Immunotherapy in NSCLC: state of the art

Sandip Pate, MD

Assistant Professor, UCSD

Cancer Immunotherapy Program

Experimental Therapeutics, Thoracic Oncology Units

Division of Hematology & Oncology and Center for Personalized Cancer Therapy

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Disclosures: Sandip Patel, MD

- Research Support: Amgen, Genentech, MedImmune, Pfizer, Xcovery, Lilly, Bristol-Myers Squibb, Incyte

- Honoraria/Consulting: Boehringer Ingelheim, Merck

- I will **not** be discussing off-label use in my presentation

Overview

- Biomarker development
  - PD-L1 IHC Landscape
- Summary of recent clinical trial data in NSCLC
- Adverse Event Management
- Case Discussion
- A path forward

Immunotherapy Biomarkers

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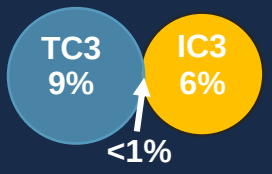
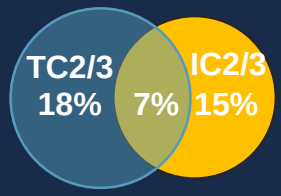
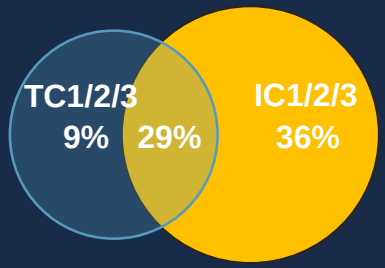
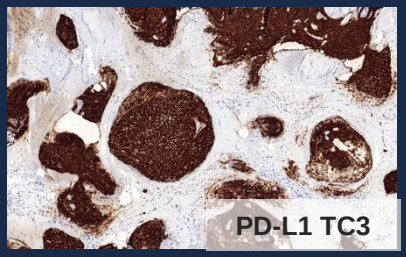
SP142 PD-L1 Expression Level in NSCLC

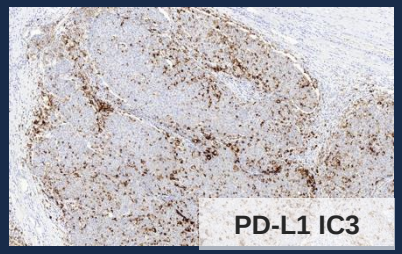


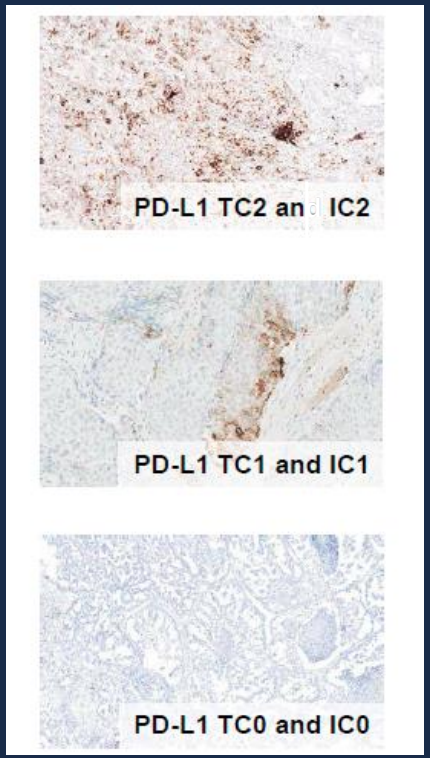




IC=immune cells; TC=tumor cells







- TC3 and IC3 represent distinct populations with <1% overlap in NSCLC
- Membranous expression is predictive
  - Tumor cell membrane
  - Immune cell membrane

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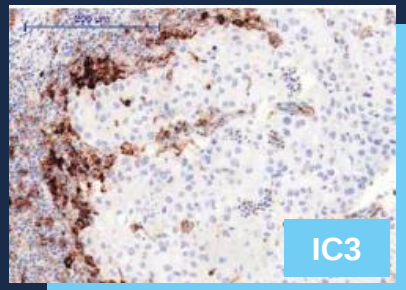
Schmid P, et al. Poster. ESMO. 2015 (abstr P269).

Characteristics for TC3 and IC3 NSCLC Tumors

Sclerotic
Desmoplastic
Associated with EMT
Regulated by methylation
Intrinsic PD-L1 regulation

PD-L1 TC3 tumors exhibit a desmoplastic and sclerotic TME with low intra-epithelial and stromal IC

PD-L1 TC3 vs IC3 NSCLC tumors have distinct tumor TME



PD-L1 IC3 tumors represent immune-rich/CD8 high tumors

Adaptive PD-L1 regulation
Intra-epithelial/stromal IC
Presence of T_{eff} cells
CD8 IHC

- Despite the differences in TME, both TC and IC predict for clinical benefit to atezolizumab

IC=immune cells; TC=tumor cells; TME=tumor microenvironment

Schmid P, et al. Poster. ESMO. 2015 (abstr P269).

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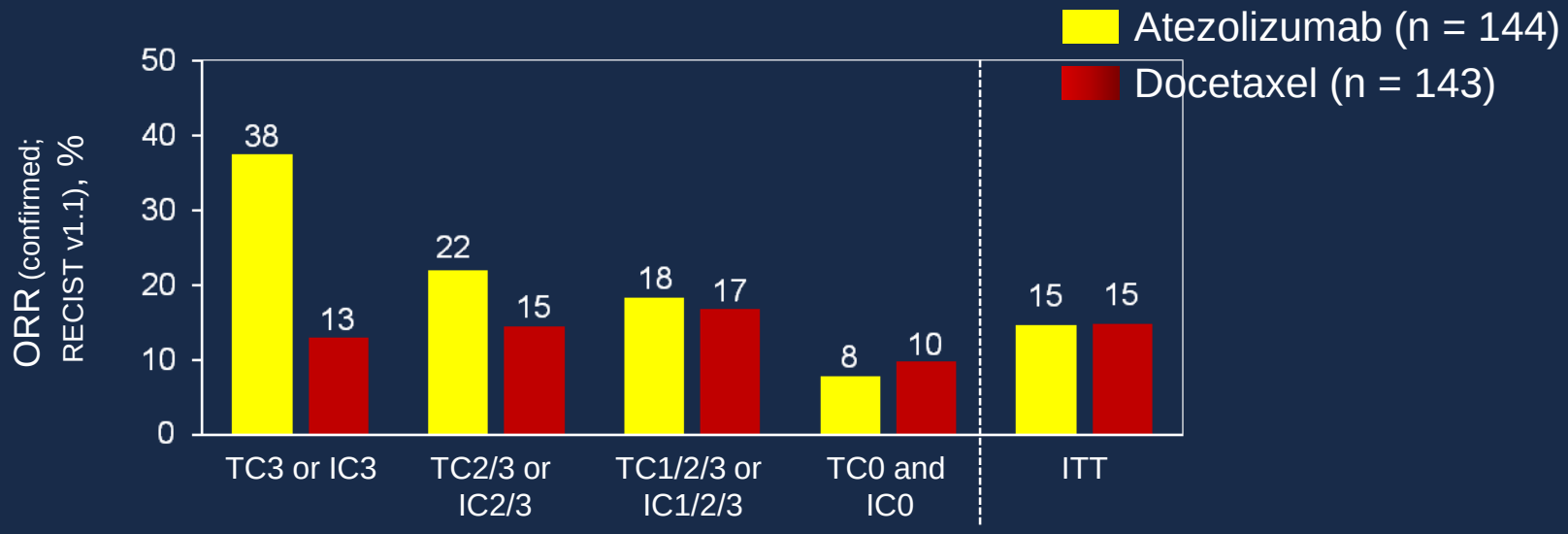
POPLAR: Overall Response and Duration of Response (Atezolizumab= anti-PD-L1)



	ITT	
	Atezolizumab (n = 21)	**Docetaxel (n = 21)**
Median duration of response, mo (95% CI)	14.3 (11.6, NE)	7.2 (5.6, 12.5)
HR[a] (95% CI) *P* value[b]	0.41 (0.18, 0.96) 0.033	
Responders with ongoing response[c], n (%)	12 (57%)	5 (24%)

[a]Unstratified HR.
[b]For descriptive purposes only.
[c]Ongoing without experiencing a PFS event.
Data cut-off May 8, 2015.

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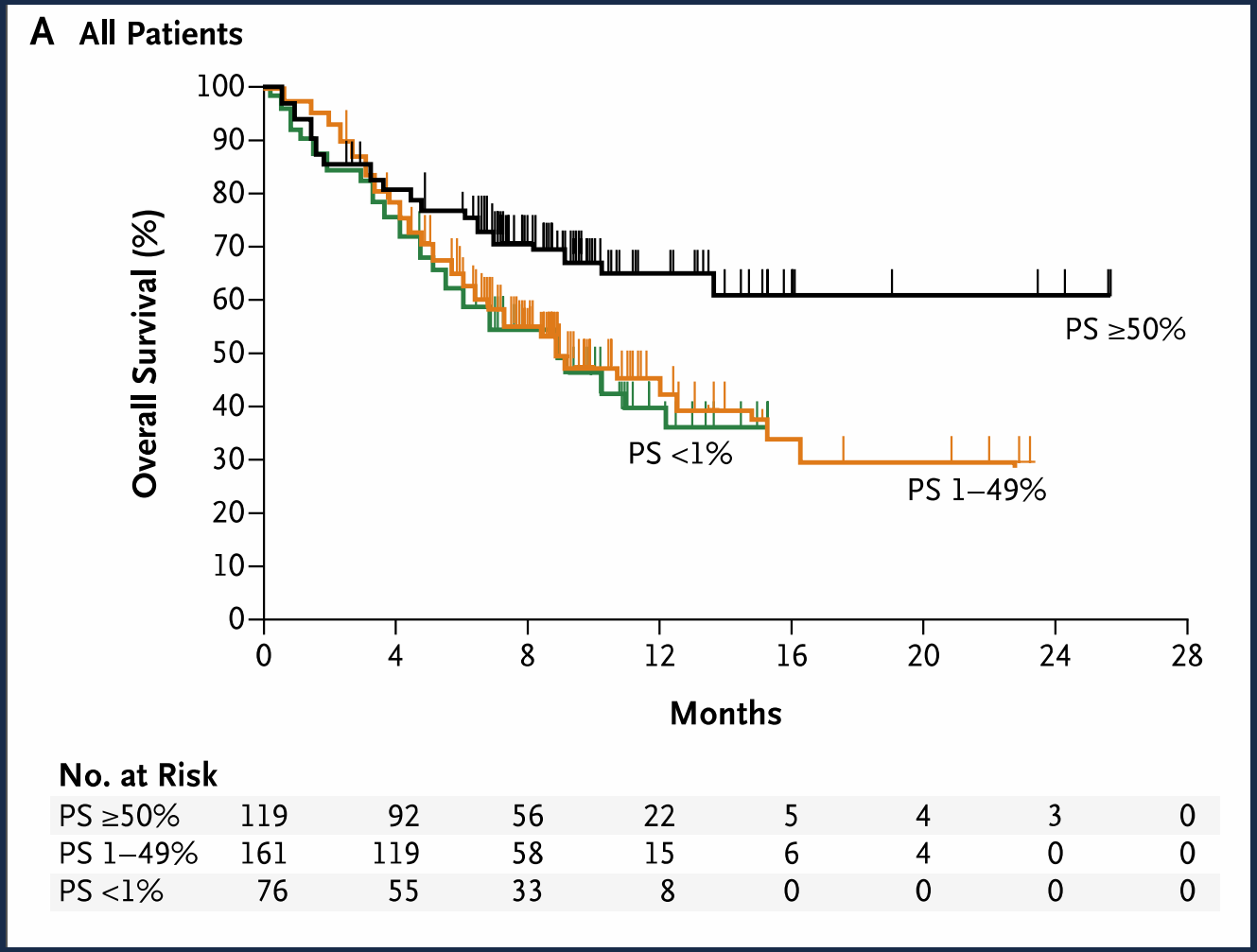
Biomarker Enrichment- OS in NSCLC with Pembrolizumab (anti-PD-1)



- PD-L1 expression on tumor membrane
- 50% cutoff point
- Pembrolizumab FDA dosing:
  - 2mg/kg iv q3 weeks

Garon et al. NEJM 2015

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Response Rate by PD-L1 IHC Expression

Therapy	Histology	PD-L1 IHC strata	ORR
Nivolumab (anti-PD-1, BMS)	Melanoma	+ -	44% 17%
	NSCLC	+ -	67% 9%
	Multiple (melanoma, RCC, NSCLC, CRC, mCRPC)	+ -	36% 0%
Pembrolizumab (anti-PD-1, Merck)	Melanoma	+ -	51% 6%
	NSCLC	+ -	67% 0%
MPDL3280A (anti-PD-L1, Roche)	Multiple (melanoma, RCC, NSCLC, CRC, gastric)	+ -	39% 13%
	NSCLC	+ -	100% 15%
	Bladder	+ -	52% 11%

Patel, Kurzrock Mol Canc Ther 2015

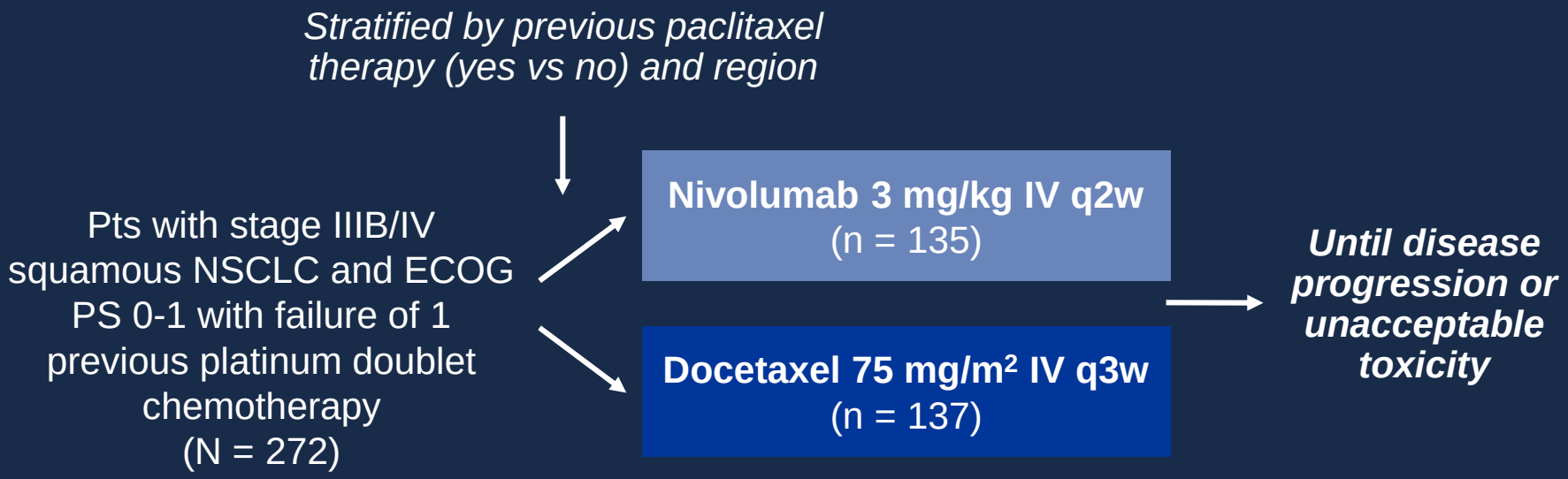
NSCLC: A Tale of Two Histologies

- Same drug: nivolumab
  - FDA approved dose:
    - nivolumab 3mg/kg iv q2 weeks
- Same disease: NSCLC
- Same setting: refractory, metastatic NSCLC

- Different histologies: squamous vs nonsquamous (mainly adenoCA)

CheckMate 017: Nivolumab vs Docetaxel in Previously Treated Squamous NSCLC

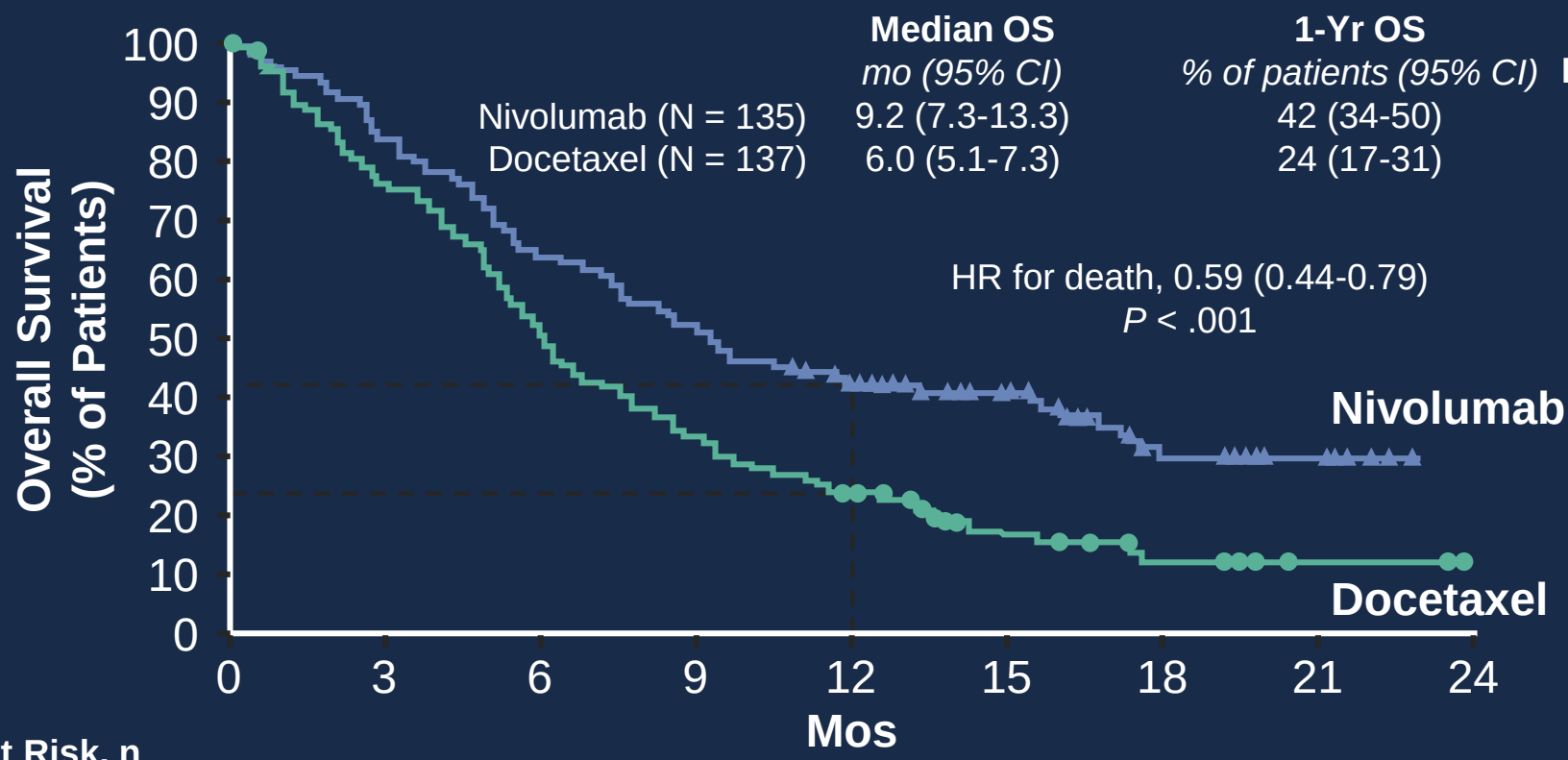
- Open-label, randomized phase III trial



- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

Spigel DR, et al. ASCO 2015. Abstract 8009. Brahmer J, et al. N Engl J Med. 2015; [Epub ahead of print].

CheckMate 017: OS in the ITT Population (Squamous)



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

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Spigel DR, et al. ASCO 2015. Abstract 8009. Brahmer J, et al. N Engl J Med. 2015;[Epub ahead of print].

CheckMate 017: OS by PD-L1 Expression (Squamous)

- OS benefit seen with nivolumab vs docetaxel independent of PD-L1 expression; similar trend in PFS, ORR

Median OS by PD-L1 Expression Level,* Mos	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1% < 1%	9.3 8.7	7.2 5.9	0.69 (0.45-1.05) 0.58 (0.37-0.92)	.56
≥ 5% < 5%	10.0 8.5	6.4 6.1	0.53 (0.31-0.89) 0.70 (0.47-1.02)	.47
≥ 10% < 10%	11.0 8.2	7.1 6.1	0.50 (0.28-0.89) 0.70 (0.48-1.01)	.41
Not quantifiable			0.39 (0.19-0.82)	

* PD-L1 expression measured in pre-treatment tumor biopsies with validated, automated immunohistochemical assay using PD-L1 antibody clone 28–8.

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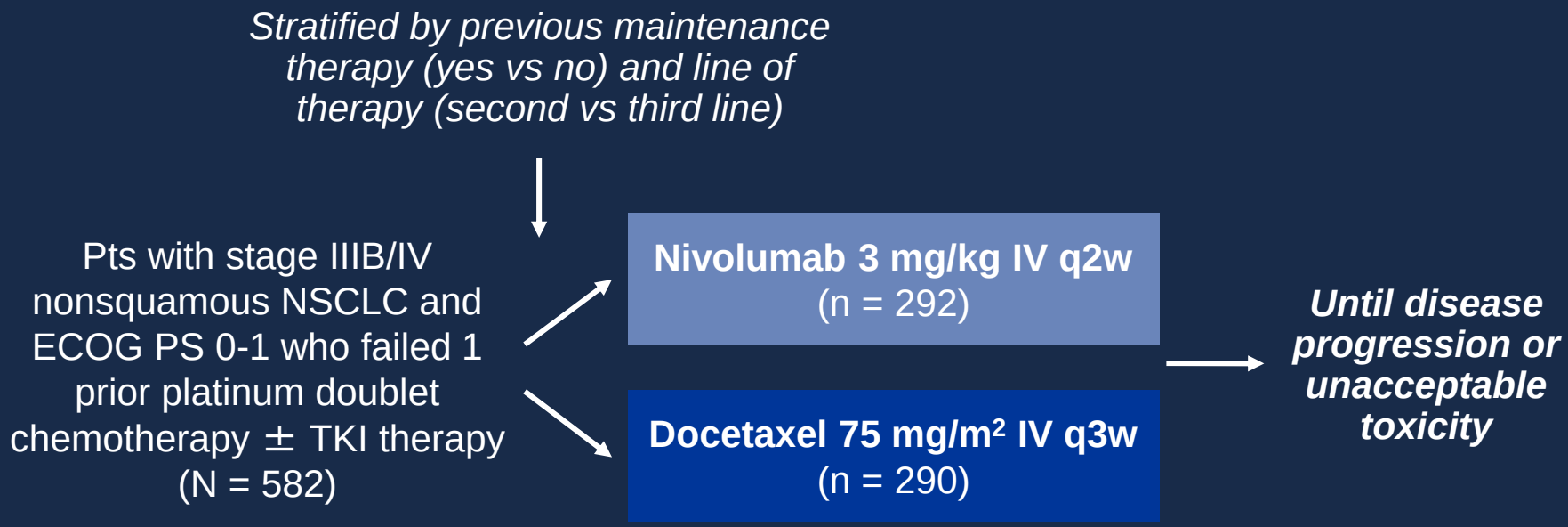
Spigel DR, et al. ASCO 2015. Abstract 8009. Brahmer J, et al. N Engl J Med. 2015; [Epub ahead of print].

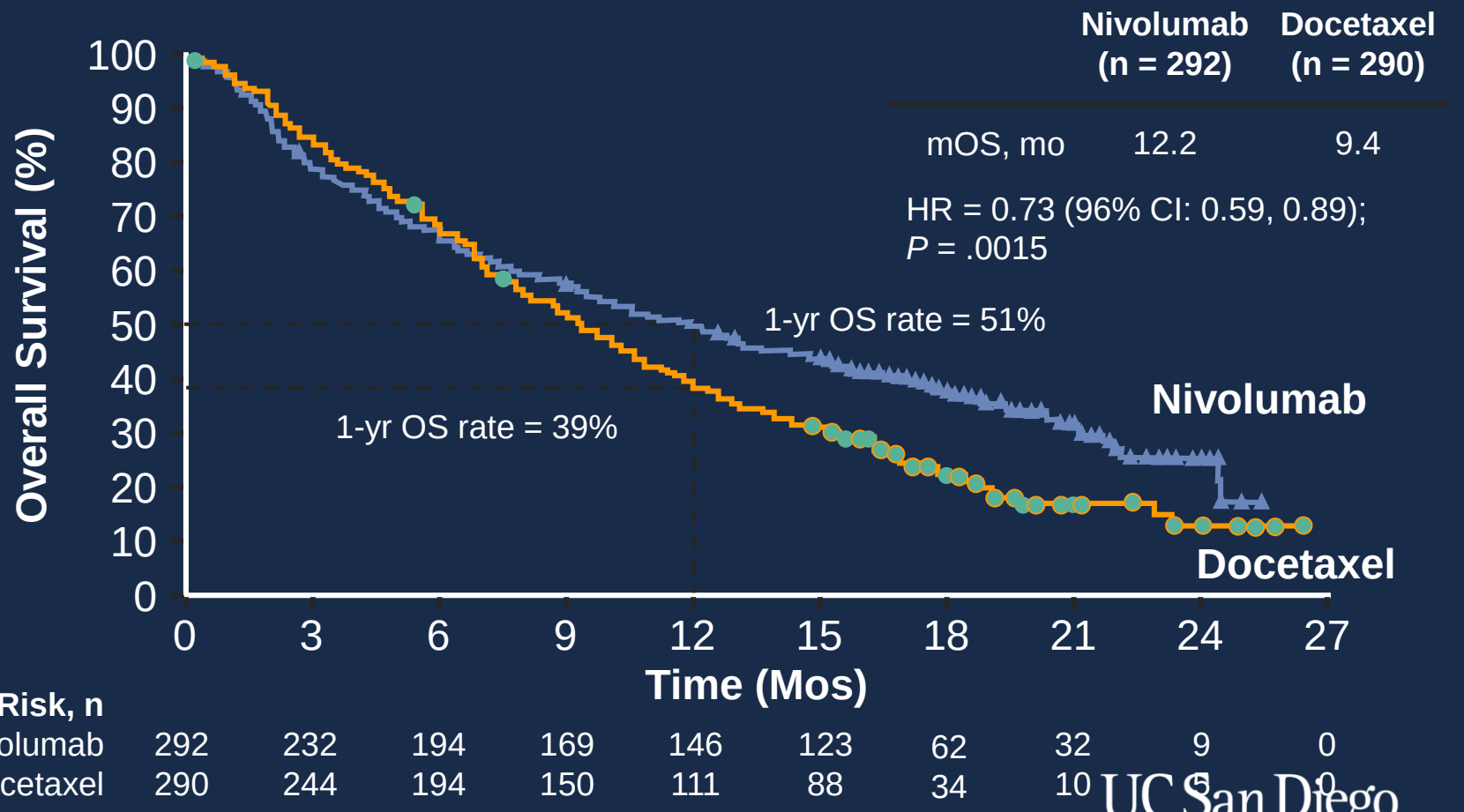
CheckMate 057: Nivolumab vs Docetaxel in Previously Treated Nonsquamous NSCLC



- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, efficacy by PD-L1 expression, safety, QoL

Paz-Ares L, et al. ASCO 2015. Abstract LBA109.

CheckMate 057: OS in the ITT Population (Nonsquamous)



Paz-Ares L, et al. ASCO 2015. Abstract LBA109. Reprinted with permission.

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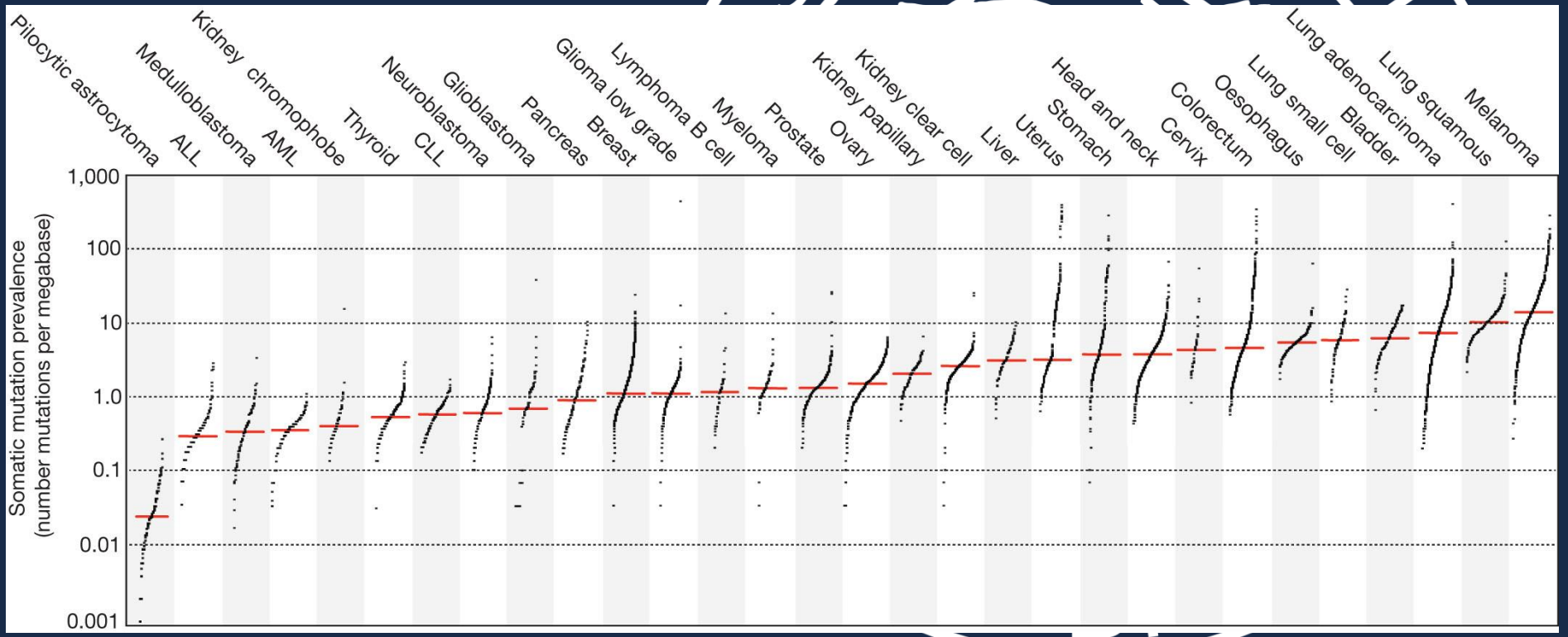
CheckMate 057: OS by PD-L1 Expression (Nonsquamous)

Median OS by PD-L1 Expression Level, mos	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction *P* Value
≥ 1%	17.2	9.0	0.59 (0.43-0.82)	.0646
< 1%	10.4	10.1	0.90 (0.66-1.24)	
≥ 5%	18.2	8.1	0.43 (0.30-0.63)	.0004
< 5%	9.7	10.1	1.01 (0.77-1.34)	
≥ 10%	19.4	8.0	0.40 (0.26-0.59)	.0002
< 10%	9.9	10.3	1.00 (0.76-1.31)	

- Similar interaction results based on baseline PD-L1 expression observed for PFS and ORR

Paz-Ares L, et al. ASCO 2015. Abstract LBA109. Reprinted with permission.

The prevalence of somatic mutations across human cancer types



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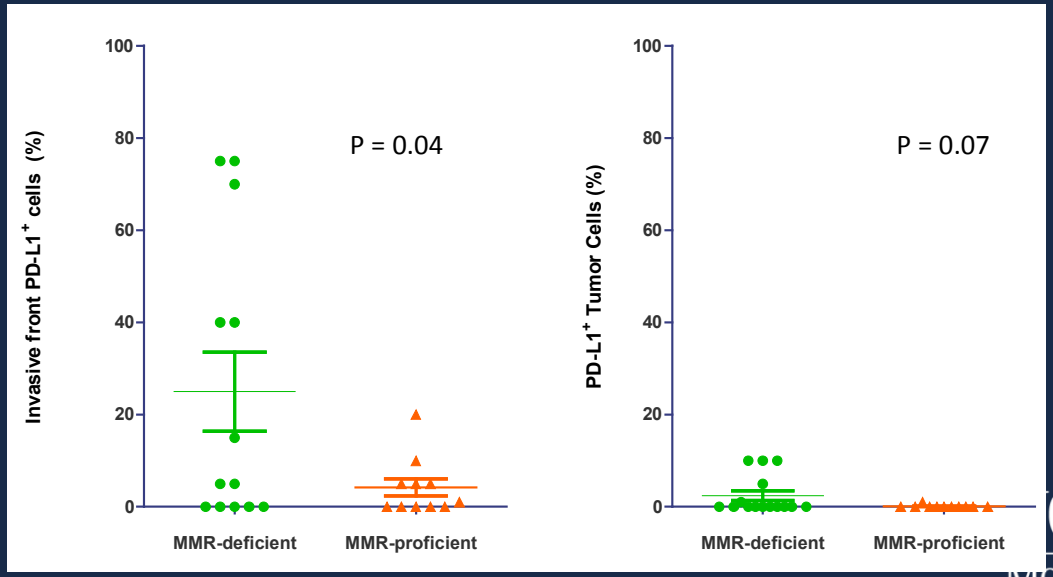
LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

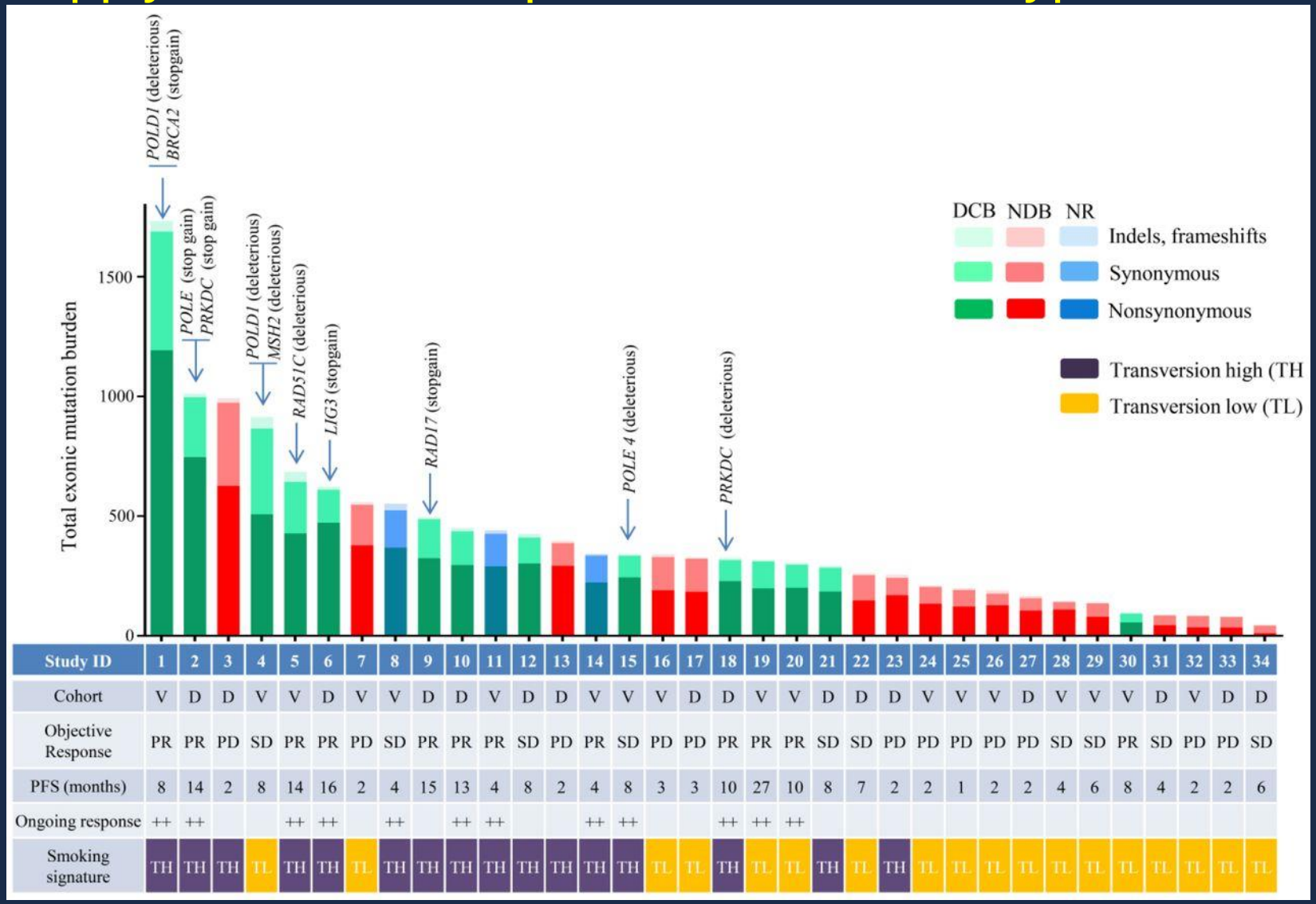
Mutational Burden

- Patients with mismatch-repair deficient GI malignancies have improved responses to anti-PD-1 therapy
  - MSI-H patients had 1782 mutations per tumor vs 73 in MSS
  - 40% ORR in MSI-H vs 0% in MSS mCRC with pembrolizumab
- PD-L1 expression is relatively associated with mutational burden
- PD-L1 expression not associated with response rate or survival
  - Does this help explain PD-L1 negative responders?



Le et al. NEJM 2015

Can Apply Same Techniques Across Tumor Types: NSCLC



Study ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34
Cohort	V	D	D	V	V	D	V	V	D	D	V	D	D	V	V	V	D	D	V	V	D	D	D	V	V	V	D	V	V	V	D	V	D	D
Objective Response	PR	PR	PD	SD	PR	PR	PD	SD	PR	PR	PR	SD	PD	PR	SD	PD	PD	PR	PR	PR	SD	SD	PD	PD	PD	PD	PD	SD	SD	PR	SD	PD	PD	SD
PFS (months)	8	14	2	8	14	16	2	4	15	13	4	8	2	4	8	3	3	10	27	10	8	7	2	2	1	2	2	4	6	8	4	2	2	6
Ongoing response	++	++			++	++		++		++	++			++	++			++	++	++														
Smoking signature	TH	TH	TH	TL	TH	TH	TL	TH	TH	TH	TH	TH	TH	TH	TH	TL	TL	TH	TL	TL	TH	TL	TH	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL	TL

Rizvi NA et al. Science 3/12/14

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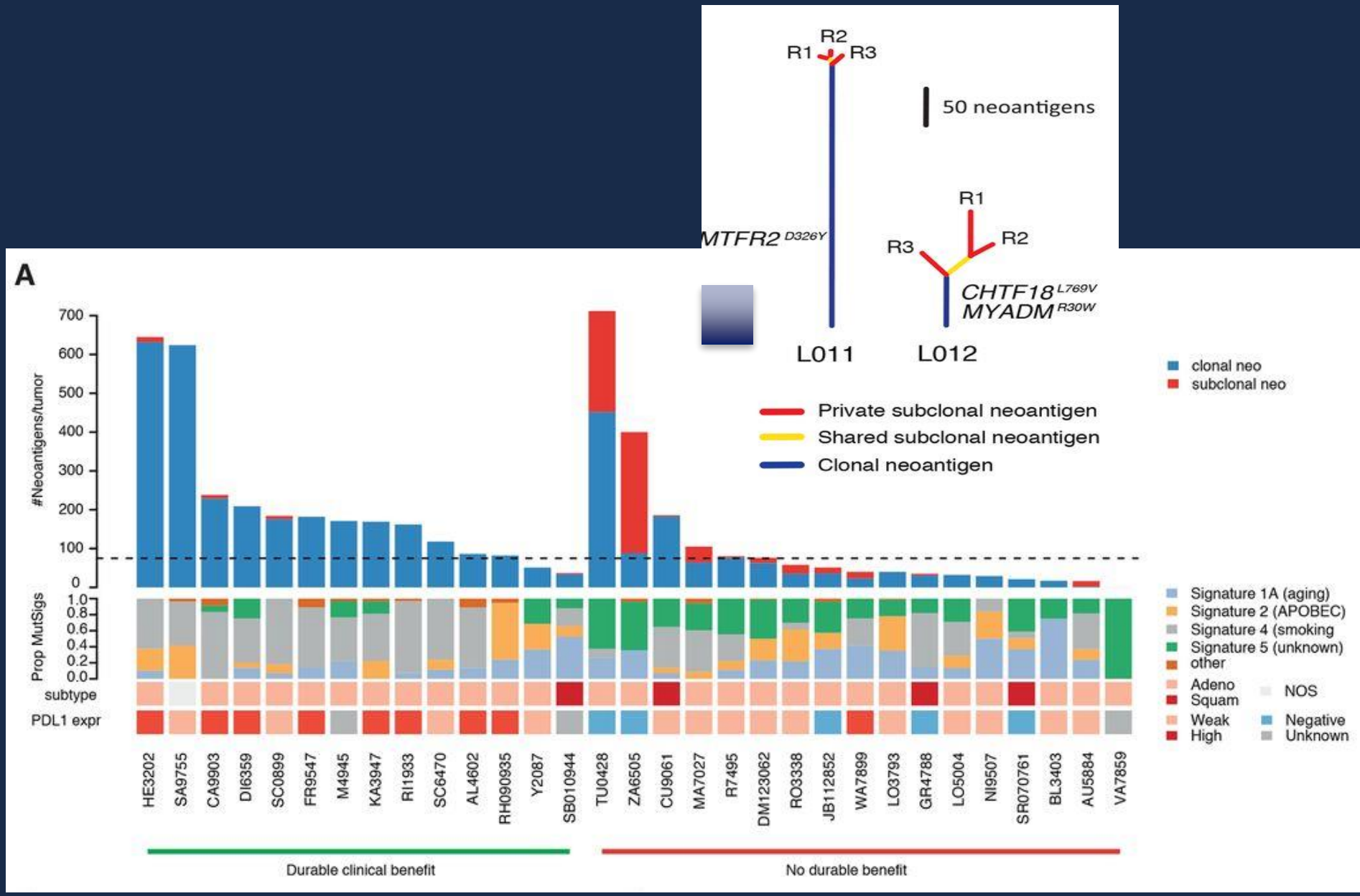
Neoantigen clonal architecture and clinical benefit of immune checkpoint blockade



Nicholas McGranahan et al. Science 2016;science.aaf1490

CTLA-4 and PD-1 Combinations

- Remarkable efficacy in melanoma
  - With substantial toxicity

- What about in NSCLC?

Is two better than one in NSCLC?

Nivolumab Plus Ipilimumab in First-line NSCLC: Summary of Efficacy

	Nivo 3 Q2W + Ipi 1 Q12W (n = 38)	Nivo 3 Q2W + Ipi 1 Q6W (n = 39)	Nivo 3 Q2W (n = 52)
Confirmed ORR, % (95% CI)	**47** (31, 64)	**39** (23, 55)	**23** (13, 37)
Median duration of response, mo (95% CI)	NR (11.3, NR)	NR (8.4, NR)	NR (5.7, NR)
Median length of follow-up, mo (range)	12.9 (0.9–18.0)	11.8 (1.1–18.2)	14.3 (0.2–30.1)
Best overall response, %			
Complete response	0	0	8
Partial response	47	39	15
Stable disease	32	18	27
Progressive disease	13	28	38
Unable to determine	8	15	12
Median PFS, mo (95% CI)	8.1 (5.6, 13.6)	3.9 (2.6, 13.2)	3.6 (2.3, 6.6)
1-year OS rate, % (95% CI)	NC	69 (52, 81)	73 (59, 83)

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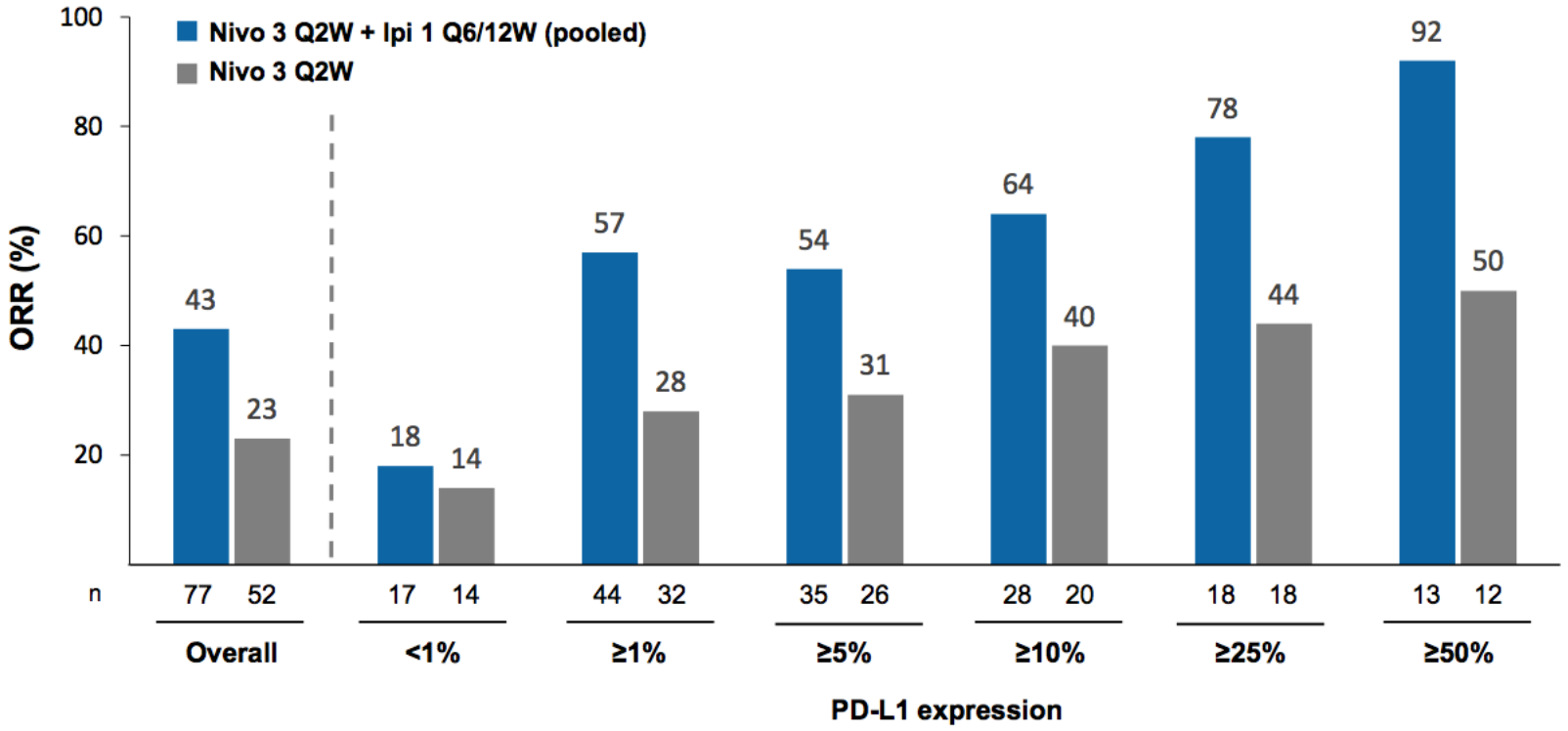
CheckMate 012 presented at ASCO 2016

PD-L1 IHC Expression and Response to Combination Immune Checkpoint Blockade

Nivolumab Plus Ipilimumab in First-line NSCLC: Efficacy Across All Tumor PD-L1 Expression Levels



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CheckMate 012 presented at ASCO 2016

What about SCLC?

Nivolumab +/- Ipilimumab in Recurrent SCLC: Summary of Response

	Nivolumab-3 (n = 98)	Nivolumab-1 + Ipilimumab-3 (n = 61)	Nivolumab-3 + Ipilimumab-1 (n = 54)
Objective response rate, % (n/N)			
Overall	**10 (10/98)**	**23 (14/61)**	**19 (10/54)**
Platinum-sensitive[a]	11 (6/55)	28 (7/25)	19 (4/21)
Platinum-resistant[a]	10 (3/30)	17 (4/23)	10 (2/21)
Best overall response, %			
Complete response	0	2	0
Partial response	10	21	19
Stable disease	22	21	17
Progressive disease	53	38	54
Unable to determine	12	13	11
Not evaluable (no tumor assessment follow-up)	2	5	0

[a]Platinum sensitivity was unknown for 29 patients as follows: nivo-3, n = 10; nivo-1/ipi-3, n = 11; nivo-3/ipi-1, n = 8. 3 pts in the nivo-3 arm, 2 pts in the nivo-1/ipi-3 arm, and 4 pts in the nivo-3/ipi-1 arm did not receive first-line platinum therapy and did not meet eligibility criteria, although they were treated and included in the analysis

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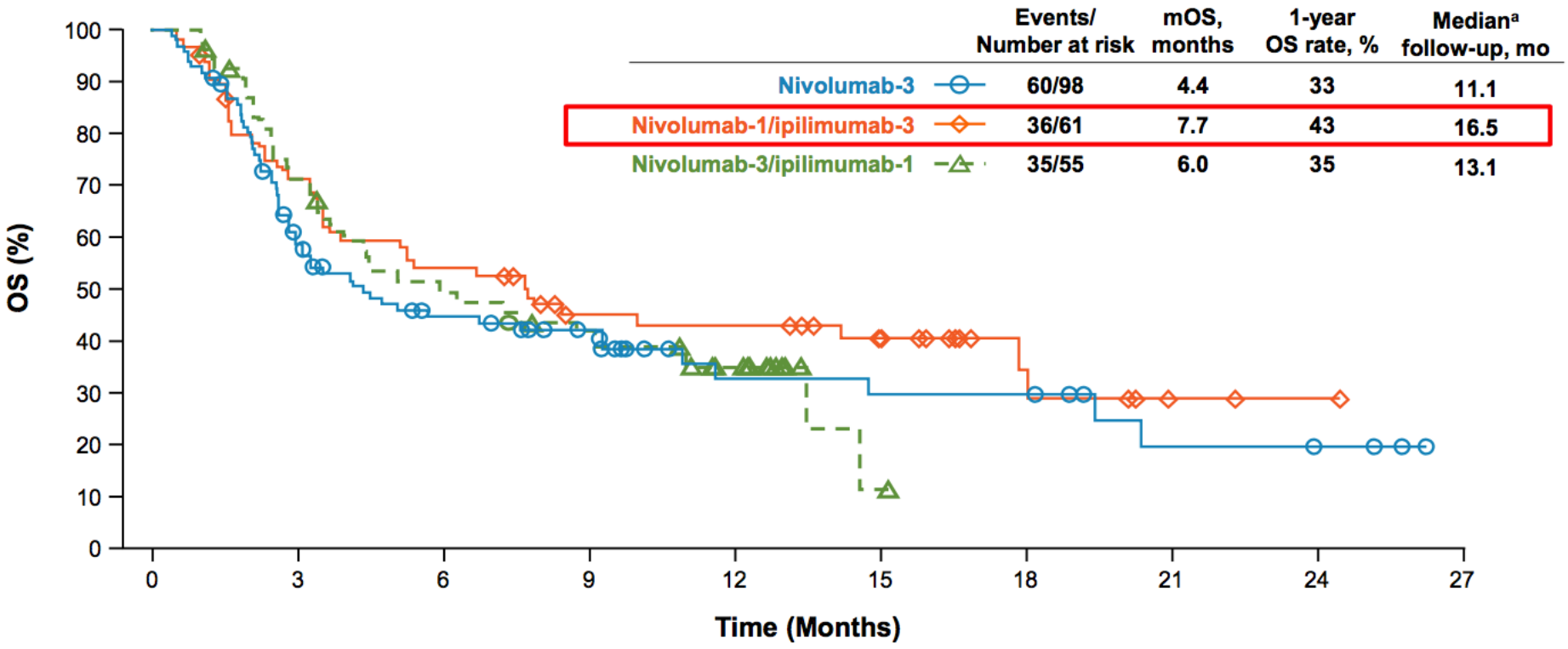
CheckMate 032 presented at ASCO 2016

Some patients with long-term response in refractory SCLC

Nivolumab +/- Ipilimumab in Recurrent SCLC: Overall Survival



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What about the side effects?

Nivolumab +/- Ipilimumab in Recurrent SCLC: Treatment-Related AEs in ≥10% of Patients

	Nivolumab-3 (n = 98)		Nivolumab-1 + Ipilimumab-3 (n = 61)		Nivolumab-3 + Ipilimumab-1 (n = 54)	
	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %	Any grade, %	Grade 3–4, %
Total treatment-related AEs	**53**	**13**	**79**	**30**	**74**	**19**
Fatigue	11	1	26	0	22	0
Pruritus	11	0	20	2	9	0
Diarrhea	7	0	21	5	17	2
Nausea	7	0	11	2	7	0
Decreased appetite	6	0	7	0	11	0
Hypothyroidism	3	0	16	2	7	0
Hyperthyroidism	2	0	11	0	6	0
Rash	2	0	20	3	7	0
Rash, maculopapular	1	0	13	3	4	0
Lipase increased	0	0	11	8	0	0
Treatment-related AEs leading to discontinuations	**6**		**11**		**7**	

- Two treatment-related deaths occurred in the nivolumab-1 + ipilimumab-3 arm: one due to myasthenia gravis and one due to worsening of renal failure. One treatment-related death due to pneumonitis occurred in the nivolumab-3 + ipilimumab-1 arm
- Treatment-related limbic encephalitis was reported in 2 (1%) patients; 1 case resolved, and outcome for 1 case was not reported
- Treatment-related pneumonitis occurred in 8 (4%) patients; 6 cases resolved, outcome for 1 case is unknown, and 1 case was fatal

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Immune-related Adverse Events: A Case Report

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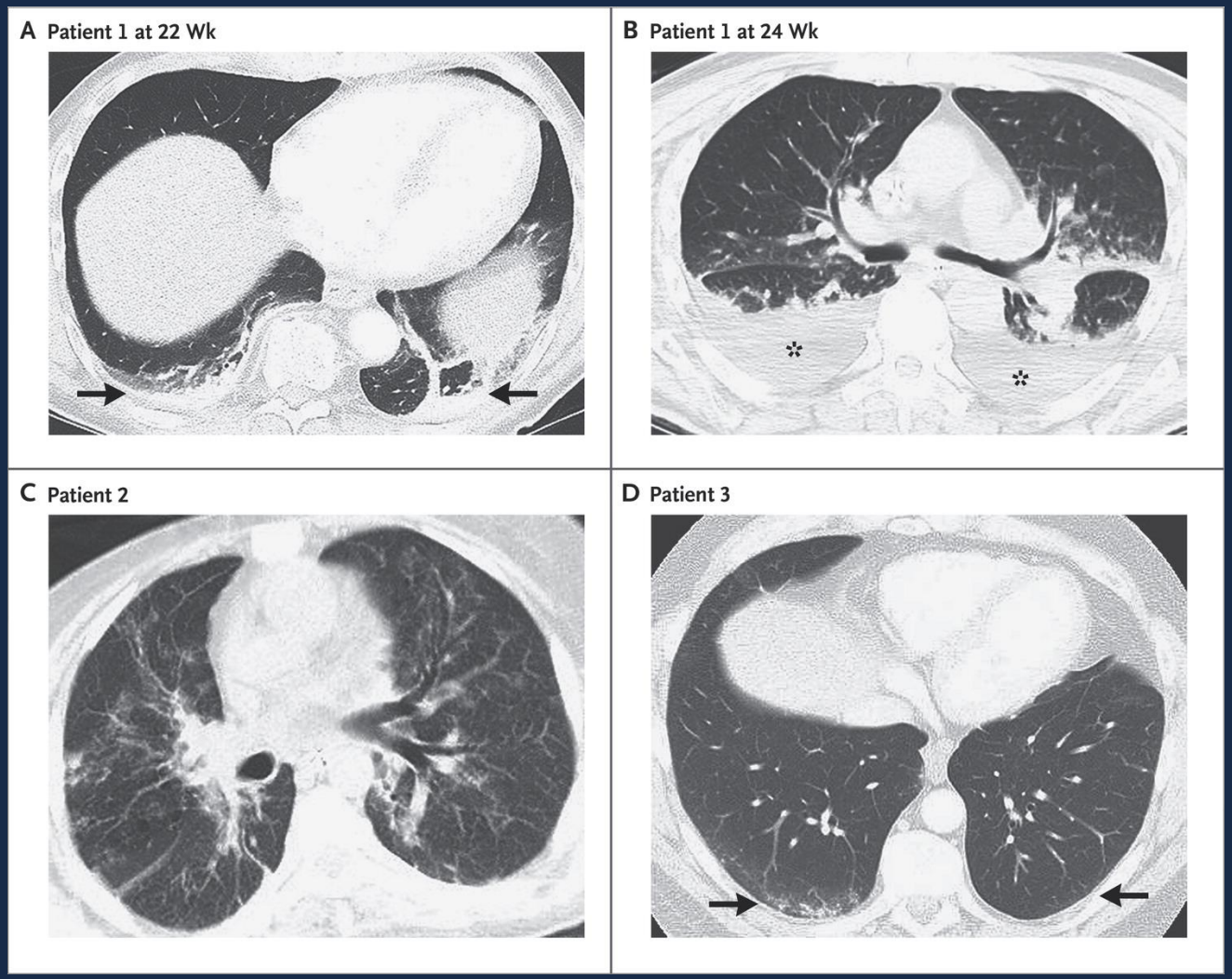
Case

- 72 year old, former 40 pack-year smoker has new back pain
  - Found to have Stage IV NSCLC-squamous with metastasis to liver
  - Received carboplatin/gemcitabine, but progression on initial scan
  - PD-L1 IHC sent on liver biopsy, 3+ intensity, >50% tumor cell membranous staining
  - Patient started on anti-PD-1 agent
  - Doing well clinically, but after cycle 3 develops acute SOB, fever

CT of the Chest Performed in Three Patients with Pneumonitis Associated with the Use of Anti–Programmed Cell Death 1 Antibodies.



Nishino M et al. N Engl J Med 2015;373:288-290.

The NEW ENGLAND JOURNAL of MEDICINE

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Pneumonitis

- Rare but potentially fatal side effect
- No gold standard diagnostic criteria aside from biopsy
- By symptoms hard to distinguish from URI, pneumonia, COPD flare
- Can happen at any time (week 6-24 as onset)

- Tips:
  - Disproportionate hypoxia relative to baseline and overall clinical condition
  - Multilobar involvement
  - CT chest with contrast to rule out PE, PNA, pneumonitis
- Common characteristics for immune-related pneumonitis
  - Multilobal involvement, often ALL lung fields involved
  - Diffuse ground glass opacities
  - Diffuse reticular opacities
  - Multifocal consolidations
  - Traction bronchiectasis

Case

- O2 sat found to be 82%
- CT: diffuse infiltrates and ground glass opacities across all lung fields, improvement in underlying tumor mass
- Admitted to hospital, started on iv methylprednisolone 125mg iv q8hrs
  - Empiric antibiotics
  - Nasal cannula @4L with improvement to 98%
- Improvement in symptoms in 6 hours, started on oral prednisone 1mg/kg po daily (60mg po daily) tapered by 20mg each week over 3 weeks
- Resumed anti-PD-1 after steroid taper completed
  - Risk of recurrent pneumonitis is lowered with prolonged steroid taper (~3 weeks)

Summary

- Immune checkpoint blockade has revolutionized oncology
  - NSCLC, historically not considered an “immunogenic” tumor, has been transformed by development of immune checkpoint blockade
- Anti-PD-1/Anti-PD-L1-based combinatorial approaches are the future of NSCLC immunotherapy
  - Nivolumab and pembrolizumab are both FDA-approved in refractory NSCLC
    - Pembrolizumab requires a positive PD-L1 IHC result per its label
  - Combinations of immunotherapy may have higher efficacy
    - With higher toxicity
- PD-L1 IHC (tumor and immune membranous) positive patients have superior clinical responses, but some patients with PD-L1 negative tumors will respond as well
- Immune-related pneumonitis is the major immune-related toxicity seen in patients in NSCLC, and is a diagnostic dilemma given its presentation is similar to a COPD-flare or pneumonia in a prior smoker
    - Early imaging and intervention with steroids are key
- Anti-PD-1/PD-L1 based approaches likely represent the floor, not the ceiling, in NSCLC

Questions?

- Sandip Patel
- sandippatel@ucsd.edu

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