

# Immunotherapy for the Treatment of Lung Cancer

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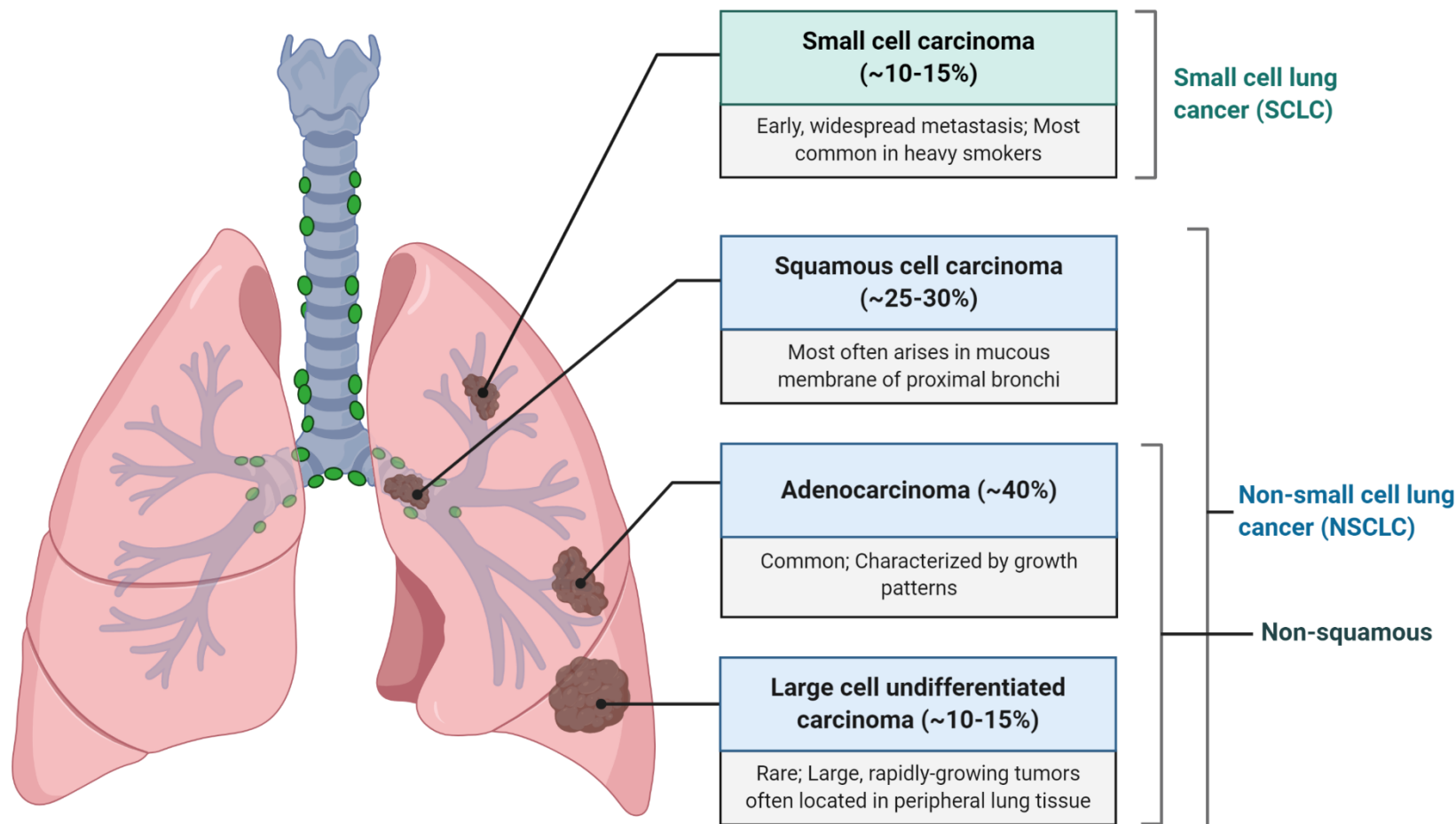
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# Disclosures

- Consulting Fees: AstraZeneca, Genentech/Roche, EMD Serono, Blueprint Medicines, Daiichi Sankyo/Lilly, Janssen Oncology, MacroGenics
- Contracted Research: Investigator sponsored research support: Merck, AstraZeneca
- Other: Panel expert, symposium presenter, educational presentations, travel support: AstraZeneca, Amgen
- I will be discussing non-FDA approved indications during my presentation.

# Lung cancer



# Treatment options for NSCLC

## Local disease

- Surgery
- Stereotactic body radiation therapy
- Chemotherapy

## Stage III unresectable disease

- Concurrent chemo-radiation
- Immunotherapy

## Metastatic disease

- Chemotherapy
- Targeted therapies
- Immunotherapy
- Radiation therapy

# Metastatic NSCLC treatment options overview

| Drug type                   | Molecular format | Administration route           | Example for NSCLC              | Typical dosing regimen                                 |
|-----------------------------|------------------|--------------------------------|--------------------------------|--------------------------------------------------------|
| Chemotherapy                | Small molecule   | Intravenous, occasionally oral | Nab-paclitaxel                 | 100 mg/m <sup>2</sup> on days 1, 8, 15 of 21-day cycle |
| Targeted therapy            | Small molecule   | Oral                           | Osimertinib (kinase inhibitor) | 80 mg tablet once a day                                |
| Targeted antibody therapy   | Antibody         | Intravenous                    | Bevacizumab (VEGF-A inhibitor) | 15 mg/kg Q3W                                           |
| Immune checkpoint inhibitor | Antibody         | Intravenous                    | Pembrolizumab (PD-1 inhibitor) | 200 mg Q3W or 400 mg Q6W                               |

# Immune checkpoint inhibitors in lung cancer

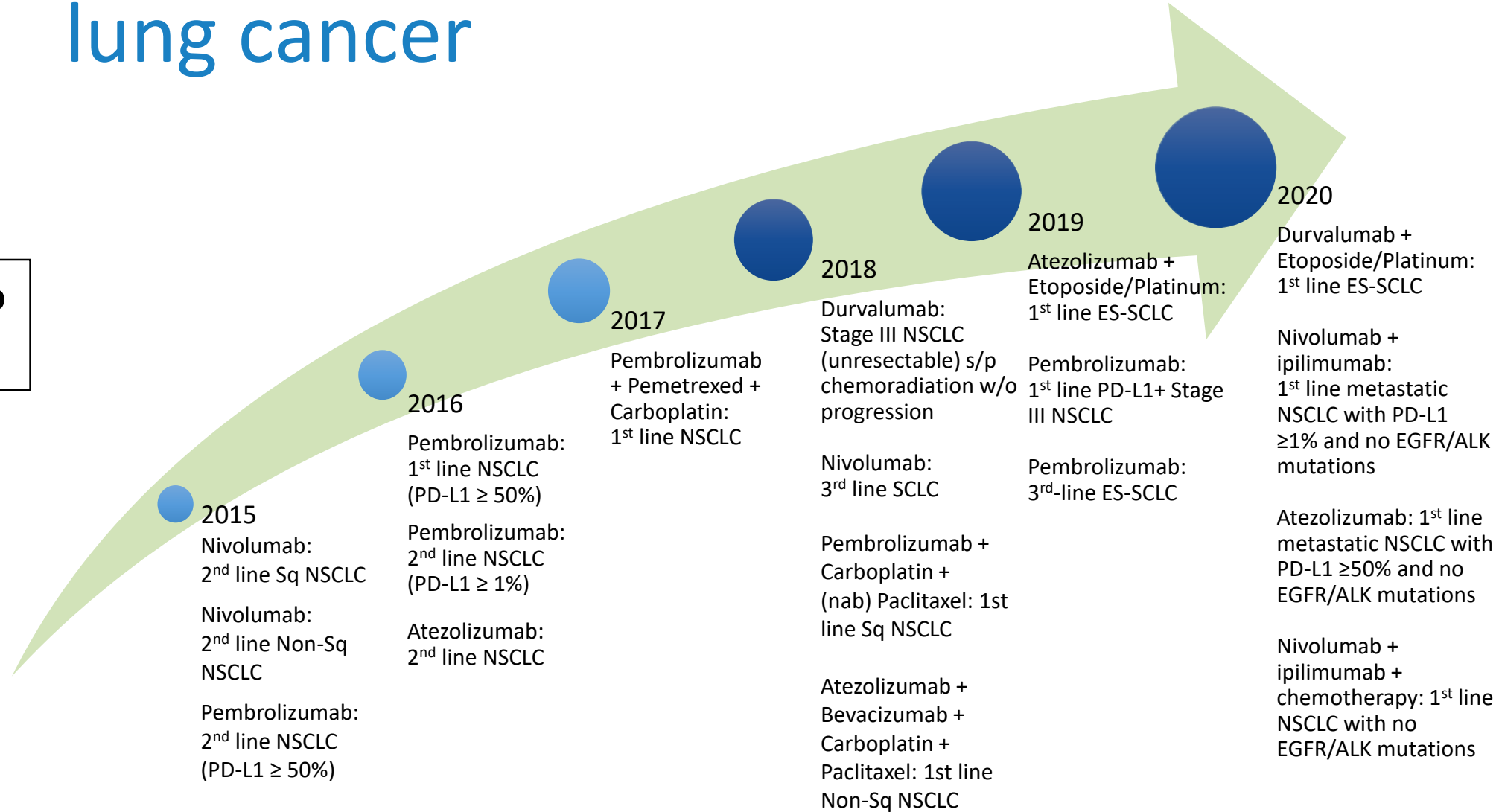
**Nivolumab**  
Y → PD-1

**Pembrolizumab**  
Y → PD-1

**Atezolizumab**  
Y → PD-L1

**Durvalumab**  
Y → PD-L1

**Ipilimumab**  
Y → CTLA-4



# Outline

- Non-small cell lung cancer
  - Front-line – PD-L1-selected and unselected
  - Later lines of treatment
  - Stage III
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

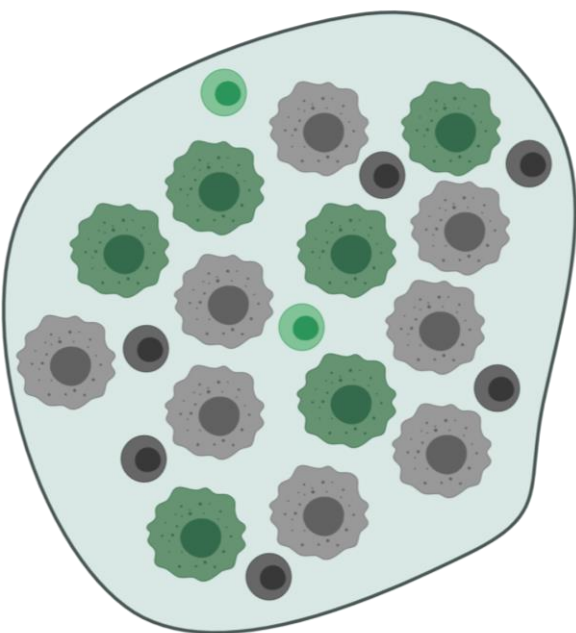
# Immunotherapy for first-line treatment of metastatic NSCLC

| 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                                                                              |
| Cemiplimab                                              | 1 <sup>st</sup> line advanced/metastatic NSCLC with <b>PD-L1 TPS ≥ 50%</b> and no EGFR/ALK/ROS1 mutations                        | 350 mg Q3W                                                                                                                  |
| 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<br>Maintenance: 840 mg Q2W, 1200 mg Q3W, or 1680 mg Q4W             |

# Brief aside: PD-L1 TPS vs CPS

$$TPS = \frac{\# \text{ of PD-L1 positive tumor cells}}{\text{number of viable tumor cells}} \times 100$$

$$CPS = \frac{\# \text{ of PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{total number of tumor and immune cells}} \times 100$$



-  PD-L1-positive immune cell
-  PD-L1-negative immune cell
-  PD-L1-positive tumor cell
-  PD-L1-negative tumor cell

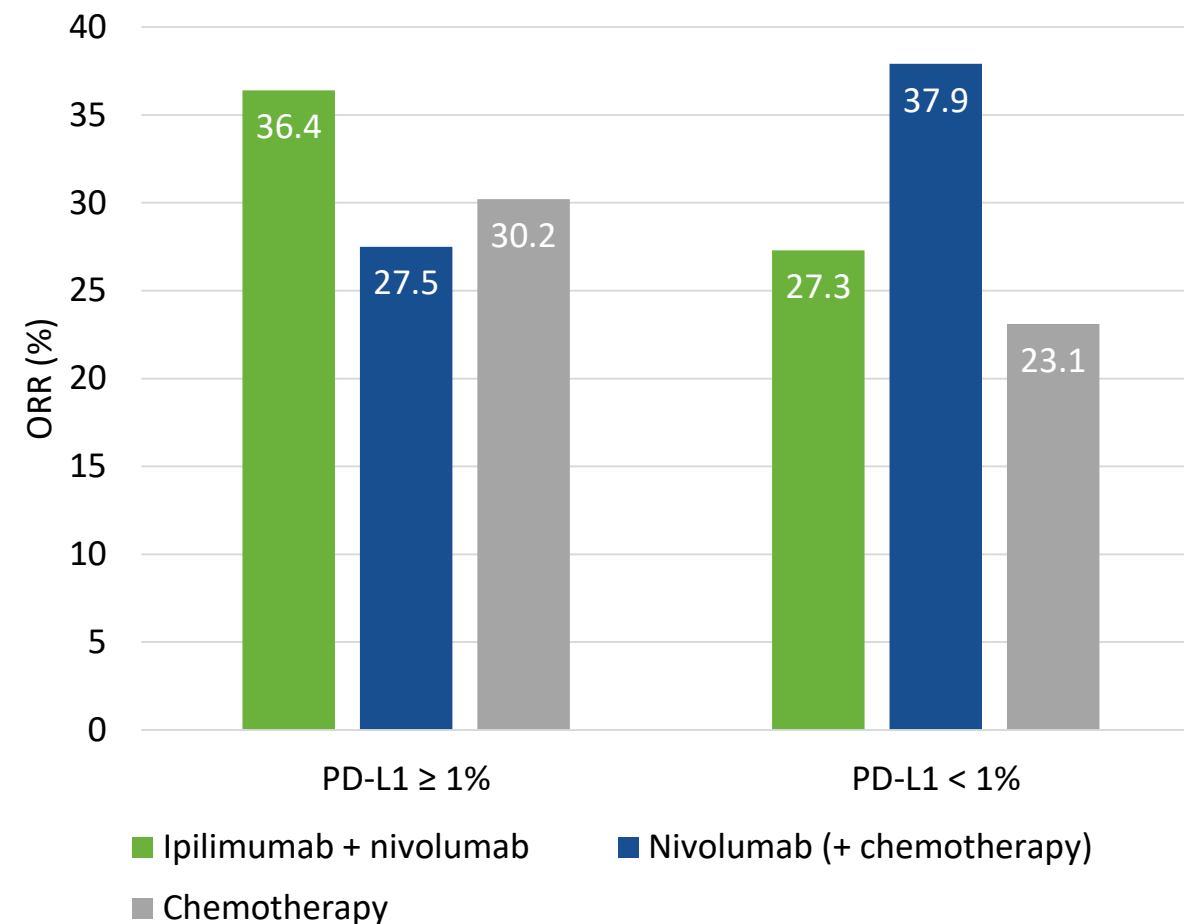
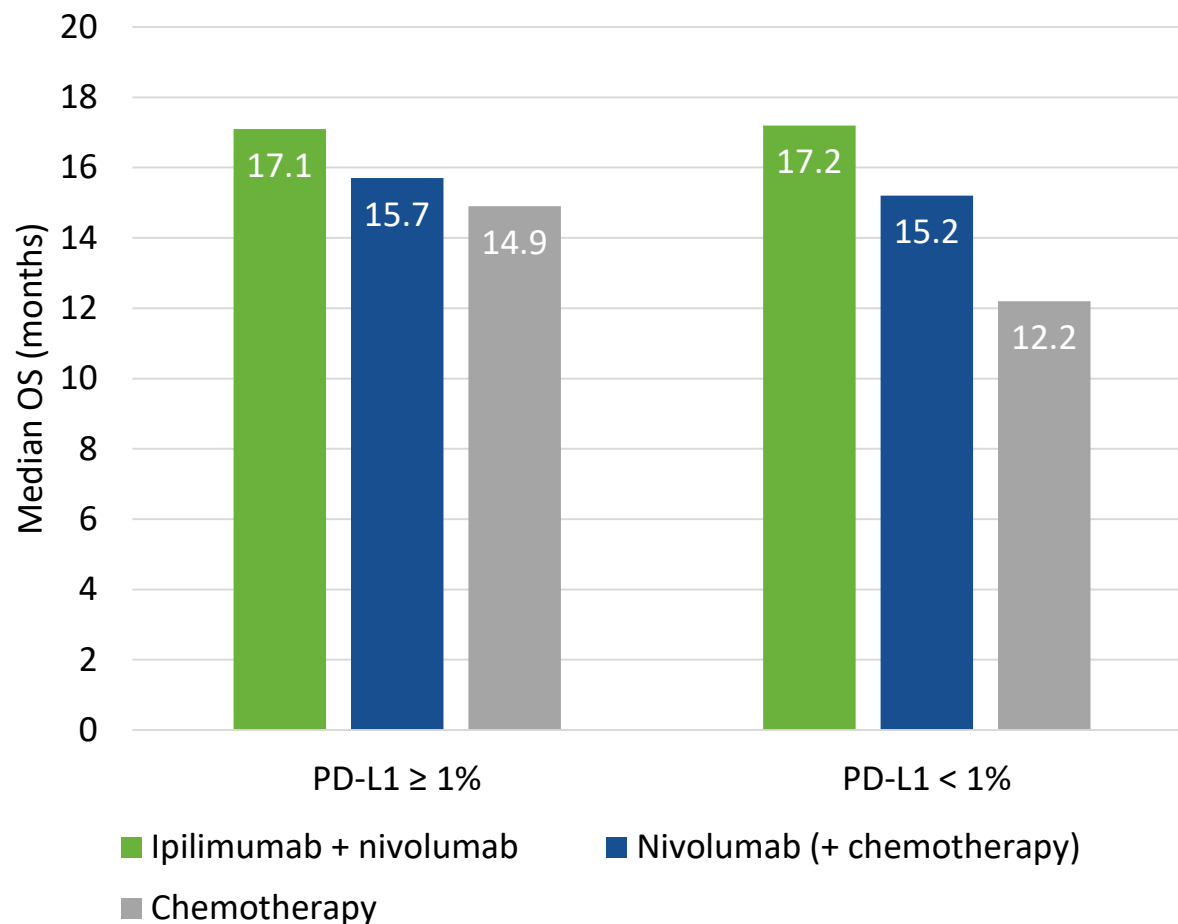
$$TPS = \frac{6 \text{ positive tumor cells}}{14 \text{ total tumor cells}} \times 100 = 43$$

$$CPS = \frac{6 \text{ positive tumor cells} + 2 \text{ positive immune cells}}{22 \text{ total cells}} \times 100 = 36$$

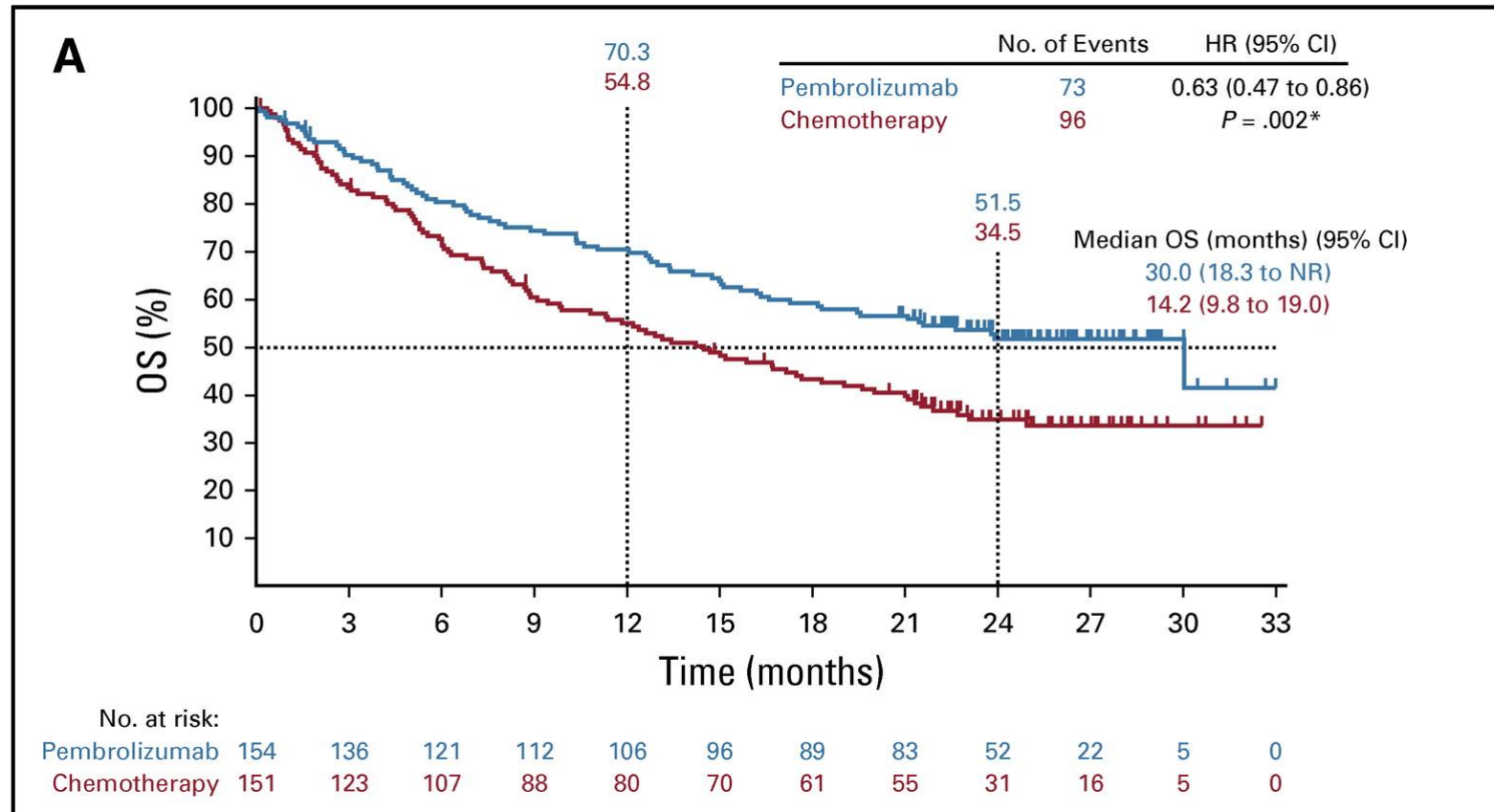
# Treatment Naïve Regimens: Competing Strategies in NSCLC by biomarker status

| PD-L1-selected                                 | PD-L1-unselected                                                  |
|------------------------------------------------|-------------------------------------------------------------------|
| Nivolumab + ipilimumab<br><i>CheckMate 227</i> | Nivolumab + ipilimumab + platinum-doublet<br><i>CheckMate 9LA</i> |
| Pembrolizumab<br><i>KEYNOTE-024, -042</i>      | Pembrolizumab + chemotherapy<br><i>KEYNOTE-189, -407</i>          |
| Atezolizumab<br><i>IMpower110</i>              | Atezolizumab + bevacizumab + chemotherapy<br><i>IMpower150</i>    |
|                                                | Atezolizumab + chemotherapy<br><i>IMpower130</i>                  |

# CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC

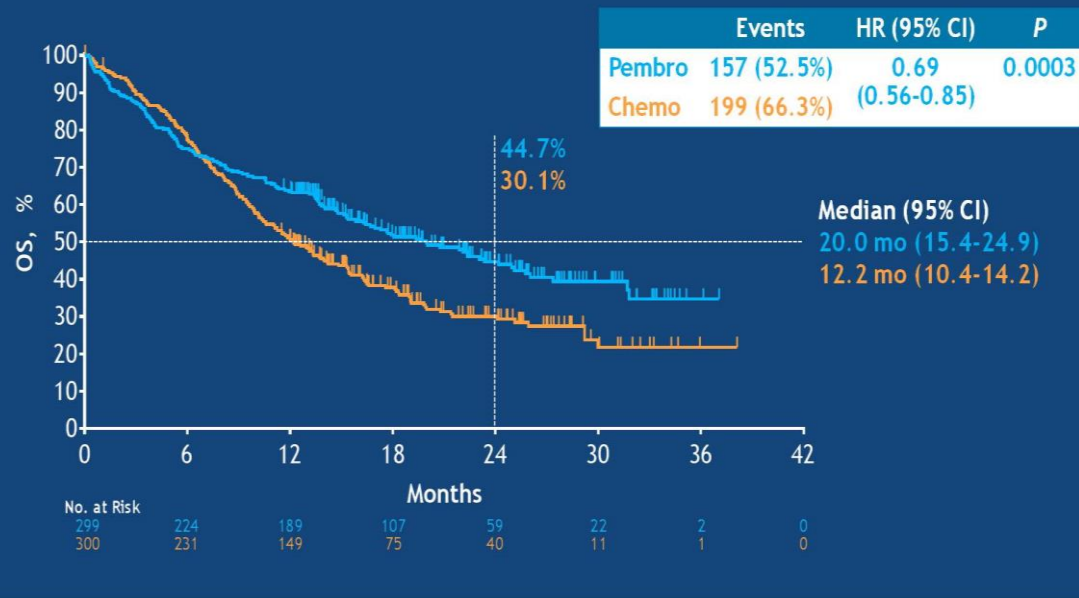


# KEYNOTE-024: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 50% NSCLC

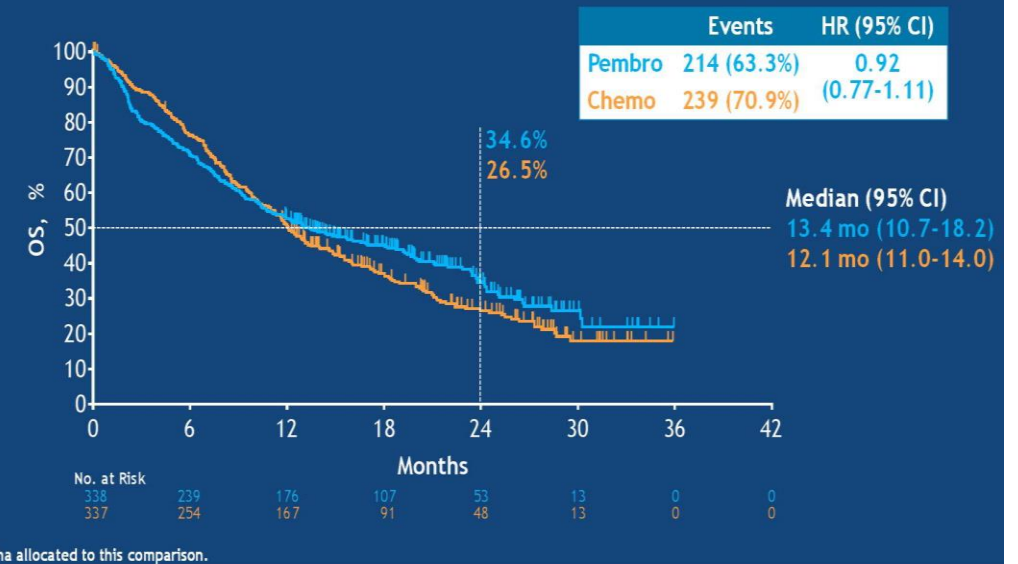


# KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 $\geq 1\%$ NSCLC

## Overall Survival: TPS $\geq 50\%$



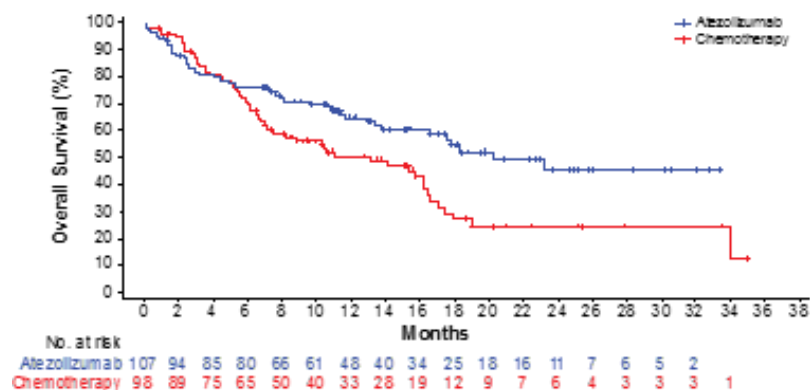
## Overall Survival: TPS $\geq 1-49\%$ (Exploratory Analysis<sup>a</sup>)



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

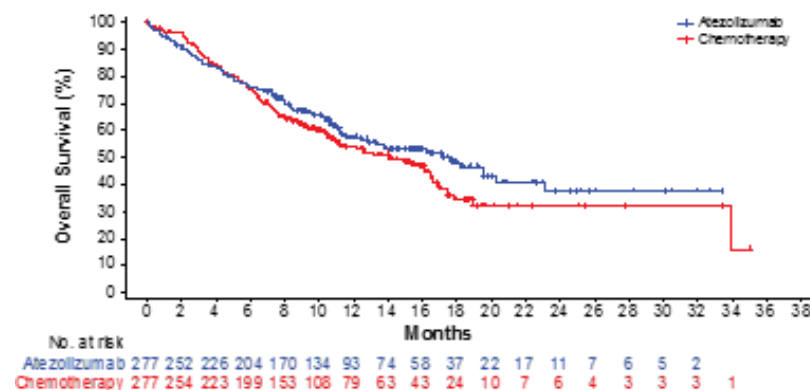
# IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

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



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

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

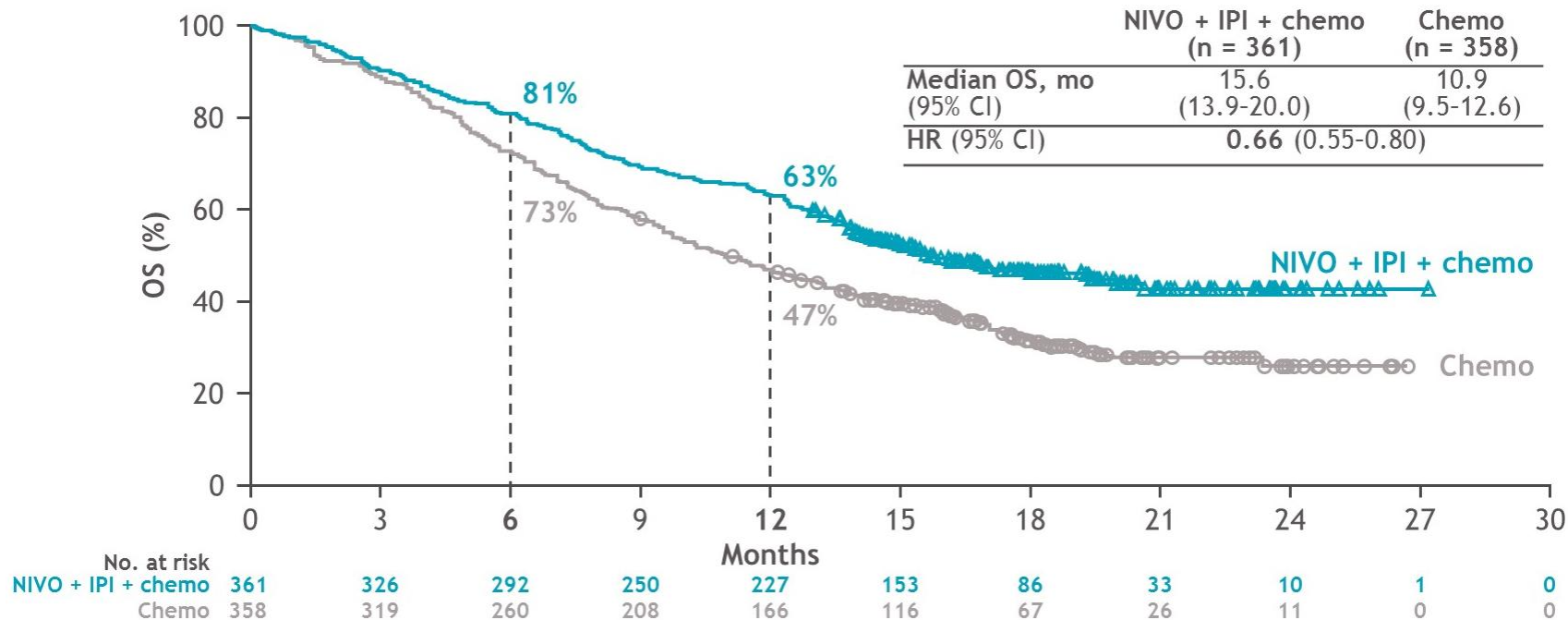


|                             | Atezo<br>(n = 277)   | Chemo<br>(n = 277) |
|-----------------------------|----------------------|--------------------|
| mOS, mo                     | 17.5                 | 14.1               |
| HR <sup>b</sup><br>(95% CI) | 0.83<br>(0.65, 1.07) |                  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

|                    |                      |
|--------------------|----------------------|
| TC3<br>IC3         | TC ≥ 50%<br>IC ≥ 10% |
| TC2/3<br>IC2/3     | TC ≥ 5%<br>IC ≥ 5%   |
| TC1/2/3<br>IC1/2/3 | TC ≥ 1%<br>IC ≥ 1%   |

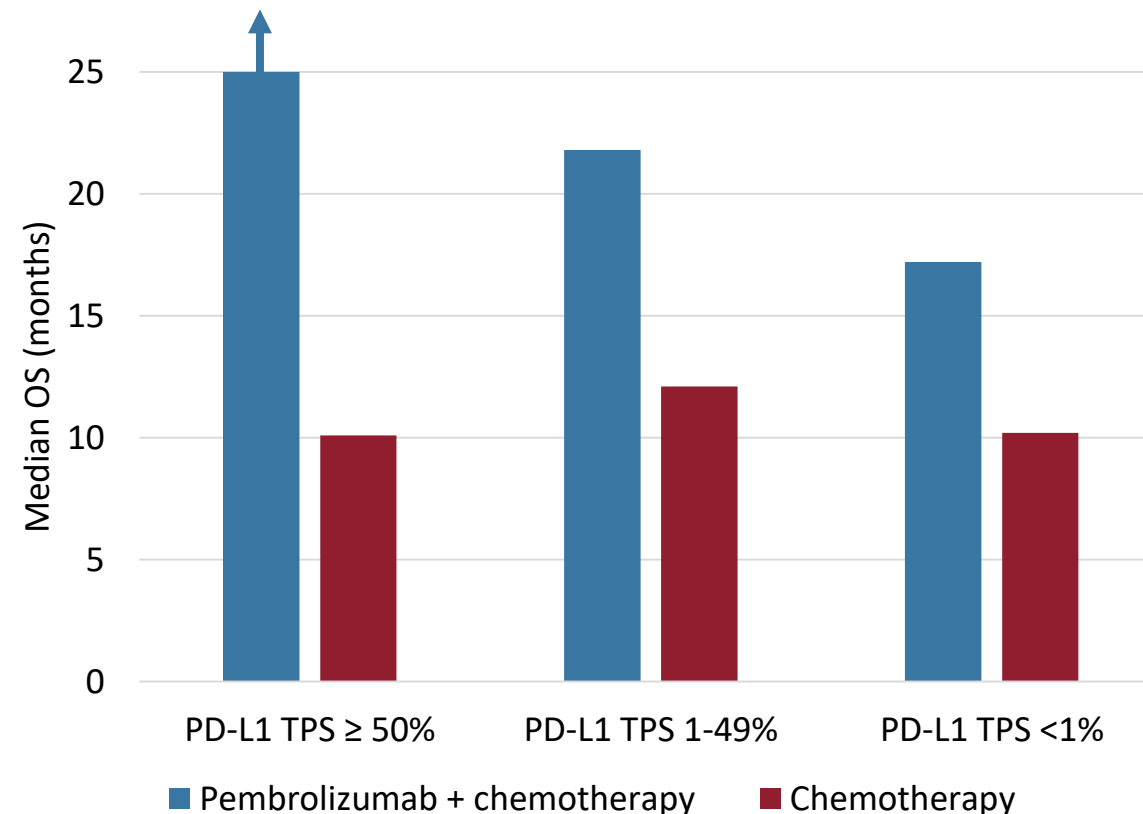
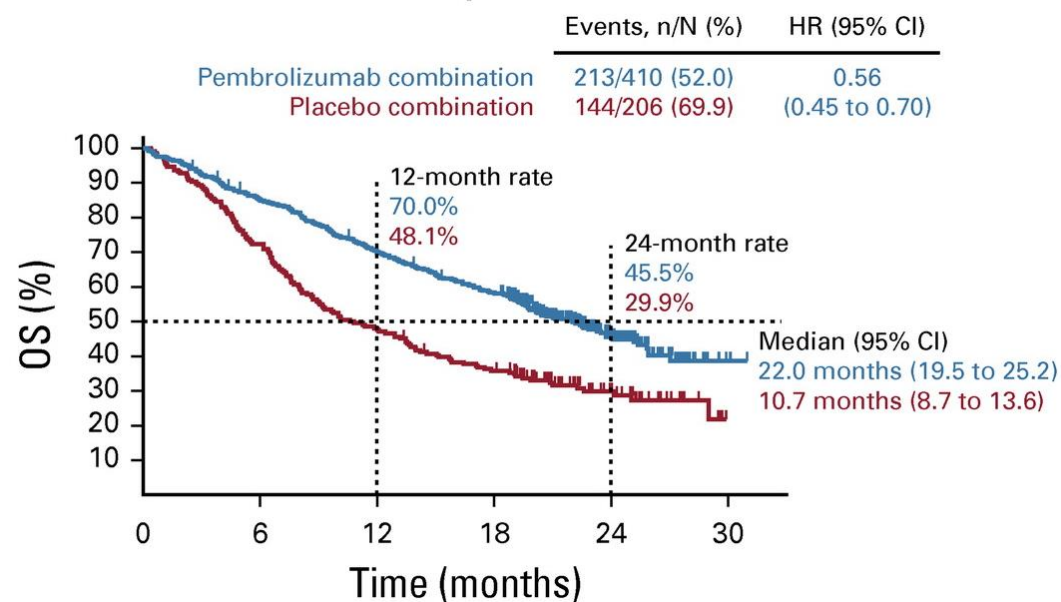
# Treatments not reliant on PD-L1 expression

# CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo



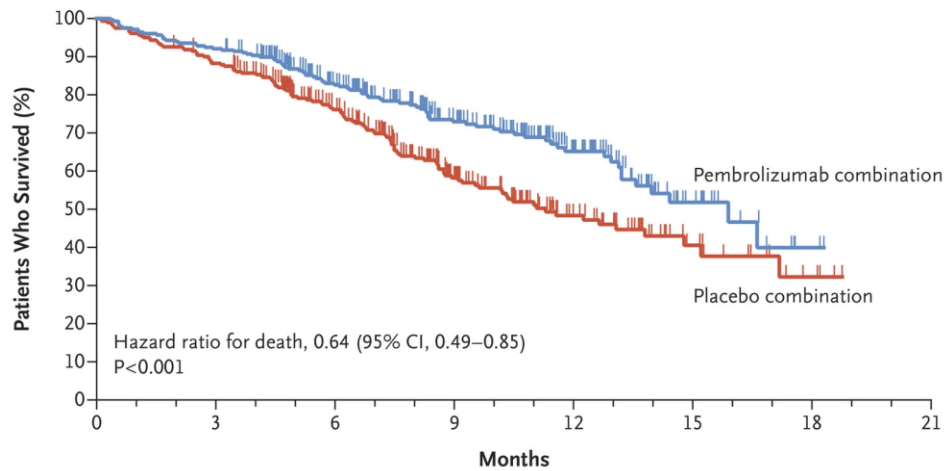
|                        | NIVO + IPI +<br>chemo<br>(n = 361) | Chemo<br>(n = 358) |
|------------------------|------------------------------------|--------------------|
| ORR, n (%)             | 138 (38)                           | 89 (25)            |
| Odds ratio<br>(95% CI) | 1.9<br>(1.4-2.6)                   |                    |
| 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)           |

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



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

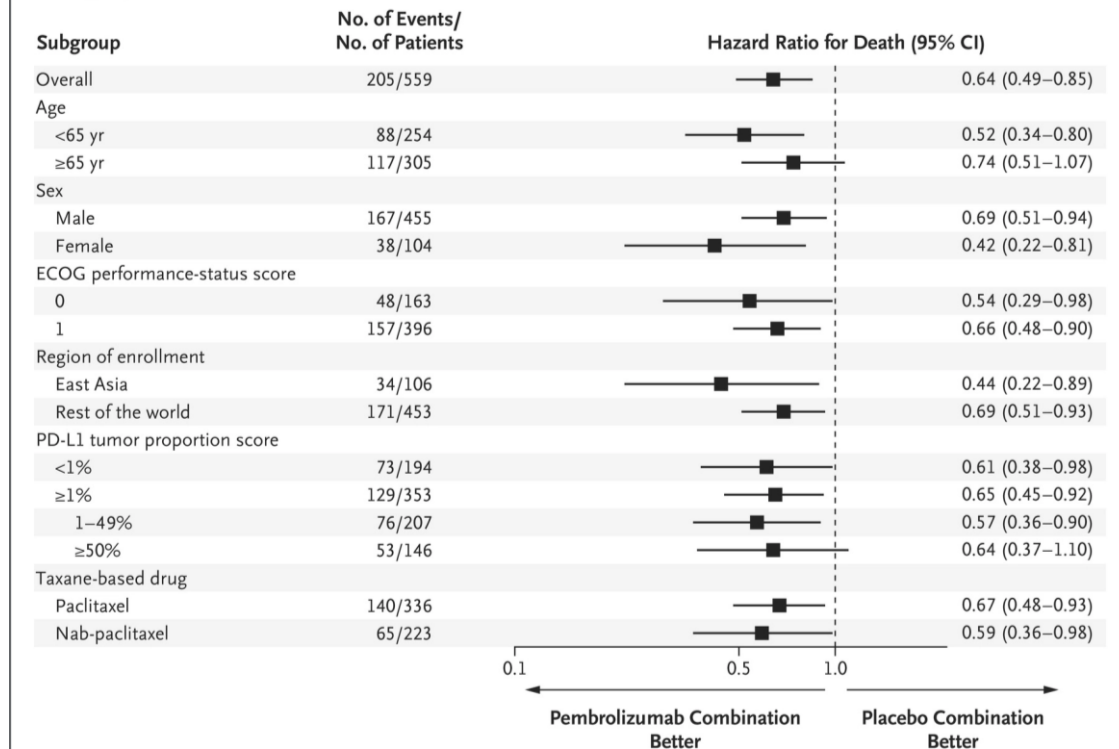
**A Overall Survival**



**No. at Risk**

|                           |     |     |     |     |    |    |   |   |
|---------------------------|-----|-----|-----|-----|----|----|---|---|
| Pembrolizumab combination | 278 | 256 | 188 | 124 | 62 | 17 | 2 | 0 |
| Placebo combination       | 281 | 246 | 175 | 93  | 45 | 16 | 4 | 0 |

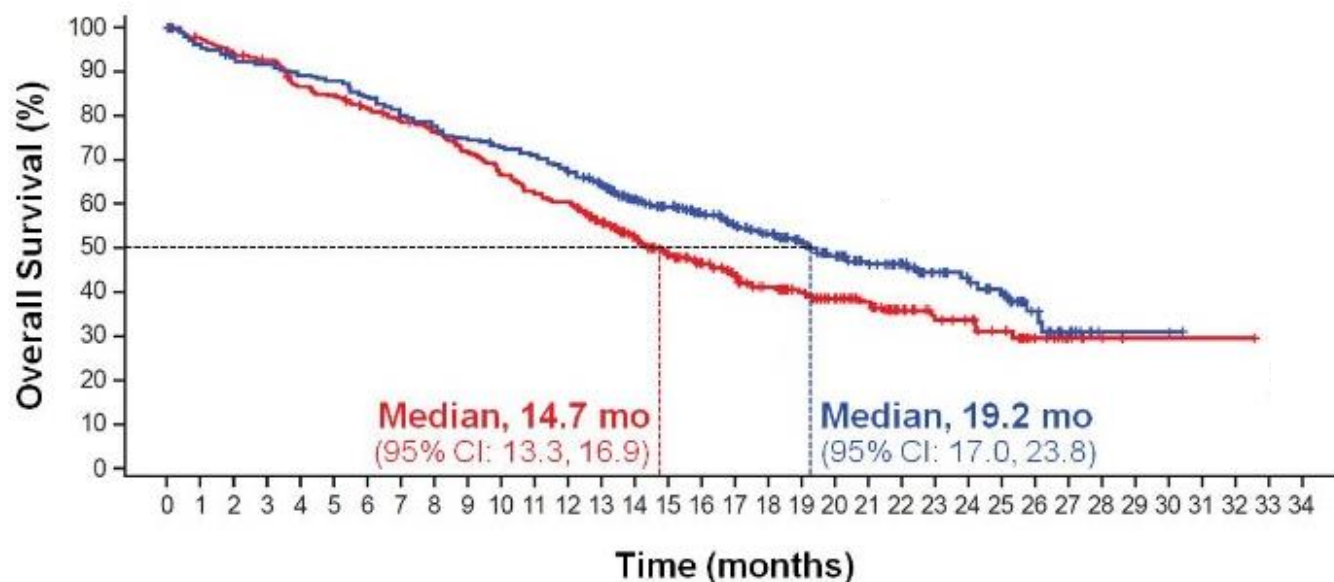
**B Subgroup Analysis of Overall Survival**



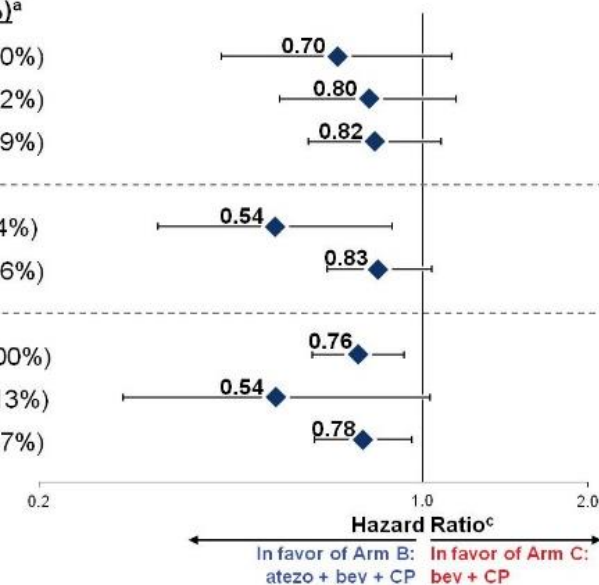
# IMpower150: Atezolizumab/Carboplatin/ Paclitaxel/Bevacizumab vs Carboplatin/ Paclitaxel/ Bevacizumab in Advanced Non-Squamous NSCLC

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

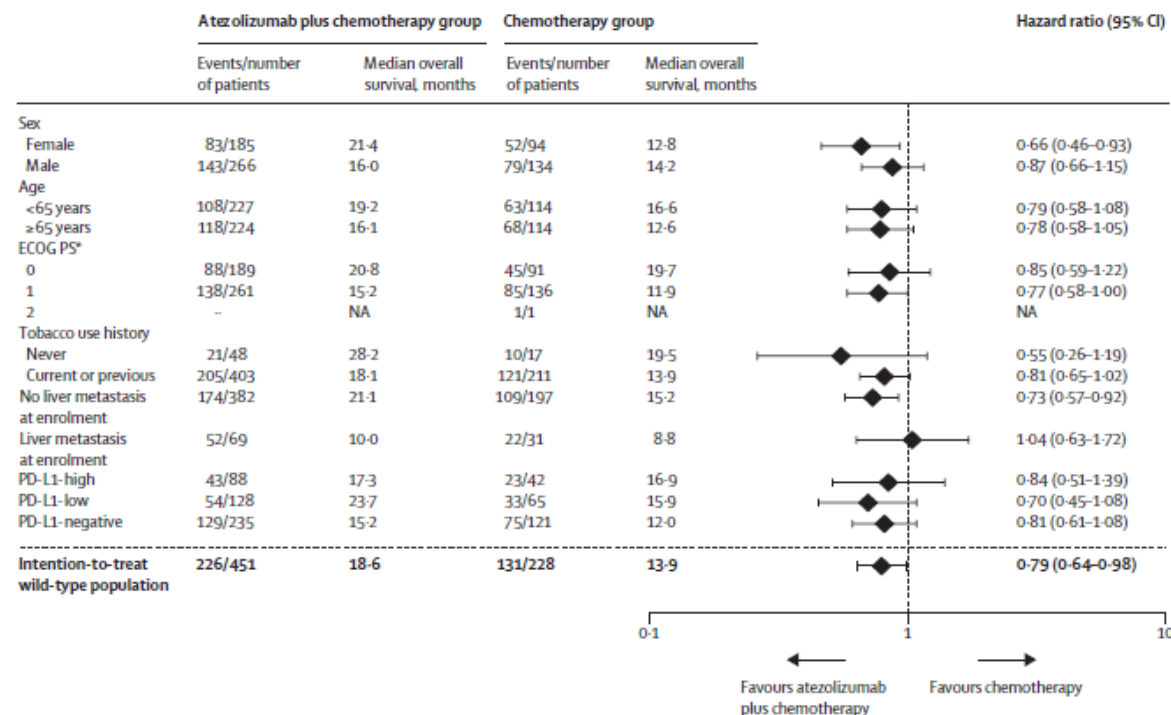
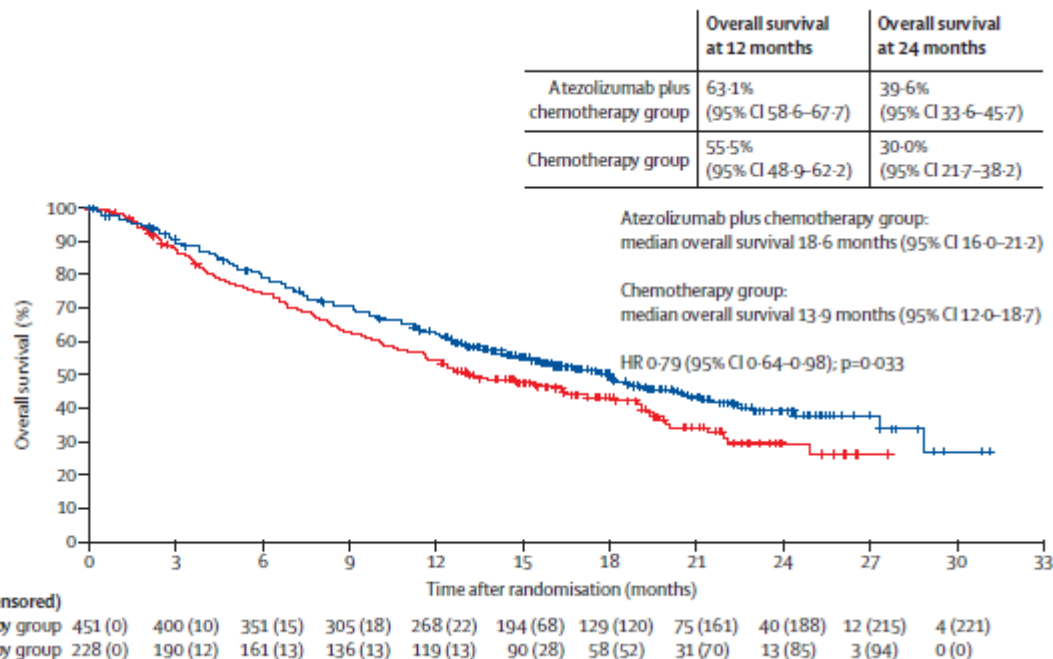
**HR<sup>a</sup>, 0.78**  
(95% CI: 0.64, 0.96)  
**P = 0.0164**  
Median follow-up: ~20 mo



| 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%)              |



# IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC



# 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 ≥ 1%</b>                                 | 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 |

# Second-line use of ICIs in NSCLC

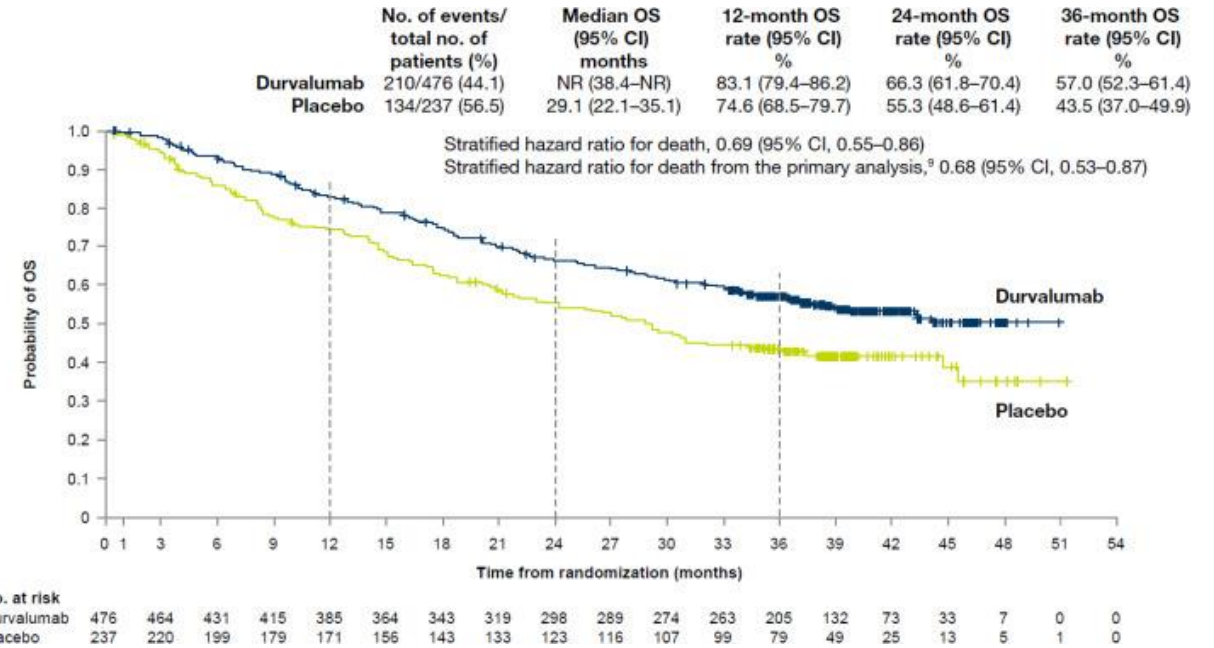
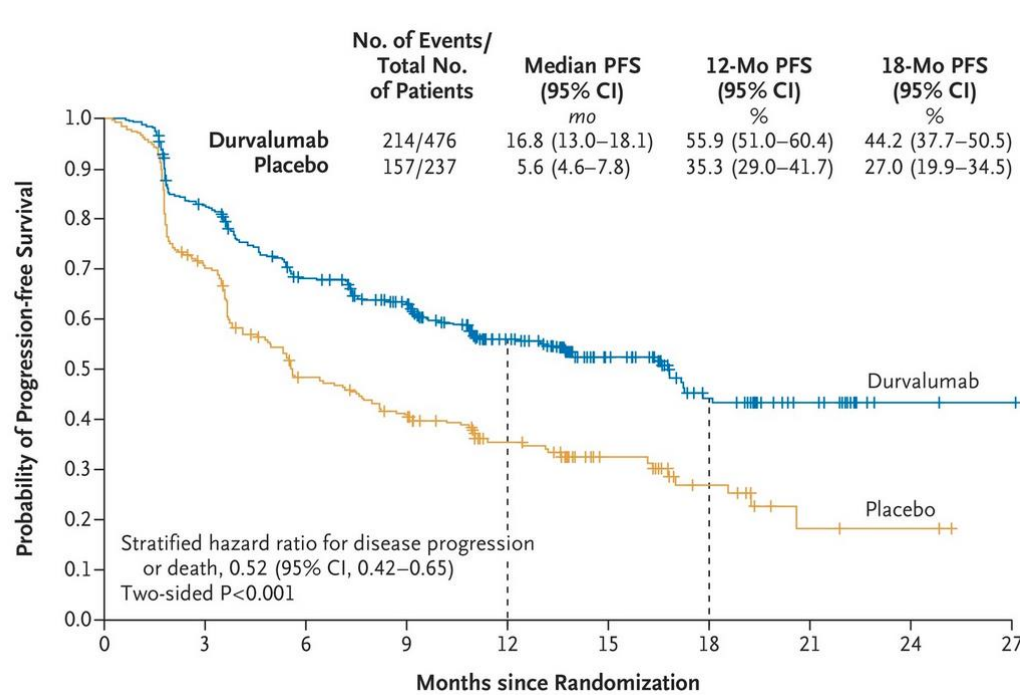
| Study                           | Treatment arms | ORR | Median PFS (months) | Median OS (months) |
|---------------------------------|----------------|-----|---------------------|--------------------|
| CheckMate 017 and CheckMate 057 | Nivolumab      | 19% | 2.56                | 11.1               |
|                                 | Docetaxel      | 11% | 3.52                | 8.1                |
| KEYNOTE-010 (PD-L1 TPS ≥ 1%)    | Pembrolizumab  | 18% | 4.0                 | 12.7               |
|                                 | Docetaxel      | 9%  | 4.0                 | 8.5                |
| OAK                             | Atezolizumab   | 14% | 2.8                 | 13.8               |
|                                 | Docetaxel      | 13% | 4.0                 | 9.6                |

Vokes, Ann Oncol 2018.  
 Herbst, Lancet 2016.  
 Fehrenbacher, J Thorac Oncol 2018.

# Immunotherapy for stage III NSCLC

| Drug          | Indication                                                                                                                 | Dose                     |
|---------------|----------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Durvalumab    | Stage III NSCLC, ineligible for surgery and without progression after chemoradiation                                       | 10 mg/kg Q2W             |
| Pembrolizumab | 1 <sup>st</sup> line stage III NSCLC (not candidate for resection or definitive chemoradiation) with <b>PD-L1 TPS ≥ 1%</b> | 200 mg Q3W or 400 mg Q6W |

# PACIFIC: durvalumab consolidation therapy for stage III NSCLC



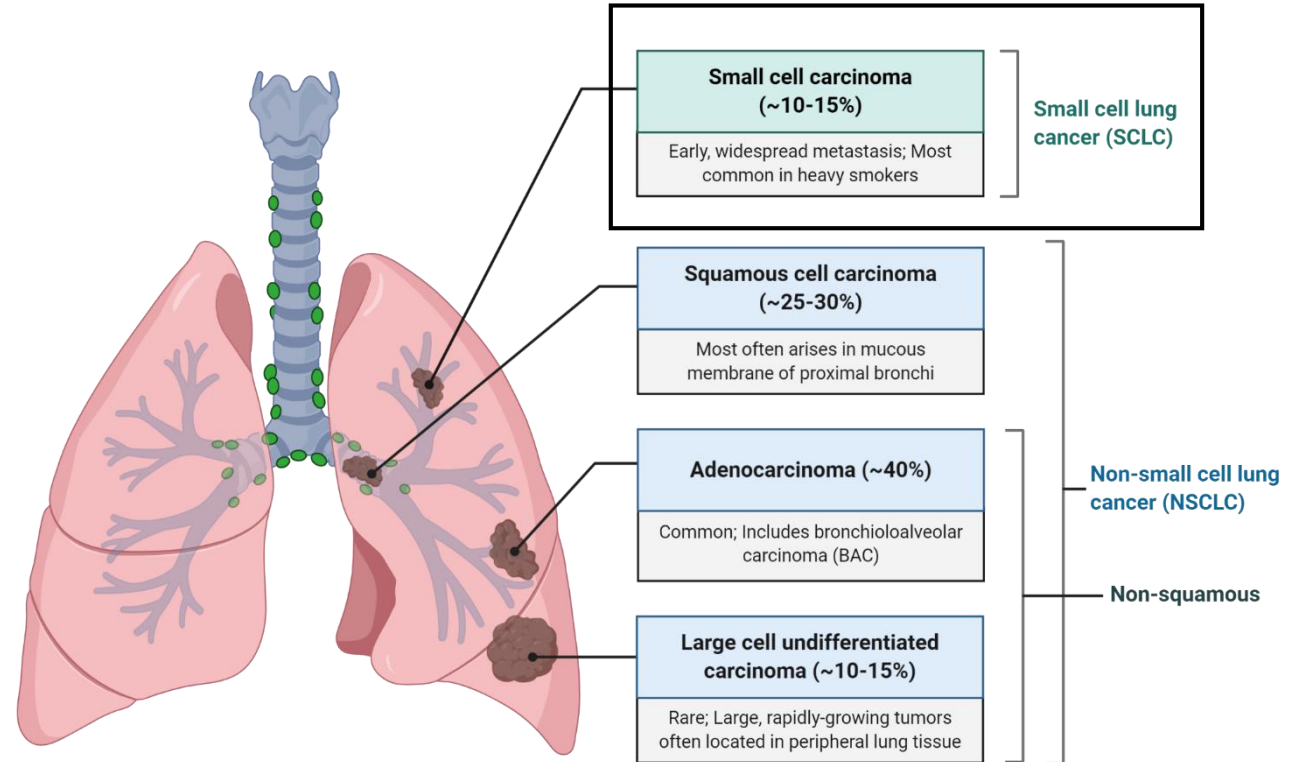
Antonia, N Engl J Med 2017.  
Gray, J Thorac Oncol 2020.

# Outline

- Non-small cell lung cancer
  - Front-line – PD-L1-selected and unselected
  - Later lines of treatment
  - Stage III
- Small cell lung cancer
- Future directions for lung cancer immunotherapy

# Small cell lung cancer

- 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

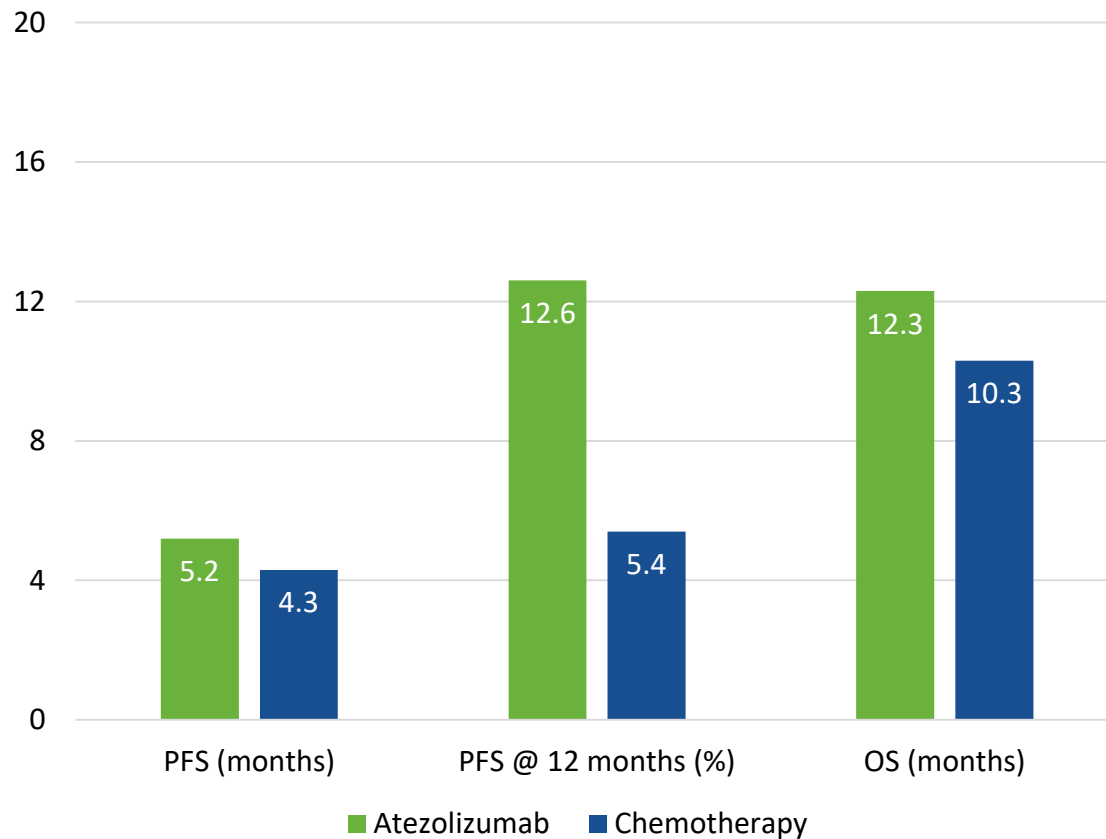


# Approved checkpoint inhibitors in SCLC

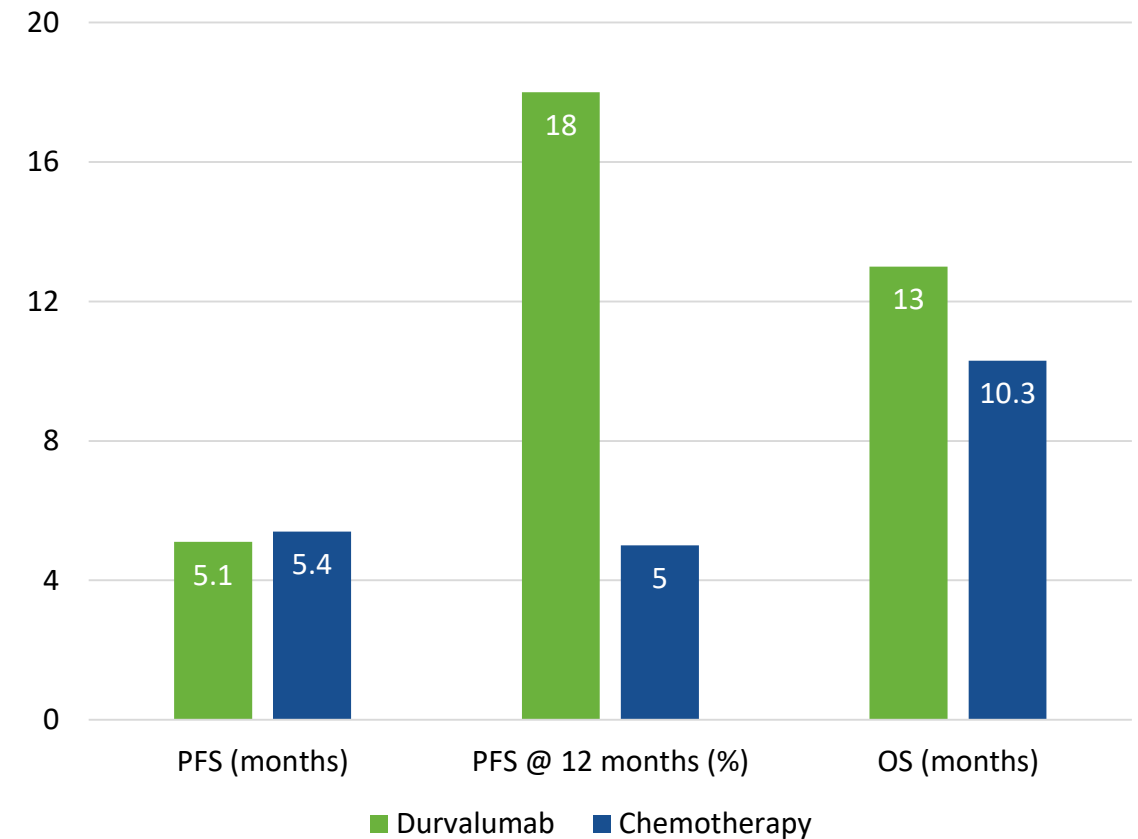
| Drug                                                  | Indication                                      | Dose                                                                                                                     |
|-------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| <b>Atezolizumab + carboplatin + etoposide</b>         | <b>1<sup>st</sup> line</b> extensive stage SCLC | For 4 cycles: atezolizumab 1200 mg + carboplatin + etoposide Q3W<br>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                                 |

# Front-line ICI in SCLC

IMpower133



CASPIAN



# Outline

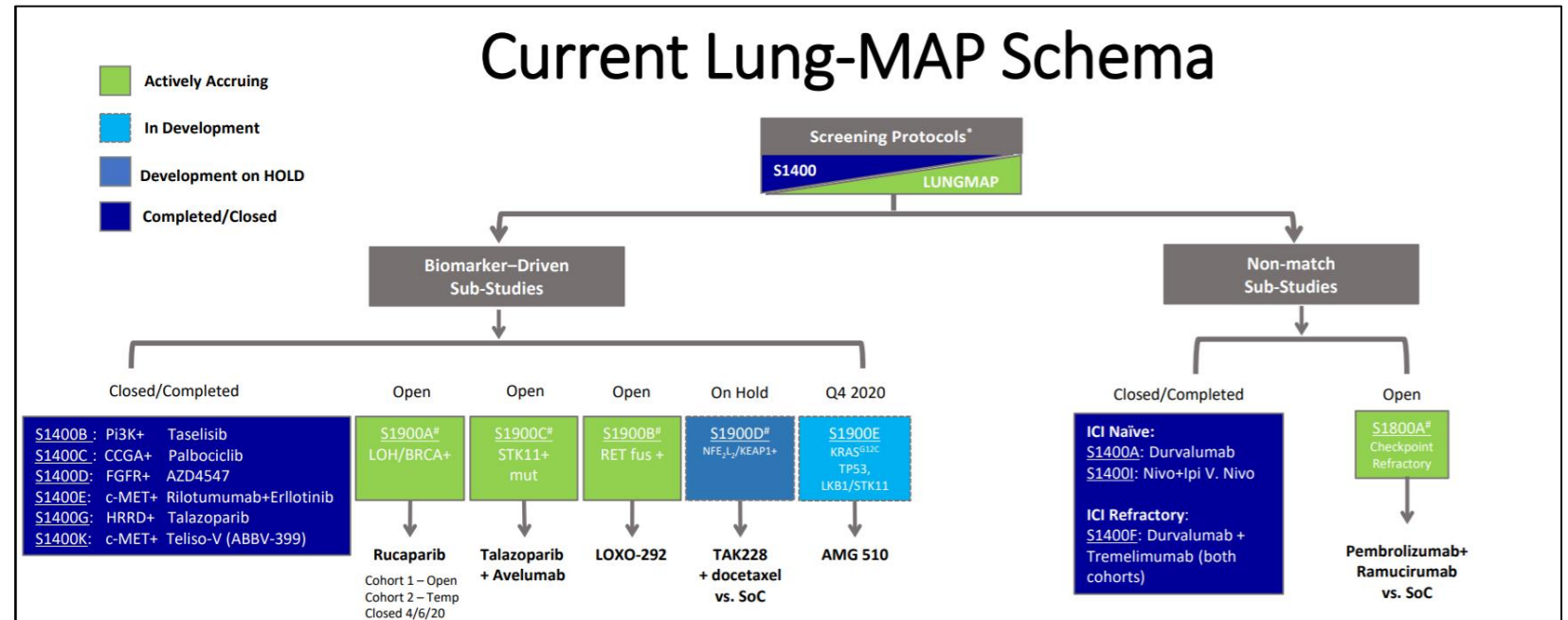
- Non-small cell lung cancer
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# In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities

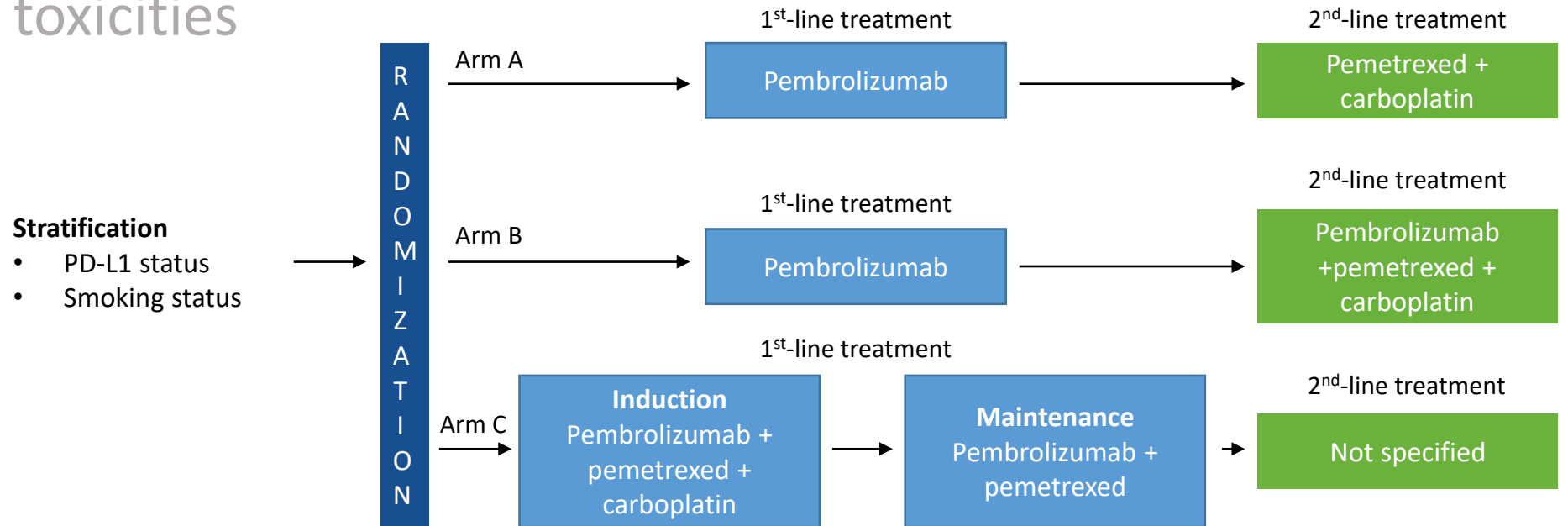
# In development: answering outstanding questions

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# In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
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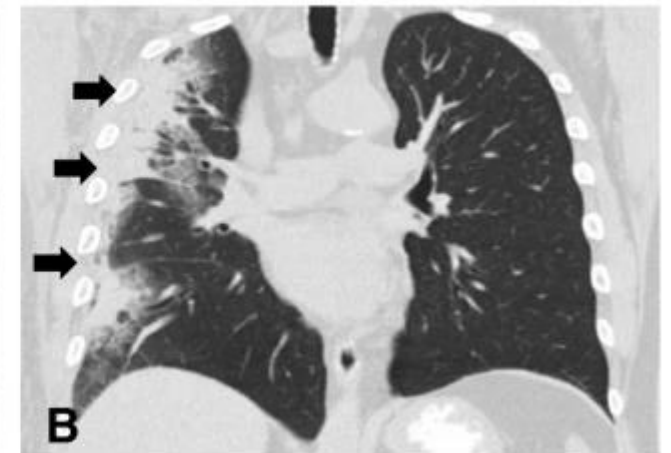
# In development: answering outstanding questions

- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities – radiation and ICIs



Axillary radiation treatment field from September-October 2017 demonstrating overlap with peripheral lung.

Chest CT performed 5 months after completing right axillary radiotherapy (March 2018) and 1.5 months after initiating nivolumab therapy



# 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

# Conclusions

- NSCLC has been a proving ground for checkpoint inhibitors
- Many front-line options available for NSCLC
- Clear-cut biomarkers still lacking
- SCLC and mesothelioma are beginning to benefit from immune checkpoint inhibitor treatments

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**

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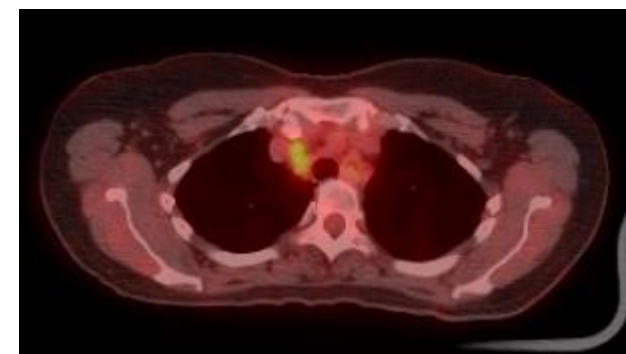
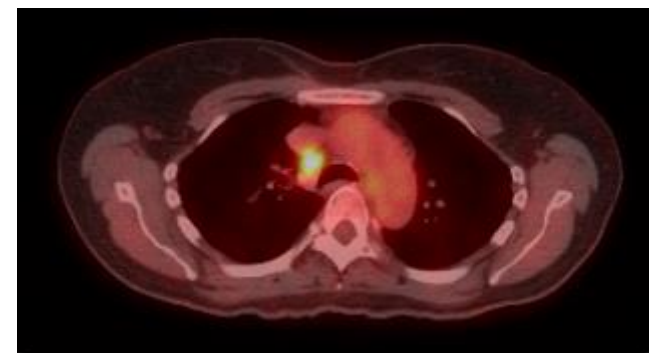
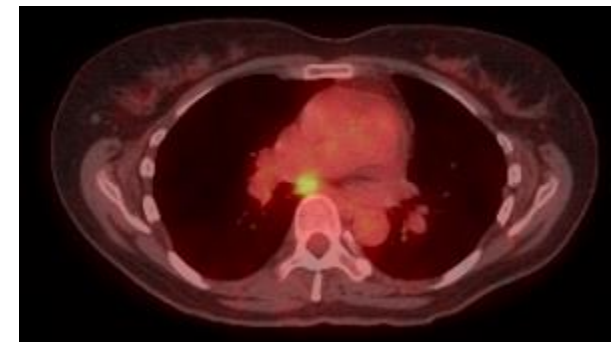
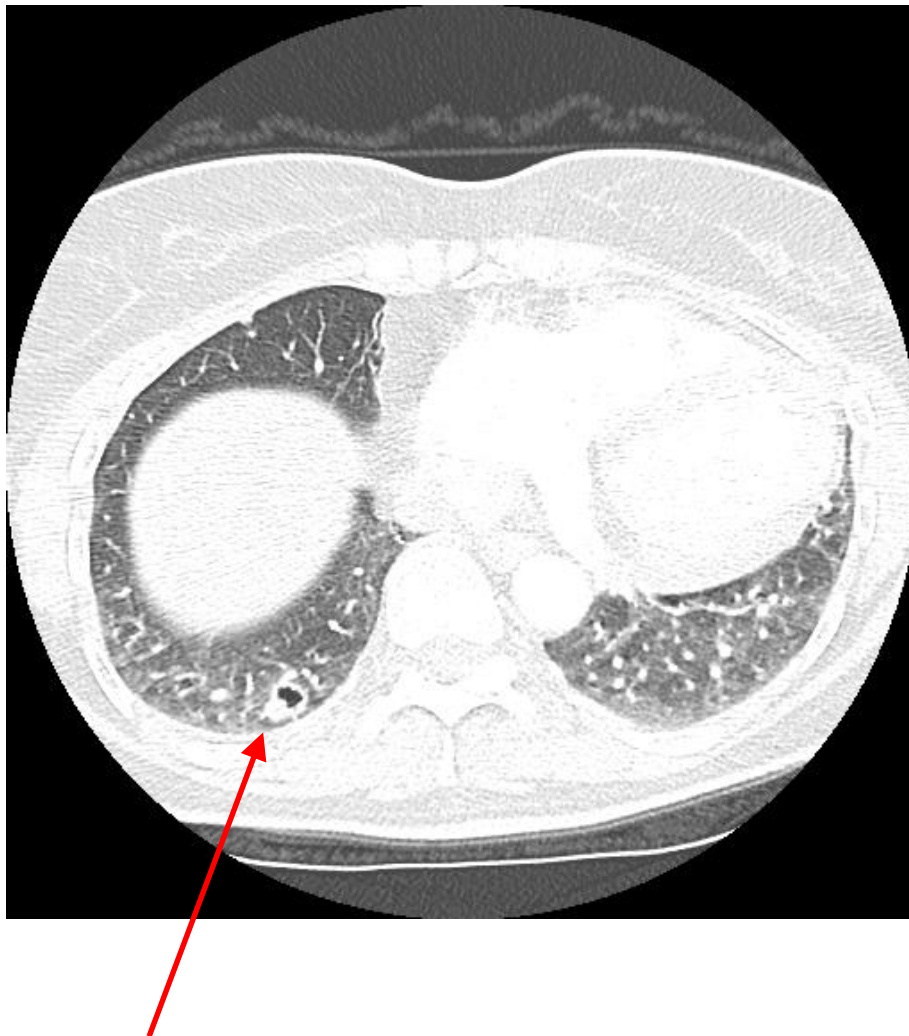
## The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC)

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

- 58 y.o. woman, new pulmonary embolism, no smoking history
- CT: Small cavitary right lower lobe nodule
- PET: Multi-station node uptake, no metastatic disease (MRI Brain negative)
- EBUS: Pathologic confirmation adenocarcinoma
- (No driver mutation; PD-L1: 10%)
- Stage IIIA, T1AN2M0

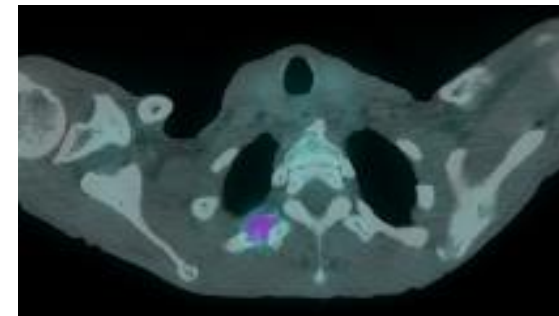
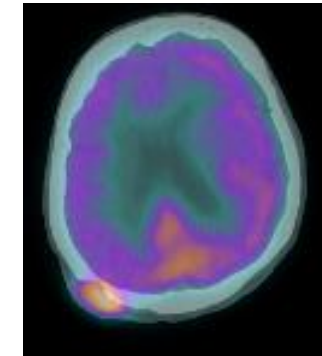
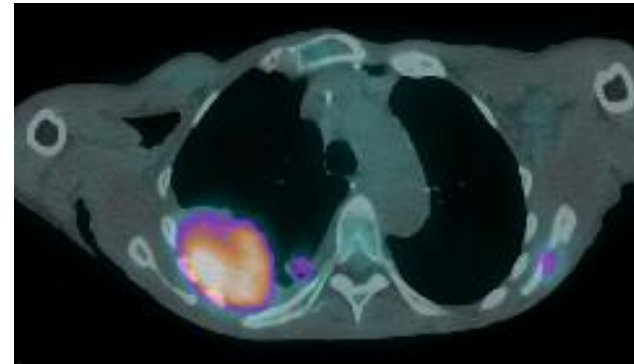
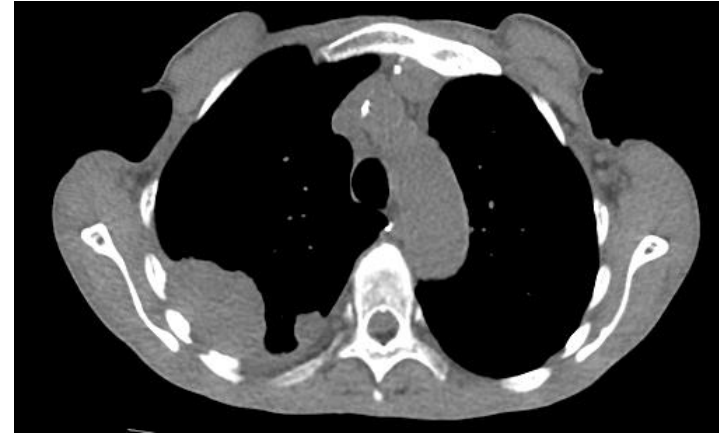


# Case Study 1—Stage IIIA NSCLC

- What treatment options?
- A. Definitive chemoradiation
- B. Definitive chemoradiation, then consolidation immunotherapy
- C. Chemotherapy and immunotherapy in combination

## Case Study 2

- 62 y.o. woman, prior tobacco abuse, follow up after pneumonia
- CT Chest: Multiple pleural-based masses
- CT-guided biopsy: Squamous cell carcinoma
- PET: Lung and pleural mass uptake, mediastinal nodes, multiple bone mets
- Stage: IVB (T3N2M1C)
- No activating mutation
- PD-L1: 10%



# Case Study 2—Stage IVB Squamous

- What treatment options?
  - A. Pembrolizumab alone
  - B. Pembrolizumab + Chemotherapy
  - C. Nivolumab/Ipilimumab +/- Chemotherapy
  - D. Any of the above

## Case Study 2, Follow Up

- This case predated Option C (Nivo/Ipi or Nivo/Ipi/Chemo)
- We chose Chemo/Pembrolizumab
- Now Cycle 35 Pembro
- (After completion 4 cycles Chemo/Pembro)
- Bone mets have sclerosed
- Patient reports good quality of life



# Questions