# Imunoterapia v liečbe pokročilého nemalobunkového karcinómu pľúc

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Workshop Eso Tour, 13. 10. 2020, Košice

# Vyhlásenie o konflikte záujmov autora

□ Nemám potenciálny konflikt záujmov
x□ Deklarujem nasledujúci konflikt záujmov

| Forma finančného prepojenia | Spoločnosť |
|---|---|
| Participácia na klinických štúdiách/firemnom grante | áno |
| Nepeňažné plnenie (v zmysle zákona) | |
| Prednášajúci | Roche, Boehringer inh., MSD, Astra Zeneca, Sandoz, |
| Akcionár | |
| Konzultant/odborný poradca | |
| Ostatné príjmy (špecifikovať) | |

Podľa UEMS (upravené v zmysle slovenskej legislatívy)

# Prednáška je podporená

Spoločnosťou MSD

# NSCLC- čo vieme ?

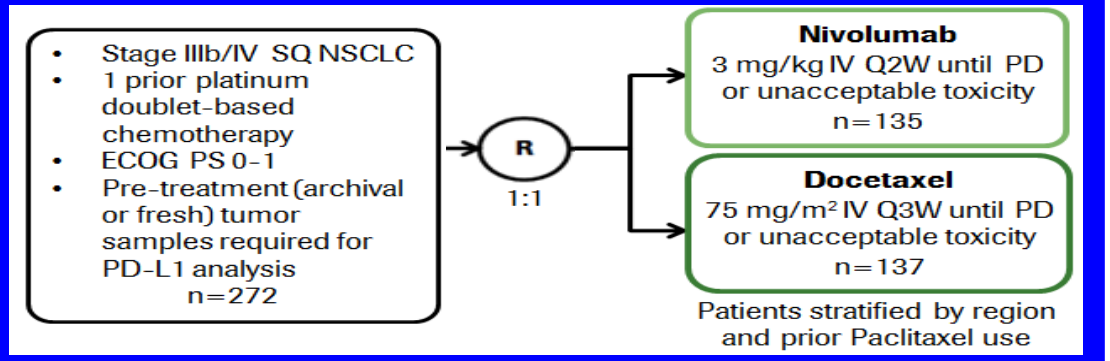
- viac ako 10 rokov imunoterapia (IO) v liečbe NSCLC
- 50-60% všetkých NSCLC sú PD-L1 pozitívne
- prvé výsledky zlepšenia OS v porovnaní s ChT priniesli v 2.línii liečby a neskorších líniach
- minoritný podiel pacientov s dlhotrvajúcim benefitom z imunoterapie
- benefit IO v OS v 1.línii
- zlepšenie OS u oboch histológii nezávisle od expresie PD-L1

Reck et al. Annals of Oncology 2019: 884-896

# Imunoterapia u predliečených pacientov

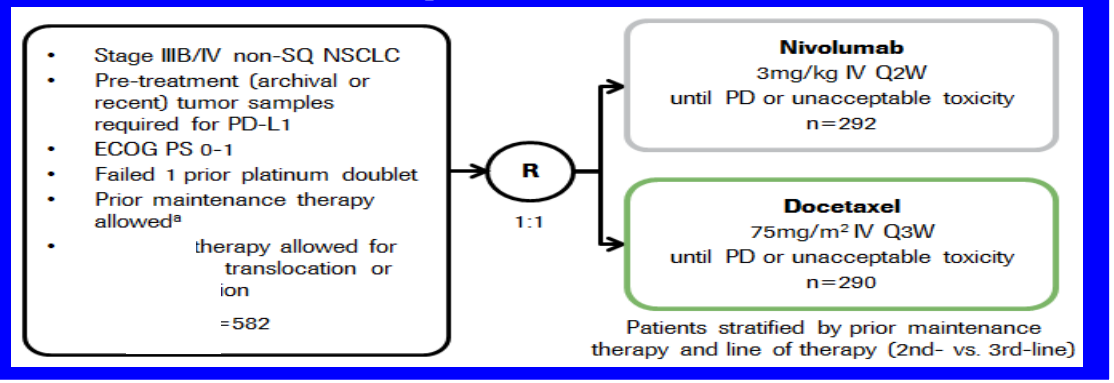
## Nivolumab – CheckMate 017 (PIII)[1]

2.línia , skvamózny, PD-L1 All-Comer



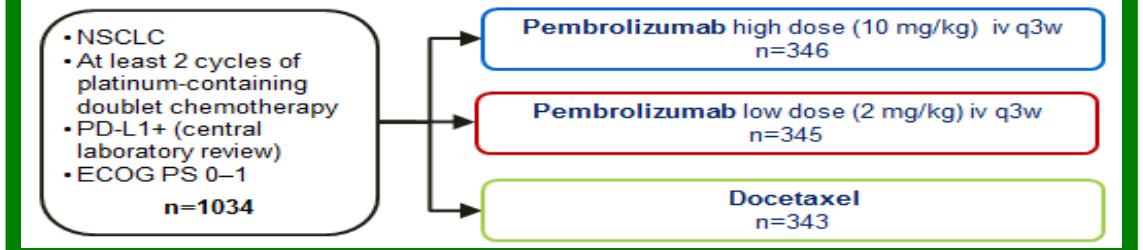

## Nivolumab – CheckMate 057 (PIII)[2]

2.línia, non-squamous, PD-L1 All-Comer



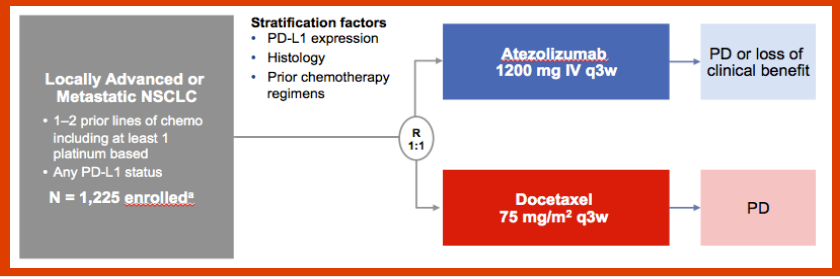

## Pembrolizumab - Keynote 010 (PII/III)[3]

2nd+ Line, PD-L1 TPS ≥1%

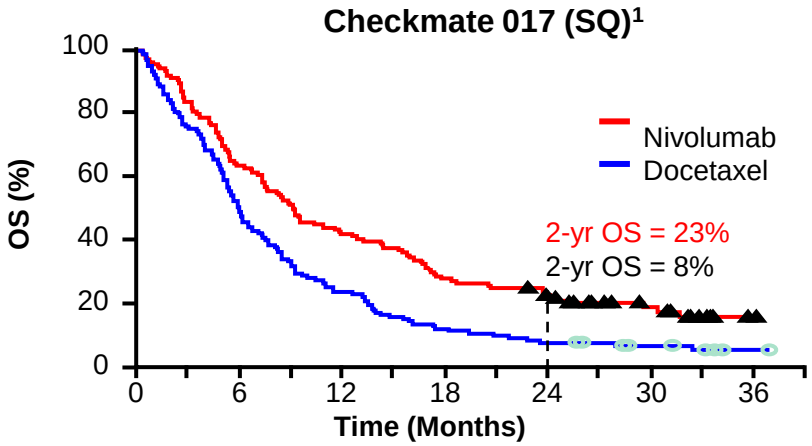


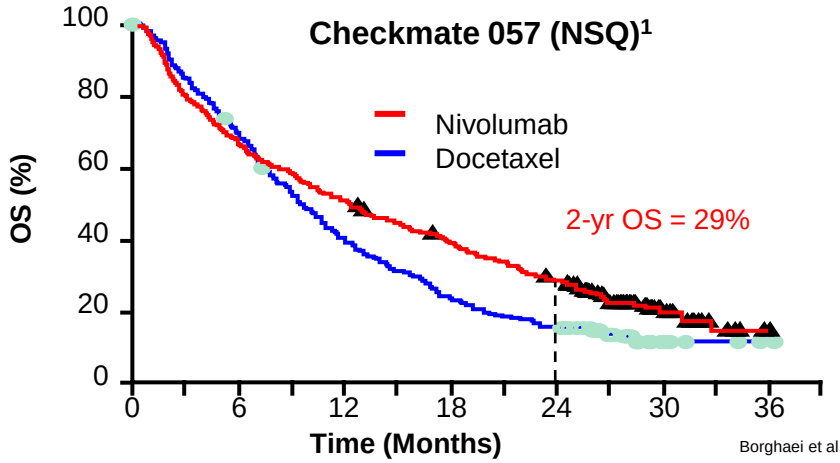

## Atezolizumab – OAK (PIII)[4]

2nd+ Line, PD-L1 All-Comer

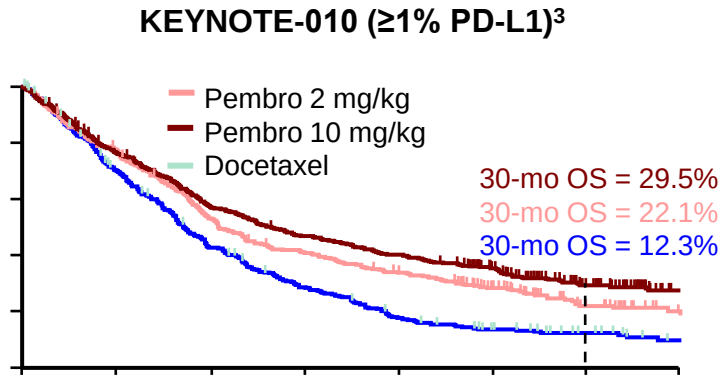


# Konzistentný benefit v OS



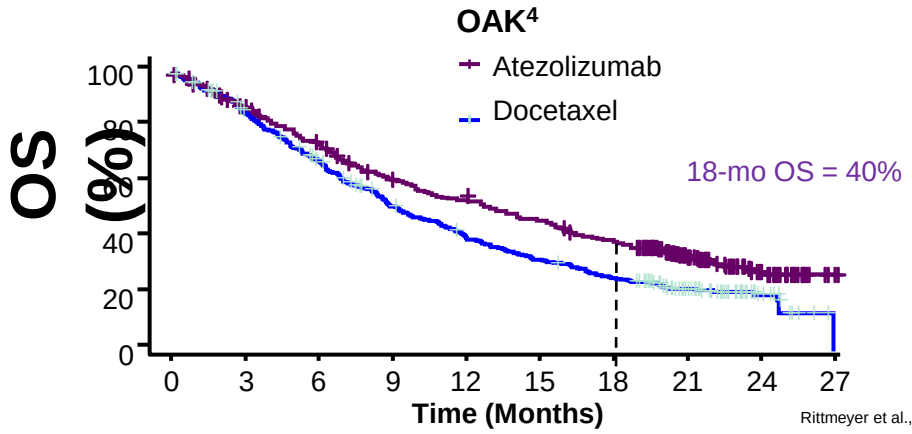




Borghaei et al., 2016, ASCO.[1]




Herbst et al., 2017, ASCO.[3]

3rOS **35%** vs 13% (ESMO,2018)

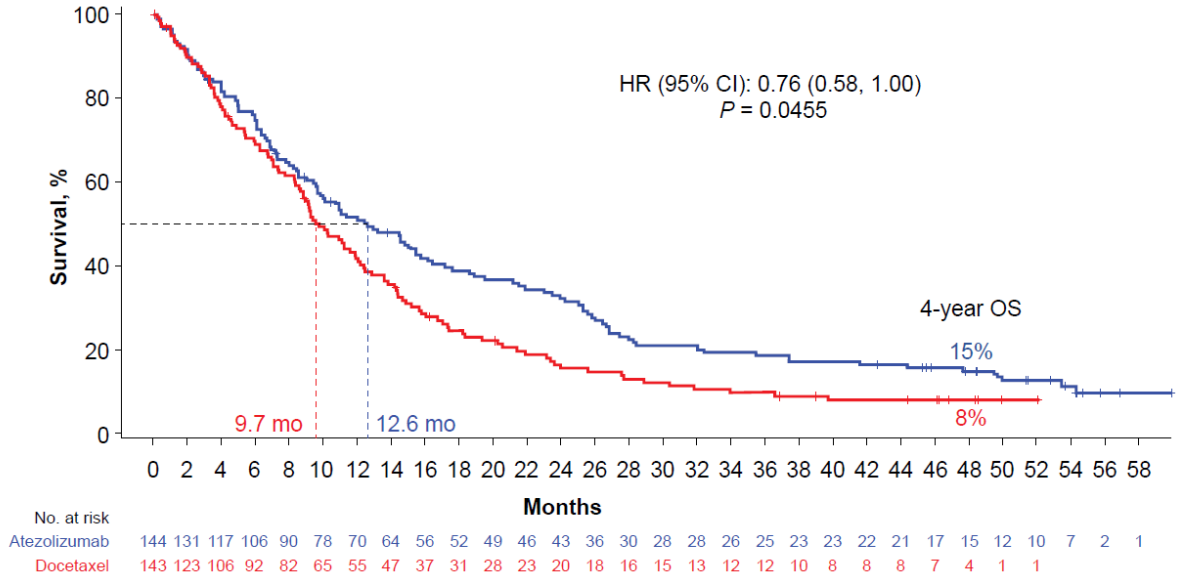



Rittmeyer et al., 2017, *Lancet*.[4]

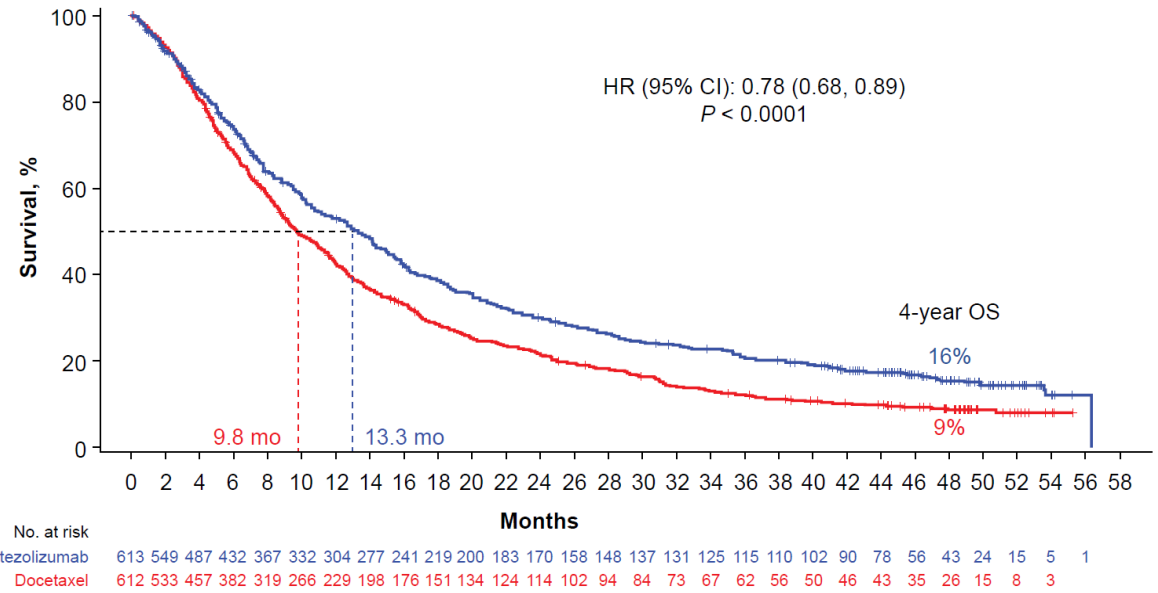
# Štvorročné celkové prežívanie u ITT populácie

## ESMO 2020

*POPLAR*



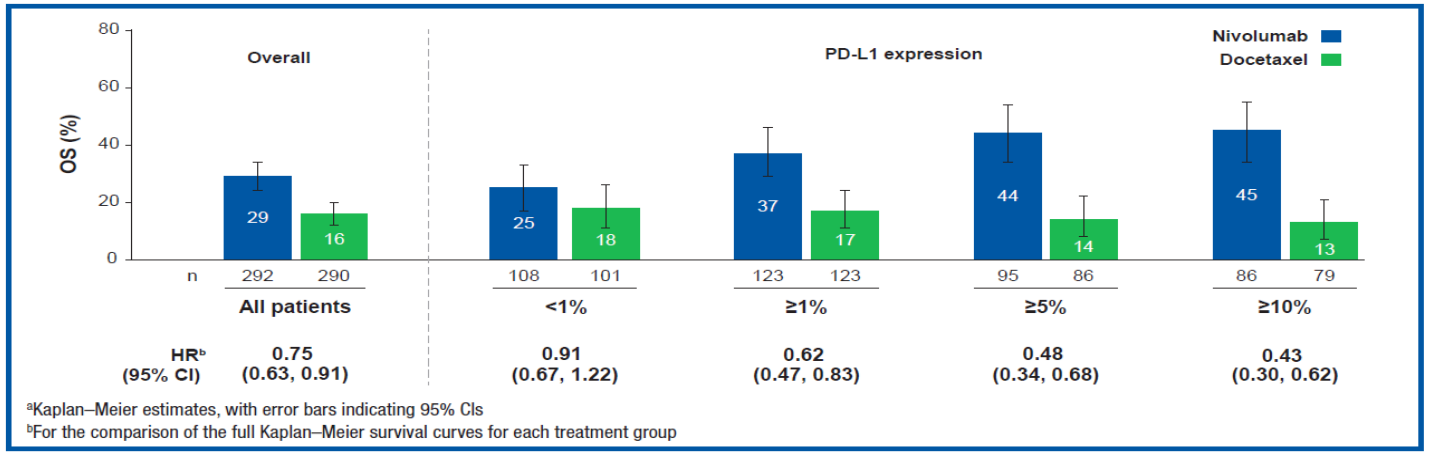

*OAK*



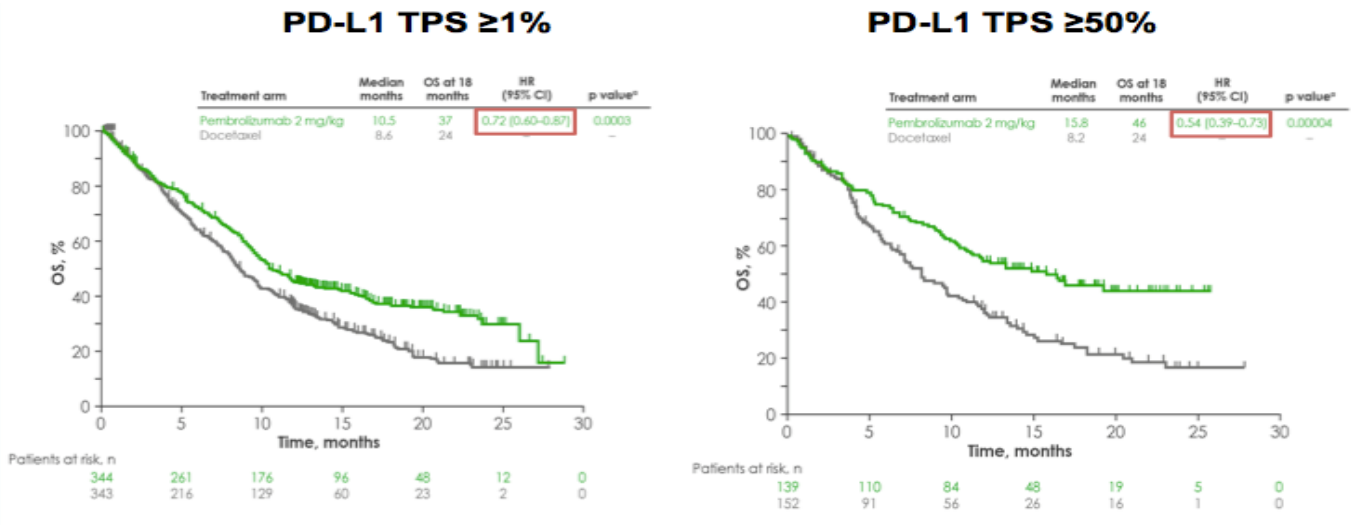

Mazières J, et al. ESMO 2020 [Abstract 1907/Poster 1271].

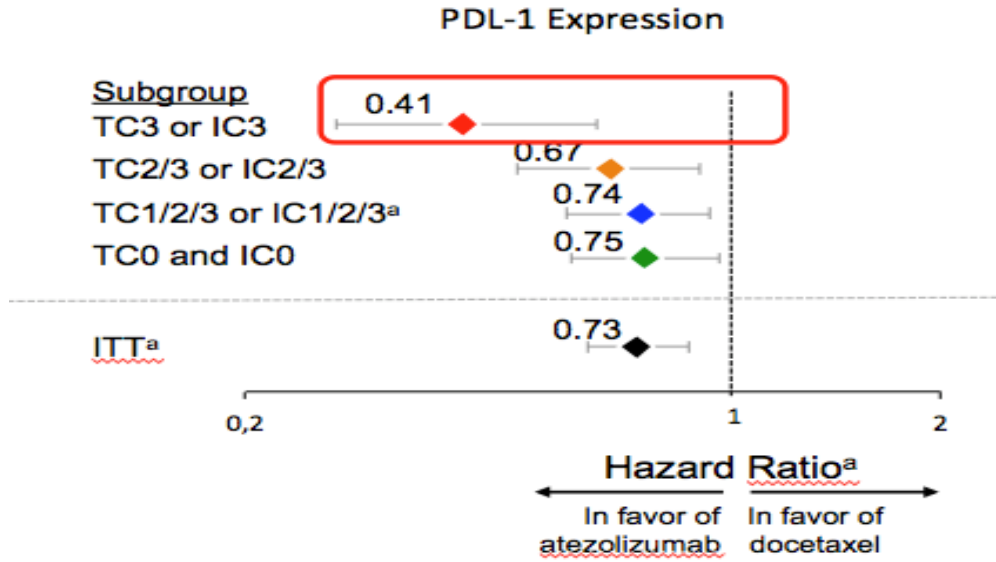
# Korelácia medzi PD-L1 expresiou a účinnosťou

**Figure 6.** 2-year OS rates[a] overall and by PD-L1 expression level in CheckMate 057 (non-SQ NSCLC)




[a]Kaplan–Meier estimates, with error bars indicating 95% CIs
[b]For the comparison of the full Kaplan–Meier survival curves for each treatment group



# Účinnosť imunoterapie u PD-L1 negatívnych pacientov

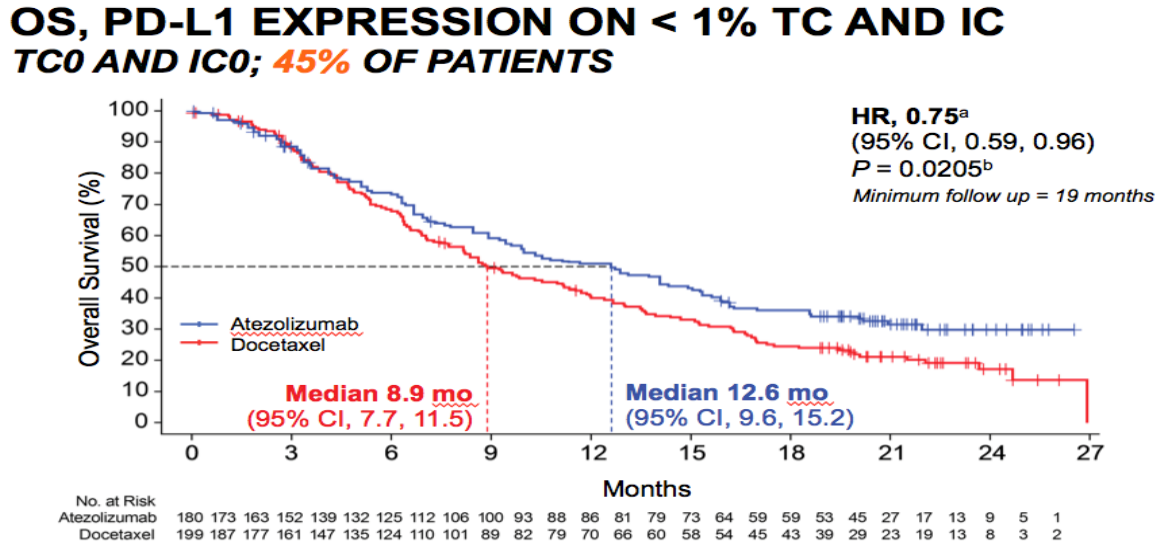
Nivolumab – CM 57

| PD-L1 expression level | ORR,[a] % | | Median DOR, mos | |
|---|---|---|---|---|
| | Nivolumab | Docetaxel | Nivolumab | Docetaxel |
| ≥1% | 31 | 12 | 16.0 | 5.6 |
| ≥5% | 36 | 13 | 16.0 | 5.6 |
| ≥10% | 37 | 13 | 16.0 | 5.6 |
| <1% | 9 | 15 | 18.3 | 5.6 |
| <5% | 10 | 14 | 18.3 | 5.6 |
| <10% | 11 | 14 | 18.3 | 5.6 |
| Not quantifiable | 13 | 9 | 7.3 | 6.6 |

Response Rate lower in PD-L1 negative patients but there are responses
Duration of response independent from PD-L1 status

RR: 9%
DOR: 18.3 months

Atezolizumab - Oak



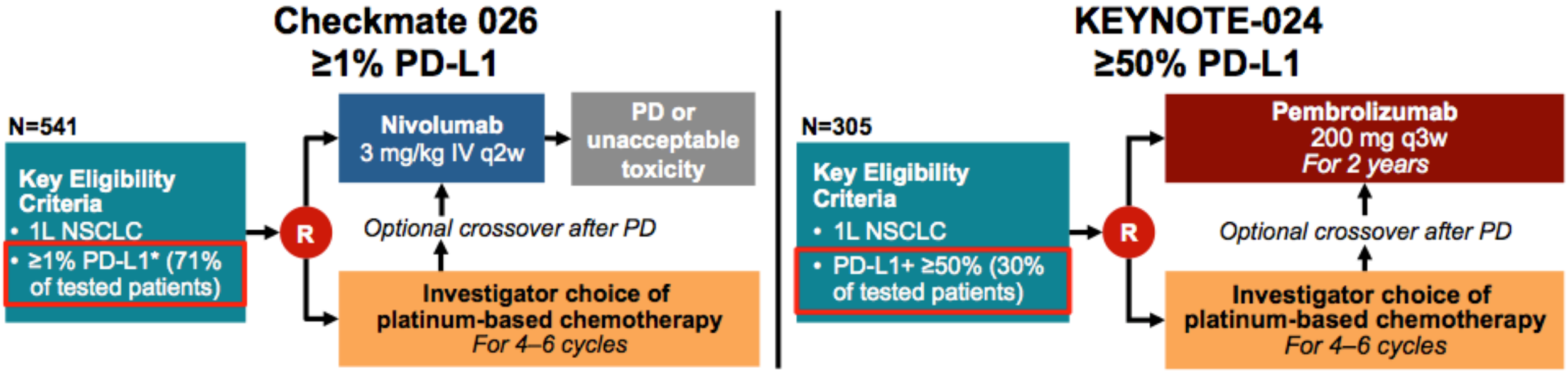

OS: 12.6 vs 8.9 months (HR 0.75)

# Prvá línia IO v liečbe NSCLC bez driver mutácie

- najvhodnejší komparátor: chemoterapia na báze platiny +/- bevacizumab
- najvhodnejší prediktívny faktor : vhodný biomarker sa stáva nutnosťou
- najhodnejší cieľ:: PFS?, OS?, ďalšie ?

perspektíva :zvýšená účinnosť s redukciou toxicity

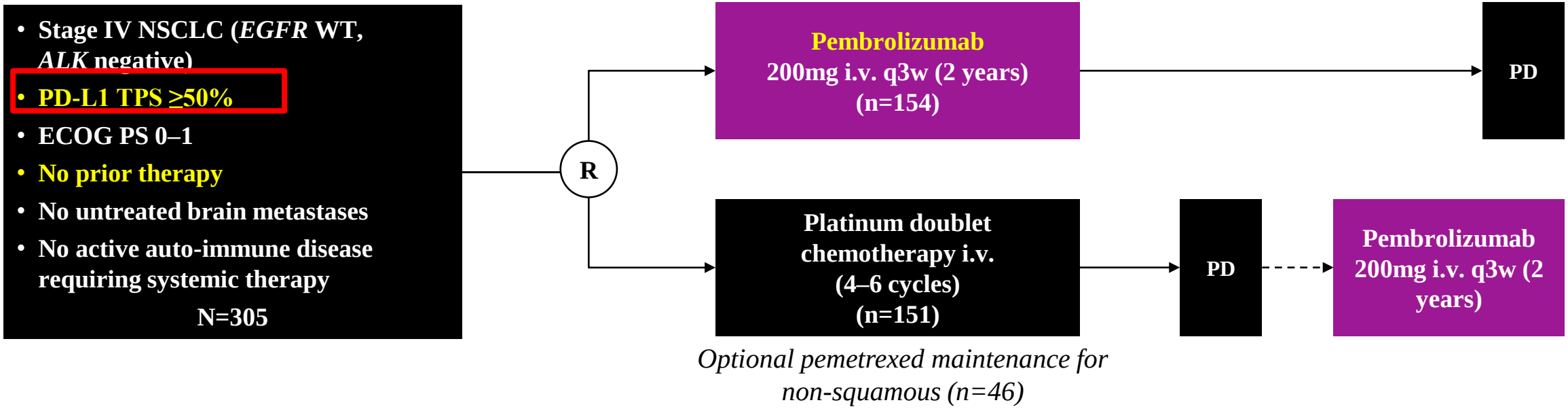
# Dve „podobné” štúdie……




**...avšak úplne rozdielne výsledky...**

Carbone D et al, NEJM 2017; 376 (25): 2415-2426; Reck M et al, NEJM 2016; 375 (19): 1823-1833

# KEYNOTE-024: dizajn štúdie




**1 Primary endpoint**
- PFS*

**2 Secondary endpoints**
- OS
- ORR*
- Safety

**3 Exploratory endpoint**
- DoR*

TPS = tumour proportion score (the proportion of viable tumour cells showing partial or complete membrane PD-L1 expression)
*RECIST v1.1 by blinded, independent central review
PD-L1 expression measured on TCs using Dako 22C3 IHC assay

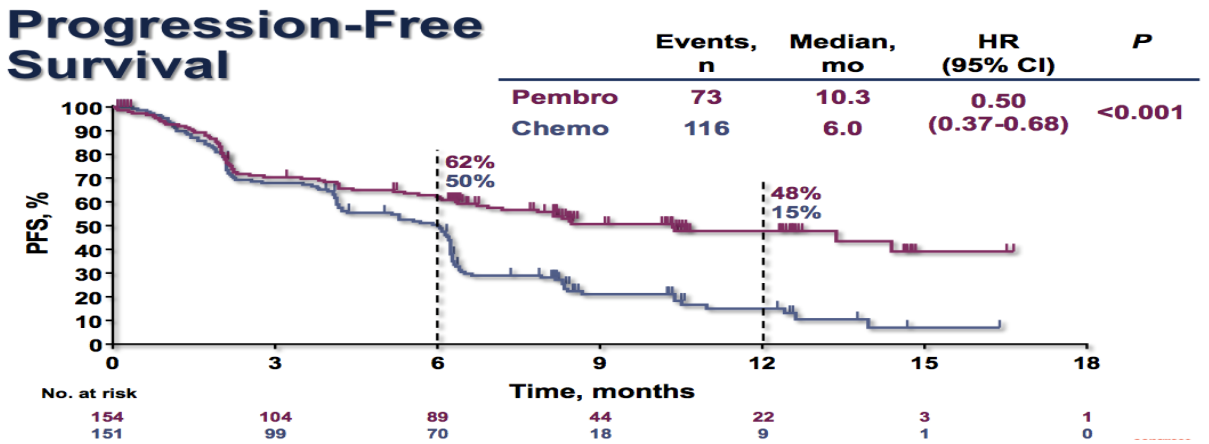
NCT02142738
Reck, et al. N Engl J Med 2016

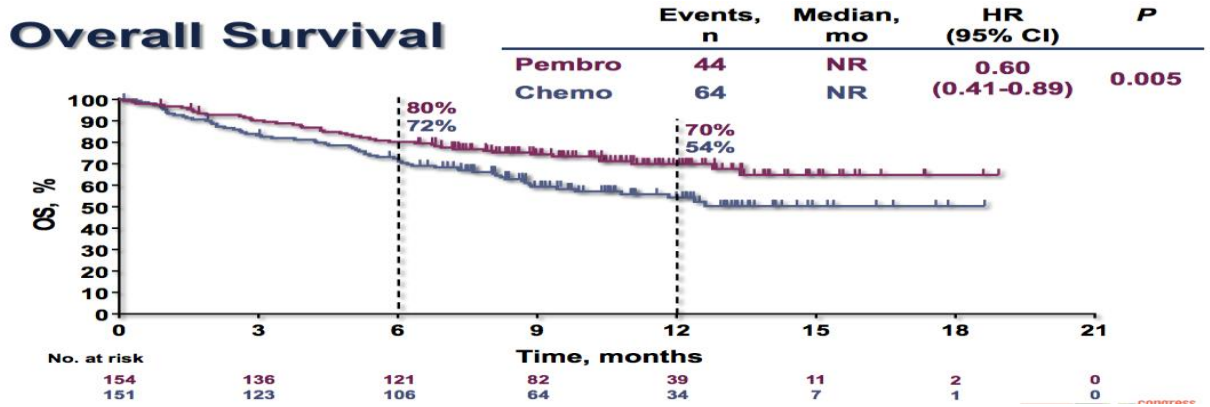
# KEYNOTE – 024: výsledky primárnej analýzy

**median FU: 11.2 mesiaca**

**PFS: 10.3** vs 6.0 m (HR 0.5; p<0.001)

- **RR**: **45%** vs 28% (chemo)
- **OS**: HR 0.60, p=0.005
  - 80.2%vs 72.4%(chemo
  - Median nebol dosiahnuty v pembro
- **TRAE** ¾: 26% vs 51%




Reck M et al, NEJM 2016; 375 (19): 1823-1833

# ESMO 2020, KEYNOTE-024: analýza po 5 rokoch

## KEYNOTE-024 5-Year OS Update: First-Line Pembrolizumab vs Platinum-Based Chemotherapy in Patients with Metastatic Non–Small-Cell Lung Cancer and PD-L1 Tumor Proportion Score ≥50%

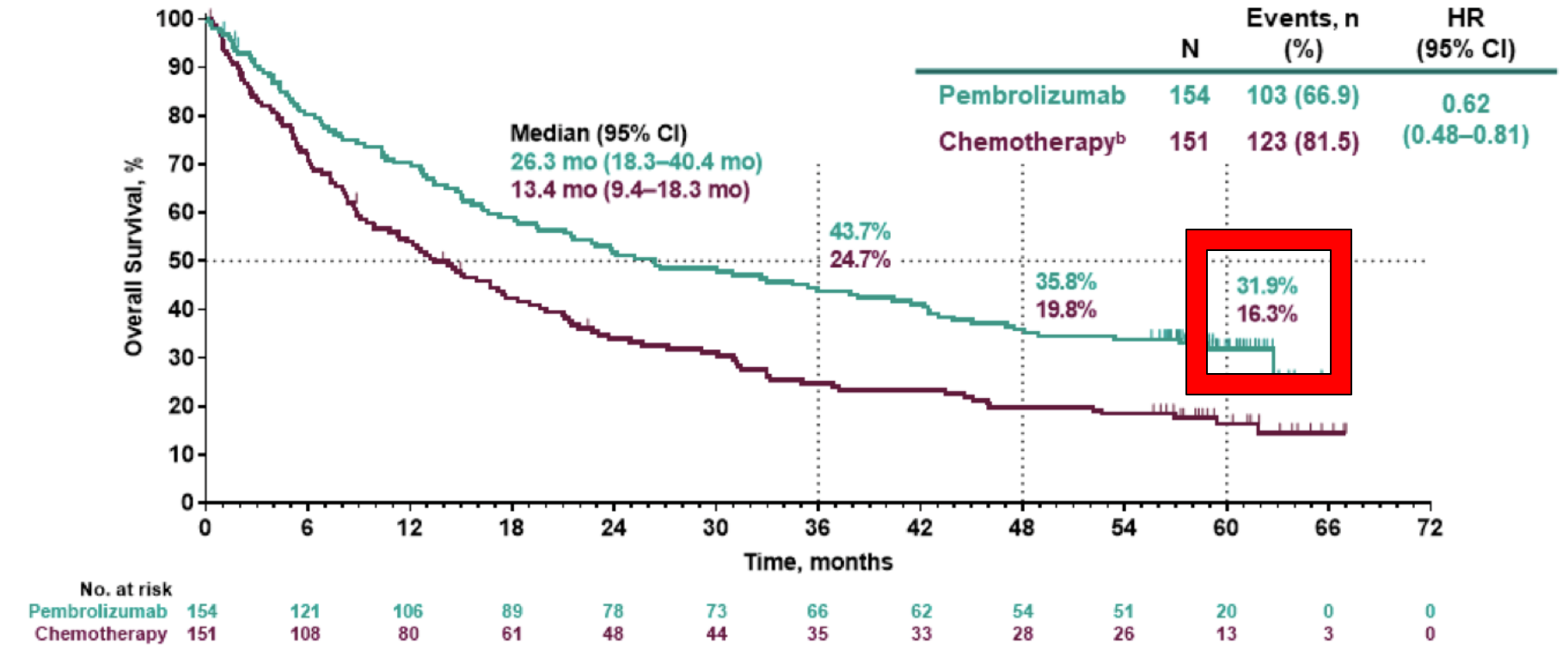
Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Ticiana A. Leal,[14] Jonathan W. Riess,[15] Erin Jensen,[16] Bin Zhao,[16] M. Catherine Pietanza,[16] Martin Reck[17]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Soroka Cancer Center, Ben Gurion University, Beer Sheva, Israel; [9]Wollongong Private Hospital and University of Wollongong, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, Sutton, Surrey, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Carbone Cancer Center, University of Wisconsin, Madison, WI, USA ; [15]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany

- výsledky u pacientov, ktorí mali kompletne 35ck (2 roky) pembrolizumabu
- ITT populácia

Brahmer et al. ESMO 2020

# KEYNOTE 0-24: 5-ročné celkové prežívanie

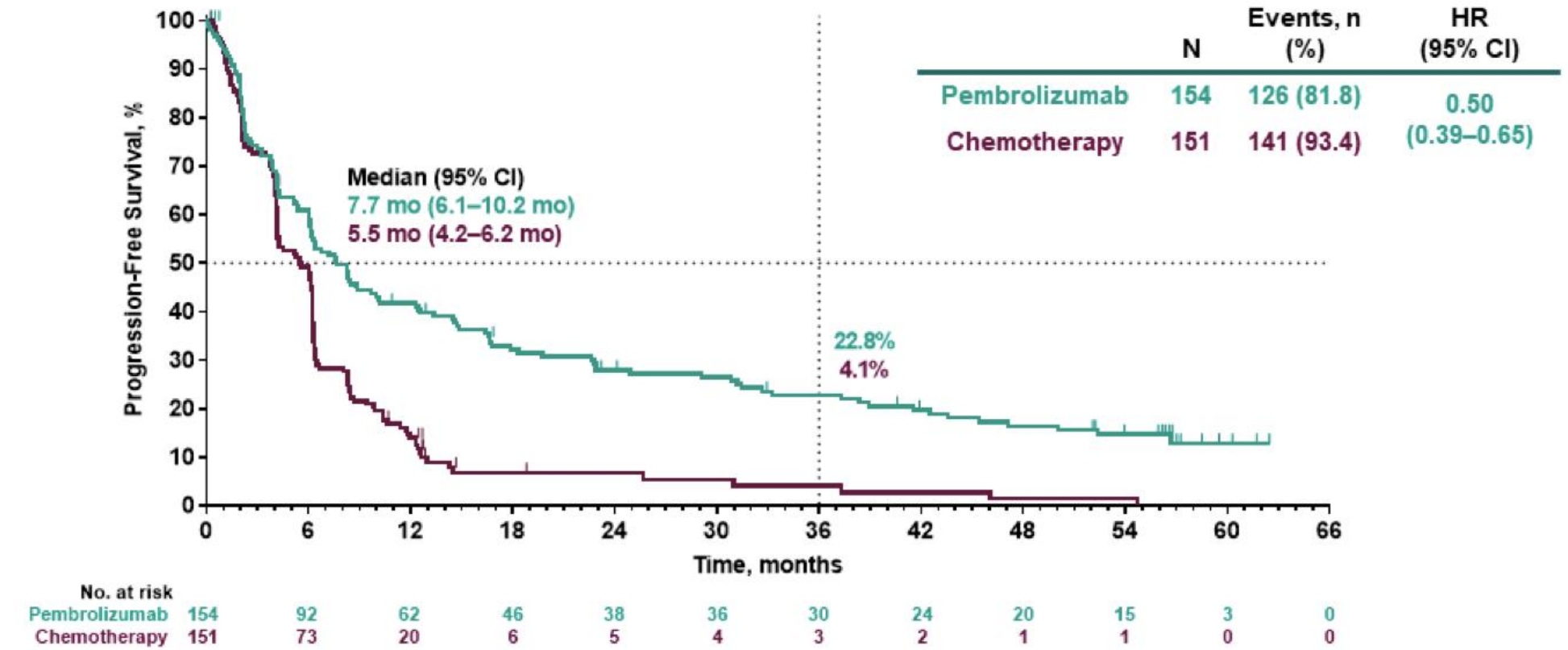



[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-(L)1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-[L]1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-[L]1 therapy). Data cutoff: June 1, 2020.

Brahmer et al. ESMO 2020

# KEYNOTE 024: PFS

## RECIST v1.1




NR, not reached.
[a]ITT population. [b]Secondary endpoint; primary endpoint was PFS assessed per blinded, independent, central radiology review.
Data cutoff: June 1, 2020.

Brahmer: ESMO 2020

# KEYNOTE-024: bezpečnosť (NU súvisiace s liečbou)

| | Pembrolizumab (n=154) | | Chemotherapy (n=150) | |
|---|---|---|---|---|
| | Any grade | Grade 3–5 | Any grade | Grade 3–5 |
| Any treatment-related AE, % | 73 | 27 | 90 | 53 |
| Treatment-related AEs occurring in ≥10% of patients, %* | | | | |
| Nausea | 10 | 0 | 43 | 2 |
| Anaemia | 5 | 2 | 44 | 19 |
| Fatigue | 10 | 1 | 29 | 3 |
| Decreased appetite | 9 | 0 | 26 | 3 |
| Diarrhoea | 14 | 4 | 13 | 1 |
| Neutropenia | 1 | 0 | 23 | 13 |
| Vomiting | 3 | 1 | 20 | 1 |
| Pyrexia | 10 | 0 | 5 | 0 |
| Constipation | 4 | 0 | 11 | 0 |
| Stomatitis | 3 | 0 | 12 | 1 |
| Decreased neutrophil count | 0 | 0 | 13 | 4 |
| Increased blood creatinine level | 2 | 0 | 10 | <1 |
| Decreased platelet count | 0 | 0 | 12 | 6 |
| Thrombocytopenia | 0 | 0 | 11 | 5 |
| Decreased white-cell count | 1 | 0 | 11 | 2 |
| Dysgeusia | 1 | 0 | 10 | 0 |
| Median treatment duration, months | 7.0 | | 3.5 | |
| Discontinued drug due to treatment-related AEs, % | 7 | | 11 | |

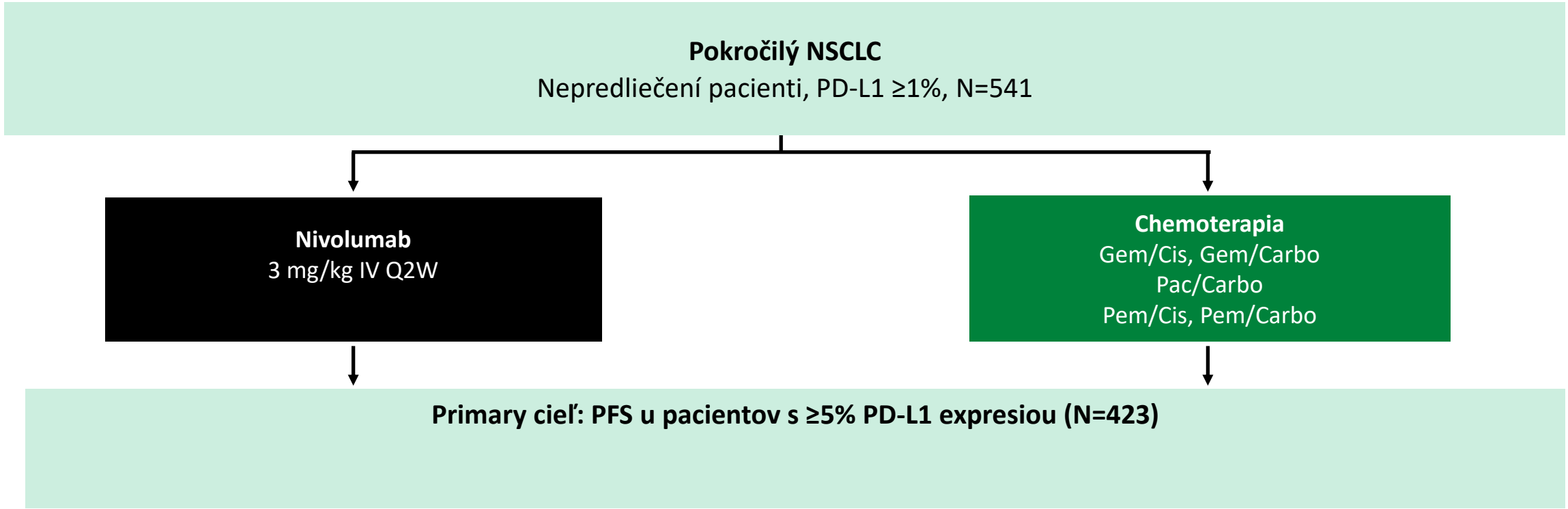
**Pembrolizumab safety was favourable versus chemotherapy; AEs profiles were as expected**

**Most common treatment-related AEs highlighted in red; cytopenias were more frequent with chemotherapy, consistent with MoA**

There were four grade 5 treatment-related AEs (pembrolizumab, n=1; chemotherapy, n=3)

Reck, et al. N Engl J Med 2016

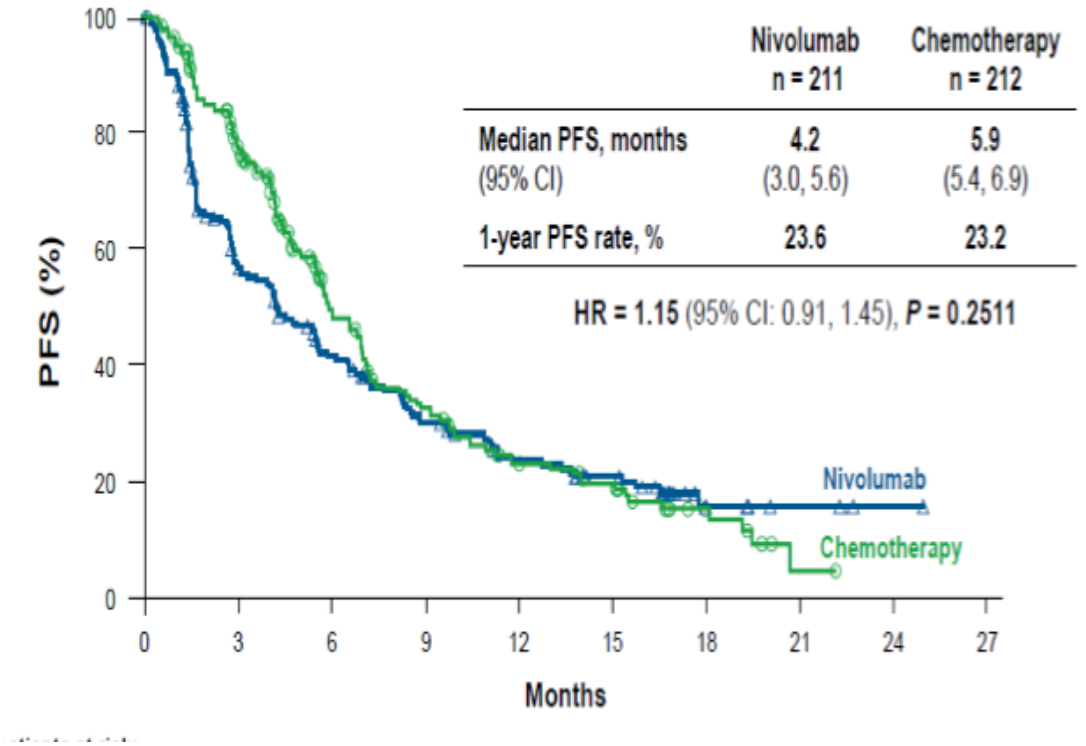
# CheckMate 026 – 1.línia s nivolumabom




Socinski et al, ESMO 2016

# CheckMate - 026

- **PFS:** 4.2 vs 5.9 m (chemo) (HR 1.15, p=0.25)
- **RR**: 26% vs 33% (chemo)
- **OS**: 13.2 vs 14.4 m (chemo) (HR1.02)
- bez rozdielu u pct s PDL-expression =/> 50%
- TRAE 3/4: 18% vs 51% (chemo)
- explorácia nového biomarkeru  (TMB)
- nehomogenita u populácie pacientov

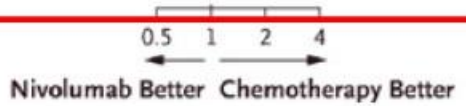



Carbone D et al, NEJM 2017; 376 (25): 2415-2426

# Nivolumab vs Chemotherapy in First-Line NSCLC, CheckMate 026 PFS and OS Subgroup Analyses

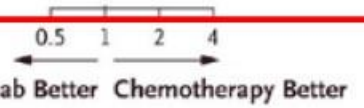
**A Progression-free Survival**

| Subgroup | Nivolumab No. of Patients | Nivolumab Median Progression-free Survival *mo* | Chemotherapy No. of Patients | Chemotherapy Median Progression-free Survival *mo* | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| Overall | 271 | 4.2 | 270 | 5.8 | 1.19 (0.97–1.46) |
| Age | | | | | |
| ≥65 yr | 123 | 4.2 | 137 | 5.4 | 1.21 (0.91–1.62) |
| <65 yr | 148 | 4.5 | 133 | 6.8 | 1.17 (0.88–1.56) |
| Sex | | | | | |
| Male | 184 | 5.1 | 148 | 5.5 | 1.05 (0.81–1.37) |
| Female | 87 | 3.6 | 122 | 6.6 | 1.36 (0.98–1.90) |
| ECOG performance-status score | | | | | |
| 0 | 85 | 5.4 | 93 | 7.2 | 1.69 (1.18–2.42) |
| ≥1 | 185 | 4.0 | 177 | 5.4 | 1.01 (0.79–1.30) |
| Tumor histologic findings | | | | | |
| Squamous | 65 | 5.1 | 64 | 4.6 | 0.83 (0.54–1.26) |
| Nonsquamous | 206 | 4.2 | 206 | 6.8 | 1.29 (1.02–1.63) |
| Smoking status | | | | | |
| Never smoked | 30 | 2.8 | 29 | 6.8 | 2.51 (1.31–4.83) |
| Former smoker | 186 | 4.2 | 182 | 5.7 | 1.14 (0.89–1.47) |
| Current smoker | 52 | 5.4 | 55 | 6.8 | 1.03 (0.66–1.62) |
| ≥50% PD-L1 expression level | 88 | 5.4 | 126 | 5.8 | 1.07 (0.77–1.49) |



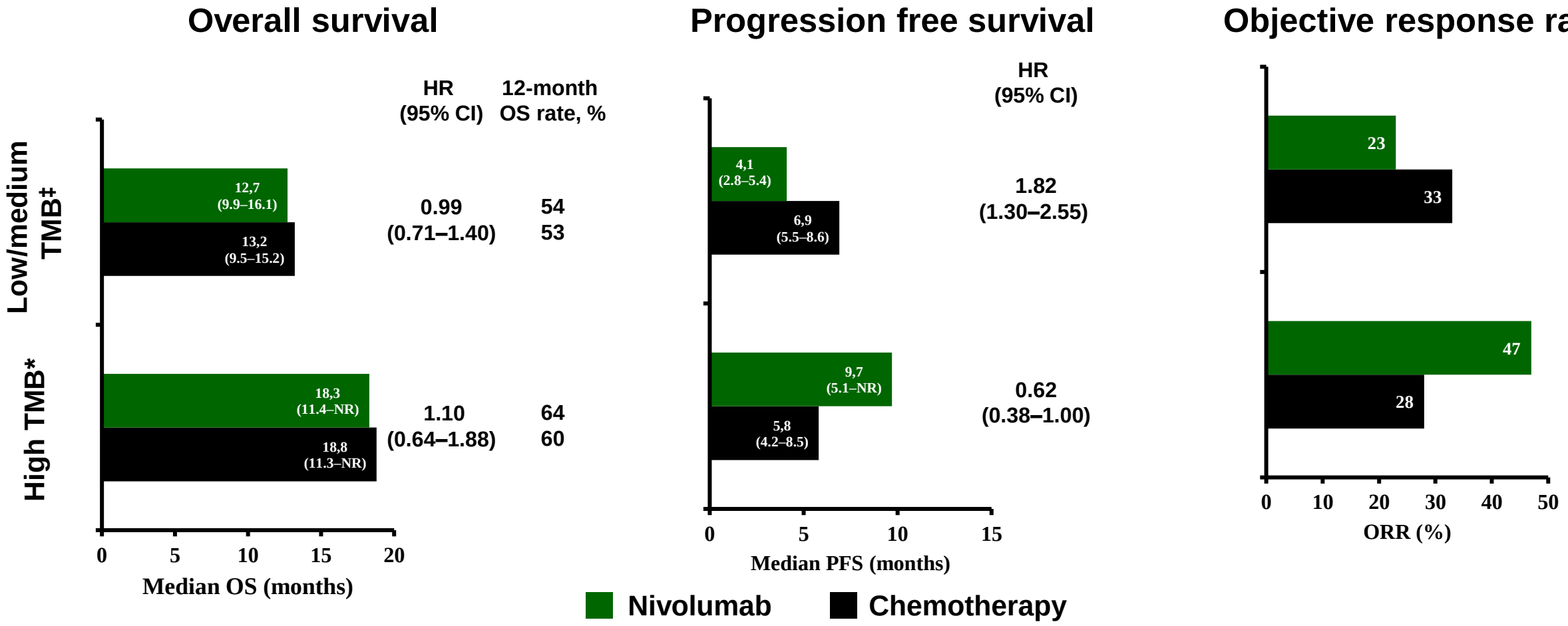

**B Overall Survival**

| Subgroup | Nivolumab No. of Patients | Nivolumab Median Overall Survival *mo* | Chemotherapy No. of Patients | Chemotherapy Median Overall Survival *mo* | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| Overall | 271 | 13.7 | 270 | 13.8 | 1.08 (0.87–1.34) |
| Age | | | | | |
| ≥65 yr | 123 | 13.3 | 137 | 11.0 | 1.04 (0.77–1.41) |
| <65 yr | 148 | 14.1 | 133 | 16.7 | 1.13 (0.83–1.54) |
| Sex | | | | | |
| Male | 184 | 13.1 | 148 | 10.8 | 0.97 (0.74–1.26) |
| Female | 87 | 16.6 | 122 | 17.3 | 1.15 (0.79–1.66) |
| ECOG performance-status score | | | | | |
| 0 | 85 | 16.6 | 93 | 18.0 | 1.11 (0.74–1.66) |
| ≥1 | 185 | 12.7 | 177 | 11.0 | 1.02 (0.79–1.32) |
| Tumor histologic findings | | | | | |
| Squamous | 65 | 10.5 | 64 | 10.2 | 0.82 (0.54–1.24) |
| Nonsquamous | 206 | 14.5 | 206 | 16.7 | 1.17 (0.91–1.52) |
| Smoking status | | | | | |
| Never smoked | 30 | 13.7 | 29 | 12.5 | 1.02 (0.54–1.93) |
| Former smoker | 186 | 14.1 | 182 | 13.3 | 1.09 (0.84–1.42) |
| Current smoker | 52 | 14.3 | 55 | 17.1 | 1.05 (0.63–1.74) |
| ≥50% PD-L1 expression level | 88 | 15.9 | 126 | 13.9 | 0.90 (0.63–1.29) |




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

# CheckMate 026: exploratívna analýza účinnosti na základe TMB (n=312)

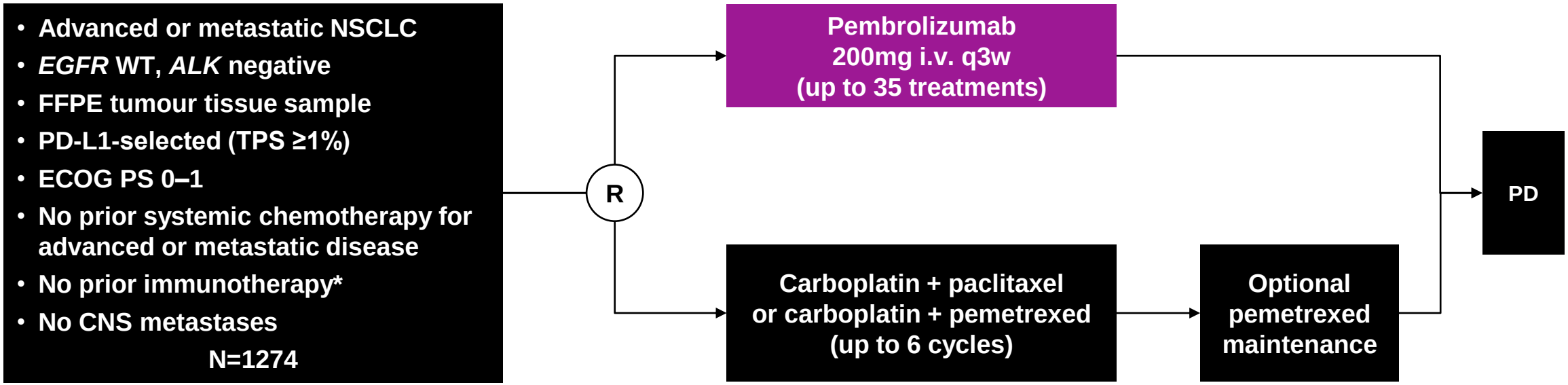



*≥243 total missense mutations; nivolumab n=47, chemotherapy n=60

‡0–242 total missense mutations (low TMB was 0 to <100 total missense mutations and medium TMB was 100 to 242 total missense mutations; data for patients with low and medium TMB were pooled; nivolumab n=111, chemotherapy n=94

Carbone, et al. N Engl J Med 2017

# KEYNOTE-042: dizajn štúdie



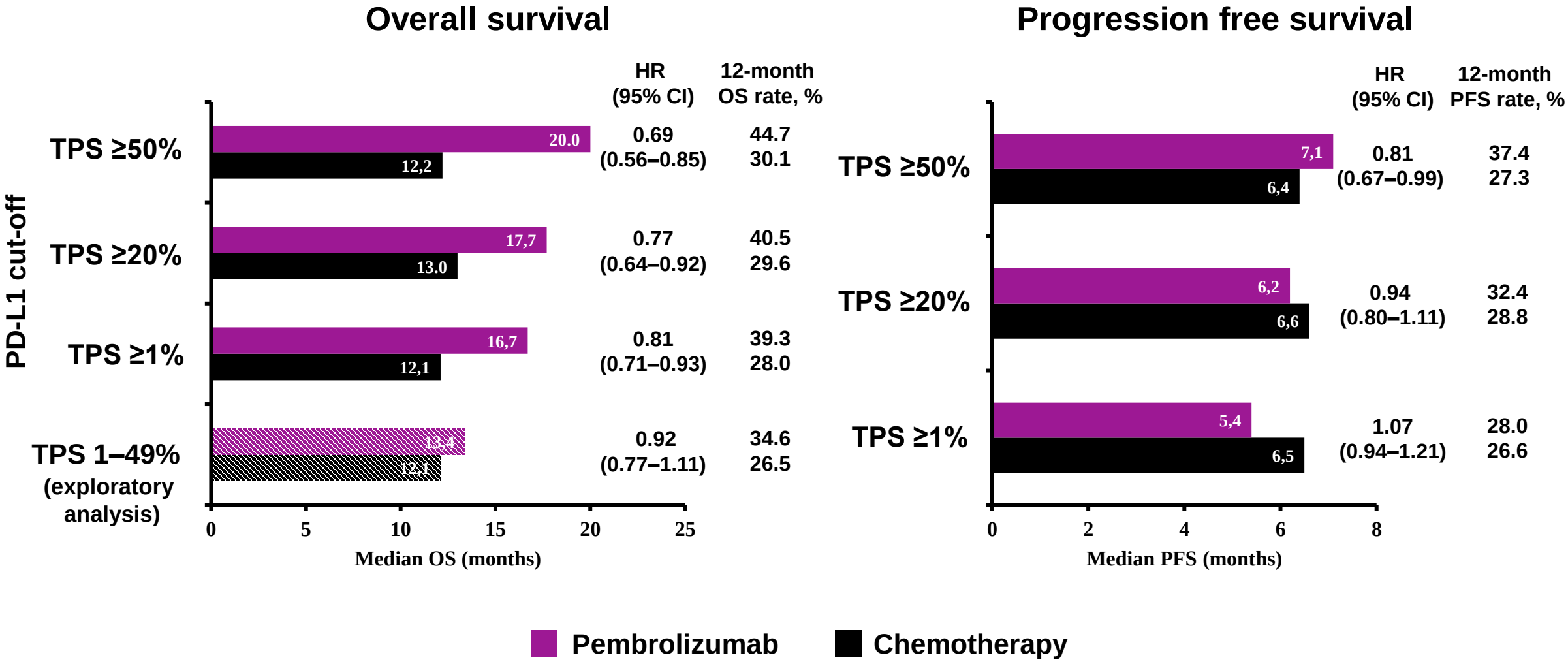

**1 Primary endpoint**
- OS

**2 Secondary endpoint**
- PFS (by central review)

*No prior anti-PDL1, anti-PD1, anti-PDL2, anti-CD137 or anti-CTLA4 therapy
Carboplatin dose: AUC 5 (max dose 750mg) or AUC 6 (max dose 900mg) i.v. q3w (up to 6 cycles)
Paclitaxel dose: 200mg/m$^2$ i.v. q3w (up to 6 cycles)
Pemetrexed dose: 500mg/m$^2$ i.v. q3w (up to 6 cycles)

NCT02220894
Lopes, et al. ASCO 2018 (Abs LBA4)

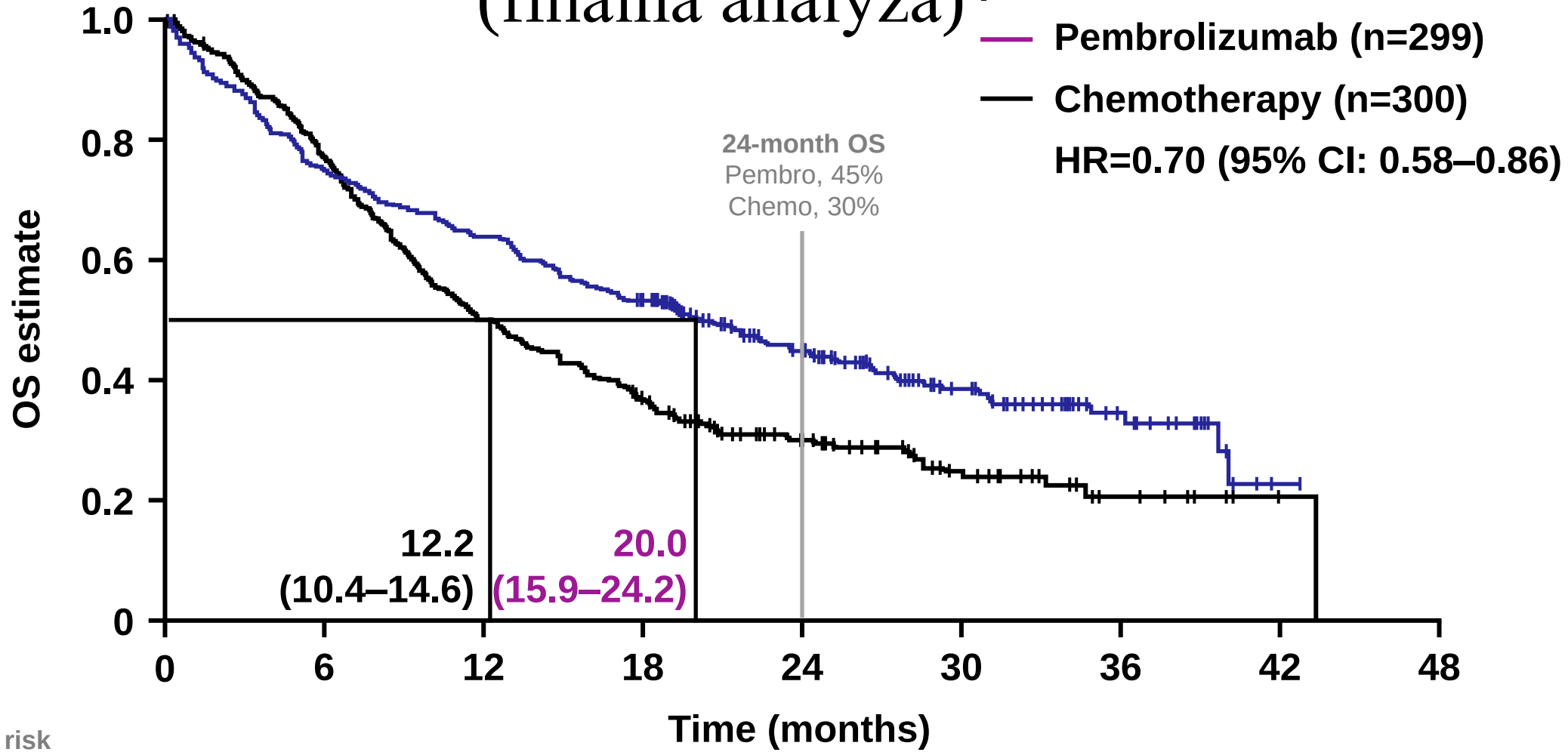
# KEYNOTE-042: prehľad OS a PFS podľa PD-L1 poskupín (primárna analýza)




**Median follow-up 12.8 months; data cut-off: 26 Feb, 2018**

Lopes, et al. ASCO 2018 (Abs LBA4)
Mok, et al. Lancet 2019

# KEYNOTE-042: OS u TPS ≥50% populácie (finálna analýza)*



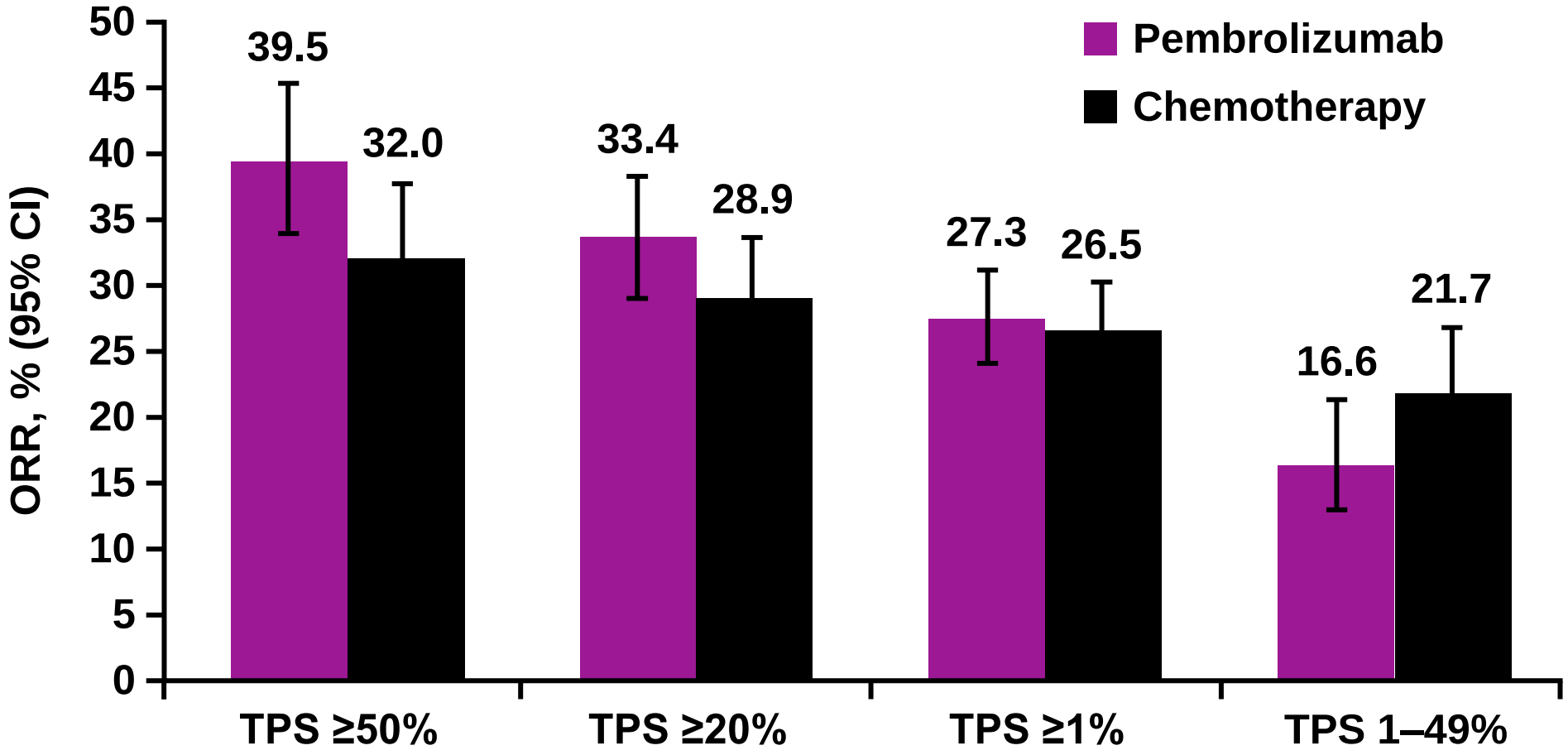

| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Pembrolizumab | 299 | 224 | 190 | 157 | 94 | 50 | 21 | 1 | 0 |
| Chemotherapy | 300 | 231 | 151 | 113 | 59 | 31 | 8 | 2 | 0 |

*No alpha was allocated, as the primary hypotheses for OS were met at the interim analysis

**Data cut-off: 4 Sept, 2018**

Mok, et al. ELCC 2019 (Abs 102O)

# KEYNOTE-042: dosiahnuté odpovede podľa PD-L1 podskupiny (primárna analýza)




**Median follow-up 12.8 months; data cut-off: 26 Feb, 2018**

Lopes, et al. ASCO 2018 (Abs LBA4)
Mok, et al. Lancet 2019

# KEYNOTE-042: záver

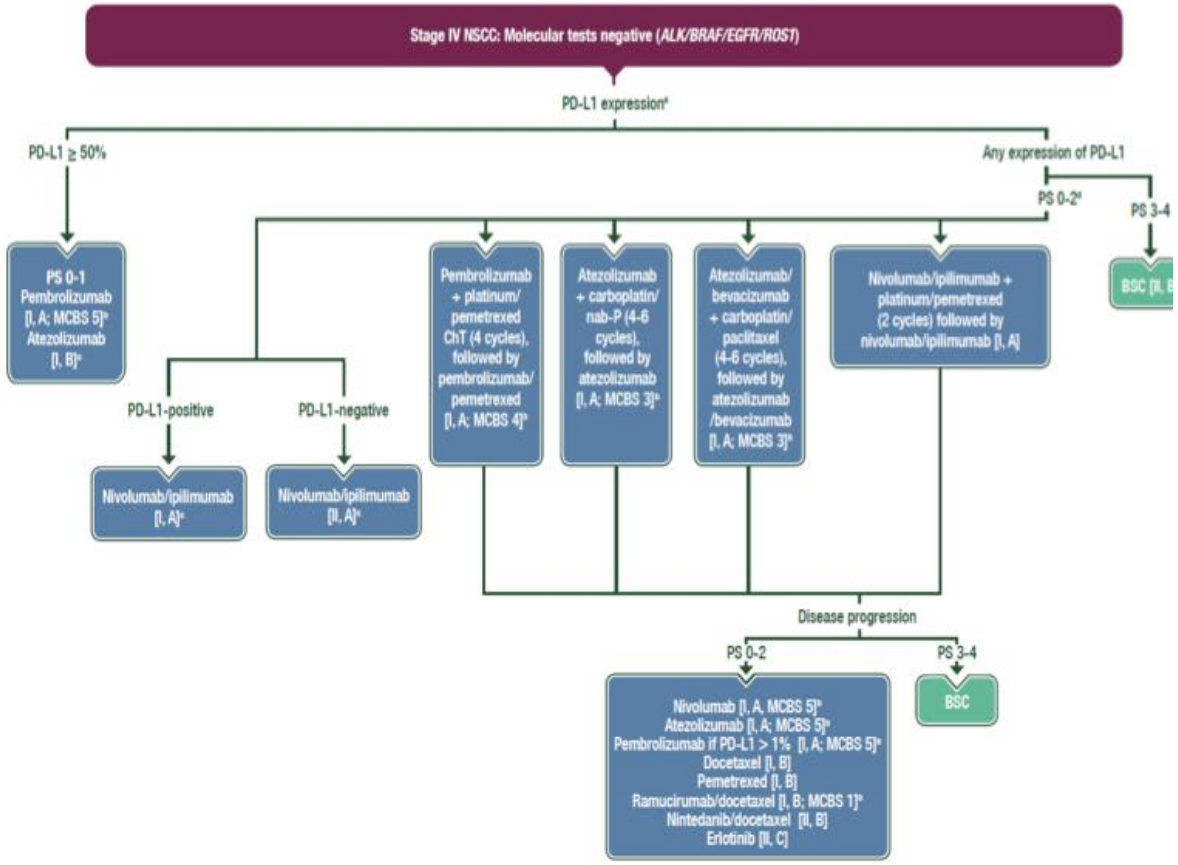
KEYNOTE-042 potvrdila výsledky štúdie KEYNOTE -024, že  TPS ≥50% by mohla byť hladina expresie pre identifikáciu pacientov , ktorí by profitovali z monoterapie pembrolizumabom

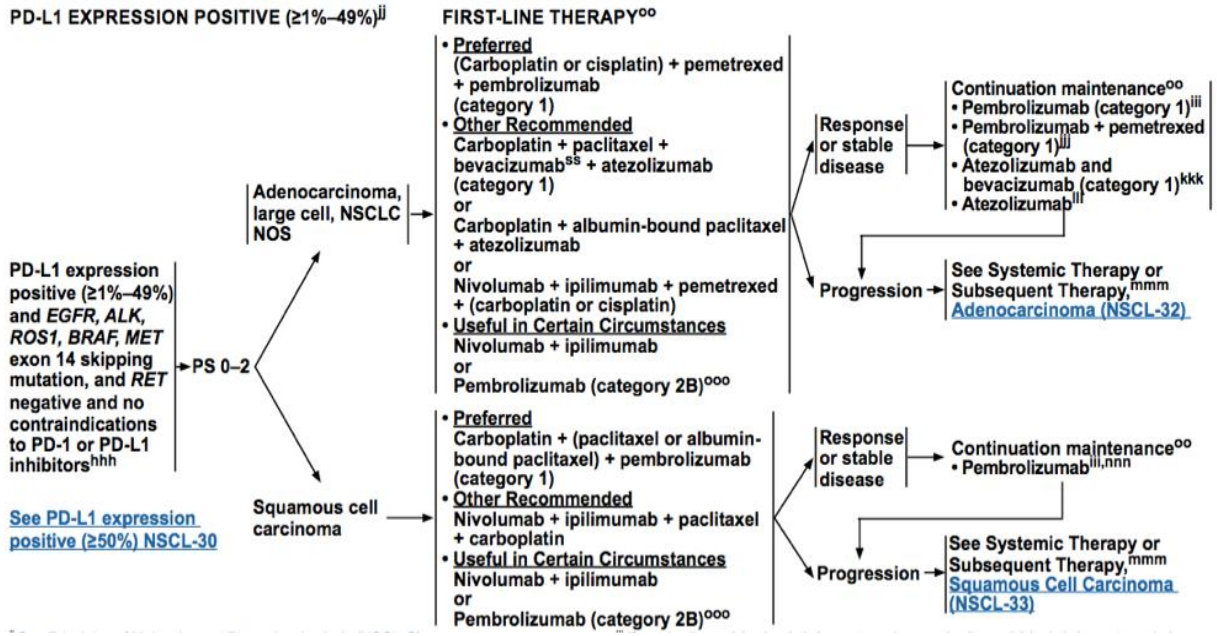
aj  keď…

**V aprili 2019 FDA rozšírila registráciu pembrolizumabu v monoterapii pre 1L pokročilých alebo  metastatických NSCLC a zahrnula pacientov s PD-L1 TPS ≥1%, na základe výsledkov zo štúdie KEYNOTE-042**

Lopes, et al. ASCO 2018 (Abs LBA4)
Mok, et al. Lancet 2019
Mok, et al. ELCC 2019 (Abs 102O)

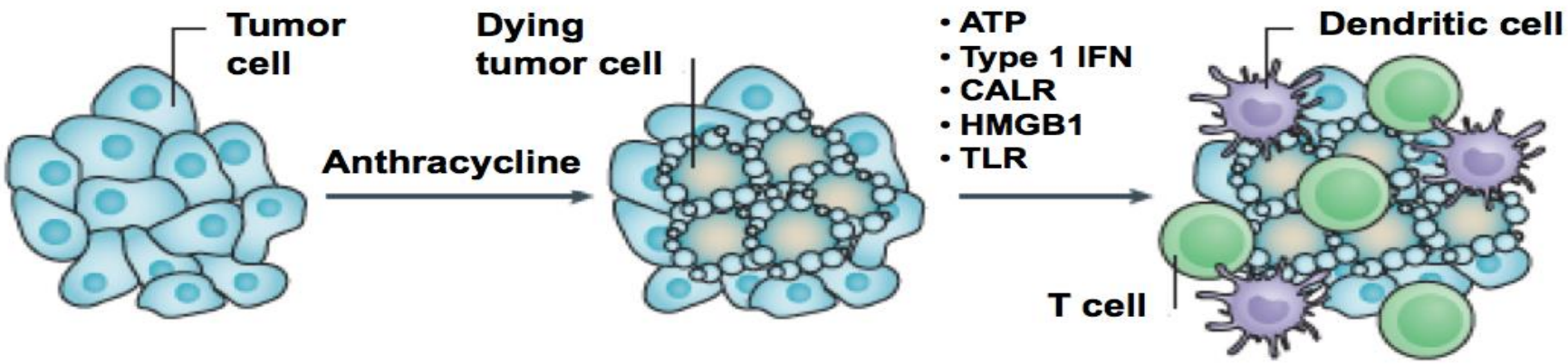
# ESMO vs NCCN



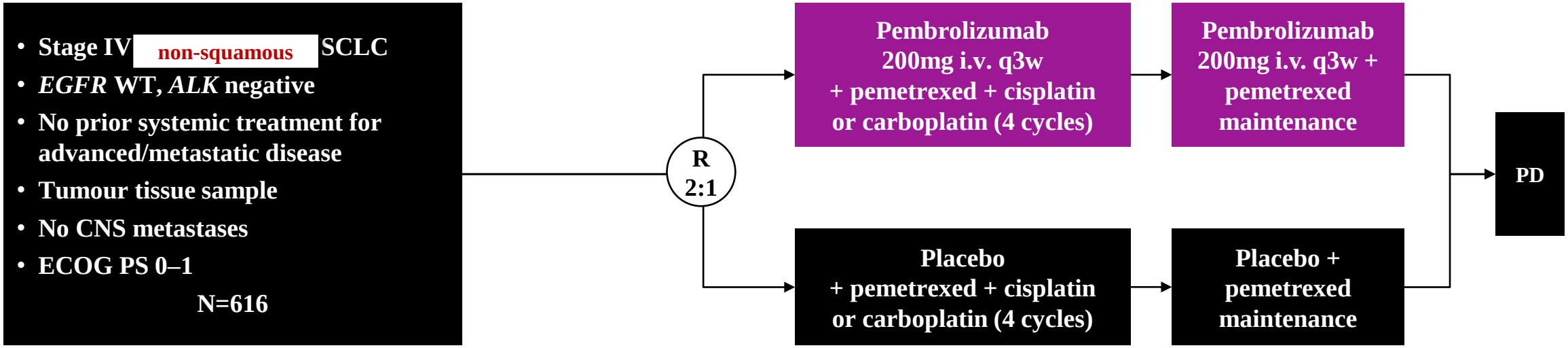

ESMO guidelines, 18.9.2019 version
NCCN: Version 8.2020 — September 15, 2020

# Chemoterapiou indukovaná imunogenicita




Gotwals P, et al. *Nat Rev Cancer.* 2017;17(5):286-301.

# KEYNOTE-189: dizajn štúdie




**Kombinácia pembrolizumabu s chemoterapiou je skúmaná u -naïve NSCLC v dvoch štúdiach fázy III: KEYNOTE-407 (skvamózny) a KEYNOTE-189 (neskvamózny )**

**1 Co-primary endpoints**
- PFS*
- OS

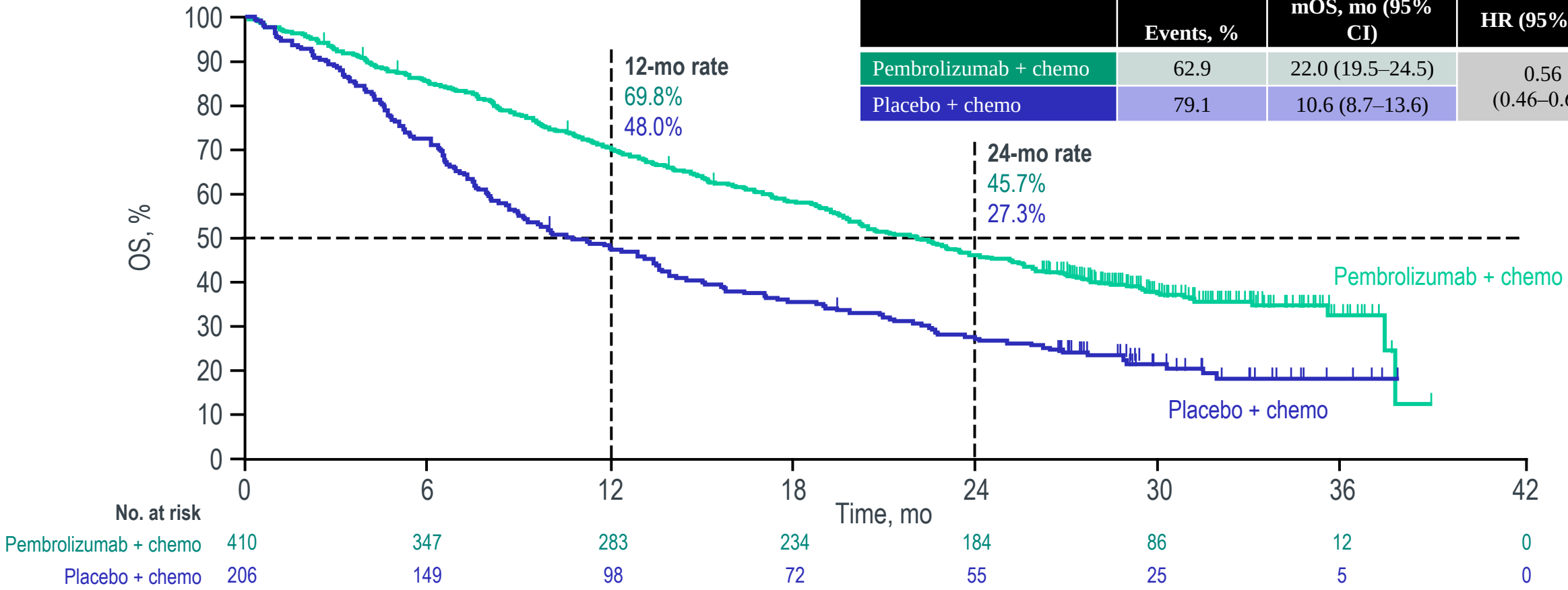
**2 Secondary endpoints**
- ORR* and DoR*
- PFS* in PD-L1 TPS ≥ 1%
- PFS (investigator-assessed per irRECIST)
- Safety and tolerability

*Centrally assessed per RECIST v1.1
Pemetrexed dose: 500mg/m$^2$ i.v. q3w; cisplatin dose: 75mg/m$^2$ i.v. q3w; carboplatin AUC 5 i.v. q3w

NCT02578680
Hall, et al. ASCO 2016 (Abs TPS9104)

# KN-189: finálna analýza pre Pembrolizumab + Chemotherapia vs Placebo + Chemotherapia (ITT Population)

| | Events, % | mOS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembrolizumab + chemo | 62.9 | 22.0 (19.5–24.5) | 0.56 (0.46–0.69) |
| Placebo + chemo | 79.1 | 10.6 (8.7–13.6) | |

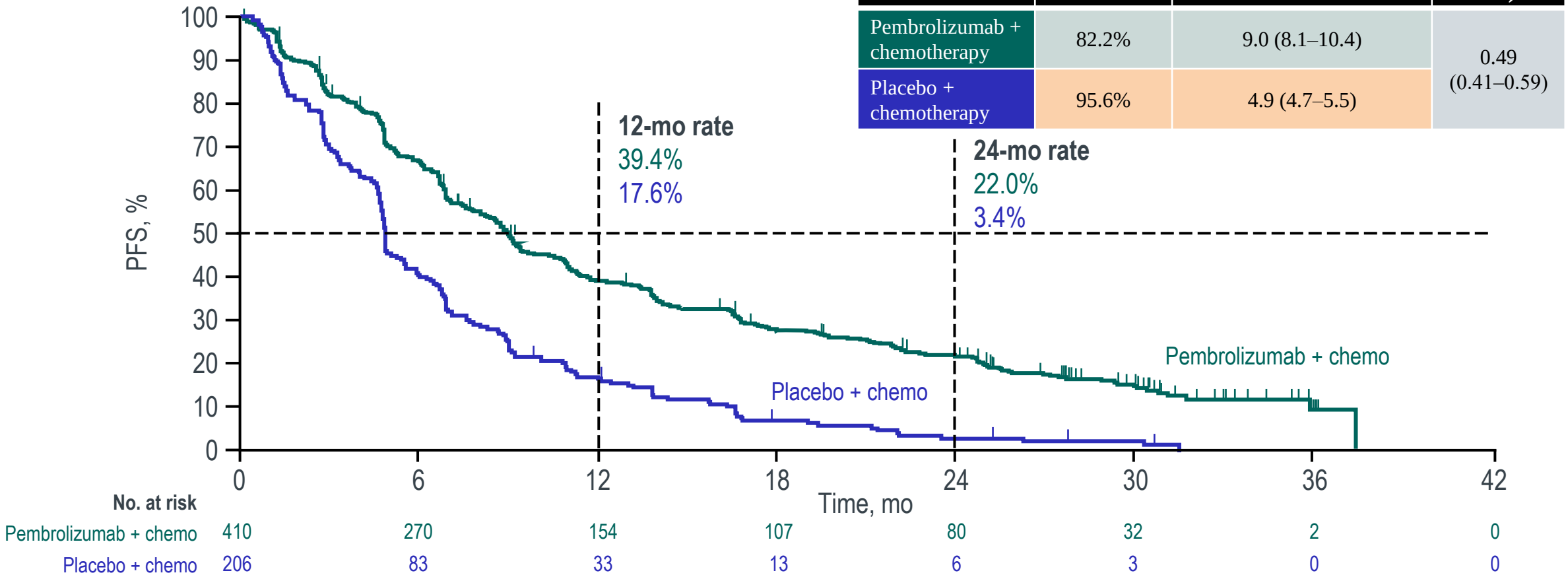



Data cutoff: May 20, 2019. Median follow-up = 31.0 mo (range: 26.5–38.8 mo).

Rodríguez-Abreu D et al. Presented at ASCO Annual Meeting 2020; May 29–31, 2020, Virtual Meeting. Abstract 9582.

# KN-189: finálna analýza PFS
# Pembrolizumab + Chemotherapia vs Placebo + Chemotherapia (ITT populácia )[1]

| | Events | mPFS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembrolizumab + chemotherapy | 82.2% | 9.0 (8.1–10.4) | 0.49 (0.41–0.59) |
| Placebo + chemotherapy | 95.6% | 4.9 (4.7–5.5) | |



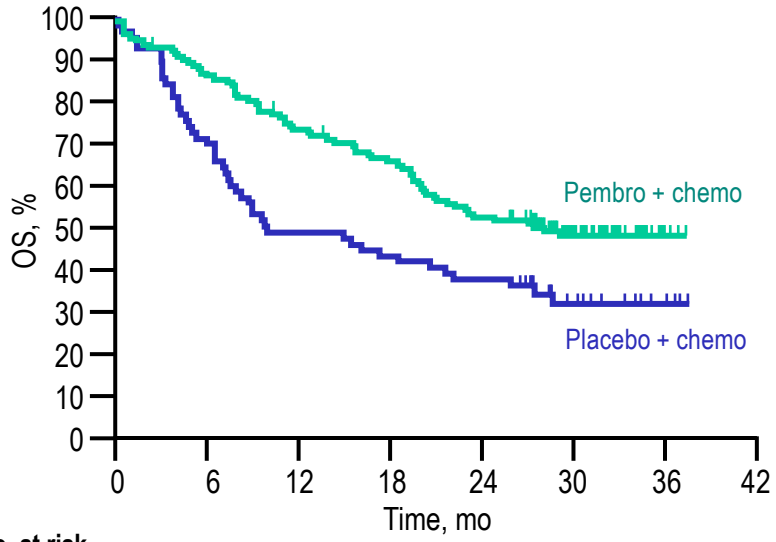

Data cutoff: May 20, 2019. Median follow-up = 31.0 mo (range: 26.5–38.8 mo).

Rodríguez-Abreu D et al. Presented at ASCO Annual Meeting 2020; May 29–31, 2020; Virtual Meeting. Abstract 9582.

# KN-189: finálna analýza OS podľa PD-L1
# Pembrolizumab + Chemotherapia vs Placebo + Chemotherapia

## TPS ≥50%

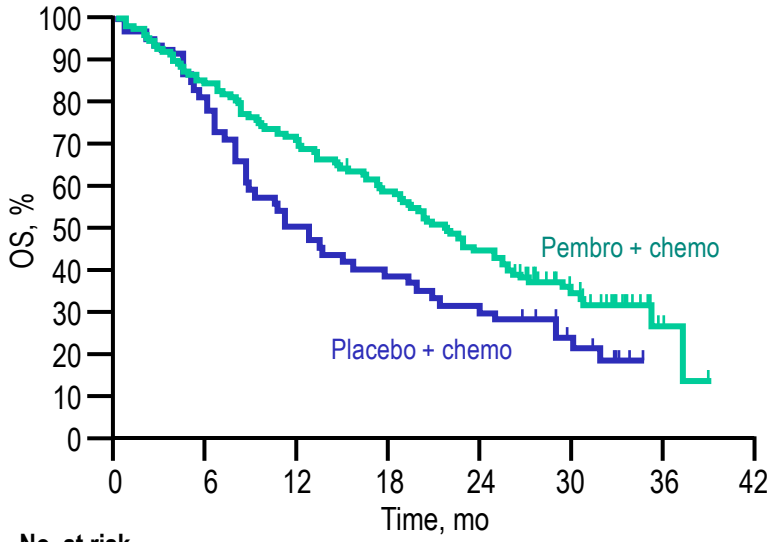
| | Events | mOS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembro + chemo | 50.8% | 27.7 (20.4–NR) | 0.59 (0.40–0.86) |
| Placebo + chemo | 67.1% | 10.1 (7.5–22.0) | |




| No. at risk | | | | |
|---|---|---|---|---|
| Pembro + chemo | 132 | 95 | 67 | 5 |
| Placebo + chemo | 70 | 34 | 26 | 4 |

## TPS 1%–49%

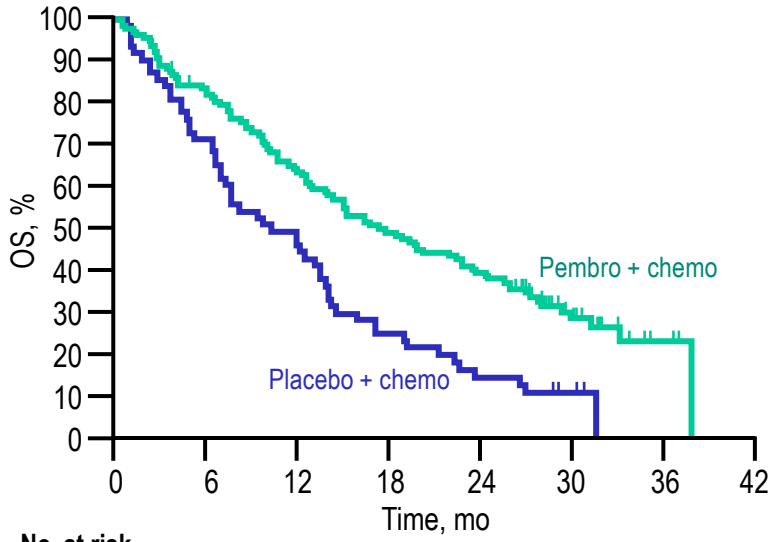
| Events | mOS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| 67.2% | 21.8 (17.7–25.6) | 0.66 (0.46–0.96) |
| 79.3% | 12.1 (8.7–19.4) | |




| No. at risk | | | | |
|---|---|---|---|---|
| | 128 | 91 | 56 | 3 |
| | 58 | 29 | 18 | 0 |

## TPS <1%

| Events | mOS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| 70.9% | 17.2 (13.8–22.8) | 0.51 (0.36–0.71) |
| 88.9% | 10.2 (7.0–13.5) | |




| No. at risk | | | | |
|---|---|---|---|---|
| | 127 | 79 | 49 | 3 |
| | 63 | 29 | 8 | 0 |

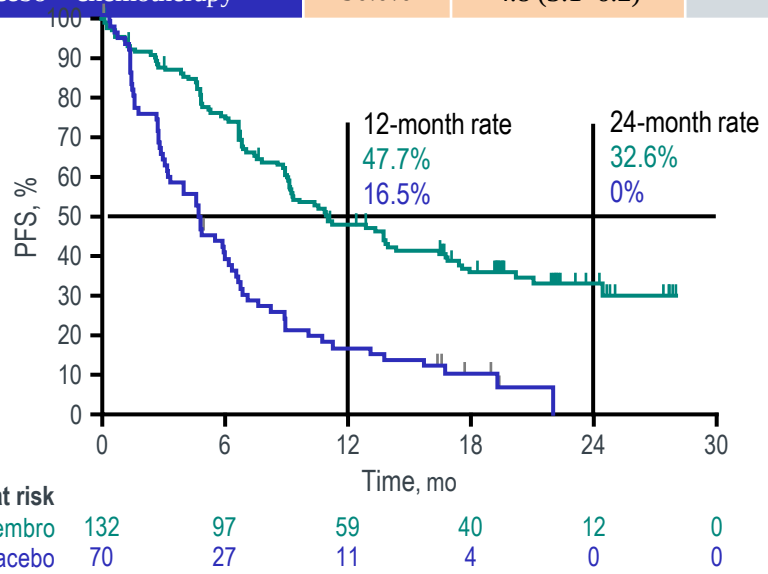
Data cutoff: May 20, 2019.

Rodríguez-Abreu D et al. Presented at ASCO Annual Meeting 2020; May 29–31, 2020; Virtual Meeting. Abstract 9582.

# KN-189: PFS podľa PD-L1 TPS pre Pembrolizumab + Chemotherapia vs Placebo + Chemotherapia (Updated Analýza)

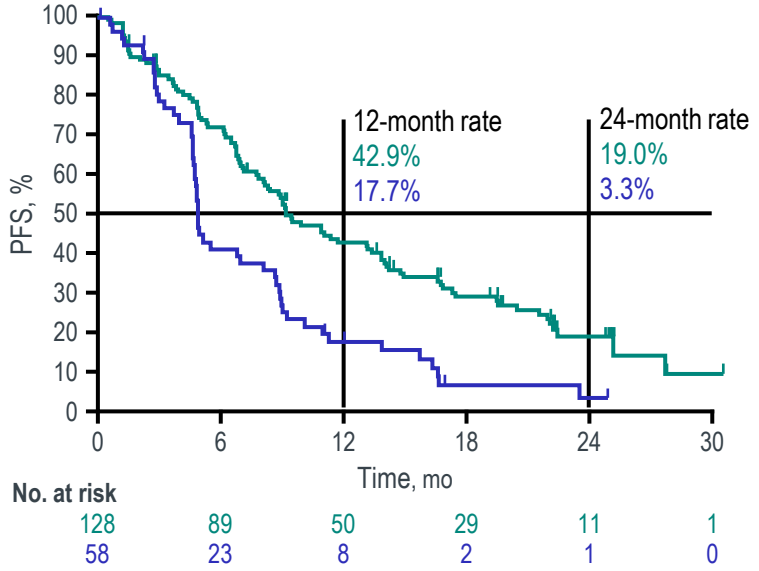
## TPS ≥50%

| | Events | mPFS, mo (95% CI) | HR (95% CI) |
|---|---|---|---|
| Pembrolizumab + chemotherapy | 63.6% | 11.1 (9.1–14.4) | 0.36 (0.26–0.51) |
| Placebo + chemotherapy | 90.0% | 4.8 (3.1–6.2) | |



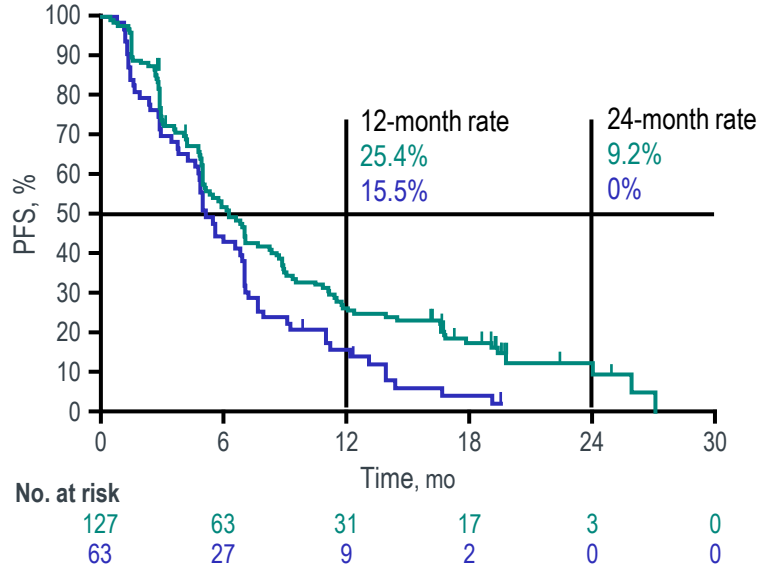

## TPS 1%–49%

| Events | mPFS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| 74.2% | 9.2 (7.8–13.1) | 0.51 (0.36–0.73) |
| 89.7% | 4.9 (4.7–6.9) | |




## TPS <1%

| Events | mPFS, mo (95% CI) | HR (95% CI) |
|---|---|---|
| 84.3% | 6.2 (4.9–8.1) | 0.64 (0.47–0.89) |
| 95.2% | 5.1 (4.5–6.8) | |




Data cutoff: September 21, 2018.

Gadgeel S et al. *J Clin Oncol.* 2020;38(14):1505-1517.

# Finálna analýza ORR v KEYNOTE-189

| | All Patients | | TPS ≥50% | | TPS 1–49% | | TPS <1% | |
|---|---|---|---|---|---|---|---|---|
| | Pembrolizumab Combination n=410 | Placebo Combination n=206 | Pembrolizumab Combination n=132 | Placebo Combination n=70 | Pembrolizumab Combination n=128 | Placebo Combination n=58 | Pembrolizumab Combination n=127 | Placebo Combination n=63 |
| **ORR, %** (95% CI) | **48.3** (43.4–53.2) | **19.9** (14.7–26.0) | **62.1** (53.3–70.4) | **25.7** (16.0–37.6) | **50.0** (41.0-59.0) | **20.7** (11.2-33.4) | **33.1** (25.0-42.0) | **14.3** (6.7-25.4) |

Data cutoff: May 20, 2019.

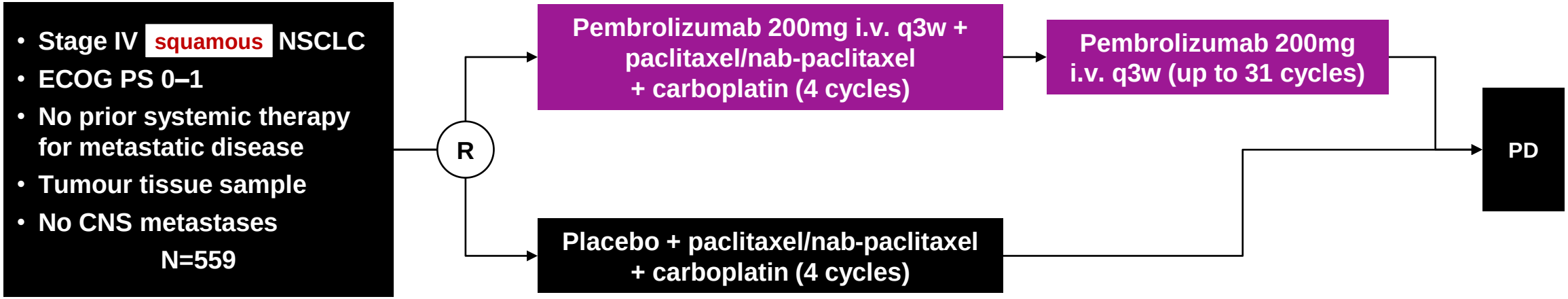
Rodríguez-Abreu D et al. Presented at ASCO Annual Meeting 2020; May 29–31, 2020; Virtual Meeting. Abstract 9582.

# KN-189: Finálna analýza  AEs v celkovej populácii

| | All-cause | | imAEs and Infusion Reactions | |
|---|---|---|---|---|
| | Pembrolizumab + chemo n=405 | Placebo + chemo n=202 | Pembrolizumab + chemo n=405 | Placebo + chemo n=202 |
| Any grade, n (%) | 404 (99.8) | 200 (99.0) | 110 (27.2) | 26 (12.9) |
| Grade 3–5, n (%) | 292 (72.1) | 135 (66.8) | 49 (12.1) | 9 (4.5) |
| Led to death,[a] n (%) | 29 (7.2) | 14 (6.9) | Not reported in final analysis | Not reported in final analysis |
| Led to discontinuation of any treatment component, n (%) | 146 (36.0) | 35 (17.3) | Not reported in final analysis | Not reported in final analysis |

[a]Eight (2.0%) participants in the pembrolizumab plus chemotherapy group and 2 (1.0%) participants in the placebo plus chemotherapy group died from AEs attributed to study treatment by the investigator.
Data cutoff: May 20, 2019.
Rodríguez-Abreu D et al. Presented at ASCO Annual Meeting 2020; May 29–31, 2020; Virtual Meeting. Abstract 9582.

# KEYNOTE-407: dizajn štúdie




**The combination of pembrolizumab plus chemotherapy is being investigated for treatment-naïve NSCLC in two phase III studies: KEYNOTE-407 (squamous) and KEYNOTE-189 (non-squamous)**

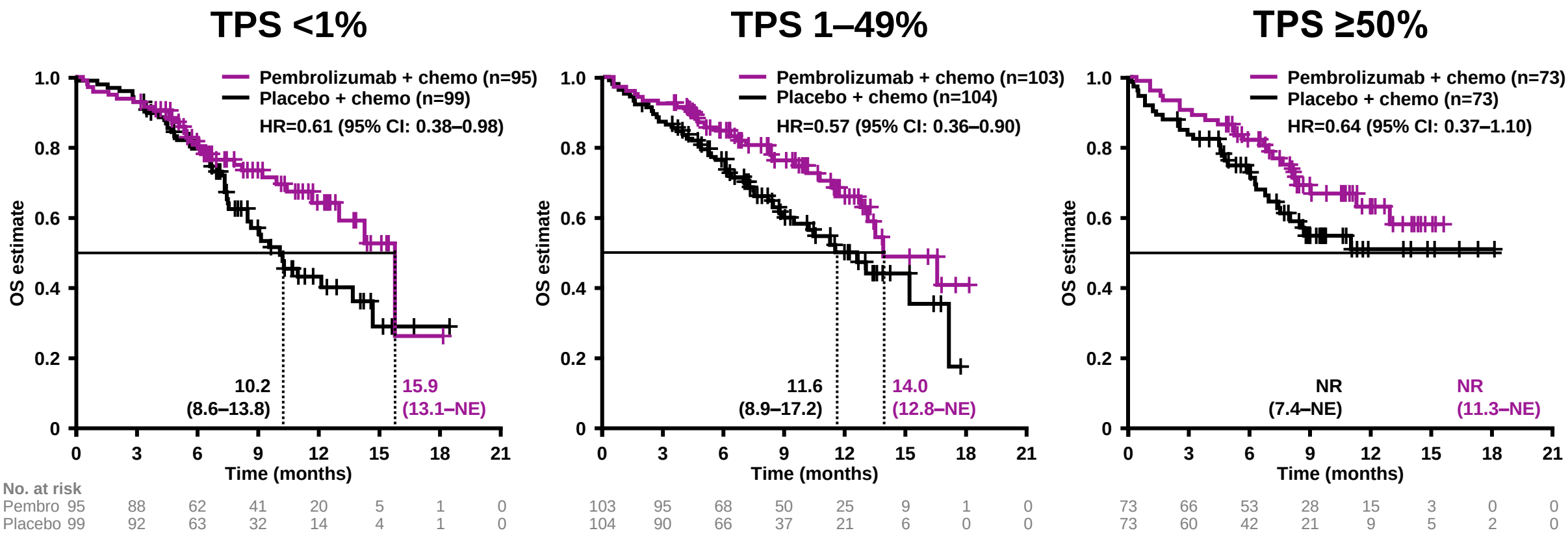
**1 Co-primary endpoints**
- PFS (central review per RECIST v1.1)
- OS

**2 Secondary endpoint**
- ORR (central review per RECIST v1.1)

Paclitaxel dose: 200 mg/m$^2$ i.v. q3w
Nab-paclitaxel dose: 100 mg/m$^2$ i.v. q1w
Carboplatin dose: AUC 6 i.v. q3w

NCT02775435

# KEYNOTE-407: OS v podskupinách

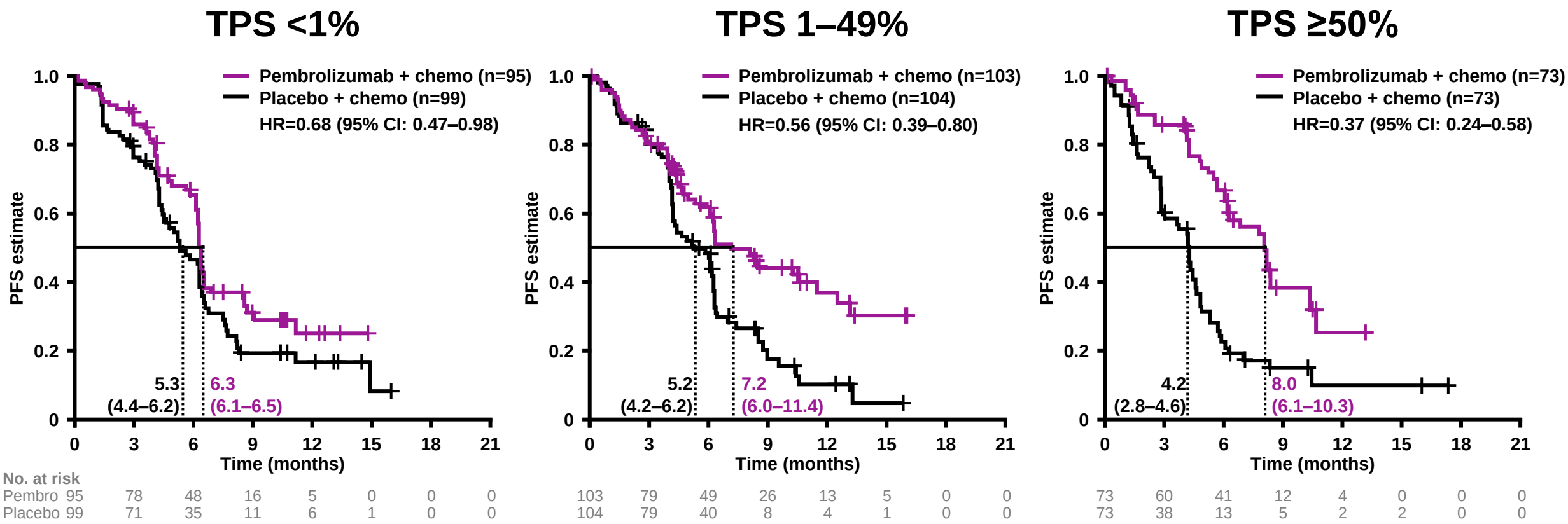



Data cutoff: 3 April 2018

**Median follow-up 7.8 months**

Paz-Ares, et al. ASCO 2018 (Abs 105); Paz-Ares, et al. N Engl J Med 2018

# KEYNOTE-407: PFS podľa PD-L1 expresie




Data cutoff: 3 April 2018

**Median follow-up 7.8 months**

Paz-Ares, et al. ASCO 2018 (Abs 105); Paz-Ares, et al. N Engl J Med 2018

# 1L NSCLC štúdie s IO

## MONOTHERAPY[1–6]

**CheckMate 026**
Nivolumab monotherapy

**KEYNOTE-024**
Pembrolizumab monotherapy

**KEYNOTE-042**
Pembrolizumab monotherapy

**MYSTIC**
Durvalumab monotherapy

**IMpower110**
Atezolizumab monotherapy

**B-FAST (cohort C)***
Atezolizumab monotherapy

**IPSOS***
Atezolizumab monotherapy

**EMPOWER-lung 1**
Cemiplimab monotherapy

## CHEMOTHERAPY COMBINATIONS[7–13]

**KEYNOTE-189**
Pembrolizumab + cisplatin/ carboplatin + pemetrexed

**IMpower150**
Atezolizumab + bevacizumab + carboplatin + paclitaxel

**IMpower130**
Atezolizumab + carboplatin + nab-paclitaxel

**CheckMate 9LA**
Nivolumab + ipilimumab + chemotherapy

**IMpower132**
Atezolizumab + cisplatin/ carboplatin + pemetrexed

**POSEIDON***
**Durvalumab + tremelimumab + chemotherapy**

**CheckMate 227**
Nivolumab + chemotherapy

## CIT + CIT COMBINATIONS[4,14]

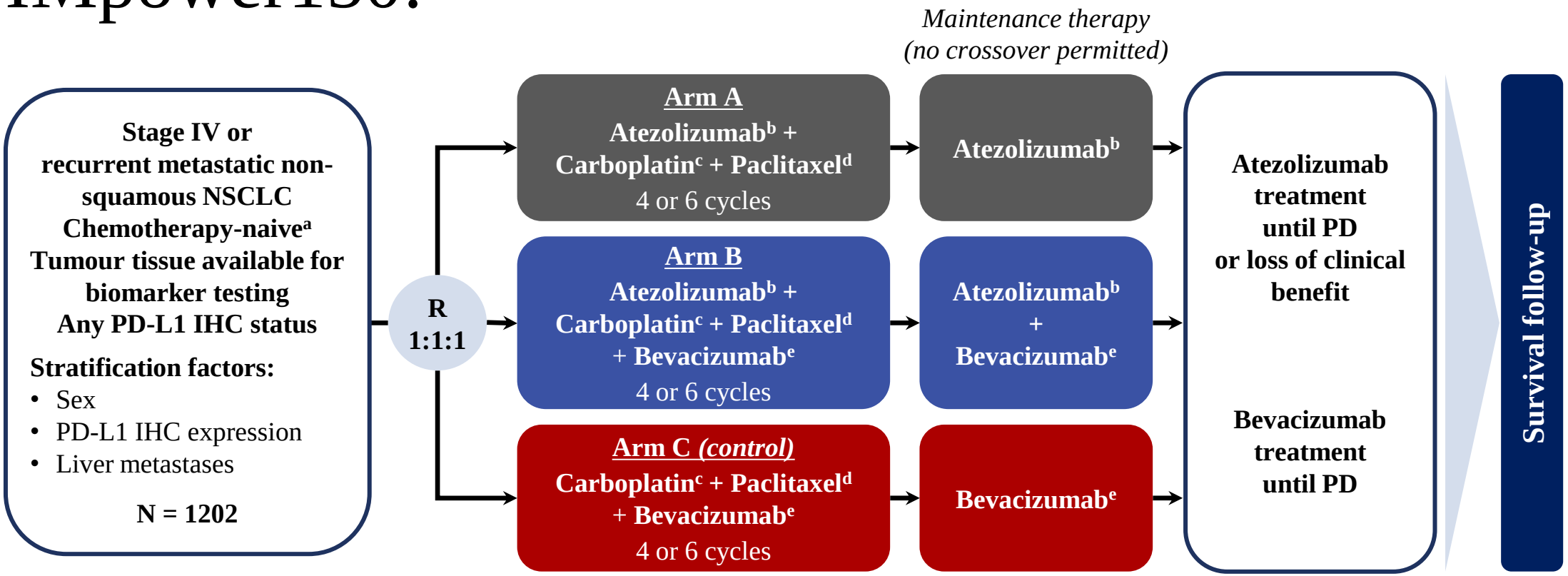
**CheckMate 227**
Nivolumab + ipilimumab

**MYSTIC**
Durvalumab + tremelimumab

- *Data not yet made public


- 1. Carbone et al. N Engl J Med 2017; 2. Reck et al. N Engl J Med 2016; 3. Mok et al. Lancet 2019; 4. Rizvi et al. JAMA Oncol 2020; 5. Spigel et al. ESMO 2019 (Abs LBA78); 6. Regeneron press release (5 November 2019)
7. Gandhi et al. N Engl J Med 2018; 8. Socinski et al. N Engl J Med 2018; 9. West et al. Lancet Oncol 2019
10. Papadimitrakopoulou et al. WCLC 2018 (Abs OA05.07); 11. Paz-Ares et al. ESMO IO 2019 (Abs LBA3); 12. Reck et al. ASCO 2020 (Abs 9501); 13. AstraZeneca press release (28 October 2019); 14. Hellmann et al. N Engl J Med 2018

# IMpower150:




a Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance to treatment with one or more approved targeted therapies.
b Atezolizumab: 1200 mg IV q3w. c Carboplatin: AUC 6 IV q3w. d Paclitaxel: 200 mg/m2 IV q3w. e Bevacizumab: 15 mg/kg IV q3w.
Socinski M, et al. *N Engl J Med,* 2018.

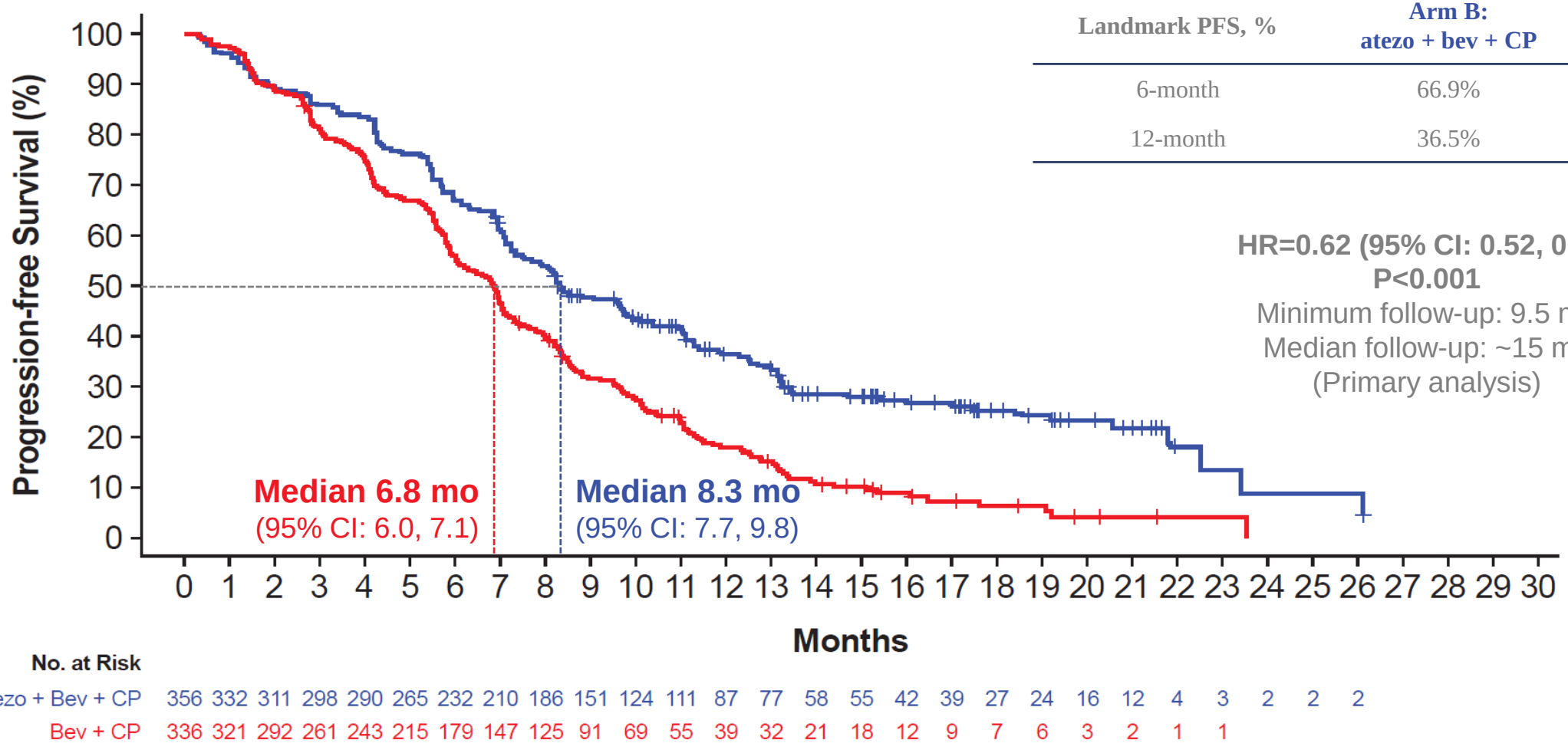
# Imunomodulácia v kombinácii s anti-VEGF+chemoterapiou

- Anti-VEGF liečba :
  - normalizácia vaskulatúry v tumore a tým vyšší prienik lymfocytov do nádoru
- ↑ Infiltracia proliferujúcich CD8+ T a myeloidných bb

- Anti-VEGF liečba antagonizuje imunosupresívny efekt VEGF
- ↑ anti-tumorovú imunitnú odpoveď

# IMpower150: PFS (rameno B vs rameno C u ITT-WT)

| Landmark PFS, % | Arm B: atezo + bev + CP | Arm C: bev + CP |
|---|---|---|
| 6-month | 66.9% | 56.1% |
| 12-month | 36.5% | 18.0% |



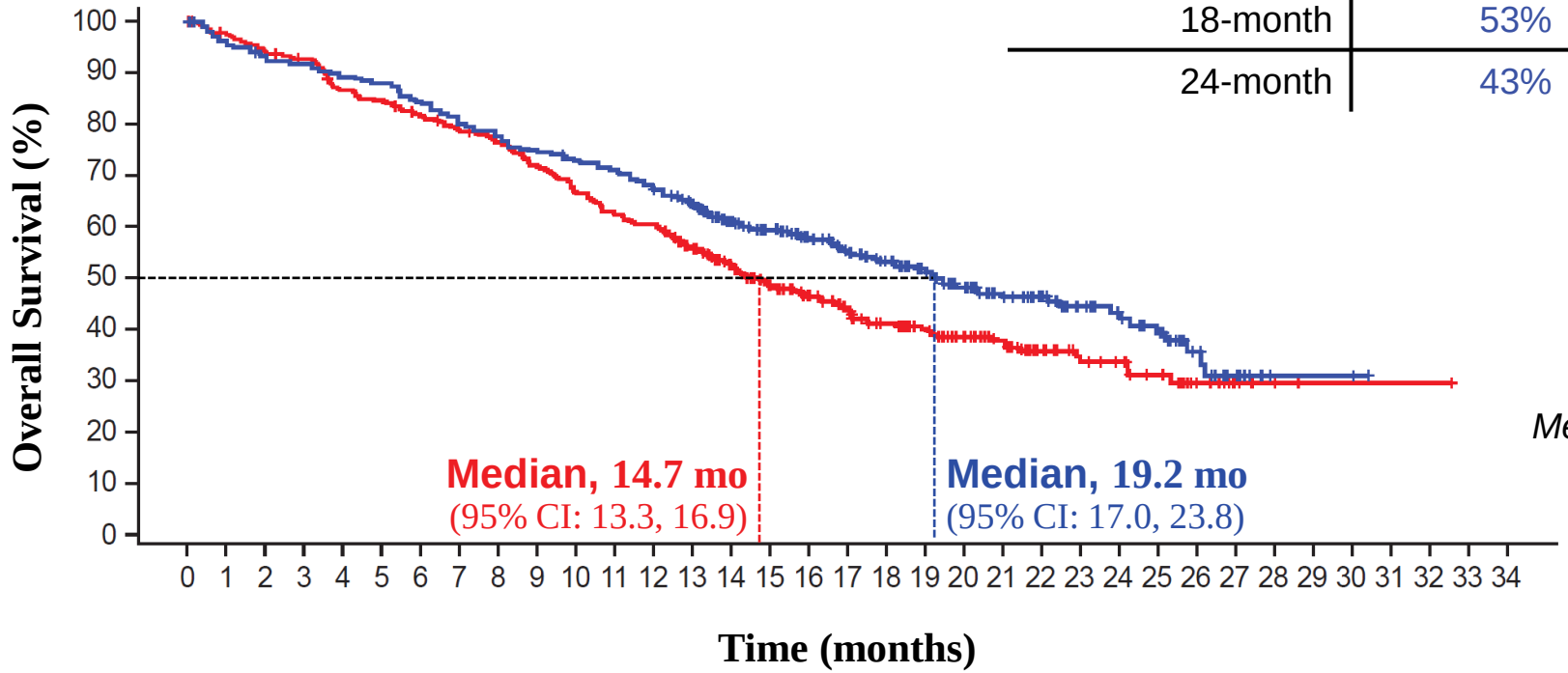

**HR=0.62 (95% CI: 0.52, 0.74)**
**P<0.001**
Minimum follow-up: 9.5 mo
Median follow-up: ~15 mo
(Primary analysis)

- **Data cut-off: 15 September, 2017.**
- WT: wildtype (excluding EGFR+/ALK+).


- 1. Socinski et al. N Engl J Med 2018
  2. Socinski et al. ASCO 2018 (9002)

# IMpower150: Signifikatne dlhšie OS pri pridaní atezolizumabu u ITT-WT (rameno B vs rameno C)

| Landmark OS, % | Arm B: atezo + bev + CP | Arm C: bev + CP |
|---|---|---|
| 12-month | 67% | 61% |
| 18-month | 53% | 41% |
| 24-month | 43% | 34% |



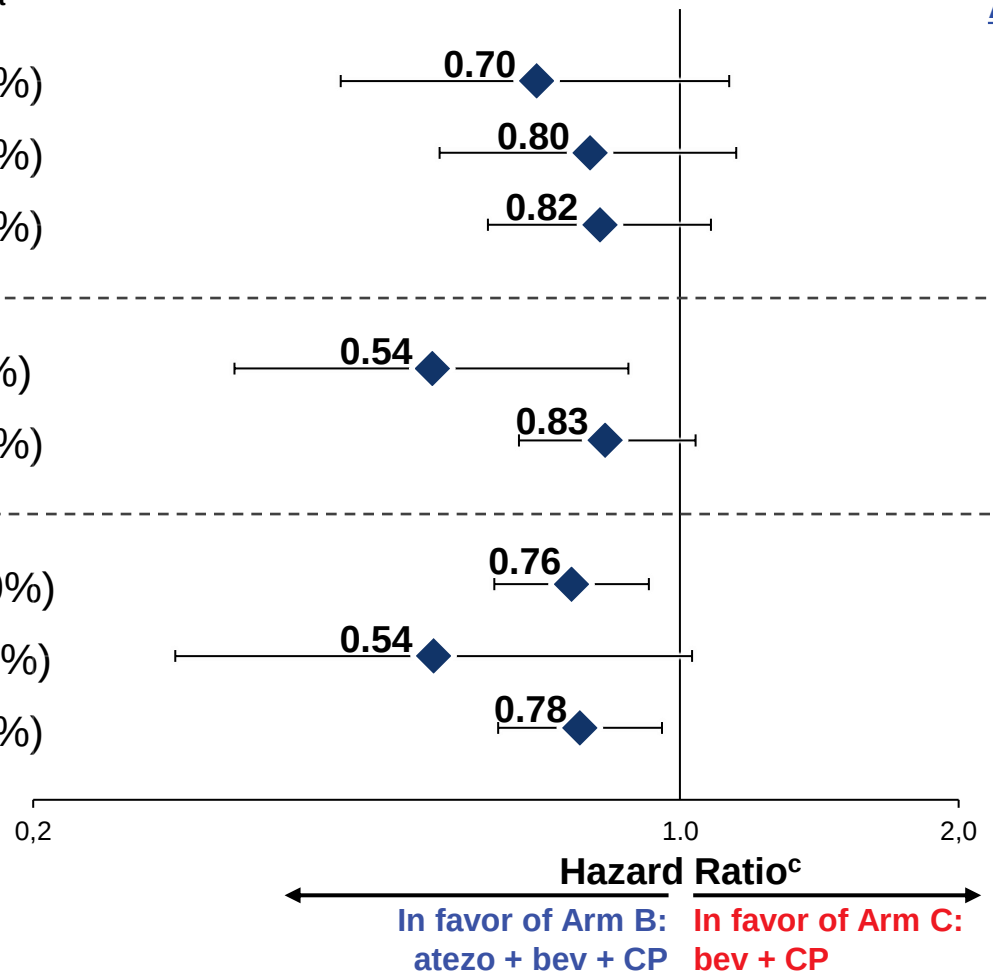

**HR[a], 0.78**
**(95% CI: 0.64, 0.96)**
***P* = 0.02**
*Median follow-up: ~20 mo*

| No. at Risk | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Atezo+Bev+CP | 359 | 339 | 328 | 323 | 314 | 310 | 296 | 284 | 273 | 264 | 256 | 250 | 235 | 218 | 188 | 167 | 147 | 133 | 119 | 103 | 84 | 66 | 57 | 41 | 34 | 28 | 16 | 9 | 2 | 2 | 2 |
| Bev+CP | 337 | 326 | 315 | 308 | 287 | 280 | 268 | 255 | 247 | 233 | 216 | 203 | 196 | 174 | 152 | 129 | 115 | 101 | 87 | 77 | 66 | 56 | 40 | 32 | 29 | 22 | 13 | 6 | 3 | 1 | 1 | 1 | 1 |

a Stratified HR.
Data cutoff: January 22, 2018
Socinski M, et al. *N Engl J Med,* 2018. Socinski M, et al. ASCO 2018. 9002.

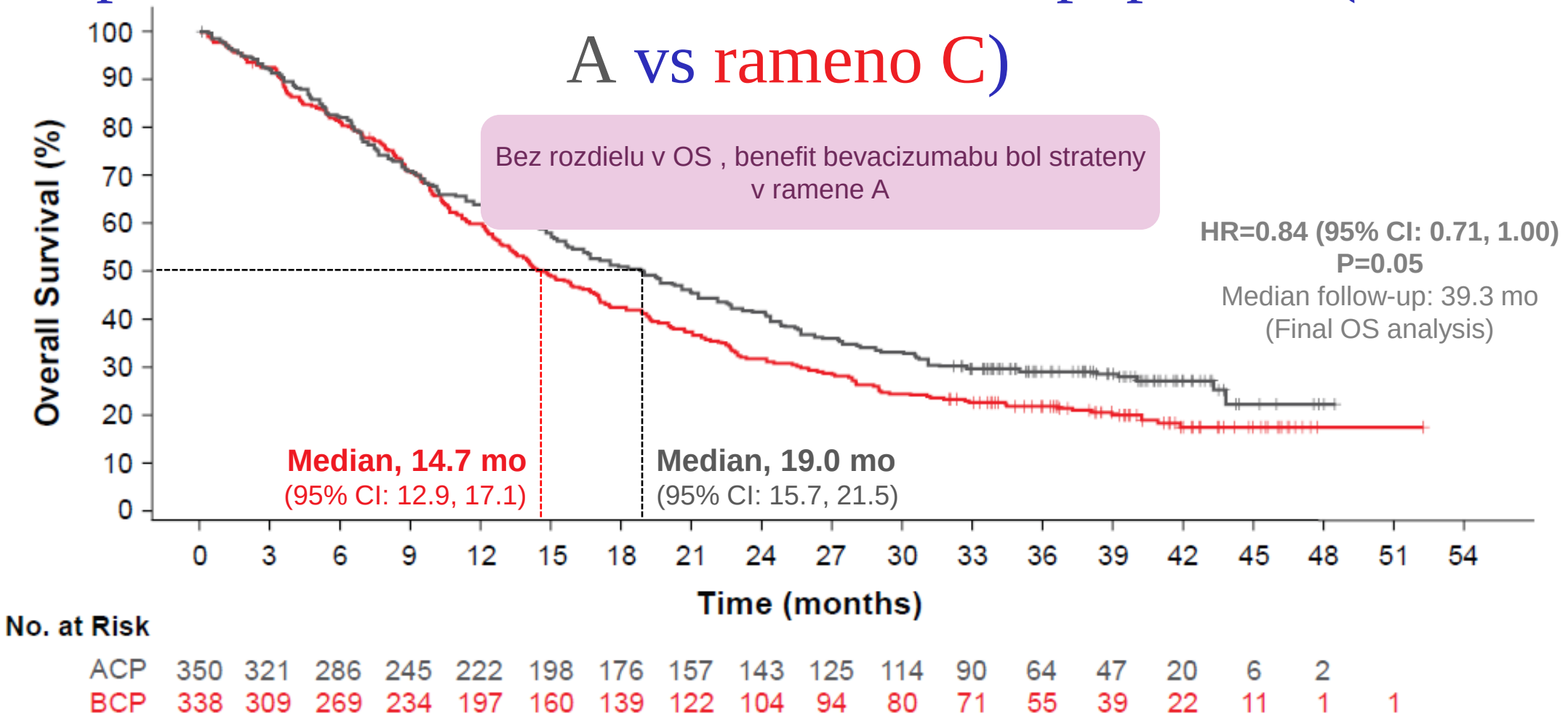
# IMpower150: OS v najdôležitejších podskupinách (rameno B vs rameno C)

| Subgroup | n (%)[a] | Median OS, mo | |
|---|---|---|---|
| | | Arm B | Arm C |
| PD-L1–High (TC3 or IC3) WT | 136 (20%) | 25.2 | 15.0 |
| PD-L1–Low (TC1/2 or IC1/2) WT | 226 (32%) | 20.3 | 16.4 |
| PD-L1–Negative (TC0 and IC0) WT | 339 (49%) | 17.1 | 14.1 |
| Liver Metastases WT | 94 (14%) | 13.2 | 9.1 |
| No Liver Metastases WT | 602 (86%) | 19.8 | 16.7 |
| ITT (including *EGFR/ALK*+) | 800 (100%) | 19.8 | 14.9 |
| *EGFR/ALK*+ only | 104[b] (13%) | NE | 17.5 |
| ITT-WT | 696 (87%) | 19.2 | 14.7 |




NE, not estimable.
a Prevalence % for PD-L1 IHC and liver metastases subgroups out of ITT-WT (n=696); prevalence of ITT, *EGFR/ALK*+, and ITT-WT out of ITT (n=800).
b One patient had *EGFR* exon 19 deletion and also tested *ALK* positive per central lab.
c Stratified HR for ITT and ITT-WT; unstratified HR for all other subgroups. Data cutoff: January 22, 2018. Socinski M, et al. ASCO 2018. 9002.

# IMpower150: Finálne OS v ITT-WT populácii (rameno A vs rameno C)

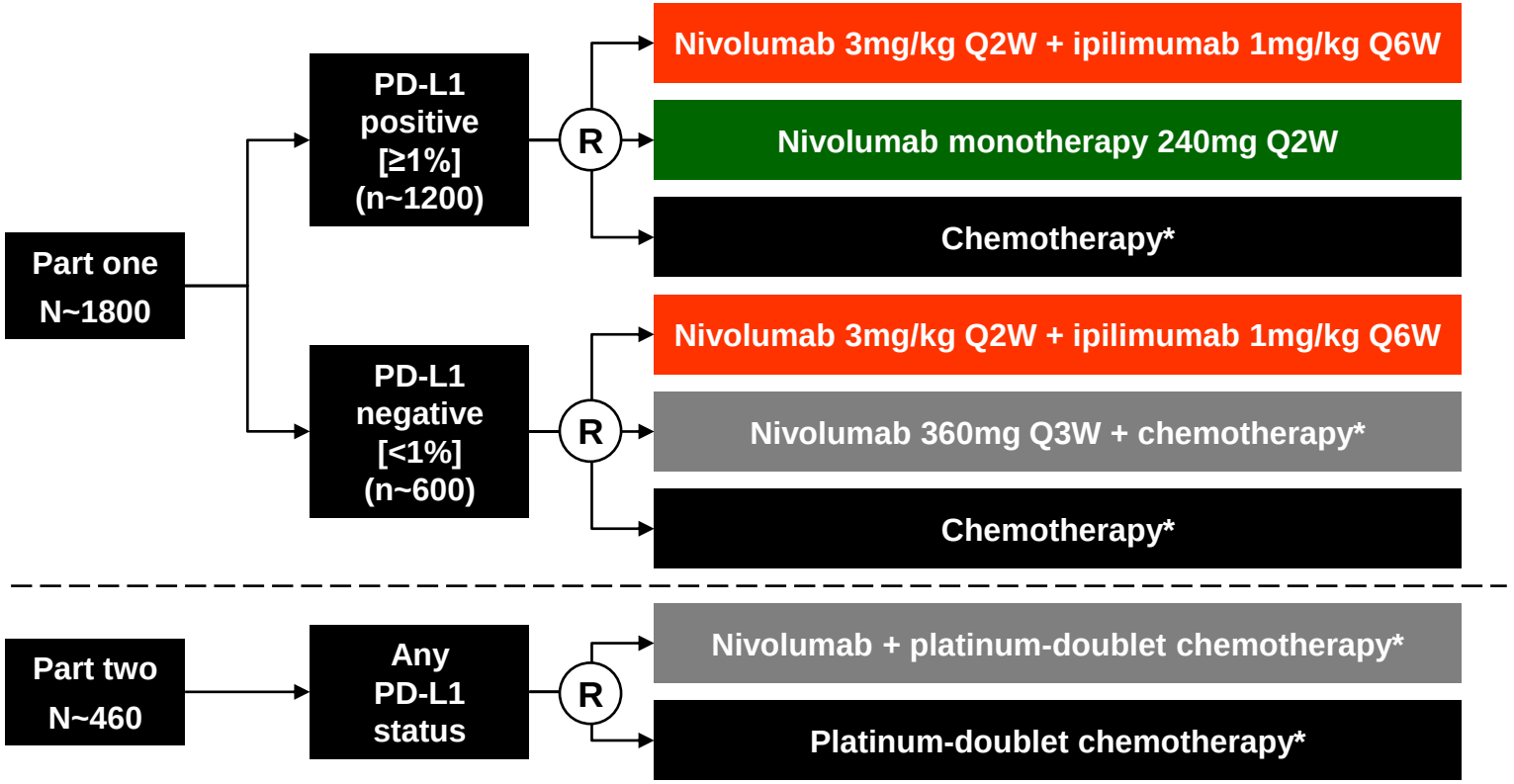



- **Data cut-off: 13 September, 2019.**

- Socinski et al. AACR 2020 (CT216)

# CheckMate 227: IPI+NIVO

- Stage IV or recurrent NSCLC
- No prior systemic therapy for advanced or metastatic disease
- No *EGFR/ALK* mutations sensitive to available targeted inhibitor therapy
- Squamous or non-squamous disease
- No untreated brain metastases
- ECOG PS 0–1
- PD-L1 status known




**1 Co-primary endpoints**

- PFS u high TMB (≥10mut/Mb)
- OS in PD-L1 TC ≥1%

**2 Secondary endpoints**

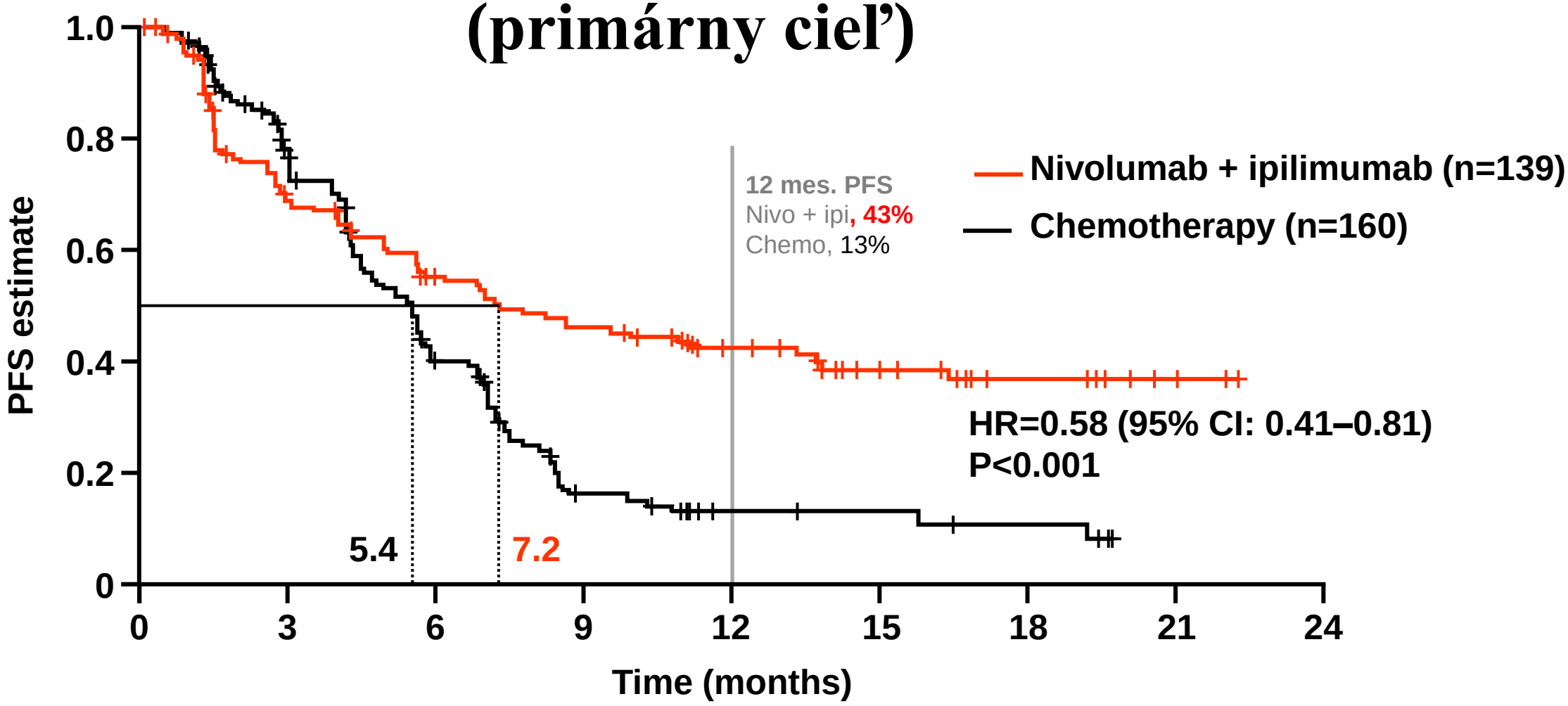
- ORR
- Disease-related symptom improvement by week 12

*In all arms, selection of chemotherapy is based on histology

NCT02477826

Paz-Ares, et al. AACR 2017 (Abs 144TiP)

# CheckMate 227: PFS (TMB high) (primárny cieľ)




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab | 139 | 85 | 66 | 55 | 36 | 24 | 11 | 3 | 0 |
| Chemotherapy | 160 | 103 | 51 | 17 | 7 | 6 | 4 | 0 | 0 |

Median PFS for low TMB (<10mut/Mb): 3.2 months for nivo + ipi vs 5.5 months for chemotherapy (HR 1.07; 95% CI: 0.84–1.35)

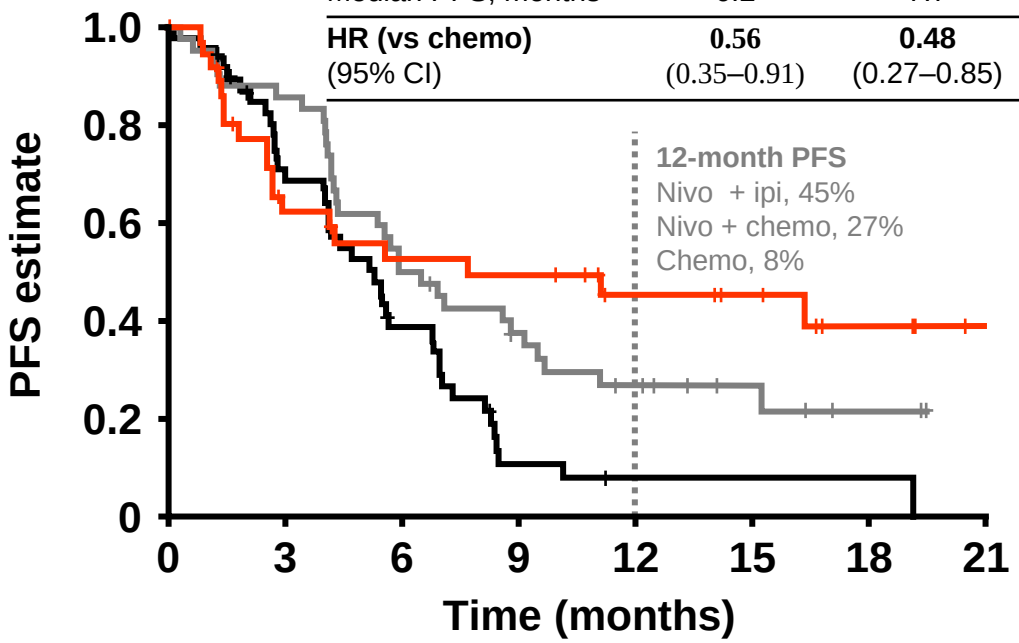
**Minimum follow-up 11.2 months**

Hellmann, et al. N Engl J Med 2018

# CheckMate 227: PFS podl'a TMB (PD-L1 TC <1%)

## TMB ≥10mut/Mb and <1% tumour PD-L1 expression

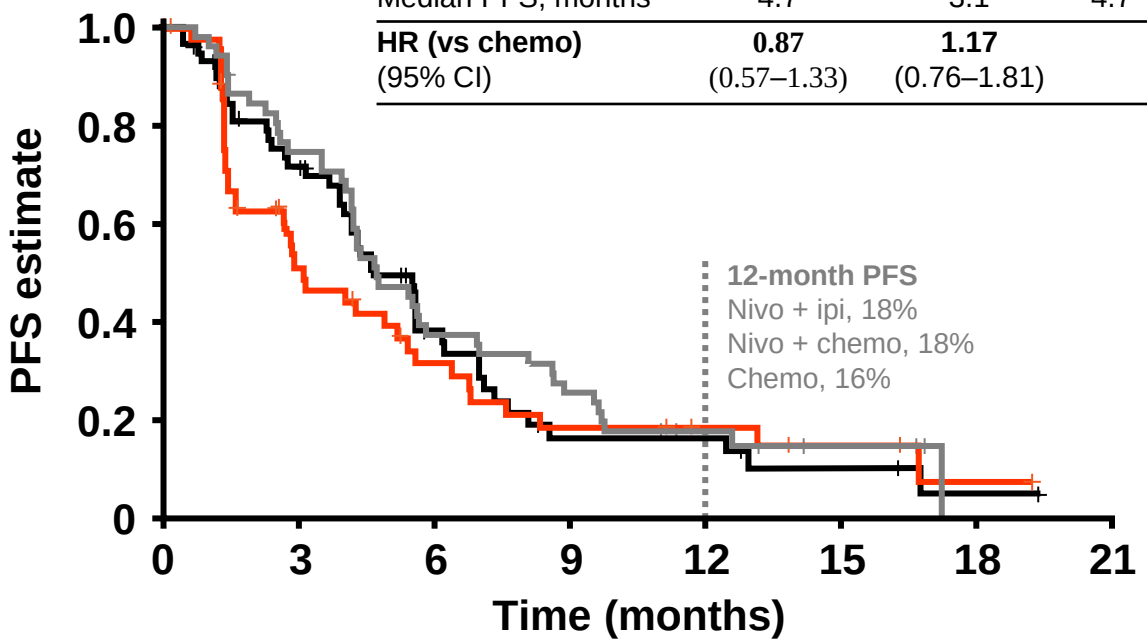
| | Nivo + chemo (n=43) | Nivo + ipi (n=38) | Chemo (n=48) |
|---|---|---|---|
| Median PFS, months | 6.2 | 7.7 | 5.3 |
| **HR (vs chemo)** (95% CI) | **0.56** (0.35–0.91) | **0.48** (0.27–0.85) | |




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Nivo + chemo | 43 | 36 | 21 | 14 | 9 | 5 | 2 | 0 |
| Nivo + ipi | 38 | 20 | 16 | 15 | 10 | 8 | 4 | 1 |
| Chemo | 48 | 30 | 16 | 4 | 1 | 1 | 1 | 0 |

## TMB <10mut/Mb and <1% tumour PD-L1 expression

| | Nivo + chemo (n=54) | Nivo + ipi (n=52) | Chemo (n=59) |
|---|---|---|---|
| Median PFS, months | 4.7 | 3.1 | 4.7 |
| **HR (vs chemo)** (95% CI) | **0.87** (0.57–1.33) | **1.17** (0.76–1.81) | |




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Nivo + chemo | 54 | 38 | 19 | 13 | 6 | 3 | 0 | 0 |
| Nivo + ipi | 52 | 22 | 12 | 7 | 5 | 3 | 1 | 0 |
| Chemo | 59 | 39 | 16 | 6 | 6 | 3 | 1 | 0 |

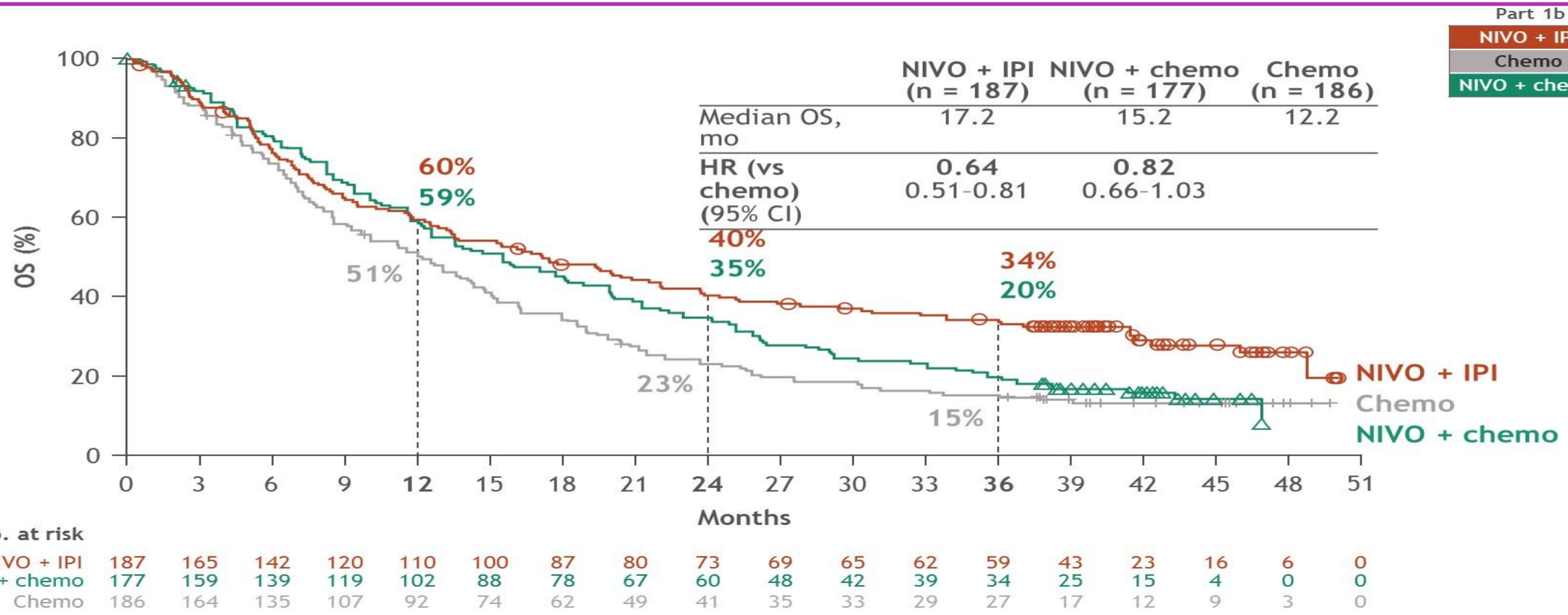
**Minimum follow-up 11.2 months**

Borghaei, et al. ASCO 2018 (Abs 9001)

# ASCO 2020



## 3-year update: OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1 < 1%)



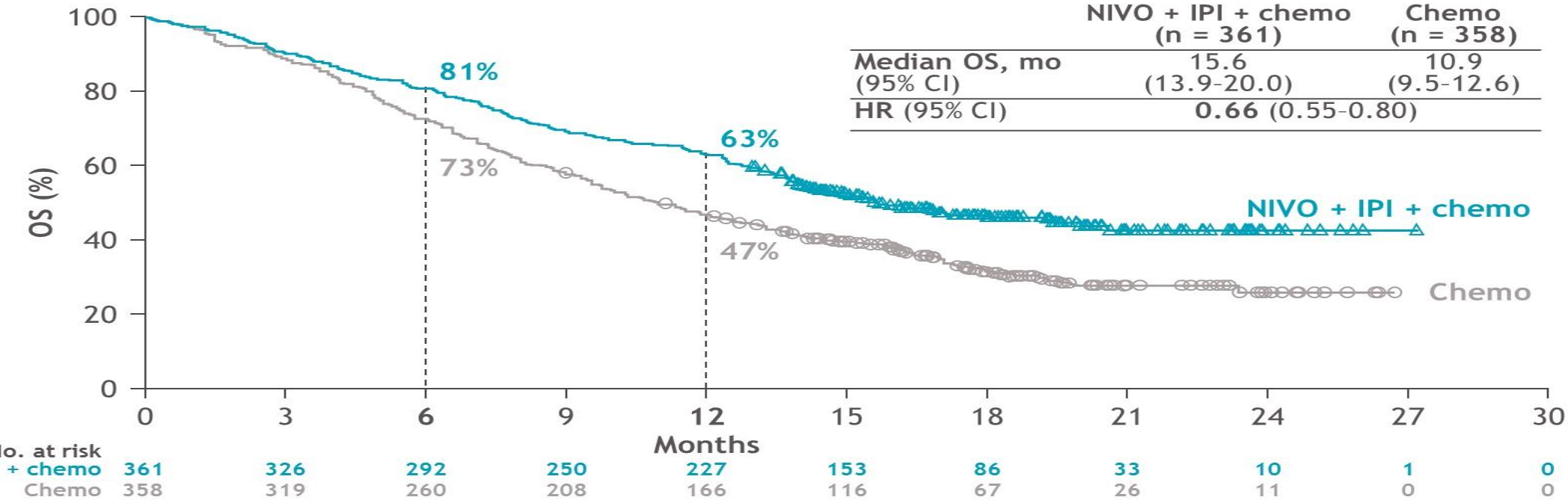

**Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.**

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

# CheckMate 9LA: Nivo+IPI+ 2 cykly chemo v 1.línii NSCLC



## Primary endpoint (updated): Overall survival[a]




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

**Minimum follow-up: 12.7 months.**

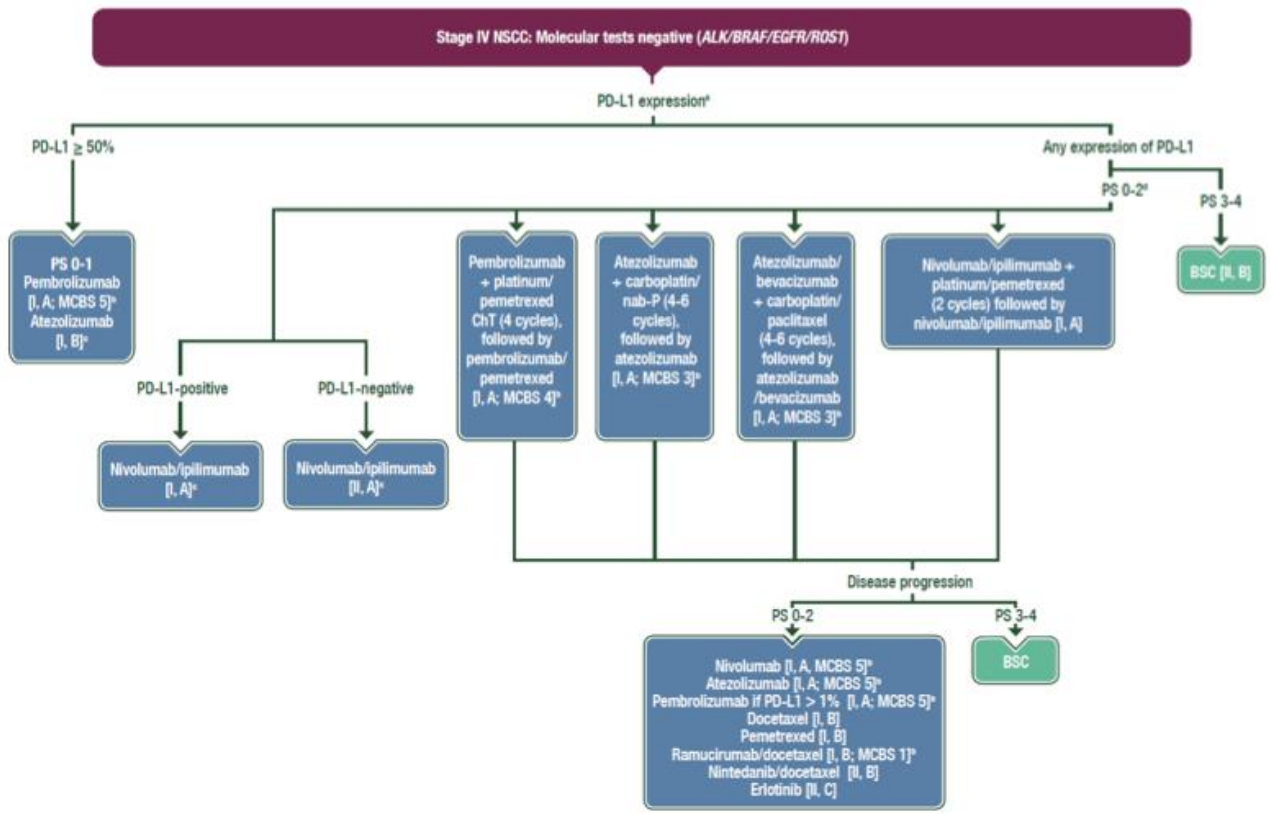
[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively



Presented By Benjamin Levy at TBD

# Závery u NSCLC

- **imunoterapia nový štandart u väčšiny pct s NSCLC v 1.línii**
  - *KEYNOTE-024, IMpower150, KEYNOTE-189,IMpower130, CheckMate 227,KEYNOTE-407 a IMpower131*
- hľadanie vhodnejších prediktívnych faktorov
  - najsilnejšia validita pre PD-L1 expresiu
  - NGS, RNA sekvenácia, vyšetrenie plazmatických vzoriek
- presun do skorších štádii?


Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)
PD-L1 expression[a]
PD-L1 ≥ 50%
Any expression of PD-L1
PS 0-2[a]
PS 3-4
PS 0-1
Pembrolizumab
[I, A; MCBS 5][a]
Atezolizumab
[I, B][a]
Pembrolizumab + platinum/ pemetrexed ChT (4 cycles), followed by pembrolizumab/ pemetrexed
[I, A; MCBS 4][a]
Atezolizumab + carboplatin/ nab-P (4-6 cycles), followed by atezolizumab
[I, A; MCBS 3][a]
Atezolizumab/ bevacizumab + carboplatin/ paclitaxel (4-6 cycles), followed by atezolizumab /bevacizumab
[I, A; MCBS 3][a]
Nivolumab/ipilimumab + platinum/pemetrexed (2 cycles) followed by nivolumab/ipilimumab [I, A]
BSC [II, B]
PD-L1-positive
PD-L1-negative
Nivolumab/ipilimumab
[I, A][a]
Nivolumab/ipilimumab
[II, A][a]
Disease progression
PS 0-2
PS 3-4
Nivolumab [I, A, MCBS 5][a]
Atezolizumab [I, A; MCBS 5][a]
Pembrolizumab if PD-L1 > 1% [I, A; MCBS 5][a]
Docetaxel [I, B]
Pemetrexed [I, B]
Ramucirumab/docetaxel [I, B; MCBS 1][a]
Nintedanib/docetaxel [II, B]
Erlotinib [II, C]
BSC

# ĎAKUJEM ZA POZORNOSŤ!