Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

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Levine Cancer Institute – Atrium Health

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

- Takeda (honoraria), AstraZeneca (advisory role), Merck (speakers' bureau), Celgene (research funding)
- 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**	

American Cancer Society

Society for Immunotherapy of Cancer
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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 mNSCLC

Nivolumab: 2nd line Non-Sq mNSCLC

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

2016

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

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

Atezolizumab: 2nd line mNSCLC

2017

Pembrolizumab + Pemetrexed/ Carboplatin: 1st line Non-Sq mNSCLC

2018

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

Nivolumab: 3rd line ES-SCLC

Pembrolizumab + Taxane/ Carboplatin: 1st line Sq-mNSCLC

2019

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

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

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

Atezolizumab + Paclitaxel protein-bound/Carboplatin: 1st line Non-Sq mNSCLC (December)

AAEM American Academy of Emergency Medicine · ACCC Association of Community Cancer Centers · HOPA Hematology/Oncology Pharmacy Association · sitc Society for Immunotherapy of Cancer

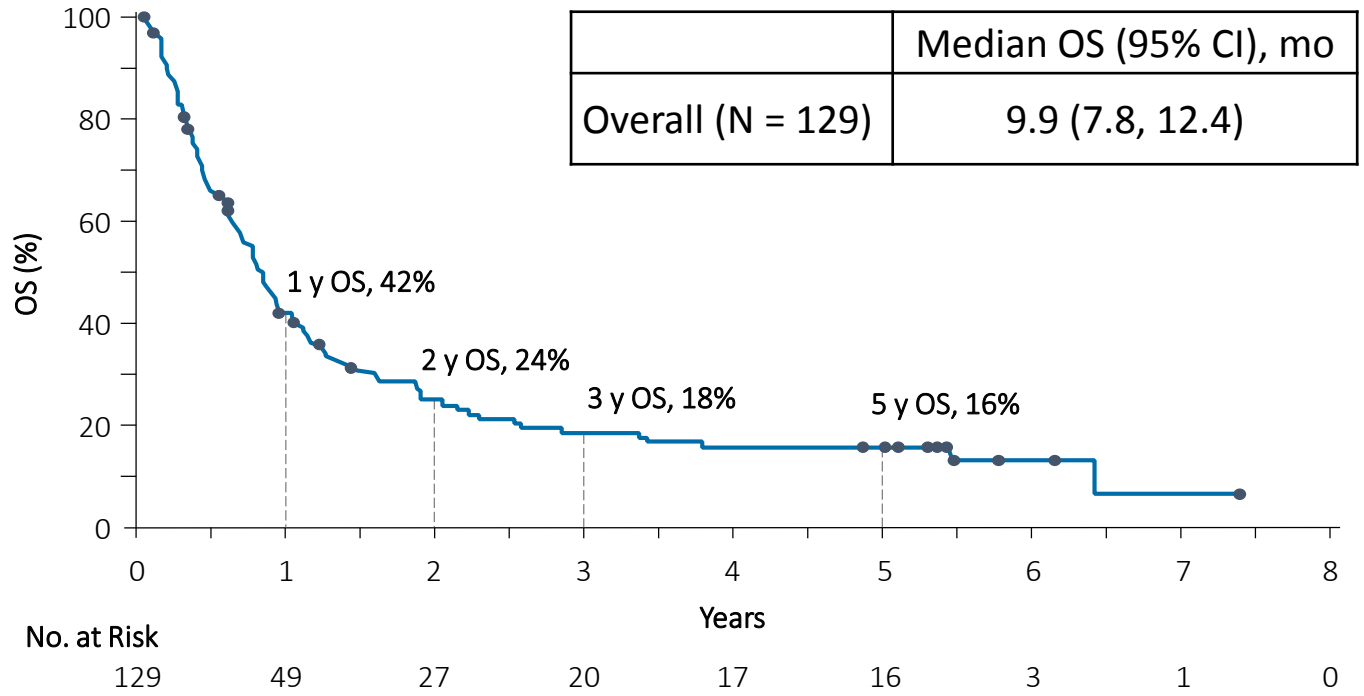
CA209-003: Nivolumab in heavily-pretreated advanced NSCLC (NCT00730639)

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-001: Pembrolizumab in advanced NSCLC

Phase I, 5-Year Update

101 treatment-naïve mNSCLC

- mOS = 22.3 months (95% CI, 17.1 - 32.3 mos)
- Estimated 5-year OS was 23.2%
- With PD-L1 TPS ≥ 50%, 5-year OS = 29.6%

449 previously treated mNSCLC

- mOS = 10.5 months (95% CI, 8.6 - 13.2 mos)
- Estimated 5-year OS = 15.5%
- With PD-L1 TPS ≥ 50%, 5-year OS = 25.0%

Compared with analysis at 3 years, only three new-onset treatment-related grade 3 adverse events occurred (hypertension, glucose intolerance, and hypersensitivity reaction, all resolved).
No late-onset grade 4 or 5 treatment-related adverse events occurred.
Median follow-up was 60.6 months (range, 51.8 to 77.9 months). At data cutoff—November 5, 2018—450 patients (82%) had died.

Garon et al. ASCO 2019

Treatment Naïve Regimens: Competing Strategies in NSCLC

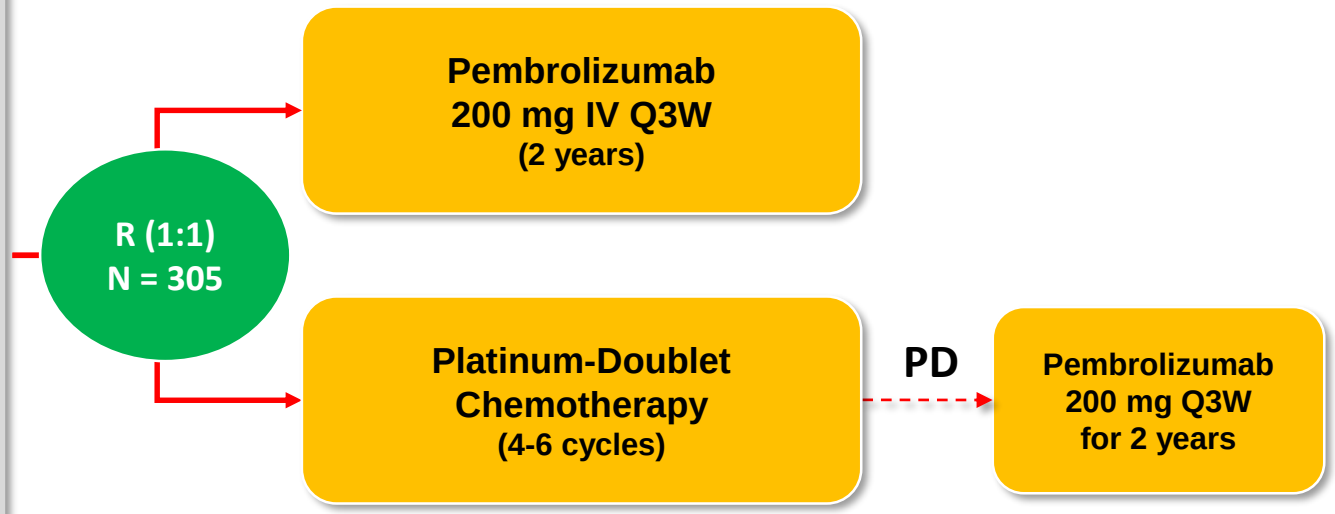
- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
- **KEYNOTE 189** – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in advanced non-squamous NSCLC
- **IMPOWER 150** – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy (Bev) in advanced non-squamous NSCLC
- **IMPOWER 130** – Atezolizumab + Chemotherapy vs. Chemotherapy 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 (≥10 mut/Mb)

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

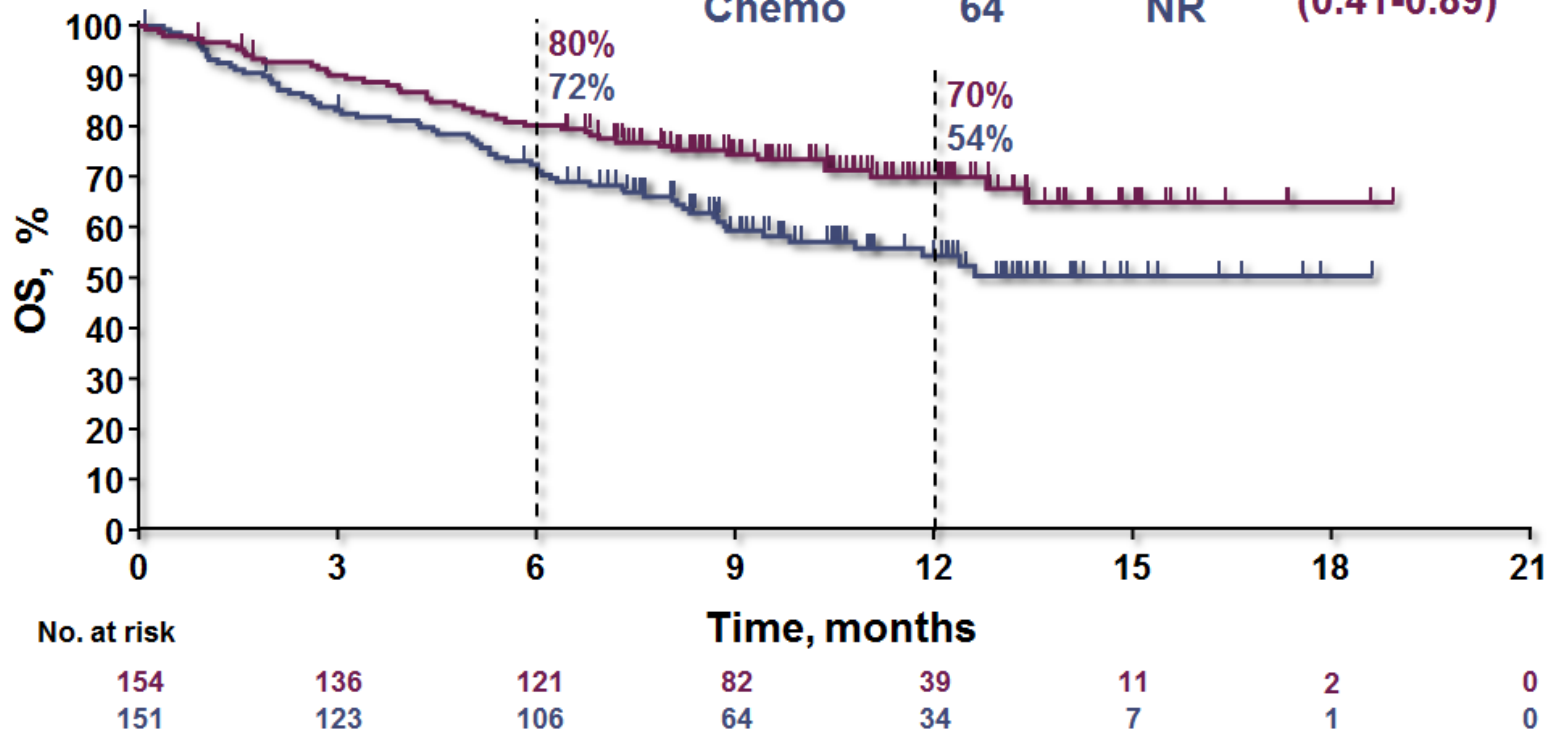


Reck M et al, ESMO 2016, NEJM 2016

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

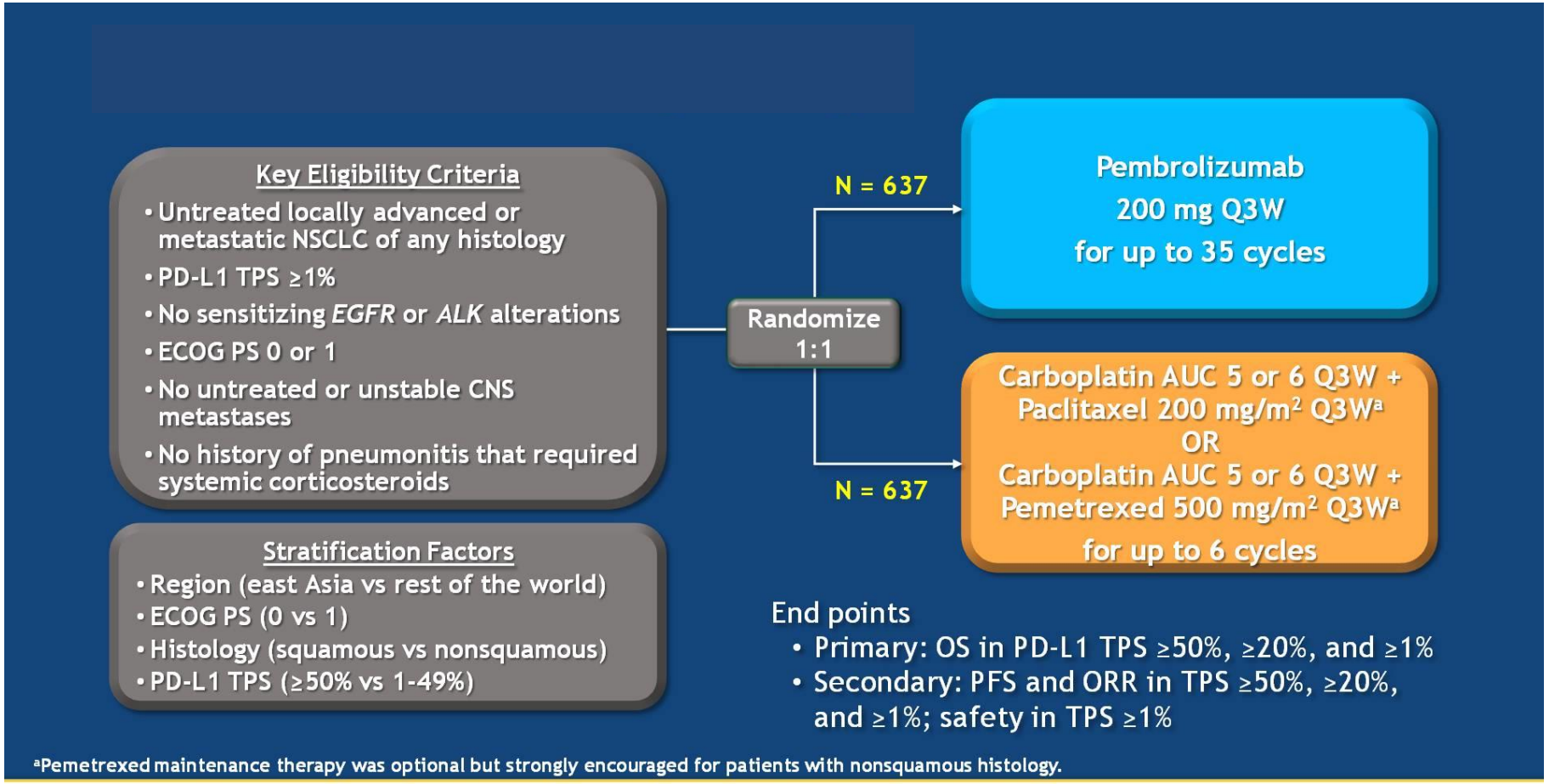
Overall Survival

	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

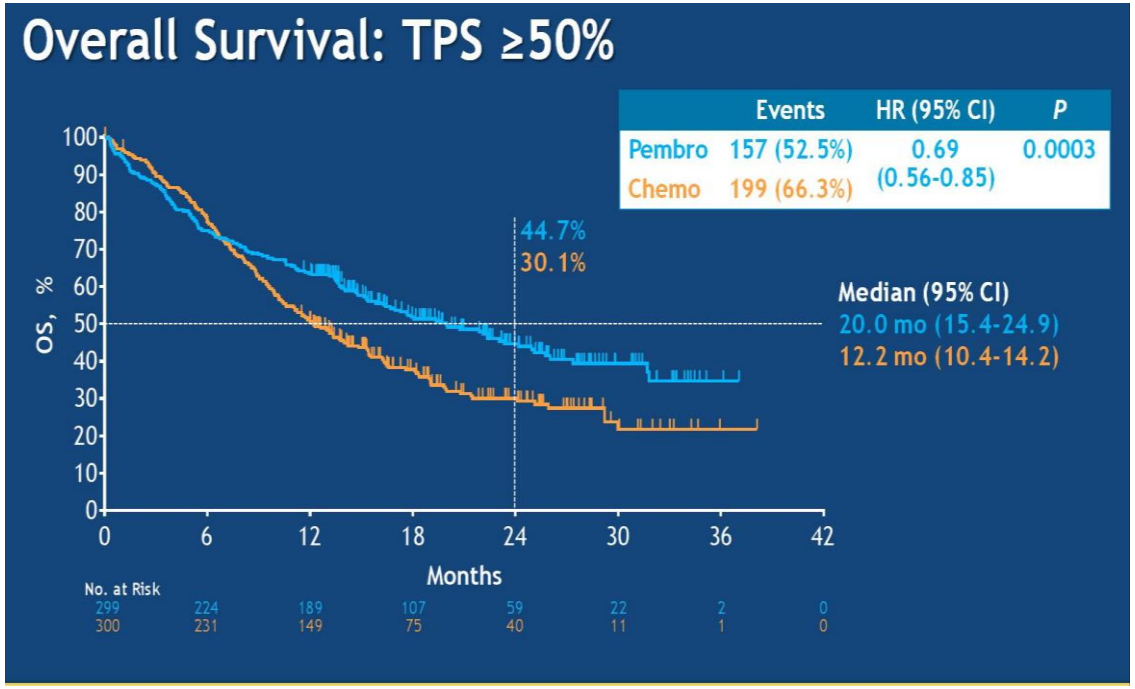
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

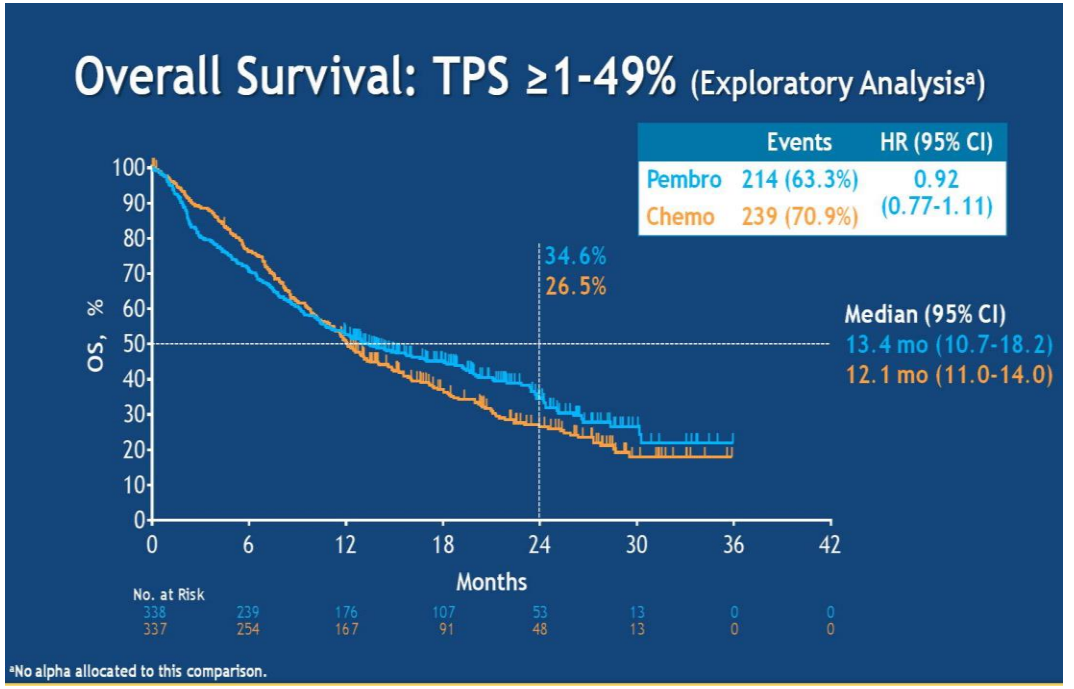


Lopes et al, ASCO 2018

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

Overall Survival

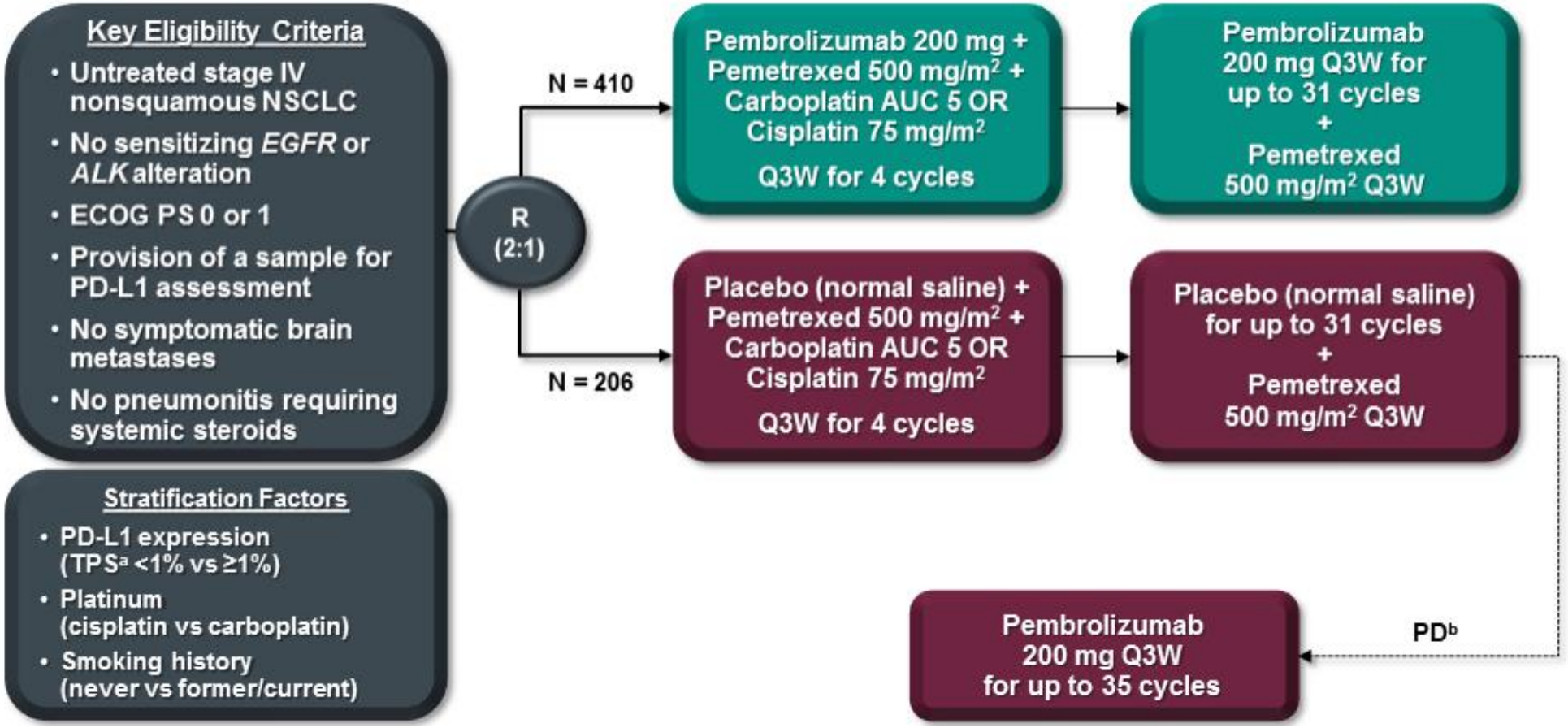




Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

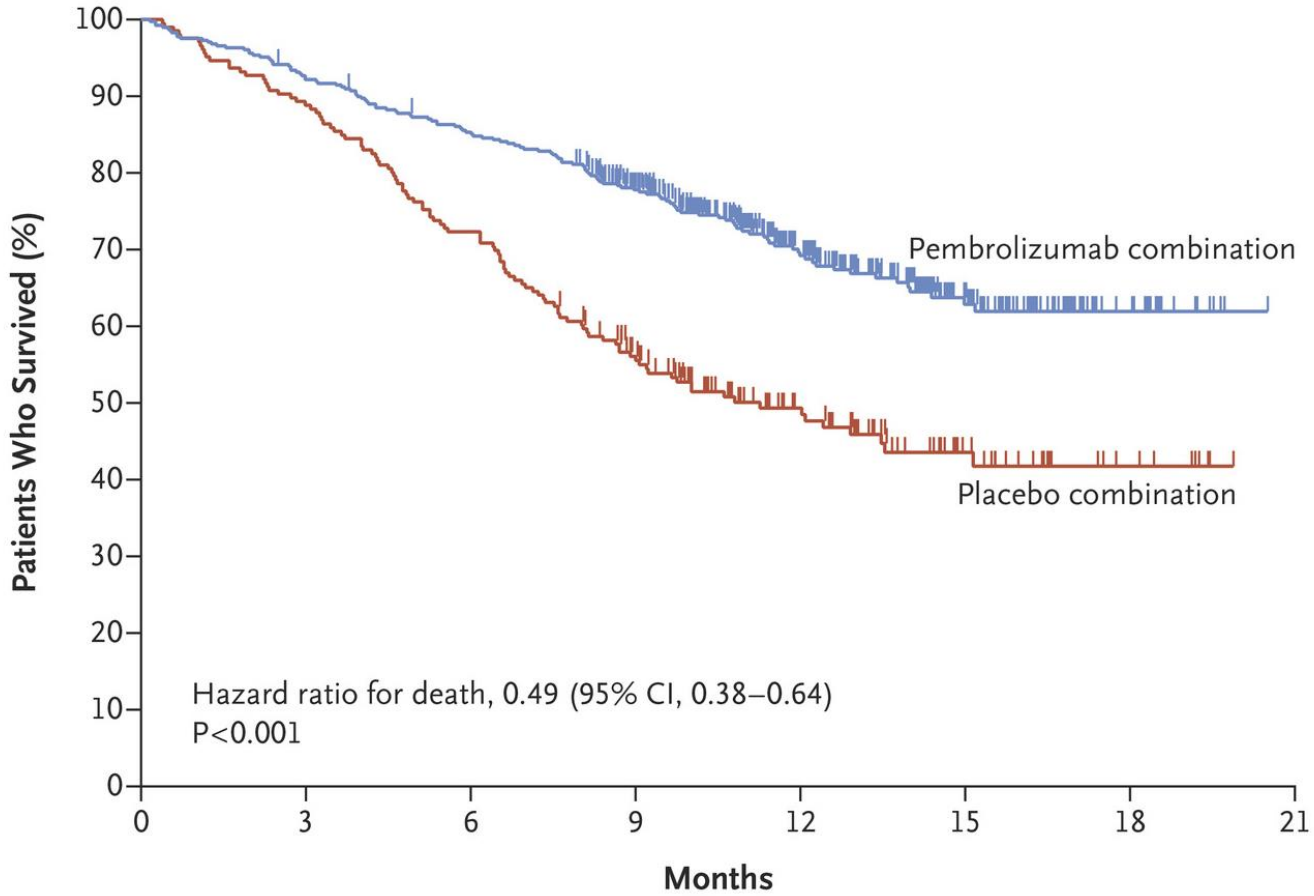
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

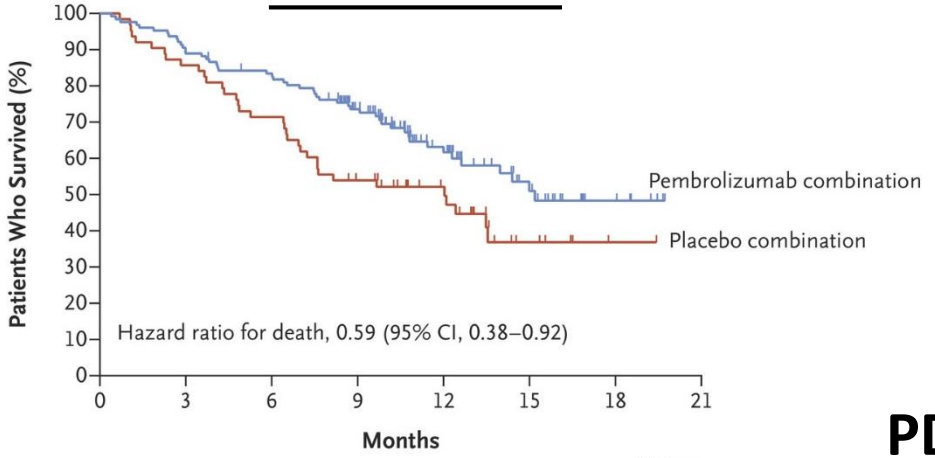
KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



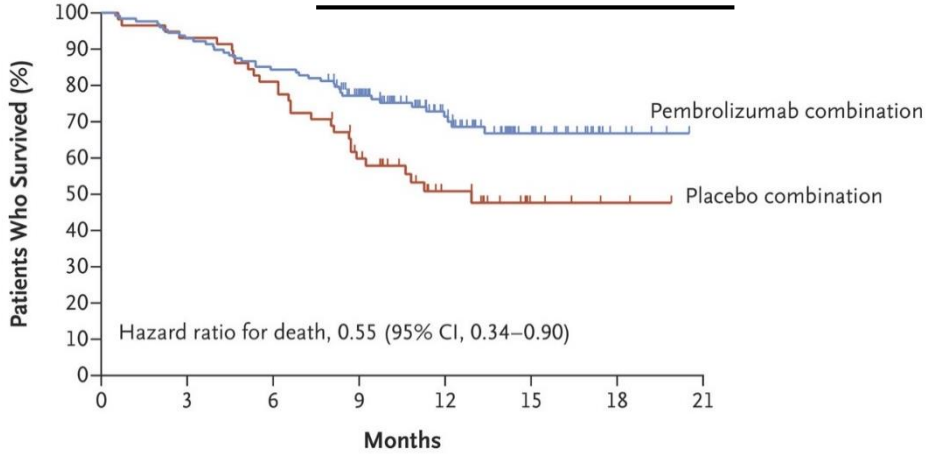
Ghandi et al, NEJM 2018

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

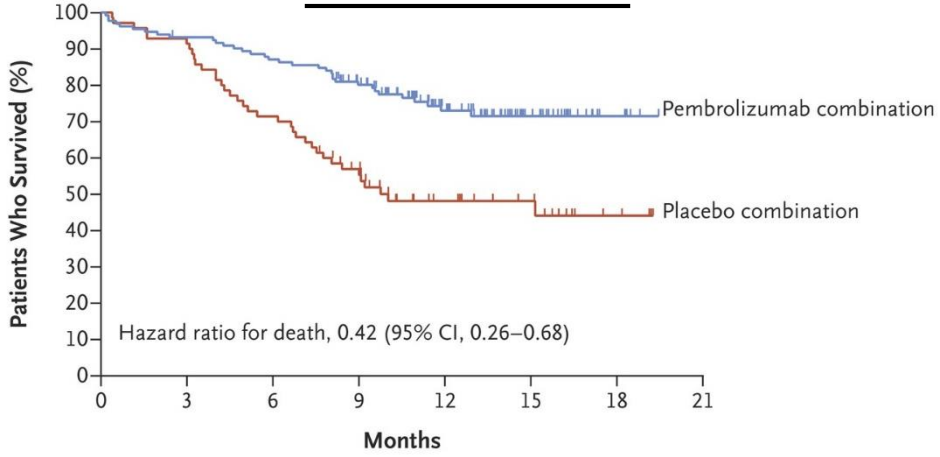
PD-L1 < 1%



PD-L1 = 1 – 49%

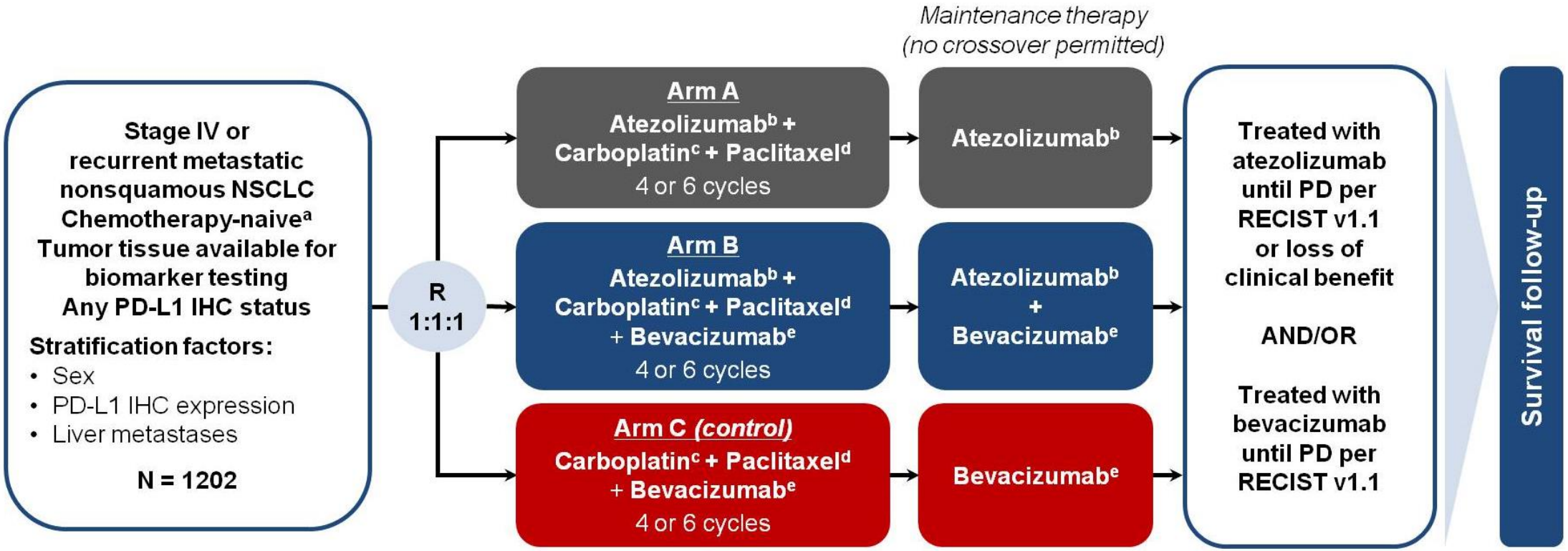


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

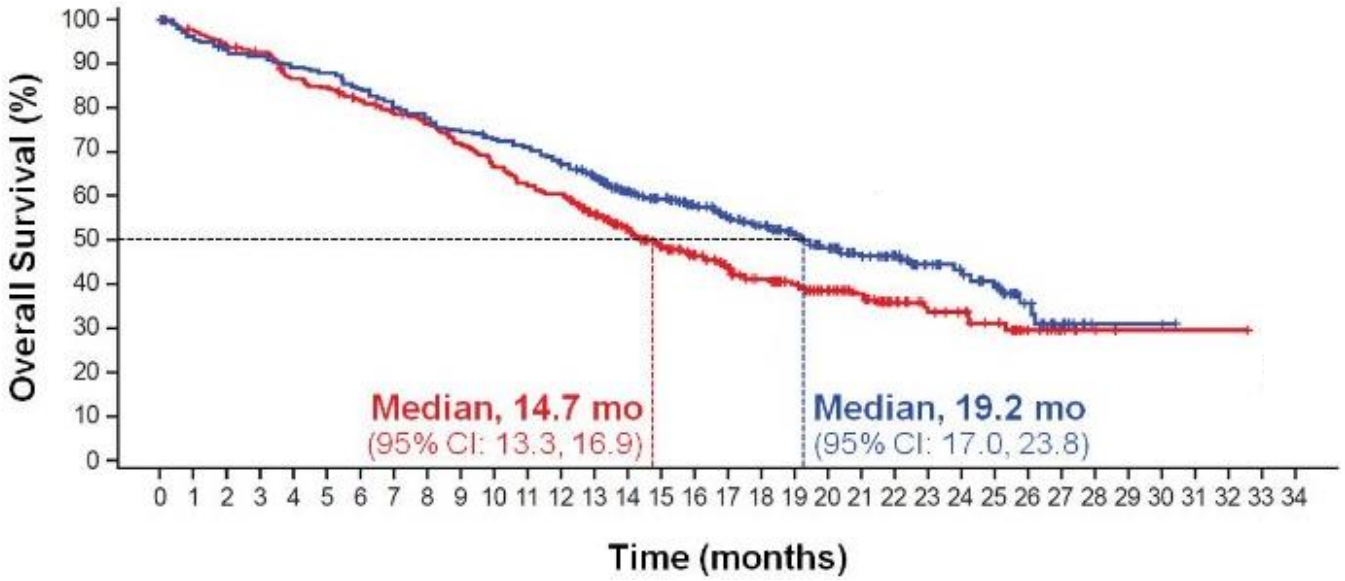


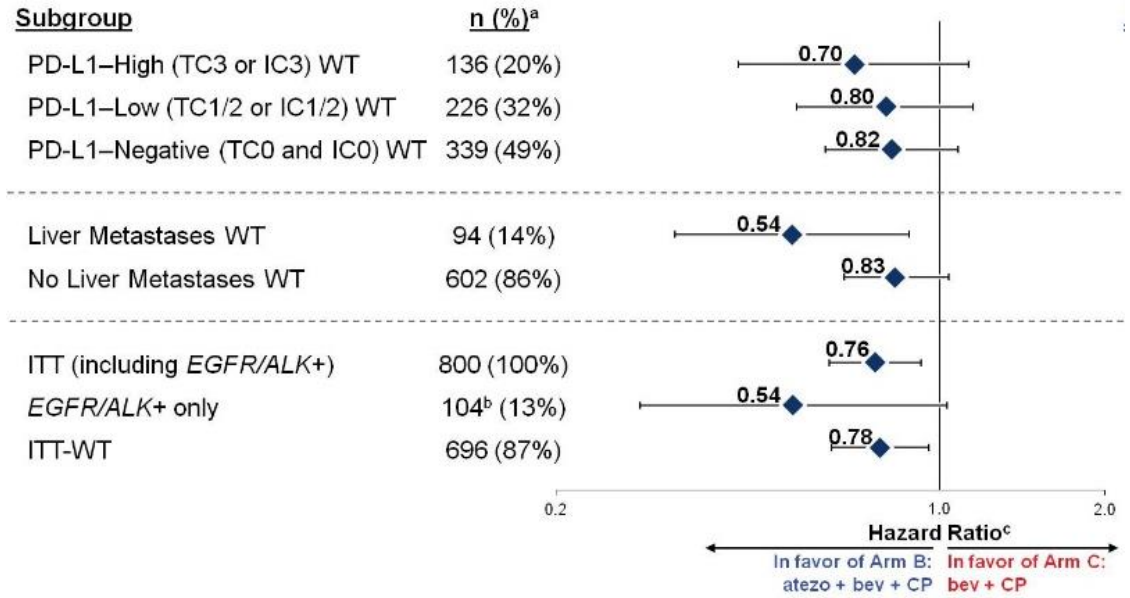
Socinski et al, NEJM 2018

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 130: Atezolizumab/Carboplatin/ Nab-paclitaxel vs Carboplatin/Nab-paclitaxel in Advanced Non-squamous NSCLC

- 681 patients randomized (2:1)
- Carboplatin D1 + nab-paclitaxel D1, D8, D15 +/- atezolizumab every 21 days for 4-6 cycles followed by maintenance (atezolizumab vs BSC)
- mPFS = 7.2 vs 6.5 months; HR=0.75; 95% CI: 0.63-0.91; p=0.0024
- mOS = 18.6 vs 13.9 months; HR=0.80; 95% CI: 0.64-0.99; p=0.0384

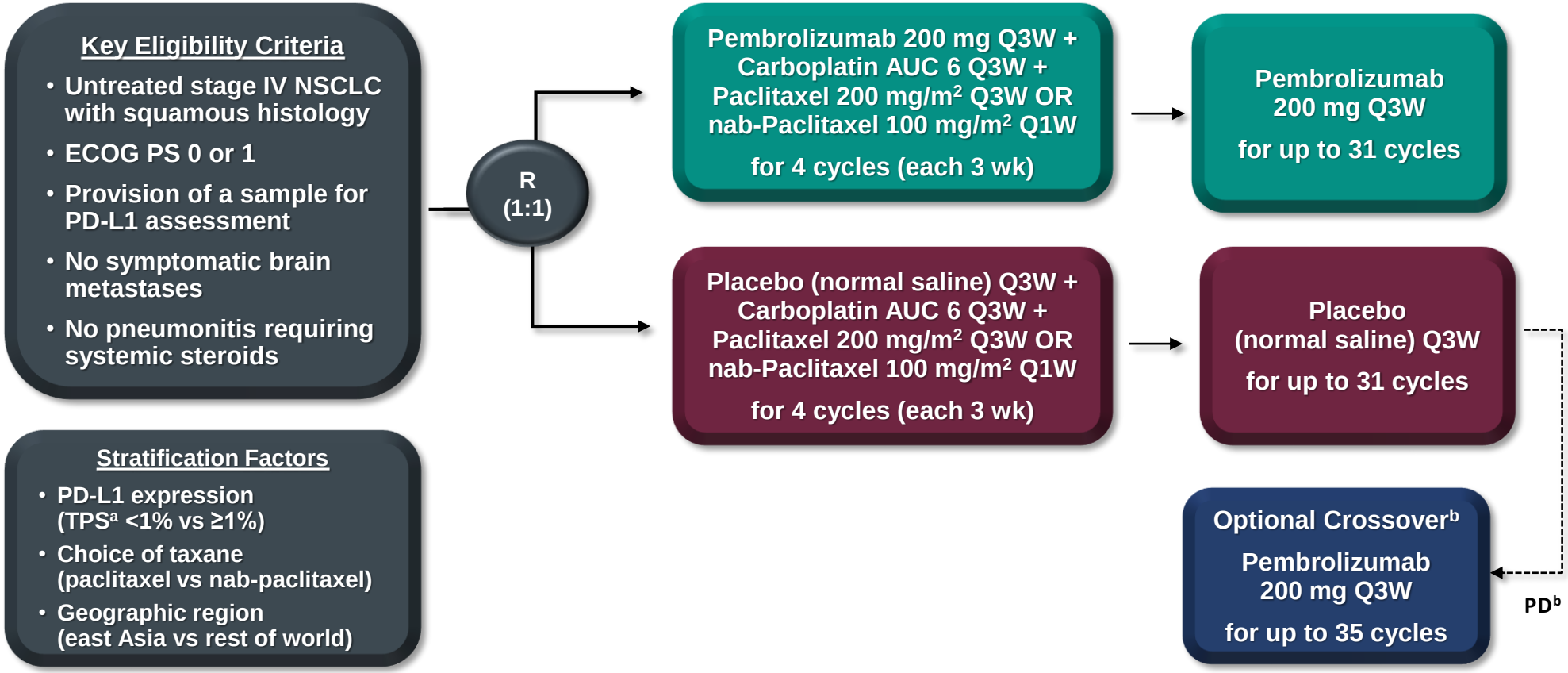
CHECKMATE 227: Nivolumab plus Ipilimumab in Advanced NSCLC

- PD-L1 >= 1% randomized 1:1:1 to nivo+ipi vs nivo vs chemo
- PD-L1 < 1% randomized 1:1:1 nivo+ipi vs nivo+chemo vs chemo

- Primary endpoint reported in NEJM (2019; 381:2020-2031) was OS with nivo + ipi vs chemo in patients with PD-L1 >= 1%
  - mOS = 17.1 vs 14.9 months (p=0.007)
  - 2-year OS rates = 40.0% vs 32.8%

- mDOR = 23.2 vs 6.2 months (chemo) vs 15.5 months (nivo alone)
- In those with PD-L1 < 1%, mDOR = 17.2 vs 12.2 months.

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

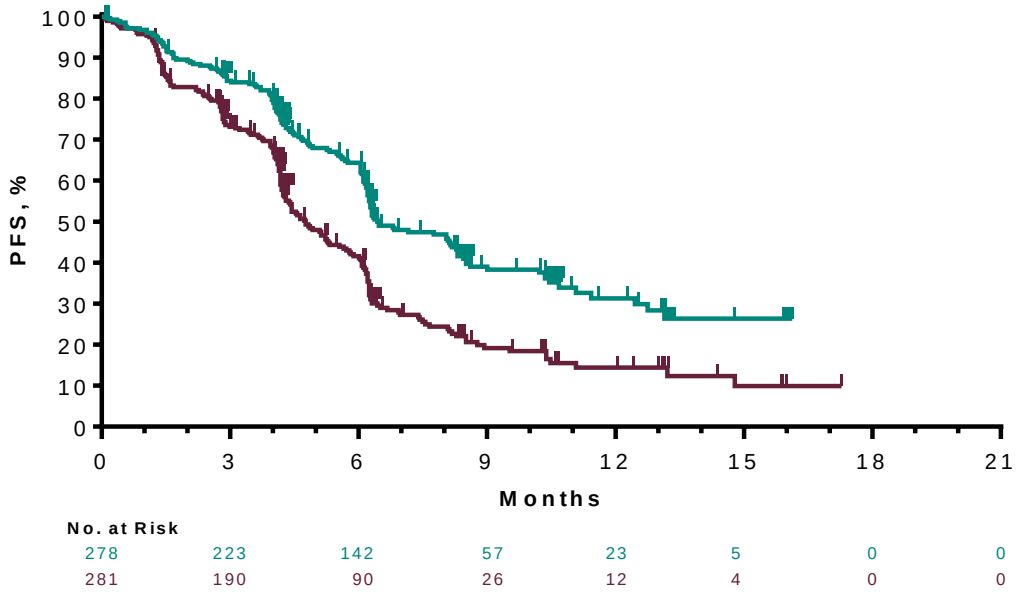


Paz-Ares et al, ASCO 2018

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

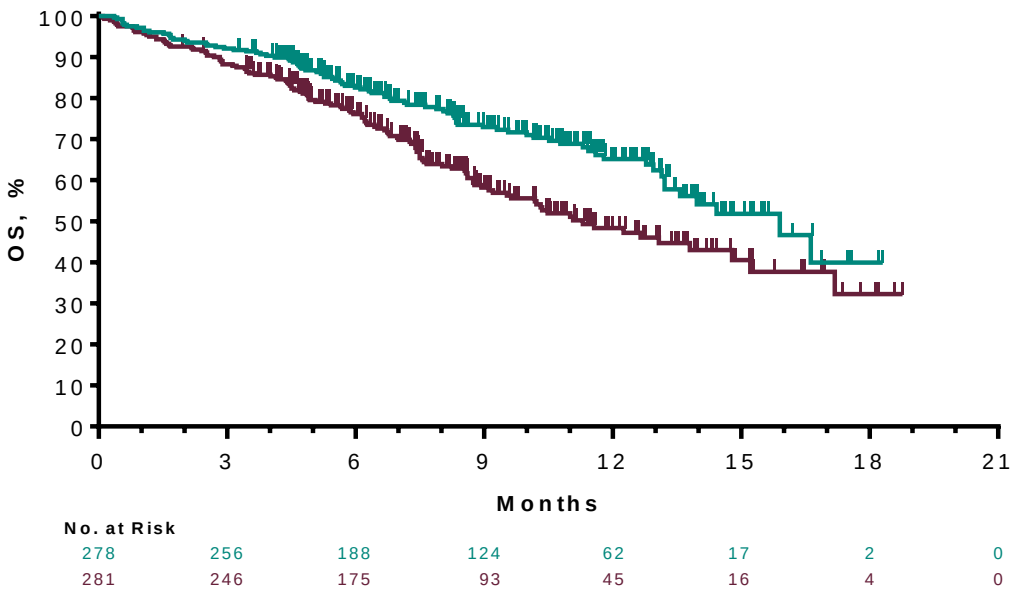
PFS (RECISTv1.1, BICR)

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



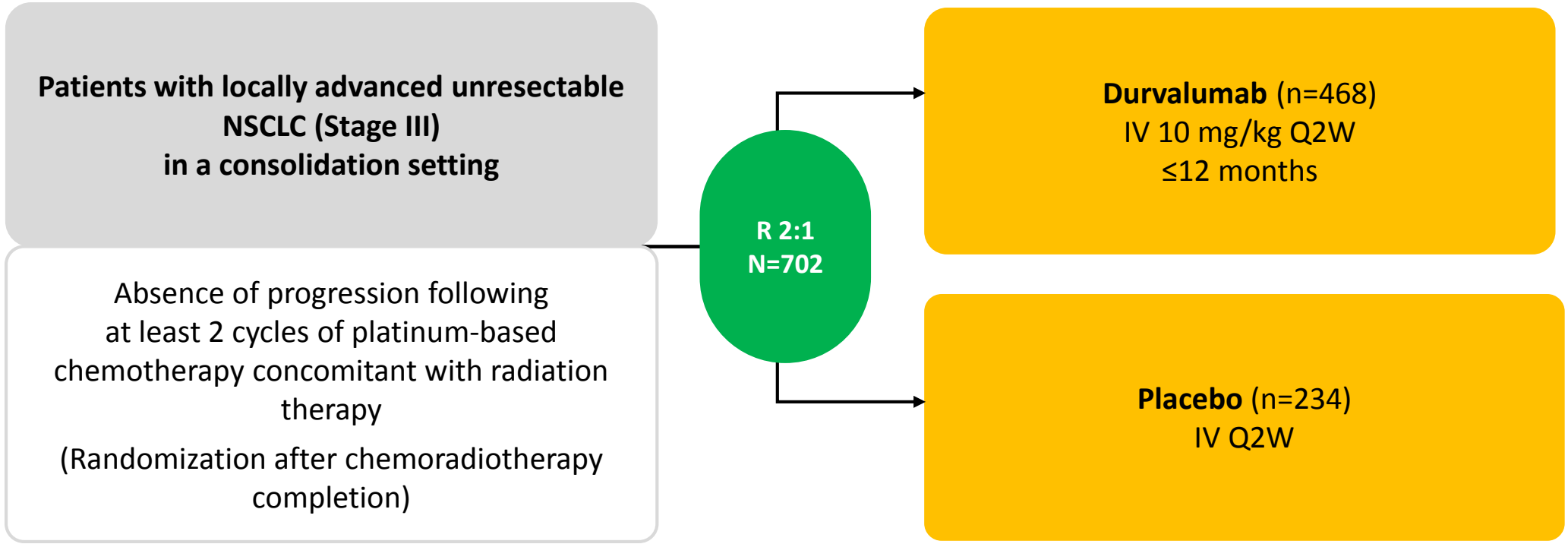
Overall Survival

	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

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

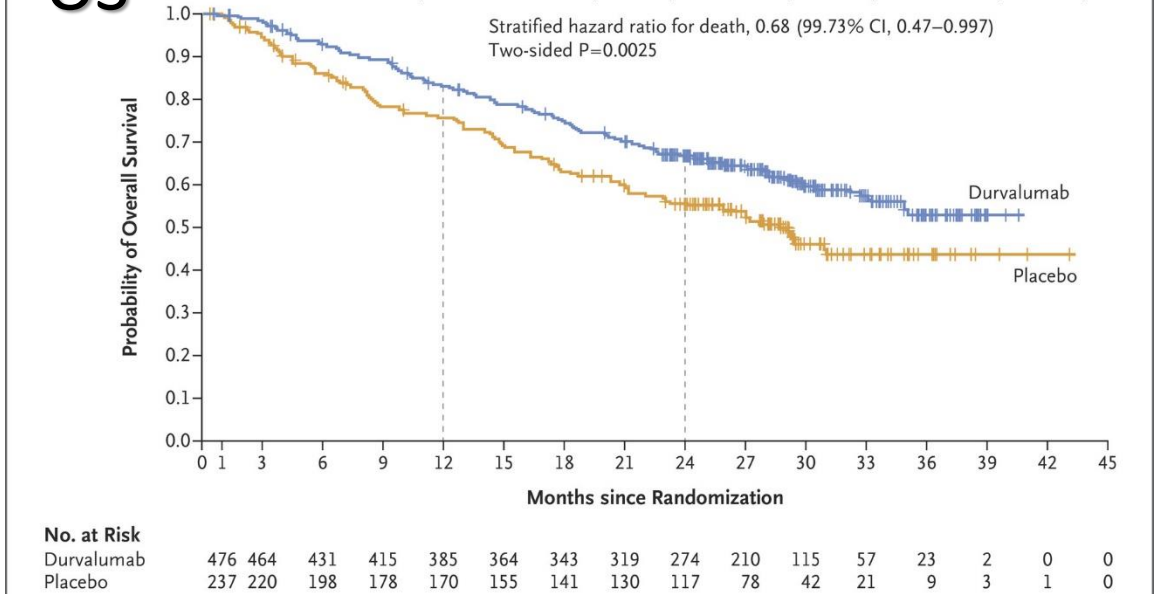


Antonia et al, NEJM 2018

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

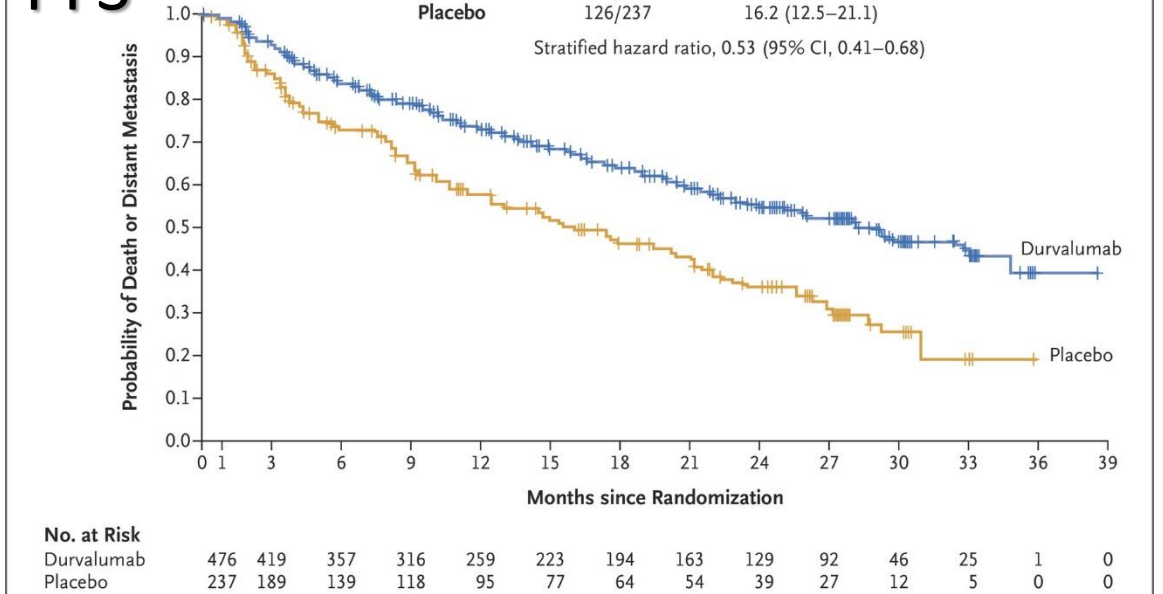
OS

	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)



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)

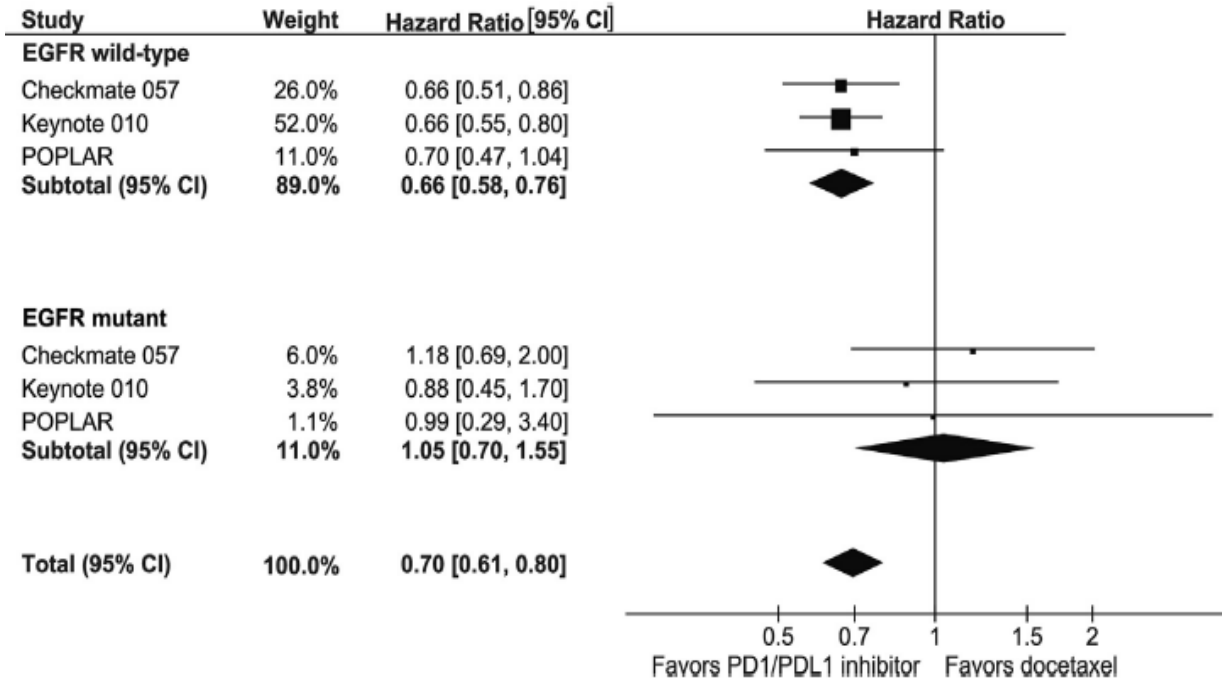


3-year OS update (stratified HR 0.69, 95% CI, 0.55–0.86) = median OS NR with durvalumab vs 29.1 months with placebo. 12-, 24- and 36-month OS rates were 83.1% versus 74.6%, 66.3% versus 55.3%, and 57.0% versus 43.5%, respectively.

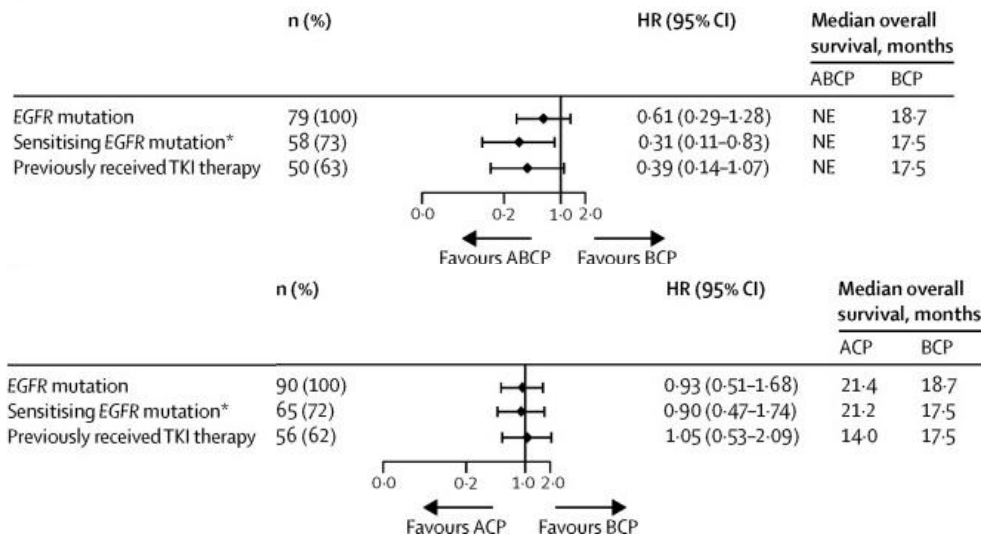
Antonia et al, NEJM 2018
Gray et al, JTO 2019

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

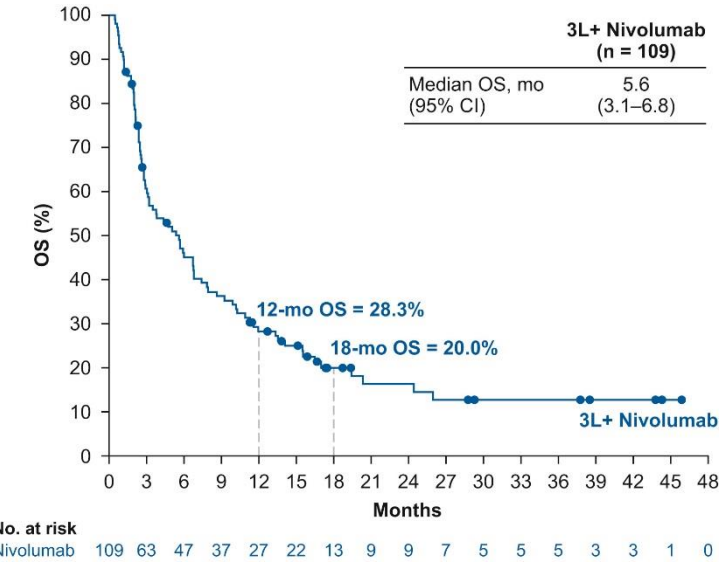
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

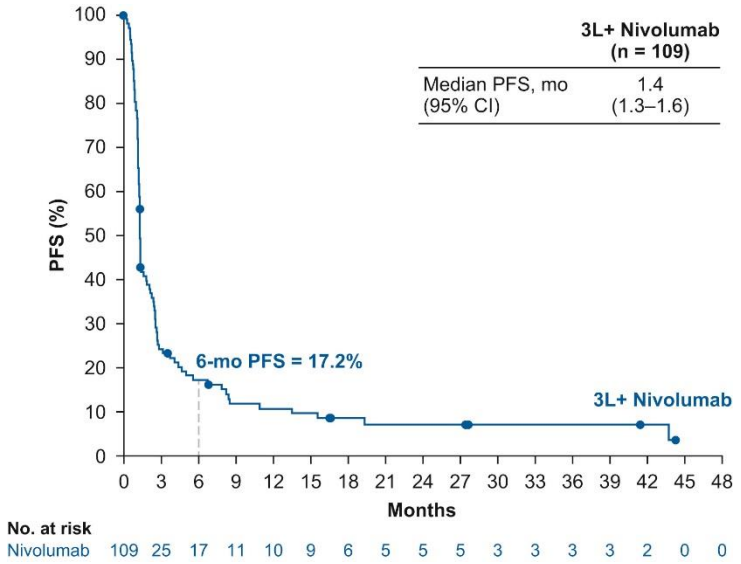
Approved checkpoint inhibitors in SCLC

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



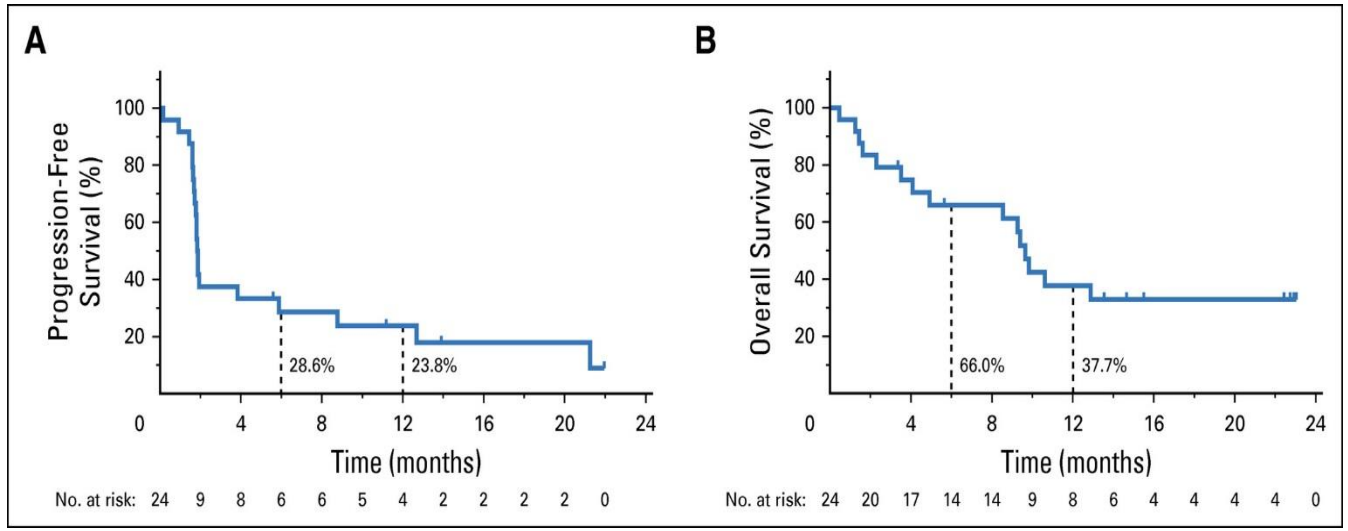


Ready, J Thorac Oncol 2019

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

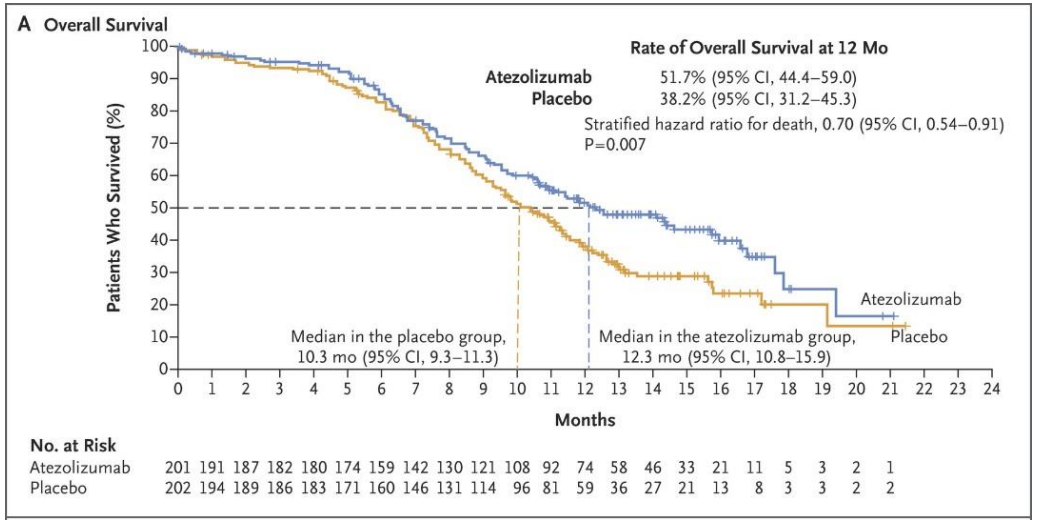
PD-L1+ (KEYNOTE-028)



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) 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.
- 2nd and 3rd line options have moved to first line treatment.
- All patients with lung cancer without contraindications to immunotherapy should receive immunotherapy.
  (regardless of PD-L1, TMB, histologic subtype)
- Those with driver mutations should receive targeted therapy first.

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)

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Case Studies

Case Study 1

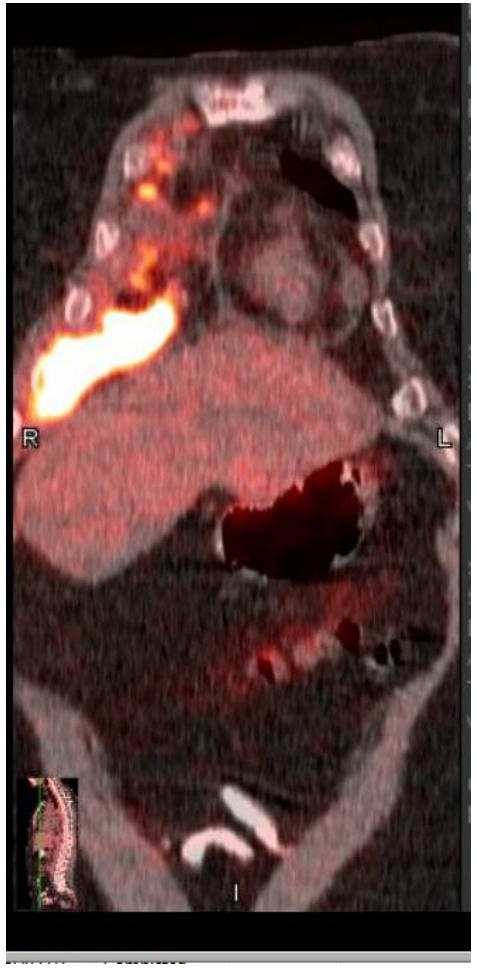
- A 46-year-old female never-smoker presents to medical oncology with a new diagnosis of metastatic adenocarcinoma of the lung based on contrasted CT chest and pleural fluid cytology.
- She has a remote history of Hodgkin lymphoma treated with MOPP-ABVD (and no radiation).
- She initially presented with a right pleural effusion under tension and underwent emergent thoracentesis with the removal of 1700cc of pleural fluid.
- Cytology was positive for malignancy: CK-7 and TTF-1 positive; GATA-3, PAX-8, CDX-2 and CK20 are negative; mucicarmine is negative; napsin and estrogen receptor staining is weak.
- She has recurrent pleuritic pain, shortness of breath, cough, and nausea without emesis. However, her ECOG PS is still zero.

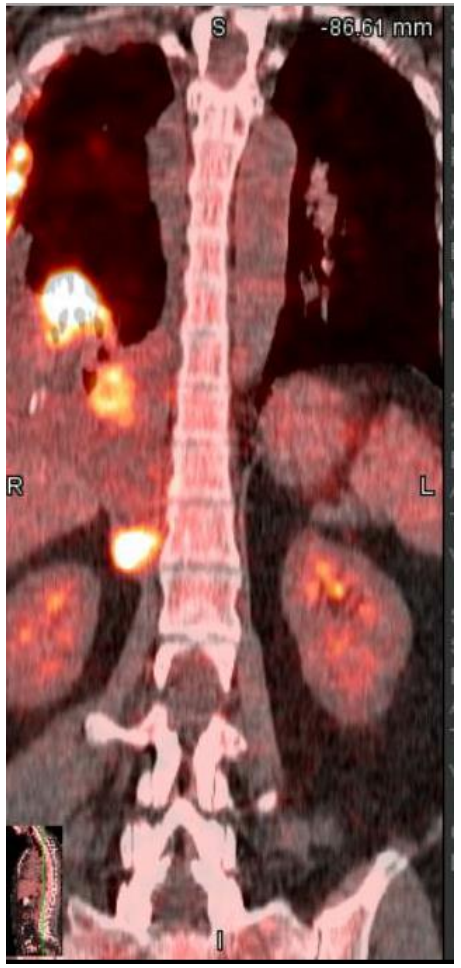
Case Study 1: What additional information do you need?

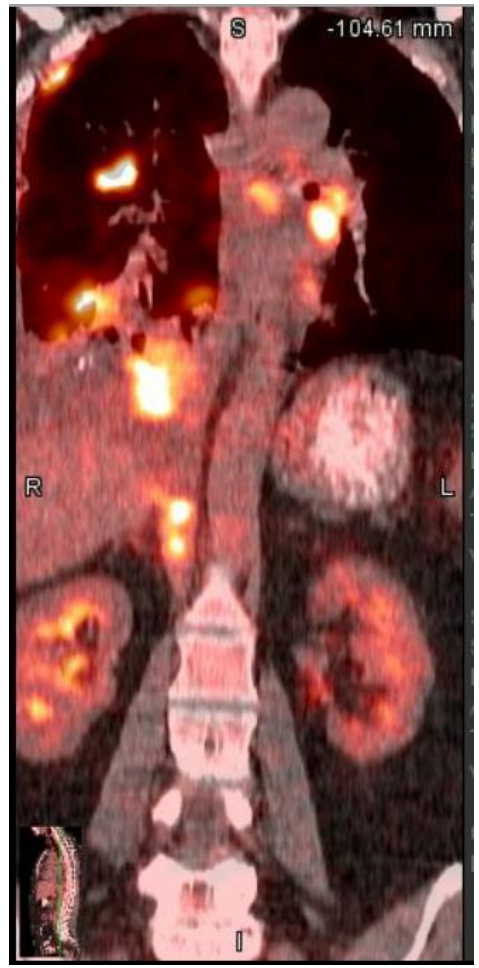
1. Brain MRI with and without contrast
    1. Standard of care to complete staging
    2. Patient has nausea
2. PET/CT
    1. Standard of care to complete staging
    2. Patient already has known metastatic disease and primary tumor was not identified on contrasted CT with voluminous effusion
3. Molecular studies
    1. Standard of care with metastatic non-squamous non-small cell lung cancer
    2. Recommended with metastatic squamous cell non-small cell lung cancer in never smokers
    3. These should include but are not limited to EGFR, ALK, ROS1, BRAF, PD-L1, +/- NTRK.

Case Study 1: Additional Information

1. Brain MRI with and without contrast – negative for malignancy
2. PET/CT – as demonstrated
3. Molecular studies
    1. EGFR, ALK, ROS1, BRAF non-mutated on tissue
    2. No driver aberrations on plasma
    3. PD-L1 TPS zero







Case Study 1: What is the next step?

A. Carboplatin-pemetrexed
   A. Incorrect. This is no longer the standard of care.

B. Pembrolizumab monotherapy
   A. Incorrect. The PD-L1 TPS is zero.

C. Carboplatin-pemetrexed-pembrolizumab
   A. Correct. Based on KEYNOTE-189, this regimen can improve RR, PFS, OS regardless of PD-L1 TPS when compared with carboplatin-pemetrexed.

D. Carboplatin-paclitaxel-bevacizumab-atezolizumab
   A. Correct. Based on IMPOWER-150, this regimen can improve outcome regardless of PD-L1 TPS when compared with carbo-taxol-bevacizumab.

E. EGFR tyrosine kinase inhibitor
   A. Incorrect. Just because she is a never smoker does not mean that she will respond to an EGFR TKI. There was no EGFR sensitizing mutation.

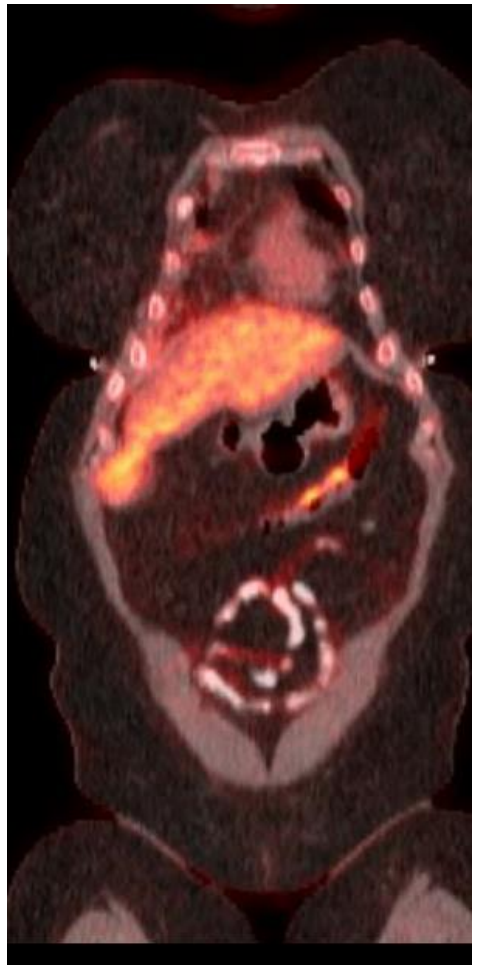
F. Obtain more information prior to starting treatment
   A. This is no indication for delay treatment in a symptomatic patient with the current information.
   B. The cell block was sent for broader molecular sequencing and was not revealing.

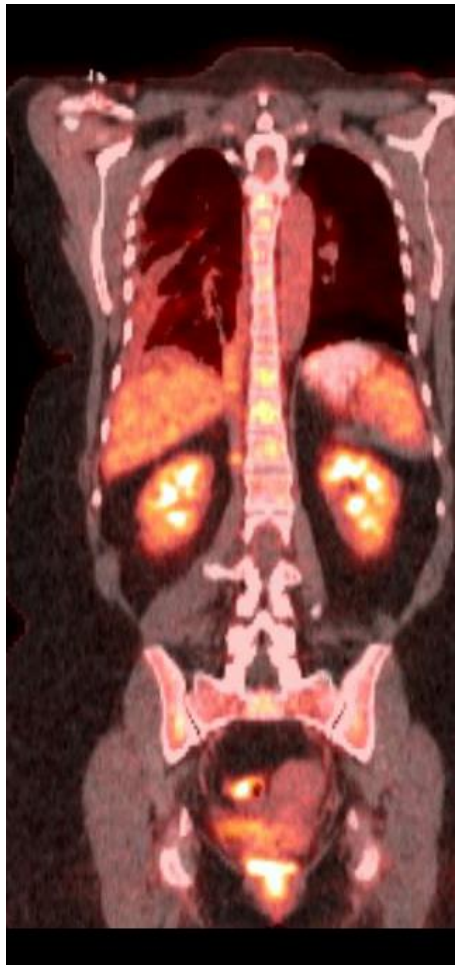
G. Pursue clinical trial
   A. This is always an appropriate option.
   B. She was excluded due to history of lymphoma.

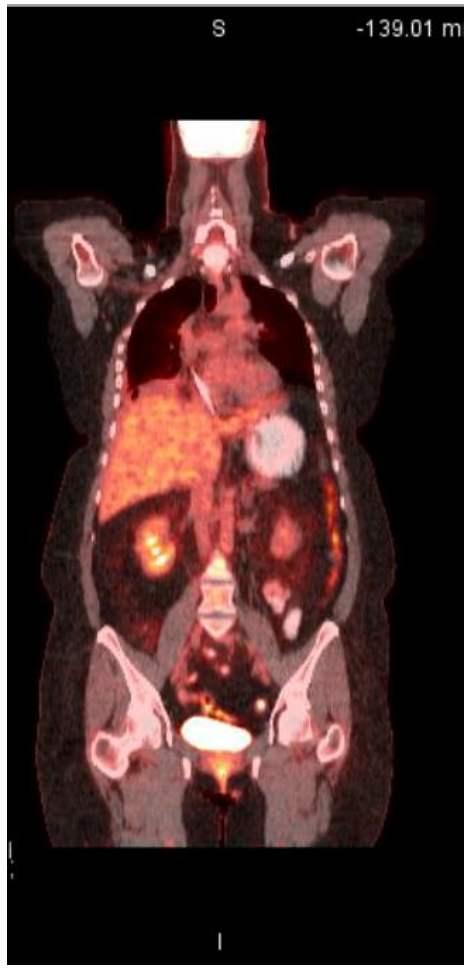
H. Provide other supportive interventions
   A. Consulting palliative medicine, nutrition, social work, navigation, integrative medicine is always an appropriate option.
   B. She had no indication for palliative radiation. She did have a pleural based catheter placed.

Case Study 1: Results

- This patient was diagnosed on 3/30/2017.
- The data from IMPOWER150 were not available.
- She was treated with four cycles of pembrolizumab-carboplatin-pemetrexed.
- She then transitioned to pembrolizumab-pemetrexed maintenance.
- She completed 35 cycles of pembrolizumab.
- She continued pemetrexed maintenance.







Case Study 2

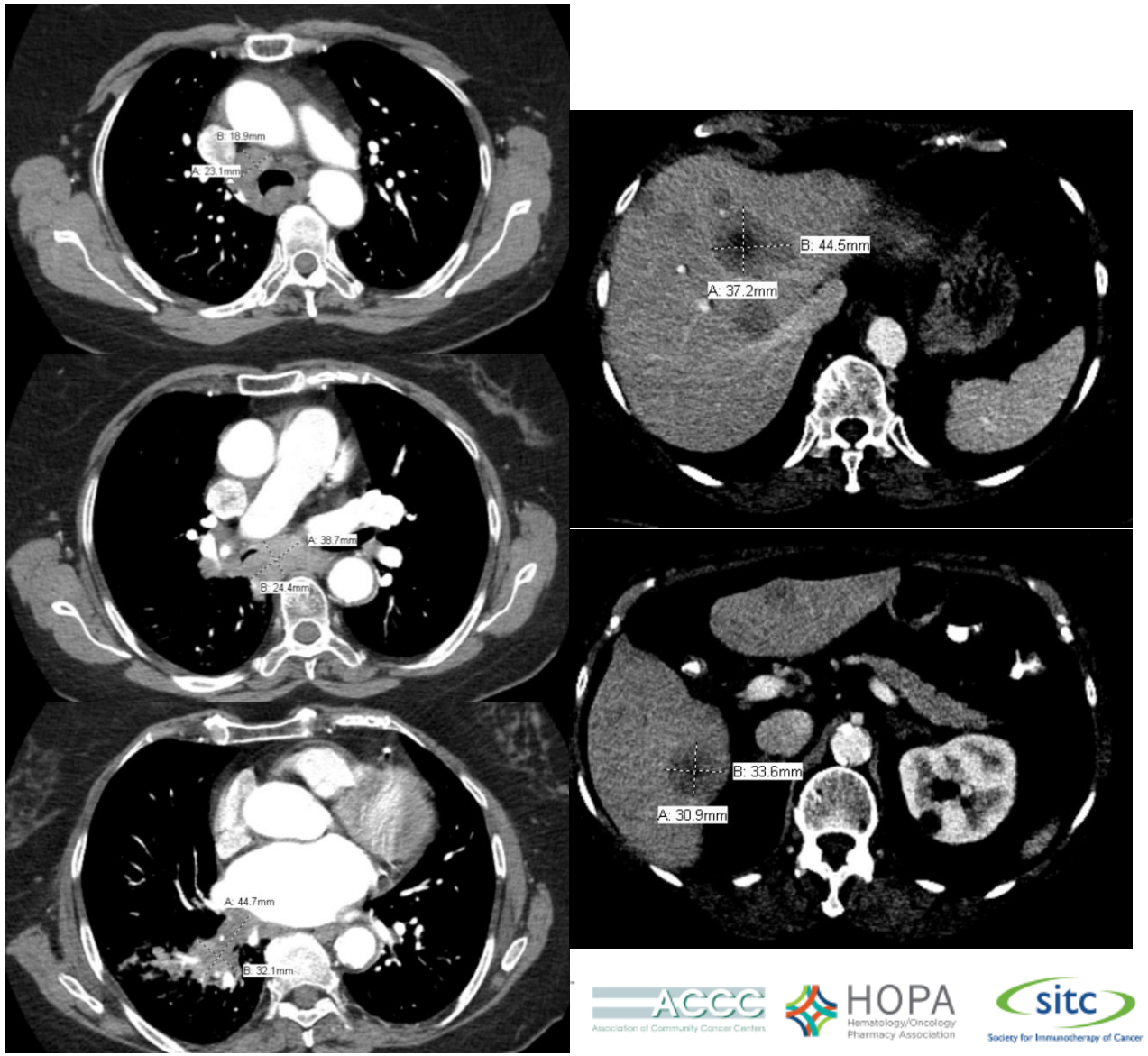
- 78-year-old female with a history of hypertension and hyperlipidemia presents with a new diagnosis of extensive stage small cell lung cancer.
- She smoked 2 packs of cigarettes daily for 20 years and quit in 1990.
- She initially presented with unresolving cough and progressive dyspnea.
- CT angiogram of the chest was negative for pulmonary embolus but revealed a right lung mass, adenopathy, post-obstructive consolidation and metastatic findings in the subcutaneous tissue and liver.
- She underwent endobronchial ultrasound with biopsy via bronchoscopy and pathology was consistent with small cell lung cancer (Positive IHC for Synaptophysin, Cytokeratin Cam 5.2, CD56 and TTF-1).

Case Study 2: What additional information do you need?

- Brain MRI with and without contrast
  - Standard of care to complete staging
- CT abdomen/pelvis with contrast
  - Standard of care to complete staging
- PET/CT
  - Not required if extensive stage is already established but recommended and if not available, then bone scan may be used to identify metastases
- Labs including sodium
  - SIADH and other paraneoplastic processes are not uncommon in small cell lung cancer
- PD-L1 TPS
  - No indication for PD-L1 TPS or TMB testing in small cell lung cancer
- ECOG PS
  - Good PS (0-2) and poor PS (3-4) due to SCLC should be treated per standard

Case Study 2: Additional Information

1. Brain MRI with and without contrast – negative for malignancy
2. CT abdomen/pelvis – confirmed extensive metastatic disease in liver; negative for bone involvement
3. PET/CT – not completed
4. Sodium – 141 (normal)
5. ECOG PS – one

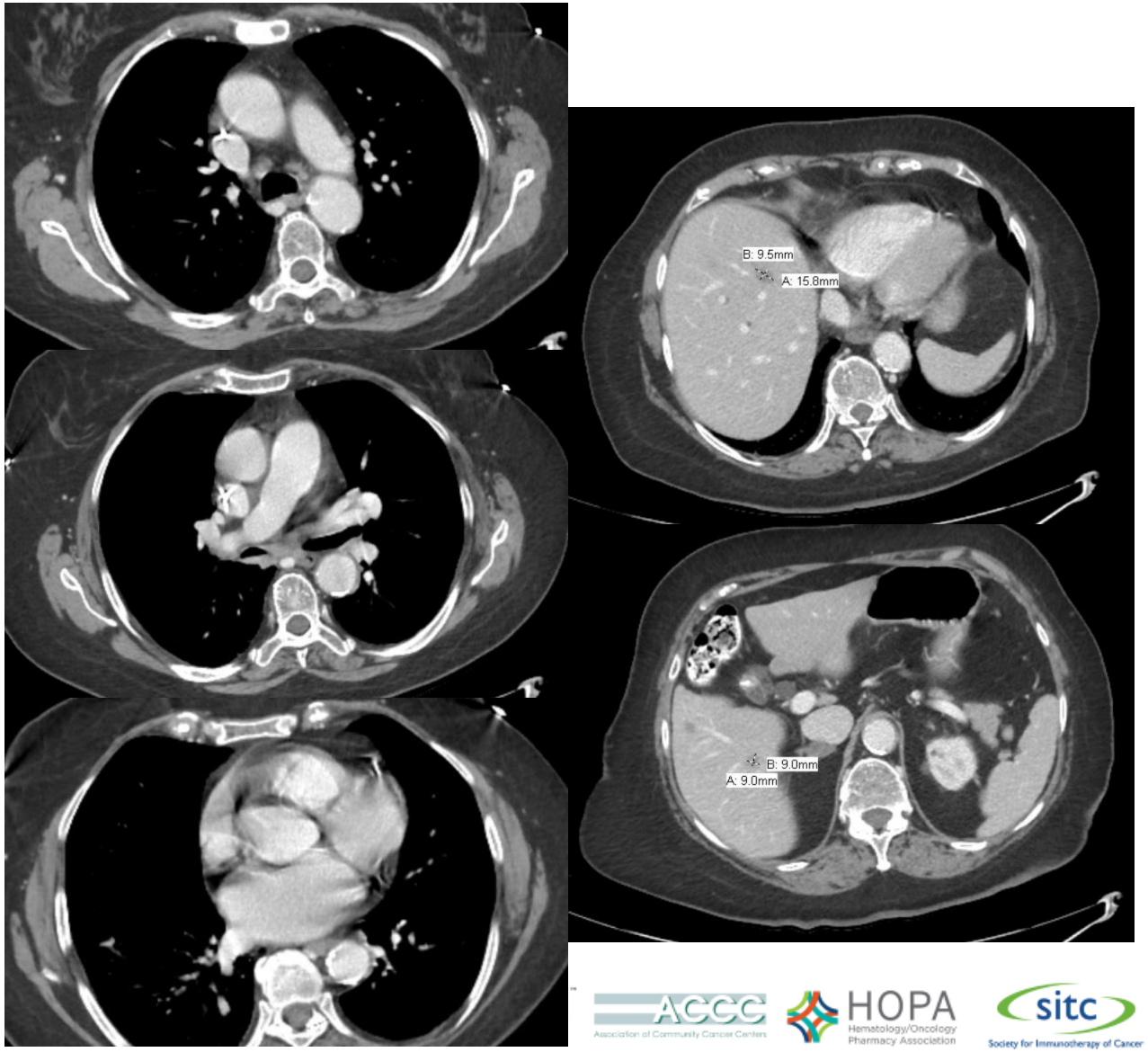


Case Study 2: What is the next step?

A. Carboplatin-etoposide
   A. Incorrect. This is no longer the preferred standard of care, however it remains an appropriate first line treatment option.
B. Carboplatin-etoposide-atezolizumab
   A. Correct. Based on IMPOWER133, this regimen can improve PFS, OS regardless of PD-L1 TPS when compared with carboplatin-etoposide.
   B. However based on cost analyses, potential toxicities, and still challenging outcomes, it has been slow for wide adoption.
C. Platinum-etoposide-durvalumab
   A. Although listed in NCCN guidelines based on the CASPIAN trial (Paz-Ares et al, The Lancet 10/4/2019), this regimen does not yet have FDA approval.
D. Pursue clinical trial
   A. This is always an appropriate option.
E. Provide other supportive interventions
   A. Consulting palliative medicine, nutrition, social work, navigation, integrative medicine is always an appropriate option.
   B. She had no indication for palliative radiation.

Case Study 2: Results

- This patient received carboplatin-etoposide-atezolizumab.
- After four cycles, she transitioned to atezolizumab maintenance.
- She declined prophylactic cranial irradiation.



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Thank you for your attention.