# II SESSIONE: Immunoterapia nel tumore del polmone

## I risultati dell'immunoterapia

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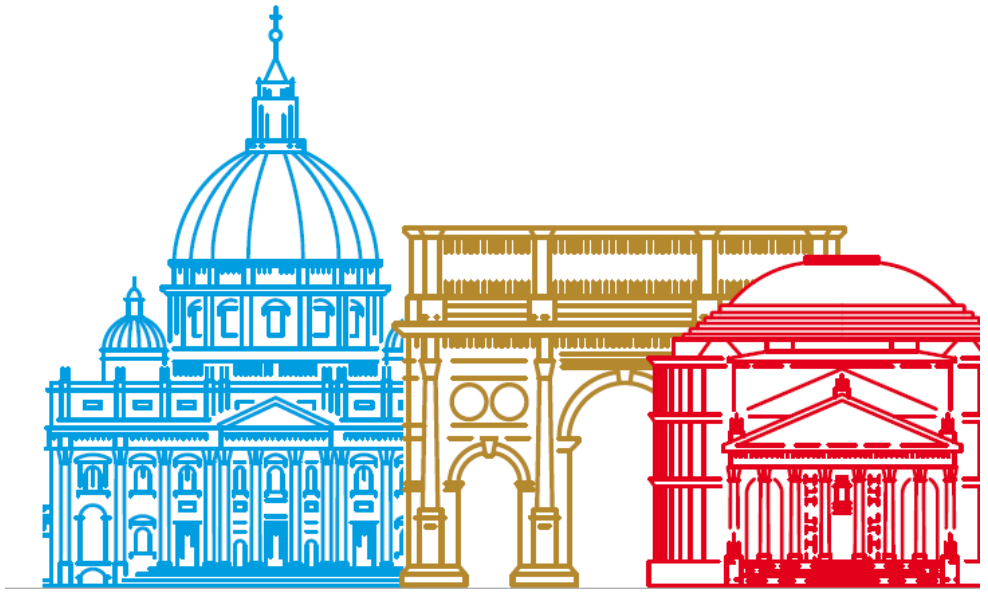


# DISCLOSURES SLIDE (last 3 yrs)

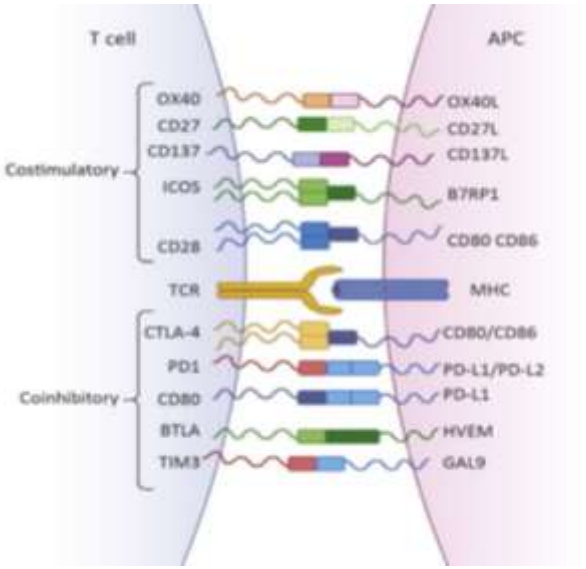
**Advisory functions:**

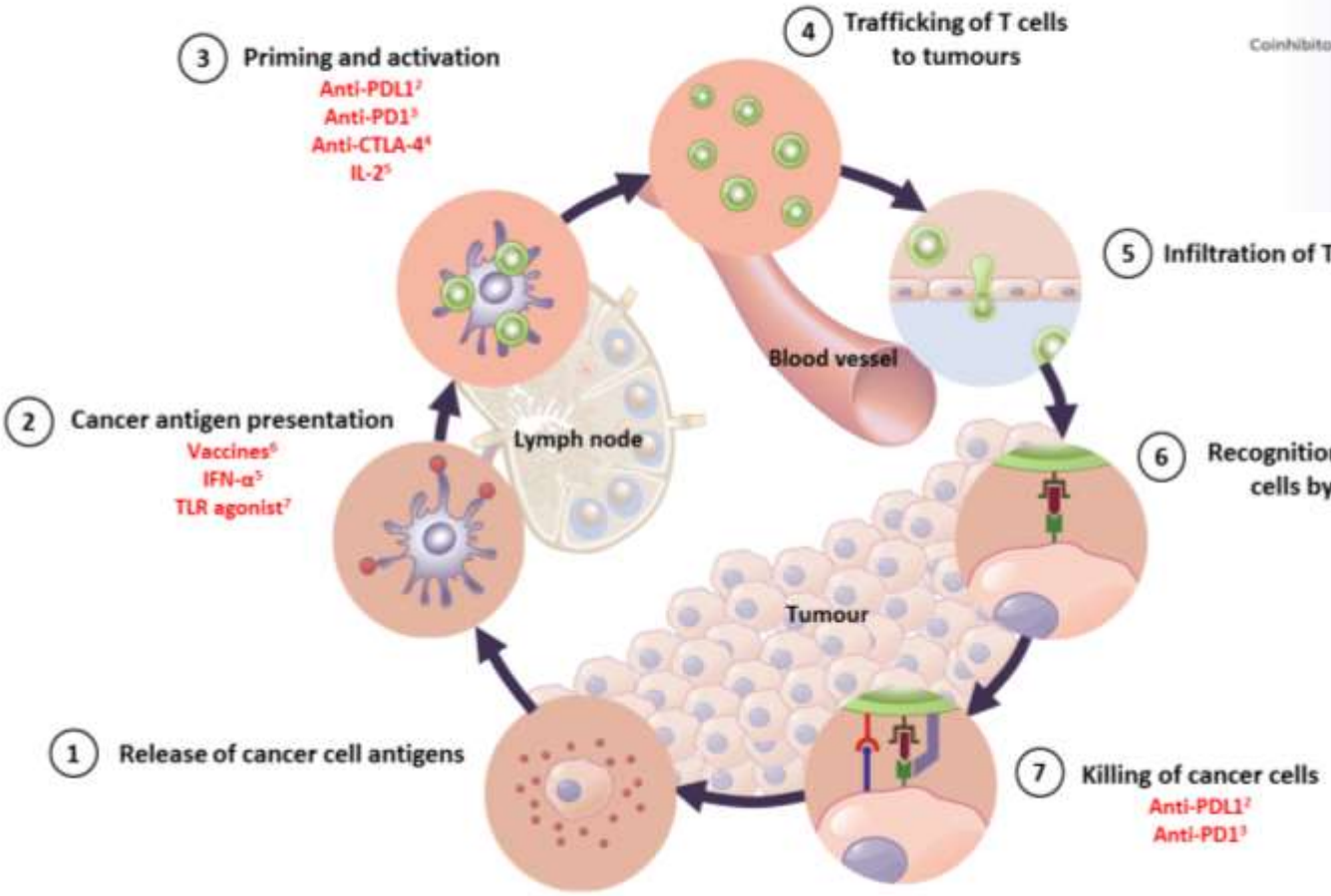
- AstraZeneca
- BMS
- Boehringer Ingelheim
- Novartis
- Roche/Genentech

# Agenda

- **Rationale for checkpoint inhibitors**
- **Available evidence:**
  - **Second-line**
  - **First-line: monotherapy / combo-treatments**
- **Side effects**
- **Conclusions**

# Avoiding immune destruction is a hallmark of cancer



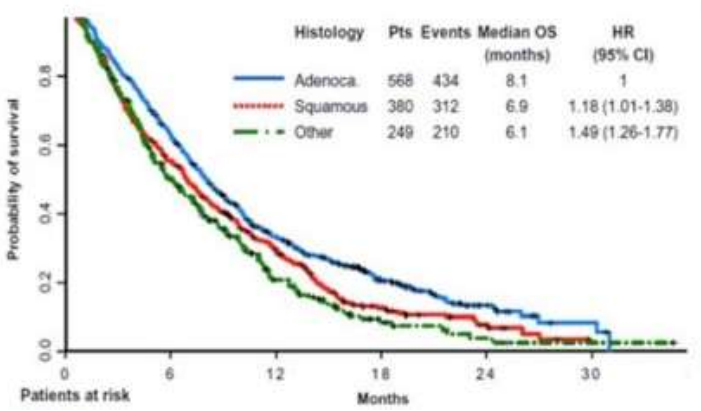

Chen & Mellman. Immunity 2013

# Agenda

- Rationale for checkpoint inhibitors
- **Available evidence:**
  - **Second-line**
  - **First-line: monotherapy / combo-treatments**
- Side effects
- Conclusions

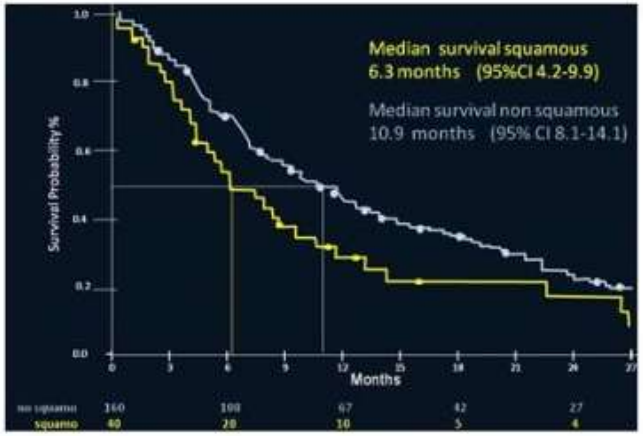
# Survival in advanced NSCLC: Expectation in 2nd Line

**Meta-analysis of Randomized Trials [Chemotherapy]**




*Di Maio M et al, EJC 2010*

**Meta-analysis of Randomized Trials [Chemo vs. Erlotinib]**




*Torri V et al , ASCO 2015*

**6-7 months for Squamous**

**8-9 months for Non-squamous**

**Second-line therapy endpoints**

**'Better life'**

- Symptom improvement
- Prolonged time to progression
- Improved disease-control rate
- Reduced toxicity
- Improved QoL

**Adapted from Brie E, AIOM 2016**

# Published Phase III Trials of PD-1/PD-L1 Agents in 2nd-Line NSCLC

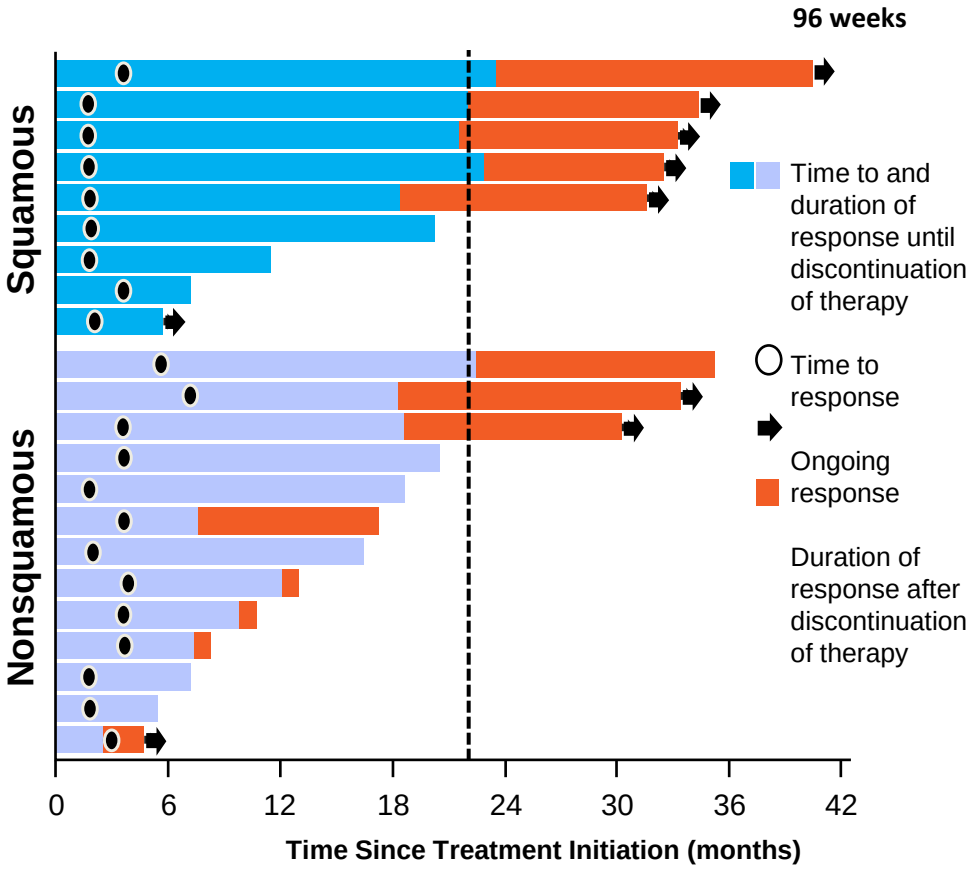
| Immuno Agent | Target | Trial | Histology | N | Drug Comparison | Primary Endpoint | Outcome |
|---|---|---|---|---|---|---|---|
| NIVOLUMAB | Anti-PD1 | CHECKMATE 017 [1] | Squamous NSCLC | 272<br>100%<br>2nd line | vs Docetaxel | OS | Positive<br>HR 0.62<br>(95% CI, 0.44 to 0.79)<br>p<0.001 |
| | Anti-PD1 | CHECKMATE 057 [2] | Non Squamous NSCLC | 582<br>88%<br>2nd line | vs Docetaxel | OS | Positive<br>HR 0.73<br>(96% CI, 0.59 to 0.89)<br>p=0.002 |
| PEMBROLIZUMAB * | Anti-PD1 | KEYNOTE 010 [3] | NSCLC PDL-1 >1% | 1034<br>69%<br>2nd line | vs Docetaxel | OS | Positive<br>HR 0.71<br>(95% CI, 0·58–0·88)<br>p=0·0008 |
| ATEZOLIZUMAB | Anti-PDL! | OAK [4] | NSCLC | 850<br>75%<br>2nd line | vs Docetaxel | OS | Positive<br>HR 0.73<br>(95% CI 0·62–0·87)<br>p=0·0003 |

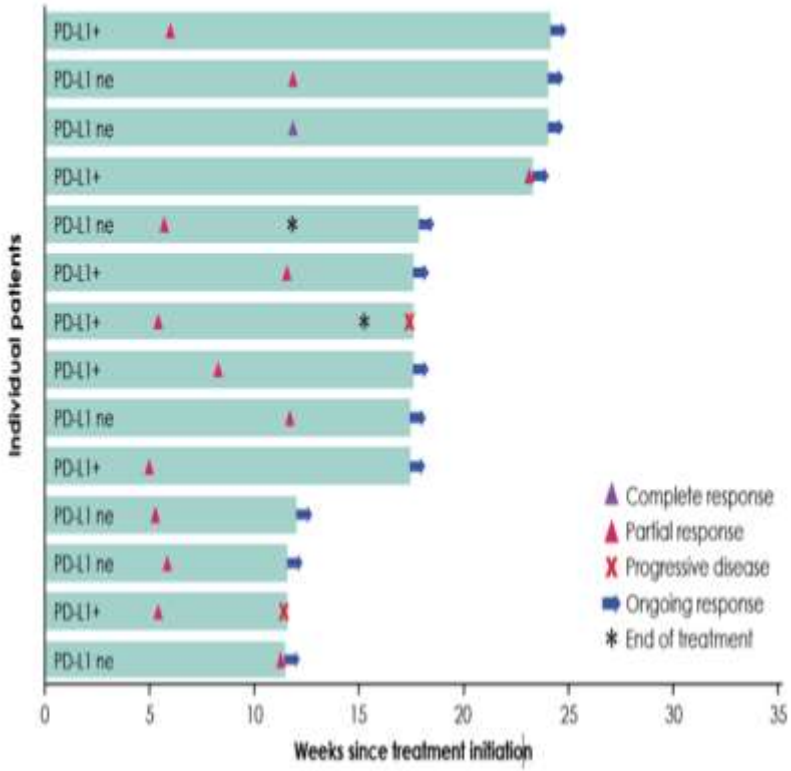
* 2mg/kg


[1] Brahmer et al, NEJM 2015
[2] Borghaei et al, NEJM 2015
[3] Herbst et al, Lancet 2016
[4] Rittermeyer et al, Lancet 2017

# Time to response is short

## Nivolumab & Avelumab monotherapy in ≥2nd-line



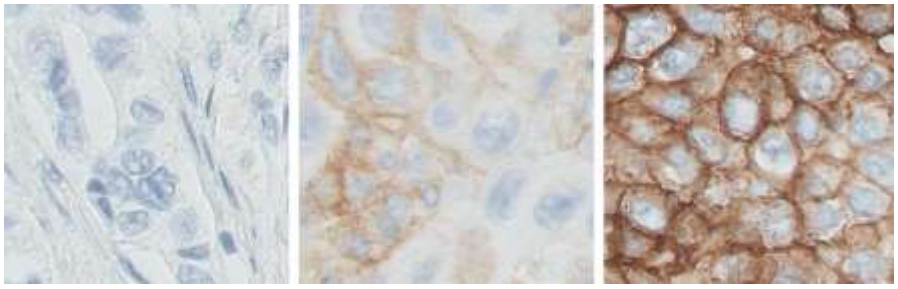

- **Most responses occurred early and were durable**
  - **50% of responders (11/22) demonstrated response at the first tumor assessment (8 weeks)**
  - **Responses were ongoing in 41% of patients (9/22) at the time of analysis**

Gettinger SN, et al. *J Clin Oncol*. 2015;33:2004–2012.

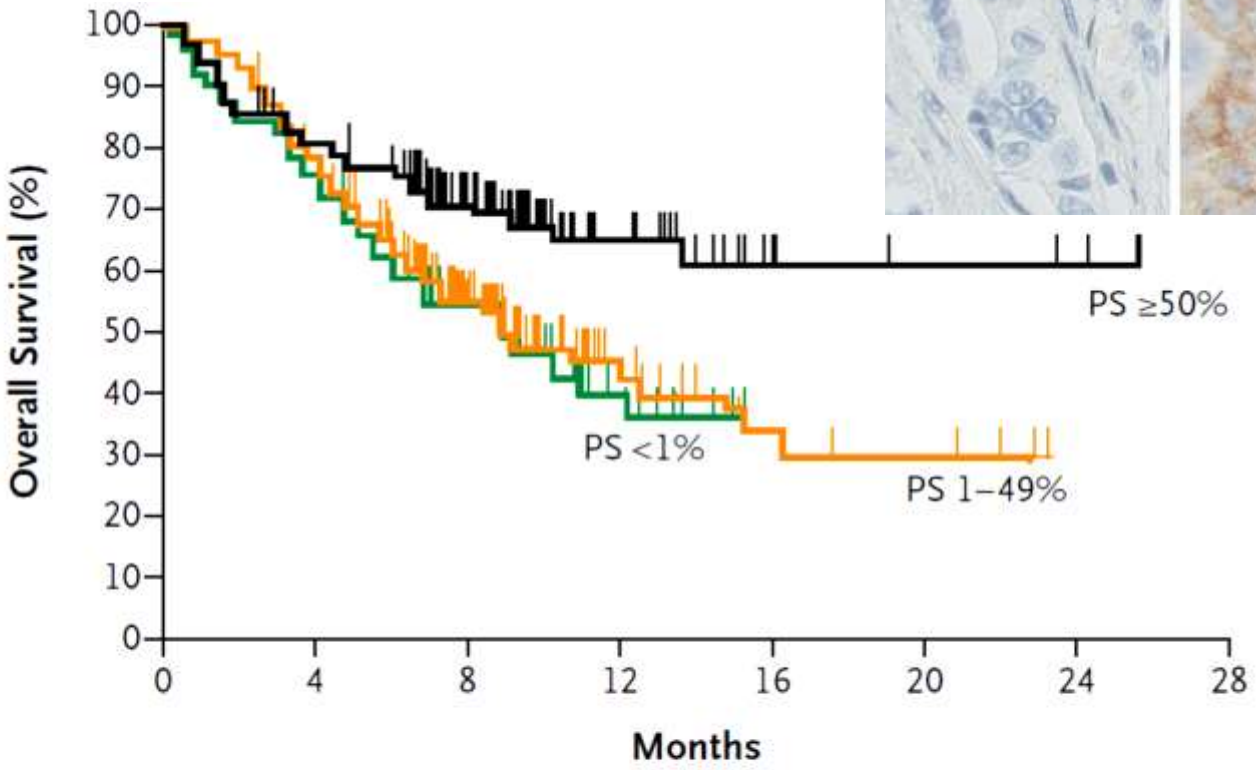
Versraegen et al., ESMO 2016

# PD-L1 Expression Matters

## Pembrolizumab - OS by PD-L1 expression




Dako 22C3 clone



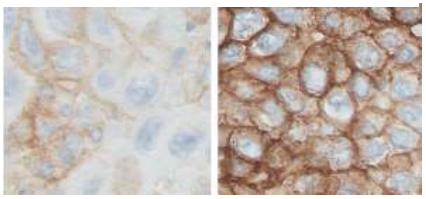

**No. at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PS ≥50% | 119 | 92 | 56 | 22 | 5 | 4 | 3 | 0 |
| PS 1–49% | 161 | 119 | 58 | 15 | 6 | 4 | 0 | 0 |
| PS <1% | 76 | 55 | 33 | 8 | 0 | 0 | 0 | 0 |

Garon, NEJM 2015

# Pembrolizumab in KEYNOTE-010: Phase II/III Trial

*Stratified by:*
- *ECOG PS (0 vs 1)*
- *region (east Asia vs not east Asia)*
- *PD-L1 expression (≥ 50% vs 1% to 49%)*




**Dako 22C3 clone**

Pts with NSCLC after platinum-based chemotherapy (and TKI if *EGFR*+ or *ALK*+); ≥ 1% PD-L1+ tumor cells; ECOG PS 0-1 (N = 1034)

**Pembrolizumab 2 mg/kg IV Q3W (n = 345)**

**Pembrolizumab 10 mg/kg IV Q3W (n = 346)**

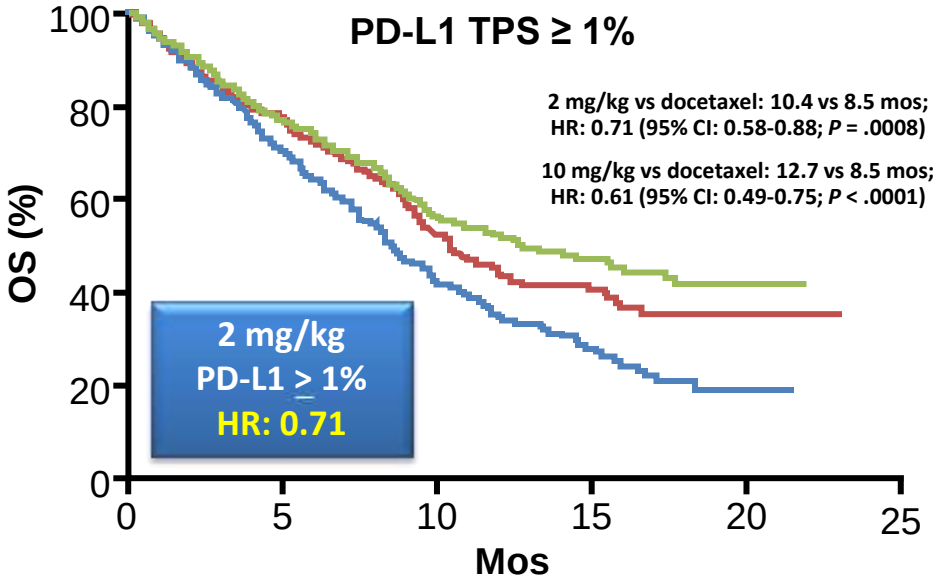
**Docetaxel* 75 mg/m² IV Q3W (n = 343)**

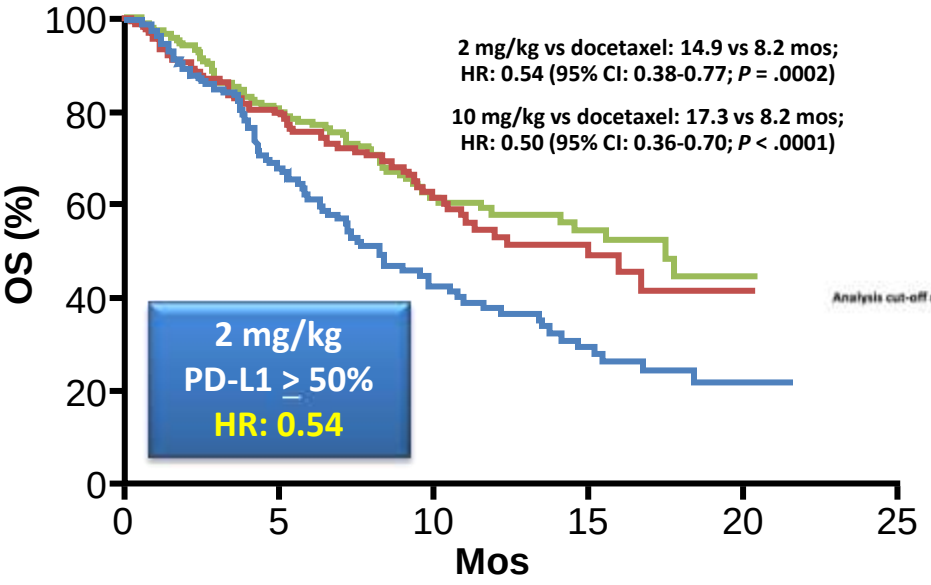
***Treatment continued for 24 mos or until PD† or unacceptable toxicity***

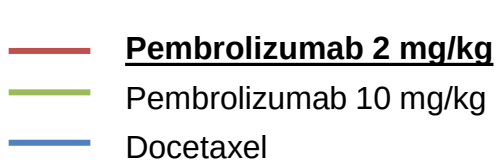
*Corticosteroid premedication allowed.
†Disease progression determined by radiological imaging.
In the case of investigator-assessed clinical disease progression, treatment permitted until confirmatory scan completed 4-6 wks later.

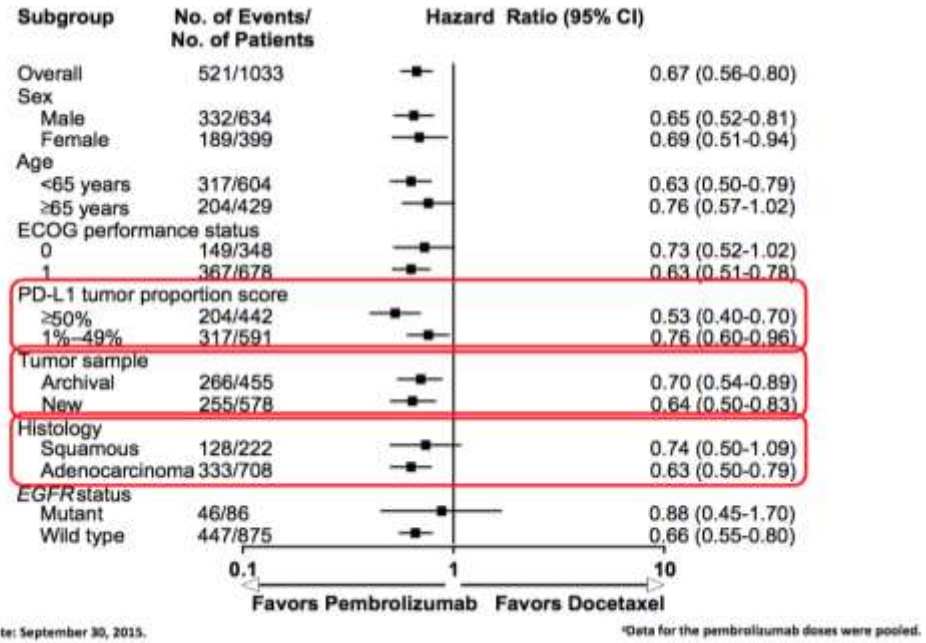
Herbst RS, et al. Lancet. 2015.

# KEYNOTE-010: Overall Survival



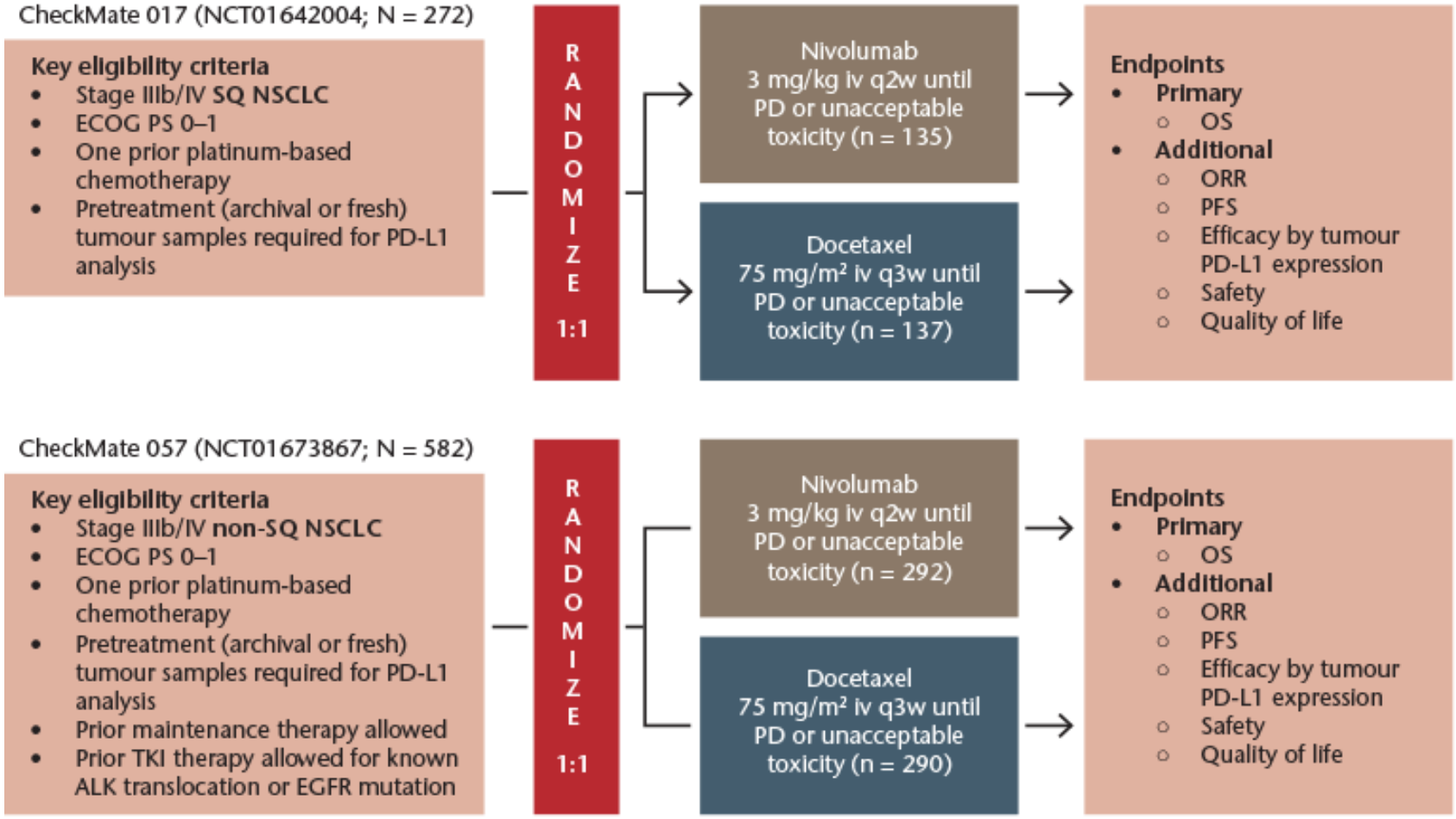




Herbst RS, et al. Lancet. 2015

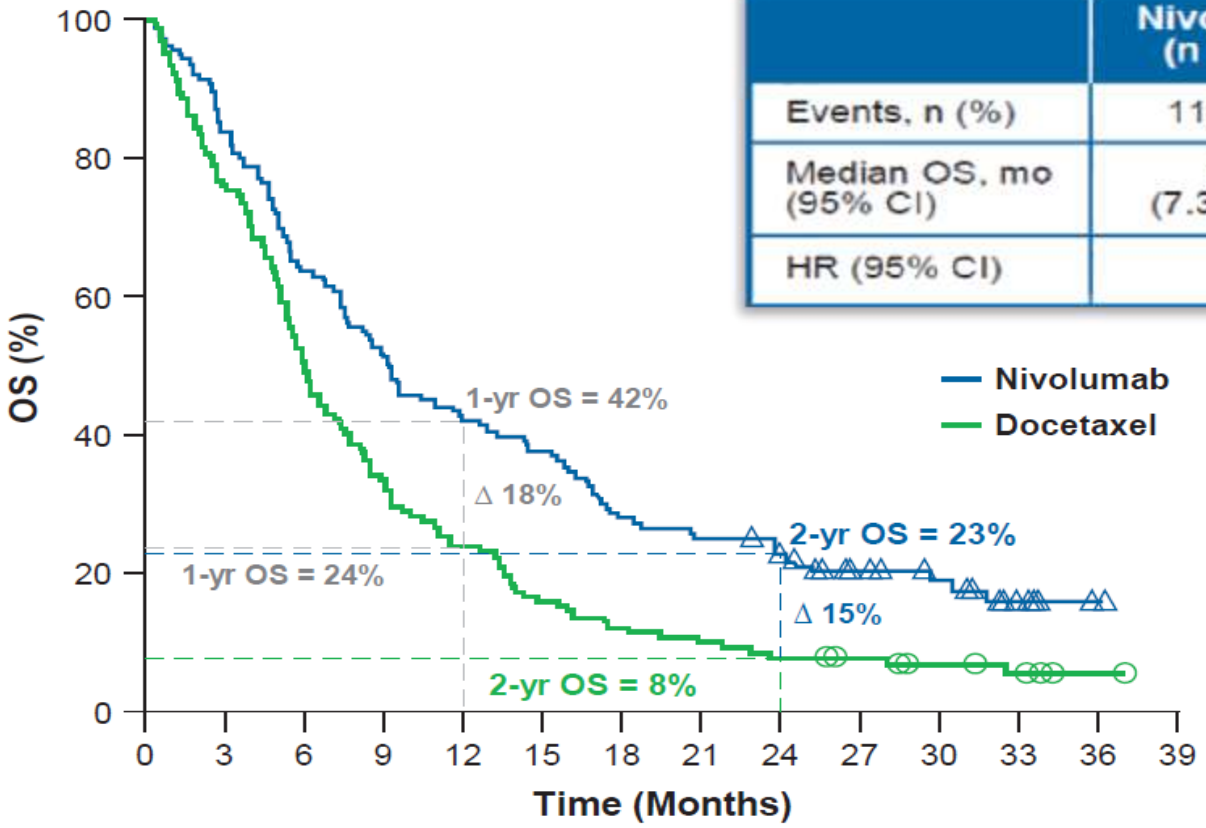
# Nivolumab in CheckMate 017 and 057: twin Phase 3 trials




*ALK = anaplastic lymphoma kinase; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; iv = intravenous; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PD = progressive disease; PFS = progression-free survival; q2w = every two weeks; q3w = every three weeks; SQ = squamous; TKI = tyrosine kinase inhibitor*

# CheckMate-017: Overall Survival in Previously Treated SQ NSCLC

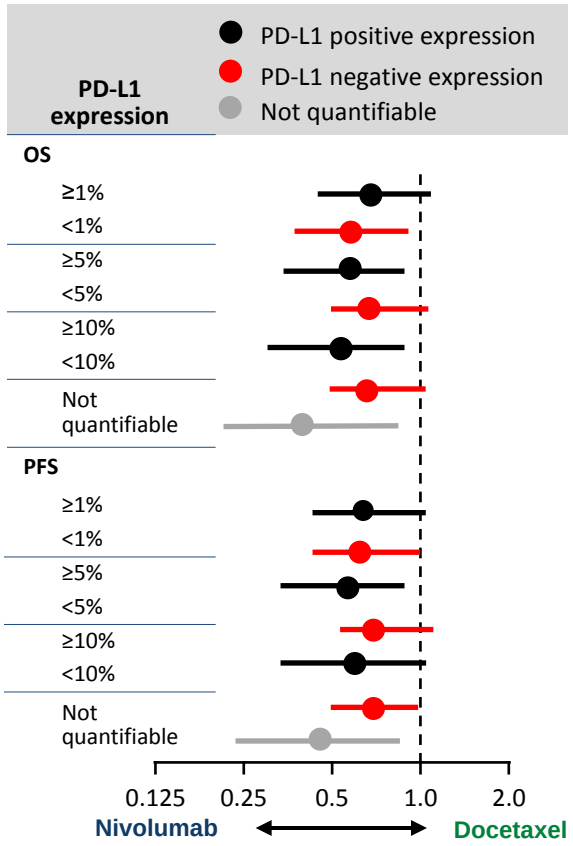
| | Nivolumab (n = 135) | Docetaxel (n = 137) |
|---|---|---|
| Events, n (%) | 110 (81) | 128 (93) |
| Median OS, mo (95% CI) | **9.2** (7.3, 12.6) | **6.0** (5.1, 7.3) |
| HR (95% CI) | 0.62 (0.47, 0.80) | |




No. of patients at risk:

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 135 | 113 | 86 | 69 | 57 | 51 | 38 | 34 | 29 | 19 | 14 | 7 | 1 | 0 |
| Docetaxel | 137 | 104 | 69 | 46 | 33 | 22 | 17 | 14 | 11 | 9 | 6 | 4 | 1 | 0 |

| PD-L1 expression,[b] % | | |
|---|---|---|
| ≥1% | 47 | 41 |
| ≥5% | 31 | 29 |
| ≥10% | 27 | 24 |
| Not quantifiable | 13 | 21 |

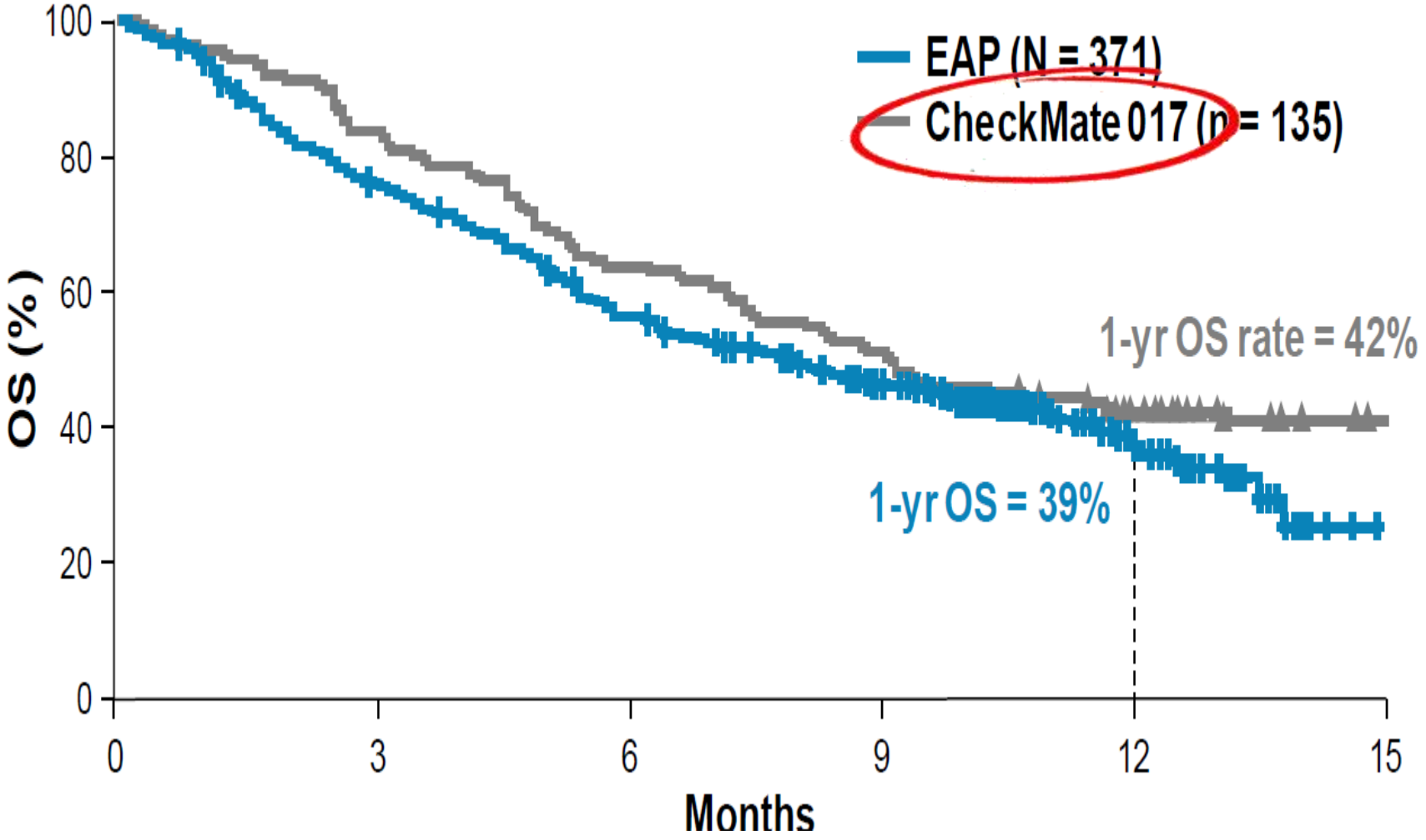



- 83% (225/272) of patients had quantifiable PD-L1 expression

# Italian Nivolumab EAP: Efficacy in Squamous NSCLC pts

IASLC WCLC 2016

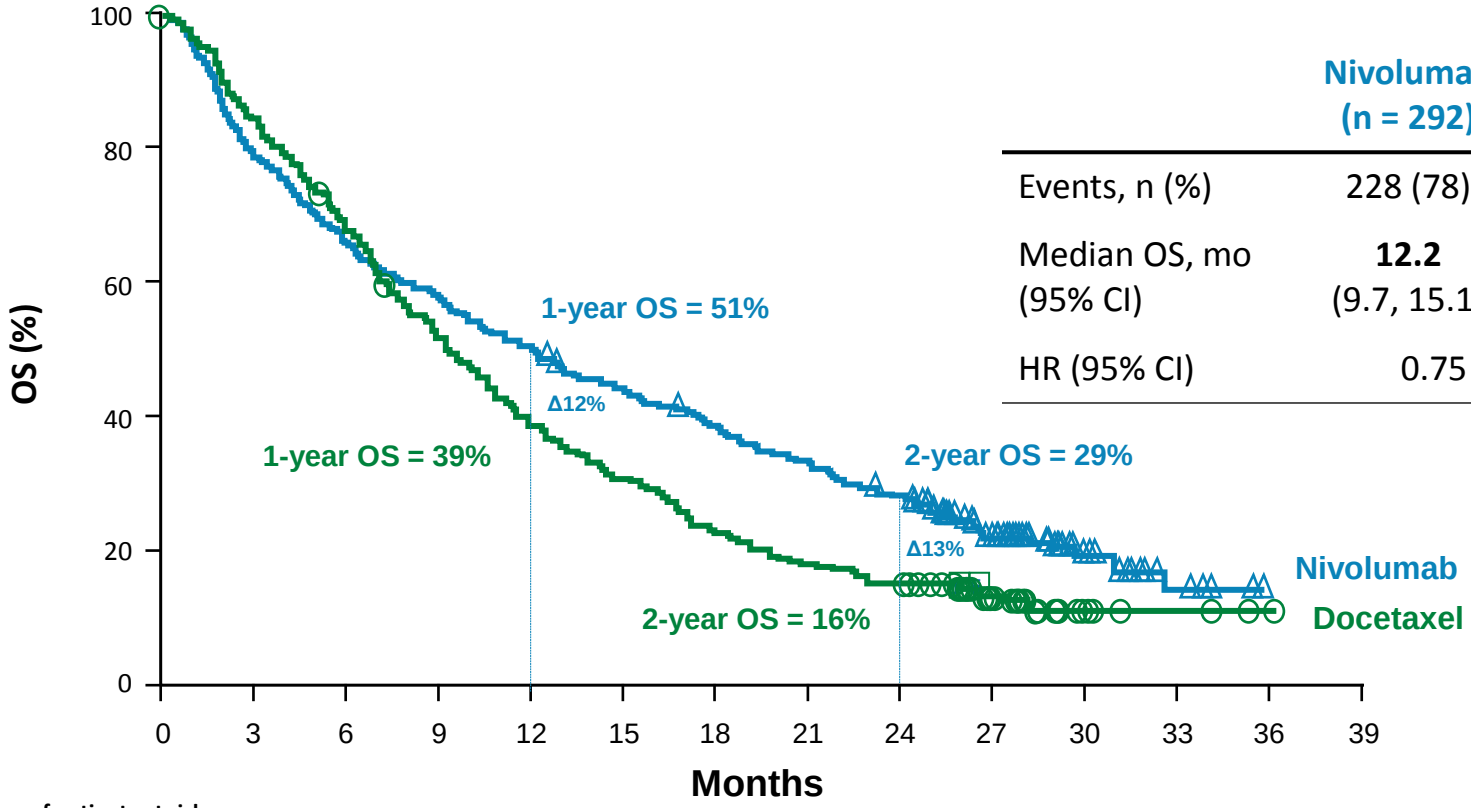
- 371 patients with SQ NSCLC participated in the EAP at 96 centers in Italy




- 209 (56%) patients received nivolumab after >2 previous lines of therapy

L Crinò et al, P WCLC 2016

# CheckMate-057: Overall Survival in Previously Treated NSQ NSCLC




| | Nivolumab (n = 292) | Docetaxel (n = 290) |
|---|---|---|
| Events, n (%) | 228 (78) | 247 (85) |
| Median OS, mo (95% CI) | **12.2** (9.7, 15.1) | **9.5** (8.1, 10.7) |
| HR (95% CI) | 0.75 (0.63, 0.91) | |

**Number of patients at risk**

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 292 | 233 | 194 | 171 | 148 | 128 | 112 | 97 | 81 | 46 | 18 | 6 | 0 | 0 |
| Docetaxel | 290 | 243 | 194 | 150 | 111 | 89 | 66 | 53 | 45 | 25 | 6 | 3 | 1 | 0 |

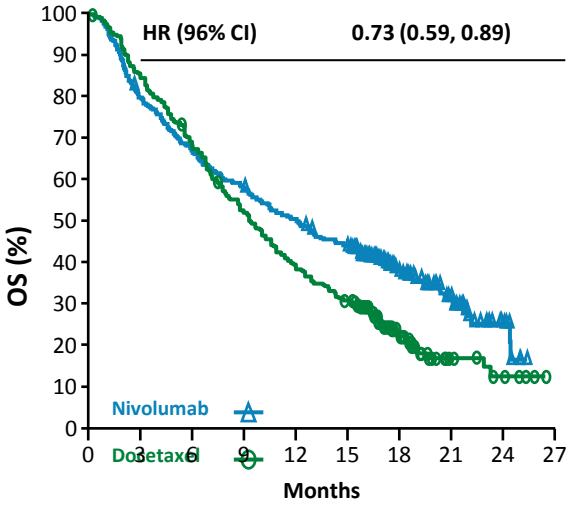
| | Nivolumab (n = 292) | Docetaxel (n = 290) |
|---|---|---|
| **Baseline PD-L1 expression** | | |
| **Quantifiable (% of evaluable patients)** | | |
| **≥1%** | 53 | 55 |
| **≥5%** | 41 | 38 |
| **≥10%** | 37 | 35 |
| **Not quantifiable (% of randomized patients)** | 21 | 23 |

Borghaei, NEJM 2016

# CheckMate-057: OS by PD-L1 Expression NSQ NSCLC

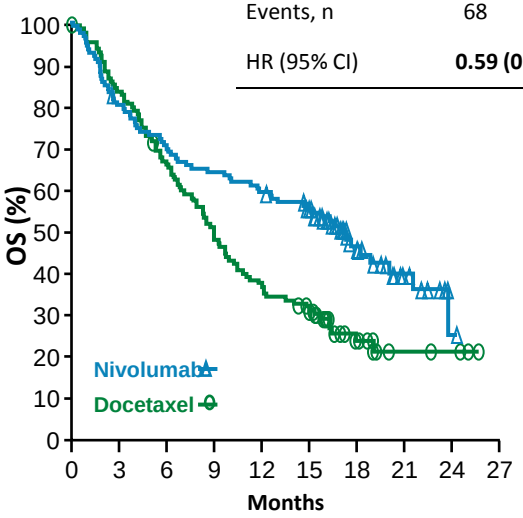
**ITT Population**[1]

| | Nivo (n = 292) | Doc (n = 290) |
|---|---|---|
| Median OS, mo | **12.2** | **9.4** |
| Events, n | 190 | 223 |
| **HR (96% CI)** | **0.73 (0.59, 0.89)** | |



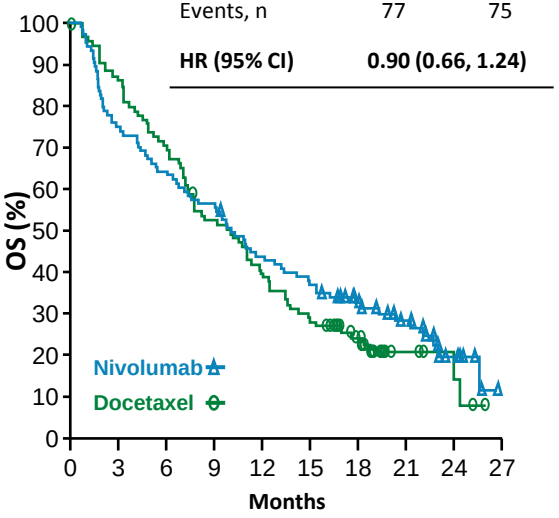

**≥1% PD-L1 Expression**

| | Nivo (n = 123) | Doc (n = 123) |
|---|---|---|
| Median OS,mo | **17.2** | **9.0** |
| Events, n | 68 | 93 |
| HR (95% CI) | **0.59 (0.43, 0.82)** | |

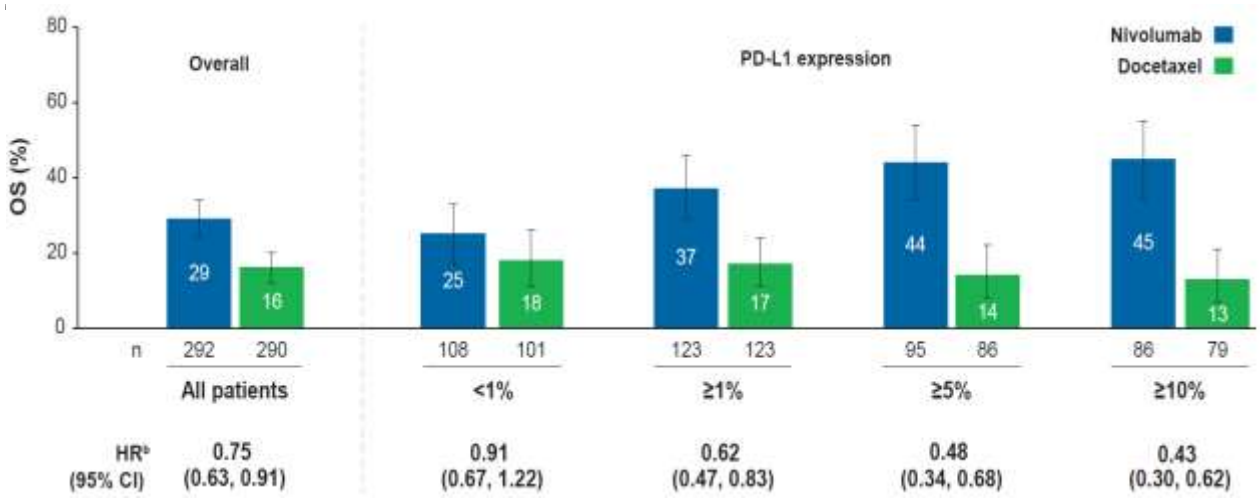



**<1% PD-L1 Expression**

| | Nivo (n = 108) | Doc (n = 101) |
|---|---|---|
| Median OS, mo | **10.4** | **10.1** |
| Events, n | 77 | 75 |
| **HR (95% CI)** | **0.90 (0.66, 1.24)** | |



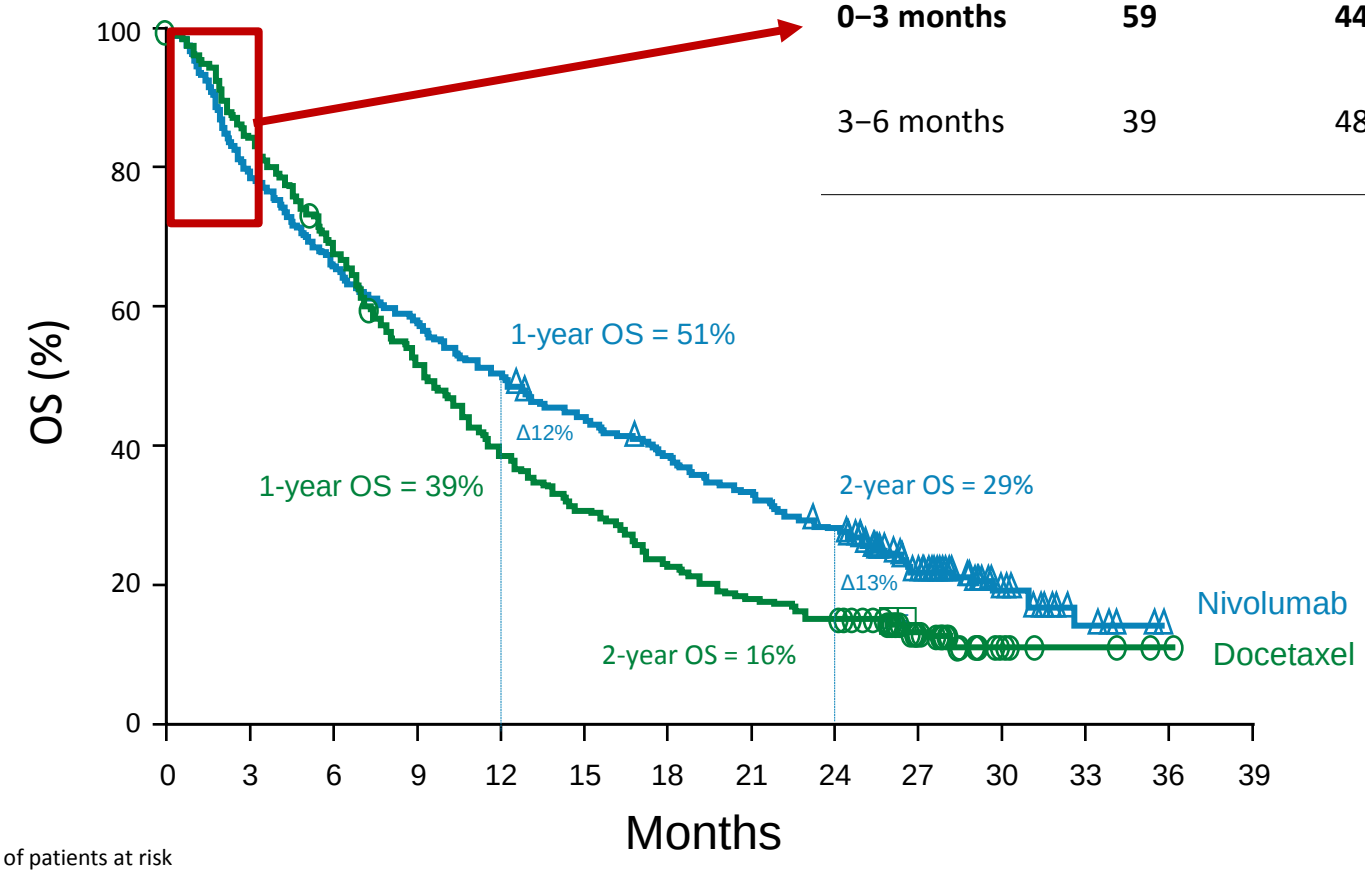

## CheckMate 057: 2-year OS Rates Overall and by PD-L1 Expression Level[2]




Paz-Ares L, ASCO 2015
Peters S , WCLC 2016

# CheckMate057: post-HOC analysis on outcome during the first 3 months

| Events | Nivolumab (n = 292) n | Docetaxel (n = 290) n | Difference n |
|---|---|---|---|
| **0–3 months** | **59** | **44** | **15** |
| 3–6 months | 39 | 48 | [9] |




Number of patients at risk

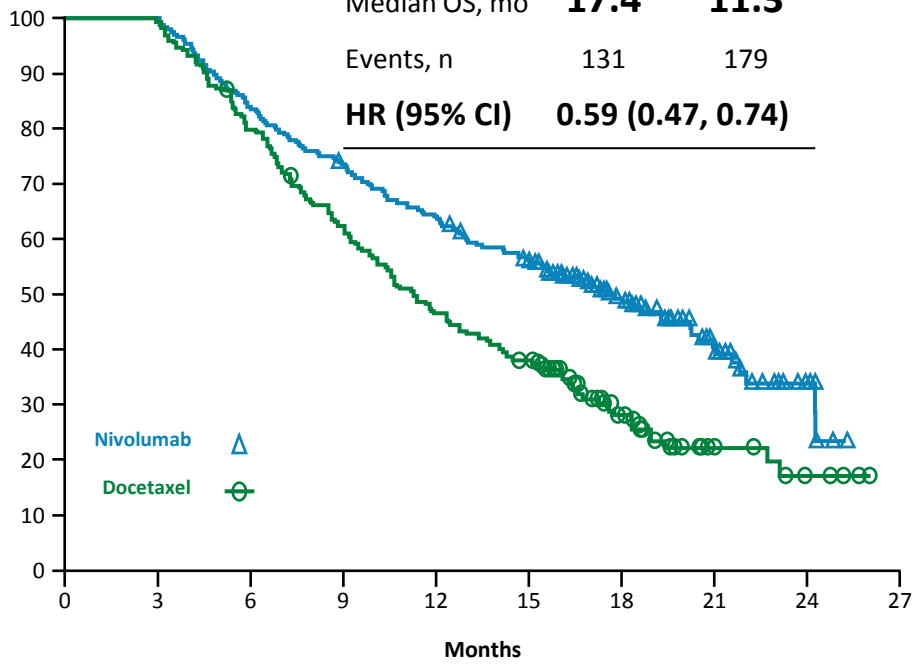
| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab | 292 | 233 | 194 | 171 | 148 | 128 | 112 | 97 | 81 | 46 | 18 | 6 | 0 | 0 |
| Docetaxel | 290 | 243 | 194 | 150 | 111 | 89 | 66 | 53 | 45 | 25 | 6 | 3 | 1 | 0 |

Peters S, WCLC 2016

# 3-Month Landmark Analysis of OS

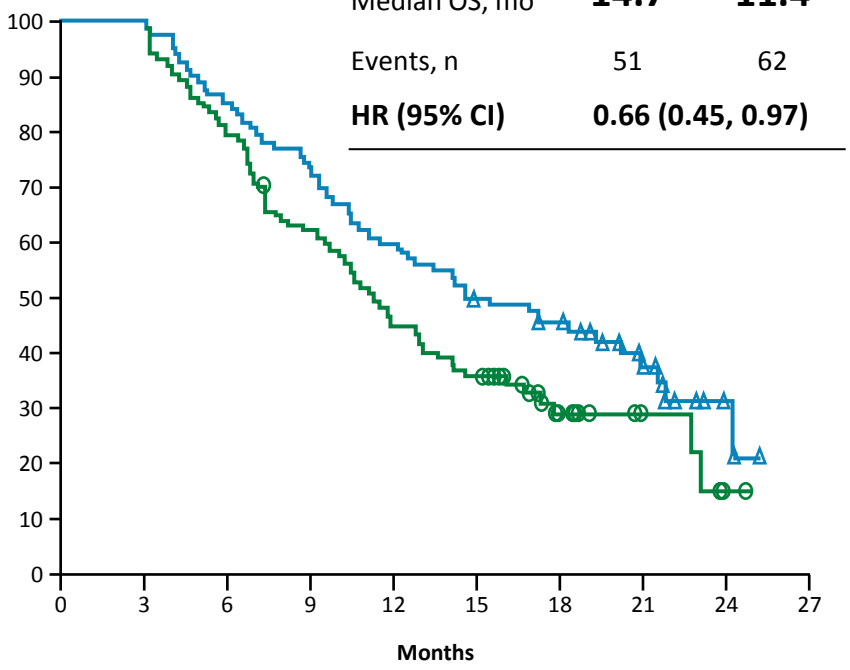
## Alive at 3 Months –All Patients

| | Nivo (n = 232) | Doc (n = 244) |
|---|---|---|
| Median OS, mo | **17.4** | **11.3** |
| Events, n | 131 | 179 |
| **HR (95% CI)** | **0.59 (0.47, 0.74)** | |




## Alive at 3 Months – Patients With <1% PD-L1 Expression

| | Nivo (n = 82) | Doc (n = 87) |
|---|---|---|
| Median OS, mo | **14.7** | **11.4** |
| Events, n | 51 | 62 |
| **HR (95% CI)** | **0.66 (0.45, 0.97)** | |



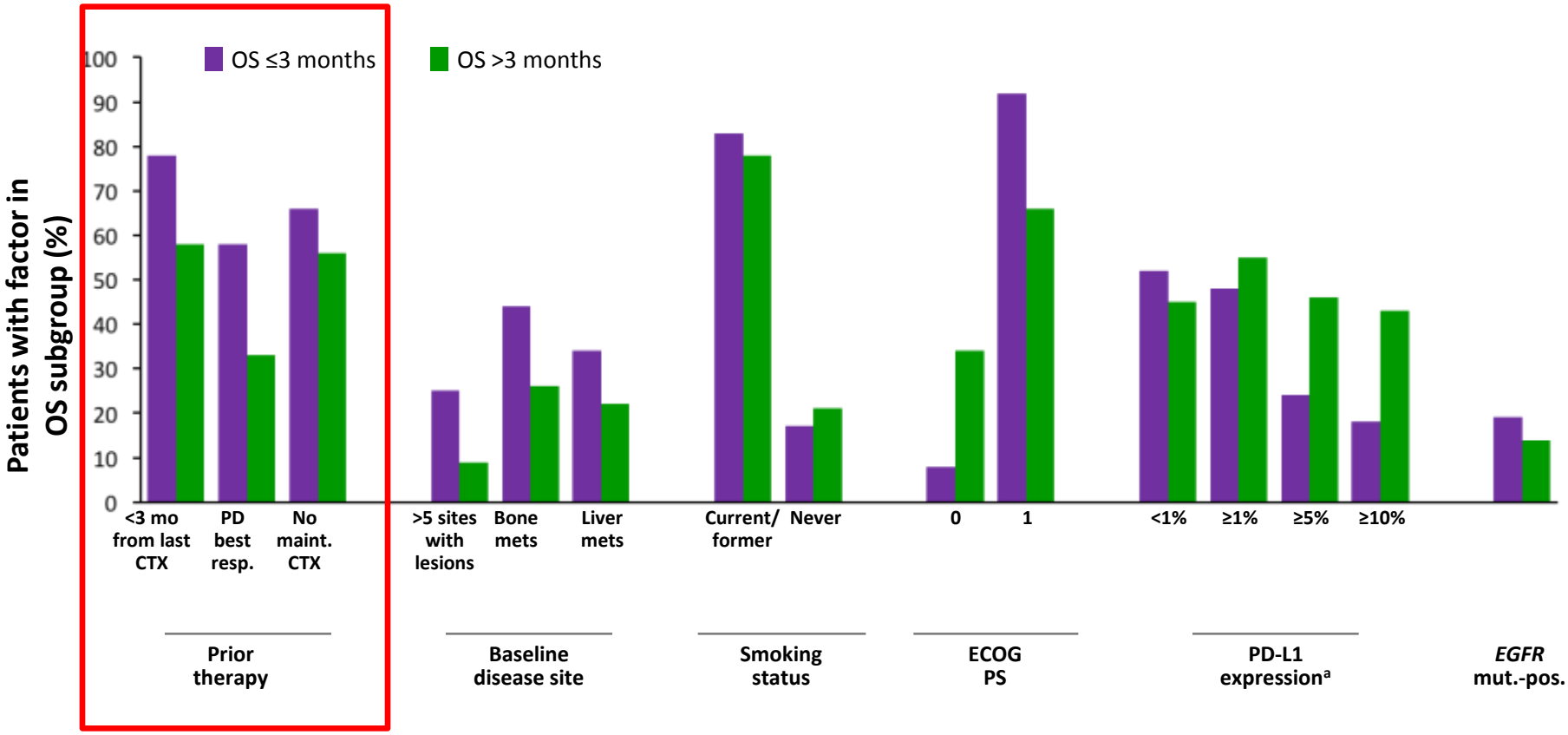

Based on a March 18, 2015 database lock

1. Borghaei H, et al. *N Engl J Med* 2015;373:1627–1639.

Peters S, WCLC 2016

# Combination of clinical factors and PD-L1 expression

## Which patients are not candidate for second-line immunotherapy?




- Post-hoc, exploratory multivariate analysis suggested that nivolumab-treated patients **with poorer prognostic features and/or aggressive disease when combined with lower or no tumor PD-L1 expression may be at higher risk of death within the first 3 months**
  - **These included the following known prognostic factors: <3 months since last treatment, PD as best response to prior treatment, and ECOG PS = 1**

S Peters et al, WCLC 2016

# Phase III OAK study design (squamous and non-squamos)

**Locally Advanced or Metastatic NSCLC[3]**

- N = 1225 enrolled[a]
- 1–2 prior lines of chemo including ≥ 1 platinum-based
- Any PD-L1 status[b]
- Stratification factors: PD-L1 expression, histology, prior chemotherapy regimens

R 1:1

- **Atezolizumab 1200 mg IV q3w** → PD or loss of clinical benefit
- **Docetaxel 75 mg/m² q3w** → PD

**Primary Endpoints (first 850 enrolled patients)**

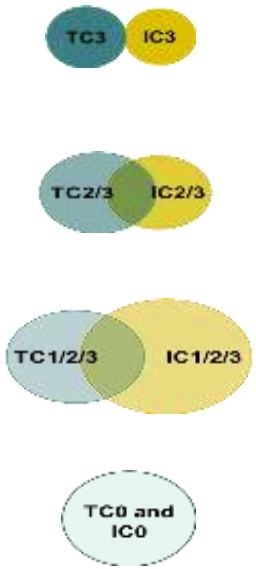
- OS in the ITT population
- OS in patients with PD-L1 expression on ≥ 1% TC or IC

**Secondary Endpoints**
ORR, PFS, DoR, Safety

**Ventana SP142**

***Intrinsic*** PD-L1 expression in tumor cells (TC)

***Adaptive*** PD-L1 expression in tumor-infiltrating immune cells (IC)

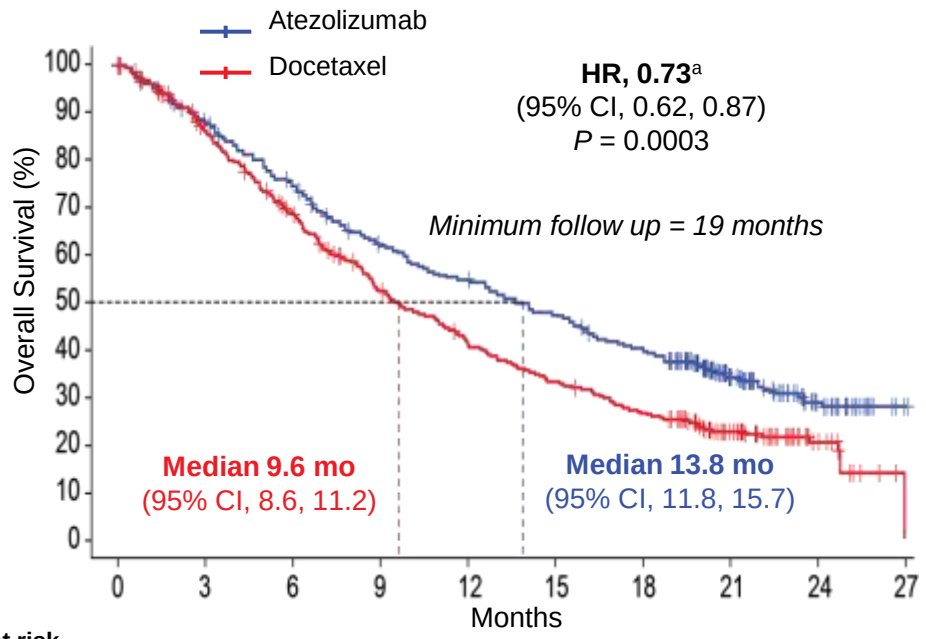



- SP142 IHC assay is sensitive and specific for PD-L1 expression on both TC and IC
- Distinct TC and IC sub-populations exist at each of four cutoff levels[a] Gettinger et al., ASCO 2015
- PD-L1 expression on TC and IC was independently predictive of response Horn et al. and Spigel et al., ASCO 2015

[a]A prespecified analysis of the first 850 patients provided sufficient power to test the co-primary endpoints of OS in the ITT and TC1/2/3 or IC1/2/3 subgroup (≥ 1% PD-L1 expression).
[b]PD-L1 expression assessed with VENTANA SP142 IHC assay

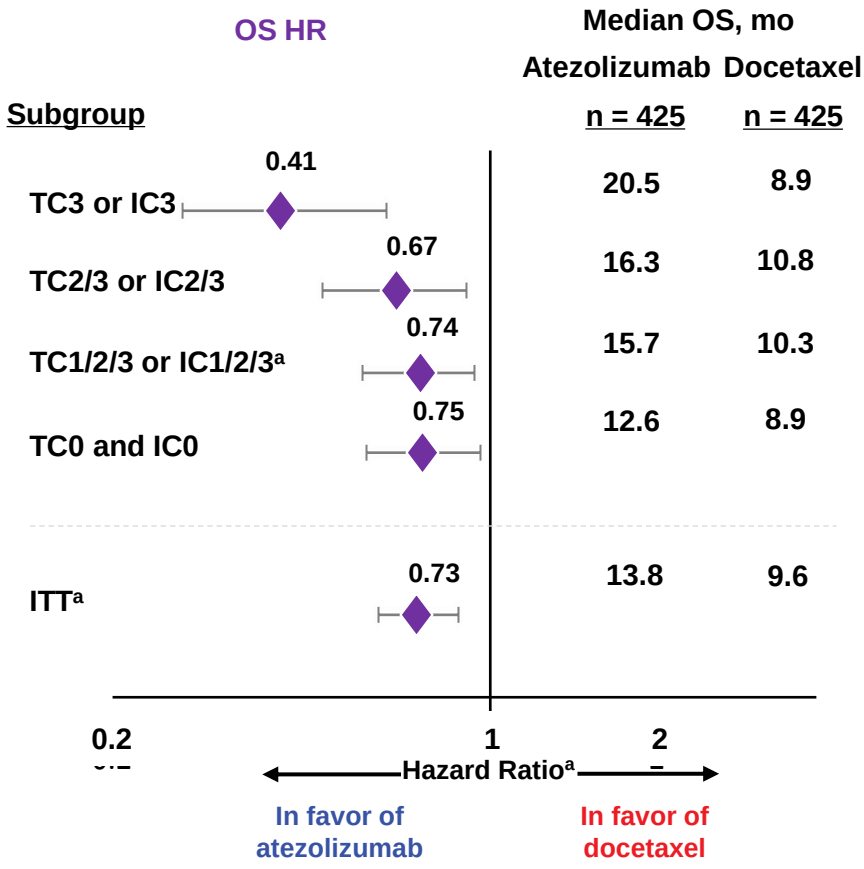
Rittermeyer et al. Lancet, 2017

# Overall survival, ITT (n = 850) and PD-L1 subgroups




**No. at risk**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 425 | 363 | 305 | 248 | 218 | 188 | 157 | 74 | 28 | 1 |
| Docetaxel | 425 | 336 | 263 | 195 | 151 | 123 | 98 | 51 | 16 | 0 |

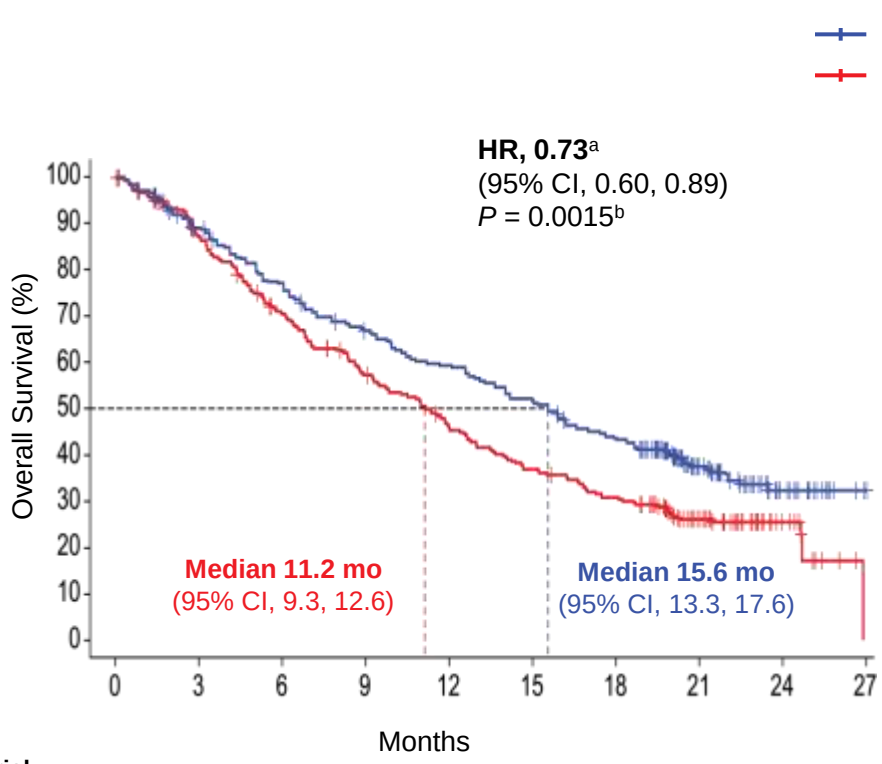



[a]Stratified HR for ITT and TC1/2/3 or IC1/2/3. Unstratified HR for other subgroups.
TC, tumor cells; IC, tumor-infiltrating immune cells; OS, overall survival.

Rittermeyer et al. Lancet, 2017

# OS by histology

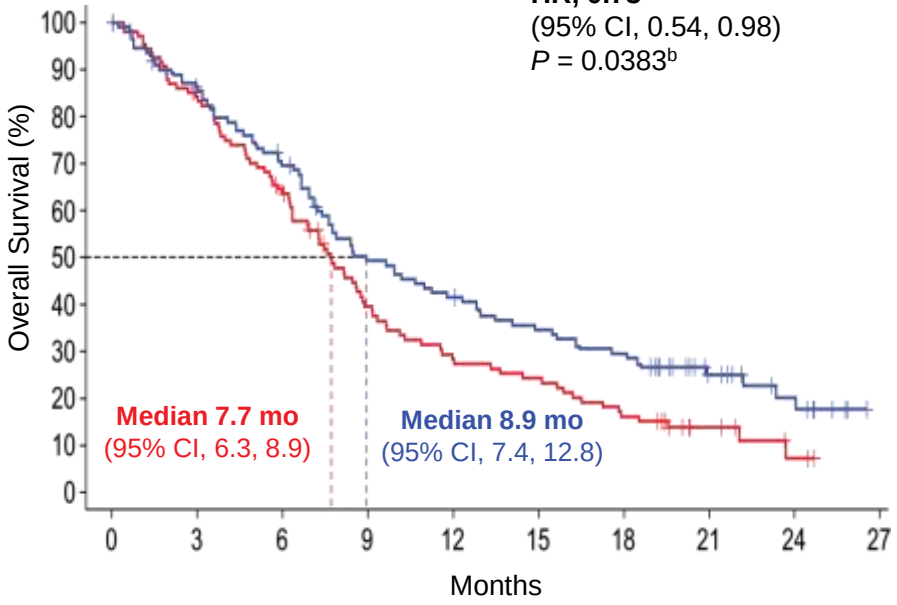
## Non-squamous




No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 313 | 270 | 231 | 197 | 175 | 153 | 127 | 59 | 20 | 1 |
| Docetaxel | 315 | 246 | 196 | 156 | 123 | 99 | 82 | 44 | 14 | 0 |

## Squamous



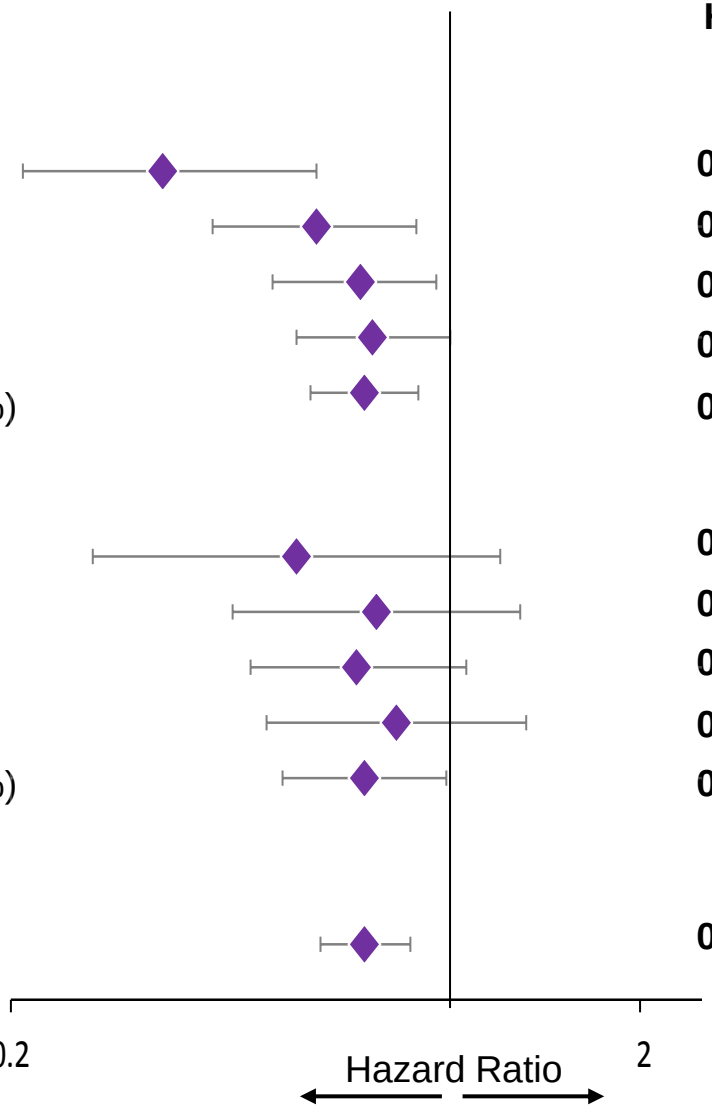

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Atezolizumab | 112 | 93 | 74 | 51 | 43 | 35 | 30 | 15 | 8 | 0 |
| Docetaxel | 110 | 90 | 67 | 39 | 28 | 24 | 16 | 7 | 2 | 0 |

Minimum follow up = 19 months.
[a]Unstratified HRs. [b]P values for descriptive purpose only.
Histology information from eCRF. OS, overall survival.
Barlesi et al. ESMO 2016 LBA44

Rittermeyer et al. Lancet, 2017

# Histology by PD-L1 status: Overall survival

| Subgroup | n (%) | HR[a] | Median OS, mo Atezolizumab | Median OS, mo Docetaxel |
|---|---|---|---|---|
| **Nonsquamous** | | | | |
| TC3 or IC3 | 96 (15%) | **0.35** | 22.5 | 8.7 |
| TC2/3 or IC2/3 | 188 (30%) | **0.61** | 18.7 | 11.3 |
| TC1/2/3 or IC1/2/3 | 333 (53%) | **0.72** | 17.6 | 11.3 |
| TC0 and IC0 | 290 (46%) | **0.75** | 14.0 | 11.2 |
| All nonsquamous | 628 (100%) | **0.73** | 15.6 | 11.2 |
| **Squamous** | | | | |
| TC3 or IC3 | 41 (18%) | **0.57** | 17.5 | 11.6 |
| TC2/3 or IC2/3 | 77 (35%) | **0.76** | 10.4 | 9.7 |
| TC1/2/3 or IC1/2/3 | 130 (59%) | **0.71** | 9.9 | 8.7 |
| TC0 and IC0 | 89 (40%) | **0.82** | 7.6 | 7.1 |
| All squamous | 222 (100%) | **0.73** | 8.9 | 7.7 |
| ITT | 850 | **0.73** | 13.8 | 9.6 |




In favor of atezolizumab

In favor of docetaxel

Rittermeyer et al. Lancet, 2017

# Second-line therapy of Sq and N-sq NSCLC: comparison across studies

## SQUAMOUS NSCLC

| | CheckMate-017[1] | | Keynote-010[2] | | OAK [3] | |
|---|---|---|---|---|---|---|
| **Drugs** | NIVO | DOC | PEMBRO * 2-10mg/kg | DOC | ATEZO | DOC |
| **mOS** | 9.2 | 6.0 | NA | | 8.9 | 7.7 |
| **HR** | 0.62 (0,48-0,81) | | 0.74 (0,50-1,09) | | 0.73 (0,54-0,98) | |
| **2 years-OS** | **23%** | **8%** | NA | | NA | |

## NON-SQUAMOUS NSCLC

| | CheckMate-057[4] | | Keynote-010[2] | | OAK [3] | |
|---|---|---|---|---|---|---|
| **Drugs** | NIVO | DOC | PEMBRO * 2-10 mg/kg | DOC | ATEZO | DOC |
| **mOS** | 12.2 | 9.5 | NA | | 15.6 | 11.2 |
| **HR** | 0.75 (0,63-0,91) | | 0.63 (0,50-0,79) | | 0.73 (0,60-0,89) | |
| **2 years-OS** | 29% | 16% | NA | | NA | |

*** PDL-1 >1%**

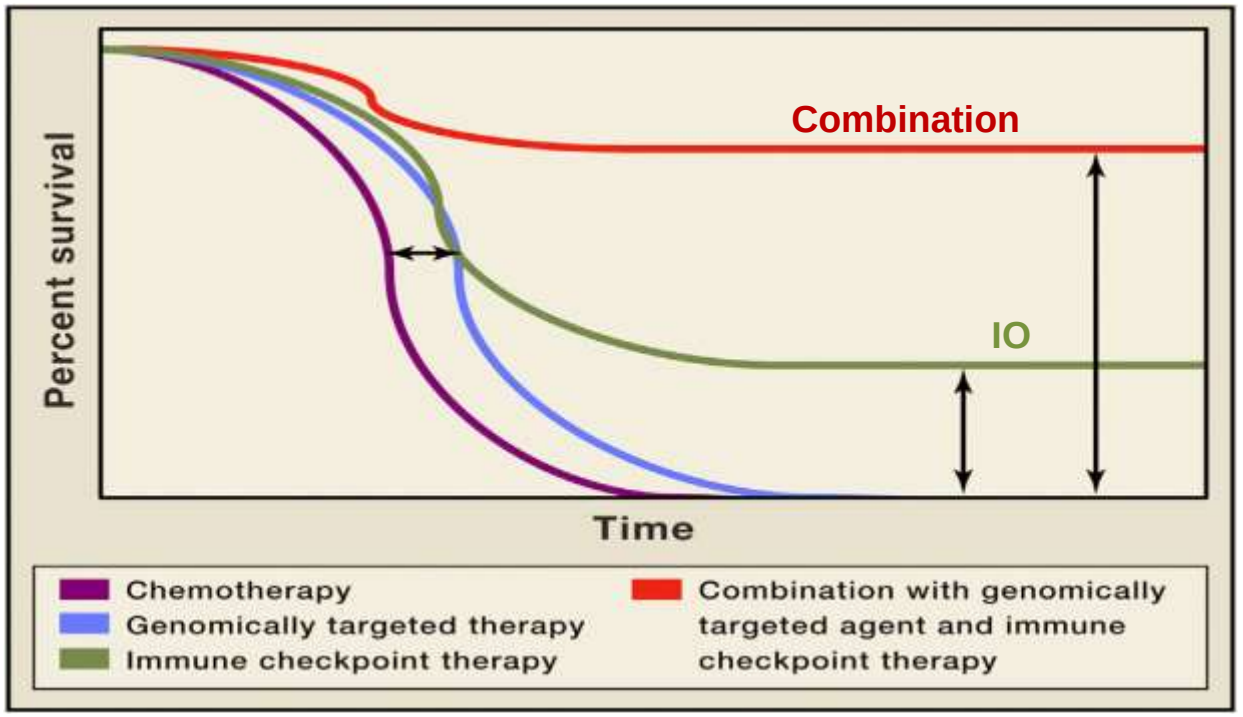
[1] Brahmer, NEJM 2015; [2] Herbst, Lancet 2016; [3] Ryttmeier, Lancet 2017; Borghaei, NEJM 2015

# Firs-line I-O

**Monoterapy with anti-PD1/PDL1**

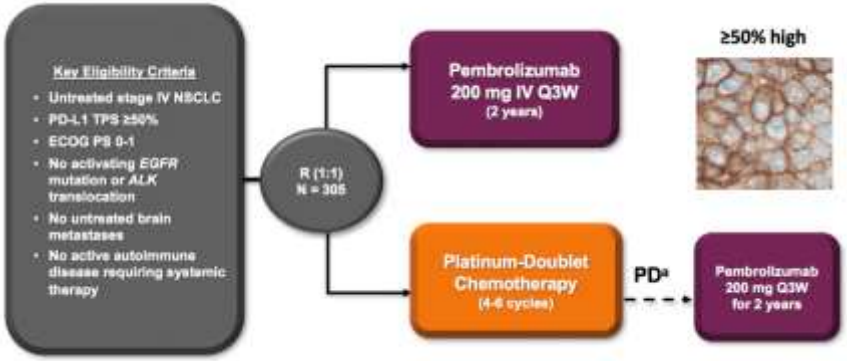
**Chemotherapy + Checkpoint Inhibitors**

**PD-1 / PD-L1 + CTLA-4 Combinations**



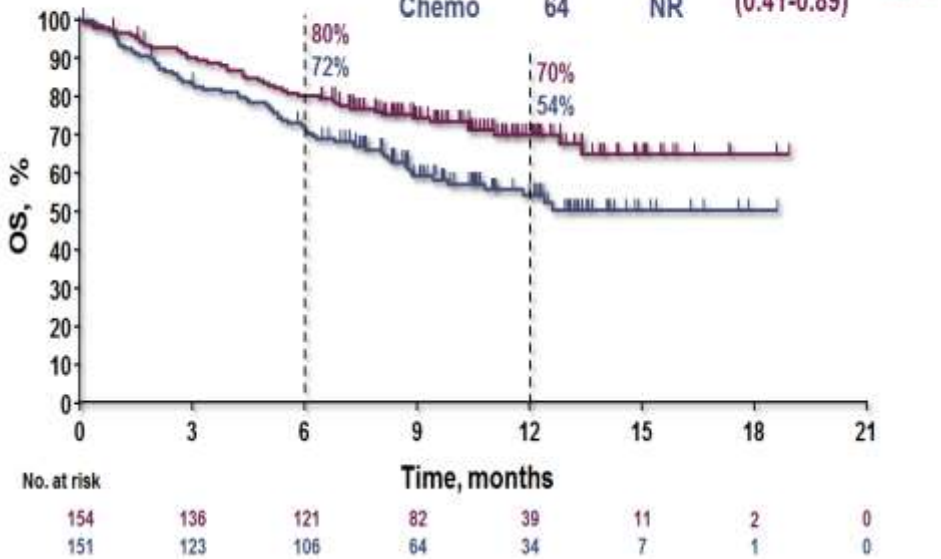
# First-line immunotherapy race

# First-line Pembrolizumab in KEYNOTE-024: efficacy outcomes



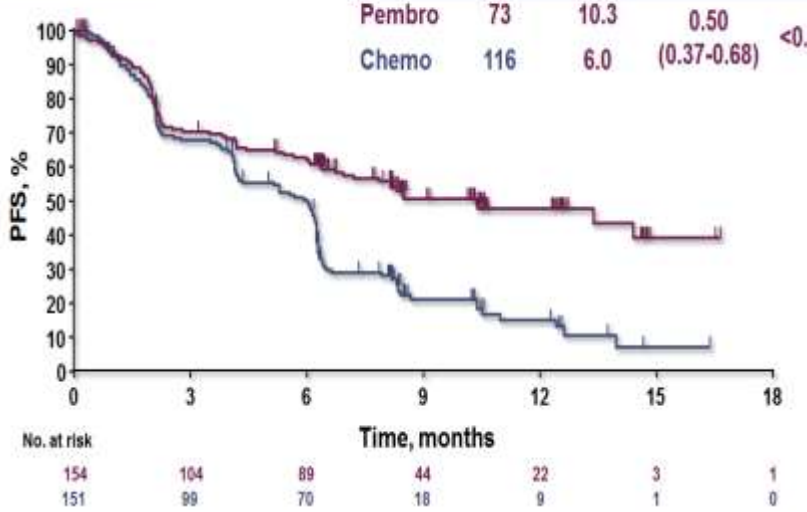

## Overall Survival

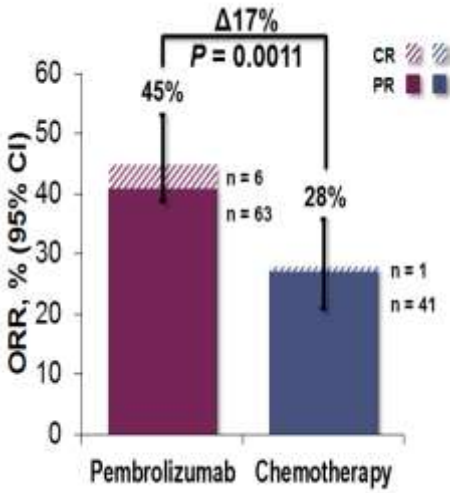
| | Events, n | Median, mo | HR (95% CI) | P |
|---|---|---|---|---|
| Pembro | 44 | NR | 0.60 (0.41-0.89) | 0.005 |
| Chemo | 64 | NR | | |




## Progression-Free Survival

| | Events, n | Median, mo | HR (95% CI) | P |
|---|---|---|---|---|
| Pembro | 73 | 10.3 | 0.50 (0.37-0.68) | <0.001 |
| Chemo | 116 | 6.0 | | |




•cross-over **in 50% of the patients**

Reck et al, NEJM 2016

# First-line Nivolumab in CheckMate-026: efficacy outcomes

**Key eligibility criteria:**

- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- ≥1% PD-L1 expression[a]
- CNS metastases permitted if adequately treated at least 2 weeks prior to randomization

**Randomize 1:1**

**Nivolumab**
3 mg/kg IV Q2W
n = 271

→ Disease progression or unacceptable toxicity

Tumor scans Q6W until wk 48 then Q12W

**Chemotherapy**
(histology dependent)[b]
Maximum of 6 cycles
n = 270

→ Disease progression → Crossover nivolumab[c] (optional)

**Stratification factors at randomization:**

- PD-L1 expression (<5% vs ≥5%)[a]
  Histology (squamous vs non-squamous)

**Primary endpoint:** PFS (≥5% PD-L1+)[d]

**Secondary endpoints:** PFS (≥1% PD-L1+)[d], OS, ORR[d]

## OS in ≥5% PD-LI+

| | 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)

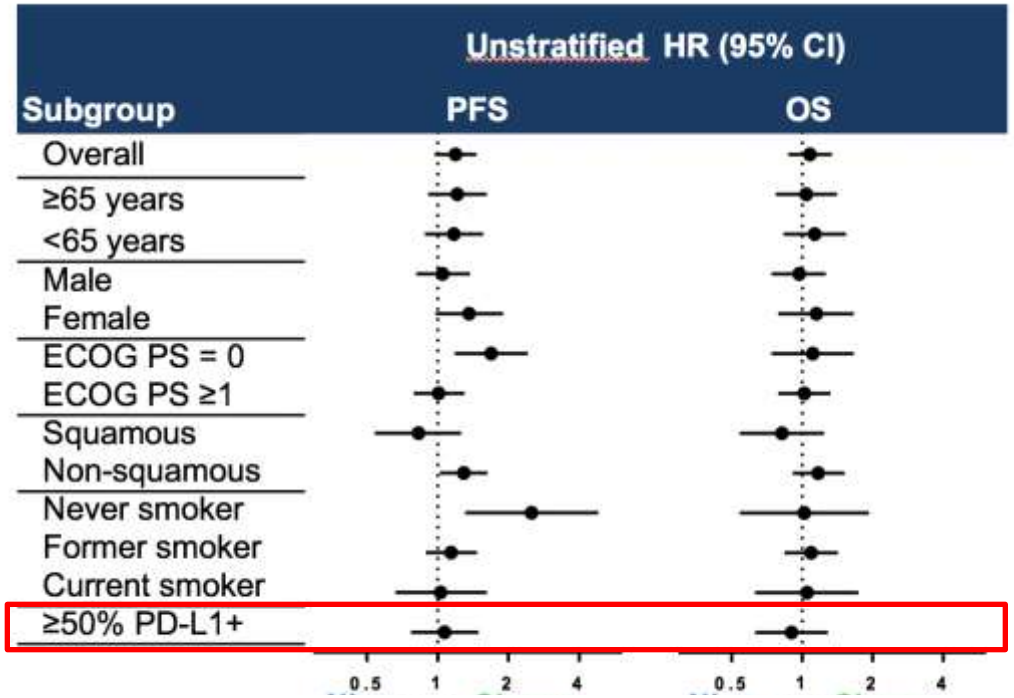
All randomized patients (≥1% PD-L1+): HR = 1.07 (95% CI: 0.86, 1.33)

## PFS in ≥5% PD-LI+

| | Nivolumab n = 211 | Chemotherapy n = 212 |
|---|---|---|
| Median PFS, months (95% CI) | <4.2 (3.0, 5.6) | 5.9 (5.4, 6.9) |
| 1-year PFS rate, % | 23.6 | 23.2 |

HR = 1.15 (95% CI: 0.91, 1.45), *P* = 0.2511

All randomized patients (≥1% PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)



# CheckMate 026 vs Keynote 024

| | Keynote 024 | CheckMate 026 |
|---|---|---|
| Tumor biopsy | After metastatic diagnosis | Within 6 months |
| PD-L1 cut off | 50% (22C3 clone) | 5% (28-8 clone) |
| Prevalence | 20-30% | 50% |
| Imaging interval | Q 9 weeks | Q 6 weeks for first 48 weeks |
| Primary endpoint | PFS (RECIST) | PFS (IRRC) |
| Never smokers (PD-1) | 3% | 11% |
| Squamous histology | 19% | 24% |
| Time from diagnosis to treatment | ? | 2 months |
| Prior radiation | ? [1] | 37.6 % |

[1] Prior radiation therapy of > 30 Gy disallowed within 6 months of first dose of trial treatment

Socinski et al, ESMO 2016
Reck et al, ESMO 2016, NEJM 2016

# BIRCH: Phase II Trial of Atezolizumab in PD-L1– Selected Advanced NSCLC

- Locally advanced or metastatic NSCLC
- Tumor PD-L1 expression (TC2/3 and/or IC2/3)
- ECOG PS 0 or 1 / No brain metastases

N = 667

→ **Cohort 1 (1L)**
**No prior chemo**
**n = 138**

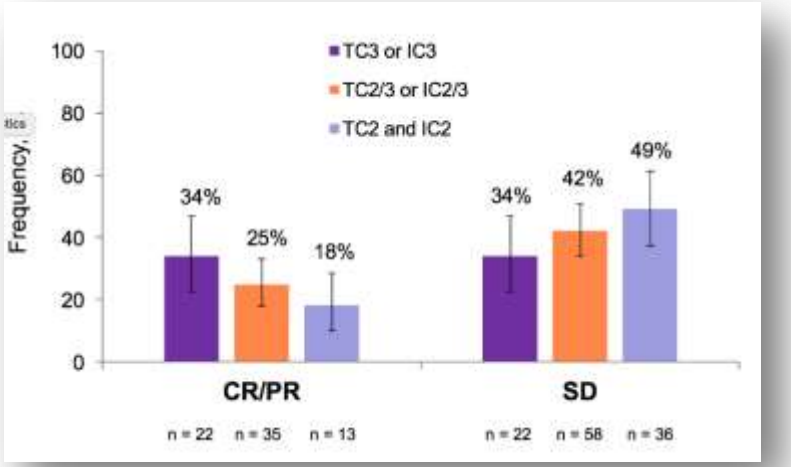
→ **PD**

**Atezolizumab dosed at 1200 mg IV q3w in all cohorts**

Primary endpoint: Objective response rate (ORR) per RECIST v1.1

Secondary endpoints:

- IRF-assessed PFS, DOR per RECIST v1.1
- Investigator ORR, PFS and DOR per RECIST v1.1 and mod-RECIST
- OS
- Safety




| Endpoint | TC2/3 or IC2/3 n = 138 | TC3 or IC3 n = 65 | TC2 and IC2 n = 73 |
|---|---|---|---|
| mDOR (95% CI) | 16.5 mo (9.9, NE) | NE (8.5, NE) | 12.3 mo (8.3, 17.9) |
| mPFS (95% CI) | 7.3 mo (5.7, 9.7) | 7.3 mo (4.9, 12.0) | 7.6 mo (4.0, 9.7) |
| 12-mo PFS rate (95% CI) | 32.5% (24.2, 40.8) | 36.5% (24.0, 48.9) | N/A |

Garassino M, WCLC 2016

***Median duration of survival follow-up = 22.5 months***

| TC3 or IC3 (n = 65) | |
|---|---|
| mOS (95% CI) | 26.9 mo (12.0, NE) |

| TC2/3 or IC2/3 (n = 138) | |
|---|---|
| mOS (95% CI) | 23.5 mo (18.1, NE) |

| TC2 and IC2 (n = 73) | |
|---|---|
| mOS (95% CI) | 23.5 mo (18.1, NE) |

# Combination Immunotherapy in first-line:

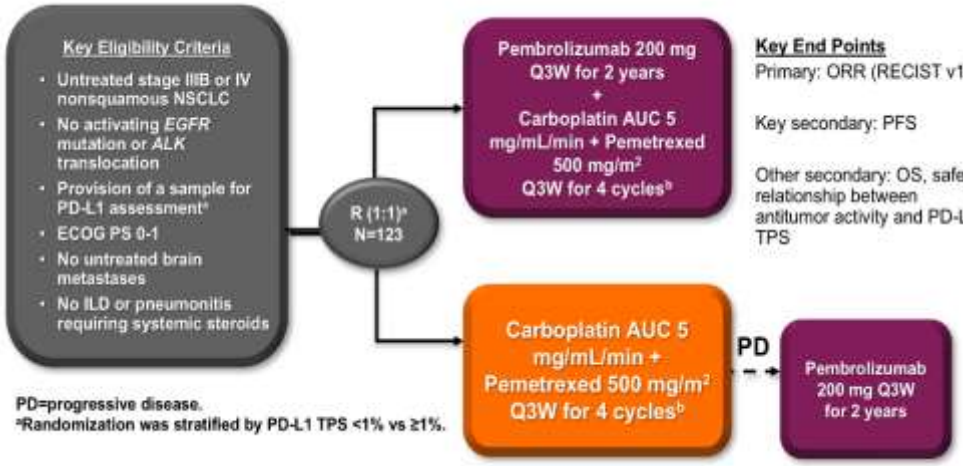
**Kind of combination:**

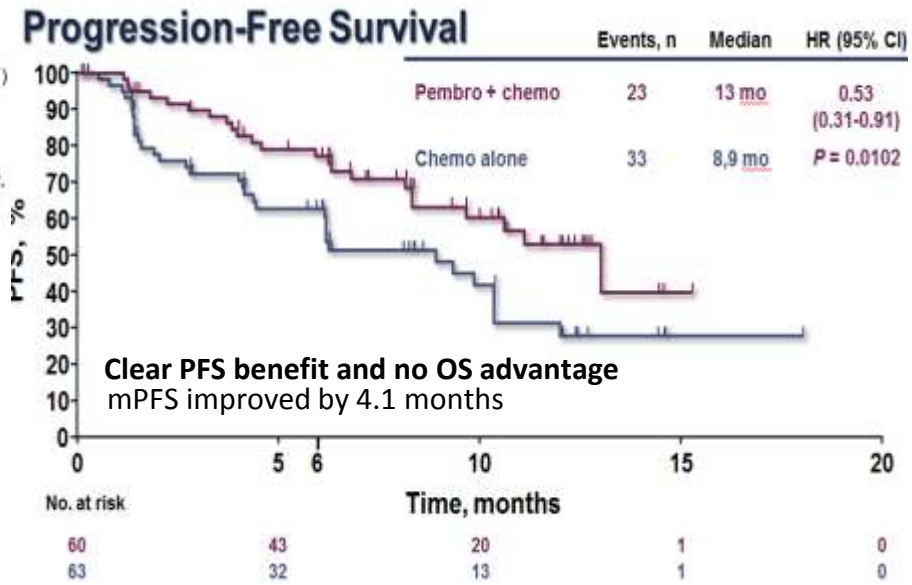
- **Chemotherapy + Checkpoint Inhibitors**
- **PD-1 / PD-L1 + CTLA-4 Combinations**

**Rationale:**

- **Improve the number of people who benefit from single-agent immunotherapy**
- **Reduce the time to response and symptom control**
- **Extend the depth and duration of tumor response for individual patients**

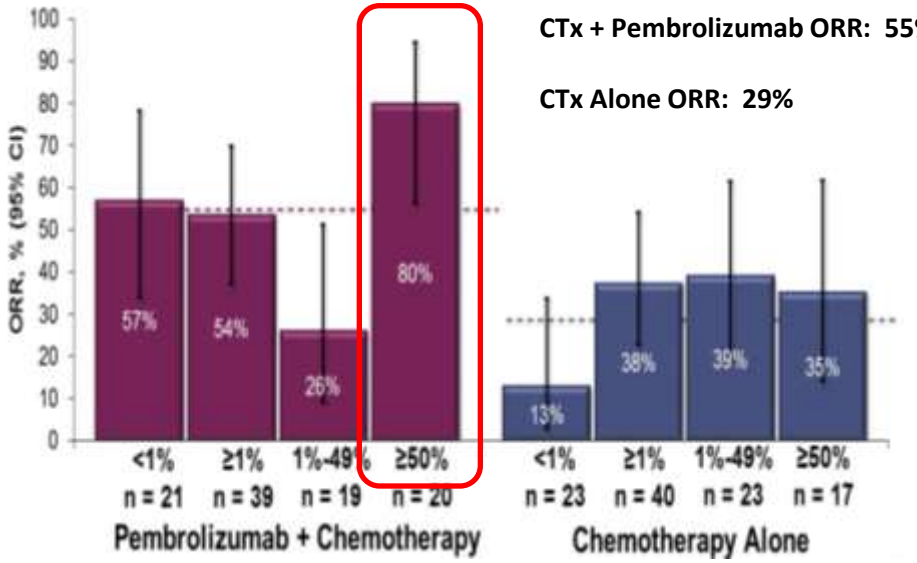
# Ph2 KEYNOTE-021: chemo plus pembrolizumab in first-line



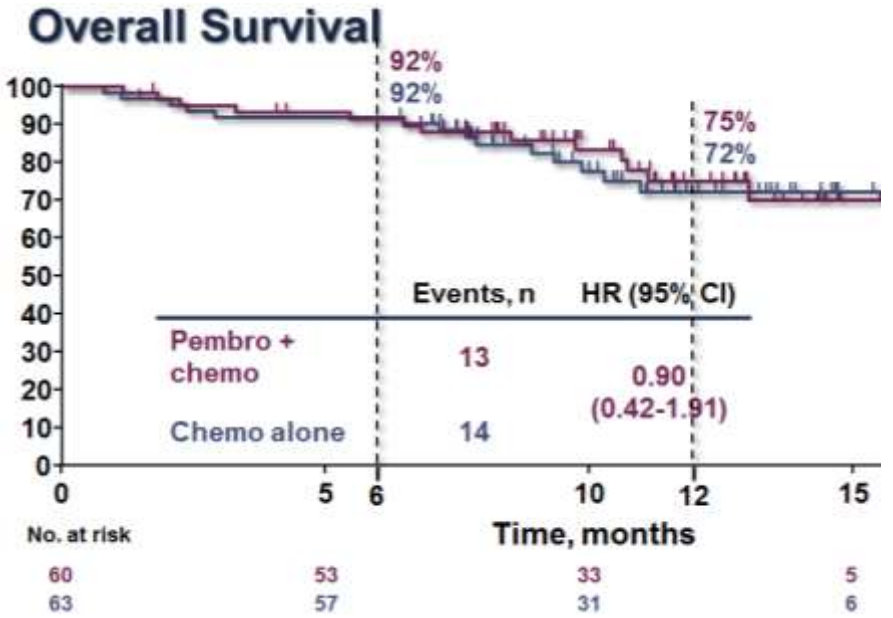

**Clear PFS benefit and no OS advantage**
mPFS improved by 4.1 months

## Objective Response Rate by PD-L1 Status




**CTx + Pembrolizumab ORR: 55%**

**CTx Alone ORR: 29%**




Estimated rate of OS @ 12 months: 75% (Combo) vs 72% (CT)
In CT arm cross-over is 51% to PD(L)1 therapies (pembro & others)

Langer et al, 2016

# Ph1 CheckMate 012: first-Line Nivolumab ± Ipilimumab in NSCLC

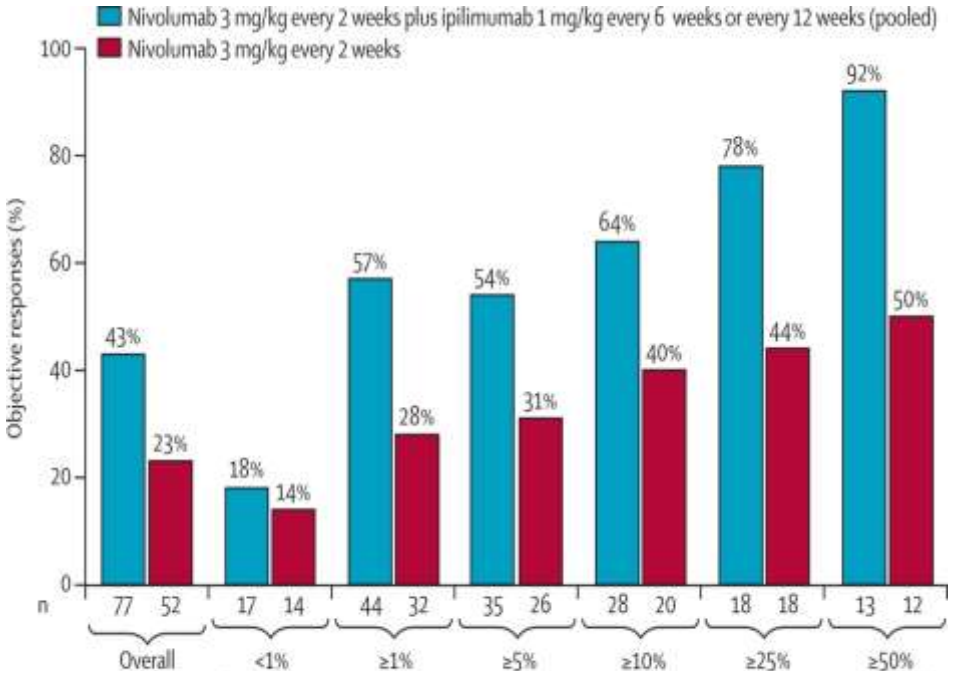
**Stage IIIB/IV NSCLC (any histology), no prior chemotherapy for advanced disease, ECOG PS 0 or 1**

| Nivolumab 3 mg/kg IV Q2W[a] | Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q12W[b] | Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg IV Q6W[b] |
|---|---|---|

**Until disease progression[c] or unacceptable toxicity**

**Primary endpoint:** safety and tolerability
**Secondary endpoints:** ORR (RECIST v1.1) and PFS rate at 24 weeks assessed by investigators
**Exploratory endpoints:** OS, efficacy by PD-L1 expression

| | Nivo 3 Q2W (n = 32) | Nivo 3 Q2W + Ipi 1 Q12W (n = 23) | Nivo 3 Q2W + Ipi 1 Q6W (n = 23) |
|---|---|---|---|
| **ORR, n (%)** | 9 (28) | 13 (57) | 13 (57) |
| **Median PFS, mo (95% CI)** | 3.5 (2.2, 6.6) | 10.4 (6.4, NR) | 13.2 (3.5, 23.0) |
| **1-year OS rate, %** | 69 | 91 | 83 |




**Hellmann, Lancet Onc 2016**

# The challenges of combination immunotherapy

- **More is not always better**
  ***Risk for increased (and new) toxicity***
  ***Modest gains in efficacy***
  ***Increased expense***

- **Drug development is outpacing our understanding of biology and potential biomarker development**

- **Where to begin?**
  ***Multiple agents and potential combinations***

# Agenda

- Rationale for checkpoint inhibitors
- Available evidence
- **Side effects**
- Conclusions

# Overall view of IO monoterapy toxicities

anti PD1 | anti PD-1 | anti PD-L1

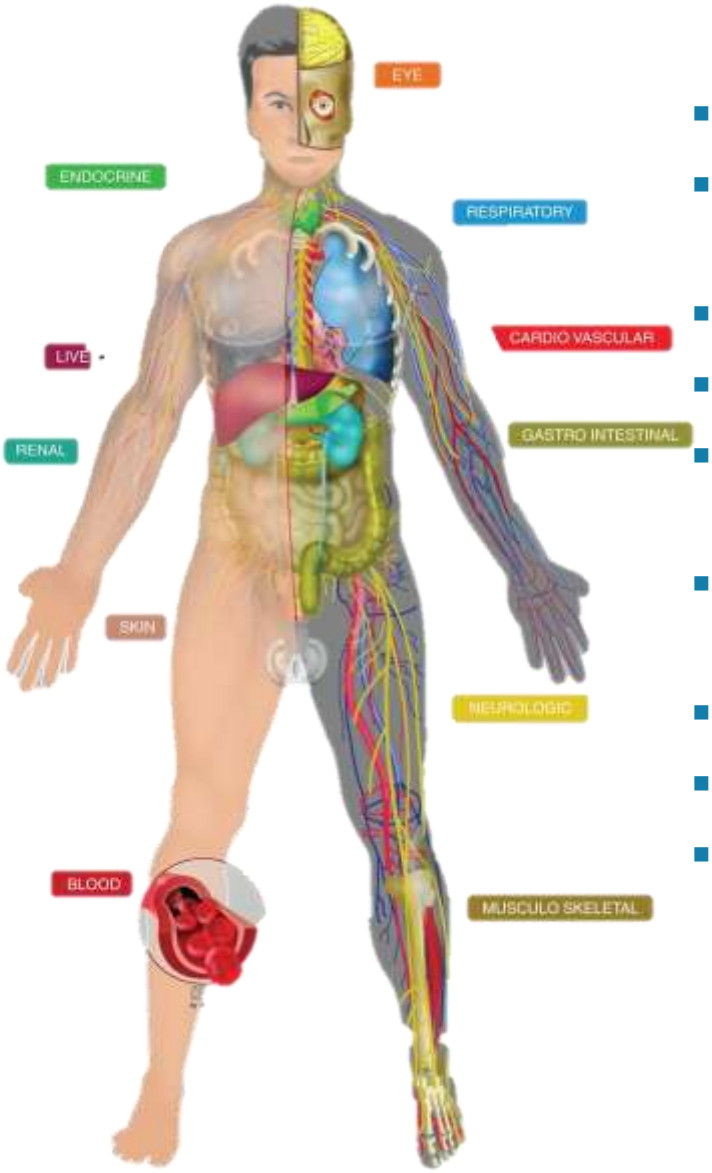
| | Nivolumab *[Checkmate 017-057]* | | Pembrolizumab *[KEYNOTE-010]* | | Atezolizumab *[POPLAR]* | |
|---|---|---|---|---|---|---|
| | **All Grade** | **G3-4** | **All Grade** | **G3-4** | **All Grade** | **G3-4** |
| **All** | **58-69** | **7-10** | **63** | **10** | **67** | **12** |
| **Fatigue** | **16** | 1 | **14** | 1 | **20** | 1 |
| **Decrease appetite** | **10-11** | 1 | **14** | 1 | **17** | 1 |
| **Asthenia** | **10** | 0 | **6** | 1 | **6** | 1 |
| **Nausea** | **9-12** | 1 | **11** | 1 | **12** | 1 |
| Diarrhea | 8 | 1 | 7 | 1 | 7 | 1 |
| Arthralgia | 5 | 0 | - | - | - | - |
| Pyrexia | 5 | 0 | - | - | - | - |
| Pneumonitis | 5 | 2 | 5 | 2 | - | - |
| Rash | 4 | 0 | 9 | 1 | - | - |
| Myalgia | 2 | 0 | 1 | 0 | - | 1 |
| Anemia | 2 | 0 | 3 | 1 | - | - |

Brahmer et al NEJM, 2015 | Borghaei H et al NEJM, 2015 | Herbst RS et al Lancet, 2015 | Fehrenbacher L et al Lancet, 2016

# Spectrum of Immuno-related toxicities of Immune checkpoint agents

- Fatigue
- Arthralgia
- Diarrhea
- Rash, Pruritus
- Hepatitis
- Liver Disorder
- Pneumonitis
- Thyroid Disorder

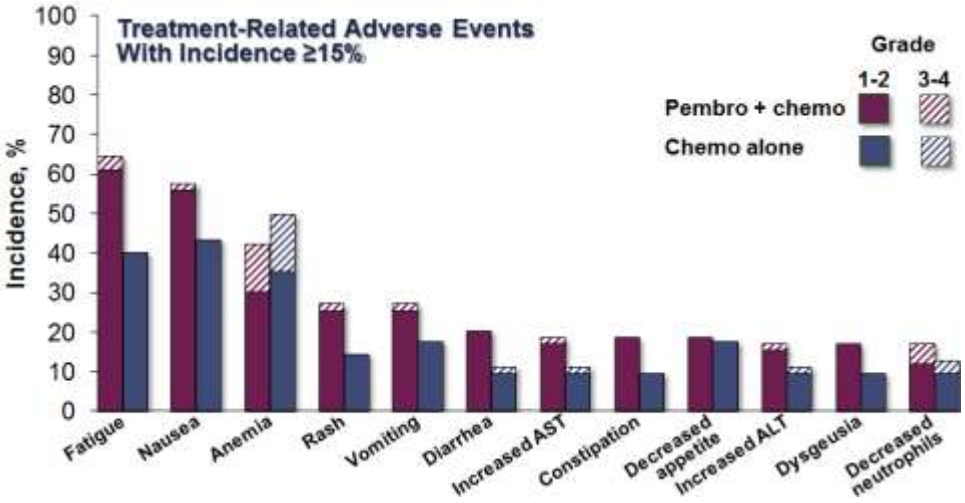
**„WELL KNOWN“ irAEs**




- Dry Mouth Syndrom (5%)
- Hypophysitis (up to 10%) – mostly central hypothyroidism
- Adrenal Insufficiency
- Diabetes Mellitus
- Ophtalmological irAEs (Uveitis, Conjunctivitis..)
- Neurological ir AEs (Meningitis, Guillain Barre Syndrom...)
- Renal Disorder
- Pancreatic Disorder
- Haematologic syndromes (Cytopenia)

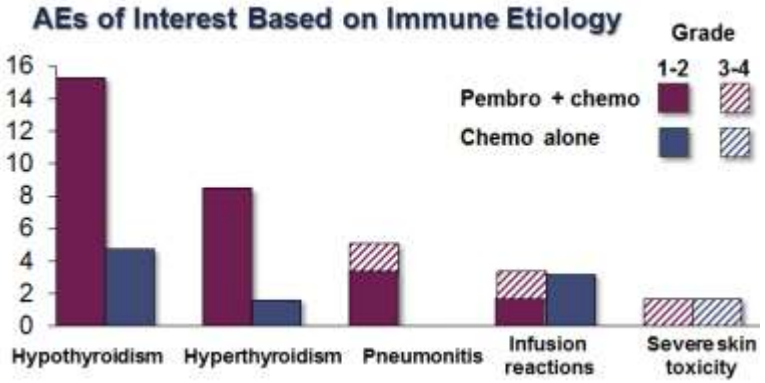
S. Champiat et al. Ann Oncol 2016;27:559-574

# Safety profile in combo-immuno treatements




## CheckMate 012 Safety Results

| | Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg | | |
|---|---|---|---|
| | Ipilimumab Dosed Every 12 wk | Ipilimumab Dosed Every 6 wk | Nivolumab Alone |
| N | 38 | 39 | 52 |
| Any grade TRAE, % | 82 | 72 | 71 |
| Grade 3-4 TRAE, % | 37 | 33 | 19 |
| Discontinuation due to TRAE,% | 11 | 13 | 10 |




Hellmann MD, et al. *J Clin Oncol*. 2016;349(suppl).

# Key-points regarding safety of Immunotherapy

- **Toxicities with IOi are different than with standard chemo**
- **PD-1 and PD-L1 inhibitor safety profiles appear similar**
- **Most toxicities are manageable, low-grade, reversible, and potentially time sensitive. Rarely lead to treatment discontinuation**
- **Presentation of side effects can be subtle (endocrinopathies) or rapid (pneumonitis)!!!**
- **Combinations w/ CTLA-4 antibodies have more severe toxicity**
- **Suspension of dosing and early use of steroids maximize safety, with no loss of efficacy**

# Agenda

- Rationale for checkpoint inhibitors
- Available evidence
- Side effects and management
- **Conclusions**

# Conclusions

- We are only at the beginning of the IO revolution in thoracic oncology
- In 2L of NSCLC (EGFR-wt/ ALK-wt), different PD-1/PD-L1 inhibitors (Atezo|Nivo|Pembro) improves efficacy outcomes, regardless histology
  - Gender and age: no influence
  - PS: all available data are in PS0-1 (activity in PS to be explored)
  - Smoking history in general is associated with better response e more outcome benefit
- In patients at risk of death within the first 3 months ( NSqNSCLC patients with poorer prognostic features and/or aggressive disease when combined with lower or no tumor PD-L1 expression ) IO is probably not indicated (based on Nivo post-Hoc Landmark analysis CheckMate-057)
- Safety and tolerability offered by IO represent an important end-point in 2$^{nd}$-line setting .
- Pembrolizumab is the new stardard care for pts with PD-L1 ≥ 50%, EGFRwt/ALKwt, steroids-free (Not yet approved in Italy) [≃ 15/20%]
- Different combo treatment in first-line setting are under evaluation and appear very promising considering efficacy endpoints.

# Articulated conclusions

**Second-line setting**

Atezolizumab | Nivolumab | Pembrolizumab beat docetaxel!

Undirect comparison is not the best way to compare these IO agents:

- **Nivolumab**: 2 different prospectively histology-based trials, regardless PD-L1
- **Pembrolizumab**: 2 different doses (2/10 mg/kg), 2 different PD-L1 evaluation (PD-L1 ≥ 1/ 50%), combo results about histology
- **Atezolizumab**: regardless histology and PD-L1 espression

PD-L1 expression appear to be not critical for 2$^{nd}$ -line immunotherapy with Nivolumab (plus clinical selection) and Atezolizumab; mandatory in first-line with Pembrolizumab.
Under evaluation considering combo-treatments in first-line.

**First-line setting**

Safety will be potentially limiting with some combinations
It is unclear whether combinations with obviate the need for a biomarker

Oncogene-addicted disease (i.e EGFR/ALK/ROS1 driven) needed a tailored trials.
Nowadays, IO not the best indication in this setting.

# THANK YOU
# for your attention

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