Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Lung Cancer

Hossein Borghaei, DO

Professor and Chief, Thoracic Oncology

Fox Chase Cancer Center

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

- **Research Support (Clinical Trials):**
  - Millennium, Merck/Celgene, BMS/Lilly
- **Advisory Board/Consultant:**
  - BMS, Lilly, Genentech, Celgene, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, Astra Zeneca, Novartis, Genmab, Regeneron, BioNTech, Cantargia AB, Amgen, Abbvie, Axiom, PharmaMar, Takeda, Huya Bio, GLG, Daiichi
- **Data and Safety Monitoring Board:**
  - University of Pennsylvania, CAR T Program
  - Takeda
- **Employment:**
  - Fox Chase Cancer Center
- I will discuss non-FDA Approved drugs and combinations.

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
ADVANCES IN Cancer IMMUNOTHERAPY™

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

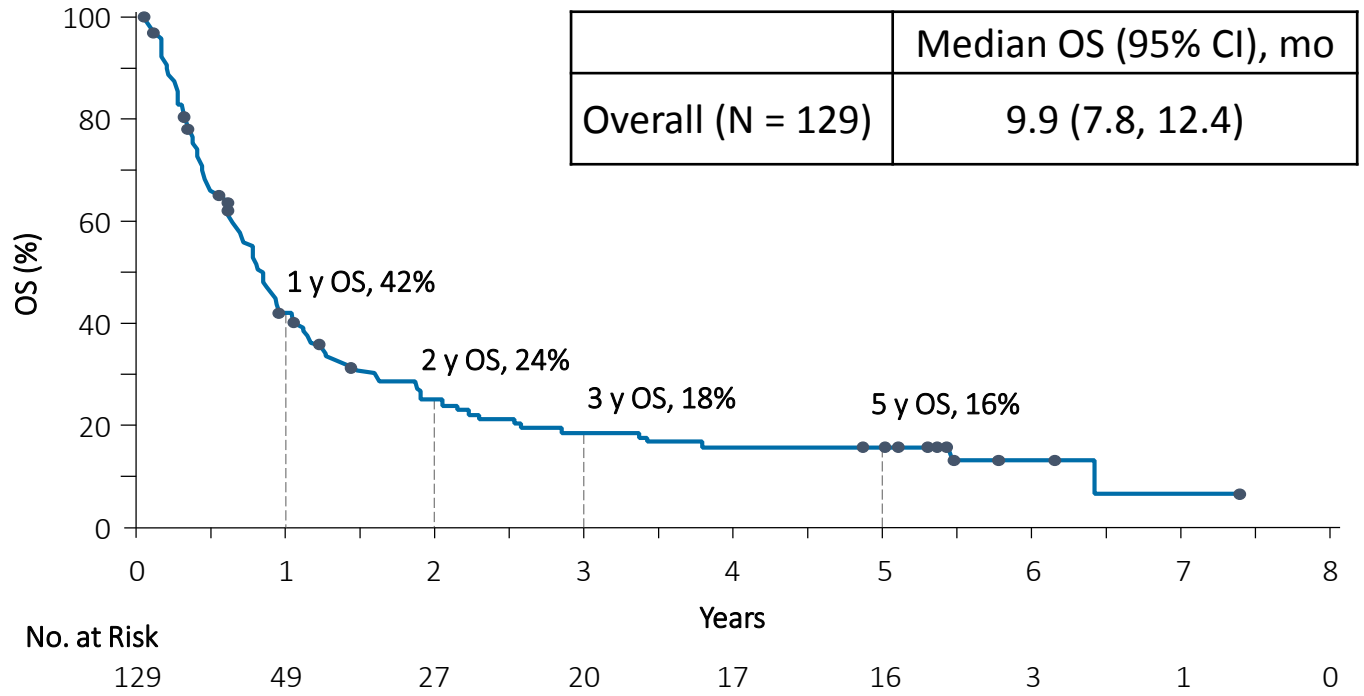
CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

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

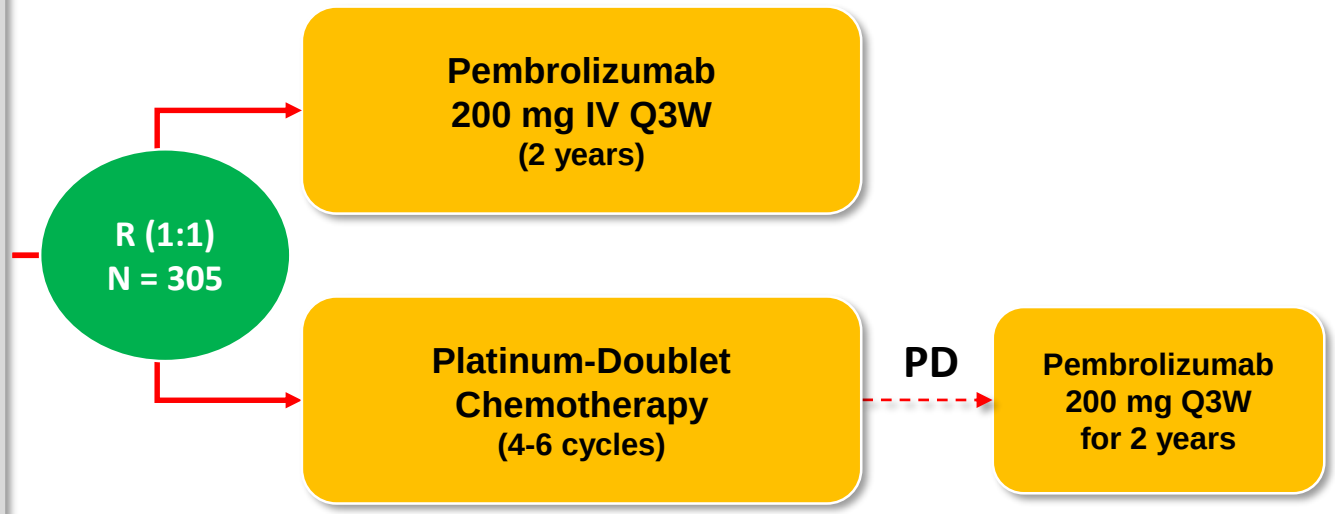
Front Line Trials with Single Agent IO

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

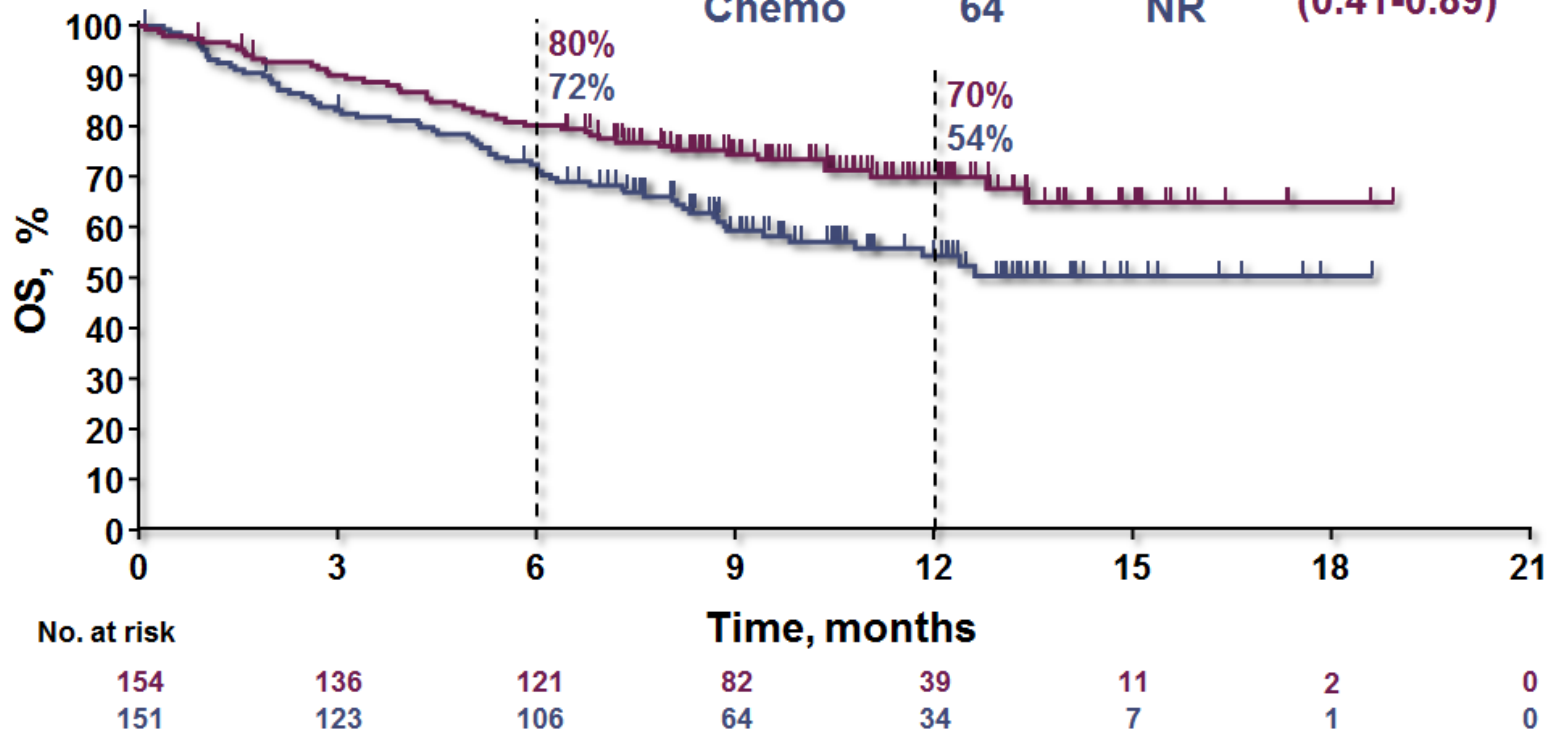


Reck M et al, ESMO 2016, NEJM 2016

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

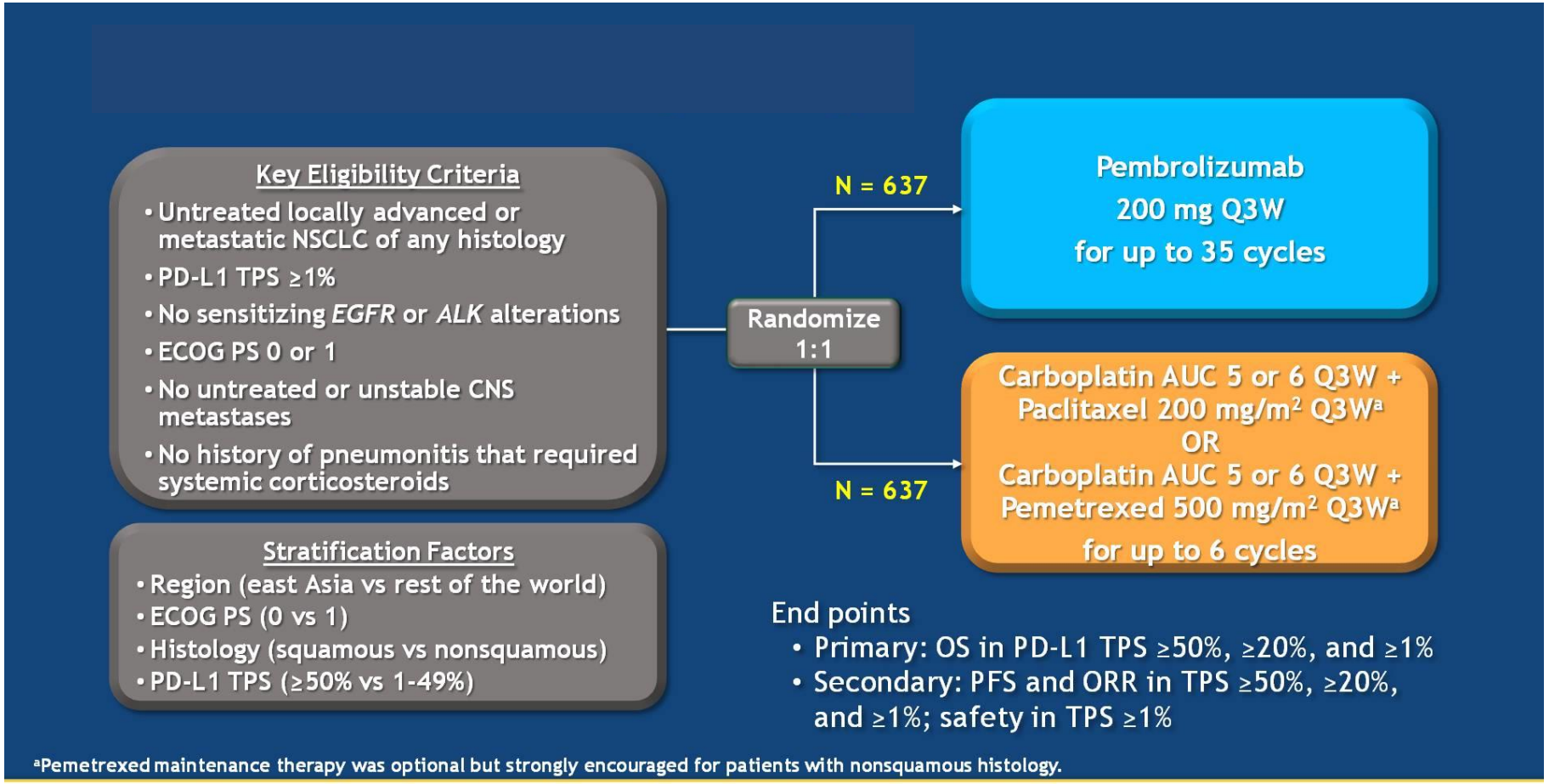
Overall Survival

	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

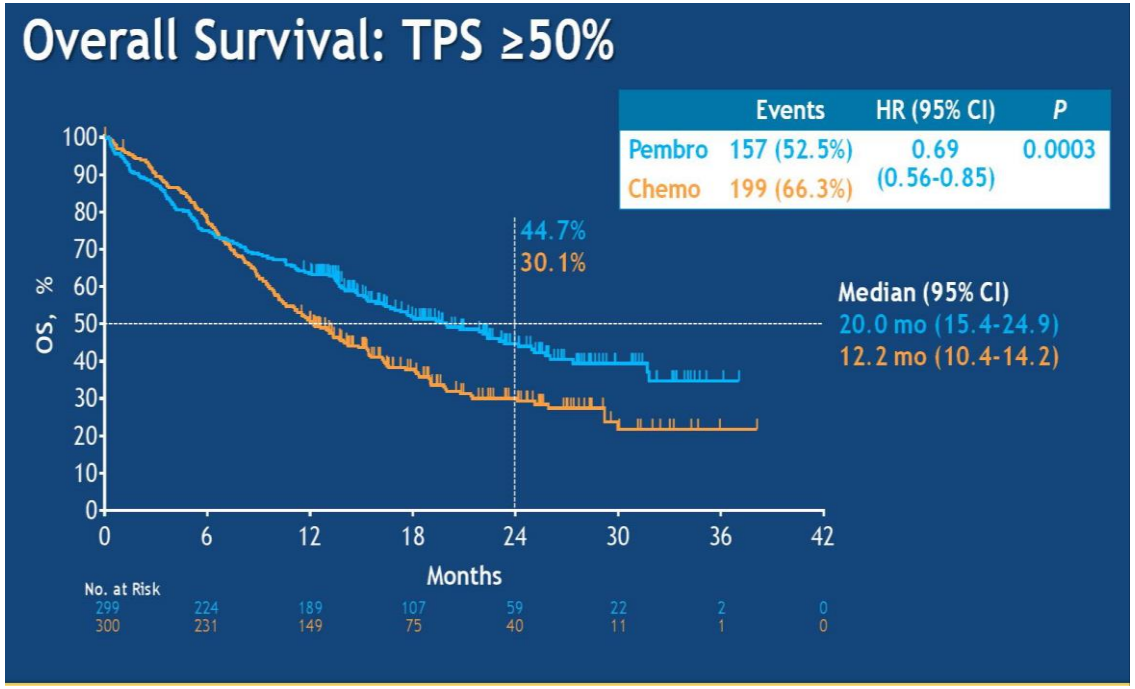
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

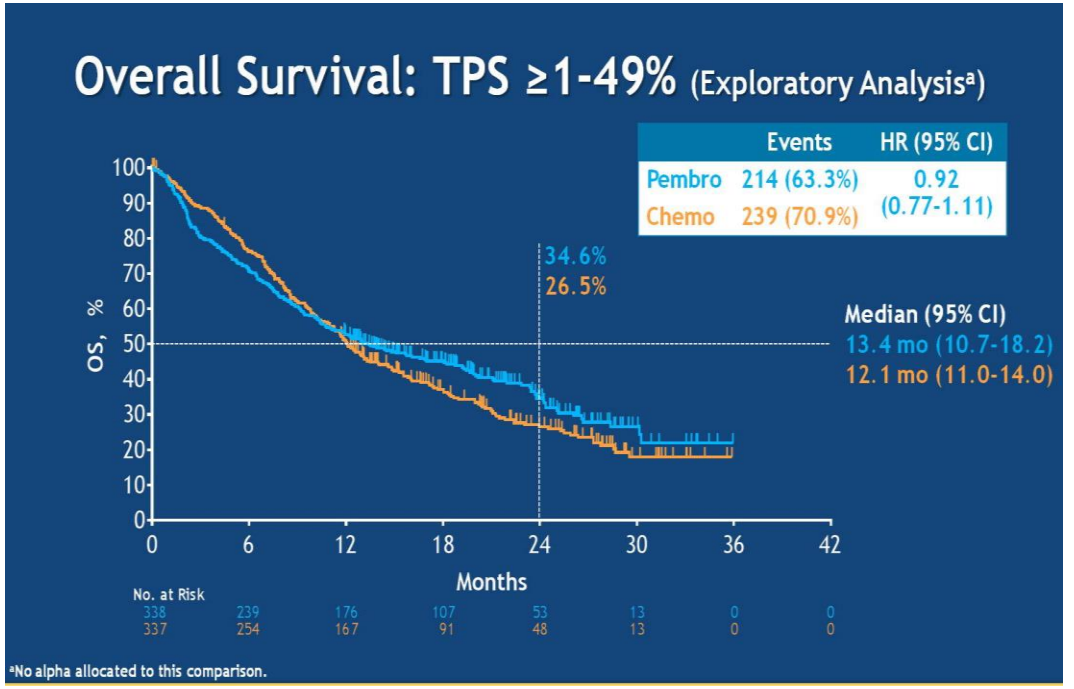


Lopes et al, ASCO 2018

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

Overall Survival



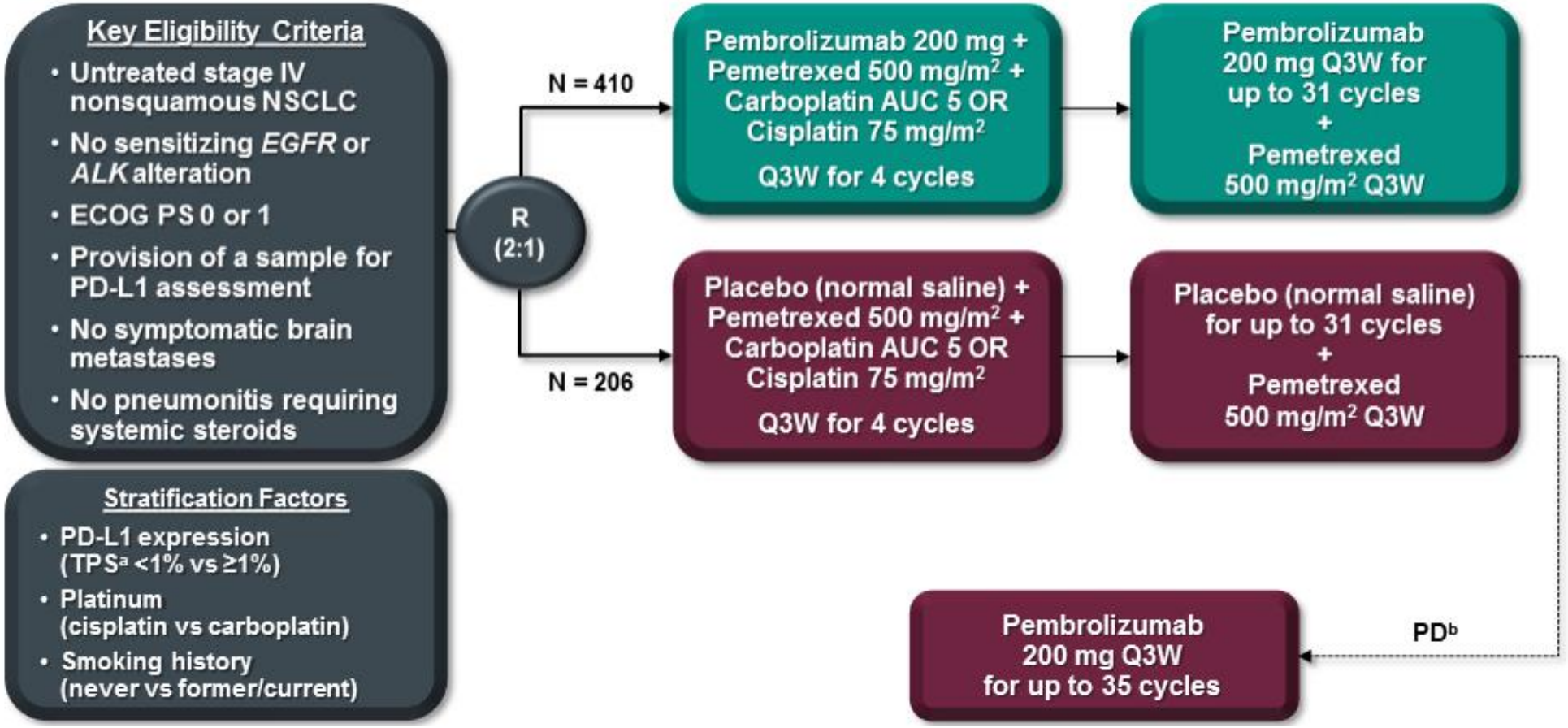


Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

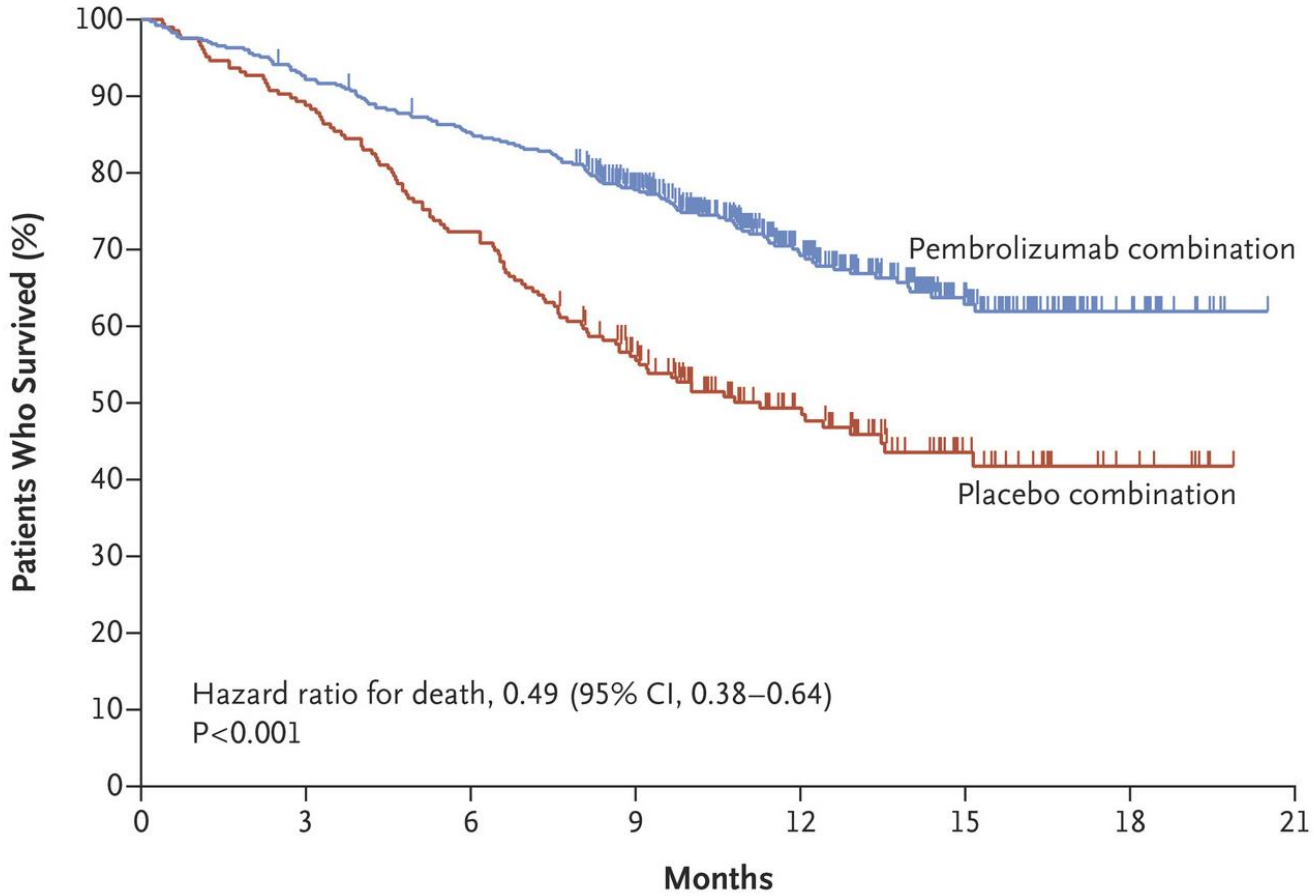
Chemotherapy Plus IO Combinations

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



Ghandi et al, NEJM 2018

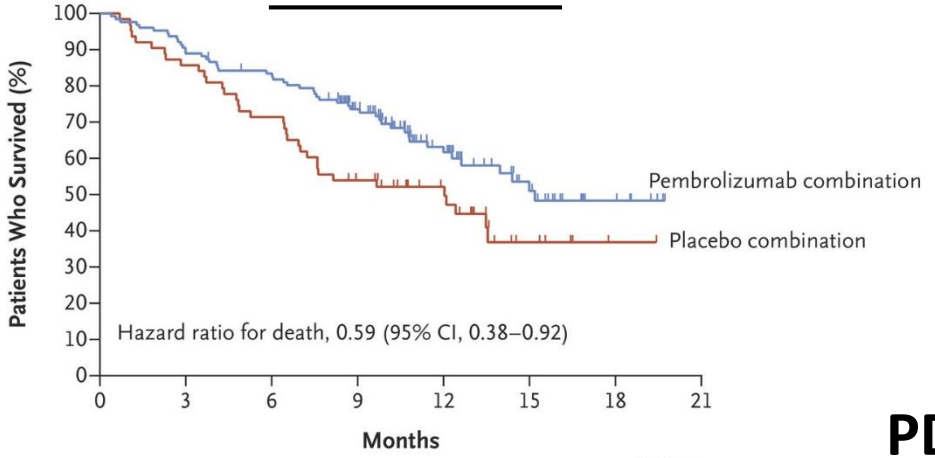
KEYNOTE-189: Pembrolizumab/Platinum /Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



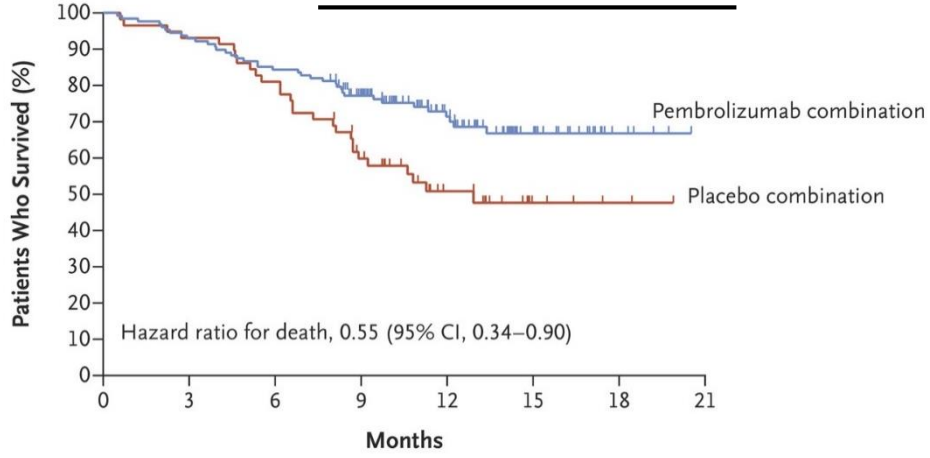
Ghandi et al, NEJM 2018

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

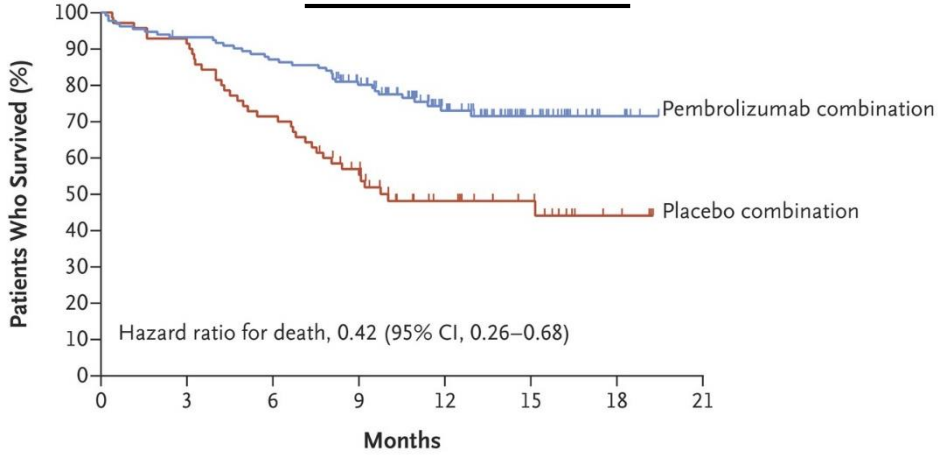
PD-L1 < 1%



PD-L1 = 1 – 49%

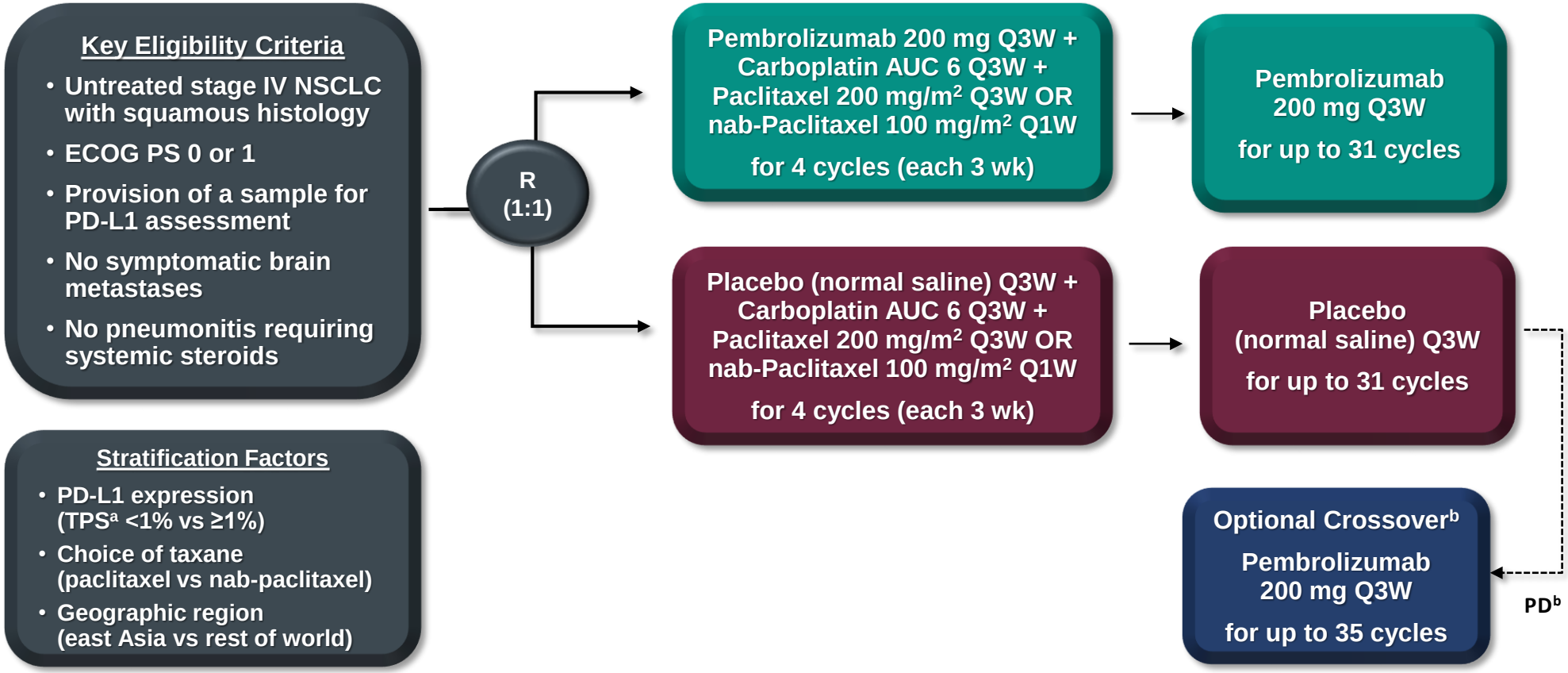


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

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

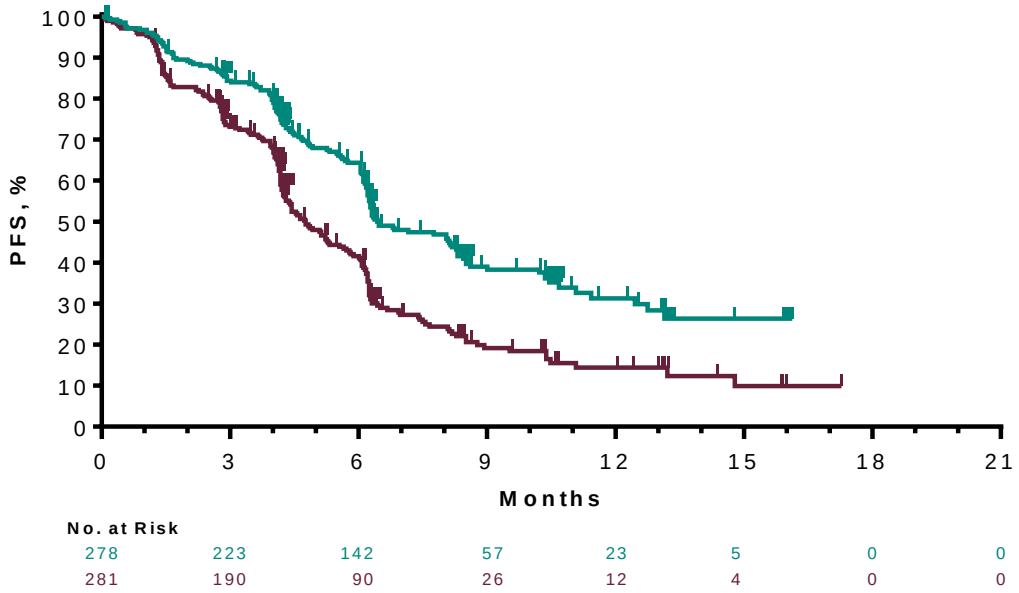


Paz-Ares et al, ASCO 2018

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

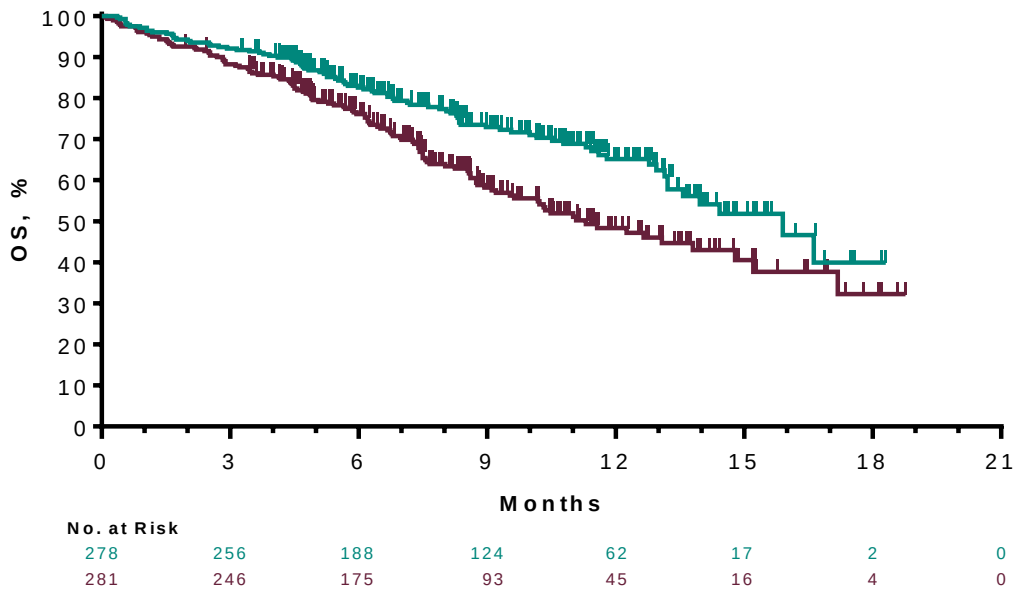
PFS (RECISTv1.1, BICR)

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



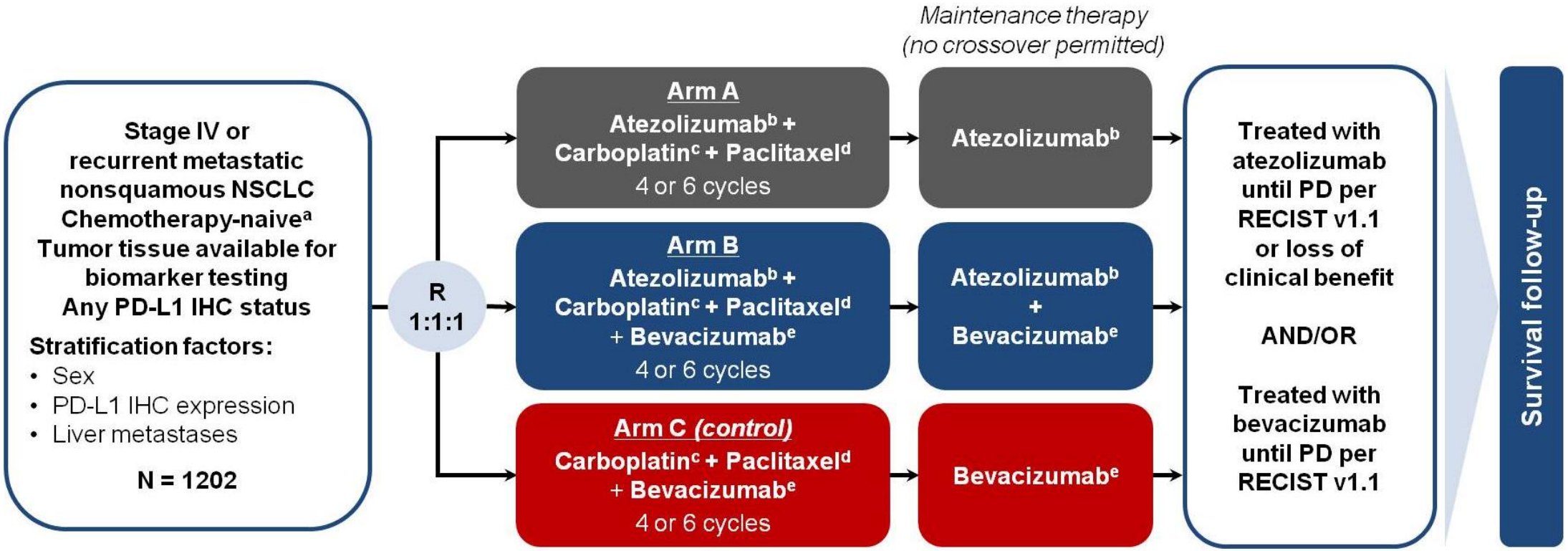
Overall Survival

	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

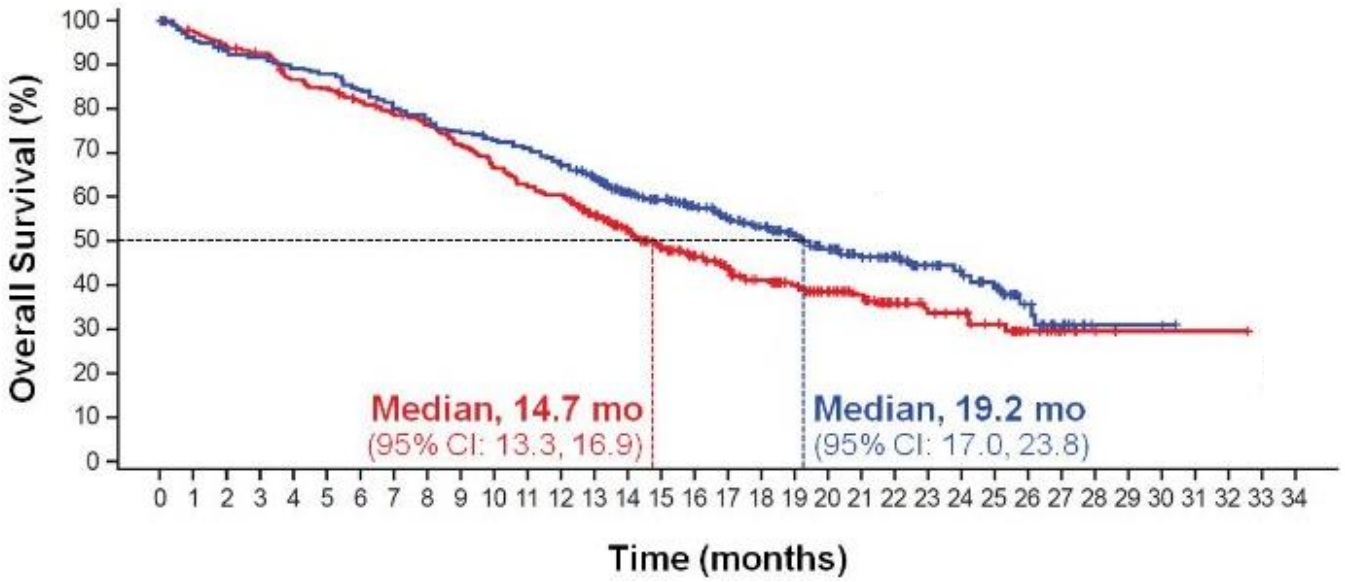


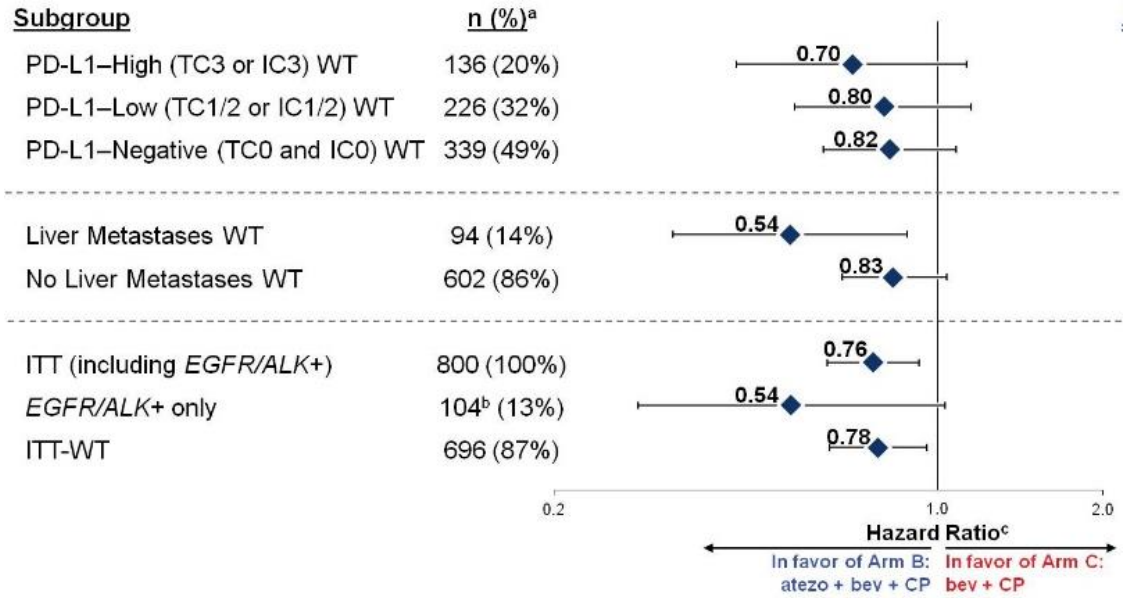
Socinski et al, NEJM 2018

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



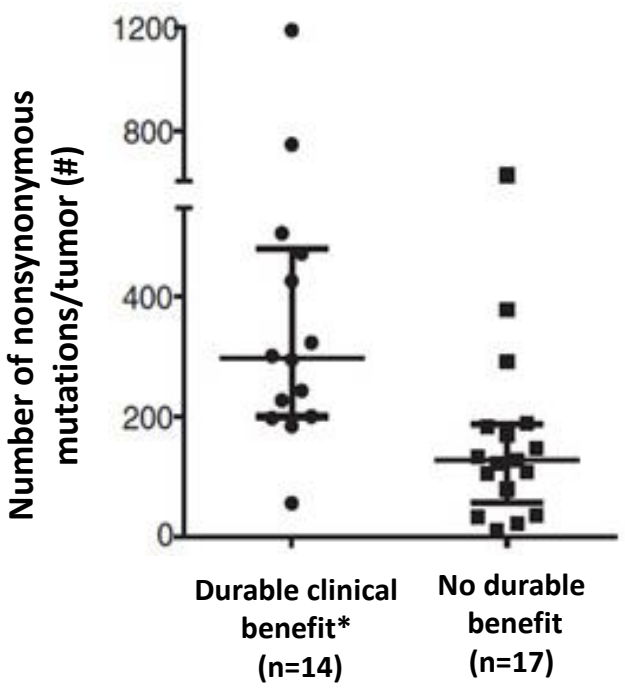


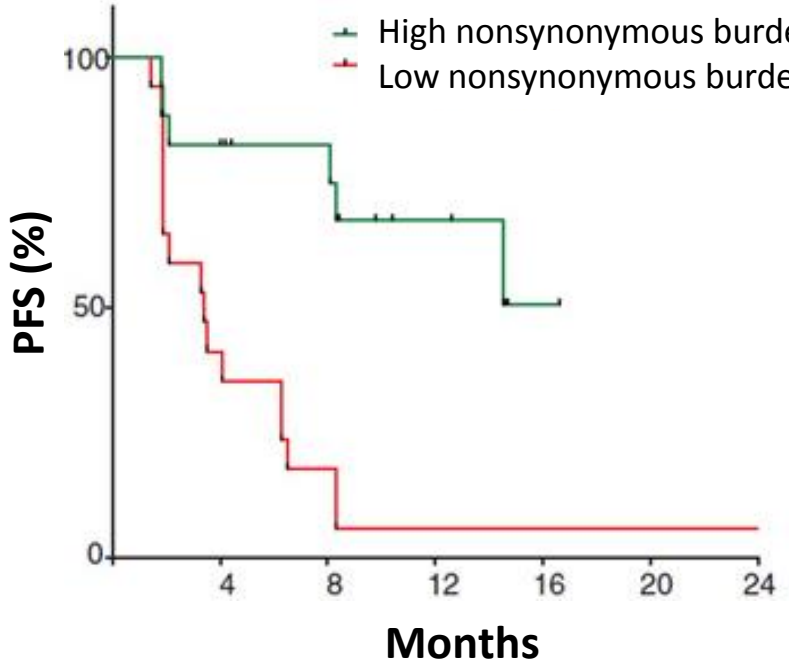
Socinski et al, NEJM 2018

TMB As a Biomarker?

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.



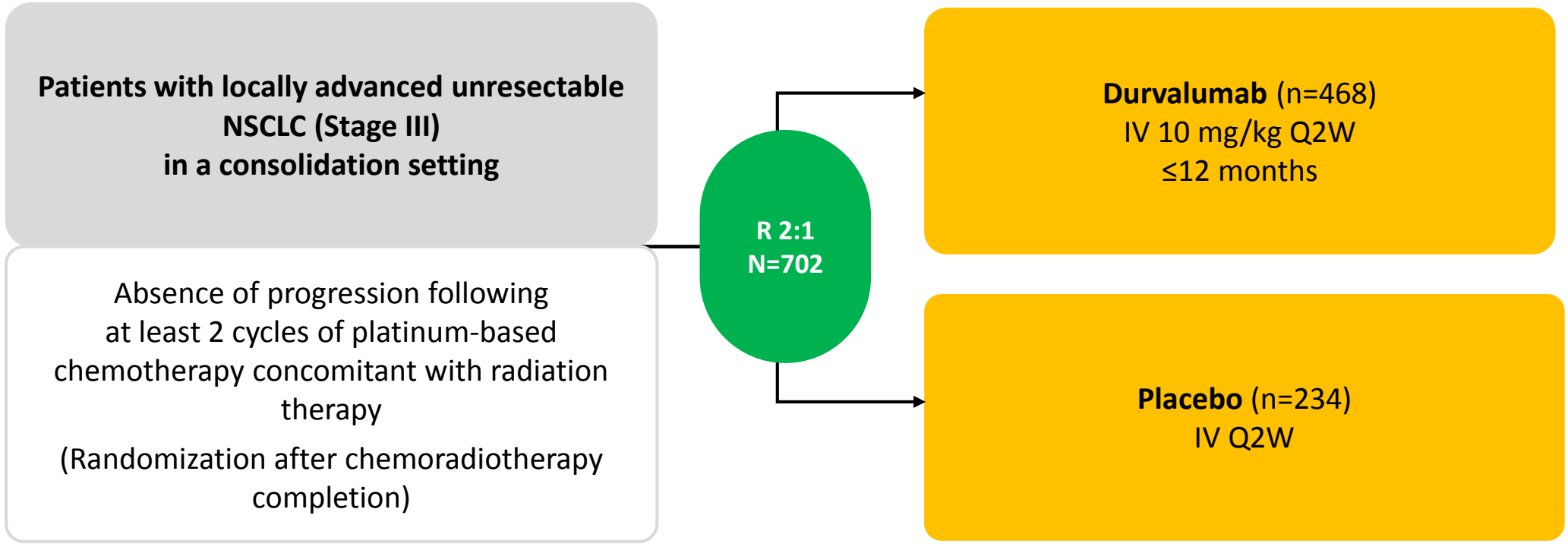


*Partial or stable response lasting > 6 mo

Rizvi N et al, Science, 2015

Locally Advanced Disease

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

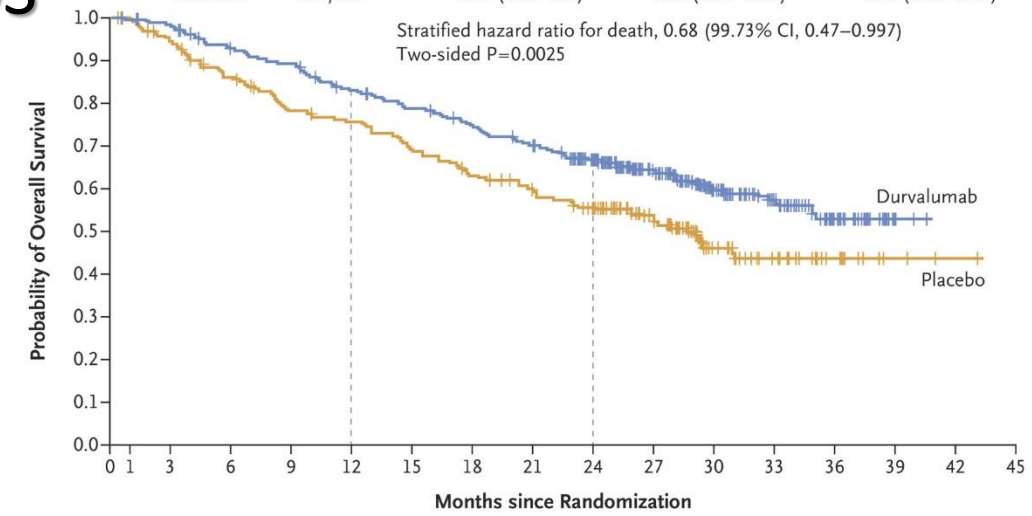


In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

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

OS

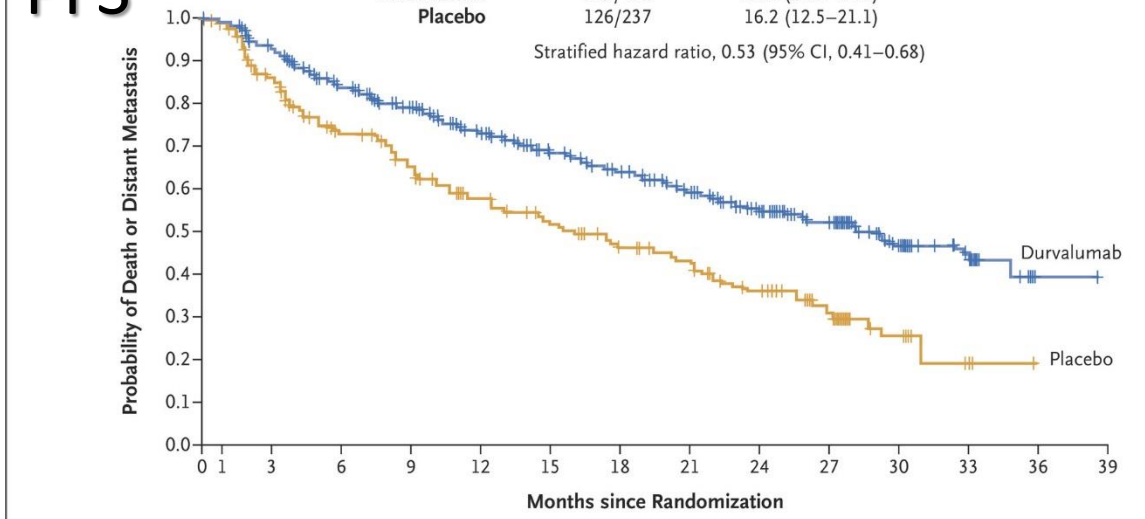
	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



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)



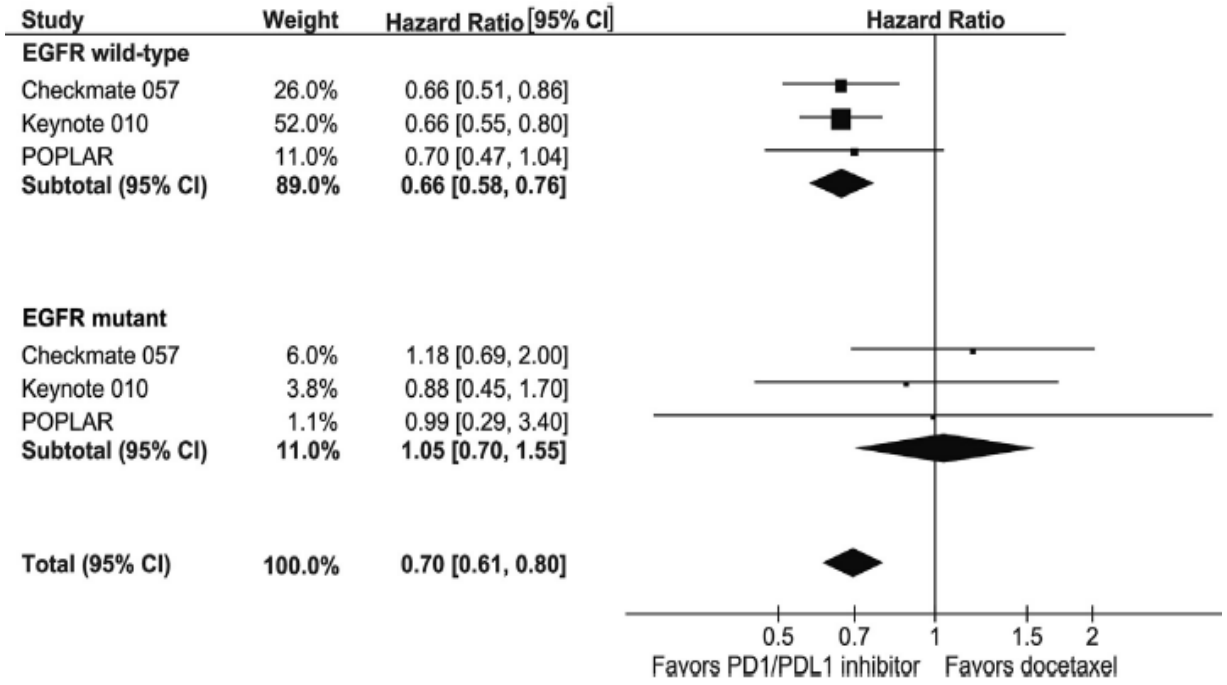
No. at Risk														
Durvalumab	476	419	357	316	259	223	194	163	129	92	46	25	1	0
Placebo	237	189	139	118	95	77	64	54	39	27	12	5	0	0

Antonia et al, NEJM 2018

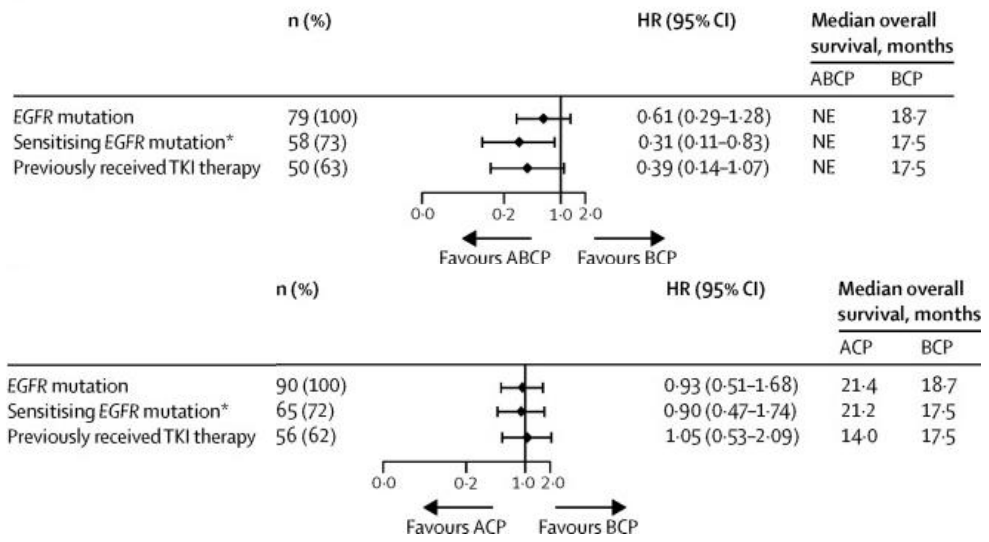
Immunotherapy in EGFR Mutation Positive Lung Cancer

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

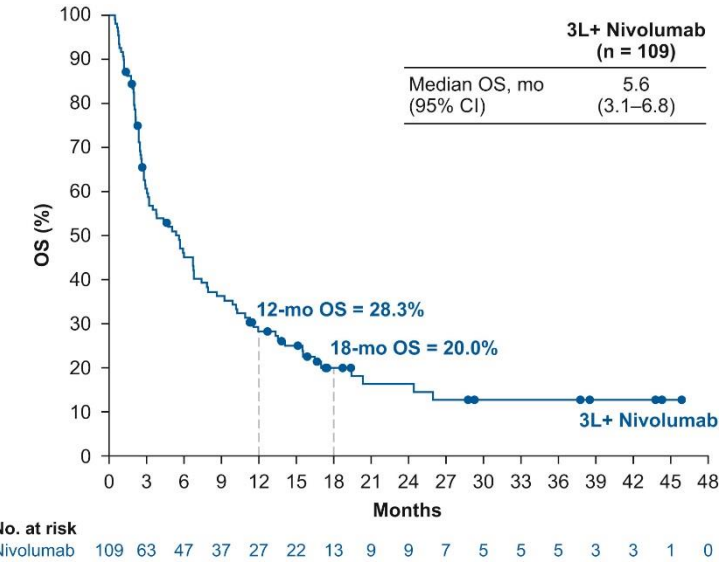
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

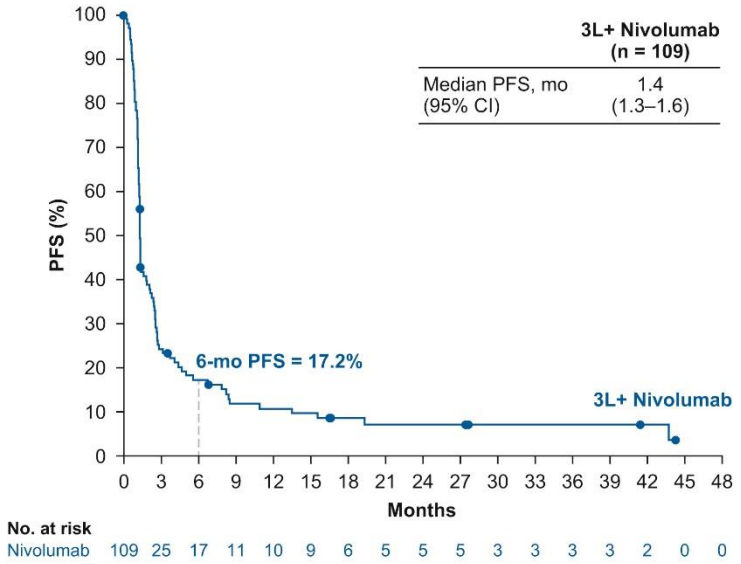
Approved checkpoint inhibitors in SCLC

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



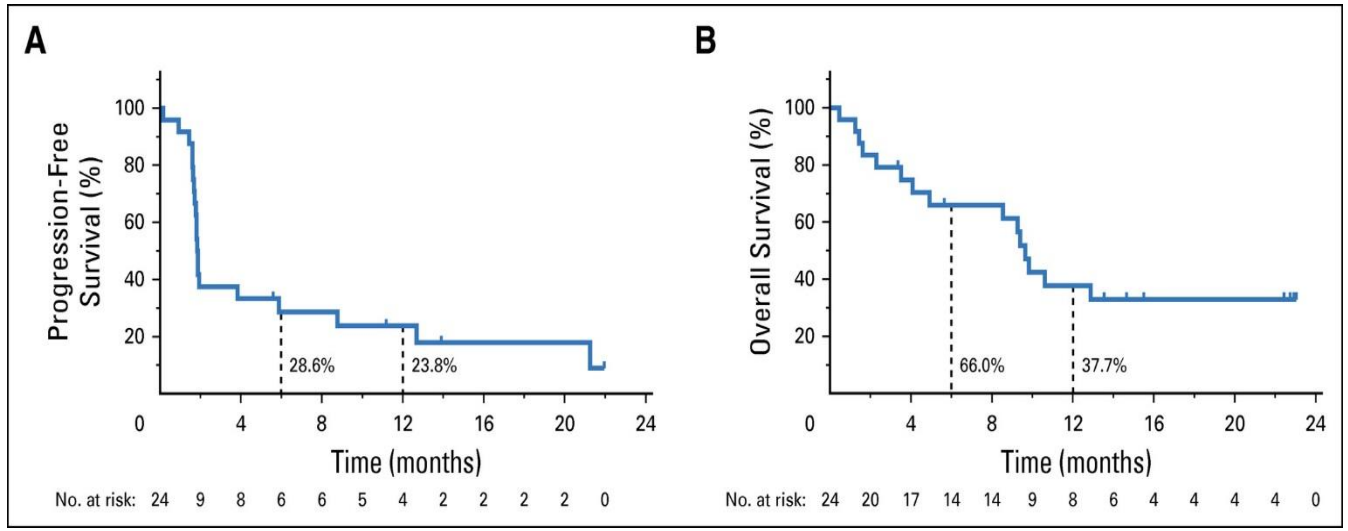


Ready, J Thorac Oncol 2019

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

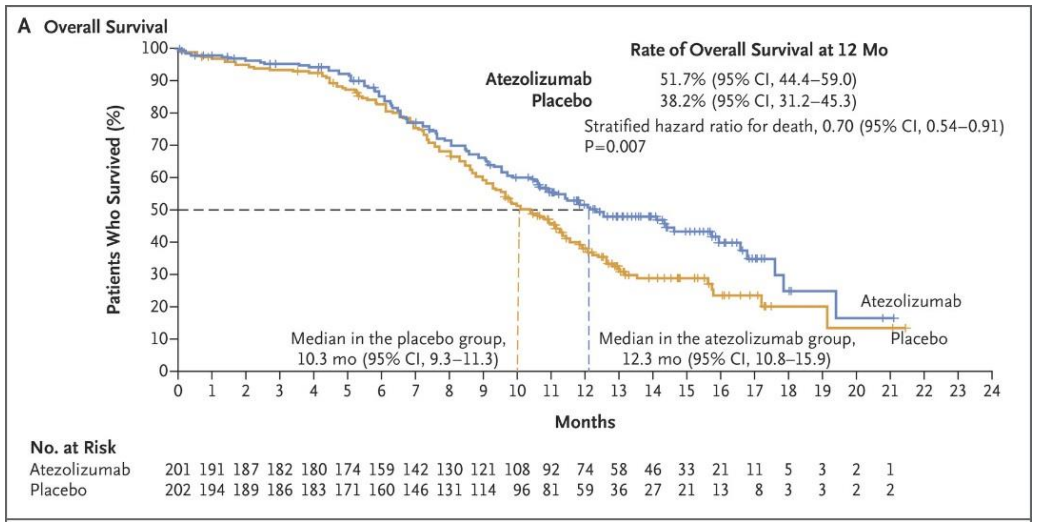
PD-L1+ (KEYNOTE-028)



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)

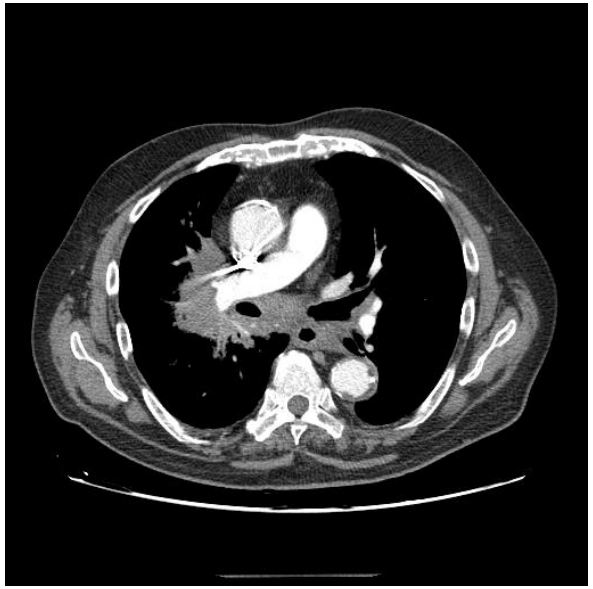
Julie R. Brahmer[1], Ramaswamy Govindan[2], Robert A. Anders[3], Scott J. Antonia[4], Sarah Sagorsky[5], Marianne J. Davies[6], Steven M. Dubinett[7], Andrea Ferris[8], Leena Gandhi[9], Edward B. Garon[10], Matthew D. Hellmann[11], Fred R. Hirsch[12], Shakuntala Malik[13], Joel W. Neal[14], Vassiliki 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

- A 70 year old male, former smoker presents for an initial consultation. He had been experiencing a cough and shortness of breath for several weeks. He was treated with antibiotics but his symptoms did not improve. Eventually he is seen by a pulmonologist who obtained a CT of chest. Biopsy of the right middle lobe mass shows Adenocarcinoma. Brain MRI is negative. PET shows bone metastasis. ECOG 1.



What would you recommend next?

1. Start Treatment with a platinum doublet chemotherapy
2. Obtain PD-L1 status
3. Obtain Molecular Testing with an NGS platform
4. Both 2 and 3

Case Study 1

- Molecular testing shows the following:

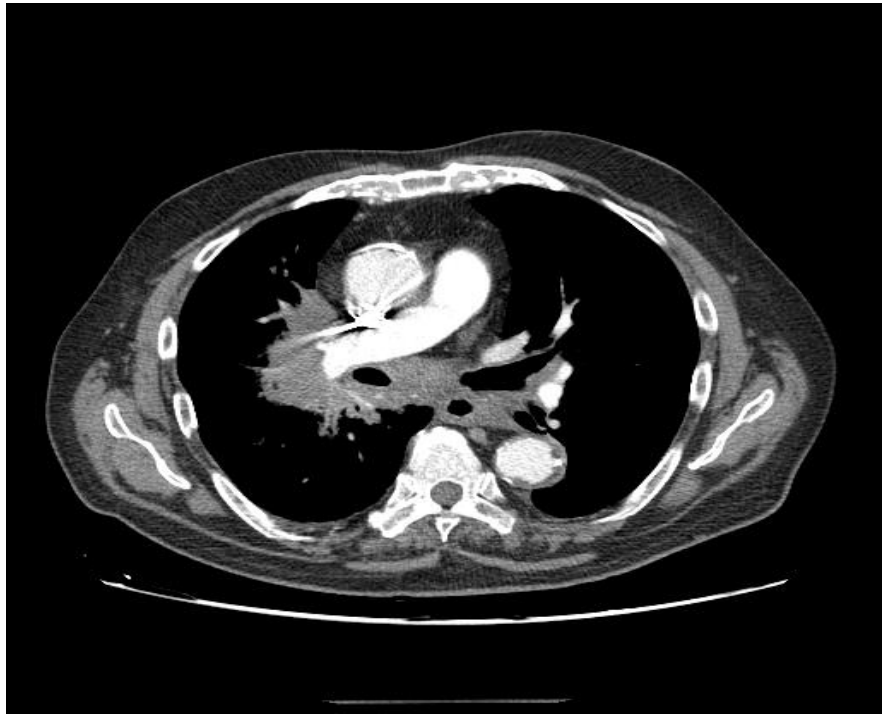
Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
NF1	splice site 7181_7189+2delT TTTAAAAGGT	None	Temsirolimus (C.2), Binimetinib (C.2), Trametinib (C.2), Everolimus (C.2), Cobimetinib (D)	None	Yes
KRAS	G12D	None	Binimetinib (C.2)	None	Yes

- PD-L1 80%
- How would you proceed now?

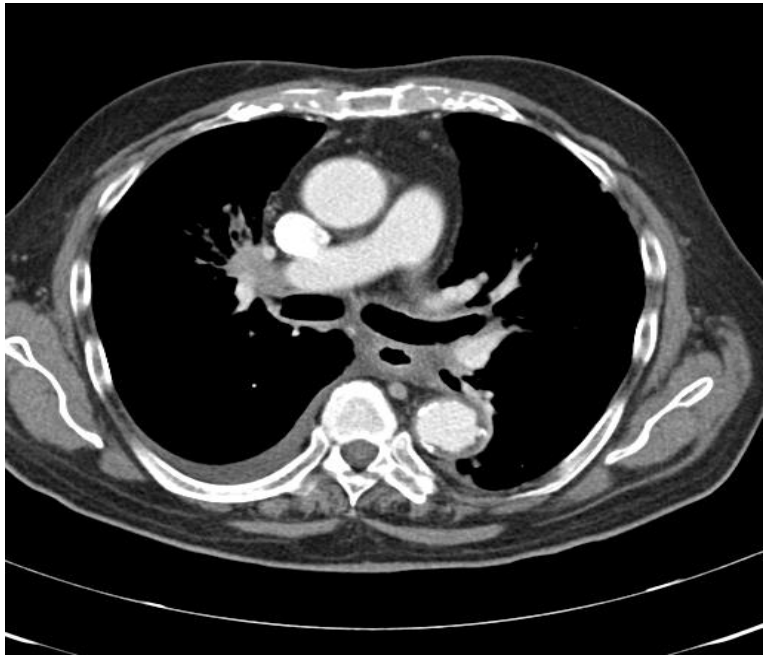
A. Pembrolizumab alone
B. Platinum doublet chemo plus a checkpoint inhibitor
C. Platinum doublet chemo alone
D. Radiation to the right lung

Case Study 1

- Treatment with pembrolizumab was initiated. After two cycles of treatment a repeat CT shows the following:



Before Treatment



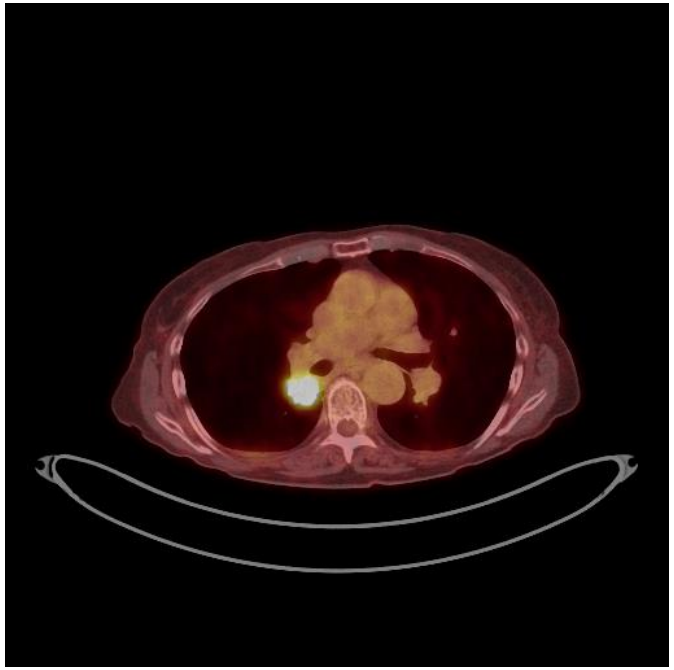
After Treatment

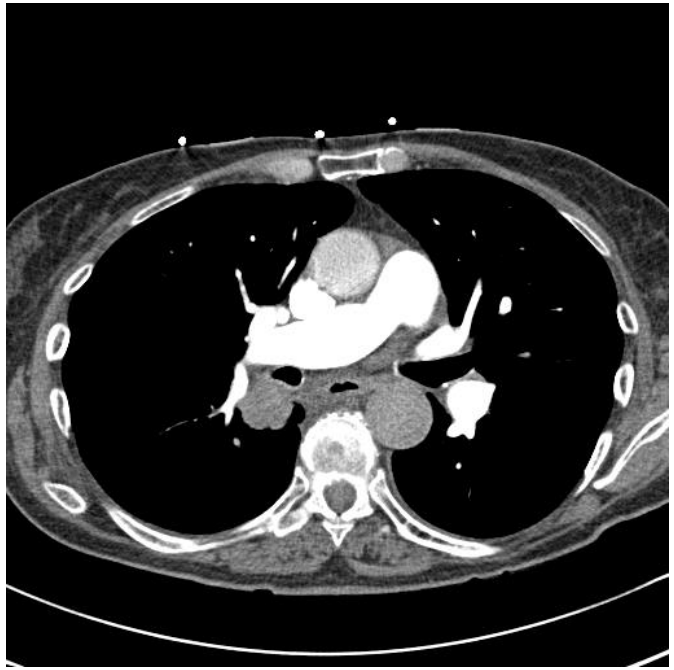
Case Study 1

- What is the next best option assuming that the patient is asymptomatic and tolerating treatment well?
  A. Continue pembrolizumab for two years in the absence of progression or toxicities
  B. Add chemotherapy since the patient has not had a CR
  C. Offer a clinical trial now
  D. Add bevacizumab since CR is not achieved.

Case Study 2

- A 76 year old female, former smoker has been referred to you for further management. Her history indicates a non productive cough and shortness of breath. Imaging studies had shown a right peri-hilar mass. A PET scan shows this lesion without evidence of distance metastasis. ECOG 1.





Case Study 2

- Biopsy shows and adenocarcinoma. Brain MRI is negative. She appears to have Stage III disease. What is the next step?
  - Referral to Surgery
  - Referral to Radiation Oncology
  - Molecular Testing
  - All of the above

Case Study 2

- She is not a surgical candidate based on surgical consultation and she is not interested in it at any rate. Radiation oncology consultation is completed and patient is a candidate for radiation. What is the best option for her?
- Concurrent chemo-RT followed by a year of durvalumab based on the PACIFIC trial
- Sequential chemo-RT
- Concurrent chemo-RT followed by two more cycles of chemotherapy
- Immunotherapy only

Cast Study 2

- She starts on treatment with concurrent chemo-RT. She completes 6 weeks of combined treatment and is back to see you. She has no molecular alterations. PD-L1 is 30%. What would you recommend now?
- Check a CT of her chest before starting durvalumab
- Start durvalumab immediately
- Start Atezolizumab
- Start Nivolumab

Case Study 2

- She starts durvalumb after an interim CT confirms lack of progression. What is the duration of treatment?
- One year
- Two years
- Until Progression
- No specific time limit