Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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ACCC Association of Community Cancer Centers

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Disclosures

- Consulting/Advisory Board: Takeda, AstraZeneca, Novartis, AbbVie, BMS

- I will be discussing non-FDA approved indications during my presentation.

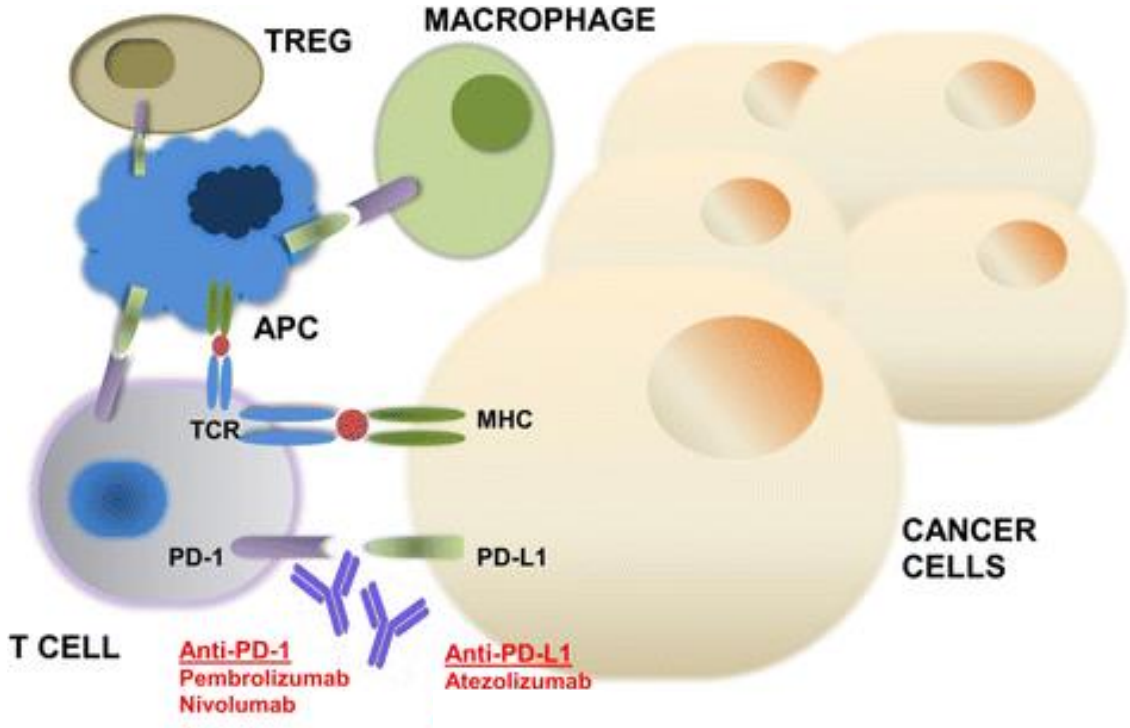
Presentation Outline

- Background: Checkpoint inhibitors for the treatment of lung cancer
- Overview of clinical trial results that led to current FDA approval of immunotherapies for the treatment of advanced/refractory and advanced/treatment naïve NSCLC
- Overview of clinical trial results that led to current FDA approval of immunotherapies for locally advanced NSCLC
- Overview of established and emerging predictive biomarkers (PD-L1, TMB) for treatment with immunotherapies for NSCLC
- Case Studies

Immunotherapy for the Treatment of Lung Cancer

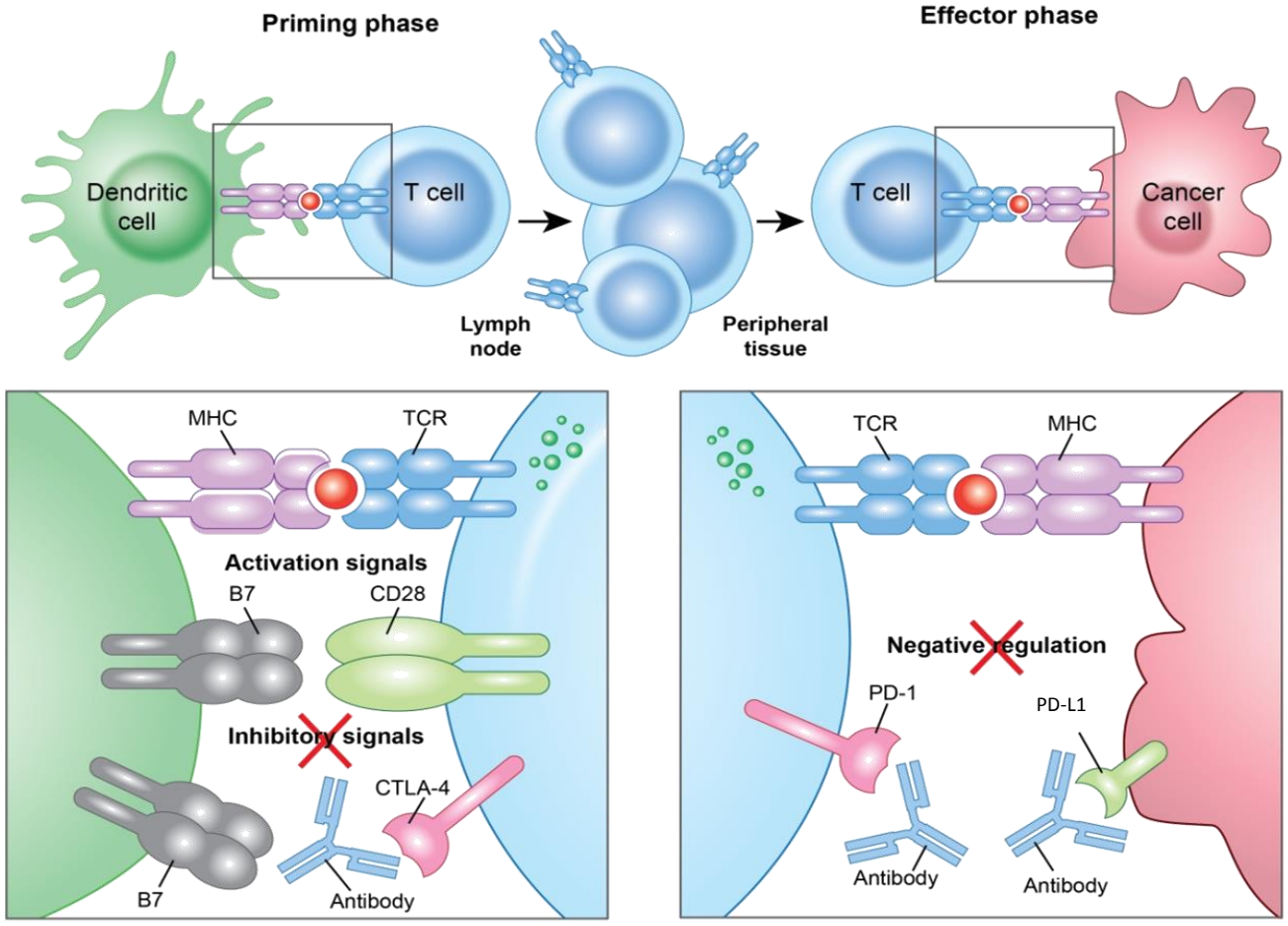
Checkpoint Inhibitors: PD-1 and PD-L1

- **Checkpoint inhibitors for the treatment of metastatic disease**
  - PD-1 acts as “off-switch” for T-Cells 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



Ribas A, NEJM, 2012

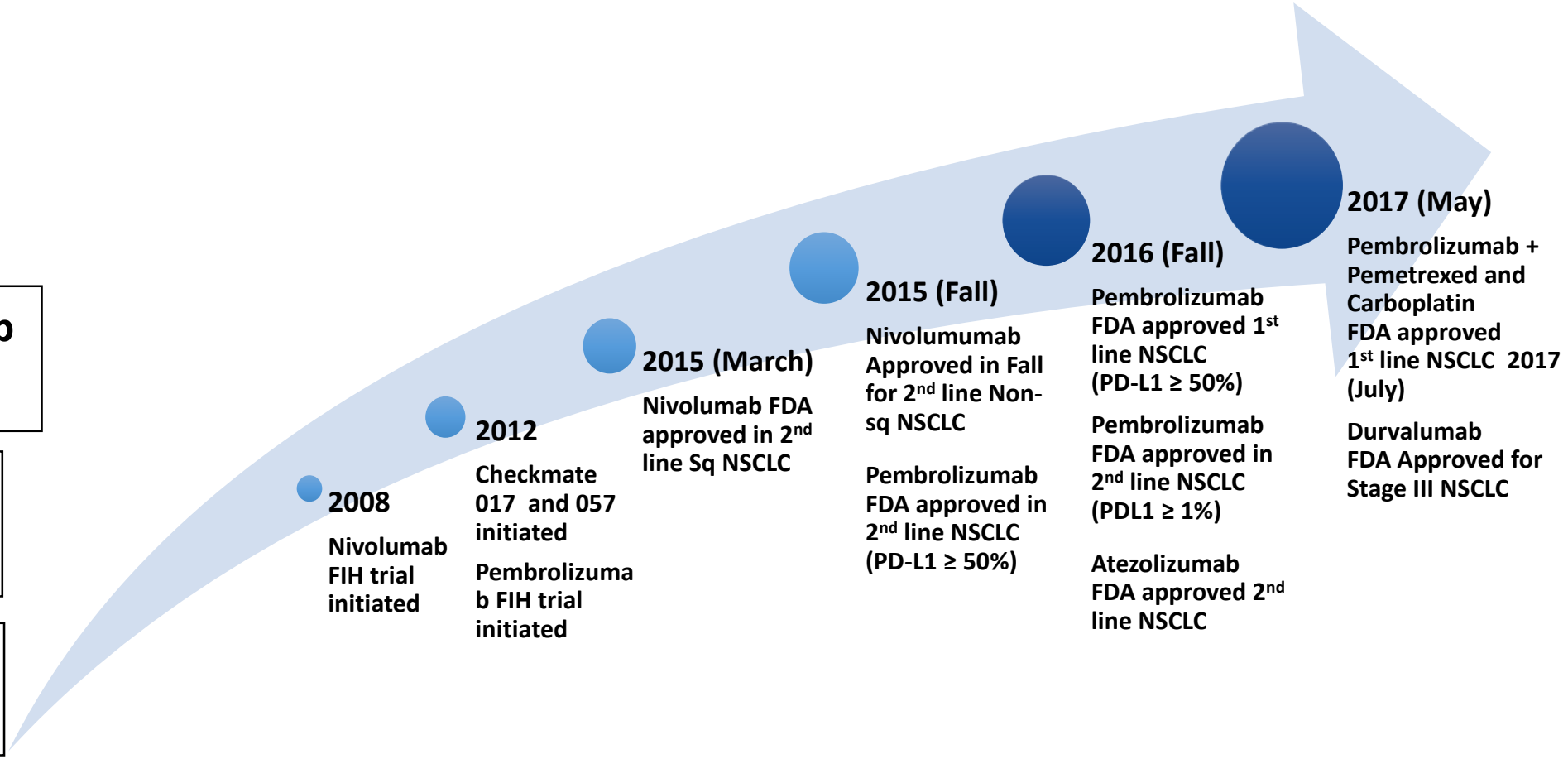
FDA-approved Checkpoint Inhibitors for use in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

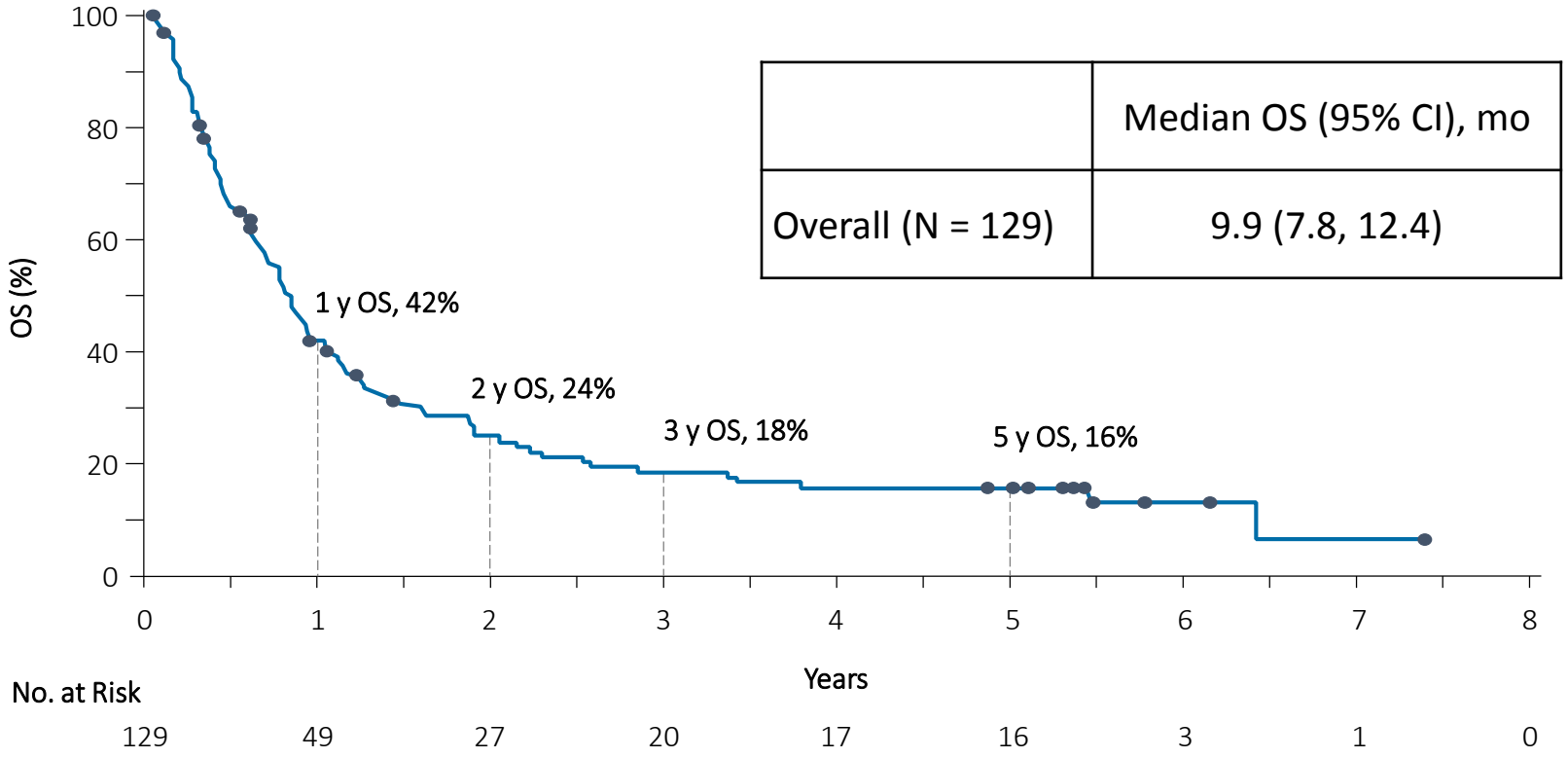


CA209-003: Nivolumab in Heavily Pretreated Advanced NSCLC (NCT00730639)

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)

Brahmer et al, AACR 2017

NCI SEER data, Lung and Bronchus Cancer, 2014

Treatment Naïve Regimens: Competing Strategies

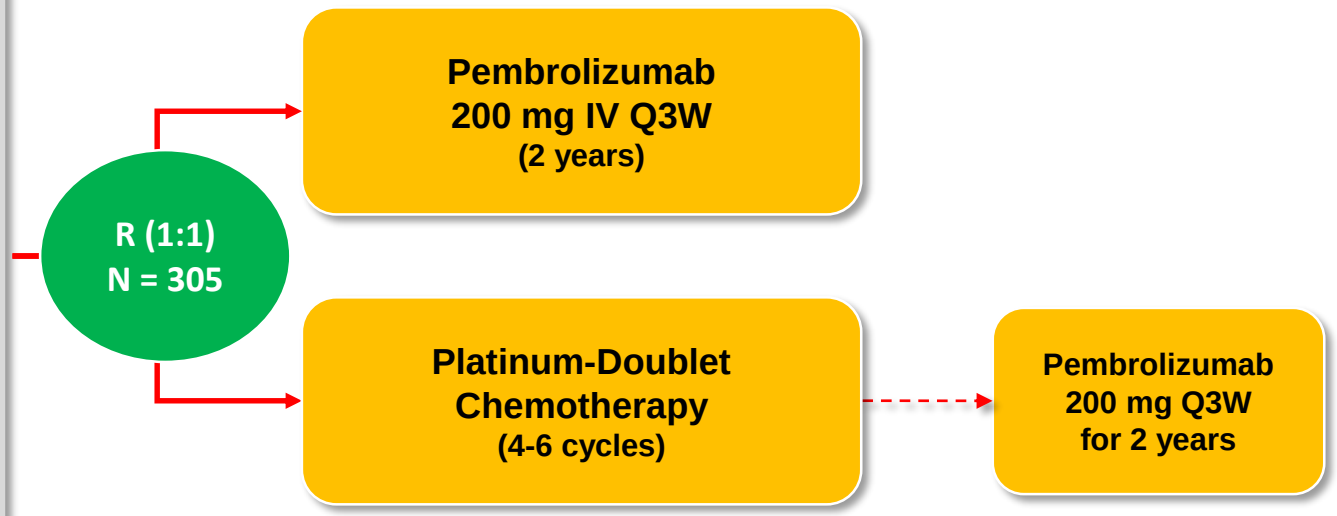
- KEYNOTE 024 – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
- KEYNOTE 042 – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
- KEYNOTE 189 – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in patients with advanced non-squamous NSCLC
- IMPOWER 150 – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (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%)

NSCLC 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



Key End Points

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

Secondary: OS, ORR, Safety

Exploratory: DOR

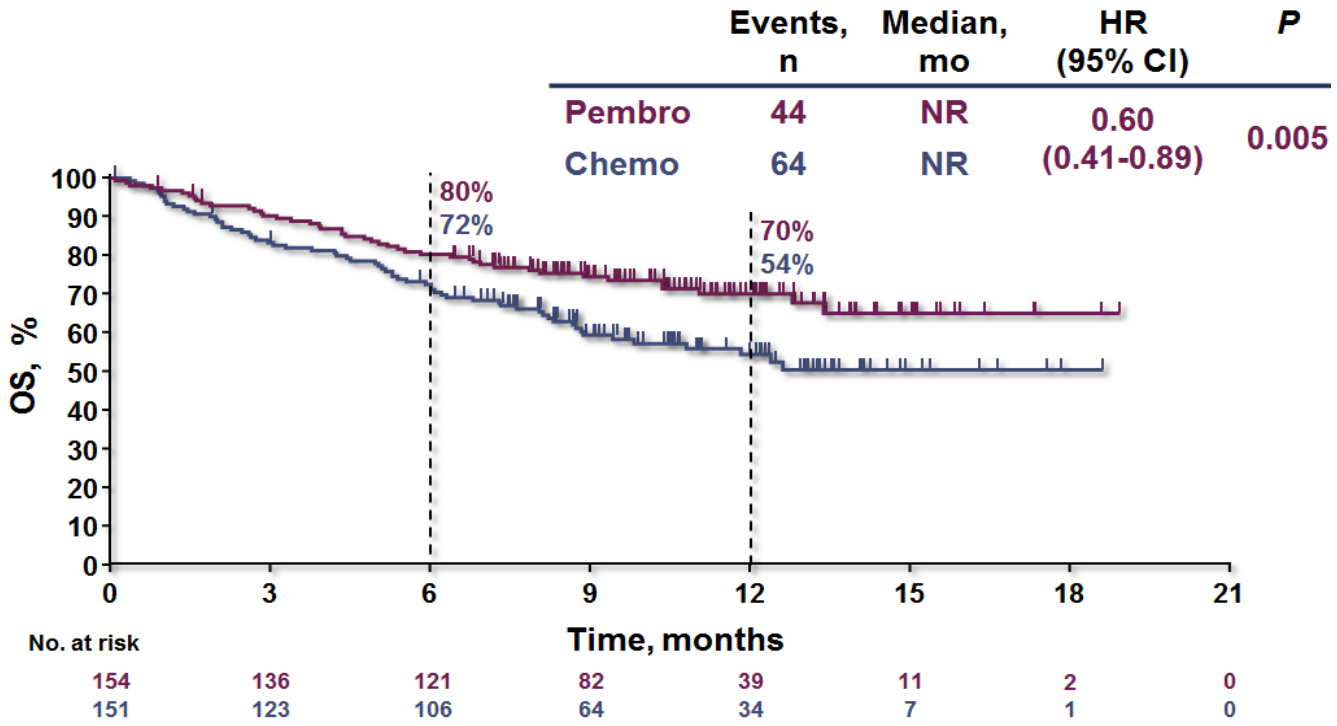
Reck M et al, ESMO 2016, NEJM 2016

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

Overall Survival

Survival benefit

- Estimated Overall Survival at 12 months: 70% (Pembrolizumab) vs 54% (Chemotherapy)
- Hazard Ratio for death: 0.60
- Significantly longer OS in Pembrolizumab group despite cross-over in 50% of patients in control arm
- Median OS not reached in either group



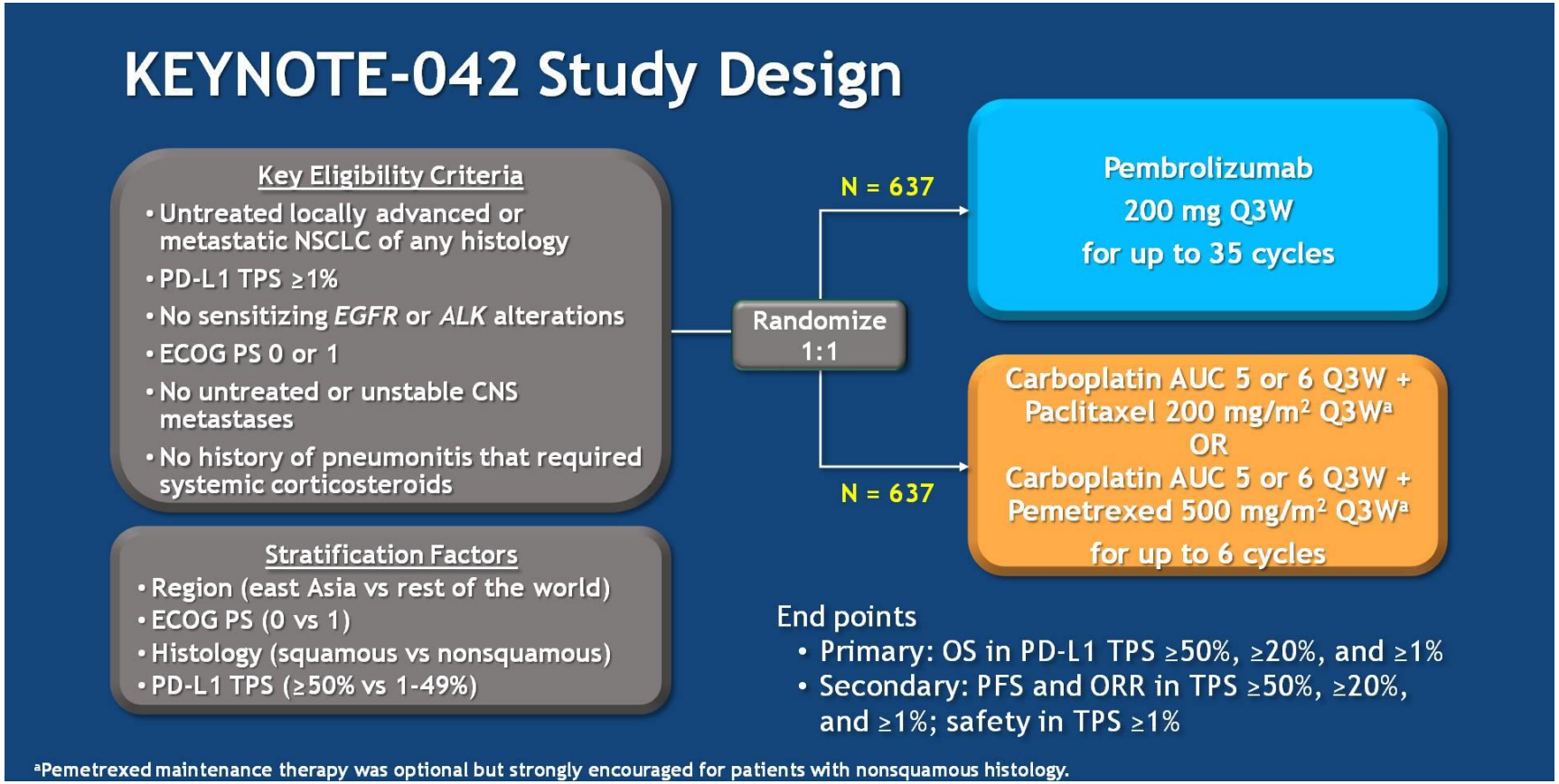
Reck M et al, ESMO 2016, NEJM 2016

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

Key End Points

Primary: OS in PD-L1 TPS ≥ 50%, ≥ 20%, and ≥ 1%

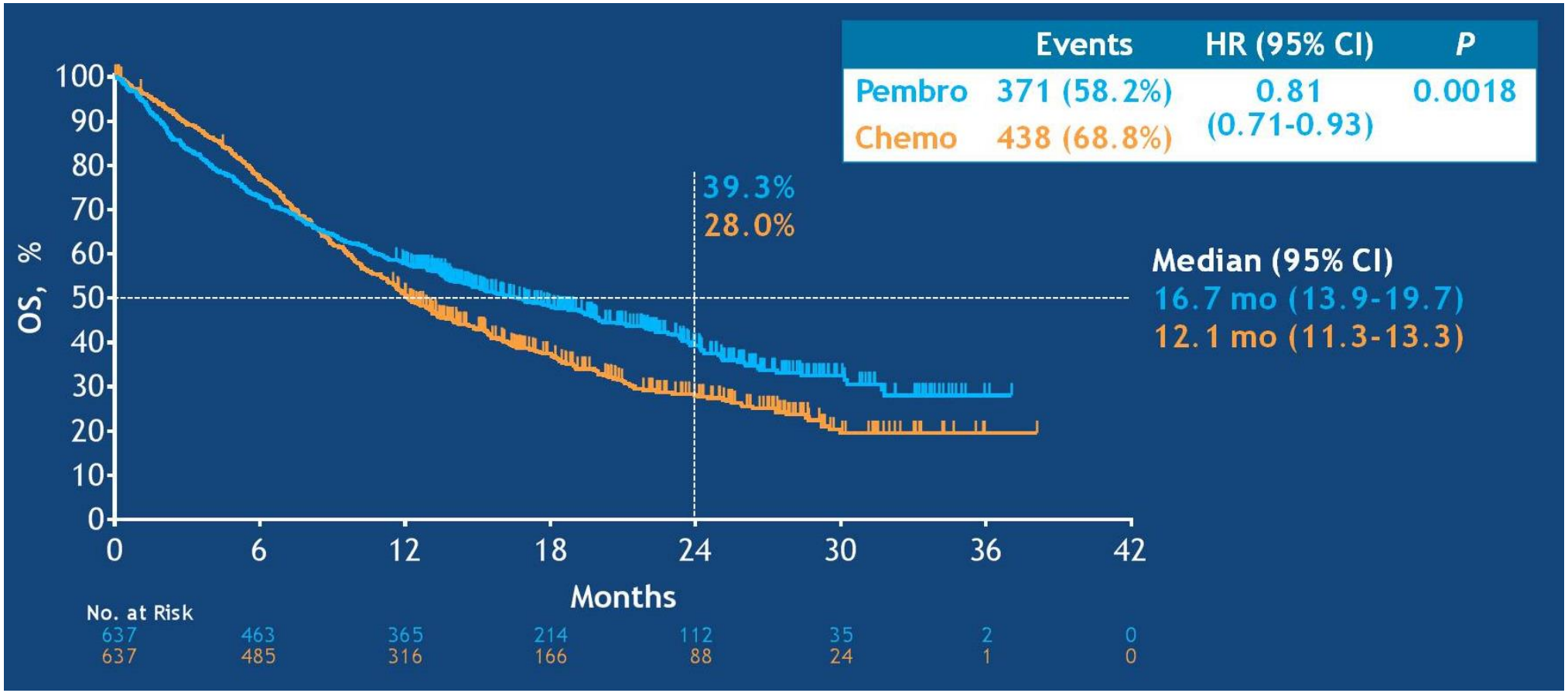
Secondary: PFS and ORR in TPS ≥ 50%, ≥ 20%, and ≥ 1%; safety in TPS ≥ 1%



Lopes et al, ASCO 2018

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

Overall Survival



Lopes et al, ASCO 2018

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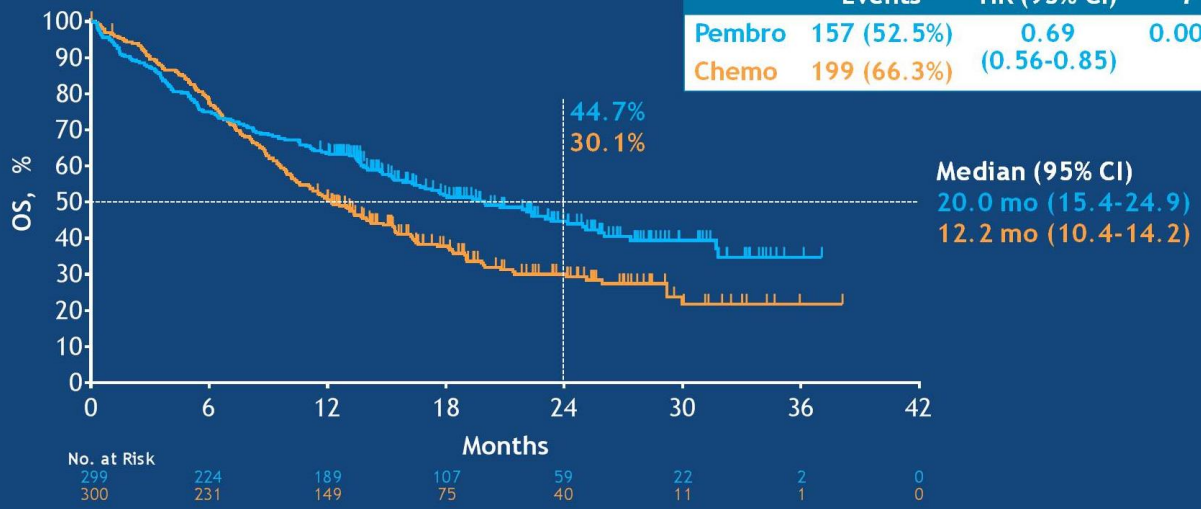
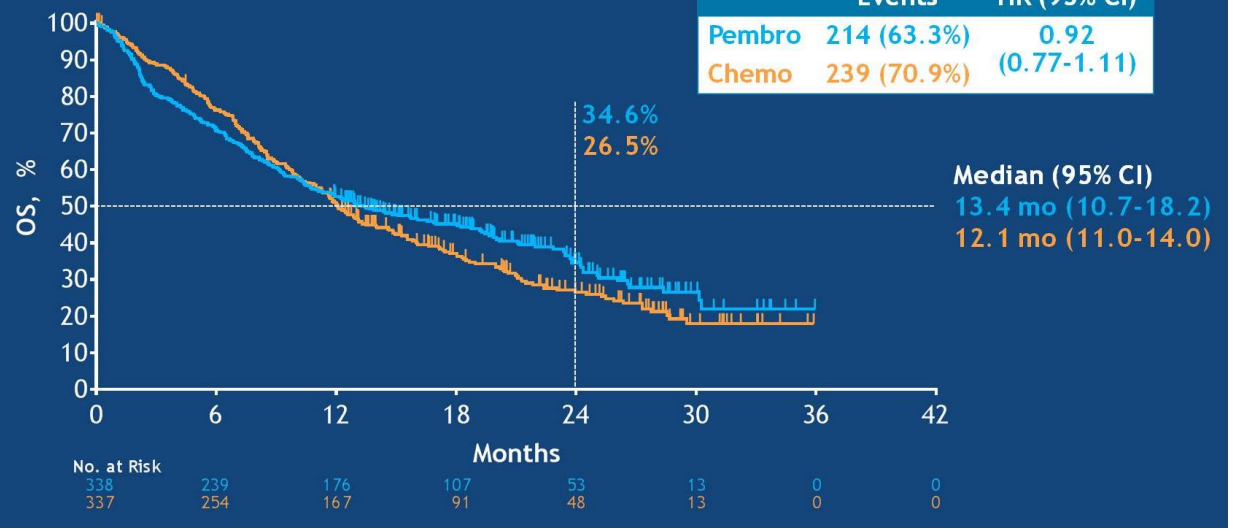
Survival benefit seemed to be driven by the TPS ≥ 50% subset with no OS benefit in the subset TPS ≥ 1- 49%

Overall Survival: TPS ≥50%

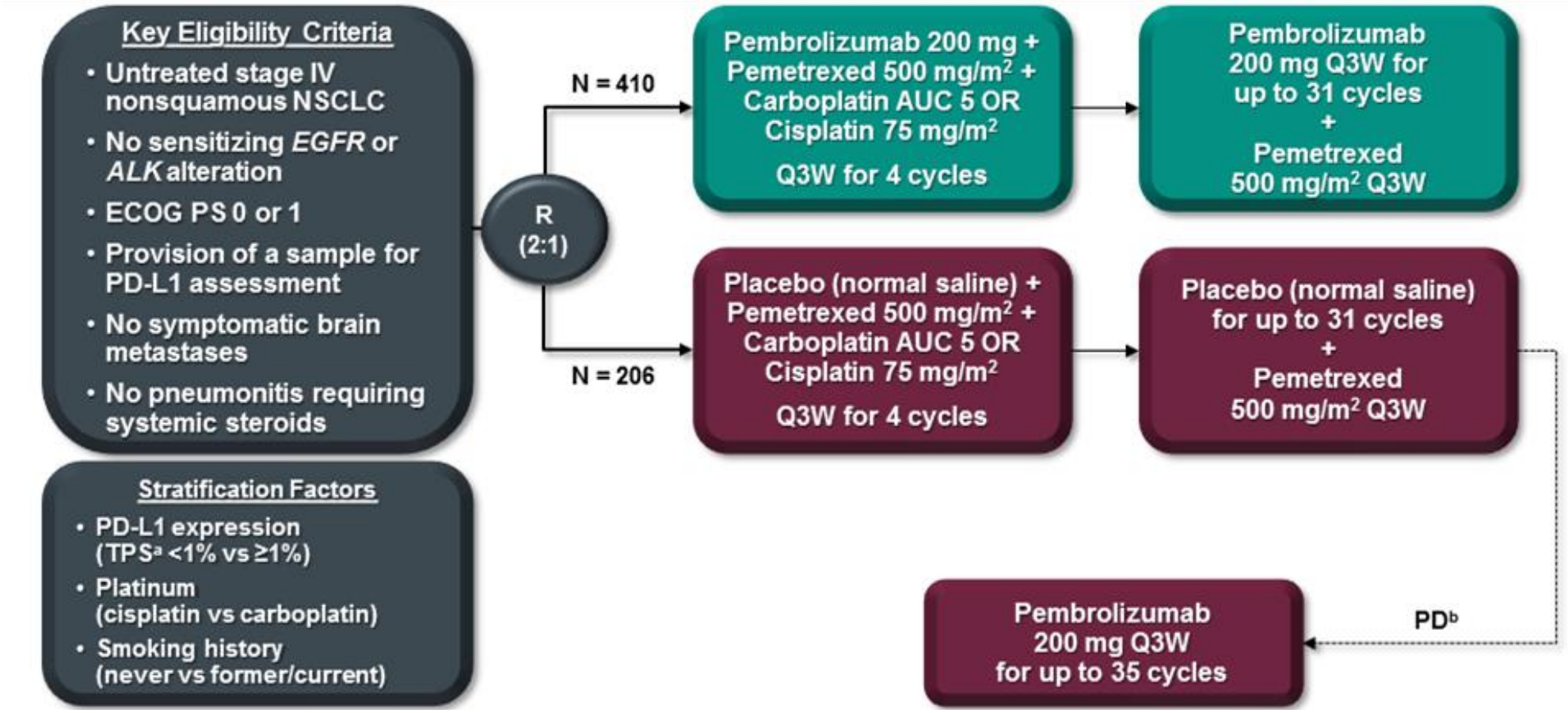


Lopes et al, ASCO 2018

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



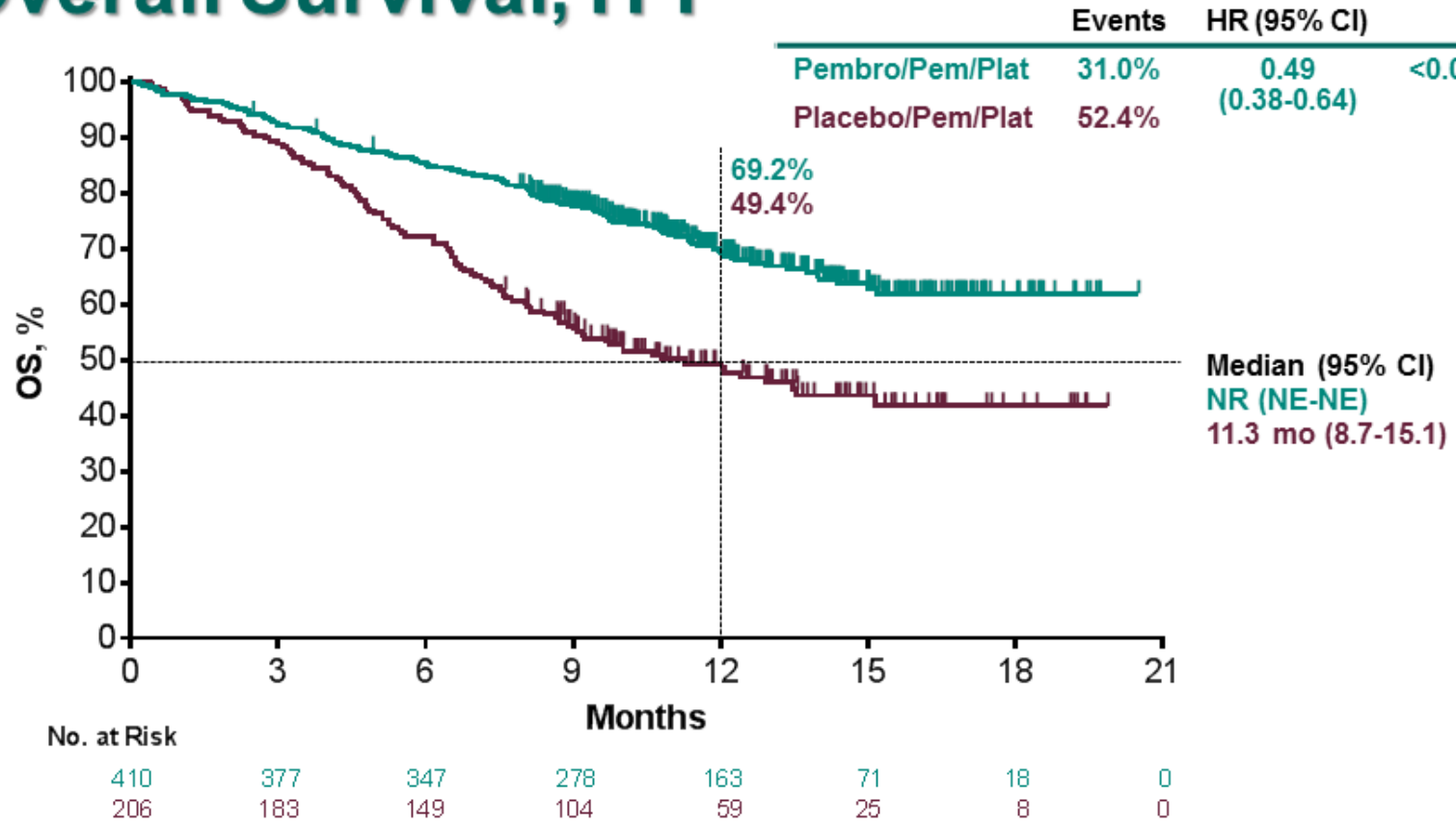
KEYNOTE-189: Carboplatin-Pemetrexed-Pembrolizumab vs. Chemotherapy for Advanced Non-squamous NSCLC



Ghandi et al, NEJM 2018

KEYNOTE-189: Carboplatin-Pemetrexed-Pembrolizumab vs. Chemotherapy for Advance Non-squamous NSCLC: OS Results

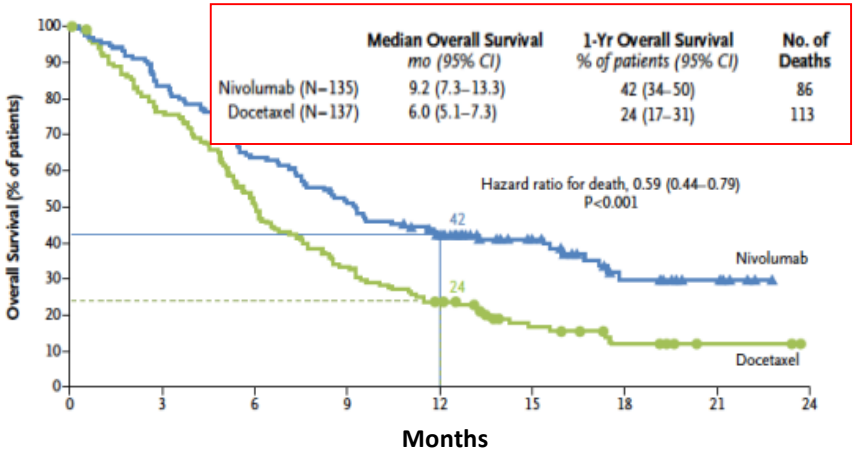
Overall Survival, ITT



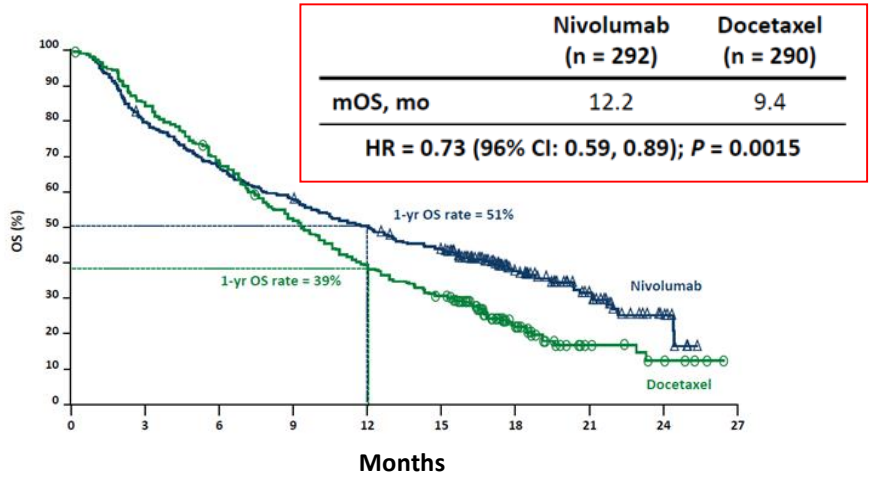
Ghandi et al, NEJM 2018

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

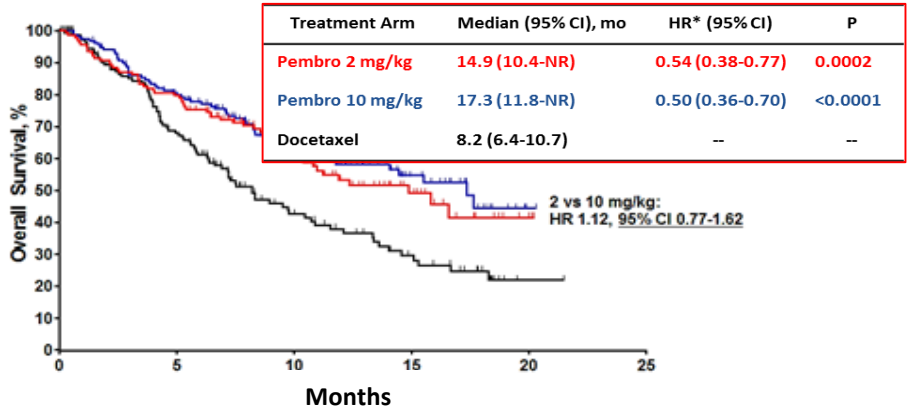
CHECKMATE 017



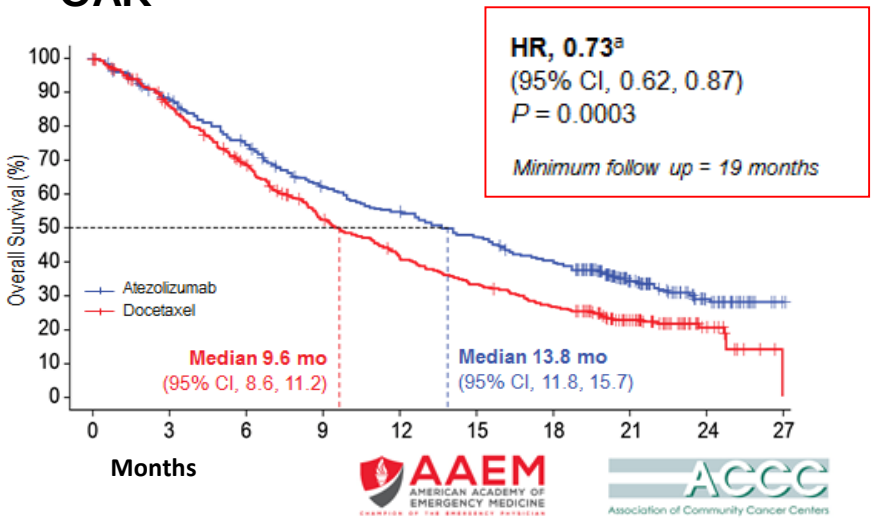
CHECKMATE 057



KEYNOTE 010 (TPS ≥ 1%)



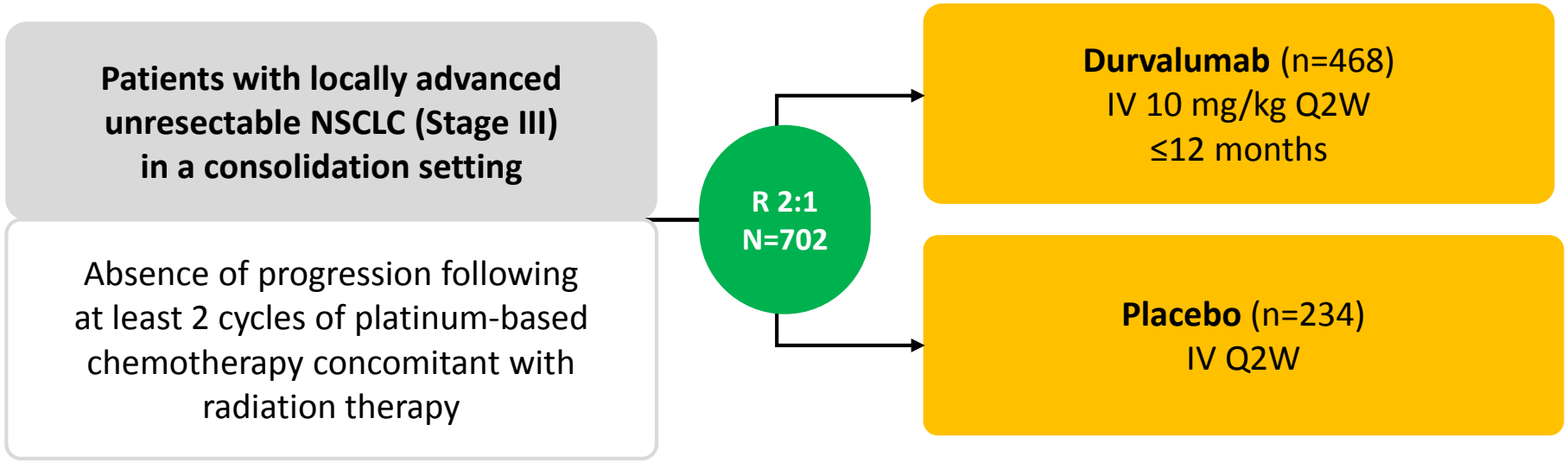
OAK



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

PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

Phase 3, randomized, double-blind, placebo-controlled trial (NCT02125461)



Primary endpoints: PFS, OS

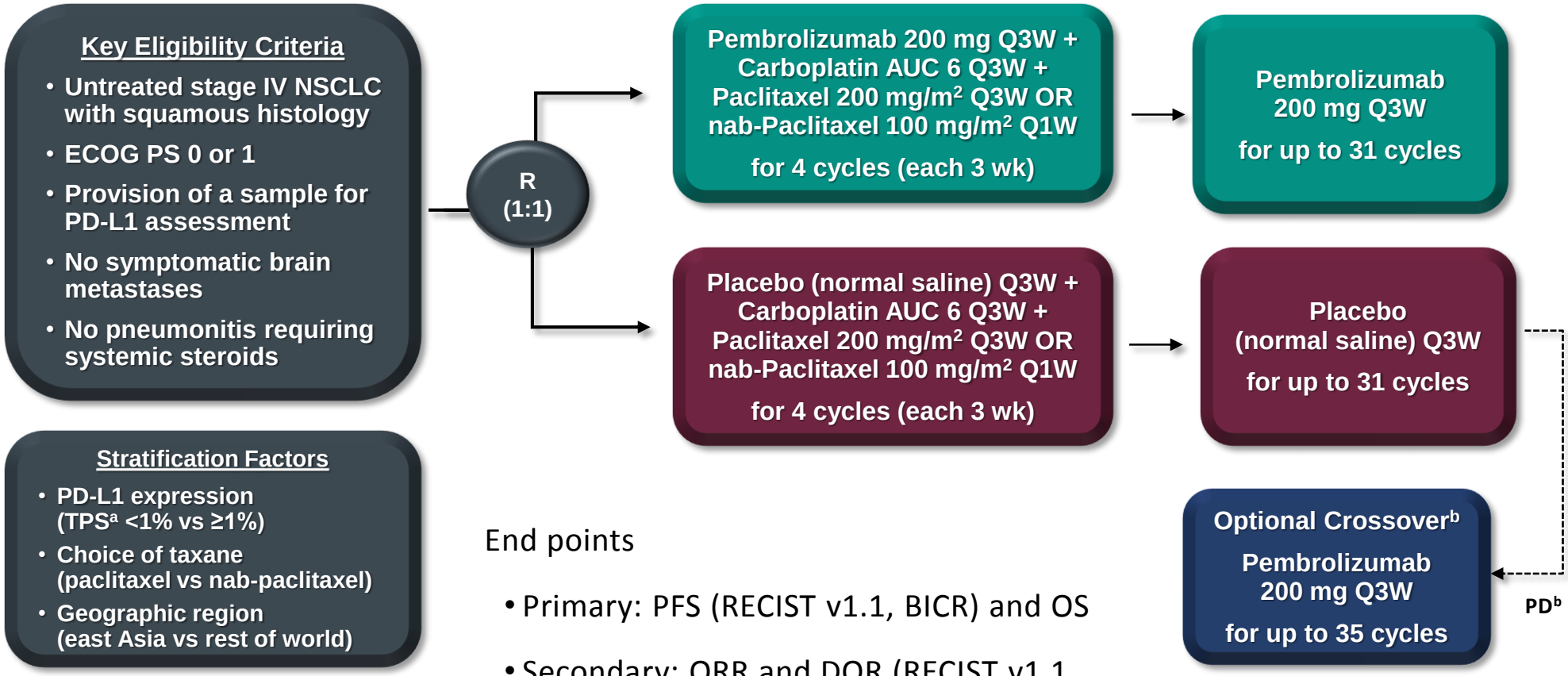
Secondary endpoints: ORR, DoR, DSR, Safety/tolerability, PK, immunogenicity, QoL

Results: Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer; PFS was significantly longer with durvalumab than with placebo.

DoR = duration of response; DSR = deep sustained response;
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.

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.

KEYNOTE-407: Chemotherapy-Pembrolizumab vs. Chemotherapy for Advanced Squamous NSCLC: Toxicity



End points

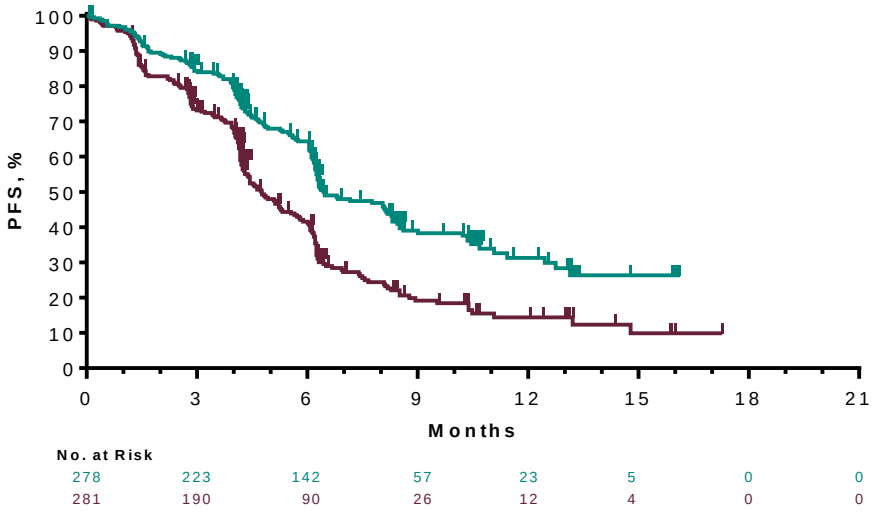
- Primary: PFS (RECIST v1.1, BICR) and OS
- Secondary: ORR and DOR (RECIST v1.1, BICR), safety

Paz-Ares et al, ASCO 2018

KEYNOTE-407: Carboplatin-Taxane - Pembrolizumab vs. Chemotherapy for advanced squamous NSCLC: PFS and OS

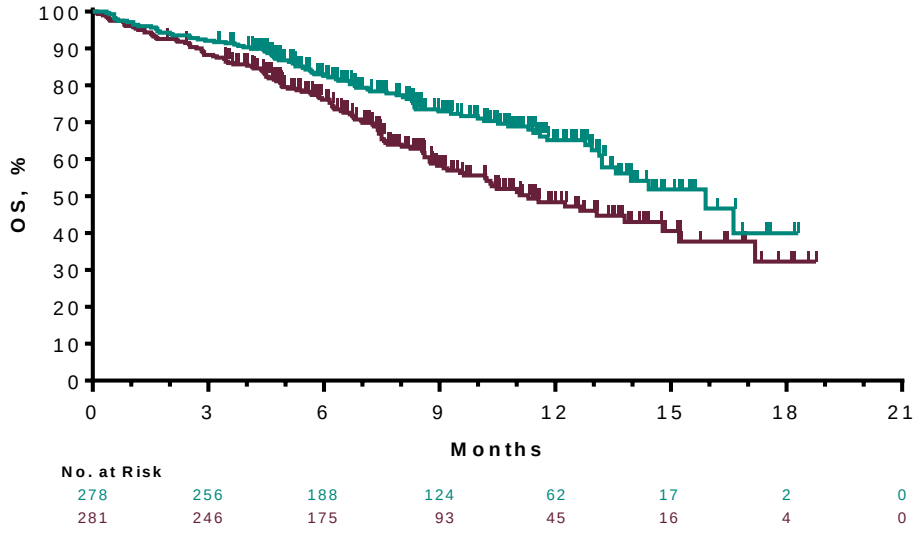
PFS (RECISTv1.1, BICR)

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



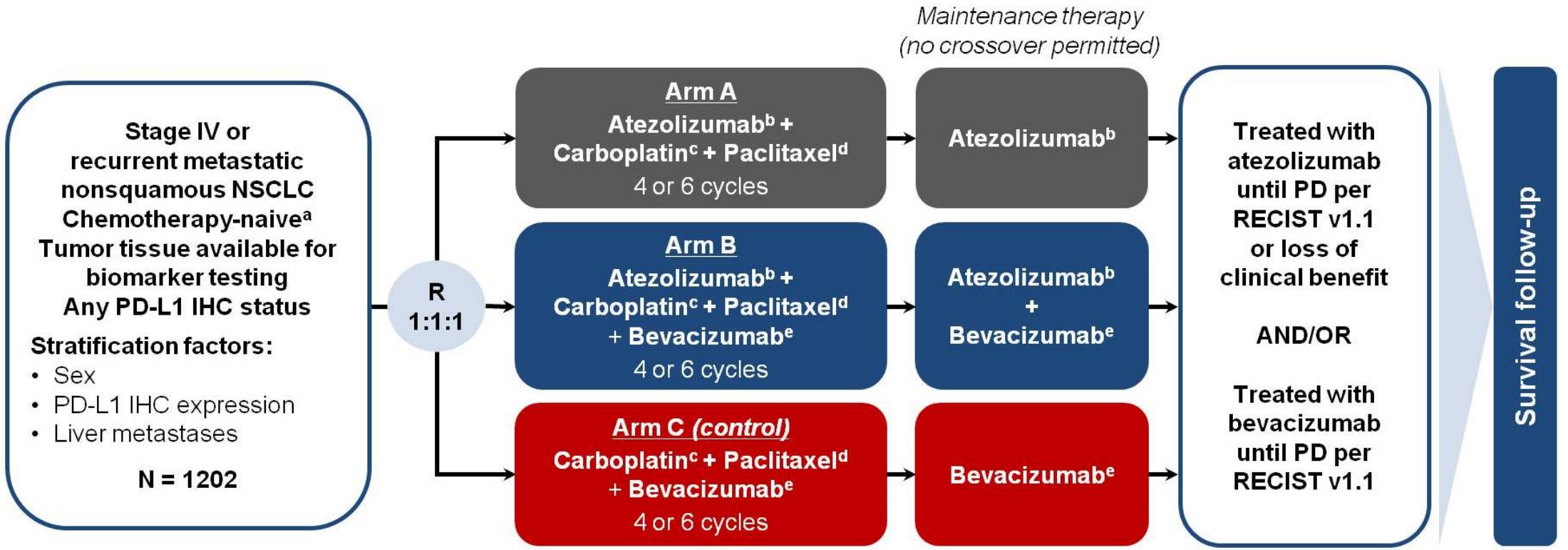
Overall Survival

	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

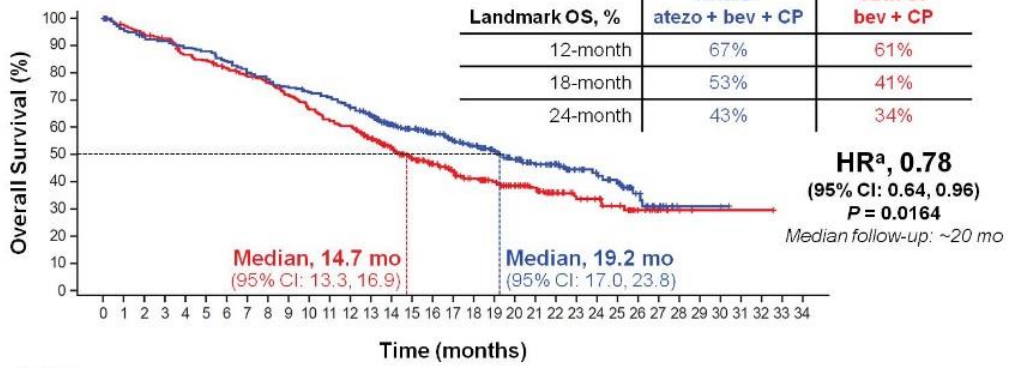
IMPOWER 150: Carboplatin/Paclitaxel/ Bevacizumab/ Atezolizumab vs. Carboplatin/Paclitaxel/Bevacizumab in advanced non-squamous NSCLC



Socinski et al, NEJM 2018

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

OS in the ITT-WT (Arm B vs Arm C)



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

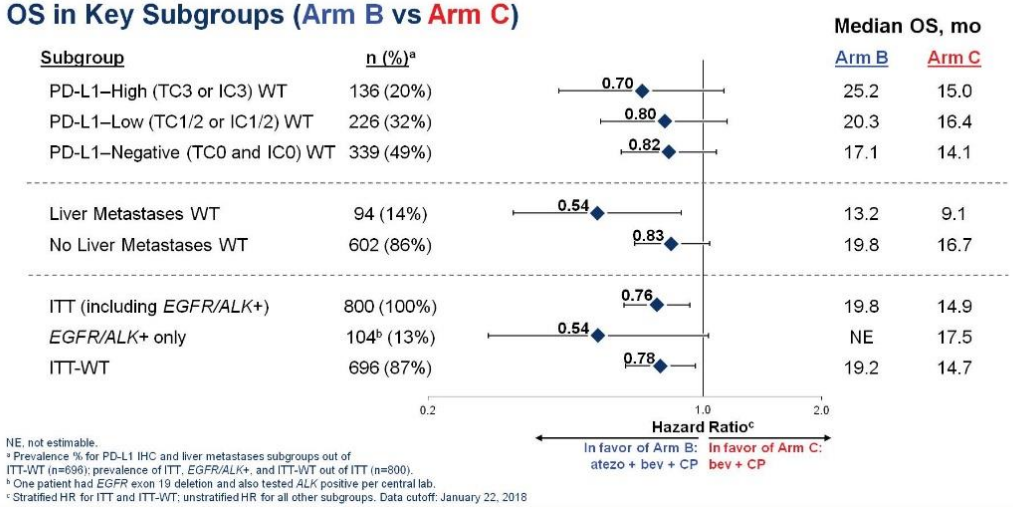
Safety

Incidence, n (%)	Arm A: atezo + CP (n = 400)		Arm B: atezo + bev + CP (n = 393)		Arm C (*control*): bev + CP (n = 394)	
Median doses received (range), n						
Atezolizumab	10 (1-43)		12 (1-44)		NA	
Bevacizumab	NA		10 (1-44)		8 (1-38)	
Treatment-related AE[a]	377 (94%)		370 (94%)		377 (96%)	
Grade 3-4	172 (43%)		223 (57%)		191 (49%)	
Grade 5[b]	4 (1%)		11 (3%)		9 (2%)	
Serious AE	157 (39%)		174 (44%)		135 (34%)	
AE leading to withdrawal from any treatment	53 (13%)		133 (34%)		98 (25%)	
Immune-related AEs[c] in > 5 patients in any arm	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**	**All grade**	**Grade 3-4**
Rash	119 (30%)	14 (4%)	117 (30%)	9 (2%)	53 (14%)	2 (1%)
Hepatitis[d]	42 (11%)	12 (3%)	54 (14%)	20 (5%)	29 (7%)	3 (1%)
Laboratory abnormalities	36 (9%)	10 (3%)	48 (12%)	18 (5%)	29 (7%)	3 (1%)
Hypothyroidism	34 (9%)	1 (<1%)	56 (14%)	1 (<1%)	18 (5%)	0
Pneumonitis[d]	23 (6%)	8 (2%)	13 (3%)	6 (2%)	5 (1%)	2 (1%)
Hyperthyroidism	11 (3%)	0	16 (4%)	1 (<1%)	5 (1%)	0
Colitis	3 (1%)	2 (1%)	11 (3%)	7 (2%)	2 (1%)	2 (1%)

- The safety profiles of ABCP and ACP were similar to A, B and C+P individually; no new safety signals were identified with the combinations

[a] Related to any study treatment. [b] Including fatal hemorrhagic AEs: Arm A: 2; Arm B: 6; Arm C: 3. [c] Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. [d] In Arm A, 1 patient had grade 5 acute hepatitis and 1 patient had grade 5 interstitial lung disease. Data cutoff: January 22, 2018

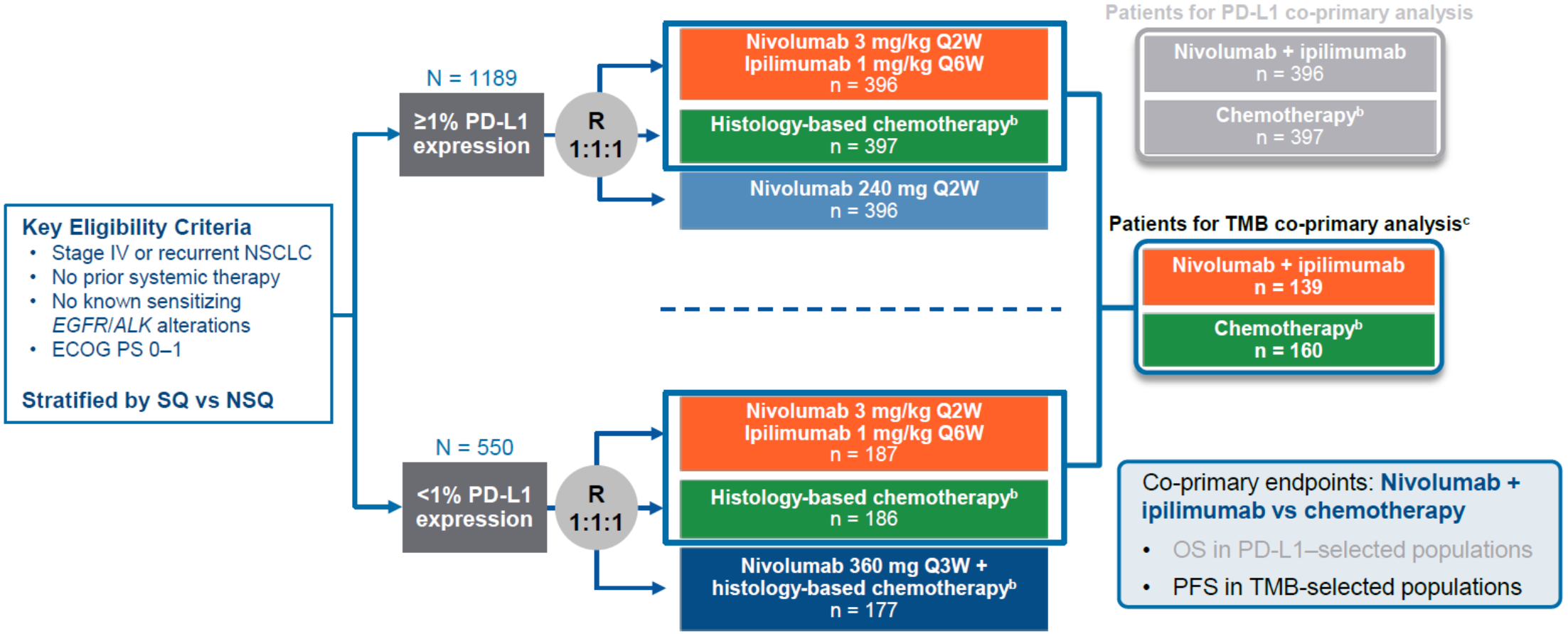
OS in Key Subgroups (Arm B vs Arm C)



NE, not estimable.
[a] Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
[b] One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
[c] Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018

Socinski et al, NEJM 2018

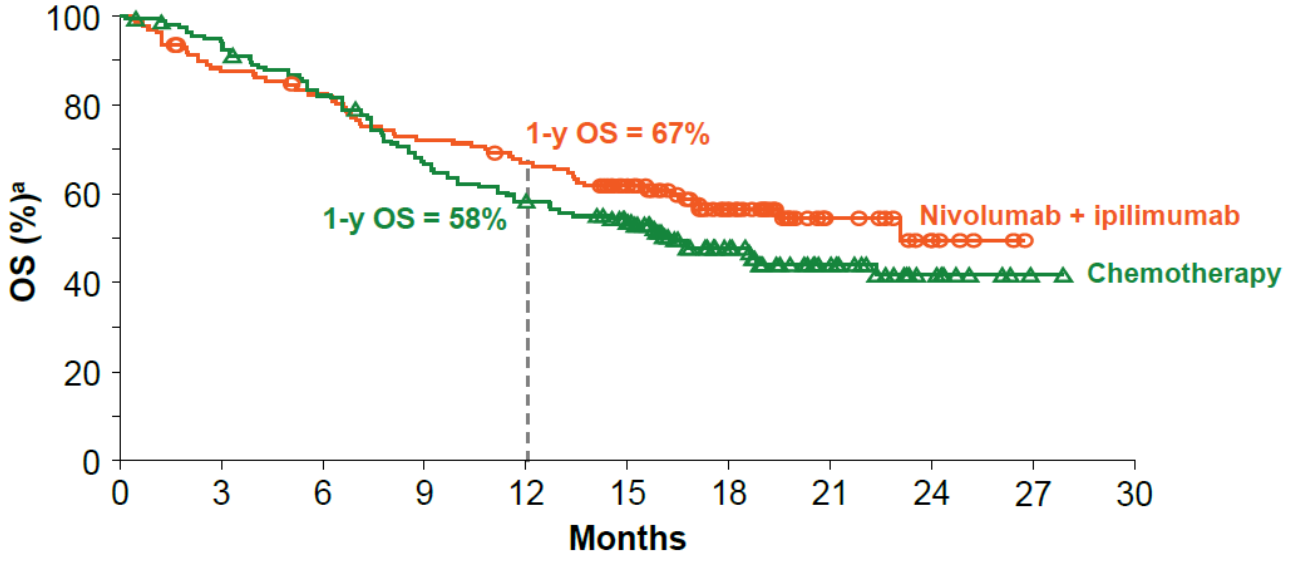
CheckMate 227: Ipilimumab + Nivolumab vs. Chemotherapy in TMB-high patients



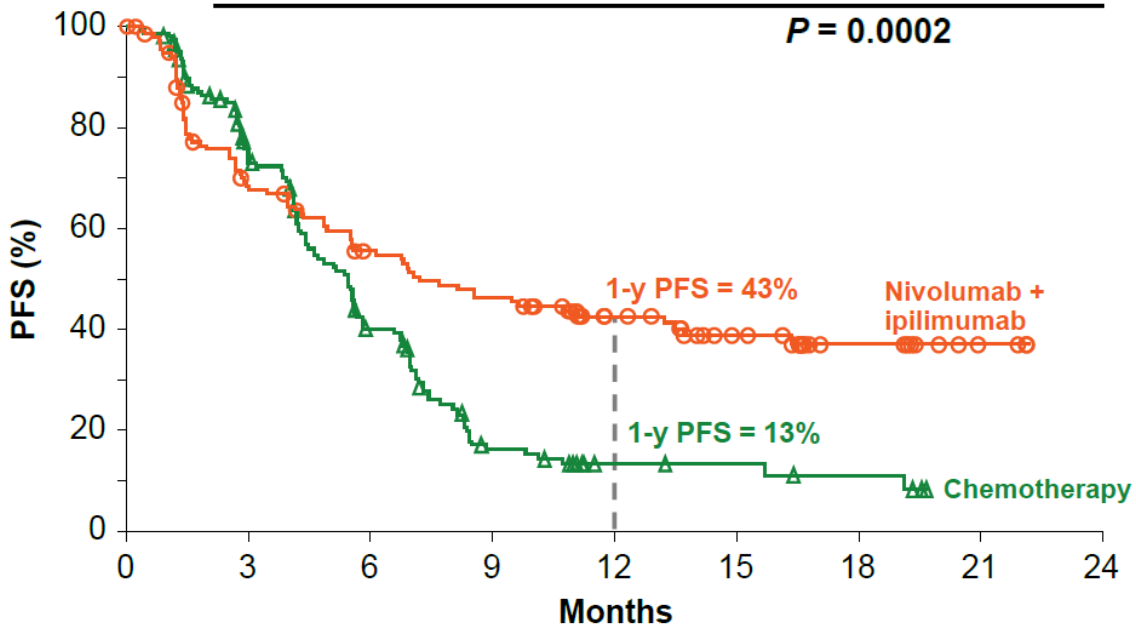
Hellman et al, NEJM, 2018

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

	Nivo + ipi (n = 139)	Chemo (n = 160)
Median OS,[b] mo	23.0	16.4
HR	**0.79**	
95% CI	0.56, 1.10	



	Nivo + ipi (n = 139)	Chemo (n = 160)
Median PFS,[b] mo	7.2	5.4
HR[c]	**0.58**	
97.5% CI	0.41, 0.81	
	***P* = 0.0002**	

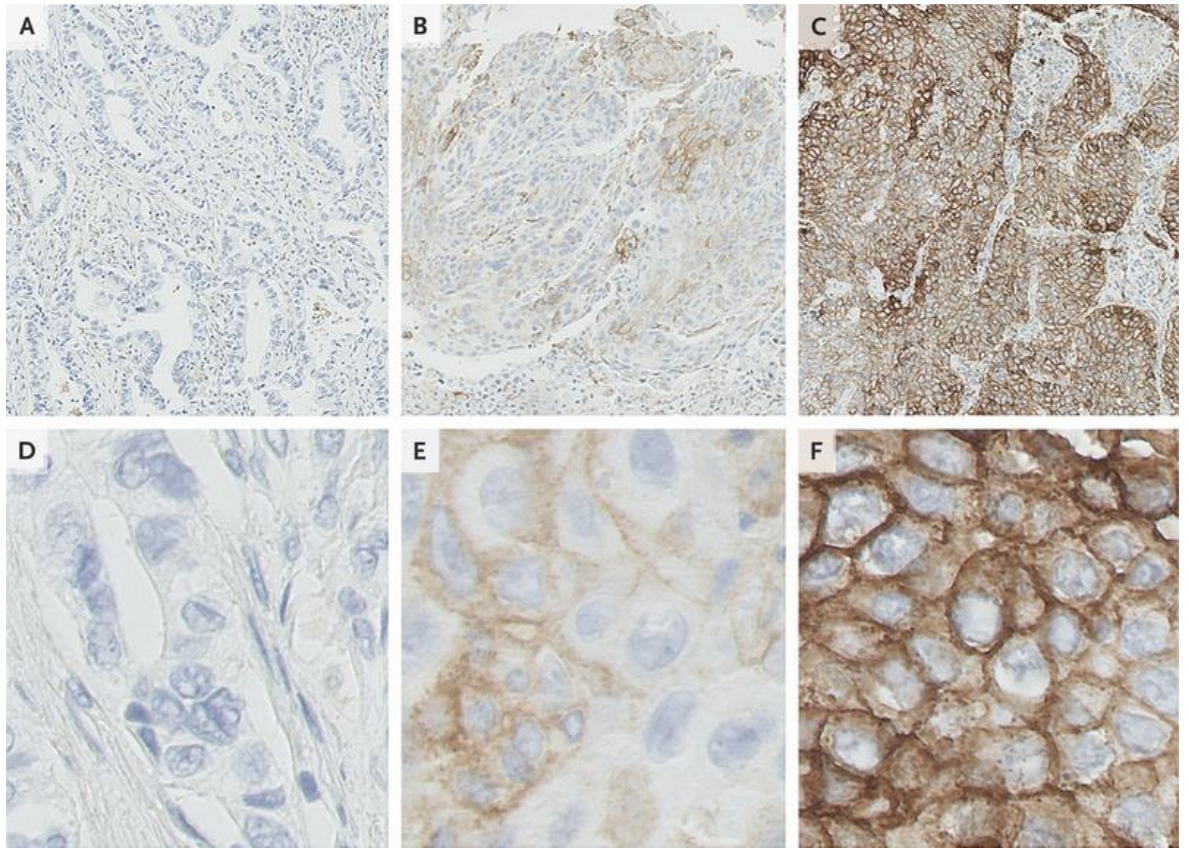


Hellman et al, NEJM, 2018

PD-L1 staining of NSCLC with increasing levels of expression

PD-L1 IHC

- Percentage of neoplastic cells showing membranous staining of PD-L1 proportion score (PS)
- Need > 100 cancer cells in order to calculate PS

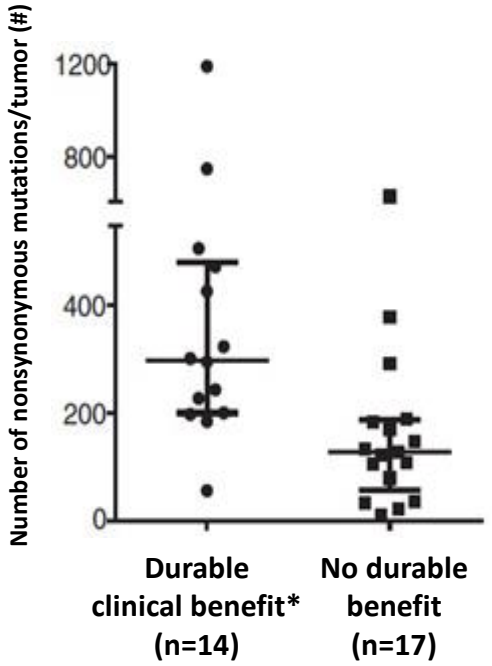


PS <1% PS 1-49% PS ≥50%

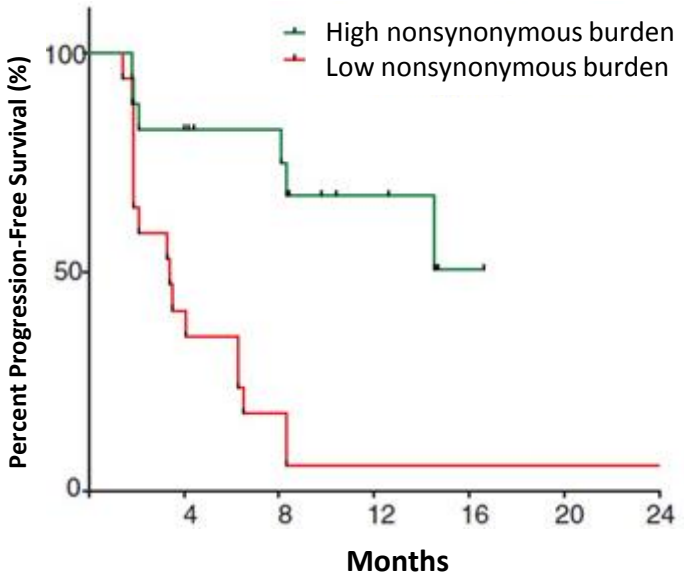
Garon EB et al, N Engl J Med 2015

Mutation Burden Determines Sensitivity to PD-1 Blockade in NSCLC

Data for All Sequenced Tumors



*Partial or stable response lasting > 6 mo

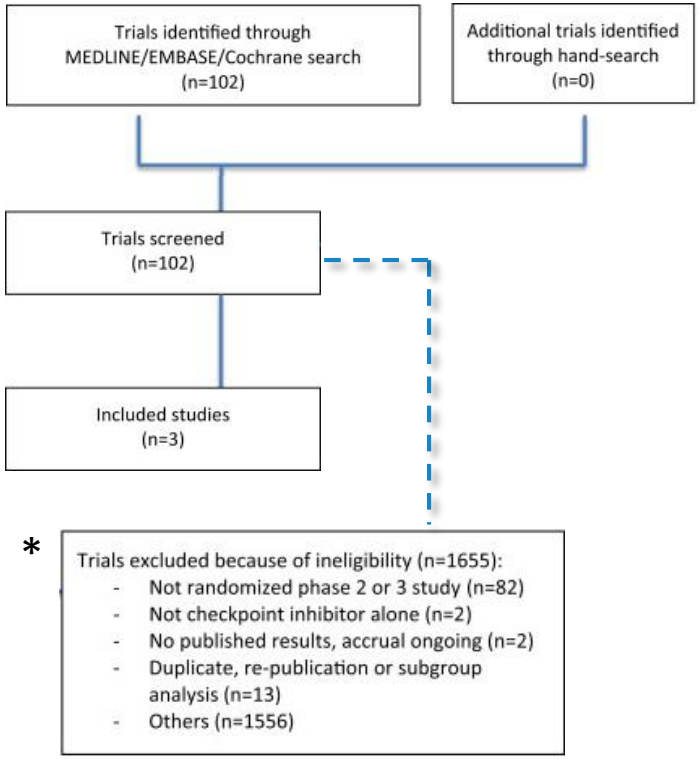


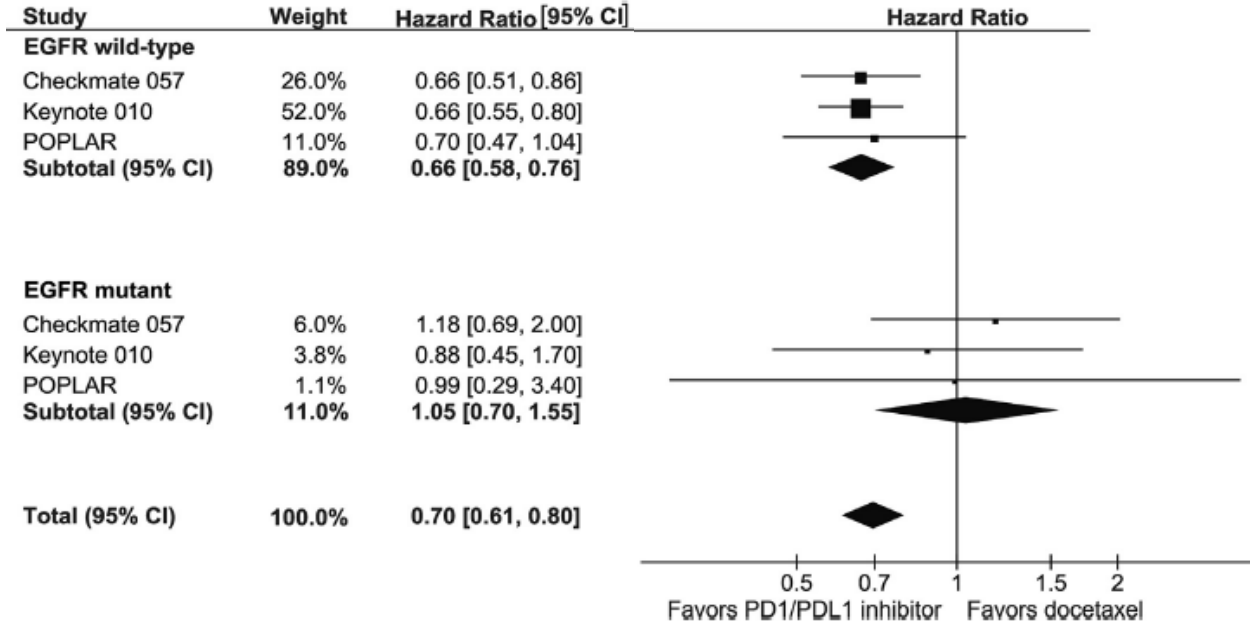
Rizvi N et al, Science, 2015

- Whole-exome sequencing of NSCLCs treated with pembrolizumab
- In two independent cohorts, higher nonsynonymous mutation burden in tumors was associated with improved objective response, durable clinical benefit (left panel), and progression-free survival (right panel)

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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





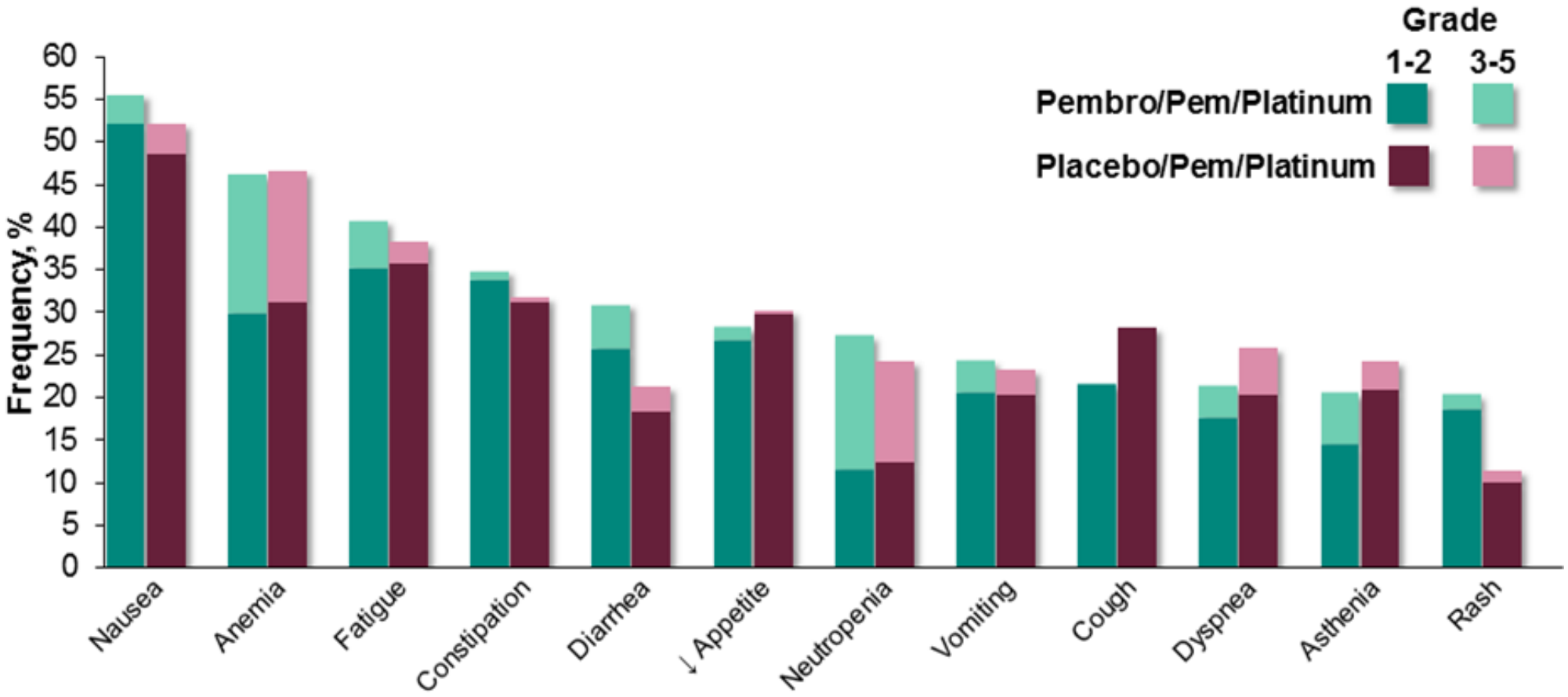
CK Lee et al., JTO 2016

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%

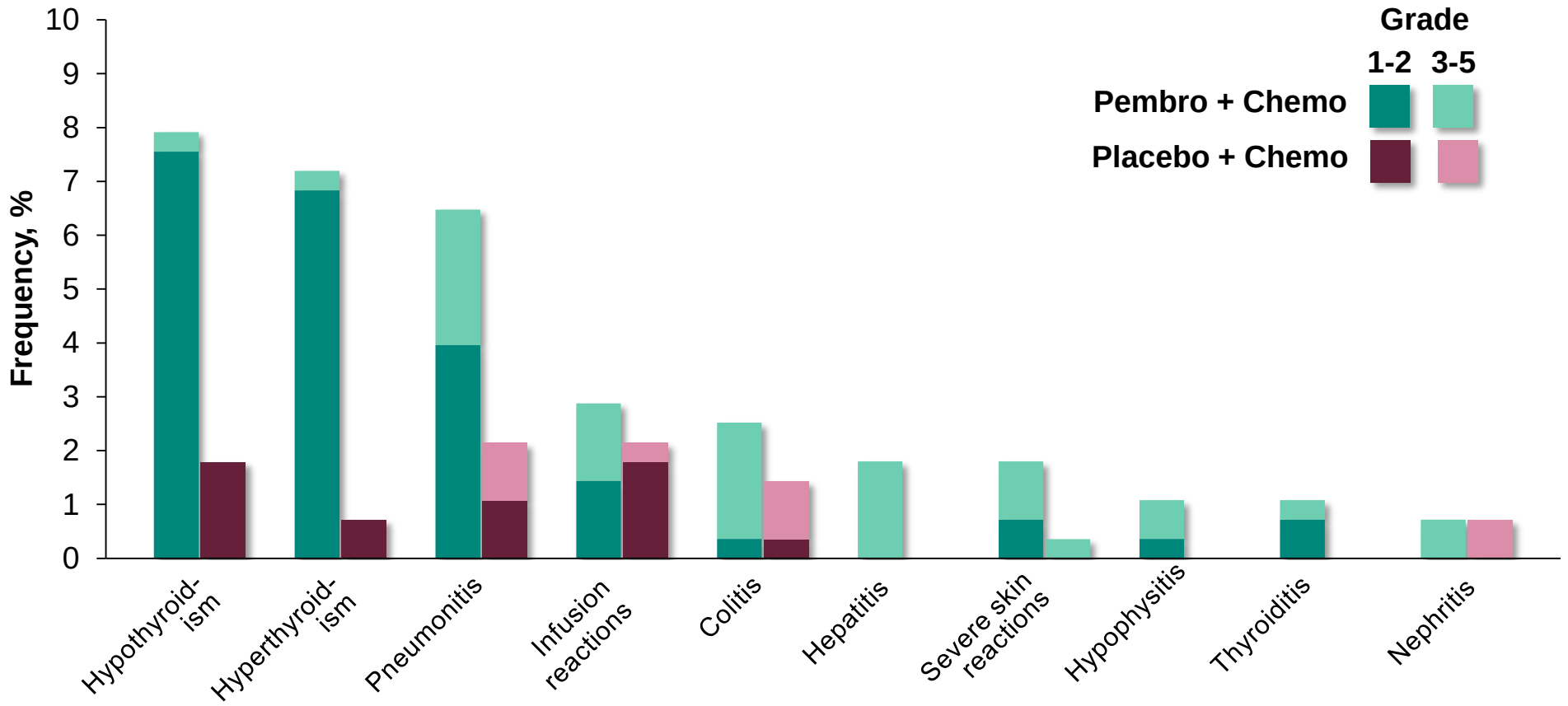
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

KEYNOTE-189: Carboplatin-Pemetrexed-Pembrolizumab vs. Chemotherapy for advance NSCLC: Toxicity



Ghandi et al, NEJM 2018

KEYNOTE-407: Carboplatin-Taxane-Pembrolizumab vs. Chemotherapy for advanced squamous NSCLC: Toxicity



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

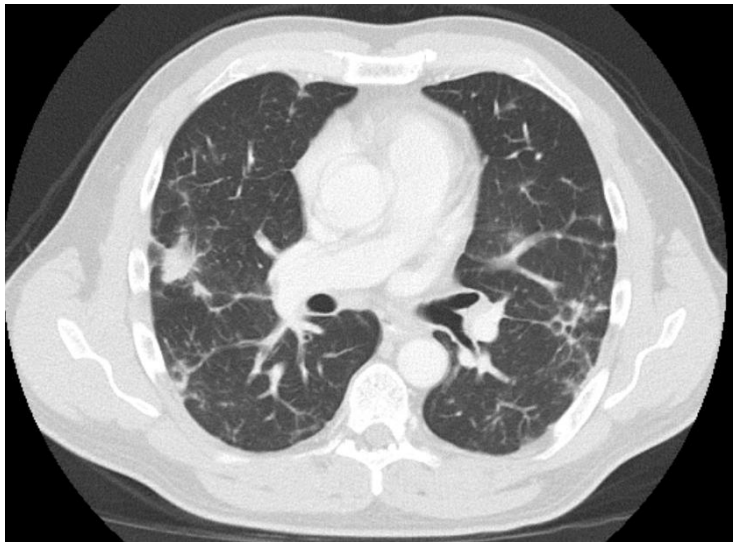
Summary of Frontline Strategies in Advanced NSCLC

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:
  - 58 year-old male, never smoker
  - Bilateral lung metastases
  - Biopsy shows:
    - Adenocarcinoma
    - KRAS mutation and TP53
    - PD-L1 is 20% positive (22C3 assay)
    - TMB is intermediate 8 mutations/MB
- What do you recommend?
  1. Pembrolizumab
  2. Pembrolizumab + carboplatin/pemetrexed
  3. Carboplatin/Pemetrexed
  4. Atezolizumab + carboplatin/paclitaxel/bevacizumab

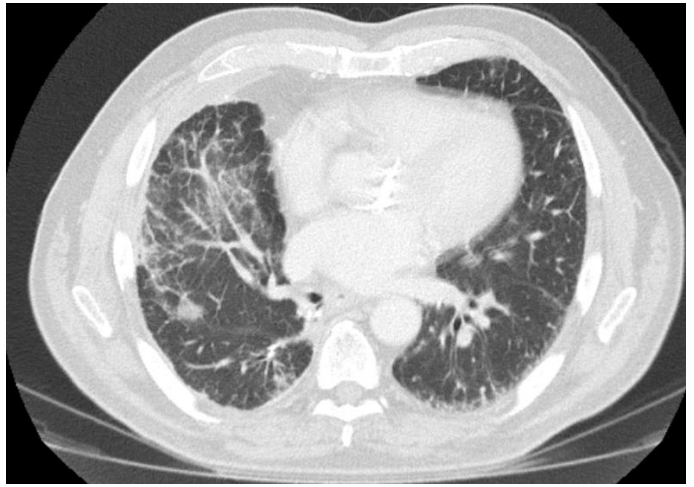


Presentation Outline

Patient Background

- 65-year-old female never smoker
- Presents with cough in June 2017
- CT imaging reveals bilateral disease
- Biopsy consistent with EGFR exon 19 adenocarcinoma
- Patient started on erlotinib and achieves response
- March 2018 CT scan demonstrates progressive disease
- Rebiopsy confirms EGFR mutation, T790M negative, PD-L1 80%

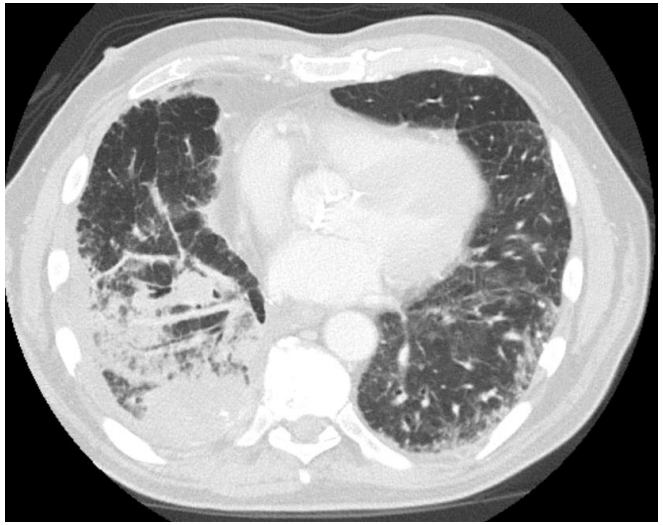
September 2017



What is your management recommendation ?

1. Osimertinib
2. Pembrolizumab
3. Carboplatin/Pemetrexed/Pembrolizumab
4. Carboplatin/Pemetrexed
5. Carboplatin/Paclitaxel/Bevacizumab/Atezo
6. Ipilimumab + Nivolumab

March 2018



Thank you!

Questions?