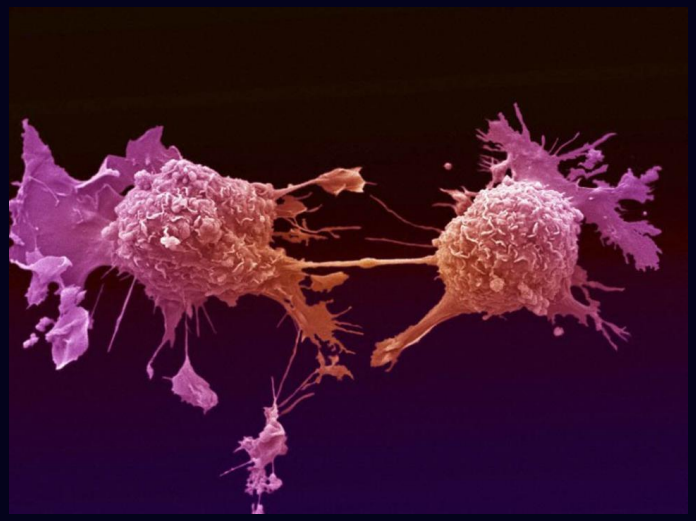


Checkpoint Inhibitors: State of the Art

Solange Peters, MD-PhD
Oncology Department
CHUV Lausanne

Disclosures

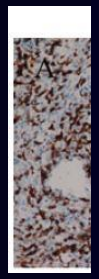
I have provided consultation, attended advisory boards and/or provided lectures for:

F. Hoffmann–La Roche, Ltd; Eli Lilly and Company Oncology, AstraZeneca, Pfizer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Morphotek, Merrimack , Merck Serono, Amgen, Clovis and Tesaro, for which I received honoraria.

I declare no conflict of interest.

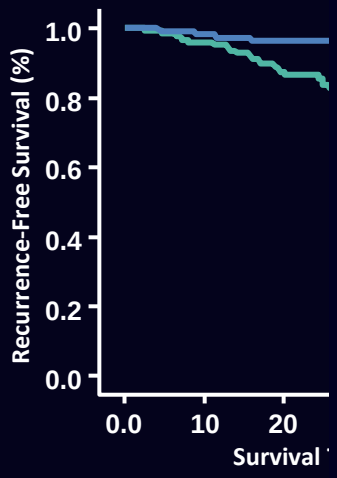
Ratio

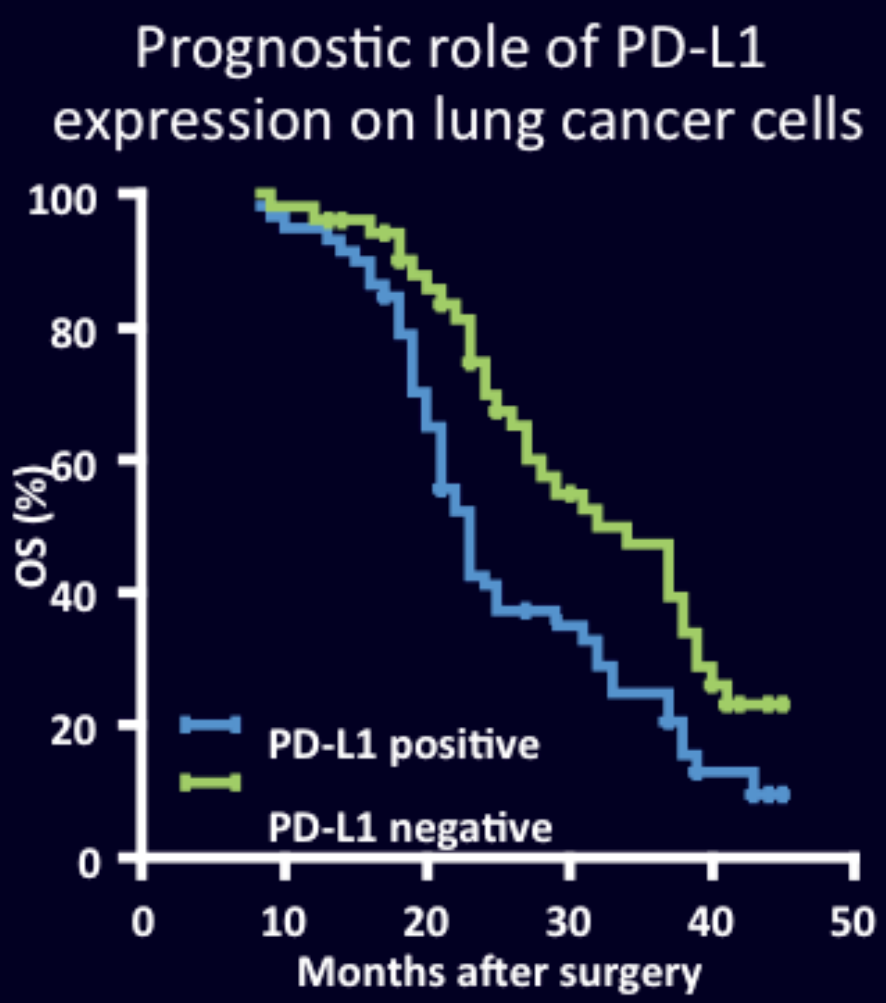
NSCLC



mmunother 2012

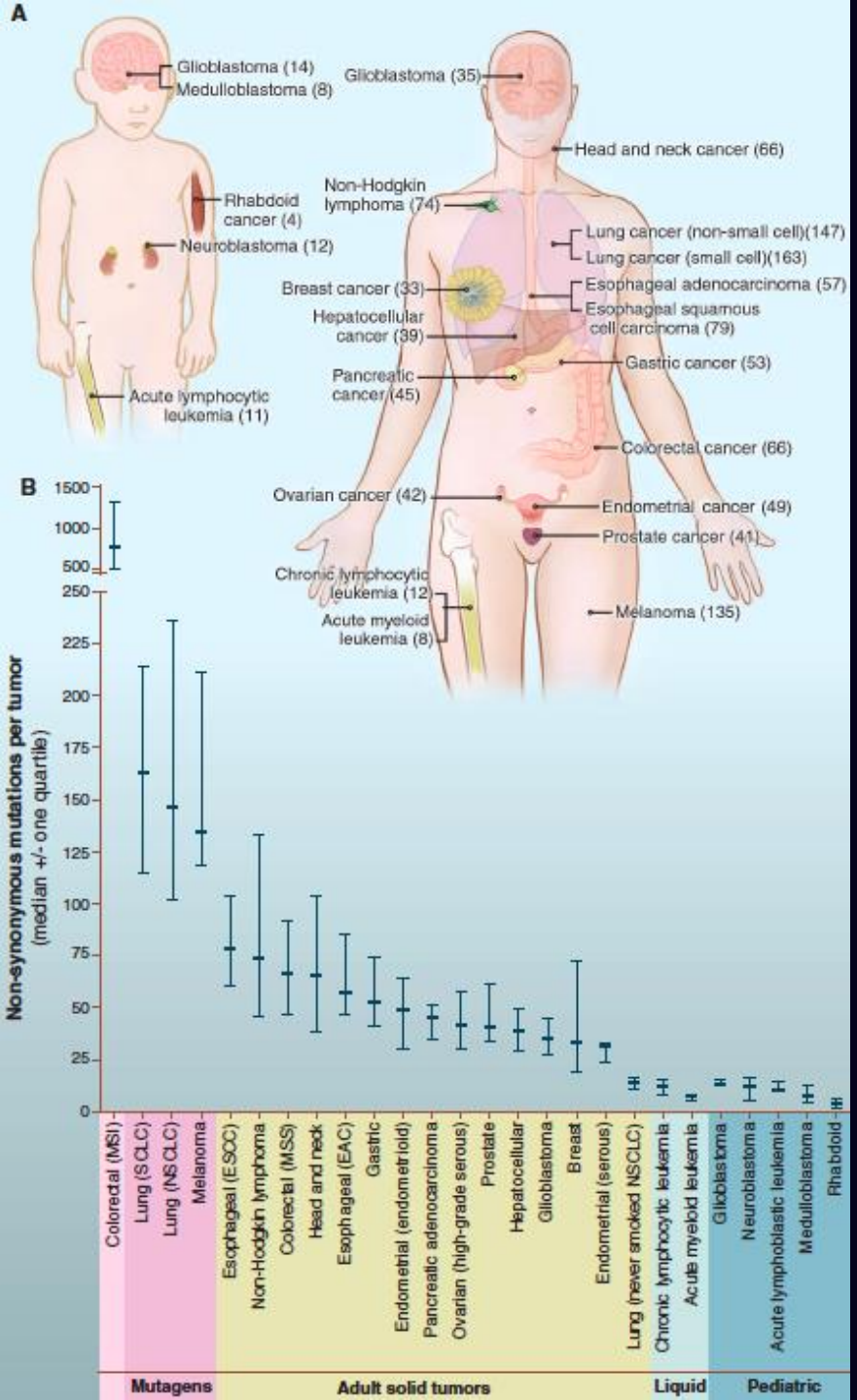
Presence of TILs as
increased recurrenc





1. Shimizu K, et al.
J Thorac Oncol. 2010

2. Horne ZD, et al.
J Surg Res. 2011

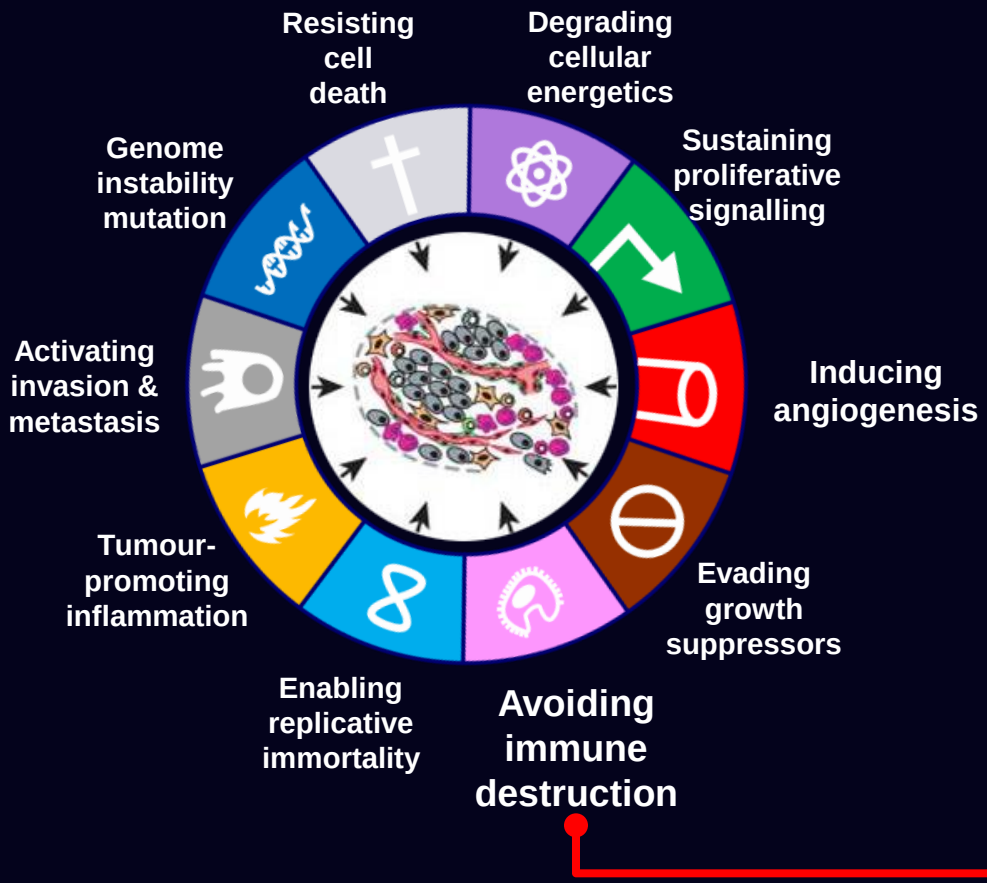


Melanomas and lung tumors display many more mutations than average, with~200 nonsynonymous mutations per tumor.

These larger numbers reflect the involvement of potent mutagens. Accordingly, lung cancers from smokers have 10 times as many somatic mutations as those from nonsmokers.

Vogelstein, Science 2013

Therapeutic Intervention at Cancer Hallmarks



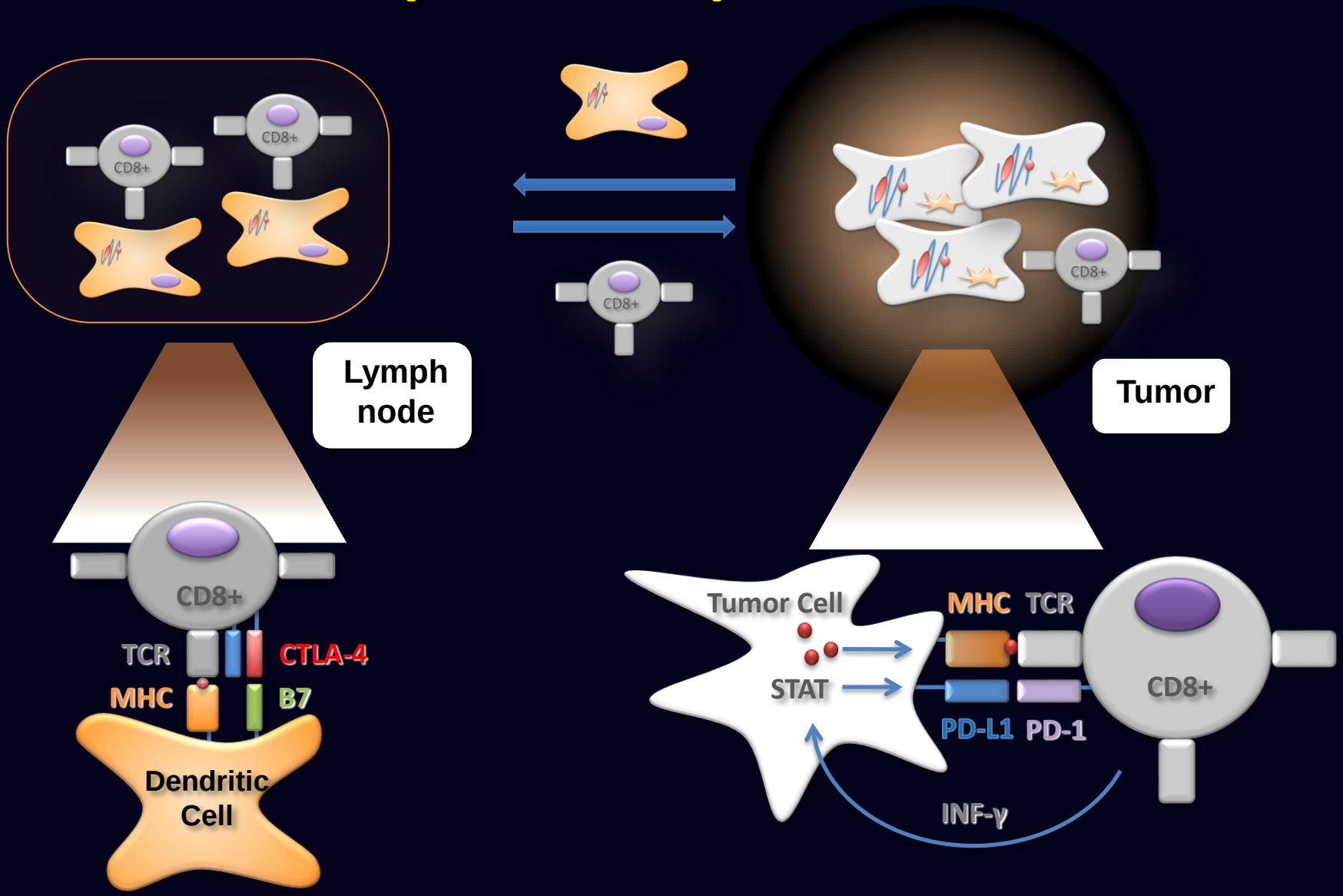
PD-1

PDL-1

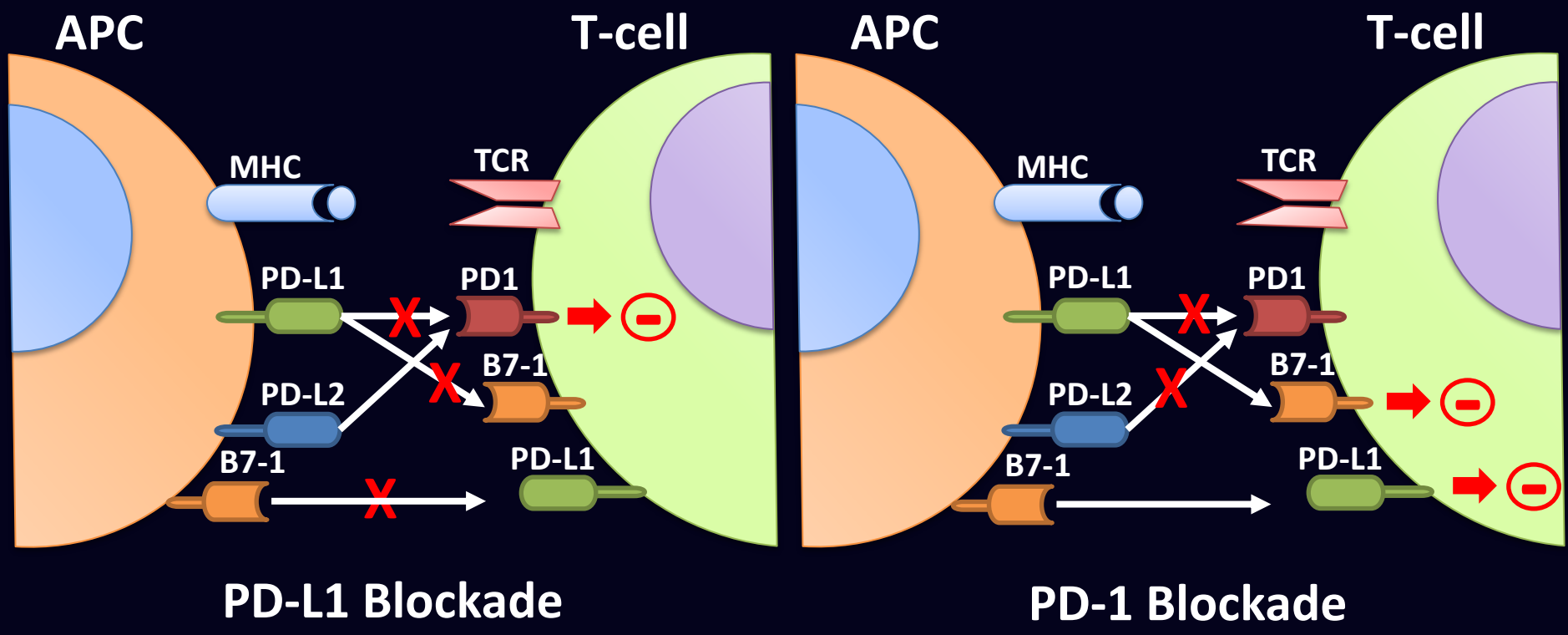
CTLA-4

Hanahan & Weinberg. Cell 2011

Immune Checkpoint Receptor: CTLA-4 & PD-1

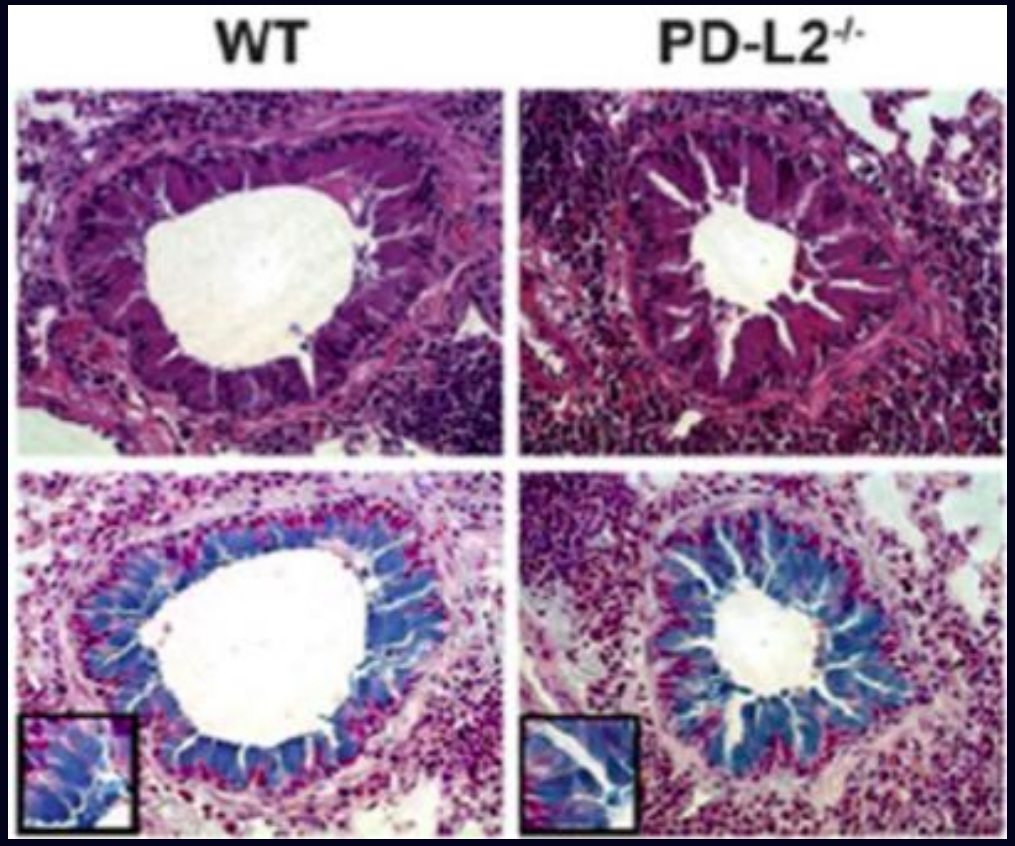


Truth is more complicated



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

Which might affect treatment tolerability



PD-L2 acts as a negative regulator of lung inflammation.
PD-L2−/− mice have enhanced disease severity, resulting in death.

Kerzerho, Allergy Clin Immunol. 2013

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

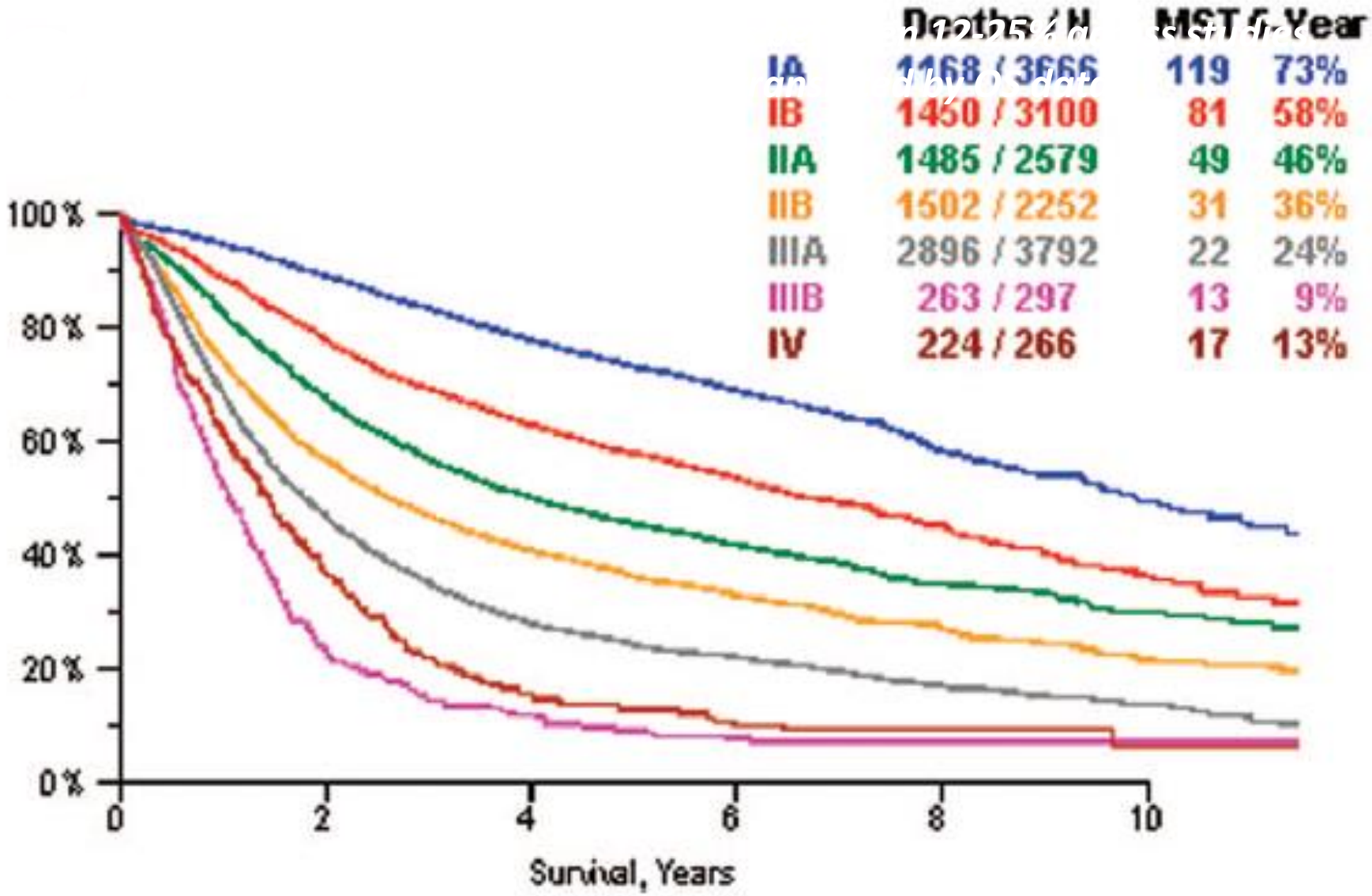
PD-1	Nivolumab-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase III
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II
	Pembrolizumab MK-3475	Humanized IgG4 mAb	Merck	Phase III
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase I
	MedI-4736	Engineered human IgG1 mAb	MedImmune	Phase III
	MPDL-3280A	Engineered human IgG1 mAb	Genentech	Phase III
	MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase II (III)

Nivolumab

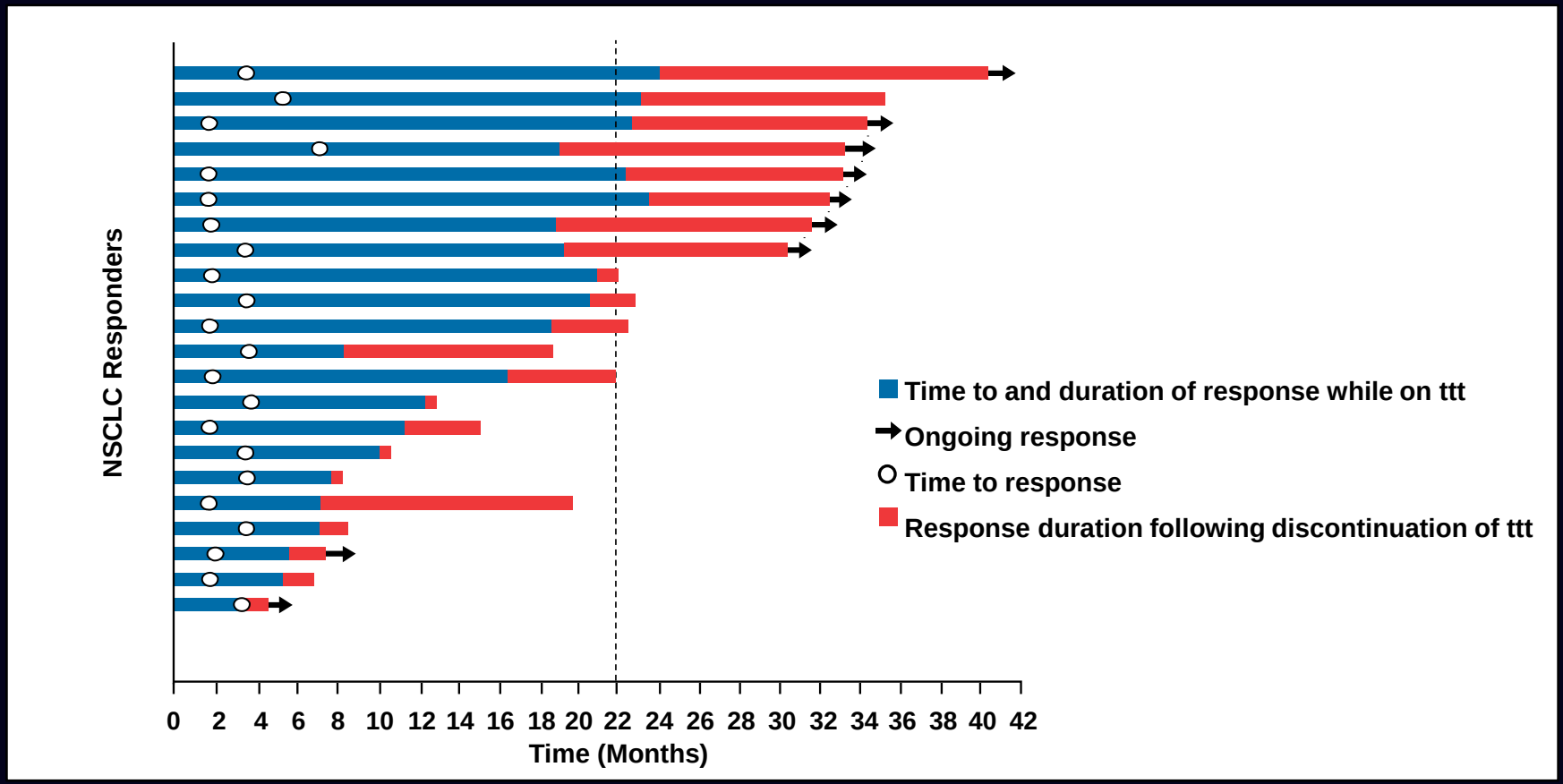
≥2 ND LINE, PHASE 1 DATA

Gettinger et al, ASCO 2014 and CMSTO 2014

OS by Dose (phase 1)

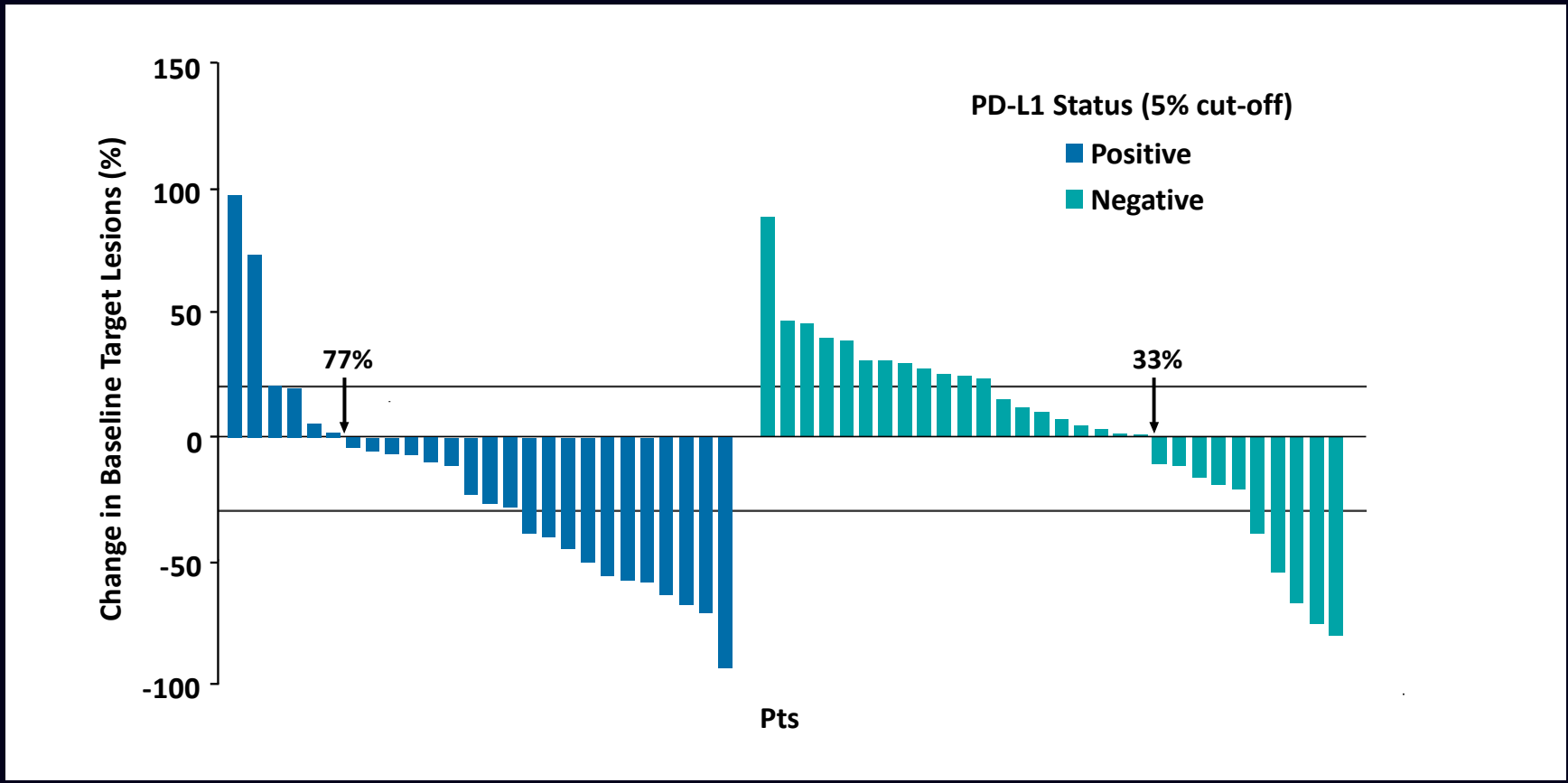


Characteristics of NSCLC checkpoint responses



- 5% unconvientional “immune-related” responses, with persistent reduction in target lesions in the presence of new lesions or regression following initial progression
- Manageable safety (low grade fatigue, nausea, diarrhea. Cave pneumonitis: 0-6%). No new safety signals with >3 year of follow-up.

Best Change in Target Lesion Tumor Burden by Tumor PD-L1 Expression



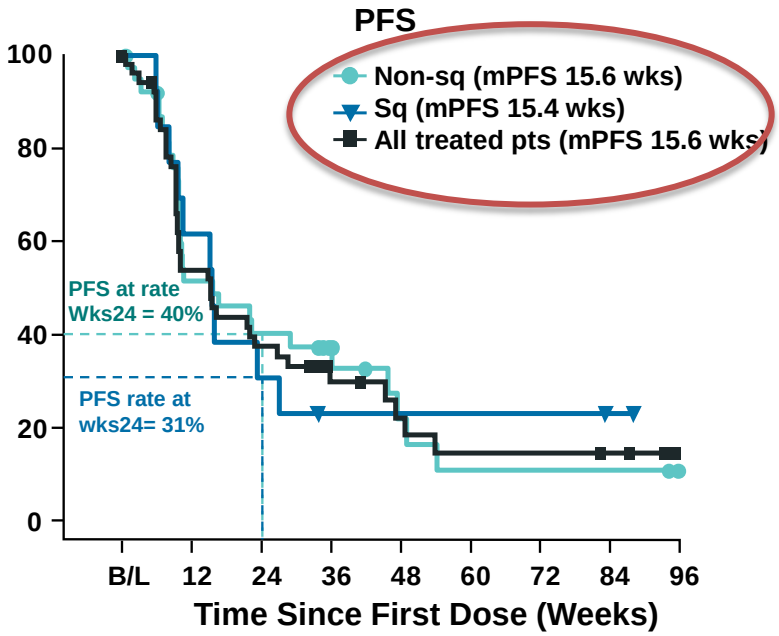
There was no clear association between PD-L1 expression and RR, PFS or OS (archival samples)

Nivolumab

1ST LINE, PHASE 1 DATA MONOTHERAPY

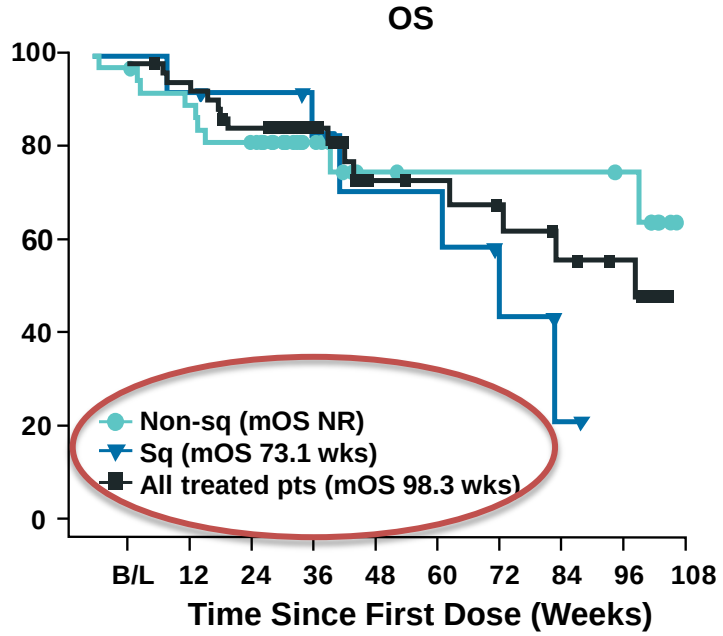
Rizvi et al; Antonia et al, CMSTO 2014

PFS and OS With Nivolumab monotherapy frontline



Number of Pts at Risk

All treated pts	52	27	18	10	6	4	4	3	0
Sq	13	8	4	2	2	2	2	1	0
Non-sq	39	19	14	8	4	2	2	2	0



Number of Pts at Risk

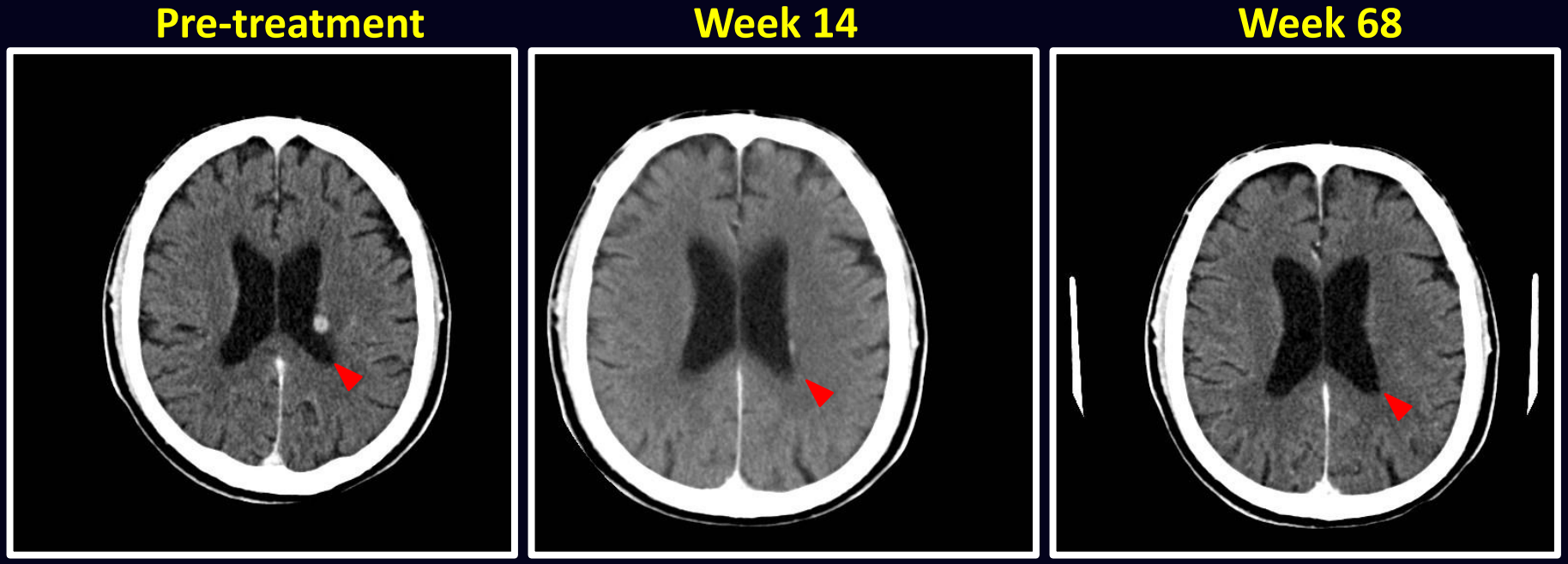
All treated pts	52	48	42	30	15	14	12	9	7	0
Sq	13	13	11	11	6	6	4	1	0	0
Non-sq	39	35	31	19	9	8	8	8	7	0

Nivolumab

SQUAMOUS ≥2 ND LINE,
PHASE 2 MONOTHERAPY DATA

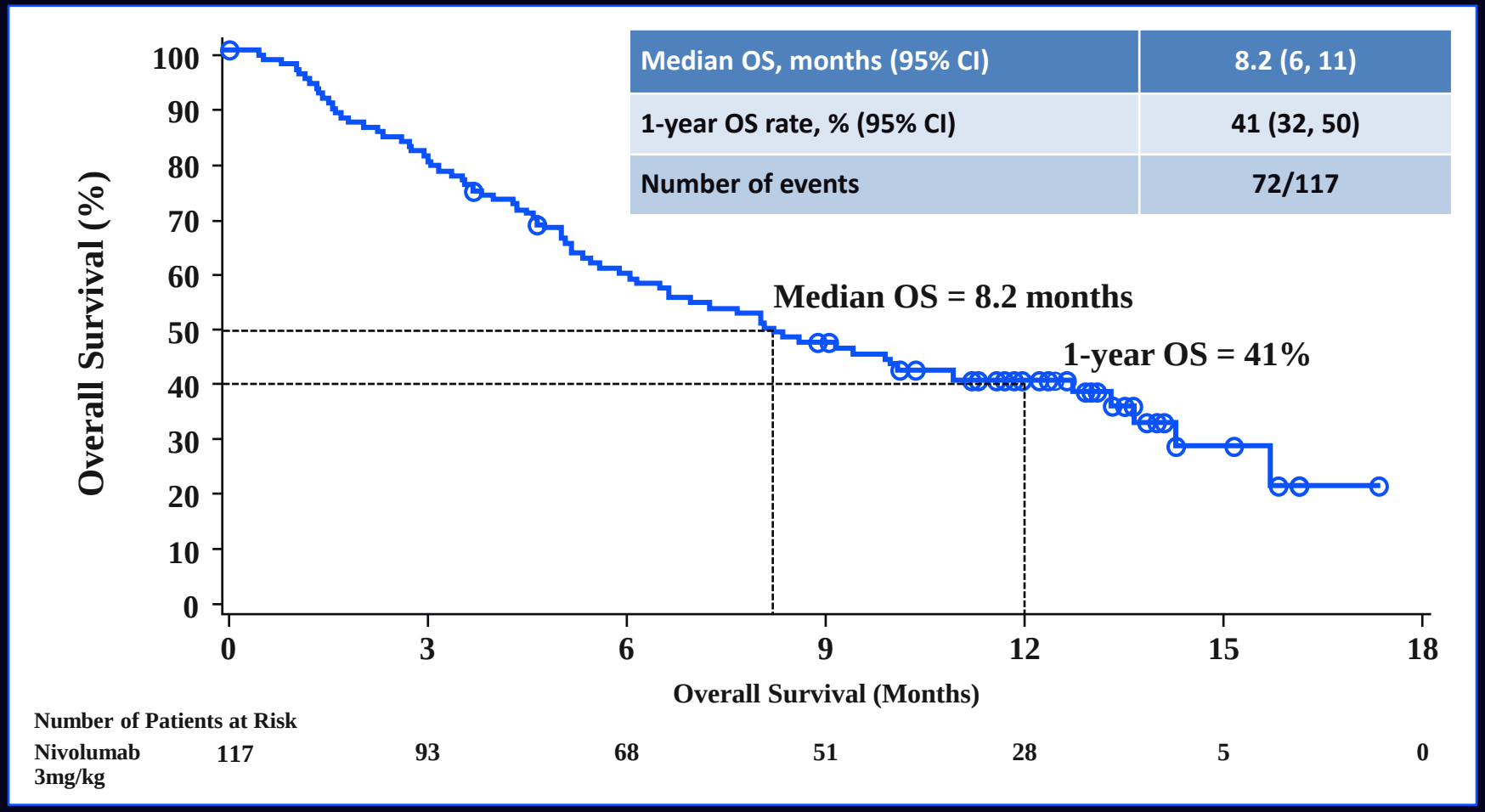
Ramalingam et al, CMSTO 2014

Response to Nivolumab in SQ NSCLC Brain Metastasis



- 73 year-old male, stage IIIB, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed radiotherapy

Overall Survival : All Treated Patients



Median follow-up for survival: 8 months (range, 0–17 months)

Nivolumab

SQUAMOUS

DOCETAXEL VS NIVOLUMAB

PHASE 3 RANDOMIZED TRIAL

Nivolumumab Phase III Trials

Bristol-Myers Squibb

CheckMate -017, A Phase 3 Study of Opdivo (Nivolumab) Compared to Docetaxel in Patients with Second-Line Squamous Cell Non-small Cell Lung Cancer, Stopped Early

Opdivo demonstrates superior overall survival in this Phase 3 trial

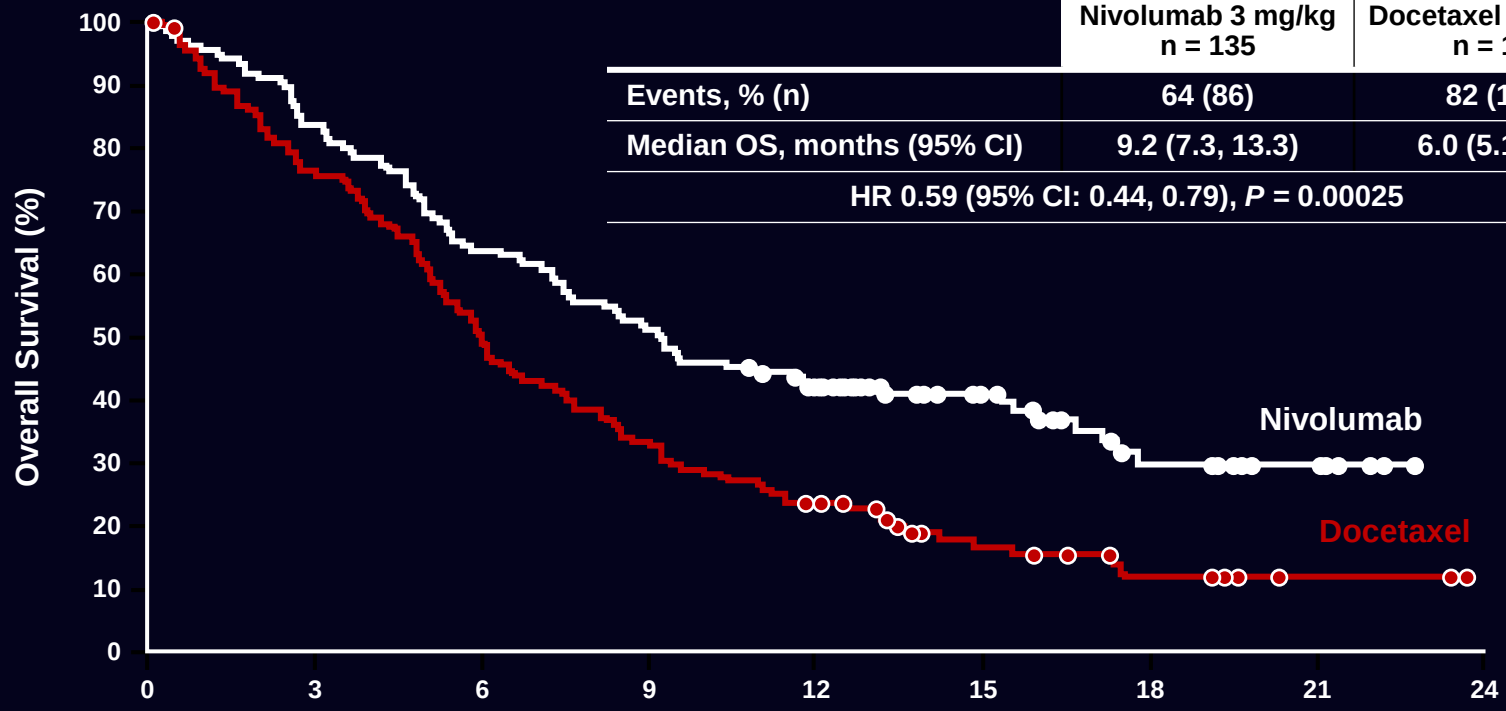
Sunday, January 11, 2015 9:06 pm EST

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE:BMY) today announced that an open-label, randomized Phase 3 study evaluating *Opdivo* versus docetaxel in previously treated patients with advanced, squamous cell non-small cell lung cancer (NSCLC) was stopped early because an assessment conducted by the independent Data Monitoring Committee (DMC) concluded that the study met its endpoint, demonstrating superior overall survival in patients receiving *Opdivo* compared to the control arm. The company will share these data – which for the first time indicate a survival advantage with an anti-PD1 immune checkpoint inhibitor in lung cancer – with health authorities.

Nivolumab phase 3 study CA209-017

Nivolumab vs docetaxel (second-line) in stage IIIB/IV squamous NSCLC

	Nivolumab 3 mg/kg n = 135	Docetaxel 75 mg/m^2 n = 137
Events, % (n)	64 (86)	82 (113)
Median OS, months (95% CI)	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
HR 0.59 (95% CI: 0.44, 0.79), *P* = 0.00025		



Number of patients at risk

Nivolumab	135	113	86	69	52	31	15	7	0
Docetaxel	137	103	68	45	30	14	7	2	0

CI = confidence interval; HR = hazard ratio; OS = overall survival.

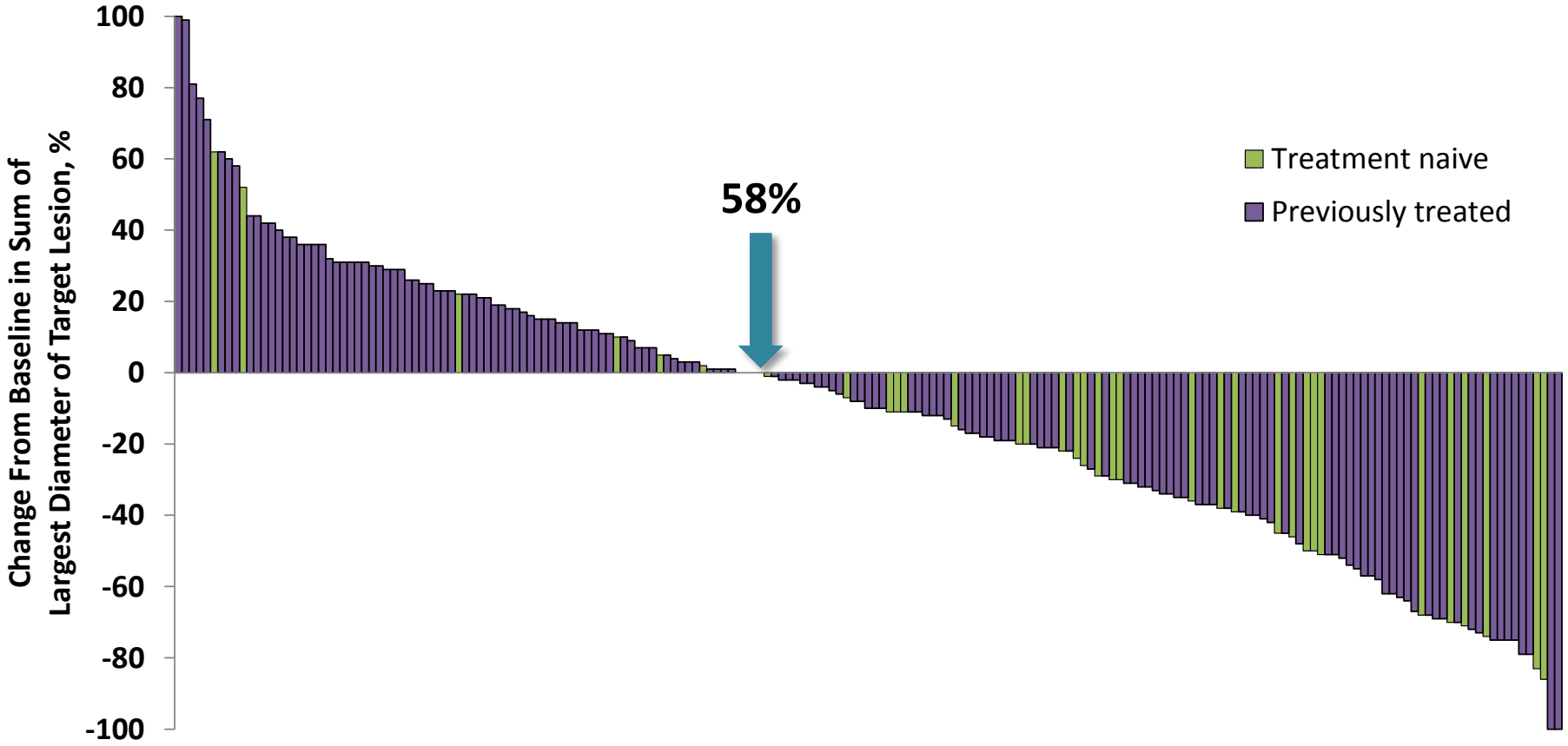
OPDIVO [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2015.

Pembrolizumab

NSCLC POOLED ANALYSIS 1ST AND SUSEQUENT LINES, MONOTHERAPY

Garon et al, ESMO 2014

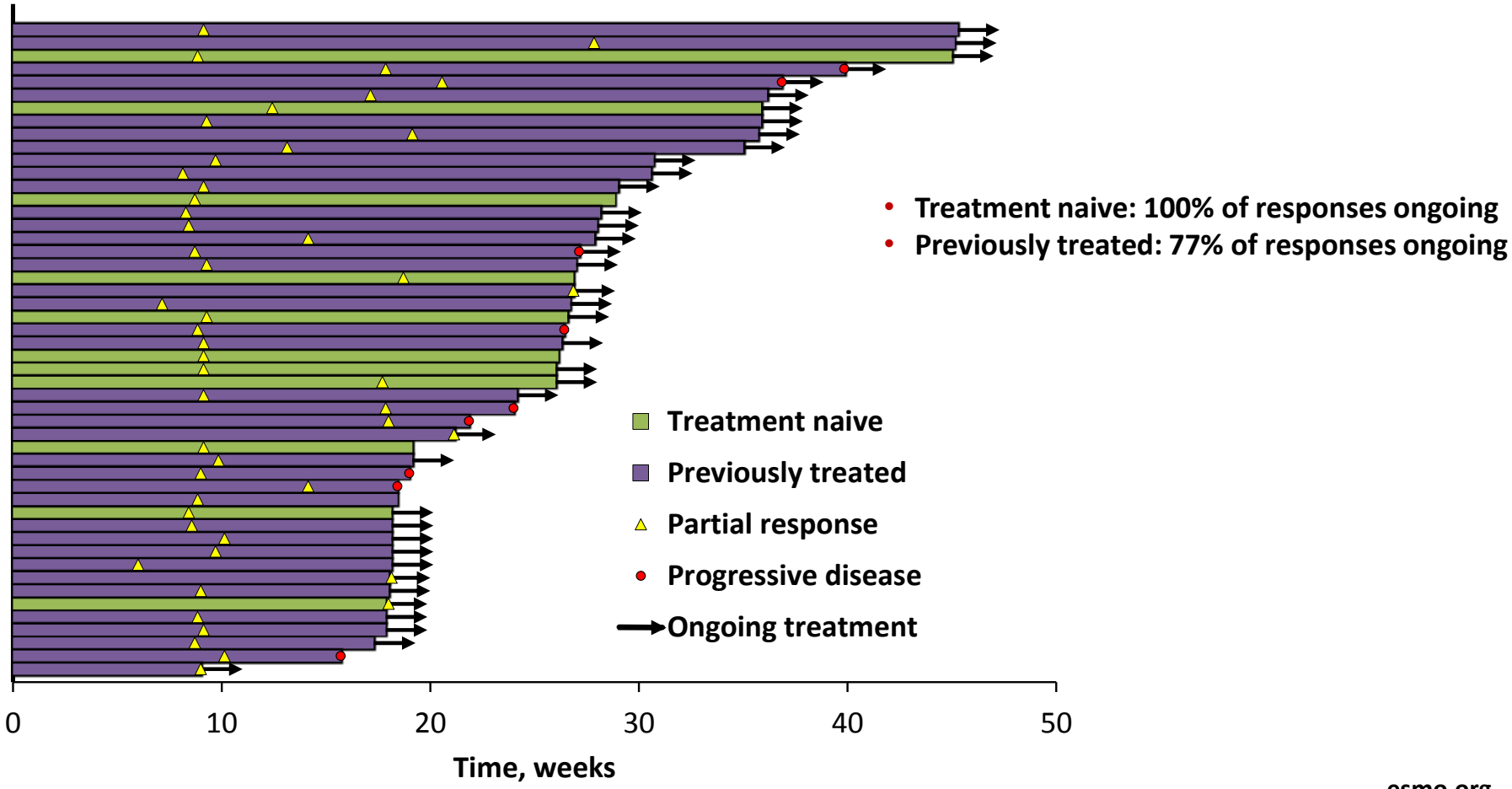
Maximum Percent Change From Baseline in Tumor Size[a] (RECIST v1.1, Central Review)



[a] [illegible].

Analysis cut-off date: March 3, 2014.

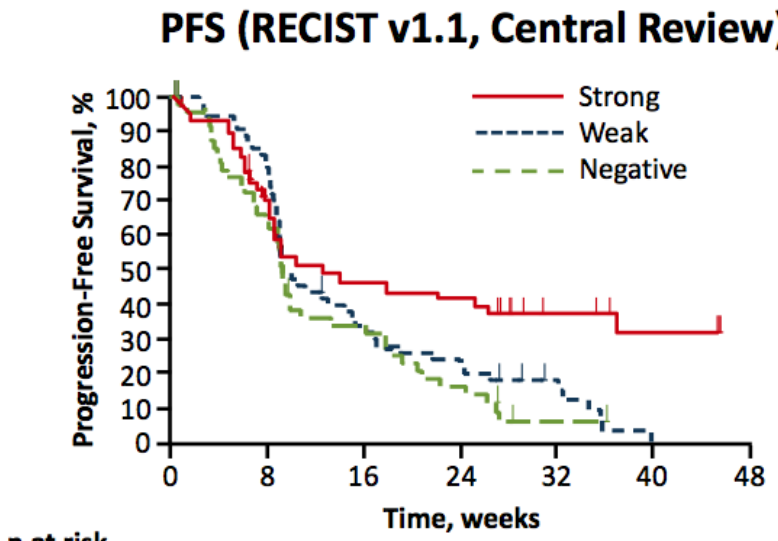
Time to and Durability of Response
(RECIST v1.1, Central Review)[a]



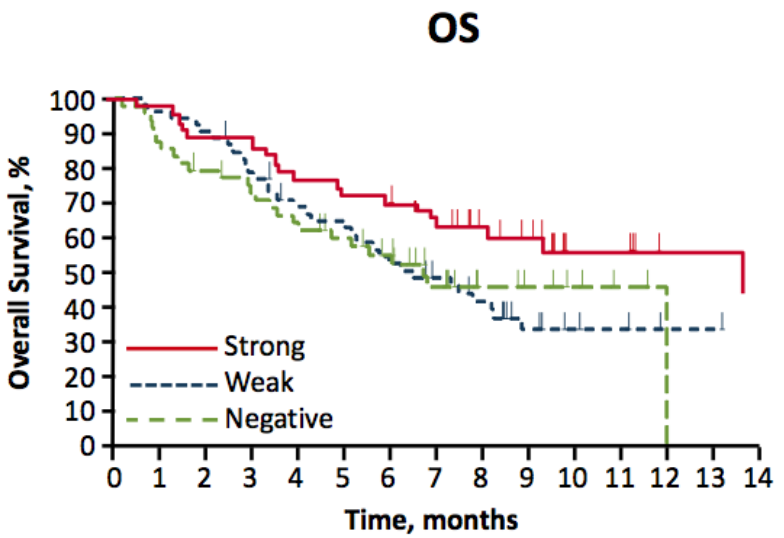
esmo.org

[a]Includes confirmed and unconfirmed responses.
Analysis cutoff date: March 3, 2014.

Pembrolizumab and PD-L1 biomarker



n at risk							
Strong	44	28	18	17	9	6	3
Weak	53	43	17	12	6	0	0
Negative	49	30	15	7	1	0	0



Strong	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
Weak	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
Negative	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

- PFS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.52; 95% CI, 0.33-0.80)
- OS was longer in patients with PD-L1 strong-positive versus PD-L1 weak-positive/ negative tumors (HR, 0.59; 95% CI, 0.35-0.99)

Garon, ESMO 2014

Kaplan-Meier Estimates of Survival

- Immunosuppressive properties of previous cytotoxic agents through lymphocytes depletion?
- Impact of steroids as antiemetic co-medication on the immune system?
- Progressive T cell exhaustion during tumor progression?
- Increase in expression of PD-L1 in the course of the disease?

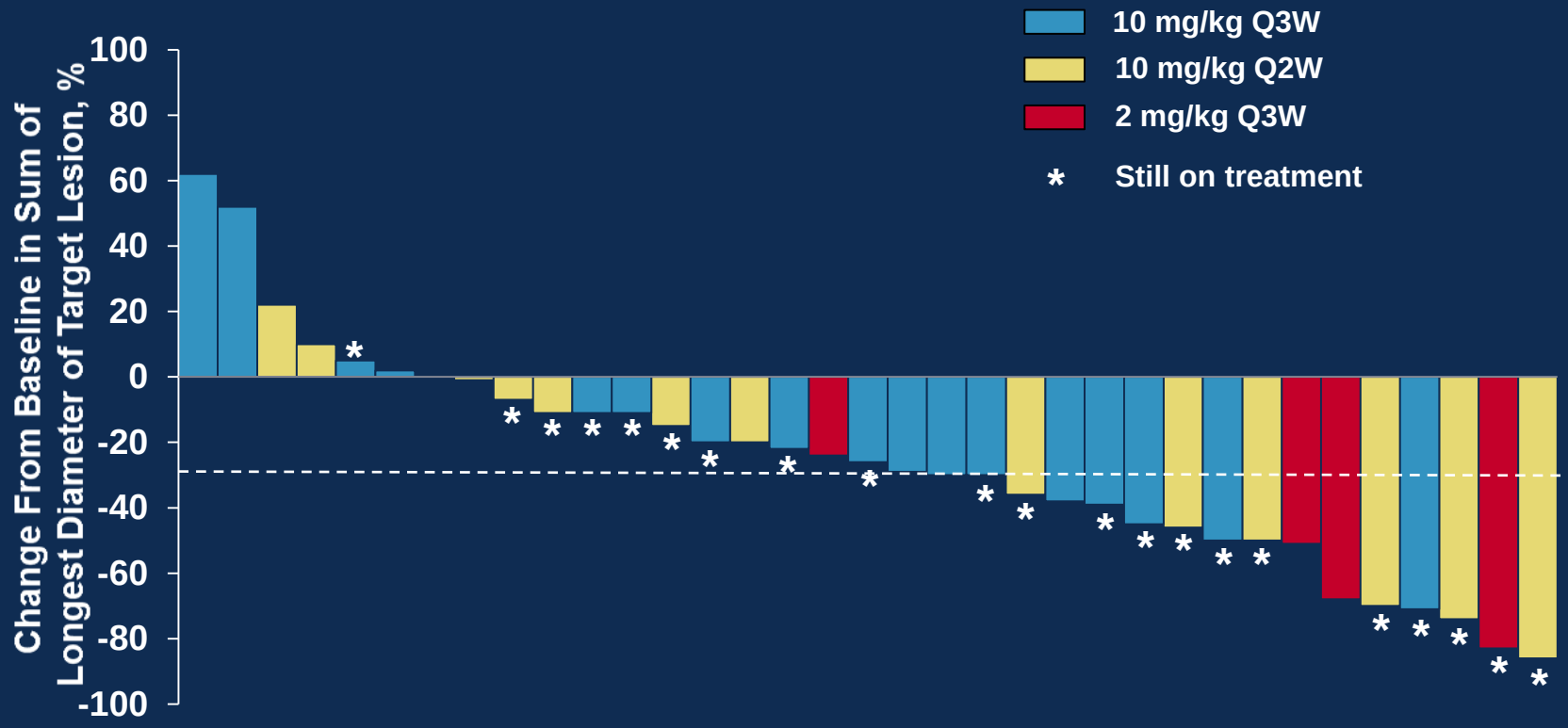
n at risk
Treatmen
Previously

- T
  - Median PFS: 27 weeks (95% CI, 14-45)
  - 24-week PFS: 51%
- Previously treated
  - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

- Median OS: NR (95% CI, NE-NE)
- 6-month OS: 86%
- Previously treated
  - Median OS: 8.2 months (7.3-NR)
  - 6-month OS: 59%

Analysis cutoff date: March 3, 2014.

Focus on pembrolizumab first line data



- Interim median PFS[c]:
  - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
  - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

MPLD3280A and MEDI4736

≥2 ND LINE, PHASE 1 DATA

Soria et al , WCLC 2013 and Brahmer et al, 2014

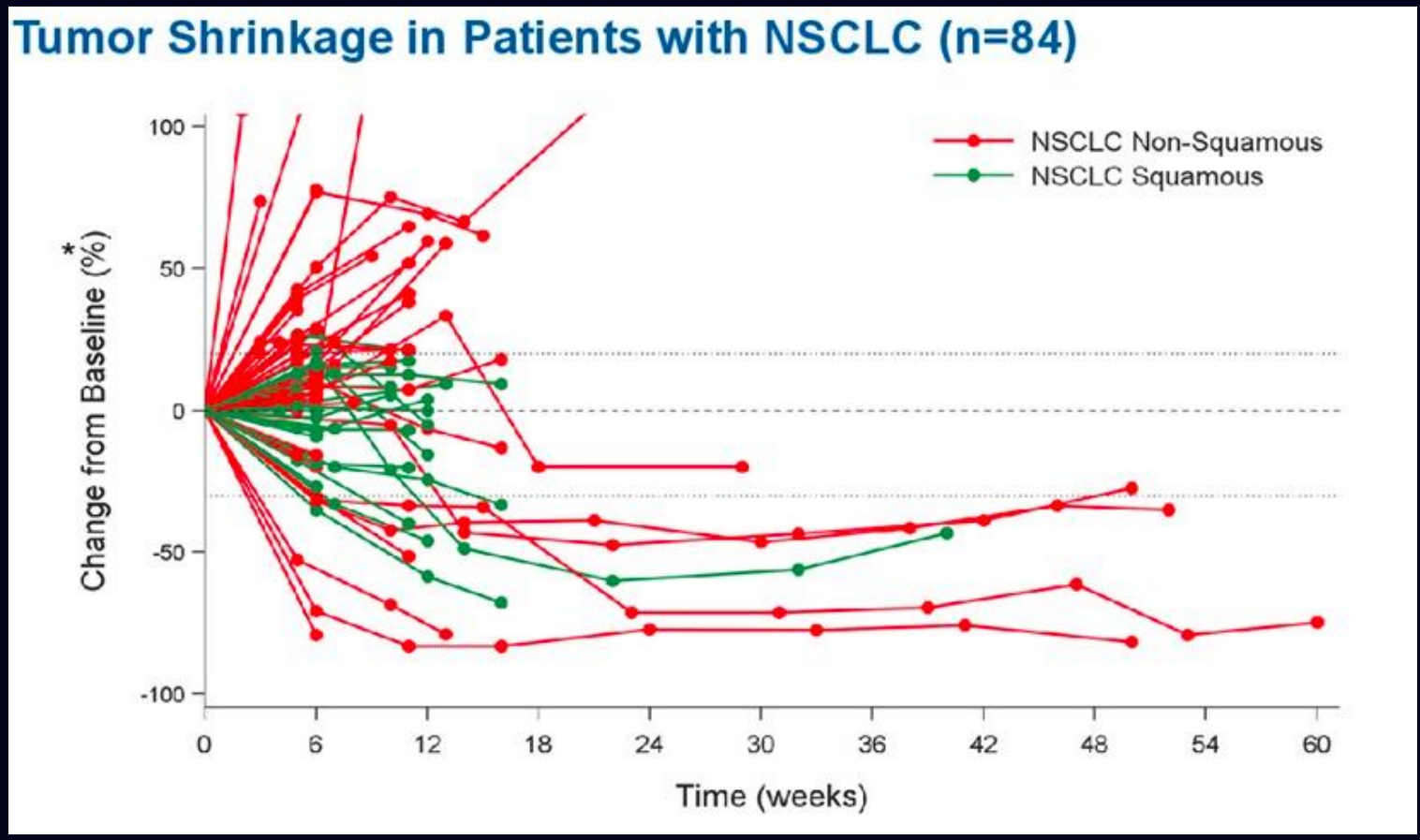
MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status

Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	**83%** (5/6)	**17%** (1/6)
IHC 2 and 3	**46%** (6/13)	**23%** (3/13)
IHC 1/2/3	**31%** (8/26)	**38%** (10/26)
All Patients[c]	**23%** (12/53)	**40%** (21/53)

OVERALL RESPONSE RATE: 21% (N=175)

Soria, ESMO 2013

MEDI4736 Phase I (spider plot)



Overall Response Rate: 16% (n=58)

Brahmer, ASCO 2014

SUBGROUPS?

Histology is not predictive

	Squamous Carcinoma	Non-squamous
Nivolumab (PD-1)	17% (9/54)	18% (13/74)
MPDL3280A (PD-L1)	27% (3/11)	21% (9/42)
Pembrolizumab (PD-1, irRECIST)	25% (66/262)	23% (60/262)

Anti PD1/PD-L1 Inhibitors Response Rate by Smoking Status

	Anti PD1		Anti PD-L 1	
	MK-3475	Nivolumab	MEDI4736	MPDL3280A
All, N	236	129	58	53
RR	**21%**	**17%**	**16%**	**23%**
Smokers	165 **27%**	75 **20%**	?	43 **26%**
Never/minimal Smokers	65 **9%**	13 **0%**	?	10 **10%**

Garon E, ESMO 2014; Hellman M ESMO 2014; Soria JC, ESMO 2013

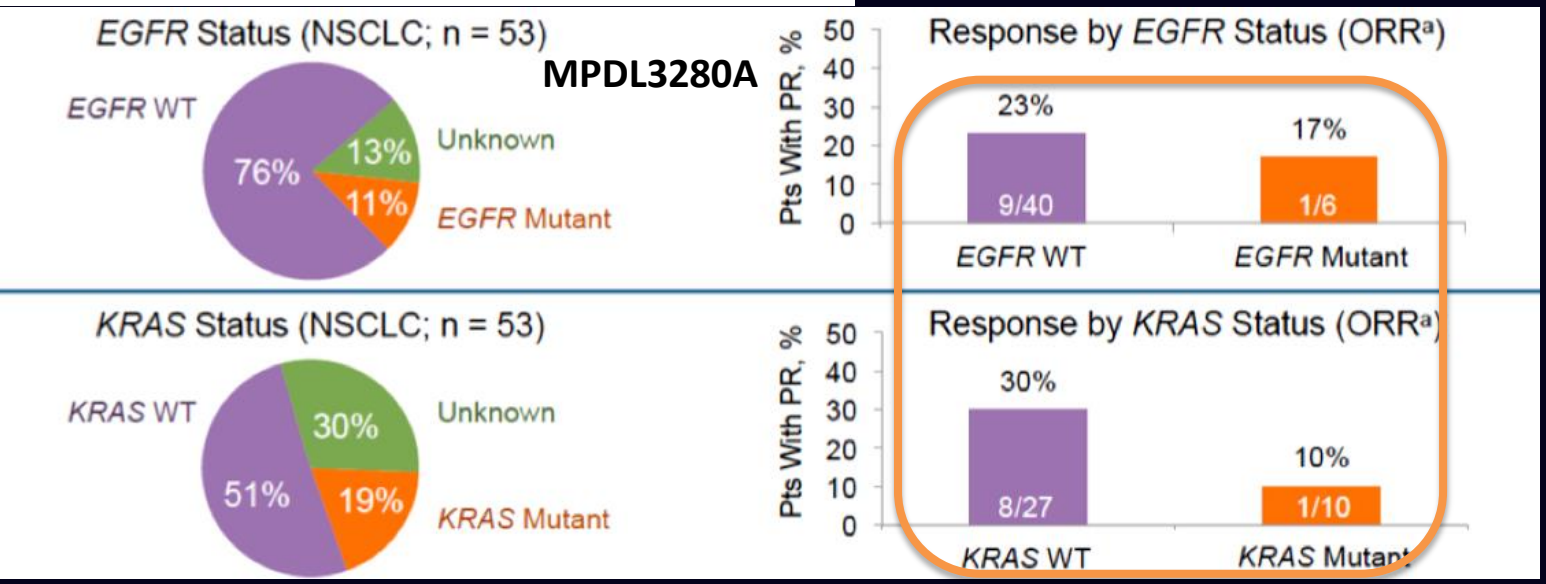
Checkpoint inhibitors in « oncogene-addicted » NSCLC ?

CA209-003: phase 1 follow-up study, up to 5 prior lines of therapy, NSCLC cohort

Subgroup	ORR, % (n/N) [95% CI]
***EGFR* status**	
Mutant	17 (2/12) [2.1−48.4]
Wild-type	20 (11/56) [10.2−32.4]
Unknown	15 (9/61) [7.0−26.2]

MK-3475	N	ORR[a] % (95% CI)
EGRFR mutation	36	14 (5-30)
KRAS mutation	39	28 (15-45)
ALK rearrangement	6	17 (0-64)

MPDL3280A



Gettinger, ASCO 2014
Garon, ESMO 2014
Horn, WLCC 2013

PD-L1 as a predictive biomarker / inclusion criteria

THE CHALLENGE OF THE BIOMARKER

Intricate role of PD-1 signalling with different cell types

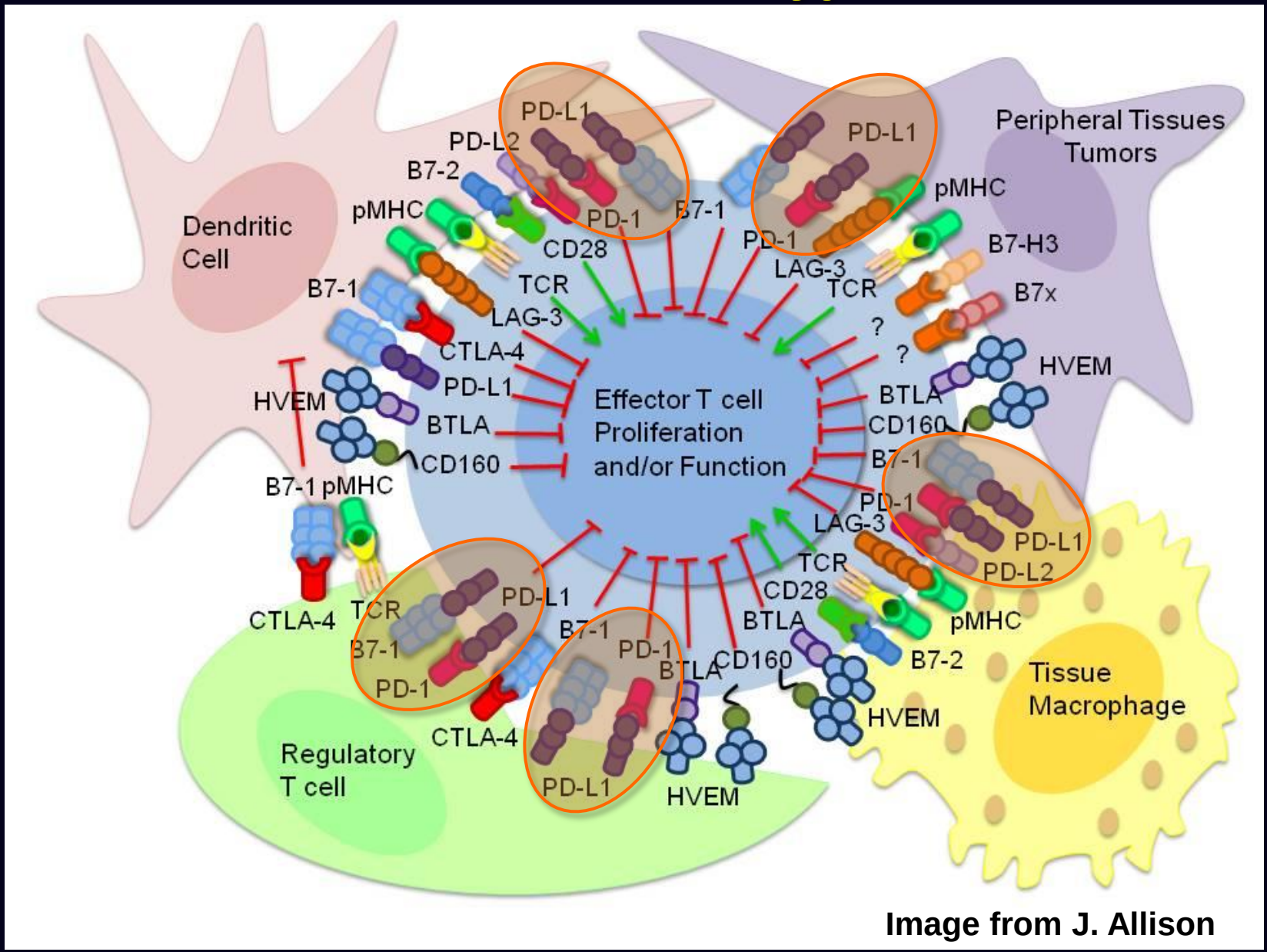


Image from J. Allison

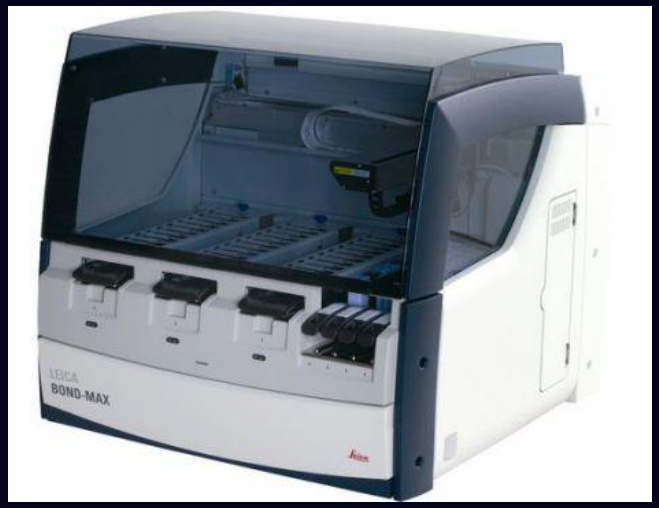
PD-L1 analysis: differences in evaluation and interpretation

Assay	Analysis	Definition of positivity	PD-L1 expression	Observed response
Nivolumab Manual Assay (5H1 – Topalian) Dako Automated Assay (28-8 – Antonia)	• Tumour cells • Archival tissue	• Positive staining defined as plasma membrane staining at any intensity • Assessment of ORR at 1% and 5% cut-off	• 56%: 1% cut-off • 49%: 5% cut-off	Topalian (n=42) • PD-L1 positive: 36% • PD-L1 negative: 0% Brahmer 2014 (n=68) • PD-L1 positive: 15% • PD-L1 negative: 14% Gettinger 2014 (n=17) • PD-L1 positive: 50% • PD-L1 negative: 0%
MPDL 3280A Ventana Automated Assay	• Tumour infiltrating immune cells • Archival tissue?	• Staining intensity by IHC	• 25% PD-L1 high (IHC 2,3) • 75% PD-L1 low (IHC 0,1)	Rizvi 2014 (n=53) • IHC 3 (n=6): 83% • IHC 2,3 (n=13): 46% • All patients (n=53): 23%
Pembrolizumab (MK-3475;) DAKO IHC Assay (22C3)	• Surface expression of PD-L1 on tumor cells and stroma • Tumour specimen <60 days before study entry	• Strong (≥50 of tumour cells) vs weak (1–49% tumour cells) expression by IHC	• 67% PD-L1 positive (strong and weak staining) • 33% PD-L1 negative (no staining)	Garon 2014 (n=194) • PD-L1 positive: 23% • PD-L1 negative: 9%
MEDI4736 (anti-PD-L1) First-generation or Ventana Automated Assay	• IHC assay to detect PD-L1 in FFPE tumour samples is being developed in collaboration with VENTANA	• Not reported	• Not reported	Brahmer 2014 (n=58) • PD-L1 positive: 25% • PD-L1 negative: 3%

DAKO Autostainer

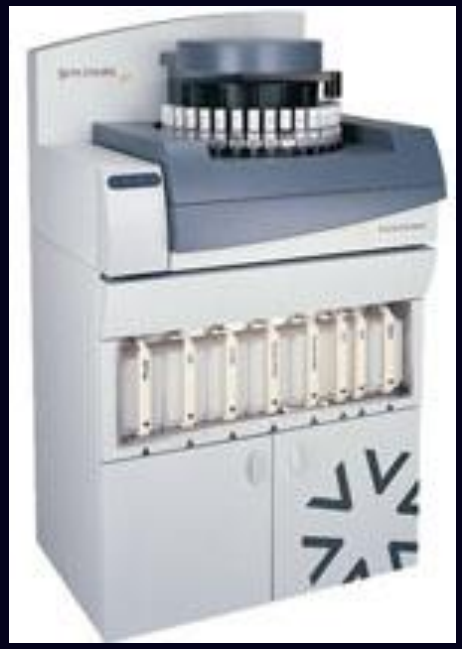
Clone 28-8
Dako

22C3 PharmDx kit
Dako



Leica BondMax

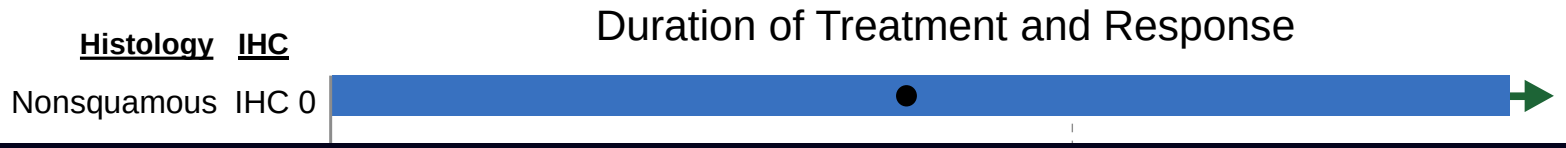
E1L3N™ XP®
(Cell Signaling)



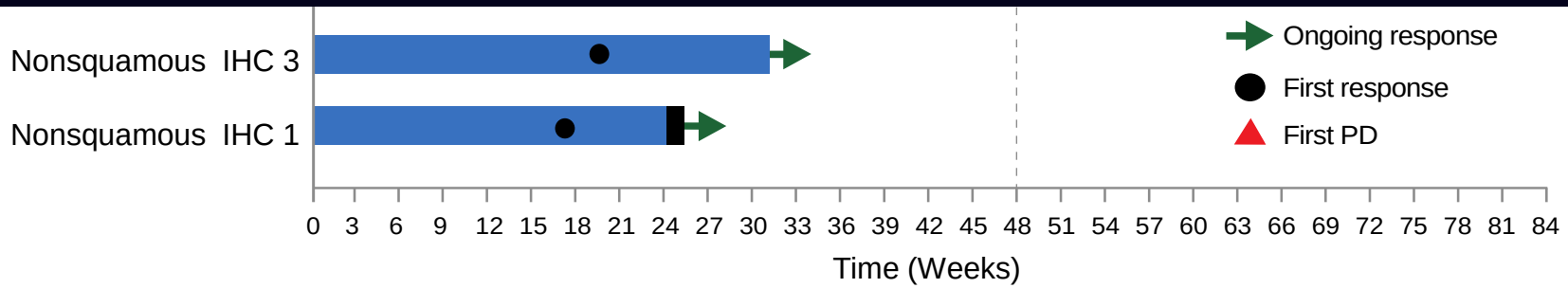
Ventana
Benchmark XT

SP142
(Ventana/
Spring Bioscience)

MPDL3280A Phase Ia: Duration of Treatment in Responders - NSCLC



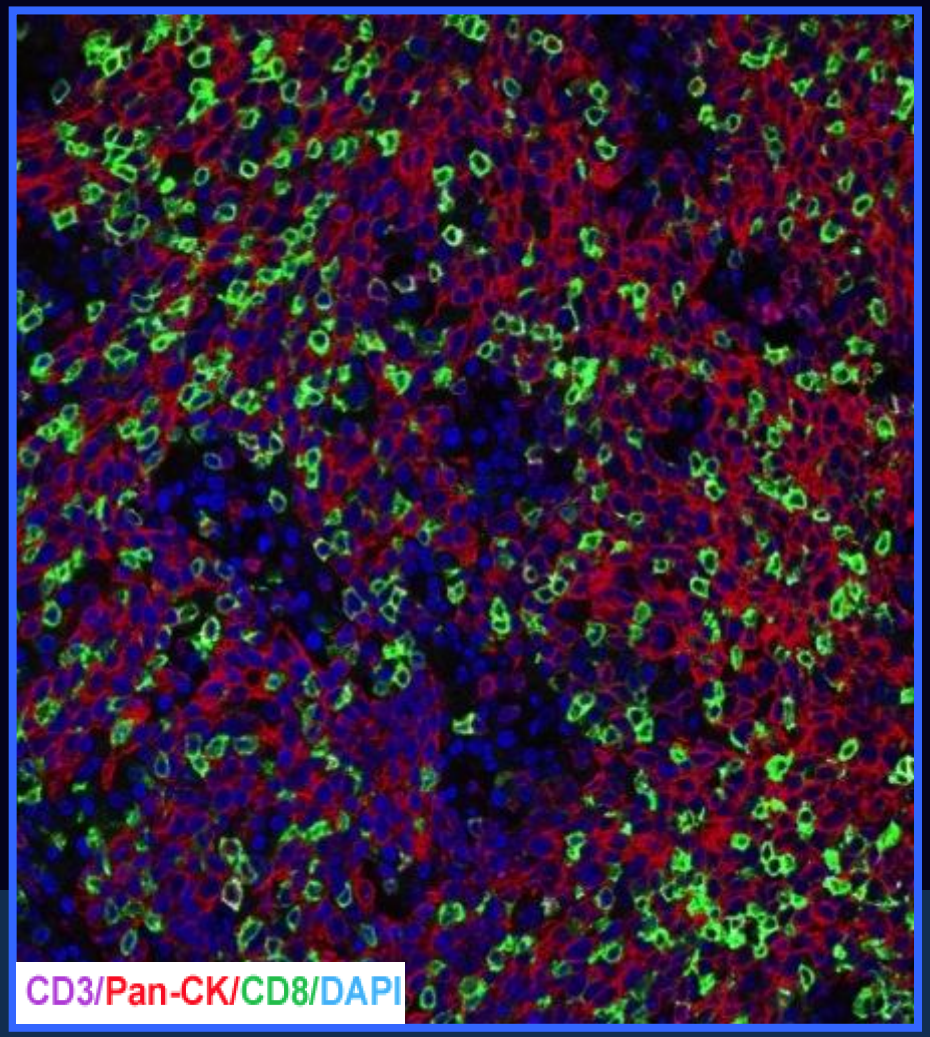
- PD-L1 “threshold” is to be defined (tumour material, mAB, technique, sampling, criteria)
- PD-L1 expression is dynamic
- PD-L1 is heterogeneous within tissue
- Importance of co-localization with TILs



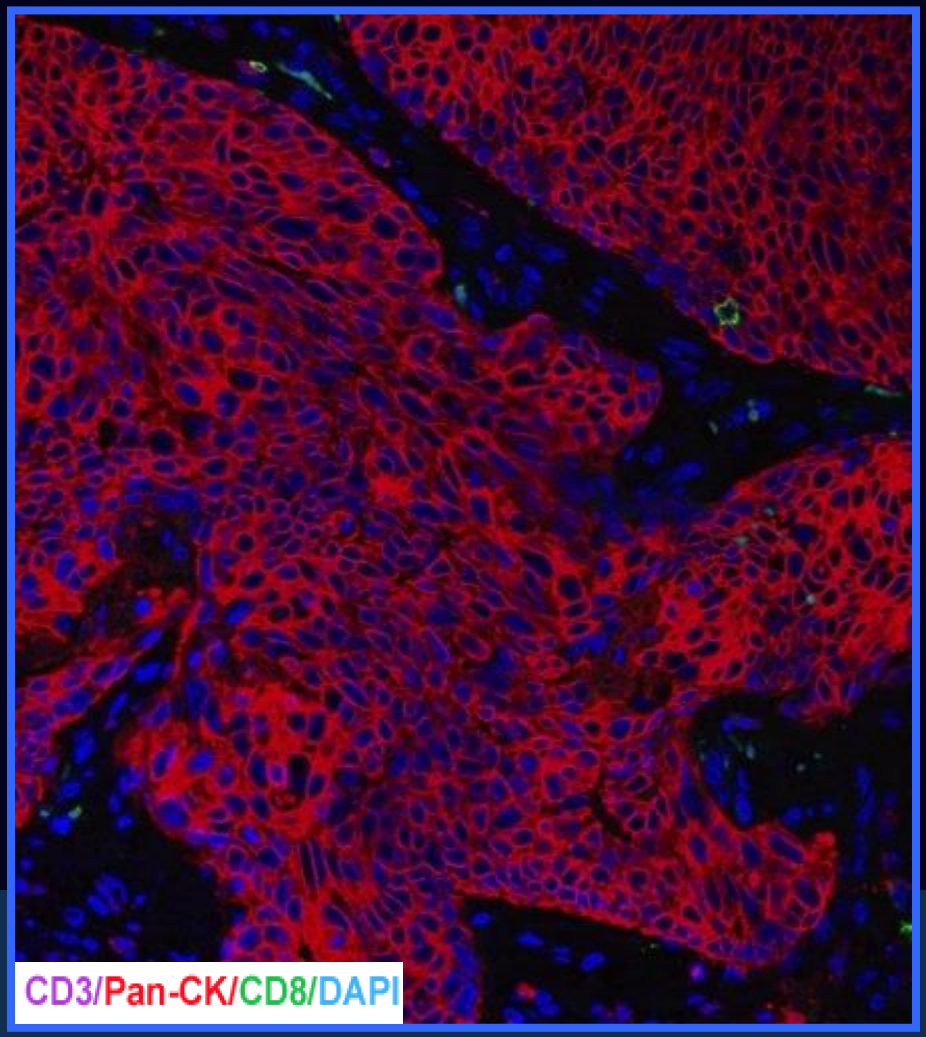
[a] Patient experiencing ongoing benefit per investigator.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Tumor Infiltrating Lymphocytes as a biomarker? The HNSCC example

Diffuse infiltration with CD8+ TILs in HNSCC



Absence of TILs in HNSCC



Tumors and/or Immune cells?

LETTER

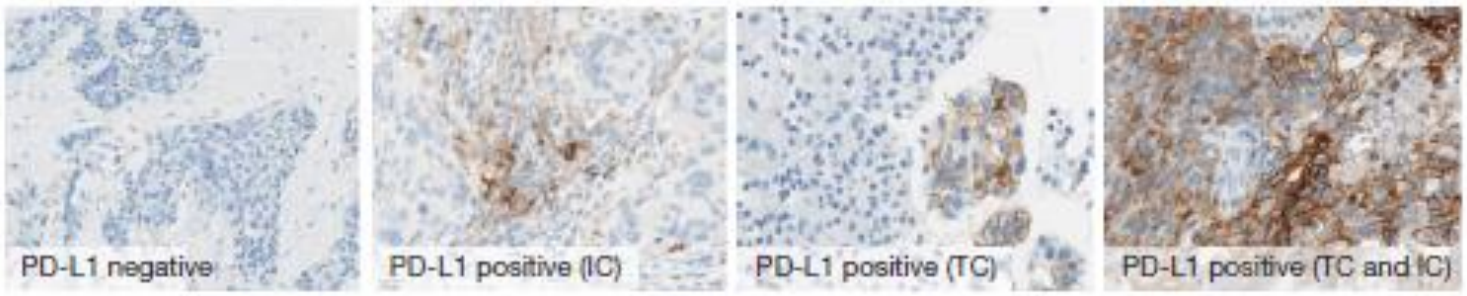
doi:10.1038/nature14011

Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients

Roy S. Herbst[1], Jean-Charles Soria[2], Marcin Kowanetz[3], Gregg D. Fine[3], Omid Hamid[4], Michael S. Gordon[5], Jeffery A. Sosman[6], David F. McDermott[7], John D. Powderly[8], Scott N. Gettinger[1], Holbrook E. K. Kohrt[9], Leora Horn[10], Donald P. Lawrence[11], Sandra Rost[3], Maya Leabman[3], Yuanyuan Xiao[3], Ahmad Mokatrin[3], Hartmut Koeppen[3], Priti S. Hegde[3], Ira Mellman[3], Daniel S. Chen[3] & F. Stephen Hodi[12]

PD-L1 prevalence determined with a Genentech/Roche anti-PD-L1 IHC assay

Indication	*n*	Percentage of PD-L1 positive (IC)	Percentage of PD-L1 positive (TC)
NSCLC	184	26	24
RCC	88	25	10
Melanoma	58	36	5
HNSCC	101	28	19
Gastric cancer	141	18	5
CRC	77	35	1
Pancreatic cancer	83	12	4



NSCLC checkpoint inhibitors

Clear evidence of anti PD1/PD-L1 activity

- Optimal dose?
- Treatment sequence?
- Combination strategy: (Martin Reck)
  - Chemotherapy
  - Other checkpoint inhibitor
  - Targeted therapy (TKI)
- Will we identify a robust & reproducible biomarker?

Sciencexpress

Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer

Genomic landscape of lung cancers shapes response to anti-PD-1 therapy

Whole-exome sequencing of non–small cell lung cancers treated with pembrolizumab.

In two independent cohorts, higher nonsynonymous mutation burden in tumors associated with improved objective response, durable clinical benefit, and progression-free survival.
Efficacy also correlated with the molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations

Rizvi, Science 2015

Thanks for your attention