Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Jonathan Riess, MD
Assistant Professor of Medicine
UC Davis Comprehensive Cancer Center

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
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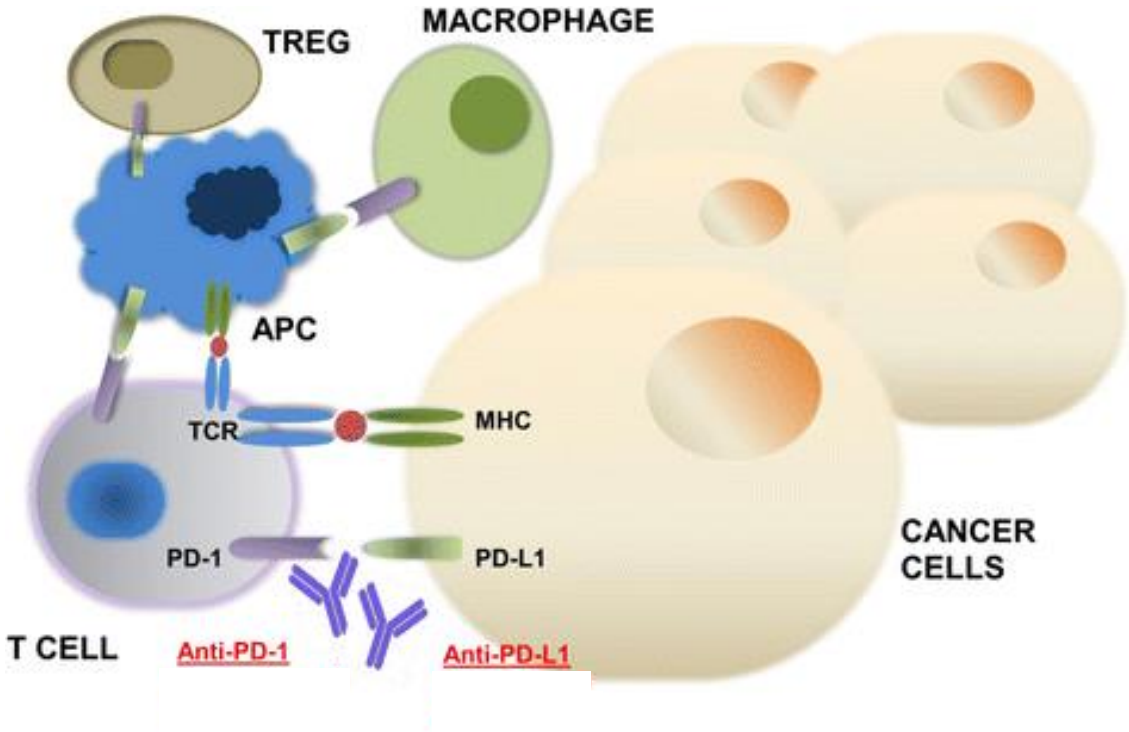
Disclosures

- Consulting Fees:
  - Celgene, Takeda, AbbVie, Spectrum, LOXO Oncology, Heron Therapeutics
- Contracted Research:
  - Merck, Novartis, Boehringer Ingelheim, Spectrum, AstraZeneca
- I will not be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

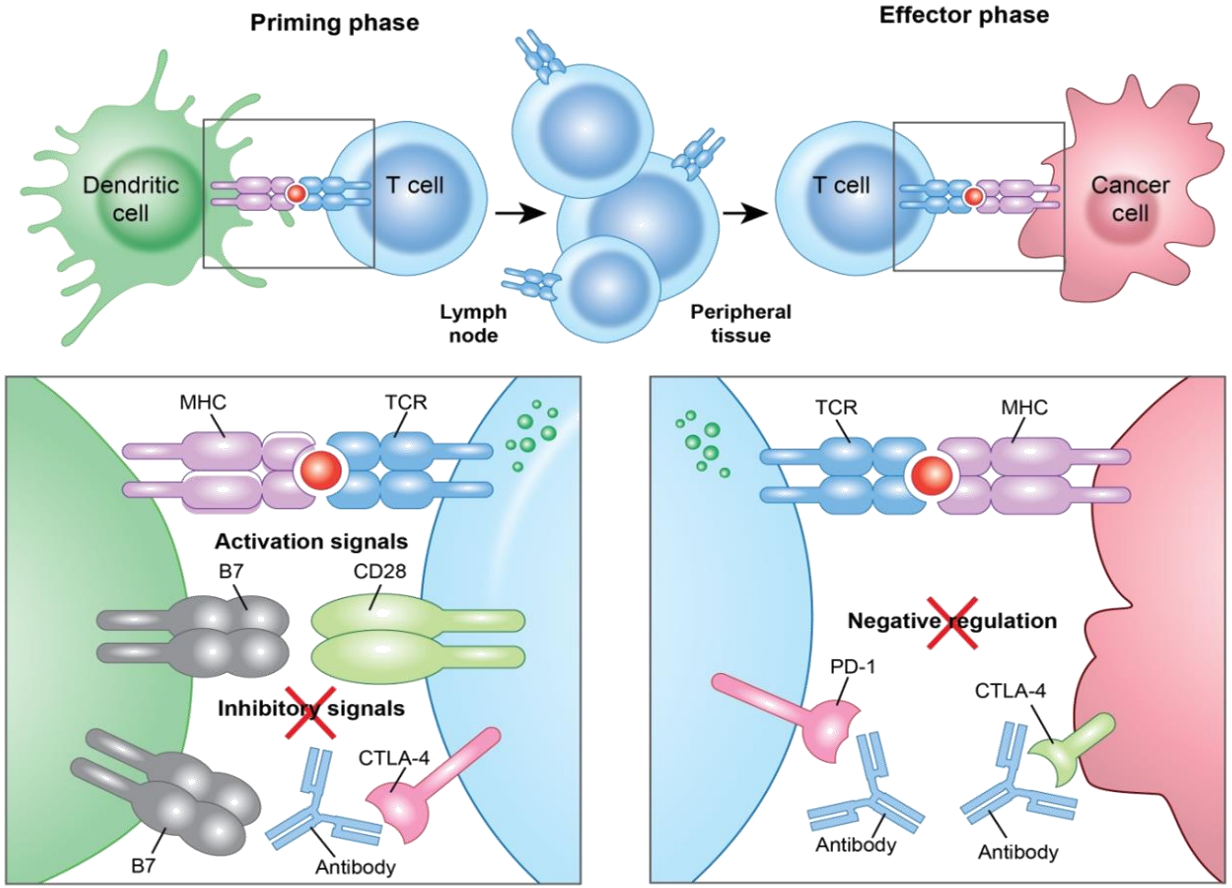
- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells



Gong J, Journal for ImmunoTherapy of Cancer, 2018

Combination Immune Checkpoint Blockade

- CTLA-4 acts as an “off-switch” for T cells when interacting with B7
- Combination strategies combine both CTLA-4 and PD-1/PD-L1 blockade



Ribas A, NEJM, 2012

FDA-approved Checkpoint Inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

2008

Nivolumab FIH trial initiated

2012

Checkmate 017 and 057 initiated

Pembrolizumab FIH trial initiated

2015 (March)

Nivolumab FDA approved in 2nd line Sq NSCLC

2015 (Fall)

Nivolumab Approved in Fall for 2nd line Non-sq NSCLC

Pembrolizumab FDA approved in 2nd line NSCLC (PD-L1 > 50%)

2016 (Fall)

Pembrolizumab FDA approved 1st line NSCLC (PD-L1 > 50%)

Pembrolizumab FDA approved in 2nd line NSCLC (PDL1 > 1%)

Atezolizumab FDA approved 2nd line NSCLC

2017 (May)

Pembrolizumab + Pemetrexed and Carboplatin FDA approved 1st line NSCLC 2017 (July)

Durvalumab FDA Approved for Stage III NSCLC

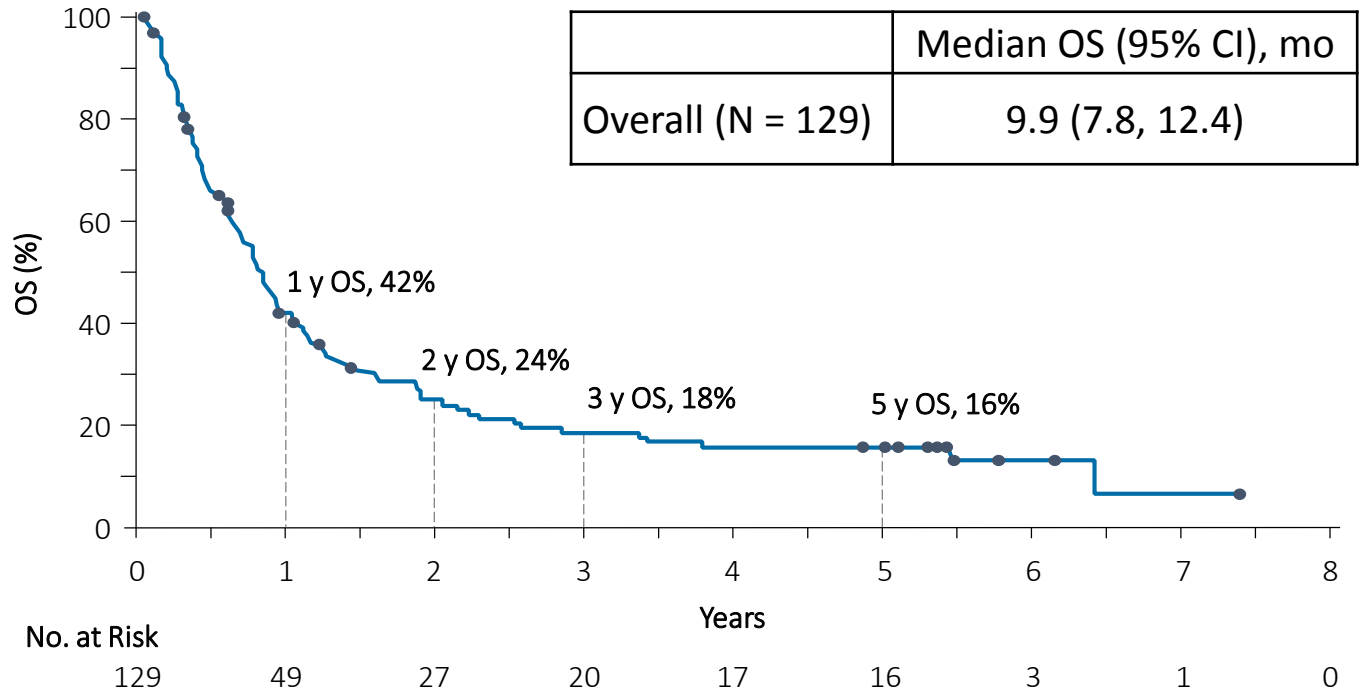
CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

Phase 1, 5-Year Update

- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor
- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%

5-Year Survival

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



Gettinger et al. JCO 2018
Brahmer et al, AACR 2017
NCI SEER data, Lung and Bronchus Cancer, 2014

Treatment Naïve Regimens: Competing Strategies

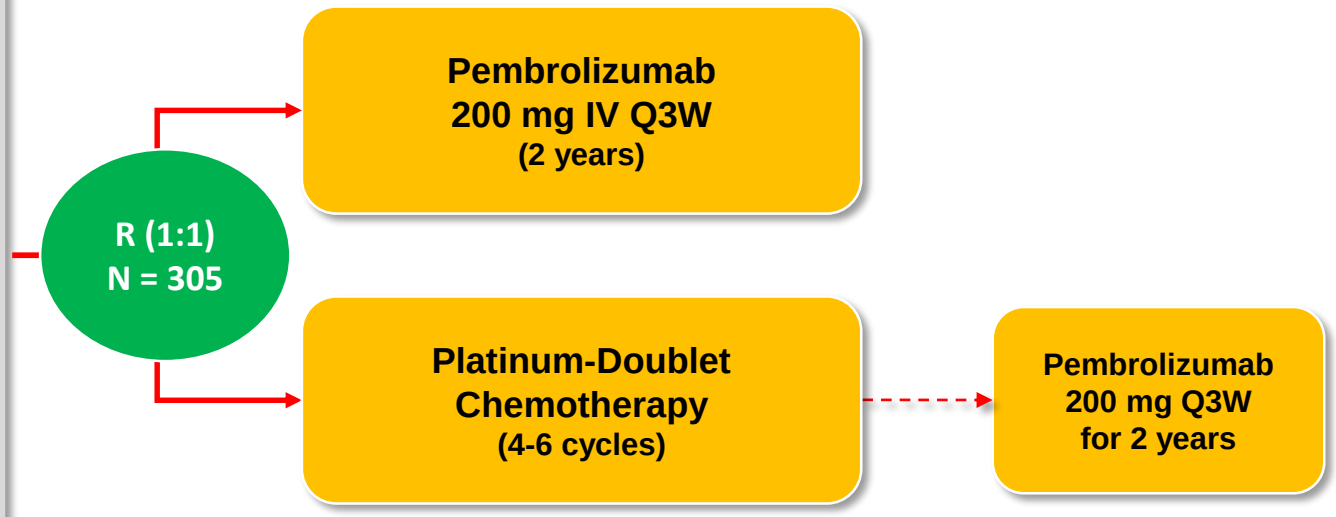
- KEYNOTE 024 – Pembrolizumab vs. Chemotherapy in PD-L1 > 50%
- KEYNOTE 042 – Pembrolizumab vs. Chemotherapy in PD-L1 > 1%
- KEYNOTE 189 – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in patients with advanced non-squamous NSCLC
- IMPOWER 150 – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (Bev) in patients in advanced non-squamous NSCLC
- KEYNOTE 407 – Pembrolizumab + Chemotherapy vs. Chemotherapy in advanced squamous cell lung cancer
- Checkmate 227 – Ipilimumab + Nivolumab vs. Chemotherapy in advanced NSCLC with high TMB

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (>50%)

NSCLS Study Design (NCT021427389)

Key Eligibility Criteria

- ***Untreated*** stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

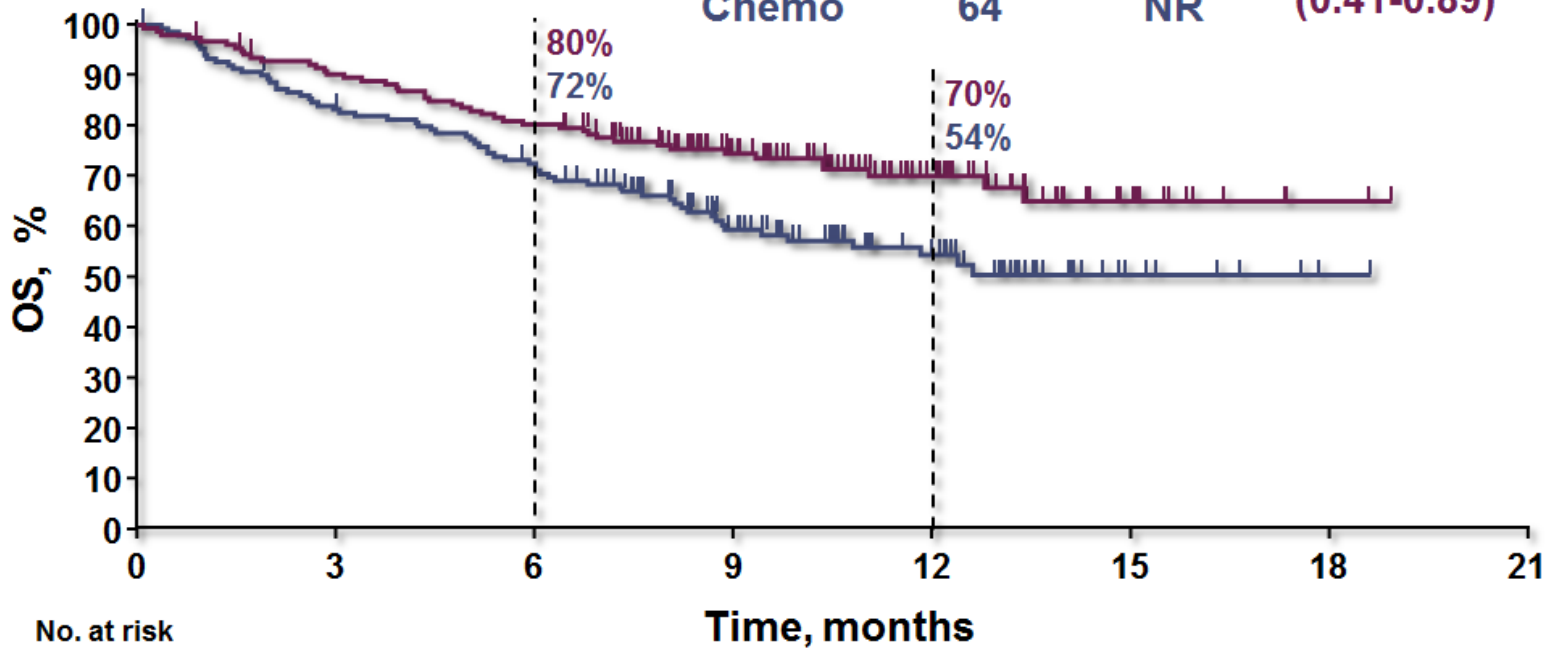


Reck M et al, ESMO 2016, NEJM 2016

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 >50% NSCLC

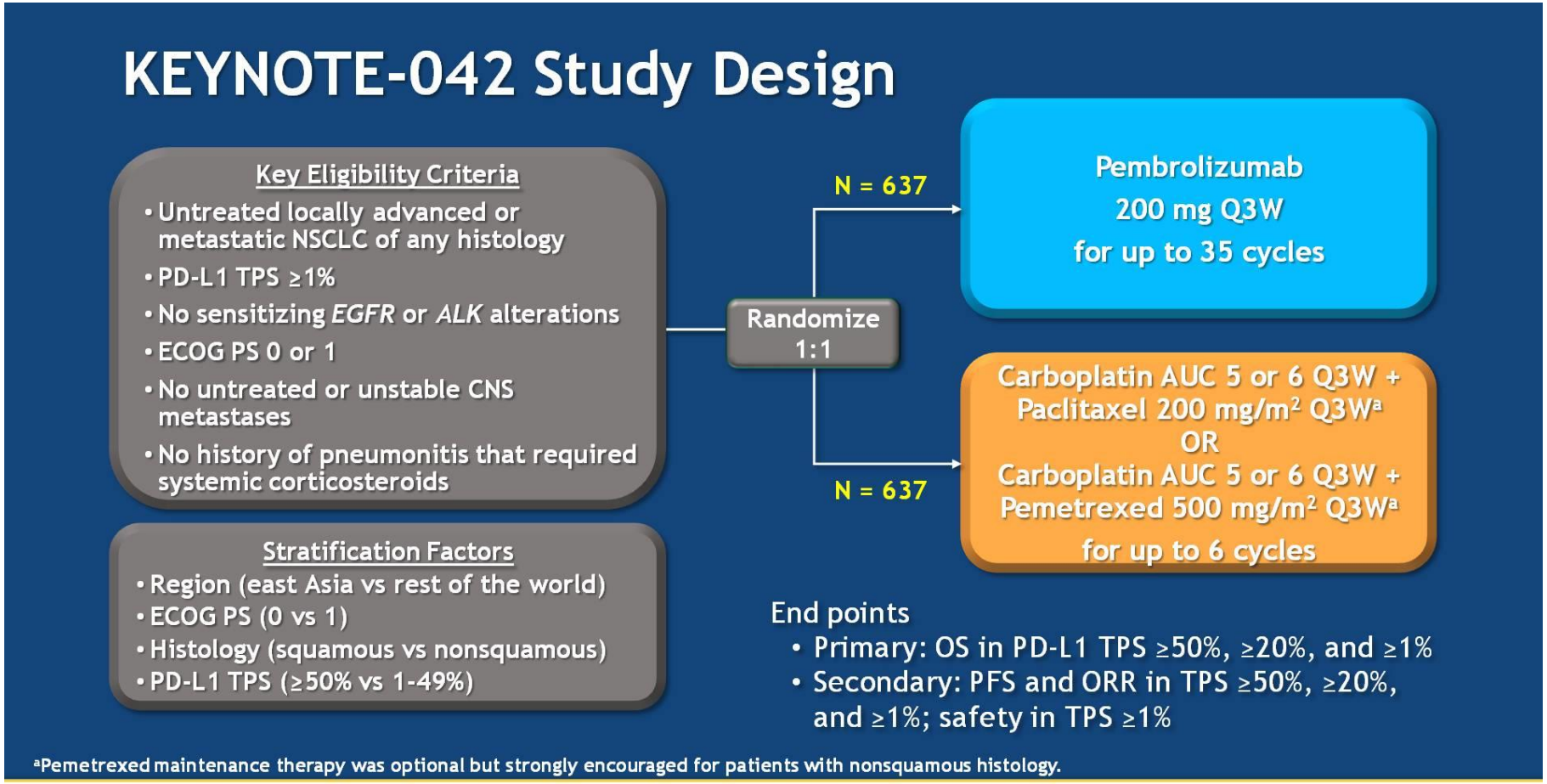
Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		



Reck M et al, ESMO 2016, NEJM 2016

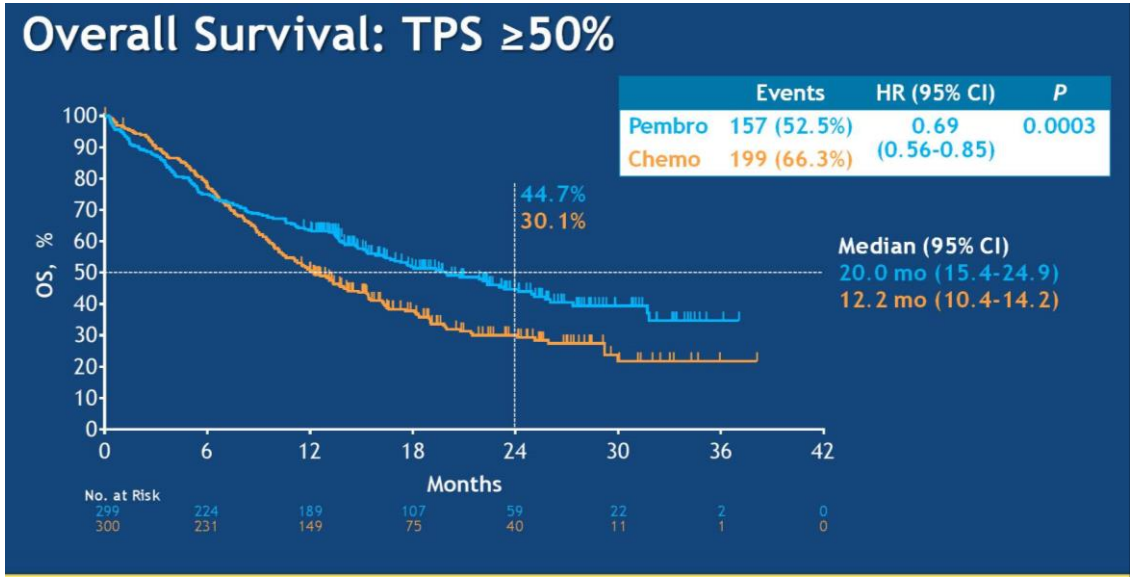
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 > 1% NSCLC

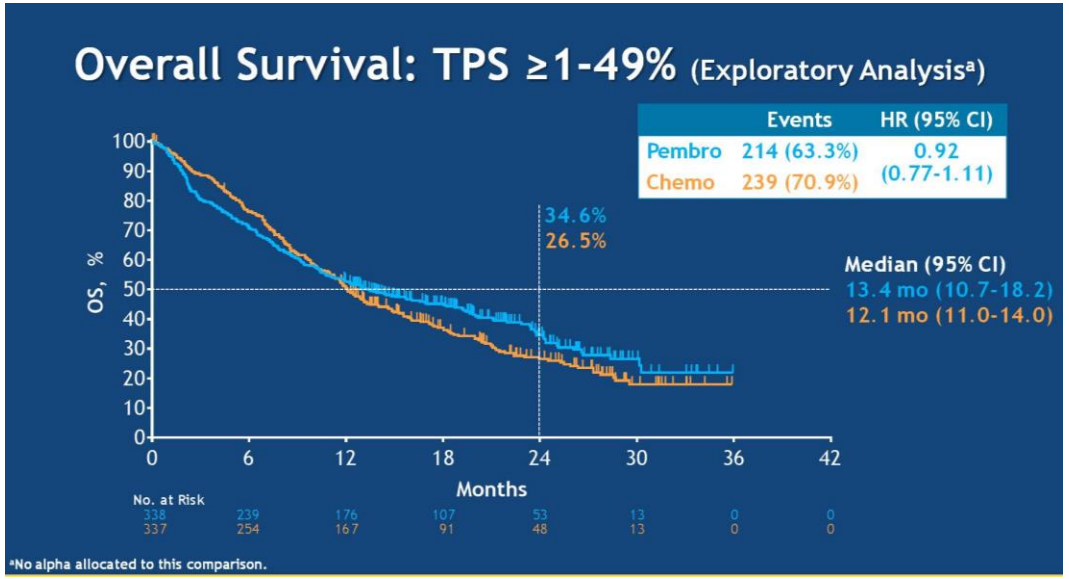


Lopes et al, ASCO 2018

KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 > 1% NSCLC

Overall Survival

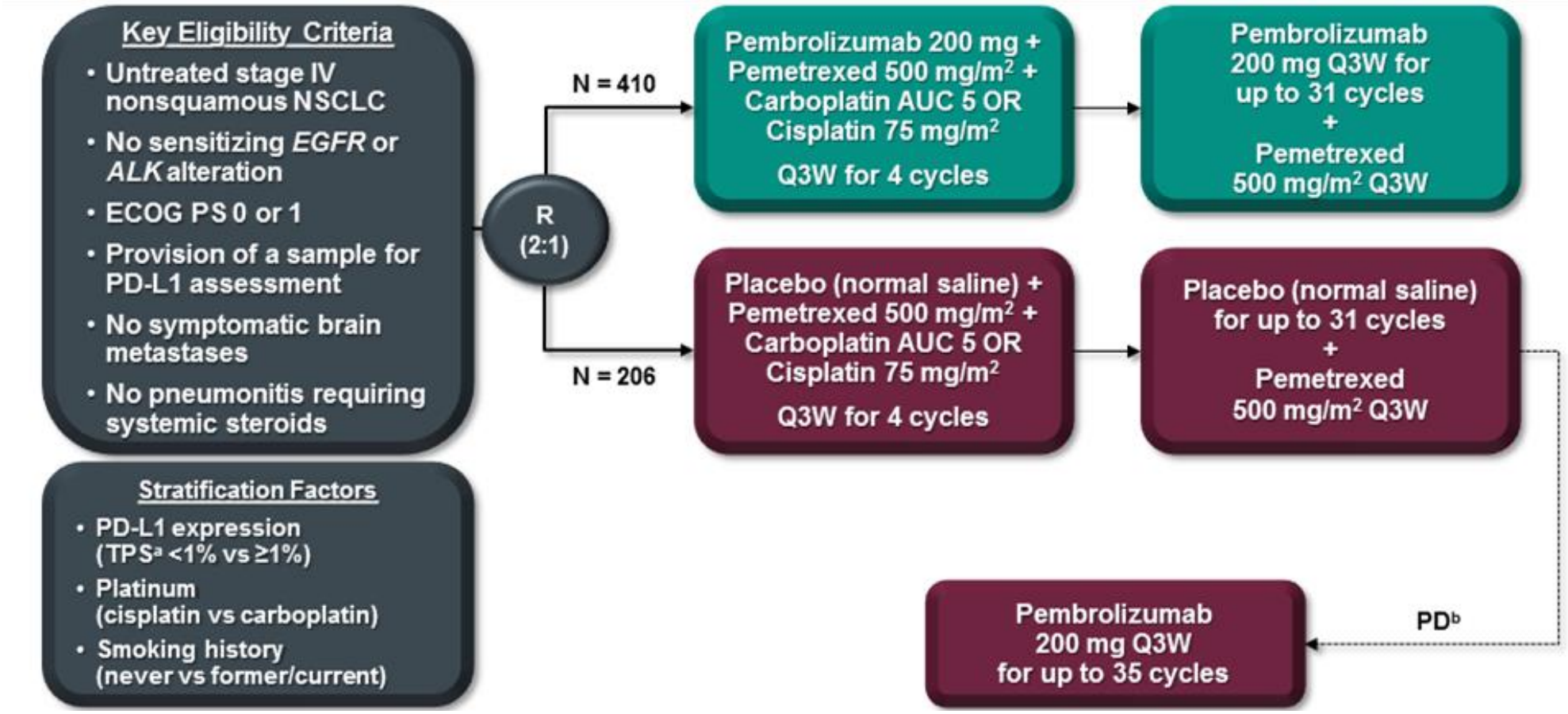




Survival benefit seemed to be driven by the TPS > 50% subset with little benefit witnessed in the subset TPS > 1- 49%

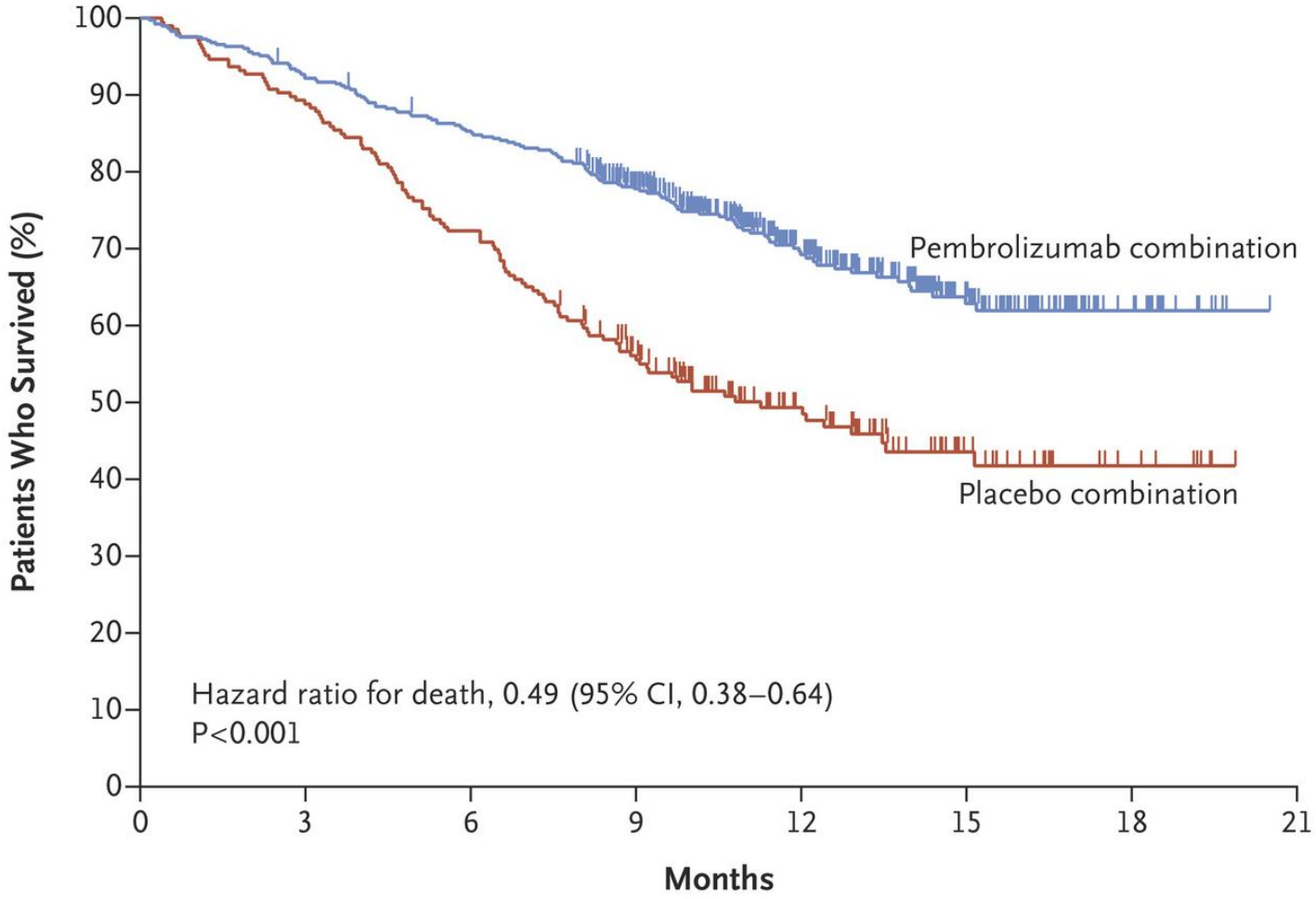
Lopes et al, ASCO 2018

KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



Ghandi et al, NEJM 2018

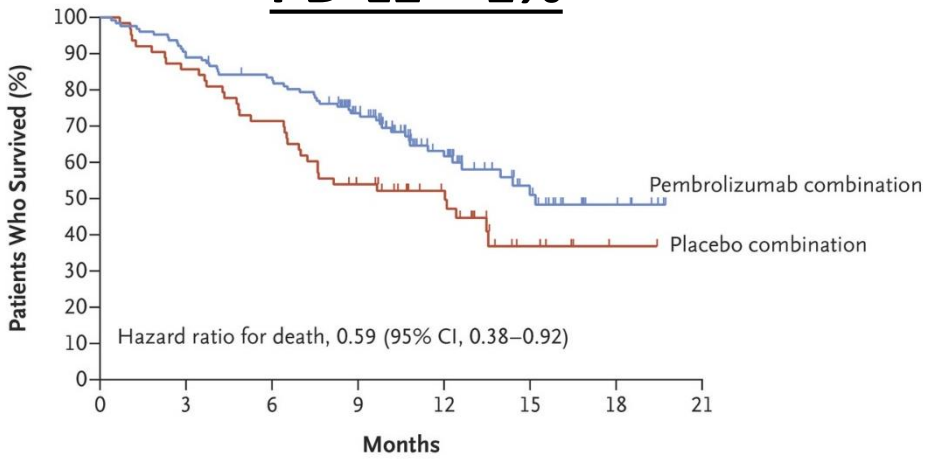
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



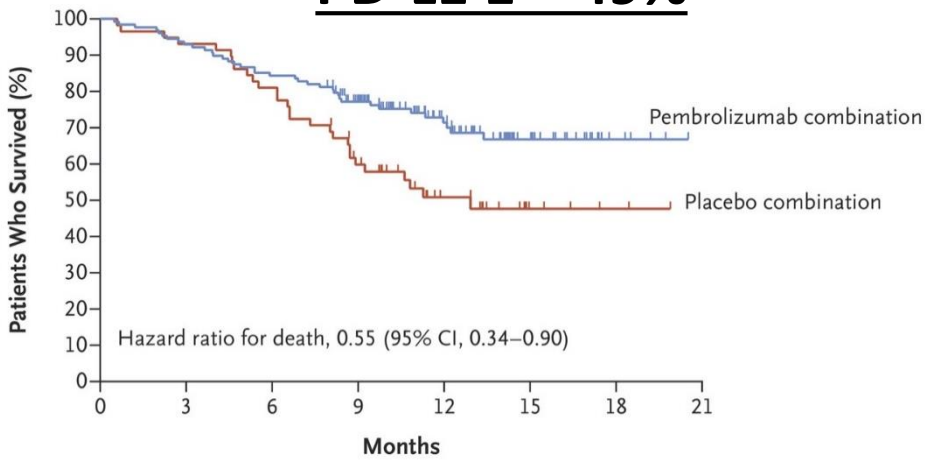
Ghandi et al, NEJM 2018

KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC

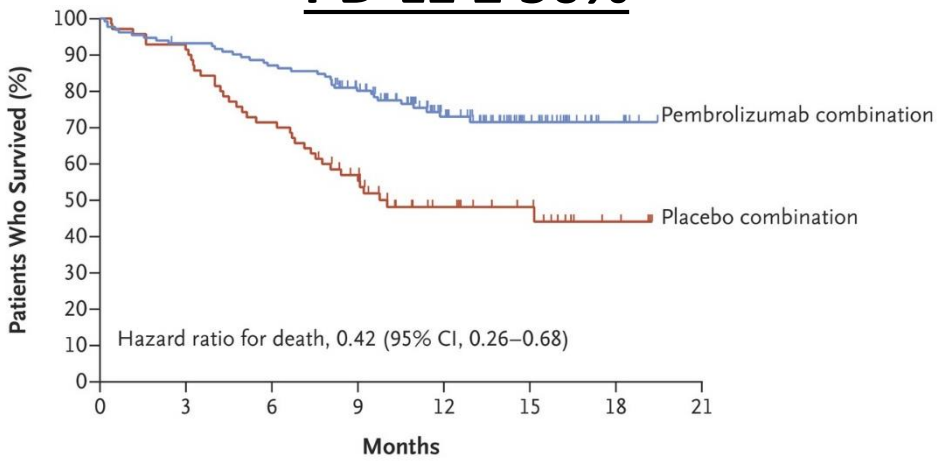
PD-L1 < 1%



PD-L1 1 – 49%

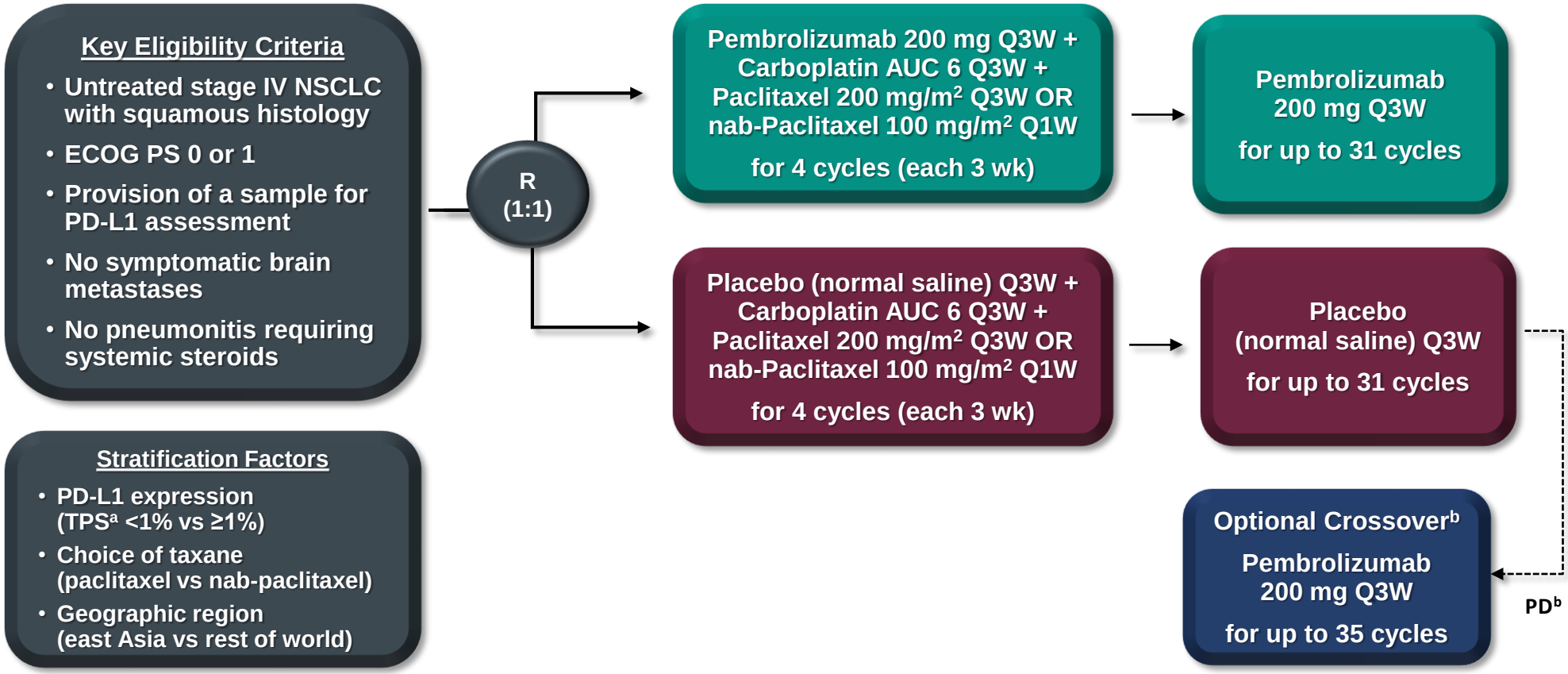


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC

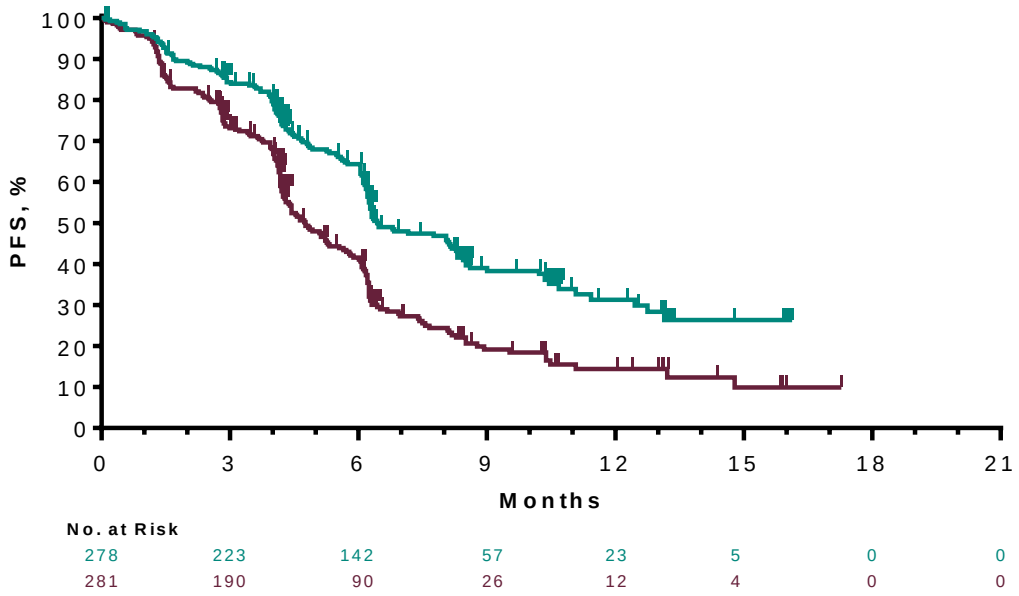


Paz-Ares et al, ASCO 2018

KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC

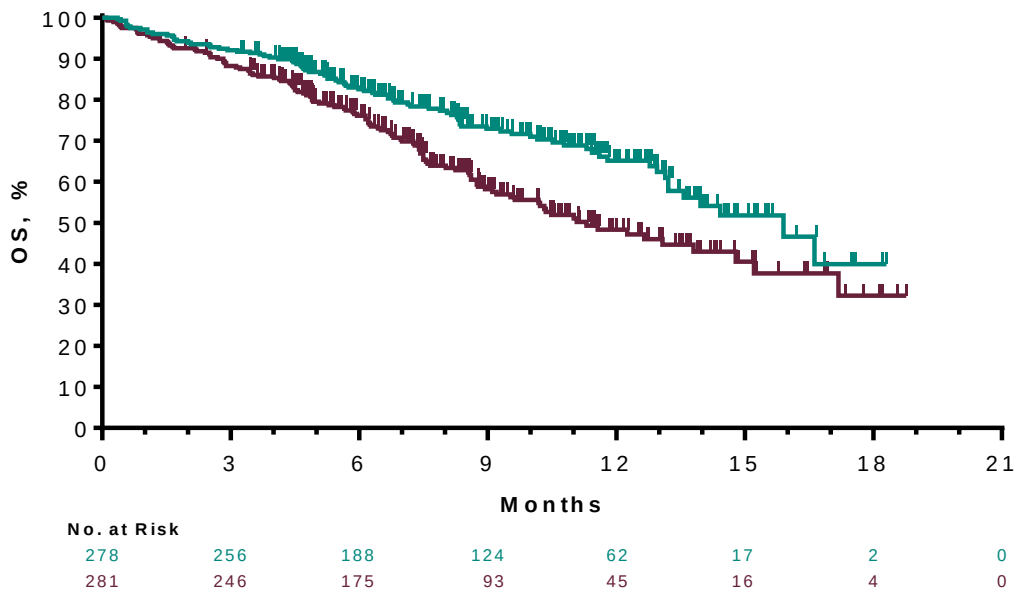
PFS (RECISTv1.1, BICR)

	Events	HR (95% CI)	*P*
Pembro + Chemo	54.7%	0.56 (0.45-0.70)	<0.0001
Placebo + Chemo	70.1%		



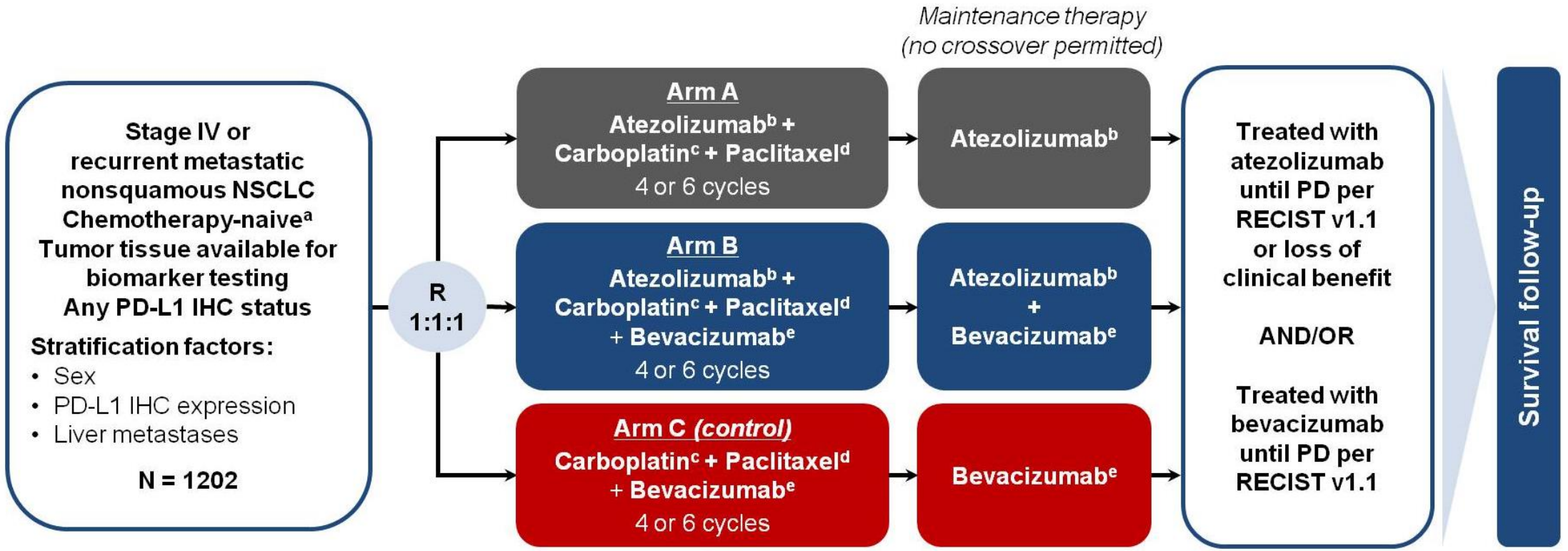
Overall Survival

	Events	HR (95% CI)	*P*
Pembro + Chemo	30.6%	0.64 (0.49-0.85)	0.0008
Placebo + Chemo	42.7%		



Paz-Ares et al, ASCO 2018

IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in advanced non-squamous NSCLC

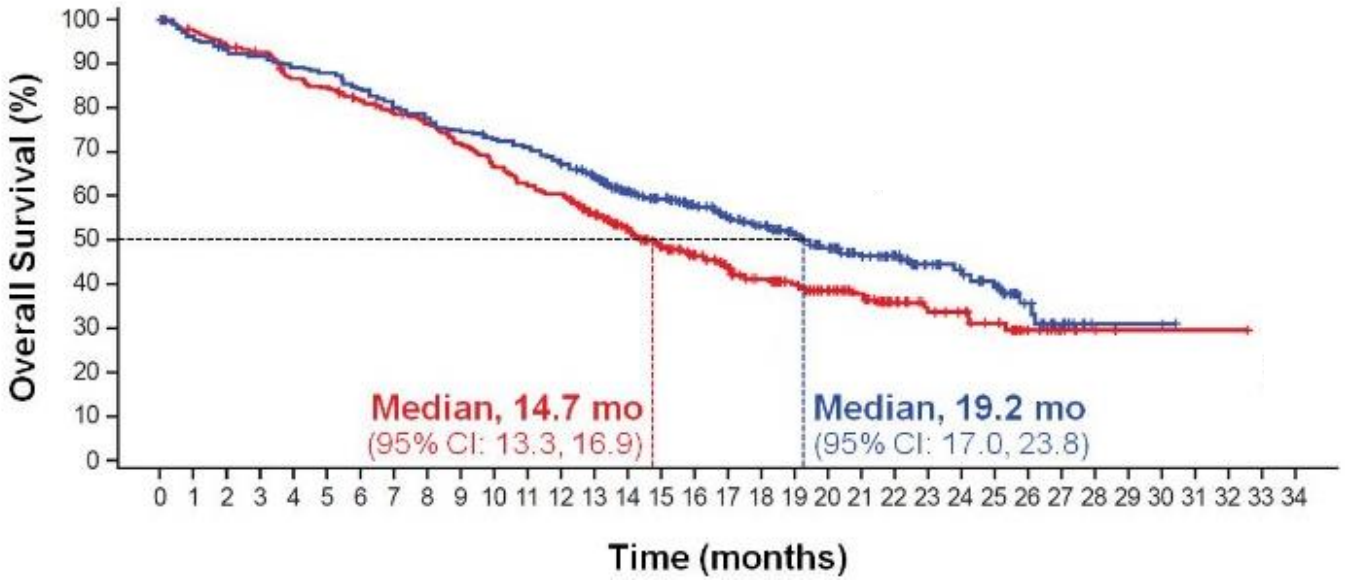


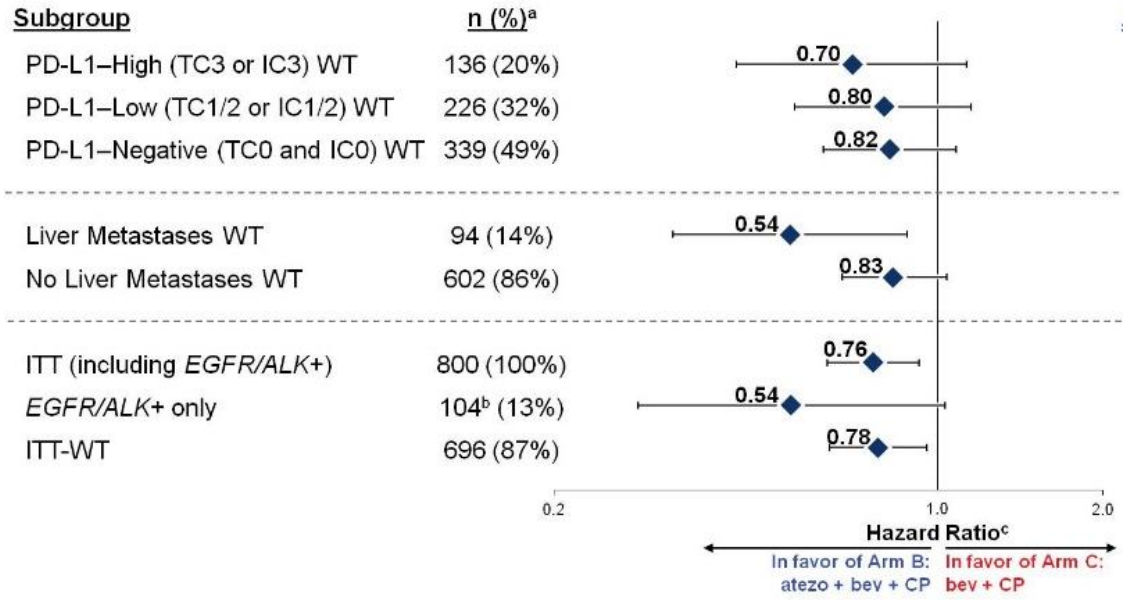
Socinski et al, NEJM 2018

IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in advanced non-squamous NSCLC

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo

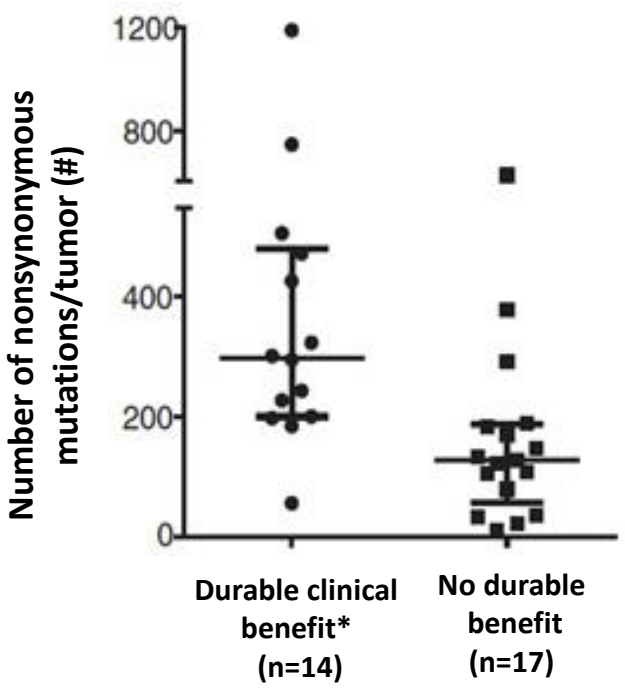


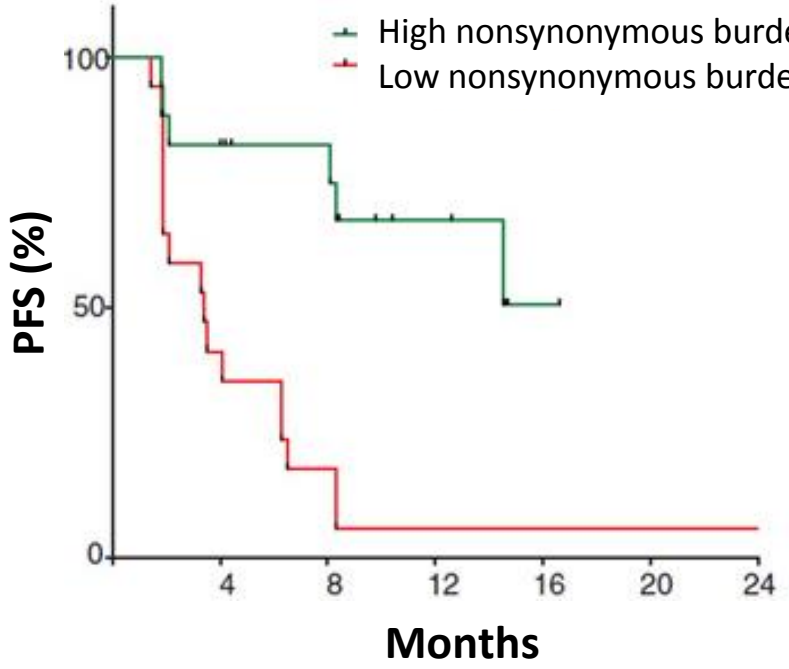


Socinski et al, NEJM 2018

Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

- In two independent cohorts, higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit, and PFS.

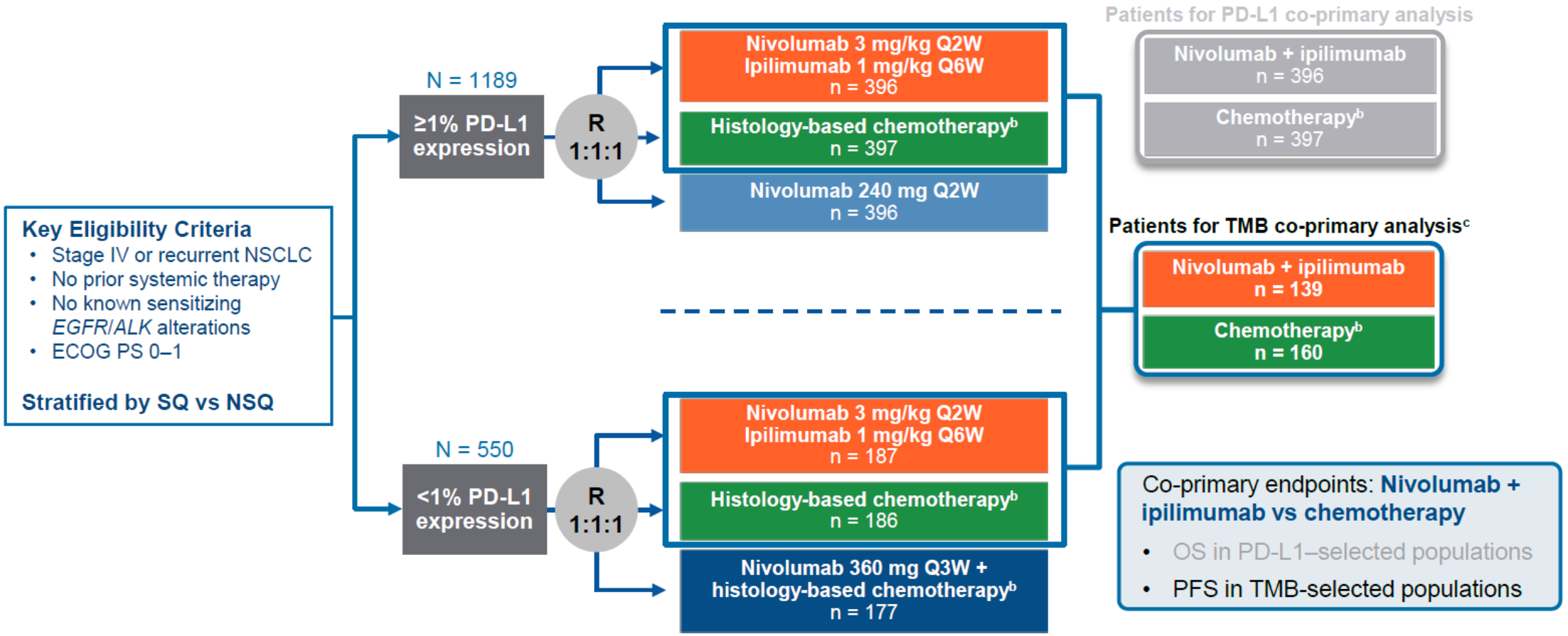




*Partial or stable response lasting > 6 mo

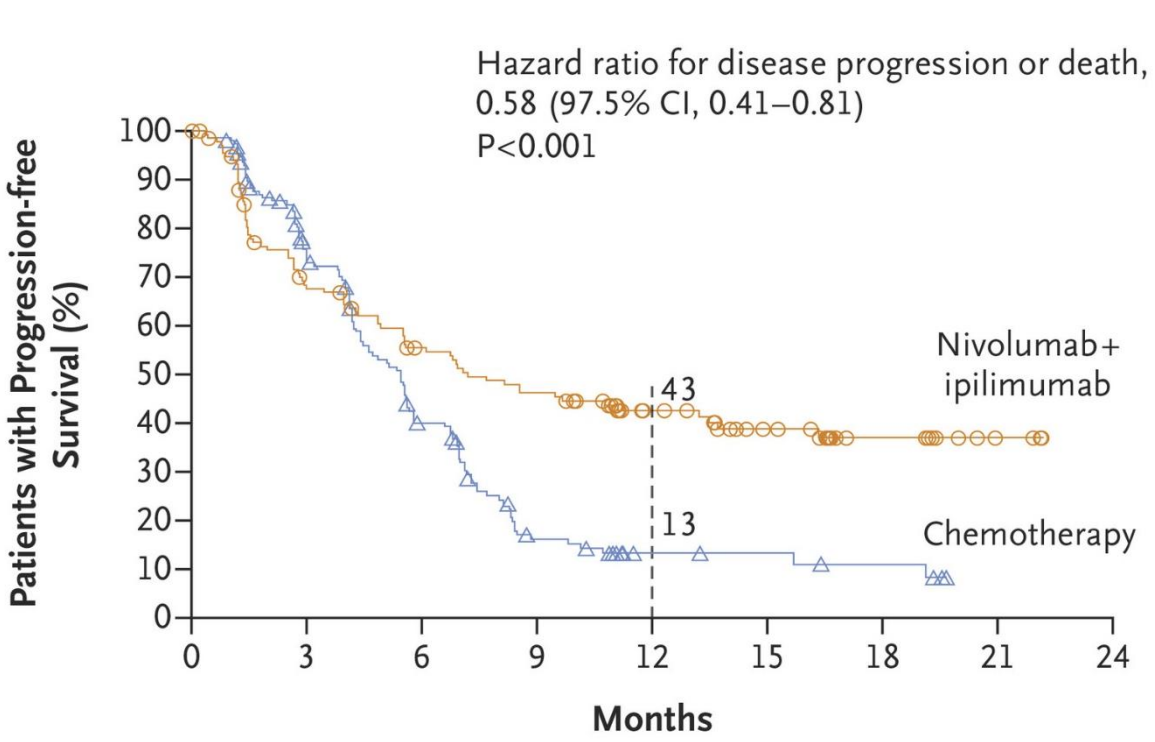
Rizvi N et al, Science, 2015

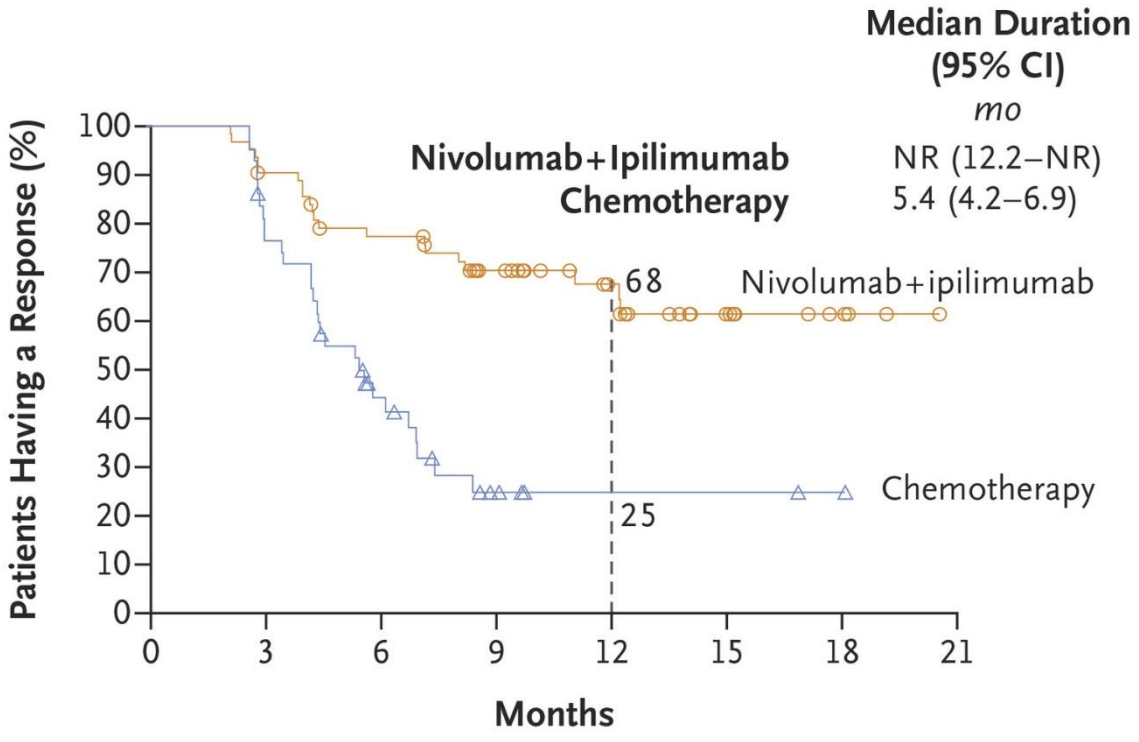
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients



Hellman et al, NEJM, 2018

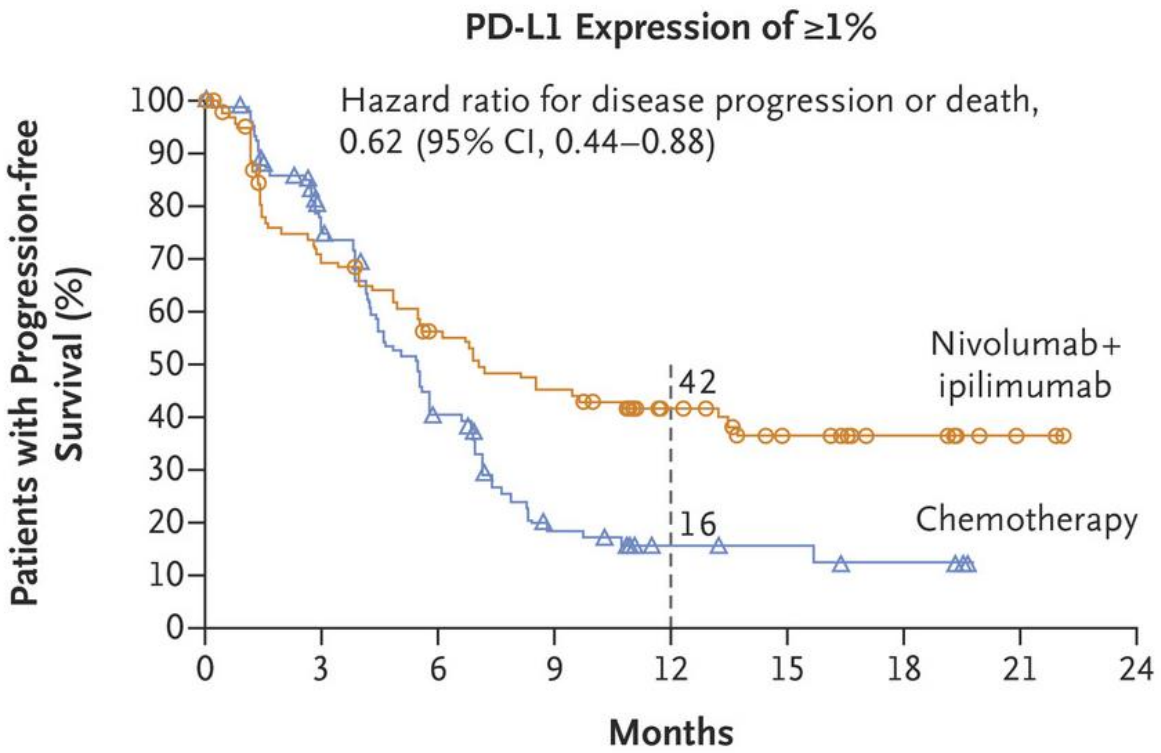
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

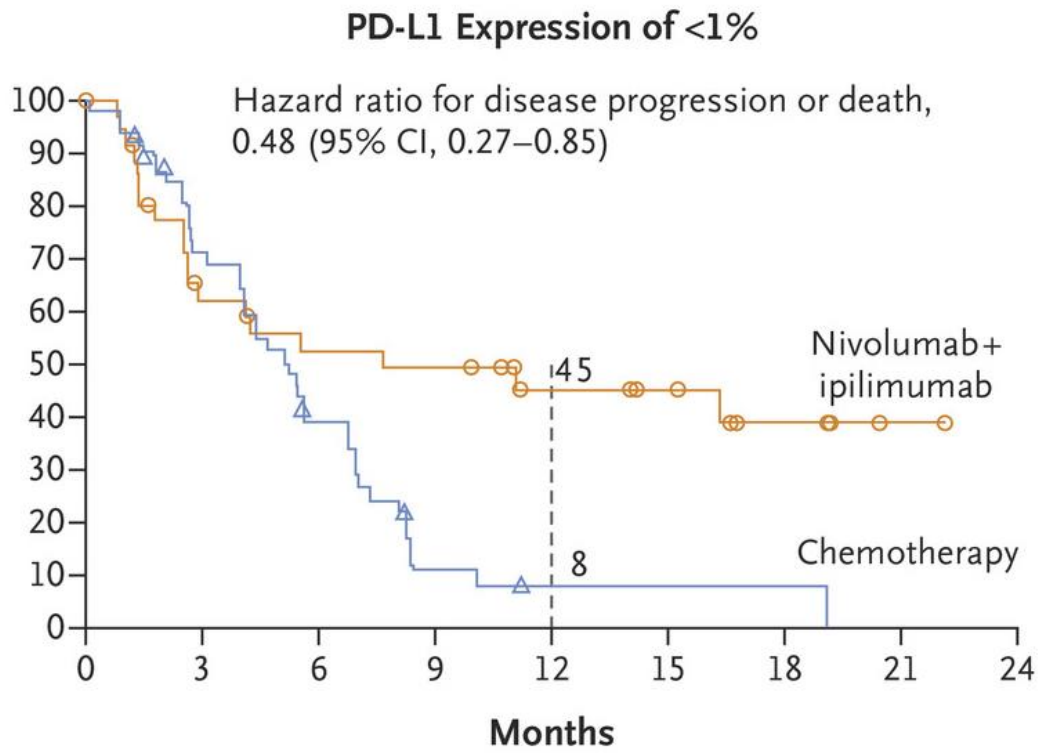




Hellman et al, NEJM, 2018

CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients





Hellman et al, NEJM, 2018

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

CHECKMATE 017 (nivolumab)

	Median Overall Survival *mo (95% CI)*	1-Yr Overall Survival *% of patients (95% CI)*	No. of Deaths
Nivolumab (N–135)	9.2 (7.3–13.3)	42 (34–50)	86
Docetaxel (N–137)	6.0 (5.1–7.3)	24 (17–31)	113

CHECKMATE 057 (nivolumab)

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	12.2	9.4

HR = 0.73 (96% CI: 0.59, 0.89); *P* = 0.0015

KEYNOTE 010 (TPS ≥ 1%) (pembrolizumab)

Treatment Arm	Median (95% CI), mo	HR* (95% CI)	P
Pembro 2 mg/kg	14.9 (10.4-NR)	0.54 (0.38-0.77)	0.0002
Pembro 10 mg/kg	17.3 (11.8-NR)	0.50 (0.36-0.70)	<0.0001
Docetaxel	8.2 (6.4-10.7)	--	--

OAK (atezolizumab)

HR, 0.73[a]
(95% CI, 0.62, 0.87)
P = 0.0003

Minimum follow up = 19 months

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

PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC

Patients with locally advanced unresectable NSCLC (Stage III) in a consolidation setting

Absence of progression following at least 2 cycles of platinum-based chemotherapy concomitant with radiation therapy

R 2:1
N=702

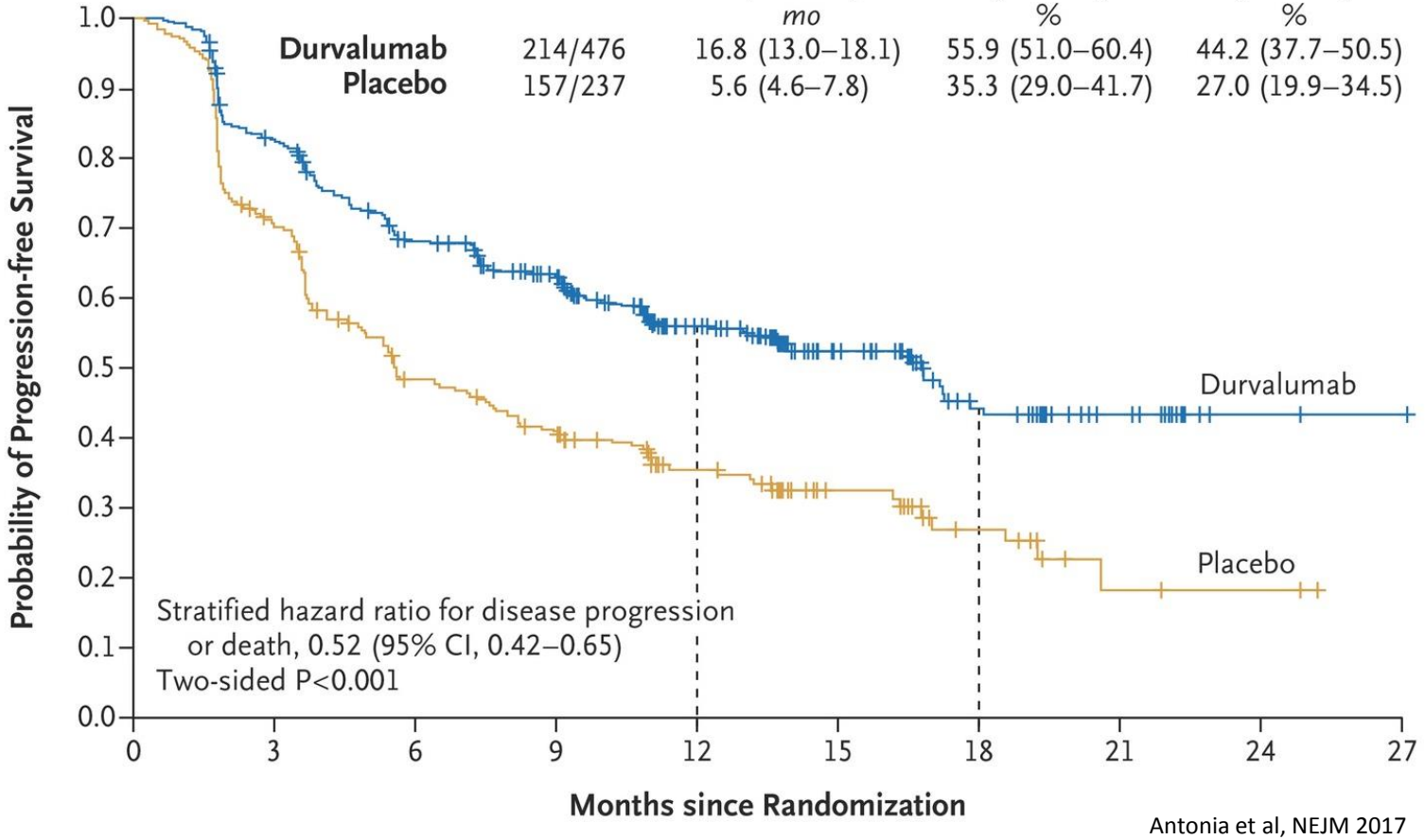
Durvalumab (n=468)
IV 10 mg/kg Q2W
≤12 months

Placebo (n=234)
IV Q2W

1. In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
2. NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
3. Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
4. Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC

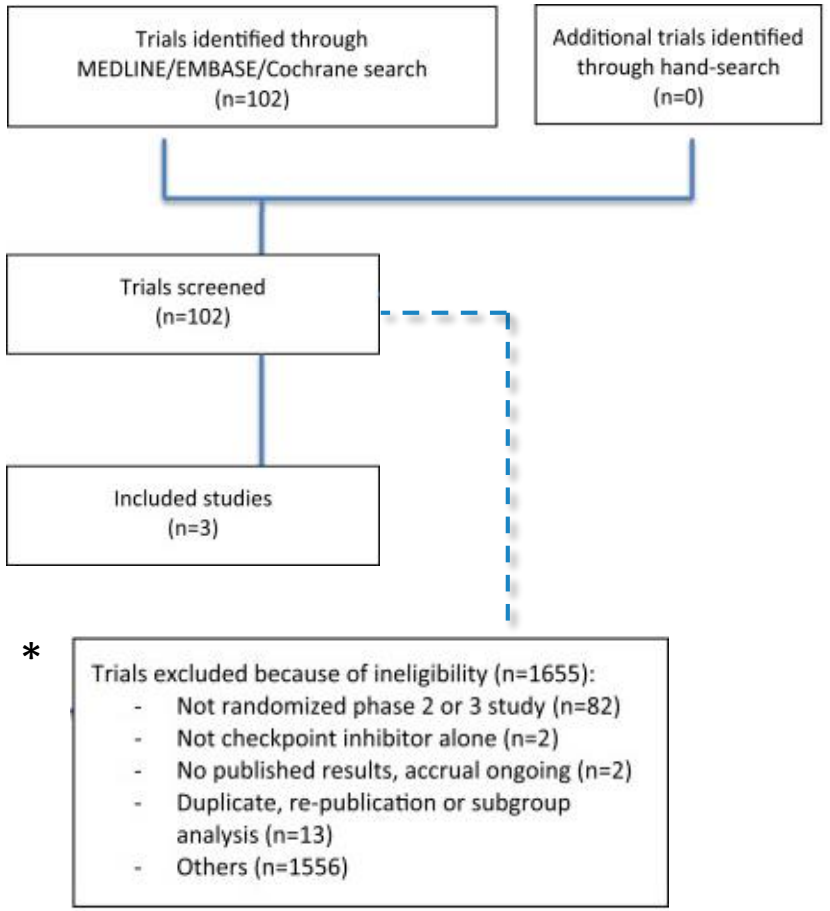
	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-Mo PFS (95% CI)	18-Mo PFS (95% CI)
		mo	%	%
Durvalumab	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
Placebo	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)

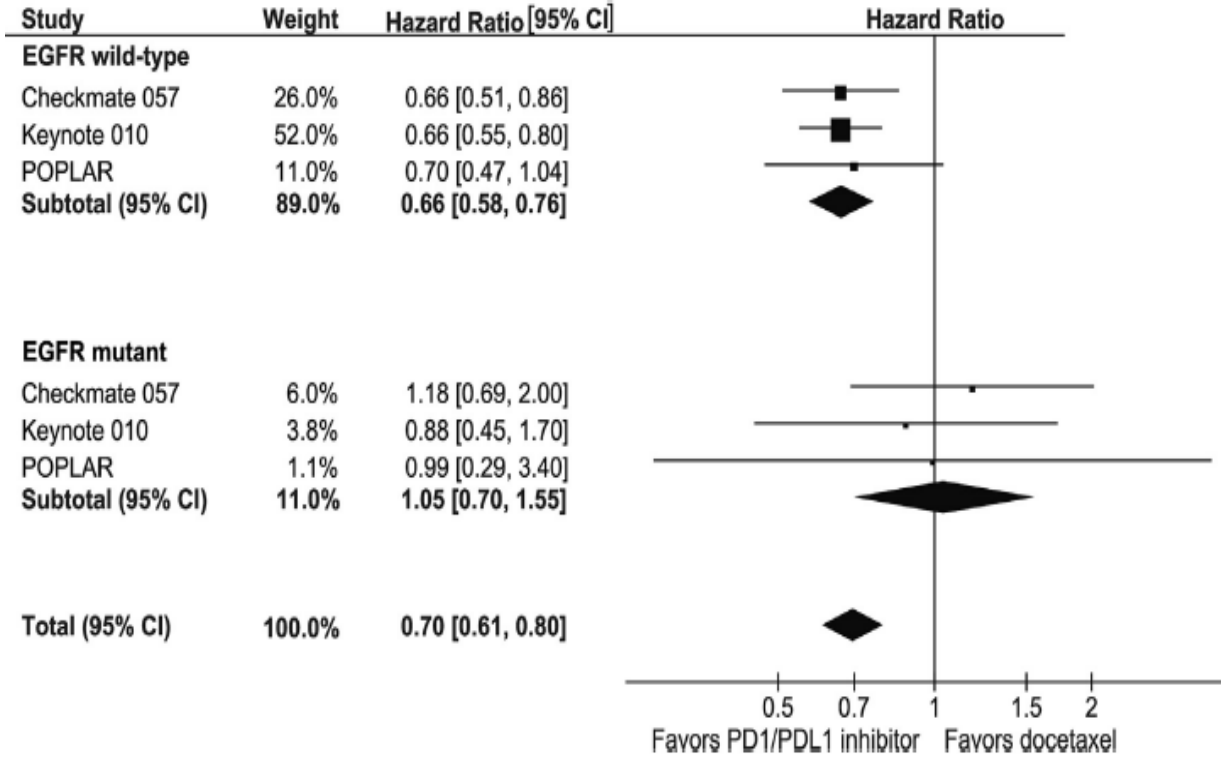


Antonia et al, NEJM 2017

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

Meta-Analysis: CM-057, KN-010, POPLAR





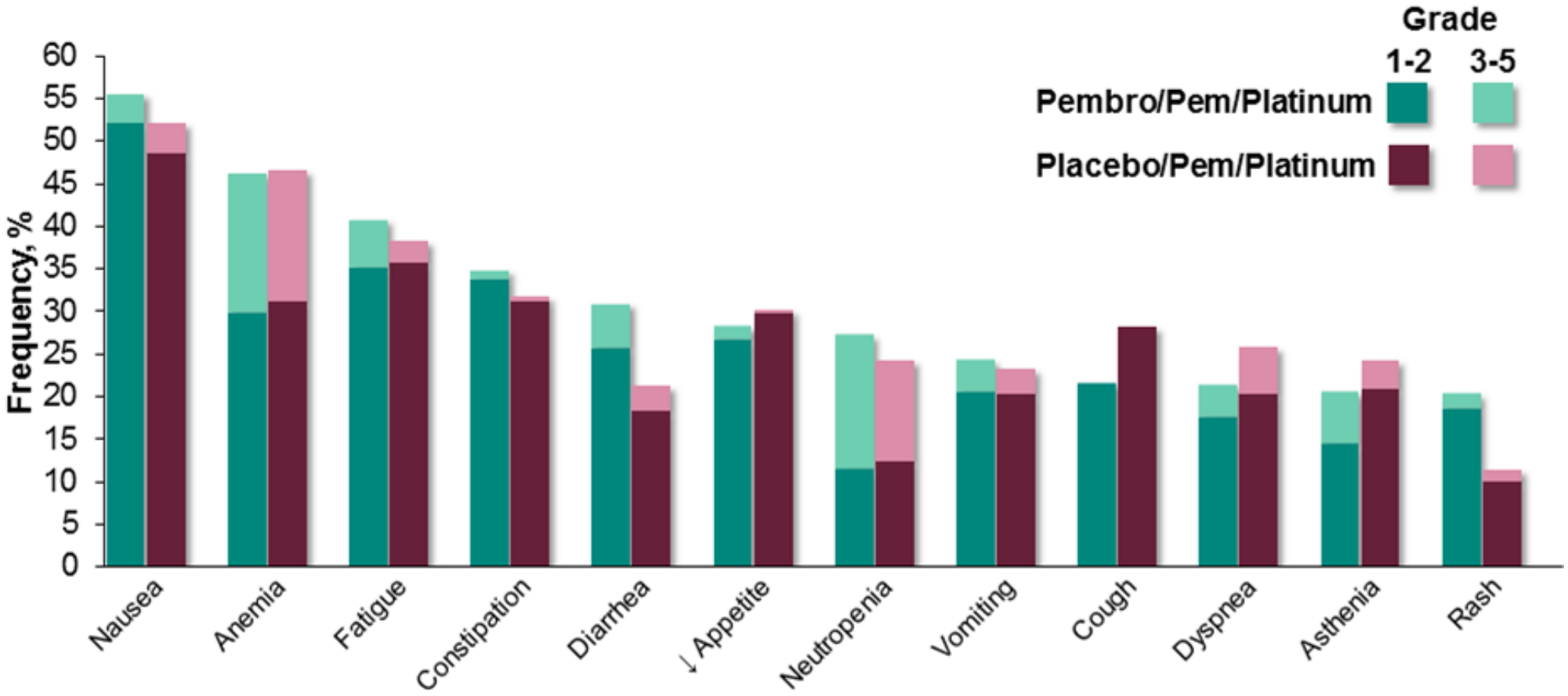
CK Lee et al., JTO 2016

Single-agent Toxicities in 2/3L Randomized Trials

	Atezolizumab OAK	Nivolumab SQ: CM 017 (updated OS; 2L)	Nivolumab NSQ:CM 057 (updated OS; 2/3L)	Pembrolizumab 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%

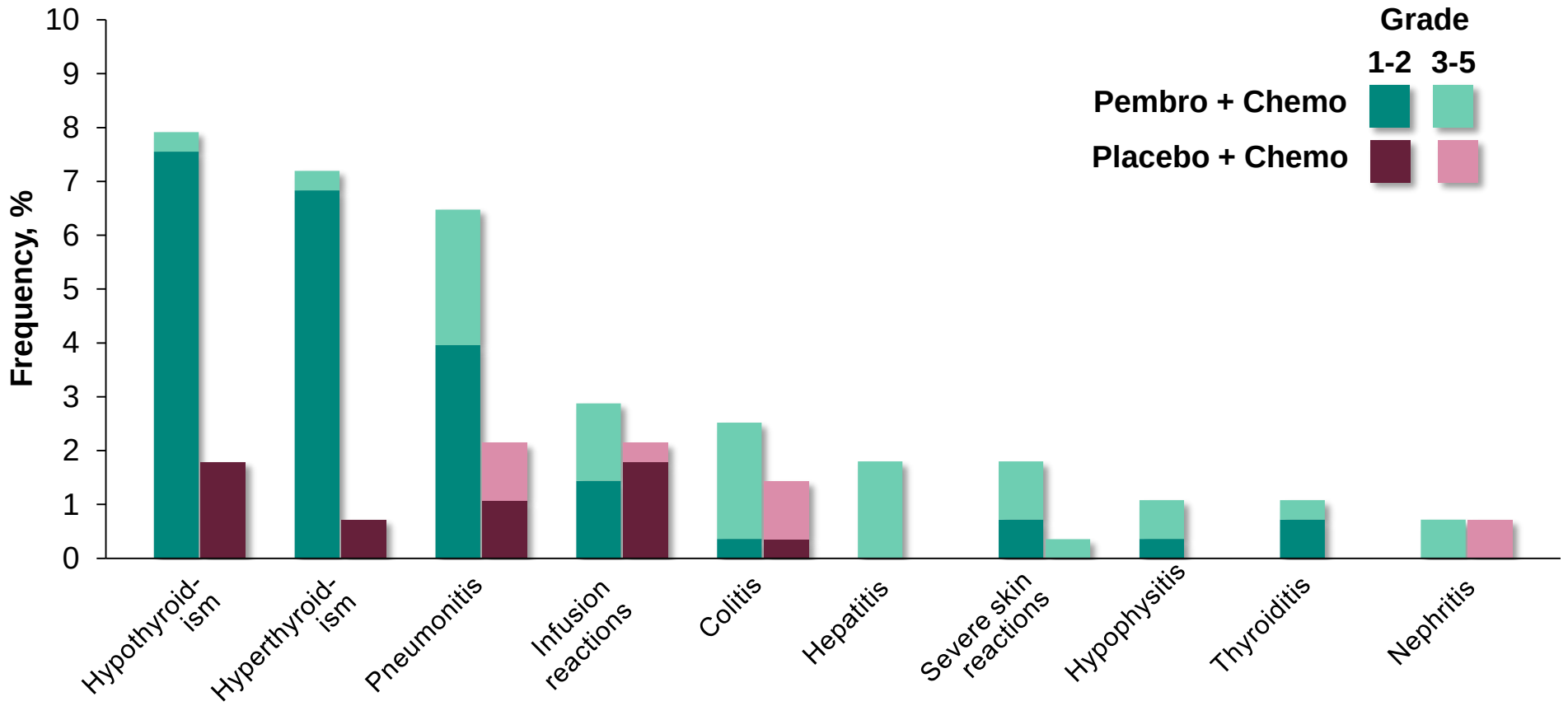
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



Ghandi et al, NEJM 2018

KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC



Paz-Arez et al, ASCO, 2018

CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

TRAE,[a] %	Nivolumab + ipilimumab (n = 576)		Chemotherapy (n = 570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	75	31	81	36
TRAE leading to discontinuation[b]	17	12	9	5
Most frequent TRAEs (≥15%)				
Rash	17	2	5	0
Diarrhea	16	2	10	1
Fatigue	13	1	18	1
Decreased appetite	13	<1	19	1
Nausea	10	<1	36	2
Constipation	4	0	15	<1
Anemia	4	2	32	11
Neutropenia	<1	0	17	9
Treatment-related deaths[c]	1		1	

Hellman et al, NEJM, 2018

Summary of Frontline Strategies in Advanced NSCLC

Clinical Trial	Drug	PFS (Months)	OS (Months)	PFS HR in PD-L1 neg	Toxicities Grade 3 - 5
KEYNOTE-024 PD-L1 ≥ 50%	Pembro	10.3	30	NA	31% vs 53%
	Plat/Pem or Gem or Pacli	6	14.2		
KEYNOTE-042 PD-L1 ≥ 1%	Pembro	5.4	16.7	NA	18% vs 41%
	Plat/Pem or Pacli	6.5	12.1		
IMpower150 Non-squamous	Atezo + Beva + Carbo/Pacli	8.3	19.2	0.77	60 vs 51%
	Beva + Carbo/Pacli	6.8	14.7		
KEYNOTE-189 Non-squamous	Pembro + Plat/Pem	8.8	NR	0.75	67% vs 66%
	Plat/Pem	4.9	11.3		
KEYNOTE-407 Squamous	Pembro + Carbo/Pacli or NabPacli	6.4	15.9	0.68	70% vs 68%
	Carbo/Pacli or NabPacli	4.8	11.3		
CheckMate 227 TMB≥10mut/Mb	Nivo + Ipi	7.2	23	0.48	31% vs 36%
	Plat/Pem or Gem	5.4	16.7		

Adapted from Solange Peters, 2018 ASCO Annual Meeting * *This is for illustration purposes only and comparing different trials is challenging as populations, indications, and other characteristics vary.*

Lung Cancer Case

How would you treat this 62 year-old woman, with a new diagnosis of stage IV lung adenocarcinoma, without targetable mutations, PD-L1 5% and TMB high.

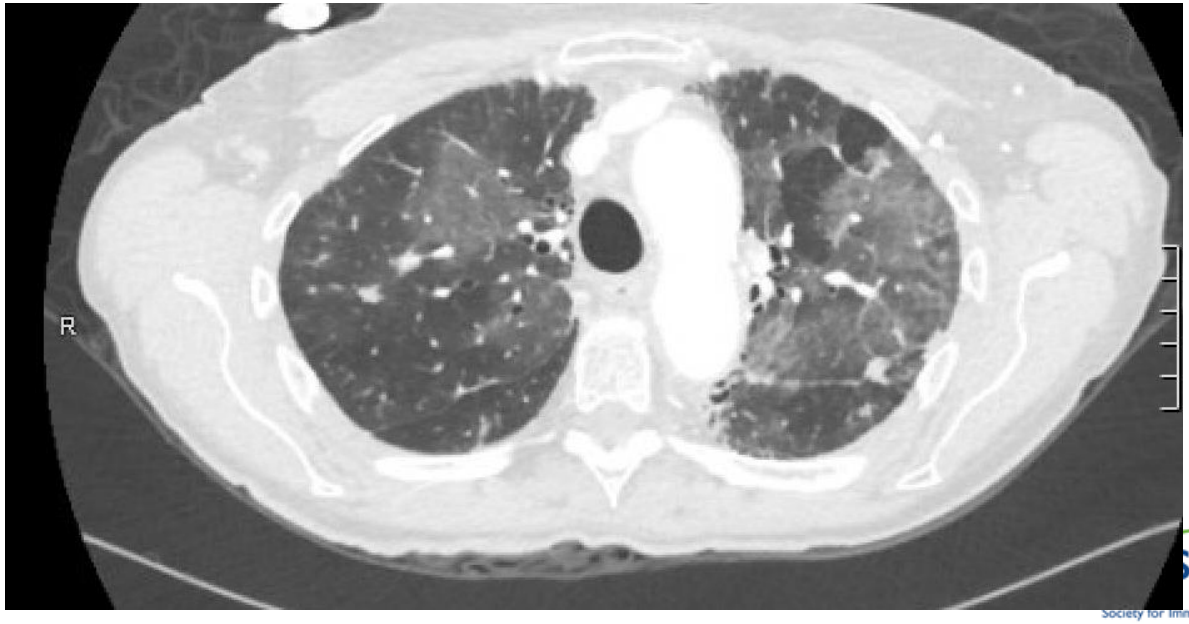
1. Carboplatin/paclitaxel +/- bevacizumab
2. Carboplatin/pemetrexed +/- bevacizumab
3. Pembrolizumab
4. Carboplatin/pemetrexed/pembrolizumab
5. Carboplatin/paclitaxel/bevacizumab + atezolizumab
6. Nivolumab/ipilumumab

Lung Cancer Case

Your patient with stage IV adenocarcinoma with begins therapy with pembrolizumab/pemetrexed/carboplatin with an excellent partial response.

After 6 months of treatment, the patient is hospitalized with a new progressive dry cough and marked shortness of breath. O2 saturation is 88% RA (previously 98%).

- The patient is afebrile, and without leukocytosis.
- A Chest CT performed.



What is the most likely cause of this clinical event and these new CT scan findings?

1. Progressive cancer
2. Infection
3. Pembrolizumab-related immune pneumonitis
4. Pulmonary edema

How would you manage this patient with new dyspnea/cough, hypoxia and bilateral ground glass opacities during treatment with pembrolizumab?

1. Begin antibiotic therapy; continue pembrolizumab
2. Refer for bronchoscopy with cultures and lung biopsy
3. Continue pembrolizumab and initiate prednisolone at 1 mg/kg
4. Hold pembrolizumab and initiate prednisolone at 1 mg/kg
5. Combined #2 and #4

Lung Cancer Case

- A presumptive diagnosis of immunotherapy-related pneumonitis is made on clinical grounds. Pembrolizumab is held and the patients symptoms improve dramatically over the next 2 weeks with prednisolone at 1 mg/kg daily.
- Steroids are tapered off over a 6 week period without recurrence of symptoms.
- A follow up CT chest shows complete resolution.
- The patient asks whether she should resume pembrolizumab, which she has now received for 8 months.

1. **Yes, resume pembrolizumab.**
2. **No, do not resume pembrolizumab.**