Apports cliniques des Immunothérapies

(y compris les virus oncolytiques!)

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Drug Development Dpt, Prof JC Soria

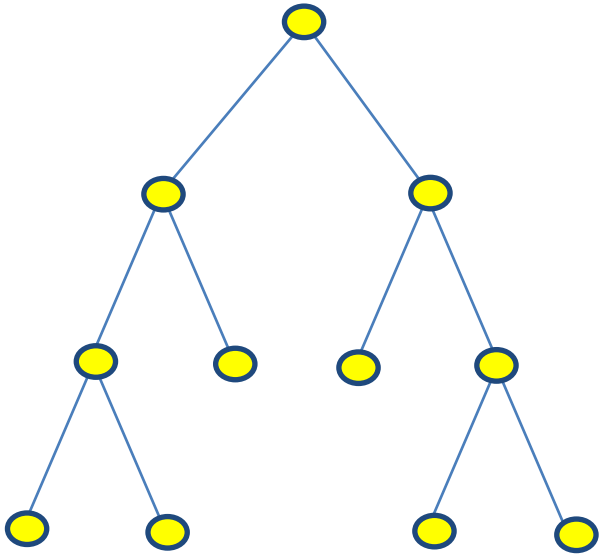
INSERM 1015, Prof L Zitvogel

SFPO, Oct 13th 2016

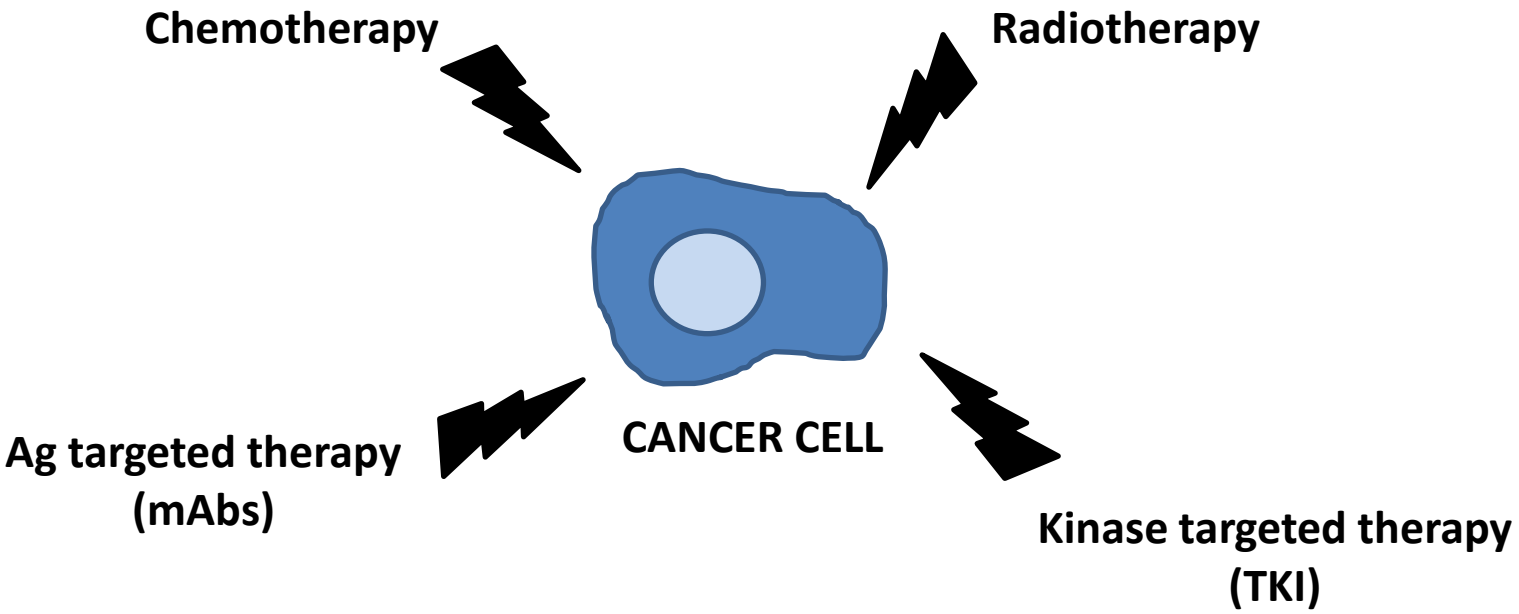
GUSTAVE ROUSSY

CANCER CAMPUS GRAND PARIS

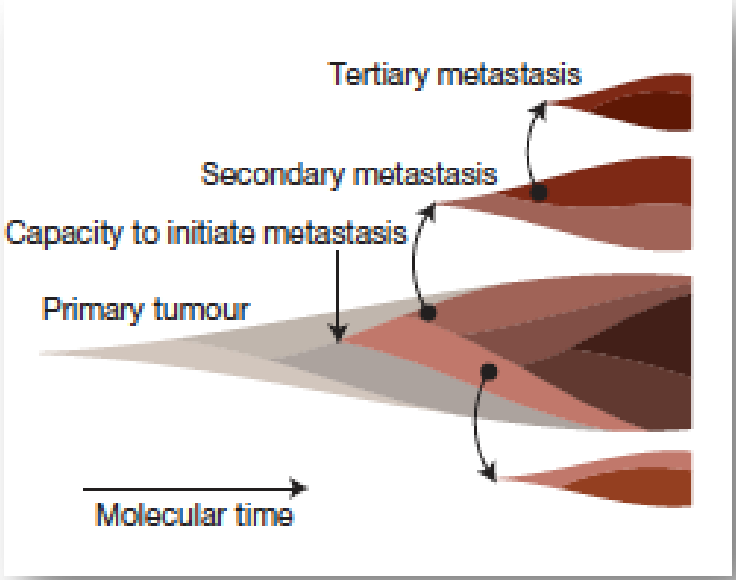
Cancer (1970-2010)



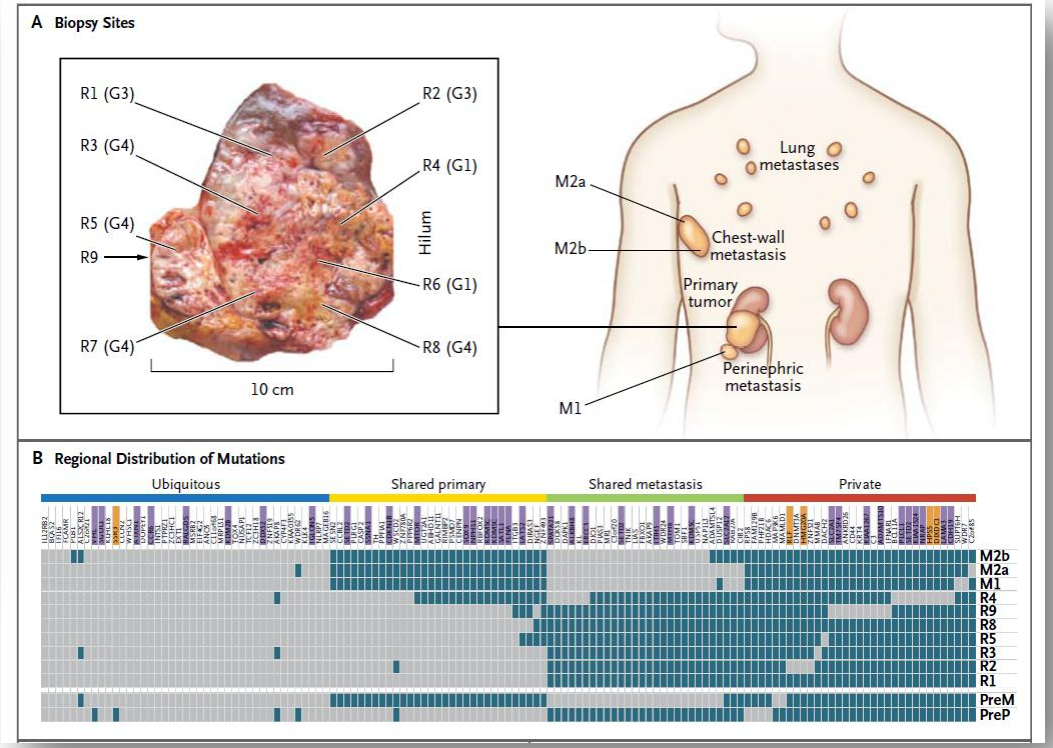
Cancer Therapies so far…



…but most Cancers become Polyclonal

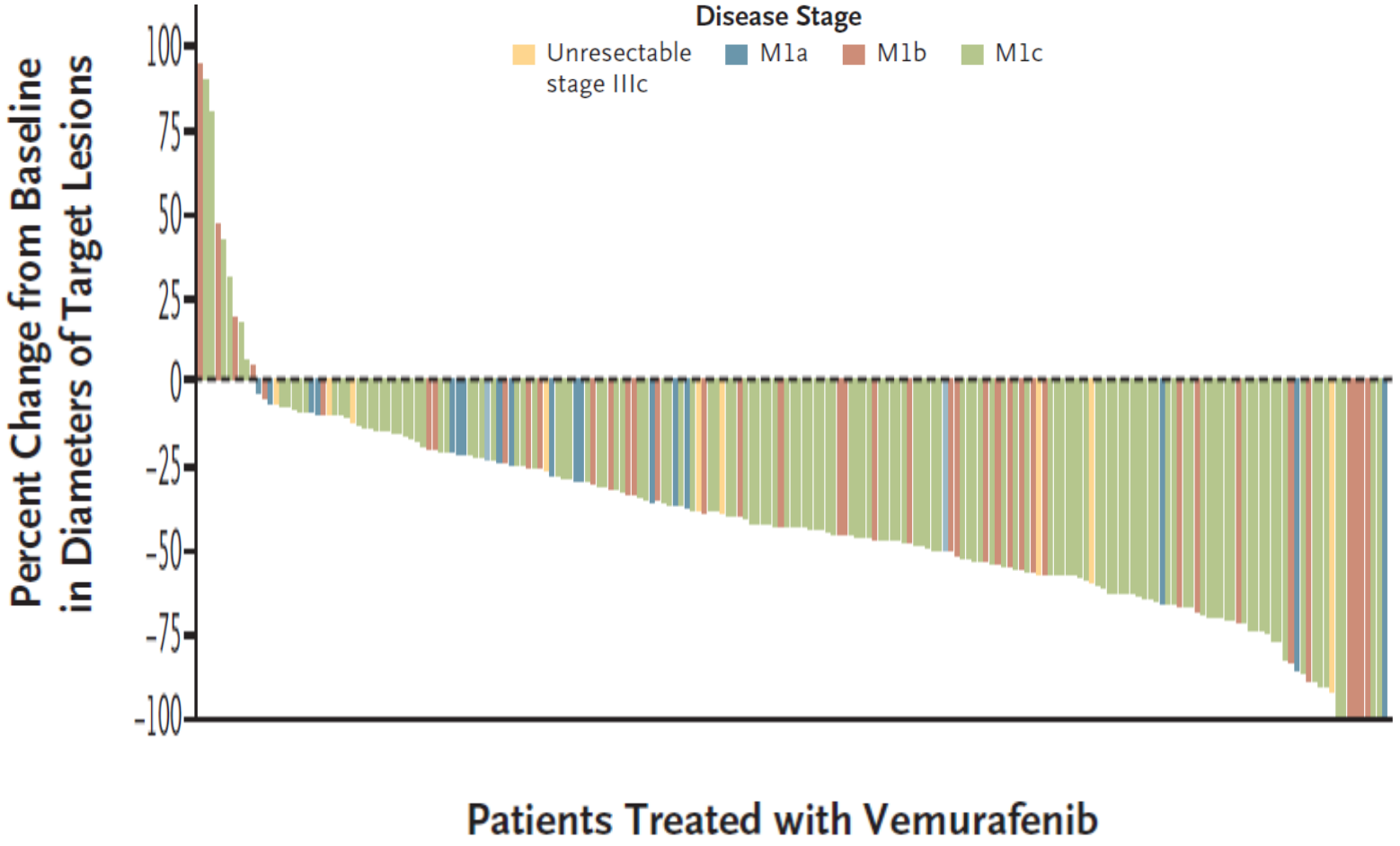


Campbell, PJ et al. Nature 2010 467: 1109-13,



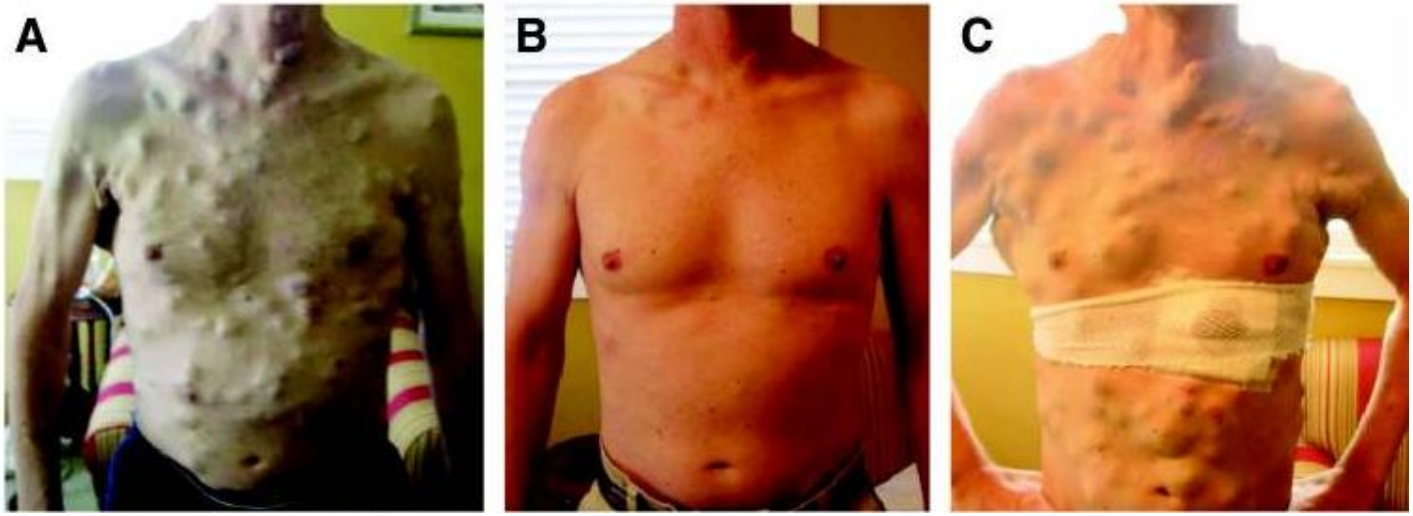
Gerlinger M, et al. N Engl J Med. 2012 Mar 8;366(10):883-92.

TUMOR TARGETED THERAPIES



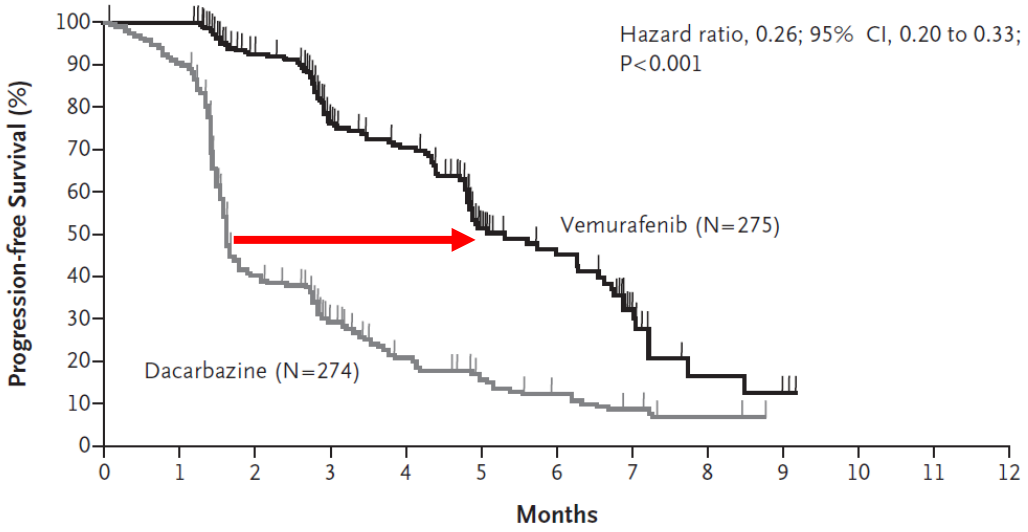
Chapman PB, et al. N Engl J Med 2011;364:2507–16.

TUMOR TARGETED THERAPIES



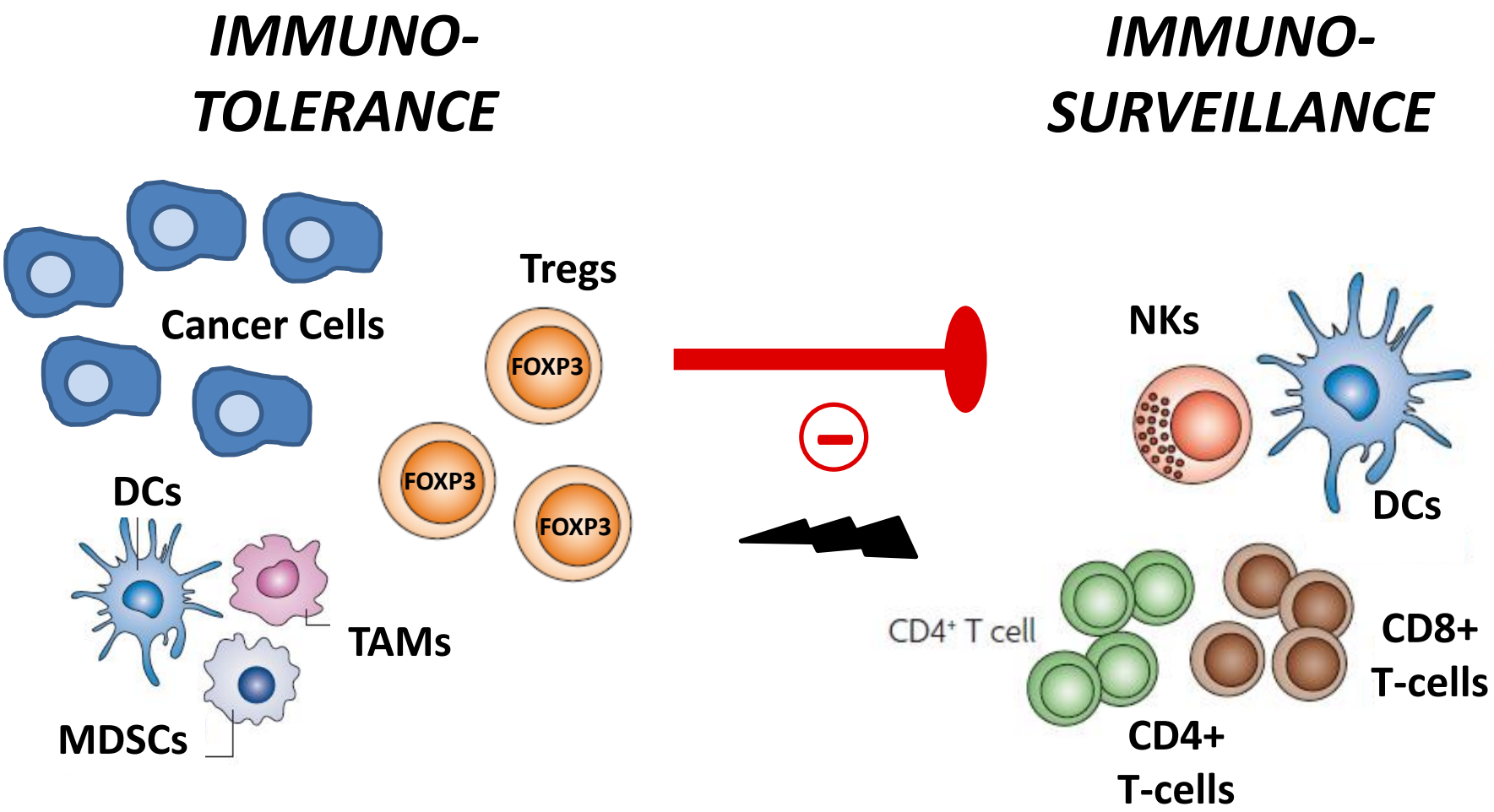
Wagle N, et al.
JCO. 2011
Aug 1;29(22):3085-96

Before BRAFi | **After 15 weeks of BRAFi** | **After 23 weeks of BRAFi**



Chapman PB et al. N Engl J Med 2011;364:2507–16.

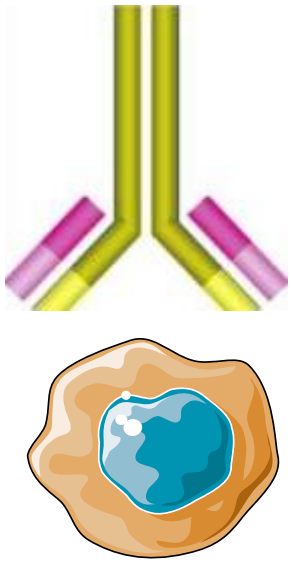
Subsets of Immune Cells can also Promote Cancers !



Adapted from Colombo MP, et al Nat Rev Cancer. 2007 Nov;7(11):880-7.

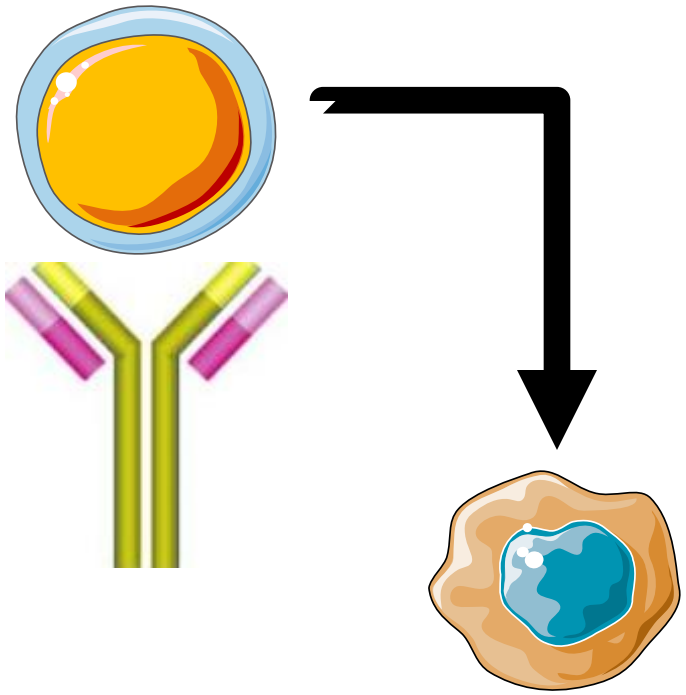
Paradigm Shift in Cancer Therapy

Historical Paradigm: Targeting Tumor Cells	New Paradigm: Targeting Immune Cells

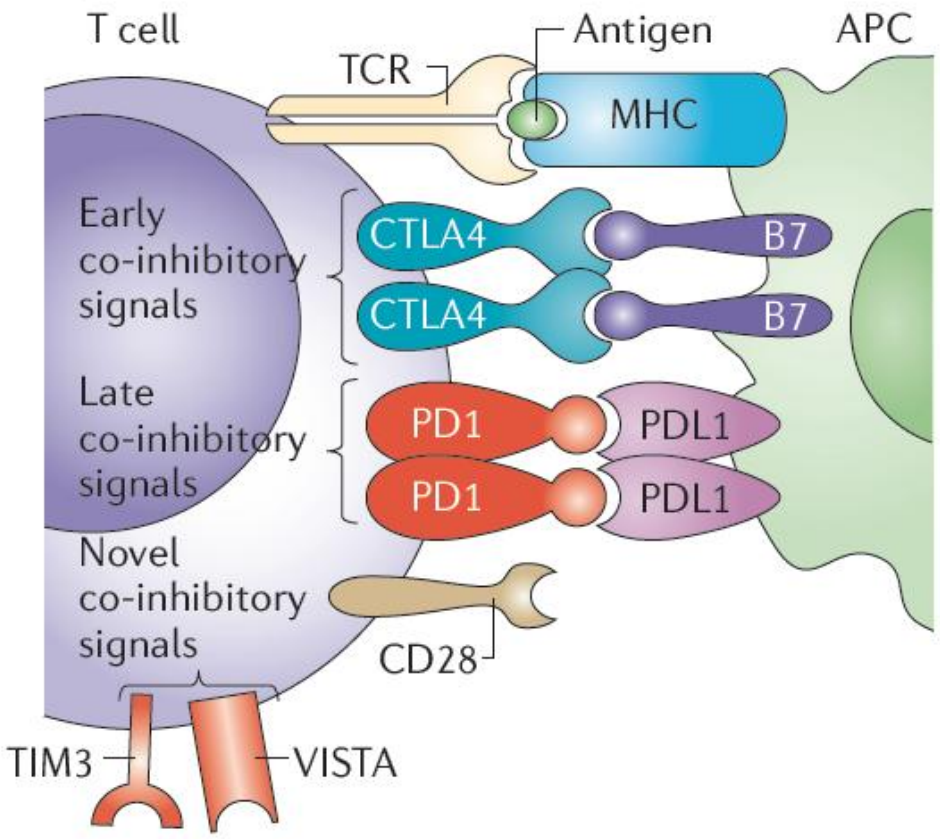


Tumor Cell

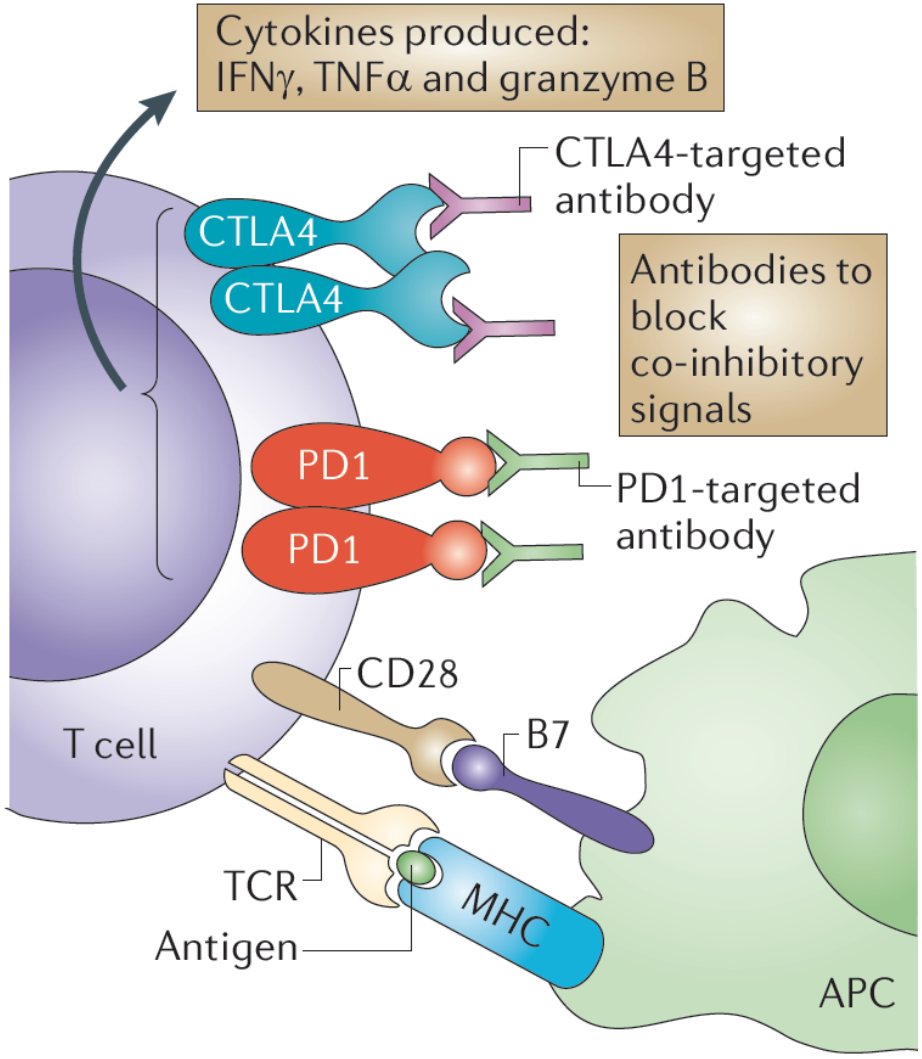
Lymphocyte



Lymphocyte Inhibition



Immune Checkpoint Blockade Therapy

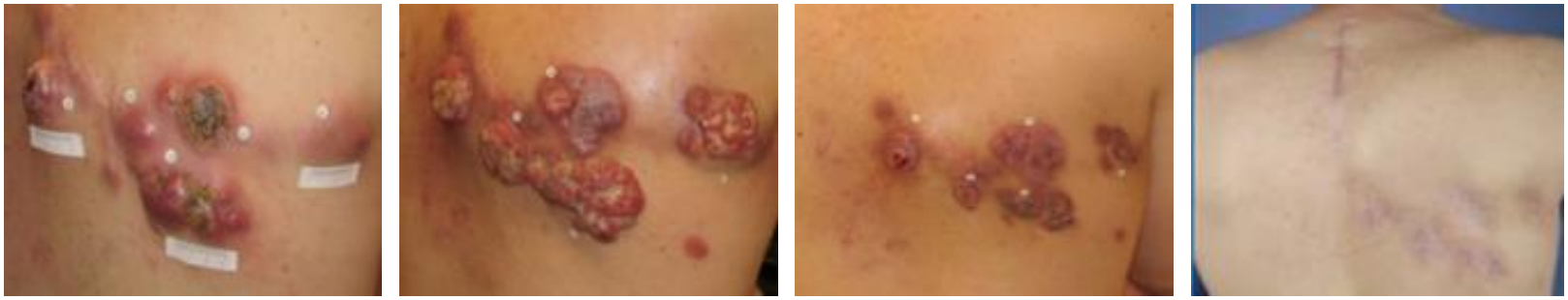


Cancer Immunotherapies

	PASSIVE	ACTIVE
NON SPECIFIC	LAK, CIK NK	Cytokines
SPECIFIC	TILs CARs Tumor targeted mAbs	Vaccines Immune targeted mAbs

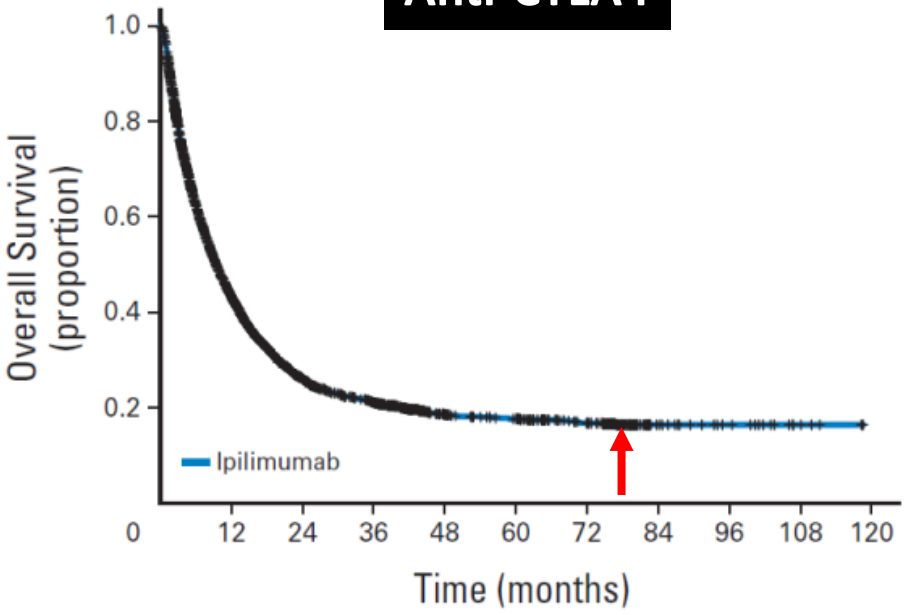
IMMUNE TARGETED THERAPY

Screening | Week 12 | Week 14 | Week 72



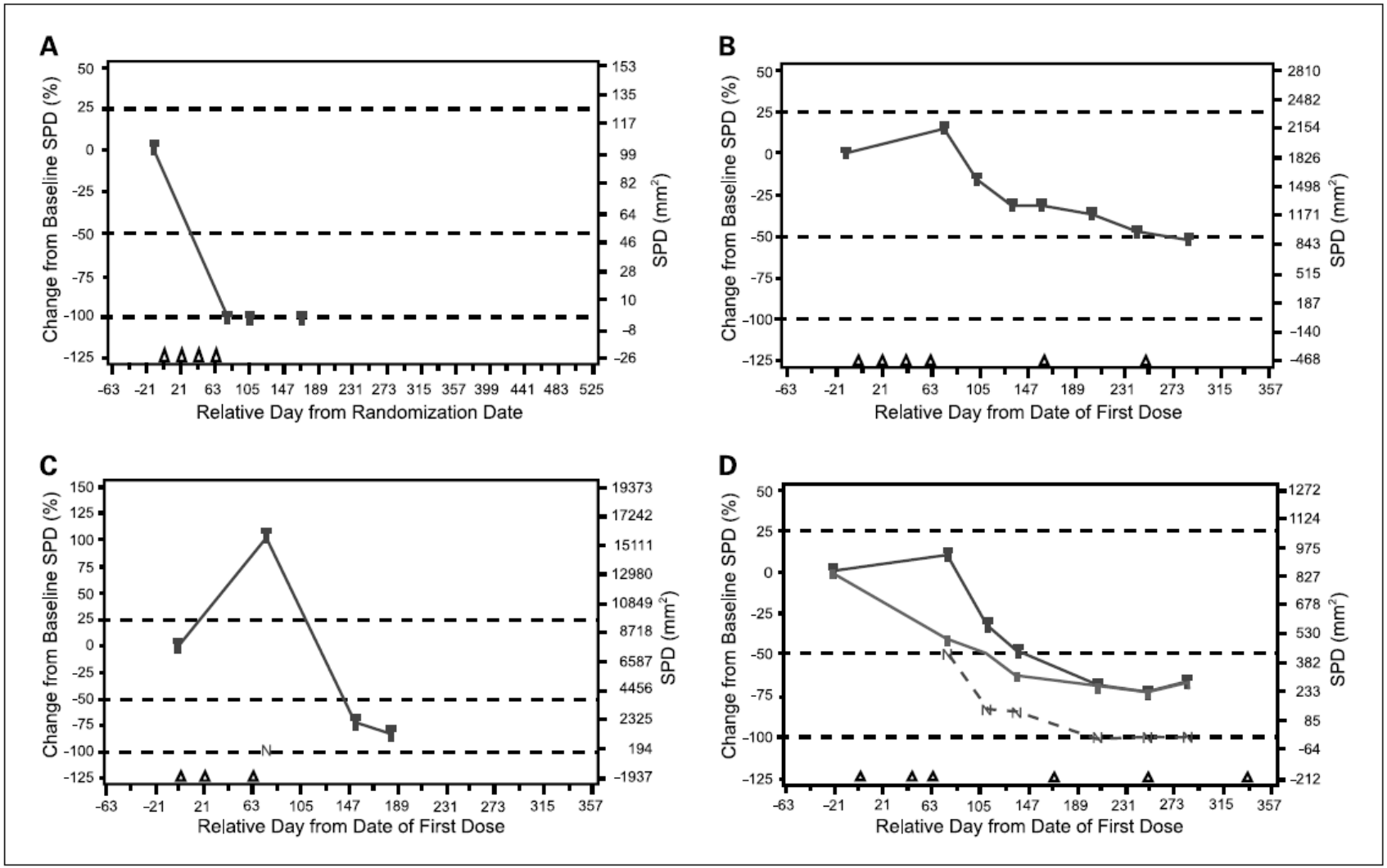
Hodi et al. Abstract #3008 ASCO 2008

Anti-CTLA4



Schadendorf D, J Clin Oncol 2015.

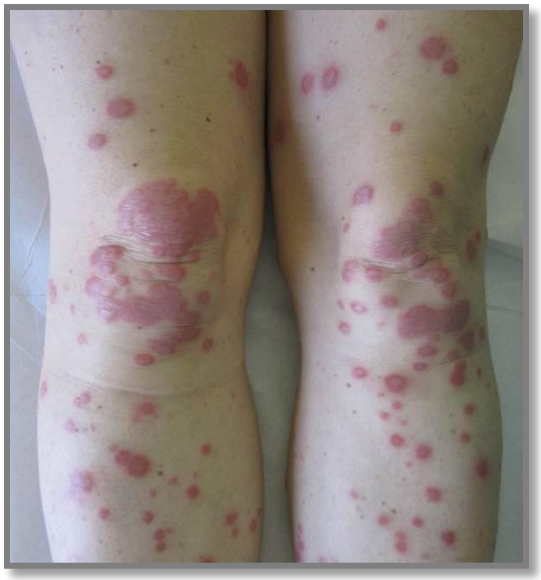
New Types of Responses in Oncology

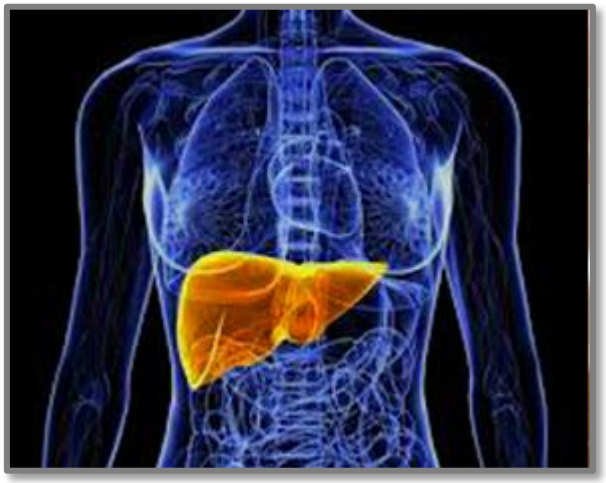


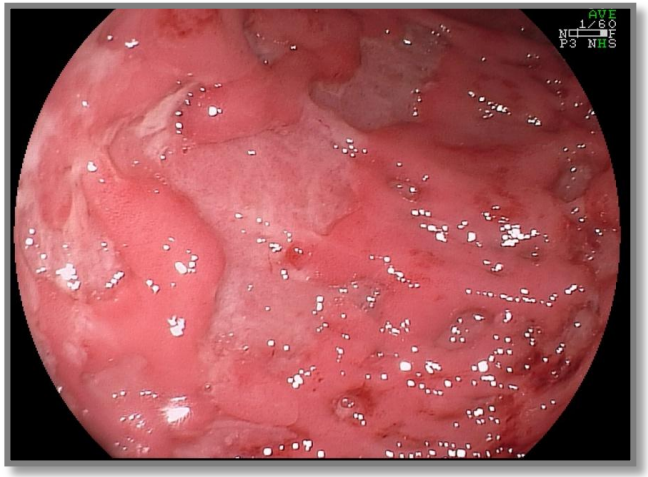
Immune-Related Response Criteria

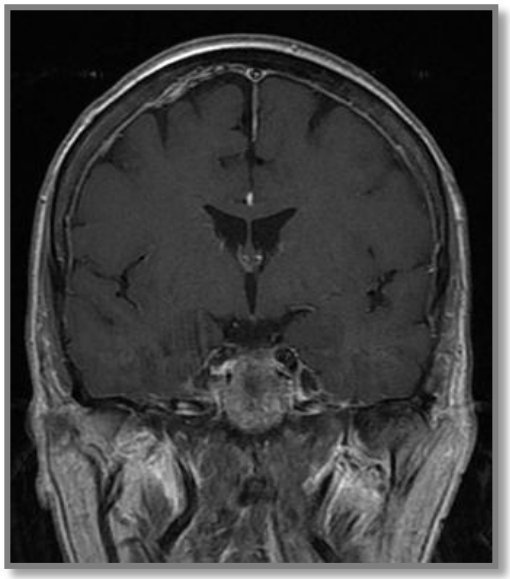
Clin Cancer Res 2009;15(23) December 1, 2009

New Types of Toxicities in Oncology



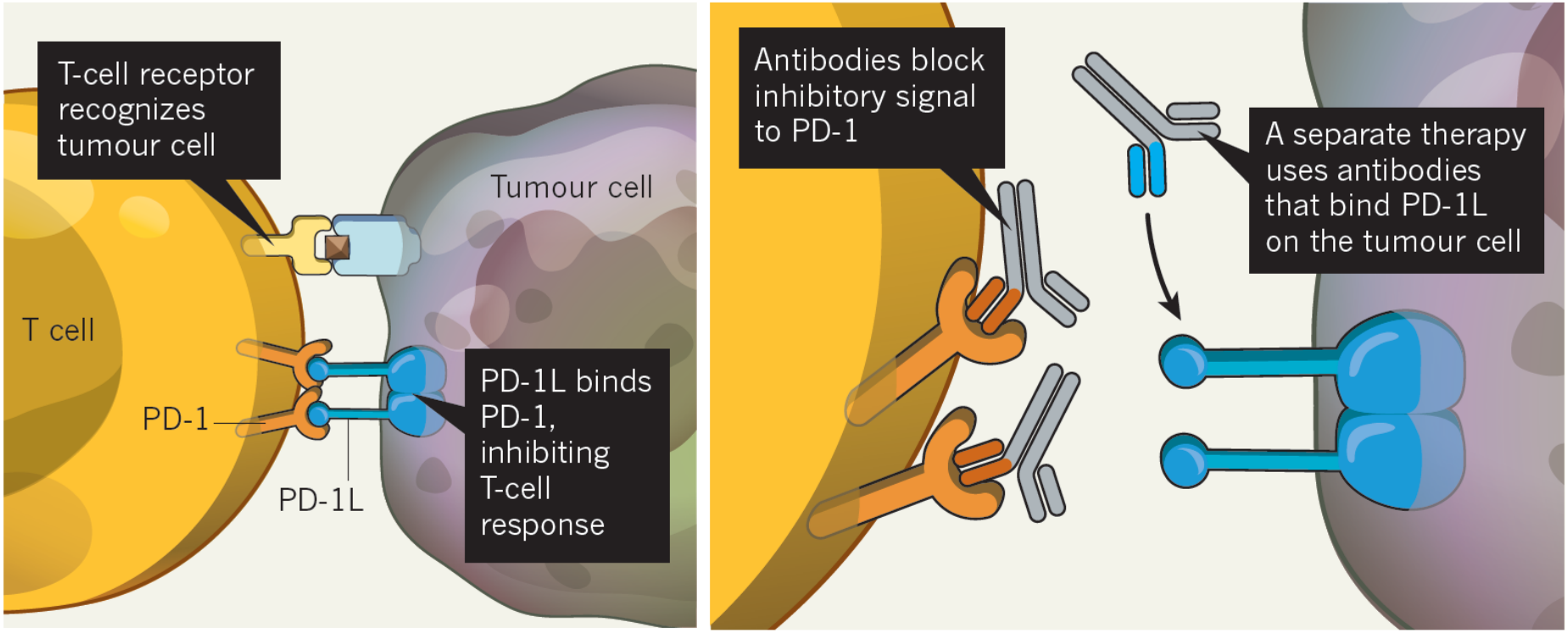






Bompaire et al Invest New drugs 2012

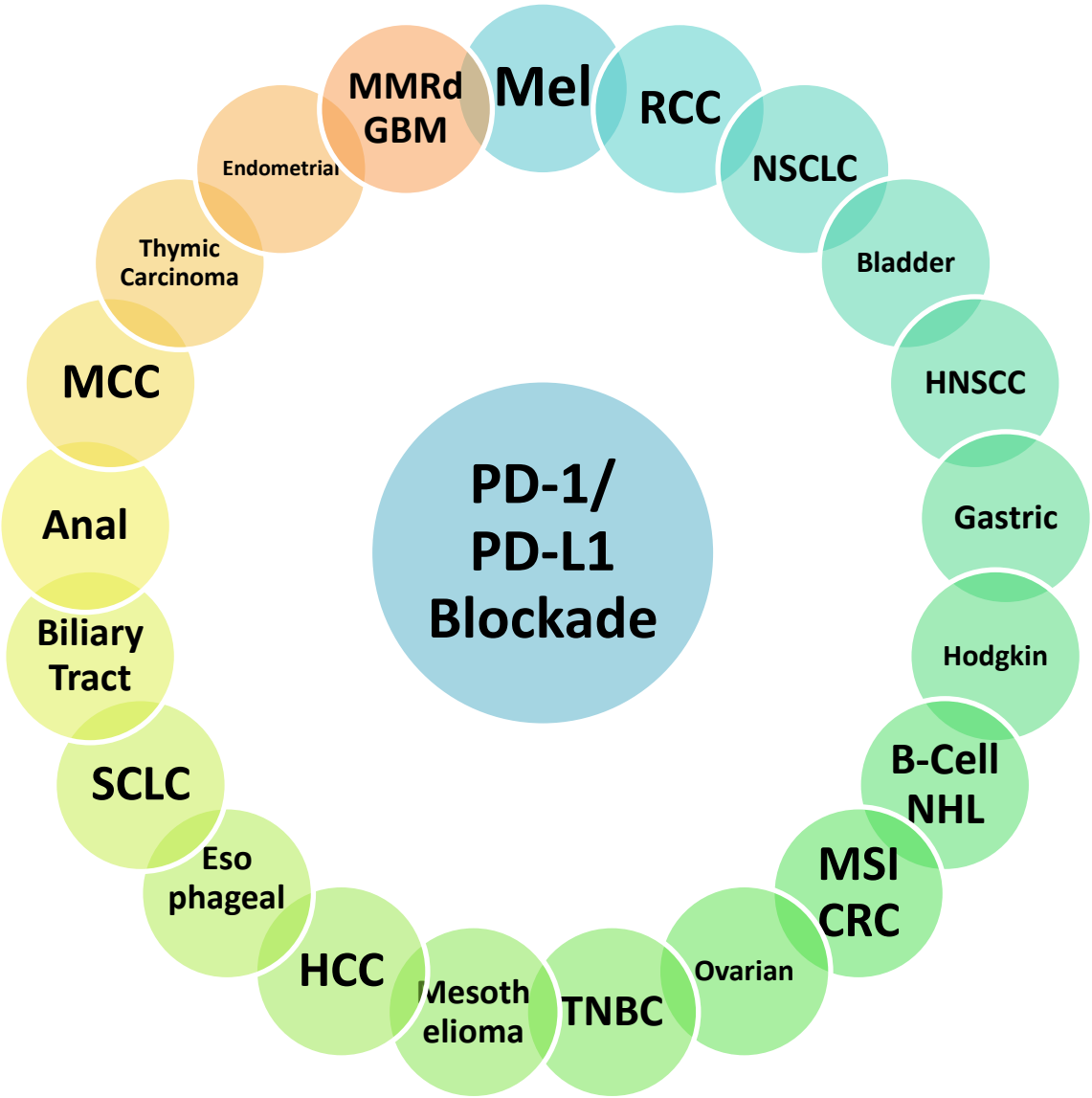
anti-PD-1 / anti-PD-L1 immunotherapy



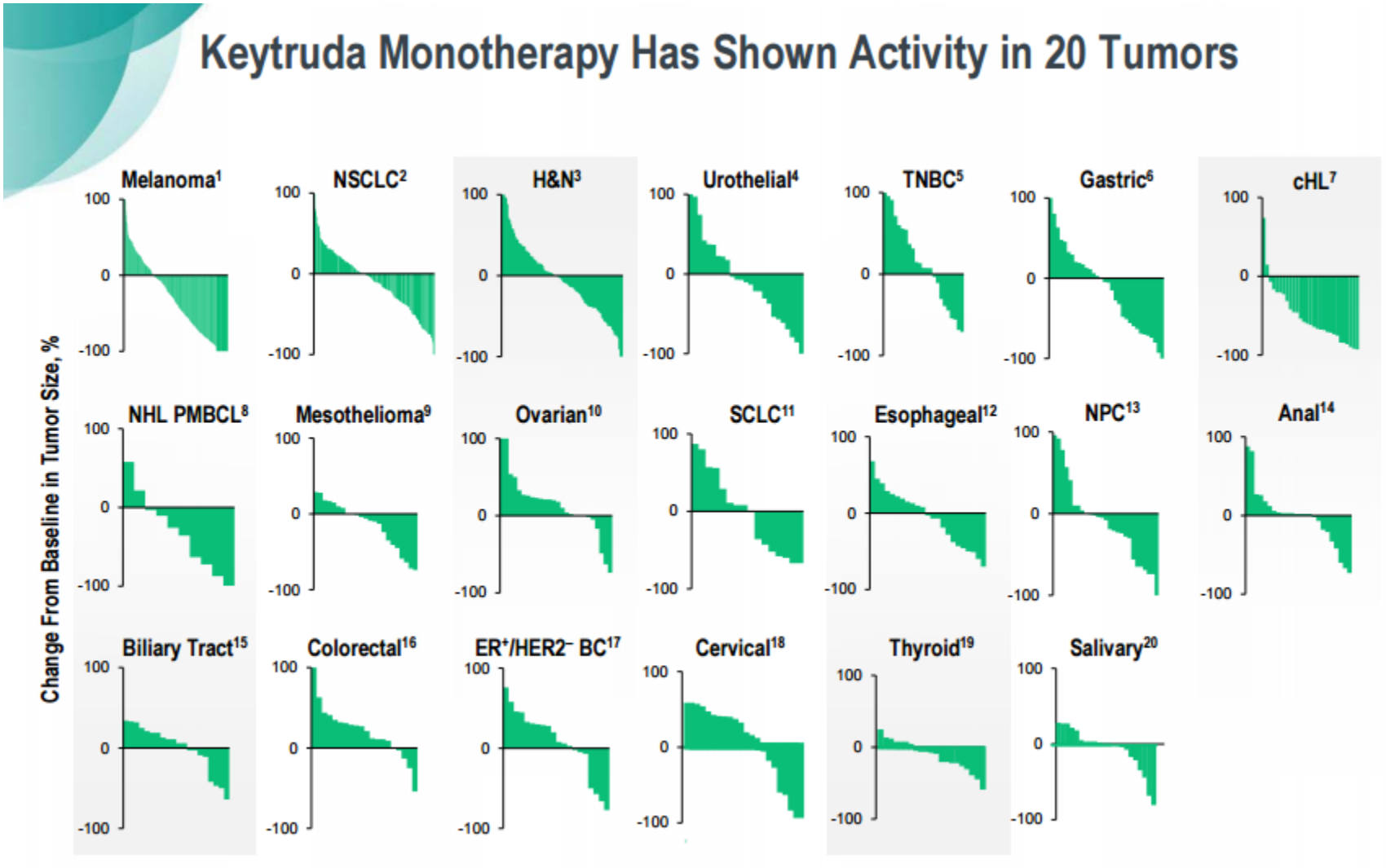
16 | NATURE | VOL 486 | 7 JUNE 2012

Hayden EC. Antibody alarm call rouses immune response to cancer. Nature. 2012 Jun 6;486(7401):16.

PD-Lomas 2016

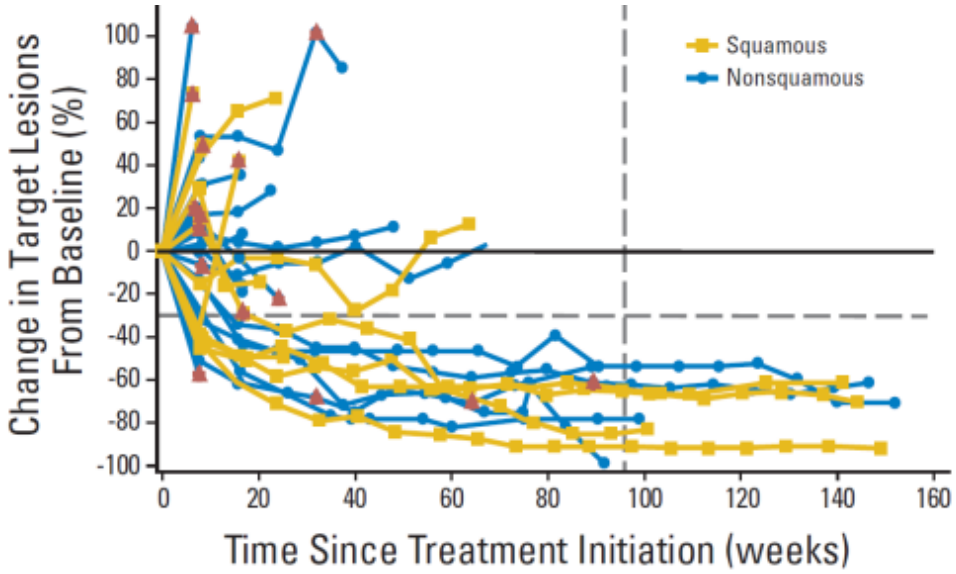


Variable Sensitivity to Immunotherapy



1. Daud A et al. 2014 SMR; 2. Garon EB et al. ESMO 2014; 3. Chow LQ et al. ESMO 2014; 4. O'Donnell P et al. 2015 Genitourinary Cancers Symposium;
5. Muro K et al. 2015 Gastrointestinal Cancers Symposium; 6. Nanda R et al. SABCS 2014; 7. Moskowitz C et al. 2014 ASH Annual Meeting; 8. Alley EA et al. 2015 AACR.

Long Duration of Responses



JCO, April 20, 2015.

Why Immune Targeted Therapies provide Survival Benefits?

Adaptive anti-tumor immunity is polyclonal:

➔ ***better control of tumor heterogeneity***

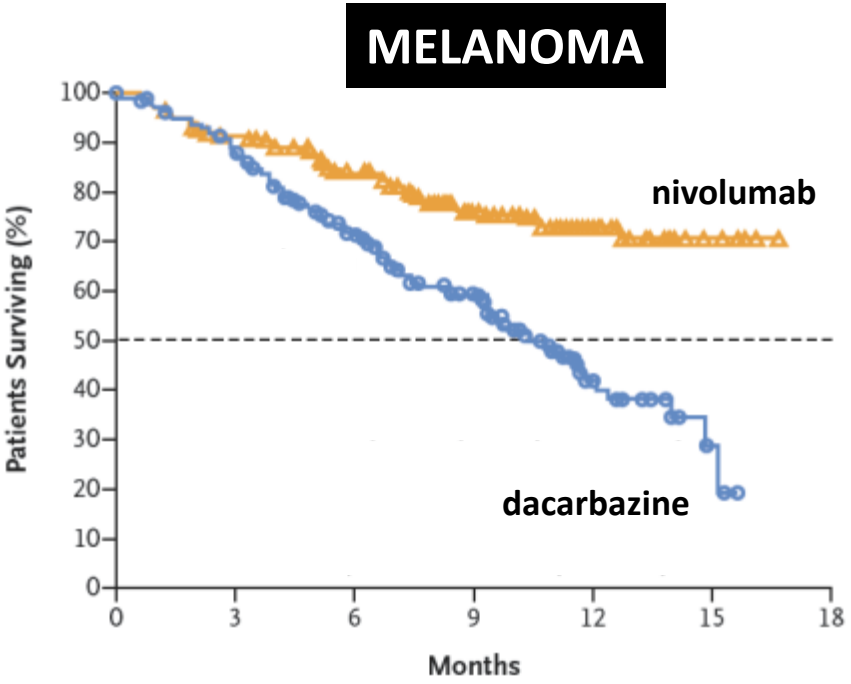
Adaptive anti-tumor immunity has memory:

➔ ***durable remissions***

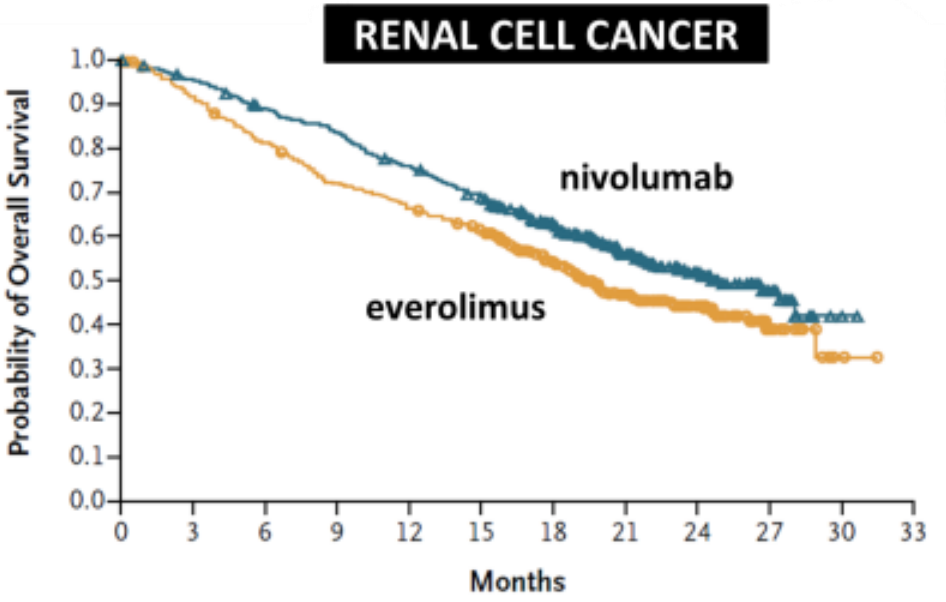
And immune cells can cross the BBB

(whereas most drugs can't)

Immune-Targeted mAbs provide Survival Benefits



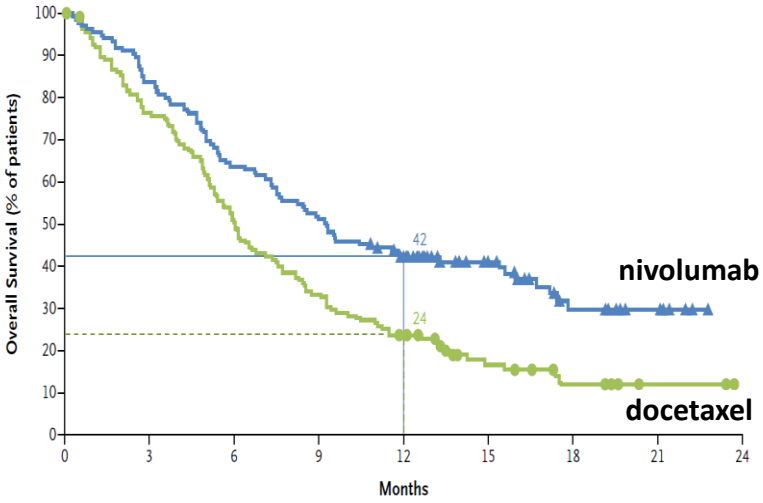
Robert C et al. NEJM 2014.



Motzer RJ, et al. NEJM 2015.

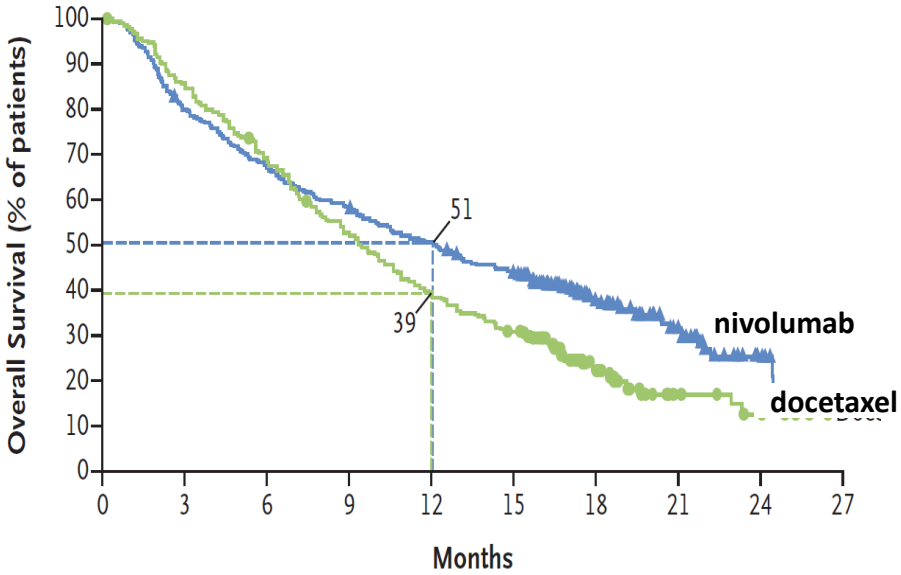
Immune-Targeted mAbs provide Survival Benefits

Sq NSCLC



Brahmer J et al. NEJM 2015.

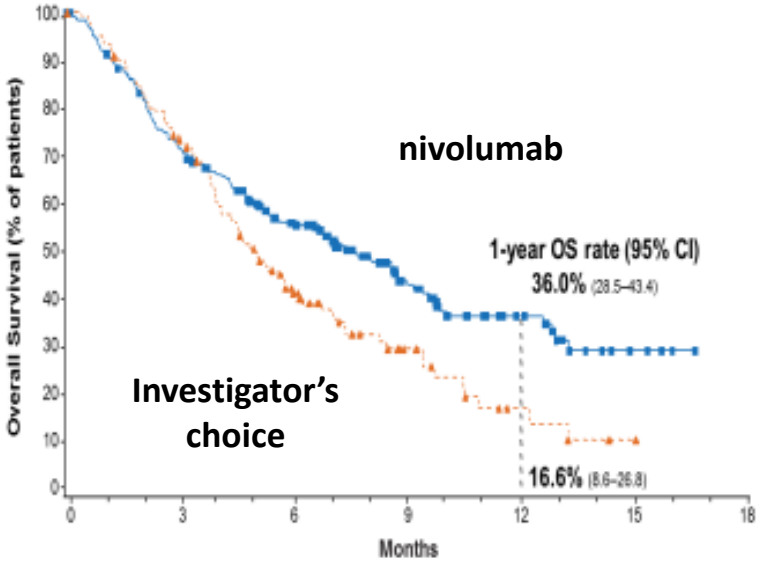
Non Sq NSCLC



Borghaei H, et al. NEJM 2015.

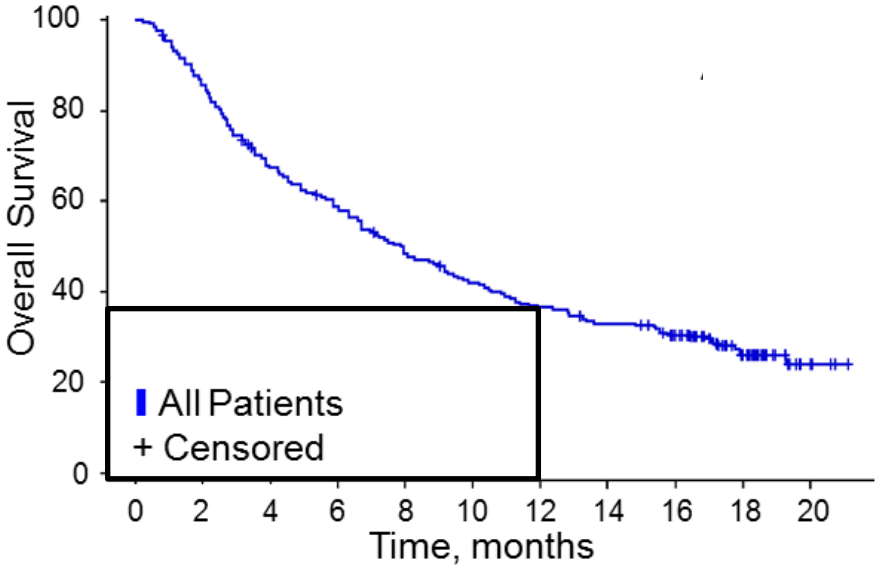
Immune-Targeted mAbs provide Survival Benefits

HNSCC



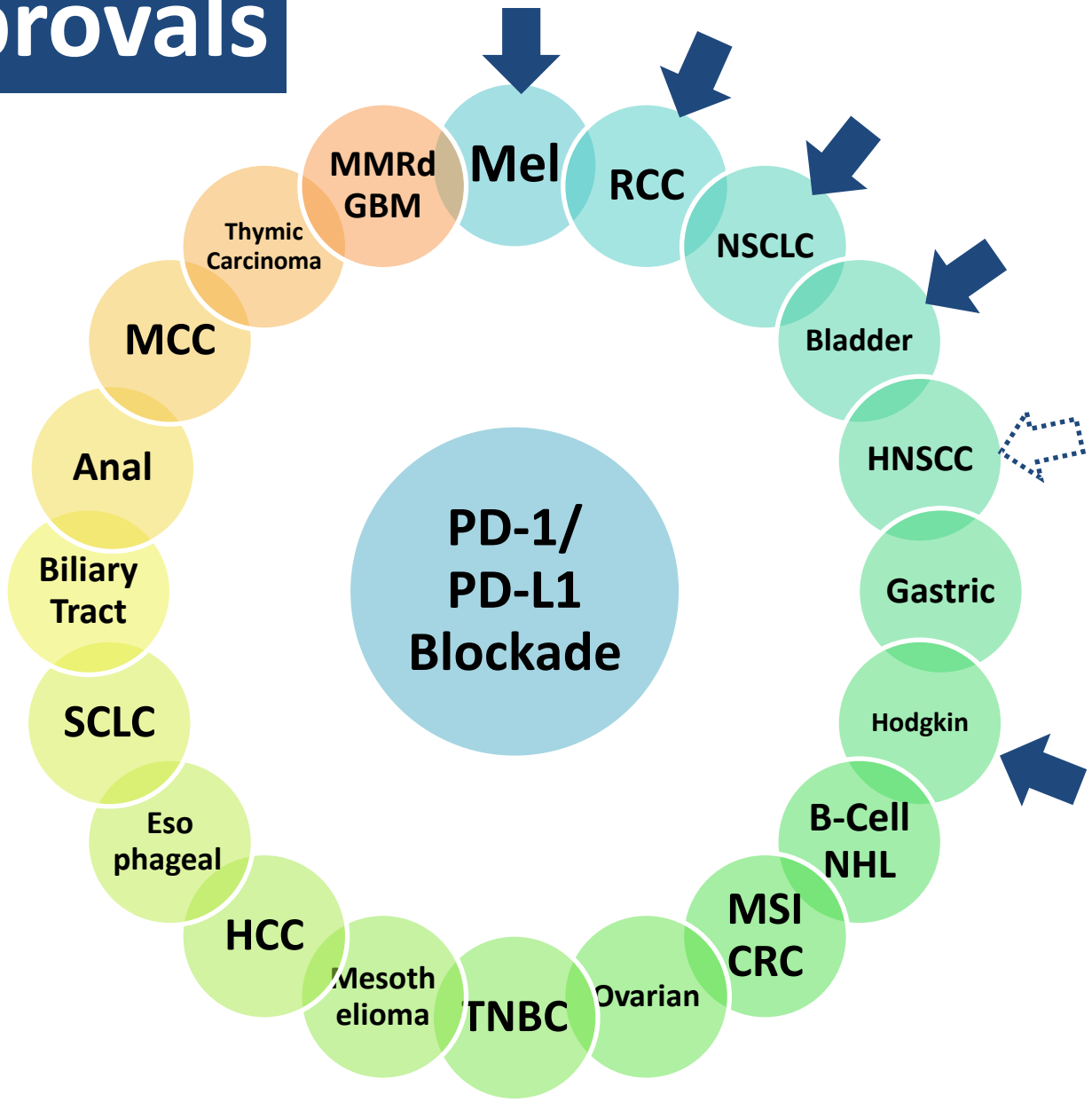
AACR 2016

Bladder

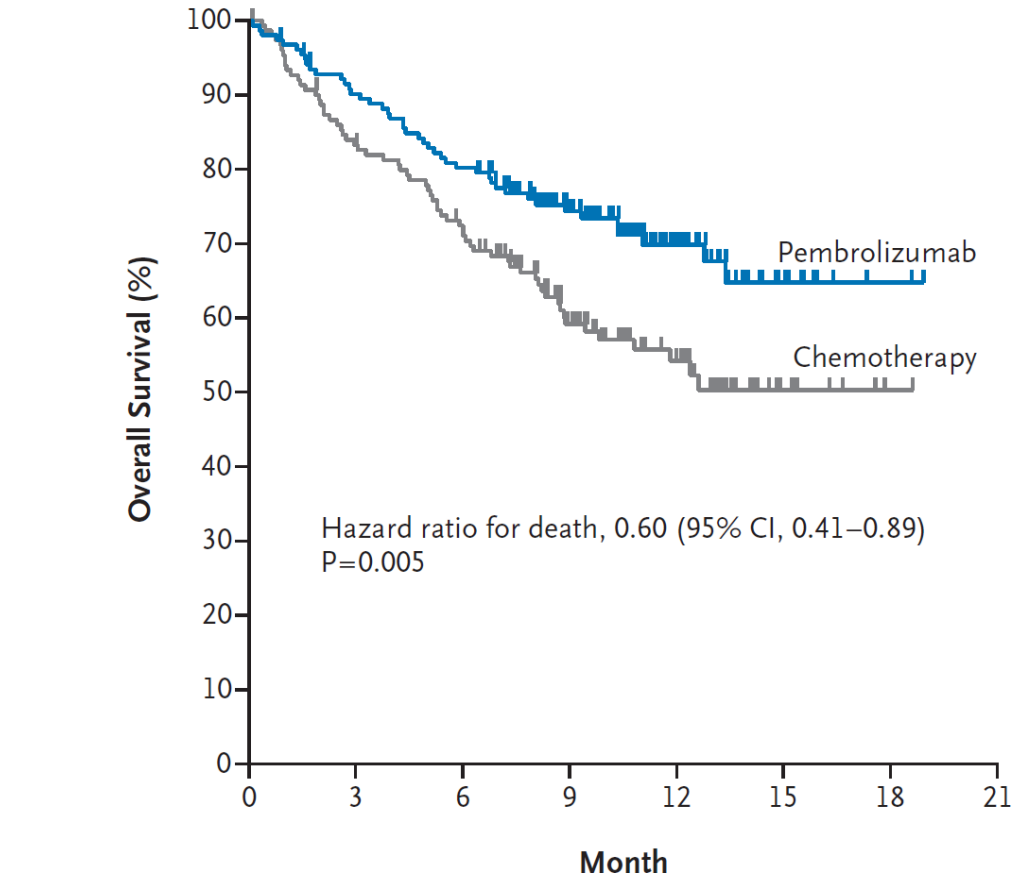


ASCO 2016

US approvals



Anti-PD-1 1st line in PD-L1^{high} NSCLC



Reck M, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive NSCLC. N Engl J Med; 2016

Know your Immune Checkpoint Antibodies

Anti-CTLA-4

Tremelimumab (AZ)

Ipilimumab (BMS)

Approved

Anti-PD-1

Nivolumab (BMS) & Pembrolizumab (MSD)

Approved

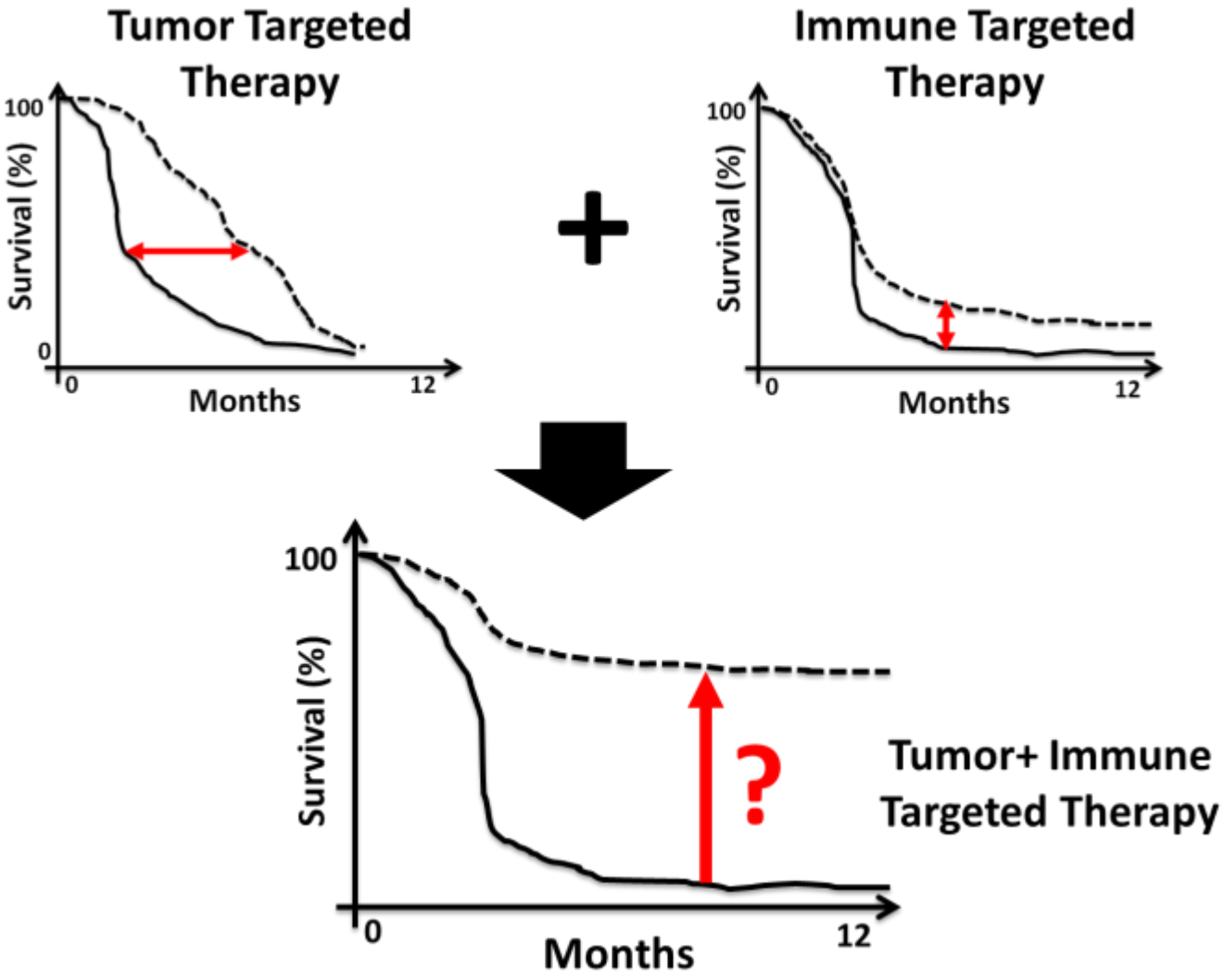
Anti-PD-L1

Durvalumab (AZ/Medimmune)
Avelumab (Pfizer)

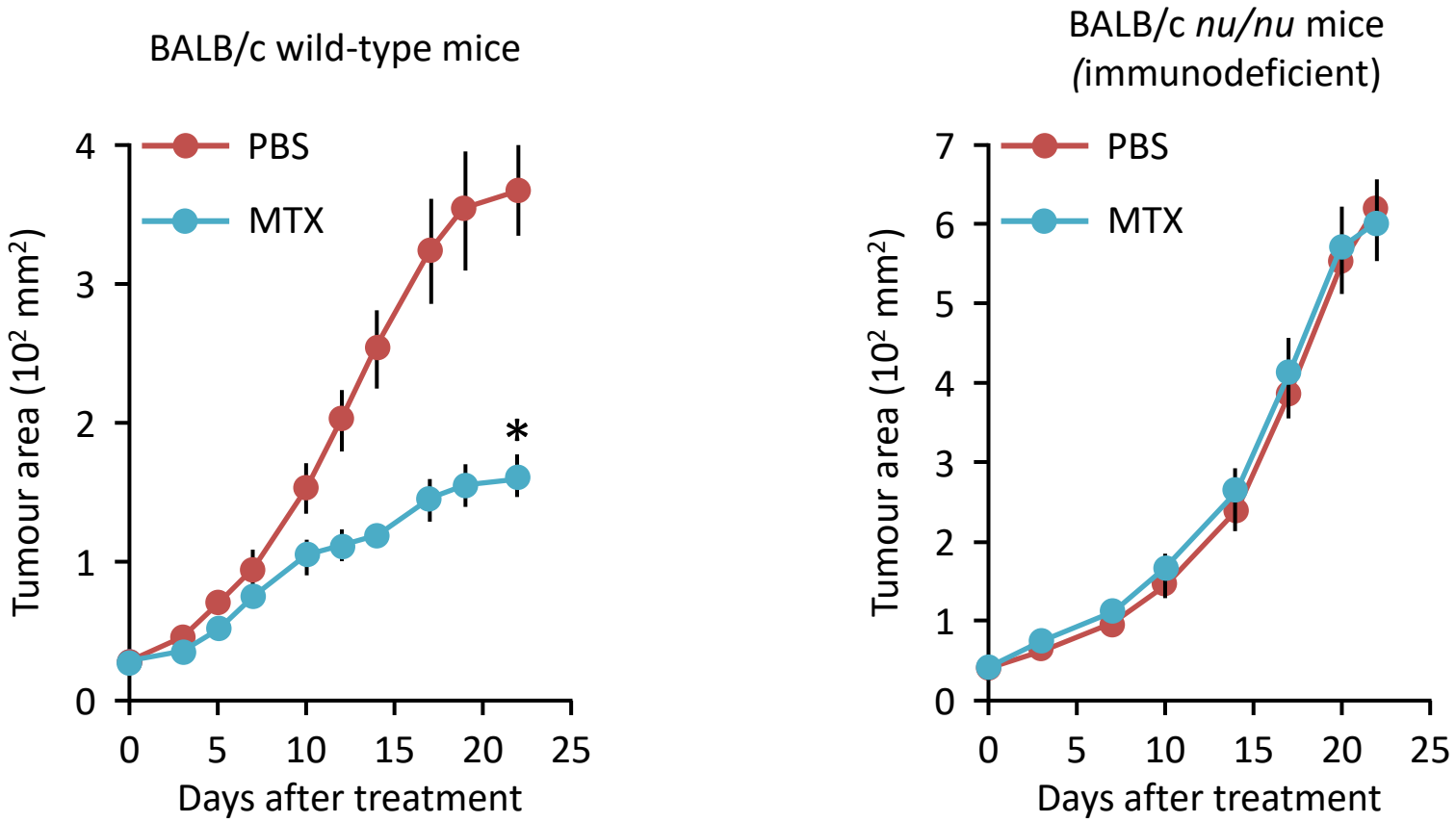
Atezolizumab (Roche/Genentech)

Approved

What is the Future of Oncology ?



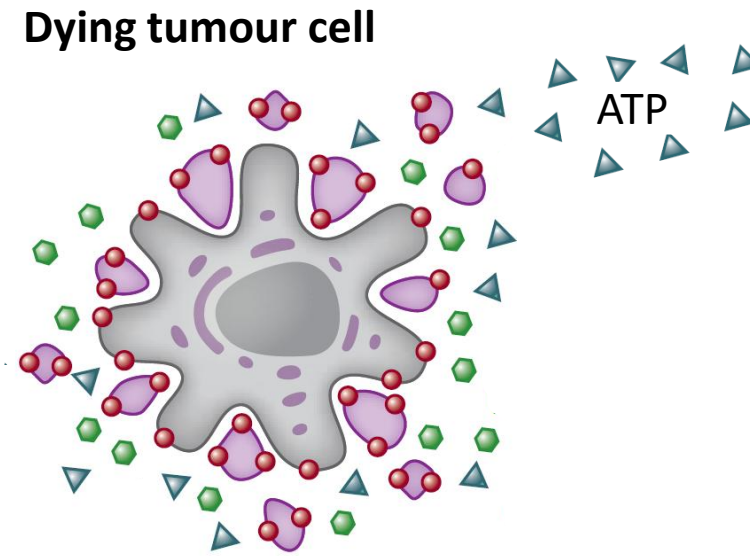
Chemotherapy Efficacy & the Immune System



*P < 0.05; n = 10 mice per group; means ± SEM are shown.
MTX, mitoxantrone; PBS, phosphate-buffered saline (control).

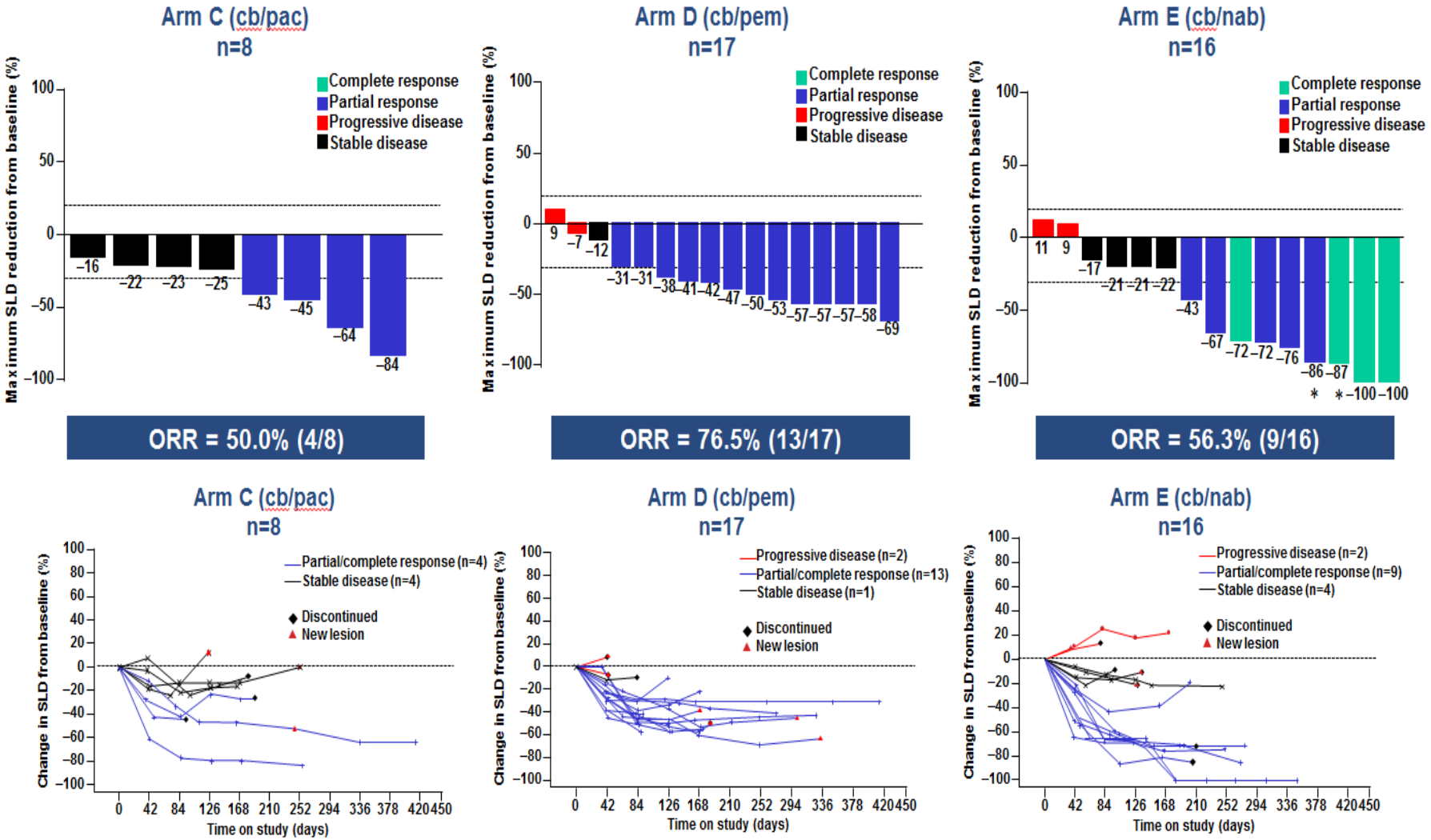
Michaud M, et al. Science 2011;334:1573–7.

Immunogenic cell death



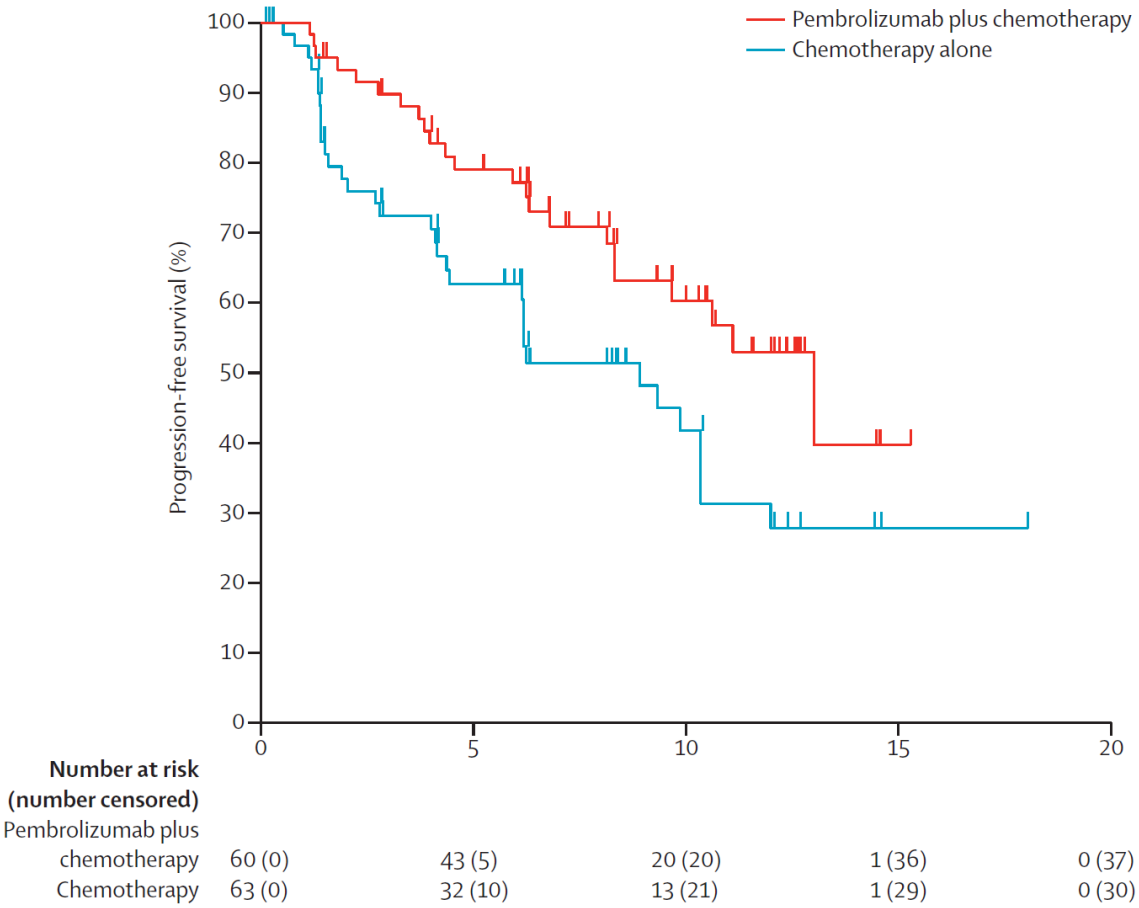
Adapted from Kroemer G *et al. Annu Rev Immunol*. 2013;31:51-72

Chemotherapy + αPD-1/PD-L1 in 1st line NSCLC



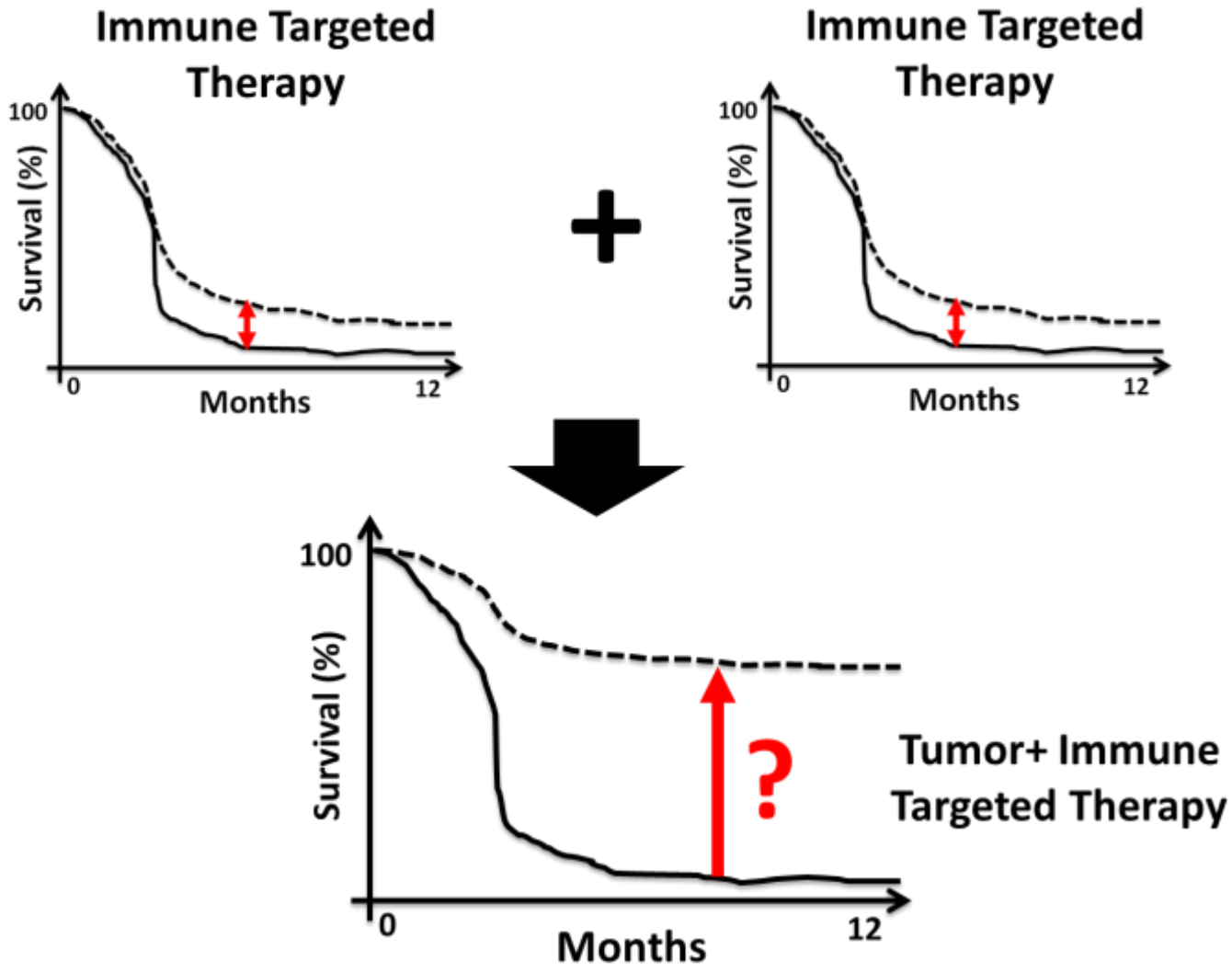
Giaccone et al, ESMO 2015

Chemo + αPD-1 1st line NSCLC



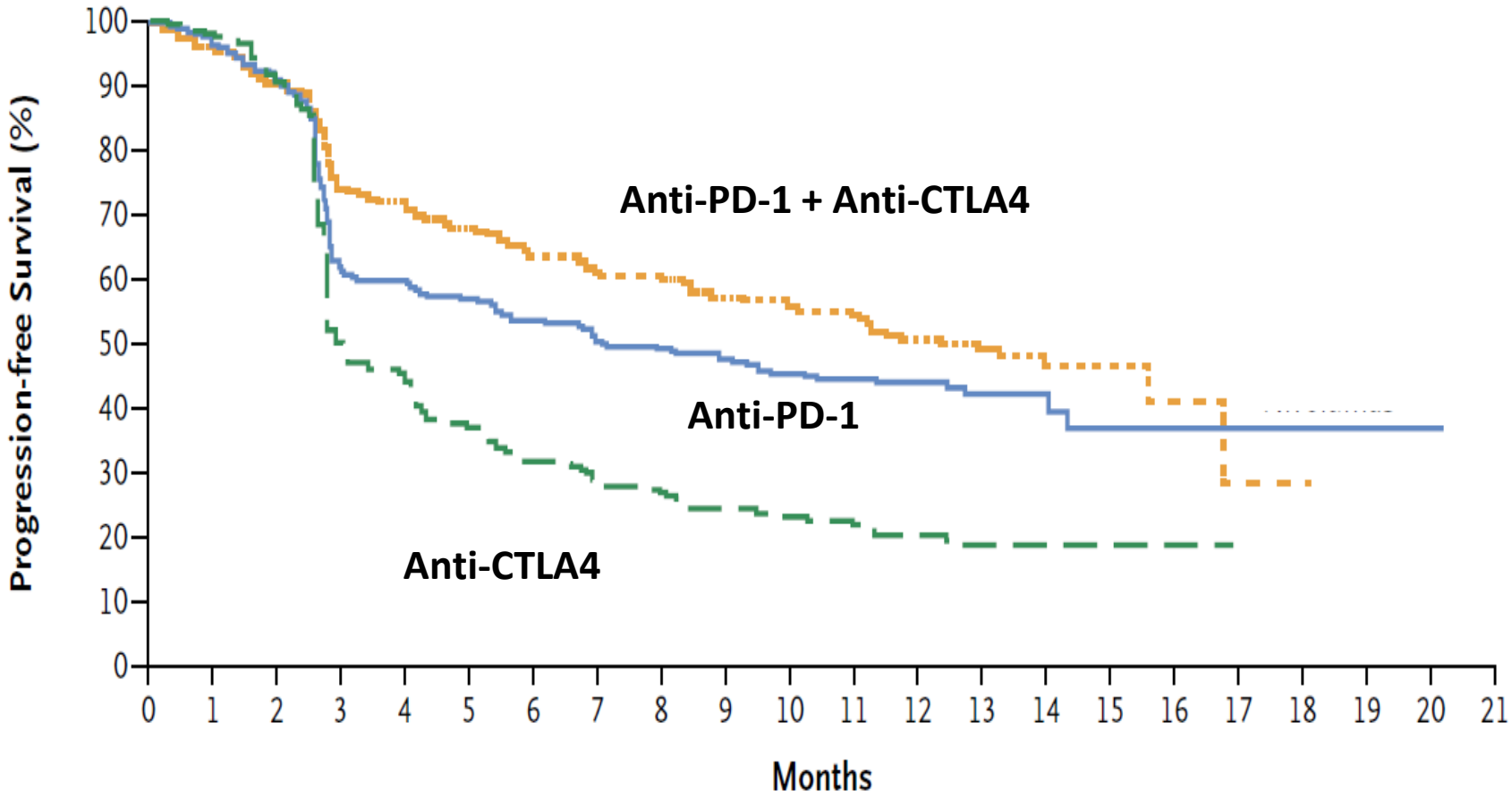
Langer CJ, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016

The Future of Oncology ?



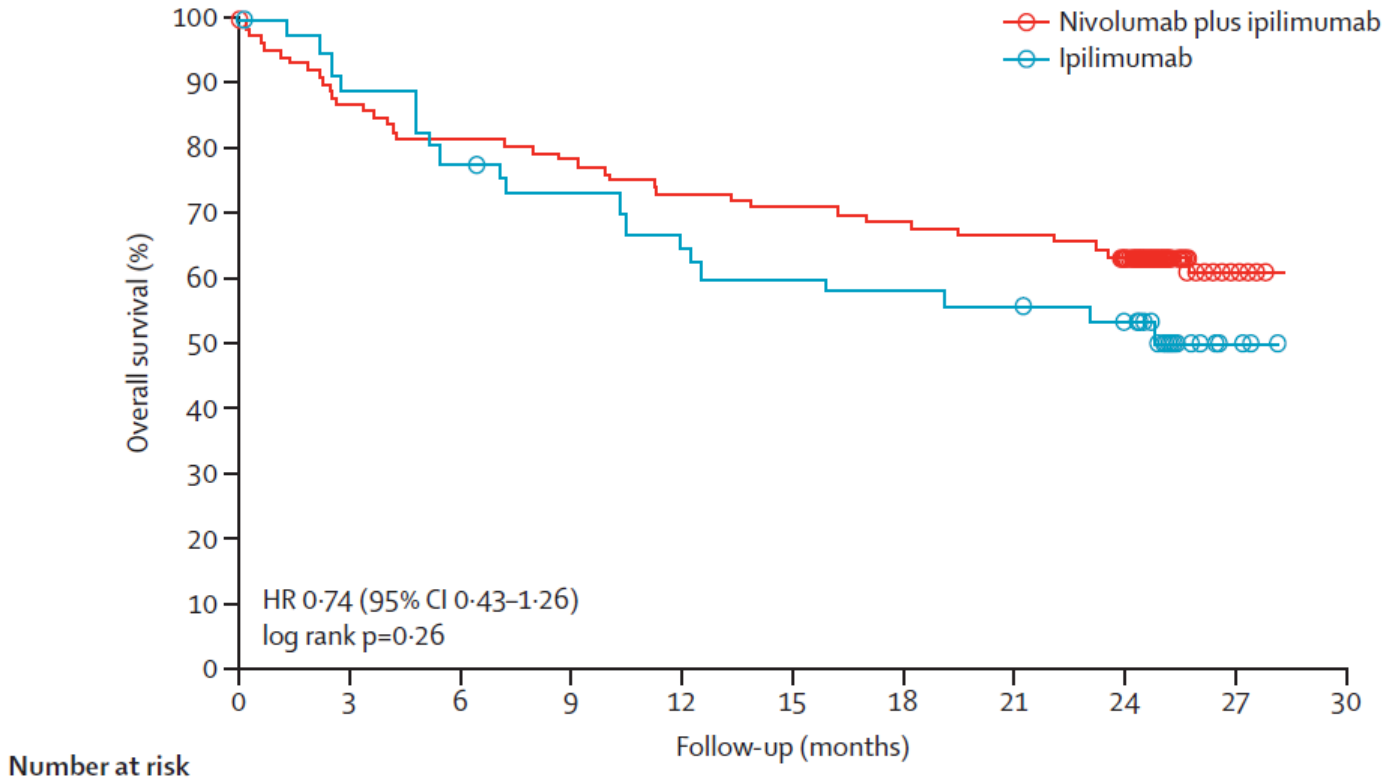
The NEW ENGLAND JOURNAL of MEDICINE

Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma



Larkin J, et al. N Engl J Med 2015.

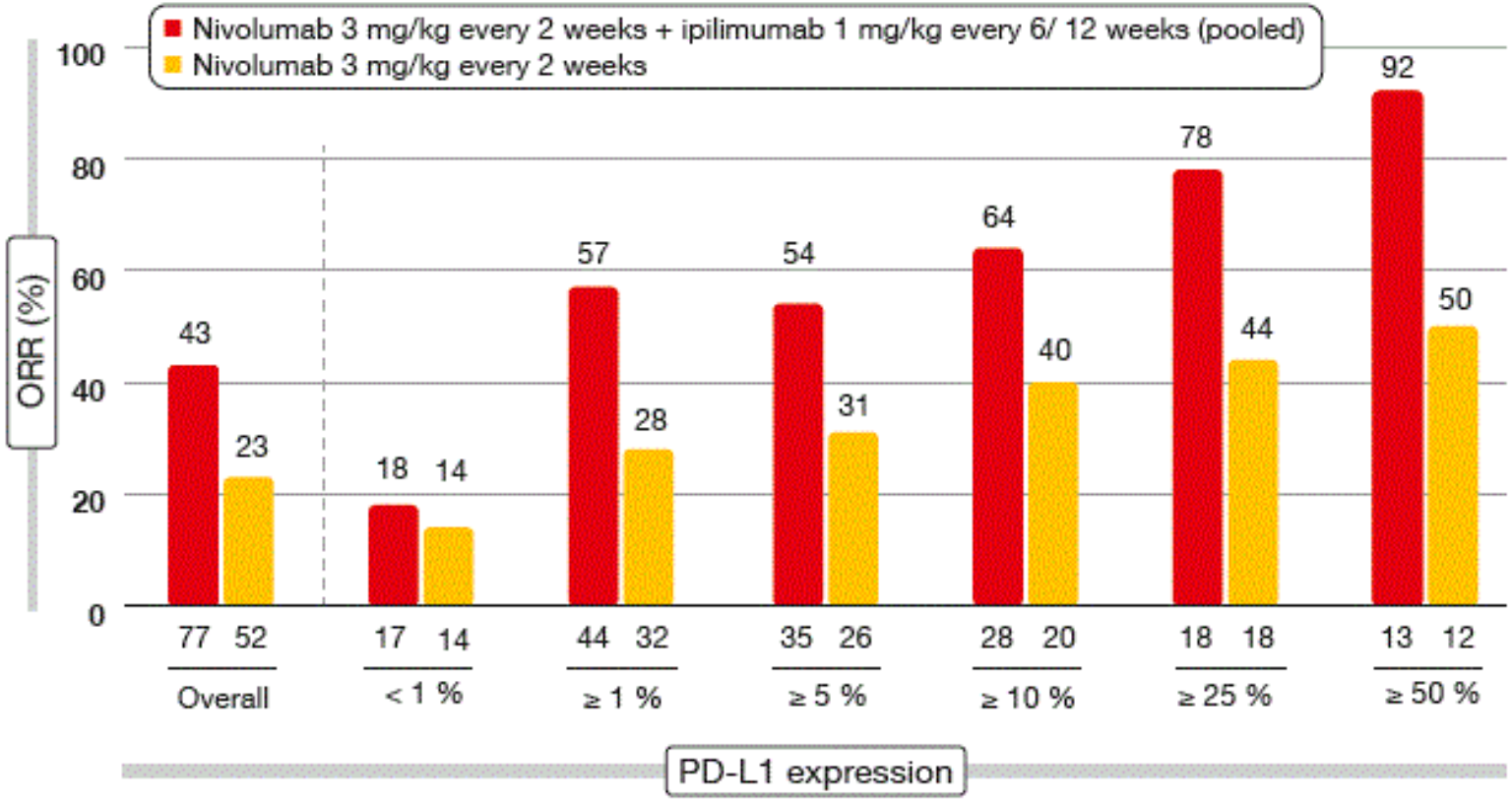
Ipilimumab + nivolumab OS in Melanoma



Number at risk (censored)											
Nivolumab plus ipilimumab	95 (0)	82 (1)	77 (1)	74 (1)	69 (1)	67 (1)	65 (1)	63 (1)	57 (4)	6 (54)	0 (60)
Ipilimumab	47 (0)	41 (1)	36 (1)	33 (2)	29 (2)	27 (2)	26 (2)	25 (2)	22 (4)	3 (22)	0 (25)

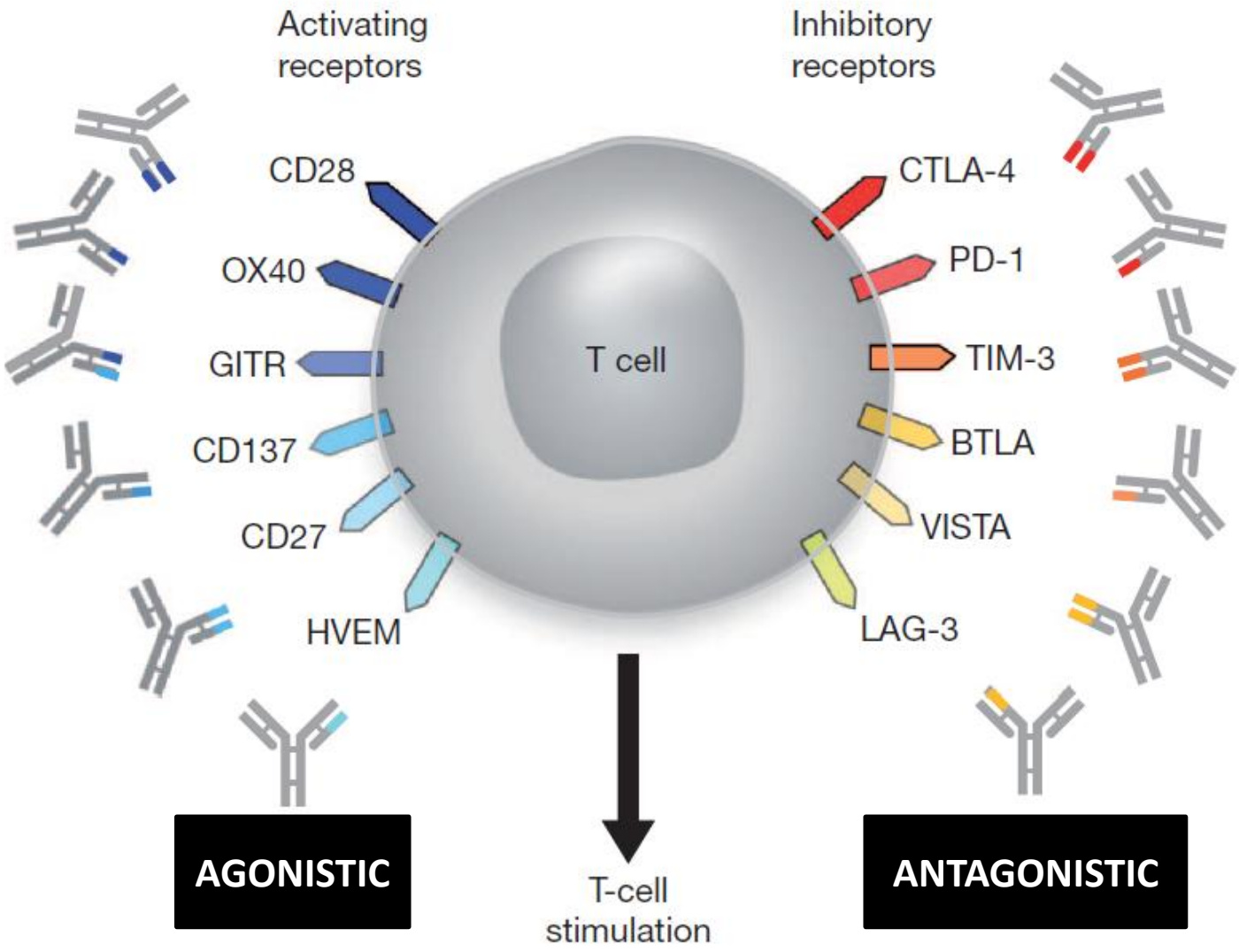
Hodi FS, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol. 2016;

Ipilimumab + nivolumab in 1st line NSCLC

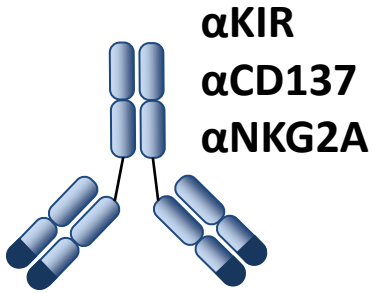


Hellmann M et al. CheckMate 012: Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC. ASCO 2016

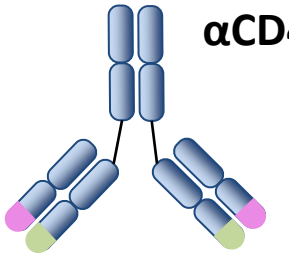
This is just the beginning

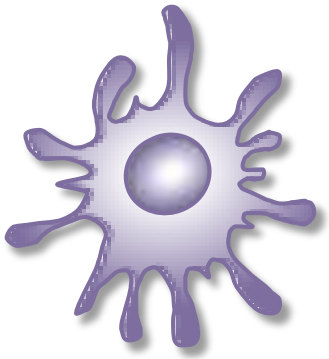


But also Target Innate Immune Cells!

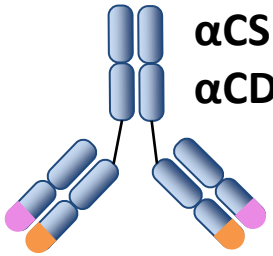


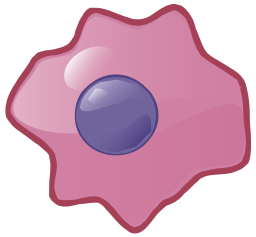
NK Cells





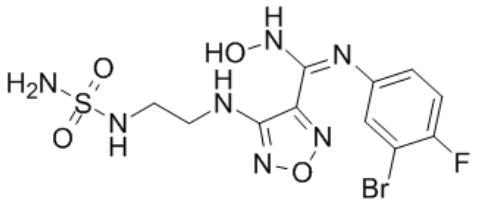
DCs
B-cells

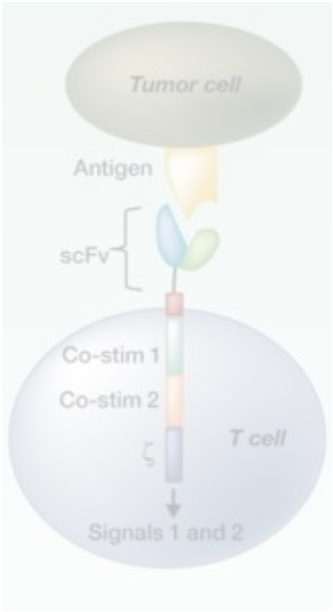




TAMs

OTHER IMMUNOTHERAPIES

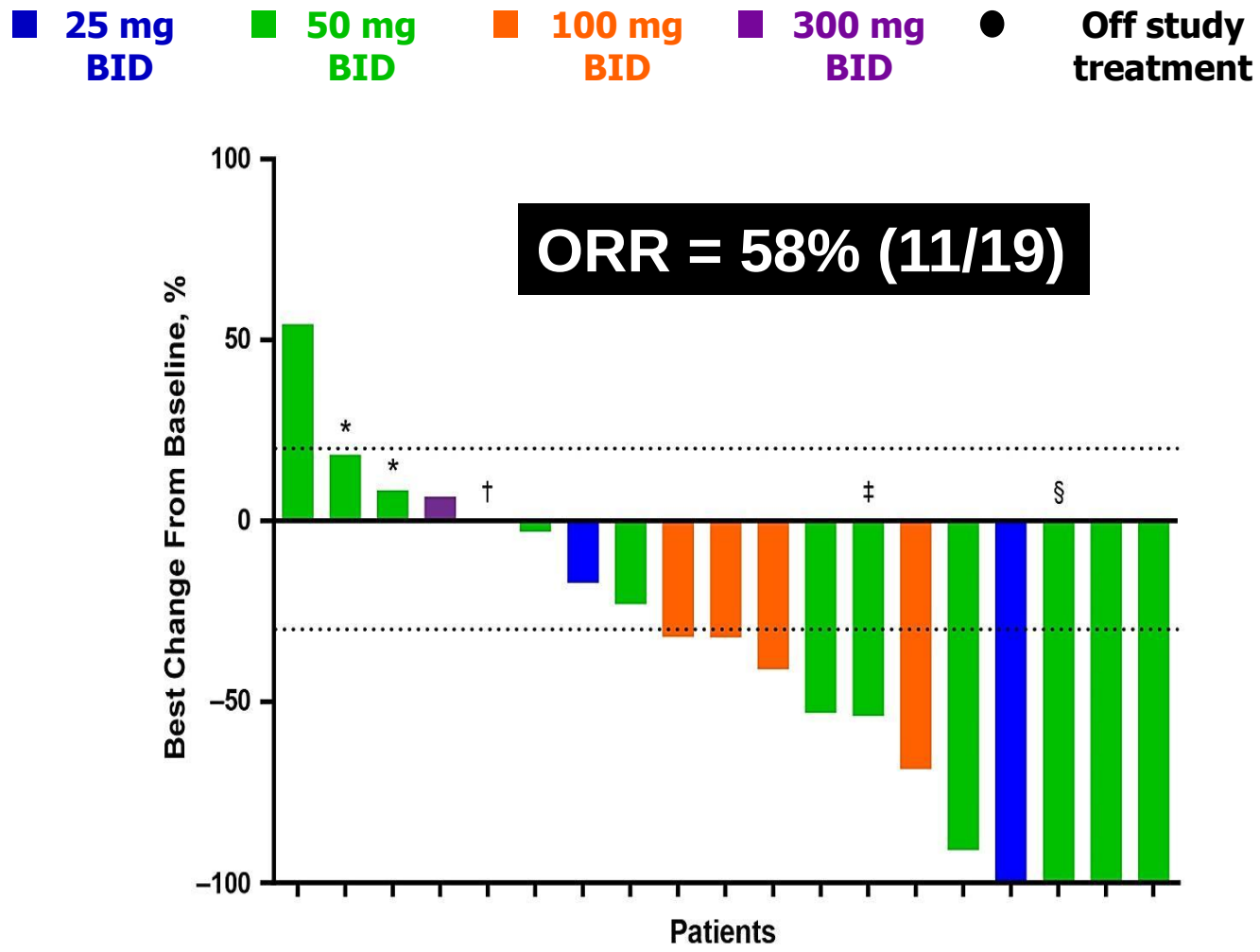




Oral Immuno Modulator	Oncolytic Virus	CAR T-cells	Bi Spe	Cytokines

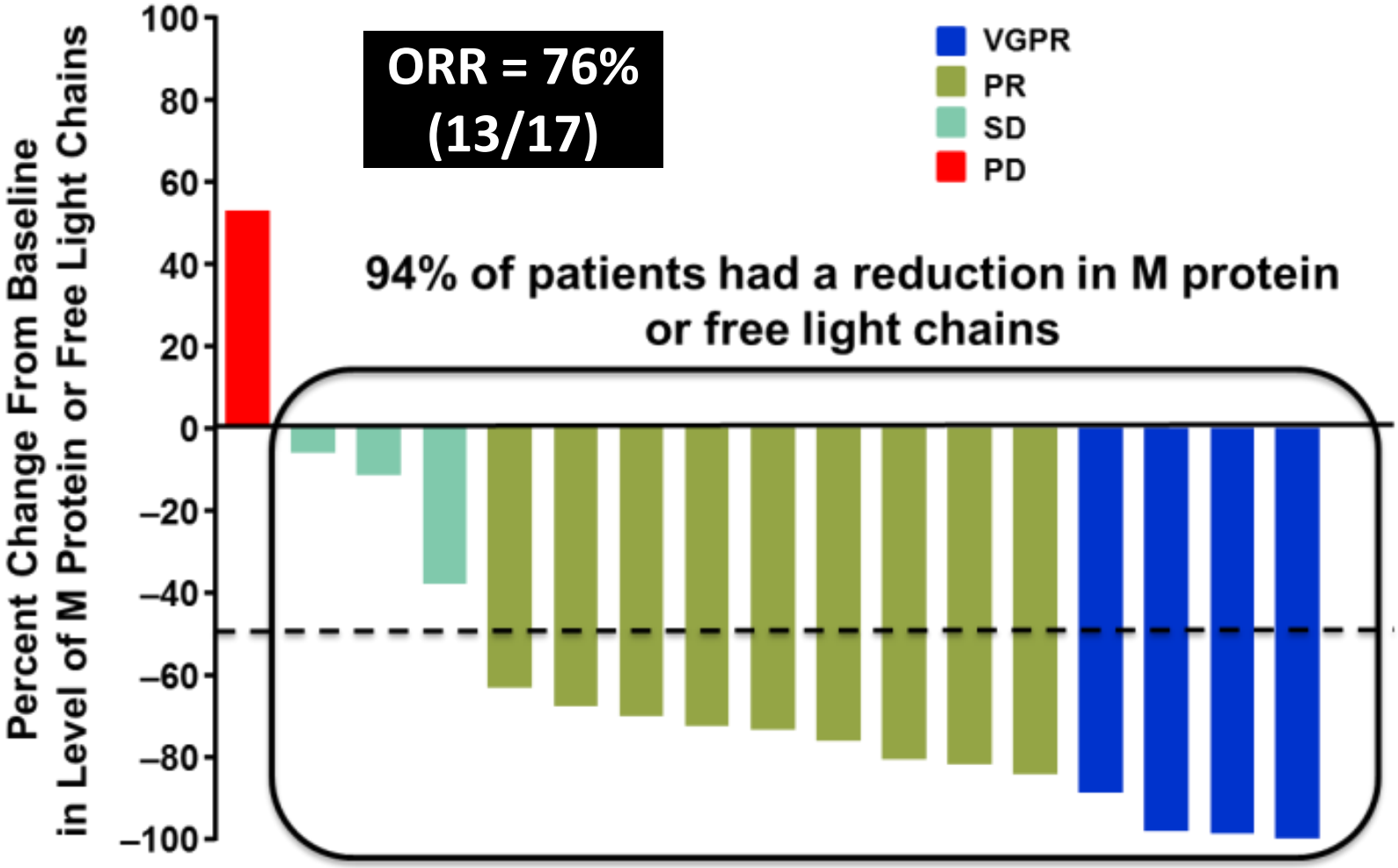
Epacadostat + pembrolizumab in Metastatic Melanoma

(Incyte, NCT02178722)



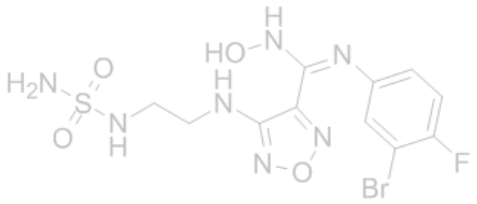
Gangadhar et al. SITC 2015. Abstract #07

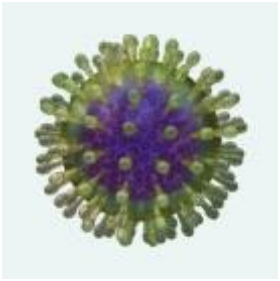
Lenalidomide + aPD-1 in Multiple Myeloma

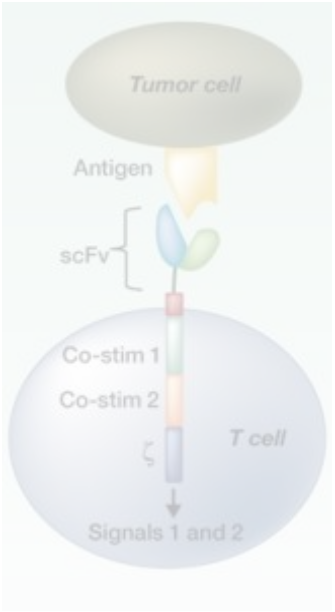


San Miguel et al, ASH 2015

The Future is Bright







IDO inhibitors

Oncolytic Virus

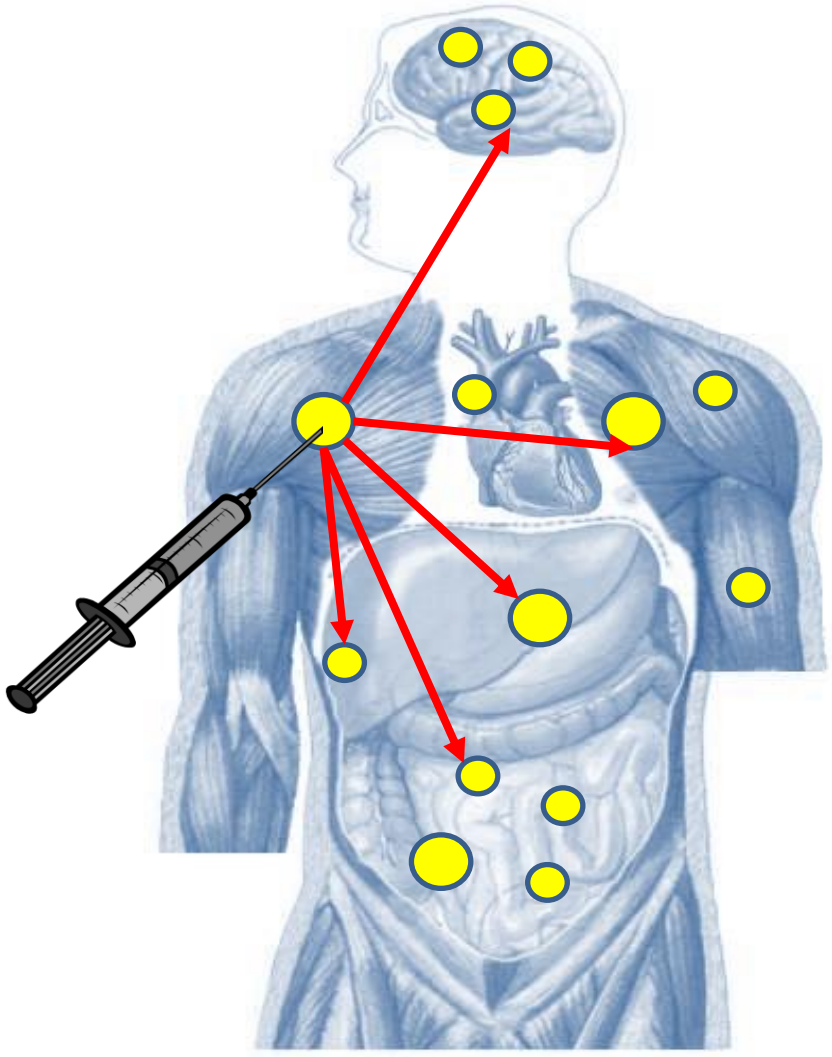
CAR T-cells

Bi Spe

Cytokines

T-VEC EMA approval Q4 2015

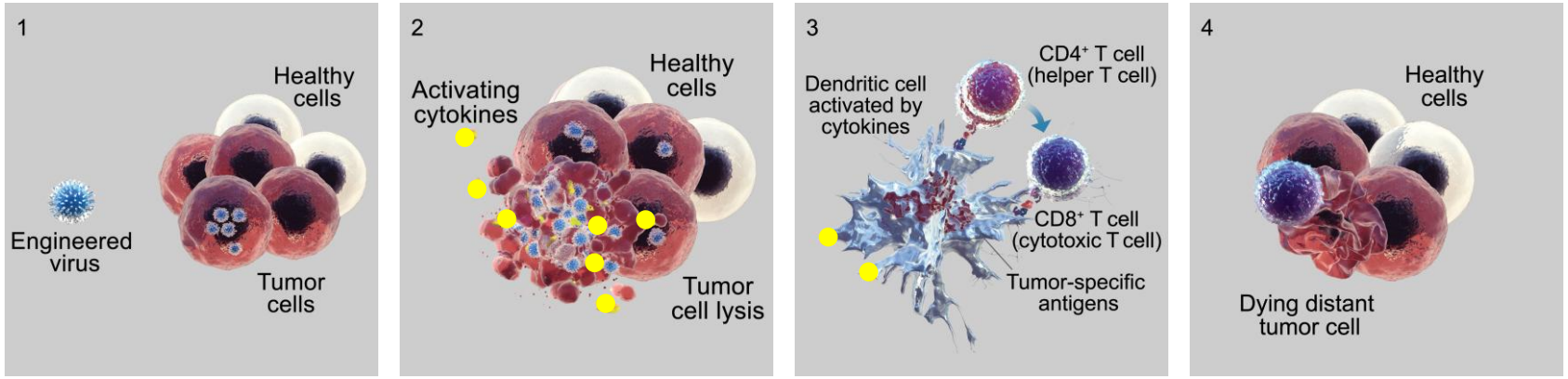
in situ immunization



Oncolytic immunotherapy designed to produce local and systemic effects

Local effect: virus-induced tumour-cell lysis

Systemic effect: tumour-specific immune response



Selective viral replication in tumour tissue[1,2]

Tumour cells rupture for an oncolytic effect[1–3]

Systemic tumour-specific immune response[4,5]

Death of distant cancer cells[4–6]

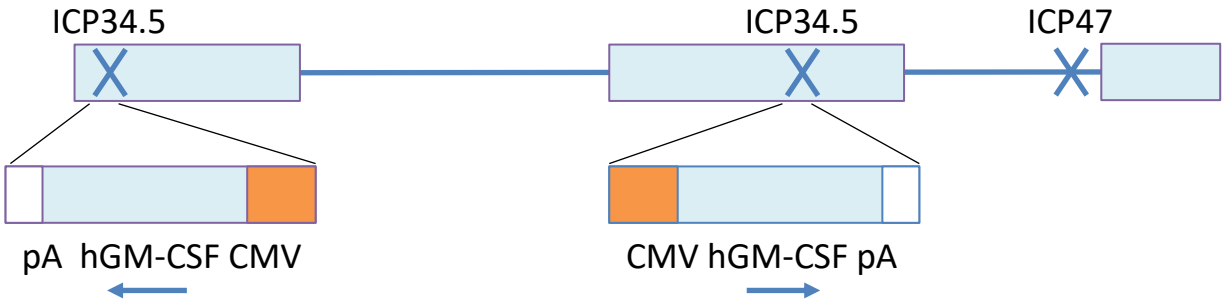
Proposed mechanism of action for T-VEC.

1. Hawkins LK, et al. Lancet Oncol 2002;3:17–26; 2. Fukuhara H, Todo T. Curr Cancer Drug Targets 2007;7:149–155;
3. Pol JG, et al. Virus Adapt Treat 2012;4:1–21; 4. Melcher A, et al. Mol Ther 2011;19:1008–16;
5. Dranoff G. Oncogene 2003;22:3188–92; 6. Liu BL, et al. Gene Ther 2003;10:292–303.

T-VEC – an oncolytic HSV-1 strain engineered for tumour-selective replication and antitumour immune responses

Modification	Rationale
HSV-1 strain, JS1	Improves tumour-cell lysis compared with other strains
Deletion of ICP34.5	Provides tumour-selective replication
Deletion of ICP47	Prevents ICP47 from blocking antigen presentation (restores antitumour immune response)
Early/increased US11 (as a result of ICP47 deletion)	Increases replication of ICP34.5-deleted HSV-1 in tumour cells
Insertion of human GM-CSF (2 copies replacing ICP34.5)	Enhances antitumour immune response

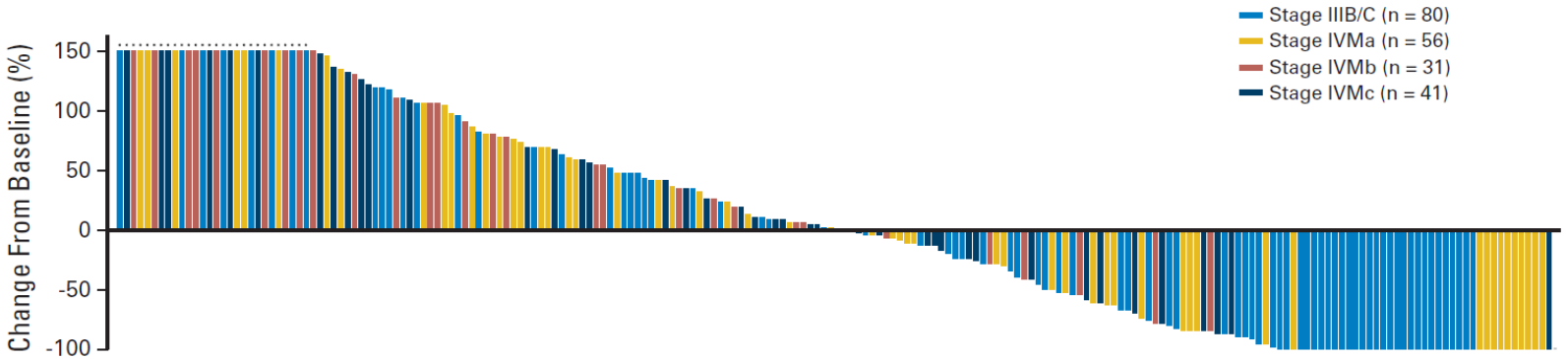
JS1/ICP34.5-/
ICP47-/hGM-CSF



CMV, cytomegalovirus promoter; hGM-CSF, human granulocyte-macrophage colony-stimulating factor; ICP, infected cell protein; pA, polyadenylation (from bovine growth hormone); US11, unique short 11.

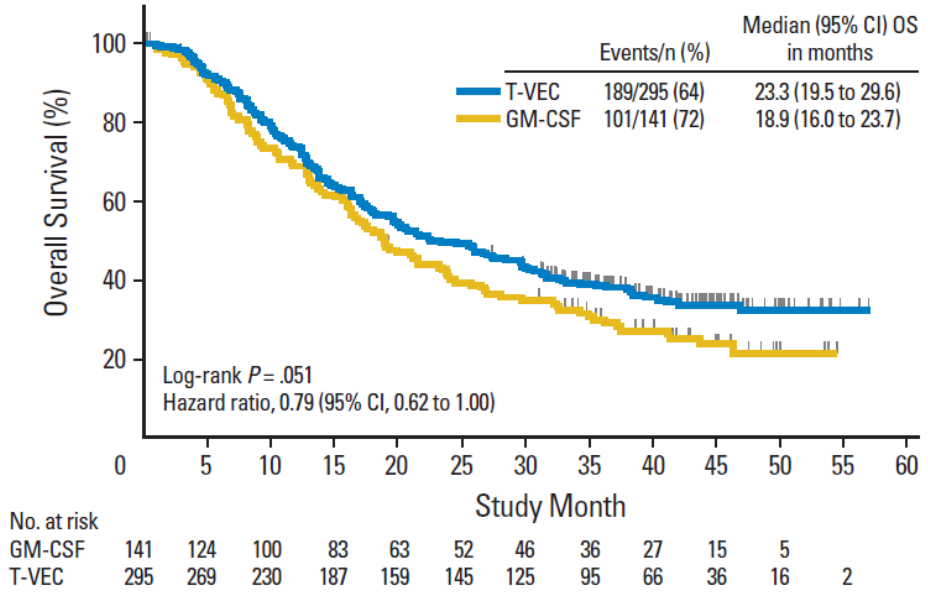
Liu BL, et al. Gene Ther 2003;10:292–303; Kaufman HL, Bines SD. Future Oncol 2010;6:941–9.

T-VEC Safety & Efficacy



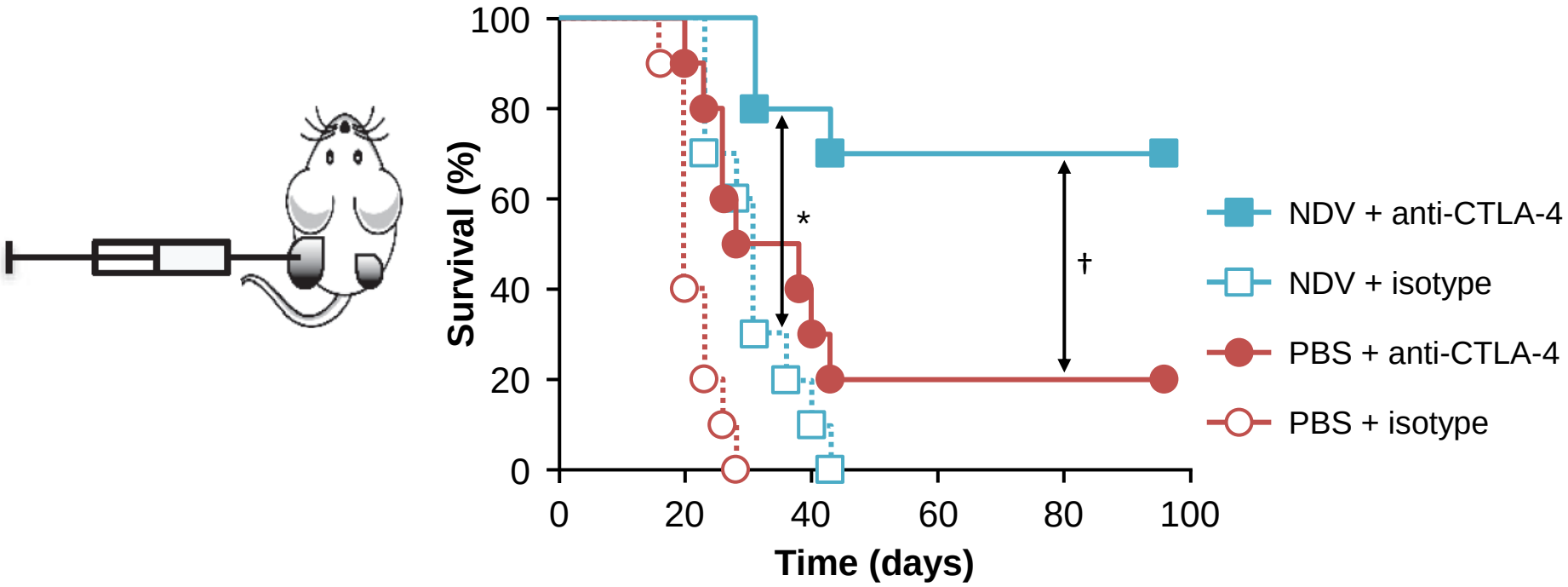
Grade 3-4 (n=292Pts)

- Cellulitis = 2,1%
- Pain = 2,1%
- Vomiting = 1,7%
- Fatigue = 1,7%
- Injection site pain = 1%



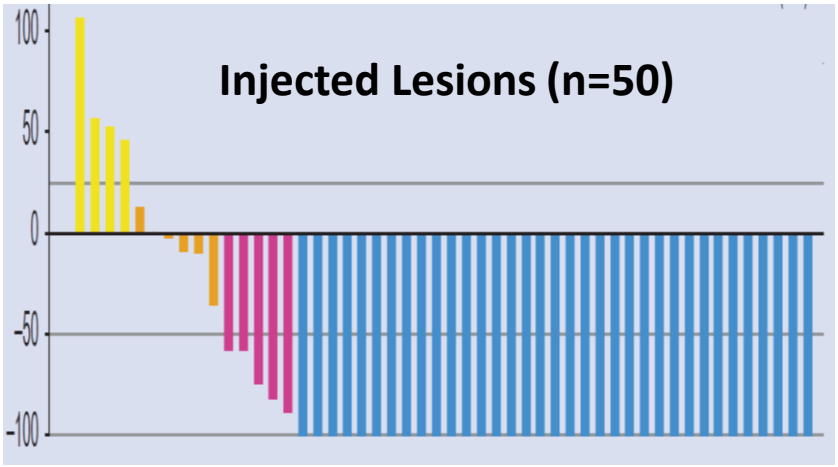
Andtbacka RHI, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. J Clin Oncol. 2015;33:2780–8.

Localised oncolytic virotherapy can overcome systemic tumour resistance to immune checkpoint blockade therapy



Zamarin D, et al. Sci Transl Med 2014;6,:226ra32.

IT T-VEC + pembrolizumab in Melanoma



ORR = 57% (irRC)

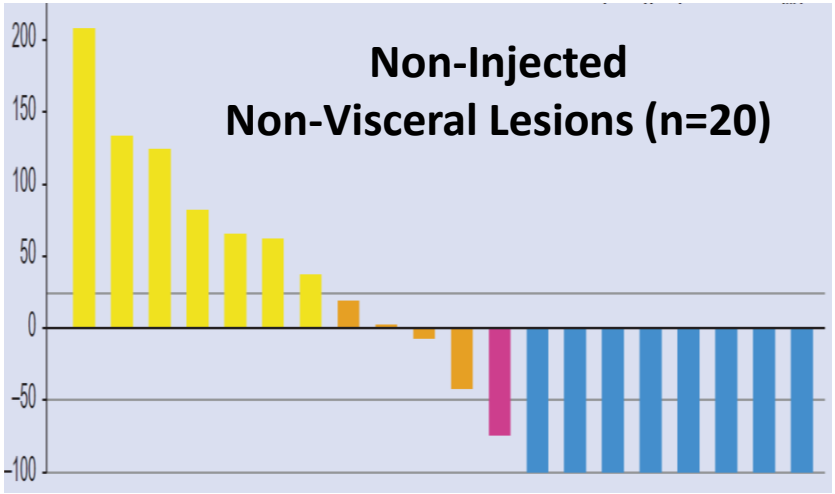
ORR pembro alone ~ 33%

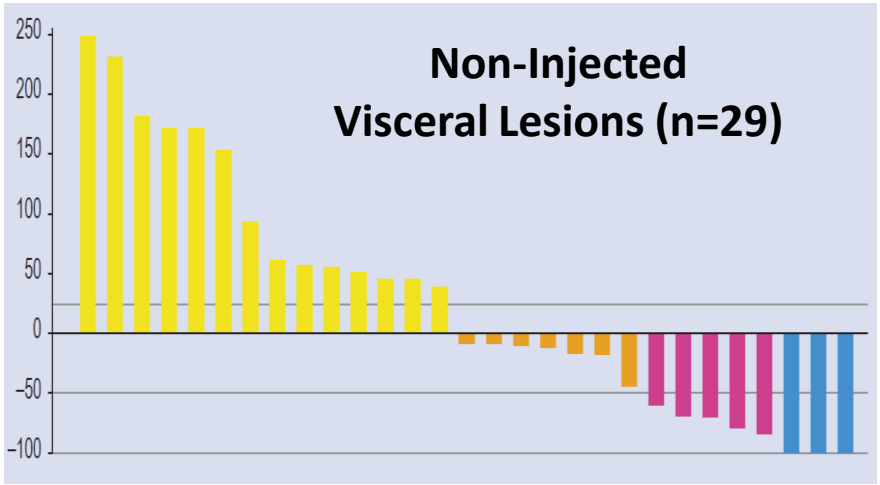
CR rate = 24% (irRC)

CR rate pembro alone ~ 6% (RECIST)

PFS at 9 month = 71%

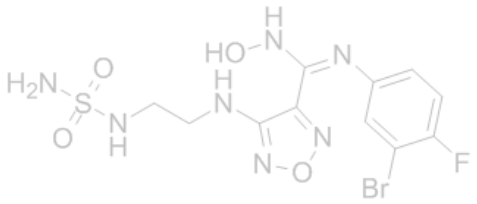
PFS at 9 months pembro alone ~40%

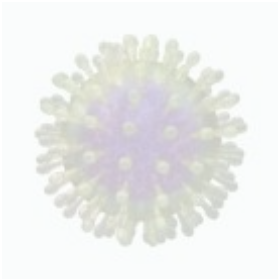


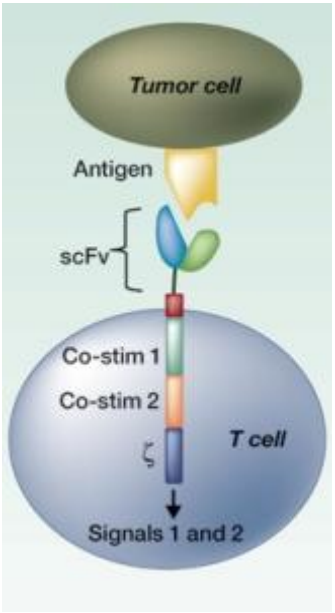


G.Long, ASCO 2016

The Future is Bright







IDO inhibitors

Oncolytic Virus

CAR T-cells

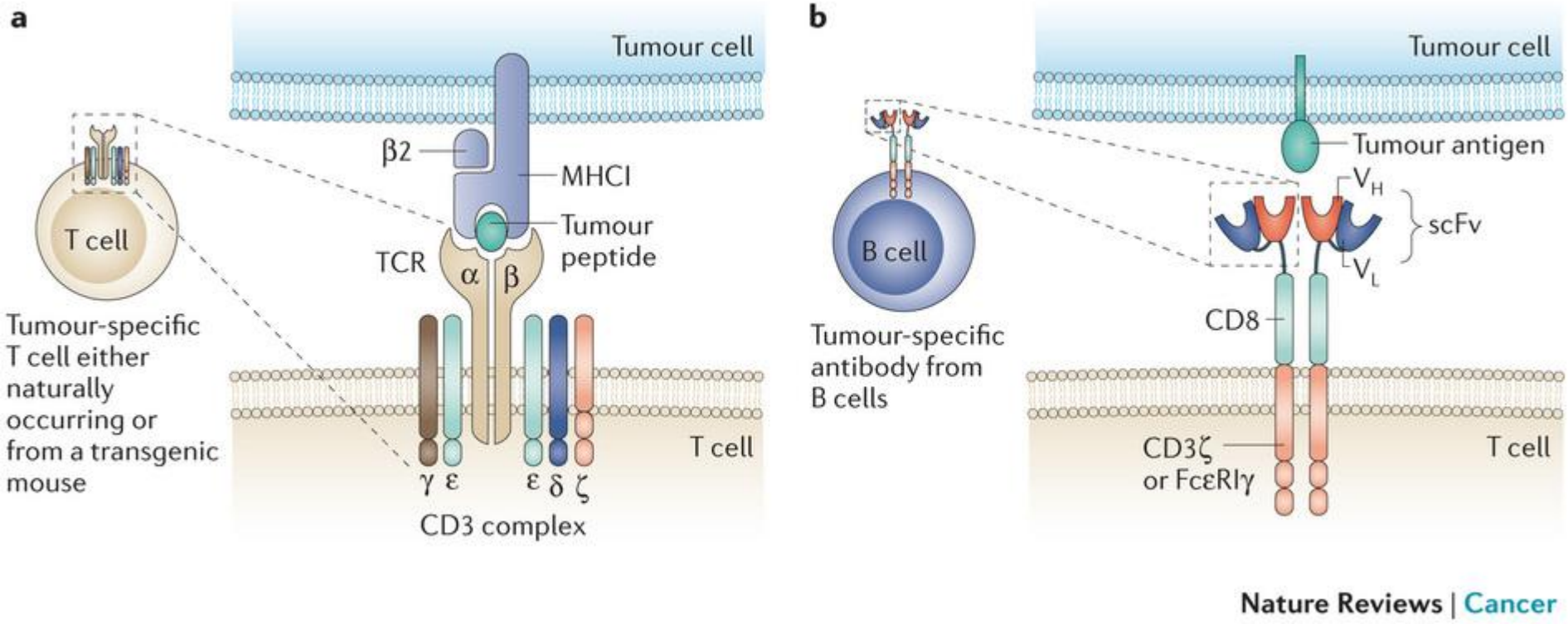
Bi Spe

Cytokines

Adoptive T-cell Therapy

T-CELL

CAR T-CELL

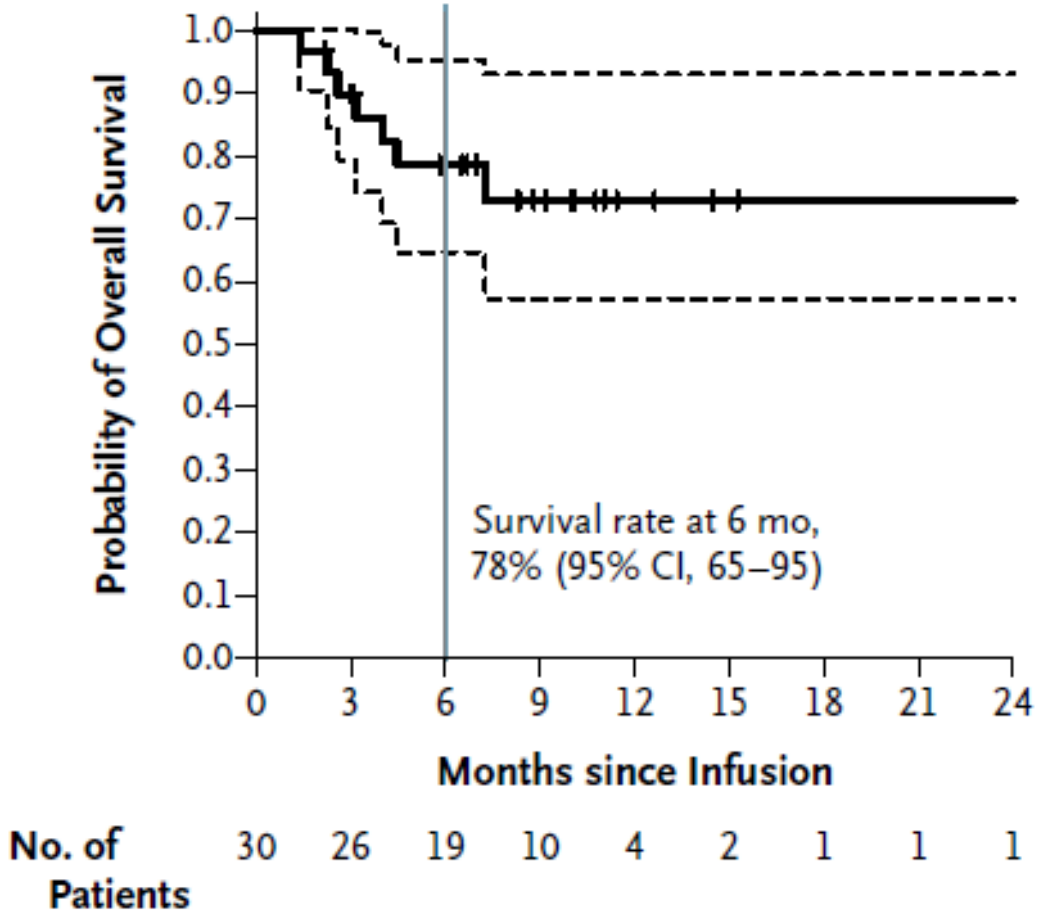


Nature Reviews Cancer, **13**, 525–541 (2013)

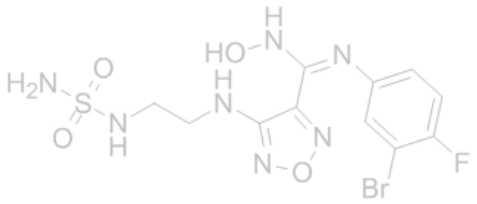
The NEW ENGLAND JOURNAL of MEDICINE

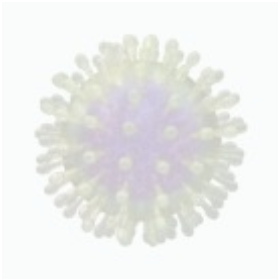
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

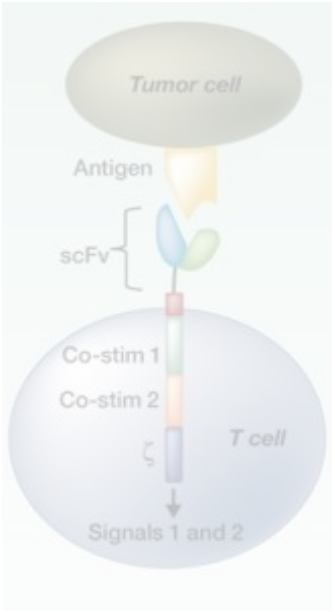
N Engl J Med. 2014 Oct 16;371(16):1507-17

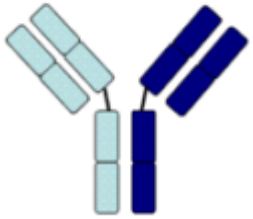


The Future is Bright









IDO inhibitors

Oncolytic Virus

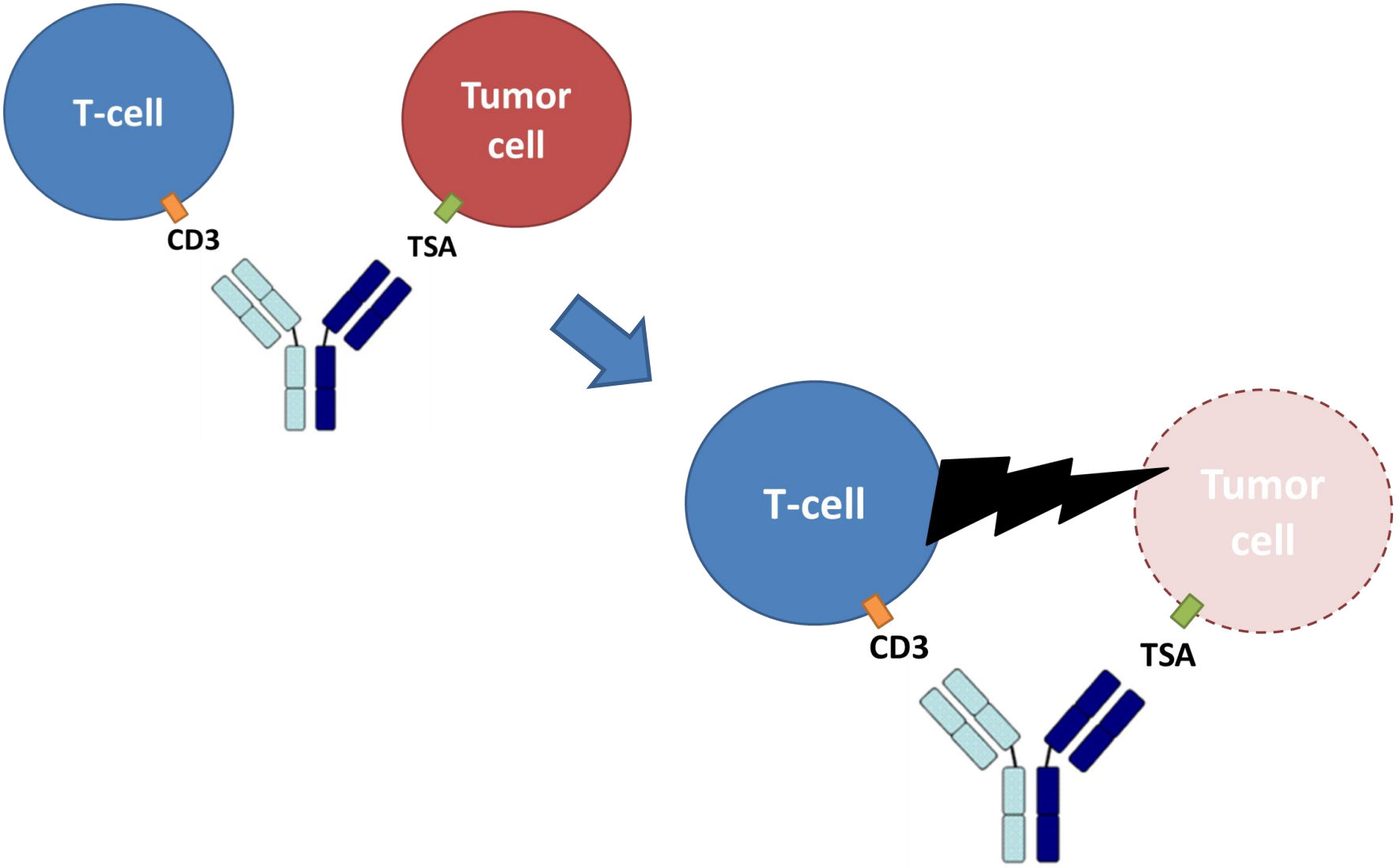
CAR T-cells

Bi Spe

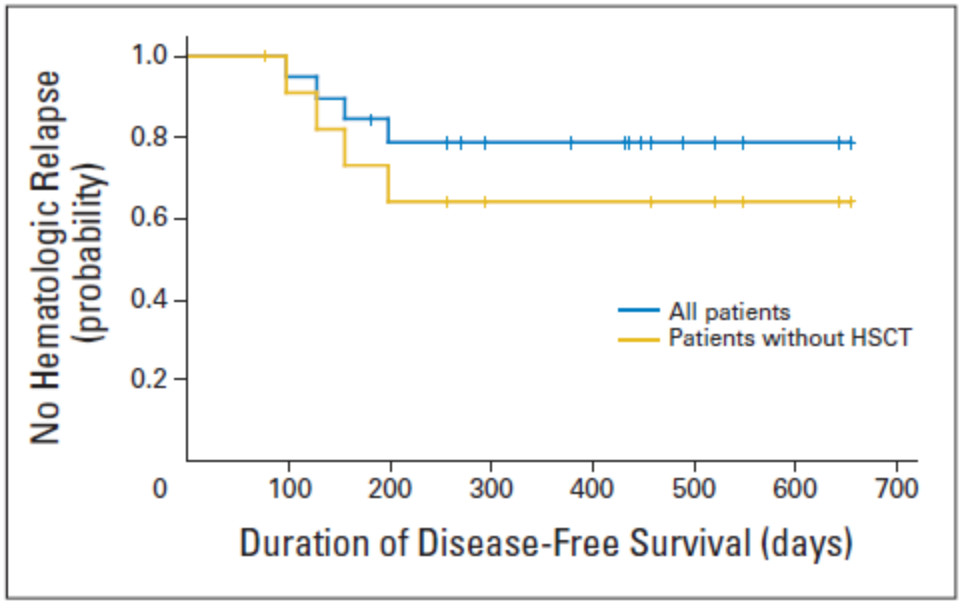
Cytokines

Blinatumomab EMA approval Q4 2015

Bispecific T-cell Engaging mAbs



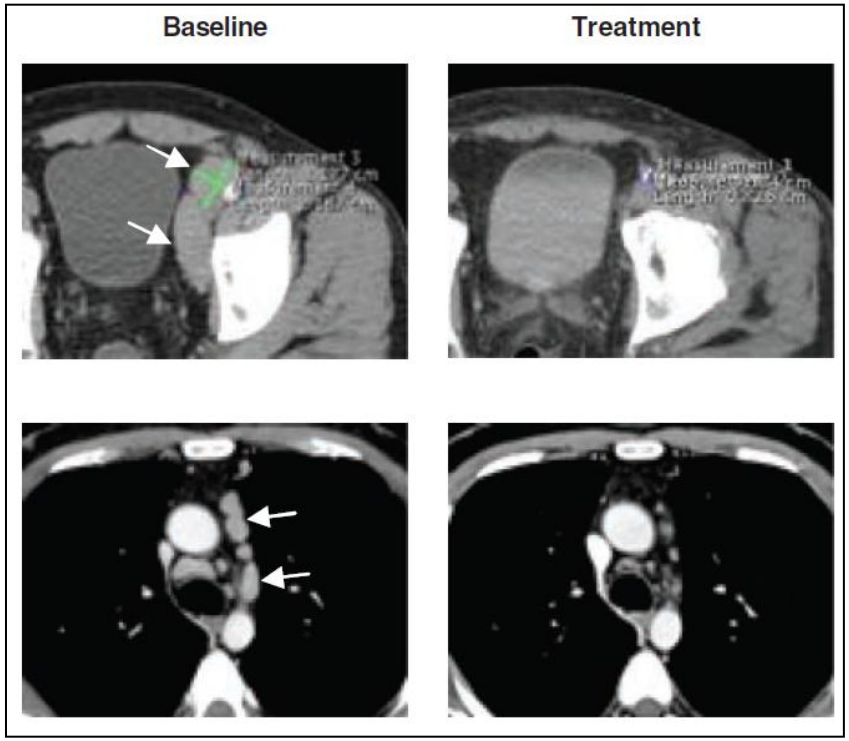
Blinatumomab in ALL & NHL



Blinatumomab on Chemotherapy-Refractory MRD in B-ALL

VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

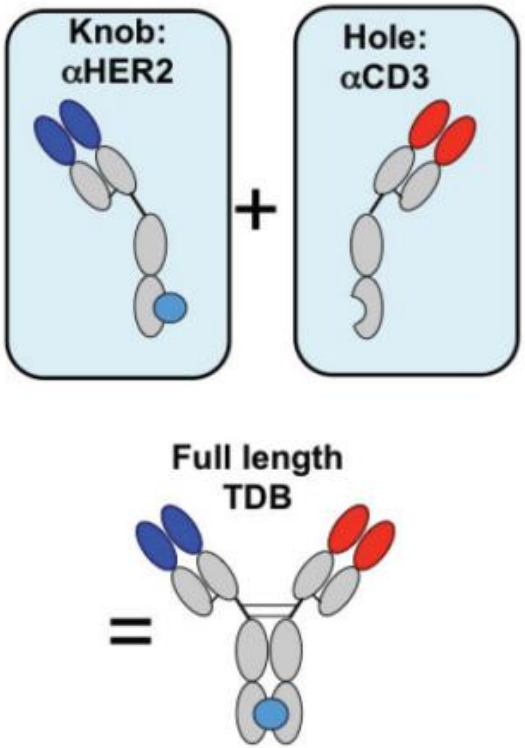


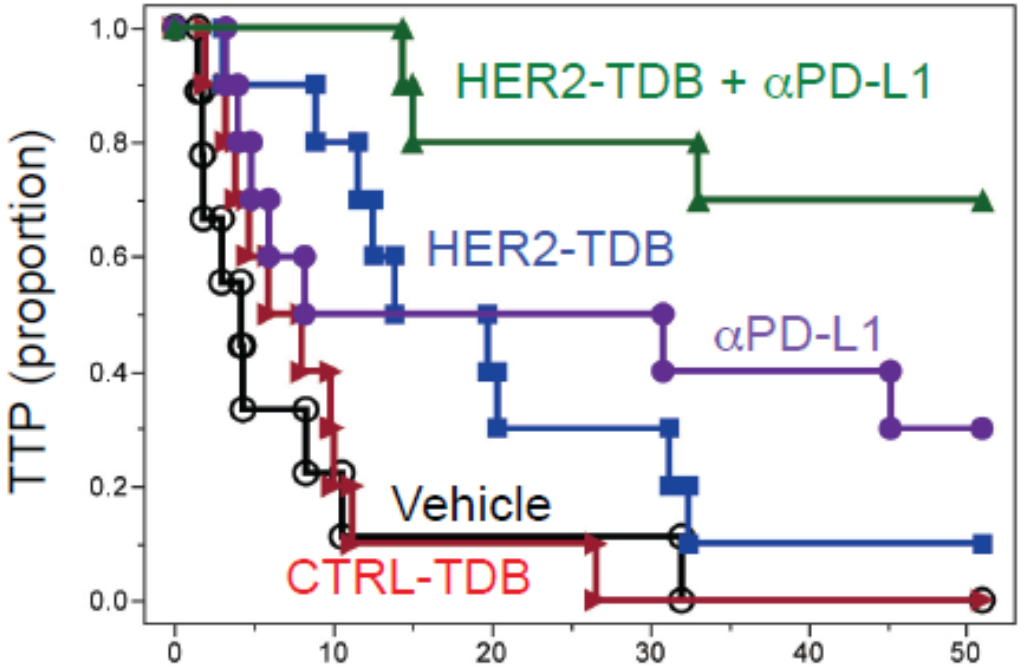
Tumor Regression in Cancer Patients by Very Low Doses of a T Cell–Engaging Antibody

Ralf Bargou *et al.*
Science **321**, 974 (2008);
DOI: 10.1126/science.1158545

Science
AAAS

T-cell Engaging Bispecifics & Immune Checkpoint Blockade

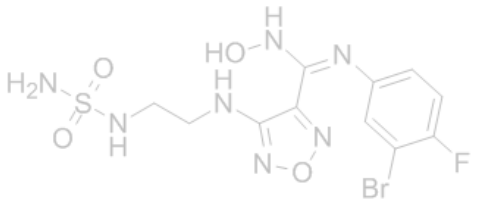


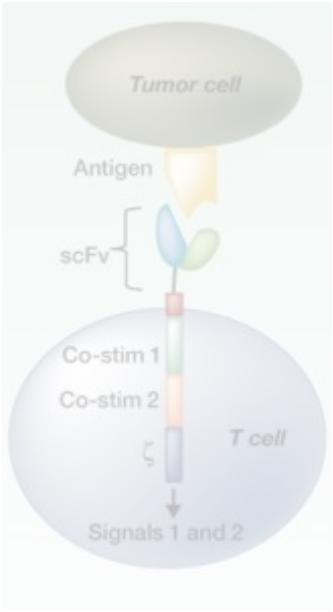


*Junttila, et al. (2014) Cancer Res., **74**,5561–5571.*

NCT02879695: Blinatumomab and Nivolumab With or Without Ipilimumab in Treating Patients With Poor-Risk Relapsed or Refractory CD19+ Precursor B-Lymphoblastic Leukemia -

The Future is Bright



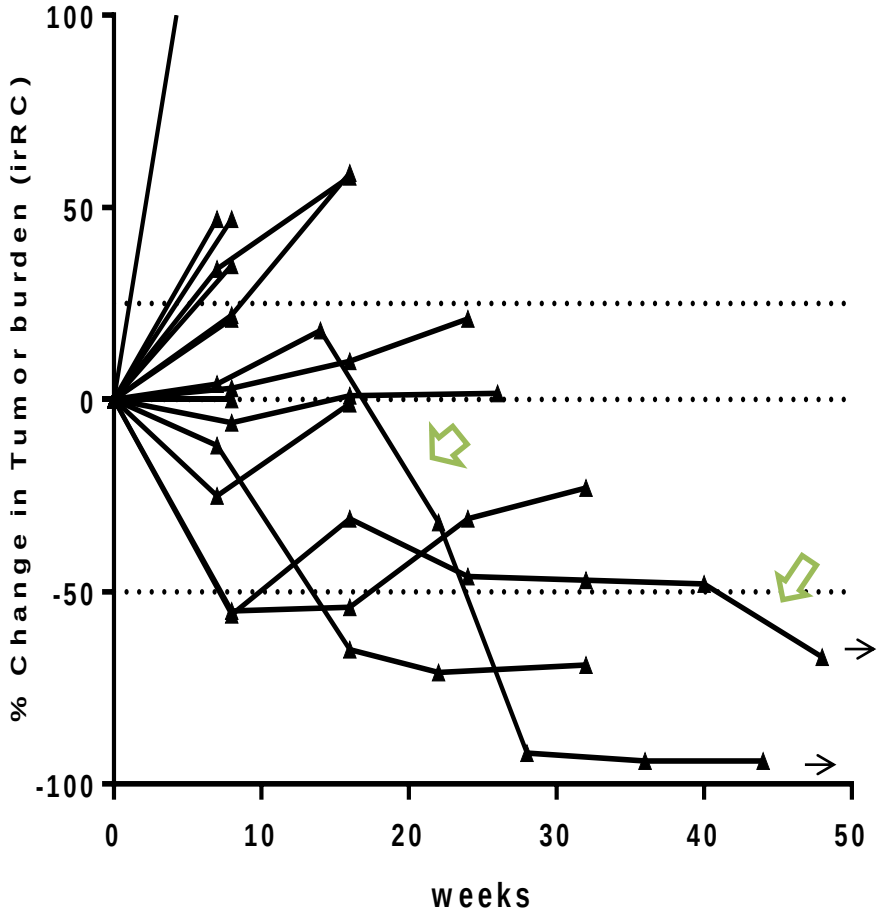


IDO inhibitors	Oncolytic Virus	CAR T-cells	Bi Spe	Cytokines

Expect the Unexpected

AM0010 (PegIL-10) Monotherapy - Activity in RCC

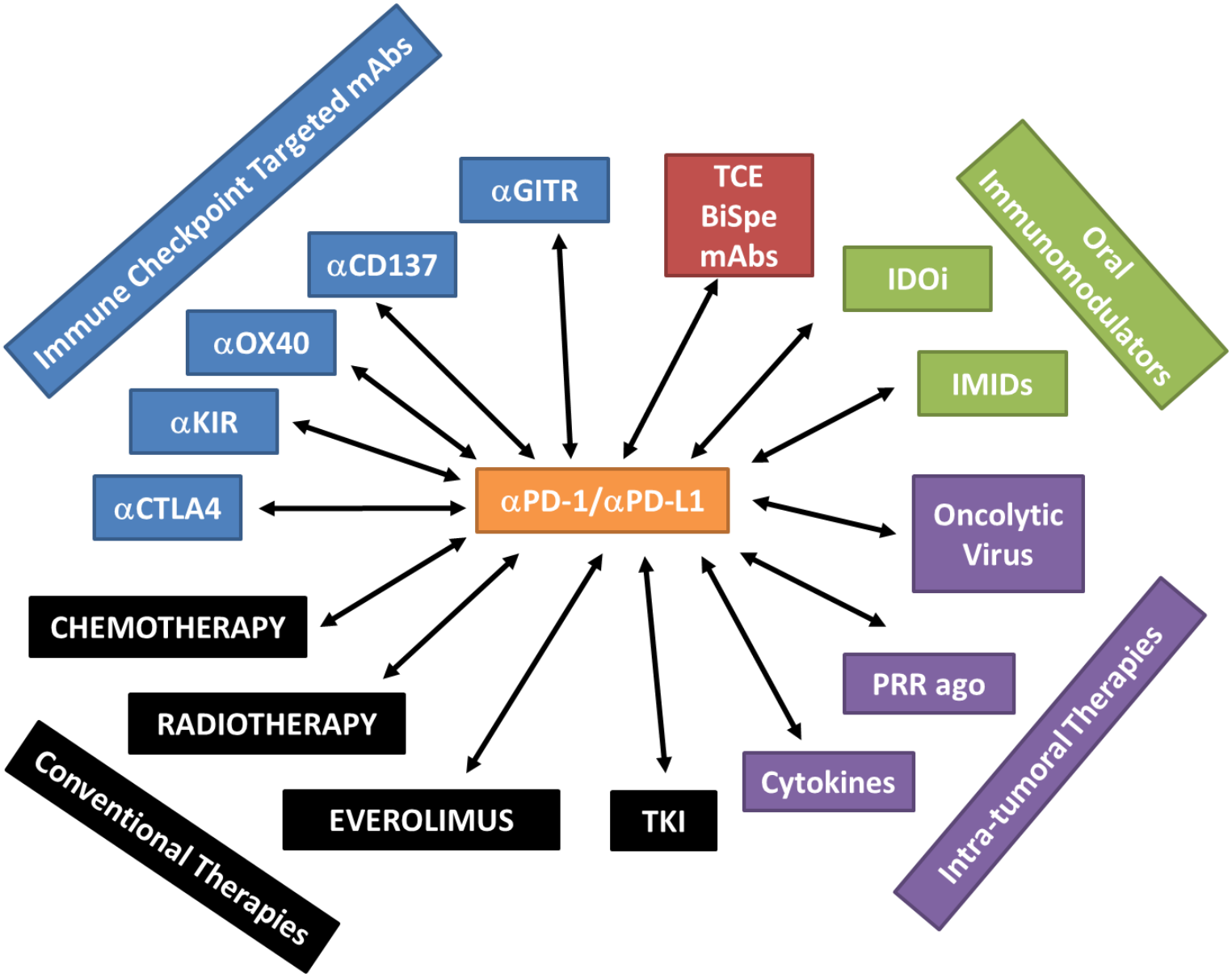
- RCC treated at 20 μg/kg AM0010
- ORR: 27% objective responses (n=15(18))
- Delayed responses after 20+ weeks (⇩)



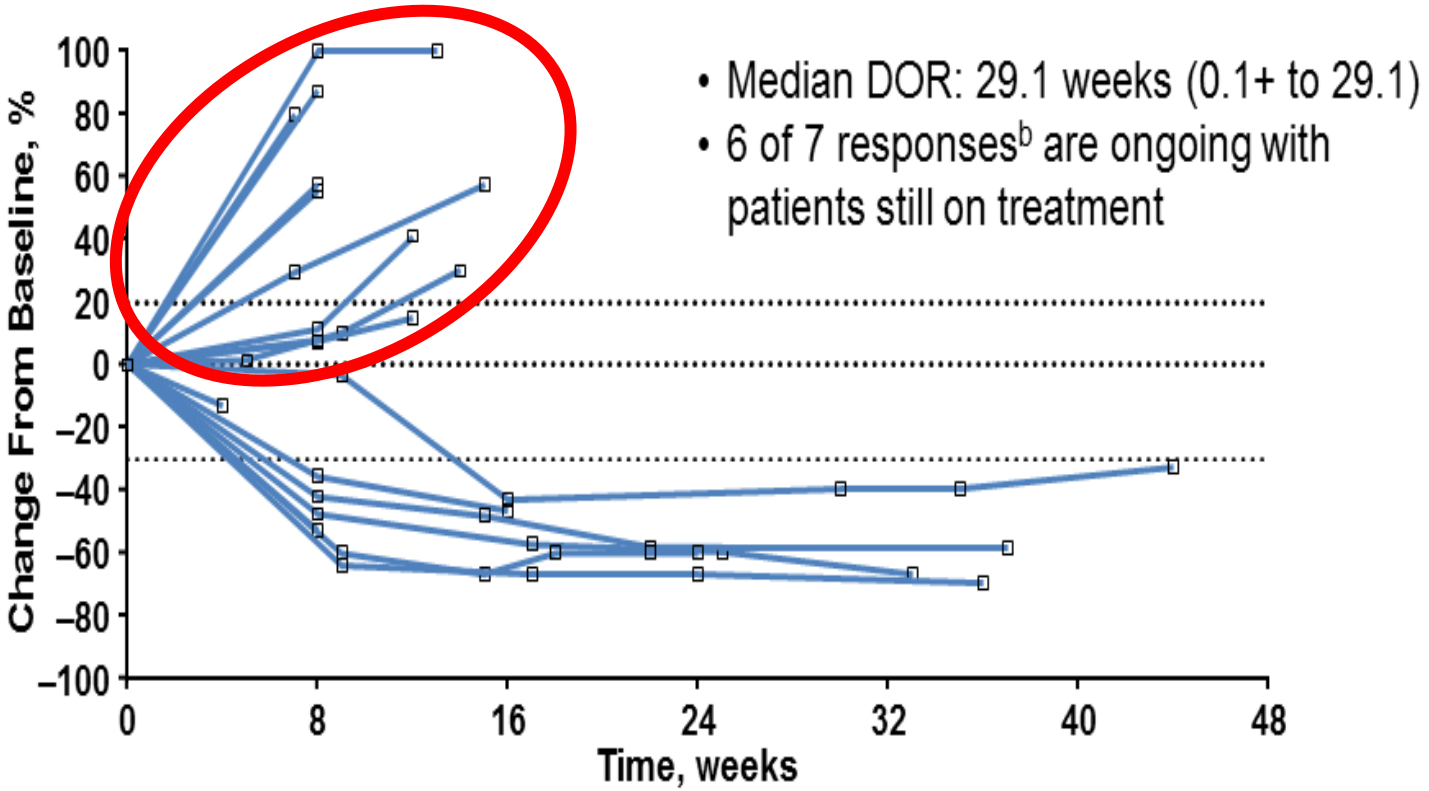
ARMO – AACR 2016

→ Continuing on study

Ongoing Clinical Combinations

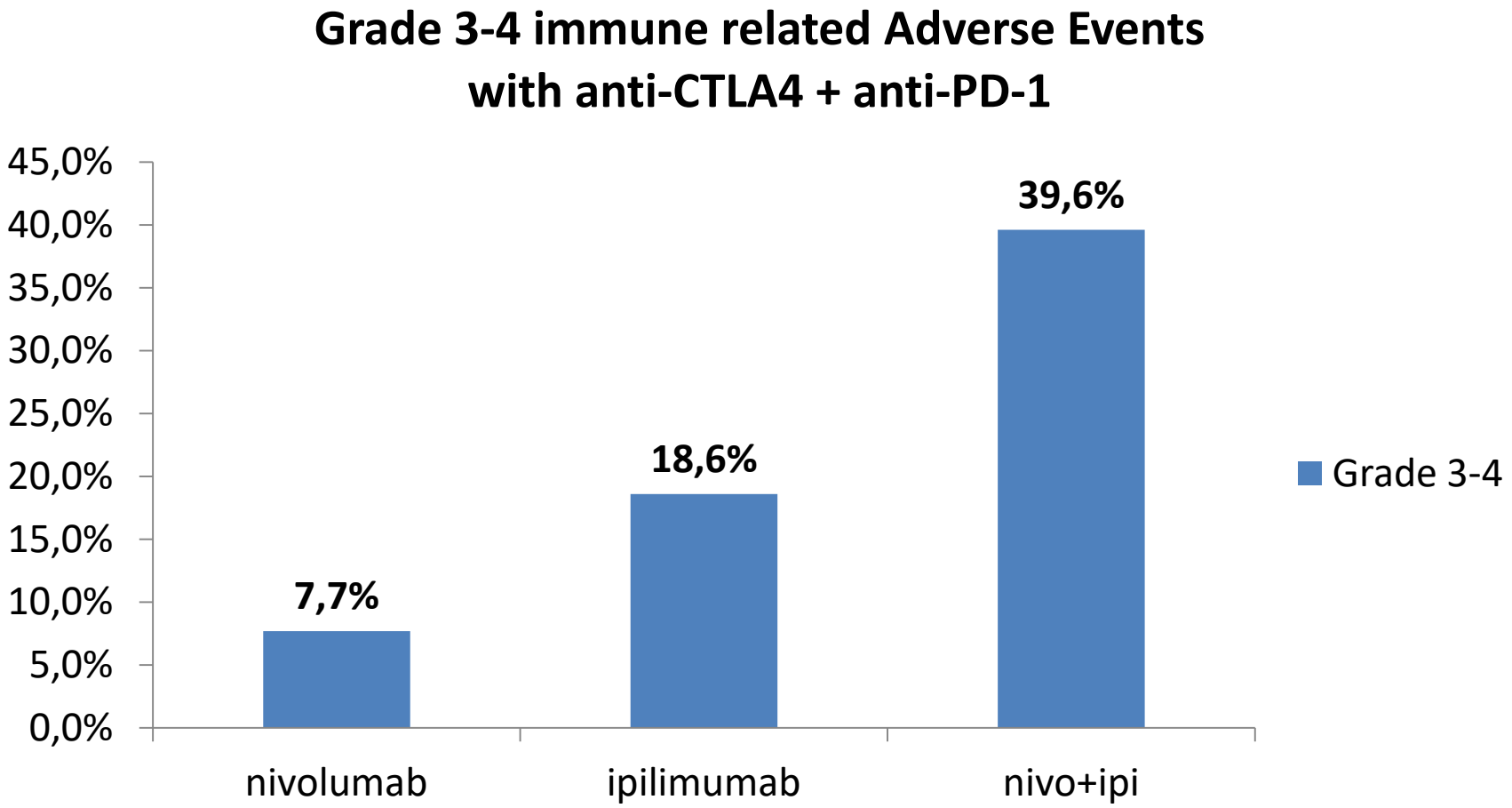


Challenge #1: How do we overcome resistance to immune checkpoint blockade therapy?



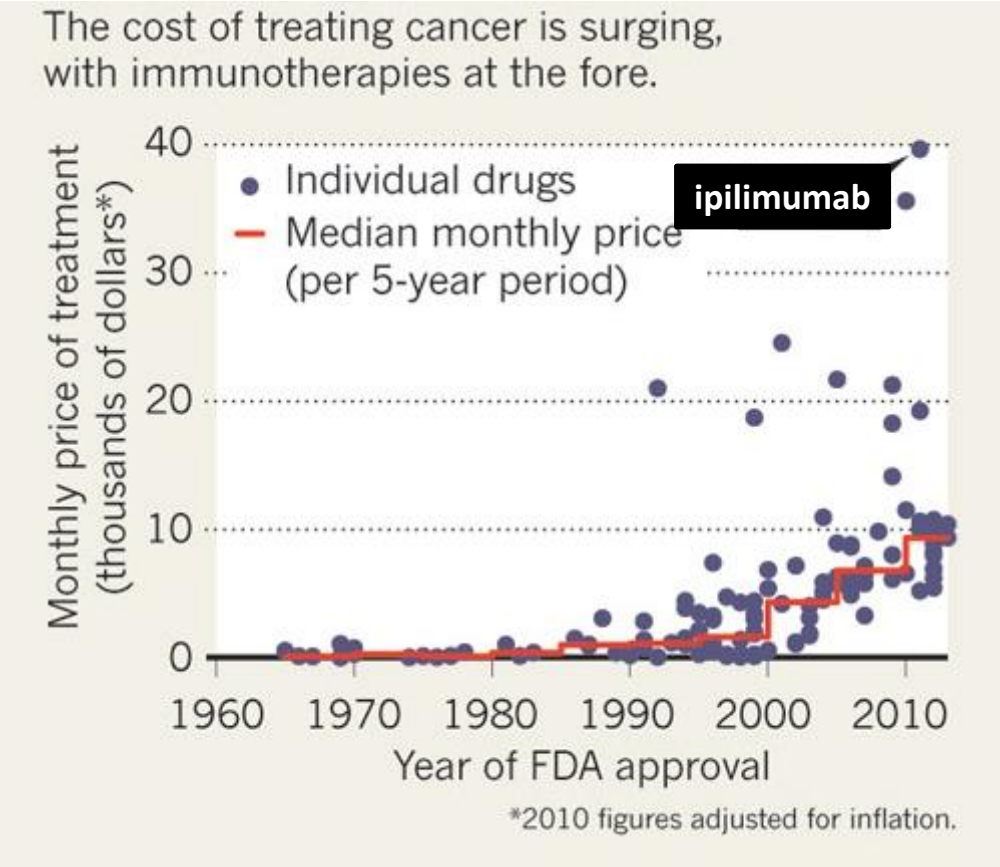
Ott et al. Pembrolizumab in SCLC. WCLC 2015

Challenge #2: Immune Toxicity



Larkin et al, N Engl J Med 2015.

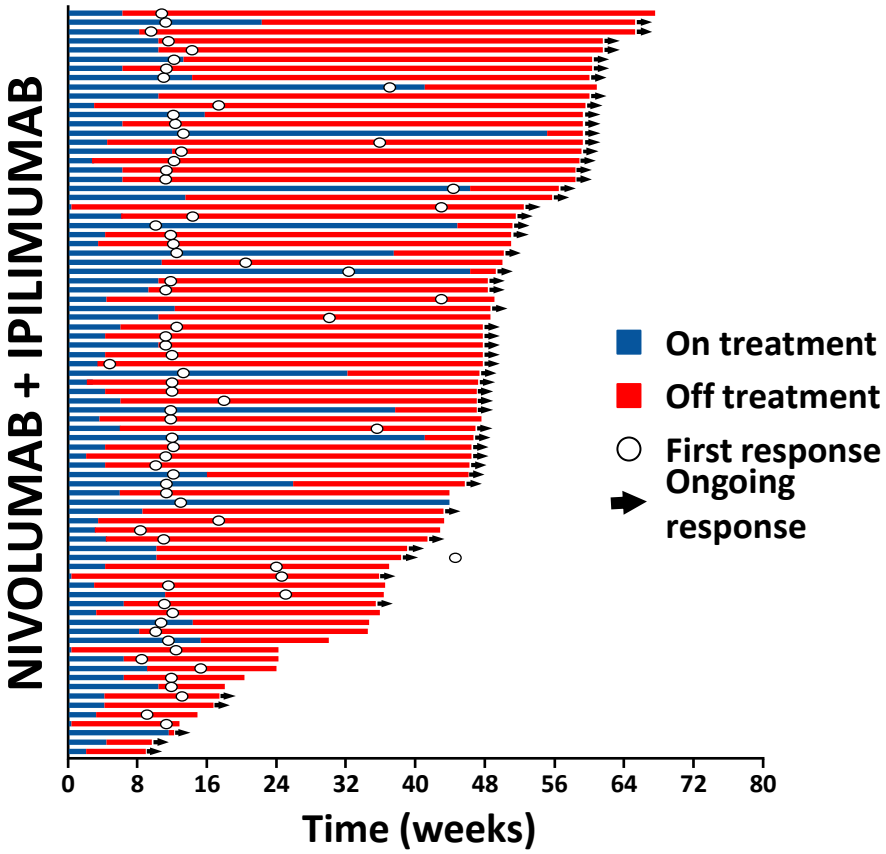
Challenge #3: Financial Toxicity



Nature. 2013 May 30;497(7451)
Immunotherapy's cancer remit widens. Ledford H.

The Good News:
We Might Not Need To Treat for Long

Time to and Durability of Response in Patients Who Discontinued Due to Toxicity



Larkin et al. Abstract Number 3303. ESMO 2015.

Apports cliniques des Immunothérapies

(y compris les virus oncolytiques!)

Aurélien Marabelle, MD, PhD

Clinical Director, Cancer Immunotherapy Pgm

Drug Development Dpt, Prof JC Soria

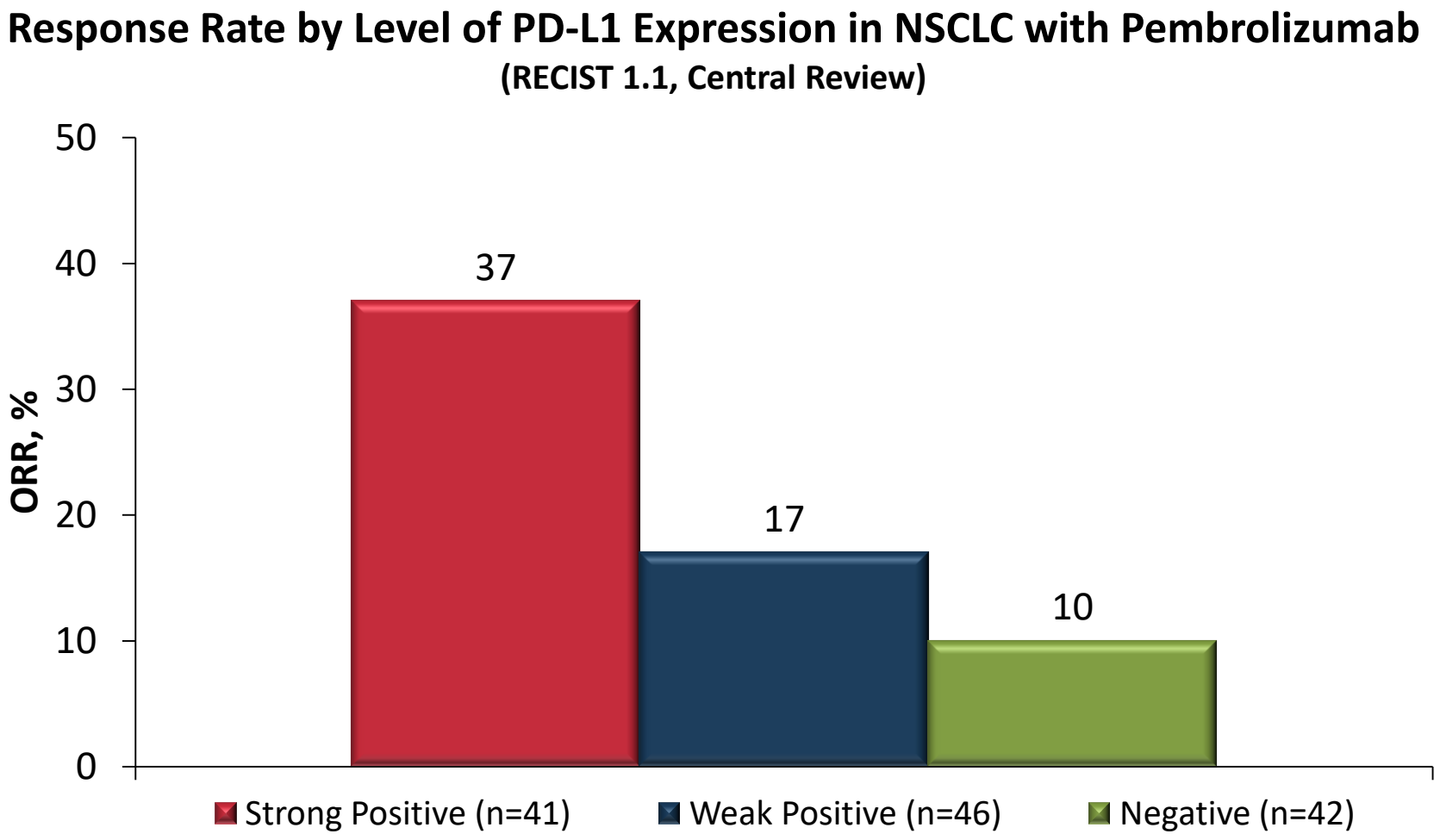
INSERM 1015, Prof L Zitvogel

SFPO, Oct 13th 2016

GUSTAVE ROUSSY

CANCER CAMPUS GRAND PARIS

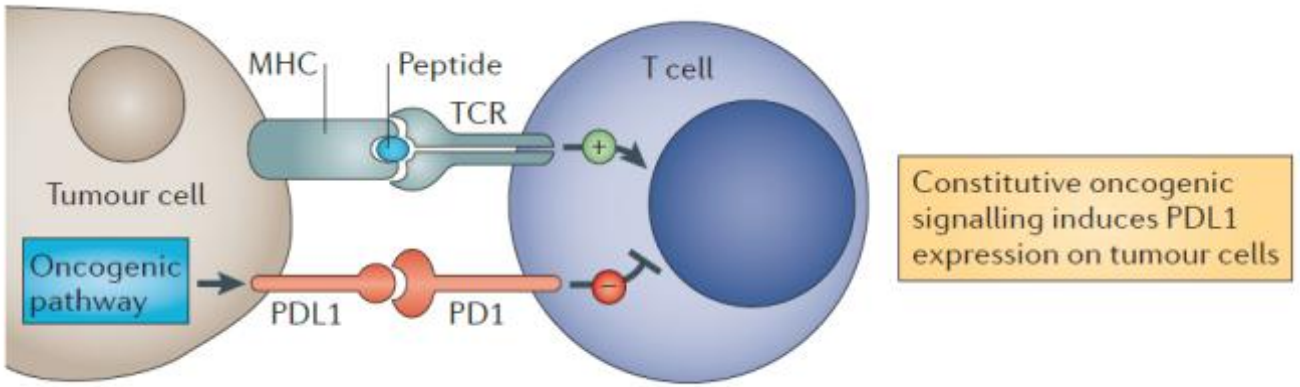
PREDICTIVE VALUE OF PD-L1 EXPRESSION



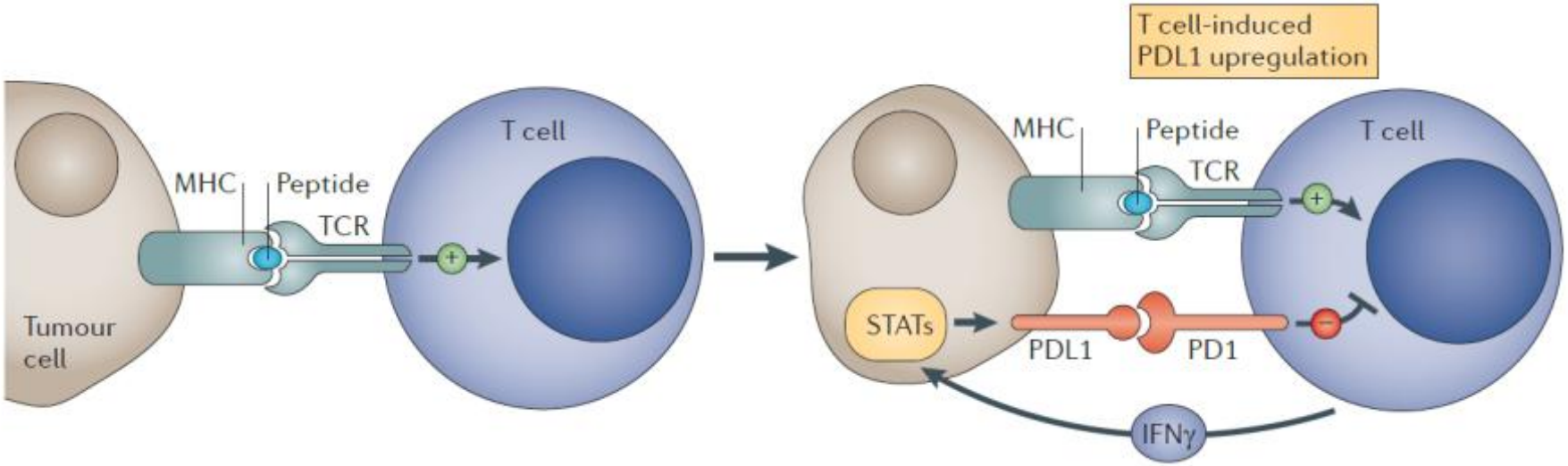
[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression who had measurable disease at baseline per imaging assessment criteria.
Analysis cut-off date: March 3, 2014.

PD-L1 can be expressed in 2 ways

CONSTITUTIVE

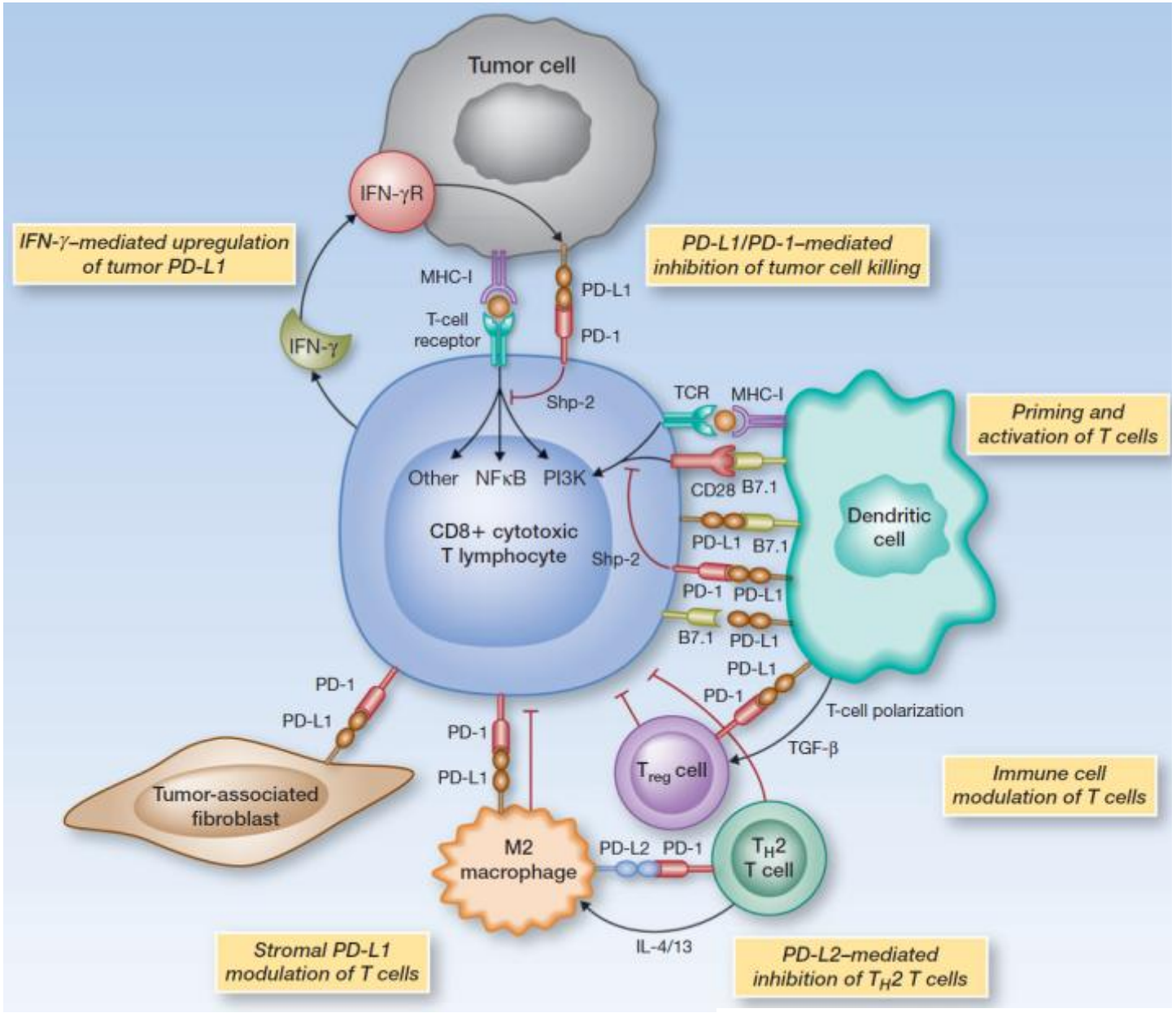


INDUCTIBLE



Nat Rev Cancer. 2012 Mar 22;12(4):252-64

Many Cell Types can be PD-L1+



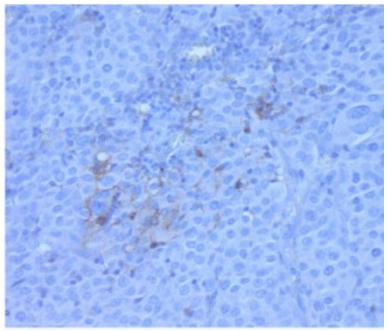
Clin Cancer Res; 18(24) December 15, 2012

PD-L1 Diagnostic assays

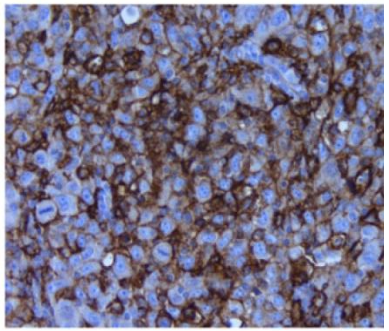
Test	Ventana SP263[14]	Dako 22C3[15]	Dako 28-8[16]	Ventana SP142*[17]
Developed as companion diagnostic assay for:	Durvalumab (AstraZeneca/ MedImmune)	Pembrolizumab (Merck)	Nivolumab (Bristol-Myers Squibb)	Atezolizumab (Roche)
Instrument	Ventana BenchMark Ultra	Dako Autostainer Link 48	Dako Autostainer Link 48	Ventana BenchMark Ultra
PD-L1 antibody	Clone SP263 (rabbit monoclonal)	Clone 22C3 (mouse monoclonal)	Clone 28.8 (rabbit monoclonal)	Clone SP142 (rabbit monoclonal)
Compartment	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane	Tumor cells Tumor-infiltrating immune cells
Cutoff(s) for PD-L1 positivity	≥25% of tumor cells[10]	≥1%; ≥50% of tumor cells[4]	≥1%; ≥5%; ≥10% of tumor cells[3]	≥1%; ≥5%; ≥50% of tumor cells ≥1%; ≥5%; ≥10% of tumor area[18]
Approval status	CE-IVD IVD Class I	IVD companion diagnostic	IVD complementary diagnostic	IVD complementary diagnostic

Intrapatient PD-L1 Discordance

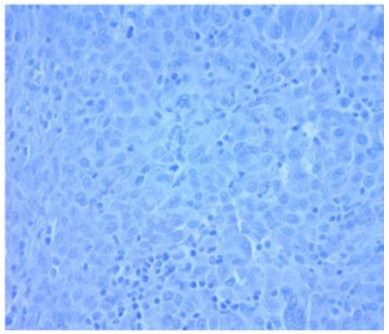
Brain Metastasis



Lymph Node Metastasis



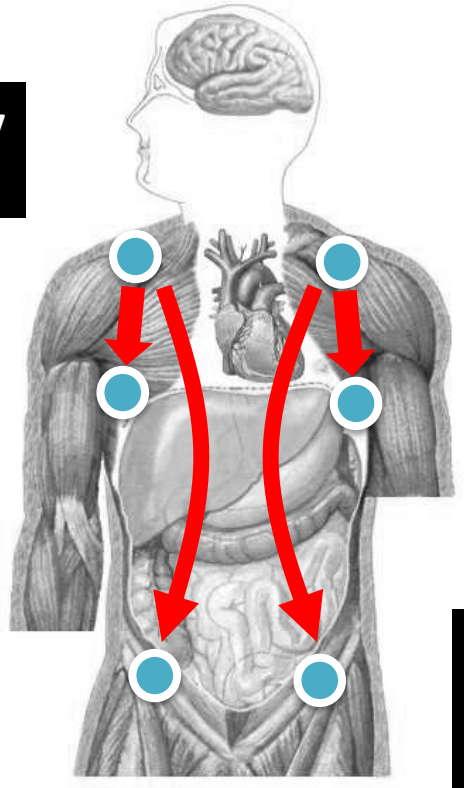
Primary Melanoma



anti-PD-L1, Merck 22C3 IHC clone, 40x

Primary PD-L1+

Primary PD-L1-



18% PD-L1- Loco-Regionale Metastases

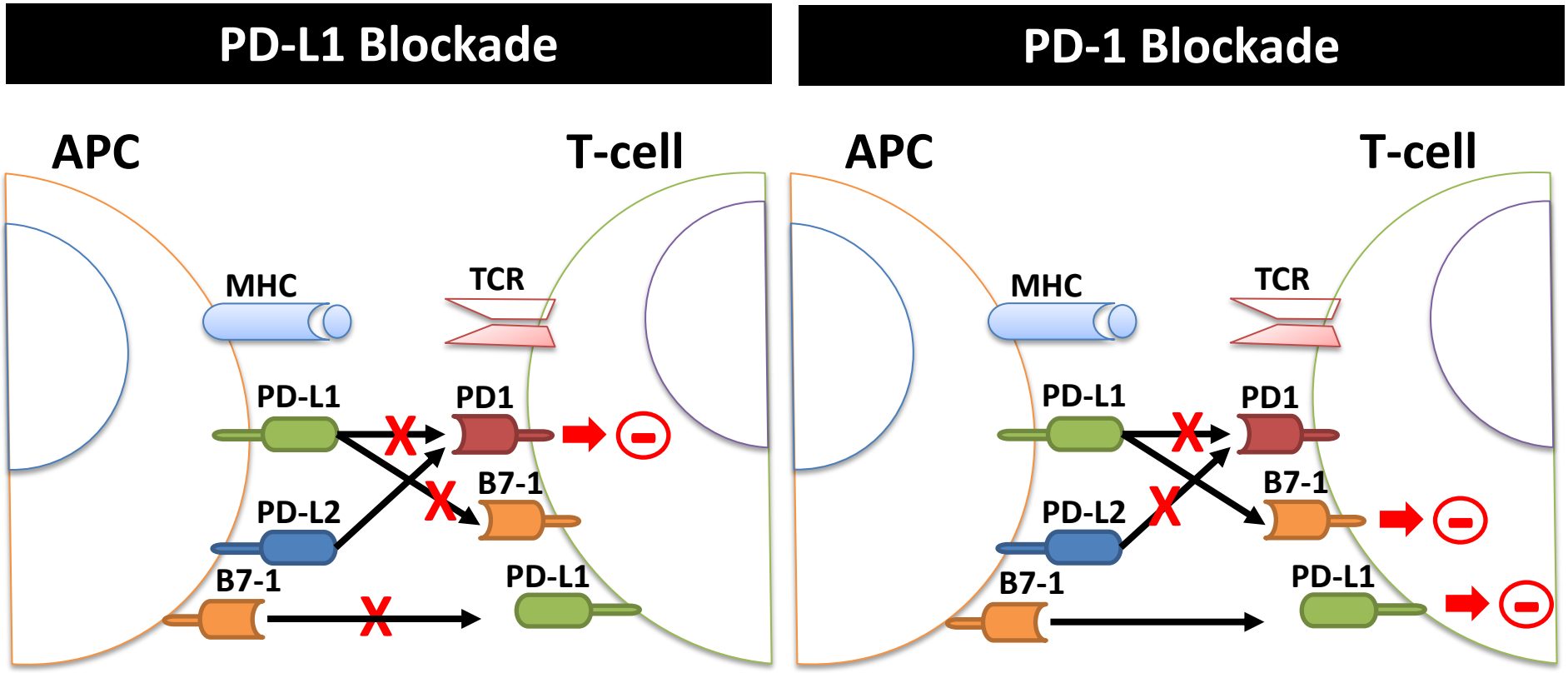
36% PD-L1+ Loco-Regionale Metastases

42% PD-L1- Distant Metastases

55% PD-L1+ Distant Metastases

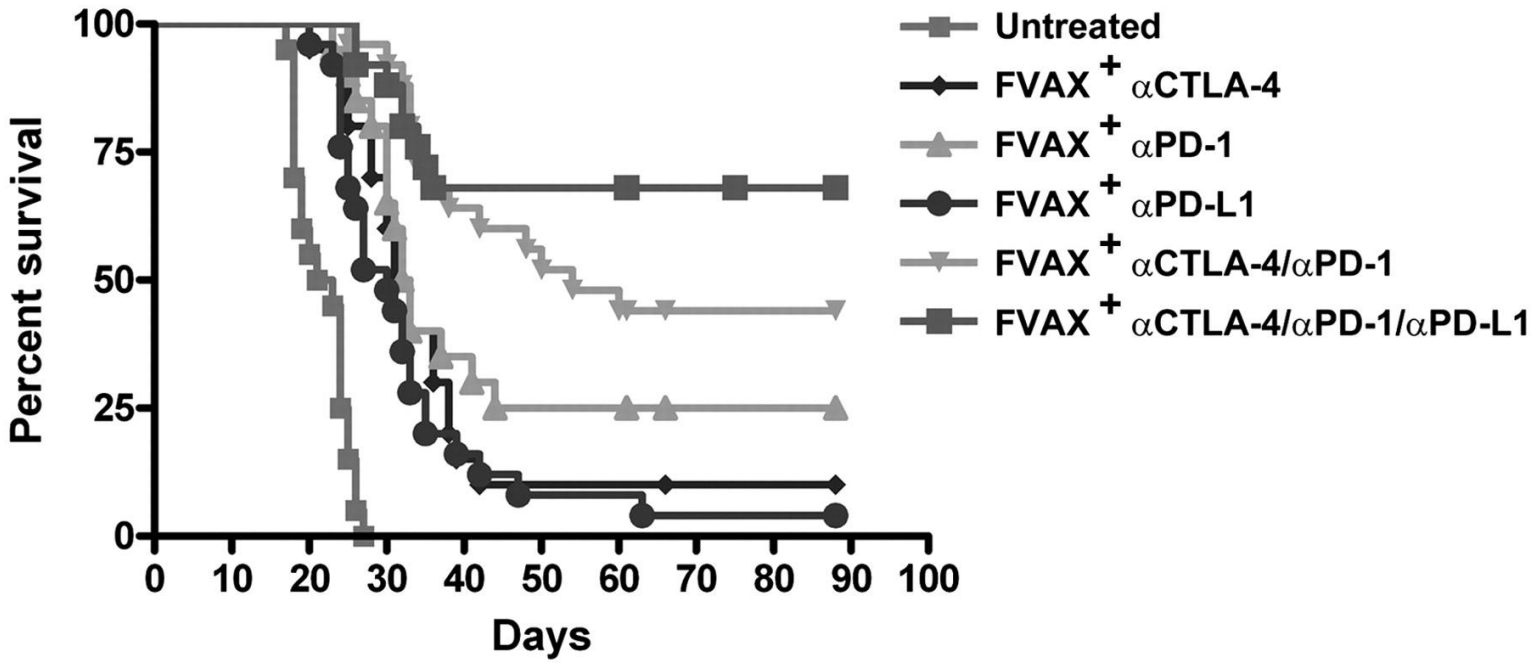
Adapted from Madore J, et al. Pigment Cell Melanoma Res 2015

PD-1/PD-L1 Blockades are not Redundant



Adapted from Annu. Rev. Immunol. 2008. 26:677–704

Anti-PD-1 + Anti-PD-L1 > Anti-PD-1



Curran M, Montalvo W, Yagita H, Allison JP. PNAS 2010;107:4275–80.

ecco

Impact of PD-L2 on response to anti-PD-1 in HNSCC

Overall Response Rate by PD-L1 and PD-L2 Status

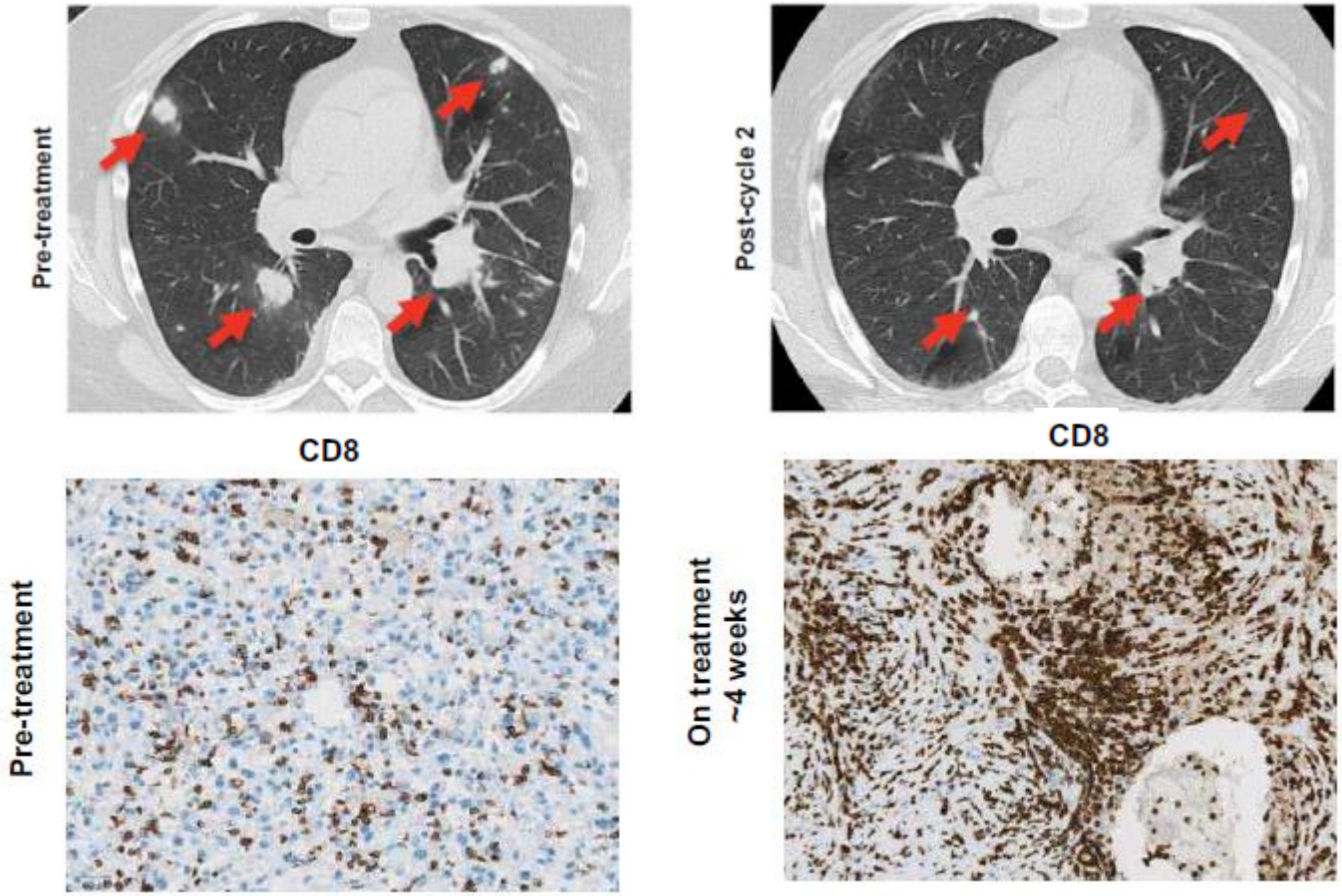
	PD-L2 Status	
PD-L1 Status	**0%**	**≥1%**
0%	**1/18 = 5.6%**	**0/3 = 0%**
≥1%	**4/34 = 11.7%**	**22/89 = 24.7%**

144 HNSCC Pts

- Logistic regression suggests PD-L2 expression is associated with higher ORR after adjusting for PD-L1 expression ($P = 0.072$)
- PD-L2 is positively associated with longer PFS after adjusting for impact of PD-L1 status ($P = 0.031$)

Data suggests that PD-L2 status is associated with outcome in pembrolizumab treated patients

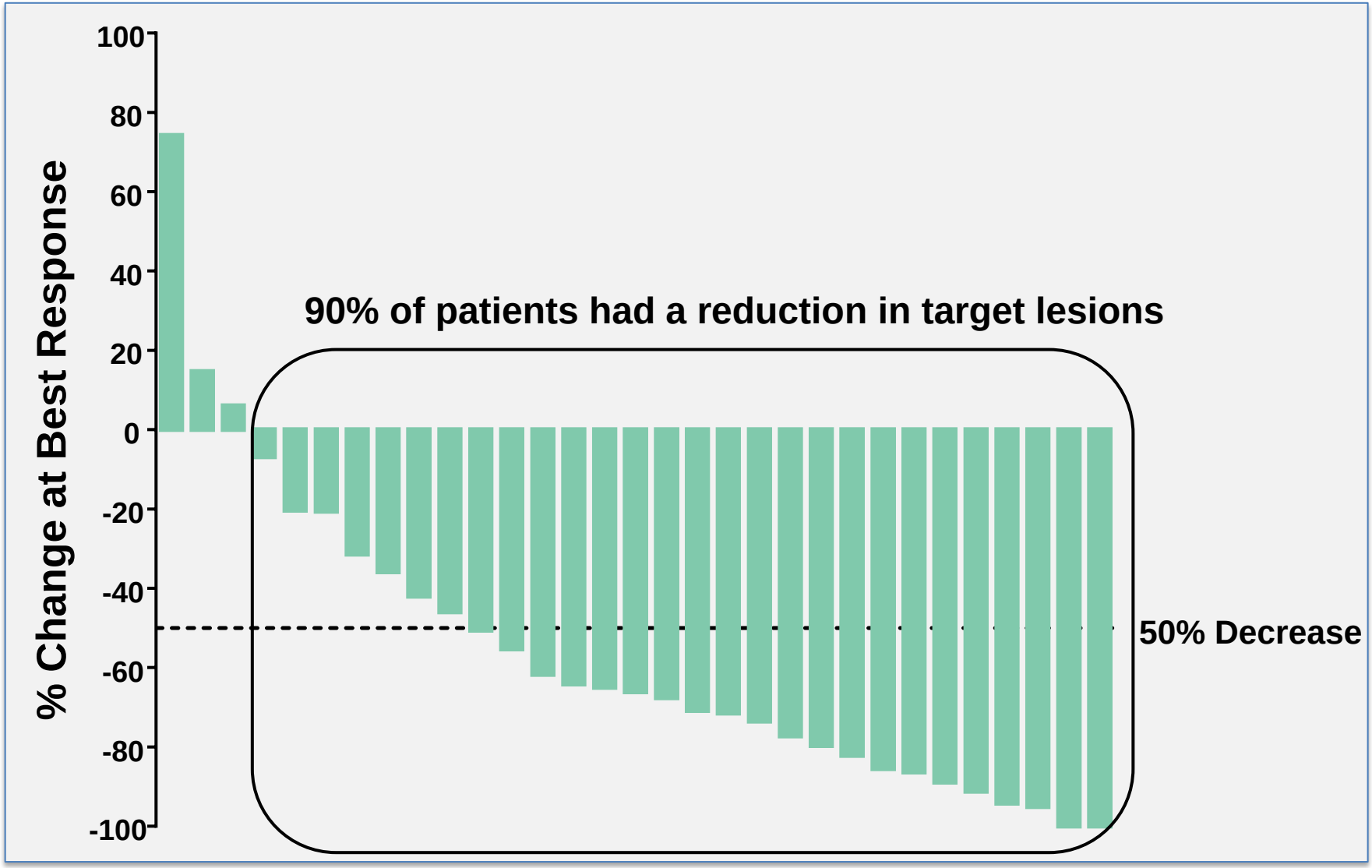
PD-1/PD-L1 blockade leads to a CD8+ T-cell anti-tumor immune response



MPDL3280A in RCC

Herbst RS *et al. Nature*. 2014 Nov 27;515(7528):563-7

Hodgkin: Highest Efficacy of anti-PD1…

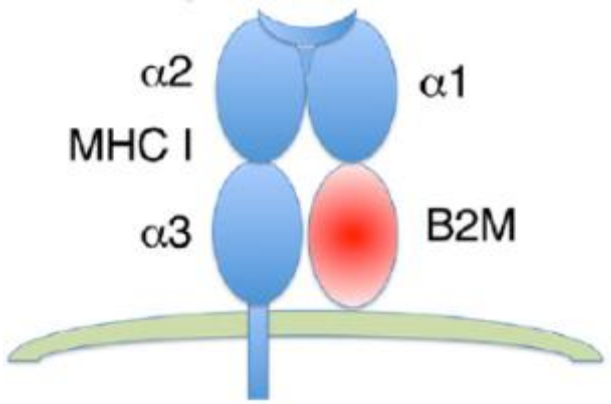


Armand P. PD-1 Blockade With Pembrolizumab in Patients With Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Safety, Efficacy, and Biomarker Assessment. P-013. ASH 2015.

…but most Hodgkins are MHC-I neg!

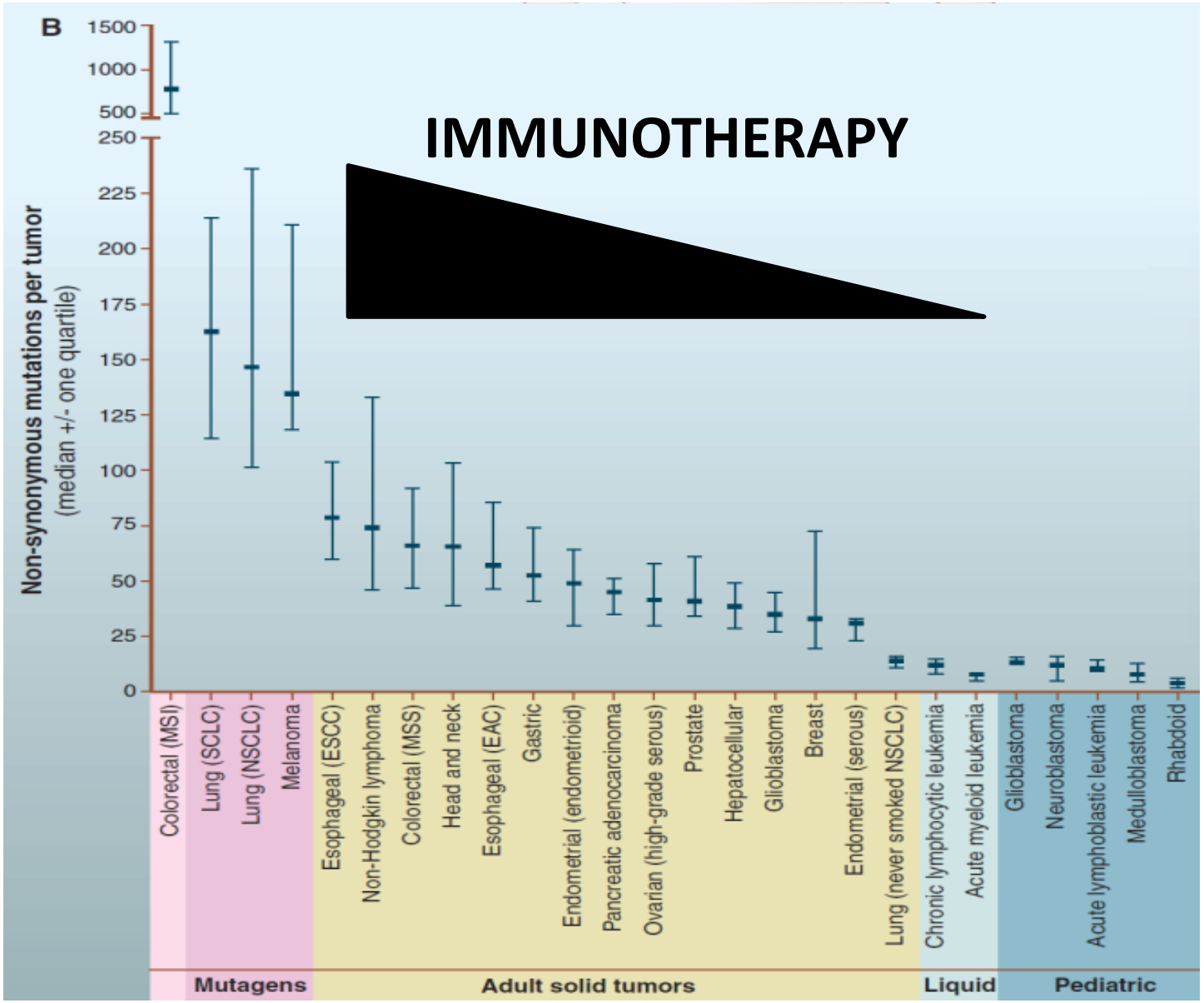
b-2-microglobulin (B2M) is the most commonly altered gene in HRS cells, with inactivating mutations that lead to loss of MHC-I expression

Presumed Function	% Primary Cases
Antigen presentation	
Ubiquitin-editing, NFkB activity	
Chromatin structure	
RNA translation	
BCR signaling, B cell survival	
Cytokine signaling	
SWI/SNF associated protein	
Cytokine signaling	
Transcription, B cell development	
Histone ubiquitination, DNA repair	
Protein ubiquitination, apoptosis	
Cytoskeleton regulation	
Transcription, BCR signaling	
G protein signal transduction	



Reichel J *et al. Blood.* 2015 Feb 12;125(7):1061-72

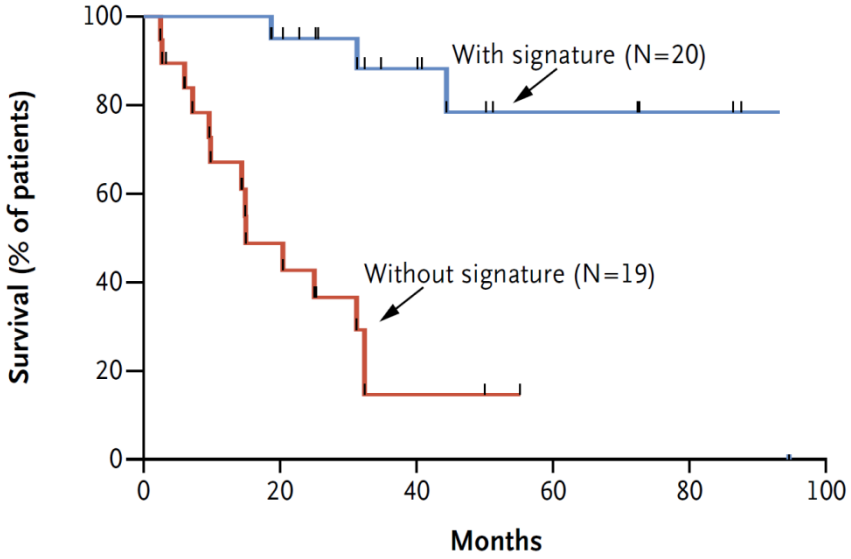
Immunogenicity of Cancers



Vogelstein B *et al. Science*. 2013 Mar 29;339(6127):1546-58

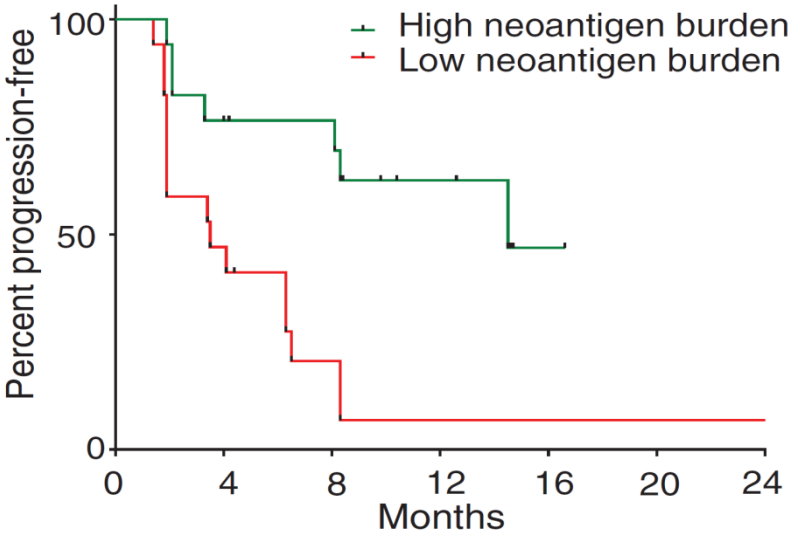
Anti-Neoepitopes Immune Responses

MELANOMA



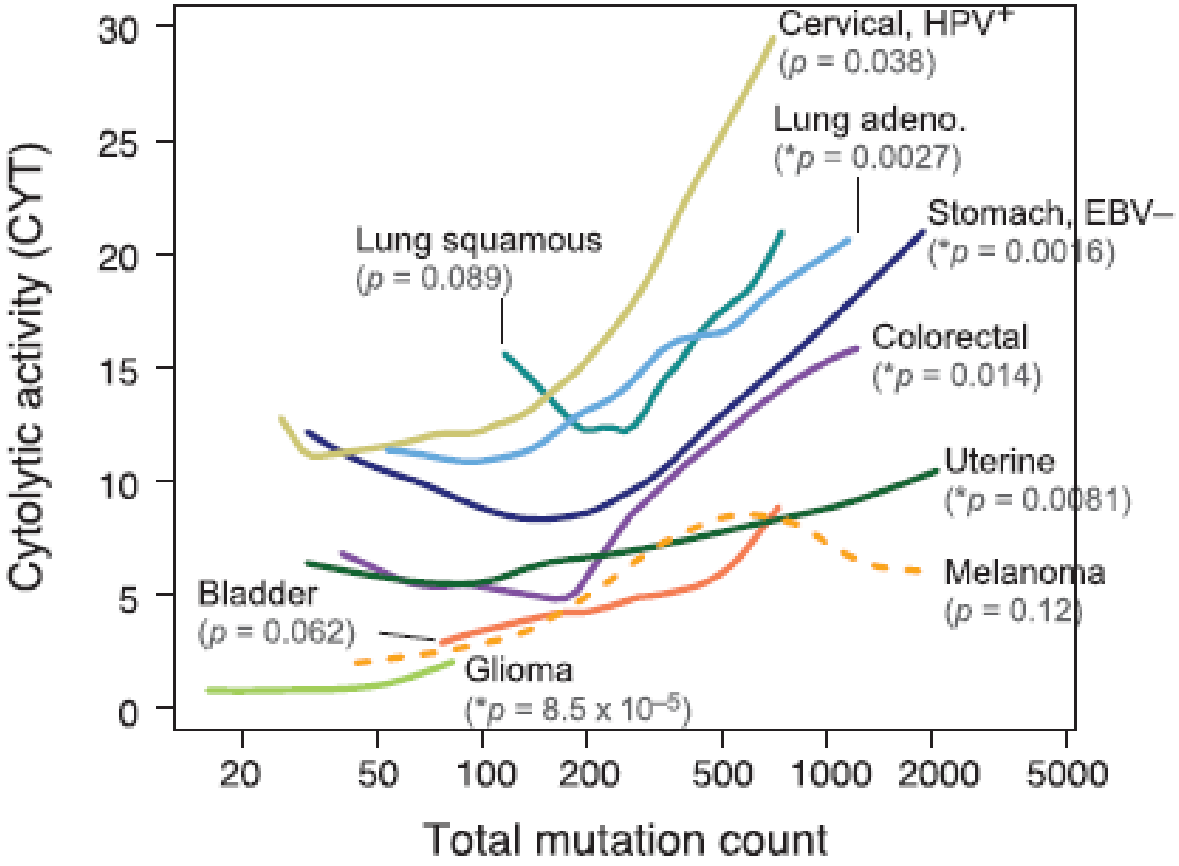
Snyder A, et al. N Engl J Med 2014.

NSCLC



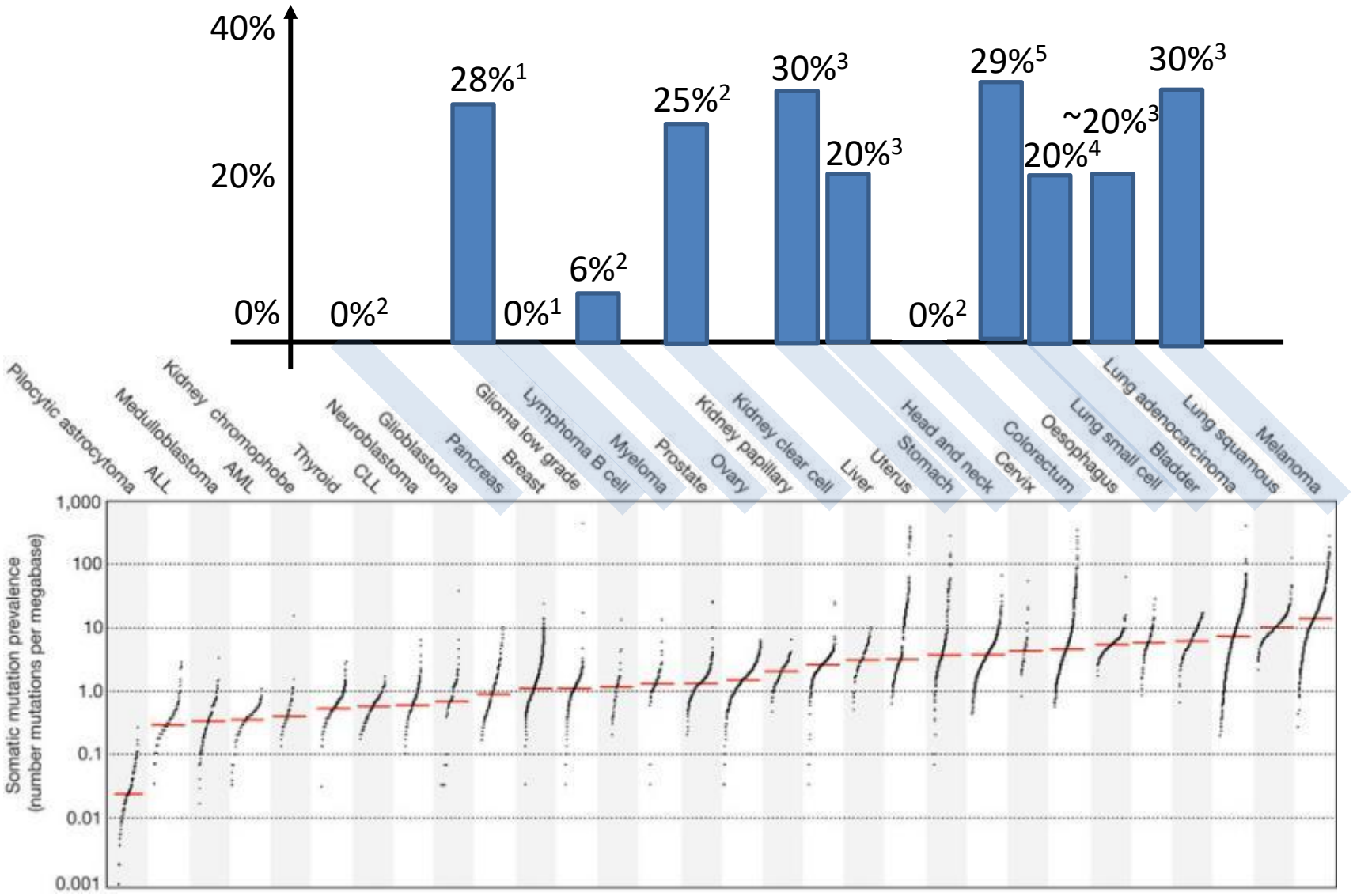
Rizvi NA, et al. Science (80) 2015.

Molecular and Genetic Properties of Tumors Associated with Local Immune Cytolytic Activity



Cell *160*, 48–61, January 15, 2015

Impact of Mutational Load on PD-1/PD-L1 Blockade ORR



Nature **500**, 415–421 (22 August 2013)

1: nivolumab, ASH 2014; 2:nivolumab, NEJM 2015; 3: pembrolizumab, ESMO 2014; 4: MPDL3280A, Nature 2014; [5] Ott, pembrolizumab WCLC2015

Impact of Somatic Genome Abnormalities on the Tumor Immunogenicity