Society for Immunotherapy of Cancer

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# 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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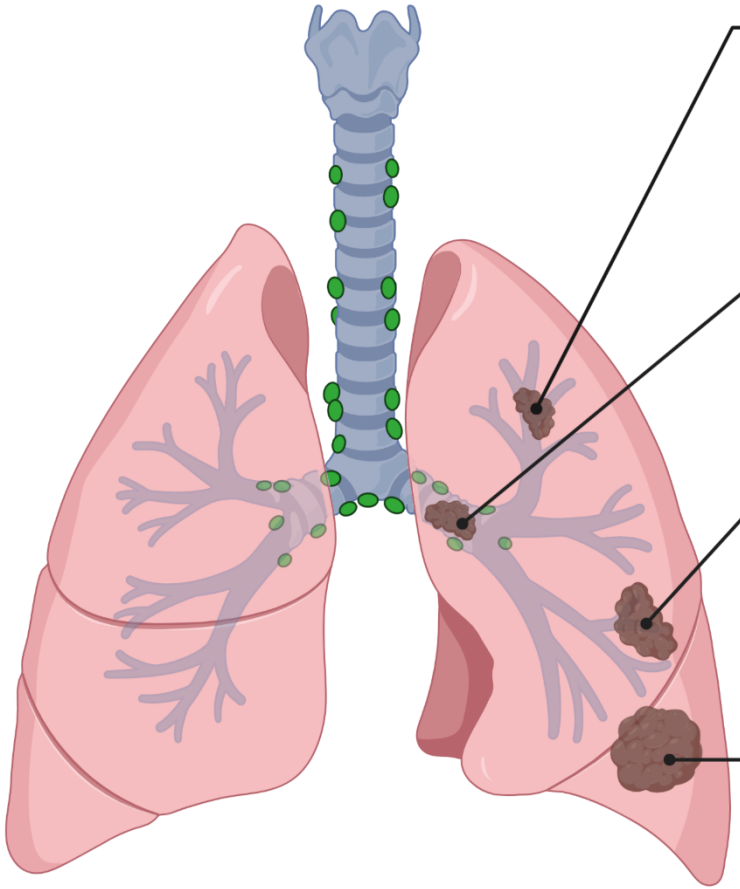
# Disclosures

- Consulting Fees: AstraZeneca, G1 Therapeutics
- I will be discussing non-FDA approved indications during my presentation.

# Lung cancer



**Small cell carcinoma (~10-15%)**
Early, widespread metastasis; Most common in heavy smokers

**Small cell lung cancer (SCLC)**

**Squamous cell carcinoma (~25-30%)**
Most often arises in mucous membrane of proximal bronchi

**Adenocarcinoma (~40%)**
Common; Characterized by growth patterns

**Large cell undifferentiated carcinoma (~10-15%)**
Rare; Large, rapidly-growing tumors often located in peripheral lung tissue

**Non-small cell lung cancer (NSCLC)**

**Non-squamous**

# Treatment options for NSCLC

**Local disease**

- Surgery
- Stereotactic body radiation therapy
- Chemotherapy

**Metastatic disease**

- Chemotherapy
- Targeted therapies
- Immunotherapy
- Radiation therapy

**Stage III unresectable disease**

- Concurrent chemo-radiation
- Consolidation immunotherapy

# 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$^2$ 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 |

Mancheril, Hosp Pharm 2014.

# Immune checkpoint inhibitors in lung cancer

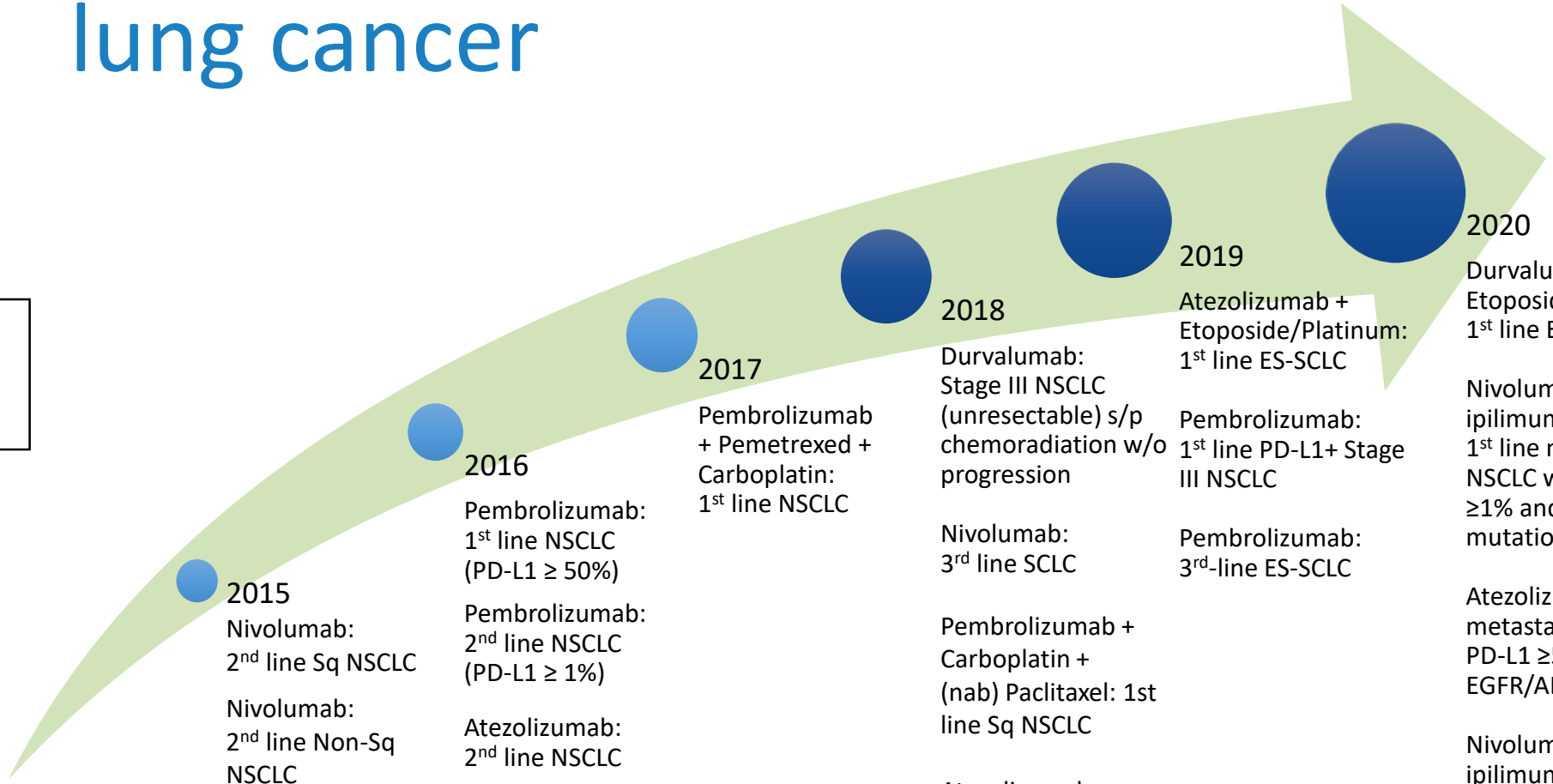
**Nivolumab**
**PD-1**

**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

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# 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

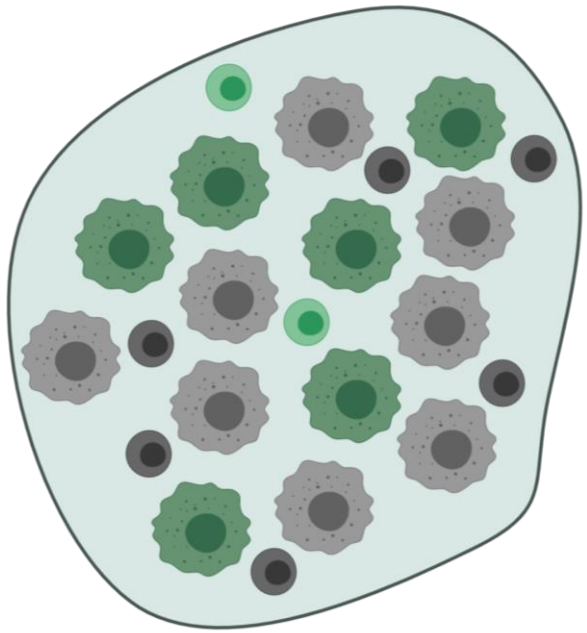
# Immunotherapy for first-line treatment of metastatic NSCLC

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

# Brief aside: PD-L1 TPS vs CPS

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

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



PD-L1-positive immune cell

PD-L1-negative immune cell

PD-L1-positive tumor cell

PD-L1-negative tumor cell

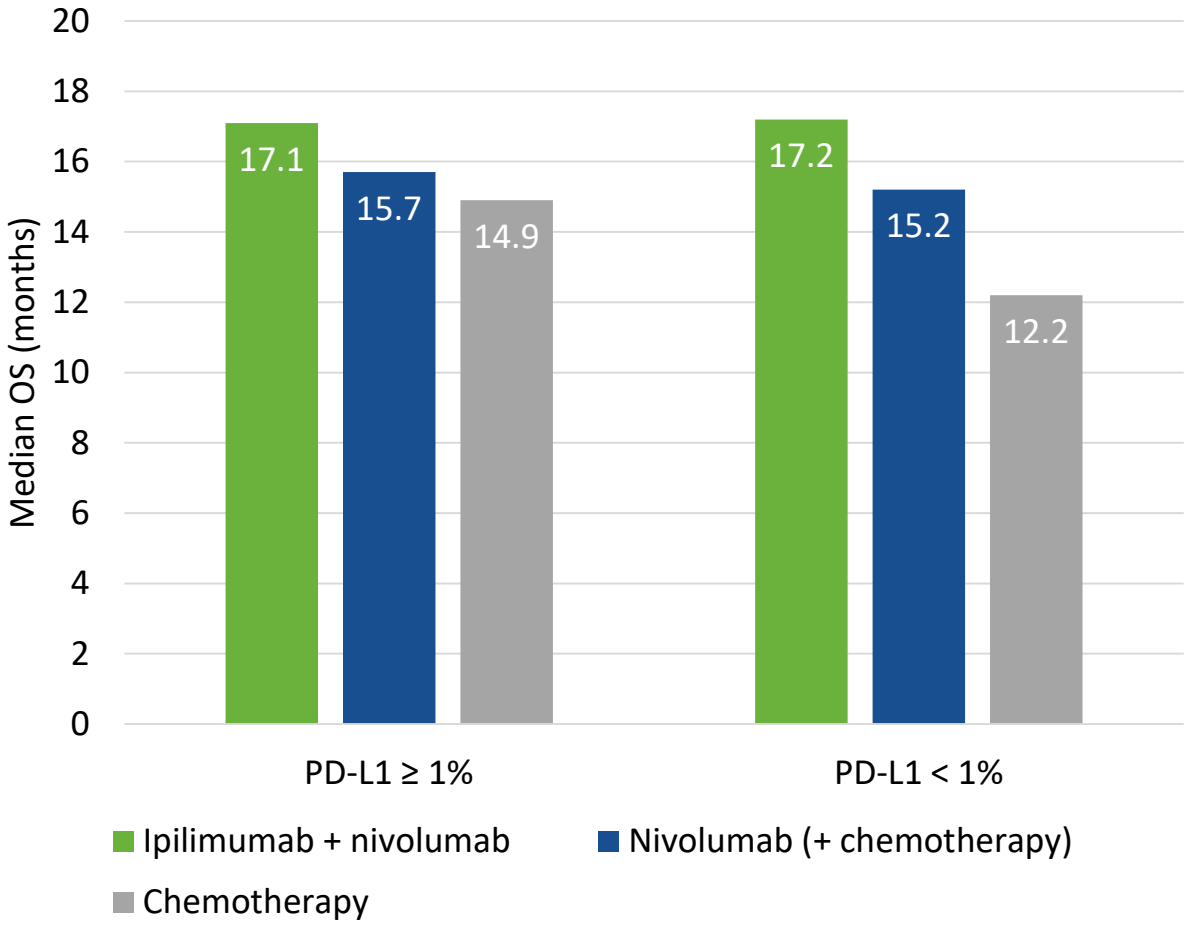
$$TPS = \frac{6\ positive\ tumor\ cells}{14\ total\ tumor\ cells} \times 100 = 43$$

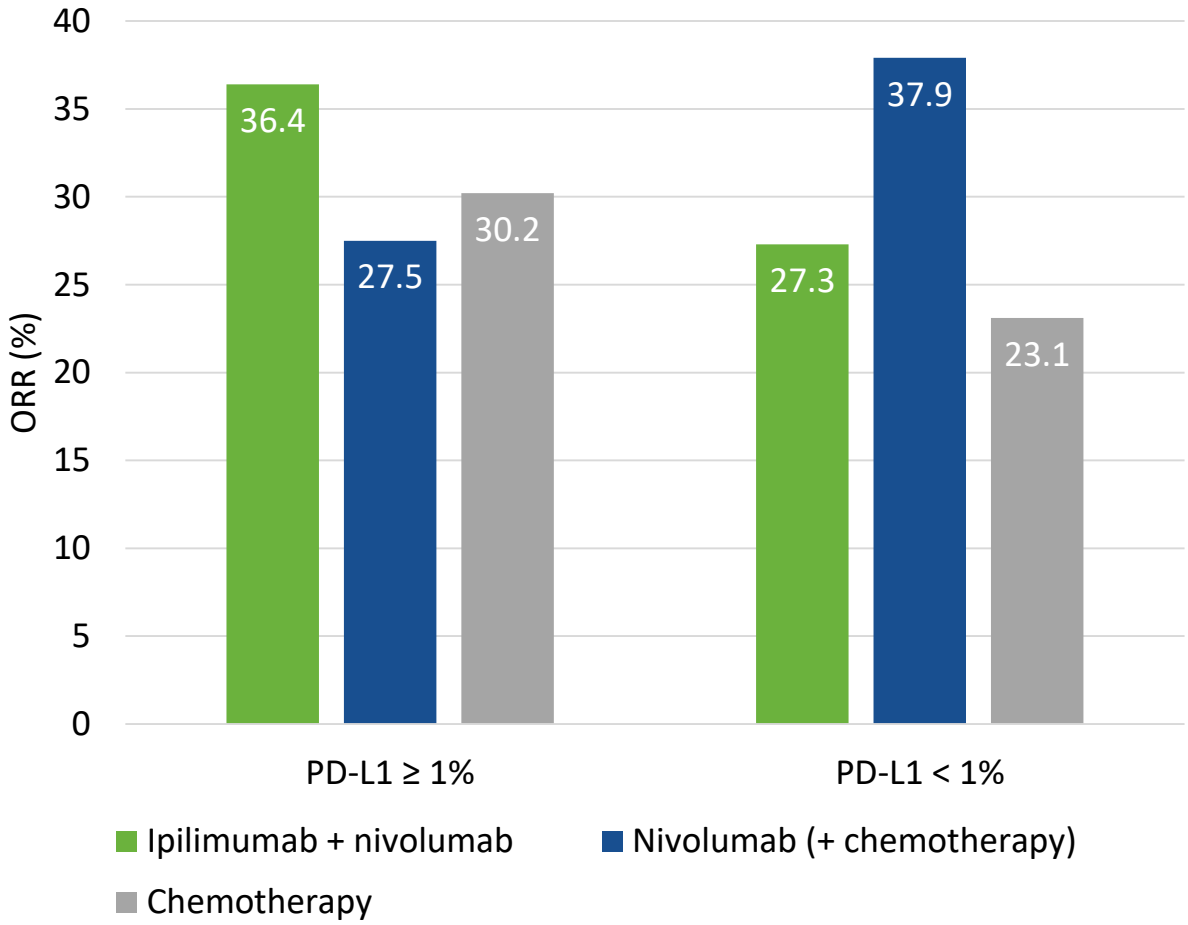
$$CPS = \frac{6\ positive\ tumor\ cells + 2\ positive\ immune\ cells}{22\ total\ cells} \times 100 = 36$$

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

| PD-L1-selected | PD-L1-unselected |
|---|---|
| Nivolumab + ipilimumab<br>*CheckMate 227* | Nivolumab + ipilimumab + platinum-doublet<br>*CheckMate 9LA* |
| Pembrolizumab<br>*KEYNOTE-024, -042* | Pembrolizumab + chemotherapy<br>*KEYNOTE-189, -407* |
| Atezolizumab<br>*IMpower110* | Atezolizumab + bevacizumab + chemotherapy<br>*IMpower150* |
| | Atezolizumab + chemotherapy<br>*Impower130* |

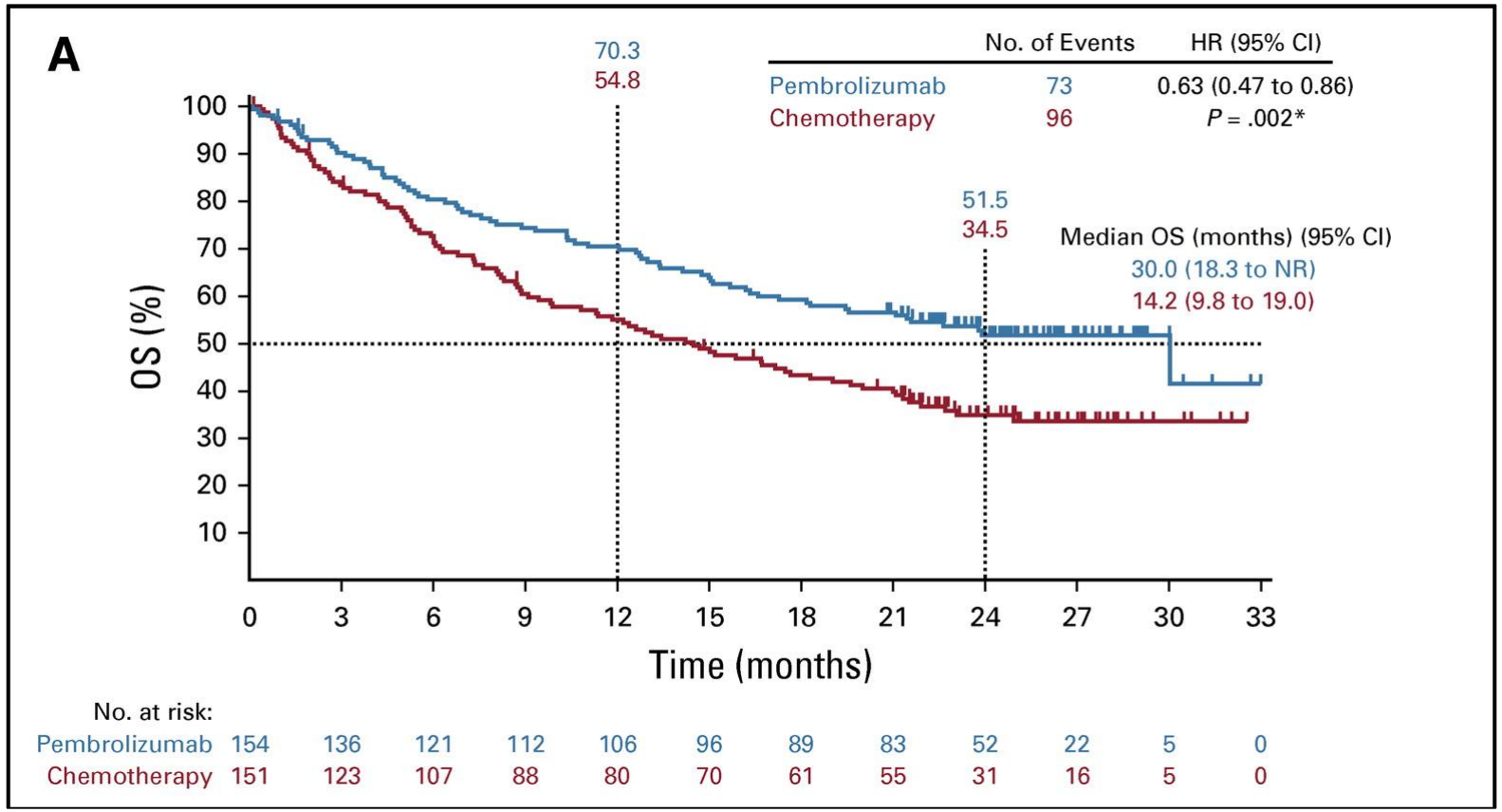
# CheckMate 227: Ipilimumab + nivolumab vs chemotherapy for 1L NSCLC




Ramalingam, ASCO 2020.

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




Reck, J Clin Oncol 2019.

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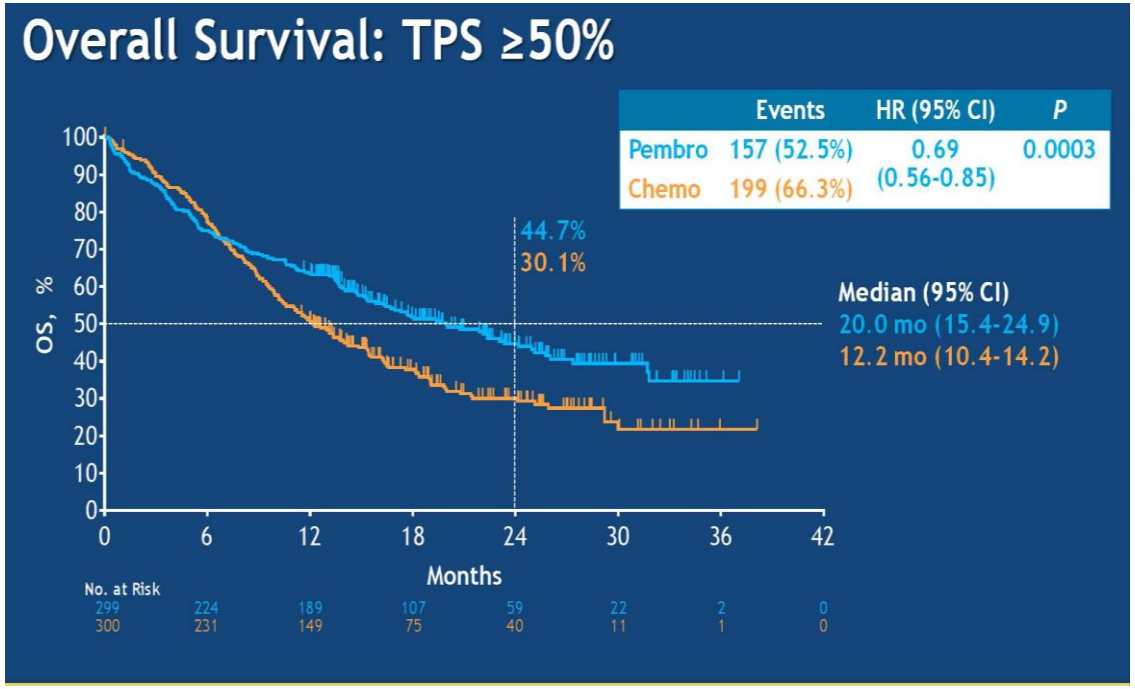
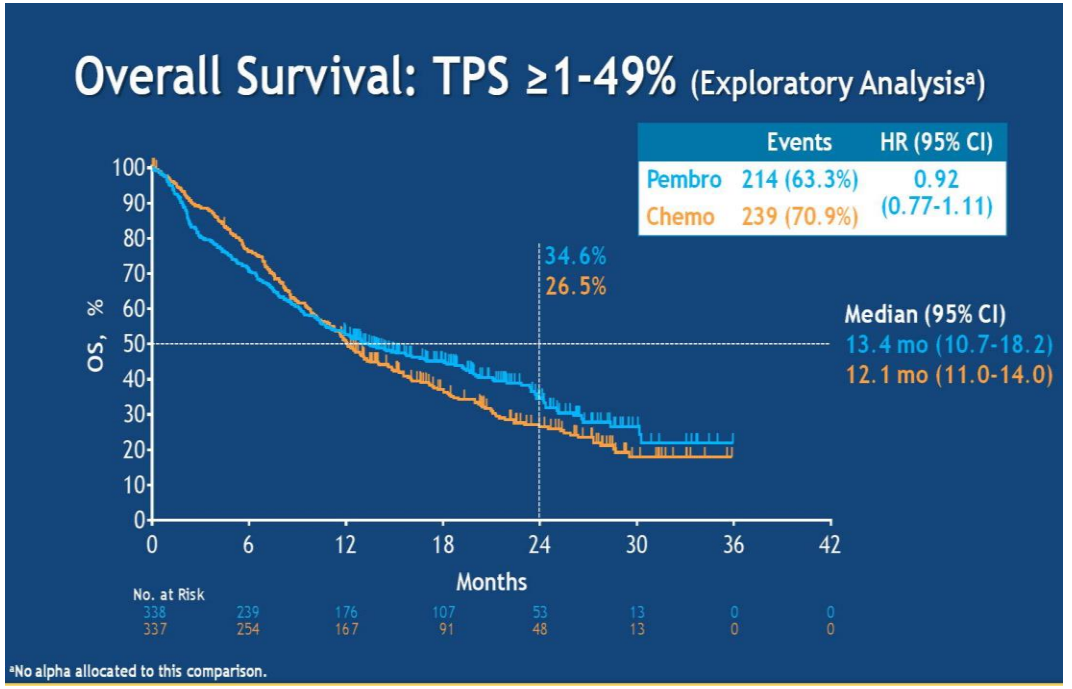
# KEYNOTE-042: Pembrolizumab vs. Chemotherapy for PD-L1 ≥ 1% NSCLC



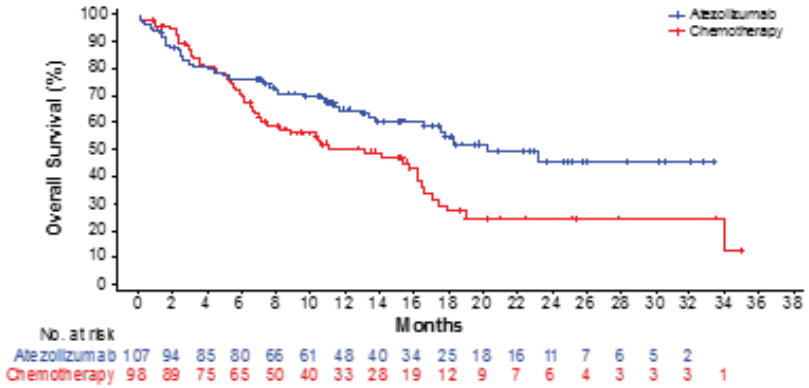




Survival benefit seemed to be driven by the TPS ≥ 50% subset with little benefit witnessed in the subset TPS = 1 - 49%

Lopes et al, ASCO 2018

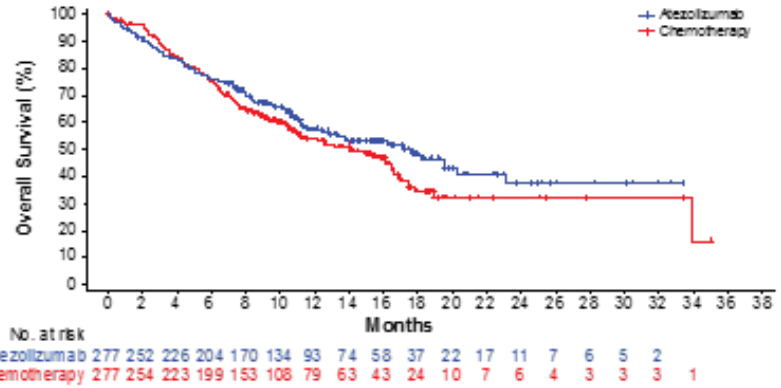
# IMpower110: Atezolizumab vs chemotherapy in 1L NSCLC

## 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]



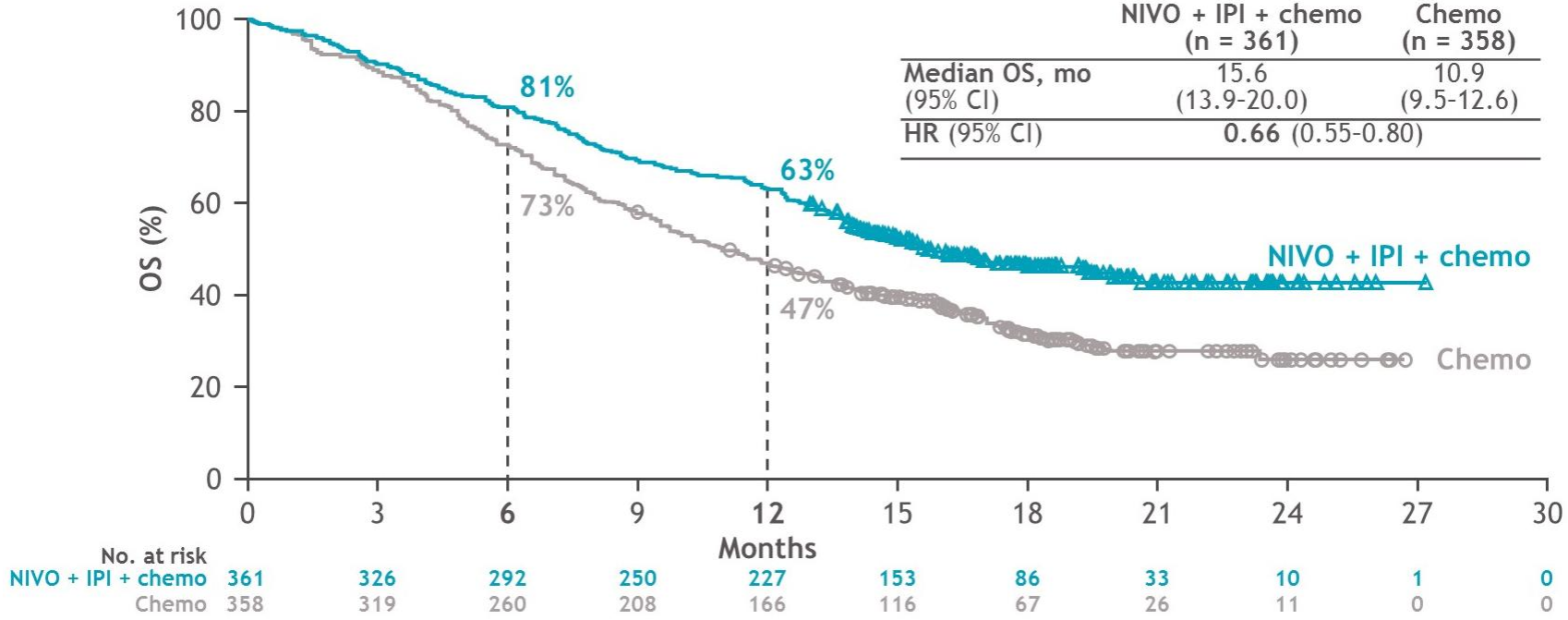

| | Atezo (n = 277) | Chemo (n = 277) |
|---|---|---|
| mOS, mo | 17.5 | 14.1 |
| HR[b] (95% CI) | 0.83 (0.65, 1.07) | |

| | |
|---|---|
| **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% |

Herbst, ESMO-IO 2019.

# Treatments not reliant on PD-L1 expression

# CheckMate 9LA: Nivolumab/Ipilimumab + limited chemo

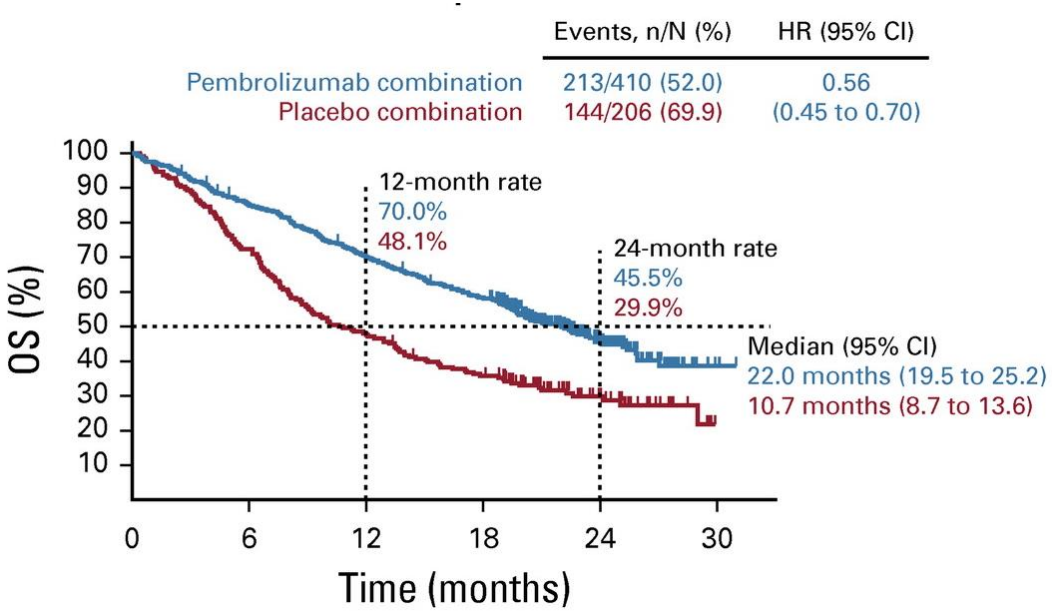


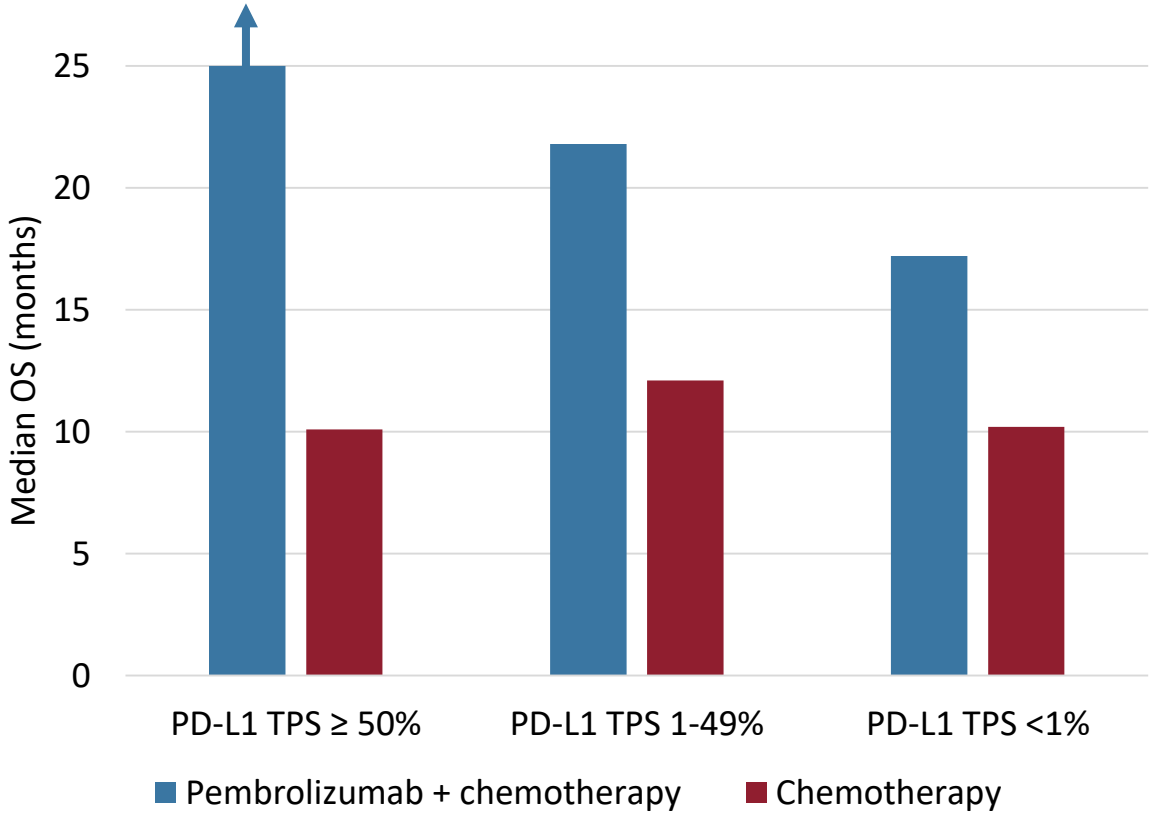

| | NIVO + IPI + chemo (n = 361) | Chemo (n = 358) |
|---|---|---|
| Median OS, mo (95% CI) | 15.6 (13.9-20.0) | 10.9 (9.5-12.6) |
| HR (95% CI) | 0.66 (0.55-0.80) | |

| | 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.

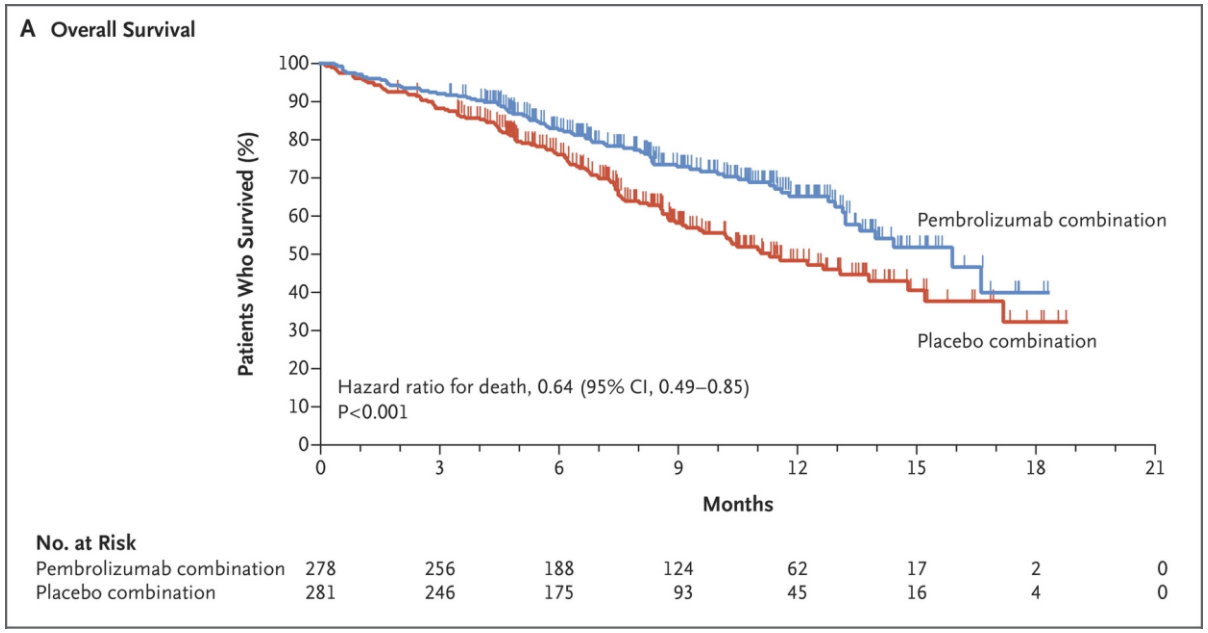
# KEYNOTE-189: Pembrolizumab/chemotherapy vs Chemotherapy Alone for Advanced Non-Squamous NSCLC

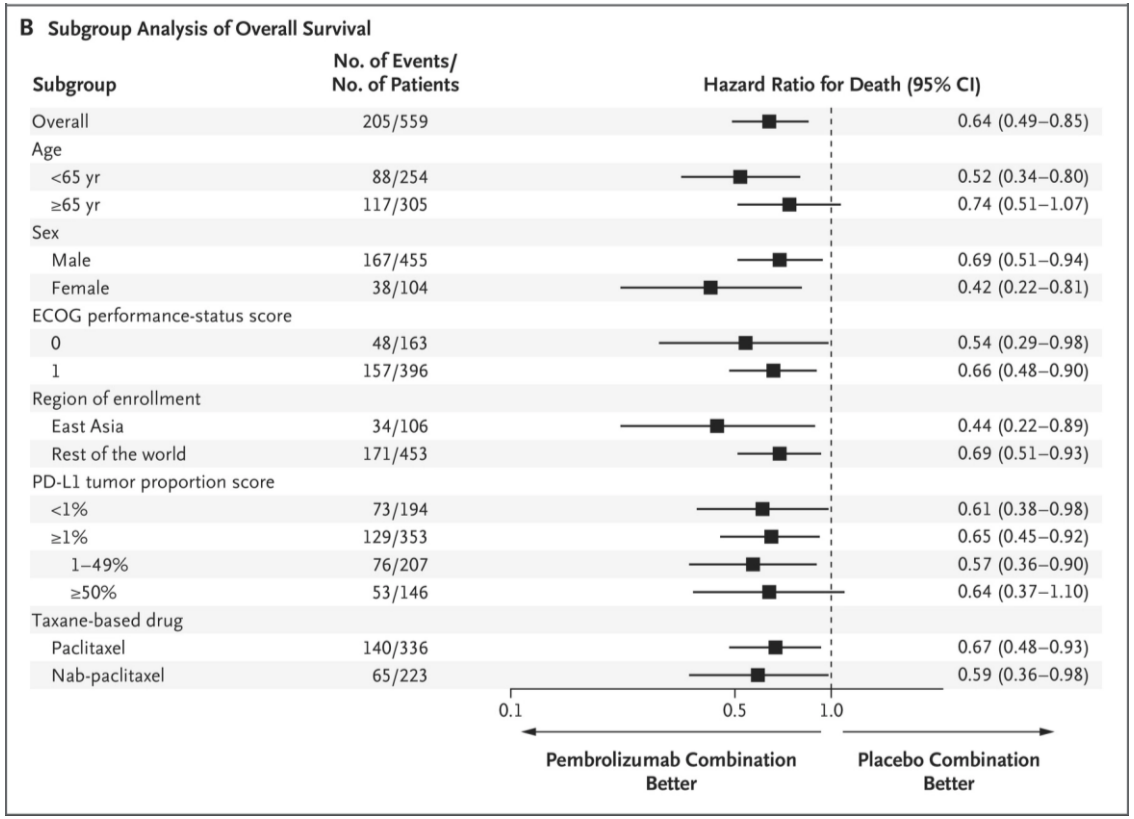



Gadgeel, J Clin Oncol 2020.

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



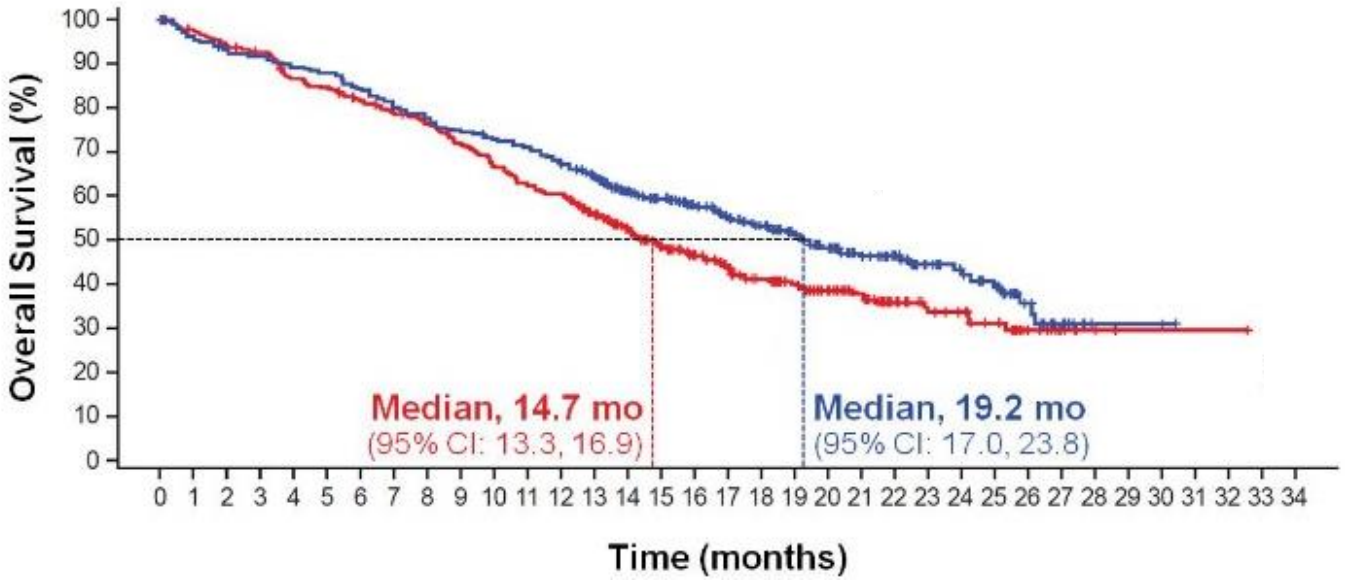



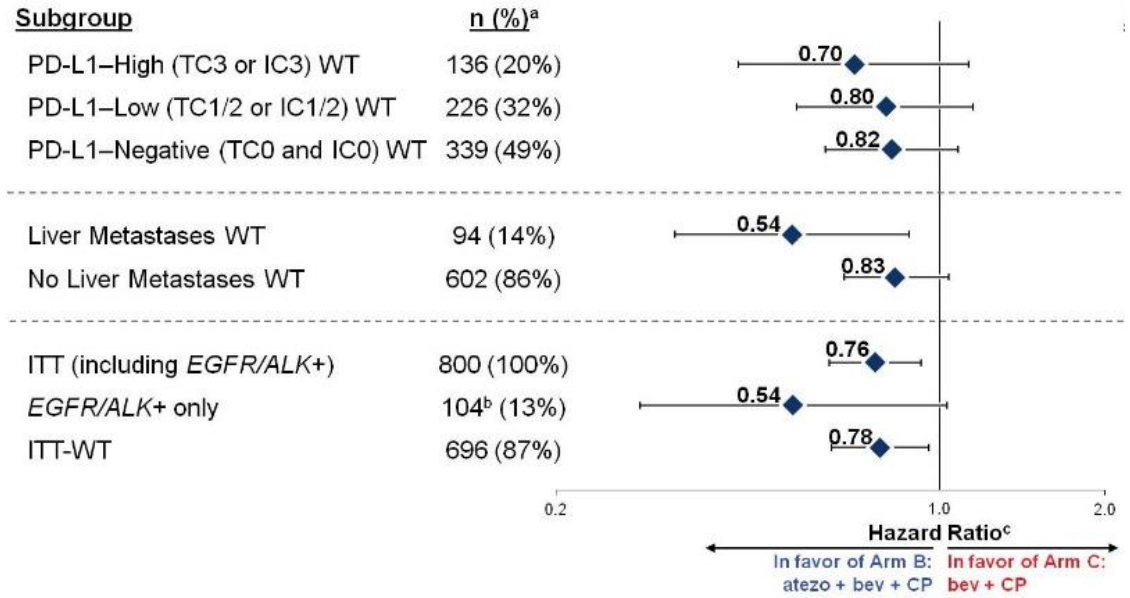

Paz-Ares et al, N Engl J Med 2018.

# IMpower150: 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

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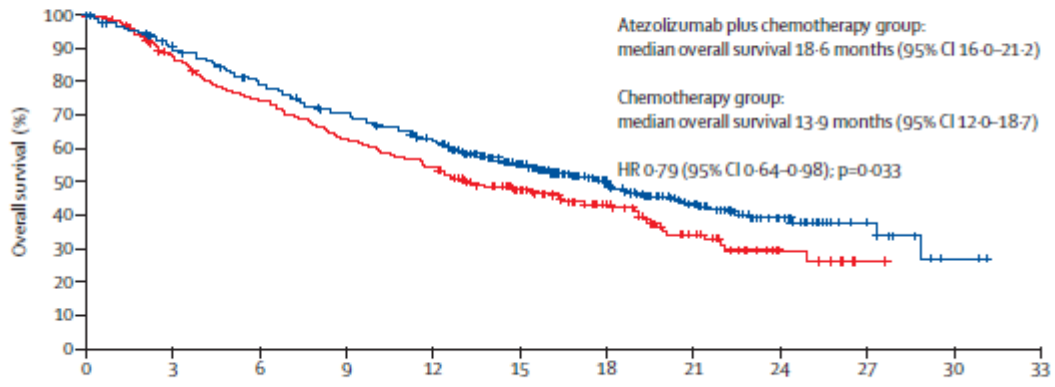
# IMpower130: Atezolizumab + chemo vs chemo alone for non-squamous NSCLC

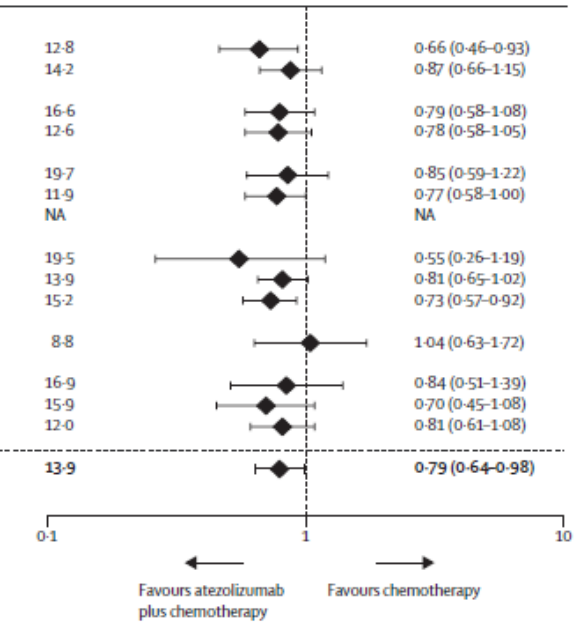
| | Overall survival at 12 months | Overall survival at 24 months |
|---|---|---|
| Atezolizumab plus chemotherapy group | 63·1% (95% CI 58·6–67·7) | 39·6% (95% CI 33·6–45·7) |
| Chemotherapy group | 55·5% (95% CI 48·9–62·2) | 30·0% (95% CI 21·7–38·2) |




**Number at risk (number censored)**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab plus chemotherapy group | 451 (0) | 400 (10) | 351 (15) | 305 (18) | 268 (22) | 194 (68) | 129 (120) | 75 (161) | 40 (188) | 12 (215) | 4 (221) |
| Chemotherapy group | 228 (0) | 190 (12) | 161 (13) | 136 (13) | 119 (13) | 90 (28) | 58 (52) | 31 (70) | 13 (85) | 3 (94) | 0 (0) |

| | Atezolizumab plus chemotherapy group | | Chemotherapy group | | Hazard ratio (95% CI) |
|---|---|---|---|---|---|
| | Events/number of patients | Median overall survival, months | Events/number of patients | Median overall survival, months | |
| Sex | | | | | |
| Female | 83/185 | 21·4 | 52/94 | 12·8 | 0·66 (0·46–0·93) |
| Male | 143/266 | 16·0 | 79/134 | 14·2 | 0·87 (0·66–1·15) |
| Age | | | | | |
| <65 years | 108/227 | 19·2 | 63/114 | 16·6 | 0·79 (0·58–1·08) |
| ≥65 years | 118/224 | 16·1 | 68/114 | 12·6 | 0·78 (0·58–1·05) |
| ECOG PS* | | | | | |
| 0 | 88/189 | 20·8 | 45/91 | 19·7 | 0·85 (0·59–1·22) |
| 1 | 138/261 | 15·2 | 85/136 | 11·9 | 0·77 (0·58–1·00) |
| 2 | .. | NA | 1/1 | NA | NA |
| Tobacco use history | | | | | |
| Never | 21/48 | 28·2 | 10/17 | 19·5 | 0·55 (0·26–1·19) |
| Current or previous | 205/403 | 18·1 | 121/211 | 13·9 | 0·81 (0·65–1·02) |
| No liver metastasis at enrolment | 174/382 | 21·1 | 109/197 | 15·2 | 0·73 (0·57–0·92) |
| Liver metastasis at enrolment | 52/69 | 10·0 | 22/31 | 8·8 | 1·04 (0·63–1·72) |
| PD-L1-high | 43/88 | 17·3 | 23/42 | 16·9 | 0·84 (0·51–1·39) |
| PD-L1-low | 54/128 | 23·7 | 33/65 | 15·9 | 0·70 (0·45–1·08) |
| PD-L1-negative | 129/235 | 15·2 | 75/121 | 12·0 | 0·81 (0·61–1·08) |
| **Intention-to-treat wild-type population** | **226/451** | **18·6** | **131/228** | **13·9** | **0·79 (0·64–0·98)** |




West, Lancet 2019

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# Immunotherapy for relapsed/refractory NSCLC

| Drug | Indication | Dose |
|---|---|---|
| Nivolumab | Metastatic squamous or non-squamous NSCLC with progression after chemotherapy (2nd line) | 240 mg Q2W or 480 mg Q4W |
| Pembrolizumab | Metastatic NSCLC with progression after chemotherapy and **PD-L1 ≥ 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 |

# Second-line use of ICIs in NSCLC

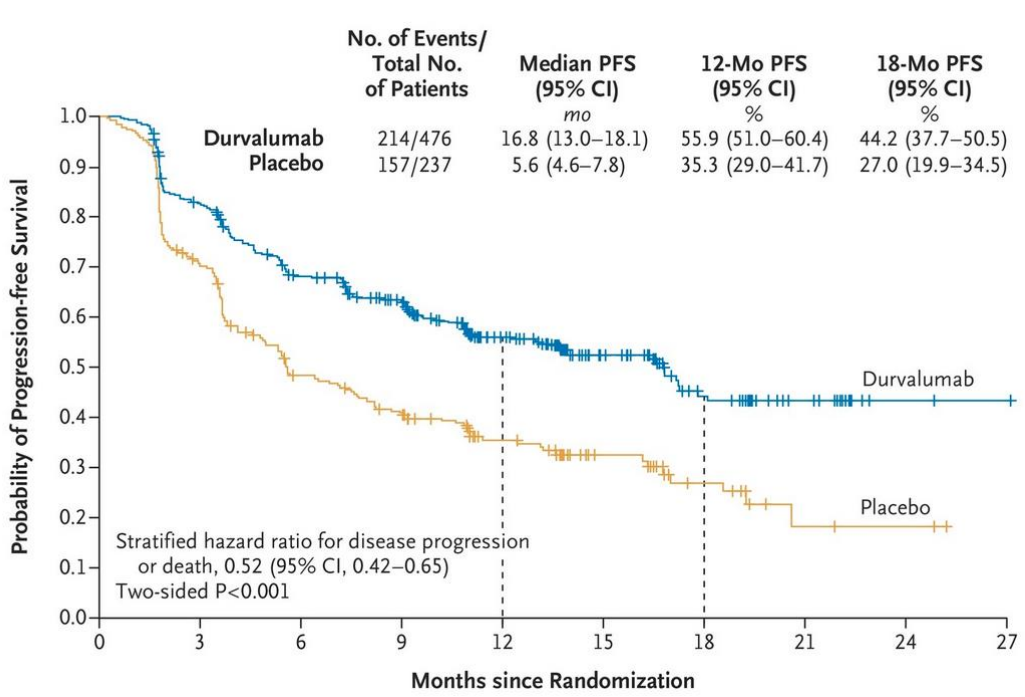
| Study | Treatment arms | ORR | Median PFS (months) | Median OS (months) |
|---|---|---|---|---|
| CheckMate 017 and CheckMate 057 | Nivolumab | 19% | 2.56 | 11.1 |
| | Docetaxel | 11% | 3.52 | 8.1 |
| KEYNOTE-010 (PD-L1 TPS ≥ 1%) | Pembrolizumab | 18% | 4.0 | 12.7 |
| | Docetaxel | 9% | 4.0 | 8.5 |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

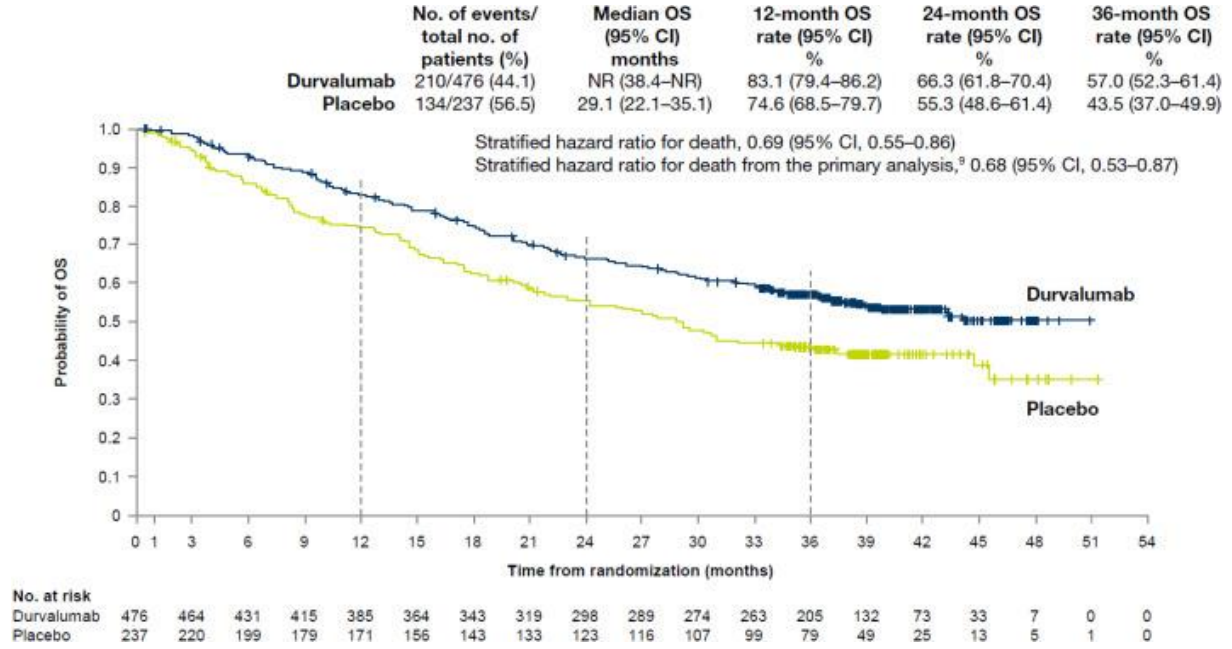
Vokes, Ann Oncol 2018.
Herbst, Lancet 2016.
Fehrenbacker, J Thorac Oncol 2018.

# 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 | 1st line stage III NSCLC (not candidate for resection or definitive chemoradiation) with **PD-L1 TPS ≥ 1%** | 200 mg Q3W or 400 mg Q6W |

# PACIFIC: Durvalumab consolidation therapy for stage III NSCLC



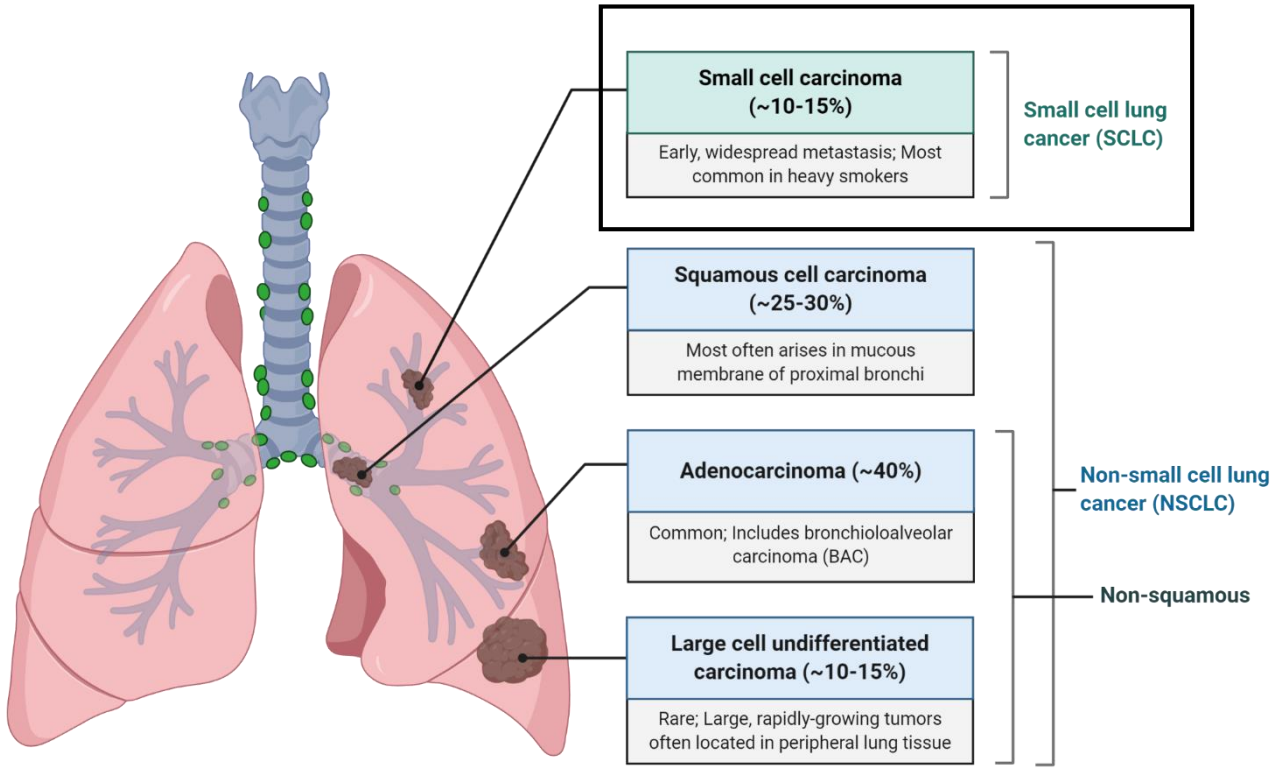

Antonia, N Engl J Med 2017.
Gray, J Thorac Oncol 2020.

# 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

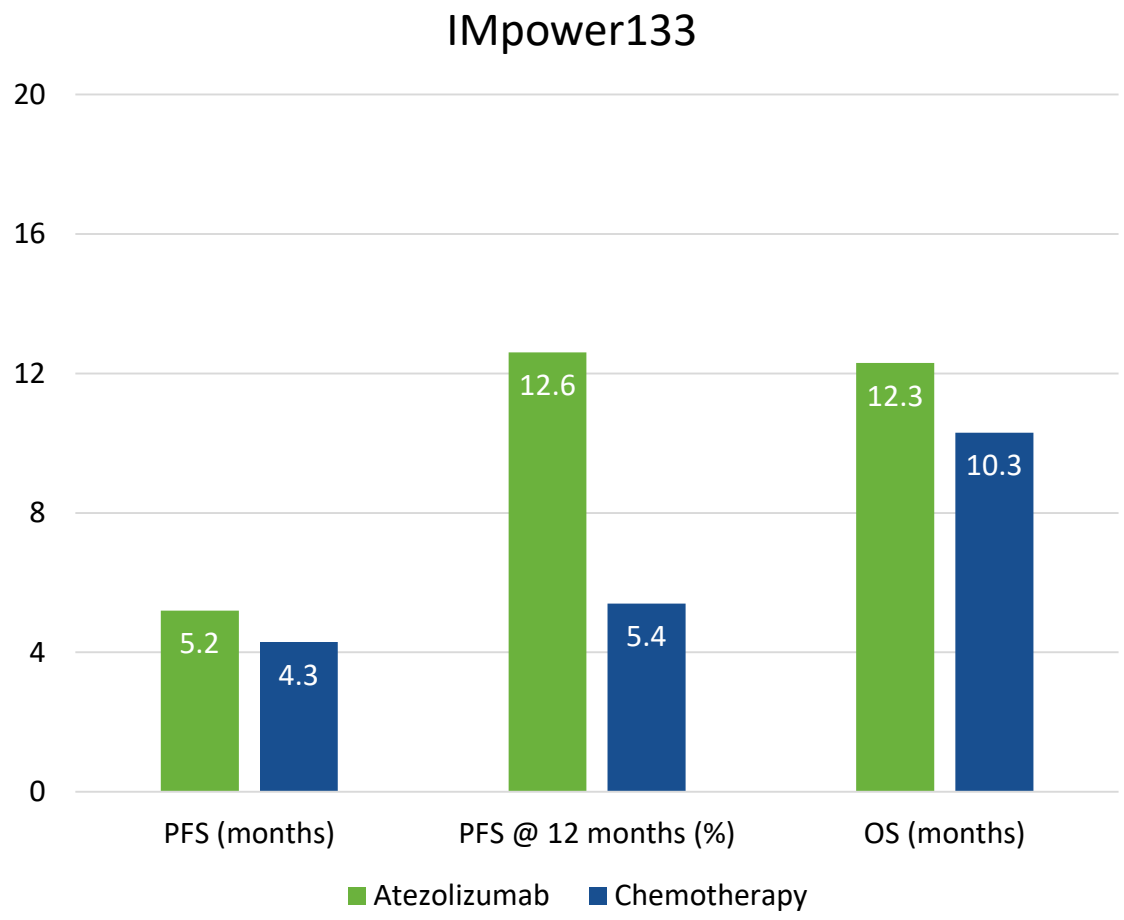
- Median survival 1-2 years after diagnosis
- Until recently, only one FDA-approved 2nd line option: topotecan – DOR: 3.3 months
- Recent approvals of immunotherapies mark the first progress in decades

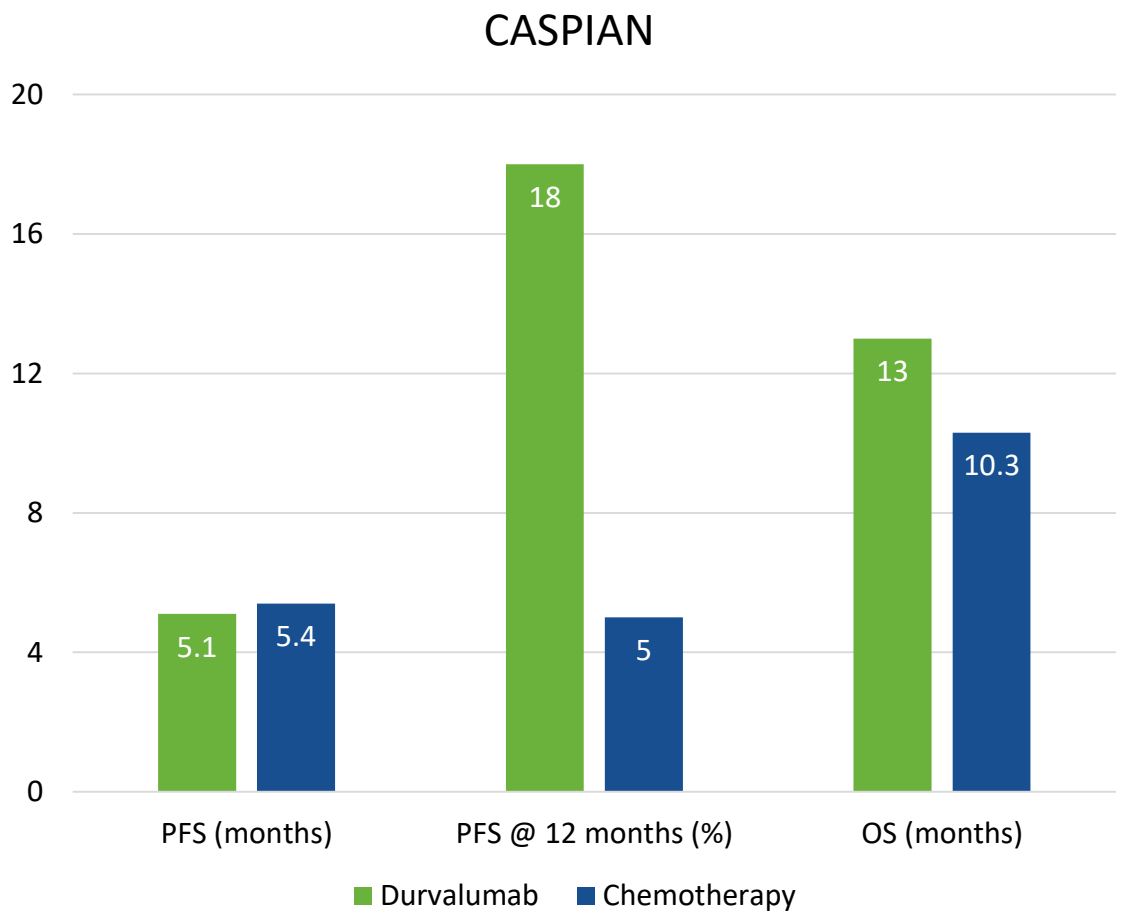


# Approved checkpoint inhibitors in SCLC

| Drug | Indication | Dose |
|---|---|---|
| **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 |

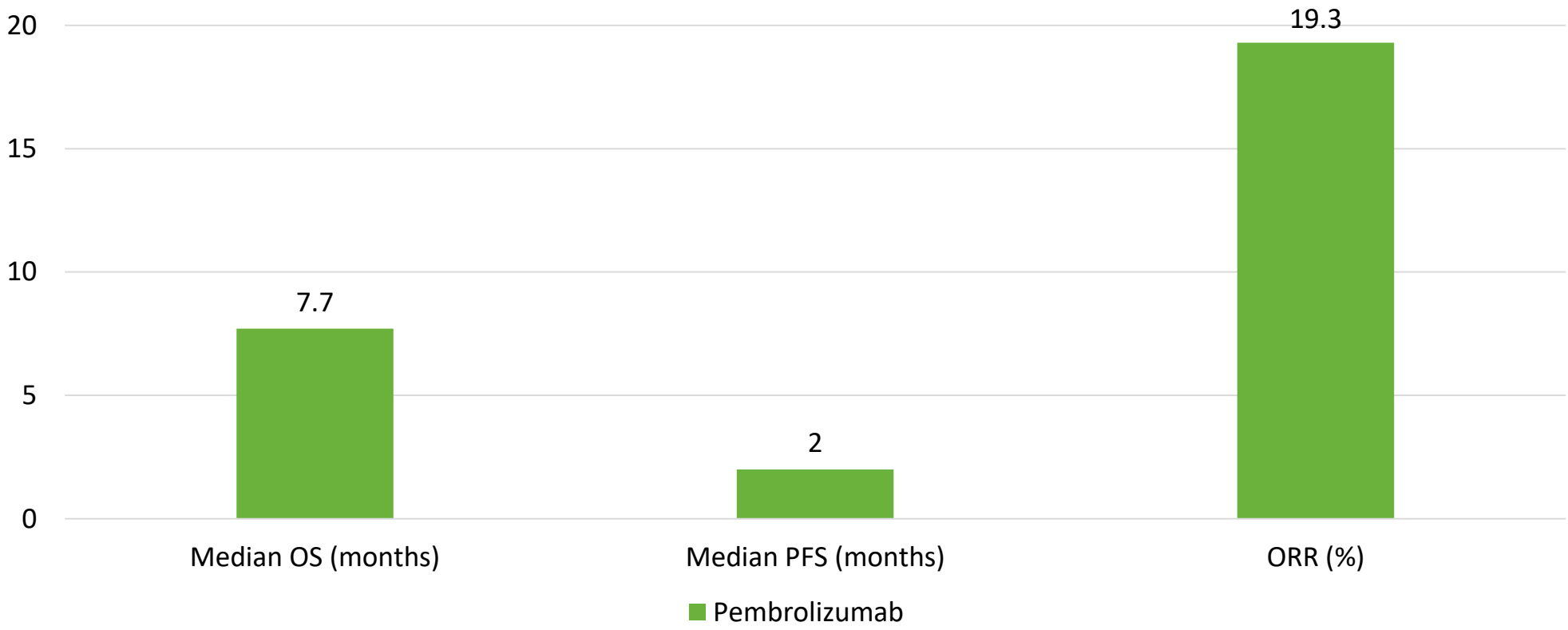
# Front-line ICIs in SCLC




Huang, J Hematol Oncol 2020.

# Later-line ICIs in SCLC




Ready, J Thorac Oncol 2019.
Chung, J Thorac Oncol 2020.
Ott, J Clin Oncol 2017.

# 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

# In development: answering outstanding questions

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

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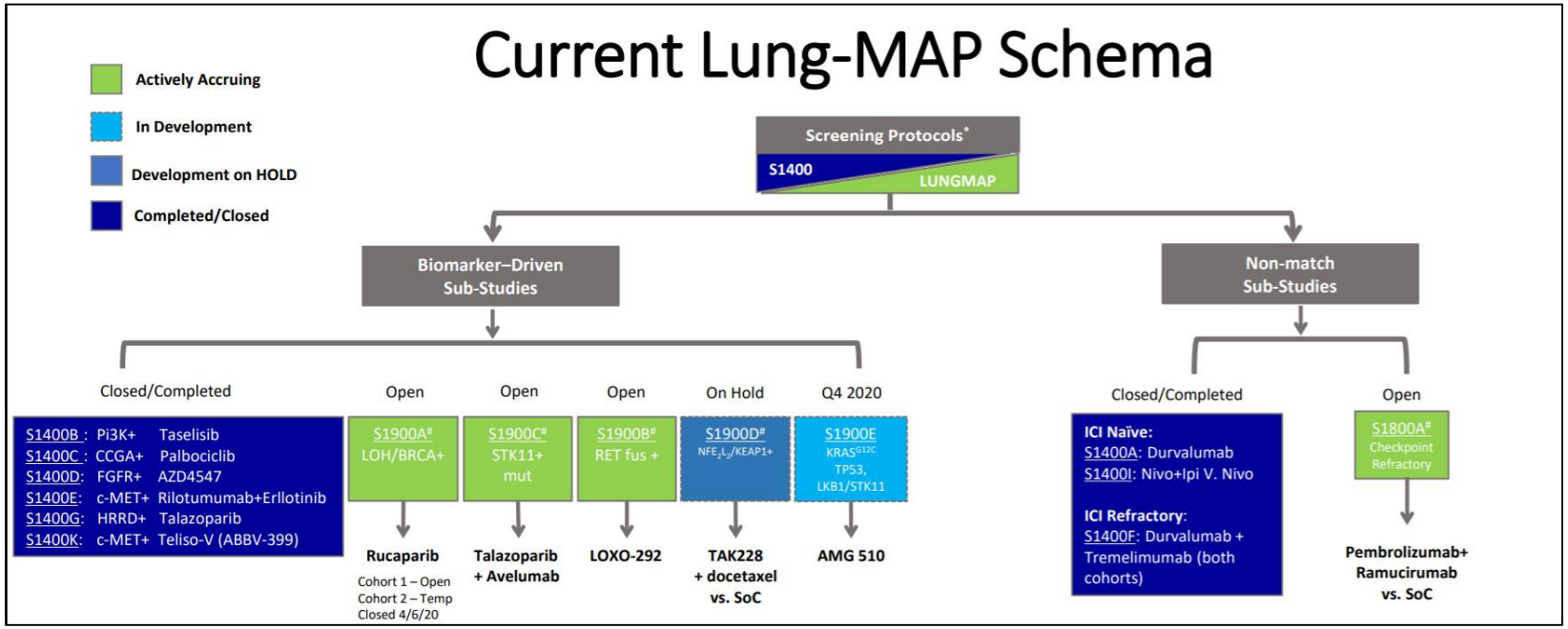
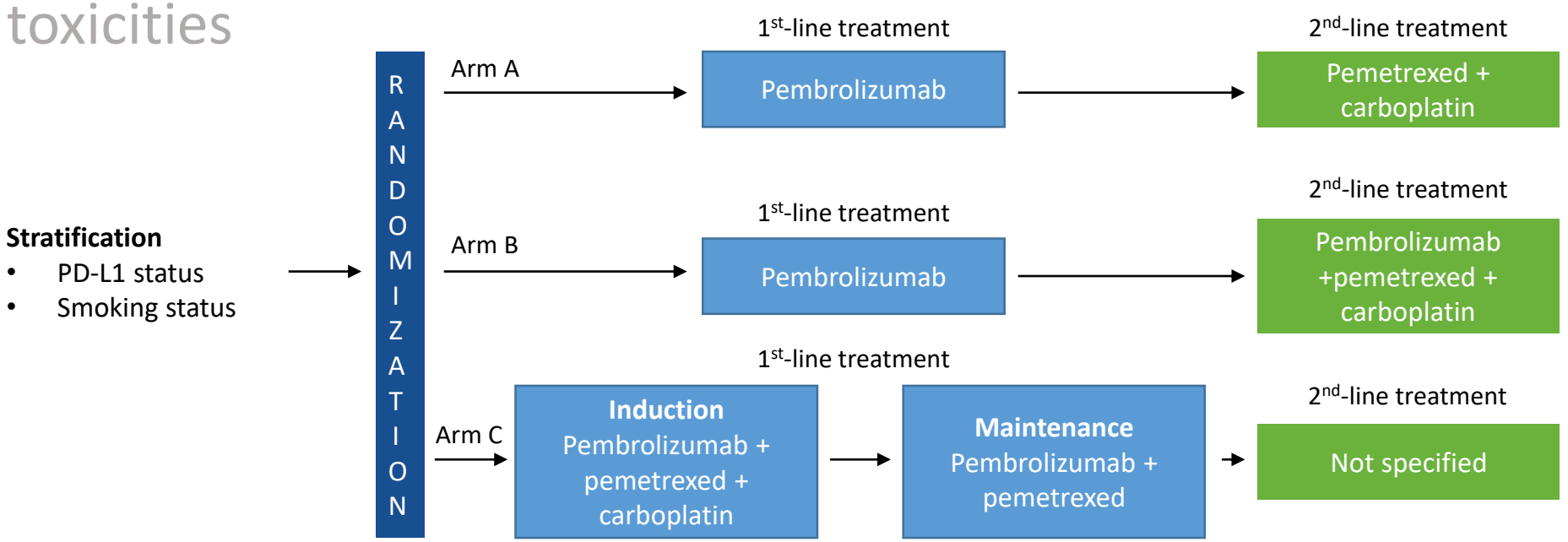



Lung-map.org

#LearnACI

# In development: answering outstanding questions

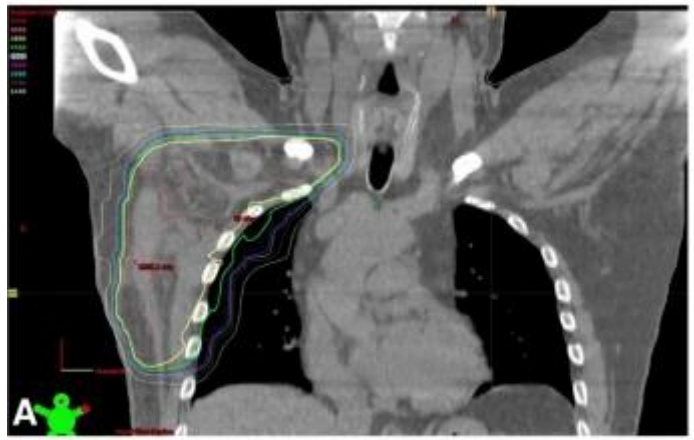
- Biomarker-driven treatment
- Timing of different treatments and combinations
- Emerging toxicities




INSIGNIA trial

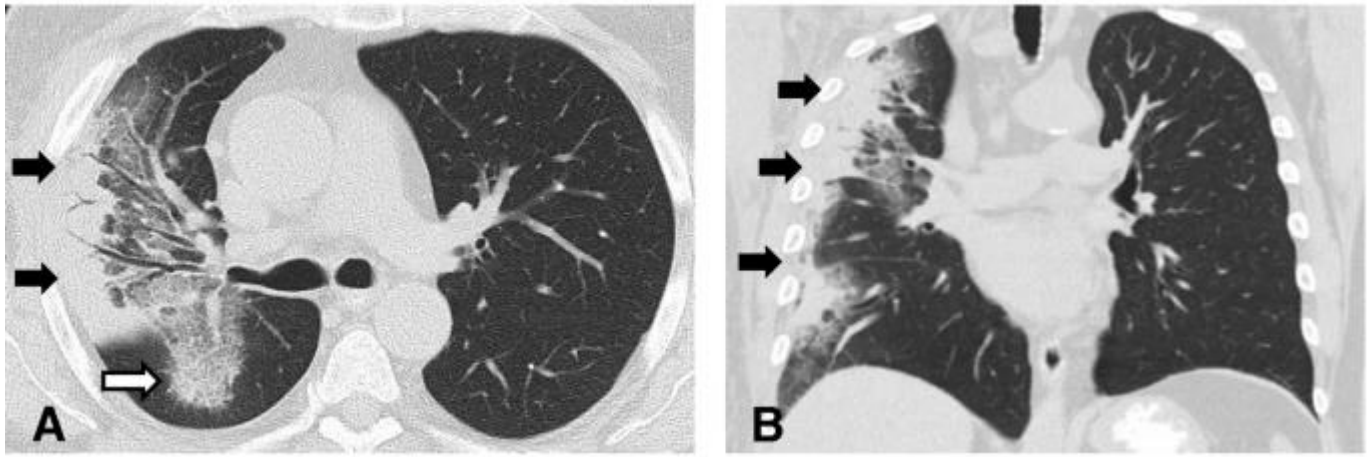
# In development: answering outstanding questions

- 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




Schoenfeld, J Immunother Cancer 2019.

# Immunotherapy for mesothelioma

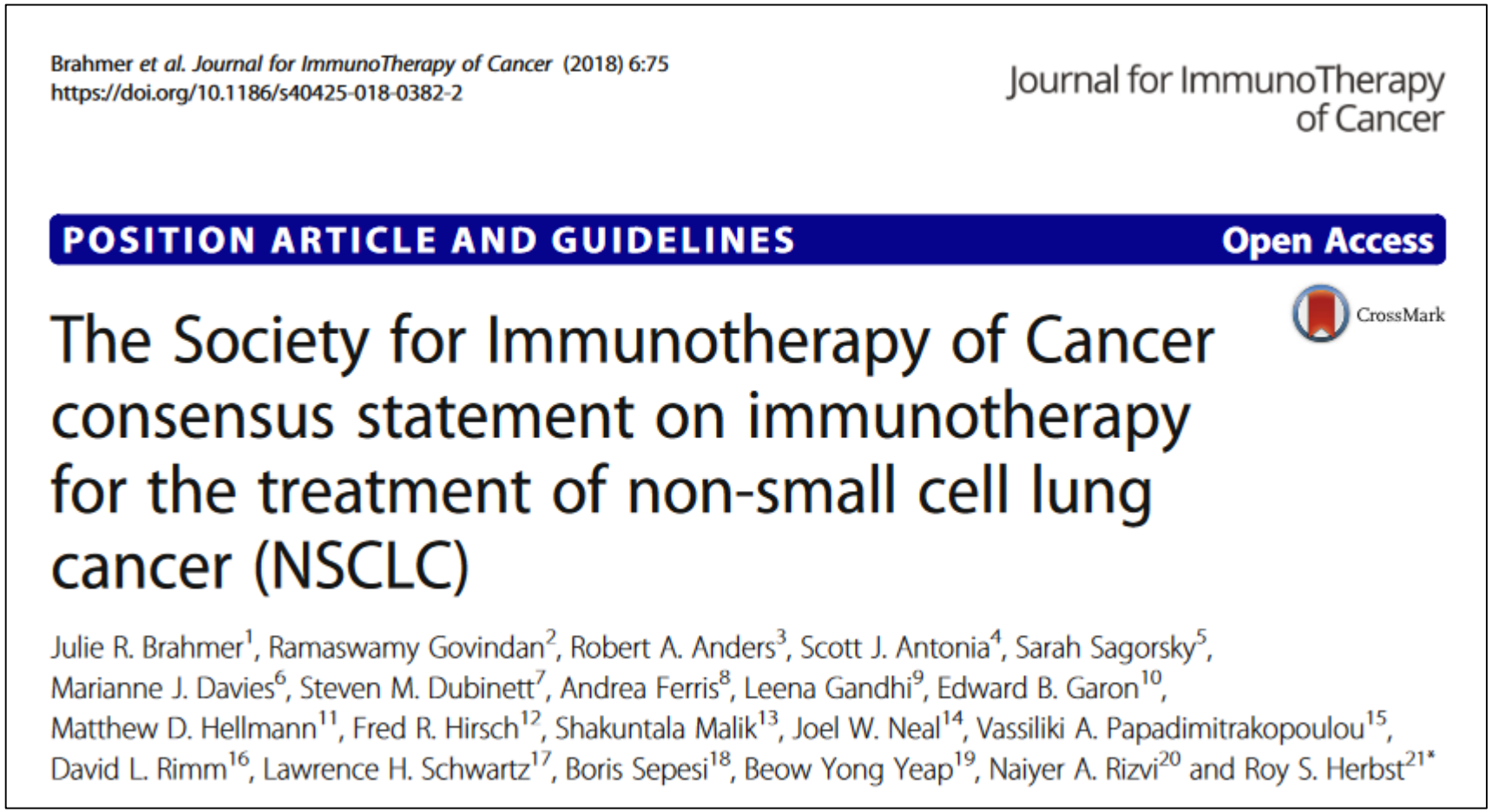
| Drug | Indication | Dose |
|---|---|---|
| Nivolumab + ipilimumab | Frontline unresectable malignant pleural mesothelioma | Nivolumab 360 mg Q3W + ipilimumab 1 mg/kg Q6W |

- 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

# Resources



Brahmer *et al. Journal for ImmunoTherapy of Cancer* (2018) 6:75
https://doi.org/10.1186/s40425-018-0382-2

Journal for ImmunoTherapy of Cancer

POSITION ARTICLE AND GUIDELINES Open Access

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

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

# Case Study

# Case Presentation

Mr Y is 61 y.o male never smoker who was diagnosed with Stage IV adenocarcinoma from lung primary with an EGFR exon 19 deletion on tumor next generation sequencing and a tumor PD-L1 TPS (22C3) of 80%. He was started on 1st line therapy with EGFR Tyrosine Kinase inhibitor Osimertinib , with a good response to treatment that lasted for 2 years before he developed widespread progression of disease. A plasma- based next generation panel was checked and he currently does not have any potentially targetable actionable mutations. He presents in clinic today to discuss options for next line treatment. Which of the following would NOT be preferred as an option for second line treatment for him ?

1. Carboplatin + pemetrexed with or without bevacizumab
2. Carboplatin + paclitaxel + bevacizumab plus atezolizumab
3. Single agent nivolumab , pembrolizumab or atezolizumab

# Case Study 1

Mr Y is 61 y.o male never smoker who was diagnosed with Stage IV adenocarcinoma from lung primary with an EGFR exon 19 deletion on tumor next generation sequencing and a tumor PD-L1 TPS (22C3) of 80%. He was started on 1st line therapy with EGFR Tyrosine Kinase inhibitor Osimertinib , with a good response to treatment that lasted for 2 years before he developed widespread progression of disease. A plasma- based next generation panel was checked and he currently does not have any potentially targetable actionable mutations. He presents in clinic today to discuss options for next line treatment. Which of the following regimens would NOT be preferred as an option for second line treatment for him ?

1. Carboplatin + pemetrexed with or without bevacizumab
2. Carboplatin + paclitaxel + bevacizumab plus atezolizumab
3. **Single agent nivolumab , pembrolizumab or atezolizumab**

# Immunotherapy in driver mutated NSCLC

## IMMUNOTHERAPY IN TREATMENT OF NSCLC WITH MUTATIONS IN EGFR OR ALK: When and how?

- Patients harboring EFGR sensitizing and ALK mutations failed to demonstrate benefit from PD-1/PD-L1 therapy in the phase III trials that evaluated single agent immunotherapy vs Docetaxel in relapse/ refractory advanced NSCLC. [1-5]
- PD-L1 expression has been described as mechanism of immune invasion for EGFR mutant NSCLC in preclinical studies ad may not be a marker of adaptive immune response. [6]
- Most of the first line chemo-immunotherapy trials excluded patients with EGFR sensitizing or ALK mutations except IMpower150 that included a subset of chemotherapy and immunotherapy naïve patients with EGFR or ALK mutations
    - In subset analysis chemotherapy and immunotherapy naïve patients with EGFR sensitizing mutations showed an improvement in OS (HR:0.31, 95% CI 0.11,0.83) and PFS (HR: 0.41  95% CI 0.23,0.75)when treated with combination of carboplatin, (nab)paclitaxel, atezolizumab and bevacizumab compared to carboplatin, (nab)paclitaxel and bevacizumab. [7]
- There are several ongoing studies evaluating the role of immunotherapy combinations in this unique subset of patients with NSCLC (NCT03786692, NCT03515837)

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