Immunotherapy for the Treatment of Lung Cancer

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Disclosures

- Contracted Research: Mirati Therapeutics
- 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

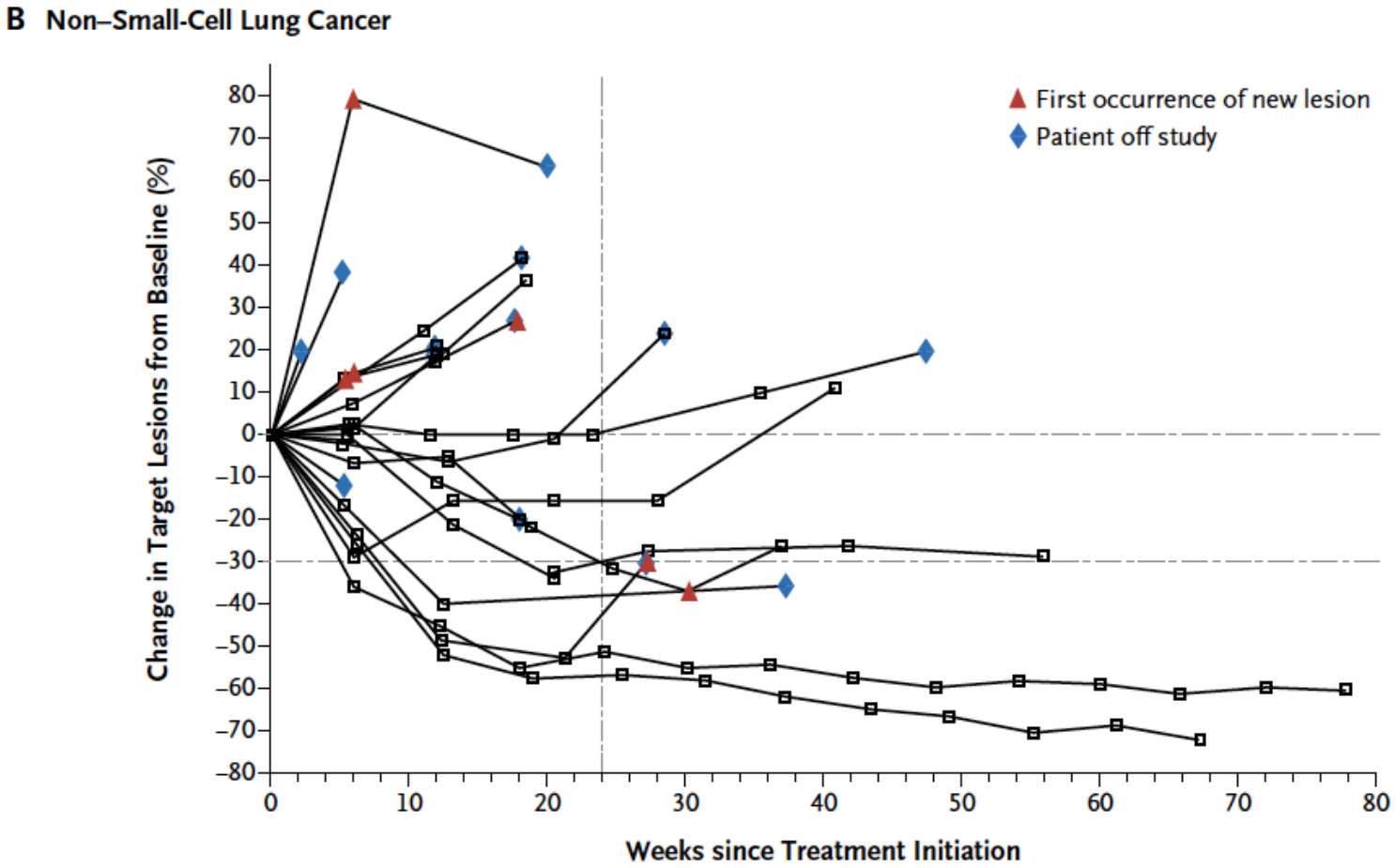
Estimated Deaths

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

Safety and activity of anti–PD-L1 antibody in patients with advanced cancer



Brahmer JR. N Engl J Med 2012; 366:2455-2465

Immune checkpoint inhibitors in lung cancer

Nivolumab
PD-1

Pembrolizumab
PD-1

Atezolizumab
PD-L1

Durvalumab
PD-L1

Ipilimumab
CTLA-4

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 + Carboplatin: 1st line NSCLC

2018
Durvalumab: Stage III NSCLC (unresectable) s/p chemoradiation w/o progression

Nivolumab: 3rd line SCLC

Pembrolizumab + Carboplatin + (nab) Paclitaxel: 1st line Sq NSCLC

Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel: 1st line Non-Sq NSCLC

2019
Atezolizumab + Etoposide/Platinum: 1st line ES-SCLC

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

Pembrolizumab: 3rd-line ES-SCLC

2020
Durvalumab + Etoposide/Platinum: 1st line ES-SCLC

Nivolumab + ipilimumab: 1st line metastatic NSCLC with PD-L1 ≥1% and no EGFR/ALK mutations

Atezolizumab: 1st line metastatic NSCLC with PD-L1 ≥50% and no EGFR/ALK mutations

Nivolumab + ipilimumab + chemotherapy: 1st line NSCLC with no EGFR/ALK mutations

#LearnACI

Outline

- NSCLC – the bulk of the talk
- SCLC
- Mesothelioma
- Cases

NSCLC

- This has been the area of the greatest growth with hundreds of trials and >10 FDA approvals
- There are several indications with a variety of evidence-based approaches with no clear “best regimen”
- I will discuss a general approach to treatment and not get too into the weeds on the details of specific clinical trials
- I will not discuss immunotherapy in second line as most approaches favor 1st line use

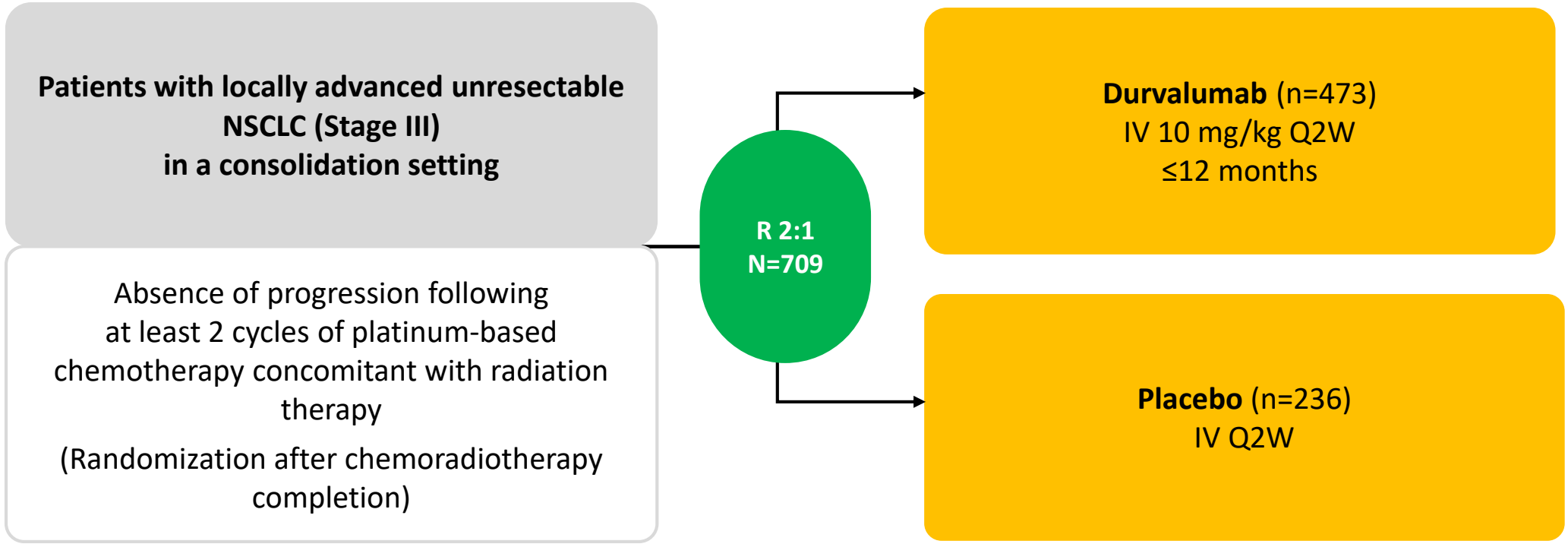
The scenarios

- PDL1 high (>50%) and no driver
- PDL1 not high (<1% and 1-49%) and no driver
- Driver mutation (EGFR, ALK; NTRK, MET, RET, BRAF)

The approaches to immunotherapy

- Chemo + PD1/PDL1
- Limited chemo + PD1/CTLA4
- Monotherapy (PD1/PDL1)
- Dual therapy (PD1/CTLA4)

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

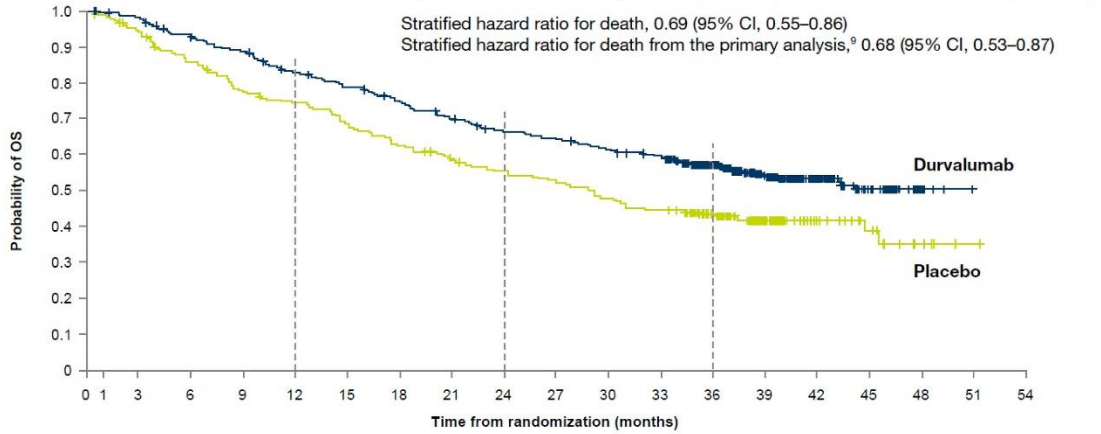


Antonia et al, NEJM 2018

PACIFIC – 3 and 4 year update

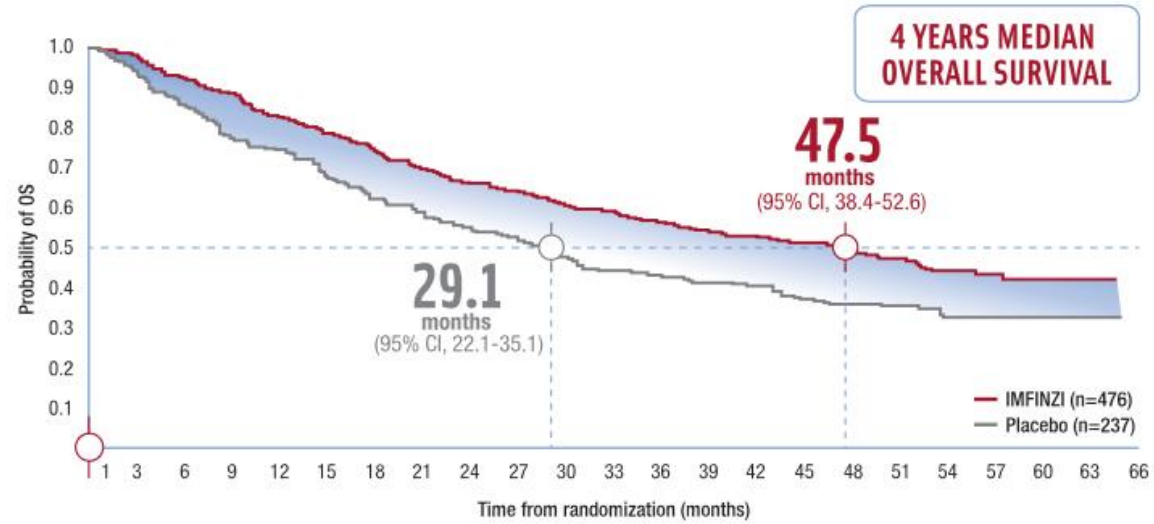
	No. of events/ total no. of patients (%)	Median OS (95% CI) months	12-month OS rate (95% CI) %	24-month OS rate (95% CI) %	36-month OS rate (95% CI) %
Durvalumab	210/476 (44.1)	NR (38.4–NR)	83.1 (79.4–86.2)	66.3 (61.8–70.4)	57.0 (52.3–61.4)
Placebo	134/237 (56.5)	29.1 (22.1–35.1)	74.6 (68.5–79.7)	55.3 (48.6–61.4)	43.5 (37.0–49.9)

Stratified hazard ratio for death, 0.69 (95% CI, 0.55–0.86)
Stratified hazard ratio for death from the primary analysis,[9] 0.68 (95% CI, 0.53–0.87)



No. at risk

Durvalumab	476	464	431	415	385	364	343	319	298	289	274	263	205	132	73	33	7	0	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	79	49	25	13	5	1	0



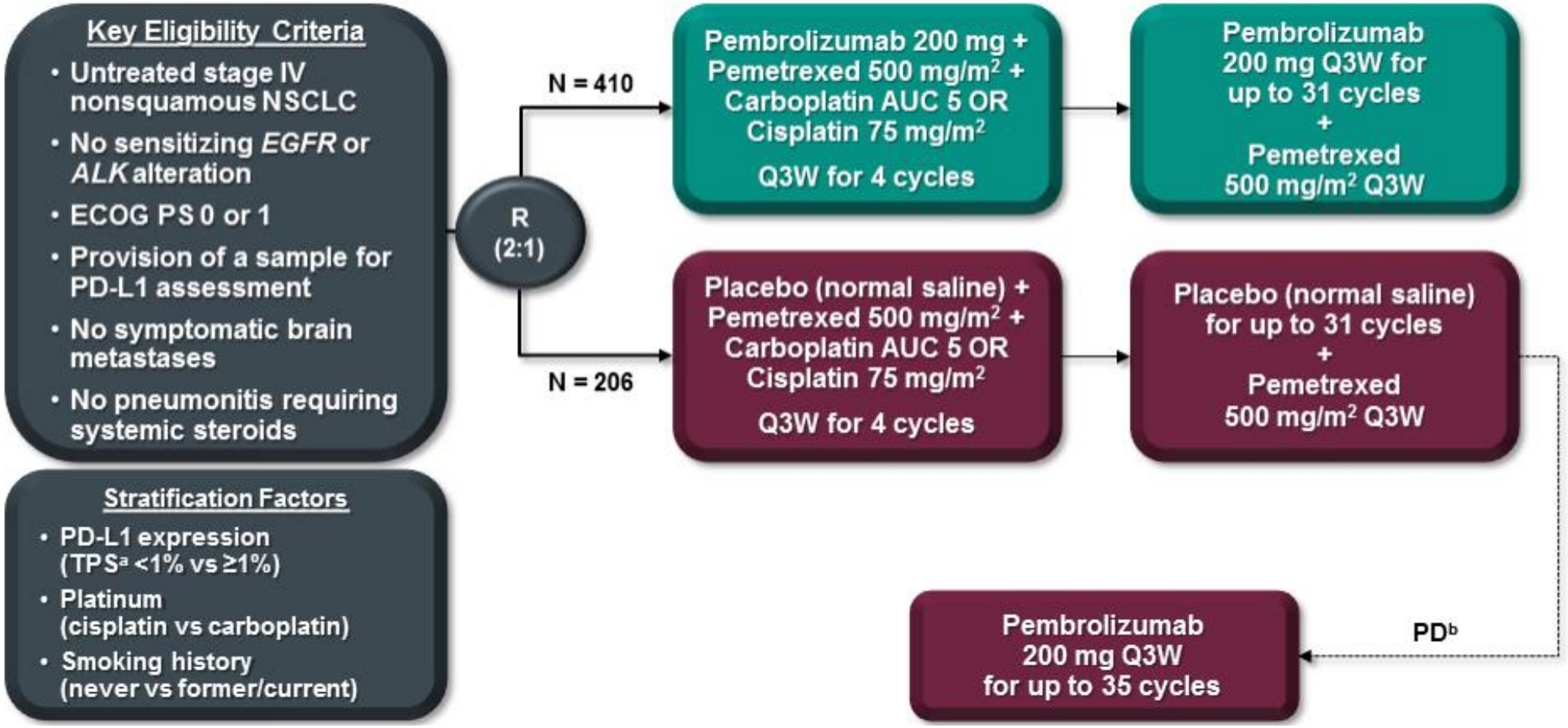
Number of patients at risk

IMFINZI	476	464	431	414	385	364	343	319	299	290	274	265	252	241	235	225	195	138	75	36	15	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	75	53	29	15	7	2	0

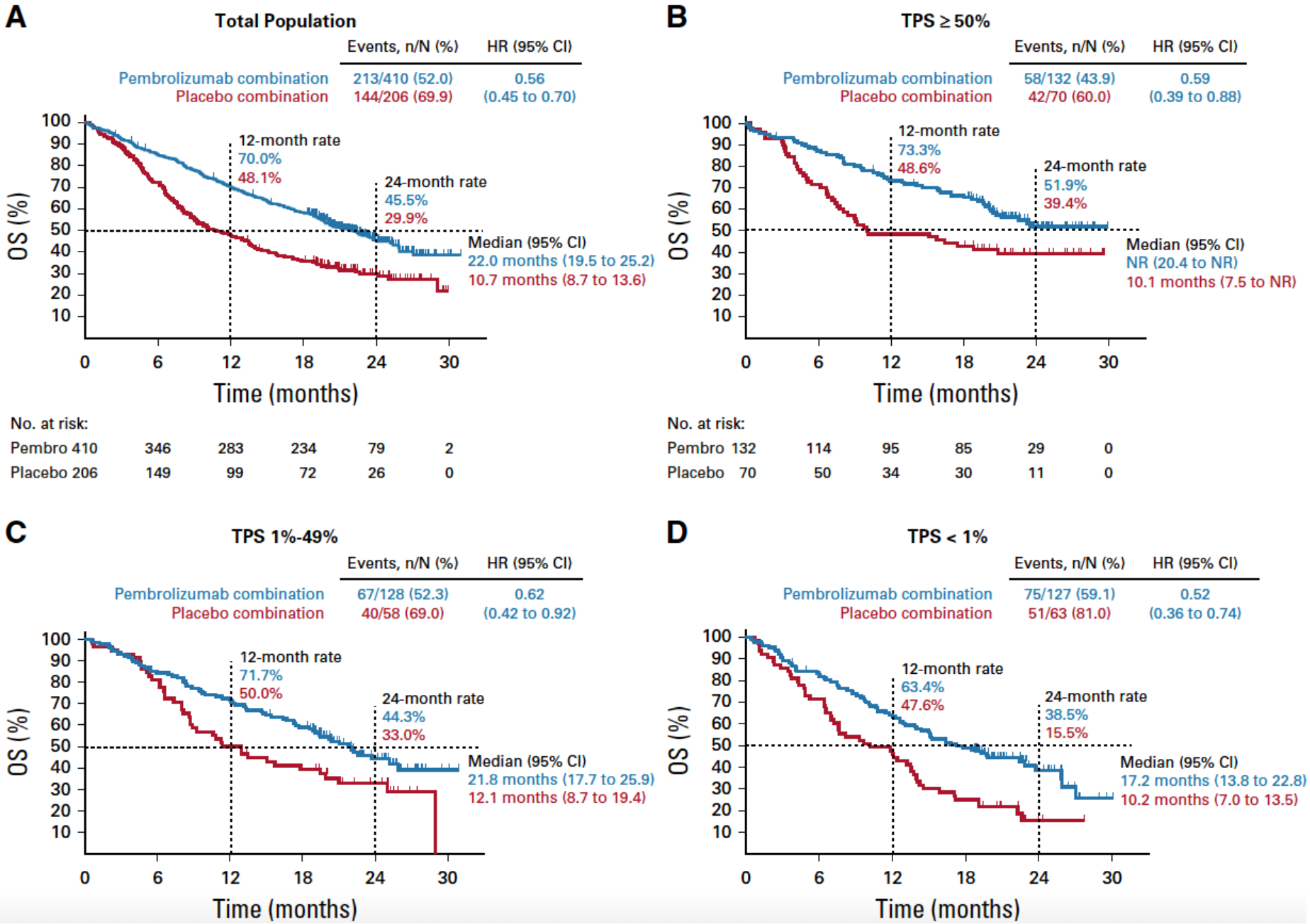
Gray JE. *Journal of Thoracic Oncology* 2020

https://www.imfinzihcp.com/non-small-cell-lung-cancer.html

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

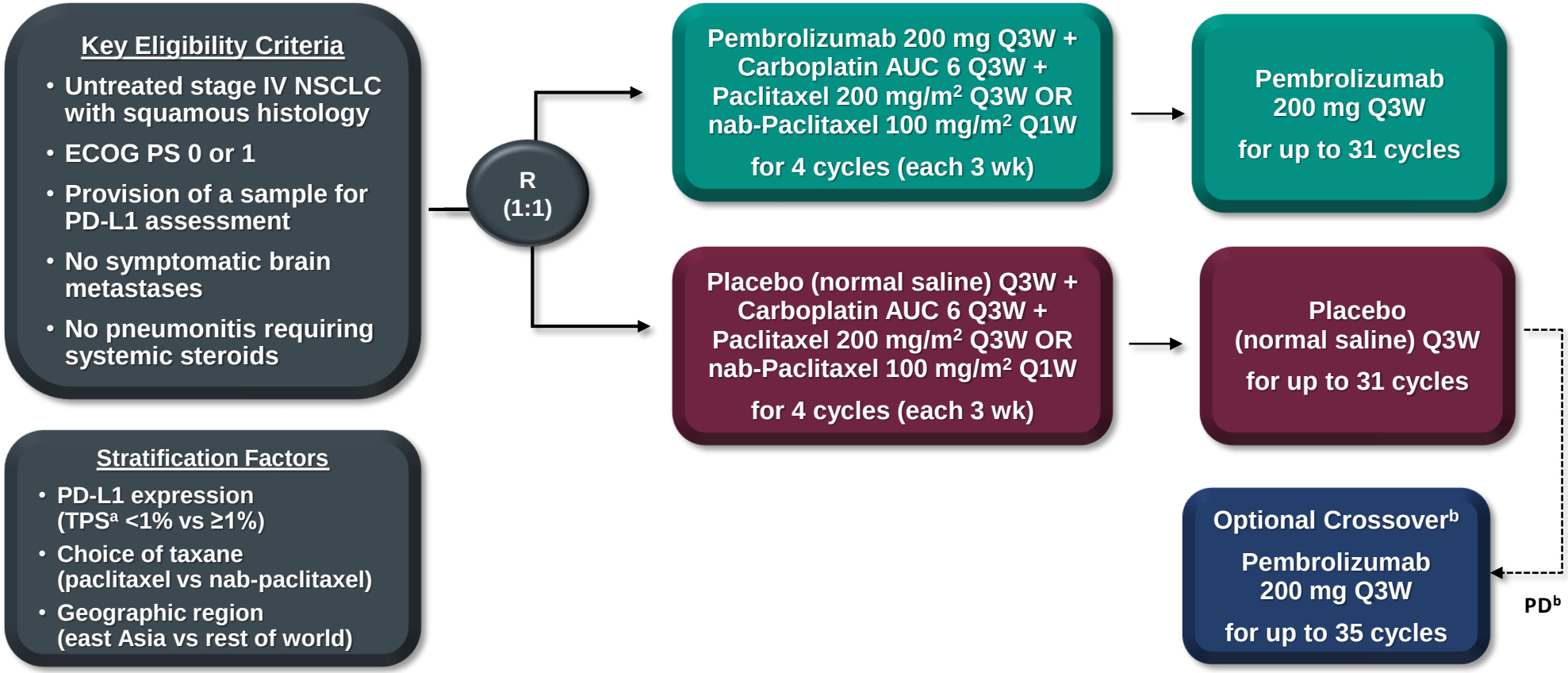


Ghandi et al, NEJM 2018



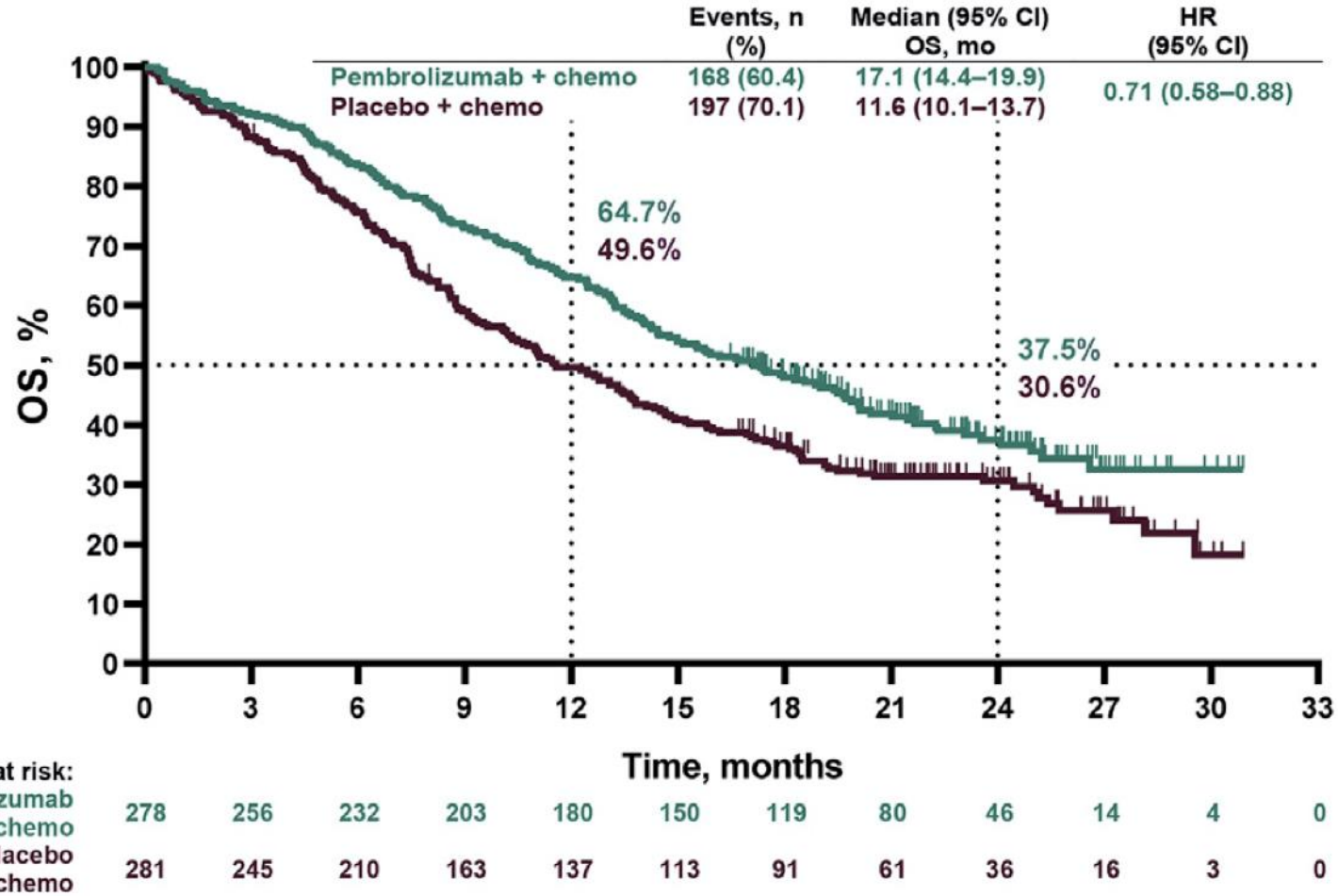
Ghandi et al, NEJM 2018, Gadgeel JCO 2020

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



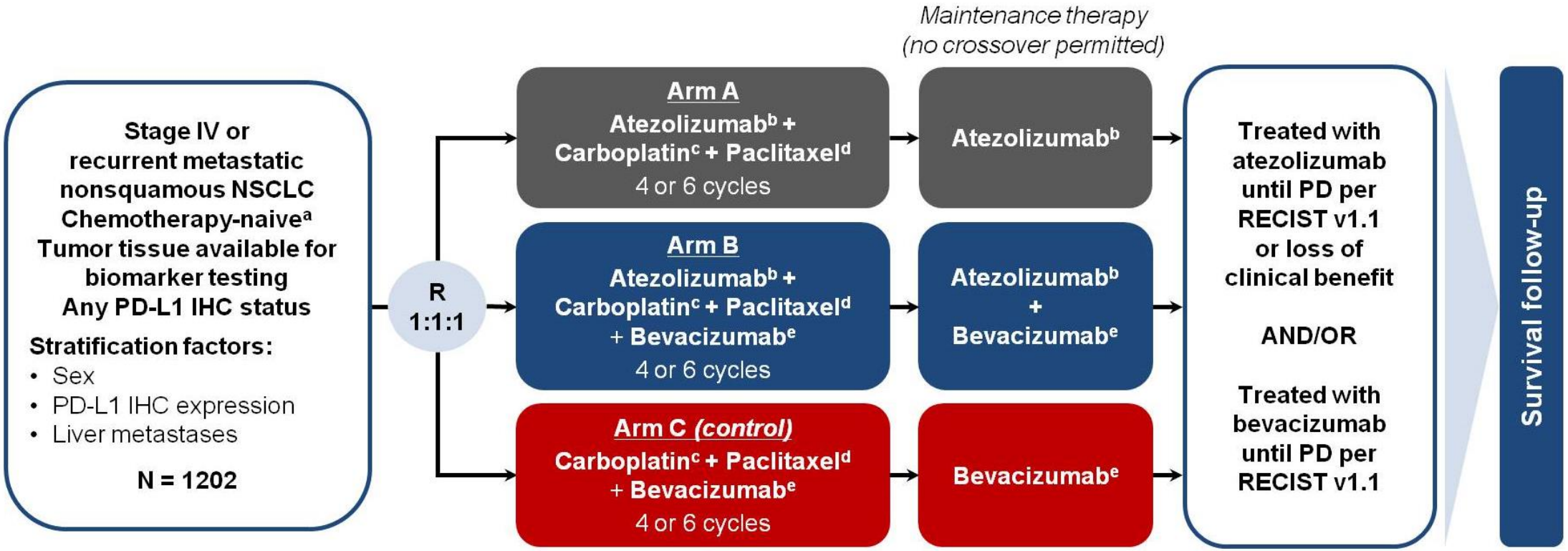
Paz-Ares et al, ASCO 2018

KEYNOTE-407: Advanced Squamous-Cell NSCLC



Paz-Ares et al, JTO 2020

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

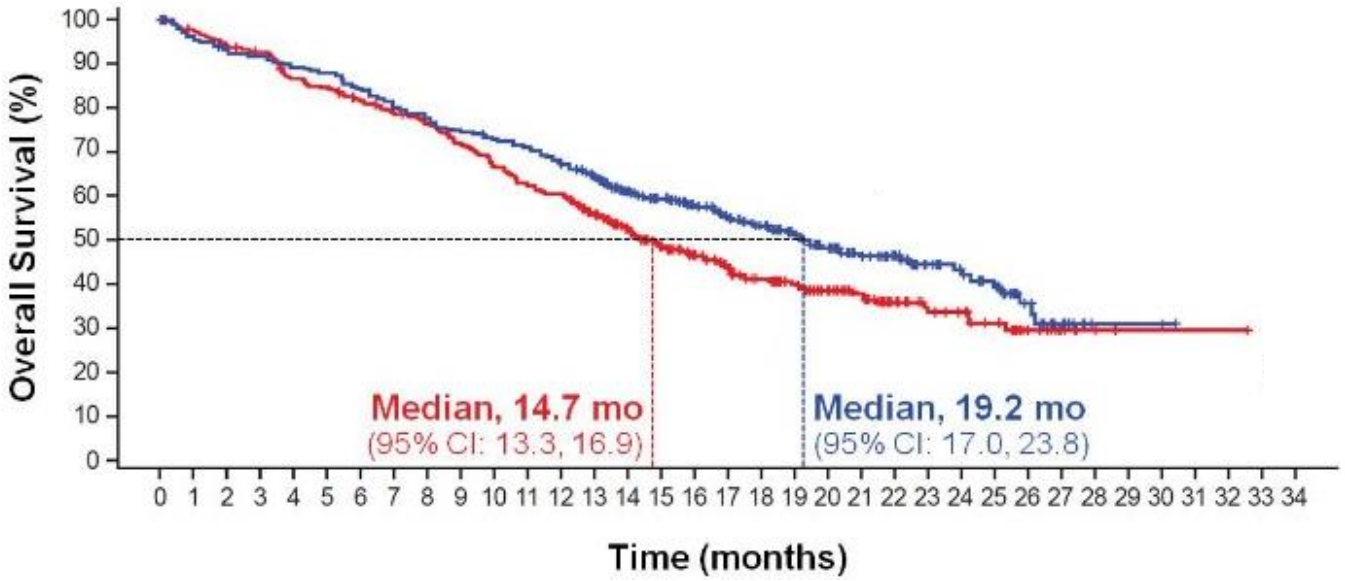


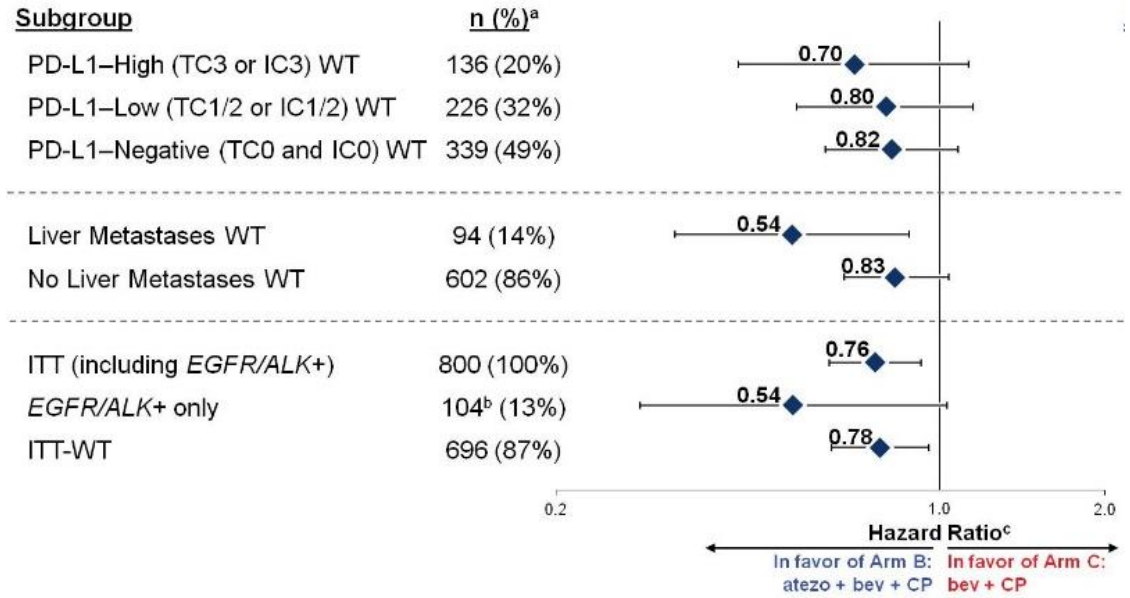
Socinski et al, NEJM 2018

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

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)

N = 719

R 1:1

n = 361

NIVO 360 mg Q3W + **IPI** 1 mg/kg Q6W + **Chemo[d]** Q3W (2 cycles)

n = 358

Chemo[d] Q3W (4 cycles) with optional pemetrexed maintenance (NSQ)

Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

Primary endpoint

- OS

Secondary endpoints

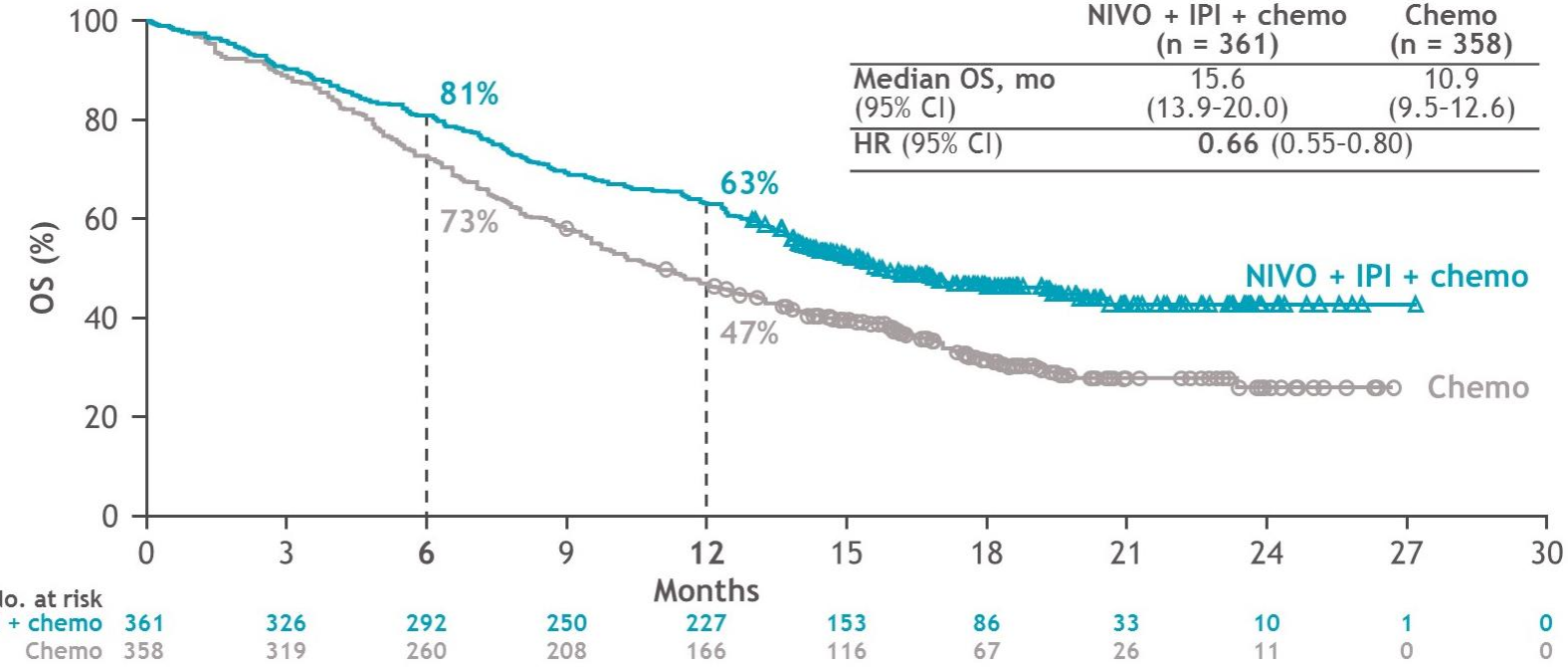
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]**NSQ**: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Reck M et al, ASCO 2020.

CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo



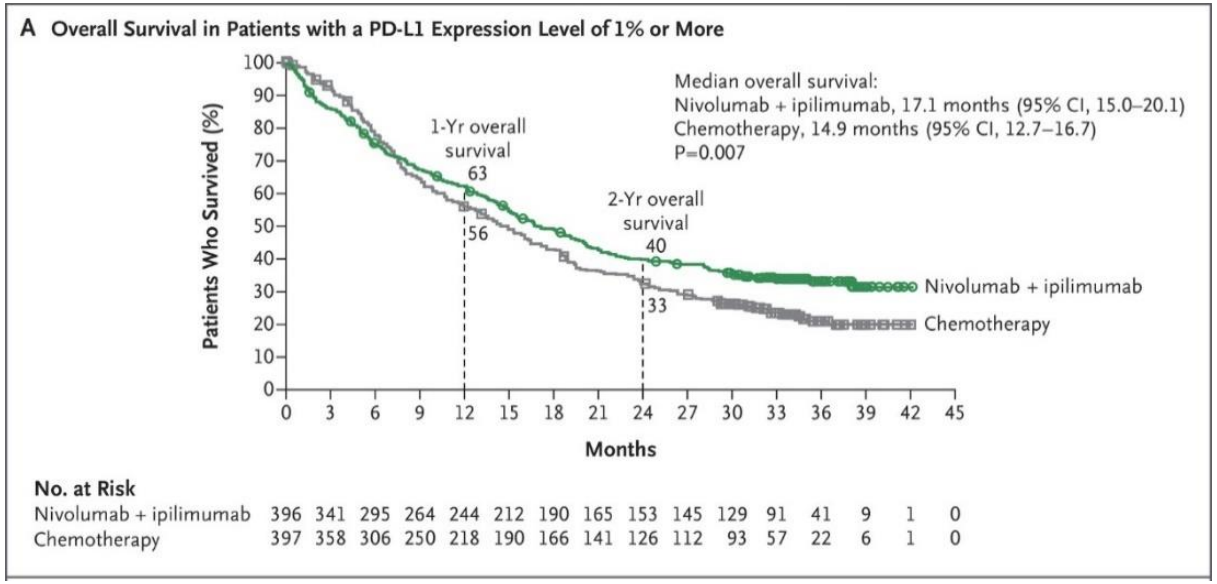
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	0.66 (0.55-0.80)	

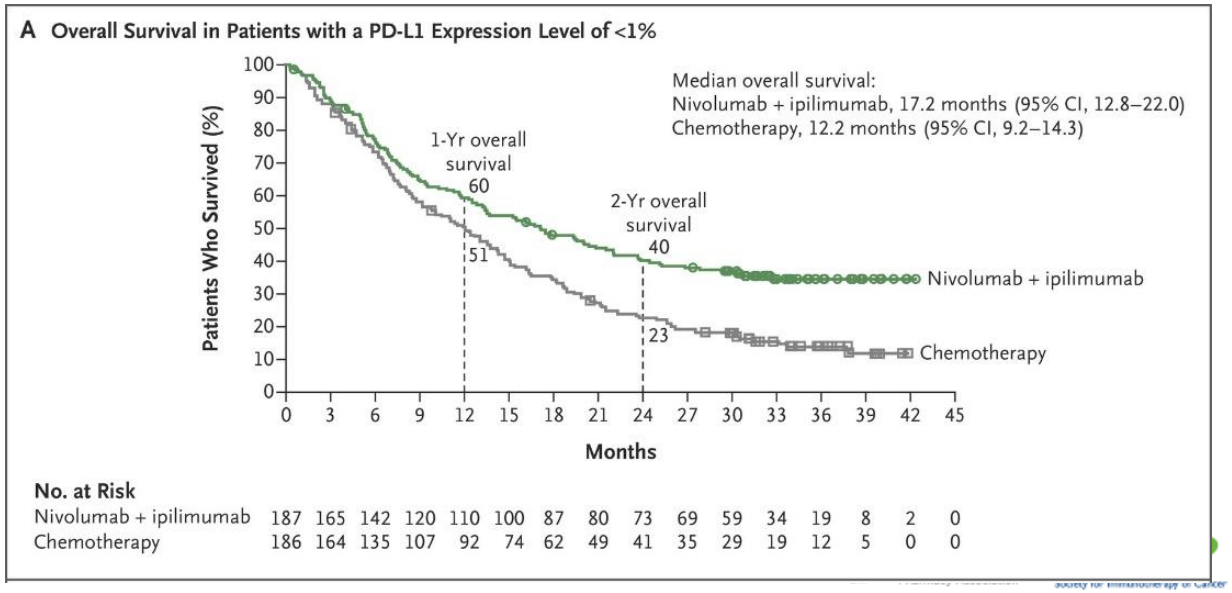
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	138 (38)	89 (25)
Odds ratio (95% CI)	1.9 (1.4-2.6)	
BOR, n (%)		
CR	8 (2)	4 (1)
PR	130 (36)	85 (24)
SD	164 (45)	185 (52)
PD	32 (9)	45 (13)
DCR, n (%)	302 (84)	274 (76)

Reck M et al, ASCO 2020.

CheckMate 227

- Primary endpoint: OS in PD-L1 ≥ 1% (tumor cells)
  - Nivo/ipi: 17.1 months
  - Chemo: 14.9 months
- Longer duration of response with nivo/ipi over chemo
- Benefit of nivolumab + ipilimumab seen regardless of PD-L1 status in this study





Hellmann, NEJM 2019.

PDL1 assays (definition of high) "as determined by an FDA-approved test"

Pembrolizumab - Dako 22C3

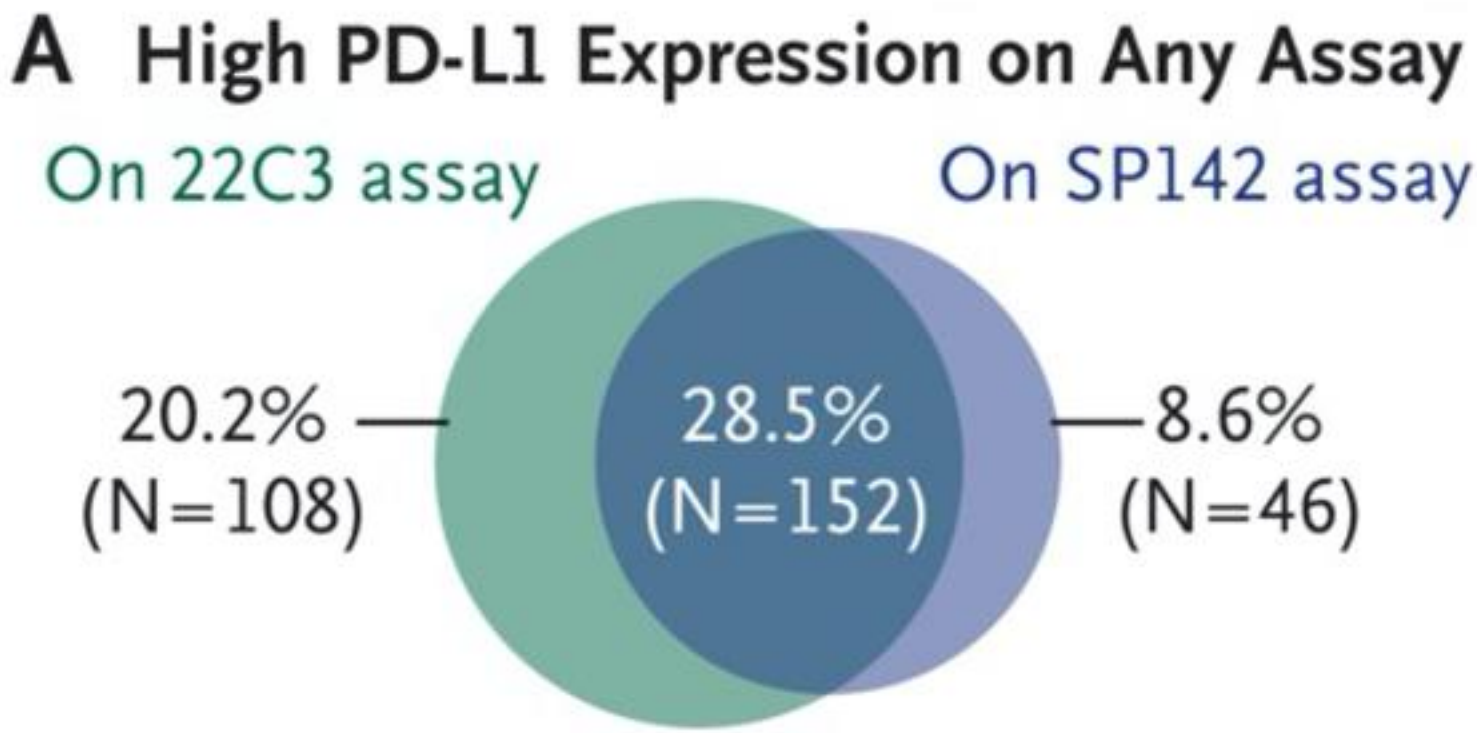
PD-L1 [Tumor Proportion Score (TPS) ≥50/ 1%]

Atezolizumab - SP142 Ventana

PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10]

Nivolumab + ipilimumab - PD-L1 IHC 28-8 pharmDx (>=1%)

no EGFR or ALK genomic tumor aberrations. (and no driver)

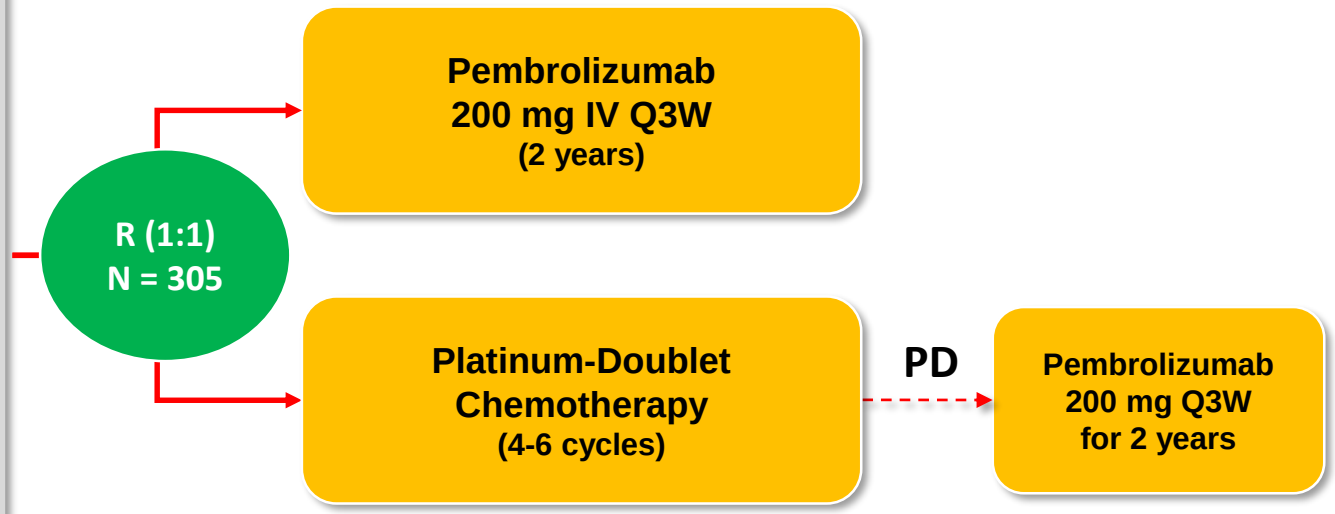


Herbst RS et al. N Engl J Med 2020

KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive (≥ 50%)

Key Eligibility Criteria

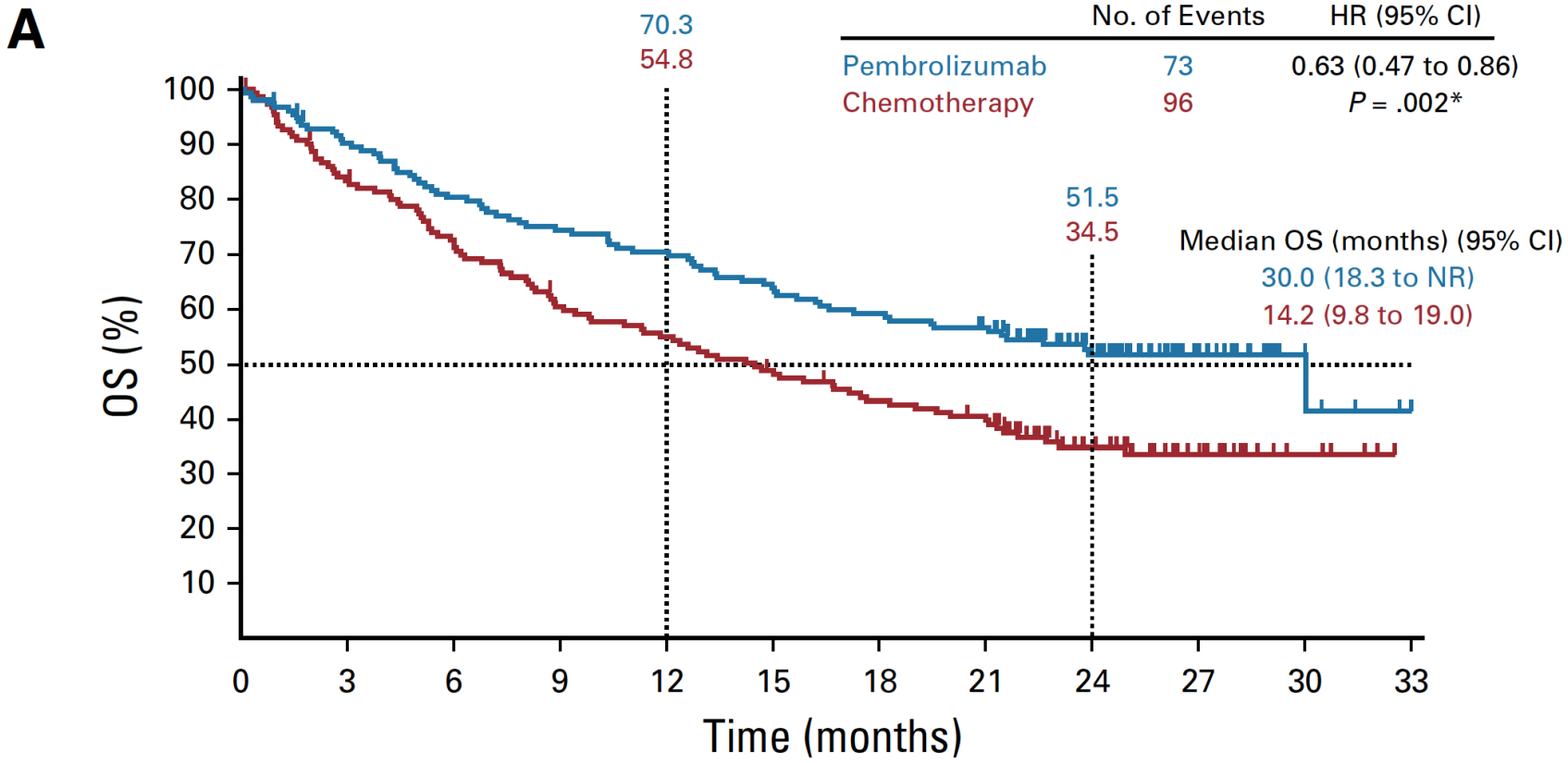
- ***Untreated*** stage IV NSCLC
- PD-L1 TPS ≥50%
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy



Reck M et al, ESMO 2016, NEJM 2016

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

Overall Survival



No. at risk:

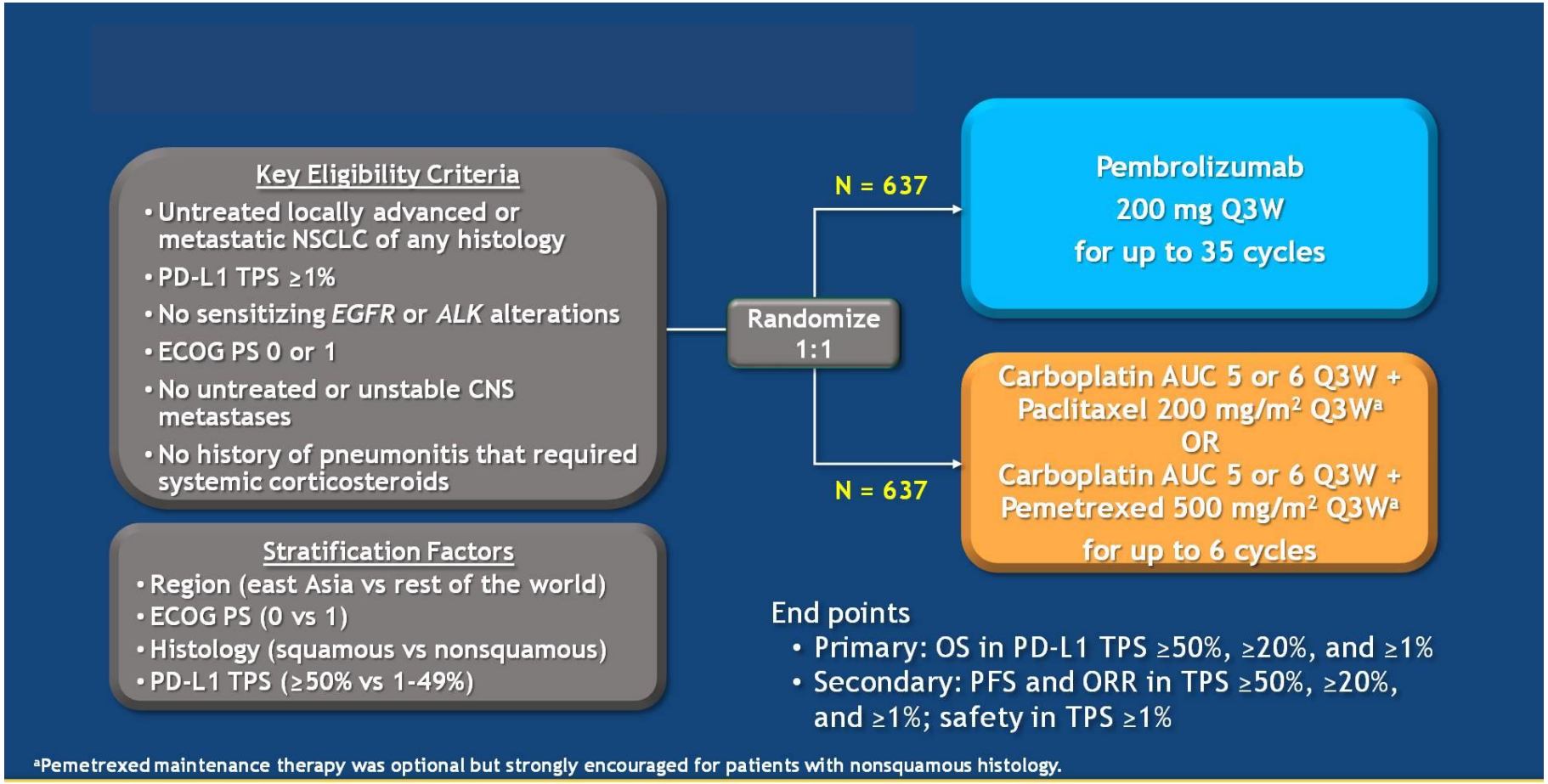
Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0
Chemotherapy	151	123	107	88	80	70	61	55	31	16	5	0

Reck M et al, ESMO 2016, NEJM 2016, JCO 2019

Keynote-024 Update
ESMO Virtual 2020 Brahmer

- Crossover to pembro allowed (83/151 = 55%)
- 5 years of follow up
- Fewer grade 3-5 SAEs 31.2 vs 53.3%
- Median OS 26.3 vs 13.4 months
- Kaplan-Meier **5-yr OS 31.9 vs 16.3%**

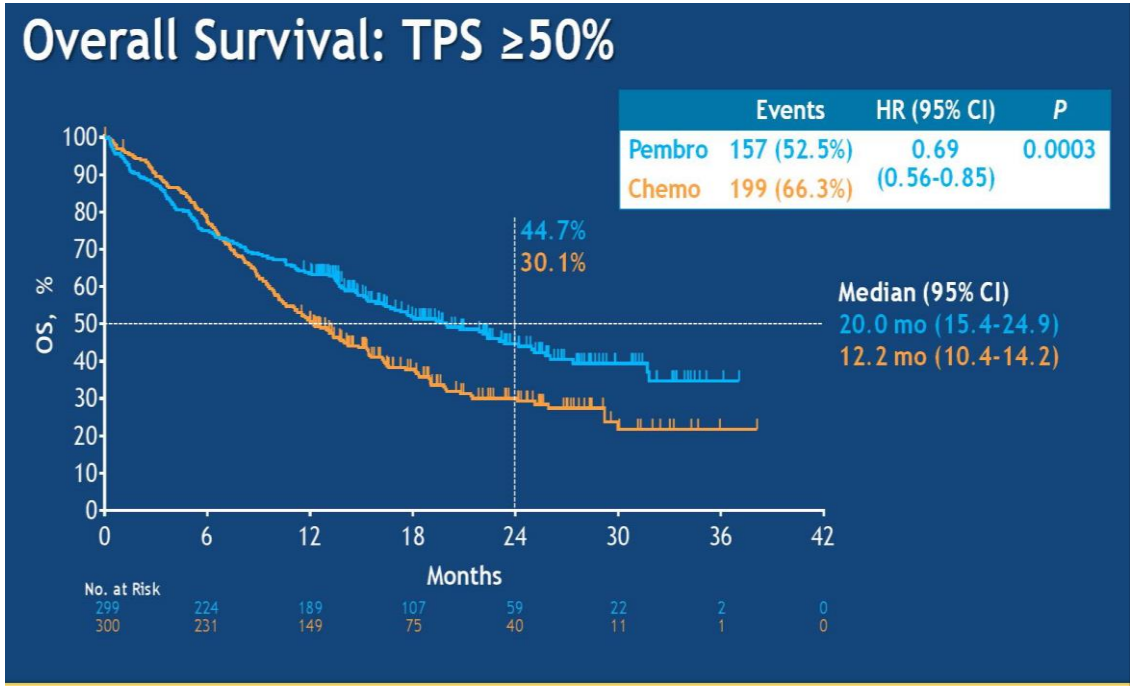
KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC

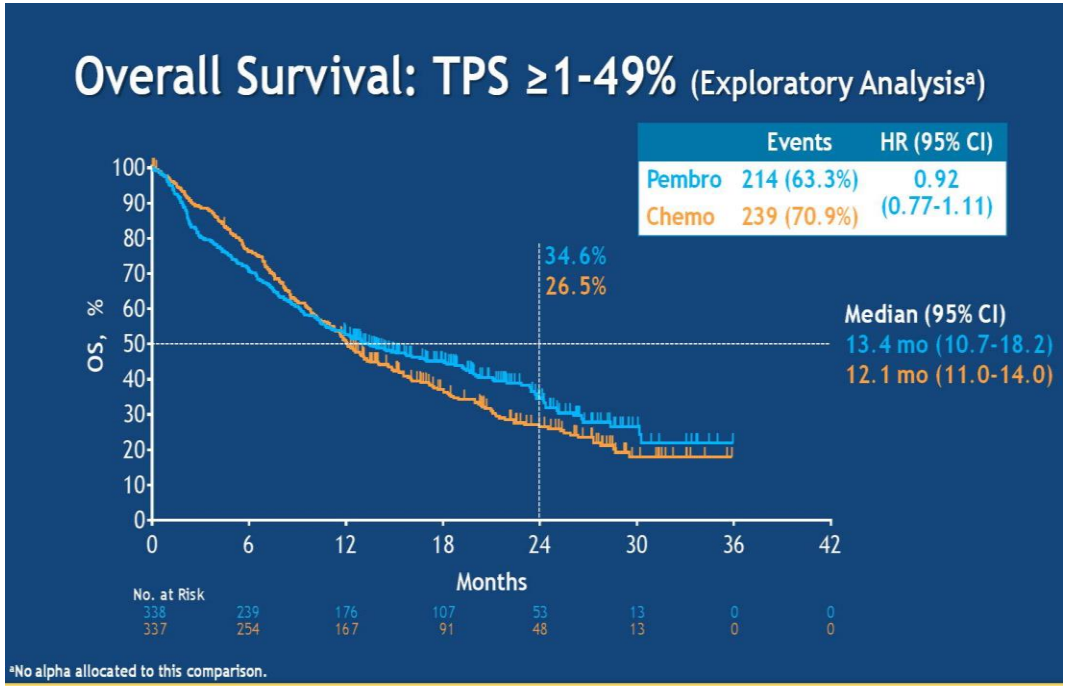


Lopes et al, ASCO 2018

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

Overall Survival



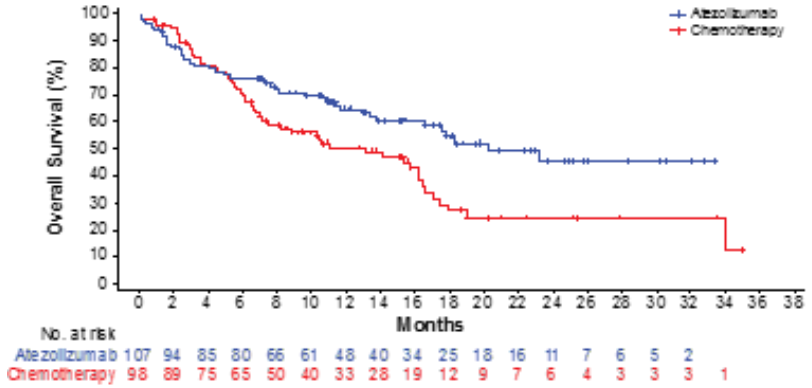


Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

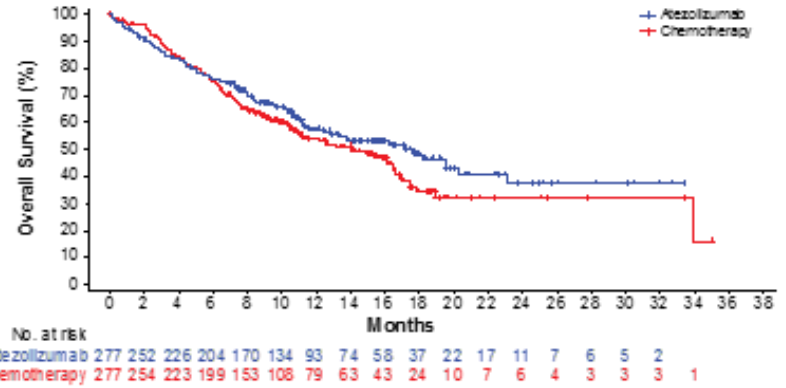
IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

SP142 (TC3 or IC3-WT)[a]



	Atezo (n = 107)	Chemo (n = 98)
mOS, mo	20.2	13.1
HR[b] (95% CI)	0.59 (0.40, 0.89)	

SP142 (TC1/2/3 or IC1/2/3-WT)[a]



	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR[b] (95% CI)	0.83 (0.65, 1.07)	

Herbst, ESMO-IO 2019.

Trial		experimental	Chemo comparator	HR	delta
KN024 (PDL1>=50%)	Pembro	26.3	13.4	0.56	12.9
KN042 (PDL1>=50%)	Pembro	20	12.2	0.69	7.8
KN042 (PDL1 1-49%)	Pembro	13.4	12.1	0.92 (NS)	1.3
IM 110 (TC3/IC3)	Atezo	20.2	13.1	0.59	7.1
KN189(non-SQ)	Chemo+pembro	22	10.7	0.56	11.3
KN407(SQ)	Chemo+pembro	17.1	11.6	0.71	5.5
IM150 (non-SQ)	CBP+ atezo	19.2	14.7	0.78	4.5
Checkmate227 (>1%)	nivo+ipi	17.1	14.9	0.79	2.2
Checkmate227 (<1%)	nivo+ipi	17.2	12.2	0.62	5
Checkmate9LA	nivo+ipi+limited chemo	15.6	10.9	0.66	4.7

Options Non-Squamous PD-L1<50% – NCCN guidelines 8.2020

ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred

- **Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d]**
- **Pembrolizumab/cisplatin/pemetrexed (category 1)[2,d]**

Other Recommended

- **Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,d,f,g,h]**
- **Atezolizumab/carboplatin/albumin-bound paclitaxel[4,d]**
- **Nivolumab + ipilimumab[5,d]**
- **Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)[6,d]**

Options Squamous PD-L1<50% – NCCN guidelines 8.2020

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[c]

Preferred

- **Pembrolizumab/carboplatin/paclitaxel[34,d] (category 1)**
- **Pembrolizumab/carboplatin/albumin-bound paclitaxel[34,d] (category 1)**

Other recommended

- **Nivolumab + ipilimumab[5,d]**
- **Nivolumab + ipilimumab + paclitaxel + carboplatin[6,d]**

Options Non-Squamous PD-L1>=50% – NCCN guidelines 8.2020

- **Preferred**
  Pembrolizumab (category 1)
  or
  (Carboplatin or cisplatin) + pemetrexed + pembrolizumab (category 1)
  or
  Atezolizumab
- **Other Recommended**
  Carboplatin + paclitaxel + bevacizumab[ss] + atezolizumab (category 1)
  or
  Carboplatin + albumin-bound paclitaxel + atezolizumab
  or
  Nivolumab + ipilimumab + pemetrexed + (carboplatin or cisplatin)
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab

Options Squamous PD-L1>=50% – NCCN guidelines 8.2020

- **Preferred**
  Pembrolizumab (category 1)
  or
  Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)
  or
  Atezolizumab
- **Other Recommended**
  Nivolumab + ipilimumab + paclitaxel + carboplatin
- **Useful in Certain Circumstances**
  Nivolumab + ipilimumab

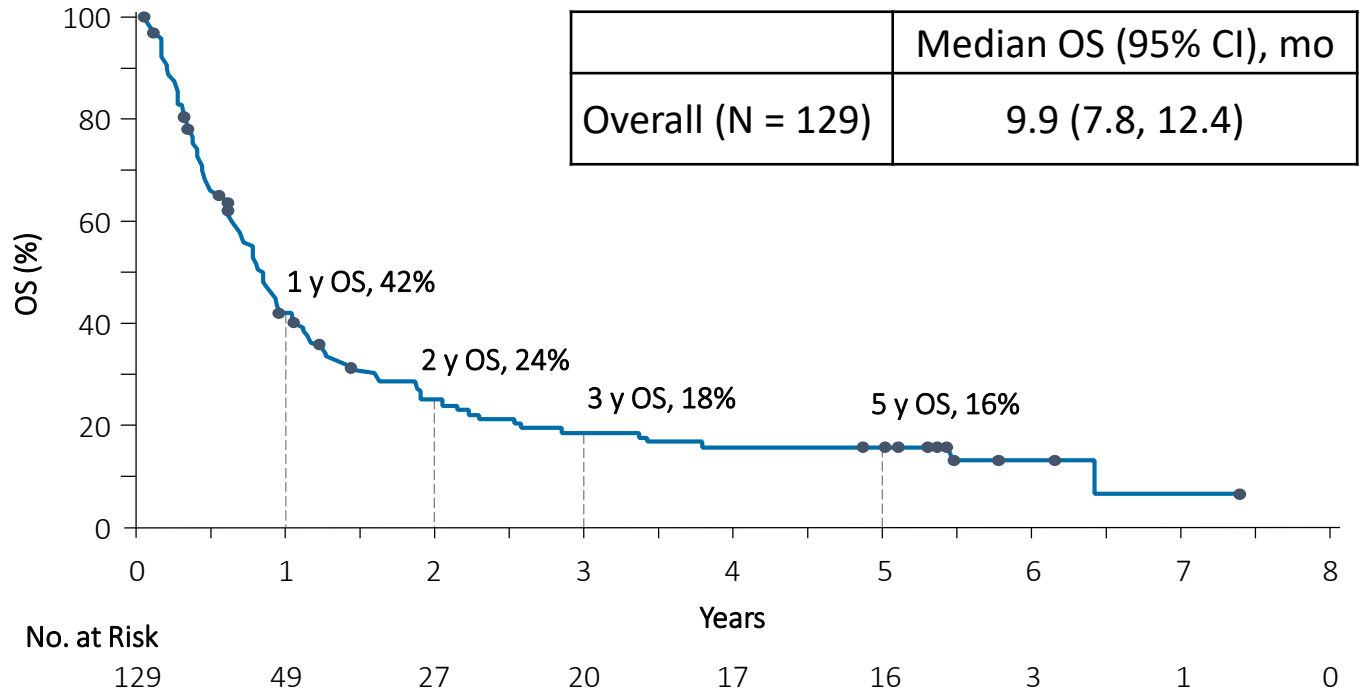
CA209-003: Nivolumab in Heavily-pretreated Advanced NSCLC (NCT00730639)

Phase 1, 5-Year Update

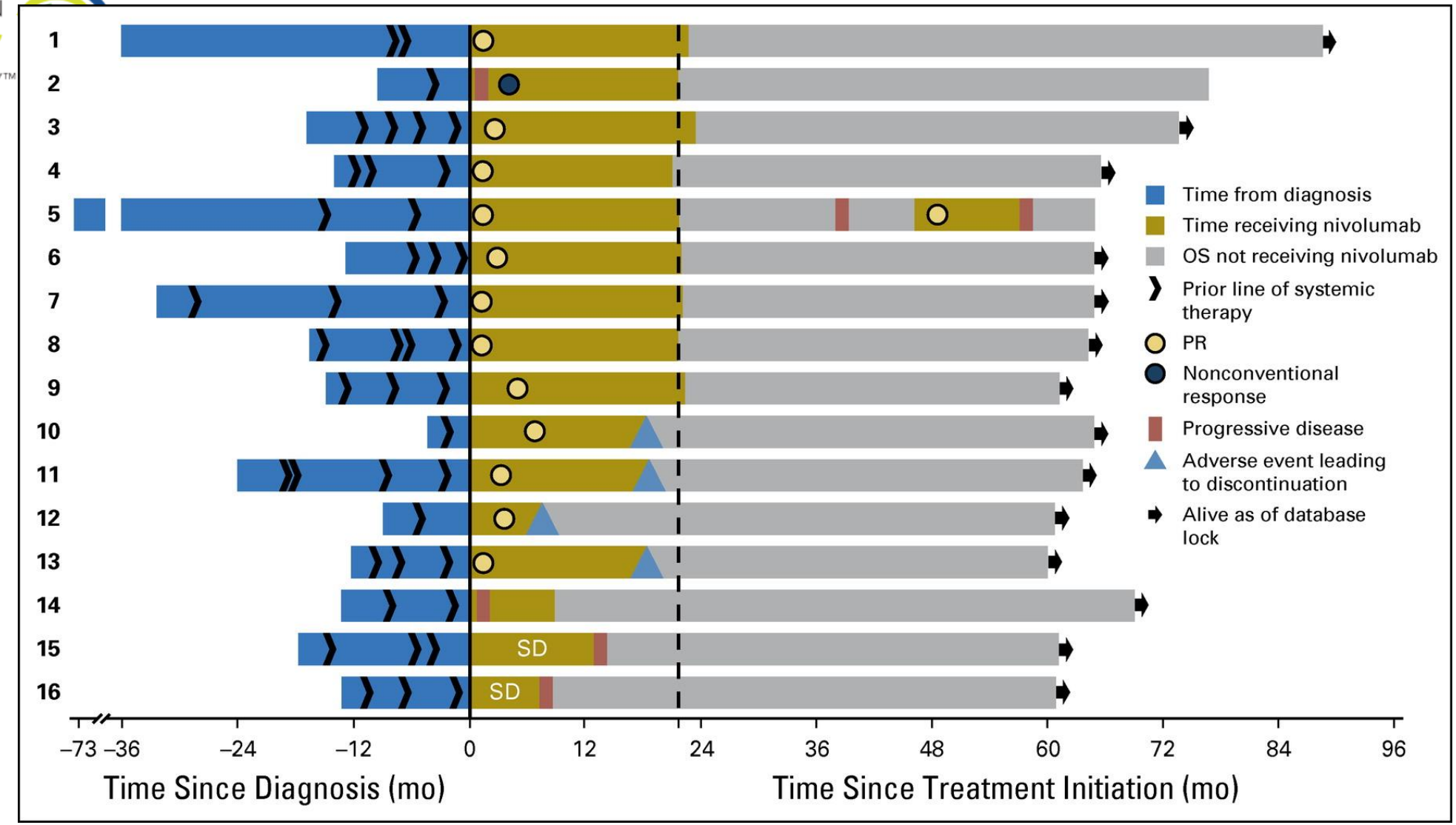
- First report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor
- According to the National Cancer Institute's SEER data, 5-year survival rate for patients with advanced NSCLC is 4.9%
- The median is not the message

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



Continuous Versus 1-Year Fixed-Duration Nivolumab in Previously Treated Advanced Non–Small-Cell Lung Cancer: CheckMate 153

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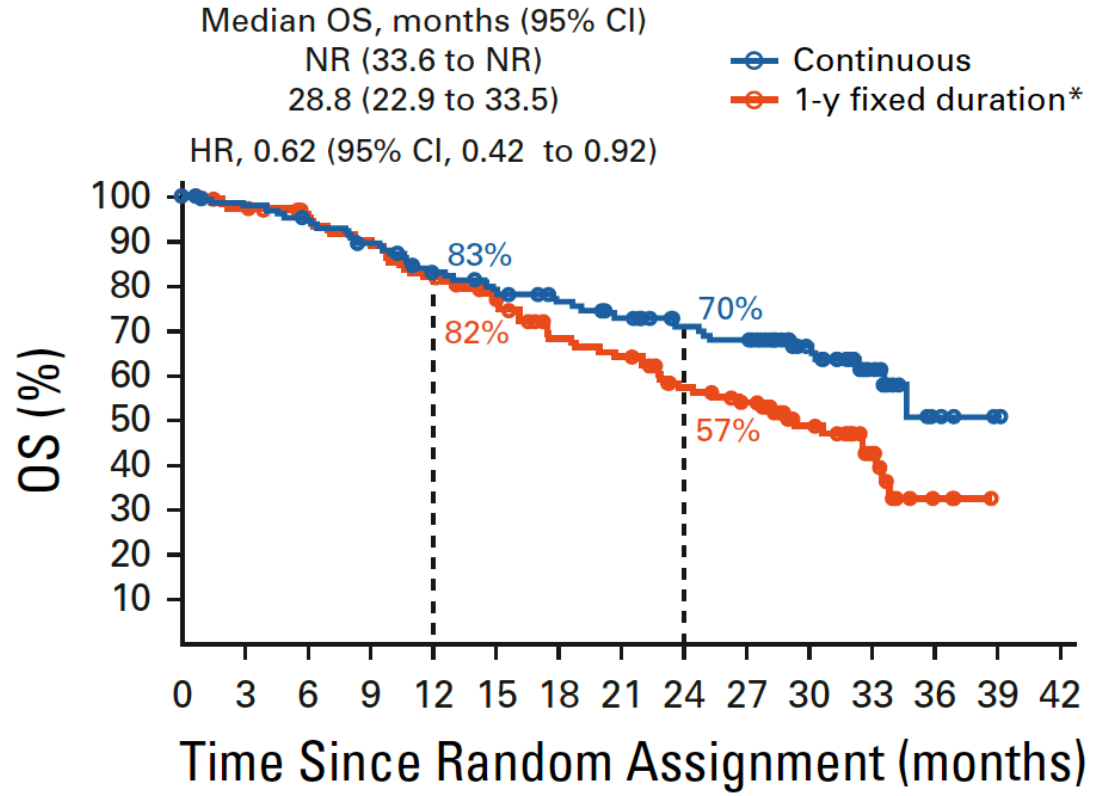
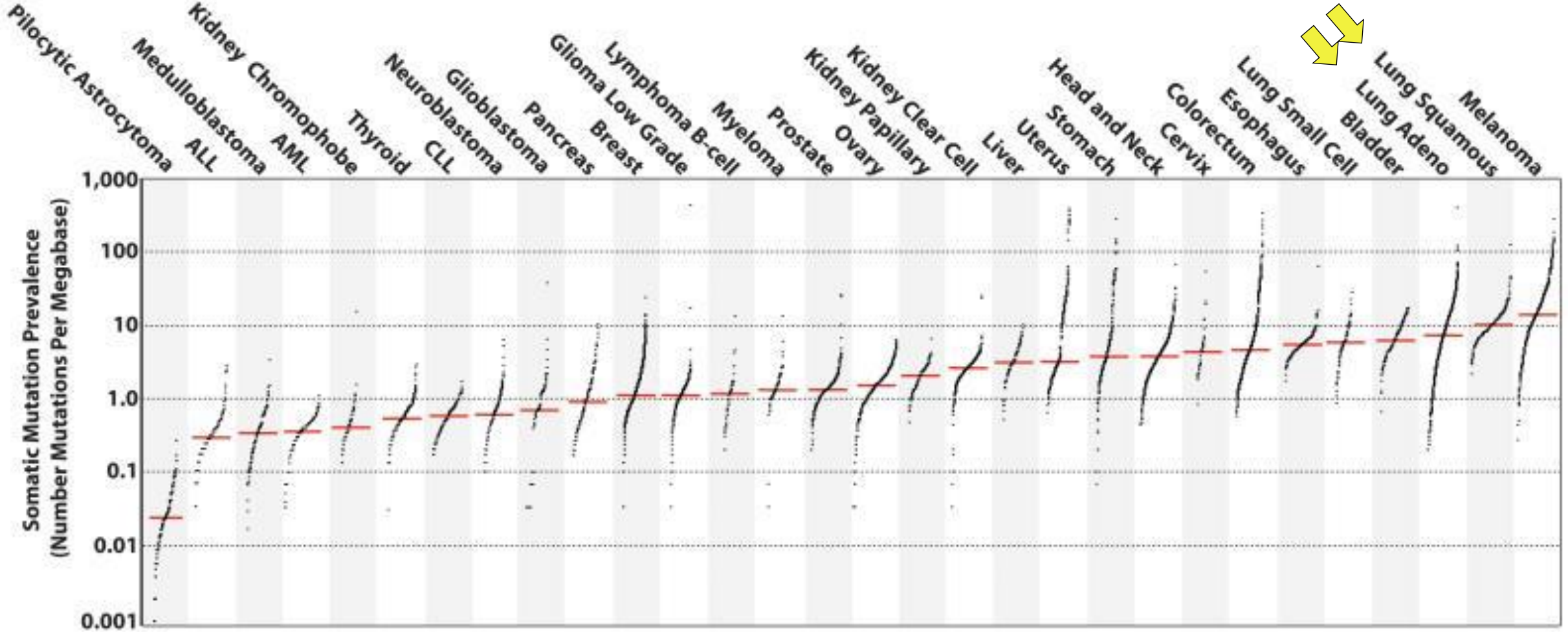


No. at risk:

Continuous	127	121	116	109	98	92	86	79	70	67	44	22	4	1	0
1-y fixed duration	125	116	109	102	93	85	70	66	53	47	32	15	4	0	0

Waterhouse DM. JCO 2020

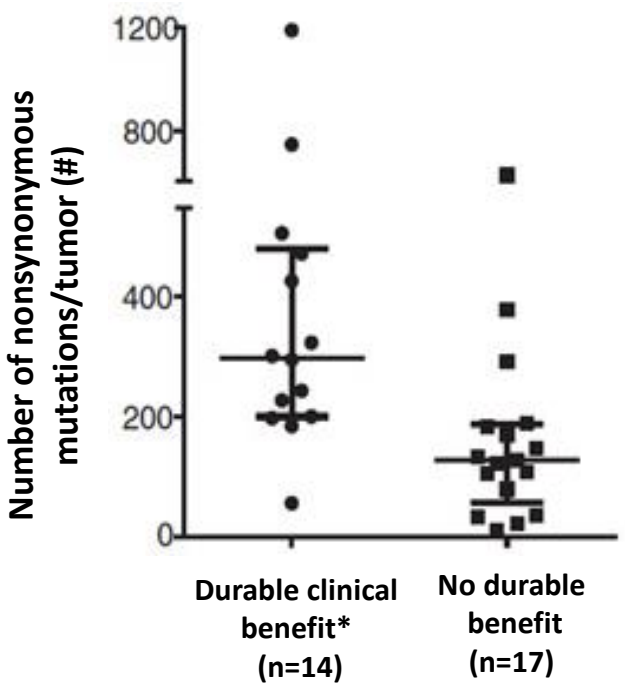
Lung Cancer has a high mutational burden

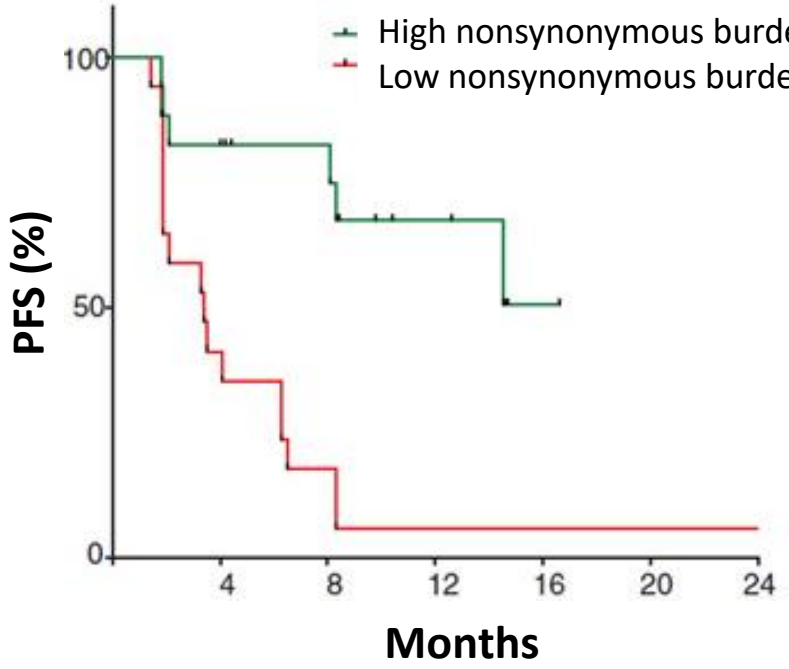


Alexandrov et al, Nature, 2013.

Tumor Mutational Burden (TMB) may Determine Sensitivity to PD-1 Blockade in NSCLC

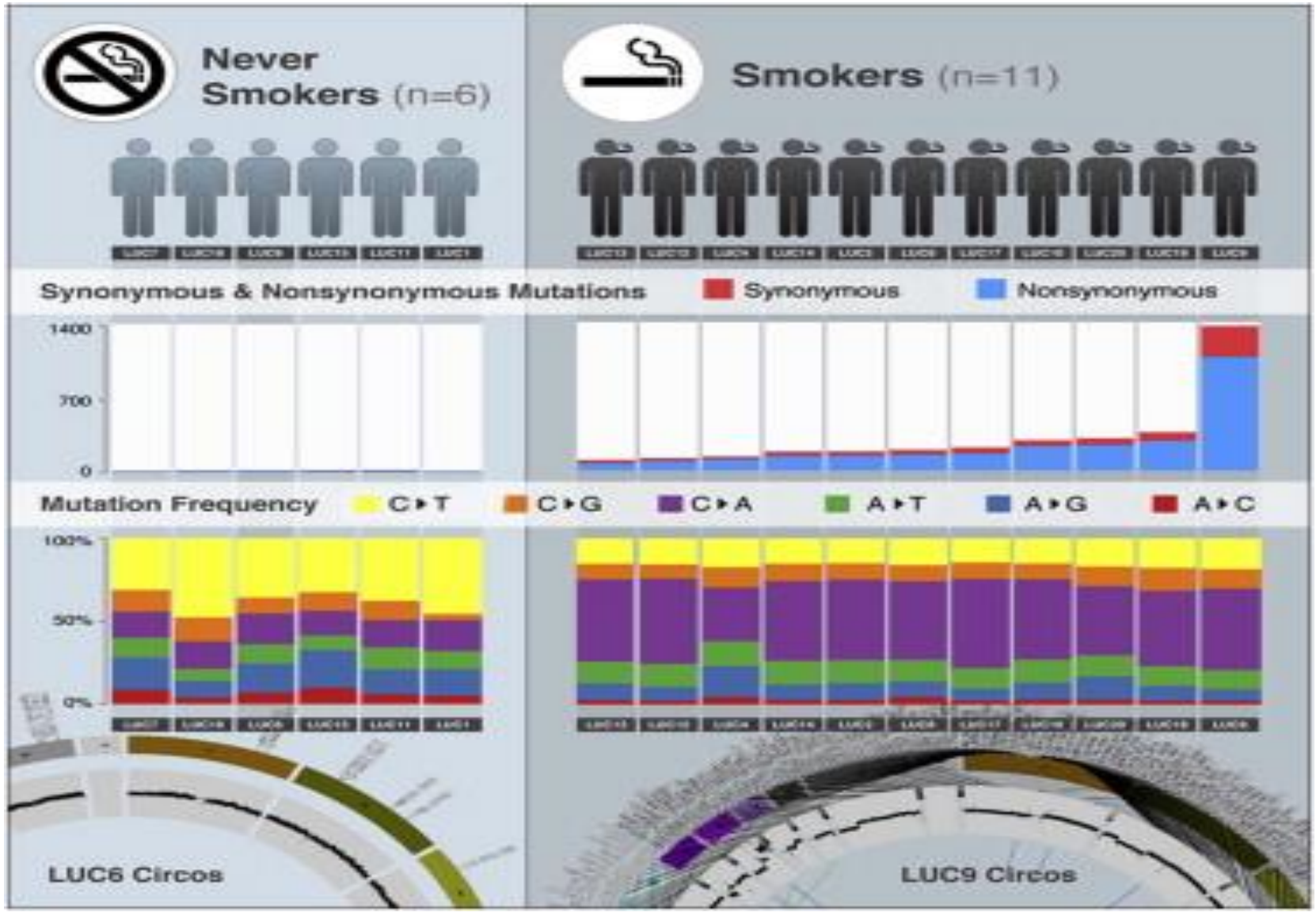
In two independent cohorts, higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit, and PFS.





*Partial or stable response lasting > 6 mo

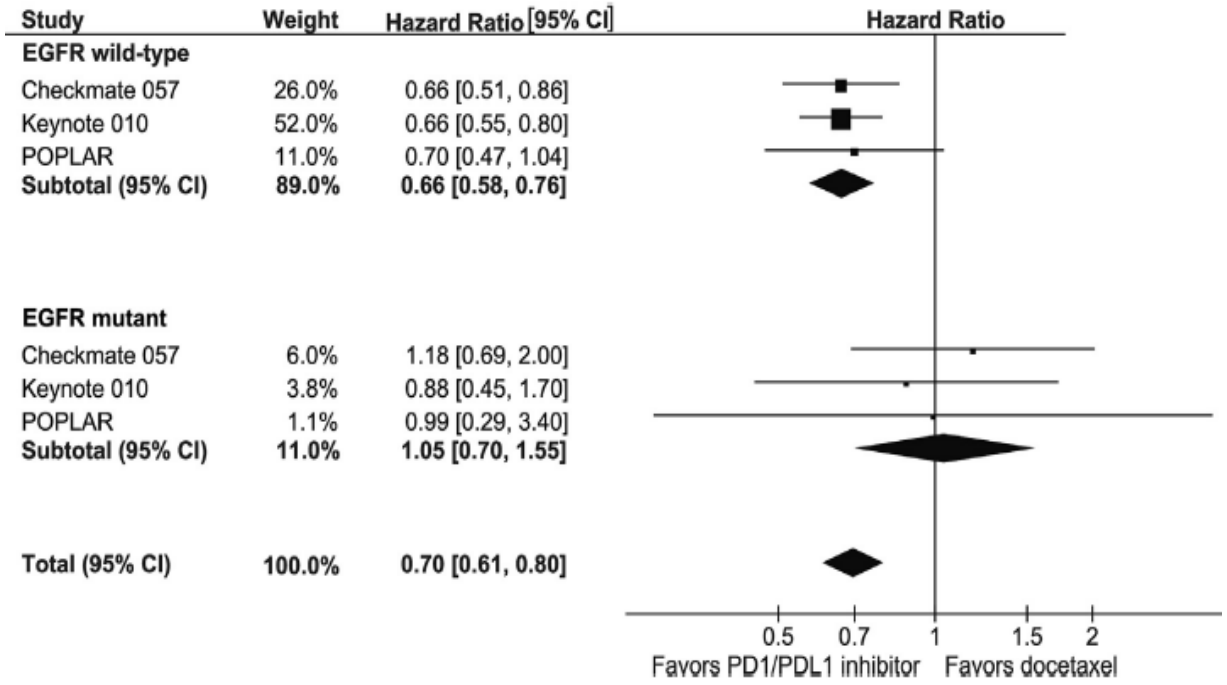
Rizvi N et al, Science, 2015



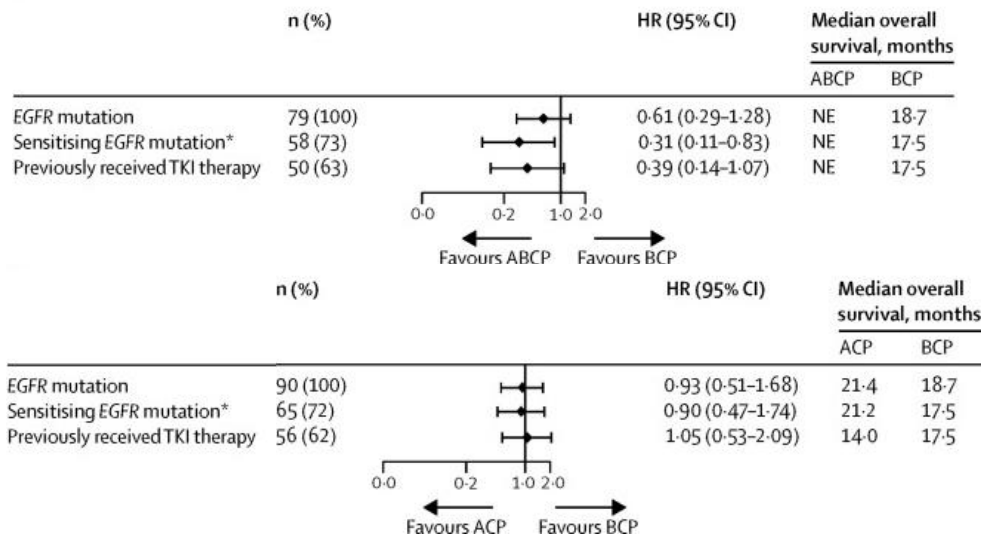
Govindan. Cell 150 (6) 1121-34, 2012

Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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



IMPOWER-150



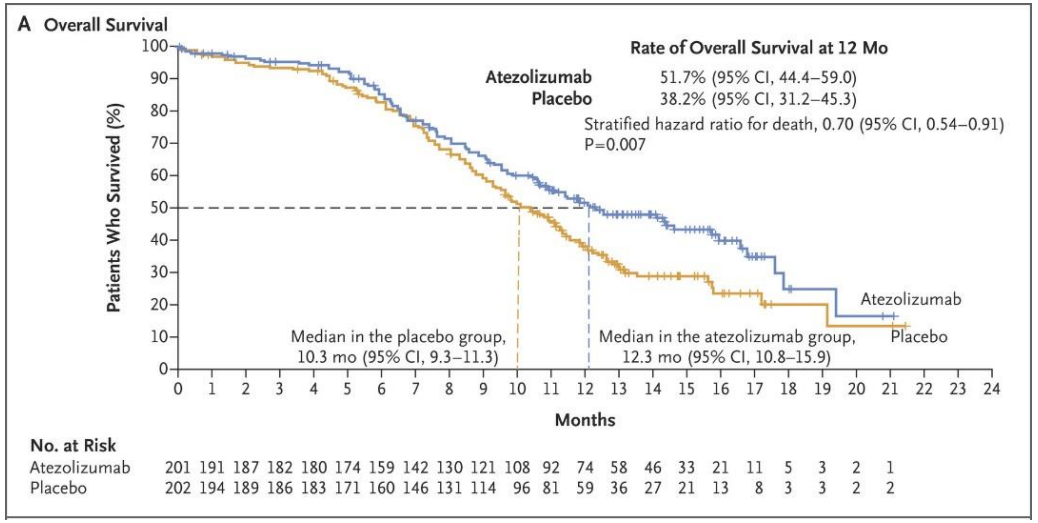
CK Lee et al., JTO 2016
M Reck et al., Lancet Resp Med 2019

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

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.

Approved checkpoint inhibitors in SCLC

Drug	Indication	Dose
Nivolumab	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (**3rd line**)	240 mg Q2W
Pembrolizumab	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy (**3rd line**)	200 mg Q3W or 400 mg Q6W
Atezolizumab + carboplatin + etoposide	**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
Durvalumab + etoposide + carboplatin/cisplatin	**1st line** extensive stage SCLC	For 4 cycles: 1500 mg durvalumab Q3W + chemotherapy; Maintenance: 1500 mg durvalumab Q4W

Immunotherapy for mesothelioma

Drug	Indication	Dose
Nivolumab + ipilimumab	Frontline unresectable malignant pleural mesothelioma	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W

- Approval based on CheckMate 743
  - Nivolumab + ipilimumab vs platinum-based chemotherapy
  - Median OS: 18.1 months vs 14.1 months
  - 2-year OS: 41% vs 27%
  - Median PFS: 6.8 months vs 7.2 months
- First FDA approval for mesothelioma since 2004

Case Studies

Case Study 1

- 71 year-old Asian female, 40 pack year current smoker, presents with L chest pain
- PMH : CVA, COPD, chronic low back pain
- Imaging PET: multiple lymph nodes R neck, mediastinum, L sided tumor; MRI brain negative
- Neck node FNA at outside facility – poorly differentiated malignancy, QNS for IHC
- Plan is for core needle biopsy for additional testing, but patient becomes symptomatic with pain, dysphagia and decline in PS from 0 to 2
- The patient is initially hesitant to initiate chemotherapy, but then decides to proceed

Case Study 1

Which would be the best option for treatment?

A. pembrolizumab monotherapy

B. carboplatin/pemetrexed and pembrolizumab

C. carboplatin/paclitaxel

D. carboplatin/paclitaxel/pembrolizumab

Case Study 1

Answer: B. carboplatin/pemetrexed and pembrolizumab (CPP)

This case is challenging due to absence of adequate tissue specimen. The patient's rapid progression gives a small window for treatment and the time to biopsy and results may be too long for PS to remain adequate for treatment.

Pembrolizumab monotherapy cannot be given (within label) without PDL1 22C3 >=1%

Carbo/taxol is appropriate for Cancer of Unknown primary, but this is clinically clearly lung cancer.

Carbo/taxol/pembrolizumab is indicated for squamous cell lung cancer

CPP – has an indication for non-squamous NSCLC without driver mutations – the patient meets this criteria.

Case Study 1

Follow-up:

The patient underwent core needle biopsy of neck node and initiated CPP therapy

Biopsy showed TTF1+ adenocarcinoma

Molecular testing was negative for EGFR/ALK/ROS1/BRAF and extended NGS

PDL1 22C3 was 80-90%

The patient had a dramatic symptomatic response to CPP, imaging is pending

Case Study 2

- 38 year-old male never-smoker and no PMH presents with stage IV , moderately differentiated p40+ squamous cell carcinoma.
- PET shows hypermetabolic LLL lesion, pleural effusion, and extensive lymph node involvement in neck, mediastinum, and upper abdomen. MRI brain is negative.
- Molecular testing (NGS) reveals no driver mutation. The patient has excellent performance status and is interested in aggressive treatment

Case Study 2

Which would be the best option for treatment?

A. pembrolizumab monotherapy

B. carboplatin/pemetrexed and pembrolizumab

C. carboplatin/paclitaxel

D. carboplatin/paclitaxel/pembrolizumab

Case Study 2

Answer: D. carboplatin/paclitaxel/pembrolizumab

In the presence of a clear lung primary, this should be treated as lung cancer and not cancer of unknown primary – thus carboplatin/paclitaxel is not favored

Squamous cell carcinoma in never smokers is rare – these patients should undergo molecular testing.

Pembroluzimab monotherapy would be an option if PDL1 high, but patient was interested in aggressive therapy.

Pemetrexed based regimens are not indicated in squamous cell carcinoma.

The carboplatin/paclitaxel/pembrolizumab regimen is indicated for stage IV squamous cell carcinoma of the lung

Case Study 2

- The patient receives 3 cycles of carbo/taxol/pembroluzimab with response by CT, but presents in DKA and is diagnosed with T1DM.

PET/CT: Decreased size and activity of primary and lymph nodes with residual minimal uptake suggestive of mild residual disease.

Case Study 2

What is the next best step in his management?

A. Watchful waiting

B. Resume carbo/taxol/pembrolizumab

C. Pembrolizumab

D. Consolidative radiation

Case Study 2

Answer: D. Consolidative radiation – this is what the patient opted for. The initial extent of his disease was likely more than that allowed in the Gomez (JCO 2019) trial, but the response to chemoimmunotherapy was remarkable

Watchful waiting would also be a reasonable option – patients who have SAEs with immunotherapy have improved survival relative to those who do not despite discontinuation of immunotherapy. (eg Haratani K, Jama Onc 2018)

One could also argue for continuation of immunotherapy after an endocrine related irAE as the process is unlikely to worsen and there is replacement therapy (insulin). This is done with thyroid dysfunction.

THANKS FOR YOUR ATTENTION!