Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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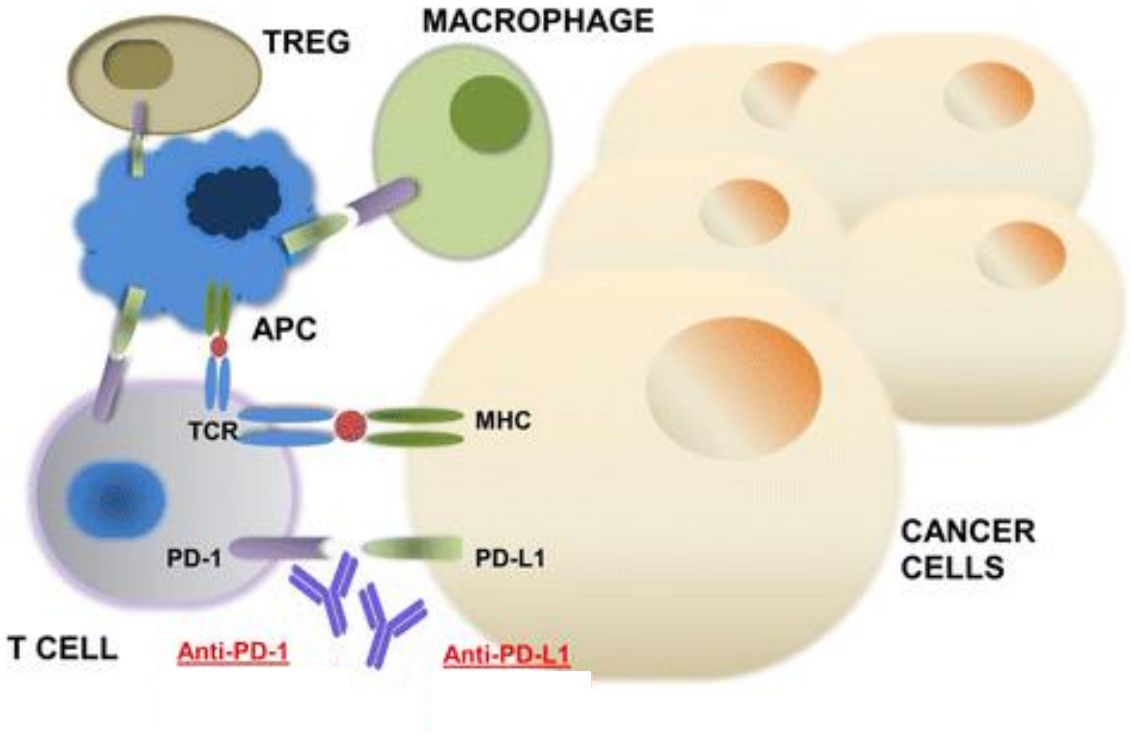
Disclosures

- Disclosures:
  - Advisory board/honorarium: Astrazeneca, Bristol-myers squibb, Pfizer, Merck, and Novartis
- I will be discussing non-Health Canada approved indications during my presentation.

Immunotherapy for the Treatment of Lung Cancer

Checkpoint Inhibitors: PD-1 and PD-L1

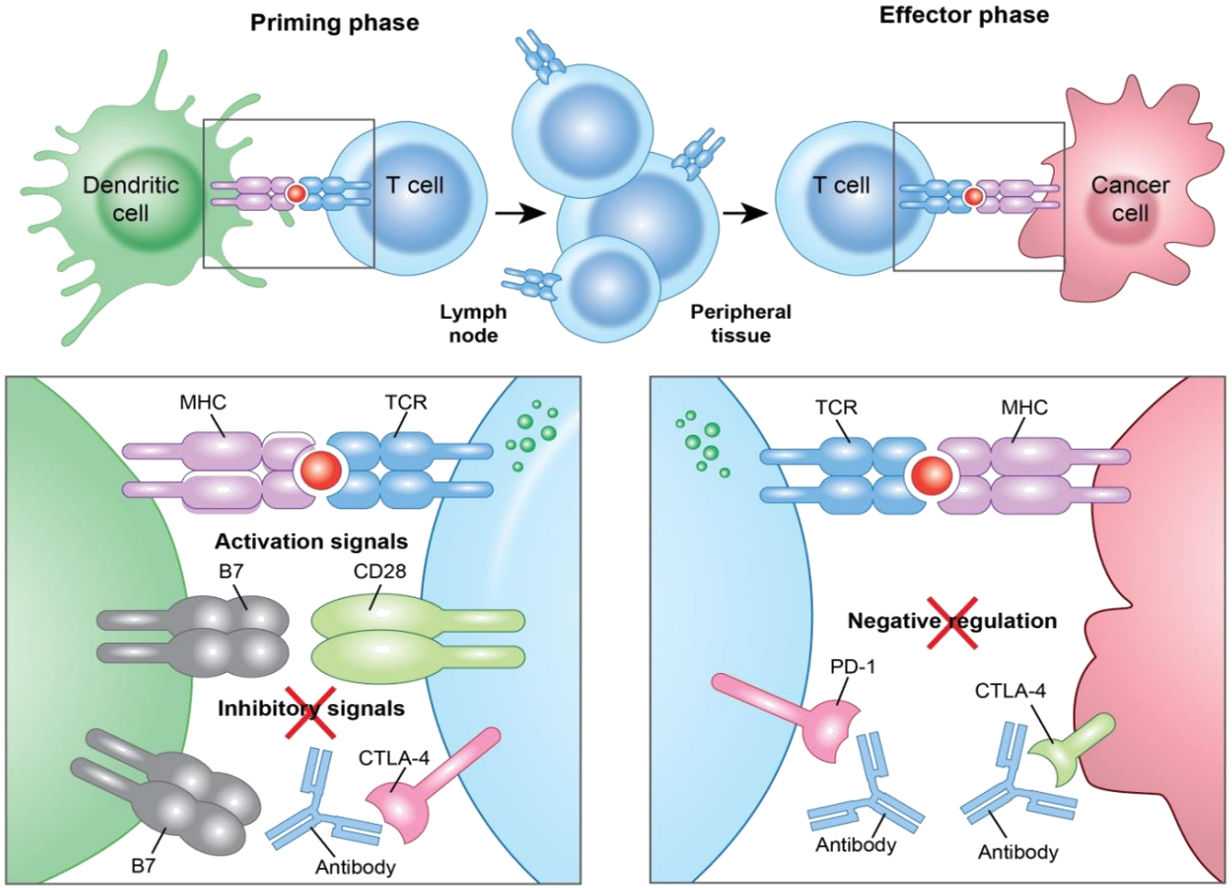
- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells



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

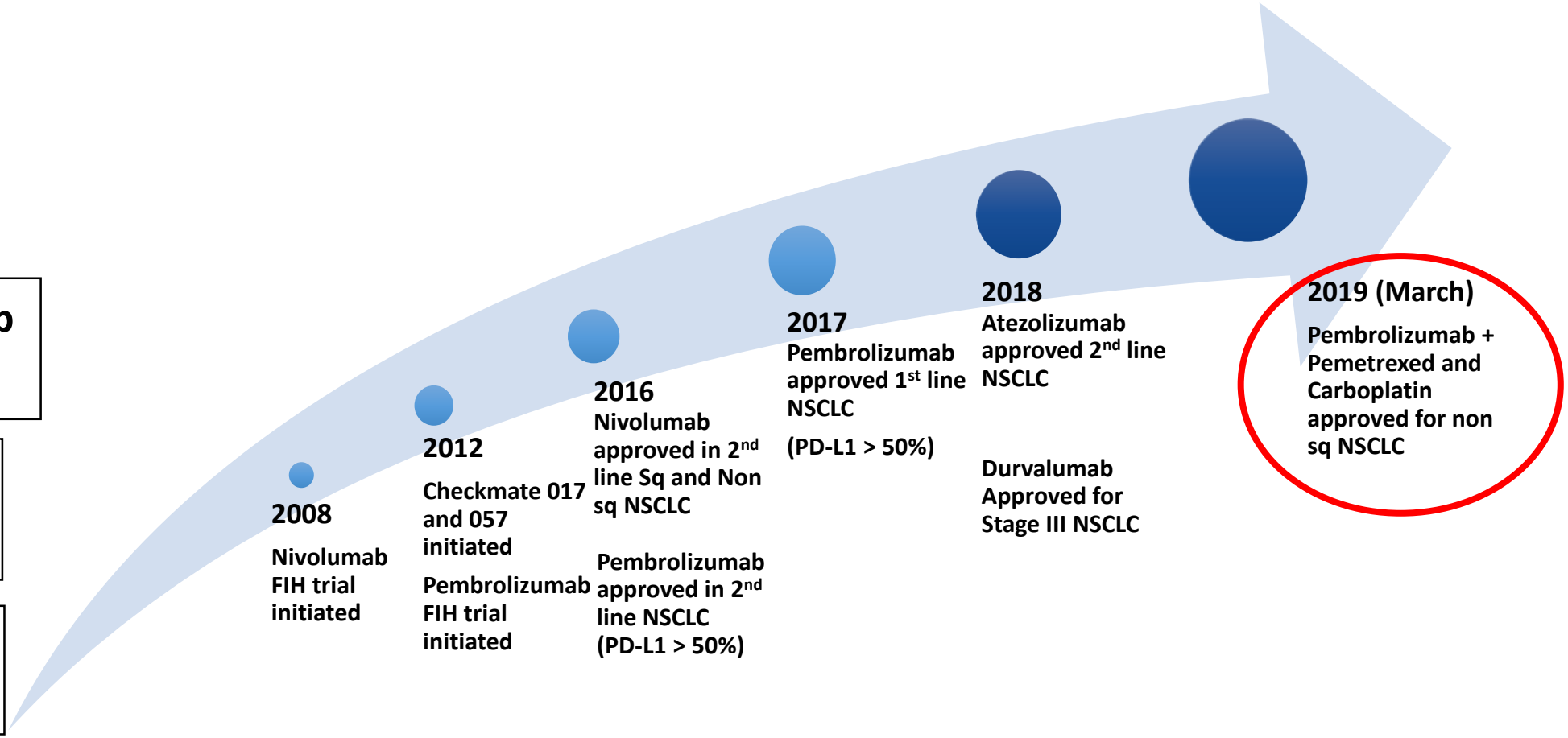
Health Canada -approved Checkpoint Inhibitors in NSCLC

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

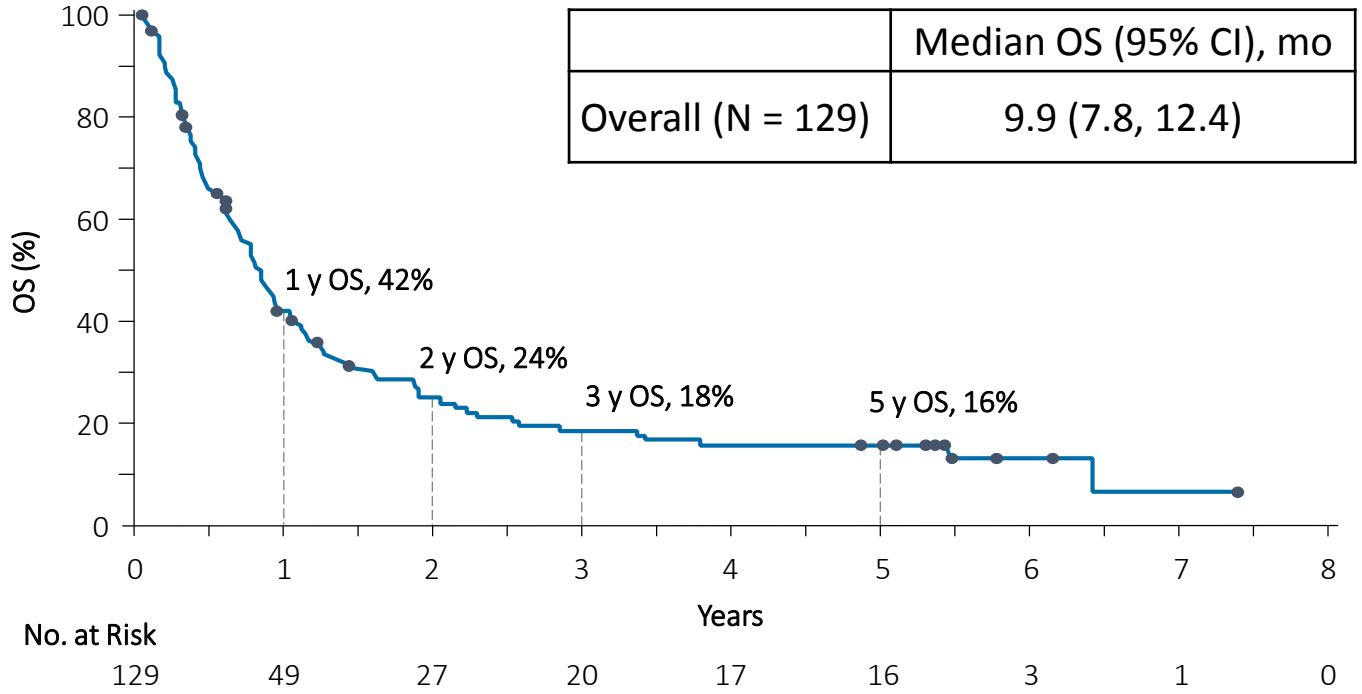


CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

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)

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

Treatment Naïve Regimens: Competing Strategies

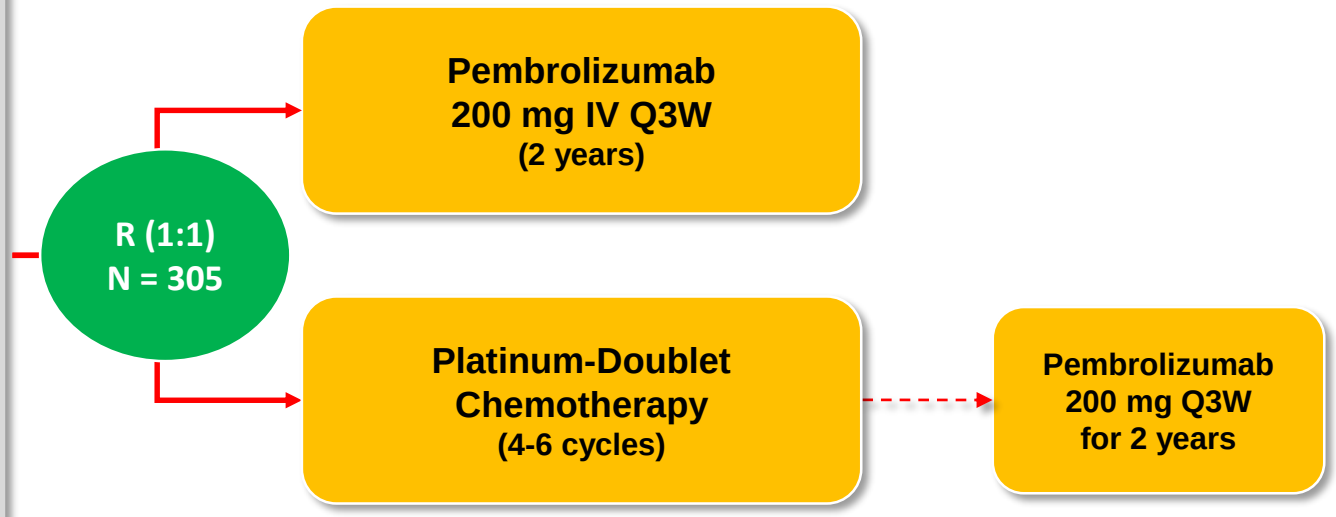
- KEYNOTE 024 – Pembrolizumab vs. Chemotherapy in PD-L1 > 50%
- KEYNOTE 042 – Pembrolizumab vs. Chemotherapy in PD-L1 > 1%
- KEYNOTE 189 – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in patients with advanced non-squamous NSCLC
- IMPOWER 150 – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy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

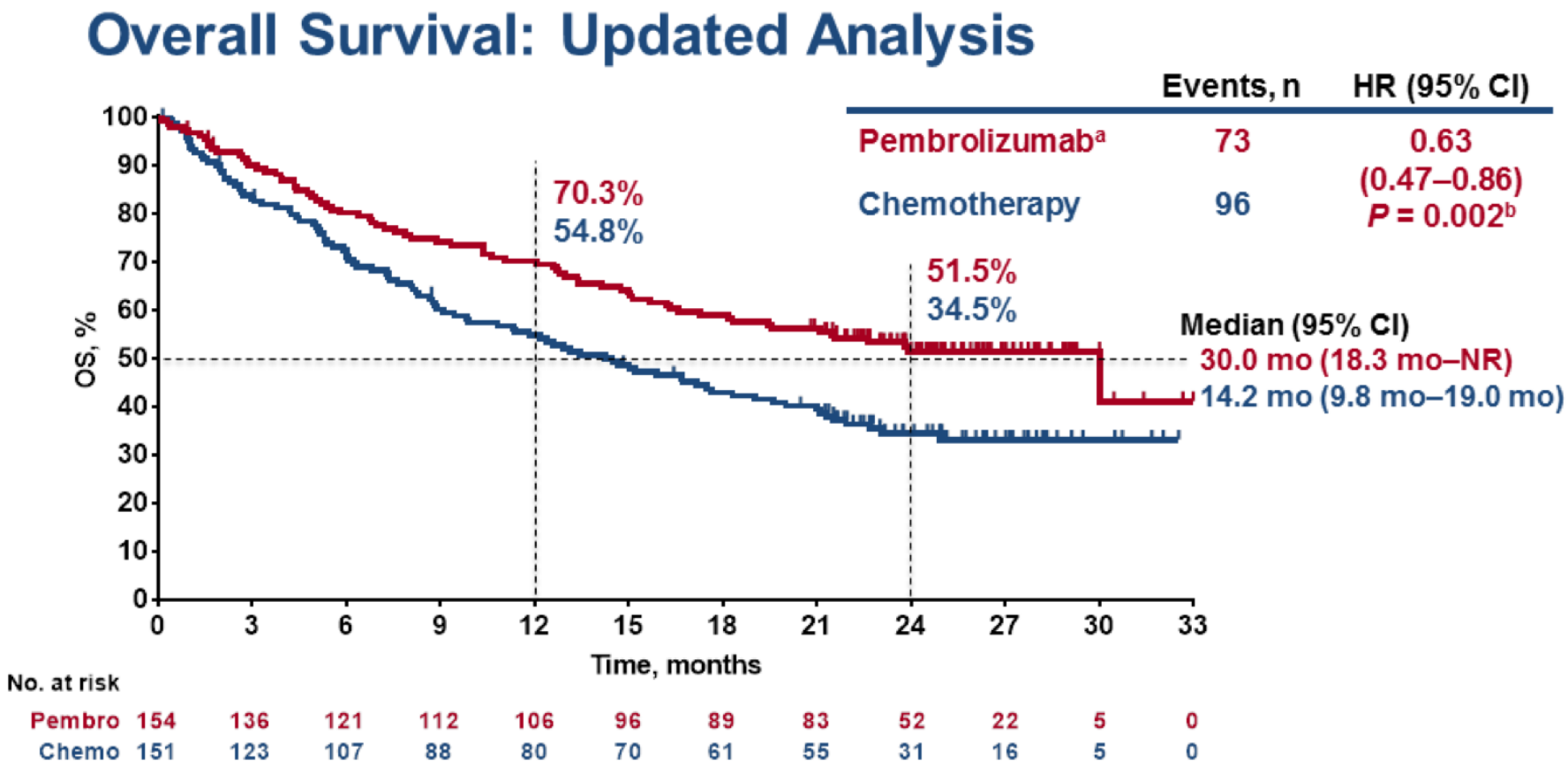
- ***Untreated*** stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



Reck M et al, ESMO 2016, NEJM 2016

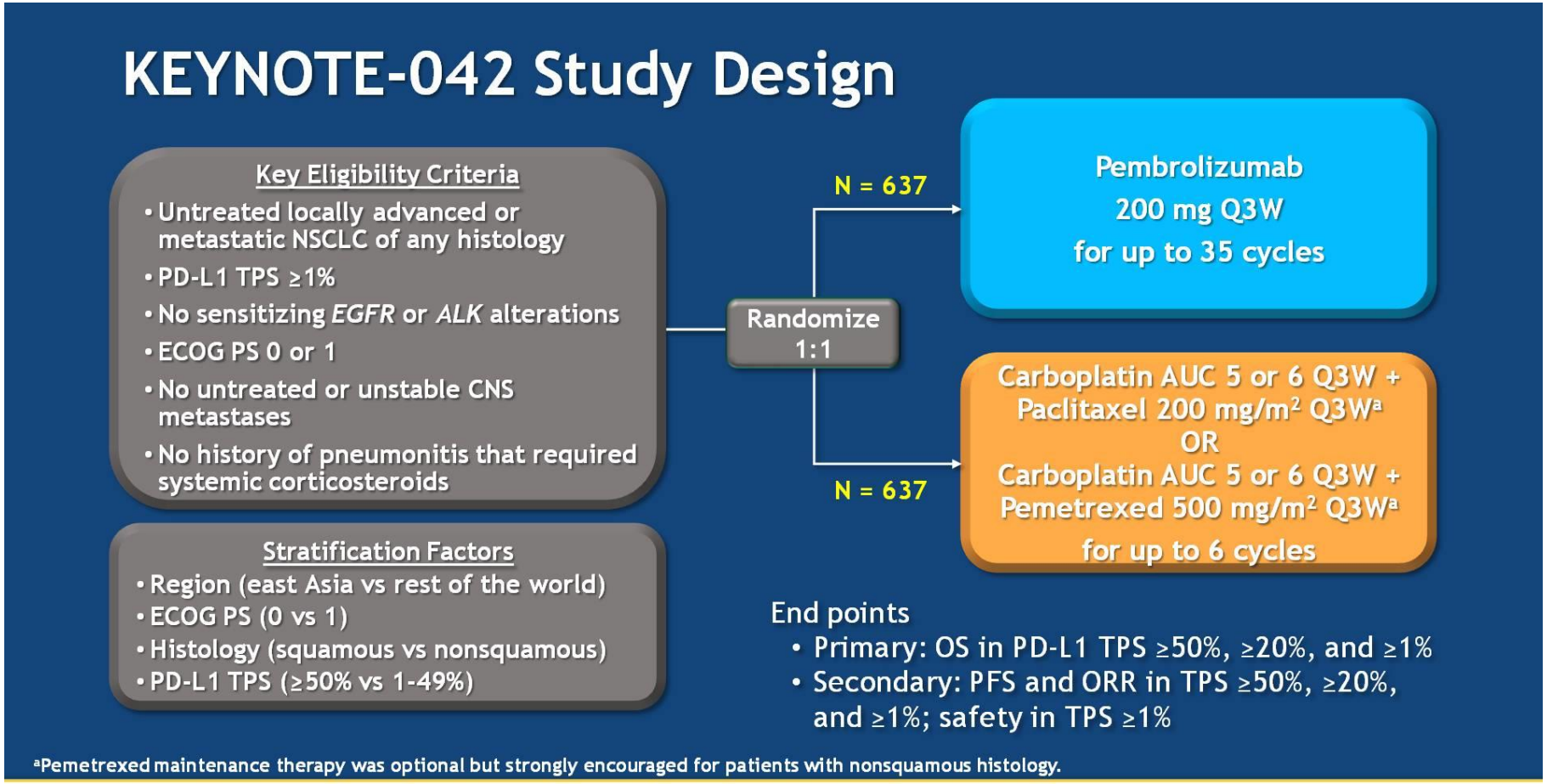
KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 >50% NSCLC

Overall Survival



Brahmer WCLC 2017

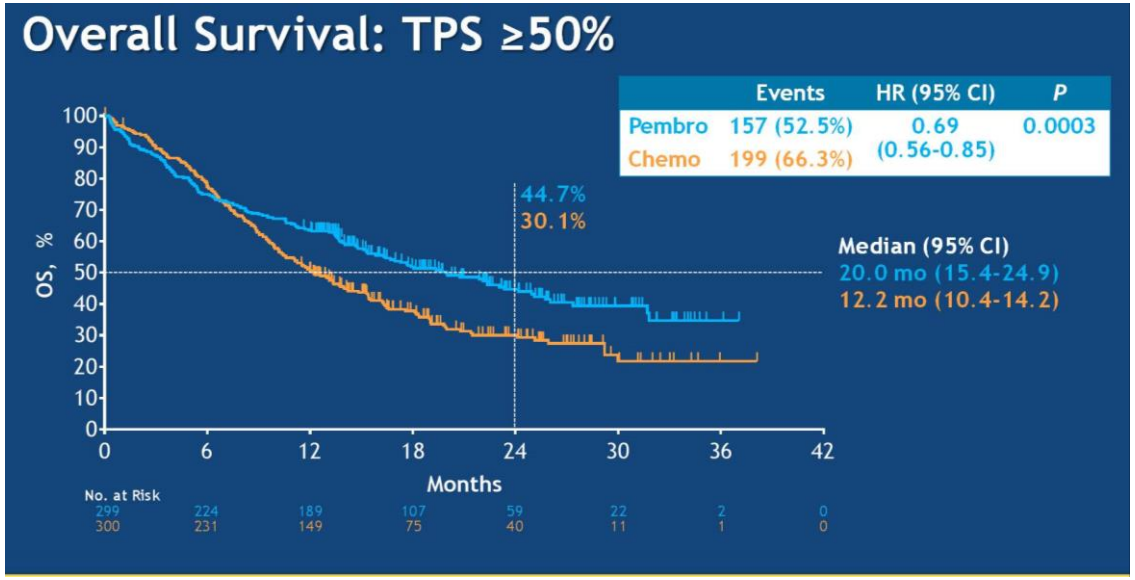
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 > 1% NSCLC

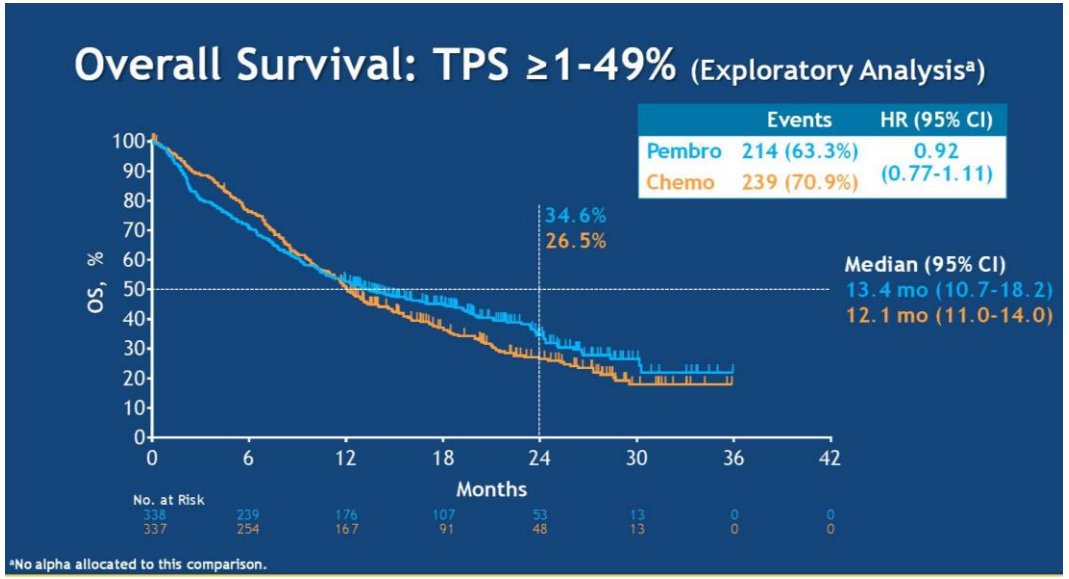


Lopes et al, ASCO 2018

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

Overall Survival

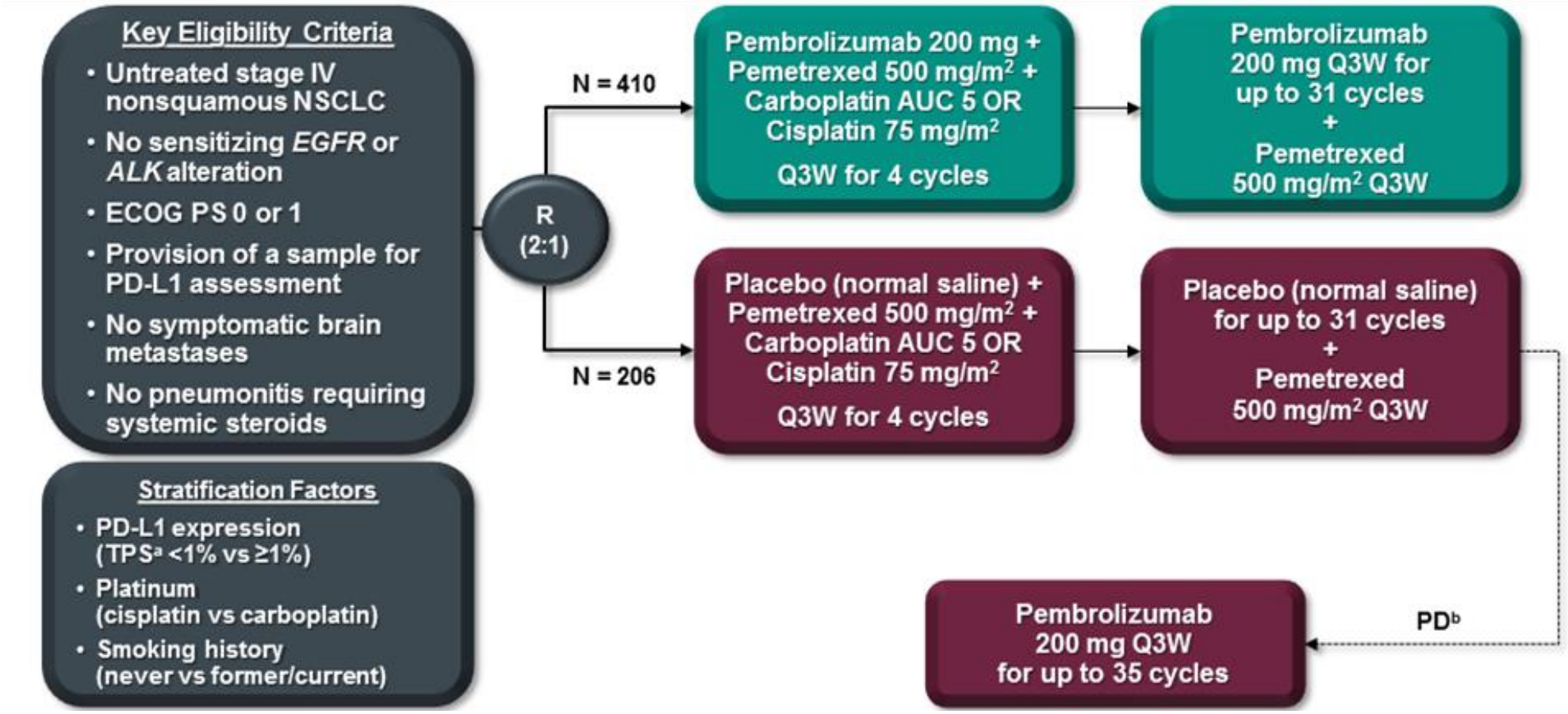




Survival benefit seemed to be driven by the TPS > 50% subset with little benefit witnessed in the subset TPS > 1- 49%

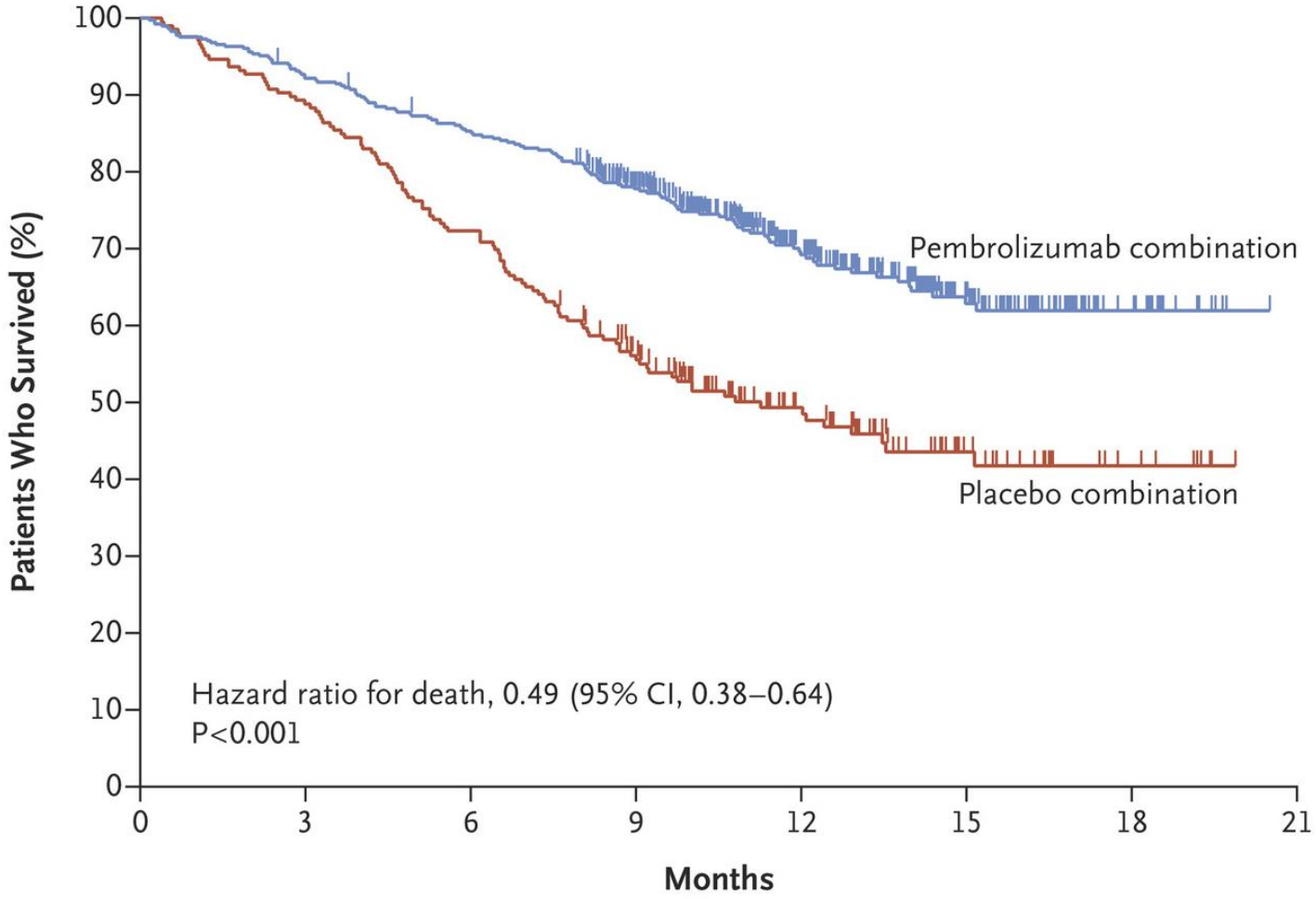
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

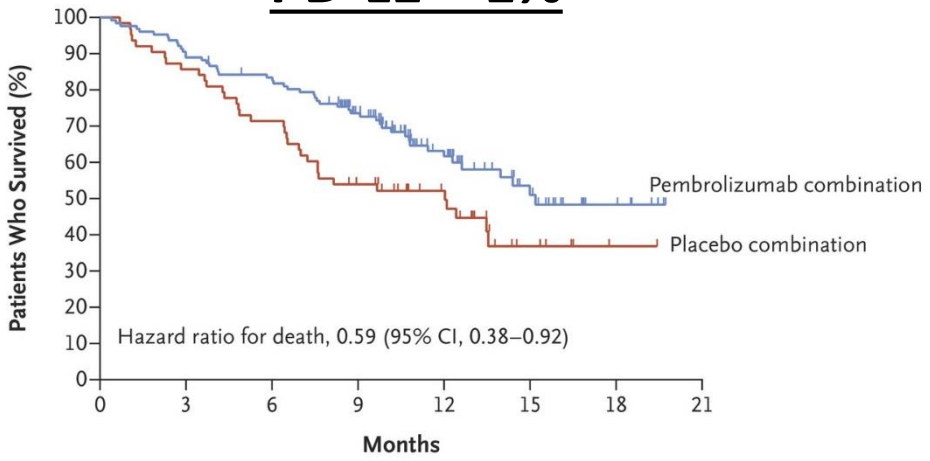
KEYNOTE-189: Pembrolizumab/Carboplatin /Pemetrexed vs Chemotherapy for Advanced Non-squamous NSCLC



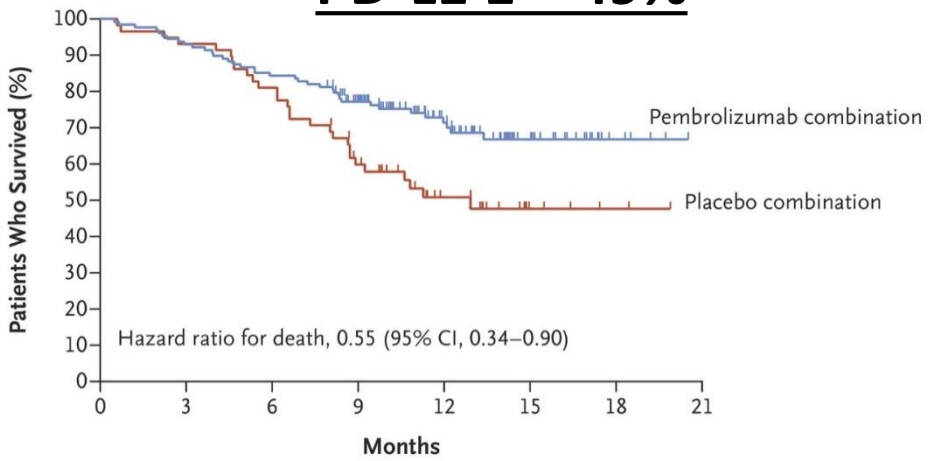
Ghandi et al, NEJM 2018

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

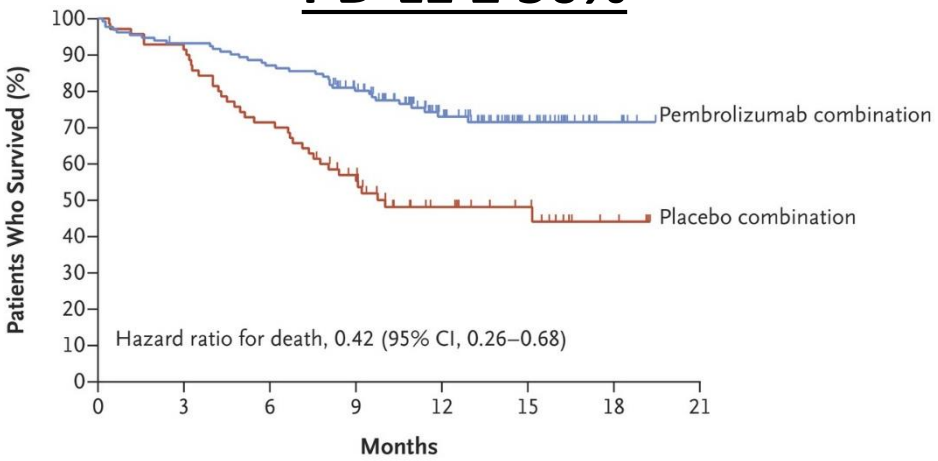
PD-L1 < 1%



PD-L1 1 – 49%

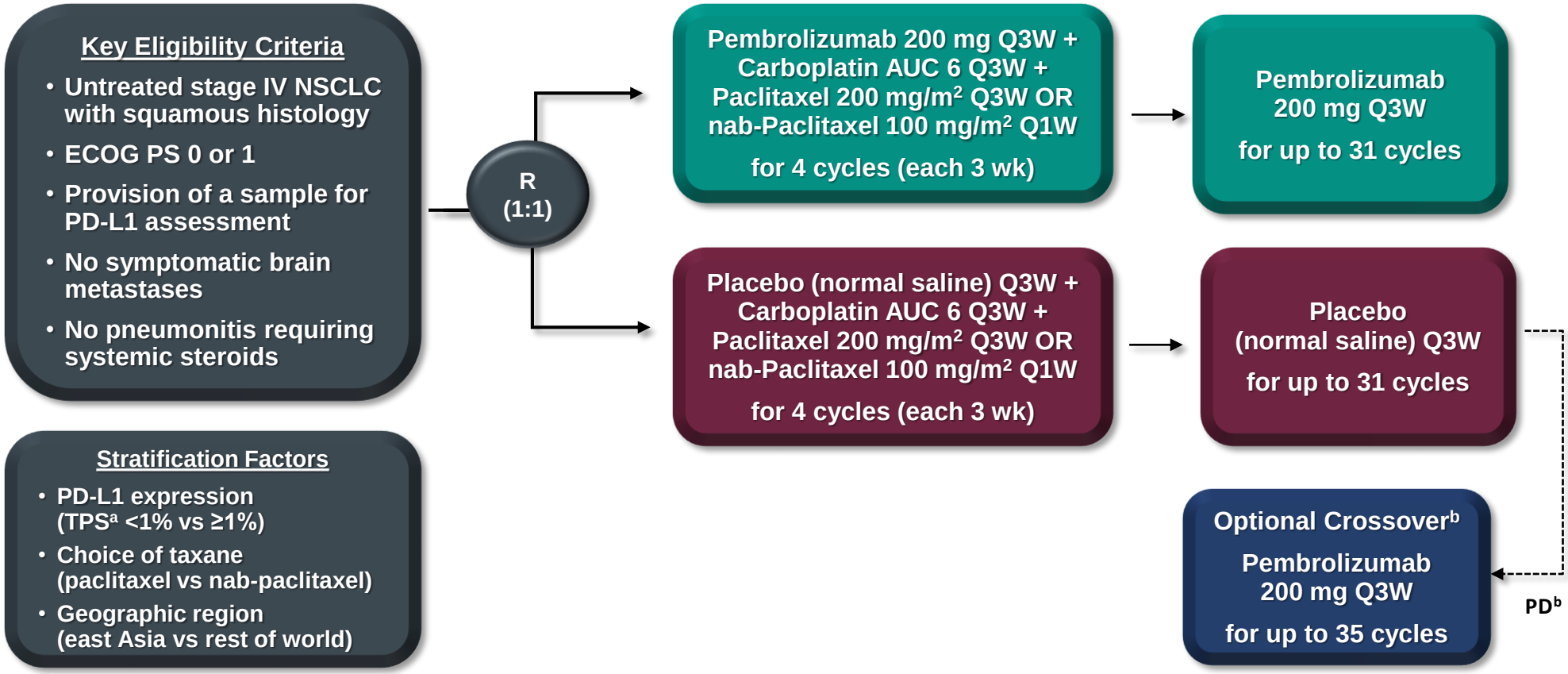


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

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

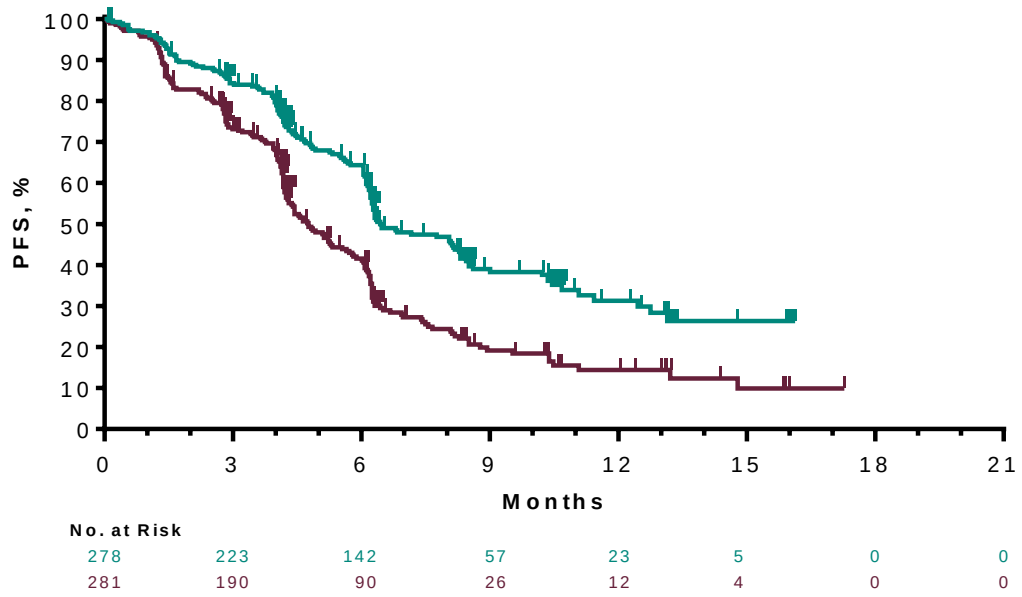


Paz-Ares et al, ASCO 2018

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

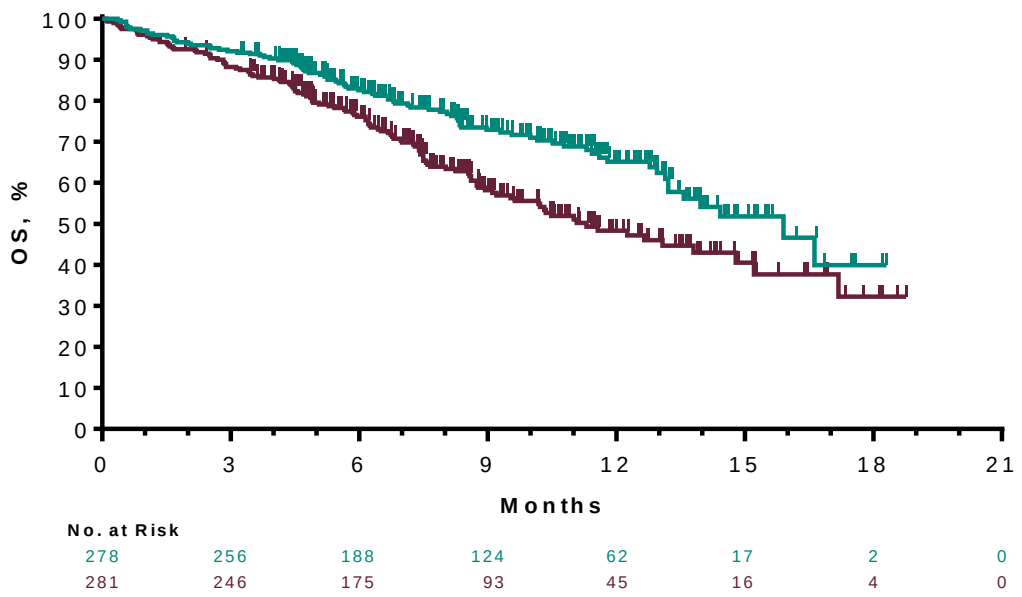
PFS (RECISTv1.1, BICR)

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



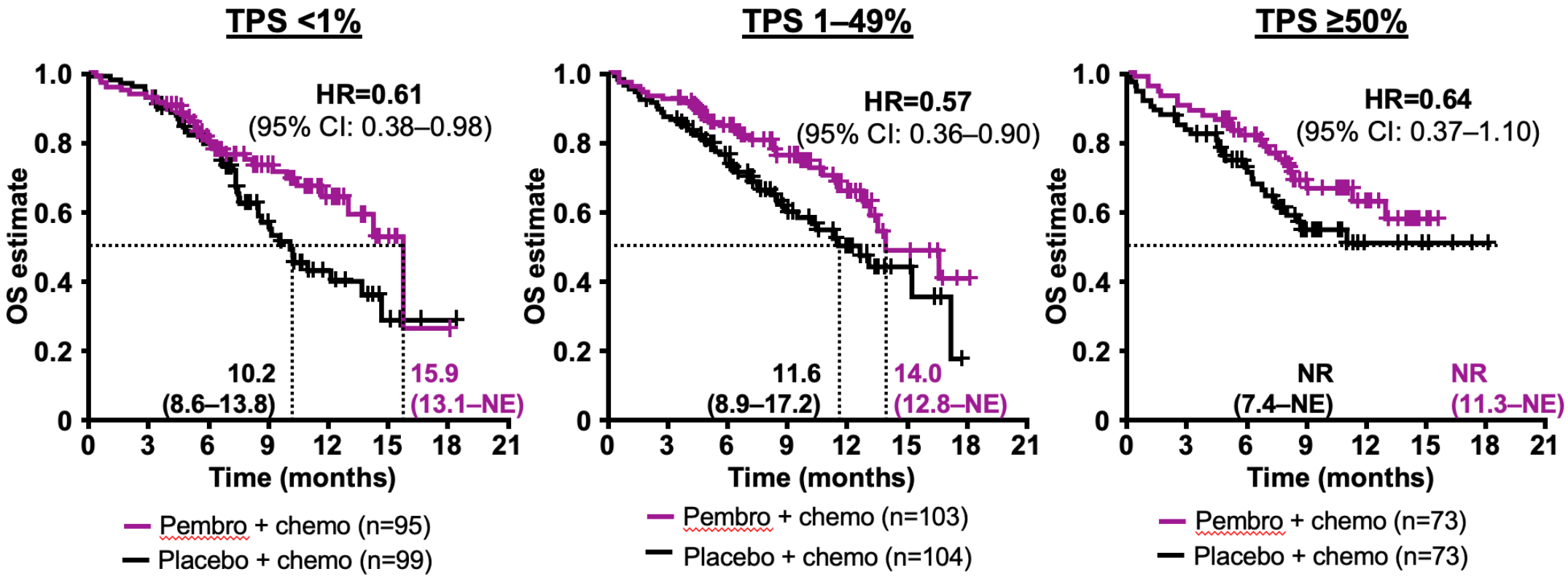
Overall Survival

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

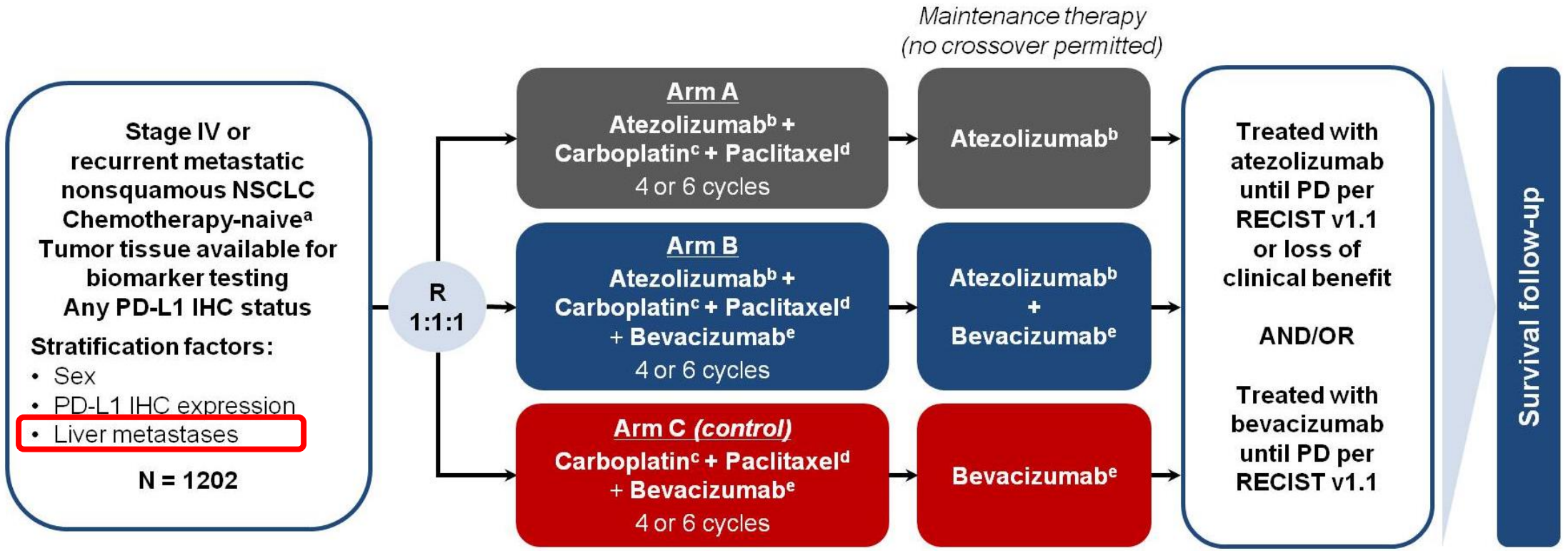


Paz-Ares et al, ASCO 2018

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



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

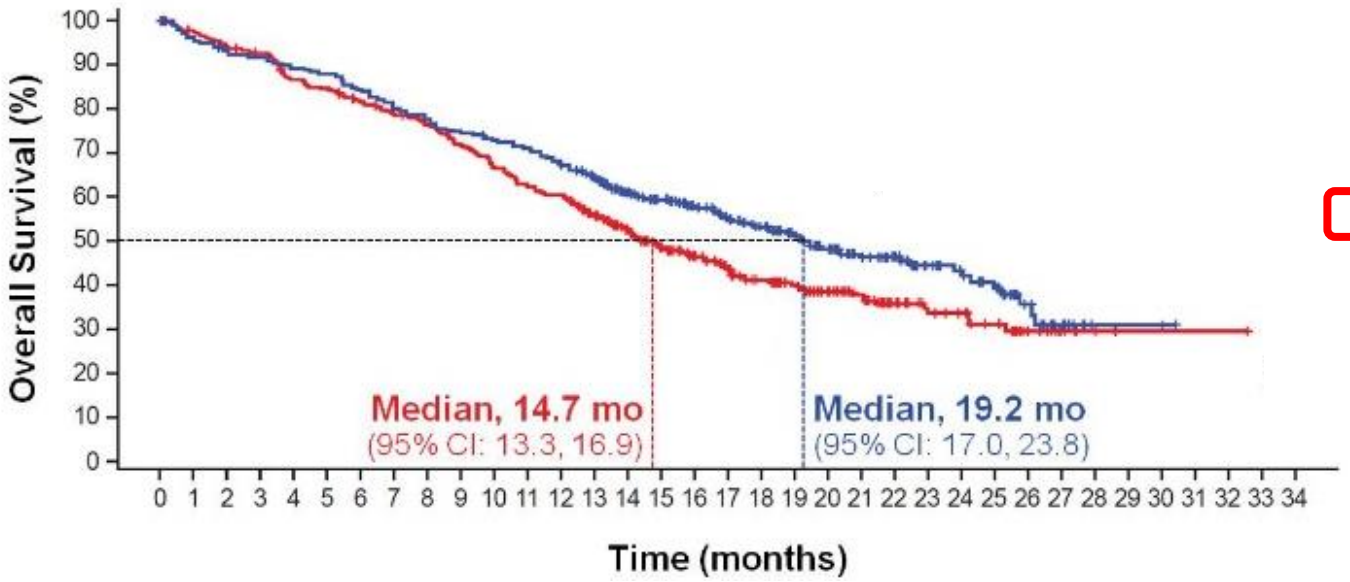


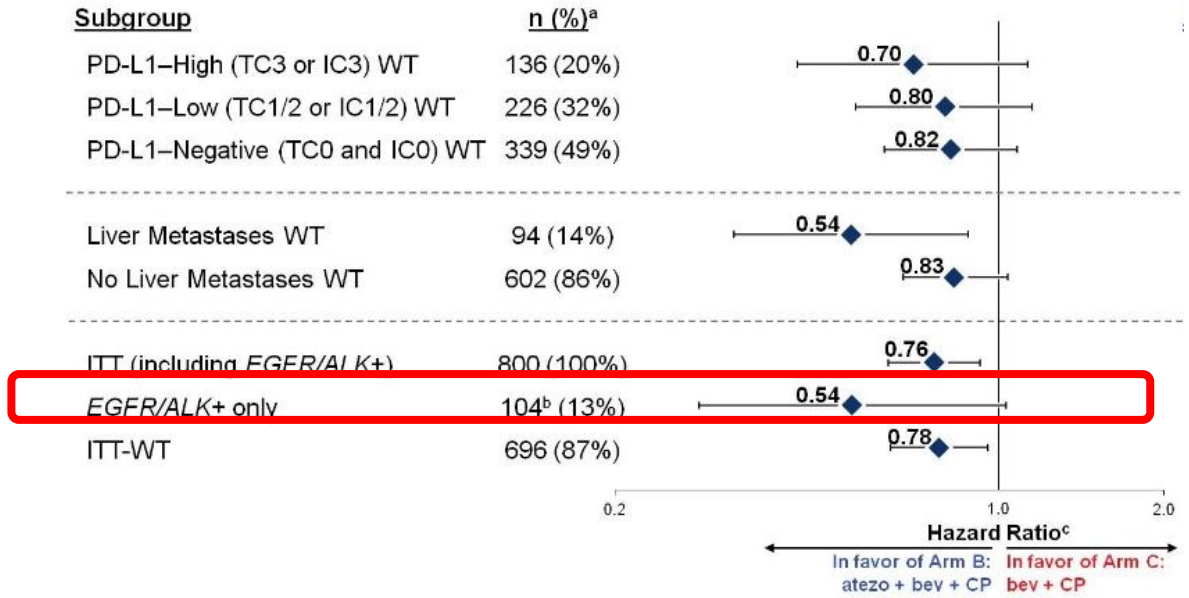
Socinski et al, NEJM 2018

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

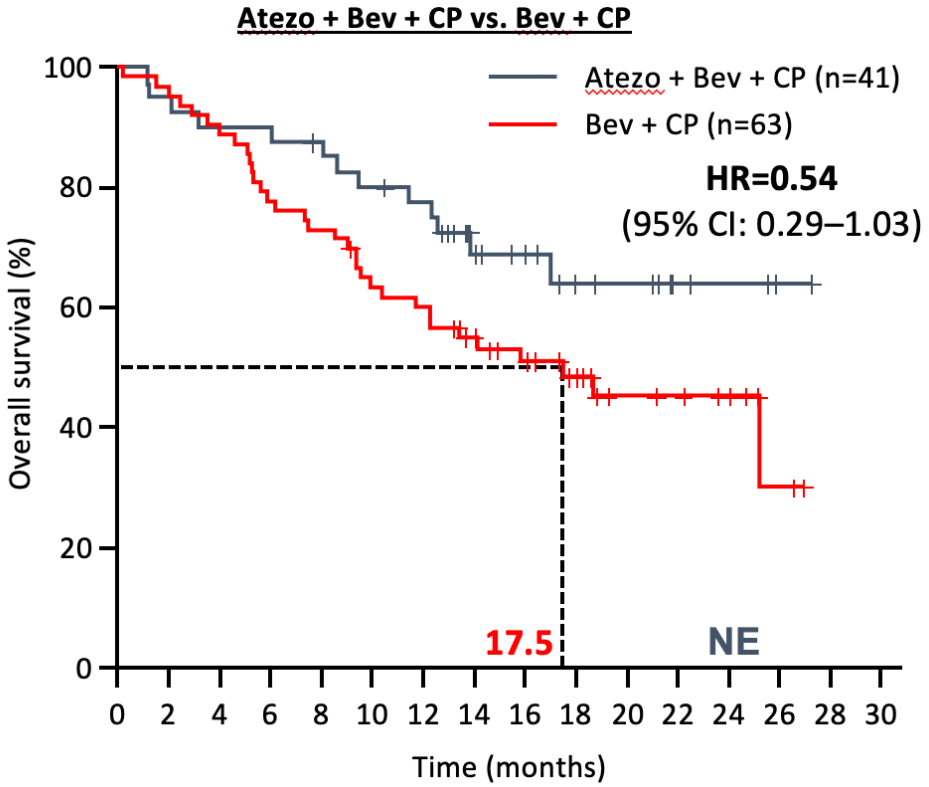




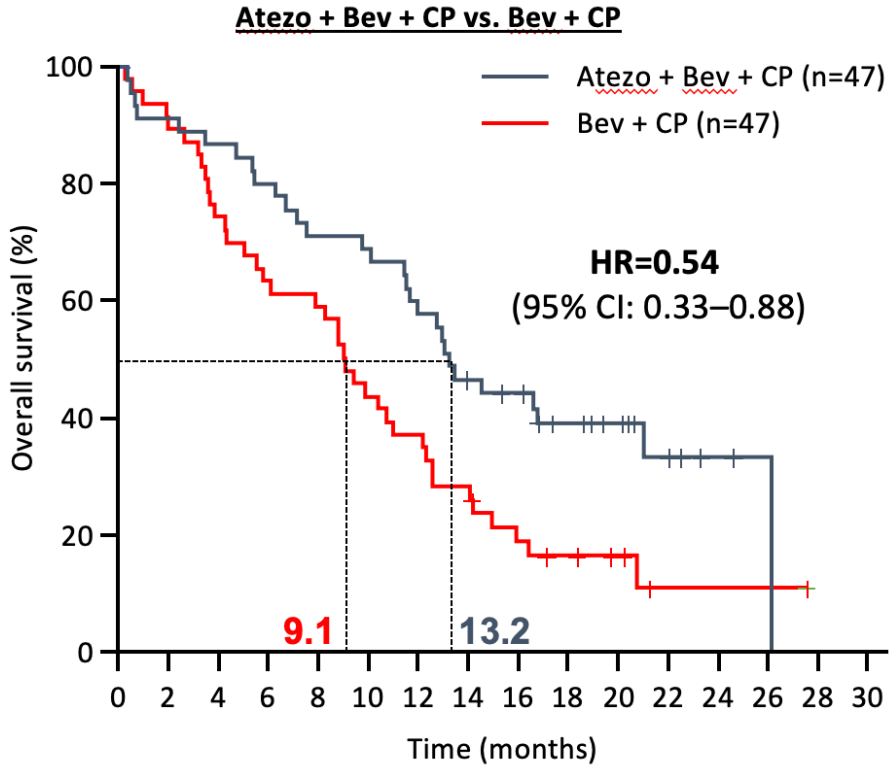
Socinski et al, NEJM 2018

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

EGFR/ALK + after prior targeted therapy

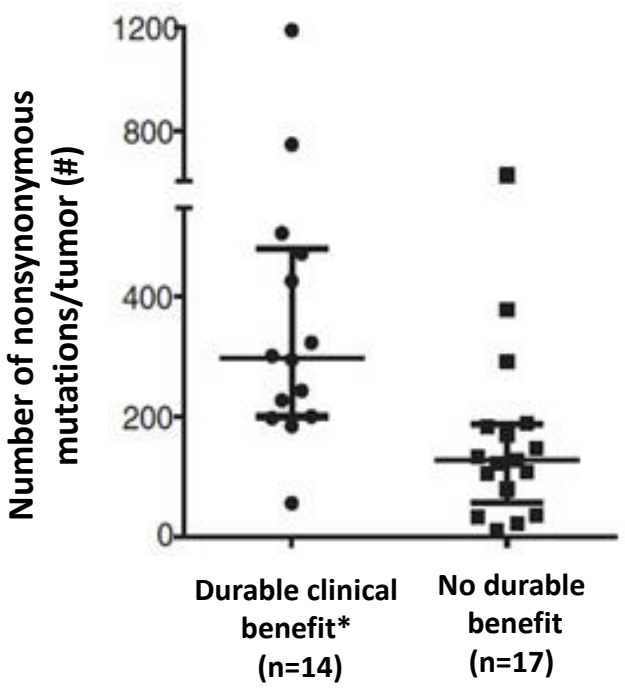


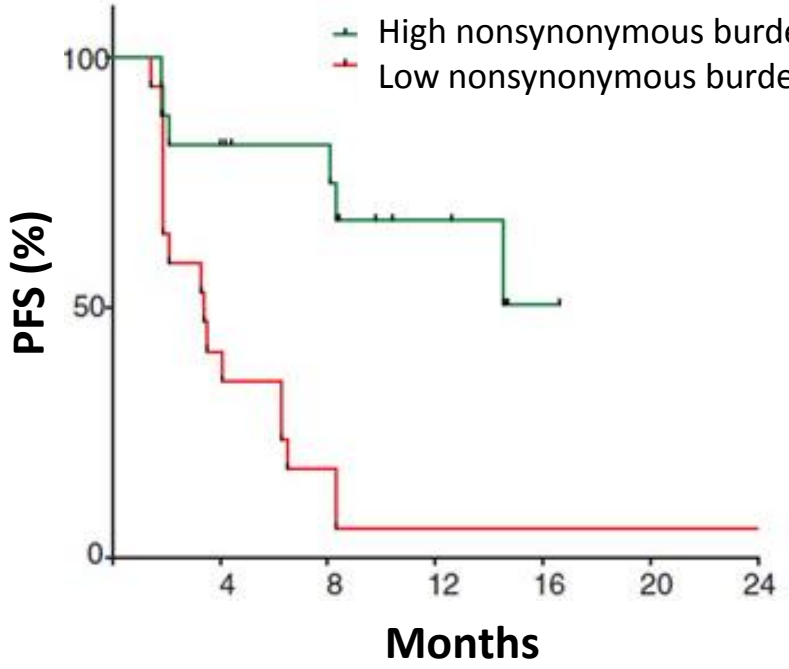
Liver metastases



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.

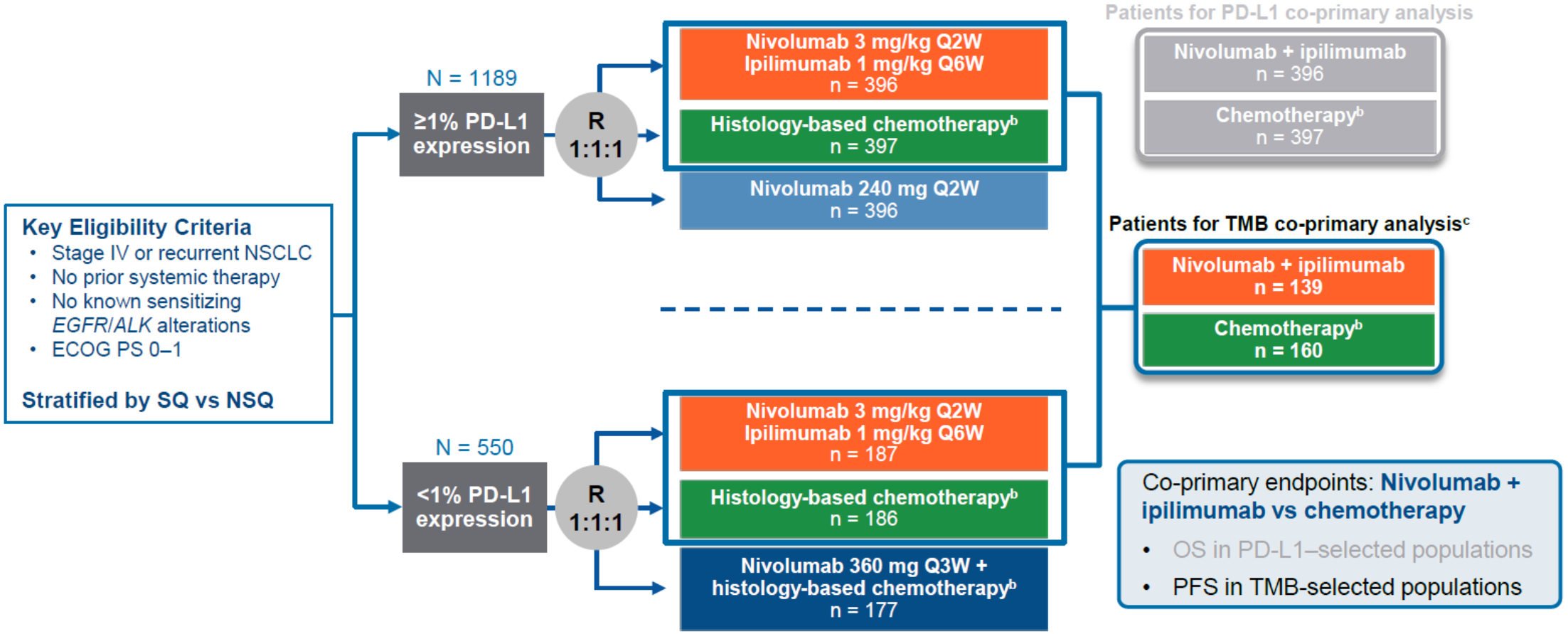




***Partial or stable response lasting > 6 mo**

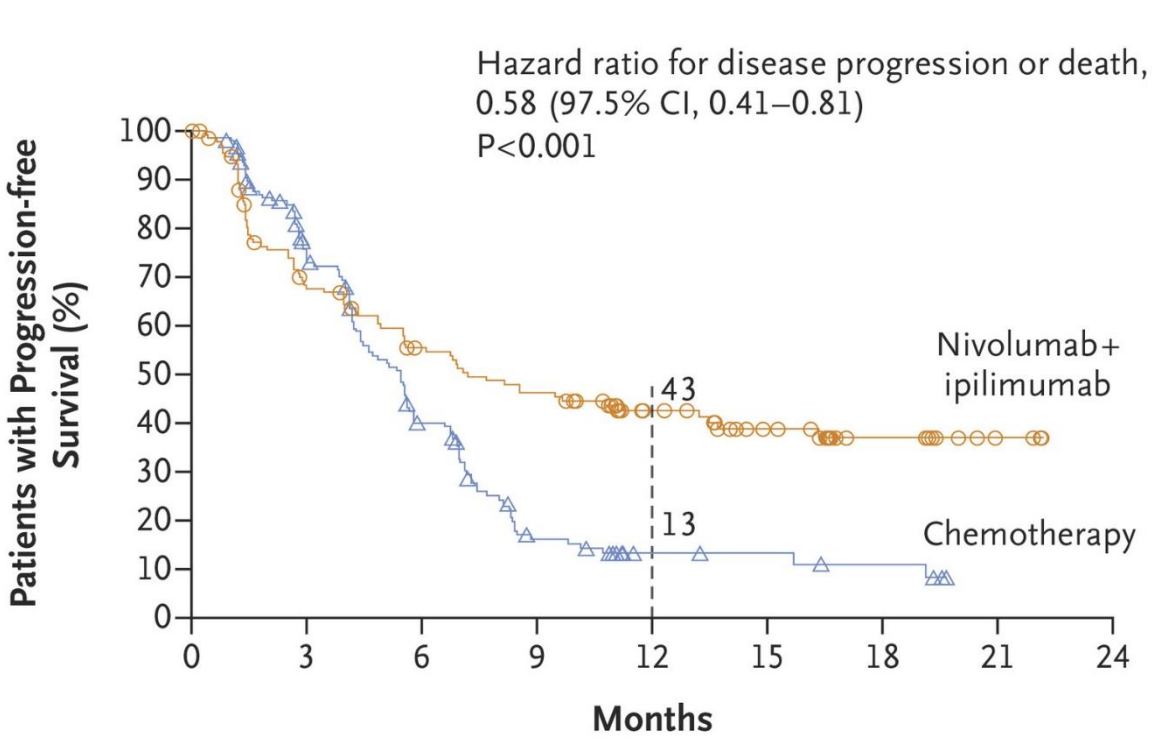
Rizvi N et al, Science, 2015

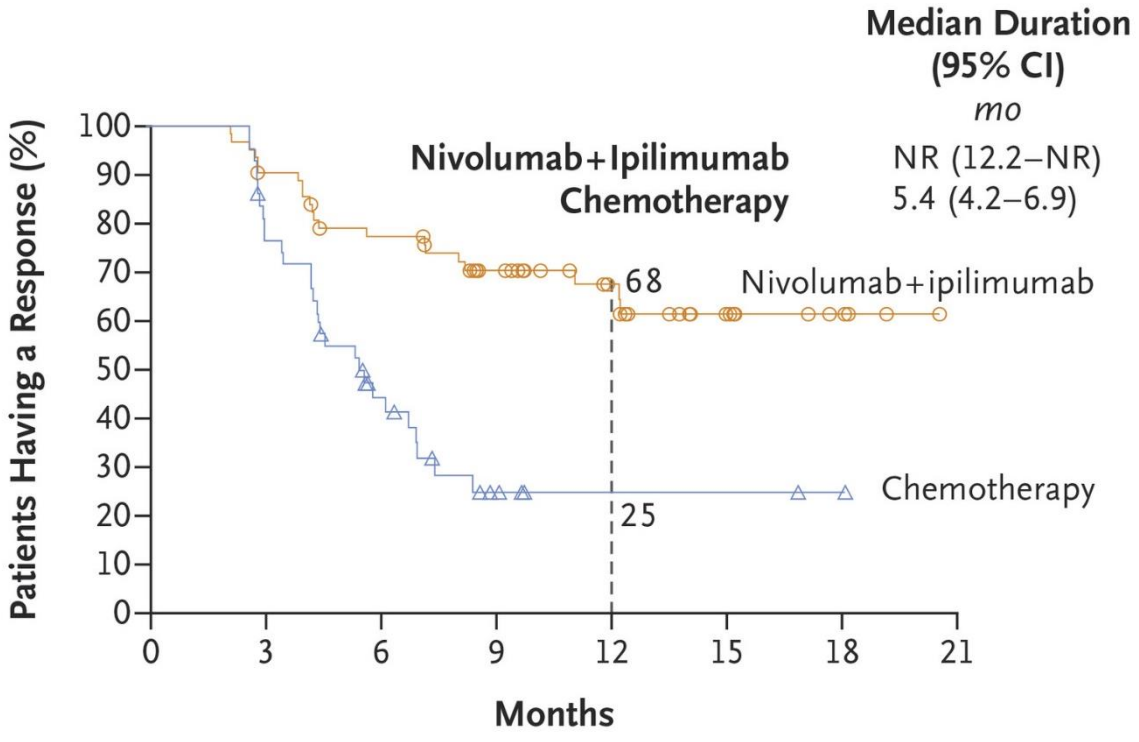
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients



Hellman et al, NEJM, 2018

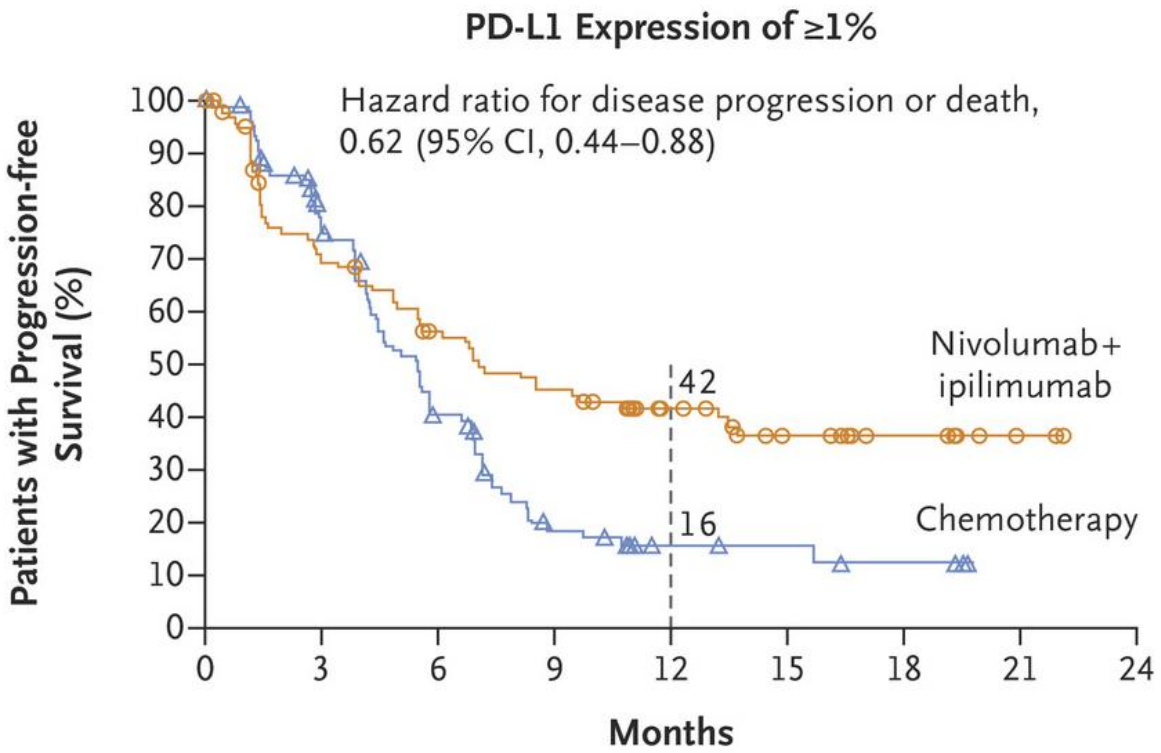
CheckMate 227: Ipilimumab + Nivolumab vs Chemotherapy in TMB-high patients

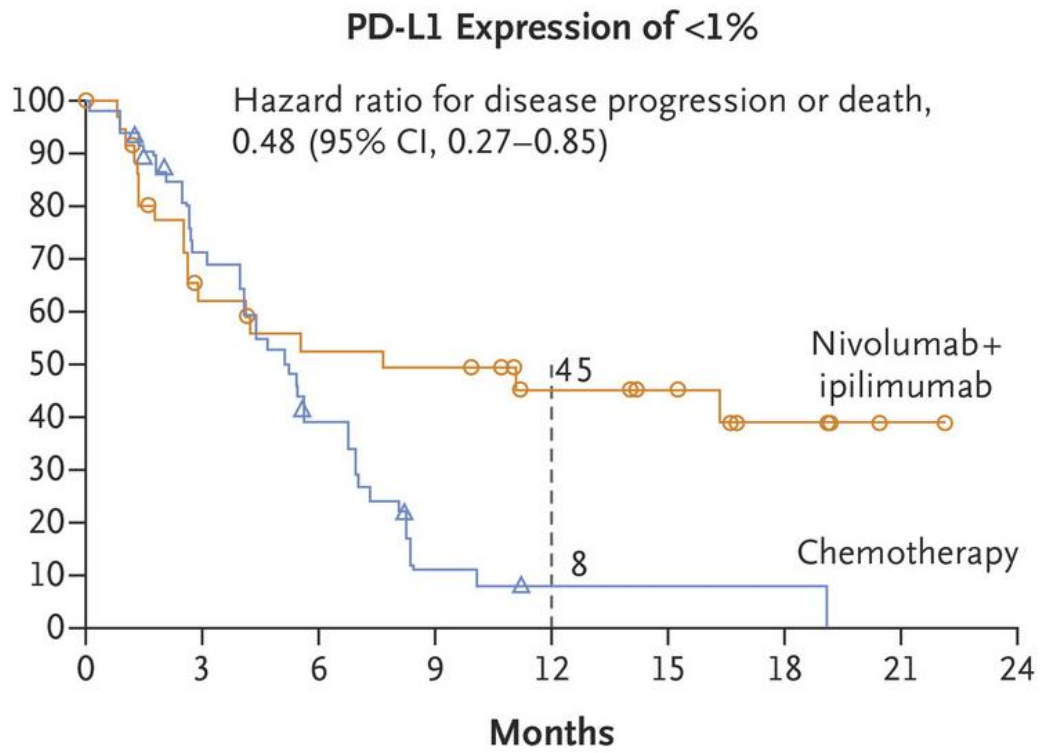




Hellman et al, NEJM, 2018

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)	--	--

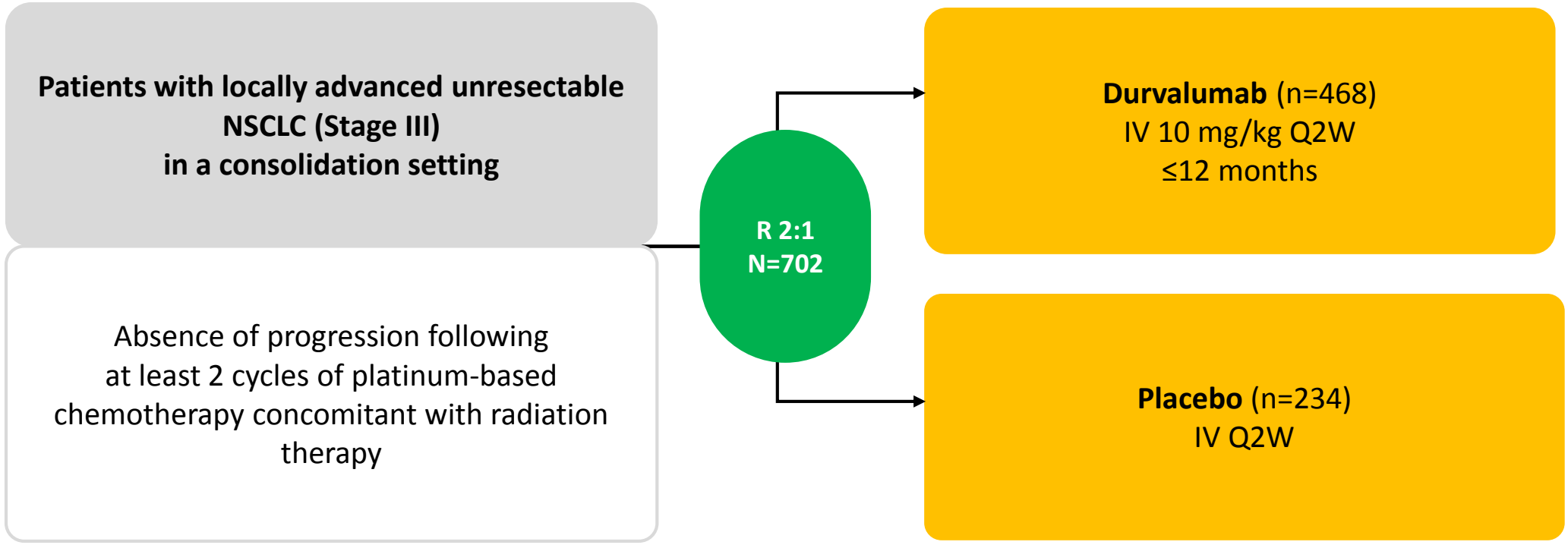
OAK (atezolizumab)

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

Minimum follow up = 19 months

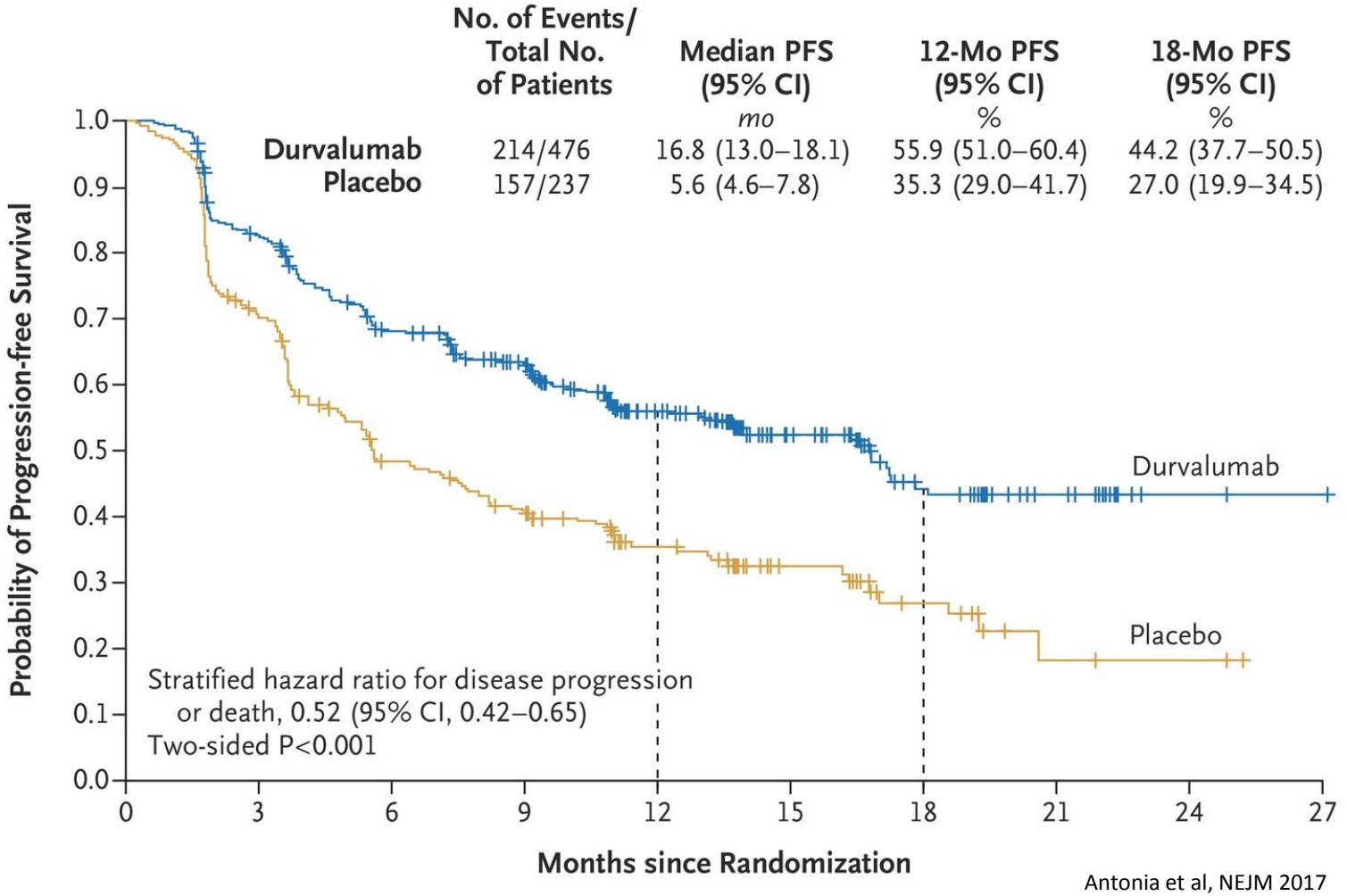
Brahmer NEJM 2015; Borghaei, NEJM 2015; Herbst Lancet 2016; Rittmeyer Lancet 2017

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



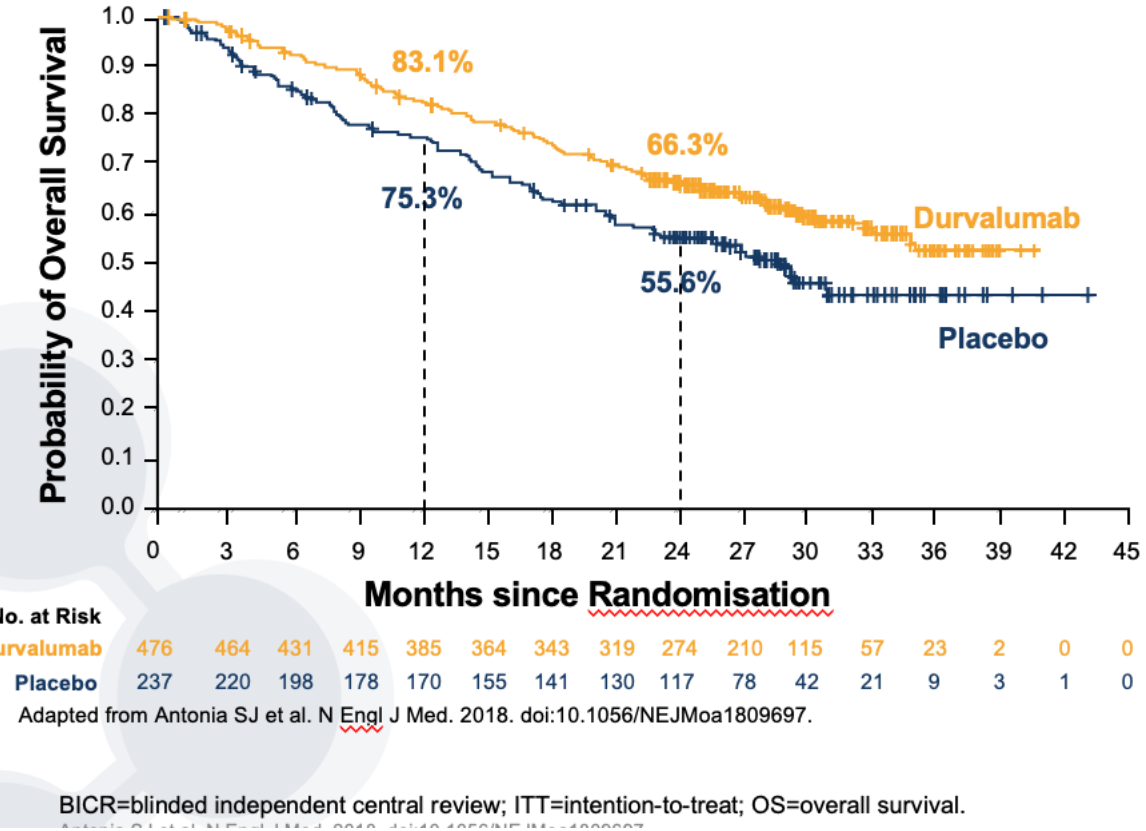
1. In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
2. NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
3. Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
4. Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

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



Antonia et al, NEJM 2017

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



Adapted from Antonia SJ et al. N Engl J Med. 2018. doi:10.1056/NEJMoa1809697.

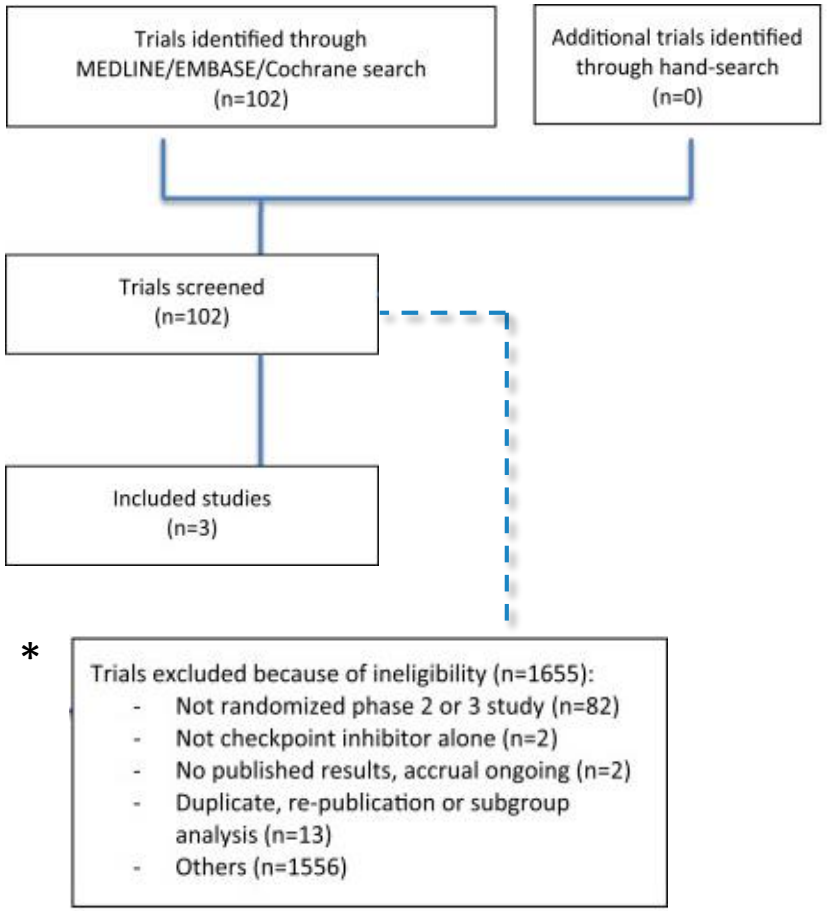
Stratified hazard ratio: 0.68 (99.73% CI: 0.47–0.997)
Two-sided P=0.0025

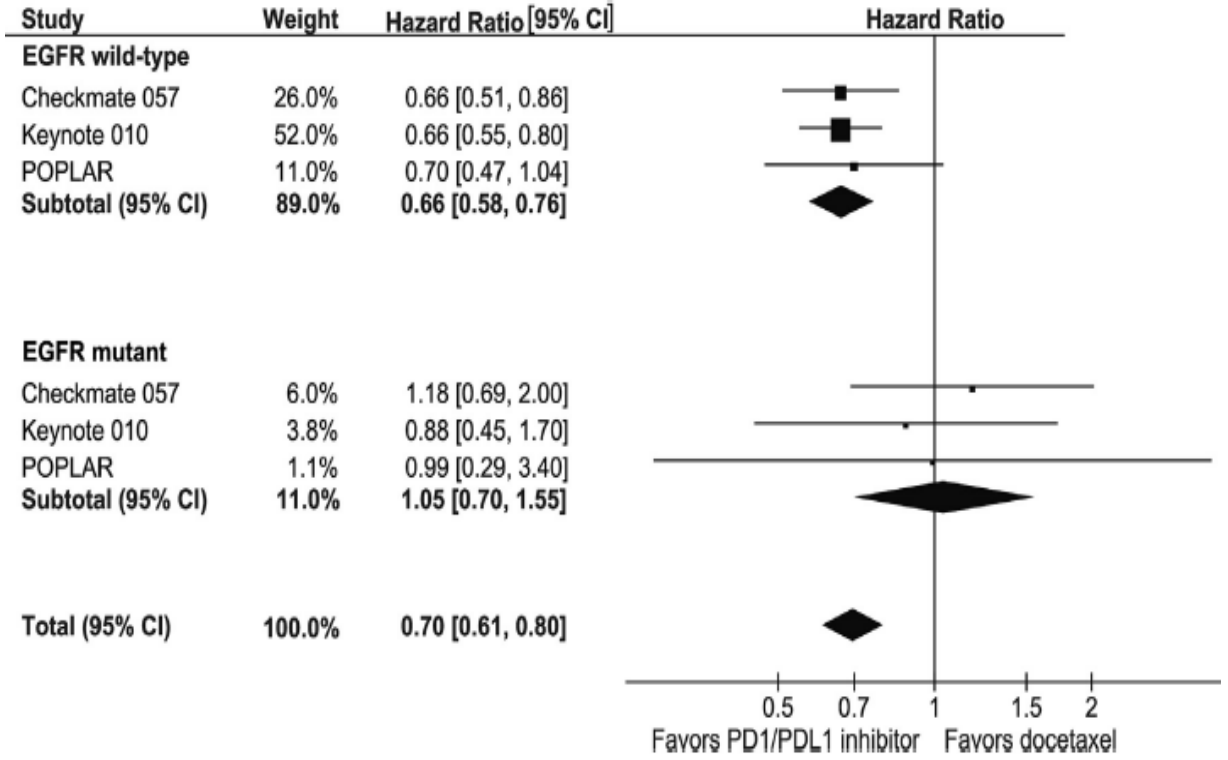
	Durvalumab (N=476)	Placebo (N=237)
Median OS (95% CI), months	**NR (34.7–NR)**	**28.7 (22.9–NR)**
12-month PFS rate (95% CI)	83.1% (79.4–86.2)	75.3% (69.2–80.4)
24-month PFS rate (95% CI)	66.3% (61.7–70.4)	55.6% (48.9–61.8)

BICR=blinded independent central review; ITT=intention-to-treat; OS=overall survival.

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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





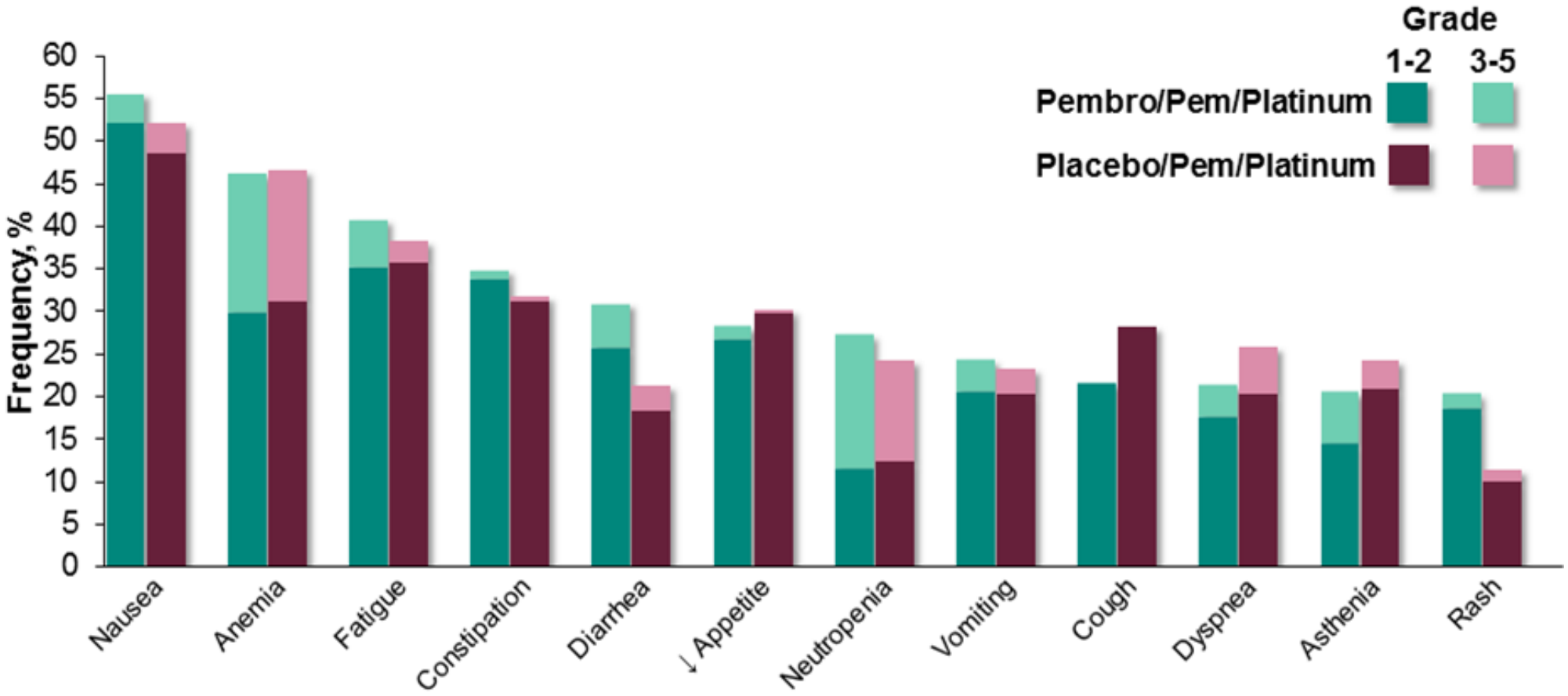
CK Lee et al., JTO 2016

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%

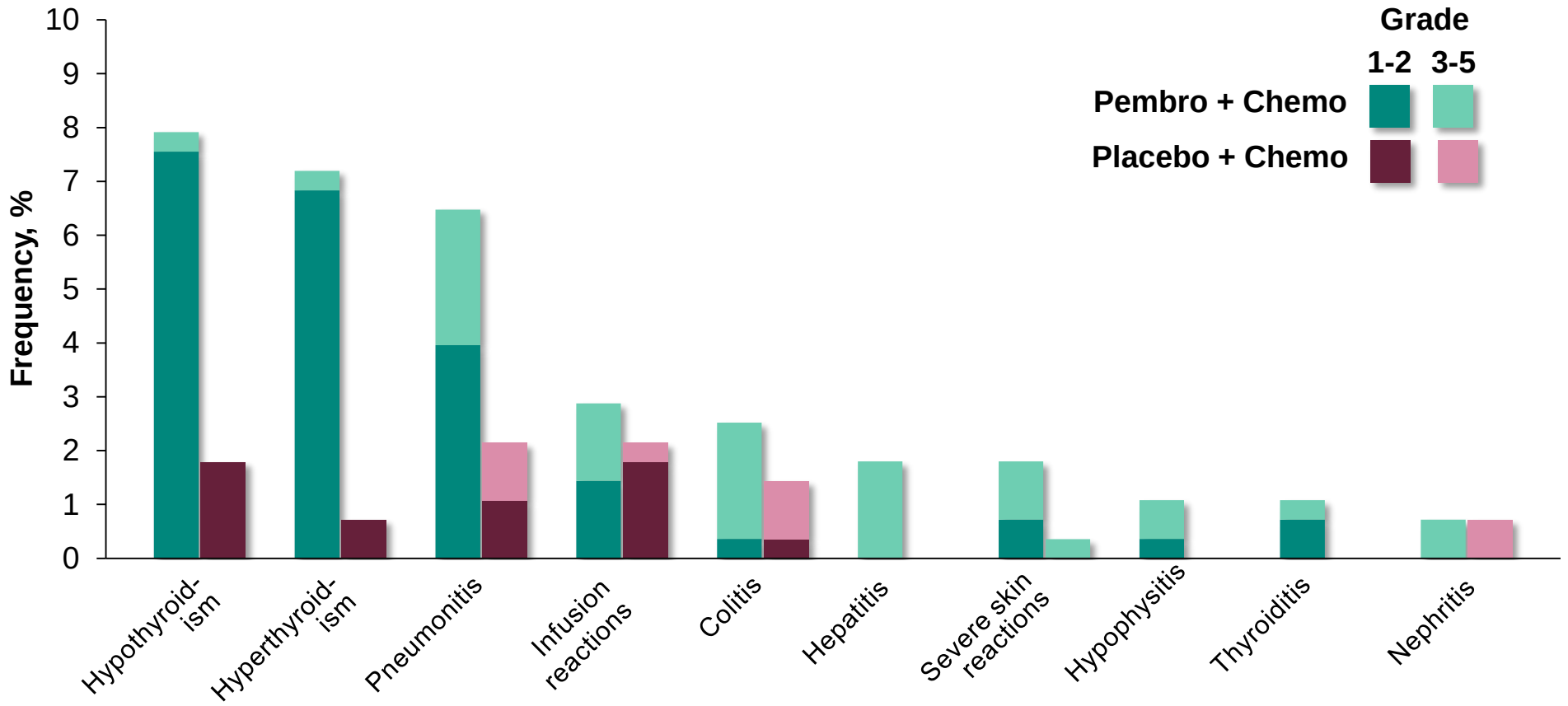
Rittmeyer, et al., *Lancet* 2017
Brahmer, et al., *NEJM* 2015
Borghaei, et al., *NEJM* 2015
Herbst, et al., *Lancet* 2015

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

Trial		PFS / OS (months)	PFS HR in PD-L1 neg.	Toxicities Grade 3-5
KEYNOTE-024 PD-L1≥50%	Pembro	10.3 / 30	NA	27 vs 53%
	Plat/Pem or Gem or Pacli	6 / 14.2		
KEYNOTE-042 PD-L1≥1%	Pembro	5.4 / 16.7	NA (in 1-49%: 0.92, NS)	18 vs 41%
	Plat/Pem or Pacli	6.5 / 12.1		
IMPower150 Non-squamous	Atezo + Beva + Plat/Pacli	8.3 / 19.2	0.72	59 vs 50%
	Plat/Pacli	6.8 / 14.4		
KEYNOTE-189 Non-squamous	Pembro + Plat/Pem	8.8 / 21.5	0.59	67 vs 65%
	Plat/Pem	4.9 / 11.3		
KEYNOTE-407 Squamous	Pembro + Plat/Pacli or NabPacli	6.4 / 15.9	0.68	70 vs 68%
	Plat/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 / 16.4		

Solange Peters, 2018 ASCO Annual Meeting

Case Study 1

- 72M, ex smoker, presented with right hand weakness to ER
- Past Medical History: Diabetes, hypertension
- Imaging
  - MRI brain: Solitary 15 mm occipital lobe lesion
  - CT chest/abdo/pelvis: RUL spiculated mass 3.1 cm, 2 other pulmonary masses, multiple bone metastases and bilateral adrenal metastases.
- Pathology:
  - Lung biopsy: Adenocarcinoma (TTF1+)
  - Biomarkers: EGFR negative, ALK negative, ROS1 negative, PDL1 > 50%
  - What would be recommended first line systemic therapy?

Case Study 1: Treatment

- Surgical resection of solitary brain radiation
- Radiation: Cavitary radiation to resected brain metastases, and palliative radiation to bone metastases
- Systemic therapy:
  - First line Pembrolizumab monotherapy
  - In US: Platinum/pemetrexed/pembrolizumab combination available

- Response:
  - CT chest/abdo/pelvis at 3 months: Response to adrenals, bone and lung
  - CT head – increase in rim enhancing lesion in brain
    - Felt to be pseudoprogression vs radionecrosis

Case Study: Course on Treatment

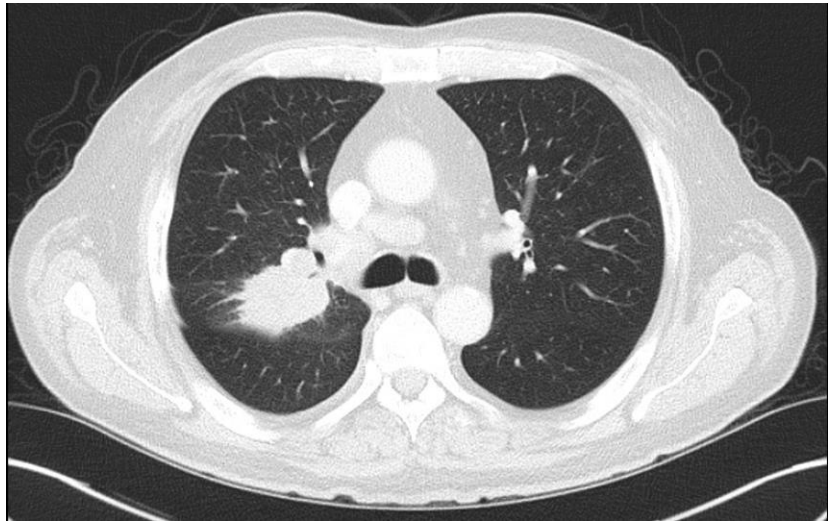
- After 12th cycle
  - 2-4 loose BM per day
- Held cycle 13
  - Started on Imodium
  - Stool cultures
  - Follow up in 2 days
  - Referred for an outpatient colonoscopy
- Stool cultures negative
- Initial improvement: then reoccurrence of 2-5 BM per day, including at night
- Started on prednisone 1 mg/kg
- Patient improved in 48 hours
- Started slow prednisone taper over 4 weeks, weekly monitoring with our centre immunotherapy nurse
- Colonoscopy: 4 days later showed mild patches of erythema
  - Colon biopsy: Colitis

Case Study 1: Course on treatment

- During taper at prednisone 40 mg daily started to have increase in BM x 2-4
- Admitted to hospital
  - Prednisone increased to 1.5 mg/day
  - Infliximab 5mg/kg IV x 1 dose
- Improved in 48 hours, and discharged on tapering steroids
- Remains off treatment x 9 months
  - Developed a choroidal metastases, treated with radiation, all other disease remains stable

Case Study 2 – 71M, metastatic NSCLC adenocarcinoma

- 56M ex smoker developed cough, fatigue
- Past Medical Hx: Nil, ECOG 1
- Imaging:
  - RUL mass: 5.3 cm with hilar adenopathy
  - PET scan: diffuse liver metastases, bone metastases, no brain metastases



Case Study 2 (continued)

- Biopsy:
  - Adenocarcinoma, TTF1+
  - Biomarkers: plasma broad molecular testing:
    - KRAS mutated (EGFR/ALK/ROS1/Braf/Met exon skipping all negative)
    - pTMB low to intermediate
    - PD-L1 1%
- Symptoms: ECOG1, increasing RUQ pain within one week, and progression on scans → rapidly progressing.

Case Study 2 - Treatment

- What treatment would you recommend?
  1. Impower 150: Carboplatin/paclitaxel/bevacizumab/atezolizumab
  2. Carboplatin/pemetrexed/pembrolizumab
  3. Carboplatin/pemetrexed
  4. Pembrolizumab

Case Study 2 - Treatment

- Rapidly progressing disease
- Combination IO would be first choice, patient did not have private coverage for immunotherapy
- Started on carboplatin/pemetrexed x 4 cycles → progressed
- Now which treatment would you recommend?
  1. Atezolizumab
  2. Pembrolizumab
  3. Nivolumab