LUNG CANCER UPDATES

ESMO HIGHLIGHTS

19-23 DE OCTUBRE 2018, MUNICH

INMUNOTERAPIA I

Dra. Virginia Calvo

Iniciativa científica de:

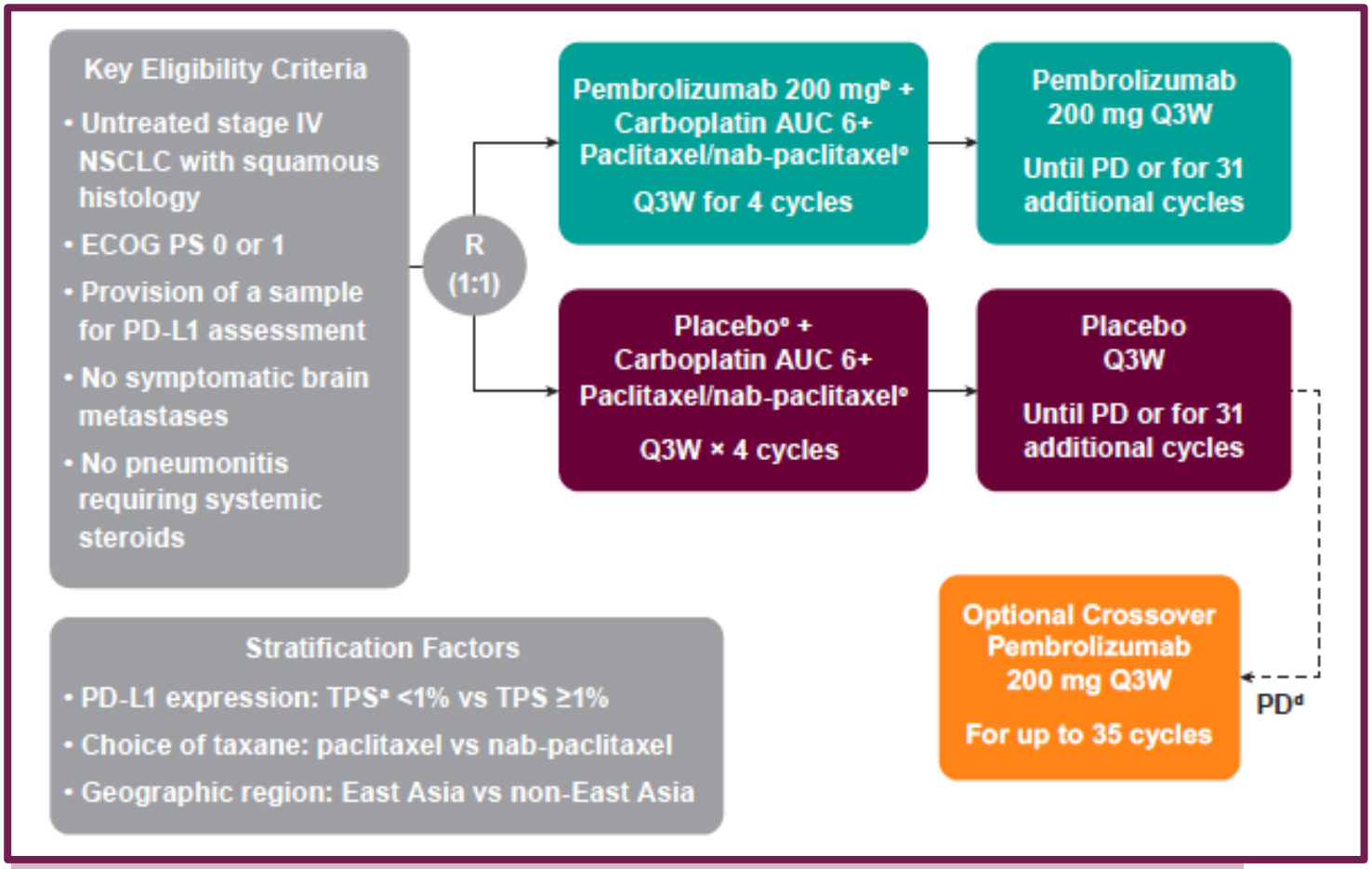
GECP

Grupo Español de Cáncer de Pulmón

Spanish Lung Cancer Group

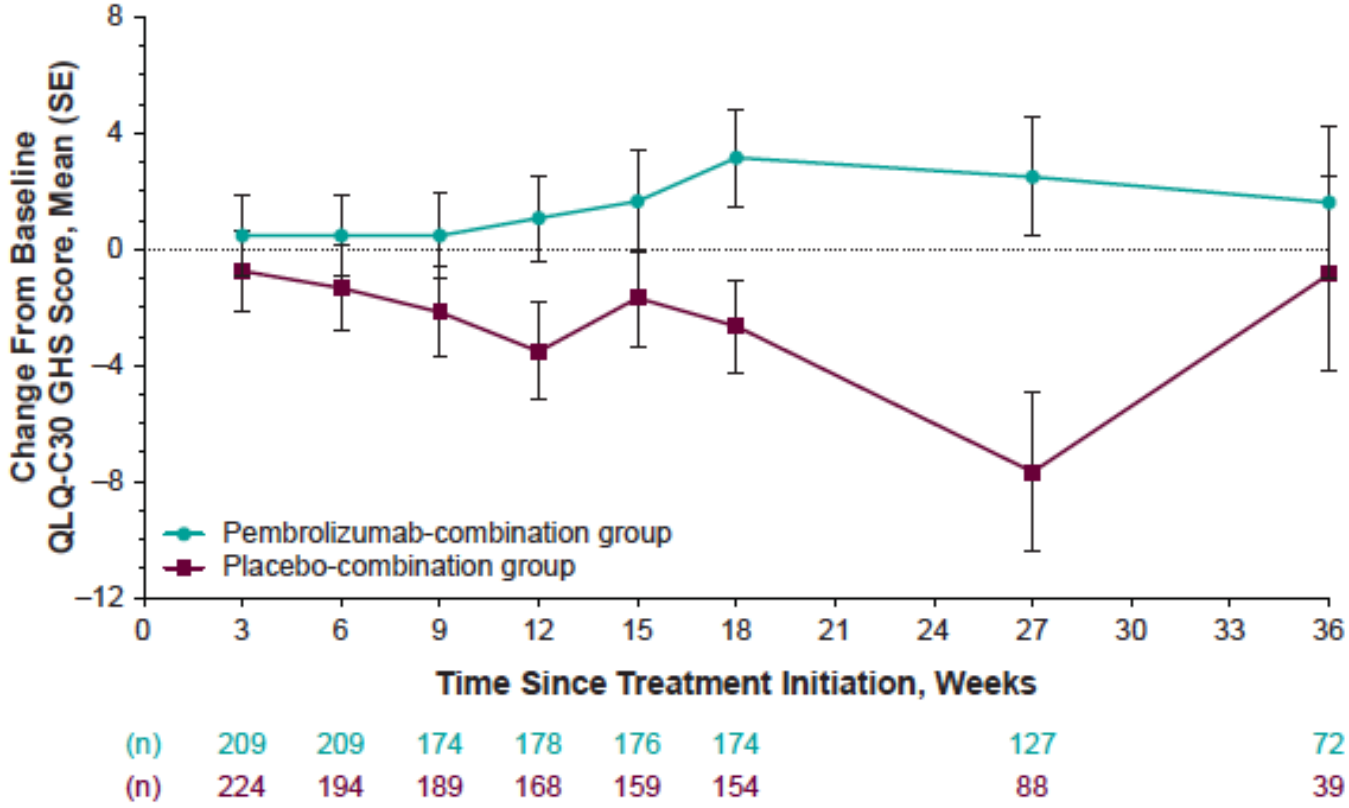
LBA62. Health-related quality of life (HRQoL) for Pembrolizumab or placebo plus Carboplatin and Paclitaxel or nab-Paclitaxel in patients with metastatic squamous NSCLC: data from KEYNOTE-407

STUDY DESING



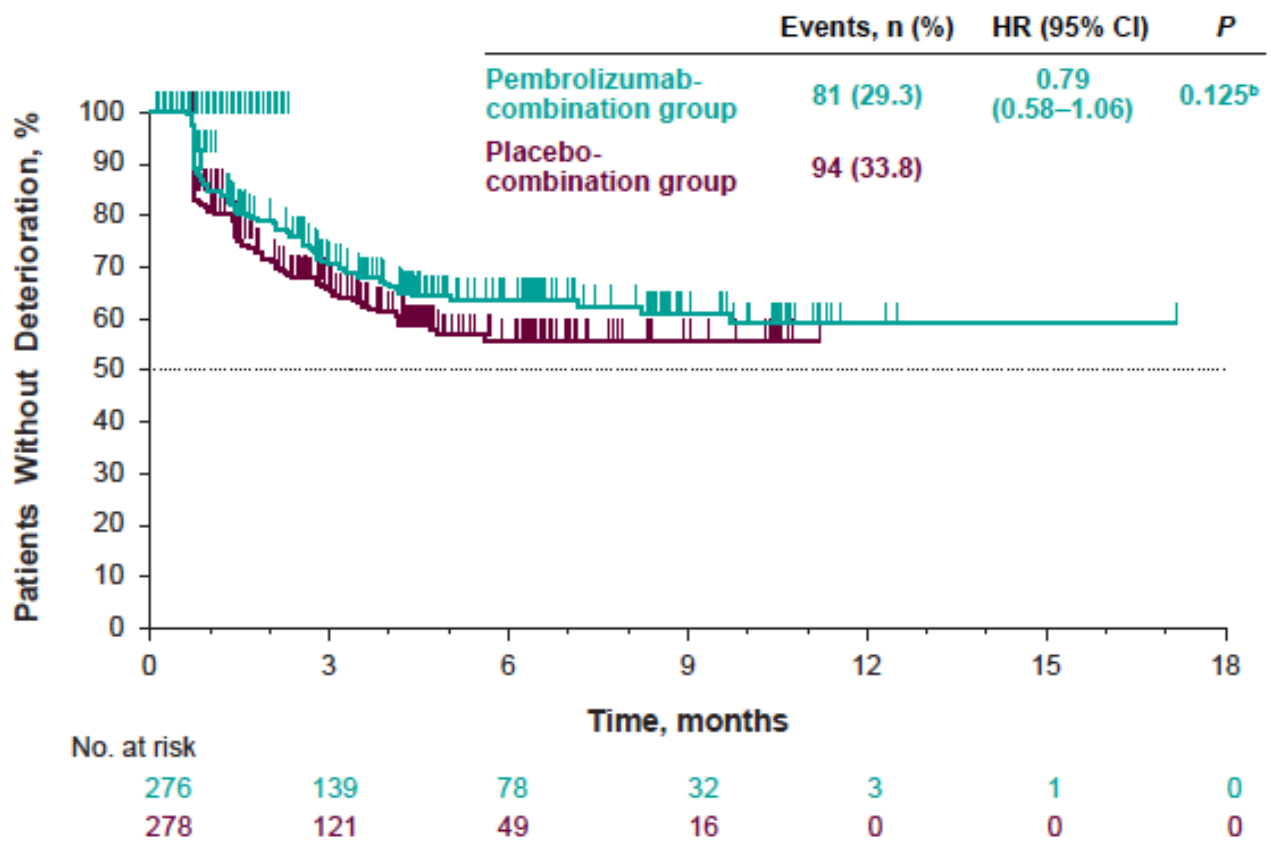
Primary endpoint: PFS by RECIST v1.1 (BICR), OS
Secondary endpoint: ORR and DoR by RECIST v1.1 (BIRC), safety

Mean change from baseline in QLC-C30 Global Health status/quality of life scores by visit



LBA62. Health-related quality of life (HRQoL) for Pembrolizumab or placebo plus Carboplatin and Paclitaxel or nab-Paclitaxel in patients with metastatic squamous NSCLC: data from KEYNOTE-407

Kaplan-Meier estimate of time to deterioration in composite endpoint of cough, chest pain, or dyspnea

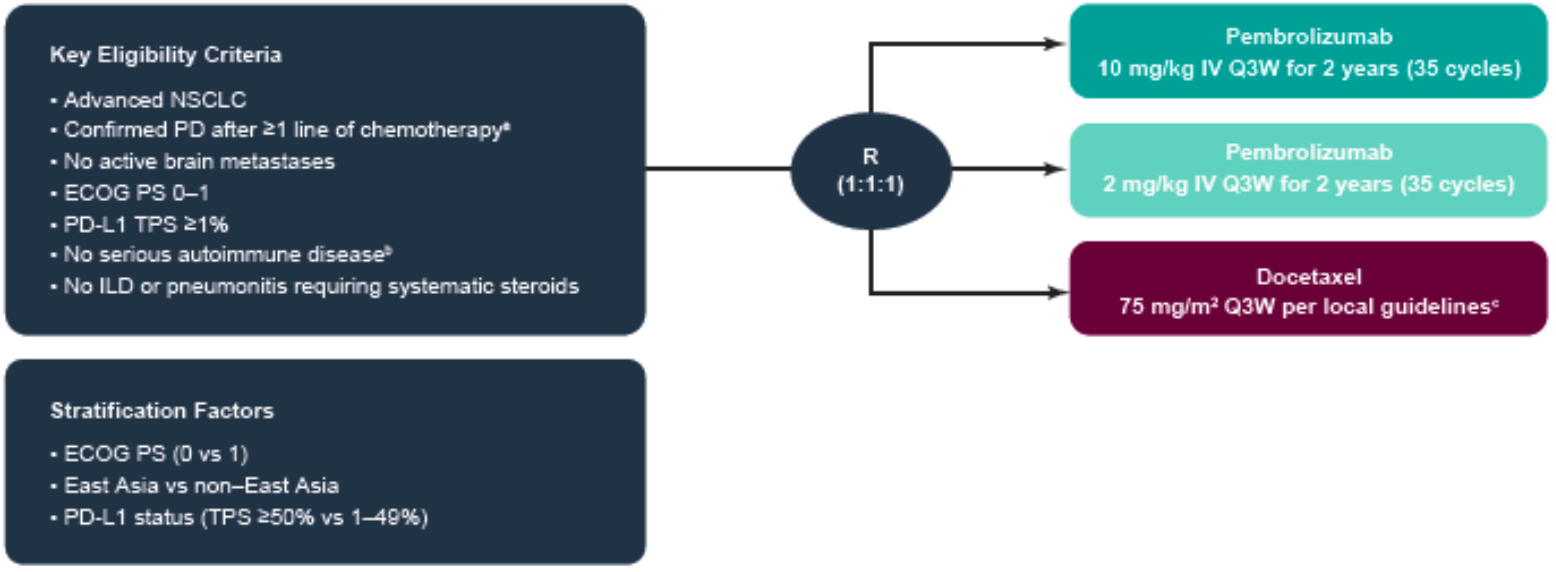


[a]Key PRO endpoint; based on the stratified Cox model, with treatment as a covariate.
[b]*P* value is 2-sided and nominal, based on the stratified log-rank test.

- Pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel maintained or improved quality of life compared with baseline and improved quality of life compared with placebo plus carboplatin and paclitaxel or nab-paclitaxel

- Pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel showed a numerical improvement in time to deterioration in cough, chest pain, or dyspnea compared with the control group (HR, 0.79; 95% CI, 0.58-1.06; p=0.125); the median time to deterioration in this endpoint was not reached in either group

LBA63. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in patients who completed 2 years of Pembrolizumab



ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; IV, intravenous; R, randomization.

[a]Must have included ≥2 cycles of platinum-doublet chemotherapy. An appropriate tyrosine kinase inhibitor was required for patients with an *EGFR*-sensitizing mutation or an *ALK* translocation.

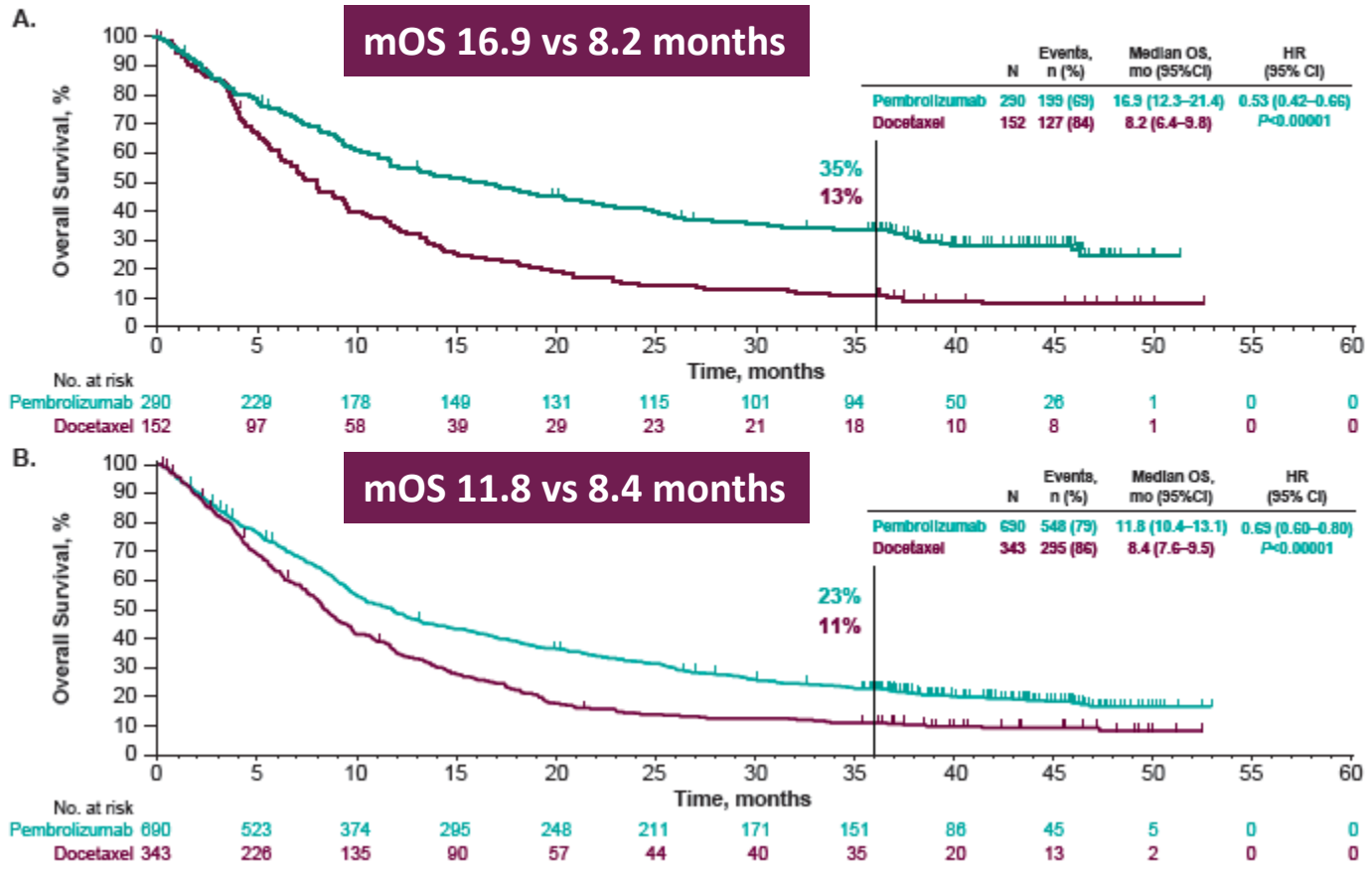
[b]No active or documented history of any autoimmune disease or syndrome that required systemic steroids or immunosuppressive agents, excluding patients with vitiligo, resolved childhood asthma/atopy, or those requiring inhaled steroids or local steroid injections.

[c]Patients received the maximum number of cycles permitted by the local regulatory authority.

LBA63. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in patients who completed 2 years of Pembrolizumab

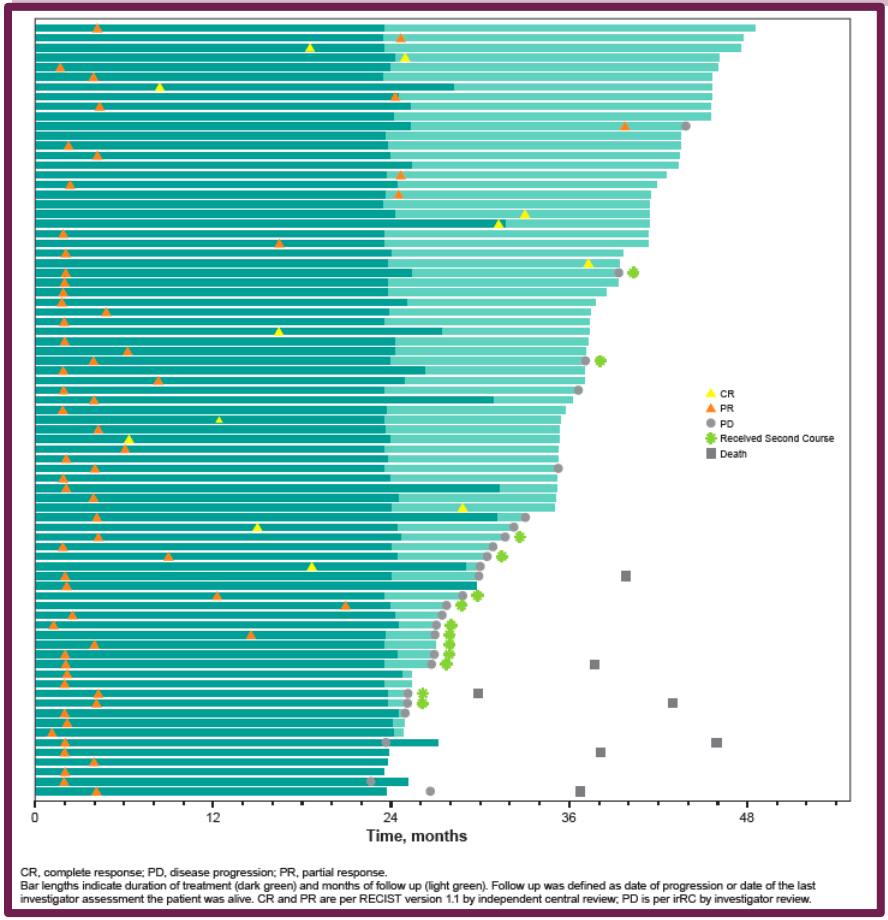
Efficacy in the PD-L1 TPS ≥50% and ≥1% Populations

Figure 2. Kaplan-Meier Estimates of OS. (A) PD-L1 TPS ≥50% Population. (B) PD-L1 TPS ≥1% Population.



LBA63. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in patients who completed 2 years of Pembrolizumab

Treatment duration and time to response in patients who completed 35 cycles or 2 years of Pembrolizumab



CR, complete response; PD, disease progression; PR, partial response.
Bar lengths indicate duration of treatment (dark green) and months of follow up (light green). Follow up was defined as date of progression or date of the last investigator assessment the patient was alive. CR and PR are per RECIST version 1.1 by independent central review; PD is per irRC by investigator review.

- 79 patients completed 35 cycles or 2 years with median follow-up of 43.4 (35.7-49.8) months
- 75 of 79 (95%) of patients had CR o PR as best response per RECIST version 1.1 by independent central review
  - 48 patients (64%) had ongoing response
  - Median duration of response: NR
- Median OS was NR
- 25 patients (32%) had PD by investigator review after stopping 35 cycles or 2 years
  - 13 (52%) started second-course Pembrolizumab

LBA63. Long-term survival in patients (pts) with advanced NSCLC in the KEYNOTE-010 study overall and in patients who completed 2 years of Pembrolizumab

- With 42.6 months of follow-up, Pembrolizumab continued to prolong OS vs Docetaxel in patients with previously treated, PD-L1 expressing advanced NSCLC
- Pembrolizumab had a manageable long-term safety profile including in patients who completed 35 cycles or 2 years of treatment
- Most patients who completed 35 cycles or 2 years of treatment of Pembrolizumab therapy had durable response, with ongoing response in 64% of patients at median follow-up of 43.4 months
- 13 (52%) patients who had progressive disease after stopping Pembrolizumab were able to receive a second course of Pembrolizumab treatment
- Of the 14 patients who received second course of Pembrolizumab, 6 (43%) had a partial response and 5 (36%) had stable disease per RECIST version 1.1 by independent central review

1384PD. Pembrolizumab in performance status 2 patients with non-small lung cancer (NSCLC): results of the PePS2 trial

LUNG CANCER UPDATES
ESMO HIGHLIGHTS
19-23 DE OCTUBRE 2018, MUNICH

Primary & Secondary Outcomes

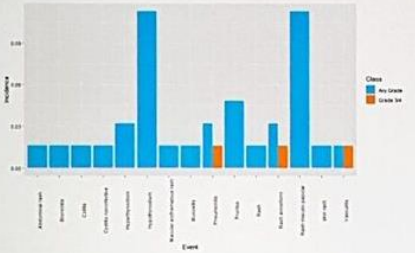
	DCB (%)	Toxicity (%)	PR (%)	No RECIST	Median OS (95% CI)	Median PFS (95% CI)
All (*n* = 60)	20 (33.3)	13 (21.7)	17 (28.3)	16 (26.7)	11.7 (6.8 - NR)	5.4 (3.5 - 8.5)
Line of therapy						
First line (*n* = 9)	1 (11.1)	3 (33.3)	0 (0.0)	3 (33.3)	6.8 (2.4 - NR)	2.9 (1.9 - NR)
Subsequent line (*n* = 51)	19 (37.3)	10 (19.6)	17 (33.3)	13 (25.5)	12.1 (8.1 - NR)	6.0 (3.5 - 11.4)
PD-L1 Proportion Score						
< 1% (*n* = 27)	6 (22.2)	7 (25.9)	4 (14.8)	6 (22.2)	9.8 (4.5 - NR)	3.7 (2.1 - 8.1)
1-49% (*n* = 15)	5 (33.3)	0 (0.0)	5 (33.3)	3 (20.0)	NR	6.8 (3.5 - NR)
≥ 50%, (*n* = 15)	8 (58.3)	4 (26.7)	7 (46.7)	6 (40.0)	16.6 (4.6 - NR)	8.5 (1.9 - NR)
Unknown PD-L1 (*n* = 3)	1 (33.3)	2 (66.7)	1 (33.3)	1 (33.3)		

DCB=Durable Clinical Benefit. Toxicity=treatment-related dose delay or treatment discontinuation due to adverse event. PR=Partial Response by RECIST. No RECIST=patients that did not have an assessment CT scan post-baseline due to disease progression or clinical deterioration. OS=Overall Survival & PFS=Progression-free Survival, measured in months. NR=Not reached.

@CRCTU Cancer Research UK Clinical Trials Unit
UNIVERSITY OF BIRMINGHAM
9

Treatment-Related Adverse Events

Immune-related



Non-immune-related

	All grades (%)	Grades 3/4 (%)
Overall incidence (n=60)	30 (85.0)	7 (11.7)
Event-level, n (%)		
Fatigue	14 (23.3)	0 (0.0)
Anorexia	6 (10.0)	0 (0.0)
Nausea	6 (10.0)	0 (0.0)

There were no grade 5 adverse events, and no cases of hyperprogression.

@CRCTU Cancer Research UK Clinical Trials Unit
UNIVERSITY OF BIRMINGHAM

- PS2 patients frequently excluded from clinical trials
- Poor prognosis vs PS 0-1 patients
- Chemotherapy and targeted agents prolong survival and improve quality-of-life in PS2 advanced NSCLC patients

- PS2 patients
  - Clinical efficacy with Pembrolizumab comparable to PS 0-1 patients beyond 1L and with tolerable toxicity

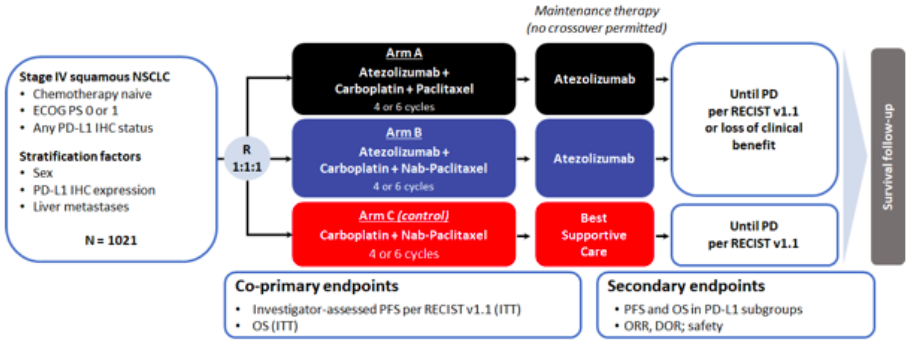
Iniciativa científica de:
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

IMpower131: Background and Study Design

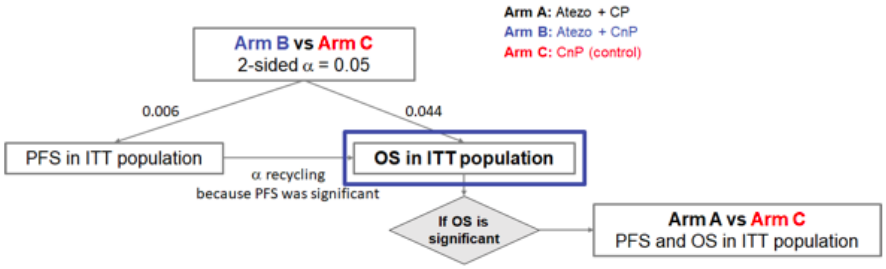
MUNICH 2018 ESMO congress

- The combination of chemotherapy and atezolizumab (atezo) may lead to enhanced anti-tumour activity
- IMpower131 is an open-label, randomised Phase III study of atezo in combination with carboplatin plus paclitaxel (CP) or nab-paclitaxel vs carboplatin plus nab-paclitaxel (CnP) in patients with first-line Stage IV squamous NSCLC
- In the primary analysis, PFS benefit was observed with atezo + CnP vs CnP (HR, 0.71; 95% CI: 0.60, 0.85; *P* = 0.0001), with a safety profile that was consistent with the known risks of the individual agents[1]
- The co-primary endpoints were tested first between Arms B and C

Study Design



Statistical Testing Plan

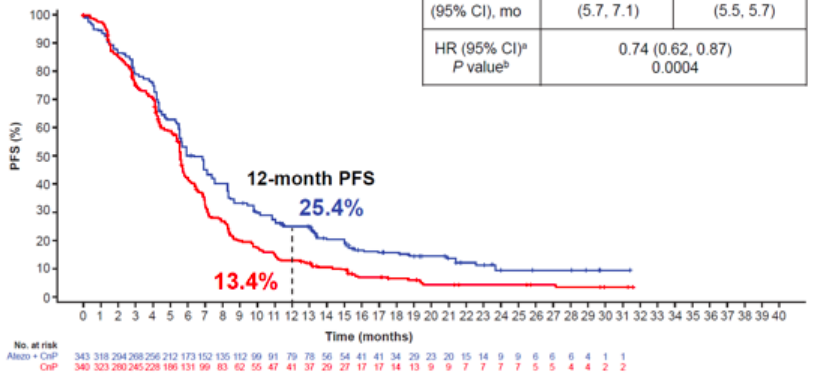


Updated PFS at the Second Interim OS Analysis

MUNICH 2018 ESMO congress

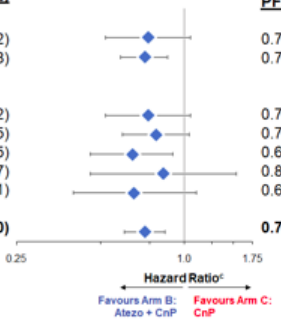
PFS in the ITT Population

	Arm B: Atezo + CnP (n = 343)	Arm C: CnP (n = 340)
Median PFS (95% CI), mo	6.5 (5.7, 7.1)	5.6 (5.5, 5.7)
HR (95% CI)[a] *P* value[b]	0.74 (0.62, 0.87) 0.0004	



PFS by Geographic Region of Enrolment

Subgroup	n (%)	PFS HR (95% CI)	Median PFS, mo Arm B	Median PFS, mo Arm C
Region				
Eastern Europe	152 (22)	0.74 (0.52, 1.05)	7.2	5.6
Rest of world	531 (78)	0.72 (0.59, 0.87)	6.0	5.6
Region				
Eastern Europe	152 (22)	0.74 (0.52, 1.05)	7.2	5.6
Rest of Europe	240 (35)	0.79 (0.60, 1.04)	5.7	5.6
North America/Australia	168 (25)	0.65 (0.46, 0.91)	7.4	5.5
Central/South America	47 (7)	0.84 (0.46, 1.53)	5.6	4.9
Asia Pacific	76 (11)	0.66 (0.40, 1.10)	7.0	5.6
ITT population	**683 (100)**	**0.74 (0.62, 0.87)**	**6.5**	**5.6**



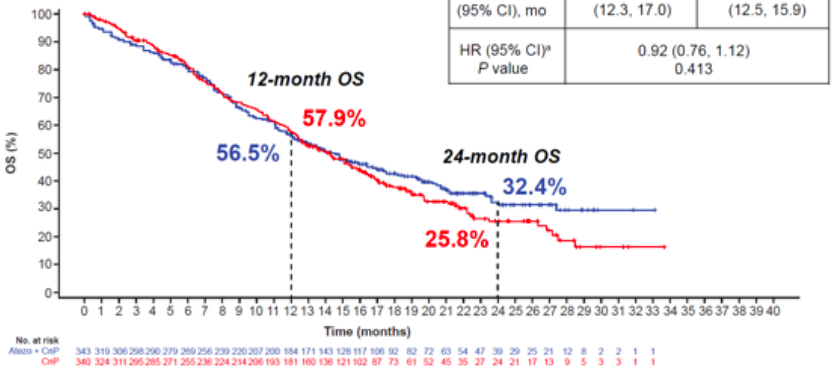
- PFS benefit with atezo + CnP vs CnP was observed in the ITT population, as well as in subgroups by geographic region of enrolment, though PFS was not formally tested in these patient groups
  - Analysis in subgroups with a smaller number of patients (Central/South America and Asia Pacific) resulted in wide CIs

OS at the Second Interim OS Analysis

MUNICH 2018 ESMO congress

OS in the ITT Population

	Arm B: Atezo + CnP (n = 343)	Arm C: CnP (n = 340)
Median OS (95% CI), mo	14.6 (12.3, 17.0)	14.3 (12.5, 15.9)
HR (95% CI)[a] *P* value	0.92 (0.76, 1.12) 0.413	



Subsequent Anti-Cancer Therapy

	Arm B: Atezo + CnP (n = 343)	Arm C: CnP (n = 340)
≥ 1 subsequent anti-cancer therapy, n (%)	116 (34%)	196 (58%)
Immunotherapy	19 (6%)	145 (43%)
Nivolumab	13 (4%)	124 (37%)
Pembrolizumab	4 (1%)	15 (4%)
Atezolizumab	2 (1%)	6 (2%)
Ipilimumab	1 (< 1%)	3 (1%)
Durvalumab	0	2 (1%)
Other	0	3 (1%)
Chemotherapy	102 (30%)	90 (26%)
Targeted therapy	22 (6%)	20 (6%)

- At the second interim OS analysis, the comparison of OS between Arms B and C did not meet the efficacy boundary, and OS continues to be followed

Safety and Conclusions

MUNICH 2018 ESMO congress

Safety Summary

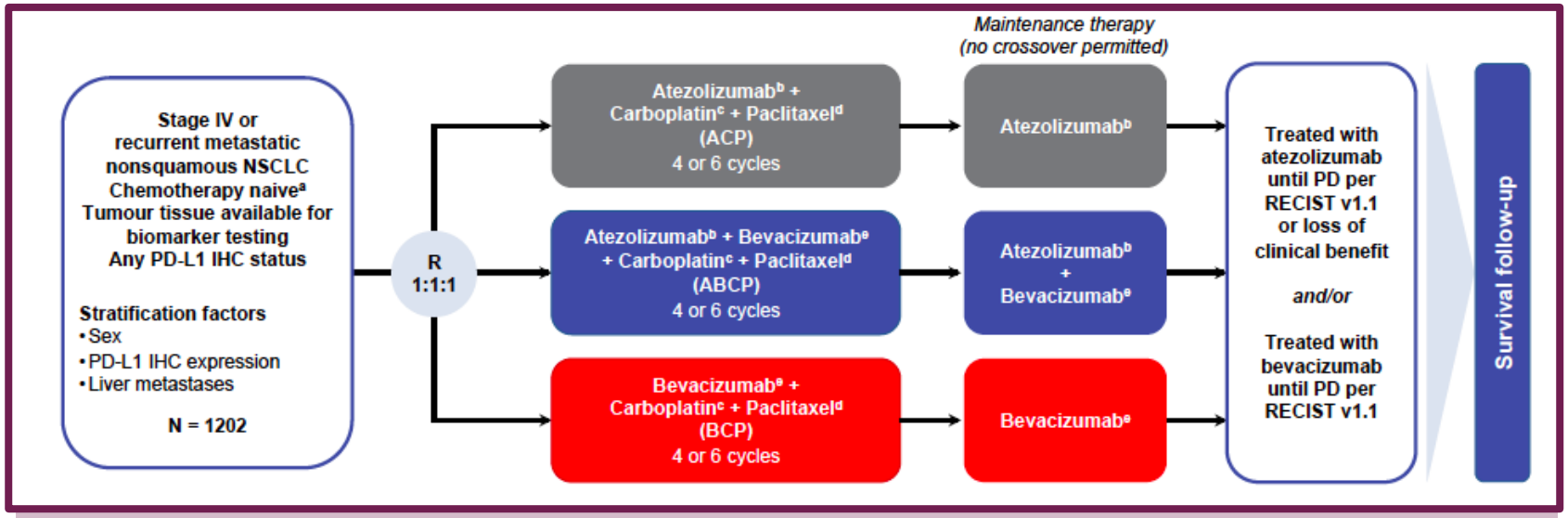
	Arm B: Atezo + CnP (n = 334)	Arm C: CnP (n = 334)
Median treatment duration (range), mo		
Atezolizumab	6.7 (0-33)	NA
Carboplatin	2.6 (0-7)	2.4 (0-7)
Nab-paclitaxel	3.0 (0-7)	2.8 (0-7)
Any AE	332 (99%)	324 (97%)
Treatment related[a]	316 (95%)	303 (91%)
Grade 3/4 AE	244 (73%)	220 (66%)
Treatment related[a]	227 (68%)	191 (57%)
Serious AE	154 (46%)	96 (29%)
Treatment related[a]	68 (20%)	35 (10%)
Grade 5 AE	32 (10%)	14 (4%)
Treatment related[a]	4 (1%)	3 (1%)
AE leading to any treatment withdrawal	99 (30%)	58 (17%)
AE leading to any dose modification/interruption	260 (78%)	219 (66%)

Conclusions:

- Updated PFS results show continued PFS benefit with atezo + CnP vs CnP in the ITT population
  - The PFS HR for atezo + CnP vs CnP in the ITT population was 0.74 (median PFS, 6.5 vs 5.6 months, respectively)
  - PFS benefit was observed across geographic subgroups
- At the second interim OS analysis in IMpower131, OS did not cross the efficacy boundary and continues to be followed
  - The OS HR for atezo + CnP vs CnP in the ITT population was 0.92 (median OS, 14.6 vs 14.3 months, respectively)
  - Nearly 43% of patients in the CnP arm received cancer immunotherapy in subsequent treatment lines, which may have contributed to the notable median OS of > 14 months in these patients with metastatic squamous NSCLC. Further analyses are required to investigate this hypothesis
- The safety of atezo + CnP was manageable and consistent with the profile for each agent; no new or unexpected signals were identified
- Final analyses are expected to be presented in 2019

1386PD. IMpower150: clinical safety, tolerability and immune-related adverse events in a Phase III study of Atezolizumab + chemotherapy +/- Bevacizumab vs chemotherapy + Bevacizumab in 1L nonsquamous NSCLC

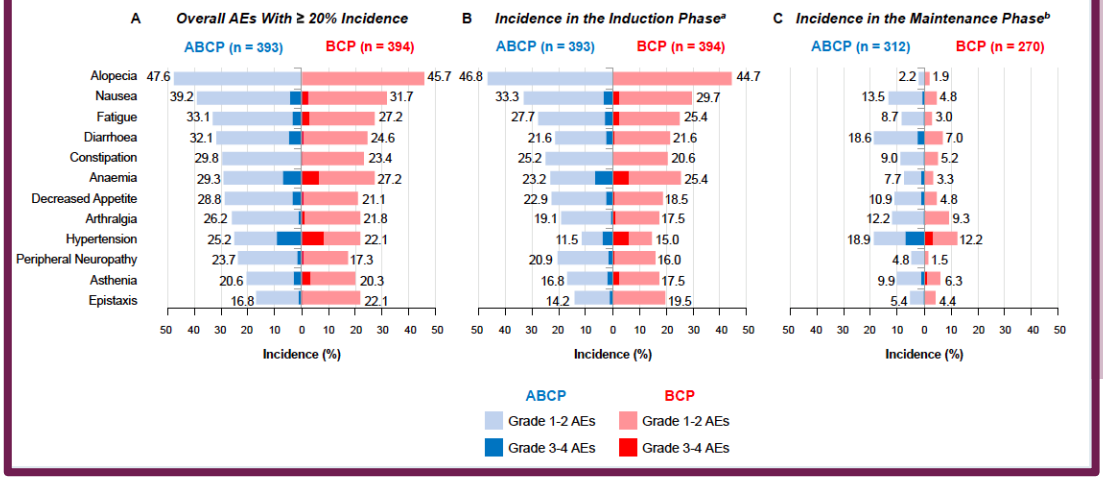
STUDY DESIGN



- IMpower150 is a randomized, open-label, international, Phase III study in 1L in patients with metastatic nonsquamous NSCLC designed to evaluated the efficacy and safety of ABCP vs BCP
- In this analysis, the safety and tolerability of the ABCP and BCP treatment regimens in the safety-evaluable population by treatment phase (induction vs maintenance) are presented

1386PD. IMpower150: clinical safety, tolerability and immune-related adverse events in a Phase III study of Atezolizumab + chemotherapy +/- Bevacizumab vs chemotherapy + Bevacizumab in 1L nonsquamous NSCLC

LUNG CANCER UPDATES
ESMO HIGHLIGHTS
19-23 DE OCTUBRE 2018, MUNICH



Most common all-causes Aes by phase of treatment

The majority of the most common Aes reported across treatment phases were grade 1-2 for both treatment arms

	ABCP			BCP		
Incidence, n (%)	**Induction[a] (n = 393)**	**Maintenance[b] (n = 312)**	**Overall (n = 393)**	**Induction[a] (n = 394)**	**Maintenance[b] (n = 270)**	**Overall (n = 394)**
Patients with ≥ 1 AE	380 (96.7)	289 (92.6)	386 (98.2)	389 (98.7)	219 (81.1)	390 (99.0)
Grade 3-4	211 (53.7)	115 (36.9)	250 (63.6)	204 (51.8)	61 (22.6)	230 (58.4)
Grade 5	15 (3.8)	8 (2.6)	24 (6.1)	11 (2.8)	9 (3.3)	21 (5.3)
Patients with ≥ 1 TRAE	362 (92.1)	221 (70.8)	370 (94.1)	375 (95.2)	147 (54.4)	377 (95.7)
Grade 3-4	191 (48.6)	66 (21.2)	223 (56.7)	176 (44.7)	30 (11.1)	191 (48.5)
Grade 5	10 (2.5)	1 (0.3)	11 (2.8)	5 (1.3)	3 (1.1)	9 (2.3)
Patients with ≥ 1 SAE	112 (28.5)	82 (26.3)	174 (44.3)	104 (26.4)	35 (13.0)	135 (34.3)
Patients with ≥ 1 AESI[c]	129 (32.8)	118 (37.8)	206 (52.4)	84 (21.3)	36 (13.3)	112 (28.4)
Grade 3-4	29 (7.4)	20 (6.4)	49 (12.5)	12 (3.0)	1 (0.4)	13 (3.3)

AE incidence by phase of treatment

The rates of grade 3-4 AEs, TRAEs, and SAEs were lower in the maintenance vs induction phases for all treatments arms

Iniciativa científica de:
GECP
Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

Most Common irAEs, Onset and Duration

Reck M. IMpower150 Safety Analysis
http://bit.ly/2Oex61e

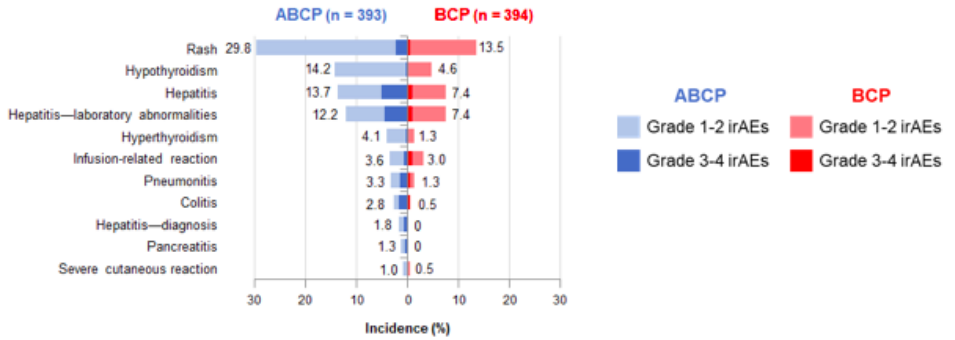
MUNICH 2018 ESMO congress

- Most irAEs in the ABCP arm appeared within the first 3 to 4 months of treatment and persisted for approximately 2 months
- Incidences of irAEs were similar across treatment phases for ABCP, with the exception of hypothyroidism, which had greater incidence in the maintenance phase vs the induction phase of treatment

Time to Onset, Duration, and Corticosteroid Use for the Most Common irAEs in the ABCP Arm

irAEs with ≥1% overall incidence in the ABCP arm (n =393)[a]	Median time to onset (range), mo	Median duration (range), mo	Corticosteroids used, n (%)
Hypothyroidism	5.9 (1.4-15.4)	NE (0.3-28.3[b])	4 (1.0)
Hepatitis – laboratory abnormalities	2.6 (0.2-17.3)	1.2 (0.1-16.3[b])	18 (4.6)
Hyperthyroidism	3.2 (1.4-7.6)	3.2 (0.7-20.9[b])	2 (0.5)
Pneumonitis	3.6 (0.3-17.2)	1.3 (0.2-10.6[b])	11 (2.8)
Colitis	3.4 (0.3-16.3)	2.0 (0.8-23.1[b])	8 (2.0)
Hepatitis – diagnosis	3.3 (0.4-6.8)	2.2 (0.1-16.5[b])	4 (1.0)
Pancreatitis	4.4 (0.7-9.4)	2.3 (0.4[b]-8.3[b])	3 (0.8)

Overall irAEs With ≥1% Incidence



- This analysis confirms the relative safety of the ABCP 4-drug regimen compared with the BCP 3-drug regimen, whilst significantly prolonging PFS and OS and maintaining patient-reported HRQOL, in the randomised phase III IMpower150 study

- The addition of Atezolizumab to BCP did not lead to premature withdrawal from chemotherapy compared with the BCP arm; therefore, the results support the use of this 4-drug ABCP treatment regimen for patients with 1L NSCLC

- The safety of the ABCP regimen appears to be tolerable and manageable compared with BCP, with minimal increase in the incidence of all-cause AEs, TRAEs and SEAs, despite longer treatment exposure