

# Immunotherapy for the Treatment of Lung Cancer

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# Disclosures

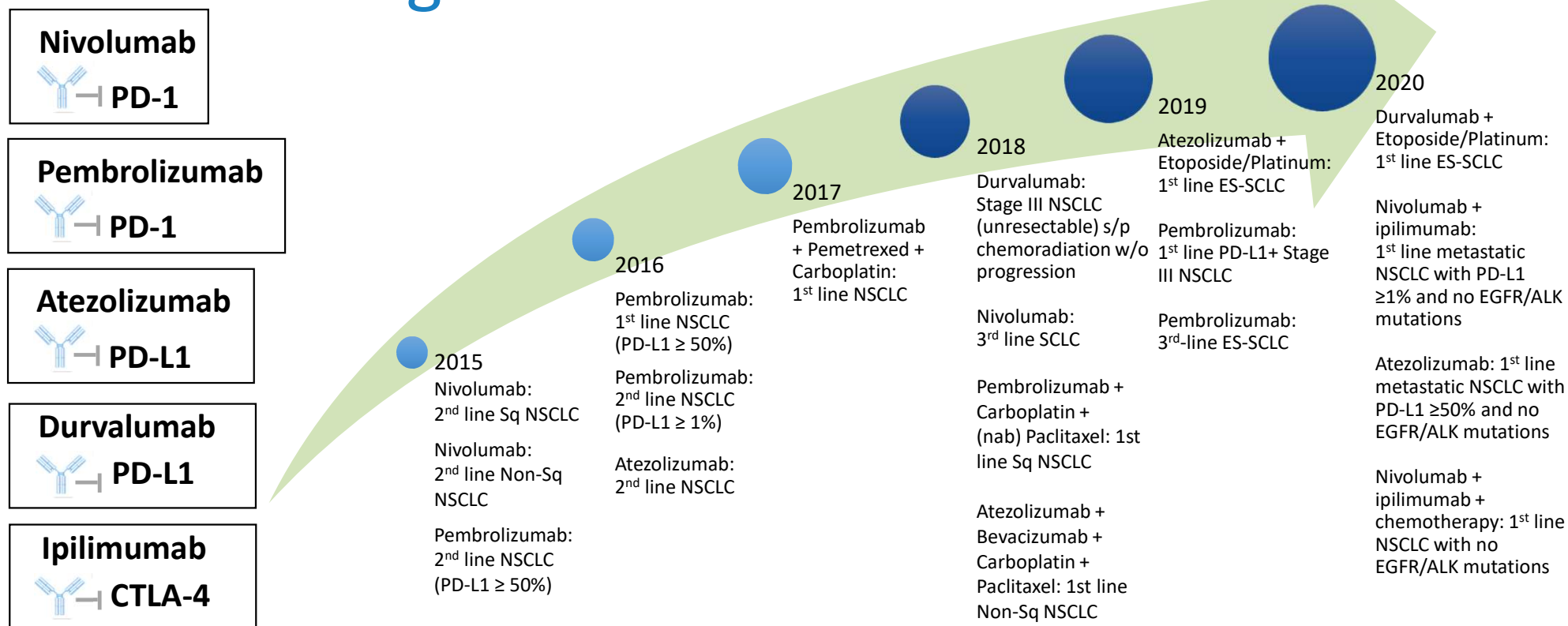
- Consulting Fees:
  - Amgen, AstraZeneca, Merck, Genentech-Roche, Bayer, BMS, Pfizer, Tesaro, KisoJi
- Contracted Research:
  - Genentech-Roche
- I will be discussing non-FDA approved indications during my presentation.

# Lung cancer

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

	Male				Female		
Estimated Deaths	Lung & bronchus	76,650	24%	 	Lung & bronchus	66,020	23%
	Prostate	31,620	10%		Breast	41,760	15%
	Colon & rectum	27,640	9%		Colon & rectum	23,380	8%
	Pancreas	23,800	7%		Pancreas	21,950	8%
	Liver & intrahepatic bile duct	21,600	7%		Ovary	13,980	5%
	Leukemia	13,150	4%		Uterine corpus	12,160	4%
	Esophagus	13,020	4%		Liver & intrahepatic bile duct	10,180	4%
	Urinary bladder	12,870	4%		Leukemia	9,690	3%
	Non-Hodgkin lymphoma	11,510	4%		Non-Hodgkin lymphoma	8,460	3%
	Brain & other nervous system	9,910	3%		Brain & other nervous system	7,850	3%
	All sites	321,670			All sites	285,210	

# Immune checkpoint inhibitors in lung cancer



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# Immunotherapy for first-line treatment of metastatic NSCLC

Drug	Indication	Dose
Pembrolizumab	1 <sup>st</sup> line metastatic NSCLC with <b>PD-L1 TPS ≥ 1%</b> and no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Atezolizumab	1 <sup>st</sup> line metastatic NSCLC with <b>PD-L1 ≥ 50% of tumor cells or ≥ 10% of immune cells</b> with no EGFR/ALK mutations	840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
Nivolumab + ipilimumab	1 <sup>st</sup> line metastatic NSCLC with <b>PD-L1 ≥ 1%</b> and no EGFR/ALK mutations	Nivolumab 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W
Nivolumab + ipilimumab + platinum-doublet chemotherapy	1 <sup>st</sup> line metastatic NSCLC with no EGFR/ALK mutations	Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W + 2 cycles of chemotherapy
Pembrolizumab + pemetrexed + platinum	1 <sup>st</sup> line metastatic non-squamous NSCLC with no EGFR/ALK mutations	200 mg Q3W or 400 mg Q6W
Pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel	1 <sup>st</sup> line metastatic squamous NSCLC	200 mg Q3W or 400 mg Q6W
Atezolizumab + bevacizumab + paclitaxel + carboplatin	1 <sup>st</sup> 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
Atezolizumab + nab-paclitaxel + carboplatin	1 <sup>st</sup> line metastatic non-squamous NSCLC with no EGFR/ALK mutations	For 4-6 cycles: atezolizumab 1200 mg Q3W + chemotherapy Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W

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# Immunotherapy for relapsed/refractory NSCLC

Drug	Indication	Dose
Nivolumab	Metastatic squamous or non-squamous NSCLC with progression after chemotherapy (2 <sup>nd</sup> line)	240 mg Q2W or 480 mg Q4W
Pembrolizumab	Metastatic NSCLC with progression after chemotherapy and <b>PD-L1</b> ≥ 1%	200 mg Q3W or 400 mg Q6W
Atezolizumab	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

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# Treatment Naïve Regimens: Competing Strategies in NSCLC

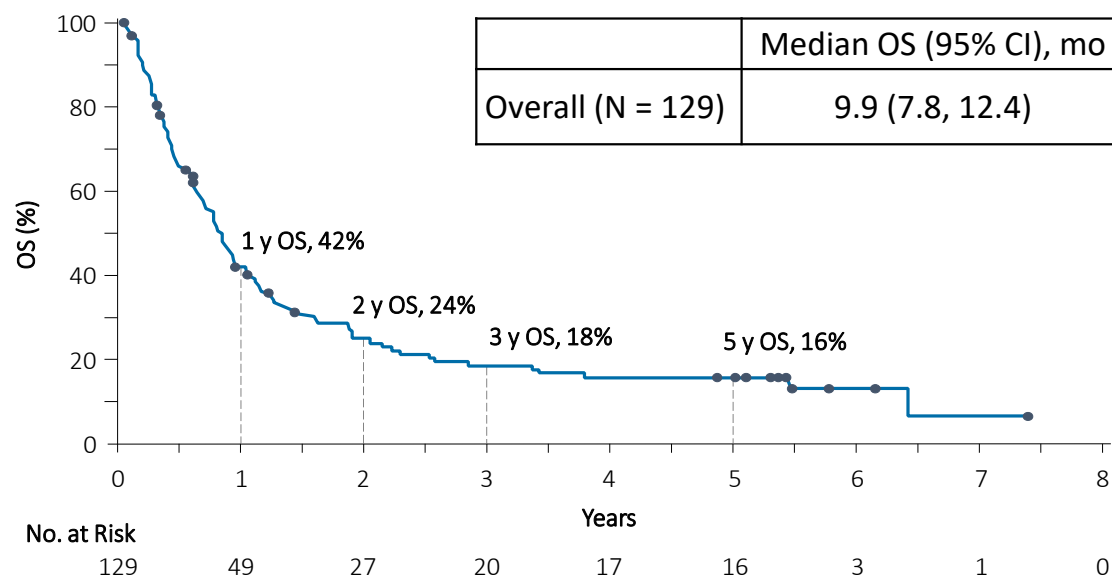
- **KEYNOTE 024** – Pembrolizumab vs. Chemotherapy in PD-L1  $\geq$  50%
- **KEYNOTE 042** – Pembrolizumab vs. Chemotherapy in PD-L1  $\geq$  1%
- **KEYNOTE 189** – Pembrolizumab + Chemotherapy vs. Chemotherapy alone in advanced non-squamous NSCLC
- **IMPOWER150** – Atezolizumab + Chemotherapy (Bev) 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
- **IMPOWER110** – Atezolizumab vs. chemotherapy in PD-L1  $\geq$  1%
- **CHECKMATE 9LA** – Nivolumab/ipilimumab with limited chemotherapy vs. chemotherapy in squamous and nonsquamous NSCLC

# 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%

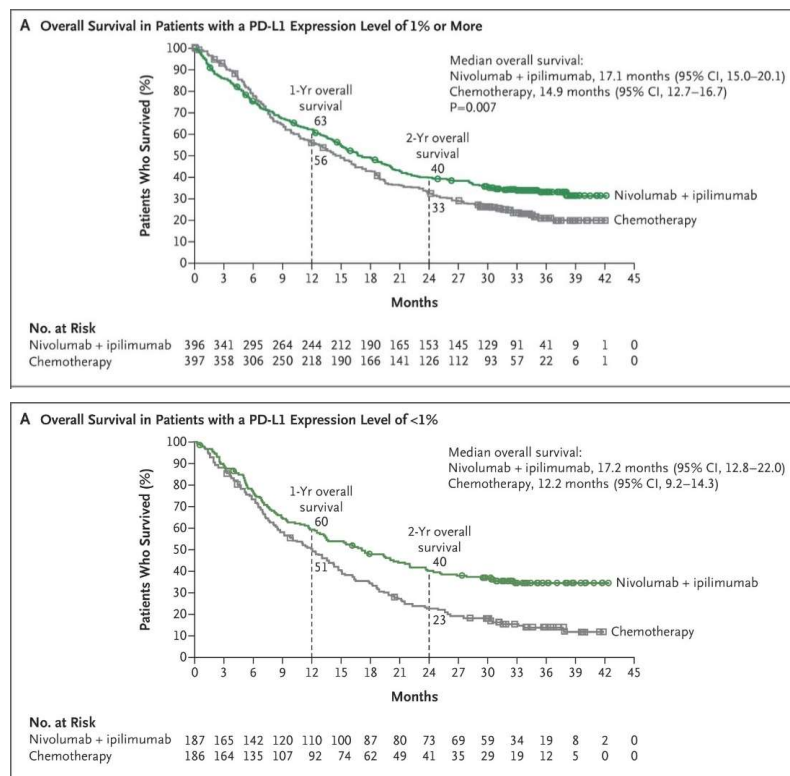
### 5-Year Survival



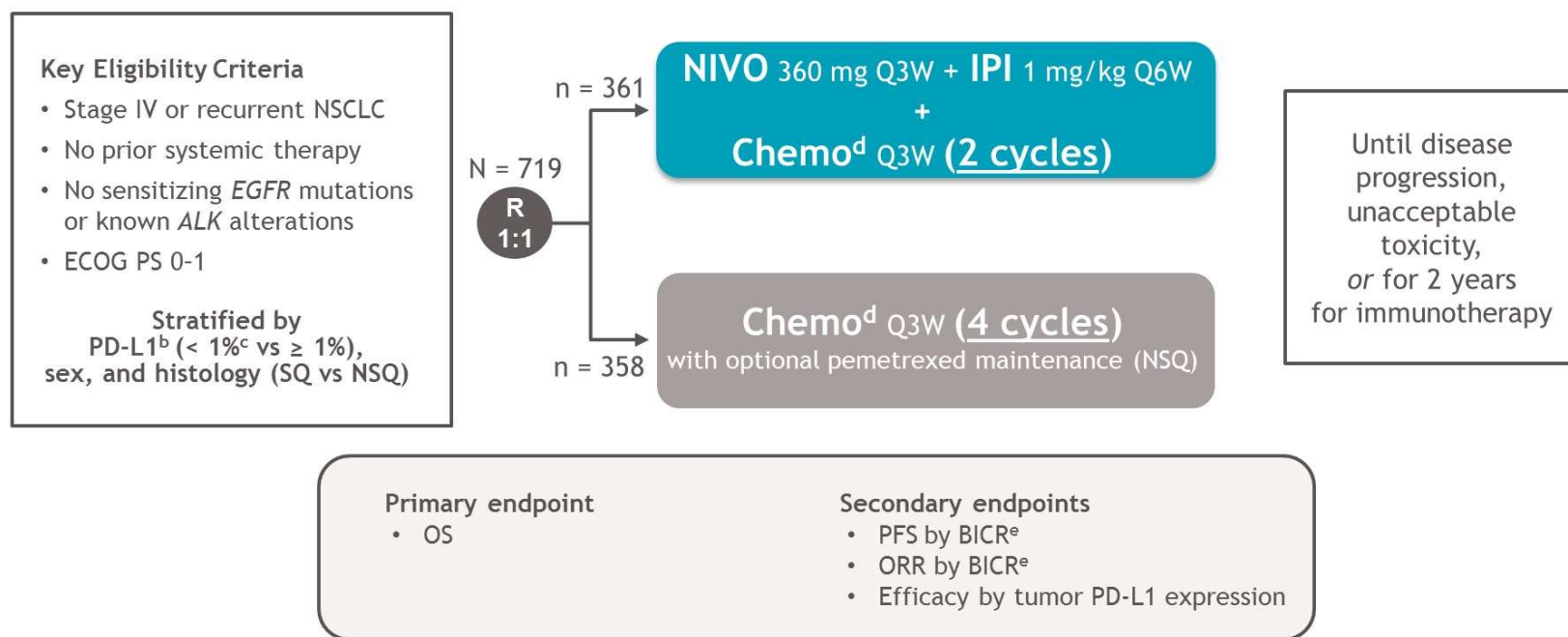


# CheckMate 227

- Primary endpoint: OS in PD-L1  $\geq 1\%$  (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



# CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo



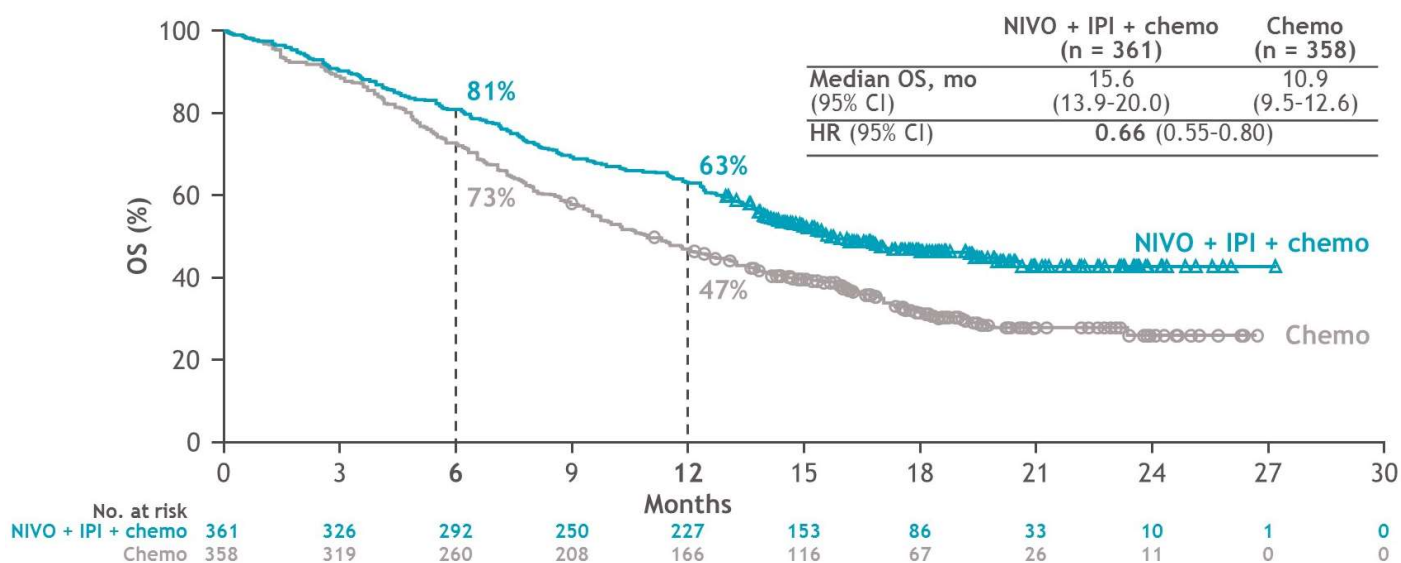
Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.

Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

<sup>a</sup>NCT03215706; <sup>b</sup>Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); <sup>c</sup>Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients;

<sup>d</sup>NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; <sup>e</sup>Hierarchically statistically tested.

# CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo



	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)

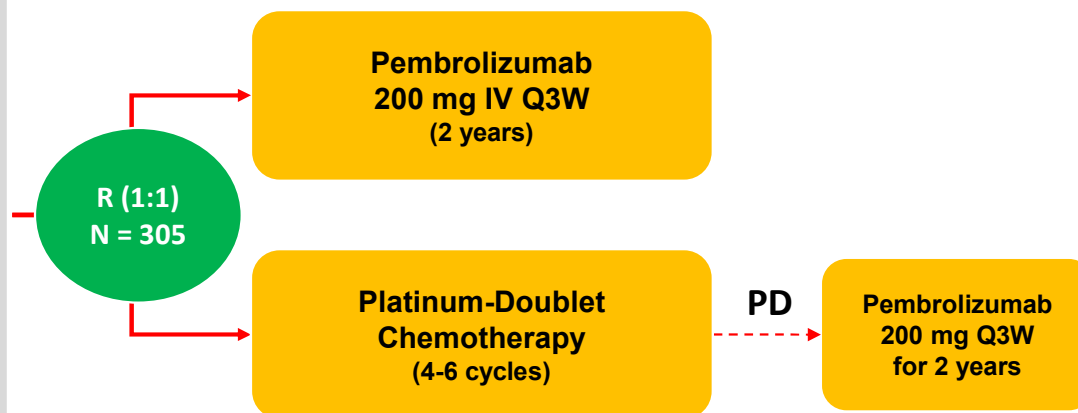
Reck M et al, ASCO 2020.

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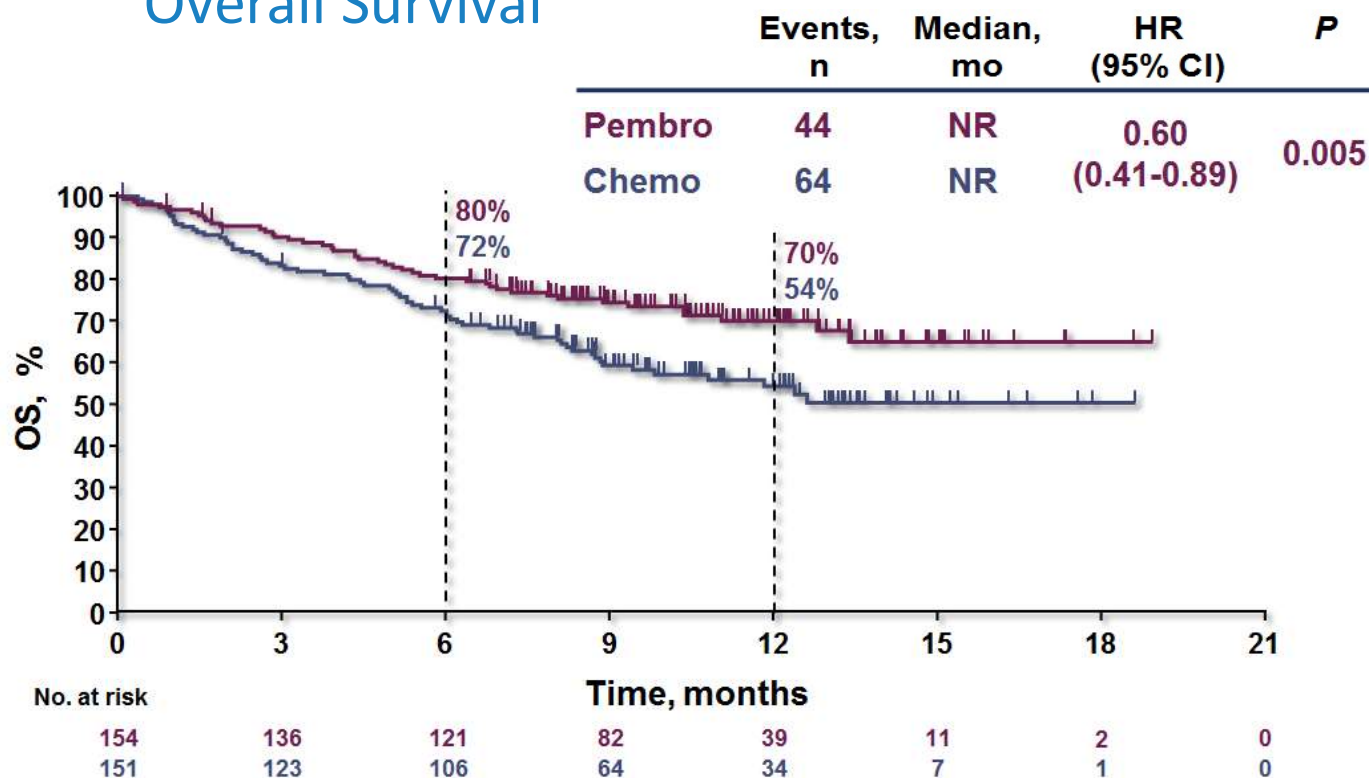
# KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 Positive ( $\geq 50\%$ ) NSCLC Study Design (NCT021427389)

## Key Eligibility Criteria

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



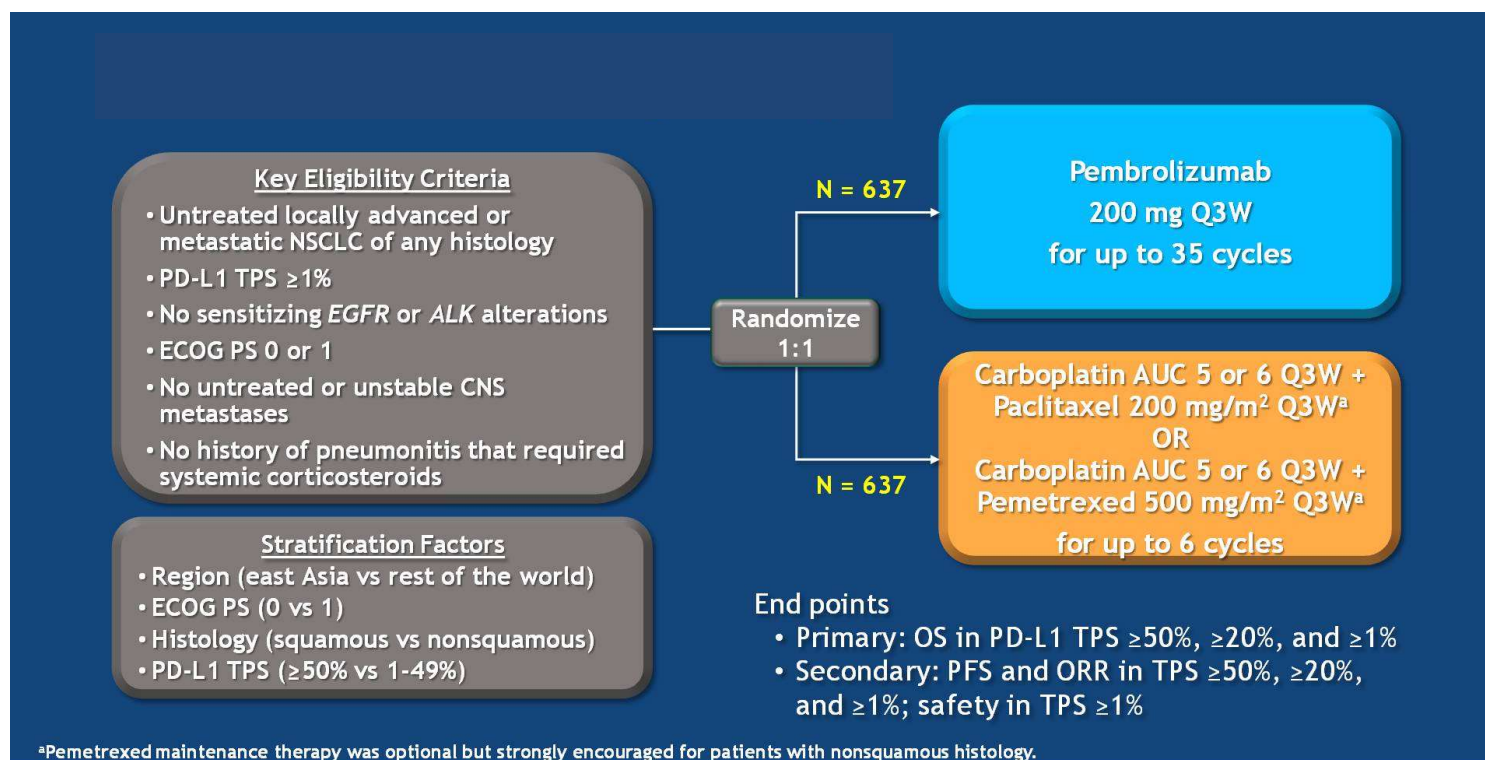
# KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 50\%$ NSCLC Overall Survival



Reck M et al, ESMO 2016, NEJM 2016

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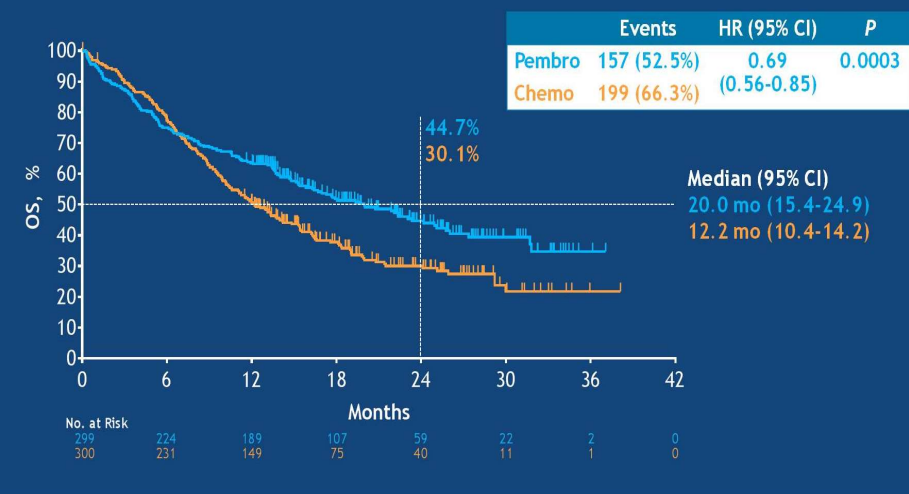
# KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 1\%$ NSCLC



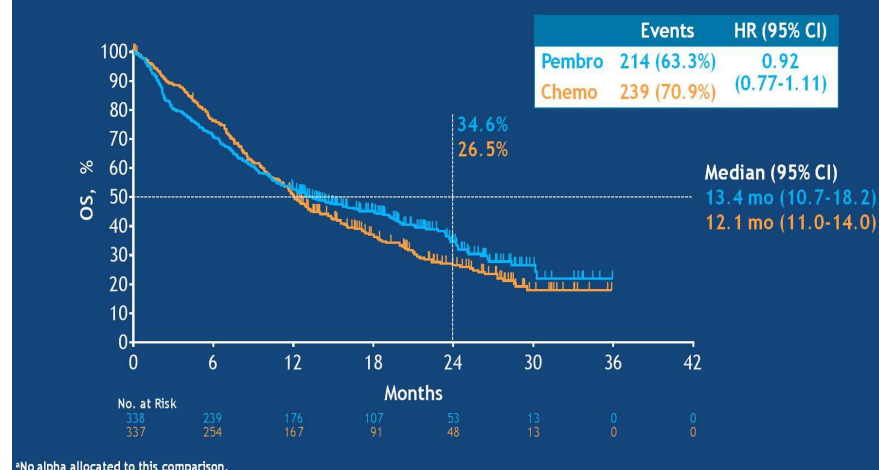


# KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC Overall Survival

## Overall Survival: TPS ≥ 50%

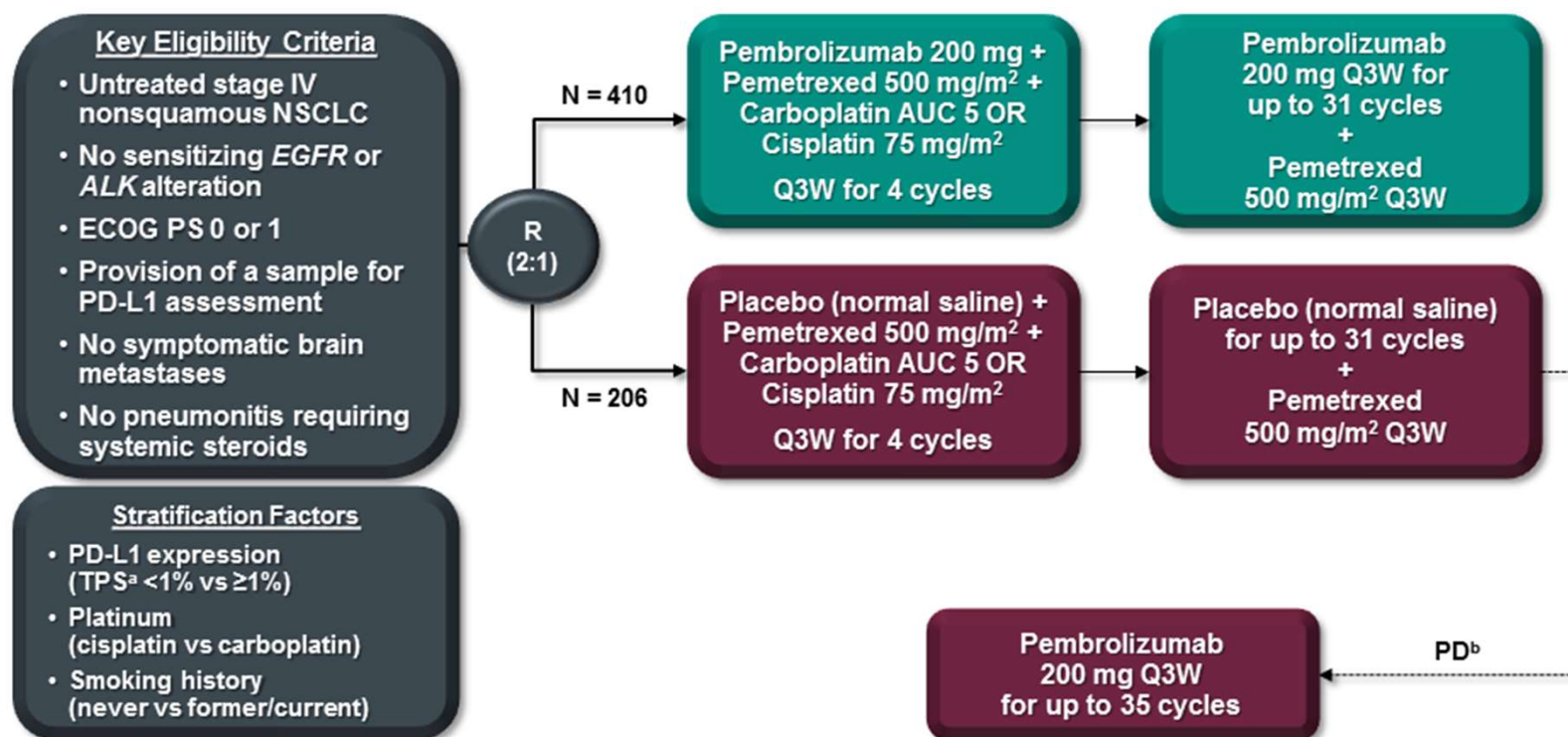


## Overall Survival: TPS ≥ 1-49% (Exploratory Analysis<sup>a</sup>)



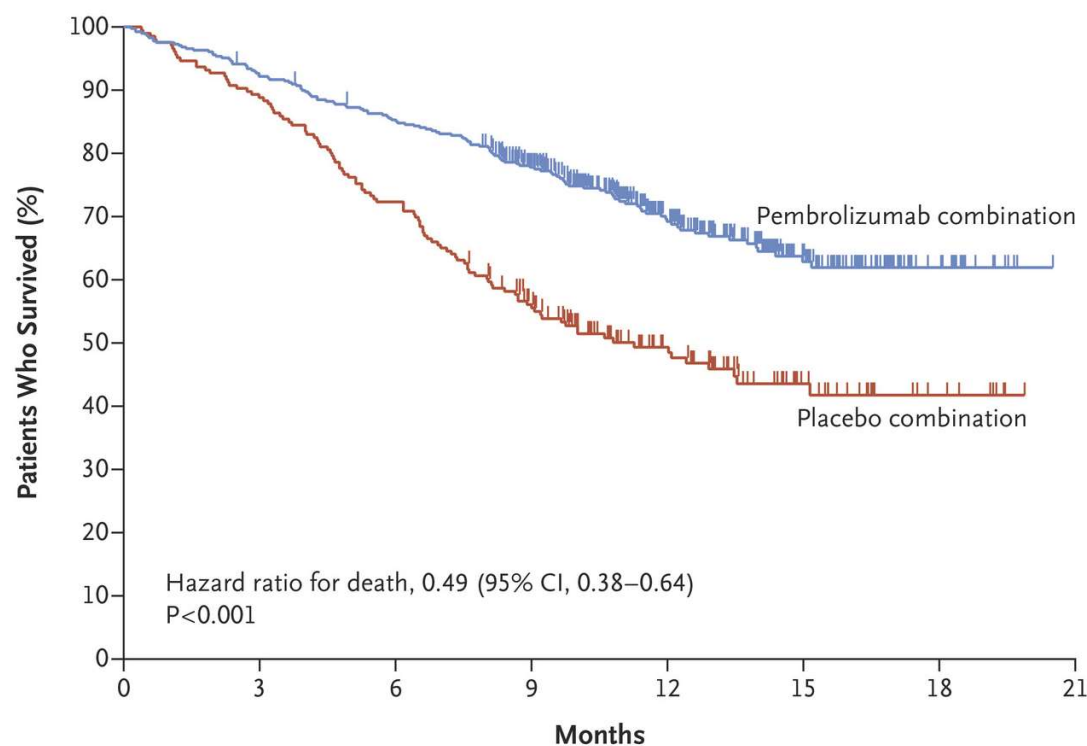
Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

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





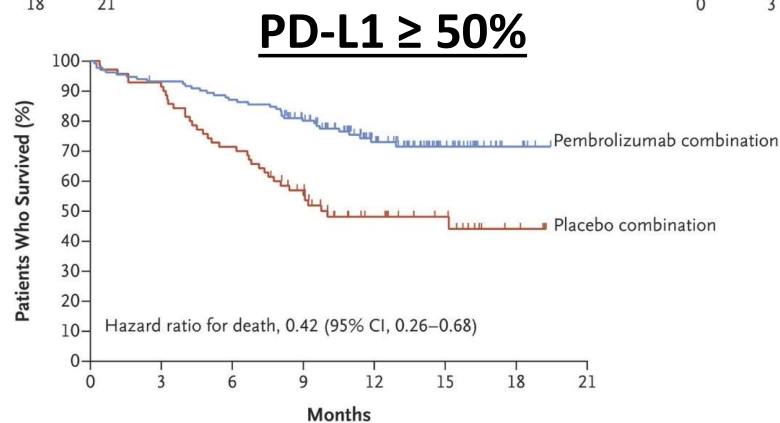
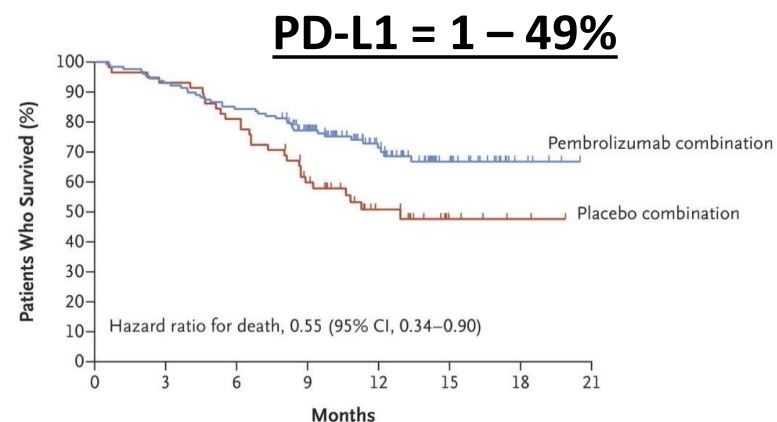
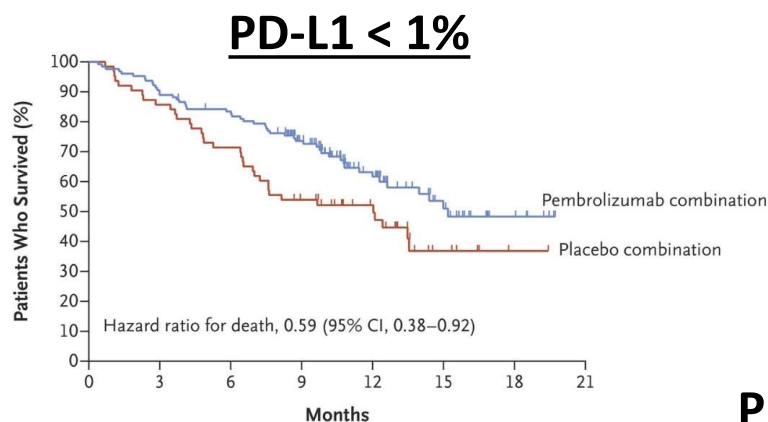
# KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



Ghandi et al, NEJM 2018

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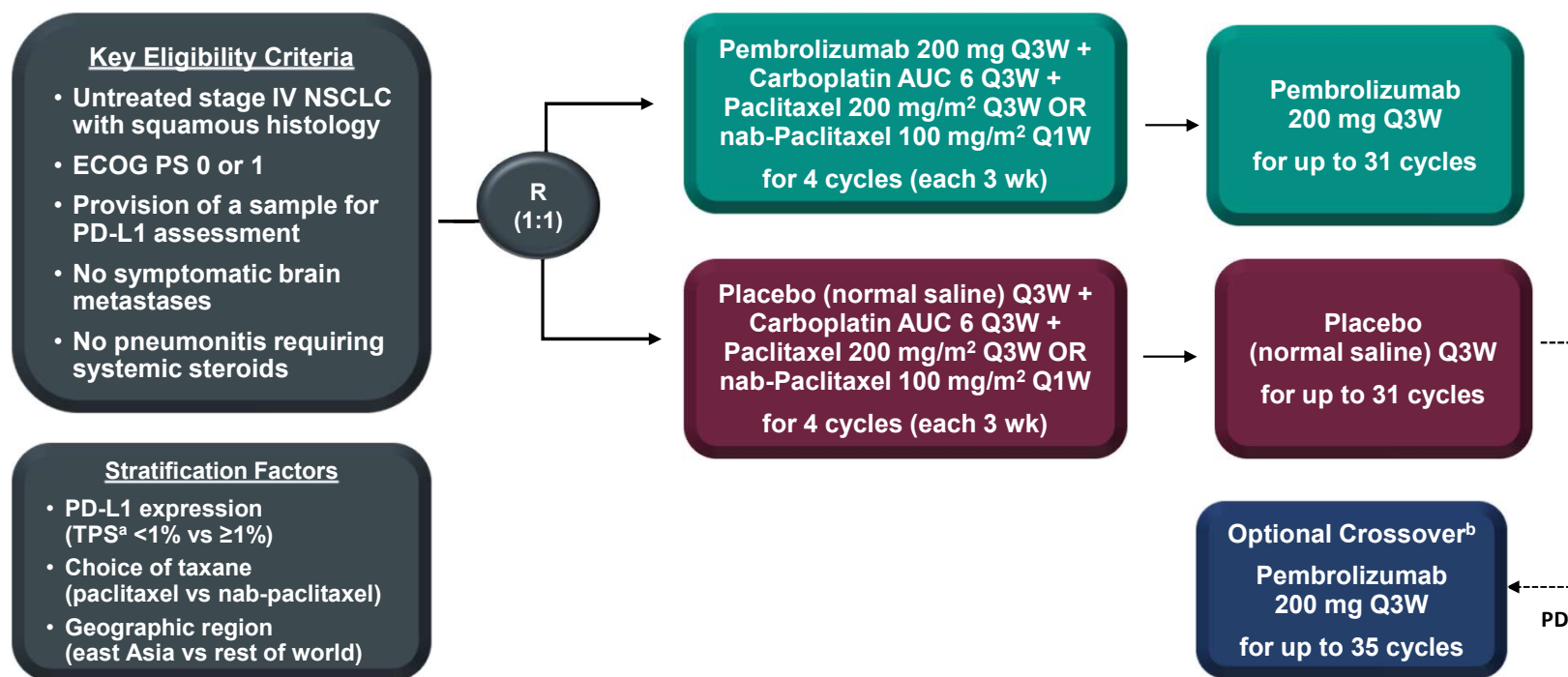
# KEYNOTE-189: Pembrolizumab/Platinum/Pemetrexed vs Chemotherapy Alone for Advanced Non-Squamous NSCLC



Ghandi et al, NEJM 2018

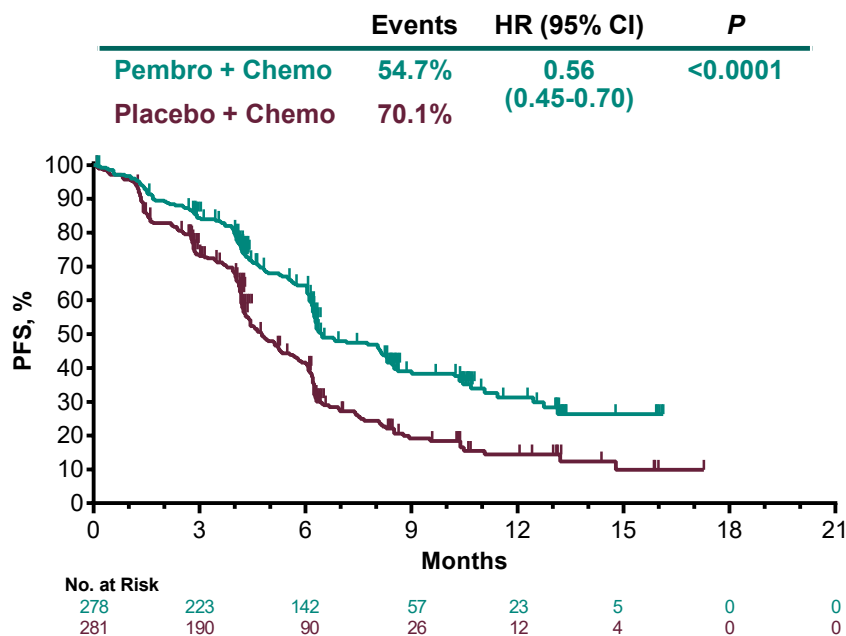
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# KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

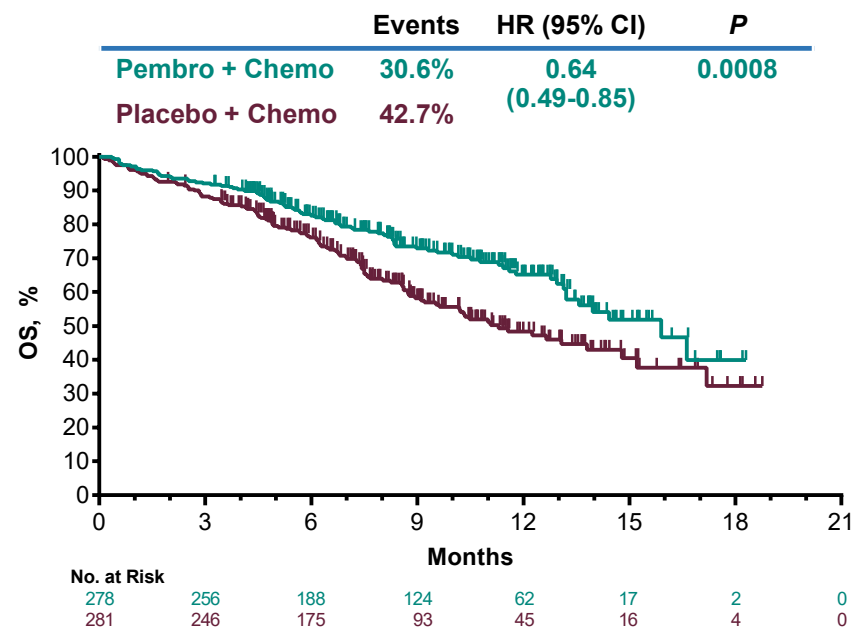


# KEYNOTE-407: Pembrolizumab/Chemotherapy vs Chemotherapy Alone for Advanced Squamous-Cell NSCLC

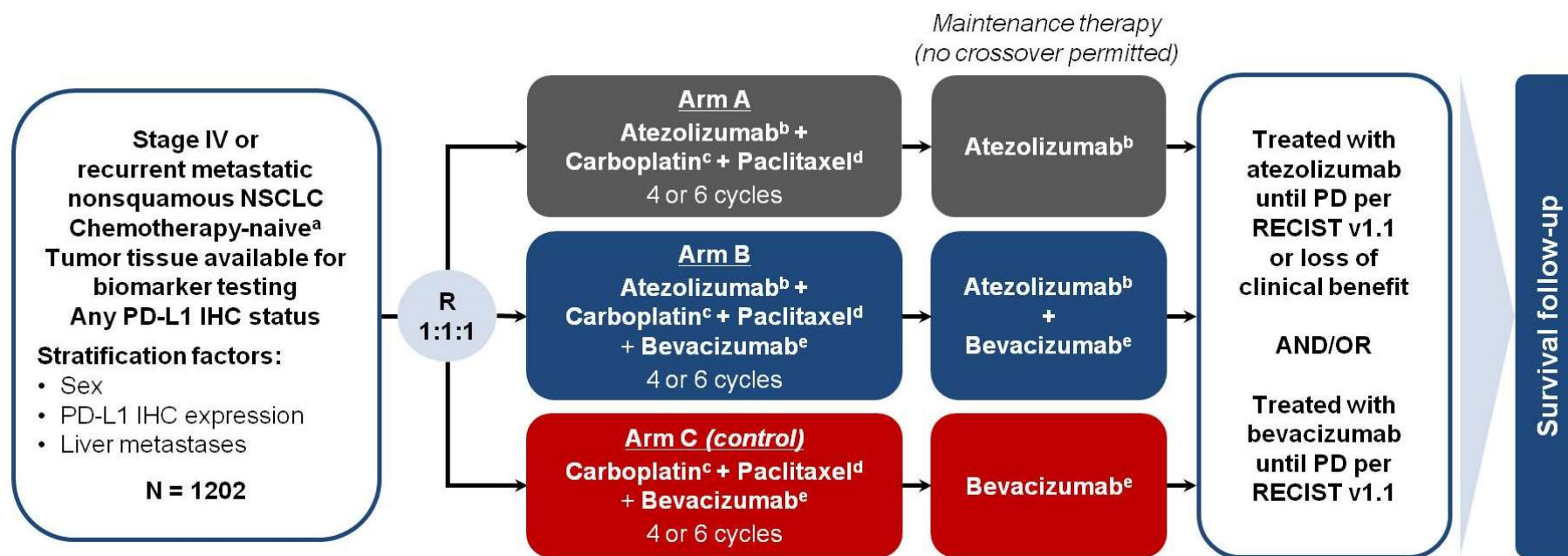
## PFS (RECISTv1.1, BICR)



## Overall Survival



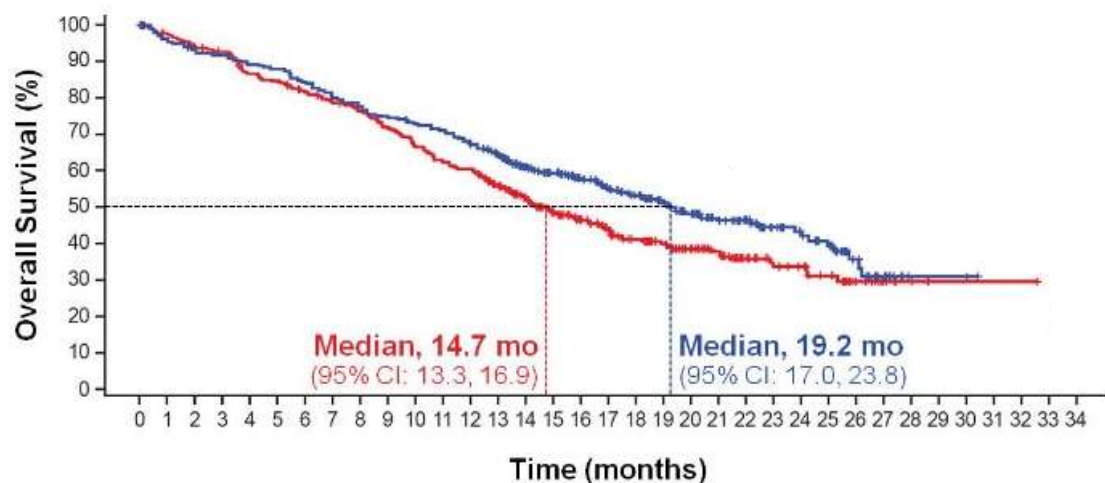
# IMPOWER 150: Atezolizumab/Carboplatin/Paclitaxel/Bevacizumab vs Carboplatin/Paclitaxel/Bevacizumab in Advanced Non-Squamous NSCLC



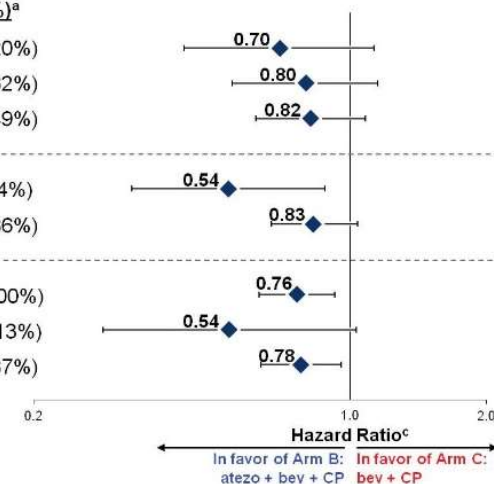
# IMPOWER 150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/ Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

Landmark OS, %	Arm B: atezo + bev + CP	Arm C: bev + CP
12-month	67%	61%
18-month	53%	41%
24-month	43%	34%

**HR<sup>a</sup>, 0.78**  
 (95% CI: 0.64, 0.96)  
**P = 0.0164**  
 Median follow-up: ~20 mo



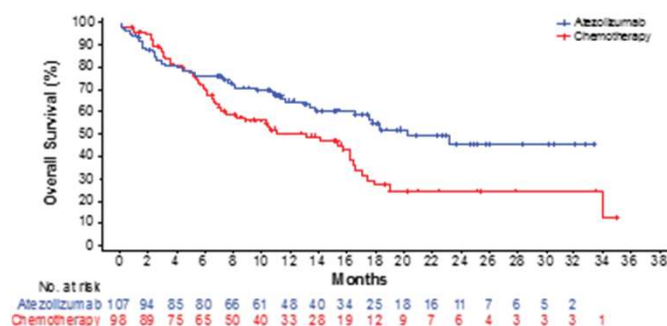
Subgroup	n (%) <sup>a</sup>
PD-L1–High (TC3 or IC3) WT	136 (20%)
PD-L1–Low (TC1/2 or IC1/2) WT	226 (32%)
PD-L1–Negative (TC0 and IC0) WT	339 (49%)
Liver Metastases WT	94 (14%)
No Liver Metastases WT	602 (86%)
ITT (including EGFR/ALK+)	800 (100%)
EGFR/ALK+ only	104 <sup>b</sup> (13%)
ITT-WT	696 (87%)





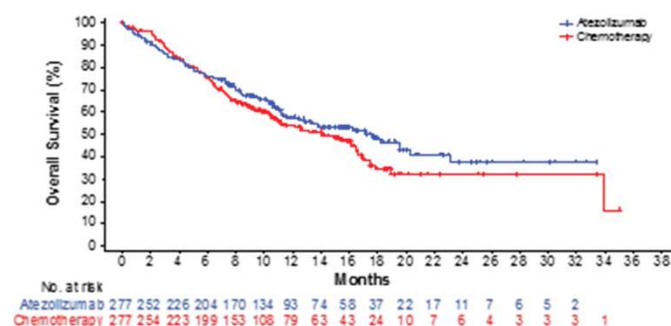
# IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

**SP142 (TC3 or IC3-WT)<sup>a</sup>**



	Atezo (n = 107)	Chemo (n = 98)
mOS, mo	20.2	13.1
HR <sup>b</sup>	0.59	
(95% CI)	(0.40, 0.89)	

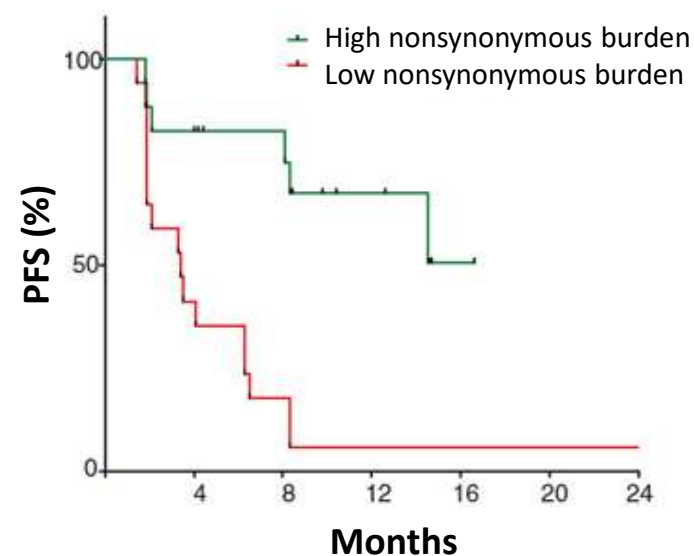
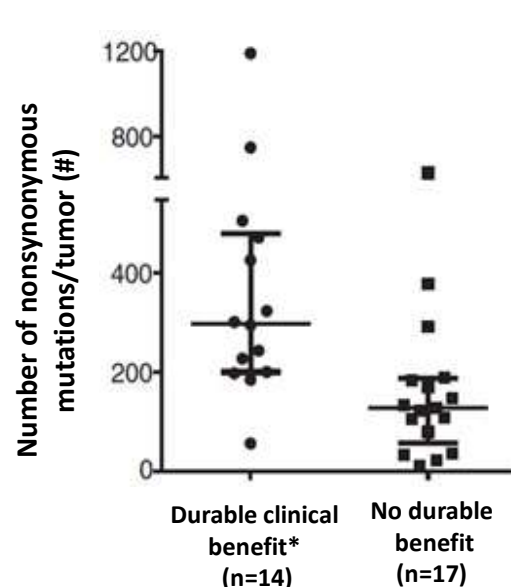
**SP142 (TC1/2/3 or IC1/2/3-WT)<sup>a</sup>**



	Atezo (n = 277)	Chemo (n = 277)
mOS, mo	17.5	14.1
HR <sup>b</sup>	0.83	
(95% CI)	(0.65, 1.07)	

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

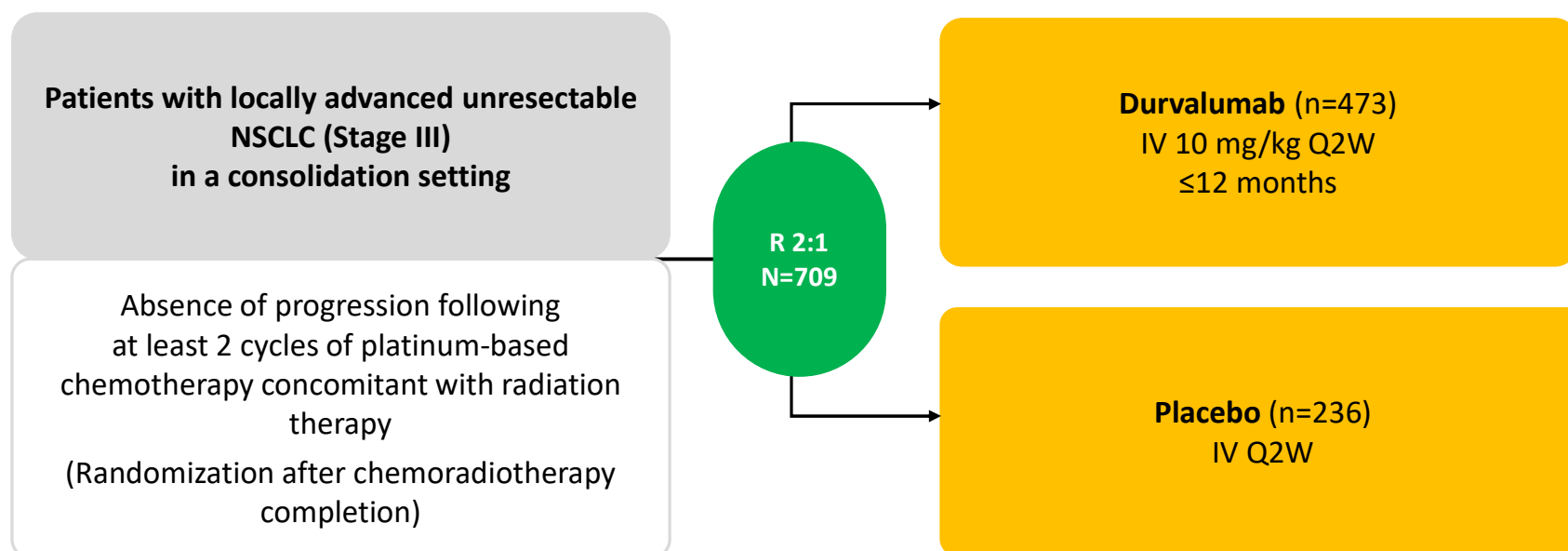
In two independent cohorts, higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit, and PFS.



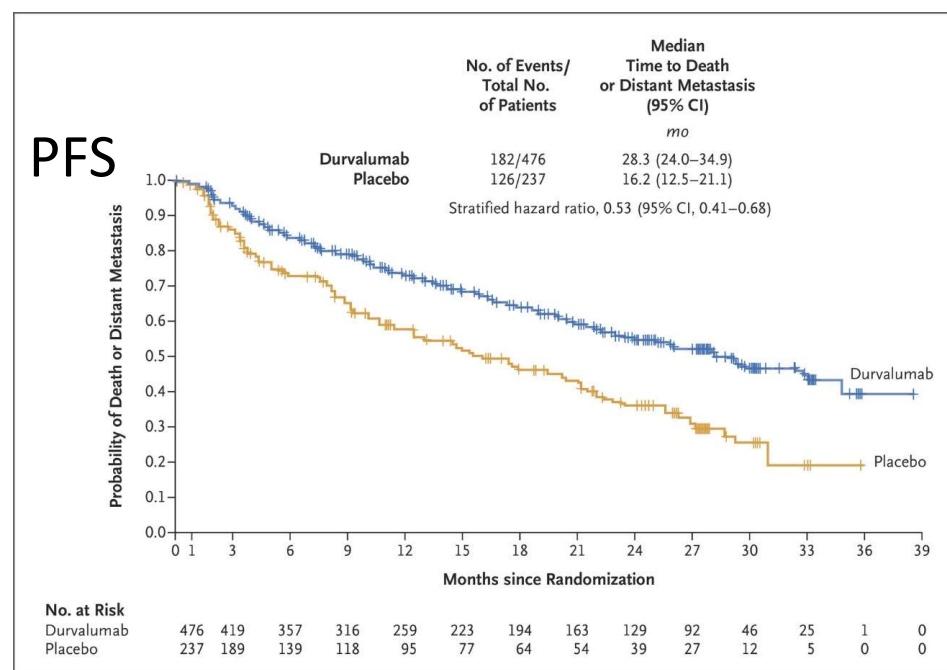
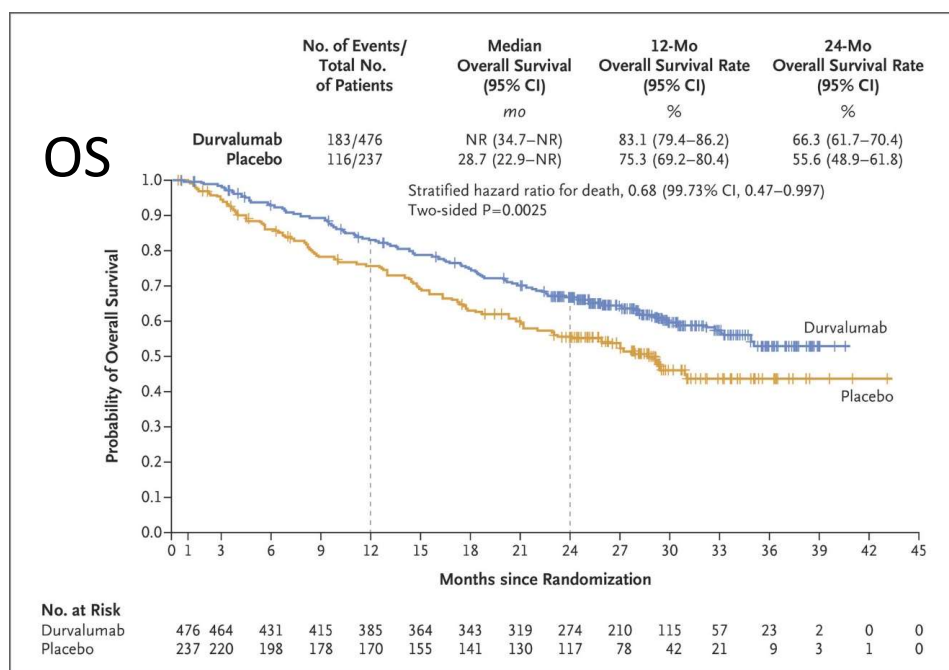
\*Partial or stable response lasting > 6 mo



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

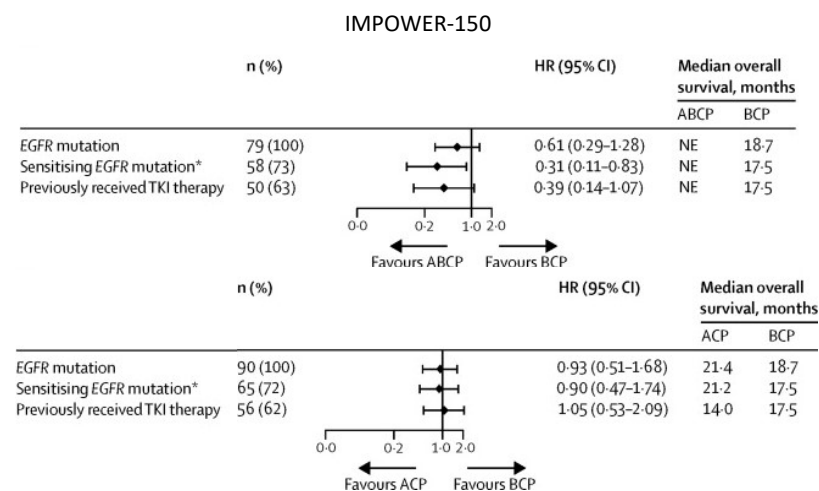
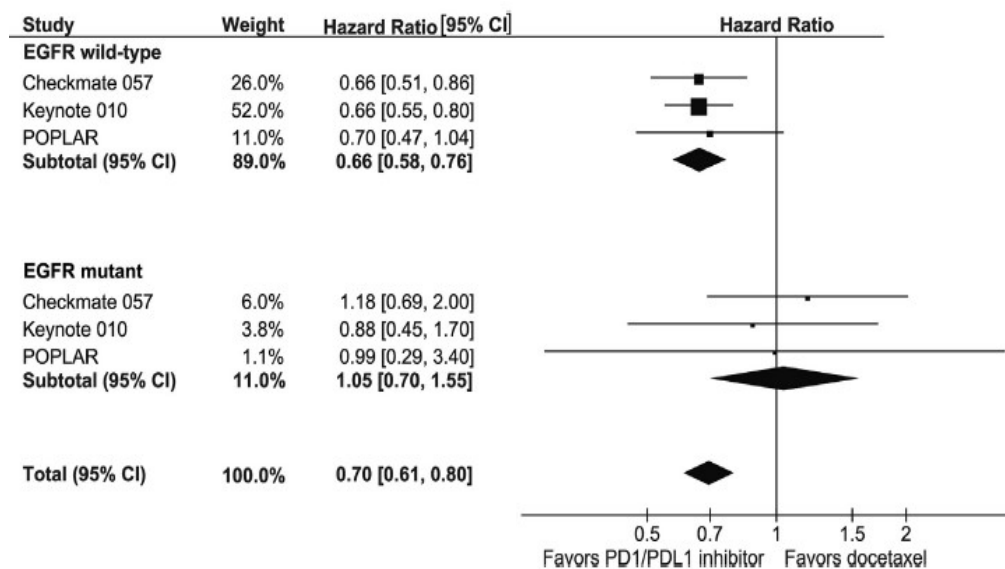


# PACIFIC (NCT02125461): Durvalumab after chemoradiotherapy in Stage III NSCLC



# Checkpoint Inhibitors in Metastatic EGFR-Mutated NSCLC

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



# 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
<b>Pembro 2 mg/kg</b>	<b>14.9 (10.4-NR)</b>	<b>0.54 (0.38-0.77)</b>	<b>0.0002</b>
<b>Pembro 10 mg/kg</b>	<b>17.3 (11.8-NR)</b>	<b>0.50 (0.36-0.70)</b>	<b>&lt;0.0001</b>
Docetaxel	8.2 (6.4-10.7)	--	--

## OAK (atezolizumab)

**HR, 0.73<sup>a</sup>**  
 (95% CI, 0.62, 0.87)  
 P = 0.0003  
 Minimum follow up = 19 months

# Small cell lung cancer

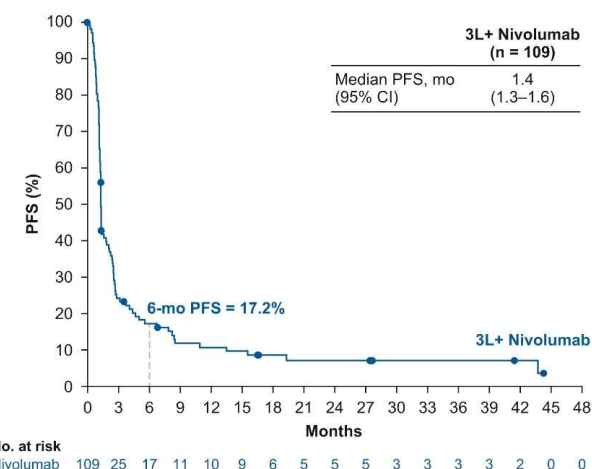
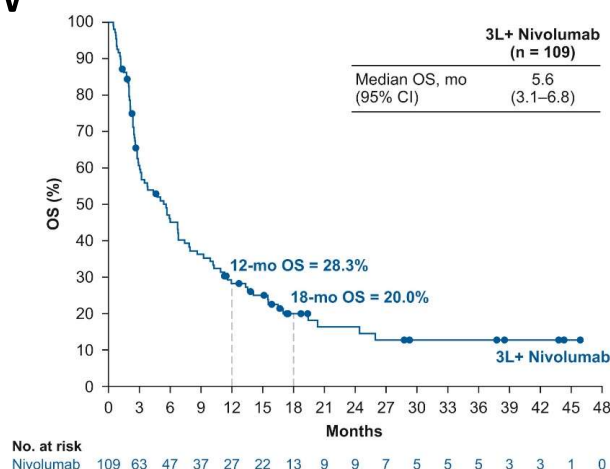
- 10-15% of lung cancers
- Almost exclusively former/current smokers
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2<sup>nd</sup> line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

# Approved checkpoint inhibitors in SCLC

Drug	Indication	Dose
<b>Nivolumab</b>	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy ( <b>3<sup>rd</sup> line</b> )	240 mg Q2W
<b>Pembrolizumab</b>	Metastatic small cell lung cancer with progression on Pt-chemotherapy and one other therapy ( <b>3<sup>rd</sup> line</b> )	200 mg Q3W or 400 mg Q6W
<b>Atezolizumab + carboplatin + etoposide</b>	<b>1<sup>st</sup> line</b> extensive stage SCLC	For 4 cycles: atezolizumab 1200 mg + carboplatin + etoposide Q3W Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W
<b>Durvalumab + etoposide + carboplatin/cisplatin</b>	<b>1<sup>st</sup> line</b> extensive stage SCLC	For 4 cycles: 1500 mg durvalumab Q3W + chemotherapy; Maintenance: 1500 mg durvalumab Q4W

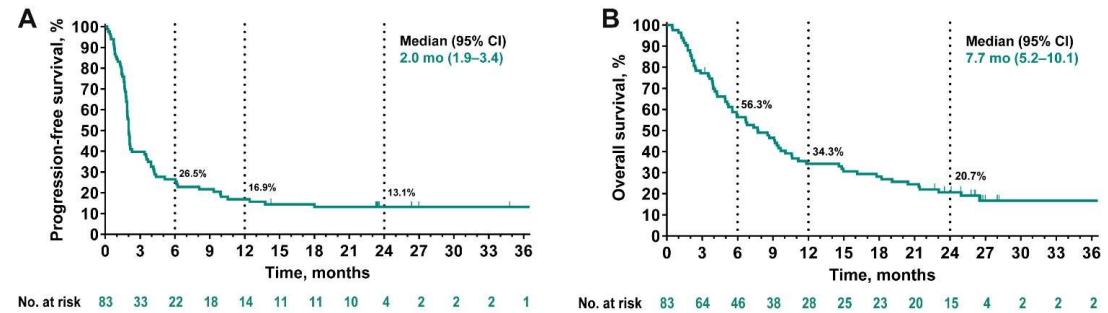
# CheckMate-032: Nivolumab in 3<sup>rd</sup> line SCLC

- 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



# Pembrolizumab in 3<sup>rd</sup>-line SCLC

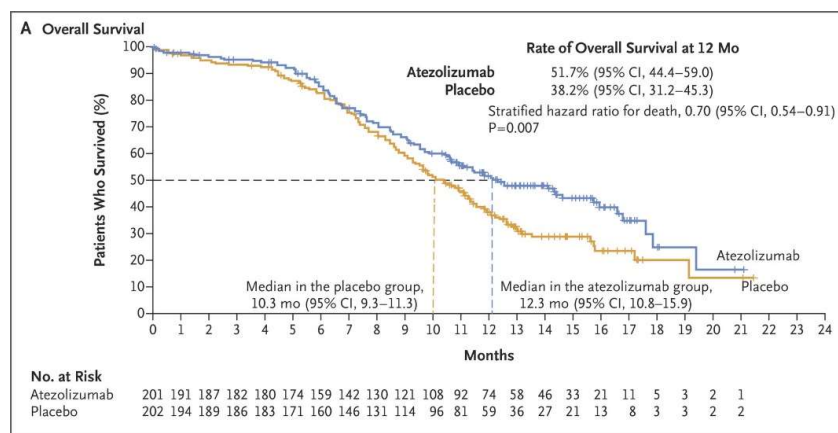
- KEYNOTE-028: PD-L1+ only (Cohort C1)
- KEYNOTE-158: PD-L1 +/- (Cohort G)
- Combined analysis:
- ORR: 19.3%
  - 2 CR, 14 PR
  - 14/16 responders were PD-L1+
  - 9/16 responders had response ≥18 mo.
- mOS: 7.7 months





# IMpower133: Atezolizumab + chemo in 1<sup>st</sup>-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



# 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

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## Conclusions

- NSCLC has been a proving ground for checkpoint inhibitors
- Moving from 2<sup>nd</sup>/3<sup>rd</sup> line options to the front line
- Optimal initial immunotherapy is rapidly evolving
- Clear-cut biomarkers still lacking

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

# Case Studies

## Case Study 1

- A 65 y.o. gentleman is referred to you with newly diagnosed metastatic lung adenocarcinoma.
- The patient initially presented with a chronic cough and subsequently underwent a CXR and CT chest with his family MD. This revealed a large RLL mass which was biopsied revealing lung adenocarcinoma. Subsequent reflex NGS was negative and PDL1 was 15%.
- The patient has undergone a recent MRI brain and PET/CT which reveals a 4 cm RLL mass, mediastinal LN, bone and liver metastases. The patient has no significant pain associated with bone metastases and is ECOG 1.
- Physical examination and bloodwork are unremarkable.
- What initial therapy would you recommend to this patient and why?

## Case Study 1

- What initial therapy would you recommend to this patient and why?
  - Pembrolizumab
  - Carboplatin-Pemetrexed-Pembrolizumab
  - Ipilimumab-Nivolumab with initial Carboplatin-Pemetrexed
  - Carboplatin-Paclitaxel-Atezolizumab-Bevacizumab

## Case Study 1

- The patient undergoes 3 cycles of carboplatin-pemetrexed-pembrolizumab with an excellent radiographic response on subsequent restaging CT CAP.
- The patient subsequently completes 4 cycles of carboplatin-pemetrexed-pembrolizumab and then transitions to pemetrexed-pembrolizumab maintenance.
- 6 months after beginning treatment, he develops blisters over his hands, arms and feet. He does not have associated fever or involvement of any mucosal surfaces.
- What is the most likely diagnosis and appropriate management?



# Case Study 1

- What is the most likely diagnosis and appropriate management?
  - SJS/TEN – hold drug, obtain skin biopsy, admit to burn unit and treat with cyclosporine + prednisone
  - Bullous Pemphigoid – hold drug, obtain skin biopsy, treat with topical steroids + rituximab or omalizumab
  - Cellulitis exacerbated by immunotherapy – admit for IV antibiotics
  - Pemetrexed rash – discontinue pemetrexed and treat supportively

## Case Study 2

- A 54 y.o. woman is referred to you with newly diagnosed Stage IIIA squamous cell lung cancer (T2N2M0).
- She initially presented with a chronic cough and small volume hemoptysis. She subsequently underwent a CT chest and bronchoscopy revealing a 4.3 cm RLL mass with biopsy consistent with squamous cell carcinoma (PDL1 5%). EBUS biopsy revealed multi-station N2 disease.
- Subsequent MRI brain and PET/CT did not reveal evidence of distant metastases or LN involvement beyond the aforementioned N2 stations.
- What would you recommend as initial management?

## Case Study 2

- What would you recommend as initial management?
  - Surgical resection then adjuvant chemotherapy and PORT
  - Neoadjuvant chemotherapy, surgical resection then PORT
  - Chemoradiotherapy then surgical resection
  - Chemoradiotherapy then durvalumab

## Case Study 2

- The patient completes chemoradiotherapy complicated by esophagitis. She undergoes a repeat CT CAP after completion of chemoradiotherapy revealing no evidence of disease progression.
- She then completes 1 year of durvalumab without complication.
- Ongoing surveillance imaging at 2 years reveals no evidence of disease recurrence.