# Maximizing Personalized Approaches Through Composite Biomarkers in METASTATIC NSCLC:

## An Innovative 2D View

## TUESDAY, SEPTEMBER 14, 2021

7:00 PM – 8:00 PM ET

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*Maximizing Personalized Approaches Through Composite Biomarkers in Metastatic NSCLC: An Innovative 2D View*

**FACULTY**

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**PROGRAM OVERVIEW**

This live virtual satellite symposium consists of presentations from expert faculty and 2D animation technology to explain immune dysfunction and the pathogenesis of non-small cell lung cancer (NSCLC), currently available and emerging immuno-oncology used alone and in combination with chemotherapy for NSCLC, and the usefulness and application of biomarkers to guide treatment selection for NSCLC.

**TARGET AUDIENCE**

This activity is designed to meet the educational needs of pulmonologists, thoracic surgeons, oncologists, pathologists, and advanced practitioners in oncology (NP/PA/PharmD) involved in the management of patients with advanced NSCLC.

**LEARNING OBJECTIVES**

Upon the completion of this program, attendees should be able to:

- Apply immune therapy biomarkers in the management of patients with advanced NSCLC
- Describe the immune dysfunction integral to the pathogenesis of non-small cell lung cancer
- Examine late stage, clinical trial data of emerging PD-1 inhibitors in the first-line and second-line treatment of advanced non-small cell lung cancer

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Purpose: This program would be beneficial for nurses involved in the long-term treatment and management of patients with non-small cell lung cancer. CNE Credits: 1.0 ANCC Contact Hour.

**CNE Accreditation Statement**: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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**Mark A. Socinski, MD** reports that he has served on speakers bureaus for Amgen, AZ, BMS, Genentech, Guardant, Jazz, Lilly, and Regeneron, and has contracted research from Genentech, AZ, Novartis, Spectrum, Cullinan, and Takeda

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The reviewer of this activity has nothing to disclose.

**CNE Content Review**

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3. Complete pre-and-post surveys and evaluation.

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## AGENDA

**I. Tumorigenesis Primer: Immune System Dysfunction in NSCLC**

1. Immune surveillance processes and tumor effects
    a. Function of CTLA-4, PD-1 and PD-L1 in T-cell regulation
    b. **Animation: Depiction of immune cellular functions and cytokine effects on tumorigenesis**

**II. Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC**

1. Currently available immuno-oncology (IO) options
    a. Approved checkpoint inhibitors
    b. Clinical trials of monotherapy and combination with chemotherapy
    c. **Animation: Depiction of the complementary anti-tumor effects of IO and chemotherapy in NSCLC**
2. Emerging data in monotherapy
    a. Cemiplimab clinical trials - review of efficacy and safety
    b. Pembrolizumab clinical trial - review of efficacy and safety
    c. ASCO update

**III. Application of Biomarkers to Immuno-oncology Treatment**

1. Case study
2. Association between PD-L1 expression and clinical outcomes
3. Interpreting and applying PD-L1 levels
4. Standardization of laboratory methods in PD-L1 testing
5. Is tumor mutational burden ready for prime time?
6. Oncogenic biomarkers as negative biomarkers

**IV. Conclusions**

**V. Questions and Answers**

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## Learning Objectives

- Apply immune therapy biomarkers in the management of patients with advanced non-small cell lung cancer (NSCLC)
- Describe the immune dysfunction integral to the pathogenesis of NSCLC
- Examine late-stage clinical trial data of emerging programmed death-ligand 1 (PD-L1) inhibitors in the first-line and second-line treatment of advanced NSCLC

# Tumorigenesis Primer

## Immune System Dysfunction in NSCLC

**Mark A. Socinski, MD**
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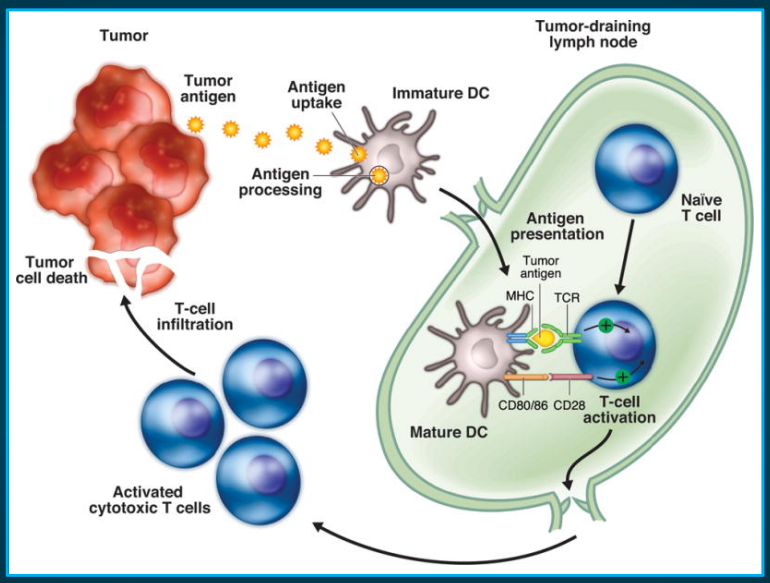
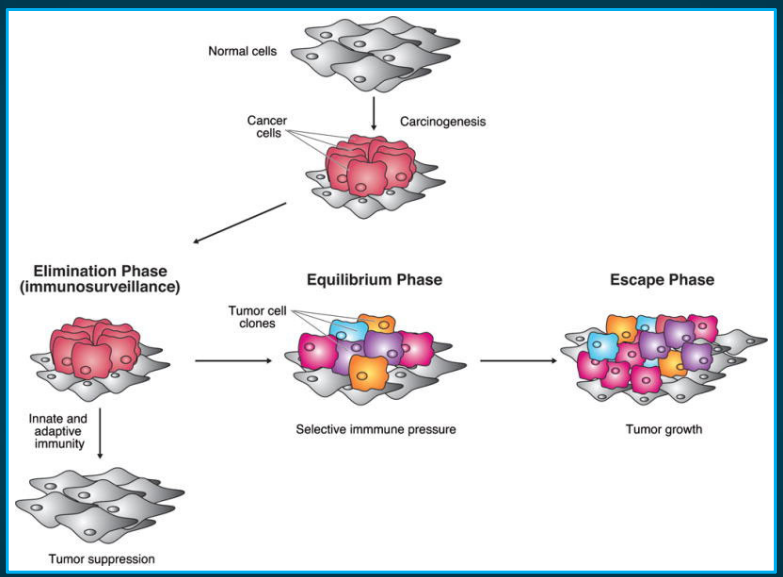
# Adaptive Anticancer Immunity



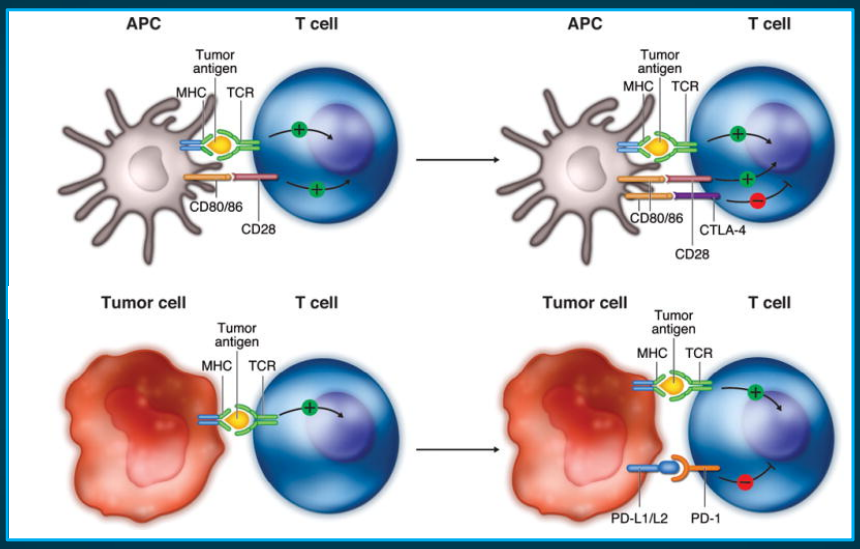

DC = dendritic cell; MHC = major histocompatibility complex; TCR = T-cell receptor; CD = cluster of differentiation.
Carbone DP, et al. J Thoracic Oncol. 2015;10(7):974-984.

# Cancer Immunoediting




Carbone DP, et al. J Thoracic Oncol. 2015;10(7):974-984.

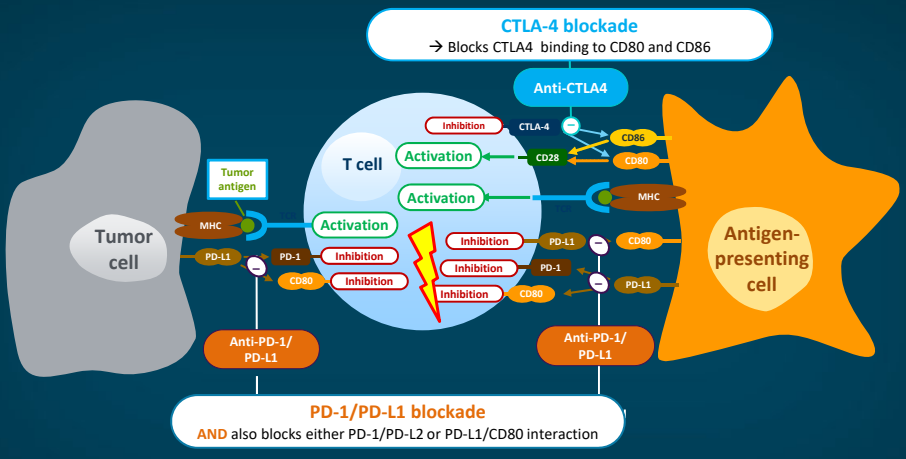
# Immune Checkpoints




**APC = antigen-presenting cell; CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed (cell) death 1; PD-L1 = PD-1 ligand.**

Carbone DP, et al. J Thoracic Oncol. 2015;10(7):974-984.

# Suppressing Antitumor Immunity




**Modified from Singh PP, et al. *Gastroenterol Rep* (Oxf). 2015;3:289-297. Modified from Chen DS, et al. *Clin Cancer Res*. 2012;18:6580-6587.**

Please click here to watch a video depicting the immune cellular functions and cytokine effects of tumorigenesis

# Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC

Immunotherapy

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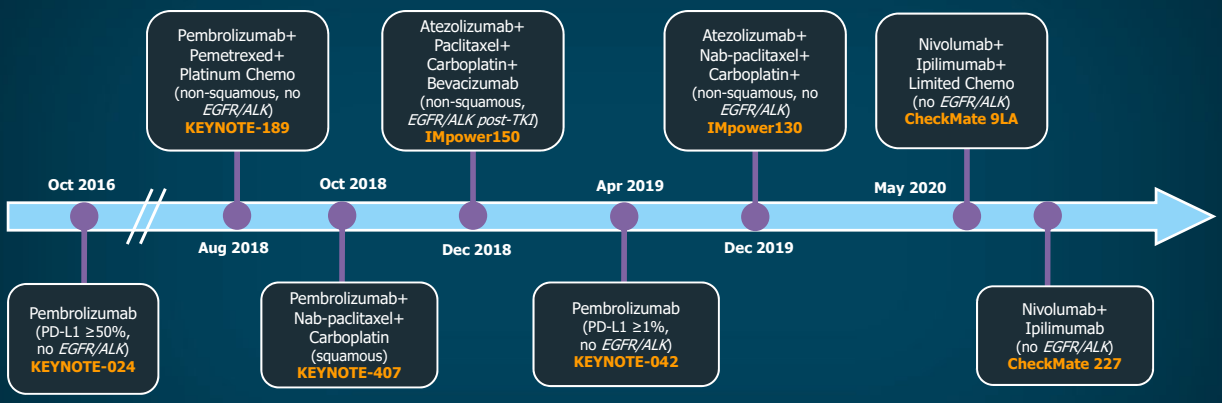
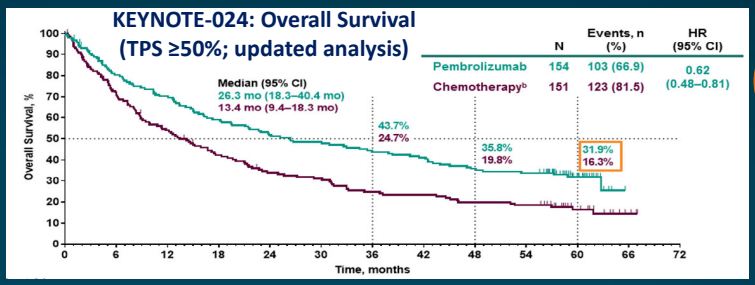
# FDA First-line Approvals for Immunotherapy in Stage IV NSCLC




- 8 randomized trials have demonstrated efficacy with ICI + concurrent chemotherapy in the first-line setting in patients without an EGFR- or ALK-positive tumor (KEYNOTE-021G, -189, -407, IMpower130, -131, -132, Checkmate-9LA; IMpower150 allowed EGFR/ALK post-TKI).
- 4 randomized trials have demonstrated that ICI are appropriate as first-line treatment for selected patients based on tumor PD-L1 expression level and no EGFR- or ALK-driven alteration (KEYNOTE-024, -042, IMpower110 and EMPOWER-Lung-1).

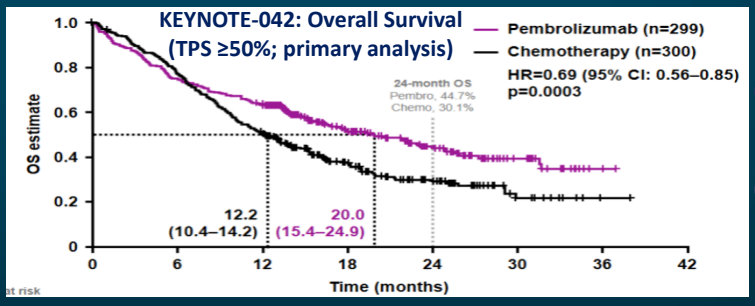
# Pembrolizumab Monotherapy Versus Chemotherapy

- PD-L1 selected
- Squamous and non-squamous NSCLC
- KEYNOTE-024 and KEYNOTE-042




mOS **26.3** months

OS HR **0.62**

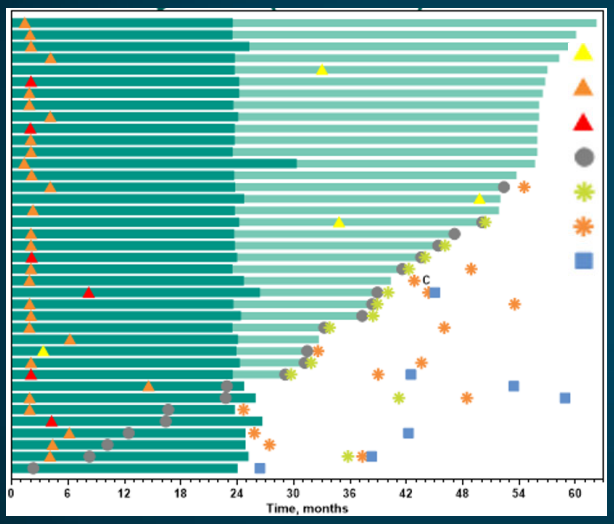



mOS **20.0** months

OS HR **0.69**

Brahmer J, et al. *Ann Oncol*. 2020;31(Suppl 4):S1142-S1215. Mok TSK, et al. *Ann Aoncol*. 2019;30(Suppl 2):I38.

# Treatment Duration and Time to Response
## 35 Cycles (2 Years) of Pembrolizumab Completed



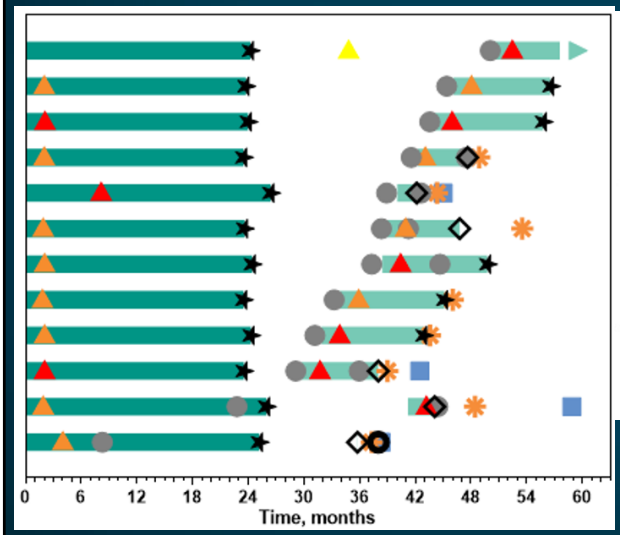

CR
PR
SD
PD
Received Second Course
Received Subsequent Therapy
Death

- At data cutoff, 18/39 patients (46%) were alive without PD or subsequent therapy for NSCLC per investigator assessment
- 1 patient developed secondary malignancy and was treated accordingly

| | N = 39 |
|---|---|
| 3-year OS rate from completion of pembrolizumab | 81 % |
| Objective response, n (%) | 32 (82) |
| Best objective response, n (%) | |
| Complete response | 4 (10) |
| Partial response | 28 (72) |
| Stable disease | 6 (15) |
| Progressive disease | 1 (3) |

Brahmer J, et al. *Ann Oncol*. 2020;31(Suppl 4):S1142-S1215.

# Treatment Duration and Time to Response
## Second Course of Pembrolizumab




CR
PR
SD
PD
NE
End of First Course
Second Course Ongoing
Completed Second Course
Discontinued Second Course
Received Subsequent Therapy
Death

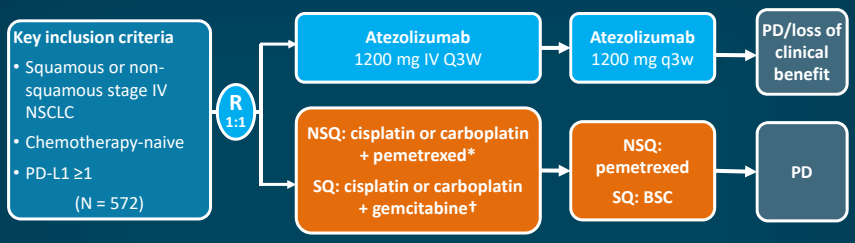
- At data cutoff, 5/12 patients (42%) were alive without PD per investigator assessment
- 3 (25%) did not receive subsequent therapy

| | N = 12 |
|---|---|
| Alive at data cutoff, n (%) | 8 (67) |
| Objective response during second course, n (%) | 4 (33) |
| Best objective response, n (%) | |
| Complete response | 0 |
| Partial response | 4 (33) |
| Stable disease | 6 (50) |
| Progressive disease | 1 (8) |

Brahmer J, et al. *Ann Oncol*. 2020;31(Suppl 4):S1142-S1215.

# IMpower110: Atezolizumab Monotherapy vs Platinum-Based Chemotherapy

## Phase 3 study of first-line treatment in patients with PD-L1 positive NSCLC




- **Primary endpoint: O**S (tested in a hierarchical manner according to PD-L1 expression status)
- **Secondary endpoints:** PFS (investigator assessed), ORR, DoR
- Stratification by sex, ECOG PS, PD-L1 expression, histology

***cisplatin 75 mg/m² or carboplatin AUC 6 + pemetrexed 500 mg/m² Q3W; †cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² q3w.**

**NSQ = nonsquamous; SQ = squamous; BSC = best supportive care.**

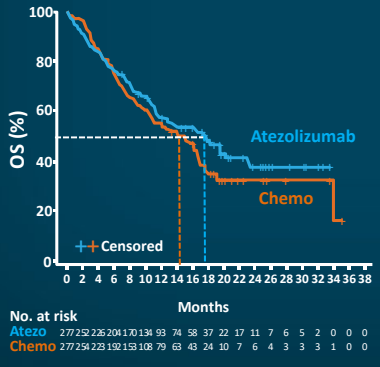
Herbst RS, et al. *N Engl J Med.* 2020;383:1328-1339. Spigel D, et al. *Ann Oncol.* 2019;30(suppl 5):v915 (abstract LBA78).

# IMpower110: OS

## Any PD-L1 expression

| | Pts | mOS (95% CI) | 6-Mo OS (95% CI) | 12-Mo OS (95% CI) |
|---|---|---|---|---|
| Atezo | 277 | 17.5 mos (12.8–23.1) | 76.2% (71.1–81.3) | 57.6% (51.2–64.0) |
| Chemo | 277 | 14.1 mos (11.0–16.6) | 75.7% (70.5–80.9) | 54.3% (47.7–60.8) |

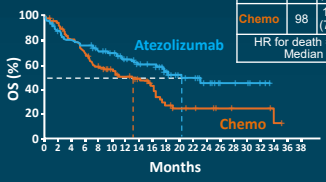
HR for death = 0.83 (95% CI, 0.65–1.07) *P*= .04
Median F/U = 13.4 mos (range, 0–35)




## High PD-L1 expression

| | Pts | mOS (95% CI) | 6-Mo OS (95% CI) | 12-Mo OS (95% CI) |
|---|---|---|---|---|
| Atezo | 107 | 20.2 mos (16.5–NE) | 76.3% (68.2–84.4) | 64.9% (55.4–74.4) |
| Chemo | 98 | 13.1 mos (7.4–16.5) | 70.1% (60.8–79.4) | 50.6% (40.0–61.3) |

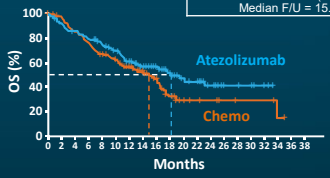
HR for death = 0.59 (95% CI, 0.40–0.89) *P*= .01
Median F/U = 15.7 mos (range, 0–35)




## High or intermediate PD-L1 expression

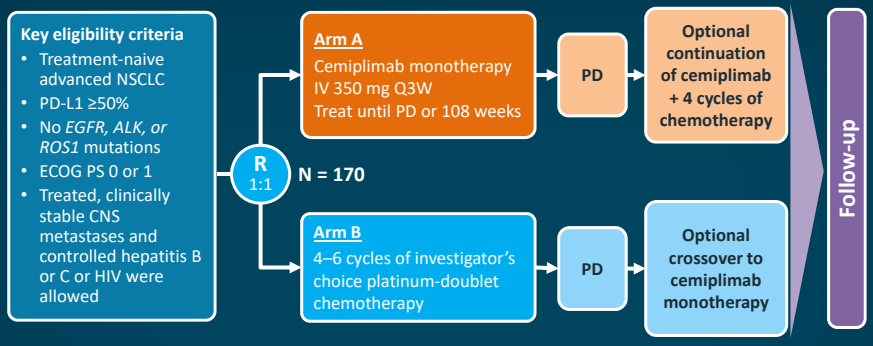
| | Pts | mOS (95% CI) | 6-Mo OS (95% CI) | 12-Mo OS (95% CI) |
|---|---|---|---|---|
| Atezo | 166 | 18.2 mos (13.3–NE) | 79.3% (73.1–85.5) | 60.7% (52.6–68.7) |
| Chemo | 162 | 14.9 mos (10.8–16.6) | 76.1% (69.3–82.8) | 56.0% (47.7–64.3) |

HR for death = 0.72 (95% CI, 0.52–0.99) *P*= .04
Median F/U = 15.2 mos (range, 0–35)




Herbst RS, et al. *N Engl J Med.* 2020;383:1328-1339.

# EMPOWER-Lung 1 Study Design



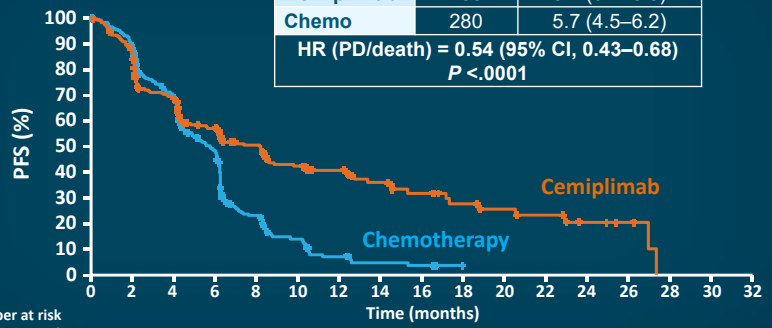

- **Endpoints**
  - Primary: OS and PFS
  - Secondary: ORR (key), DoR, HRQoL, and safety
- Stratification based on histology (squamous vs nonsquamous and region (Europe, Asia, rest of world)

**CNS = central nervous system; HIV = human immunodeficiency virus; HRQoL = health-related quality of life.**

Sezer A, et al. *Lancet.* 2021;397:592-604.

# EMPOWER-Lung 1: PFS in PD-L1 ≥50% Population

| | Patients n | Median PFS mos (95% CI) |
|---|---|---|
| Cemiplimab | 283 | 8.2 (6.1–8.8) |
| Chemo | 280 | 5.7 (4.5–6.2) |
| HR (PD/death) = 0.54 (95% CI, 0.43–0.68) *P* <.0001 | | |

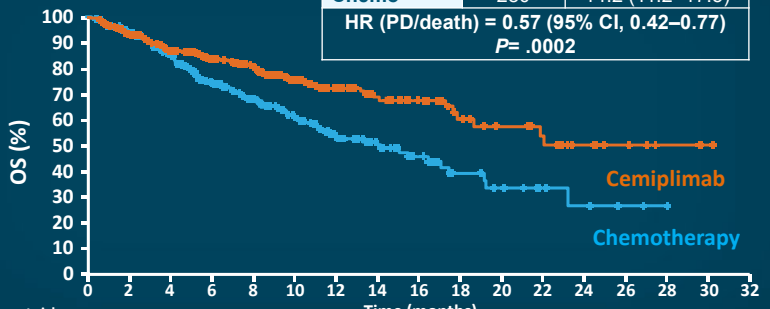



| Number at risk (number censored) | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cemiplimab | 283 (0) | 221 (24) | 162 (42) | 123 (55) | 92 (73) | 59 (93) | 43 (107) | 28 (118) | 20 (123) | 14 (127) | 11 (129) | 9 (130) | 5 (133) | 3 (135) | 0 (136) | 0 (136) | 0 (136) |
| Chemo | 280 (0) | 220 (31) | 157 (48) | 104 (56) | 42 (67) | 20 (75) | 8 (78) | 4 (80) | 3 (80) | 0 (83) | 0 (83) | 0 (83) | 0 (83) | 0 (83) | 0 (83) | 0 (83) | 0 (83) |

Sezer A, et al. *Lancet.* 2021;397:592-604.

# EMPOWER-Lung 1: OS in PD-L1 ≥50% Population

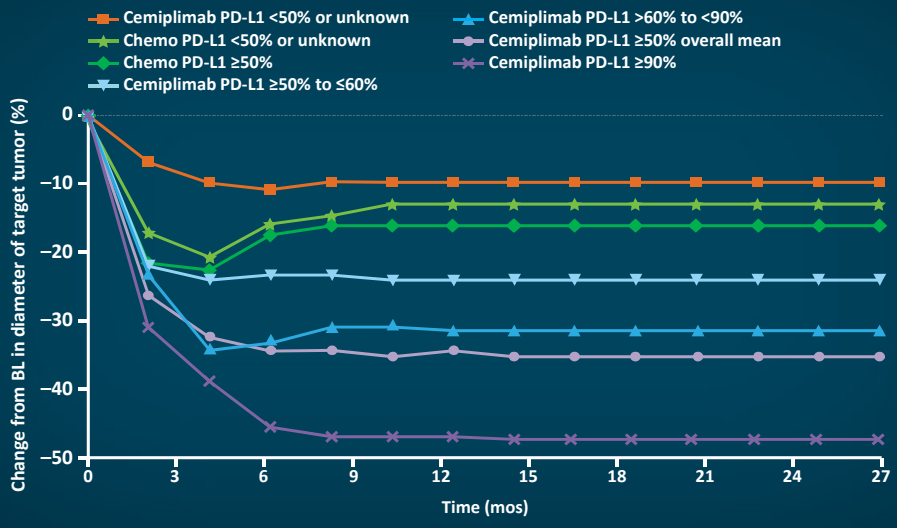
| | Patients n | Median OS mos (95% CI) |
|---|---|---|
| Cemiplimab | 283 | NR (17.9–NE) |
| Chemo | 280 | 14.2 (11.2–17.5) |
| HR (PD/death) = 0.57 (95% CI, 0.42–0.77) *P*= .0002 | | |




| Number at risk (number censored) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cemiplimab | 283 (0) | 244 (21) | 203 (46) | 177 (65) | 154 (82) | 108 (119) | 83 (140) | 55 (165) | 42 (177) | 24 (192) | 18 (197) | 15 (199) | 10 (203) | 6 (207) | 3 (210) | 1 (212) | 0 (213) |
| Chemotherapy | 280 (0) | 239 (24) | 198 (45) | 153 (66) | 125 (82) | 87 (110) | 57 (130) | 41 (144) | 25 (156) | 15 (163) | 11 (165) | 6 (170) | 4 (171) | 2 (173) | 1 (174) | 0 (175) | 0 (175) |

Sezer A, et al. *Lancet.* 2021;397:592-604.

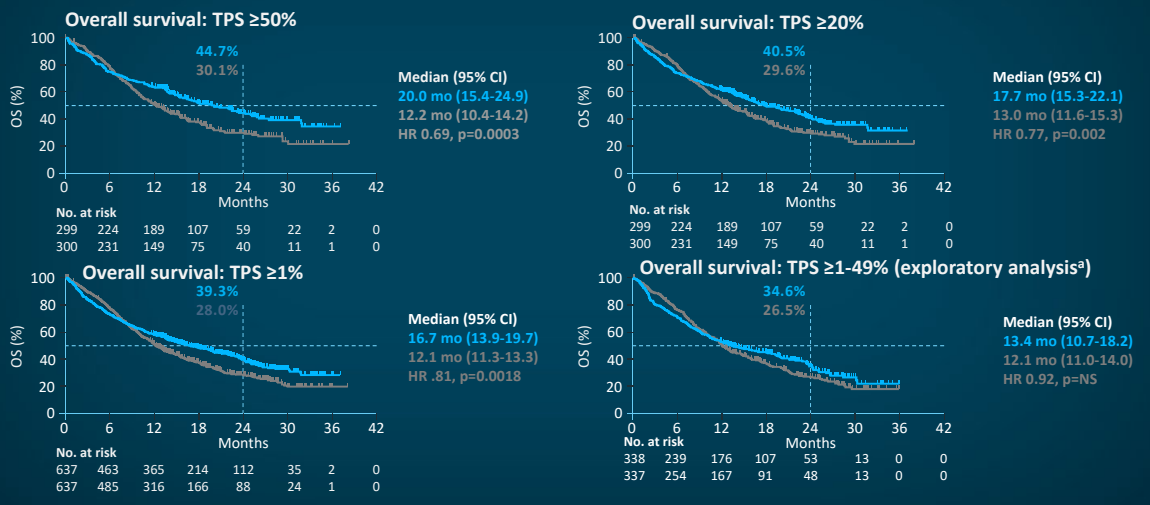
# EMPOWER-Lung 1: Measurement of Target Tumor Based on BL PD-L1




BL = baseline.

Sezer A, et al. *Lancet.* 2021;397:592-604.

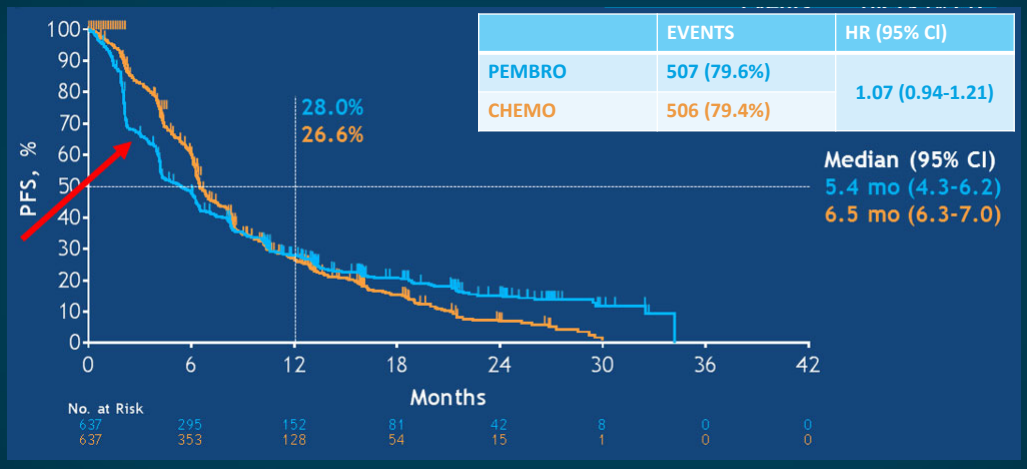
# KEYNOTE 042: Pembrolizumab Versus Chemotherapy in PD-L1+ (> 1%): OS by PD-L1 TPS




Lopes G, et al. *J Clin Oncol*. 2018;36(Suppl 18):LBA4.

# KEYNOTE 042: Progression Free Survival, TPS ≥ 1%

(RECIST v1.1, BICR)

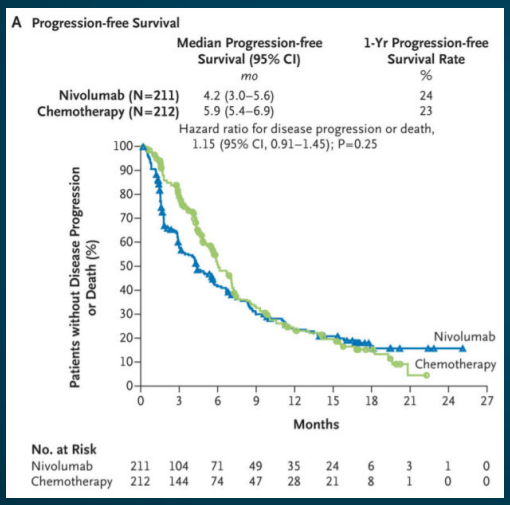


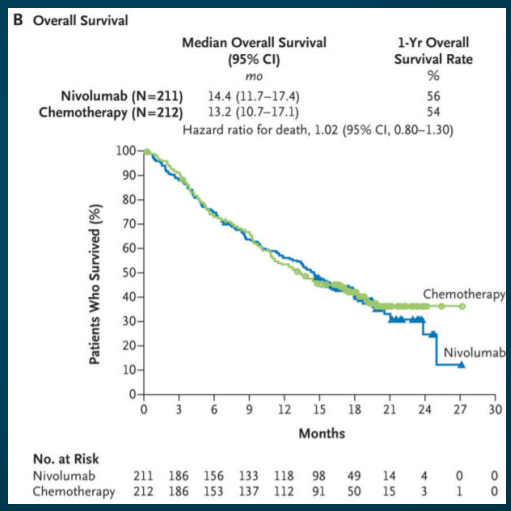

| | EVENTS | HR (95% CI) |
|---|---|---|
| PEMBRO | 507 (79.6%) | 1.07 (0.94-1.21) |
| CHEMO | 506 (79.4%) | |

Formal comparison of pembrolizumab vs chemotherapy no performed based on hierarchical testing strategy.
Data cutoff date, February 26, 2018

Lopes G, et al. *J Clin Oncol*. 2018;36(Suppl 18):LBA4.

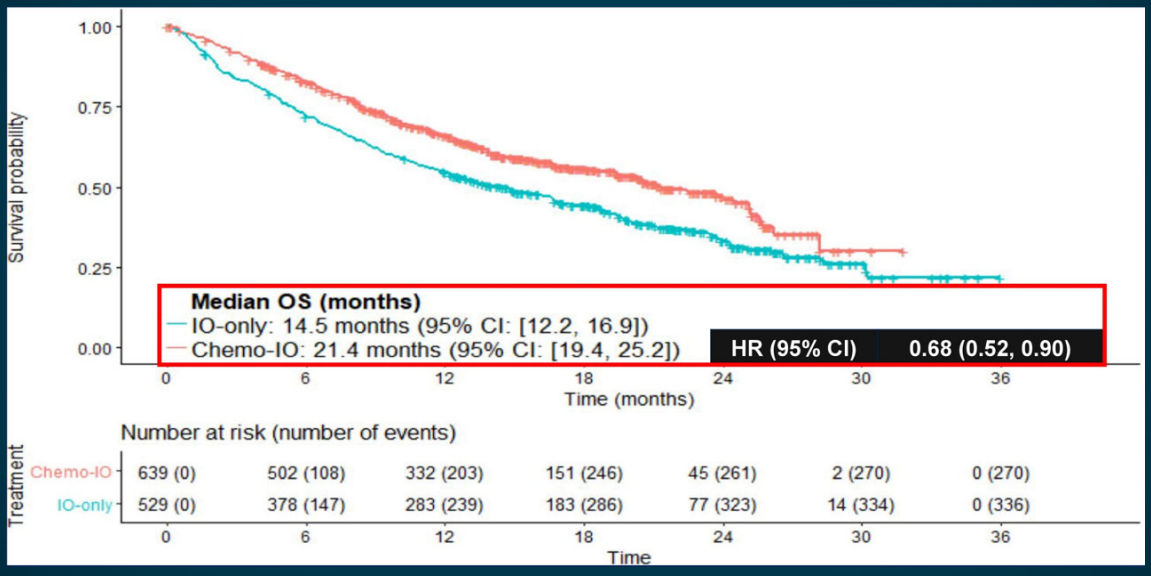
# PFS and OS Among Patients With PD-L1 Expression ≥ 5% CheckMate-026: Nivolumab Versus Chemotherapy




Carbone DP, et al. *N Engl J Med*. 2017;376(25):2415-2426.

# Exploratory Overall Survival: NSCLC PD-L1 (1-49% Subgroup Analysis)




Akinboro O, et al. *J Clin Oncol*. 2021 [published online before print].

## Considerations Regarding Immuno-monotherapy in Advanced NSCLC

When to treat with immuno-monotherapy?

- Low volume disease
- Relatively asymptomatic
- Very high PD-L1 expression (≥ 90%)

When not to treat with immuno-monotherapy?

- High volume disease
- Heavy symptom burden
- Lesser PD-L1 expression
- PD-L1 < 50%

# Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC

Immunotherapy Plus Chemotherapy

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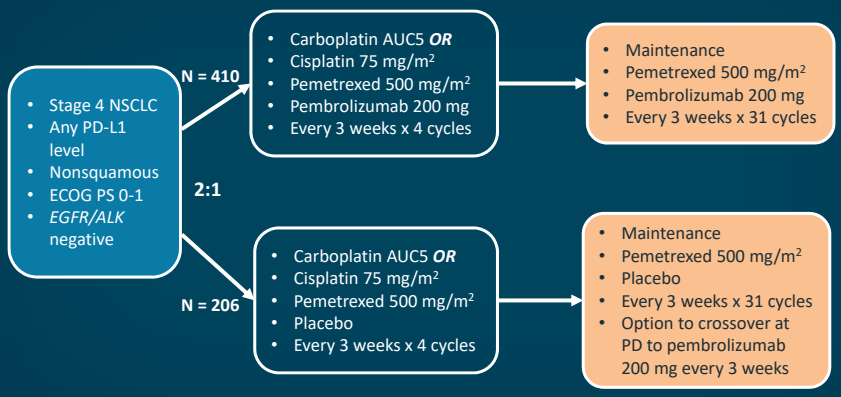
# KEYNOTE-189: Platinum/Pemetrexed +/- Pembrolizumab



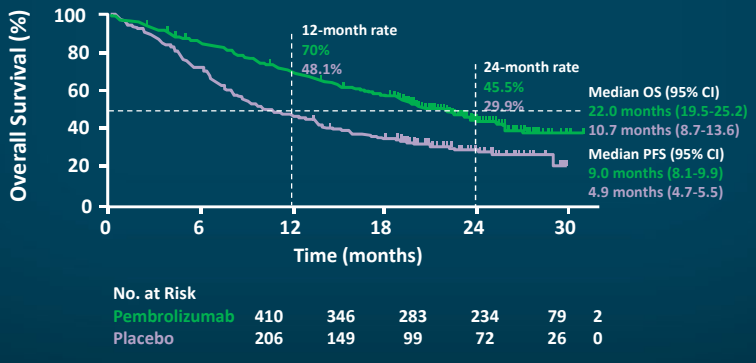

Randomization stratified by: PD-L1 <1% vs ≥1%, tobacco Y vs N, carboplatin vs cisplatin.
Primary endpoints: progression-free survival (PFS), overall survival (OS).
Secondary endpoints: objective response rate (ORR), duration of response, safety.

**ECOG = Eastern Cooperative Oncology Group; PS = performance status; AUC = area under the curve dosing cap; *EGFR/ALK* = epidermal growth factor receptor/anaplastic large-cell lymphoma kinase.**

**Gandhi L, et al. *N Engl J Med*. 2018;378:2078-2092.**

# KEYNOTE-189: Platinum/Pemetrexed +/- Pembrolizumab—Total Population

| | Events, n/N (%) | HR OS (95% CI) | HR PFS (95% CI) |
|---|---|---|---|
| Pembrolizumab/Chemo | 213/410 (52.0) | 0.56 (0.45-0.70) | 0.48 (0.4-0.58) |
| Placebo/Chemo | 144/206 (69.9) | | |



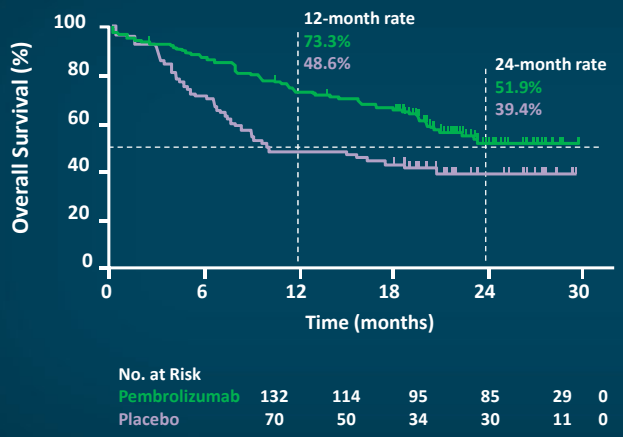

No. at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Pembrolizumab | 410 | 346 | 283 | 234 | 79 | 2 |
| Placebo | 206 | 149 | 99 | 72 | 26 | 0 |

**HR = hazard ratio; CI = confidence interval.**

**Gadgeel S, et al. *J Clin Oncol*. 2020;38(4):1505-1517.**

# KEYNOTE-189: PD-L1 Status—TPS ≥50%



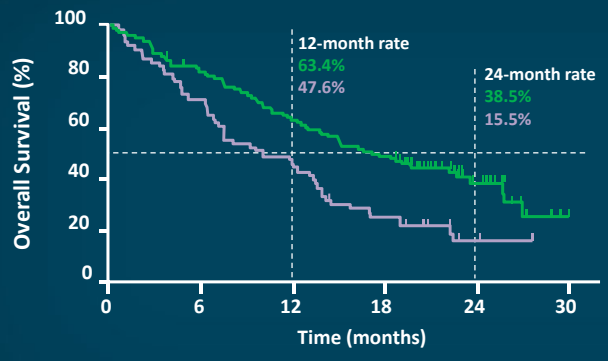

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Pembrolizumab | 132 | 114 | 95 | 85 | 29 | 0 |
| Placebo | 70 | 50 | 34 | 30 | 11 | 0 |

**Median OS (95% CI)**
NR (20.4-NR)
10.1 months (7.5-NR)

**PD-L1 TPS ≥50%** (n = 202)
**PFS** NR vs 10.1 months
**ORR** 62.1% vs 24.3%

TPS = tumor proportion score; NR = not reached.
Gadgeel S, et al. *J Clin Oncol*. 2020;38(4):1505-1517.

# KEYNOTE-189: PD-L1 Status—TPS <1%



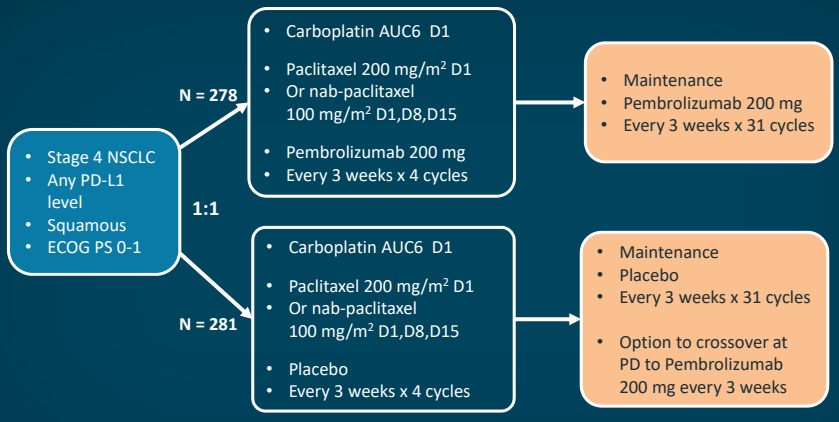

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| Pembrolizumab | 127 | 104 | 79 | 61 | 17 | 0 |
| Placebo | 63 | 45 | 30 | 15 | 2 | 0 |

**Median OS (95% CI)**
17.2 months (13.8-22.8)
10.1 months (7.0-13.5)

**PD-L1 TPS <1%** (n = 192)
**PFS** 17.2 vs 10.2 months
**ORR** 32.3% vs 14.3%

Gadgeel S, et al. *J Clin Oncol*. 2020;38(4):1505-1517.

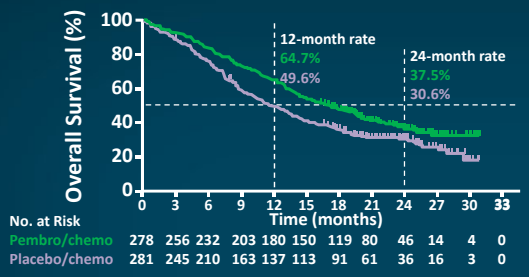
# KEYNOTE-407: Platinum/Taxane +/- Pembrolizumab

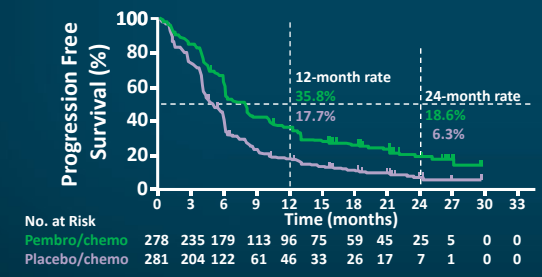



Randomization stratified by: PD-L1 <1% vs ≥1%, geographic region, choice of taxane.
Primary endpoints: PFS, OS.
Secondary endpoints: ORR, duration of response, safety.

Paz-Ares L, et al. *J Thoracic Oncol*. 2020;15(10):1657-1669.

# KEYNOTE-407: Overall Population



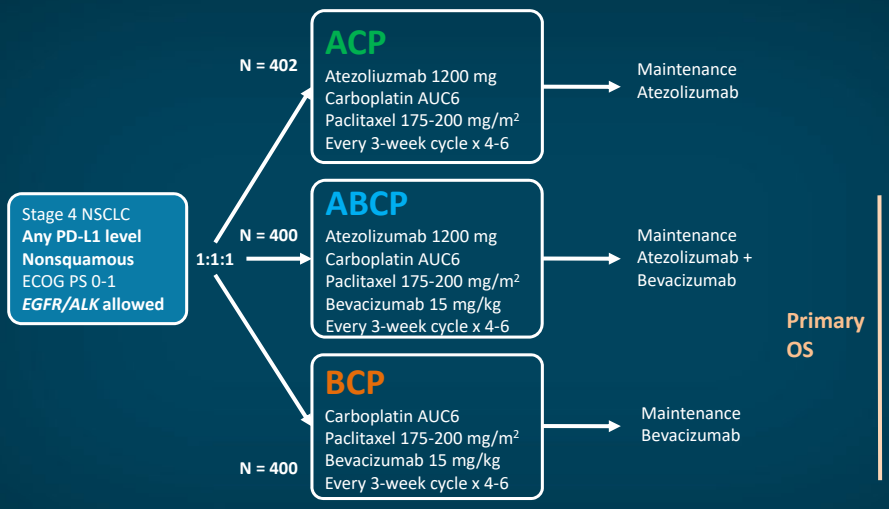

| | Events, n (%) | Median (95% CI) OS, mo | HR (95% CI) |
|---|---|---|---|
| Pembro/ Chemo | 168 (60.4) | 17.1 (14.4-19.9) | 0.71 (0.58-0.88) |
| Placebo/ Chemo | 197 (70.1) | 11.6 (10.1-13.7) | |

| | Pembro/ Chemo N = 278 | Placebo/ Chemo N = 281 |
|---|---|---|
| ORR, % | 62.6% (56.6-68.3) | 38.4% (32.7 – 44.4) |
| CR | 6 (2.2) | 9 (3.2) |
| PR | 168 (60.4) | 99 (35.2) |
| SD | 65 (23.4) | 103 (36.7) |
| PD | 17 (6.1) | 40 (14.2) |

| | Events, n (%) | Median (95% CI) PFS, mo | HR (95% CI) |
|---|---|---|---|
| Pembro/ Chemo | 217 (78.1) | 8.0 (6.3-8.4) | 0.57 (0.47-0.69) |
| Placebo/ Chemo | 252 (89.7) | 5.1 (4.3-6.0) | |

pembro = pembrolizumab; chemo = chemotherapy.
Paz-Ares L, et al. J Thoracic Oncol. 2020;15(10):1657-1669.

# IMpower150: Carbo/Taxol +/-Atezolizumab/Bevacizumab

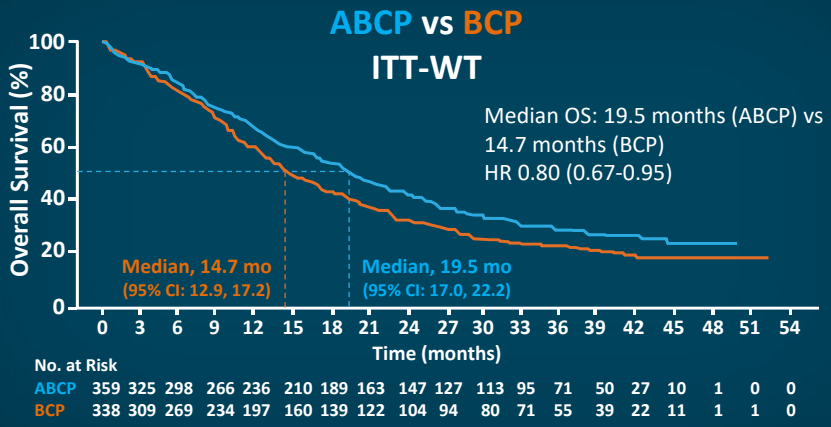



Randomization stratified by: PD-L1, gender, presence of liver metastases.
Primary endpoints: PFS, OS for ABCP vs BCP in *EGFR/ALK* wild-type.

**Carbo = carboplatin; ACP = atezolizumab-carboplatin-paclitaxel; ABCP = atezolizumab-bevacizumab-carboplatin-paclitaxel; BCP = bevacizumab-carboplatin-paclitaxel.**

**Socinski MA, et al. *J Thoracic Oncology*. 2021 [Article in press]. (https://doi.org/10.1016/j.jtho.2021.07.009).**

# IMpower150: Overall Survival Outcomes

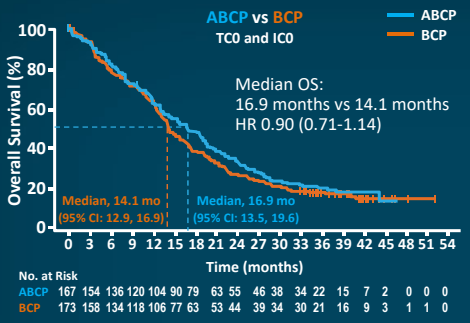



**ITT-WT = intention-to-treat wild-type.**

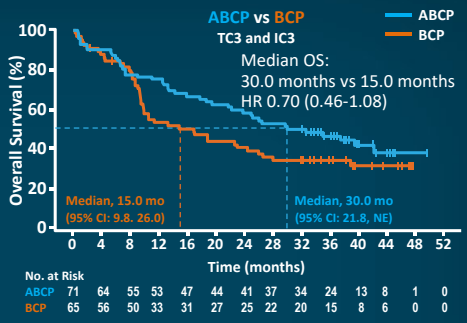
**Socinski MA, et al. *J Thoracic Oncology*. 2021 [Article in press]. (https://doi.org/10.1016/j.jtho.2021.07.009).**

# IMpower150: Final Overall Analysis

## PD-L1 TC0 or IC0




## PD-L1 TC3 or IC3




### SP142 or SP263 PD-L1 Antibodies

| Tumor Cell (TC) Score | | Immune Cell (IC) Score | |
|---|---|---|---|
| **TC3** | ≥50% | **IC3** | ≥10% |
| **TC2** | ≥5% and <50% | **IC2** | ≥5% and <10% |
| **TC1** | ≥1% and <5% | **IC1** | ≥1% and <5% |
| **TC0** | <1% | **IC0** | <1% |

Socinski MA, et al. *J Thorac Oncol*. 2021 [Article in Press]. (https://doi.org/10.1016/j.jtho.2021.07.009).

**Please click here to watch a video of the complementary anti-tumor effects of immunotherapy in combination with chemotherapy**

# Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC

## Immunotherapy Combinations

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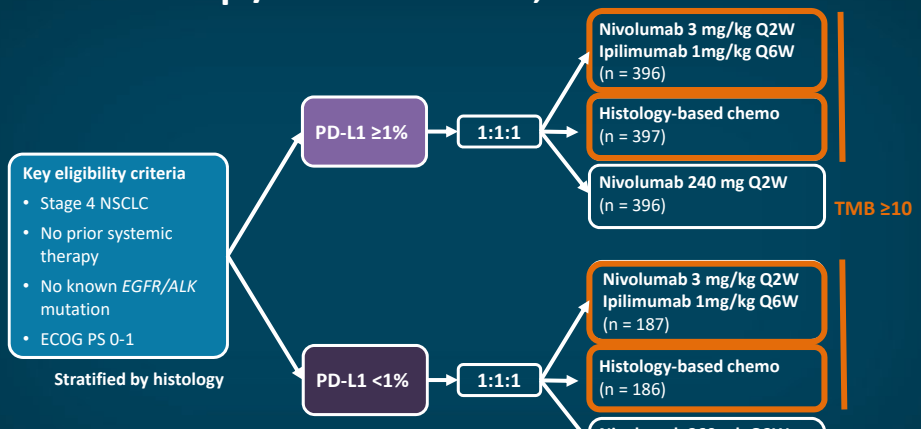
## CheckMate 227: PFS Primary Endpoint Ipi/Nivo vs Chemo, TMB ≥10

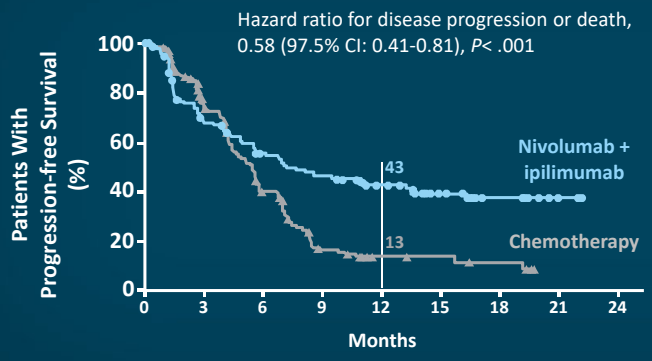



**Coprimary endpoints**
- **OS: Ipi/nivo vs chemo for patients with PD-L1 ≥1%**
- **PFS: Ipi/nivo vs chemo for patients with TMB ≥10 mut/mb**

ipi = ipilimumab; nivo = nivolumab; TMB = tumor mutation burden.
Hellmann MD, et al. *N Engl J Med.* 2019;381:2020-2031.

# CheckMate 227: PFS Primary Endpoint
# Ipi/Nivo vs Chemo, TMB ≥10

## Progression-Free Survival



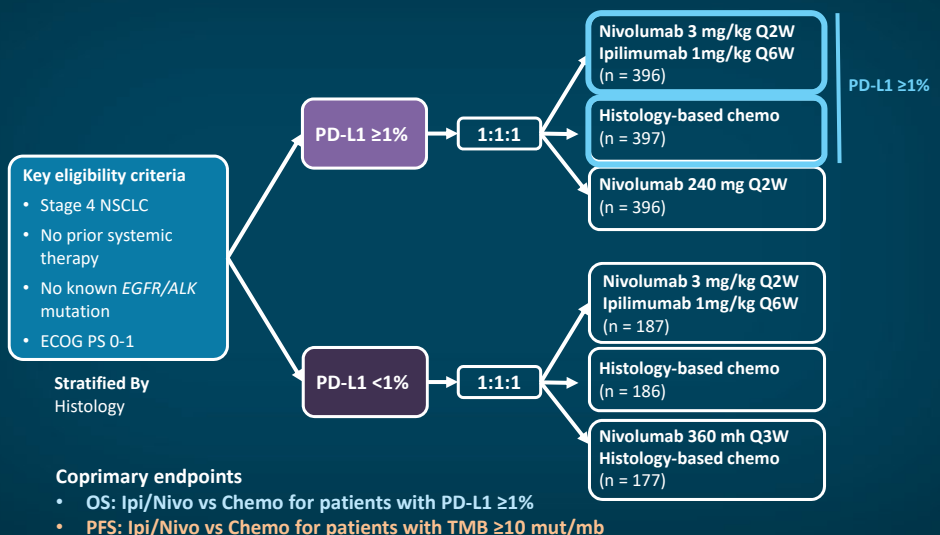

**Median PFS**
7.2 vs 5.5 months
HR 0.58 (0.41-0.81)

**1-Yr PFS-Rate**
43% vs 13%

| No. at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nivo/ipi | 139 | 85 | 66 | 55 | 36 | 24 | 11 | 3 | 0 |
| Chemo | 160 | 103 | 51 | 17 | 7 | 6 | 4 | 0 | 0 |

Hellmann MD, et al. *N Engl J Med*. 2018;378:2093-2104.

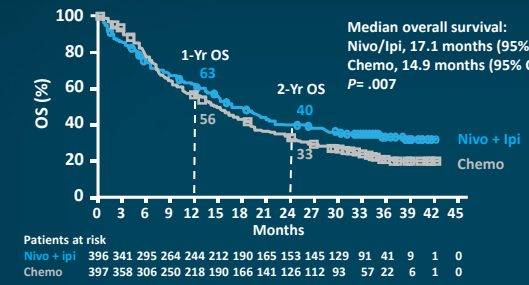
# CheckMate 227: Ipi/Nivo vs Chemo




**Coprimary endpoints**
- **OS: Ipi/Nivo vs Chemo for patients with PD-L1 ≥1%**
- **PFS: Ipi/Nivo vs Chemo for patients with TMB ≥10 mut/mb**

Hellmann MD, et al. *N Engl J Med*. 2018;378:2093-2104.

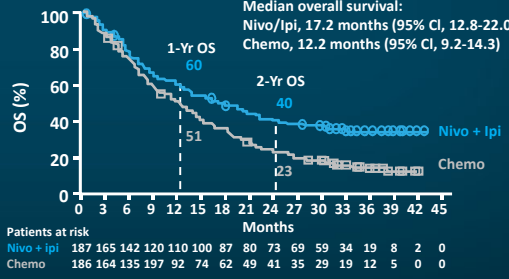
# CheckMate 227: OS Primary Endpoint
# Ipi/Nivo vs Chemo, PD-L1 Positive




Median overall survival:
Nivo/Ipi, 17.1 months (95% CI, 15.0-20.1)
Chemo, 14.9 months (95% CI, 12.7-16.7)
*P*= .007

**Overall Survival**
**PD-L1 ≥1%**

**Overall Survival**
**PD-L1 <1%**

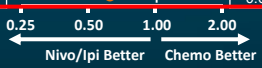



Median overall survival:
Nivo/Ipi, 17.2 months (95% CI, 12.8-22.0)
Chemo, 12.2 months (95% CI, 9.2-14.3)

Hellmann MD, et al. *N Engl J Med*. 2019;381:2020-2031.

# CheckMate 227: OS Primary Endpoint
# Ipi/Nivo vs Chemo, PD-L1 Positive

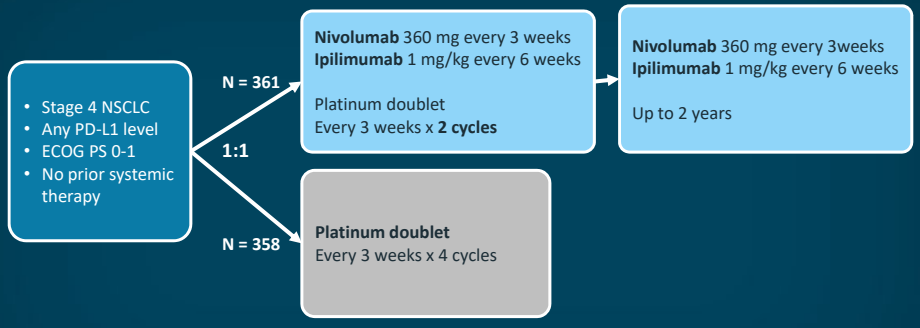
| Subgroup | No. of Patients | Median Overall Survival (months) Nivo/ipi (N = 583) | Median Overall Survival (months) Chemo (N = 583) | Unstratified Hazard Ratio for Death (95% CI) |
|---|---|---|---|---|
| **Randomized Groups** | | | | |
| PD-L1 | | | | |
| All randomized | 1166 | 17.1 | 13.9 | 0.73 (0.64-0.84) |
| <1% | 373 | 17.2 | 12.2 | 0.62 (0.49-0.79) |
| ≥1% | 793 | 17.1 | 14.9 | 0.79 (0.65-0.96) |
| **Additional Exploratory Subgroup Analysis** | | | | |
| PD-L1 | | | | |
| 1-49% | 396 | 15.1 | 15.1 | 0.94 (0.75-1.18) |
| ≥50% | 397 | 21.2 | 14.0 | 0.70 (0.55-0.90) |
| Tumor mutational burden | | | | |
| Low, <10 mut/Mb | 380 | 16.2 | 12.6 | 0.75 (0.59-0.94) |
| High, ≥10 mut/Mb | 299 | 23.0 | 16.4 | 0.68 (0.51-0.91) |
| **PD-L1 and tumor mutational burden (mut/Mb) combined** | | | | |
| PD-L1 <1% | | | | |
| TMB <10 | 111 | 15.5 | 13.0 | 0.69 (0.46-1.05) |
| TMB ≥10 | 86 | 20.4 | 11.2 | 0.51 (0.30-0.87) |
| PD-L1 ≥1% | | | | |
| TMB <10 | 269 | 16.2 | 12.1 | 0.78 (0.59-1.02) |
| TMB ≥10 | 213 | 24.4 | 18.1 | 0.77 (0.54-1.09) |
| PD-L1 ≥50% | | | | |
| TMB <10 | 125 | 18.1 | 8.1 | 0.67 (0.44-1.03) |
| TMB ≥10 | 111 | NR | 17.2 | 0.63 (0.37-1.07) |




TMB = tumor mutational burden.

Hellmann MD, et al. *N Engl J Med*. 2019;381:2020-2031.

# CheckMate 9LA: Ipi/Nivo/Chemo vs Chemo

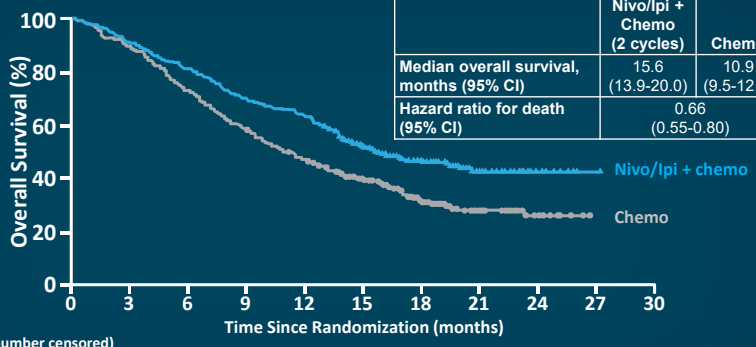



Randomization stratified by: PDL1 <1% vs ≥1%, histology, gender.
Primary endpoints: OS.
Secondary endpoints: PFS ,ORR, duration of response, safety.

Paz-Ares L, et al. *Lancet Oncol*. 2021;22(2):198-211.

# CheckMate 9LA: Ipi/Nivo/Chemo vs Chemo

## Overall Survival: 15.6 Months vs 10.9 Months




| | Nivo/Ipi + Chemo (2 cycles) | Chemo |
|---|---|---|
| Median overall survival, months (95% CI) | 15.6 (13.9-20.0) | 10.9 (9.5-12.6) |
| Hazard ratio for death (95% CI) | 0.66 (0.55-0.80) | |

| No. at Risk (number censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivo/Ipi + Chemo | 361 (0) | 326 (0) | 292 (0) | 250 (0) | 227 (0) | 153 (38) | 86 (90) | 33 (138) | 10 (161) | 1 (170) | 0 (171) |
| Chemo | 358 (0) | 319 (0) | 260 (0) | 208 (0) | 166 (2) | 116 (27) | 67 (56) | 26 (91) | 11 (105) | 0 (116) | 0 (116) |

Overall survival advantage, however, versus chemo monotherapy

Paz-Ares L, et al. *Lancet Oncol*. 2021;22(2):198-211.

# KEYNOTE-598: Pembrolizumab/Ipilimumab for PD-L1 ≥50%

- Stage 4 NSCLC
- PD-L1 ≥50%
- No prior systemic therapy
- No *EGFR/ALK*

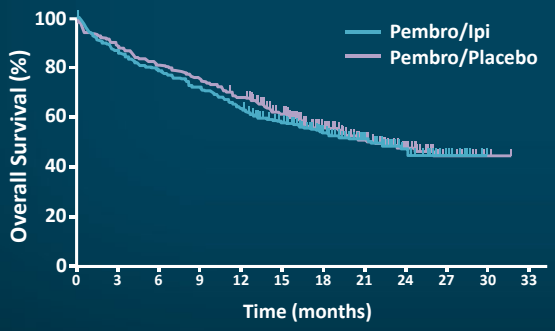
1:1

N = 284 — **Pembrolizumab** 200 mg Q3W x 35 **Ipilimumab** 1 mg/kg Q6W x 18

N = 284 — **Pembrolizumab** 200 mg Q3W x 35 **Placebo** Q6W x 18

**Primary endpoints**
OS and PFS by BICR

**Secondary endpoints**
ORR, duration response, safety

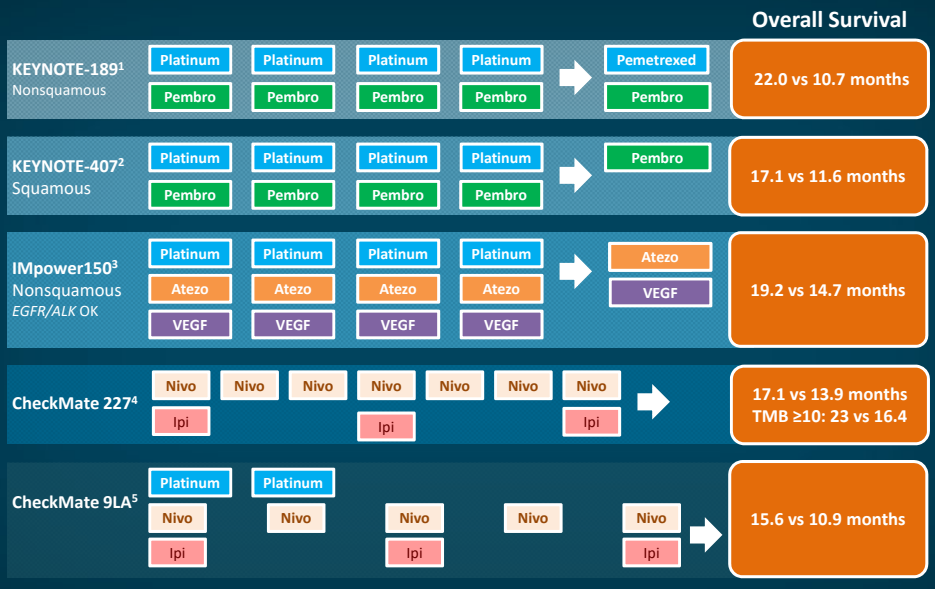



No difference in survival outcomes.

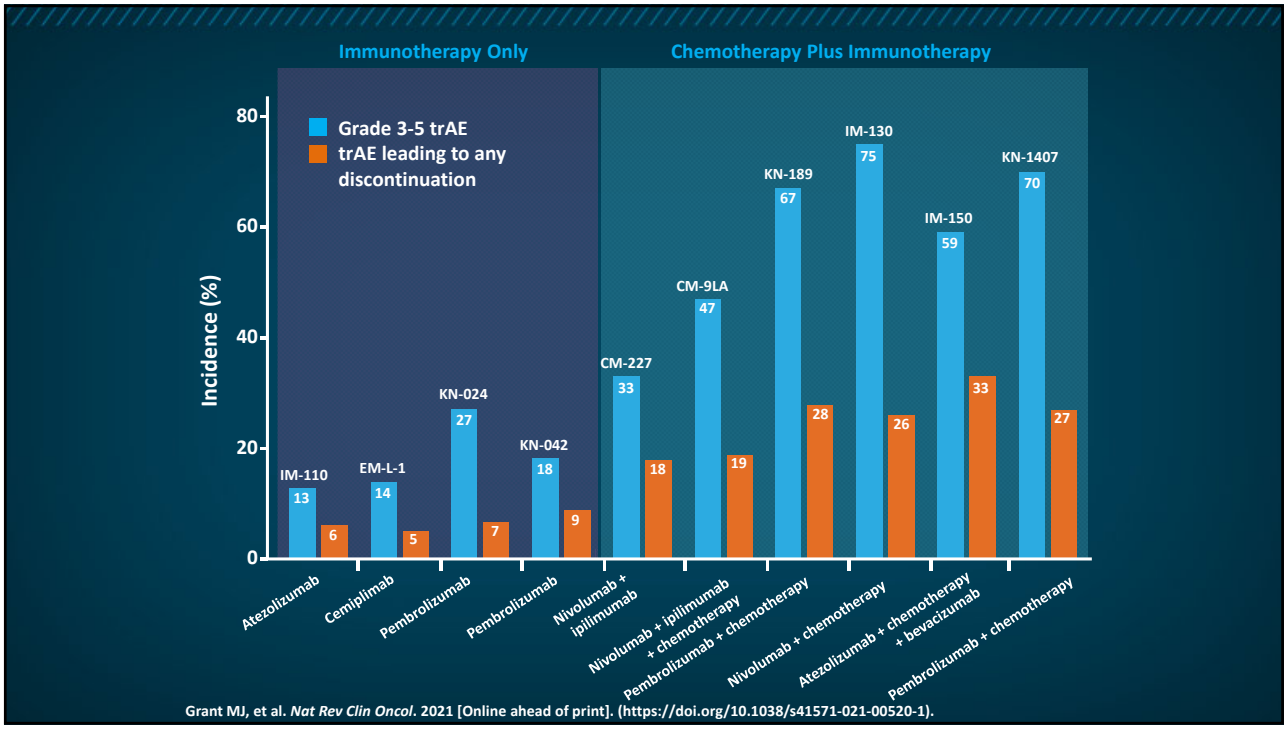
Median OS: 21.4 vs 21.9 months
Median PFS: 8.2 vs 8.4 months

BICR = Blinded independent central review.

Boyer M, et al. *J Clin Oncol*. 2021;39(21):2327-2338.




1. Gandhi L, et al. *N Engl J Med*. 2018;378:2078-2092. 2. Paz-Ares L, et al. *N Engl J Med*. 2018;379:2040-2051. 3. Socinski MA, et al. *N Engl J Med*. 2018;378:2288-2301. 4. Hellmann MD, et al. *N Engl J Med*. 2019;381:2020-2031. 5. Paz-Ares L, et al. *Lancet Oncol*. 2021;22(2):198-211.




Grant MJ, et al. *Nat Rev Clin Oncol*. 2021 [Online ahead of print]. (https://doi.org/10.1038/s41571-021-00520-1).

# Application of Biomarkers to Immuno-Oncology Treatment

## A 64-Year-Old Man With a History of Tobacco Use…

Medical history

Chronic obstructive pulmonary disease (COPD)

Current diagnosis

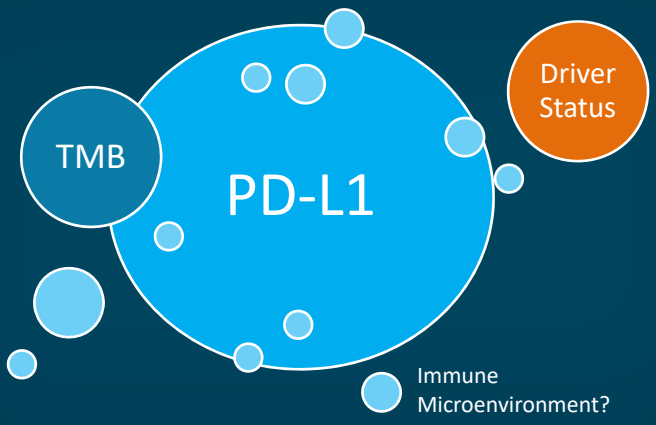
Lung adenocarcinoma involving the right upper lobe, mediastinal lymph nodes, bones, and pleura

Medical examination and workup

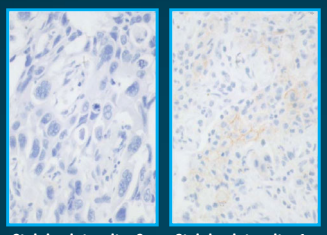
- He remains active
- ECOG PS of 1
- PD-L1 TPS returns at 30%
- Next-generation sequencing (NGS) assay identifies a *KRAS G12C* mutation, as well as a TMB of 16 mutations/megabase

**What first-line therapy do you offer this patient?**

## Biomarkers Impacting Immunotherapy in NSCLC



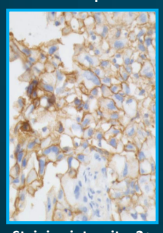
# The Story of PD-L1 as a Biomarker:
## PD-L1+ NSCLC (>50%)—KEYNOTE Studies



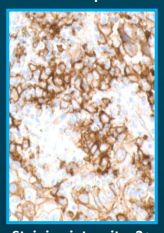
Staining intensity: 0+
PD-L1 = 0% positive



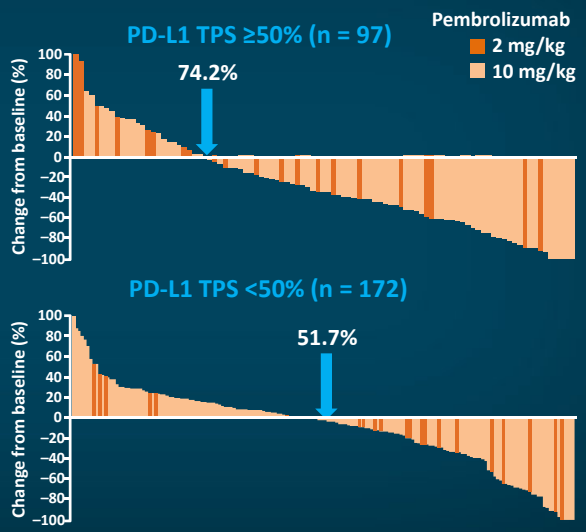
Staining intensity: 1+
PD-L1 = 2% positive



Staining intensity: 2+
PD-L1 = 100% positive



Staining intensity: 3+
PD-L1 = 100% positive

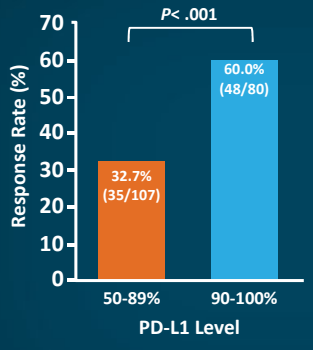


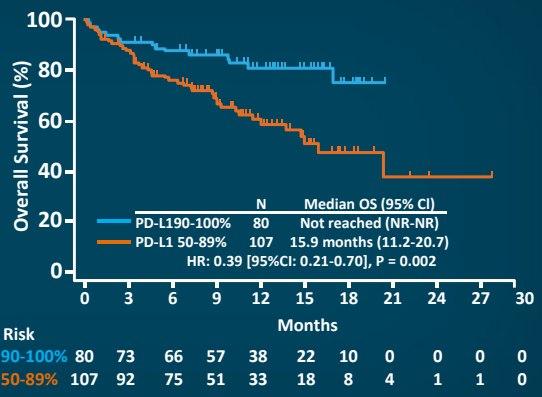

TPS = tumor proportion score.

Soria JC, et al. European Cancer Congress 2015. Abstract 33LBA.

# PD-L1 as a Continuous Variable

## First-Line Pembrolizumab, Retrospective Review



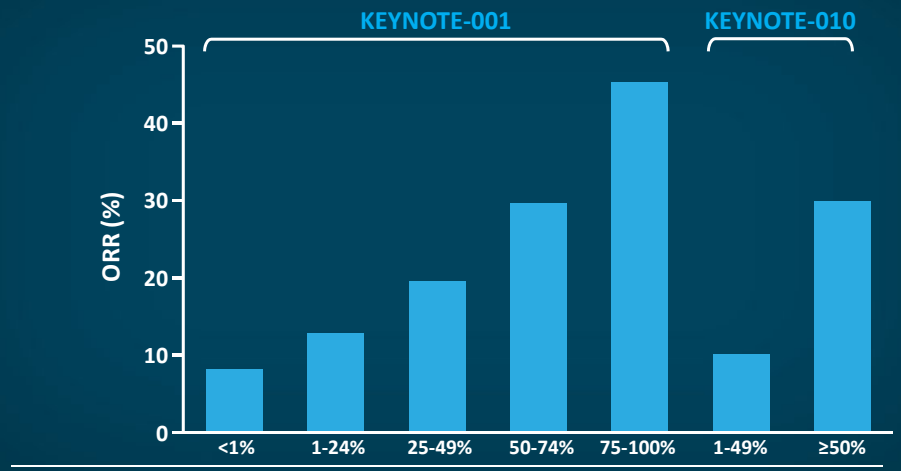

No. at Risk

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PD-L1 90-100% | 80 | 73 | 66 | 57 | 38 | 22 | 10 | 0 | 0 | 0 | 0 |
| PD-L1 50-89% | 107 | 92 | 75 | 51 | 33 | 18 | 8 | 4 | 1 | 1 | 0 |

While studies incorporate fixed PD-L1 thresholds (eg, 1%, 50%), PD-L1 functions as a continuous variable.

Aguilar EJ, et al. *Ann Oncol*. 2019;30(10):1653-1659

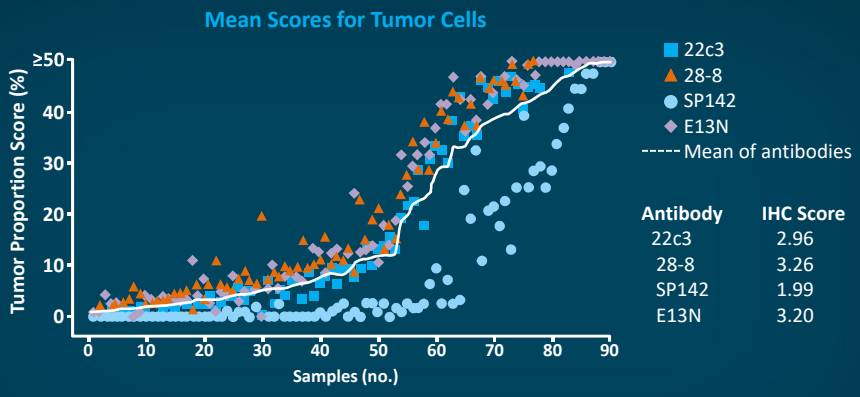
# PD-L1 TPS and ORR to Pembrolizumab KEYNOTE-001 and KEYNOTE-010




| | <1% | 1-24% | 25-49% | 50-74% | 75-100% | 1-49% | ≥50% |
|---|---|---|---|---|---|---|---|
| Response rate (%) | 8.1 | 12.9 | 19.4 | 29.6 | 45.4 | 10/0 | 30.0 |
| Prevalence (%) | 39.2 | 31.0 | 6.7 | 8.6 | 14.6 | 37.9 | 28.4 |

Grigg C, et al. *J Immunother Cancer*. 2016;4:48.

# Mean PD-L1 IHC Score Across Assays



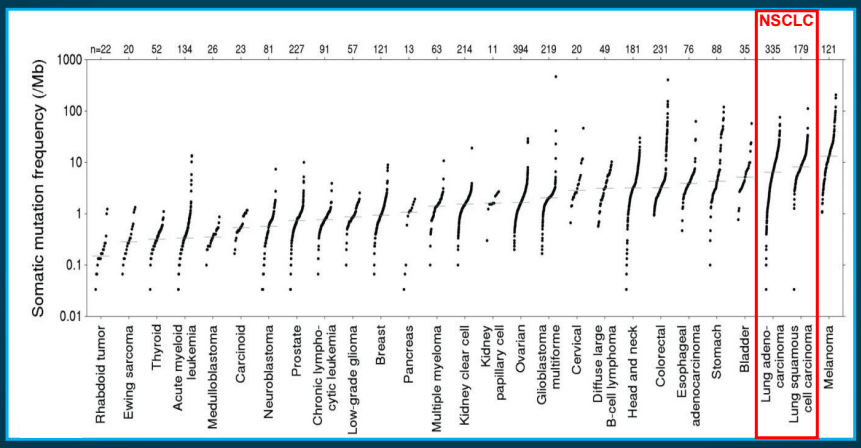

| Antibody | IHC Score |
|---|---|
| 22c3 | 2.96 |
| 28-8 | 3.26 |
| SP142 | 1.99 |
| E13N | 3.20 |

- Lower mean tumor PD-L1 expression score for the SP142 assay compared to the other assays
- High concordance between pathologists for tumor PD-L1 measurement
- Low concordance for immune cell PD-L1 scoring

Rimm DL, et al. *JAMA Oncol*. 2017;3(8):1051-1058.

# Beyond PD-L1: Tumor Mutation Burden (TMB)

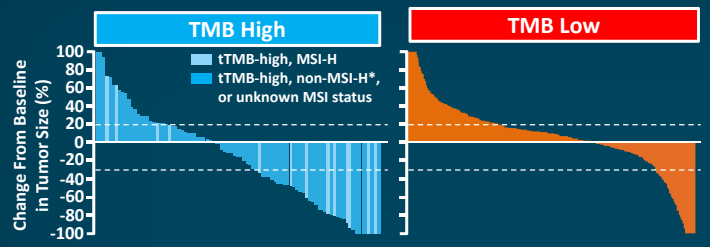
## Somatic Mutation Frequencies in Different Tumors




Lawrence MS, et al. *Nature.* 2013;499:214-218.

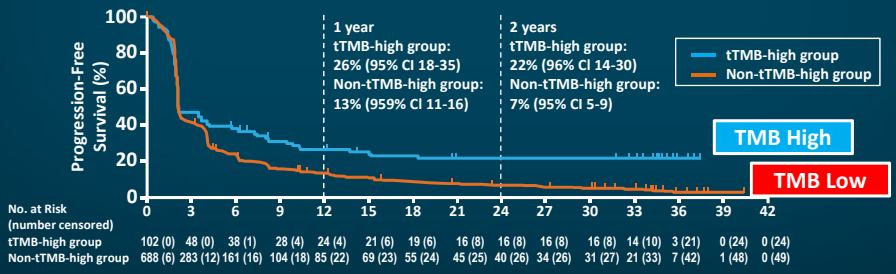
# KEYNOTE-158

- Pembrolizumab has FDA approval for TMB-high solid tumors, based on KEYNOTE-158
  - Phase 2, previously treated solid tumors (n = 102, TMB high, 688 TMB low)
  - Single-arm: pembrolizumab 200 mg every 3 weeks for up to 35 cycles




ORR 29% vs 6%
Median PFS 2.1 months in both groups

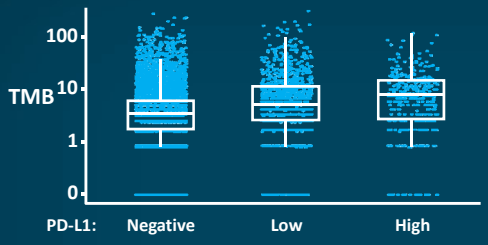
Majority of patients SCLC or gynecologic malignancies

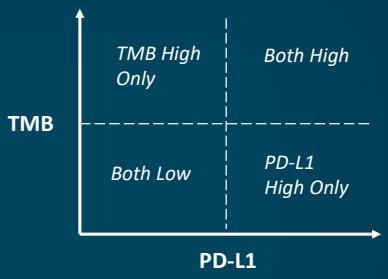



FDA= US Food and Drug Administration. Marabelle A, et al. *Lancet Oncol.* 2020;21(10):1353-1365.

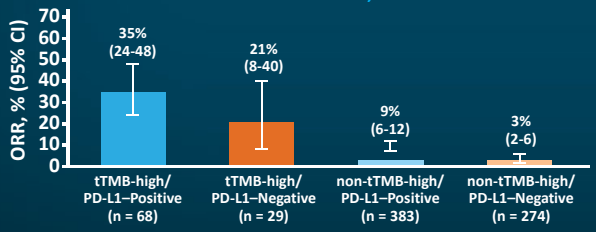
# Are TMB and PD-L1 Independent Biomarkers for Immuno-Oncology (IO) Response?

**Across Solid Tumors PD-L1 and TMB Do Not Correlate**



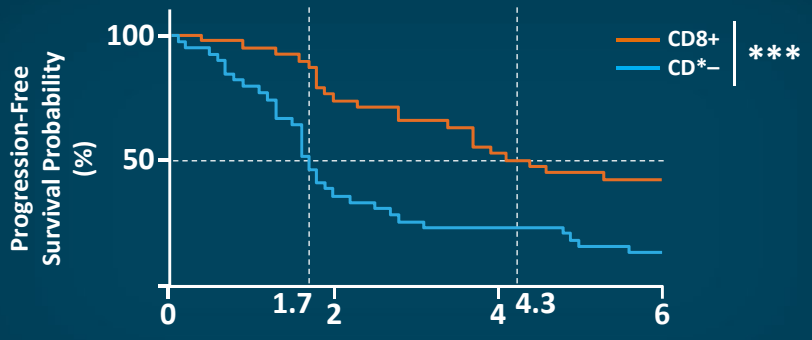

**KEYNOTE-158: Pembrolizumab, Solid Tumors**




Marabelle A, et al. *Lancet Oncol*. 2020;21(10):1353-65. Yarchoan M, et al. *JCI Insight*. 2019;4(6):e126908.

# Immunologic Microenvironment

**Number of Tumor Infiltrating Lymphocytes?**
**Phenotype of Infiltrating Immune Cells?**

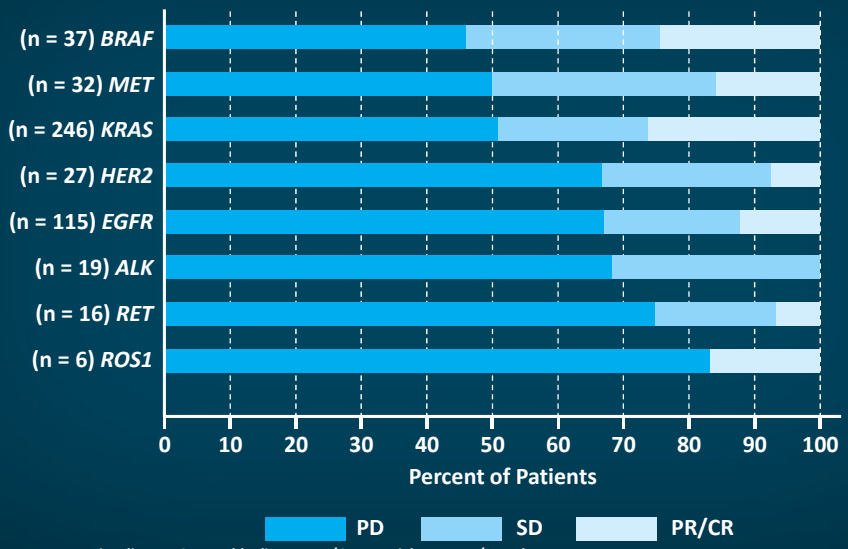



**Nivolumab PFS by CD8 Immunohistochemistry (IHC) Status**

**"Hot" vs "Cold" Immunologic Microenvironment**

Fumet JD, et al. *Br J Cancer*. 2018;119(8):950-960.

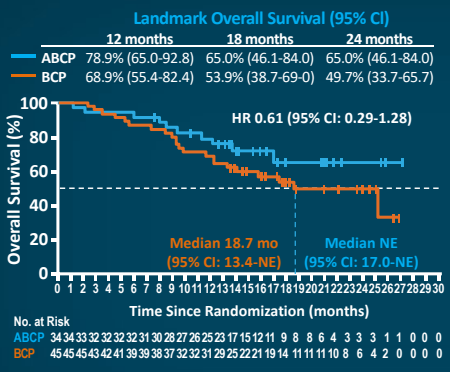
# Driver Mutation Status as a Negative Biomarker




PD = progressive disease; SD = stable disease; PR/CR = partial response/complete response.

Mazieres J, et al. *Ann Oncol*. 2019;30(8):1321-1328.

# Impower 150 *EGFR*m Population

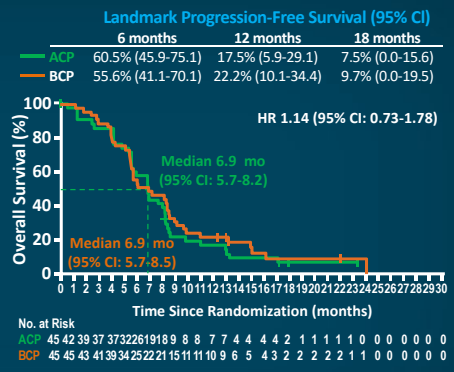



**ABCP vs BCP**

Median OS 18.7 months vs NR

HR 0.61 (0.29-1.28)

*Adding IO + VEGF*




**ACP vs BCP**

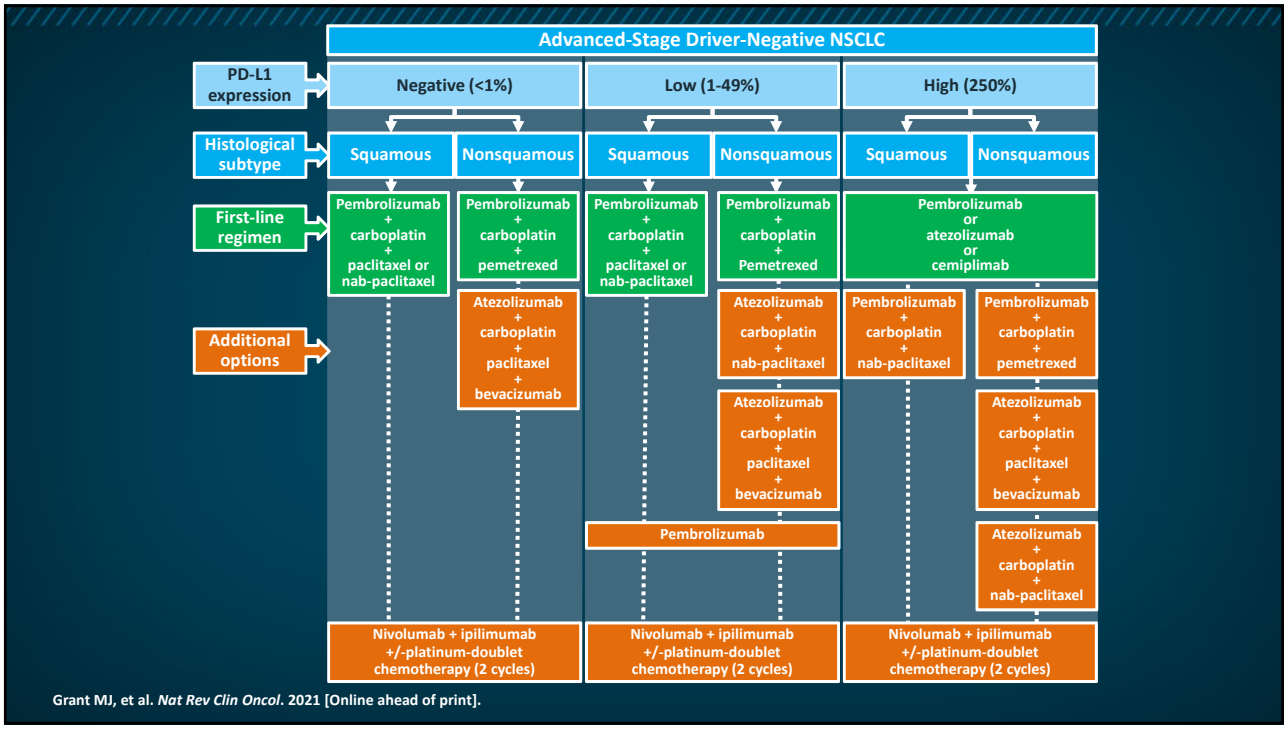
Median OS 6.9 vs 6.9 months

HR 1.14 (0.73-1.78)

*Adding IO only*

VEGF = vascular endothelial growth factor; NE = not estimable.

Reck M, et al. *Lancet Resp Med*. 2019;7(5):387-401.




Grant MJ, et al. *Nat Rev Clin Oncol*. 2021 [Online ahead of print].

## A 64-Year-Old Man With a History of Tobacco Use…

### Medical history

COPD

### Current diagnosis

Lung adenocarcinoma involving the right upper lobe, mediastinal lymph nodes, bones, and pleura

### Medical examination and work-up

- He remains active
- ECOG PS of 1
- PD-L1 TPS returns at 30%
- NGS assay identifies a KRAS G12C mutation, as well as a TMB of 16 mutations/megabase

**What first-line therapy do you offer this patient?**

**Carboplatin/pemetrexed/pembrolizumab** as per KEYNOTE-189

## Clinical Pearls

- Immune dysfunction is integral to the pathogenesis of lung cancer and can be harnessed to treat lung cancers
- Several checkpoint inhibitors are approved by the US Food and Drug Administration for advanced NSCLC, as well as those directed by PD-L1 and TMB as biomarkers
- Several immunomonotherapies and multiple combinations are under investigation
- Patients benefit from clinical trial enrollment whenever possible
- Immunotherapies are also being used in earlier-stage disease and are demonstrating significant improvement in outcomes

## Thank you!

## Tumorigenesis Primer: Immune System Dysfunction in NSCLC

| Resource | Address |
|---|---|
| **Carbone DP, Gandara DR, Antonia SJ, Zielinski C, Paz-Ares L. Non-small-cell lung cancer: Role of the immune system and potential for immunotherapy. *J Thorac Oncol*. 2015;10:974-984.** | https://pubmed.ncbi.nlm.nih.gov/26134219/ |
| **Singh PP, Sharma PK, Krishnan G, Lockhart AC. Immune checkpoints and immunotherapy for colorectal cancer. *Gastroenterol Rep (Oxf)*. 2015;3:289-297.** | https://pubmed.ncbi.nlm.nih.gov/26510455/ |

## Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC: Emerging Data of Immunotherapy Monotherapy

| Resource | Address |
|---|---|
| **Gadgeel S, Rodríguez-Abreu D, Speranza G, et al. Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell cancer. *J Clin Oncol*. 2020;38:1505-1517.** | https://pubmed.ncbi.nlm.nih.gov/32150489/ |
| **Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.** | https://www.nejm.org/doi/10.1056/NEJMoa1801005 |
| **Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med*. 2020;383:1328-1339.** | https://www.nejm.org/doi/full/10.1056/NEJMoa1917346 |
| **Paz-Ares L, Vicente D, Tafreshi A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: Protocol-specified final analysis of KEYNOTE-407. *J Thorac Oncol*. 2020;15:1657-1669.** | https://pubmed.ncbi.nlm.nih.gov/32599071/ |
| **Sezer A, Kilickap, Gümüş M, et al. LBA52 - EMPOWER-Lung 1: Phase III first-line (1L) cemiplimab monotherapy vs platinum-** | https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/empower-lung-1-phase-iii-first-line-1l- |

| | |
|---|---|
| **doublet chemotherapy (chemo) in advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) ≥50%. *Ann Oncol*. 2020;31(suppl 4):S1142-S1215.** | cemiplimab-monotherapy-vs-platinum-doublet-chemotherapy-chemo-in-advanced-non-small-cell-lung-cancer-n |
| **Socinski MA, Nishio M, Jotte RM, et al. Impower150 final overall survival analyses for atezolizumab plus bevacizumab and chemotherapy in first-line metastatic nonsquamous non-small cell lung cancer. *J Thorac Oncol*. 2021;S1556-0864(21)02322-4.** | https://www.jto.org/article/S1556-0864(21)02322-4/fulltext |
| **Spigel D, de Marinis F, Giaccone G, et al. Impower110: Interim overall (OS) analysis of a phase III study of atezolizumab (atezo) vs platinum-based chemotherapy (chemo) as first-line (1L) treatment (tx) in PD-L1-selected NSCLC. *Ann Oncol*. 2019:30(suppl 5):V915.** | https://www.annalsofoncology.org/article/S0923-7534(19)60359-5/fulltext |

## Checkpoint Inhibitor Regimens in Treating Advanced/Metastatic NSCLC: Immunotherapy Combinations

| Resource | Address |
|---|---|
| **Boyer M, Şendur MAN, Rodríguez-Abreu D, et al. Pembrolizumab plus ipilimumab or placebo for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50%: Randomized, double-blind phase III KEYNOTE-598 study. *J Clin Oncol*. 2021;39:2327-2338.** | https://pubmed.ncbi.nlm.nih.gov/33513313/ |
| **Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078-2092.** | https://www.nejm.org/doi/10.1056/NEJMoa1801005 |
| **Grant MJ, Herbst RS, Goldberg SB. Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. *Nat Rev Clin Oncol*. 2021;10.1038/s41571-021-00520-1.** | https://pubmed.ncbi.nlm.nih.gov/34168333/ |
| **Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in** | https://www.nejm.org/doi/full/10.1056/nej |

| | |
|---|---|
| **advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381:2020-2031.** | moa1910231 |
| **Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): An international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:198-211.** | https://pubmed.ncbi.nlm.nih.gov/33476593/ |
| **Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378:2288-2301.** | https://www.nejm.org/doi/10.1056/NEJMoa1716948 |

## Application of Biomarkers to Immuno-oncology Treatment

| Resource | Address |
|---|---|
| **Aguilar EJ, Ricciuti B, Gainor JF, et al. Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. *Ann Oncol*. 2019;30:1653-1659.** | https://pubmed.ncbi.nlm.nih.gov/31435660/ |
| **Fumet JD, Richard C, Ledys F, et al. Prognostic and predictive role of CD8 and PD-L1 determination in lung tumor tissue of patients under anti-PD-1 therapy. *Br J Cancer*. 2018;119:950-960.** | https://pubmed.ncbi.nlm.nih.gov/30318514/ |
| **Grant MJ, Herbst RS, Goldberg SB.. Selecting the optimal immunotherapy regimen in driver-negative metastatic NSCLC. *Nat Rev Clin Oncol*. 2021;10.1038/s41571-021-00520-1.** | https://pubmed.ncbi.nlm.nih.gov/34168333/ |
| **Grigg C, Rizvi NA. PD-L1 biomarker testing for non-small cell lung cancer: Truth or fiction? *J Immunother Cancer*. 2016;4:48.** | https://jitc.bmj.com/content/jitc/4/1/48.full.pdf |
| **Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med*. 2018;378:2093-2104.** | https://pubmed.ncbi.nlm.nih.gov/29658845/ |
| **Herbst RS, Lopes G, Kowalski DM, et al.** | https://oncologypro.esmo.org/meeting- |

| | |
|---|---|
| **Association between tissue TMB (tTMB) and clinical outcomes with pembrolizumab monotherapy (pembro) in PD-L1-positive advanced NSCLC in the KEYNOTE-010 and -042 trials. *Ann Oncol*. 2019;30(suppl 5):v851-v934.** | resources/esmo-2019-congress/Association-between-tissue-TMB-tTMB-and-clinical-outcomes-with-pembrolizumab-monotherapy-pembro-in-PD-L1-positive-advanced-NSCLC-in-the-KEYNOTE-010-and-042-trials |
| **Lawrence M, Stpjanov P, Polak P, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. *Nature*. 2013;499:214-218.** | https://www.nature.com/articles/nature12213 |
| **Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: Prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. 2020;21:1353-1365.** | https://pubmed.ncbi.nlm.nih.gov/32919526/ |
| **Mazieres J, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30:1321-1328.** | https://pubmed.ncbi.nlm.nih.gov/31125062/ |
| **Paz-Ares L, Drilon A, Lusque A, et al. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: Protocol-specified final analysis of KEYNOTE-407. *Ann Oncol*. 2019;30:1321-1328.** | https://pubmed.ncbi.nlm.nih.gov/32599071/ |
| **Ramos-Paradas J, Hernández-Prieto S, Lora D, et al. Tumor mutational burden assessment in non-small-cell lung cancer samples: Results from the TMB$^2$ harmonization project comparing three NGS panels. *J Immunother Cancer*. 2021;9:e001904.** | https://pubmed.ncbi.nlm.nih.gov/33963008/ |
| **Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (Impower150): Key subgroup analyses of** | https://pubmed.ncbi.nlm.nih.gov/30922878/ |

| | |
|---|---|
| **patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387-401.** | |
| **Rimm DL, Han G, Taube JM, et al. A prospective, multi-institutional, pathologist-based assessment of 4 immunohistochemistry assays for PD-L1 expression in non-small cell lung cancer. *JAMA Oncol*. 2017;3:1051-1058.** | https://jamanetwork.com/journals/jamaoncology/fullarticle/2608280 |
| **Soria JC, Mauguen A, Reck M, et al. Systematic review and meta-analysis of randomised phase II/III trials adding bevacizumab to platinum-based chemotherapy as first-line treatment in patients with advanced non-small-cell lung cancer. *Ann Oncol*. 2013;24:20-30.** | https://pubmed.ncbi.nlm.nih.gov/23180113/ |
| **Yarchoan M, Albacker LA, Hopkins AC, et al. PD-L1 expression and tumor mutational burden are independent biomarkers in most cancer. *JCI Insight*. 2019;4:e126908.** | https://pubmed.ncbi.nlm.nih.gov/30895946/ |

Maximizing Personalized Approaches Through Composite Biomarkers in

# METASTATIC NSCLC:

## An Innovative 2D View

# ANIMATIONS

**Pathogenesis of Immune System Dysfunction** https://youtu.be/fDdUzUI2Fz0

**Anti-tumor Effects of IO Plus Chemotherapy** https://youtu.be/tJn2ZsCzAgk

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*This activity is co-provided by Ultimate Medical Academy/Complete Conference Management.*
*This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc and Sanofi Genzyme.*

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