ES-SCLC: Changing Paradigms with Immune-oncology Combinations

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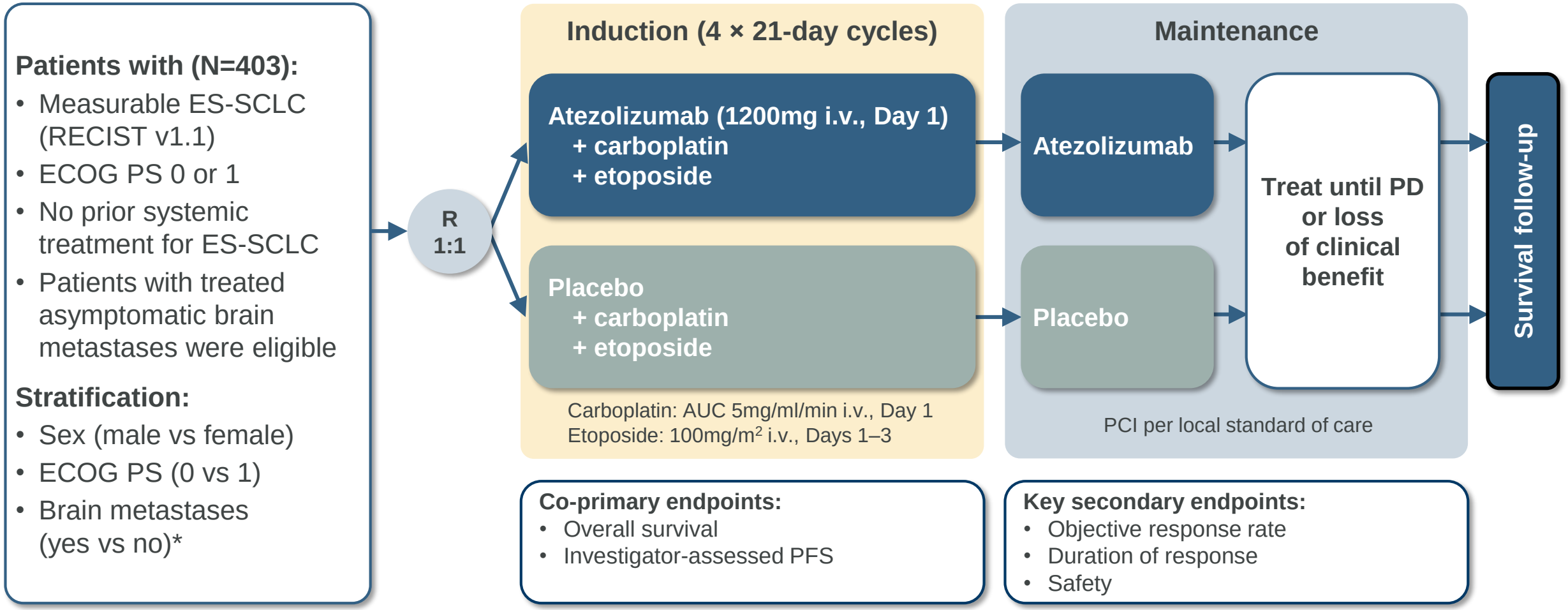
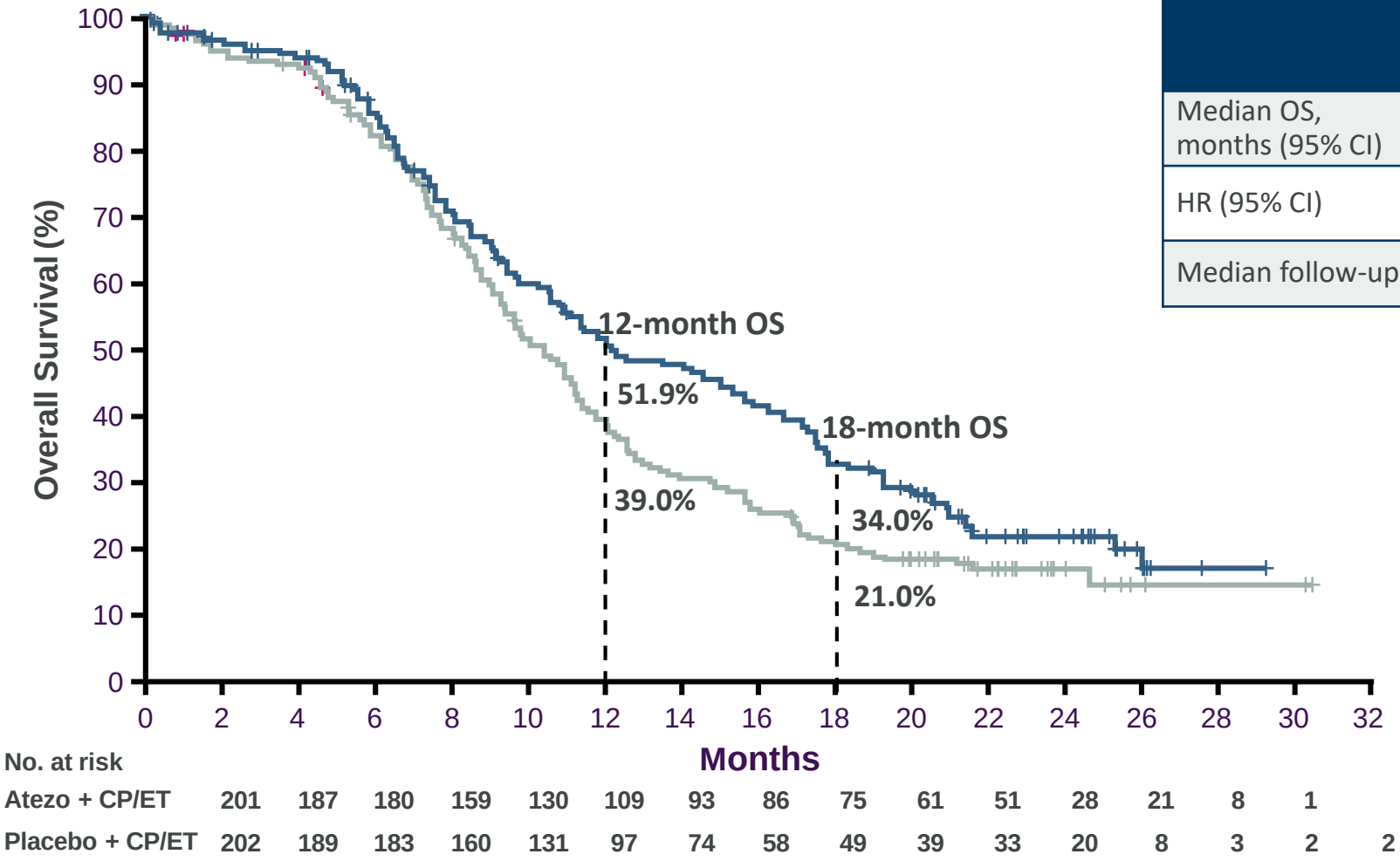
IMpower133: Atezolizumab+chemotherapy versus chemotherapy in 1L ES-SCLC



PCI, prophylactic cranial irradiation

*Only patients with treated brain metastases were eligible

IMpower133: OS in the ITT population (updated analysis)



	Atezolizumab + CP/ET (N=201)	Placebo + CP/ET (N=202)
Median OS, months (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*	
Median follow-up, months	22.9	

*p-value is provided for descriptive purposes

Clinical data cut-off date: 24 January 2019

Horn, et al. AACR 2020 (Abs CT220)

Reck, et al. ESMO 2019 (Abs 1736O)

CASPIAN Study Design

Phase 3, global, randomized, open-label, active-controlled, multicenter study

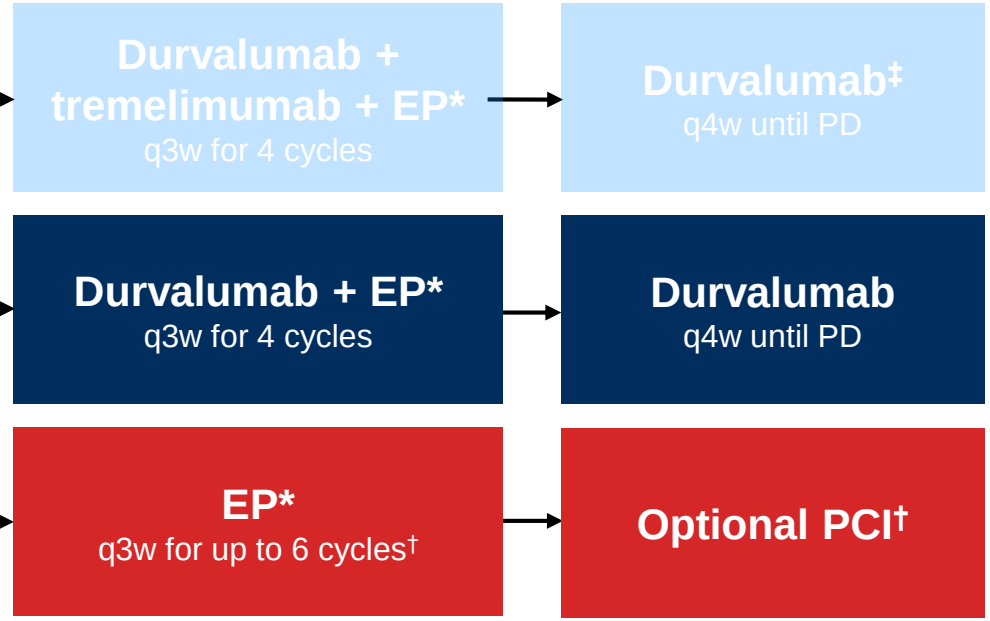
- Treatment-naïve ES-SCLC
- WHO PS 0 or 1
- Asymptomatic or treated and stable brain metastases permitted
- Life expectancy ≥12 weeks
- Measurable disease per RECIST v1.1

N=805 (randomized)

1:1:1

R

Stratified by planned platinum (carboplatin vs cisplatin)



Primary endpoint

- OS

Secondary endpoints

- PFS§
- ORR§
- Safety & tolerability
- PROs

*EP consists of etoposide 80–100 mg/m^2 with either carboplatin AUC 5–6 or cisplatin 75–80 mg/m^2, durvalumab dosed at 1500 mg, tremelimumab dosed at 75 mg
†Patients could receive an additional 2 cycles of EP (up to 6 cycles total) and PCI at the investigator's discretion
‡Patients received an additional dose of tremelimumab post-EP
§By investigator assessment per RECIST v1.1
AUC, area under the curve; ORR, objective response rate; PCI, prophylactic cranial irradiation; PD, disease progression; PFS, progression-free survival; PROs, patient-reported outcomes; PS, performance status; q3w, every 3 weeks; q4w, every 4 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1

Paz-Ares L et al., WCLC 2019, PL02.11; ESMO 2019 Paz-Ares L et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934 ; ASCO 2020, Paz-Ares L et al. J Clin Oncol 38: 2020 (suppl; abstr 9002)

Baseline Characteristics

	Durvalumab + EP (n=268)	EP (n=269)
Median age (range), years	62 (28–82)	63 (35–82)
Male, %	70.9	68.4
White / Asian / Other, %	85.4 / 13.4 / 1.1	82.2 / 15.6 / 2.2
WHO PS 0 / 1, %	36.9 / 63.1	33.5 / 66.5
Disease stage III / IV*, %	10.4 / 89.6	8.9 / 91.1
Current / Former / Never smoker, %	44.8 / 47.0 / 8.2	46.8 / 47.6 / 5.6
Brain or CNS metastases, %	10.4	10.0

*All patients were confirmed as having ES-SCLC

CNS, central nervous system

Paz-Ares L et al., WCLC 2019, PL02.11; ESMO 2019 Paz-Ares L et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934 ; ASCO 2020, Paz-Ares L et al. J Clin Oncol 38: 2020 (suppl; abstr 9002)

Patient Disposition

	Durvalumab + EP (n=268)	EP (n=269)
Received treatment, n	265	266
Ongoing treatment, n (%)	43 (16)	0
Completed EP / Discontinued EP*, n	223 / 42	190 / 76
PCI post-EP†, n (%)	–	21 (8)
Did not receive treatment, n	3	3
Received subsequent anticancer therapy, n (%)	113 (42)	119 (44)

- Median duration of follow-up in censored patients: 14.2 months (range 0.1–23.1)

*The most common reason for treatment discontinuation was disease progression in both arms
†PCI was only permitted in the EP arm at the investigator's discretion

Paz-Ares L et al., WCLC 2019, PL02.11; ESMO 2019 Paz-Ares L et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934 ; ASCO 2020, Paz-Ares L et al. J Clin Oncol 38: 2020 (suppl; abstr 9002)

Treatment Exposure

Chemotherapy	D+EP (n=265)	EP (n=266)
Platinum agent received†, n (%)		
Carboplatin	208 (78.5)	208 (78.2)
Cisplatin	65 (24.5)	67 (25.2)
Median number of cycles of EP‡, n (range)	4 (1–6)	6 (1–6)
Number of cycles of EP‡, n (%)		
≥4 cycles	230 (86.8)	225 (84.6)
6 cycles	1 (0.4)	151 (56.8)
Immunotherapy	**(n=265)**	**(n=266)**
Median total duration of durvalumab, weeks	28.0	–
Median number of durvalumab doses, n (range)	7 (1–37)	–
Median total duration of tremelimumab, weeks	–	–
Patients receiving 5 planned tremelimumab doses, n (%)	–	–

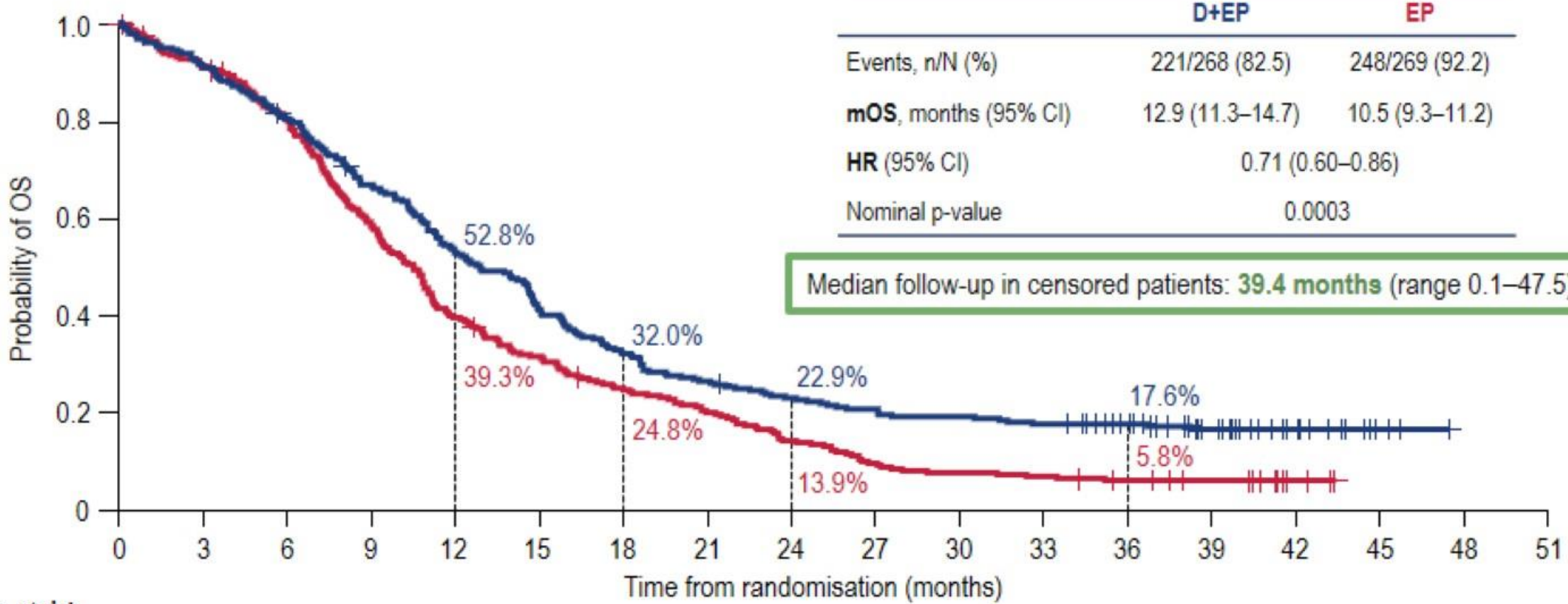
*2 patients discontinued due to AEs during the immunotherapy infusions before receiving any EP
†Patients were allowed to switch between carboplatin and cisplatin at the investigator's discretion
‡Based on etoposide exposure

Paz-Ares L et al., WCLC 2019, PL02.11; ESMO 2019 Paz-Ares L et al., Annals of Oncology (2019) 30 (suppl_5): v851-v934 ; ASCO 2020, Paz-Ares L et al. J Clin Oncol 38: 2020 (suppl; abstr 9002)

3-year Overall Survival Update: D+EP vs EP

	D+EP	EP
Events, n/N (%)	221/268 (82.5)	248/269 (92.2)
mOS, months (95% CI)	12.9 (11.3–14.7)	10.5 (9.3–11.2)
HR (95% CI)	0.71 (0.60–0.86)	
Nominal p-value	0.0003	

Median follow-up in censored patients: **39.4 months** (range 0.1–47.5)

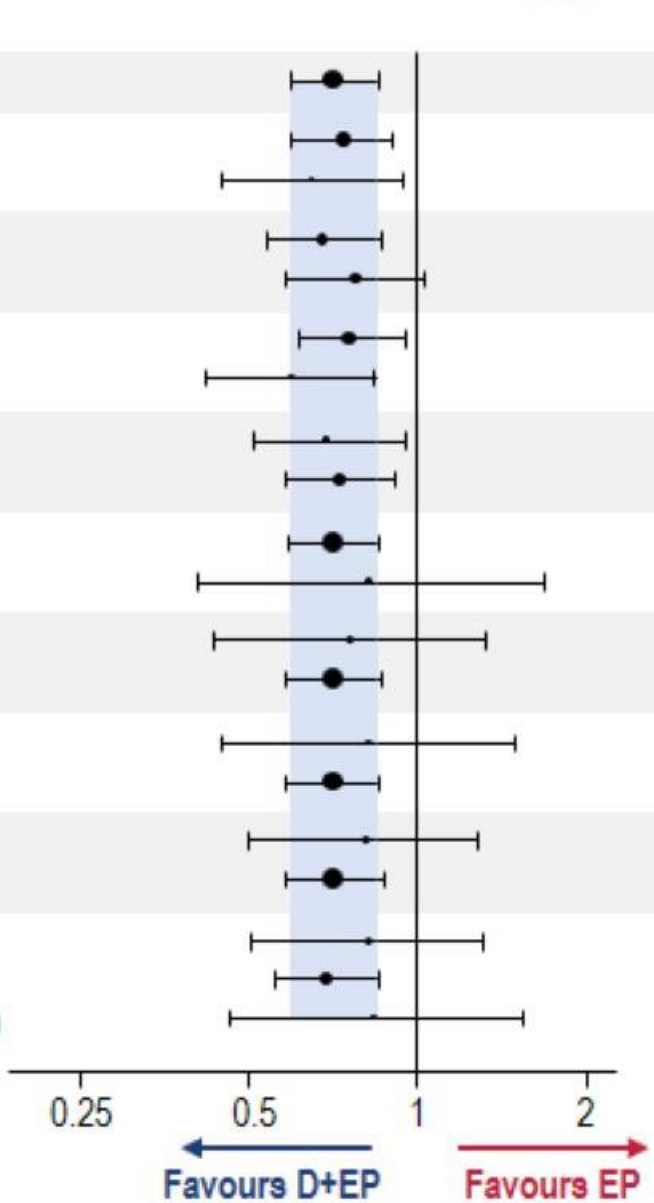


No. at risk

D+EP	268	244	214	177	140	109	85	70	60	54	50	46	39	25	13	3	0	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0	0

Data cutoff: 22 March 2021

3-year Overall Survival Update: D+EP vs EP Subgroup Analysis



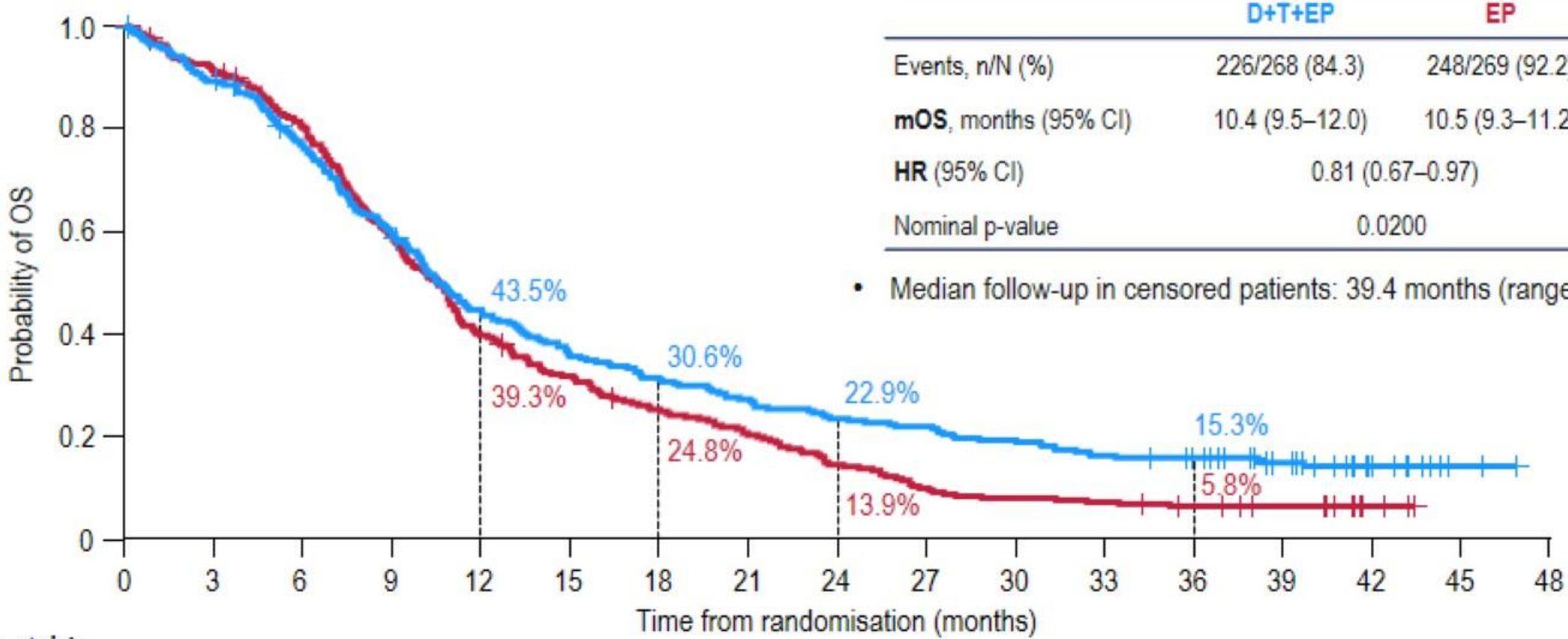
Data cutoff: 22 March 2021; Size of circle is proportional to the number of events across both treatment groups

AJCC, American Joint Committee on Cancer; CNS, central nervous system

3-year Overall Survival Update: D+T+EP vs EP

	D+T+EP	EP
Events, n/N (%)	226/268 (84.3)	248/269 (92.2)
mOS, months (95% CI)	10.4 (9.5–12.0)	10.5 (9.3–11.2)
HR (95% CI)	0.81 (0.67–0.97)	
Nominal p-value	0.0200	

- Median follow-up in censored patients: 39.4 months (range 0.1–47.5)

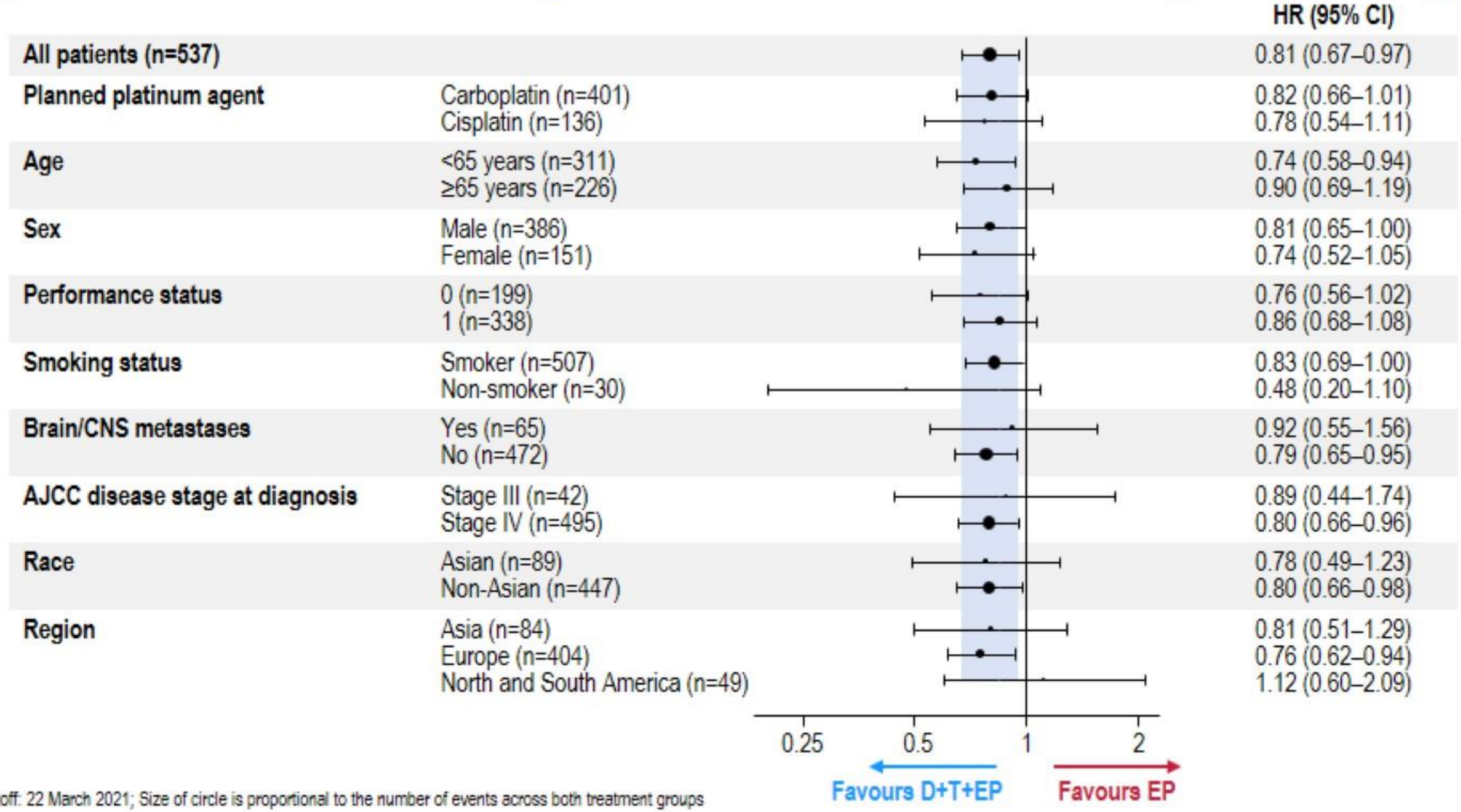


No. at risk

D+T+EP	268	238	200	156	114	92	80	70	60	56	48	41	37	26	11	2	0
EP	269	243	212	156	104	82	64	51	36	24	19	17	13	10	3	0	0

Data cutoff: 22 March 2021

3-year Overall Survival Update: D+T+EP vs EP Subgroup Analysis



Data cutoff: 22 March 2021; Size of circle is proportional to the number of events across both treatment groups

Durvalumab Treatment Exposure (Safety Population)

	D+EP (n=265)	D+T+EP (n=266)
Ongoing durvalumab at data cutoff, n (%)	27 (10.2)	19 (7.1)
Median number of durvalumab doses (range)	7.0 (1–52)	6.0 (1–46)
Total duration of durvalumab exposure, n (%)		
≥1 year	54 (20.4)	49 (18.4)
≥2 years	32 (12.1)	30 (11.3)
≥3 years	24 (9.1)	21 (7.9)
Median total duration of durvalumab, weeks (range)	28.0 (0.3–198.7)	23.1 (0.1–190.0)

- The majority of patients at risk at 3 years in the immunotherapy arms remained on durvalumab treatment at the data cutoff
- Exposure to chemotherapy and tremelimumab had not changed at this data cutoff compared with the previous analysis[1]

Data cutoff: 22 March 2021

1. Goldman JW, et al. Lancet Oncol 2021;22:51–65

Serious Adverse Events: 3-year Update

	D+EP (n=265)	D+T+EP (n=266)	EP (n=266)
Serious AEs (all cause), n (%)*	86 (32.5)	126 (47.4)	97 (36.5)
Febrile neutropenia	12 (4.5)	11 (4.1)	12 (4.5)
Pneumonia	6 (2.3)	16 (6.0)	11 (4.1)
Anaemia	5 (1.9)	9 (3.4)	12 (4.5)
Thrombocytopenia	1 (0.4)	6 (2.3)	9 (3.4)
Hyponatremia	2 (0.8)	9 (3.4)	4 (1.5)
Neutropenia	2 (0.8)	5 (1.9)	7 (2.6)
Diarrhoea	2 (0.8)	7 (2.6)	4 (1.5)
Pulmonary embolism	1 (0.4)	7 (2.6)	0
AEs leading to death (all cause), n (%)†	14 (5.3)	29 (10.9)	16 (6.0)
Treatment-related AEs leading to death	6 (2.3)	12 (4.5)	2 (0.8)

Data cutoff: 22 March 2021; *Serious AEs occurring in ≥2% patients in any treatment arm are shown

†Four additional deaths were reported since the previous analysis (none considered treatment related): one in the D+EP arm (aspiration), two in the D+T+EP arm (drowning and pneumocystis jirovecii pneumonia), and one in the EP arm (small intestine leiomyosarcoma)

OS Based on Baseline Brain Metastases

Durvalumab + EP consistently improved OS versus EP in patients regardless of the presence of baseline brain metastases

- HR 0.69 [0.35–1.31] and 0.74 [0.59–0.93]

Figure 2. Forest plot for OS by brain metastases at baseline

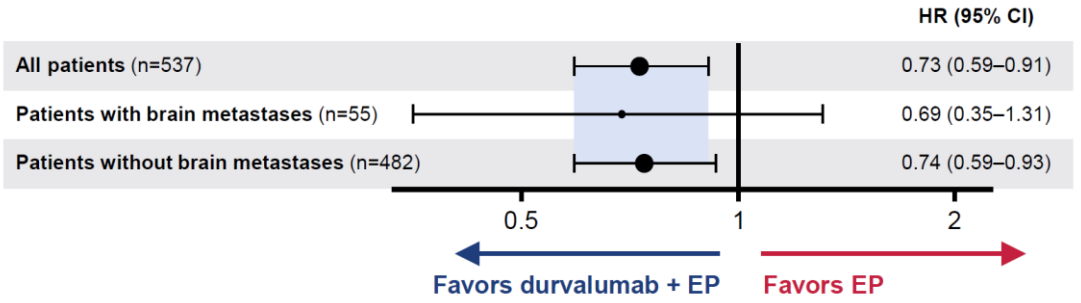
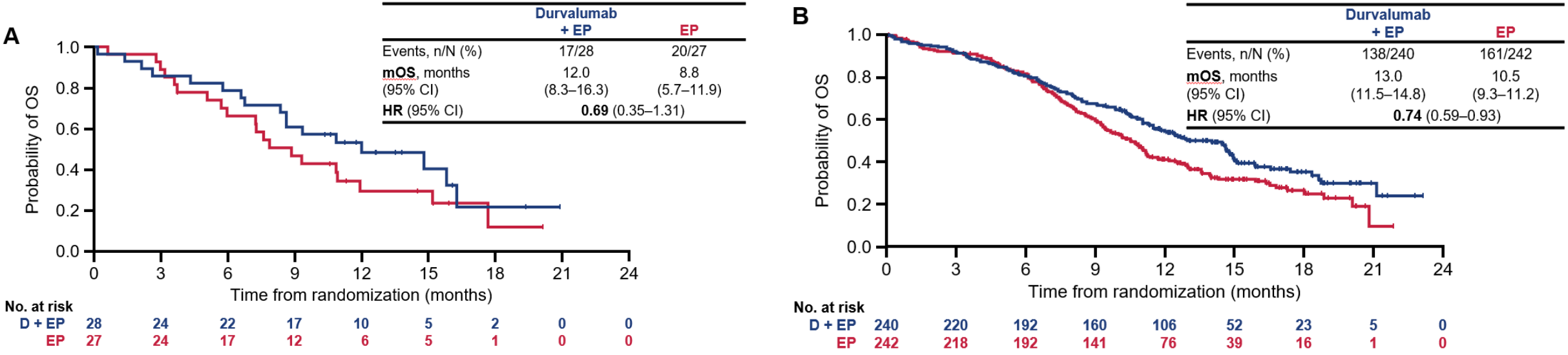


Figure 3. OS in patients with (A) or without (B) brain metastases at baseline



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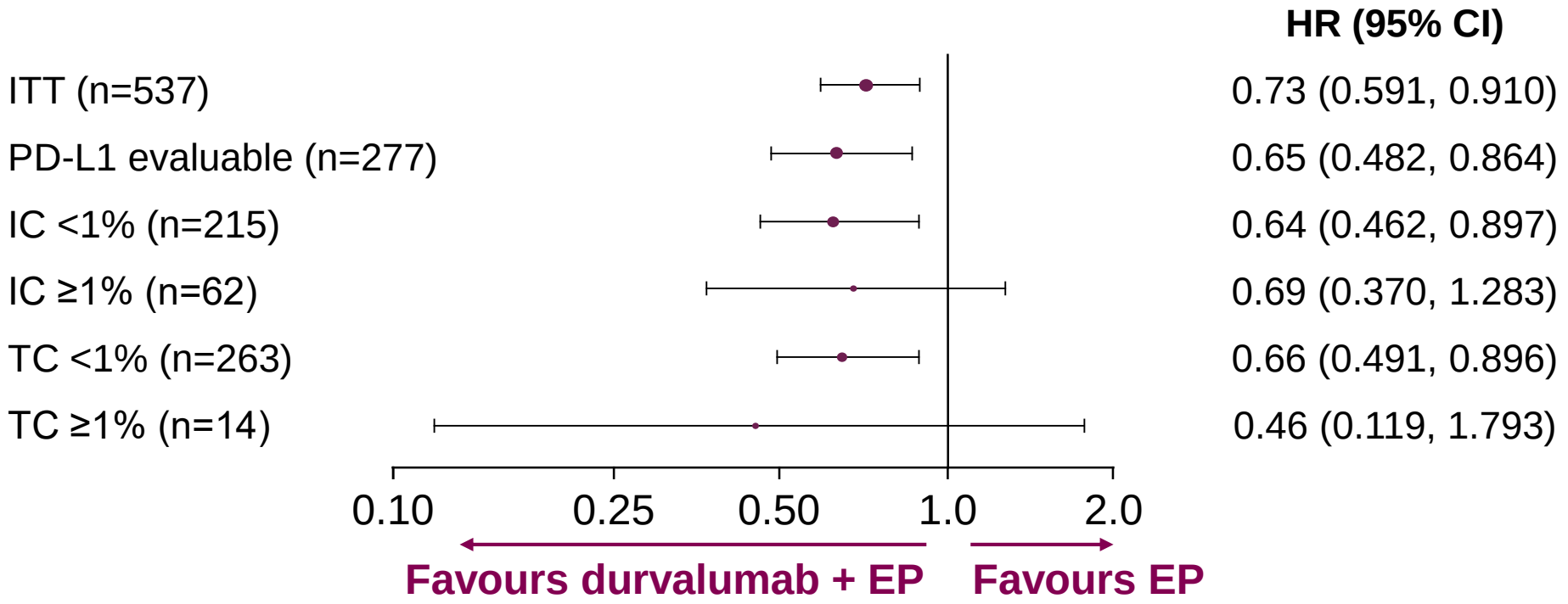
CASPIAN: Overall survival based on PD-L1 expression



- 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

- The size of the HR dot represents the total number of events across both arms
- CI, confidence interval; EP, etoposide–platinum; HR, hazard ratio; IC, immune cell; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival; TC, tumour cell
- Paz-Ares L, et al. Presented at European Society for Medical Oncology Congress; 27th September – 1st October 2019; Barcelona, Spain

CASPIAN: Overall safety summary

	D+EP (n=265)	EP (n=266)
Any-grade all-cause AEs, n (%)	260 (98.1)	258 (97.0)
Grade 3/4 AEs	165 (62.3)	167 (62.8)
Serious AEs	85 (32.1)	97 (36.5)
AEs leading to treatment discontinuation*	27 (10.2)	25 (9.4)
Immune-mediated AEs†	53 (20.0)	7 (2.6)
AEs leading to death	13 (4.9)	15 (5.6)
Treatment-related AEs leading to death‡	6 (2.3)	2 (0.8)

*Includes patients who permanently discontinued at least one study drug
†An event that is associated with drug exposure and consistent with an immune-mediated mechanism of action, where there is no clear alternate etiology and the event required treatment with systemic corticosteroids or other immunosuppressants and/or, for specific endocrine events, endocrine therapy; majority of immune-mediated AEs were low grade and thyroid related
‡AEs assessed by the investigator as possibly related to any study treatment. Causes of death were death, febrile neutropenia, and pulmonary embolism (two patients each), and enterocolitis, general physical health deterioration/multiple organ dysfunction syndrome, pneumonia, pneumonitis/hepatitis, respiratory failure, and sudden death (one patient each) in the durvalumab + tremelimumab + EP arm; cardiac arrest, dehydration, hepatotoxicity, interstitial lung disease, pancytopenia, and sepsis (one patient each) in the durvalumab + EP arm; pancytopenia and thrombocytopenia/haemorrhage (one patient each) in the EP arm
AE, adverse event; D, durvalumab; EP, etoposide–platinum; T, tremelimumab
Paz-Ares L, et al. Presented at ASCO 2020 May 29th–31st, Virtual; abstract 9002

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Small Cell Lung Cancer

PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of systemic therapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimen
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1, for all)[b,5]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]

Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]

Useful In Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

[a] Cisplatin contraindicated or not tolerated.
[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

Patient-reported Outcomes (PROs)

CASPIAN[1]	IMpower133[2]
Time to deterioration in all patient-reported symptoms and functional domains favored durvalumab + EP arm versus EP arm	Time to deterioration of treatment-related symptoms were similar between arms.

QLQ-C30	Events/ patients, n	Median TTD, months Durvalumab + EP	Median TTD, months EP	HR (95% CI)	Nominal *P* value
Global health status/QoL	240/470	8.4	7.2	0.81 (0.626–1.054)	0.1166
Cognitive functioning	261/486	8.4	6.0	0.61 (0.472–0.776)	<0.0001
Emotional functioning	216/481	12.9	7.3	0.61 (0.464–0.800)	0.0003
Physical functioning	246/483	8.5	6.5	0.75 (0.581–0.970)	0.0276
Role functioning	262/456	7.4	5.9	0.71 (0.550–0.904)	0.0059
Social functioning	264/472	7.6	6.2	0.70 (0.549–0.897)	0.0048
Appetite loss	251/454	8.3	6.6	0.70 (0.542–0.899)	0.0054
Constipation	225/468	11.1	7.3	0.65 (0.499–0.855)	0.0018
Diarrhea	208/487	14.6	7.7	0.59 (0.442–0.774)	0.0002
Dyspnea	220/442	9.0	7.4	0.75 (0.574–0.989)	0.0406
Fatigue	309/475	5.5	4.3	0.82 (0.653–1.027)	0.0835
Nausea/vomiting	260/488	8.4	6.6	0.80 (0.626–1.027)	0.0809
Pain	250/472	7.8	6.7	0.79 (0.615–1.021)	0.0718
Insomnia	220/435	8.6	7.3	0.75 (0.568–0.980)	0.0349
QLQ-LC13					
Cough	221/459	9.3	7.7	0.78 (0.600–1.026)	0.0747
Dyspnea	284/480	6.5	5.5	0.79 (0.625–1.006)	0.0578
Hemoptysis	165/487	18.3	10.5	0.64 (0.469–0.876)	0.0049
Arm/shoulder pain	224/478	9.9	7.5	0.70 (0.535–0.915)	0.0088
Chest pain	215/478	10.6	7.8	0.76 (0.575–0.996)	0.0464
Other pain	255/466	7.8	6.4	0.72 (0.558–0.923)	0.0096

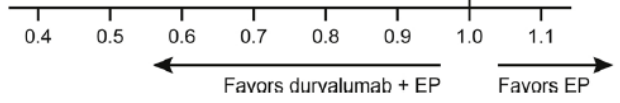


Table 1. Mean (SD) baseline EORTC QLQ-C30 and QLQ-LC13 scores

Baseline score, mean (SD)	Atezolizumab + CP/ET (*N* = 201)	Placebo + CP/ET (*N* = 202)
EORTC QLQ-C30 scales	*n* = 179	*n* = 175
Fatigue[a]	42.0 (26.4)	38.7 (26.9)
Appetite loss[a]	28.9 (32.3)	27.4 (31.9)
Constipation	22.7 (30.5)	22.7 (32.8)
Diarrhea	6.3 (15.7)	7.4 (17.9)
Dyspnea	41.9 (31.8)	36.4 (33.4)
Financial difficulties	24.8 (31.6)	22.9 (31.7)
Insomnia	37.6 (33.3)	34.1 (34.6)
Nausea/vomiting	9.6 (18.9)	10.5 (21.8)
Pain	33.6 (31.0)	31.9 (30.9)
Physical functioning	70.7 (22.7)	71.9 (23.5)
Role functioning	67.1 (31.3)	66.4 (32.9)
Social functioning	71.1 (29.1)	73.3 (28.8)
Emotional functioning	68.6 (23.9)	69.9 (24.0)
Cognitive functioning	81.8 (21.1)	83.3 (20.6)
Global health status	51.6 (22.4)	53.7 (23.4)
EORTC QLQ-LC13 scales	*n* = 176	*n* = 168
Cough[a]	42.2 (27.7)	42.9 (29.2)
Chest pain[a]	22.9 (26.6)	22.2 (25.7)
Dyspnea[a]	34.3 (25.9)	29.6 (25.9)
Arm/shoulder pain[a]	22.2 (30.6)	19.4 (27.4)
Alopecia	5.1 (16.9)	3.6 (15.1)
Dysphagia	11.2 (20.4)	10.1 (22.4)
Hemoptysis	5.3 (13.7)	8.5 (17.5)
Pain in other parts	24.1 (29.1)	27.4 (30.8)
Peripheral neuropathy	9.9 (20.3)	9.9 (21.8)
Sore mouth	5.5 (14.7)	8.9 (19.8)

1. Goldman JW et al. *Lung Cancer*. 2020;149:46-51. 2. Mansfield AS et al. *Ann Oncol.* 2020;31:310-317.

CASPIAN vs IMPOWER 133: Efficacy Outcomes

	CASPIAN	IMPOWER 133
ORR	67.9% vs 57.6%	60% vs 64%
mPFS	5.1m vs 5.4m (HR 0.78)	5.2m vs 4.4m (HR 0.77)
12m PFS	17.5% vs 4.7%	12.6% vs 5.4%
mOS	13.0m vs 10.3m (HR 73)	12.5m vs 10.3m (HR 0.76)
Biomarker	none yet	bTMB ≥16?

Case 2

- 64 year old male, current smoker, found to have shortness of breath and cytopenias with ANC of 800, Hgb of 8, Plt- 17
- Viral etiologies rule out by PCR, imaging showed 2cm lung nodule, multiple enlarged hilar lymph nodes, and multiple areas of osseous changes
- Bone marrow biopsy performed and shows infiltrated marrow with small blue cells with high proliferation rate consistent with small cell lung cancer
- CNS imaging shows no evidence of brain metastasis

Case (cont.)

- Patient underwent blood transfusion and decision to initiate treatment as an inpatient for close monitoring of blood counts and given patient's condition
- Patient was started on cisplatin and etoposide and required transfusion and GCSF support
- He is subsequently discharged and presents in outpatient clinic for discussion around continuation of treatment
- His blood counts and breathing are improved, however his ANC is 1500, his Hgb remains at 8, his platelets at 47
- What would be your optimal treatment regimen to continue from here?

Case (cont.)

- Given cytopenias, decision to continue cisplatin (less cytopenias than carboplatin) and etoposide with the addition of anti-PD-L1 immunotherapy

- Treatment with cisplatin/etoposide/durvalumab as per CASPIAN was continued and patient remained in remission for almost a year

Thank you

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