PRECISION IN CANCER IMMUNOTHERAPY

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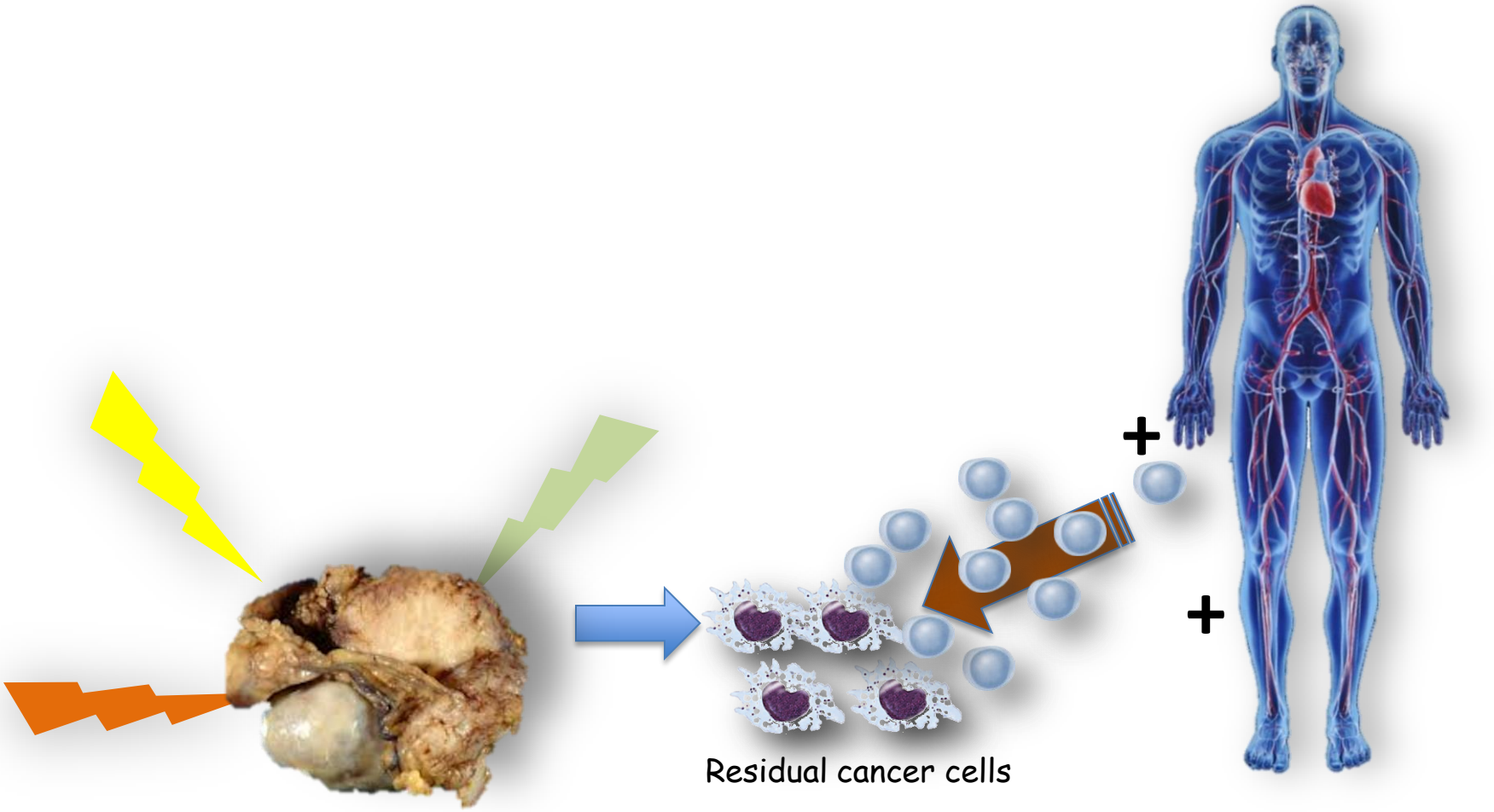
CHUV

Penn Medicine

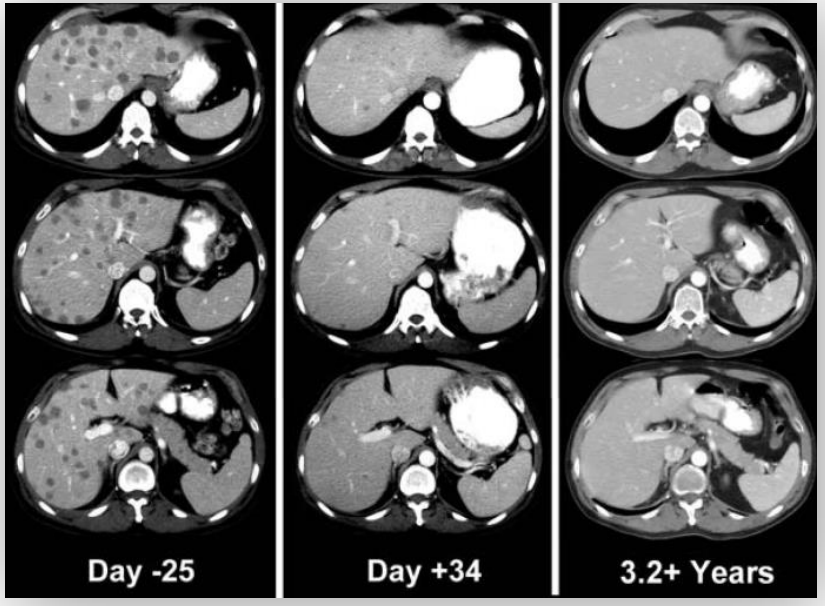
INTEGRATIVE THERAPY ADDRESSING MULTIPLE HALLMARKS OF CANCER

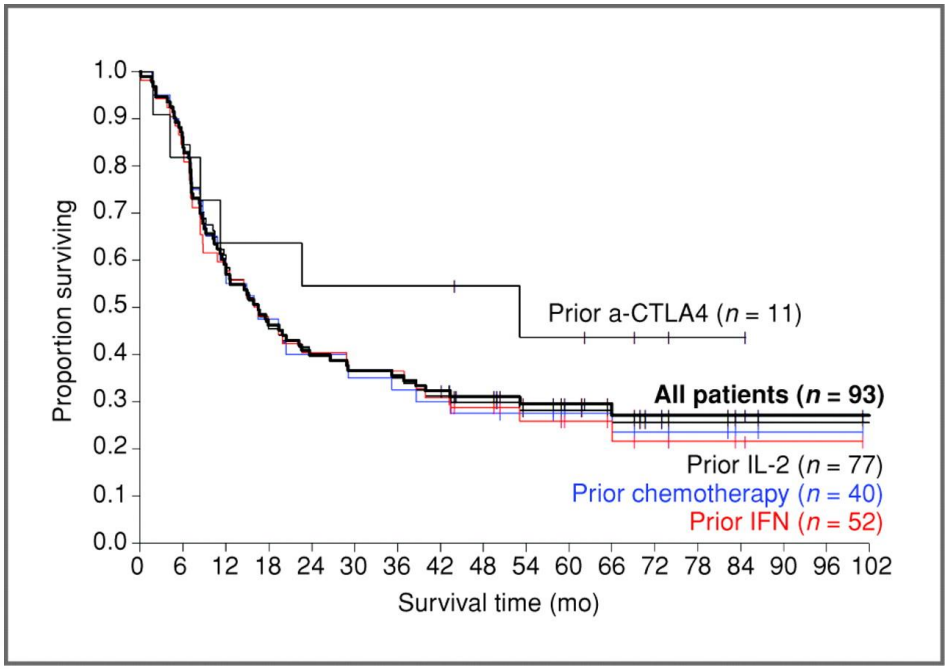


Combination targeted therapy
Radiation
Chemotherapy

Immunomodulation
Active/passive immunotherapy
Therapy of the tumor microenvironment

Tumor Therapy with Adoptive Transfer of Reactive TILs



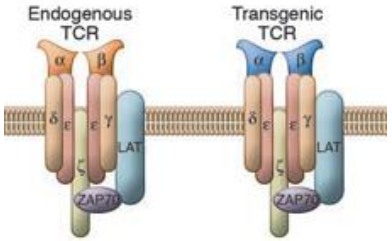


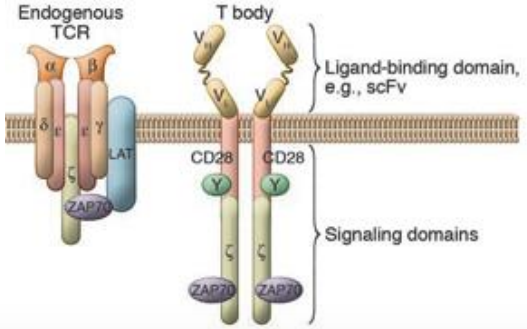
Rosenberg S A et al. *Clin Cancer Res* 2011

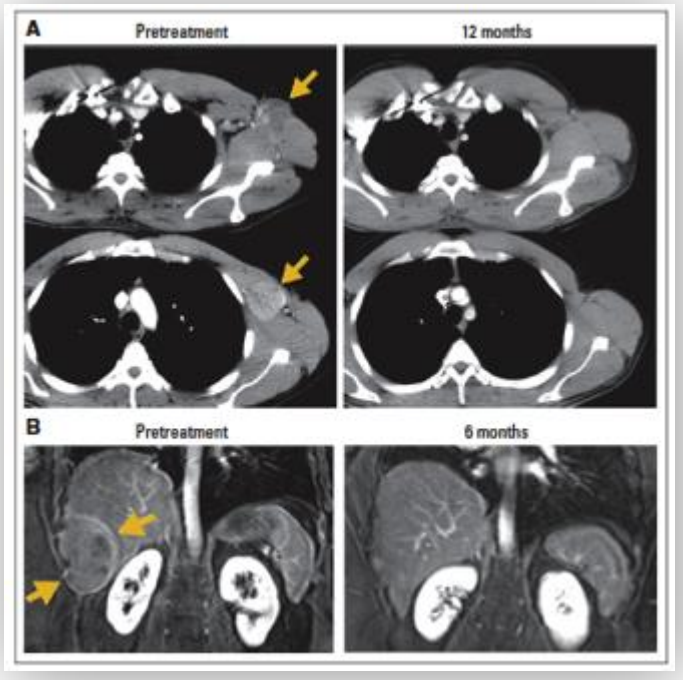
From July 2002 to July 2007, 787 tumors from 402 patients were processed for TIL.
Active, specific TILs were identified in 269 patients (67%), leading to the eventual treatment of 107 patients (27%).

Goff SL et al. *J Immunother* 2010

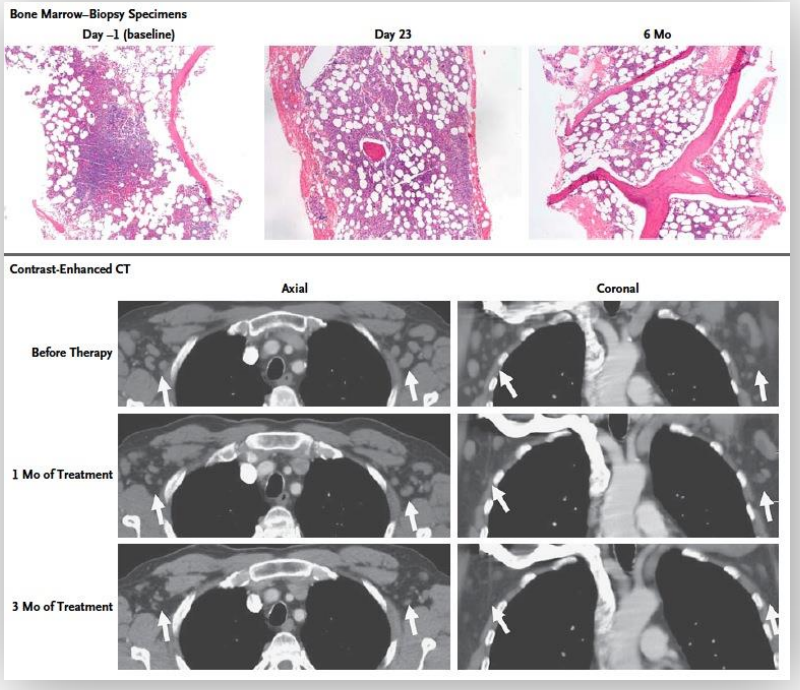
Tumor Therapy with Engineered T Cells





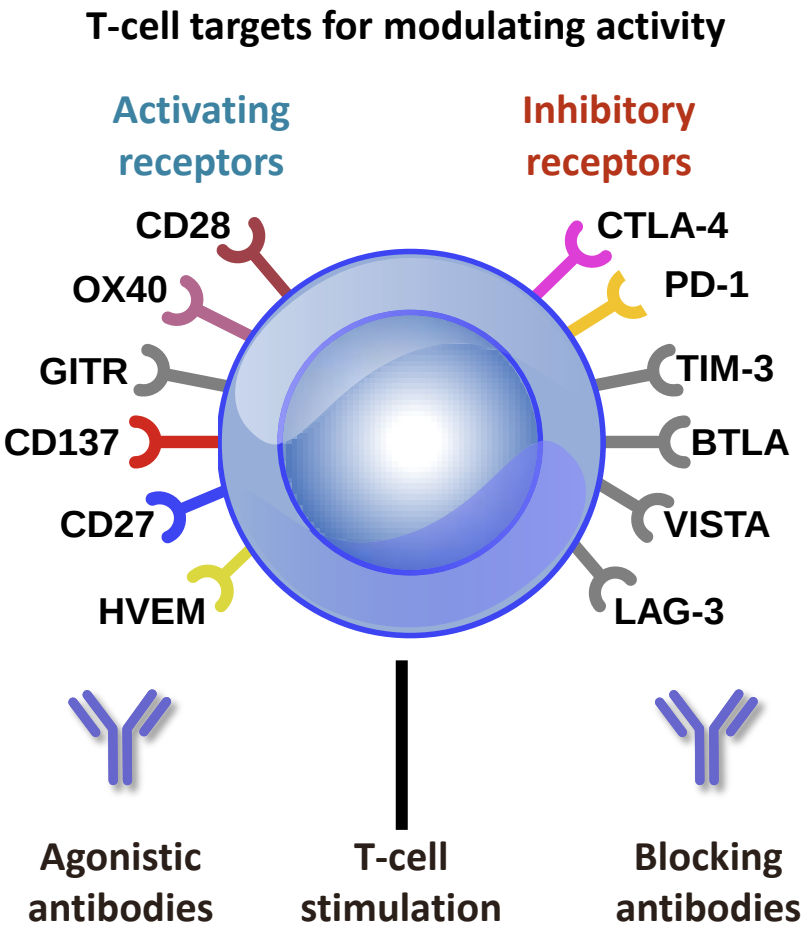


Robbins *JCO* 2011



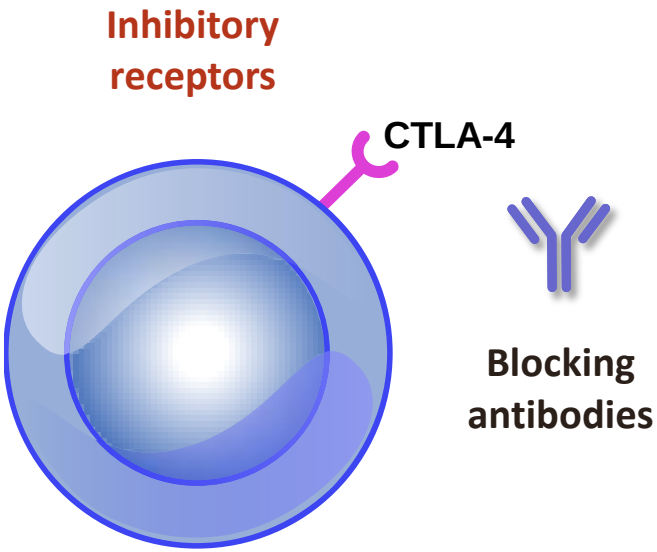
Porter *NEJM* 2011

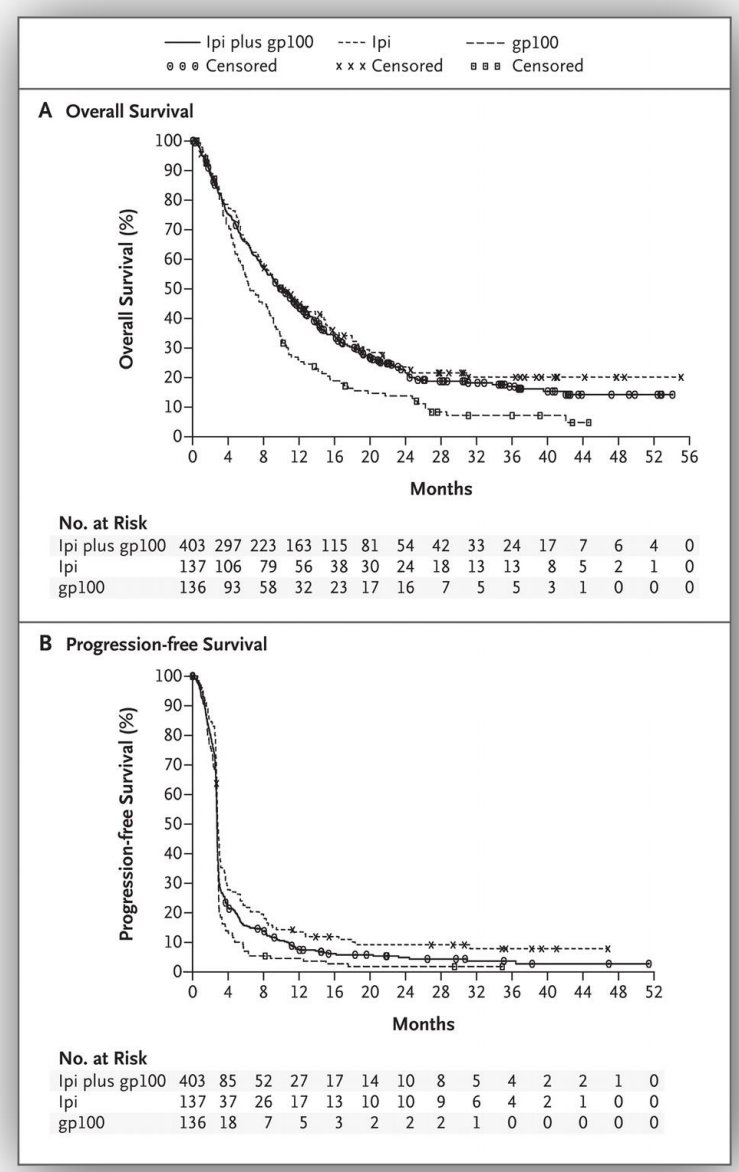
T-cell targets for immunoregulatory antibody therapy



Mellman, et al. Nature 2011

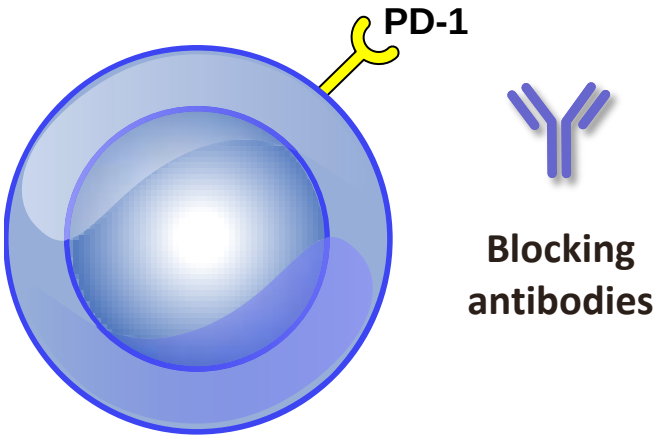
Patients with melanoma benefit from CTLA-4 blockade

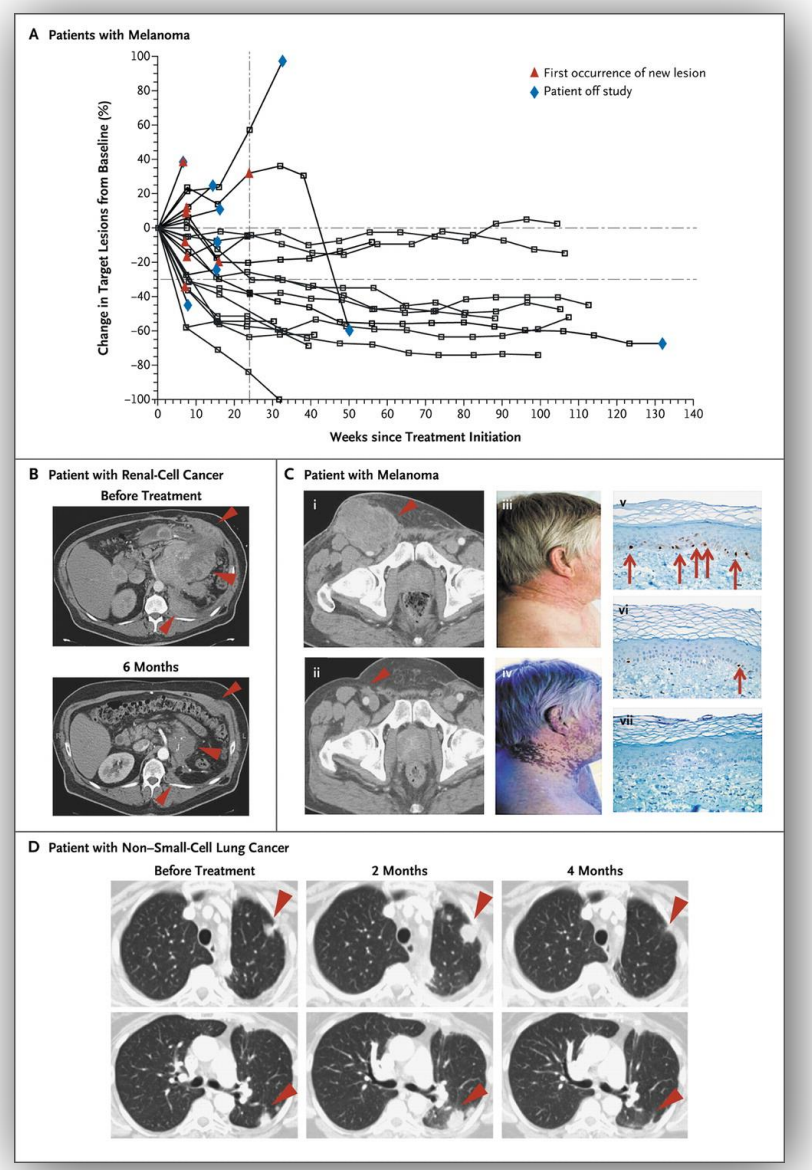




Hodi FS et al. N Engl J Med 2010;363:711-723.

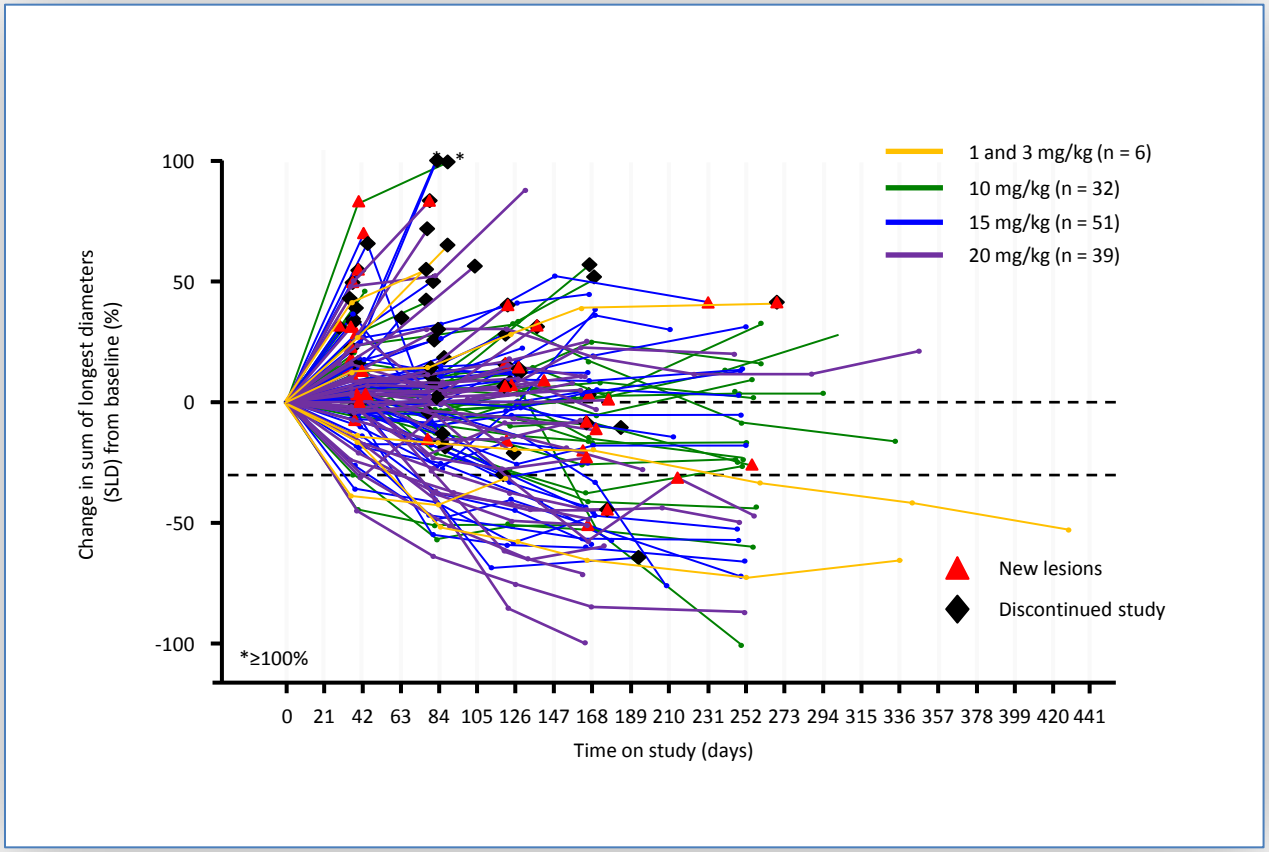
Patients with solid tumors benefit from PD-1 blockade





Topalian SL et al. N Engl J Med 2012;366:2443-2454.

Patients with solid tumors benefit from PD-L1 blockade



Patients first dosed at 1–20 mg/kg prior to 1 Aug 2012 with at least 1 post-baseline evaluable tumour assessment; data cut-off 1 Feb 2013

Herbst, et al. ASCO 2013

Important challenges for personalization

- Identify robust predictive biomarkers
- Understand the mechanism of the therapeutic effect
- Identify mechanisms of resistance
  - Constitutive
  - Adaptive
- Rapid testing in preclinical models and in the clinic

In search for biomarkers….

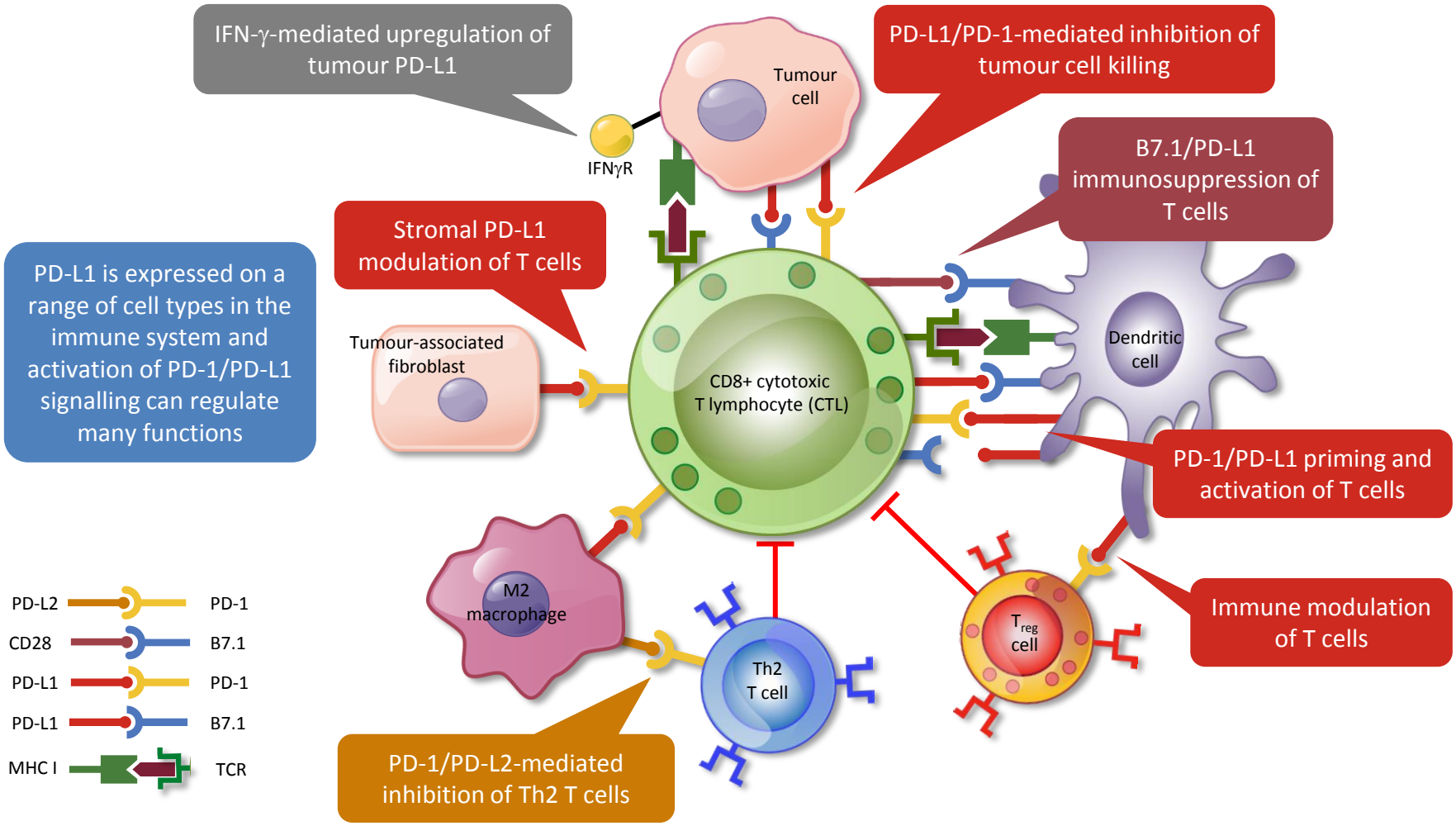
1) Mobilizing endogenous immunity

- Checkpoint blockade
- TIL therapy

2) Passive or active immunotherapy against defined targets

- CARs: Surface antigens (CD19, CD20, PSMA etc)
- TCRs and molecularly defined vaccines: Expression of the surface peptide-MHC complex

PD-L1 plays an important role in dampening the anti-tumour immune response

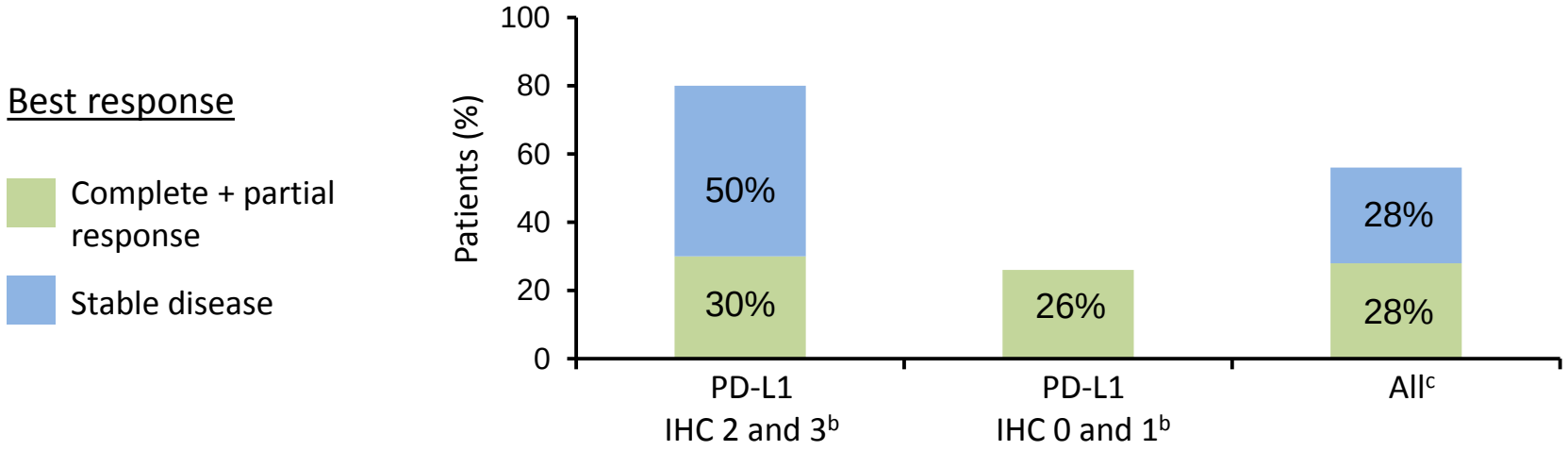


Chen, et al. Clin Cancer Res 2012

MPDL3280A phase Ia: tumour response by PD-L1 IHC status – melanoma

- Estimated PD-L1 prevalence in melanoma is ≈40% (non-clinical trial samples)[a]

Investigator-assessed best overall response rate (RECIST 1.1 confirmed ORR) (n = 43)			
	PD-L1 IHC 2 and 3[b]	**PD-L1 IHC 0 and 1[b]**	**All[c]**
Melanoma RECIST 1.1 ORR	6/20 (30%)	5/19 (26%)	12/43 (28%)
Melanoma CR + PR + SD	16/20 (80%)	5/19 (26%)	24/43 (56%)



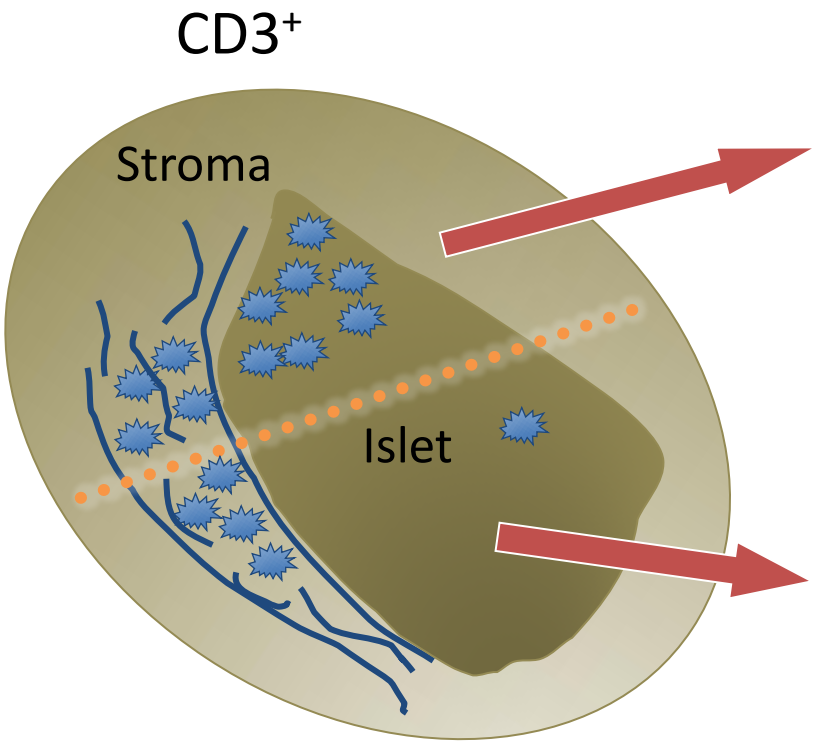
[a]Surgical tumour specimens (internal Genentech data from non-trial samples). Koeppen and Kowanetz, Genentech
[b]IHC 2 and 3: ≥5% tumour-infiltrating immune cells positive for PD-L1; IHC 0 and 1: <5% tumour-infiltrating immune cells positive for PD-L1
[c]All patients includes 39 patients with known and four patients with unknown tumour PD-L1 status
Patients first dosed at 1–20 mg/kg by 1 Oct 2012; data cut-off 30 Apr 2013. One patient without post-baseline scan was included as a non-responder

The NEW ENGLAND JOURNAL of MEDICINE

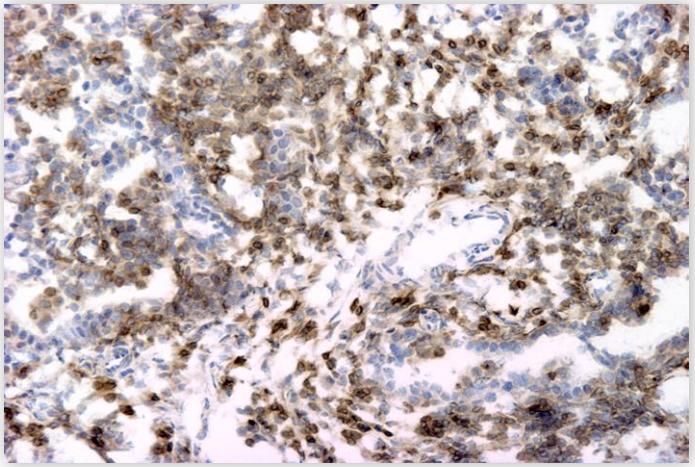
ORIGINAL ARTICLE

Intratumoral T Cells, Recurrence, and Survival in Epithelial Ovarian Cancer

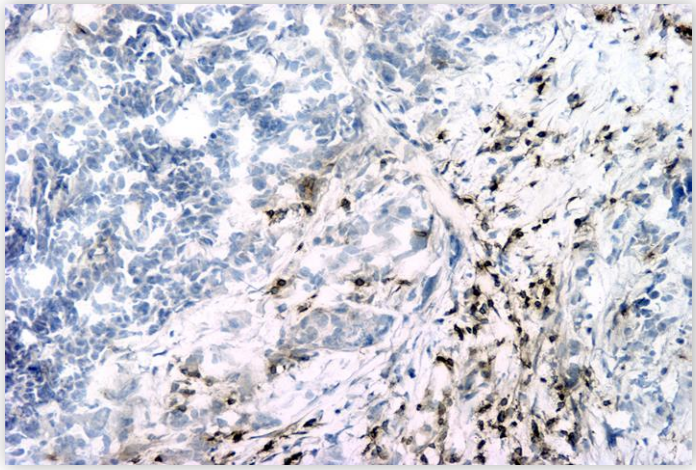
Lin Zhang, M.D., Jose R. Conejo-Garcia, M.D., Ph.D., Dionyssios Katsaros, M.D., Ph.D., Phyllis A. Gimotty, Ph.D., Marco Massobrio, M.D., Giorgia Regnani, M.D., Antonis Makrigiannakis, M.D., Ph.D., Heidi Gray, M.D., Katia Schlienger, M.D., Ph.D., Michael N. Liebman, Ph.D., Stephen C. Rubin, M.D., and George Coukos, M.D., Ph.D.



Present
54.8%



Absent
38.7%

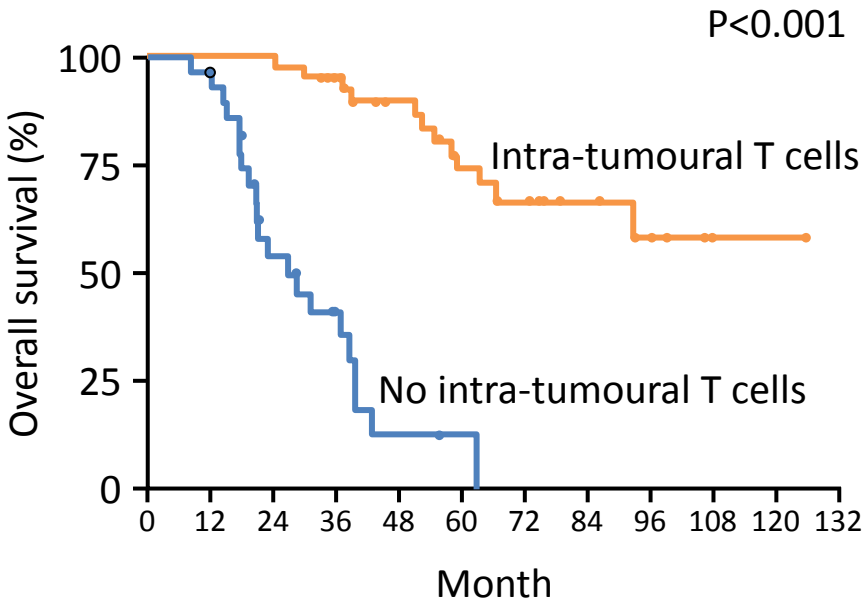


Zhang, et al. N Engl J Med 2003

After successful chemotherapy, only patients with anti-tumour T cells survive long term or are cured

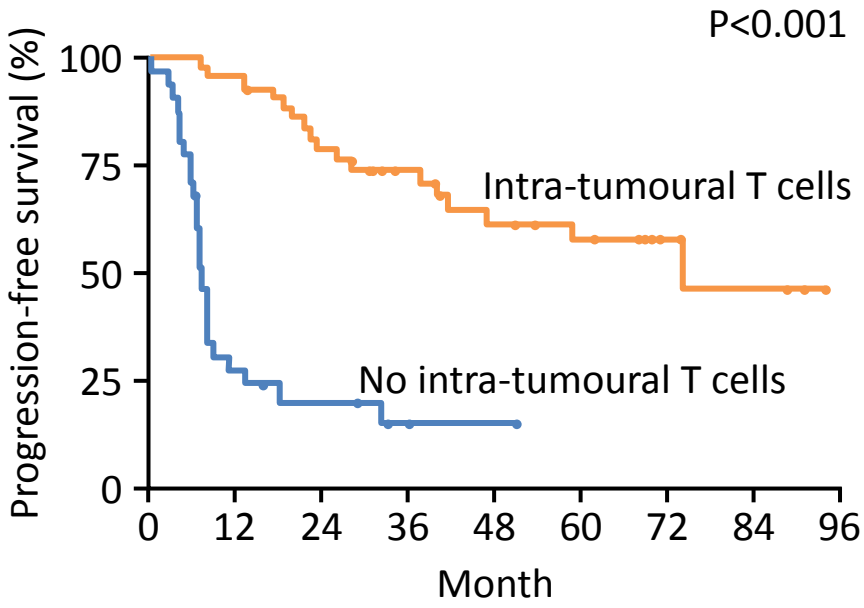
At 96–132 months:

>60% alive



At 96 months:

50% cure



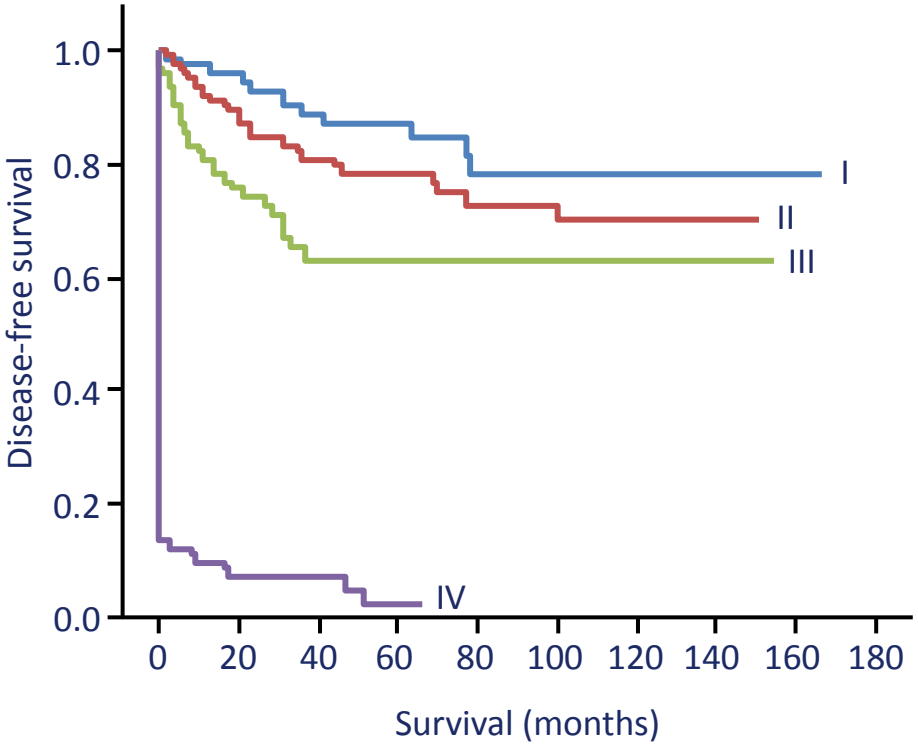
Zhang, et al. N Engl J Med 2003

The adaptive immune response more than tumour stage predicts clinical outcome

Tumour histopathological findings

UICC-TNM (Dukes' staging)

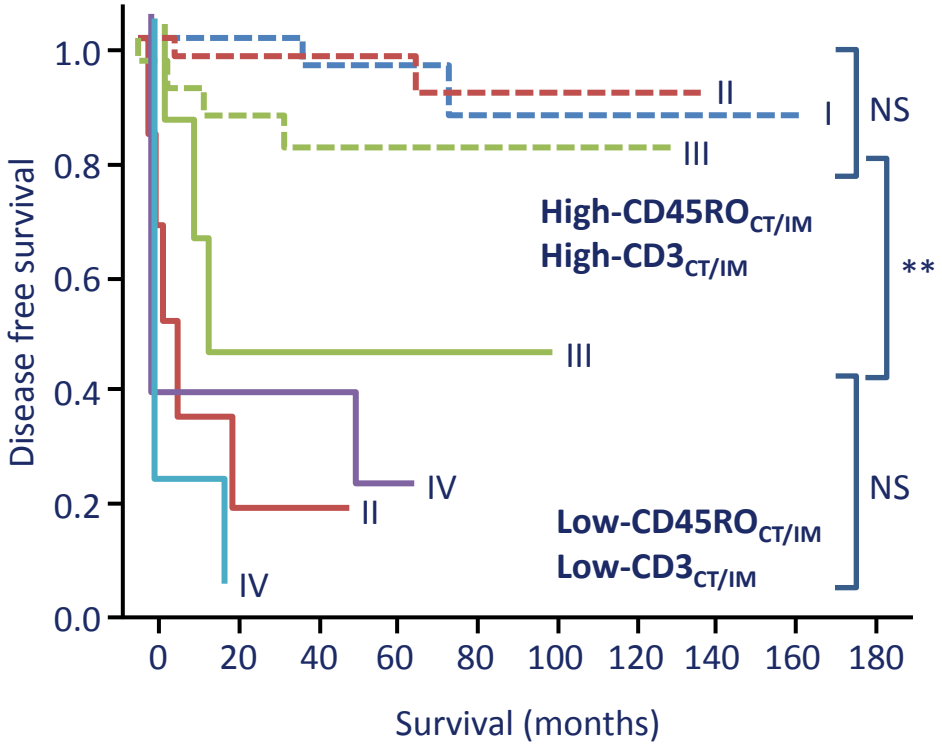
Current prognosis classification



Immune cells analysis

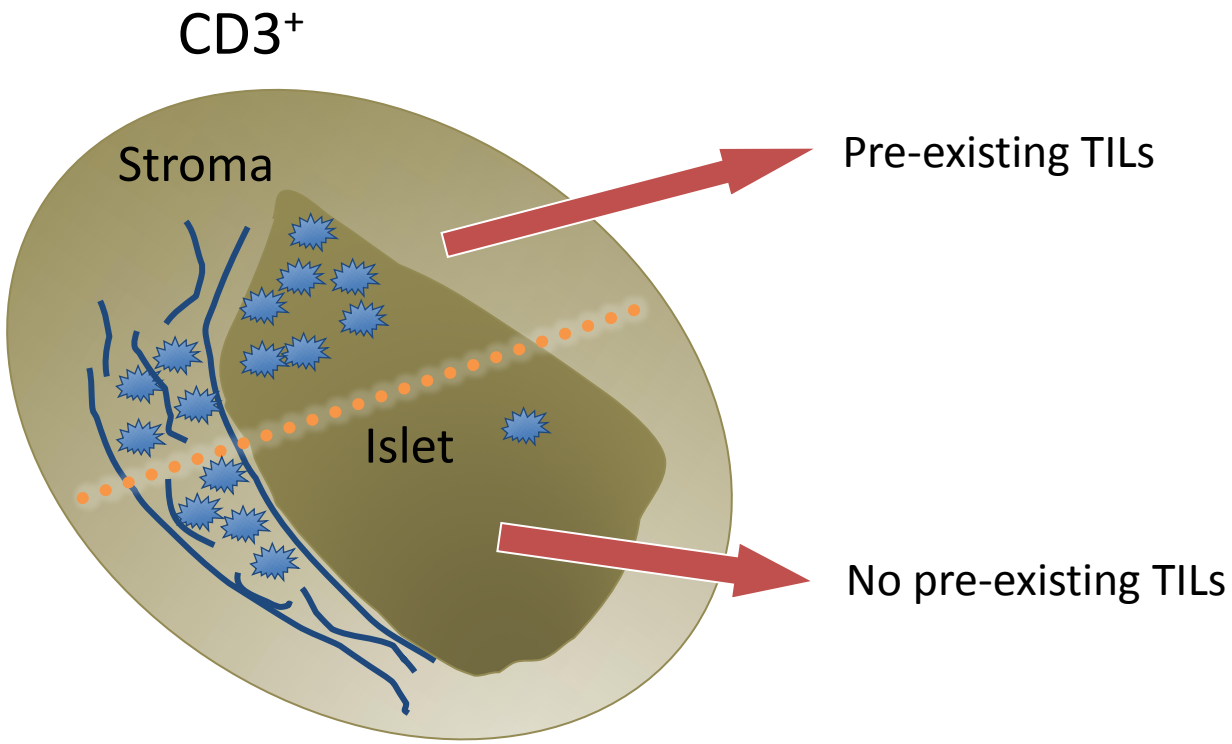
$CD3_{CT}/CD3_{IM}$ evaluation plus

$CD45RO_{CT}/CD45RO_{IM}$ evaluation

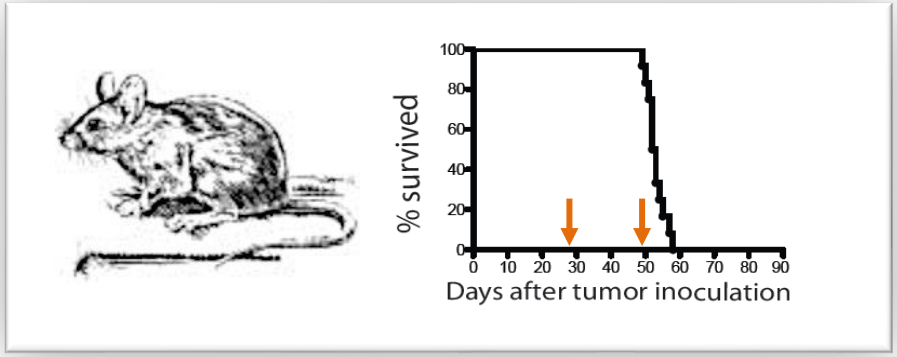


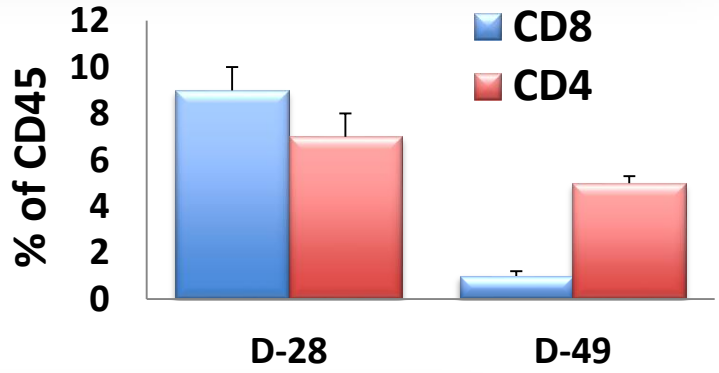
Galon, et al. Science 2006

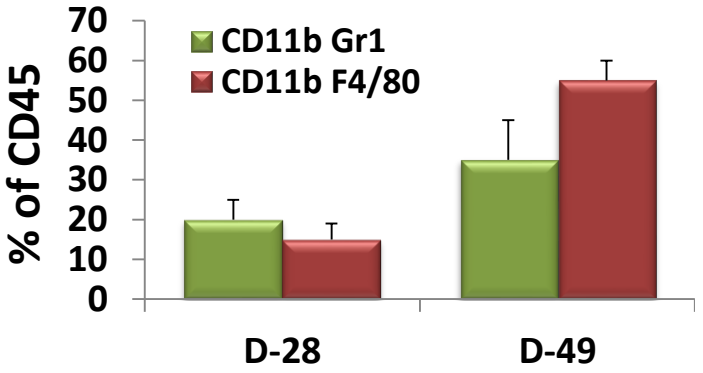
Classification of tumours

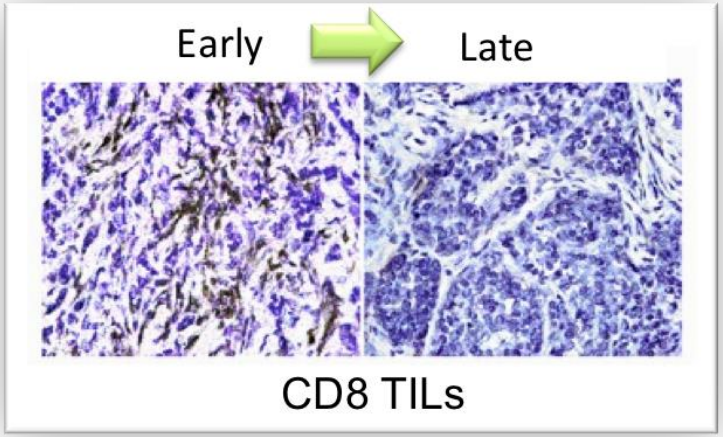


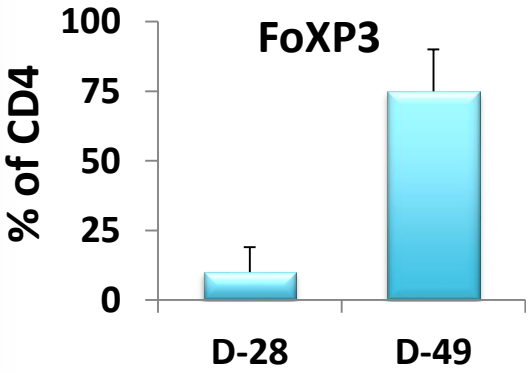
Should one expect similar response to checkpoint blockade?

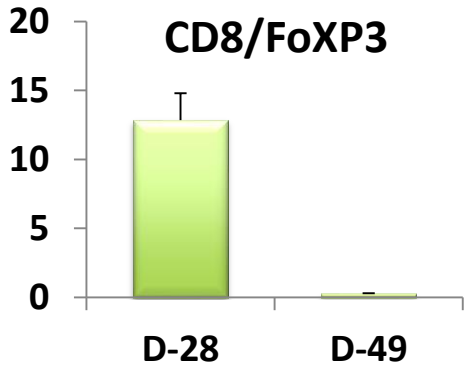

% survived
100
80
60
40
20
0
0 10 20 30 40 50 60 70 80 90
Days after tumor inoculation


% of CD45
12
10
8
6
4
2
0
CD8
CD4
D-28
D-49

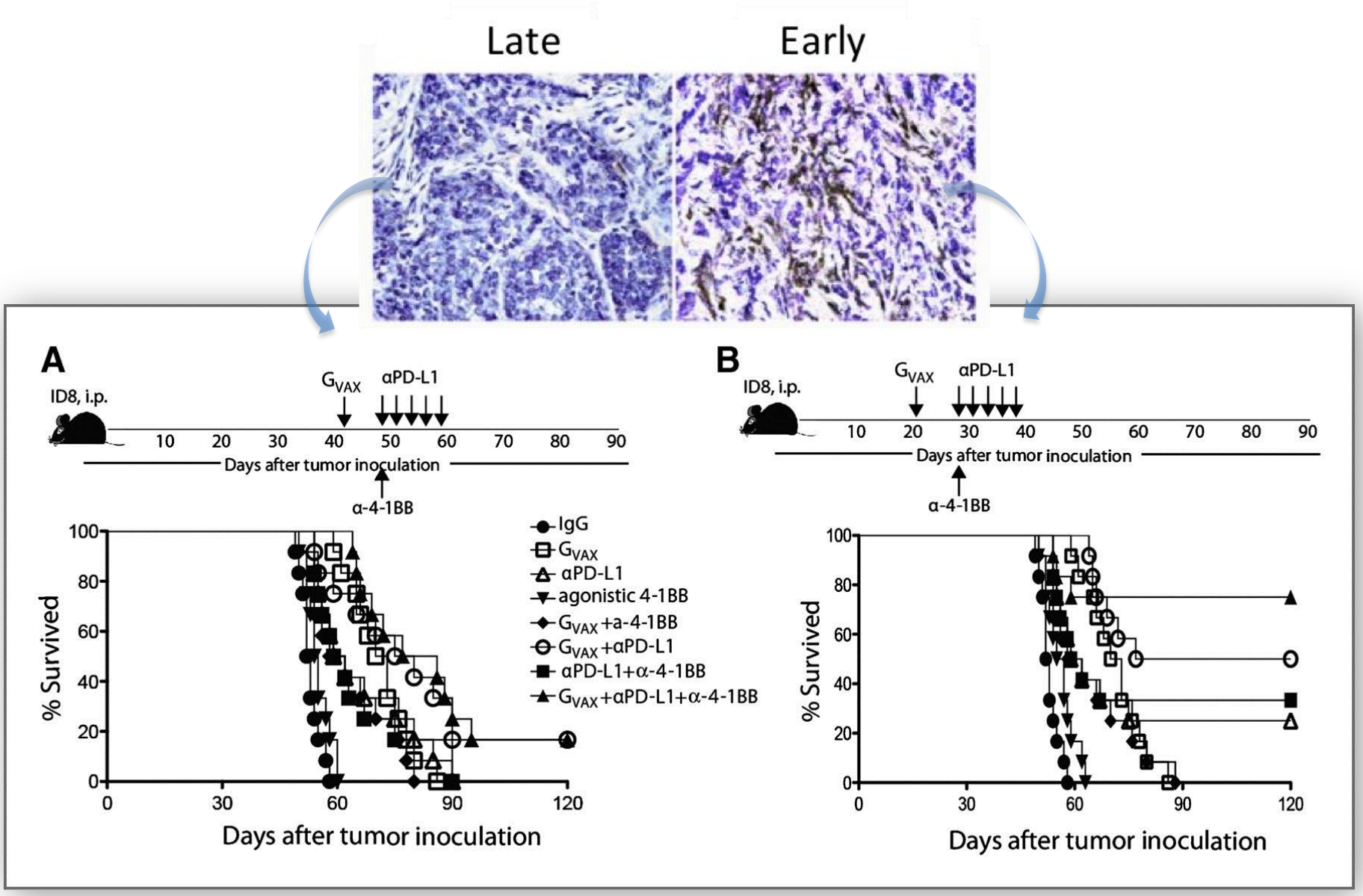

% of CD45
70
60
50
40
30
20
10
0
CD11b Gr1
CD11b F4/80
D-28
D-49


Early
Late
CD8 TILs

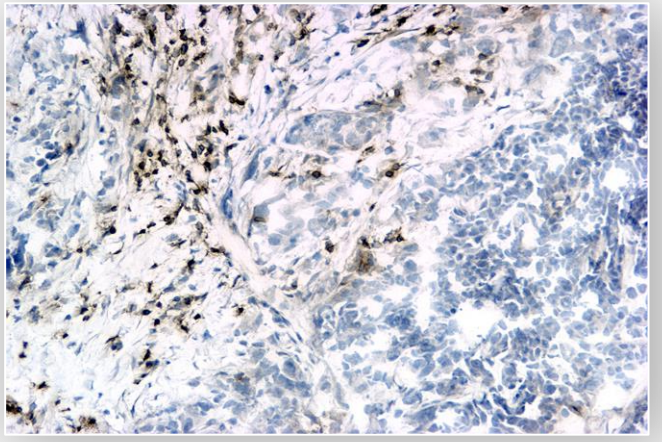

% of CD4
100
75
50
25
0
FoXP3
D-28
D-49

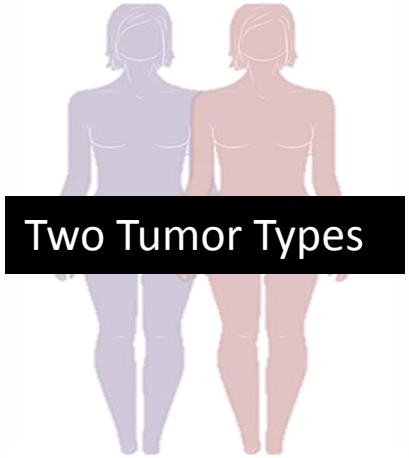

20
15
10
5
0
CD8/FoXP3
D-28
D-49

Absence of TILs predicts failure of PD-L1 blockade

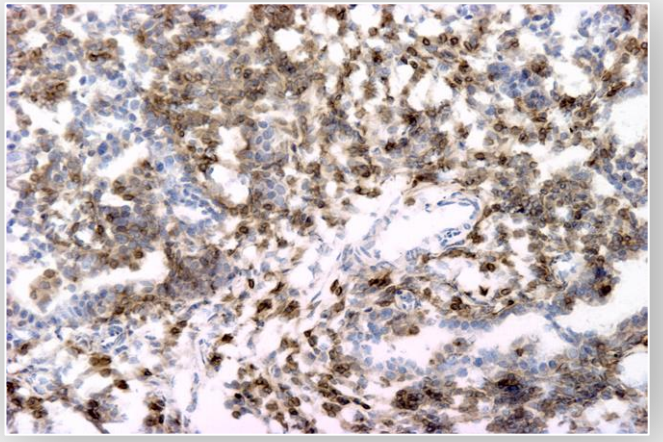


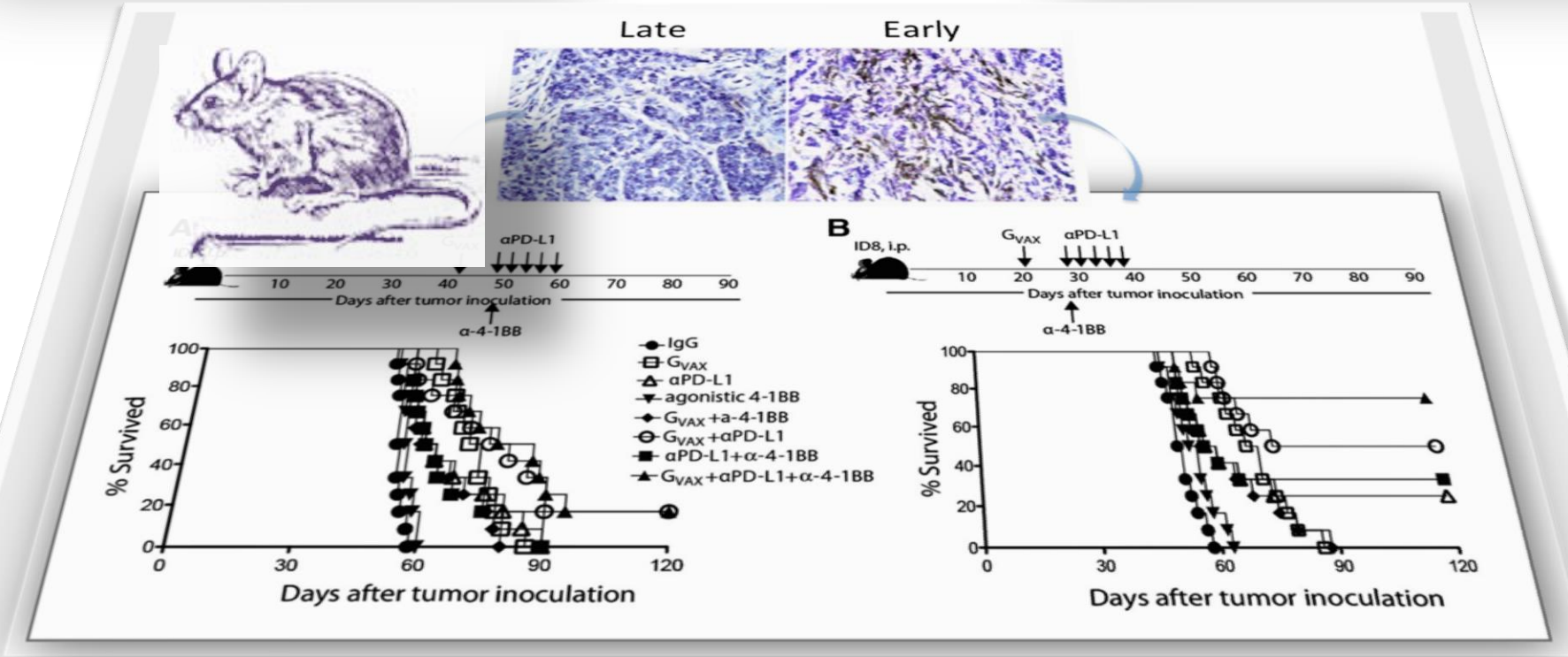
Duraiswamy J et al. Cancer Res 2014;74:633-634

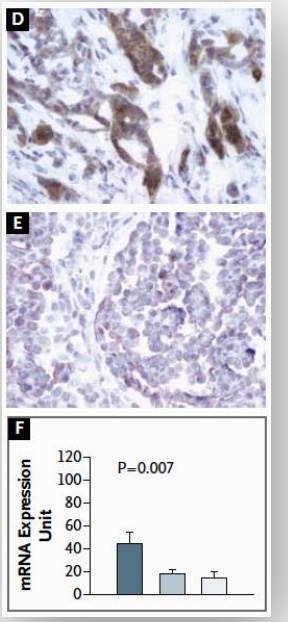


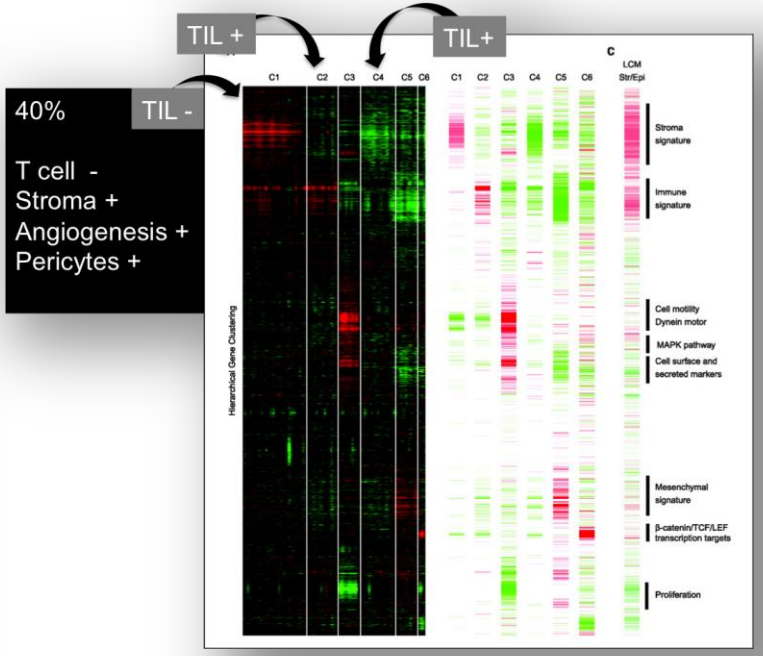


Two Tumor Types

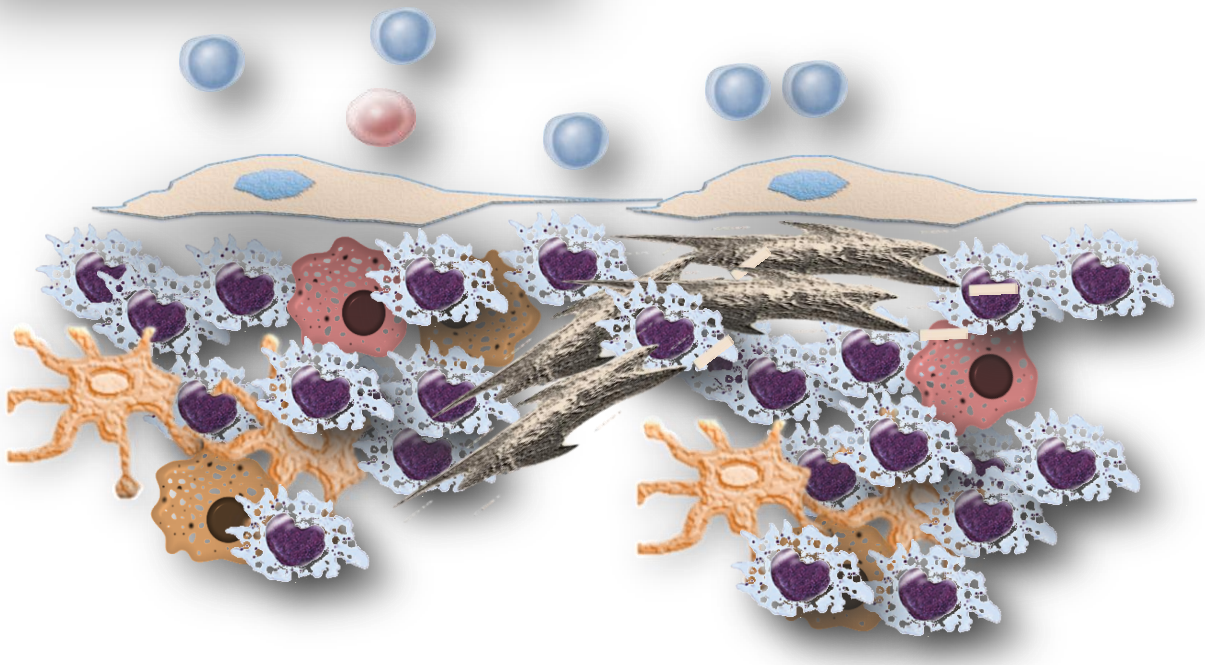








The Endothelial Barrier Hypothesis

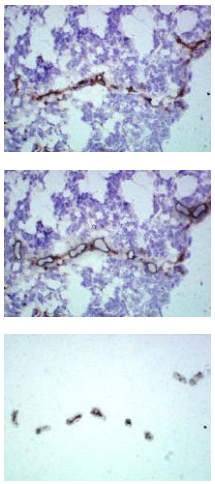


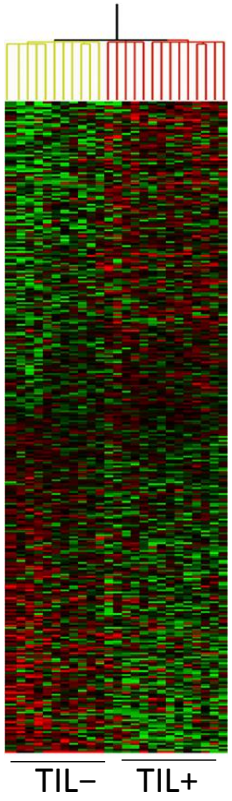
nature medicine

Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy

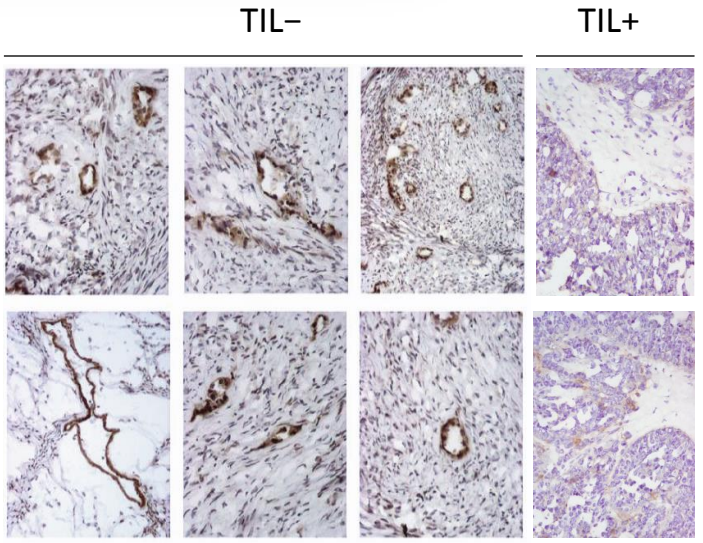
Ronald J Buckanovich[1,2,7,8], Andrea Facciabene[1,8], Sarah Kim[1], Fabian Benencia[1,3], Dimitra Sasaroli[1,4], Klara Balint[1], Dionysios Katsaros[6], Anne O'Brien-Jenkins[1], Phyllis A Gimotty[1,5] & George Coukos[1,3]

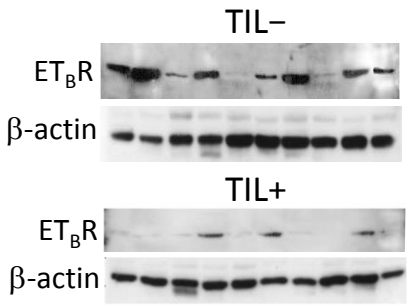
CD31 LCM

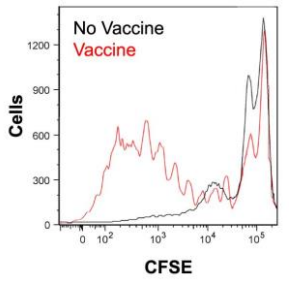


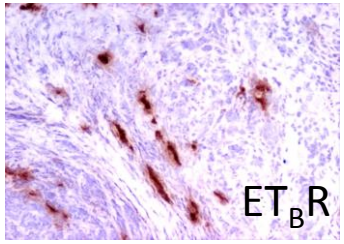


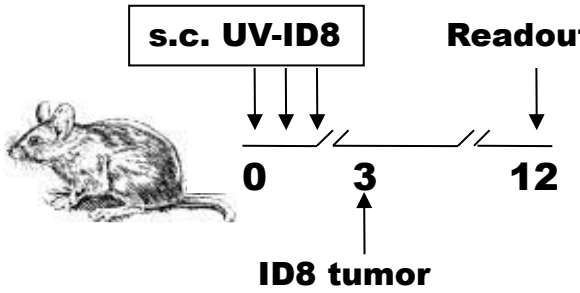
TIL–			TIL+		
Fold Change	Common Name	Genbank Acc	Fold Change	Common Name	Genbank Acc
3.627	MEG3	AI291123	5.412	C3	NM_000064
2.886	SEC61G	NM_014302	3.746		AW262311
2.873	KIAA1609	AA195124	3.455	ZNFN1A5	BF056303
2.82	ACTR6	NM_022496	3.141	LOC283663	AI926479
2.784		AK026659	3.096	IGLJ3	X57812
2.746	ATP9A	AB014511	2.872	ZNF521	AK021452
2.665		R38110	2.831		AK000119
2.642	NCOA1	BF576458	2.682	CALD1	BF063186
2.584	WIT-1	NM_015855	2.678	CYP1B1	NM_000104
2.539		AI343000	2.65	EIF5B	BG261322
2.513	MSI2	BE220026	2.618		AA903710
2.502	ETRB	NM_000115	2.587	HSPC056	BF942281
2.473	PAPSS2	AW299958	2.576	FLJ32949	AI039361
2.372	ALDOA	NM_000034	2.48	CFLAR	AI634046
2.372	ZNF423	AW149417	2.467		N54783
2.358	ENPP2	L35594	2.457	FLJ10330	N32872
2.344	HSU79266	NM_013299	2.455	C18orf14	NM_024781
2.34	KIAA0146	D63480	2.45		AI417595
2.316		AI300126	2.448	GBP1	AW014593
2.279	EMX2	AI478455	2.438		AA417078
2.273	MYBL1	AW592266	2.427	SFRS1	AA046439
2.27	MPHOSPH9	X98258	2.426	NICAL	NM_022765
2.267		AI083578	2.419	NOL7	NM_016167
2.233	ETRB	M74921	2.41	MYCBP2	AA488899
2.214		H37807	2.382	ESR1	NM_000125
2.212		AI800895	2.382		AI683805
2.17	TAF3	AI123516	2.356	ADRBK2	AI651212
2.148	SLC1A4	BF340083	2.348		AW954199
2.141	HES1	BE973687	2.346	SCAP2	NM_003930
2.135	DLK1	U15979	2.328	STK3	NM_006281
2.122	SGCB	U29586	2.324	AKAP10	AU147278

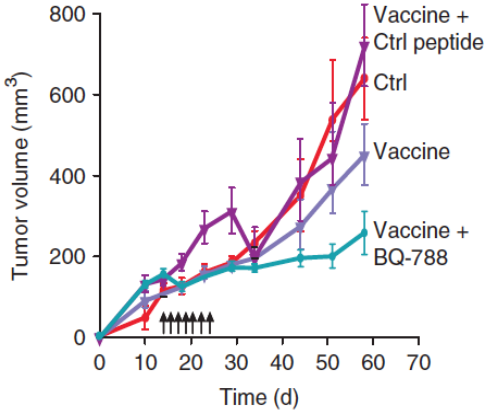


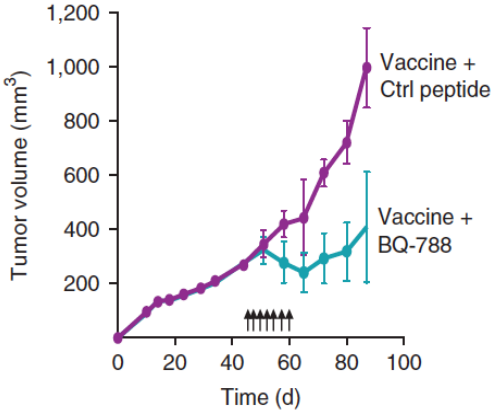


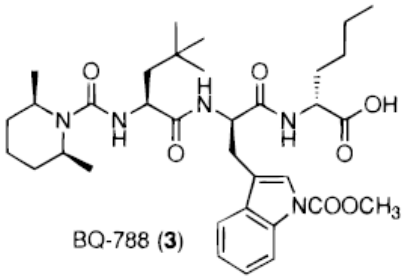

No Vaccine
Vaccine
Cells
CFSE

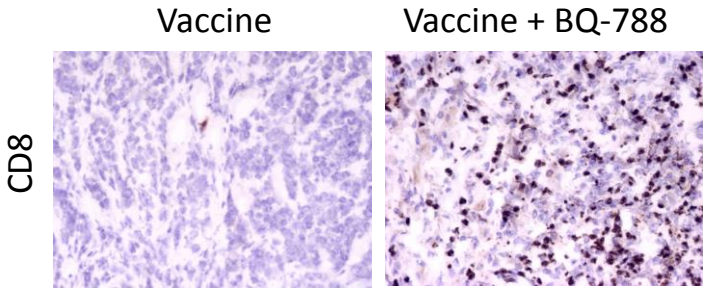

ET$_B$R

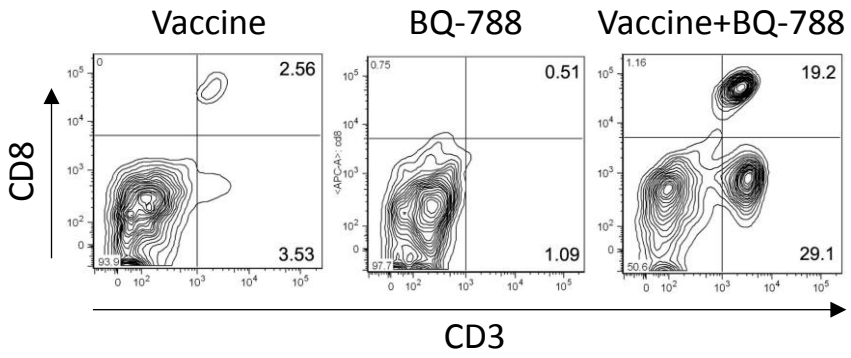

s.c. UV-ID8
Readouts
0
3
12
ID8 tumor


Tumor volume (mm^3)
Time (d)
Vaccine + Ctrl peptide
Ctrl
Vaccine
Vaccine + BQ-788


Tumor volume (mm^3)
Time (d)
Vaccine + Ctrl peptide
Vaccine + BQ-788


OH
NCOOCH$_3$
BQ-788 (3)

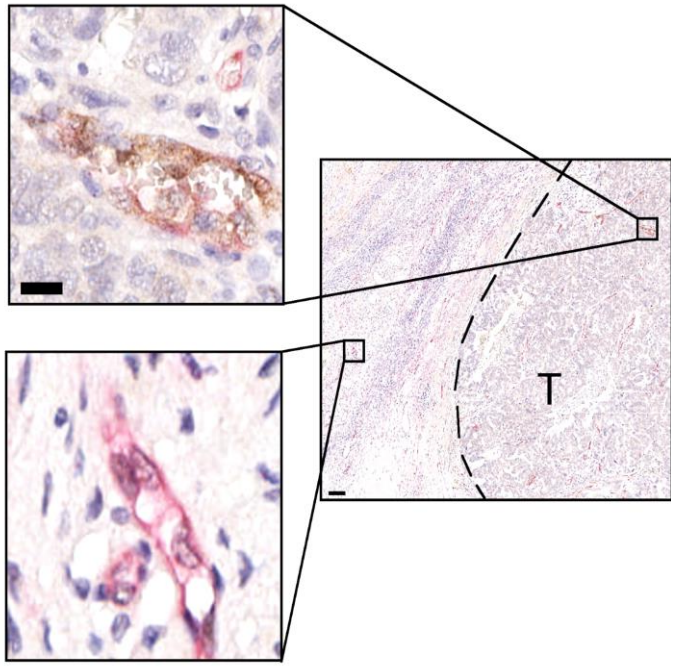

Vaccine
Vaccine + BQ-788
CD8

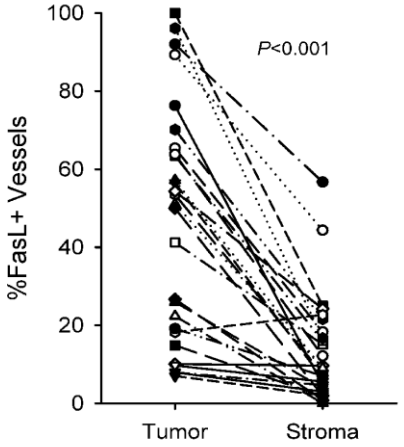

Vaccine
BQ-788
Vaccine+BQ-788
CD8
CD3
2.56
3.53
0.51
1.09
19.2
29.1

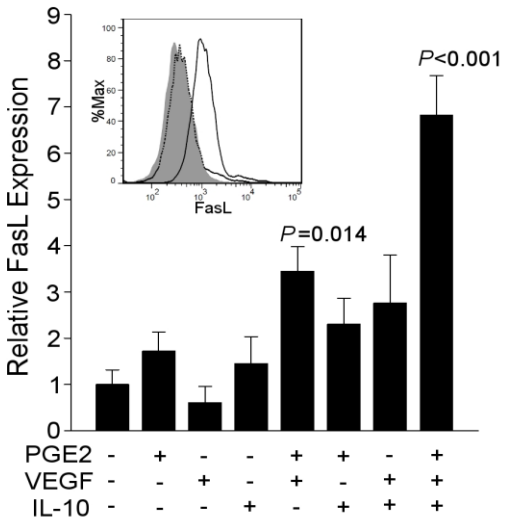
nature medicine

Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors

Gregory T Motz[1], Stephen P Santoro[1], Li-Ping Wang[2], Tom Garrabrant[1], Ricardo R Lastra[2], Ian S Hagemann[2], Priti Lal[2], Michael D Feldman[2], Fabian Benencia[1] & George Coukos[1,3]

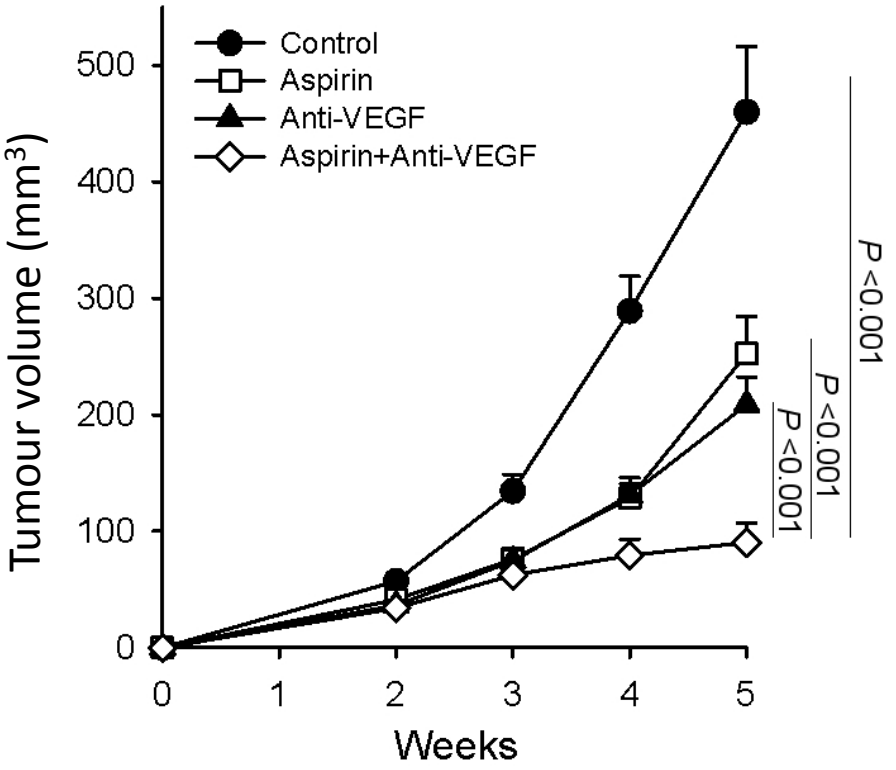


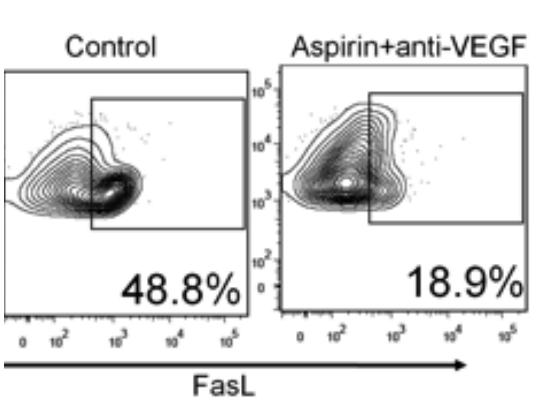




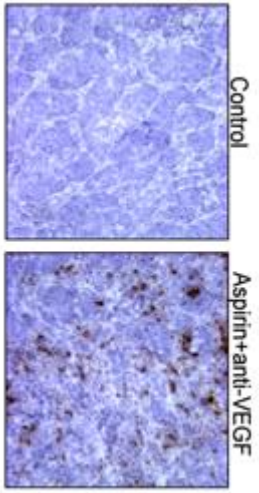
Blockade of PGE2 + VEGF-A enhances CD8 T-cell infiltration

ID8-VEGF tumours



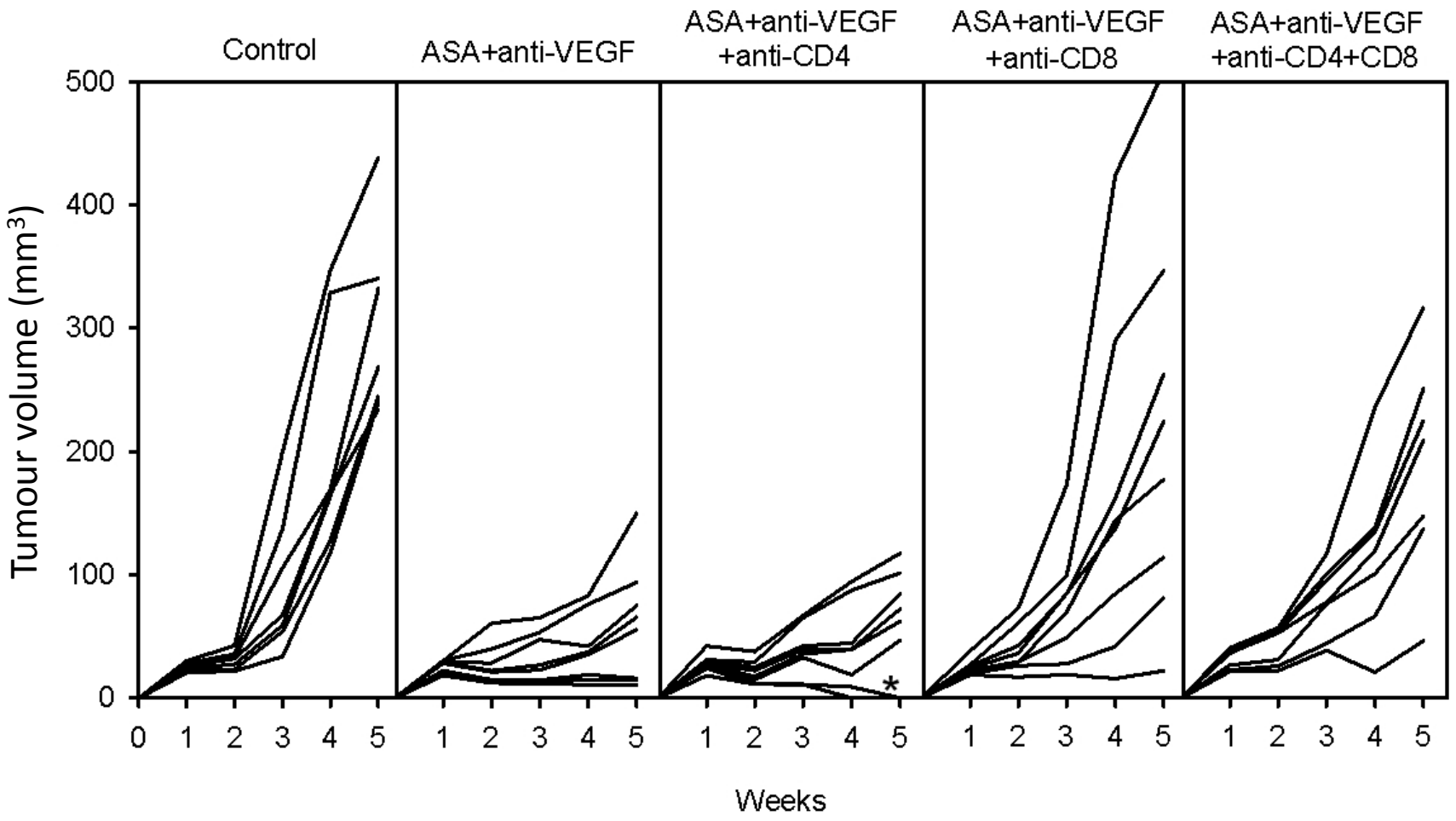


CD8



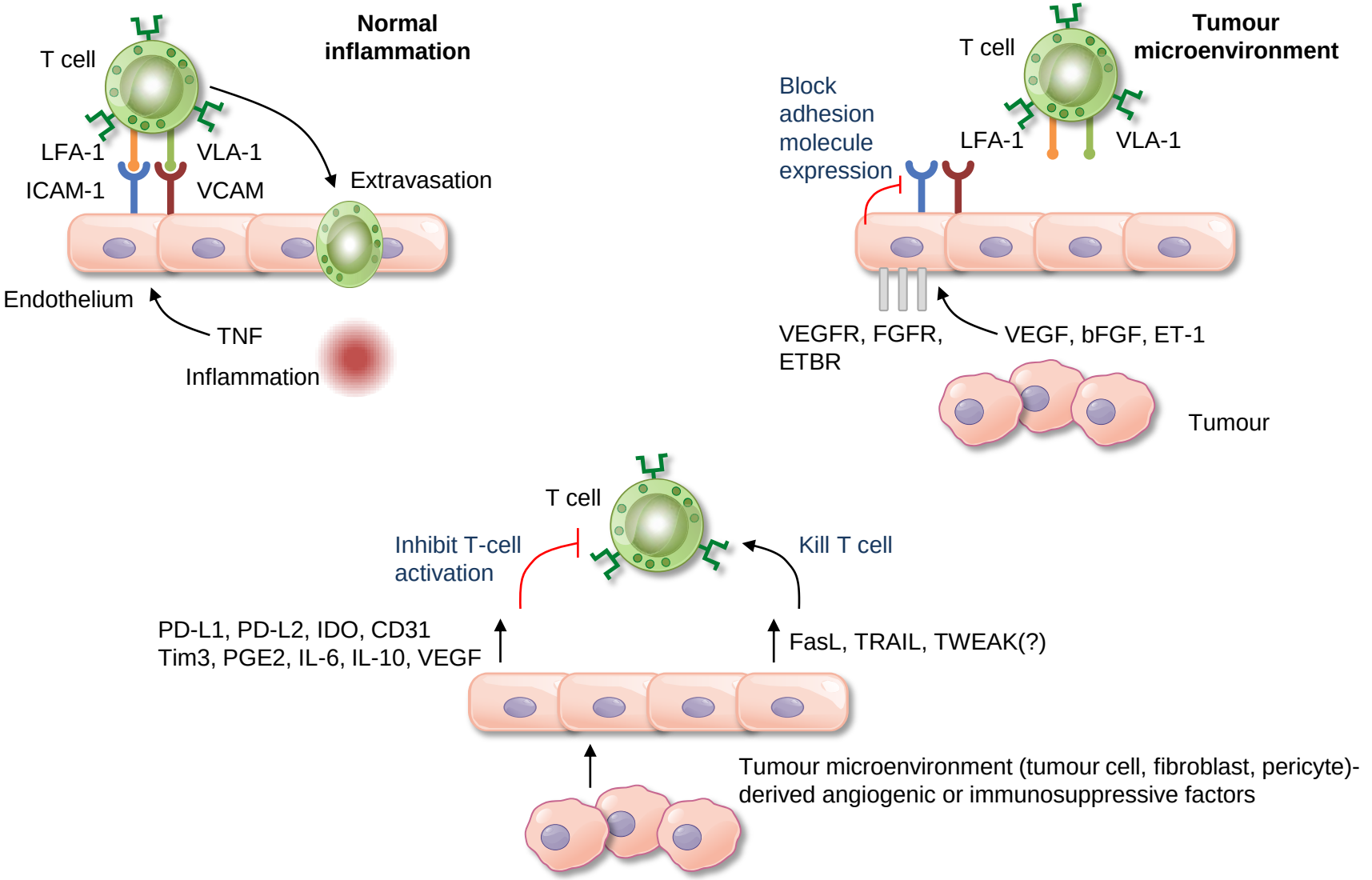
Motz, et al. Nature Med (in press) 2014

CD8 cells mediate the effect of αVEGF Ab + ASA



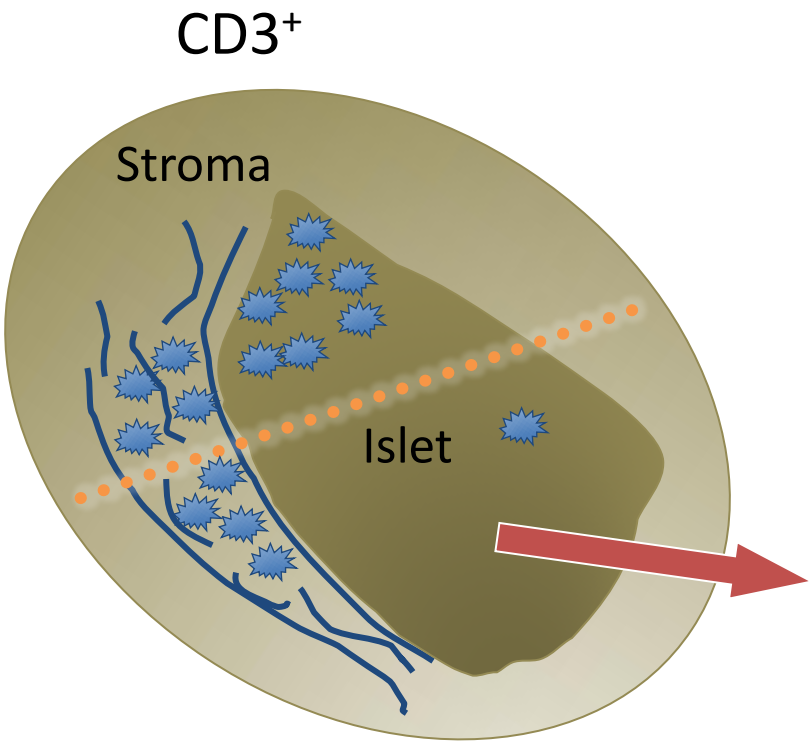
Motz, et al. Nature Med (in press) 2014

Immunity
Review



Motz and Coukos. Immunity 2013

Classification of tumours

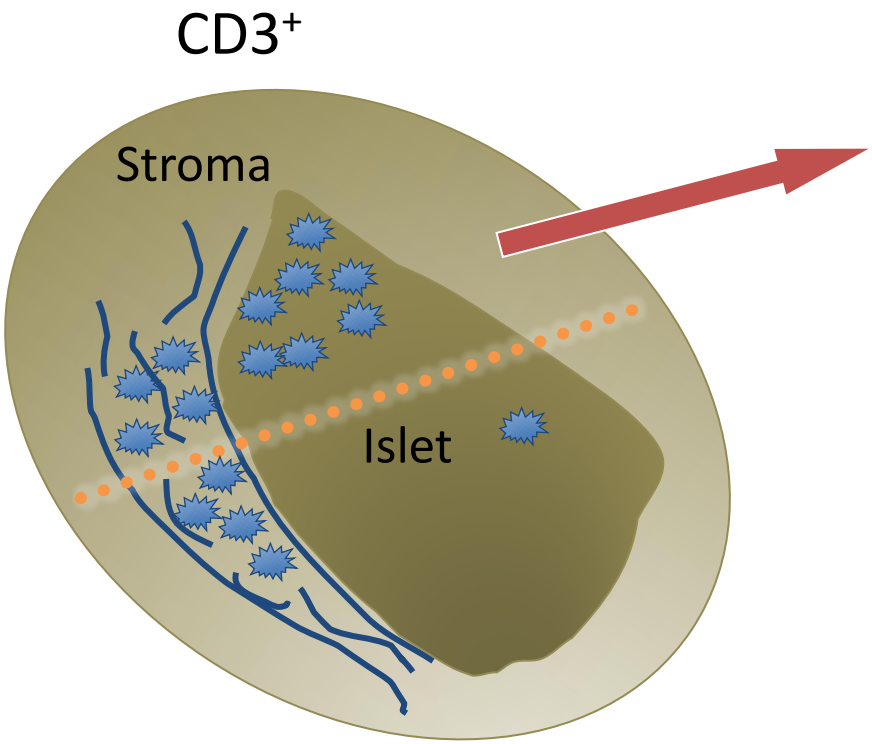


No pre-existing immunity:

Tumour barriers must be attenuated (endothelial barrier etc.)

Immunity must be induced

Classification of tumours

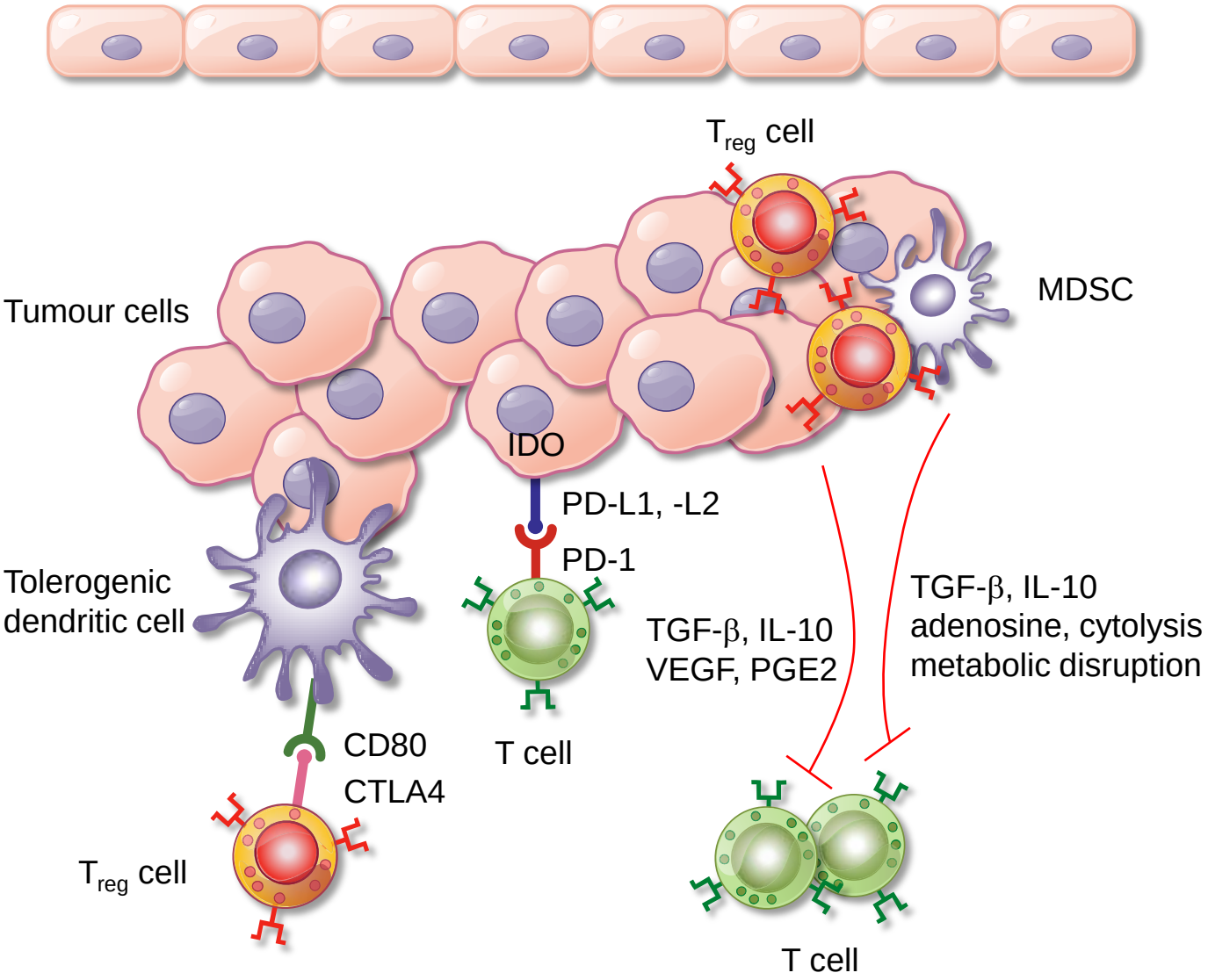


Pre-existing immunity:
can be activated

Is PD-1 pathway blockade enough?

Immunity
Review

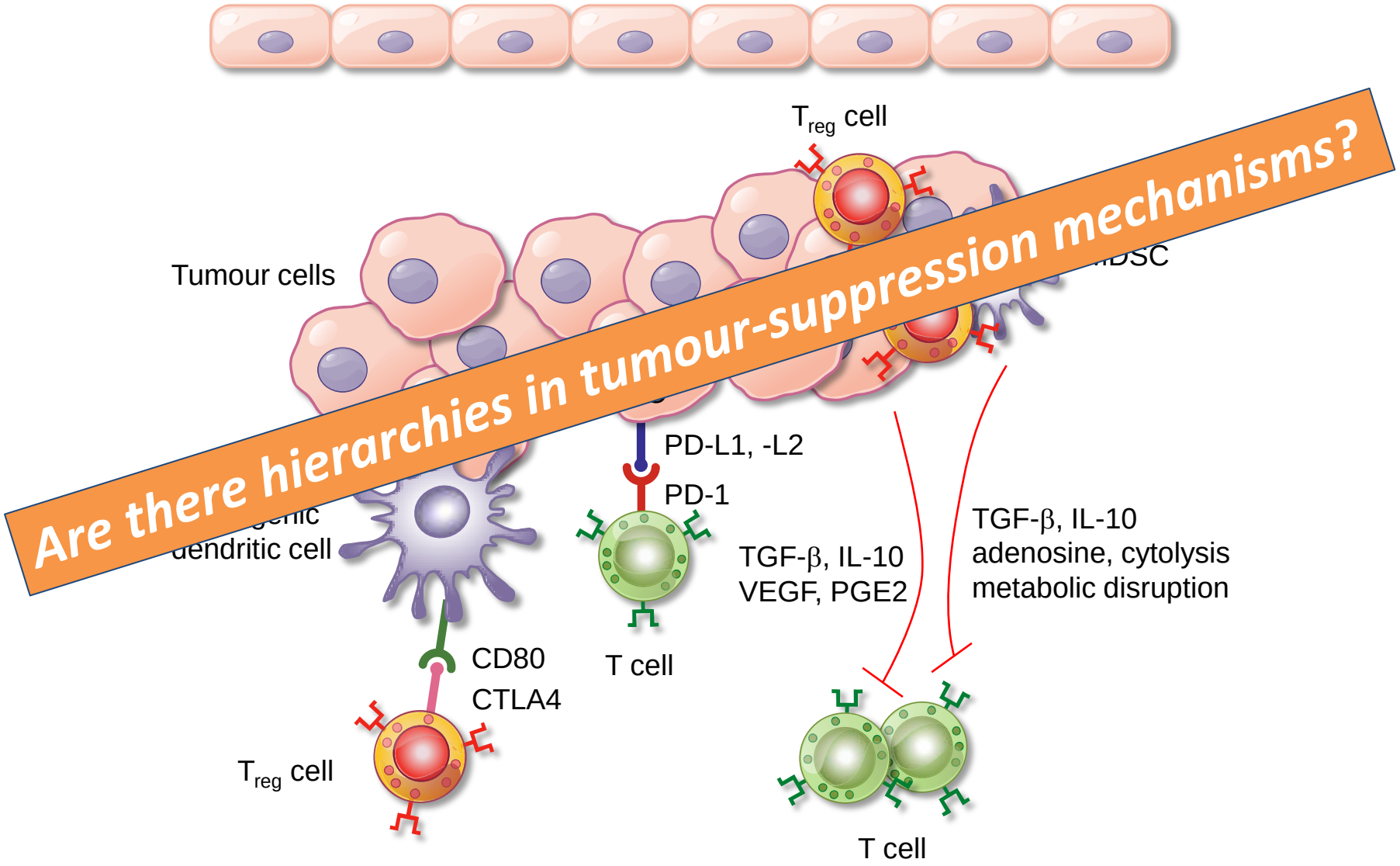
A multitude of targets



Motz and Coukos. Immunity 2013

Immunity
Review

A multitude of targets



Motz and Coukos. Immunity 2013

Critical components of immune therapy

Disruption of homeostatic regulatory mechanisms

Angiogenesis blockade

Expansion of tumour-reactive T cells

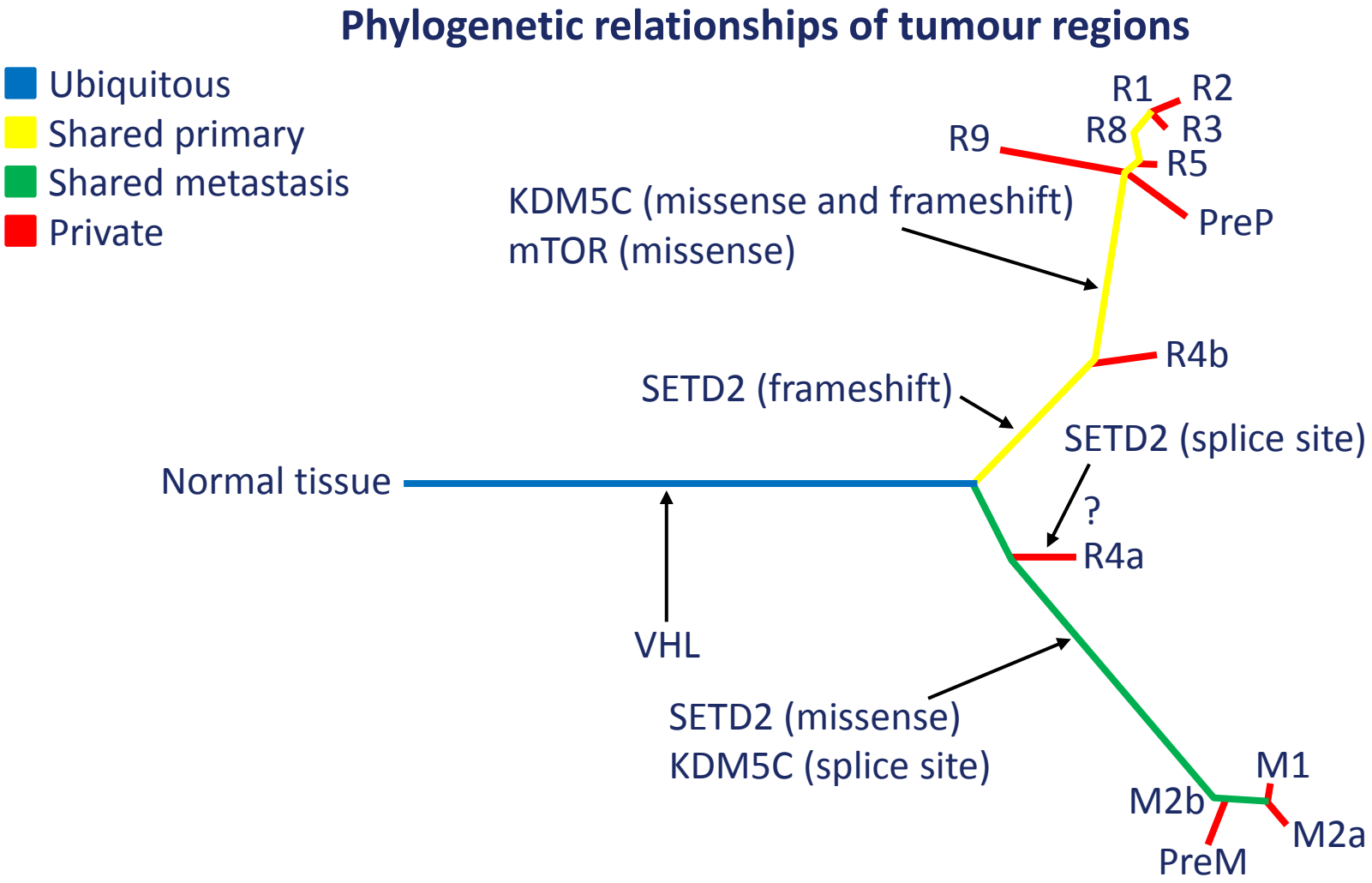
Critical components of immune therapy

Disruption of homeostatic regulatory mechanisms

Angiogenesis blockade

Expansion of tumour-reactive T cells

Molecular heterogeneity at different biopsy sites in patients with kidney cancer



Gerlinger, et al. N Engl J Med 2012