Translational Data for Durvalumab from the ADRIATIC Trial

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Durvalumab vs placebo after concurrent chemoradiotherapy in limited-stage small-cell lung cancer: Outcomes by PD-L1 expression in ADRIATIC

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Previously presented as a Poster Presentation by Dr. Christine Hann at AACR 2025 on 08 Apr 2025.

Background on outcomes by PD-L1 expression in ADRIATIC

- PD-L1 expression is an approved immunotherapy biomarker used to guide treatment decisions in NSCLC
- Although PD-L1 is generally expressed at low levels in SCLC and is not currently a validated immunotherapy biomarker in this tumor type, PD-L1 was evaluated as a potential biomarker in ADRIATIC
- **PD-L1 expression on TCs or ICs was assessed by central retrospective testing of pre-cCRT tissue samples using the VENTANA PD-L1 (SP263) immunohistochemistry assay**
- **OS and PFS were assessed in the PD-L1-evaluable population and in subgroups with PD-L1 expression ≥1% on TCs and/or ICs (secondary endpoint) and <1% on TCs and ICs**
- Data cutoff: 15 January 2024

Patient demographics & baseline characteristics

- Among 162 (61.4%) and 171 (64.3%) patients in the durvalumab and placebo arms who were evaluable for PD-L1, baseline characteristics were generally balanced across the treatment arms and consistent with the ITT population

- As in the ITT population, a majority of patients received prior cisplatin CT (67.0%), once-daily RT (70.6%), and PCI (54.7%)

- Of the PD-L1-evaluable patients, 51.9% in the durvalumab arm and 57.3% in the placebo arm had PD-L1 TC or IC ≥1%

Table 1. Baseline characteristics and prior treatment in the PD-L1-evaluable population

	Durvalumab (n=162)	Placebo (n=171)
Median age (range), years	61.0 (28–84)	62.0 (28–79)
Age, years, n (%)		
≥65	61 (37.7)	65 (38.0)
Sex, n (%)		
Male	116 (71.6)	118 (69.0)
Female	46 (28.4)	53 (31.0)
Race, n (%)		
White	70 (43.2)	82 (48.0)
Asian	90 (55.6)	85 (49.7)
Other	2 (1.2)	4 (2.3)
WHO PS, n (%)		
0	76 (46.9)	82 (48.0)
1	86 (53.1)	89 (52.0)
Smoking history, n (%)		
Current/former	145 (89.5)	149 (87.1)
Never	17 (10.5)	22 (12.9)
AJCC stage at diagnosis, n (%)		
I or II	20 (12.3)	23 (13.5)
III	142 (87.7)	148 (86.5)
PD-L1 expression status, n (%)		
TC or IC ≥1%	84 (51.9)	98 (57.3)
TC and IC <1%	78 (48.1)	73 (42.7)
Prior CT regimen, n (%)*		
Cisplatin-etoposide	108 (66.7)	115 (67.3)
Carboplatin-etoposide	54 (33.3)	56 (32.7)
Prior RT schedule, n (%)		
Once daily	118 (72.8)	117 (68.4)
Twice daily	44 (27.2)	54 (31.6)
Best response to prior cCRT, n (%)		
Complete response	14 (8.6)	23 (13.5)
Partial response	120 (74.1)	129 (75.4)
Stable disease	28 (17.3)	19 (11.1)
End of cCRT to randomization, n (%)		
<14 days	18 (11.1)	20 (11.7)
≥14 days to <28 days	49 (30.2)	51 (29.8)
≥28 days	95 (58.6)	100 (58.5)
Received prior PCI, n (%)	92 (56.8)	90 (52.6)

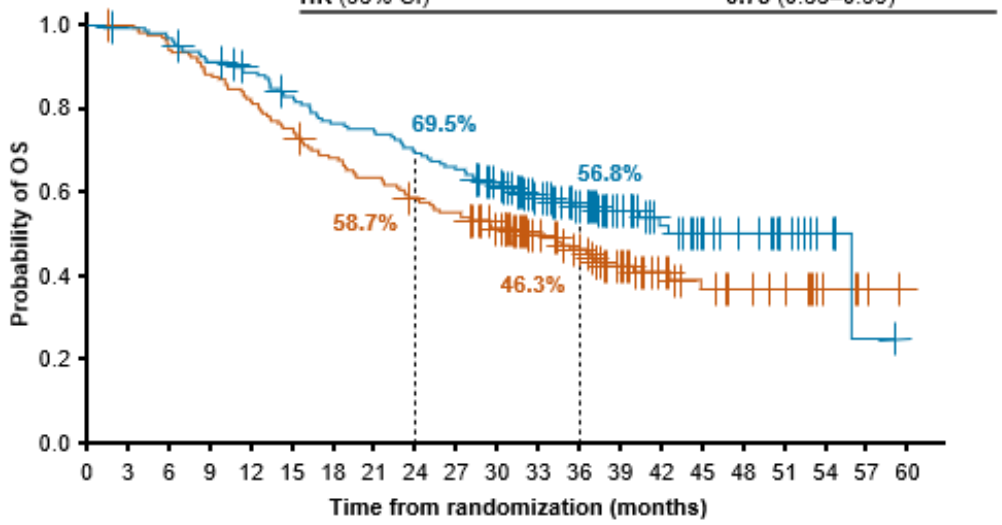
*Based on the first cycle of chemotherapy received.

OS & PFS by BICR in the PD-L1-evaluable population

- In the PD-L1-evaluable population, improvements in OS and PFS with durvalumab vs placebo were of similar magnitude to those previously reported in the ITT population.

A.

	Durvalumab	Placebo
Events/patients, n/N	71/162	95/171
Median OS (95% CI), months	**55.9** (34.0–NE)	**32.2** (24.2–39.9)
HR (95% CI)*	**0.73** (0.53–0.99)	

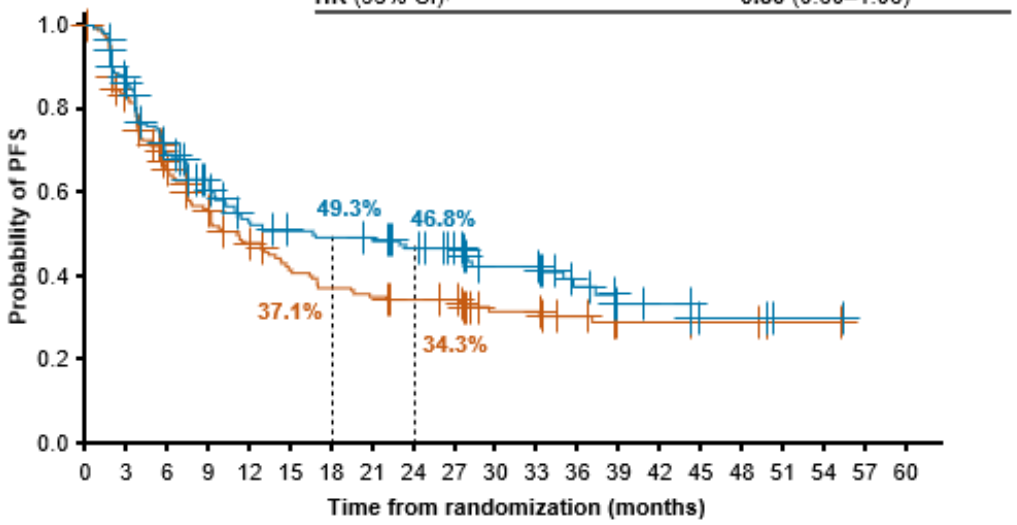


No. at risk

Durvalumab	162	160	156	146	139	129	119	116	108	102	90	71	57	40	28	21	16	10	5	1	0
Placebo	171	170	160	150	139	128	115	107	98	92	78	60	50	35	23	16	13	11	5	3	1

B.

	Durvalumab	Placebo
Events/patients, n/N	89/162	107/171
Median PFS (95% CI), months	**16.8** (9.5–33.1)	**11.0** (7.7–14.6)
HR (95% CI)†	**0.80** (0.60–1.06)	



No. at risk

Durvalumab	162	134	105	89	71	66	64	62	55	50	35	35	20	12	11	5	5	1	1	0	0
Placebo	171	136	99	83	68	58	52	49	44	43	28	28	22	12	12	8	8	3	3	0	0

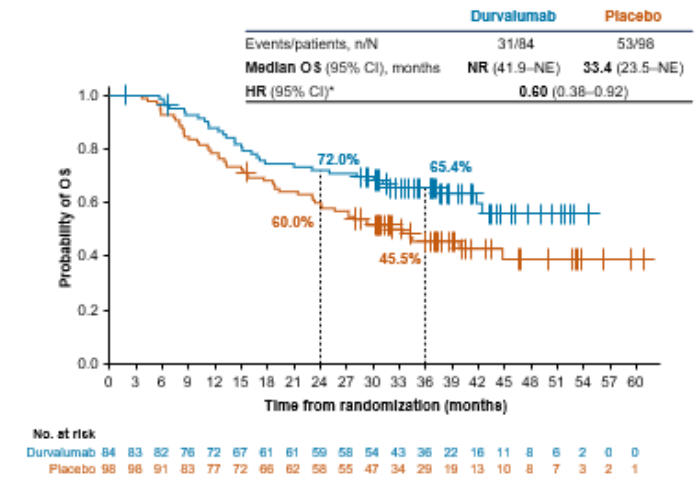
*HR and CI calculated using a stratified Cox proportional hazards model adjusted for receipt of PCI (yes vs no).
†HR and CI calculated using a stratified Cox proportional hazards model adjusted for disease stage (stage I/II vs III) and receipt of PCI (yes vs no).

OS & PFS by PD-L1 expression level

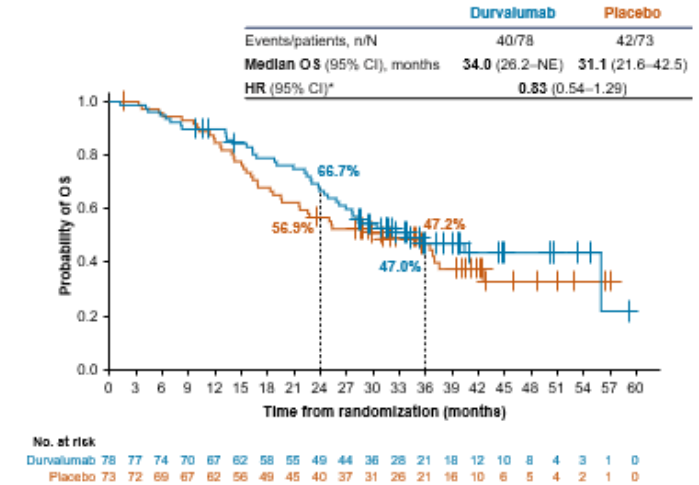
- Durvalumab appeared to improve OS and PFS vs placebo in subgroups with PD-L1 TC or IC ≥1% and with TC and IC <1%, consistent with the ITT population.

OS by PD-L1 expression level

A. TC or IC ≥1%



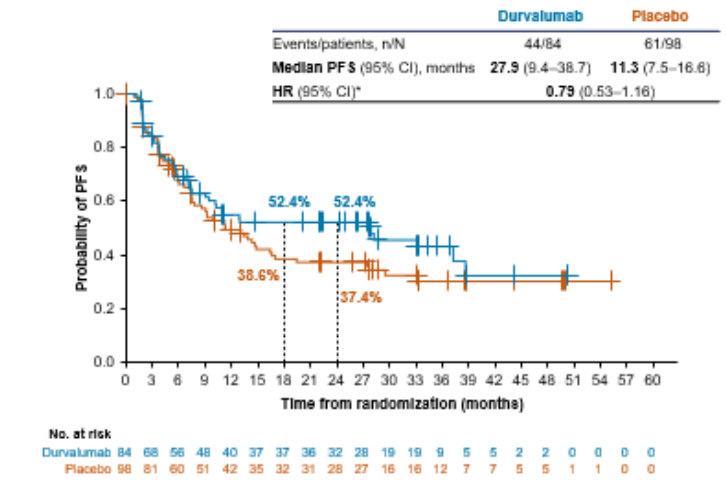
B. TC and IC <1%



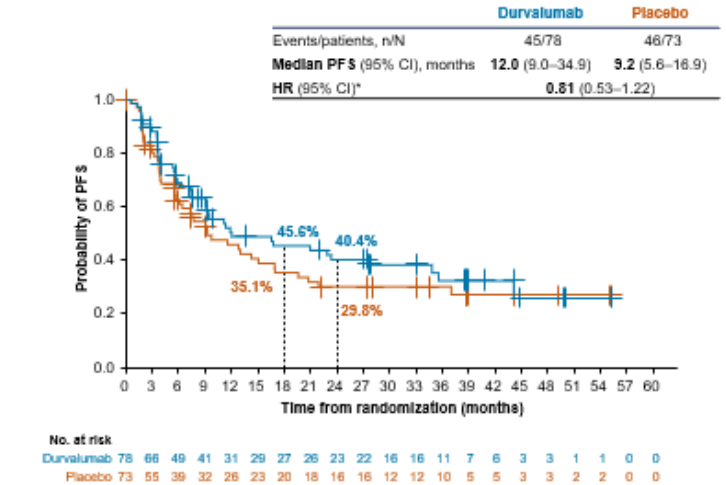
*HRs and CIs calculated using an unstratified Cox proportional hazards model.

PFS by PD-L1 expression level

A. TC or IC ≥1%



B. TC and IC <1%



*HRs and CIs calculated using an unstratified Cox proportional hazards model.

Safety summary in the PD-L1 evaluable safety population

- Overall safety profile in the PD-L1-evaluable safety population was generally consistent with that previously reported in the ITT population

	Durvalumab (n=162)	Placebo (n=170)
Any-grade all-cause AEs, n (%)	152 (93.8)	148 (87.1)
Maximum grade 3/4 AEs	32 (19.8)	36 (21.2)
Serious AEs	48 (29.6)	37 (21.8)
AEs leading to discontinuation of durvalumab or placebo	23 (14.2)	22 (12.9)
AEs leading to death	3 (1.9)	4 (2.4)
Treatment-related† AEs leading to death	2 (1.2)‡	0

*All patients with evaluable PD-L1 data who received at least 1 dose of study drug.
†As assessed by the investigator. ‡Causes of death were encephalopathy and pneumonitis.

Conclusions on outcomes by PD-L1 expression in ADRIATIC

- Approximately two-thirds of patients were evaluable for PD-L1 in ADRIATIC; baseline characteristics in these patients were consistent with the ITT population and improvements in OS and PFS were of similar magnitude to those in the ITT population.
- Among the PD-L1-evaluable population, 54.7% of patients had PD-L1 TC or IC ≥1%
- Consolidation durvalumab appeared to improve OS and PFS vs placebo irrespective of PD-L1 expression based on a cutoff of 1% on TCs and/or ICs
- These data further support consolidation durvalumab as the new standard of care in patients with LS-SCLC with no progression after cCRT

Clinical and molecular characteristics of early progressors and long-term progression-free survivors from the phase 3 ADRIATIC trial of consolidation durvalumab versus placebo after concurrent chemoradiotherapy in limited-stage small-cell lung cancer

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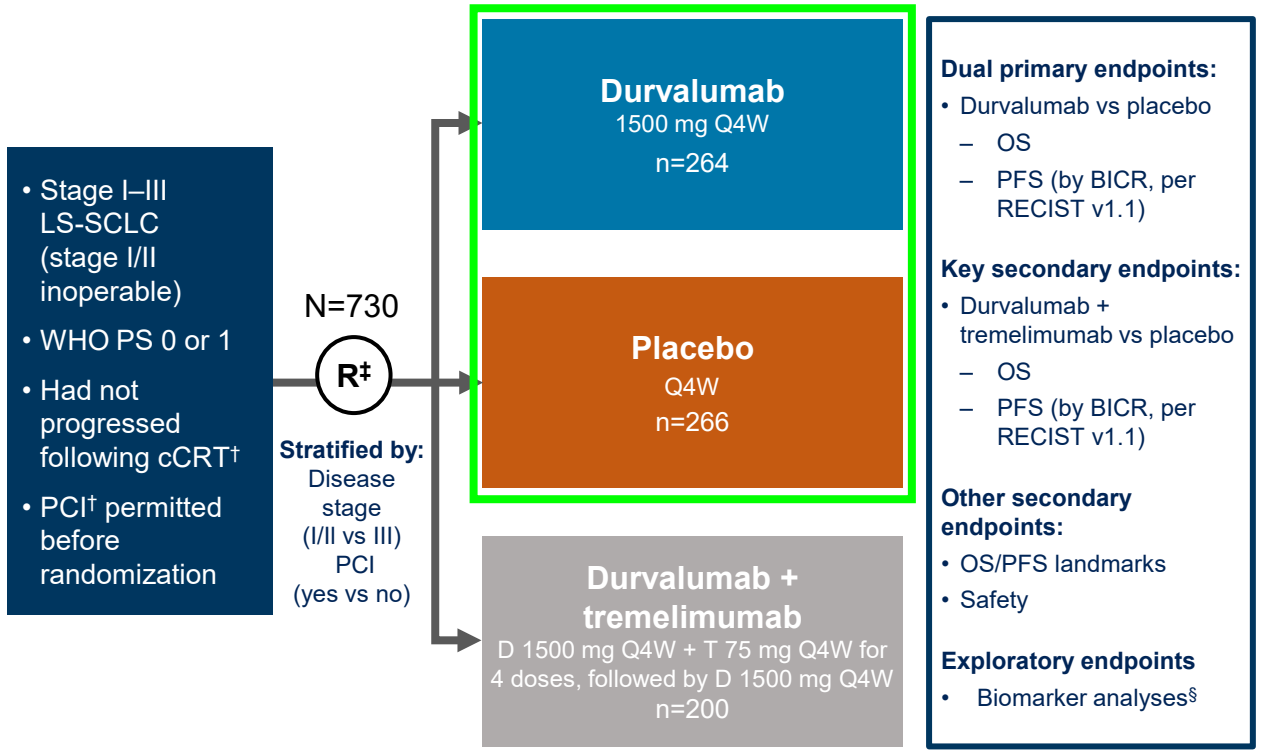
Background

- Consolidation durvalumab has become the new standard of care in patients with LS-SCLC and no progression after cCRT, based on the results of the ongoing ADRIATIC study
  - At the first planned interim analysis, durvalumab significantly improved the dual primary endpoints of OS and PFS vs placebo[1]
  - Durvalumab was well tolerated, with a manageable safety profile[1]
- Here we report post-hoc, exploratory analyses of clinical characteristics, patterns of progression, and associated immune-related biomarkers (CD8, MHC I, and PD-L1 by IHC; T-cell inflamed signature [TIS], *CD8A*, and STING pathway by RNA sequencing)* in:
  - Early progressors (EPs; patients with PFS <6 months)
  - Long-term progression-free survivors (LTPs; PFS or censored after >12 months)

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international ADRIATIC study (NCT03703297)



Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

1. Cheng Y, et al. N Engl J Med 2024;391:1313–27

*In the biomarker-evaluable populations using pre-cCRT tumor samples collected at screening

†cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization

‡The first 600 patients were randomized in a 1:1:1 ratio to the three treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo

§Not applicable for China

BICR, blinded independent central review; cCRT, concurrent chemoradiotherapy; D, durvalumab; IHC, immunohistochemistry; LS-SCLC, limited-stage small-cell lung cancer; OS, overall survival; PCI, prophylactic cranial irradiation; PFS, progression-free survival; PS, performance status; Q4W, every 4 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; T, tremelimumab; WHO, World Health Organization

Clinical characteristics of EPs and LTPs

Higher proportions of stage I/II disease, prior BID radiotherapy and prior PCI were seen in LTPs vs EPs in both arms; there was a higher proportion of patients with WHO PS 0 in LTPs vs EPs in the durvalumab arm

	Durvalumab (n=264)		Placebo (n=266)	
	EP	LTP	EP	LTP
n (% of ITT population)	83 (31.4)	113 (42.8)	97 (36.5)	100 (37.6)
Median age, years (range)	61.0 (36–77)	63.0 (28–84)	61.0 (39–79)	63.0 (28–79)
Sex, %				
Male / female	67.5 / 32.5	61.1 / 38.9	74.2 / 25.8	72.0 / 28.0
Race, %				
White / Asian	48.2 / 50.6	50.4 / 48.7	58.8 / 38.1	48.0 / 52.0
WHO PS, %				
0	43.4	54.9	49.5	45.0
1	56.6	45.1	50.5	55.0
Disease stage, %				
I or II	6.0	17.7	7.2	19.0
III	94.0	82.3	92.8	81.0
Smoking history, %				
Current or former / never smoker	90.4 / 9.6	89.4 / 10.6	91.8 / 8.2	89.0 / 11.0
Prior platinum agent, %				
Carboplatin / cisplatin	30.1 / 69.9	38.1 / 61.9	35.1 / 64.9	32.0 / 68.0
Prior radiotherapy, %				
BID	20.5	31.9	24.7	35.0
QD	79.5	68.1	75.3	65.0
Response to prior cCRT, %				
CR or PR / SD	89.2 / 10.8	81.4 / 18.6	86.6 / 13.4	89.0 / 11.0
Prior PCI, %	45.8	61.9	45.4	62.0

BID, twice daily; CR, complete response; EP, early progressor; ITT, intent-to-treat; LTP, long-term progression-free survivor; PR, partial response; QD, once daily; SD, stable disease

Data cutoff: January 15, 2024

Patterns of disease progression in EPs and LTPs

Rates of intrathoracic and extrathoracic progression were similar for EPs in both arms; among LTPs with RECIST progression, progression was mostly intrathoracic

	Durvalumab		Placebo	
	EP (n=83)	**LTP (n=113)**	**EP (n=97)**	**LTP (n=100)**
No PFS events, n (%)	N/A	88 (77.9)	N/A	67 (67.0)
Progression-free at DCO	N/A	84 (74.3)	N/A	65 (65.0)
Censored for PFS prior to DCO	N/A	4 (3.5)*	N/A	2 (2.0)†
RECIST progression, n (%)	78 (94.0)	19 (16.8)	96 (99.0)	25 (25.0)
Intrathoracic progression only‡	36 (43.4)	16 (14.2)	42 (43.3)	16 (16.0)
Extrathoracic progression only§¶	39 (47.0)	3 (2.7)	44 (45.4)	9 (9.0)
Simultaneous intrathoracic and extrathoracic progression¶	3 (3.6)	0	10 (10.3)	0
Death in absence of progression, n (%)	5 (6.0)	6 (5.3)	1 (1.0)	8 (8.0)

Data cutoff: January 15, 2024

*Censored deaths in two patients and censored due to withdrawal of consent in two patients

†Censored death in one patient and censored due to withdrawal of consent in one patient

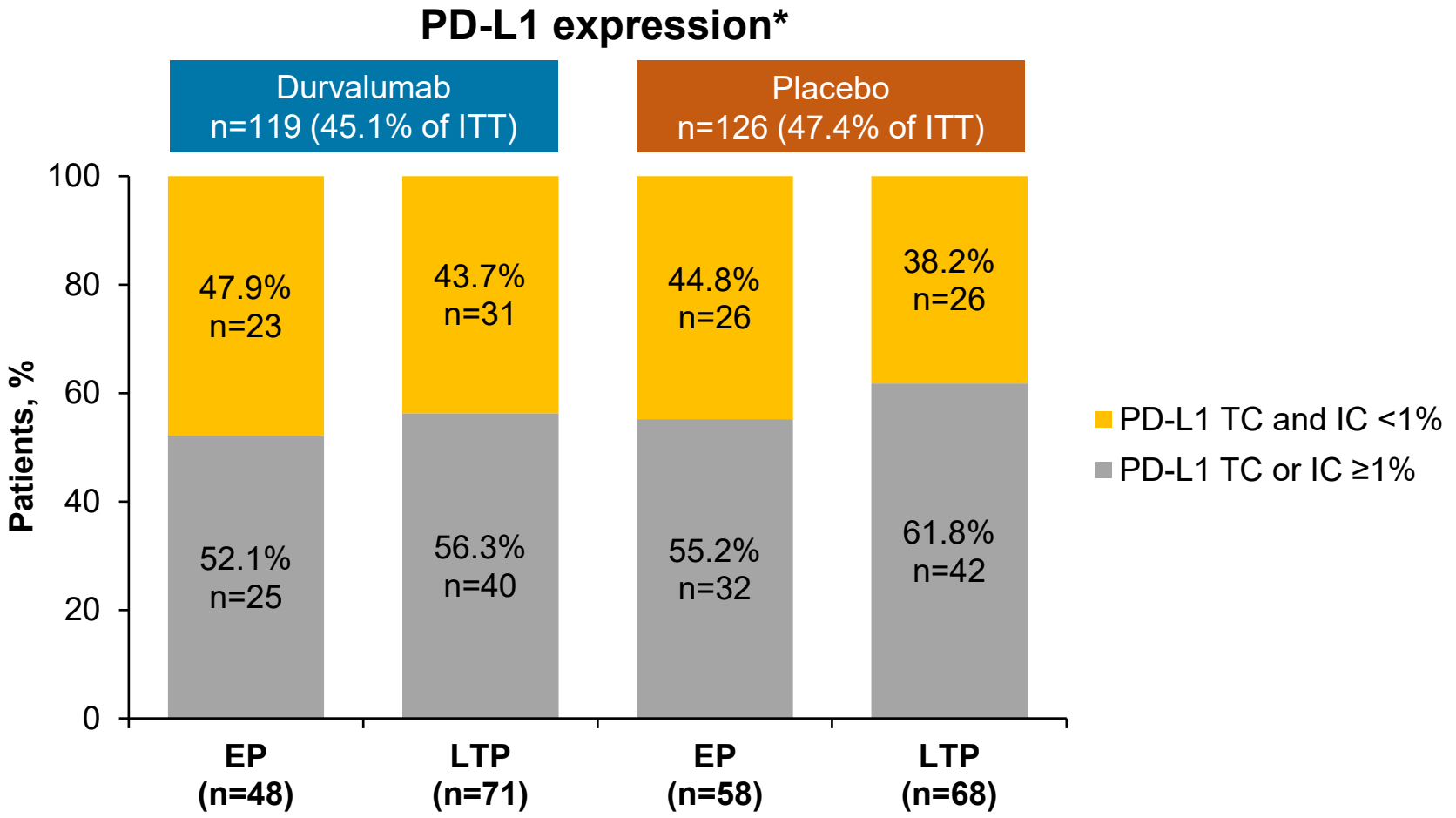
‡Any lesion within the lungs and mediastinum

§Any lesions outside the lungs, including the chest wall/diaphragm

¶Among patients with extrathoracic progression, two EPs in the durvalumab arm and two EPs in the placebo arm had two new lesions, the remainder all had one new lesion

PD-L1 expression in EPs and LTPs

Similar rates of tumors with PD-L1 expression on TC or IC ≥1% were seen in EPs and LTPs in both arms



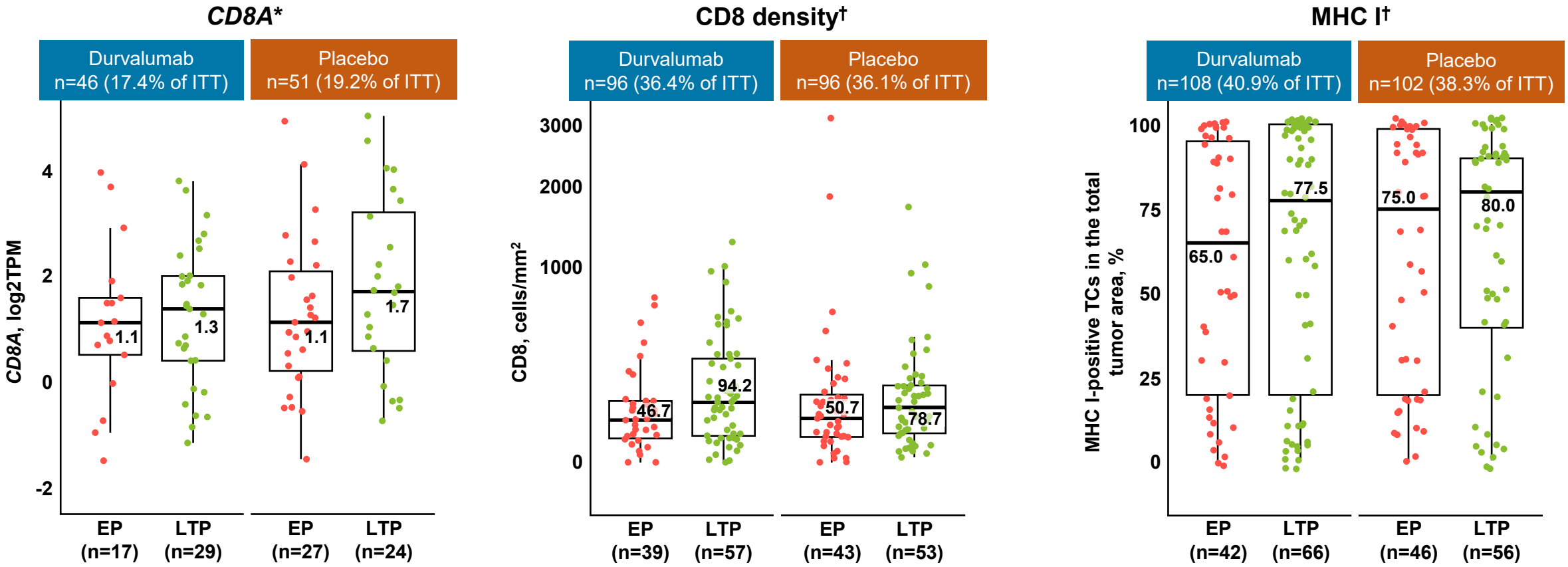
Data cutoff: January 15, 2024

*Assessed by VENTANA PD-L1 (SP263) IHC assay in pre-cCRT tumor samples collected at screening

IC, immune cell; PD-L1, programmed cell death ligand-1; TC, tumor cell

CD8A, CD8 density, and MHC I in EPs and LTPs

CD8A expression, CD8 density, and MHC I expression appeared higher in LTPs vs EPs in both arms



Data cutoff: January 15, 2024

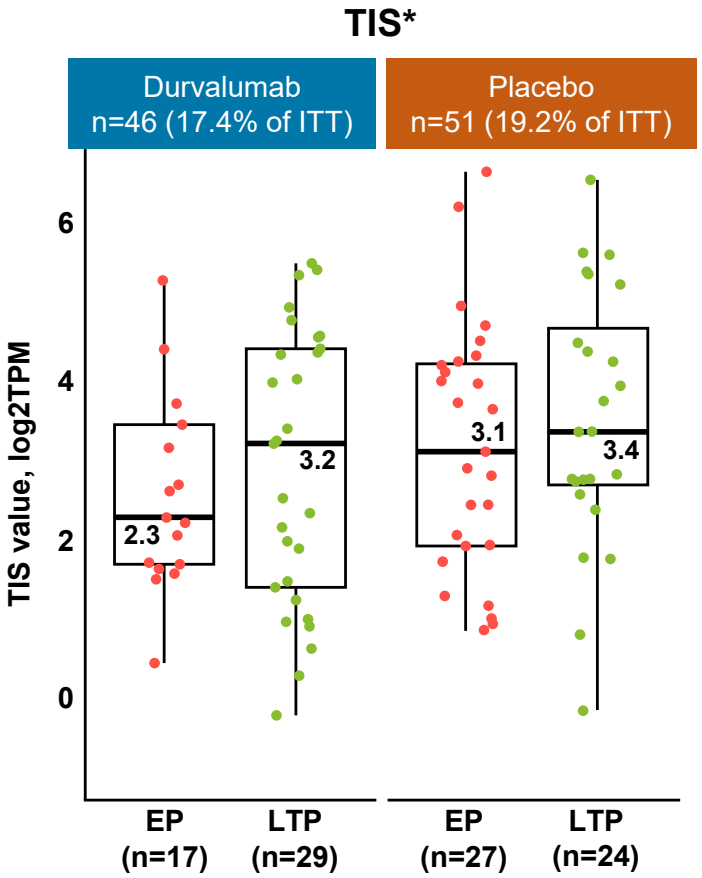
*Assessed by RNA sequencing in pre-cCRT tumor samples collected at screening

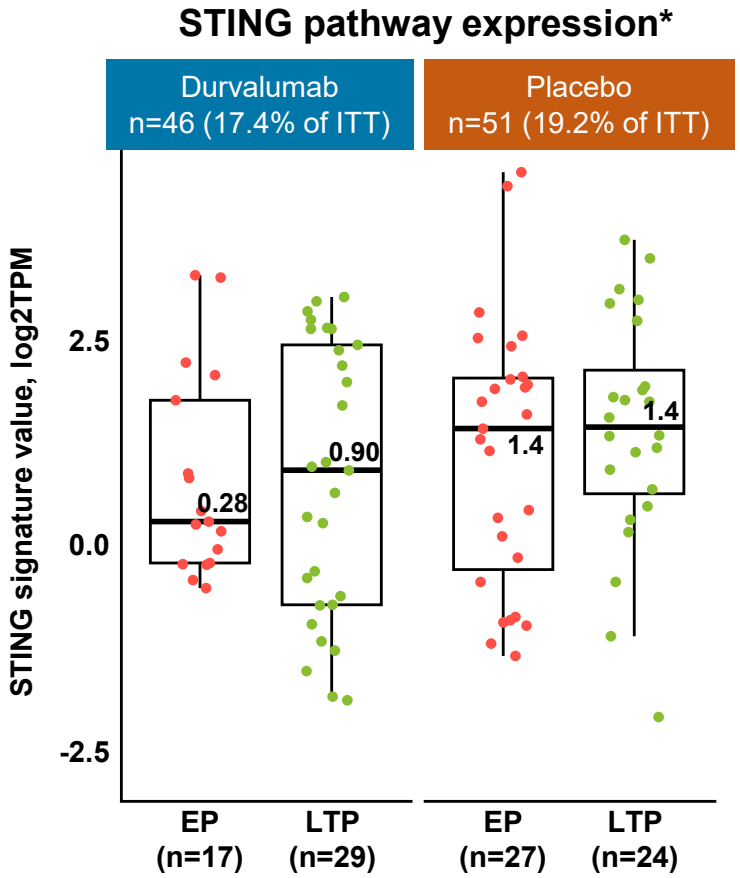
†Assessed by IHC in pre-cCRT tumor samples collected at screening

CD8, cluster of differentiation 8; MHC I, major histocompatibility complex class I

TIS and STING pathway in EPs and LTPs

Trends for higher TIS and STING pathway expression were seen in LTPs vs EPs in the durvalumab arm but not the placebo arm





Data cutoff: January 15, 2024

*Assessed by RNA sequencing in pre-cCRT tumor samples collected at screening

STING, stimulator of interferon genes; TIS, T-cell inflamed signature

Conclusions

- Higher proportions of stage I/II disease, prior BID radiotherapy and prior PCI were seen in LTPs vs EPs in both arms; there was a higher proportion of patients with WHO PS 0 in LTPs vs EPs in the durvalumab arm
- Rates of intrathoracic and extrathoracic progression were similar for EPs in both arms; among the LTPs who had RECIST progression events, progression was mostly intrathoracic
- Compared with EPs, LTPs were generally characterized by a pre-cCRT tumor microenvironment more conducive to fostering a response to immunotherapy
  - CD8 density, and *CD8A* and MHC I expressions appeared higher in LTPs vs EPs, regardless of treatment arm; trends for higher TIS and STING pathway expression were seen in LTPs vs EPs in the durvalumab arm but not the placebo arm
    - The higher antigen presentation and cytotoxic marker expression observed in LTPs could potentially enhance durvalumab's mechanism of action in these patients
- Findings should be prospectively validated in a larger dataset, given the limited sample sizes of the biomarker evaluable populations (18–46% of ITT population); additional integrative spatial analyses may also be informative
- **These exploratory analyses suggest that outcomes in durvalumab LTPs are potentially explained by molecular characteristics of the tumor microenvironment associated with the mechanism of action of durvalumab**

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