sitc Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

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

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Disclosures

- Consulting: AstraZeneca, Beyond Spring, Boehringer Ingelheim, Bristol Myers Squibb, Inivata, Takeda
- Contracted research (paid to institution for clinical trials): Celgene, Merck, Novartis, OncoMed, Roche

- 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 one of the earliest approved indications for immunotherapy

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

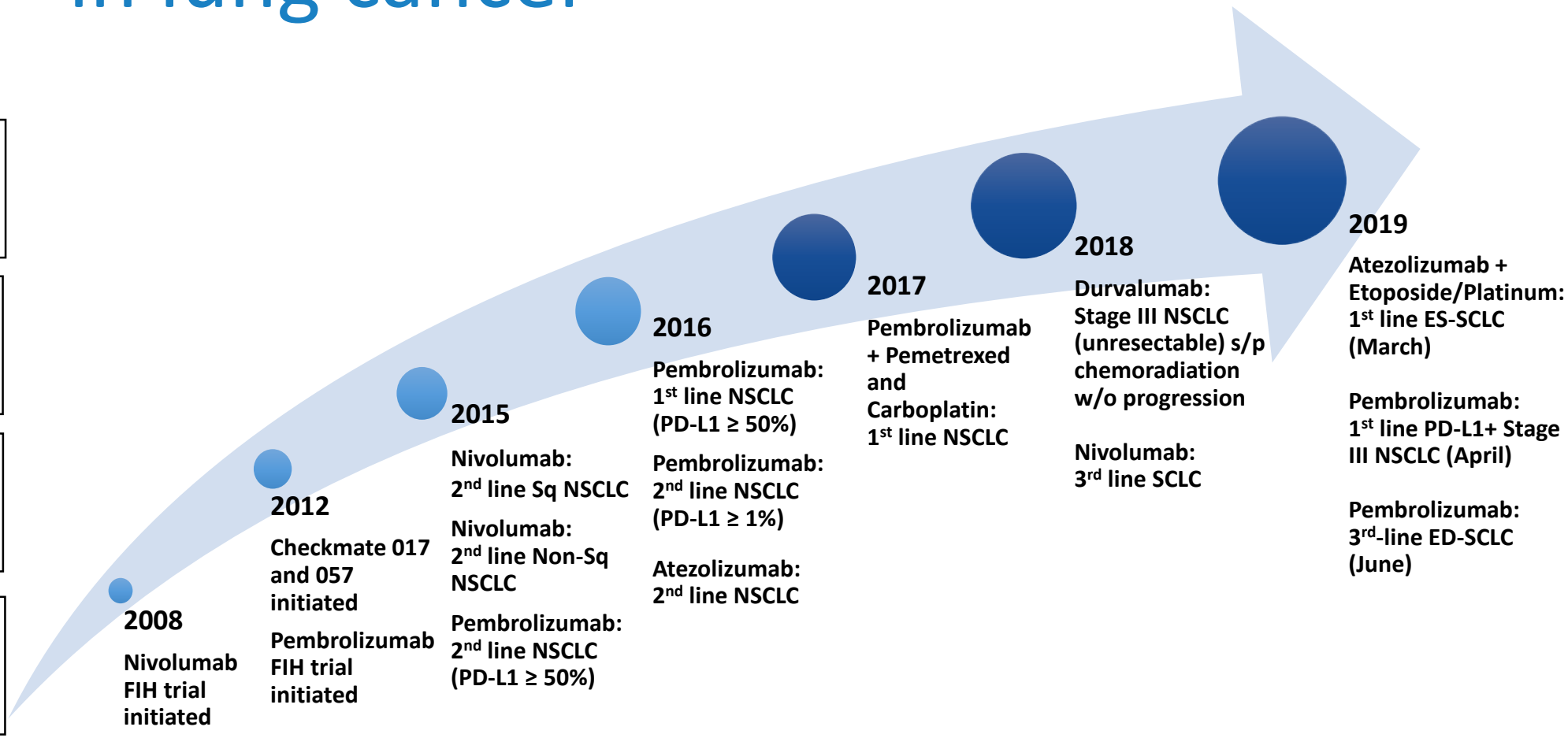
FDA-approved checkpoint inhibitors in lung cancer

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1



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 metastatic NSCLC, with PD-L1 TPS ≥ 1% and no EGFR/ALK mutations and 1st line stage III NSCLC (not candidate for resection or definitive chemoradiation)	
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

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

Treatment-naïve regimens: Competing strategies in NSCLC

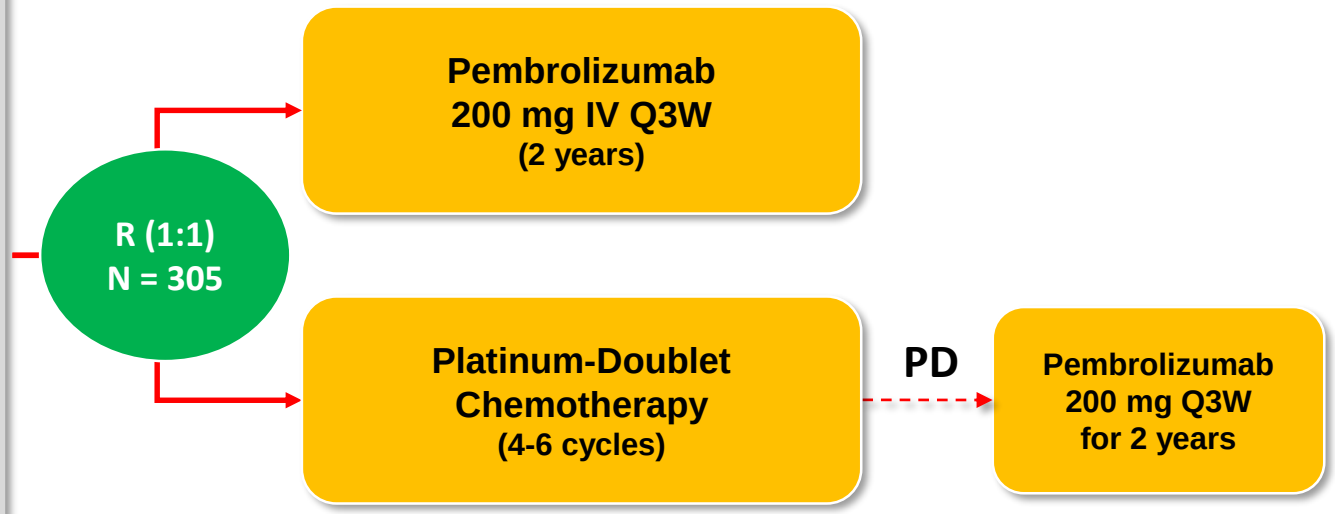
- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1 ≥ 1%
- **KEYNOTE 189** – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in advanced non-squamous NSCLC
- **IMPOWER 150** – Atezolizumab + Chemotherapy (Bev) vs. Chemotherapy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

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

Study Design

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

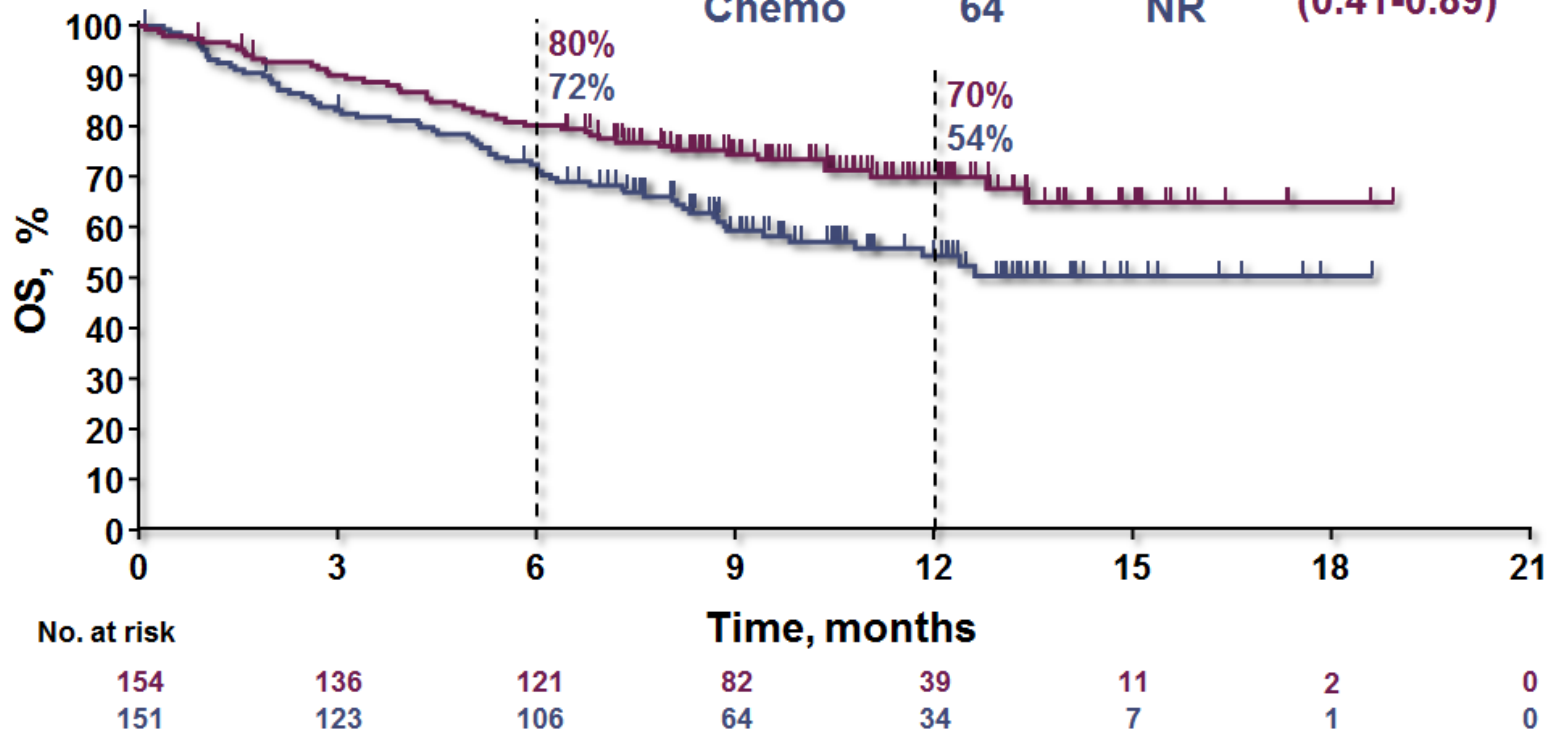


Reck M et al, ESMO 2016, NEJM 2016

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

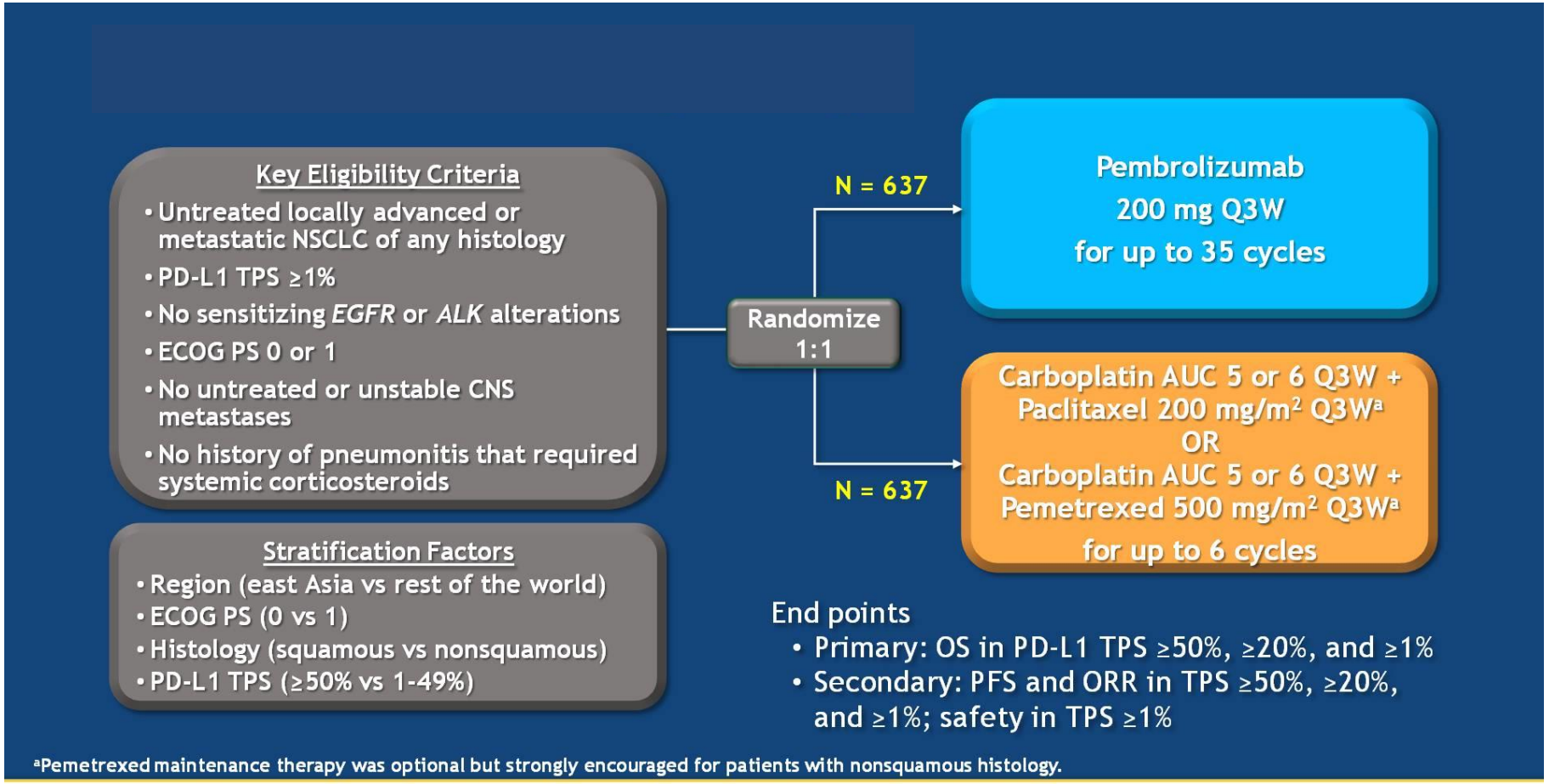
Overall Survival

	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

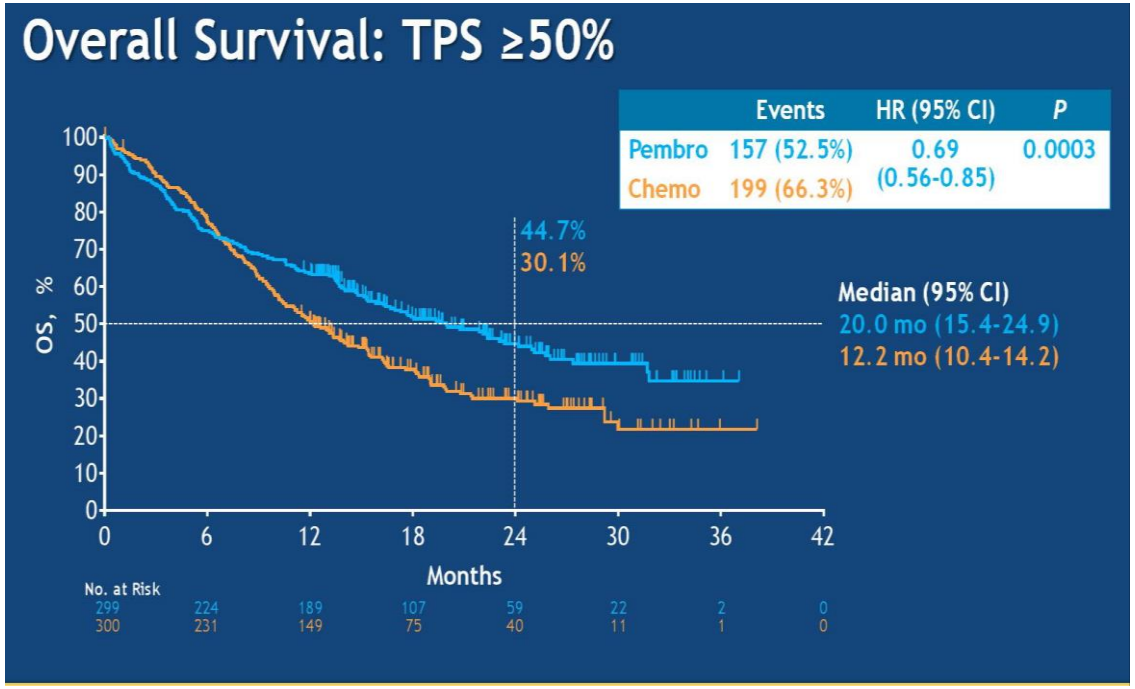
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC



Lopes et al, ASCO 2018

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

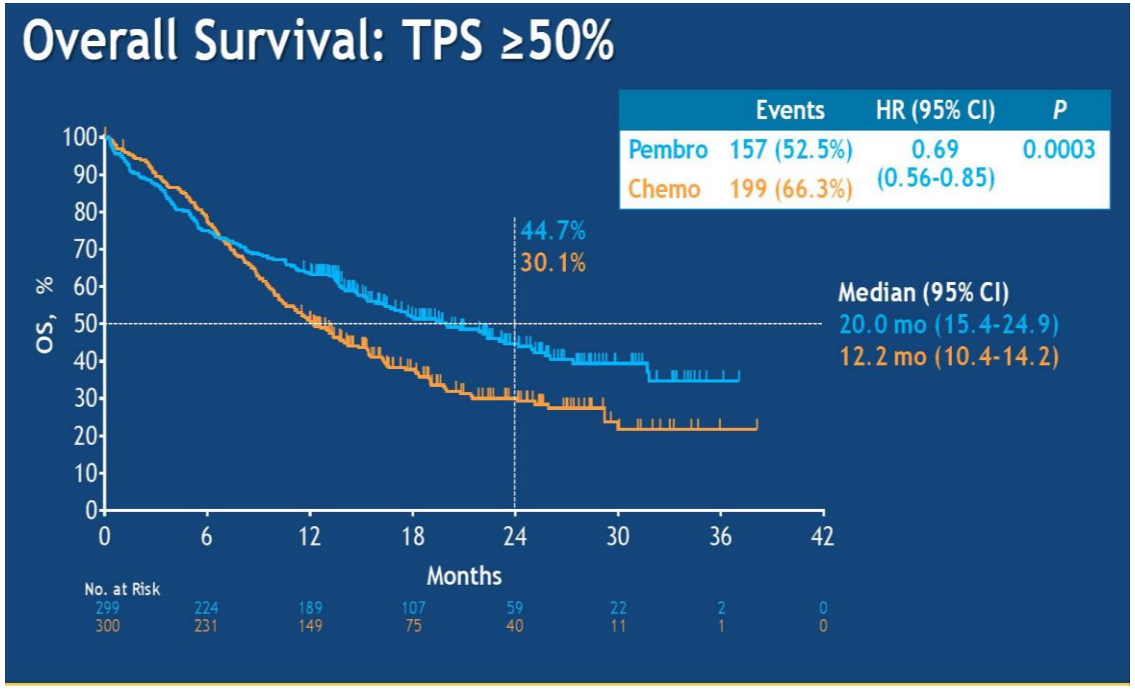
Overall Survival

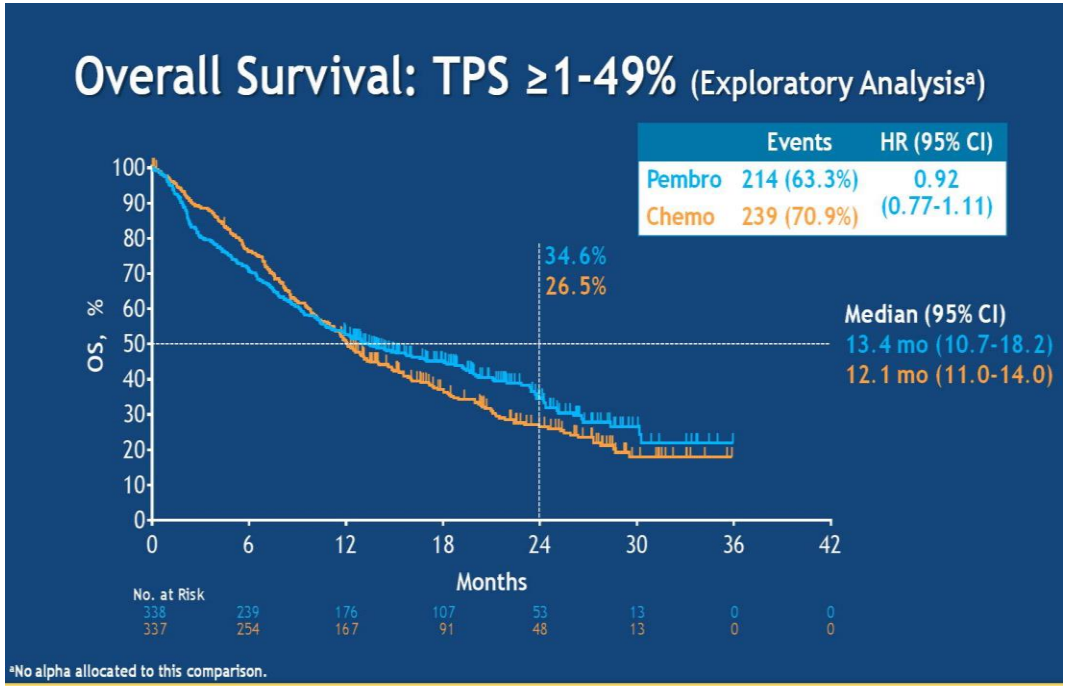


Lopes et al, ASCO 2018

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

Overall Survival





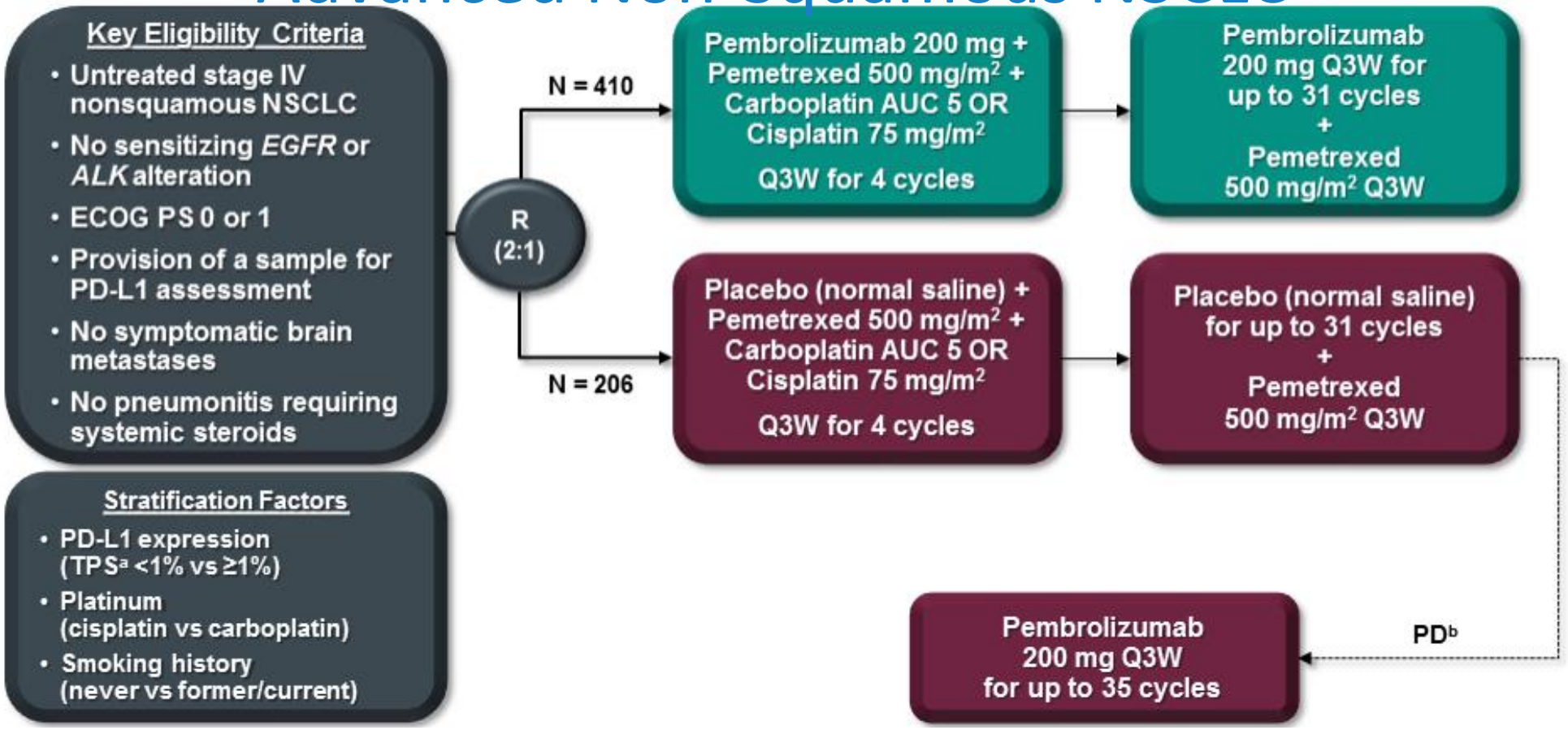
Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Only 20% of chemo arm later had immunotherapy

FDA approved but NOT recommended by SITC Consensus Statement or NCCN Guidelines for most PD-L1 1-49%

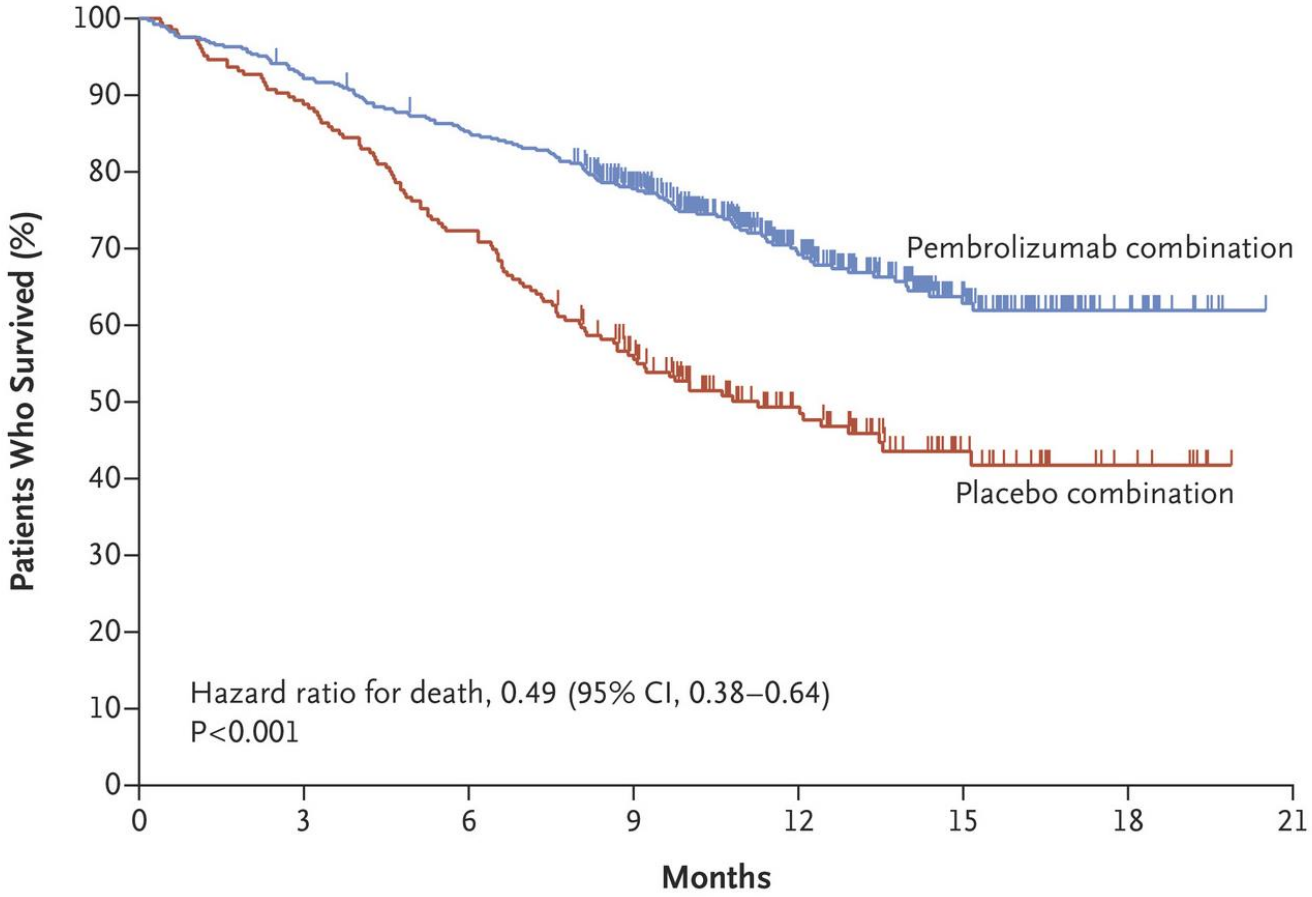
Lopes et al, ASCO 2018

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



Ghandi et al, NEJM 2018

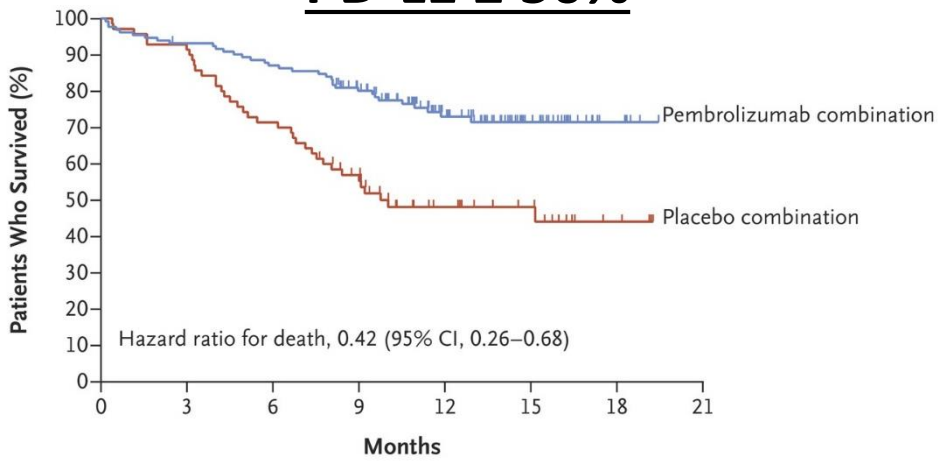
KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



Ghandi et al, NEJM 2018

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

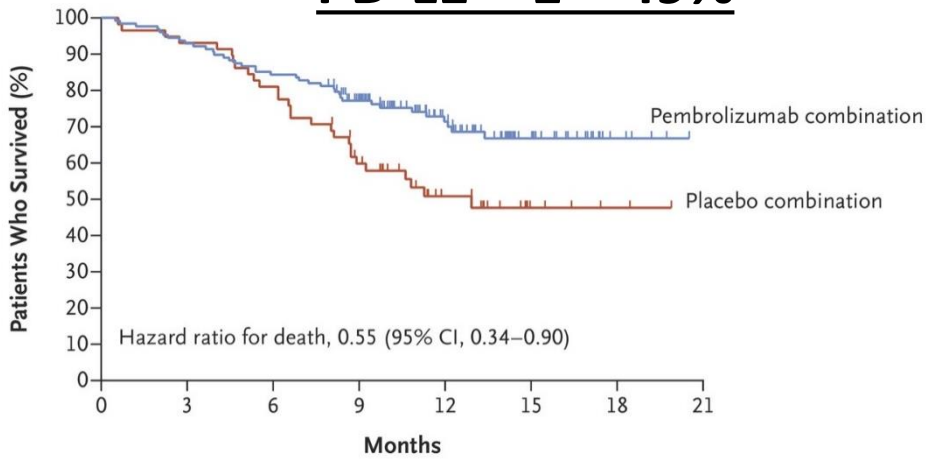
PD-L1 ≥ 50%



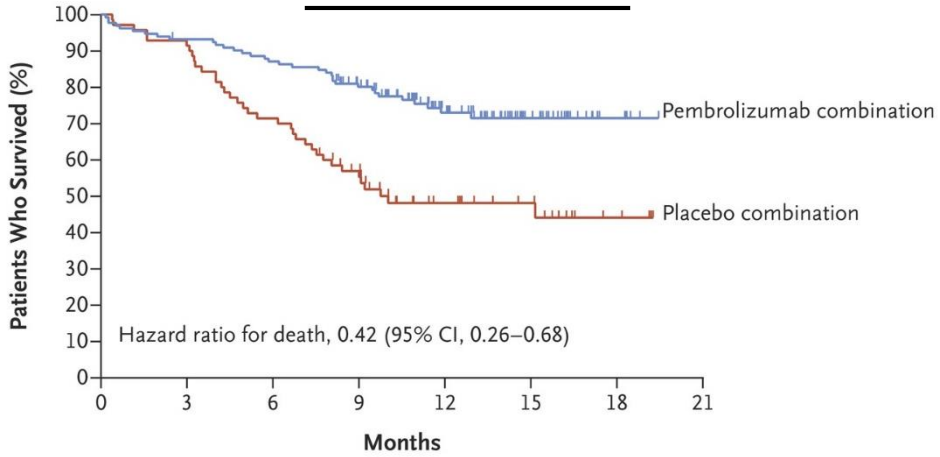
Ghandi et al, NEJM 2018

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

PD-L1 = 1 – 49%



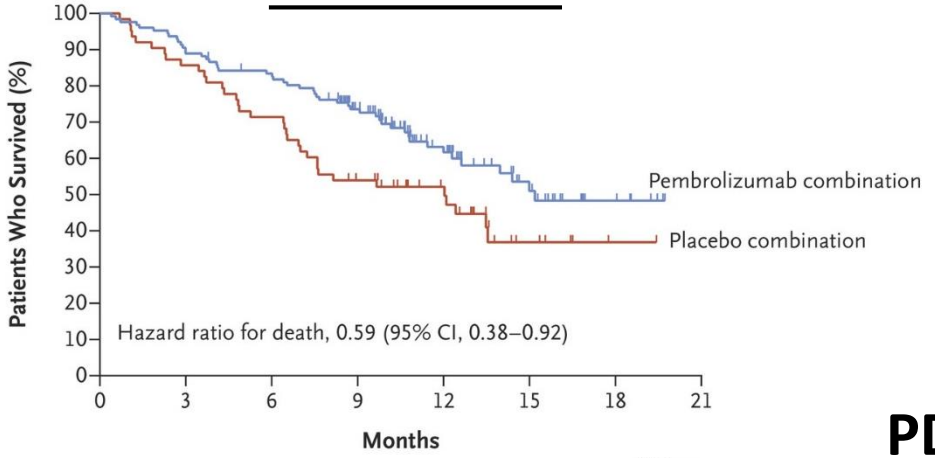
PD-L1 ≥ 50%



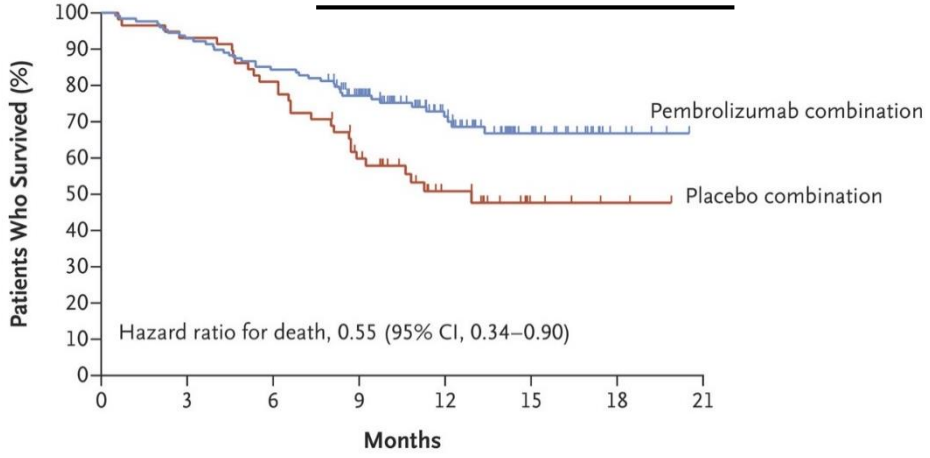
Ghandi et al, NEJM 2018

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

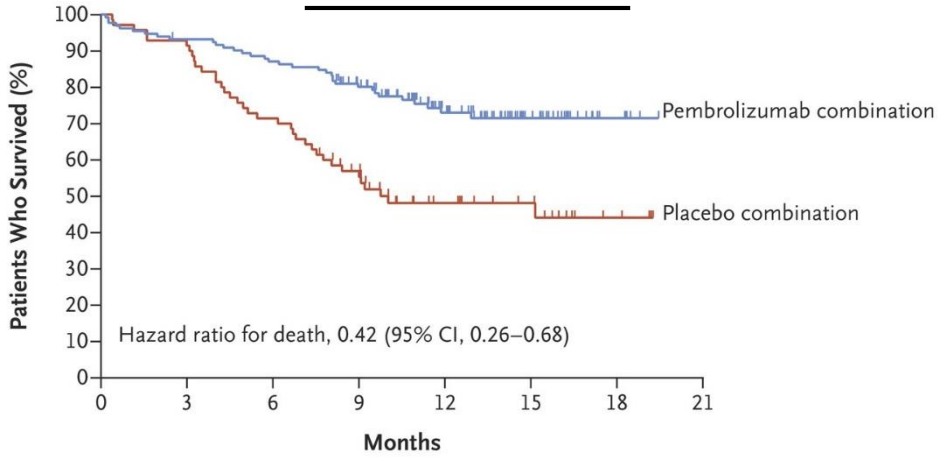
PD-L1 < 1%



PD-L1 = 1 – 49%

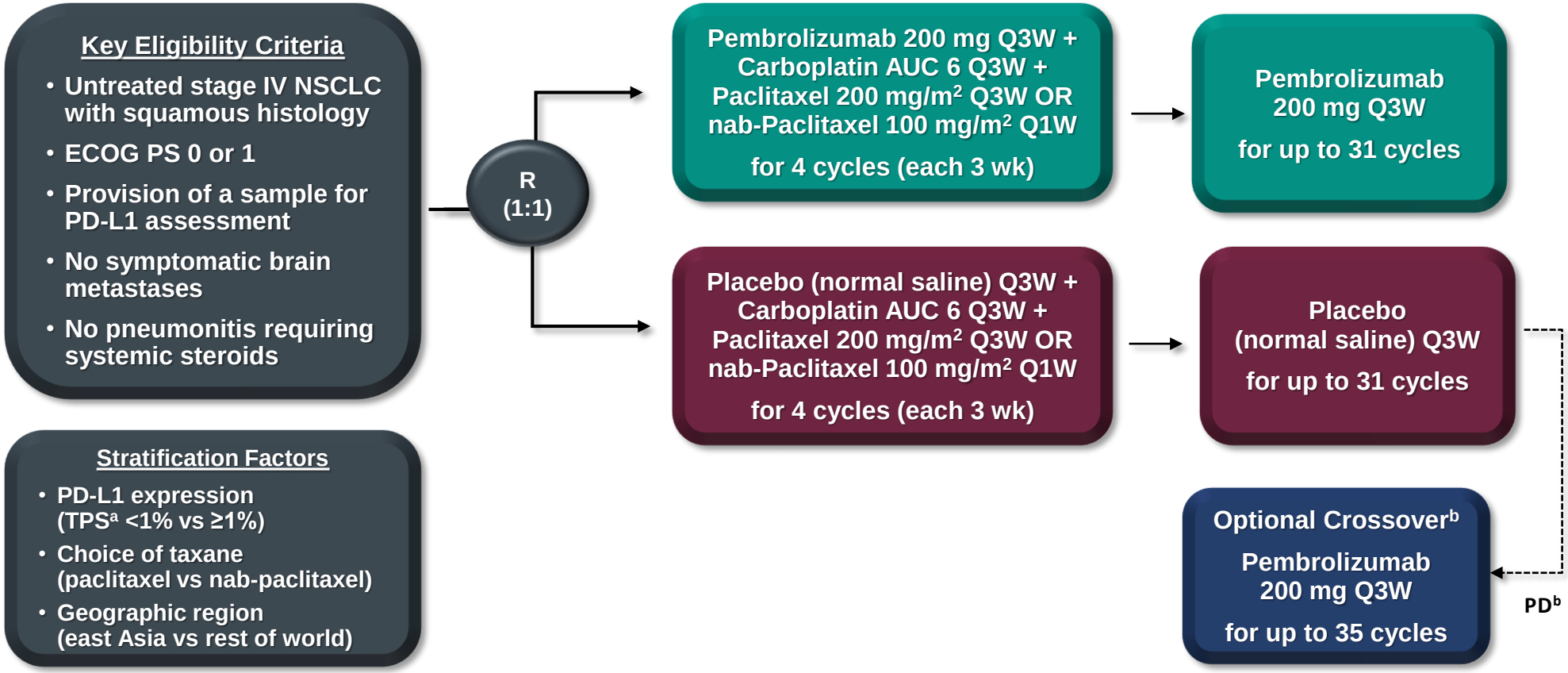


PD-L1 ≥ 50%



Ghandi et al, NEJM 2018

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

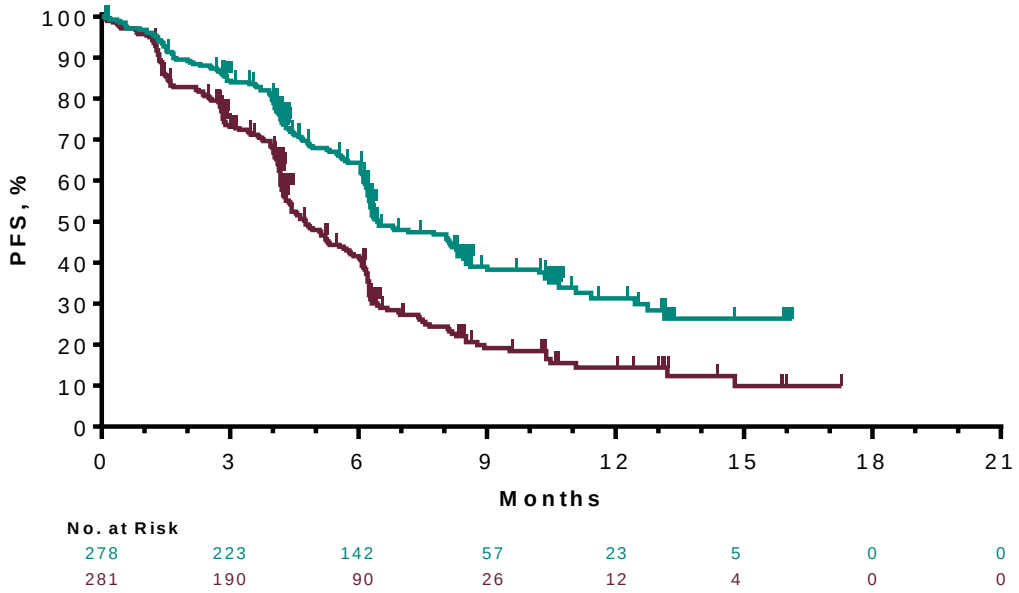


Paz-Ares et al, ASCO 2018

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

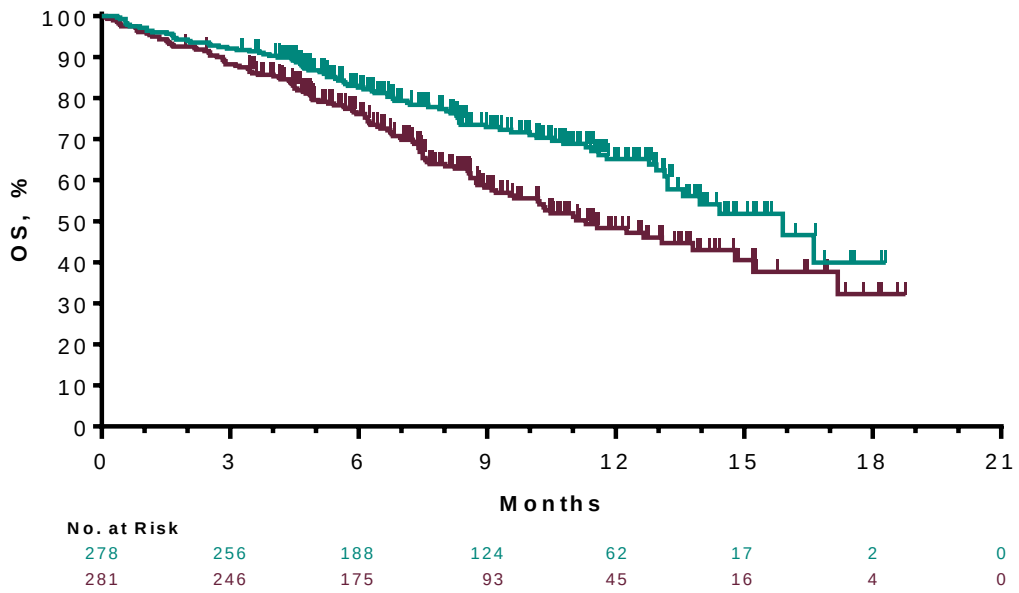
PFS (RECISTv1.1, BICR)

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



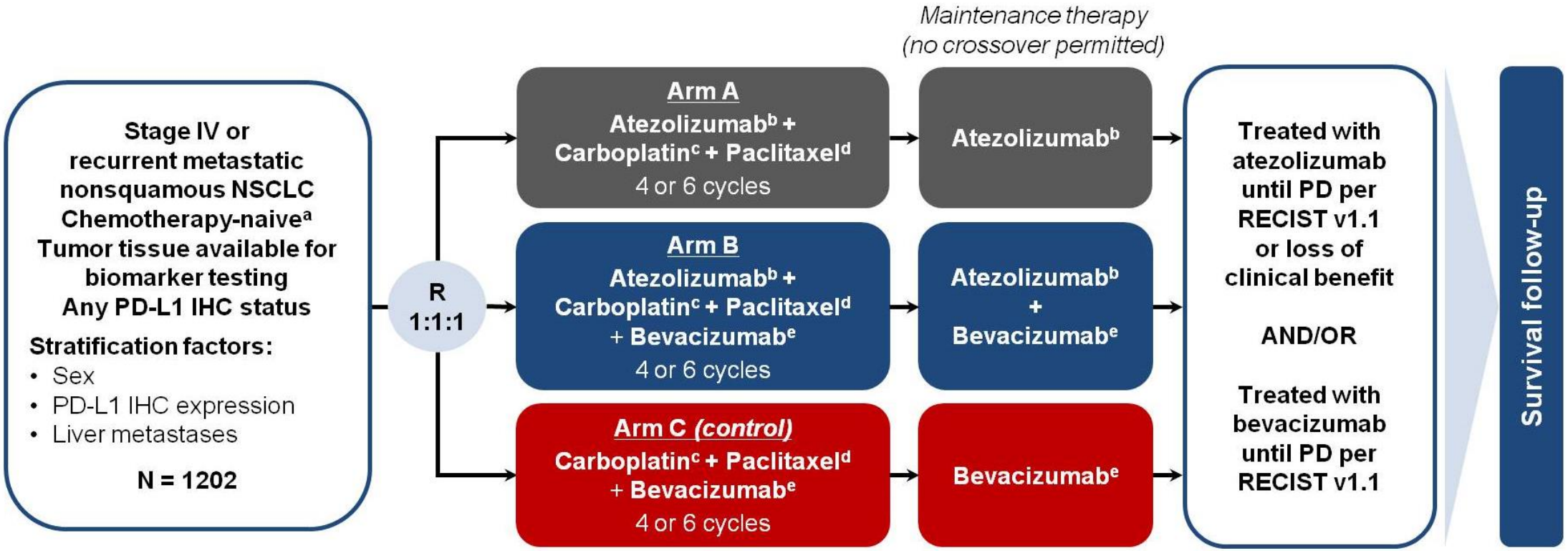
Overall Survival

	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

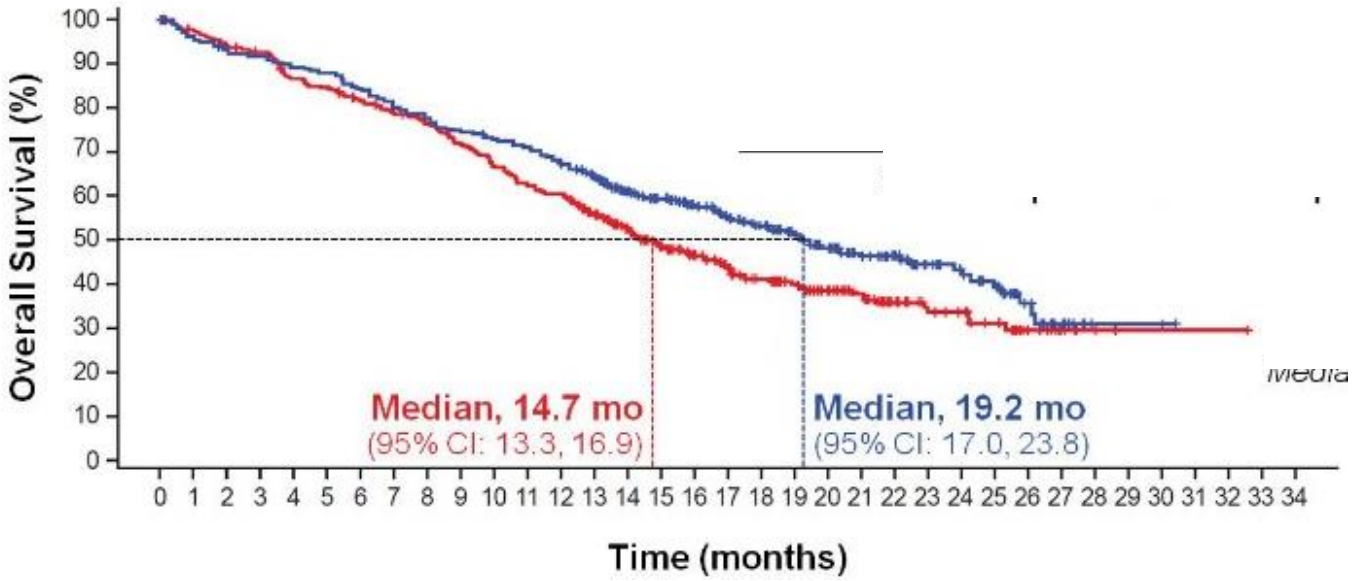


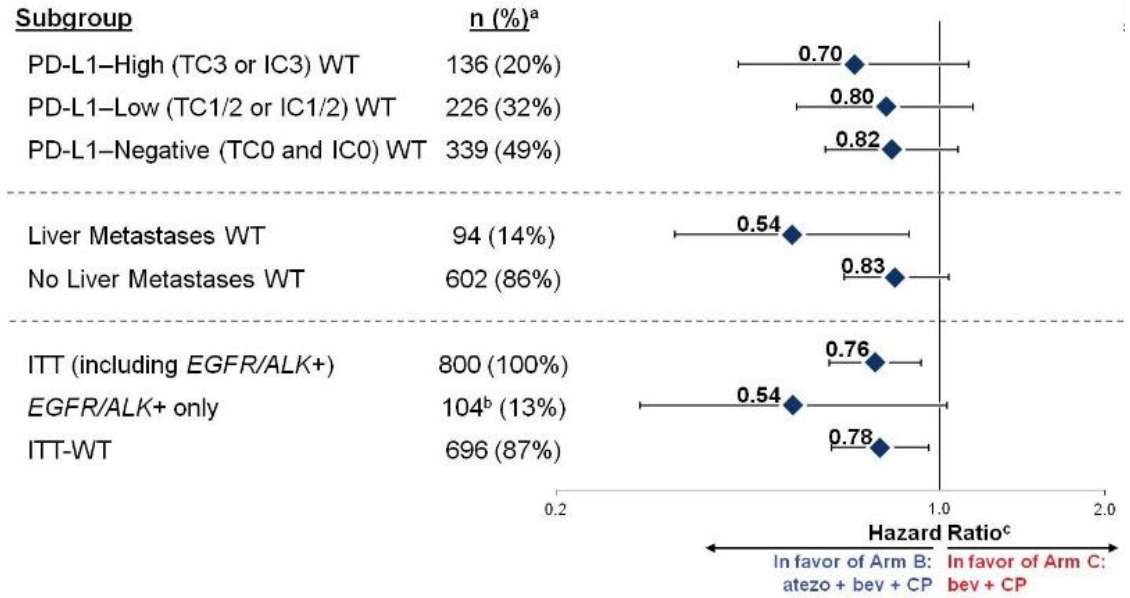
Socinski et al, NEJM 2018

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%	

HR[a], 0.78
(95% CI: 0.64, 0.96)
***P* = 0.0164**





Socinski et al, NEJM 2018

Long-term Outcomes in the Immunotherapy Era

- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%

Garon et al. JCO 2019
NCI SEER data, Lung and Bronchus Cancer, 2014

Long-term Outcomes in the Immunotherapy Era

- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%
- KEYNOTE-001
  - Pembrolizumab monotherapy in previously treated patients
  - 5 year overall survival

Garon et al. JCO 2019
NCI SEER data, Lung and Bronchus Cancer, 2014

Long-term Outcomes in the Immunotherapy Era

- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%
- KEYNOTE-001
  - Pembrolizumab monotherapy in previously treated patients
  - 5 year overall survival

	#	All	PD-L1 >=50%
Treatment-naïve	101	23.2%	29.6%
Previously treated	449	15.5%	25.0%

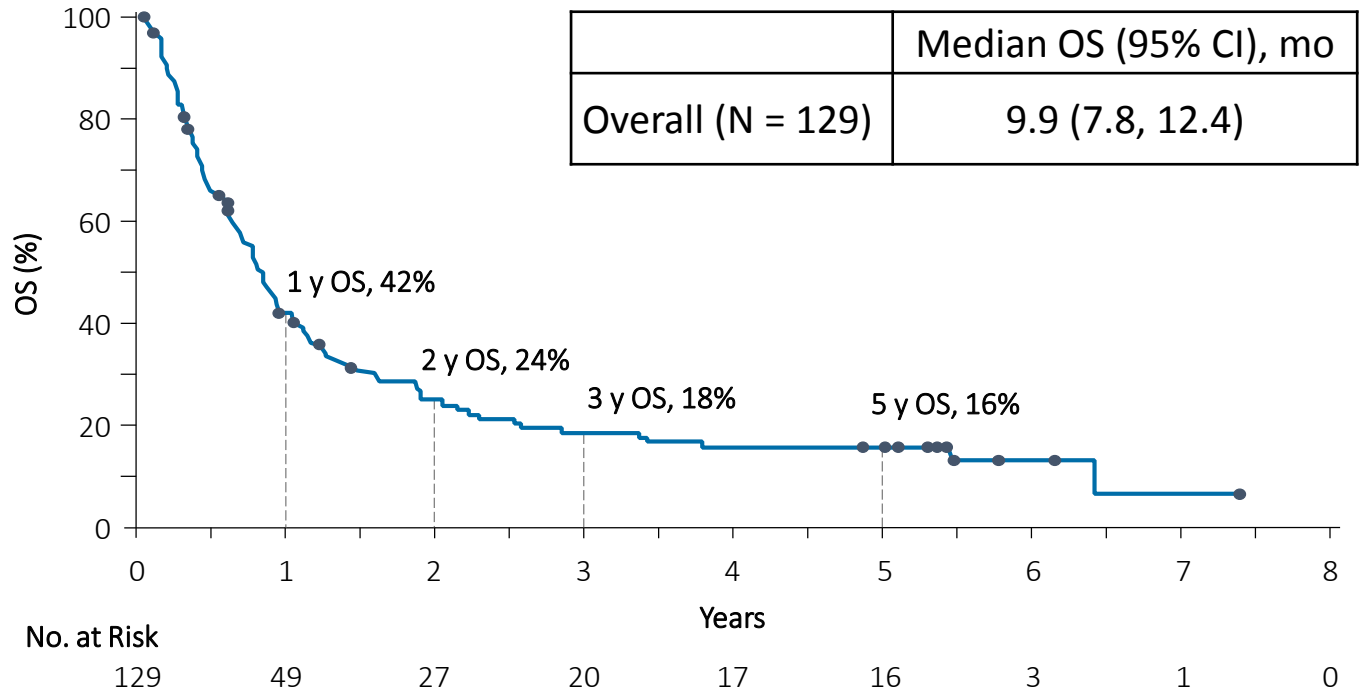
Garon et al. JCO 2019
NCI SEER data, Lung and Bronchus Cancer, 2014

Long-term Outcomes in the Immunotherapy Era

- CA209-003
- Nivolumab monotherapy in previously treated patients

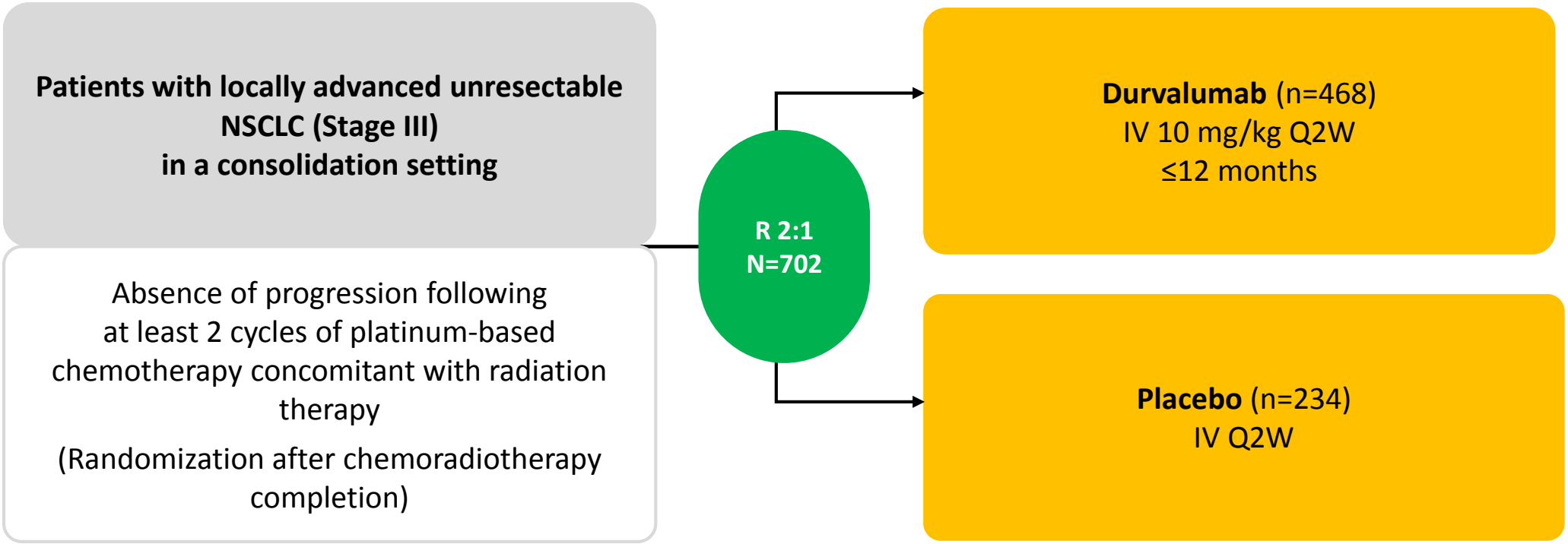
5-Year Survival

	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

PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

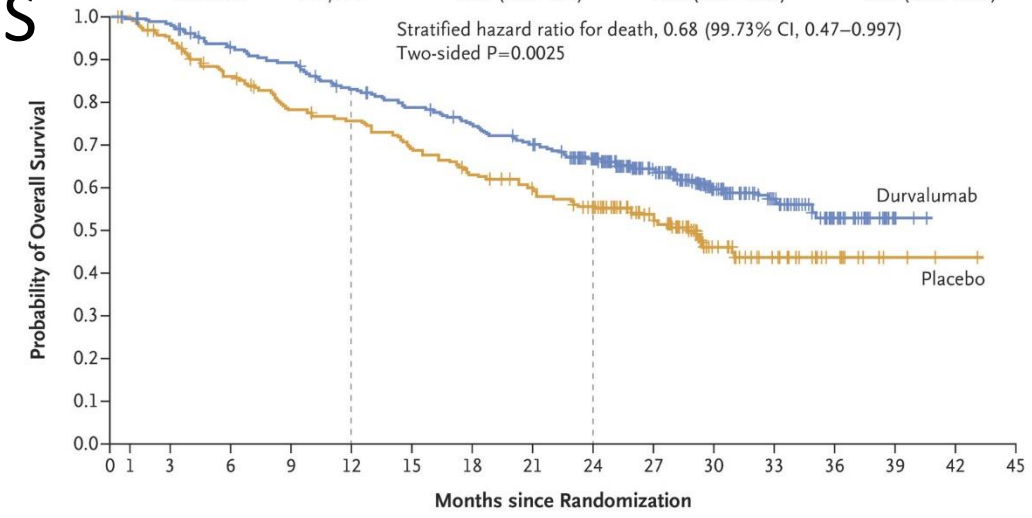


In House Data, AstraZeneca Pharmaceuticals LP. PACIFIC Protocol. 2014.
NIH 2015 NCT02125461, http://clinicaltrials.gov/ct2/show/NCT02125461.
Creelan B, Iannotti NO, Salamat MA, et al. 2016. (PHRR150325-000989)
Ann Oncol. 2015;26 (supplement 1): i24-i28, abstract 95TiP.

PACIFIC: Durvalumab after Chemoradiotherapy in Stage III NSCLC

OS

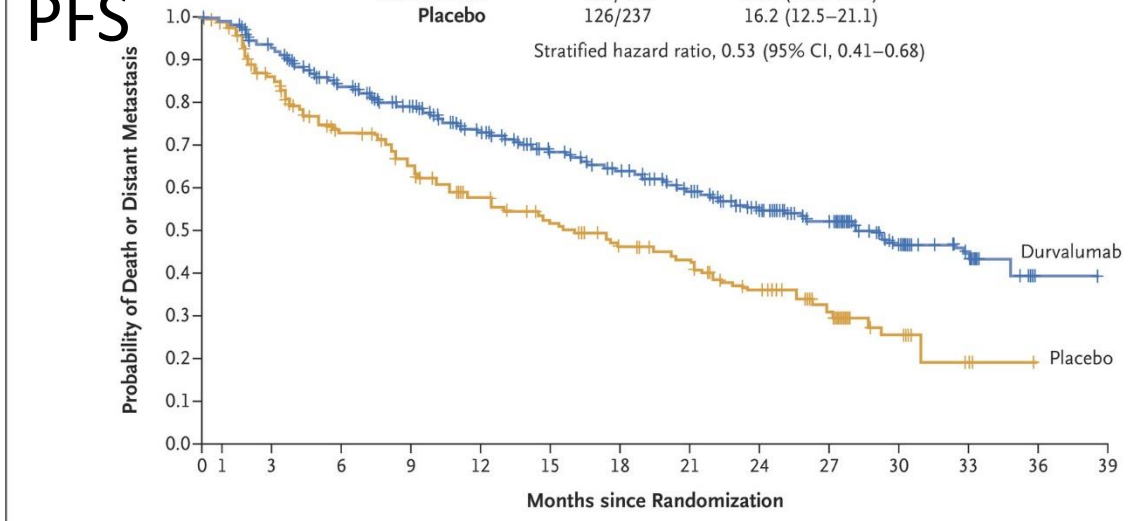
	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



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

Grade 3/4 toxicity 29.9 vs 26.1%, pneumonitis 3.4 vs 2.6%, d/c rate 15.4 vs 9.8%

Antonia et al, NEJM 2018

Small cell lung cancer

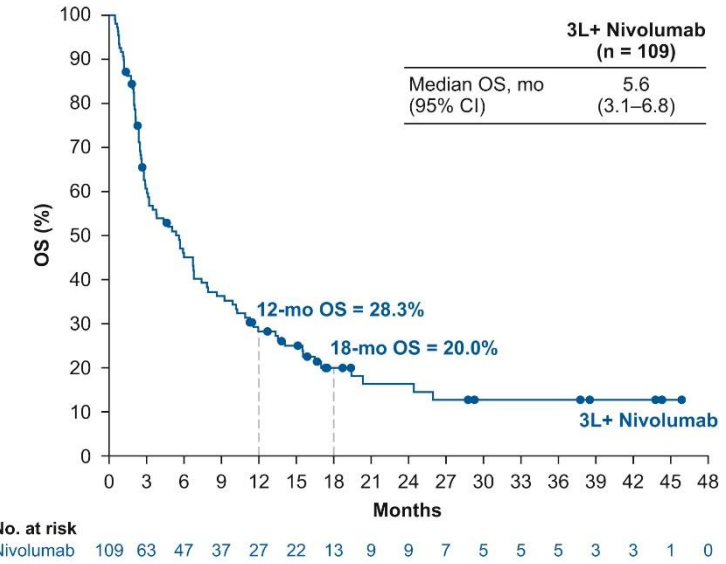
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

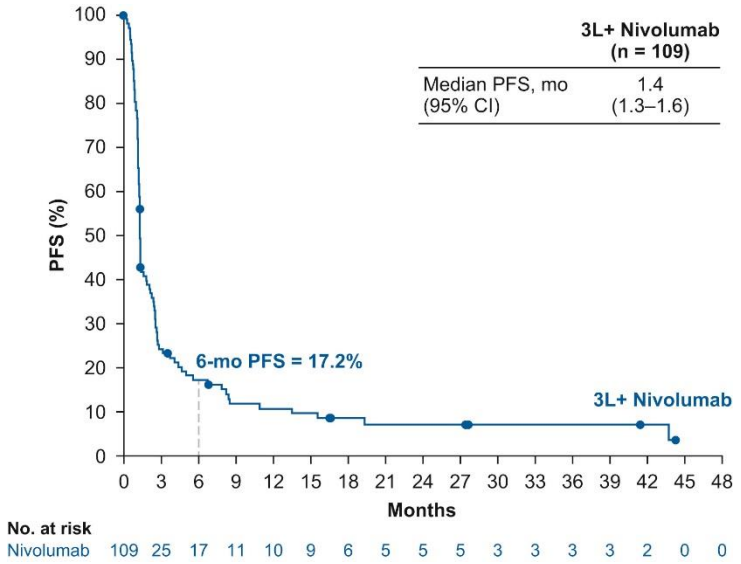
Approved checkpoint inhibitors in SCLC

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



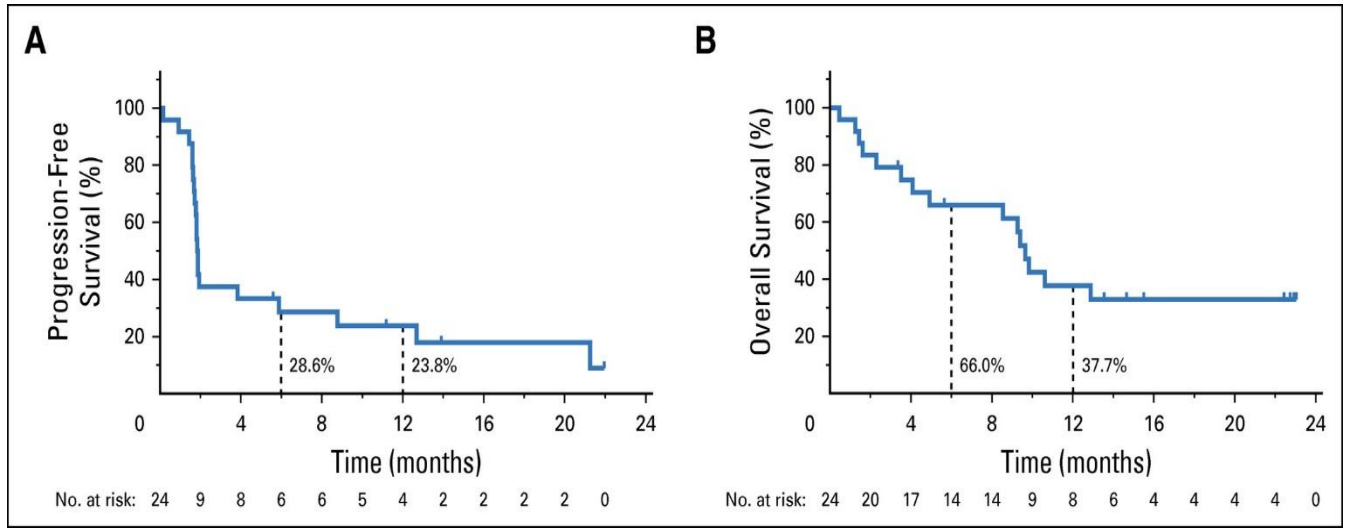


Ready, J Thorac Oncol 2019

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

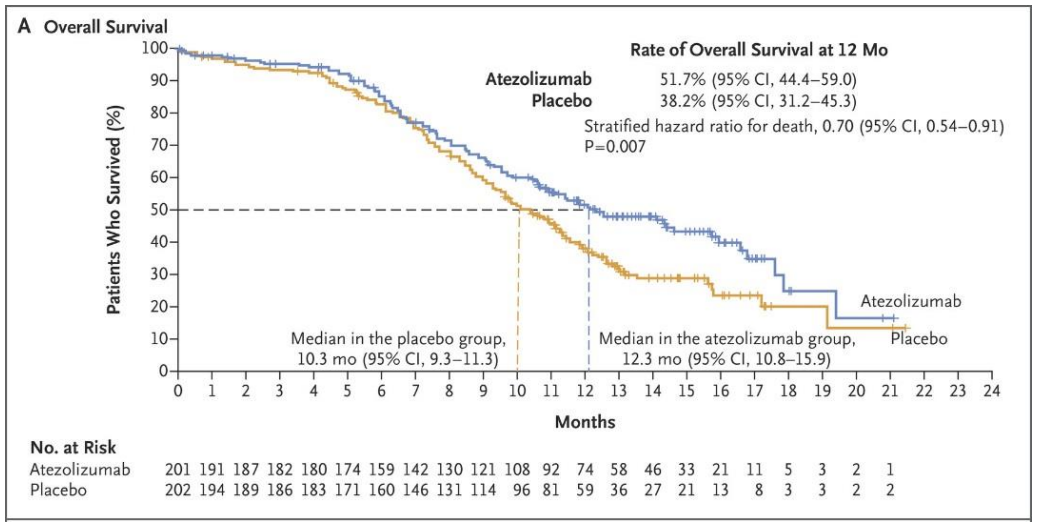
PD-L1+ (KEYNOTE-028)



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
- PD-1 and PD-L1 inhibitors have moved from 2nd/3rd line options to the front line for nearly all NSCLC patients
- Already seeing durable long-term responders from early phase 1 trials
- Clear-cut biomarkers still lacking
- Clear need for immuno-refractory strategies

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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Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Case Studies

Case Study 1

- 49yo Caucasian man presents with cough, progressive SOB and back pain
  - CXR shows L pleural effusion
    - Thoracentesis: 1.2L, cytology sent to lab
  - CT after thoracentesis shows 3.4cm left upper lung mass with near total collapse of left lung, large conglomerate mediastinal LAD
  - PET/CT also reveals multiple bone metastases and a left adrenal mass, hypermetabolic
  - MRI brain negative

- Patient still quite dyspneic after thoracentesis, PS 1
- Works as a foreman, but no toxic exposures
- Tobacco: 5PY in his teens, quit at 20. EtOH: None.

Case Study 1

- 49yo Caucasian man presents with cough, progressive SOB and back pain, found to have metastatic stage IV adenocarcinoma involving pleura, bone, and adrenal
  - Cytology: Adenocarcinoma
  - IHC
    - CK7+, CK20-, TTF1+ and NapsinA+
    - PD-L1 22C3 70%, 3+

Case Study 1

- 49yo Caucasian man presents with cough and progressive SOB with metastatic stage IV adenocarcinoma involving pleura, bone, adrenal, symptomatic, PD-L1 high at 70%

- What do you want to treat with now?
  - Carboplatin, paclitaxel, bevacizumab and atezolizumab
  - Carboplatin, pemetrexed and pembrolizumab
  - Pembrolizumab
  - Other

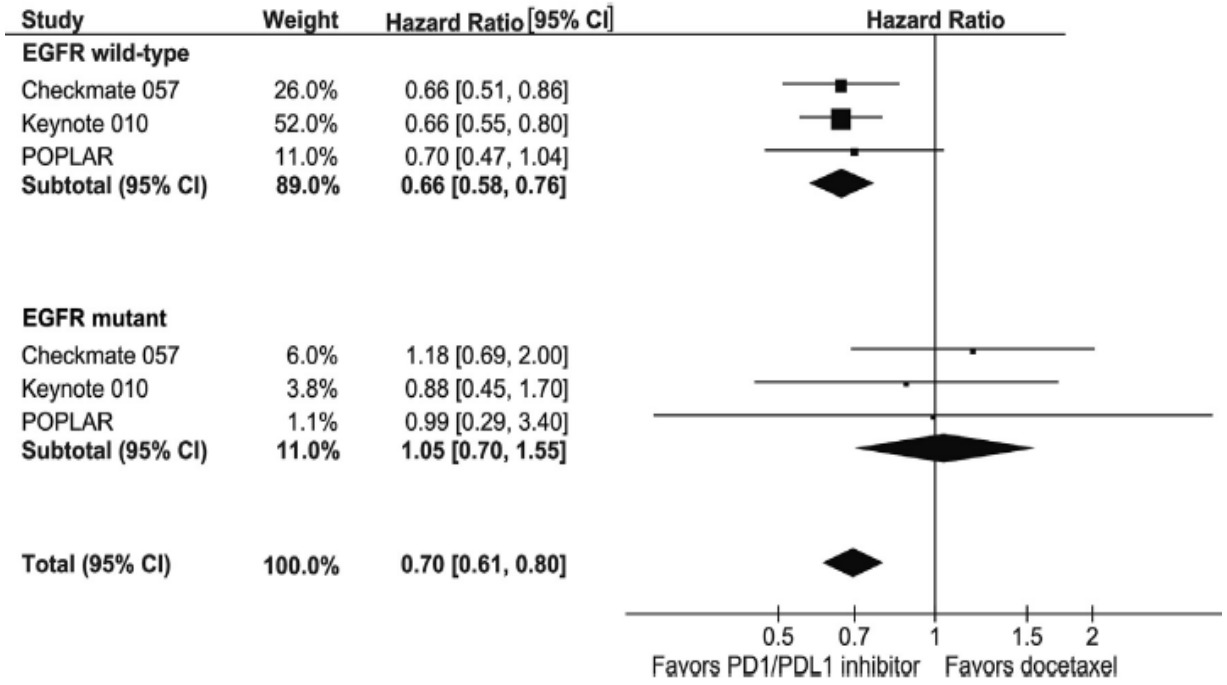
Case Study 1

- 49yo Caucaisn man presents with cough and progressive SOB with metastatic stage IV adenocarcinoma involving pleura, bone, adrenal, symptomatic, PD-L1 high at 70%

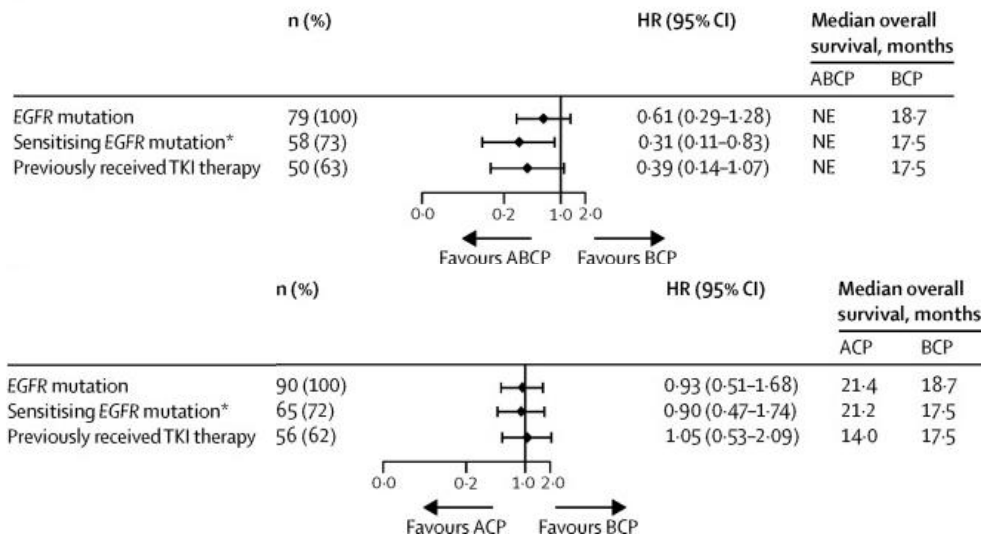
- NGS returns 10 days later with EGFR exon 19 deletion, TMB 0 Muts/Mb

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

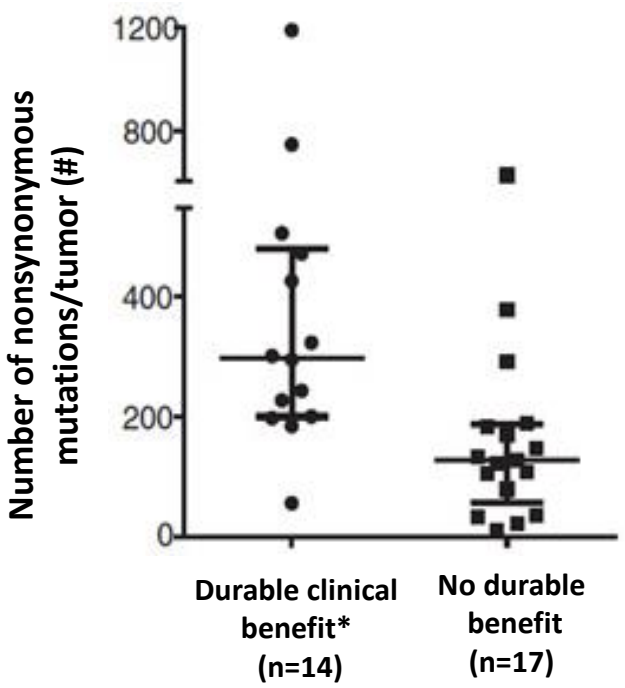
Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

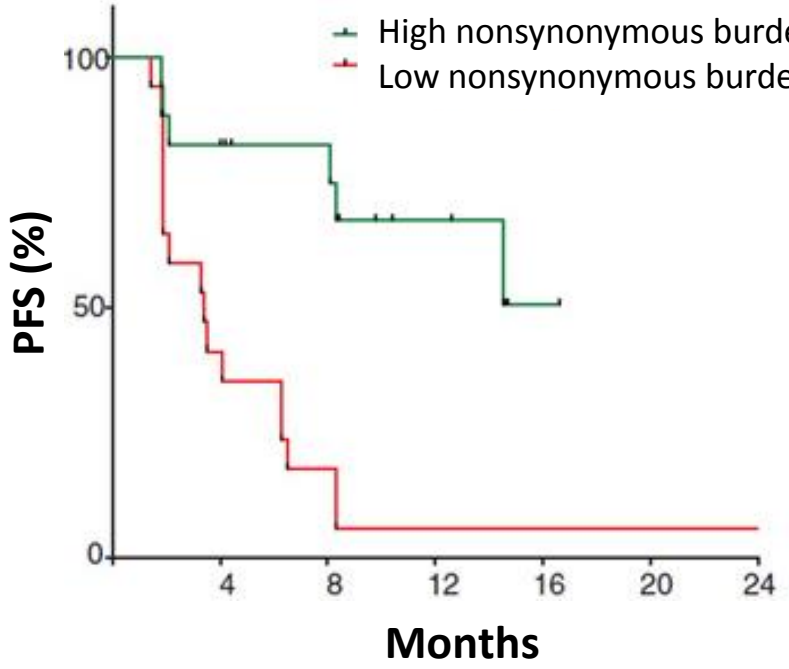
1st line study from UCLA: Lisberg et al ASCO 2017

- Phase 2 study, planned 25 EGFR+ TKI-naïve patients with advanced dz
  - Pembrolizumab single agent
  - Primary endpoint ORR
- Results: Stopped after stage 1, 11 patients
  - 1/11 had an objective response
  - …and that patient was later found to be EGFR negative
  - This despite 73% with PD-L1 expression >=50%
  - 2 deaths within 6 months of enrollment, including 1 attributed to pneumonitis
- Take-home messages: first line IO not appropriate for EGFR and likely other driver mutations where targeted therapy available– poor effectiveness even with high PD-L1 and potential interaction with TKI

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

Case Study 1

- 49yo Caucasian man presents with cough and progressive SOB with metastatic stage IV adenocarcinoma involving pleura, bone, adrenal, PD-L1 high at 70%, EGFR exon 19 del
- Osimertinib with disease response x 26 months, then multifocal progression
- Repeat biopsy with EGFR exon 19 del, TP53 mut

- What next?
  - Carboplatin, paclitaxel, bevacizumab and atezolizumab
  - Carboplatin, pemetrexed and bevacizumab
  - Carboplatin, pemetrexed and pembrolizumab
  - Pembrolizumab

Case Study 2

- 69yo Asian woman presents with fever and productive cough x 1 week
- CXR shows left lung/hilar consolidation, 4.8cm
- After 1 week of antibiotics, fever resolves but cough continues to worsen
- CT chest shows 5.1 cm left lower lobe mass and also hilar, prevascular, subcarinal and paratracheal LAD up to 1.6cm short axis
- PET/CT shows uptake only in the lung mass and hilar and ipsilateral mediastinal nodes
- MRI brain negative

- Patient feeling ok aside from cough, PS1.

- Never smoker. Homemaker.

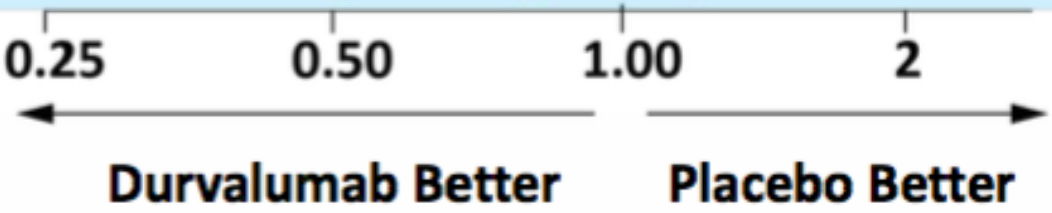
Case Study 2

- 69yo Asian woman with clinical stage IIIB (T3N2M0) lung cancer
- EBUS subcarinal node: Adenocarcinoma, TTF1+
  - PD-L1 30%by 22C3, EGFR exon 19 del
- Thoracic surgery deems her unresectable

- How would you treat?
  - Concurrent chemoradiation with carboplatin and paclitaxel
  - Concurrent chemoradiation with carboplatin and paclitaxel, then durvalumab
  - Concurrent chemoradiation with carboplatin and paclitaxel, then osimertinib
  - Osimertimib

PACIFIC trial subsets

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death
	no. of patients		
All patients	476	237	0.55
PD-L1 status			
≥25%	115	44	0.41
<25%	187	105	0.59
Unknown	174	88	0.59
EGFR mutation			
Positive	29	14	0.76
Negative	315	165	0.47
Unknown	132	58	0.79



Case Study 2

- 69yo Asian woman with clinical stage IIIB (T3N2M0) lung adenocarcinoma
- She completes chemoradiation with 66Gy in 6 weeks with weekly carboplatin/paclitaxel
- Imaging at end of treatment shows treatment response
- She starts on durvalumab

Case Study 2

- 69yo Asian woman with clinical stage IIIB (T3N2M0) lung adenocarcinoma s/p chemoradiation, now on durvalumab
- At 3 months, TSH 12 and FT4 2
  - Started on levothyroxine with normalization of TSH 6 weeks later
- At 6 months, glucose 330 on routine labs → fasting 230, A1c 8.2
  - Sent to endocrinology
  - Started on long-acting and short-acting insulin with good control

- Do you resume durvalumab to complete a year?
  - Yes
  - No

Thank you!