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# LUNG CANCER UPDATES

## ESMO HIGHLIGHTS

**27 SEPTIEMBRE - 1 OCTUBRE 2019**


Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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BARCELONA

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# Inmunoterapia (I)

Dr. Óscar Juan-Vidal

Con la colaboración de:

Bristol-Myers Squibb

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Lilly

# IMpower110: Interim OS Analysis of a phase III Study of Atezolizumab vs Platinum-based CT as 1L Tx in PD-L1-sledted NSCLC

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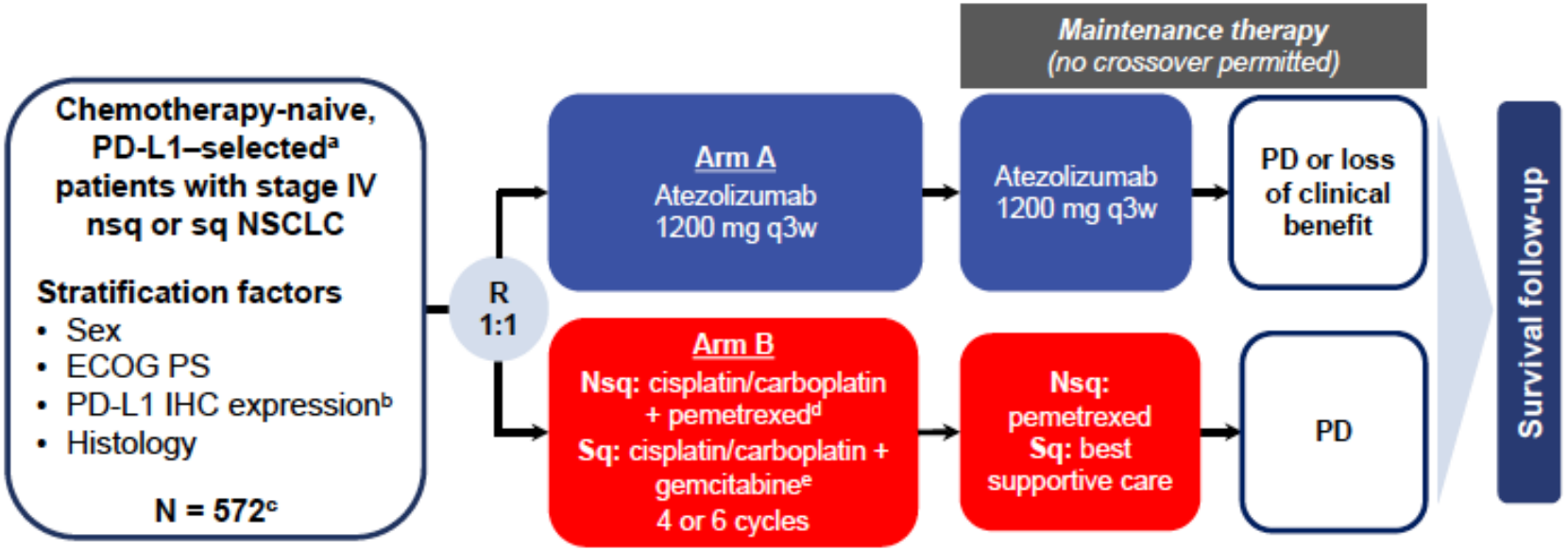
## IMpower110 Study Design




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

IC, tumour-infiltrating immune cells; IHC, immunohistochemistry; nsq, non-squamous; PD, progressive disease; q3w, every 3 weeks; R, randomised; sq, squamous; TC, tumour cells; WT, wild-type. [a] PD-L1 expression (VENTANA SP142 IHC assay) ≥ 1% on TC or IC. [b] TC1/2/3 and any IC vs TC0 and IC1/2/3. [c] 554 patients in the WT population. [d] Cisplatin 75 mg/m² or carboplatin area under the curve (AUC) 6 + pemetrexed 500 mg/m² IV q3w. [e] Cisplatin 75 mg/m² + gemcitabine 1250 mg/m² or carboplatin AUC 5 + gemcitabine 1000 mg/m² IV q3w. [f] WT population excludes patients with *EGFR*+ and/or *ALK*+ NSCLC.

Spigel et al. IMpower110 Interim OS Analysis https://bit.ly/2lxRNHQ

# Statistical Testing Plan

**Arm A vs Arm B**
OS IA in TC3 or IC3 WT
n = 205

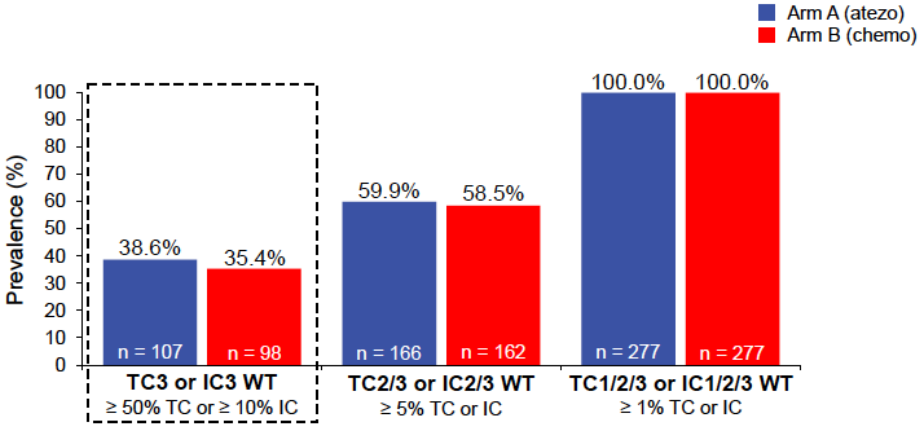
↓

**Arm A vs Arm B**
OS IA in TC2/3 or IC2/3 WT
n = 328

↓

**Arm A vs Arm B**
OS IA in TC1/2/3 or IC1/2/3 WT
n = 554

## Prevalence of PD-L1 Expression



# OS: TC3 or IC3 WT

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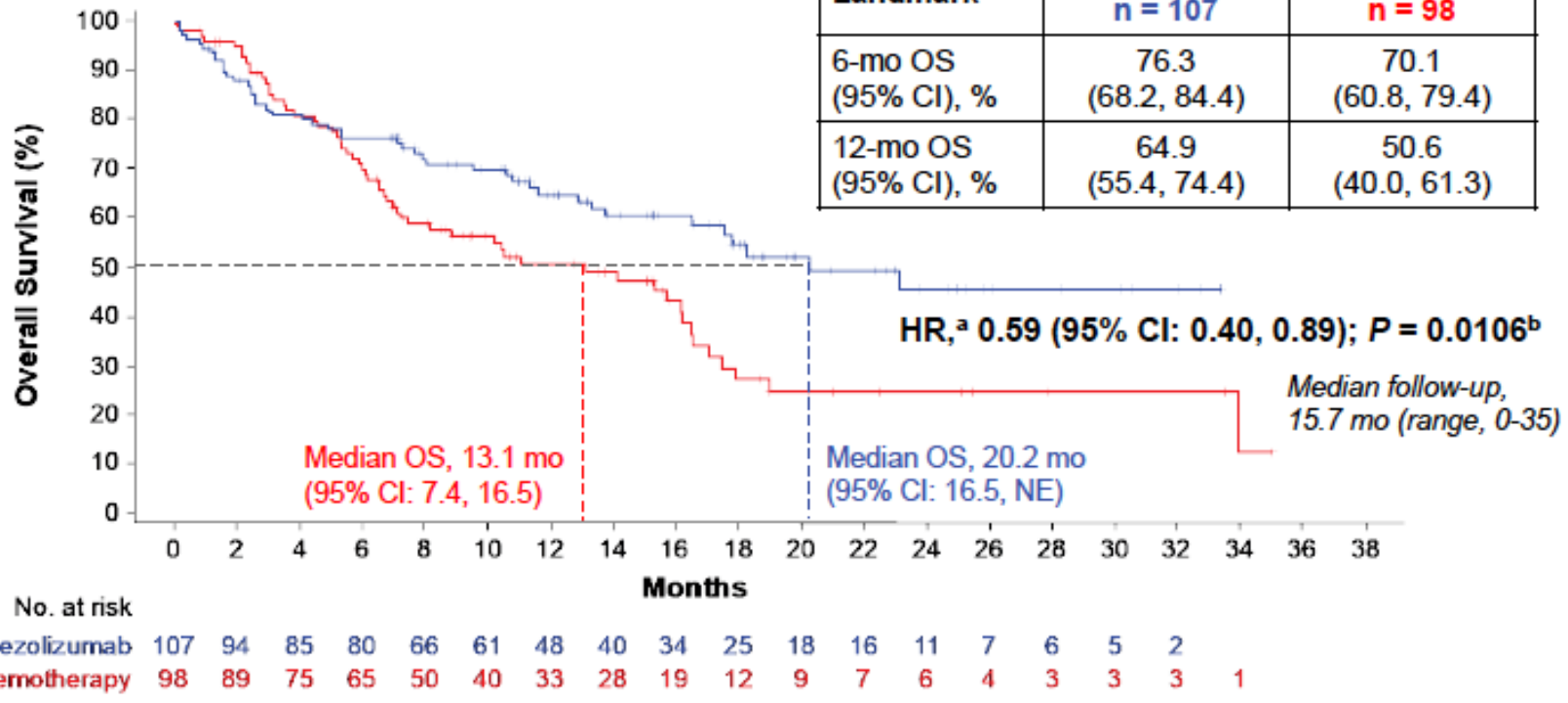
| Landmark | Arm A (atezo) n = 107 | Arm B (chemo) n = 98 |
|---|---|---|
| 6-mo OS (95% CI), % | 76.3 (68.2, 84.4) | 70.1 (60.8, 79.4) |
| 12-mo OS (95% CI), % | 64.9 (55.4, 74.4) | 50.6 (40.0, 61.3) |



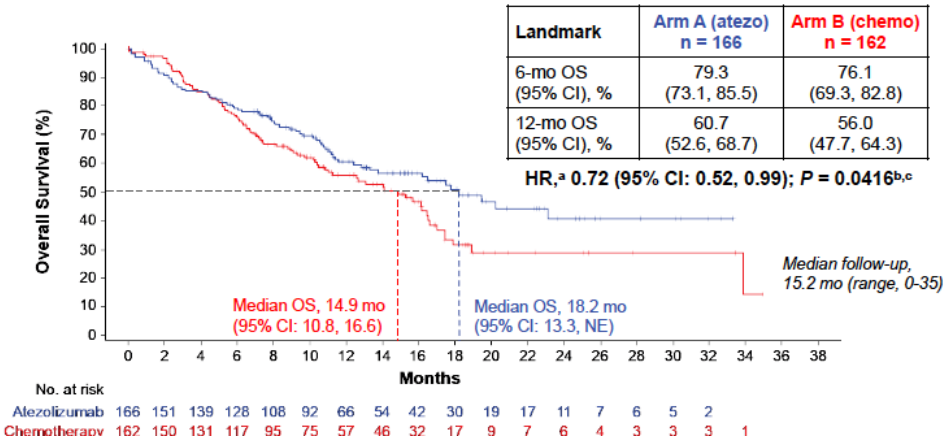

NE, not estimable. * Stratified. [b] Stratified log-rank.
Data cutoff: 10 September 2018.

Spigel et al. IMpower110 Interim OS Analysis
https://bit.ly/2IxRNHQ

# IMpower110: Interim OS Analysis of a phase III Study of Atezolizumab vs Platinum-based CT as 1L Tx in PD-L1-sledted NSCLC



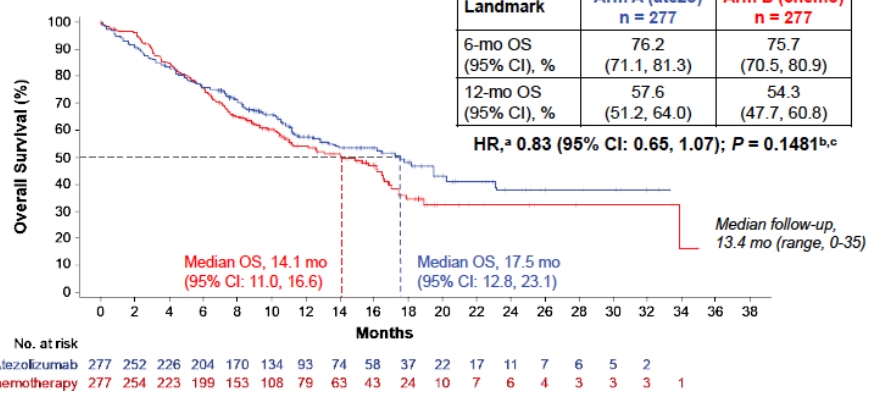
## OS: TC2/3 or IC2/3 WT




| Landmark | Arm A (atezo) n = 166 | Arm B (chemo) n = 162 |
|---|---|---|
| 6-mo OS (95% CI), % | 79.3 (73.1, 85.5) | 76.1 (69.3, 82.8) |
| 12-mo OS (95% CI), % | 60.7 (52.6, 68.7) | 56.0 (47.7, 64.3) |

HR,[a] 0.72 (95% CI: 0.52, 0.99); *P* = 0.0416[b,c]

## OS: TC1/2/3 or IC1/2/3 WT




| Landmark | Arm A (atezo) n = 277 | Arm B (chemo) n = 277 |
|---|---|---|
| 6-mo OS (95% CI), % | 76.2 (71.1, 81.3) | 75.7 (70.5, 80.9) |
| 12-mo OS (95% CI), % | 57.6 (51.2, 64.0) | 54.3 (47.7, 60.8) |

HR,[a] 0.83 (95% CI: 0.65, 1.07); *P* = 0.1481[b,c]

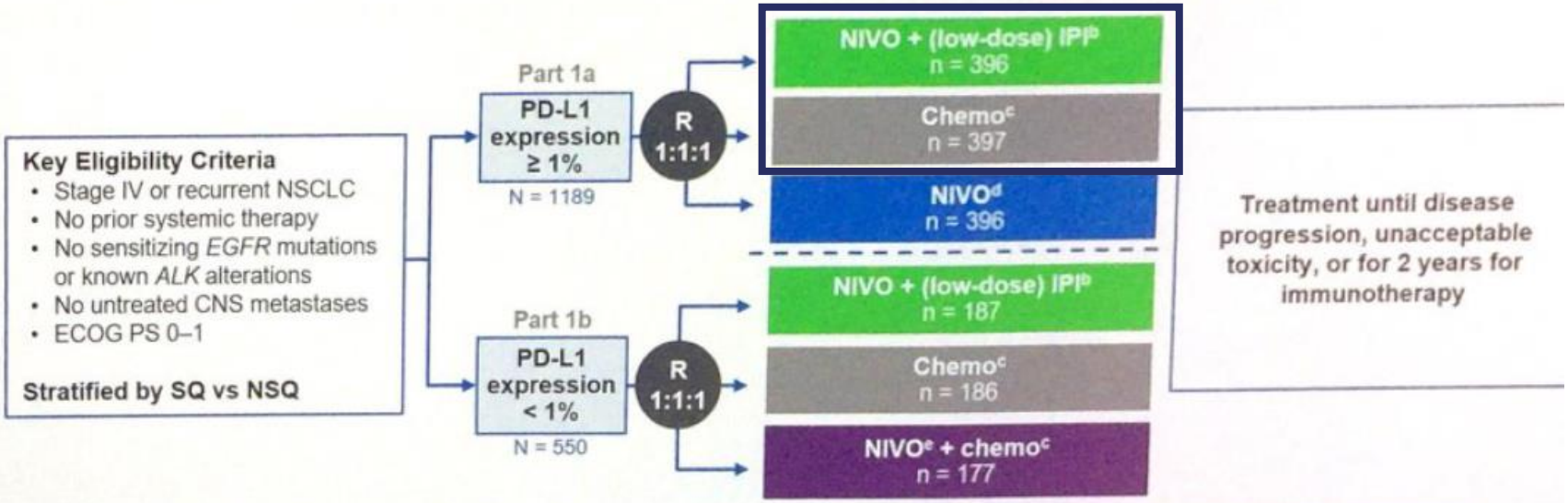
# Subsequent therapies

| | TC1/2/3 or IC1/2/3 WT | |
|---|---|---|
| | Arm A (atezo) n = 277 | Arm B (chemo) n = 277 |
| Patients with ≥ 1 therapy, n (%) | 82 (29.6) | 137 (49.5) |
| Chemotherapy | 77 (27.8) | 68 (24.5) |
| Immunotherapy | 7 (2.5) | 80 (28.9) |
| Targeted therapy | 14 (5.1) | 12 (4.3) |

# LBA4_PR - Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced NSCLC: CheckMate 227 part 1 final analysis



## CheckMate 227 Part 1 Study Design[a]




**Independent co-primary endpoints: NIVO + IPI vs chemo**
- PFS in high TMB (≥10 mut/Mb) population[f]
- OS in PD-L1 ≥ 1% population[g]

**Secondary endpoints (PD-L1 hierarchy):**
- PFS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO + chemo vs chemo** in PD-L1 < 1%
- OS: **NIVO vs chemo** in PD-L1 ≥ 50%

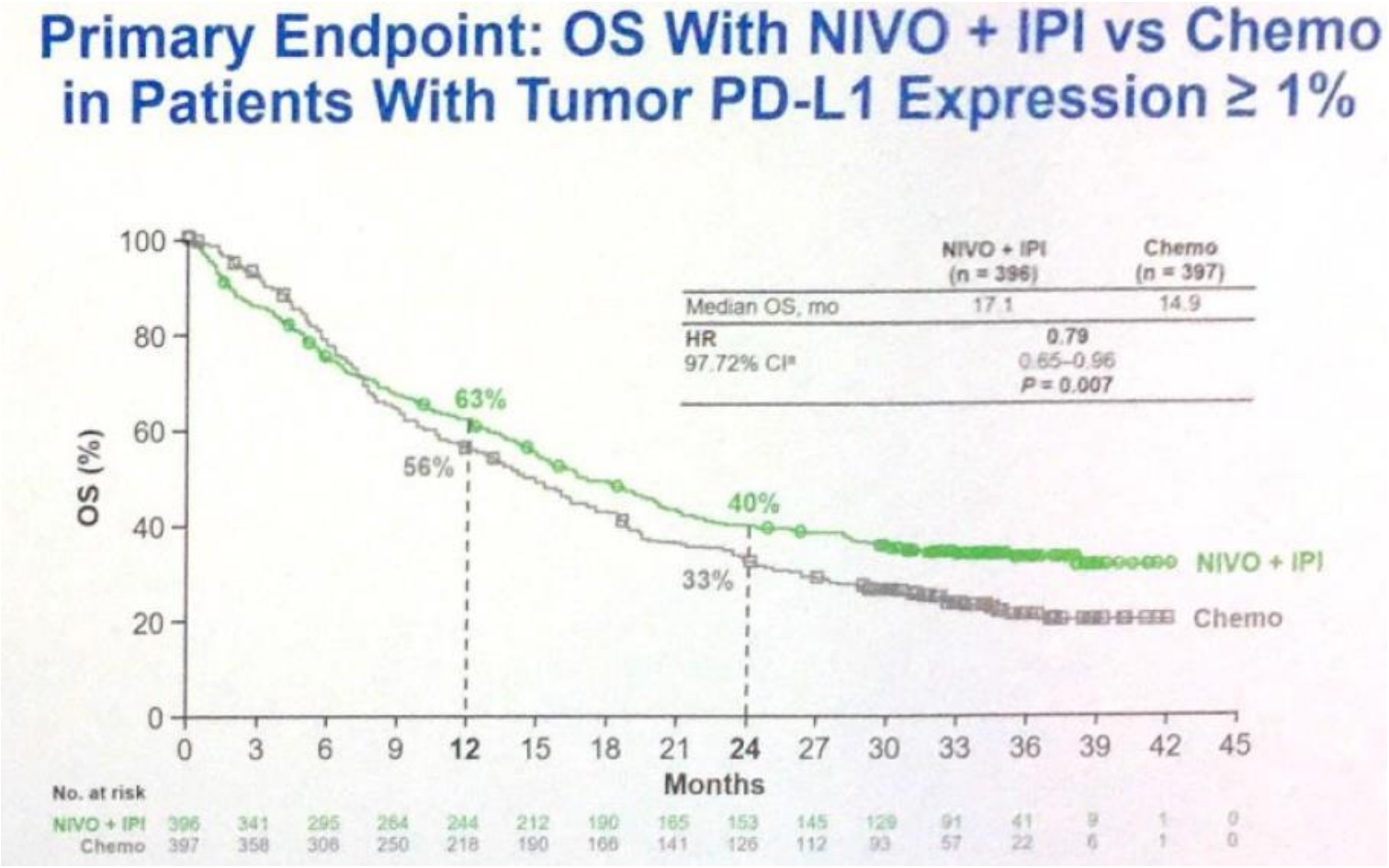
Database lock: July 2, 2019; **minimum follow-up for primary endpoint: 29.3 months**

[a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]TMB primary endpoint analysis conducted at January 24, 2018 database lock in subset of patients randomized to NIVO + IPI or chemo; alpha allocated was 0.025; [g]Alpha allocated was 0.025 overall (0.023 for final analysis)

# LBA4_PR - Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced NSCLC: CheckMate 227 part 1 final analysis

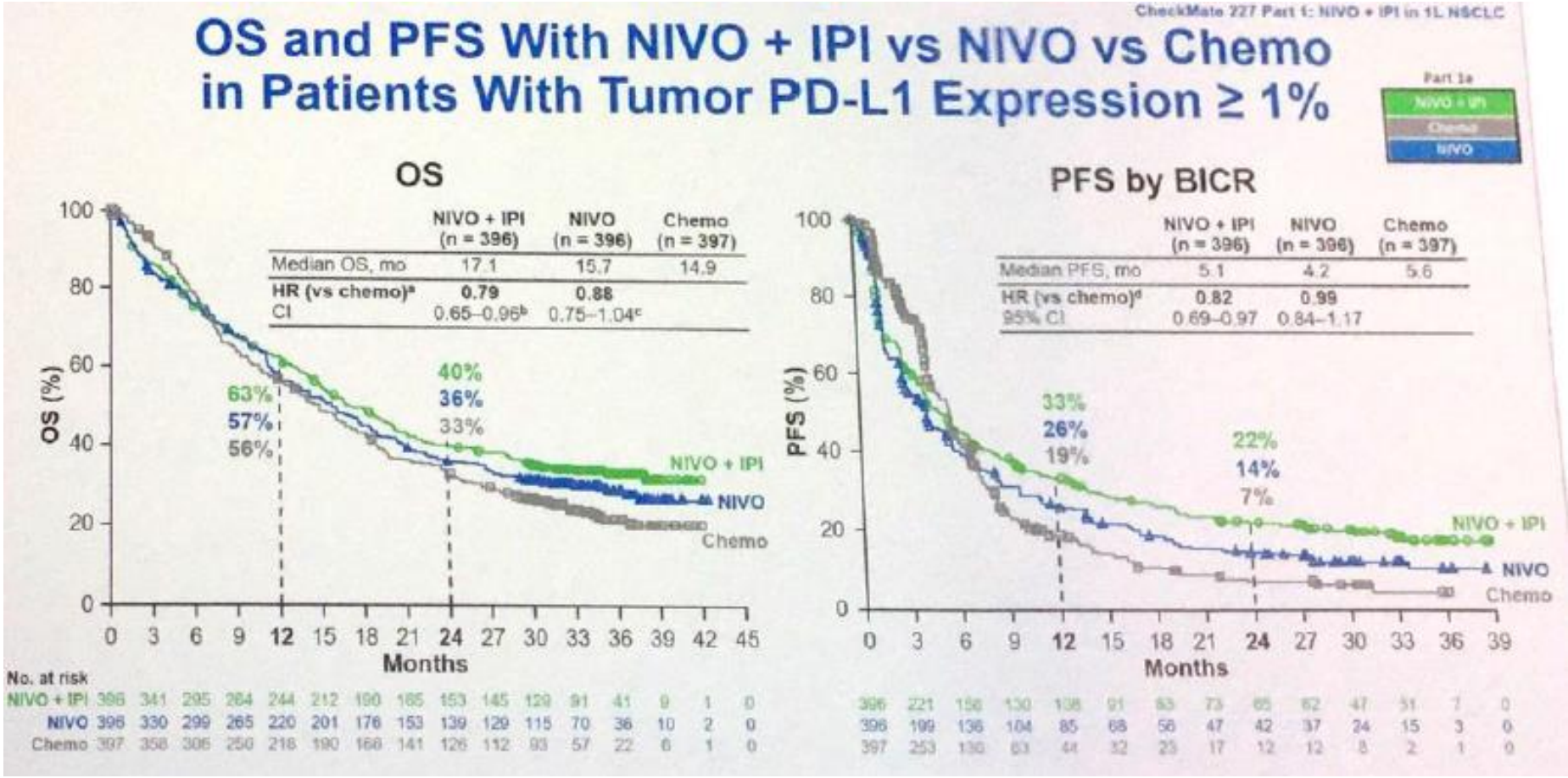


## Primary Endpoint: OS With NIVO + IPI vs Chemo in Patients With Tumor PD-L1 Expression ≥ 1%



# LBA4_PR - Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced NSCLC: CheckMate 227 part 1 final analysis



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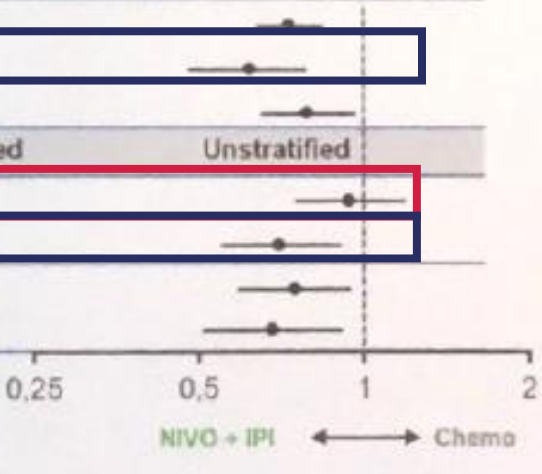
# LBA4_PR - Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced NSCLC: CheckMate 227 part 1 final analysis



## OS for NIVO + IPI vs Chemo by Tumor PD-L1 Expression, TMB Status, and Combined Subgroups in All Randomized Patients

| | | Median OS, months NIVO + IPI n = 583 | Chemo n = 583 | HR | HR (95% CI) |
|---|---|---|---|---|---|
| **Randomized groups** | | | | Stratified | Stratified |
| | All randomized (N = 1166) | 17.1 | 13.9 | 0.73 | |
| PD-L1 | PD-L1 < 1% (n = 373) | 17.2 | 12.2 | 0.62 | |
| | PD-L1 ≥ 1% (n = 793) | 17.1 | 14.9 | 0.79[b] | |
| **Additional exploratory subgroups analyses[b,c]** | | | | Unstratified | Unstratified |
| PD-L1 | 1–49% (n = 396) | 15.1 | 15.1 | 0.94 | |
| | ≥ 50% (n = 397) | 21.2 | 14.0 | 0.70 | |
| TMB[d] (mut/Mb) | low, < 10 (n = 380) | 16.2 | 12.6 | 0.75 | |
| | high, ≥ 10 (n = 299) | 23.0 | 16.4 | 0.68 | |



# LBA4_PR - Nivolumab (NIVO) + low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced NSCLC: CheckMate 227 part 1 final analysis



## Safety Summary of Treatment-Related AEs in All Patients Treated With NIVO + IPI, Chemo, or NIVO

| TRAE,[a] % | NIVO + IPI (n = 576) | | Chemo (n = 570) | | NIVO[b] (n = 391) | |
|---|---|---|---|---|---|---|
| | Any grade | Grade 3–4 | Any grade | Grade 3–4 | Any grade | Grade 3–4 |
| Any TRAE | 77 | 33 | 82 | 36 | 66 | 19 |
| TRAE leading to discontinuation[c] | 18 | 12 | 9 | 5 | 12 | 7 |
| **Most frequent TRAEs (≥ 15%)** | | | | | | |
| Diarrhea | 17 | 2 | 10 | 1 | 12 | < 1 |
| Rash | 17 | 2 | 5 | 0 | 11 | 1 |
| Fatigue | 14 | 2 | 19 | 1 | 11 | < 1 |
| Decreased appetite | 13 | 1 | 20 | 1 | 7 | 0 |
| Nausea | 10 | < 1 | 36 | 2 | 6 | < 1 |
| Anemia | 4 | 1 | 33 | 12 | 3 | < 1 |
| Constipation | 4 | 0 | 15 | < 1 | 2 | 0 |
| Neutropenia | < 1 | 0 | 17 | 10 | < 1 | 0 |
| Treatment-related deaths[d] | 1 | | 1 | | < 1 | |

- With 18 months more follow-up, safety was consistent with the previous report[1] and did not increase
- Median duration of therapy (range) was 4.2 mo (0.03–25.5) with NIVO + IPI, 2.6 mo (0.03–37.6+) with chemo, and 4.6 mo (0.03–26.5) with NIVO

# TMB and clinical outcomes with Pembrolizumab





## Association Between Tissue TMB and Clinical Outcomes with Pembrolizumab Monotherapy in PD-L1-Positive Advanced NSCLC in the KEYNOTE-010 and 042 Trials

Roy S. Herbst[1], Gilberto Lopes[2], Dariusz M. Kowalski[3], Makoto Nishio[4]; Yi-long Wu[5], Gilberto de Castro Jr[6], Paul Baas[7], Dong-Wan Kim[8], Matthew A. Gubens[9], Razvan Cristescu[10], Deepti Aurora-Garg[10], Andrew Albright[10], Mark Ayers[10], Andrey Loboda[10], Jared Lunceford[10], Julie Kobie[10], Gregory Lubiniecki[10], M. Catherine Pietanza[10], Bilal Piperdi[10], Tony SK Mok[11]

[1]Yale University School of Medicine, Yale Cancer Center, New Haven, CT, USA; [2]Sylvester Comprehensive Cancer Center at the University of Miami, Miami, FL, USA; [3]The Maria Sklodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [4]Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5]Guandong Lung Cancer Institute, Guangdong General Hospital, and Guangdong Academy of Medical Sciences, Guangdong, China; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]Netherlands Cancer Institute, Amsterdam, Netherlands; [8]Seoul National, University Hospital, Seoul, Republic of Korea; [9]University of California, San Francisco, CA, USA; [10]Merck &Co., Inc, Kenilworth, NJ, USA; [11]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Shatin, Hong Kong, China

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KEYNOTE-010: phase 1/2, 2L+
KEYNOTE-042: phase 3, 1L, PD-L1≥1%



## Pembrolizumab Plus Platinum-Based Chemotherapy for Metastatic NSCLC: Tissue TMB (tTMB) and Outcomes in KEYNOTE-021, 189, and 407

Luis Paz-Ares,[1] Corey J. Langer,[2] Silvia Novello,[3] Balazs Halmos,[4] Ying Cheng,[5] Shirish M. Gadgeel,[6] Rina Hui,[7] Shunichi Sugawara,[8] Hossein Borghaei,[9] Razvan Cristescu,[10] Deepti Aurora-Garg,[10] Andrew Albright,[10] Andrey Loboda,[10] Julie Kobie,[10] Jared Lunceford,[10] Mark Ayers,[10] Gregory M. Lubiniecki,[10] M. Catherine Pietanza,[10] Bilal Piperdi,[10] Marina C. Garassino[11]

[1]Hospital Universitario 12 de Octubre, Spanish National Cancer Research Center, Universidad Complutense and Ciberonc, Madrid, Spain; [2]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [3]University of Turin, Orbassano, Italy; [4]Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA; [5]Jilin Cancer Hospital, Changchun, China; [6]Karmanos Cancer Institute, Detroit, MI, USA (currently at University of Michigan, Ann Arbor, MI, USA); [7]Westmead Hospital and University of Sydney, Sydney, NSW, Australia; [8]Sendai Kousei Hospital, Miyagi, Japan; [9]Fox Chase Cancer Center, Philadelphia, PA, USA; [10]Merck & Co., Inc., Kenilworth, NJ, USA; [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

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KEYNOTE-021: phase 1/2, 1L, NSQ
KEYNOTE-189: phase 3, 1L, NSQ
KEYNOTE-407: phase 3, 1L, SQ

# Association of tTMB with efficacy

## KEYNOTE-010

| Nominal *P* Value[b] | Pembro (n = 164) | Chemo (n = 89) |
|---|---|---|
| OS | 0.006 (one-sided) | 0.410 (two-sided) |
| PFS | 0.001 (one-sided) | 0.579 (two-sided) |
| ORR | 0.009 (one-sided) | 0.330 (two-sided) |

tTMB was associated with outcomes for pembr as a continuous variable but not with chemo based on α = 0.05 significance level and AUROC analysis

## KEYNOTE-024

| Nominal *P* Value[b] | Pembro (n = 414) | Chemo (n = 379) |
|---|---|---|
| OS | <0.001 (one-sided) | 0.060 (two-sided)[c] |
| PFS | <0.001 (one-sided) | 0.174 (two-sided)[c] |
| ORR | <0.001 (one-sided) | 0.035 (two-sided) |

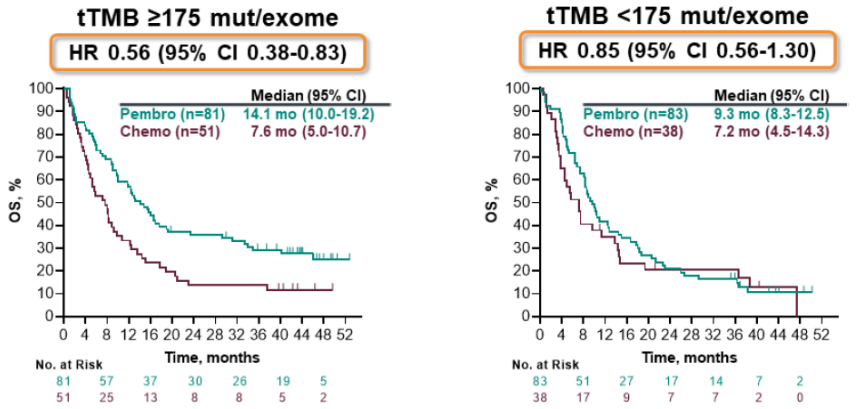
tTMB was associated with outcomes for pembro as a continuous variable but not chemo in general, based on α = 0.05 significance level and AUROC

# TMB and clinical outcomes with Pembrolizumab

## Association of tTMB with efficacy

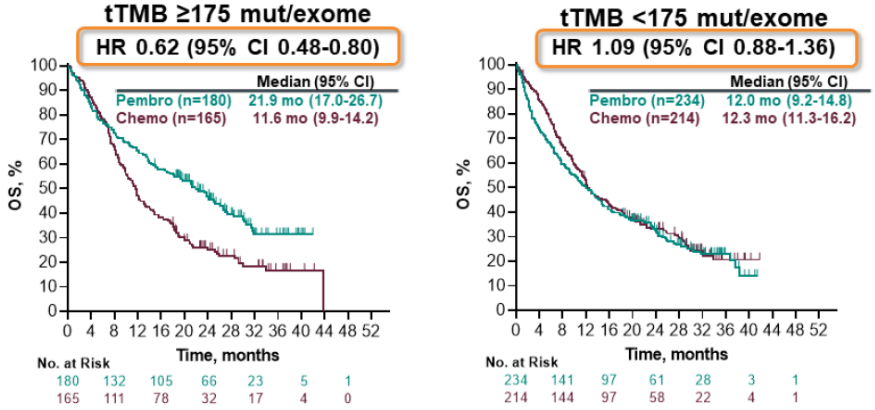
### KEYNOTE-010

**Clinical Utility for OS (KEYNOTE-010[a]): tTMB Cutpoint of 175 mut/exome**




### KEYNOTE-024

**Clinical Utility for OS (KEYNOTE-042[a]): tTMB Cutpoint of 175 mut/exome**



# Association of tTMB ($log_{10}$) With Efficacy

| | KEYNOTE-021 C and G | | KEYNOTE-189 | | KEYNOTE-407 | |
|---|---|---|---|---|---|---|
| Nominal *P* Value[a] | Pembro + Chemo (n = 44) | Chemo Alone (n = 26) | Pembro + Chemo (n = 207) | Placebo + Chemo (n = 86) | Pembro + Chemo (n = 143) | Placebo + Chemo (n = 169) |
| ORR | 0.180 | 0.279 | 0.072 | 0.434 | 0.393 | 0.086 |
| PFS | 0.187 | 0.409 | 0.075 | 0.055 | 0.052 | 0.560 |
| OS | 0.081 | 0.475 | 0.174 | 0.856 | 0.160 | 0.818 |

**No association between tTMB (continuous, $log_{10}$-transformed) and efficacy for pembrolizumab + chemotherapy or chemotherapy ± placebo in any study based on α = 0.05 significance level**

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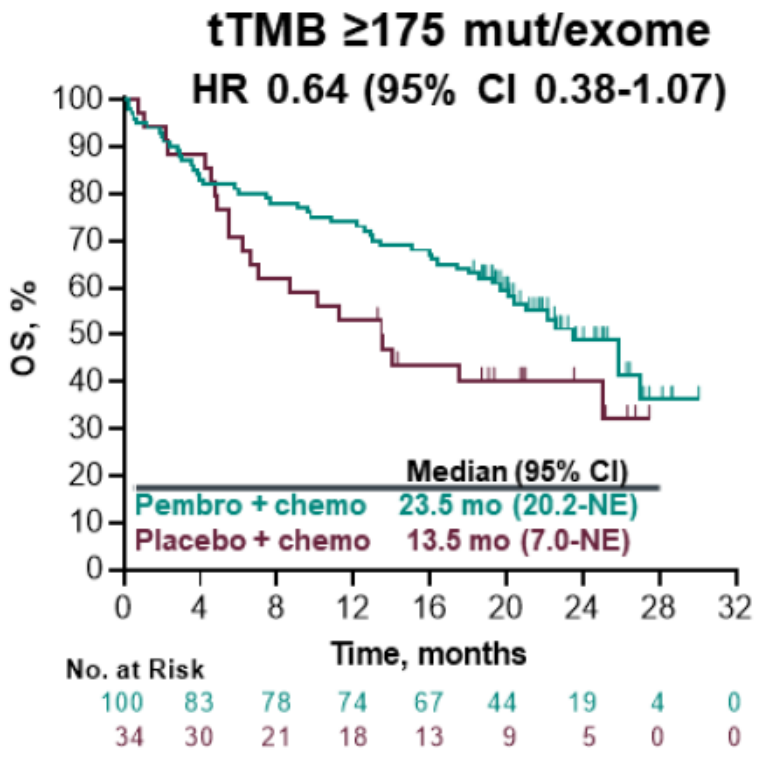
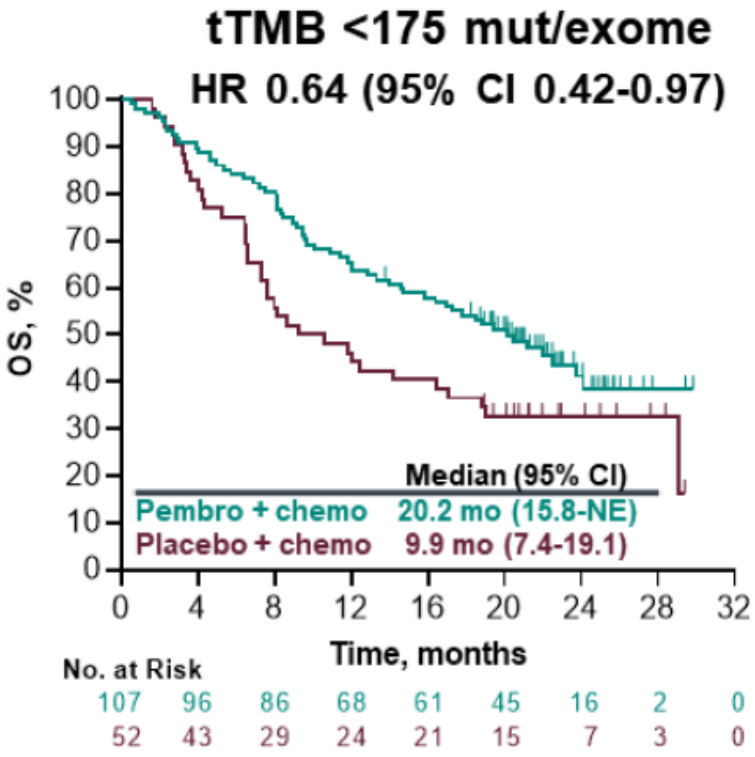
# Clinical Utility for OS in KEYNOTE-189: tTMB Cutpoint of 175 mut/exome

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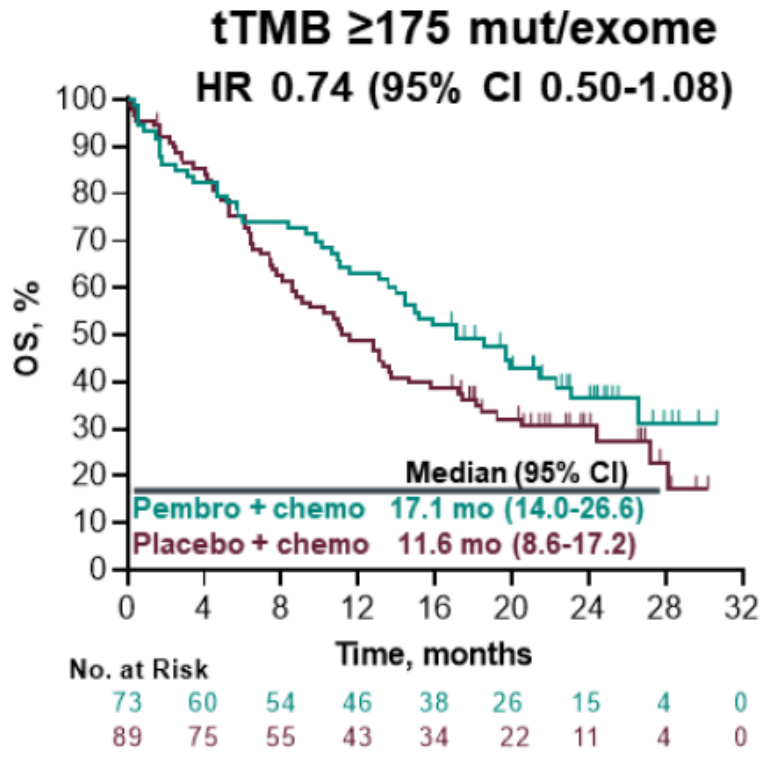
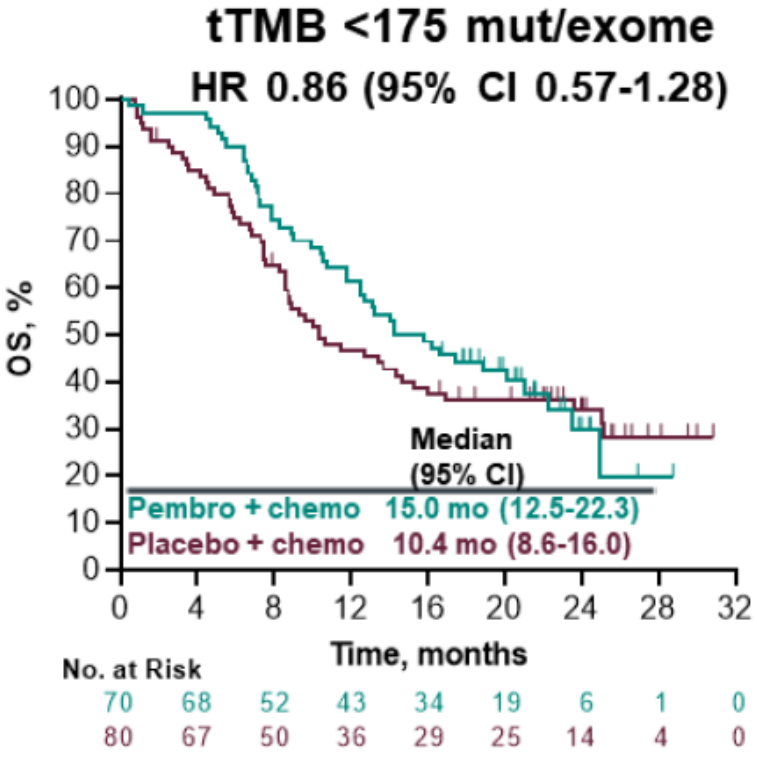
# Clinical Utility for OS in KEYNOTE-407: tTMB Cutpoint of 175 mut/exome



# LBA89 – PD-L1 expression, patterns of progression and PROs with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN



## CASPIAN STUDY DESIGN

Phase 3, global, randomised, open-label, sponsor-blind, multicentre study

- Treatment-naive ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomised)

1:1:1 R — Stratified by planned platinum agent (carboplatin vs cisplatin)

- **Durvalumab + EP*** — Durvalumab 1500 mg + EP q3w for up to 4 cycles → **Durvalumab** 1500 mg q4w until disease progression
- **EP*** q3w for up to 6 cycles† → **Optional PCI†**
- Durvalumab + tremelimumab + EP* → Durvalumab†

**Primary endpoint**
- OS

**Secondary endpoints**
- PFS, ORR
- Safety & tolerability
- PROs

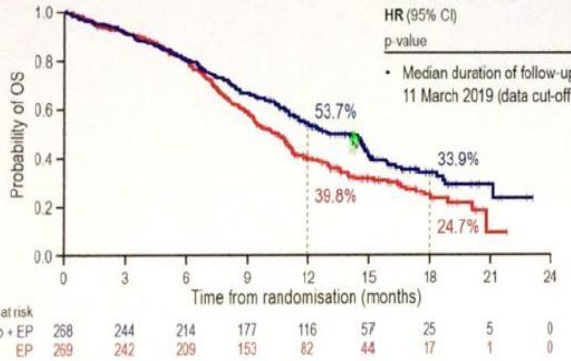
**Exploratory endpoints**
- PD-L1 biomarker analysis (tissue mandatory if available)

Following pre-planned interim analysis by the IDMC, the durvalumab + tremelimumab + EP arm remains sponsor-blind and continues to final analysis

## OVERALL SURVIVAL (PRIMARY ENDPOINT)

| | Durvalumab + EP | EP |
|---|---|---|
| Events, n/N (%) | 155/268 (57.8) | 181/269 (67.3) |
| **mOS**, months (95% CI) | **13.0** (11.5–14.8) | **10.3** (9.3–11.2) |
| **HR** (95% CI) | **0.73** (0.591–0.909) | |
| p-value | 0.0047 | |

- Median duration of follow-up in censored patients as of 11 March 2019 (data cut-off): 14.2 months (range 0.1–23.1)



# LBA89 – PD-L1 expression, patterns of progression and PROs with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN



## PATTERNS OF FIRST PROGRESSION

### Types of progression

| | Durvalumab + EP (N=268) | EP (N=269) |
|---|---|---|
| **Total progression events**, n (%) | 226 (84.3) | 233 (86.6) |
| **RECIST-defined progression**, n (%) | 192 (71.6) | 194 (72.1) |
| Target lesions | 115 (42.9) | 106 (39.4) |
| Non-target lesions | 66 (24.6) | 61 (22.7) |
| New lesions | 111 (41.4) | 127 (47.2) |
| **Death in absence of progression**, n (%) | 34 (12.7) | 39 (14.5) |

### Sites of new lesions (>5% patients)

| | Durvalumab + EP (N=268) | EP (N=269) |
|---|---|---|
| **New lesions**, n (%) | 111 (41.4) | 127 (47.2) |
| Lung | 23 (8.6) | 41 (15.2) |
| Brain/CNS | 31 (11.6) | 31 (11.5) |
| Liver | 15 (5.6) | 24 (8.9) |
| Bone | 12 (4.5) | 19 (7.1) |
| Regional lymph nodes | 15 (5.6) | 12 (4.5) |

- Numerically fewer patients developed new lesions at first progression with durvalumab + EP versus EP
- No difference in the incidence of new brain/CNS lesions between arms

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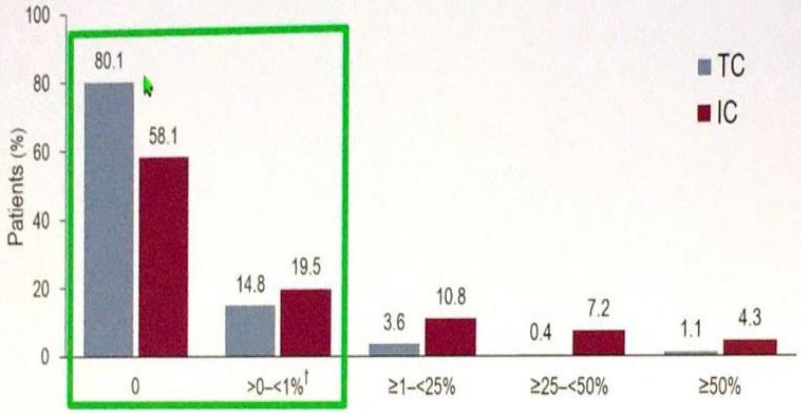
# LBA89 – PD-L1 expression, patterns of progression and PROs with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN

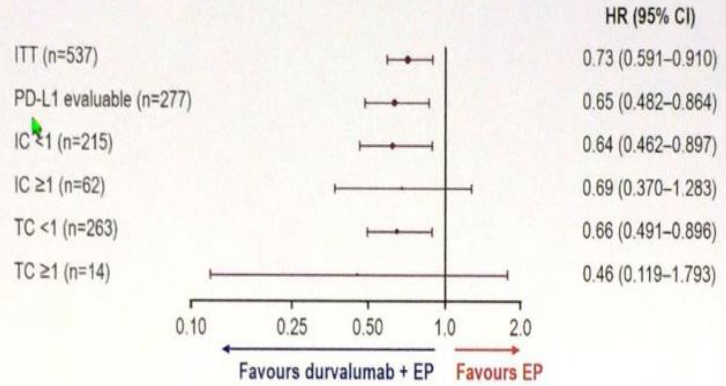


## PREVALENCE OF PD-L1 EXPRESSION ON TCs OR ICs*




- 94.9% and 77.6% of patients had PD-L1 expression <1% on TCs and ICs, respectively
- Due to low PD-L1 expression, a 1% cut-off was used in post-hoc analyses

## OVERALL SURVIVAL BASED ON PD-L1 EXPRESSION

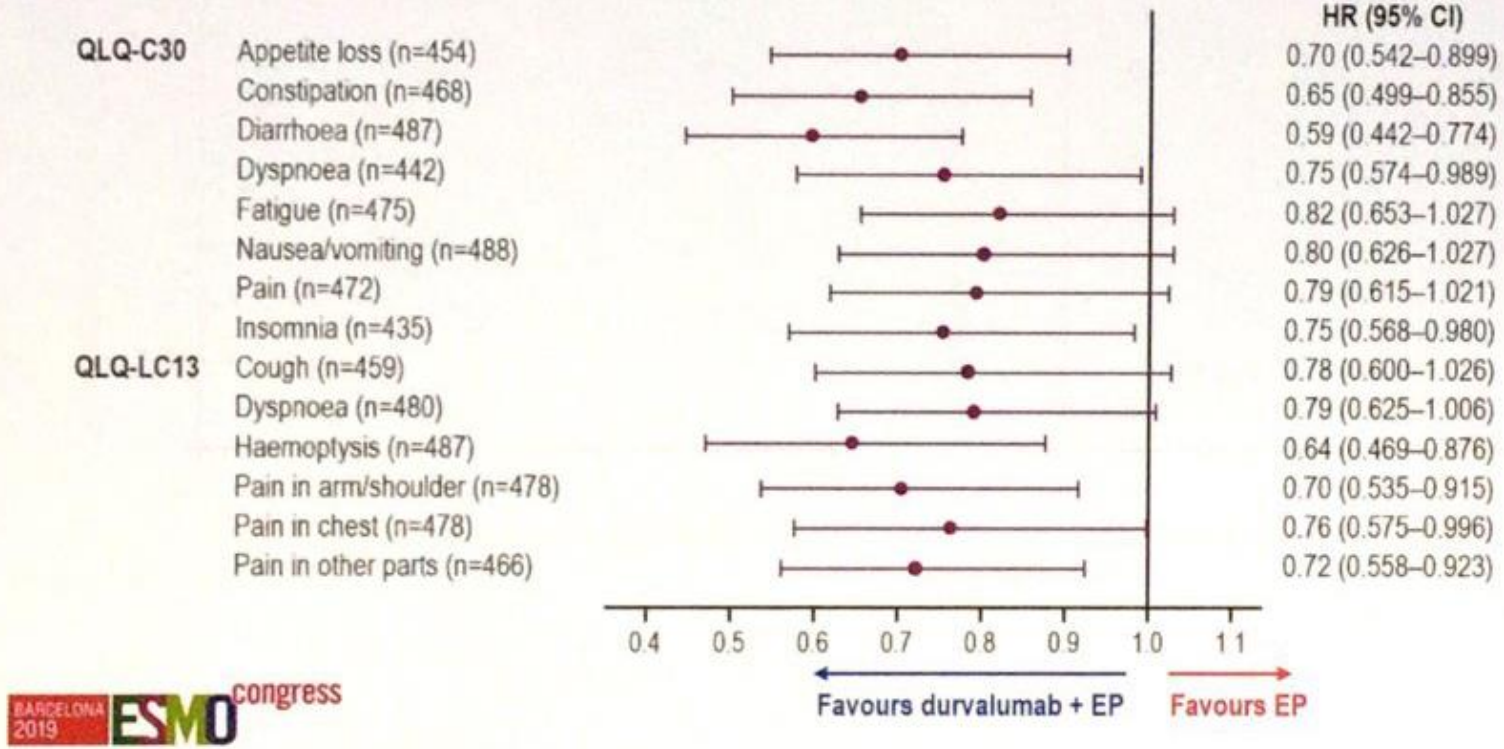



- Durvalumab + EP was associated with improved OS vs EP, regardless of PD-L1 expression with a 1% cut-off
- No significant interaction was observed with OS based on PD-L1 expression as a continuous variable (TC, p=0.54; IC, p=0.23); similar results were observed with PFS and ORR

# LBA89 – PD-L1 expression, patterns of progression and PROs with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN

## TIME TO DETERIORATION IN SYMPTOMS

- Durvalumab + EP was favoured across all symptoms




BARCELONA 2019 ESMO congress

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# 1736O- IMPOWER133: UPDATED OS ANALYSIS OF 1L ATEZOLIZUMAB +CARBOPLATIN+ETOPOSIDE IN ES-SCLC



## IMpower133 study design

**Patients with (N = 403)**
- Measurable ES-SCLC (RECIST version 1.1)
- ECOG PS 0 or 1
- No prior systemic treatment for ES-SCLC
- Patients with treated asymptomatic brain metastases were eligible

**Stratification**
- Sex (male vs female)
- ECOG PS (0 vs 1)
- Brain metastases (yes vs no)[a]

R 1:1

| | *Induction* | *Maintenance* |
|---|---|---|
| Atezolizumab arm | Atezolizumab + carboplatin + etoposide, Four 21-day cycles | Atezolizumab |
| Placebo arm | Placebo + carboplatin + etoposide, Four 21-day cycles | Placebo |

Treat until PD or loss of clinical benefit

Survival follow-up

Co-primary end points
- ✓ Overall survival
- ✓ Investigator-assessed PFS

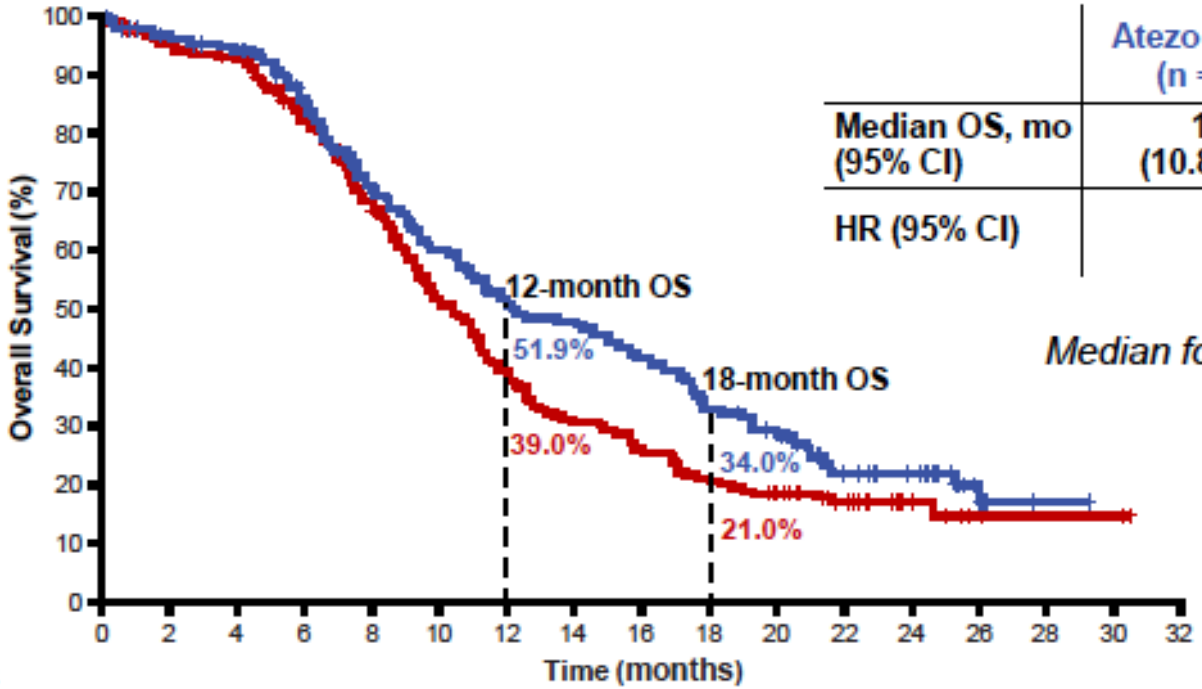
Key secondary end points
- ✓ Objective response rate
- ✓ Duration of response
- ✓ Safety

- ❑ Updated OS in ITT and by PD-L1 subgroups
- ❑ Updated DOR/ORR in ITT
- ❑ Updated Safety

Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m² IV, Days 1–3.
▪ Only patients with treated brain metastases were eligible.

# 1736O- IMPOWER133: UPDATED OS ANALYSIS OF 1L ATEZOLIZUMAB +CARBOPLATIN+ETOPOSIDE IN ES-SCLC

## Updated OS in ITT




| | Atezo + CP/ET (n = 201) | Placebo + CP/ET (n = 202) |
|---|---|---|
| Median OS, mo (95% CI) | 12.3 (10.8, 15.8) | 10.3 (9.3, 11.3) |
| HR (95% CI) | 0.76 (0.60, 0.95) p = 0.0154[a] | |

*Median follow-up, 22.9 months*

[a]p-value is provided for descriptive purpose.
CCOD 24 January 2019

GECP lung cancer research

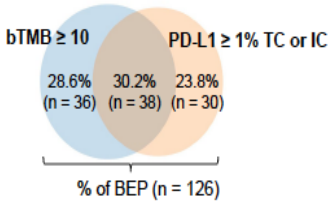
# 1736O- IMPOWER133: UPDATED OS ANALYSIS OF 1L ATEZOLIZUMAB +CARBOPLATIN+ETOPOSIDE IN ES-SCLC



## Biomarker analysis: bTMB and PD-L1 expression

- PD-L1 and bTMB biomarkers identify distinct patient populations in ES-SCLC
- Post-hoc exploratory analysis conducted for OS by PD-L1 expression
  - The PD-L1 IHC biomarker evaluable population (BEP) comprised 34% of the ITT population
  - VENTANA SP263 assay was used to determine PD-L1 status on slide sections ≤ 1 year old
  - PD-L1 expression was observed mostly on immune cells (IC), with limited expression on tumour cells (TC)
  - Efficacy analyses were conducted using PD-L1 expression cut-offs of 1% and 5%

**bTMB – PD-L1 IHC overlap**




| PD-L1 IHC expression in ES-SCLC (n = 137) | | | |
|---|---|---|---|
| IC | % BEP (n) | TC | % BEP (n) |
| < 1% | 49.6% (68) | < 1% | 94.2% (129) |
| ≥ 1% | 50.4% (69) | ≥ 1% | 5.8% (8) |
| ≥ 5% | 20.4% (28) | ≥ 5% | 1.5% (2) |

## Updated OS in PD-L1 expression subgroups