

Immunotherapy for the Treatment of Lung Cancer

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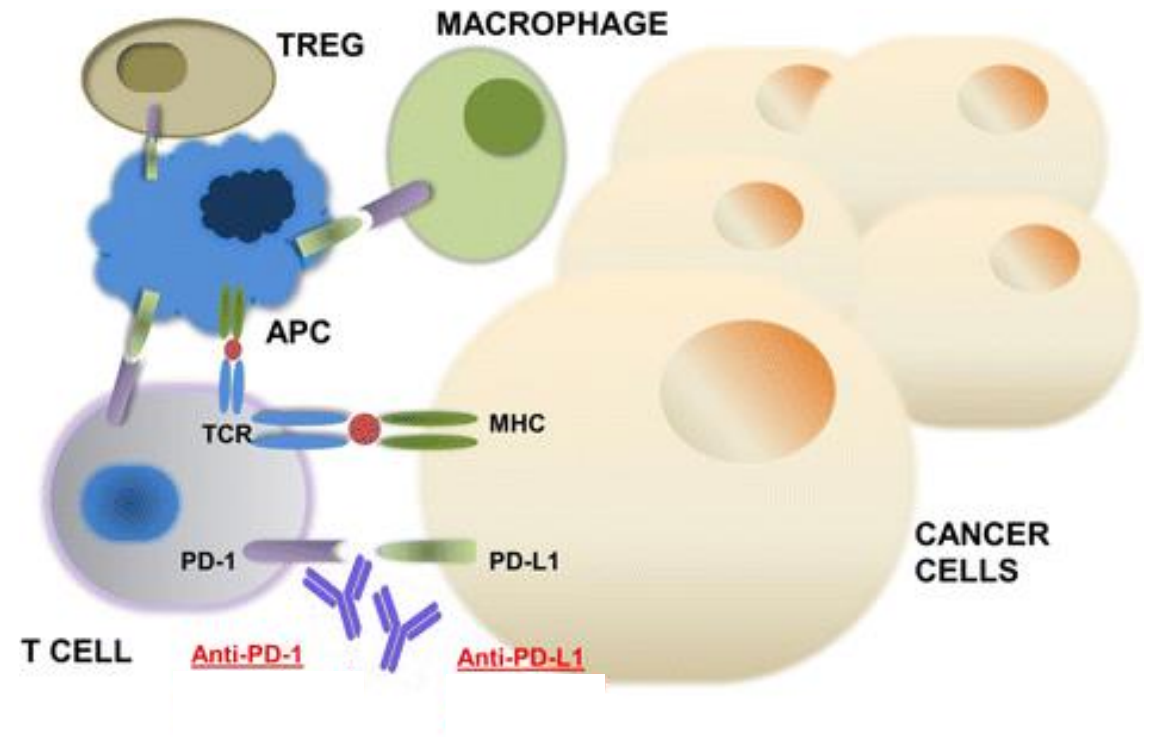
Disclosures

- No relevant financial relationships to disclose.
- I will be discussing some non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

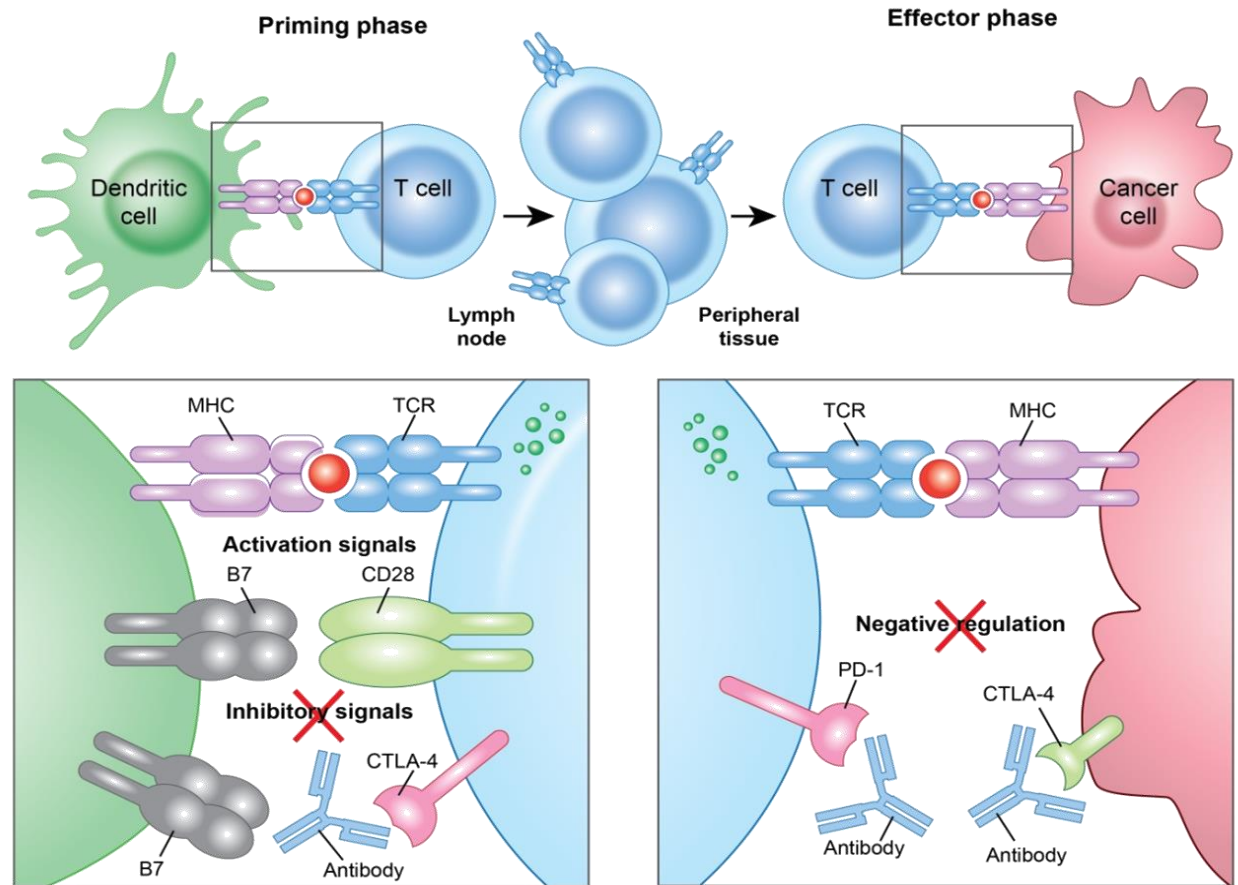
- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells



Gong J, Journal for Immunotherapy of Cancer, 2018

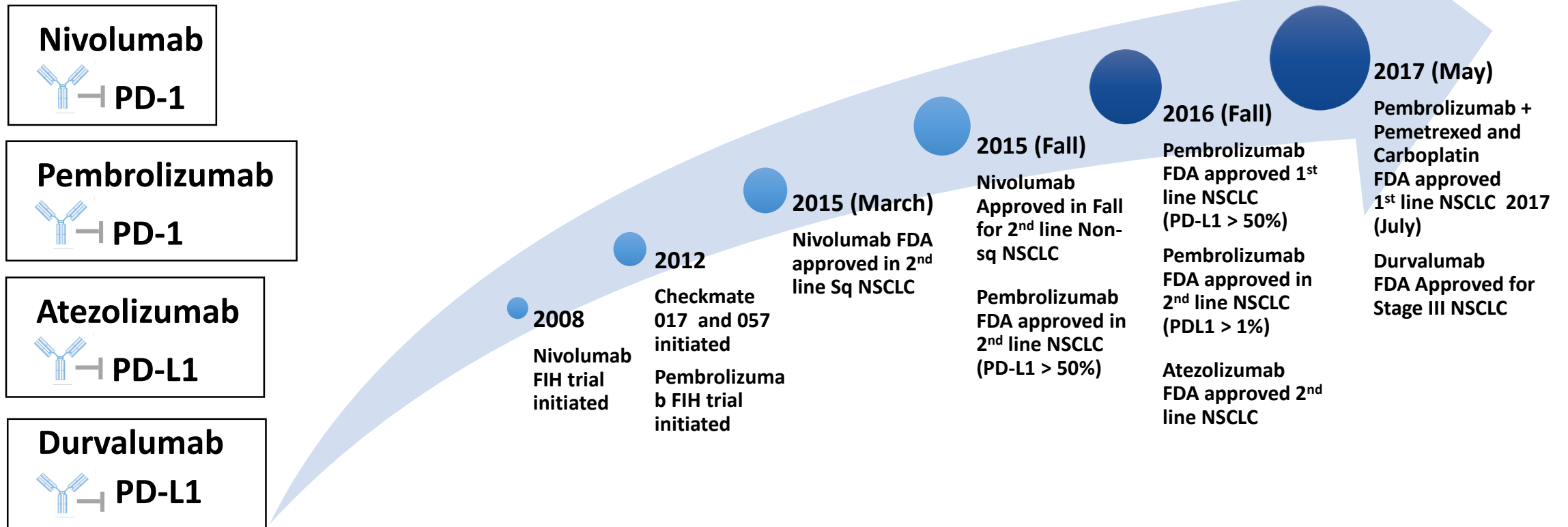
Combination Immune Checkpoint Blockade

- 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

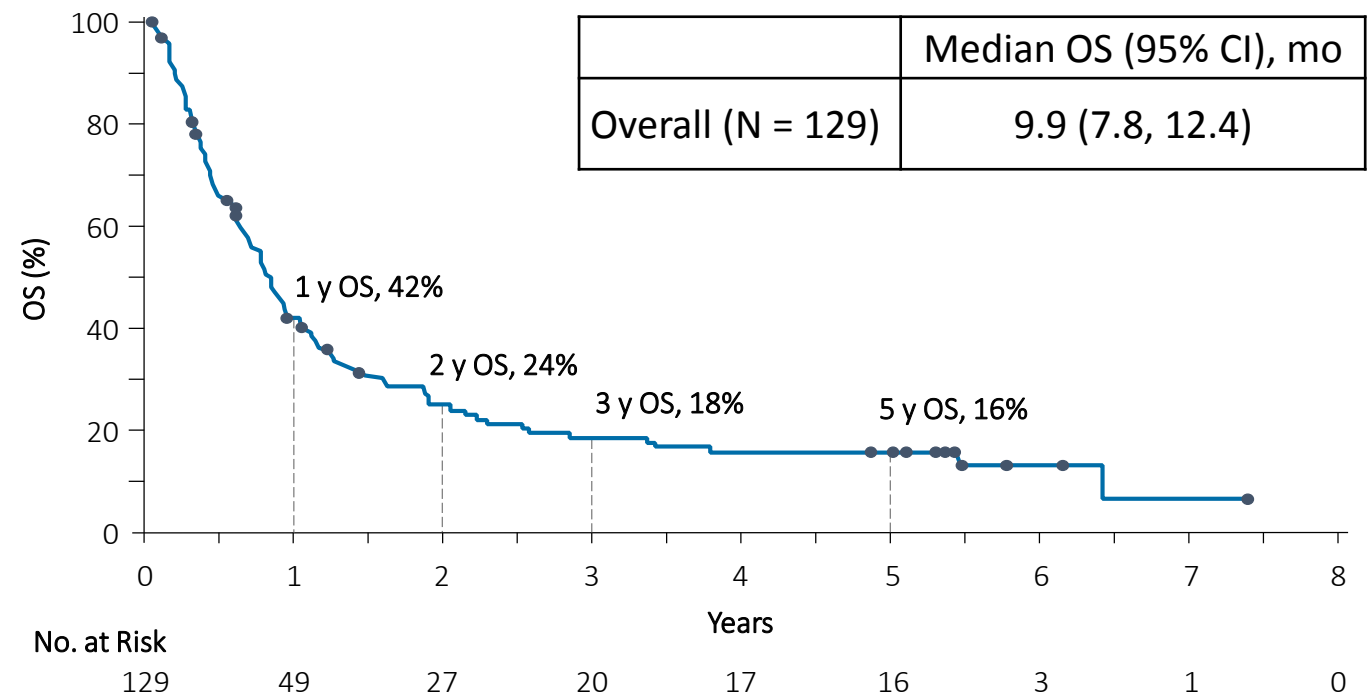


CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

Phase 1, 5-Year Update

5-Year Survival

- 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%



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

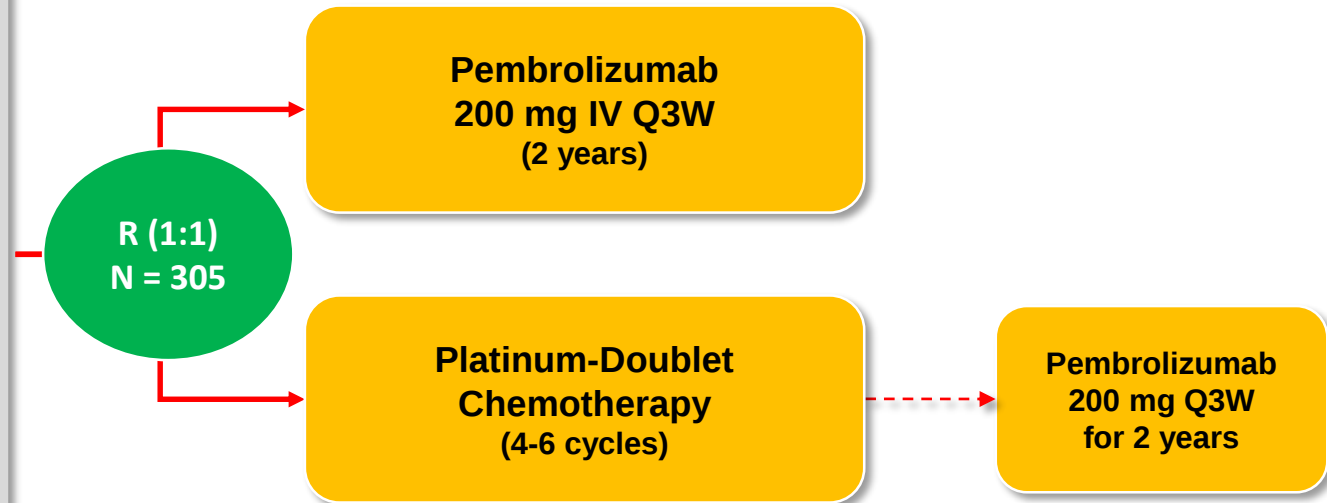
Treatment Naïve Regimens: Competing Strategies

- 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)

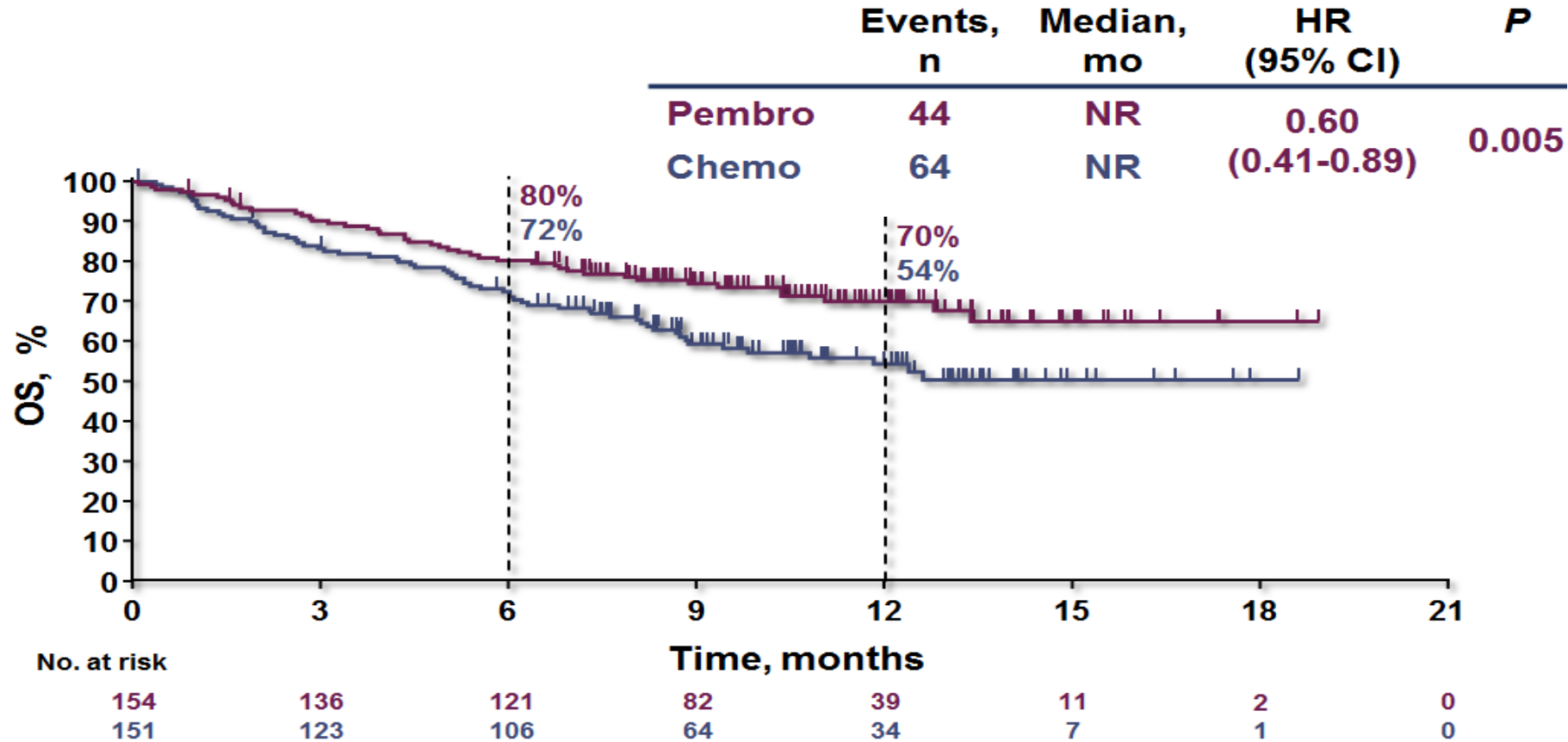
Key Eligibility Criteria

- **Untreated** stage IV NSCLC
- PD-L1 TPS $\geq 50\%$
- 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



Reck M et al, ESMO 2016, NEJM 2016

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

KEYNOTE-042 Study Design

Key Eligibility Criteria

- Untreated locally advanced or metastatic NSCLC of any histology
- PD-L1 TPS $\geq 1\%$
- No sensitizing *EGFR* or *ALK* alterations
- ECOG PS 0 or 1
- No untreated or unstable CNS metastases
- No history of pneumonitis that required systemic corticosteroids

Stratification Factors

- Region (east Asia vs rest of the world)
- ECOG PS (0 vs 1)
- Histology (squamous vs nonsquamous)
- PD-L1 TPS ($\geq 50\%$ vs 1-49%)

Randomize
1:1

N = 637

Pembrolizumab
200 mg Q3W
for up to 35 cycles

N = 637

Carboplatin AUC 5 or 6 Q3W +
Paclitaxel 200 mg/m² Q3W^a
OR
Carboplatin AUC 5 or 6 Q3W +
Pemetrexed 500 mg/m² Q3W^a
for up to 6 cycles

End points

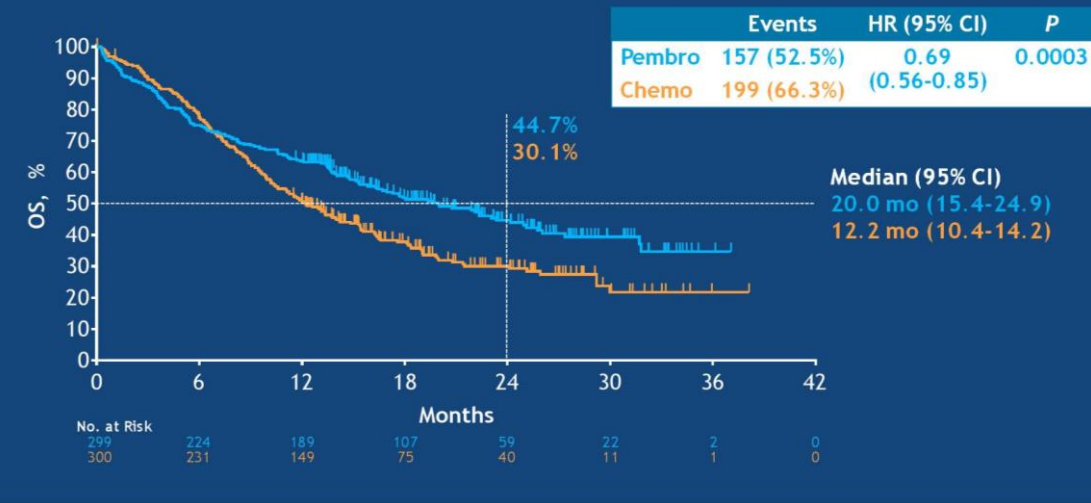
- Primary: OS in PD-L1 TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$
- Secondary: PFS and ORR in TPS $\geq 50\%$, $\geq 20\%$, and $\geq 1\%$; safety in TPS $\geq 1\%$

^aPemetrexed maintenance therapy was optional but strongly encouraged for patients with nonsquamous histology.

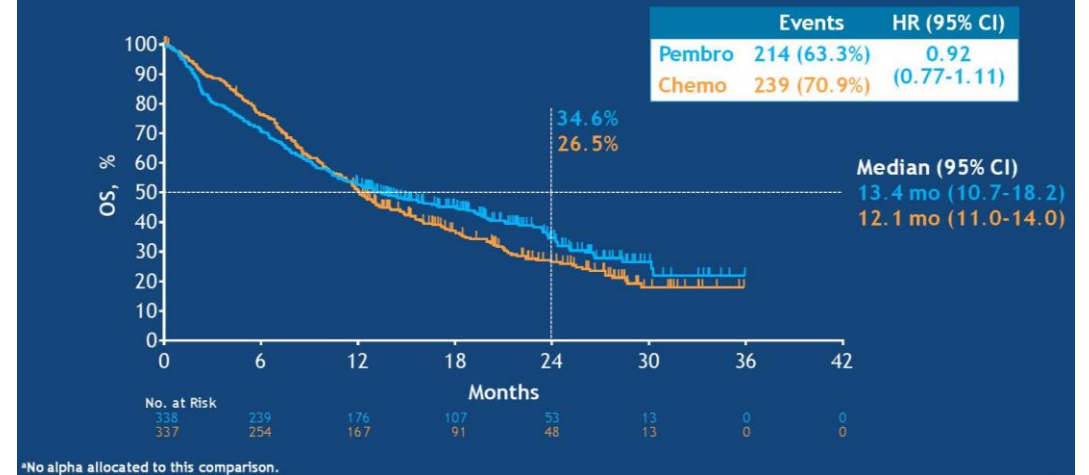
Lopes et al, ASCO 2018

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

Overall Survival: TPS ≥50%



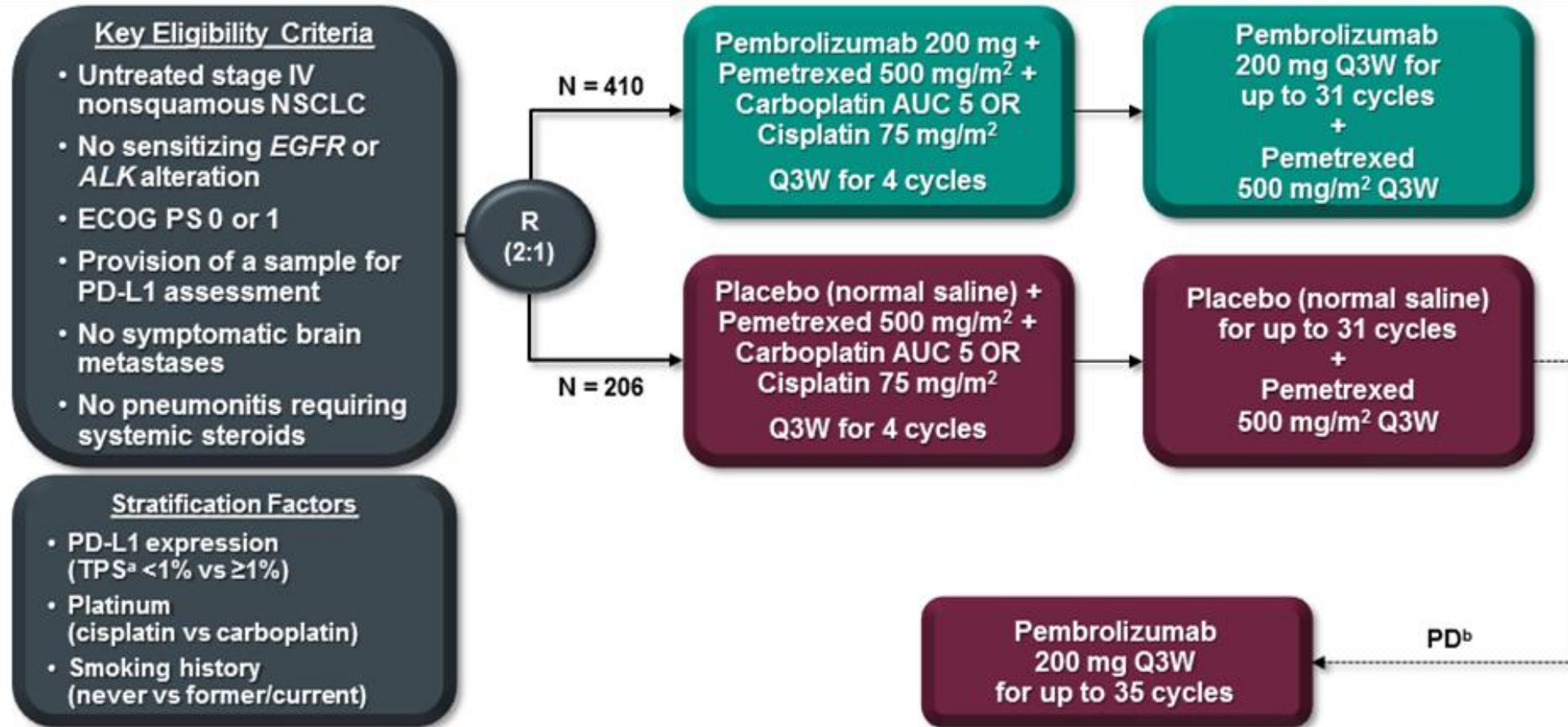
Overall Survival: TPS ≥1-49% (Exploratory Analysis^a)



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

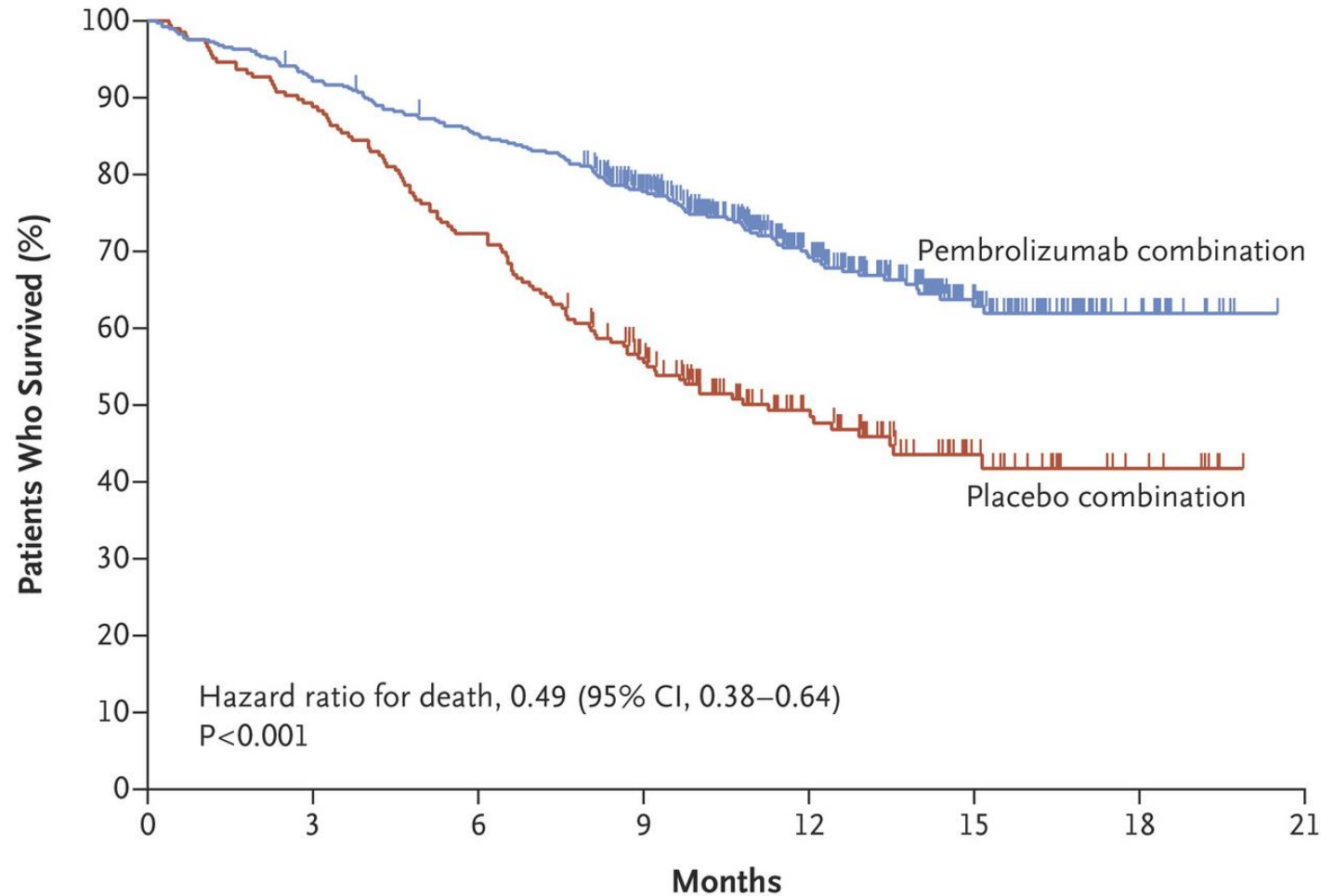
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

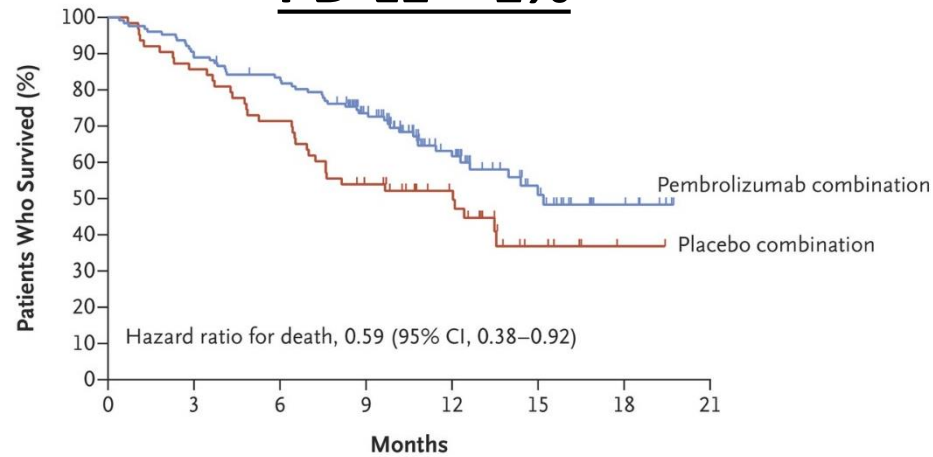
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



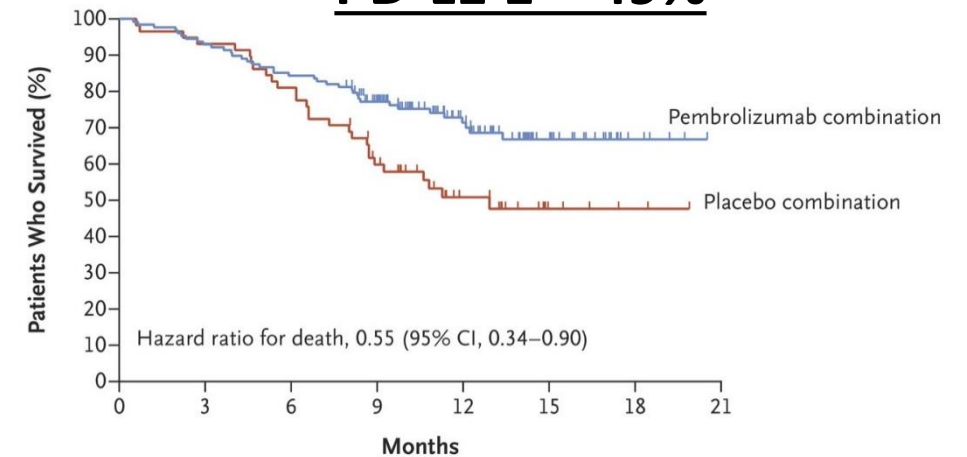
Ghandi et al, NEJM 2018

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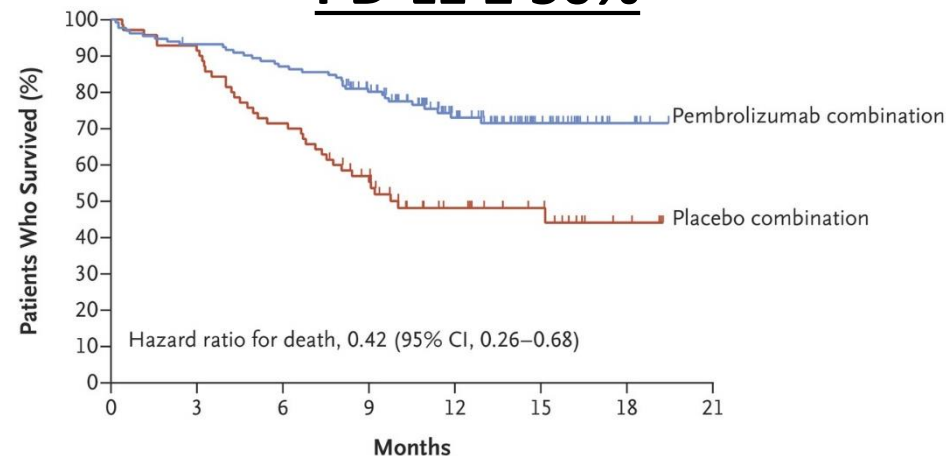
PD-L1 < 1%



PD-L1 1 – 49%

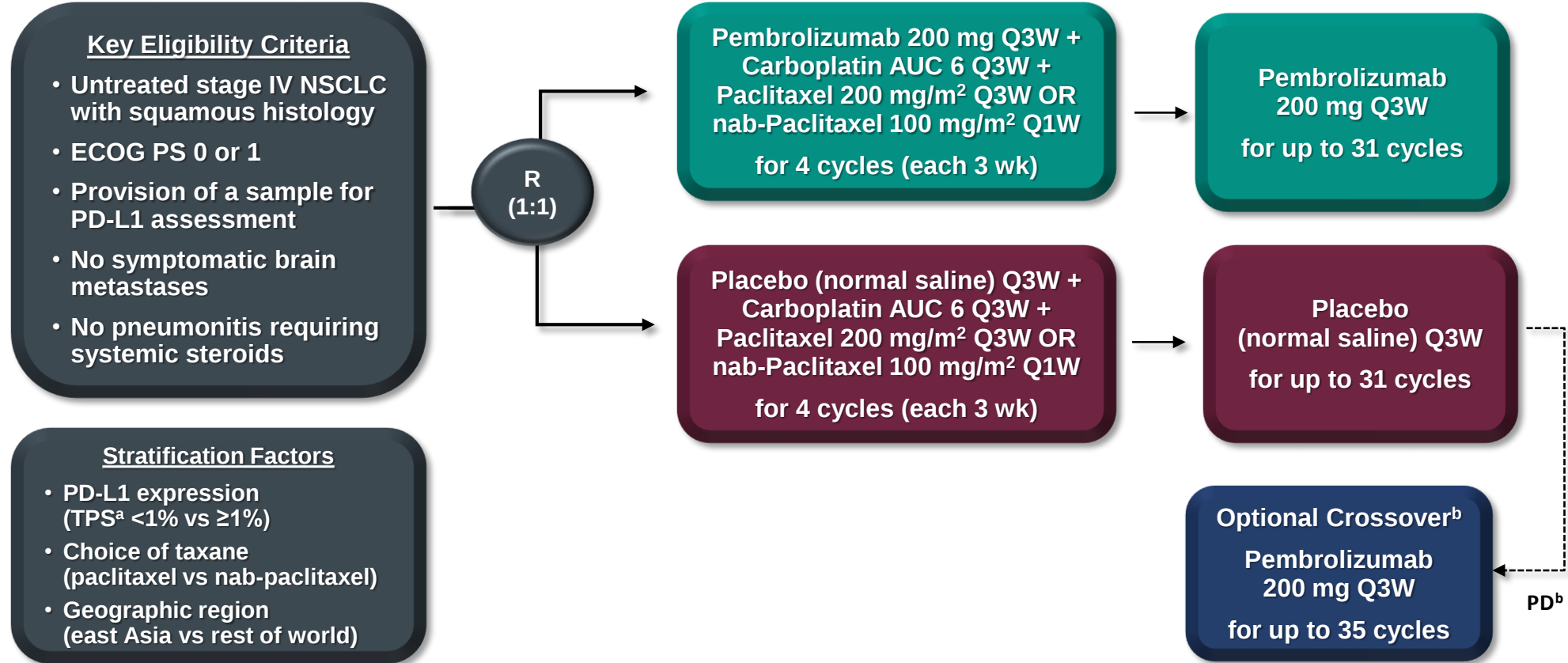


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

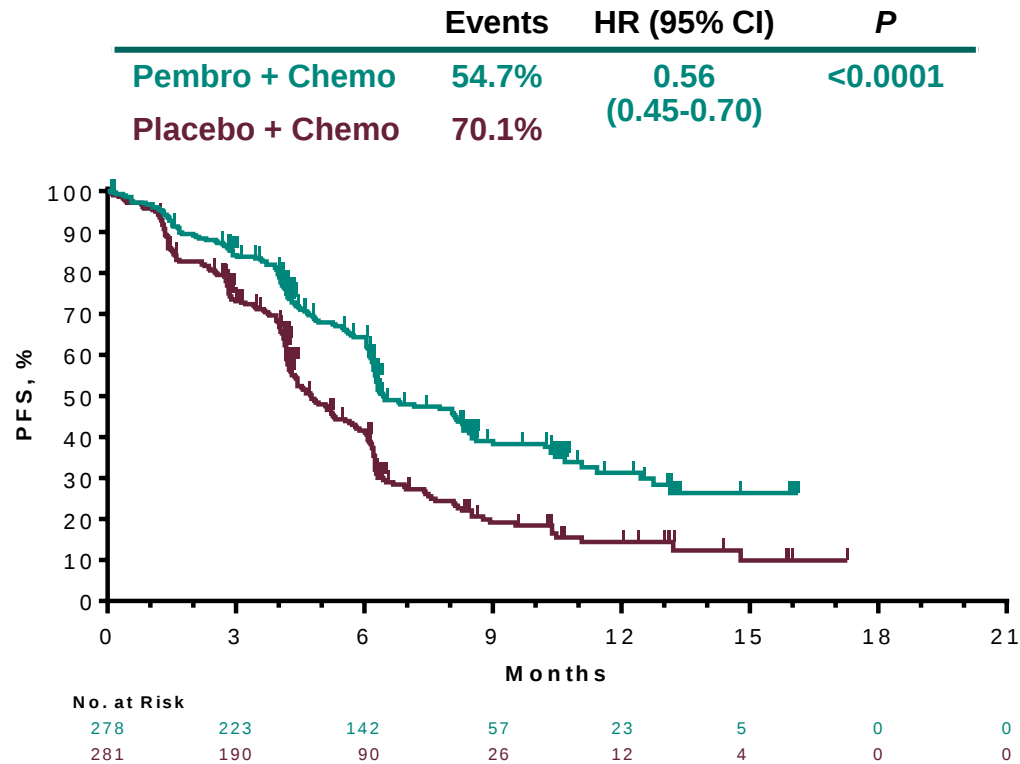
KEYNOTE-407: Pembrolizumab/chemotherapy vs Chemotherapy for Advanced Squamous-cell NSCLC



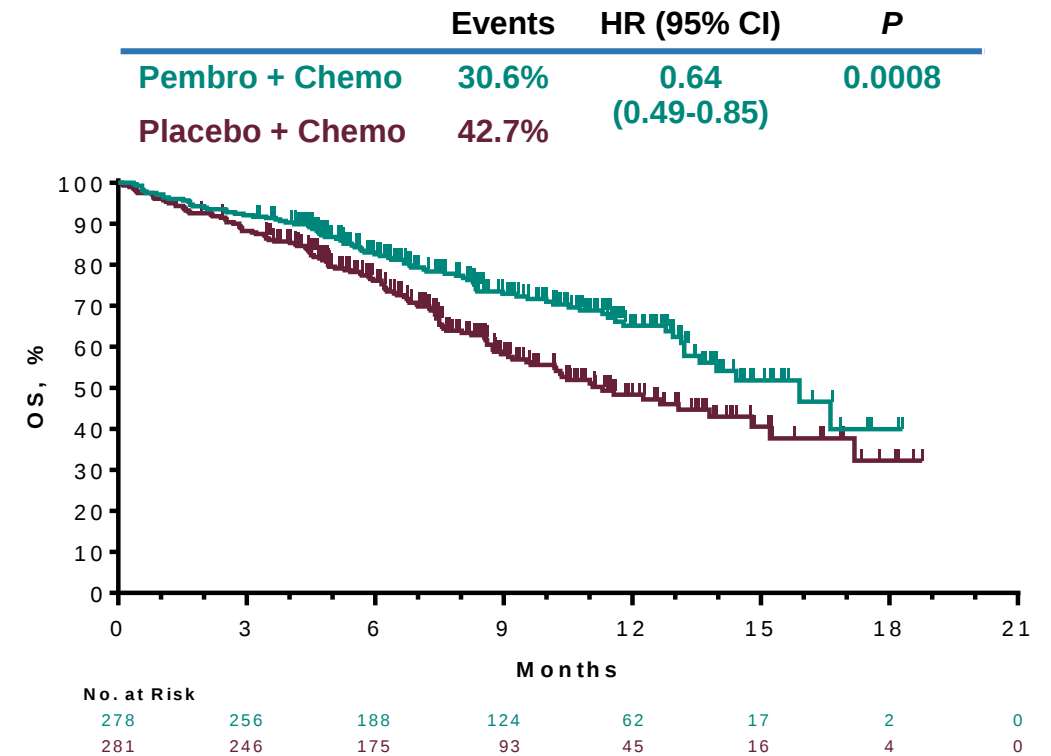
Paz-Ares et al, ASCO 2018

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

PFS (RECISTv1.1, BICR)

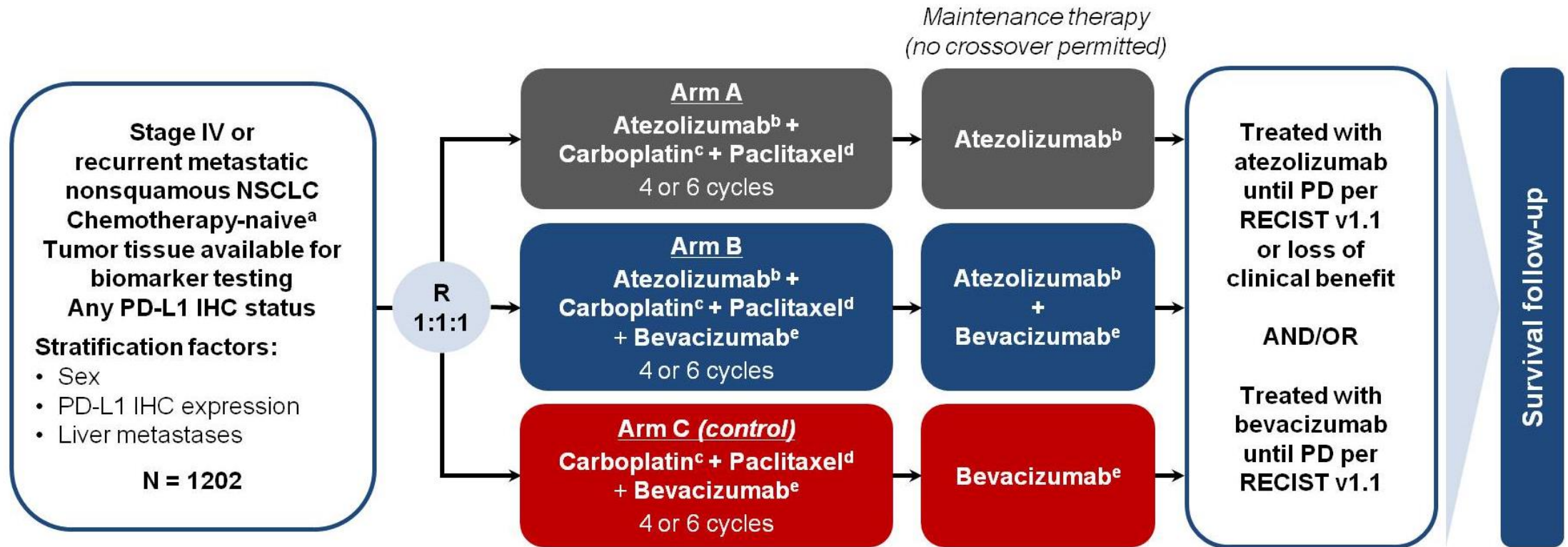


Overall Survival



Paz-Ares et al, ASCO 2018

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

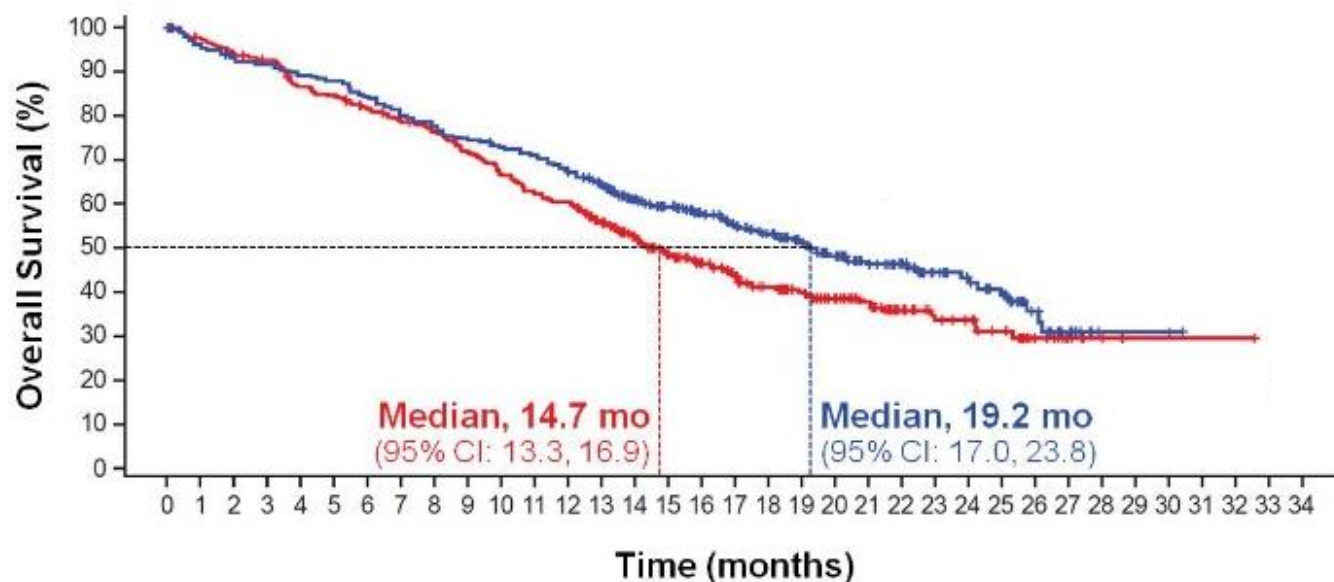


Socinski et al, NEJM 2018

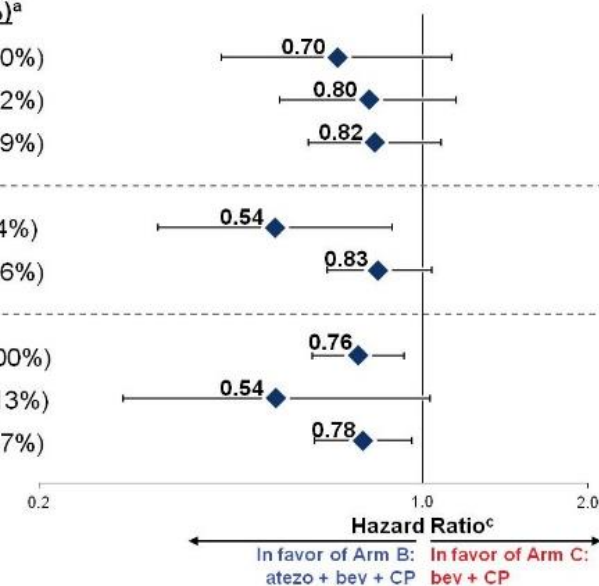
IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/ Paclitaxel/Bevacizumab in advanced non-squamous NSCLC

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



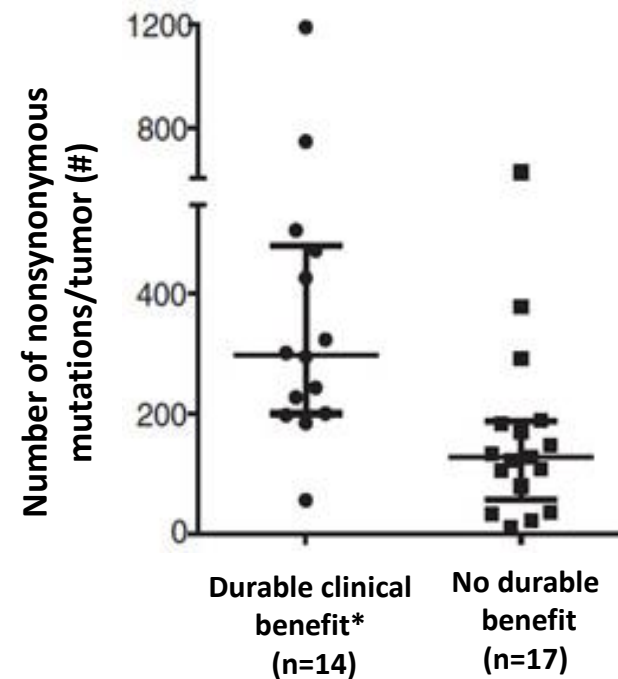
Subgroup	n (%) ^a
PD-L1–High (TC3 or IC3) WT	136 (20%)
PD-L1–Low (TC1/2 or IC1/2) WT	226 (32%)
PD-L1–Negative (TC0 and IC0) WT	339 (49%)
Liver Metastases WT	94 (14%)
No Liver Metastases WT	602 (86%)
ITT (including EGFR/ALK+)	800 (100%)
EGFR/ALK+ only	104 ^b (13%)
ITT-WT	696 (87%)



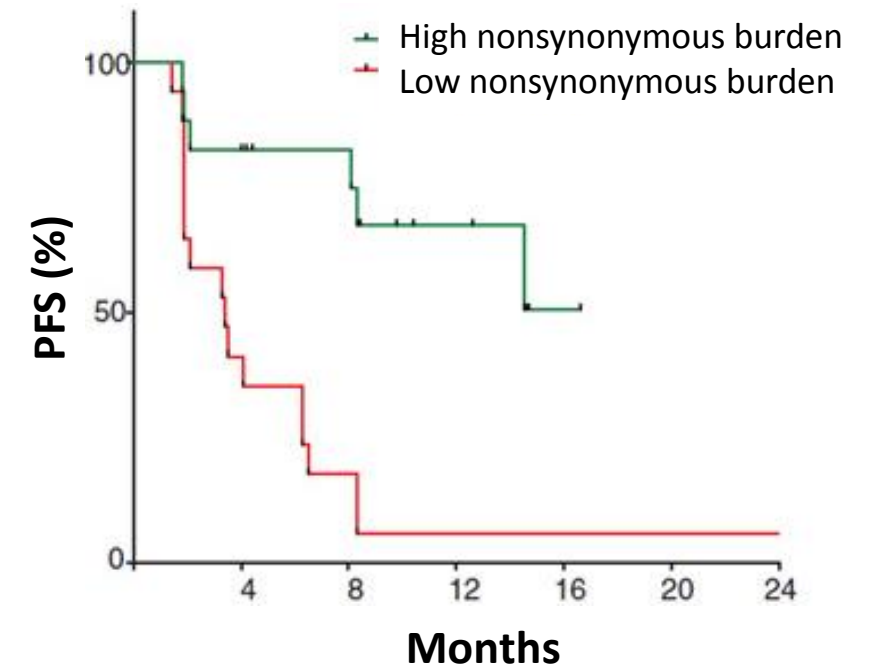
Socinski et al, NEJM 2018

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.

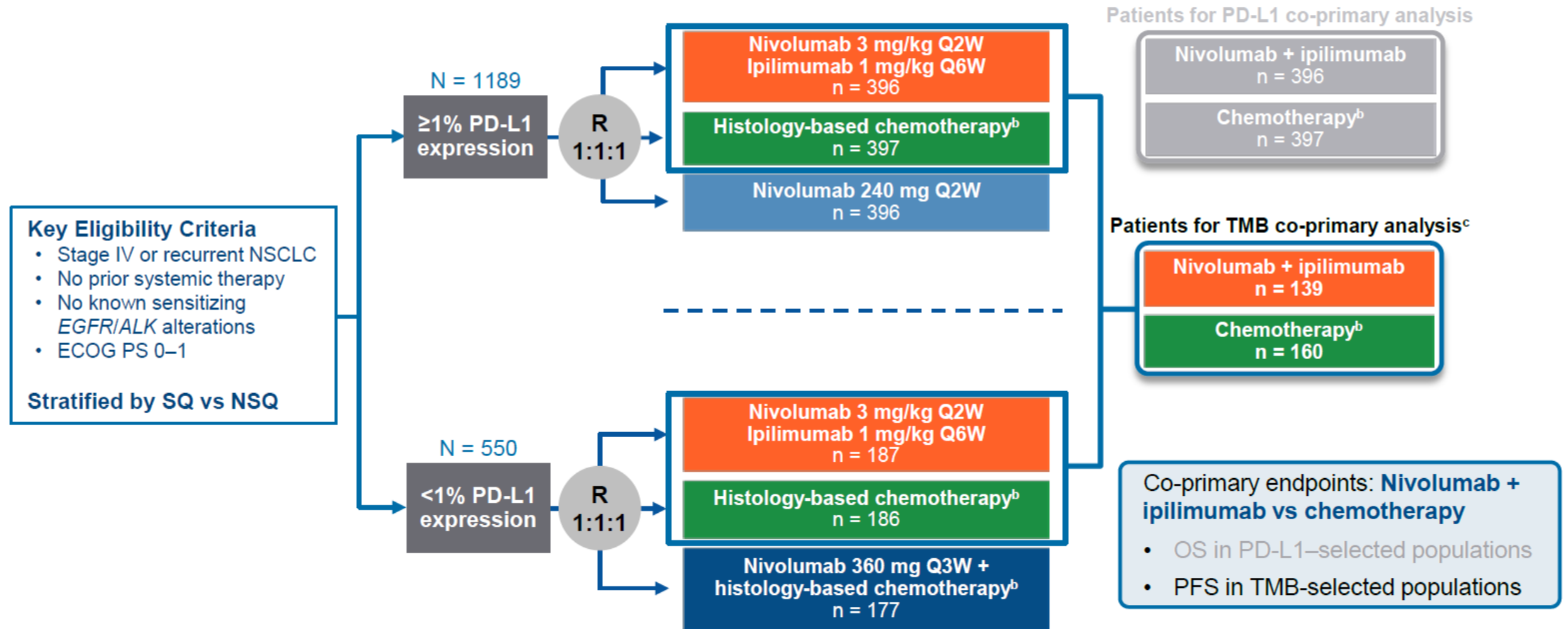


*Partial or stable response lasting > 6 mo



Rizvi N et al, Science, 2015

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

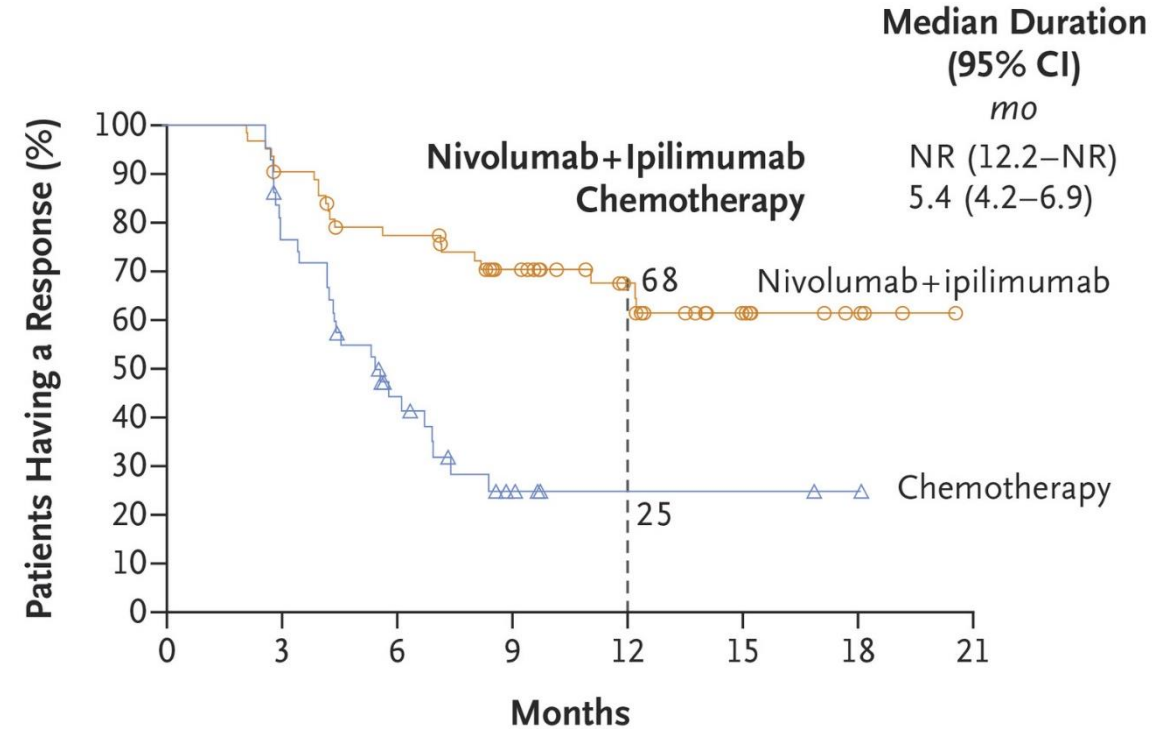
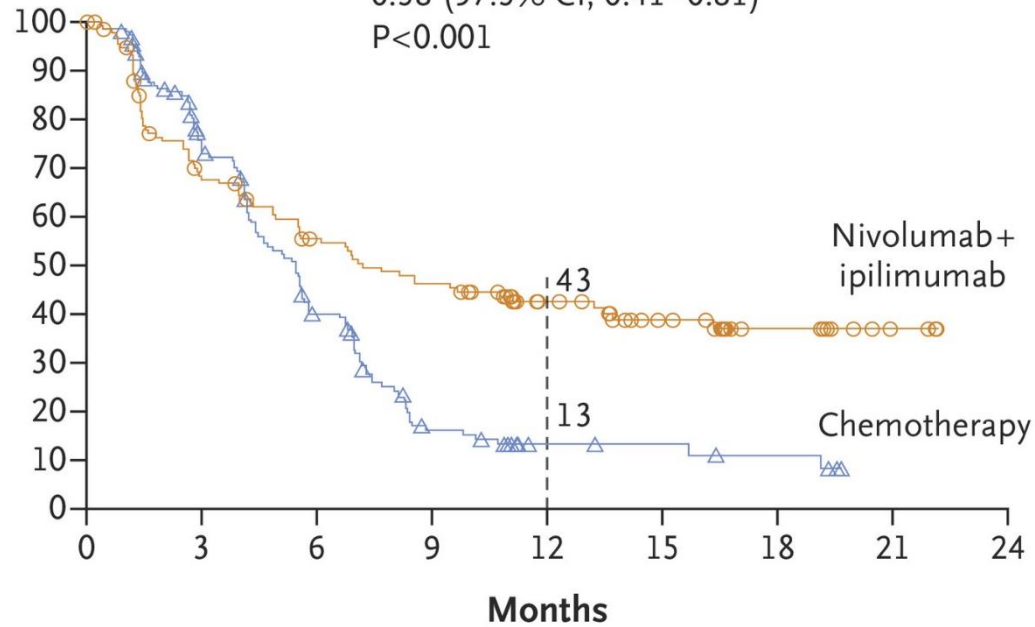


Hellman et al, NEJM, 2018

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

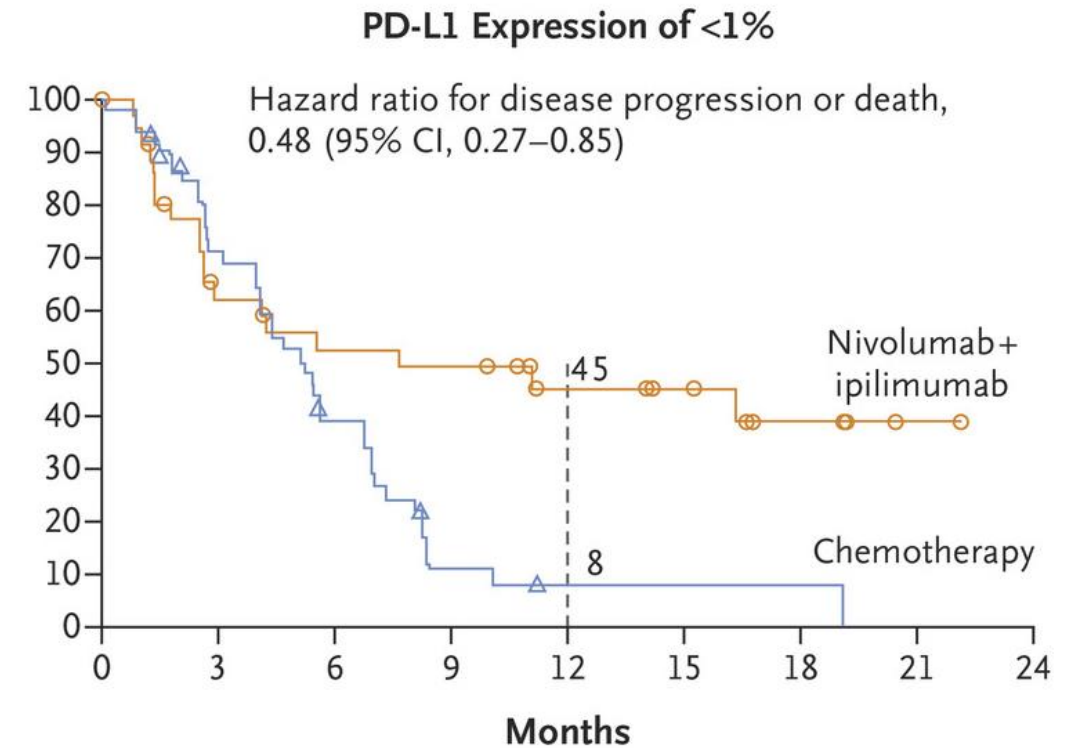
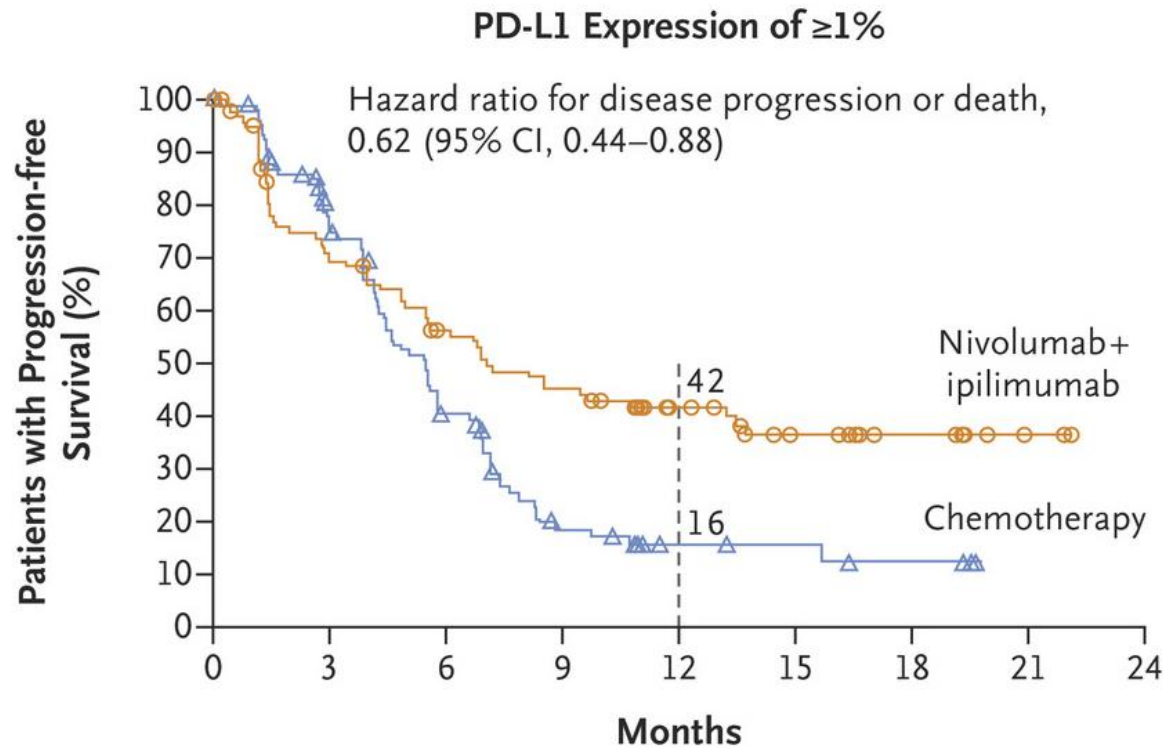
Hazard ratio for disease progression or death,
0.58 (97.5% CI, 0.41–0.81)
P<0.001

Patients with Progression-free
Survival (%)



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		

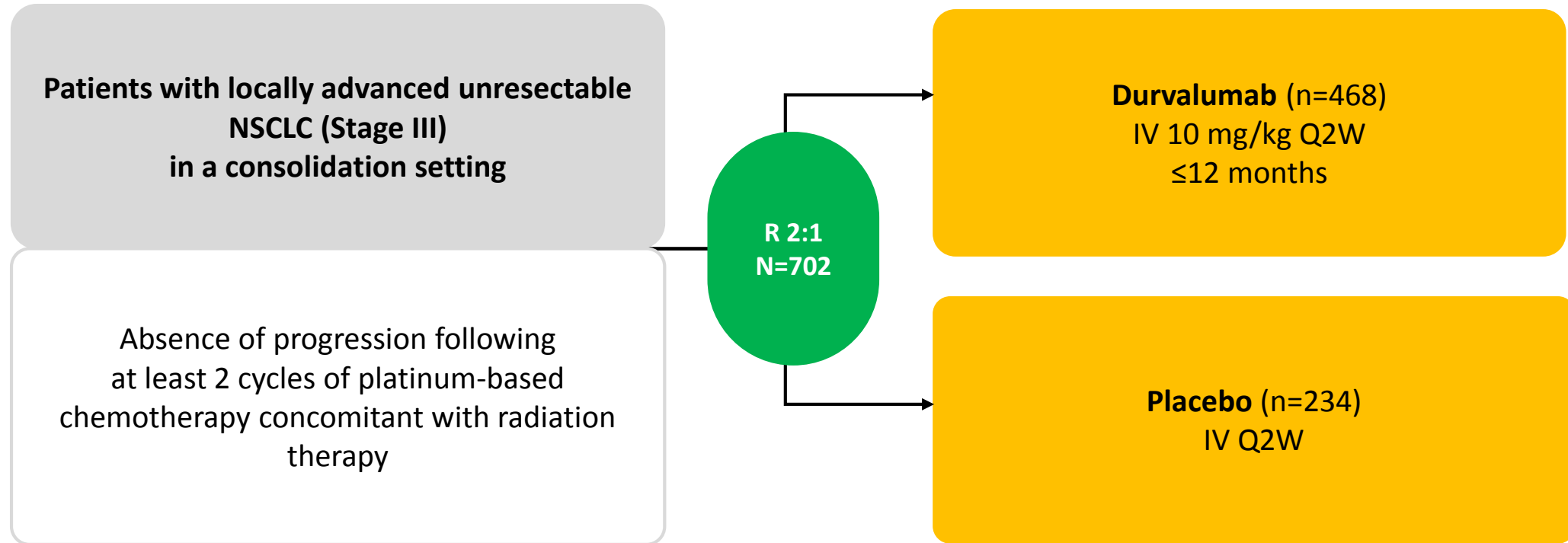
KEYNOTE 010 (TPS ≥ 1%) (pembrolizumab)

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)

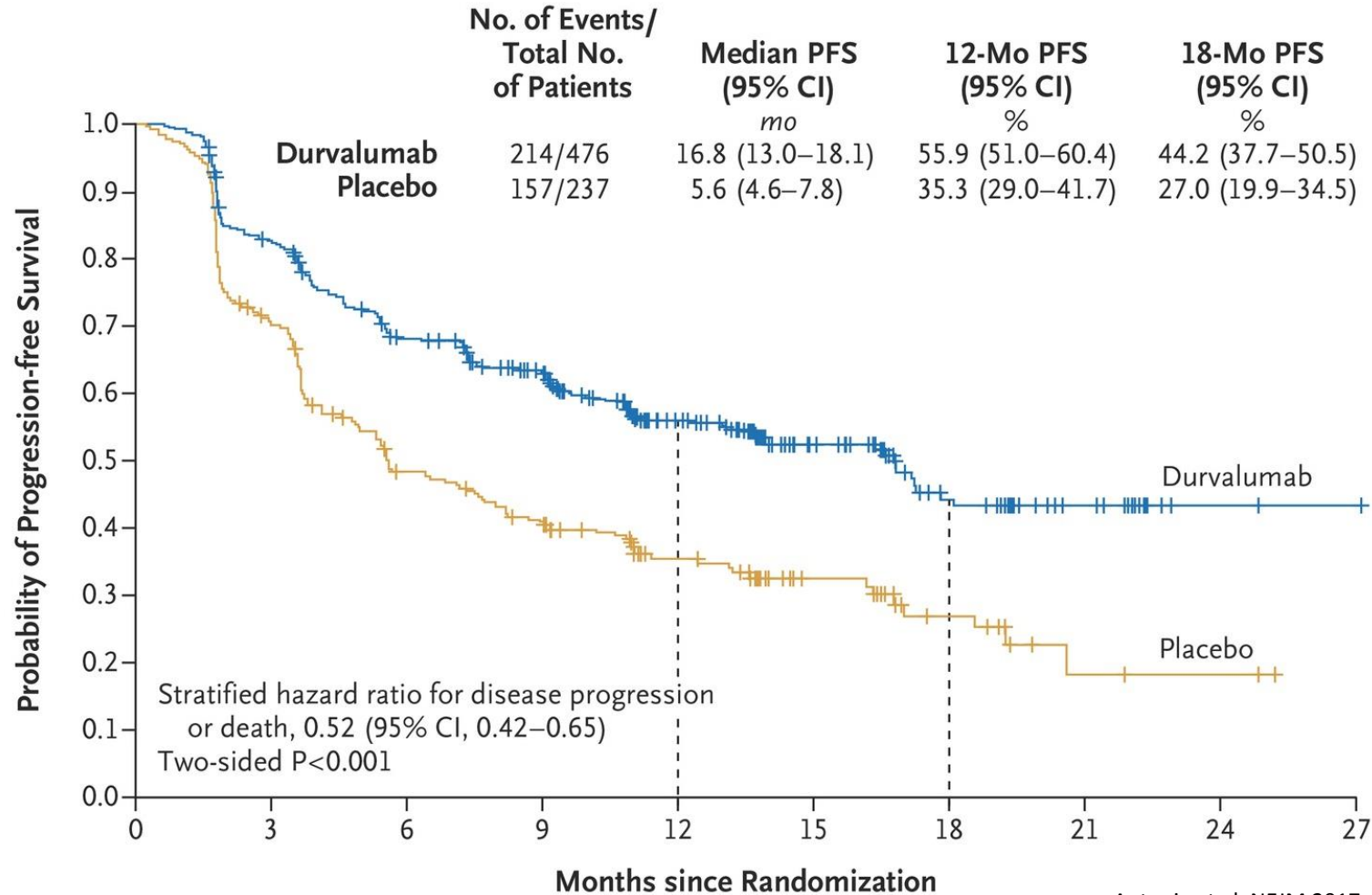
HR, 0.73^a
 (95% CI, 0.62, 0.87)
 P = 0.0003
Minimum follow up = 19 months

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



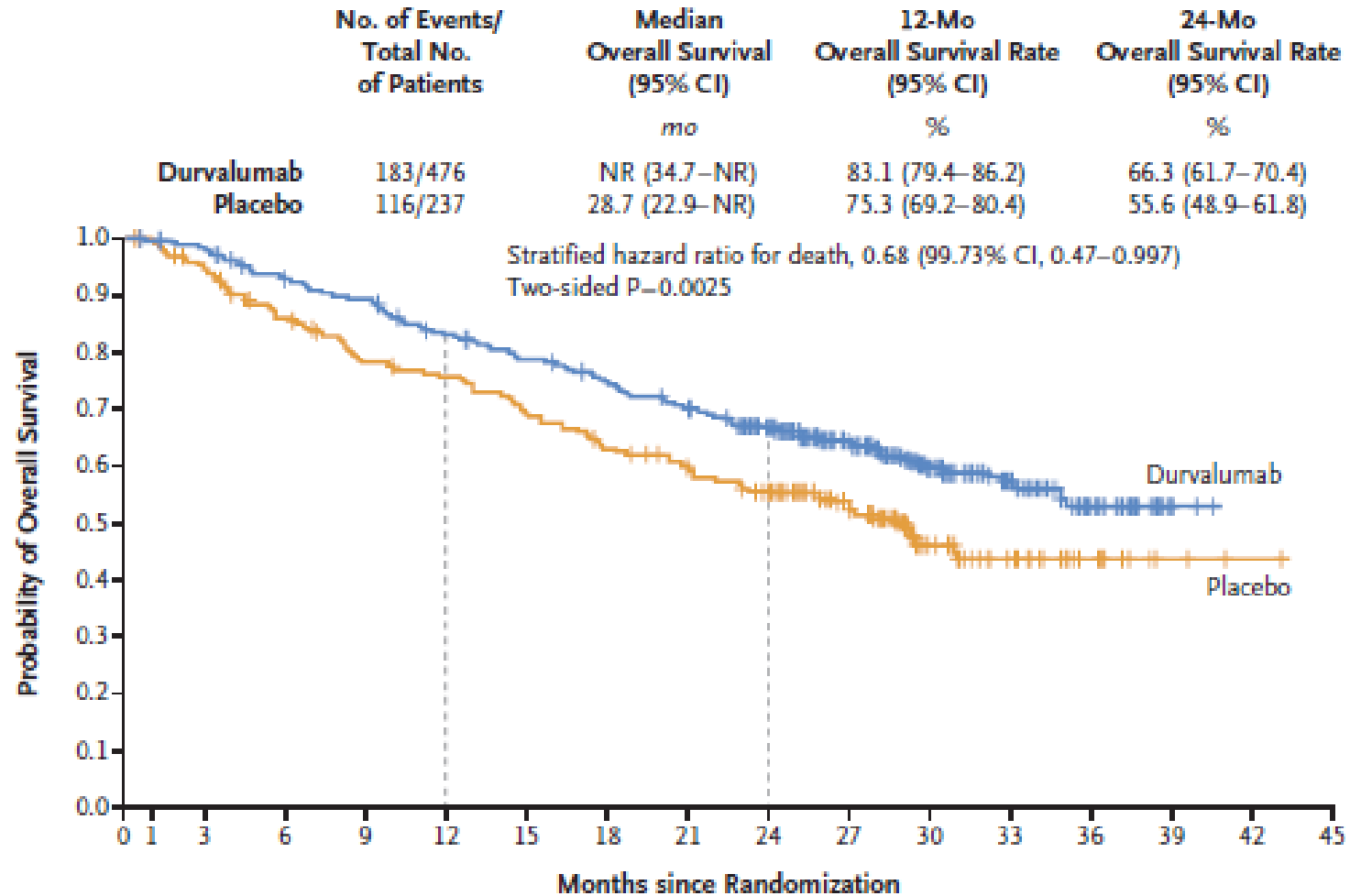
1. In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
2. NIH 2015 NCT02125461, <http://clinicaltrials.gov/ct2/show/NCT02125461>.
3. Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
4. Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TIP.

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



Antonia et al, NEJM 2017

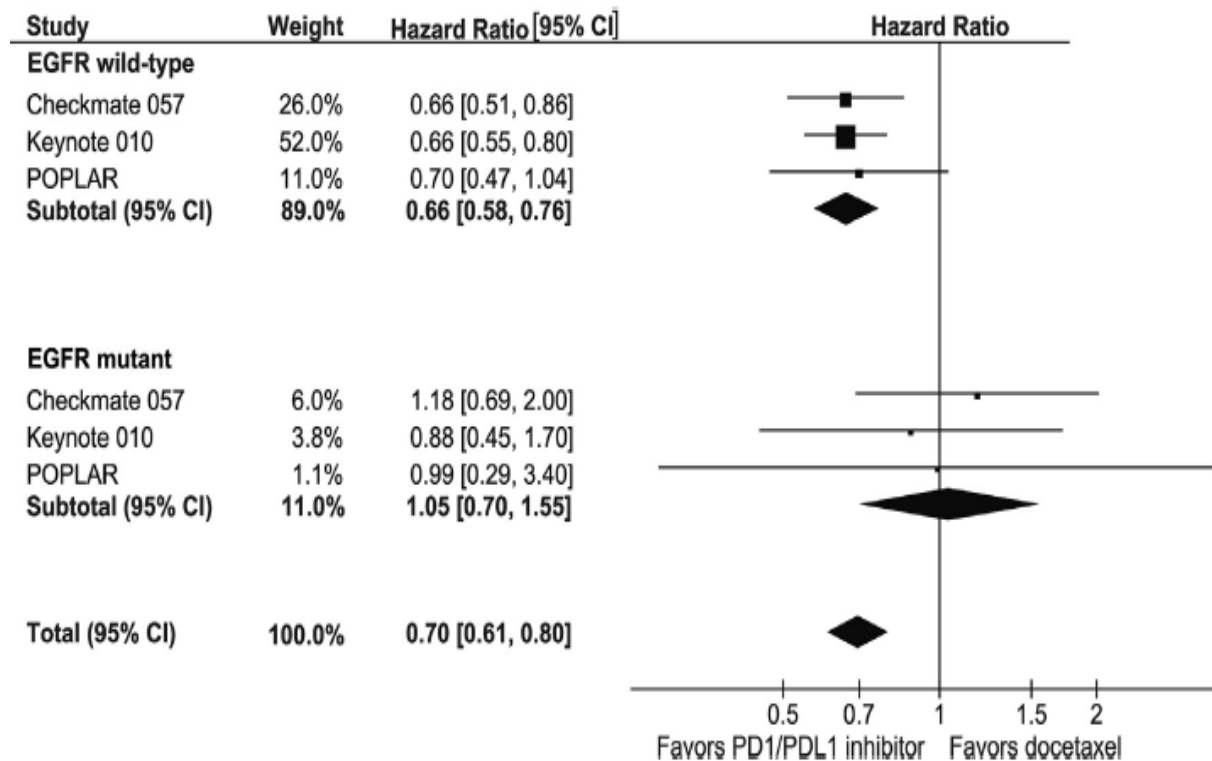
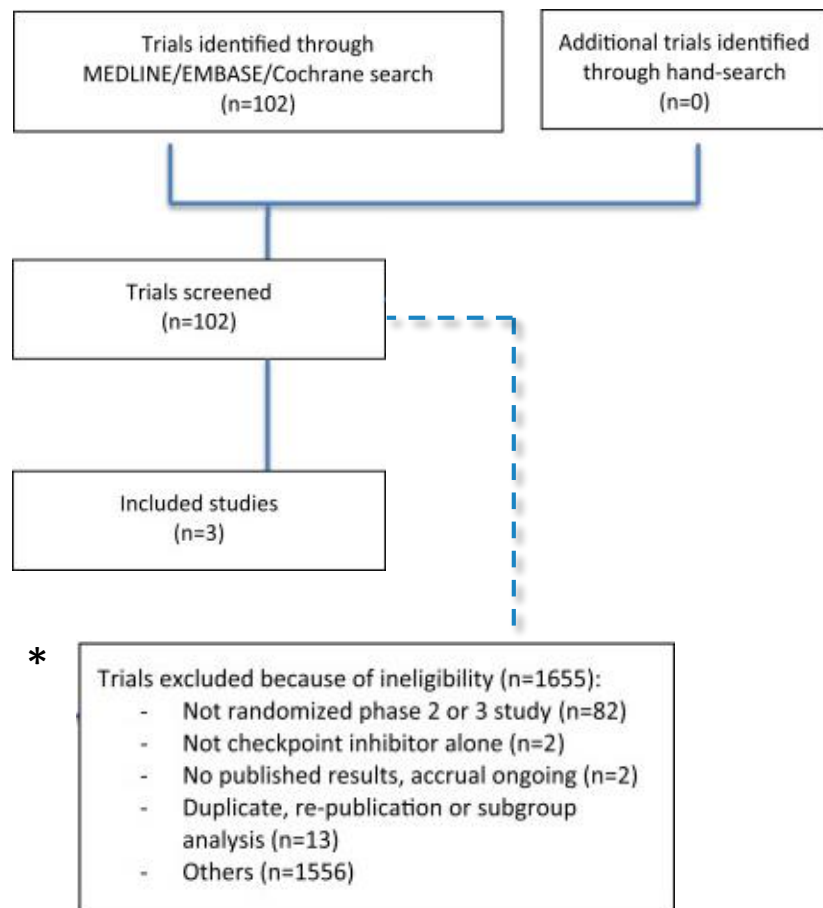
PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC



No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	0

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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



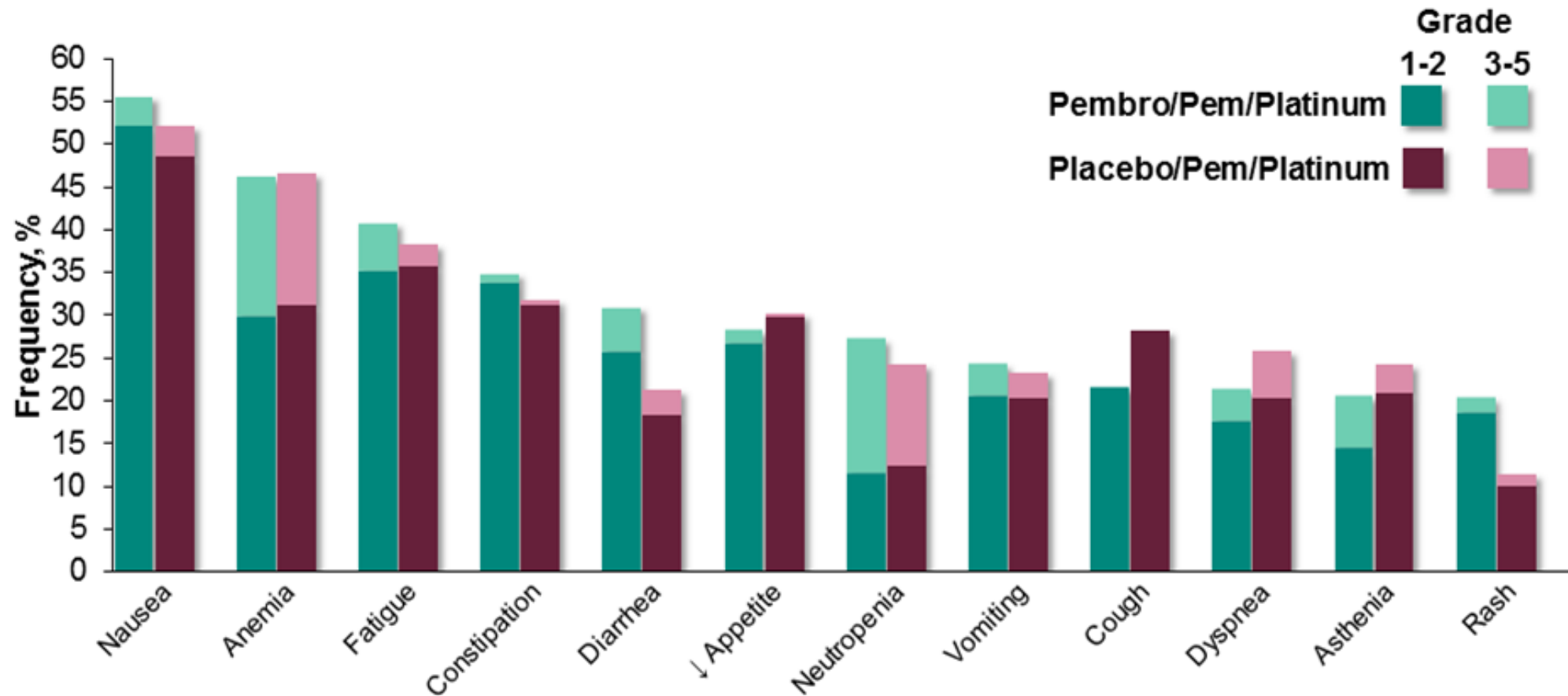
CK Lee et al., JTO 2016

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%

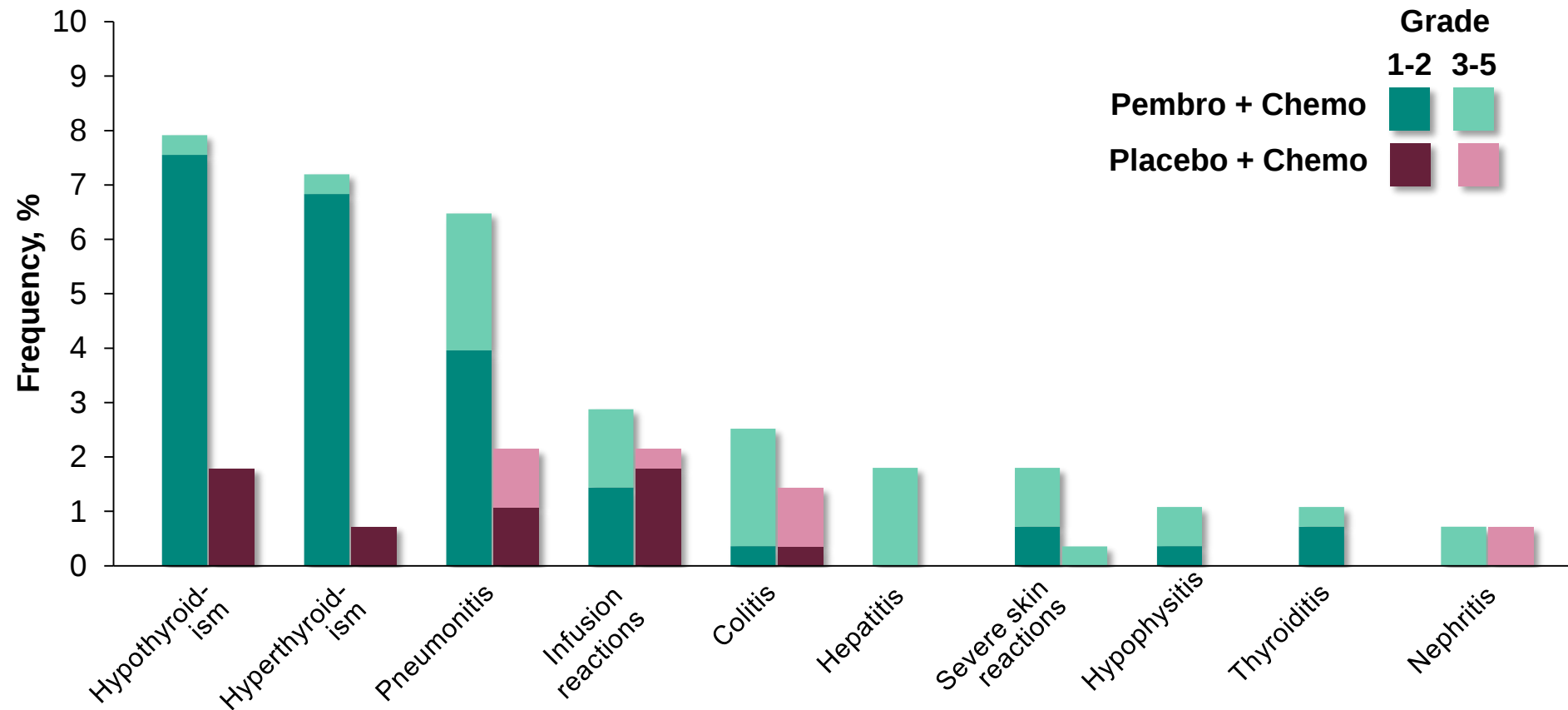
Rittmeyer, et al., *Lancet* 2017
 Brahmer, et al., *NEJM* 2015
 Borghaei, et al., *NEJM* 2015
 Herbst, et al., *Lancet* 2015

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.

Case Study 1

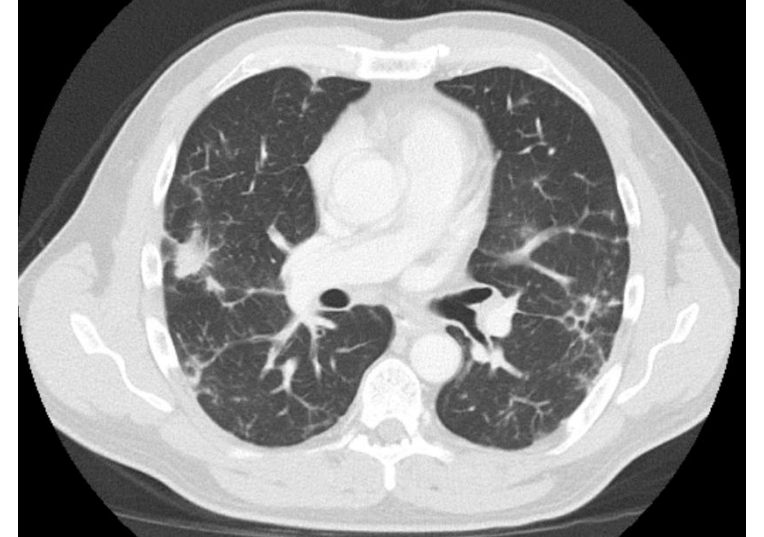
Background:

65 year-old male, 30 pack/year history of tobacco use

Presents with bilateral lung metastases, minimally symptomatic

Biopsy shows:

- Adenocarcinoma
- KRAS G12C mutation
- PD-L1 is 80% (22C3 assay)



Case Study 1

Background:

65 year-old male, 30 pack/year history of tobacco use

Presents with bilateral lung metastases, **minimally symptomatic**

- Biopsy shows:
 - Adenocarcinoma
 - KRAS G12C mutation
 - PD-L1 is 80% (22C3 assay)
- Treatment course:
 - Pembrolizumab IV every 3 weeks
 - CT scans at 6 weeks, 15 weeks, 24 weeks show interval response without progression; grade 1 hypothyroidism for which levothyroxine initiated, no other IRAEs to date
 - Plan for continued therapy barring toxicity/progression for minimum 2 years

Case Study 2

Background

65-year-old female with prior 20 p/y tobacco use

Presents with dyspnea after hiking trip

CT shows innumerable cavitating bilateral lung masses,
liver metastases

- Biopsy shows:
 - Adenocarcinoma of the lung
 - EGFR/ALK/ROS1/BRAF/KRAS-, TP53 mutation
 - PD-L1 is 1% (22C3 assay)
 - TMB is low (3 mutations/MB)



Case Study 2

What are your care options?



Case Study 2

What do you recommend? (By a show of hands)

- Carboplatin/Pemetrexed?
- Pembrolizumab? (off-label)
- Carboplatin/Pemetrexed/Pembrolizumab?
- Targeted therapy?

Why?



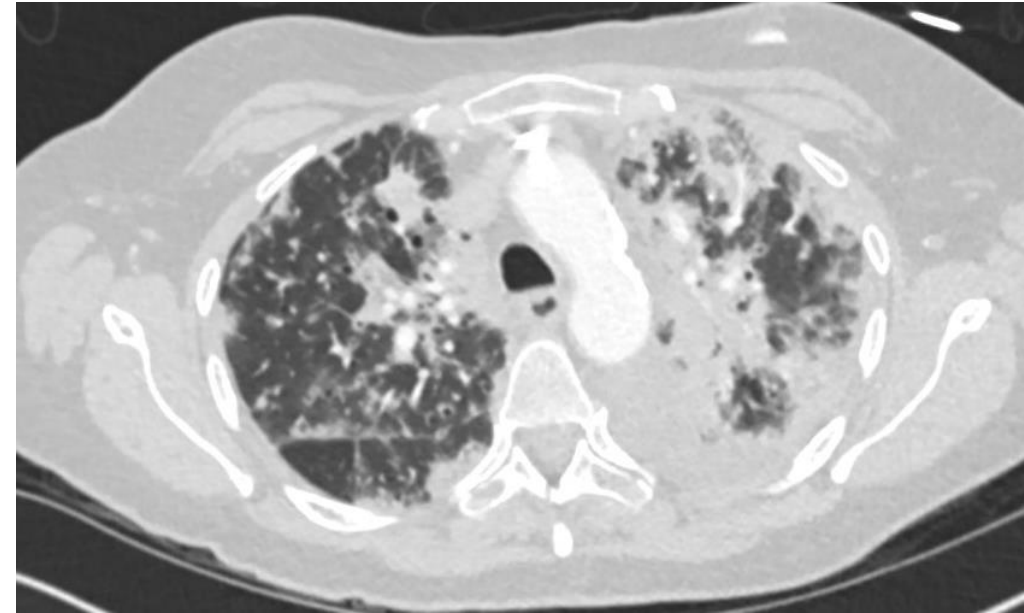
Case Study 2

She is treated with Carboplatin/Pemetrexed/Pembrolizumab IV every 3 weeks.

Three months into therapy, she is admitted with 1 week of fever, cough, and dyspnea after returning from a family vacation...

What are you concerned about?

What are your next steps?



Case Study 2

Grade 4 pneumonitis

Bronchoscopy/BAL → cultures negative

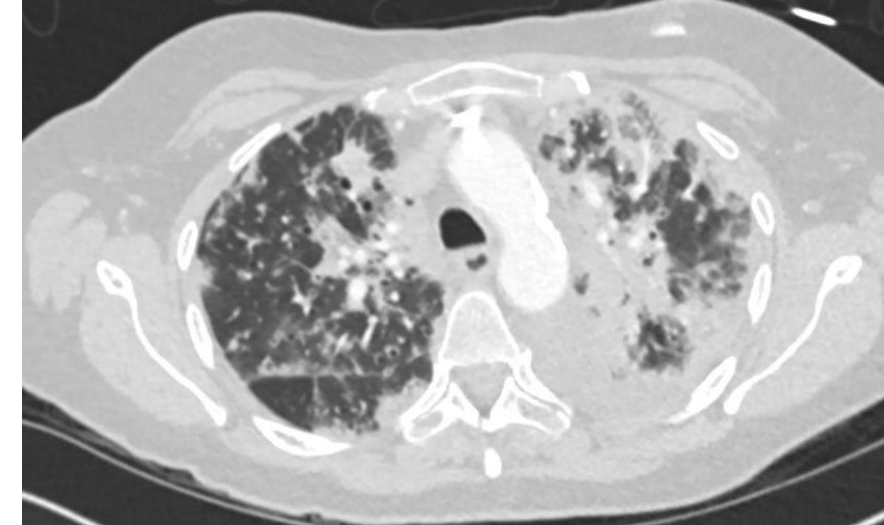
Intubated, treated with high-dose steroids
(methylprednisolone IV 2mg/kg/day)

Extubated, 1 month hospitalization, rehab x 2 weeks

Pembrolizumab permanently discontinued...

... 2 months later, resumes Pemetrexed IV every 3 weeks
alone for maintenance therapy

Before



After

