Gli agenti anti-PD1 e anti-PD-L1

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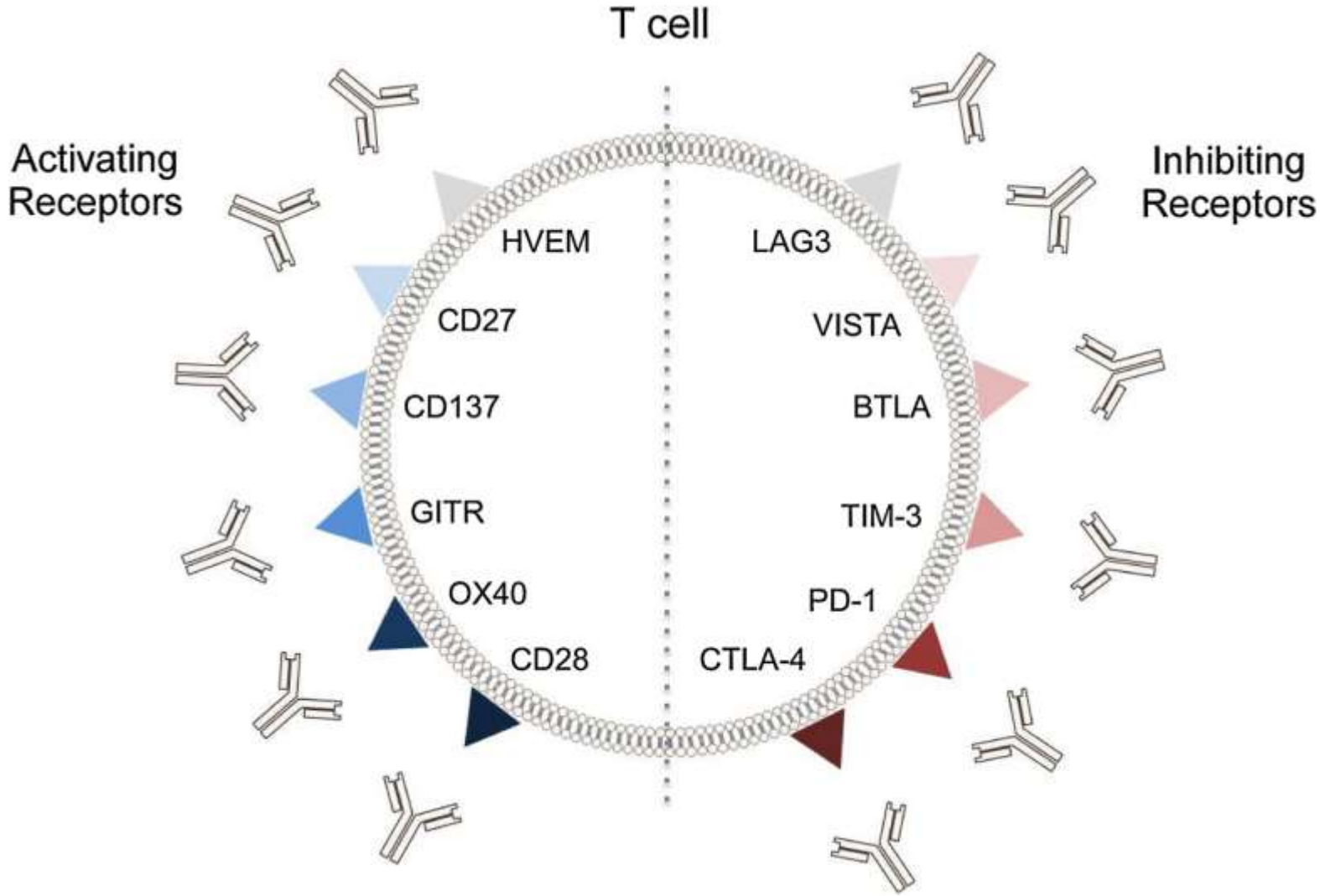
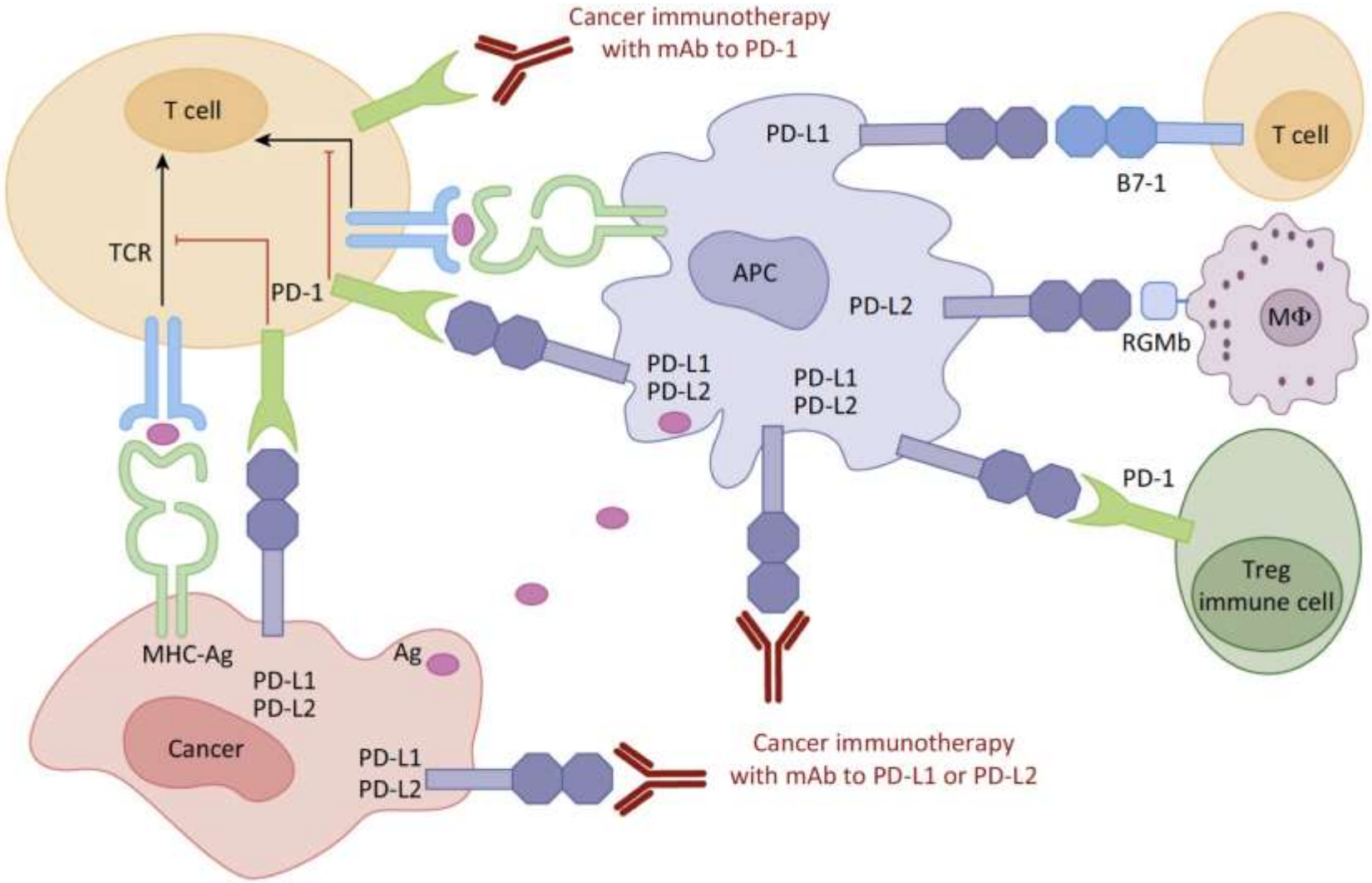
Immunotherapeutic targets



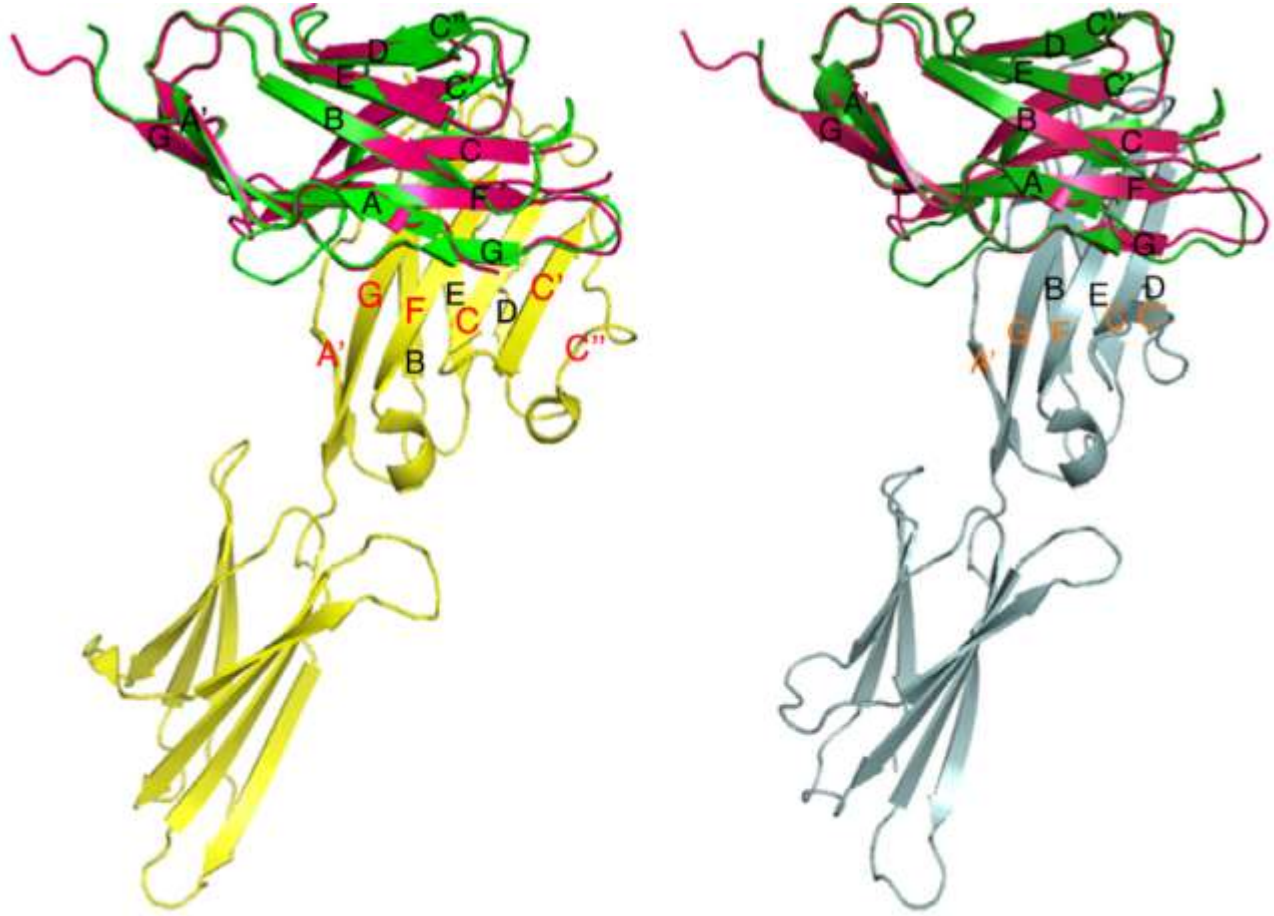
Merelli et al. Critical Reviews in Oncology/Hematology 2014; 89: 140

Cancer immunotherapy with anti-PD-1 and anti-PD-L1/L2 antibodies



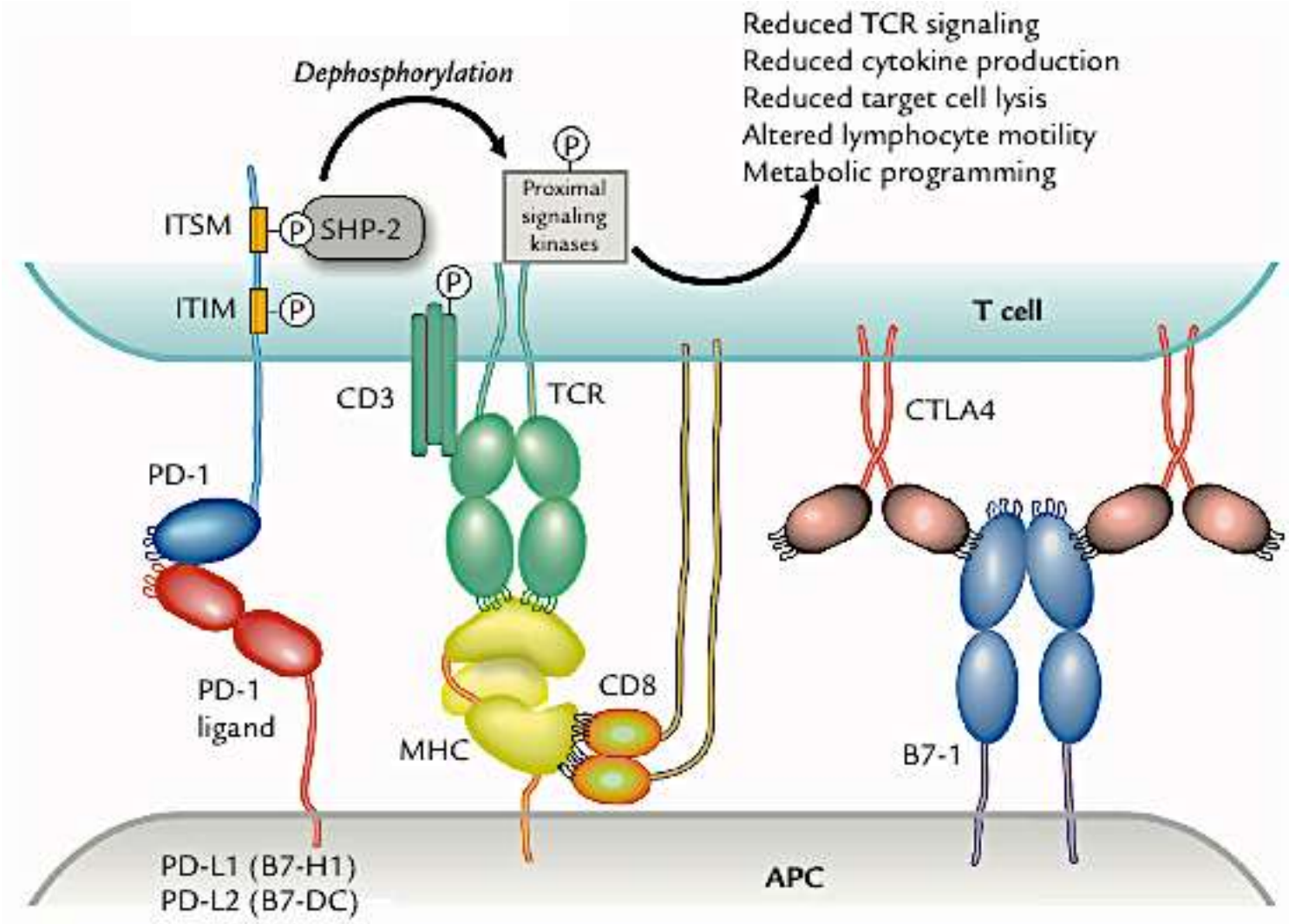
Kim C. Ohaegbulam et al. Trends in Molecular Medicine 2015, Vol. 21, No. 1

Crystal structures of PD-1/PD-L1 (left) and PD-1/PD-L2 complexes (right)



Kim C. Ohaegbulam et al. Trends Mol Med 2015, Vol. 21, No. 1

PD1/PD-L1 signal transduction



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

Biological agents targeting PD-1 or PD-L1 in cancer clinical trials

Biological agent	Class	Target
CT-011 (pidilizumab)	Humanized IgG1	PD-1
MK-3475 (lambrolizumab, pembrolizumab)	Humanized IgG4	PD-1
BMS-936558 (nivolumab)	Human IgG4	PD-1
AMP-224 (B7-DC-Fc fusion protein)	PD-L2 IgG2a fusion protein	PD-1
BMS-936559	Human IgG4	PD-L1
MEDI4736 (durvalumab)	Humanized IgG	PD-L1
MPDL3280A (atezolizumab)	Human IgG	PD-L1
MSB0010718C (avelumab)	Human IgG1	PD-L1

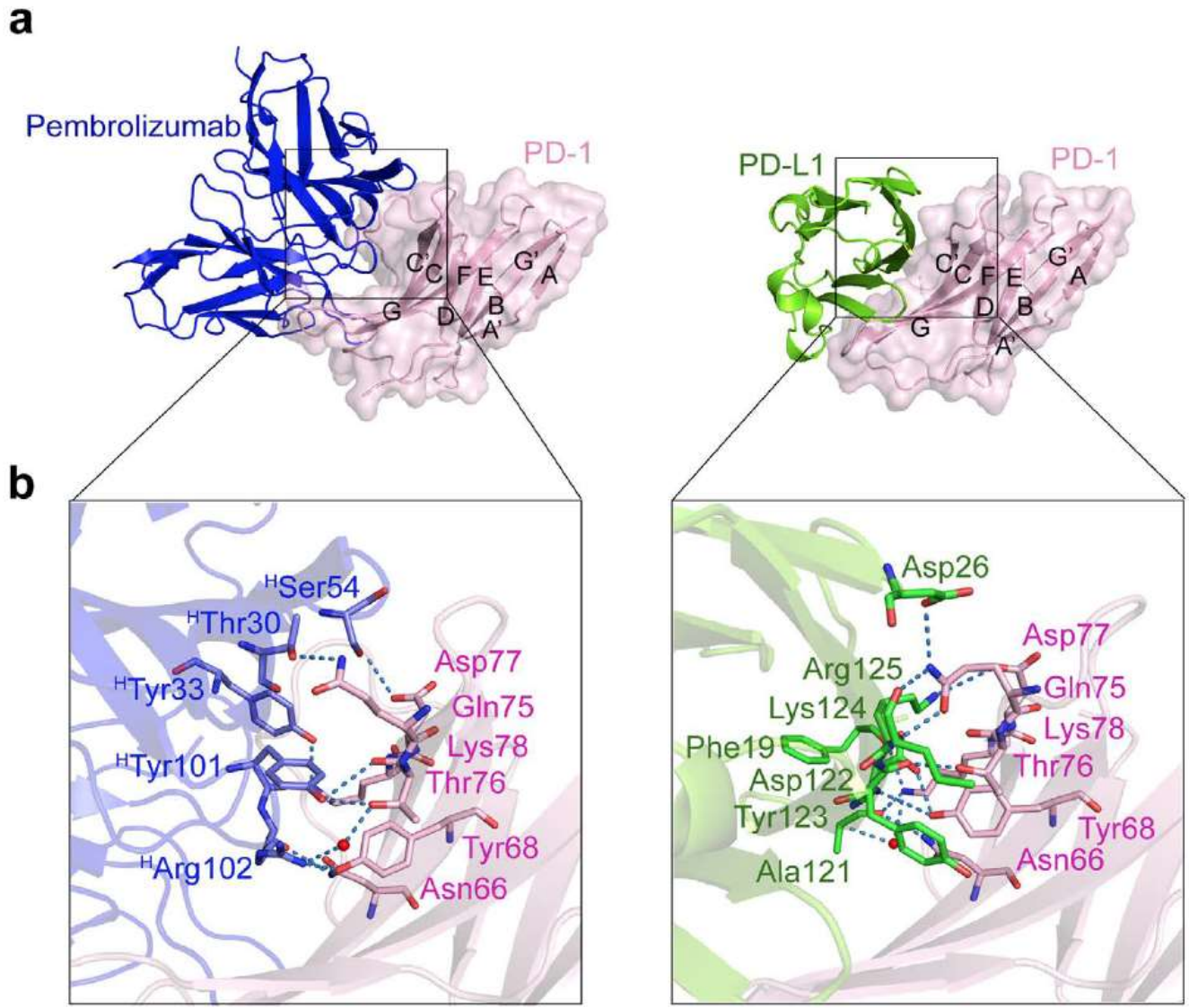
Kim C. Ohaegbulam et al. Trends Mol Med 2015, Vol. 21, No. 1

Binding affinities of B7/CD28 family members to their ligands and blocking antibodies

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[†])
PD-1:nivolumab (2.6 nM)	Brahmer et al[1] (Scatchard plots analysis)
PD-1:pembrolizumab (0.028 nM)[‡]	Hamid et al[3]
PD-1:pidilizumab (20 nM)	Atkins et al[50]
PD-L1:MPDL-3280A (0.4 nM)	Herbst et al[51]

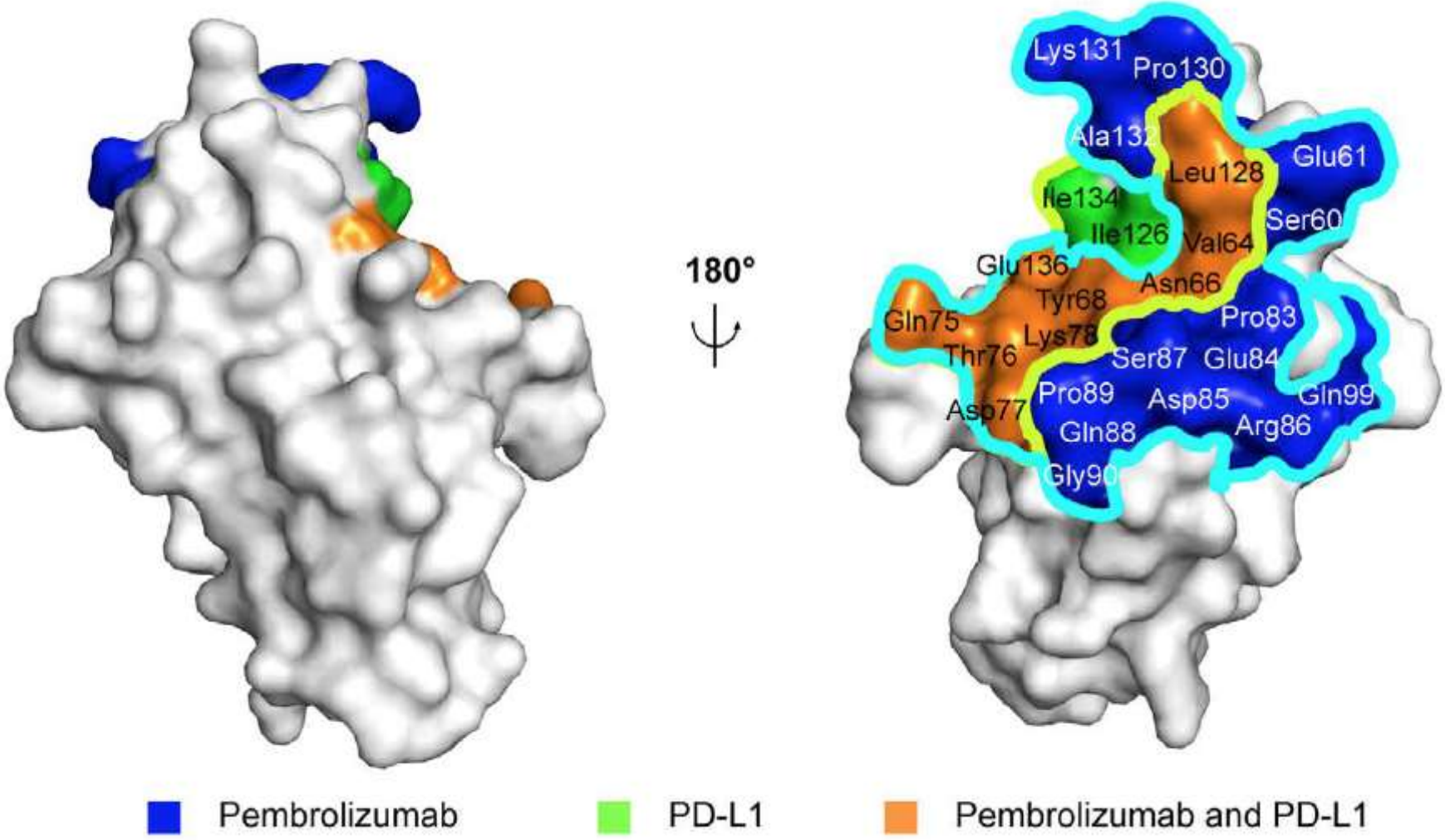
Kathleen M. Mahoney et al. Clin Ther. 2015;37:764–782

Structure of the pembrolizumab/PD-1 complex and comparison with the PD-L1/PD-1 complex



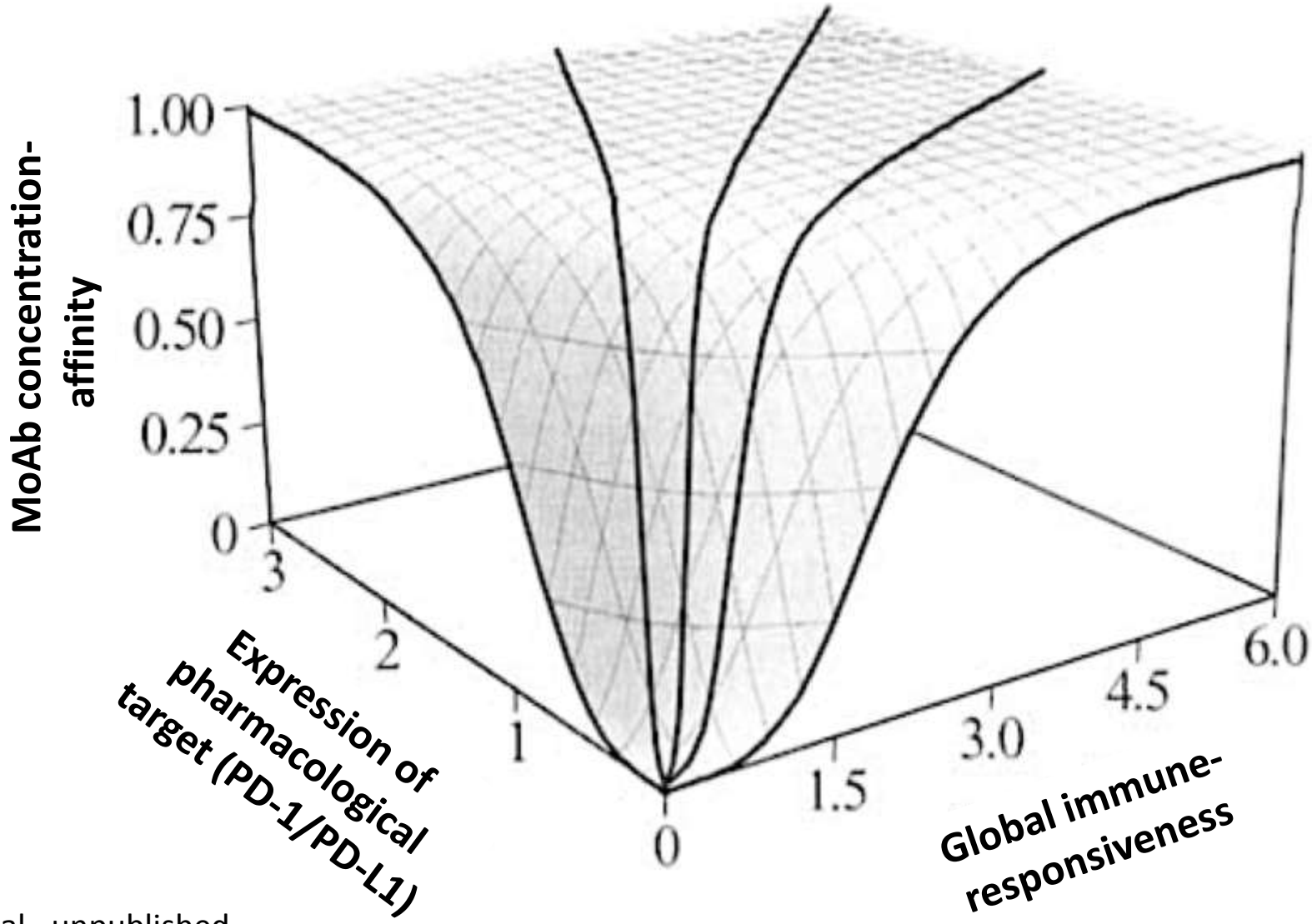
Horita S et al. Scientific Reports, 6:35297, DOI: 10.1038/srep35297

Steric overlap on the PD-1 surface that interact with pembrolizumab and PD-L1



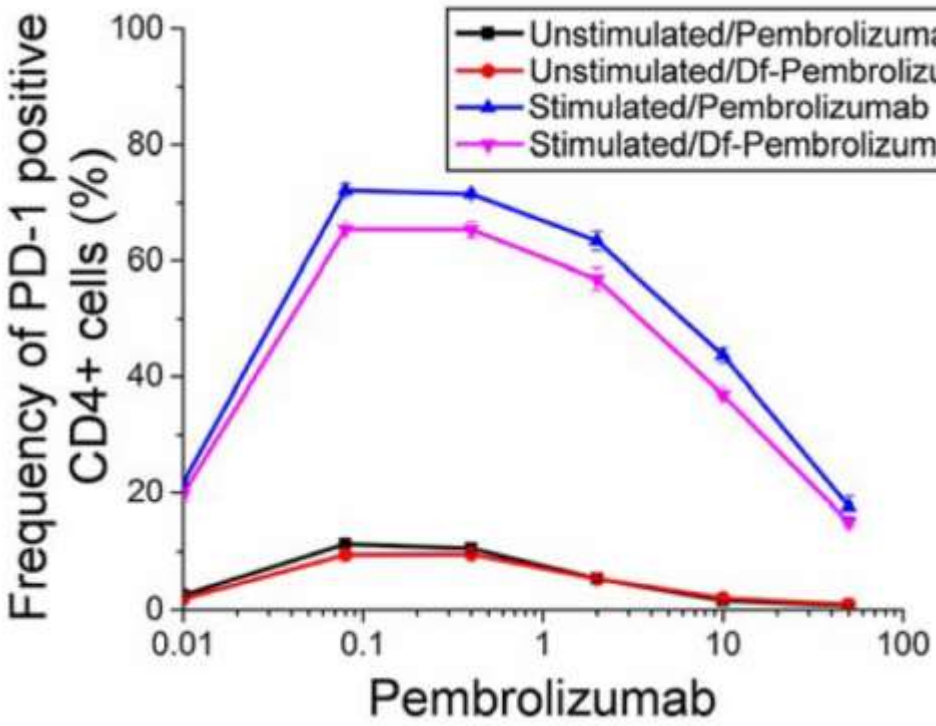
Horita S et al. Scientific Reports, 6:35297, DOI: 10.1038/srep35297

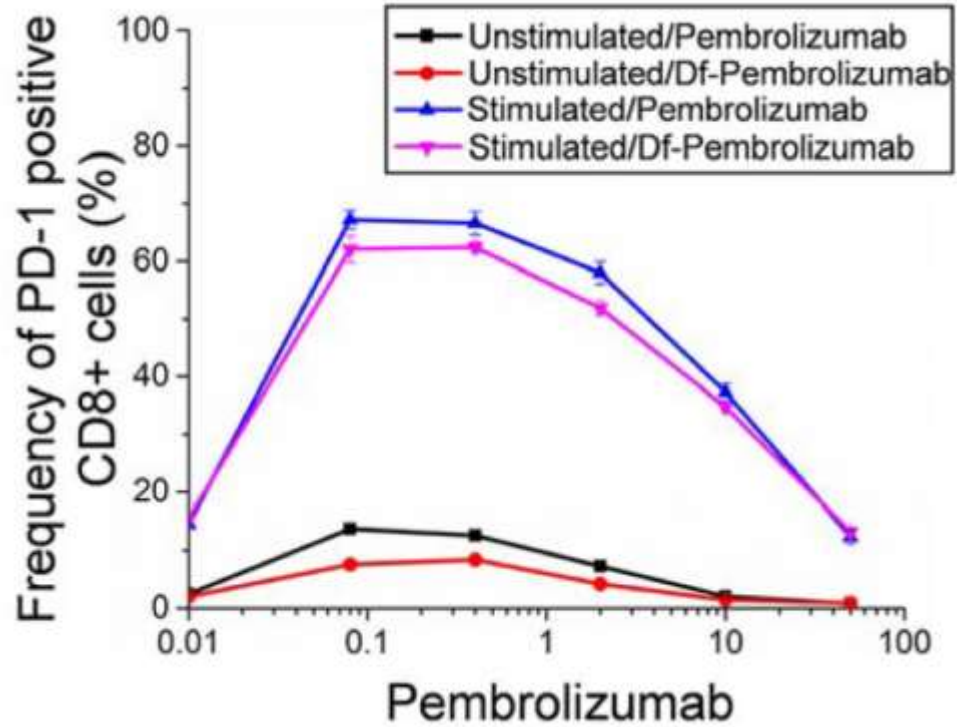
Unique tri-dimensional model of drug-target-immune-activation relationships for ICPI



Danesi et al., unpublished

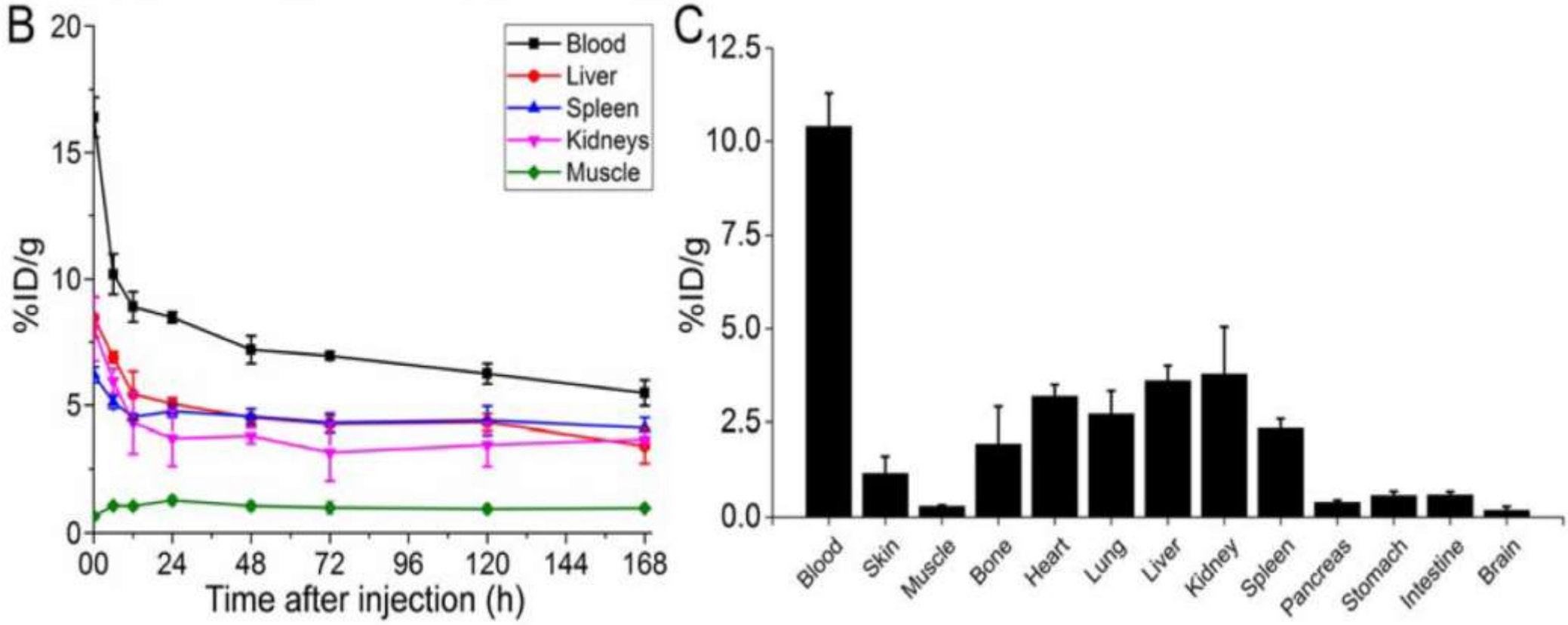
Pembrolizumab displays higher binding to stimulated T-cells expressing the PD-1 receptor





Christopher G. England et al J Nucl Med Doi: 10.2967/jnumed.116.177857

Biodistribution of 89Zr-Df-pembrolizumab in ICR mice



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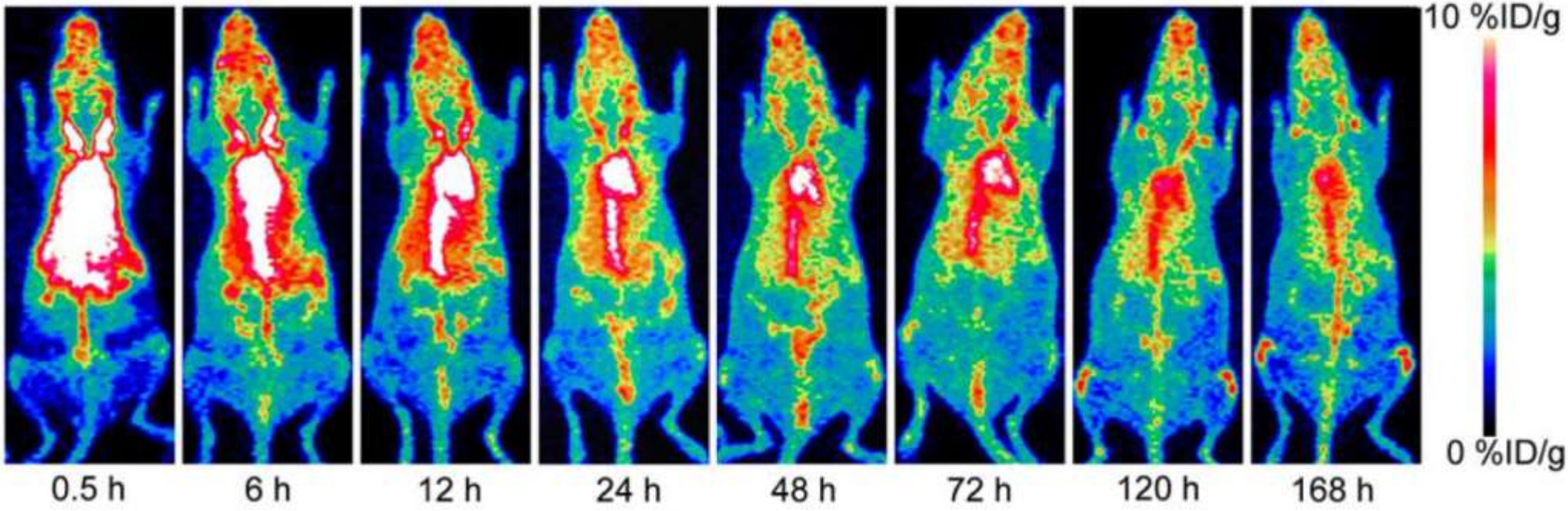
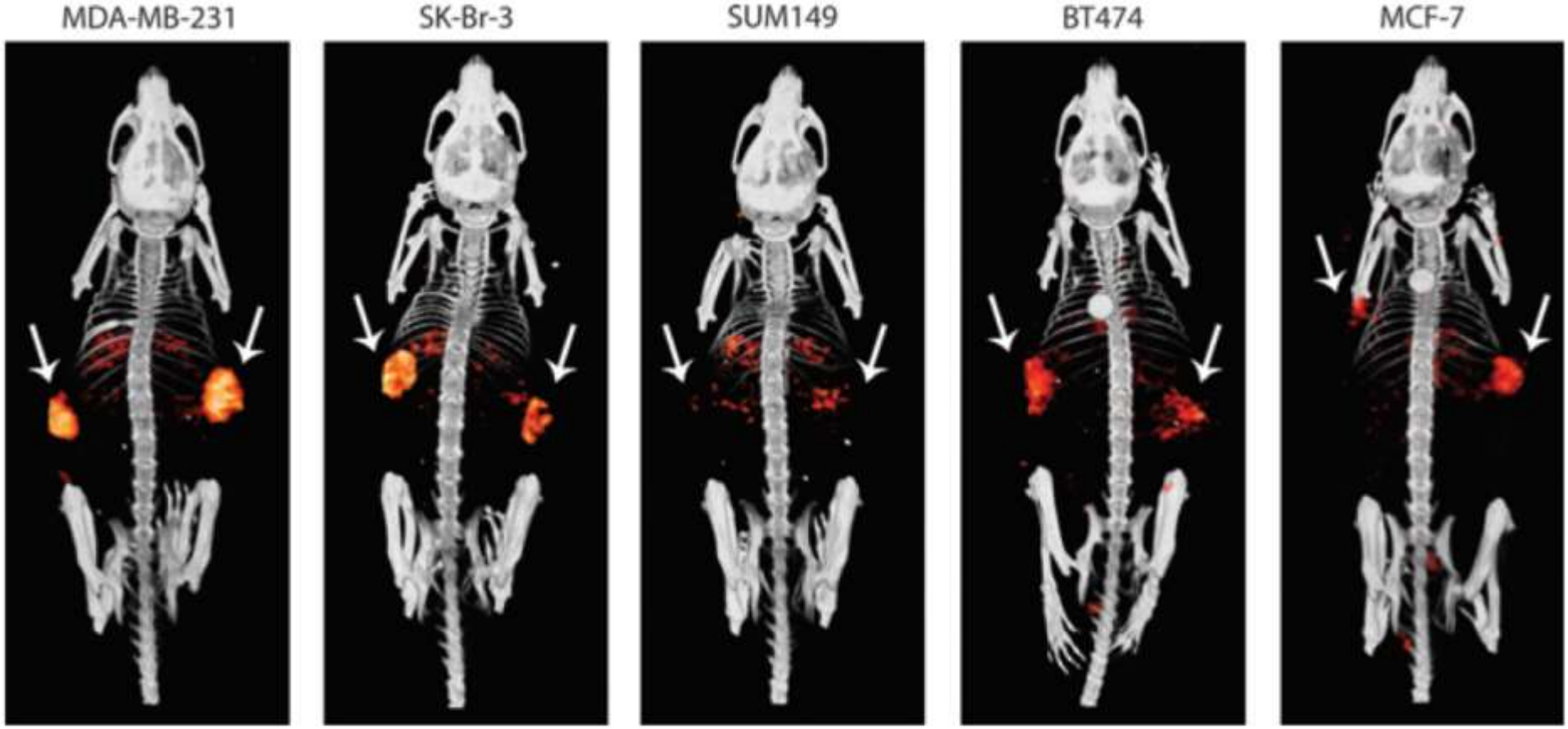


Imaging of tumor PD-L1 expression using radiolabeled anti-PD-L1 antibodies



Sandra Heskamp et al. Cancer Res 2015;75:2928-2936

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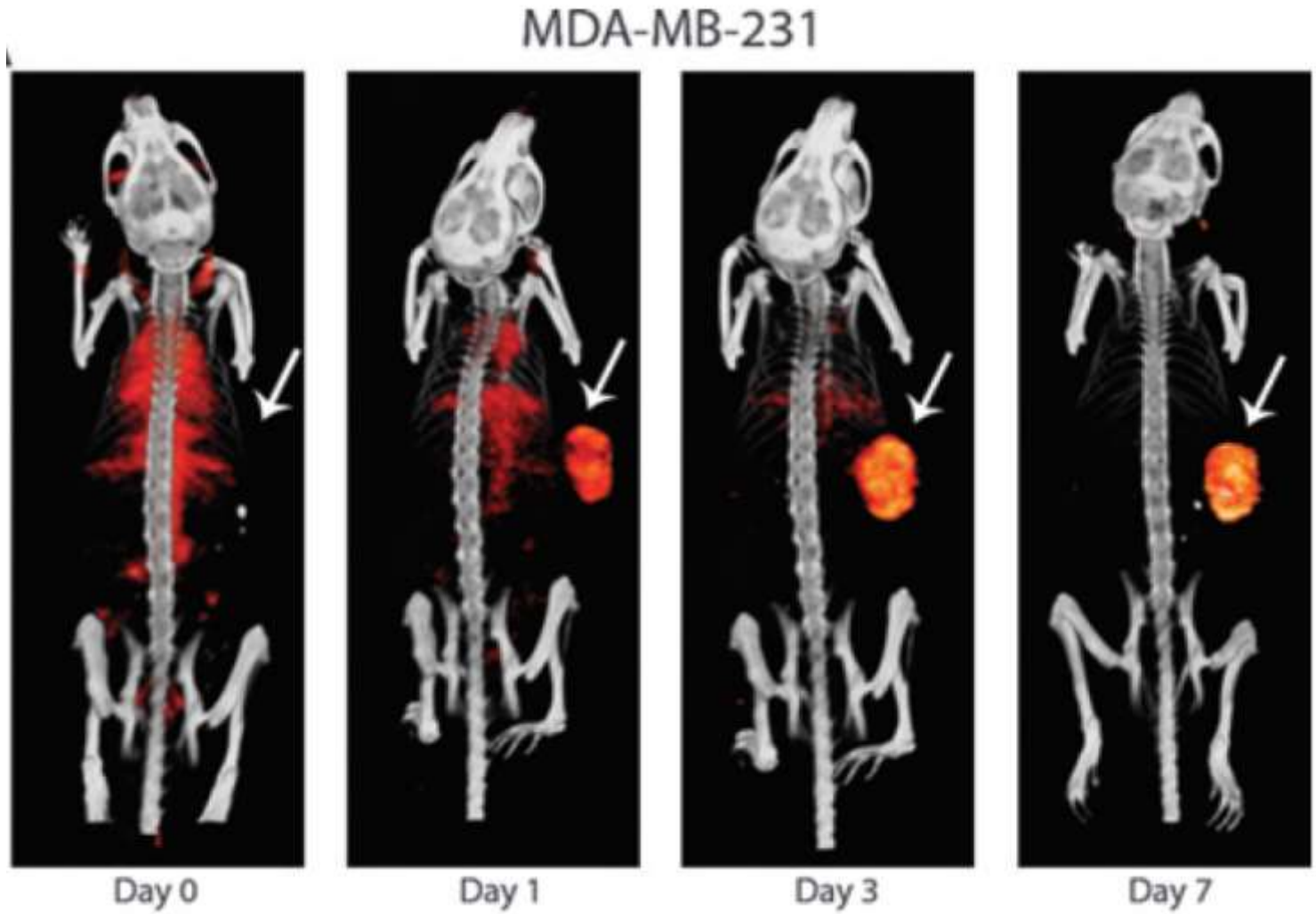

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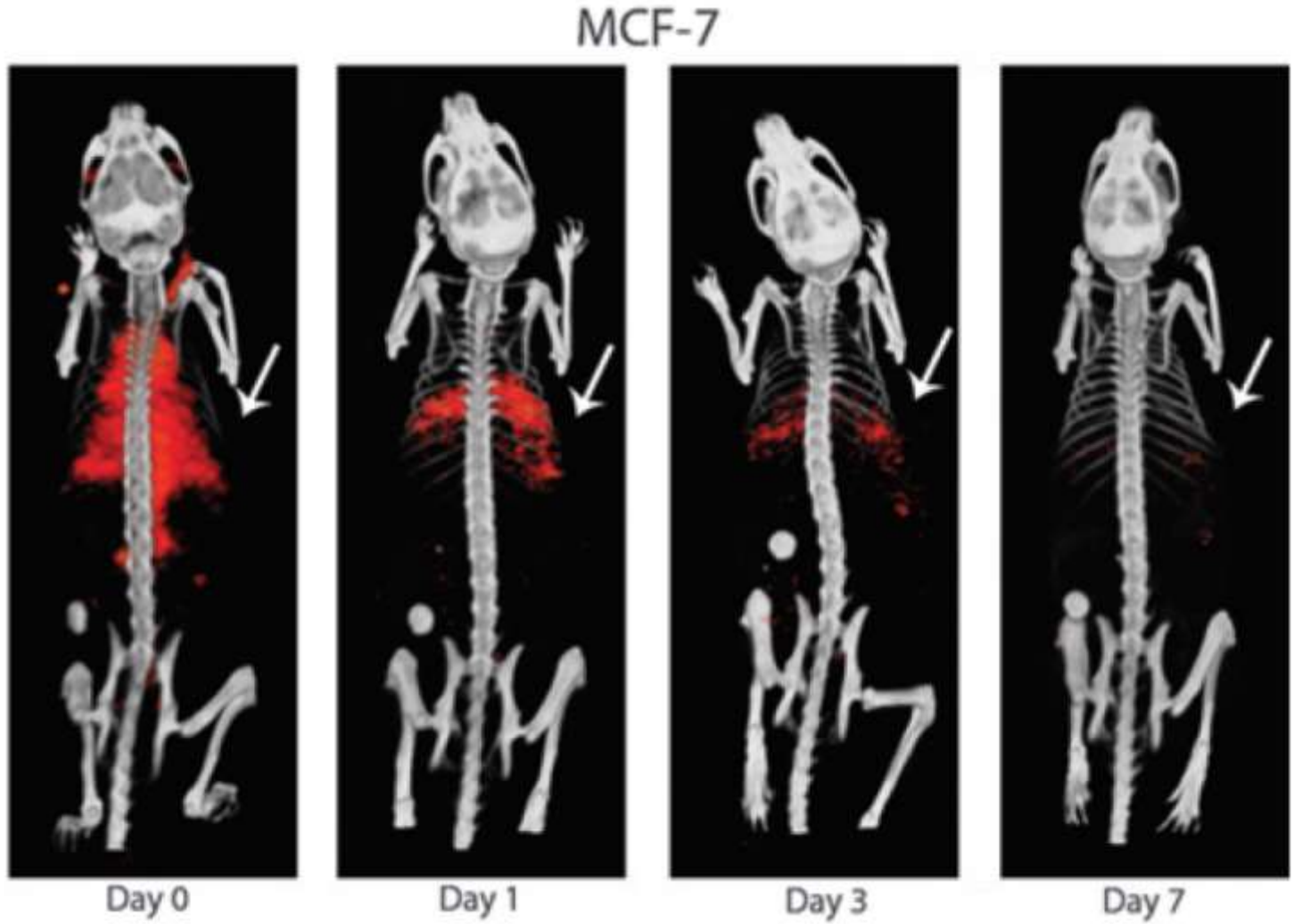

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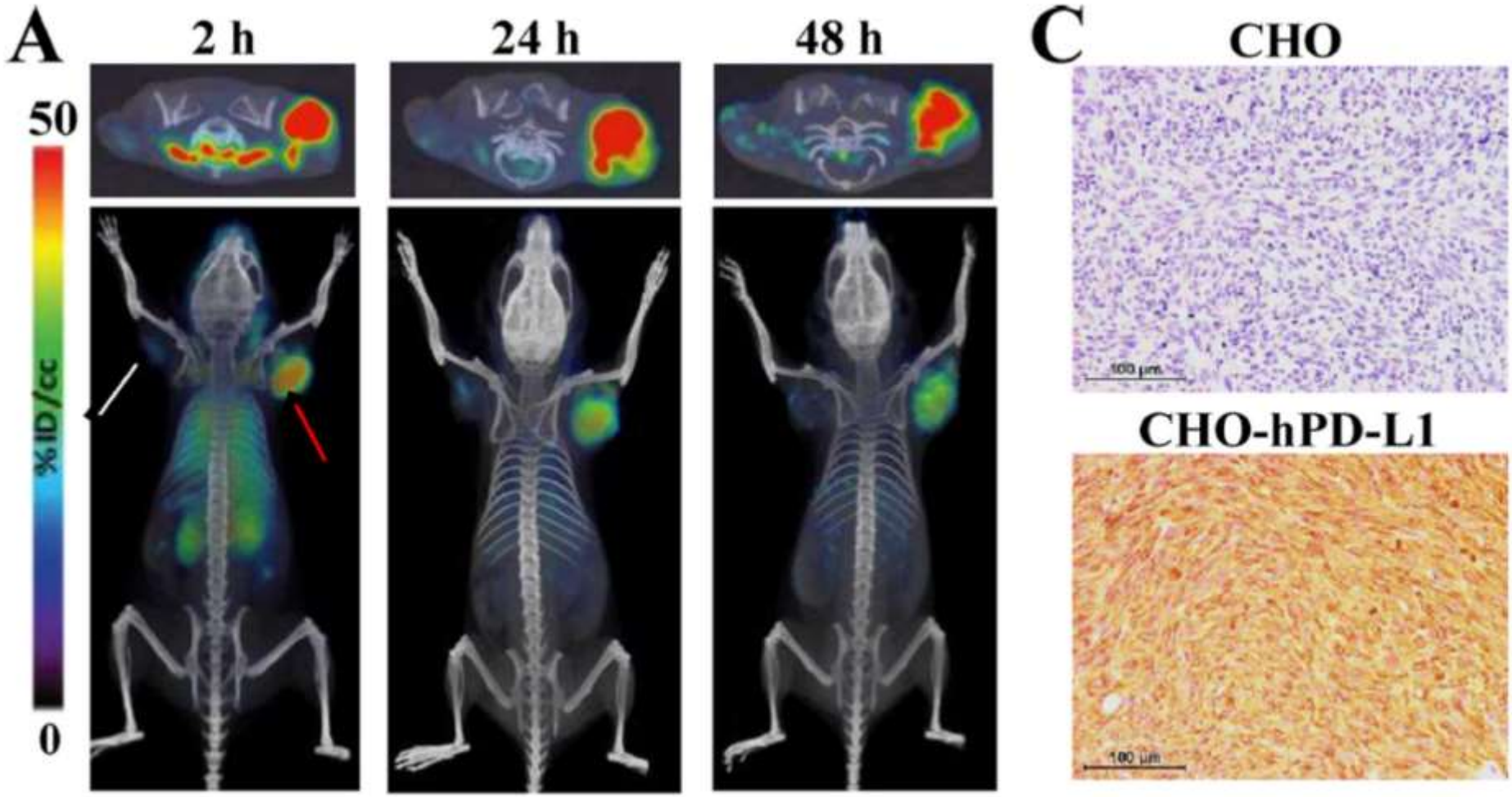
PD-L1 Detection in Tumors Using [64Cu]atezolizumab with PET



Wojciech G. Lesniak et al. Bioconjug Chem 2016; 27(9): 2103–2110

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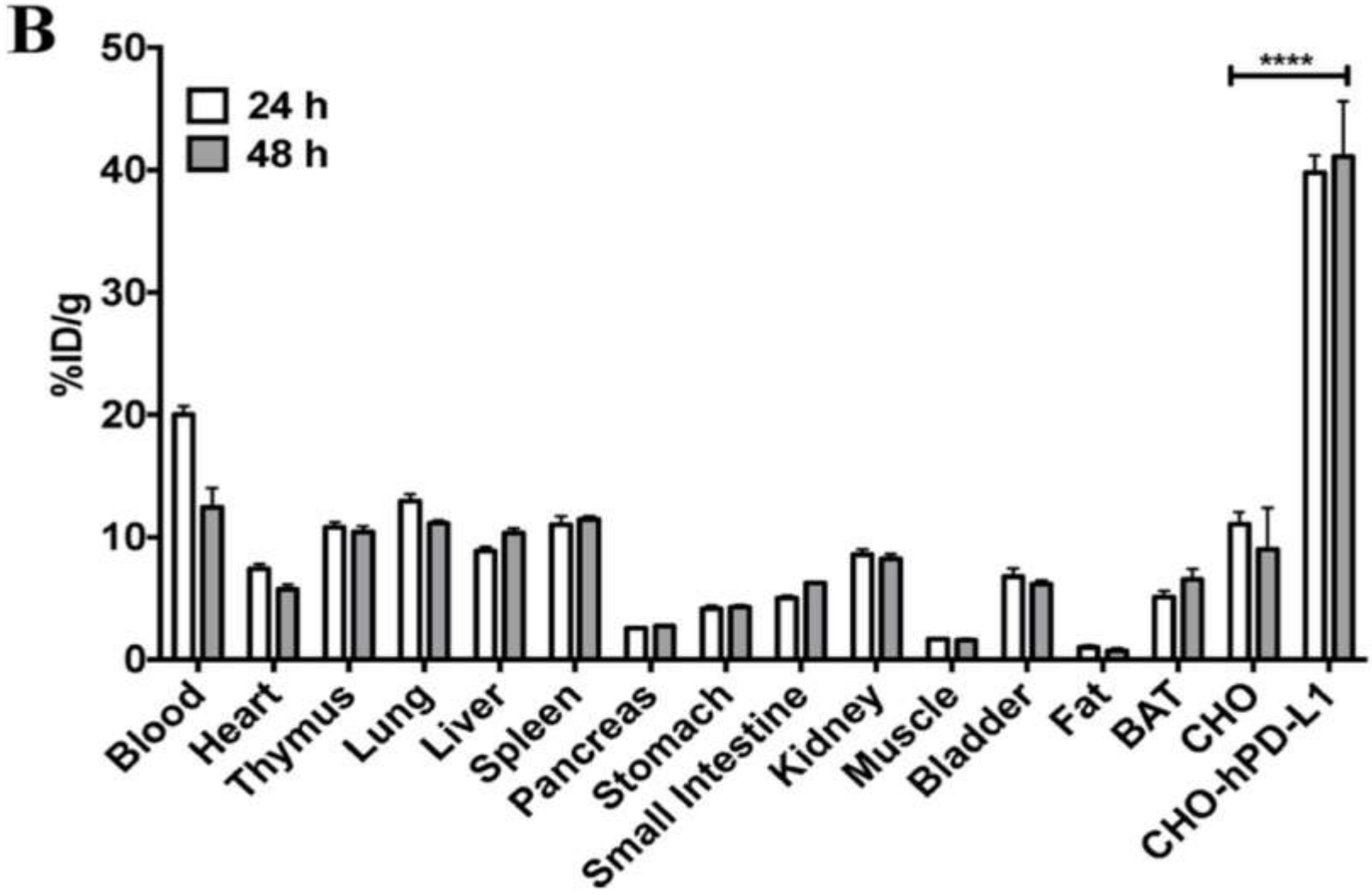
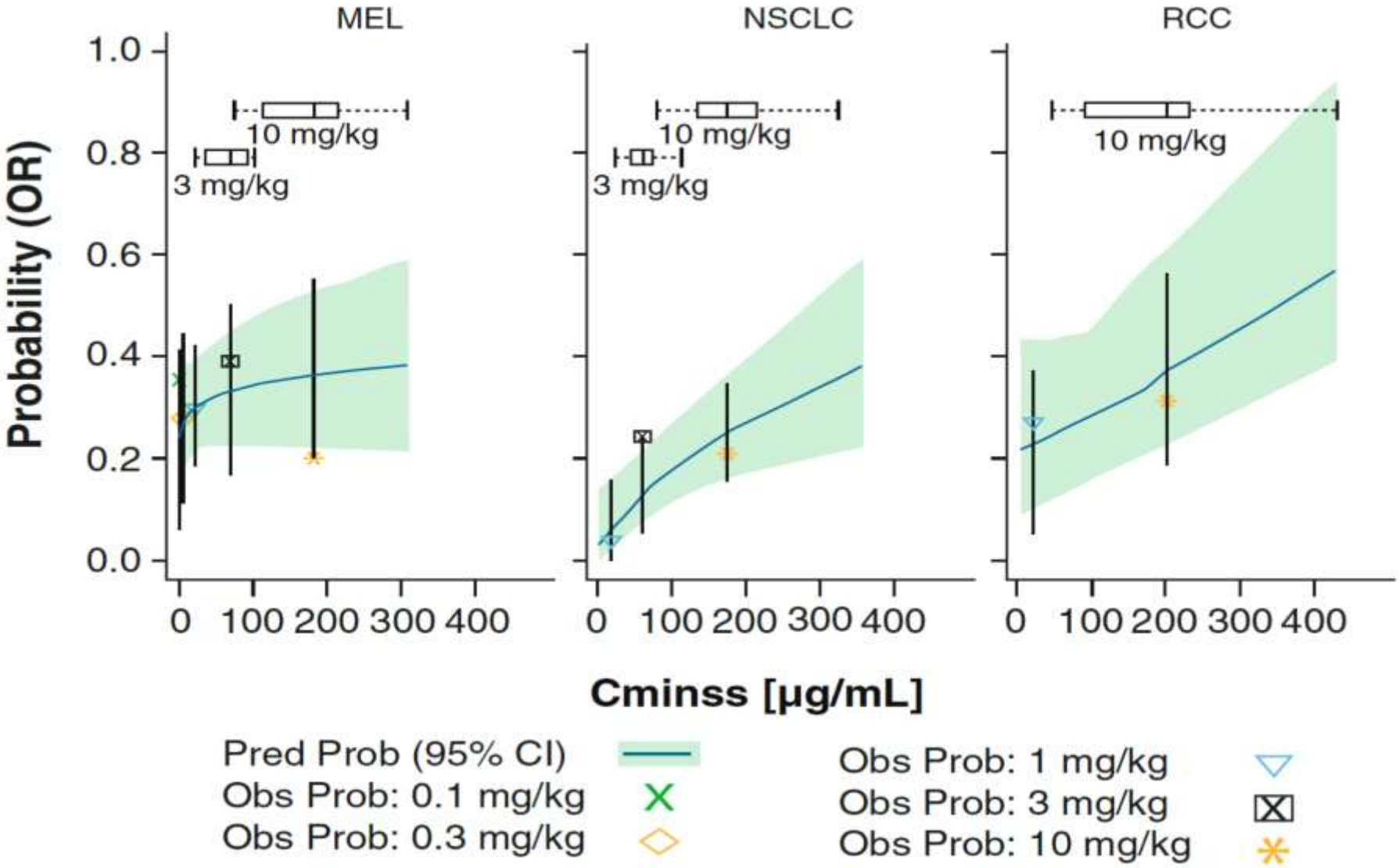


Wojciech G. Lesniak et al. Bioconjug Chem 2016; 27(9): 2103–2110

Exposure-response efficacy analysis of nivolumab by tumor type



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

Pharmacokinetics of pembrolizumab

Median (90% prediction interval) PK parameters of pembro at steady state based on popPK model.

	Pembro Dose Regimen		
PK Parameter	2 mg/kg Q3W	10 mg/kg Q3W	10 mg/kg Q2W
Cmax (µg/mL)	64.6 (43.9; 99.2)	318 (215; 488)	393 (261; 691)
Ctrough (µg/mL)	22.3 (8.84; 50.1)	110 (40.8; 257)	185 (82; 395)
AUCss, 6 wk (µg·day/mL)	1398 (713; 2730)	6859(3403; 13712)	10353 (5308; 20137)

Tara C. Gangadhar et al. J Clin Oncol 33, 2015 (suppl; abstr 3058)

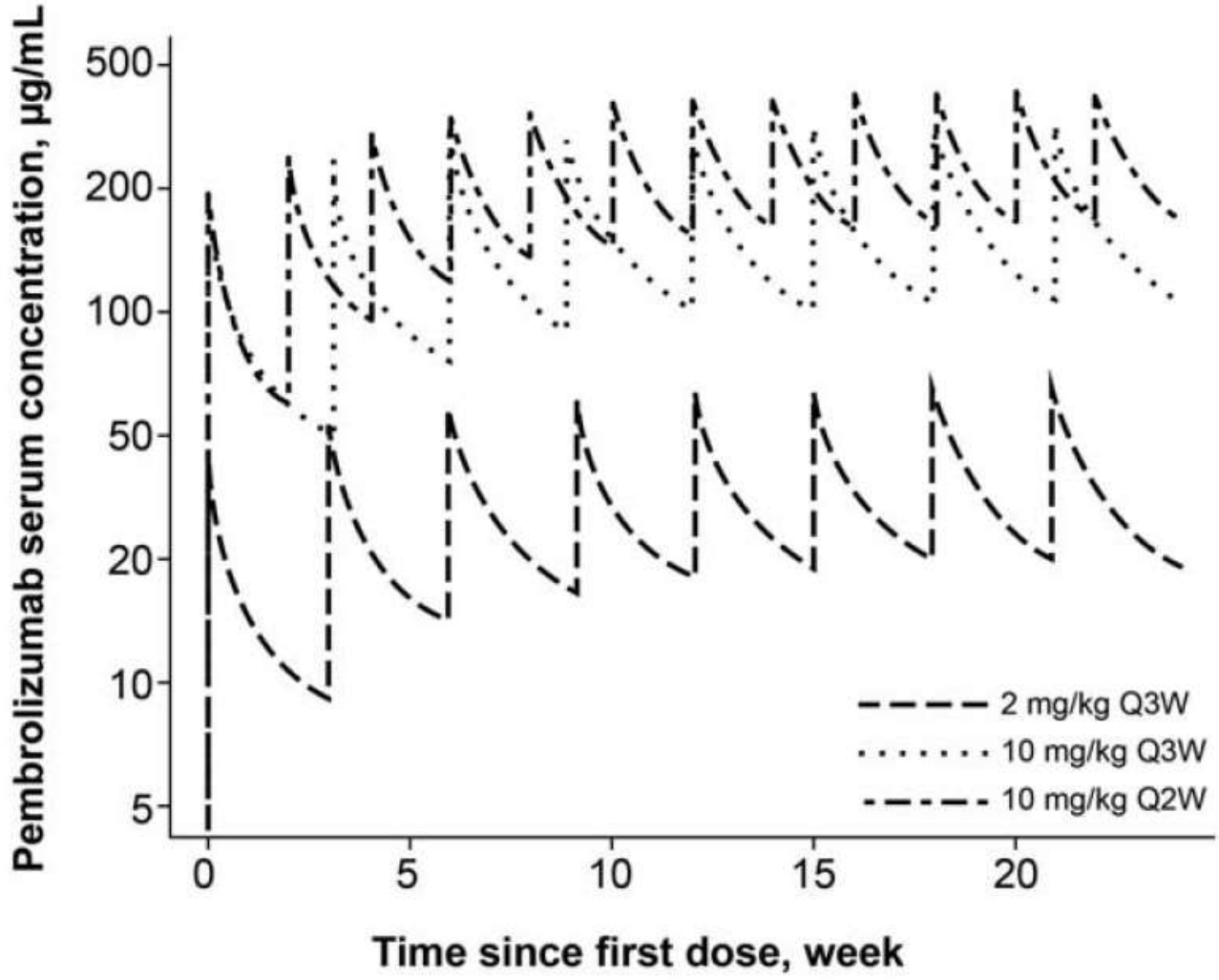
Citation: CPT Pharmacometrics Syst. Pharmacol. (2016) 00, 00; doi:10.1002/psp4.12139

ORIGINAL ARTICLE

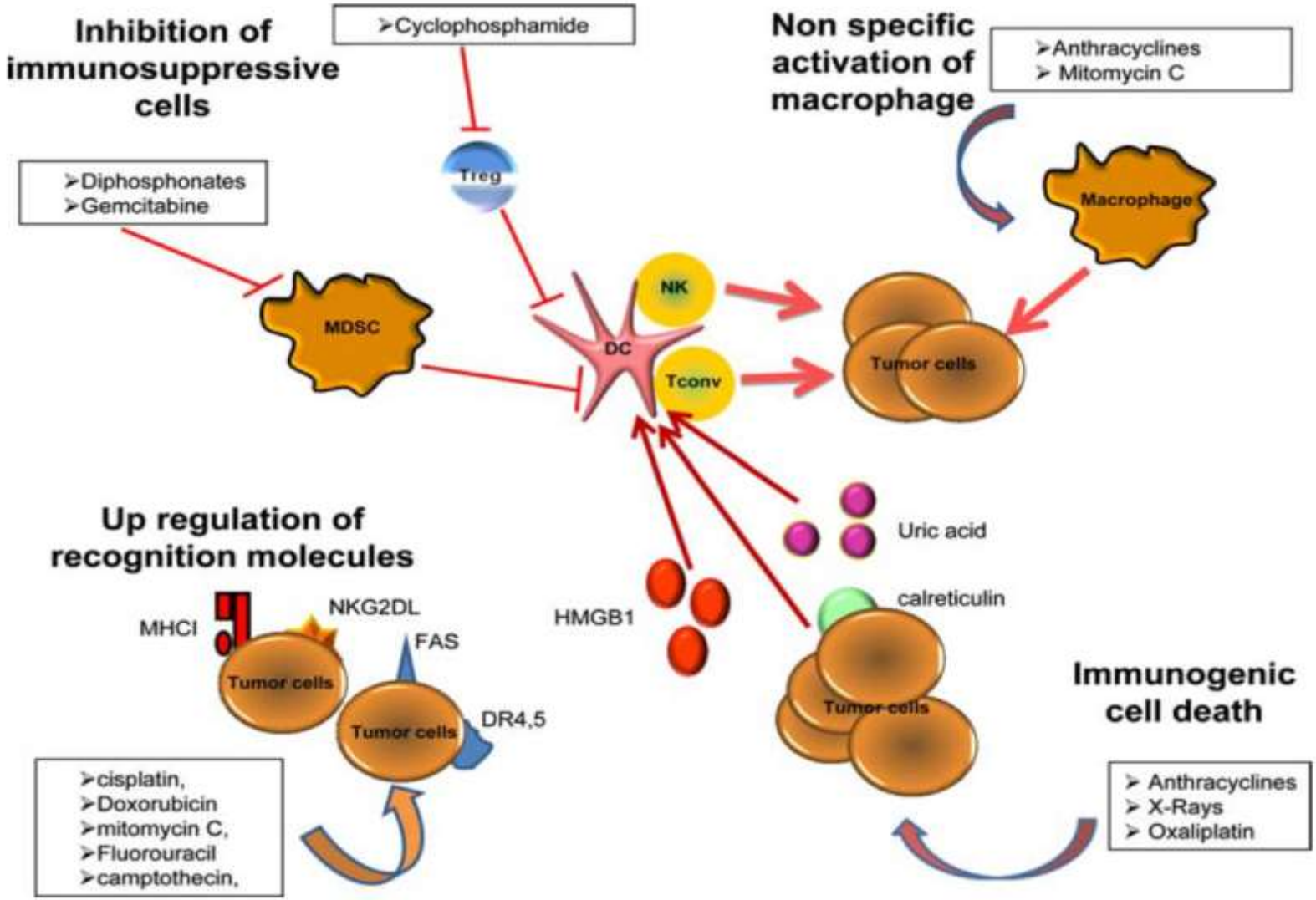
Model-Based Characterization of the Pharmacokinetics of Pembrolizumab: A Humanized Anti–PD-1 Monoclonal Antibody in Advanced Solid Tumors

M Ahamadi[1]*, T Freshwater[1], M Prohn[2], CH Li[1], DP de Alwis[1], R de Greef[3], J Elassaiss-Schaap[4], A Kondic[1] and JA Stone[1]

Predicted pembrolizumab concentration-time profiles



Chemotherapy: not only a cytotoxic effect, but also an adjuvant for antitumor immunity



Cédric Ménard et al., Cancer Immunol Immunother (2008) 57:1579–1587

Open questions

- Why are the response rates of anti-PD-1 and anti-PD-L1 variable among different cancers?
- Can response biomarkers be identified and how can these be integrated into clinical practice?
- How can anti-PD-1 and anti-PD-L1 antibodies be integrated into current treatment regimens in upfront and relapsed settings?
- Does PD-1 expressed on immune cells other than T cells play a role in anti-PD-1/PD-L1 therapy?
- Can we develop small-molecule inhibitors of the PD-1/PD-L1 interaction?