#ESMOUPDATES

Iniciativa científica de:

GECP lung cancer research

LUNG CANCER UPDATES

ESMO HIGHLIGHTS

27 SEPTIEMBRE - 1 OCTUBRE 2019

Con la colaboración de:

Bristol-Myers Squibb

illumina

Lilly

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27 SEPTIEMBRE - 1 OCTUBRE 2019

BARCELONA

Iniciativa científica de:

GECP lung cancer research

SCLC (I)

Dr. Manuel Dómine Gómez

Con la colaboración de:

Bristol-Myers Squibb

illumina

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INMUNOTERAPIA + QUIMIOTERAPIA
Carcinoma Microcítico Pulmón Enfermedad Extendida

- 17360: IMpower 133 Updated Overall survival (0S) analysis of first-line (1L) atezolizumab + carboplatin + etoposide in ES SCLC (M Reck)

- LBA89 PDL-1 expression patterns of proression and patients reported outcomes (PROs) with durvalumab plus platinum etoposide in ES-SCLC: Results from CASPIAN (M Garassino)

IMpower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC)

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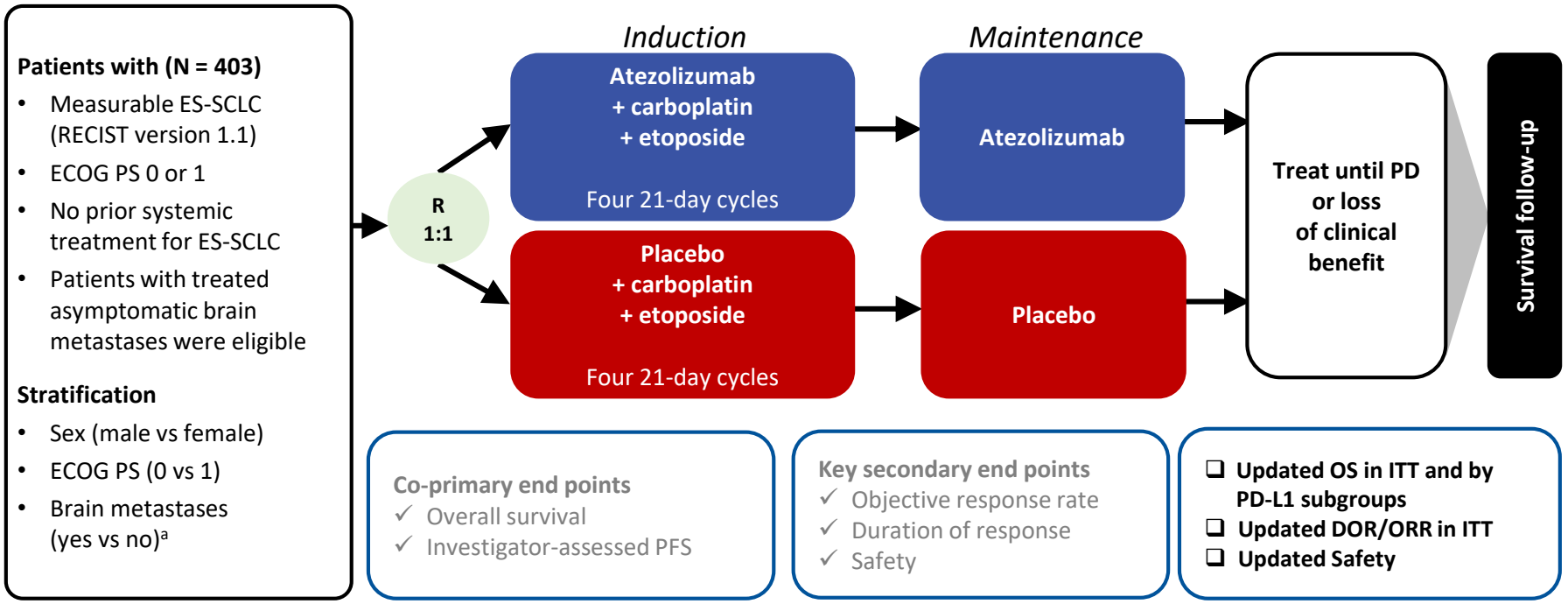
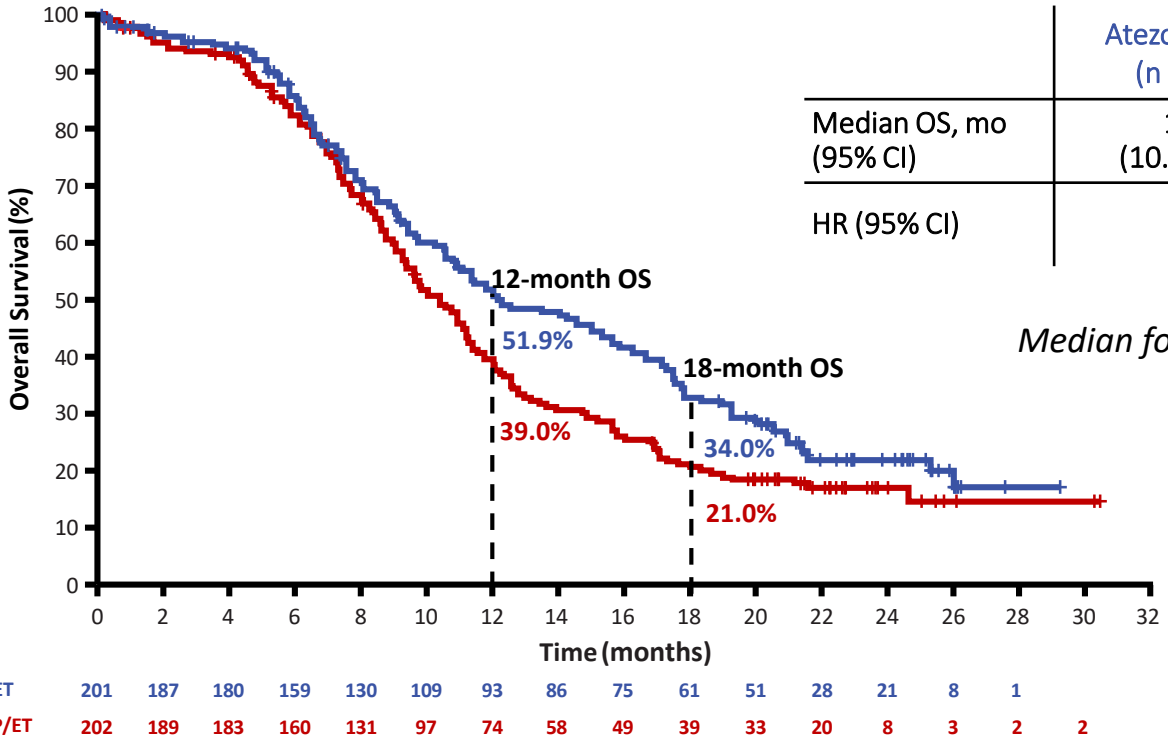
IMpower133 study design



Atezolizumab, 1200 mg IV, Day 1; Carboplatin, AUC 5 mg/mL/min IV, Day 1; Etoposide, 100 mg/m^2 IV, Days 1–3.
[a] Only patients with treated brain metastases were eligible.

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

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]	

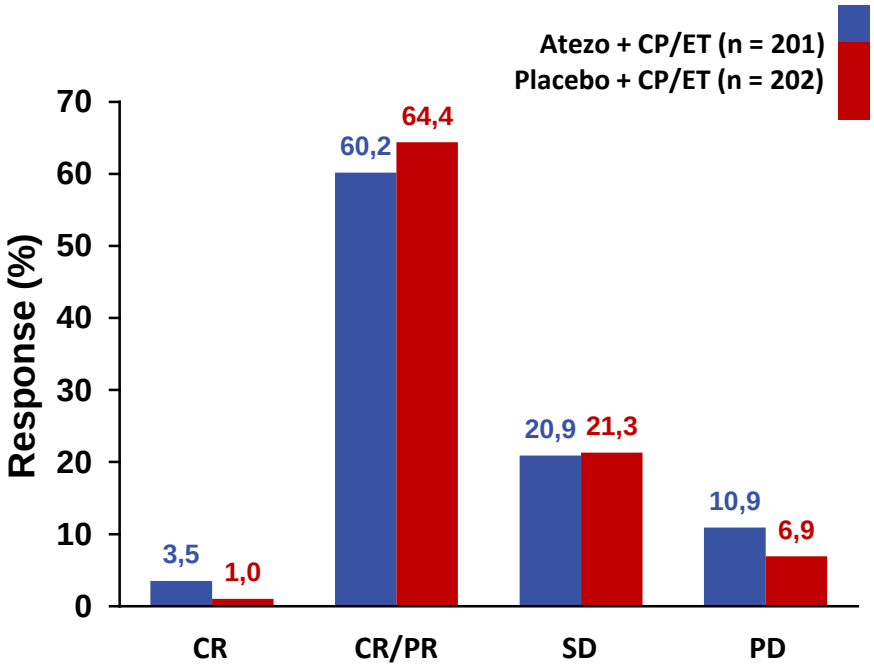
Median follow-up, 22.9 months

No. at risk															
Atezo + CP/ET	201	187	180	159	130	109	93	86	75	61	51	28	21	8	1
Placebo + CP/ET	202	189	183	160	131	97	74	58	49	39	33	20	8	3	2	2

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

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

Updated ORR and DOR in ITT



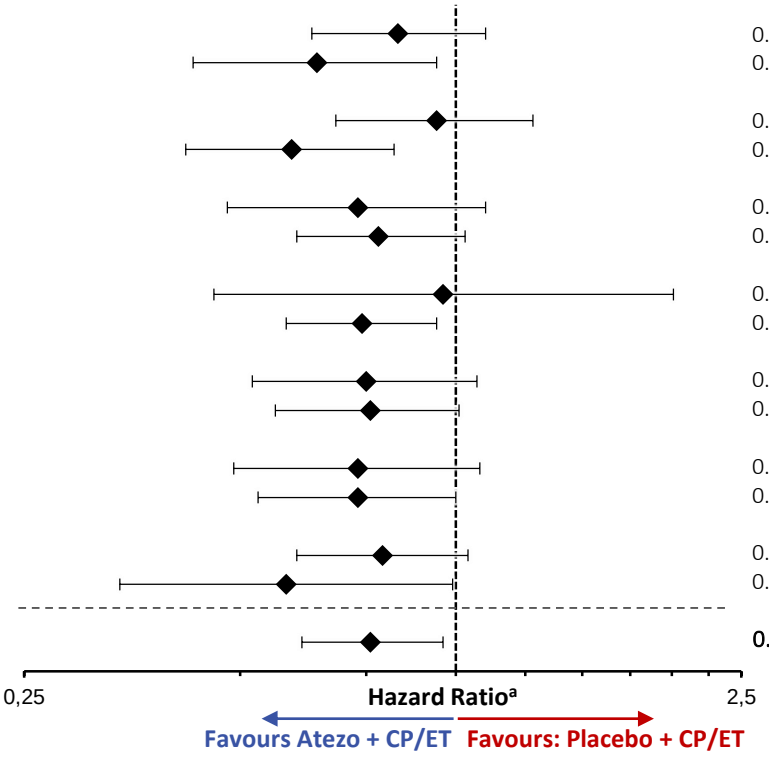
Missing or unevaluable data in atezo + CP/ET(8.0%); placebo + CP/ET (7.4%).
+Censored.
[a] defined as patients without events
CCOD 24 January 2019

Duration of response	Atezo + CP/ET (n = 121)	Placebo + CP/ET (n = 130)
mDOR, months (range)	4.2 (1.4+ to 24.3+)	3.9 (2.0 to 24.2+)
Patients with ongoing response, n (%)[a]	11 (9.1)	3 (2.3)

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

Updated OS in subgroups

Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
Male (n = 261)	12.2	10.9	0.83 (0.63, 1.10)
Female (n = 142)	13.6	9.5	0.64 (0.43, 0.94)
< 65 years (n = 217)	12.1	11.5	0.94 (0.68, 1.28)
≥ 65 years (n = 186)	14.4	9.6	0.59 (0.42, 0.82)
ECOG PS 0 (n = 140)	16.8	12.6	0.73 (0.48, 1.10)
ECOG PS 1 (n = 263)	11.3	9.3	0.78 (0.60, 1.03)
Brain metastases (n = 35)	8.5	9.7	0.96 (0.46, 2.01)
No brain metastases (n = 368)	12.6	10.4	0.74 (0.58, 0.94)
Liver metastases (n = 149)	9.3	7.8	0.75 (0.52, 1.07)
No liver metastases (n = 254)	16.3	11.2	0.76 (0.56, 1.01)
bTMB < 10 (n = 134)	11.8	9.4	0.73 (0.49, 1.08)
bTMB ≥ 10 (n = 212)	14.9	11.2	0.73 (0.53, 1.00)
bTMB < 16 (n = 266)	12.5	10.0	0.79 (0.60, 1.04)
bTMB ≥ 16 (n = 80)	17.1	11.9	0.58 (0.34, 0.99)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**



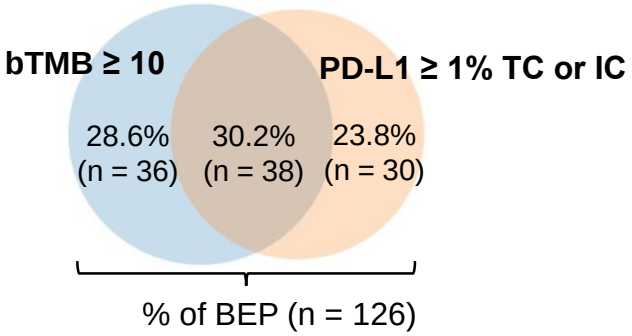
A total of 57 patients had unknown bTMB score.
bTMB, blood tumour mutational burden.
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
CCOD 24 January 2019

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

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



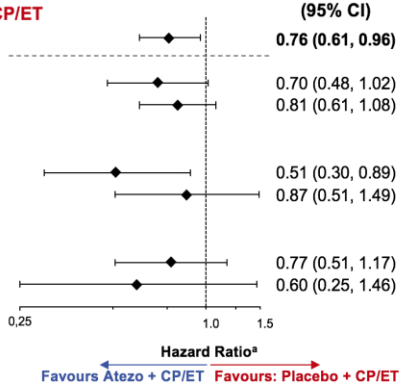
PD-L1 IHC expression in ES-SCLC (n = 137)

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)

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

Updated OS in PD-L1 expression subgroups

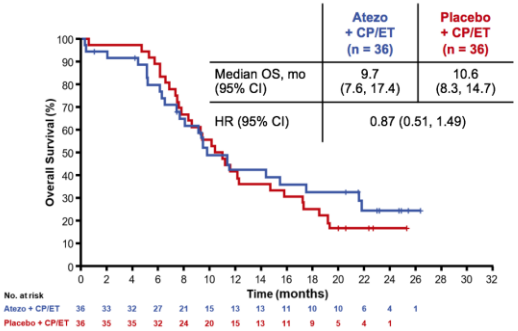
Subgroup	Median OS (months) Atezo + CP/ET	Median OS (months) Placebo + CP/ET	OS Hazard Ratio[a] (95% CI)
ITT (N = 403)	**12.3**	**10.3**	**0.76 (0.61, 0.96)**
ITT-BEP (n = 137)	9.9	8.9	0.70 (0.48, 1.02)
Non-BEP (n = 266)	14.6	11.2	0.81 (0.61, 1.08)
PD-L1 expression 1% TC or IC			
< 1% PD-L1 (n = 65)	10.2	8.3	0.51 (0.30, 0.89)
≥ 1% PD-L1 (n = 72)	9.7	10.6	0.87 (0.51, 1.49)
PD-L1 expression 5% TC or IC			
< 5% PD-L1 (n = 108)	9.2	8.9	0.77 (0.51, 1.17)
≥ 5% PD-L1 (n = 29)	21.6	9.2	0.60 (0.25, 1.46)



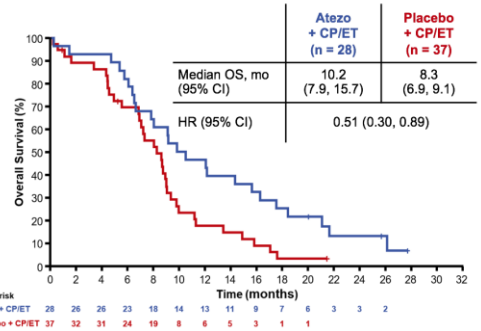
[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.
CCOD 24 January 2019

Updated OS in PD-L1 expression subgroups

PD-L1 Expression ≥ 1% TC or IC



PD-L1 Expression < 1% TC or IC



Median follow-up, 22.9 months

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

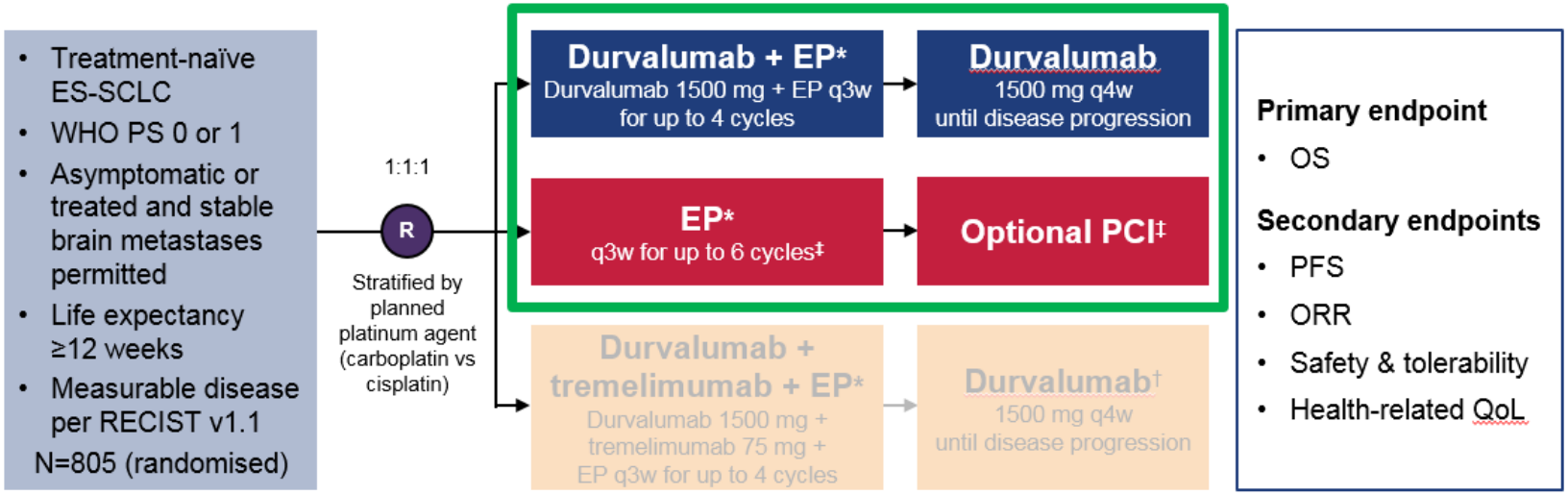
Conclusions

- Atezolizumab + CP/ET continued to demonstrate an improvement in OS for 1L ES-SCLC with 22.9 months of follow-up
  - mOS 12.3 months; HR: 0.76; 95% CI, 0.60, 0.95
  - 18-month landmark OS demonstrated a survival increase of 13% in the atezolizumab + CP/ET (34%) arm compared with the placebo + CP/ET (21%) arm
- Exploratory biomarker analyses that included both PD-L1 IHC and bTMB suggest that patients derive treatment benefit from the addition of atezolizumab regardless of biomarker status
  - PD-L1 analysis was based on a limited data set (34% of the ITT)
  - Further studies are needed to evaluate potential biomarkers and association with outcomes
- These results further support the addition of atezolizumab to CP/ET as the new standard of care for untreated ES-SCLC in an all-comer patient population

IMpower 133 Update OS Analysis: presented by Dr Martin Reck http://bit.ly/2Z32WhW

CASPIAN Study Design

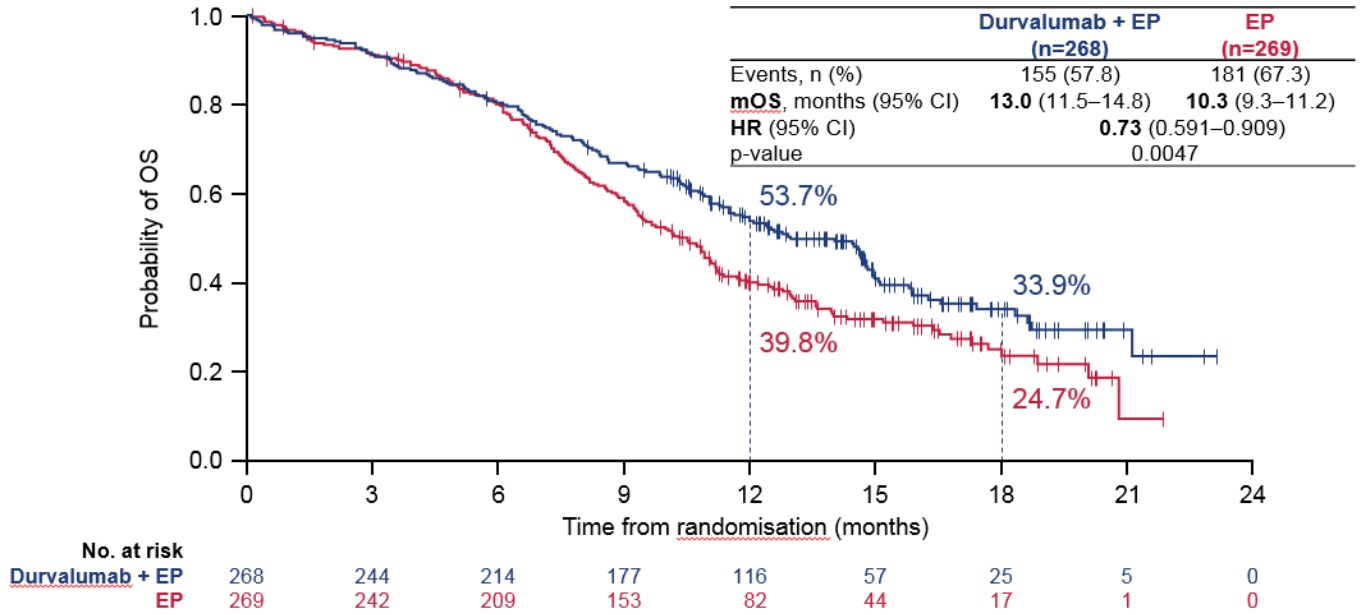
Phase 3, global, randomised, open-label, sponsor-blind multicentre study



Following preplanned interim analysis by the IDMC, the durvalumab + tremelimumab + EP versus EP comparison continues to final analysis

CASPIAN Study

Overall Survival (Primary Endpoint)

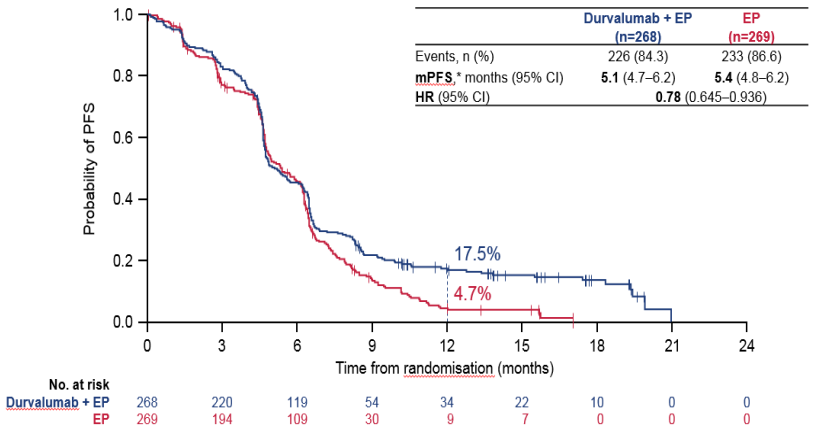


	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	155 (57.8)	181 (67.3)
mOS, months (95% CI)	**13.0** (11.5–14.8)	**10.3** (9.3–11.2)
HR (95% CI)	**0.73** (0.591–0.909)	
p-value	0.0047	

Paz-Ares L et al WCLC 2019

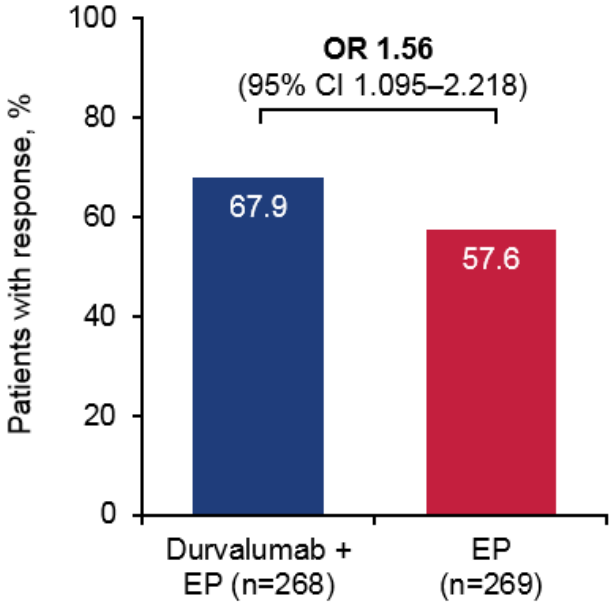
CASPIAN Study

Progression-free Survival



	Durvalumab + EP (n=268)	EP (n=269)
Events, n (%)	226 (84.3)	233 (86.6)
mPFS,* months (95% CI)	**5.1** (4.7–6.2)	**5.4** (4.8–6.2)
HR (95% CI)	**0.78** (0.645–0.936)	

ORR*



Iniciativa científica de:

GeCP lung cancer research

Paz-Ares L et al WCLC 2019

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)

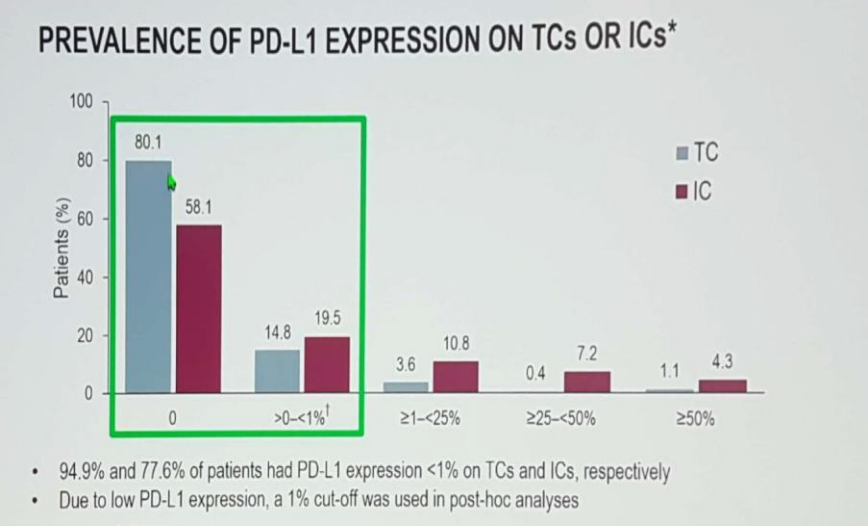
Sites of new lesions (>5% patients)

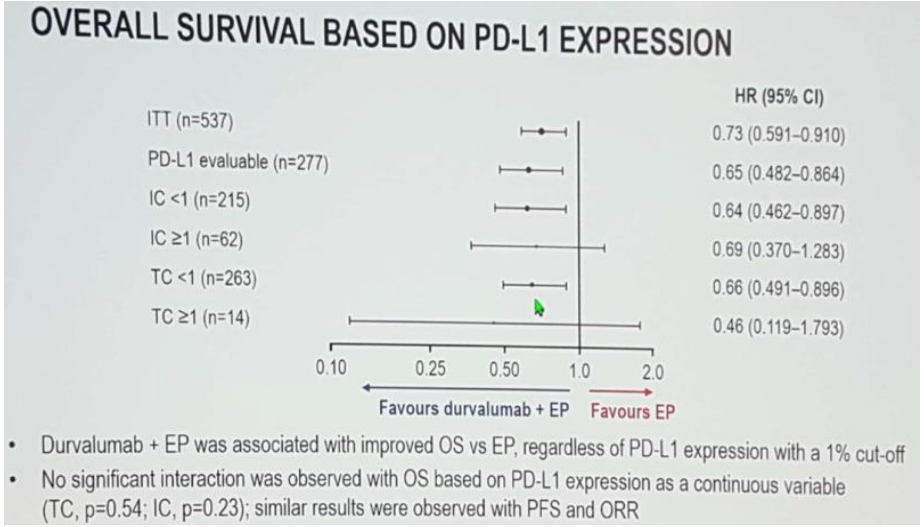
	Durvalumab + EP (N=268)	EP (N=269)
New lesions, n (%)	111 (41.4)	127 (47.2)
Lung	23 (8.6)	41 (15.2)
Brain/CNS	31 (11.6)	31 (11.5)
Liver	15 (5.6)	24 (8.9)
Bone	12 (4.5)	19 (7.1)
Regional lymph nodes	15 (5.6)	12 (4.5)

- 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

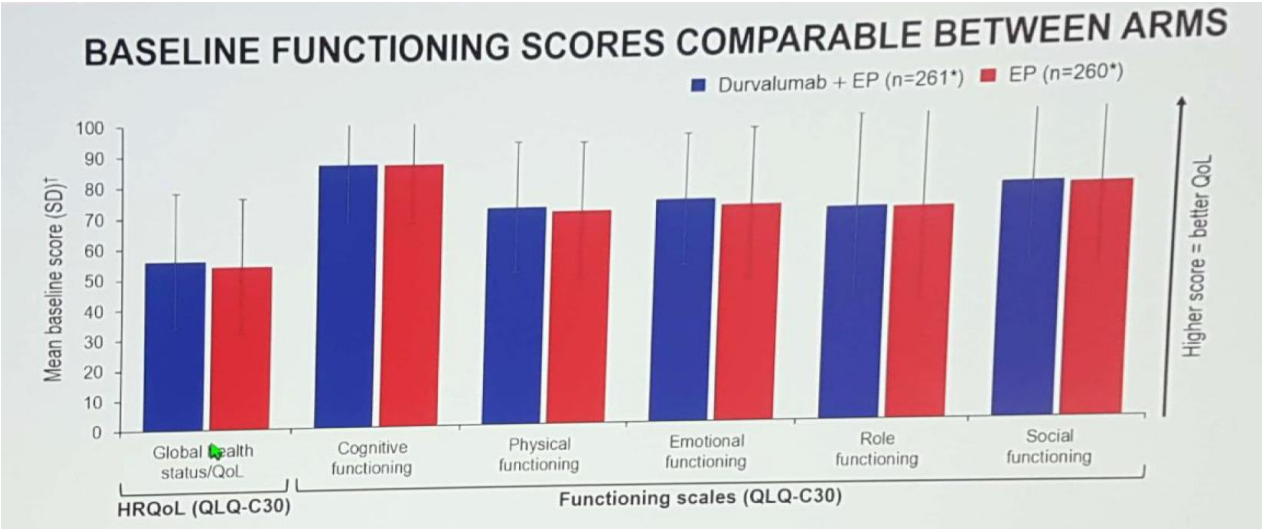
- Caspian la determinación de PD-L1 era obligatoria si había tejido, se utilizó el método Ventana SP263

- 59% tenían tumor disponible y 51.6% PD-L1 fue evaluable



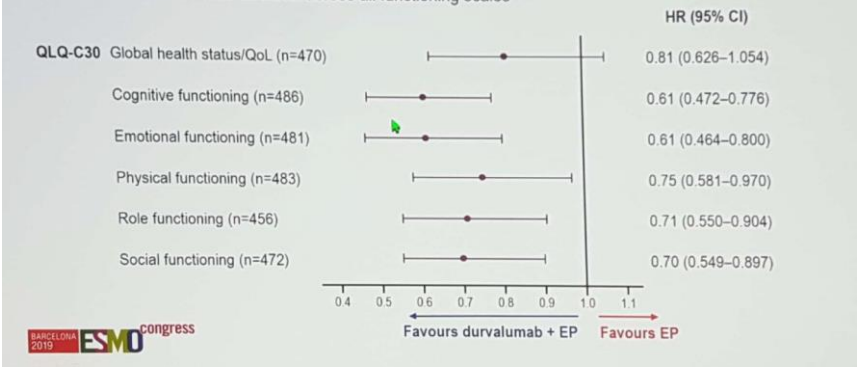


BASELINE FUNCTIONING SCORES COMPARABLE BETWEEN ARMS



TIME TO DETERIORATION IN FUNCTIONING SCALES

- Durvalumab + EP was favoured across all functioning scales



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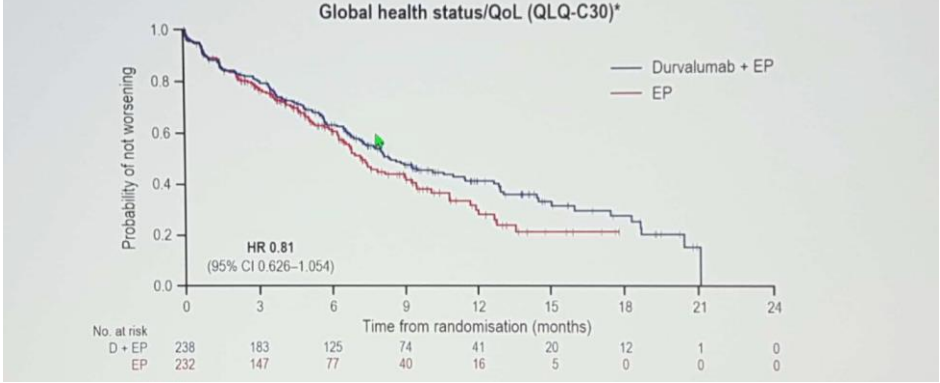
TIME TO DETERIORATION



Iniciativa científica de:

GECP lung cancer research

Conclusiones

- 1º Línea Durvalumab + EP demostró un beneficio significativo en OS HR 0.73 (0.591 0.909, p= 0OO47)

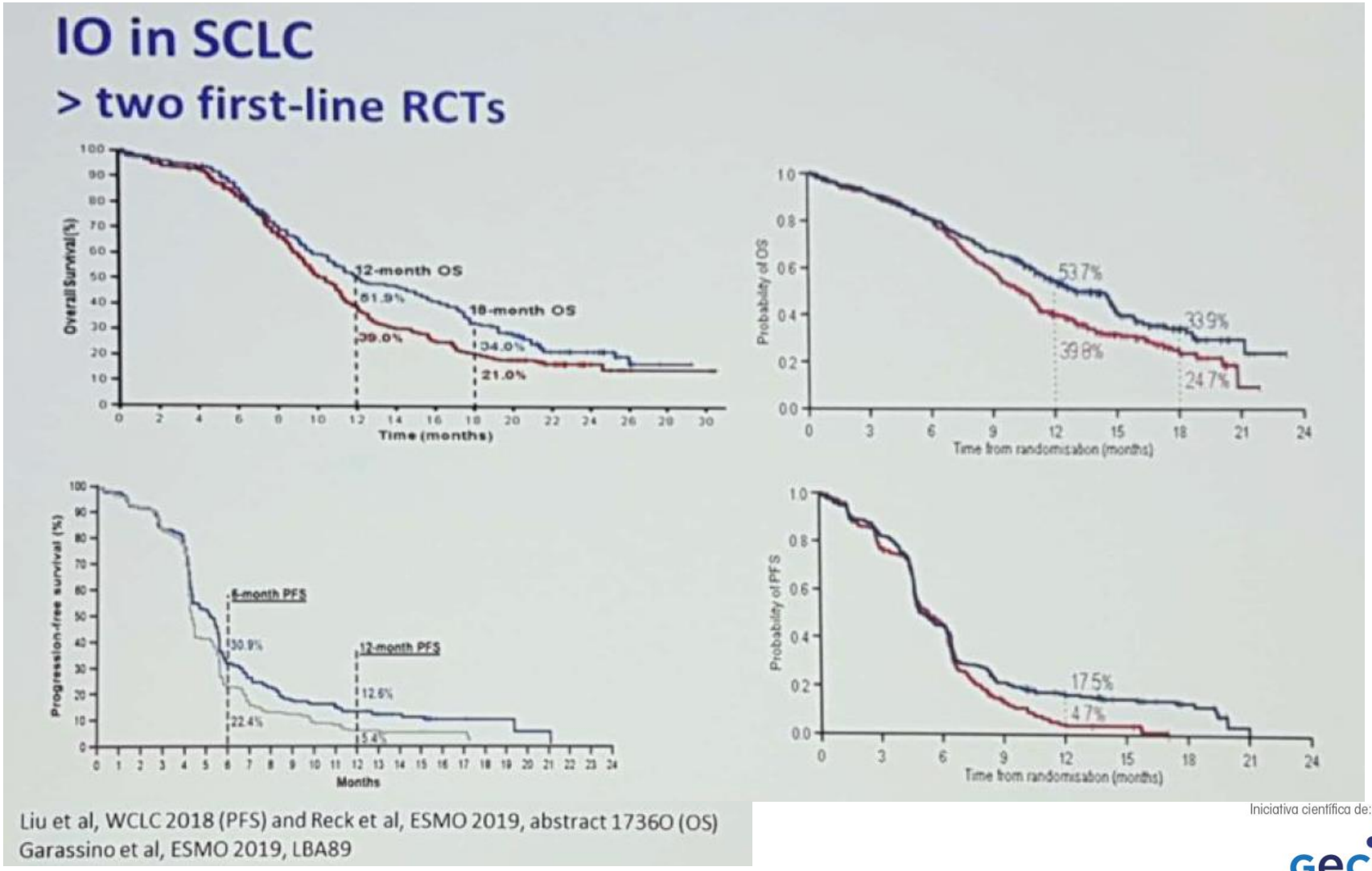
- Pacientes con durva + EP desarrollaron un menor número de nuevas lesiones incluido pulmón, hígado y hueso. Similar incidencia para metástasis cerebrales

- La expresión de PD-L1 fue baja y no se encontró correlación con los resultados clínicos

- Se están realizando análisis exploratorios con otros marcadores de biomarcadores

- Tiempo hasta el deterioro y Qol favorecen al brazo de durva + EP

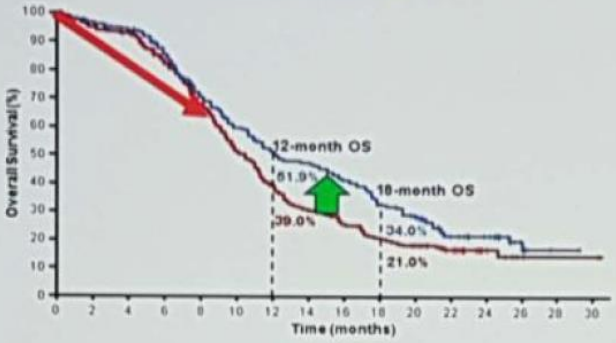
INMUNOTERAPIA + QUIMIOTERAPIA
Carcinoma Microcítico Pulmón Enfermedad Extendida

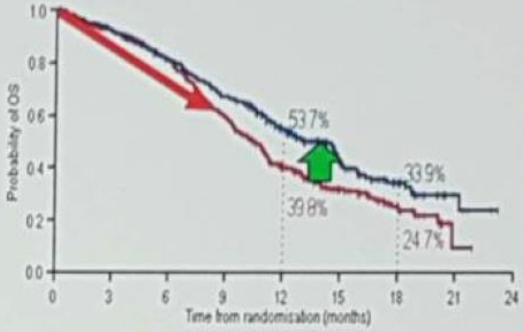


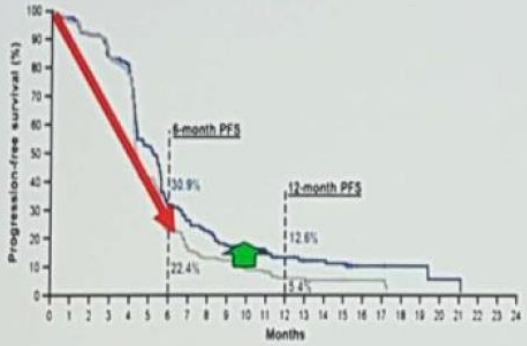
Liu et al, WCLC 2018 (PFS) and Reck et al, ESMO 2019, abstract 1736O (OS)
Garassino et al, ESMO 2019, LBA89

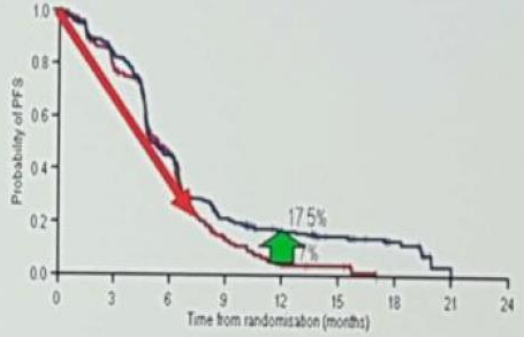
IO in SCLC

> two first-line RCTs





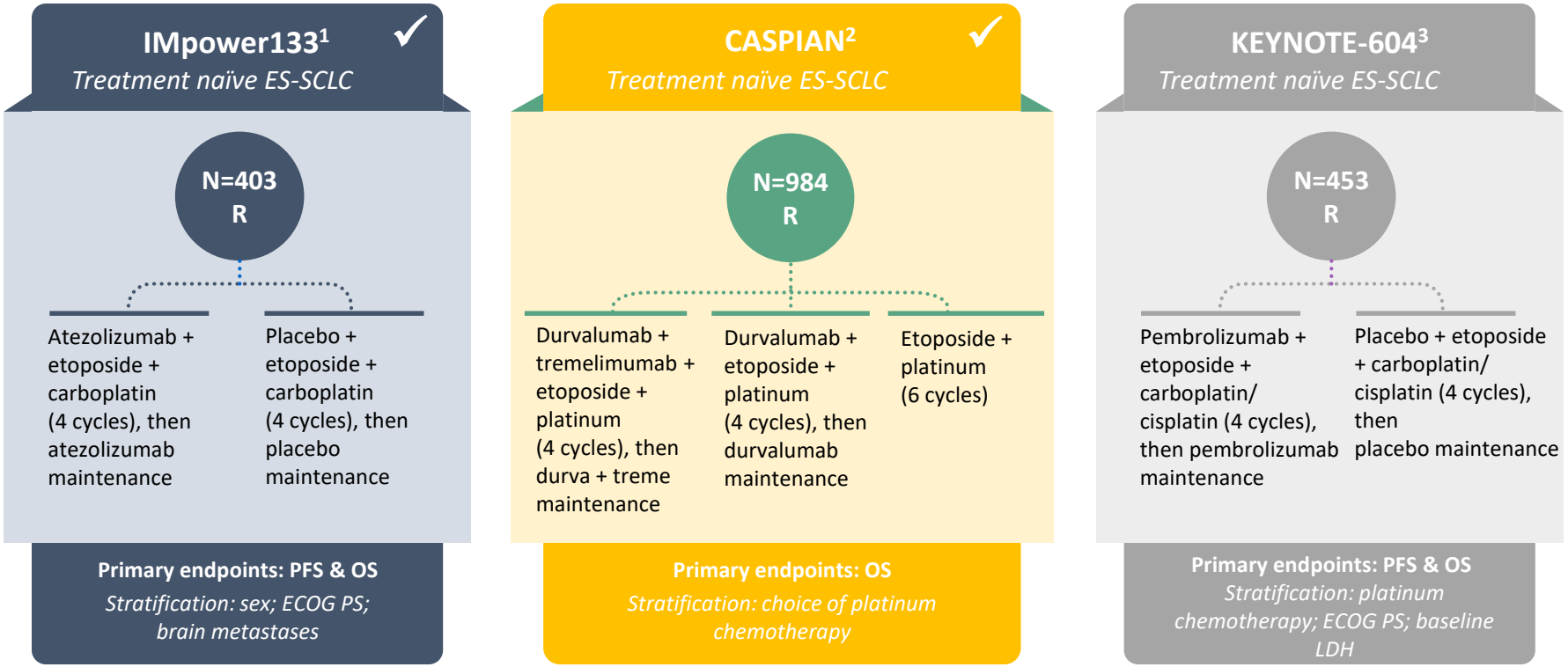




- Initially no difference
- Difference from month 6 onwards
  - Delayed effect?
  - Maintenance effect?
- A fraction of patients with a relevant effect

Liu et al, WCLC 2018 (PFS) and Reck et al, ESMO 2019, abstract 17360 (OS)
Garassino et al, ESMO 2019, LBA89

KEYNOTE-604 is an ongoing trial in ES-SCLC



1. Horn, et al. New Eng J Med 2018; 2. Paz-Ares, et al. WCLC 2019 (Abs PL02.11) 3. Rudin, et al. ESMO 2017 (Abs 153TiP)

Iniciativa científica de:
GeCP lung cancer research

Conclusiones

- Etoposide/Platinum was the preferred treatment option for ES-SCLC and median OS was consistently below 10 months
- Two randomized phase III studies confirmed improvement of OS by combination of EP with immunotherapy for patients with ES-SCLC
- Clinical relevant benefit in a fraction, split of curves after chemo period
- No Biomarkers to identify this fraction of patients in phase III trials