XVII SIMPOSIUM
BASES BIOLÓGICAS DEL CÁNCER
E INNOVACIÓN TERAPÉUTICA

MÁS DE 20 AÑOS A LA VANGUARDIA DE LA FORMACIÓN
EN LA BIOLOGÍA Y TRATAMIENTO DEL CÁNCER

SALAMANCA, 22 Y 23 DE MAYO DE 2025

# Monoterapia vs Combinación en NSCLC PD-L1 altos expresores

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# Declaration of potential conflicts of interest

**Honoraria:** AstraZeneca, Boehringer-Ingelheim, Bayer, Pfizer, Roche, Novartis, Merck Sharp & Dohme, and Bristol-Myers Squibb.

**Consulting or advisory role:** AstraZeneca, Amgen, Bayer, Boehringer-Ingelheim, Daiichi Sankyo, Johnson & Johnson, Pfizer, Roche/Genentech, Eli Lilly and Company, Novartis, Takeda, Merck Sharp & Dohme, Regeneron/Sanofi, BeiGene, Summit Therapeutics, and Bristol-Myers Squibb.

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**Stock Ownership:** None

# OUTLINE

- Background
- IO monotherapy
- IO + Chemotherapy
- IO vs IO + Chemo
- Conclusions

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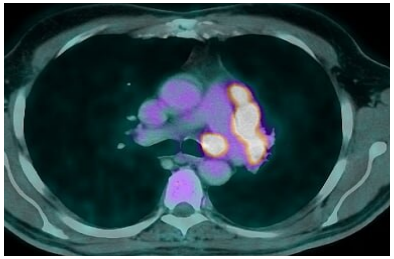
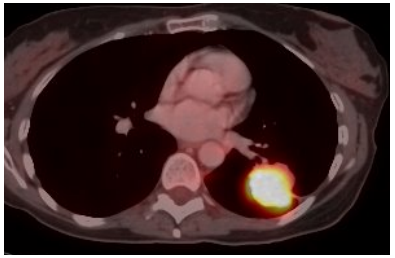
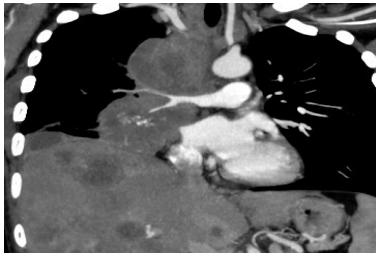
# ICI vs Chemo+ICI in NSCLC and High PD-L1: Why?

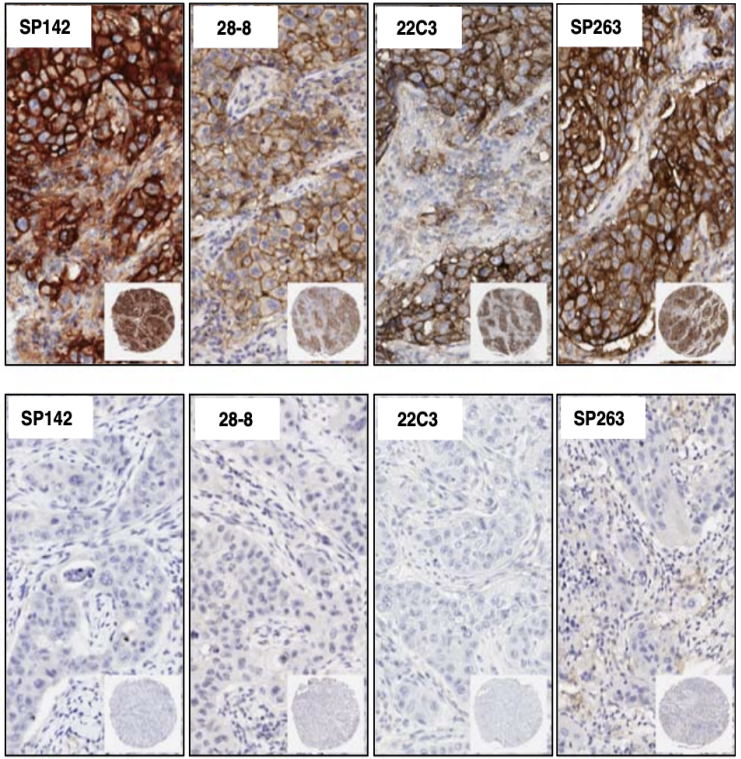
| Case 1 | Case 2 | Case 3 |
|---|---|---|
|  |  |  |
| 72 yo male, former smoker<br>Stage IV KRASmut LUAC<br>M1: Brain, liver, bone<br>PS 1<br>Steroids, WBRT | 67 yo female, never smoker<br>Stage IV wt LUAC<br>M1: Lung, bone<br>PS 0 | 59 yo former smoker<br>Stage IV wt SqCC<br>M1: liver, adrenal, bone<br>PS 2<br>SCVS, hipercalcemia |

- **PD-L1 80%, all patients treated with Pembrolizumab monotherapy**

| | | |
|---|---|---|
| Completed 35 cycles<br>CR, 5 years NED | PD at 4 cycles, added chemo w/o response<br>NGS: RET fusion<br>2 years under PR with selpercatinib | PS declined after 2 cycles<br>Died at 2 months |

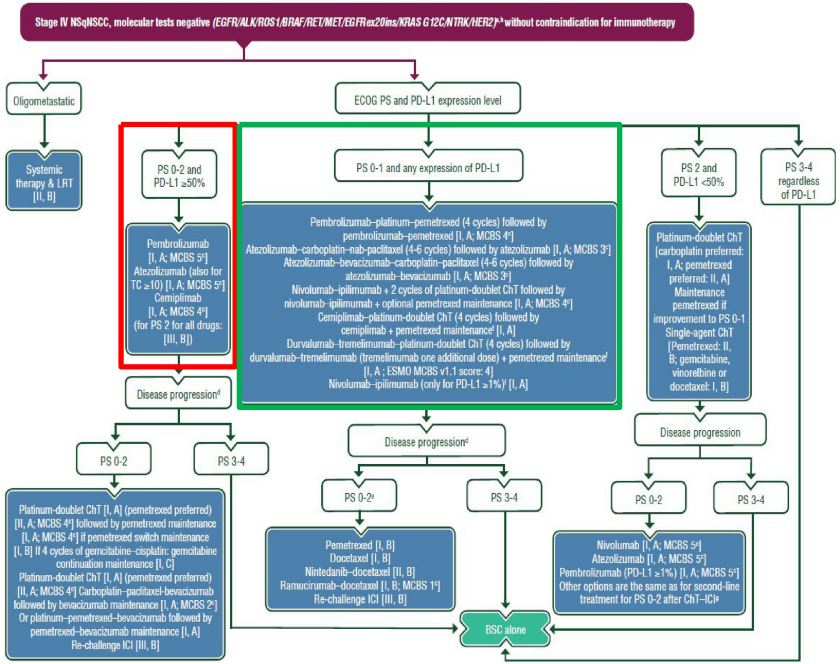
# PD-L1 in stage IV NSCLC without driver mutations

- Immunohistochemistry for PD-L1 expression by tumor proportion score (TPS) predicts response to immunotherapy in advanced NSCLC that lacks a driver mutation.
- PD-L1-high tumors (at least 50%) may be seen in approximately 30% of advanced NSCLCs
- Patients with PD-L1 expression ≥50% are offered therapy with immune checkpoint inhibitor (ICI), with or without platinum-doublet chemotherapy.
- Less than 50% of patients with advanced NSCLC ever receive second-line therapy due to rapid deterioration during disease progression.
- No randomized clinical trial compared ICI vs chemo + ICI in terms of OS, so treatment decision relies on clinical prognostic factors, tumor biology, and availability to therapeutic options.

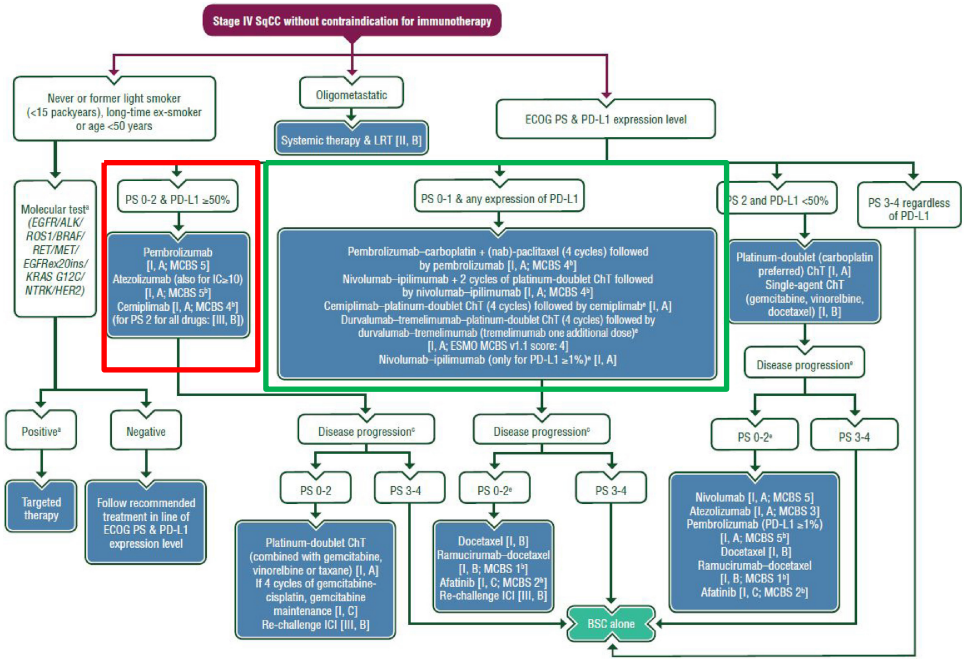


# ESMO guidelines for stage IV NSCLC and PD-L1 ≥50%

## Non-Squamous histology




## Squamous histology




*Hendriks LE, et al. Annals of Oncology DOI: (10.1016/j.annonc.2022.12.013) 2023 ESMO*

# Multiple Available Options For 1L Stage IV NSCLC w/o AGA

**No F2F IO – IO Comparisons To Date**

## High PD-L1 (TPS ≥50%)

### Monotherapy

Squamous and Non-Squamous

- Pembrolizumab — KEYNOTE-024
- Atezolizumab — IMpower-110
- Cemiplimab — EMPOWER-Lung 1

### Combination

Squamous and Non-Squamous

- Cemiplimab + ChT — EMPOWER-Lung 3
- Tislelizumab + ChT — RATIONALE-304 RATIONALE-307

Non-Squamous

- Pembroli… + ChT — …NOTE-189
- Atezo… + … — …wer-150

Squamous

- Pembroli… + ChT — …NOTE-407

Squamous a… …n-Squamous

- Nivolumab + Ipilimumab + ChT — CheckMate-9LA

## Low PD-L1 (TPS <50%) or unknown

### Combination

Squamous and Non-Squamous

- Cemiplimab + ChT (PD-L1≥1%) — EMPOWER-Lung 3
- Nivolumab + Ipilimumab + ChT — CheckMate-9LA

Non-Squamous

- Pembrolizumab + ChT — KEYNOTE-189
- Atezolizumab + ChT + Bev — IMpower-150

Squamous

- Pembrolizumab + ChT — KEYNOTE-407
- Tislelizumab + ChT — RATIONALE-307

*Not reimbursed in Spain*

Modified from Reck M. *J Clin Oncol*. 2022.

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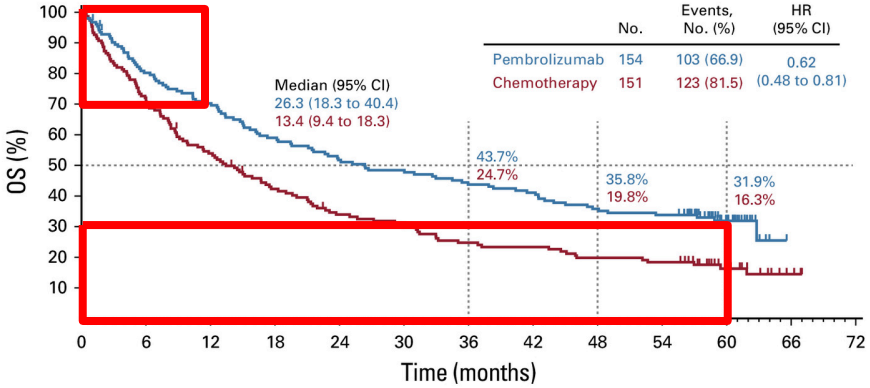
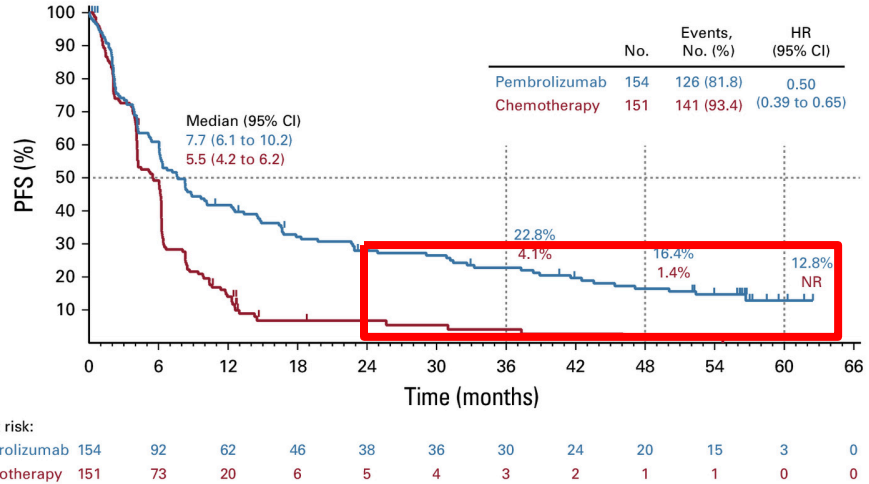
# Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50% (Keynote-024)



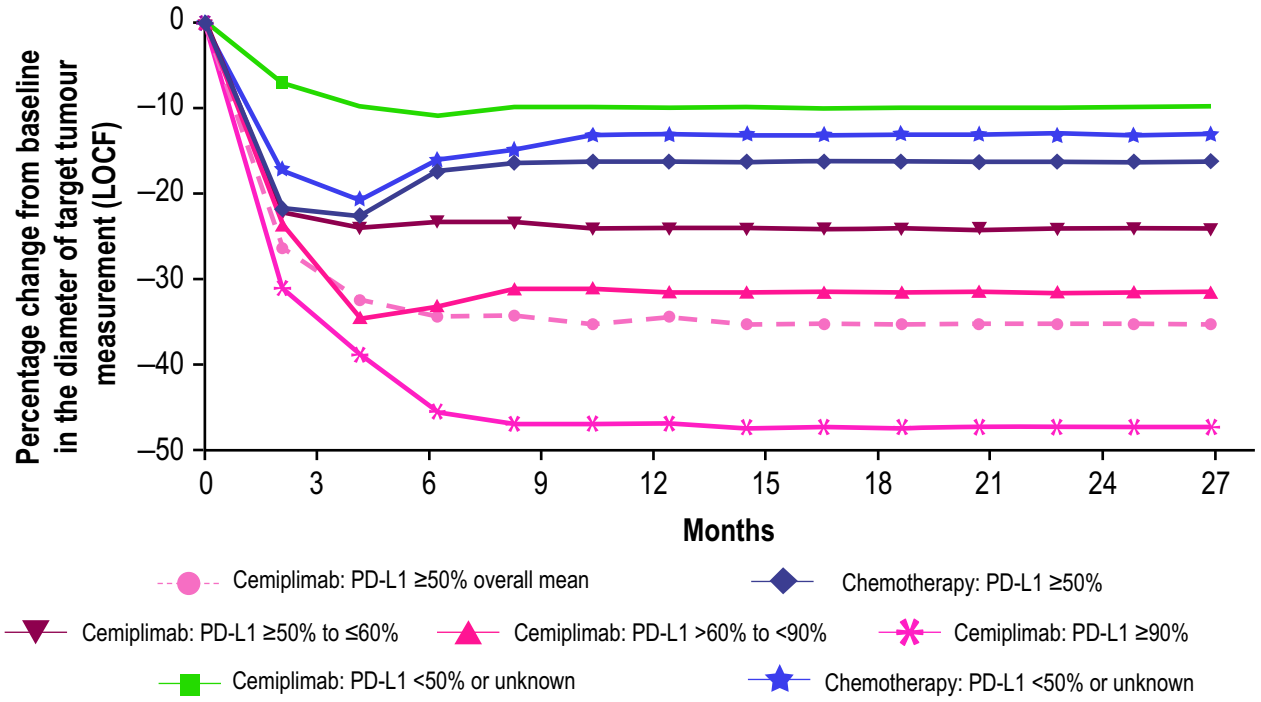




ORR 46.1% vs 31%
DOR 29.1 months vs 6.4 months
25.8% completed 35 cycles of pembrolizumab

Crossover: 66%
Pembrolizumab rechallenge:
ORR 33.3%, SD 50%

Reck M. J Clin Oncol. 2021

# PD-L1 expression correlates with response to ICI



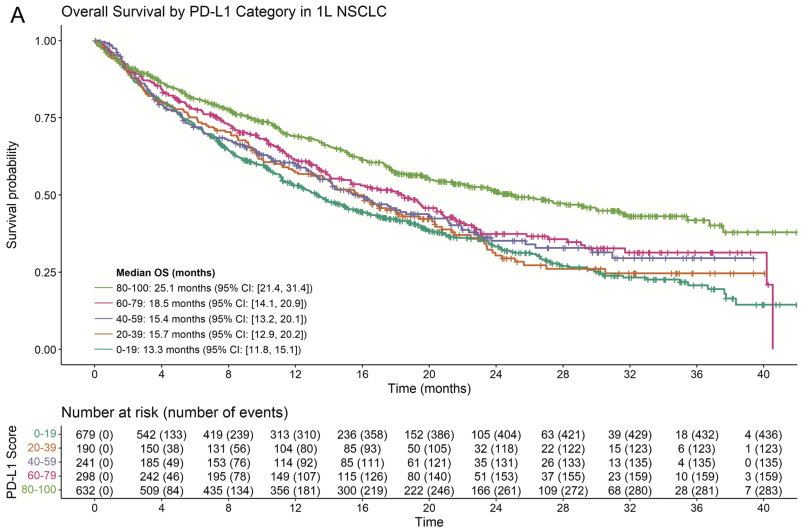

| PD-L1 levels | ORR, % (95% CI) |
|---|---|
| ≥90% | 45.9 (35.8–56.3) vs 18.1 (10.9–27.4) |
| >60 to <90% | 39.3 (29.1–50.3) vs 20.0 (12.3–29.8) |
| ≥50 to ≤60% | 32.3 (23.1–42.6) vs 22.9 (15.0–32.6) |
| 50% or unknown | 26.0 (16.5–37.6) vs 21.6 (12.9–32.7) |

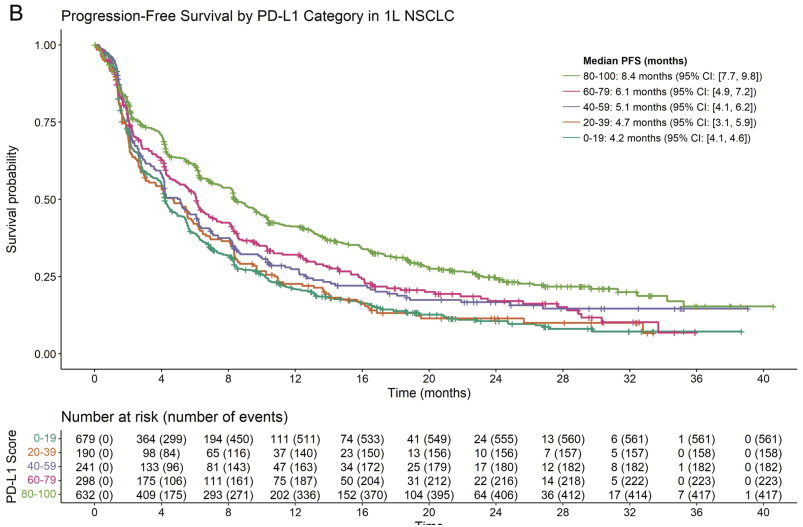
Cemiplimab
vs
Chemotherapy

# Impact of Increasing PD-L1 Levels on Outcomes to PD-1/PD-L1 Inhibition in Patients With NSCLC

**Retrospective pooled analysis FDA (2015-2022)**

**11 RCT (n=3806)**



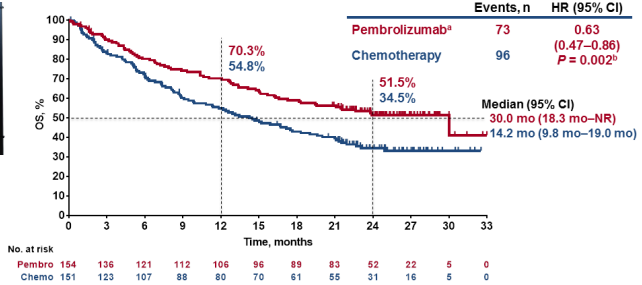

Vallejo J. Oncologist. 2024

# 1L NSCLC: Phase 3 Trials With IO Monotherapy
# Not a happy story for everyone

## KN-024

PD-L1 ≥50%: Pembrolizumab

**Overall Survival: Updated Analysis**

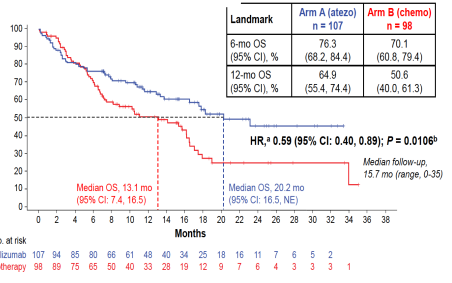



| | Events, n | HR (95% CI) |
|---|---|---|
| Pembrolizumab[a] | 73 | 0.63 (0.47–0.86) *P* = 0.002[b] |
| Chemotherapy | 96 | |

## IMpower 110

TC3 o IC3: Atezolizumab

OS:

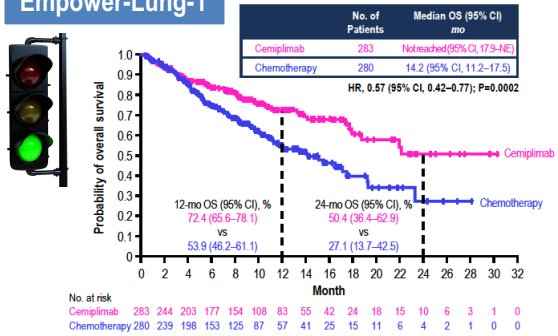



| Landmark | Arm A (atezo) n = 107 | Arm B (chemo) n = 98 |
|---|---|---|
| 6-mo OS (95% CI), % | 76.3 (68.2, 84.4) | 70.1 (60.8, 79.4) |
| 12-mo OS (95% CI), % | 64.9 (55.4, 74.4) | 50.6 (40.0, 61.3) |

## Empower-Lung-1

PD-L1 ≥50%: Cemiplimab

PD-L1 ≥50% ITT

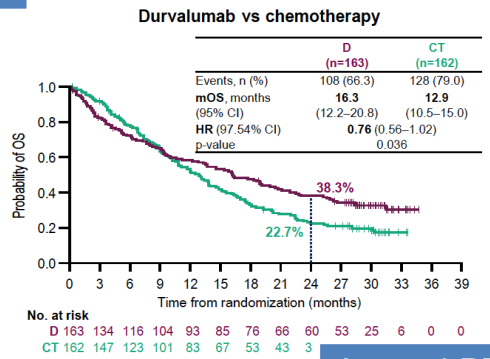



| | No. of Patients | Median OS (95% CI) *mo* |
|---|---|---|
| Cemiplimab | 283 | Not reached (95% CI, 17.9–NE) |
| Chemotherapy | 280 | 14.2 (95% CI, 11.2–17.5) |

## MYSTIC

PD-L1 ≥25%: Durvalumab

**Durvalumab vs chemotherapy**

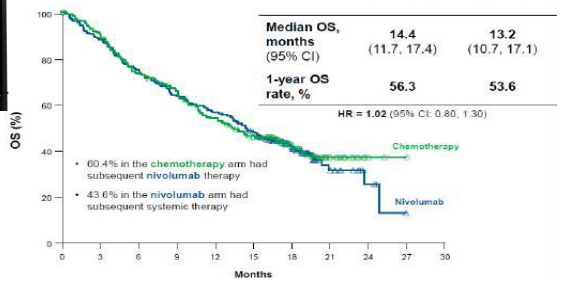



| | D (n=163) | CT (n=162) |
|---|---|---|
| Events, n (%) | 108 (66.3) | 128 (79.0) |
| **mOS**, months (95% CI) | **16.3** (12.2–20.8) | **12.9** (10.5–15.0) |
| **HR** (97.54% CI) | **0.76** (0.56–1.02) | |
| p-value | 0.036 | |

## CM-026

PD-L1 ≥5%: Nivolumab

**OS (≥5% PD-L1+)**



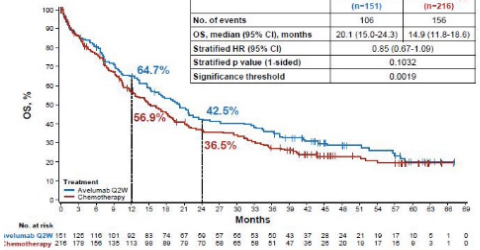

| | Nivolumab n = 211 | Chemotherapy n = 212 |
|---|---|---|
| Median OS, months (95% CI) | 14.4 (11.7, 17.4) | 13.2 (10.7, 17.1) |
| 1-year OS rate, % | 56.3 | 53.6 |

HR = 1.02 (95% CI: 0.80, 1.30)

## KN-042

PD-L1 ≥1%: Avelumab

**Avelumab Q2W vs chemotherapy**

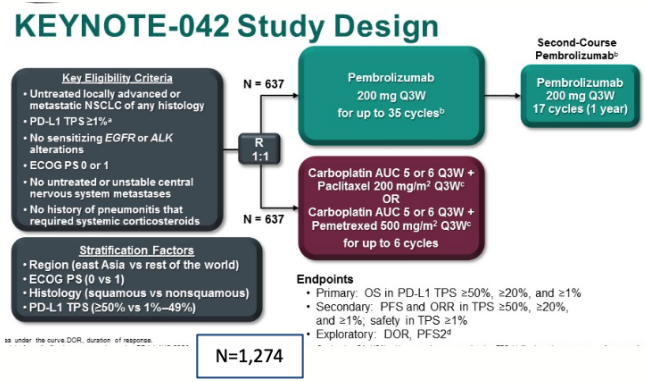


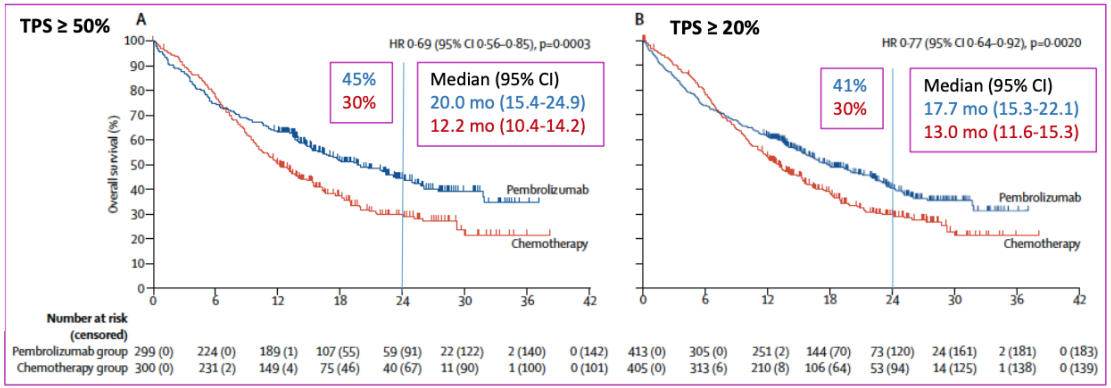

| | Avelumab Q2W (n=151) | Chemotherapy (n=216) |
|---|---|---|
| No. of events | 106 | 156 |
| OS, median (95% CI), months | 20.1 (15.0–24.3) | 14.9 (11.8–18.6) |
| Stratified HR (95% CI) | 0.85 (0.67–1.09) | |
| Stratified p value (1-sided) | 0.1032 | |
| Significance threshold | 0.0019 | |

Are anti-PD(L)-1 ICI interchangeable? Heterogeneous population?

Cross-study comparisons are not intended.

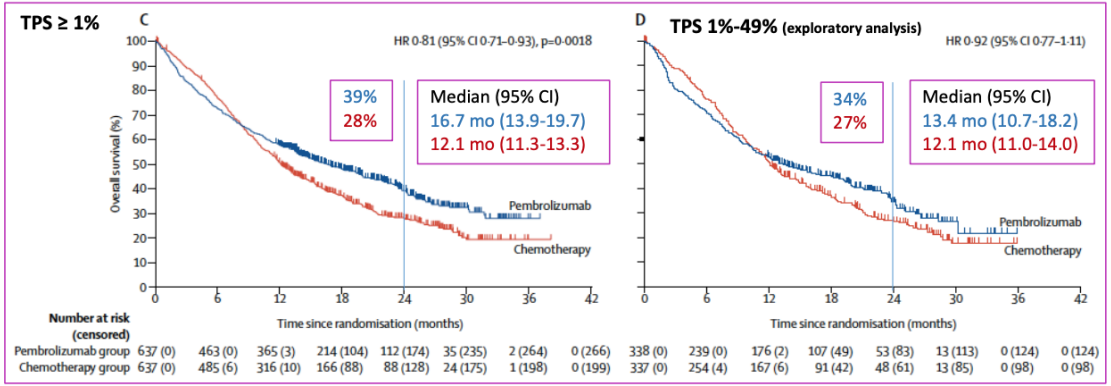
# Front Line Protocols: IO only




| | Pembrolizumab group (n=636) | | Chemotherapy group (n=615) | |
|---|---|---|---|---|
| | Any grade | Grades 3–5 | Any grade | Grades 3–5 |
| Any event | 399 (63%) | 113 (18%) | 553 (90%) | 252 (41%) |
| Event leading to discontinuation | 57 (9%) | 48 (8%) | 58 (9%) | 43 (7%) |
| Event leading to death* | 13 (2%) | 13 (2%) | 14 (2%) | 14 (2%) |

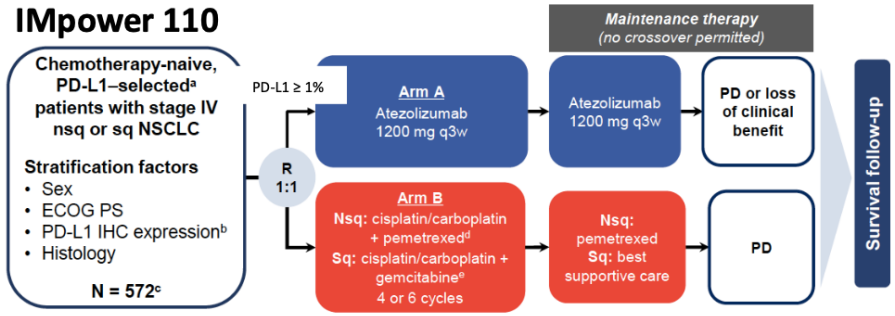
These results were confirmed with a follow-up of 47 months




*Mok TSK, et al. Lancet 2019;393(10183):1819-30; Cho BC, et al. J Thorac Oncol 2021;16:S225-S226*

# Front Line Protocols: IO only

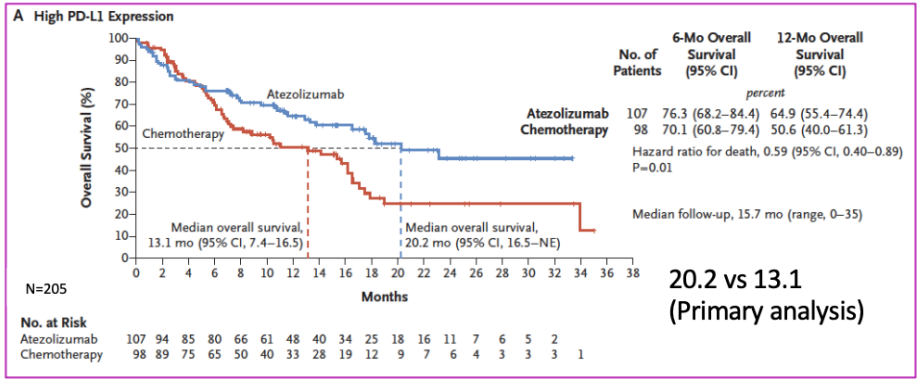
## IMpower 110



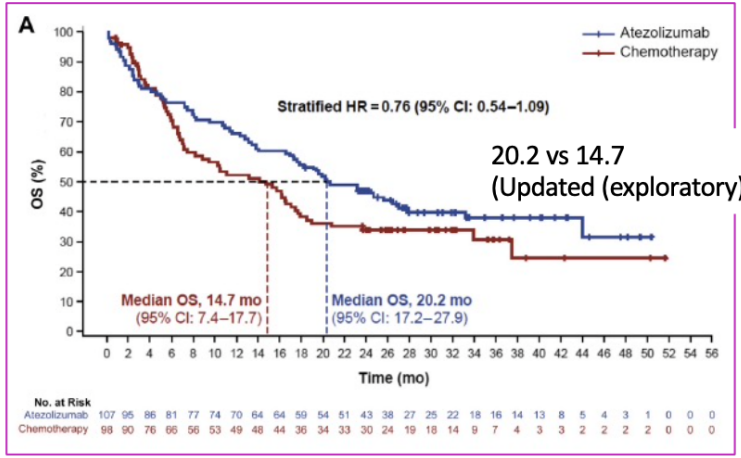

- Primary endpoint: OS in WT population[f]
- Key secondary endpoints: investigator-assessed PFS, ORR and DOR (per RECIST version 1.1)

| Outcome High PD-L1 expression WT | Atezo n=107 | Chemo n=98 |
|---|---|---|
| Median PFS, mo | 8.2 | 5.0 |
| 1-y PFS, % | 39.2 | 19.2 |
| 2-y PFS, % | 25.7 | 7.9 |
| ORR (95% CI), % | 40.2 (30.8-50.1) | 28.6 (19.9-38.6) |
| Median DOR (range), mo | 38.9 (2.8-46.3) | 8.3 (2.6-30.0) |

Updated (exploratory) analysis
Median follow-up:
31.3 mo (range, 0-52 mo)




20.2 vs 13.1
(Primary analysis)




20.2 vs 14.7
(Updated (exploratory) analysis)

*Herbst RS, et al. N Engl J Med. 2020;383(14):1328-39; Jassem J, et al. J Thorac Oncol. 2021;16(11):1872-82*

# Front Line Protocols: IO only

## EMPOWER-Lung 01

**Key eligibility criteria**
- Treatment-naive advanced NSCLC
- PD-L1 ≥50%
- No *EGFR*, *ALK* or *ROS1* mutations
- ECOG performance status 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

**Stratification factors**
- Histology (squamous vs non-squamous)
- Region (Europe, Asia or ROW)

**Endpoints**
- Primary: OS and PFS
- Secondary: ORR (key), DOR, HRQoL and safety

R 1:1

**Arm A**
Cemiplimab monotherapy
350 mg IV Q3W
Treat until Progressive Disease or 108 weeks

Progressive Disease → Optional continuation of cemiplimab + 4 cycles of chemotherapy

Crossover rate of 74%

**Arm B**
4–6 cycles of investigator's choice chemotherapy

Progressive Disease → Optional crossover to cemiplimab monotherapy

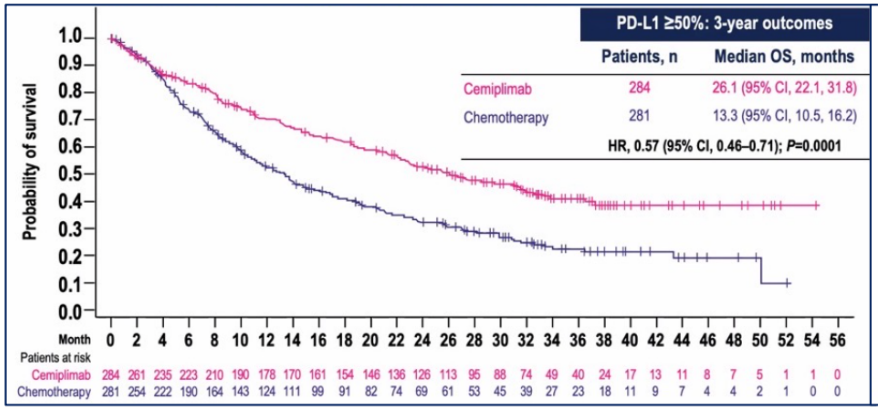
Follow-up

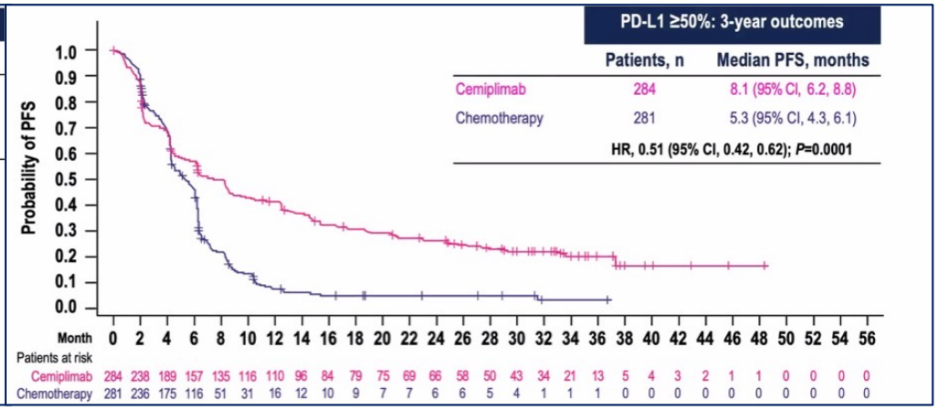
ITT (N=712[1])
Here we report data per cutoff of 4 March 2022
Median time from randomisation to data cutoff: 37.1 months (range: 24.0– 56.5)

PD-L1 ≥50% population (N=565[1])
PD-L1 testing by 22C3 assay performed per instructions for use

N=563 with PD-L1 ≥ 50%

| | PD-L1 ≥50% | |
|---|---|---|
| | Cemiplimab (n=284) | Chemotherapy (n=281) |
| Best Overall Tumor Response, n (%) | | |
| Complete Response (CR) | 23 (8.1) | 6 (2.1) |
| Partial Response (PR) | 109 (38.4) | 53 (18.9) |
| Stable Disease (SD) | 65 (22.9) | 142 (50.5) |
| Non-CR/Non-PD | 2 (0.7) | 2 (0.7) |
| Progressive Disease (PD) | 60 (21.1) | 45 (16.0) |
| Not Evaluable (NE) | 25 (8.8) | 33 (11.7) |
| Objective Response Rate (ORR: CR+PR) | 132 (46.5) | 59 (21.0) |
| 95 CI for ORR (n%) | (40.6, 52.5) | (16.4, 26.2) |
| Odds ratios (range), two-sided p-value | 3.264 (2.255, 4.724) p <0.0001 | |
| Median DOR, months (95% CI) | 23.6 (16.8, 33.0) | 5.9 (4.3, 6.5) |




*Sezer A, et al. Lancet 2021;397(10274):592-604; Özgüroglu M, et al. LBA54 presented at ESMO 2022*

# The Benefit of I-O Monotherapy Is Established in NSCLC With High PD-L1 Expression

## Outcomes in NSCLC With High PD-L1 Expression and Access in Spain

| Trial | KEYNOTE-024[1,2] | IMpower110[3] | EMPOWER-Lung 1[4,5] |
|---|---|---|---|
| Treatment | Pembrolizumab (n=154) | Atezolizumab (n=107) | Cemiplimab (n=283) |
| ORR | 44.8% | 38.3% | 39.2% |
| Median PFS (months) | 10.3 | 8.1 | 8.2 |
| Median OS (months) | 26.3 | 20.2 | 26.1 |
| | | | |
| Unresectable stage III not amenable for chemo-RT | Not evaluated | Not evaluated | Excluded |
| Unfit for chemo | No | Under evaluation | No |
| Body weight dose adjustment | Possible | No | Possible |
| q6 weeks dosing | Yes | Yes | No |
| s.c. administration | Coming soon | Yes | No |

Cross-study comparisons are not intended.

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# Front Line Protocols: IO + Chemotherapy

| Study | Drug | Control | Histology | PD-L1 Cutoffs | PFS (mo)<br>IO vs control | OS (mo)<br>IO vs control |
|---|---|---|---|---|---|---|
| KEYNOTE 407 | Carboplatin<br>Taxane<br>Pembrolizumab | Carboplatin<br>Taxane | SCC | None | 8.0 vs 5.1<br>5-year PFS (%)<br>10.8% vs 3.5% | 17.2 vs 11.6<br>5-year OS (%)<br>18.4% vs 9.7% |
| KEYNOTE 189 | Platinum<br>Pemetrexed<br>Pembrolizumab | Platinum<br>Pemetrexed | Non-SCC | None | 9 vs 4.9<br>5-year PFS (%)<br>7.5% vs 0.6% | 22 vs 10.6<br>5-year OS (%)<br>19.4% vs 11.3% |
| IMpower 150 | Carboplatin<br>Paclitaxel<br>Bevacizumab<br>Atezolizumab | Carboplatin<br>Paclitaxel<br>Bevacizumab | Non-SCC | None | 8.3 vs 6.8 | 19.5 vs 14.7 |
| IMpower 130 | Carboplatin<br>Nab-Paclitaxel<br>Atezolizumab | Carboplatin<br>Nab-Paclitaxel | Non-SCC | None | 7 vs 5.5 | 18.6 vs 13.9 |

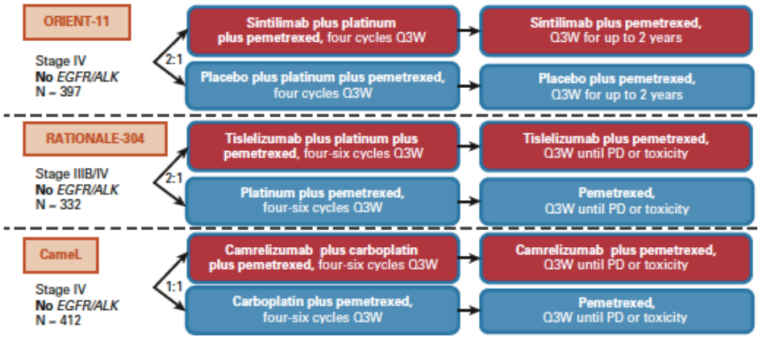
***Not approved in Spain (SNS) for PD-L1 ≥50%***

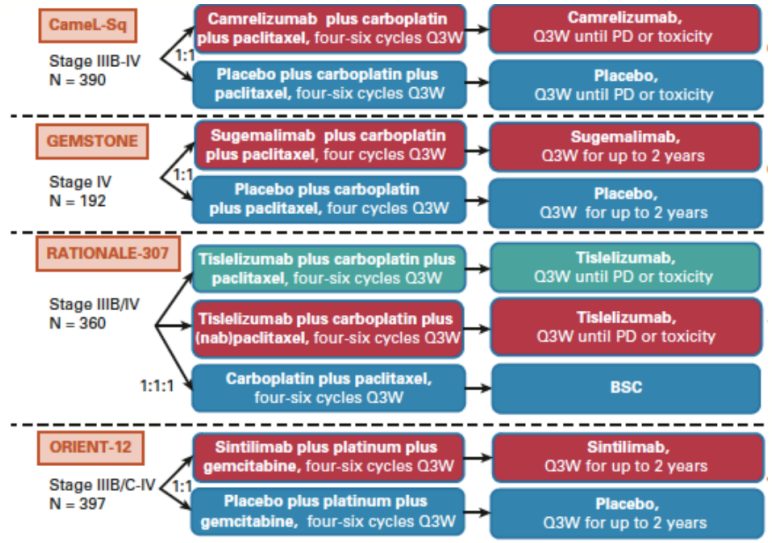
# Front Line Protocols: IO + Chemotherapy

In Chinese patients

- Other new anti-PD-1 inhibitors:
  - Sintilimab in ORIENT-11 (ELCC 2022), ORIENT-12
  - Tislelizumab in RATIONALE-304, RATIONALE-307
  - Camrelizumab in CameL, CameL-Sq

- Oher anti-PD-L1:
  - Sugemalimab in GEMSTONE-302




*Reck M. et al. J Clin Oncol 2022;40:586-97*

# EMPOWER-Lung 3: Cemiplimab in Combination With Chemotherapy in Treatment-näive Advanced NSCLC

## EMPOWER-Lung 3 (Part 2) Study Design (NCT03409614)

**Background:** Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

**Key eligibility criteria**
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c[†], IV)
- Any PD-L1 expression
- No *EGFR*, *ALK*, or *ROS1* mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases [‡]

**Stratification factors**
- PD-L1 expression: <1% vs 1–49% vs ≥50%
- Histology: non-squamous vs squamous

**Endpoints**
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

R 2:1

**Arm A** Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles[§] → PD or 108 weeks

**Arm B** Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles [§] → PD or 108 weeks

Follow-up

**N=466**

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

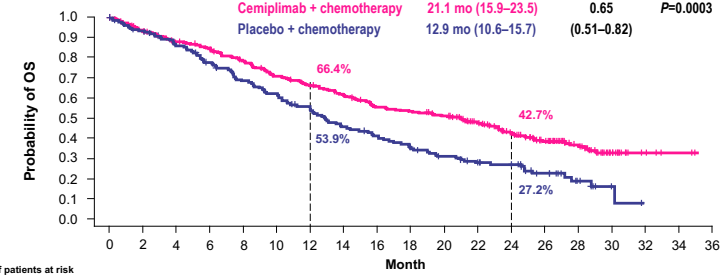
[†]Patient not a candidate for definitive chemoradiation. [‡]Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment). [§]For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen. *ALK*, anaplastic lymphoma kinase gene; BOR, best overall response; chemo, chemotherapy; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomised; *ROS1*, c-ros oncogene 1.

1. Sezer A et al. *Lancet* 2021;397:592–604.

2021 ESMO congress

## Overall survival

| | Median (95% CI) | HR (95% CI) | |
|---|---|---|---|
| Cemiplimab + chemotherapy | 21.1 mo (15.9–23.5) | 0.65 | *P*=0.0003 |
| Placebo + chemotherapy | 12.9 mo (10.6–15.7) | (0.51–0.82) | |



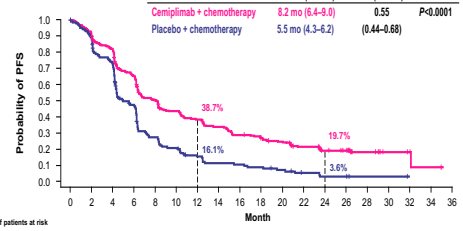

Number of patients at risk

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cemiplimab + chemotherapy | 312 | 289 | 269 | 256 | 233 | 210 | 195 | 180 | 160 | 154 | 145 | 121 | 94 | 71 | 40 | 16 | 5 | 2 | 0 |
| Placebo + chemotherapy | 154 | 141 | 126 | 112 | 98 | 89 | 75 | 64 | 57 | 48 | 40 | 34 | 31 | 19 | 8 | 2 | 0 | 0 | 0 |

Data cutoff date: 14 June 2022. Median (range) duration of follow-up[†]: 28.4 (20.5–35.9) months. [†]From randomisation to data cut-off date.
CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival.

## Progression Free Survival

| | Median (95% CI) | HR (95% CI) | |
|---|---|---|---|
| Cemiplimab + chemotherapy | 8.2 mo (6.4–9.0) | 0.55 | *P*<0.0001 |
| Placebo + chemotherapy | 5.5 mo (4.3–6.2) | (0.44–0.68) | |

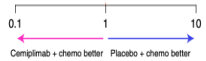



Number of patients at risk

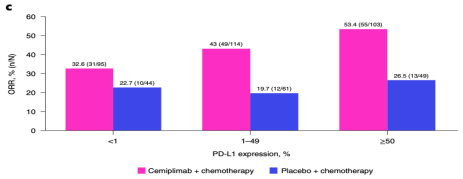
| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cemiplimab + chemotherapy | 312 | 280 | 247 | 194 | 146 | 125 | 110 | 96 | 82 | 75 | 68 | 51 | 37 | 34 | 15 | 4 | 3 | 1 | 0 |
| Placebo + chemotherapy | 154 | 134 | 107 | 66 | 38 | 29 | 20 | 15 | 14 | 12 | 9 | 5 | 3 | 3 | 1 | 1 | 0 | 0 | 0 |

**b**

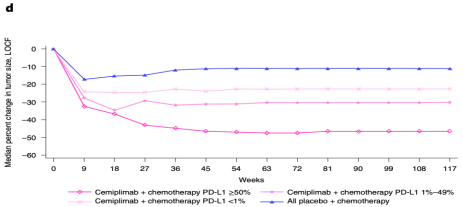
| | | Cemiplimab + chemo No. OS events/ no. patients | Placebo + chemo No. OS events/ no. patients | Hazard ratio (95% CI) |
|---|---|---|---|---|
| All patients | | 132/312 | 82/154 | 0.71 (0.53–0.93) |
| Age group | <65 years | 72/184 | 53/94 | 0.57 (0.40–0.81) |
| | ≥65 years | 60/128 | 29/60 | 0.88 (0.56–1.37) |
| Sex | Male | 113/268 | 75/123 | 0.55 (0.41–0.74) |
| | Female | 19/44 | 7/31 | 2.11 (0.89–5.03) |
| Race | White | 116/267 | 76/138 | 0.67 (0.50–0.89) |
| | Non-white | 16/45 | 6/16 | 0.79 (0.31–2.02) |
| Histology | Squamous | 57/133 | 39/67 | 0.56 (0.37–0.84) |
| | Non-squamous | 75/179 | 43/87 | 0.79 (0.54–1.14) |
| PD-L1 level | <1% | 54/95 | 27/44 | 1.01 (0.63–1.60) |
| | 1–49% | 40/114 | 31/61 | 0.52 (0.32–0.83) |
| | ≥50% | 38/103 | 24/49 | 0.61 (0.37–1.02) |
| ECOG PS | 0 | 11/51 | 6/18 | 0.55 (0.20–1.49) |
| | 1 | 119/259 | 75/134 | 0.69 (0.52–0.92) |
| Region | Europe | 118/270 | 76/138 | 0.67 (0.50–0.90) |
| | Asia | 14/42 | 6/16 | 0.72 (0.27–1.88) |
| Brain met | Yes | 11/24 | 5/7 | 0.42 (0.14–1.26) |
| | No | 121/288 | 77/147 | 0.68 (0.51–0.90) |
| Cancer stage | Locally advanced | 16/45 | 13/24 | 0.54 (0.25–1.15) |
| | Metastatic | 116/267 | 69/130 | 0.69 (0.51–0.93) |
| Smoking | Smokers | 115/269 | 75/130 | 0.61 (0.46–0.82) |
| | Never smokers | 17/43 | 7/24 | 1.28 (0.53–3.08) |




**c**




**d**




Makharadze, T et al. JTO 2023; Gogishvili M. Nature Medicine 2022

# RATIONALE-304: Tislelizumab + chemotherapy

## *1L Advanced/Metastasic Non-Squamous Histology, PD-L1 ≥50%*

**Figure 1** **Kaplan-Meier plot of PFS in BGB-A317-304 in patients with PD-L1 ≥50%**

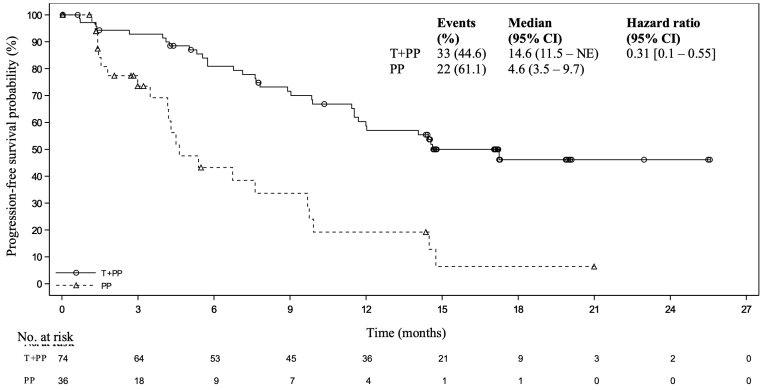
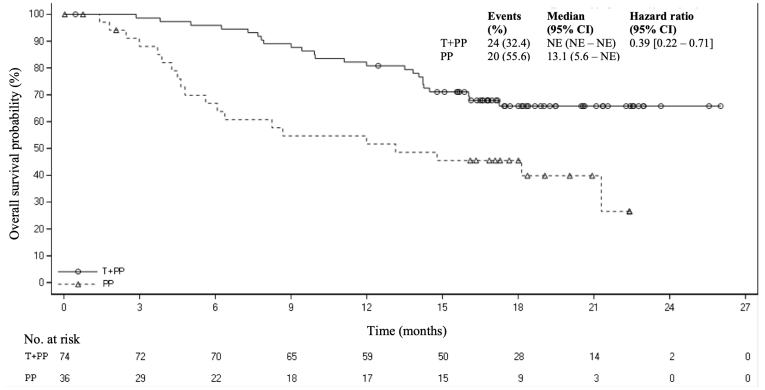



**Figure 2** **Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%**




| Endpoint | Tislelizumab + Pemetrexed + Platinum (N = 74) | Pemetrexed + Platinum (N = 36) |
|---|---|---|
| **PFS** | | |
| Events, n (%) | 33 (44.6) | 22 (61.1) |
| Median PFS (months) (95% CI) | 14.6 (11.5, NE) | 4.6 (3.5, 9.7) |
| Stratified hazard ratio[a] (95% CI) | 0.31 (0.18, 0.55) | |
| **OS** | | |
| Deaths, n (%) | 24 (32.4) | 20 (55.6) |
| Median OS (months) (95% CI) | NE (NE, NE) | 13.1 (5.6, NE) |
| Stratified hazard ratio[a] (95% CI) | 0.39 (0.22, 0.71) | |
| **Best overall response, n (%)[b]** | | |
| **ORR[b], n (%)** | 52 (70.3) | 11 (30.6) |
| 95% CI[c] | (58.5, 80.3) | (16.3, 48.1) |
| **DoR[b]** | | |
| Median DoR (months) (95% CI) | NE (13.2, NE) | 8.5 (3.3 NE) |

Lu S. ESMO Open. 2024

# RATIONALE-307: Tislelizumab + chemotherapy

## *1L Advanced/Metastasic Squamous Histology, PD-L1 ≥50%*

**Figure 3 Kaplan-Meier plot of PFS in BGB-A317-307 by IRC**

T+PC arm versus T+nPC arm versus PC arm

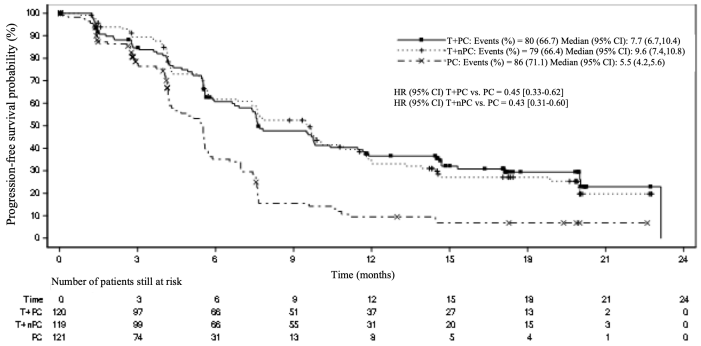
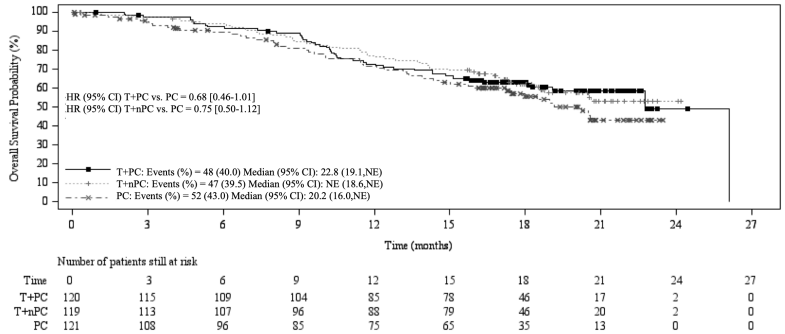



**Figure 4 Kaplan-Meier plot of OS in BGB-A317-307**

T+PC arm versus T+nPC arm versus PC arm




| Endpoint | Tislelizumab + Paclitaxel + Carboplatin (N = 120) | Tislelizumab + nab-Paclitaxel + Carboplatin (N = 119) | Paclitaxel + Carboplatin (N = 121) |
|---|---|---|---|
| **PFS** | | | |
| Events, n (%) | 80 (66.7) | 79 (66.4) | 86 (71.1) |
| Median PFS (months) (95% CI) | 7.7 (6.7, 10.4) | 9.6 (7.4, 10.8) | 5.5 (4.2, 5.6) |
| Stratified hazard ratio[a] (95% CI) | 0.45 (0.33, 0.62) | 0.43 (0.31, 0.60) | - |
| **OS** | | | |
| Deaths, n (%) | 48 (40.0) | 47 (39.5) | 52 (43.0) |
| Median OS (months) (95% CI) | 22.8 (19.1, NE) | NE (18.6, NE) | 20.2 (16.0, NE) |
| Stratified hazard ratio (95% CI) | 0.68 (0.45, 1.01) | 0.752 (0.50, 1.12) | - |
| **ORR[b]** | | | |
| ORR, n (%) | 74 (61.7) | 74 (62.2) | 45 (37.2) |
| 95% CI | (52.4, 70.4) | (52.8, 70.9) | (28.6, 46.4) |
| **DoR[b]** | | | |
| Median DoR (months) (95% CI) | 13.2 (7.85, 18.79) | 10.4 (8.34, 17.15) | 4.8 (4.04, 5.72) |

Wang J. ESMO Open. 2024

# Front Line Protocols: IO + Chemotherapy

## Outcomes in NSCLC With High PD-L1 Expression and Access in Spain

| Trial | EMPOWER-Lung 3[1,2] | RATIONALE-304[3] | RATIONALE-307[4,5] |
|---|---|---|---|
| Histology | Squamous and Non-Squamous | Non-Squamous | Squamous |
| Treatment | Cemiplimab + Chemotherapy (n=312) | Tislelizumab + Chemotherapy (n=74) | Tislelizumab + Chemotherapy (n=120) |
| ORR | 53.4% | 70.3% | 61.7% |
| Median PFS (months) | 10.8 | 14.6 | 7.7 |
| Median OS (months) | 23.5 | NE | 22.8 |
| Unresectable stage III not amenable for chemo-RT | Excluded | Included | Included |
| QoL improvement | Yes | Yes | Yes |

Cross-study comparisons are not intended.

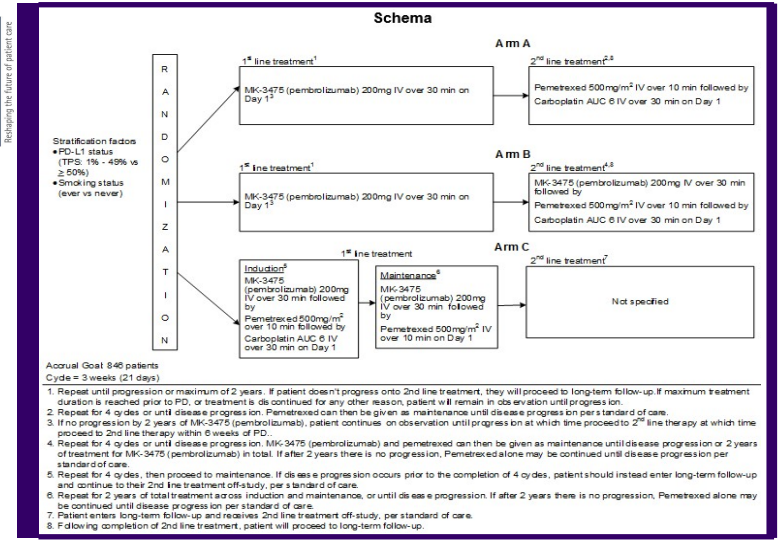
# OUTLINE

- Background
- IO monotherapy
- IO + Chemotherapy
- IO vs IO + Chemo
- Conclusions

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

- **Randomized Phase 3 trials Pembro vs Pembro + Chemotherapy**

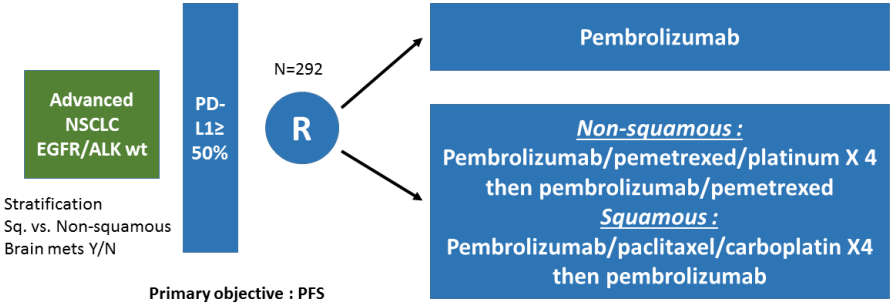
## EA5163/S1709/INSIGNA




**STATUS: CLOSED TO ACCRUAL**

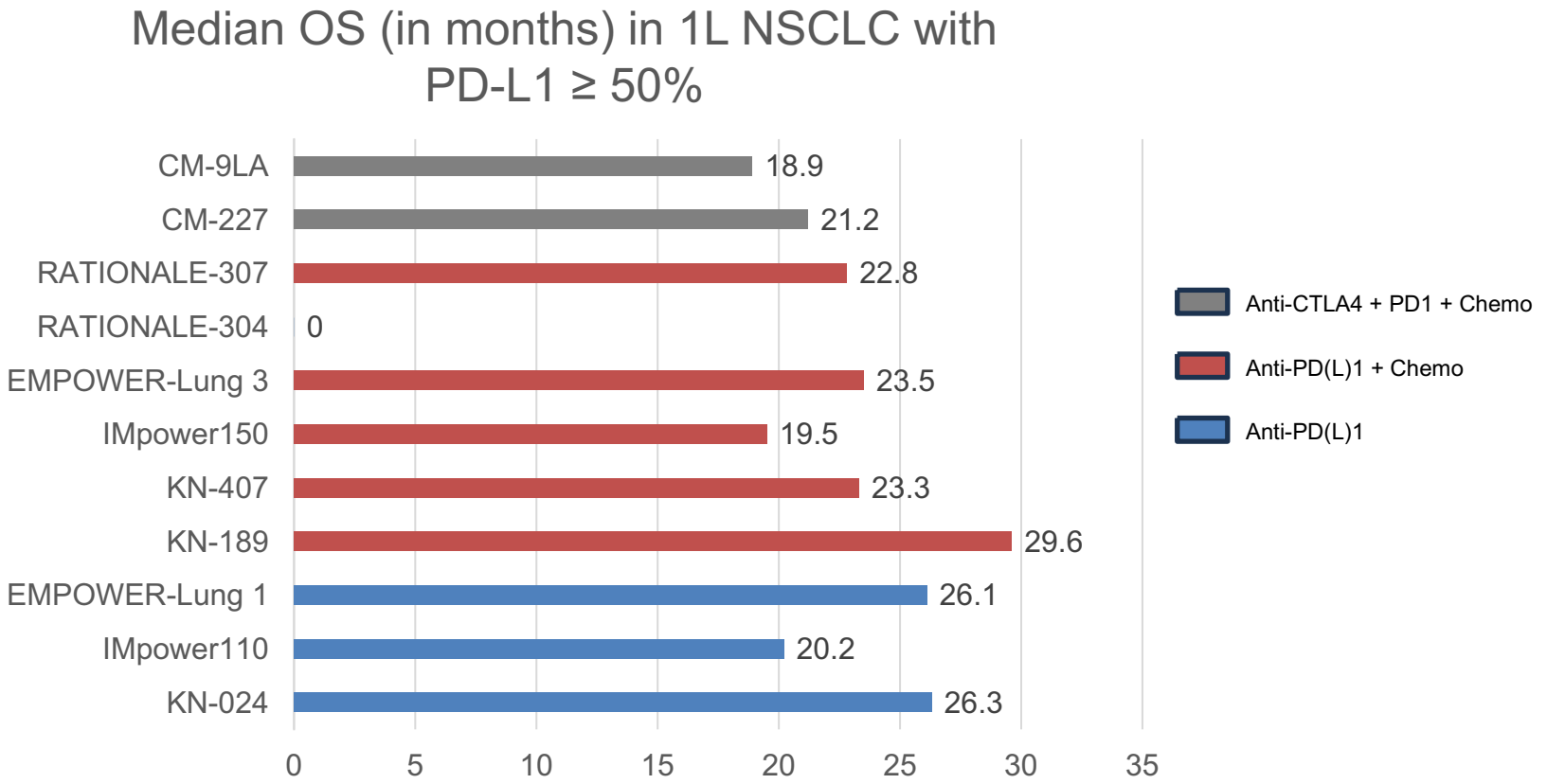
## PERSEE Trial ongoing

*NCT04547504*




**Primary objective : PFS**

# Front Line Protocols: IO mono, IO + Chemo, IO + IO

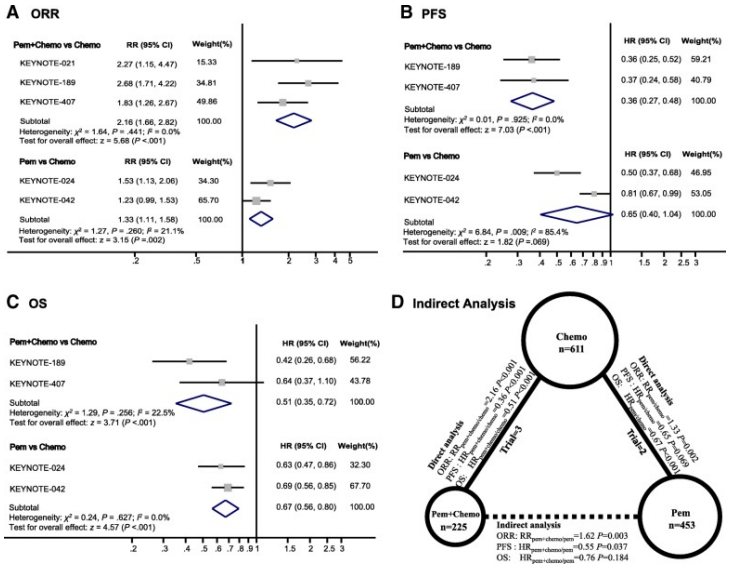



Cross-study comparisons are not intended.

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

## MA Pembrolizumab vs Pembrolizumab plus chemotherapy

5 RCT (n=1,289)




Pembrolizumab plus chemotherapy was *superior to pembrolizumab alone:*

- **Objective response rates** (ORRs; relative risk 1.6, 95% CI 1.2-2.2)
- **PFS** (hazard ratio [HR] 0.55, 95% CI 0.32-0.97)

*But no statistically significant differences in **OS***
(HR 0.76, 95% CI 0.51-1.14).

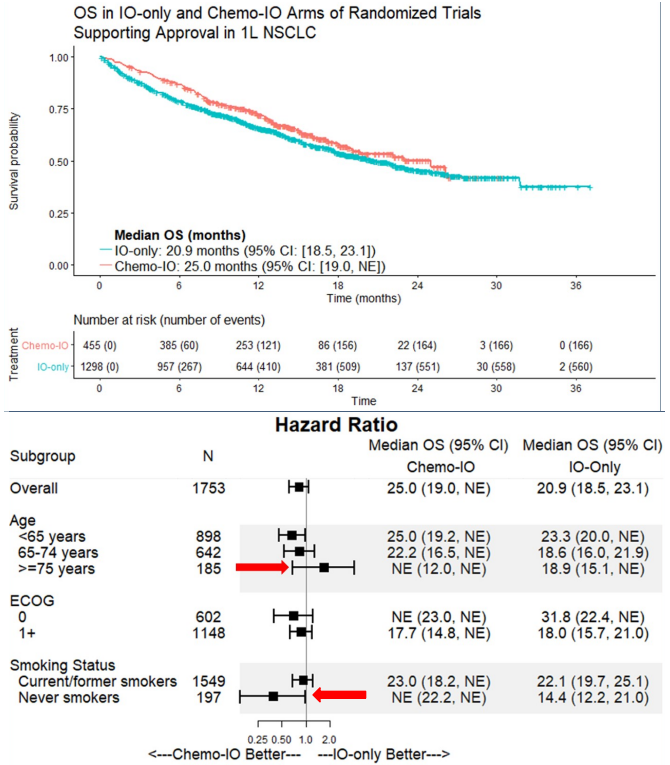
Zhou Y. J Immunother Cancer. 2019

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

## Retrospective pool analysis of FDA approved regimens

| Chemo-IO Trials | | IO-only Trials | |
|---|---|---|---|
| Trial | Investigational Regimen | Trial | Investigational Regimen |
| KEYNOTE-021* | **Pembrolizumab** + Chemo** | CheckMate 026 | **Nivolumab**** |
| KEYNOTE-189 | **Pembrolizumab** + Chemo** | KEYNOTE-024 | **Pembrolizumab**** |
| KEYNOTE-407 | **Pembrolizumab** + Chemo** | KEYNOTE-042 | **Pembrolizumab**** |
| IMpower150 | **Atezolizumab** + Bevacizumab + Chemo*** | IMpower110 | **Atezolizumab**** |
| IMpower130 | **Atezolizumab** + Chemo** | CheckMate 227 | **Nivolumab** + **Ipilimumab**** |
| CheckMate-9LA | **Nivolumab** + **Ipilimumab** + Chemo** | EMPOWER-Lung 1 | **Cemiplimab**** |

| | Chemo-IO (*N*=455) | IO-alone (*N*=1,298) |
|---|---|---|
| OS | | |
| Median, months (95% CI) | 25.0 (19.0, NE) | 20.9 (18.5, 23.1) |
| HR (95% CI) | 0.82 (0.62, 1.08) | |
| PFS | | |
| Median, months (95% CI) | 9.6 (8.4, 11.1) | 7.1 (6.3, 8.3) |
| HR (95% CI) | 0.69 (0.55, 0.87) | |
| ORR | | |
| % (95% CI) | 61 (56, 66) | 43 (41, 46) |
| Odds ratio | 1.2 (1.1, 1.3) | |

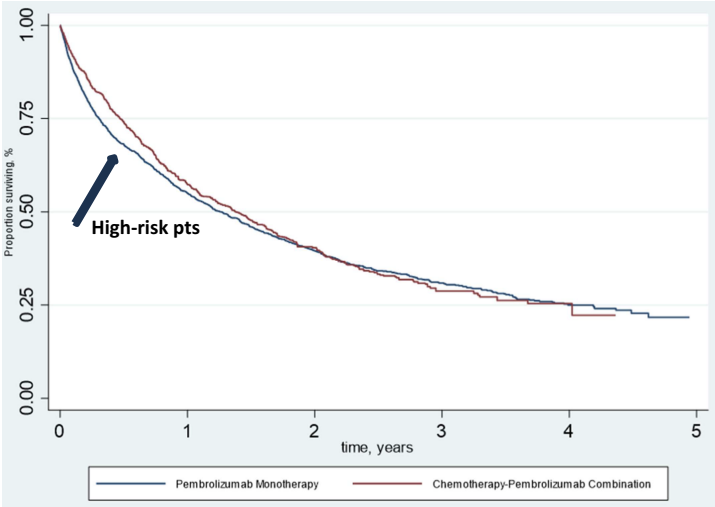



Akinboro O. J Clin Oncol 2022; 40(suppl)Abstr 9000

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

**Retrospective RWD from EHRs, 2016-2021 (Flatiron)**

280 US cancer clinics (n=3,086)




**No OS differences** (HR 0.98, 95% CI 0.86-1.12) but survival *benefit with chemo-IO during the first 6 months* (HR 0.74, 95% CI 0.61-0.90)

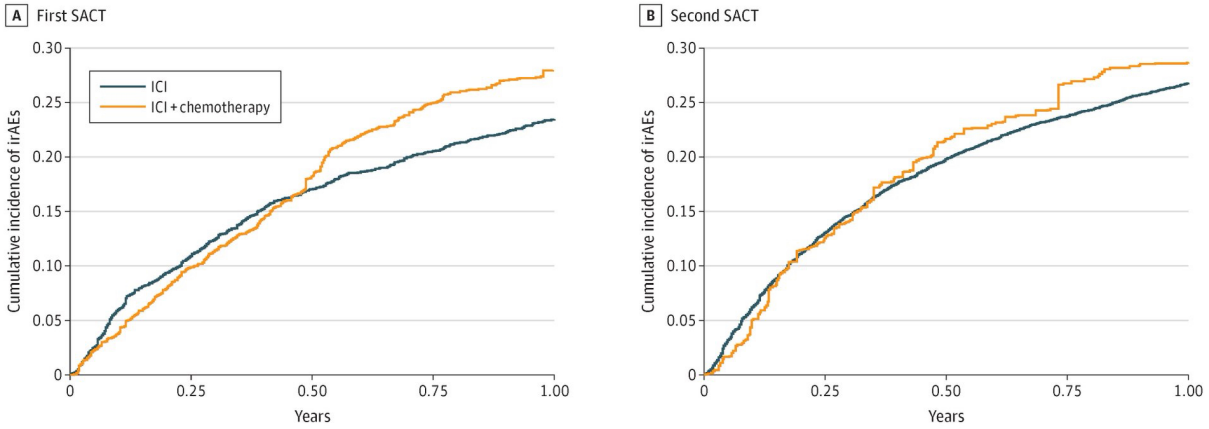
Shah M. Clin Lung Cancer. 2023

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

## Retrospective SEER Medicare, 2013-2019

(n=17,681)

Figure 1. Cumulative Incidence of Severe Immune-Related Adverse Event (irAE) by Treatment Arms Among Propensity Score Weighted Cohorts




ICI indicates immune checkpoint inhibitor; SACT, systemic anticancer therapy.

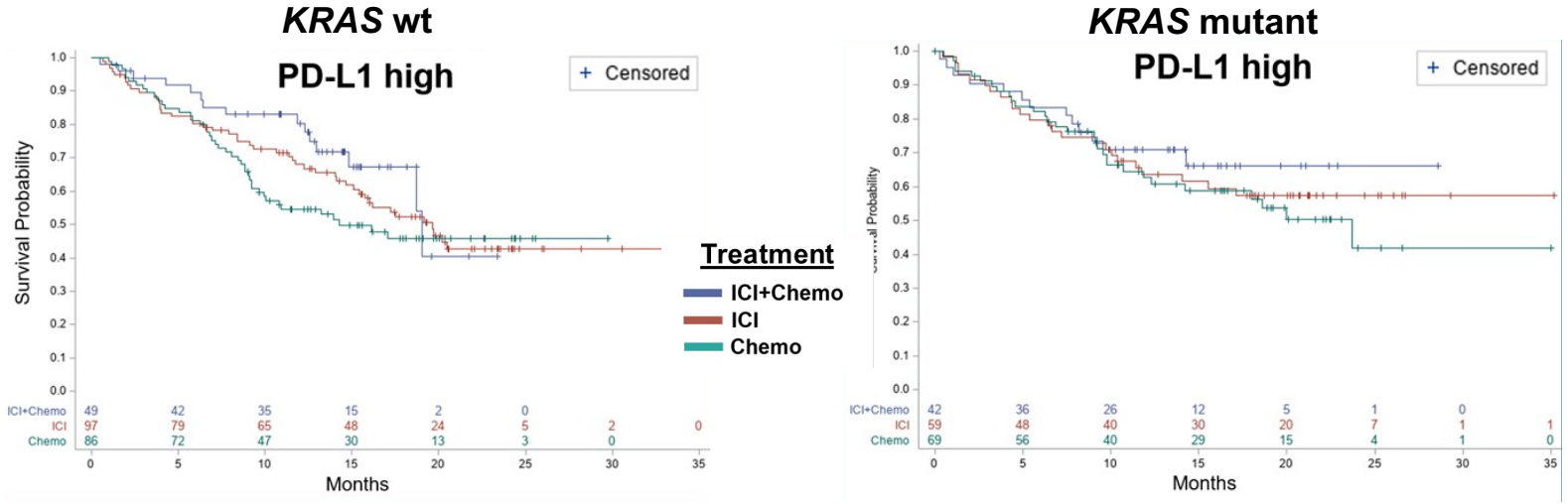
***Increased risk of severe adverse events with chemo-IO vs IO alone in older adults***

Heyward J. JAMA Oncol 2025

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

## Retrospective pool analysis of FDA approved regimens

Outcomes in KRAS mutant NSCLC



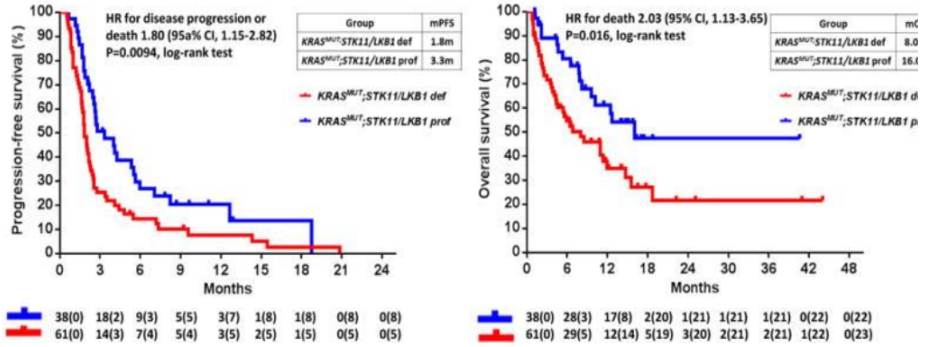

Nakajima EC. J Clin Oncol 2022; 40(suppl):Abstr 9001

# Monotherapy vs combination in advanced NSCLC and high PD-L1 expression

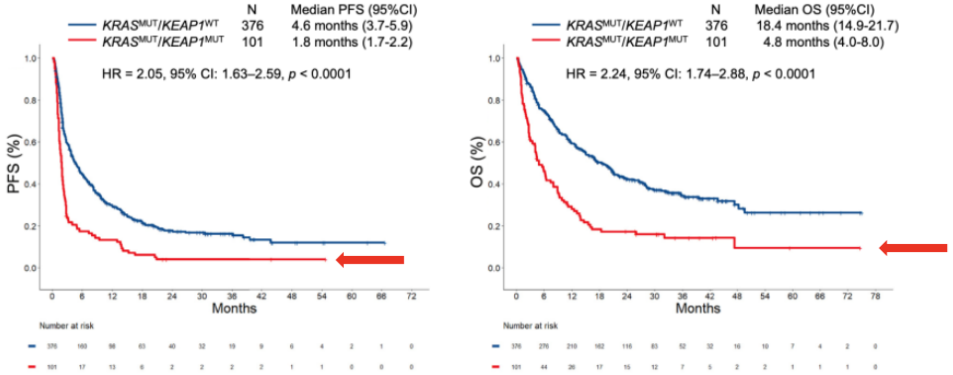
## Retrospective pool analysis

Outcomes of ICI monotherapy in *KRAS* mutant NSCLC by co-mutations in *STK11* and *KEAP1*

### *STK11*




### *KEAP1*




***STK11 and KEAP1* mutant lung cancer tumors are immune "cold" and predict resistance to ICI therapy in *KRAS* mutant lung adenocarcinoma**

Skoulidis et al. Cancer Discov. 2018; Ricciuti et al. J Thorac Oncol 2022; Scalera et al. J Thorac Oncol 2021

# OUTLINE

- Background
- IO monotherapy
- IO + Chemotherapy
- IO vs IO + Chemo
- Conclusions

# Toma de decisiones en el tratamiento de 1ª línea para pacientes con NSCLC avanzado sin mutaciones accionables

| Características clínicas | Características moleculares | Contexto |
|---|---|---|
| •Edad<br>•Sexo<br>•Hábito tabáquico<br>•ECOG<br>•Metástasis hepaticas<br>•Metástasis cerebrales<br>•Carga tumoral/OMD<br>•Esteroides/antibióticos<br>•Microbiota… | •PD-L1<br>•TMB<br>•KRAS<br>•STK11<br>•KEAP1<br>•POLEmut<br>•MSIh | •Costes<br>•Toxicidades<br>•Acceso<br>•Posología<br>•Preferencias del paciente<br>•Expectativas del paciente |

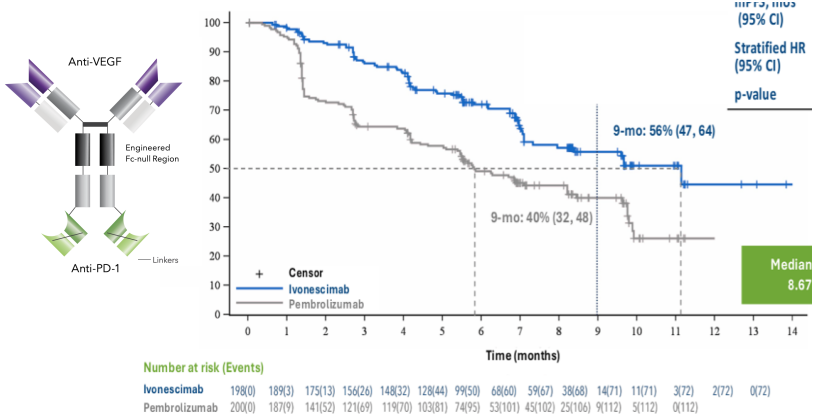
- **Variabilidad y reproducibilidad de la expresión de PD-L1**
- **Ausencia de mutaciones accionables → Necesidad de NGS**

- ***La medicina es un arte, no la convirtamos en burocracia***
- ***Demandemos más evidencia científica***

# Can we improve current SoC for NSCLC and PD-L1 ≥50%?

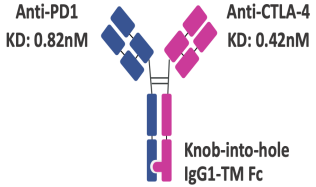
- ***Bispecifics look promising!***

## HARMONi-2: Ivonescimab (antiPD1 x VEGF) vs Pembrolizumab

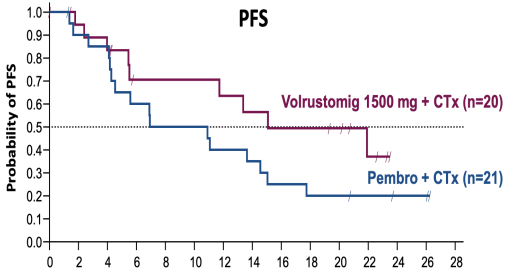



## Volrustomig (anti-PD1 x CTLA4) + chemo vs Pembrolizumab + chemo

### Volrustomig PD-1/CTLA-4 bispecific




### Volrustomig 1500 mg + CTx in 1L nonsquamous NSCLC[2]




- Multiple trials failed to improved ICI: Avelumab, bintrafusp alfa (TGF-b trap), Canakimumab (IL-1b)… IO + IO combos (CTLA4, TIGIT, TIM3, OX40, LAG3), antiangiogenics (lenvatinib),…
- Others are under evaluation: Combinations with anti-Trop2 ADCs (SG, Dato-DXd)

Zhou, C. et al. Presented at *WCLC* 2024; Spigel, D. et al. Presented at WCLC 2024; Disclaimer: The list of agents is not intended to be exhaustive.

# Conclusions

1. It may be reasonable to recommend that patients with high tumor volume to be treated with the combinatorial therapy to produce deeper and longer response, while patients with low tumor volume or with very high PD-L1 TPS can be treated with anti-PD(L)-1 ICI alone.

2. Elderly patients or unfit for chemotherapy can benefit from ICI alone.

3. Special attention to women, never-smoker patients who can derived less benefit from ICI alone than from chemo+ICI, specially if not comprenhesive genomic profiling was performed.

4. Despite recent improvements in survival, global outcomes are far away from aceptable for most of our patients, so we encourage to include them in clinical trials.

# Thanks for your attention!

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