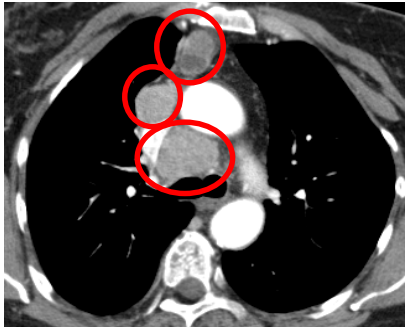


# **Combination Immunotherapy for Lung Cancer**

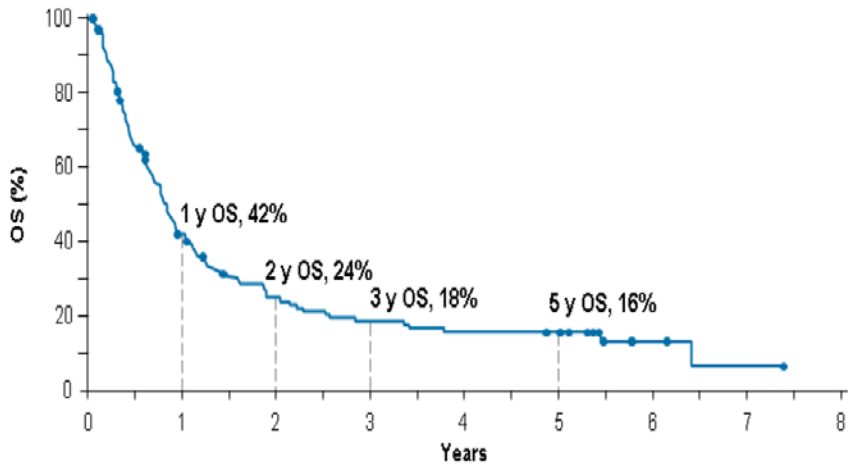
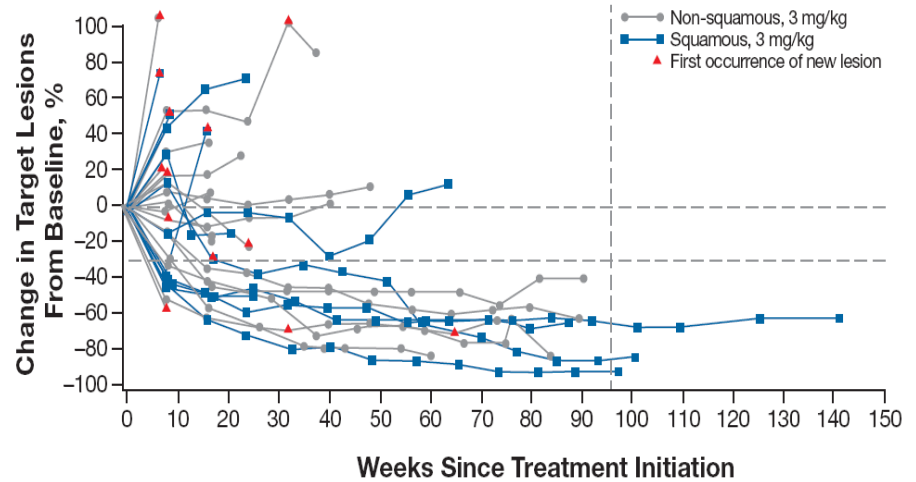
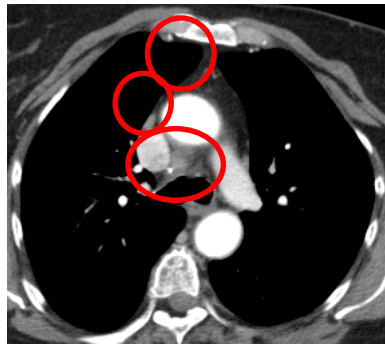
**Scott Antonia  
Moffitt Cancer Center**

# Anti-PD1/PD-L1 Responses in NSCLC

**BEFORE**

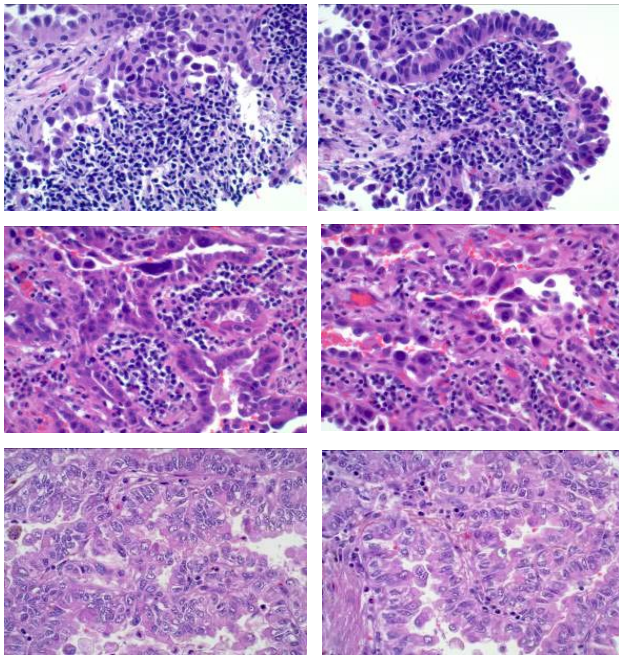


**AFTER**



- Pembrolizumab
- Nivolumab
- Atezolizumab

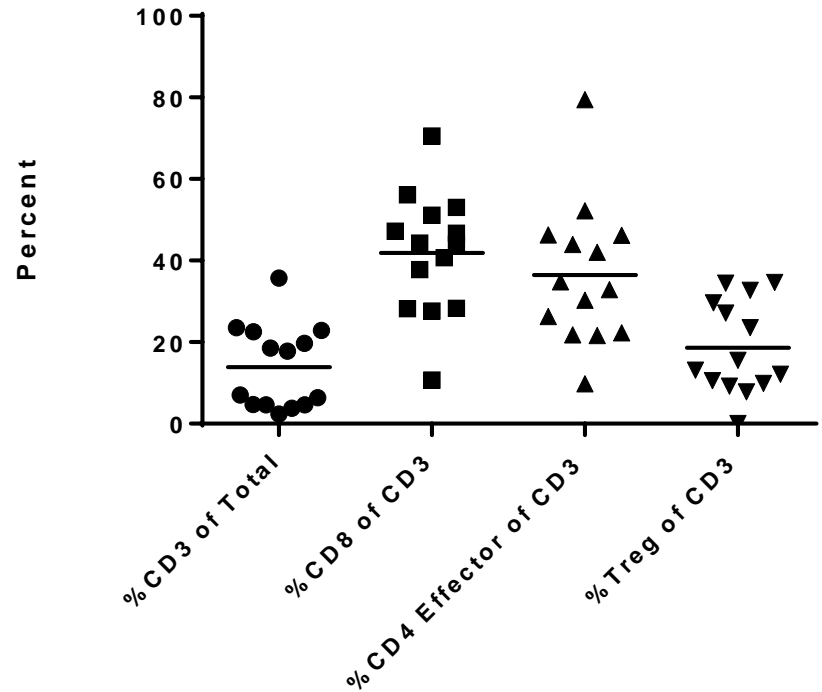
# Insufficient number of T cells present within many NSCLC tumors



High TIL

Moderate TIL

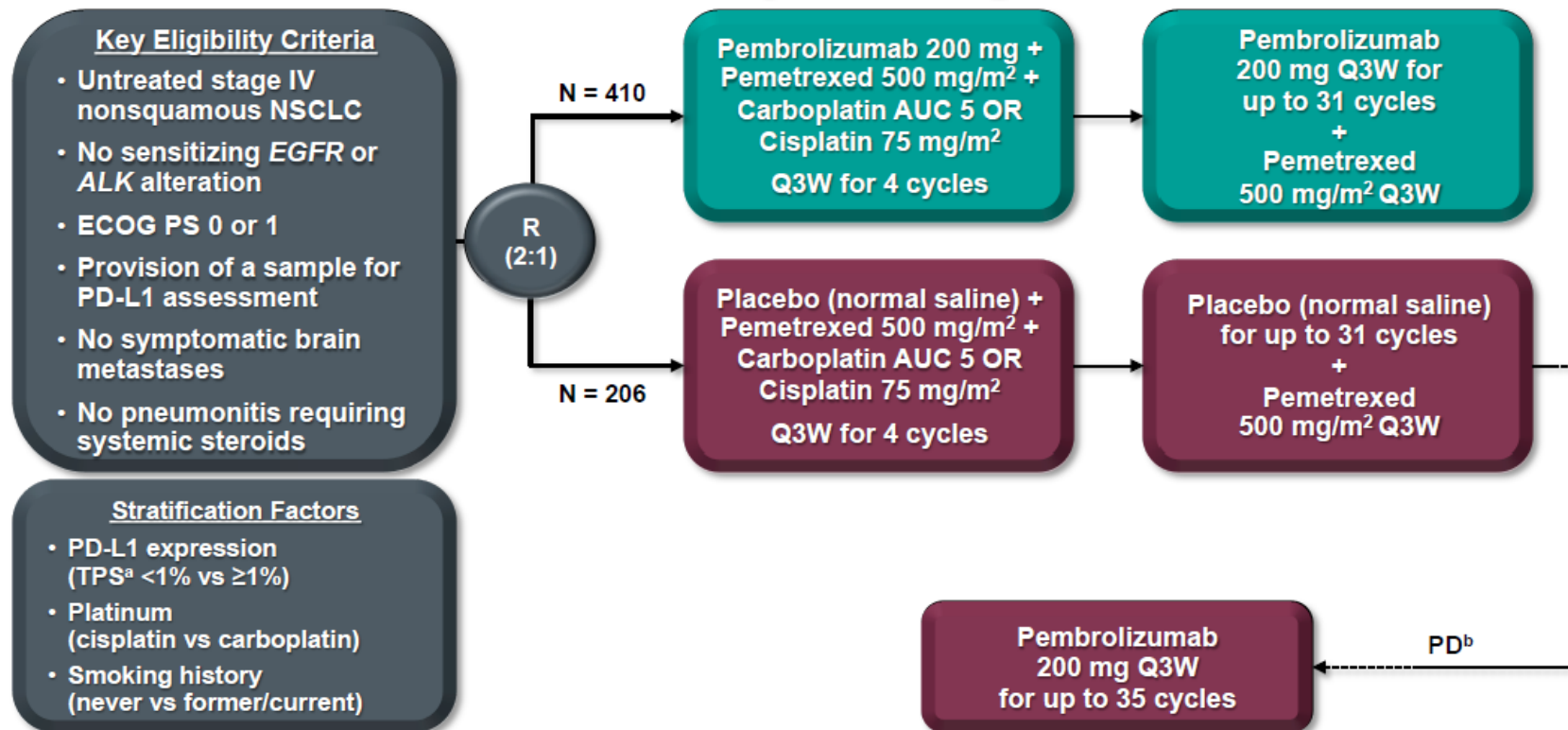
Low TIL



# Strategies to increase the number of T cells generated within the lymphoid compartment.

1. Chemotherapy
2. Anti-CTLA.4
3. Vaccines
4. Radiation
5. DC activation: CD40, TLR agonists
6. T cell stimulatory molecule agonists: GITR, OX40, 4-1BB
7. ACT with CAR or TCR transgenic T cells
8. ACT with TILs
9. IL2

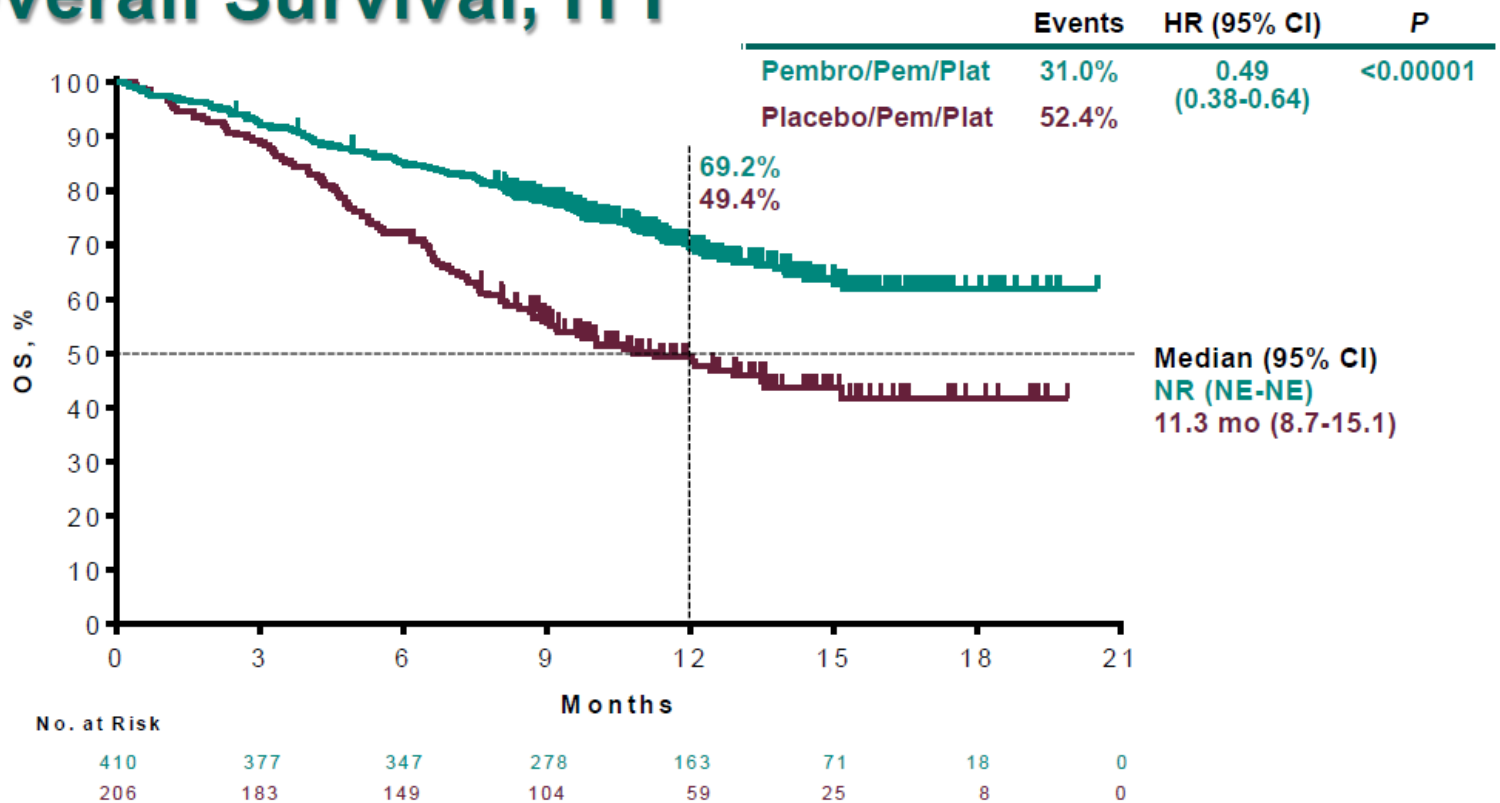
# KEYNOTE-189 Study Design (NCT02578680)



<sup>a</sup>Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. <sup>b</sup>Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

# Keynote-189

## Overall Survival, ITT



Data cutoff date: Nov 8, 2017.

# **Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicenter, Phase 1b study**

S. Antonia, S.B. Goldberg, A. Balmanoukian, J.E. Chaft, R.E. Sanborn, A. Gupta, R. Narwal, K. Steele, Y. Gu, J.J. Karakunnel, N.A. Rizvi

*Lancet Oncol* 2016

# Treme 3 & 10 mg/kg more toxic than 1 mg/kg

n (%)	D10–20 q4/2w T1 n=59	D10–20 q4/2w T3 n=34	D15 q4w T10 n=9	All cohorts N=102
Related AE	42 (71)	32 (94)	8 (89)	82 (80)
Related Grade 3/4 AE	17 (29)	19 (56)	7 (78)	43 (42)
Related death	2 (3)*	1 (3) <sup>†</sup>	0 (0)	3 (3)
Related SAE	12 (20)	18 (53)	7 (78)	37 (36)
Related AE leading to D/C	9 (15)	15 (44)	5 (56)	29 (28)



# CheckMate 012: Safety and Efficacy of First-line Nivolumab and Ipilimumab in Advanced NSCLC

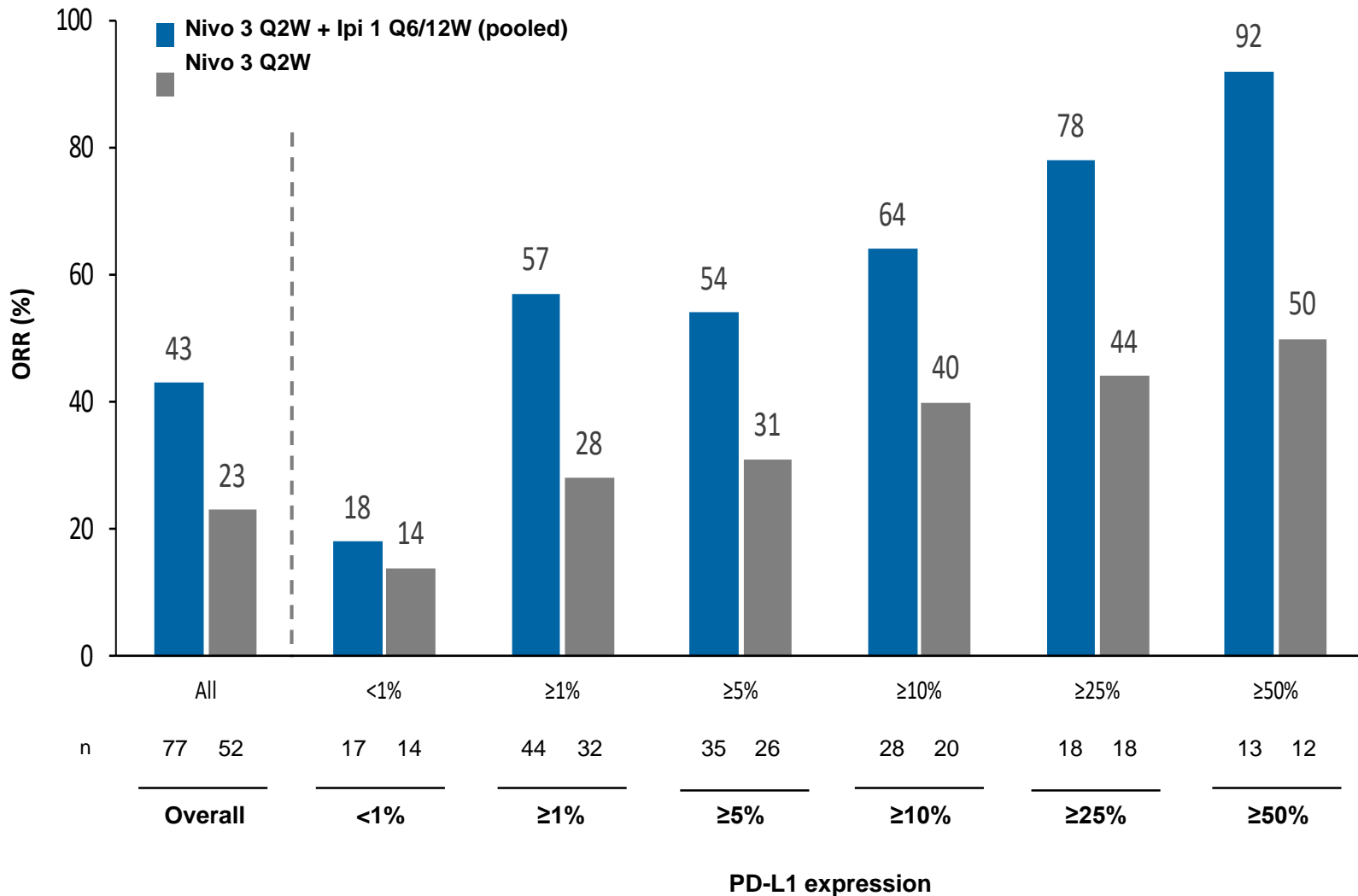
Matthew D. Hellmann, Scott N. Gettinger, Jonathan Goldman, Julie Brahmer, Hossein Borghaei, Laura Q. Chow, Neal E. Ready, David E. Gerber, Rosalyn Juergens, Frances A. Shepherd, Scott A. Laurie, Tina Young, William J. Geese, Shruti Agrawal, Xuemei Li, Scott J. Antonia

# Nivolumab Plus Ipilimumab in First-line NSCLC: Safety Summary

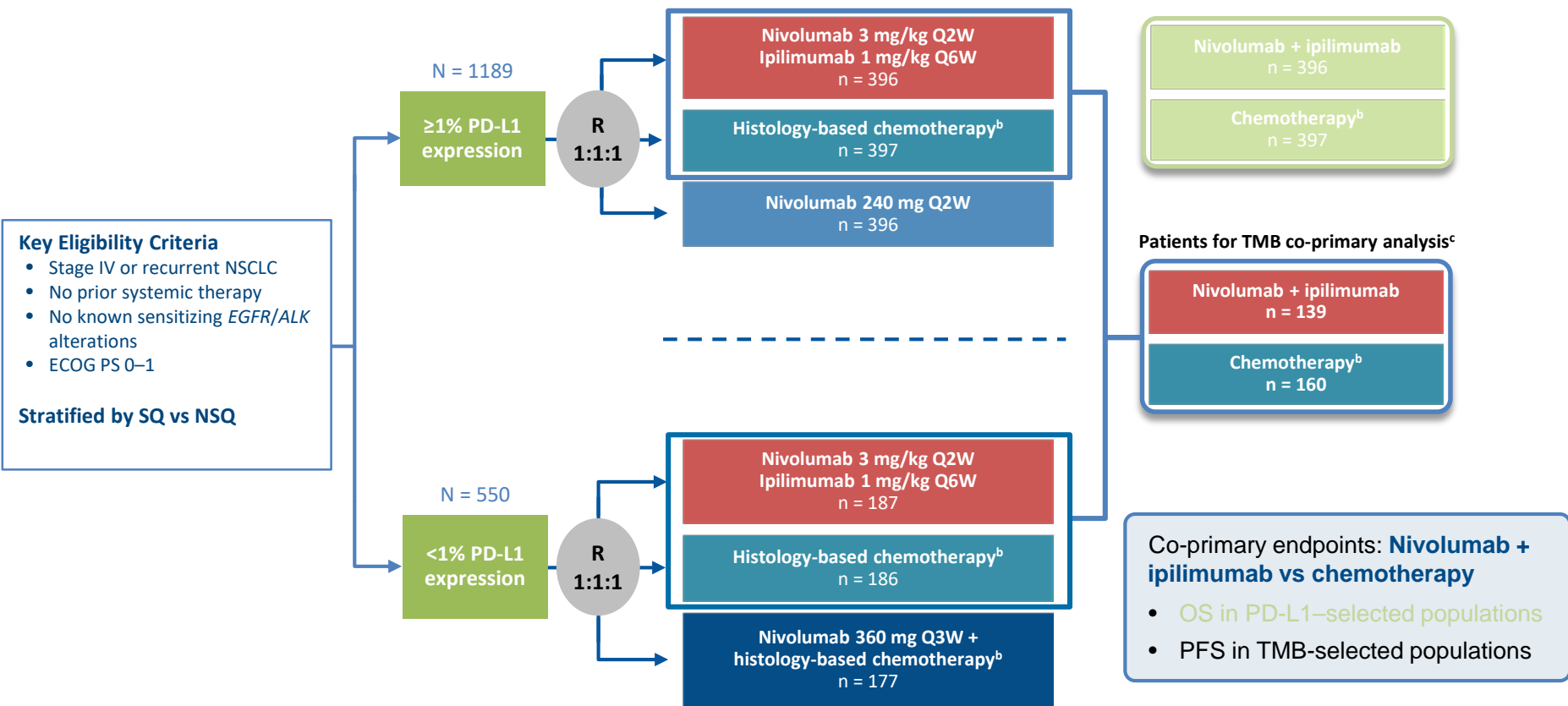
	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)		Nivo 3 Q2W + Ipi 1 Q6W (n = 39)		Nivo 3 Q2W (n = 52)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
<b>Treatment-related AEs, %</b>	82	37	72	33	71	19
<b>Treatment-related AEs leading to discontinuation, %</b>	11	5	13	8	10	10

- There were no treatment-related deaths
- Treatment-related grade 3–4 AEs led to discontinuation at a third of the rate seen with older combination arms using higher or more frequent doses of ipilimumab

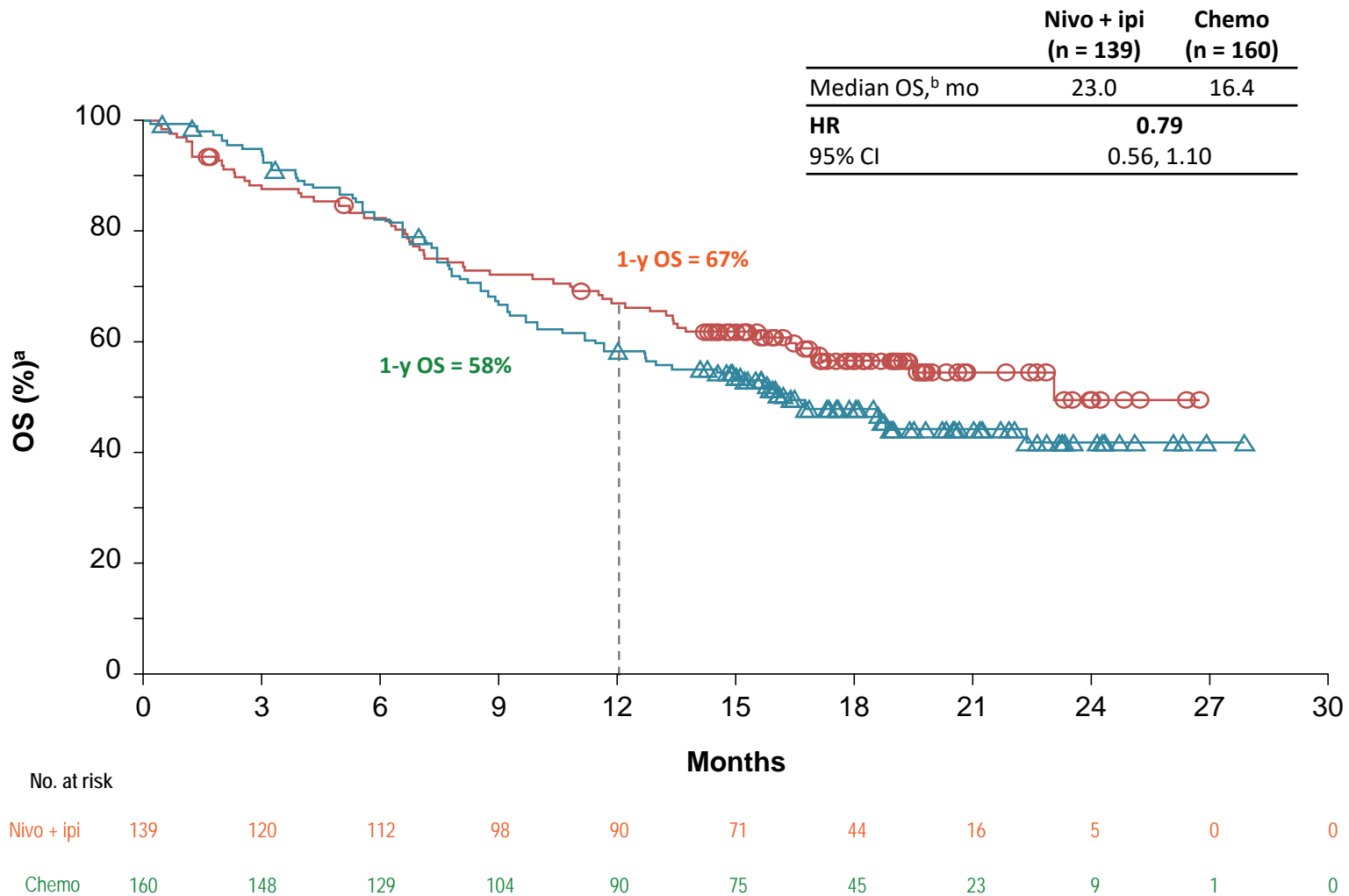
# Efficacy Across PD-L1 Expression Levels



# Checkmate-227



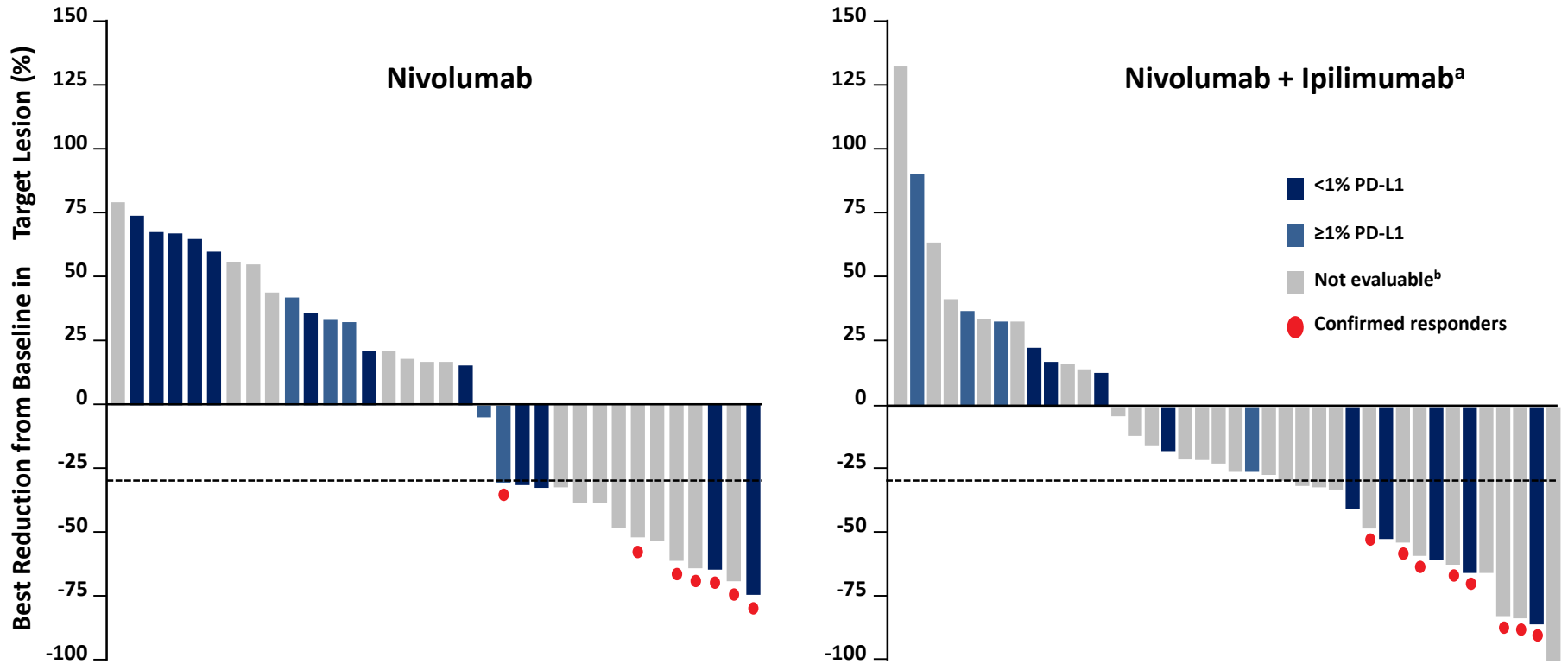
# Checkmate-227



# **Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial**

Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, Jäger D, Pietanza MC, Le DT, de Braud F, Morse MA, Ascierto PA, Horn L, Amin A, Pillai RN, Evans J, Chau I, Bono P, Atmaca A, Sharma P, Harbison CT, Lin CS, Christensen O, Calvo E

# Tumor Responses in SCLC



Evaluable samples (40 of 90)	PD-L1 expression level, n (%)	
	<1%	≥1%
Nivolumab (n = 22)	15 (68)	7 (32)
Nivolumab + Ipilimumab (n = 18)	12 (67)	6 (33)

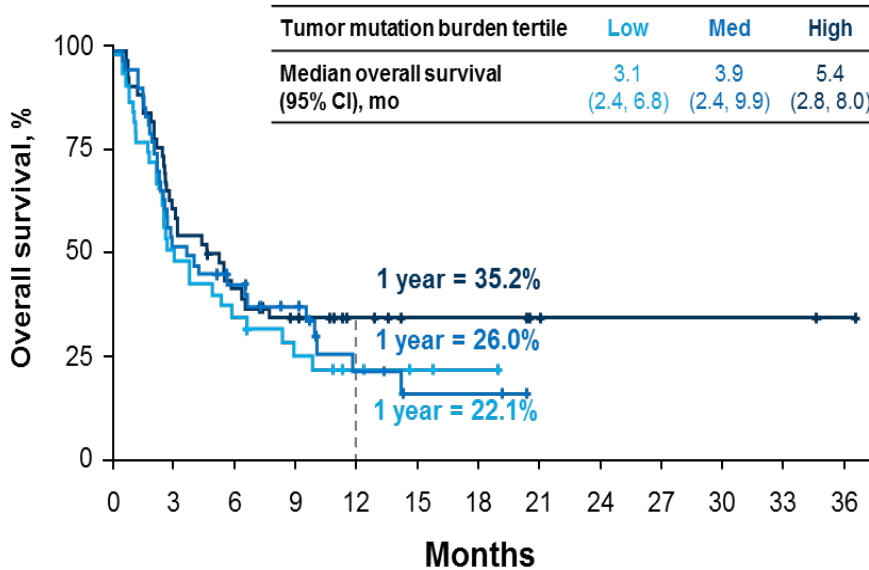
# Impact of Tumor Mutation Burden on the Efficacy of Nivolumab or Nivolumab Plus Ipilimumab in Small Cell Lung Cancer: An Exploratory Analysis of CheckMate 032

Matthew D. Hellmann, Margaret K. Callahan, Mark M. Awad, Emiliano Calvo, Paolo A. Ascierto, Akin Atmaca, Naiyer A. Rizvi, Fred R. Hirsch, Giovanni Selvaggi, Joseph D. Szustakowski, Ariella Sasson, Ryan Golhar, Patrik Vitazka, Han Chang, William J. Geese, Scott J. Antonia



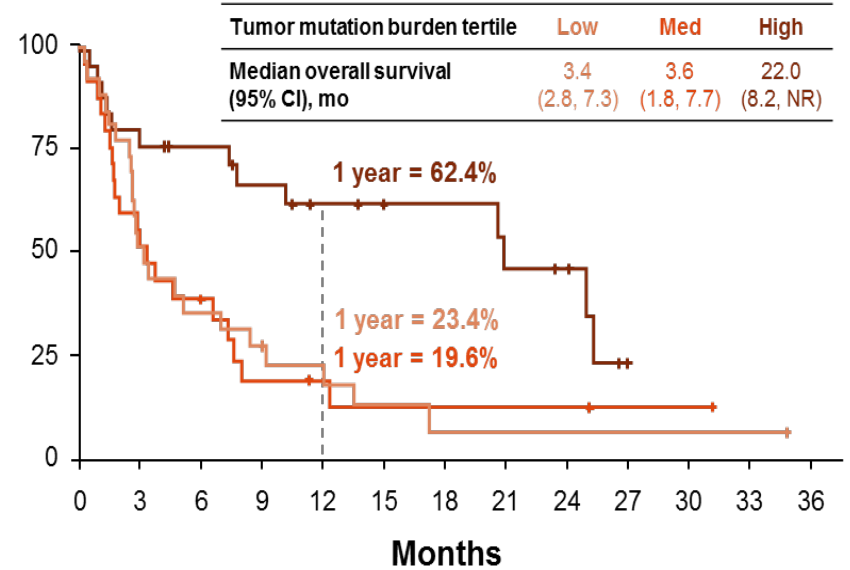
# Overall Survival

## Nivolumab



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Low	42	19	13	9	4	3	1	0	0	0	0	0	0
Medium	44	23	17	12	6	2	2	1	0	0	0	0	0
High	47	29	20	14	8	5	5	5	2	2	2	2	2

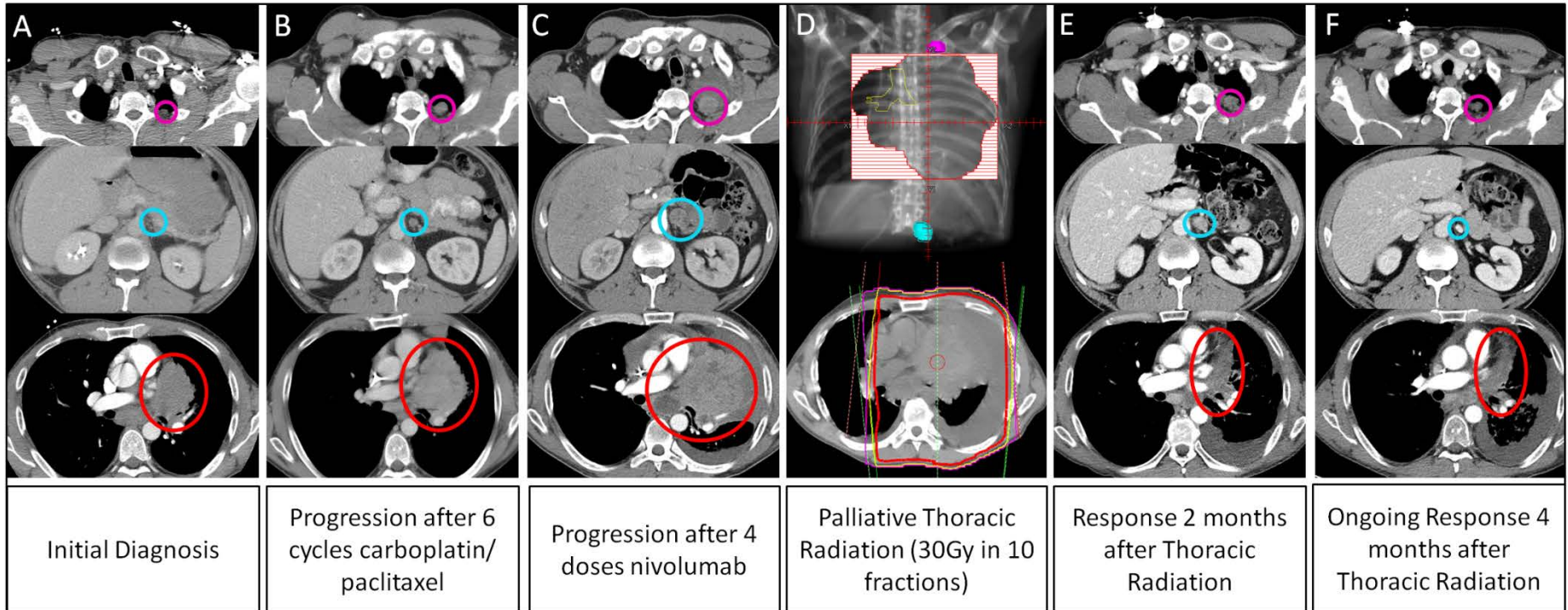
## Nivolumab + ipilimumab



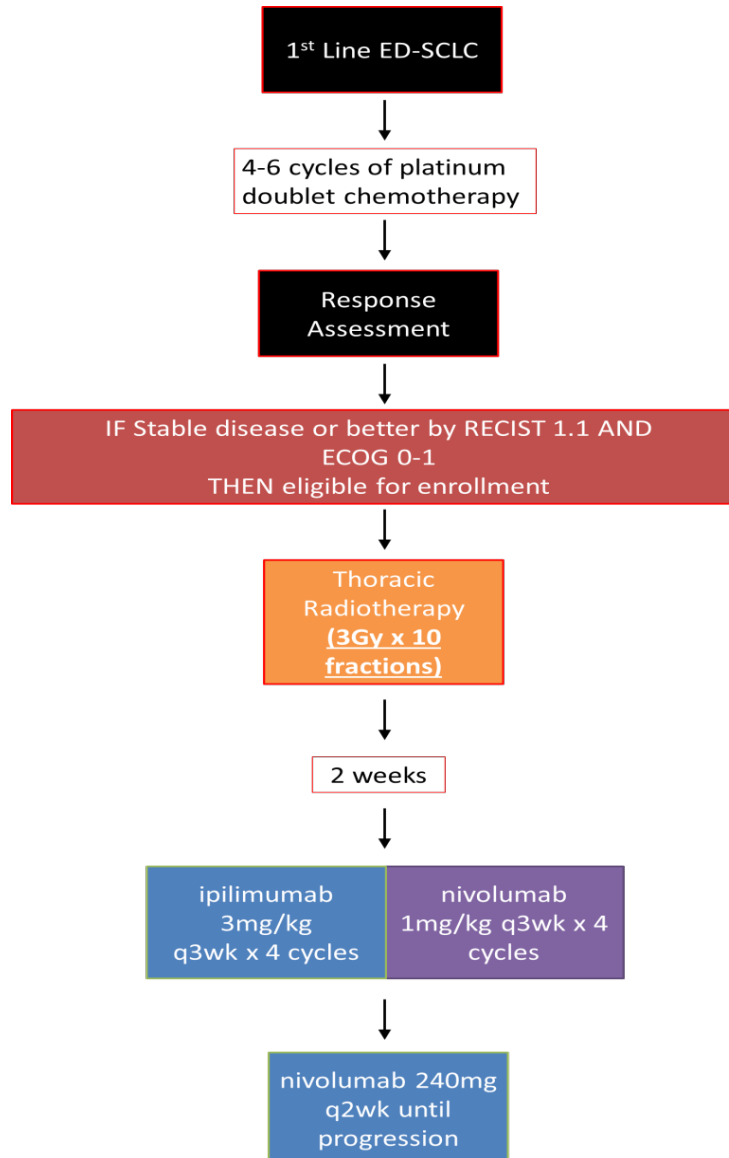
No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Low	27	15	9	7	5	2	2	1	1	1	1	1	1
Medium	25	15	9	4	3	2	2	2	2	1	1	0	0
High	26	20	17	14	10	9	8	8	6	2	0	0	0

# Thoracic Radiation to Augment Immune Responses

## Abscopal Effect



# Thoracic Radiation to Augment Immune Responses



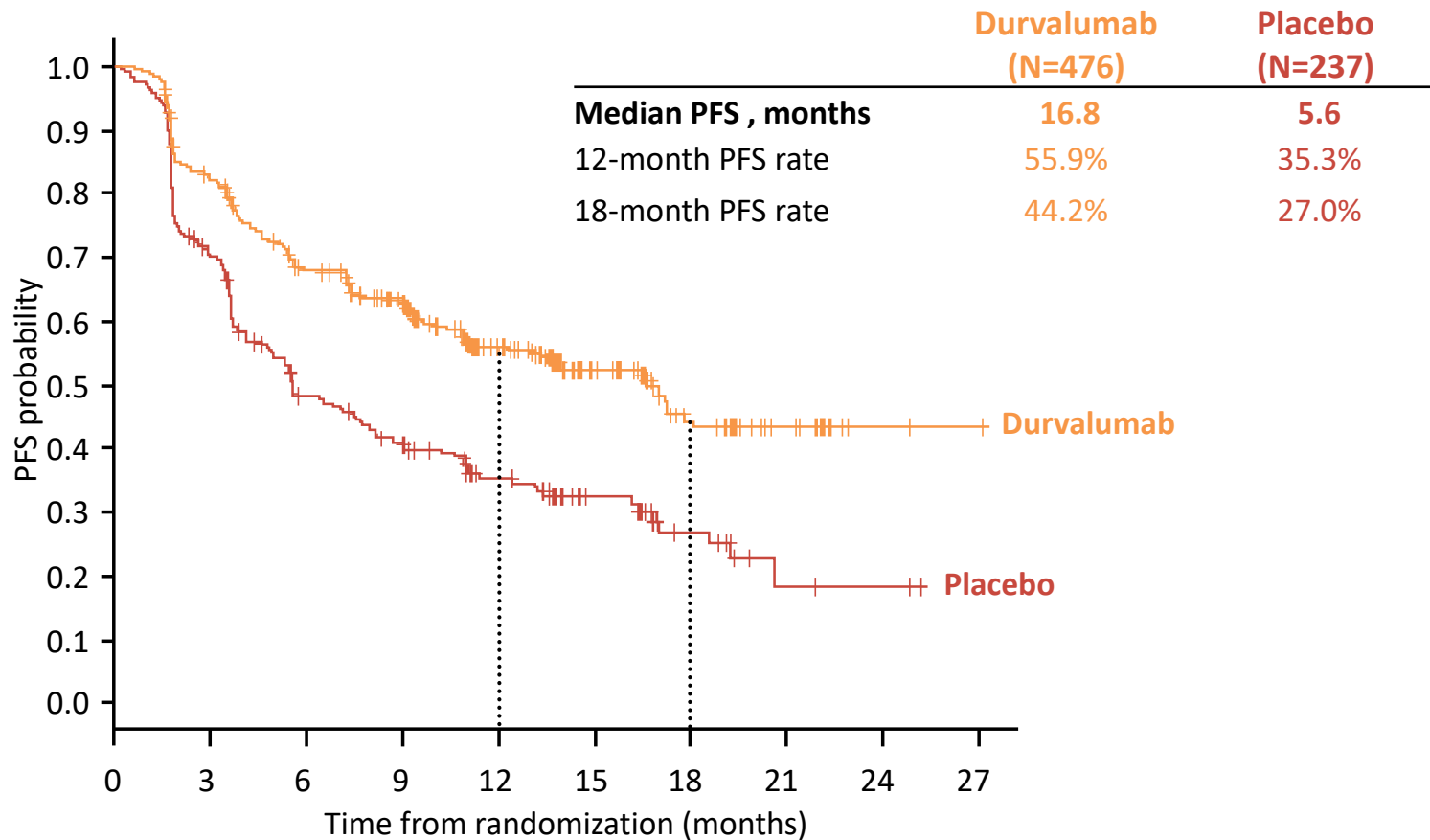
# **Durvalumab After Chemoradiotherapy in Stage III Non-Small Cell Lung Cancer**

Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim YC, Karapetis CS, Hirt S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M.

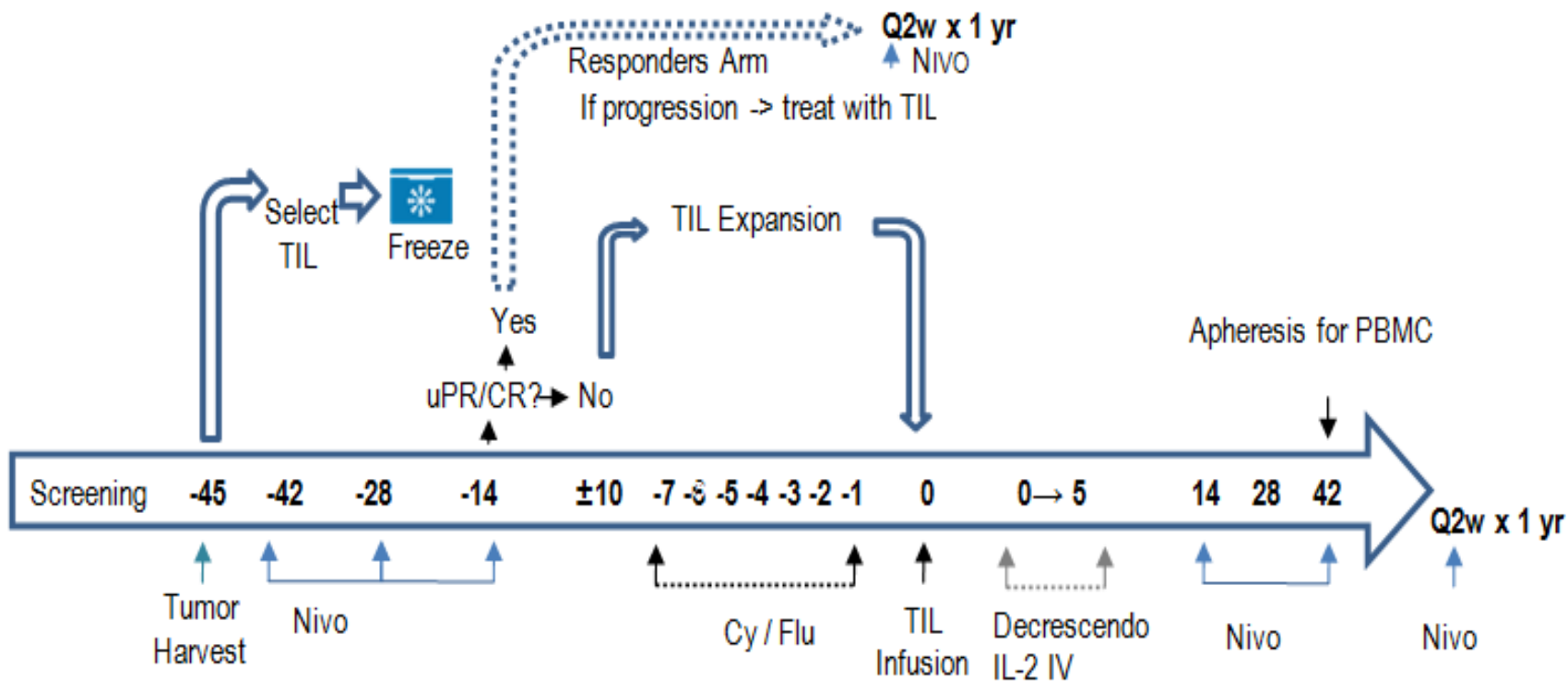
N Engl J Med. 2017

# PFS by BICR (Primary Endpoint; ITT)

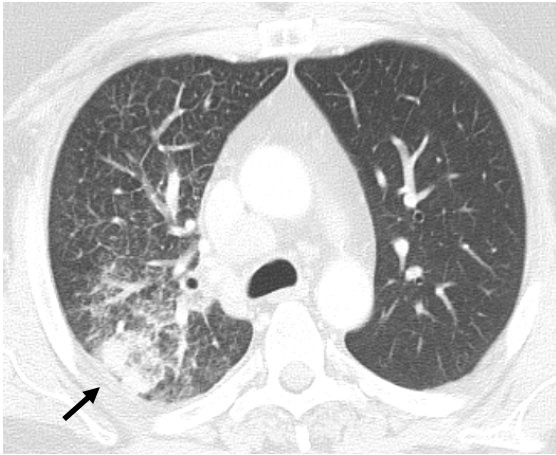
Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)



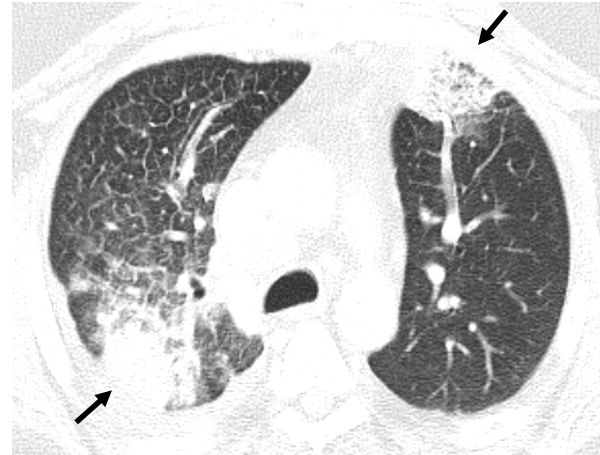
# Ex vivo expanded TIL ACT with low dose IL2 and nivolumab



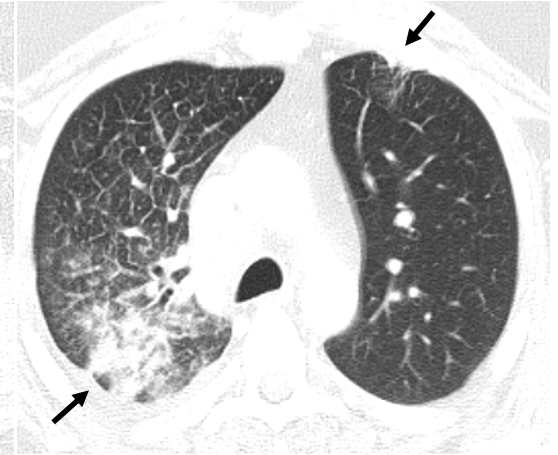
# Patient #1



**Day -63**  
**Pre nivolumab**



**Day -8**  
**Pre TIL**

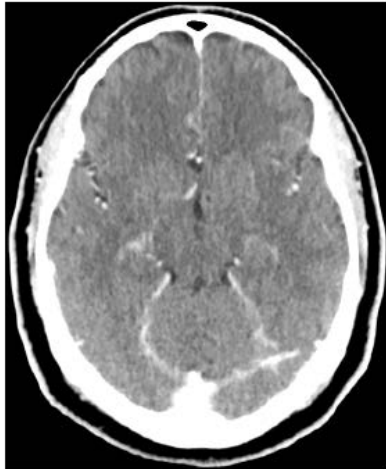
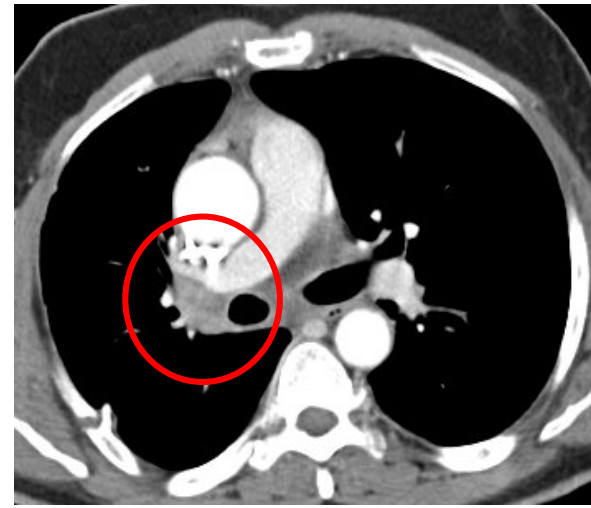
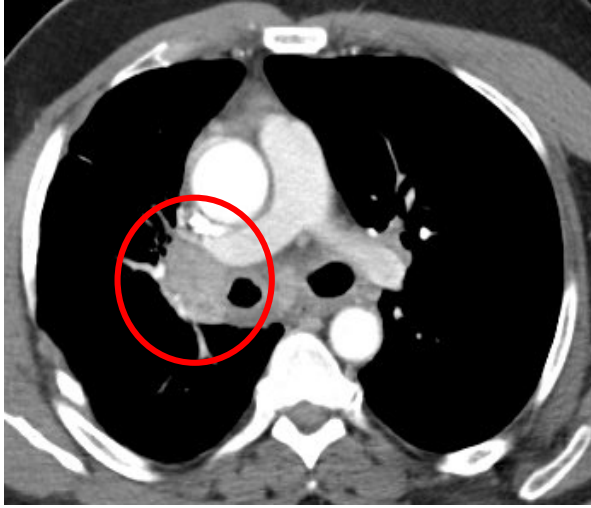


**Day +28**  
**Post TIL**

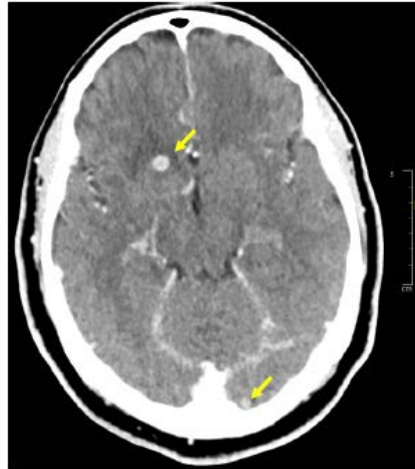
- Increasing lymphangitic pulmonary metastases during nivolumab
- **13% decrease** in target lesions 1 mo after ACT compared to Pre TIL Day -8



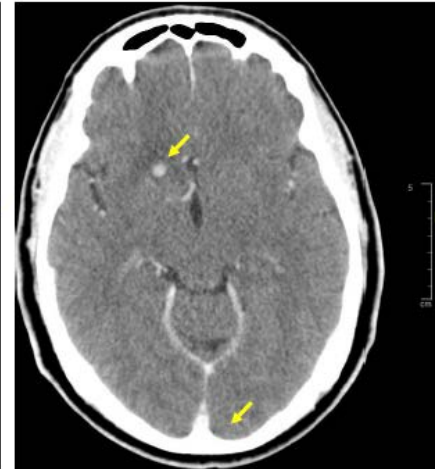
# Patient #2



Day -63  
Pre nivolumab

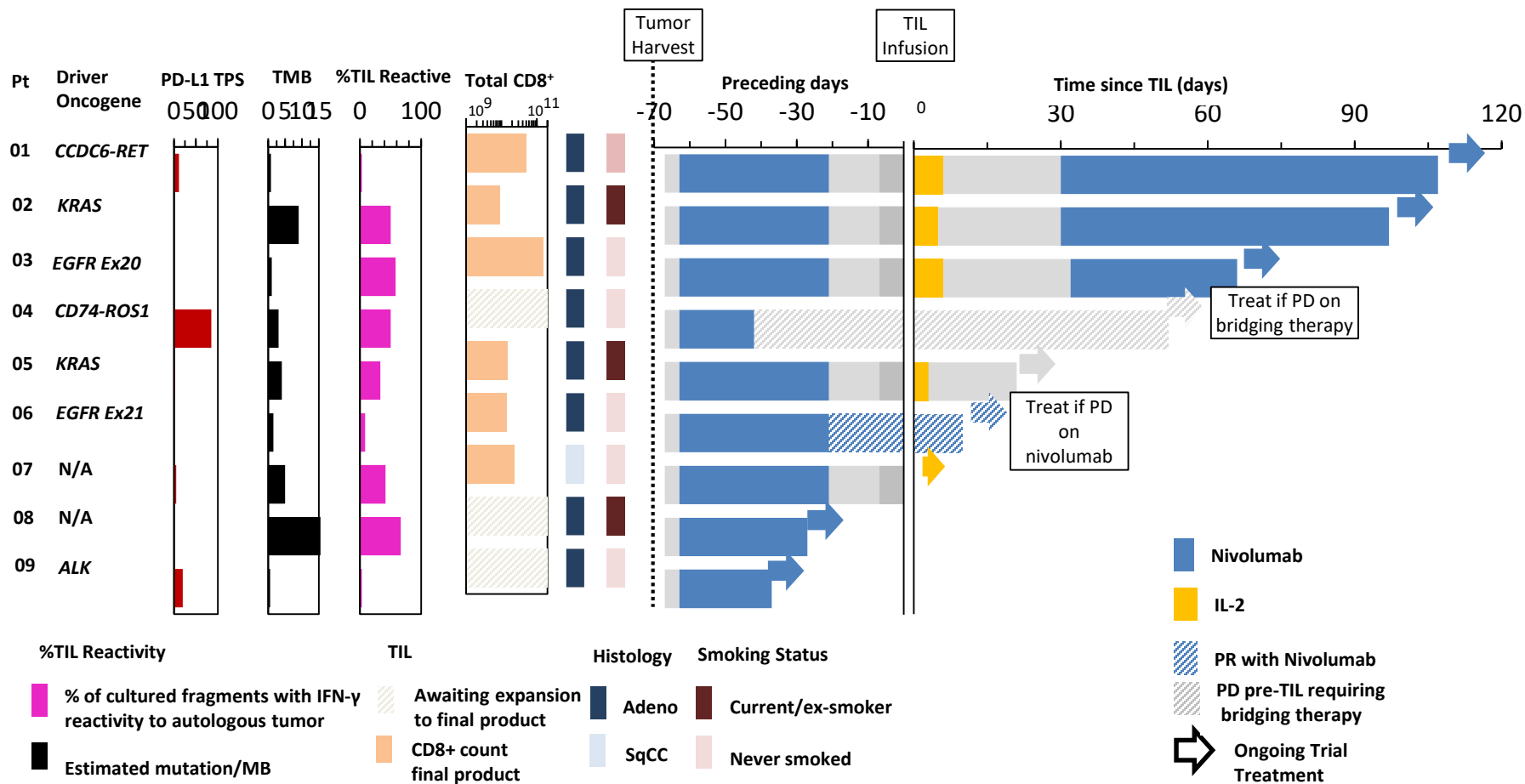


Day -8  
Pre TIL

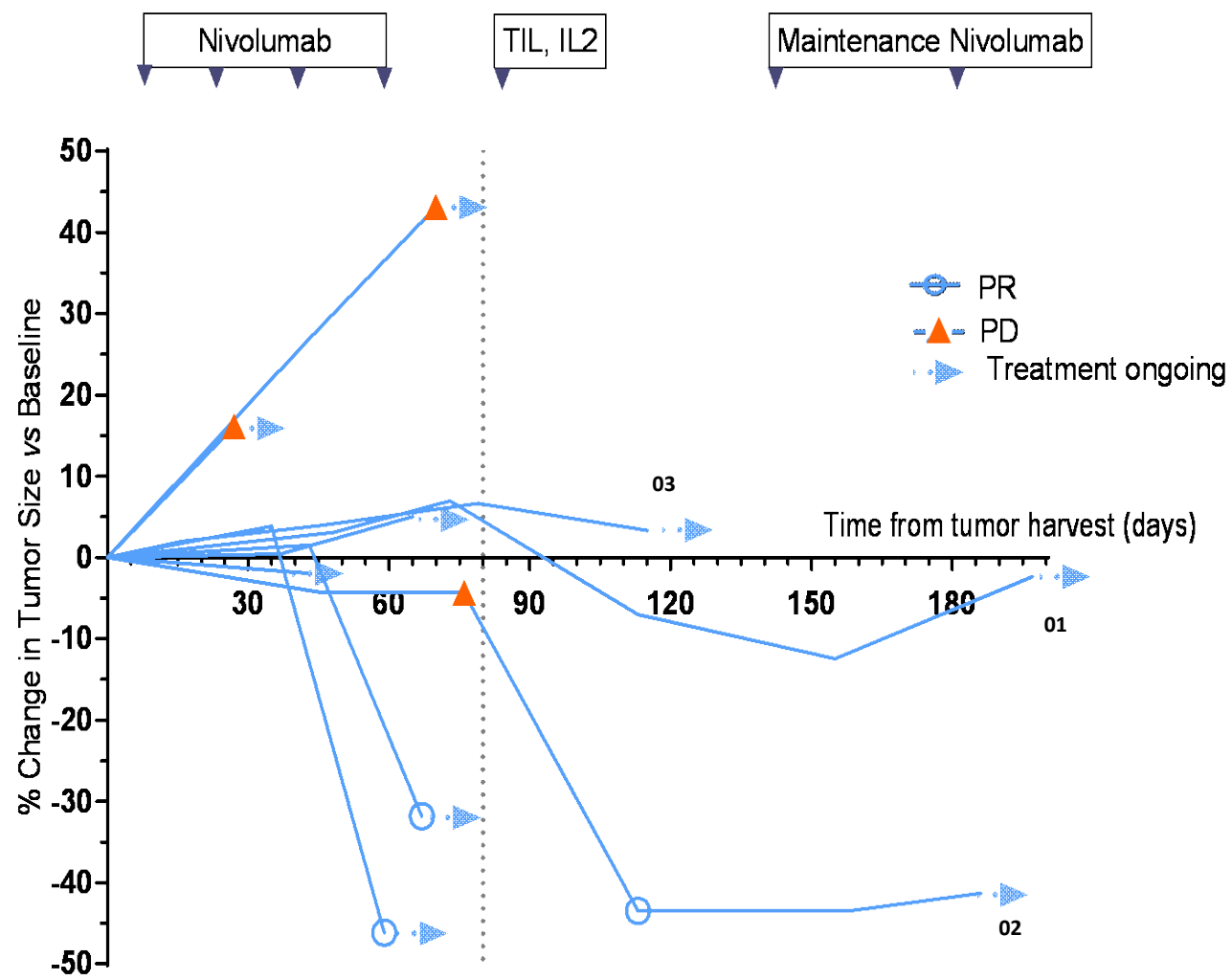


Day +28  
Post TIL





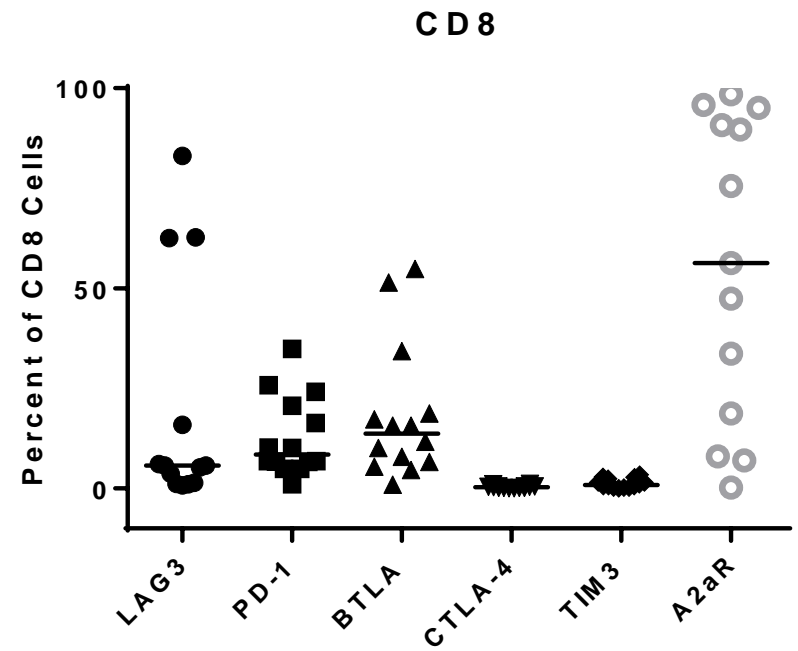
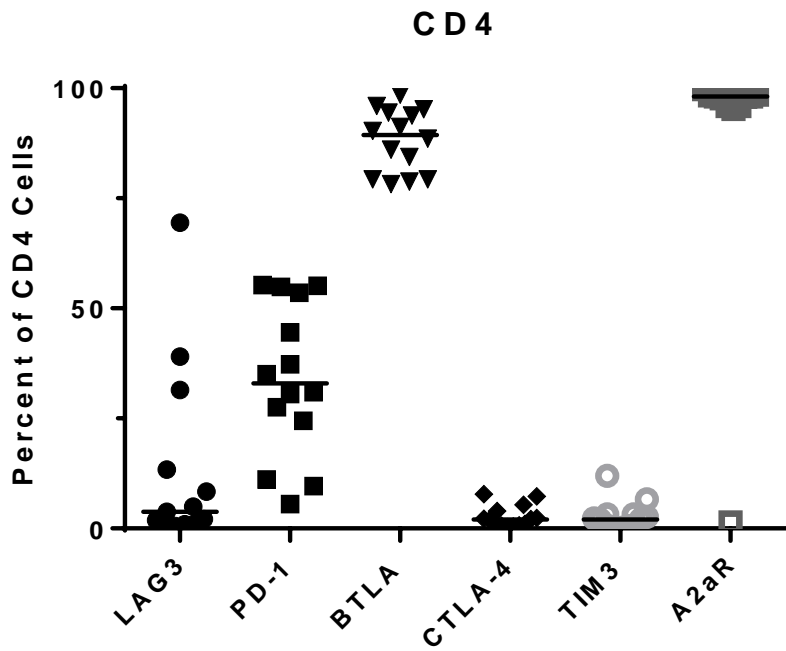
Tumor Size  
( $n = 9$ )



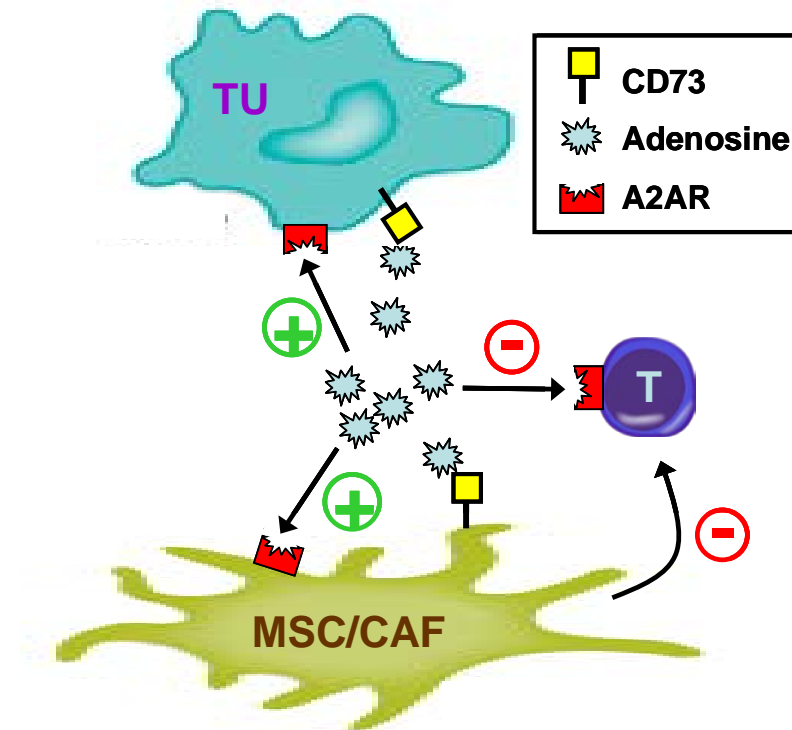
# T cells are inhibited in the tumor microenvironment

- **Surface membrane proteins- checkpoints**
  - PD1, CTLA4, LAG3, TIM3, BTLA, Adenosine A2AR
- **Soluble factors and metabolic alterations**
  - IL10, TGF $\beta$ , Adenosine, IDO, Arginase
- **Inhibitory cells**
  - Cancer Associated Fibroblasts, Regulatory T cells, Myeloid Derived Suppressor Cells, Tumor Associated Macrophages, Regulatory B cells

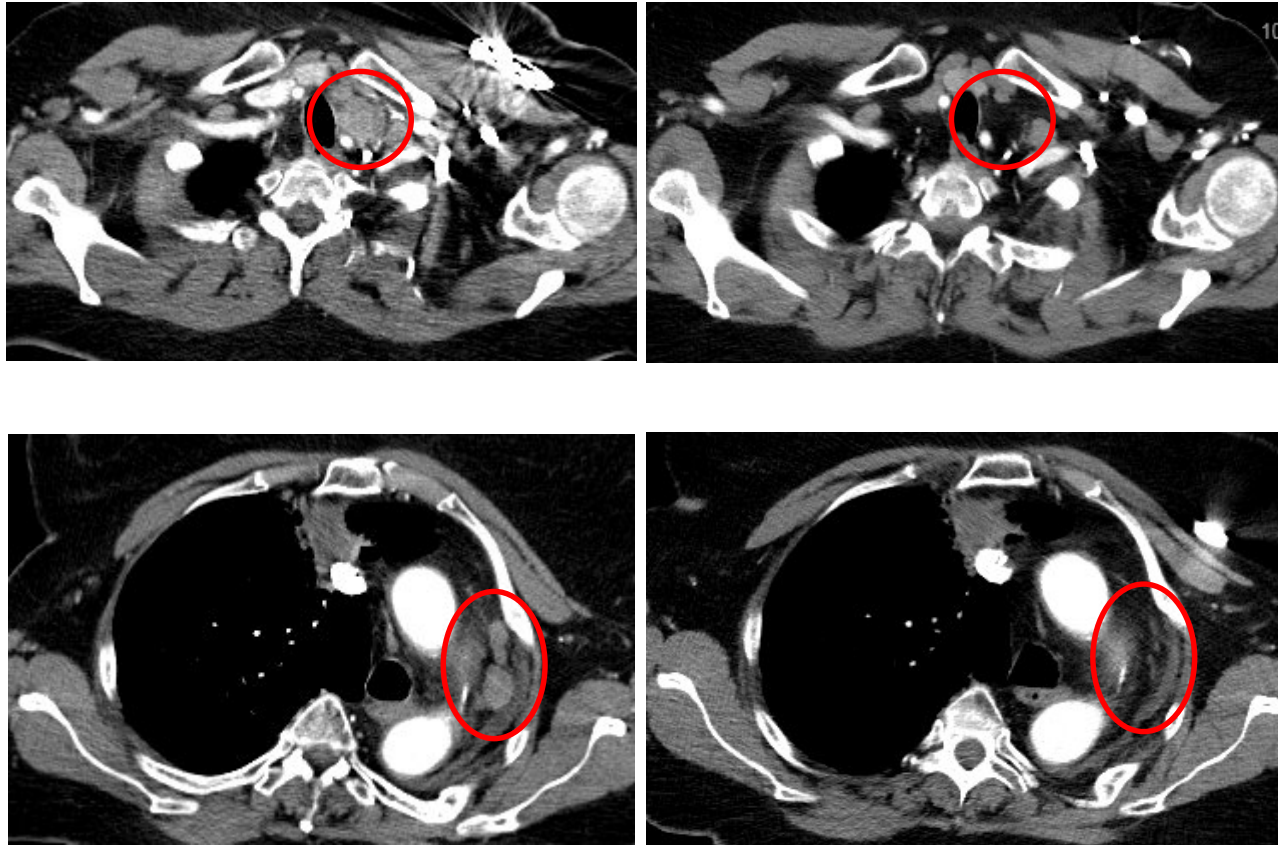
# Checkpoint Protein Expression of Fresh Lung TILs



# Adenosine in the Tumor Microenvironment



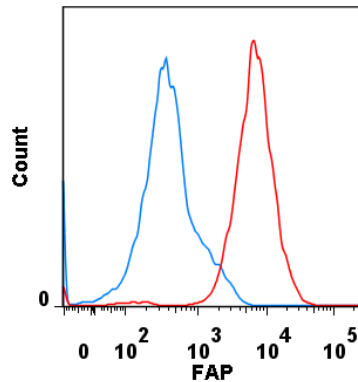
# Clinical Response to Adenosine A2AR Antagonist Monotherapy



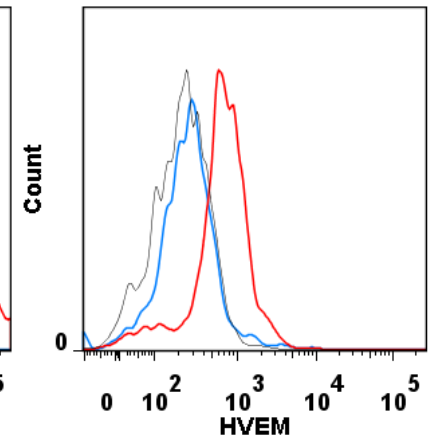
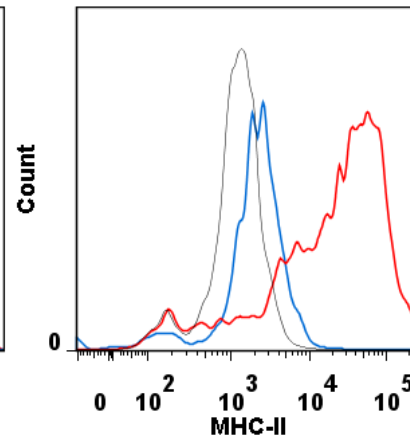
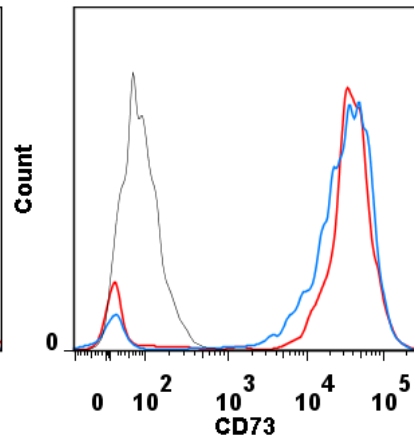
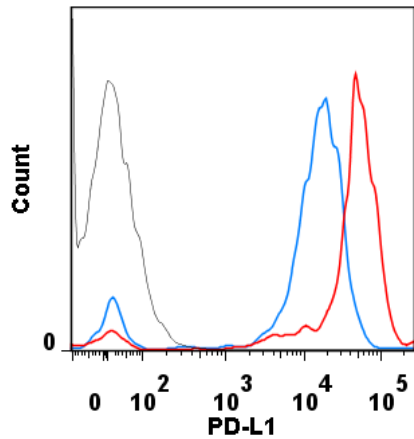
***Trial: PBF509 (A2AR antagonist) +/- PDR001 (anti-PD1)***

# Cancer Associated Fibroblasts

## Immunosuppressive in the TME



$\alpha$ -SMA



Unstained



Untreated

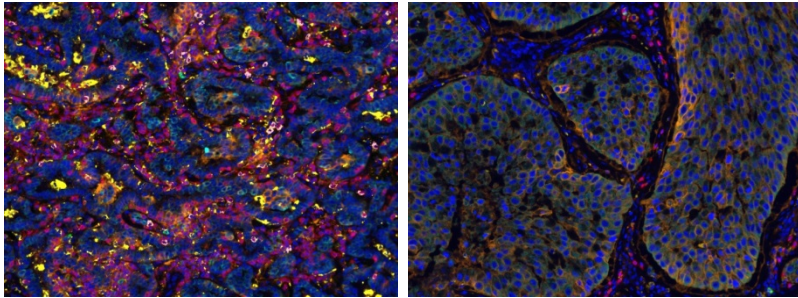


IFN- $\gamma$

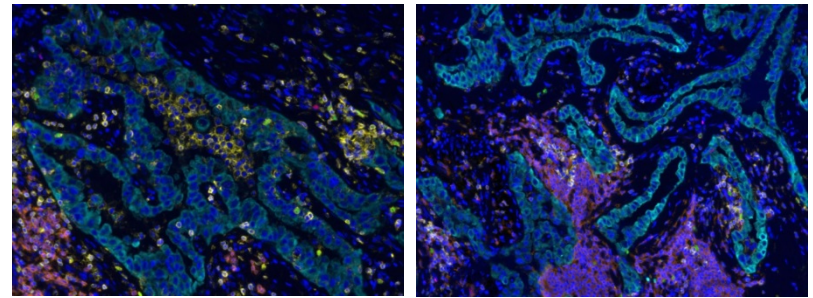
***Trial: nintedanib, ipilimumab, nivolumab; first-line NSCLC***



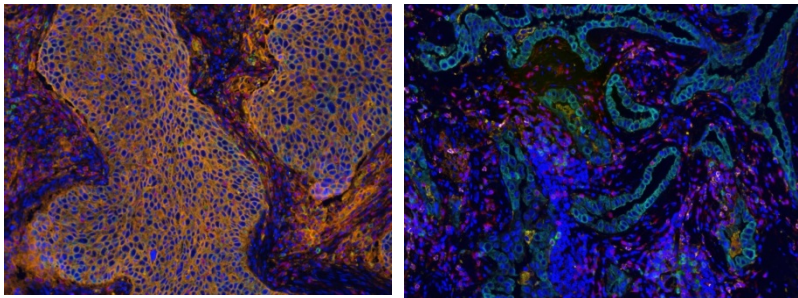
# The Challenge



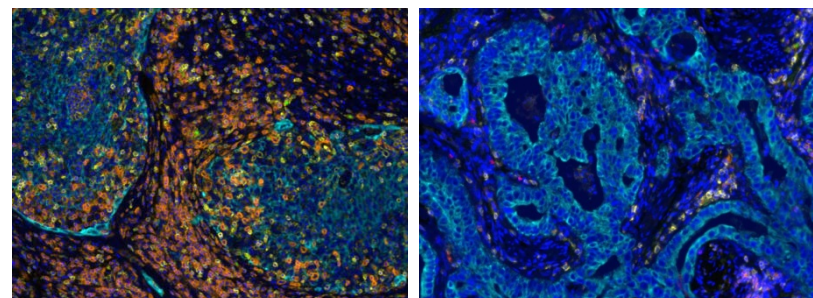
● TAMs



● CD45RO



● PD-L1



● CD20

- There are a myriad of ways tumors evade rejection by the immune system.
- There is considerable heterogeneity across patients with respect to the relevance of each of these.
- Appropriate biomarkers need to be employed to know which immunosuppressive mechanisms are operational in individual patients.



# Acknowledgements

- Melanie Mediavilla
- David Noyes
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- Jhanelle Gray
- Brad Perez
- Amod Sarnaik
- Tawee Tanvetyanon
- Charles Williams
- Eric Haura