ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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Association of Community Cancer Centers

Society for Immunotherapy of Cancer

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Disclosures

- AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Genentech, Inc., Consulting Fees
- AstraZeneca Pharmaceuticals LP , Bristol-Myers Squibb, Corvus Pharmaceuticals, Genentech, Inc., Contracted Research
- I *will not* be discussing non-FDA approved indications during my presentation.

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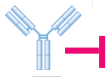
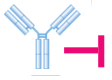
Immune checkpoint inhibitors in NSCLC

Nivolumab:



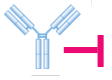
PD-1

Pembrolizumab :



PD-1

Atezolizumab:



PD-L1

2008

Nivolumab FIH trial initiated

2012

Checkmate 017 and 057 initiated

Pembrolizumab FIH trial initiated

2015

Nivolumab FDA approved in 2nd line NSCLC

2015

Pembrolizumab FDA approved in 2nd line NSCLC

(PD-L1 > 1%)

2016

Pembrolizumab FDA approved 1st line NSCLC

(PD-L1 > 50%)

2016

Atezolizumab FDA approved 2nd line NSCLC

2017

Pembrolizumab (+ pemetrexed and carboplatin)

FDA approved

1st line NSCLC

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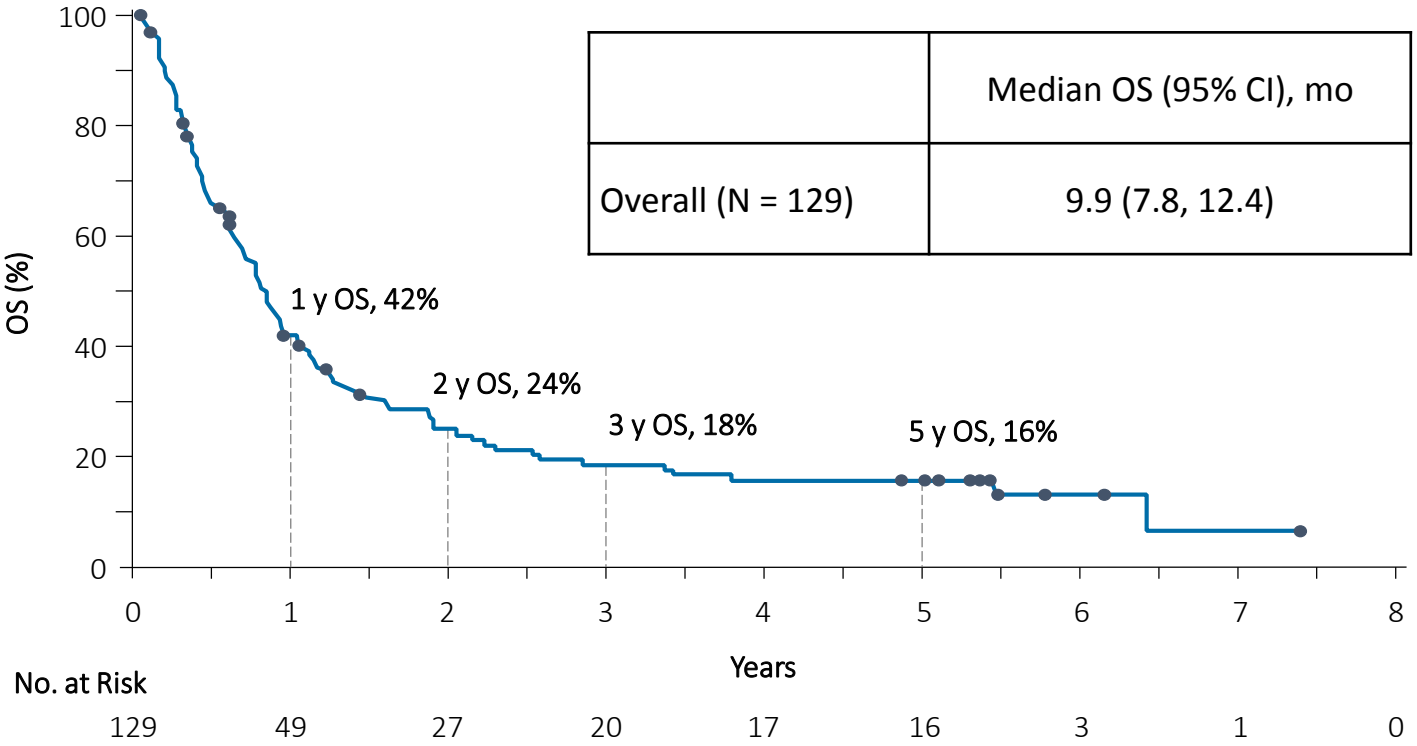
CA209-003 5-Year Update: Phase 1 Nivolumab in Advanced NSCLC

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



Brahmer et al, AACR 2017

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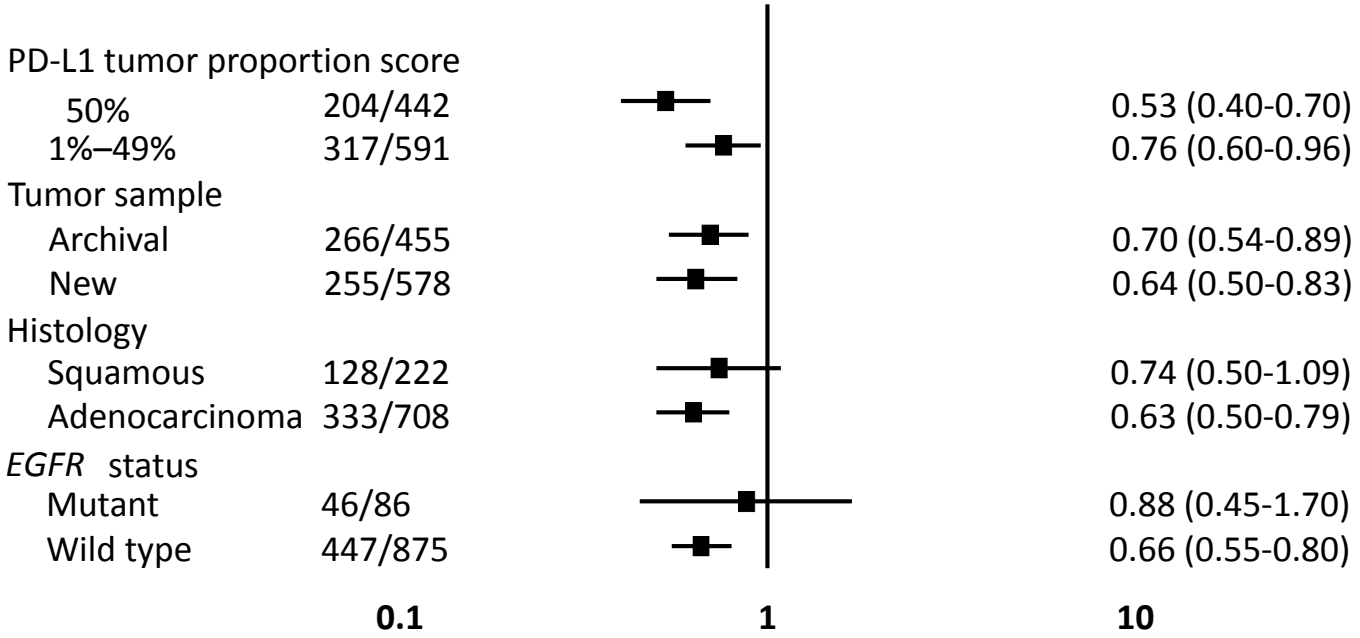
Approval in ≥ 2nd line setting (unselected for PD-L1)

		Atezo vs. doce OAK (2/3L)	Nivo vs. doce (017) (updated OS; 2L)	Nivo vs. doce (057) (updated OS; 2/3L)
ITT	HR	0.73	NA	NA
	Median OS (mo.)	13.8 vs. 9.6		
NSQ	HR	0.73	NA	0.73
	Median OS	15.6 vs. 11.2		12.2 vs. 9.4
SQ	HR	0.73	0.62	NA
	Median OS	8.9 vs. 7.7	9.2 vs. 6.0	

Barlesi ,et al., ESMO 2016
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015

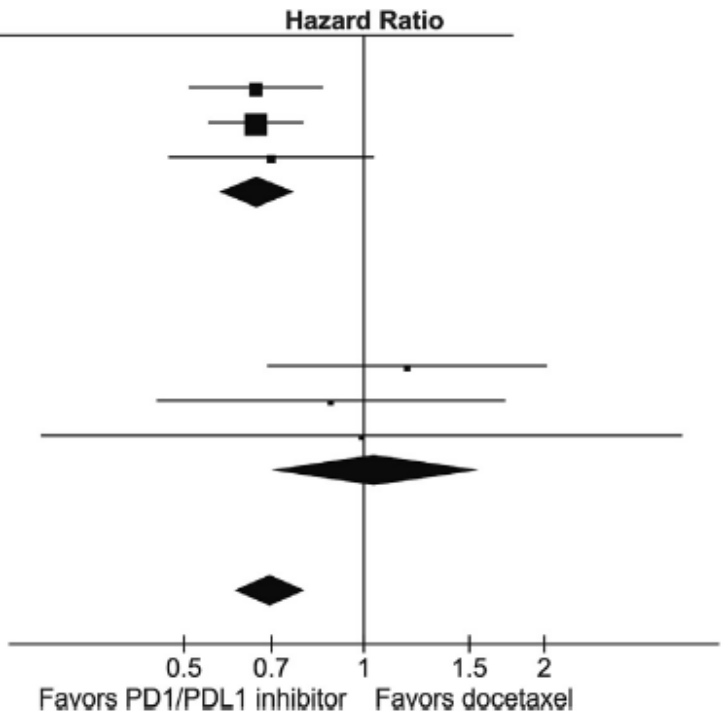
KEYNOTE 010: Pembrolizumab approval ≥ 2nd line (PD-L1 ≥ 1%)



Herbst et al, Lancet 2015

EGFRm PD-(L)-1 meta-analysis

Study	Weight	Hazard Ratio [95% CI]
EGFR wild-type		
Checkmate 057	26.0%	0.66 [0.51, 0.86]
Keynote 010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
Subtotal (95% CI)	**89.0%**	**0.66 [0.58, 0.76]**
EGFR mutant		
Checkmate 057	6.0%	1.18 [0.69, 2.00]
Keynote 010	3.8%	0.88 [0.45, 1.70]
POPLAR	1.1%	0.99 [0.29, 3.40]
Subtotal (95% CI)	**11.0%**	**1.05 [0.70, 1.55]**
Total (95% CI)	**100.0%**	**0.70 [0.61, 0.80]**



CK Lee et al., *JTO* 2016

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Toxicities in 2/3L Randomized trials

	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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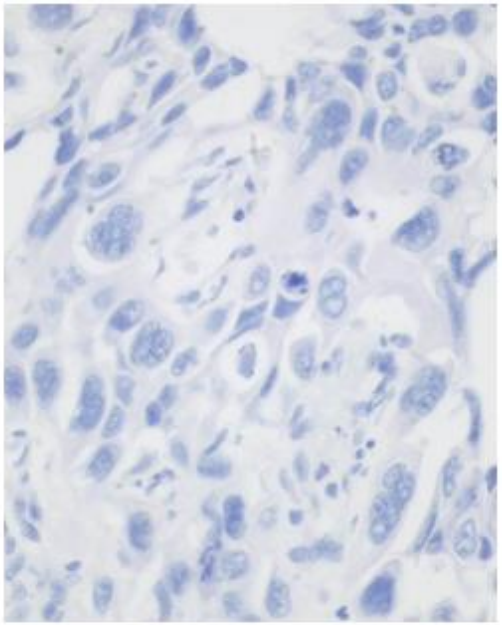
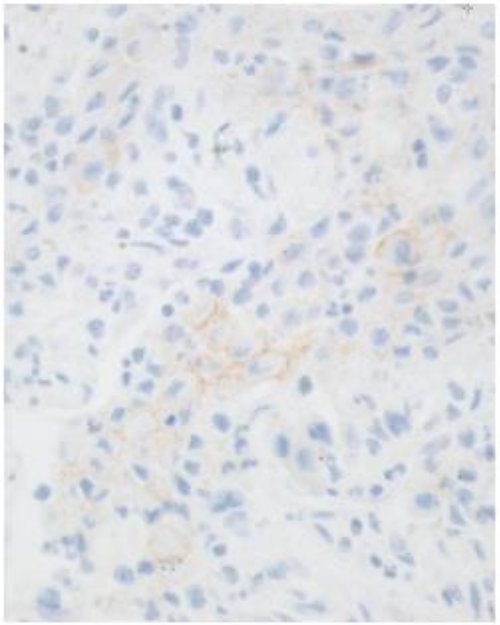
PD-L1 selection to bridge the gap ?



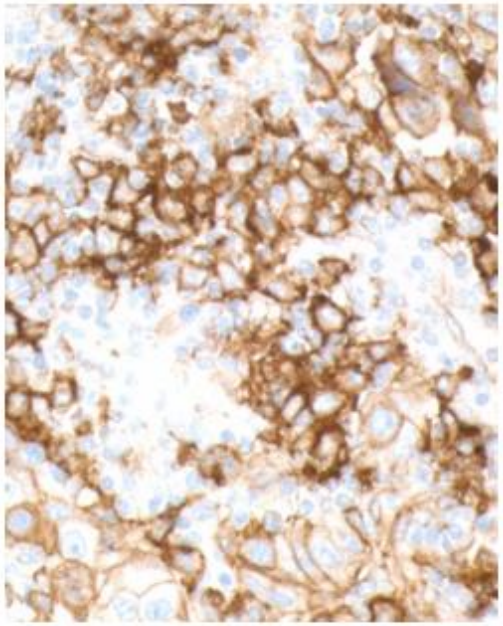
PD-L1 = 0% positive

Negative



PD-L1 = 2% positive

Weak Positive (1%-49%)

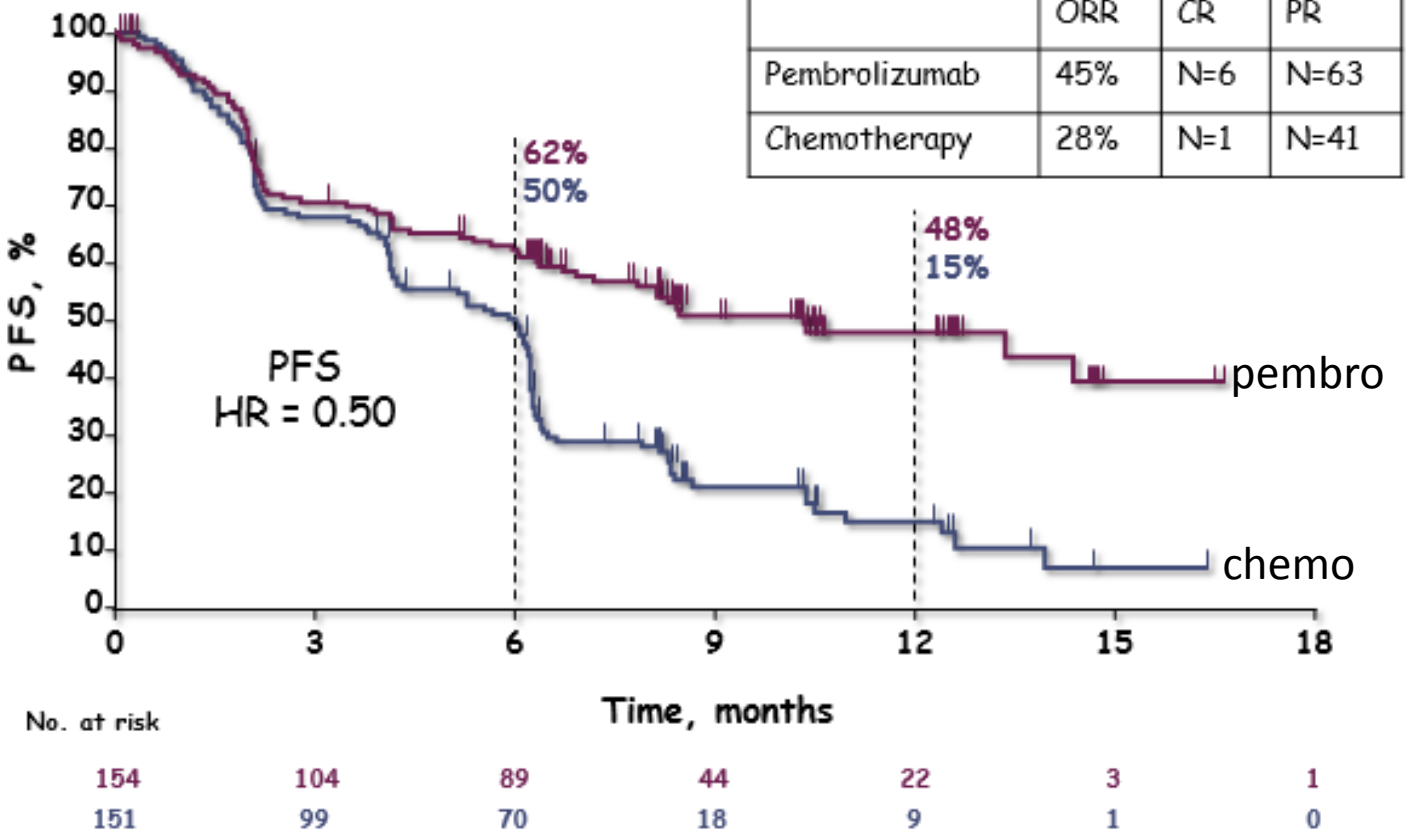


PD-L1 = 100% positive

Strong Positive (50%-100%)

KN 024: First line pembrolizumab vs. chemotherapy in PD-L1 ≥ 50%

	ORR	CR	PR
Pembrolizumab	45%	N=6	N=63
Chemotherapy	28%	N=1	N=41



Reck et al, NEJM 2016

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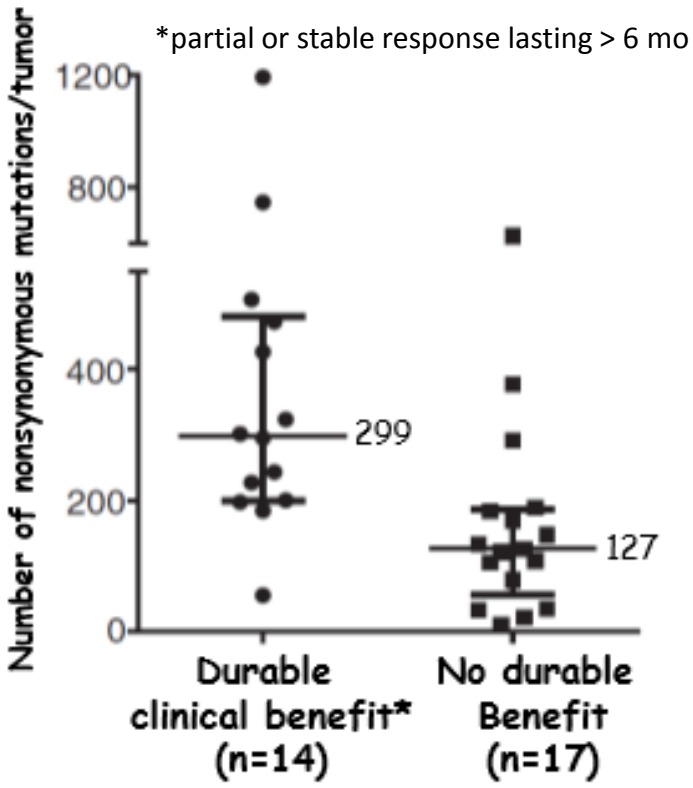
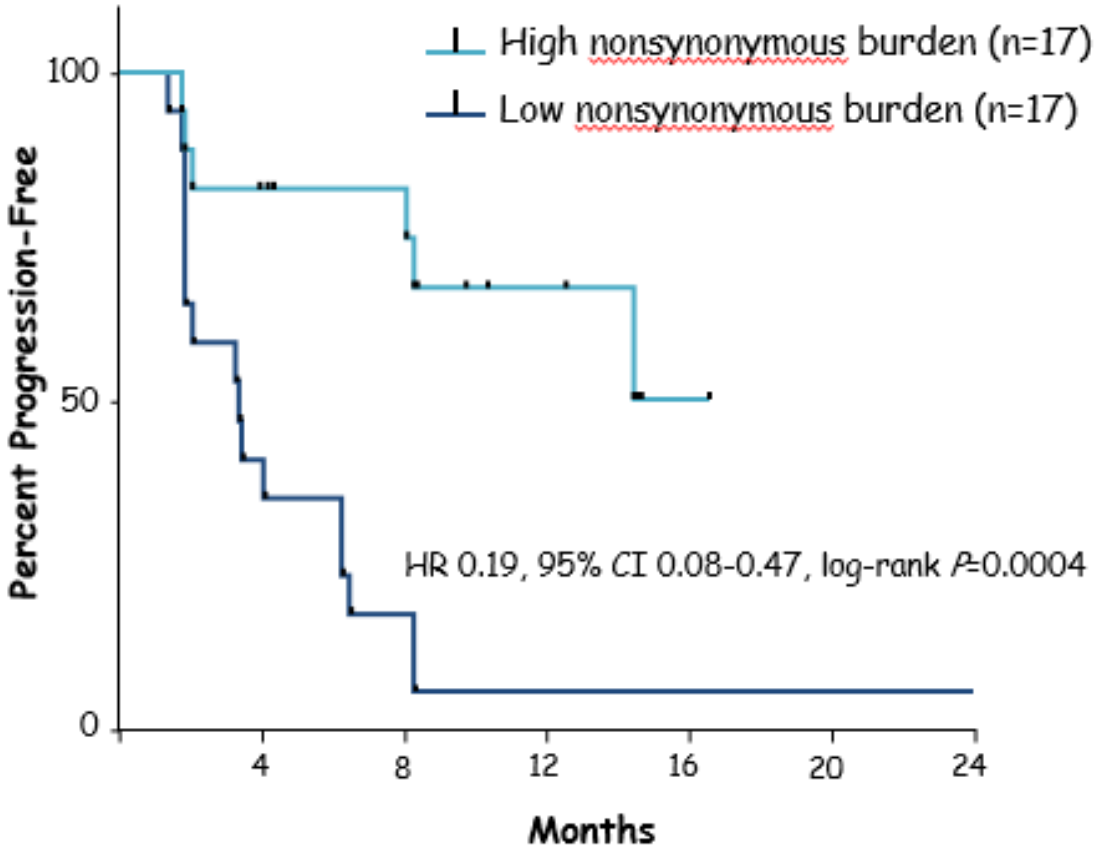
Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC



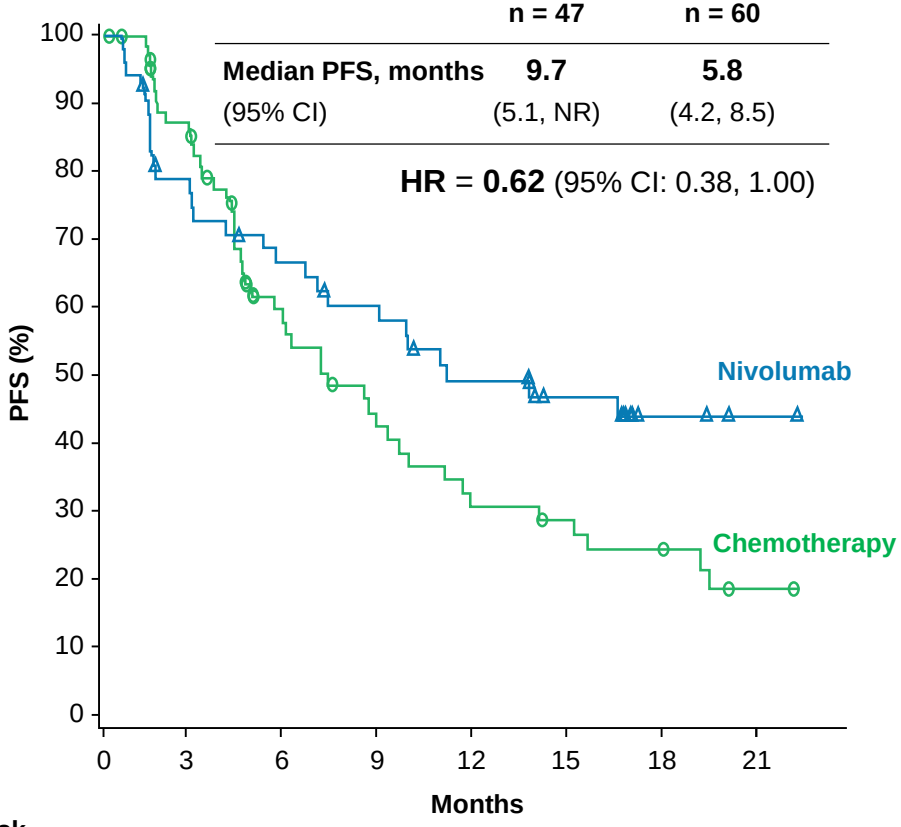


Rizvi N et al, Science 2015:348(6230):124-128

PFS by Tumor Mutation Burden Subgroup CheckMate 026 TMB Analysis

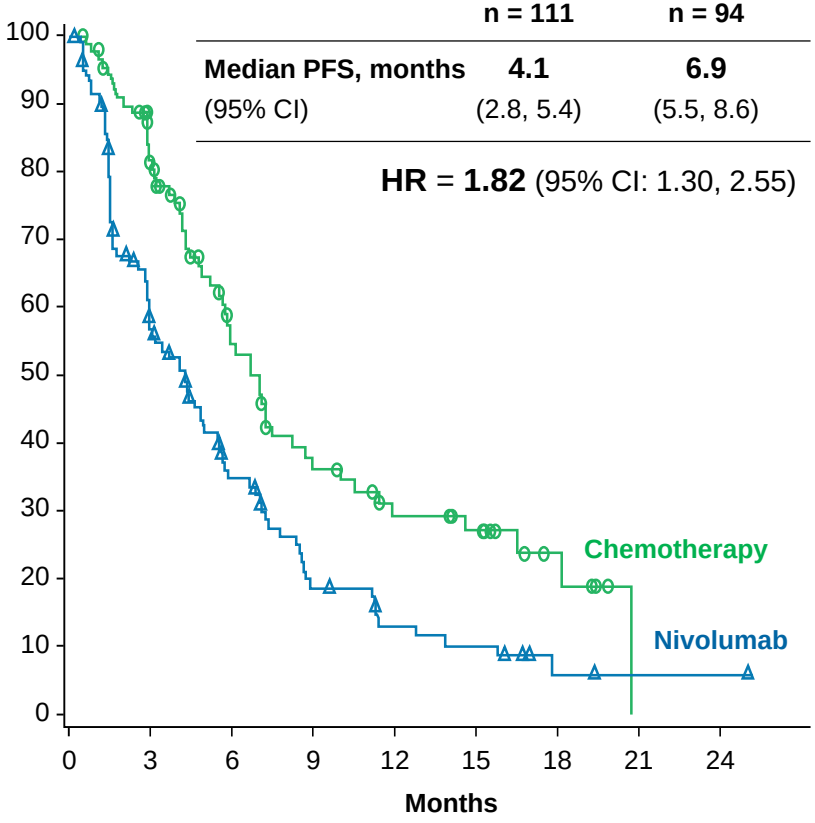
Nivolumab in First-line NSCLC

High TMB



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

Low/medium TMB

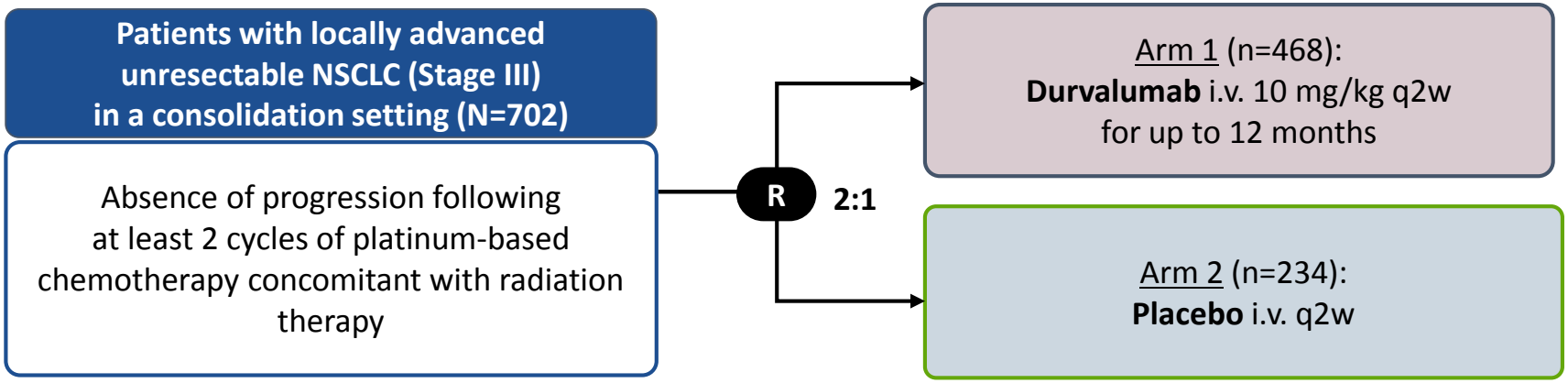


111	54	30	15	9	7	2	1	1
94	65	37	23	15	12	5	0	0

Peters, et al., AACR 2017

PACIFIC (NCT02125461/D4191C00001): Study Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)



Primary endpoints
- PFS, OS

Secondary endpoints
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

Est. completion: 2017
FPD[4] Q2 14
LPCD: Q2 16

DoR = duration of response; DSR = deep sustained response; FPD, first patient dosed; i.v. = intravenous; LPCD = last patient commenced dosing; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; q2w = every 2 weeks; QoL = quality of life.

PACIFIC (NCT02125461/D4191C00001): Study Design

- Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study (26 countries)

Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

Patients with locally advanced

therapy

Placebo i.v. q2w

Primary endpoints
- PFS, OS

Secondary endpoints
- ORR, DoR, DSR
- Safety/tolerability
- PK, immunogenicity, QoL

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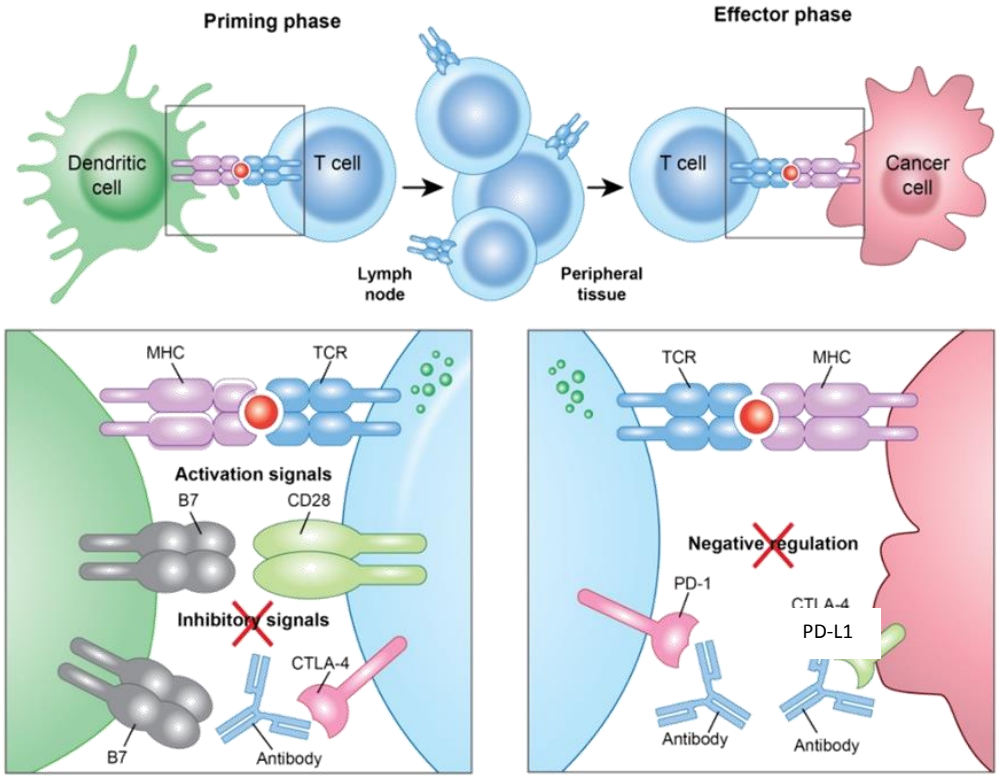
Combination Immune checkpoint blockade



Ribas A, N Engl J Med 2012; 366:2517-2519.

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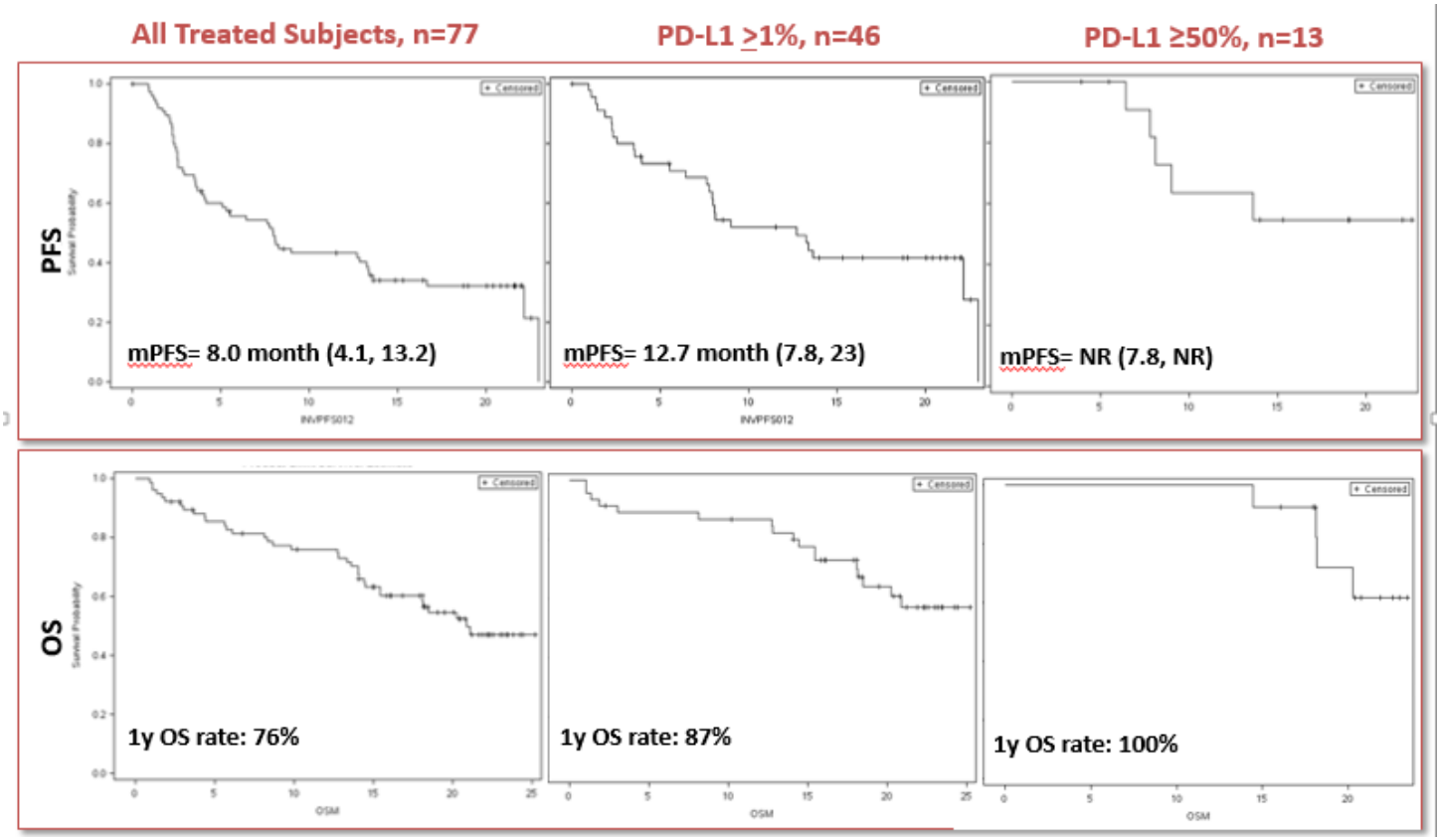
Ipilimumab: CTLA-4

Nivolumab: PD-1

Combination I-O (IPI/NIVO) potential in first line ?



CheckMate 012
Goldman, et al, ASCO Annual Meeting, 2017

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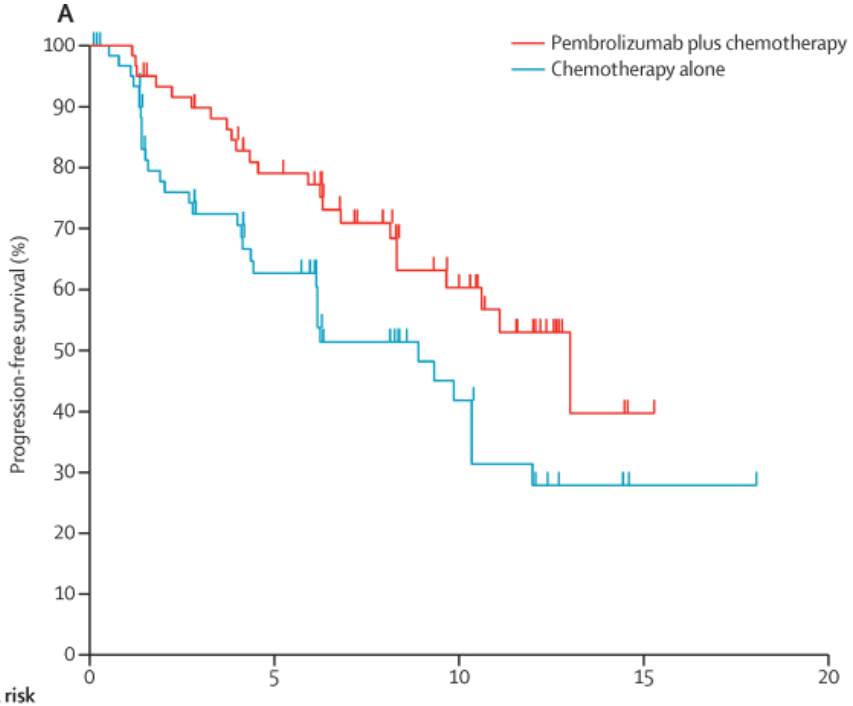
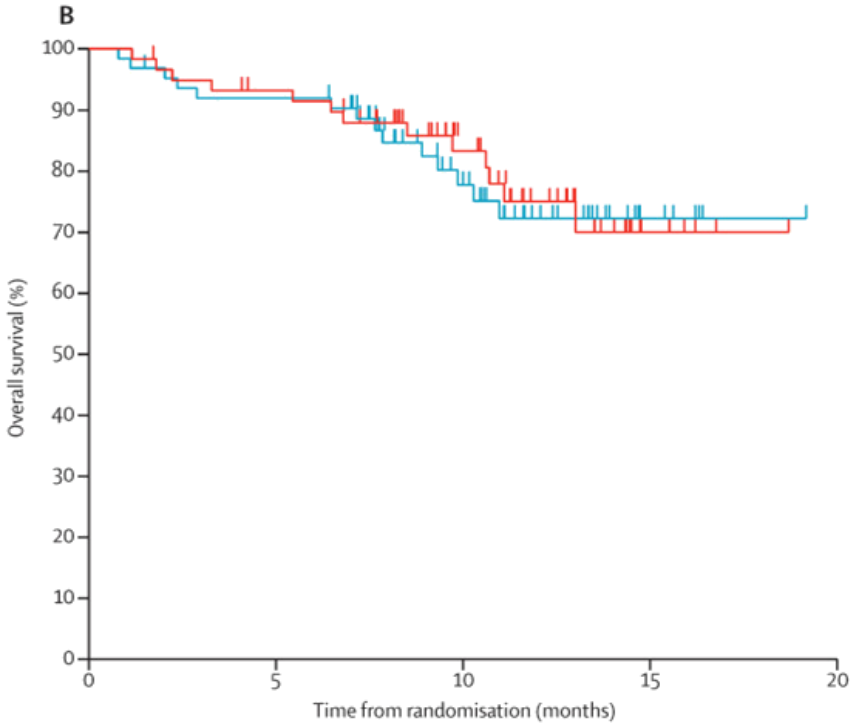
First line pemetrexed/carboplatin +/- pembrolizumab PFS



Number at risk (number censored)					
Pembrolizumab plus chemotherapy	60 (0)	43 (5)	20 (20)	1 (36)	0 (37)
Chemotherapy	63 (0)	32 (10)	13 (21)	1 (29)	0 (30)



	60 (0)	53 (3)	33 (18)	5 (42)	0 (47)
	63 (0)	57 (1)	31 (20)	6 (43)	0 (49)

KEYNOTE-021 study: Langer CL, *Lancet Oncol* 2016

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Phase 3 first-line combination trials in advanced NSCLC (all PD-L1 unselected)

Treatment	N*	Arms			Primary endpoint
Checkmate 227[1]	1980	Nivolumab, ipilimumab	Nivolumab	Plt-doublet chemotherapy	OS
MYSTIC[2]	1092	Durvalumab, tremelimumab	Durvalumab	SOC Plt-based chemotherapy	PFS
NEPTUNE[3]	800	Durvalumab, tremelimumab	SOC Plt-based chemotherapy	-	OS
IMpower 130[4]	550	Atezolizumab, nab-paclitaxel/carboplatin	nab-paclitaxel/carboplatin	-	PFS
IMpower 150[5]	1200	Atezolizumab, paclitaxel/carboplatin, bevacizumab	Atezolizumab, paclitaxel/carboplatin	Paclitaxel/ carboplatin, bevacizumab	PFS
IMpower 131[6]	1200	Atezolizumab, nab-paclitaxel/carboplatin	Atezolizumab, paclitaxel/carboplatin	Nab-paclitaxel/carboplatin	PFS

*Estimated enrolment

Plt, platinum; SOC, standard of care

1. NCT02477826; 2. NCT02453282; 3. NCT02542293; 4. NCT02367781; 5. NCT02366143; 6. NCT02367794

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Case Study #1

A 58-year-old female never smoker with bilateral lung disease, biopsy shows adenocarcinoma, EGFR mutation (L858R) and PD-L1 is 90% positive (22C3 assay). What do you recommend?

1. Erlotinib 150 mg po qd
2. Pembrolizumab
3. Pembrolizumab + pemetrexed and carboplatin combination

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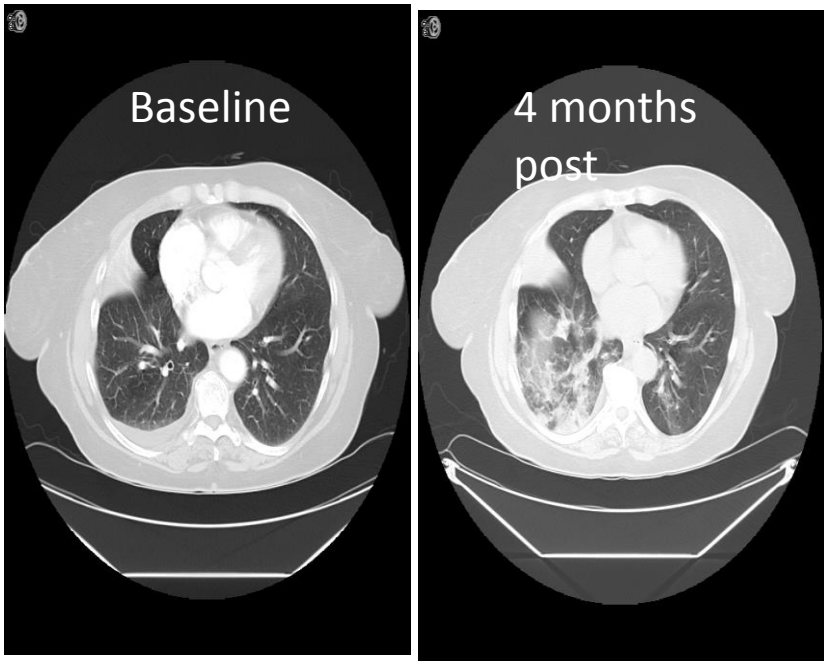
Case Study #2

A 70-year-old female ex-smoker with NSCLC with treatment response to anti-PD-1 antibody presents with increasing cough, SOB and new decline in O2 sat to 82%. 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 and start prednisone 40 mg po qd
5. Discontinue anti-PD-1 and admit for IV steroids



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