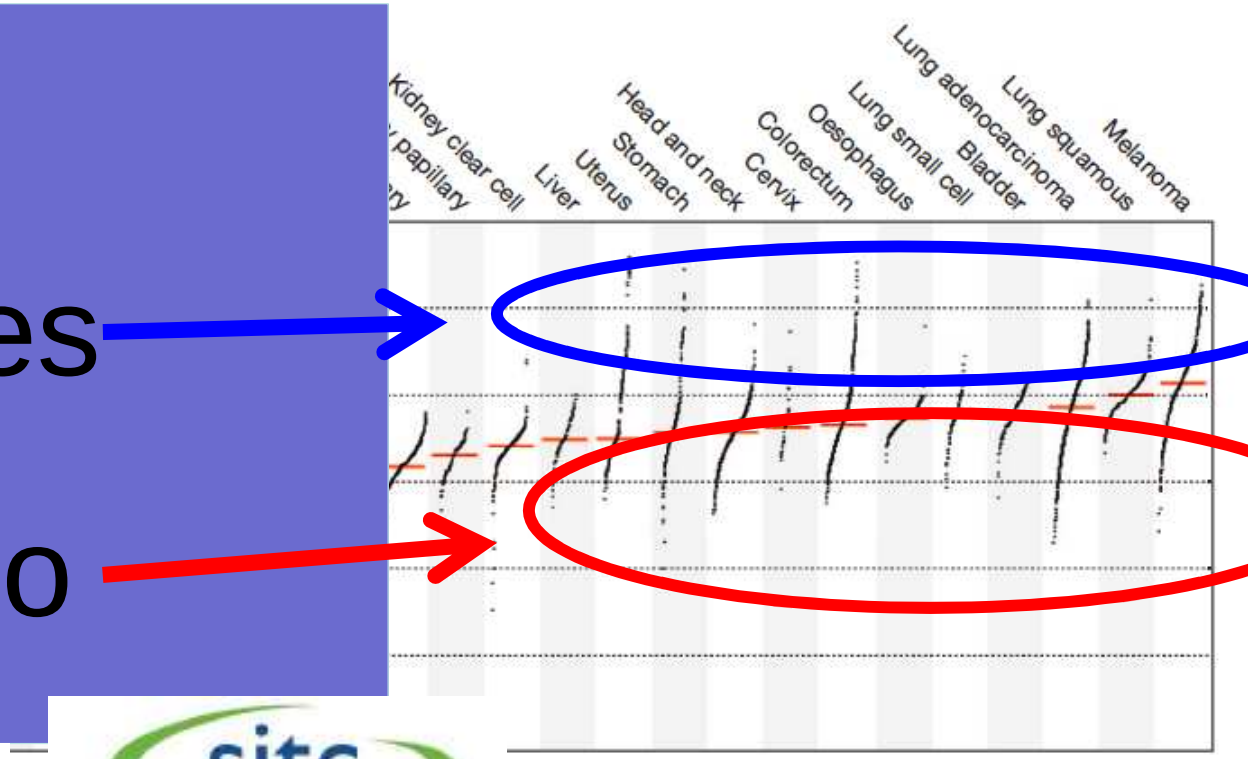
Alexandrov L et al. Nature 2013

Respond to checkpoint blockade?

Yes

Hypothesis

No



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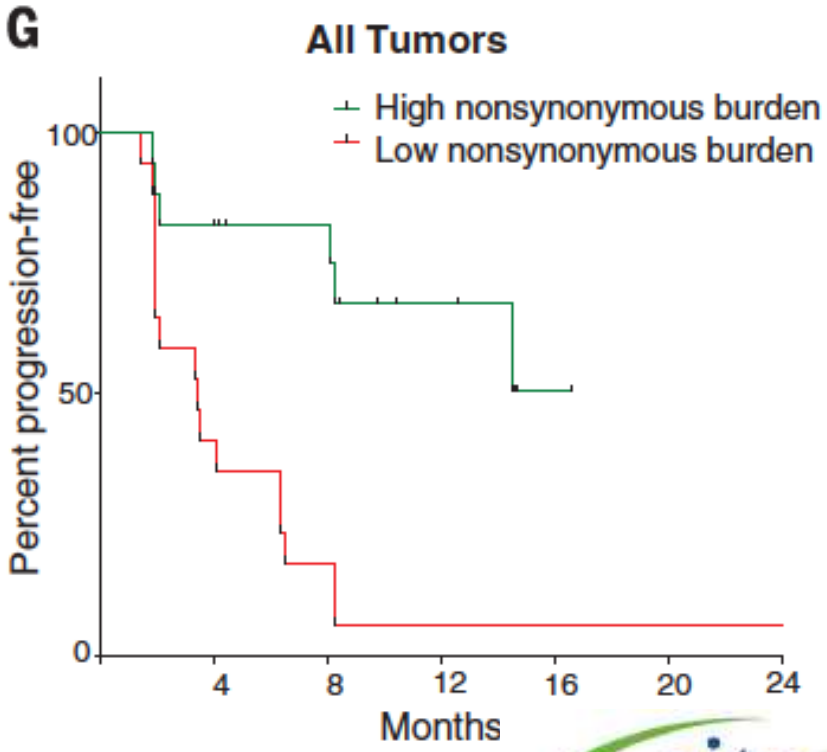
Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Naiyer A. Rizvi,[1,2*†] Matthew D. Hellmann,[1,2*] Alexandra Snyder,[1,2,3*] Pia Kvistborg,[4] Vladimir Makarov,[3] Jonathan J. Havel,[3] William Lee,[5] Jianda Yuan,[6] Phillip Wong,[6] Teresa S. Ho,[6] Martin L. Miller,[7] Natasha Rekhtman,[8] Andre L. Moreira,[8] Fawzia Ibrahim,[1] Cameron Bruggeman,[9] Billel Gasmi,[10] Roberta Zappasodi,[10] Yuka Maeda,[10] Chris Sander,[7] Edward B. Garon,[11] Taha Merghoub,[1,10] Jedd D. Wolchok,[1,2,10] Ton N. Schumacher,[4] Timothy A. Chan[2,3,5‡]

3 APRIL 2015 • VOL 348 ISSUE 6230



Hypothesis: PD-1 Blockade works in patients with a "pre-existing" immune response against their tumor.

This data supports hypothesis..

Big Question?

What will Prime Anti-Cancer Immunity

- Will combination immunotherapies?
  - Standard therapies (chemo/rads)
  - Std. vaccines + Costim (OX40, 4-1BB)
  - Ab – Ab combinations (Tim3, OX40, LAG-3, VISTA …)
- "Re-direct" immune cells - Chimeric Antigen Receptor (CAR) T cells, DARTs, Bi-specific Abs.

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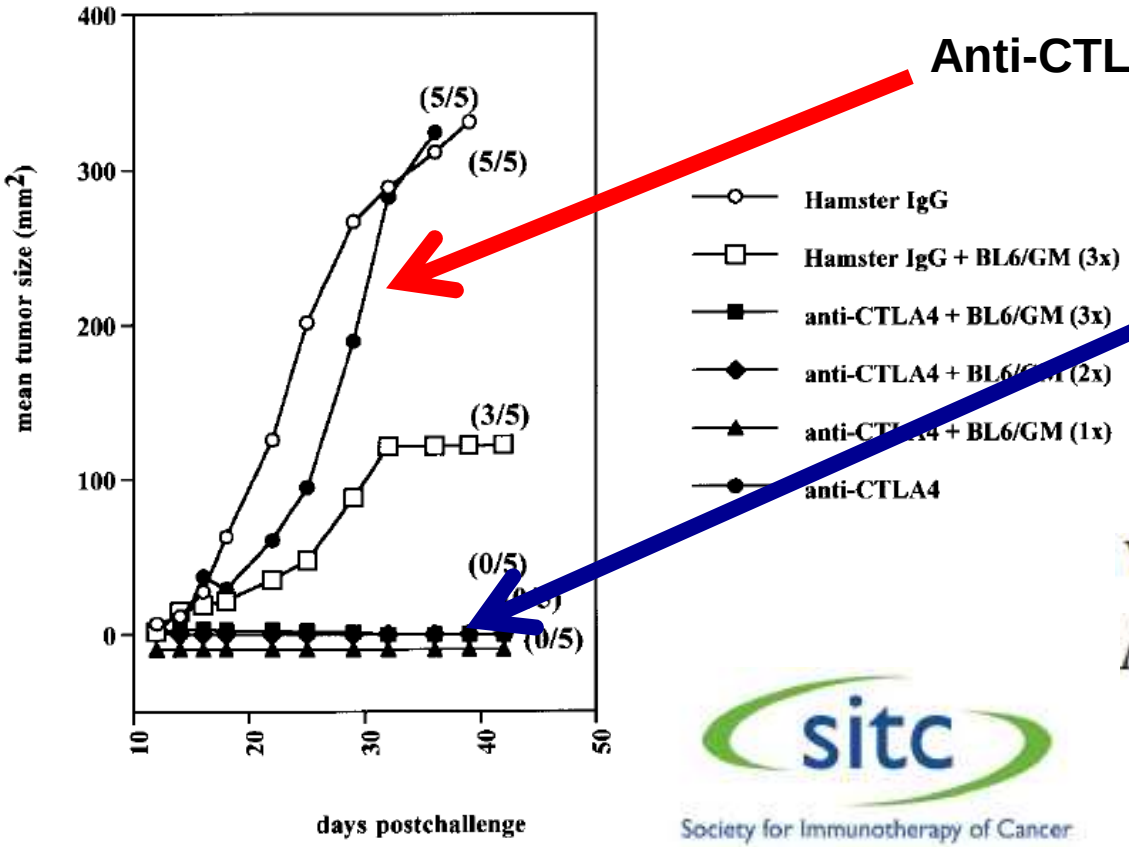
Combination Immunotherapy of B16 Melanoma Using Anti–Cytotoxic T Lymphocyte–associated Antigen 4 (CTLA-4) and Granulocyte/Macrophage Colony-Stimulating Factor (GM-CSF)-producing Vaccines Induces Rejection of Subcutaneous and Metastatic Tumors Accompanied by Autoimmune Depigmentation

By Andrea van Elsas, Arthur A. Hurwitz, and James P. Allison



Anti-CTLA-4 alone

Vaccine + Anti-CTLA-4

J. Exp. Med.
Volume 190, Number 3,
August 2, 1999 355–366

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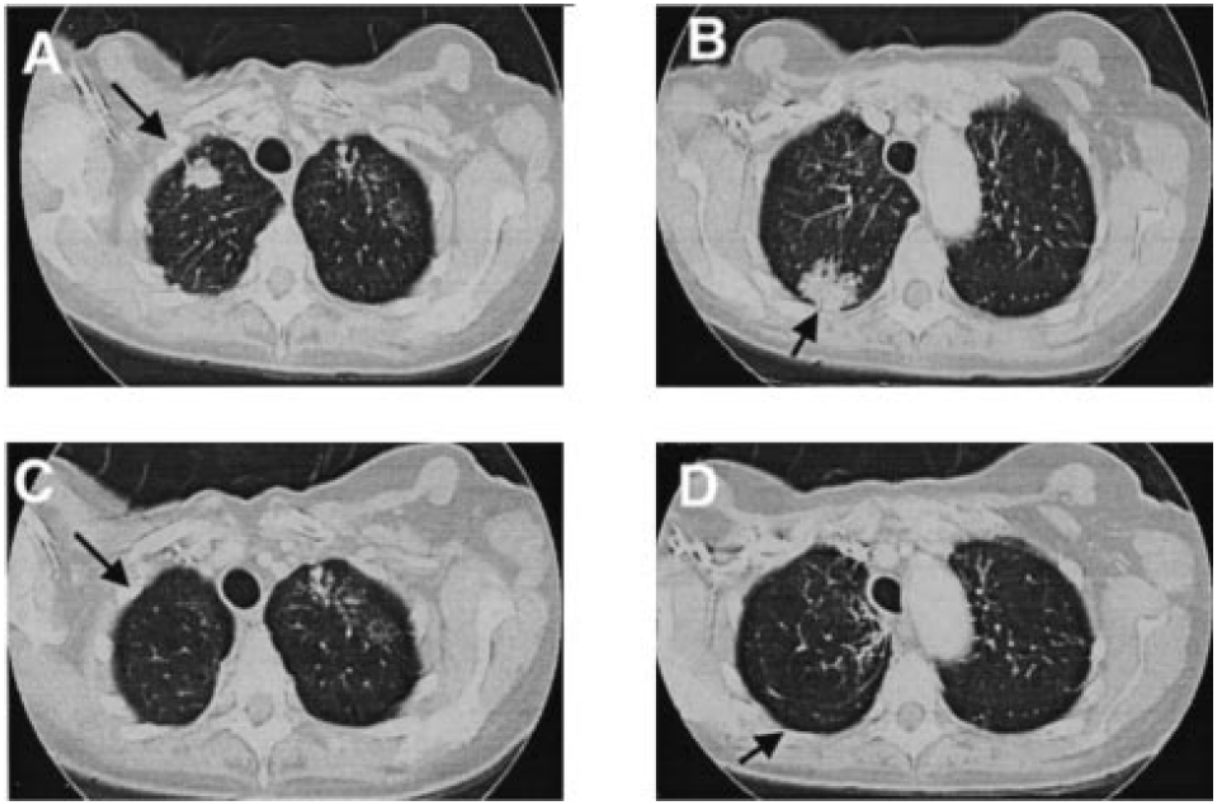
NSCLC Vaccines can induce CR (RARE)

BRIEF COMMUNICATION

Granulocyte–Macrophage Colony-Stimulating Factor Gene-Modified Autologous Tumor Vaccines in Non–Small-Cell Lung Cancer

John Nemunaitis, Daniel Sterman, David Jablons, John W. Smith II, Bernard Fox, Phil Maples, Scott Hamilton, Flavia Borellini, Andy Lin, Sayeh Morali, Kristen Hege



Journal of the National Cancer Institute, Vol. 96, No. 4, February 18, 2004

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LUNG CANCER IMMUNOTHERAPY TREATMENTS IN CLINICAL TRIALS

Treatment stratgies	Clinical trials
Non-small cell lung cancer (NSCLC)	
Therapeutic cancer vaccines	• tergenpumatucel-L (HyperAcute), which consists of genetically modified lung cancer cells • GV1001, which is specific for a protein called telomerase, found in nearly all cancers • TG4010, which targets the antigen MUC1 • CV9202 RNActive-derived cancer vaccine, which consists of six different cancer antigens • DRibble (DPV-001), which is a DC targeted vaccine containing more than 100 antigens overexpressed by the average lung cancer, plus toll-like receptor (TLR) adjuvants • racotumomab (Vaxira), which is specific for an antigen found on the surface of tumor cells • Adoptive T cell transfer as treatment for patients with lung cancers expressing the NY-ESO-1 cancer antigen

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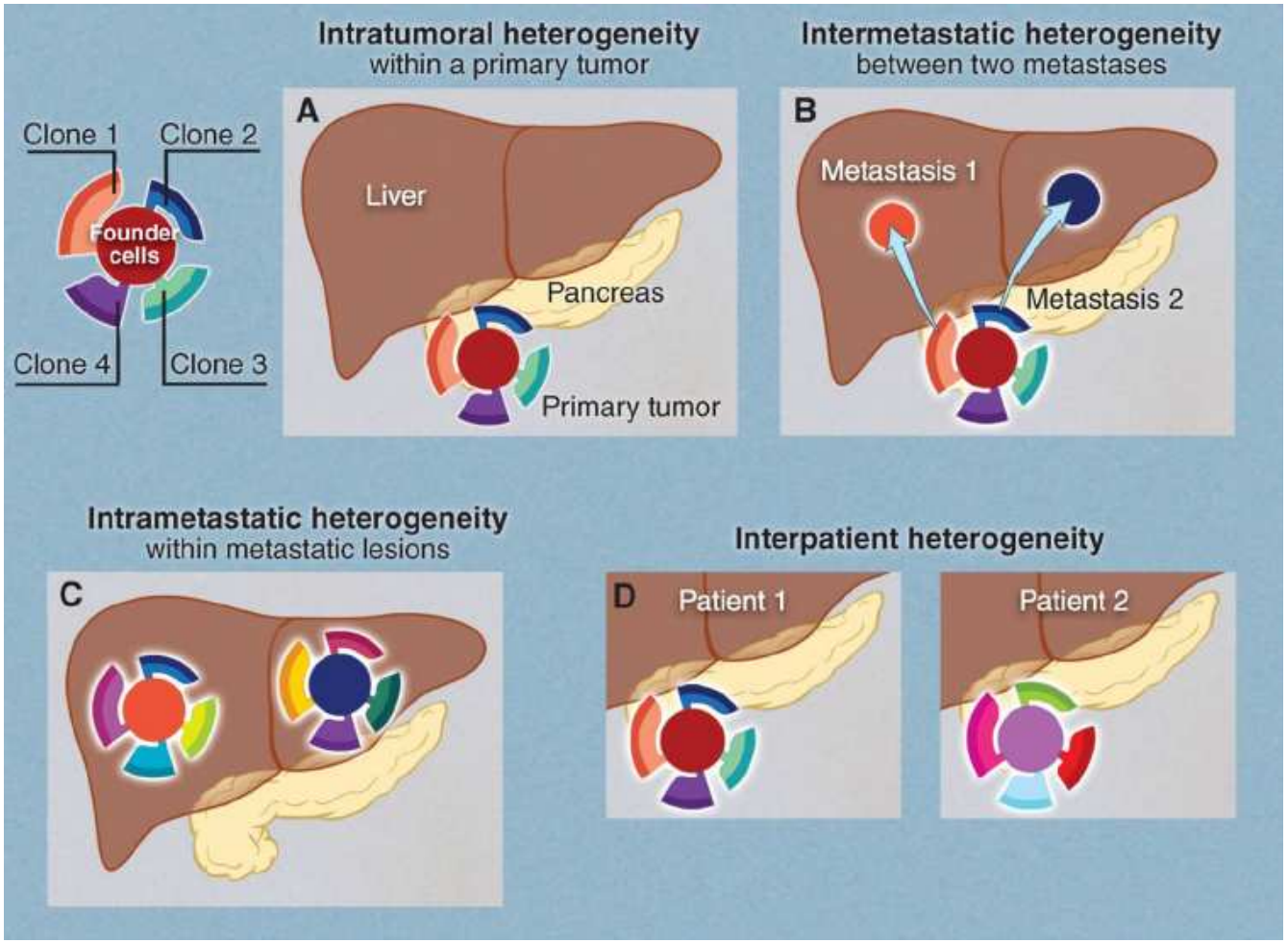
Hypothesis: Cancer Heterogeneity Mandates Requirement for Broad Immunity



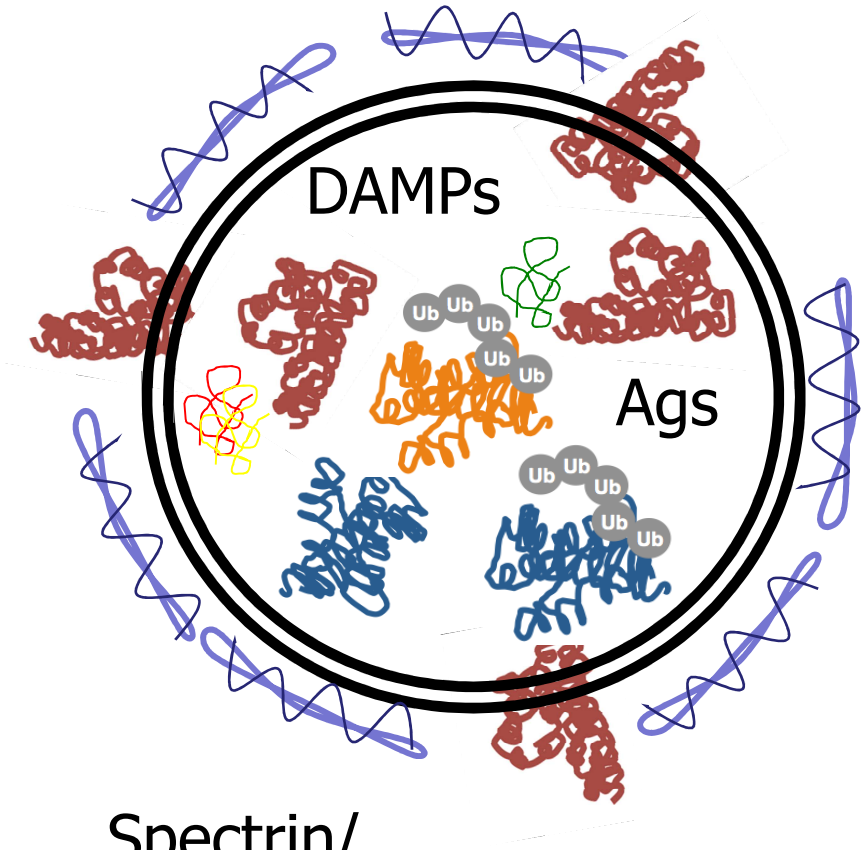
Vogelstein B, Science 339:1546, 2013

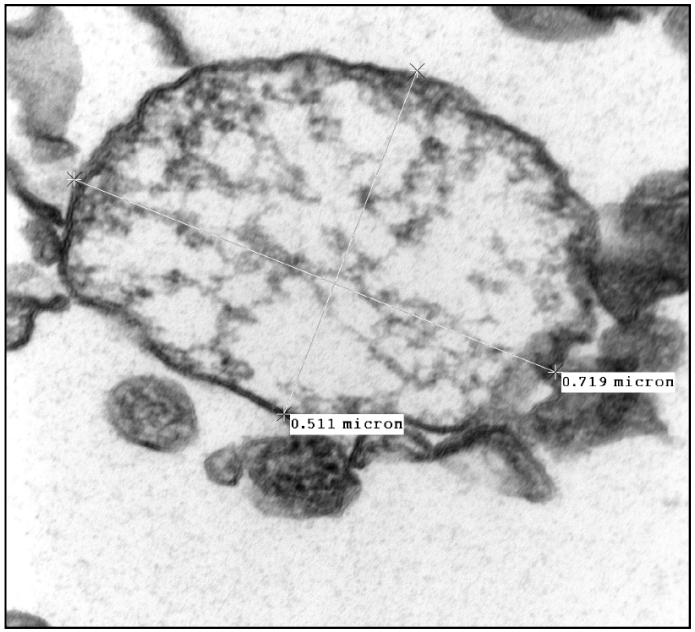
Science
AAAS

Hypothesis:

Effective treatment of metastatic cancer will require an immune response to many antigens

Characterization of DPV-001: A Cancer Autphagosome Vaccine





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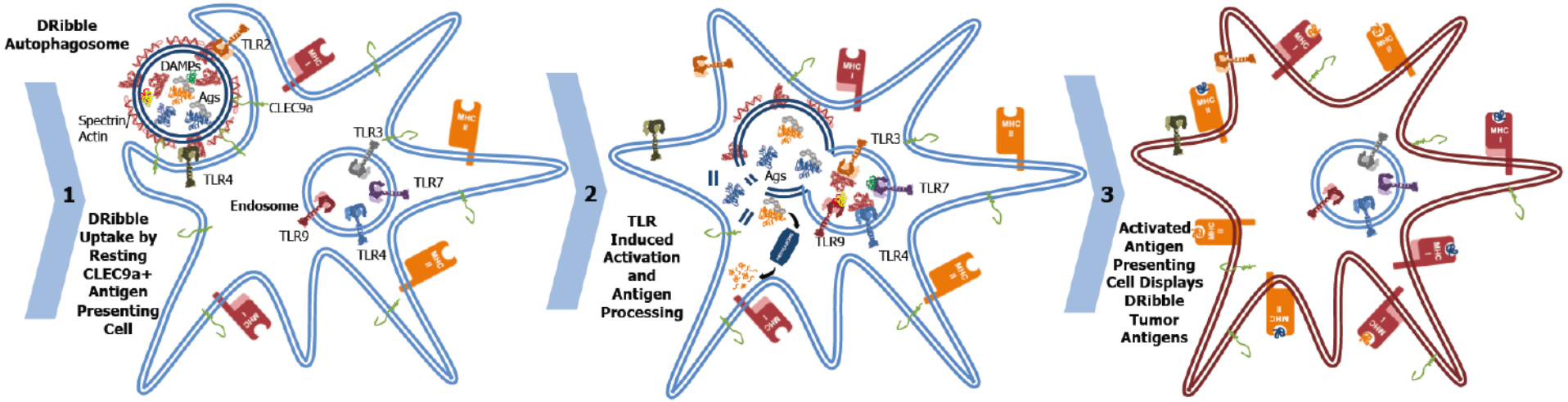
Proposed Model for DPV-001 Cross-Presentation



DPV-001: APC-Targeted delivery of a stable double membrane vesicle containing more than 100 putative cancer antigens overexpressed by NSCLC, DAMPs and agonists for TLR 2, 3, 4, 7 and 9

NCT01909752 / NCT02234921

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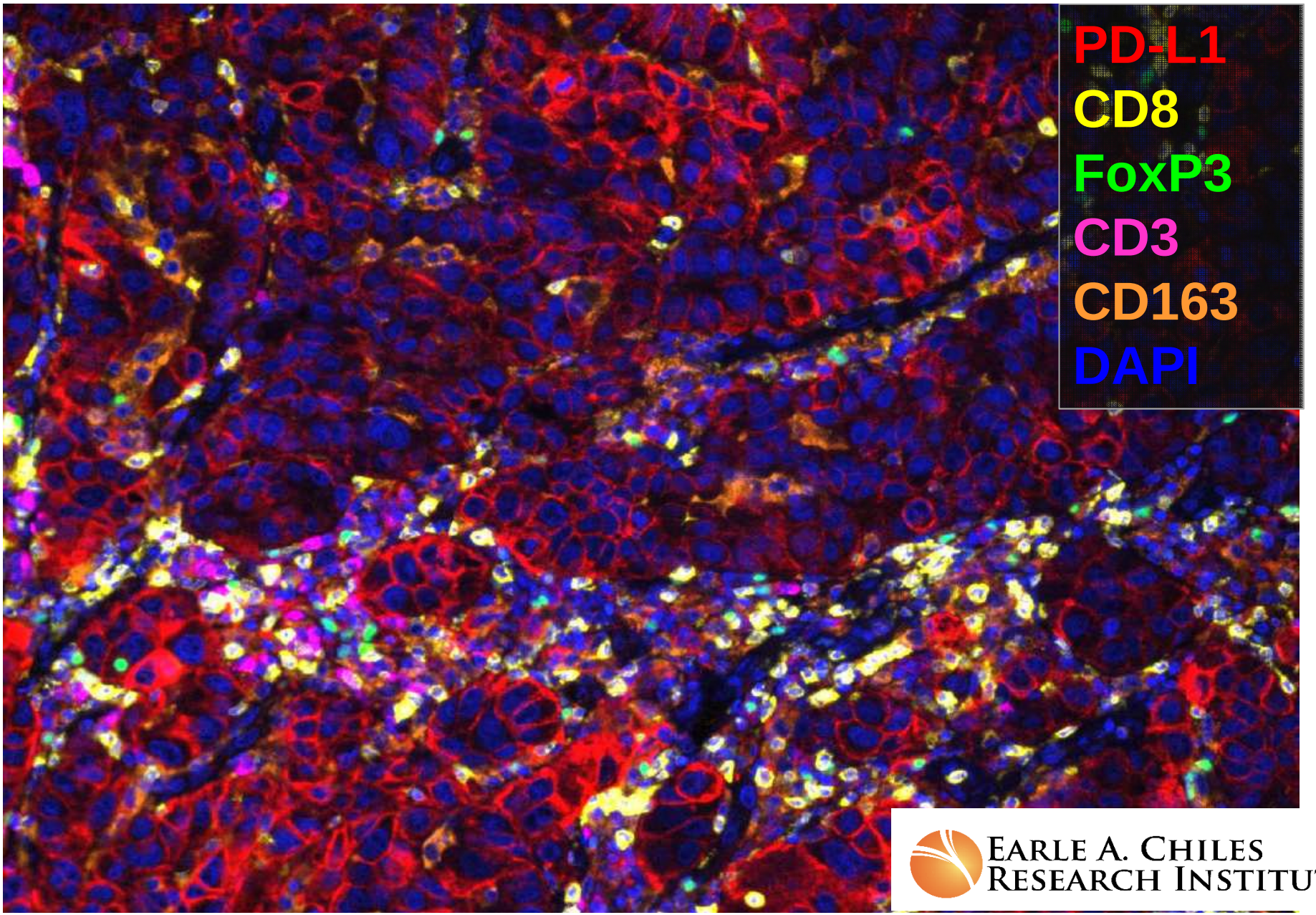
NSCLC metastasis post DPV-001 vaccination:
Tumor cells are strong PD-L1+ and infiltrated by T cells



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Phase I/II Combination: 2nd line Metastatic Squamous NSCLC DPV-001 + anti-PD-1 vs anti-PD-1 alone

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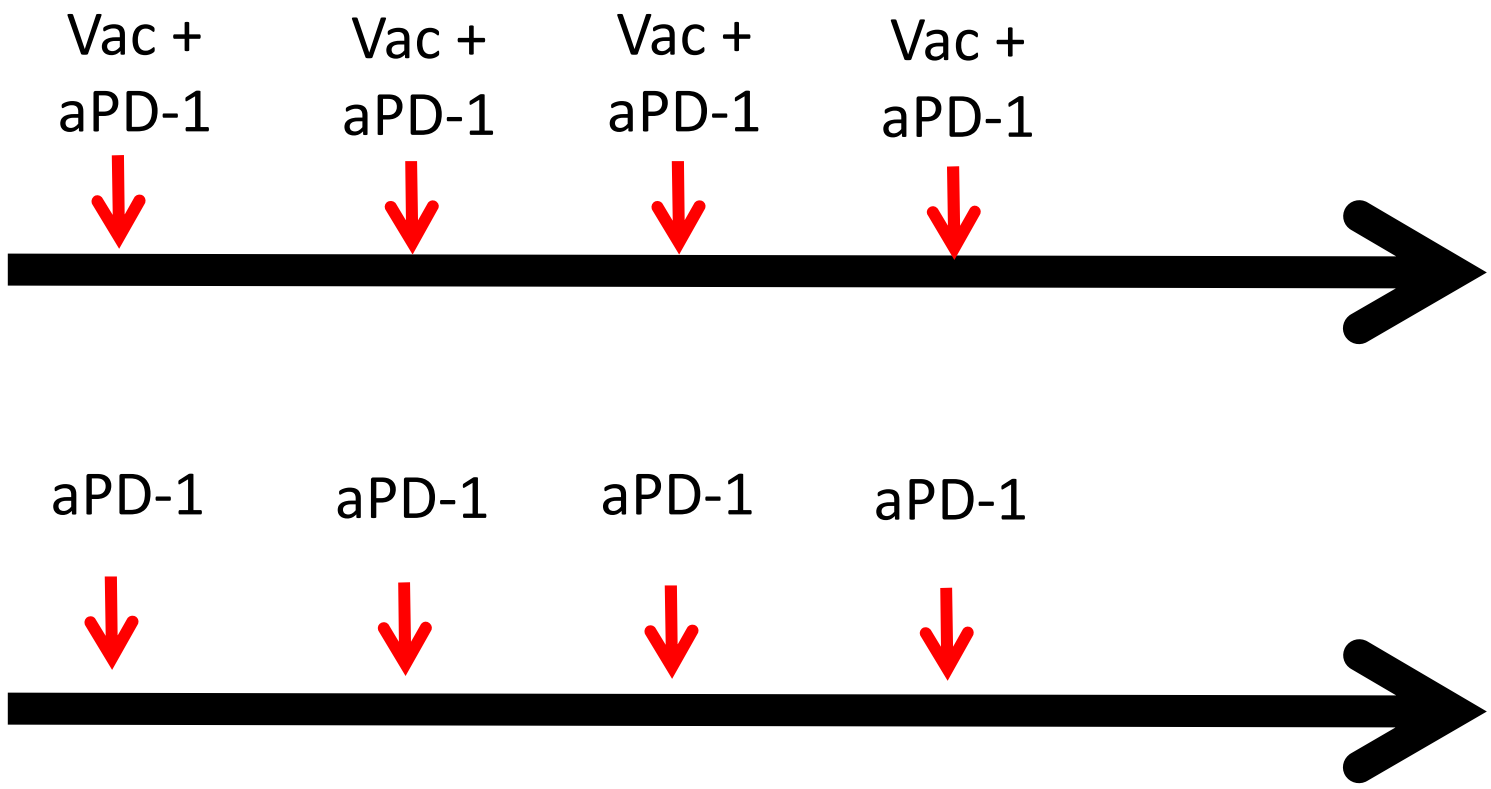

270 – 300 patients

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LUNG CANCER IMMUNOTHERAPY TREATMENTS IN CLINICAL TRIALS

Treatment stratgies	Clinical trials
Non-small cell lung cancer (NSCLC)	
Oncolytic virus therapy	• Reolysin, which uses a modified human reovirus (respiratory enteric orphan virus)
Small cell lung cancer (SCLC)	
Adjuvant immunotherapy	• MGN1703, a TLR
Checkpoint inhibitor	• ipilimumab (Yervoy)*, an anti-CTLA-4 antibody

THE NEW YORKER

"Never, ever, think outside the box."

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Antibiotics reduce effect of Oxaliplatin

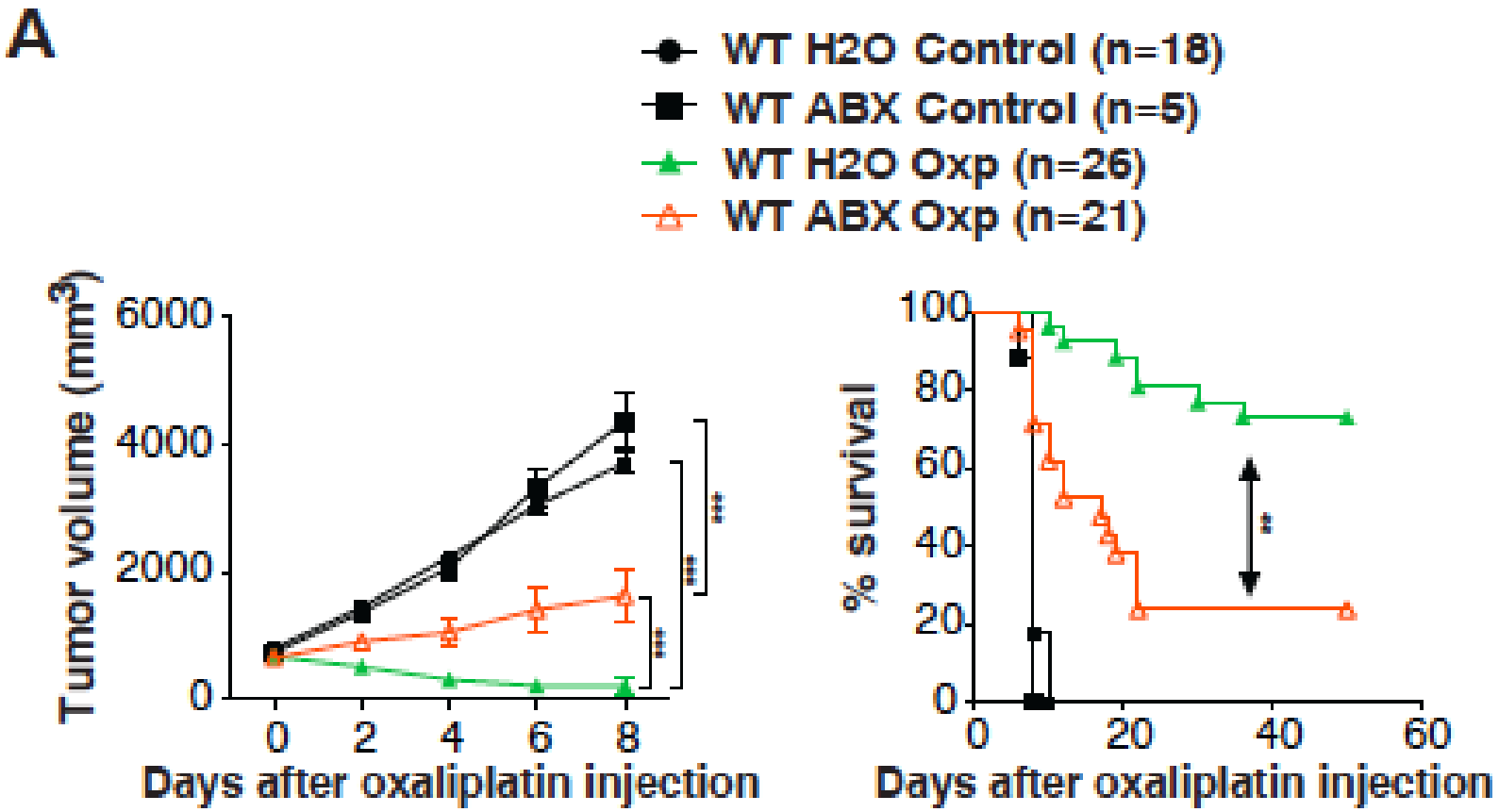

Fig. 4. Commensal bacteria control oxaliplatin therapy response by modulating ROS production. (A) Subcutaneous EL4 tumor-bearing H_2O- or ABX-treated mice were treated with oxaliplatin (10 mg per kg of weight); tumor growth (top) and survival (bottom) are shown. (B) Global gene expression

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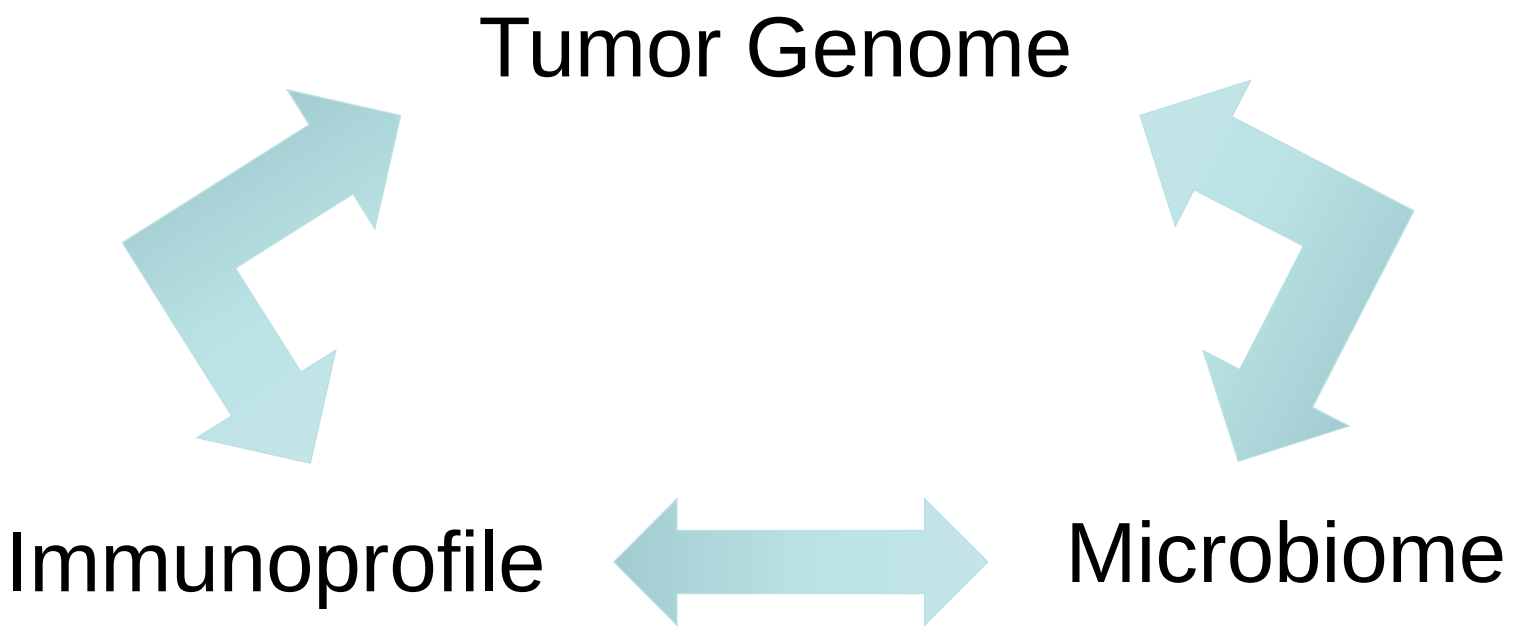

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