Check point inhibitors for NSCLC
An update

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nature**OUTLOOK**

CANCER IMMUNOTHERAPY
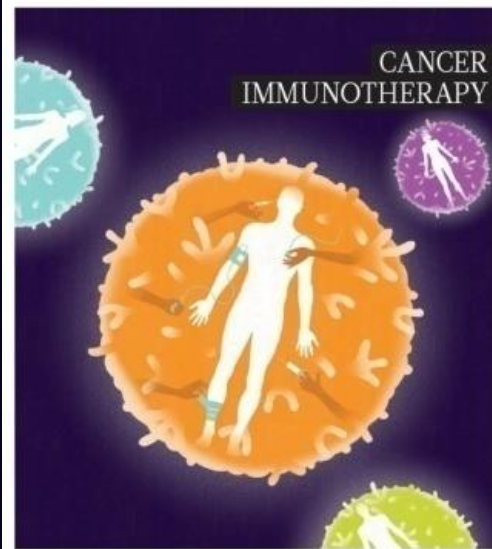
Produced with support of a medical education grant from Bristol-Myers Squibb and with support of a grant from F. Hoffmann-La Roche Ltd and Merck & Co., Inc.
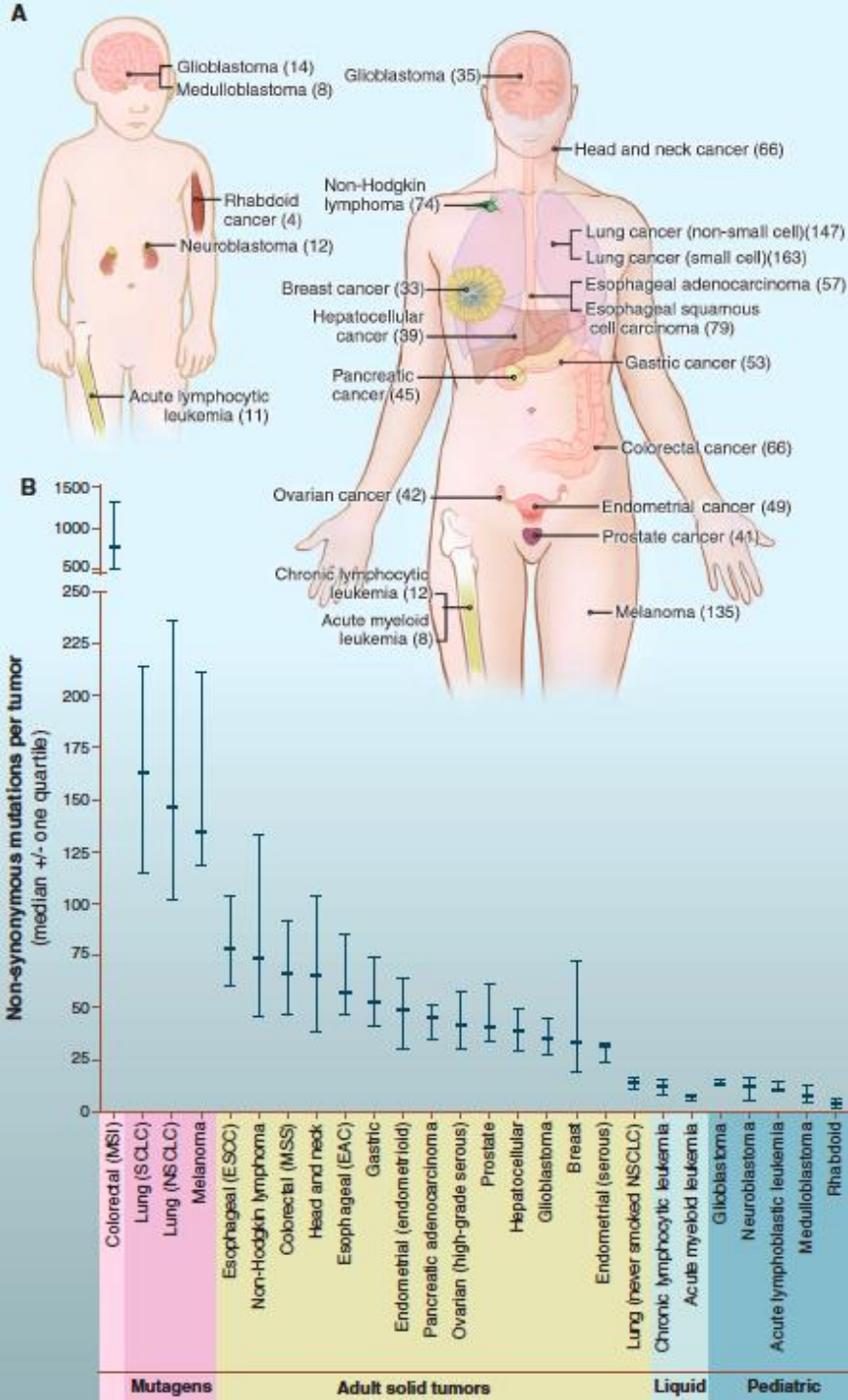
Dendreon

Enhancing natural defences

Science

29 December 2013

Breakthrough of the Year
Cancer Immunotherapy
T cells on the attack

AAAS

GOP Makeover / Drone Morality / The Marriage Test

TIME

HOW TO CURE CANCER*

*Yes, it's now possible—thanks to new cancer dream teams that are delivering better results faster
BY BILL SAPORITO

"In any trial you get the odd patient who does very well, but this is an order of magnitude above that.", **Mick Peake, Glenfield Hospital**
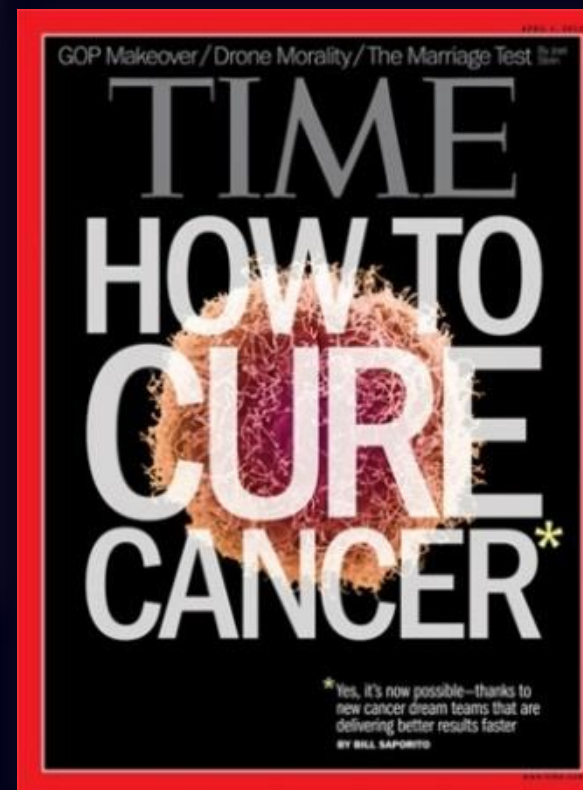
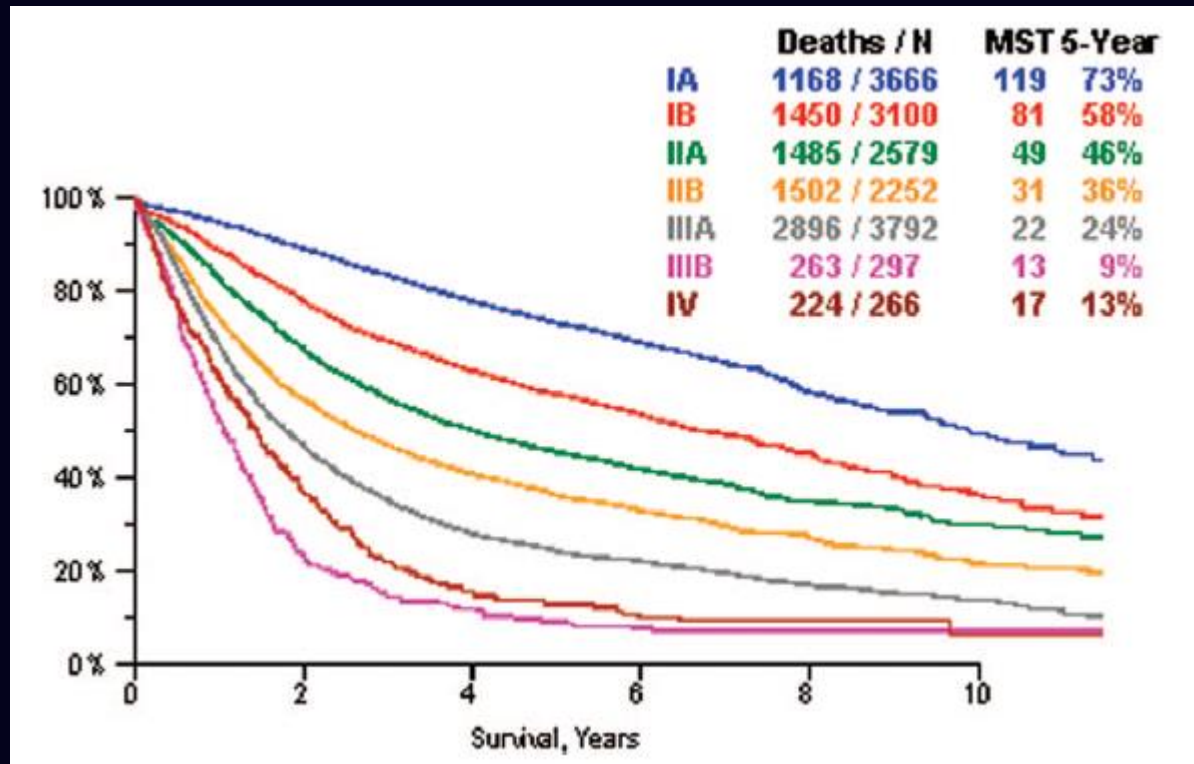# Mutations in Cancer Cells Make Them Appear Different to the Immune System

Somatic mutation frequencies observed in exomes from 3083 tumor-normal pairs
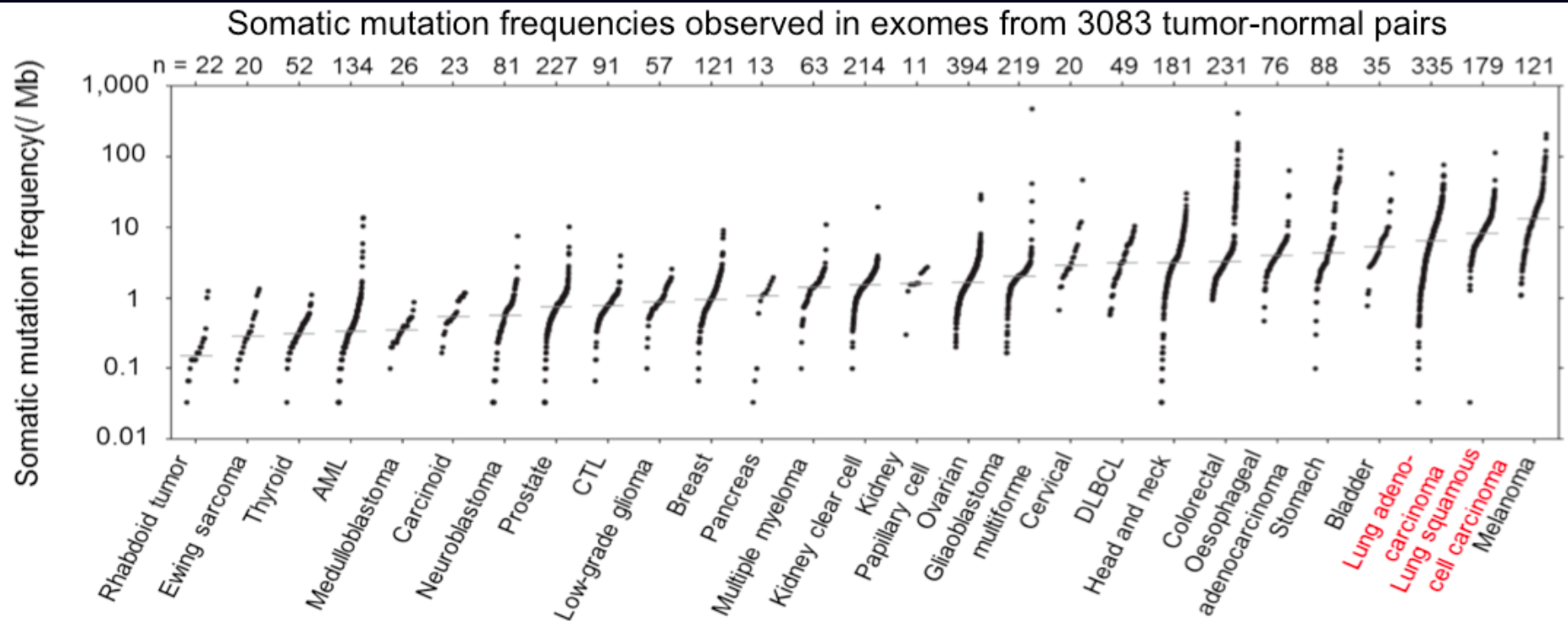
High mutational rates may contribute to increased immunogenicity
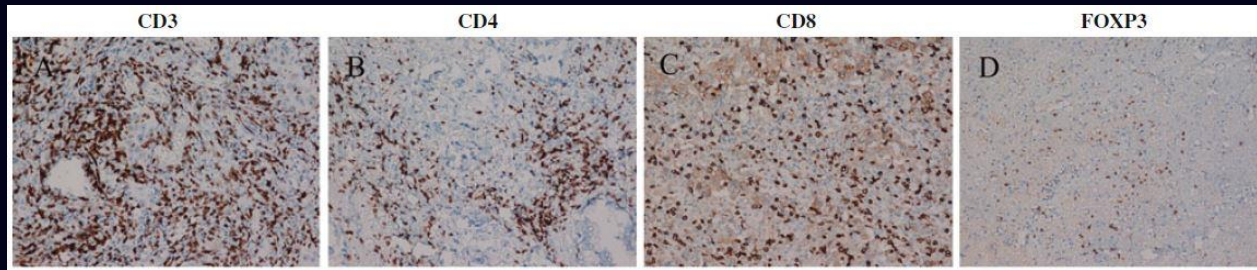
Lawrence MS, et al. *Nature*. 2013.

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

Lung cancer is the main cause of cancer death worldwide

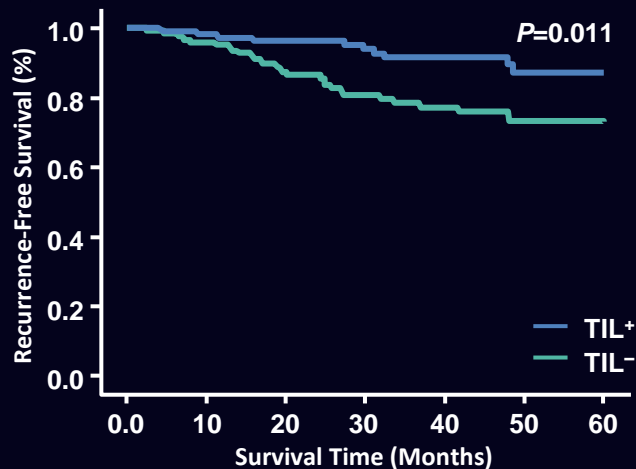|	Deaths / N	MST	5-Year
IA	1168 / 3666	119	73%
IB	1450 / 3100	81	58%
IIA	1485 / 2579	49	46%
IIB	1502 / 2252	31	36%
IIIA	2896 / 3792	22	24%
IIIB	263 / 297	13	9%
IV	224 / 266	17	13%

Survival, Years
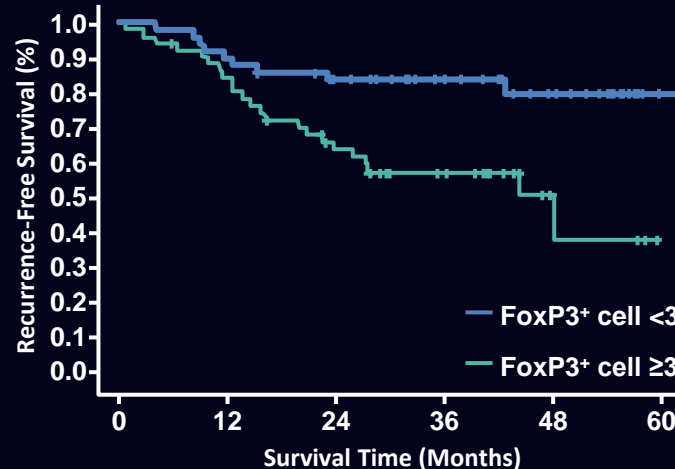
Rationale for immune therapy in NSCLC

Liu H et al. *Cancer Immunol Immunother* 2012

Presence of TILs associated with increased recurrence-free survival[1]

Higher NSCLC-Infiltrating Tregs associated with worse recurrence-free survival[2]
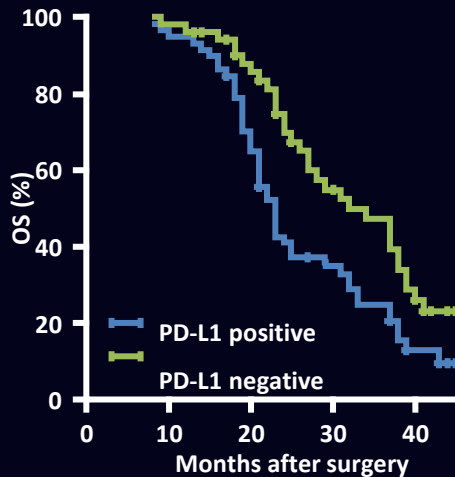

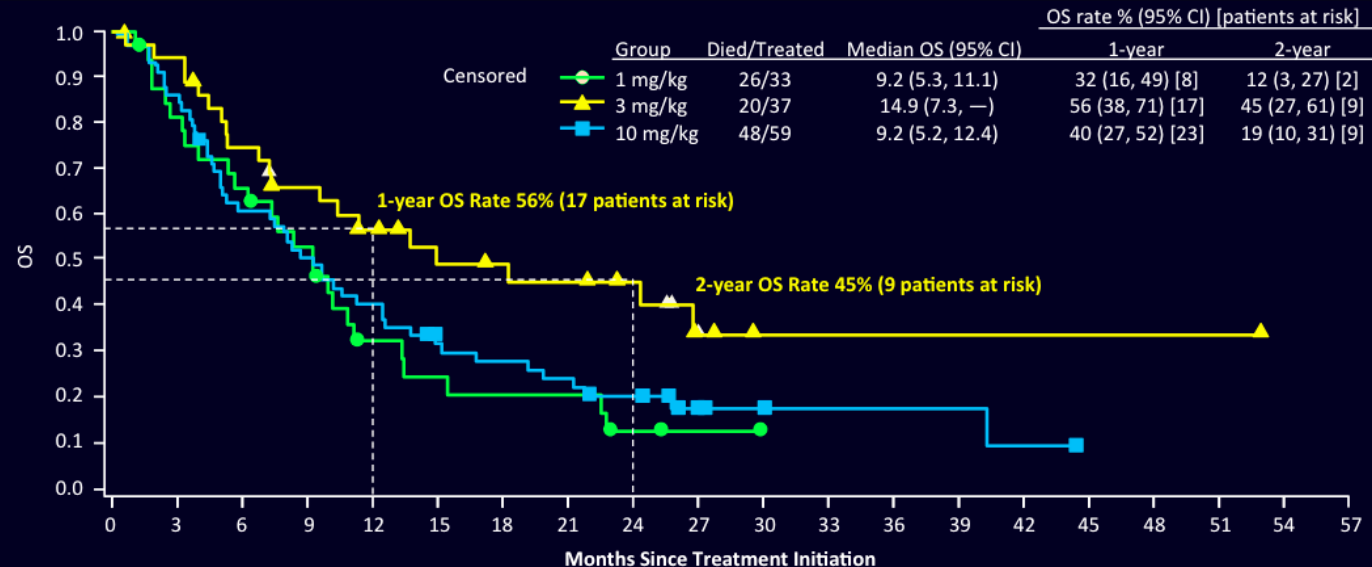1. Shimizu K, et al. *J Thorac Oncol.* 2010

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

Rationale for immune therapy in NSCLC

Prognostic role of PD-L1 expression on lung cancer cells

Mu CY, et al. *Med Oncol* 2011

Brahmer, ASCO 2014

Lung cancer immunotherapy Landscape

Cancer immunotherapy: any interaction with the immune system to treat cancer

Active: priming of the immune system

Passive: delivery of compounds that may use immune system

Antigen-specific

Non-antigen-specific

Monoclonal antibodies

Adoptive cell transfer

-> AG-specific antibodies & cytotoxic T cells

-> enhancement of immune system
- cytokines
- checkpoint inhibitors

- cetuximab
- trastuzumab

- T cells engineering
- CARs
- Dendritic cells

Cancer vaccination therapy

Cancer immunomodulation therapy

Targeted antibodies immunotherapy

Cellular immunotherapy

NSCLC: An immune driven tumor?

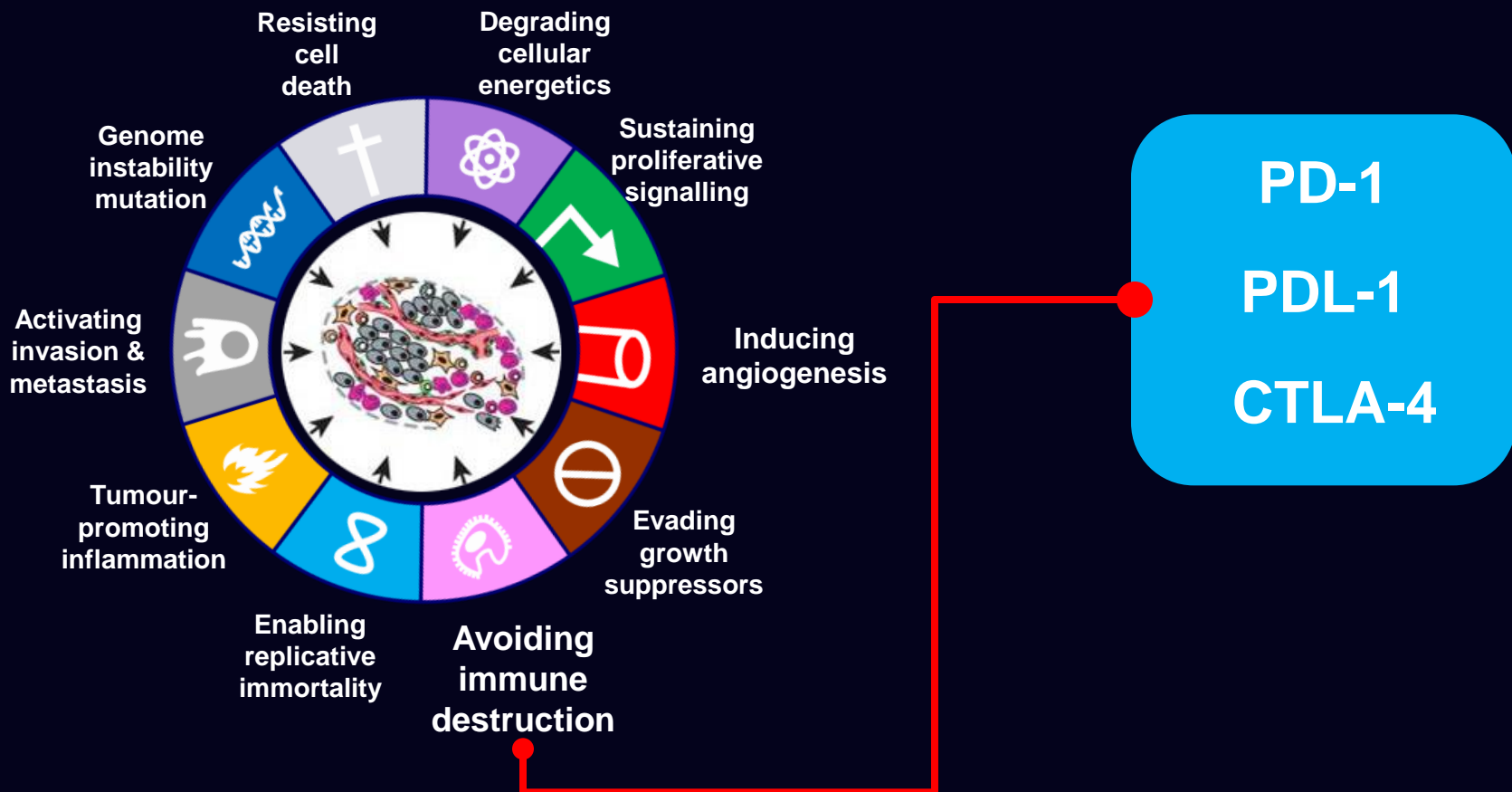| Tumour type	Prognostic[a] tumour infiltrating lymphocytes[b]	Immune-related spontaneous tumour regression[c]
NSCLC	Yes[1]	Yes[13] (rare)
CRC	Yes[2]	Yes[14]
Breast	Yes[3,4]	No
Melanoma	Yes[5,6]	Yes[15]
Renal	Yes[7,8]	Yes[16,17]
Prostate	Yes[9]	No
Ovarian	Yes[10]	No
Head and neck	Yes[11]	No
Cervical	Yes[12]	Evidence for cervical intraepithelial neoplasia 2/3[18,19]

[a]Covers correlation with improved overall or progression-free survival, disease stage, or therapy outcome
[b]The type of lymphocyte dictates where there is a correlation with improved or worsened outcome
[c]Based on PubMed search conducted in October 2013 using the terms 'spontaneous regression' and the tumour type

1. Hiraoka K, et al. *Br J Cancer*. 2006;94:275–280; 2. Galon J, et al. *Science*. 2006;29:1960–1964; 3. Mahmoud SM, et al. *J Clin Oncol*. 2011;29:1949–1955; 4. Loi S, et al. *J Clin Oncol*. 2013;31:860–867; 5. Piras F, et al. *Cancer*. 2005;104:1246–1254; 6. Azimi F, et al. *J Clin Oncol*. 2012;30:2678–2683; 7. Siddiqui SA, et al. *Clin Cancer Res*. 2007;13:2075–2081; 8. Donskov F, et al. *Br J Cancer*. 2002;87:194–201; 9. Flammiger A, et al. *APMIS*. 2012;120:901–908; 10. Zhang L, et al. *N Engl J Med*. 2003;348:203–213; 11. Badoual C, et al. *Clin Cancer Res*. 2006;12:465–472; 12. Piersma SJ, et al. *Cancer Res*. 2007;67:354–361; 13. Nakamura Y, et al. *Lung Cancer*. 2009;65:119–122; 14. Bir AS, et al. *Anticancer Res*. 2009;29:465–468; 15. Kalialis LV, et al. *Melanoma Res*. 2009;19:275–282; 16. Kawai K, et al. *Int J Urol*. 2004;11:1130–1132; 17. Kumar T, et al. *Respir Med*. 2010;104:1543–1550; 18. Øvestad IT, et al. *Mod Pathol*. 2010;23:1231–1240; 19. Castle PE, et al. *Obstet Gynecol*. 2009;113:18–25.

Therapeutic Intervention at Cancer Hallmarks

Resisting cell death

Degrading cellular energetics

Genome instability mutation

Sustaining proliferative signalling

Activating invasion & metastasis

Inducing angiogenesis

Tumour-promoting inflammation

Evading growth suppressors

Enabling replicative immortality

Avoiding immune destruction

PD-1

PDL-1

CTLA-4

Ipilimumab

NSCLC PHASE II , COMBINATION WITH CHEMOTHERAPY.
D. CARBONE

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

PD-1	Nivolumab-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase IIII multiple tumors
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	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 II (III)
	MPDL-3280A	Engineered human IgG1 mAb	Genentech	Phase III
	MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase II

Anti-PD1/Anti PDL1:
What do we know at the end of 2014?

1) **Monotherapy treatment with various drugs accross histologies and molecular subtypes**
    1) **in ≥2 line of NSCLC treatment**
    2) **In first line NSCLC treatment**
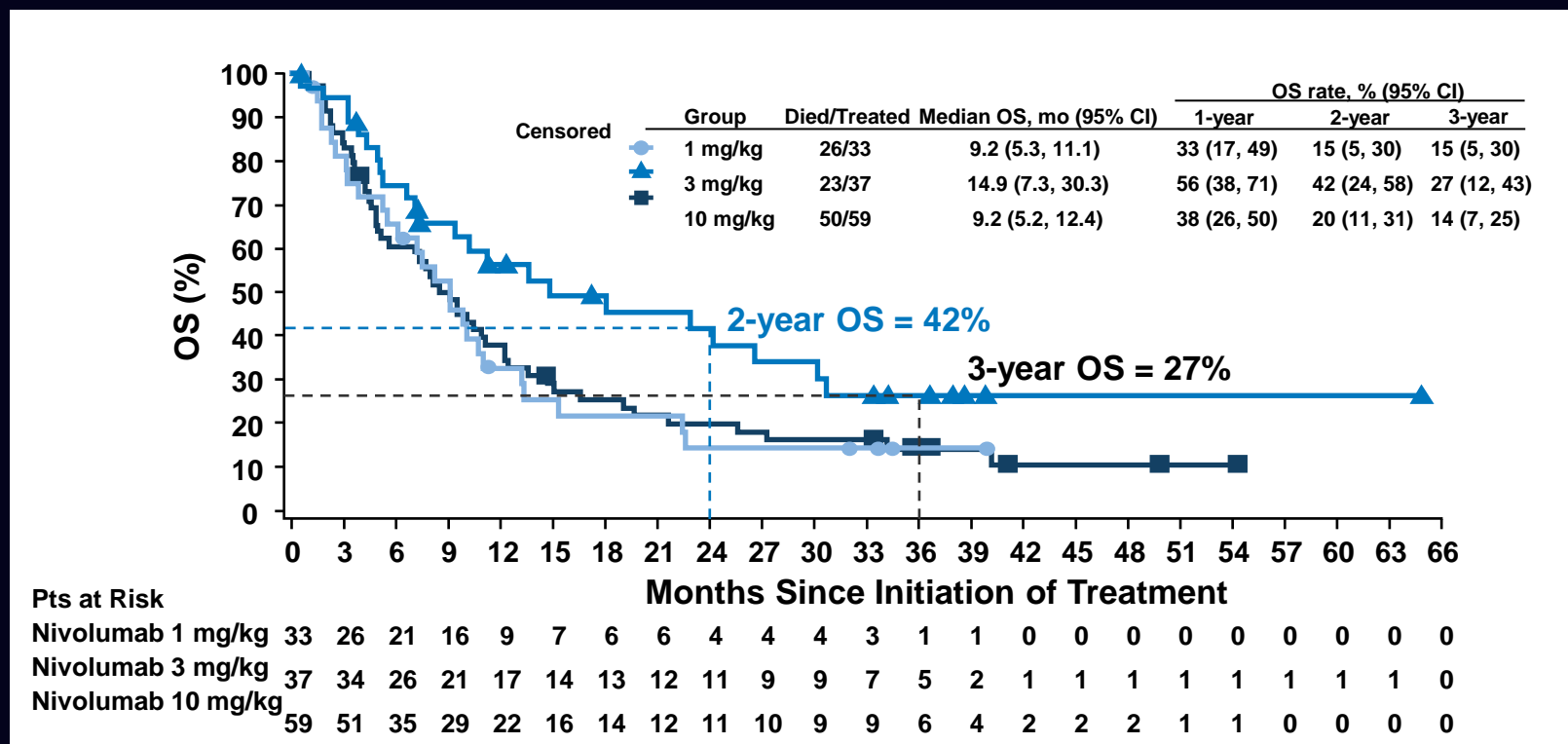
2) **The challenge of the biomarker**

Long-Term Survival, Clinical Activity and Safety of Nivolumab (Anti-PD-1; BMS-936558, ONO-4538) in Patients (pts) With Advanced Non-Small Cell Lung Cancer (NSCLC)

Gettinger et al, ASCO 2014 and CMSTO 2014

Nivolumab

>2 ND LINE, PHASE 1 DATA

Gettinger et al, ASCO 2014 and CMSTO 2014

OS by Dose (data lock 09-2014)

	Group	Died/Treated	Median OS, mo (95% CI)	OS rate, % (95% CI) 1-year	2-year	3-year
1 mg/kg	26/33	9.2 (5.3, 11.1)	33 (17, 49)	15 (5, 30)	15 (5, 30)
3 mg/kg	23/37	14.9 (7.3, 30.3)	56 (38, 71)	42 (24, 58)	27 (12, 43)
10 mg/kg	50/59	9.2 (5.2, 12.4)	38 (26, 50)	20 (11, 31)	14 (7, 25)

Pts at Risk

Nivolumab 1 mg/kg: 33 26 21 16 9 7 6 6 4 4 4 3 1 1 0 0 0 0 0 0 0 0 0

Nivolumab 3 mg/kg: 37 34 26 21 17 14 13 12 11 9 9 7 5 2 1 1 1 1 1 1 1 1 0

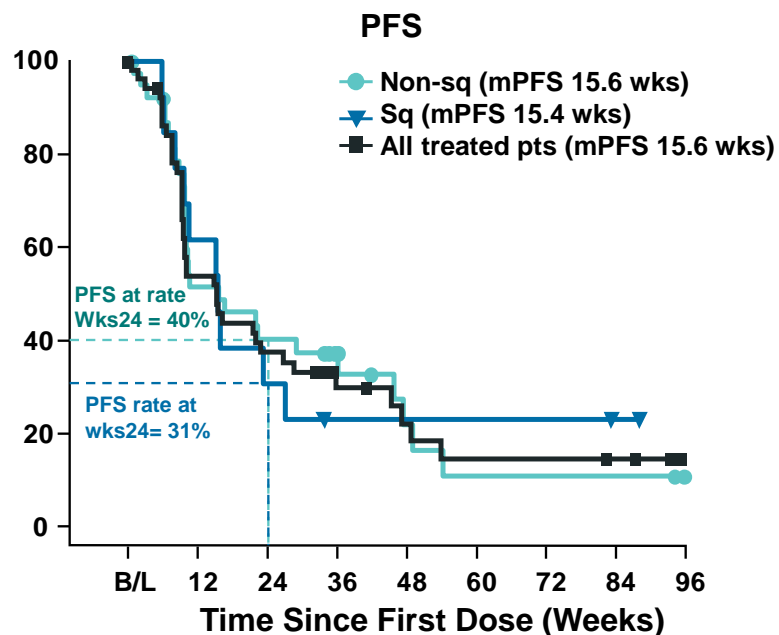Nivolumab 10 mg/kg: 59 51 35 29 22 16 14 12 11 10 9 9 6 4 2 2 2 1 1 0 0 0 0

- **Pts were heavily pretreated; 54% had 3–5 prior therapies**

- **50% of responders (11/22) demonstrated response at first assessment (8 wks)**

- **Responses were ongoing in 41% of pts (9/22) at the time of analysis**
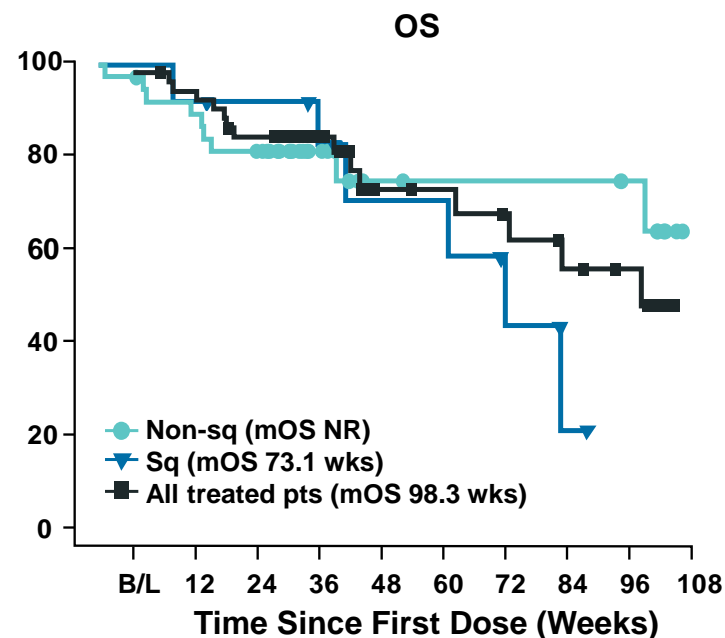
Characteristics of Responses
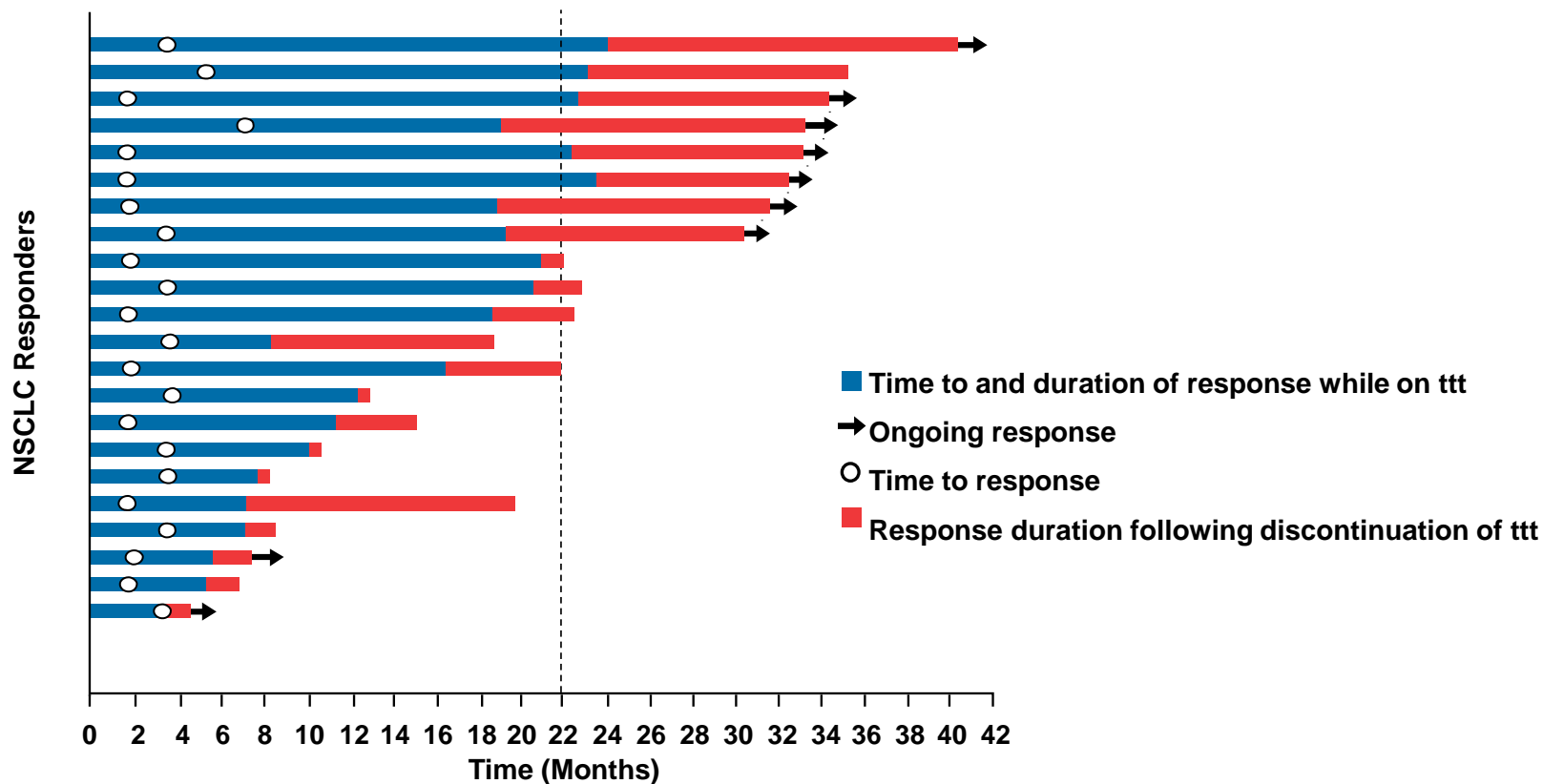
- 5% unconviential "immune-related" responses, with persistent reduction in target lesions in the presence of new lesions or regression following initial progression

- Manageable safety profile with no new safety signals emerging with all pts having >1 year of follow-up

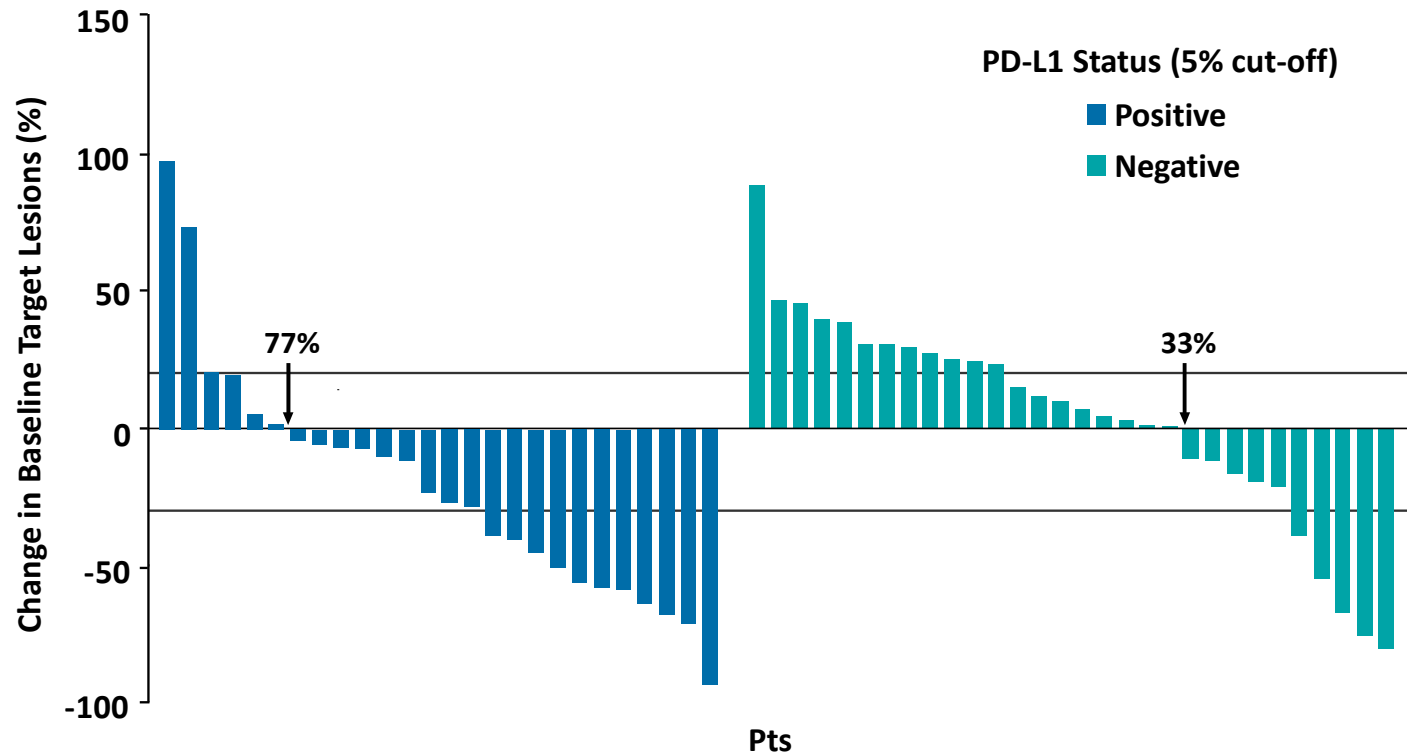# PFS and OS in NSCLC Pts Treated With Nivolumab Monotherapy

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)

Exploratory Analysis of Response by Smoking Exposure

Variable	ORR, % (n/N) [95% CI][a]
Smoking exposure	
>5 pack-years	30 (20/66) [20, 43]
≤5 pack-years[b]	0 (0/14) [0, 23]
Time since quitting (NO CORRELATION)	
>15 yrs prior	26 (6/23) [10, 48]
6–15 yrs prior	17 (2/12) [2, 48]
1–5 yrs prior	46 (6/13) [19, 75]
Current smoker	27 (6/22) [11, 50]
0/never smoker	0 (0/10) [0, 31]

Nivolumab in EGFR M+

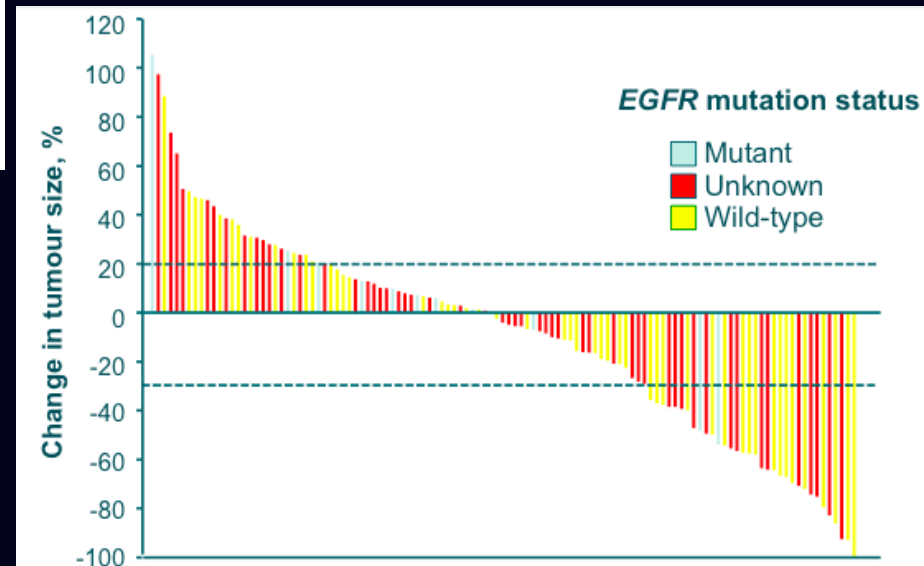**CA209-003: phase 1 follow-up study, up to 5 prior lines of therapy, NSCLC cohort**

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]

Nivolumab

1ST LINE, PHASE 1 DATA MONOTHERAPY

Rizvi et al; Antonia et al, CMSTO 2014

Nivolumab

1ST LINE, PHASE 1 DATA MONOTHERAPY
COMBINATIONS
IPILIMUMAB AND NIVOLUMAB
### NIVOLUMAB AND ERLOTINIB (EGFR M+)
NIVOLUMAB AND CHEMOTHERAPY
D.CARBONE

Rizvi et al; Antonia et al, CMSTO 2014

PFS and OS in NSCLC Pts Treated With Nivolumab Monotherapy frontline

PFS

- Non-sq (mPFS 15.6 wks)
- Sq (mPFS 15.4 wks)
- All treated pts (mPFS 15.6 wks)

PFS at rate Wks24 = 40%

PFS rate at wks24= 31%

Time Since First Dose (Weeks)

OS

- Non-sq (mOS NR)
- Sq (mOS 73.1 wks)
- All treated pts (mOS 98.3 wks)

Time Since First Dose (Weeks)
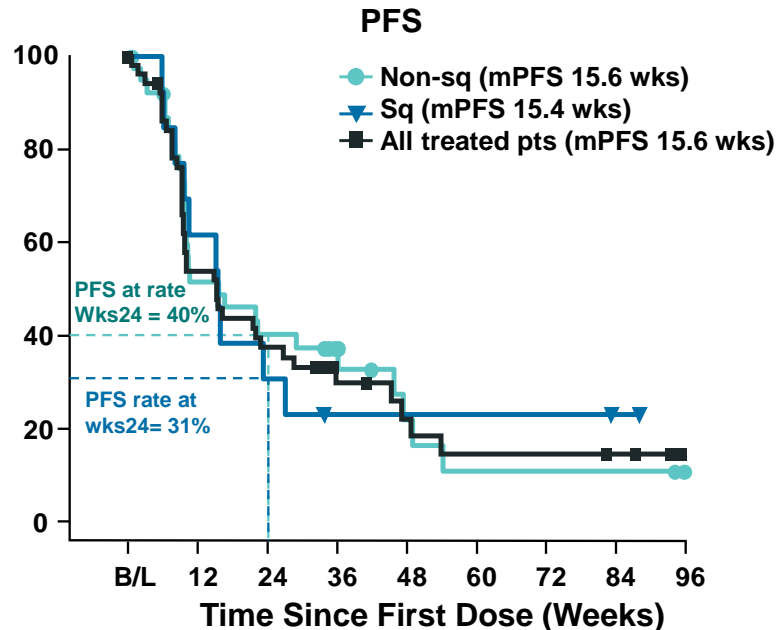
Number of Pts at Risk

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
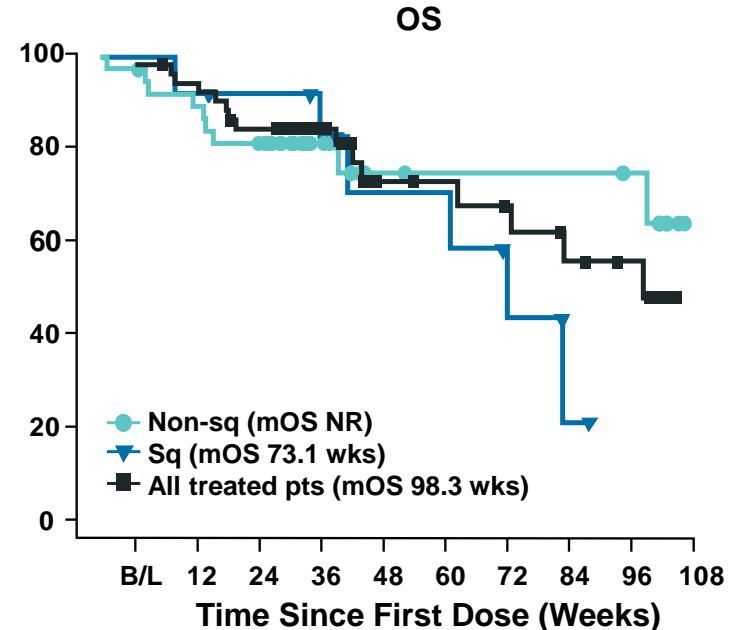
Number of Pts at Risk

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

Percent Changes in Target Lesion Tumor Burden by PD-L1 in first line

A. Percent change in target lesions from baseline

PD-L1 Status (5% cut-off)

Positive
Negative

Change From Baseline (%)

Time Since First Dose (Weeks)
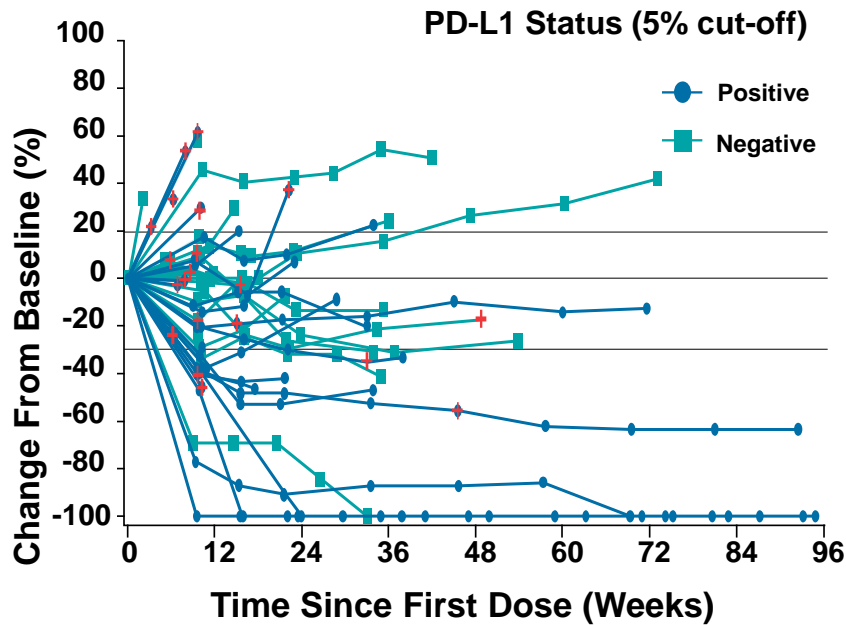
B. Best percent change in target lesion tumor burden from baseline

PD-L1 Status (5% cut-off)

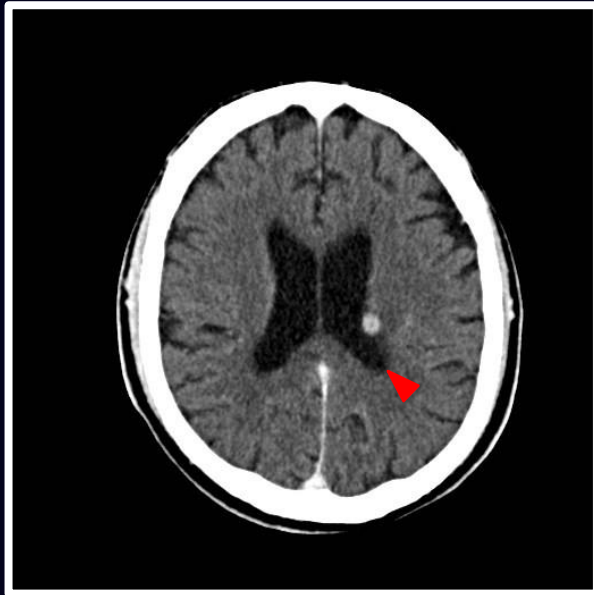Positive
Negative
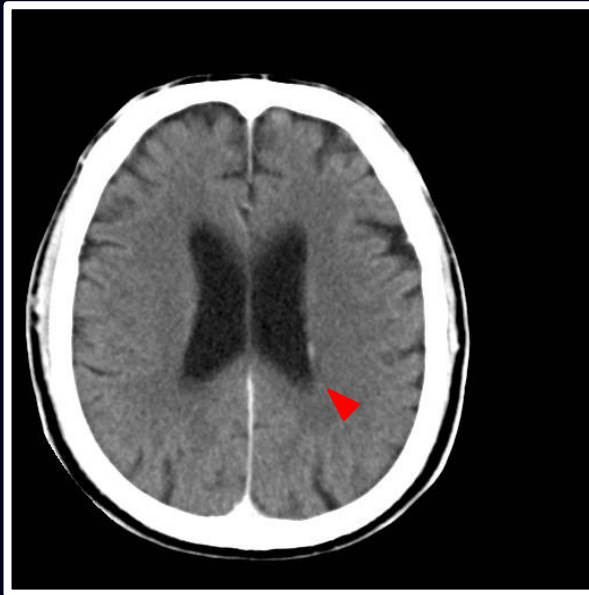
Change in Baseline Target Lesion (%)a

Pts
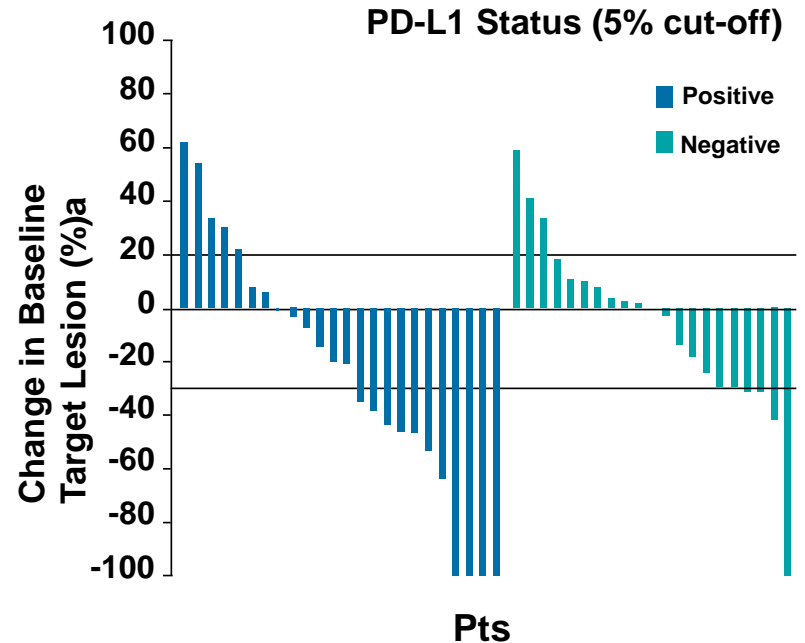
Nivolumab

SQUAMOUS >2 ND LINE, PHASE 2 MONOTHERAPY DATA

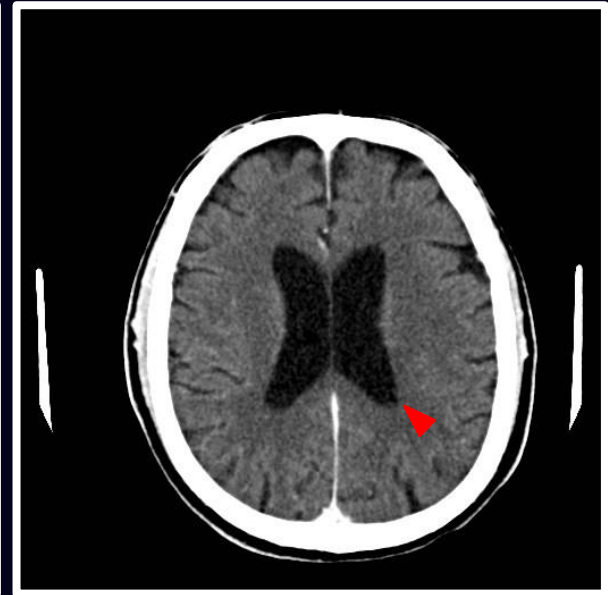# Response to Nivolumab in SQ NSCLC Brain Metastasis

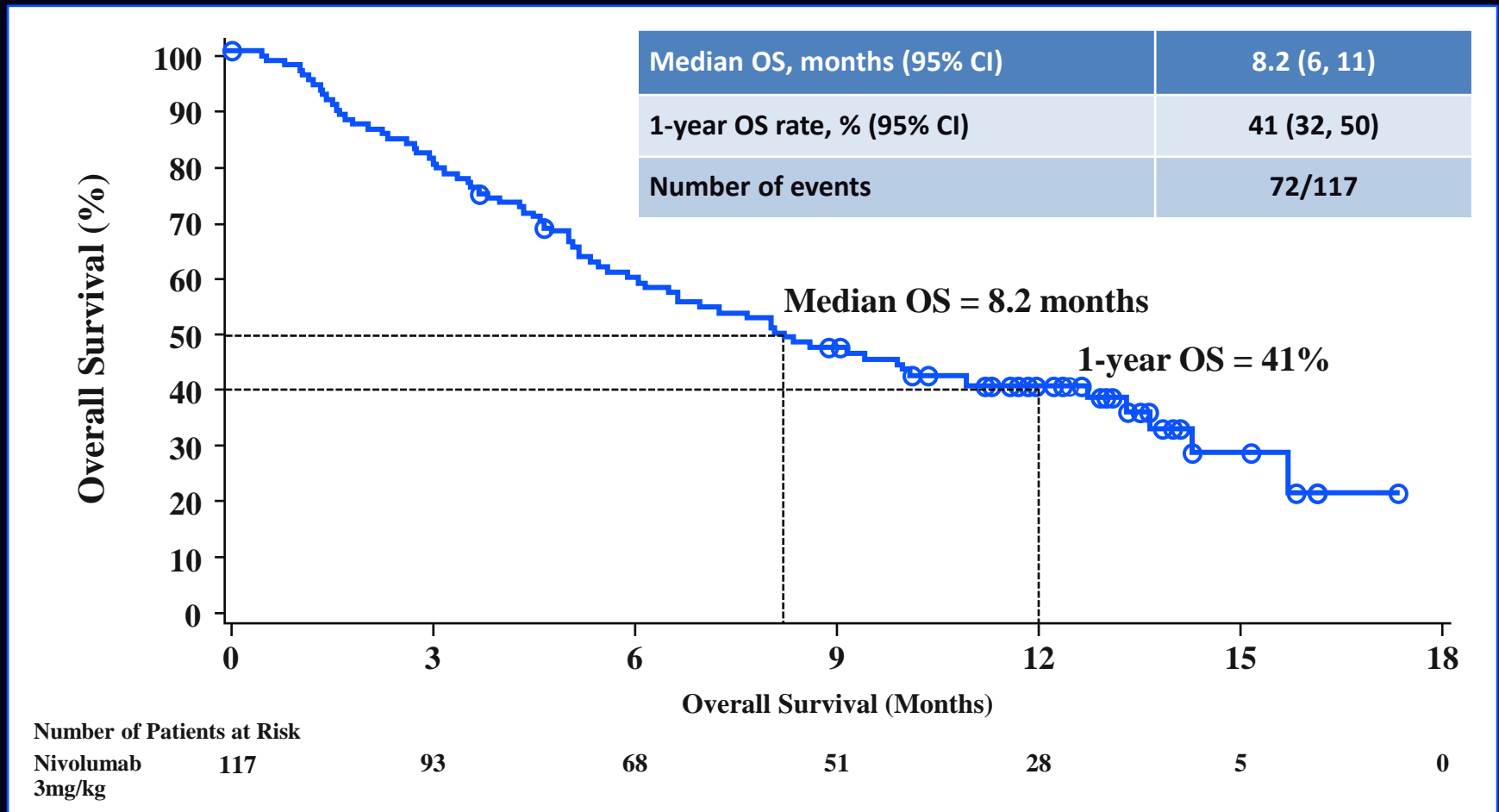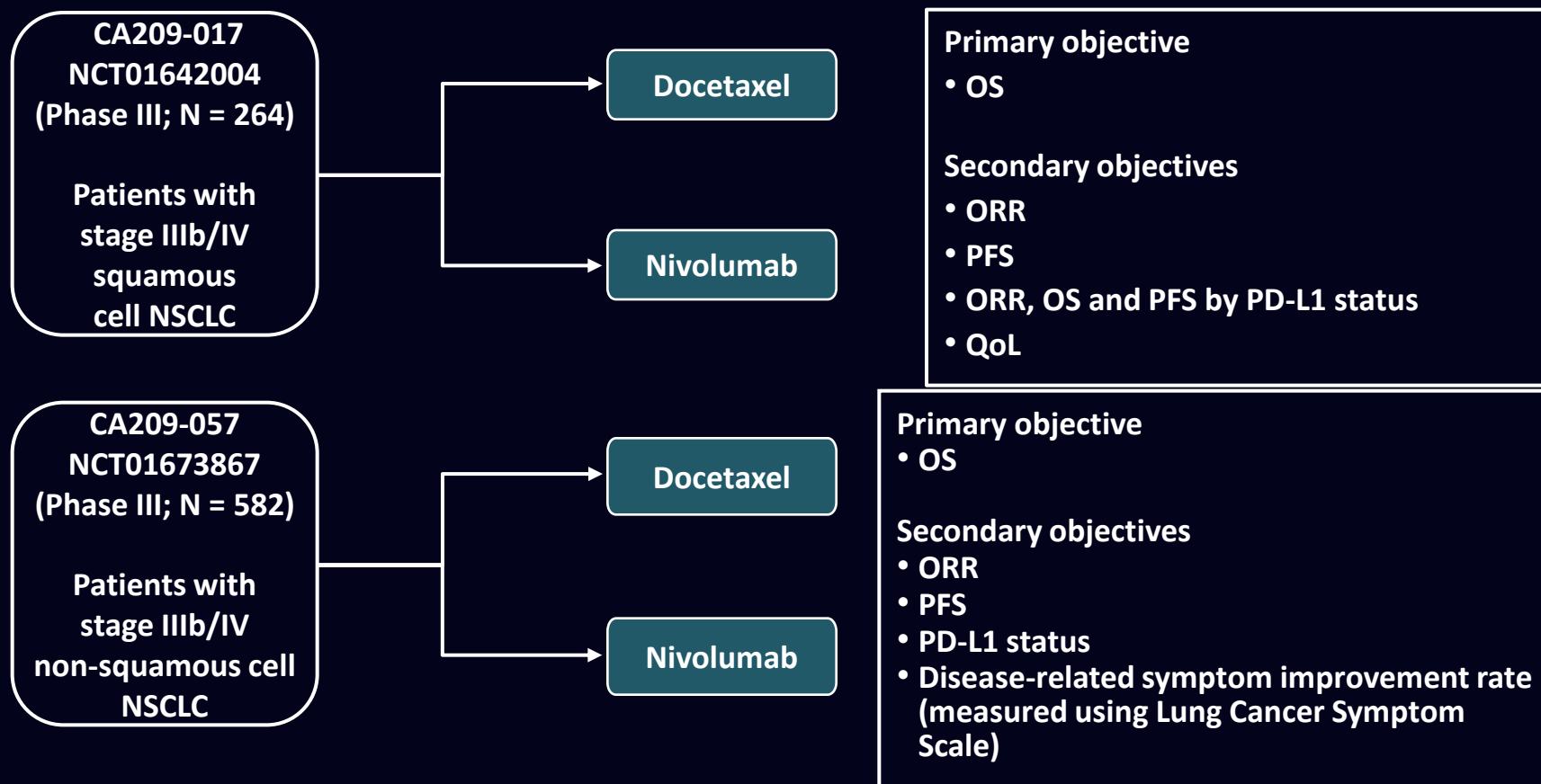**Pre-treatment** | **Week 14** | **Week 68**

- 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 OS, months (95% CI)	8.2 (6, 11)
1-year OS rate, % (95% CI)	41 (32, 50)
Number of events	72/117

Median OS = 8.2 months

1-year OS = 41%

Number of Patients at Risk

Nivolumab 3mg/kg	117	93	68	51	28	5	0

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

Randomized confirmation pending…

CA209-017
NCT01642004
(Phase III; N = 264)

Patients with stage IIIb/IV squamous cell NSCLC

→ Docetaxel

→ Nivolumab

Primary objective
- OS

Secondary objectives
- ORR
- PFS
- ORR, OS and PFS by PD-L1 status
- QoL

CA209-057
NCT01673867
(Phase III; N = 582)

Patients with stage IIIb/IV non-squamous cell NSCLC

→ Docetaxel

→ Nivolumab

Primary objective
- OS

Secondary objectives
- ORR
- PFS
- PD-L1 status
- Disease-related symptom improvement rate (measured using Lung Cancer Symptom Scale)

http://www.clinicaltrials.gov

Pembrozilumab

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)

58%

Treatment naive
Previously treated

y-axis: Change From Baseline in Sum of Largest Diameter of Target Lesion, %

[a] ⬥⬥⬥.
Analysis cut-off date: March 3, 2014.

Time to and Durability of Response
(RECIST v1.1, Central Review)[a]
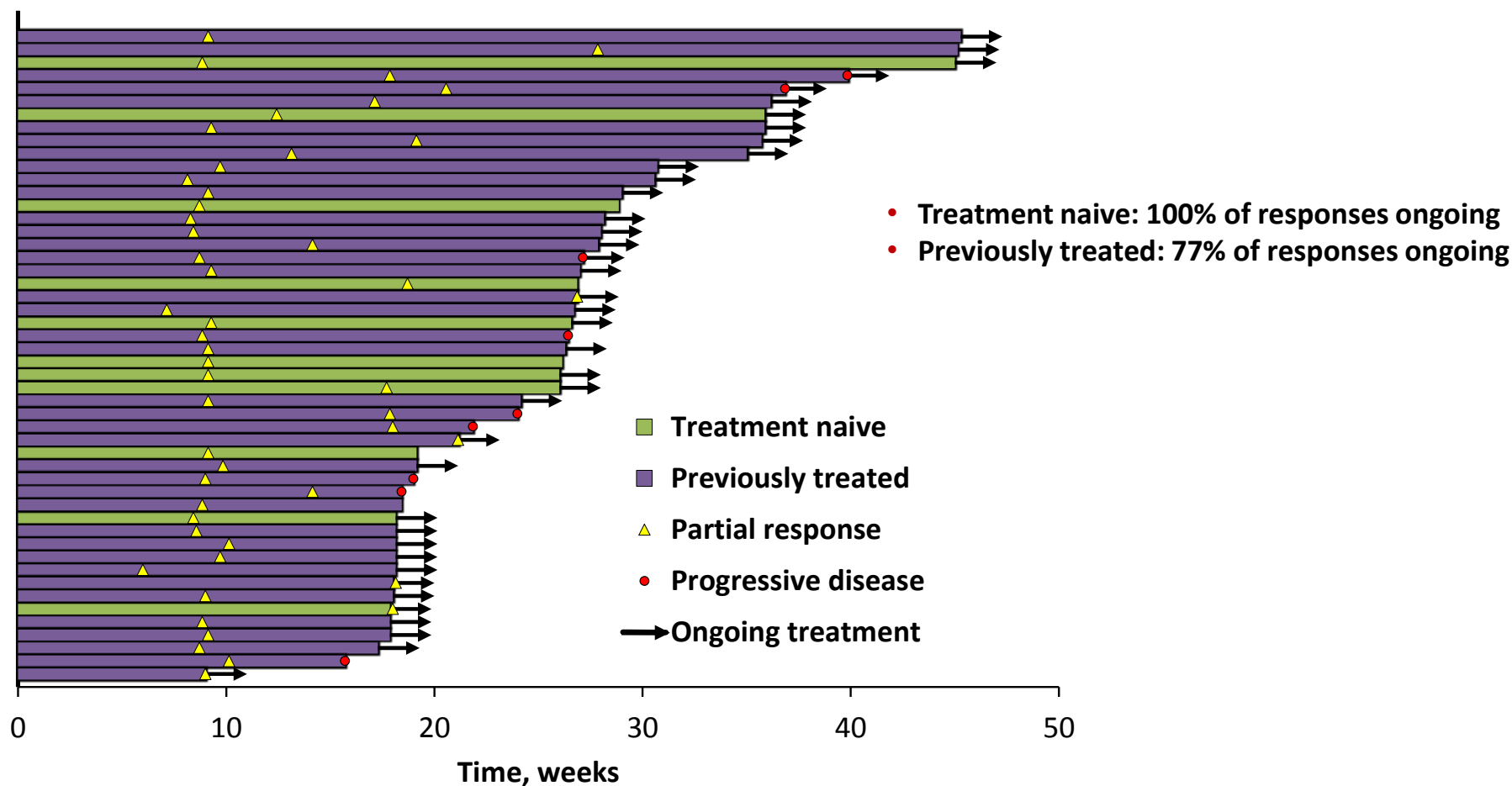
- Treatment naive: 100% of responses ongoing
- Previously treated: 77% of responses ongoing

Legend:
- ▢ Treatment naive
- ▢ Previously treated
- △ Partial response
- ● Progressive disease
- → Ongoing treatment

X-axis: Time, weeks (0, 10, 20, 30, 40, 50)

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

Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

OS
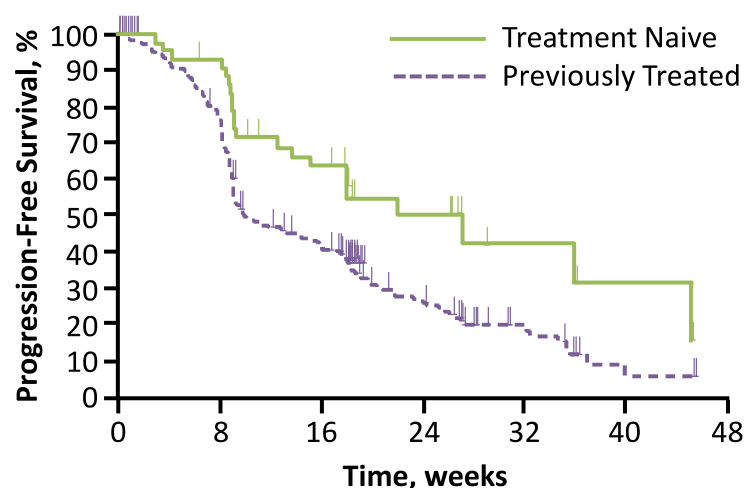
n at risk

Treatment Naive	45	39	25	11	4	2	0
Previously Treated	217	159	81	33	13	2	0

45	41	38	24	13	7	2	0
217	192	146	77	33	8	0	0

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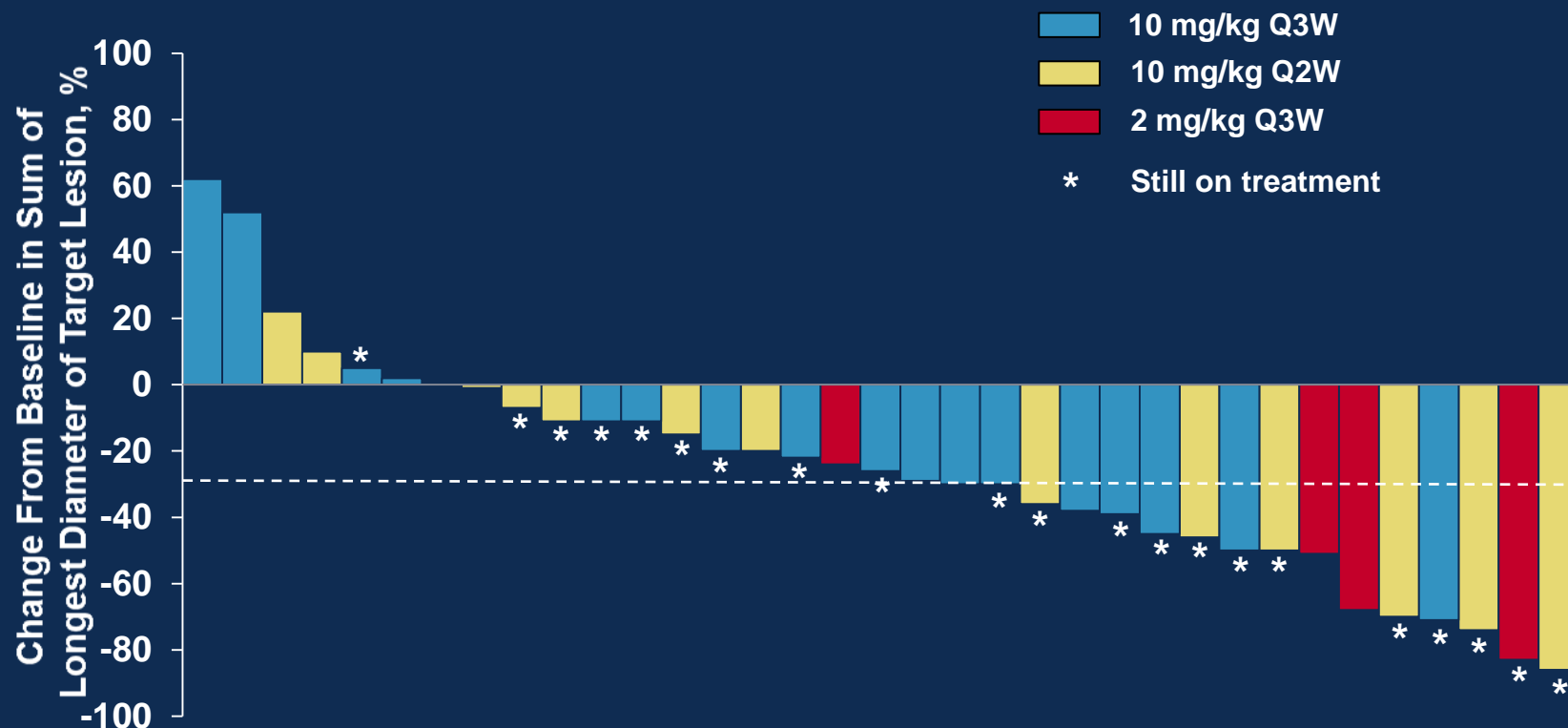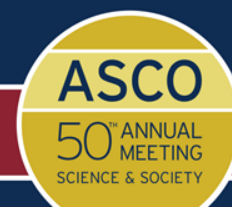 - Median PFS: 10 weeks (9.1-15.3)
  - 24-week PFS: 26%

- Treatment naive
  - 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%

26-30 September 2014, Madrid, Spain

Analysis cutoff date: March 3, 2014.
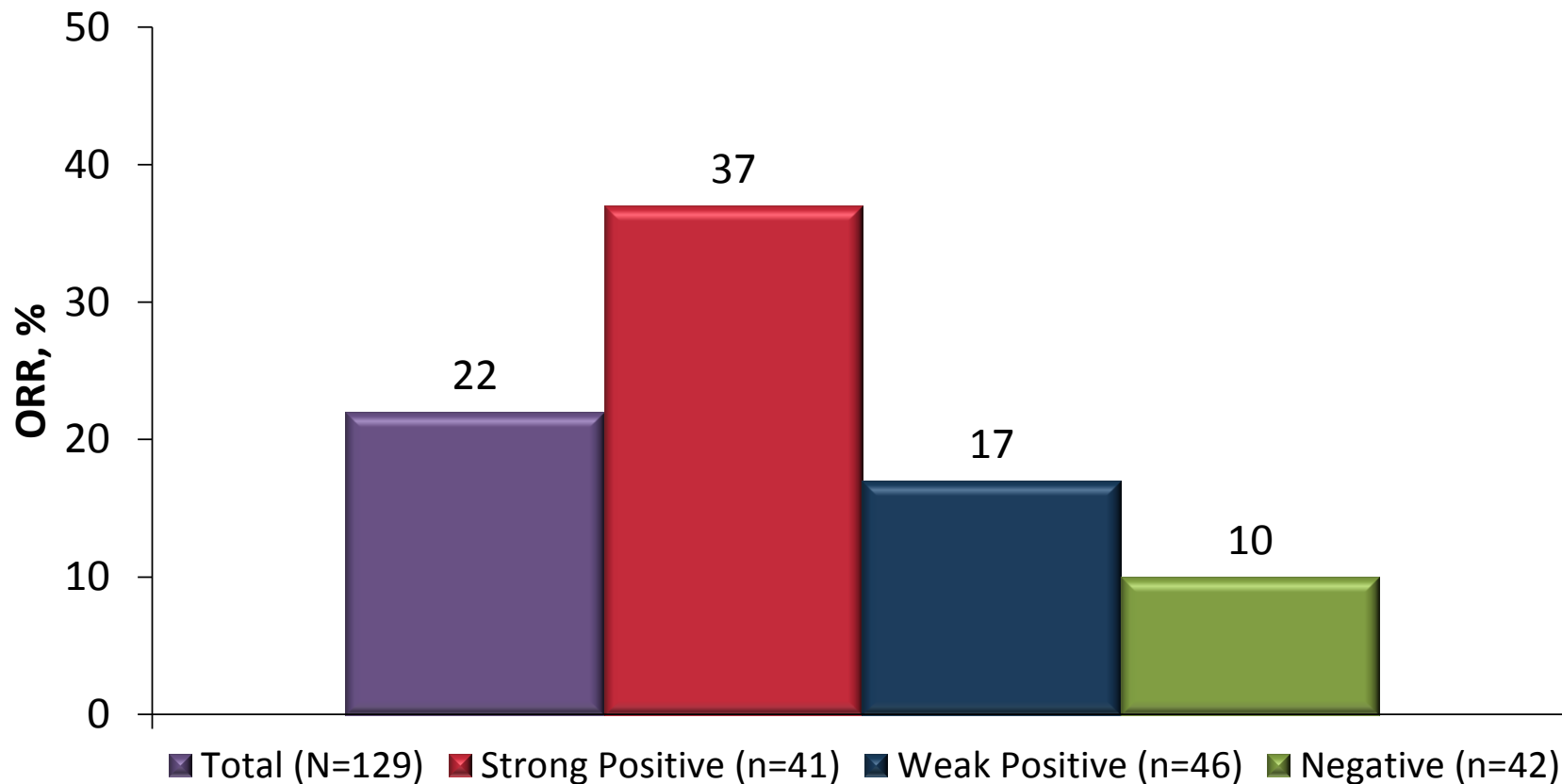
Focus on pembrozilumab first line data

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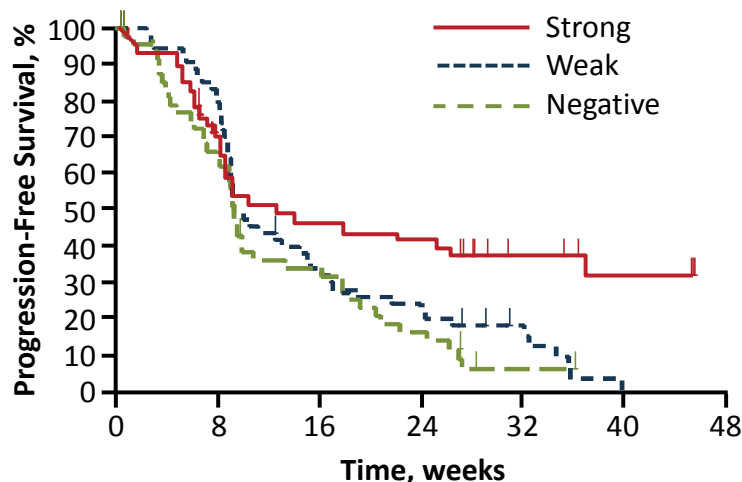 - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

Response Rate by Level of PD-L1 Expression
## (RECIST 1.1, Central Review)

[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.

Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)

OS

n at risk

PFS:

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

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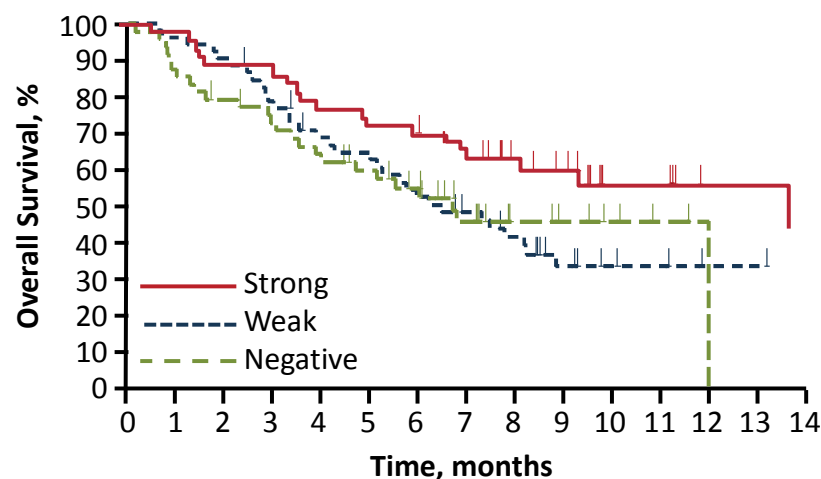
Strong	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
Weak	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
Negative	49	42	38	34	29	26	21	14	8	6	4	2	0	0	0

- 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)

[a]Evaluable patients were those patients in the training set with evaluable tumor PD-L1 expression.
Strong PD- ▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯▯-L1 positivity as staining in 1-49% of tumor cells. Negative staining is no PD-L1 staining in tumor cells.
Data cut-off: March 3, 2014.

MPLD3280A

>2 ND LINE, PHASE 1 DATA

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

MPDL3280A Phase Ia: Efficacy Summary
Investigator Assessed

	Single Agent RECIST 1.1 Response Rate (ORR[a])	SD of 24 Weeks or Longer	24-Week PFS Rate
Overall population (N = 175)	21%	19%	42%
NSCLC (n = 53)	**23%**	17%	45%
Nonsquamous (n = 42)	21%	17%	44%
Squamous (n = 11)	27%	18%	46%

[a] ORR includes investigator-assessed unconfirmed and confirmed PR.
Six patients who did not have a post-baseline scan were included as non-responders.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

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

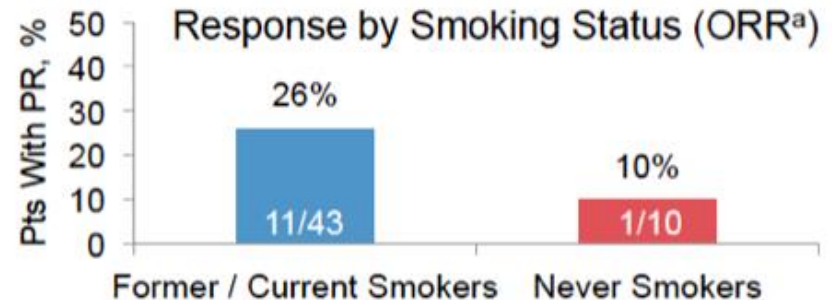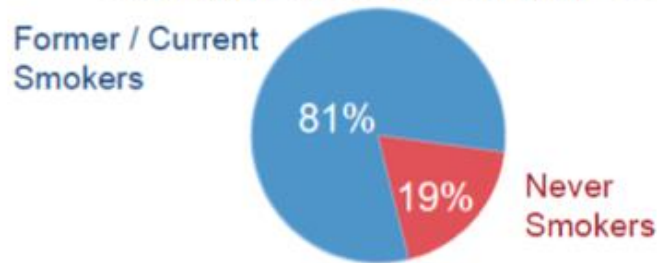| Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	83% (5/6)	17% (1/6)
IHC 2 and 3	46% (6/13)	23% (3/13)
IHC 1/2/3	31% (8/26)	38% (10/26)
All Patients[c]	23% (12/53)	40% (21/53)

[a] IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3:
≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.
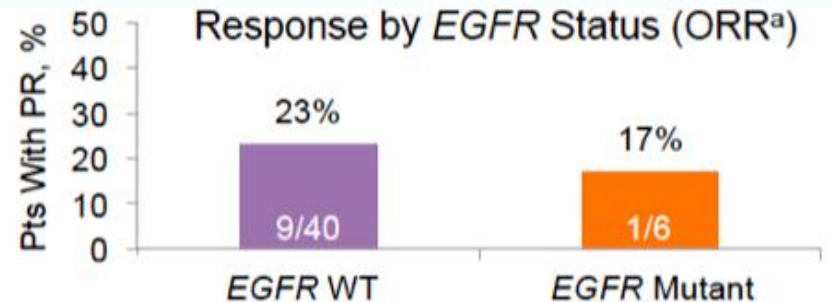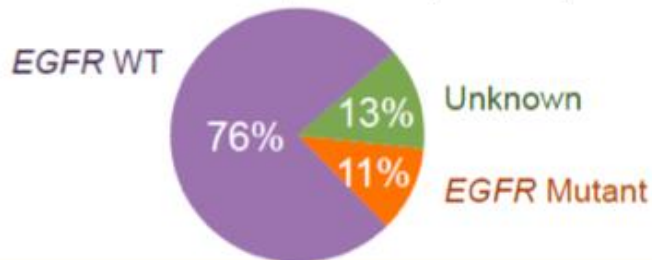[b] ORR includes investigator-assessed unconfirmed and confirmed PR.
[c] All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.
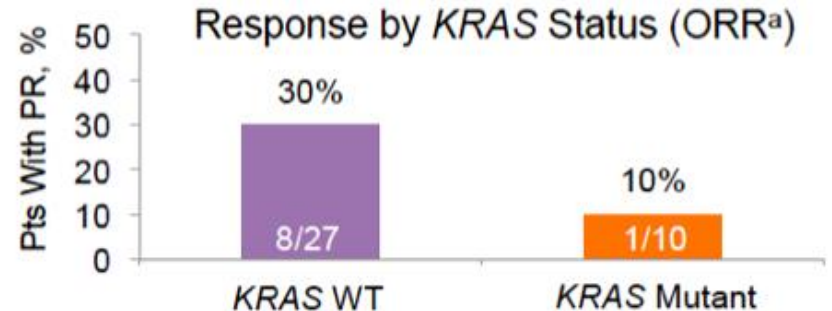
MPDL3290A: Specific predictors

Smoking Status (NSCLC; n = 53)
- Former / Current Smokers: 81%
- Never Smokers: 19%

Response by Smoking Status (ORR[a])
- Former / Current Smokers: 26% (11/43)
- Never Smokers: 10% (1/10)

EGFR Status (NSCLC; n = 53)
- EGFR WT: 76%
- Unknown: 13%
- EGFR Mutant: 11%

Response by EGFR Status (ORR[a])
- EGFR WT: 23% (9/40)
- EGFR Mutant: 17% (1/6)

KRAS Status (NSCLC; n = 53)
- KRAS WT: 51%
- Unknown: 30%
- KRAS Mutant: 19%

Response by KRAS Status (ORR[a])
- KRAS WT: 30% (8/27)
- KRAS Mutant: 10% (1/10)

Histology is not predictive through all available data

	Squamous Carcinoma	Non-squamous
Nivolumab (PD-1)	17% (9/54)	18% (13/74)
MPDL3280A (PD-L1)	33% (3/9)	19% (6/31)
Pembrolizumab (irRECIST)	25% (66/262)	23% (60/262)

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
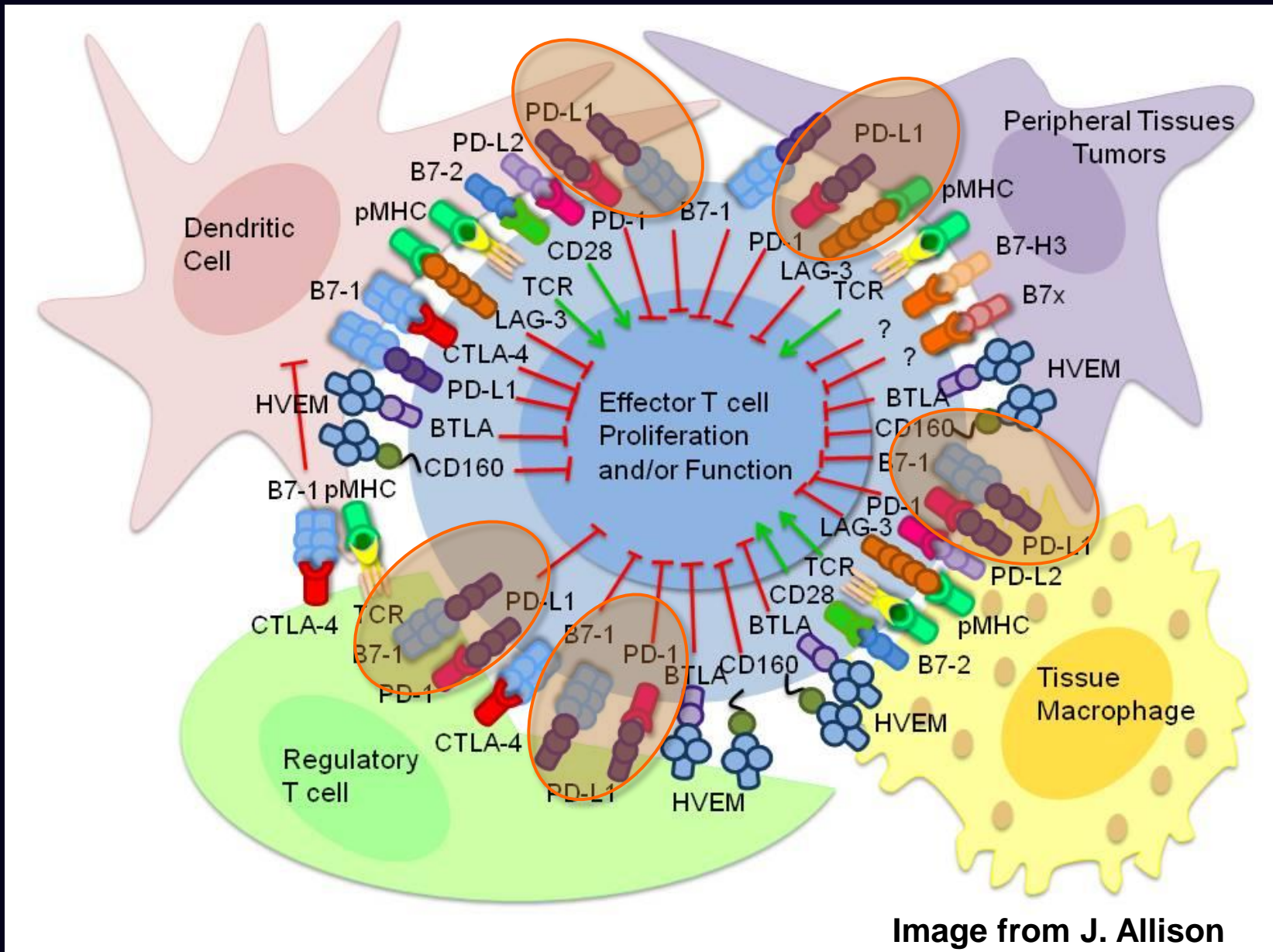
PD-L1 analysis:
differences in evaluation and interpretation

Agent	Assay	Analysis	Definition of positivity	PD-L1 expression
Nivolumab (anti-PD-1) [1-4]	Dako automated IHC assay (28-8 rabbit Ab) Analytically validated	• Archival FFPE	• 1% and 5% cut-off among >100 evaluable tumour cells	• 56%: 1% cut-off • 49%: 5% cut-off

Pembrolizumab (anti-PD-1) [5,6]	Dako automated IHC assay (22C3 mouse Ab)	• Archival FFPE	• Tumour dependent:
			  - Melanoma > 1%
			  - NSCLC
			    PD-L1 (+): Strong (≥50%) and weak staining (1–49%)
			    PD-L1 (–): no staining
				• ~25%: ≥50% staining
				• ~45–70%: ≥1% staining

MPDL3280A (anti-PD-L1) [7,8]	Ventana automated clinical research IHC assay	• Archival FFPE	• PD-L1 (+):
			  IHC 3 (≥10%),
			  IHC 2,3 (≥5%),
			  IHC 1,2,3 (≥1%)
			• PD-L1 (–):
			  IHC 1, 0 or unknown
				• 11%: IHC 3
				• 75%: IHC 1, 0

MEDI-4736 (anti-PD-L1) [9]	First-generation or Ventana IHC Automated Assay (in dev.)	• Archival FFPE	• Not reported	• Not reported

PD-L1 as a biomarker in NSCLC

|	Nivolumab BMS			Pembrolizumab MSD (Merck)			MPDL3280A Genentech			MEDI4736 MedImmune
Drug/ Sponsor	Nivolumab BMS			Pembrolizumab MSD (Merck)			MPDL3280A Genentech			MEDI4736 MedImmune
Assay	28-8			22C3						SP263
Cells scored	Tumor cell membrane			Tumor cell (and stroma)			Infiltrating immune cells			
Tissue	Archival			Recent			Arch./Recent			Arch./Recent
Setting	1st line	2L ++		1st line	2L ++		2L ++			2L ++
Cut-point	5%	1%	5%	1%	1%	50%	1%	5%	10%	
ORR in PD-L1 +	50% N=10	13% N=38	15% N=33	26-47% N=45	19-23% N=177	37% N=41	31% N=26	46% N=13	83% N=6	39% N=13
ORR in PD-L1 -	0% N=7	17% N=30	14% N=35	???	9-13% N=40	11% N=88	20% N=20	18% N=33	18% N=40	5% N=19

NIVO
Topalian, NEJM 2012
Grosso, ASCO 2013, #3016
Brahmer, ASCO 2014, #8112
Gettinger, ASCO 2014, #8024

Pembro
Daud, AACR 2014
Ghandi, AACR 2014
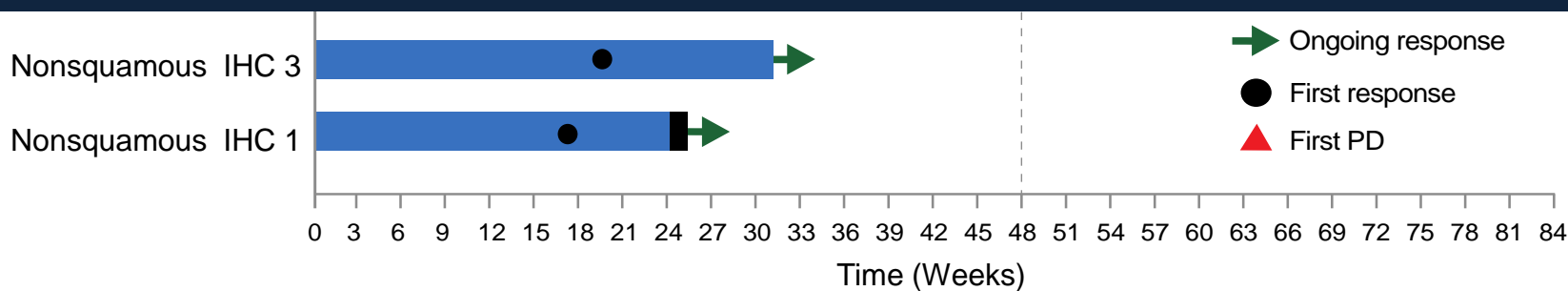Rizvi, ASCO 2014, #8009
Garon, ASCO 2014, #8020

MPDL3280A
Hamid, ASCO 2013, #9010
Herbst, ASCO 2013, #3000
Powderly, ASCO 2013, #3001
Spigel, ASCO 2013, #8008

MEDI4736
Segal, ASCO 2014, #3002
Brahmer, ASCO 2014, #8021

# MPDL3280A Phase Ia: Duration of Treatment in Responders - NSCLC

Duration of Treatment and Response

Histology   IHC

Nonsquamous IHC 0
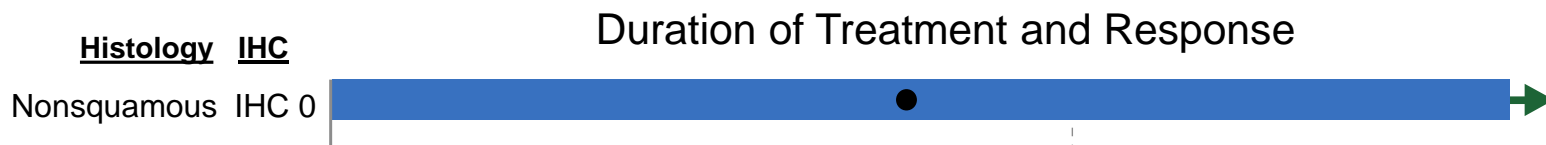
- ## PD-L1 expression is dynamic

- ## PD-L1 is heterogeneous within tissue

- ## PD-L1 "threshold" is to be defined (tumour material, mAB, technique, sampling, criteria)

- ## Importance of co-localization with TILs

Nonsquamous IHC 3

Nonsquamous IHC 1

→ Ongoing response

● First response

▲ First PD

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69 72 75 78 81 84
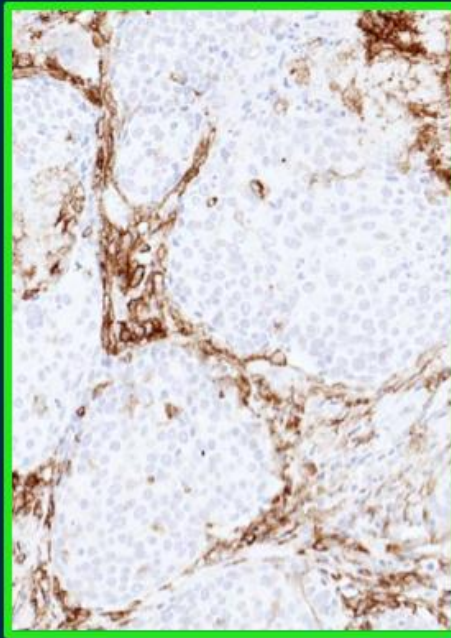
Time (Weeks)

[a] Patient experiencing ongoing benefit per investigator.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.
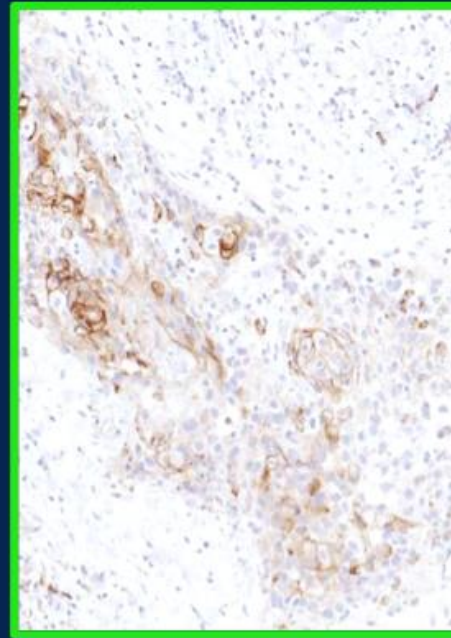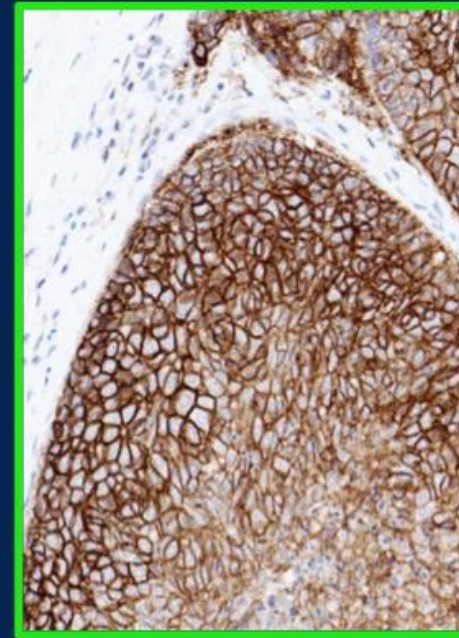
Stroma or tumour cells?
HNSCC example
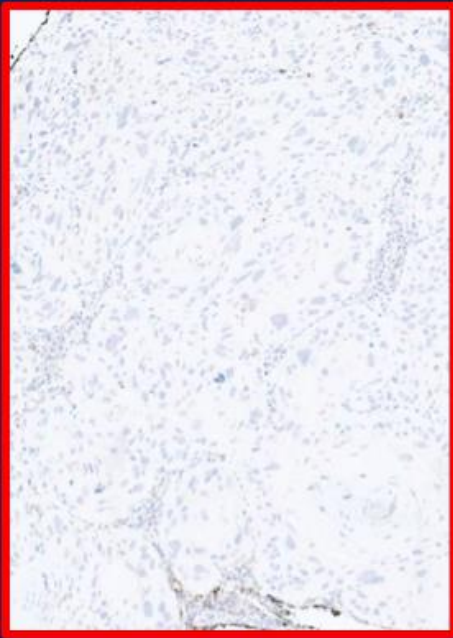
PD-L1Negative
→ Ineligible

PD-L1-Stroma
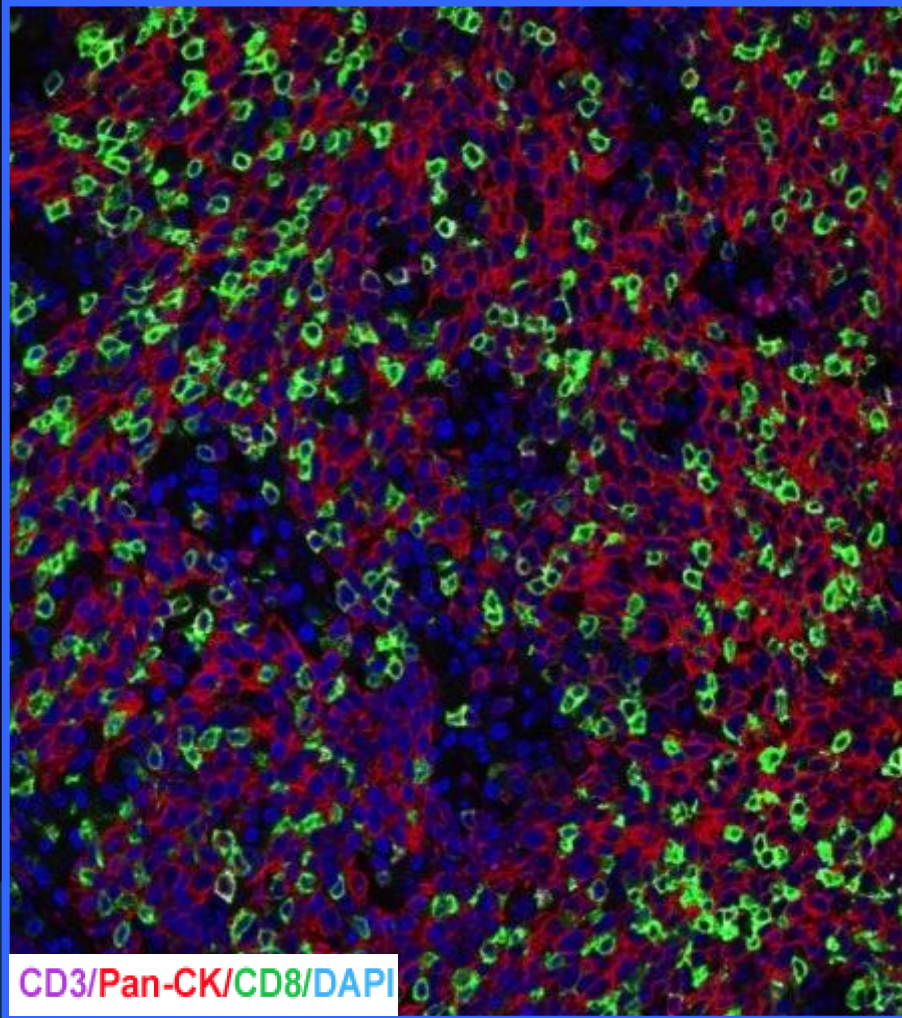Positive

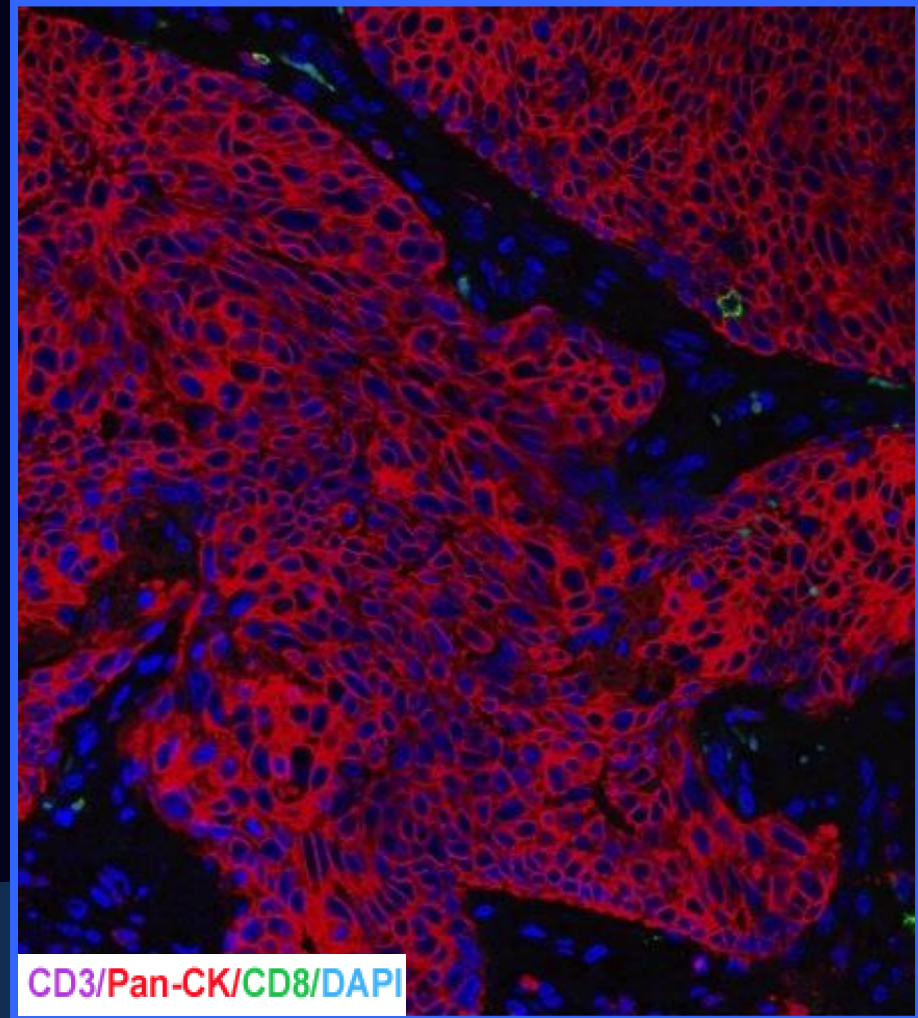PD-L1-Tumor
Positive (weak)

PD-L1-Tumor
Positive (strong)

Tumor Infiltrating Lymphocytes as a biomarker?
The HNSCC example

Diffuse infiltration with CD8+ TILs in HNSCC

Absence of TILs in HNSCC

CD3/Pan-CK/CD8/DAPI

CD3/Pan-CK/CD8/DAPI

PD1/PDL1 summary

Clear evidence of anti PD1/PD-L1 activity

	Anti PD1		Anti PDL1
	MK-3475	Nivolumab	MPDL3280A
N	236	129	53
RR	21%	17%	23%
Follow-up	6.8 m	>1 year	?
PFS Median	P: 2.5 m; 26% at 6m Naive: 6.5 m; 51% at 6m	2.3 m (Naive 9 m)	45% at 6m
OS Median	P:8.2 m; Naive: NR P:59%, Naive: 86% at 6 m	9.9 months 42% at 1y 24% at 2 y	?

PD1/PDL1 summary

Clear evidence of anti PD1/PD-L1 activity

➢ Optimal dose?

➢ Treatment sequence?

➢ Combination strategy

- Chemotherapy

- Other check point inhibitor

- Targeted therapy (TKI)

➢ Pharmacodynamic biomarkers of activity?

(circulating CD8+Ki-67+ T cells and/or plasma proteins (eg, IL-18))

PD1/PDL1 summary

Predictors of activity: PD-L1 as the biomarker?

- Selection by PD-L1 expression likely enhances response rate, but activity seen in PD-L1 neg

- How do we define PD-L1 positivity? (AB, threshold, analysis)

- How does PD-L1 evolve over time (stage/ disease course / treatments)

- Is PD-L1 more strongly expressed in defiend patients subgroups (smokers?)

- Randomized trials with PD-L1 stratification awaited!

Thanks for your attention