ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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Disclosures

- No disclosures

- I will not be discussing non-FDA approved indications during my presentation.

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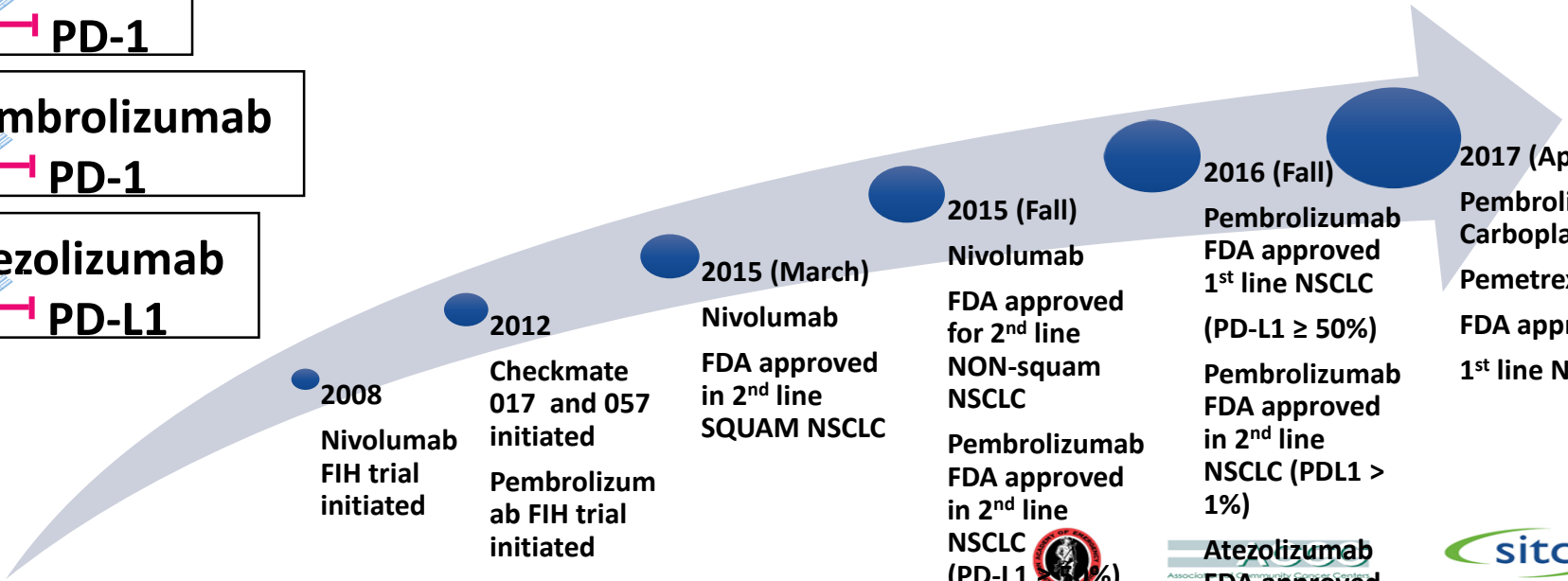
Immune checkpoint inhibitors in NSCLC

Nivolumab — **PD-1**

Pembrolizumab — **PD-1**

Atezolizumab — **PD-L1**



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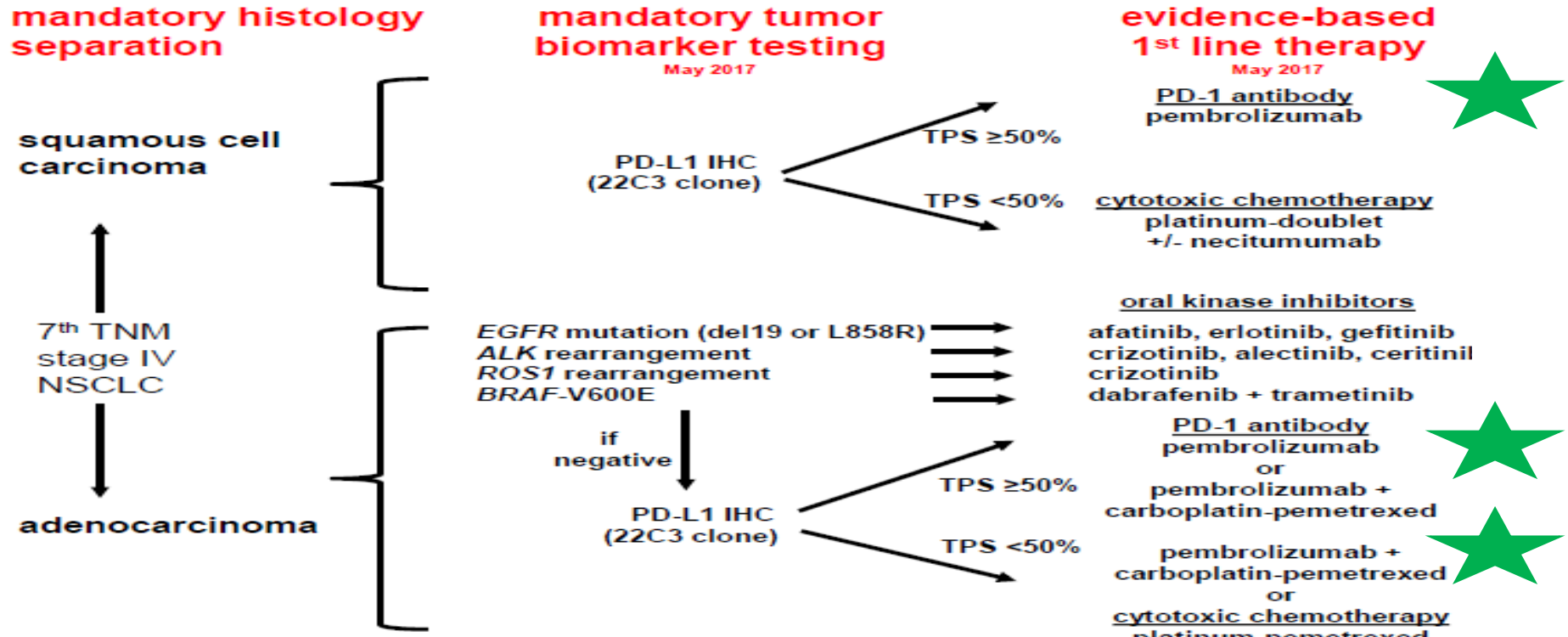
Therapeutic stratification in advanced NSCLC



Adapted from: Rangachari D, Costa DB, *Trans Cancer Resear.* 2017

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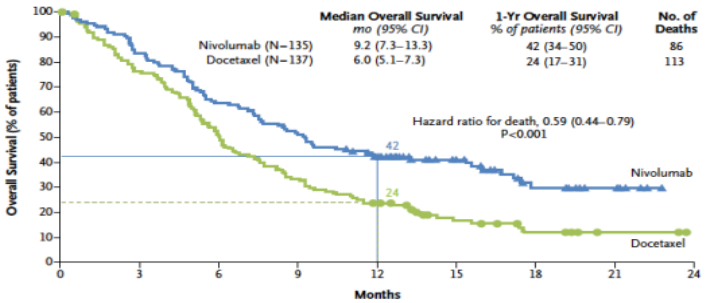
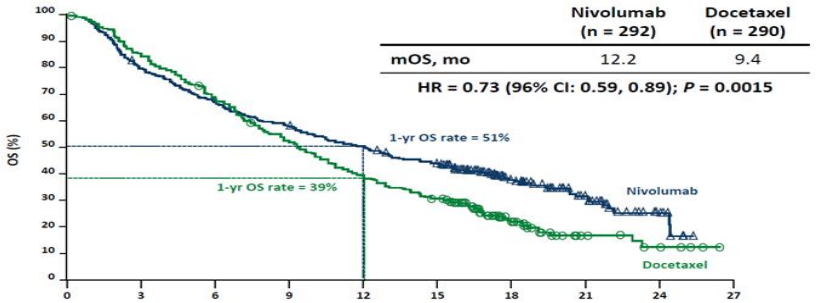
PD1/PD-L1 Inhibitors increase Overall Survival in 2L Advanced NSCLC

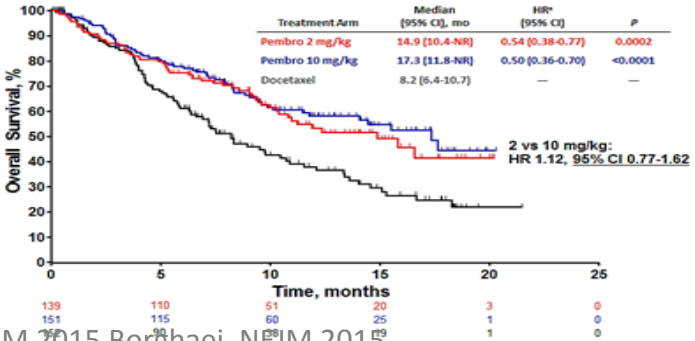
CHECKMATE 017- Nivolumab, squam



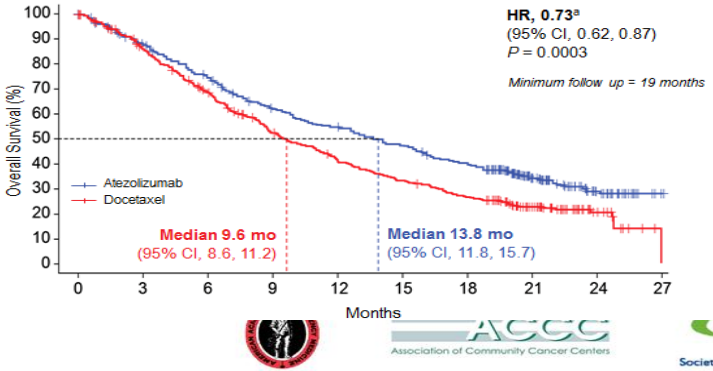
CHECKMATE 057- Nivolumab, non-squam



KEYNOTE 010- Pembrolizumab



OAK- Atezolizumab



Brahmer NEJM 2015 Borghaei, NEJM 2015
Herbst Lancet 2016. Rittmeyer Lancet 2017

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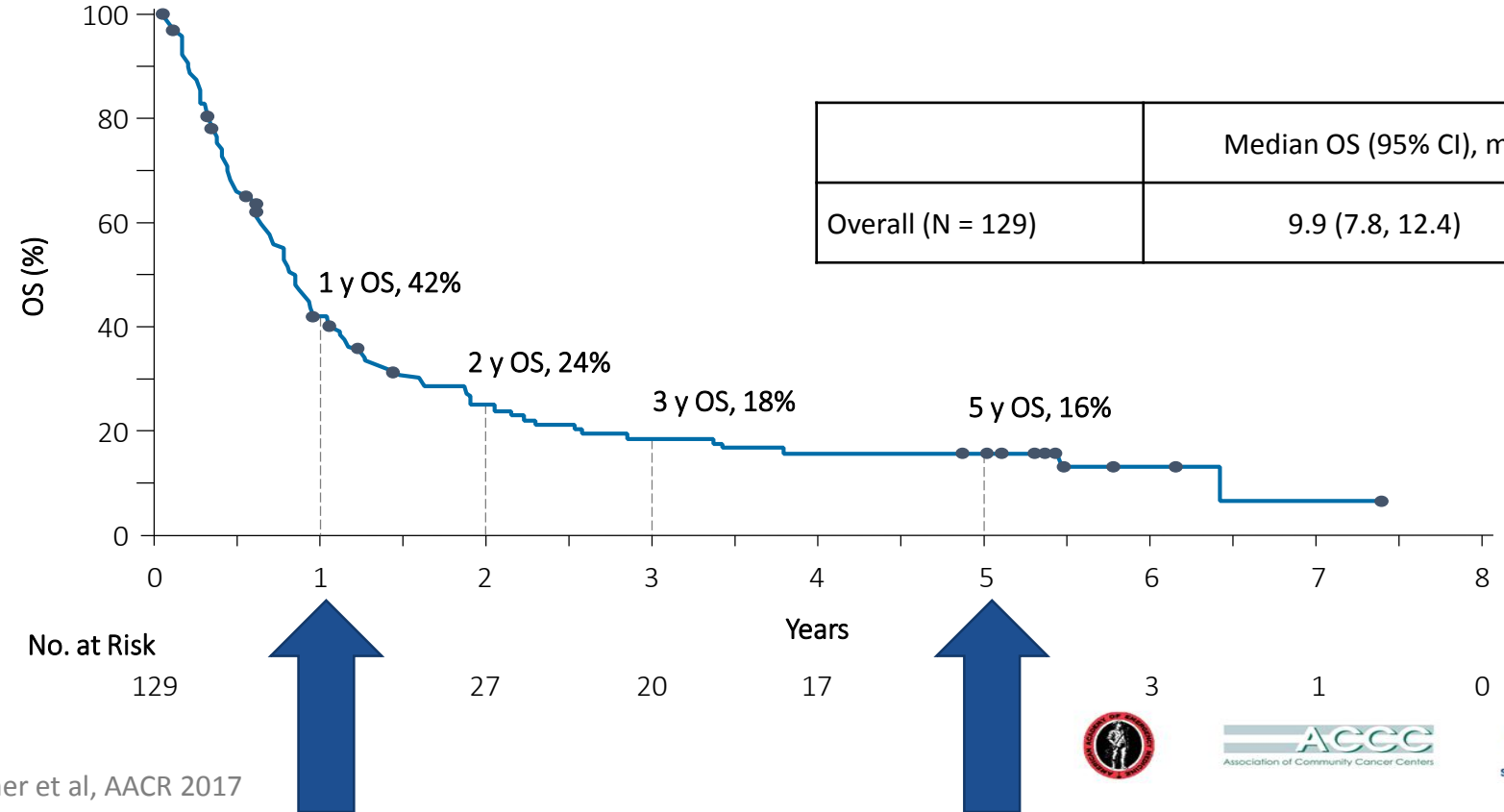
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8, 12.4)

Brahmer et al, AACR 2017

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Toxicities in 2L and 3L Studies

	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Keynote 010
Related Grade 3-5 AEs	15%	8%	11%	13-16%
Discontinuation due to related AEs	5%	6%	6%	4-5%
Pneumonitis AEs	1%	5%	3%	4-5%

Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

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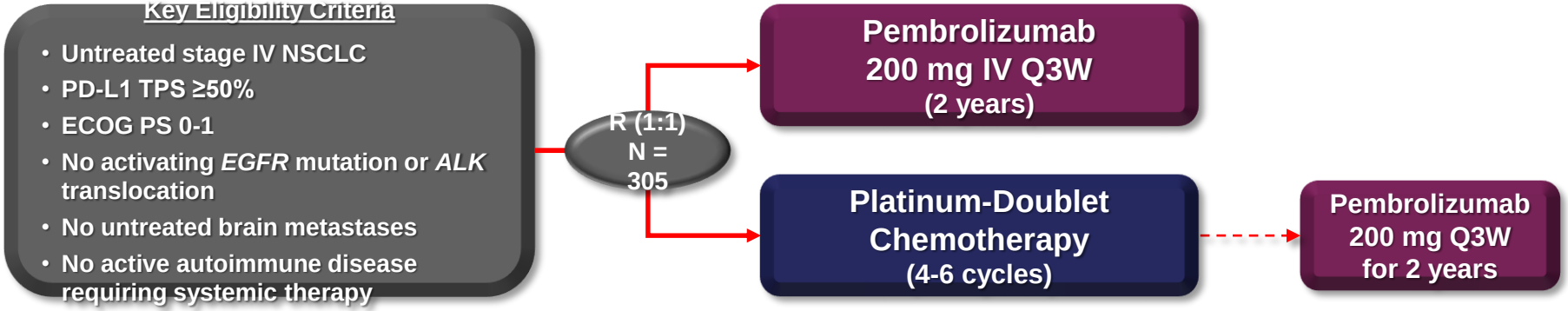
IO in the 1L setting: KEYNOTE-024 Schema (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

Secondary: OS, ORR, safety

Exploratory: DOR

Reck M et al, ESMO 2016, NEJM 2016

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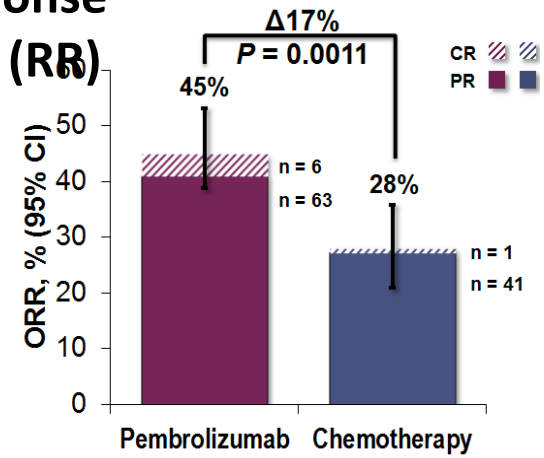
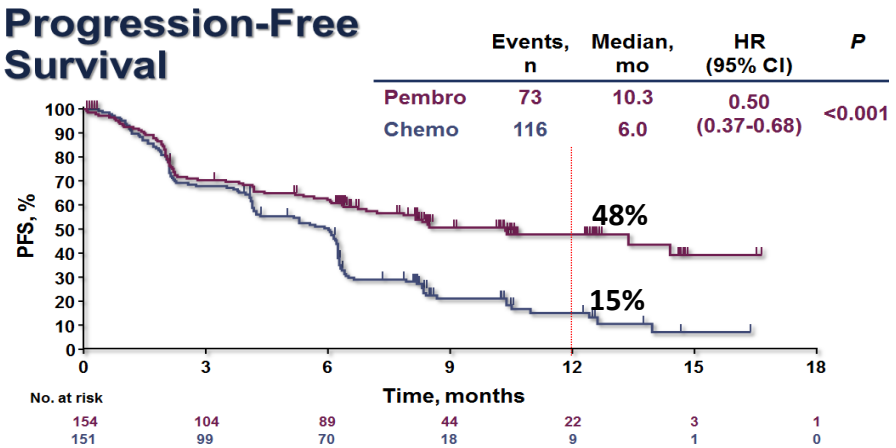
KEYNOTE-024 Efficacy

Response Rate (RR)



Progression-Free Survival



- ✓ 45% is the one of best RRs ever reported in 1st line setting – and more durable
- ✓ Time to Response is identical between Pembro and Chemo
- ✓ PFS improved by 4.3 months (HR of 0.50)

Reck M et al, ESMO 2016, NEJM 2016

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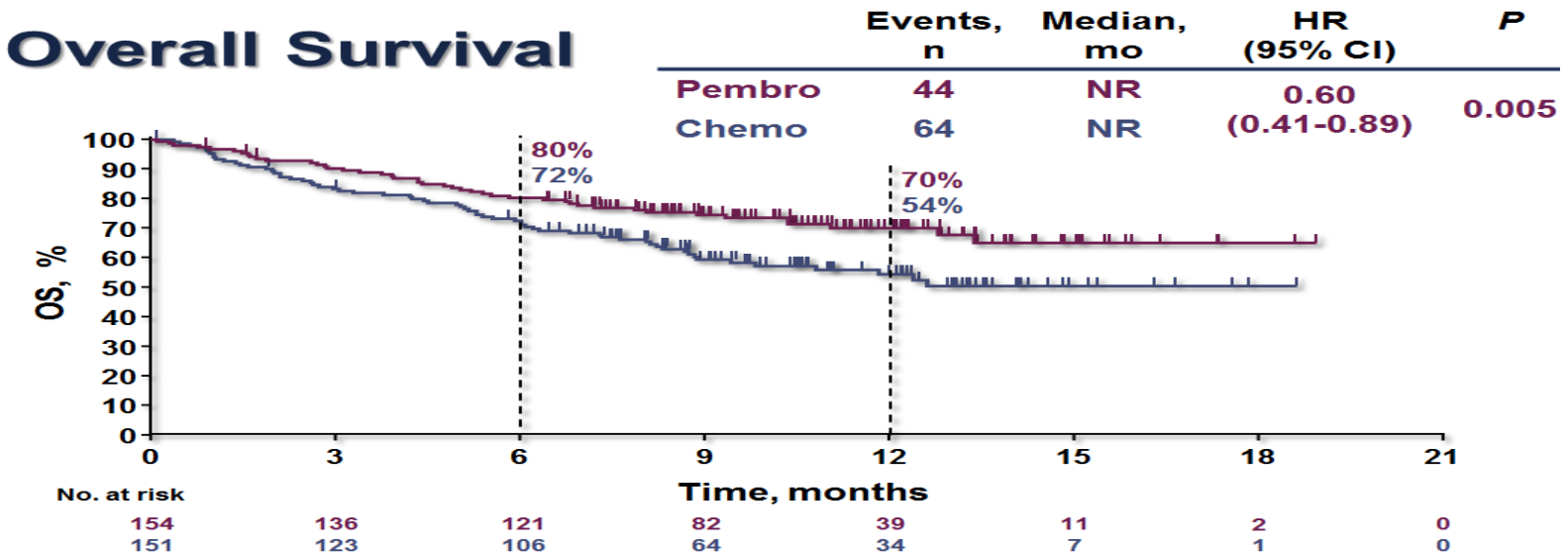
KEYNOTE-024 Survival Data



- ✓ Estimated OS @ 12 months: 70% (Pembro) vs. 54% (Chemo)
- ✓ HR for death: 0.60
- ✓ Findings despite crossover to Pembro in 50%

Reck M et al, ESMO 2016, NEJM 2016

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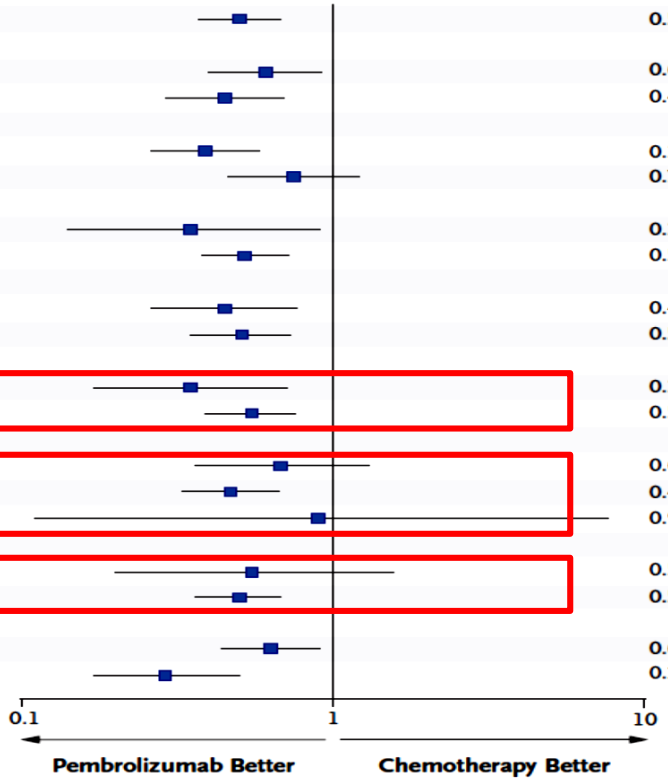
KEYNOTE-024: Improved outcomes w/Pembro across all subgroups

Subgroup	No. of Events/ No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	189/305	0.50 (0.37–0.68)
Age		
<65 yr	91/141	0.61 (0.40–0.92)
≥65 yr	98/164	0.45 (0.29–0.70)
Sex		
Male	116/187	0.39 (0.26–0.58)
Female	73/118	0.75 (0.46–1.21)
Region of enrollment		
East Asia	21/40	0.35 (0.14–0.91)
Non–East Asia	168/265	0.52 (0.38–0.72)
ECOG performance-status score		
0	59/107	0.45 (0.26–0.77)
1	129/197	0.51 (0.35–0.73)
Histologic type		
Squamous	37/56	0.35 (0.17–0.71)
Nonsquamous	152/249	0.55 (0.39–0.76)
Smoking status		
Current	44/65	0.68 (0.36–1.31)
Former	133/216	0.47 (0.33–0.67)
Never	12/24	0.90 (0.11–7.59)
Brain metastases at baseline		
Yes	17/28	0.55 (0.20–1.56)
No	172/277	0.50 (0.36–0.68)
Platinum-based chemotherapy regimen		
Included pemetrexed	120/199	0.63 (0.44–0.91)
Did not include pemetrexed	69/106	0.29 (0.17–0.50)



Reck M et al, ESMO 2016, NEJM 2016

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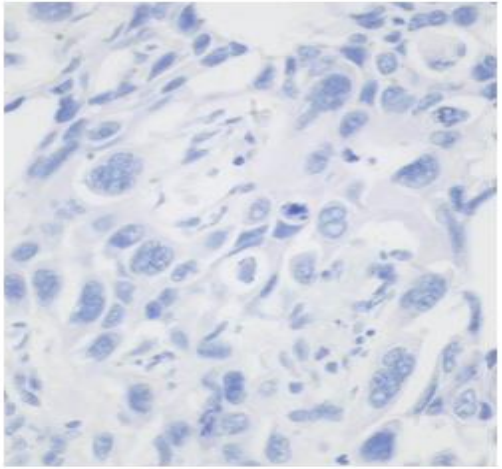
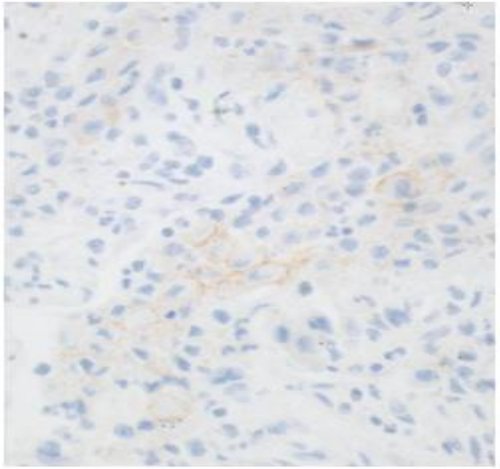
PD-L1 as an IO biomarker



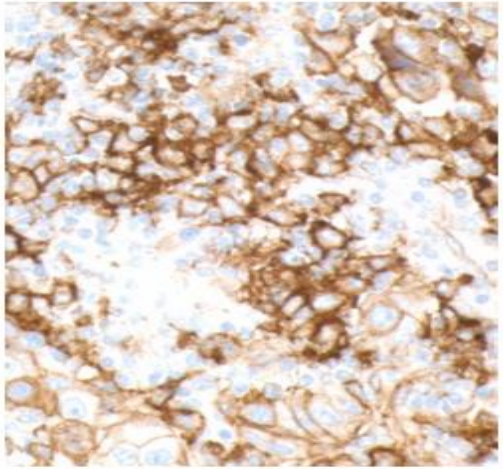
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)



PD-L1 = 100% positive

Strong Positive (50%-100%)

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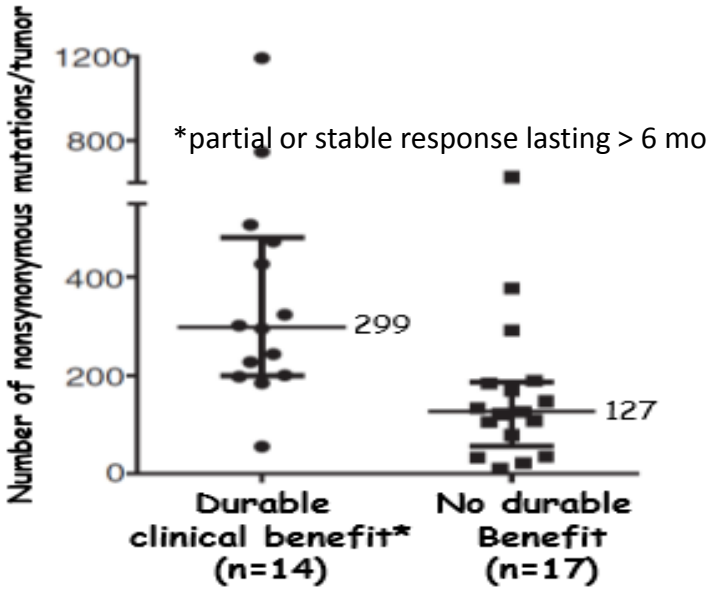
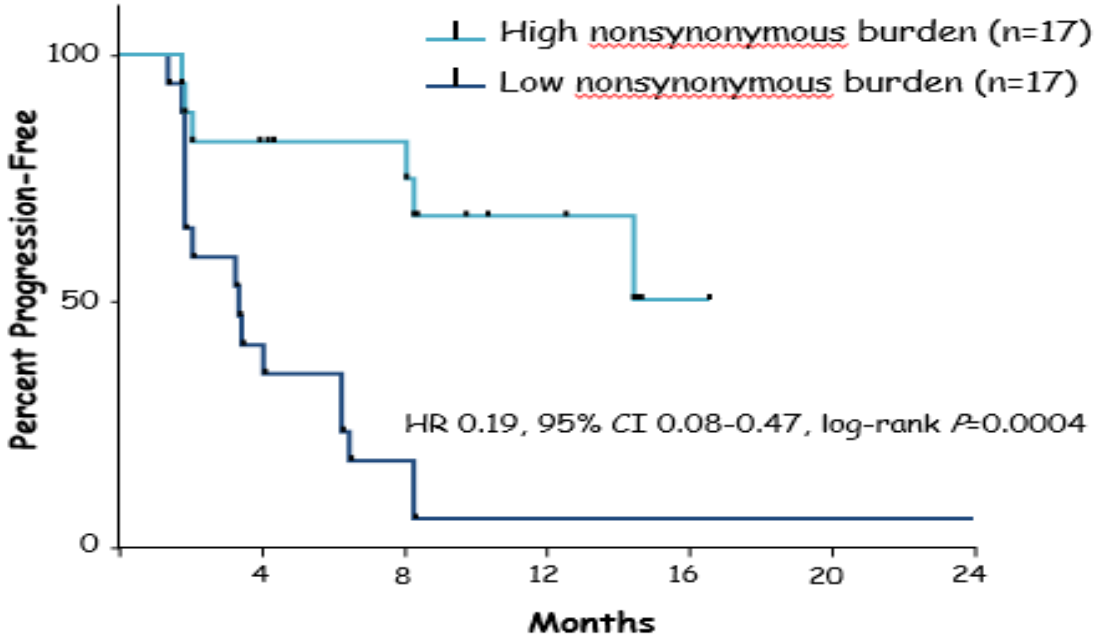
Tumor Mutation Burden as an IO biomarker



*partial or stable response lasting > 6 mo



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Rizvi N et al, Science 2015:348(6230):124-128

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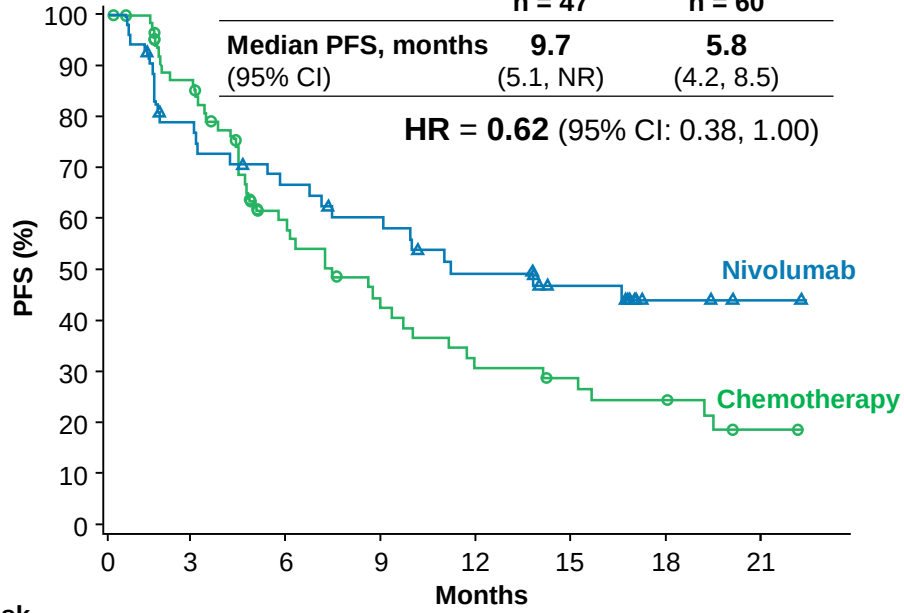
PFS by Tumor Mutation Burden CheckMate-026 (1L Nivolumab in NSCLC)

High TMB

	Nivolumab n = 47	Chemotherapy n = 60
Median PFS, months	9.7	5.8
(95% CI)	(5.1, NR)	(4.2, 8.5)

HR = 0.62 (95% CI: 0.38, 1.00)

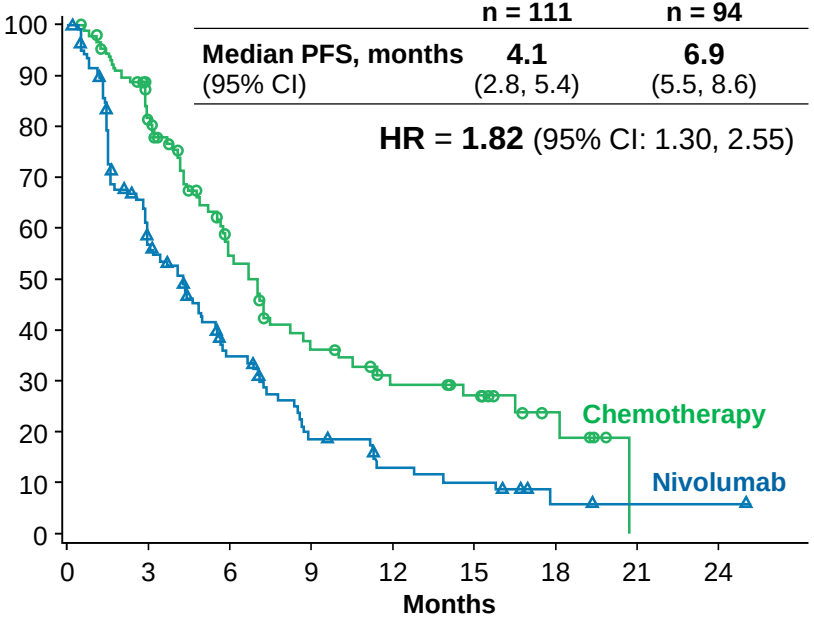


No. at Risk								
Nivolumab	47	30	26	21	16	12	4	1
Chemotherapy	60	42	22	15	9	7	4	1

Low/medium TMB

	Nivolumab n = 111	Chemotherapy n = 94
Median PFS, months	4.1	6.9
(95% CI)	(2.8, 5.4)	(5.5, 8.6)

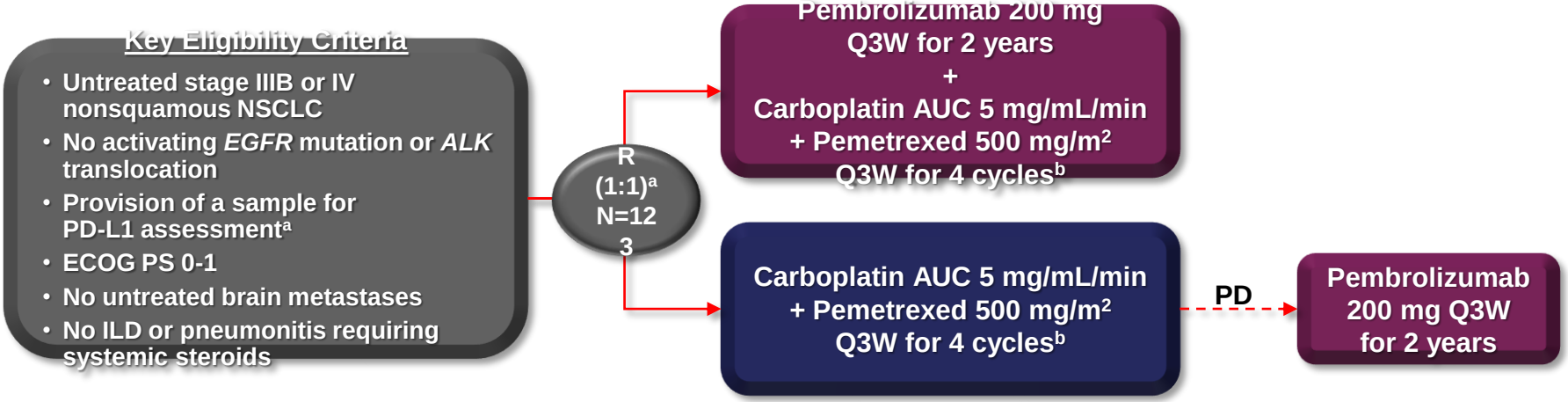
HR = 1.82 (95% CI: 1.30, 2.55)



Nivolumab	111	54	30	15	9	7	2	1	1
Chemotherapy	94	65	37	23	15	12	5	0	0

Peters, et al., AACR 2017

KEYNOTE-021 Cohort G: 1L Carboplatin/Pemetrexed + Pembrolizumab



End Points

Primary: ORR (RECIST v1.1 per blinded, independent central review)

Key secondary: PFS

Other secondary: OS, safety, relationship between antitumor activity and PD-L1 TPS

Langer, et al Lancet Oncology 2016

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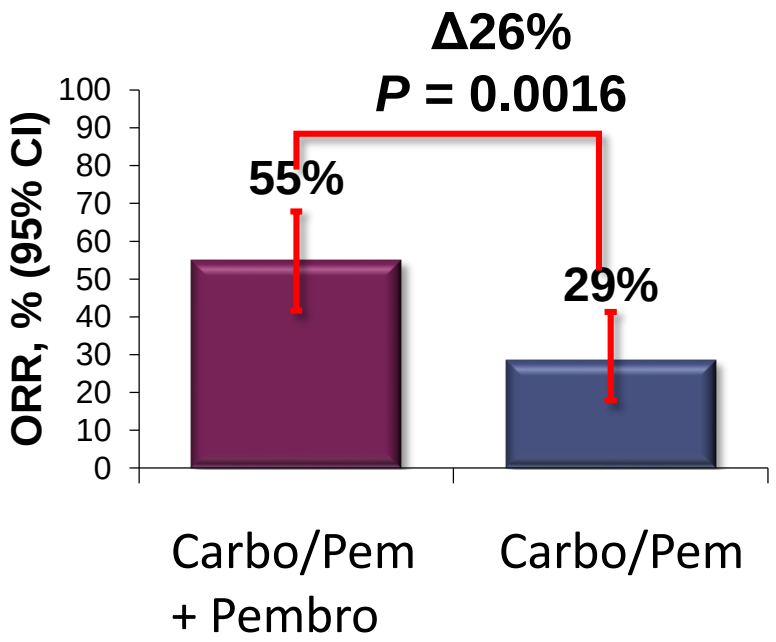
KEYNOTE-021 Efficacy

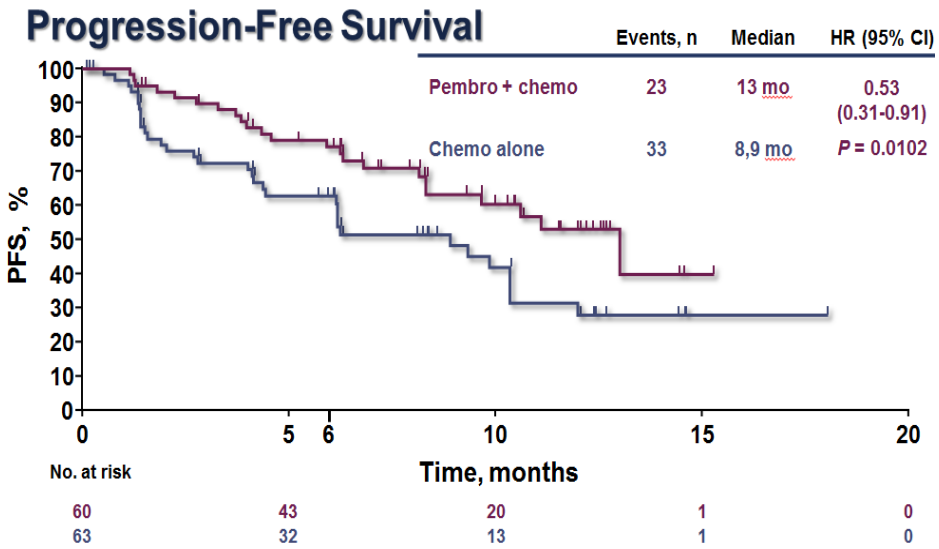


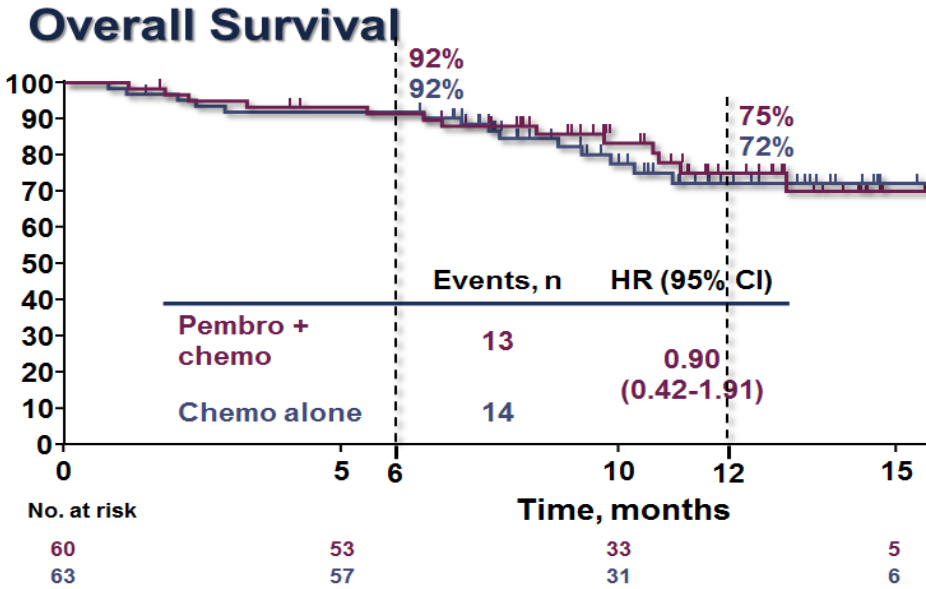
	Pembro + Chemo Responders n = 33	Chemo Alone Responders n = 18
TTR, mo median (range)	1.5 (1.2-12.3)	2.7 (1.1-4.7)
DOR, mo median (range)	NR (1.4+-13.0+)	NR (1.4+-15.2+)
Ongoing response,[a] n (%)	29 (88)	14 (78)

DOR = duration of response; TTR = time to response.
[a]Alive without subsequent disease progression.

Langer, et al Lancet Oncology 2016

KEYNOTE-021 Survival





Langer, et al Lancet Oncology 2016
Papadimitrikopolou, ASCO 2017

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Take home points

- Immune checkpoint inhibitors have improved survival in NSCLC in the 1st AND 2nd line setting

  …Survival benefit = 2-6 months

- PD-L1 is a simplistic predictive biomarker

  …Patients with PD-L1- tumors still benefit

  …Tumor mutation burden and other markers being explored

- IF response, then typically durable (>6 mos)

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Take home points

- More work needs to be done to determine which patients are best served by combination chemo-/immuno-therapy

  …I would consider combination therapies for:

  metastatic adenoCA, NO actionable mutations,

  PD-L1-, AND bulky tumor /very symptomatic

- TKIs remain the standard initial treatment for NSCLC with *EGFR, ALK, ROS1* mutations

- Immune toxicities are real, but can be managed

  …And are typically less severe than with chemotherapy

  …Early identification is essential

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Case Study #1

A 58-year-old female never smoker with bilateral lung mets and biopsy showing lung adenocarcinoma with EGFR mutation (L858R) and PD-L1 90% positive (22C3 assay).

What do you recommend?

1. Erlotinib 150 mg PO daily
2. Pembrolizumab
3. Pembrolizumab + pemetrexed and carboplatin combination

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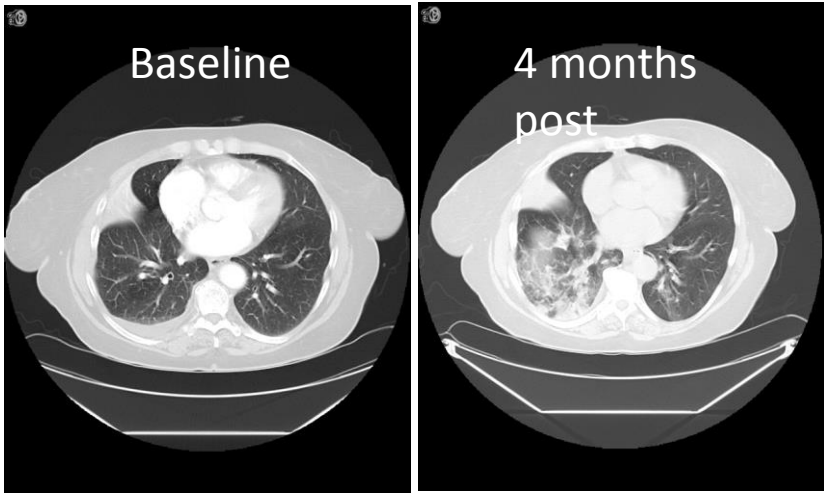
Case Study #2

A 70-year-old female ex-smoker with NSCLC currently receiving Pembrolizumab presents with increasing cough, SOB, and new decline in O2 sat to 82% on RA.

What is your management recommendation ?

1. Continue anti-PD-1 antibody
2. Continue anti-PD-1 with dose reduction
3. Hold anti-PD-1 for 2 weeks
4. Discontinue anti-PD-1 + start prednisone 40mg PO daily
5. Discontinue anti-PD-1 + admit for IV steroids



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