I farmaci immunoterapici

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History of Cancer Immunotherapy

1970s

Discovery of dendritic cell[1]

Immune component to spontaneous regressions in melanoma

1980s

Tumor-specific monoclonal Abs

Adoptive T-cell immunotherapy

1990s

BCG approved for bladder cancer

First tumor-associated antigen cloned (MAGE-1)

IFN-α as adjuvant therapy for melanoma[2]

IL-2 approved for RCC and melanoma (US)[3,4]

2000s

Discovery of checkpoint inhibitors[5-7]

2011

First immunotherapy approved for prostate cancer (sipuleucel-T)[8]

First checkpoint inhibitor (ipilimumab) approved for advanced melanoma[9]

2014

Pembrolizumab and nivolumab approved for advanced melanoma[10,11]

Nivolumab approved for NSCLC[12,13]

2015

Nivolumab approved for RCC[15]

Pembrolizumab approved for PD-L1+ NSCLC[14]

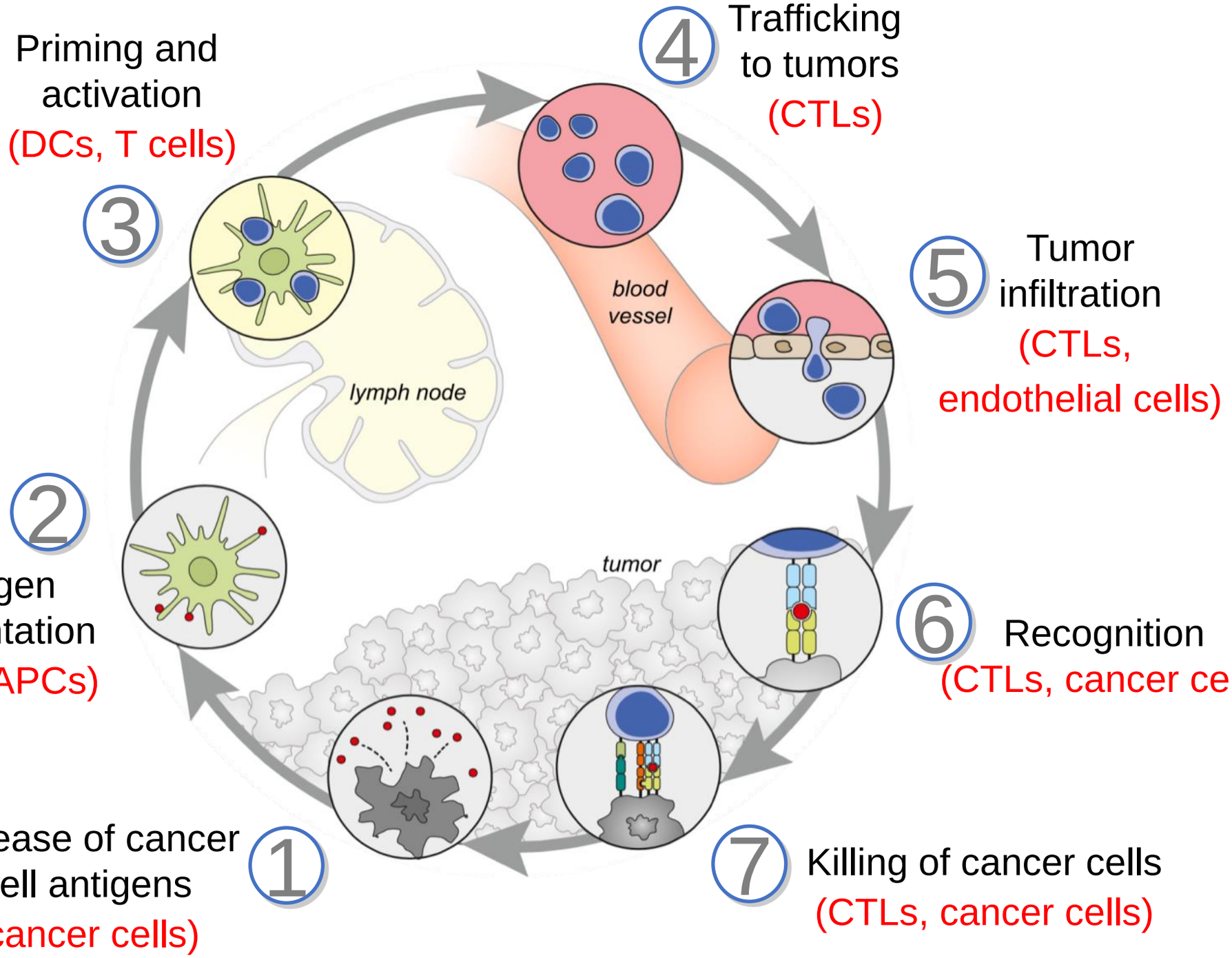
2016

Atezolizumab approved for advanced urothelial carcinoma[16]

Nivolumab approved for HL[17]

Atezolizumab granted Priority Review for PD-L1+ NSCLC

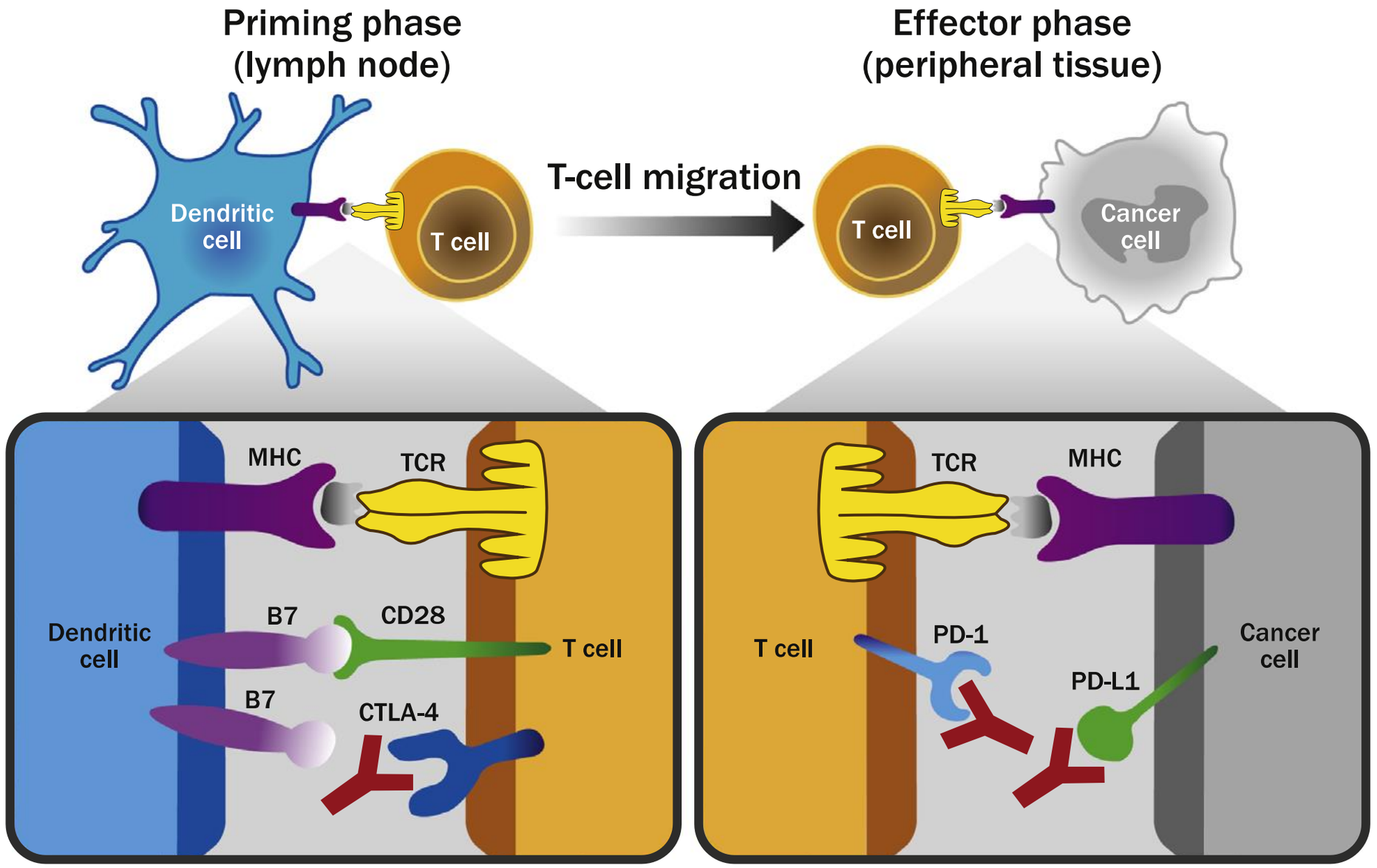
The Cancer Immunity Cycle



Slide credit: clinicaloptions.com

CTLA-4 and PD-1/L1 checkpoint blockade for cancer treatment

Pennell, N. Sem Oncol 2015, S3-S10



Classification of anti-PD-1/PD-L1 mAbs

Compound	Target	Clinical indication
Nivolumab	PD-1	Melanoma, NSCLC, RCC, Urothelial, cHL, HNSCC, +ipilimumab combos
Pembrolizumab	PD-1	NSCLC, +chemo (NSCLC), HNSCC, cHL (adult), MSI-H and dMMR tumors, Melanoma, cHL (peds), Urothelial
Atezolizumab	PD-L1	NSCLC, Urothelial
Durvalumab	PD-L1	Urothelial
Avelumab	PD-L1	Merkel cell, Urothelial

Activation of ADCC/CDC by ICIs

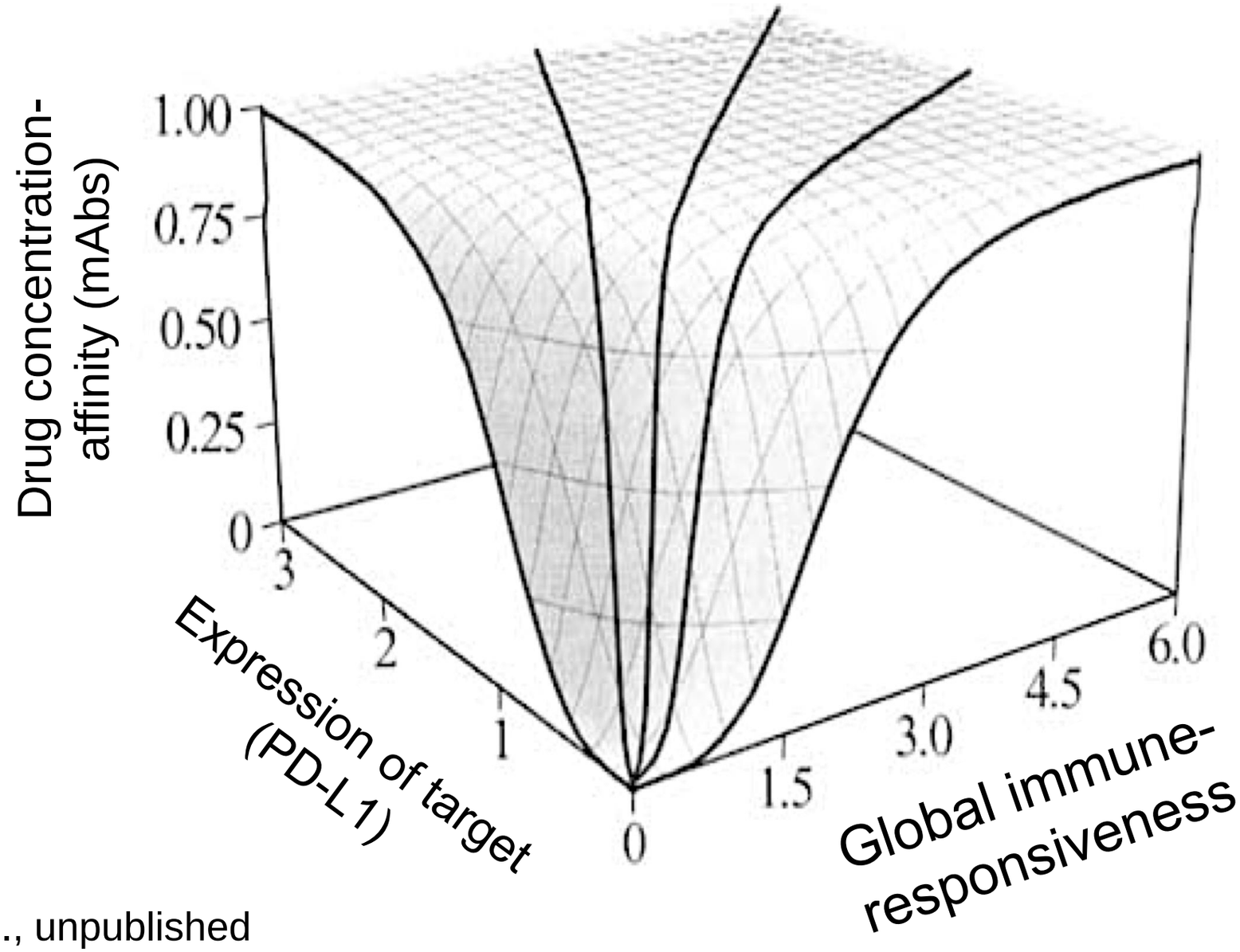
Table II. Isotype of immune-checkpoint inhibitors.

Checkpoint Inhibitor	Killer Isotype	Nonkiller Isotype
Anti-CTLA-4	Ipilimumab (IgG1)	Tremelimumab (IgG2)
Anti-PD-1	Pidilizumab (IgG1)	Nivolumab (IgG4), pembrolizumab (IgG4)
Anti-PD-L1	–	BMS-936559 (IgG4), MPDL-3280A (mutated IgG1 that eliminates ADCC and CDC)

ADCC = antibody-dependent cell-mediated cytotoxicity; CDC = complement dependent cytotoxicity; CTLA = cytotoxic T-lymphocyte antigen; Ig = immunoglobulin; PD = programmed cell death protein.

Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

3-D model of drug-target-immune-activation relationships for ICPI



Danesi et al., unpublished

Kd of PD-L1 and PD-L2 for PD-1

PD-1		
PD-1:PD-L1		
270–526 nM	Youngnak et al[49]	(Scatchard plots analysis)
590–770 nM	Butte et al[48]	(Scatchard plots analysis)
770 nM	Butte et al[48]	(equilibrium binding†)
PD-1:PD-L2		
89–106 nM	Youngnak et al[49]	(Scatchard plots analysis)
590 nM	Butte et al[48]	(equilibrium binding†)

Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

SCIENTIFIC REPORTS

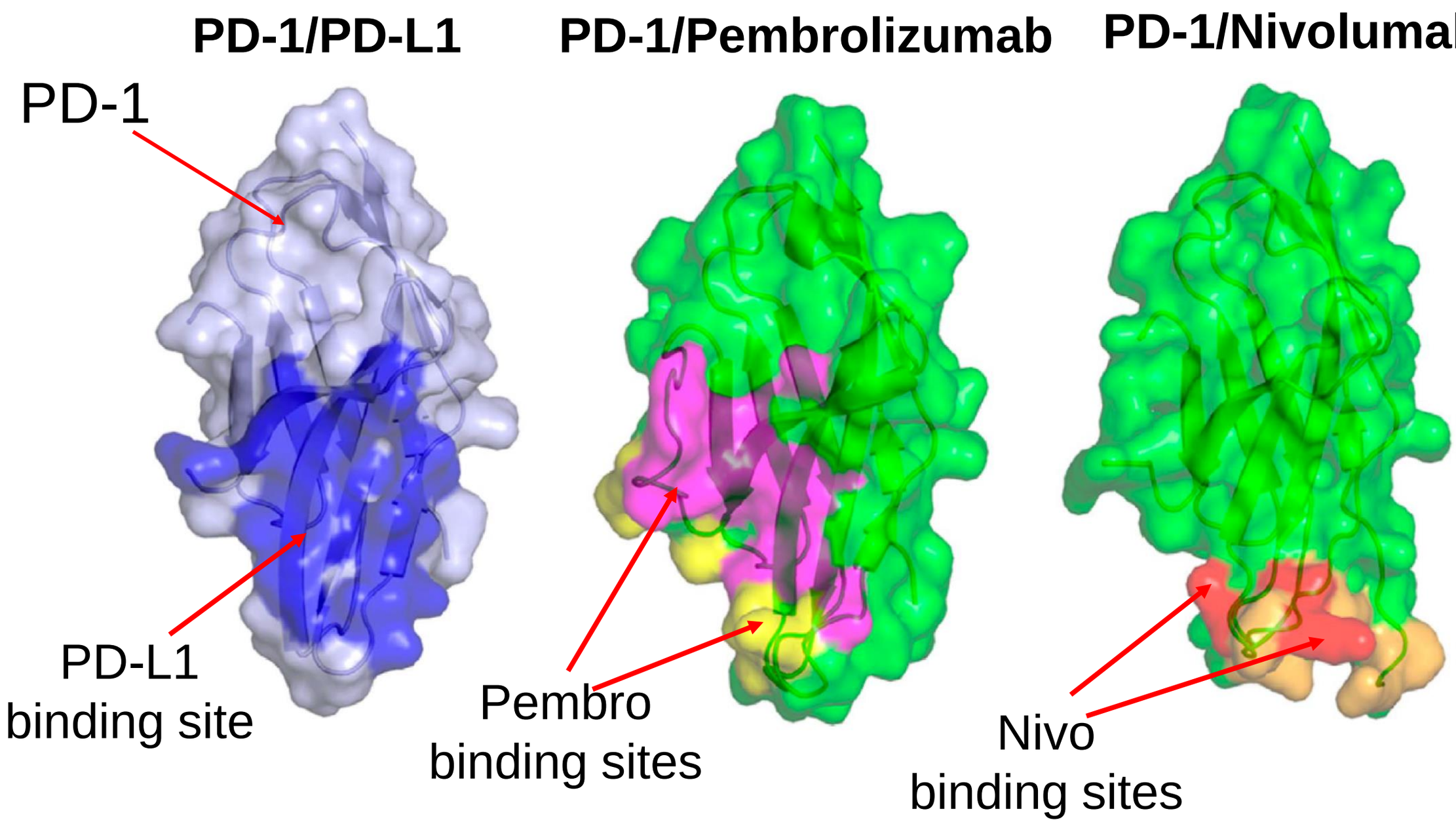
OPEN

High-resolution crystal structure of the therapeutic antibody pembrolizumab bound to the human PD-1

Received: 01 July 2016
Accepted: 27 September 2016
Published: 13 October 2016

Shoichiro Horita[1], Yayoi Nomura[1,2], Yumi Sato[1,2], Tatsuro Shimamura[1,2], So Iwata[1,2,3] & Norimichi Nomura[1,2]

Interactions between PD-1 and anti-PD-1 drugs



Ju Yeon Lee et al. Nat Commun. 2016

Binding affinity of blocking antibodies to PD-1

Agent	Target	Description	K_D Binding Affinity
Nivolumab (BMS-936558, ONO-4538, MDX-1106)	PD-1	Finally human IgG4	3 nM
Pembrolizumab (MK-3475, lambrolizumab)	PD-1	Humanized IgG4 kappa	28 pM
Pidilizumab (CT-011)	PD-1	Humanized anti–PD-1 IgG1 kappa	20 nM

Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

Agrawal *et al. Journal for ImmunoTherapy of Cancer* (2016) 4:72
DOI 10.1186/s40425-016-0177-2

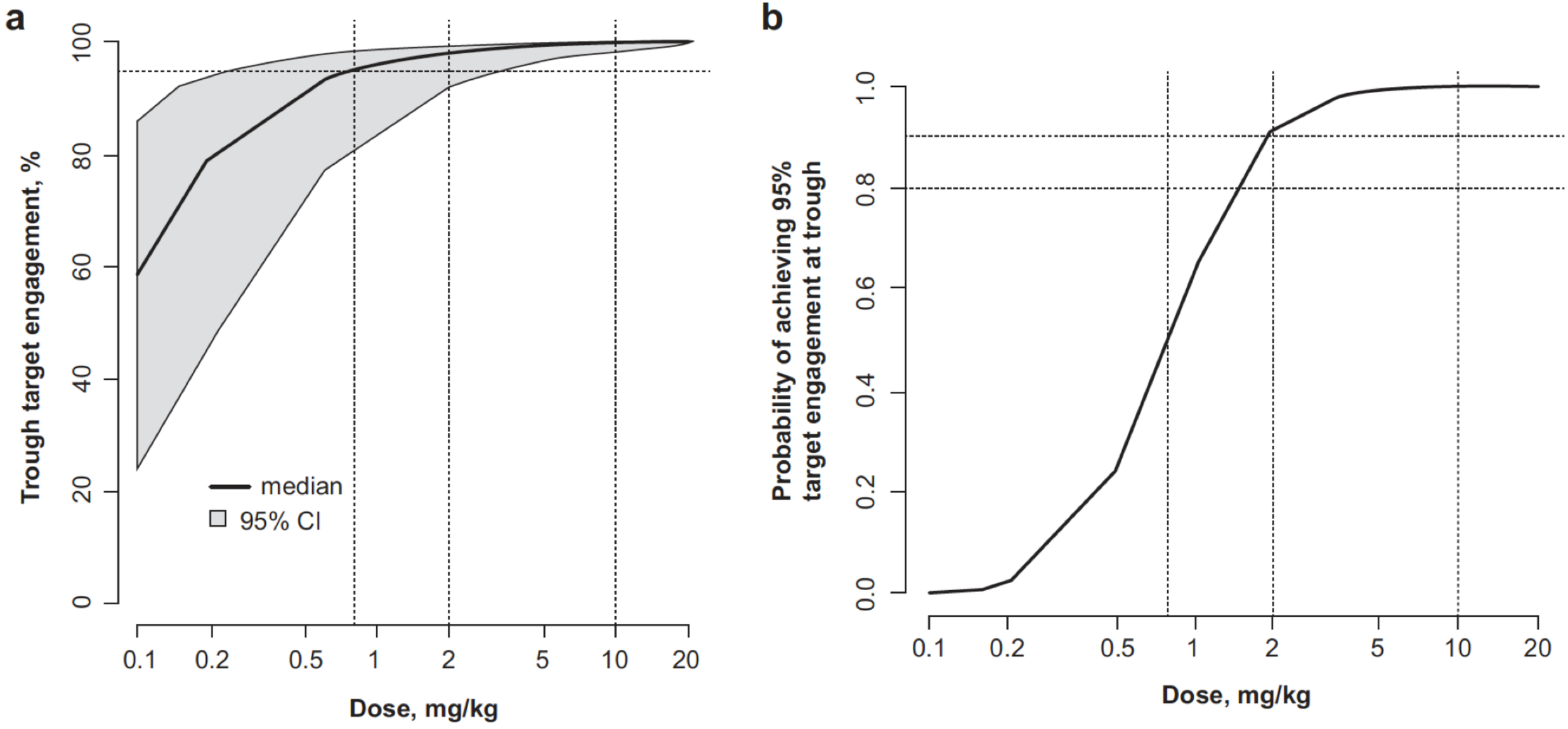
Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Nivolumab dose selection: challenges, opportunities, and lessons learned for cancer immunotherapy

Shruti Agrawal[1*], Yan Feng[1], Amit Roy[1], Georgia Kollia[2] and Brian Lestini[3]

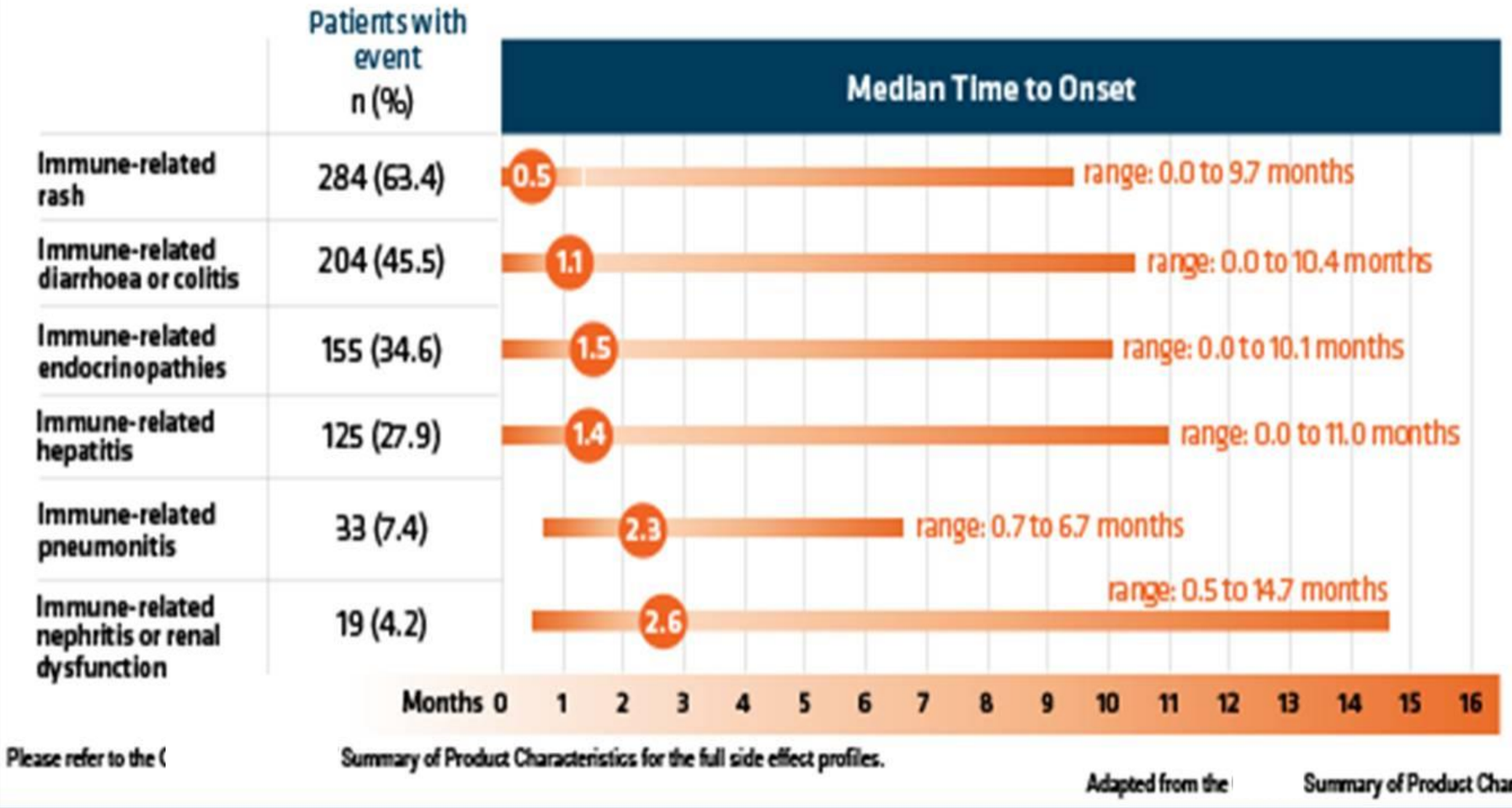
Target engagement as a function of Css



Agrawal et al. Journal for ImmunoTherapy of Cancer (2016) 4:72

Adverse Event Timing

Time to onset of treatment-related immune-related AEs (any Grade) in patients who received NIVO +IPI Regimen across three clinical studies in melanoma (n=448)[1]



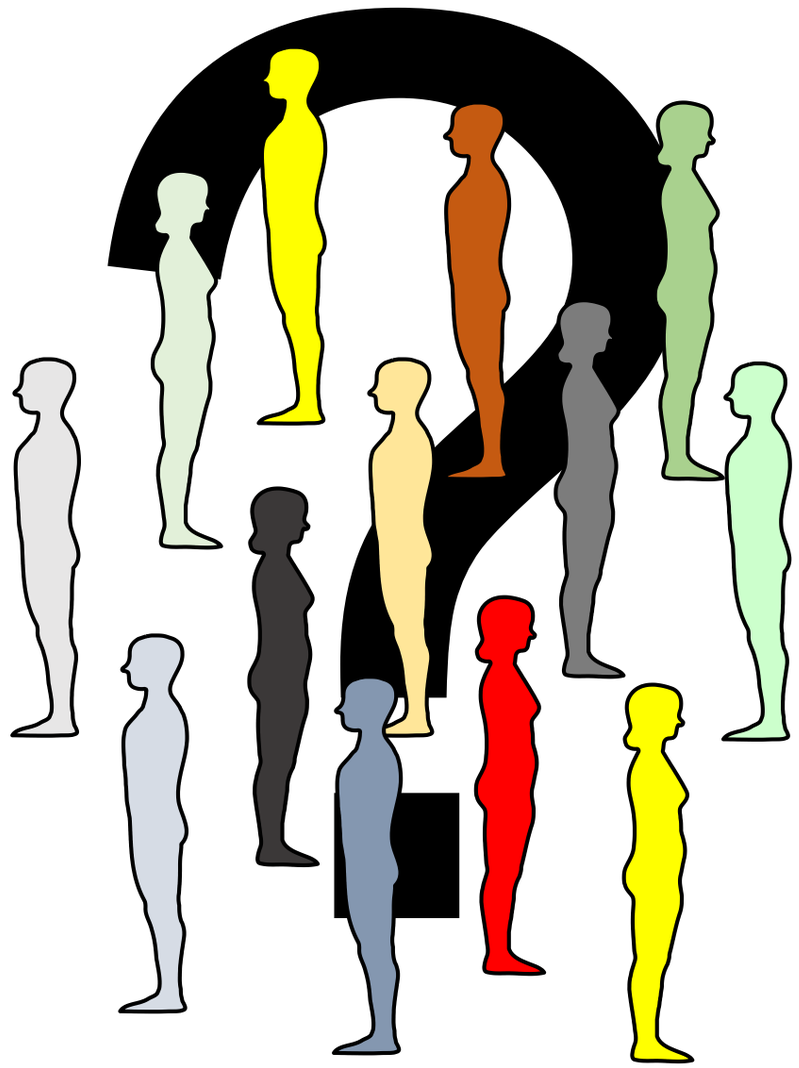
Please refer to the (Summary of Product Characteristics for the full side effect profiles.

Adapted from the Summary of Product Characteristics

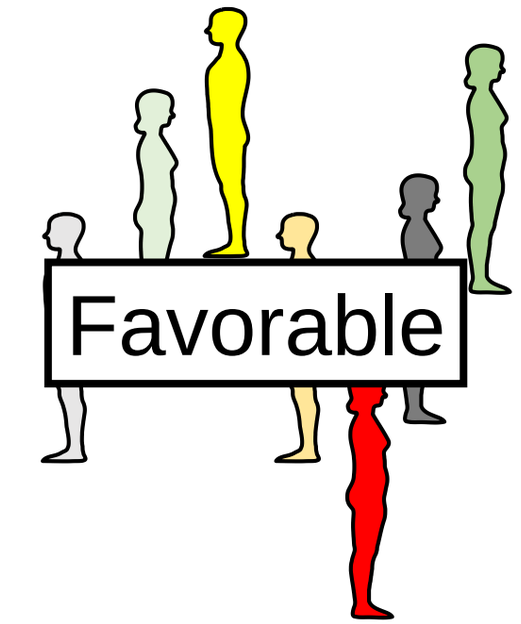
Risk to benefit ratio

Patient- and
Drug-related variables

Drug

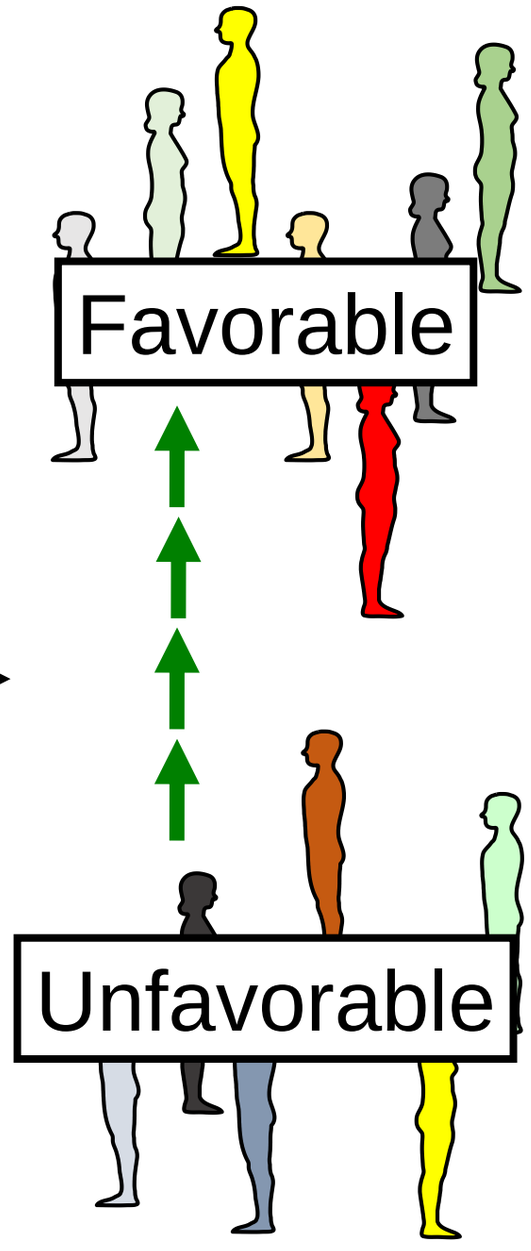


Result



Risk to benefit ratio

Drug → Biomarkers → Result



What about resistance?

- The majority of patients demonstrating innate resistance
  - Objective responses to PD-1 blockade is observed in only **30–40%** of them

- Acquired resistance to anti-PD-1 therapy is also a problem
  - **25%** of responders later demonstrating disease progression

Andrews and Wargo. J Immunother Cancer. 2017

The NEW ENGLAND JOURNAL of MEDICINE

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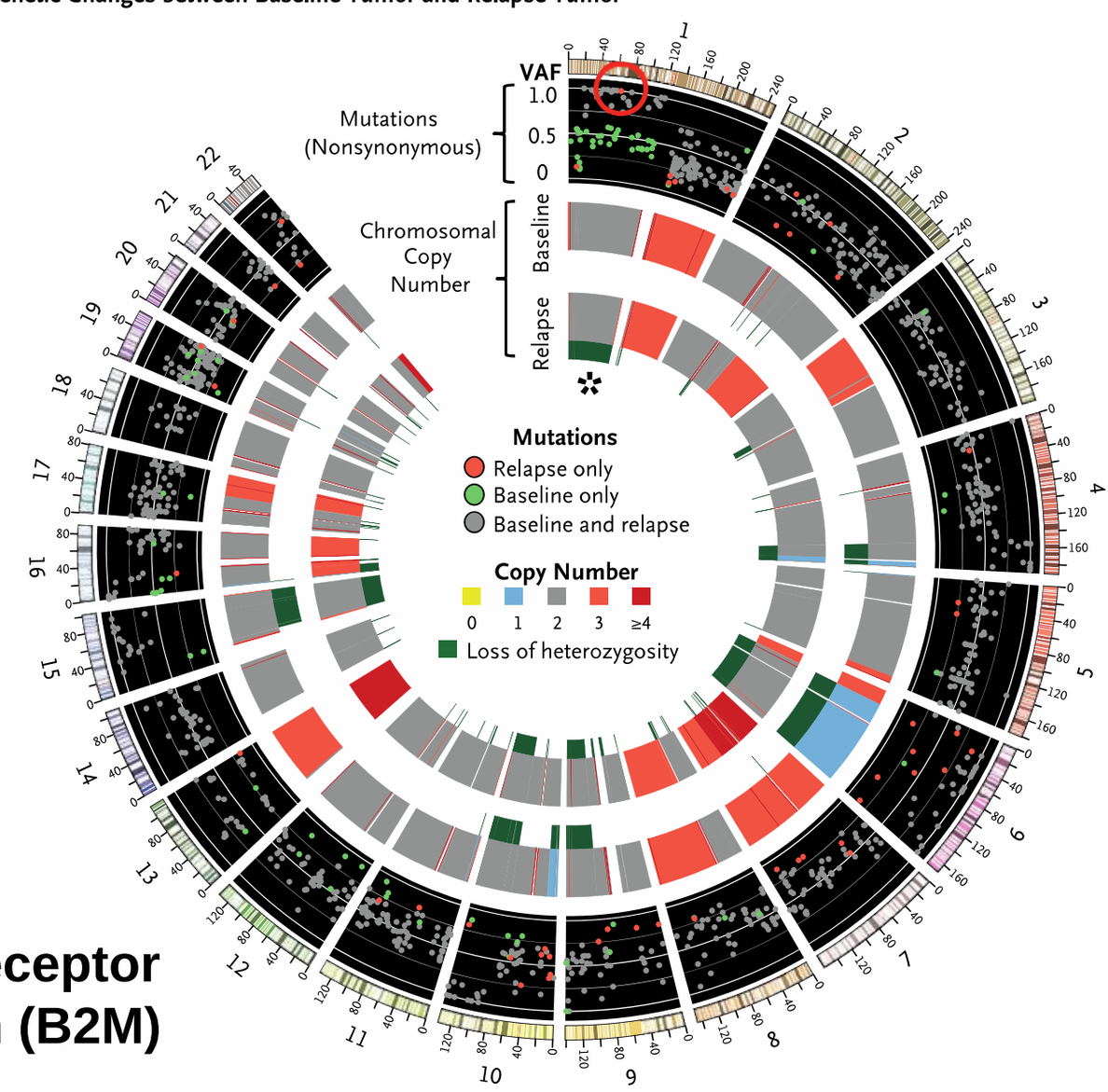
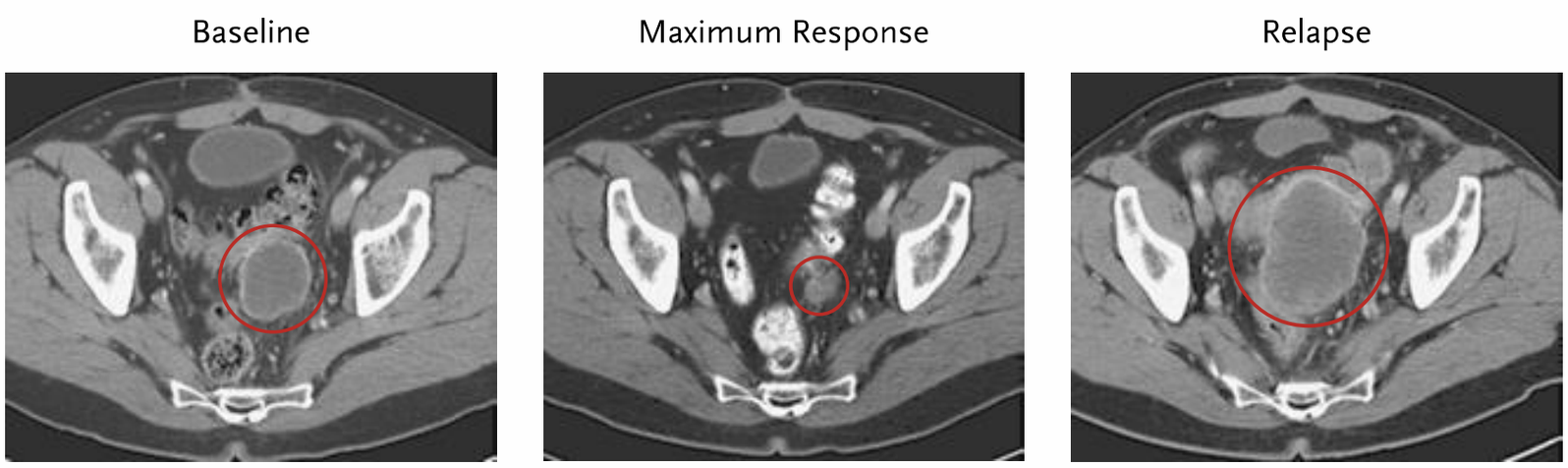
Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

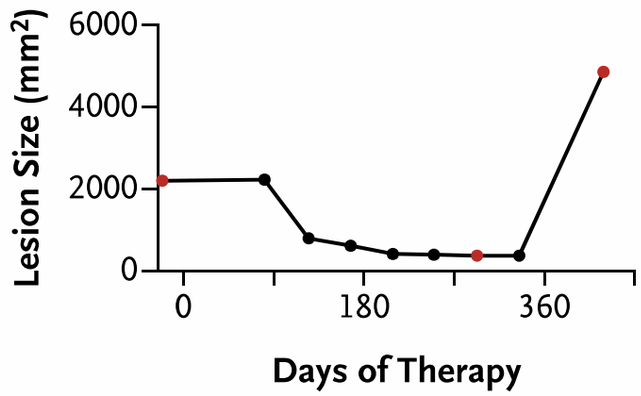
Jesse M. Zaretsky, B.S., Angel Garcia-Diaz, Ph.D., Daniel S. Shin, M.D., Helena Escuin-Ordinas, Ph.D., Willy Hugo, Ph.D., Siwen Hu-Lieskovan, M.D., Ph.D., Davis Y. Torrejon, M.D., Gabriel Abril-Rodriguez, M.Sc., Salemiz Sandoval, Ph.D., Lucas Barthly, M.Sc., Justin Saco, B.S., Blanca Homet Moreno, M.D., Riccardo Mezzadra, M.Sc., Bartosz Chmielowski, M.D., Ph.D., Kathleen Ruchalski, M.D., I. Peter Shintaku, Ph.D., Phillip J. Sanchez, Ph.D., Cristina Puig-Saus, Ph.D., Grace Cherry, R.N., N.P., Elizabeth Seja, B.A., Xiangju Kong, M.Sc., Jia Pang, B.S., Beata Berent-Maoz, Ph.D., Begoña Comin-Anduix, Ph.D., Thomas G. Graeber, Ph.D., Paul C. Tumeh, M.D., Ton N.M. Schumacher, Ph.D., Roger S. Lo, M.D., Ph.D., and Antoni Ribas, M.D., Ph.D.



Defects in the pathways involved in interferon-receptor signaling (JAK) and antigen presentation protein (B2M)

A Metastatic Lesion at Three Time Points





Nivolumab in Previously Treated Squamous NSCLC (CheckMate 017): OS by PD-L1 Expression

PD-L1 Exp. Level

1%

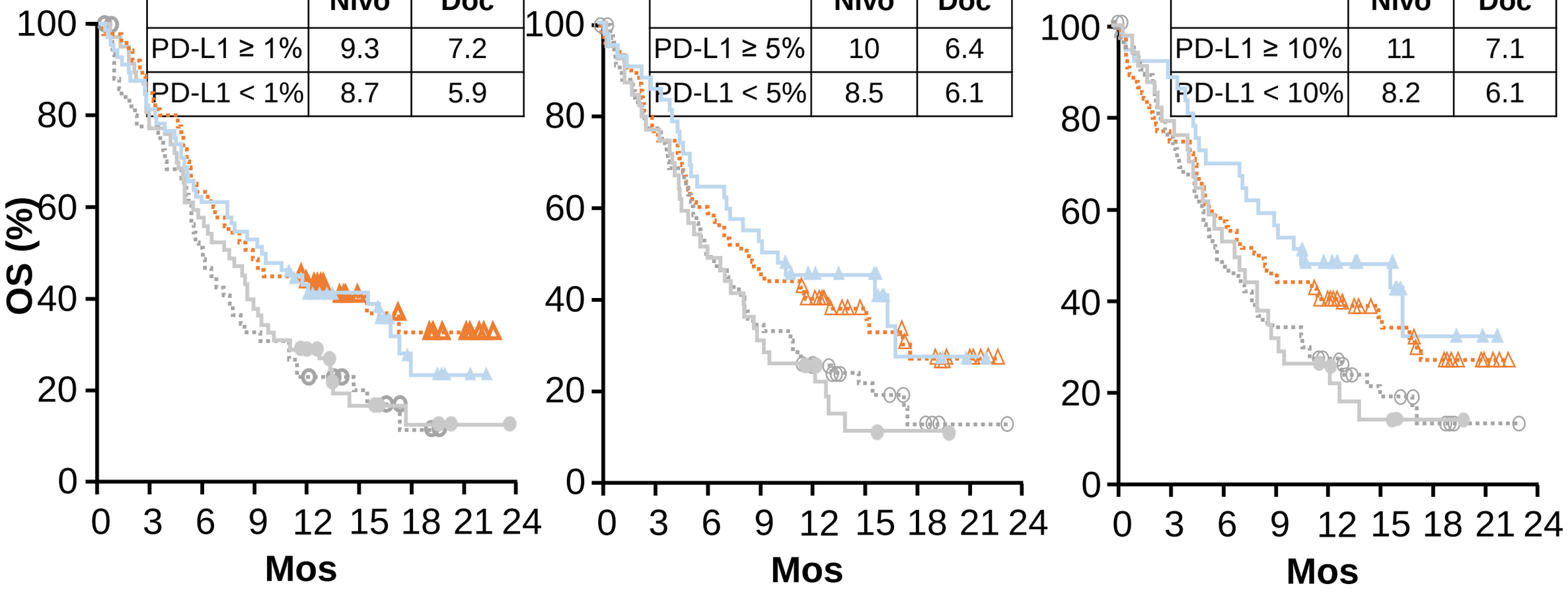
	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 1%	9.3	7.2
PD-L1 < 1%	8.7	5.9

5%

	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 5%	10	6.4
PD-L1 < 5%	8.5	6.1

10%

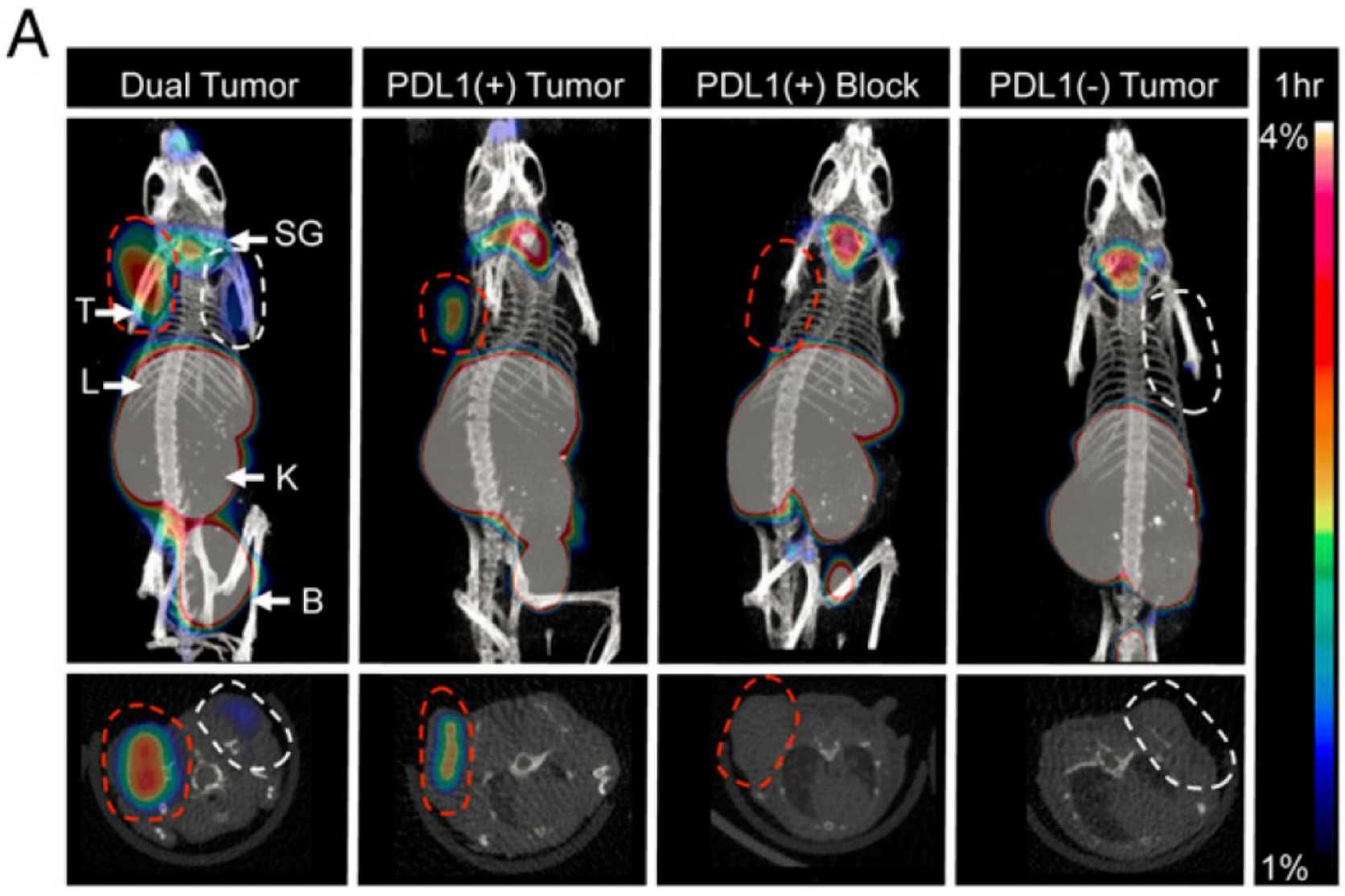
	Median OS, Mos	
	Nivo	Doc
PD-L1 ≥ 10%	11	7.1
PD-L1 < 10%	8.2	6.1

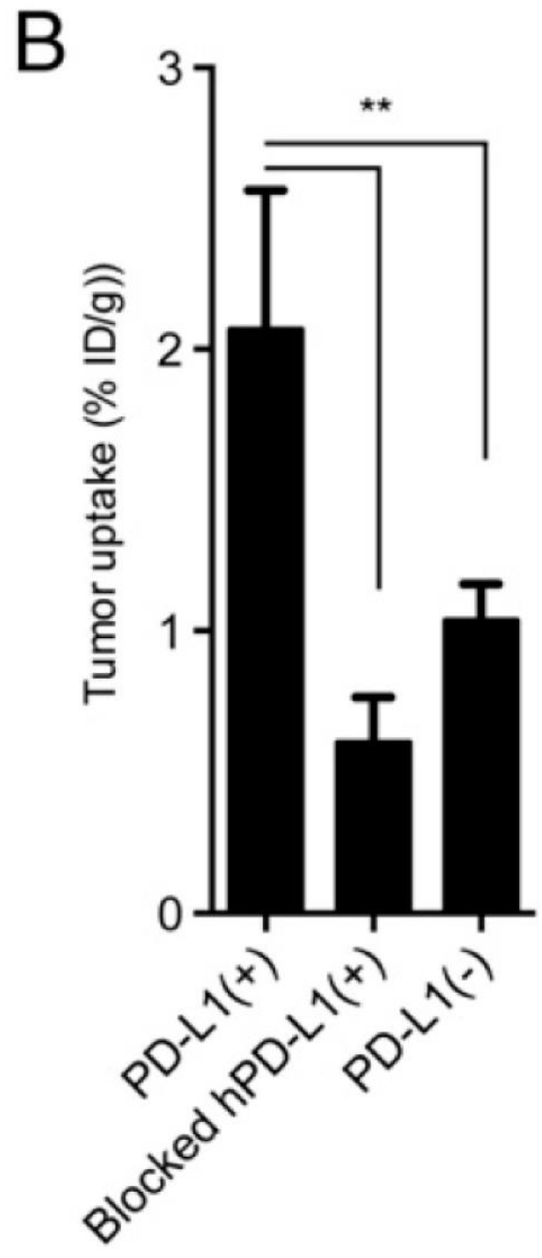


Brahmer J, et al. N Engl J Med. 2015;373:123-135.

Slide credit: clinicaloptions.com

Micro-PET imaging of hPD-L1 with ^{64}Cu–DOTA–HAC

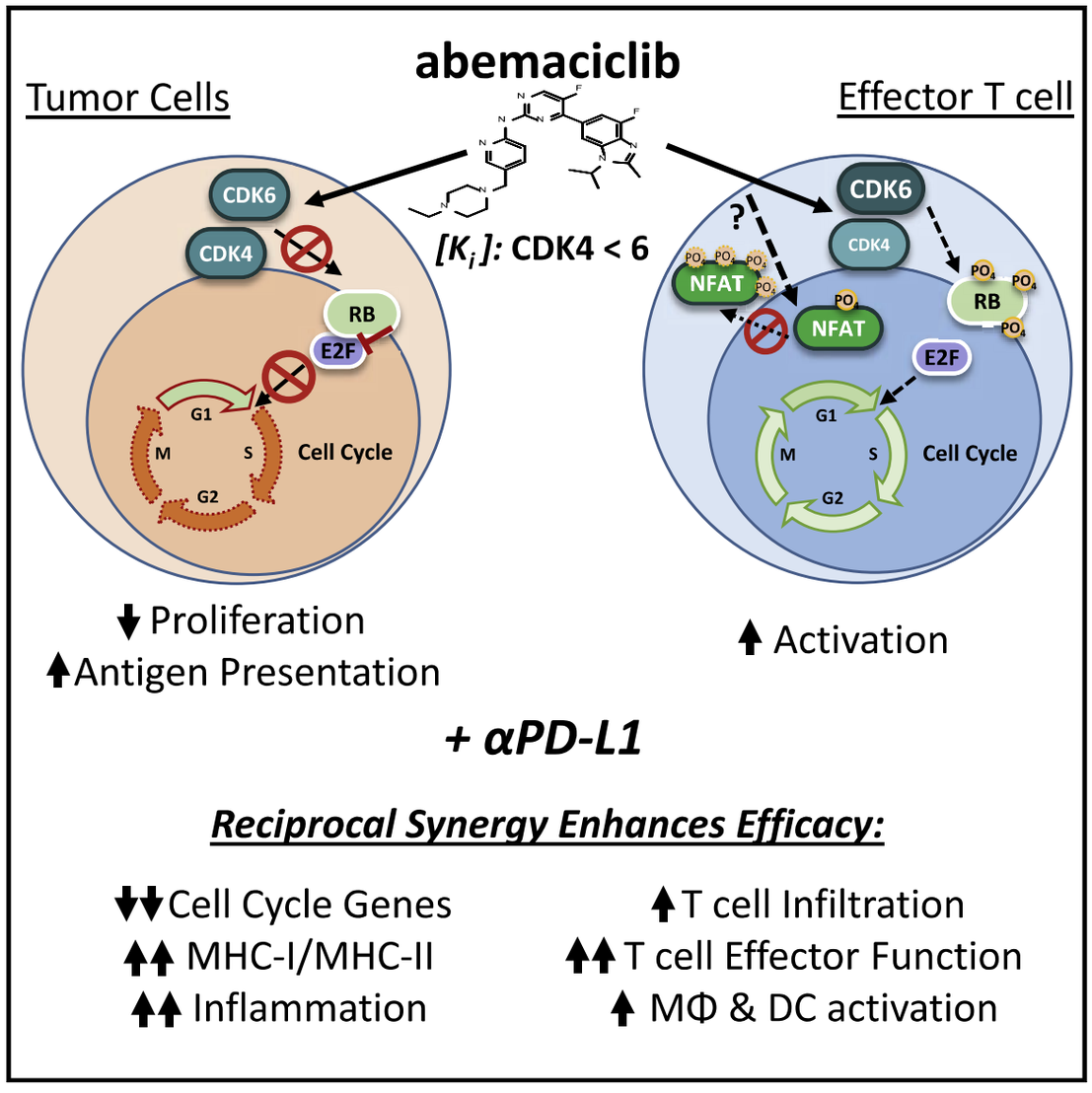




Maute et al. Proc Natl Acad Sci U S A. 2015

Scientific rational for combinations

ICIs plus CDK4/6i



Schaer et al. Cell Rep. 2018 Mar 13;22(11):2978-2994.
Goel et al. Nature. 2017 Aug 24;548(7668):471-475.

Key points

- How can anti-PD-1 and anti-PD-L1 antibodies be integrated into current treatment regimens in breast cancer patients?

- Preclinical models and hypothesis-driven clinical investigations may help to find new drugs' combinations

- Identification of predictive pharmacokinetic and pharmacogenetic biomarkers (translational approach)