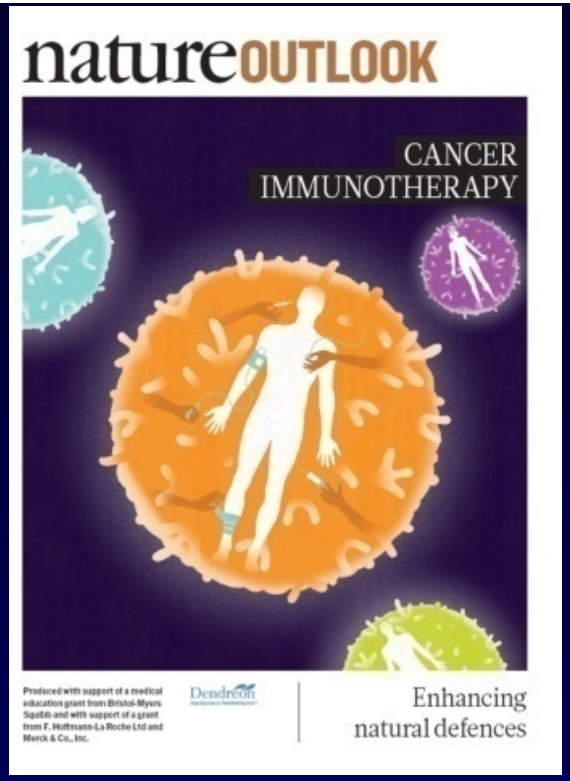
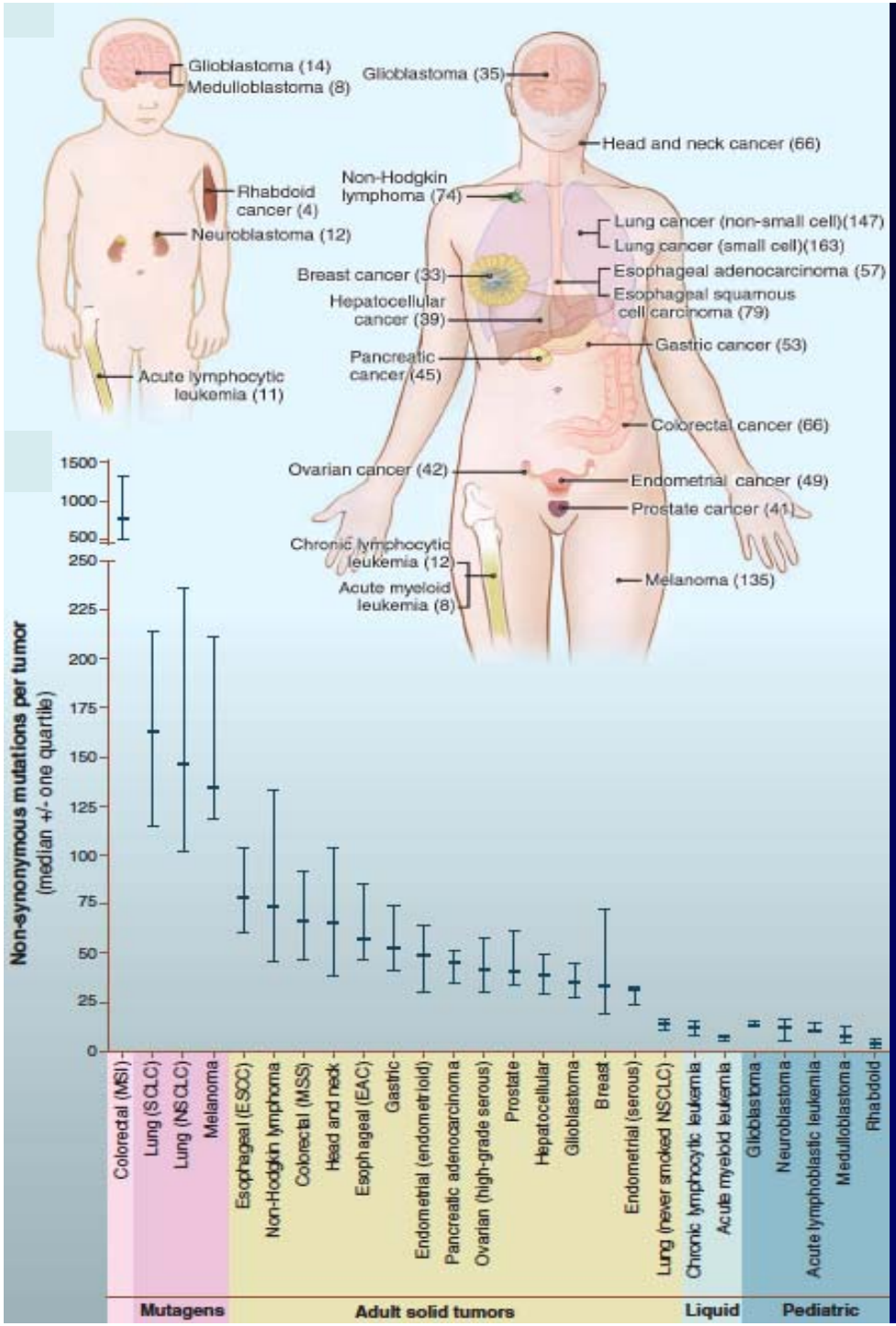
Keynote Lecture
Immunotherapy: A Step Forward in Treatment of Advanced Non-Small Cell Lung Cancer

Solange Peters, MD, PhD
Multidisciplinary Oncology Center Lausanne
Lausanne, Switzerland



"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

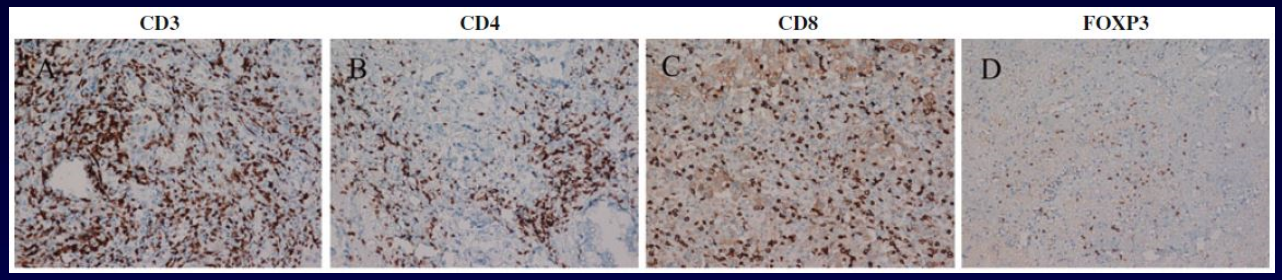


- **Melanomas and lung tumors display many more mutations than average, with ~200 nonsynonymous mutations per tumor.**

- **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.**

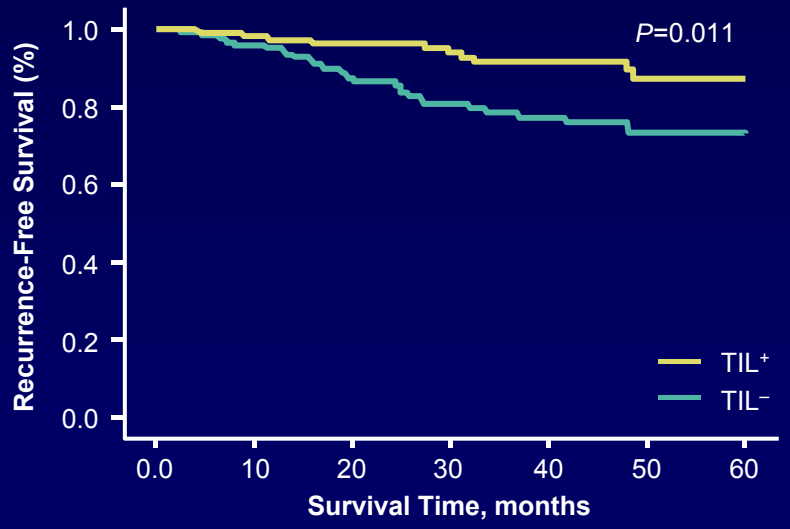
Vogelstein B, et al. *Science*. 2013;339(6127):1546-1558.
Lawrence MS, et al. *Nature*. 2013;499(7457):214-218.

Rationale for Immune Therapy in NSCLC

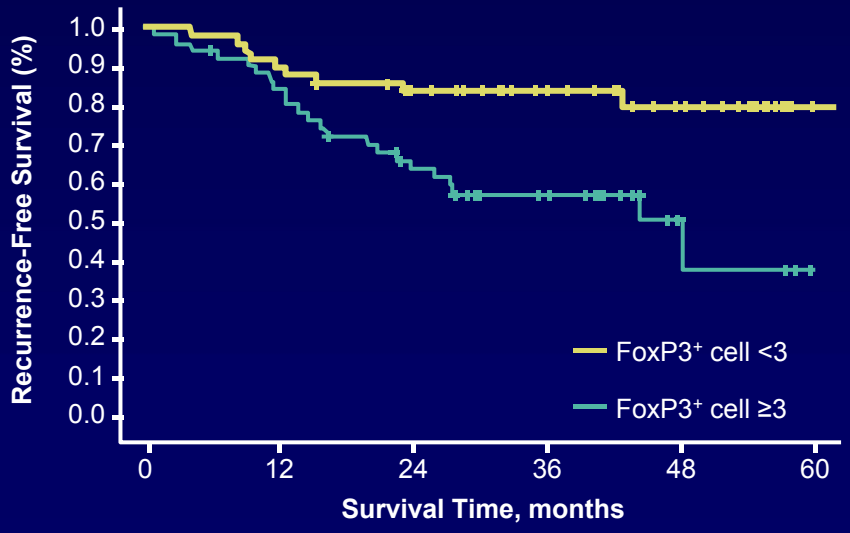


Liu H et al. *Cancer Immunol Immunother.* 2012;61(10):1849-1856

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



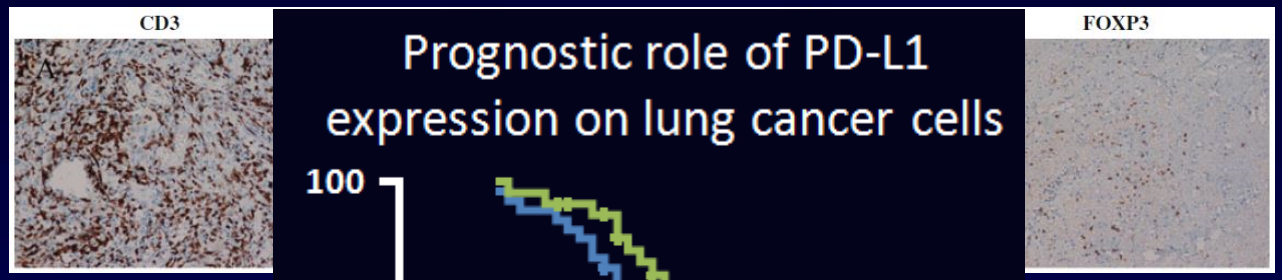
Higher NSCLC-infiltrating Tregs associated with worse recurrence-free survival[2]



TIL, tumor infiltrating lymphocytes; Tregs, regulatory T cells cells

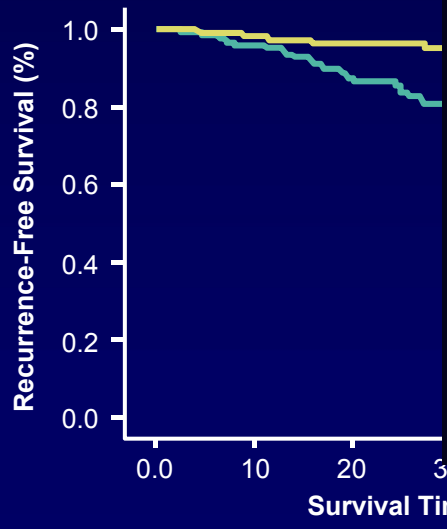
1. Shimizu K, et al. *J Thorac Oncol.* 2010;5(5):585-590. 2. Horne ZD, et al. *J Surg Res.* 2011;171(1):1-5.
3. Mu CY, et al. *Med Oncol.* 2011;28(3):682-688.

Rationale for Immune Therapy in NSCLC

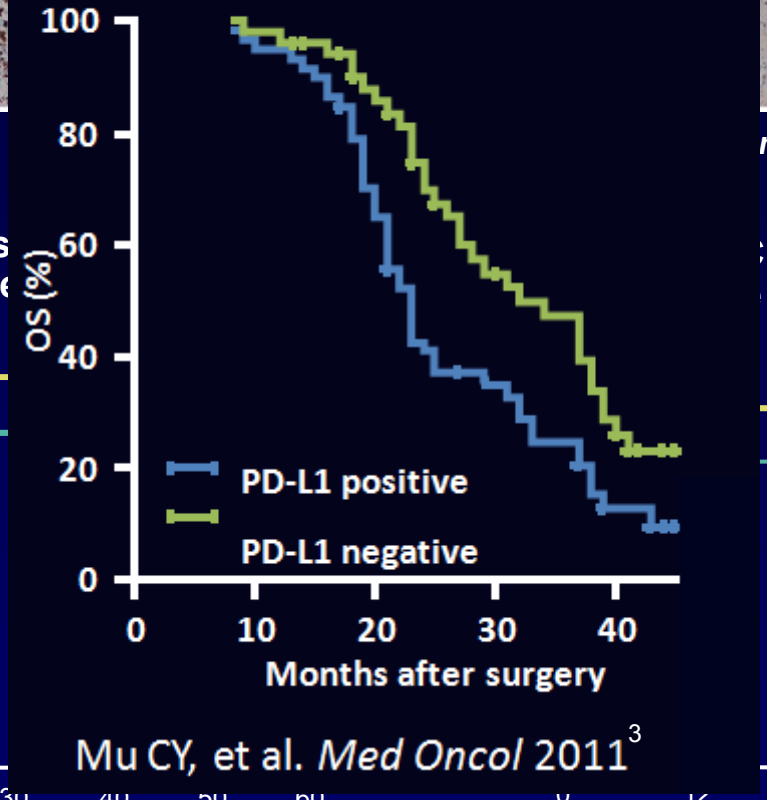


nol Immunother. 2012;61(10):1849-1856

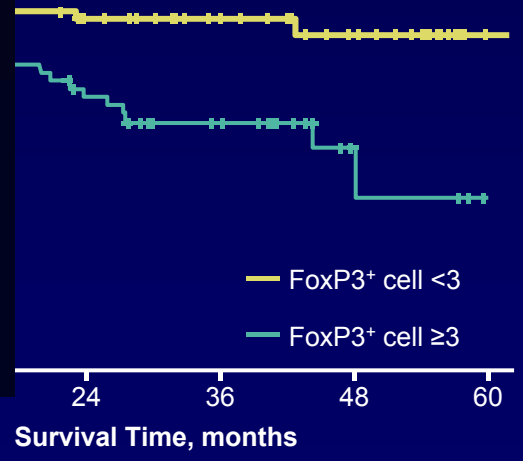
Presence of TILs as
increased recurrence



Prognostic role of PD-L1 expression on lung cancer cells



-infiltrating Tregs associated
recurrence-free survival[2]



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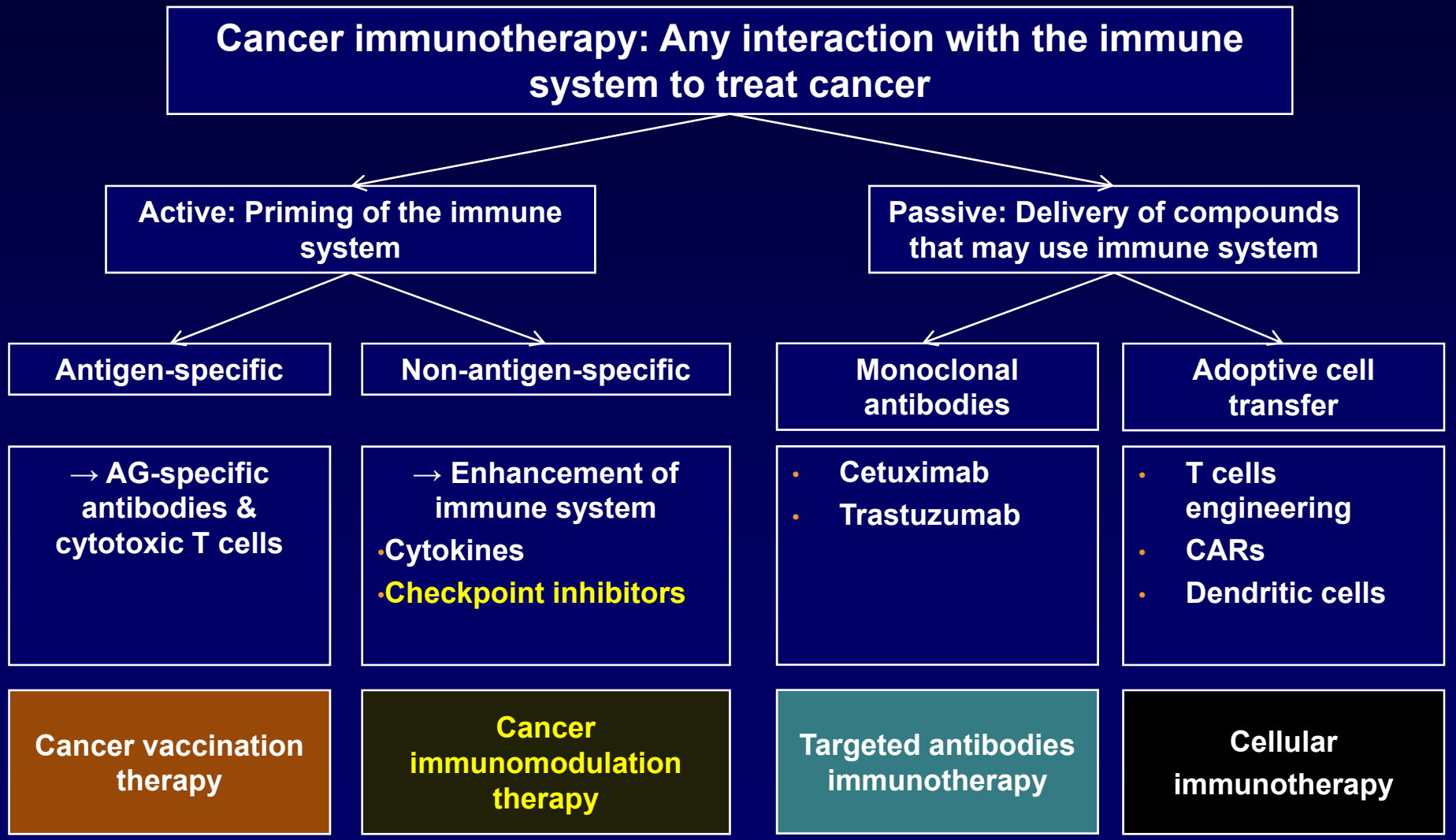
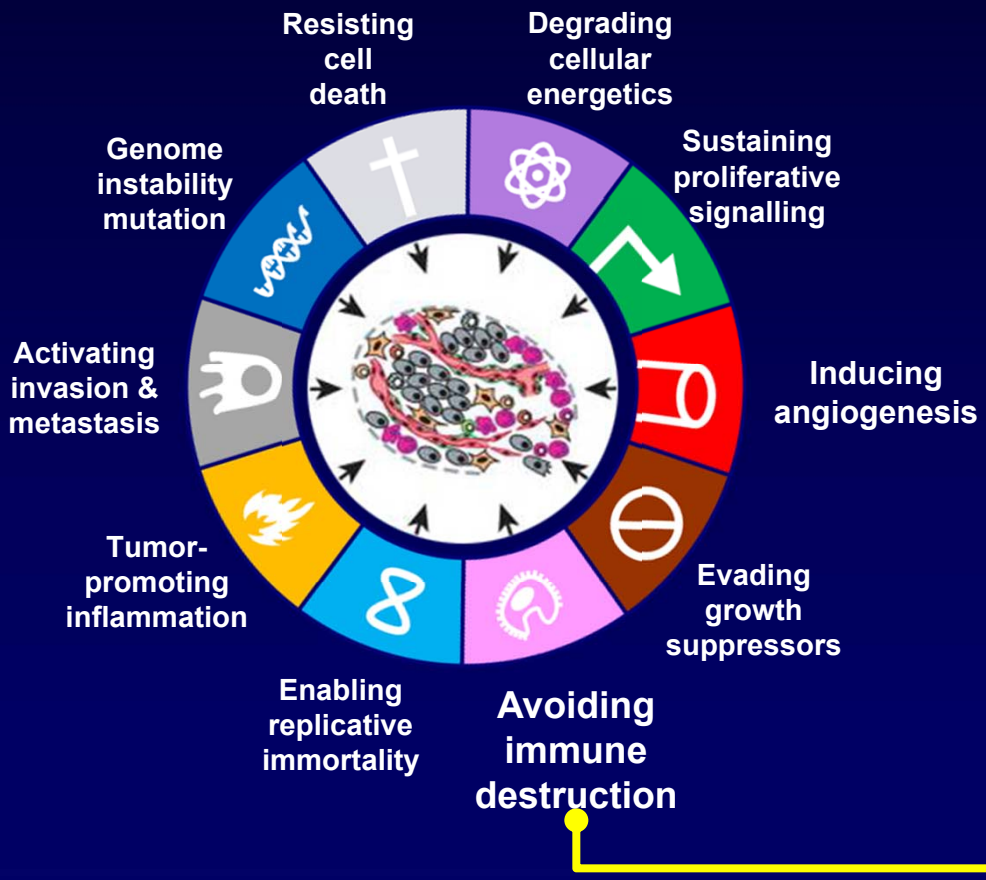
3. Mu CY, et al. *Med Oncol.* 2011;28(3):682-688.

Lung Cancer Immunotherapy Landscape



Therapeutic Intervention at Cancer Hallmarks

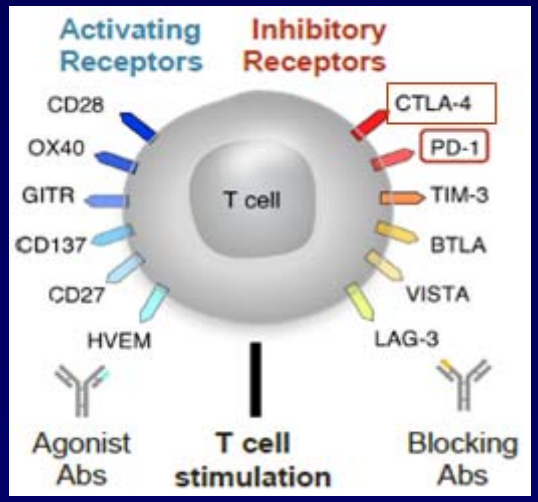


Immune checkpoints

PD-1

PDL-1

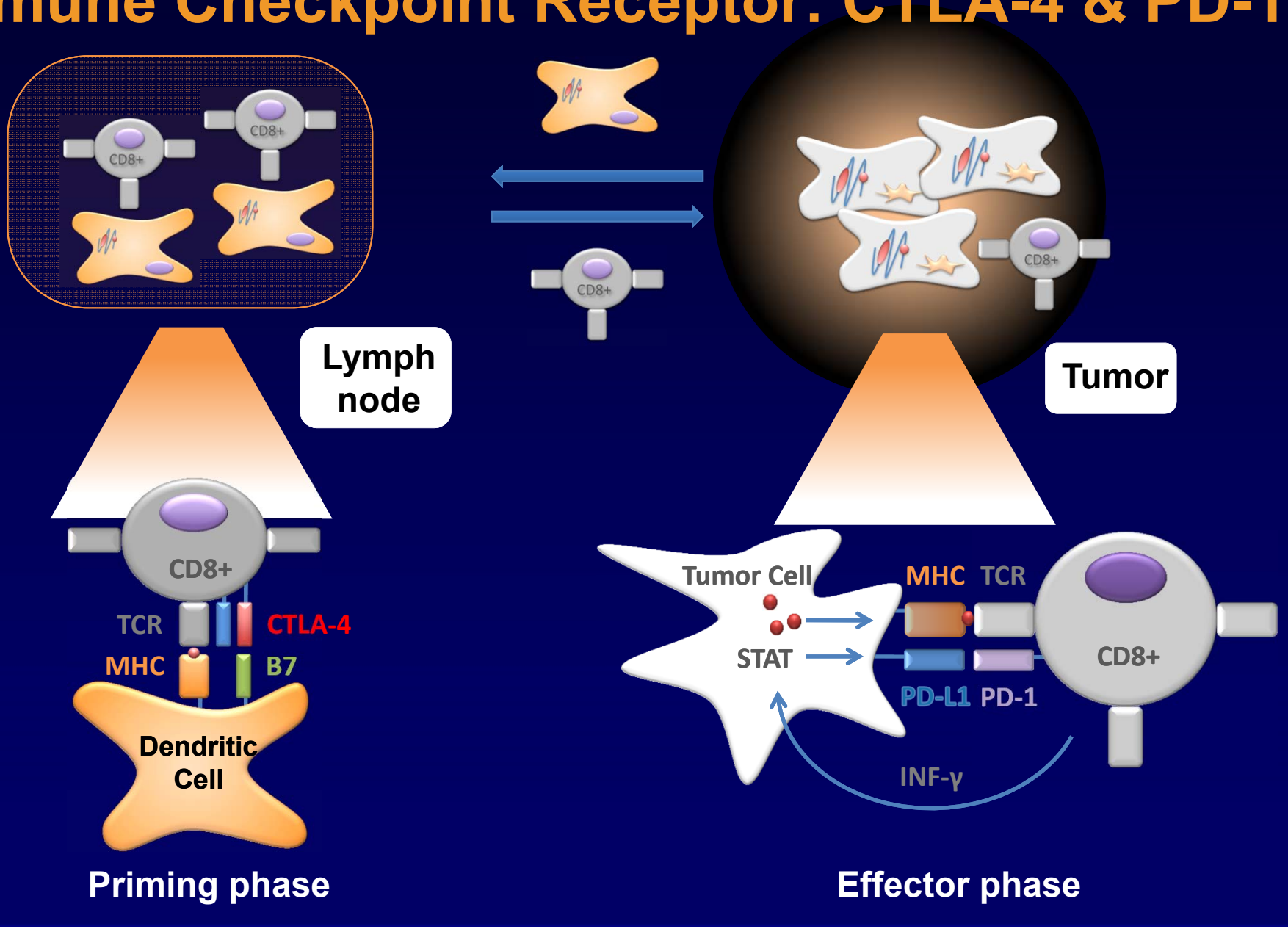
CTLA-4



Hanahan D, et al. *Cell.* 2011;144(5):646-674.

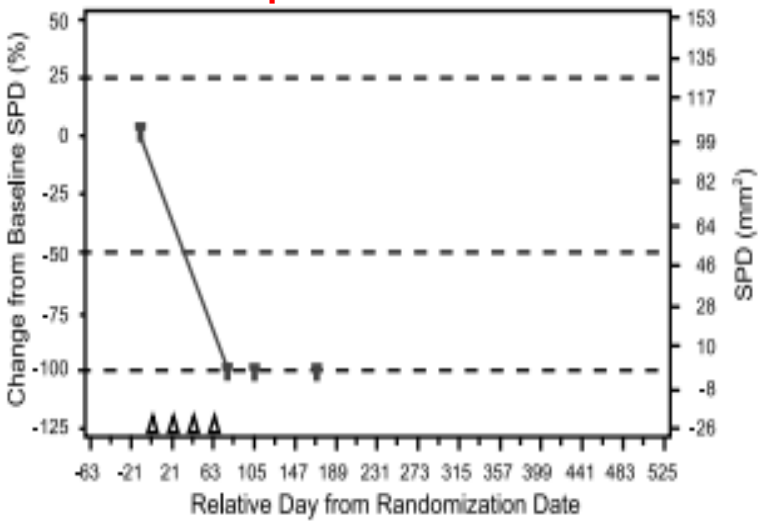
Mellman I, et al. *Nature.* 2011;480(7378):480-489.

Immune Checkpoint Receptor: CTLA-4 & PD-1

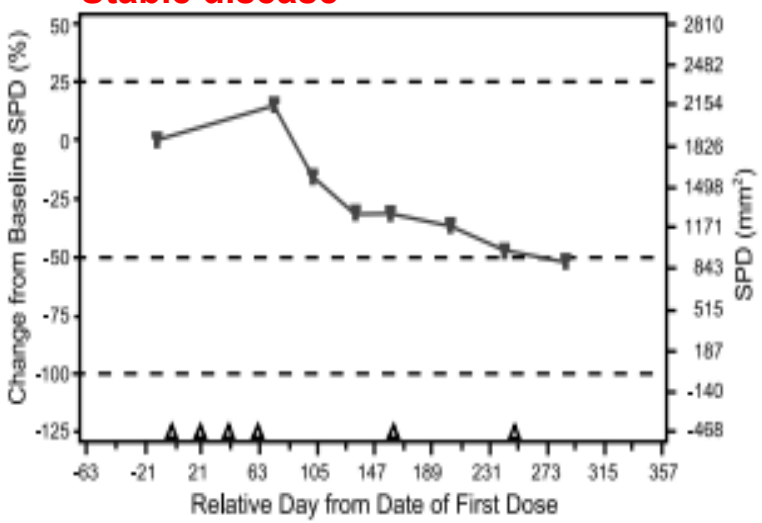


Patterns of Response to Immunotherapy

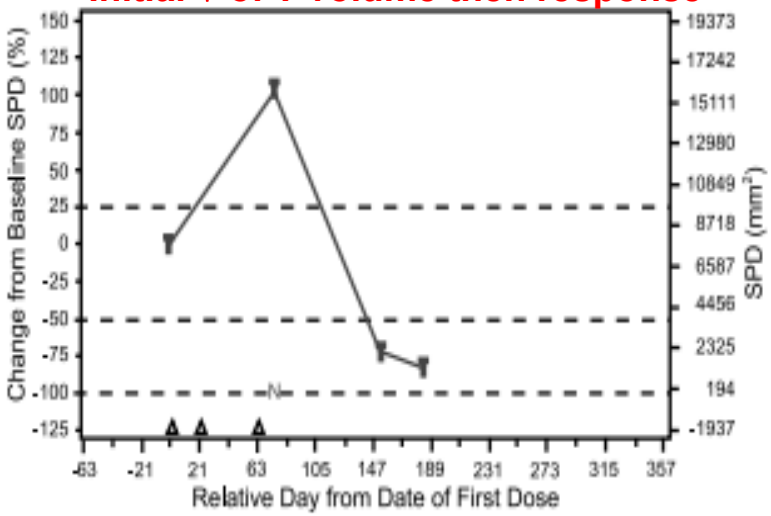
Initial response



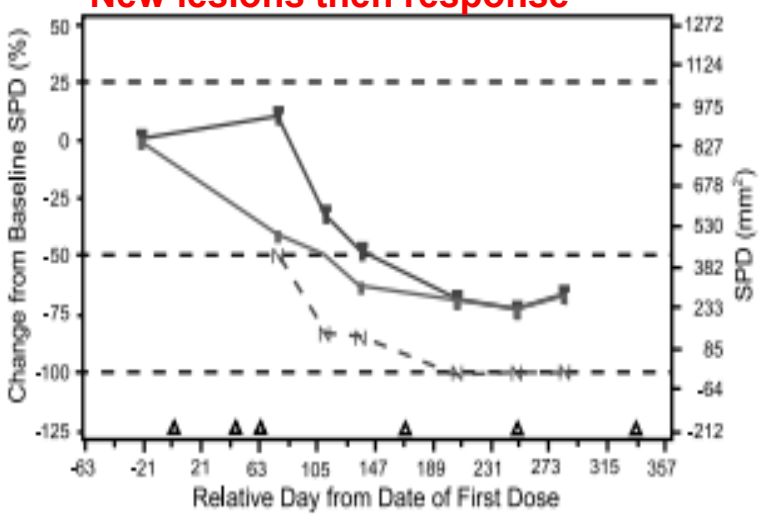
Stable disease



Initial ↑ of T volume then response



New lesions then response



Wolchock JD, et al. *Clin Cancer Res*. 2009;15:7412-7420.

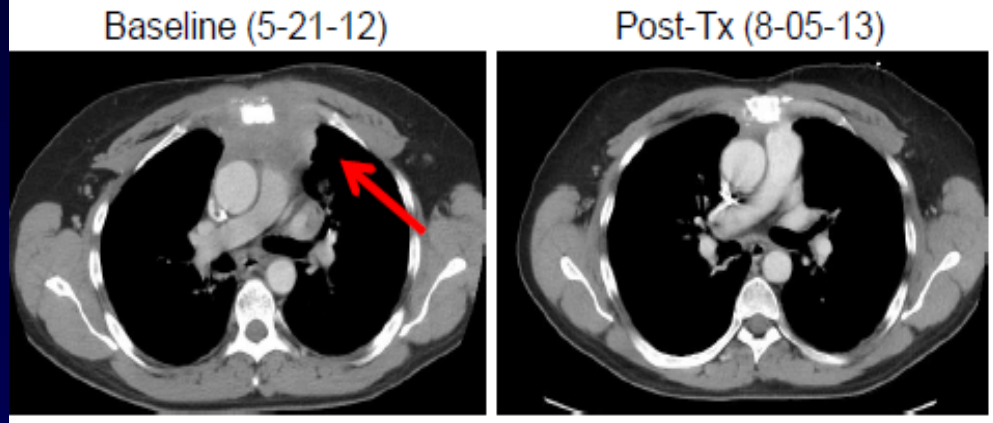
Response Criteria for Immunotherapy

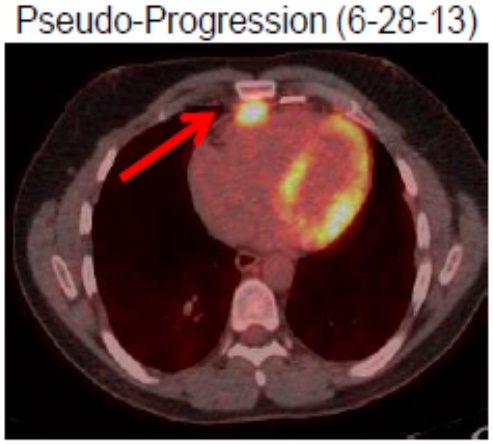
RECIST 1.1[1]			
CR	**PR**	**SD**	**PD**
Disappearance of all target lesions, reduction in short-axis diameter of pathology LN to <10 mm	≥30% decrease in sum of longest diameters of target lesions	Neither PR nor PD	≥20% increase (≥5 mm absolute increase) in sum of longest diameters, in comparison with smallest sum of longest diameters recorded during treatment
Immune-related response criteria[2]			
irCR	**irPR**	**irSD**	**irPD**
Disappearance of all lesions on 2 consecutive observations ≥4 weeks apart	≥50% decrease in tumor burden compared with baseline in 2 observations ≥4 weeks apart	50% decrease in tumor burden compared with baseline not established, nor 25% increase vs nadir	≥25% increase in tumor burden compared with nadir (at any single timepoint) in 2 consecutive observations at least 4 weeks apart

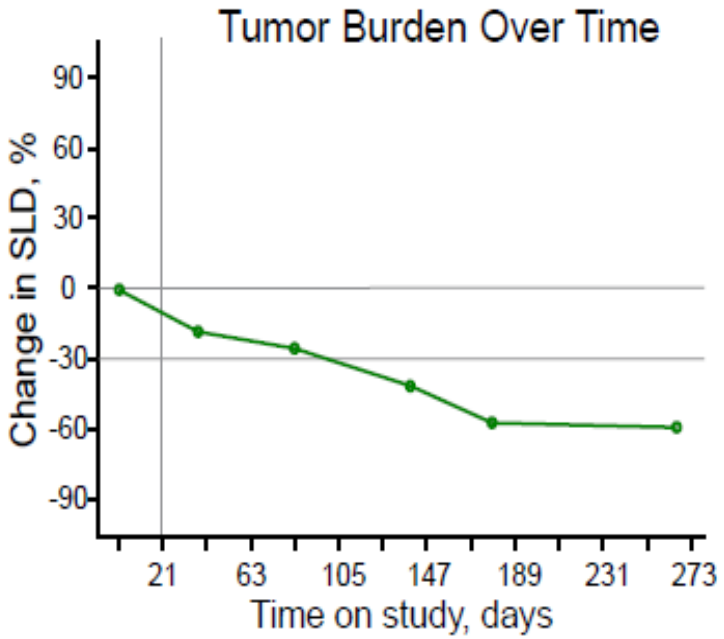
1. Eisenhauer EA, et al. *Eur J Cancer.* 2009;45(2):228-247. 2. Wolchok JD, et al. *Clin Cancer Res*. 2009;15(23):7412-7420.

Pseudo-Progression

- **After 1 year of therapy with anti-PDL1 MPDL3280A**







- Sustained response of target lesions with new/growing solitary FDG-avid nTL
- Excision of FDG-avid nTL revealed reactive lymph node without evidence of malignant involvement

Gettinger SN, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney, Australia. Abstract MO19.09.

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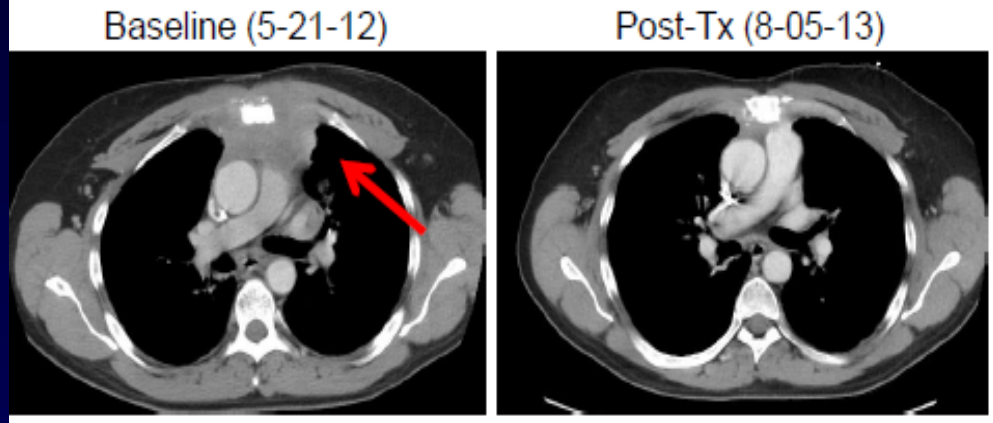

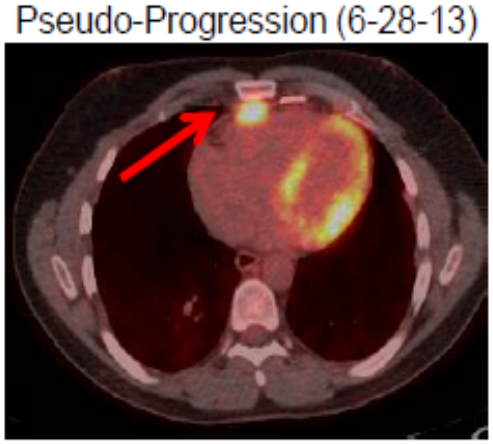

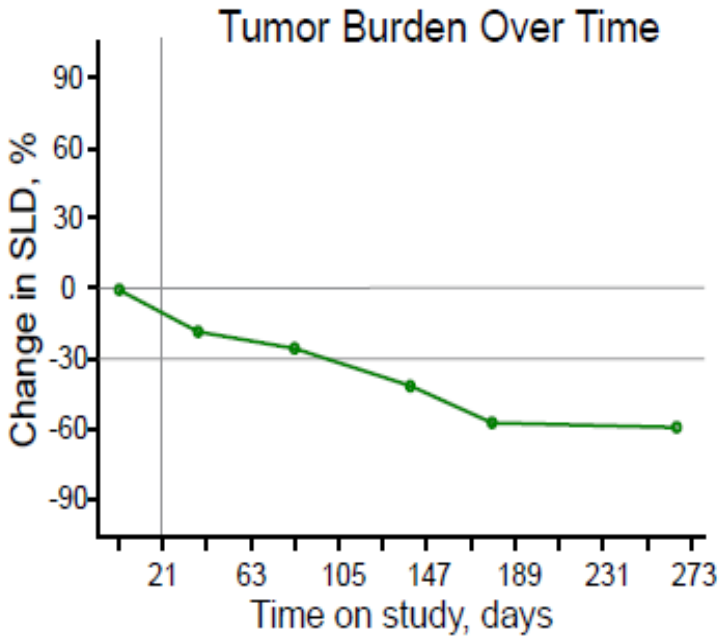

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Guidelines Helped Managing Specific Toxicities

IMMUNE-MEDIATED ADVERSE REACTIONS

Follow color code to appropriate management guide section.

GASTROINTESTINAL

GO TO PAGE 6

Signs and symptoms such as

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

LIVER

GO TO PAGE 8

Signs such as

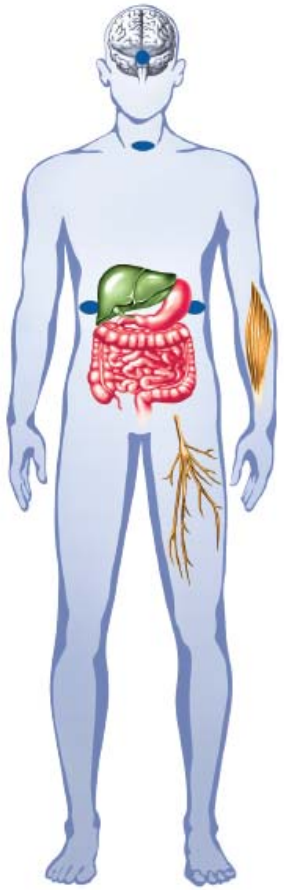
- Abnormal liver function tests (eg, AST, ALT) or total bilirubin

SKIN

GO TO PAGE 10

Symptoms such as

- Pruritus
- Rash



NEUROLOGIC

GO TO PAGE 12

Symptoms such as

- Unilateral or bilateral weakness
- Sensory alterations
- Paresthesia

ENDOCRINE

GO TO PAGE 14

Signs and symptoms such as

- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

OTHER ADVERSE REACTIONS, including ocular manifestations

GO TO PAGE 16

Please see each organ system section for related guidance.

See checklist on the next page.

Ipilimumab: Immune-Mediated Adverse Reaction Management Guide: https://www.hcp.yervoy.com/pdf/rems-management-guide.pdf

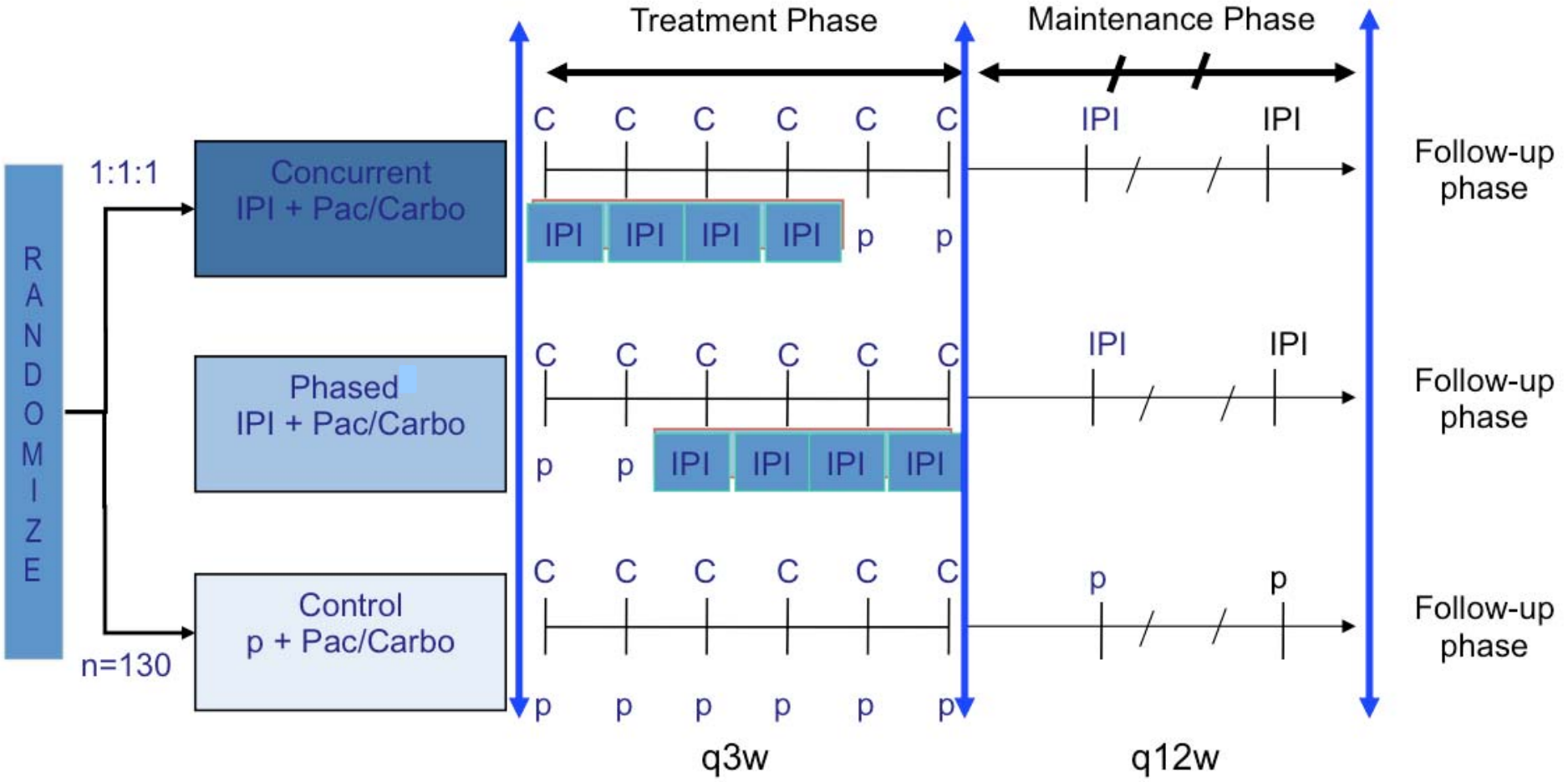
General Principles of Immune-Related Toxicity Management

Generally based on severity of symptoms:

- Grade 1: Supportive care; +/- withhold drug
- Grade 2: Withhold drug, consider redose if toxicity resolves to ≤ grade 1. Low-dose corticosteroids (prednisone 0.5 mg/kg/day or equivalent) if symptoms do not resolve within a week
- Grade 3-4: Discontinue drug; high-dose corticosteroids (prednisone 1-2 mg/kg/day or equivalent) tapered over ≥ 1 month once toxicity resolves to ≤ grade 1
- Presence of irAEs may be a biomarker for response

Anti-CTLA 4
Ipilimumab
NSCLC Phase II, Combination With Chemotherapy

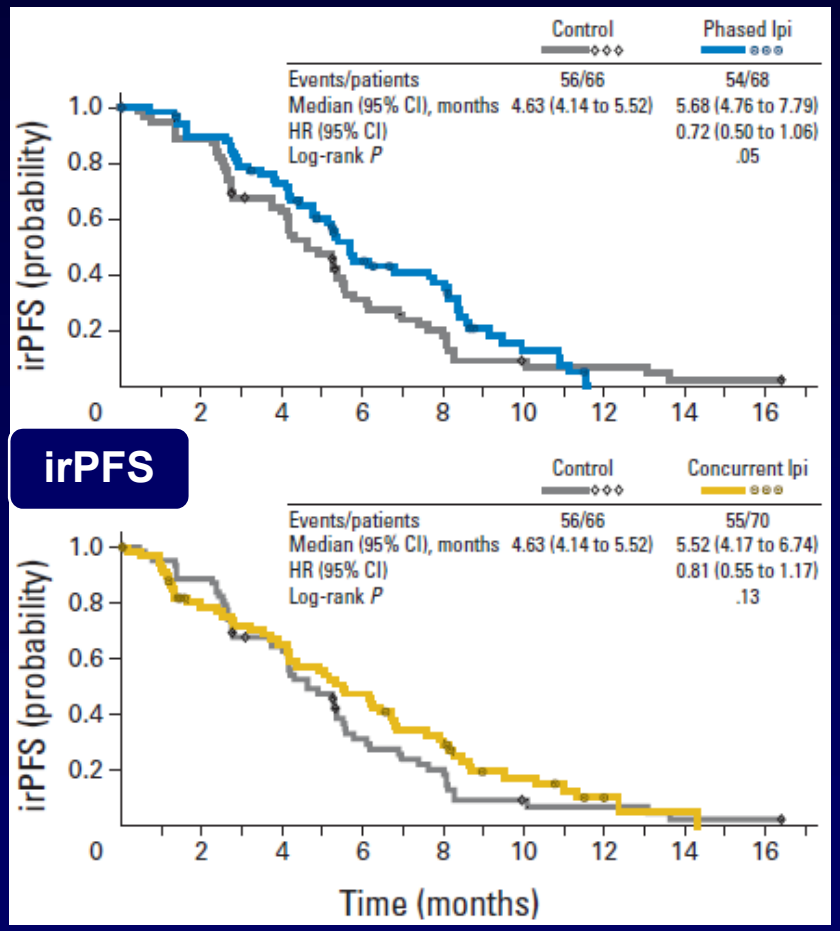
Ipilimimab Phase II CA184-041: Study Schema

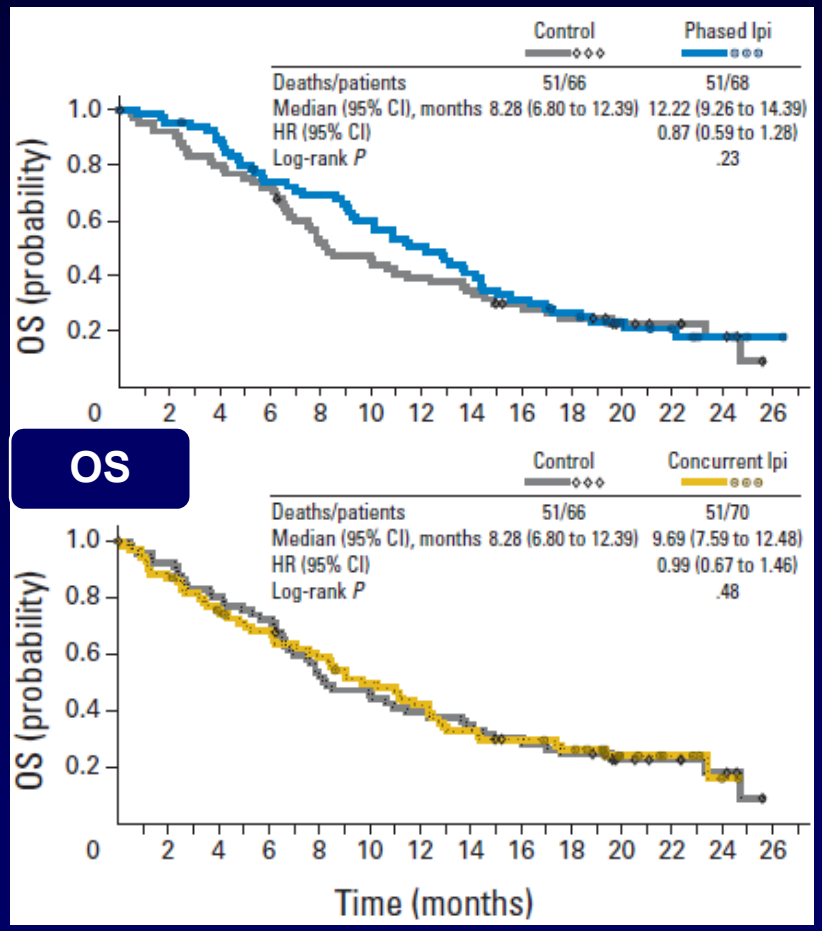


IPI, Ipilimumab; C, carboplatin, P, paclitaxel

Lynch TJ, et al. *J Clin Oncol.* 2012;30(17):2046-2054.

Lung Cancer Immunomodulation
Ipilimumab





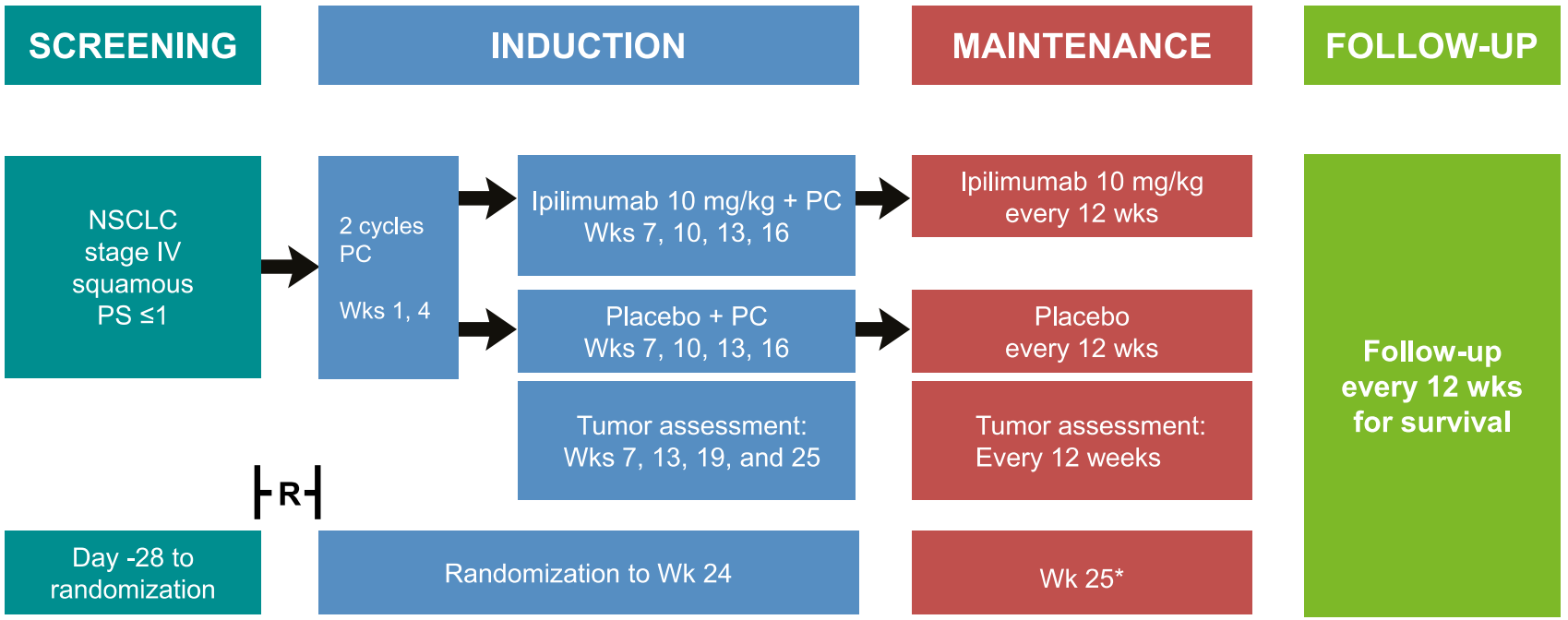
irPFS, immune-related response criteria

Lynch TJ, et al. *J Clin Oncol.* 2012;30(17):2046-2054.

Ipilimumab: NSCLC Phase III Trial

Squamous cell NSCLC, stage IV; primary end point: OS

CA184-104 study design: treatment flow



*Ends upon progressive disease or AE leading to discontinuation

PS = performance status; R = randomization; PC = chemotherapy doublet: paclitaxel 175mg/m^2 + carboplatin AUC=6; wk(s) = week(s)

N = 920, accrual completed

US National Institutes of Health. Available at: http:// clinicaltrials.gov/ct2/show/NCT01285609. Accessed 12 December 2014.

Clinical Development of Inhibitors of PD-1 and PD-L1 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
	MEDI4736	Engineered human IgG1 mAb	MedImmune	Phase III
	MPDL3280A	Engineered human IgG1 mAb	Genentech	Phase III
	MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase II

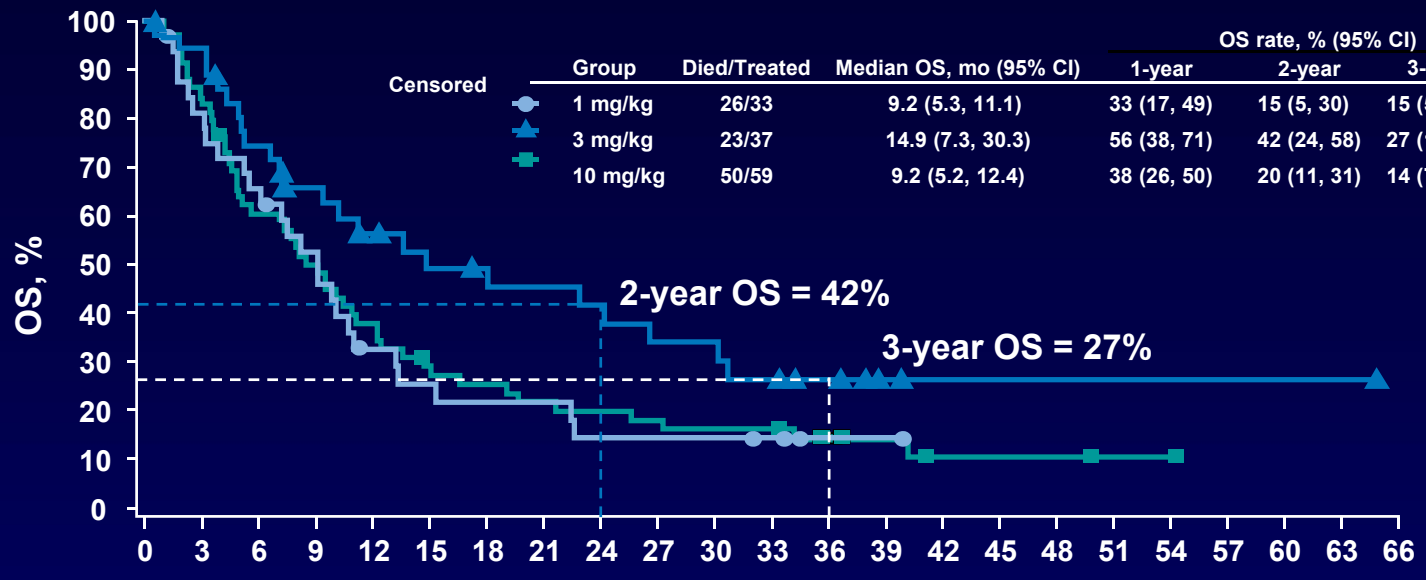
Anti-PD1/Anti PD-L1: What Do We Know at the End of 2014?

1. Monotherapy treatment with various drugs across histologies and molecular subtypes
   a. In ≥ second line of NSCLC treatment (including, maintenance)
   b. In first-line NSCLC treatment

2. The challenge of the biomarker

Anti-PD1
Nivolumab
≥ Second Line, Phase I Data

OS by Dose (Data Lock Sep 2014)



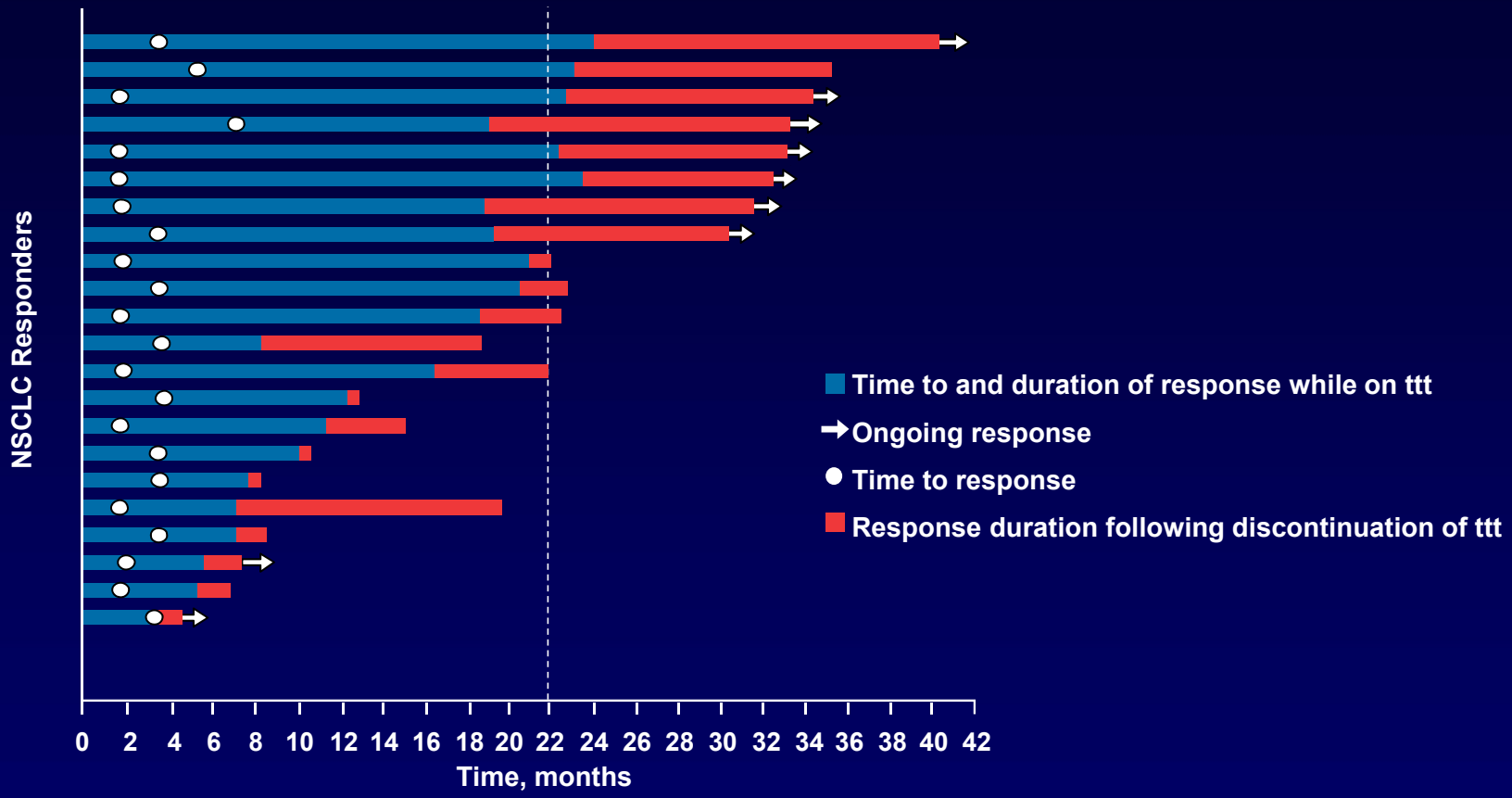
Group	Died/Treated	Median OS, mo (95% CI)	OS rate, % (95% CI) 1-year	2-year	3-year
1 mg/kg	26/33	9.2 (5.3, 11.1)	33 (17, 49)	15 (5, 30)	15 (5, 30)
3 mg/kg	23/37	14.9 (7.3, 30.3)	56 (38, 71)	42 (24, 58)	27 (12, 43)
10 mg/kg	50/59	9.2 (5.2, 12.4)	38 (26, 50)	20 (11, 31)	14 (7, 25)

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

- Patients were heavily pretreated; 54% had 3-5 prior therapies
- Responses were ongoing in 41% of patients (9/22) at the time of analysis
- 3 treatment related deaths due to pneumonitis

Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 170.

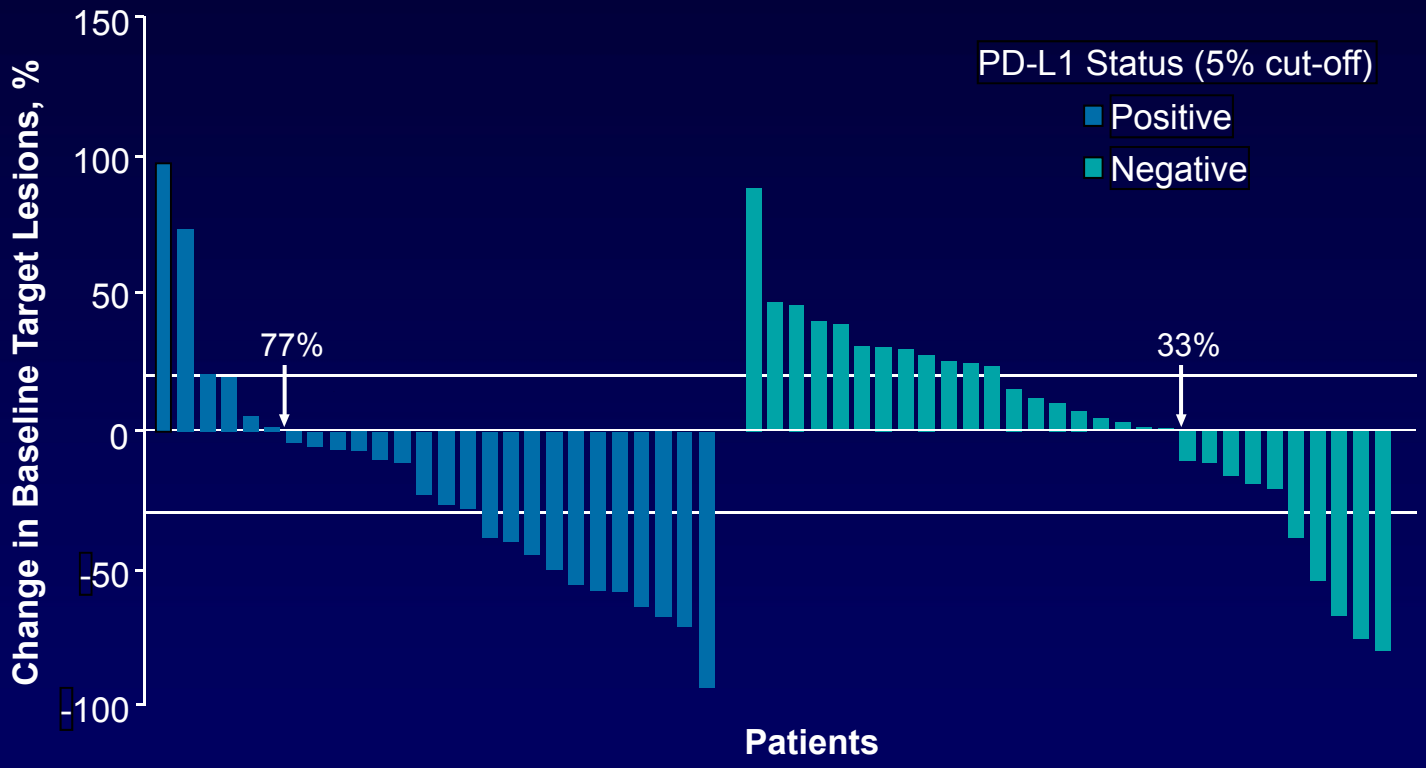
Characteristics of Responses



- **5% unconventional "immune-related" responses, with persistent reduction in target lesions in the presence of new lesions or regression following initial progression**

Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 170.

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)

Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 170.

Exploratory Analysis of Response by Smoking Exposure

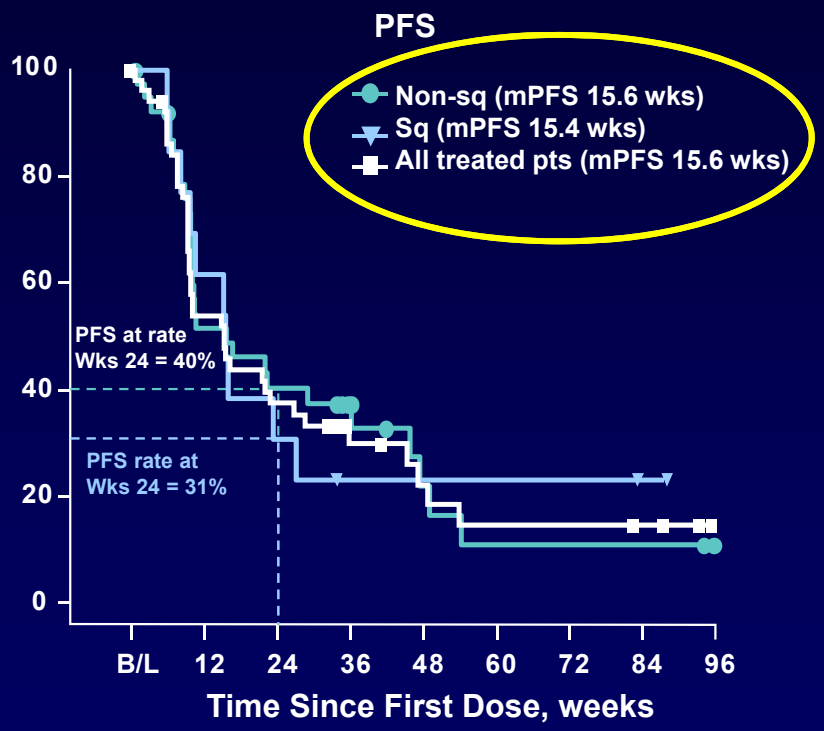
Variable	ORR, %	(n/N)	[95% CI][a]
Smoking exposure			
>5 pack-years	30	(20/66)	[20, 43]
≤5 pack-years[b]	0	(0/14)	[0, 23]
Time since quitting (NO CORRELATION)			
>15 yrs prior	26	(6/23)	[10, 48]
6-15 yrs prior	17	(2/12)	[2, 48]
1-5 yrs prior	46	(6/13)	[19, 75]
Current smoker	27	(6/22)	[11, 50]
0/never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

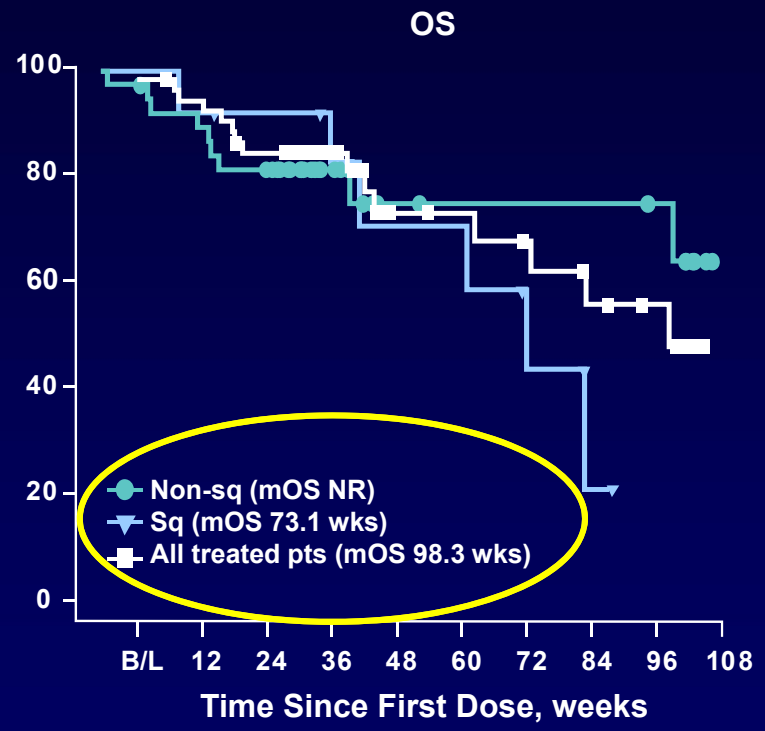
Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 170.

Nivolumab

First Line, Phase I Data
Monotherapy & Combinations

PFS and OS With Nivolumab Monotherapy Front Line





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

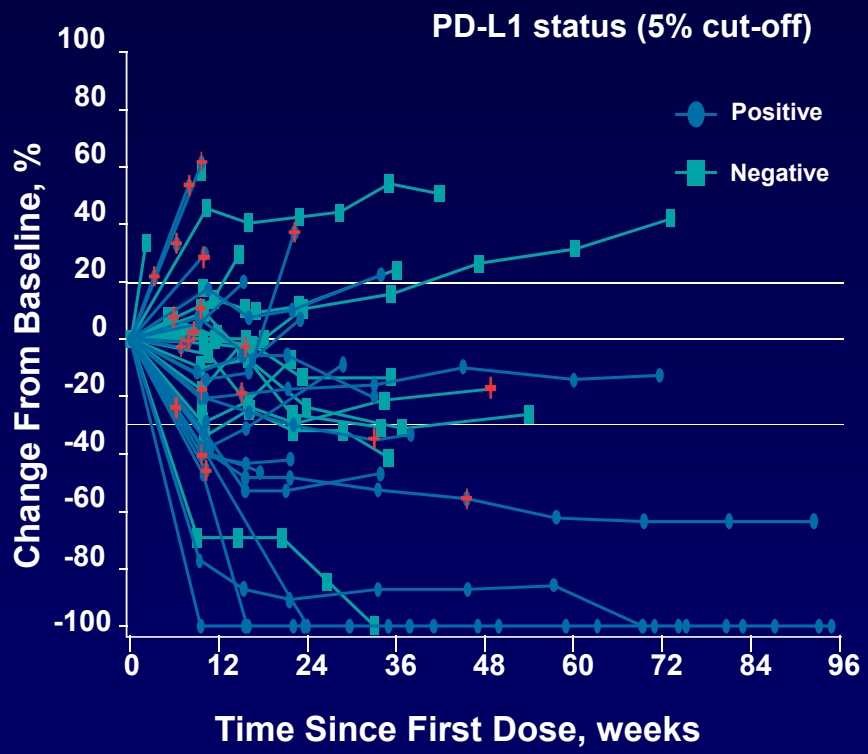
Number of Pts at Risk

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

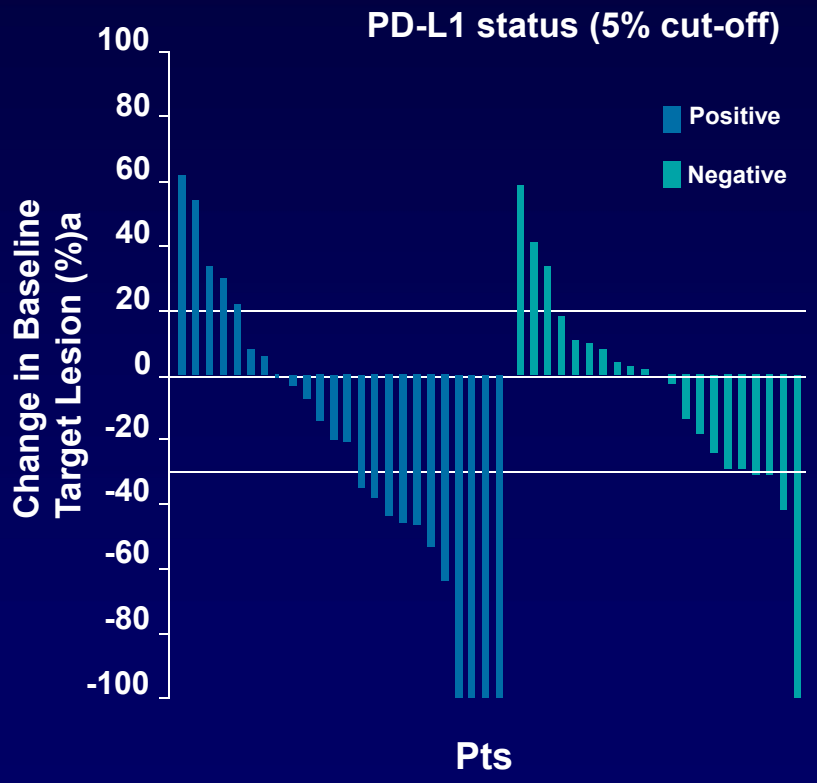
Rizvi NA, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 165.

Percent Changes in Target Lesion Tumor Burden by PD-L1 in First Line

A. Percent change in target lesions from baseline

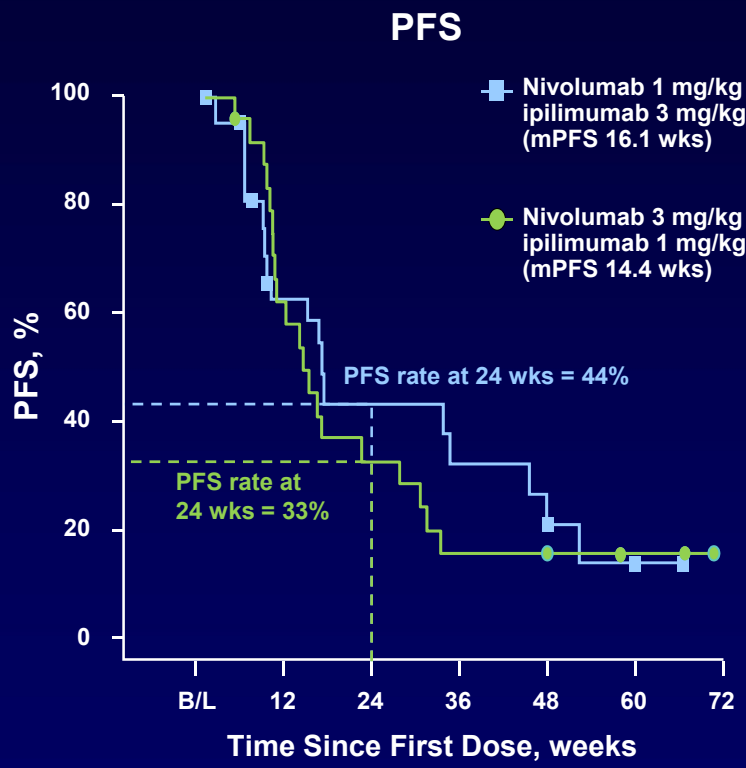


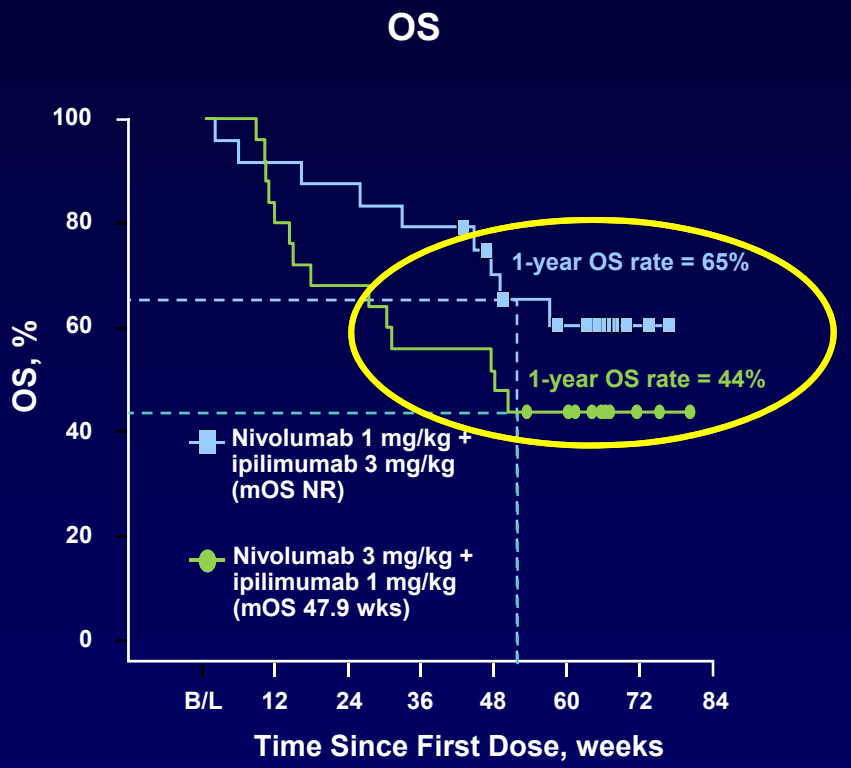
B. Best percent change in target lesion tumor burden from baseline



Rizvi NA, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 165.

PFS and OS in NSCLC Patients 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

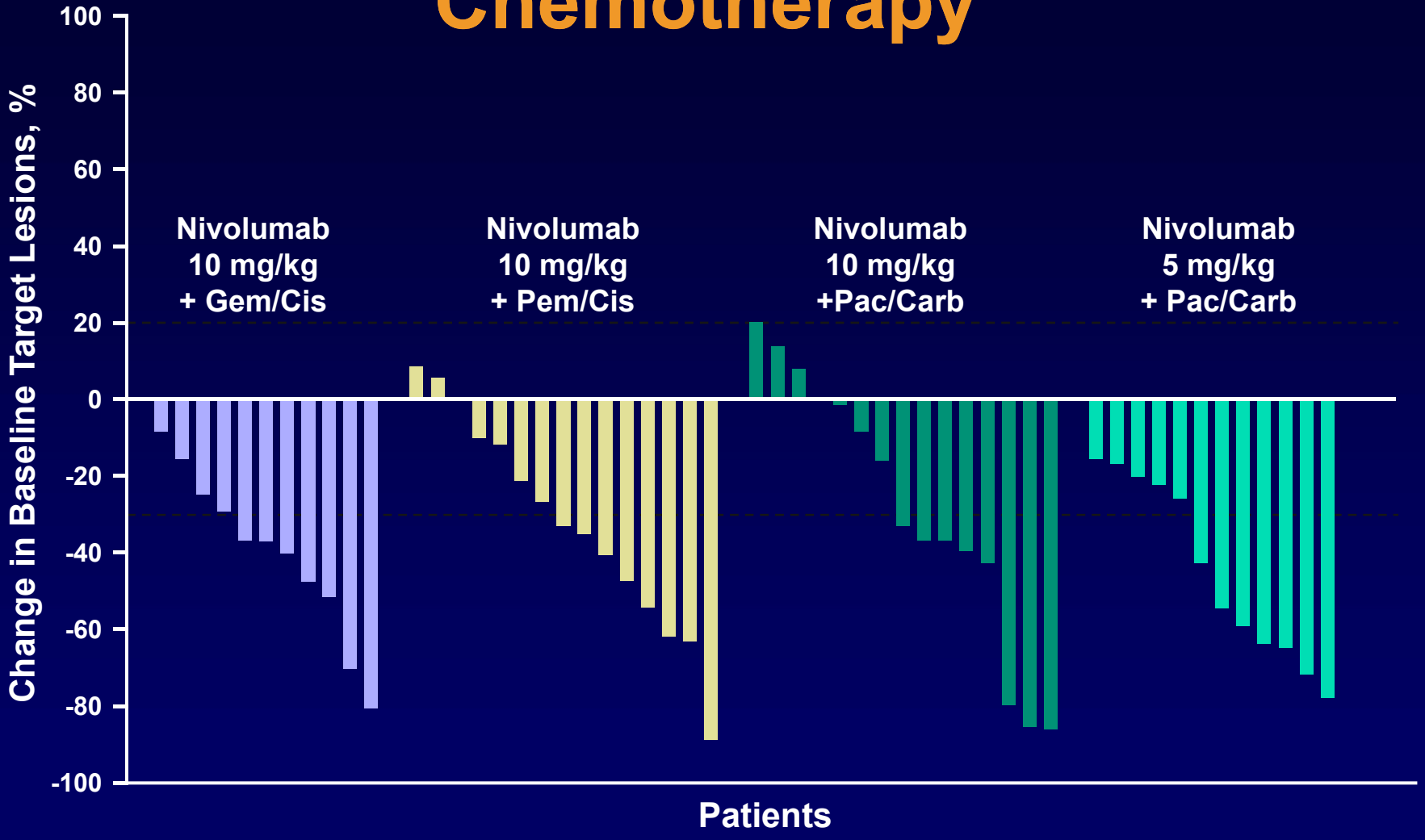
Antonia SJ , et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 168.

Safety: Nivolumab Plus Ipilimumab 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%)

Antonia SJ , et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 168.

First-Line Combination With Chemotherapy



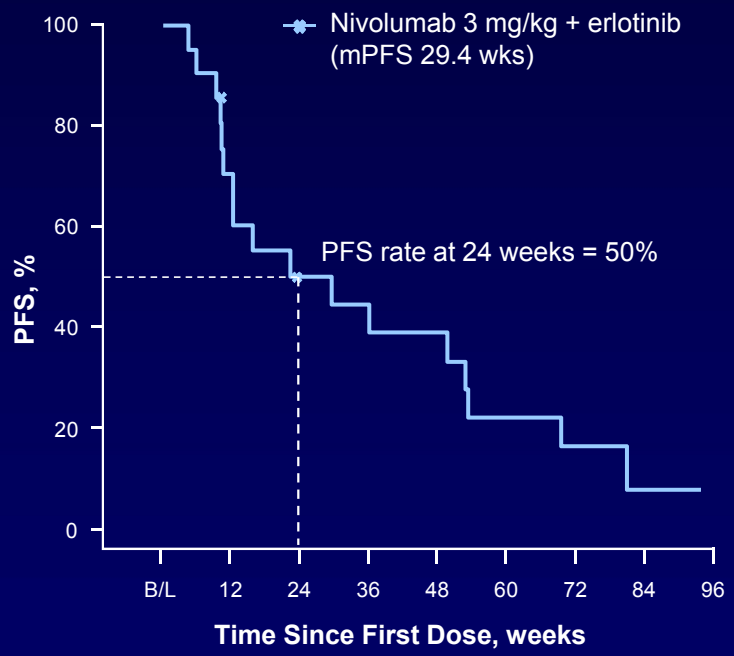
ORR for nivolumab plus chemotherapy in first-line treatment are similar to those previously reported for chemotherapy alone

Antonia SJ , et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 3.

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

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

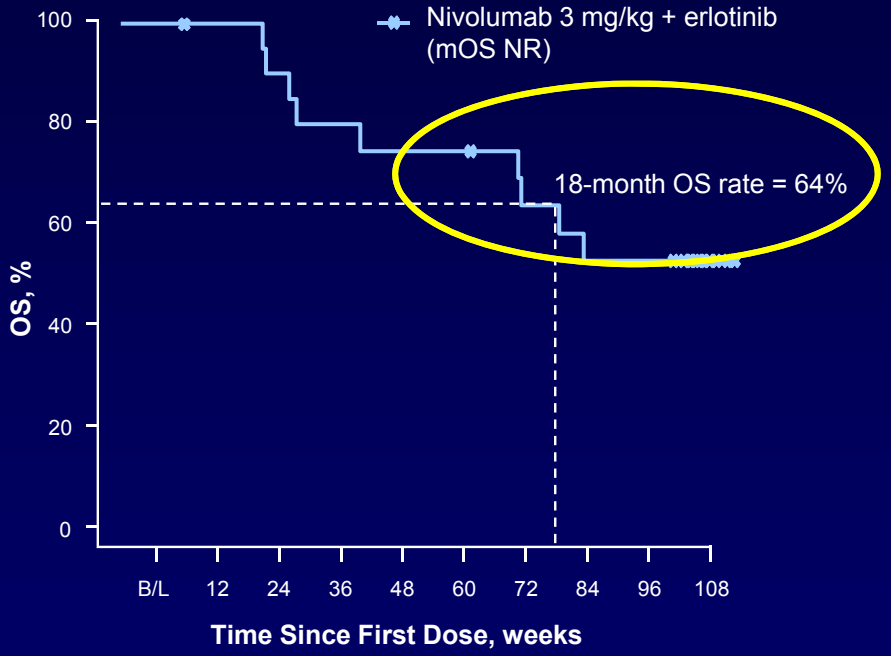
PFS



Number of Pts at Risk

Nivolumab + erlotinib	21	14	9	7	7	4	3	1	0

OS



Number of Pts at Risk

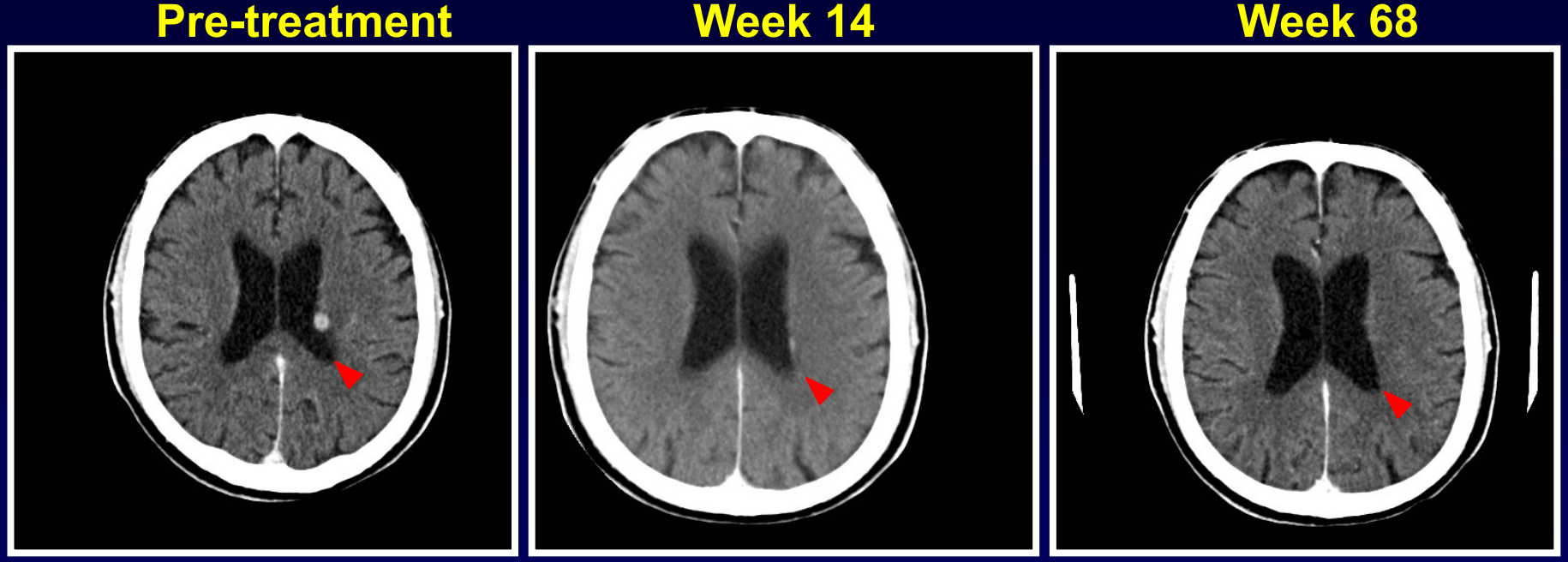
Nivolumab + erlotinib	21	20	20	16	15	15	13	10	10	2

Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 171.

Nivolumab

Squamous ≥ Second Line, Phase II Monotherapy Data

Response to Nivolumab in Squamous NSCLC Brain Metastasis

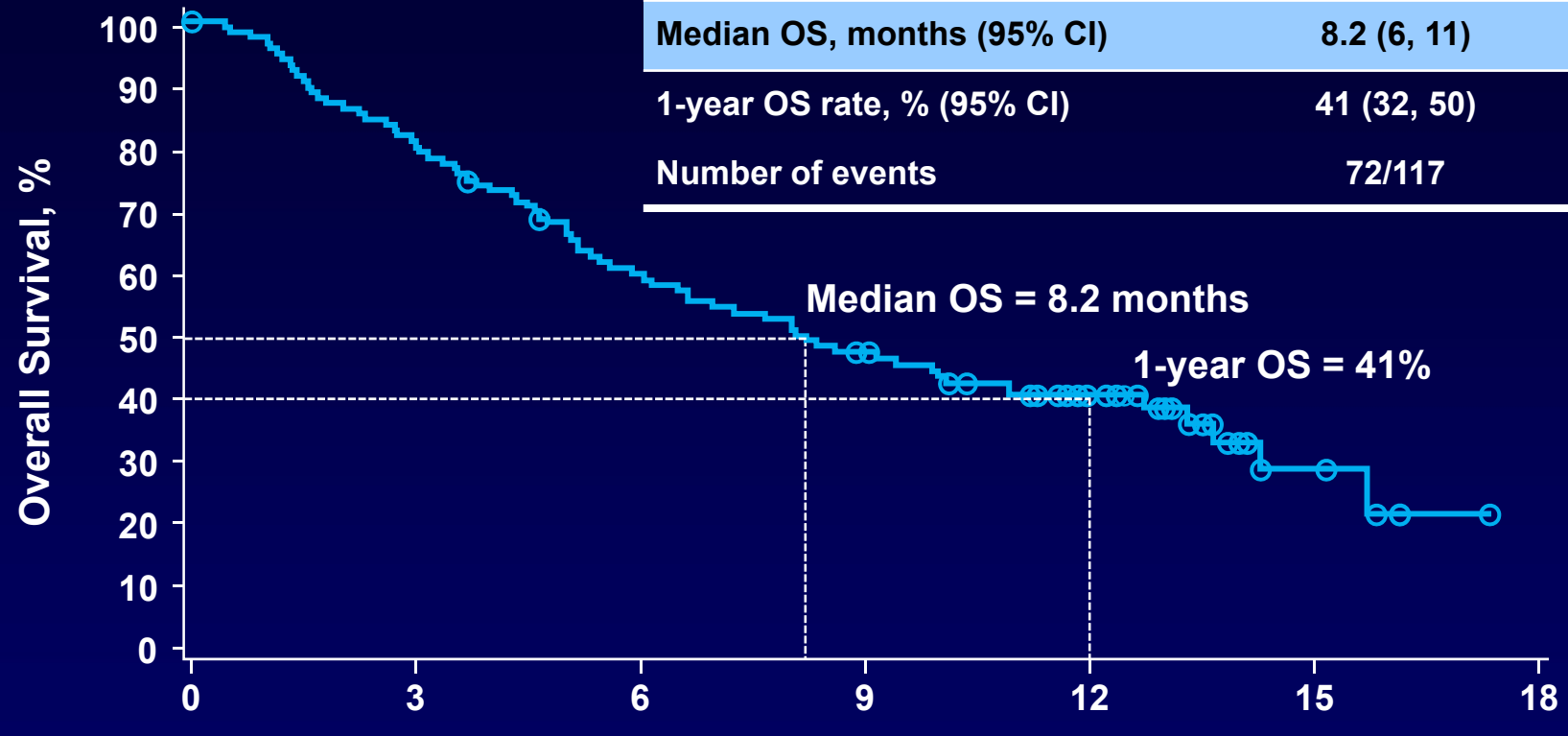


- 73 year-old male, stage IIIB, former smoker
- Prior radiotherapy (mediastinal), 3 prior systemic regimens (cisplatin/gemcitabine, docetaxel, vinorelbine)
- No prior CNS-directed radiotherapy

Ramalingam S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract LBA2.

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



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)

Ramalingam S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract LBA2.

Select Adverse Events (≥1%) Under Anti-PD1: The Example of nivolumab

- Demonstrates a safety profile managed by protocol algorithms
- No new safety signals emerging; all patients >1 year of follow-up

	Patients, n (%) [N = 129]	
	Any grade	Grade 3-4
Any treatment-related select adverse event*	41 (53)	5 (6)
Skin	16 (20)	0
Gastrointestinal	12 (15)	1 (1)
Pneumonitis	8 (6)	3 (2)†
Pulmonary	7 (9)	2 (3)
Endocrinopathies	6 (8)	0
Hepatic	5 (6)	1 (1)
Infusion reaction	4 (5)	1 (1)
Renal	3 (4)	0

*Defined as an event with potential immunological aetiologies that require more frequent monitoring and/or unique intervention

†2/3 cases were fatal

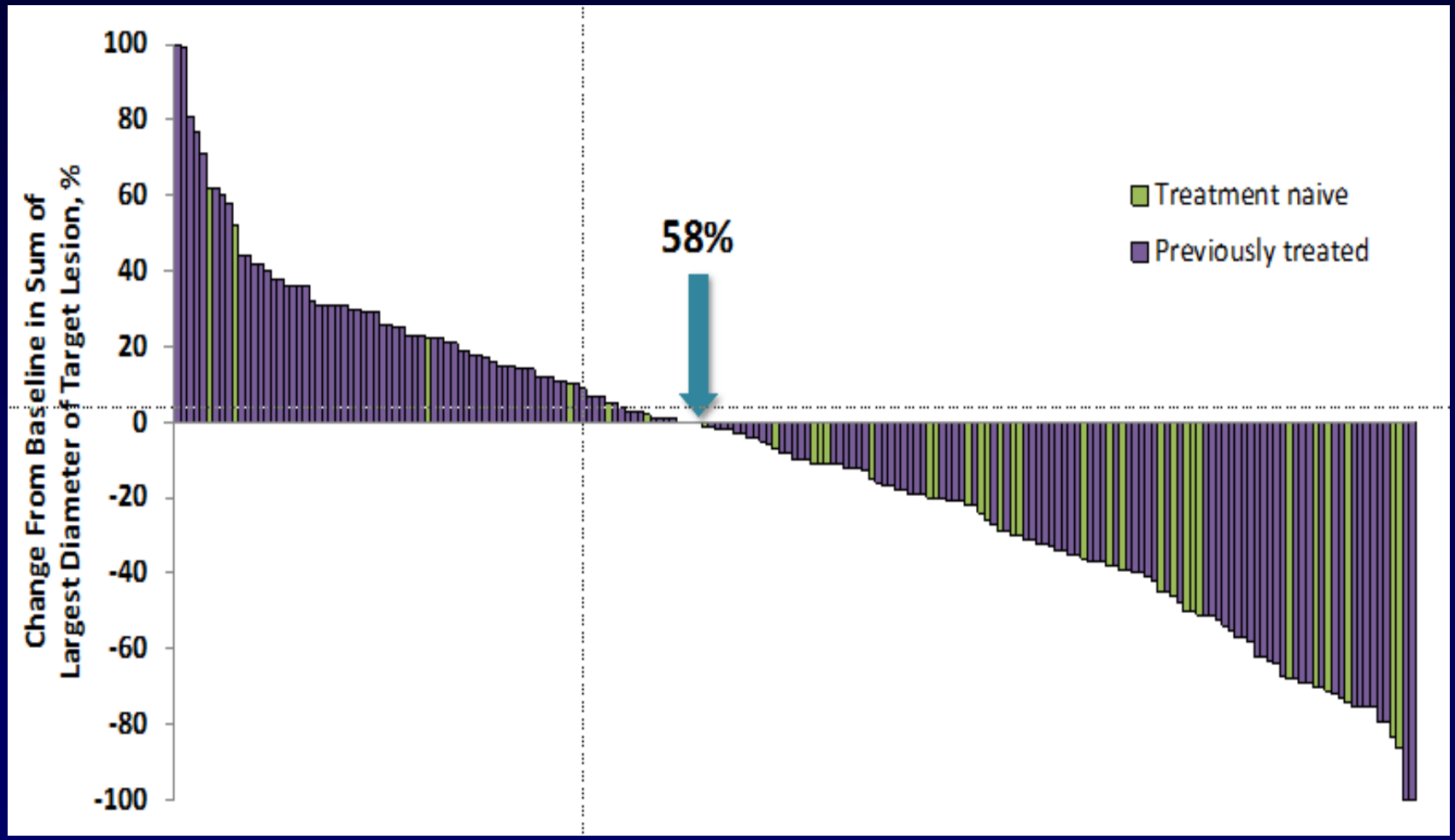
Brahmer JR, et al. *J Clin Oncol.* 2014;32 (Suppl): Abstract 8112.

Anti-PD1

Pembrozilumab

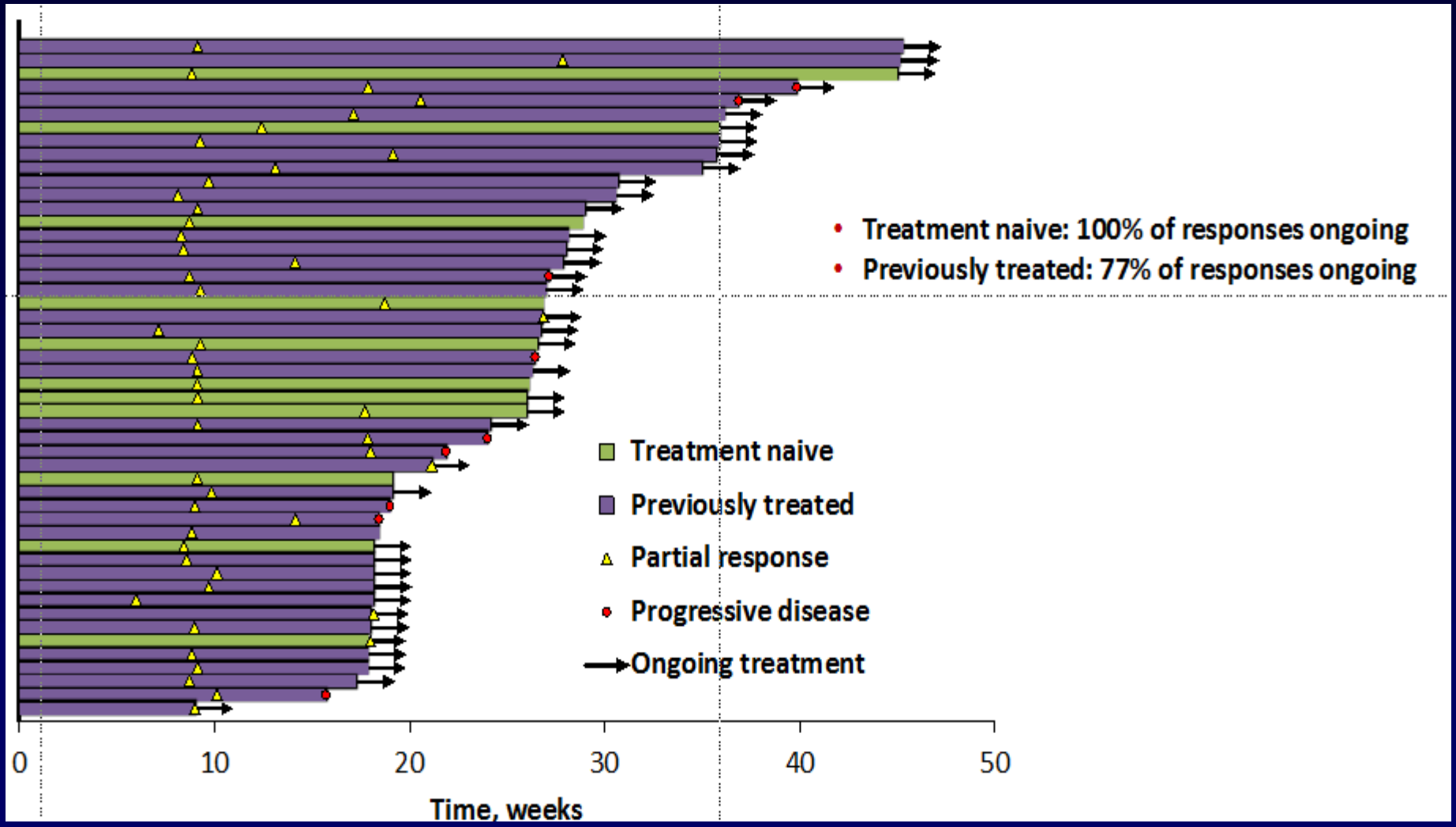
NSCLC Pooled Analysis First and Subsequent Lines, Monotherapy (Phase Ib)

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



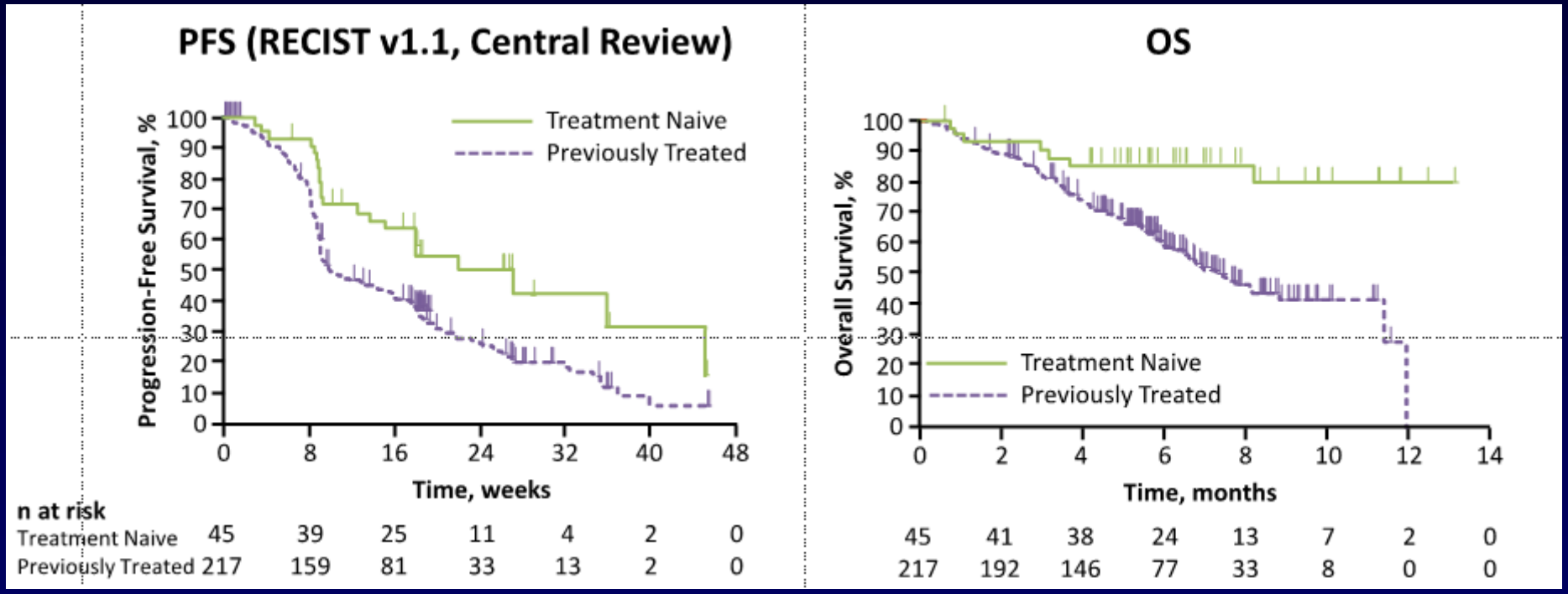
Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43.

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



Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43.

Kaplan-Meier Estimates of Survival



Treatment naive

- **Median PFS: 27 weeks (95% CI, 14-45)**
- **24-weeks 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%**

Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43.

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?

Treatment naive
- Median PFS: 27 weeks (95% CI, 14-45)
- 24-weeks PFS: 51%

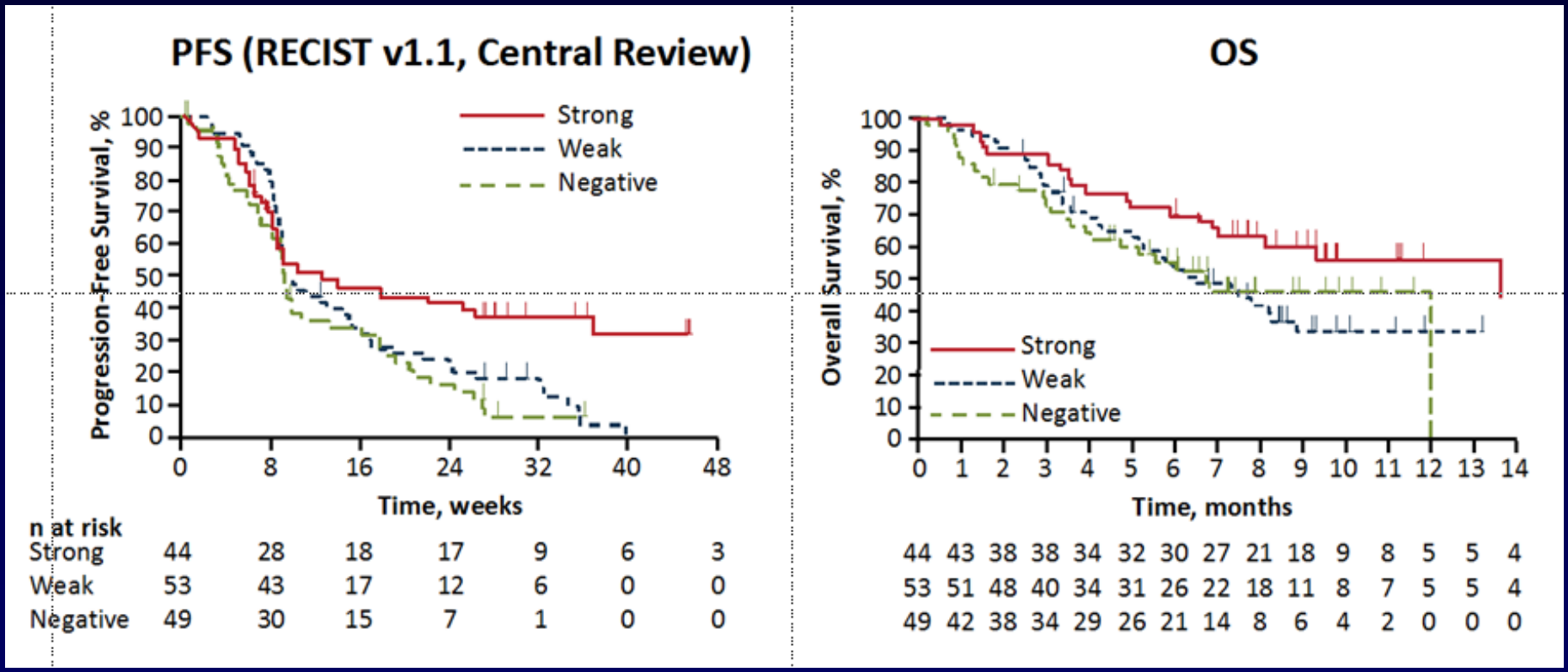
Previously treated
- Median PFS: 10 weeks (9.1-15.3)
- 24-week PFS: 26%

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%

Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43.

Kaplan-Meier Estimates of Survival



- **PFS was longer in patients with PD-L1 strong-positive vs 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 vs PD-L1 weak-positive / negative tumors (HR, 0.59; 95% CI, 0.35-0.99)**

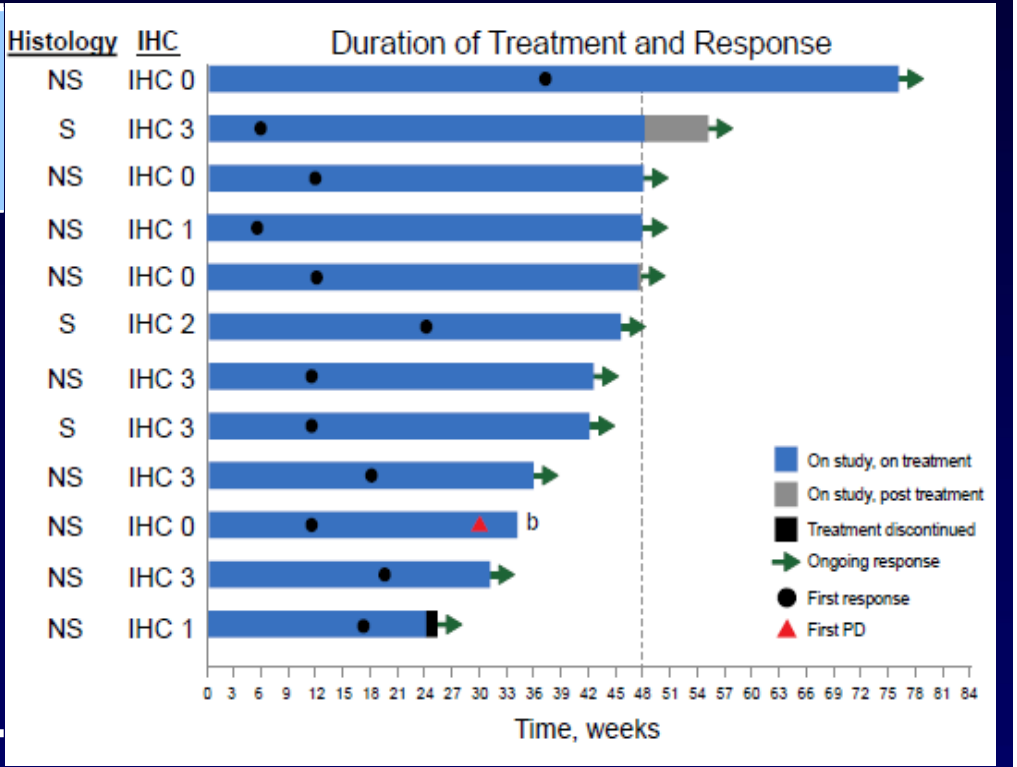
Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43.

Anti-PD-L1
MPLD3280A
≥ Second Line, Phase I Data

Soria J-C, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney, Australia.
Brahmer JR, et al. *J Clin Oncol.* 2014;32 (Suppl): Abstract 8112.

MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status, Histology and Duration of Treatment and Response – 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	23% (12/53)	40% (21/53)



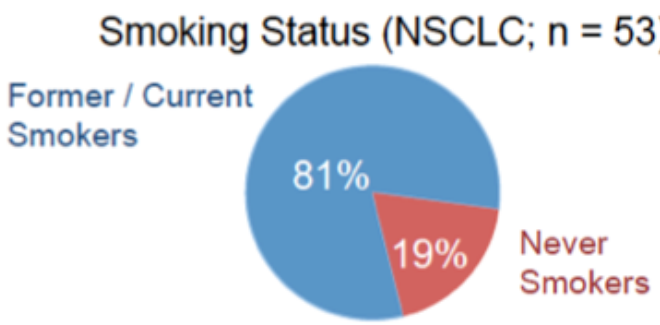
NS, nonsquamous; S, squamous

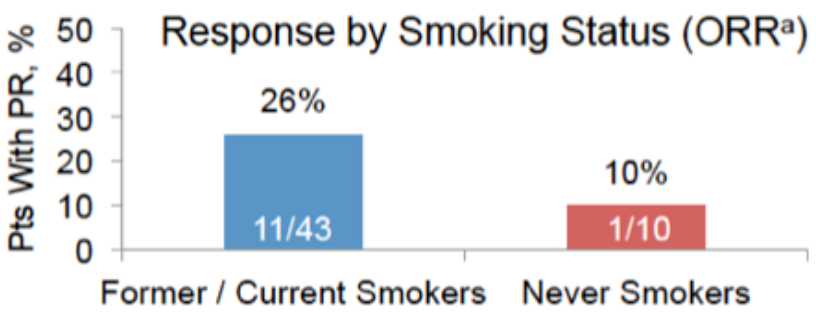
Overall response rate: 21% (n = 175)

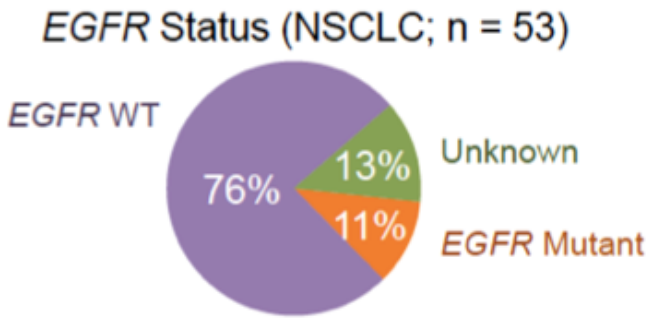
[a]ORR includes investigator-assessed unconfirmed and confirmed PR per RECIST 1.1
[b]Patient experiencing ongoing benefit per investigator

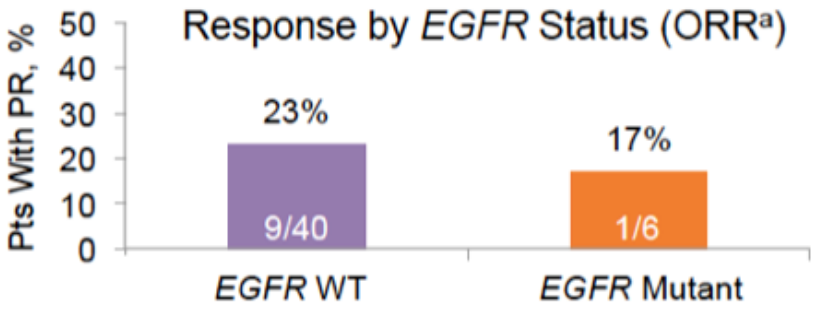
Horn L, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney, Australia. Abstract M018.01. Soria JC, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract 3408.

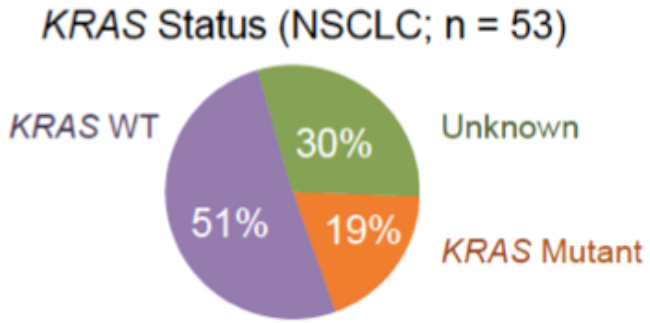
MPDL3290A: Specific Predictors

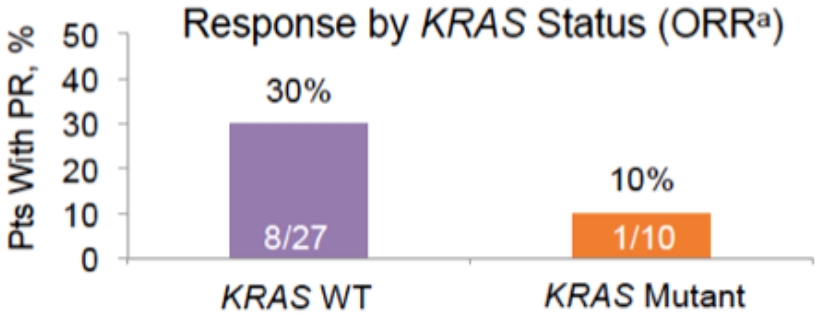








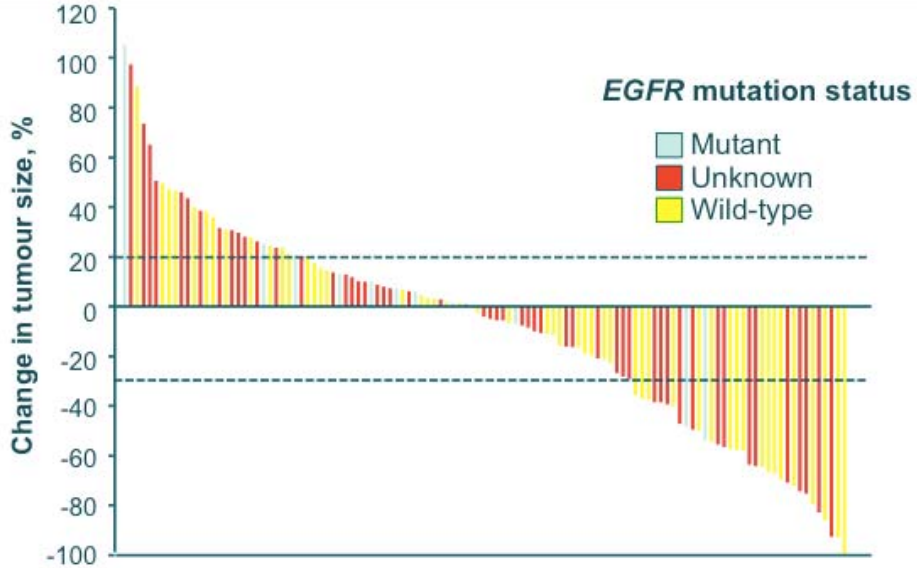


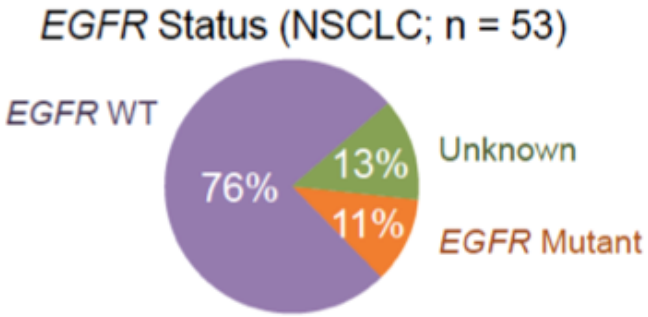


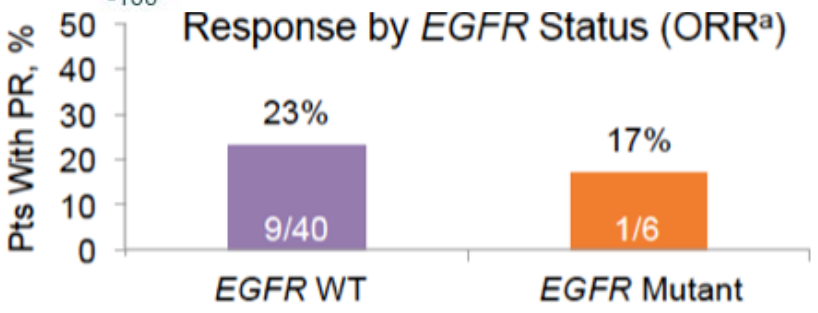
Horn L, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney Australia. Abstract M018.01.

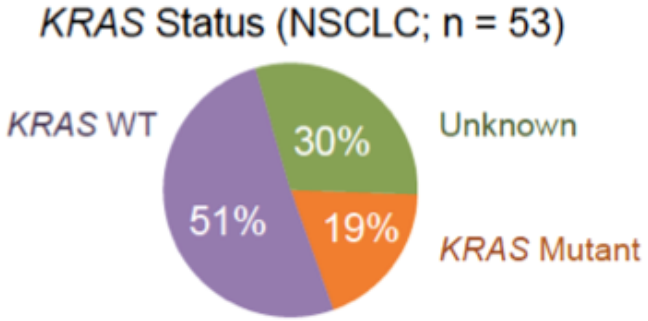
CA209-003: phase 1 follow-up study, up to 5 prior lines of therapy, NSCLC cohort

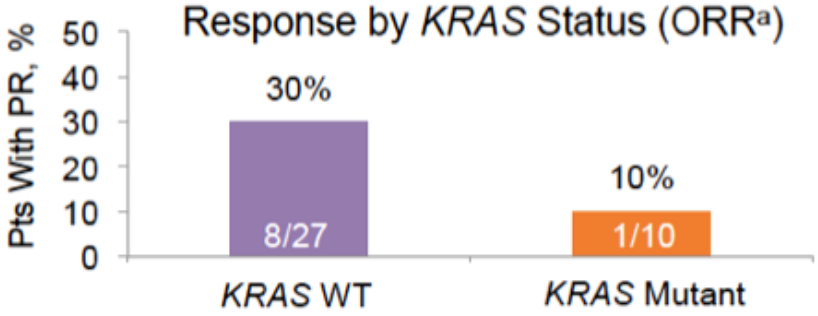
Subgroup	ORR, % (n/N) [95% CI]
***EGFR* status**	
Mutant	17 (2/12) [2.1−48.4]
Wild-type	20 (11/56) [10.2−32.4]
Unknown	15 (9/61) [7.0−26.2]











Horn L, et al. Presented at: 15th World Conference on Lung Cancer; October 27-31, 2013; Sydney Australia. Abstract M018.01.

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)

Soria JC, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract 3408. Garon EB, et al. *Ann Oncol*. 2014;25(Suppl 4): Abstract LBA43. Gettinger S, et al. Presented at: Chicago Multidisciplinary Symposium in Thoracic Oncology; October 30-November 1, 2014; Chicago, Illinois. Abstract 171.

PD-L1 as a Predictive Biomarker/Inclusion Criteria
The Challenge of the Biomarker

Intricate Role of PD-1 Signaling With Different Cell Types

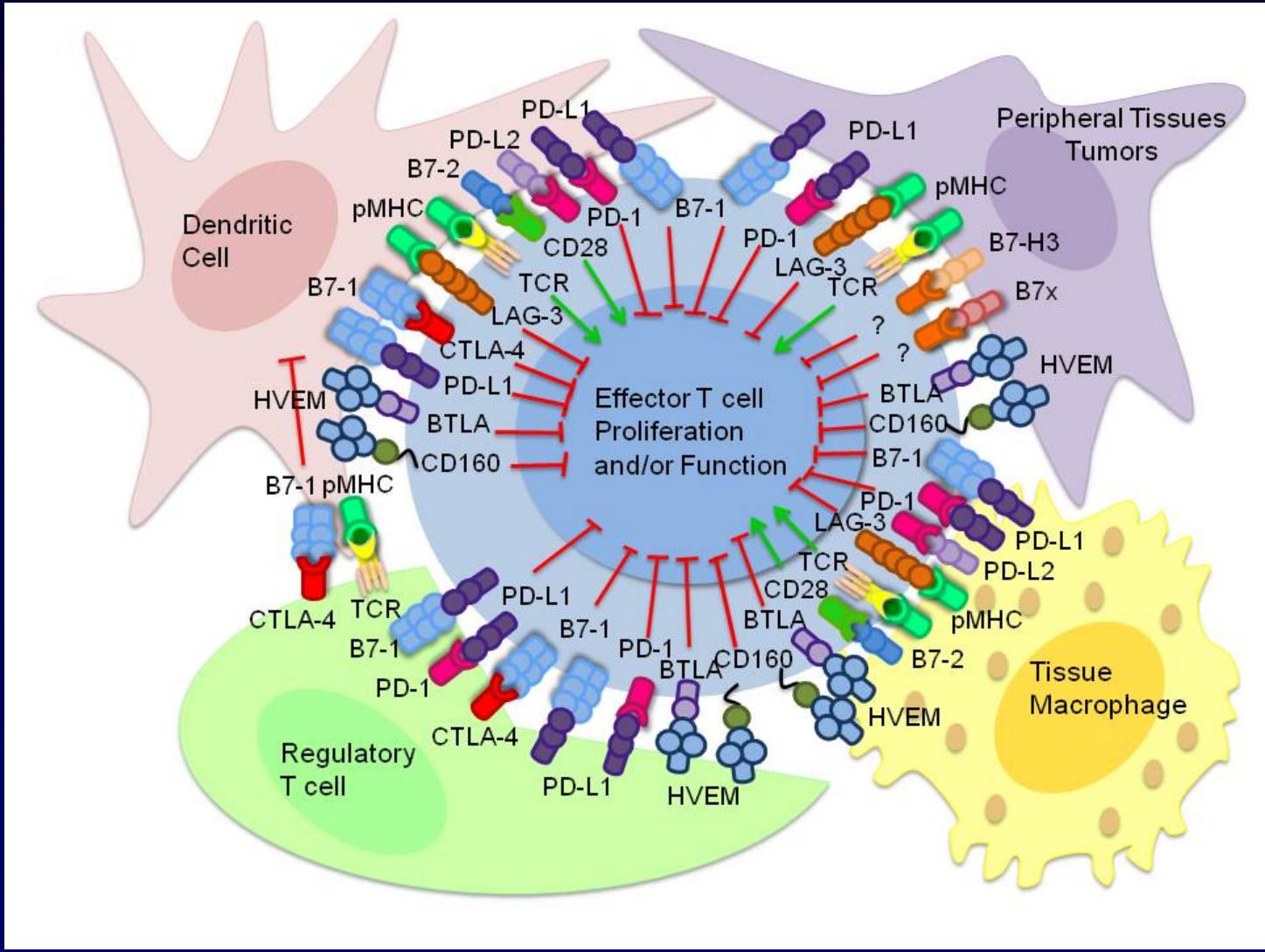


Image from J Allison

Intricate Role of PD-1 Signaling With Different Cell Types

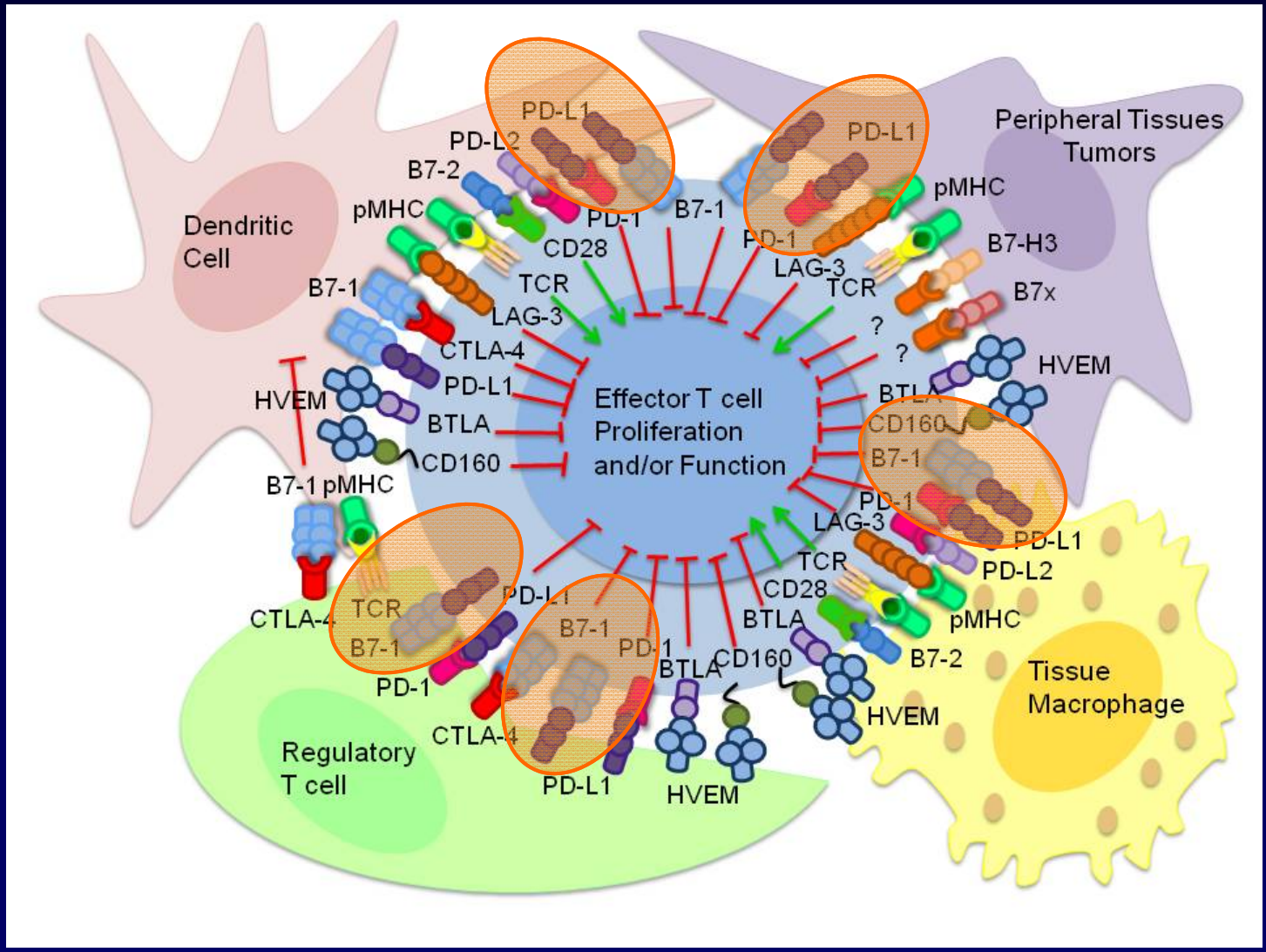


Image from J Allison

PD-L1 Analysis: Differences in Evaluation and Interpretation

Agent	Assay	Analysis	Definition of positivity	PD-L1 expression
Nivolumab (anti-PD-1)	Dako automated IHC assay (28-8 rabbit Ab) Analytically validated	• Archival FFPE	• 1% and 5% cut-off among >100 evaluable tumor cells	• 56%: 1% cut-off • 49%: 5% cut-off
Pembrolizumab (anti-PD-1)	Dako automated IHC assay (22C3 mouse Ab)	• Archival FFPE	• Tumor 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)	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)	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

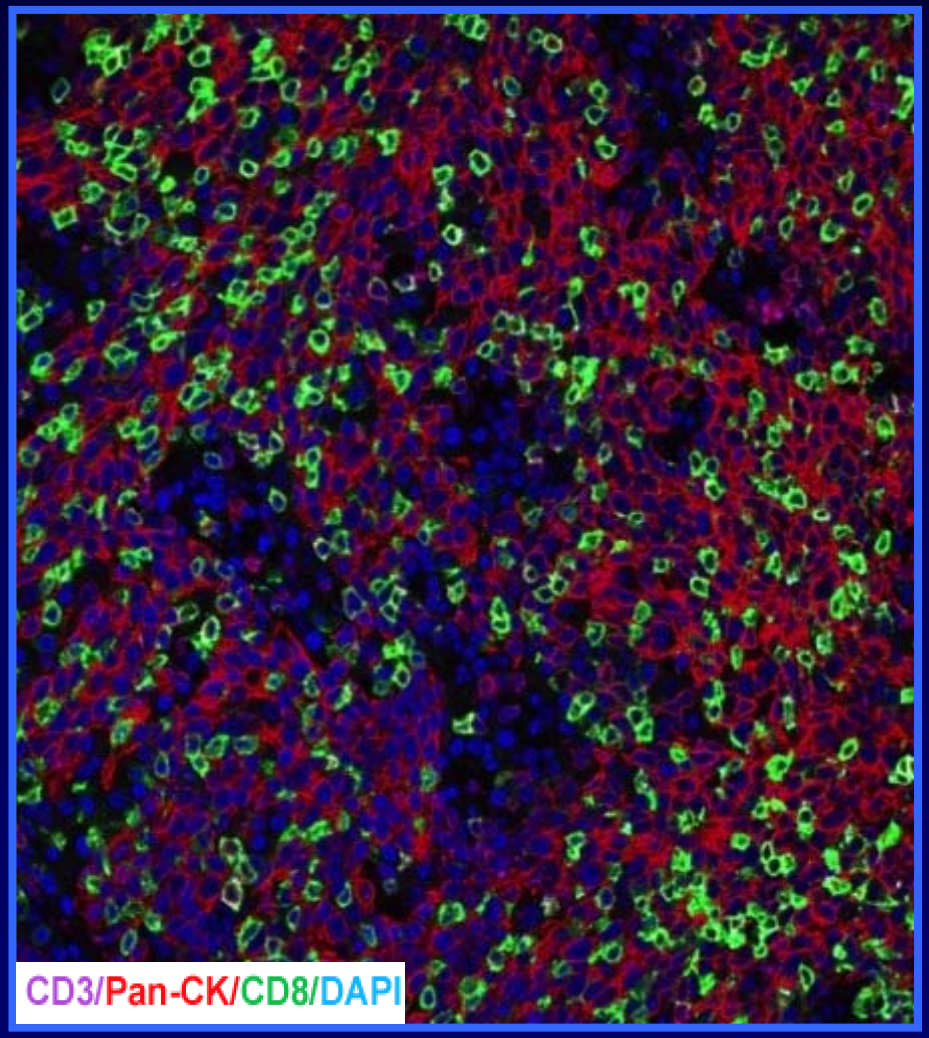
PD-L1 as a Biomarker in NSCLC

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

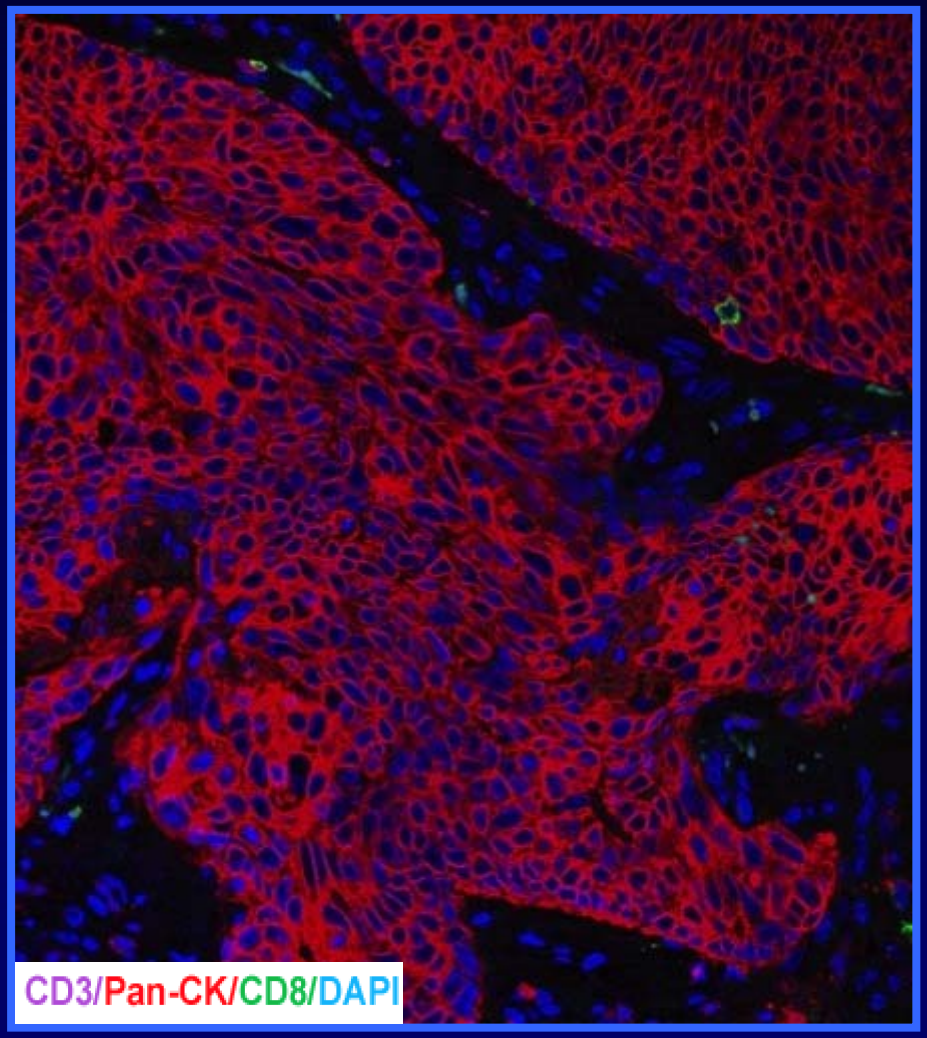
Drug/ sponsor	Nivolumab BMS	Pembrolizumab MSD (Merck)		MPDL3280A Genentech			MEDI4736 MedImmune		
PD-L1 +	N=10	N=38	N=33	N=45	N=177	N=41	N=26	N=13	N=6	N=13
ORR in PD-L1 -	0% N=7	17% N=30	14% N=35	???	9-13% N=40	11% N=88	20% N=20	18% N=33	18% N=40	5% N=19

Tumor Infiltrating Lymphocytes as a Biomarker? The HNSCC Example

Diffuse infiltration with CD8+ TILs in HNSCC



Absence of TILs in HNSCC



Seiwert TY, et al. *J Clin Oncol.* 2014;32(Suppl): Abstract 6011.

Conclusions

Clear evidence of anti PD1/PD-L1 activity

- Optimal dose?
- Treatment sequence?
- Combination strategy
  - Chemotherapy
  - Other checkpoint inhibitor
  - Targeted therapy (TKI)
- Selection by PD-L1 expression likely enhances response rate but activity seen in PD-L1 neg
- Pharmacodynamic biomarkers of activity? (circulating CD8+Ki-67+ T cells and/or plasma proteins [eg, IL-18])

Thanks for Your Attention