IMpower-133

N Engl J Med 2018; 379:2220-2229

(PD1/PDL1-161)

WCLC 2018
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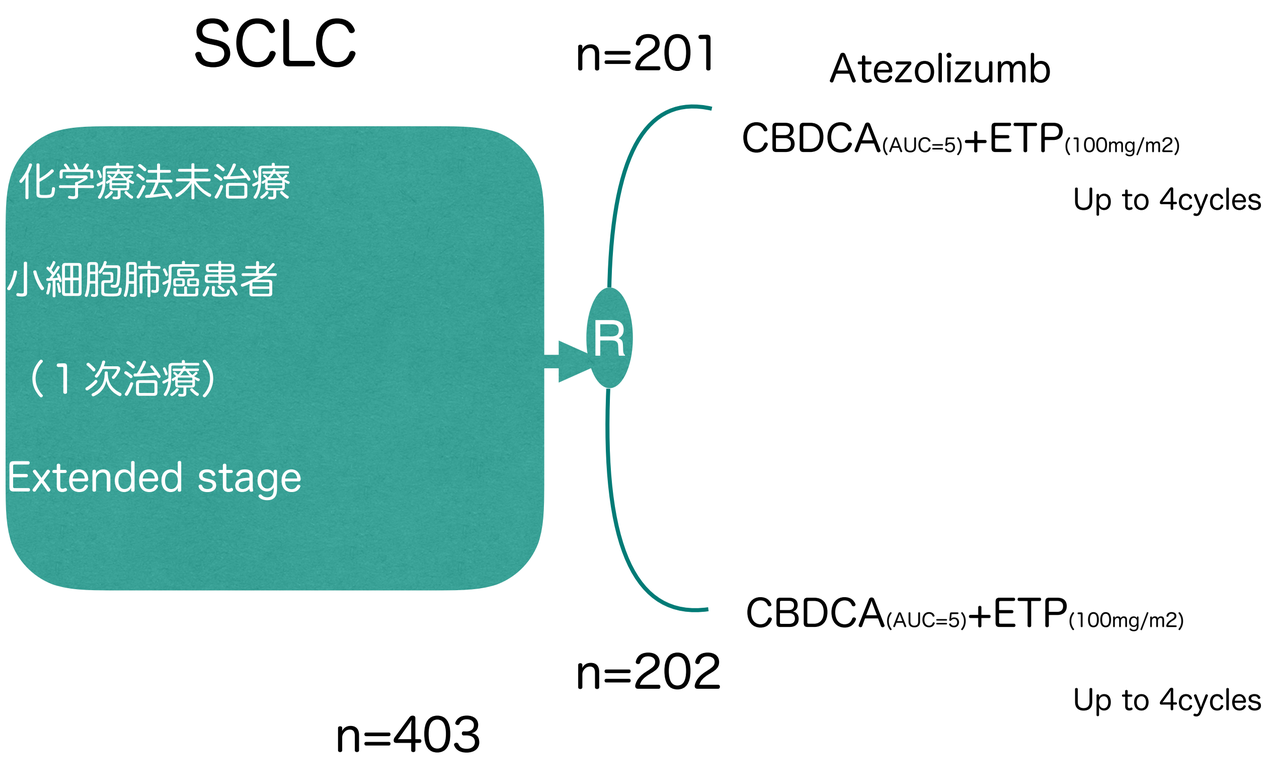
Primary Endpoint: PFS, OS

Secondary Endpoint: ORR, DOR, Safety



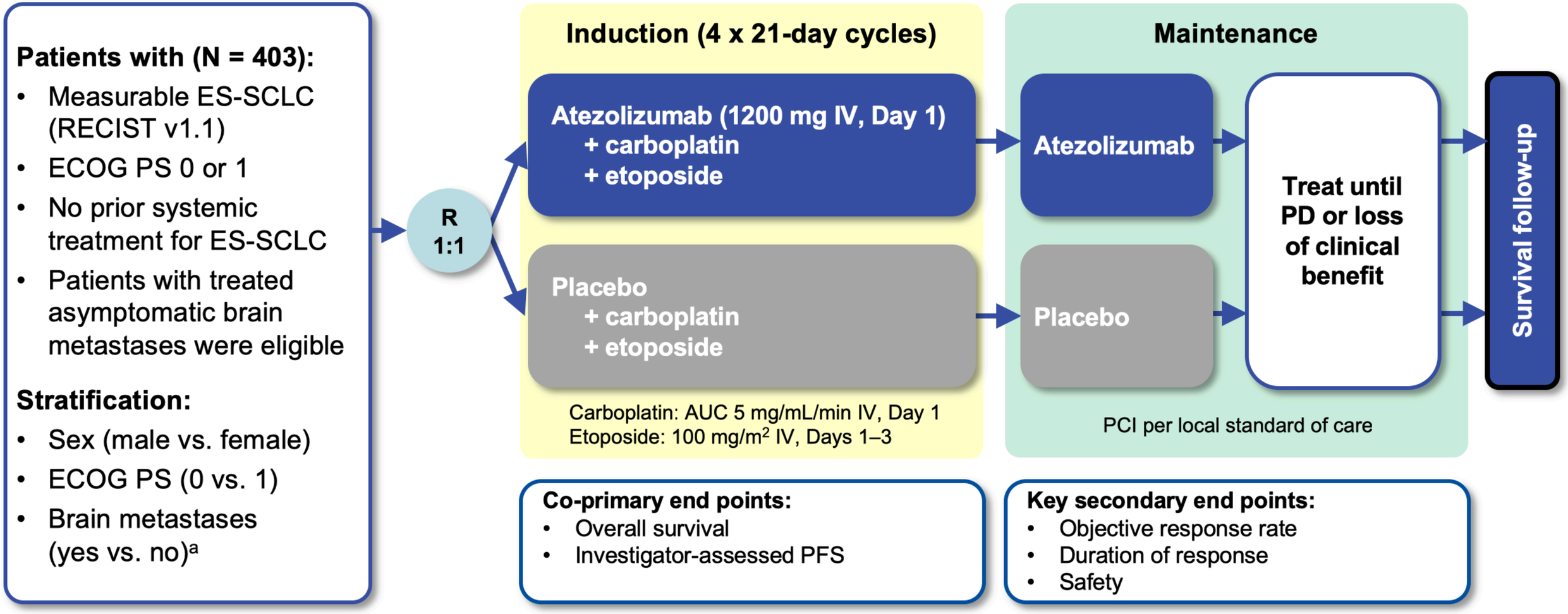
	PFS	median OS	1年生存率	1年 無増悪生存率	ORR	DoR
	5.2ヶ月	12.3ヶ月	51.7%	12.6%	60%	4.2ヶ月
	HR=0.77 p=0.017	HR=0.70 p=0.069				
	4.3ヶ月	10.3ヶ月	38.2%	5.4%	64%	3.9ヶ月

※未治療の進展型小細胞肺がん患者に対する1次治療として既存の標準治療より成績が上回る治療レジメンは20年ぶりになる。

Arm A (Tecentriq plus chemotherapy) vs Arm B (Placebo plus chemotherapy) in ITT		
	Arm A **n=201**	**Arm B** **n=202**
Median OS **(95% CI), months**	12.3 (10.8, 15.9)	10.3 (9.3, 11.3)
HR (95% CI); *P* value	0.70 (0.54, 0.91); p=0.0069	
1-year OS rate	51.7%	38.2%
ORR, %	60%	64%
Median DOR, months	4.2	3.9
HR (95% CI)	0.70 (0.53, 0.92)	
Median PFS **(95% CI), months**	5.2 (4.4, 5.6)	4.3 (4.2, 4.5)
HR (95% CI)	0.77 (0.62, 0.96) p=0.017	
1-year PFS rate	12.6%	5.4%

CI, confidence interval; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



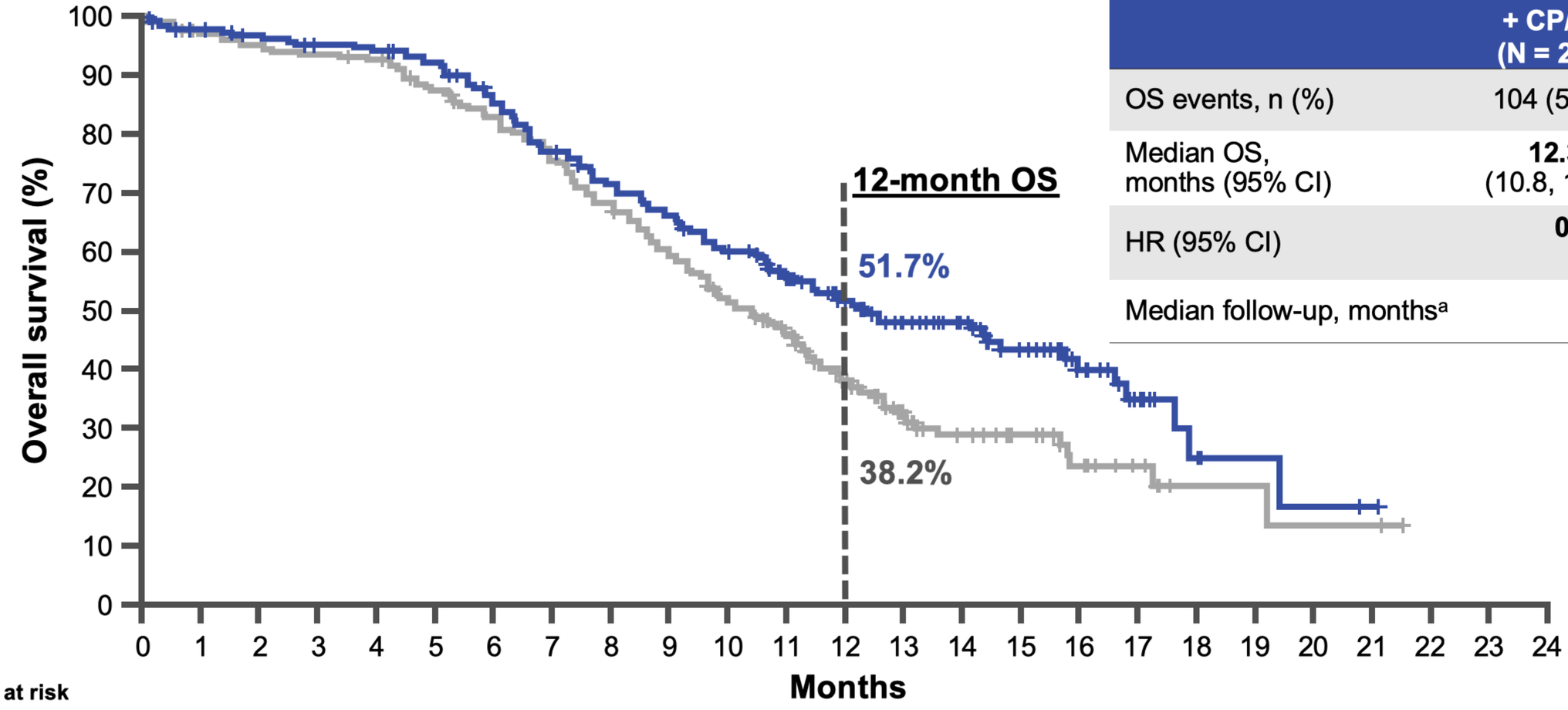
[a] Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.

Baseline characteristics

Characteristic	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Median age (range) — years	64 (28–90)	64 (26–87)
Age group — no. (%)		
< 65 years	111 (55)	106 (52)
≥ 65 years	90 (45)	96 (48)
Male sex — no. (%)[a]	129 (64)	132 (65)
Smoking status[b]		
Current smoker	74 (36.8)	75 (37.1)
Former smoker	118 (58.7)	124 (61.4)
Race — no. (%)		
White	163 (81)	159 (79)
Asian	33 (16)	36 (18)
Other	5 (2)	7 (3)
ECOG PS — no. (%)[a]		
0	73 (36)	67 (33)
1	128 (64)	135 (67)
Brain metastases — no. (%)[a]		
Yes	17 (8)	18 (9)
Liver metastases — no. (%)		
Yes	77 (38)	72 (36)

Clinical data cutoff date: April 24, 2018. [a] Data reported per electronic case report form. [b] Nine patients in the atezolizumab group and three patients in the placebo group have never smoked. CP/ET, carboplatin + etoposide.

Overall survival



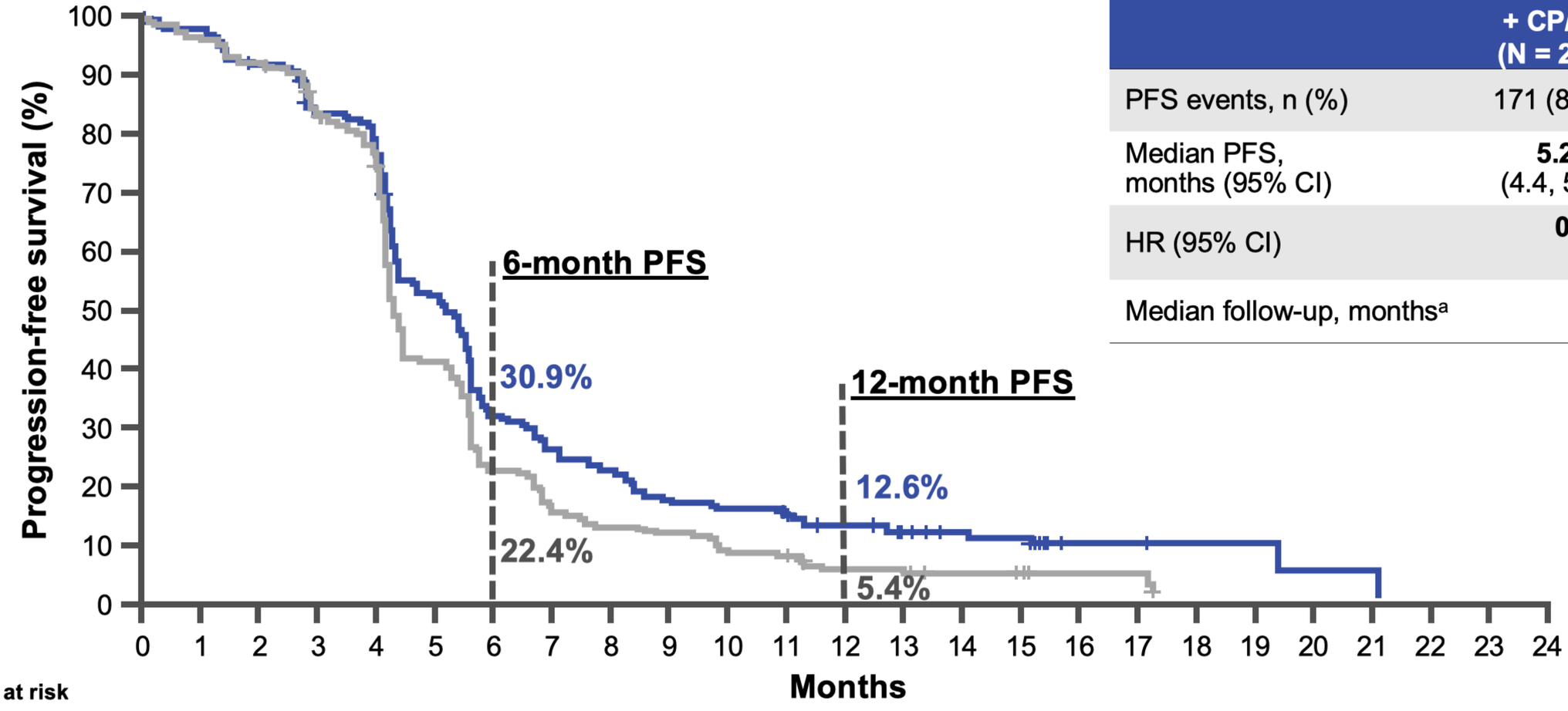
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
OS events, n (%)	104 (51.7)	134 (66.3)
Median OS, months (95% CI)	**12.3** (10.8, 15.9)	**10.3** (9.3, 11.3)
HR (95% CI)	**0.70** (0.54, 0.91) p = 0.0069	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	191	187	182	180	174	159	142	130	121	108	92	74	58	46	33	21	11	5	3	2	1
Placebo	202	194	189	186	183	171	160	146	131	114	96	81	59	36	27	21	13	8	3	3	2	2

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Investigator-assessed progression-free survival



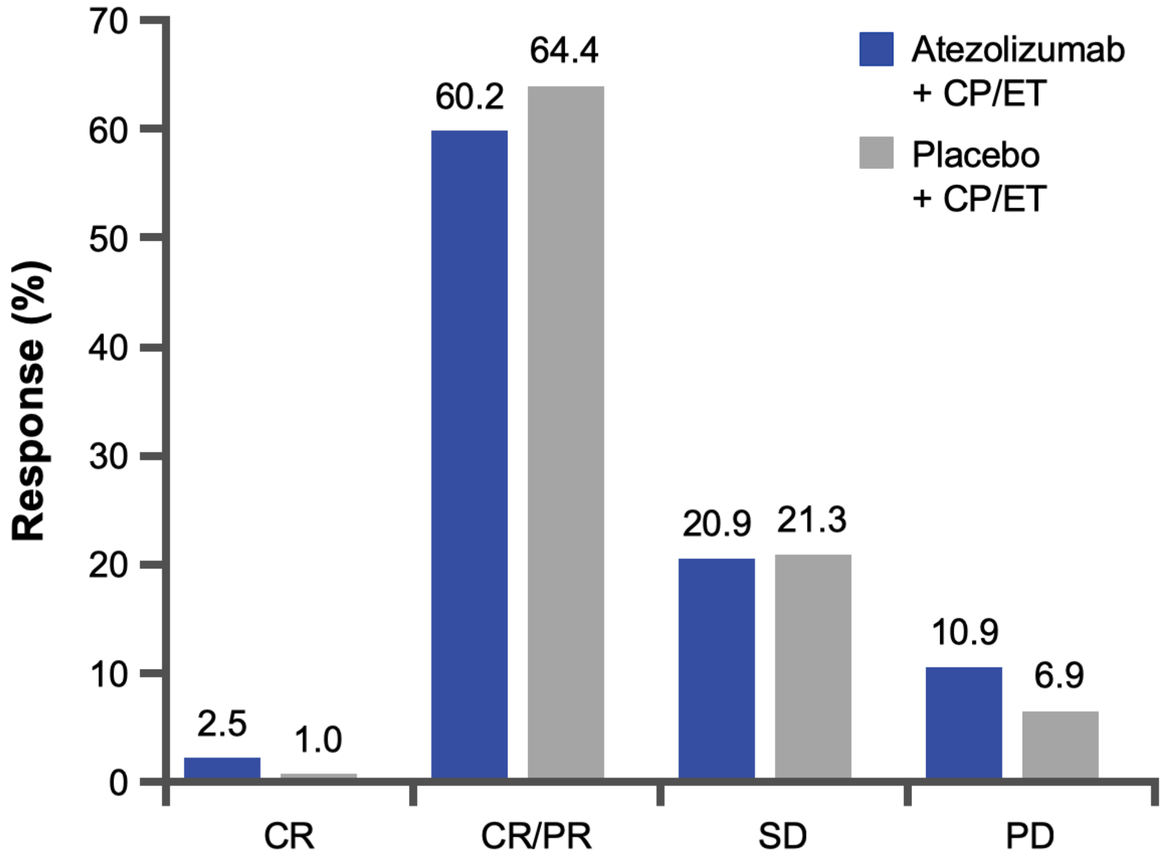
	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
PFS events, n (%)	171 (85.1)	189 (93.6)
Median PFS, months (95% CI)	**5.2** (4.4, 5.6)	**4.3** (4.2, 4.5)
HR (95% CI)	**0.77** (0.62, 0.96) p = 0.017	
Median follow-up, months[a]	13.9	

No. at risk

Atezolizumab	201	190	178	158	147	98	58	48	41	32	29	26	21	15	12	11	3	3	2	2	1	1
Placebo	202	193	184	167	147	80	44	30	25	23	16	15	9	9	6	5	3	3				

[a] Clinical data cutoff date: April 24, 2018, 11 months after the last patient was enrolled. CI, confidence interval; HR, hazard ratio; CP/ET, carboplatin + etoposide.

Confirmed objective response and duration of response

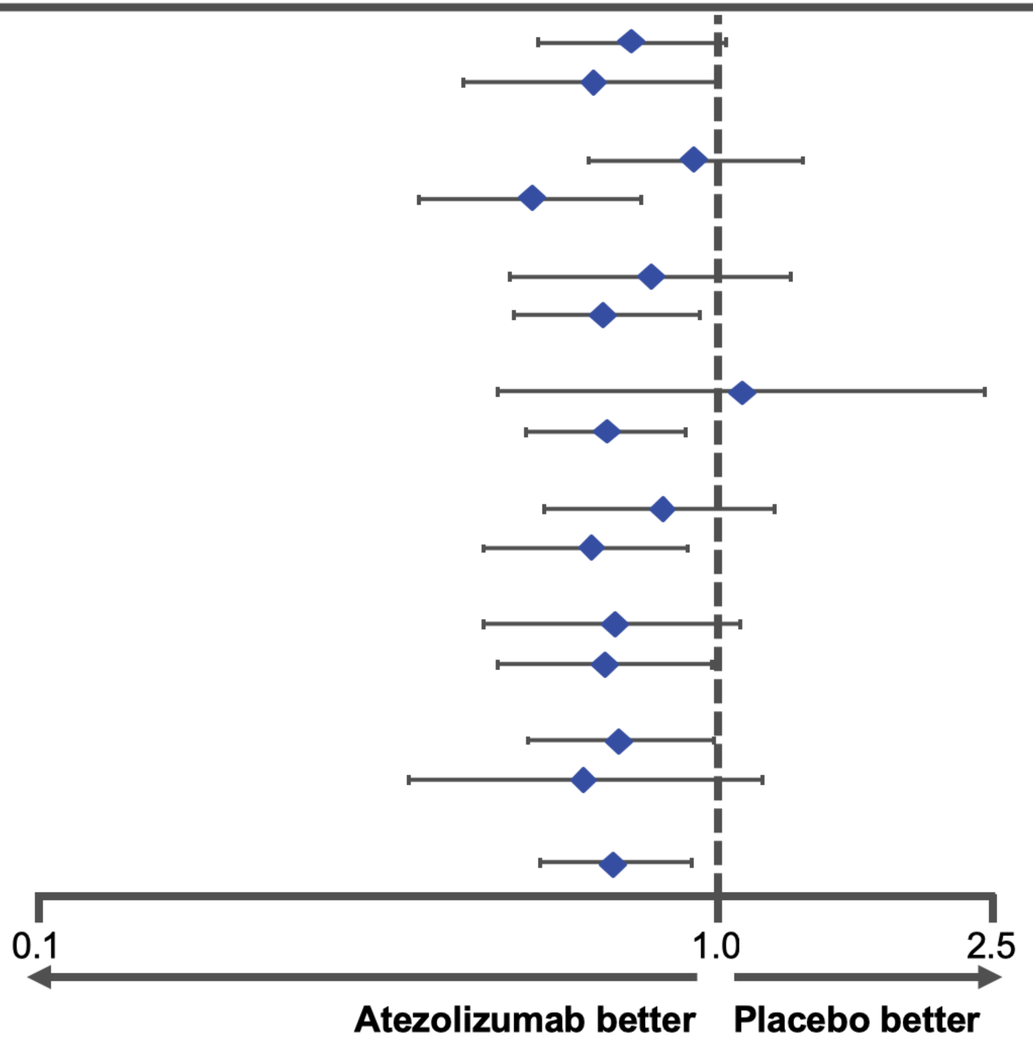


Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4[a] to 19.5)	3.9 (2.0 to 16.1[a])
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%)[b]	18 (14.9)	7 (5.4)

[a] Censored. [b] At clinical cutoff date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

Overall survival in key subgroups

Population	Median overall survival (months) Atezolizumab + CP/ET	Placebo + CP/ET	OS hazard ratio[a] (95% CI)
Male (n = 261)	12.3	10.9	0.74 (0.54, 1.02)
Female (n = 142)	12.5	9.5	0.65 (0.42, 1.00)
< 65 years (n = 217)	12.1	11.5	0.92 (0.64, 1.32)
≥ 65 years (n = 186)	12.5	9.6	0.53 (0.36, 0.77)
ECOG PS 0 (n = 140)	16.6	12.4	0.79 (0.49, 1.27)
ECOG PS 1 (n = 263)	11.4	9.3	0.68 (0.50, 0.93)
Brain metastases (n = 35)	8.5	9.7	1.07 (0.47, 2.43)
No brain metastases (n = 368)	12.6	10.4	0.68 (0.52, 0.89)
Liver metastases (n = 149)	9.3	7.8	0.81 (0.55, 1.20)
No liver metastases (n = 254)	16.8	11.2	0.64 (0.45, 0.90)
bTMB < 10 mut/mb (n = 139)	11.8	9.2	0.70 (0.45, 1.07)
bTMB ≥ 10 mut/mb (n = 212)	14.6	11.2	0.68 (0.47, 0.97)
bTMB < 16 mut/mb (n = 271)	12.5	9.9	0.71 (0.52, 0.98)
bTMB ≥ 16 mut/mb (n = 80)	17.8	11.9	0.63 (0.35, 1.15)
ITT (N = 403)	12.3	10.3	0.70 (0.54, 0.91)



Clinical data cutoff date: April 24, 2018. bTMB (blood tumor mutational burden) assessed as reported in Gandara DR, et al. *Nat Med,* 2018.

[a] Hazard ratios are unstratified for patient subgroups and stratified for the ITT.

Subsequent treatments

	Atezolizumab + CP/ET (N = 201)	Placebo + CP/ET (N = 202)
Total number of patients with at least one treatment	104 (51.7)	116 (57.4)
Line of therapy — no. (%)		
Second	101 (50.2)	116 (57.4)
Third	29 (14.4)	38 (18.8)
Fourth	3 (1.5)	15 (7.4)
Therapy type — no. (%)		
Chemotherapy/non-anthracycline	81 (40.3)	88 (43.6)
Chemotherapy/anthracycline	31 (15.4)	46 (22.8)
Immunotherapy	6 (3.0)	15 (7.4)
Other	2 (1.0)	2 (1.0)
Targeted therapy	2 (1.0)	1 (0.5)

Clinical data cutoff date: April 24, 2018.

Safety summary

Patients — no. (%)	Atezolizumab + CP/ET (N = 198)	Placebo + CP/ET (N = 196)
Patients with ≥ 1 AE	198 (100)	189 (96.4)
Grade 3–4 AEs	133 (67.2)	125 (63.8)
Treatment-related AEs[a]	188 (94.9)	181 (92.3)
Serious AEs	74 (37.4)	68 (34.7)
Immune-related AEs	79 (39.9)	48 (24.5)
AEs leading to withdrawal from any treatment[a]	22 (11.1)	6 (3.1)
AEs leading to withdrawal from atezolizumab/placebo	21 (10.6)	5 (2.6)
AEs leading to withdrawal from carboplatin	5 (2.5)	1 (0.5)
AEs leading to withdrawal from etoposide	8 (4.0)	2 (1.0)
Treatment-related deaths	3 (1.5)	3 (1.5)

- Median duration of treatment with atezolizumab was 4.7 months (range: 0 to 21)
- Median number of doses received:
  - Atezolizumab: 7 (range: 1 to 30)
  - Chemotherapy: 4 doses for carboplatin; 12 doses for etoposide (same for both treatment groups)

Clinical data cutoff date: April 24, 2018. Multiple occurrences of the same AE in one patient were counted once at the highest grade for the preferred term.
[a] Incidence of treatment-related AEs and AEs leading to withdrawal from any treatment are for any treatment component. AE, adverse event.

Most frequently observed AEs

Treatment-related AEs — no. (%) > 5% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Neutrophil count decreased	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0

Immune-related AEs — no. (%) > 1% Grade 3–4 AEs in either treatment group	Atezolizumab + CP/ET (N = 198)			Placebo + CP/ET (N = 196)		
	Grade 1–2	Grade 3–4	Grade 5	Grade 1–2	Grade 3–4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

Clinical data cutoff date: April 24, 2018.

Summary

- IMpower133 is the first study in over 20 years to show a clinically meaningful improvement in OS over the current standard-of-care in 1L ES-SCLC
- The addition of atezolizumab to carboplatin and etoposide provided a significant improvement in OS and PFS, compared with carboplatin and etoposide alone in 1L ES-SCLC
  - mOS: 12.3 vs. 10.3 months; HR: 0.70 (p = 0.0069); 12-month OS: 51.7% vs. 38.2%
  - mPFS: 5.2 vs. 4.3 months; HR: 0.77 (p = 0.017); 12-month PFS: 12.6% vs. 5.4%
- The safety profile of atezolizumab plus carboplatin and etoposide was as expected with no new findings
  - Rates of hematologic side effects were similar between treatment groups
  - Administration of atezolizumab did not compromise the ability to deliver standard carboplatin plus etoposide
  - The incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy[1–3]
- These data suggest that atezolizumab plus carboplatin and etoposide is a new standard of care for the first-line treatment of ES-SCLC

1. Rittmeyer A, et al. *Lancet*, 2017. 2. Cortinovis D, et al. *Ann Oncol*, 2017 (Suppl. 5). 3. Fehrenbacher L, et al. *Lancet*, 2016.