Current State of Checkpoint Inhibitors?

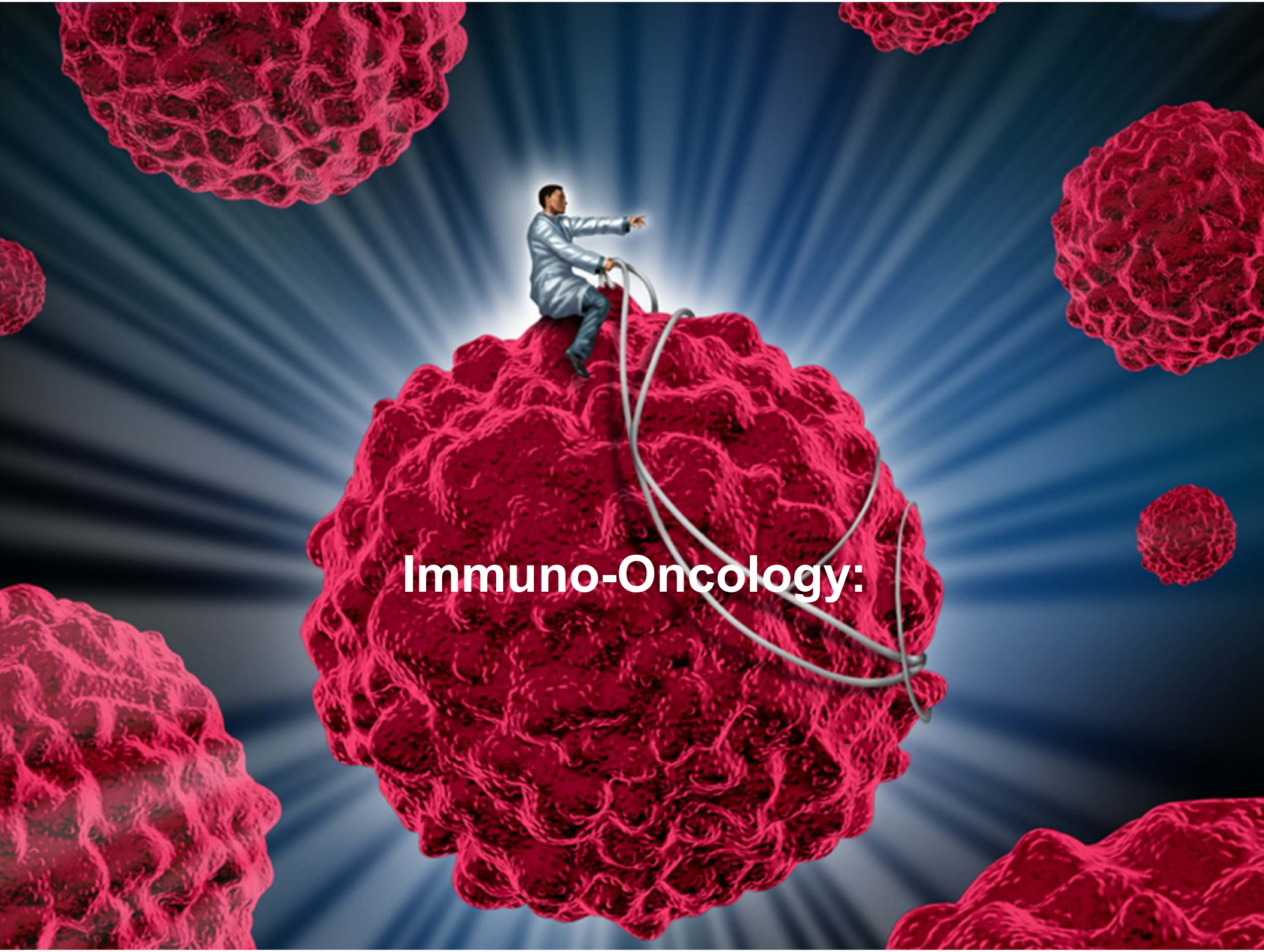
(may you live in interesting times)

Omid Hamid MD
Director, Cutaneous Oncology
Chief, Translational Research & Immunotherapy
ohamid@theangelesclinic.org

The Angeles Clinic
AND RESEARCH INSTITUTE

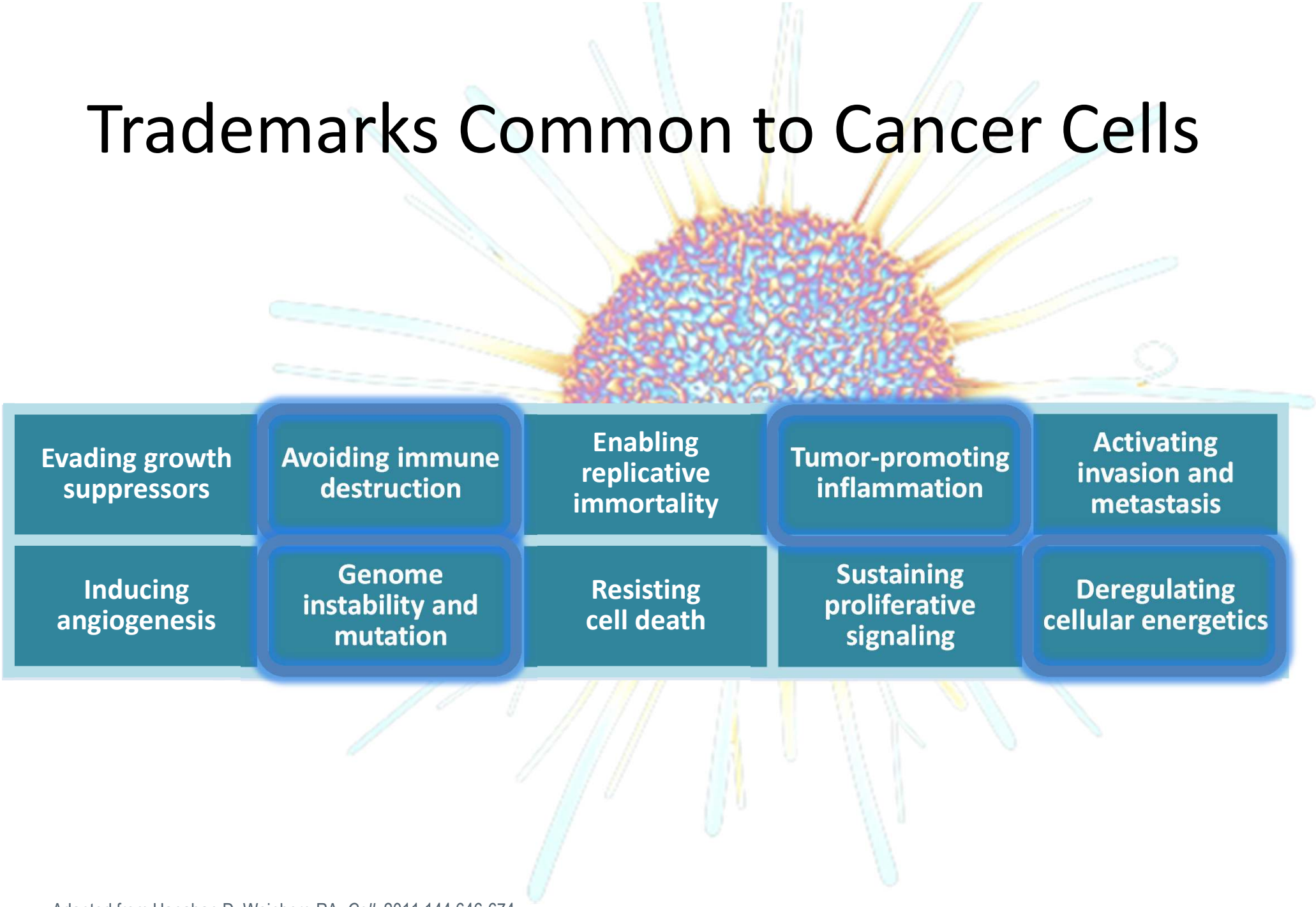
Disclosures

- Consulting: Bristol-Myers Squibb, Roche, Genentech, Amgen, Merck Rinat, Novartis, Caris
- Speaker: BMS, Genentech
- Contracted Research: Bristol-Myers Squibb, GlaxoSmithKline, Roche, Merck, Incyte, Esai , Medimmune


Immuno-Oncology:

2013 Breakthrough of the Year

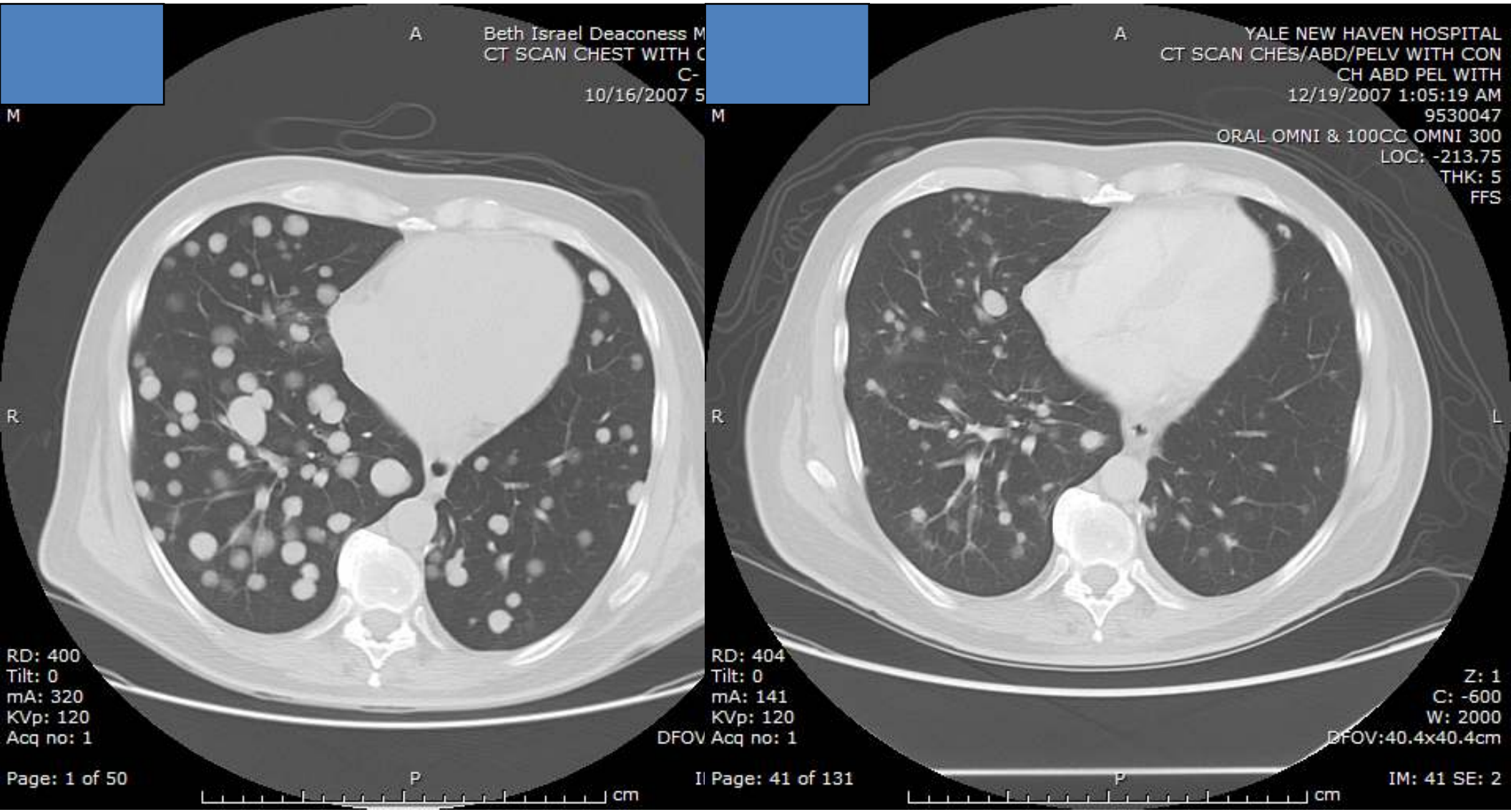
Trademarks Common to Cancer Cells



Adapted from Hanahan D, Weinberg RA. *Cell*. 2011;144:646-674.

The Promise of Immunotherapy

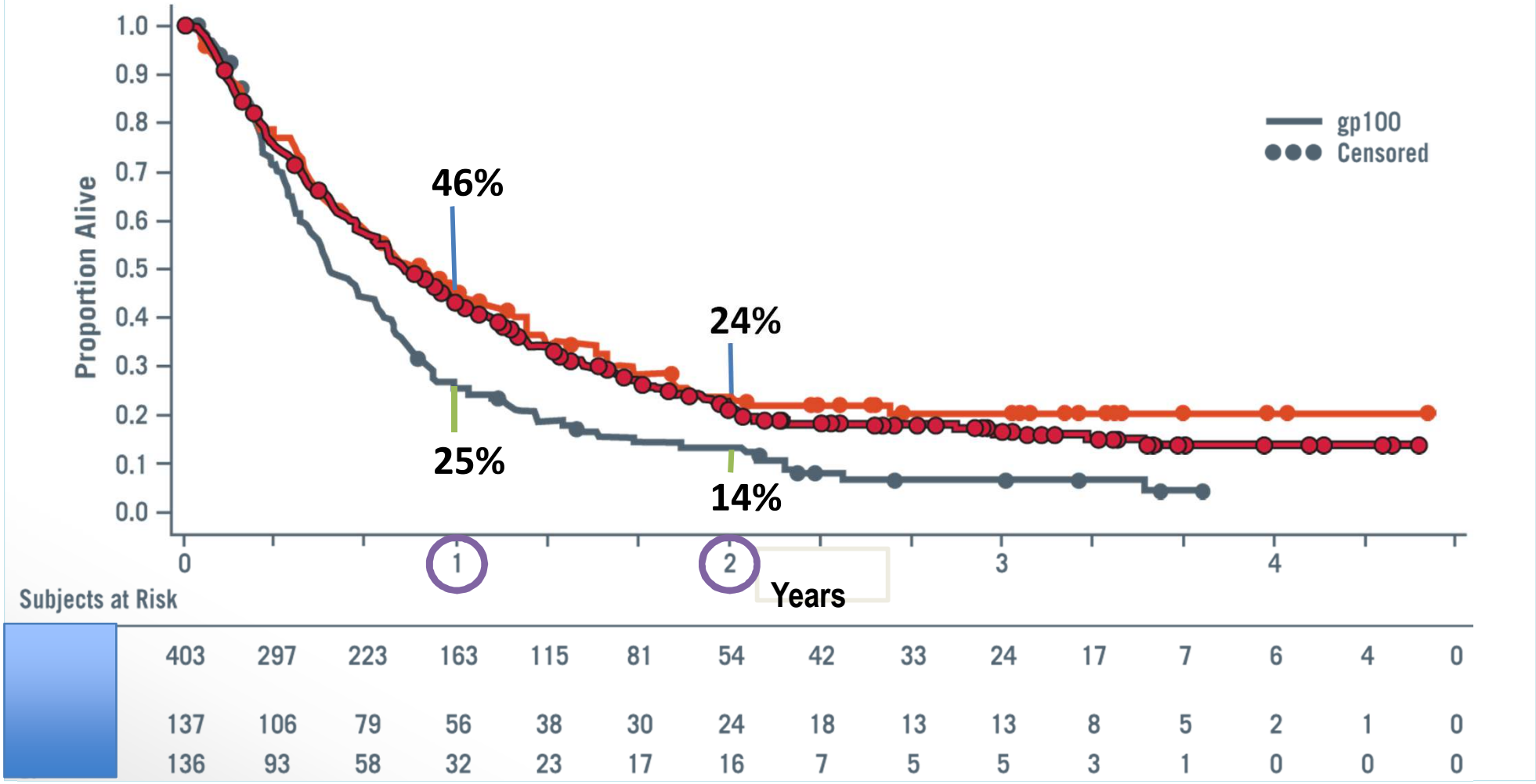
Response to Ipilimumab 10 mg/kg x 2 doses



No progression 5+ years

Ipilimumab Experience

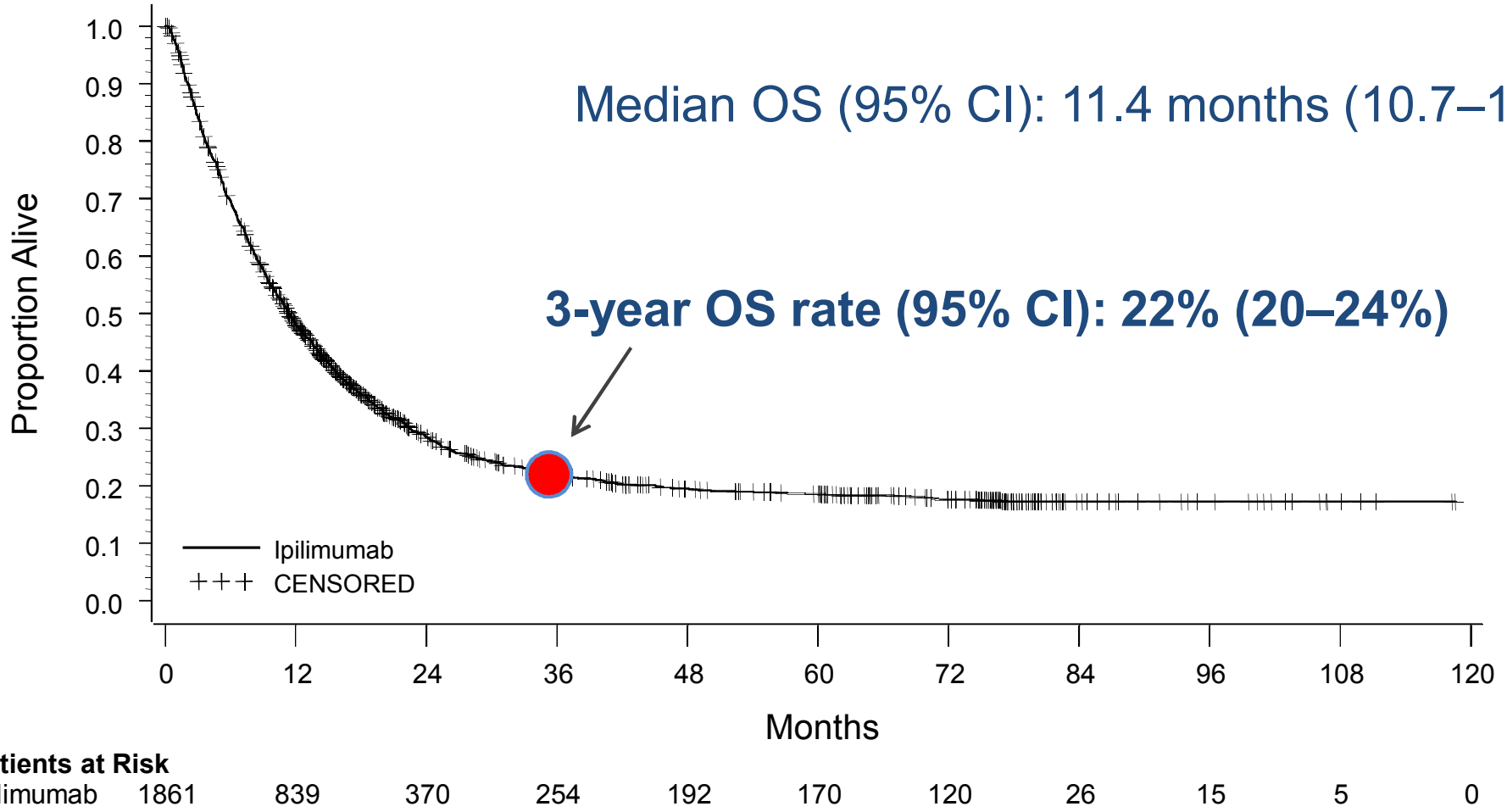
Overall survival: Kaplan-Meier estimate [1-4,a]



[a]Estimated overall survival rates as in the pivotal phase 3 study publication.[2]

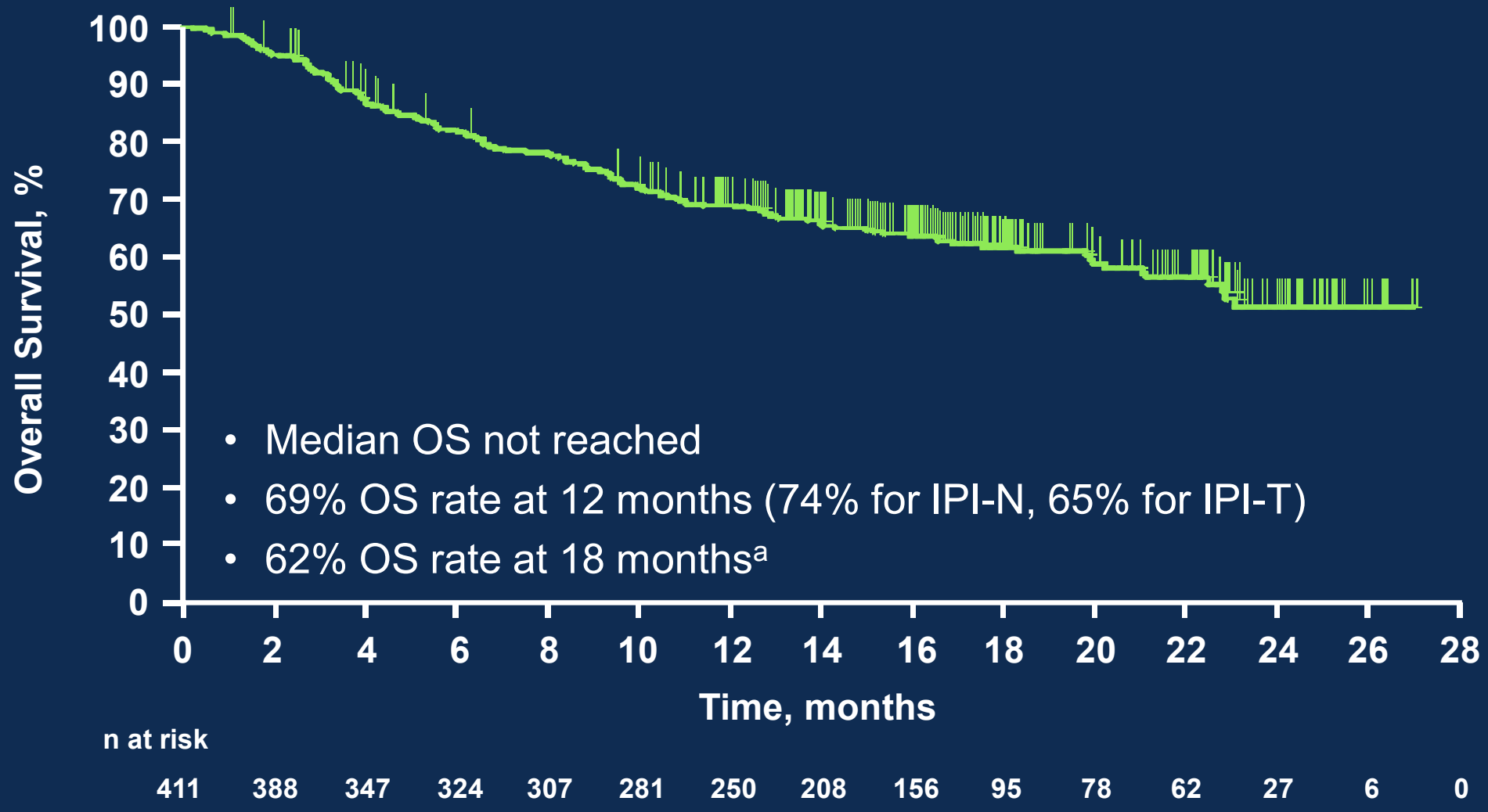
1. package insert. Princeton, NJ: Bristol-Myers Squibb; 2011.
2. FS et al. *N Engl J Med*. 2010;363:711-723.
3. Wolchuk JD et al. *Cancer Immun.* 2010;10:9.
4. Data on file. YERV 008.

Primary Analysis of Pooled OS Data on Ipilimumab in 1861 Patients



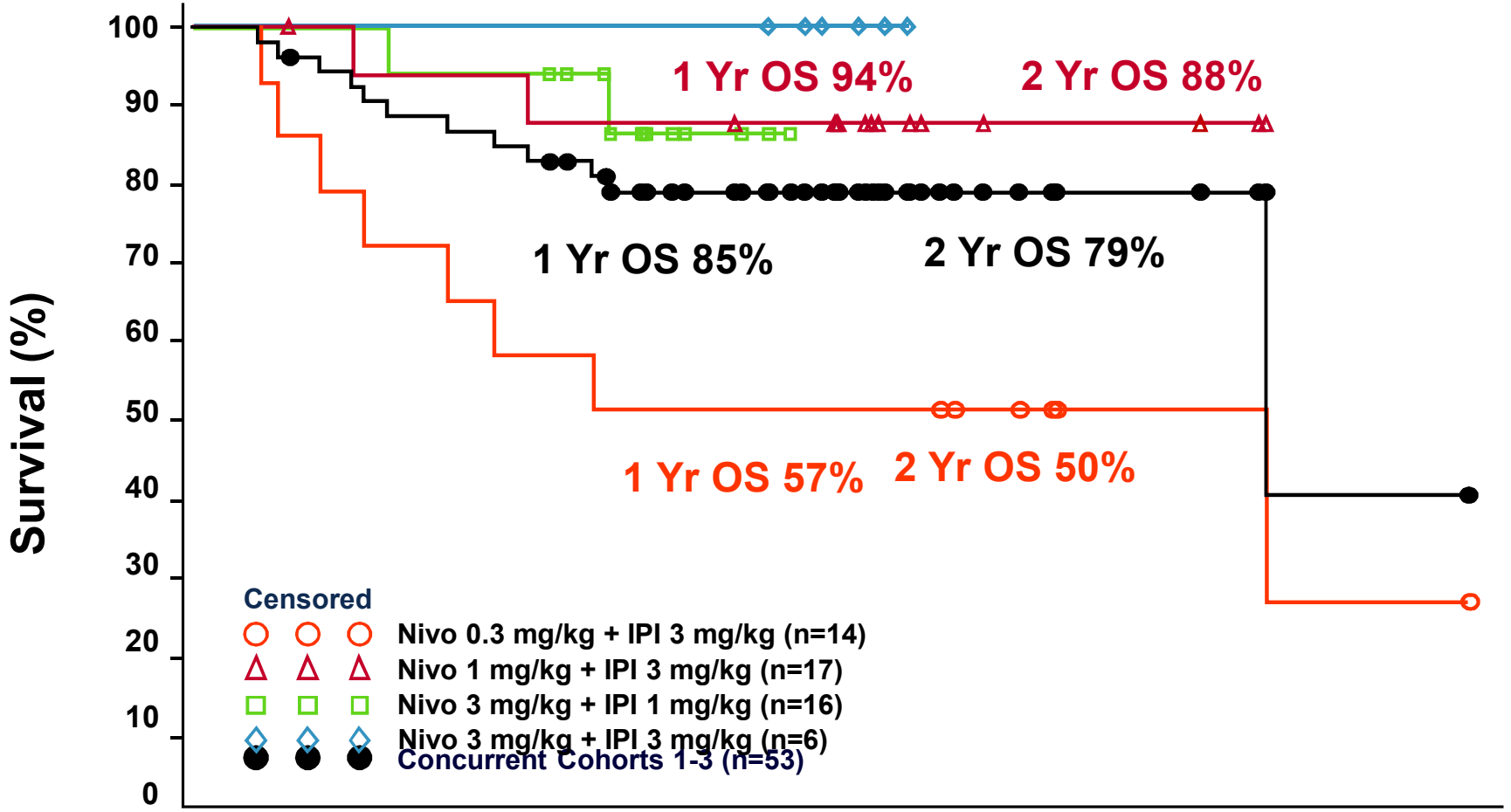
Schadendorf et al, ESMO 2013

Kaplan-Meier Estimate of Overall Survival



[a]OS rate at 18 months is driven by the 135 patients enrolled in the nonrandomized cohorts because they have the longest follow-up duration.
Analysis cut-off date: May 2014.

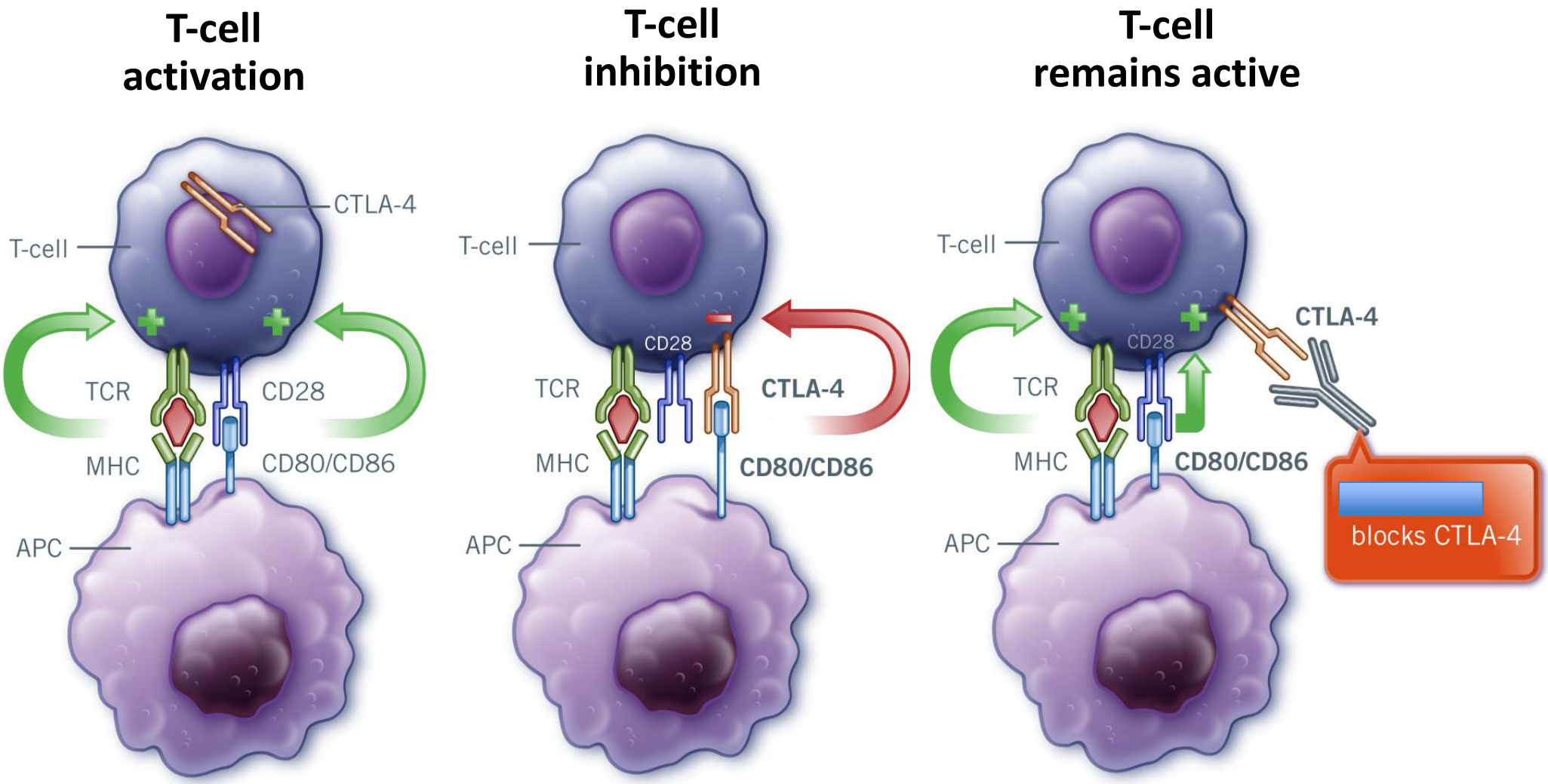
Overall Survival for Concurrent Therapy by Dose Cohort



Pts at Risk																
Nivo 0.3_IPI 3	14	13	11	10	8	7	7	7	7	7	5	2	2	2	1	1	0
Nivo 1 _IPI 3	17	17	16	15	15	14	14	13	9	4	3	3	3	2	0	0	0
Nivo 3_IPI 1	16	16	15	15	15	13	4	2	0	0	0	0	0	0	0	0	0
Nivo 3_IPI 3	6	6	6	6	6	6	6	6	3	0	0	0	0	0	0	0	0
Concurrent	53	52	48	46	44	40	31	28	19	11	8	5	5	4	1	1	0

How does this work ?

Ipilimumab: An Anti-CTLA-4 Therapy That Augments T-Cell Activation and Proliferation



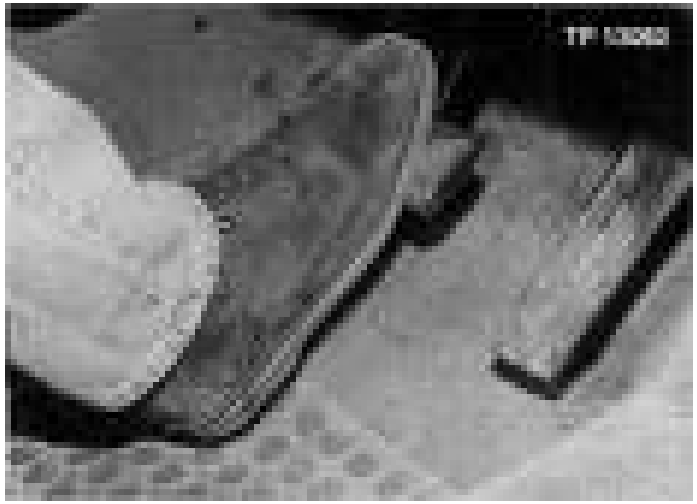
APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Adapted from. Plenary session presentation, abstract #4, ASCO 2010.

CTLA-4: The Brake on T cell Activation

T-cell receptor: Antigen-MHC

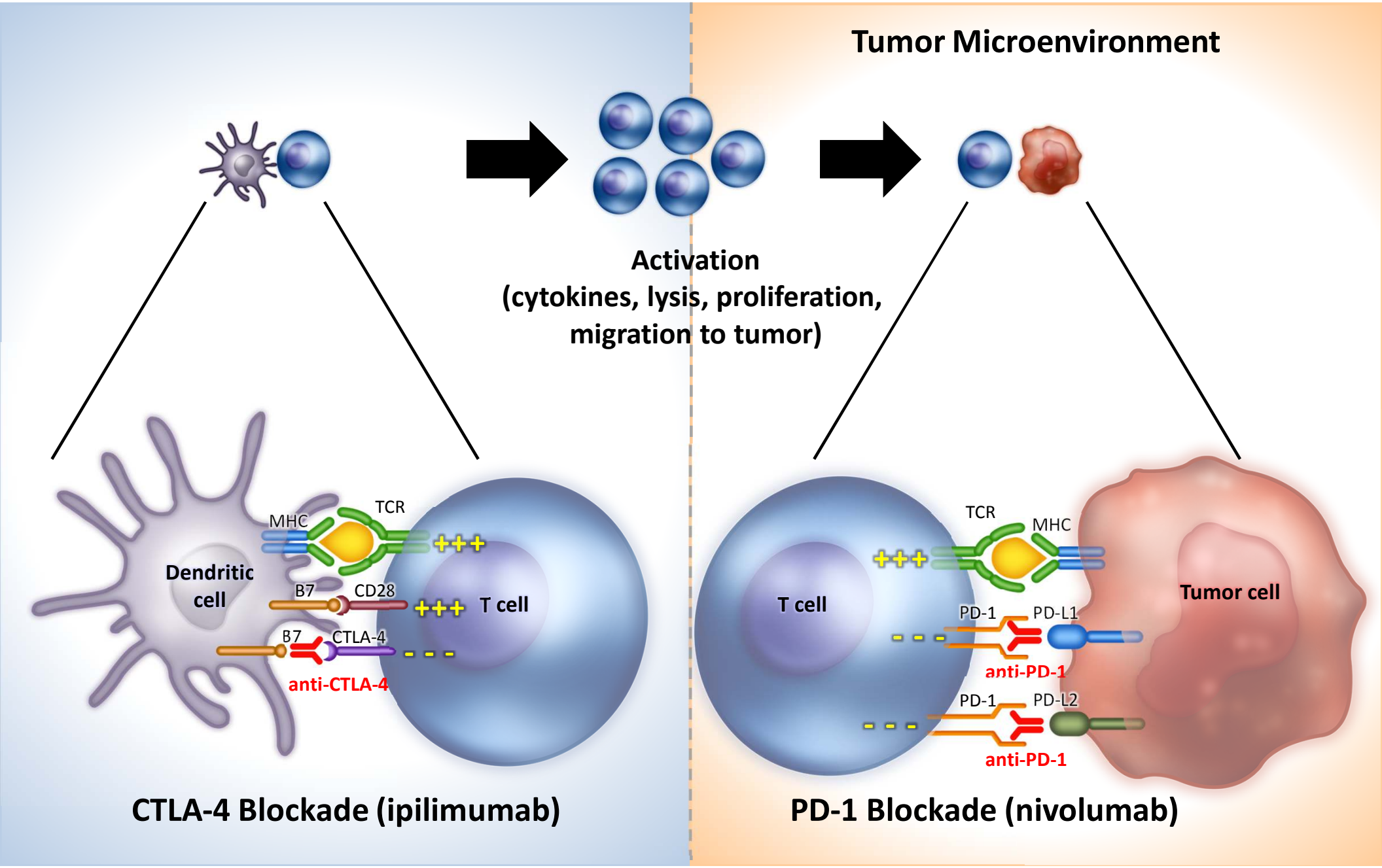
CD28: B7



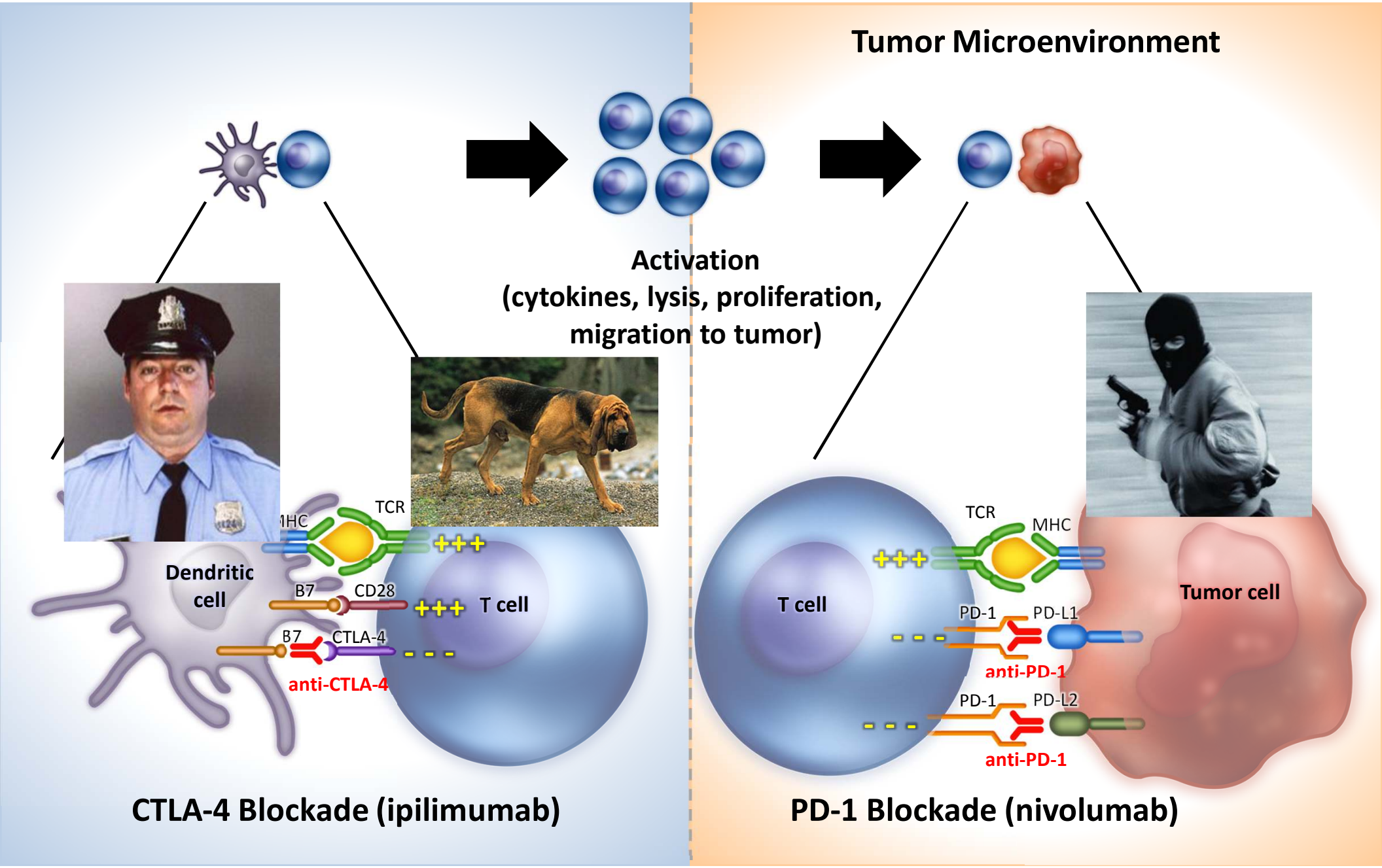
CTLA-4: B7

Vaccine?

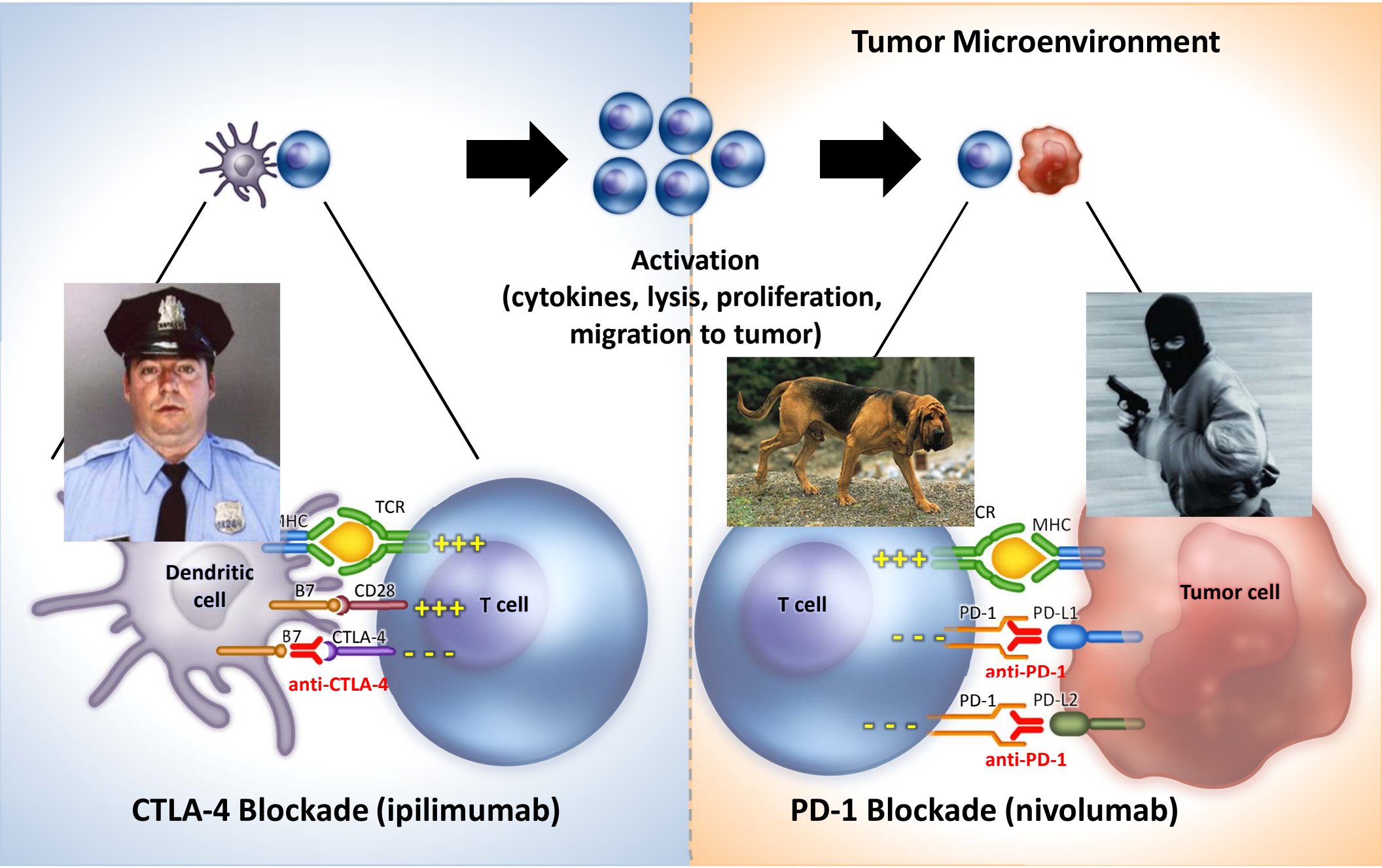
Blocking CTLA-4 and PD-1



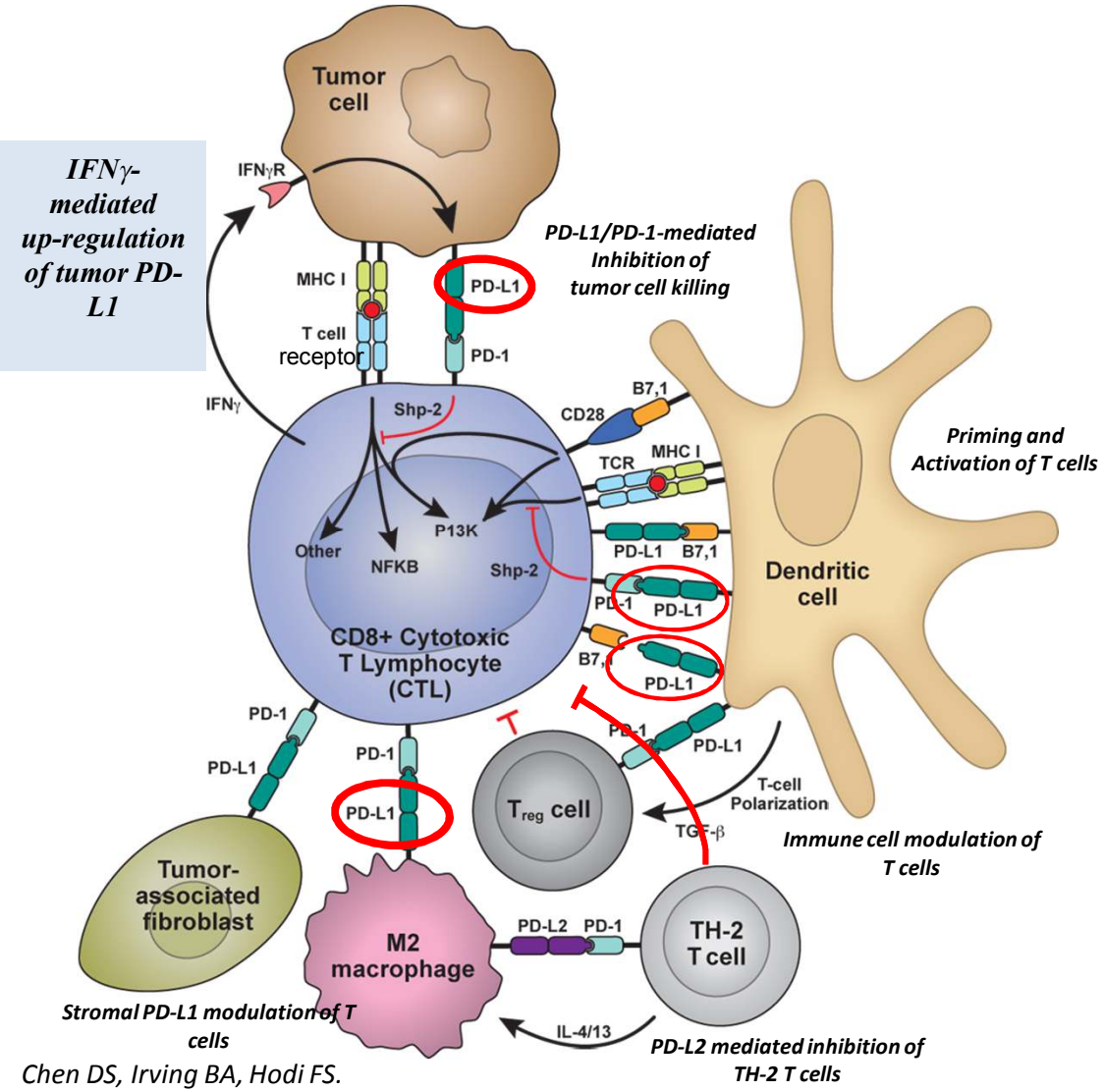
Blocking CTLA-4 and PD-1



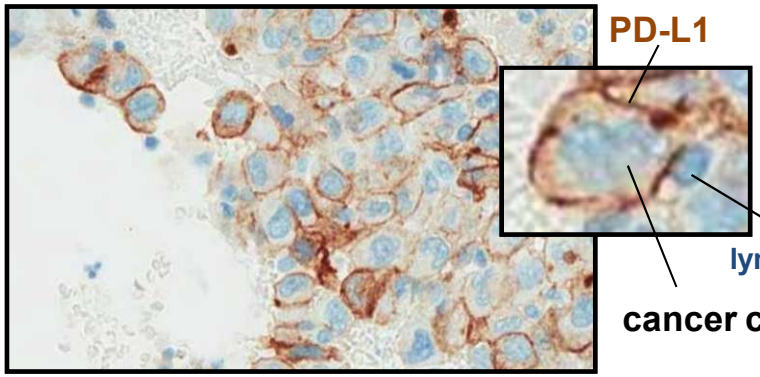
Blocking CTLA-4 and PD-1



PD-L1 dampens the anti-tumor immune response



Chen DS, Irving BA, Hodi FS.
Clin Cancer Res. 2012;18:6580.



Presence of intratumoral T-cells may lead to adaptive immune resistance

PD-L1 expression in the tumor microenvironment can inhibit anti-tumor T cell activity:

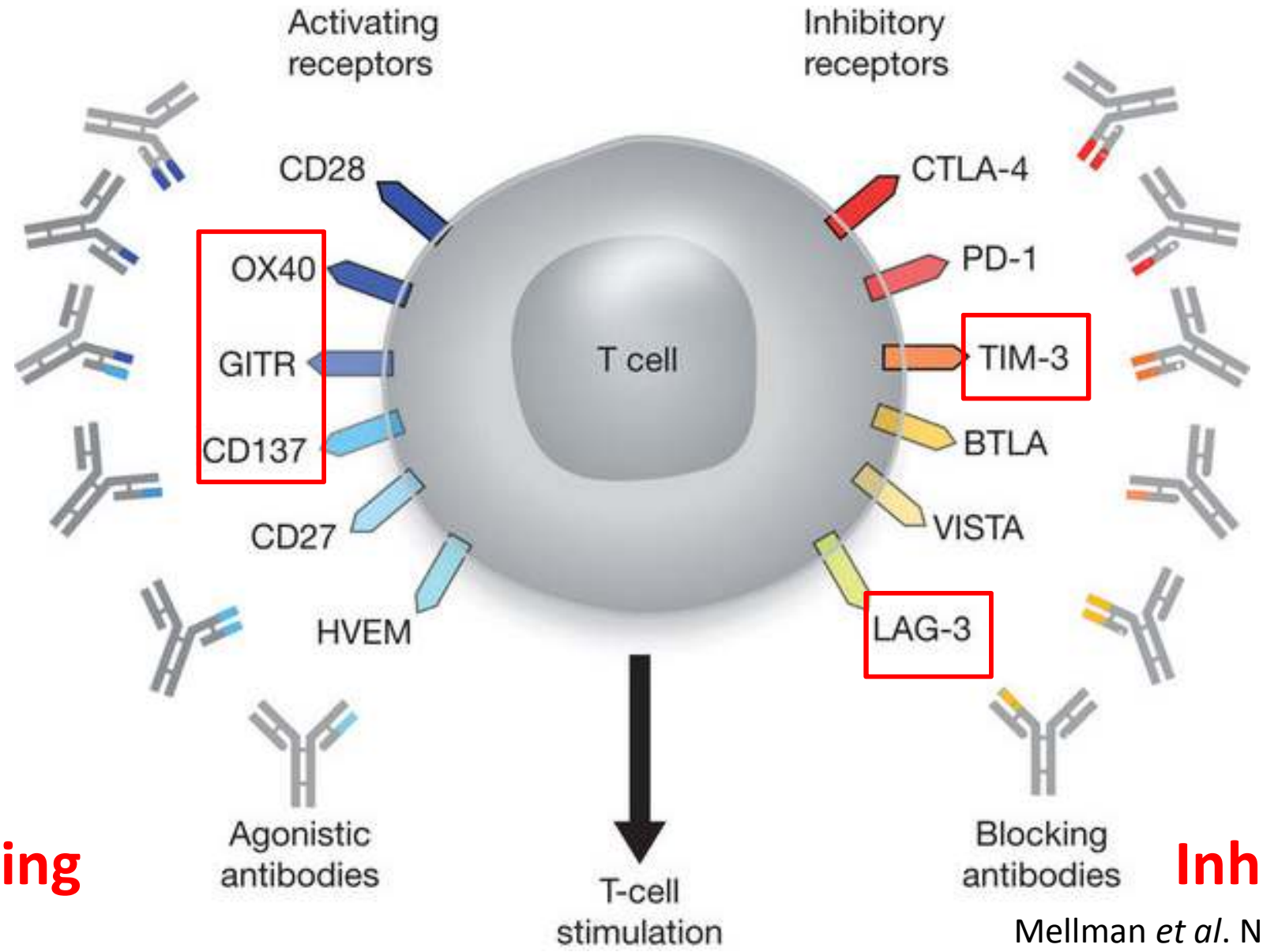
1. PD-L1 expression by tumor infiltrating ***immune cells***
2. PD-L1 expression by ***cancer cells***

Courtesy of and adapted from Omid Hamid, MD, ASCO 2013

Immune Modulatory Receptors

Turning up The Activating

Blocking the Inhibiting



Activating

Inhibiting

Mellman *et al*. Nature, 2011

Wait what?
Which Tumor Types

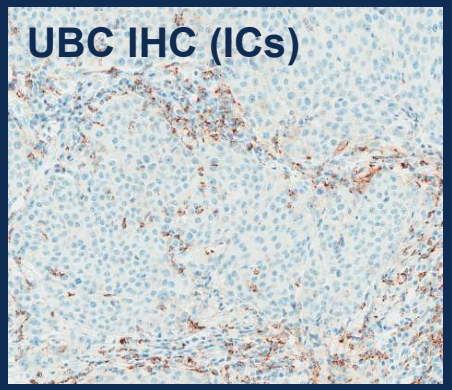
Tumor-mediated inhibition of the immune system has been observed in multiple tumor types

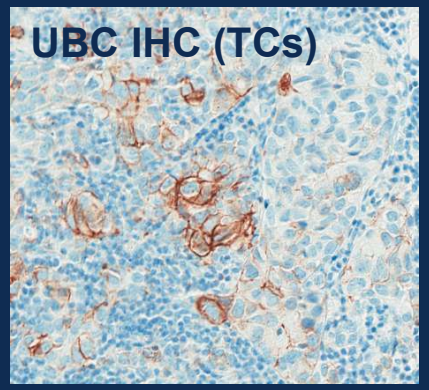
Tumor Type	Infiltrating immune cells reported	Evidence of tumor-associated immunosuppression reported	Tumor-immune system interactions known to correlate with clinical prognosis
Bladder	✓	✓	✓
Breast	✓	✓	✓
Colorectal	✓	✓	✓
Esophageal	✓	✓	✓
Gastric	✓	✓	✓
Head & neck cancer	✓	✓	✓
Hepatocellular	✓	✓	✓
Leukemia	—	✓	—
Lung cancer	✓	✓	✓
Lymphoma	—	✓	—
Melanoma	✓	✓	✓
Ovarian	✓	✓	✓
Pancreatic	✓	✓	—
Prostate	✓	—	✓
Renal cell carcinoma	✓	✓	✓

1. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264; 2. Mellman I, et al. *Nature*. 2011;480:480-489; 3. Sharma P, et al. *Proc Natl Acad Sci U S A*. 2007;104:3967-3972; 4. Pages F, et al. *N Engl J Med*. 2005;353:2654-2666; 5. Salama P, et al. *J Clin Oncol*. 2009;27:186-192; 6. Ichihara F, et al. *Clin Cancer Res*. 2003;9:4404-4408; 7. Badoual C, et al. *Clin Cancer Res*. 2006;12:465-472; 8. Gao Q, et al. *Clin Cancer Res*. 2009;15:971-979; 9. Dieu-Nosjean MC, et al. *J Clin Oncol*. 2008;26:4410-4417; 10. Taylor RC, et al. *J Clin Oncol*. 2007;25:869-875; 11. Zhang L, et al. *N Engl J Med*. 2003;348:203-213; 12. Liyanage UK, et al. *J Immunol*. 2002;169:2756-2761; 13. Kärjä V, et al. *Anticancer Res*. 2005;25:4435-4438; 14. Thompson RH, et al. *Clin Cancer Res*. 2007;13:1757-1761; 15. Hiraoka K, et al. *Br J Cancer*. 2006;94:275-280; 16. Winerdal ME, et al. *BJU Int*. 2011;108:1672-1678; 17. Kono K, et al. *Cancer Immunol Immunother*. 2006;55:1064-1071; 18. Rody A, et al. *Breast Cancer Res*. 2009;11:1-13; 19. Inman BA, et al. *Cancer*. 2007;109:1499-1505; 20. Schaefer C, et al. *Br J Cancer*. 2005;92:913-920; 21. Woo EY, et al. *J Immunol*. 2002;168;4272-4276; 22. Karube K, et al. *Br J Haematol*. 2004;126:81-84; 23. Chapon M, et al. *J Invest Dermatol*. 2011;131:1300-1307; 24. Hamanishi J, et al. *PNAS*. 2007;104:3360-3365.

PD-L1 Prevalence in Solid Tumors

Indication	PD-L1+ (IC)	PD-L1+ (TC)
NSCLC (n = 184)	26%	24%
UBC (n = 205)	**27%**	**11%**
RCC (n = 88)	25%	10%
Melanoma (n = 59)	36%	5%
HNSCC (n = 101)	28%	19%
Gastric cancer (n = 141)	18%	5%
CRC (n = 77)	35%	1%
Pancreatic cancer (n = 83)	12%	4%





ICs; tumor-infiltrating immune cells.
TCs; tumor cells.
PD-L1+ if ≥ 5% ICs or TCs were positive for PD-L1 staining (Genentech/Roche PD-L1 IHC).

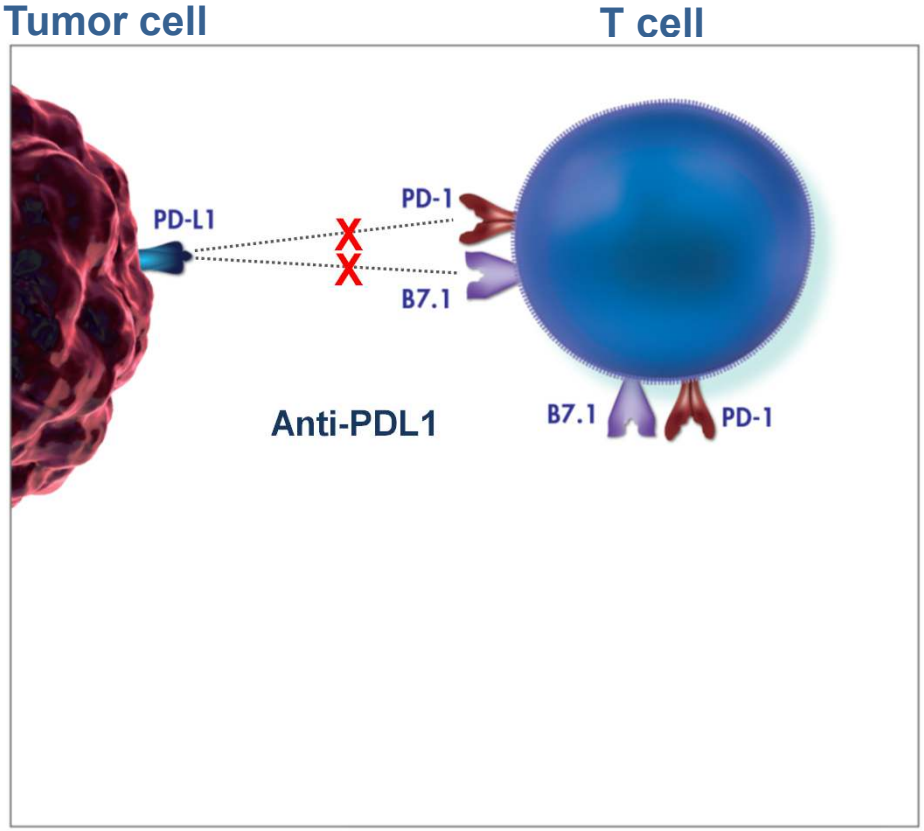
PDL1 expression - prognosis

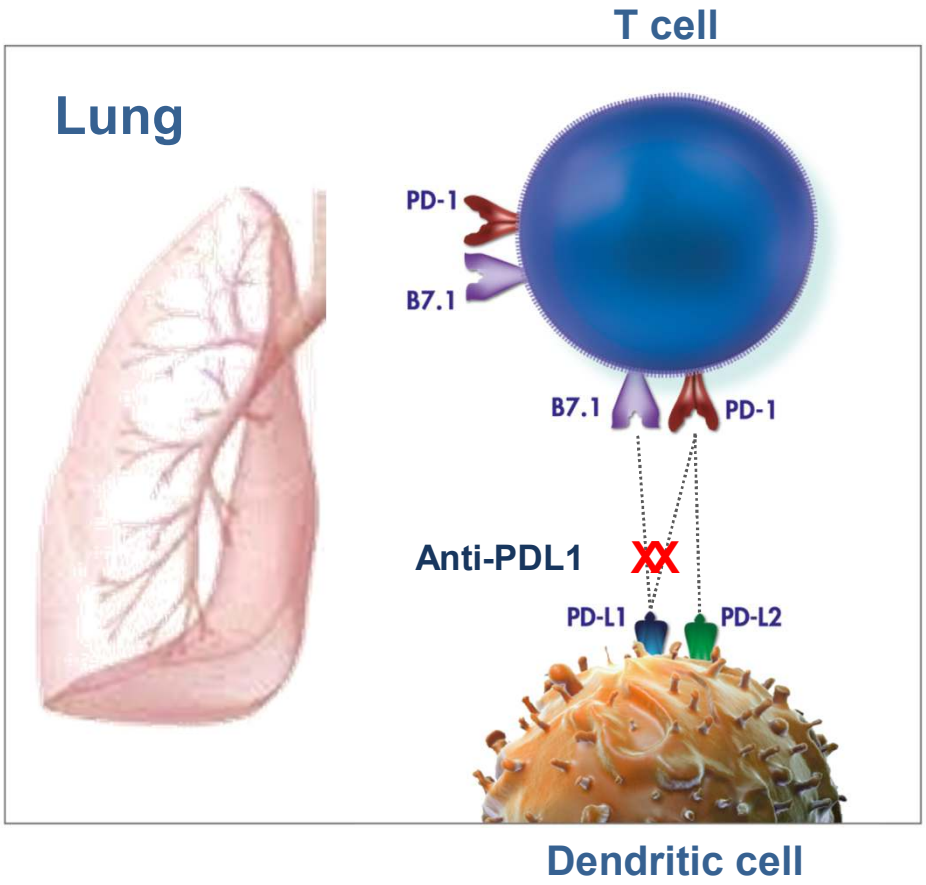
Tumor type	Prognostic and pathological associations
Cervical	Expression of PD-L1 does not appear to affect prognosis [114]
Colon	PD-L1 expression associated with poorer prognosis [115]
Gastric	PD-L1 expression correlated with tumor size, invasion, lymph node metastasis, and reduced survival [116]
HBV-related HCC	PD-L1 on circulating leukocytes associated with tumor recurrence and shorter survival after cryoablation [117]
HCC	PD-L1 expression associated with tumor aggressiveness, postoperative recurrence, and worse prognosis [84]
Melanoma	PD-L1 expression associated with more advanced disease and shorter survival [82], or, more recently, longer survival [43] than patients with PD-L1 tumors
NSCLC	Tumor expression of PD-L1 correlates with adenocarcinoma (non-squamous) histology and shorter post-lobectomy survival [83]
Ovarian	Expression of PD-L1 associated with poor prognosis [118]
RCC	PD-L1 expression associated with increased tumor stage, risk of death from RCC, and shorter survival [119]

HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; NSCLC: Non-small-cell lung cancer; RCC: Renal cell cancer.

Hamid, Carvajal, Expert Opin. Biol. Ther. 2013 [Early Online]

Anti-PDL1 Inhibits the Binding of PD-L1 to PD-1 / B7.1





- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming
- An anti-PDL1 specific antibody leaves the PD-1/PD-L2 interaction intact
  - Lung dendritic cells and macrophages express high levels of PD-L2 upon immune challenge
  - Preclinical models indicate PD-L2 plays an important role in lung immune homeostasis

Akbari O, et al. *Mucosal Immunol.* 2010; Matsumoto K, et al. *Biochem Biophys Res Commun.* 2008; Francisco L, et al. *J Exp Med*. 2009; Huber S, et al. *Blood.* 2010.

Courtesy of and adapted from Jeff Sossman, MD, SMR 2013

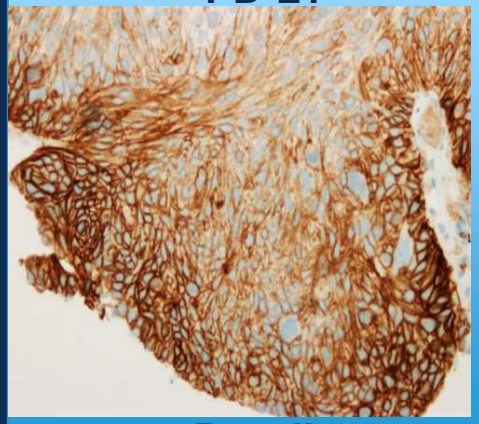
PD-1/PD-L1 Agents in Development

Target	Agent	Class
PD-1	Nivolumab (MDX1106, BMS-936558)	IgG4 fully human Ab
	Pembrolizumab (MK-3475)	IgG4 engineered humanized Ab
	Pidilizumab (CT-011)	IgG1 humanized Ab
	AMP-224	Fc of human IgG-PD-L2 fusion
PD-L1	BMS935559 (MDX-1105)	IgG4 fully human Ab
	MPDL3280A	IgG1 engineered fully human Ab
	MEDI4736	IgG1 engineered fully human Ab
	MSB0010718C	IgG1 fully human Ab

How is it given and how does it work?

PD-L1 Immunohistochemistry
Case Study in NSCLC

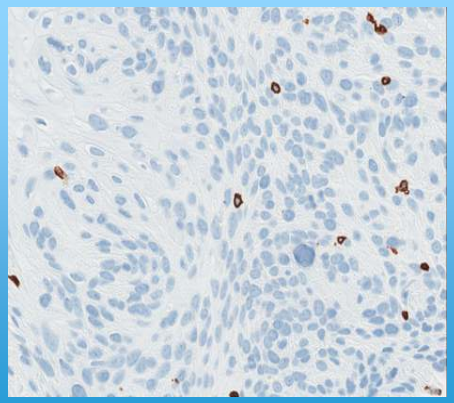
PD-L1



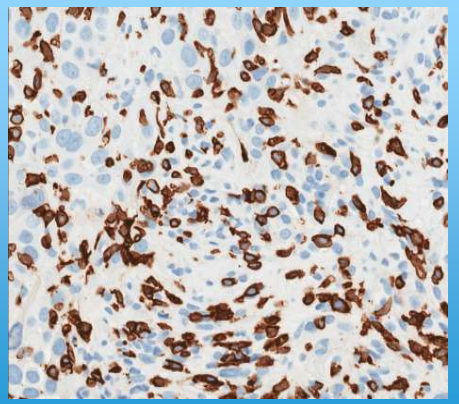
Baseline

PD-L1 staining performed on VENTANA BenchMark ULTRA using VENTANA PD-L1 (SP263) clone

CD8

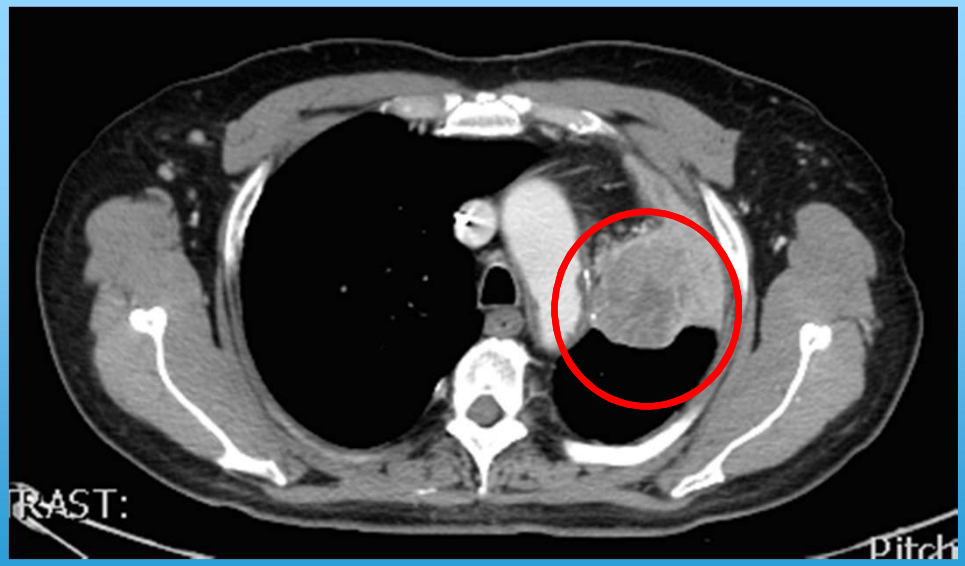


Baseline



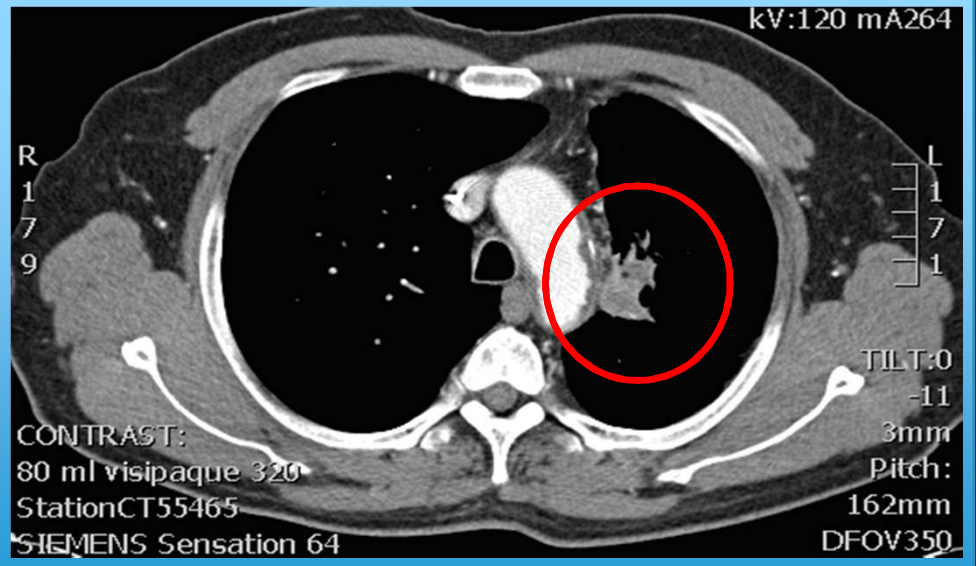
On-Treatment (week 6)

Baseline



64 yo M w/ sq NSCLC s/p Carbo/Paclitaxel + Cetuximab

On-Treatment (Week 16)



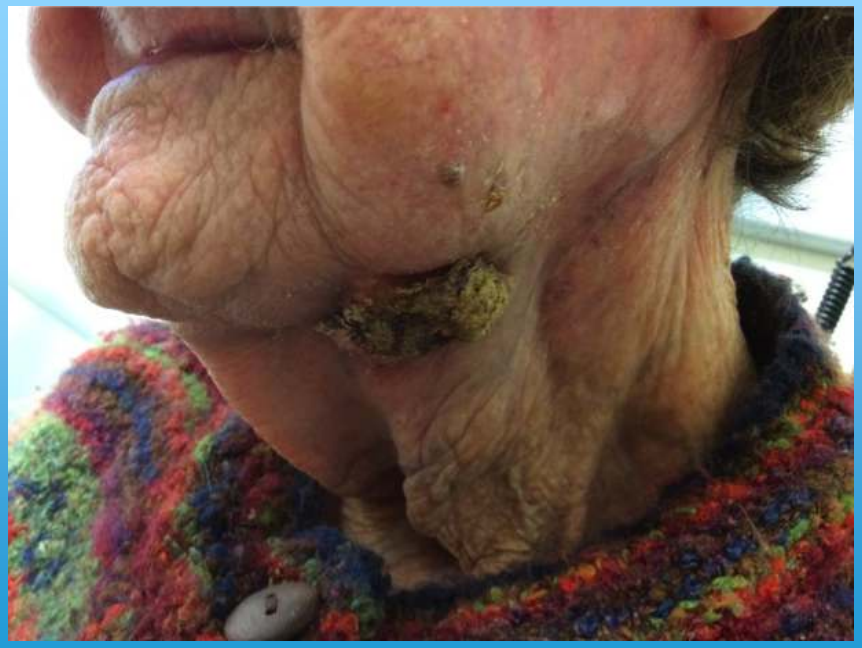
Ongoing PR

CT images courtesy of Dr. Ignatius Ou of Chao Family Comprehensive Cancer Center

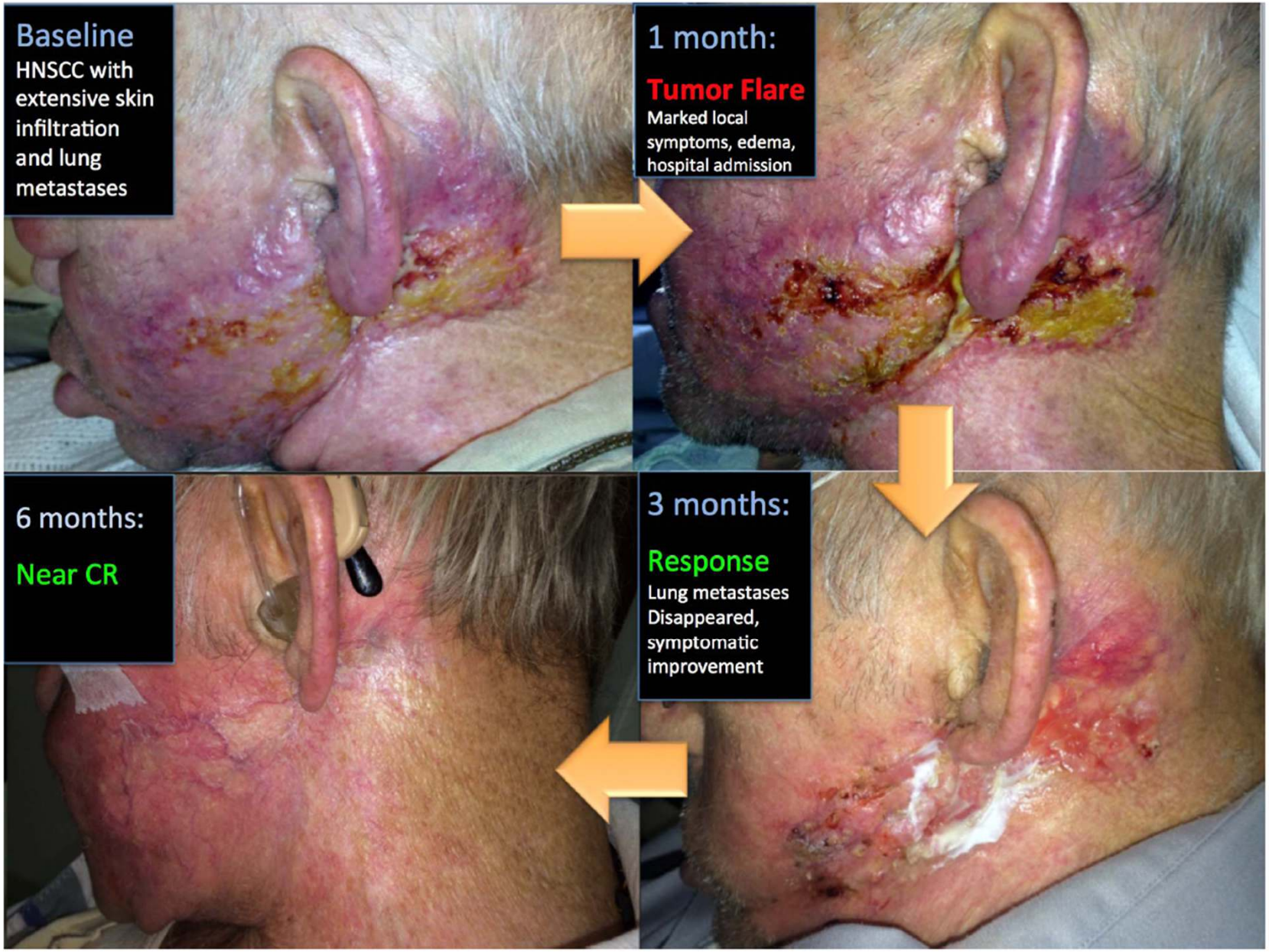
Response in Patient with Head and Neck Cancer

Baseline

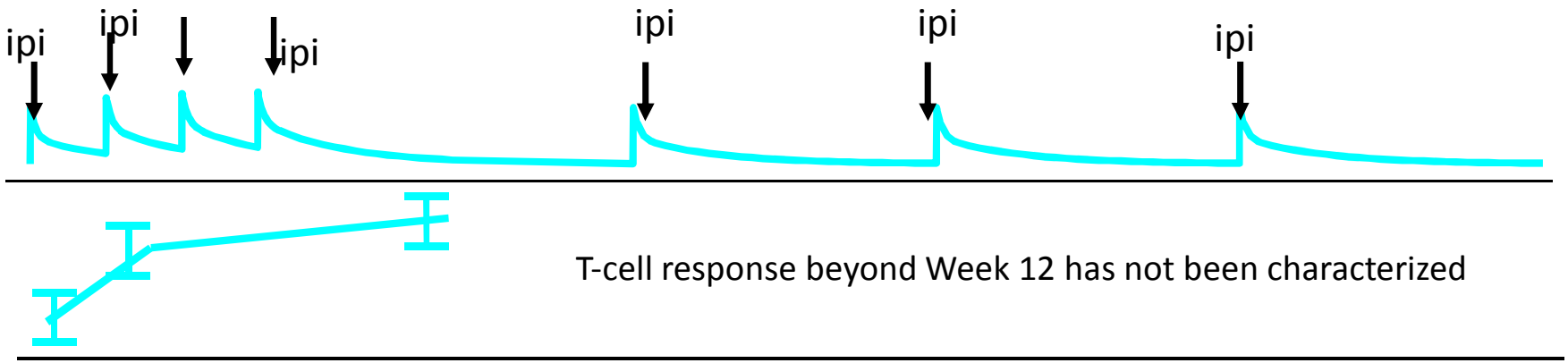
Day 28

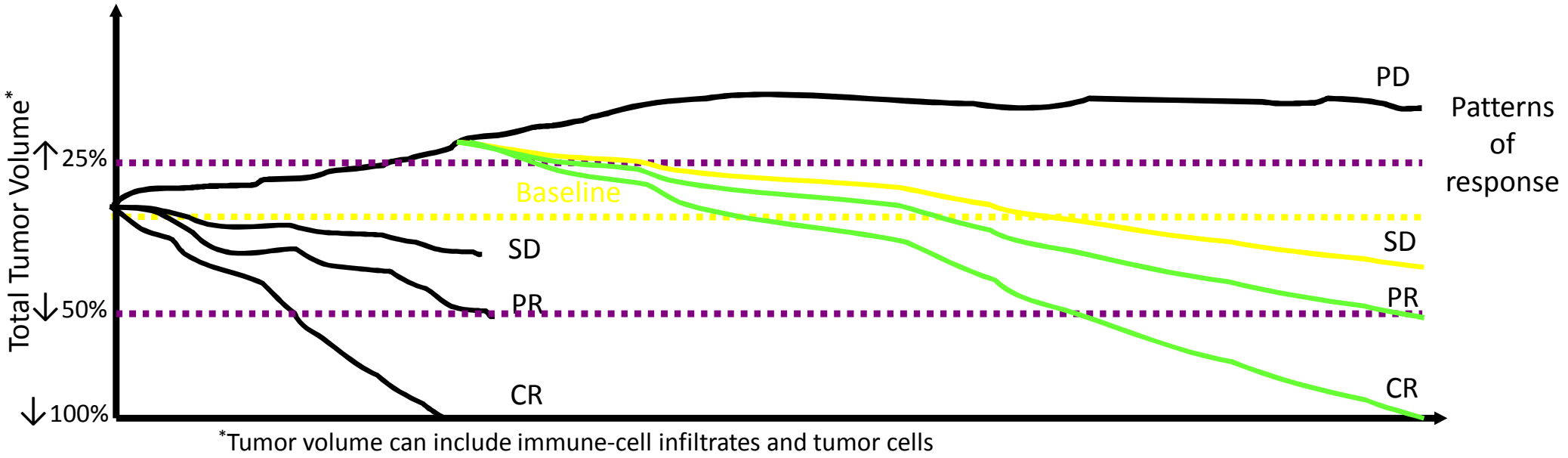


- 96 y.o. female
  - Progressed on previous cetuximab
  - HPV negative, PD-L1 positive
  - Treatment ongoing at 8 weeks


Baseline
HNSCC with extensive skin infiltration and lung metastases
1 month:
Tumor Flare
Marked local symptoms, edema, hospital admission
3 months:
Response
Lung metastases Disappeared, symptomatic improvement
6 months:
Near CR

Immunotherapy: Evolution of Anticancer Effect



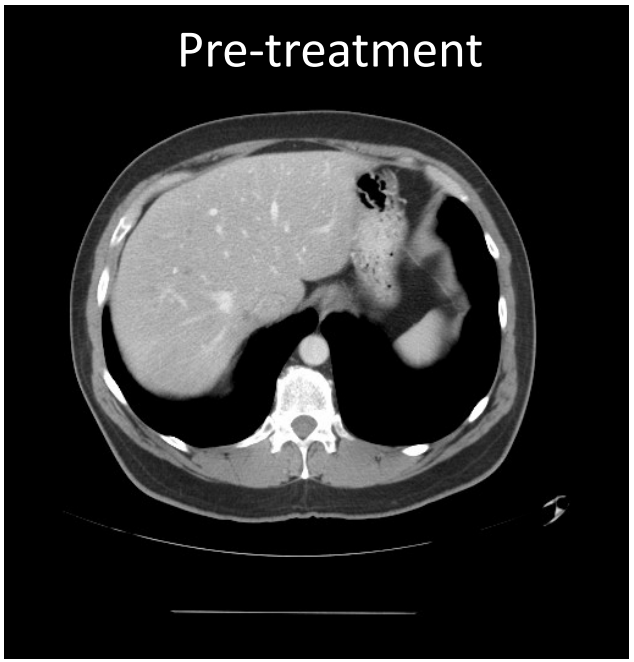


*Tumor volume can include immune-cell infiltrates and tumor cells

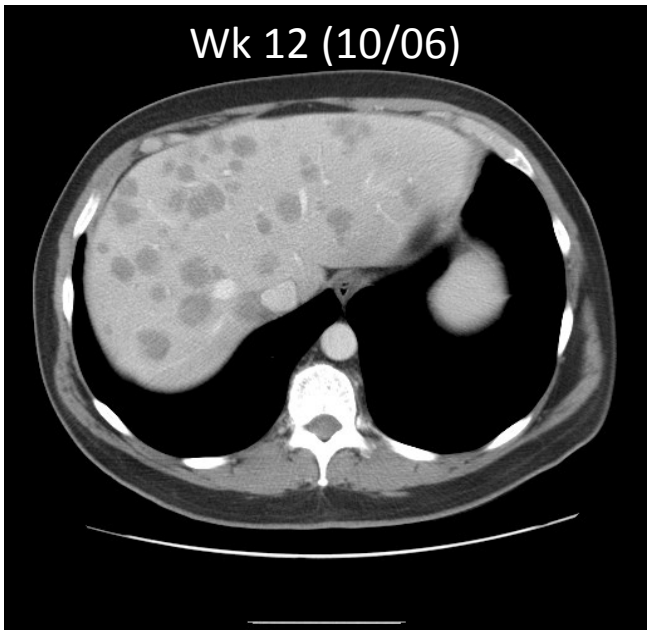
Immune-cell activation and proliferation begins early

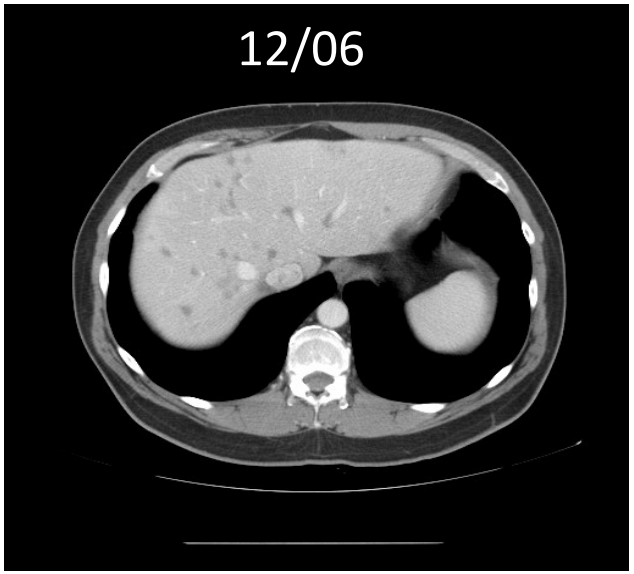
Measurable clinical effect occurs at variable time points

Unique Kinetics of Responses in Patients Treated With Ipilimumab

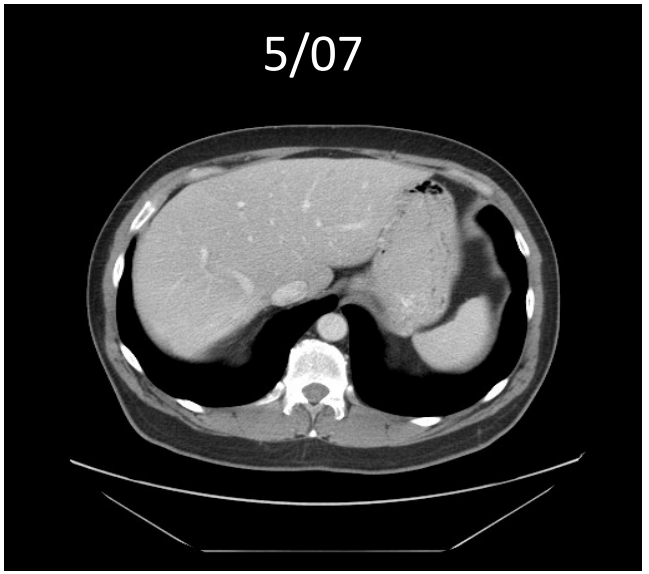


Four blinded doses ipilimumab



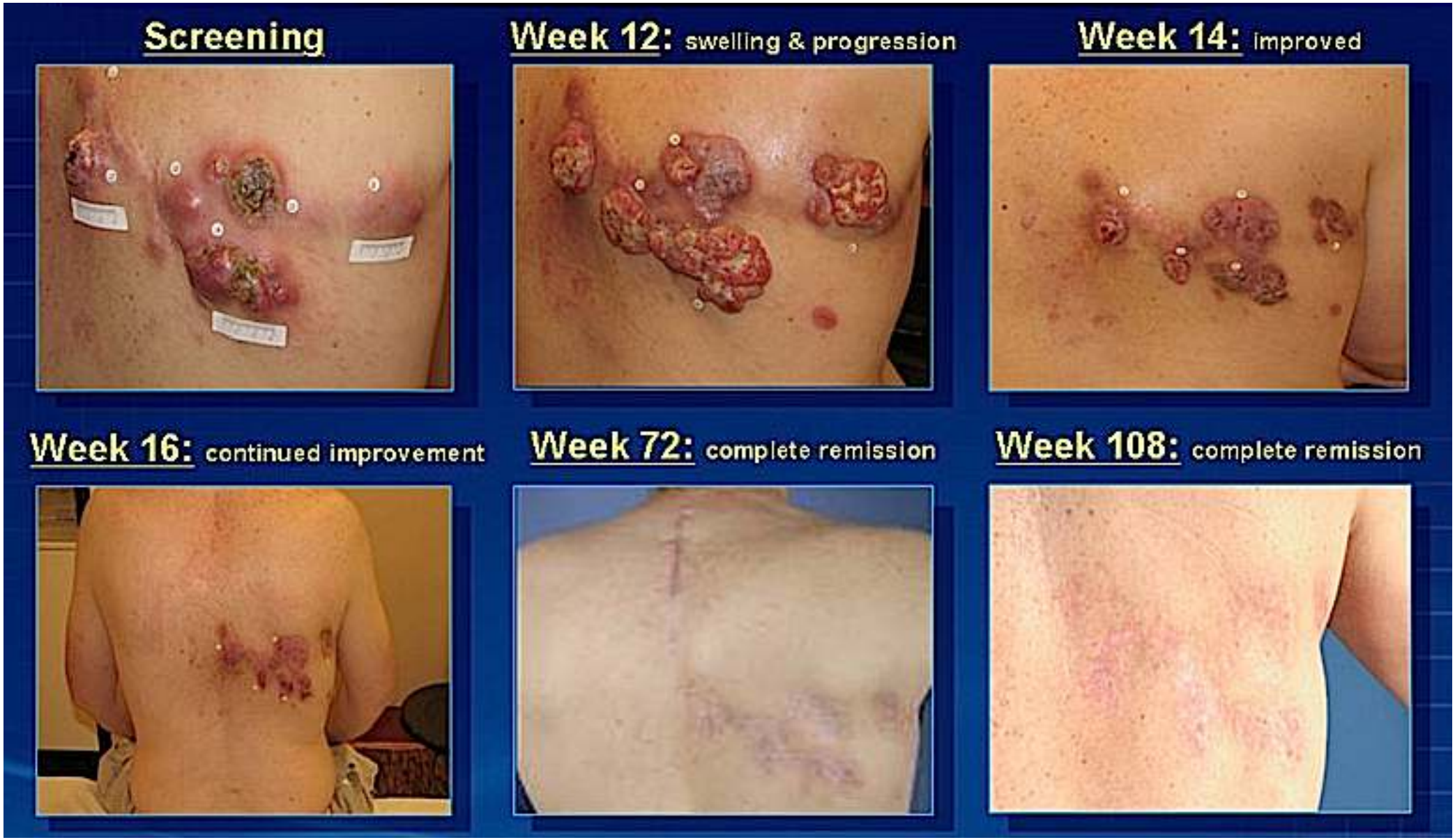


Four 10 mg/kg doses ipilimumab



Images courtesy Dr. Wolchok.

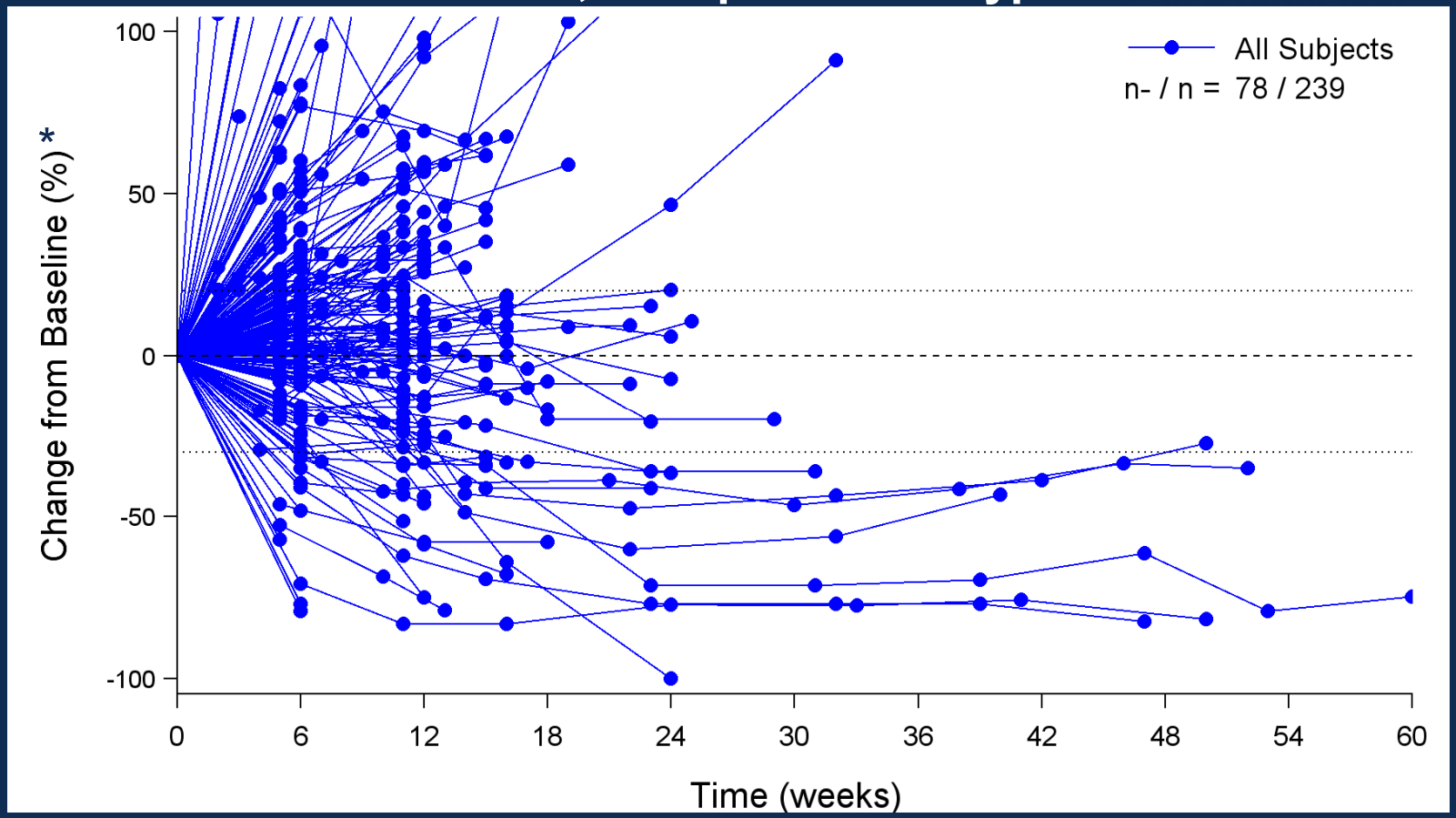
Ipilimumab Patterns of Response



All patients with ≥1 on-treatment scan (n=239)

Early and Durable Activity Observed in Some Patients

All Doses, Multiple Tumor Types



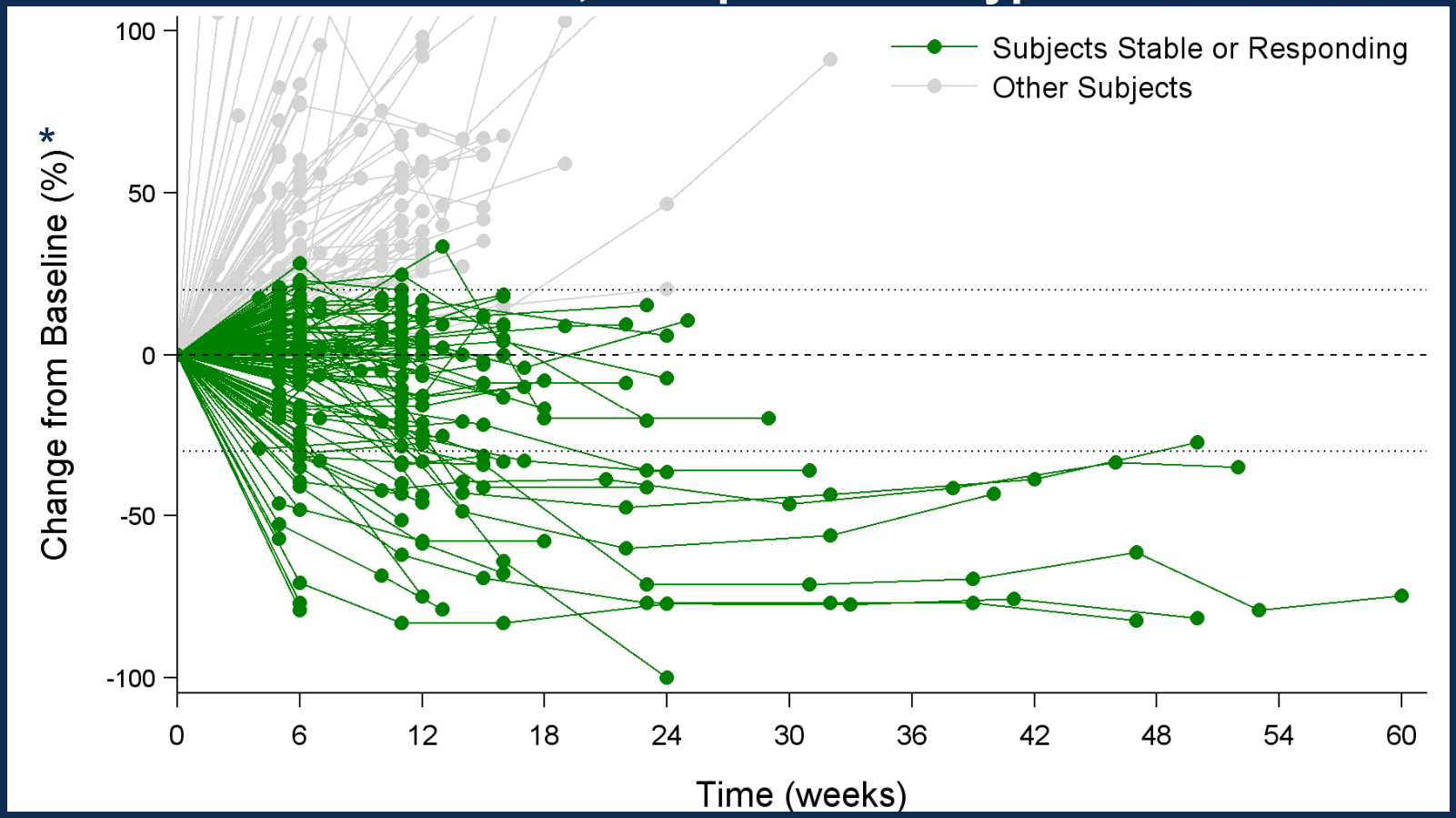
- Overall pattern of activity consistent with PD-L1/PD-1 targeting agents
- Activity can be preceded by initial progression

*Changes >100% are truncated; Data cut-off: May 18, 2014

All patients with ≥1 on-treatment scan (n=239)

Early and Durable Activity Observed in Some Patients

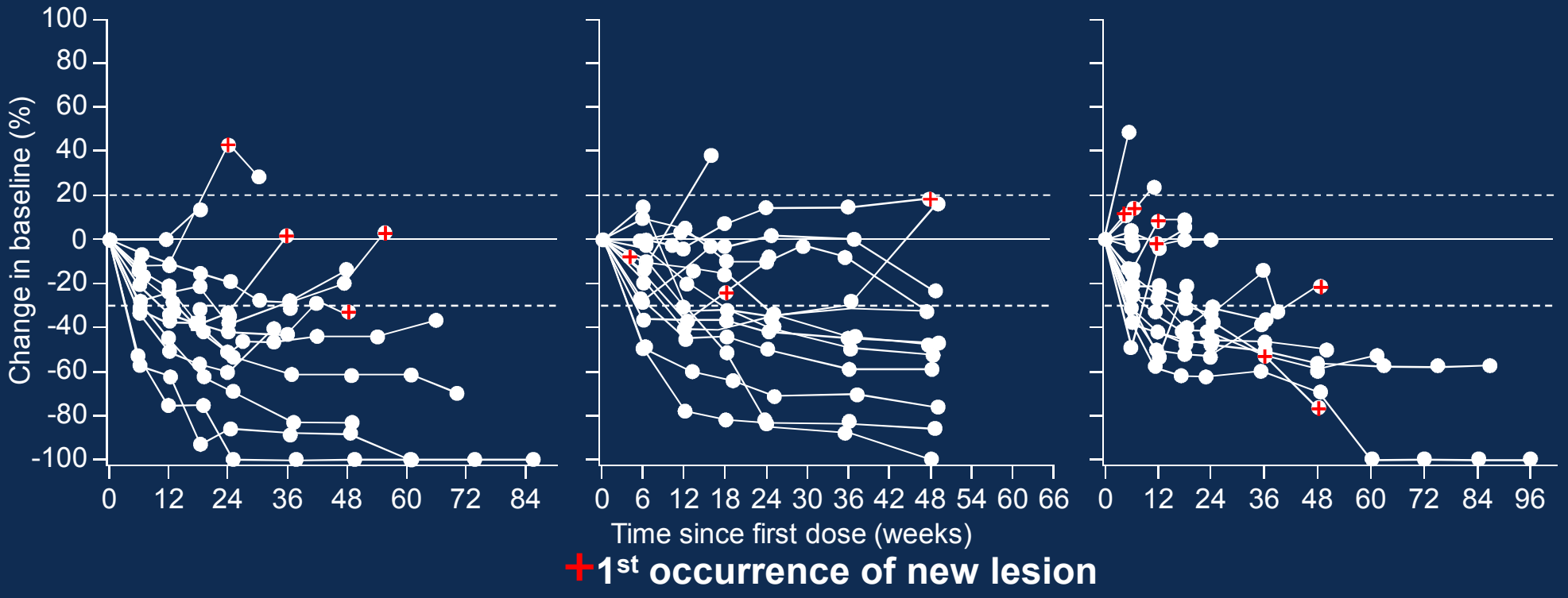
All Doses, Multiple Tumor Types



- Overall pattern of activity consistent with PD-L1/PD-1 targeting agents
- Activity can be preceded by initial progression

*Changes >100% are truncated; Data cut-off: May 18, 2014

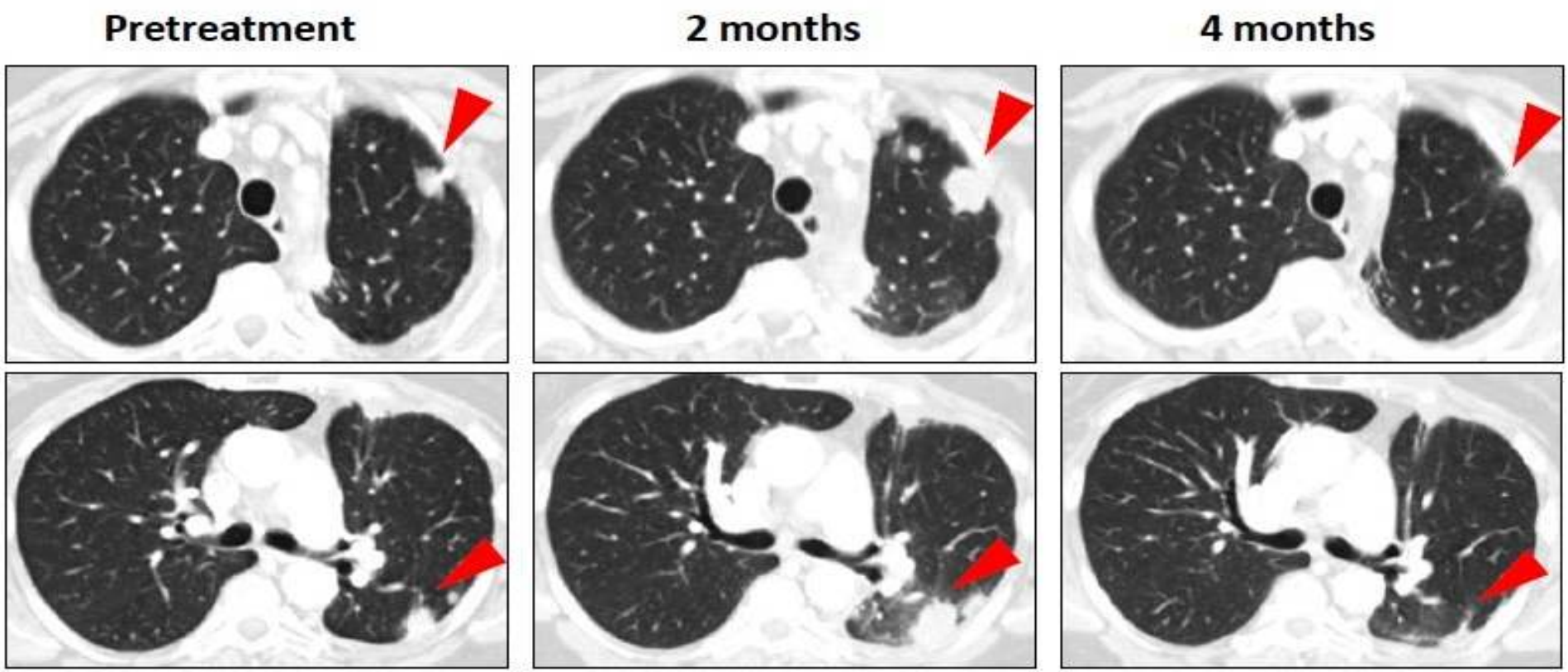
Change from baseline in target tumor burden by prior treatment status



Positive change in tumor burden indicates tumor growth; negative change indicates tumor reduction.

PRESENTED AT:
ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

PD-1 “responses” can be delayed

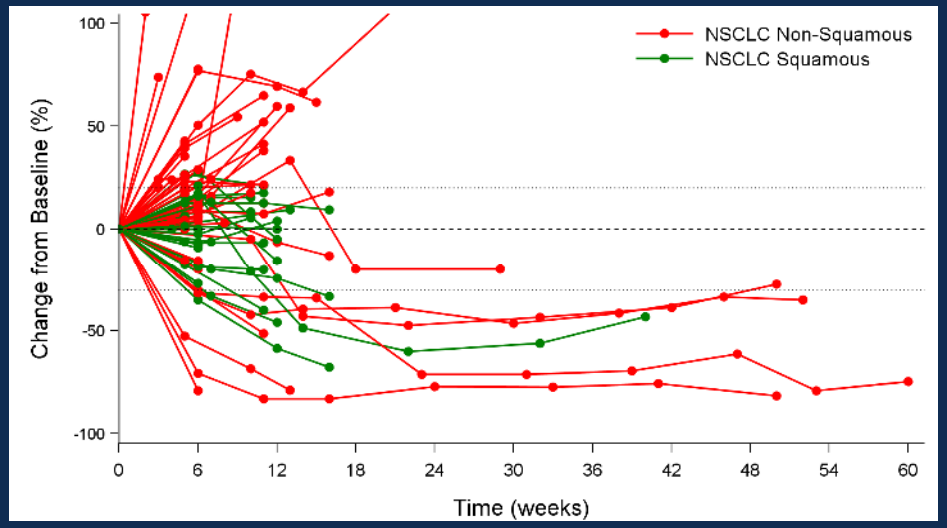


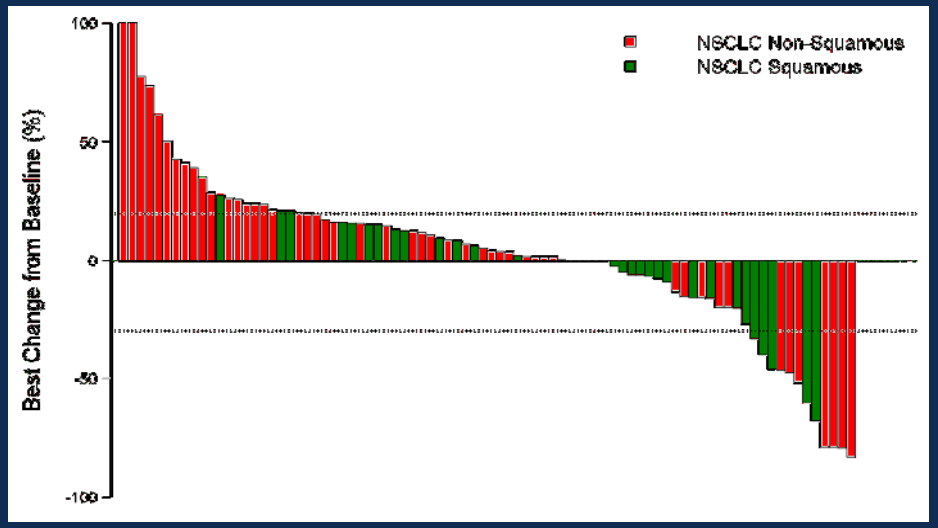
Topalian et al. *NEJM* 2012

Select tumor types from escalation and expansion with ≥1 on-treatment scan

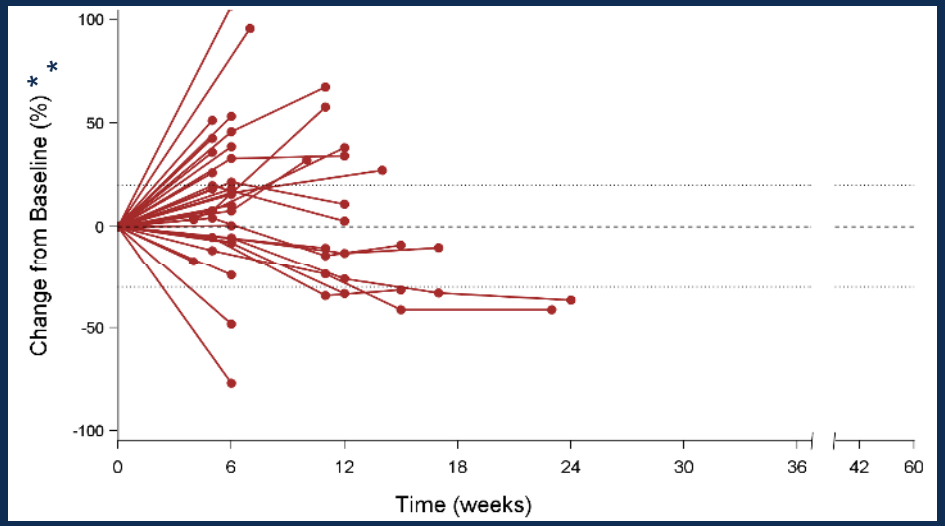
Emerging Clinical Activity in Multiple Tumors

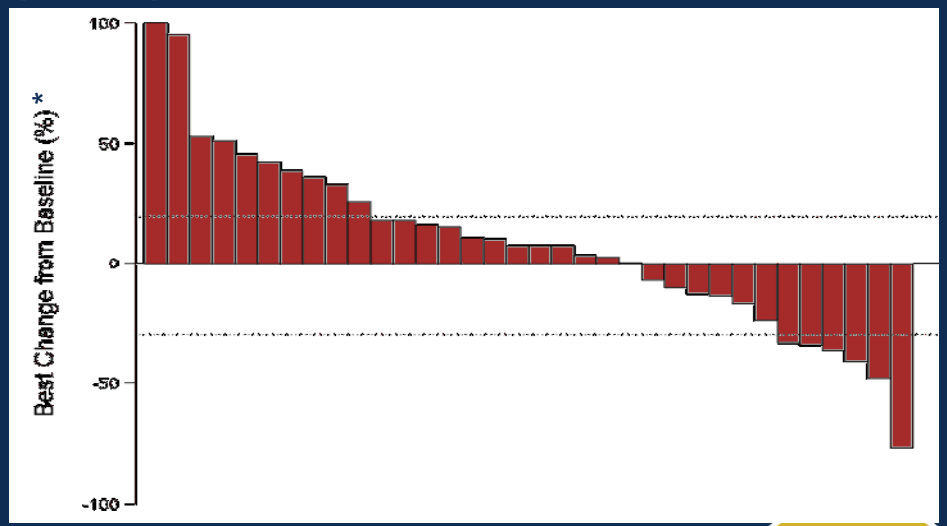
NSCLC (n = 84)





SCCHN (n=34)



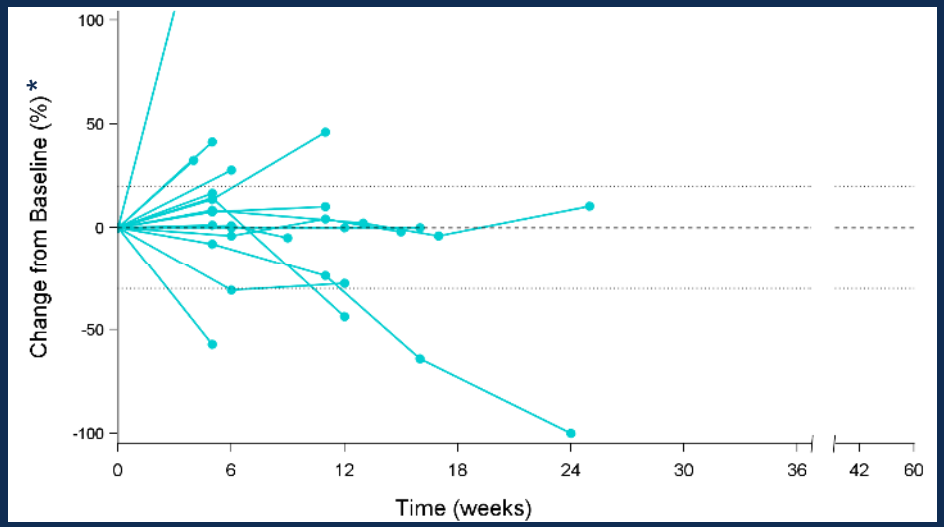


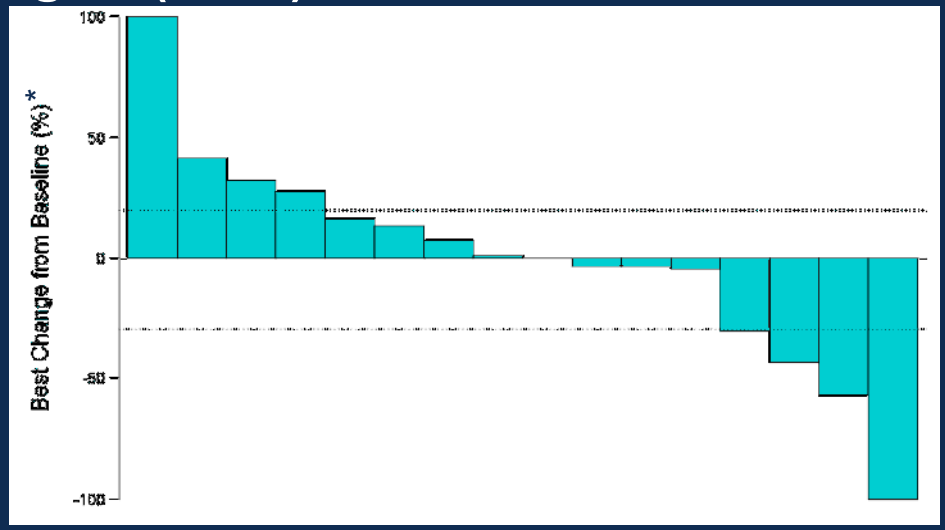
*Changes >100% are truncated; Data cut-off: May 18, 2014

Select tumor types from escalation and expansion with ≥1 on-treatment scan

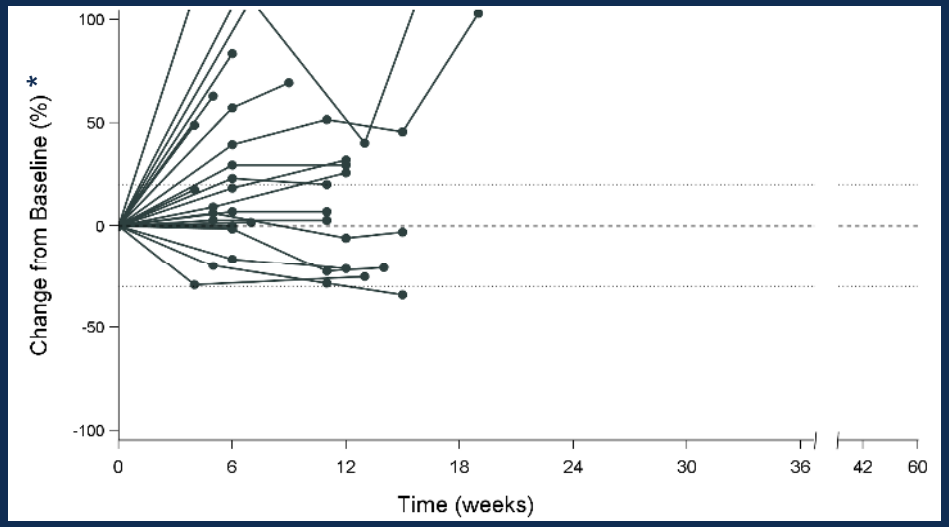
Emerging Clinical Activity in Multiple Tumors

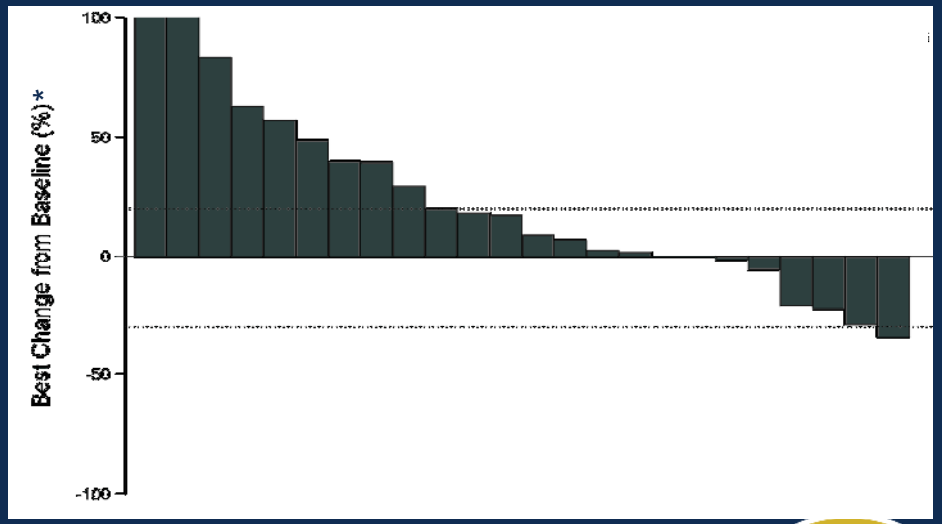
Gastroesophageal (n=16)





Pancreatic adenocarcinoma (n=24)



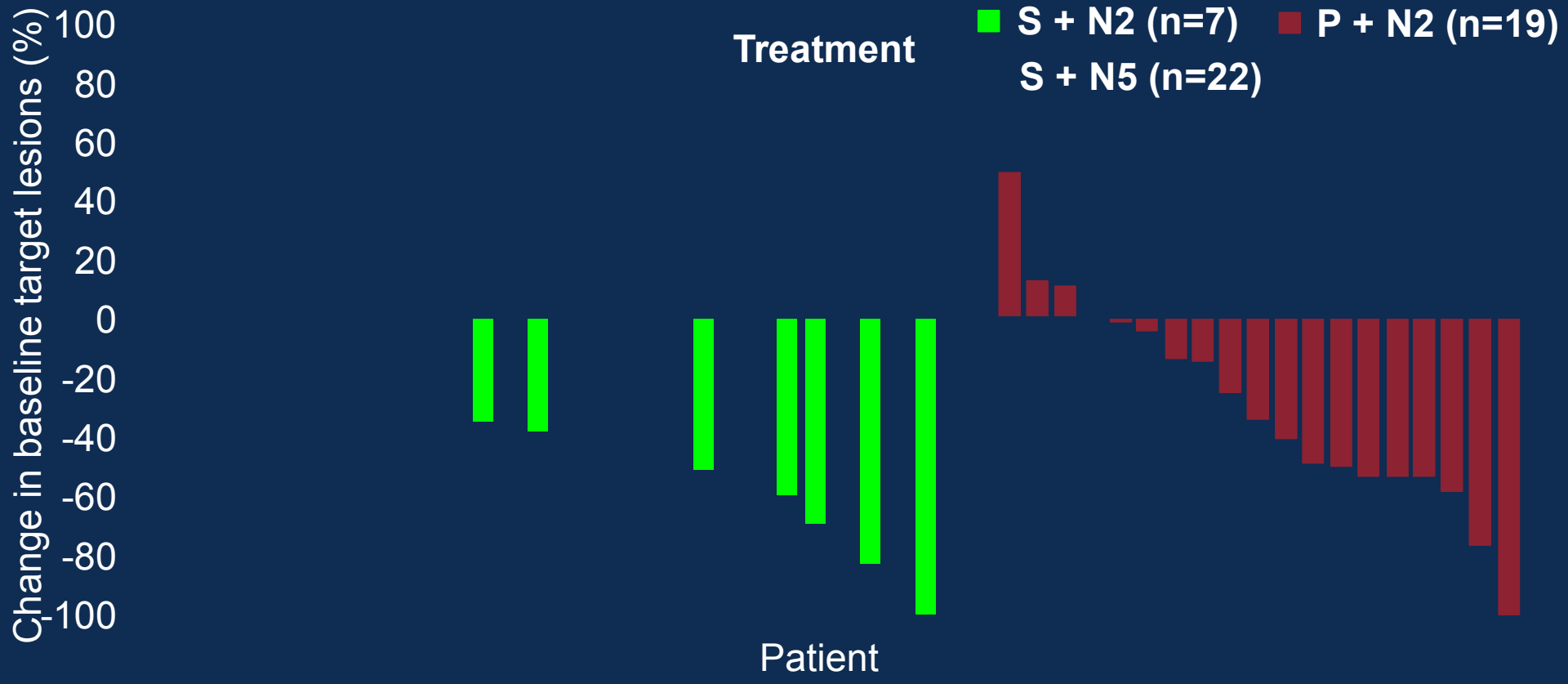


*Changes >100% are truncated; Data cut-off: May 18, 2014

Nivolumab (anti-PD-1; BMS-936558; ONO-4538) in combination with sunitinib or pazopanib in patients (pts) with metastatic renal cell carcinoma (mRCC)

A. Amin, E.R. Plimack, J.R. Infante, M.S. Ernstoff, B. Rini, D.F. McDermott, J. Knox, S.K. Pal, M.H. Voss, P. Sharma, C. Kollmannsberger, D. Heng, J. Spratlin, Y. Shen, J. Kurland, P. Gagnier, H. Hammers

Maximum tumor burden reduction in baseline target lesions by nivolumab dose

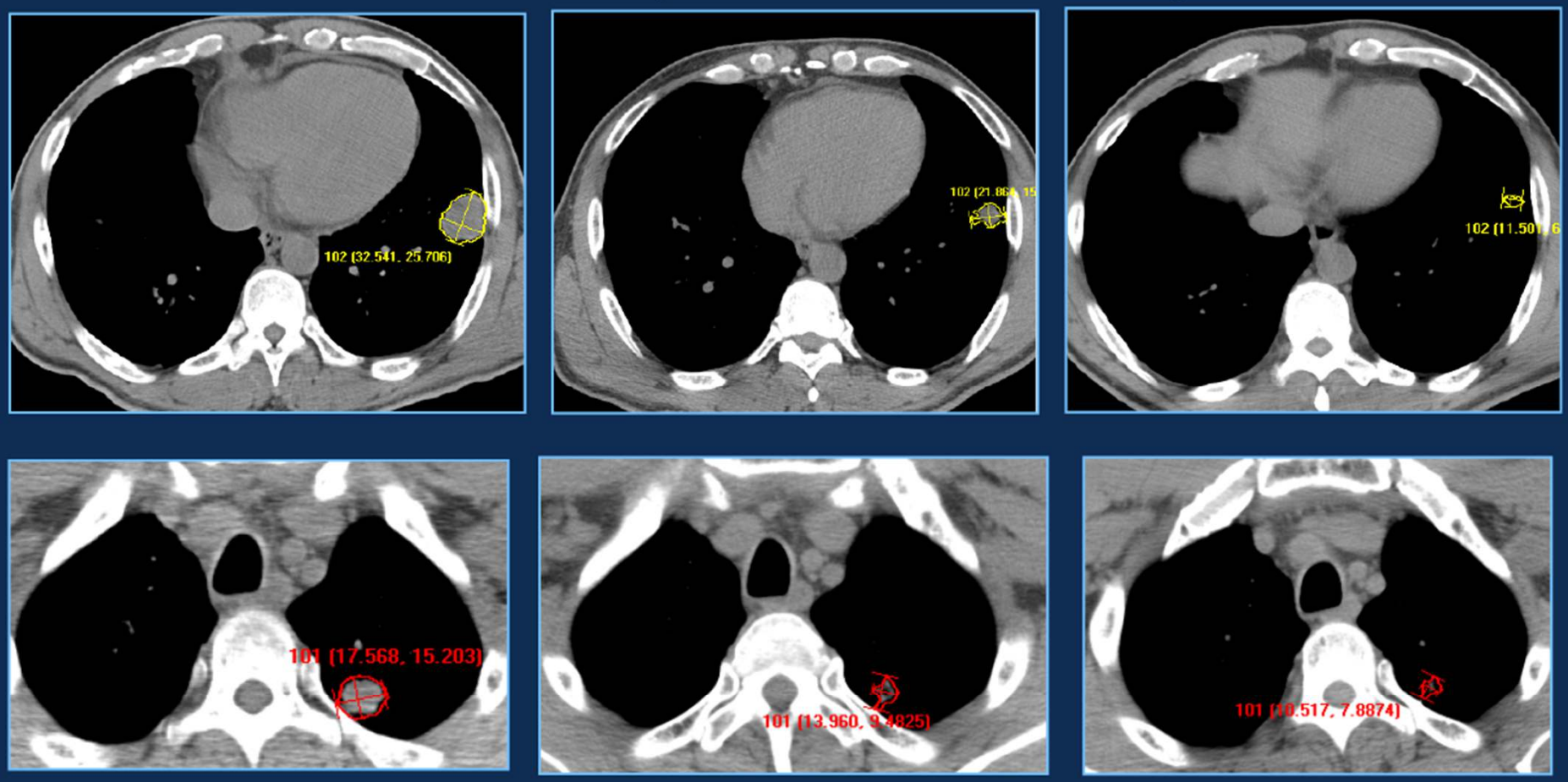


Positive change in tumor burden indicates tumor growth; negative change indicates tumor change.

PRESENTED AT:
ASCO 50TH ANNUAL MEETING SCIENCE & SOCIETY

Patient Response *(central review)*

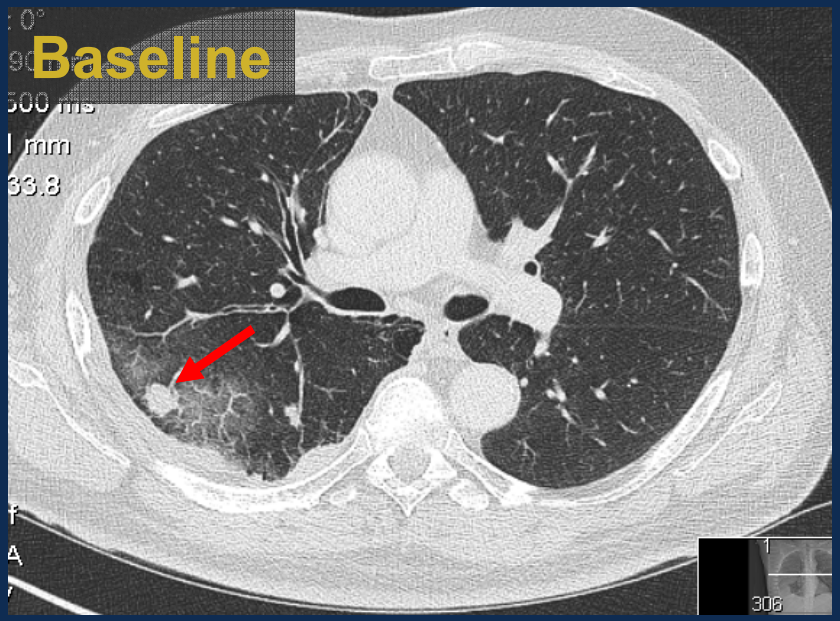
Baseline | **Cycle 4 -28.3%** | **Cycle 8 -56.1%**

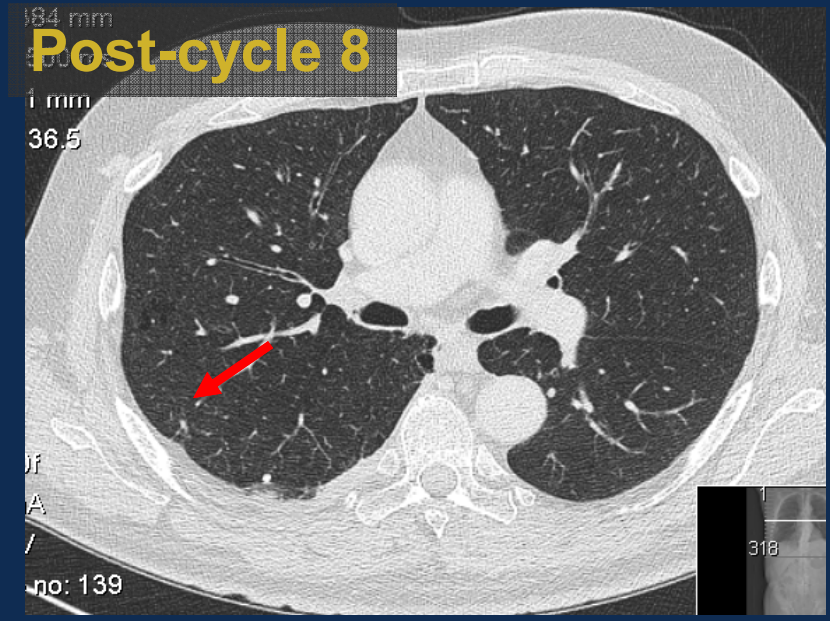


Presented by: Tanguy Seiwert

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

MPDL3280A: Regression of Lung Target Lesion in Patient With UBC



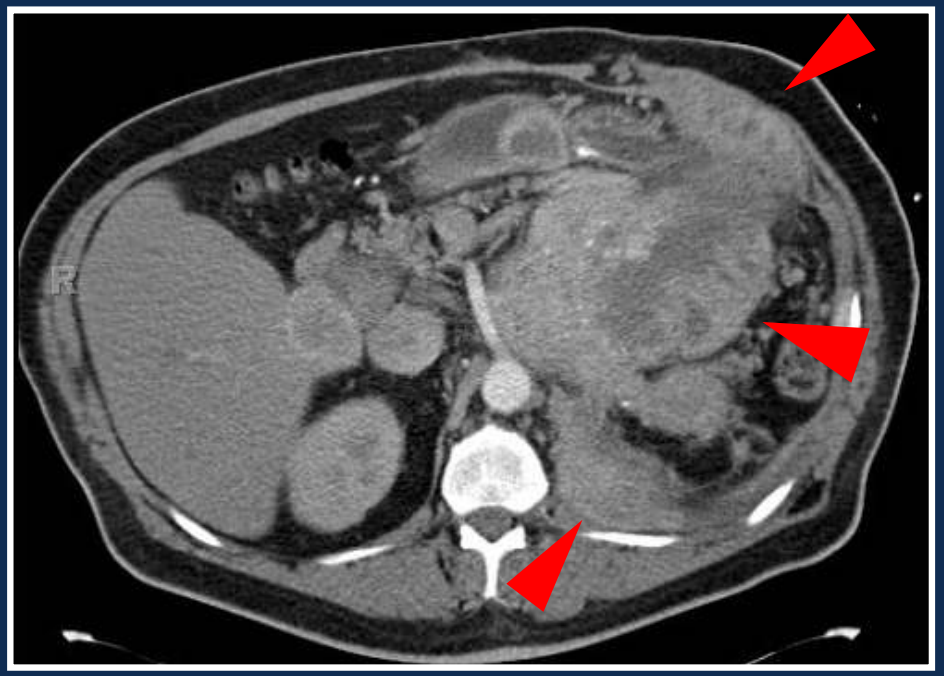


- 68-year-old male former smoker
- PD-L1 IHC positive
- Received prior cystectomy and gemcitabine + cisplatin

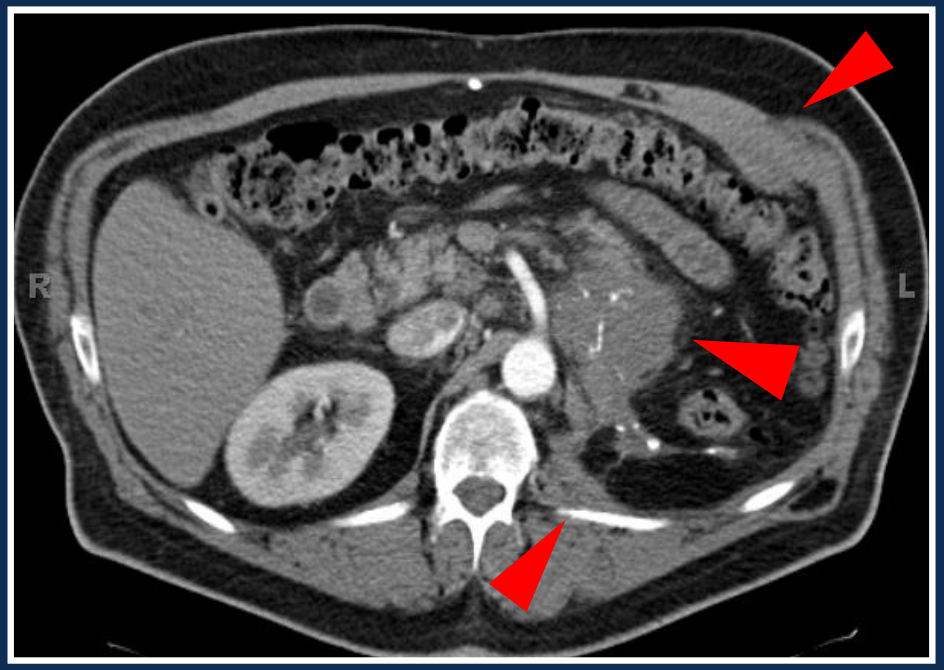
Prof. Thomas Powles, Barts Cancer Institute.

Bulky Refractory RCC Treated with PD-1 Blockade

Pretreatment



6 months



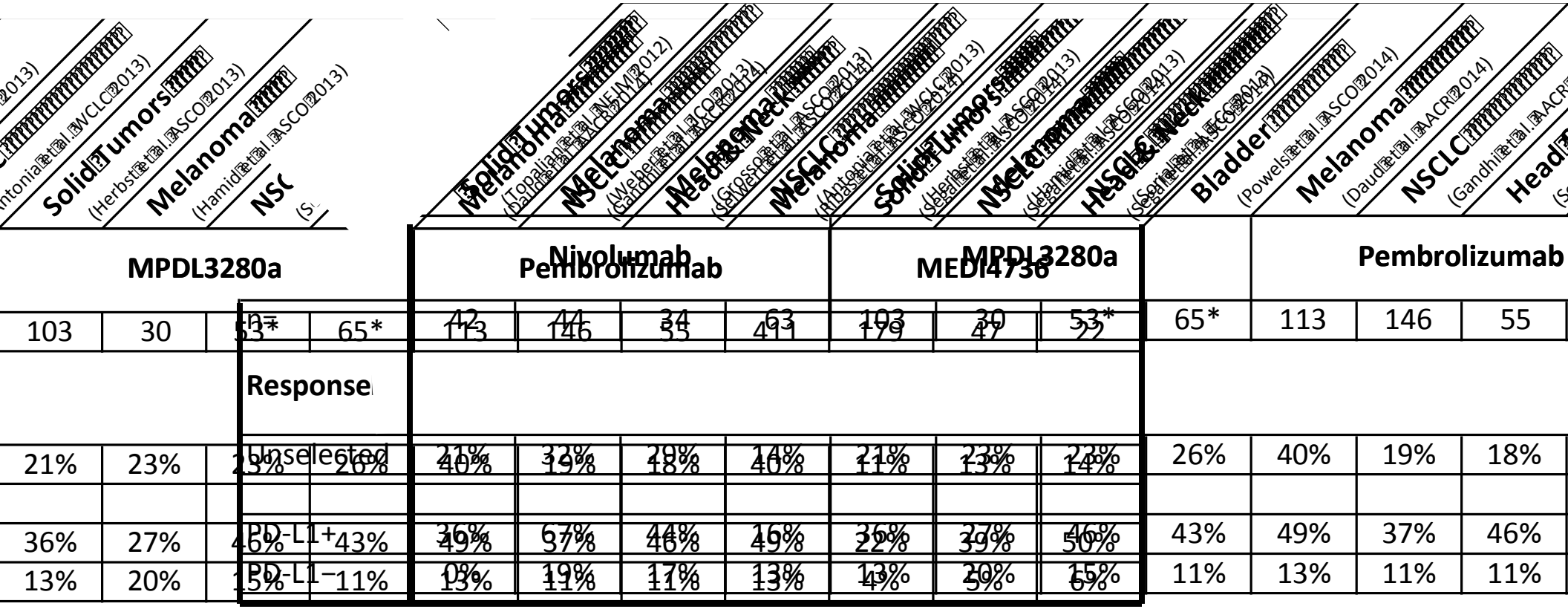
- 57-year-old patient had developed progressive disease after receiving sunitinib, temsirolimus, sorafenib, and pazopanib
- Rx with Nivolumab (anti-PD-1) at 1 mg/kg q 2 wks x 2 years
- Completed 12 cycles – now with PET Complete Response

What predicts Response ?

PD-L1+ tumors are associated with (but not required) for response

	Solid Tumors (Topalian et al. NEJM 2012)	Melanoma (Weber et al. JCO 2013)	Melanoma (Grosso et al. ASCO 2013)	NSCLC (Antonia et al. WCLC 2013)	Solid Tumors (Herbst et al. ASCO 2013)	Melanoma (Hamid et al. ASCO 2013)	NSCLC (Sorial et al. ECC 2013)	Bladder (Powels et al. ASCO 2014)	14)	I. AACR 2014)	Head & Neck (Selwert et al.	Me
	Nivolumab				**MPDL3280a**						**umab**	
n=	42	44	34	63	103	30	53*	65*			55	411
Response												
Unselected	21%	32%	29%	14%	21%	23%	23%	26%			18%	40%
PD-L1+	36%	67%	44%	16%	36%	27%	46%	43%			46%	49%
PD-L1−	0%	19%	17%	13%	13%	20%	15%	11%			11%	13%

PD-L1+ tumors are associated with (but not required) for response



MPDL3280a				Nivolumab		Pembrolizumab		MPDL3280a		MEDI4736		Pembrolizumab			
n=															
103	30	53*	65*	113	146	55	411	179	47	22	65*	113	146	55	
Response															
Unselected	21%	23%	26%	40%	19%	18%	40%	11%	13%	14%	26%	40%	19%	18%	
PD-L1+	36%	27%	43%	49%	37%	46%	49%	22%	39%	50%	43%	49%	37%	46%	
PD-L1−	13%	20%	11%	13%	11%	11%	13%	4%	5%	6%	11%	13%	11%	11%	

Efficacy of PD-1 Agents

Drug	Sponsor	Target	Disease Type	Response (n)	Reference
Nivolumab	BMS	PD-1	Solid Tumors	21% (42)	Topalian et al. *NEJM* 2012
			Melanoma	32% (44)	Weber et al. *JCO* 2013
			NSCLC	14% (63)	Antonia et al. WCLC 2013
			RCC	21% (168)	Motzer et al. ASCO 2014
			Ovarian	17% (18)	Hamanishi ASCO 2014
Pembrolizumab	Merck	PD-1	Melanoma	40% (113)	Daud et al. AACR 2014
			NSCLC	19% (146)	Gandhi et al. AACR 2014
			Melanoma	34% (411)	Ribas et al. ASCO 2014
			NSCLC	26% (45)	Rizvi et al. ASCO 2014
			Head & Neck	18% (55)	Selwert et al. ASCO 2014
CT-011	Curetech	PD-1	Hematologic Cancers	33% (17)	Berger et al. *Clin Cancer Res* 2008
			Melanoma	6% (101)	Atkins et al. ASCO 2014
AMP-224	Amplimmune/ GSK	PD-1	Solid tumors	Response, SD (42)	Infante et al. ASCO 2013

Efficacy of PD-1 Agents

Drug	Sponsor	Target	Disease Type	Response (n)	Reference
Nivolumab	BMS	PD-1	Solid Tumors	21% (42)	Topalian et al. *NEJM* 2012
			NSCLC	14% (63)	Antonia et al. WCLC 2013
			Ovarian	17% (18)	Hamanishi et al. ASCO 2014
Pembrolizumab	Merck	PD-1	NSCLC	19% (146)	Gandhi et al. AACR 2014
			NSCLC	26% (45)	Rizvi et al. ASCO 2014
			Head & Neck	18% (55)	Selwert et al. ASCO 2014
CT-011	Curetech	PD-1	Hematologic Cancers	33% (17)	Berger et al *Clin Cancer Res* 2008
AMP-224	Amplimmune/ GSK	PD-1	Solid tumors	Response, SD (42)	Infante et al. ASCO 2013

Efficacy of PD-L1 Agents

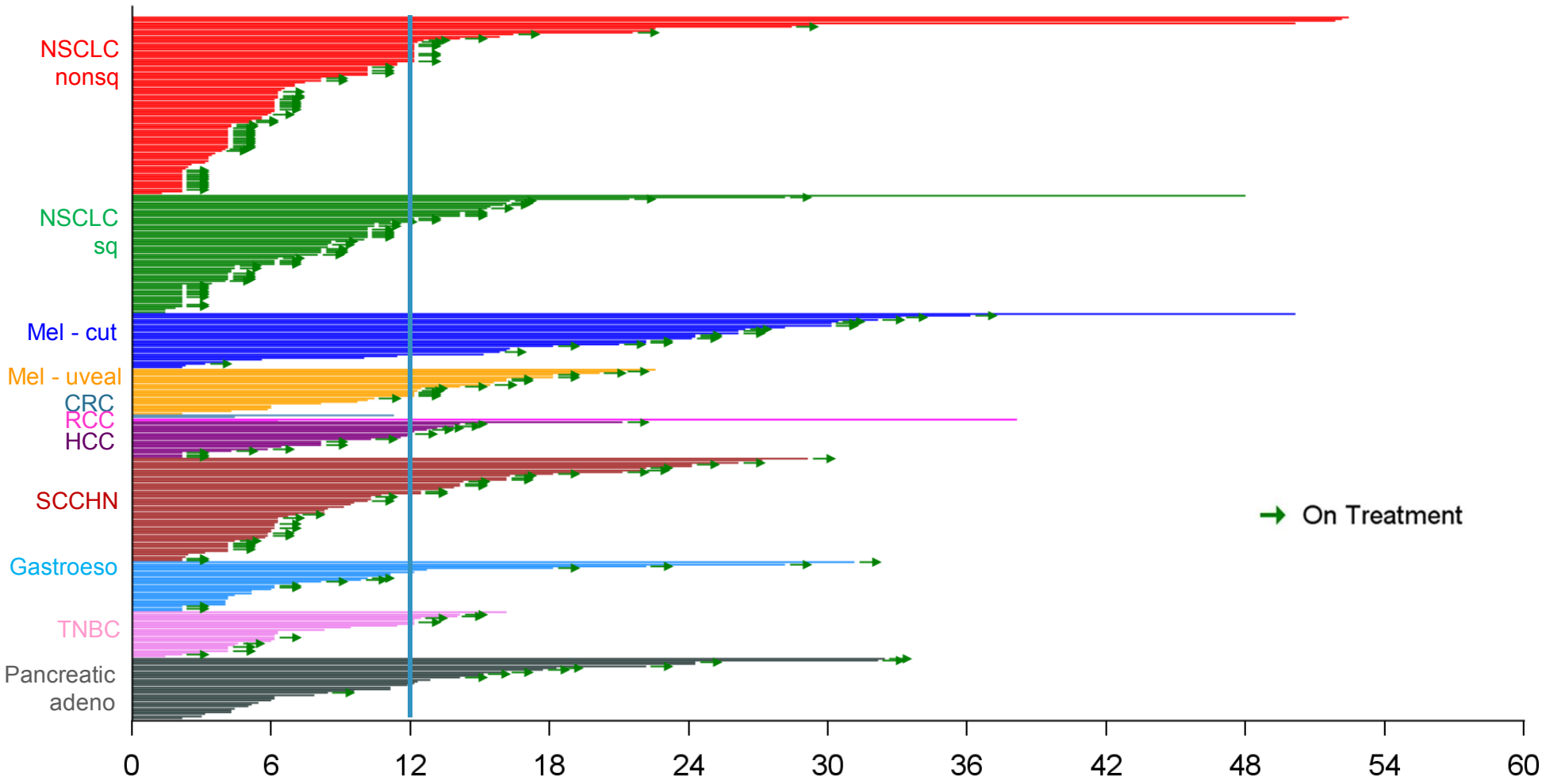
Drug	Sponsor	Target	Disease Type	Response (n)	Reference
MPDL3280a	Genentech	PD-L1	Solid Tumors	21% (103)	Herbst et al. ASCO 2013
			Melanoma	23% (30)	Hamid et al. ASCO 2013
			NSCLC	23% (53)	Sorial et al. ECC 2013
			Bladder	26% (65)	Powels et al. ASCO 2014
MEDI4736	MedImmune	PD-L1	Solid Tumors	11% (179)	Segal et al. ASCO 2014
			NSCLC	16% (58)	Brahmer et al ASCO 2014
			Head & Neck	14% (22)	Segal et al. ASCO 2014
			Gastric	19% (16)	Segal et al. ASCO 2014
MSB0010718C	EMD Serono	PD-L1	Solid tumors	Response (27)	Heery et al. ASCO 2014
MDX - 1105	BMS	PD-L1	Solid Tumors	17% (135)	Brahmer et al. *NEJM* 2012

Efficacy of PD-L1 Agents

Drug	Sponsor	Target	Disease Type	Response (n)	Reference
MPDL3280a	Genentech	PD-L1	Solid Tumors	21% (103)	Herbst et al. ASCO 2013
			[redacted]	[redacted]	[redacted]
			NSCLC	23% (53)	Sorial et al. ECC 2013
			Bladder	26% (65)	Powels et al. ASCO 2014
MEDI4736	MedImmune	PD-L1	Solid Tumors	11% (179)	Segal et al. ASCO 2014
			NSCLC	16% (58)	Brahmer et al ASCO 2014
			Head & Neck	14% (22)	Segal et al. ASCO 2014
			Gastric	19% (16)	Segal et al. ASCO 2014
MSB0010718C	EMD Serono	PD-L1	Solid tumors	Response (27)	Heery et al. ASCO 2014
MDX - 1105	BMS	PD-L1	Solid Tumors	17% (135)	Brahmer et al. *NEJM* 2012

All patients, all doses (n=367)

Majority Remain on Treatment

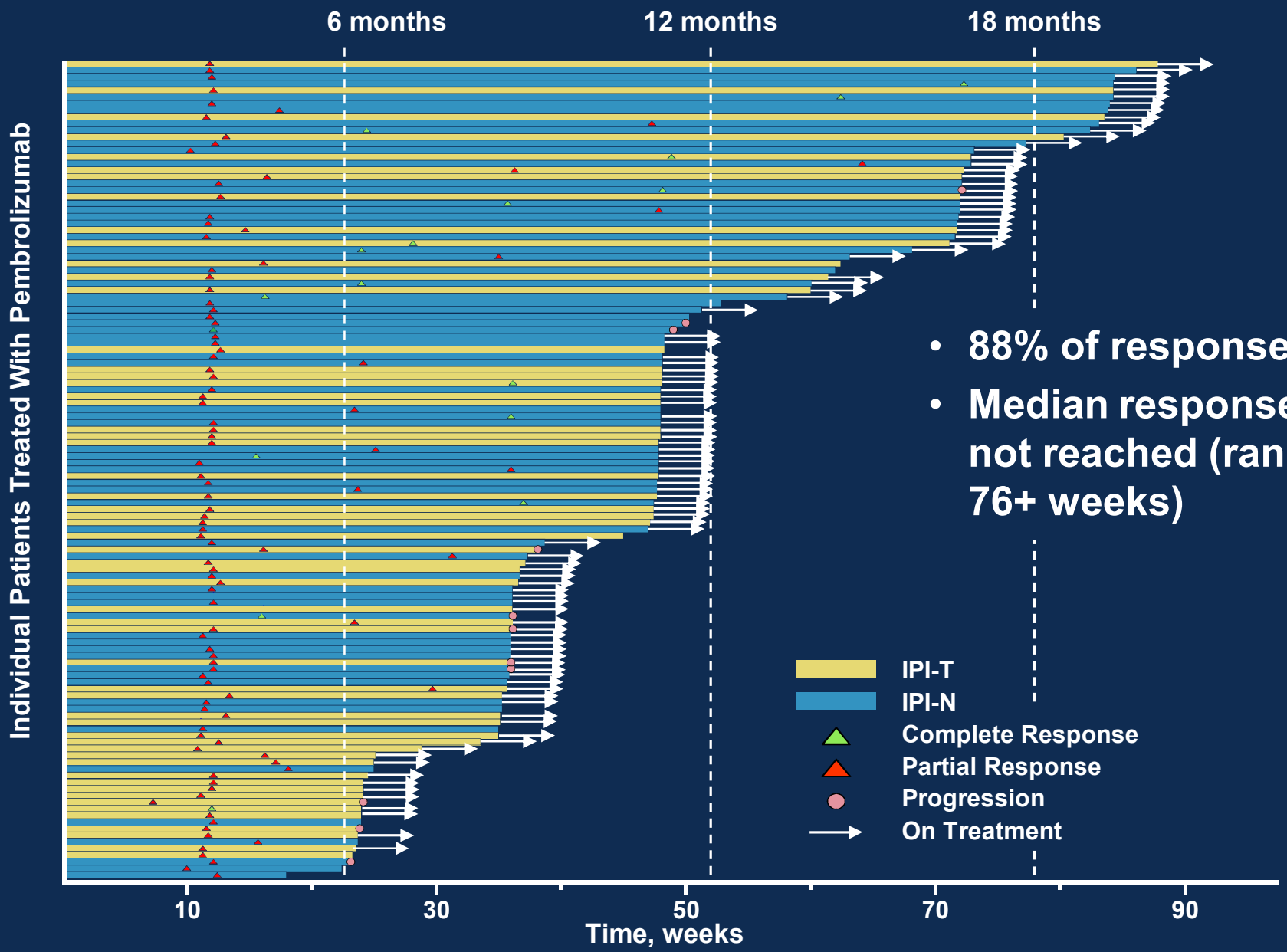


NSCLC, non-small cell lung cancer; nonsq, non-squamous; sq, squamous, Mel, melanoma; Cut, cutaneous; CRC, colorectal cancer, RCC, renal cell carcinoma; HCC, hepatocelluar carcinoma; SCCHN, squamous cell carcinoma of the head and neck; Gastroeso, gastroesophageal; TNBC, triple negative breast cancer; Adeno, adenocarcinoma

Median duration of treatment is 8 weeks (range: 0–52 weeks)

Data cut-off: May 18, 2014

Time to and Durability of Response (Central Review, RECIST v1.1)



- 88% of responses ongoing[a]
- Median response duration not reached (range, 6+ to 76+ weeks)

[a]Ongoing response defined as alive, progression free, and without new anticancer therapy.
Analysis cut-off date: October 18, 2013.

Confirmed Objective Response Rate (ORR) by Dosing Regimen and Prior Ipilimumab Treatment

Lambrolizumab Dose	Prior IPI Treatment	RECIST 1.1, Independent Central Review			irRC, Investigator Assessment	
		N	ORR, % (95% CI)	Response Duration Range, mo	N	ORR, % (95% CI)
Total		117	38 (25–44)*	1.9+ – 10.8+	135	37 (29–45)
10 mg/kg Q2W	Naive	39	49 (32–65)	1.9+ – 10.8+	41	56 (40–72)
	Treated	13	62 (32–86)	2.8+ – 8.3+	16	56 (30–80)
	Total	52	52 (38–66)	1.9+ – 10.8+	57	56 (42–69)
10 mg/kg Q3W	Naive	19	26 (9–51)	2.6 – 5.6+	24	33 (16–55)
	Treated	26	27 (12–48)	2.8+ – 8.3+	32	22 (9–40)
	Total	45	27 (15–42)	2.6 – 8.3+	56	27 (16–40)
2 mg/kg Q3W	Naive	20	25 (9–49)	2.1+ – 5.5+	22	14 (3–35)

*Including unconfirmed responses, ORR was 44% across all doses and 56% for 10 mg/kg Q2W, 36% for 10 mg/kg Q3W, and 35% for 2 mg/kg Q3W.
"+" indicates censored observation.

Reinduction – tumor activity with both ipilimumab and nivolumab

Cancer Therapy: Clinical

Clinical Cancer Research

Durable Cancer Regression Off-Treatment and Effective Reinduction Therapy with an Anti-PD-1 Antibody

Evan J. Lipson[1], William H. Sharfman[1,3], Charles G. Drake[1,2], Ira Wollner[6], Janis M. Taube[3,4], Robert A. Anders[4], Haiying Xu[4], Sheng Yao[1,3], Alice Pons[1], Lieping Chen[1,3], Drew M. Pardoll[1], Julie R. Brahmer[1], and Suzanne L. Topalian[5]

Clin Cancer Res; 19(2) January 15, 2013

Cancer Therapy: Clinical

Clinical Cancer Research

Efficacy and Safety of Retreatment with Ipilimumab in Patients with Pretreated Advanced Melanoma Who Progressed after Initially Achieving Disease Control

Caroline Robert[1], Dirk Schadendorf[2], Marianne Messina[3], F. Stephen Hodi[4], and Steven O'Day[5], for the MDX010-20 investigators

Clinical Cancer Res; 19 (8) 2232-9

What about toxicity ?

Monitor for the Following Signs and Symptoms

GASTROINTESTINAL

Signs and symptoms such as

- Diarrhea
- Abdominal pain
- Blood or mucus in stool
- Bowel perforation
- Peritoneal signs
- Ileus
- Fever

In symptomatic patients, rule out infectious etiologies

Consider endoscopic evaluation for persistent or severe symptoms

LIVER

Signs such as

- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

Rule out infectious or malignant causes

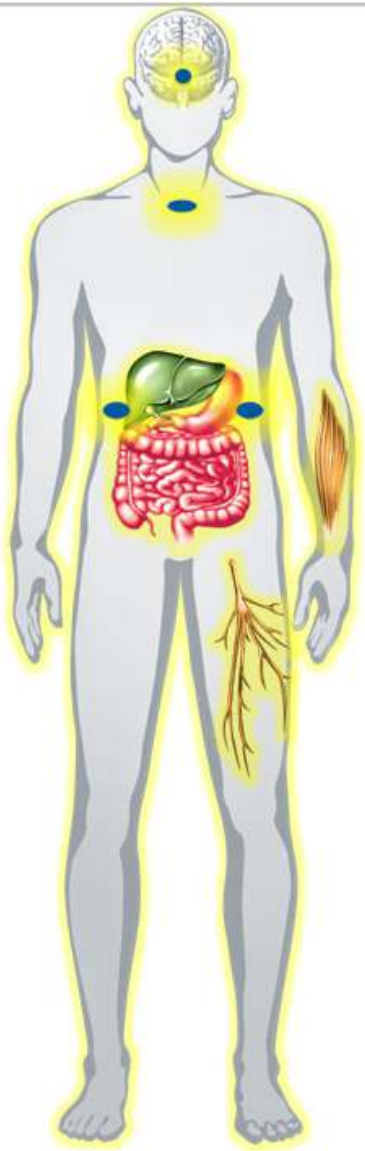
Increase frequency of LFT monitoring until resolution

SKIN

Symptoms such as

- Pruritus
- Rash

Unless an alternate etiology has been identified, signs or symptoms of dermatitis should be considered immune-mediated



NEUROLOGIC

Symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE

Signs and symptoms such as

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries
- Hypophysitis[a]
- Adrenal insufficiency (including adrenal crisis)
- Hyper- or hypothyroidism
- Nonspecific symptoms which may resemble other causes (eg, brain metastasis)

OTHER ADVERSE REACTIONS, including ocular manifestations

[a]In a limited number of patients, hypophysitis was diagnosed by imaging studies through enlargement of the pituitary gland.

® (ipilimumab) package insert. Princeton, NJ: Bristol Myers Squibb Company.

Most Common Immune-Related Adverse Events* (irAEs; All Grades)

% of Patients			
irAE	**Ipi + gp100 N=380**	**Ipi + pbo N=131**	**gp100 + pbo N=132**
All grades			
Any	**58.2**	**61.1**	**31.8**
Dermatologic	**40.0**	**43.5**	**16.7**
GI	**32.1**	**29.0**	**14.4**
Endocrine	**3.9**	**7.6**	**1.5**
Hepatic	**2.1**	**3.8**	**4.5**

***Across entire study duration**

Most Common Immune-Related Adverse Events* (Grades 3, 4 and 5)

% of Patients						
irAE	Ipi + gp100 N=380		Ipi + pbo N=131		gp100 + pbo N=132	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any	9.7	0.5	12.2	2.3	3.0	0
Dermatologic	2.1	0.3	1.5	0	0	0
GI	5.3	0.5	7.6	0	0.8	0
Endocrine	1.1	0	2.3	1.5	0	0
Hepatic	1.1	0	0	0	2.3	0
Death due to irAE	1.3		1.5		0	

*Across entire study duration

Treatment-Related AEs With Incidence >5%

Adverse Event, %	Total N = 411	
	Any Grade	Grade 3/4
Fatigue	36	2
Pruritus	24	<1
Rash	20	<1
Diarrhea	16	<1
Arthralgia	16	0
Nausea	12	<1
Vitiligo	11	0
Asthenia	9	0
Cough	9	0

Adverse Event, n (%)	Total N = 411	
	Any Grade	Grade 3/4
Myalgia	9	0
Headache	8	<1
Hypothyroidism	8	<1
Decreased appetite	7	<1
Dyspnea	7	<1
Chills	6	0
Pyrexia	6	0
ALT increased	5	<1
Total	83	12

- No treatment-related deaths
- Similar safety profiles in IPI-N and IPI-T patients

Analysis cut-off date: October 18, 2013.

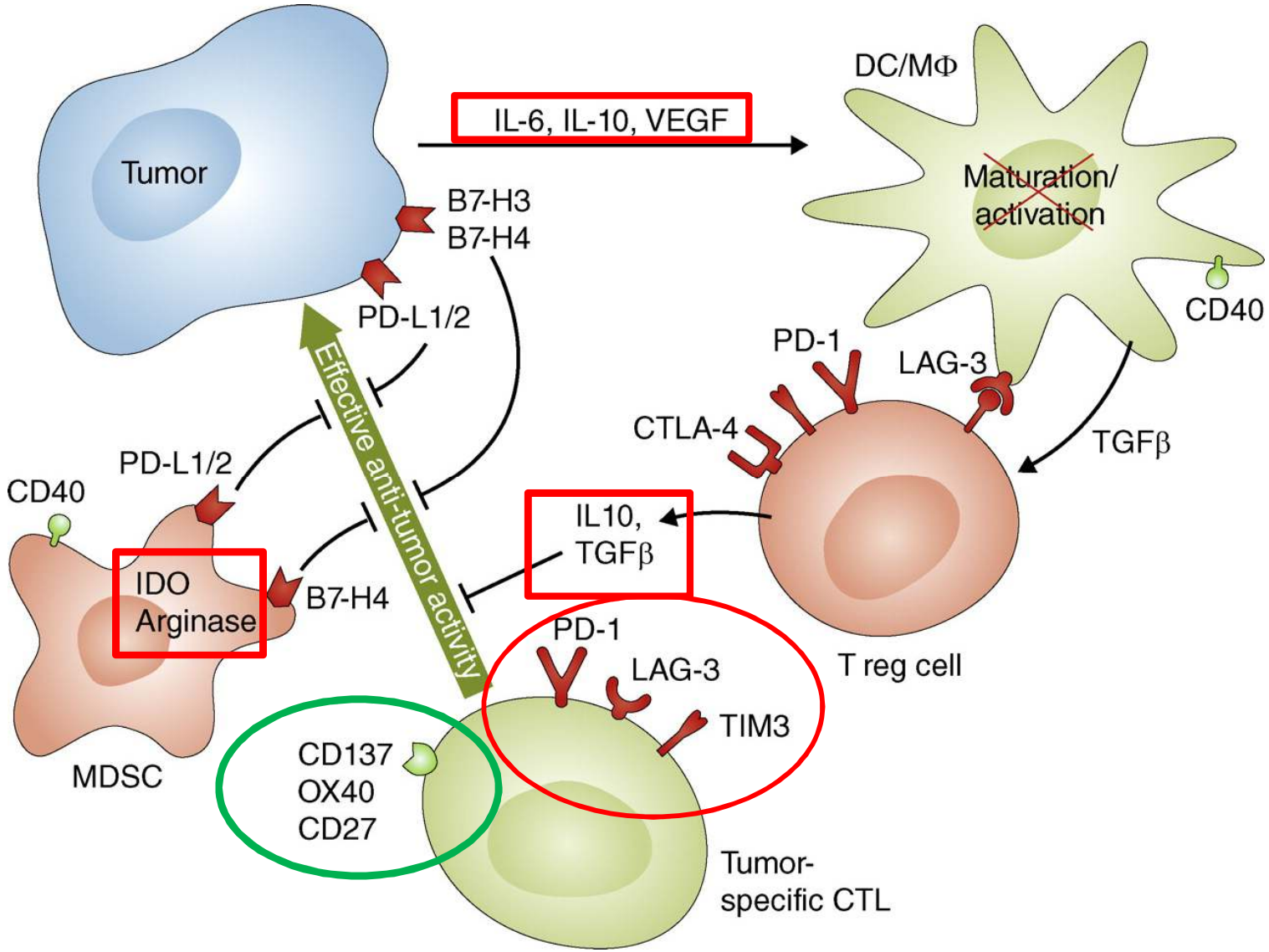
Immune-Mediated AEs

Adverse Event, n (%)	Any Grade	Grade 3-4
Hypothyroidism	32 (8)	1 (<1)
Hyperthyroidism	4 (1)	1 (<1)
Pneumonitis[a]	11 (3)	1 (<1)
Colitis	3 (<1)	2 (<1)
Hepatitis[b]	2 (<1)	1 (<1)

- Some reported skin rashes may have been immune-mediated
- The following potentially immune-mediated AEs were reported in <1% of patients: nephritis, hypophysitis, and uveitis

[a]1 additional patient experienced interstitial lung disease of grade 1-2.
[b]Includes autoimmune hepatitis.
Analysis cut-off date: October 18, 2013.

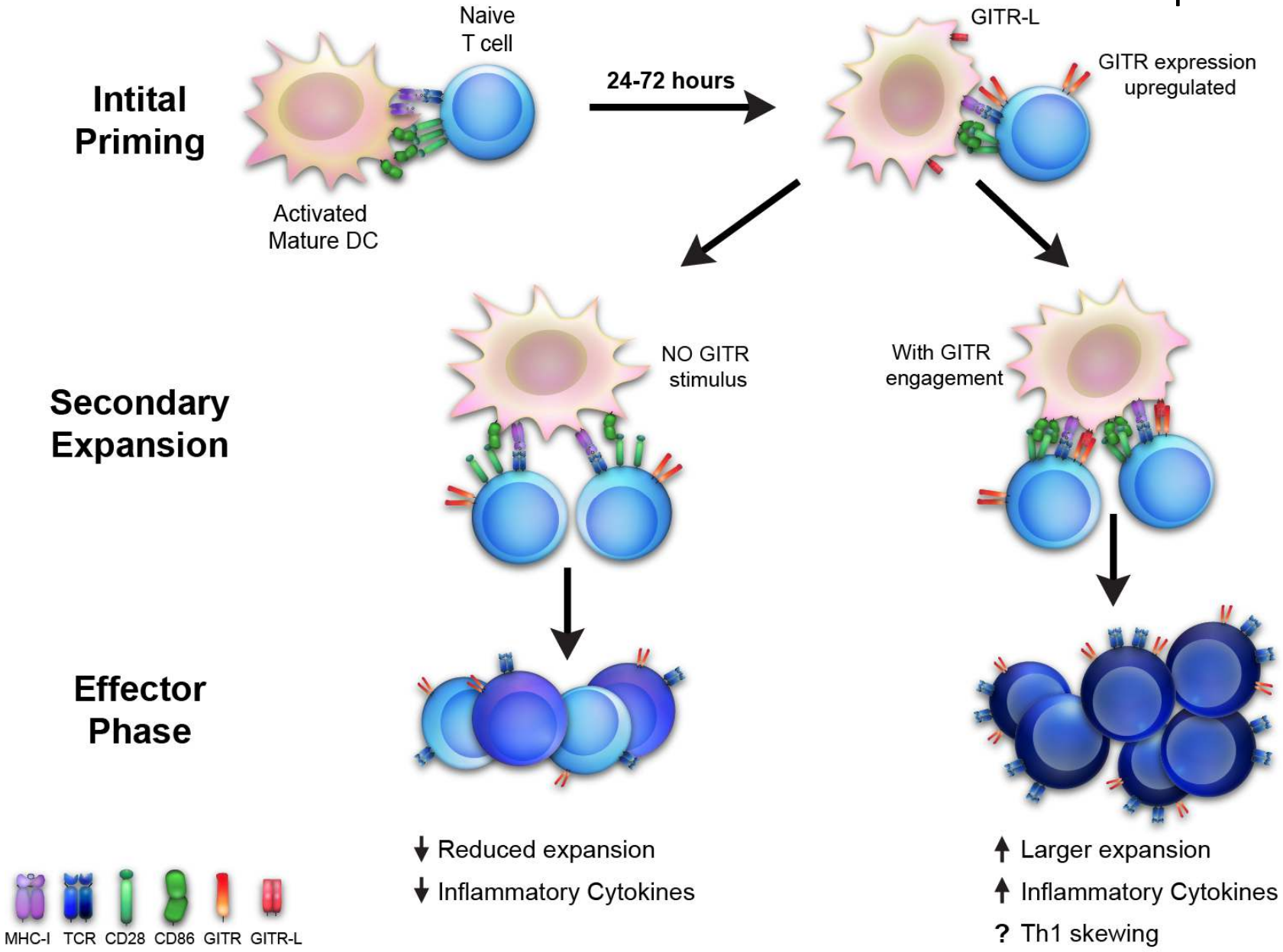
Effective anti-tumor immunotherapy



Pardoll and Drake, J Exp Med, 2012

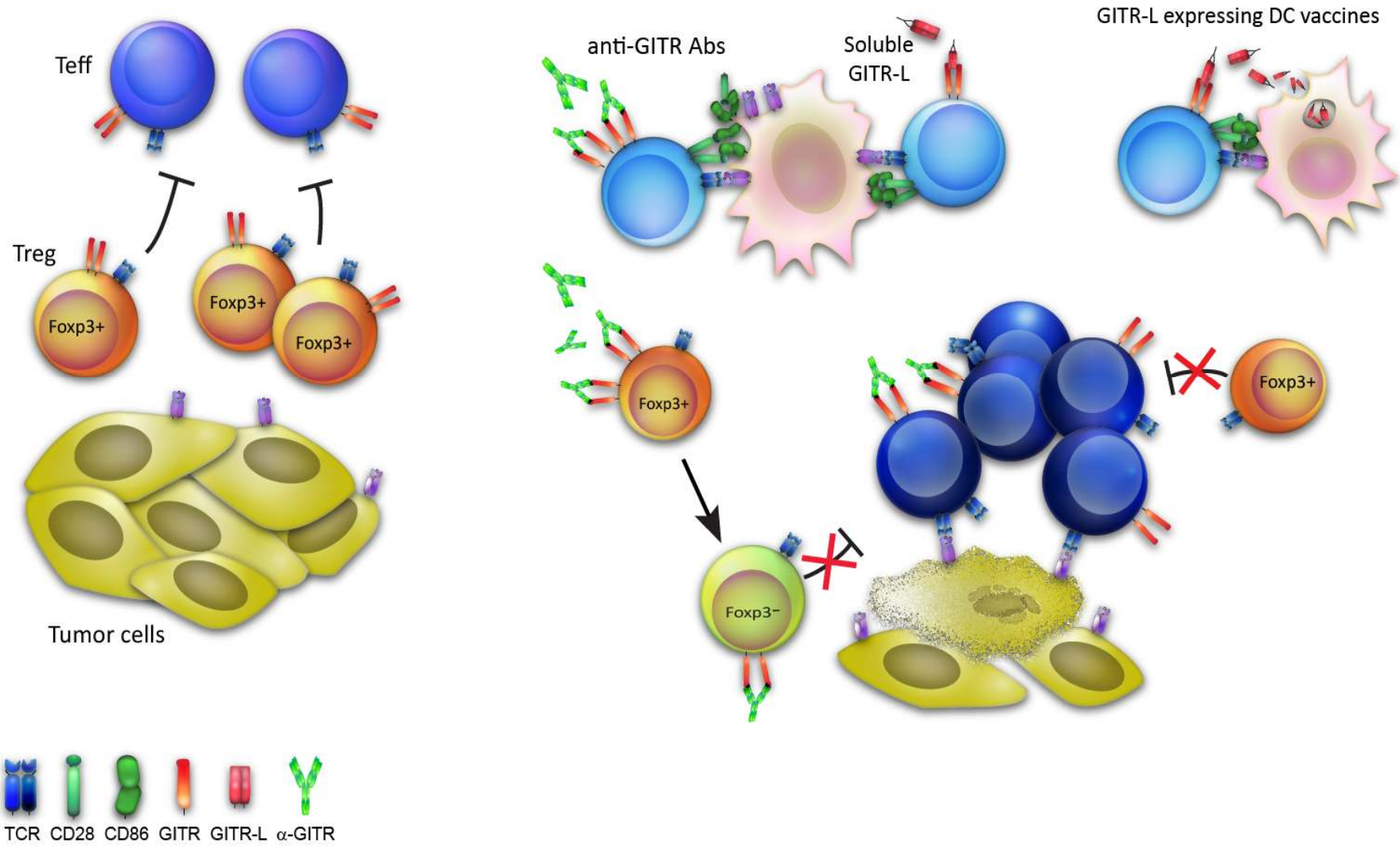
Future Checkpoint Inhibitors

GITR: a model of **AGONIST** stimulation for effector T cell expansion



Schaer, Murphy & Wolchok Current Opinion in Immunology 2012, 24:217–224

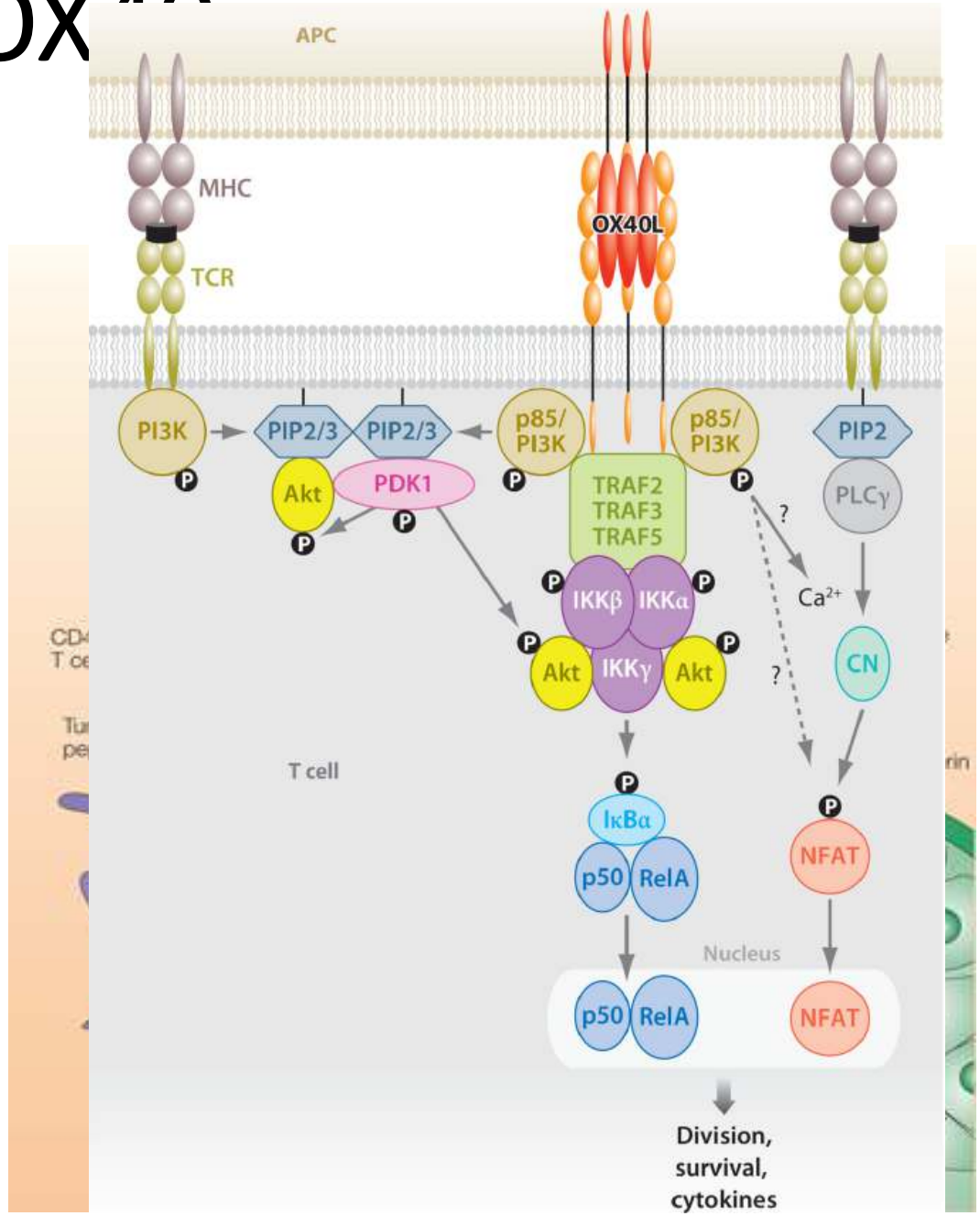
Preclinical Modeling of GITR as an Agonist T Cell Immunotherapy



Cohen & Schaer et al. PloS ONE 2010 May 3;5(5)
Schaer et al. Cancer Immunology Research 2013 Nov 5
Schaer, Murphy & Wolchok Current Opinion in Immunology 2012, 24:217–224

OX40

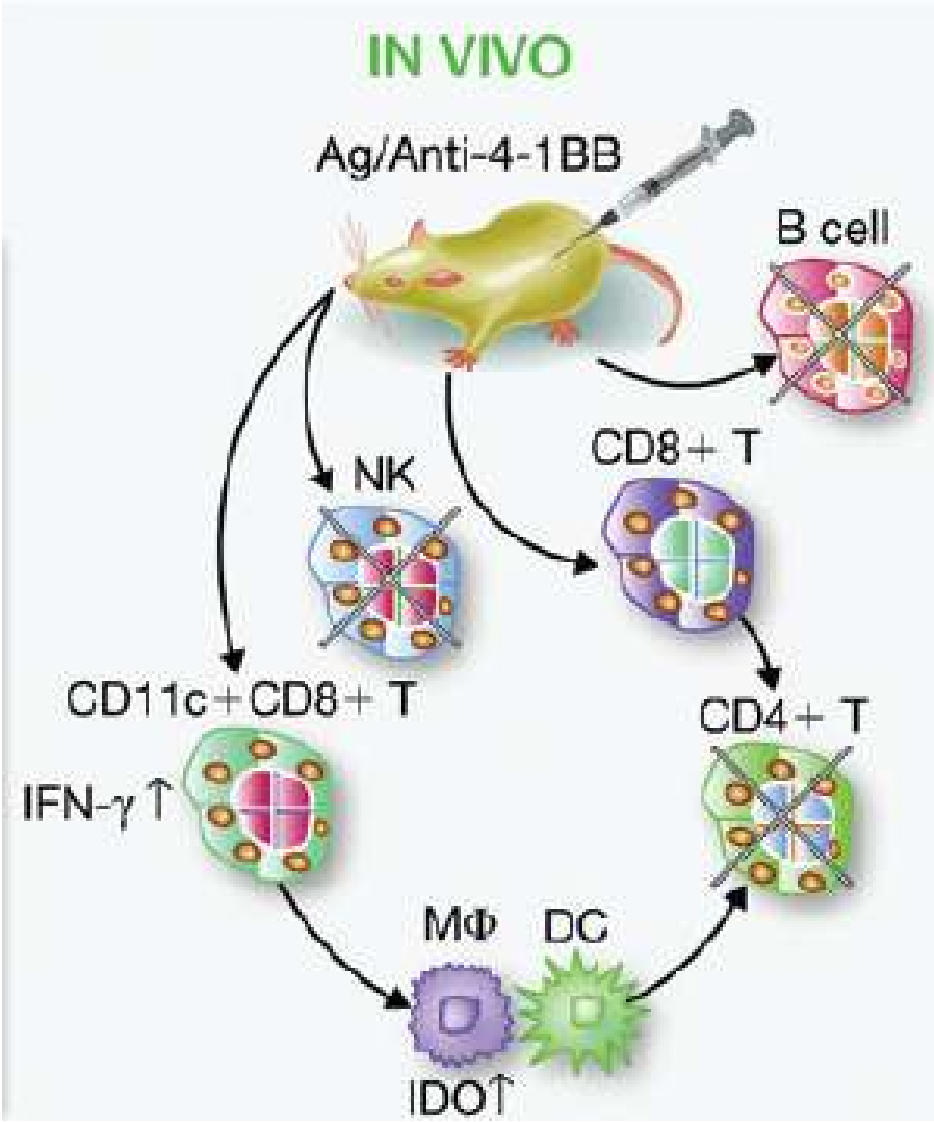
- OX40 agonism augments Ag (tumor) specific T-cell memory response
- Mechanistically distinct from anti-CTLA4
- Phase I: murine anti-human OX40 completed



Sheridan. Nature Biotechnology, 2013 and Croft. Annu Rev Immunol, 2010

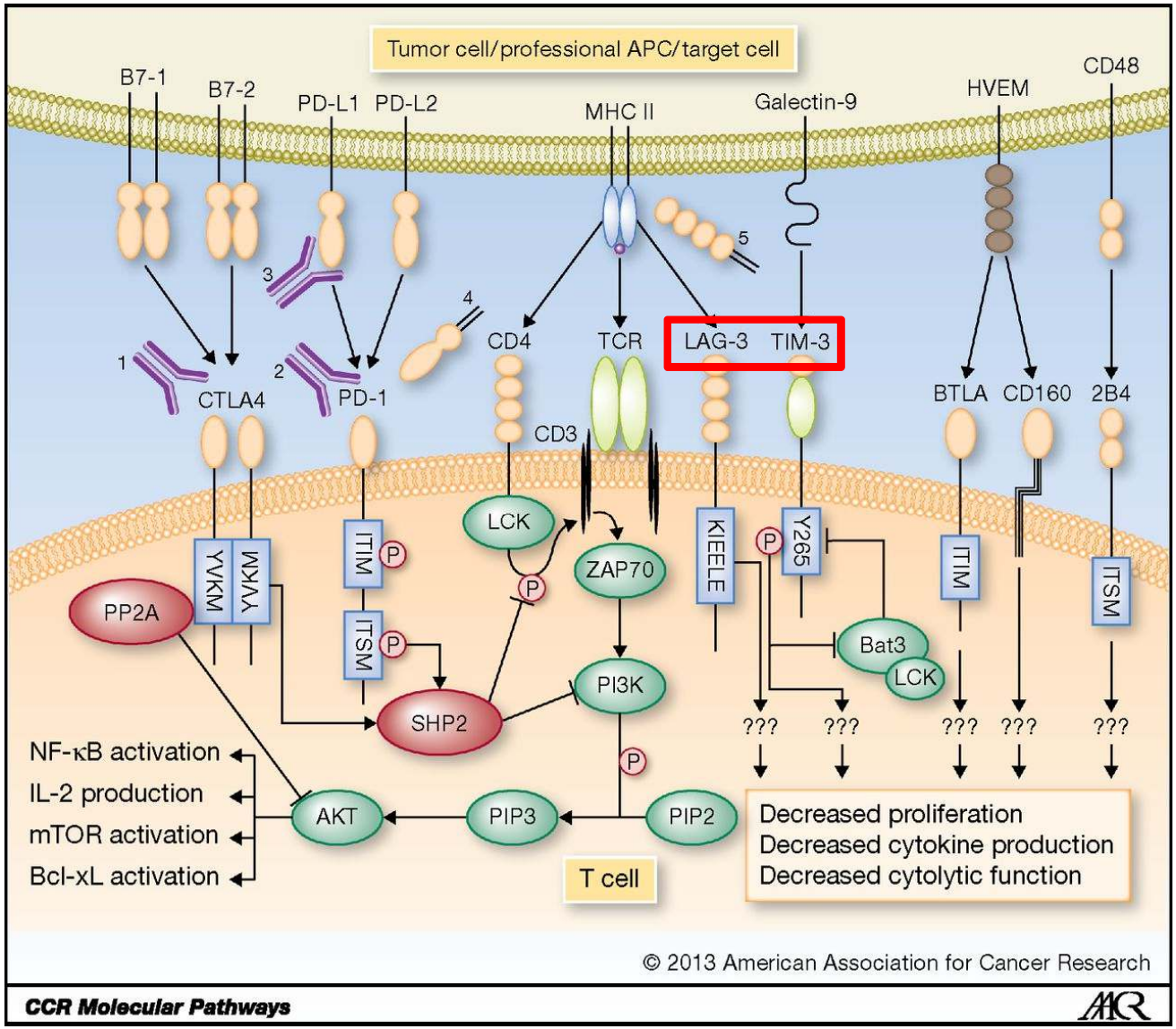
CD137 (4-1bb)

- Expressed broadly
  - $CD4^+$, $CD8^+$ T, B cells, NK, Mϕ, DC
- *In vivo*, biased $CD8^+$ activation
  - ↓ in B, NK, $CD4^+$ in IFN, TNF, TGF and IDO dependent manner
- Prior Phase I:
  - hepatic tox



Kwon. Mol Cancer Ther, 2012

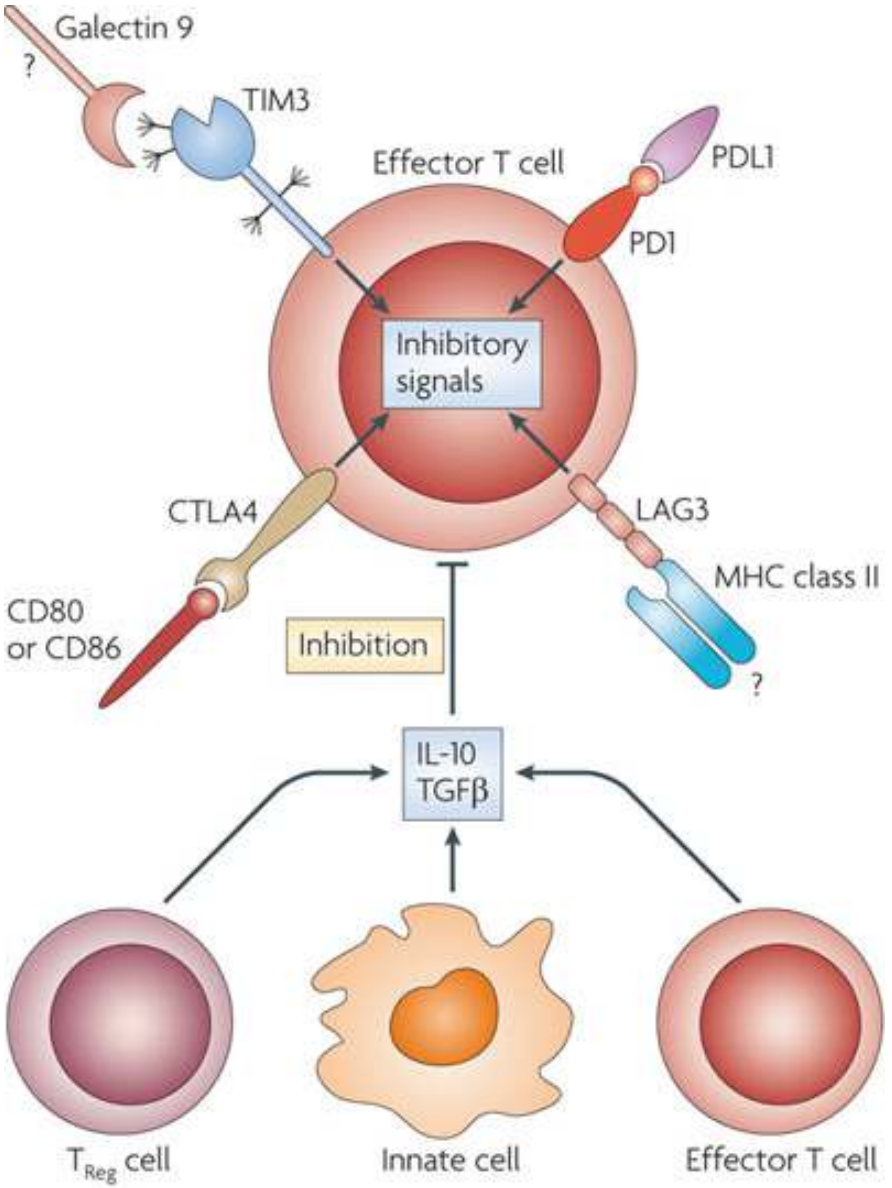
Inhibitory immune-checkpoints



Nirschl and Drake, Clin Can Res, 2013

LAG3 and TIM3

- LAG3 : MHC II
- TIM3 : Galectin 9
- No autoimmune-like phenotype in KO models
- LAG3: Expressed with PD-1 on TIL

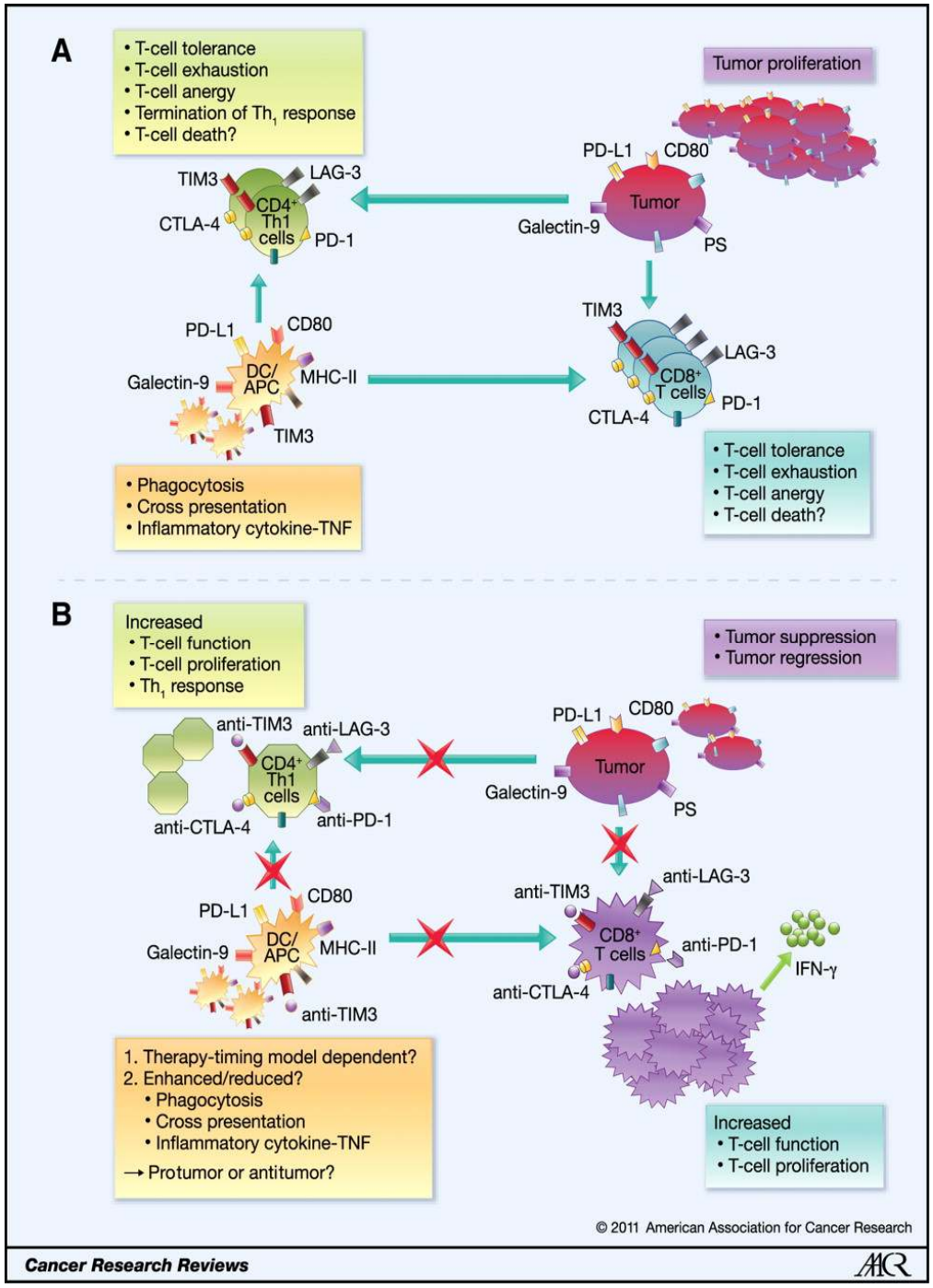


Nature Reviews | Immunology

Rouse and Sehrawat, Nature Reviews Immunology, 2010

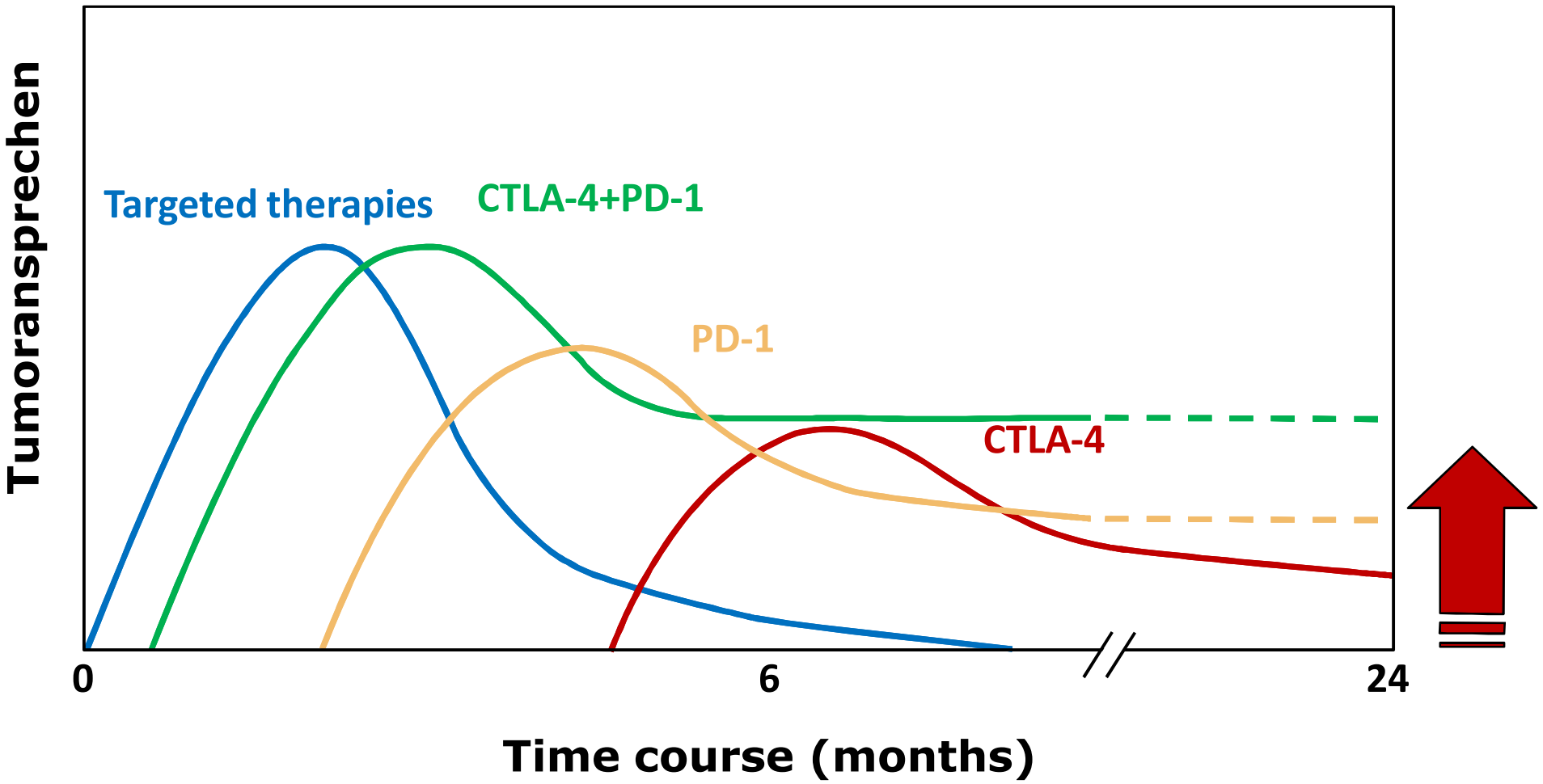
TIM3 and LAG3

- Prolonged Ag presentation by APC & (-) molecules (Gal 9, PD-L1, CD80) lead to T cell exhaustion
- Receptor blockade leads to inflammatory response (INF-γ) and increased Th1 response



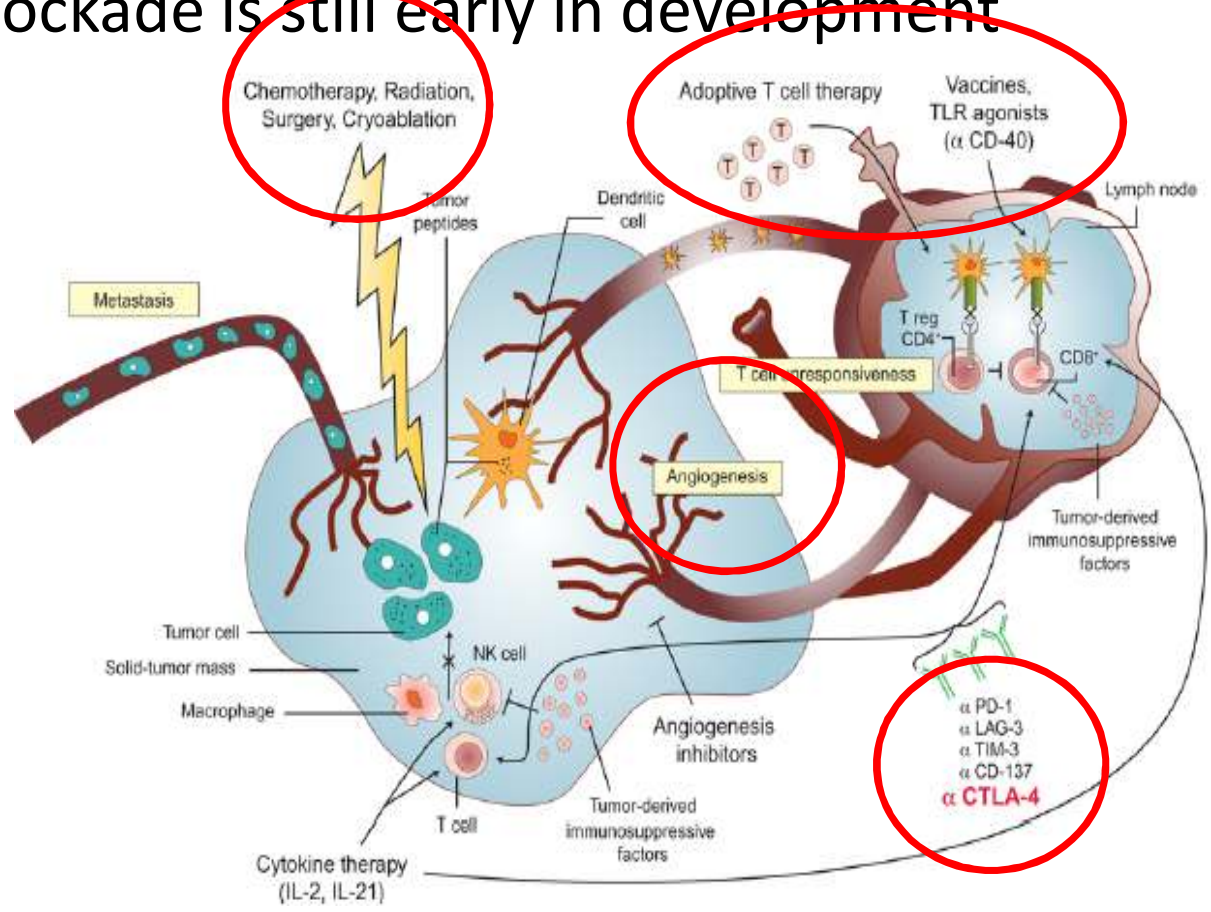
Ngiow *et al*. Cancer Res 2011

Antitumoral response: Targeted therapies vs. Immunotherapies (CTLA-4 antibodies)



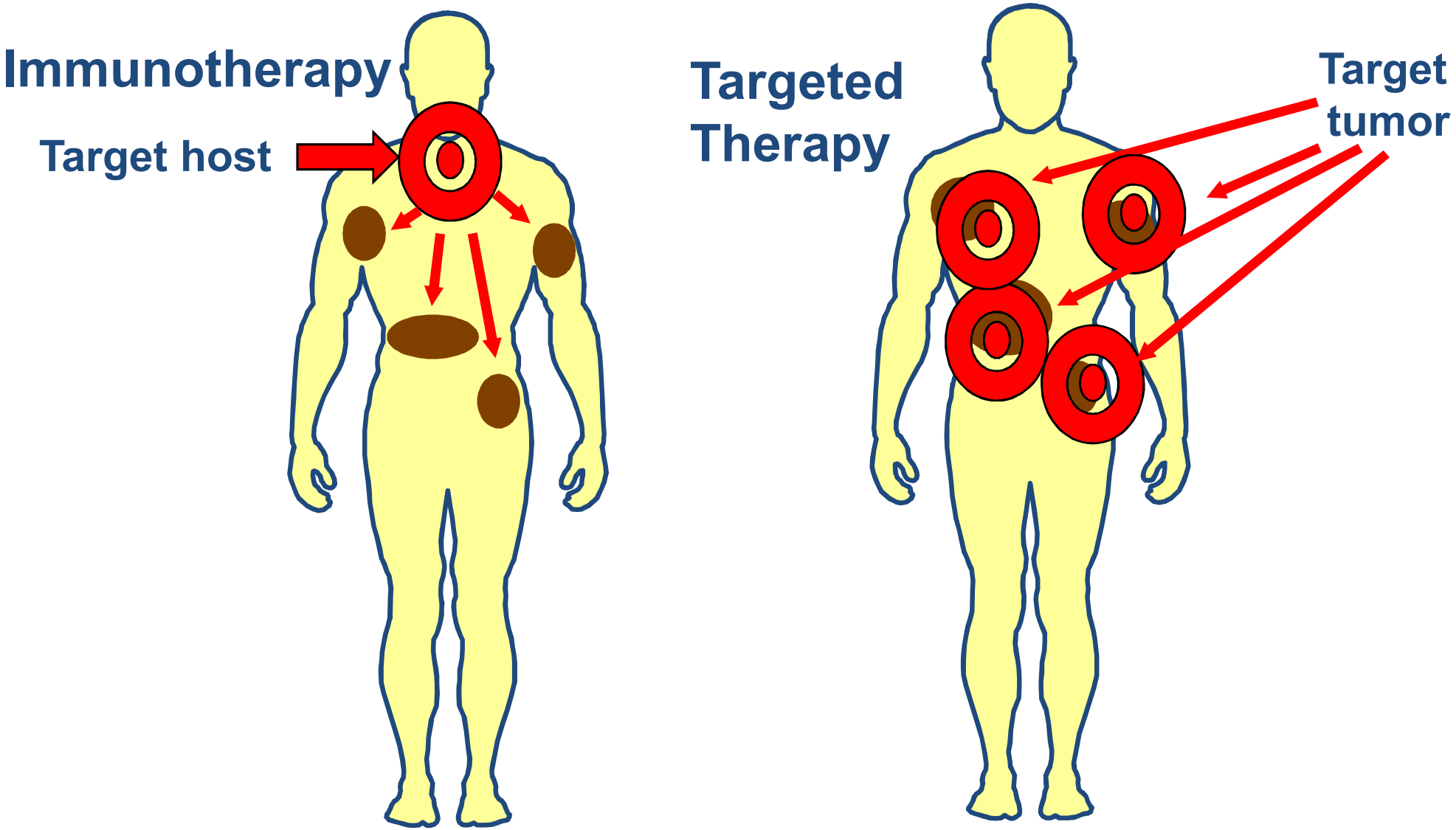
Conclusions

- Immune-checkpoint blockade is still early in development
- Future is likely in combinations
  - **Multiple checkpoints**
    - (PD-1 + LAG3 etc.)
  - **Targeted Therapy**
    - (VEGFi or iNOS modulation + PD-L1)
  - **Radiation**
    - (CTLA-4 or OX40 + RT etc.)
  - **Chemotherapy**
    - (Cyclophosphamide to deplete T_{reg} prior to checkpoint blockade)
  - **Adoptive Cell Therapy**

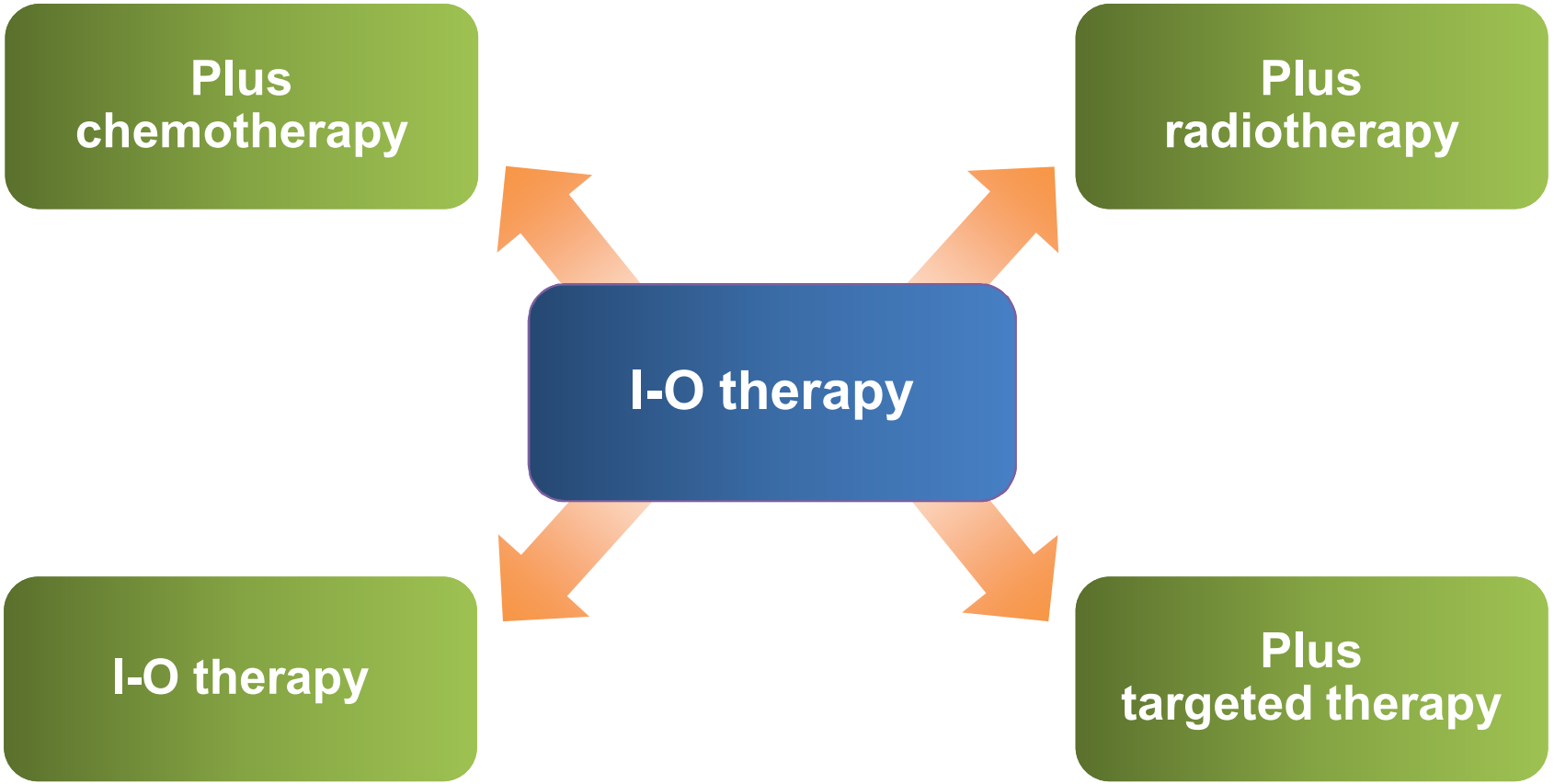


Grosso and Jure-Kunkel, Cancer Immunity, 2013

The future of treatment 2014+



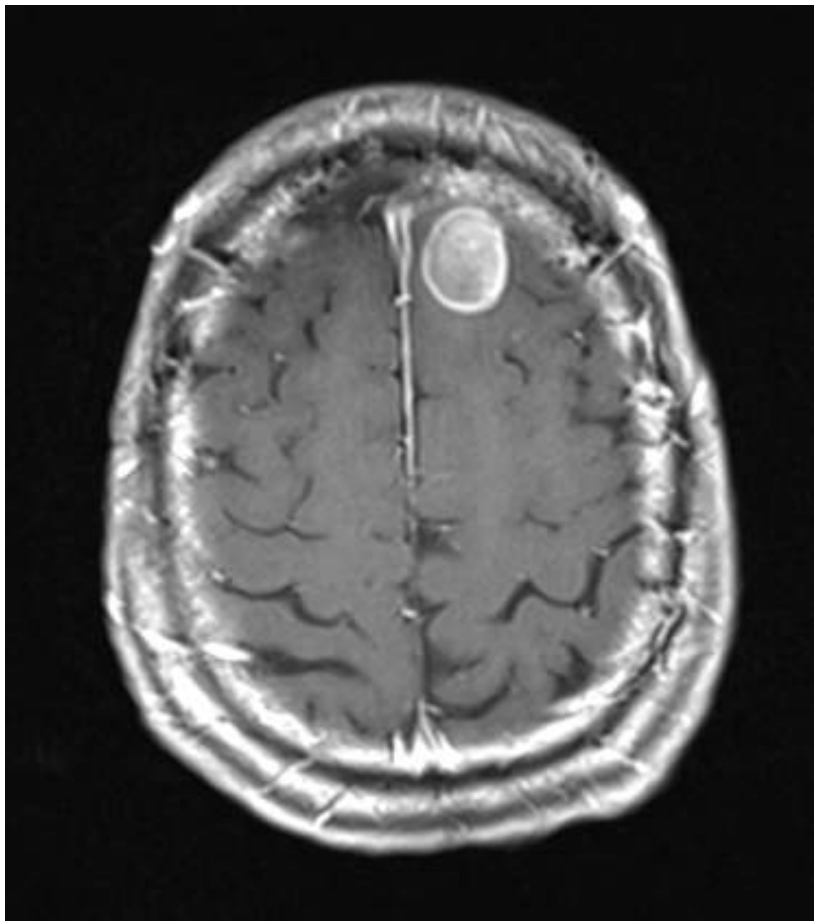
Future Combination Regimens

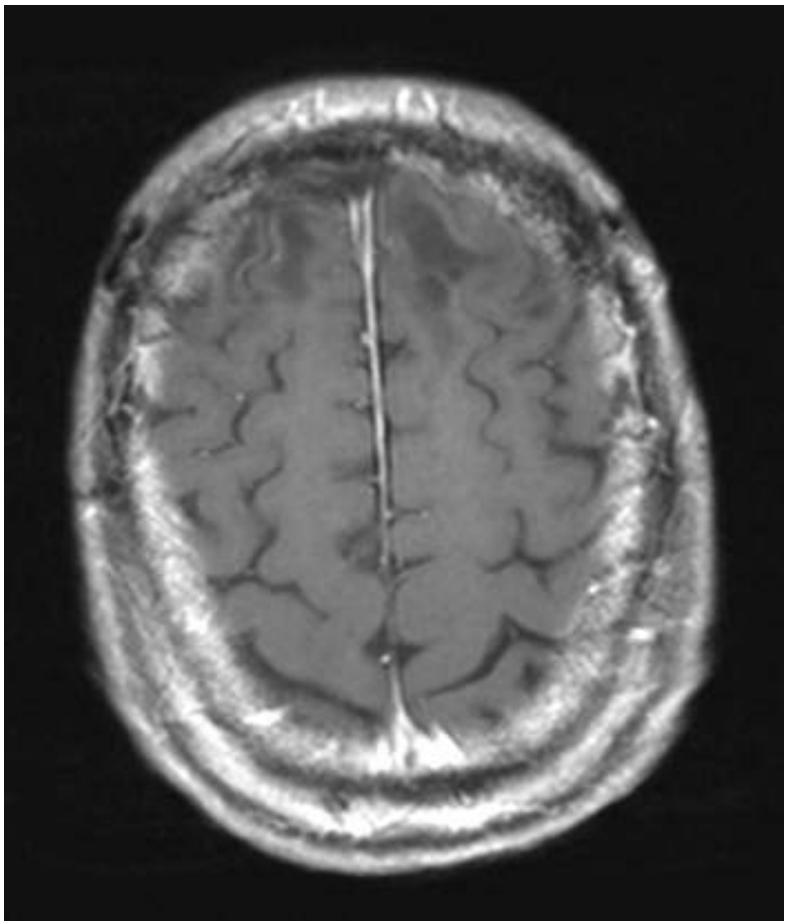


Brain metastases
The final frontier……

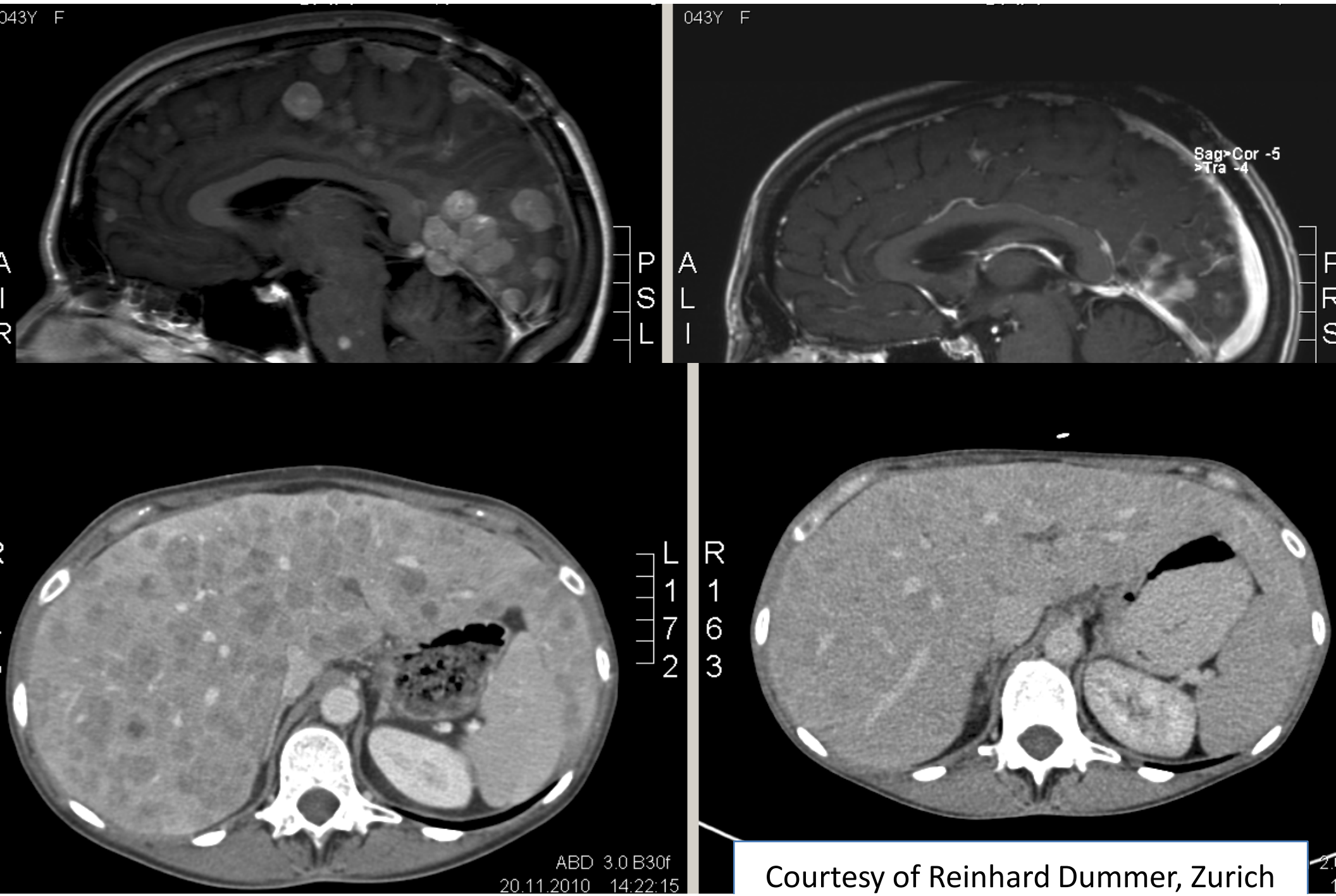
Durable brain responses in two patients

A: Partial response (PR) in brain and PR in total tumor burden, duration 11+ months



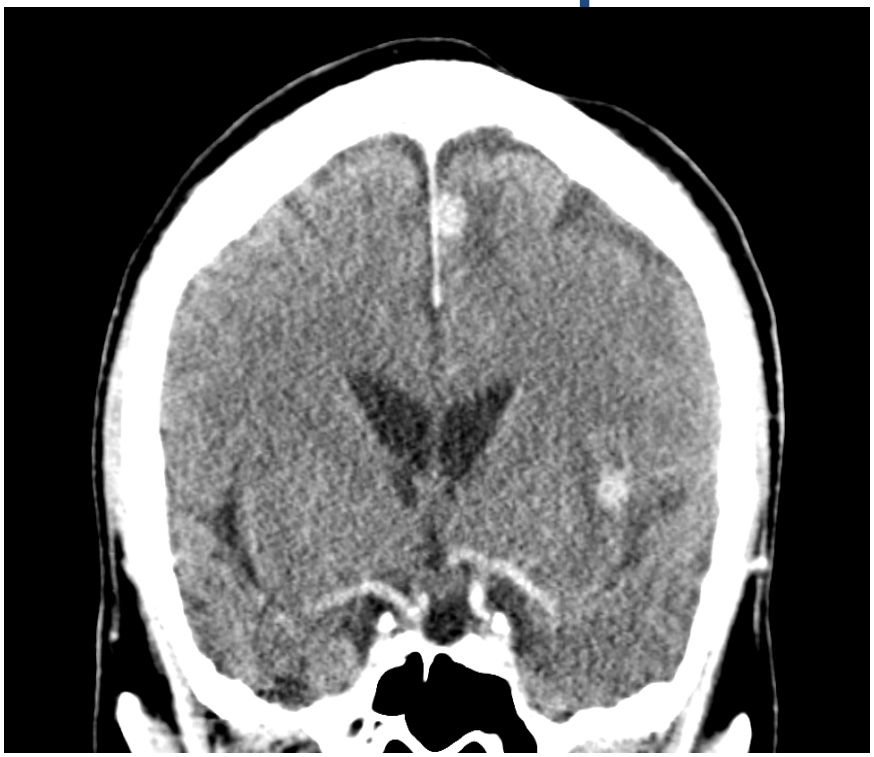


BRAF inhibitors for patients with brain mets

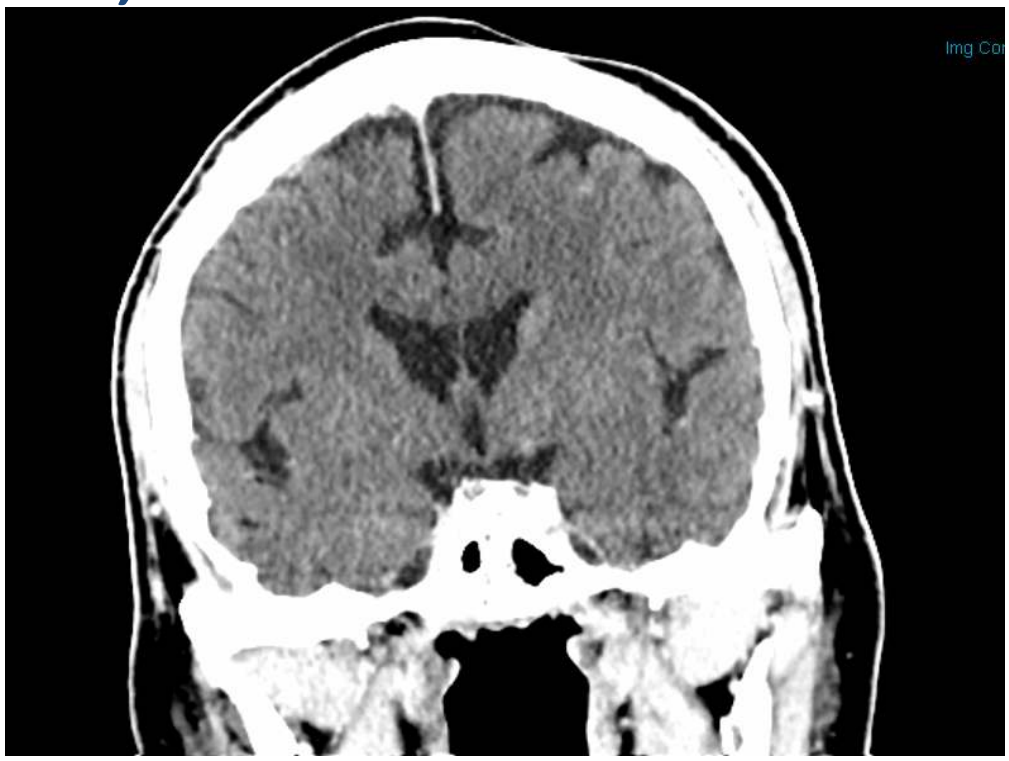


Courtesy of Reinhard Dummer, Zurich

72-year-old Male
Failed Ipilimumab, WBRT. PDL1+



Baseline



Cycle 5 Pembro 2 mg/kg Q3/52

At 30 months:

- CR in brain and lung
- Almost CR in adrenal

Presented by: Richard Kefford

Earlier ? Adjuvant ??

Ipilimumab Versus Placebo After Complete Resection of Stage III Melanoma: Initial Efficacy and Safety Results from the EORTC 18071 Phase III Trial

Eggermont AM,[1] Chiarion-Sileni V,[2] Grob JJ,[3] Dummer R,[4] Wolchok JD,[5] Schmidt H,[6] Hamid O,[7] Robert C,[1] Ascierto PA,[8] Richards JM,[9] Lebbé C,[10] Ferraresi V,[11] Smylie M,[12] Weber JS,[13] Maio M,[14] Konto C,[15] Karra Gurunath R,[16] de Pril V,[17] Suciu S,[16] Testori A[18]

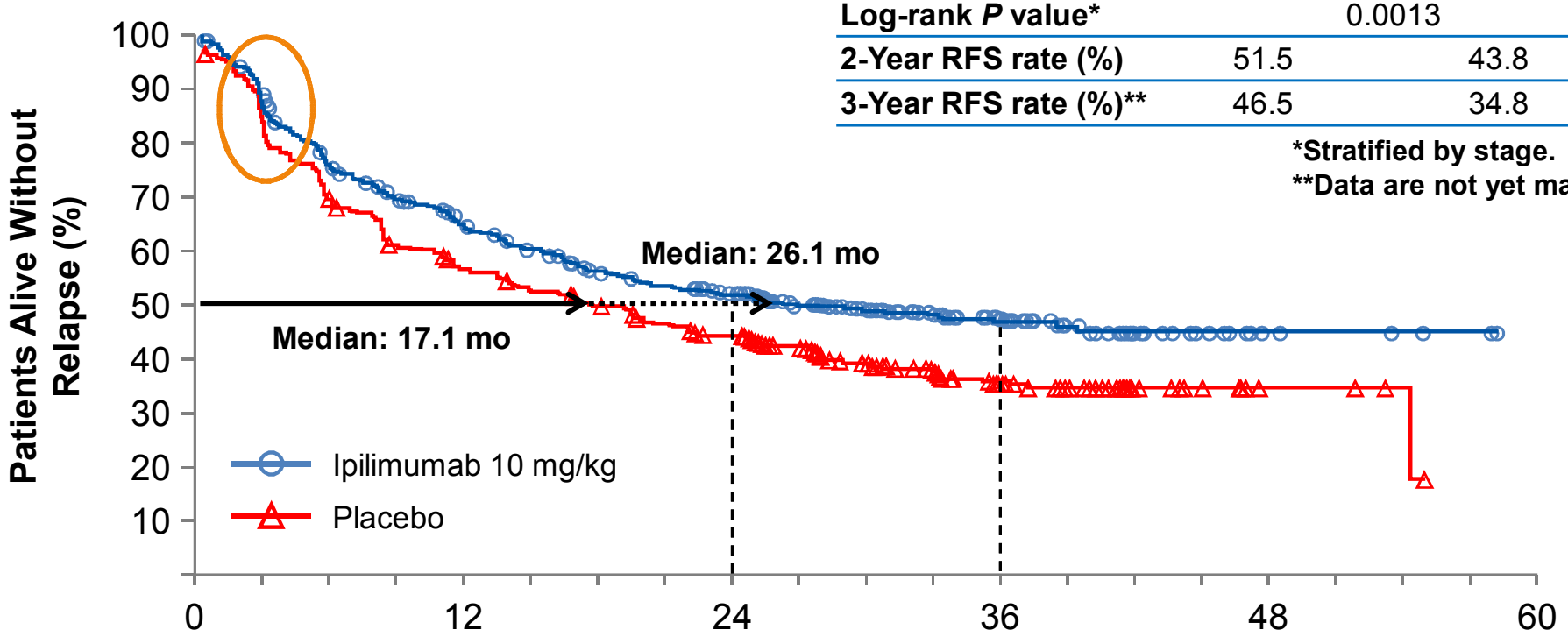
[1]Gustave Roussy Cancer Campus Grand Paris, Villejuif, France; [2]IOV-IRCCS, Melanoma Oncology Unit, Padova, Italy; [3]Hôpital de la Timone, Marseille, France; [4]University of Zürich Hospital, Zürich, Switzerland; [5]Memorial Sloan-Kettering Cancer Center, New York, NY, USA; [6]Aarhus University Hospital, Aarhus, Denmark; [7]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [8]Istituto Nazionale Tumori Fondazione "G. Pascale", Naples, Italy; [9]Oncology Specialists S.C., Park Ridge, IL, USA; [10]Hôpital Saint-Louis, Paris, France; [11]Istituti Fisioterapici Ospitalieri, Rome, Italy; [12]Cross Cancer Institute, Edmonton, Alberta, Canada; [13]H Lee Moffitt Cancer Center, Tampa, FL, USA; [14]University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy; [15]Bristol-Myers Squibb, Wallingford, CT, USA; [16]EORTC Headquarters, Brussels, Belgium; [17]Bristol-Myers Squibb, Braine-l'Alleud, Belgium; [18]European Institute of Oncology, Milan, Italy.

Abstract Number LBA9008

Primary Endpoint: Recurrence-free Survival (IRC)

	Ipilimumab	Placebo
Events/patients	234/475	294/476
HR (95% CI)*	0.75 (0.64–0.90)	
Log-rank *P* value*	0.0013	
2-Year RFS rate (%)	51.5	43.8
3-Year RFS rate (%)**	46.5	34.8

***Stratified by stage.**
****Data are not yet mature.**



Patients at Risk

	O	N					
Ipilimumab	234	475	276	205	67	5	0
Placebo	294	476	260	193	62	4	0

PD-1 in the adjuvant

- Less toxic ?
- More response ?
- Combination ?

Acknowledgments

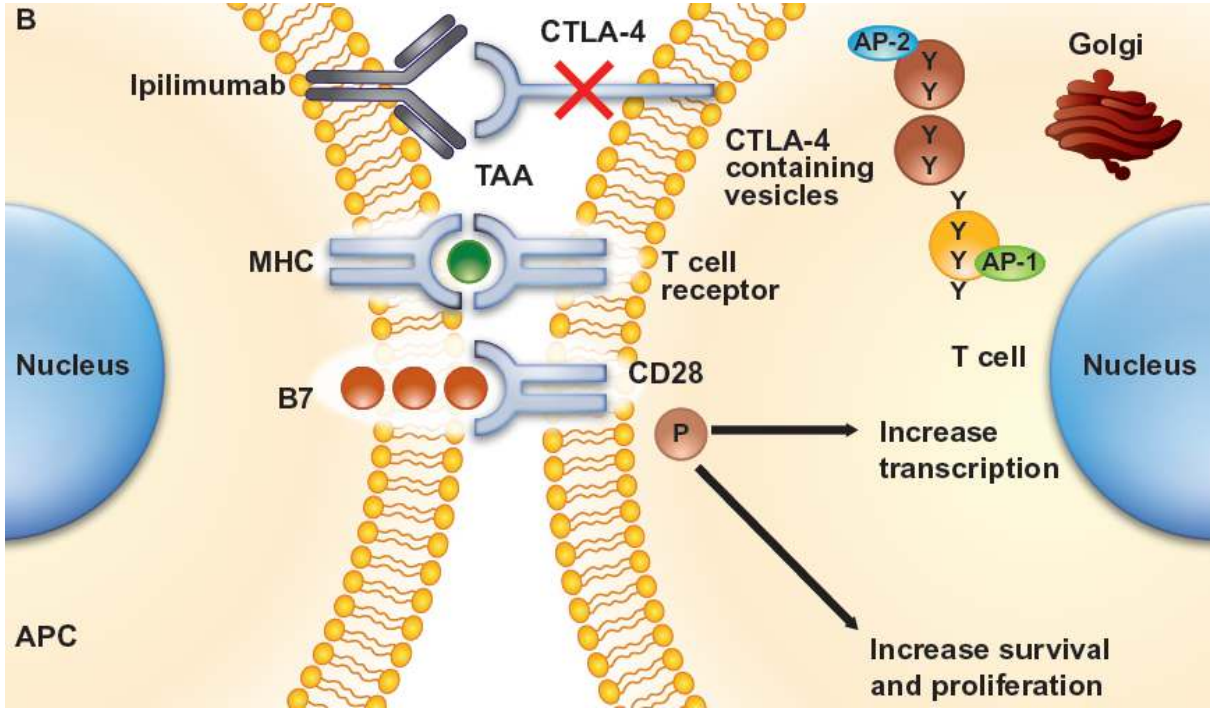
THE PATIENTS AND THEIR FAMILIES!

Categories of immunotherapeutic interventions for cancer

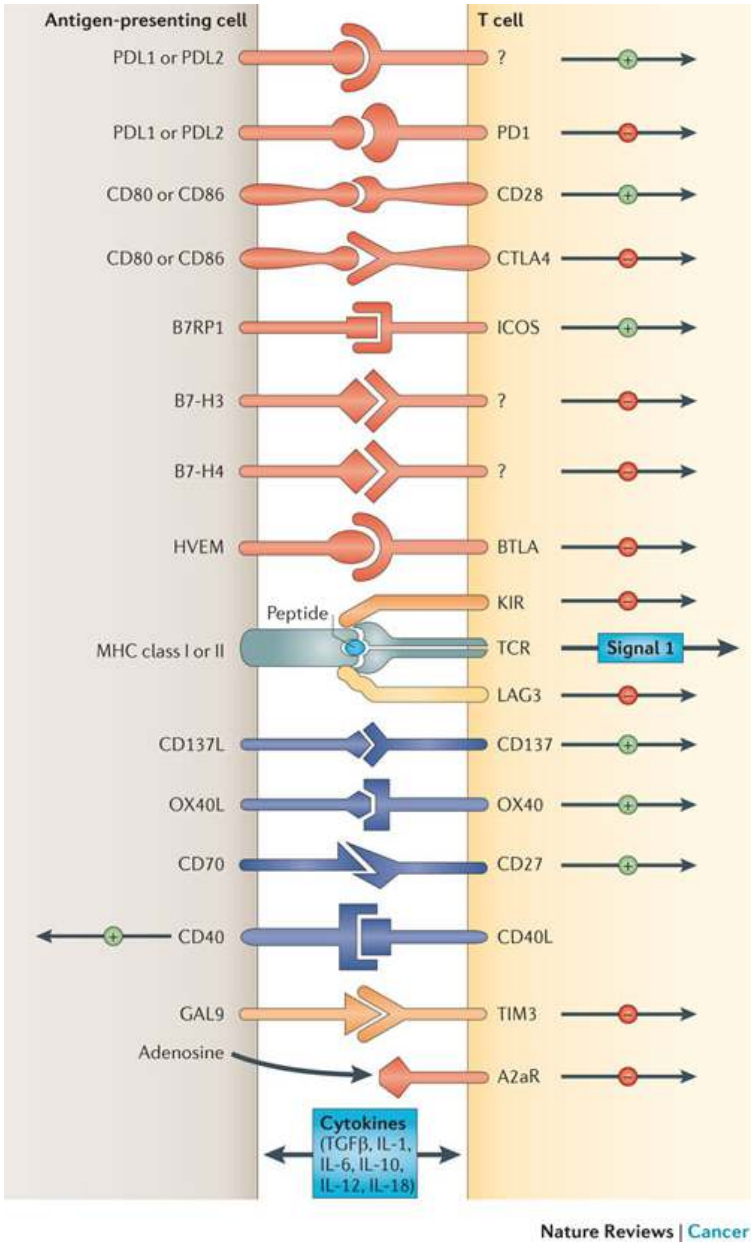
	(I) Increase of T-cell frequencies in circulation	(II) Blocking immune-inhibitory pathways within the tumor microenvironment				(III) De novo induction of immune inflammation in tumor site
		Inhibitory Molecules	Metabolic Dysregulation	Suppressive Cell Types	T-cell Anergy	
BLOCKING	αCTLA-4	PD-1/PDL-1 intervention αB7-H3 αB7-H4	IDO inhibitors Arginase inhibitors	CD25-dependant Treg depletion Depletion of MDSC	αLAG3 αTIM3 EGR2 inhibitors	Blocking inhibitory oncogene pathways (e.g., STAT 3) Blockade of MDSC function or depletion
ENGAGING	αCD28 Homeostatic cytokines Vaccines IL-2 therapy	N/A	N/A	TLR-mediated activation of MDSC	α4-1BB αOX40 Homeostatic cytokines	Induction of type I interferons TLR agonists Radiation TNF-like molecules (e.g., LIGHT)

Spranger and Gajewski, J Immunother Cancer, 2013

Ipilimumab and Immune-Checkpoint Blockade



Luke and Hodi, Oncologist 2013



Pardoll, Nat Rev Can 2012