Atelier anti-PD1 – Recherche de cible

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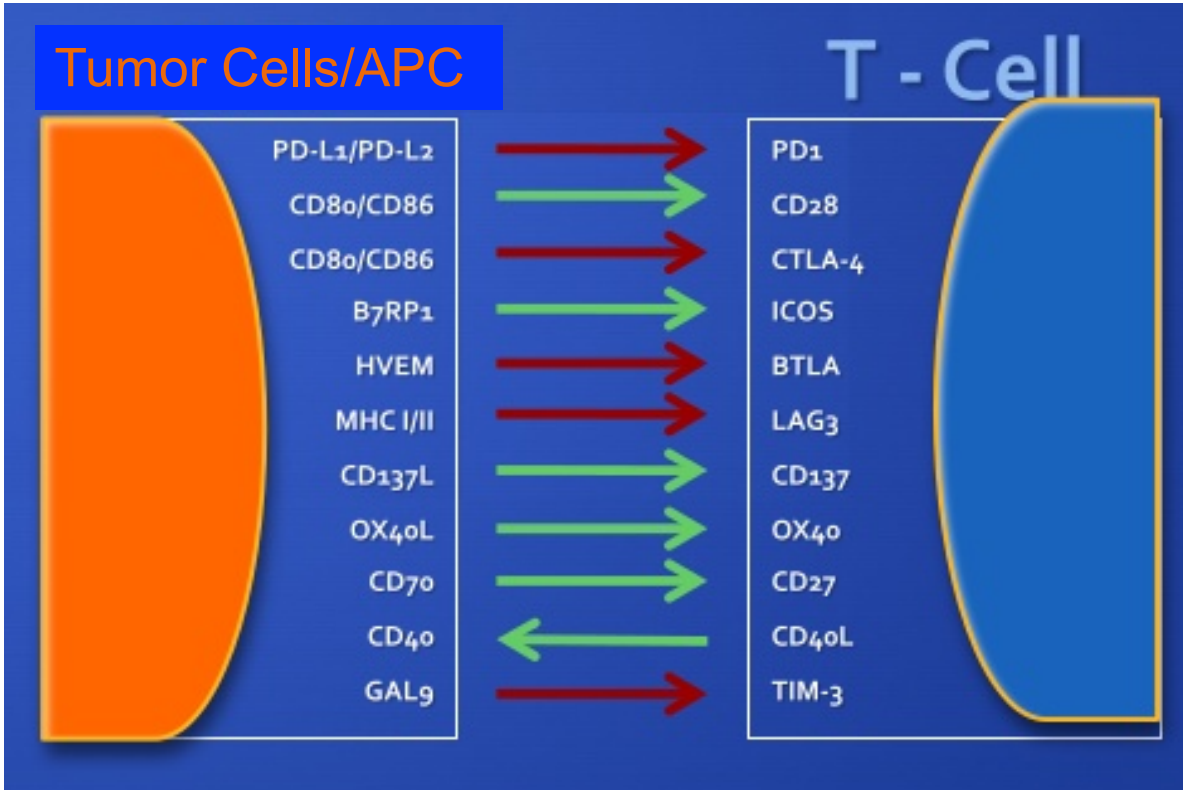
Atelier anti-PD1 – Recherche de cible

Hallmarks of Cancer

Hanahan D & Weinberg RA Immunity 2011

Atelier anti-PD1 – Recherche de cible

Functional interactions between tumor cells & their immune microenvironment

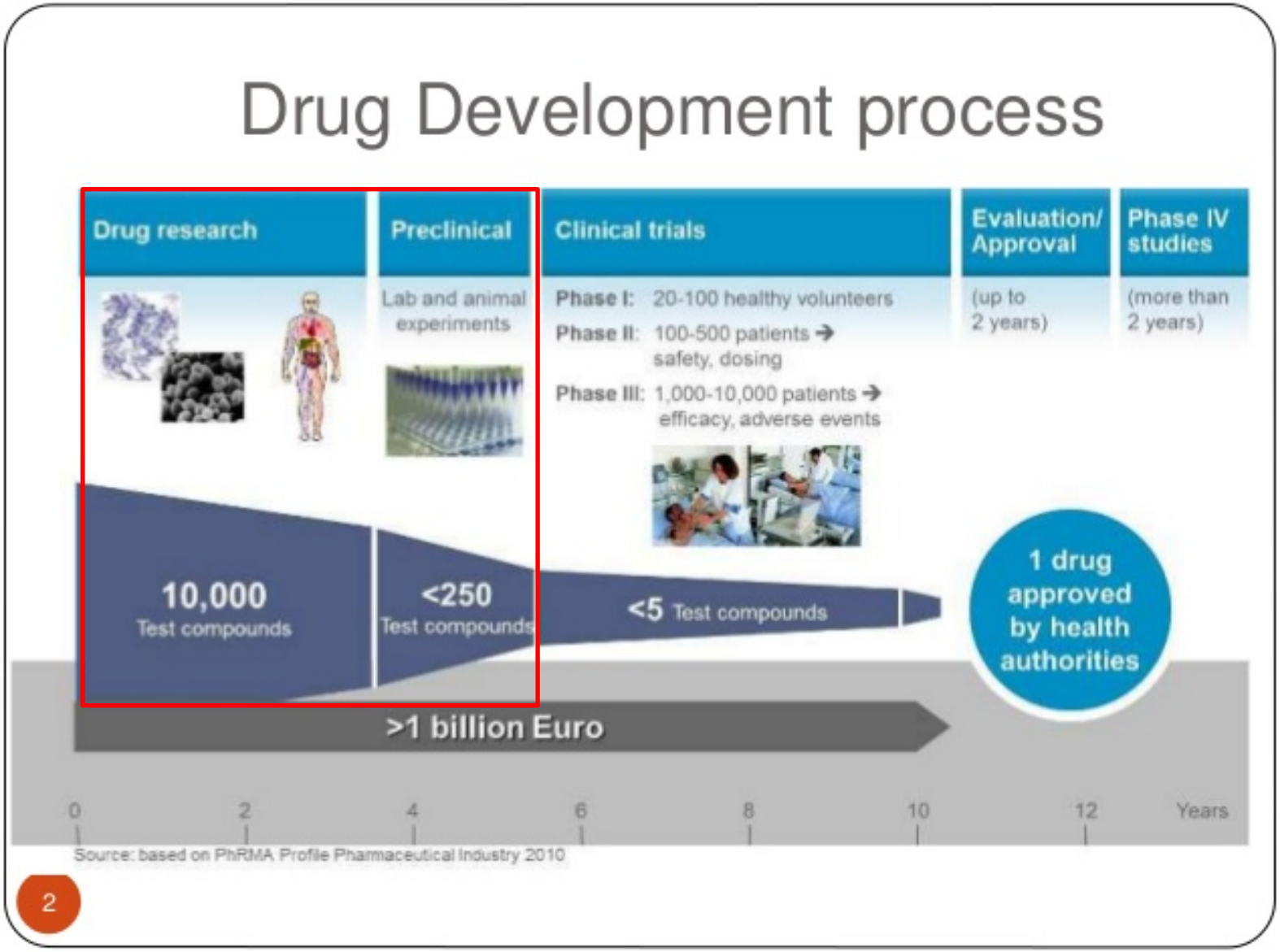


Inhibitory signal

Activation signal

APC: Antigen Presenting Cells

Atelier anti-PD1 – Recherche de cible

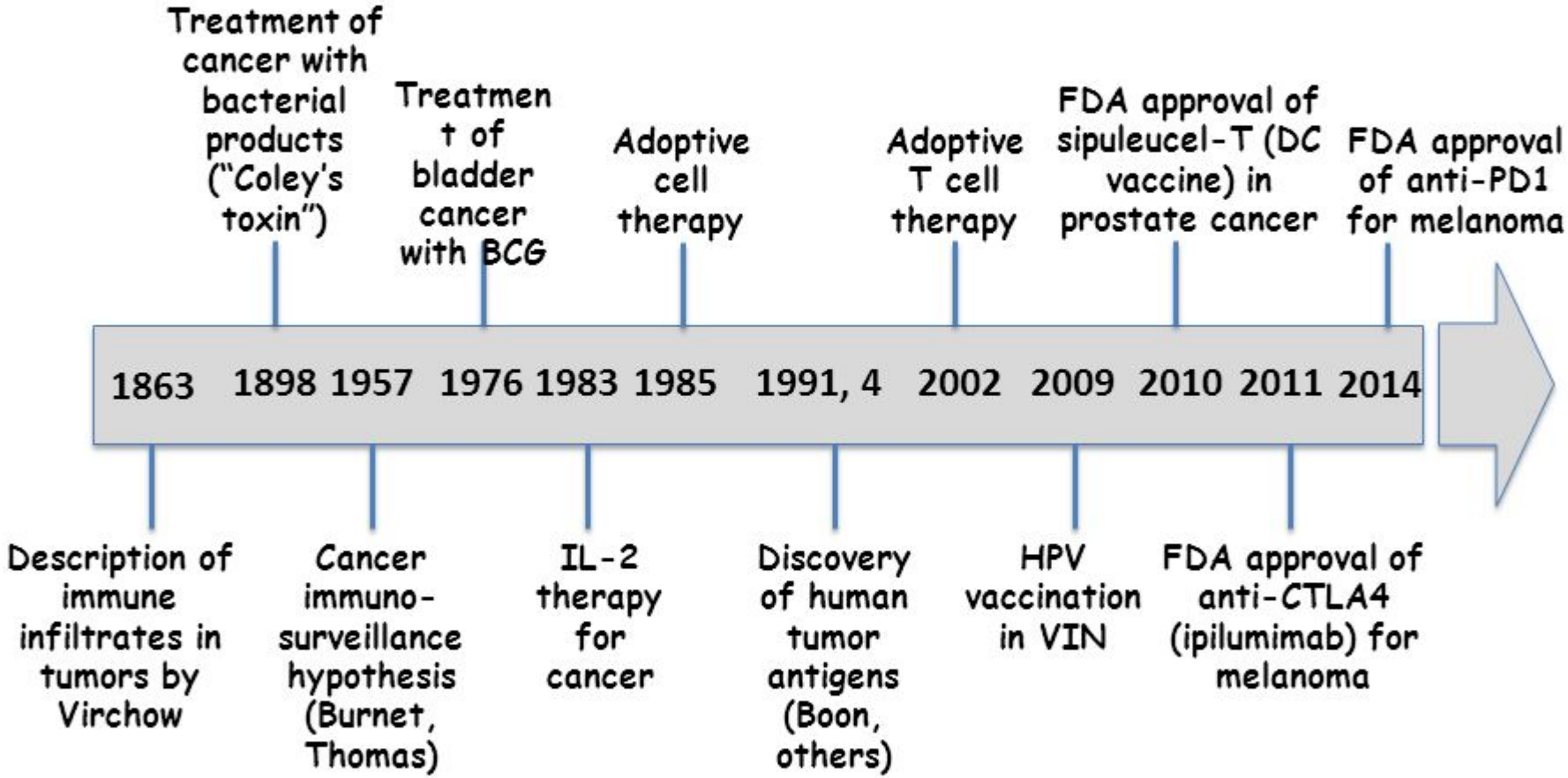


Atelier anti-PD1 – Recherche de cible

- Introduction générale
- Réponse immunitaire anti-tumorale
  - Rationnel biologique de l'utilisation des anti-immune checkpoints
- Mécanismes moléculaires de résistance aux anti-PD1
  - Combinaisons
  - Autres immunomodulateurs
- Toxicité de ces anticorps

Cancéropôle Grand Sud-Ouest

The history of cancer immunotherapy



Cancéropôle Grand Sud-Ouest

Major FDA approved PD-1 and PDL-1

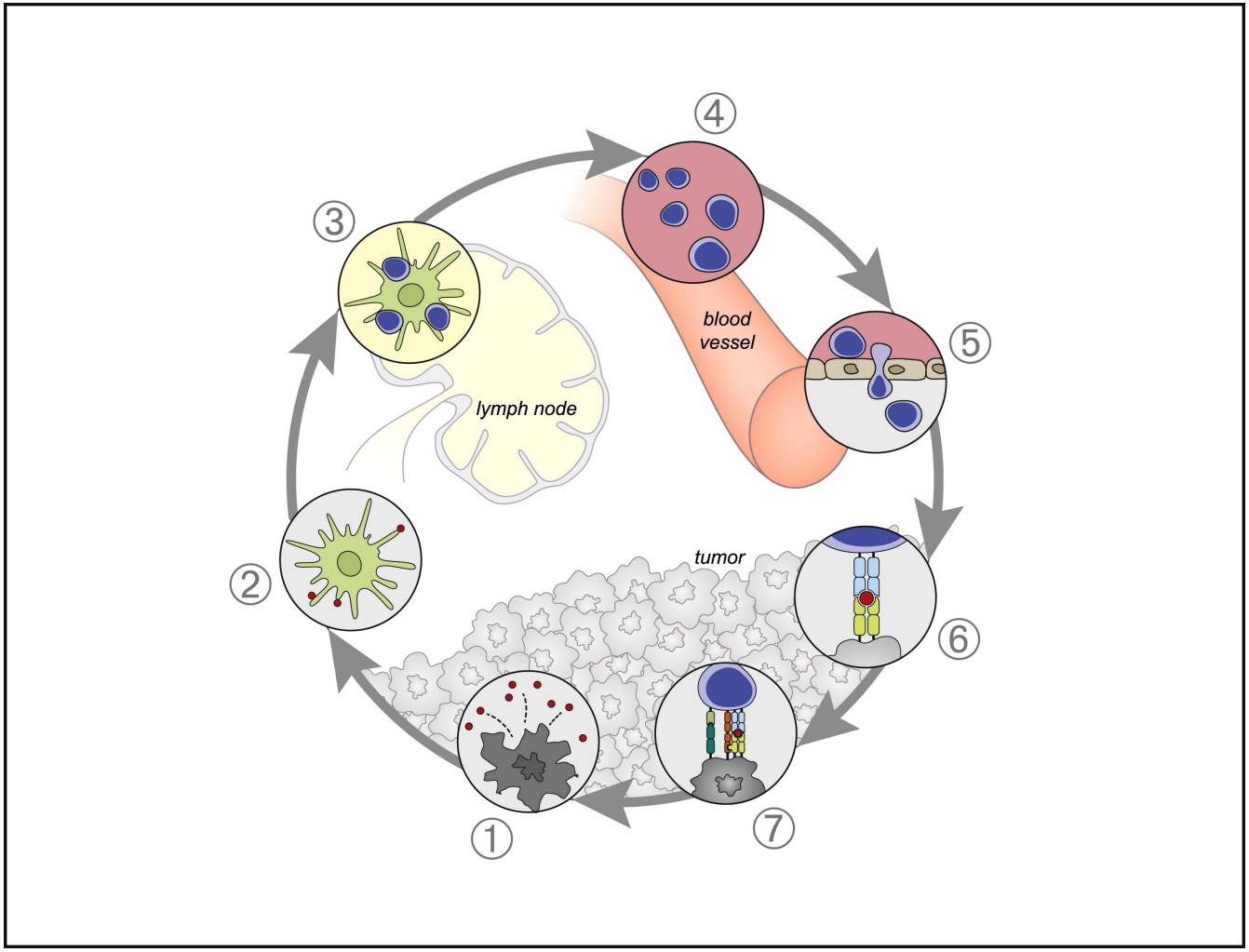
Drug	Commercial name	Owner	Target	First approval date
Pembrolizumab	Keytruda	MSD	PD-1	September 2014
Nivolumab	Opdivo	BMS	PD-1	December 2014
Atezolizumab	Tecentriq	Roche	PD-L1	May 2016
Avelumab	Bevancio	EMD and Pfizer	PD-L1	March 2017
Durmalumab	Imfinzi	AstraZeneca	PD-L1	May 2017

Source: Drugs.com

LABIOTECH.eu

The Cancer – Immunity cycle

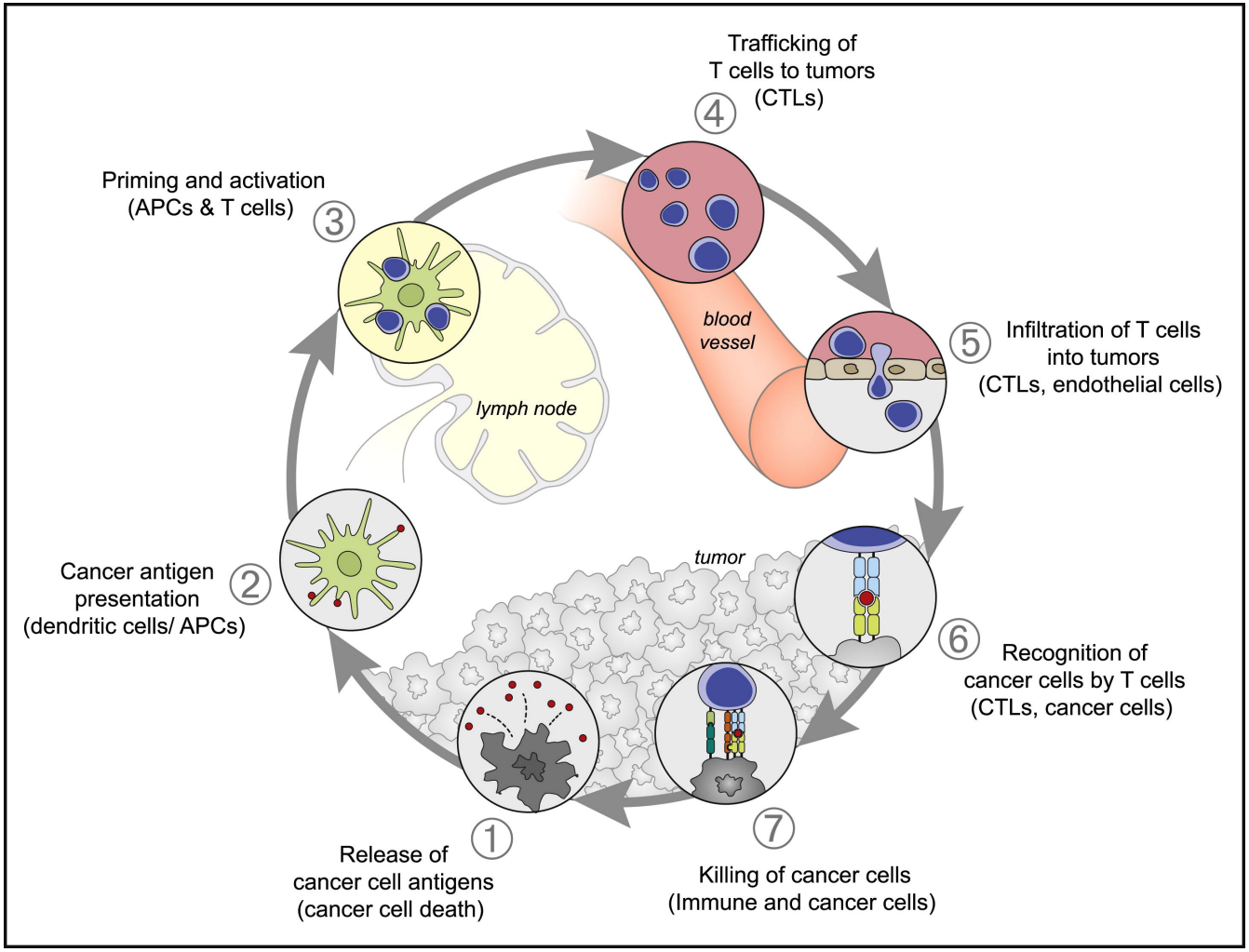
Functional interactions between tumor cells & their immune microenvironment



Un(e) volontaire pour commenter ce shéma?

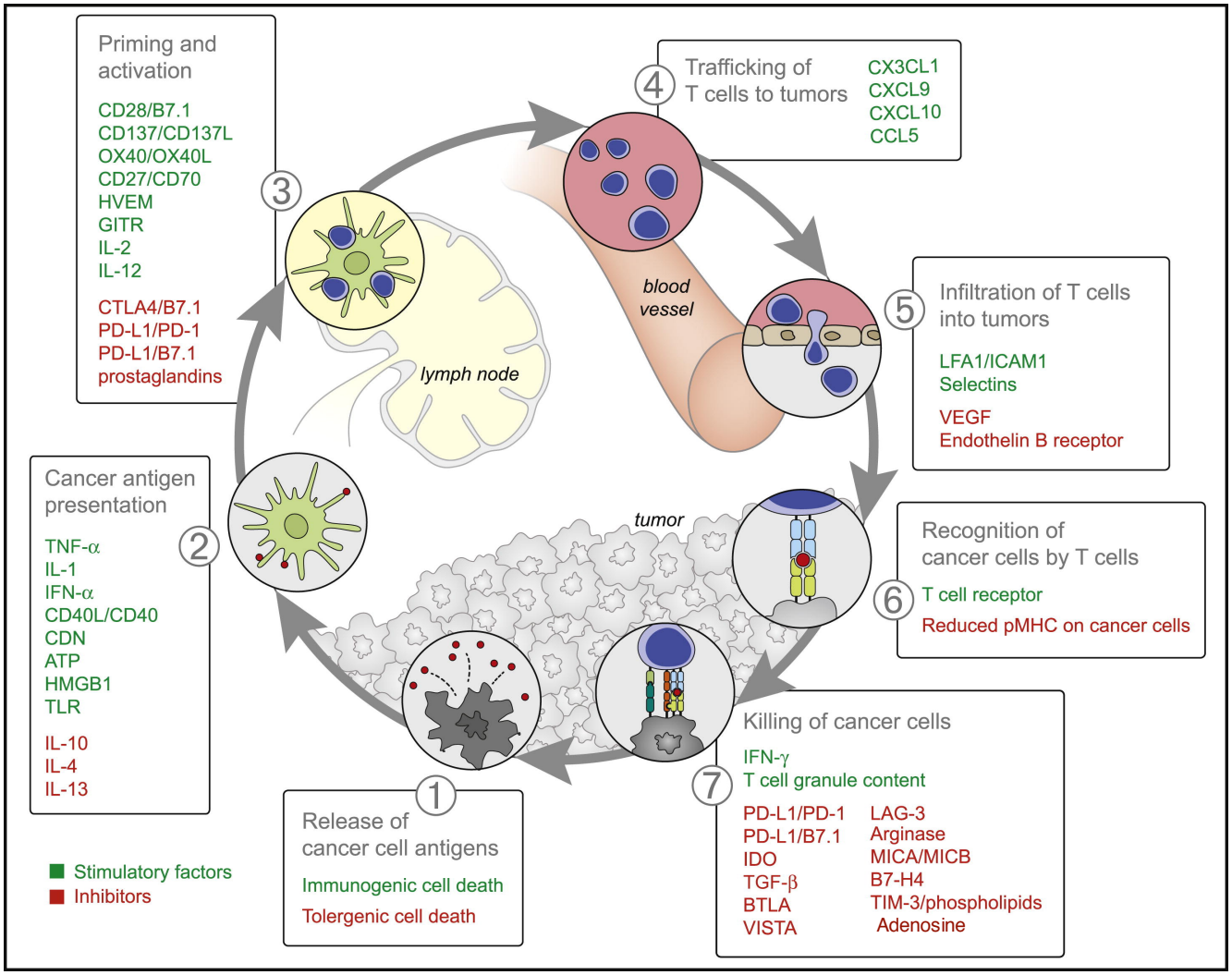
The Cancer – Immunity cycle

Functional interactions between tumor cells & their immune microenvironment



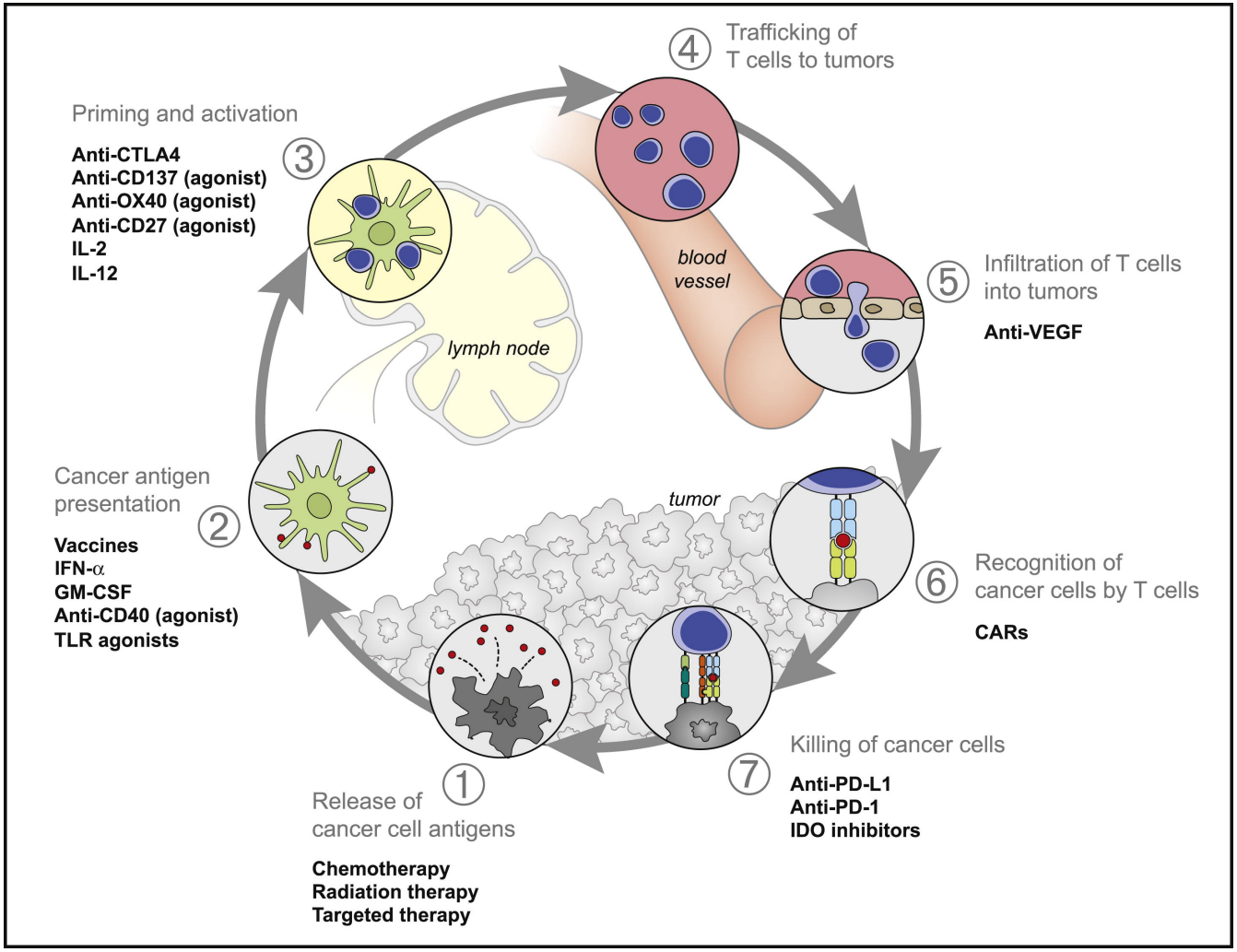
The Cancer – Immunity cycle

Functional interactions between tumor cells & their immune microenvironment



The Cancer – Immunity cycle

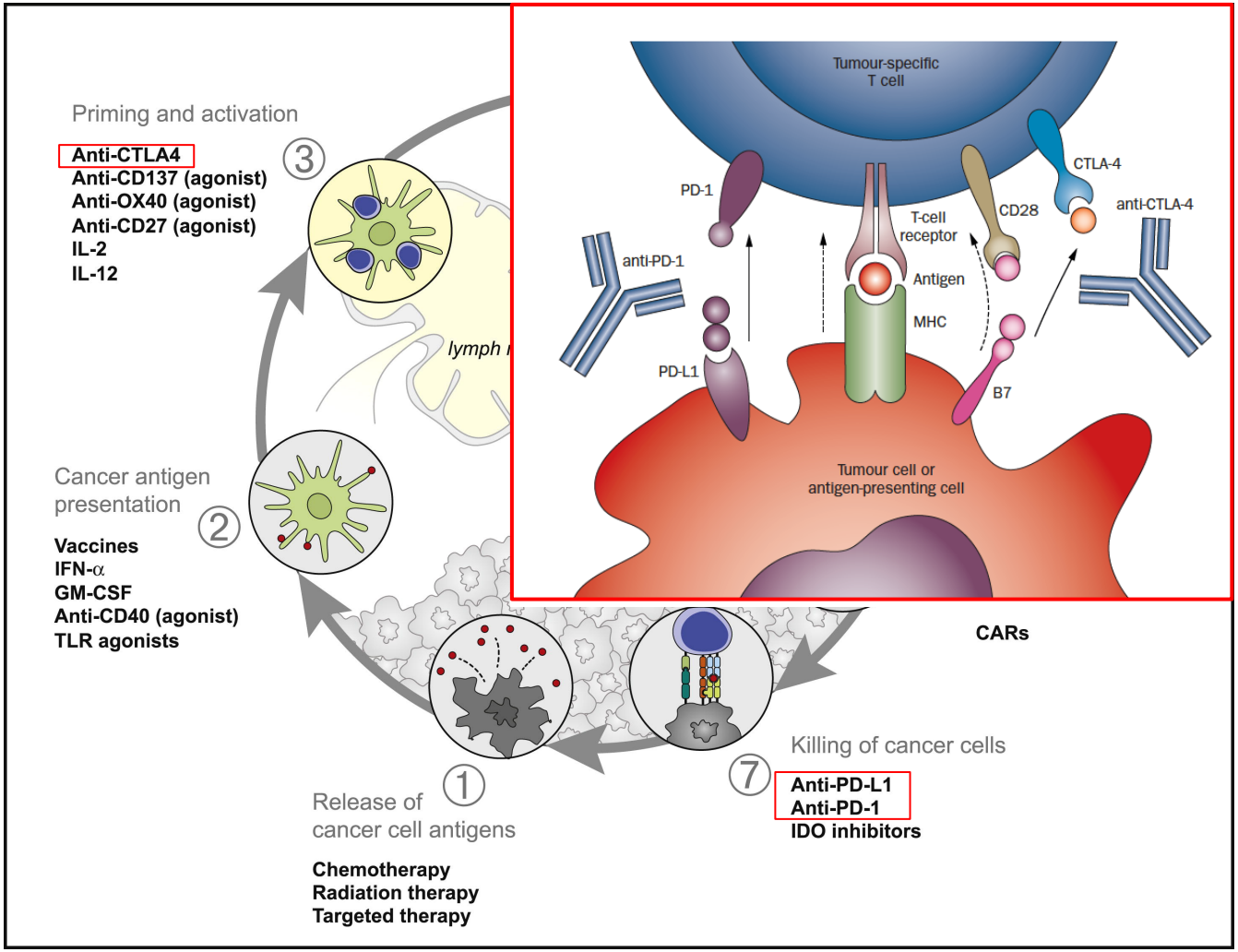
Functional interactions between tumor cells & their immune microenvironment



The goal of immunotherapy is to initiate or reinitiate endogenous anti-tumor immunity

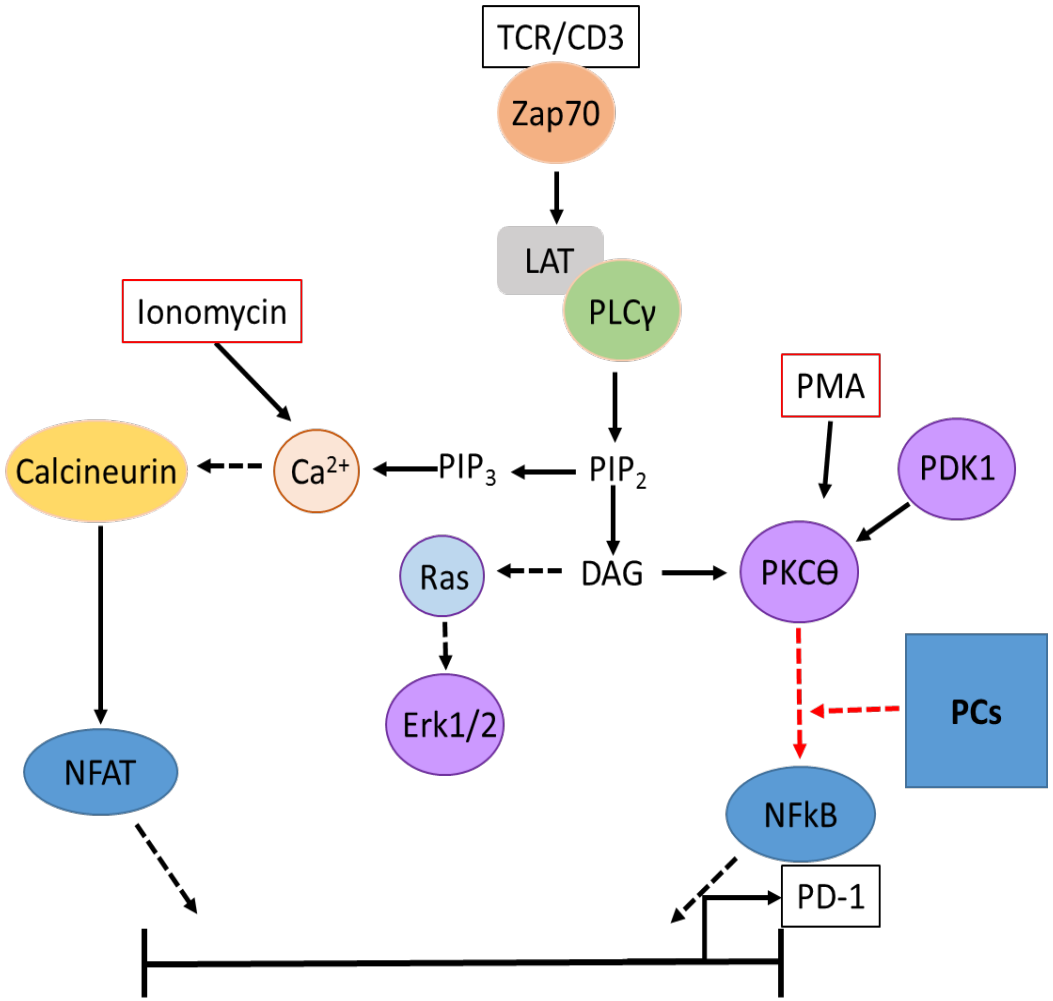
Immune checkpoints inhibitors

Functional interactions between tumor cells & their immune microenvironment



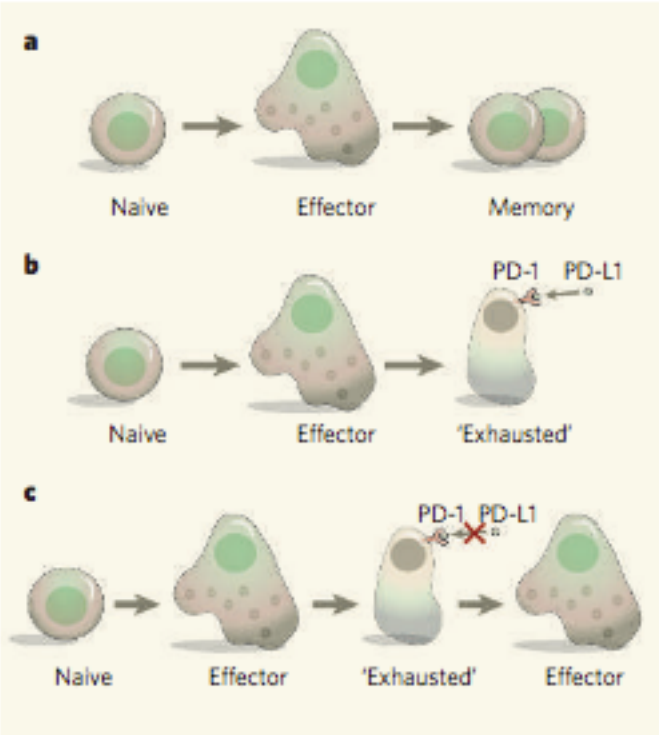
The goal of immunotherapy is to initiate or reinitiate endogenous anti-tumor immunity

PD1 Expression



Immune checkpoints inhibitors

Reviving exhausted T cells through PD1/PD-L1 blockade



a) Acute infection

b) Chronic infection / Tumor

c) Reviving exhausted T cells

The goal of immunotherapy is to initiate or reinitiate endogenous anti-tumor immunity

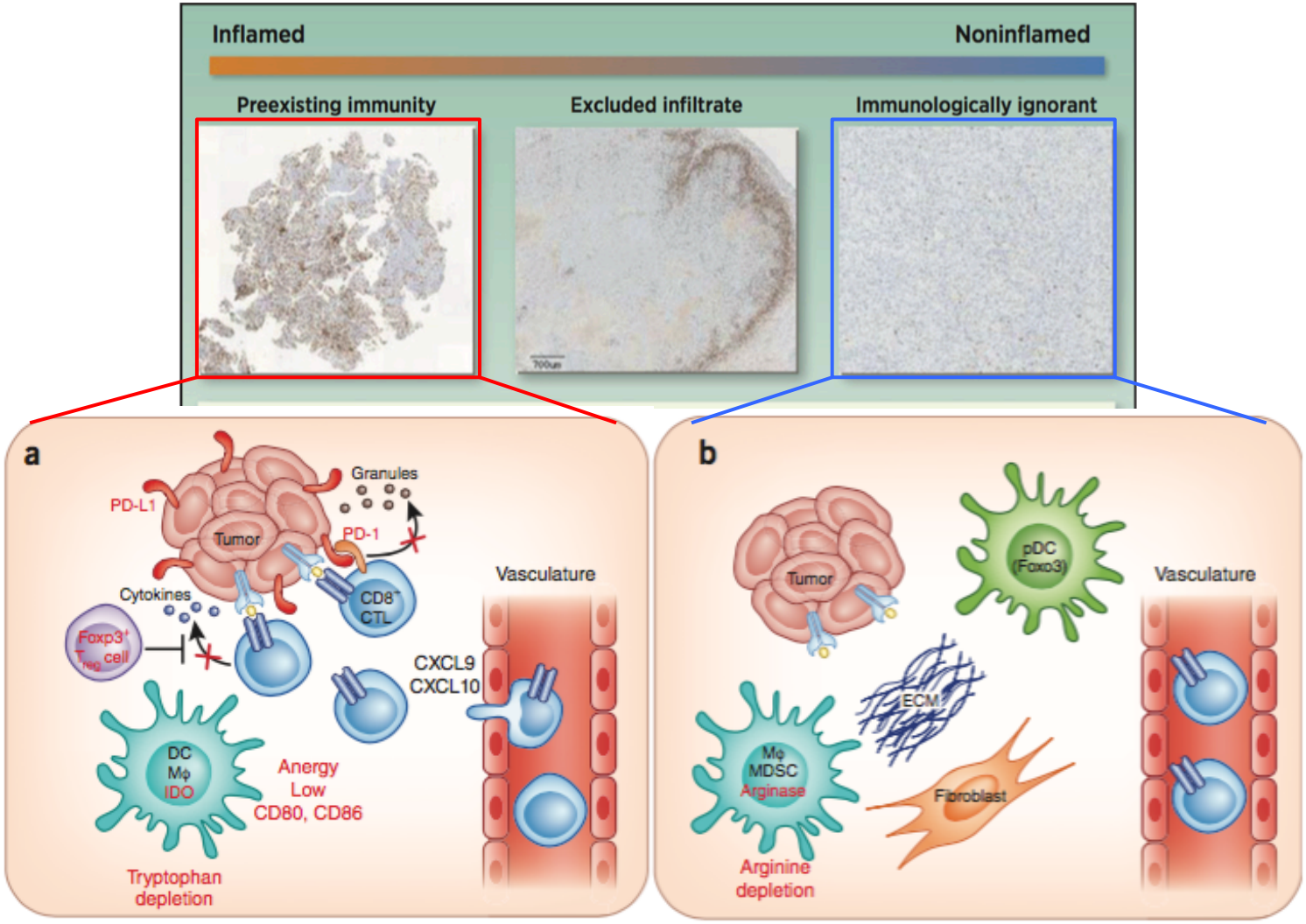
PD1 / PD-L1 blokade

Comparison of PD-1/PD-L1 Targeted Agents

	Nivolumab (BMS936558)	Pembrolizumab	MPDL3280A	Pidilizumab (CT-011)
Company	BMS	Merck	Genentech/Roche	CureTech
Target/MOA	PD-1 (blocks PD-L1/PD-L2)	PD-1 (blocks PD-L1/PD-L2)	PD-L1 (blocks PD-L1)	PD-1
Antibody	Human, **IgG4**	Humanized, **IgG4**	Human, **IgG1** (effector T-cell function)	Humanized, **IgG1** (effector T-cell function)
Targeted Tumors	Melanoma, NSCLC, RCC	Melanoma	Melanoma, NSCLC, RCC, Colon, Gastric, HNSCC, Lymphoma	Melanoma, pancreatic, lymphoma, CRC, RCC, MM
Latest Clinical Phase Development	**Phase III**/(melanoma, NSCLC, RCC) *[6-phase III trials]*	**Phase III**/(melanoma) Phase II (NSCLC)	Phase II (NSCLC)	Phase II (CRC, lymphoma, Hep-C pancreatic, PCa
Activity/response rates	**Melanoma**: all cohorts (ORR=31%) 3mg/kg Q2W cohort (ORR 41%) **NSCLC**: (17%), RCC (29%)	**Melanoma**: all cohorts (ORR>38%) 10mg/kg Q2W cohort (ORR=52%) **NSCLC**: nscc cohort ORR=23%), scc cohort (ORR=33%)	**Melanoma:** (ORR 29%, SD 87%, PFS 43%), NSCLC (24%) **NSCLC:** all cohorts (ORR=23%) **RCC:** (ORR=13%)	+50% increase in CD4, +40% increase in CD8
Efficacy	**Melanoma**: 3mg/kg Q2W cohort mOS=20.3 mths **NSCLC**: mOS=9.9 mths	**Melanoma:** mPFS=>7 mths **NSCLC**: nscc cohort mPFS=9.1 wks), scc cohort (mPFS=23.5 wks)	**All Tumors:** 39% vs. 13% **NSCLC:** 100% vs. 15%	
Fast Approval Strategy (w/phase II)	1. Squamous NSCLC 2. RCC	1. Melanoma	1. NSCLC	-
ADCC/CDC Toxicity	none	none	none	
Pneumonitis	3-4%	3-4%	none	none
Grade 3/4 Adverse Events	All Grade 3/4 = 14% • Fatigue 2% • Diarrhea 1% • Pruritus 0.3% • Nausea 0.3% • Hb decrease 0.3%	All Grades 3/4 = 12.6% • Fatigue 1.5% • Rash 2.2% • Pruritus 0.7%	All Grade 3/4 = 43% • Hyperglycemia 5% • Fatigue 4% • Increased ALT 3% • Dyspnea 3% • Hypoxia 3%	

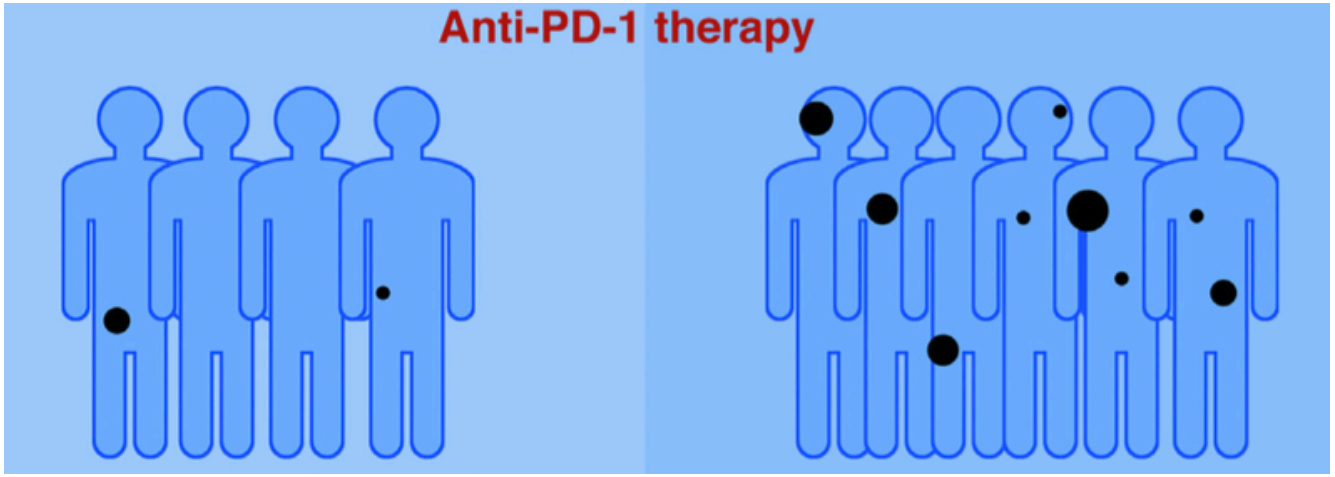
Impact of tumor infiltrate

Functional interactions between tumor cells & their immune microenvironment



Adapted from Gajewski T et al., Nature Immunology 2013

Resistance to anti-PD1



Responding

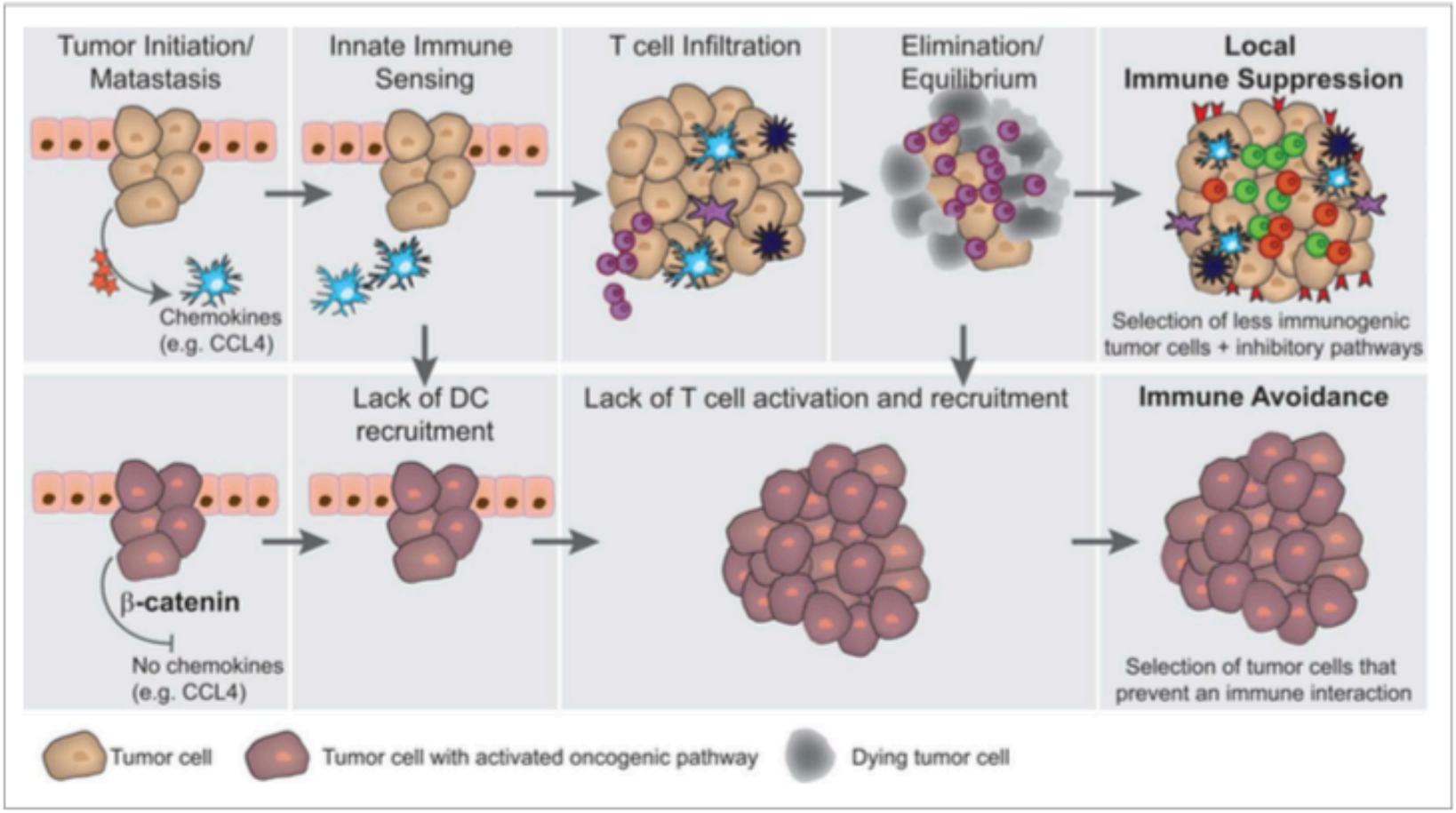
Non responding : primary resistance

Initial response with delayed tumor relapse : acquired resistance

- Mutations that inhibit activation and recruitment of T cells (β-catenin, PTEN)
  Spranger S et al., Nature 2015, Peng W et al., Cancer discovery 2016
- Mutations that favor tumor immune escape (JAK1-2, β2-microglobulin)
  Zaretsky JM et al., New Eng J Med 2016
- Increased expression of other immune checkpoints by effector T cells (TIM-3)
  Koyama S et al., Nat Com 2016

Resistance to anti-PD1

Functional interactions between tumor cells & their immune microenvironment



Tumor-intrinsic oncogene pathways mediating immune avoidance

Adapted from Spranger S et al., Oncoimmunology 2016

Resistance to anti-PD1

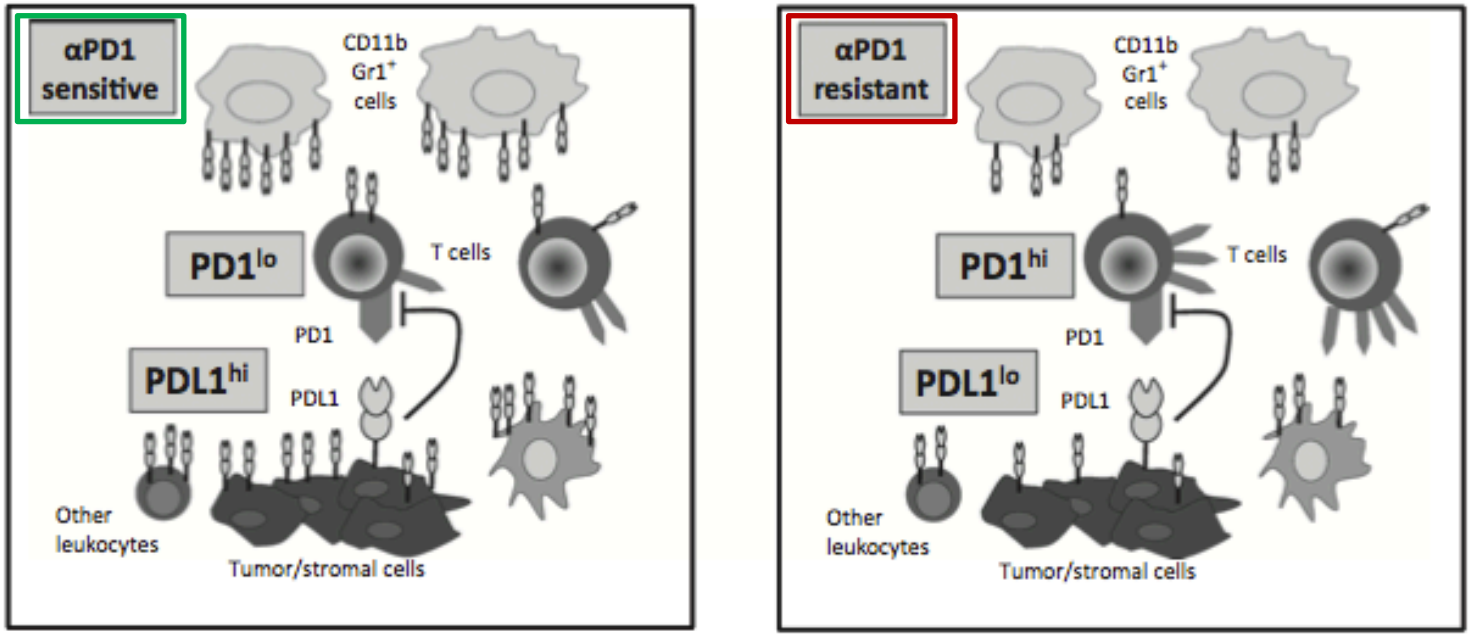
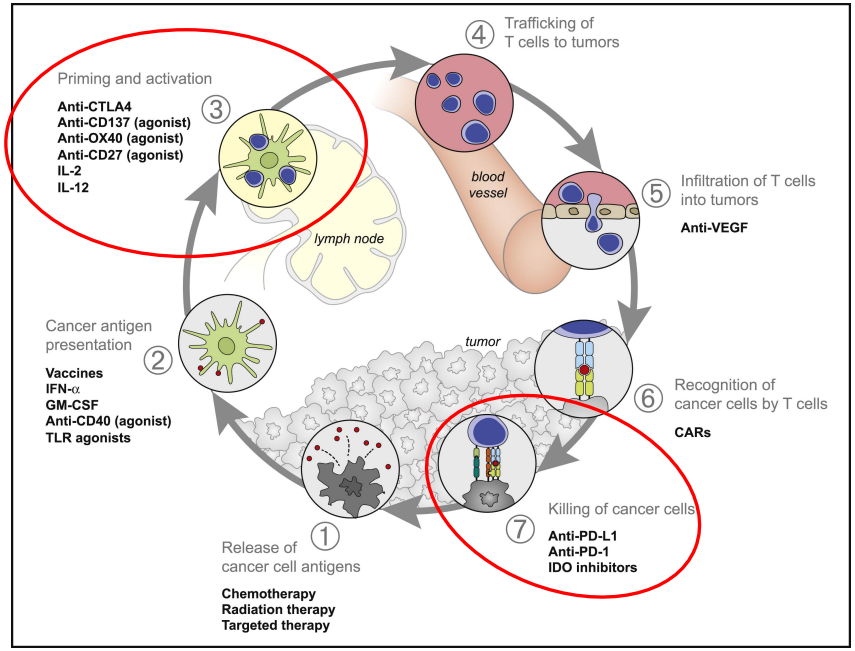


Figure 7.
Schematic diagram of the PD1/PDL1 axis in anti-PD1–sensitive and –resistant tumors. Left, in a tumor microenvironment with PD1^{lo} T cells, an increased level of PDL1 expression is present that increases the probability of PD1 ligation on T cells. Right, in contrast, in a tumor microenvironment with PD1^{hi} T cells, a low level of PDL1 expression is sufficient to ensure the ligation of PD1 on T cells.

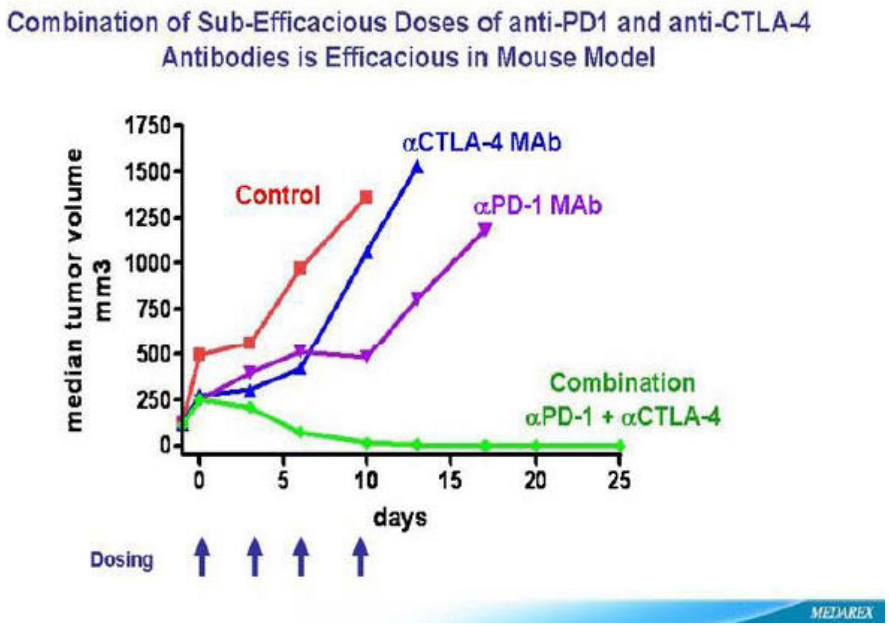
From Ngiow SF et al., Cancer Research 2015

Combined Therapies

- Combining checkpoint inhibitors in cancer therapy

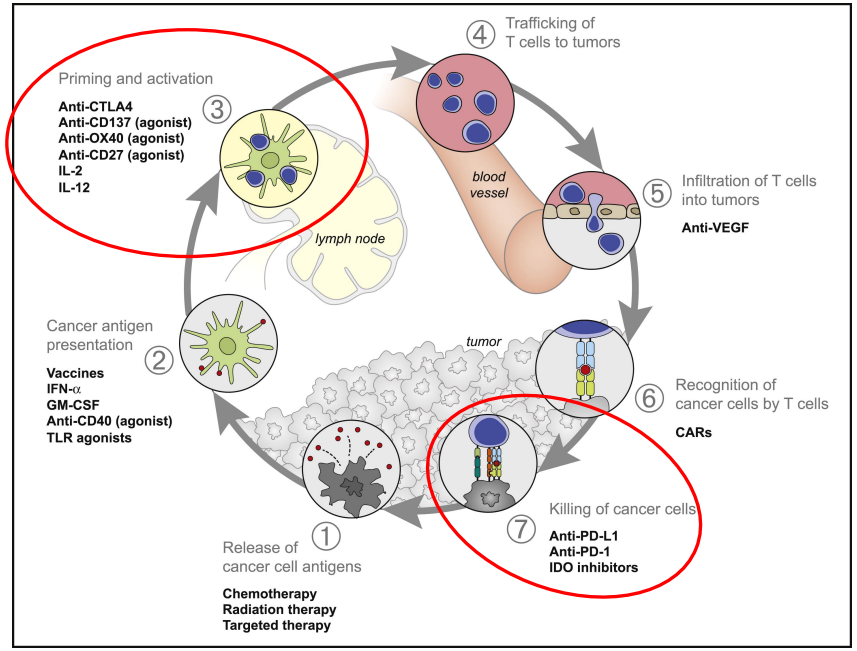


Murine melanoma model

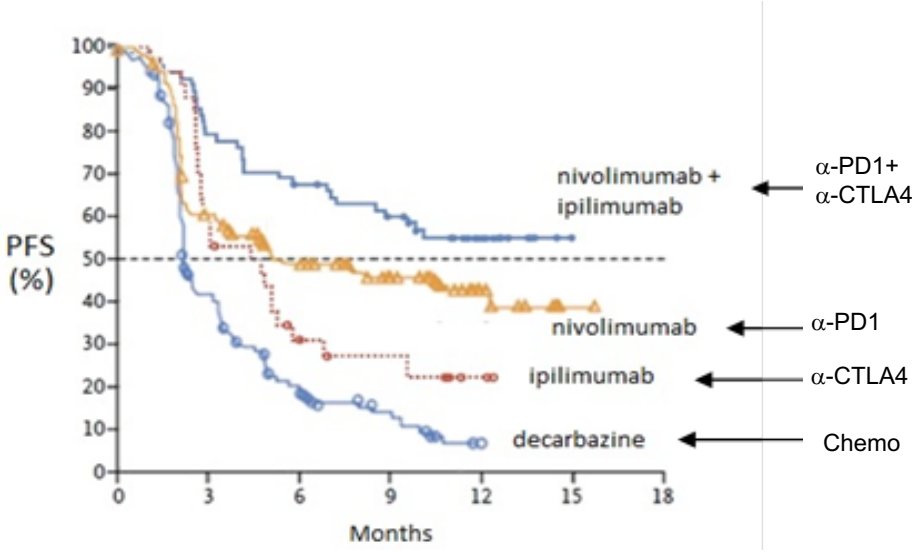


Combined Therapies

- Combining checkpoint inhibitors in cancer therapy



Human melanoma

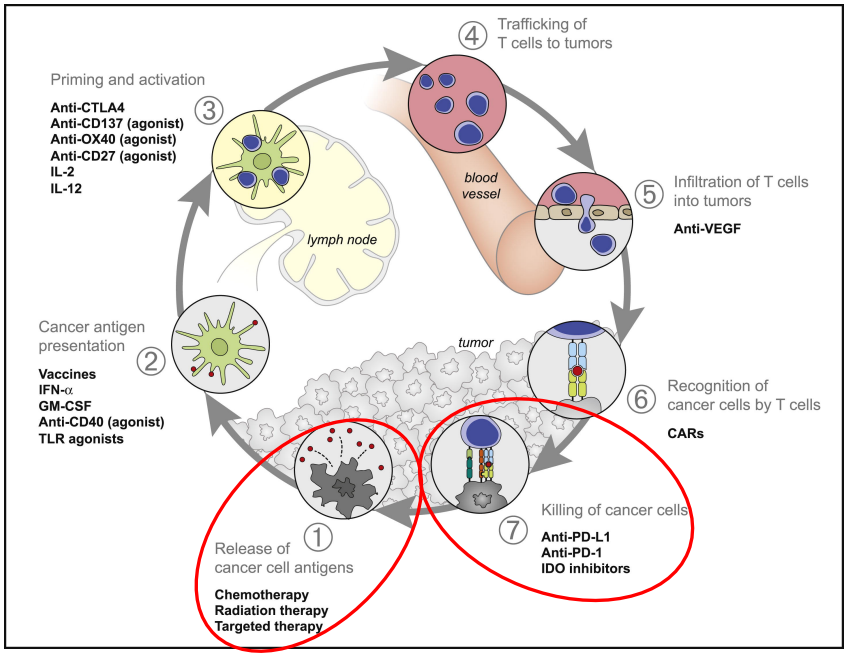


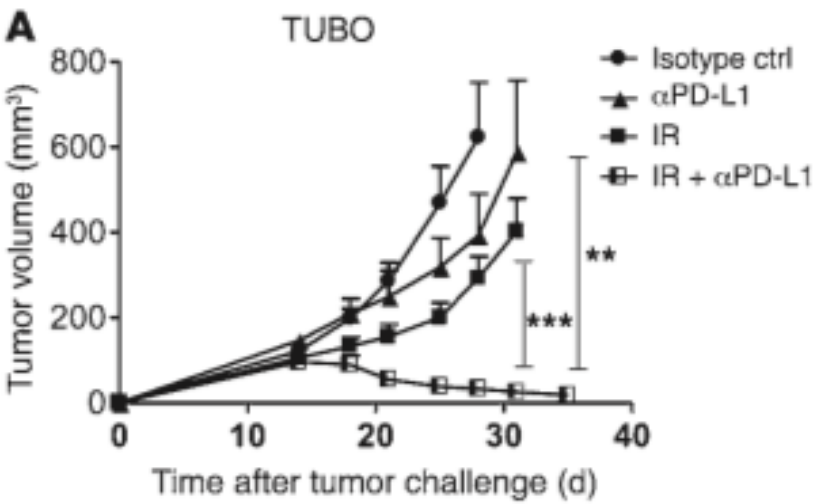
- Search for predictive markers of clinical activity of checkpoint inhibitors
- Combination with other regulators of the immune response?
- Combination with conventional therapies?

Adapted from Robert C, NEJM 2014 and Postow MA, NEJM 2015

Combined Therapies

- Combining checkpoint inhibitors with conventional therapies to reinforce anti-tumor immunity

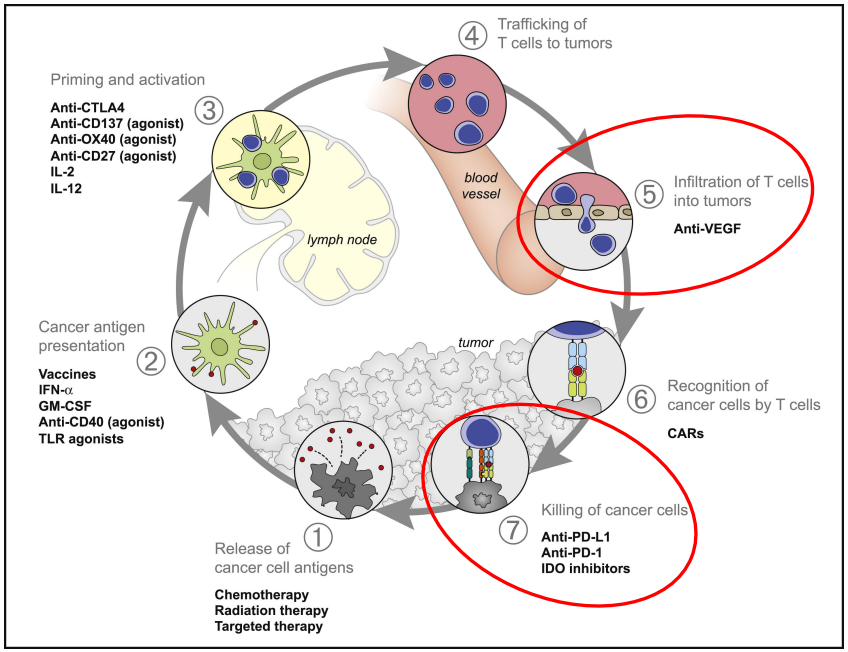


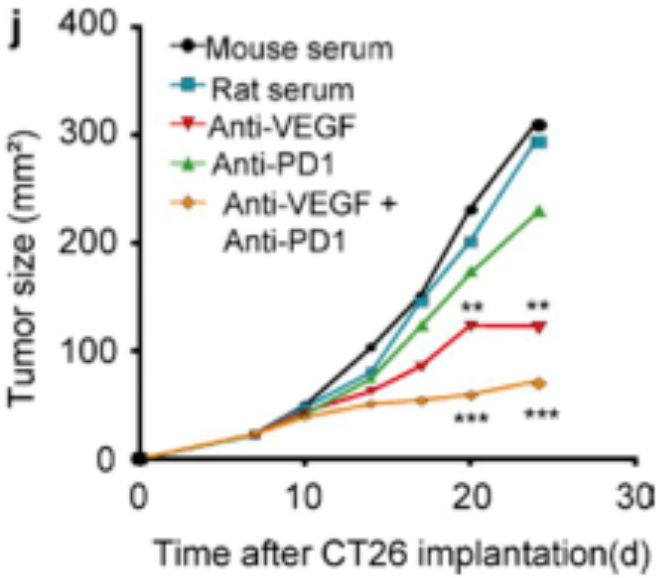


Deng L, JCI 2014

Combined Therapies

- VEGF-A blockade significantly reduced PD-1 expression on intratumoral CD8+ T cells *(CT26 - colon preclinical model)*



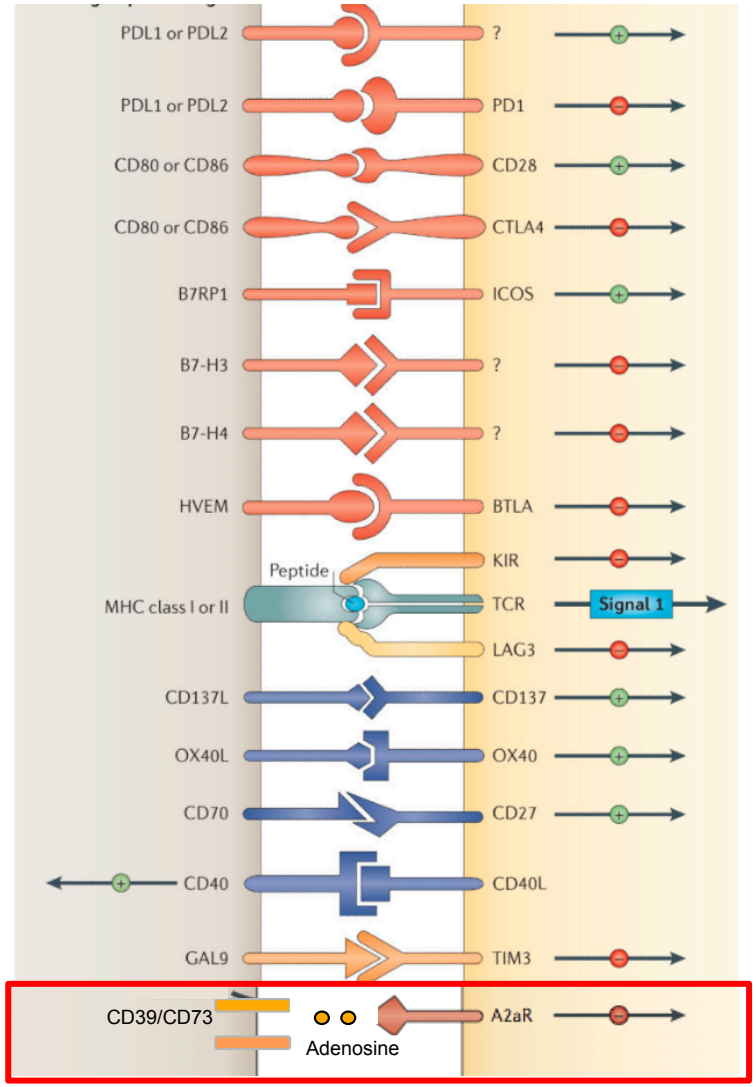


- VEGF-A blockade synergizes with anti-PD-1 to prevent tumor growth

Voron T, J Exp Med 2015

Other immunoregulators

Tumor cells
or
Immune cells

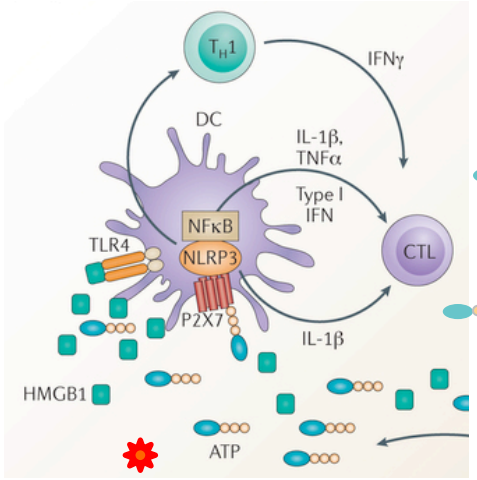


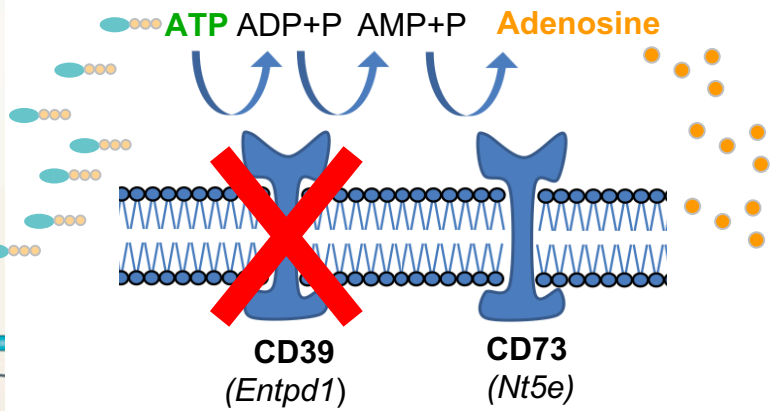
Effector T cell

CD39/CD73/adenosine immunosuppressive pathway

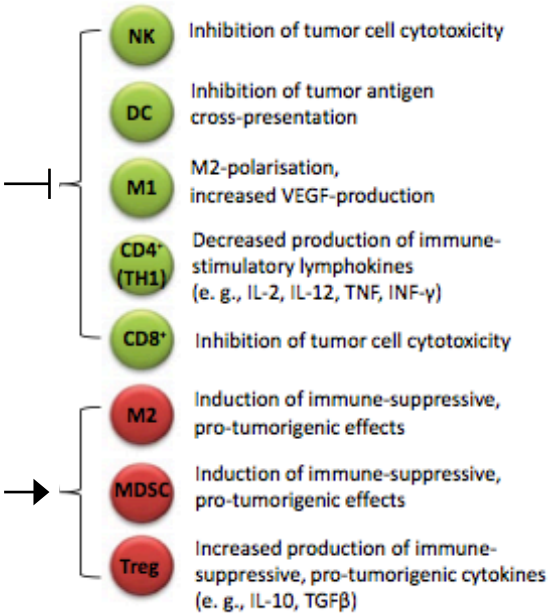
Other immunoregulators

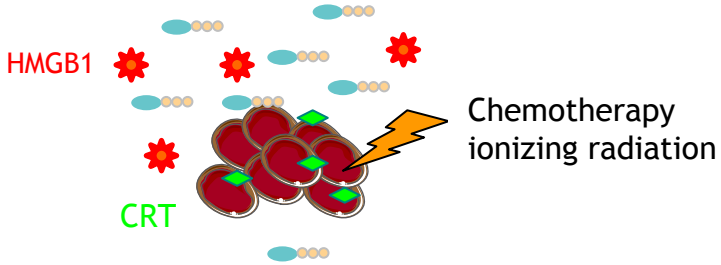
ATP is released during immunogenic cell death (DC priming)





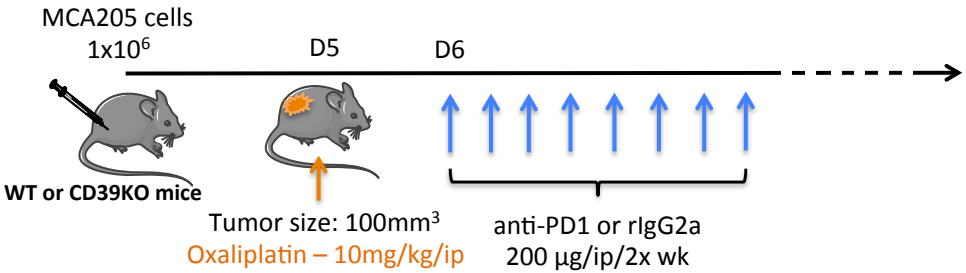
Adenosine limits anti-tumor immune response

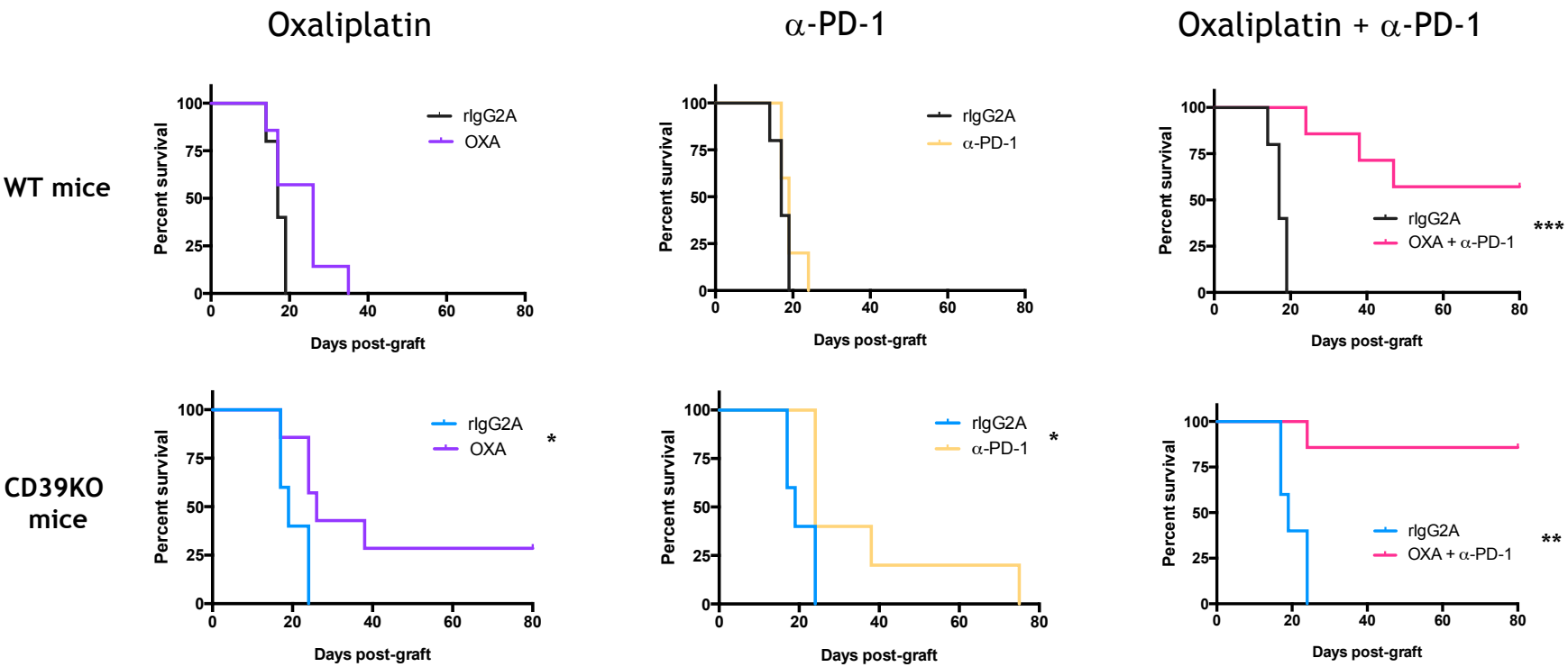




Impact of CD39 deficiency immunotherapy & chemotherapy?

Other immunoregulators





CD39 deficiency significantly increases treatment efficacy and mice survival

Cancéropôle Grand Sud-Ouest

Side effects of immune checkpoint inhibitors

Table 2 Nivolumab monotherapy and combination with ipilimumab side effect profile

Adverse event category	Nivolumab α-PD1		Ipilimumab α-CTLA4		Nivolumab + ipilimumab α-PD1 + α-CTLA4	
	Any, n (%)	Grades 3–4, n (%)	Any, n (%)	Grades 3–4, n (%)	Any, n (%)	Grades 3–4, n (%)
Endocrine						
Hypothyroidism	27 (8.6)	0	13 (4.2)	1 (0.3)	47 (15)	1 (0.3)
Hyperthyroidism	13 (4.2)	0	3 (1)	0	31 (9.9)	3 (1)
Hypophysitis	2 (0.6)	1 (0.3)	12 (3.9)	6 (1.9)	24 (7.7)	5 (1.6)
Pyrexia	18 (5.8)	0	21 (6.8)	1 (0.3)	58 (6.8)	1 (0.3)
Gastrointestinal						
Elevated ALT/AST	24 (7.7)	7 (2.2)	23 (7.3)	7 (2.2)	103 (33)	45 (14.4)
Diarrhea	60 (19.2)	7 (2.2)	103 (33.1)	19 (6.1)	138 (44.1)	29 (9.3)
Colitis	4 (1.3)	2 (0.6)	36 (11.6)	27 (8.7)	37 (11.8)	24 (7.7)
Nausea	41 (13.1)	0	50 (16.1)	2 (0.6)	81 (25.9)	7 (2.2)
Vomiting	20 (6.4)	1 (0.3)	23 (7.4)	1 (0.3)	48 (15.3)	8 (2.6)
Decreased appetite	34 (10.9)	0	39 (12.5)	1 (0.3)	56 (17.9)	4 (1.3)
Musculoskeletal						
Arthralgia	24 (7.7)	0	19 (6.1)	0	33 (10.5)	1 (0.3)
Neuropsychiatric						
Fatigue	107 (34.2)	4 (1.3)	87 (28)	3 (1)	110 (35.1)	13 (4.2)
Headache	23 (7.3)	0	24 (7.7)	1 (0.3)	32 (10.2)	1 (0.3)
Pulmonary						
Pneumonitis	4 (1.3)	1 (0.3)	5 (1.6)	1 (0.3)	20 (6.4)	3 (1)
Dyspnea	14 (4.5)	1 (0.3)	13 (4.2)	0	32 (10.2)	2 (0.6)
Skin						
Rash	81 (25.9)	2 (0.6)	102 (32.8)	6 (1.9)	126 (40.3)	15 (4.8)
Vitiligo	23 (7.3)	1 (0.3)	12 (3.9)	0	21 (6.7)	0
Pruritus	59 (18.8)	0	110 (35.4)	1 (0.3)	104 (33.2)	6 (1.9)
Discontinuation due to treatment-related AE	24 (7.7)	16 (5.1)	46 (14.8)	41 (13.2)	114 (36.4)	92 (29.4)

Note: Data from Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372(4):320–330.[42]
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

From Force J and Salama AKS ImmunoTargets and Terapy 2017