# **Case 1:** 63-year-old woman

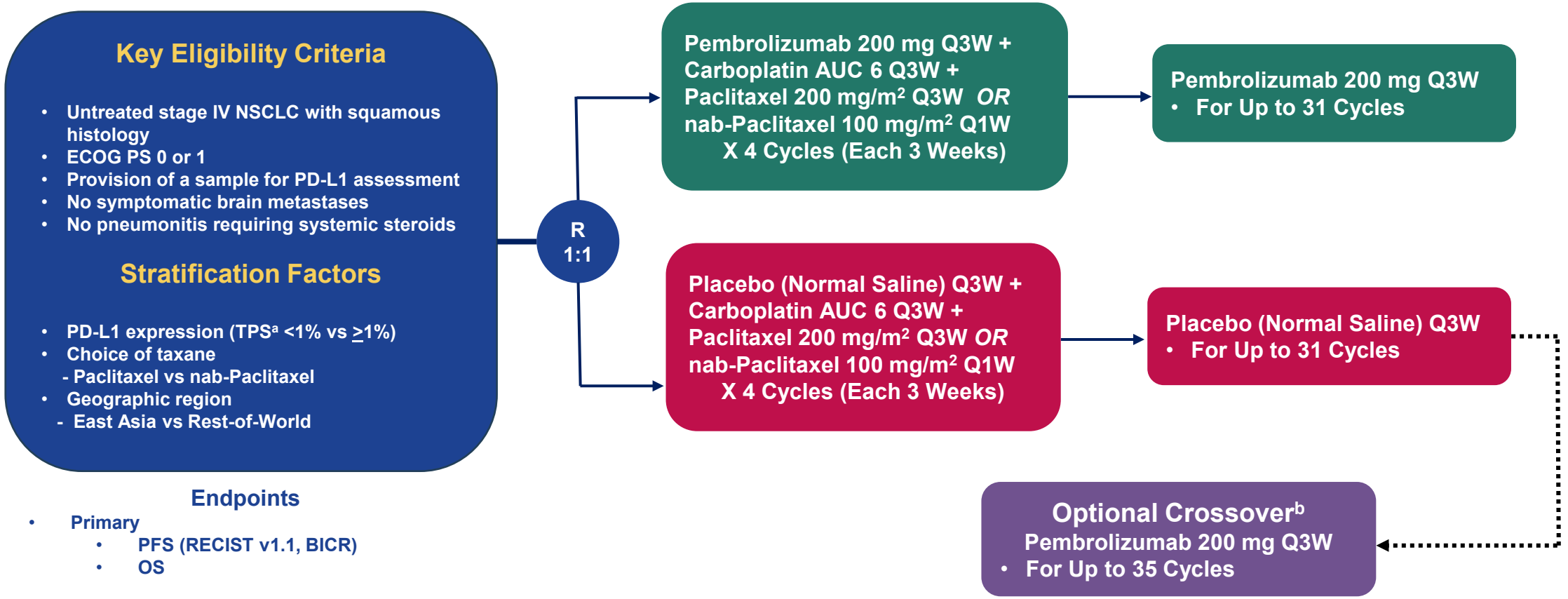
- Presented to the ED with vague complaints of dry cough and shortness of breath
  - She gave a history of a recent, 8-pound weight loss
- Past medical, family, and social history
  - Hyperlipidemia, treated with statin
  - COPD, treated with maintenance fluticasone furoate, umeclidinium, and vilanterol inhalation QD
  - Mother: deceased at 70 years-of-age from lung cancer
  - Former smoker (30 pack years) and quit tobacco habit 15 years ago
- Physical examination
  - Current weight: 110 lbs
  - ECOG PS 1

# Case 1 (Cont.)

- Diagnostic Workup
  - CT of thorax discovered a 3 cm nodule in the left, upper lobe, enlarged L hilar nodes
  - CT of abdomen revealed metastases to the liver
  - MRI of brain negative for brain metastases
- Final pathology: consistent with squamous cell carcinoma
  - Metastatic stage IV
- PD-L1 expression by IHC: <1%
- NGS: no actionable mutations

- **What treatment options should be considered?**

# KEYNOTE 407 Trial: Study Design




**Endpoints**

- **Primary**
  - **PFS (RECIST v1.1, BICR)**
  - **OS**
- **Secondary**
  - **ORR and DOR (RECIST v1.1, BICR)**
  - **Safety**

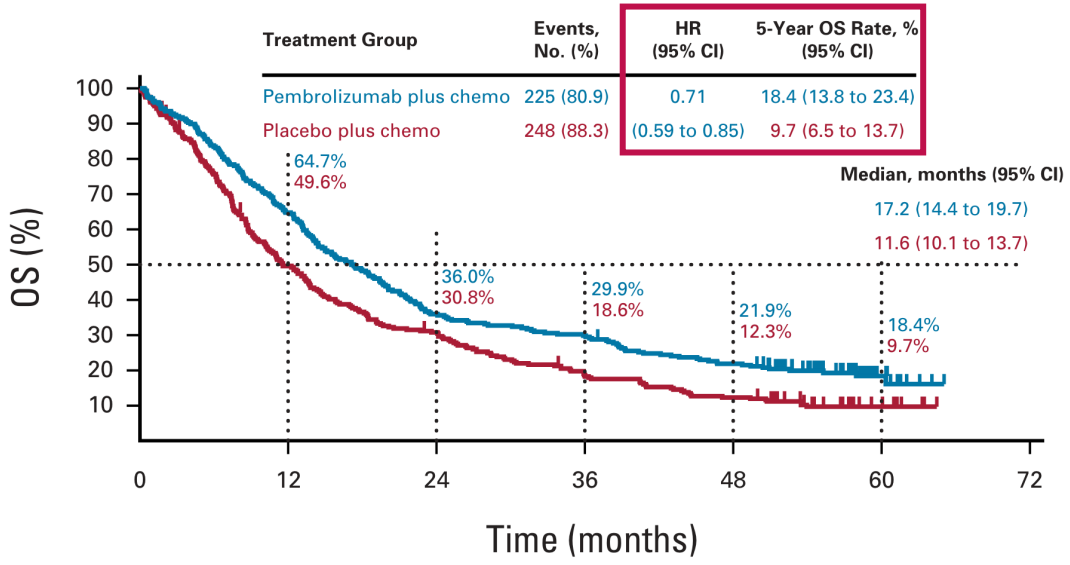
[a] Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay.
[b] Patients could crossover during combination therapy or monotherapy.
- To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

BICR, blinded independent central radiologic review; ECOG PS, Eastern Cooperative Oncology Group Performance Score; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand-1; TPS, tumor proportion score.

Paz-Ares L, et al. *N Engl J Med*. 2018;379(21):2040-2051.

# KEYNOTE-407: 5-Year OS and PFS

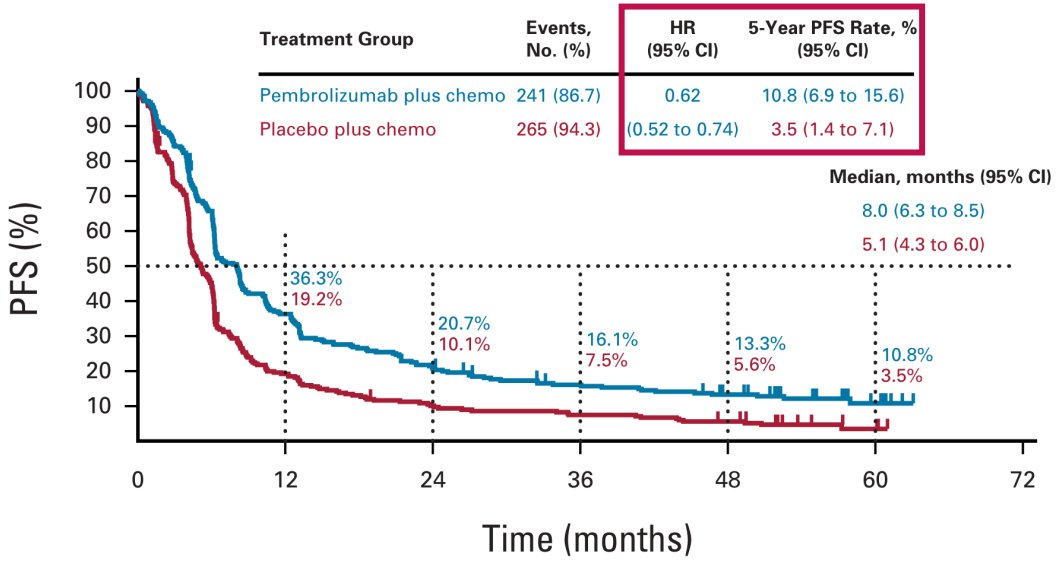
## Overall Survival (ITT Population)




No. at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pembrolizumab plus chemo | 278 | 180 | 100 | 83 | 60 | 10 | 0 |
| Placebo plus chemo | 281 | 137 | 84 | 50 | 33 | 7 | 0 |

## Progression-Free Survival (ITT Population)



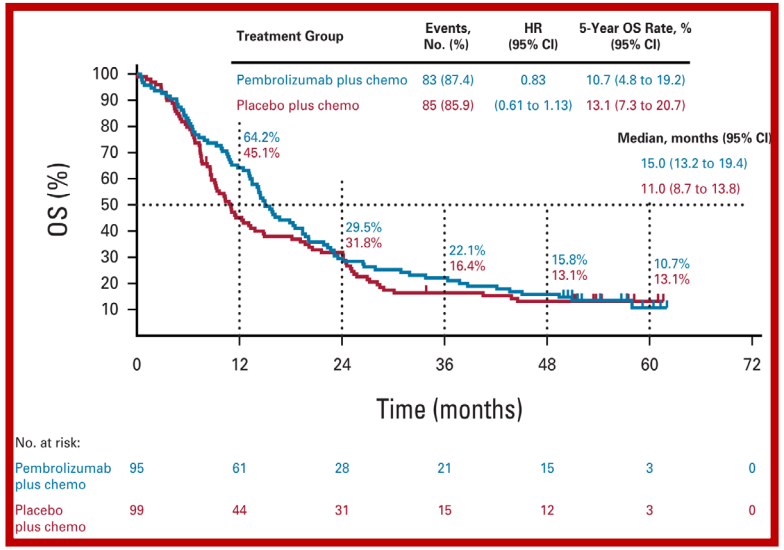

No. at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Pembrolizumab plus chemo | 278 | 100 | 56 | 40 | 30 | 7 | 0 |
| Placebo plus chemo | 281 | 53 | 27 | 20 | 14 | 1 | 0 |

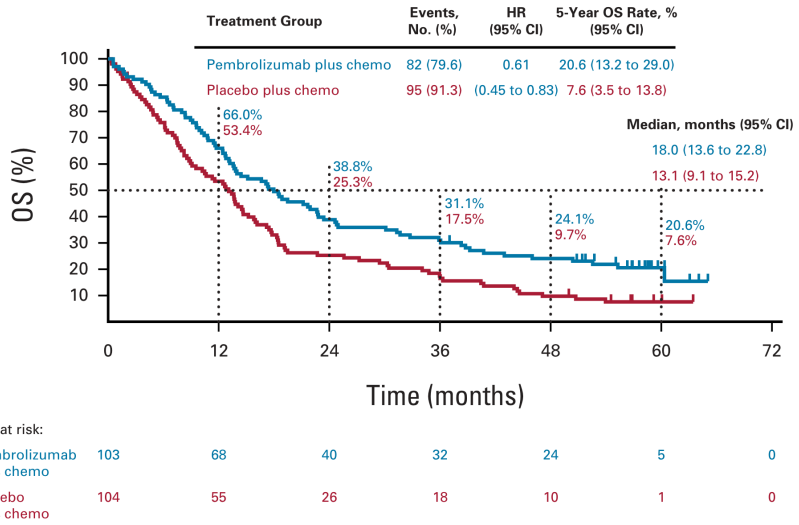
Novello S, et al. *J Clin Oncol*. 2023;41(11):1999-2006.

# KEYNOTE-407: 5-Year OS by PD-L1 Status

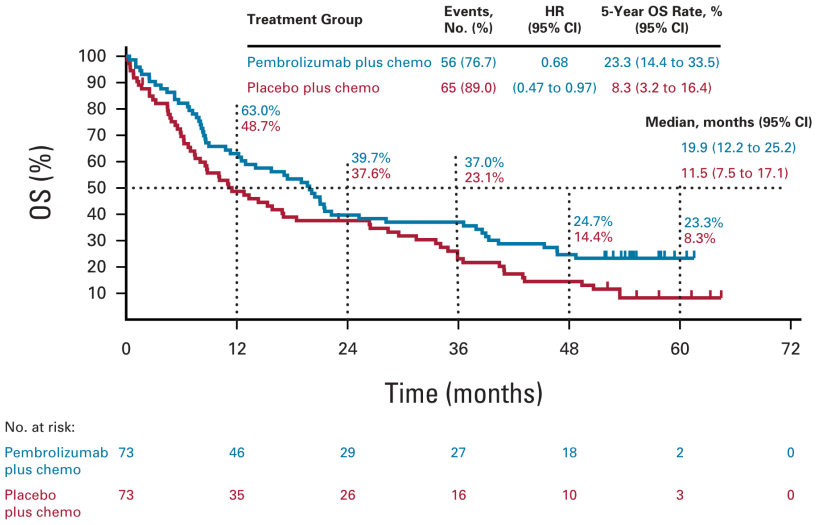
## PD-L1 Expression <1%




## PD-L1 Expression 1% - 49%

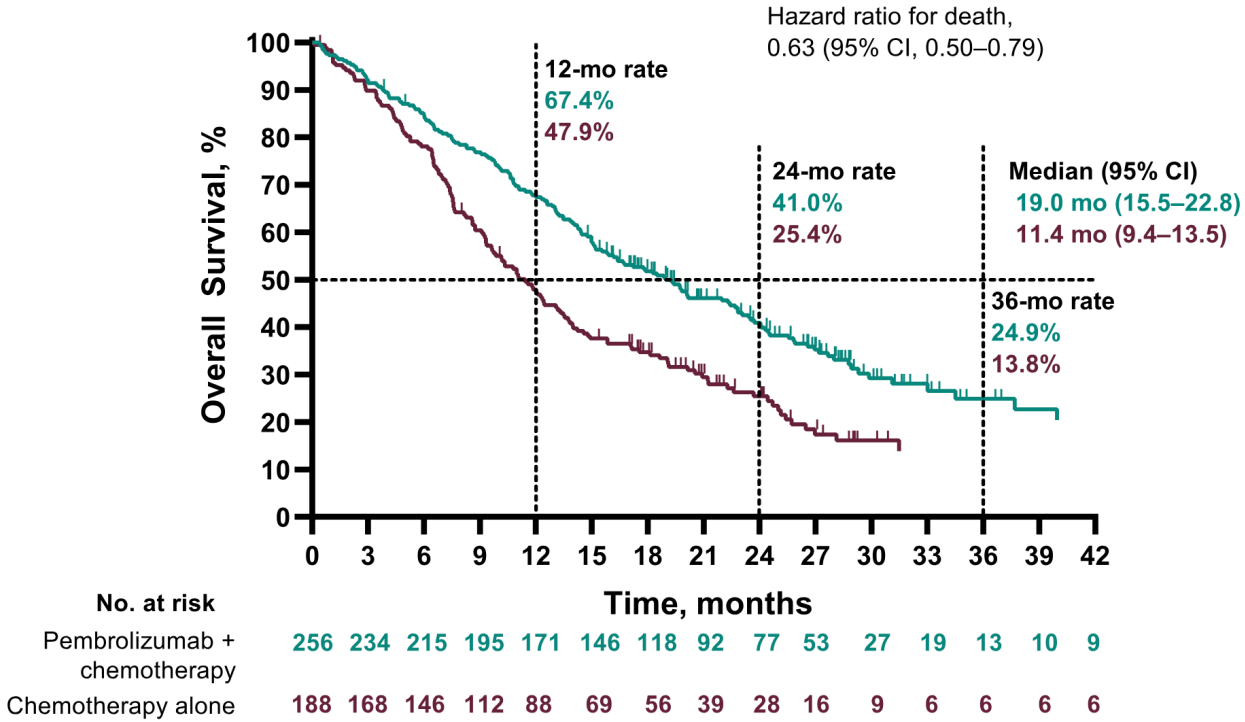


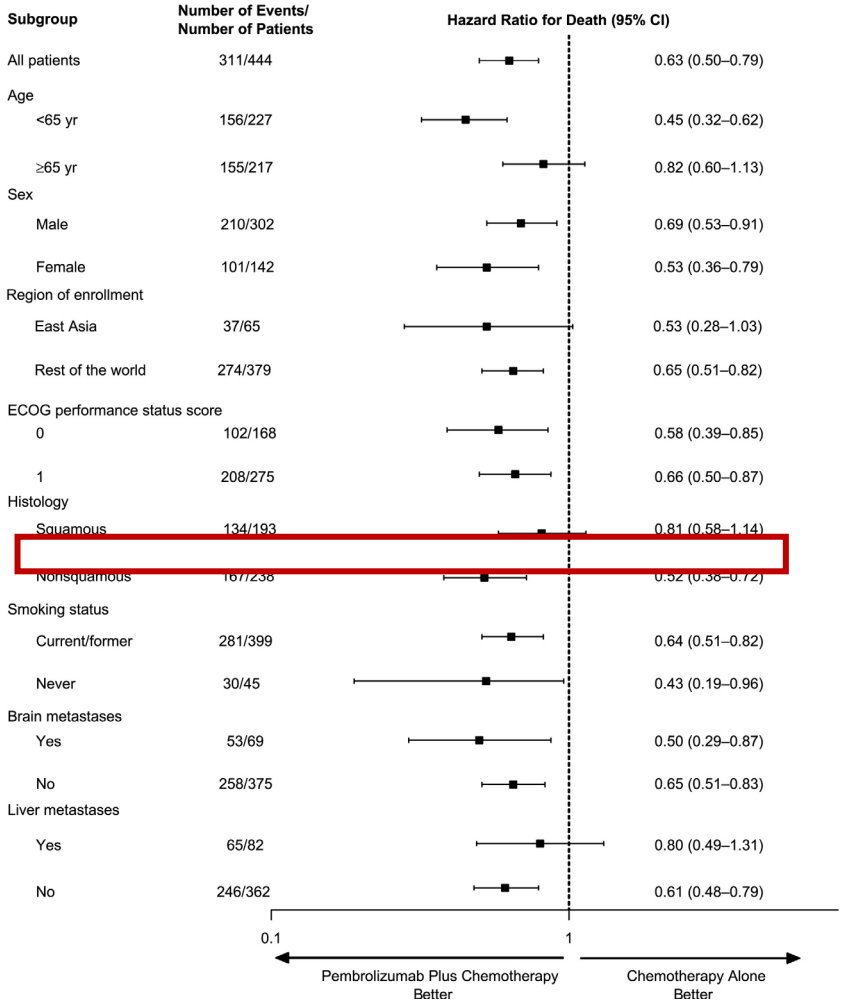

## PD-L1 Expression ≥50%




Novello S, et al. *J Clin Oncol*. 2023;41(11):1999-2006.

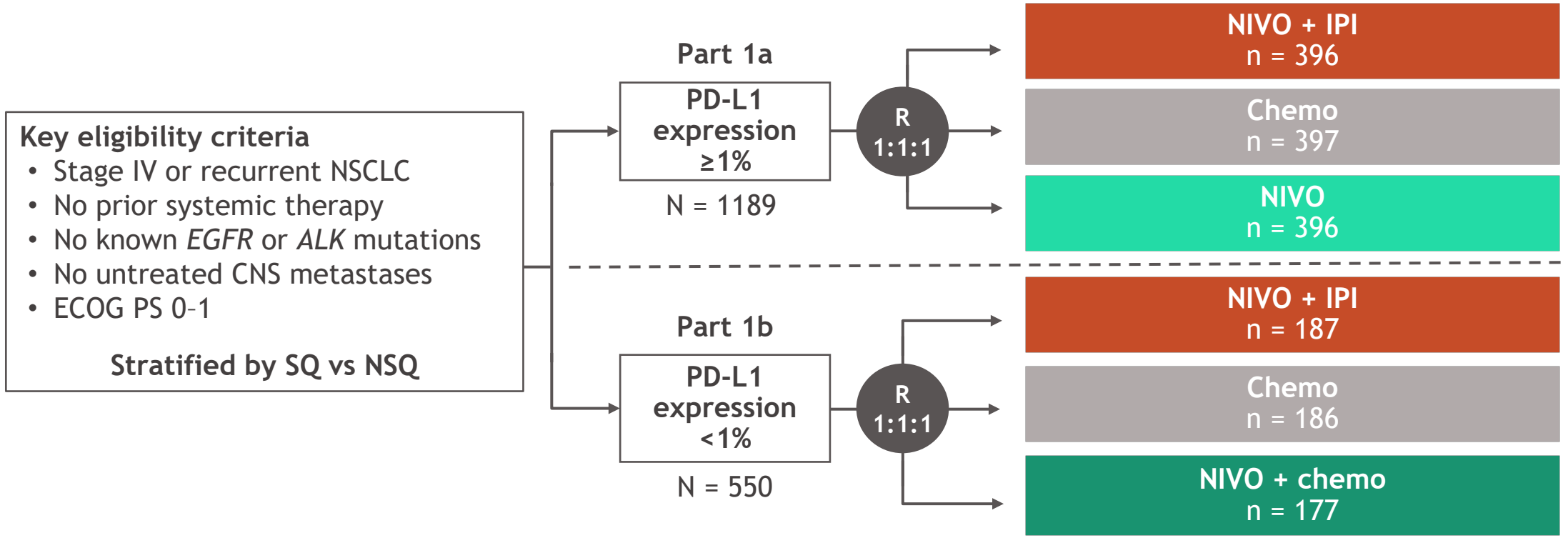
# Pembrolizumab + Chemotherapy vs Chemotherapy in Patients With Advanced NSCLC Without Tumor PD-L1 Expression: A Pooled Analysis of 3 Randomized Controlled Trials




Borghaei H, et al. *Cancer.* 2020;126(22):4867-4877.

# CheckMate 227 Part 1: Study Design




**Independent primary endpoints (NIVO + IPI vs chemo)**
- PFS in patients with high TMB (≥ 10 mut/Mb)
- OS in patients with tumor PD-L1 ≥1%

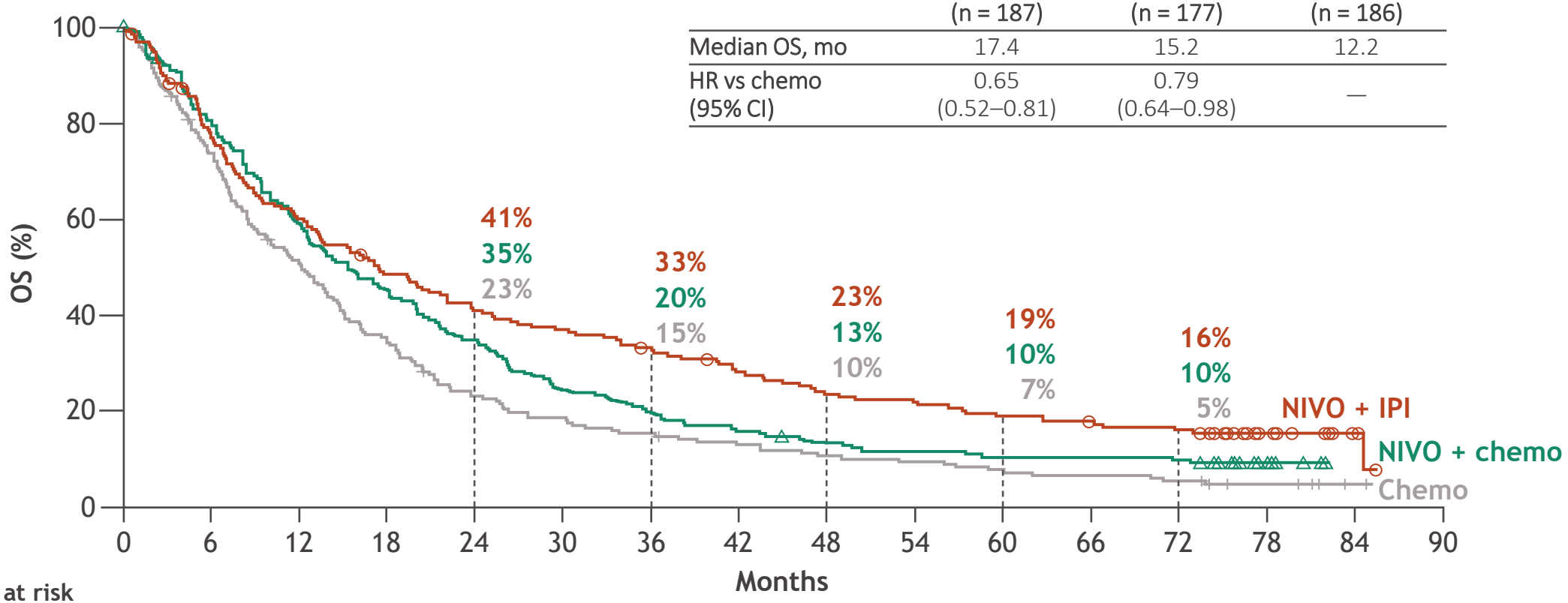
**Exploratory analyses**
- OS by response and tumor burden reduction
- OS by baseline HRQoL

Database lock: February 21, 2023; minimum/median follow-up for OS: 73.5/78.8 months.

Ramalingam SS, et al. WCLC 2023. Abstract OA14.03.

# CheckMate 227 Part 1: 6-Year OS in Patients With PD-L1 <1%

| | NIVO + IPI (n = 187) | NIVO + chemo (n = 177) | Chemo (n = 186) |
|---|---|---|---|
| Median OS, mo | 17.4 | 15.2 | 12.2 |
| HR vs chemo (95% CI) | 0.65 (0.52–0.81) | 0.79 (0.64–0.98) | — |



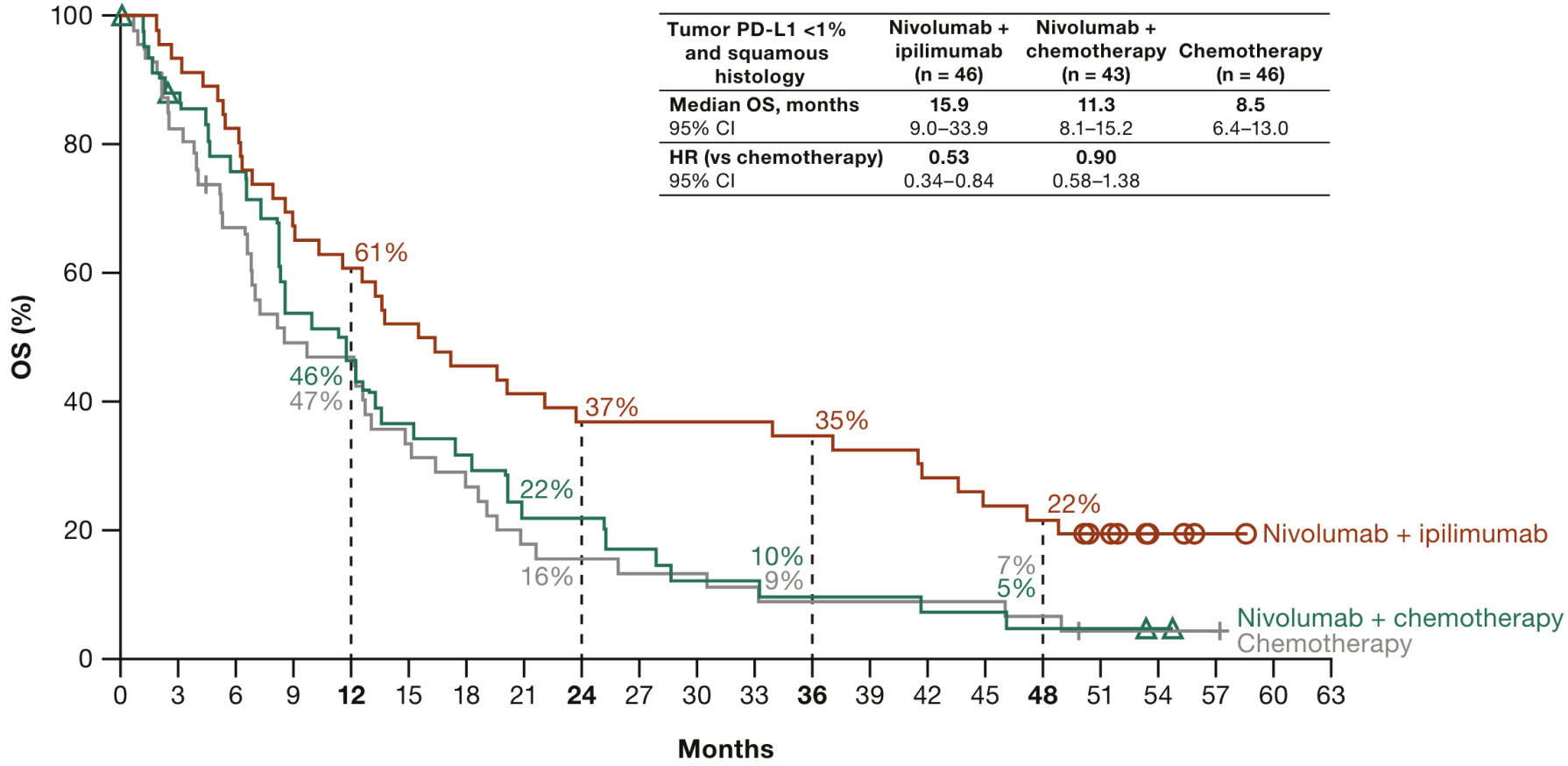

| No. at risk | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO + IPI | 187 | 142 | 110 | 88 | 74 | 67 | 59 | 49 | 41 | 38 | 33 | 30 | 27 | 11 | 3 | 0 |
| NIVO + chemo | 177 | 139 | 102 | 78 | 60 | 42 | 34 | 27 | 22 | 19 | 17 | 17 | 16 | 5 | 0 | 0 |
| Chemo | 186 | 135 | 92 | 62 | 41 | 33 | 27 | 22 | 18 | 16 | 12 | 11 | 9 | 5 | 1 | 0 |

- In an exploratory analysis of OS by histology in patients with tumor PD-L1 < 1%, 6-year OS rates with NIVO + IPI vs chemo were 15% vs 6% (NSQ) and **18% and 4% (SQ)**

Ramalingam SS, et al. WCLC 2023. Abstract OA14.03.

# CheckMate 227 Part 1: OS in Patients With PD-L1 <1% and Squamous Histology

| Tumor PD-L1 <1% and squamous histology | Nivolumab + ipilimumab (n = 46) | Nivolumab + chemotherapy (n = 43) | Chemotherapy (n = 46) |
|---|---|---|---|
| **Median OS, months** | **15.9** | **11.3** | **8.5** |
| 95% CI | 9.0–33.9 | 8.1–15.2 | 6.4–13.0 |
| **HR (vs chemotherapy)** | **0.53** | **0.90** | |
| 95% CI | 0.34–0.84 | 0.58–1.38 | |

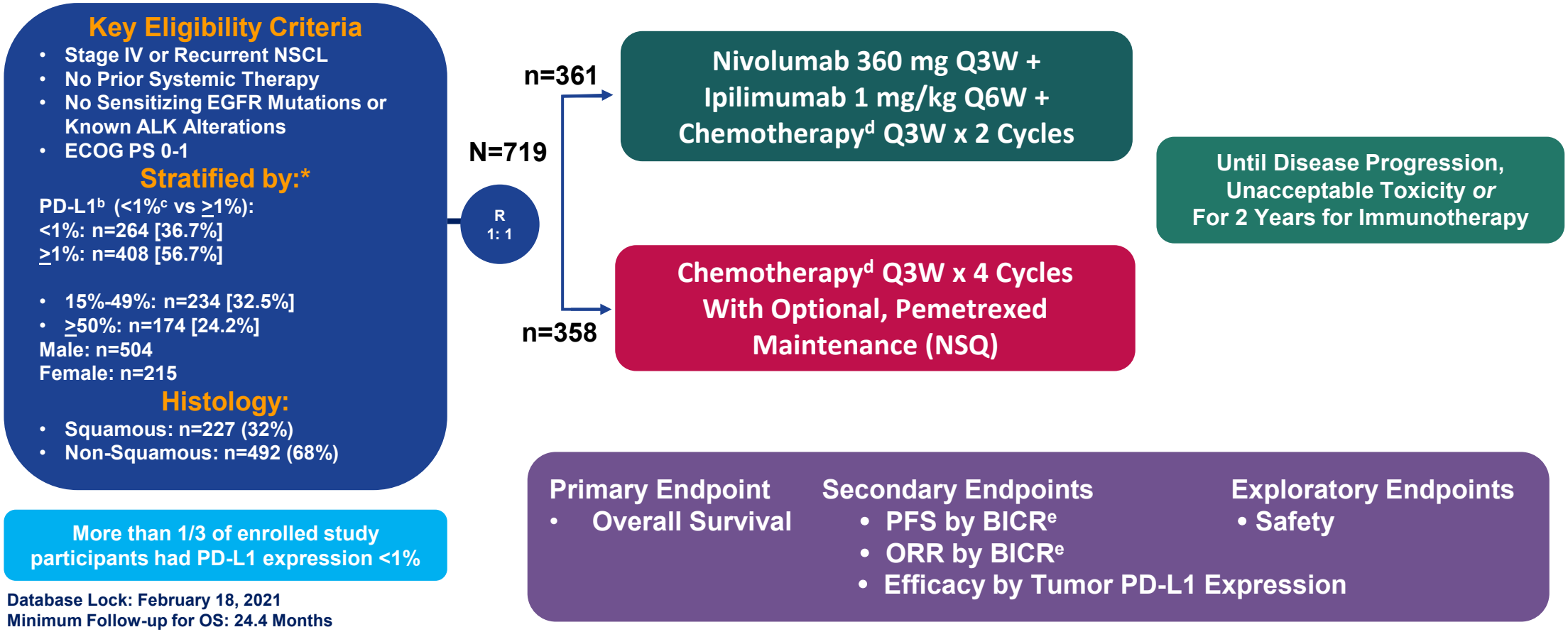



**Number of patients at risk**

| | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab | 46 | 43 | 38 | 31 | 28 | 24 | 21 | 19 | 17 | 17 | 17 | 17 | 16 | 15 | 13 | 11 | 10 | 7 | 3 | 1 | 0 | 0 |
| Nivolumab + chemotherapy | 43 | 36 | 31 | 22 | 19 | 15 | 13 | 9 | 9 | 7 | 5 | 5 | 4 | 4 | 3 | 3 | 2 | 2 | 1 | 0 | 0 | 0 |
| Chemotherapy | 46 | 38 | 30 | 22 | 21 | 15 | 12 | 8 | 7 | 6 | 6 | 5 | 4 | 4 | 4 | 4 | 3 | 1 | 1 | 1 | 0 | 0 |

Paz-Ares LG, et al. *J Thorac Oncol*. 2022;17(2):289-308.

# CheckMate 9LA Trial: Study Design



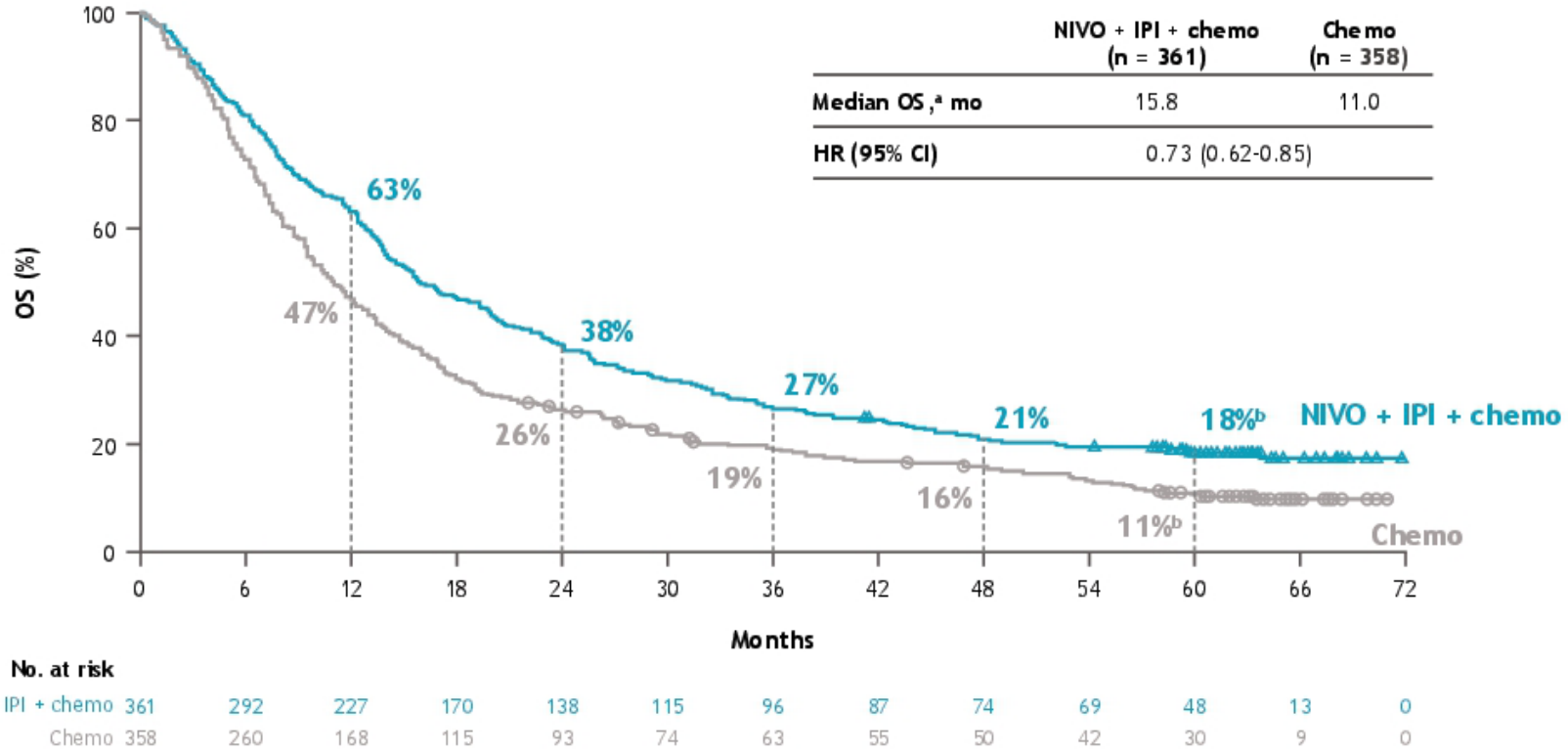

**Database Lock: February 18, 2021**
**Minimum Follow-up for OS: 24.4 Months**
**Median Follow-up for OS: 30.7 Months**

[a]NCT03215706
[b]Determined by the PD-L1 IHC 28.8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.


Reck M, et al. ASCO 2021. Abstract 9000.
Paz-Ares LG, et al. *Lancet Oncol*. 2021;22:198-211.

# CheckMate 9LA: 5-Year OS

## All Randomized

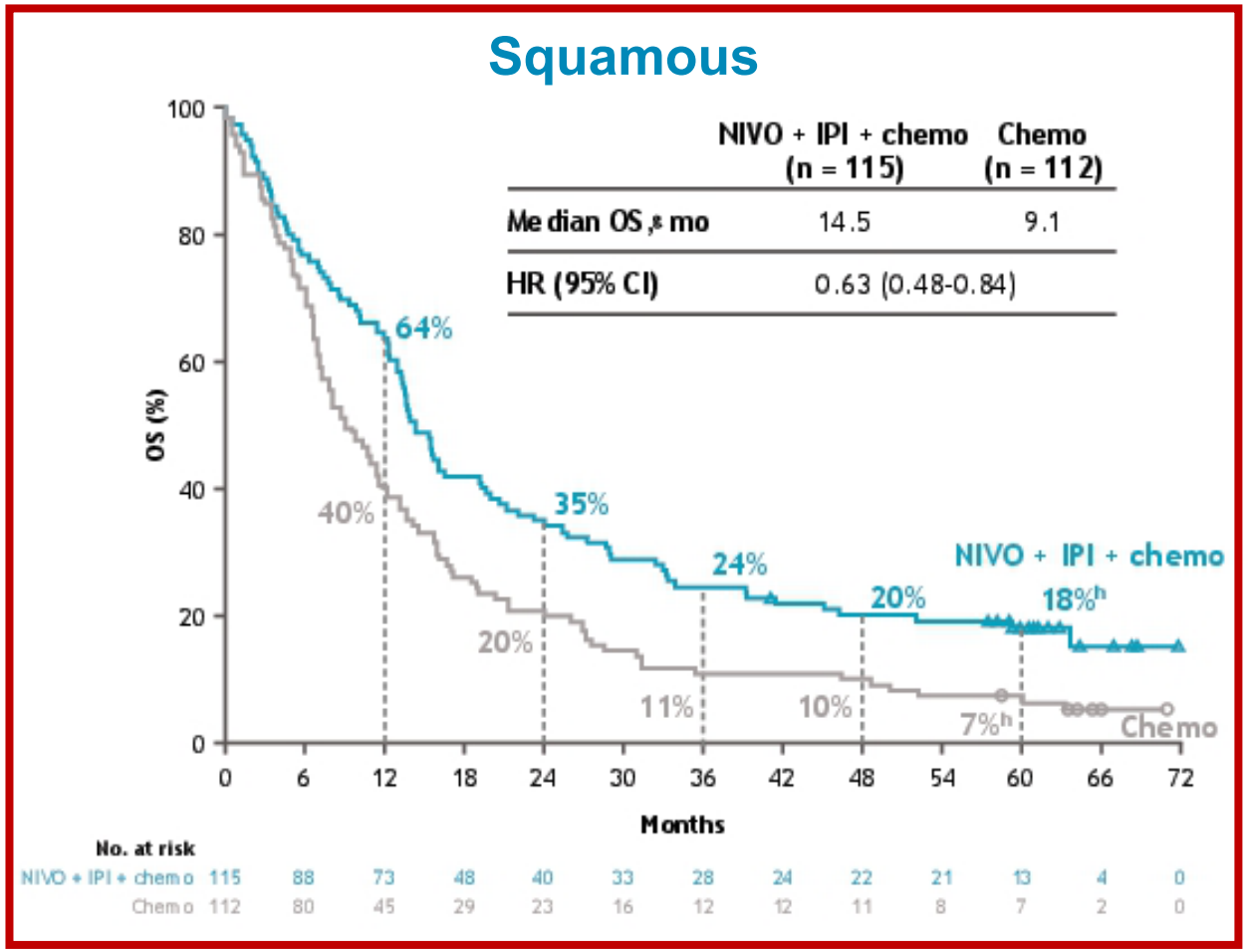



Database Lock: December 15, 2023
Minimum Follow-Up for OS: 57.3 Months
Maximum Follow-Up to OS: 64.5 Months

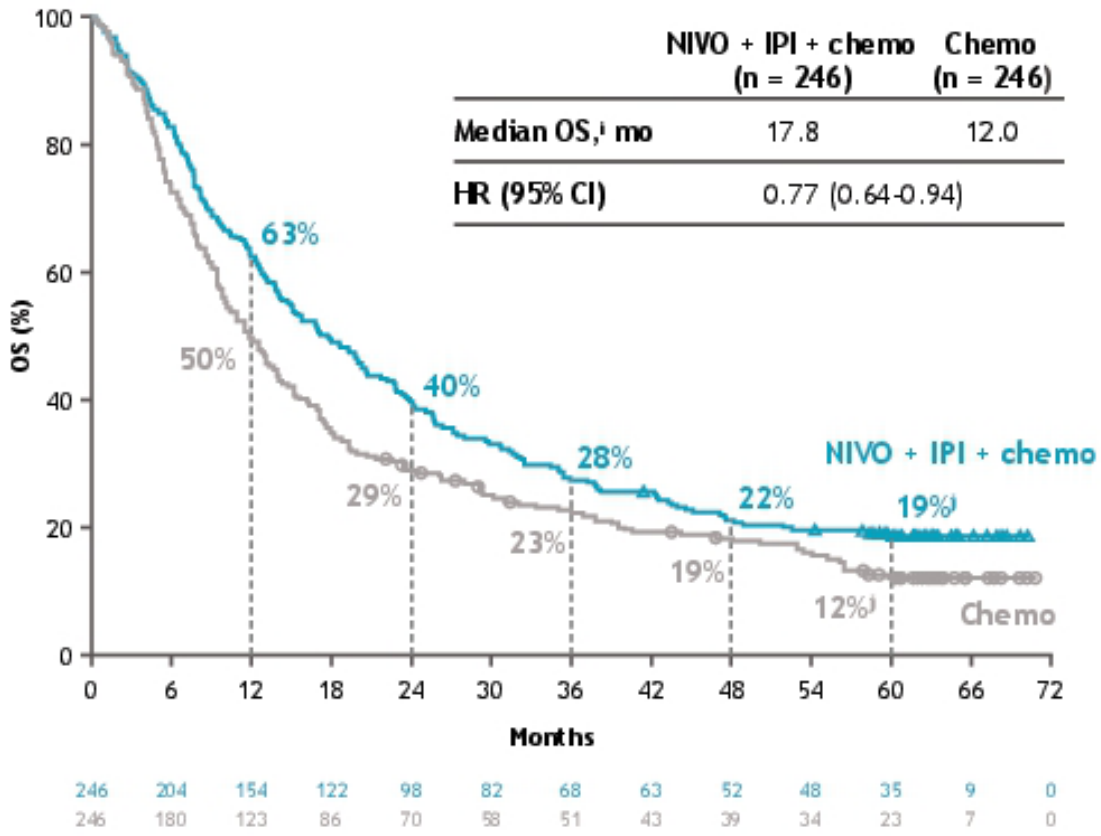

Reck M, et al. *J Clin Oncol.* 2024;42(16 suppl):8560.
Reck M, et al. ASCO 2024. Poster #424.

# CheckMate 9LA: 5-Year OS by Histology

## Squamous




## Nonsquamous

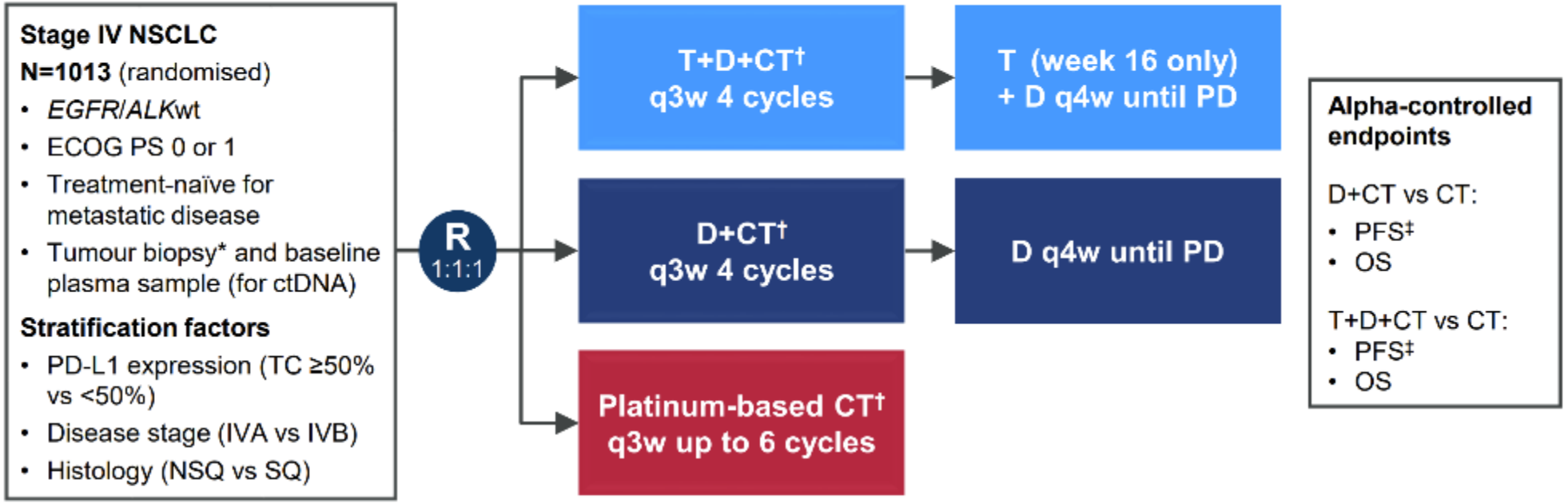




Reck M, et al. *J Clin Oncol.* 2024;42(16 suppl):8560.
Reck M, et al. ASCO 2024. Poster #424.

# Phase III POSEIDON Clinical Trial: Study Design

## Phase 3, global, randomised, open-label, multicentre study in 1L mNSCLC

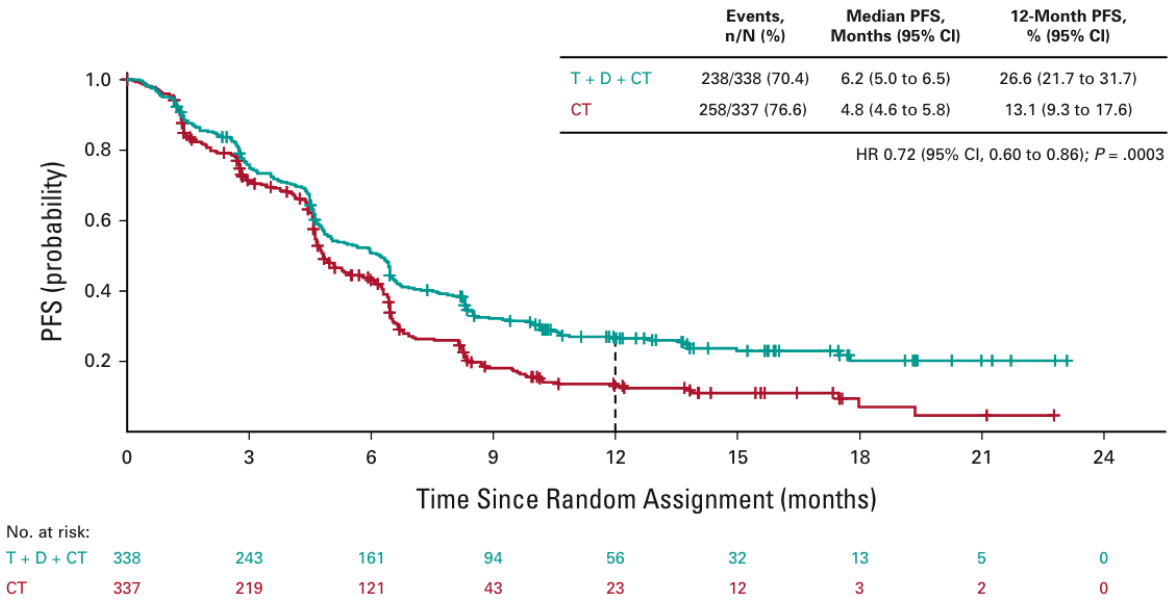


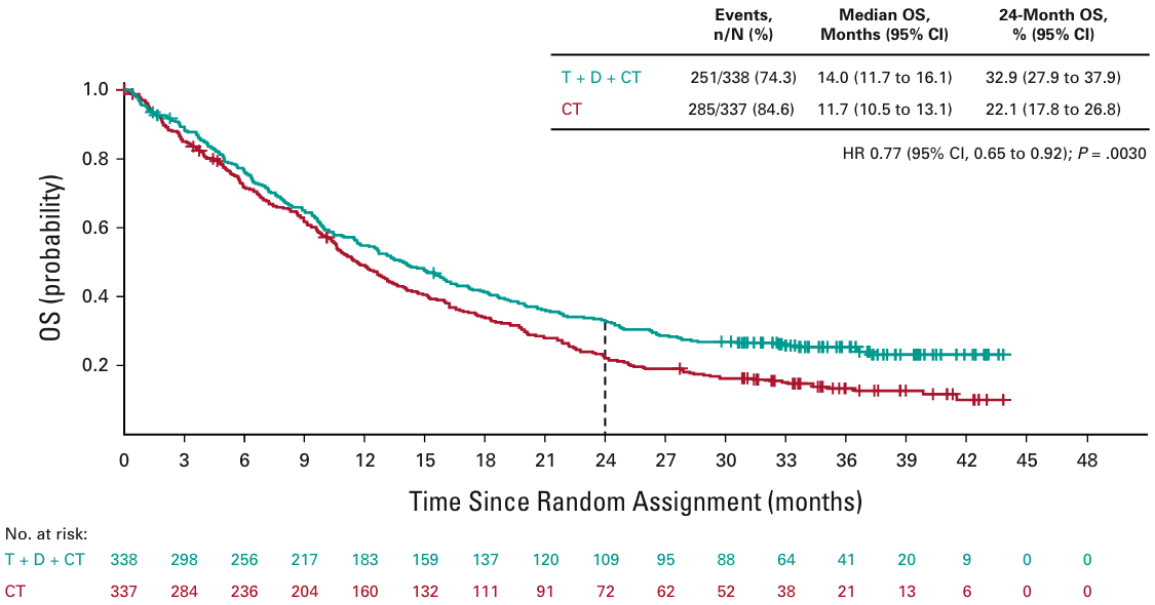

- **Durvalumab** 1500mg ± **limited-course tremelimumab** 75mg + **CT** q3w for **4 cycles**
  - One additional dose of tremelimumab post-CT (week 16; 5th dose)
- Followed by **durvalumab q4w maintenance** until PD, and optional pemetrexed q4w§

Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

ALKwt, anaplastic lymphoma kinase wild type; CT, platinum-based chemotherapy; ctDNA, circulating tumor DNA; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSG, non-squamous; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; q3w, every 3 weeks; SQ, squamous; T, tremelimumab; TC, tumor cellularity.

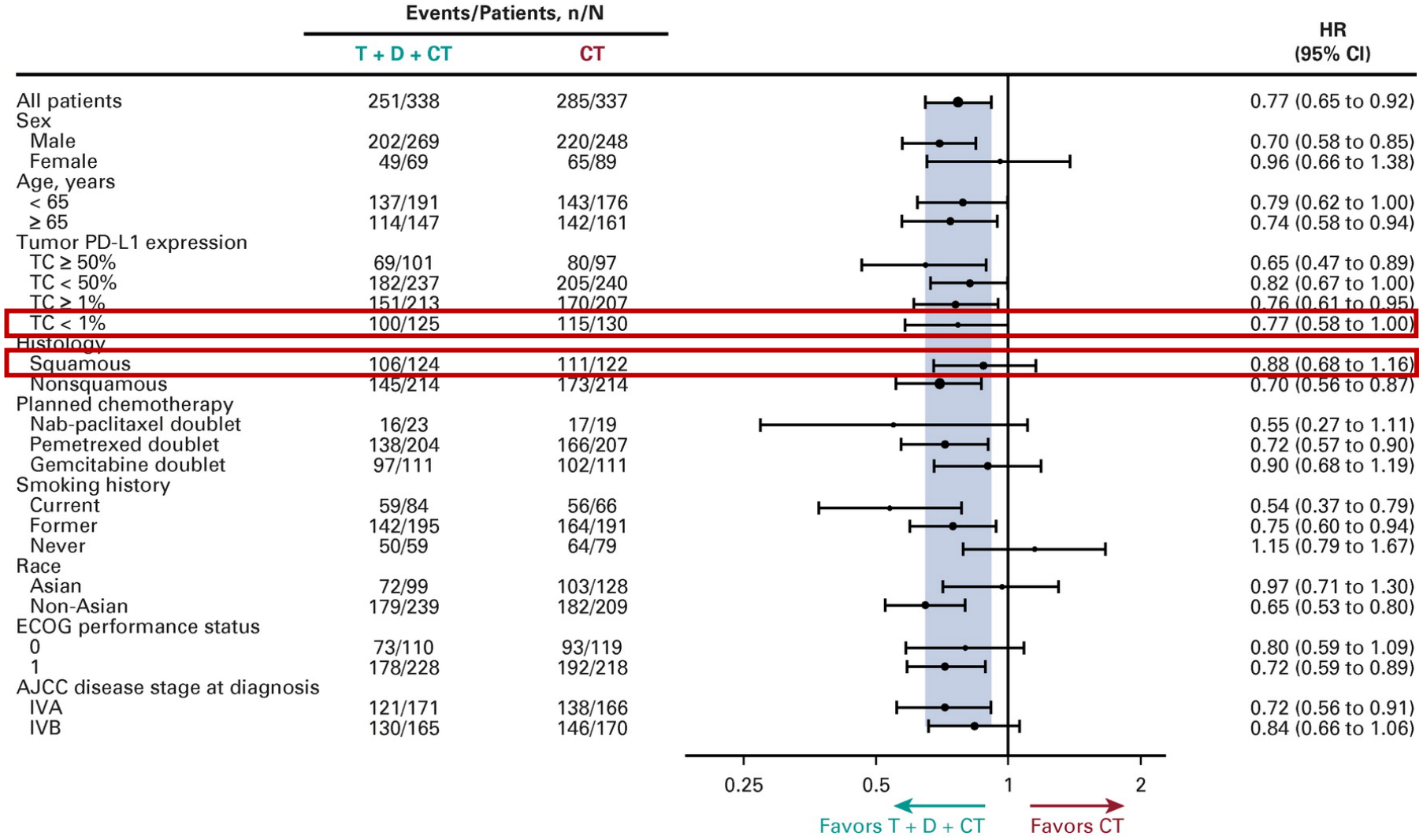
# POSEIDON: 4-Year PFS and OS




Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

# POSEIDON: OS in Patients With PD-L1 <1% or Squamous Histology



| | Events/Patients, n/N | | HR (95% CI) |
|---|---|---|---|
| | T + D + CT | CT | |
| All patients | 251/338 | 285/337 | 0.77 (0.65 to 0.92) |
| Sex | | | |
| Male | 202/269 | 220/248 | 0.70 (0.58 to 0.85) |
| Female | 49/69 | 65/89 | 0.96 (0.66 to 1.38) |
| Age, years | | | |
| < 65 | 137/191 | 143/176 | 0.79 (0.62 to 1.00) |
| ≥ 65 | 114/147 | 142/161 | 0.74 (0.58 to 0.94) |
| Tumor PD-L1 expression | | | |
| TC ≥ 50% | 69/101 | 80/97 | 0.65 (0.47 to 0.89) |
| TC < 50% | 182/237 | 205/240 | 0.82 (0.67 to 1.00) |
| TC ≥ 1% | 151/213 | 170/207 | 0.76 (0.61 to 0.95) |
| TC < 1% | 100/125 | 115/130 | 0.77 (0.58 to 1.00) |
| Histology | | | |
| Squamous | 106/124 | 111/122 | 0.88 (0.68 to 1.16) |
| Nonsquamous | 145/214 | 173/214 | 0.70 (0.56 to 0.87) |
| Planned chemotherapy | | | |
| Nab-paclitaxel doublet | 16/23 | 17/19 | 0.55 (0.27 to 1.11) |
| Pemetrexed doublet | 138/204 | 166/207 | 0.72 (0.57 to 0.90) |
| Gemcitabine doublet | 97/111 | 102/111 | 0.90 (0.68 to 1.19) |
| Smoking history | | | |
| Current | 59/84 | 56/66 | 0.54 (0.37 to 0.79) |
| Former | 142/195 | 164/191 | 0.75 (0.60 to 0.94) |
| Never | 50/59 | 64/79 | 1.15 (0.79 to 1.67) |
| Race | | | |
| Asian | 72/99 | 103/128 | 0.97 (0.71 to 1.30) |
| Non-Asian | 179/239 | 182/209 | 0.65 (0.53 to 0.80) |
| ECOG performance status | | | |
| 0 | 73/110 | 93/119 | 0.80 (0.59 to 1.09) |
| 1 | 178/228 | 192/218 | 0.72 (0.59 to 0.89) |
| AJCC disease stage at diagnosis | | | |
| IVA | 121/171 | 138/166 | 0.72 (0.56 to 0.91) |
| IVB | 130/165 | 146/170 | 0.84 (0.66 to 1.06) |



Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

# EMPOWER-Lung 3 Trial: Study Design

## Key Eligibility Criteria

- Treatment-naïve laNSCLC:
  - Non-squamous and squamous histology
- 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%
  - <1%: n=95 (30.4%)
  - 1%-49%: n=114 (36.5%)
  - ≥50%: n=103 (33.0%)
- Histology:
  - Non-squamous: n=179 (57.4%)
  - Squamous: n=133 (42.6%)

**Endpoints**

- Primary: OS
- Key Secondary: PFS and ORR
- Additional Secondary: DOR, BOR, Safety, Tolerability, and PROs

R 2:1

**Arm A**

Cemiplimab 350 mg Q3W + Investigator's Choice Platinum-Doublet Chemotherapy Q3W x 4 Cycles

**Arm B**

Placebo Q3W + Investigator's Choice Platinum-Doublet Chemotherapy Q3W x 4 Cycles

Progression or 108 Weeks

Progression or 108 Weeks

Follow-Up

**466 Patients in Full Analysis Population**

**69 Patients with laNSCLC Not Candidates for Definitive Interventions**
**Data Cutoff: June 14, 2022**

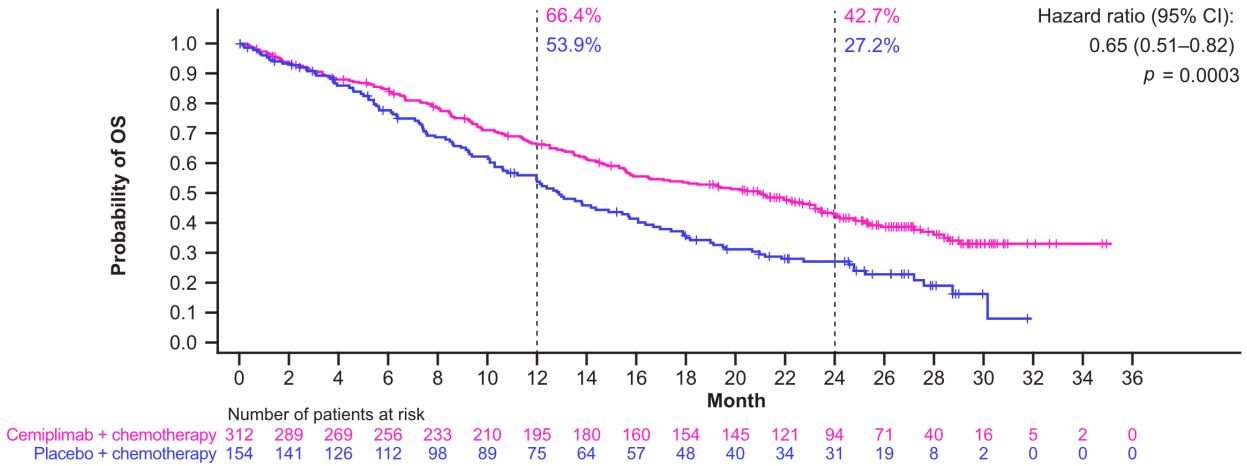
† Patient not a candidate for definitive chemoradiation.
- The indication to exclude concurrent radical chemo-radiation for stage IIIb/c patients was based on an individual decision by the principal investigator.

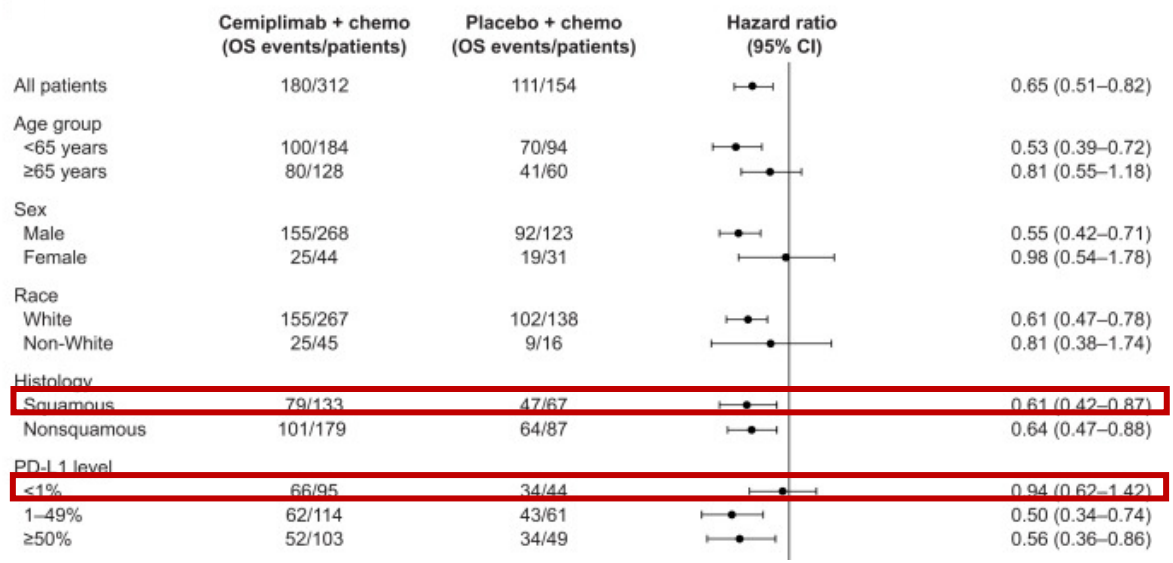
‡ Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment).
§ For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen.

Gogishvili M, et al. *Nat Med.* 2022;28:2374-2380.

ALK, anaplastic lymphoma kinase gene; BOR, best overall response; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; laNSCLC, locally advanced non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomized; ROS1, c-ros oncogene 1.

# EMPOWER-Lung 3: 2-Year OS




Makharadze T, et al. *J Thorac Oncol.* 2023;18(6):755-768.

# EMPOWER-Lung 3: OS and PFS by Histology

| Subgroup | OS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy | Median OS (months) | OS HR (95% CI) | PFS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy | Median PFS (months) | PFS HR (95% CI) | ORR % |
|---|---|---|---|---|---|---|---|
| Squamous PD-L1: <1% (n=54) | 23/38 vs 13/16 | 21.9 vs 16.7 | 0.60 (0.30-1.20) | 31/38 vs 14/16 | 8.3 vs 6.1 | 0.70 (0.37-1.32) | 50.0 vs 31.3 |
| Squamous PD-L1: 1-49% (n=81) | 31/53 vs 19/28 | 23.2 vs 8.6 | 0.52 (0.29-0.92) | 45/53 vs 25/28 | 6.7 vs 4.2 | 0.55 (0.33-0.90) | 43.4 vs 25.0 |
| Squamous PD-L1: ≥50% (n=65) | 25/42 vs 15/23 | 22.2 vs 15.1 | 0.77 (0.40-1.45) | 33/42 vs 18/23 | 8.3 vs 5.5 | 0.51 (0.28-0.92) | 47.6 vs 26.1 |
| | | | | | | | |
| Non-Squamous PD-L1: <1% (n=85) | 43/57 vs 21/28 | 9.6 vs 13.0 | 1.26 (0.74-2.12) | 46/57 vs 25/28 | 5.2 vs 4.3 | 0.79 (0.49-1.30) | 22.8 vs 14.3 |
| Non-Squamous PD-L1: 1-49% (n=94) | 31/61 vs 24/33 | 23.2 vs 12.0 | 0.48 (0.28-0.82) | 42/61 vs 30/33 | 8.5 vs 6.2 | 0.42 (0.26-0.69) | 42.6 vs 15.2 |
| Non-Squamous PD-L1: ≥50% (n=87) | 27/61 vs 19/26 | 24.8 vs 14.4 | 0.42 (0.23-0.76) | 37/61 vs 21/26 | 12.5 vs 5.2 | 0.46 (0.27-0.80) | 57.4 vs 26.9 |

Makharadze T, et al. *J Thorac Oncol.* 2023;18(6):755-768.