Immune checkpoint inhibitors in NSCLC
An update

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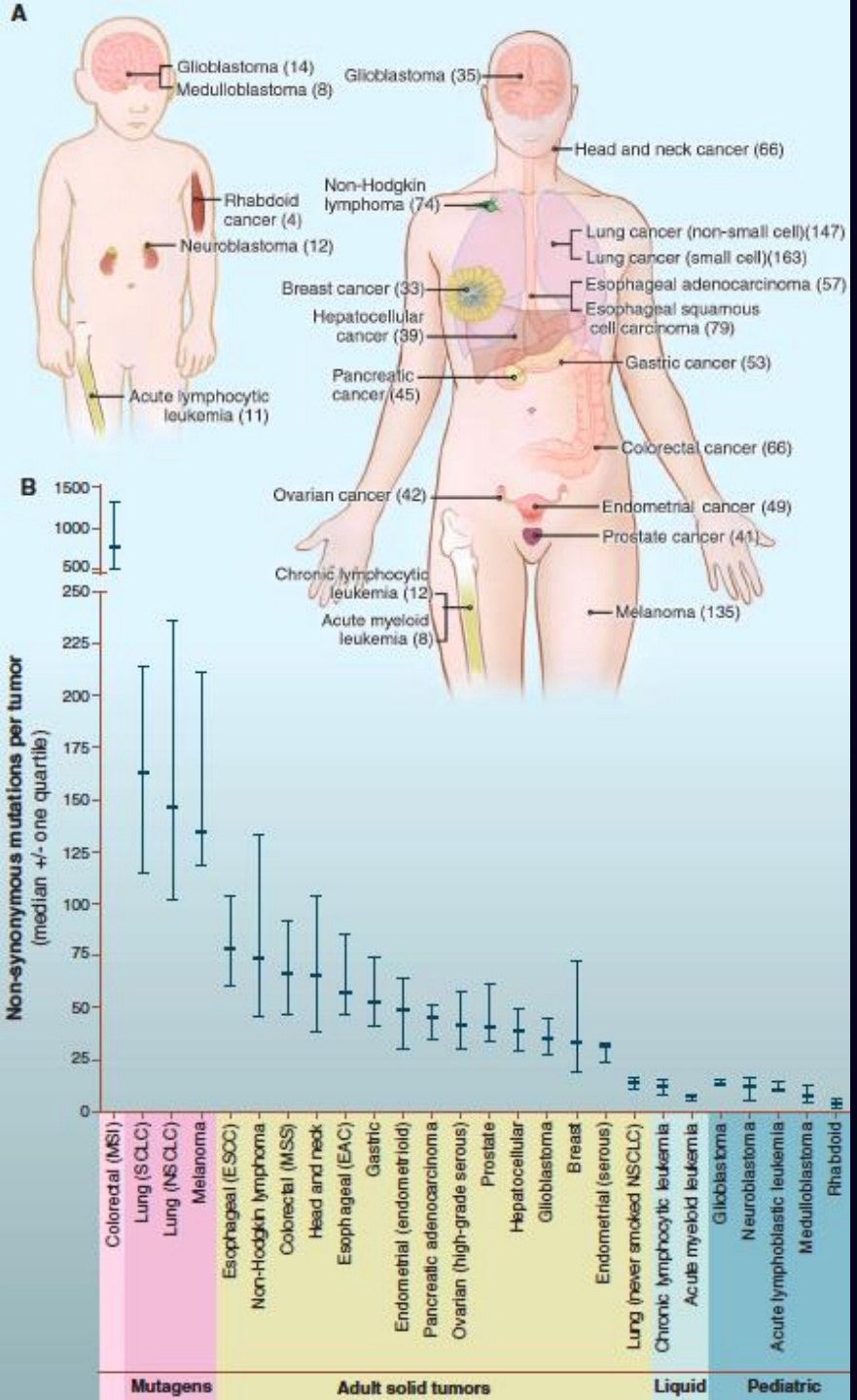
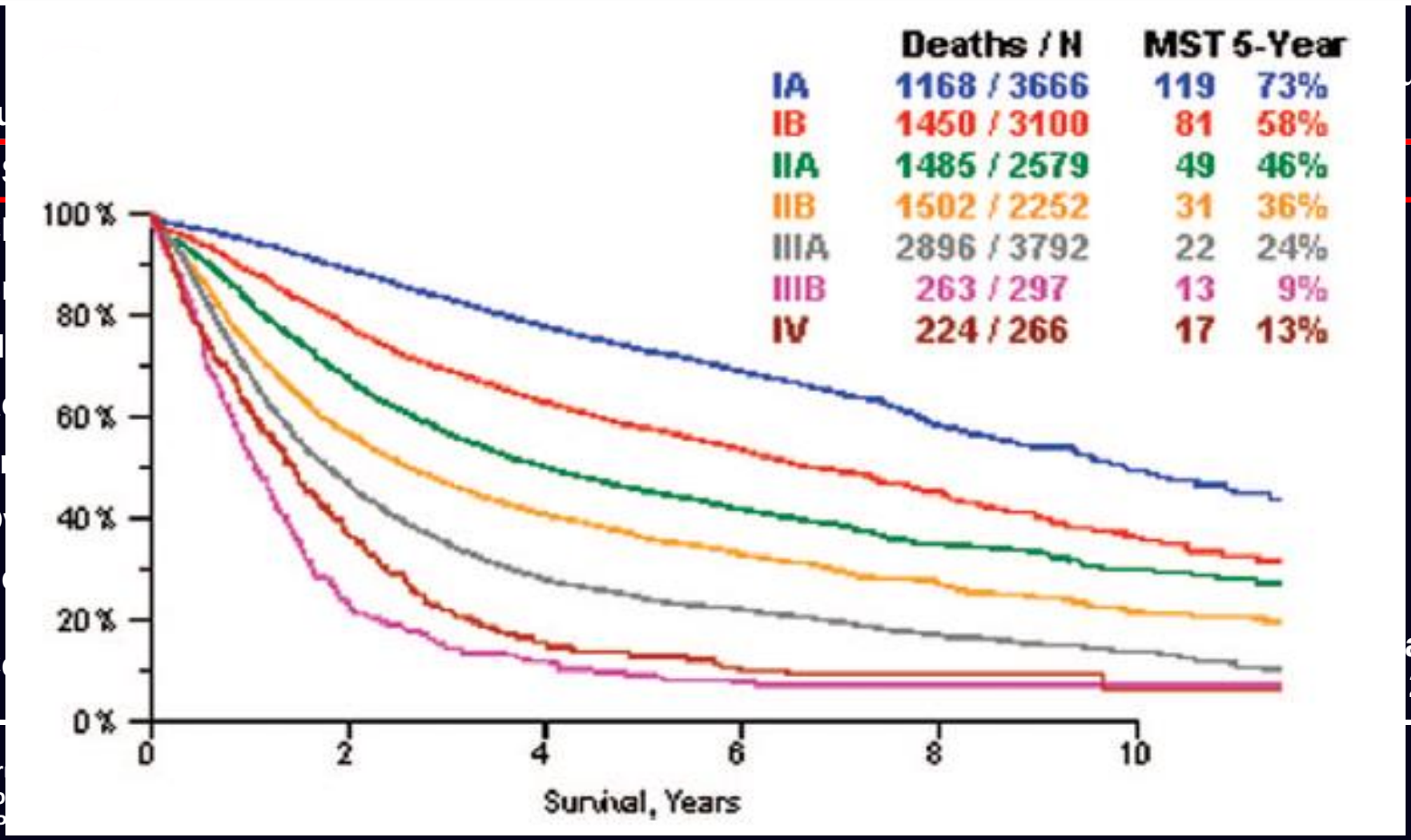


Melanomas and lung tumors display many more mutations than average, with~200 nonsynonymous mutations per tumor.

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

NSCLC: An immune driven tumor?



[a]Covers cor
[b]The type o
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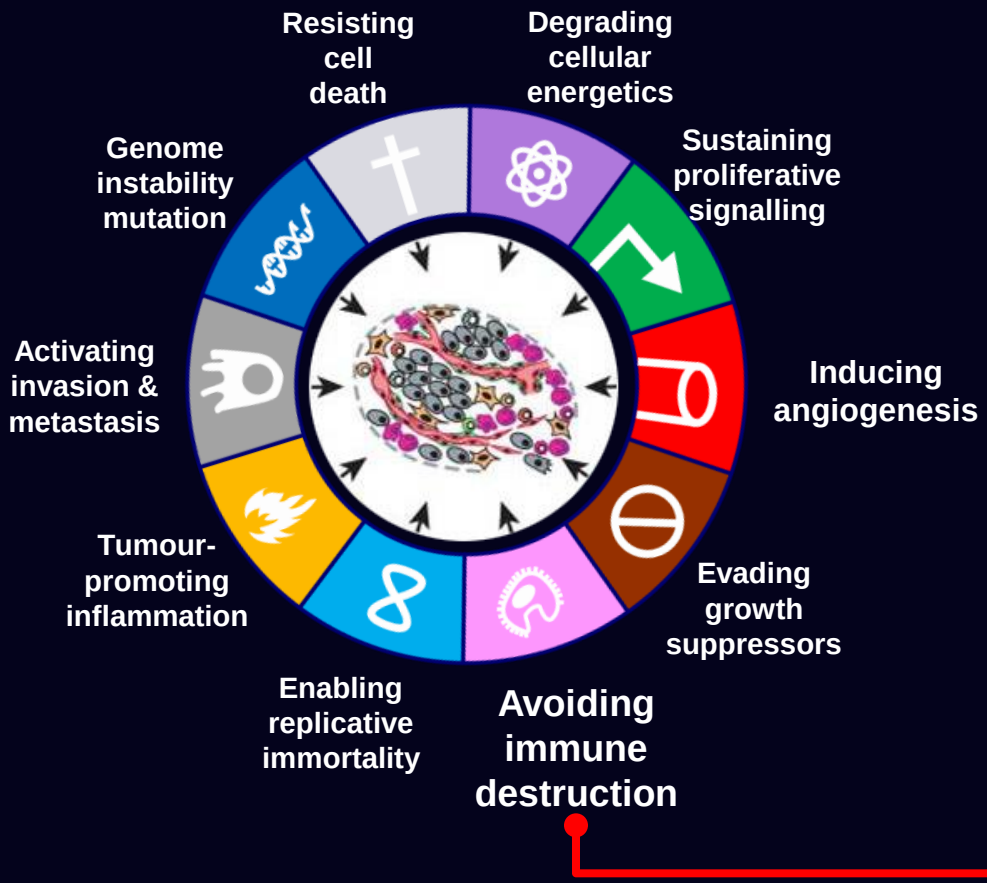
2/3[18,19]

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



PD-1

PDL-1

CTLA-4

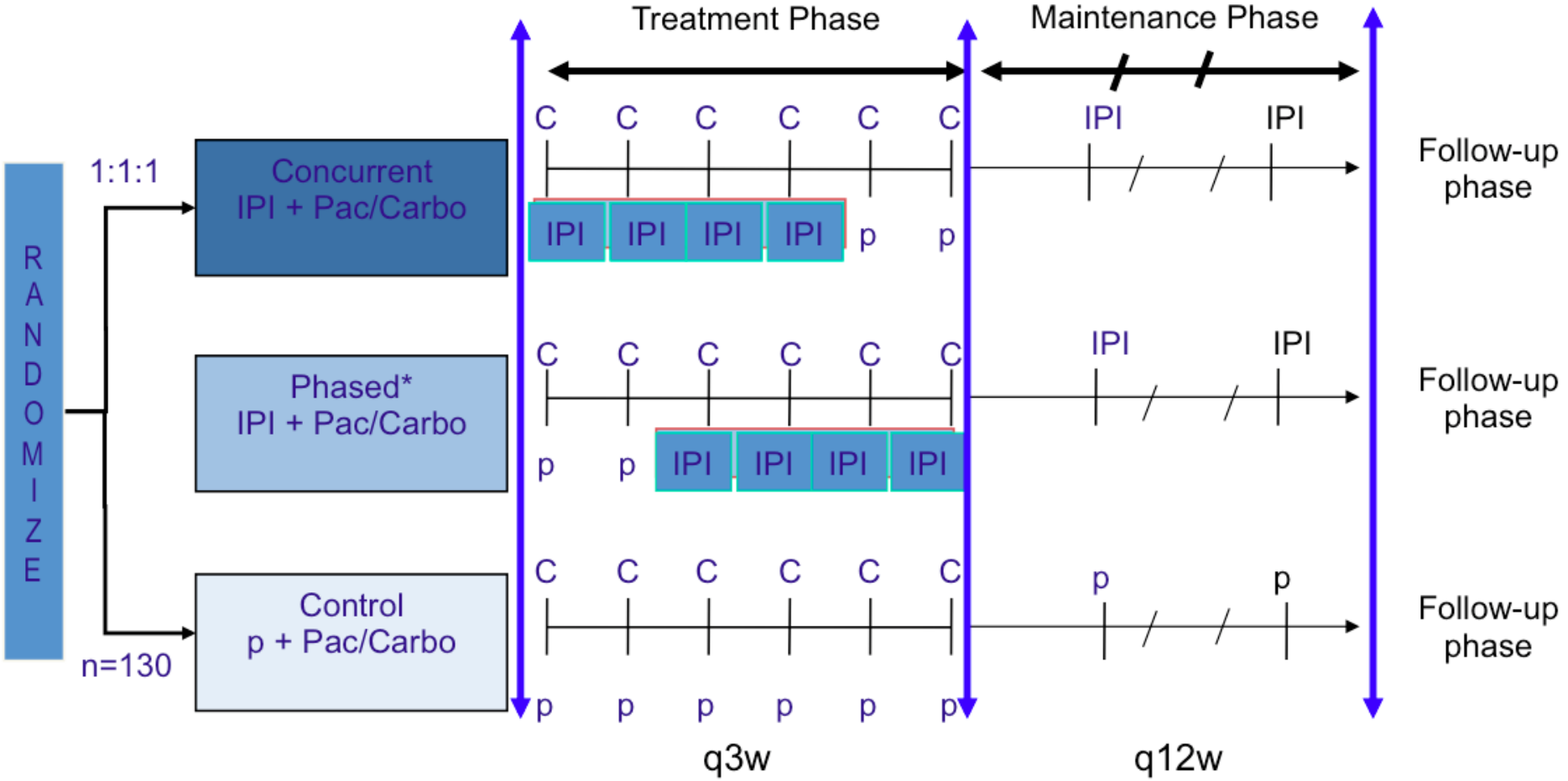
Hanahan & Weinberg. Cell 2011

Ipilimumab

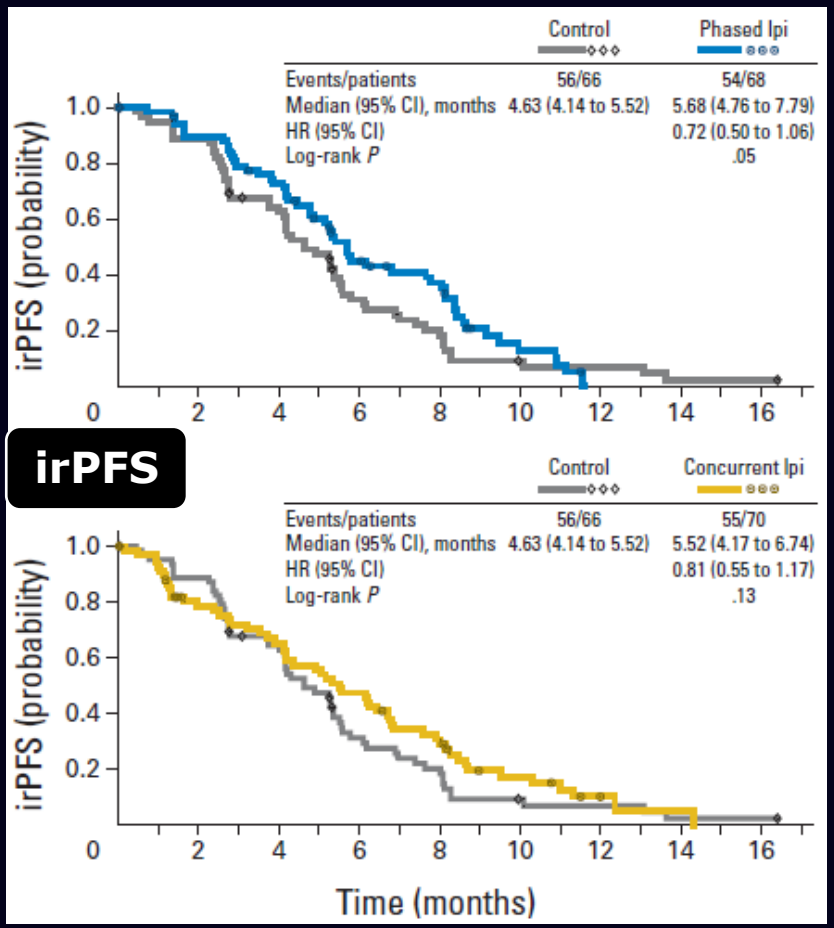
NSCLC PHASE II , COMBINATION WITH CHEMOTHERAPY

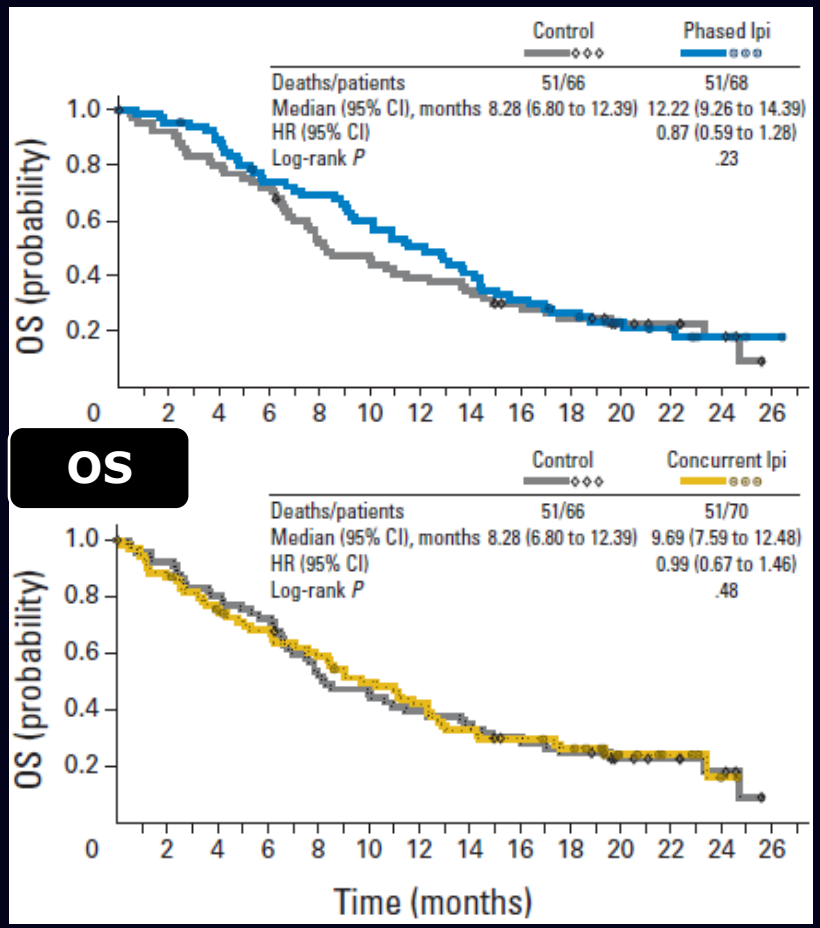
Lynxh et al, JCO 2012

Ipilimimab Phase 2 CA184-041: Study Schema



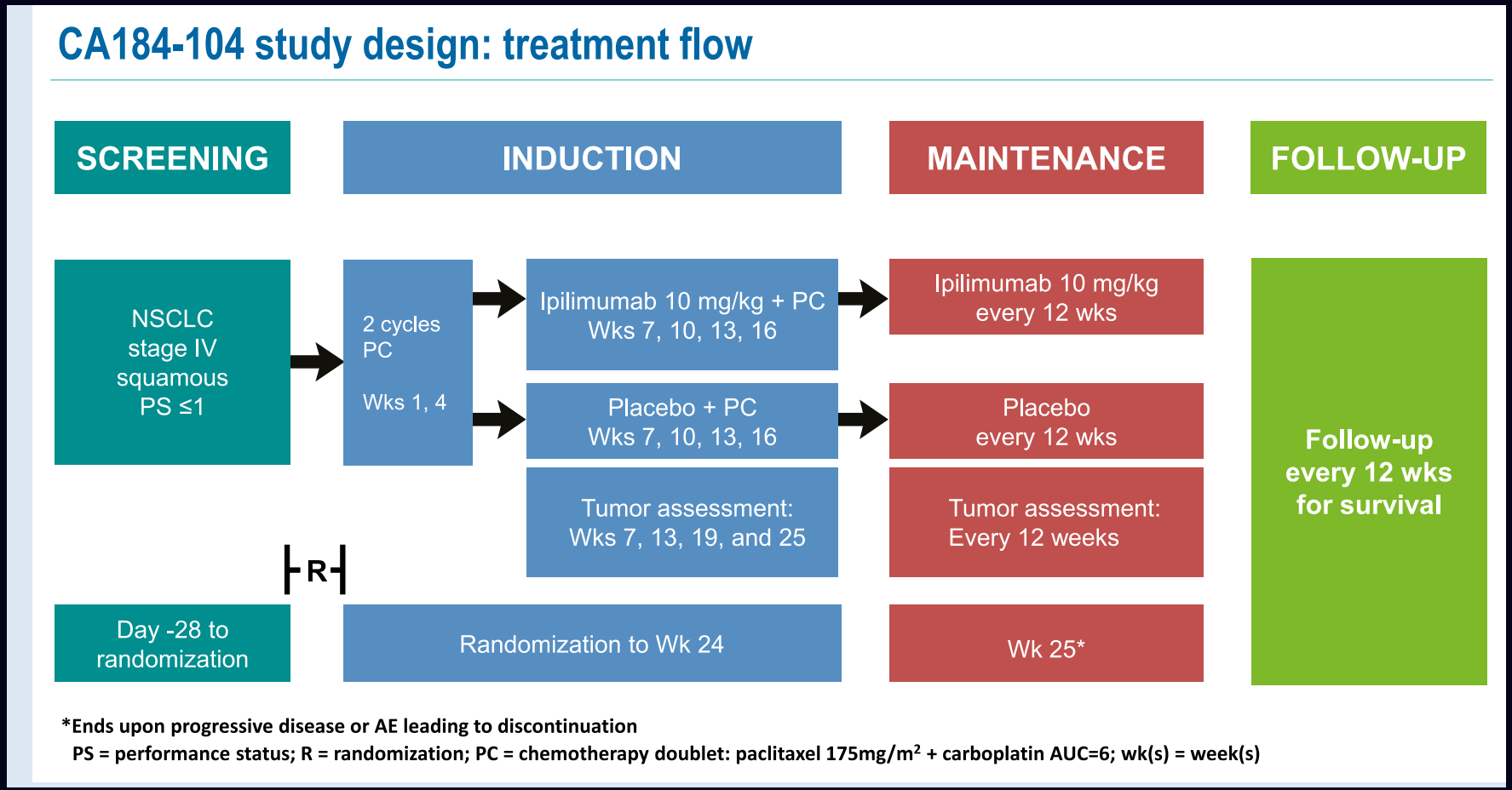
Lung cancer immunomodulation
Ipilimumab





Ipilimumab: NSCLC phase III trial

Squamous Cell NSCLC, stage IV. Primary EP: OS



N=920, accrual completed

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

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 (incl. maintenance)**
    2) **In first line NSCLC treatment**

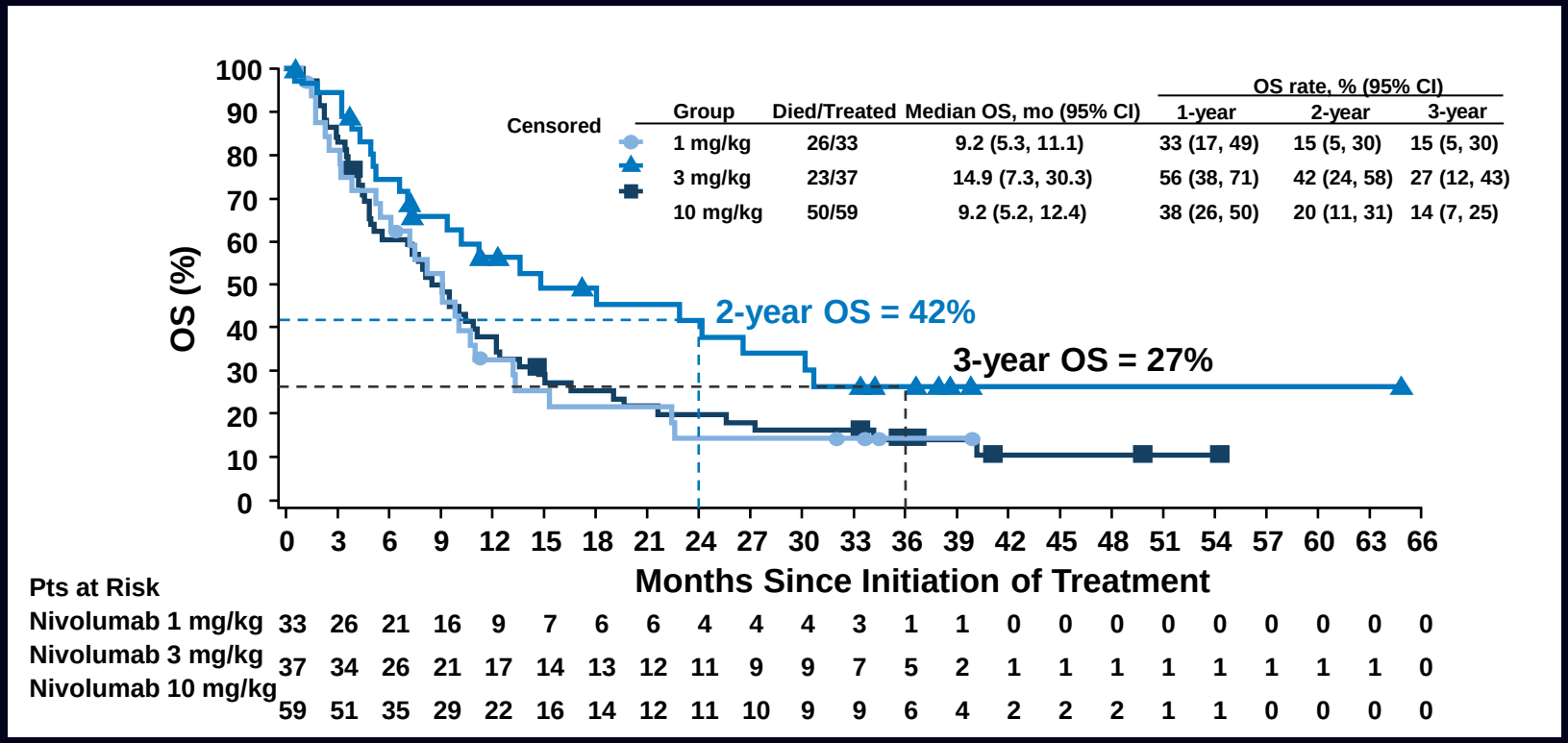
2) **The challenge of the biomarker**

Nivolumab

≥2 ND LINE, PHASE 1 DATA

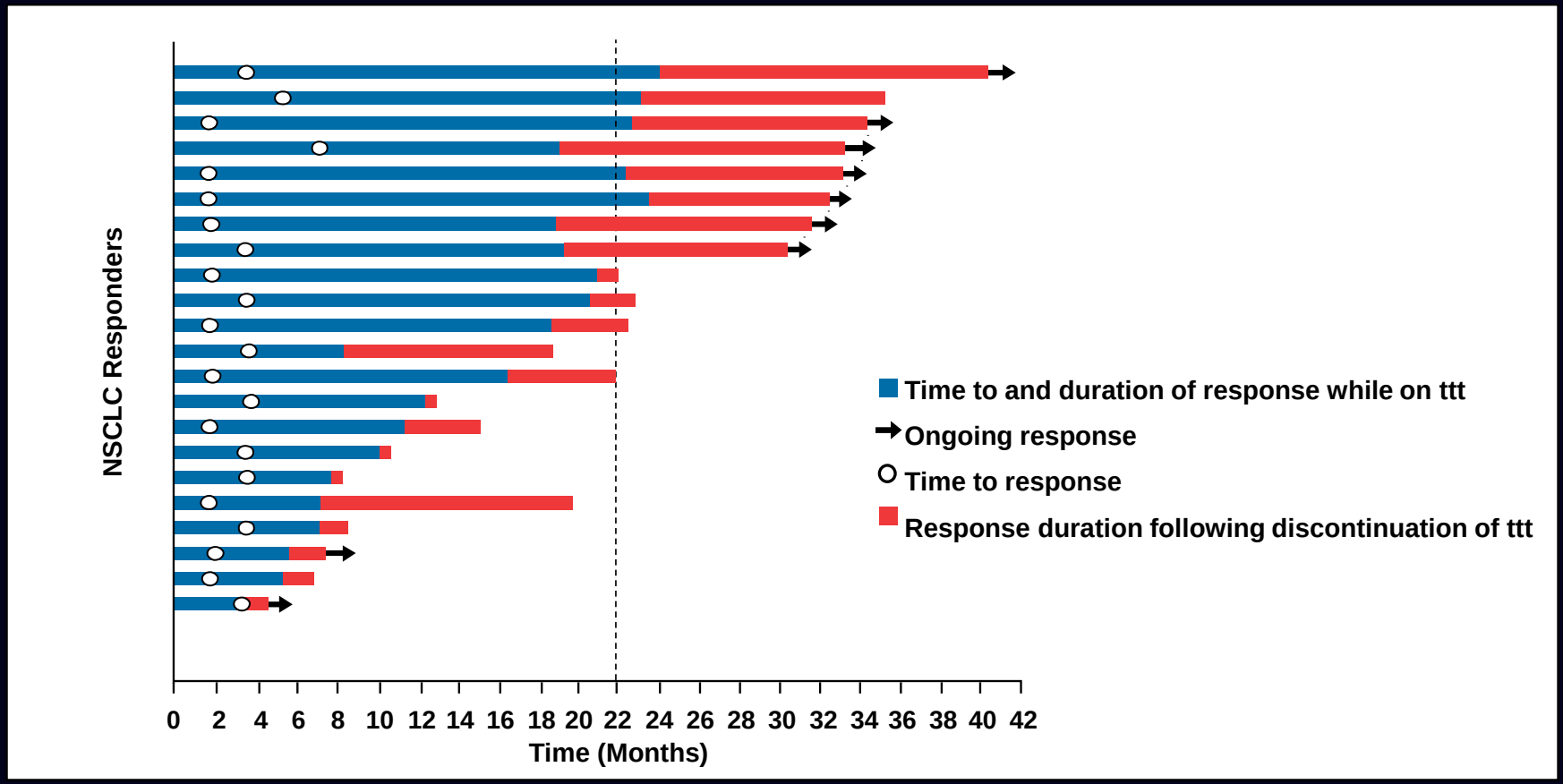
Gettinger et al, ASCO 2014 and CMSTO 2014

OS by Dose (data lock 09-2014)



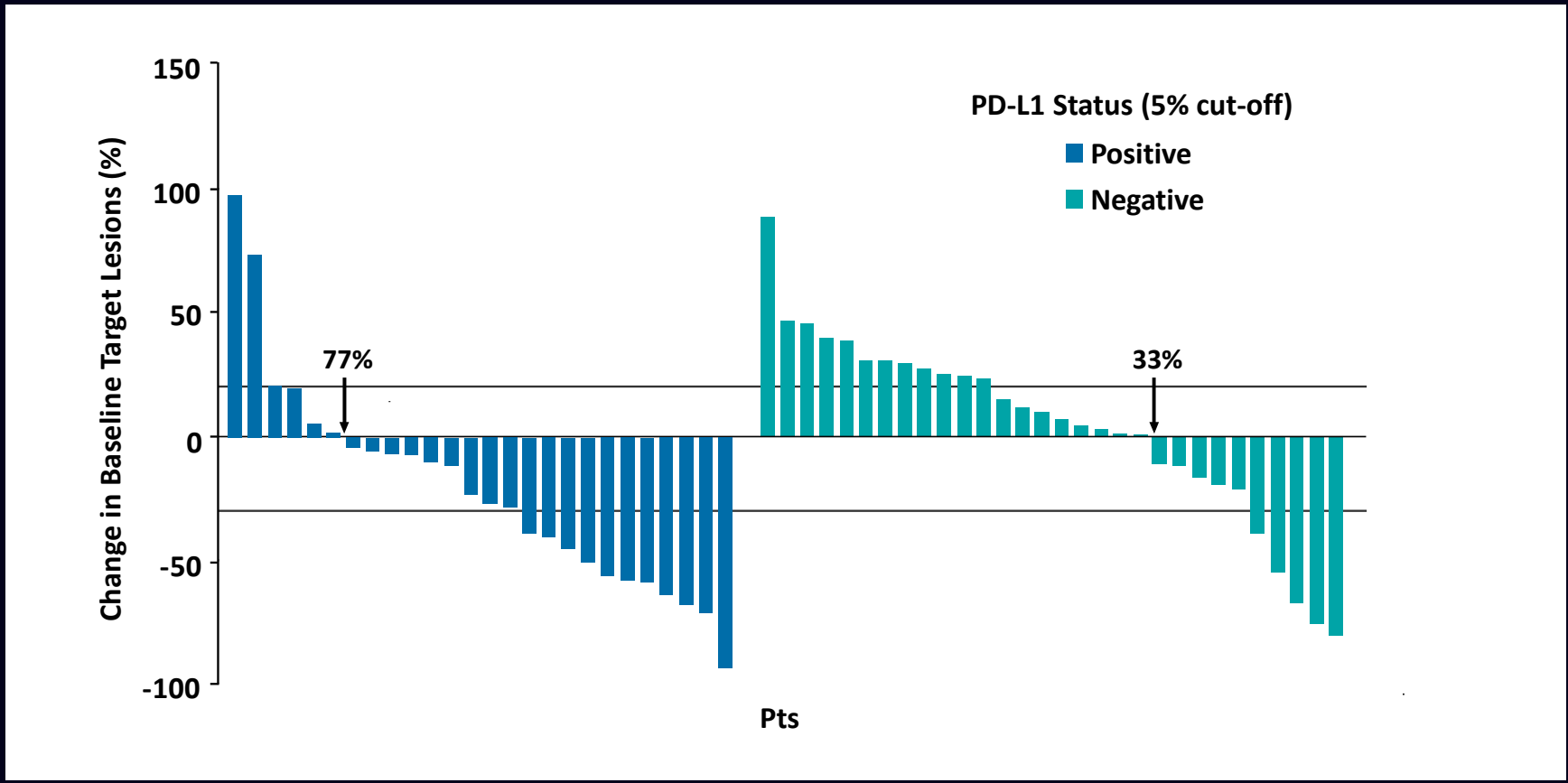
- **Pts were heavily pretreated; 54% had 3–5 prior therapies**
- **50% of responders (11/22) demonstrated response at first assessment (8 wks)**
- **Responses were ongoing in 41% of pts (9/22) at the time of analysis**

Characteristics of Responses



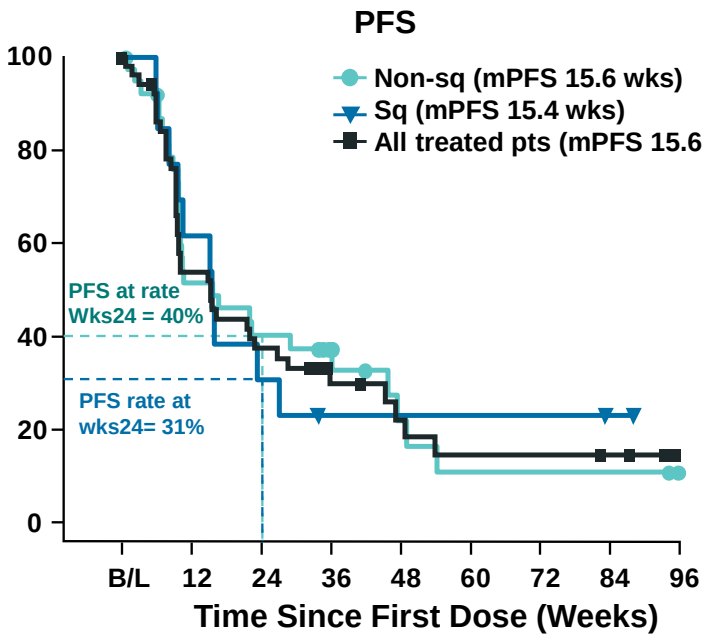
- 5% unconvientional “immune-related” responses, with persistent reduction in target lesions in the presence of new lesions or regression following initial progression
- Manageable safety profile with no new safety signals emerging with all pts having >1 year of follow-up

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



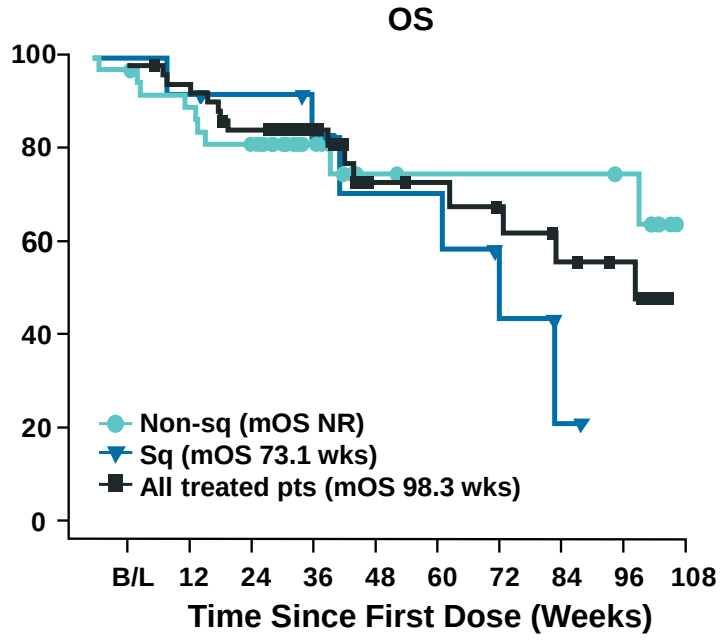
There was no clear association between PD-L1 expression and RR, PFS or OS (archival samples)

PFS and OS With Nivolumab Monotherapy



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

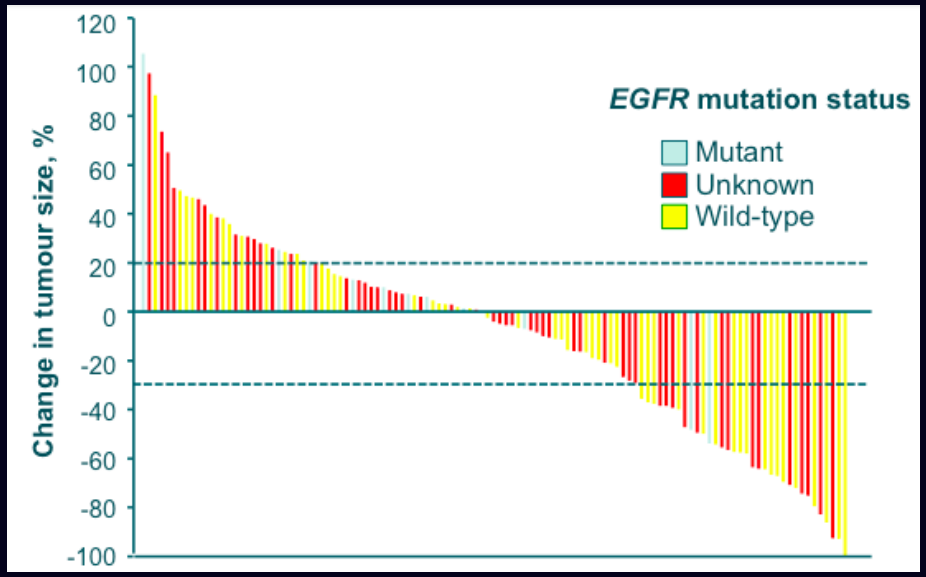
Exploratory Analysis of Response by Smoking Exposure

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]

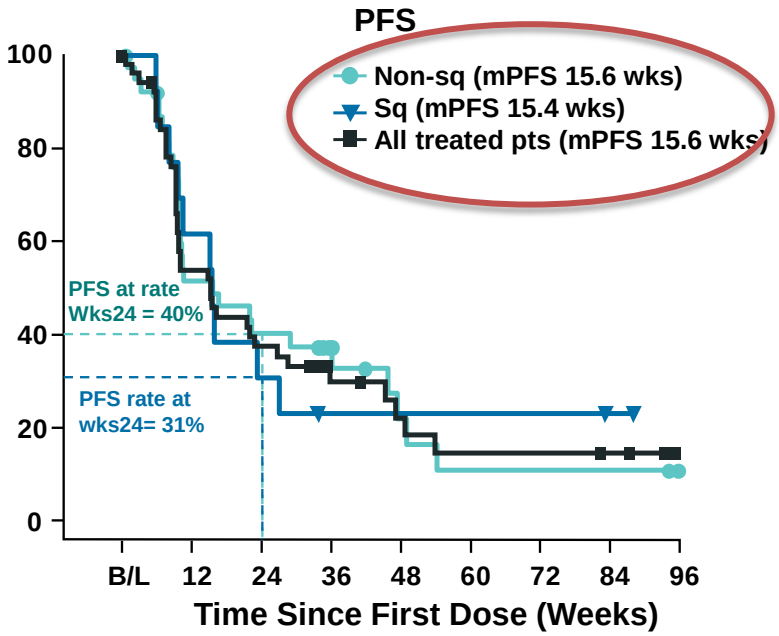


Nivolumab

1ST LINE, PHASE 1 DATA MONOTHERAPY & COMBINATIONS

Rizvi et al; Antonia et al, CMSTO 2014

PFS and OS With Nivolumab Monotherapy frontline



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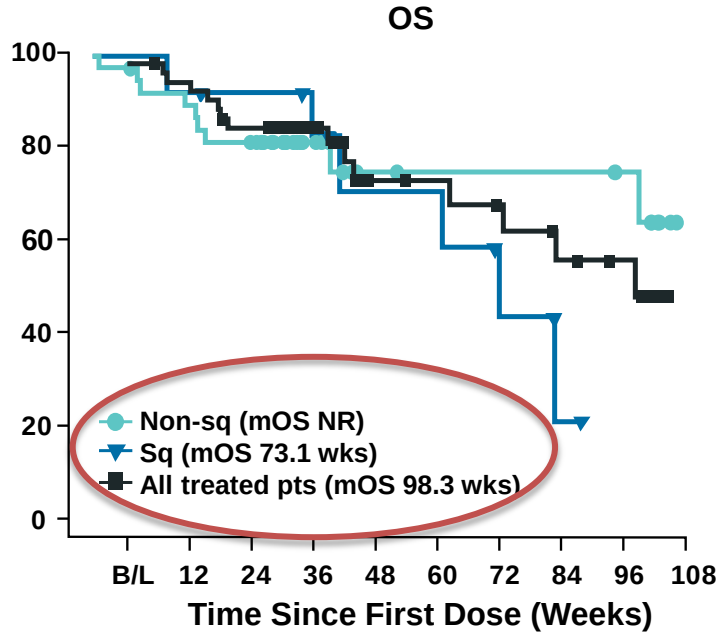
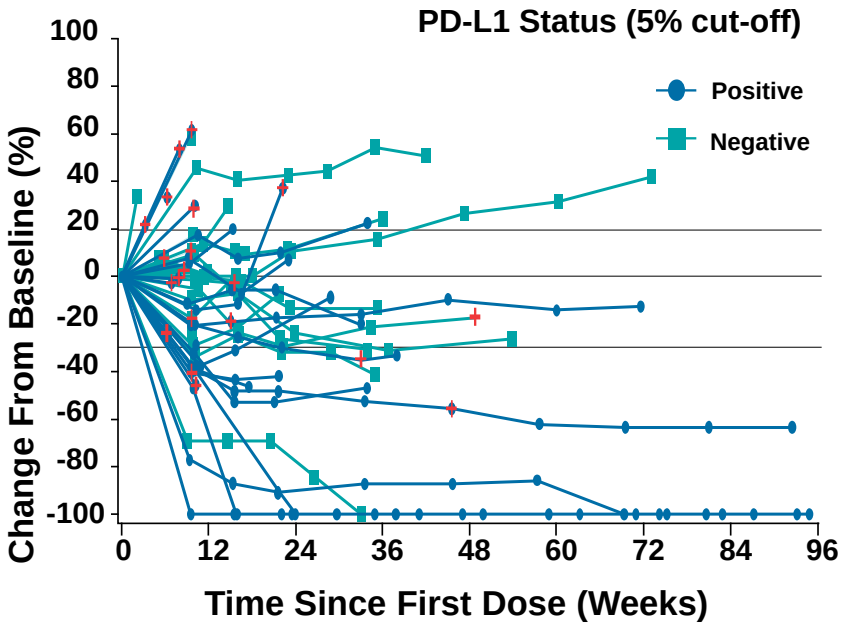


Number of Pts at Risk

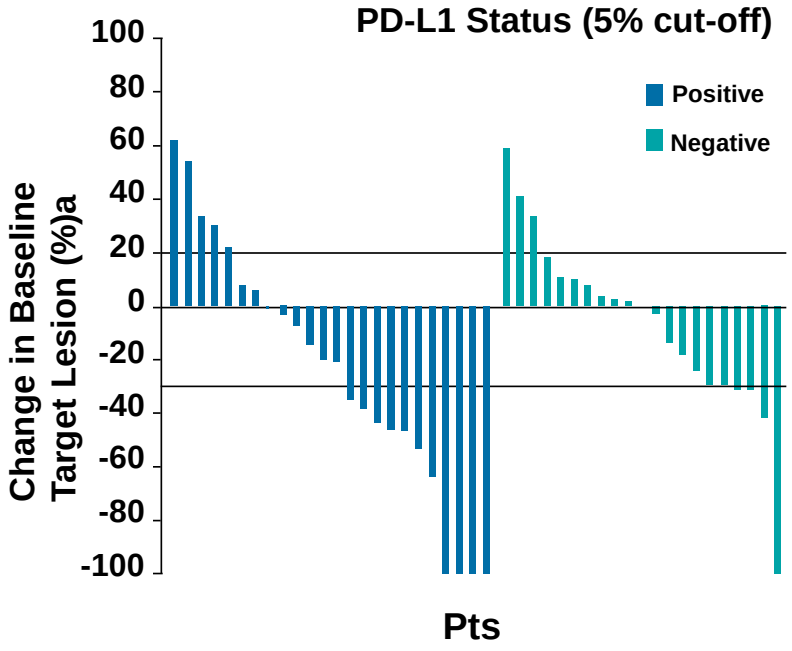
All treated pts	52	48	42	30	15	14	12	9	7	0
Sq	13	13	11	11	6	6	4	1	0	0
Non-sq	39	35	31	19	9	8	8	8	7	0

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

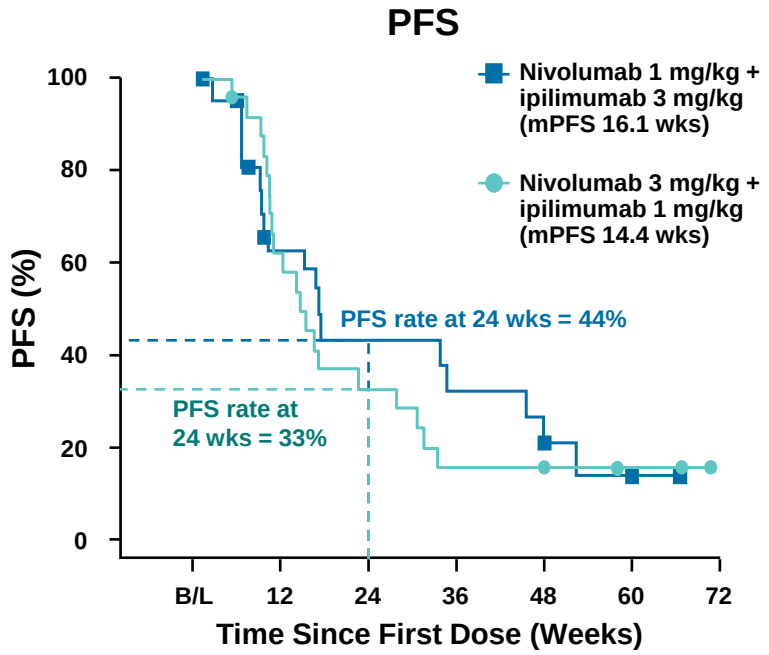
A. Percent change in target lesions from baseline



B. Best percent change in target lesion tumor burden from baseline

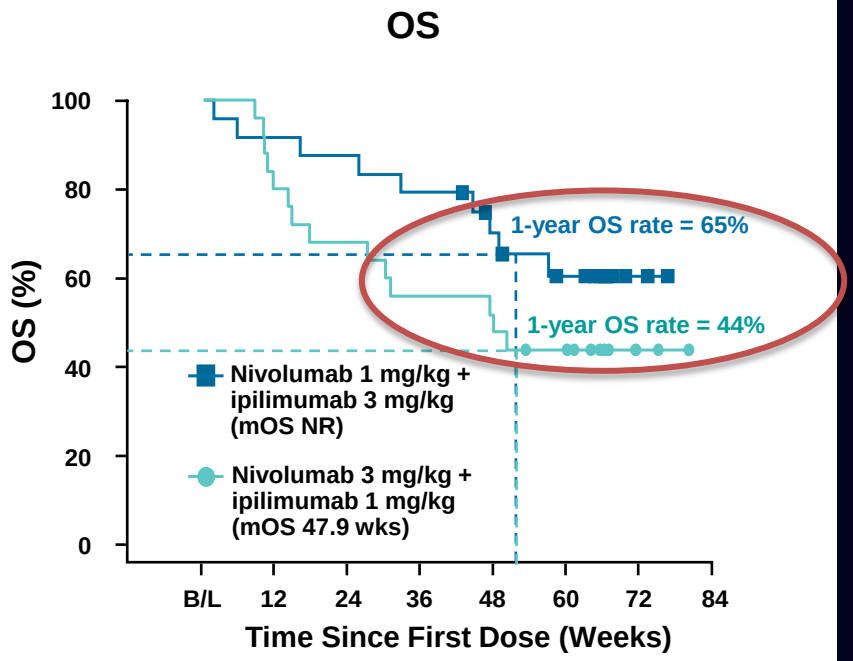


PFS and OS in NSCLC pts Treated With Nivolumab Plus Ipilimumab



Number of Pts at Risk

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	24	10	8	6	3	1	0
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	25	14	8	4	3	2	0



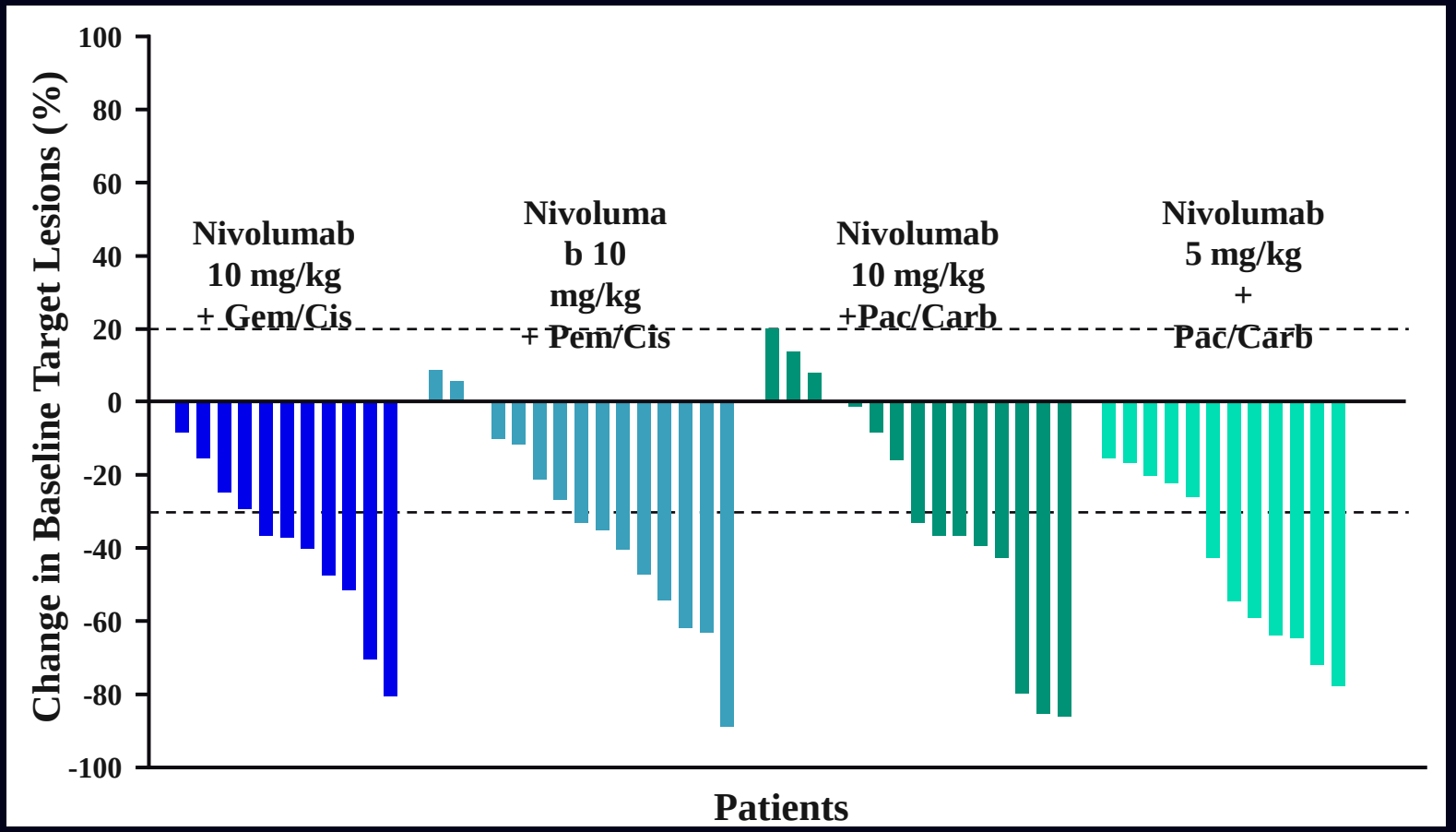
Number of Pts at Risk

Nivolumab 1 mg/kg + ipilimumab 3 mg/kg	24	22	21	19	15	11	2	0
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg	25	20	17	14	12	10	2	0

Safety : Nivo + Ipi in NSCLC

- Treatment-related AEs led to discontinuation of any study drug in 37%, and included pneumonitis, increased ALT or AST, colitis or diarrhea, and allergic nephritis, ulcerative colitis, impaired gastric emptying, Miller Fisher syndrome, and pulmonary hemorrhage
- Most treatment-related AEs leading to discontinuation occurred during induction (15 pts, 31%)

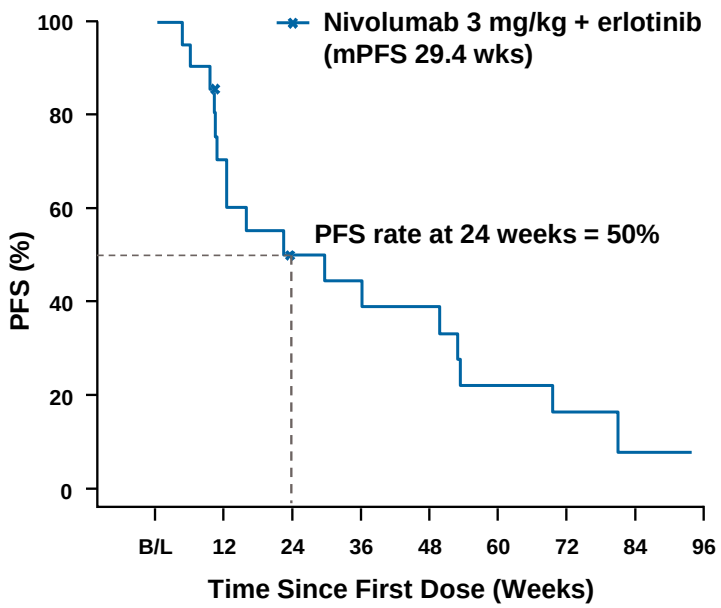
1st line combination with chemotherapy

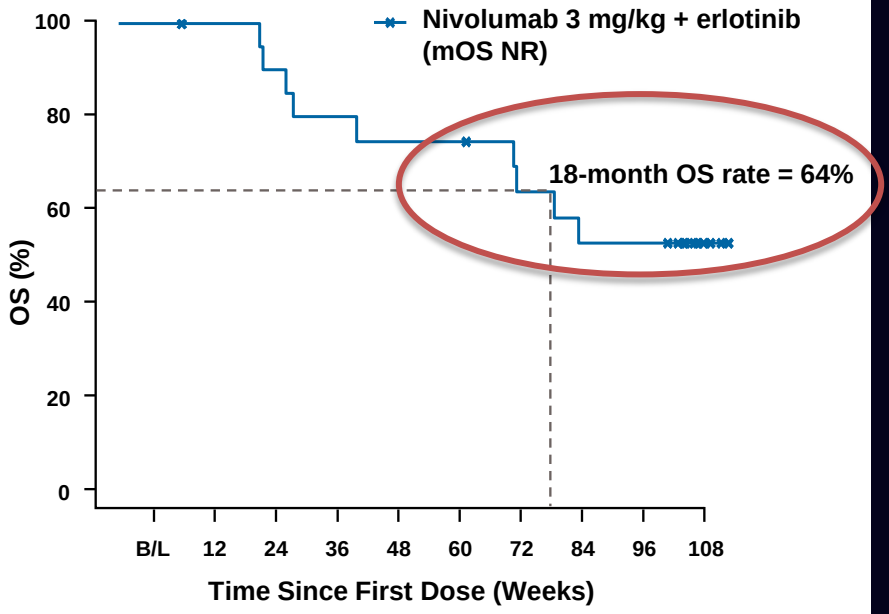


ORR for nivolumab plus chemotherapy in 1st-line treatment are similar to those previously reported for chemotherapy alone

PFS and OS in EGFR + NSCLC Treated With Nivolumab Plus Erlotinib

20 refractory after TKI failure , 1 naïve EGFR M+ patients

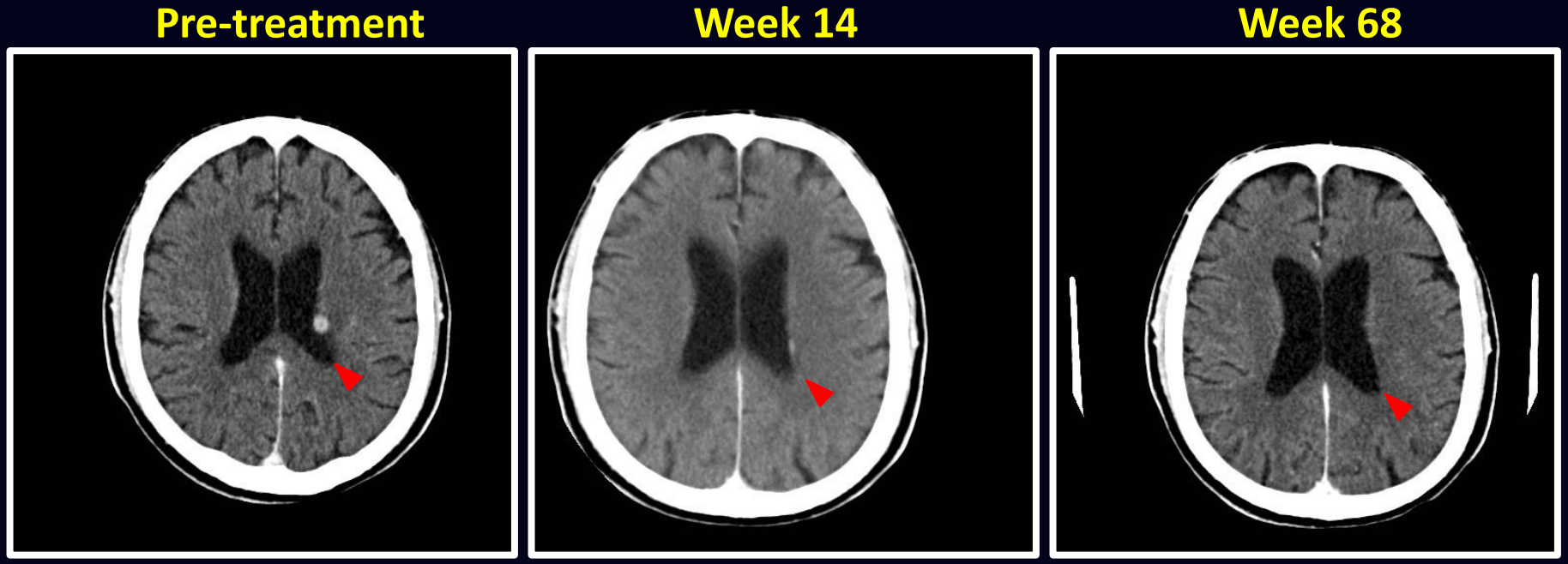




Nivolumab

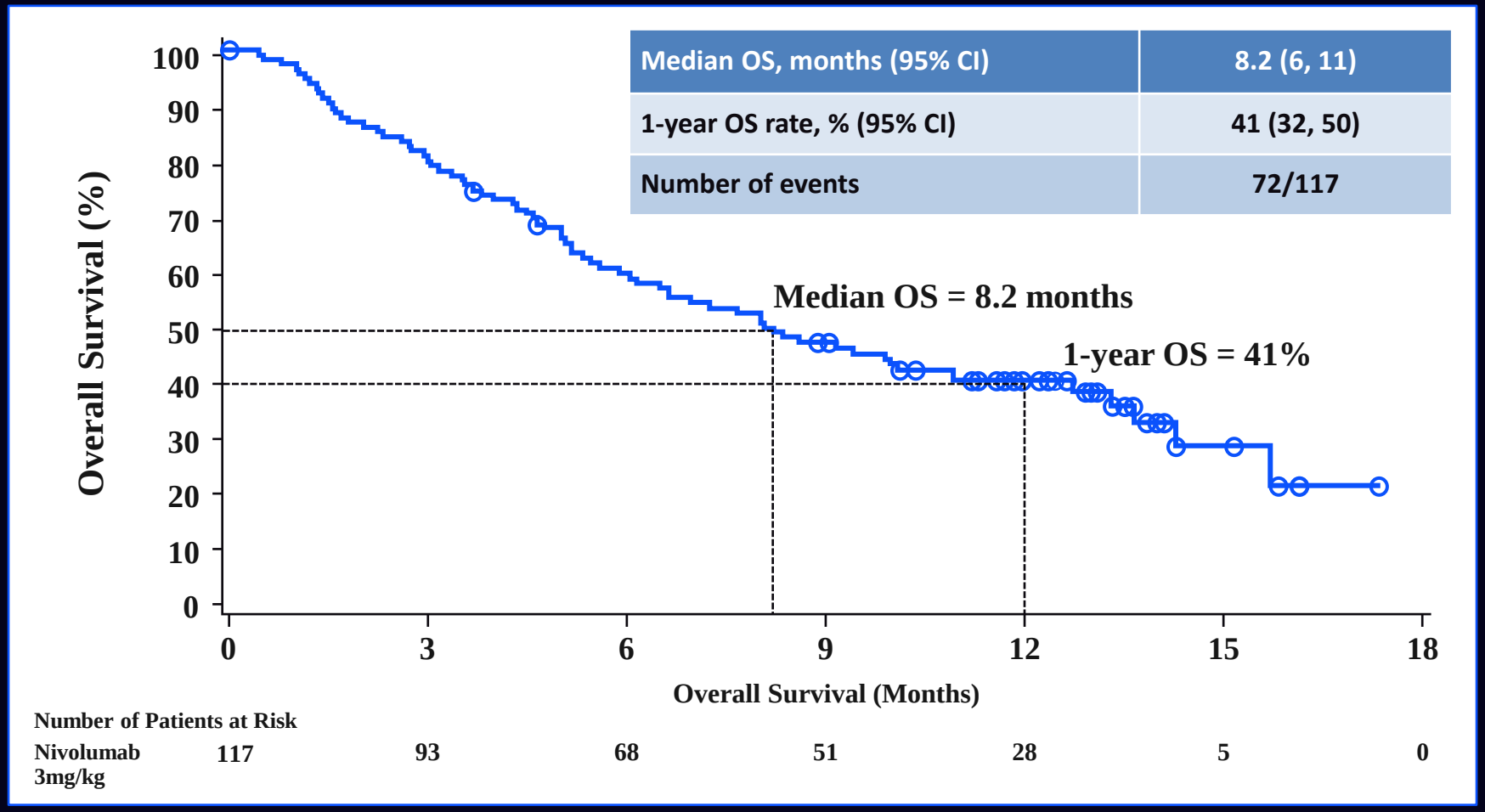
SQUAMOUS ≥2 ND LINE, PHASE 2 MONOTHERAPY DATA

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



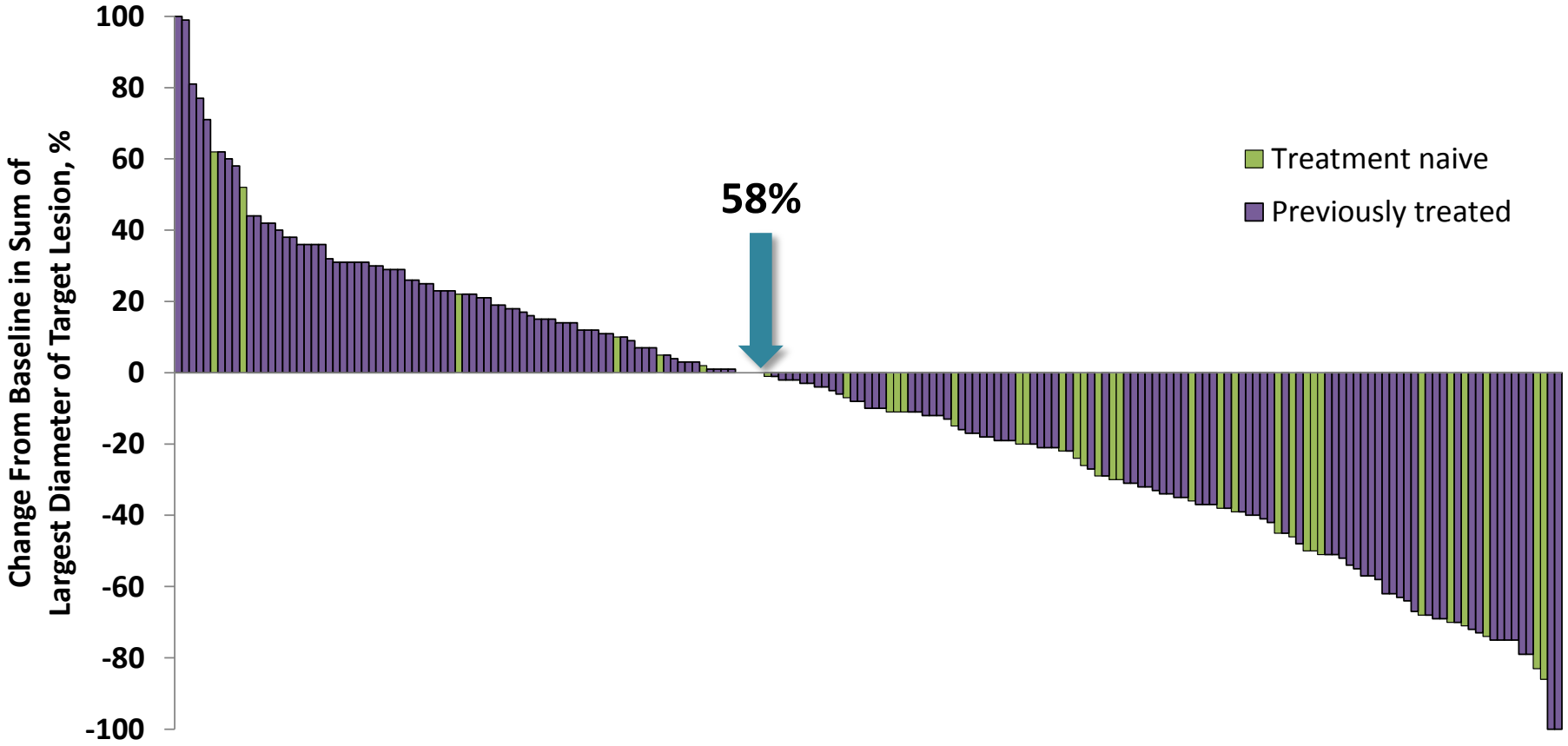
Median follow-up for survival: 8 months (range, 0–17 months)

Pembrozilumab

NSCLC POOLED ANALYSIS 1ST AND SUSEQUENT LINES, MONOTHERAPY

Garon et al, ESMO 2014

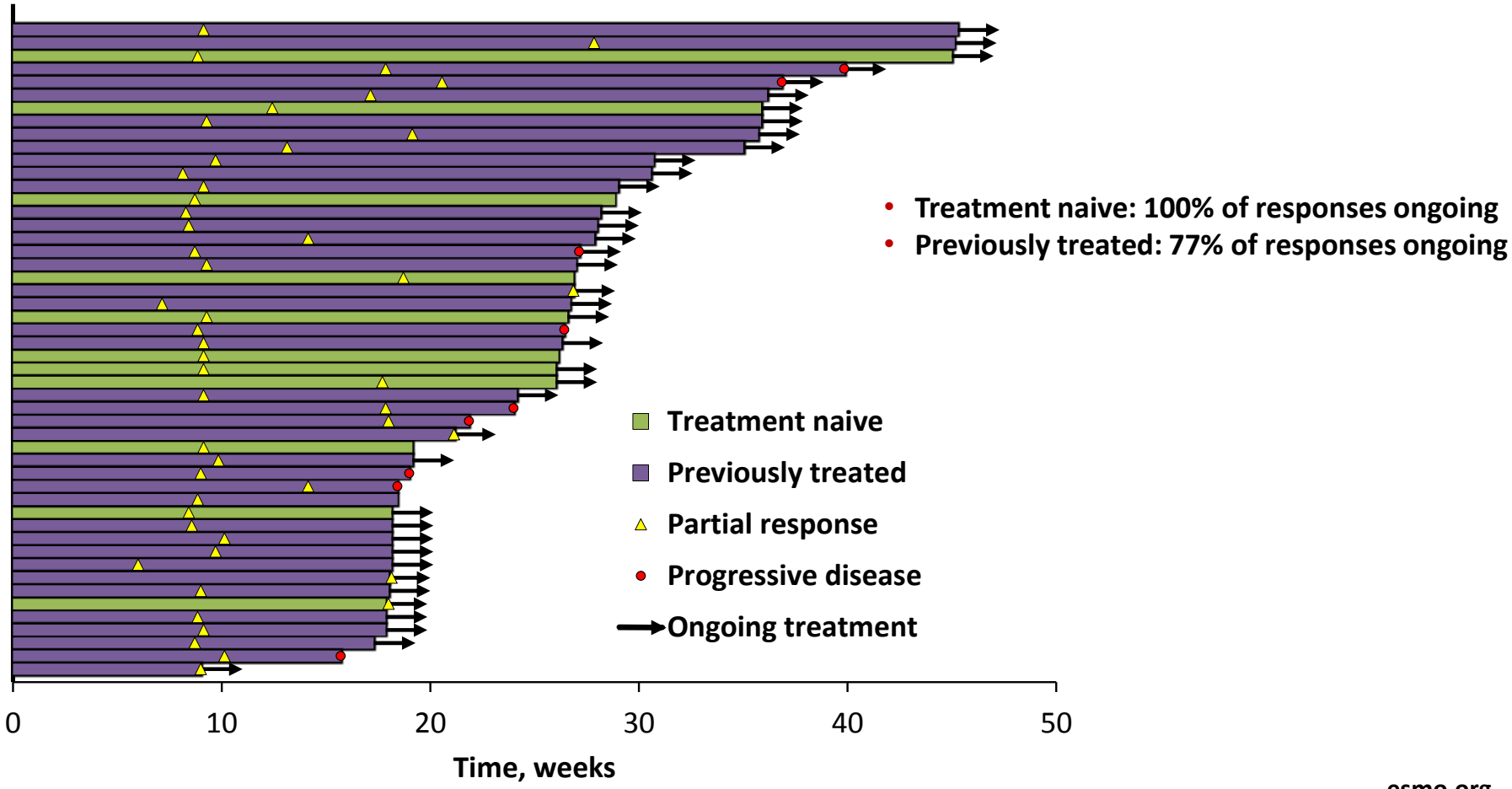
Maximum Percent Change From Baseline in Tumor Size[a] (RECIST v1.1, Central Review)



[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.

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?

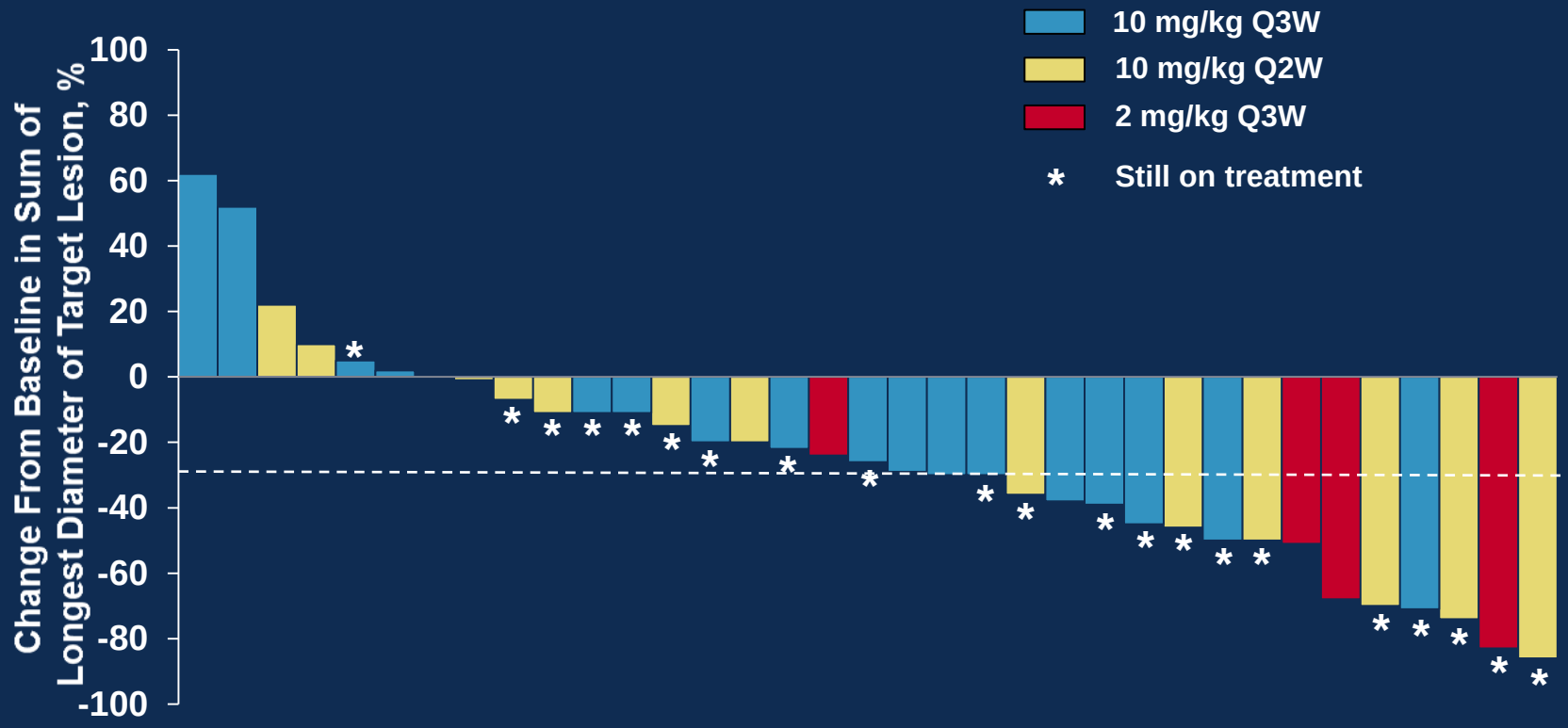
n at risk
Treatmen
Previously

- 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 pembrozilumab first line data

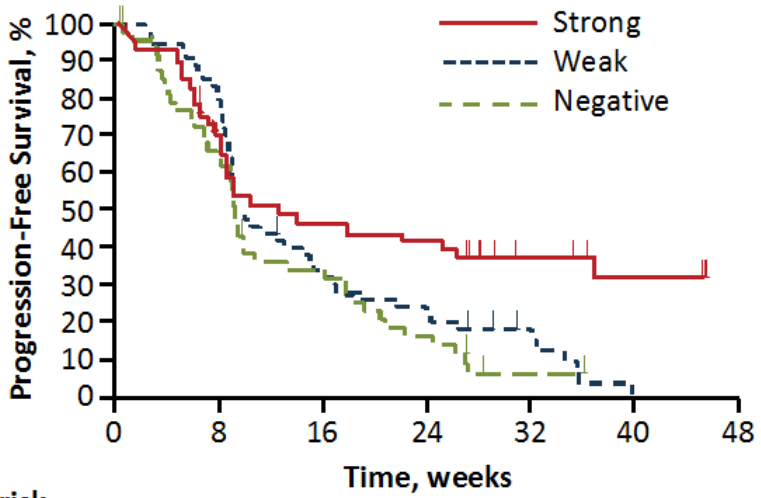


- Interim median PFS[c]:
  - 27.0 weeks (95% CI, 13.6-45.0) by RECIST v1.1 per central review
  - 37.0 weeks (95% CI, 27.0-NR) by irRC per investigator review

MADRID 2014 ESMO congress

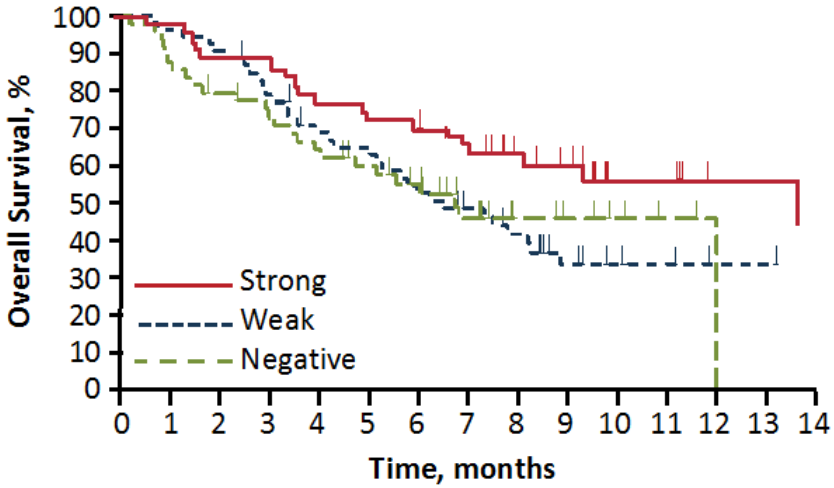
Kaplan-Meier Estimates of Survival

PFS (RECIST v1.1, Central Review)



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

OS



	44	43	38	38	34	32	30	27	21	18	9	8	5	5	4
	53	51	48	40	34	31	26	22	18	11	8	7	5	5	4
	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)

MPLD3280A

≥2 ND LINE, PHASE 1 DATA

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

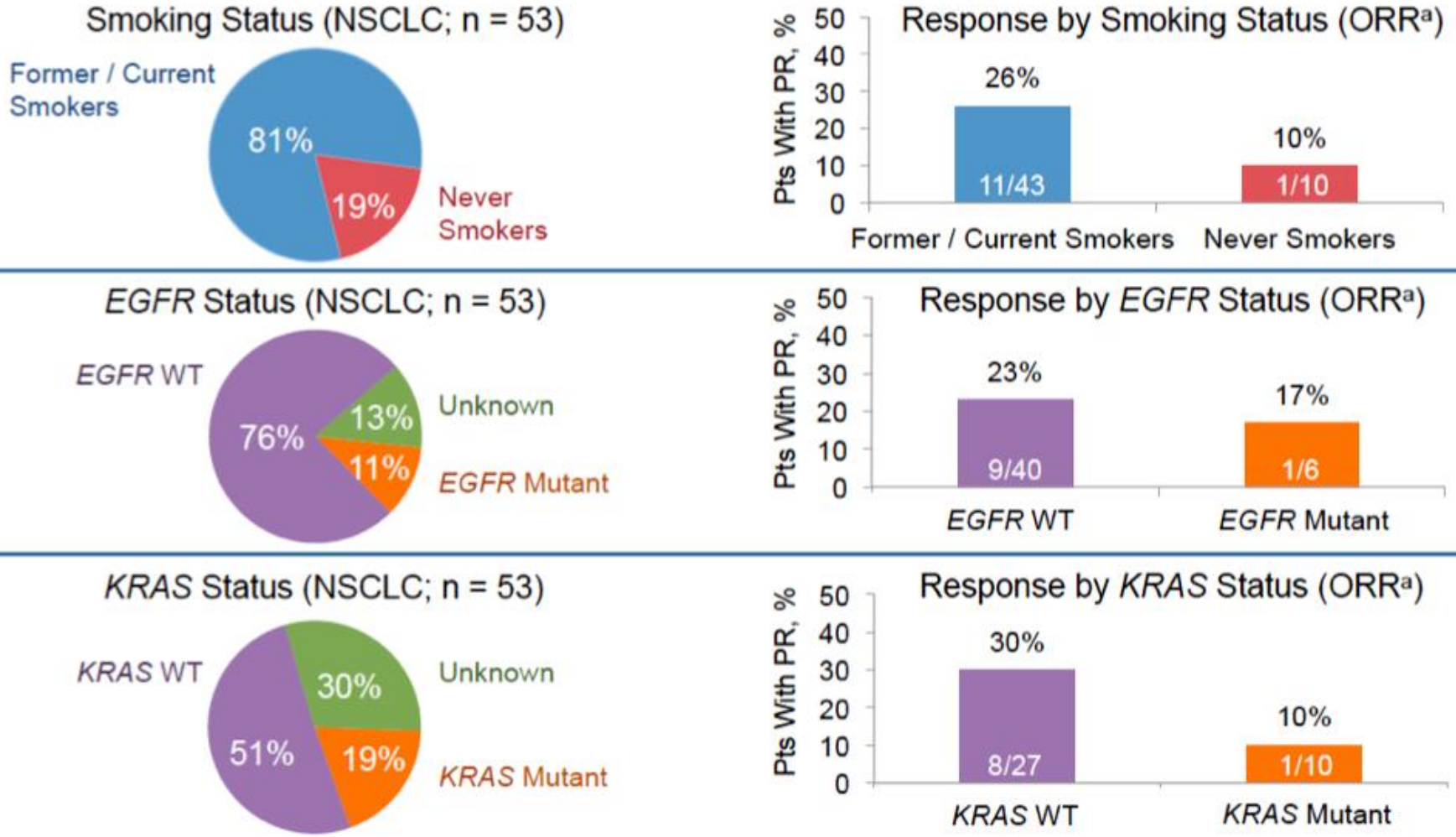
MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status - NSCLC

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)

OVERALL RESPONSE RATE: 21% (N=175)

Soria, ESMO 2013

MPDL3290A: Specific predictors



Horne et al., WLCC 2013 #MO18.1

Histology is not predictive through all available data

	Squamous Carcinoma	Non-squamous
Nivolumab (PD-1)	17% (9/54)	18% (13/74)
MPDL3280A (PD-L1)	27% (3/11)	21% (9/42)
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

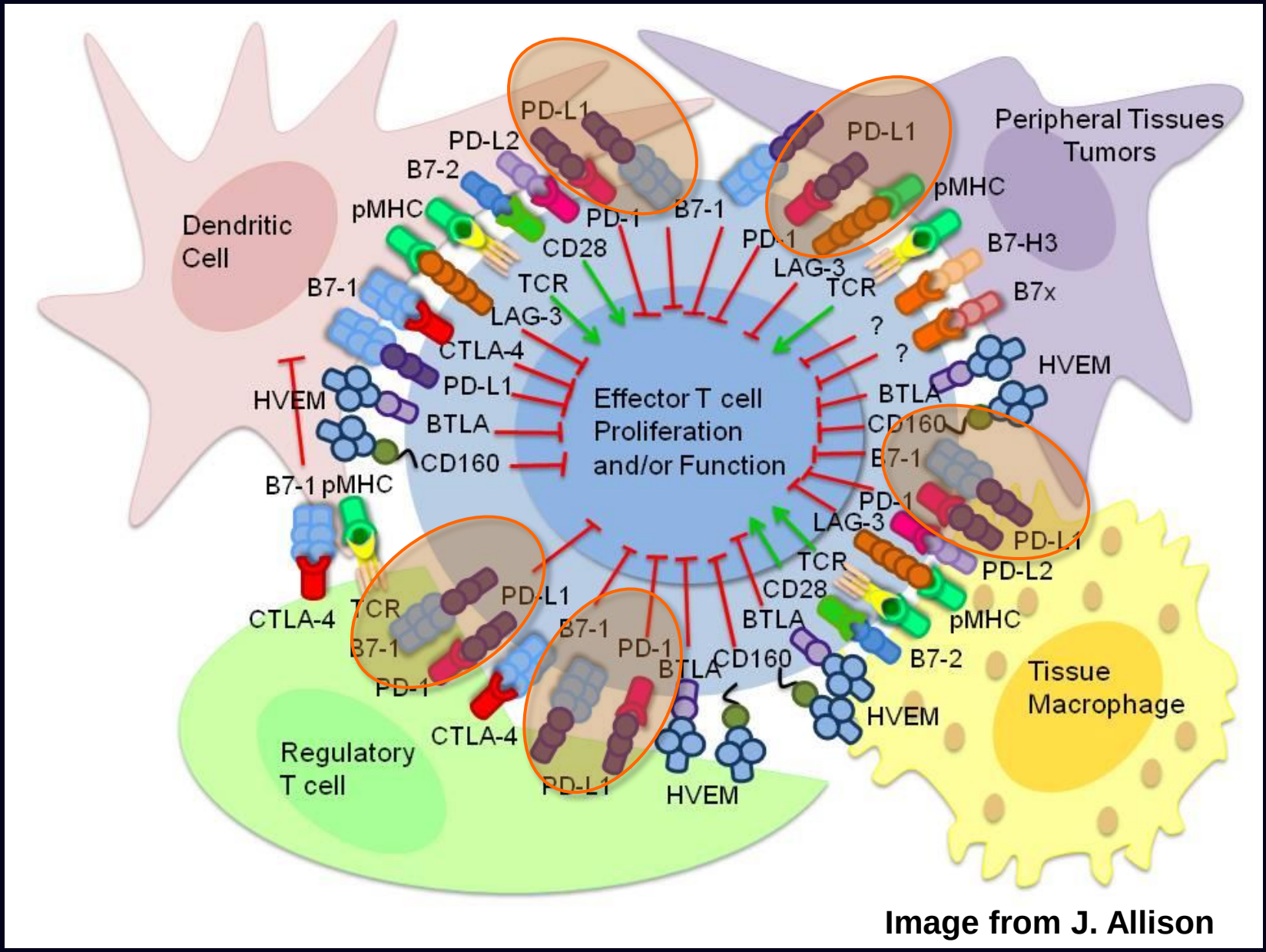


Image from J. Allison

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

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

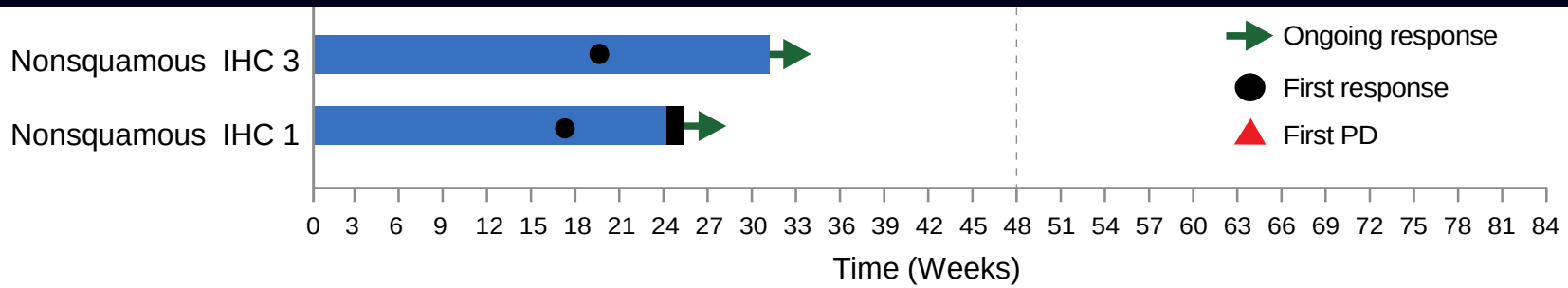
Pembro
Daud, AACR 2014
Ghandi, AACR 2014
Rizvi, ASCO 2014, #8009
Garon, ASCO 2014, #8020

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

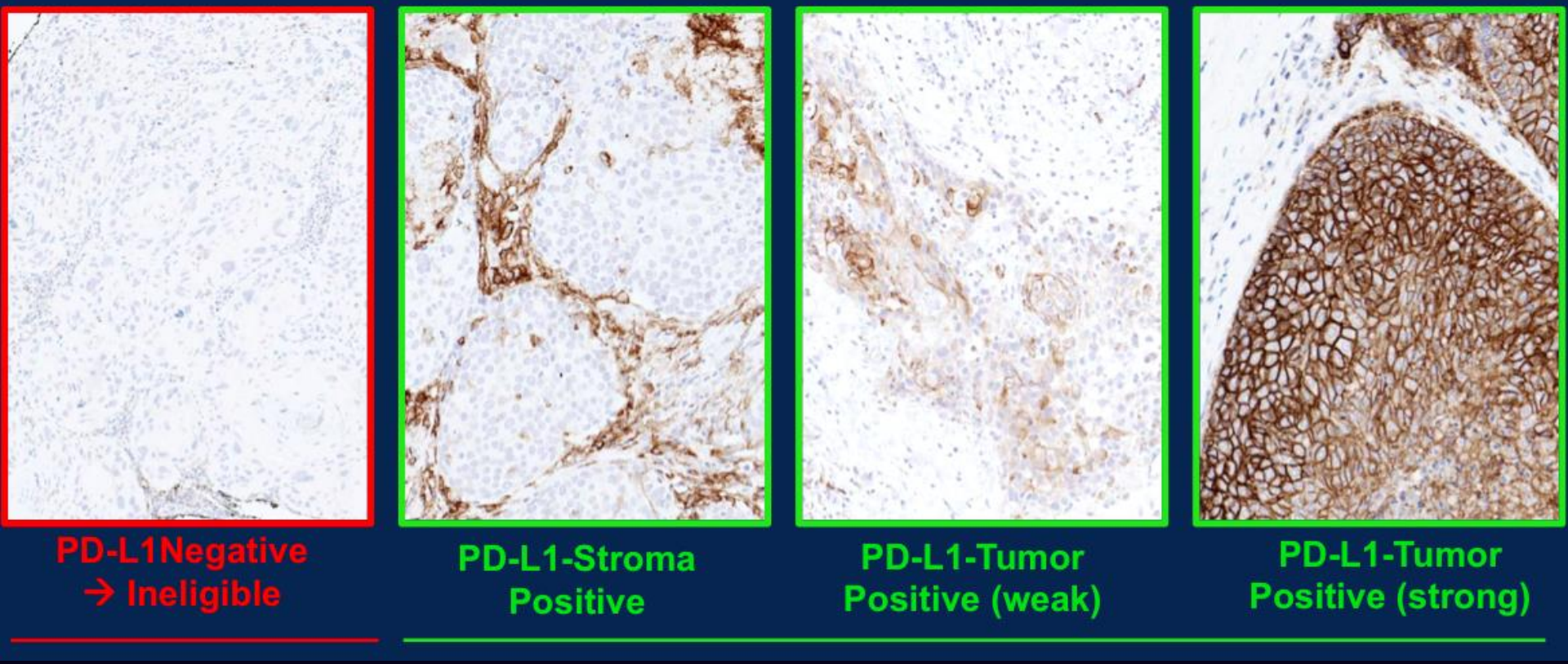
MPDL3280A Phase Ia: Duration of Treatment in Responders - NSCLC

- 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



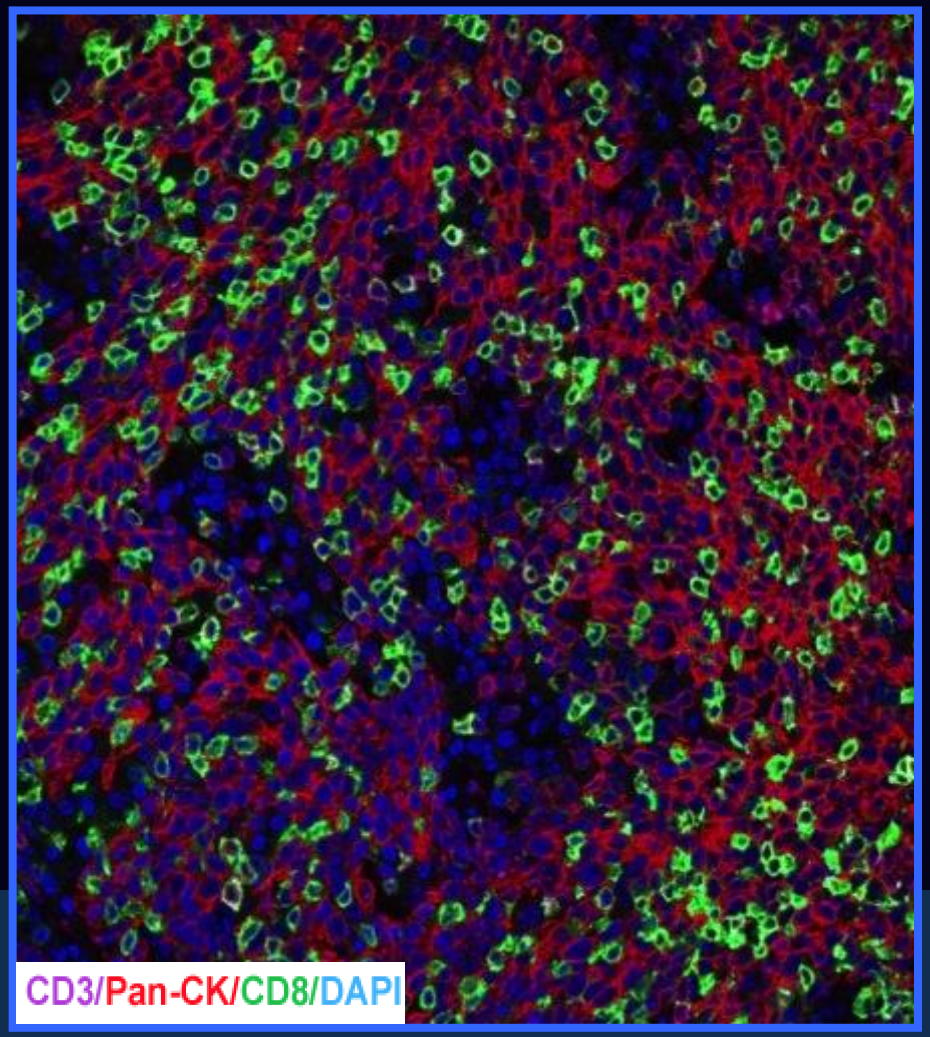
[a] Patient experiencing ongoing benefit per investigator.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Stroma or tumour cells?
HNSCC example

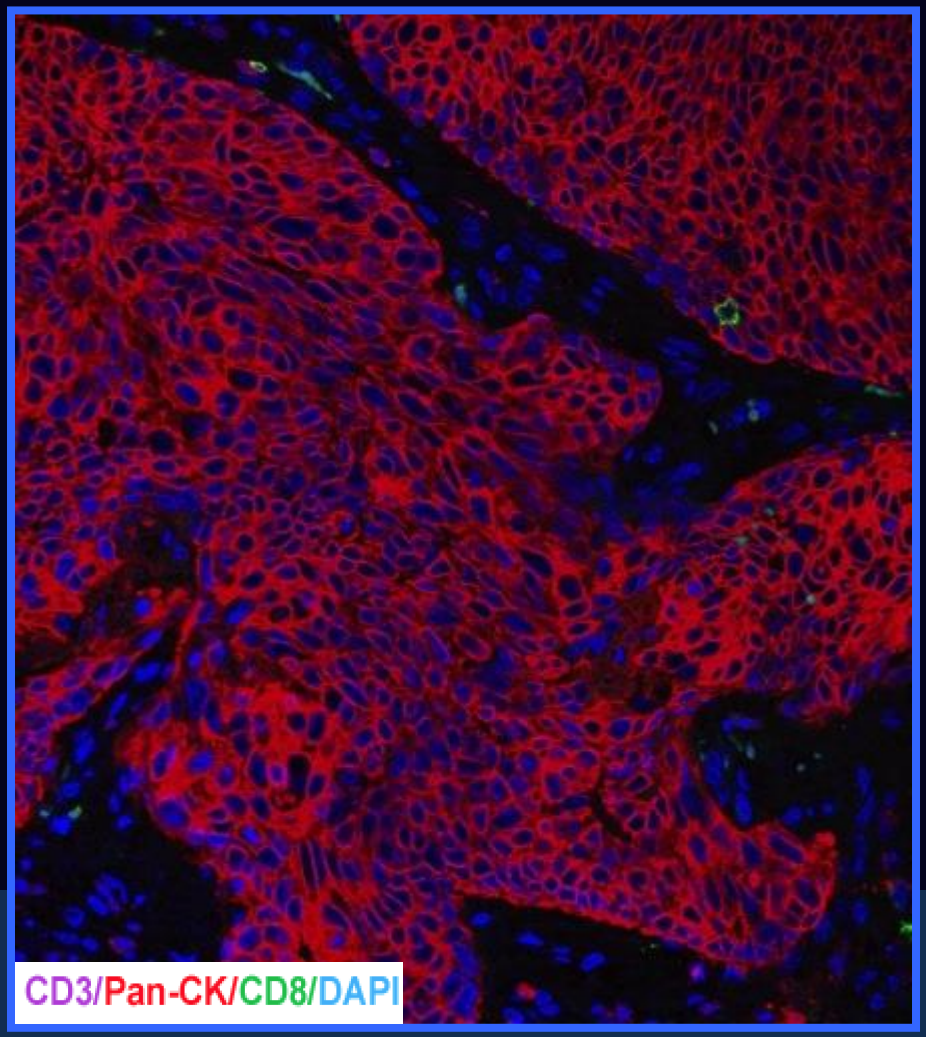


Tumor Infiltrating Lymphocytes as a biomarker? The HNSCC example

Diffuse infiltration with CD8+ TILs in HNSCC



Absence of TILs in HNSCC



PD1/PDL1 summary

Clear evidence of anti PD1/PD-L1 activity

- Optimal dose?
- Treatment sequence?
- Combination strategy
  - Chemotherapy
  - Other checkpoint 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
- Activity seen in PD-L1 neg
- How do we define PD-L1 positivity?
- How does PD-L1 evolve over time ?
- Is PD-L1 more strongly expressed in defined patients subgroups (smokers?)
- Randomized trials with PD-L1 stratification awaited!

PD1/PDL1 summary

Phase III trials:

- Ongoing in first line vs platinum-based chemotherapy in PD-L1+, with/out crossover
- Completed in second line vs docetaxel in squamous and non-squamous subtypes
- Ongoing in second line vs docetaxel in PD-L1+
- Starting in radically resected stage IB-III adjuvant setting (PDL1+ and all)
- Starting in consolidation after radical chemoradiotherapy in stage III

Thanks for your attention