Society for Immunotherapy of Cancer

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# Immunotherapy for the Treatment of Lung Cancer

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AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

# Disclosures

- Dr. Rangachari reports non-financial support (institutional research support) from Bristol-Myers Squibb, Novocure, and Abbvie/Stemcentrx.
- I will be discussing non-FDA approved indications during my presentation.

# Lung cancer

- 80-85% non-small cell lung cancer (NSCLC)
- 10-15% small cell lung cancer (SCLC)
- NSCLC has relatively long and extensive history of immunotherapy use

Estimated Deaths

| Male | | |
|---|---|---|
| Lung & bronchus | 76,650 | 24% |
| Prostate | 31,620 | 10% |
| Colon & rectum | 27,640 | 9% |
| Pancreas | 23,800 | 7% |
| Liver & intrahepatic bile duct | 21,600 | 7% |
| Leukemia | 13,150 | 4% |
| Esophagus | 13,020 | 4% |
| Urinary bladder | 12,870 | 4% |
| Non-Hodgkin lymphoma | 11,510 | 4% |
| Brain & other nervous system | 9,910 | 3% |
| **All sites** | **321,670** | |

| Female | | |
|---|---|---|
| Lung & bronchus | 66,020 | 23% |
| Breast | 41,760 | 15% |
| Colon & rectum | 23,380 | 8% |
| Pancreas | 21,950 | 8% |
| Ovary | 13,980 | 5% |
| Uterine corpus | 12,160 | 4% |
| Liver & intrahepatic bile duct | 10,180 | 4% |
| Leukemia | 9,690 | 3% |
| Non-Hodgkin lymphoma | 8,460 | 3% |
| Brain & other nervous system | 7,850 | 3% |
| **All sites** | **285,210** | |

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# FDA-approved checkpoint inhibitors in lung cancer

**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**

Nivolumab: 2nd line Sq NSCLC

Nivolumab: 2nd line Non-Sq NSCLC

Pembrolizumab: 2nd line NSCLC (PD-L1 ≥ 50%)

**2016**

Pembrolizumab: 1st line NSCLC (PD-L1 ≥ 50%)

Pembrolizumab: 2nd line NSCLC (PD-L1 ≥ 1%)

Atezolizumab: 2nd line NSCLC

**2017**

Pembrolizumab + Pemetrexed and Carboplatin: 1st line NSCLC

**2018**

Durvalumab: Stage III NSCLC (unresectable) s/p chemoradiation w/o progression

Nivolumab: 3rd line SCLC

**2019**

Atezolizumab + Etoposide/Platinum: 1st line ES-SCLC (March)

Pembrolizumab: 1st line PD-L1+ Stage III NSCLC (April)

Pembrolizumab: 3rd-line ED-SCLC (June)

# Approved checkpoint inhibitors in NSCLC

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| **Nivolumab** | 2015 | Metastatic Squamous NSCLC with progression after chemotherapy (2nd line) | 240 mg Q2W or 480 mg Q4W |
| | 2015 | Metastatic Non-Squamous NSCLC with progression after chemotherapy (2nd line) | |

# Approved checkpoint inhibitors in NSCLC

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| **Pembrolizumab** | 2015 | Metastatic NSCLC with progression after chemotherapy and PD-L1 ≥ 50% | 200 mg Q3W |
| | 2016 | Metastatic NSCLC with progression after chemotherapy and PD-L1 ≥ 1% | |
| | 2016 | 1st line metastatic NSCLC with PD-L1 TPS ≥ 50% | |
| | 2019 | 1st line stage III NSCLC (not candidate for resection or definitive chemoradiation) and Metastatic NSCLC, with PD-L1 TPS ≥ 1% and no EGFR/ALK mutations | |
| **Pembrolizumab + pemetrexed & carboplatin** | 2017 | 1st line metastatic Non-Squamous NSCLC | |
| **Pembrolizumab + pemetrexed + platinum** | 2018 | 1st line metastatic Non-Squamous NSCLC with no EGFR/ALK mutations | |
| **Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel** | 2018 | 1st line metastatic Squamous NSCLC | |

# Approved checkpoint inhibitors in NSCLC

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| **Atezolizumab** | 2016 | Metastatic NSCLC with progression after Pt-chemotherapy and targeted therapy if EGFR/ALK mutation-positive | 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W |
| **Atezolizumab + bevacizumab + paclitaxel + carboplatin** | 2018 | 1st line metastatic non-squamous NSCLC with no EGFR/ALK mutations | For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy + bevacizumab Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W |
| **Durvalumab** | 2018 | Stage III NSCLC, ineligible for surgery and without progression after chemoradiation | 10 mg/kg Q2W |

# Treatment Naïve Regimens: Competing Strategies in NSCLC

- **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 advanced non-squamous NSCLC
- **IMPOWER 150** – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (Bev) 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

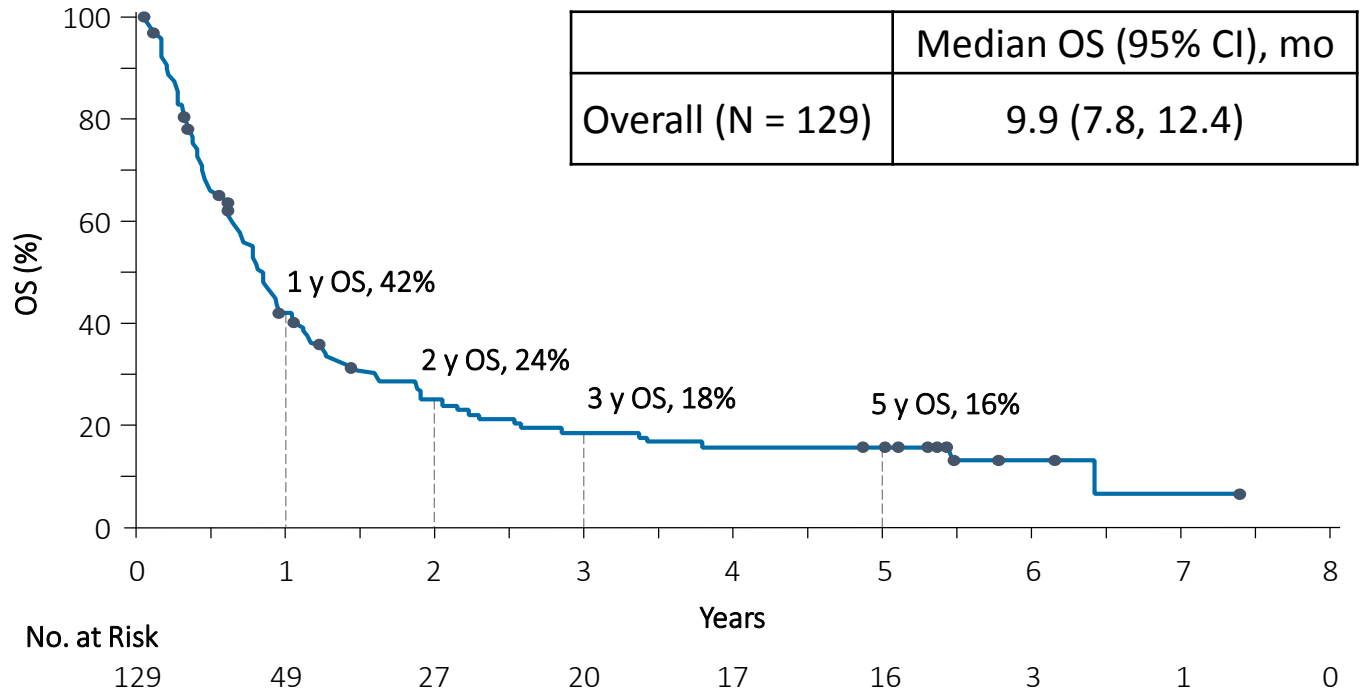
# CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

## 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) |



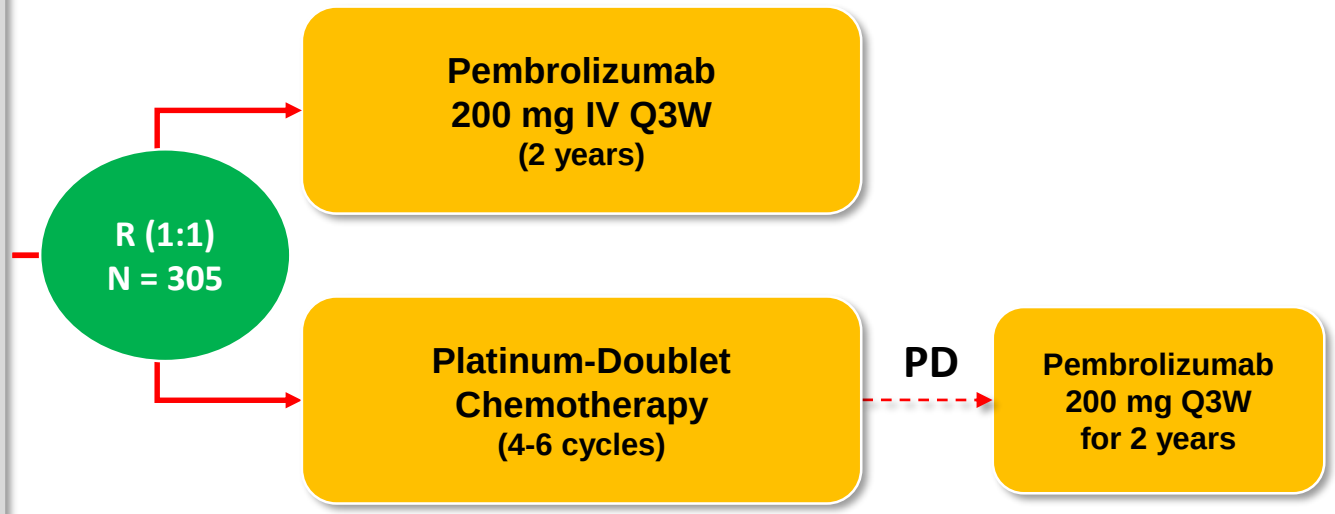

Gettinger et al. JCO 2018
Brahmer et al, AACR 2017
NCI SEER data, Lung and Bronchus Cancer, 2014

# 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

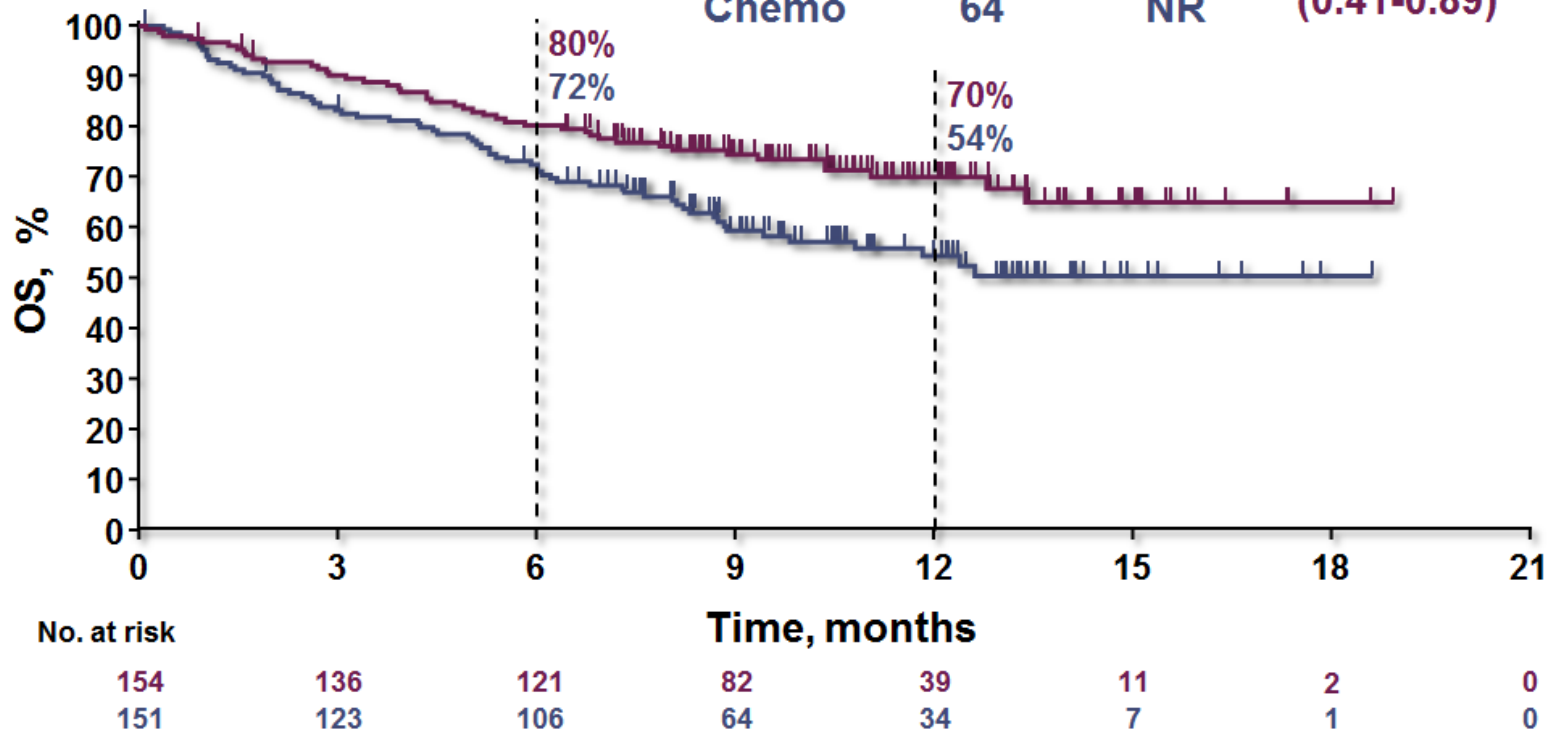



Reck M et al, ESMO 2016, NEJM 2016

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

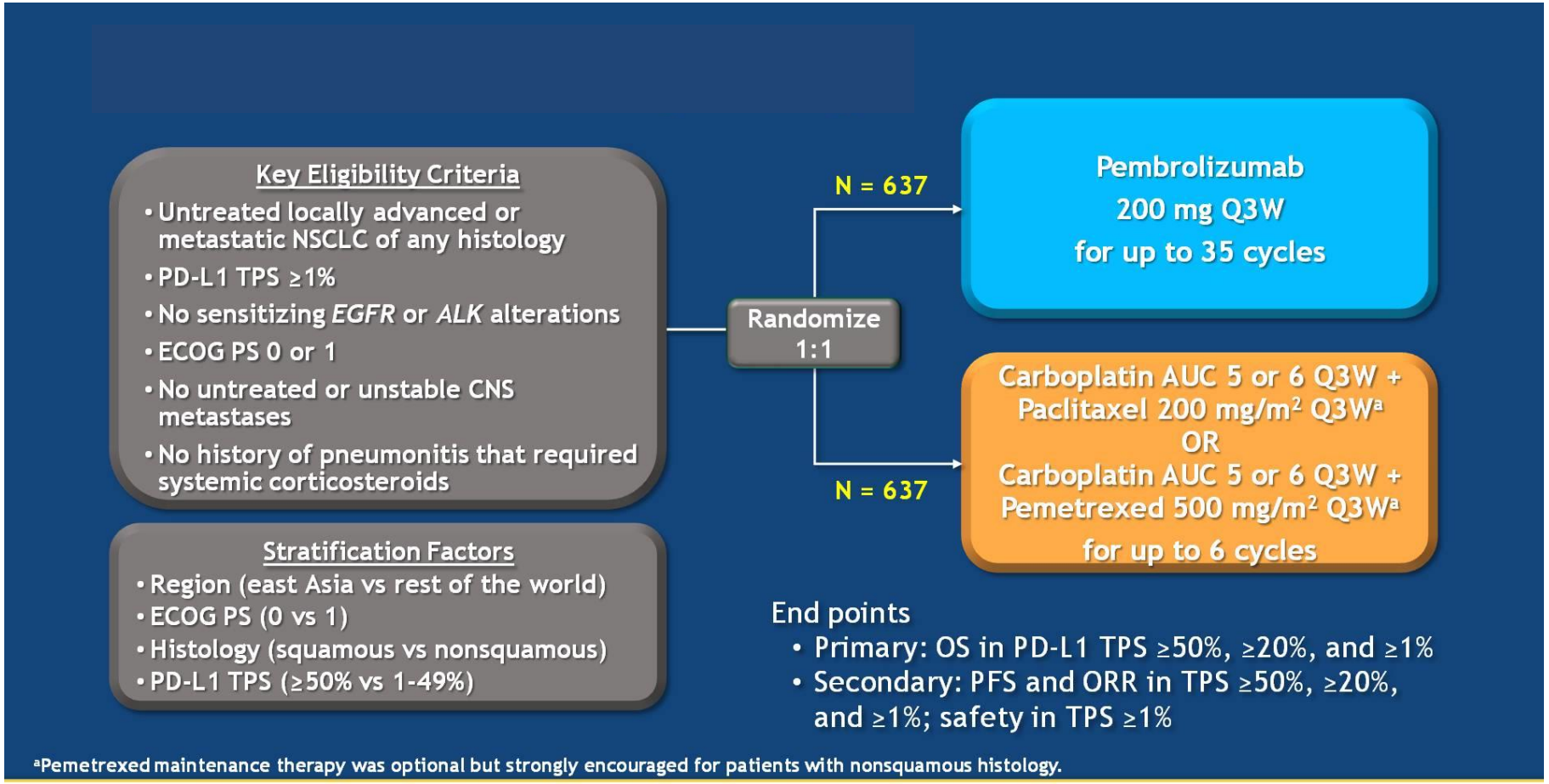
## Overall Survival

| | 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

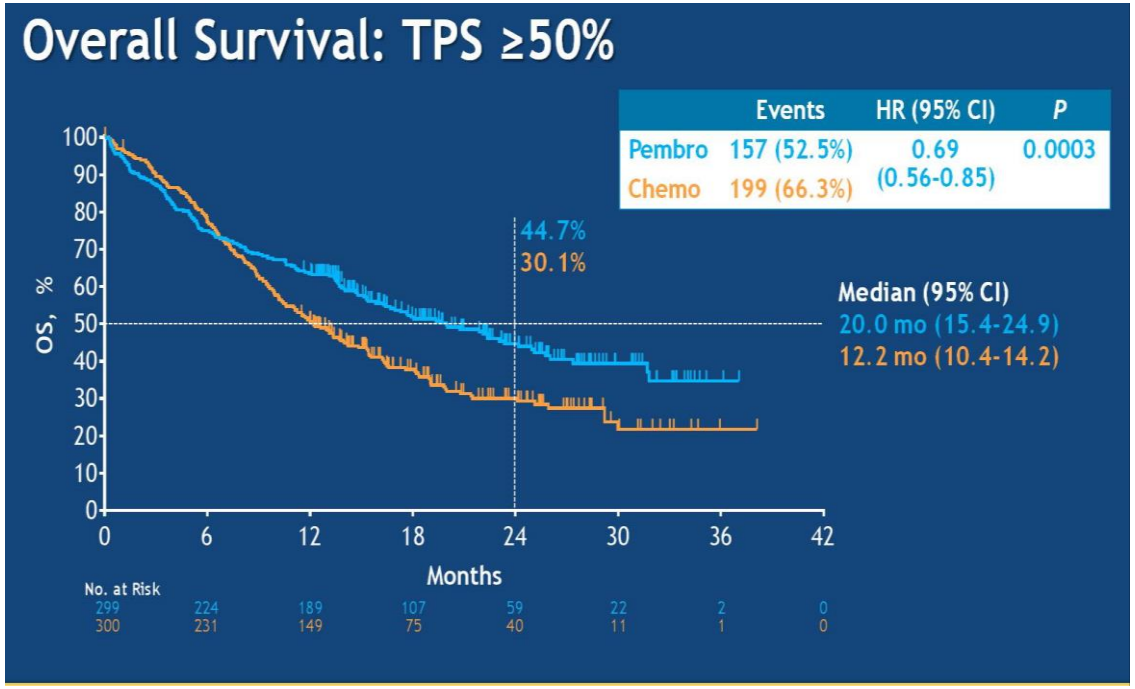
# KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

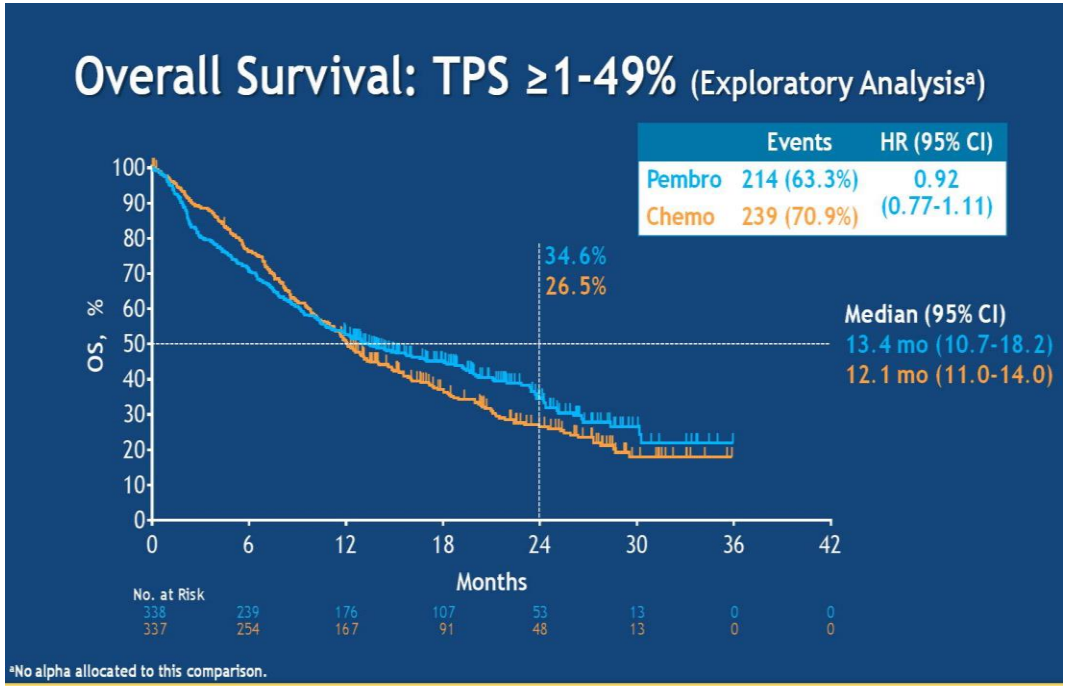



Lopes et al, ASCO 2018

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

## Overall Survival

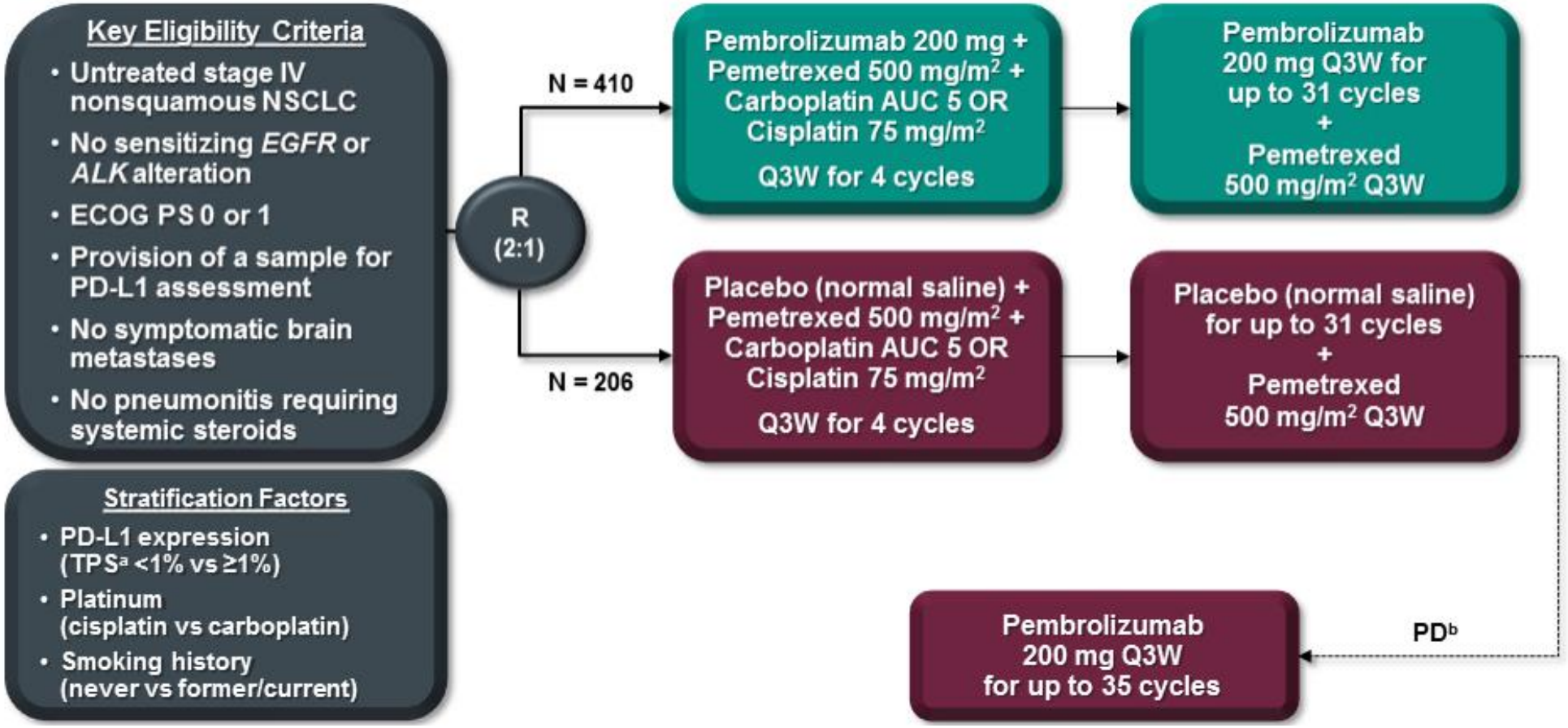



**Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%**

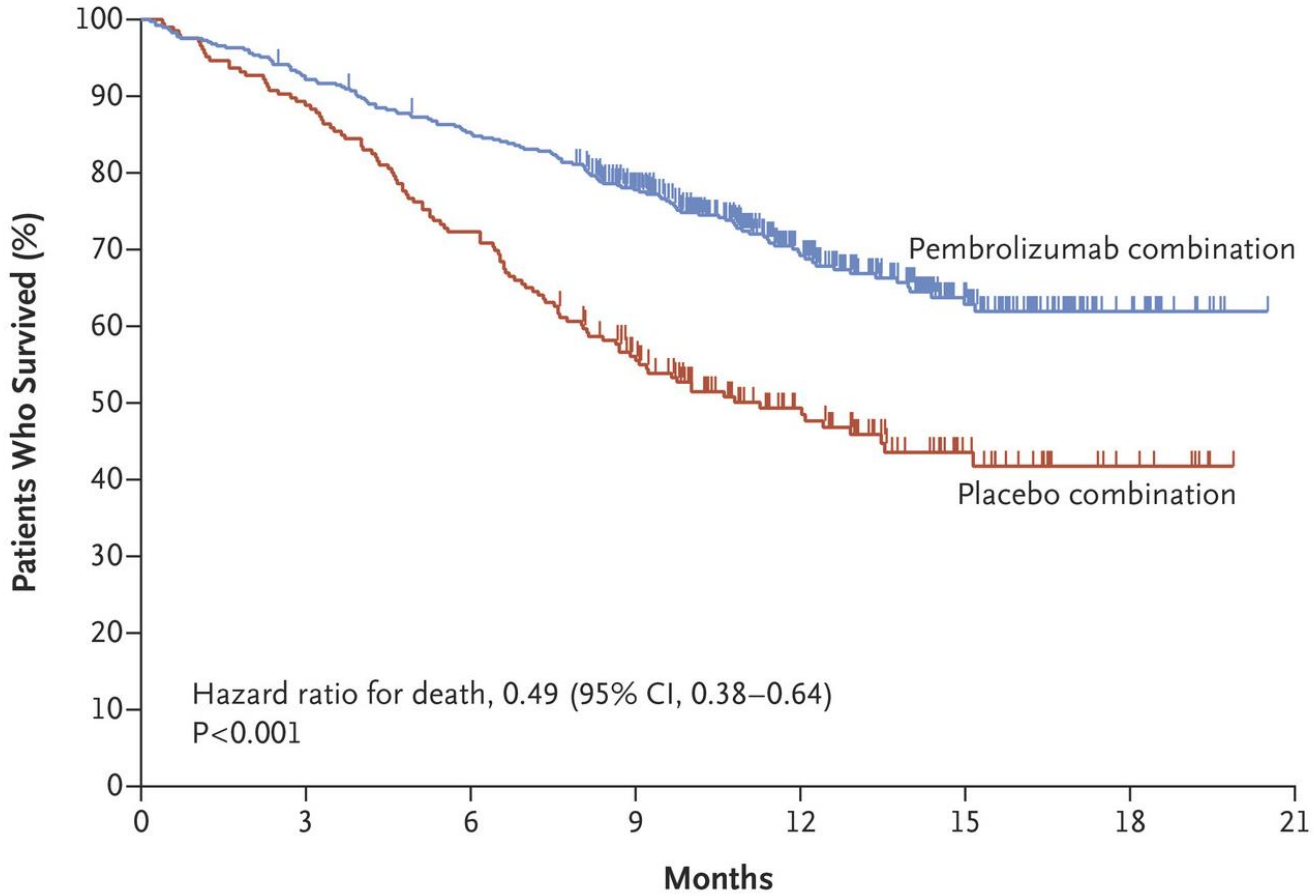
Lopes et al, ASCO 2018

# KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC




Ghandi et al, NEJM 2018

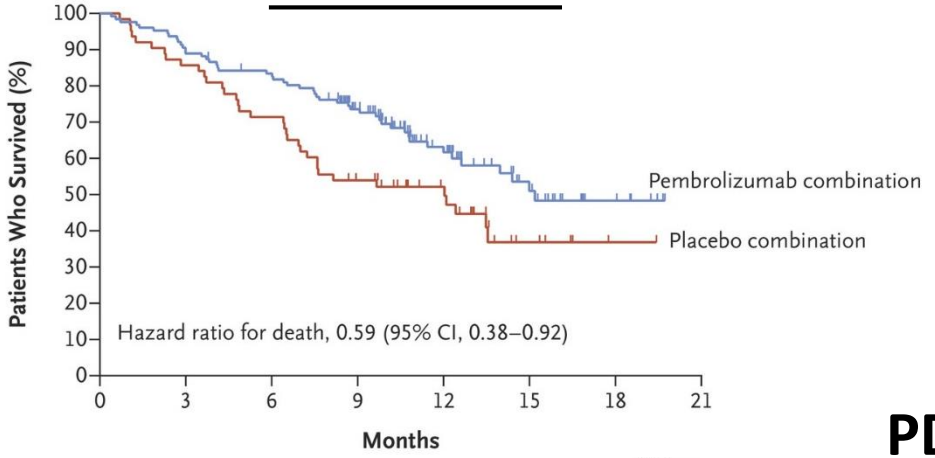
# KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



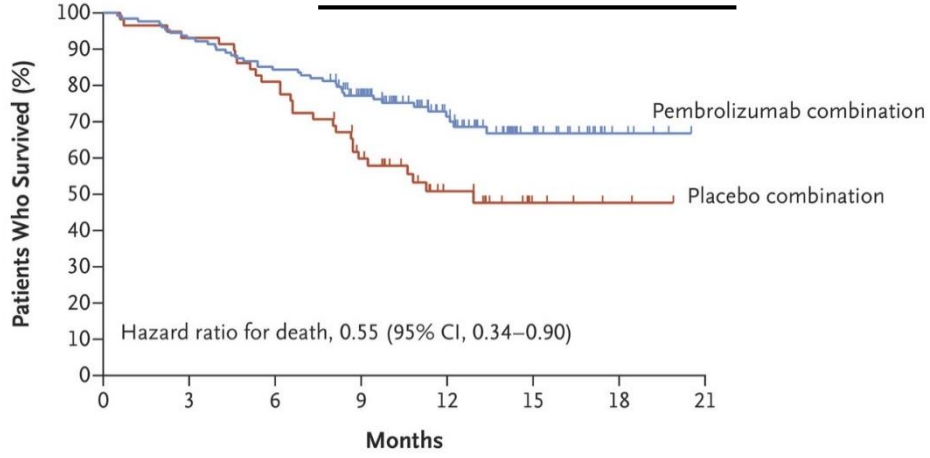

Ghandi et al, NEJM 2018

# KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

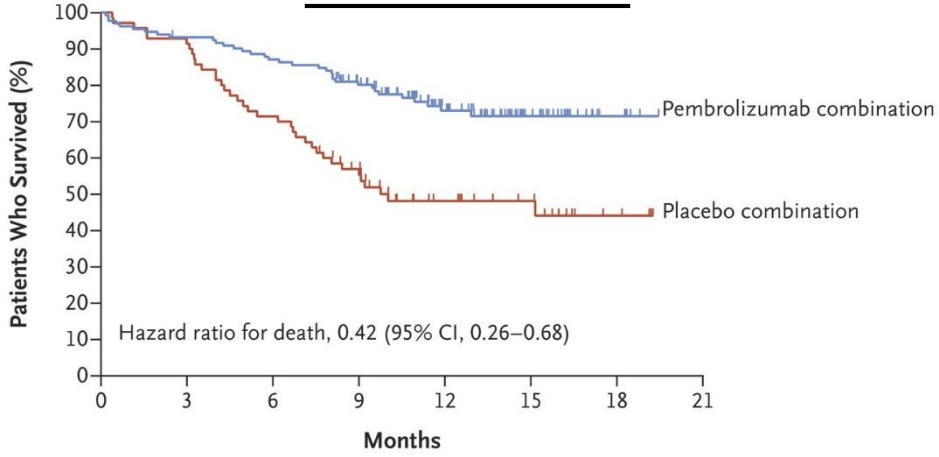
**PD-L1 < 1%**




**PD-L1 = 1 – 49%**

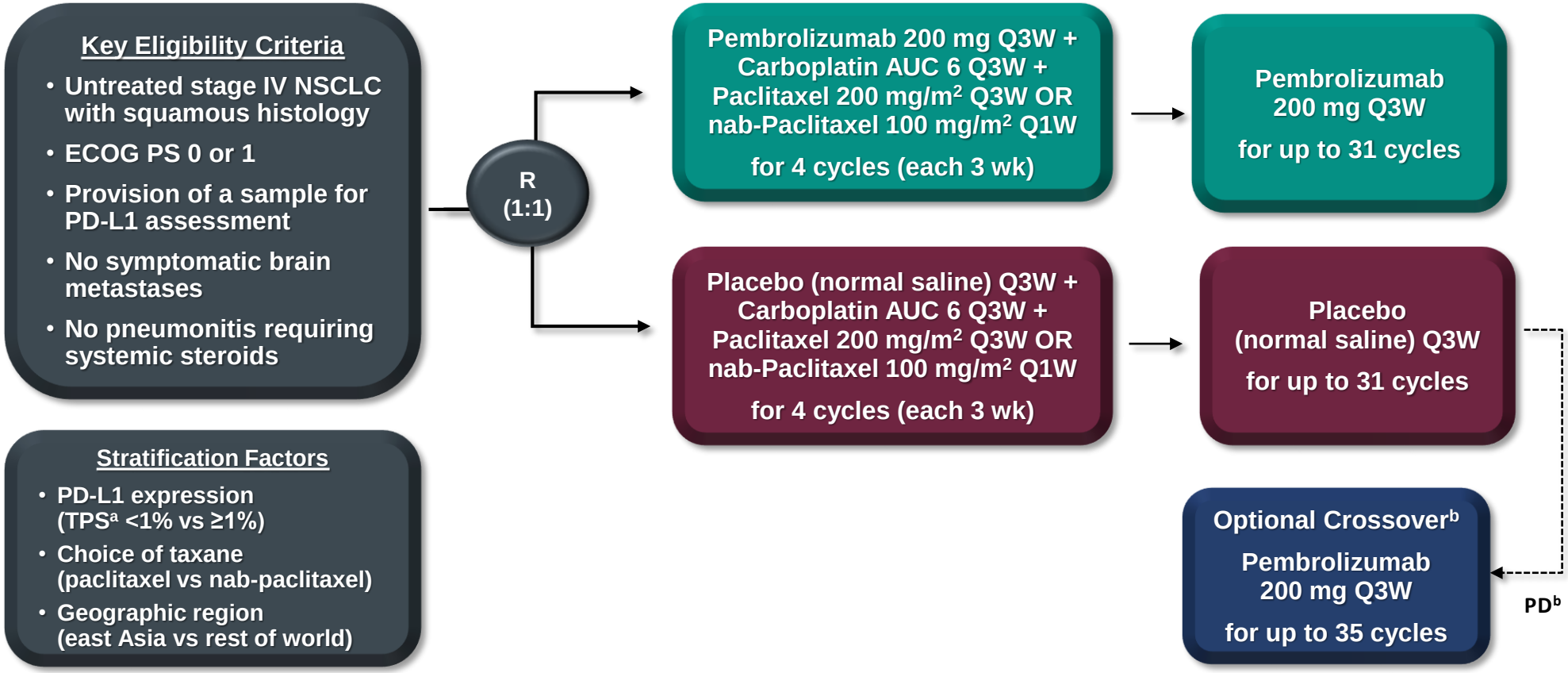



**PD-L1 ≥ 50%**




Ghandi et al, NEJM 2018

# KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

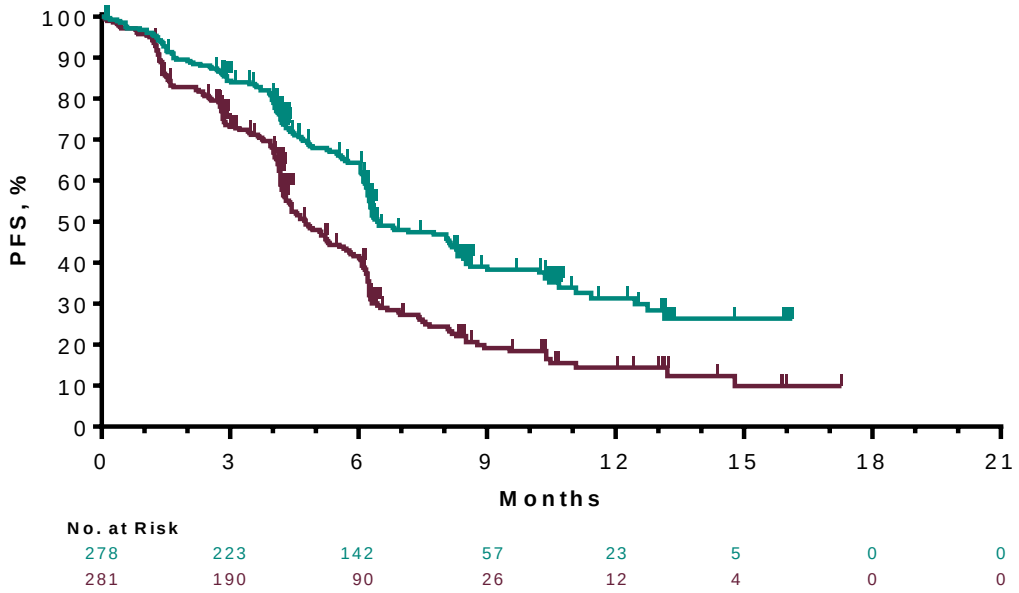



Paz-Ares et al, ASCO 2018

# KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

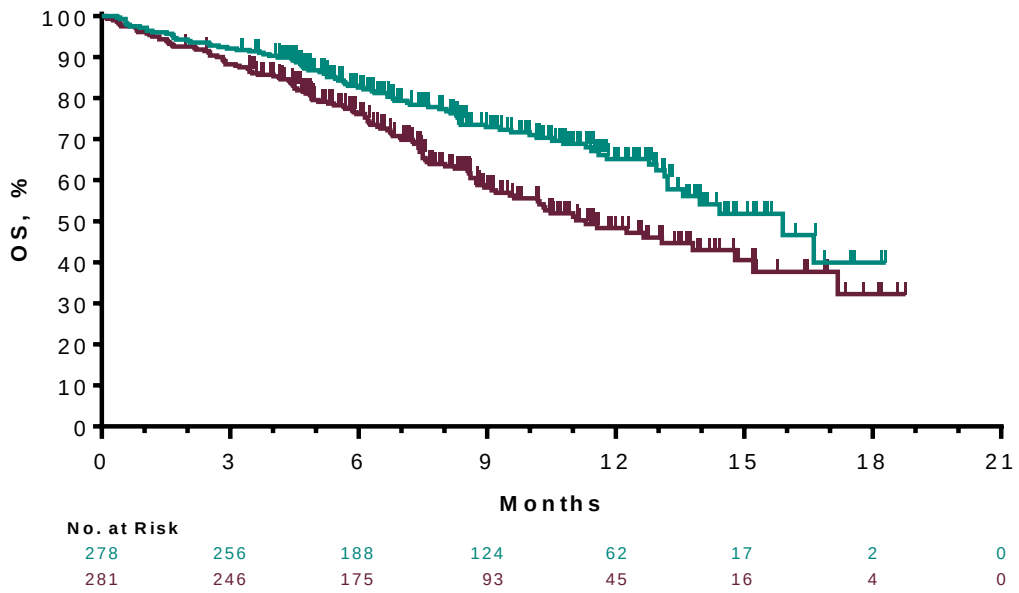
## PFS (RECISTv1.1, BICR)

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



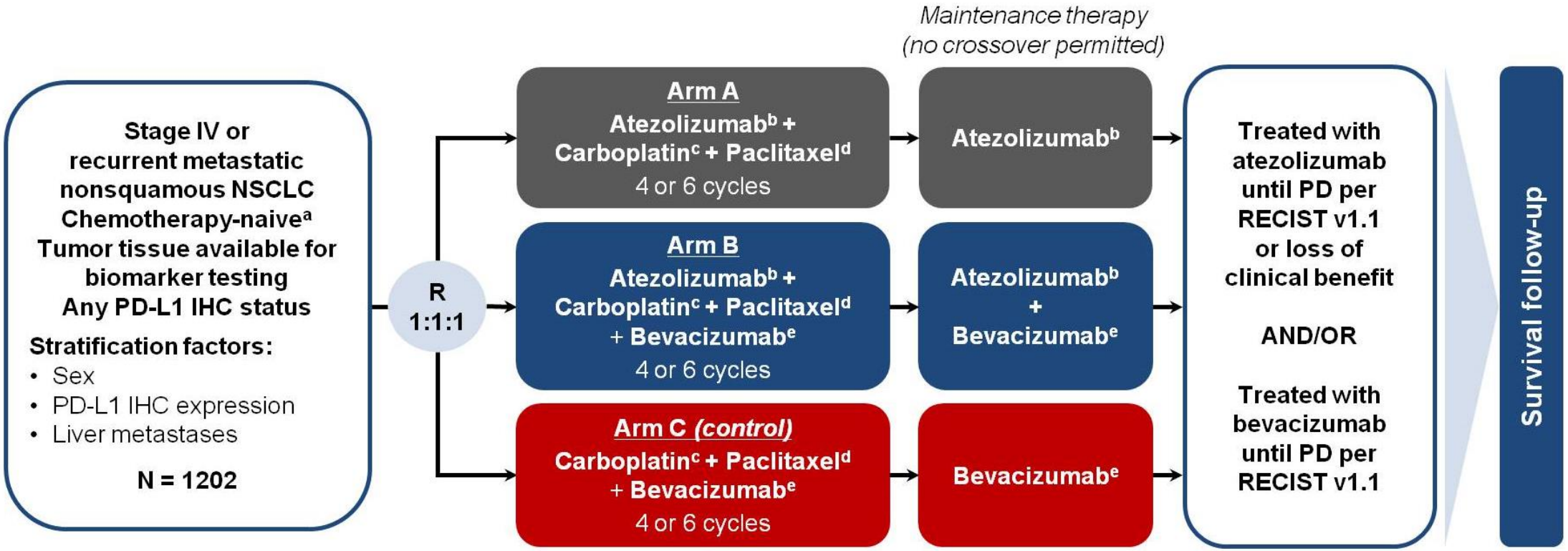

## Overall Survival

| | 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

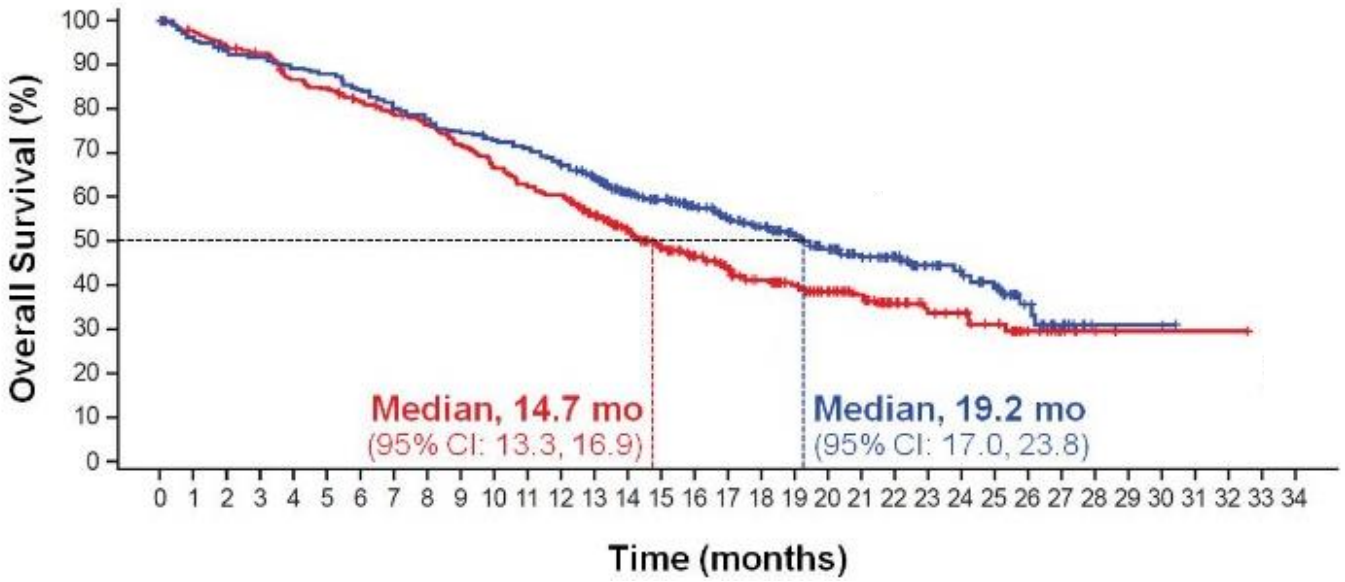


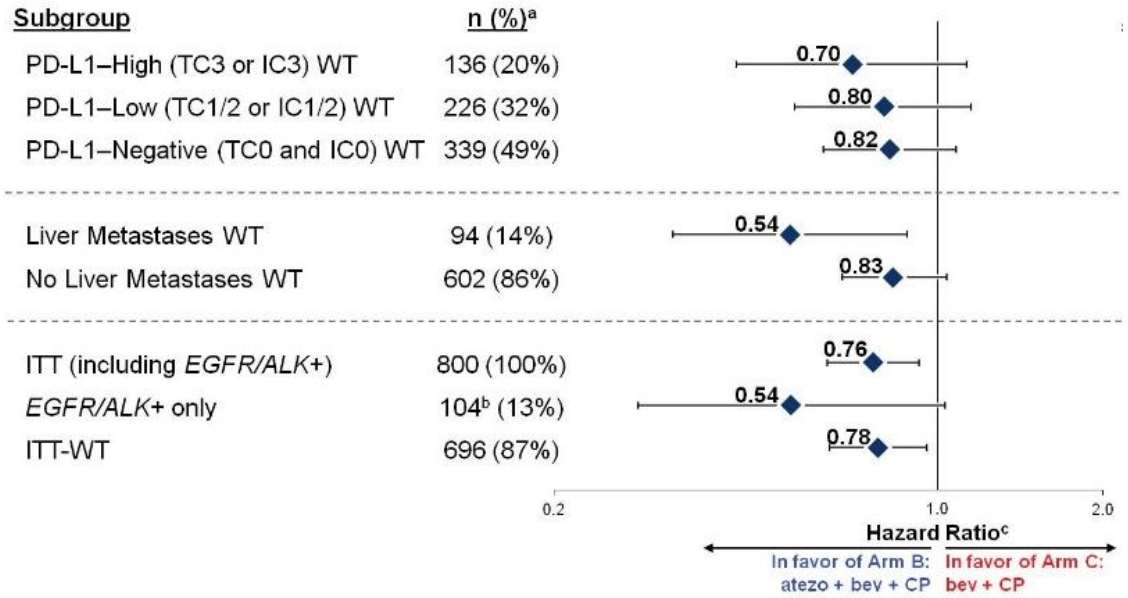

Socinski et al, NEJM 2018

# 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*

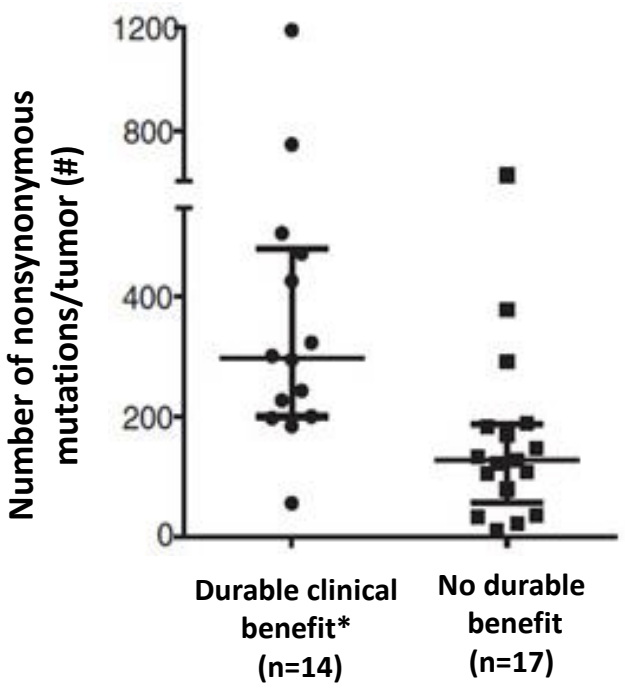


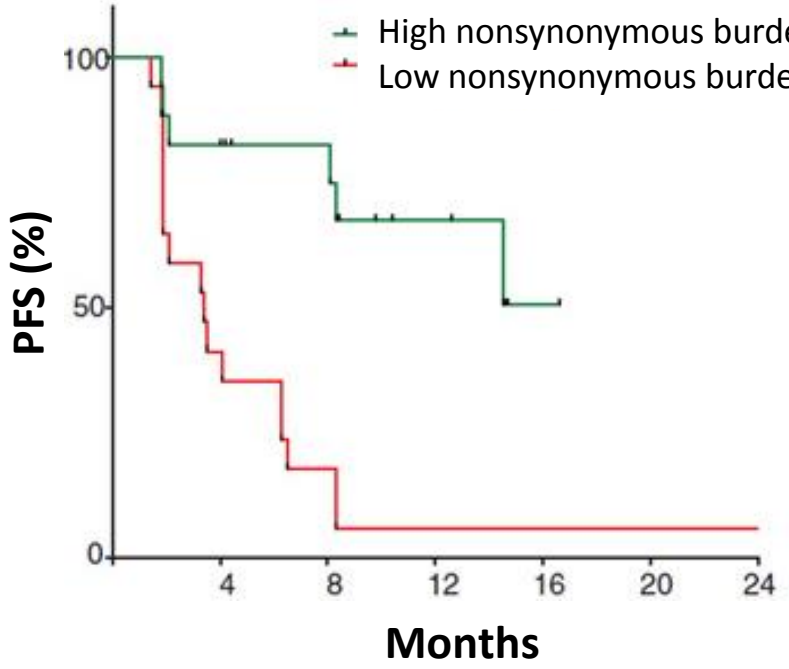




Socinski et al, NEJM 2018

# 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.

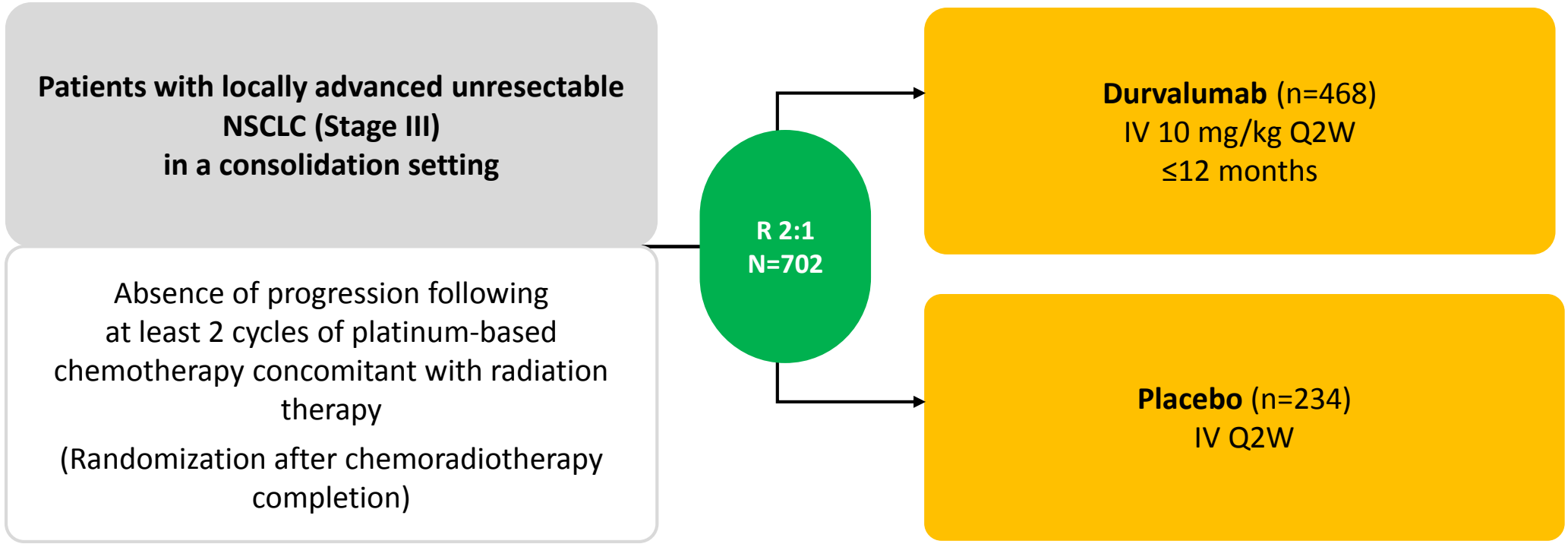



*Partial or stable response lasting > 6 mo

Rizvi N et al, Science, 2015

# PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC

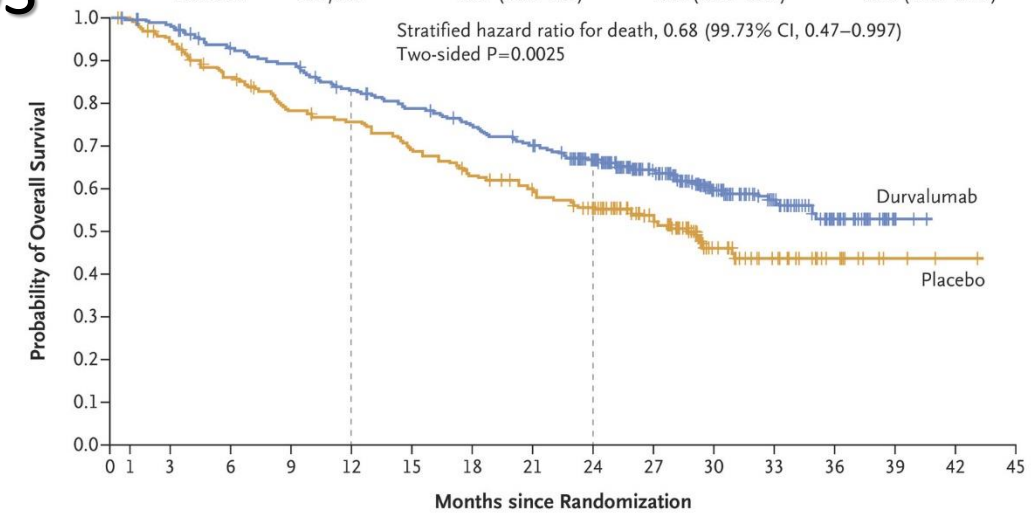



In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

# PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC

OS

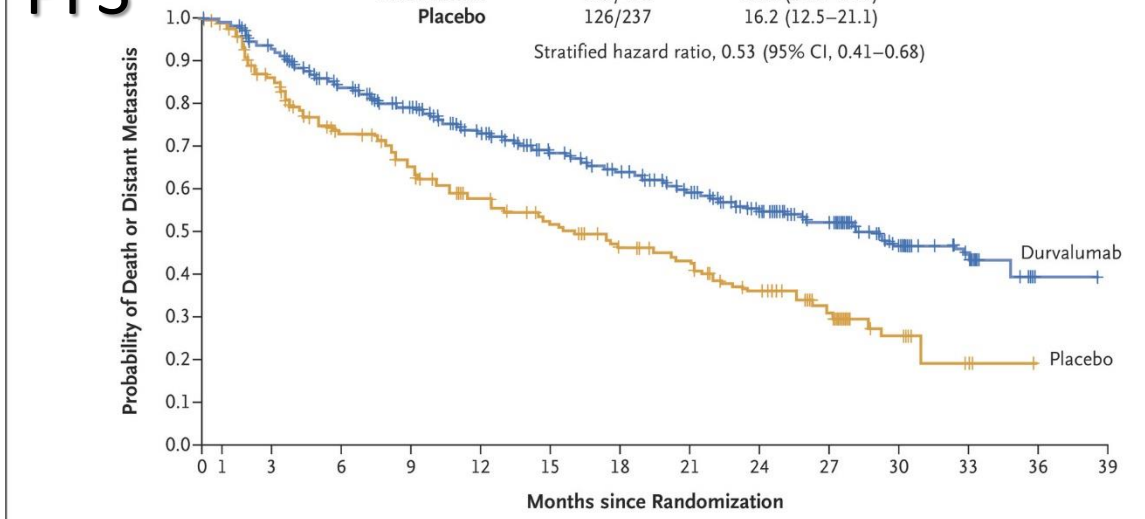
| | No. of Events/ Total No. of Patients | Median Overall Survival (95% CI) | 12-Mo Overall Survival Rate (95% CI) | 24-Mo Overall Survival Rate (95% CI) |
|---|---|---|---|---|
| | | *mo* | % | % |
| Durvalumab | 183/476 | NR (34.7–NR) | 83.1 (79.4–86.2) | 66.3 (61.7–70.4) |
| Placebo | 116/237 | 28.7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




| 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 |

PFS

| | No. of Events/ Total No. of Patients | Median Time to Death or Distant Metastasis (95% CI) |
|---|---|---|
| | | *mo* |
| Durvalumab | 182/476 | 28.3 (24.0–34.9) |
| Placebo | 126/237 | 16.2 (12.5–21.1) |

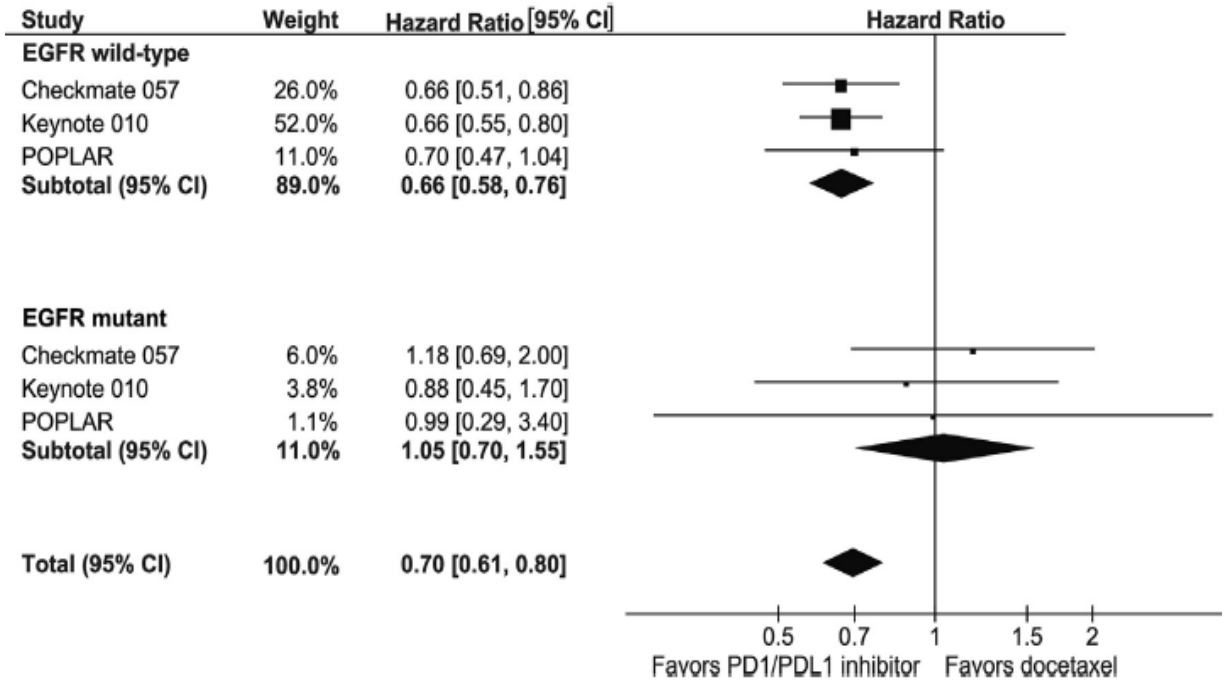



| No. at Risk | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab | 476 | 419 | 357 | 316 | 259 | 223 | 194 | 163 | 129 | 92 | 46 | 25 | 1 | 0 |
| Placebo | 237 | 189 | 139 | 118 | 95 | 77 | 64 | 54 | 39 | 27 | 12 | 5 | 0 | 0 |

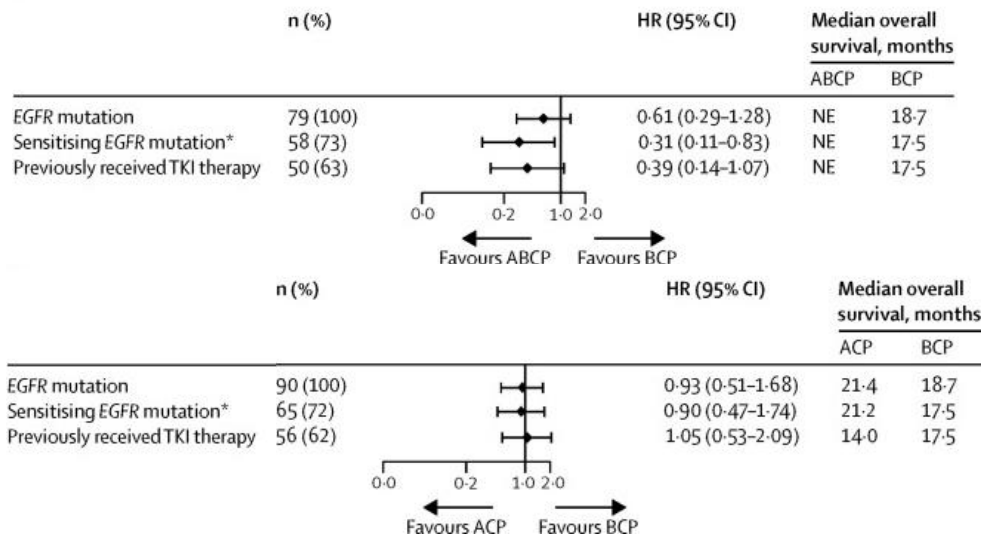
Antonia et al, NEJM 2018

# Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

## Meta-Analysis: CM-057, KN-010, POPLAR; IMPOWER-150




IMPOWER-150




CK Lee et al., JTO 2016
M Reck et al., Lancet Resp Med 2019

# PD-1/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

# Small cell lung cancer

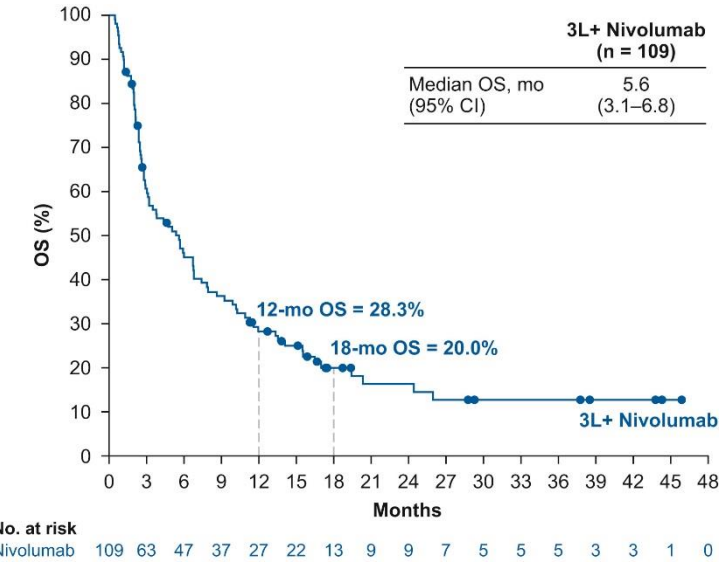
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

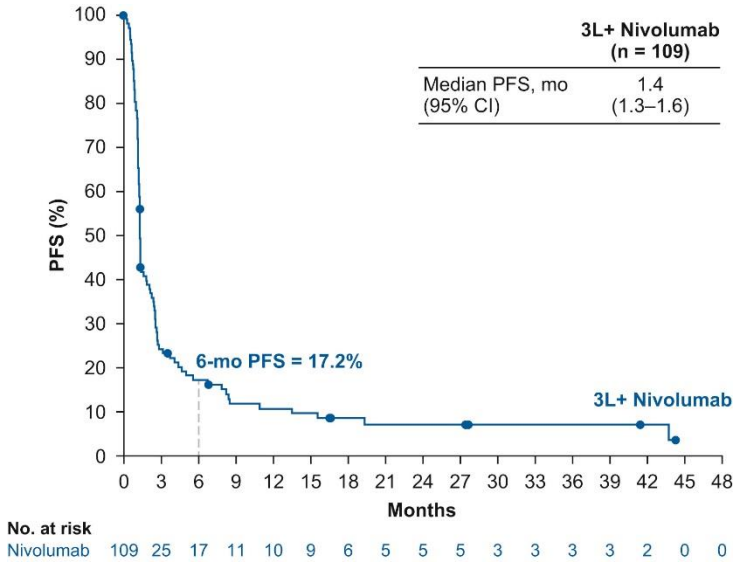
# Approved checkpoint inhibitors in SCLC

| Drug | Approved | Indication | Dose |
|---|---|---|---|
| **Nivolumab** | 2018 | Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line) | 240 mg Q2W |
| **Atezolizumab + carboplatin + etoposide** | 2019 | 1st line extensive stage SCLC | For 4 cycles: atezolizumab 1200 mg + carboplatin + etoposide Q3W Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W |
| **Pembrolizumab** | 2019 | Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (3rd line) | 200 mg Q3W |

# CheckMate-032: Nivolumab in 3rd line SCLC

- Nivolumab in SCLC with progression on platinum chemotherapy and another therapy
- Nivolumab 3 mg/kg Q2W
- @28.3 months:
  - ORR: 11.9%
  - mDOR: 17.9 months



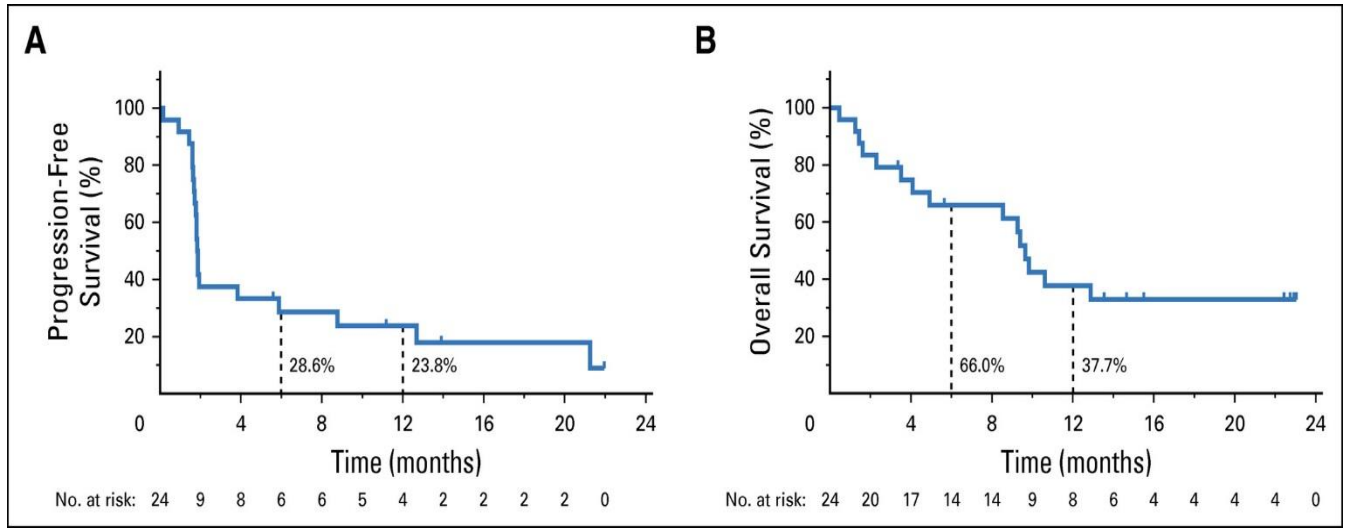




Ready, J Thorac Oncol 2019

# Pembrolizumab in 3rd-line SCLC

- KEYNOTE-028: PD-L1+ only (Cohort C1)
- KEYNOTE-158: PD-L1 +/- (Cohort G)
- Combined analysis:
- ORR: 19.3%
  - 2 CR, 14 PR
  - 14/16 responders were PD-L1+
  - 9/16 responders had response ≥18 mo.
- mOS: 7.7 months

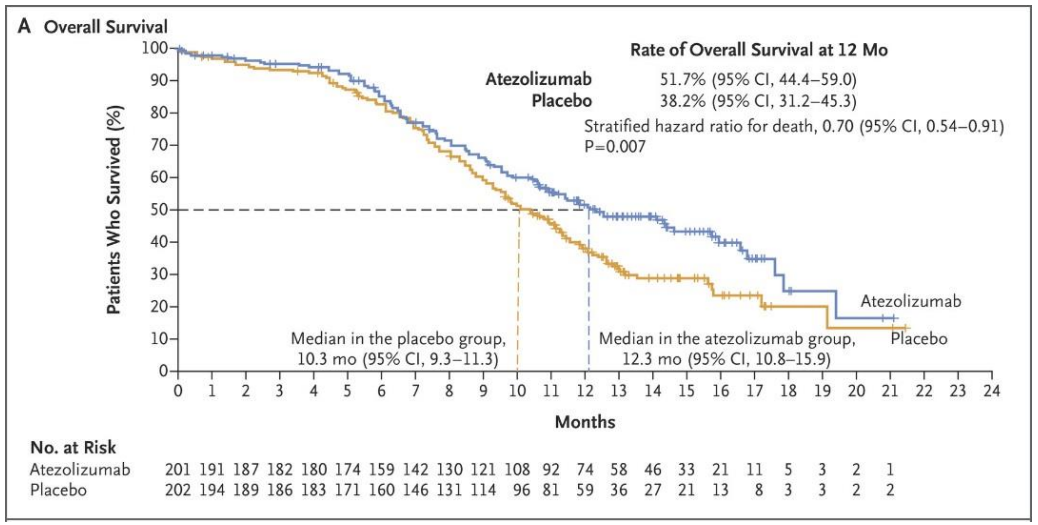
PD-L1+ (KEYNOTE-028)




Ott, J Clin Oncol 2017.

# IMpower133: Atezolizumab + chemo in 1st-line SCLC

- Induction phase: four 21-day cycles of carboplatin and etoposide + atezolizumab (1200 mg once per cycle) or placebo
- Maintenance phase: either atezolizumab or placebo
- @13.9 mo:
  - mOS = 12.3 vs 10.3 mo
  - mPFS = 5.2 vs 4.3 mo




Horn, NEJM 2018.

# Conclusions

- NSCLC has been a proving ground for checkpoint inhibitors
- Moving from 2nd/3rd line options to the front line
- Clear-cut biomarkers still lacking

# Resources

Brahmer *et al. Journal for ImmunoTherapy of Cancer* (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

Journal for ImmunoTherapy of Cancer

**POSITION ARTICLE AND GUIDELINES** **Open Access**

## The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

Julie R. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki A. Papadimitrakopoulou[15], David L. Rimm[16], Lawrence H. Schwartz[17], Boris Sepesi[18], Beow Yong Yeap[19], Naiyer A. Rizvi[20] and Roy S. Herbst[21*]

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

# Case Studies

# Case Study 1

**Your patient is a 59 y/o gentleman with a 45 pack/year tobacco history presents with R-sided weakness and falls and ultimately diagnosed with adenocarcinoma of the lung with metastases to the brain and bone.**

Following palliative brain radiotherapy for the symptomatic brain metastases, he presents to your clinic for systemic therapy counseling and planning.

Aside from tobacco use and HTN, he has no other medical problems. ECOG PS is 1.

Comprehensive tumor molecular profiling performed on a nodal aspirate shows the following: microsatellite- stable, tumor mutation burden (TMB)- 50 muts/mb, PD-L1 22C3 tumor proportion score (TPS) 50%, and KRAS G12C mutation amongst many others.

# Case Study 1

**Which of the following is advised as an evidence-based palliative systemic therapy regimen in this patient's case?**

A. Carboplatin/Pemetrexed
B. Carboplatin/Pemetrexed/Pembrolizumab
C. Pembrolizumab
D. B and C
E. All of the above

# Case Study 1

**Answer:**

A. Carboplatin/Pemetrexed
B. Carboplatin/Pemetrexed/Pembrolizumab
C. Pembrolizumab
D. B and C
E. All of the above

# Case Study 1

**Discussion:**

Notable aspects of this patient's case include the following:

59 y/o gentleman with a 45 pack/year tobacco history presents with adenocarcinoma of the lung with metastases to the brain and bone.

He has no other medical problems. ECOG PS is 1.

Comprehensive tumor molecular profiling shows: microsatellite- stable, tumor mutation burden (TMB)- 50 muts/mb, PD-L1 TPS 50%, and KRAS G12C mutation.

On the basis of the landmark KEYNOTE trials, either **Pembrolizumab** alone (**KEYNOTE-024**) OR combination chemoimmunotherapy with **Carboplatin/Pemetrexed/Pembrolizuma**b (**KEYNOTE-189**) is a reasonable FDA-approved regimen for this patient due to **high tumor PD-L1 (TPS ≥50%) and absence of other actionable genomic alterations**.

Given high likelihood of brisk response with less toxicity associated with single agent Pembrolizumab vs. combination chemoimmunotherapy, **Pembrolizumab alone** is generally favored in this setting (high tumor PD-L1)– though whether upfront combination therapy might be superior in this setting remains uncertain.

# Case Study 2

Six months into the treatment course, the patient develops a grade 3 colitis from Pembrolizumab. He is admitted and treated with high dose IV steroids and remains on a slow outpatient PO steroid taper.

Most recent CT torso and MRI brain performed just prior to hospitalization shows overall partial response to therapy since initiation of Pembrolizumab 6 months ago; there are no new sites of disease/evidence of disease progression.

# Case Study 2

**What do you advise next for your patient?**

A. Resume Pembrolizumab IV every 3 weeks.
B. Administer Pembrolizumab at extended intervals of IV every 6 weeks.
C. Switch to Carboplatin/Pemetrexed.
D. Transition to active surveillance for now.

# Case Study 2

**Answer:**

A. Resume Pembrolizumab IV every 3 weeks.

B. Administer Pembrolizumab at extended intervals of IV every 6 weeks.

C. Switch to Carboplatin/Pemetrexed.

D. Transition to active surveillance for now.

# Case Study 2

**Discussion:**

The patient has had a known, significant immune-related adverse event (colitis, grade 3).

Suspension of Pembrolizumab and treatment with high dose steroids, followed by steroid taper over a minimum of 4-6 weeks is advised.

Re-challenge with Pembrolizumab might be considered in future following detailed discussion of risks, benefits, and alternatives with the patient.

Immune-related adverse events may be accompanied by continued durable disease control even in the absence of continued regular administration of the immune checkpoint inhibitor.

**Active surveillance is a safe and viable strategy if the overall disease burden is stable.**