Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Antoinette J. Wozniak, MD, FACP, FASCO
Associate Director of Clinical Research
Director of the Lung Cancer Disease Unit
Hillman Cancer Center
University of Pittsburgh

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ACCC Association of Community Cancer Centers

Society for Immunotherapy of Cancer

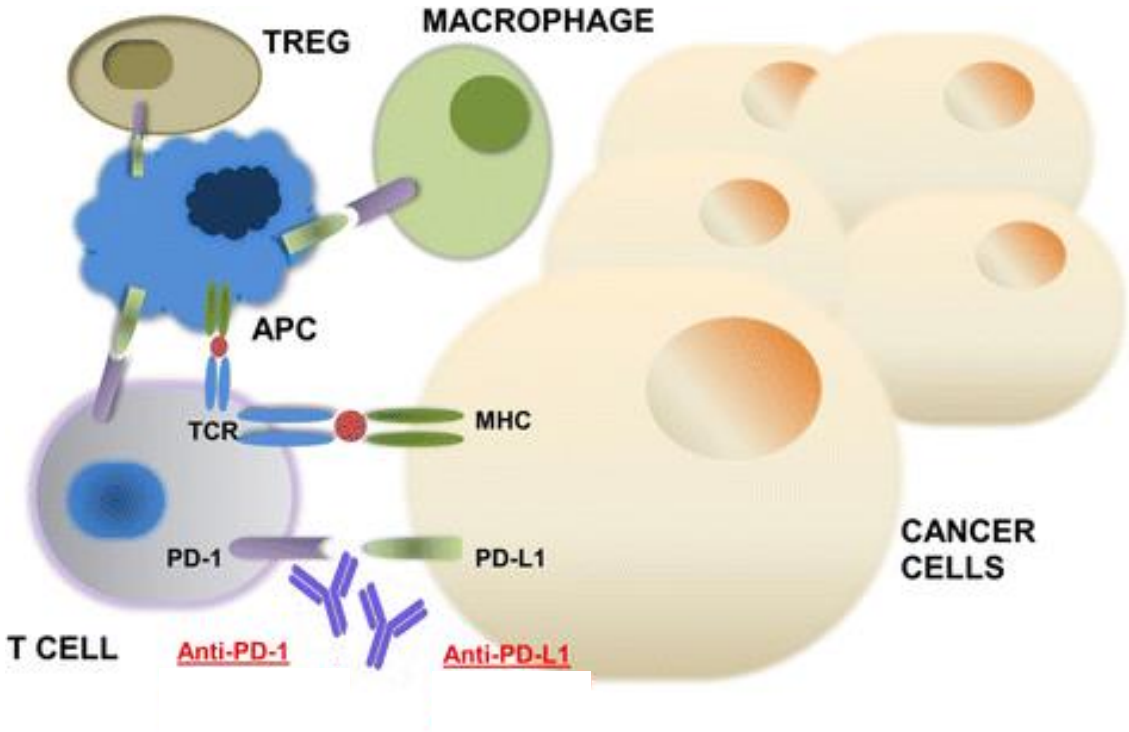
Disclosures

- Research Support – Boehringer Ingelheim, Genentech
- Advisory/Consultancy – Boehringer Ingelheim, AstraZeneca, Takeda, BeyondSpring, HUYA
- I will be discussing non-FDA approved indications during my presentation.

Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

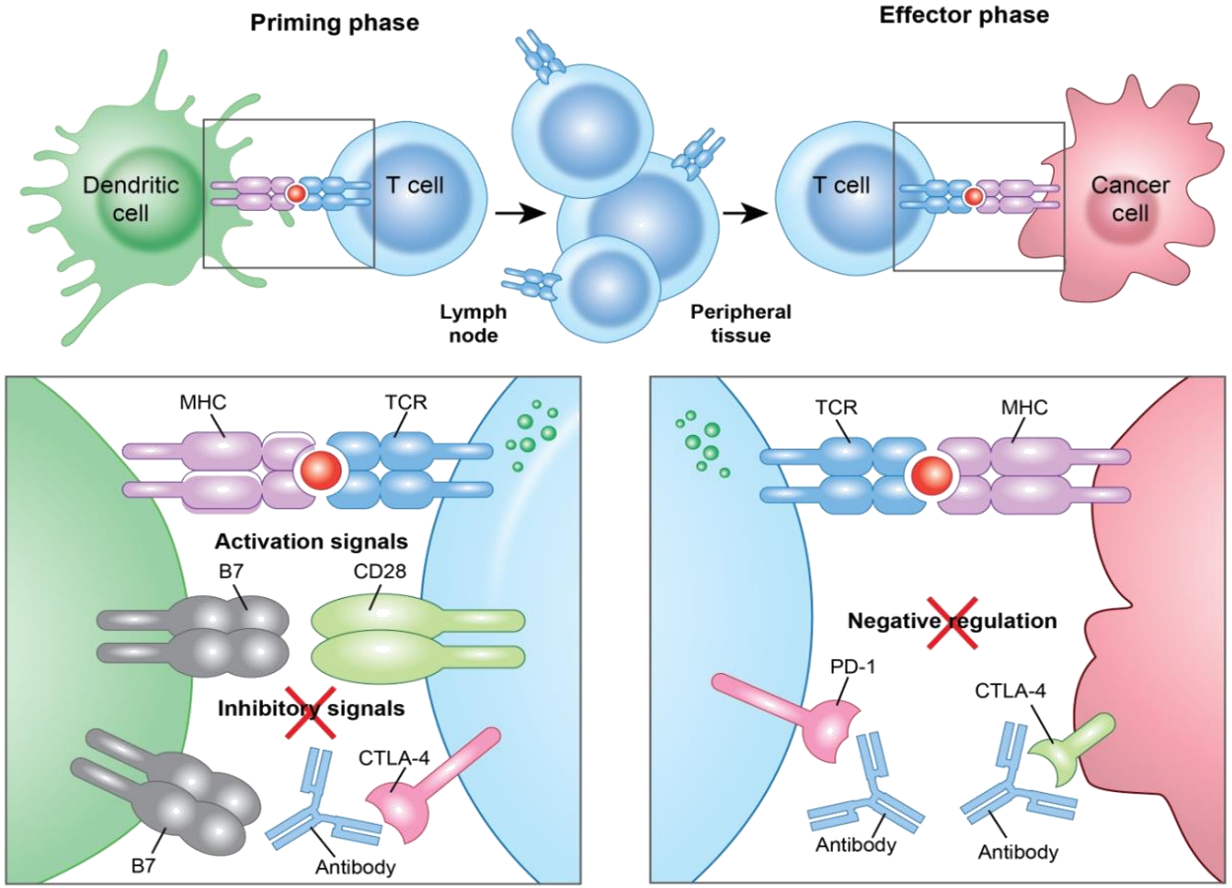
- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells



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

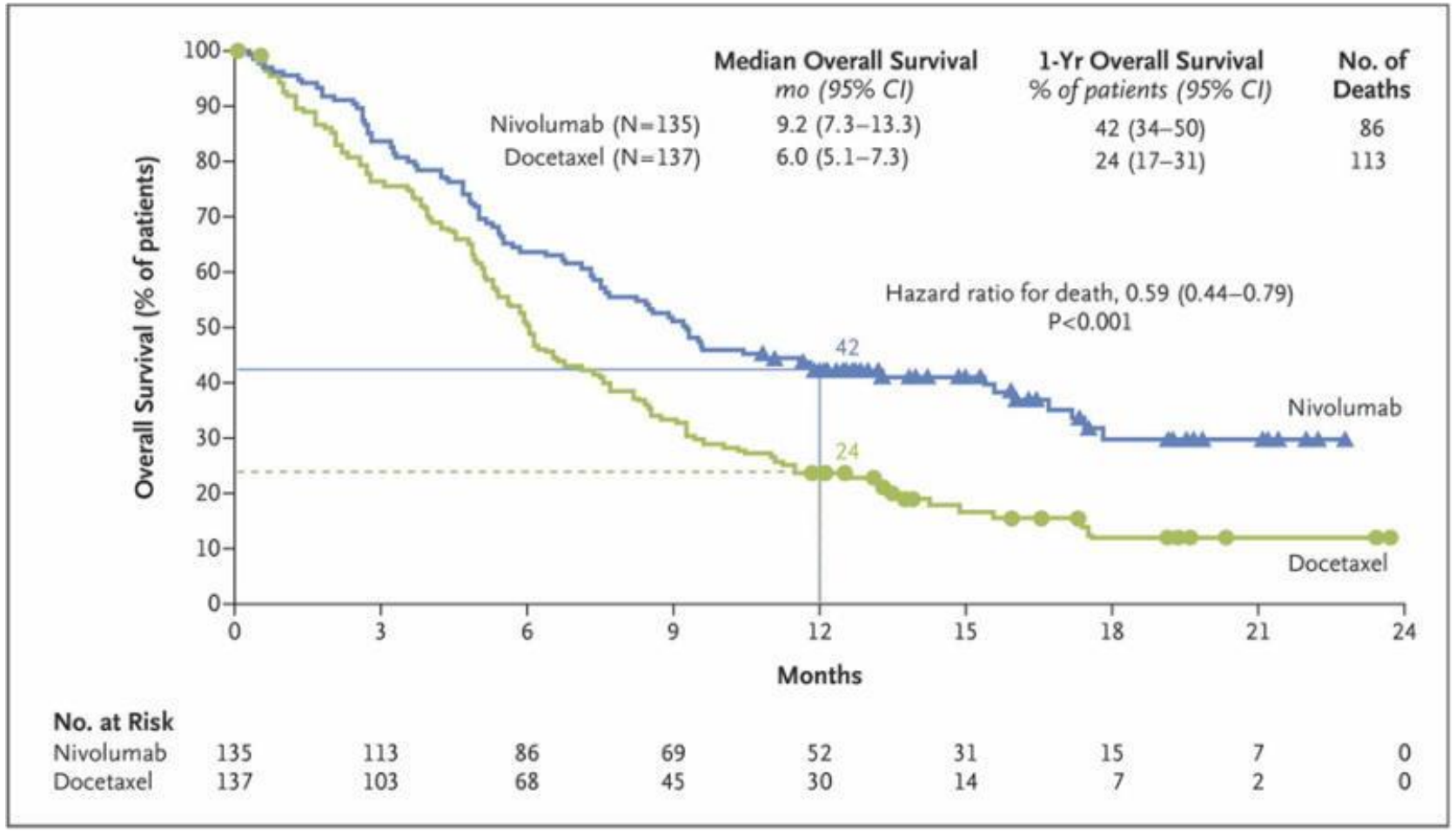
2017 (May)
Pembrolizumab + Pemetrexed and Carboplatin FDA approved 1st line NSCLC 2017 (July)

Durvalumab FDA Approved for Stage III NSCLC

2018 (Oct)
Pembrolizumab + Carboplatin and Paclitaxel/nab-Paclitaxel FDA approved 1st line squamous NSCLC

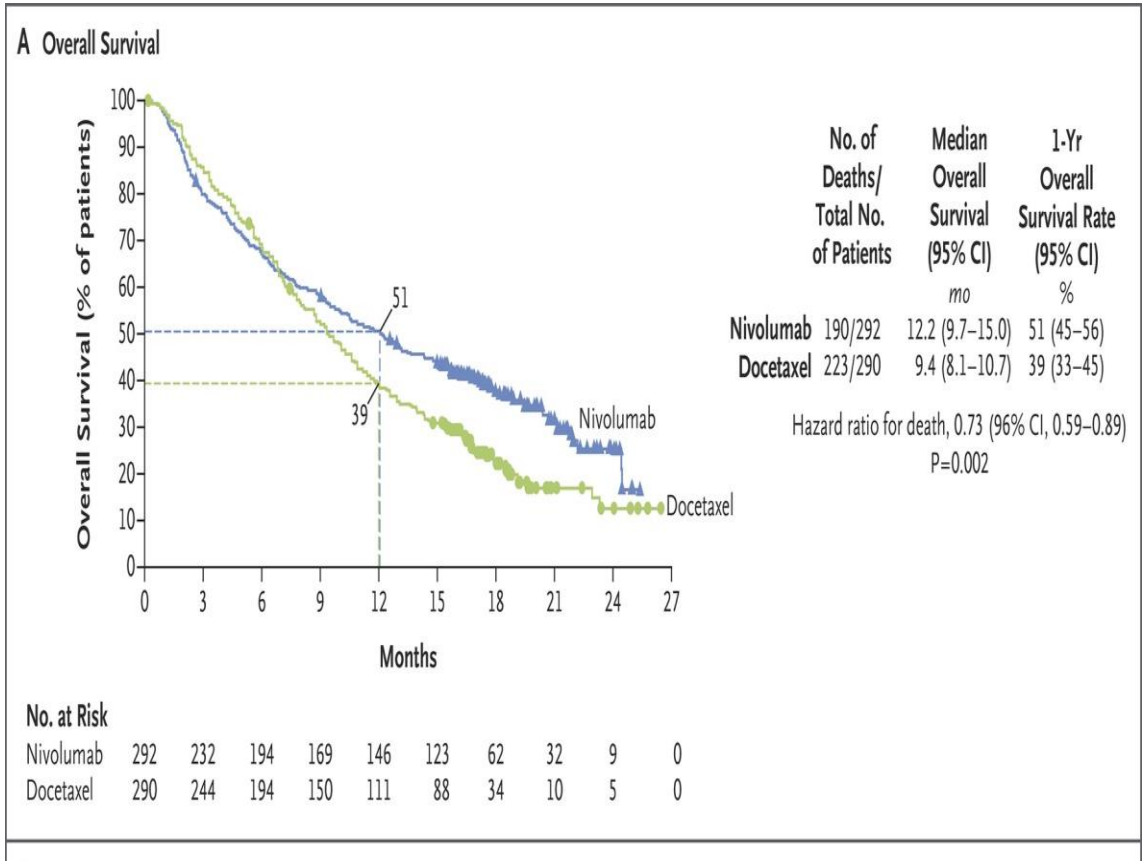
2018 (Dec)
Carbo/Pac/Bev/Atezo FDA approved 1st line non-squamous NSCLC

CheckMate 017 (Squamous) Nivolumab vs Docetaxel



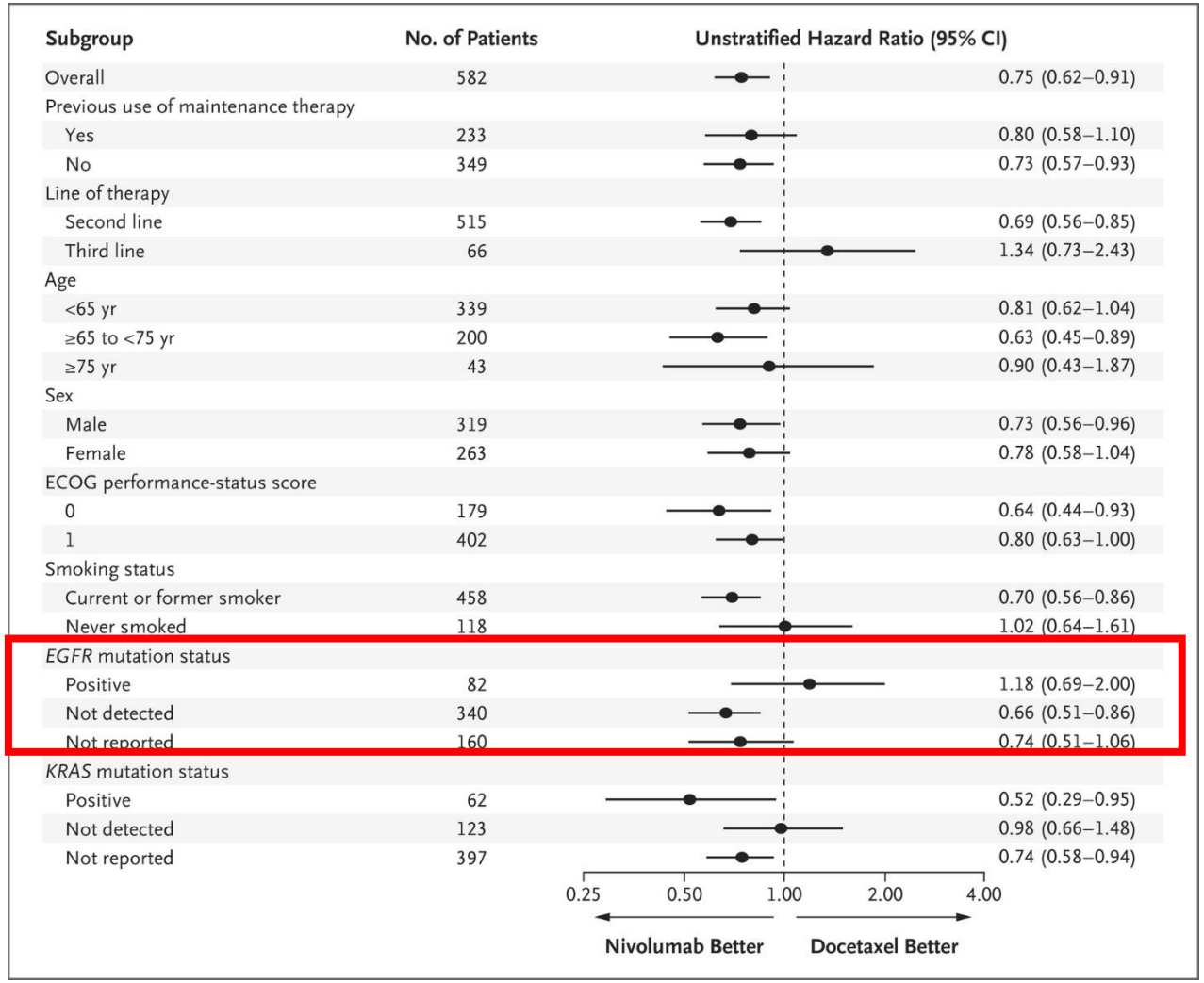
Brahmer J et al: NEJM 373:123, 2015

CheckMate 057 (NonSquamous) Nivolumab vs Docetaxel



	No. of Deaths/ Total No. of Patients	Median Overall Survival (95% CI)	1-Yr Overall Survival Rate (95% CI)
		mo	%
Nivolumab	190/292	12.2 (9.7–15.0)	51 (45–56)
Docetaxel	223/290	9.4 (8.1–10.7)	39 (33–45)

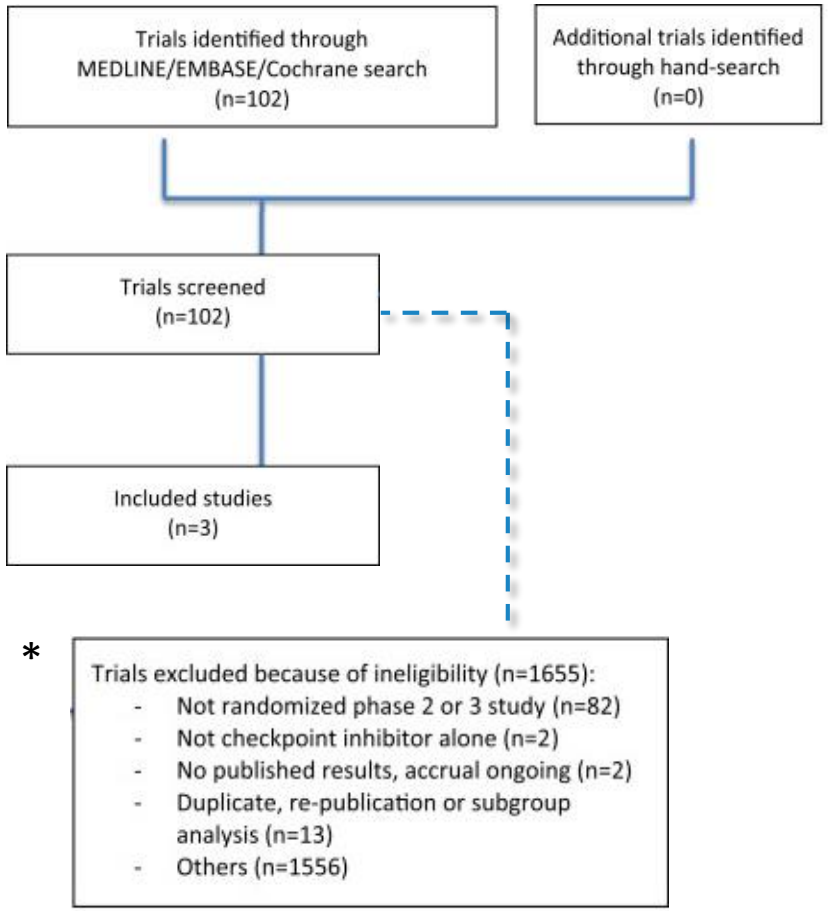
Hazard ratio for death, 0.73 (96% CI, 0.59–0.89)
P=0.002

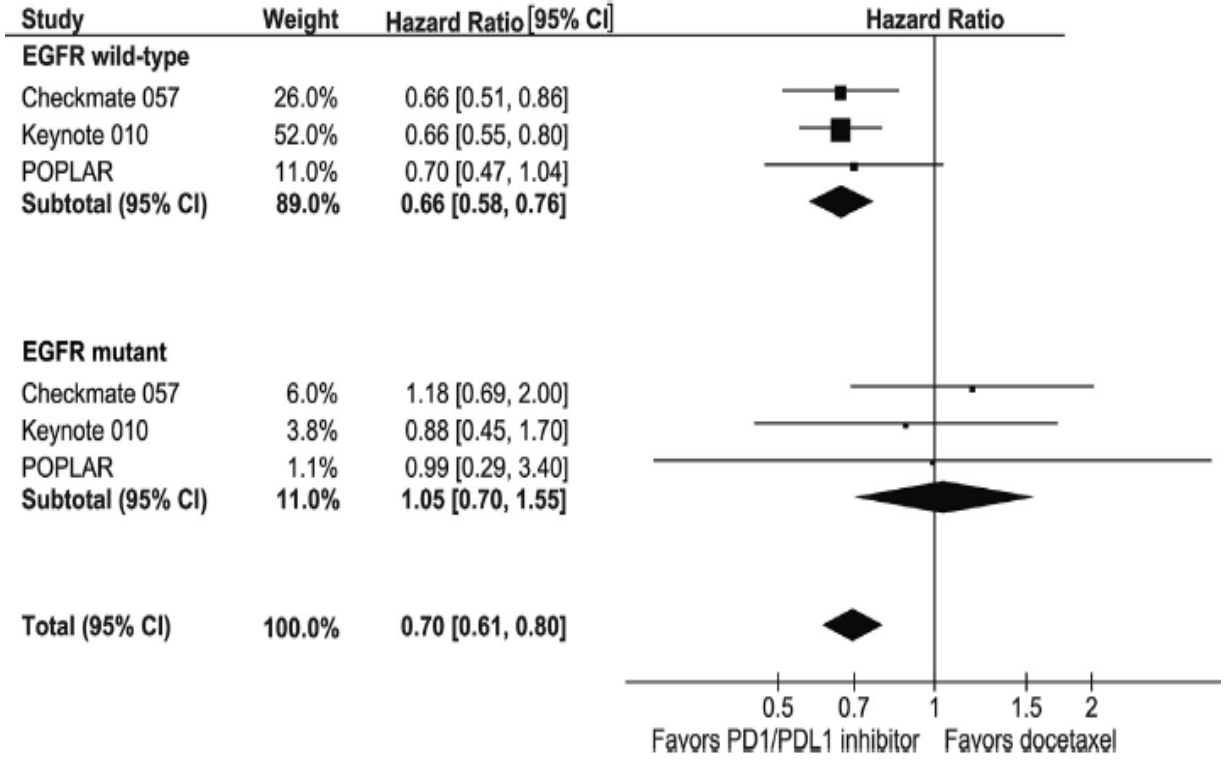


Borghaei H et al: NEJM 373:1627, 2015

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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





CK Lee et al., JTO 2016

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

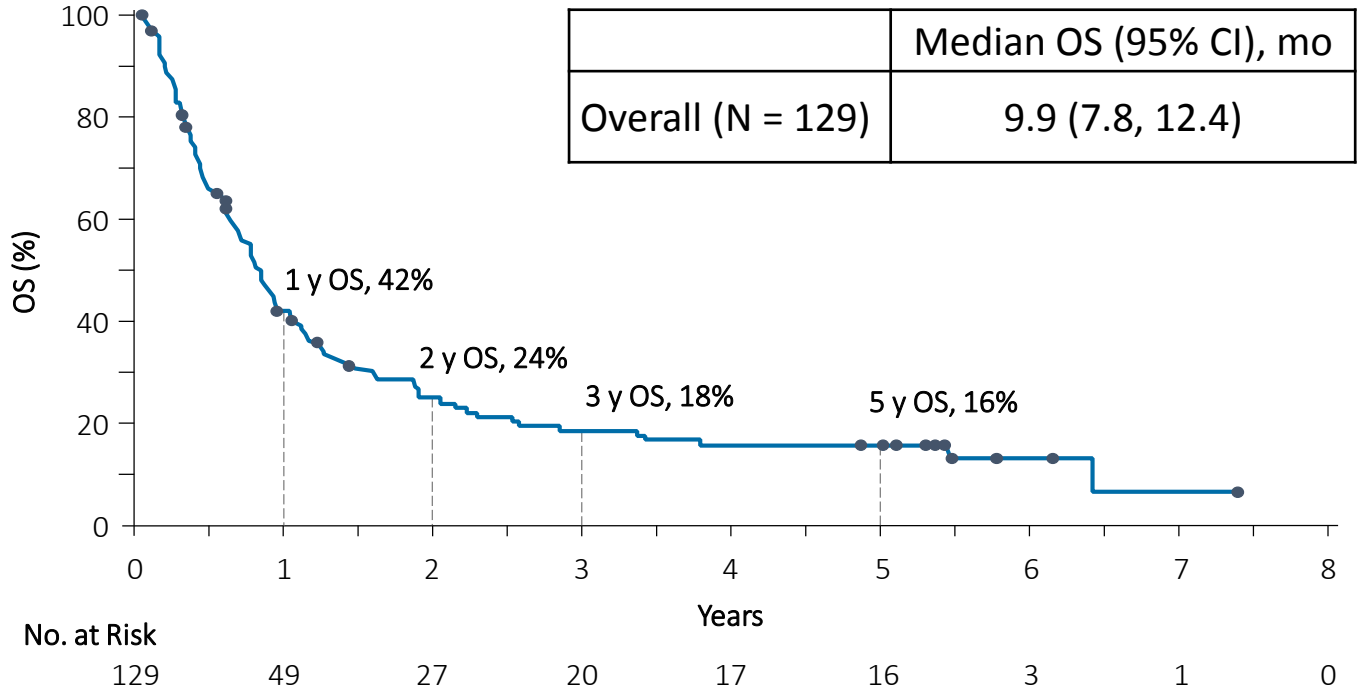
Brahmer NEJM 2015; Borghaei, NEJM 2015; Herbst Lancet 2016; Rittmeyer Lancet 2017

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

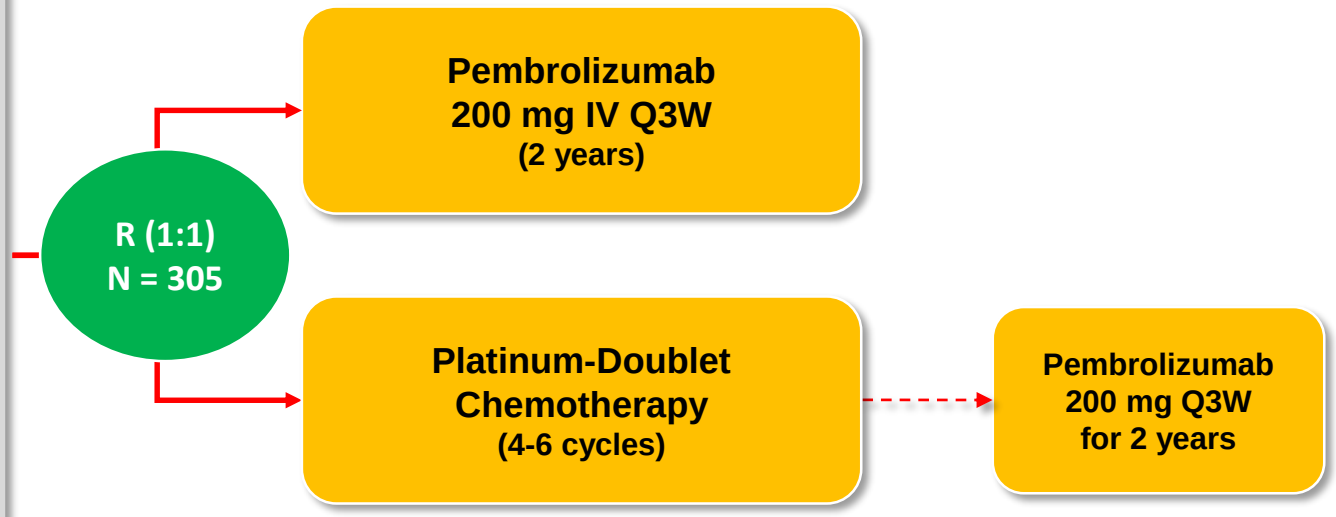
- KEYNOTE 024 – Pembrolizumab vs. Chemotherapy in PD-L1 > 50%
- KEYNOTE 042 – Pembrolizumab vs. Chemotherapy in PD-L1 > 1%
- KEYNOTE 189 – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in patients with advanced non-squamous NSCLC
- KEYNOTE 407 – Pembrolizumab + Chemotherapy vs. Chemotherapy in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

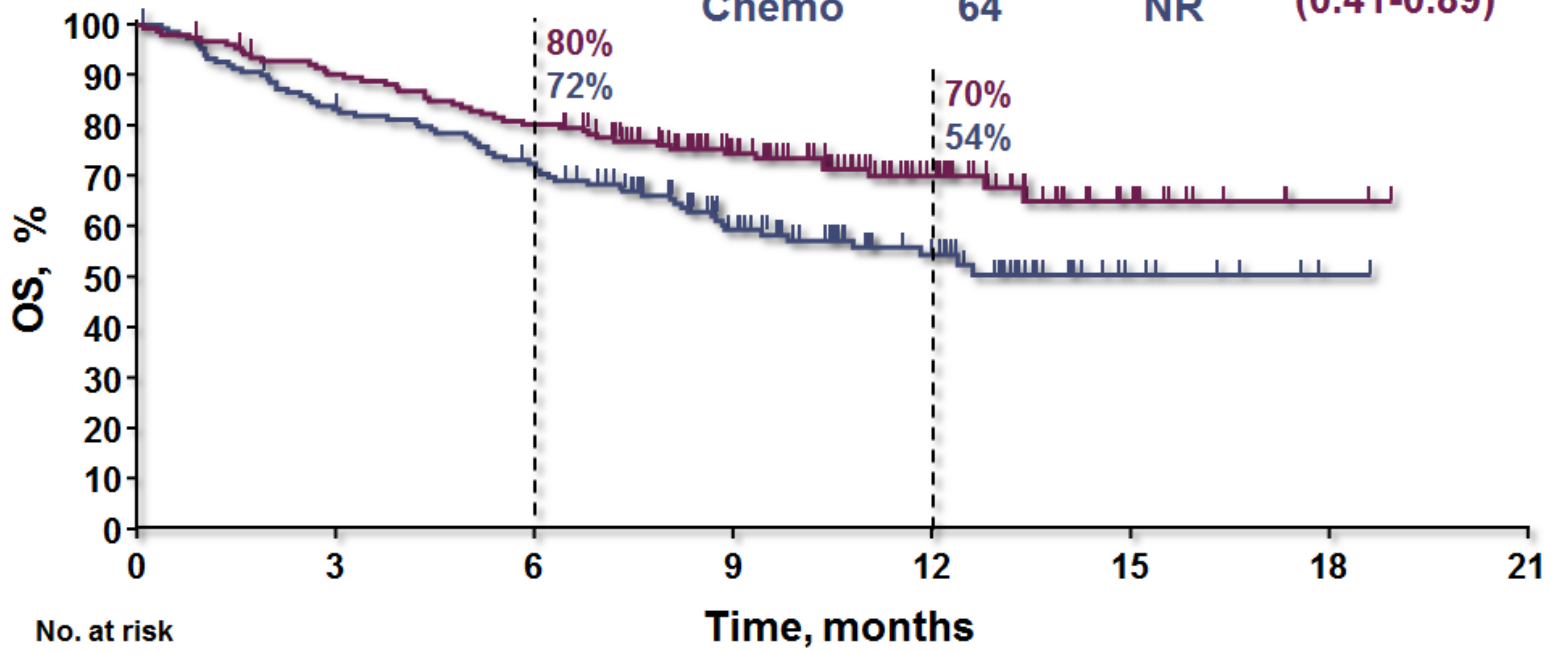


Reck M et al, ESMO 2016, NEJM 2016

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

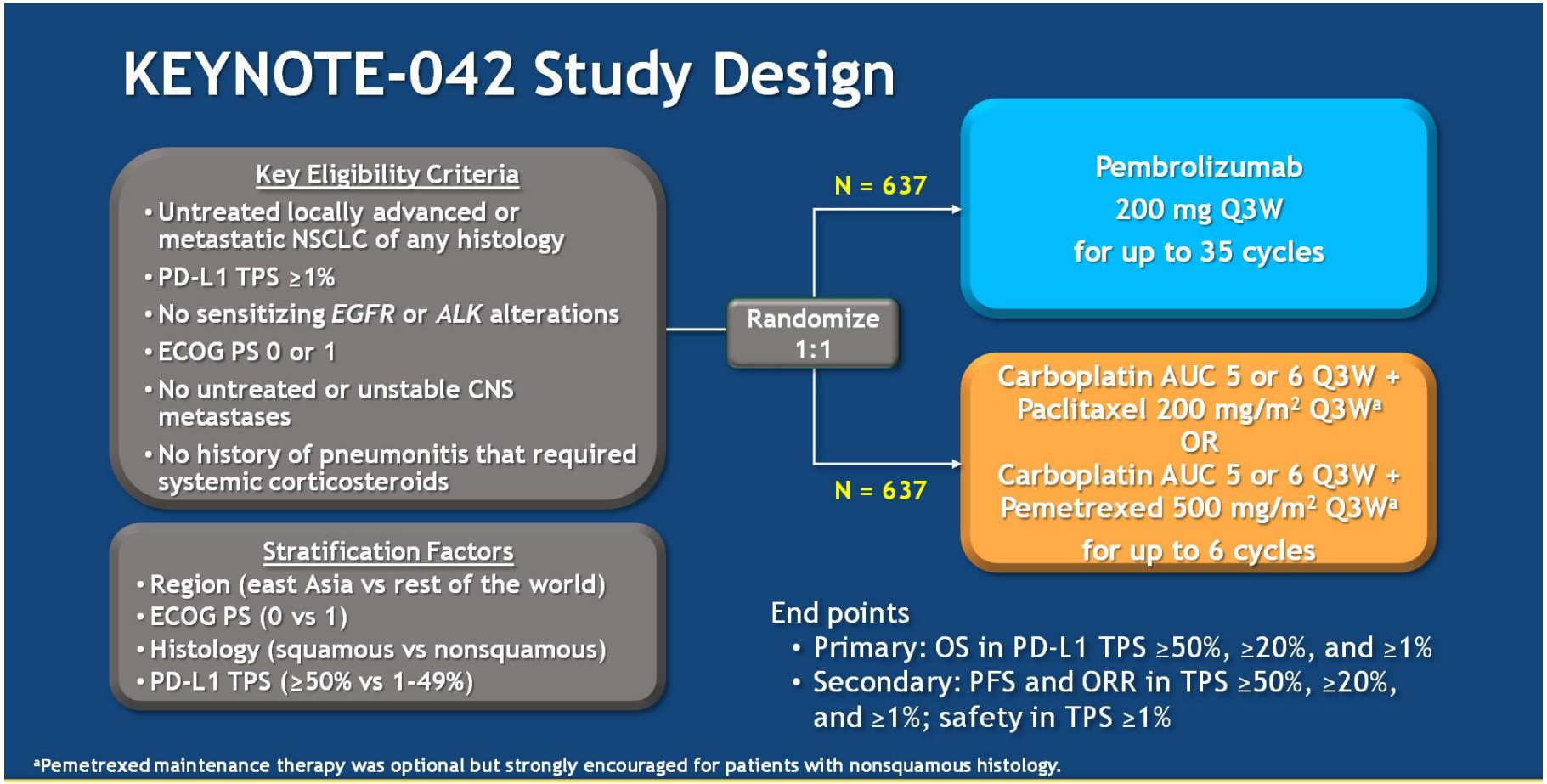
Overall Survival

	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

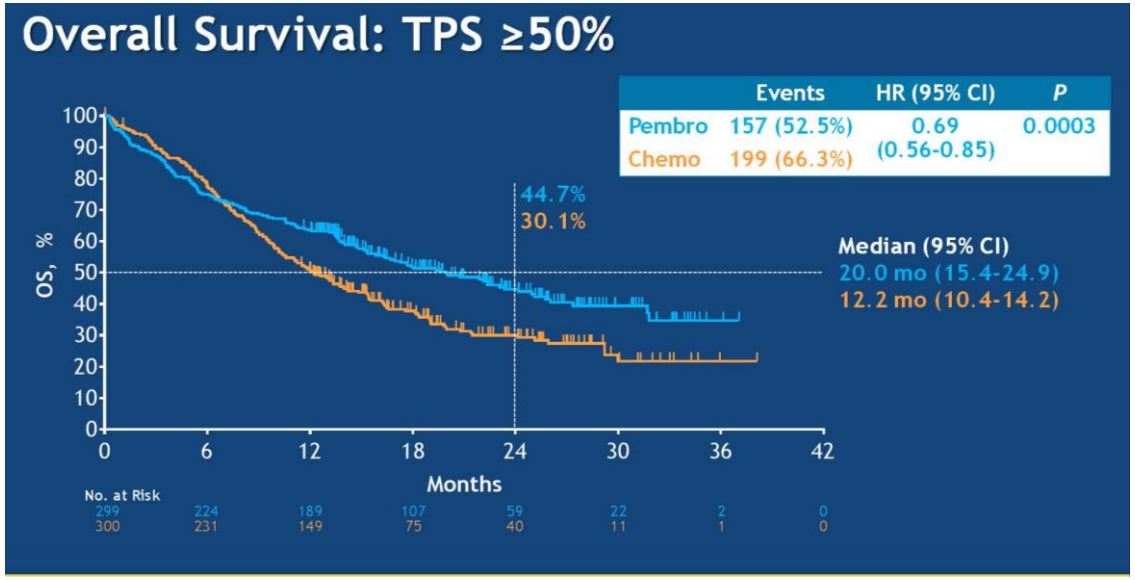
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 > 1% NSCLC

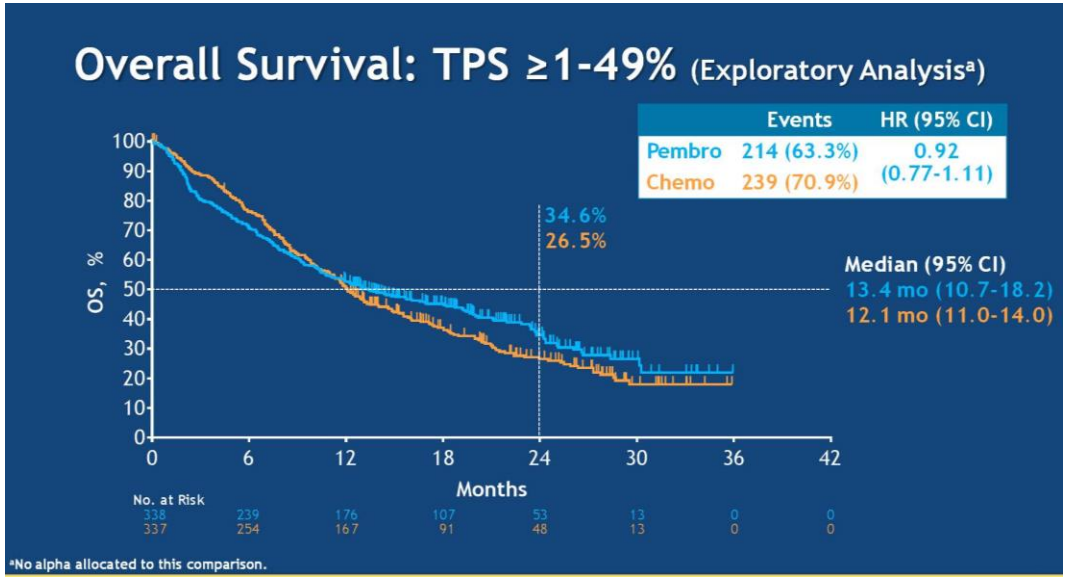


Lopes et al, ASCO 2018

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

Overall Survival

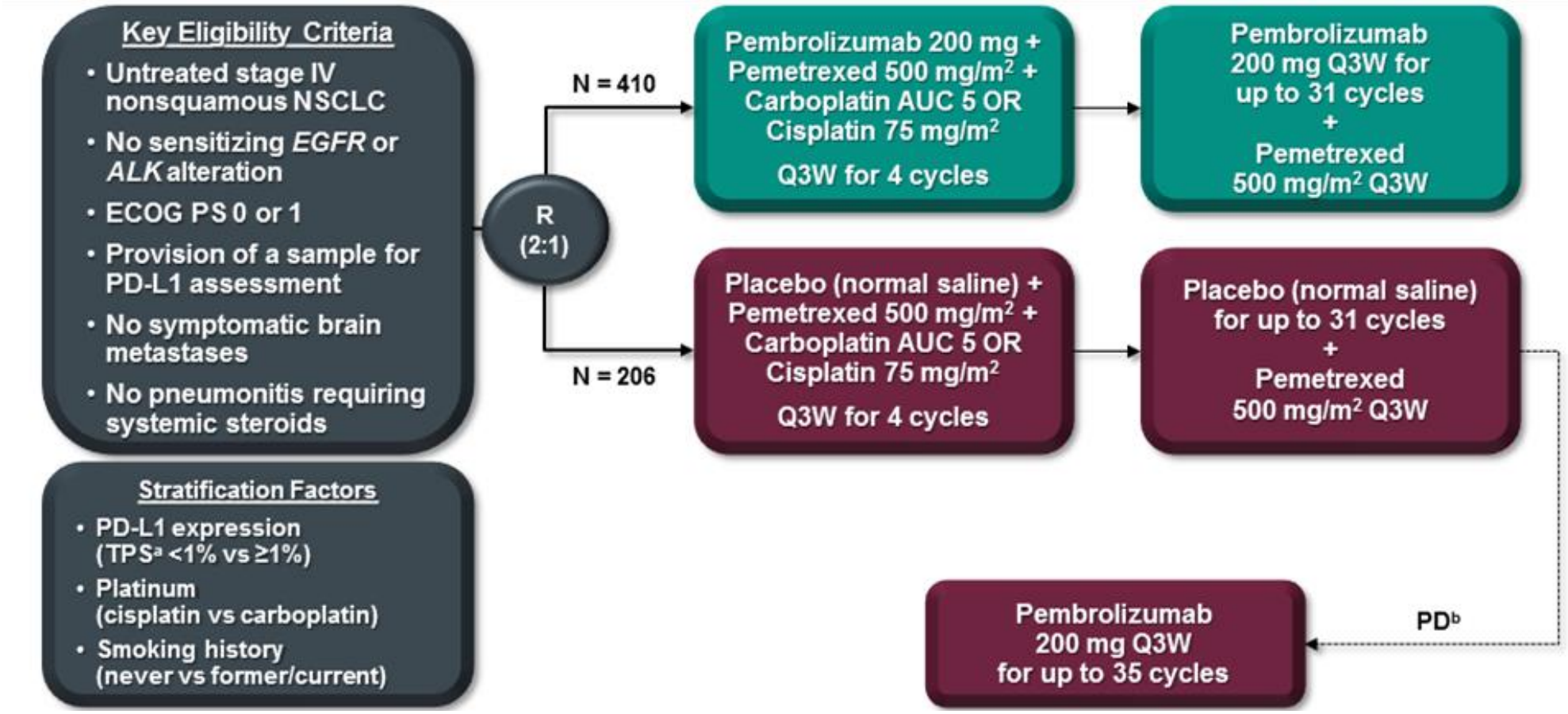




Survival benefit seemed to be driven by the TPS > 50% subset with little benefit witnessed in the subset TPS > 1- 49%

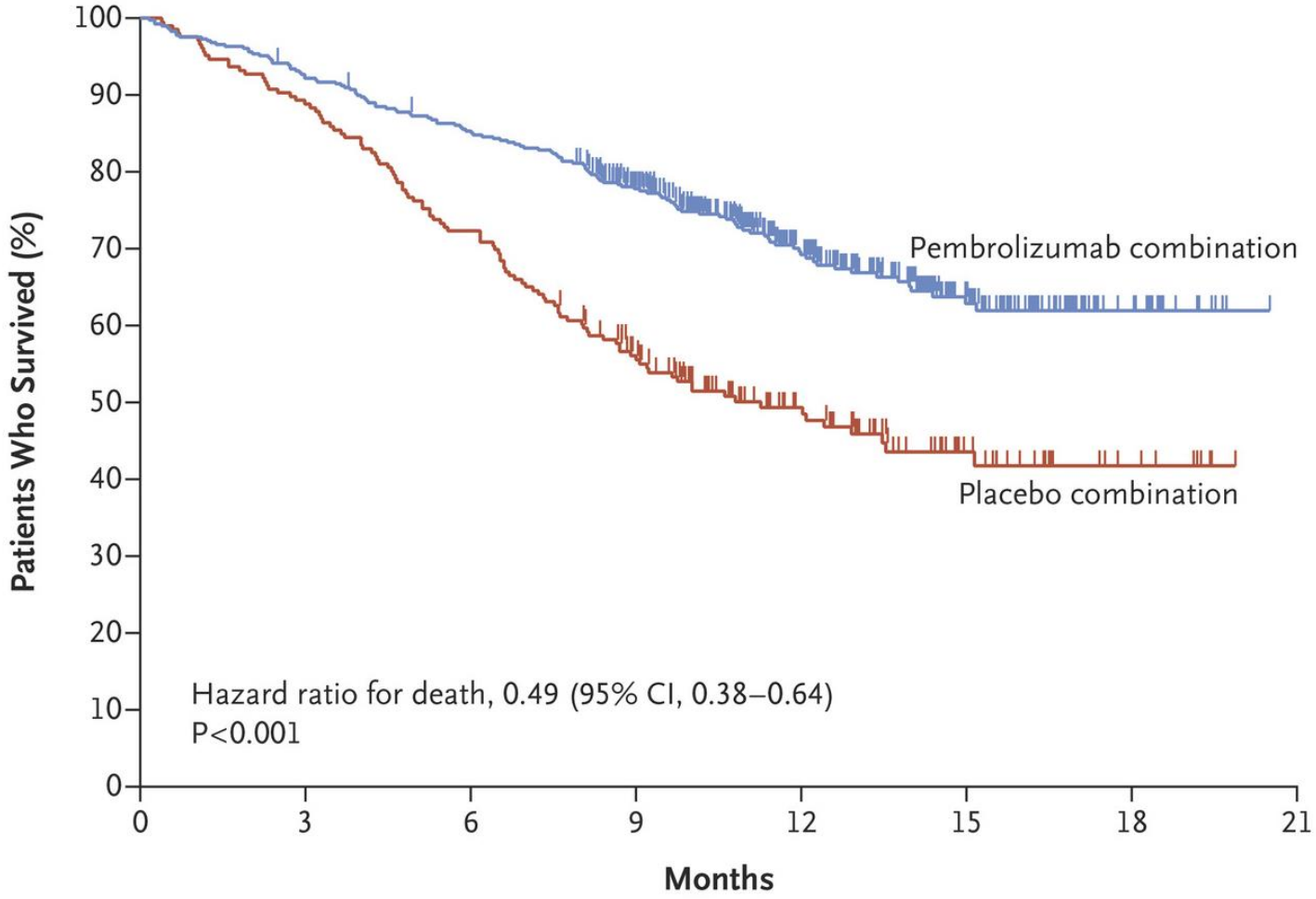
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

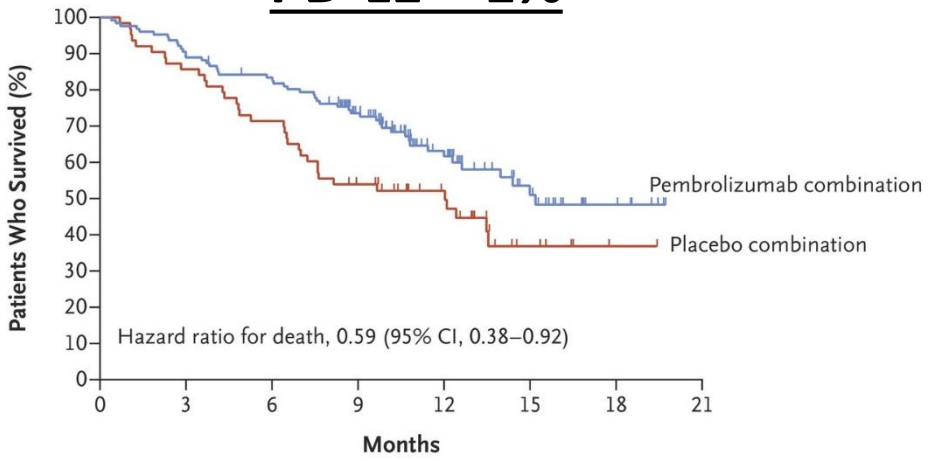
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



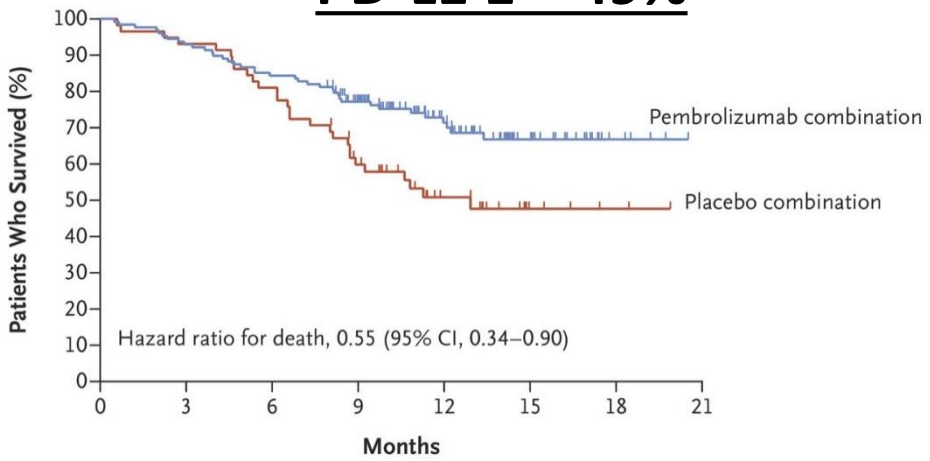
Ghandi et al, NEJM 2018

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

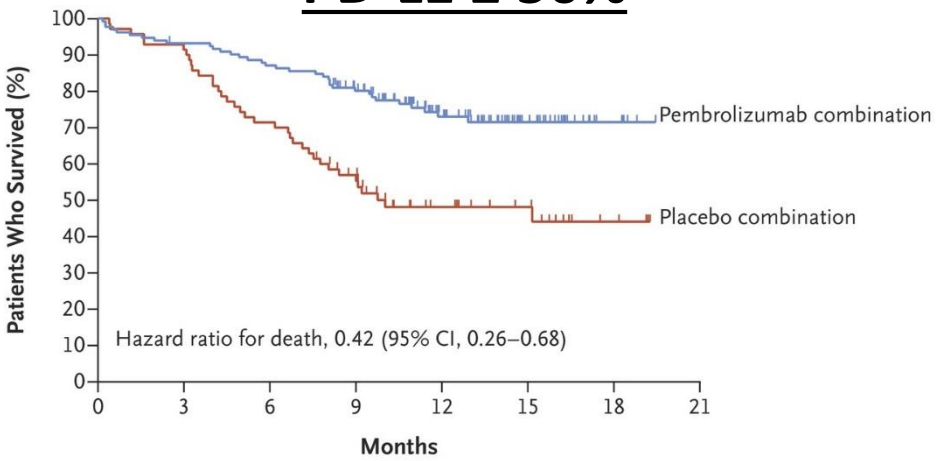
PD-L1 < 1%



PD-L1 1 – 49%

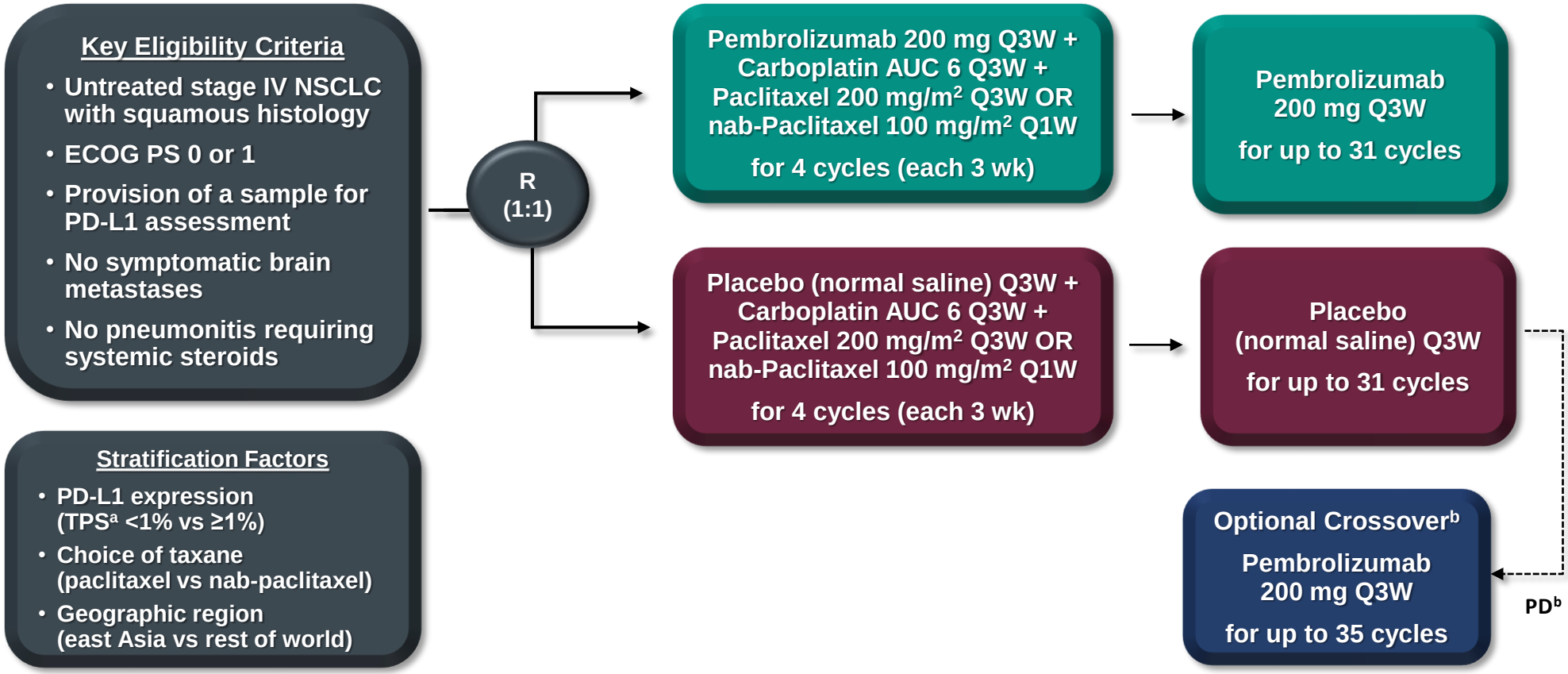


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

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

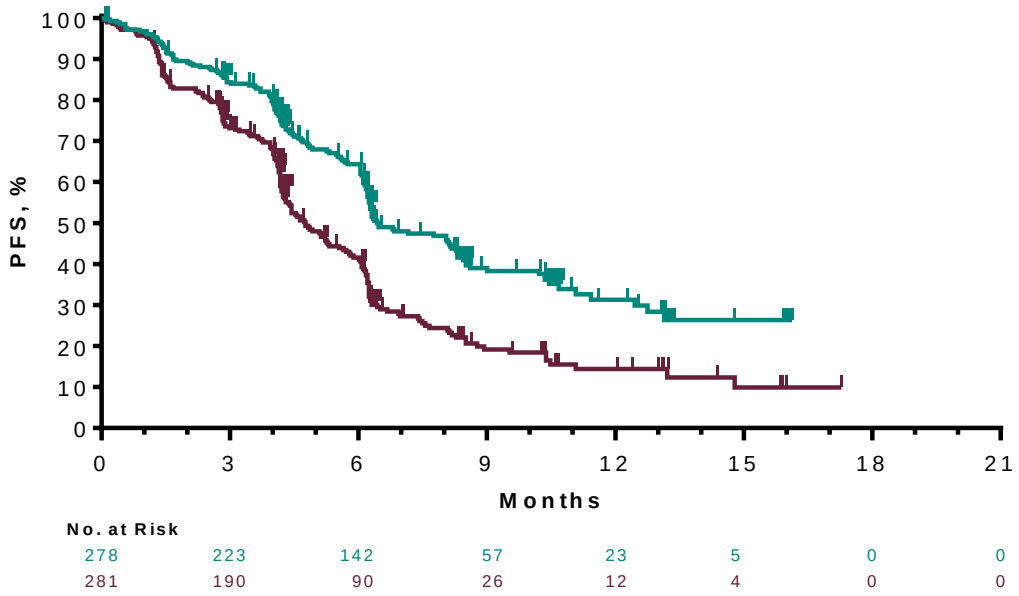


Paz-Ares et al, ASCO 2018

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

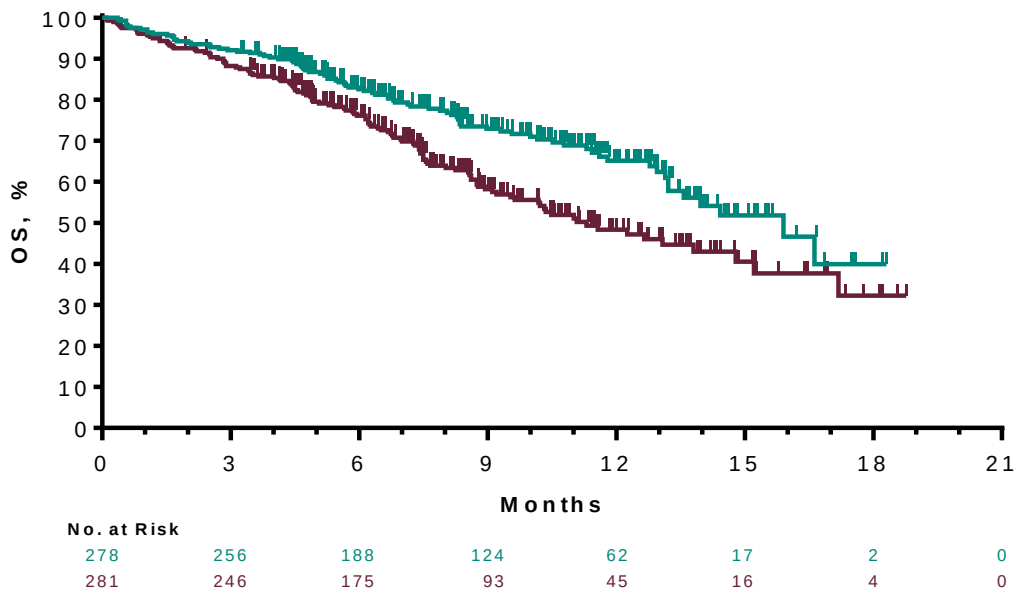
PFS (RECISTv1.1, BICR)

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



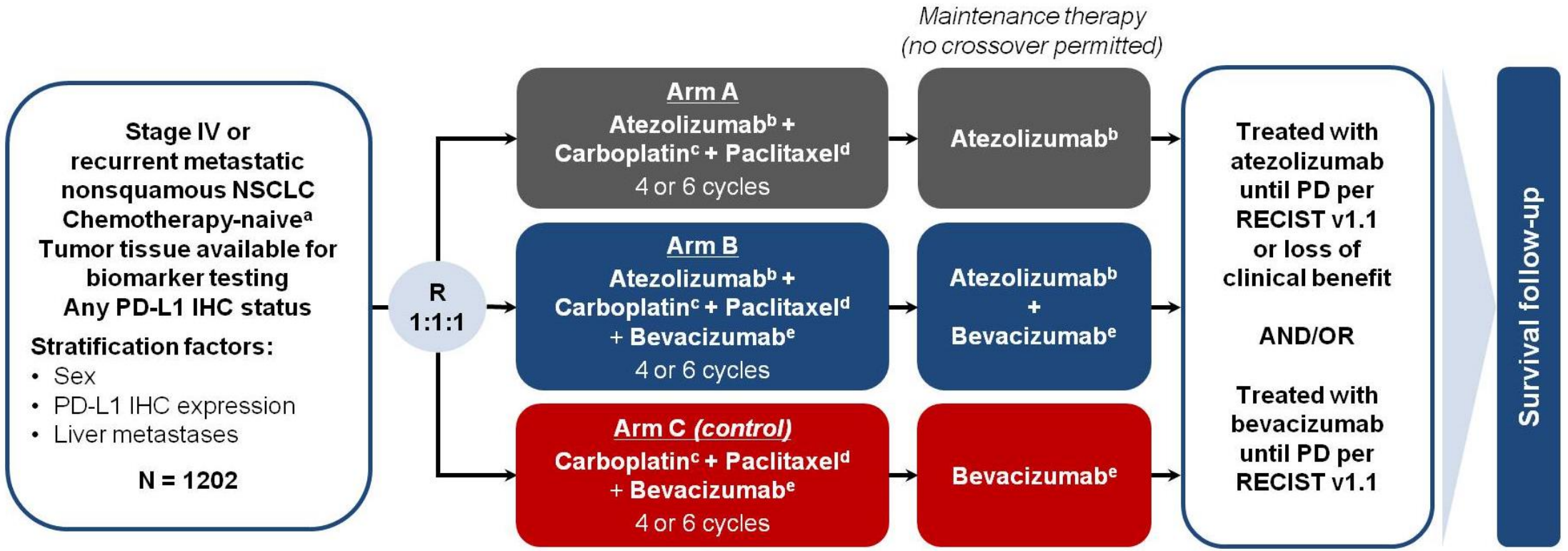
Overall Survival

	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

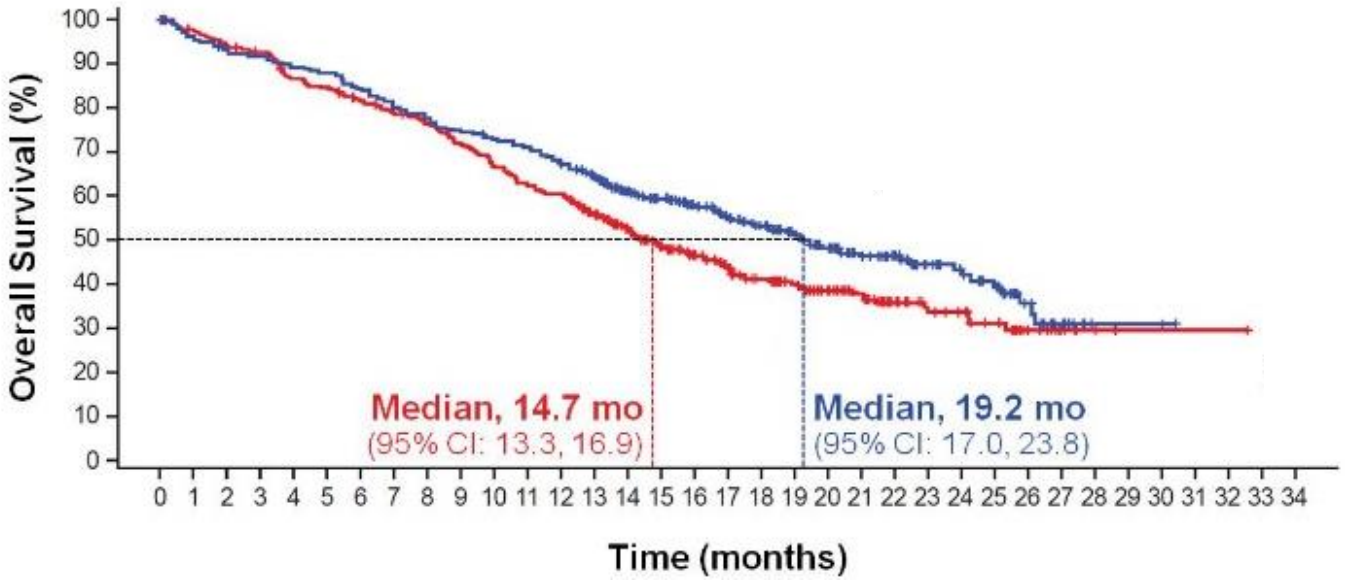


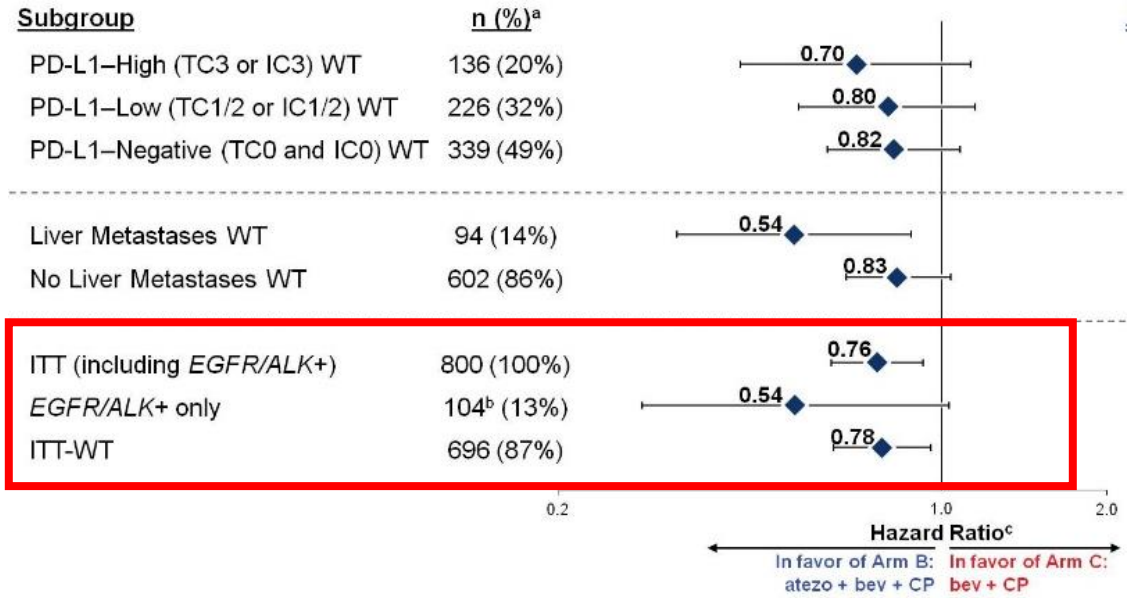
Socinski et al, NEJM 2018

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%

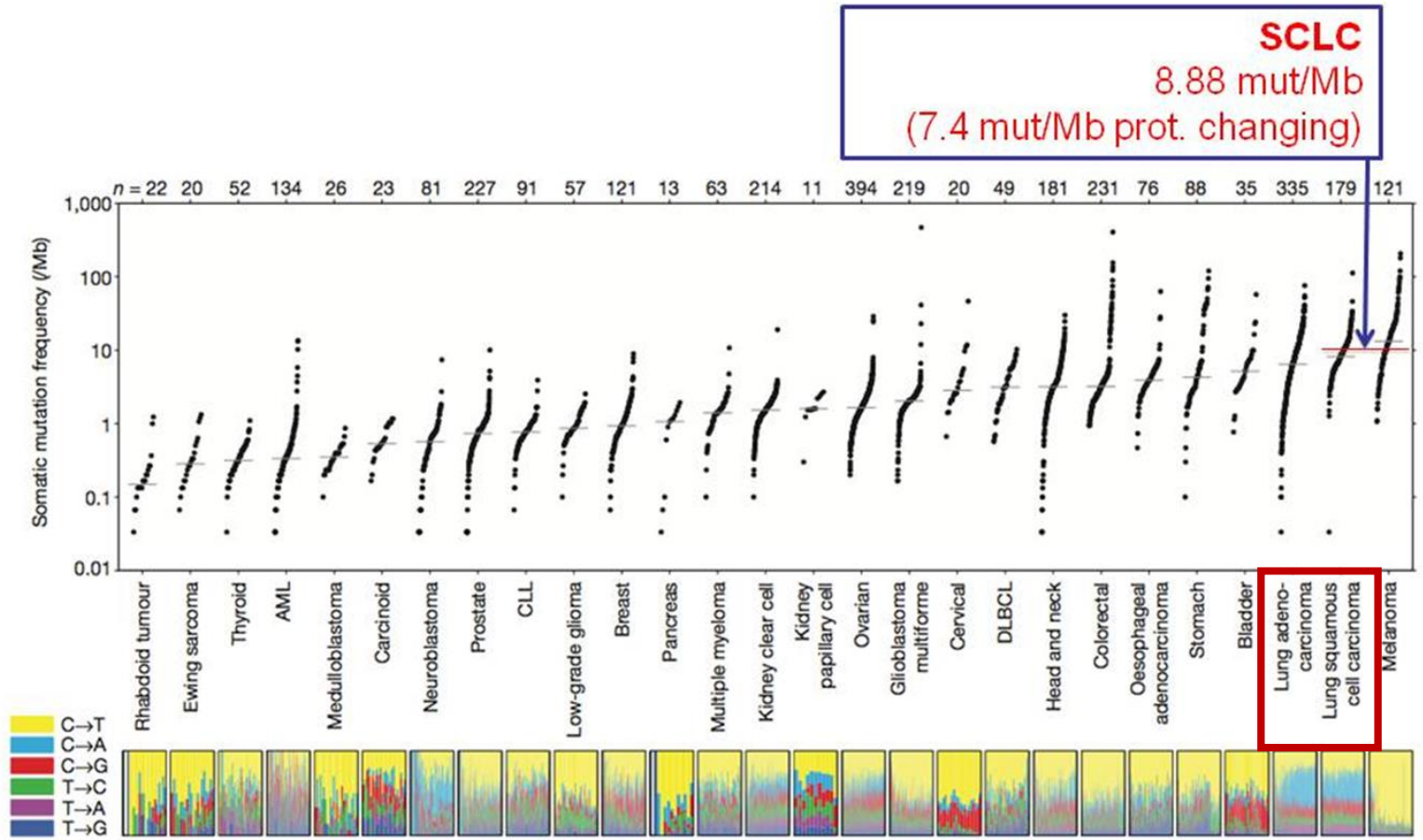
HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**
Median follow-up: ~20 mo





Socinski et al, NEJM 2018

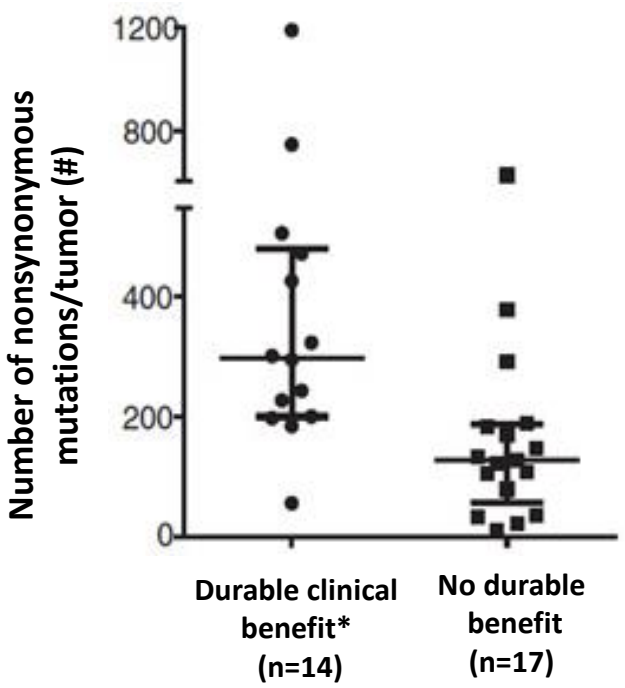
Somatic mutation frequency in lung cancer

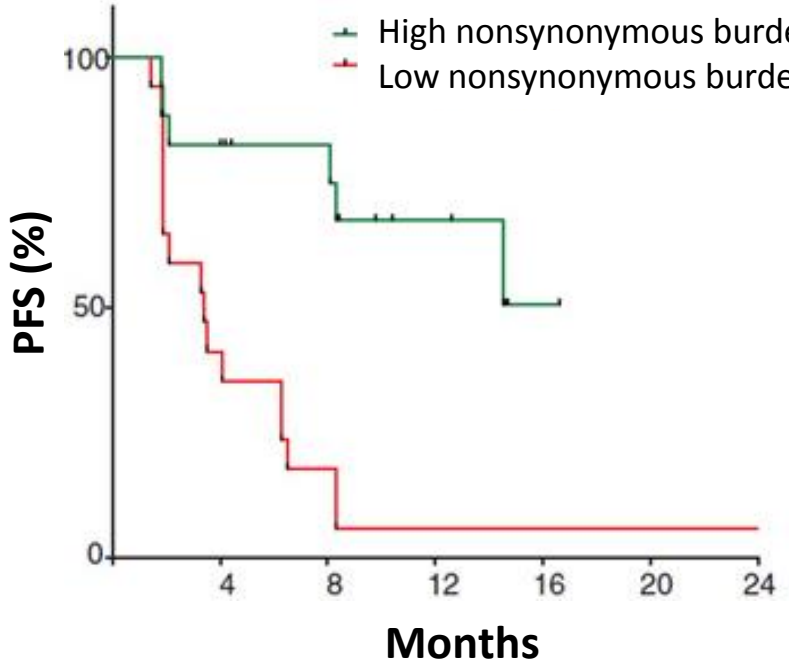


Lawrence et al. *Nature* (2013)
Peifer et al., Nat Genet (2012)

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.

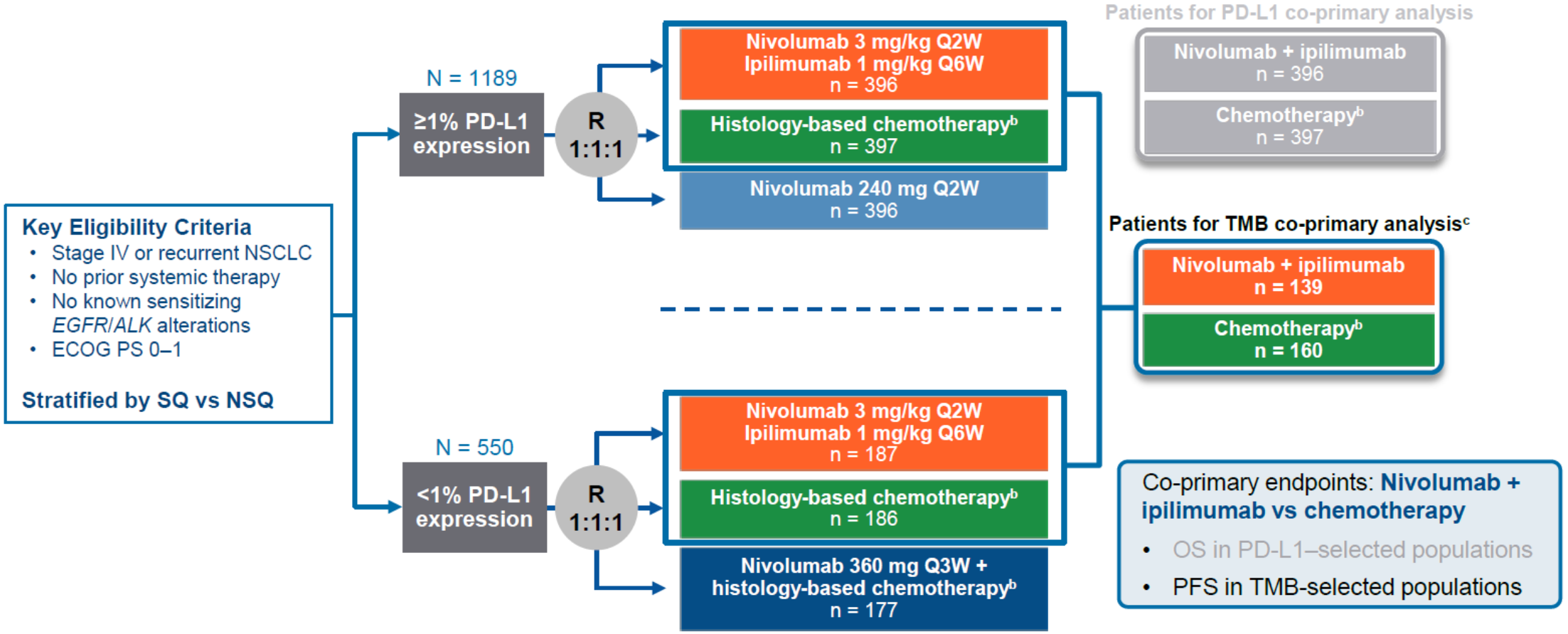




***Partial or stable response lasting > 6 mo**

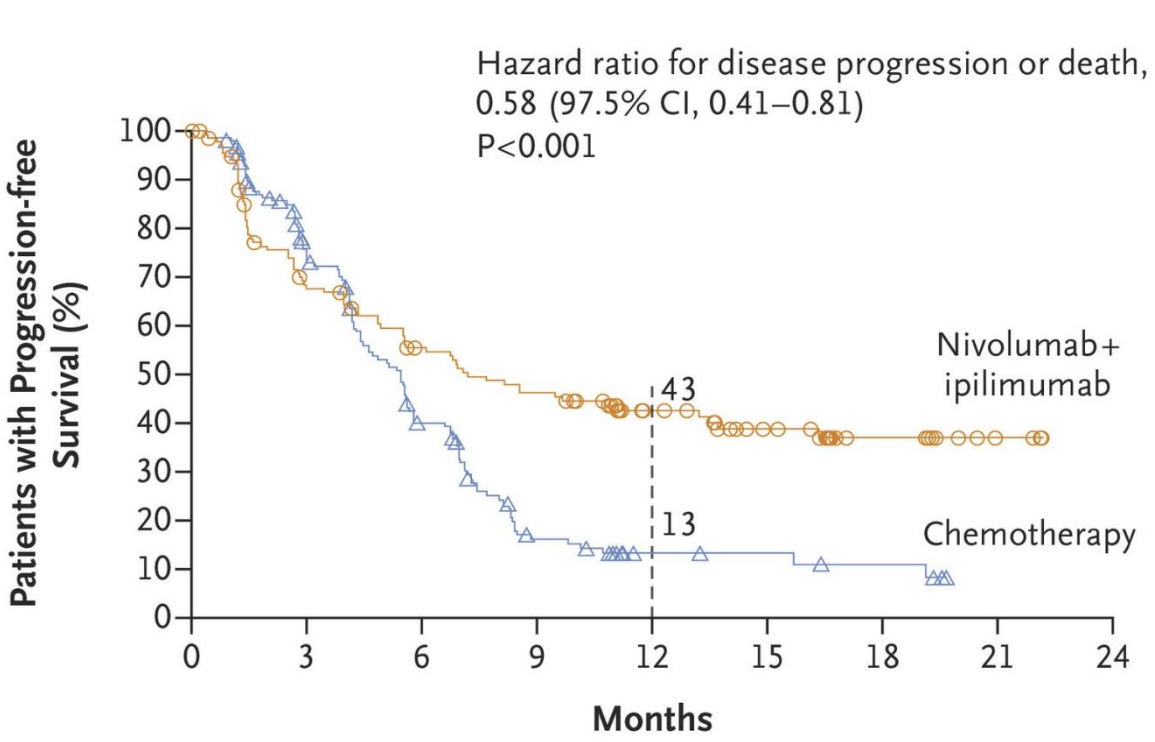
Rizvi N et al, Science, 2015

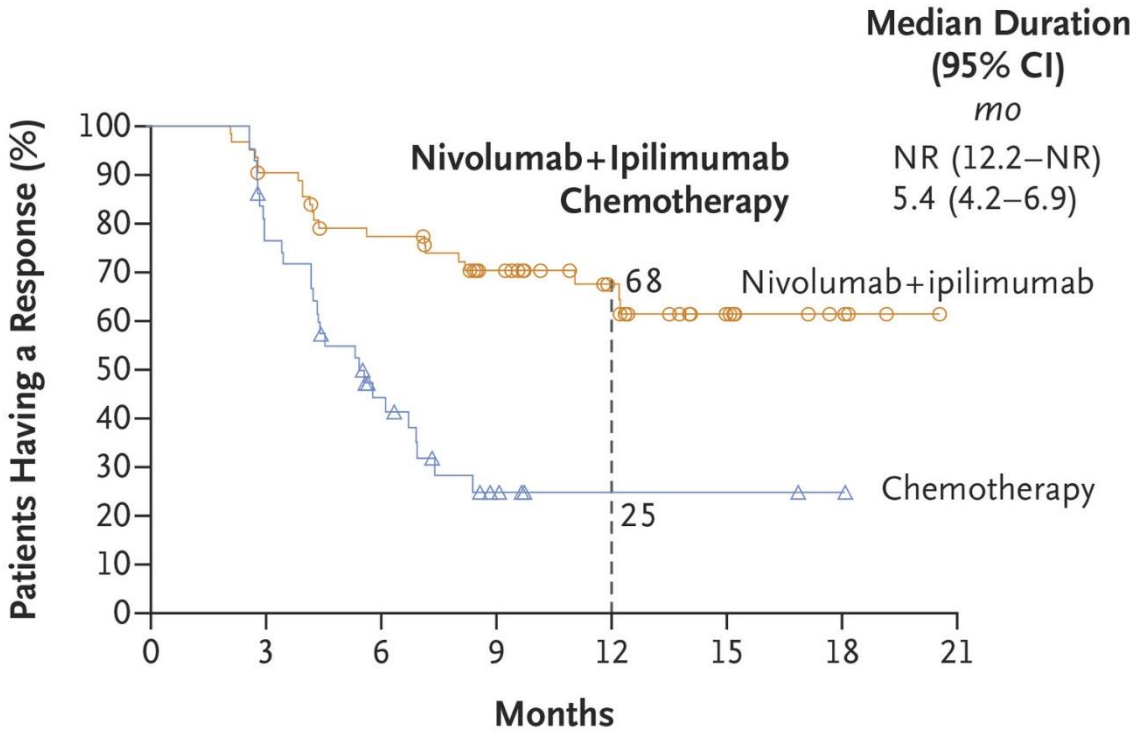
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients



Hellman et al, NEJM, 2018

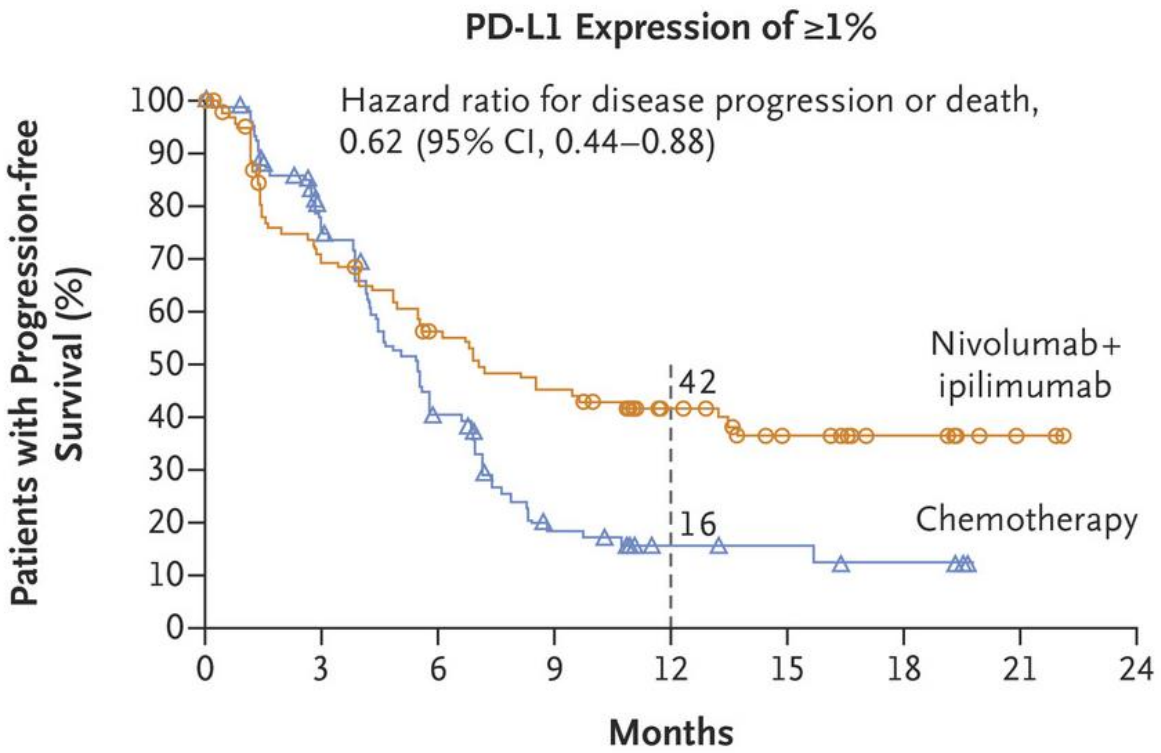
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

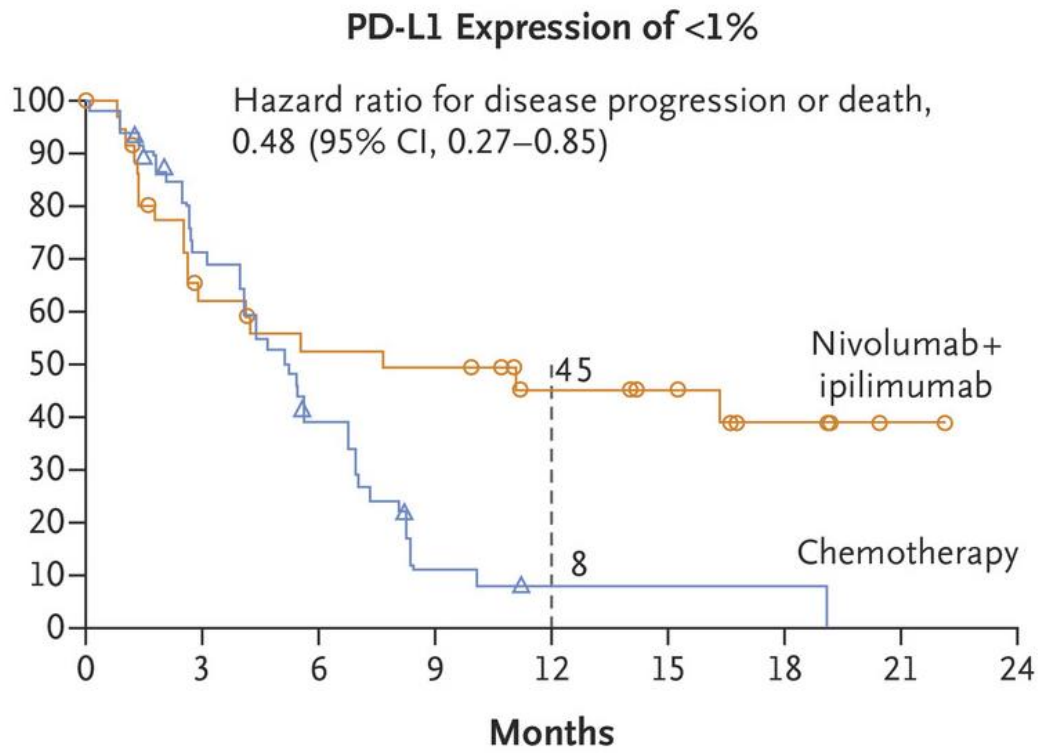




Hellman et al, NEJM, 2018

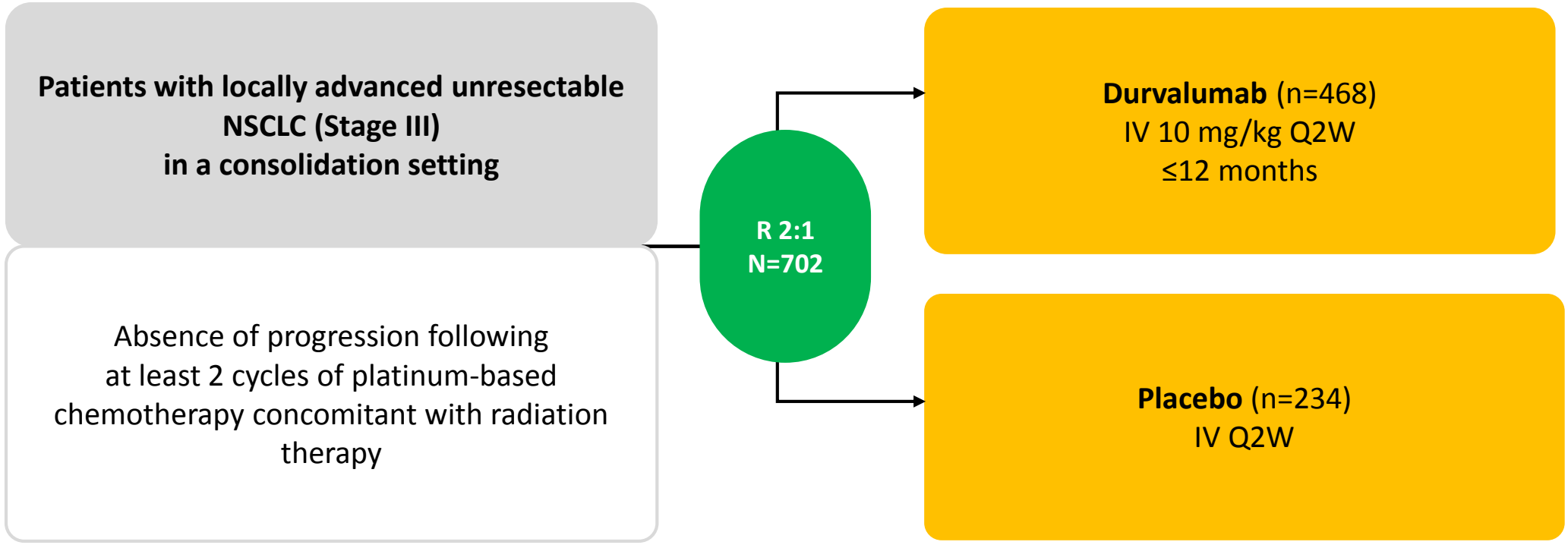
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients





Hellman et al, NEJM, 2018

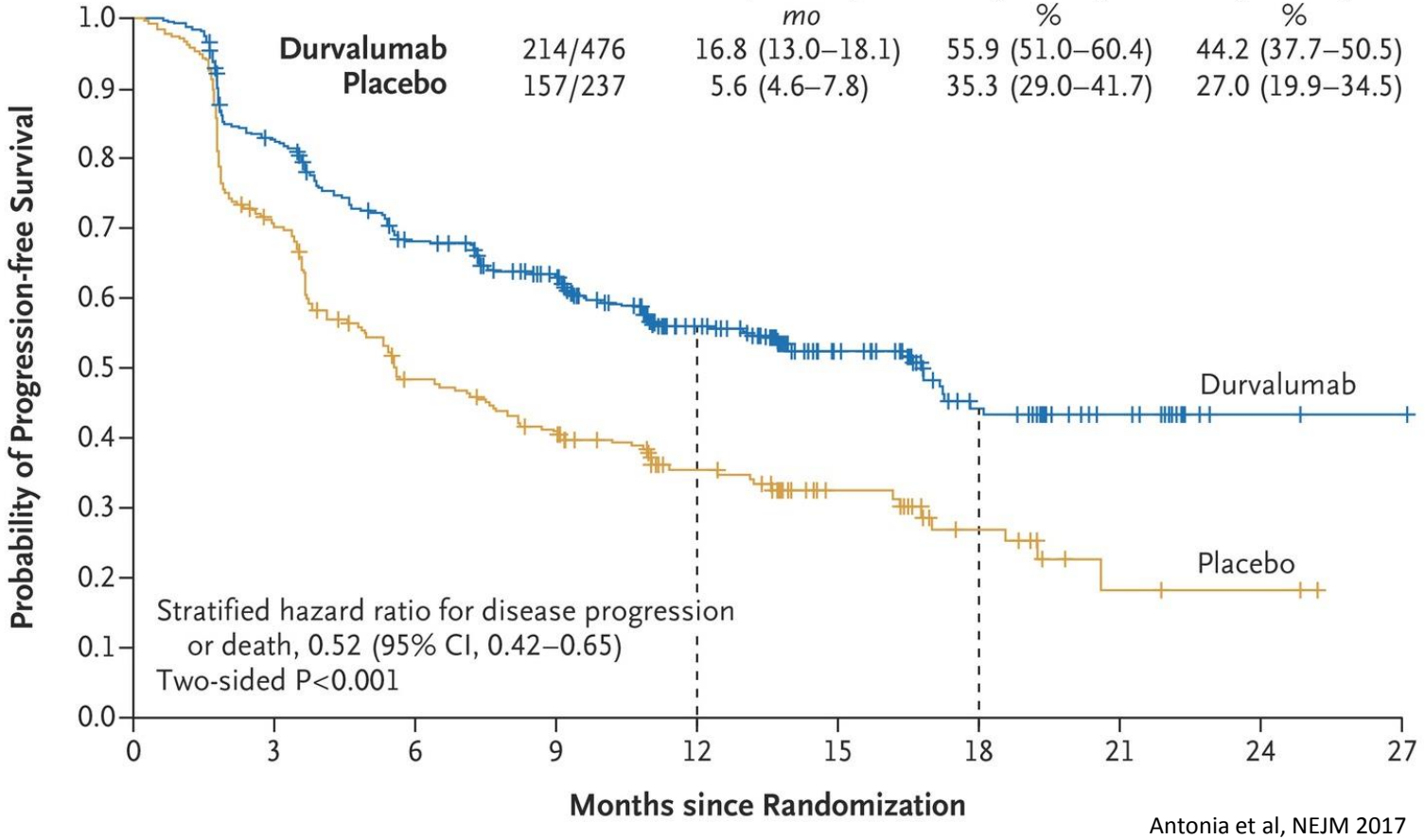
PACIFIC (NCT02125461): Durvalumab after Chemoradiotherapy in Stage III NSCLC



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

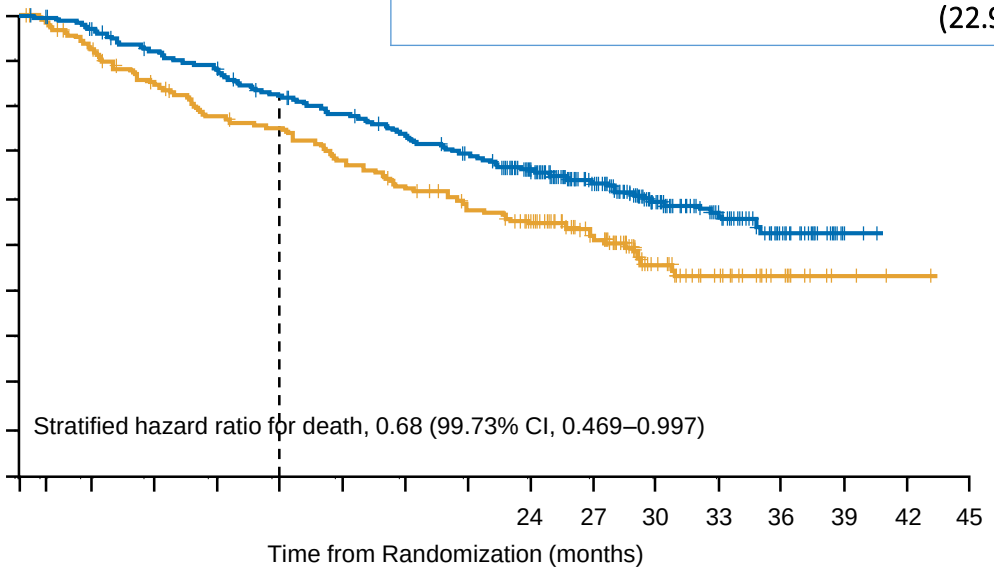
	No. of Events/ Total No. of Patients	Median PFS (95% CI)	12-Mo PFS (95% CI)	18-Mo PFS (95% CI)
		mo	%	%
Durvalumab	214/476	16.8 (13.0–18.1)	55.9 (51.0–60.4)	44.2 (37.7–50.5)
Placebo	157/237	5.6 (4.6–7.8)	35.3 (29.0–41.7)	27.0 (19.9–34.5)



Antonia et al, NEJM 2017

PACIFIC: Overall Survival* (ITT)

	No. of events / No. of patients	Median OS (95% CI) months	12-mo OS (95% CI) %	24-mo OS (95% CI) %
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)



No. at Risk																
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

*

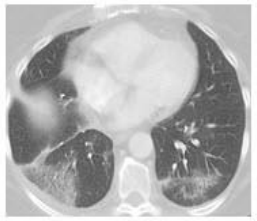
Antonia S et al, N Eng J Med, September 2018

Summary of Frontline Strategies in Advanced NSCLC

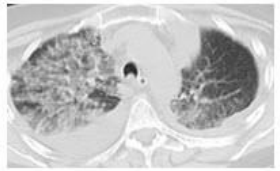
Clinical Trial	Drug	PFS (Months)	OS (Months)	PFS HR in PD-L1 neg	Toxicities Grade 3 - 5
KEYNOTE-024 PD-L1 ≥ 50%	Pembro	10.3	30	NA	31% vs 53%
	Plat/Pem or Gem or Pacli	6	14.2		
KEYNOTE-042 PD-L1 ≥ 1%	Pembro	5.4	16.7	NA	18% vs 41%
	Plat/Pem or Pacli	6.5	12.1		
IMpower150 Non-squamous	Atezo + Beva + Carbo/Pacli	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.*

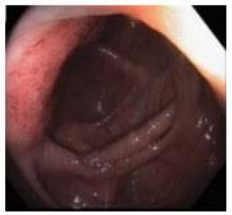
Immune Related AEs



Endocrine
Thyroiditis
Hypothyroidsim
Hyperthyroidism
Hypophysitis
Hypopituitarism
Adrenal Insufficiency

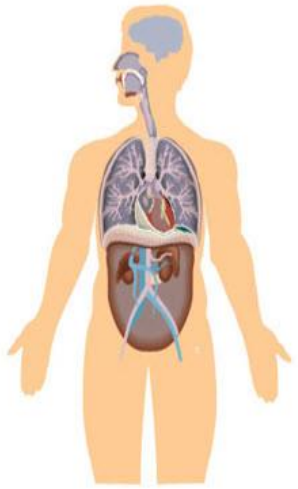


Pulmonary
Pneumonitis
Respiratory failure

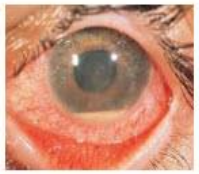


Gastrointestinal
Nausea, Emesis
Diarrhea, Colitis,
Perforation;
Pancreatitis

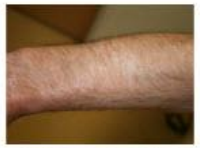
Neurologic
Neuropathy
Meningitis
Guillane-Barre Syndrome



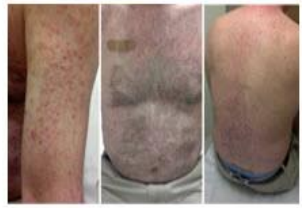
Ocular
Iritis
Uveitis
Conjunctivitis



Cardiac
Pericarditis

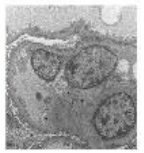


Dermatologic
Mucositis
Rash, Vitaligo



Hepatic
Transaminitis
Hepatitis

Renal
Nephritis
Renal Insufficiency



Cause of these toxicities - T cell infiltration, cytokines, auto-antibodies

Postow NEJM 2017

Common AEs in PD-(L)-1 Directed Agents*

Toxicities	Any Grade (%)	Grade 3-4 (%)
Fatigue	16-20	1
Decreased Appetite	10-14	1
Nausea	12	1
Rash	9-13	1
Diarrhea	8	1
Hypothyroidism	8-11	1
Pneumonitis	2-5	2

Hyperthyroidism, Myocarditis, Adrenal insufficiency, Myositis, Type I diabetes, Hepatitis

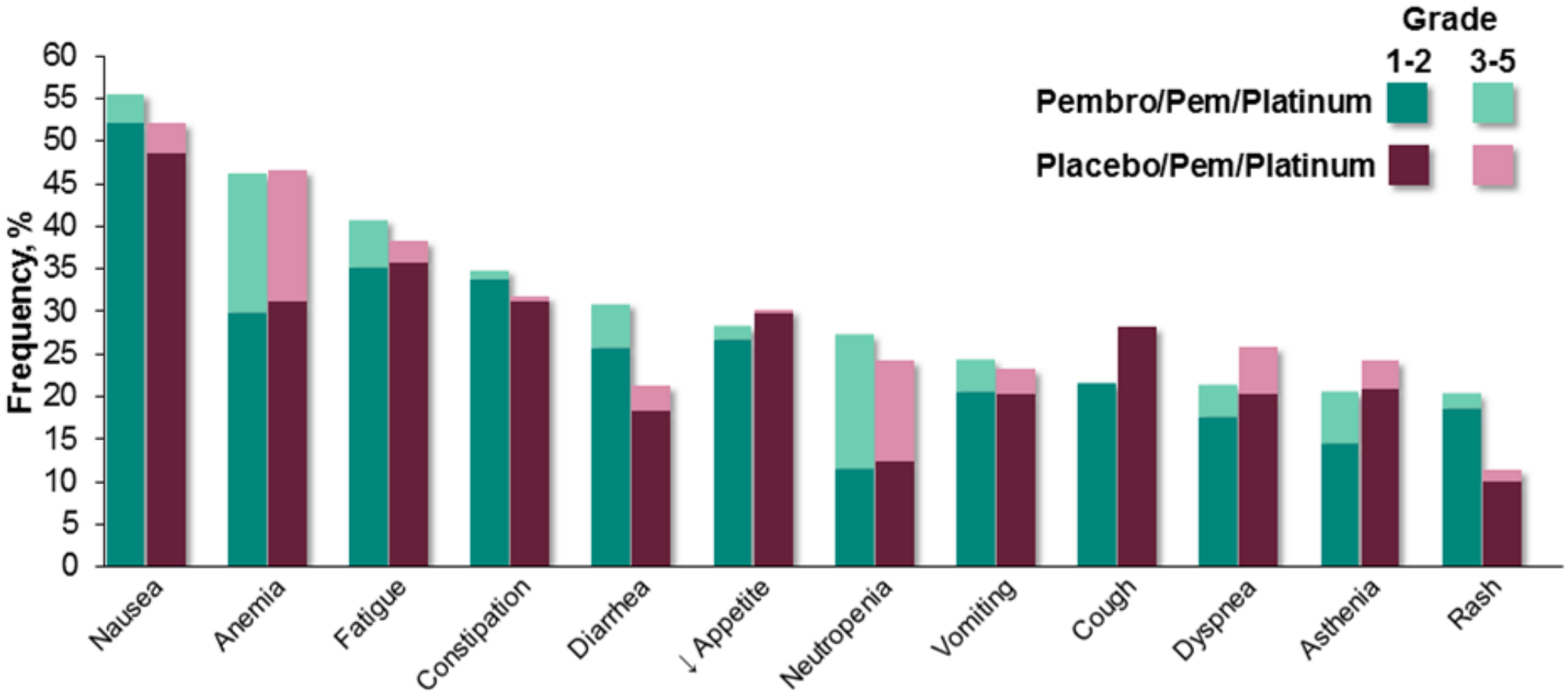
*Reviewed data from Checkmate 057, Keynote 10 and OAK

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%

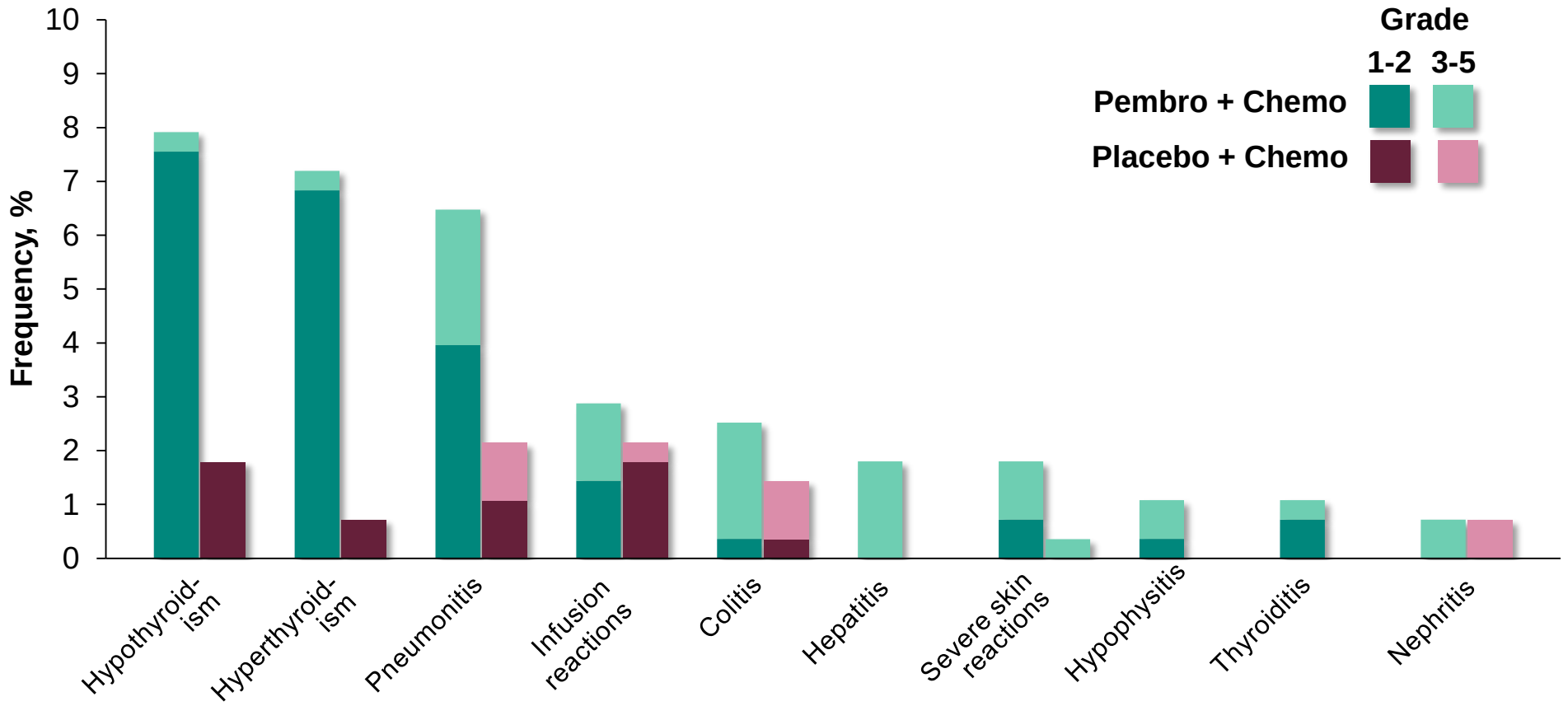
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

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



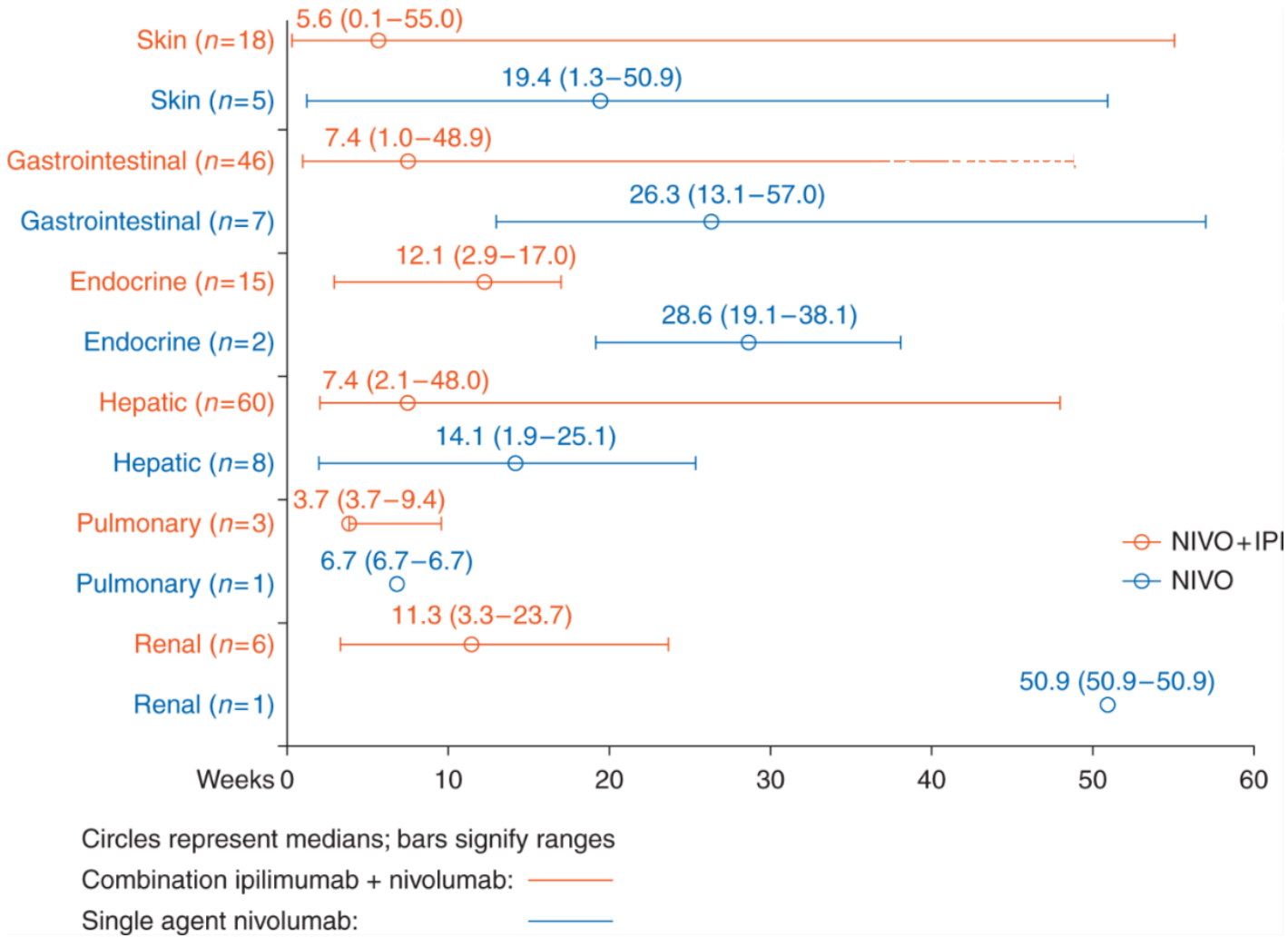
Paz-Arez et al, ASCO, 2018

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

Onset of Grade 3/4 Immune Related AEs



Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
Ann Oncol. 2017

Guidelines- Management

- irAEs higher with CTLA4 (exceptions- hypothyroidism, type I DM)
- Grade 1- symptomatic management, continue ICI
- Grade 2- Steroids 0.5-1.0mg prednisone, hold ICI, restart once grade 1 and prednisone at 10mg daily.
- Grade 3- Steroids 1-2mg prednisone, Infliximab. Steroid taper over 4-6 weeks. May restart PD-(L)-1 drugs with high level of caution.
- Grade 4- Steroids 1-2mg prednisone, Infliximab, other immunosuppressants, discontinue ICI (exception: endocrinopathies)

Brahmer, et al J Clin Oncol 2018, ASCO/NCCN guidelines on irAEs

Case Study: 1

- **Background**
  - 54 year-old female, former smoker
  - Left lung mass and malignant pleural effusion
  - Biopsy shows:
    - Adenocarcinoma
    - KRAS mutation and TP53
    - PD-L1 is 20% positive (22C3 assay)
- **What do you recommend?**
  1. Pembrolizumab
  2. Pembrolizumab + Carboplatin/Pemetrexed
  3. Carboplatin/Pemetrexed
  4. Atezolizumab + Carboplatin/Paclitaxel/Bevacizumab

- **Follow-up**
  - Patient does well
  - CT shows a response to treatment
  - She has been monitored closely and she has not had any significant side effects
  - 2 weeks after an office visit the patient comes in with facial swelling, hoarsness, and increased fatigue.
- **What do you recommend?**
  1. Stat CT scan of the chest
  2. Empiric treatment with diuretics and steroids
  3. TSH
  4. Observation

Case Study: 2

Patient Background

- 70-year-old male with a distant smoking history
- Presents with cough, mild dyspnea and mid thoracic pain
- CT imaging reveals bilateral disease, left pleural effusion and a lytic lesion at T4
- Thoracic spine MRI shows slight epidural compression at T4
- Biopsy consistent with adenocarcinoma
- Patient started on radiation to T4
- Molecular studies come back while he is getting radiation
  - EGFR Exon 18 G719C point mutation
  - PD-L1 80% (22C3 assay)

What is your management recommendation on completion of the radiation?

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