Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Jose Pacheco MD

Assistant Professor

Thoracic Oncology/Phase I

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE
CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

© 2018–2019 Society for Immunotherapy of Cancer

Disclosures

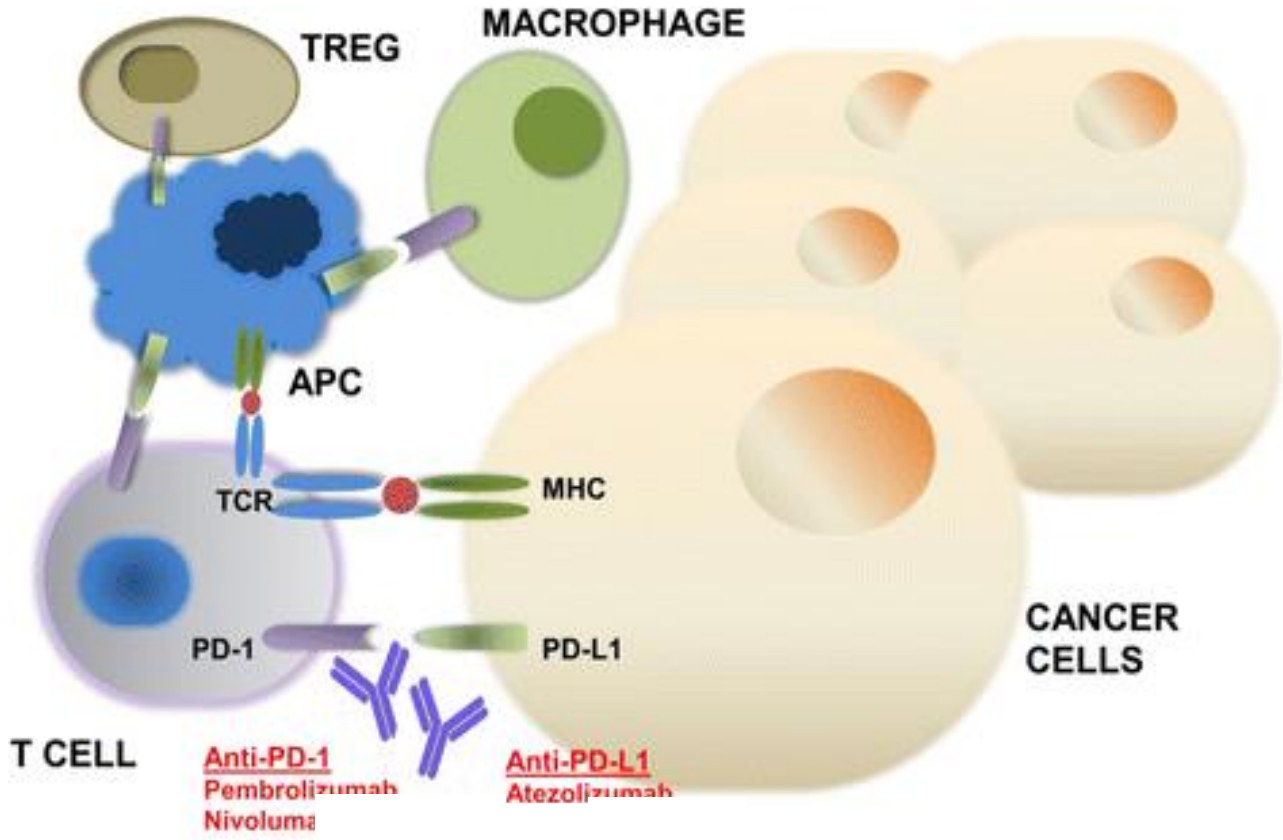
- Research funding from Pfizer
- Honorarium from Takeda
- Consulting fees from AstraZeneca and Novartis
- I will be discussing non-FDA approved indications during my presentation.

© 2018–2019 Society for Immunotherapy of Cancer

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

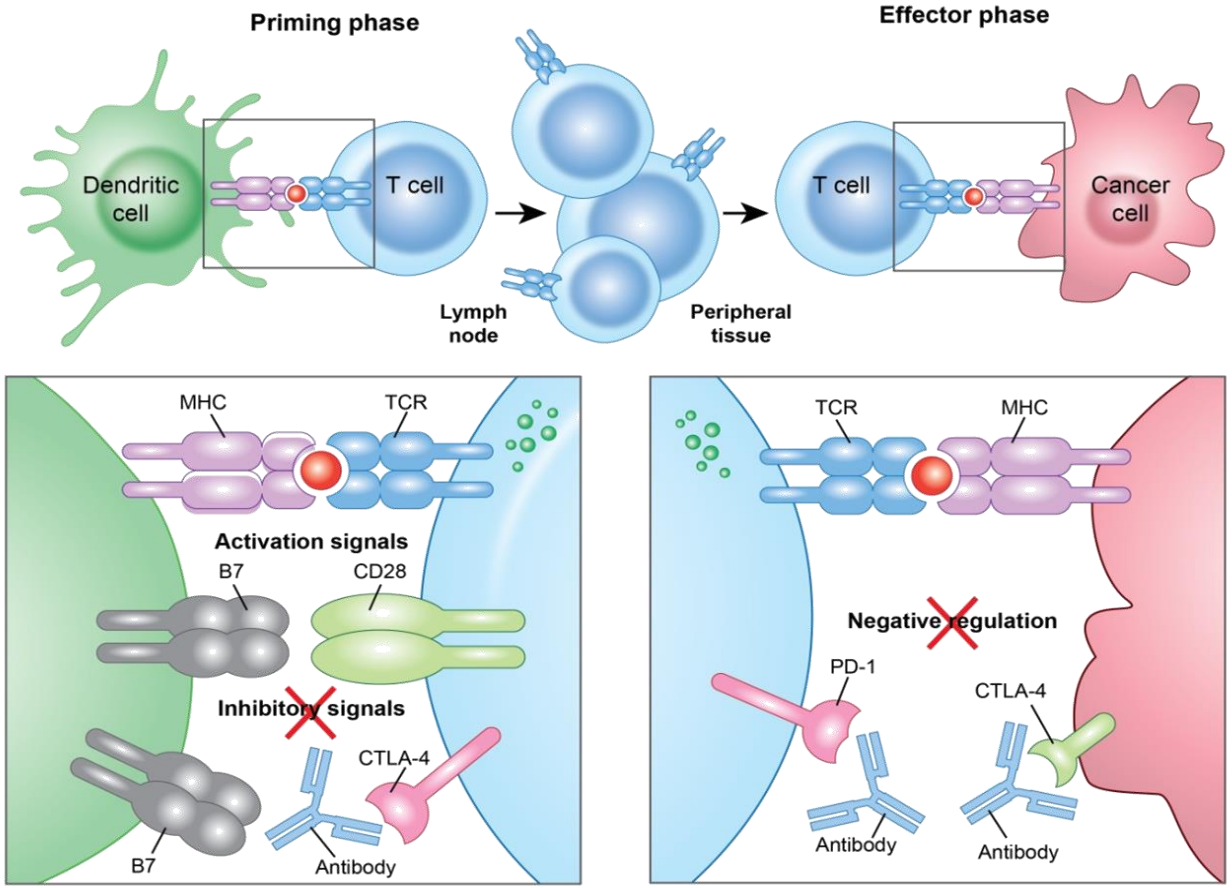


Gong J, Journal for ImmunoTherapy of Cancer, 2018

© 2018–2019 Society for Immunotherapy of Cancer

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

© 2018–2019 Society for Immunotherapy of Cancer

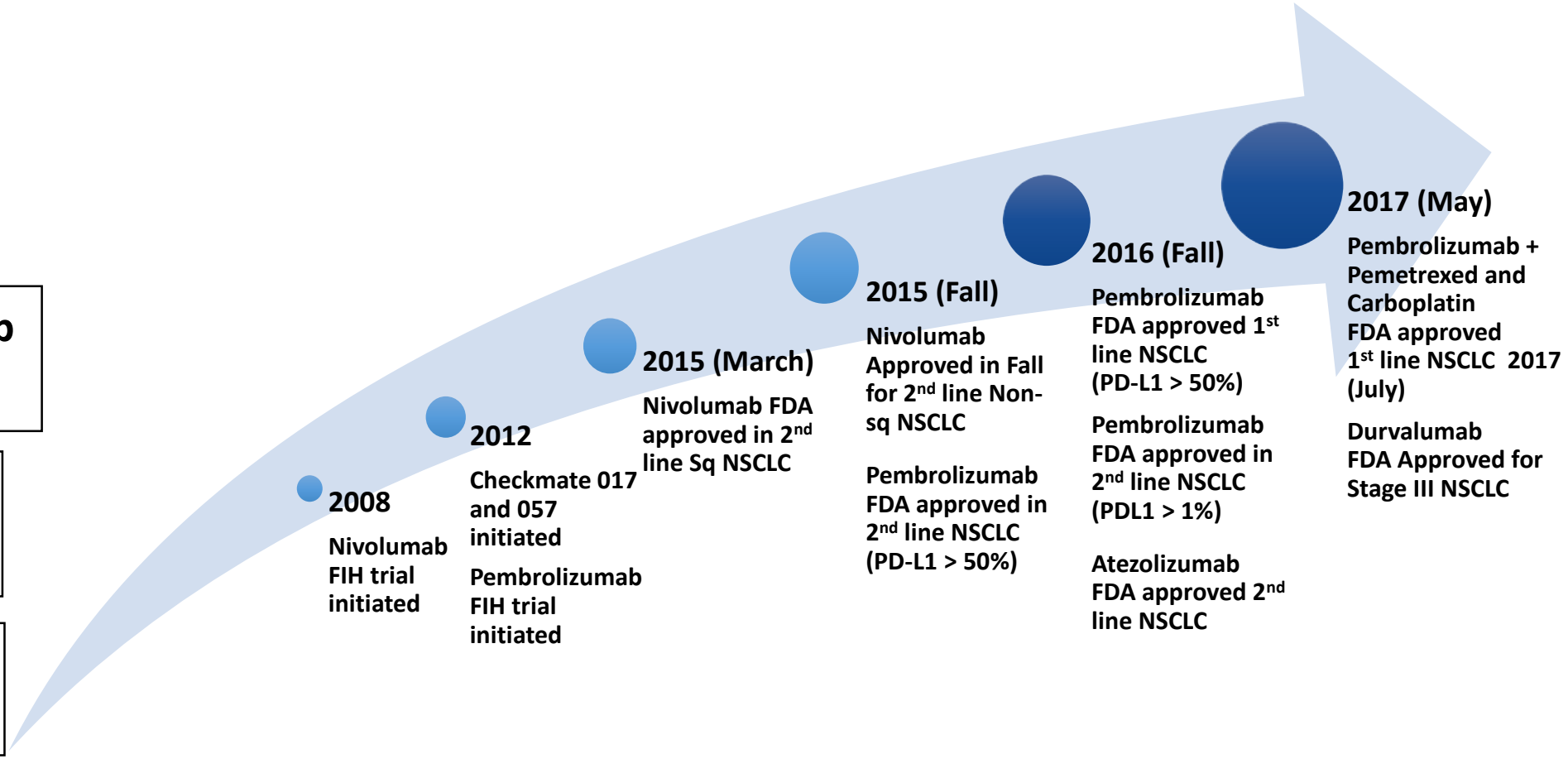
FDA-approved Checkpoint Inhibitors in NSCLC

Nivolumab — PD-1

Pembrolizumab — PD-1

Atezolizumab — PD-L1

Durvalumab — PD-L1



© 2018–2019 Society for Immunotherapy of Cancer

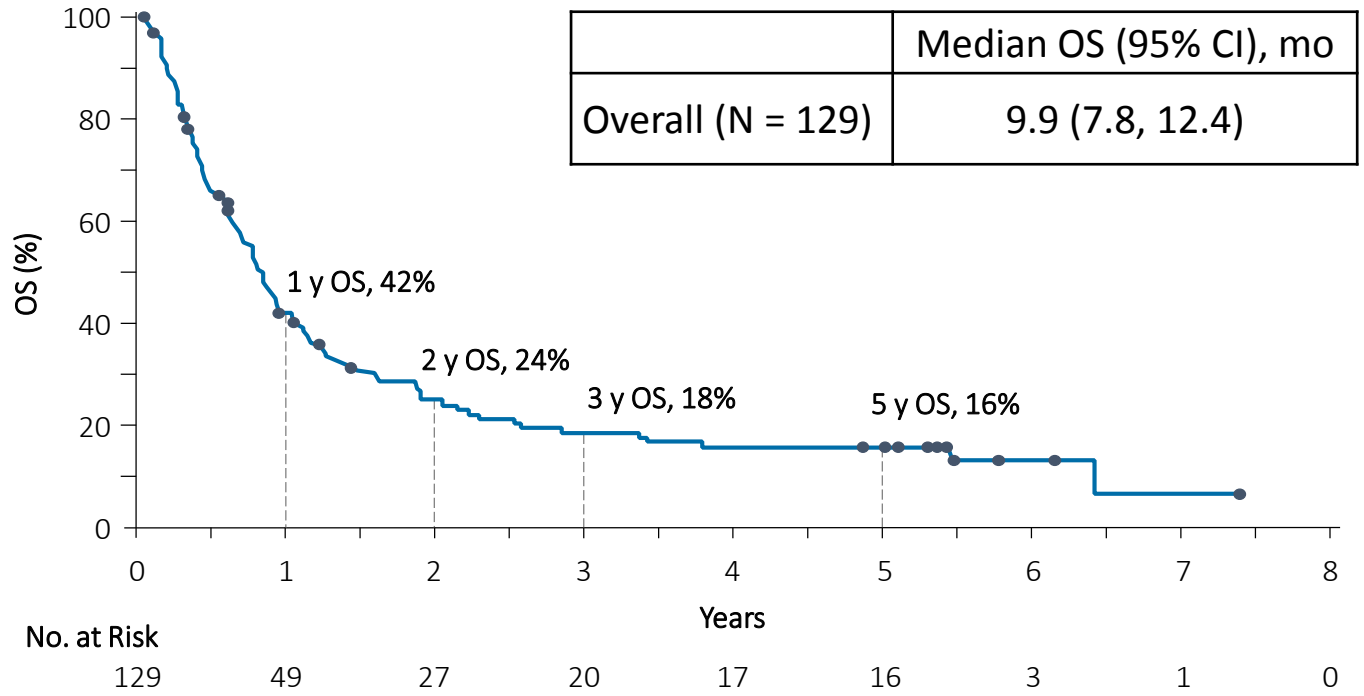
CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

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

© 2018–2019 Society for Immunotherapy of Cancer

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

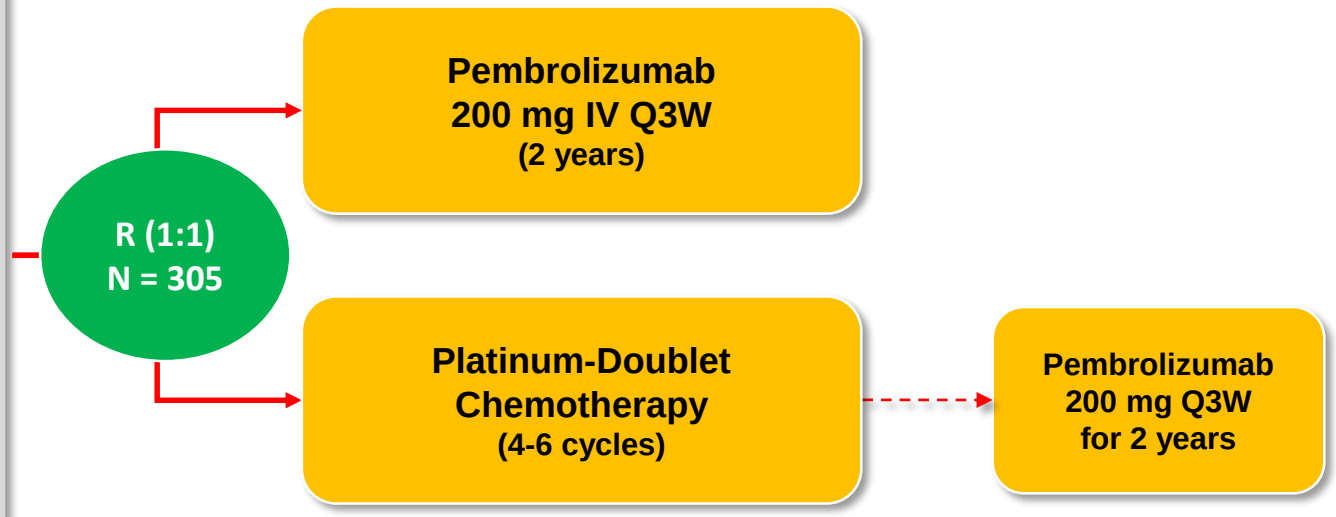
© 2018–2019 Society for Immunotherapy of Cancer

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

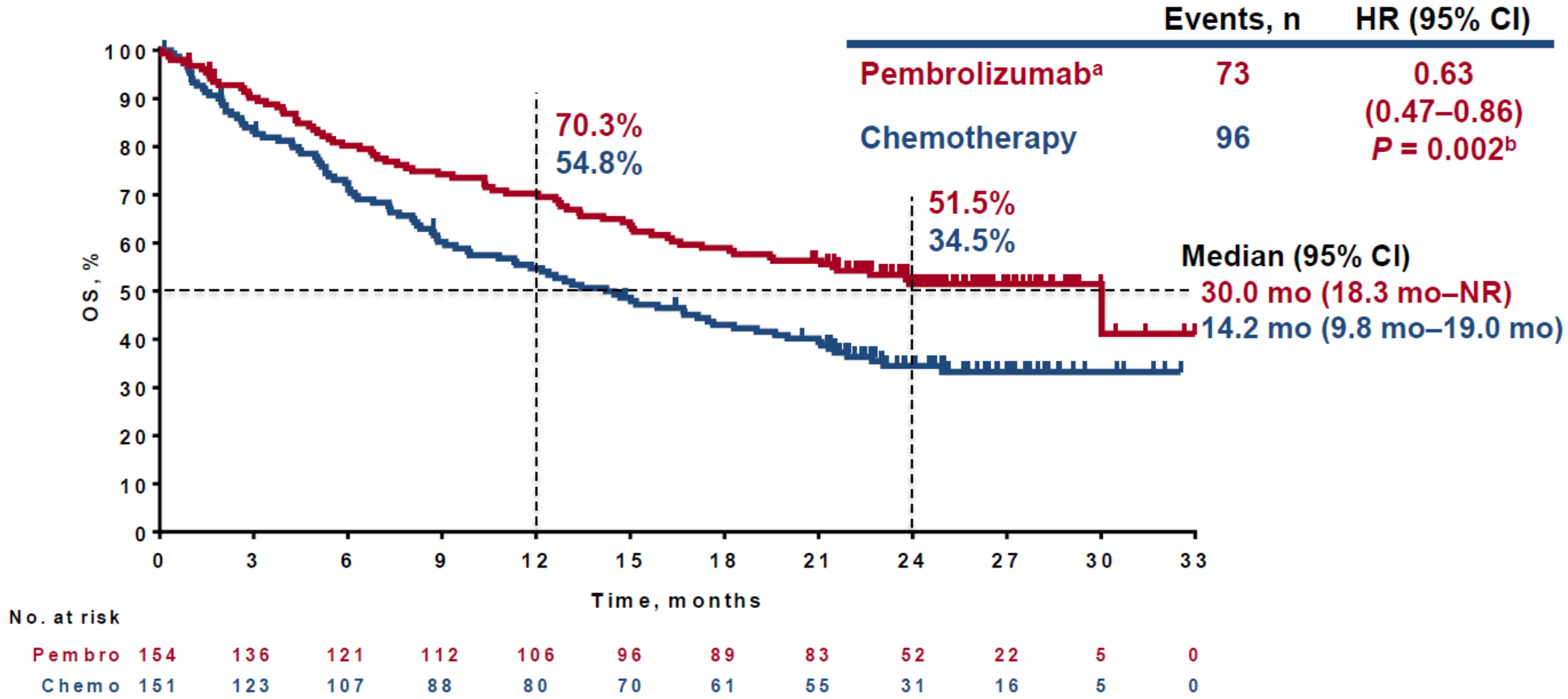


Reck M et al, ESMO 2016, NEJM 2016

© 2018–2019 Society for Immunotherapy of Cancer

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

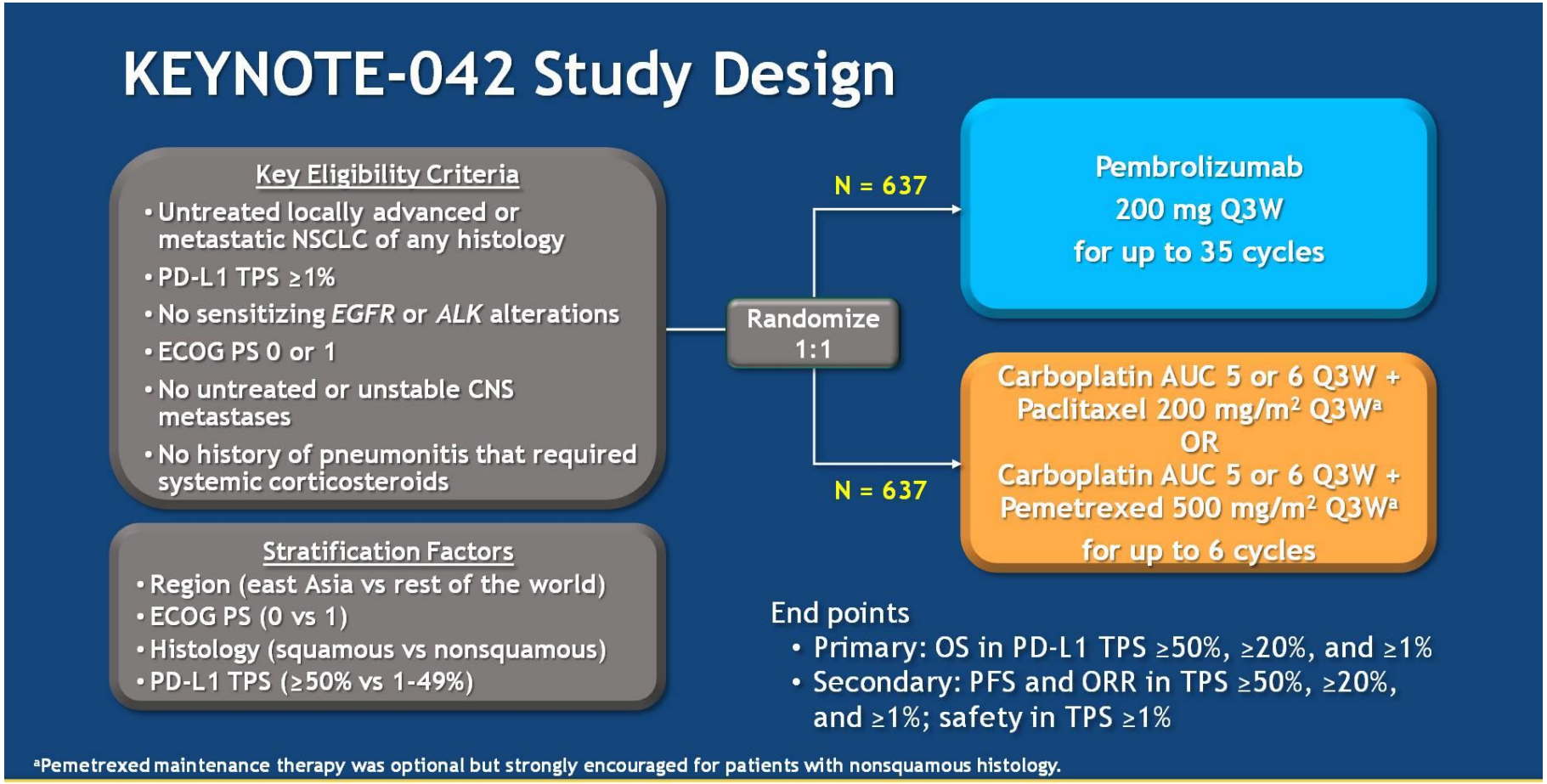
Overall Survival



1) Brahmer J et al, IASLC World Lung 2017. 2) Reck M et al. JCO 2019

© 2018–2019 Society for Immunotherapy of Cancer

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

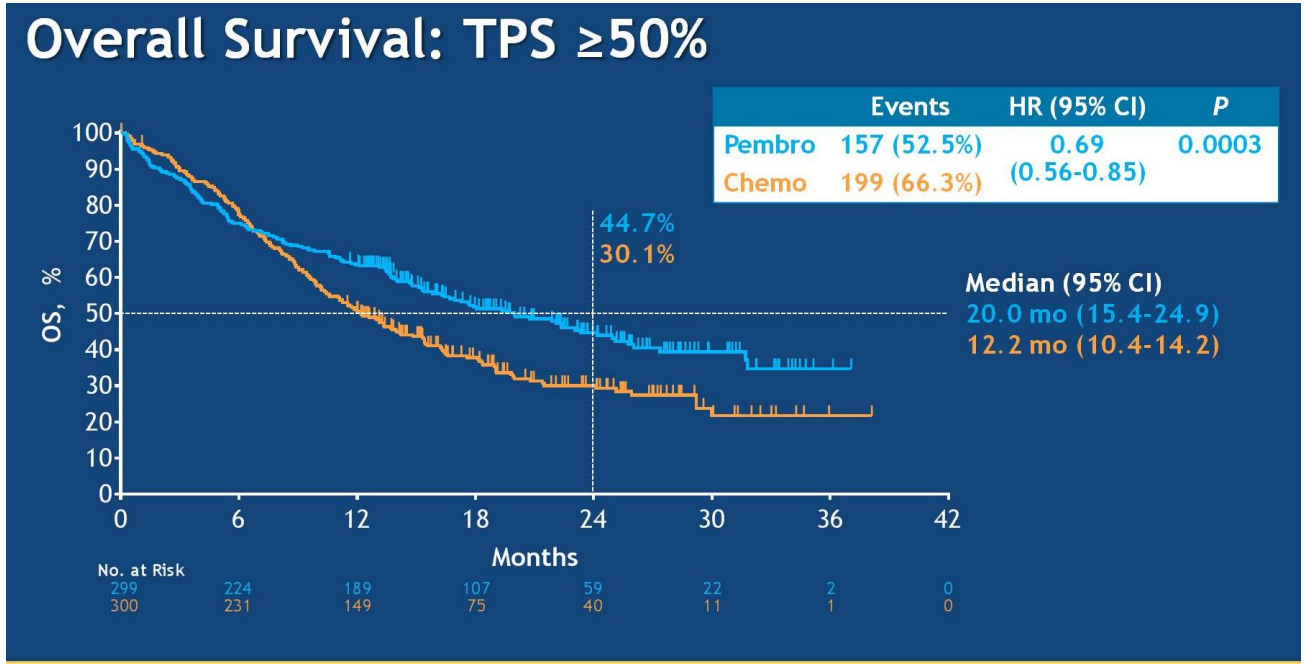


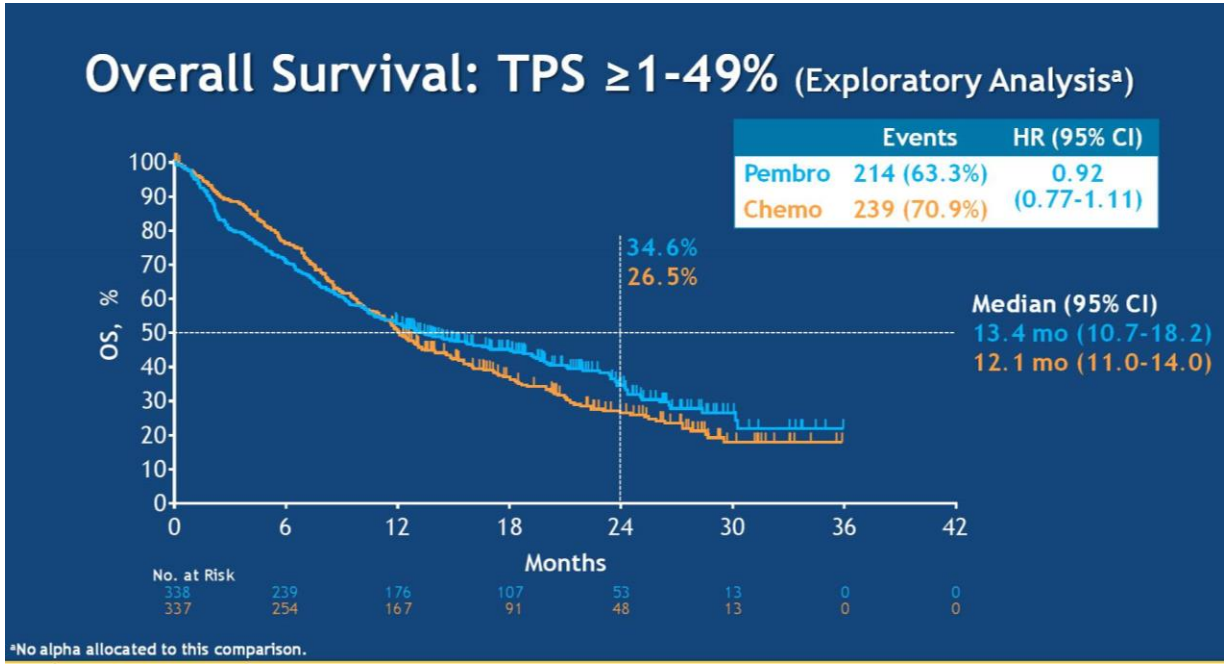
Lopes et al, ASCO 2018

© 2018–2019 Society for Immunotherapy of Cancer

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

Overall Survival



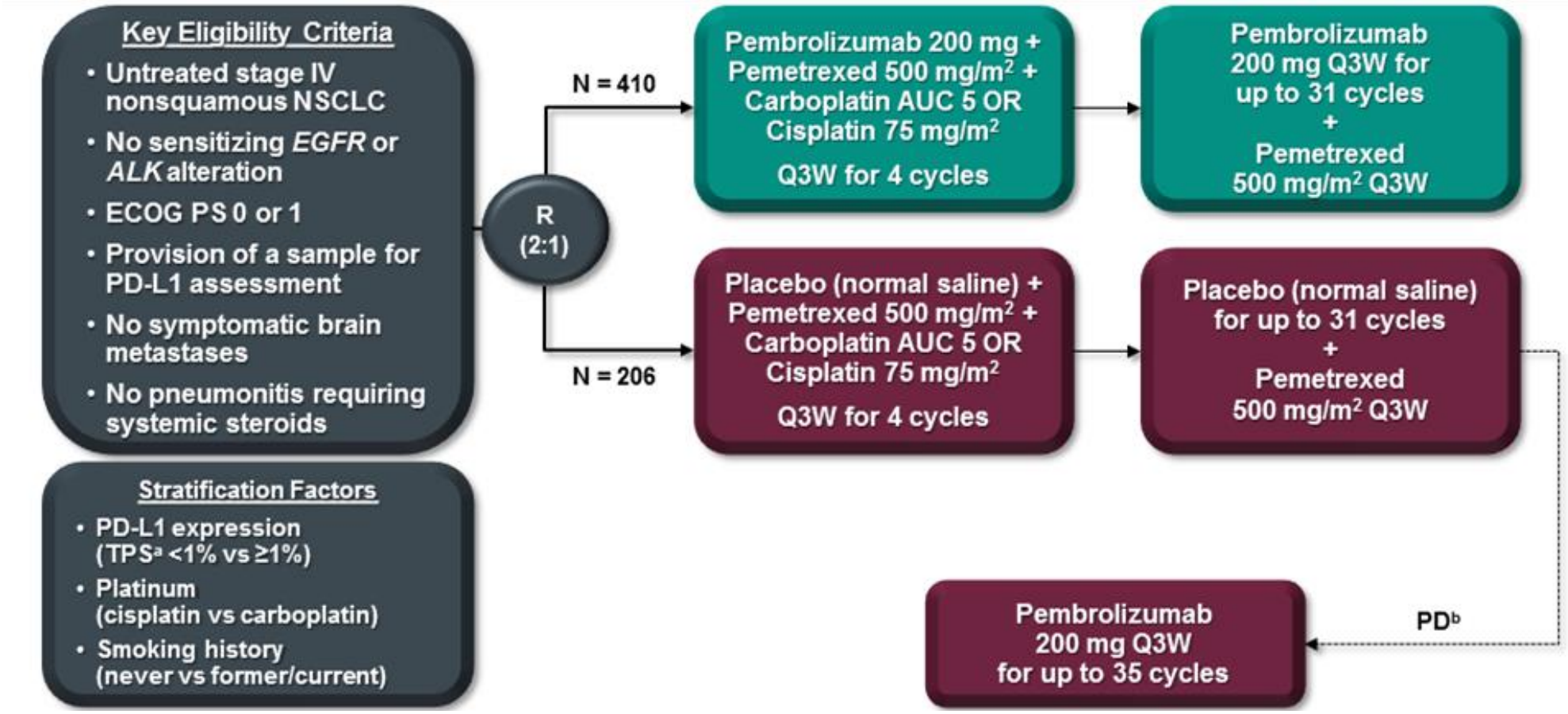


Survival benefit seemed to be driven by the TPS > 50% subset with little benefit witnessed in the subset TPS > 1- 49%

Lopes et al, ASCO 2018

© 2018–2019 Society for Immunotherapy of Cancer

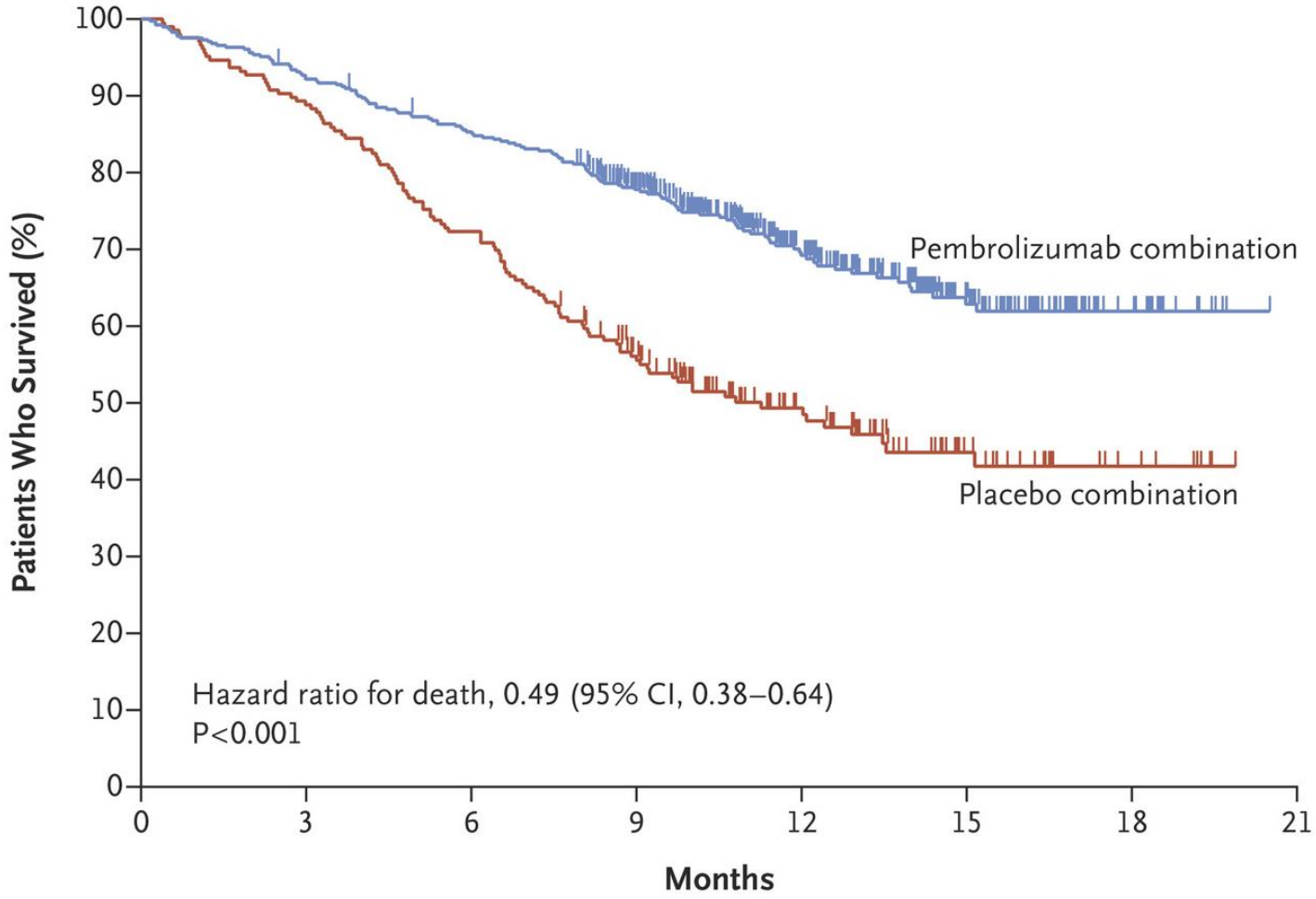
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



Ghandi et al, NEJM 2018

© 2018–2019 Society for Immunotherapy of Cancer

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



Ghandi et al, NEJM 2018

Pembrolizumab combination

Median overall survival –not reached

1-year overall survival 69.2% (95%CI, 64.1-73.8)

Placebo combination

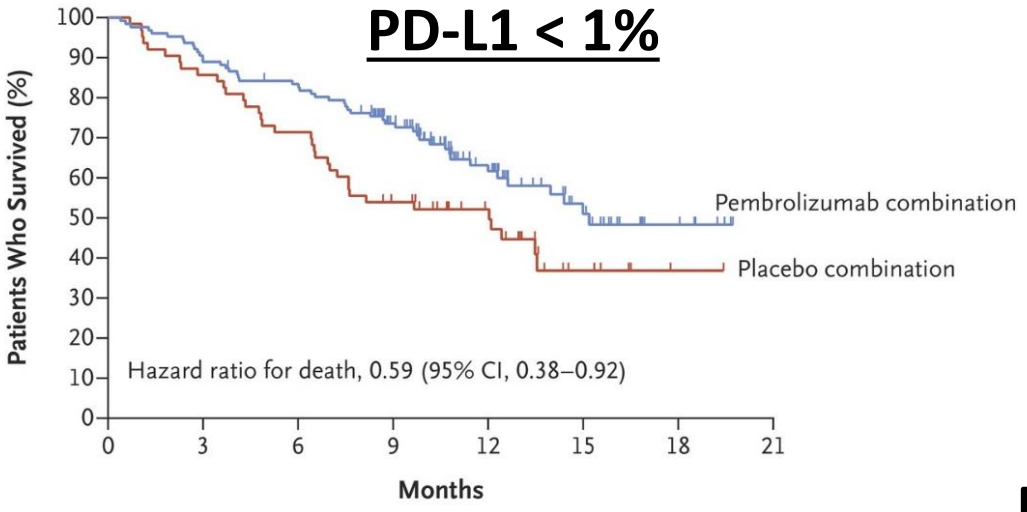
Median overall survival 11.3 months (95%CI, 8.7-15.1)

1-year overall survival 49.4% ((95%CI, 42.1-56.2)

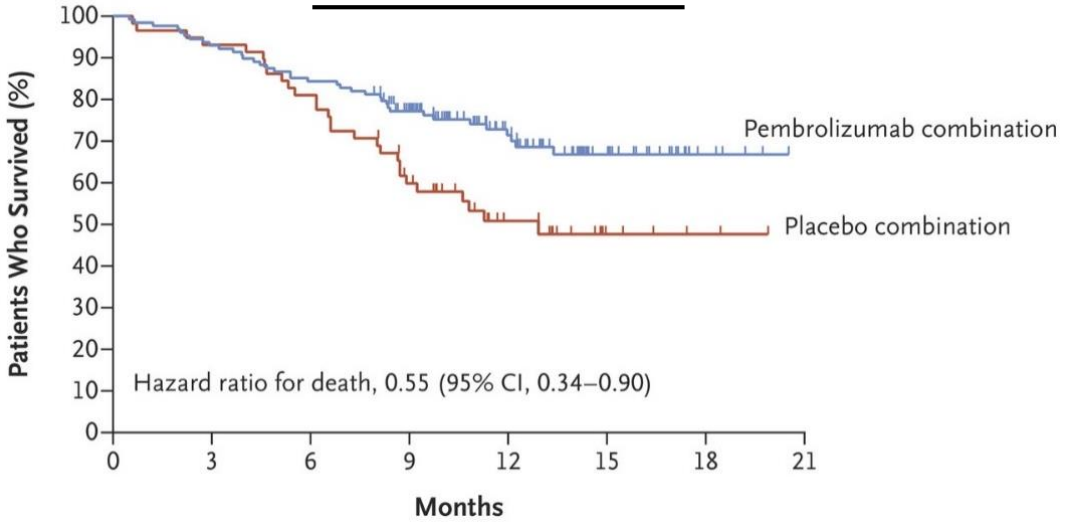
© 2018–2019 Society for Immunotherapy of Cancer

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

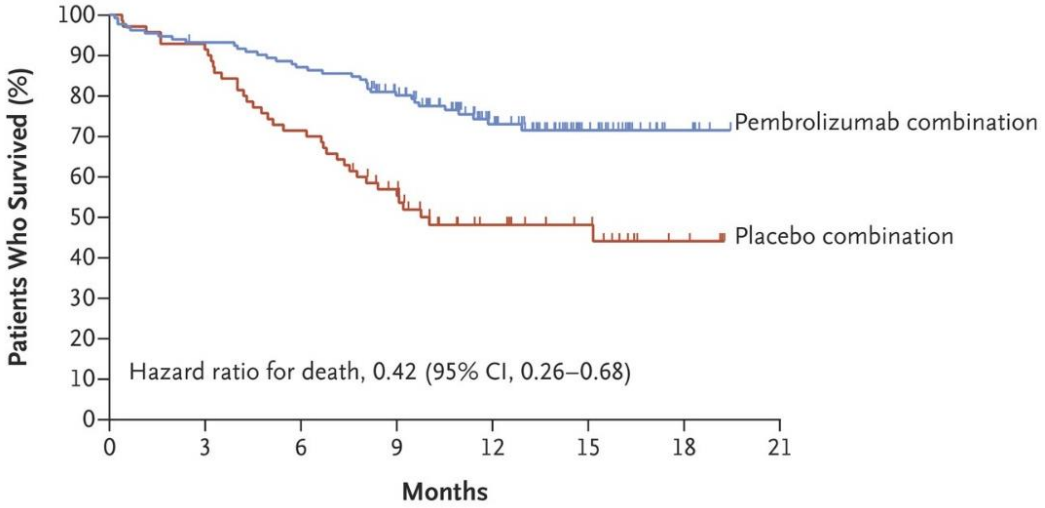
PD-L1 < 1%



PD-L1 1 – 49%



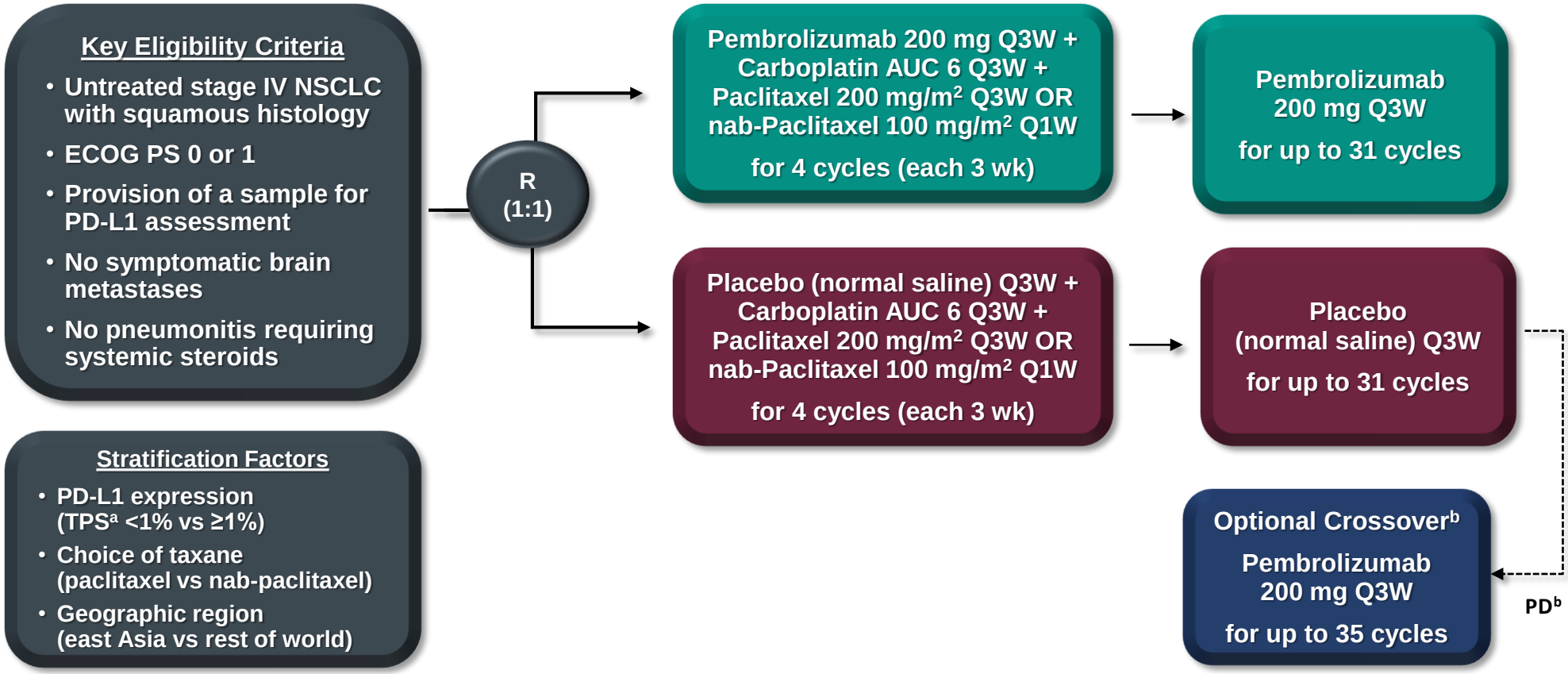
PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

© 2018–2019 Society for Immunotherapy of Cancer

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



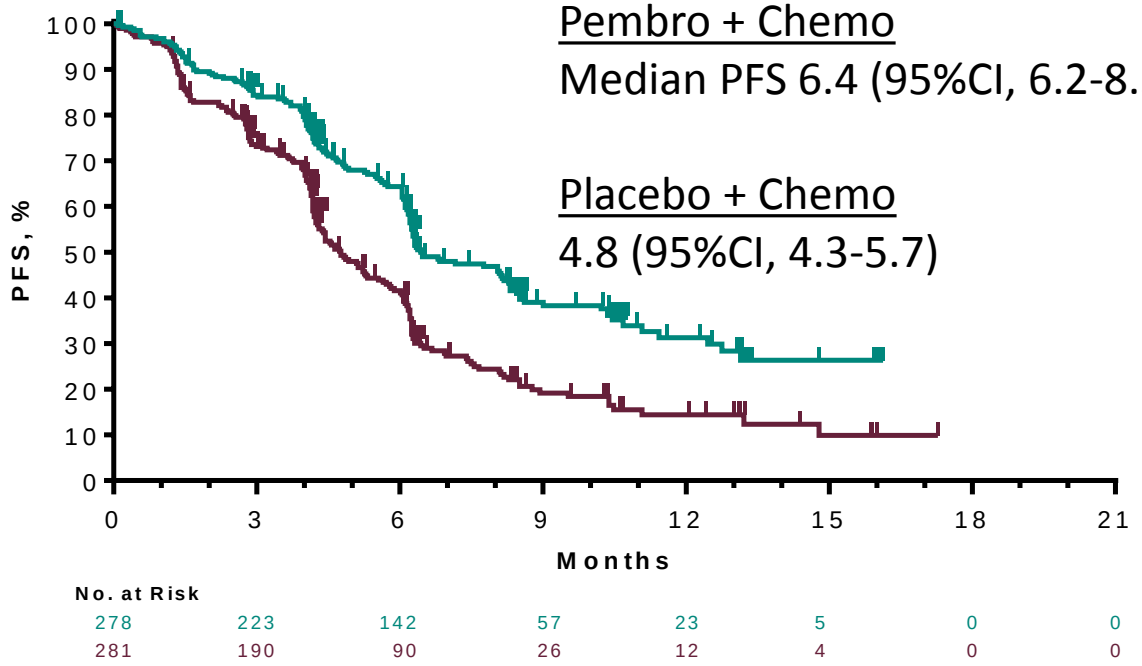
Paz-Ares et al, ASCO 2018

© 2018–2019 Society for Immunotherapy of Cancer

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%		

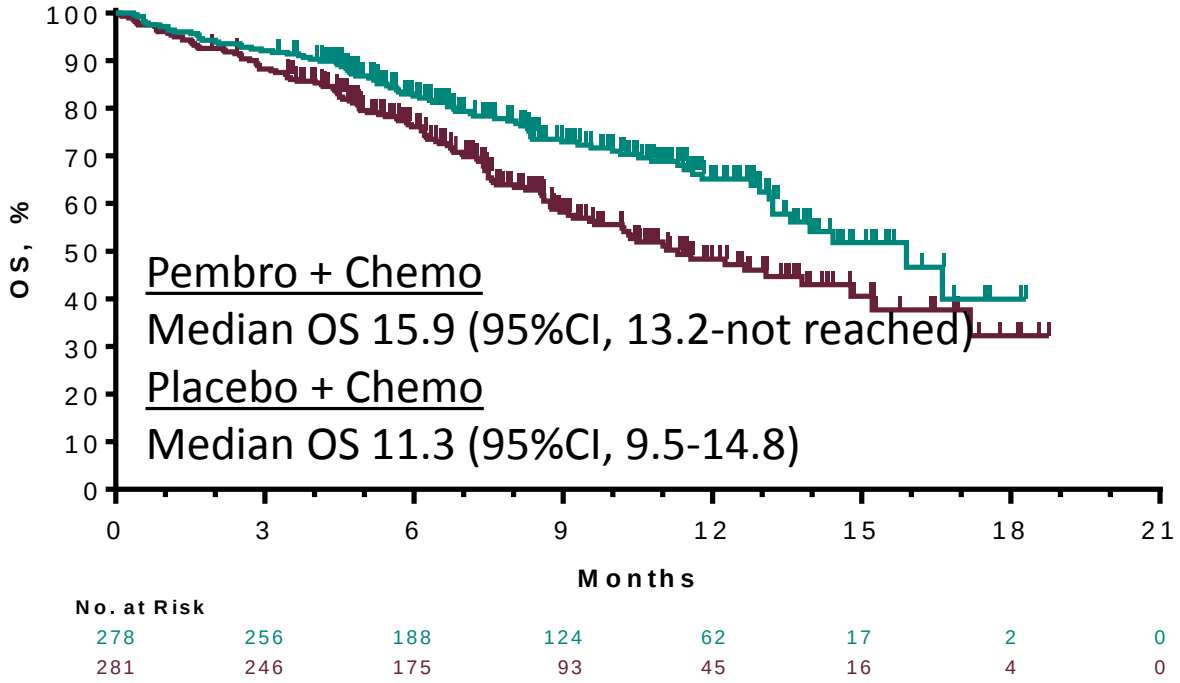


Pembro + Chemo
Median PFS 6.4 (95%CI, 6.2-8.3)

Placebo + Chemo
4.8 (95%CI, 4.3-5.7)

Overall Survival

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



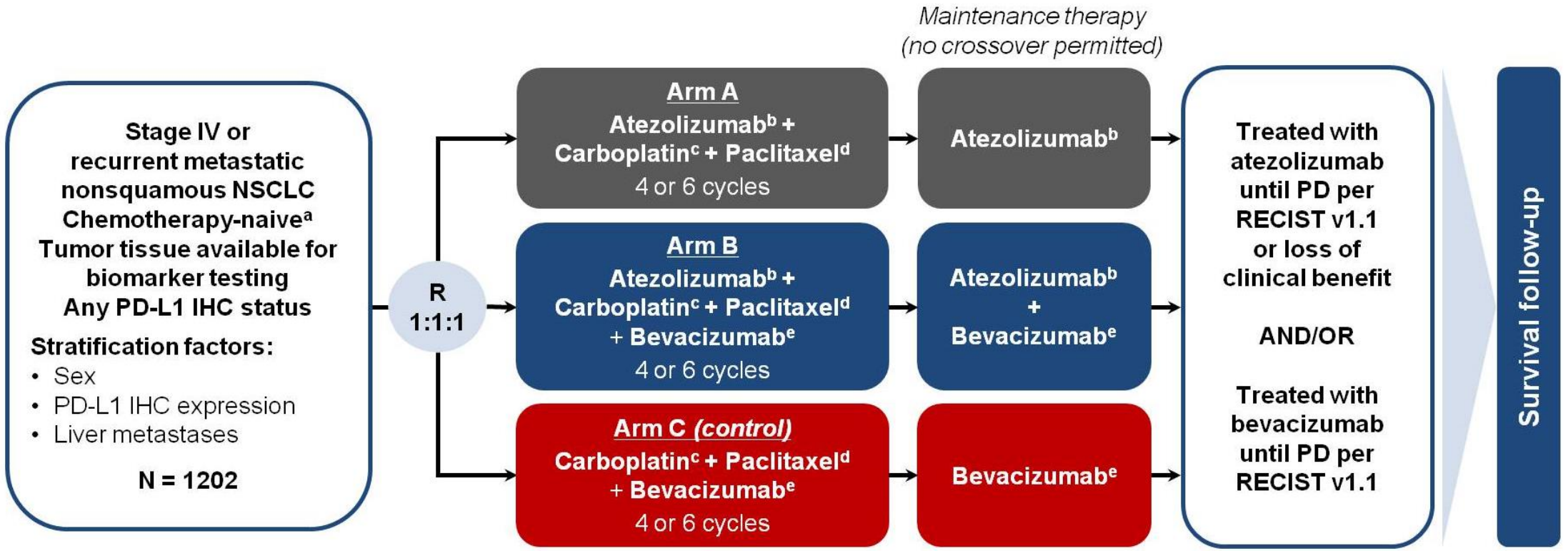
Pembro + Chemo
Median OS 15.9 (95%CI, 13.2-not reached)

Placebo + Chemo
Median OS 11.3 (95%CI, 9.5-14.8)

Paz-Ares et al, ASCO 2018

© 2018–2019 Society for Immunotherapy of Cancer

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



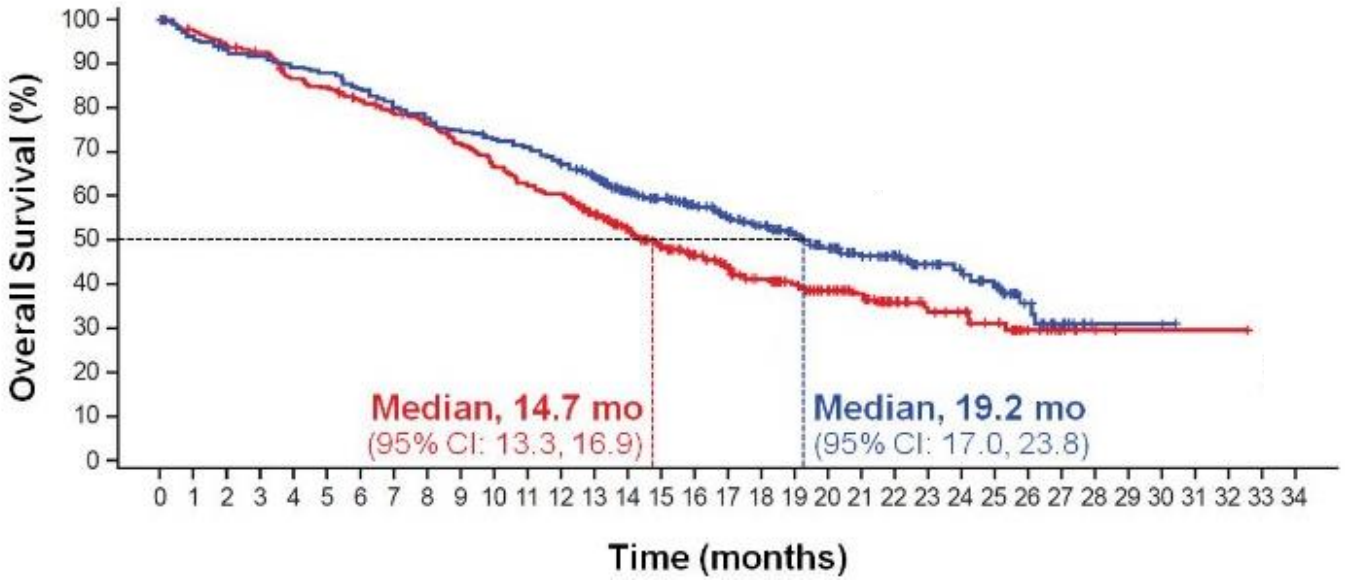
Socinski et al, NEJM 2018

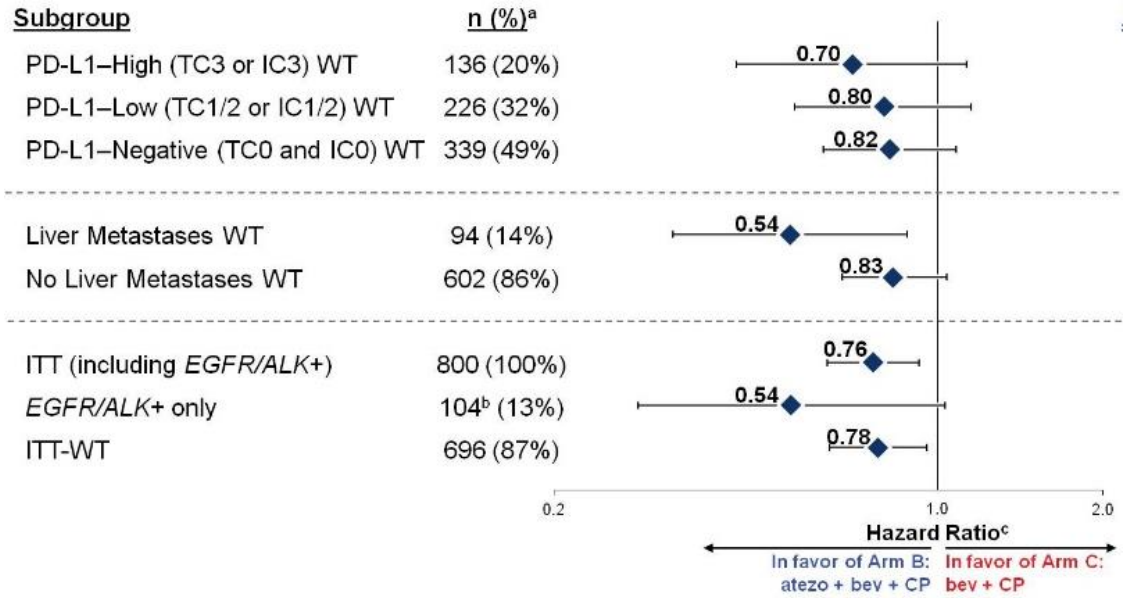
© 2018–2019 Society for Immunotherapy of Cancer

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



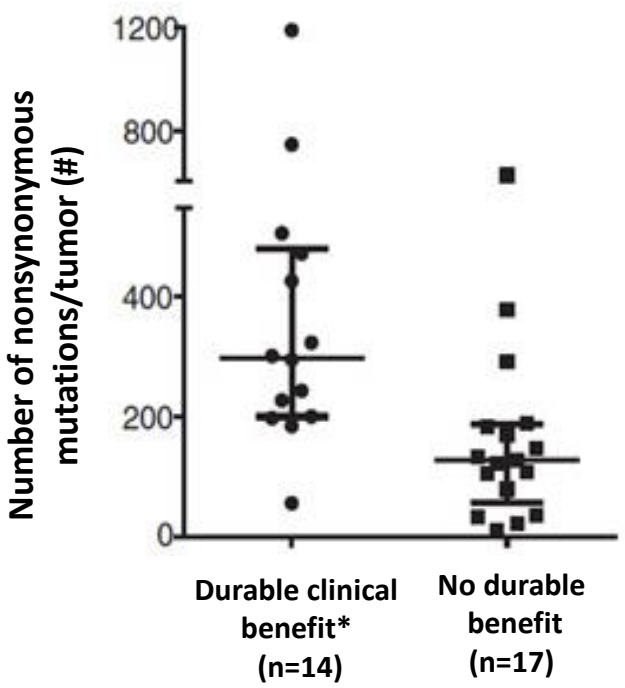


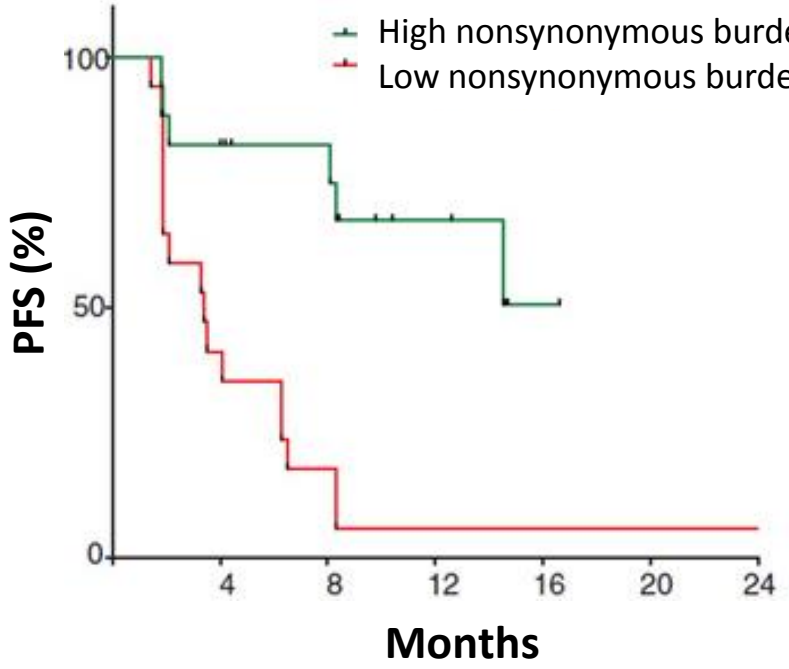
Socinski et al, NEJM 2018

© 2018–2019 Society for Immunotherapy of Cancer

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.



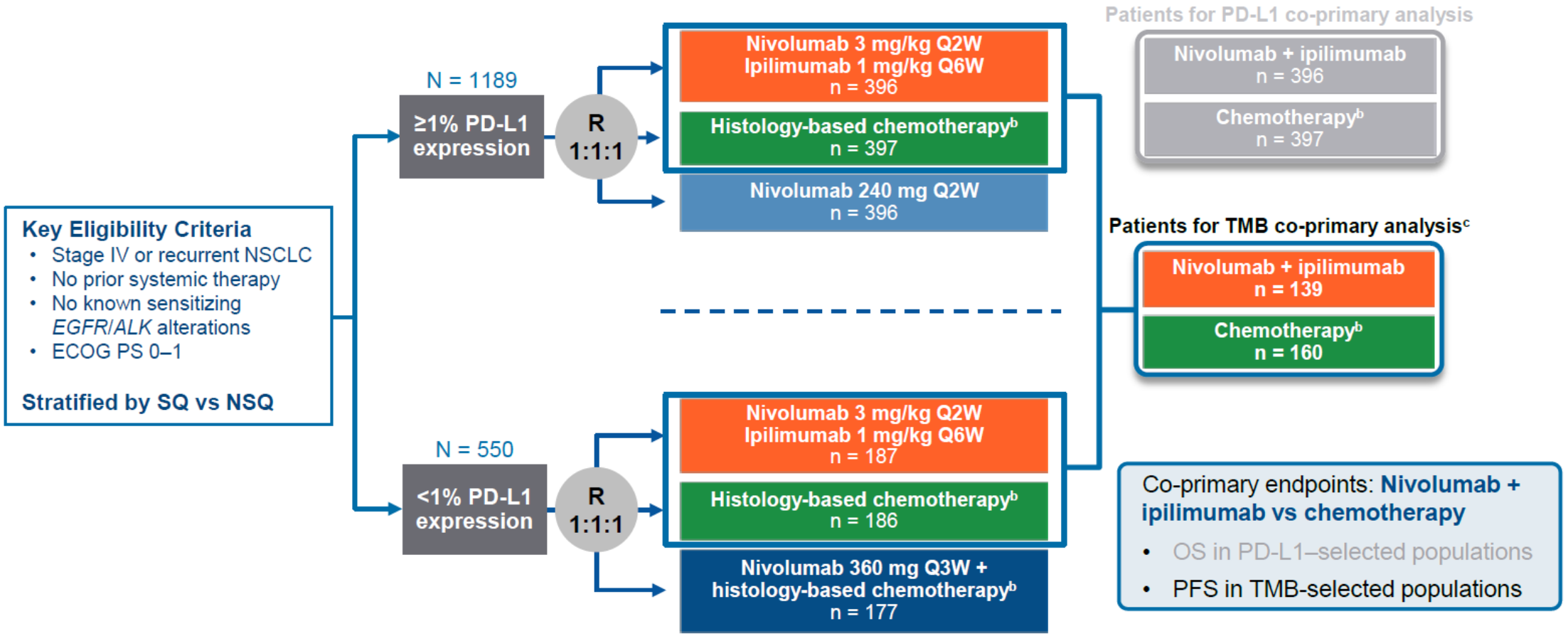


*Partial or stable response lasting > 6 mo

Rizvi N et al, Science, 2015

© 2018–2019 Society for Immunotherapy of Cancer

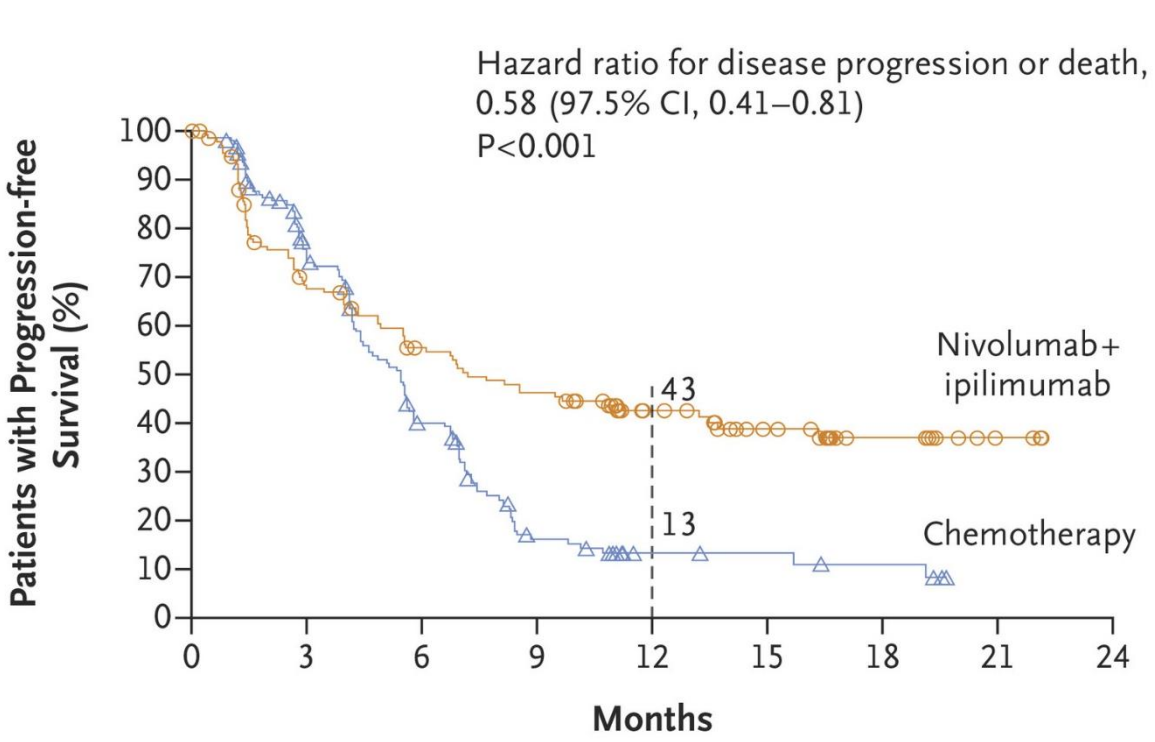
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

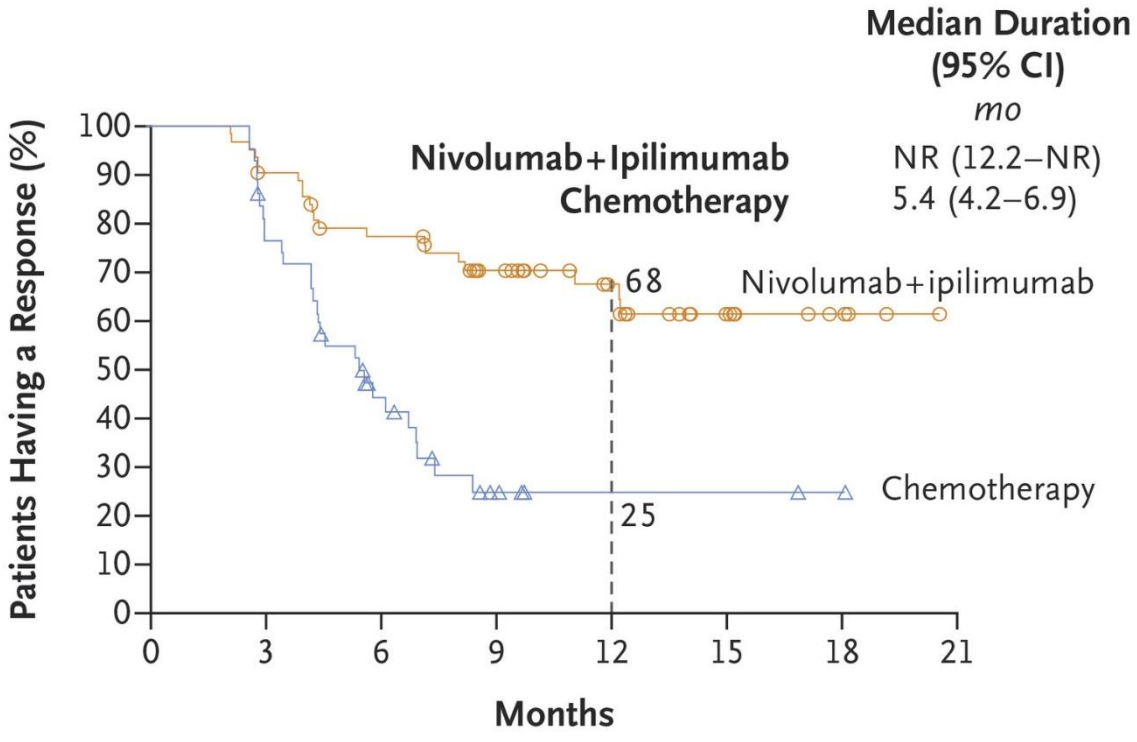


Hellman et al, NEJM, 2018

© 2018–2019 Society for Immunotherapy of Cancer

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



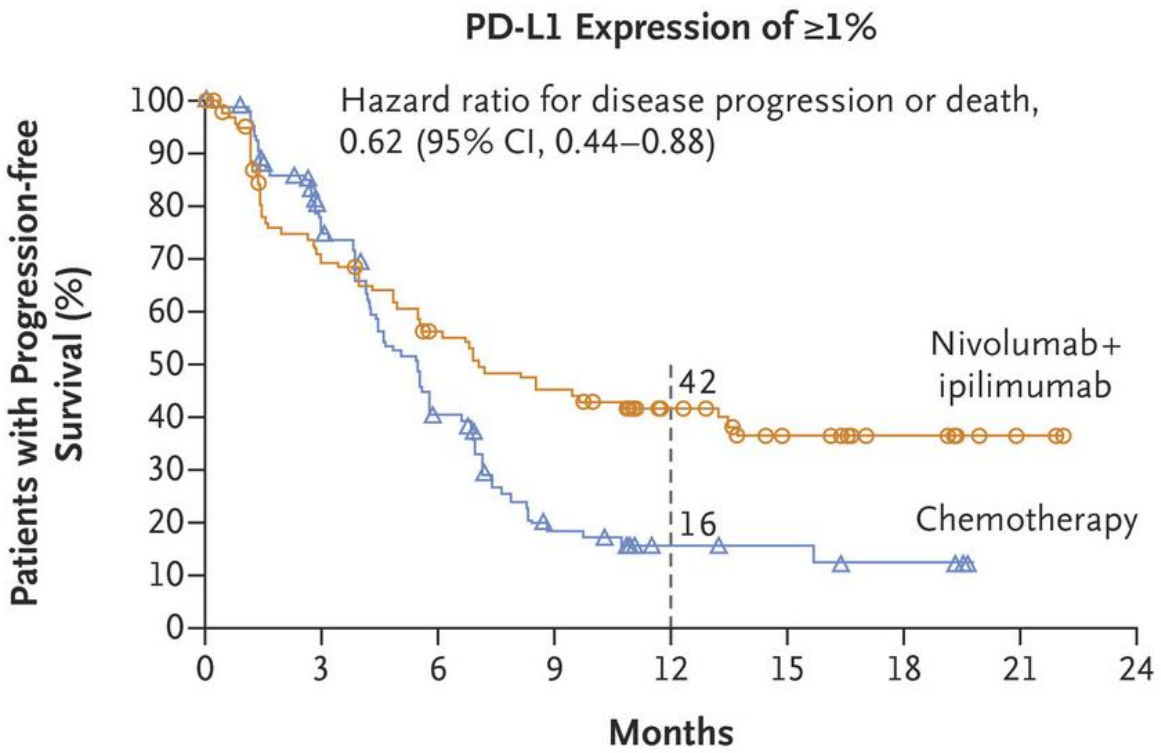


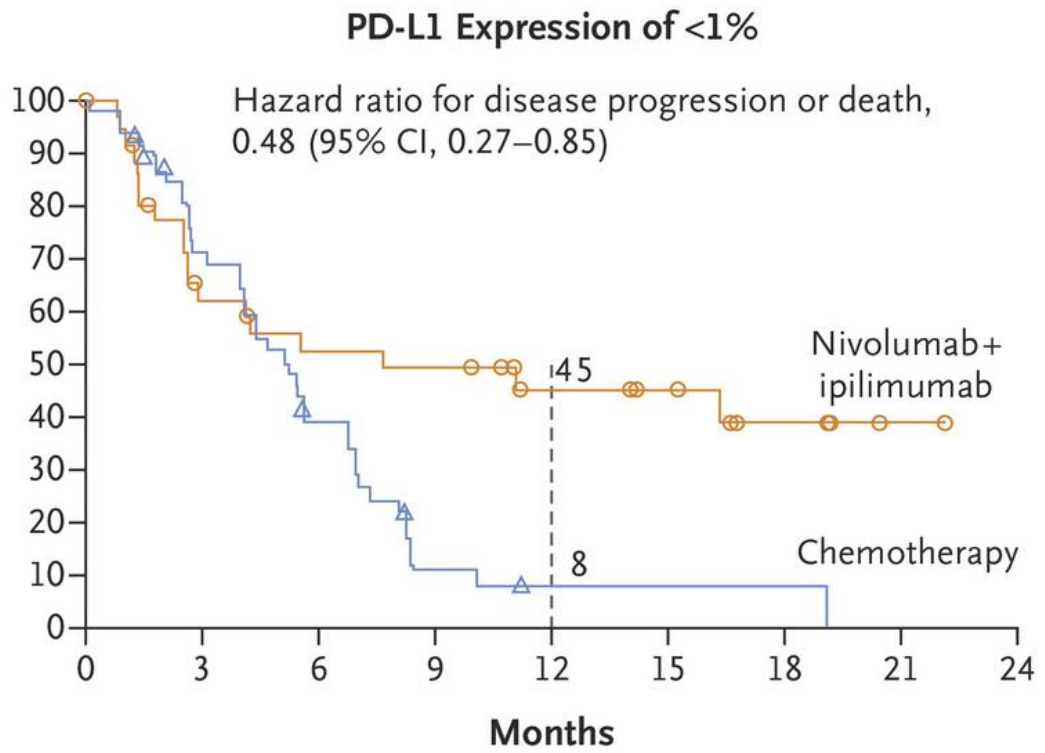
FDA approval for first-line use of nivolumab + ipilimumab in patients with high TMB is no longer being pursued due to overall survival not being statistically significantly increased vs chemotherapy.

Hellman et al, NEJM, 2018

© 2018–2019 Society for Immunotherapy of Cancer

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





Hellman et al, NEJM, 2018

© 2018–2019 Society for Immunotherapy of Cancer

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

© 2018–2019 Society for Immunotherapy of Cancer

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

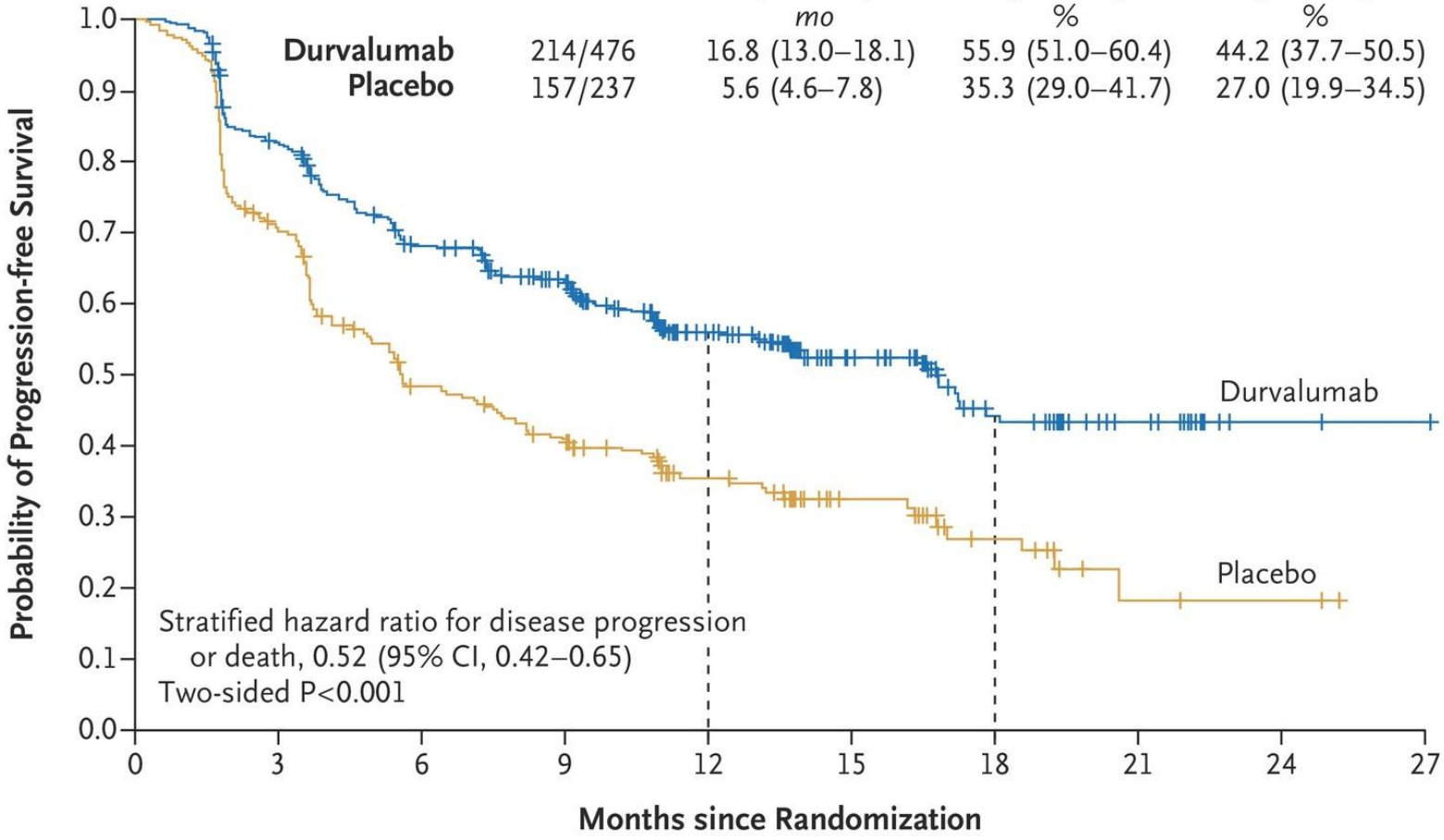
Placebo (n=234)
IV Q2W

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.

© 2018–2019 Society for Immunotherapy of Cancer

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)

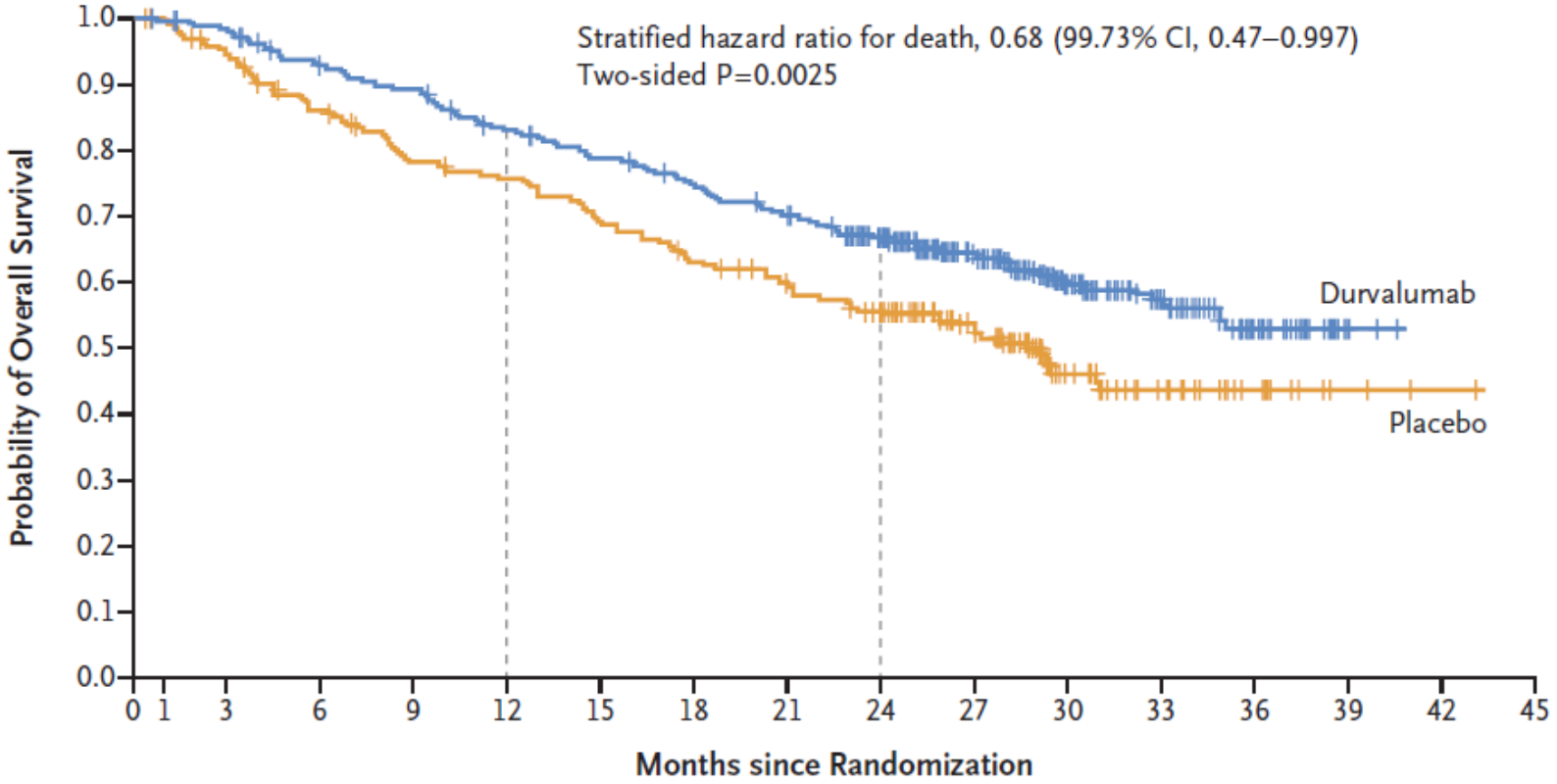


Antonia et al, NEJM 2017

© 2018–2019 Society for Immunotherapy of Cancer

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

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)

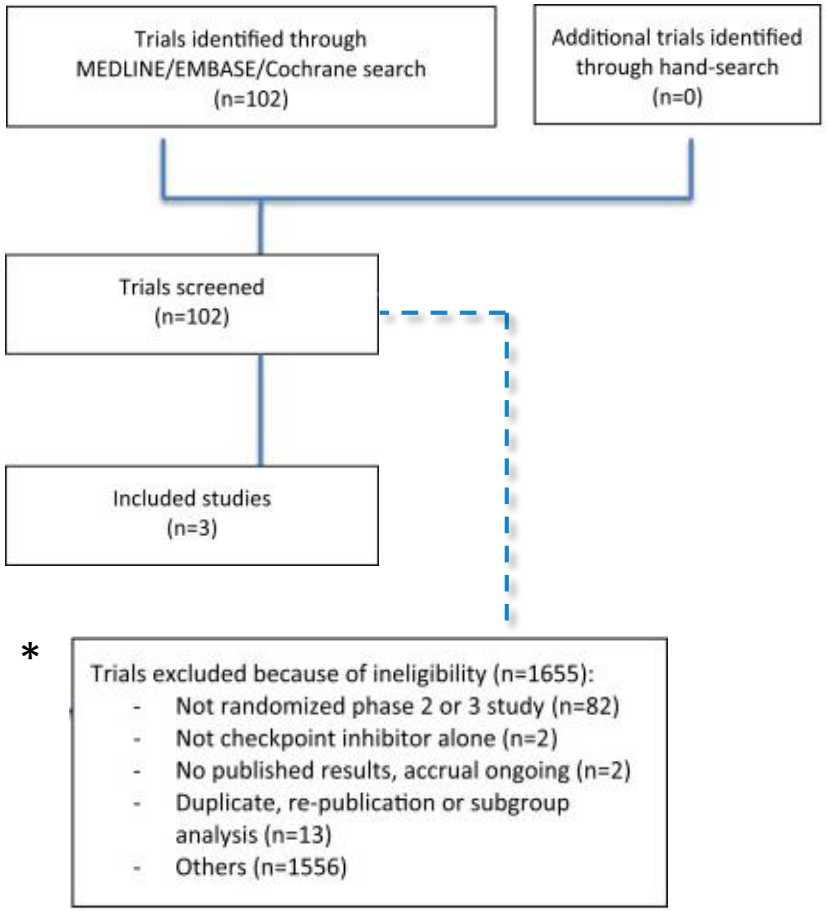


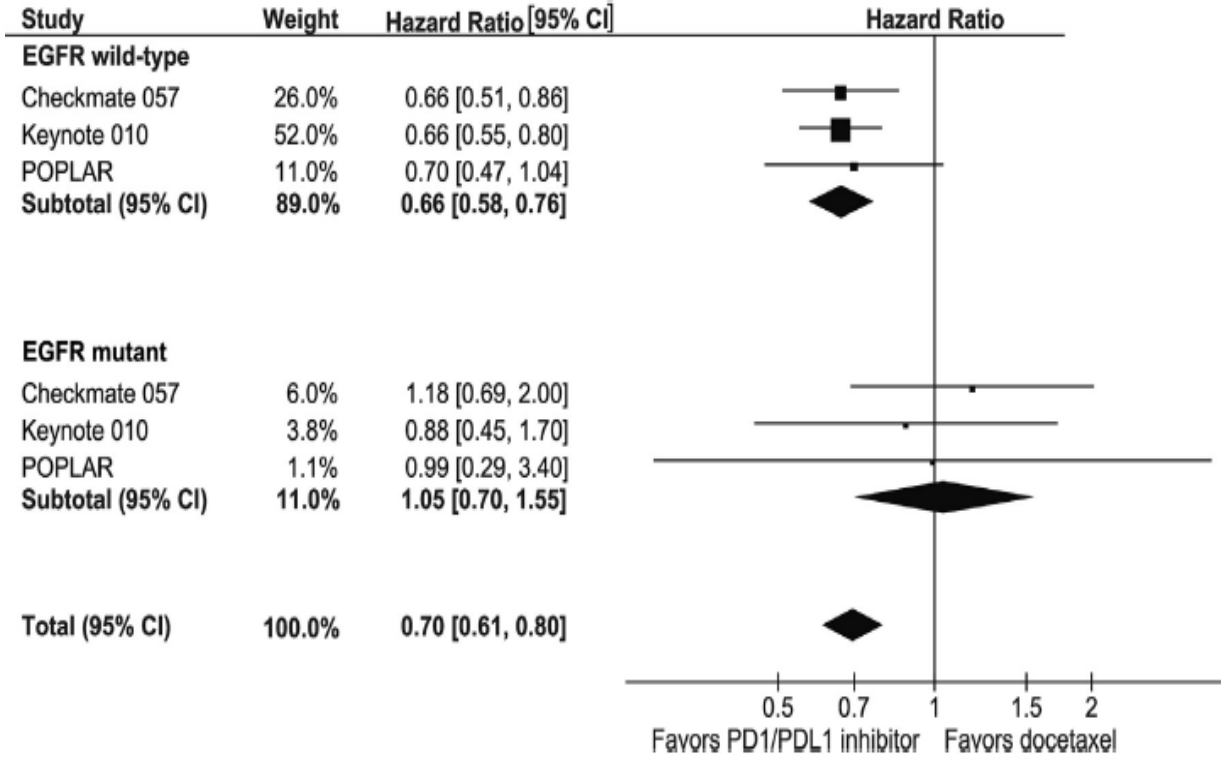
Antonia et al. NEJM 2018

© 2018–2019 Society for Immunotherapy of Cancer

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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





CK Lee et al., JTO 2016

© 2018–2019 Society for Immunotherapy of Cancer

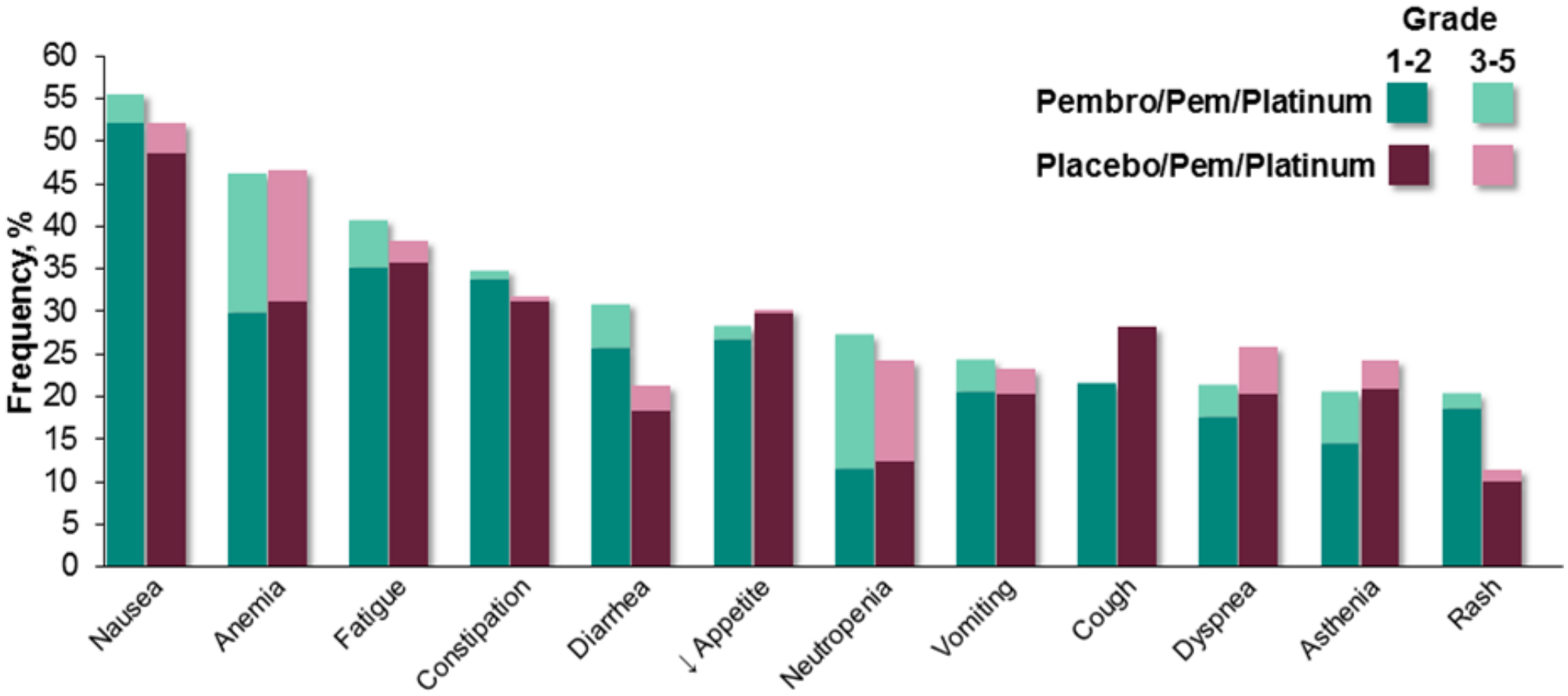
Single-agent Toxicities in 2/3L Randomized Trials

	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

© 2018–2019 Society for Immunotherapy of Cancer

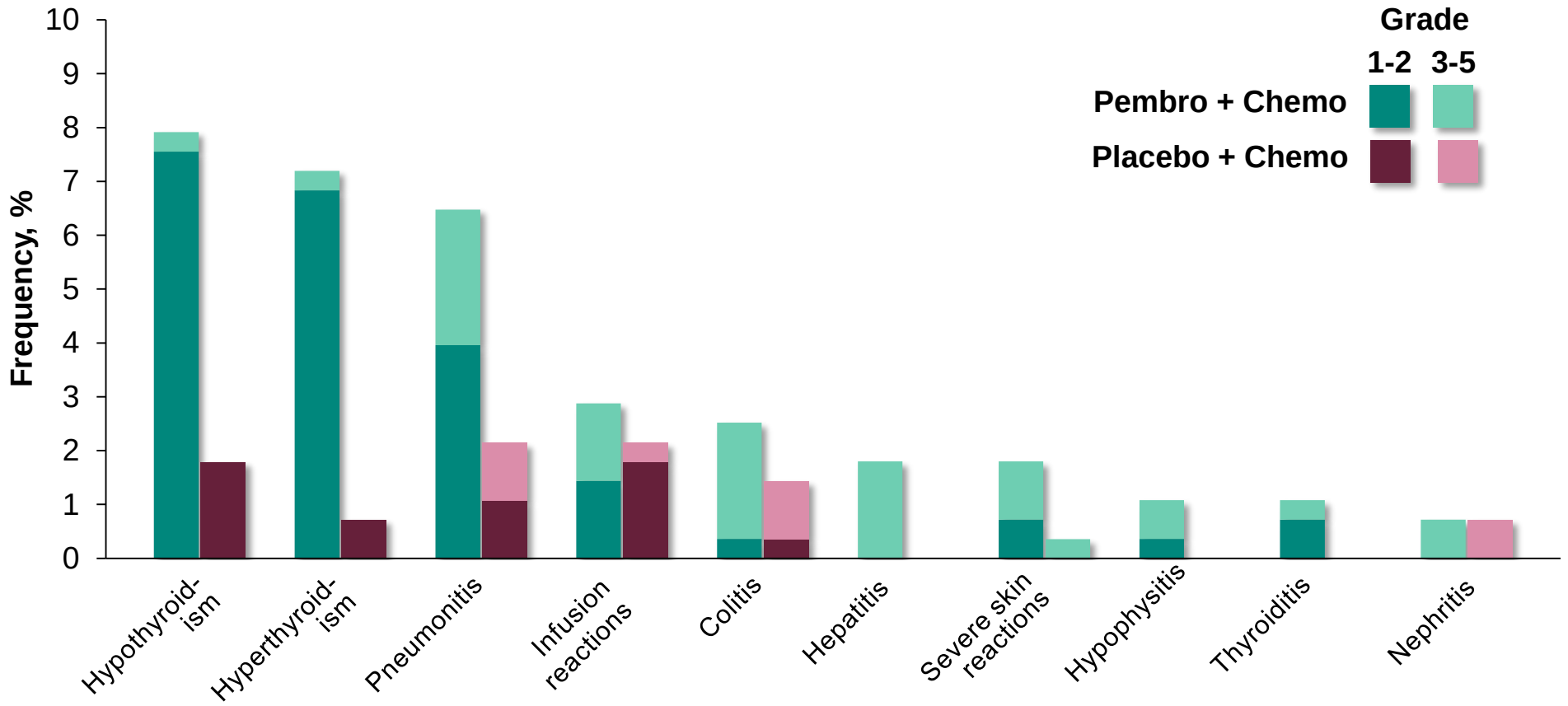
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



Ghandi et al, NEJM 2018

© 2018–2019 Society for Immunotherapy of Cancer

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



Paz-Arez et al, ASCO, 2018

© 2018–2019 Society for Immunotherapy of Cancer

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

© 2018–2019 Society for Immunotherapy of Cancer

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.*

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 1

- A 63 year old female, heavy smoker, presented with trouble moving her left upper extremity.
- MRI brain showed five brain metastases, the largest of which was 2.0 centimeters
- CT chest/abdomen/pelvis showed a large right upper lobe mass, pathologic mediastinal lymphadenopathy, supraclavicular lymphadenopathy and bilateral adrenal metastases.
- Resection of right frontal brain metastasis was performed
- Path – metastatic adenocarcinoma of lung origin, KRAS G12R mutation, PD-L1 80% on tumor cells by the 22C3 assay

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 1

- What is the treatment with the best chance of long-term survival in this patient?
  - A) Carboplatin + Pemetrexed followed by Pemetrexed maintenance
  - B) Nivolumab
  - C) Carboplatin + Paclitaxel
  - D) Pembrolizumab

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 1

D) Pembrolizumab has a median OS of 30 months for first line treatment of patients with NSCLC and PD-L1 ≥ 50%

[Pembrolizumab had superior OS when compared to platinum based doublets in patients with PD-L1 ≥ 50%, nivolumab did not have superior OS when compared to platinum based doublets in a similar patient population]

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 2

- A 60 year old male with metastatic NSCLC was treated with nivolumab + ipilimumab.
- After being on this treatment for 6 months he began to complain of significant fatigue. Recent CT scan showed a continued partial response to therapy.
- He stated the fatigue was so severe he could not get up nor do normal activities. He stated the fatigue was as bad as his cancer.
- Associated symptoms included headache and diplopia
- MRI brain showed no brain metastasis

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 2

- What is the best next step?
  - A) Lumbar puncture
  - B) Evaluate ACTH, cortisol, testosterone, FSH, LH
  - C) Ophthalmology consult
  - D) Endocrinology consult

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 2

- B) Evaluate ACTH, cortisol, testosterone, FSH, LH

[pan-hypopituitarism can occur with immune checkpoint inhibition, the incidence is higher with combination of PD-1 axis + CTLA-4 inhibition. Symptoms may include headache and severe fatigue. To diagnosis radiographic one do a pituitary protocol MRI; however, this particular image does not always show pituitary pathology in such cases.]

© 2018–2019 Society for Immunotherapy of Cancer

Case Study 2

- ACTH was 6 (normal range 7-39). 3 months earlier it was 34
- Cortisol was 4
- Testosterone was 18 (normal range 87-780)
- FSH and LH were very low
- The patient was referred to endocrinology where he was started on testosterone replacement and steroids

© 2018–2019 Society for Immunotherapy of Cancer

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Jose Pacheco
Assistant Professor
Thoracic Oncology/Phase I

Email:
jose.m.Pacheco@ucdenver.edu

© 2018–2019 Society for Immunotherapy of Cancer