

ORIGINAL RESEARCH

# Adjuvant durvalumab for esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy: a placebo-controlled, randomized, double-blind, phase II study

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**Background:** We evaluated the efficacy of adjuvant durvalumab after neoadjuvant concurrent chemoradiotherapy (CCRT) in patients with esophageal squamous cell carcinoma (ESCC).

**Patients and methods:** This randomized, double-blind, phase II study included patients with ESCC who underwent curative surgery after neoadjuvant CCRT. Patients were randomized to receive either durvalumab (20 mg/kg/i.v. every 4 weeks for 12 months) or placebo in a 1:1 ratio and were stratified by age and pathologic tumor stage. The primary endpoint was disease-free survival (DFS).

**Results:** Between March 2016 and June 2018, 86 patients were randomized to the durvalumab ( $n = 45$ ) or placebo ( $n = 41$ ) arm. The median follow-up duration was 38.7 months. There was no difference in DFS [hazard ratio (HR) 1.18, 95% confidence interval (CI) 0.62-2.27,  $P = 0.61$ ] or overall survival (HR 1.08, 95% CI 0.52-2.24,  $P = 0.85$ ) between the two arms. Subgroup analysis was performed for patients for whom the post-CCRT programmed death-ligand 1 (PD-L1) expression profile could be assessed ( $n = 54$ ). In the PD-L1-positive group, based on tumor proportion score  $\geq 1\%$ , durvalumab was associated with longer overall survival compared with the placebo (36-month survival rate: 94% versus 64%; HR 0.42, 95% CI 0.10-1.76), while in the PD-L1-negative group, it was associated with shorter overall survival (42% versus 55%; HR 1.53, 95% CI 0.48-4.83), showing the tendency of interaction between post-CCRT PD-L1 status and adjuvant durvalumab therapy for overall survival (interaction  $P = 0.18$ ).

**Conclusions:** We failed to demonstrate that adjuvant durvalumab improved survival after neoadjuvant CCRT in patients with ESCC. However, post-CCRT PD-L1 expression could predict the survival of patients who receive adjuvant durvalumab after neoadjuvant CCRT, which needs to be validated.

**Key words:** adjuvant therapy, concurrent chemoradiotherapy, durvalumab, immune checkpoint inhibitor, squamous esophageal cancer

## INTRODUCTION

Esophageal cancer, an aggressive malignancy, is the sixth leading cause of cancer-related mortality worldwide.<sup>1</sup> Geographical and ethnic features affect histologic type distribution. While esophageal squamous cell carcinoma

(ESCC) predominates in Asia, Africa, and South America, and is the most common histologic type globally, esophageal adenocarcinoma (EAC) is the most common variant in Western countries.<sup>2</sup> ESCC accounted for 90% of esophageal cancers in Korea in 2013, with EAC representing only 3%.<sup>3</sup>

Locally advanced esophageal cancers comprise more than half of all newly diagnosed esophageal malignancies.<sup>4</sup> Although the standard treatment with neoadjuvant concurrent chemoradiotherapy (CCRT) followed by surgery can achieve a cure,<sup>5-7</sup> the prognosis of locally advanced esophageal cancer remains unsatisfactory, with ~56% of patients treated with the trimodal therapy having disease progression or dying within 5 years.<sup>5</sup>

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Immune checkpoint inhibitors (ICIs) directed to programmed cell death protein 1 (PD-1) have become important therapeutic agents for recurrent or metastatic esophageal cancer, especially for ESCC. Nivolumab and pembrolizumab are superior to chemotherapy in patients with ESCC and programmed death-ligand 1 (PD-L1)-high [combined positive score (CPS)  $\geq 10$ ] ESCC, respectively, who have failed prior chemotherapy.<sup>8,9</sup> Furthermore, in a recent clinical trial, the addition of pembrolizumab to standard chemotherapy was superior to chemotherapy alone as the first-line therapy in patients with esophageal cancer.<sup>10</sup>

Considering their proven efficacy in inoperable or metastatic esophageal cancer, it is expected that the incorporation of ICIs into a trimodal therapy for locally advanced esophageal cancer will improve cure rate and survival. To date, few studies have investigated the efficacy of durvalumab in patients with metastatic ESCC. However, the PACIFIC trial demonstrated that consolidation therapy with durvalumab for 1 year after definitive CCRT improved survival in patients with stage III non-small-cell lung cancer compared with definitive CCRT alone.<sup>11,12</sup> The success of the PACIFIC trial may be partly attributed to a synergistic antitumor effect between CCRT and durvalumab therapy.

Therefore, we hypothesized that the addition of adjuvant durvalumab for patients with ESCC who undergo neoadjuvant CCRT followed by complete resection could eradicate residual or hidden tumor cells that might have become more vulnerable to immunotherapy. In this study, we investigated whether adjuvant durvalumab therapy improved survival in patients with ESCC who underwent surgery after neoadjuvant CCRT. For biomarker analysis, we explored whether PD-L1 expression changes after neoadjuvant CCRT and evaluated the predictive role of PD-L1 expression status in pre- and post-CCRT (surgical) samples to assess the efficacy of adjuvant durvalumab therapy.

## METHODS

### Study design

This single-center, prospective, randomized, double-blinded phase II study was conducted at the Samsung Medical Center, Seoul, Korea. The patients were randomized in a 1:1 ratio based on two stratification factors: age ( $\geq 65$  years versus  $< 65$  years) and pathological tumor stage (ypT0-2N0 versus ypT3-4N0 or ypT0-4N1-3) according to the American Joint Committee on Cancer, seventh edition.<sup>13</sup>

This study was managed by the Samsung Medical Center Academic Clinical Research Organization (A-CRO). The Rave Electronic Data Capture system (Medidata Solutions, New York, USA) was used for clinical data management and electronic case report form construction.

### Participants

The inclusion criteria were as follows: (i) complete resection of ESCC after neoadjuvant CCRT; (ii) clinical tumor stage T3-4N0M0 or T1-4N1-3M0 at neoadjuvant CCRT initiation; (iii)

age  $\geq 18$  years; (iv) Eastern Cooperative Oncology Group performance score of 0 or 1; (v) completion of signed informed consent form 21-56 days after esophagectomy; (vi) normal hematologic, renal, and liver function; and (vii) no significant medical problems. No specific neoadjuvant chemotherapy regimen or radiation method was required for enrollment. However, two cycles of 5-fluorouracil (4000 mg/m<sup>2</sup> over 4 days) plus cisplatin (60 mg/m<sup>2</sup> on day 1) every 3 weeks, starting on the same day of radiation therapy (44 Gy in 22 daily fractions) was strongly recommended.

Further details regarding patient enrollment are included in the study protocol (see [Supplementary Material](https://doi.org/10.1016/j.esmooop.2022.100385), available at <https://doi.org/10.1016/j.esmooop.2022.100385>). All patients provided written informed consent. This study was conducted under the supervision of the Samsung Medical Center Institutional Review Board.

### Randomization and masking

Patients who met the predefined eligibility criteria were randomly assigned in a 1:1 ratio to the durvalumab or placebo arm using a stratified randomization method. A preconstructed randomization table was uploaded to the Rave Randomization and Trial Support Management system, and stratification factors were entered to generate an individual randomization number. Subsequently, the randomization number was sent to both the pharmacist and clinical research assistant, and the study drugs were prepared based on a randomization table. During administration, all study drugs were double blinded to both the patients and the medical staff.

The durvalumab solution and its matching placebo (normal saline) were identical in color, and their respective intravenous (i.v.) bags were identical in size. To ensure double blindness during dispensation to other study personnel, both durvalumab and placebo were blinded using an opaque sleeve and fastened to the i.v. bag using tamper-evident tape.

Unblinding was conducted based on a predefined procedure if serious adverse events suspected to be causally related to the study drug occurred. A code-breaking document was filled and signed by the principal investigator and sent to the A-CRO to execute the unblinding process.

### Procedures

Durvalumab 20 mg/kg i.v. or placebo was administered every 4 weeks for a maximum of 12 months or until disease progression or unacceptable toxicity. Assessments of tumor response were performed using chest computed tomography every 12 weeks for the first 24 months after enrollment, every 4 months from 25 to 48 months, every 6 months from 49 to 60 months, and every 12 months thereafter. Positron emission tomography or esophagography was used to confirm the suspected disease.

For PD-L1 assessments, formalin-fixed paraffin-embedded tissue blocks were cut into 4- $\mu$ m thick sections, stained with a VENTANA PD-L1 (SP263) assay (Ventana

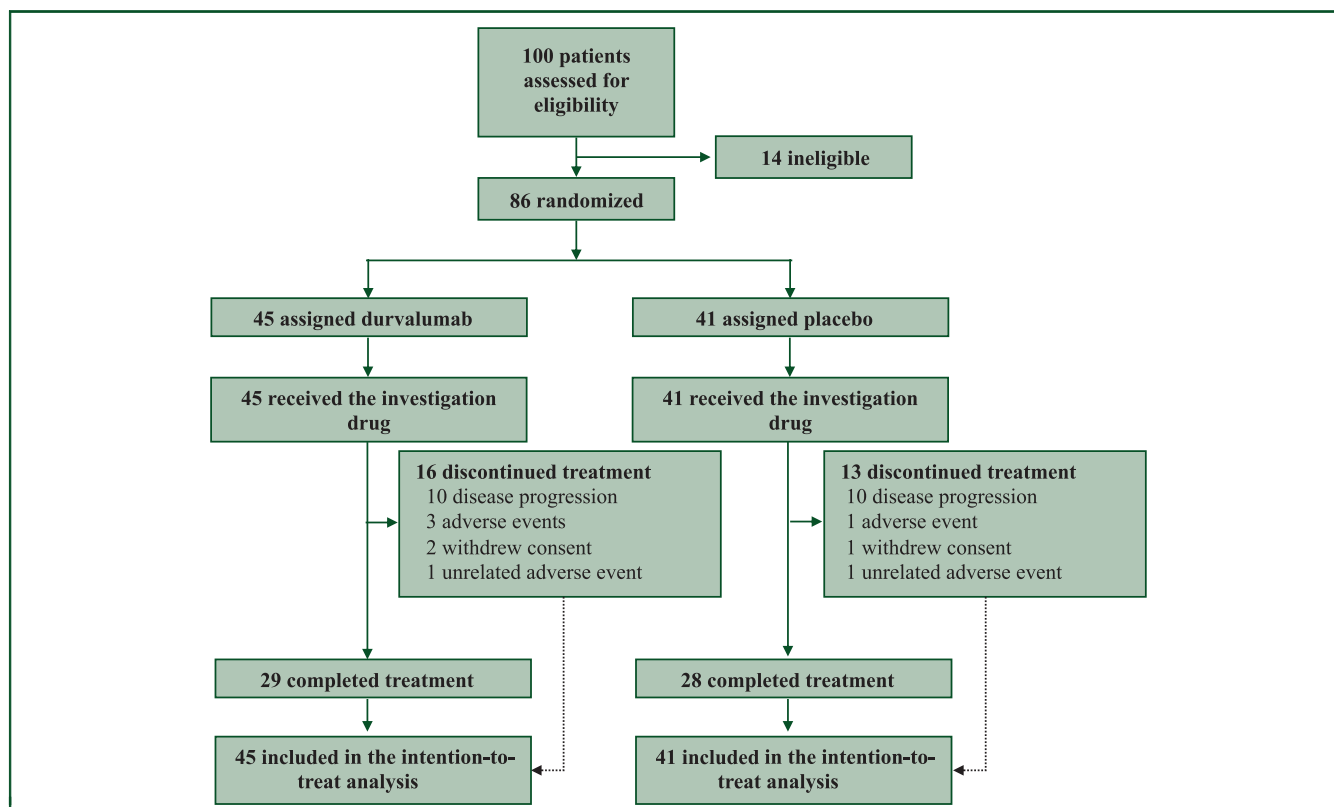


Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the study.

Medical Systems, AZ, USA), and observed with the OptiView DAB immunohistochemistry Detection Kit (Roche Diagnostics, Rotkreuz, Switzerland), according to the manufacturer's instructions. Assessment of PD-L1 expression was conducted based on tumor proportion score, defined as the percentage of viable tumor cells with partial or complete membrane staining in at least 100 viable tumor cells, which is performed independently and prospectively by two pathologists who were blind to any information about patients. Positive PD-L1 expression was defined as  $\geq 1\%$  of the tumor cells presenting with any membrane staining.

### Outcomes

The primary and secondary outcomes of this study were disease-free survival (DFS) and overall survival, respectively. Safety outcomes were evaluated according to the Common Terminology Criteria for Adverse Events version 4. As a biomarker study, changes in PD-L1 expression between pre- and post-neoadjuvant CCRT specimens and their correlation with DFS and overall survival were evaluated.

### Sample size calculation

Based on a previous trial,<sup>14</sup> the DFS rate at 12 months was expected to be  $\sim 60\%$  in the placebo arm. A positive effect in the durvalumab arm was defined as a 12-month DFS rate of  $\geq 75\%$ . Based on this hypothesis, a two-sample log-rank test with one-sided  $\alpha=10\%$  and 80% power requires 79 patients. Based on this sample size calculation, this study was planned to recruit 84 patients (42 patients per arm),

accounting for 5% of attrition due to ineligibility and dropout. We anticipated a study duration of 58 months: 34 months for patient accrual and 24 months for additional follow-up. The final analysis was planned to be conducted when 56 cases of a DFS event (defined as either disease recurrence or death) occurred.

### Statistical analysis

The data lock and study arms unblinding were performed on 11 January 2021 (58 months since the first patient was enrolled) as initially planned. Although the actual number of DFS events ( $n = 37$ ) at that time was lower than initially expected ( $D = 56$ ), we decided to perform the final analysis on time after observing only one DFS event in 2020. The analysis was conducted based on an intention-to-treat principle. The chi-square test and Student's *t*-test were used to calculate statistical differences between categorical and continuous variables, respectively. DFS was calculated as the interval between the date of randomization and the date of either disease recurrence or death due to any cause. The overall survival was calculated as the interval between the date of randomization and the date of death due to any cause. Kaplan–Meier curves were used to estimate survival distributions, and the log-rank test was used to compare survival distributions between arms. The Cox proportional hazards model was used to conduct this comparison adjusting for clinical predictors, including the interaction between post-CCRT PD-L1 status and adjuvant durvalumab. All statistical analyses were conducted using R software

(version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). This study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT02520453).

## RESULTS

### Baseline demographics

Among the 100 patients screened between March 2016 and June 2018, 86 were enrolled in the study (45 in the durvalumab arm and 41 in the placebo arm) at Samsung Medical Center, Seoul, Korea. All participants received the study drugs and were included in the intention-to-treat analysis. [Figure 1](#) shows the CONSORT (Consolidated Standards of Reporting Trials) trial profile. There was no difference between groups regarding baseline characteristics, including percentage of patients with a pathologic complete response (ypCR) and post-CCRT PD-L1 expression ([Table 1](#)).

### DFS and overall survival

The median follow-up duration for survival analysis was 38.7 months [95% confidence interval (CI) 36.8-43.3]. The median DFS was not reached (NR) in any group [durvalumab arm: 95% CI 17.0-not available (NA); placebo arm: 95% CI 20.1-NA]. The 12-, 24-, and 36-month DFS rates were 71%, 58%, and 55% in the durvalumab arm versus 73%, 61%, and 61% in the placebo arms, respectively: the hazard ratio (HR) for durvalumab was 1.18 (95% CI 0.62-2.27,  $P = 0.61$ ; [Figure 2A](#)). As a subsequent therapy after the recurrence of esophageal cancer, 15 patients (33%) received systemic antitumor therapy in the durvalumab arm, including three who received nivolumab. Similarly, in the placebo arm, nine patients (22%) received systemic antitumor therapy and two received nivolumab. The median overall survival was 50.6 months (95% CI 50.6-NA) for the durvalumab arm and NR (95% CI NA-NA) for the placebo arm (HR 1.08, 95% CI 0.52-2.24,  $P = 0.85$ ; [Figure 2B](#)). The overall survival rates of the durvalumab and placebo arms at 12, 24, and 36 months were 91% versus 88%, 73% versus 73%, and 71% versus 68%, respectively.

### Efficacy of adjuvant durvalumab in the ypCR and non-ypCR groups

In the comparison of survival according to ypCR, patients with ypCR ( $n = 28$ ) had better survival than those without ypCR ( $n = 58$ ), as indicated by higher 36-month DFS rate (71% versus 52%) and 36-month overall survival rate (79% versus 66%; [Supplementary Figure S1](#), available at <https://doi.org/10.1016/j.esmooop.2022.100385>). For both groups with and without ypCR, there was no significant difference in DFS and overall survival between the durvalumab and placebo arms ([Figure 3](#)).

### PD-L1 expression as a predictive biomarker

Pre-CCRT PD-L1 expression data were available for 72 patients, while post-CCRT PD-L1 data were available for 54 patients, after excluding 28 patients with ypCR and 4 who were unevaluable ([Table 1](#)). Analysis of paired pre- and

**Table 1. Baseline characteristics of the study population**

Characteristics	Durvalumab arm (n = 45)	Placebo arm (n = 41)	P
Age, years	64 (39-76)	66 (42-83)	0.26
Age $\geq 65$	21 (47)	21 (51)	0.83
Age $< 65$	24 (53)	20 (49)	
Gender			
Male	43 (96)	37 (90)	0.42
Female	2 (4)	4 (10)	
Smoking			
Never	7 (16)	4 (10)	0.45
Former	15 (33)	19 (46)	
Current	23 (51)	18 (44)	
Interval between operation and enrollment, days	28 (23-36)	30 (23-36)	0.78
Primary tumor site			
Cervical	0 (0)	3 (7)	0.27
Upper thoracic	8 (18)	5 (12)	
Midthoracic	19 (42)	20 (49)	
Lower thoracic	18 (40)	13 (32)	
Pre-CCRT clinical stage			
II	8 (18)	13 (32)	0.21
III	37 (82)	28 (68)	
Chemotherapy regimen of CCRT			
5-FU and cisplatin	45 (100)	45 (100)	0.55
Radiation dose of CCRT	44 (43-44)	44 (43-44)	
Post-CCRT surgical stage			
ypCR	14 (31)	14 (34)	0.98
I	2 (4)	2 (5)	
II	23 (51)	19 (46)	
III	6 (13)	6 (15)	
Number of dissected LN	37 (27-44)	38 (31-42)	0.83
LN dissection fields			
Two	26 (58)	17 (42)	0.20
Three	19 (42)	24 (59)	
Post-CCRT PD-L1 expression			
Positive	17 (38)	14 (34)	0.97
Negative	12 (27)	11 (27)	
ypCR	14 (31)	14 (34)	
Unavailable	2 (4)	2 (5)	

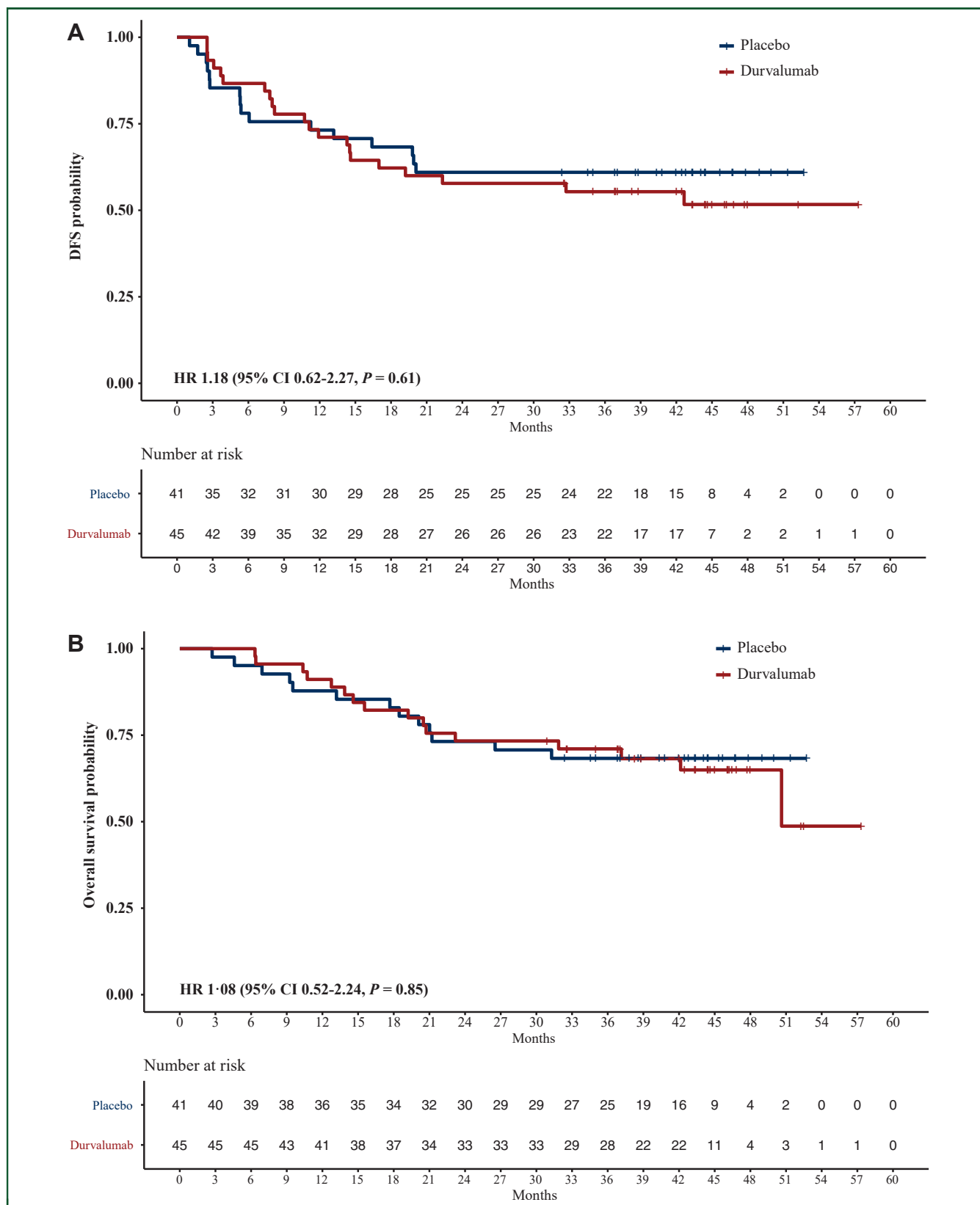
Data are presented as  $n$  (%) or median (interquartile range) unless otherwise specified.  $P$  values were calculated using the chi-square test for categorical variables and  $t$ -test for continuous variables.

CCRT, concurrent chemoradiotherapy; CR, complete response; LN, lymph node; PD-L1, programmed death-ligand 1; ypCR, pathologic complete response.

post-CCRT samples ( $n = 48$ ) revealed that after CCRT, the PD-L1 tumor proportion score increased in 20 pairs, decreased in 15, and did not change in 13 ([Supplementary Figure S2](#), available at <https://doi.org/10.1016/j.esmooop.2022.100385>). Based on the cut-off level ( $\geq 1\%$ ) for positive PD-L1 expression, positive PD-L1 shifted to negative PD-L1 in 8 paired samples, from negative PD-L1 to positive PD-L1 in 13, and remained unchanged in 27.

Pre-CCRT PD-L1 expression was not useful for predicting the efficacy of adjuvant durvalumab. In patients with positive pre-CCRT PD-L1 expression ( $n = 32$ ), durvalumab therapy did not affect DFS or overall survival. A similar result was observed in pre-CCRT PD-L1-negative patients ( $n = 40$ ; [Supplementary Figure S3](#), available at <https://doi.org/10.1016/j.esmooop.2022.100385>).

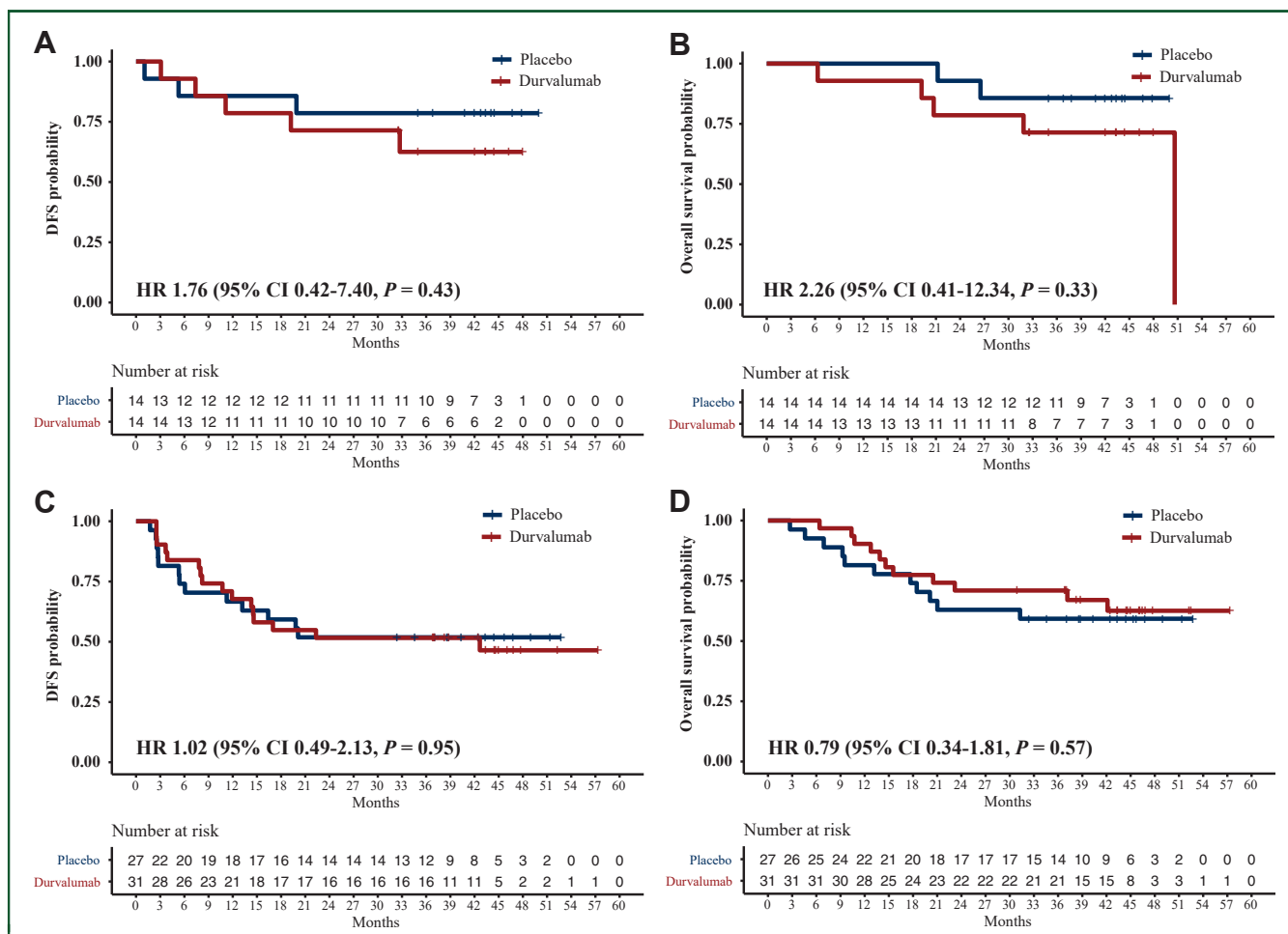
Compared with pre-CCRT PD-L1 status, post-CCRT PD-L1 expression could predict the efficacy of adjuvant durvalumab more accurately. In patients with positive post-CCRT



**Figure 2.** Kaplan–Meier curves of (A) disease-free survival and (B) overall survival of the durvalumab and placebo arms in the intention-to-treat population. CI, confidence interval; DFS, disease-free survival; HR, hazards ratio.

PD-L1 expression ( $n = 31$ ), the median DFS was 42.7 months in the durvalumab arm ( $n = 17$ ) and 20.1 months in the placebo arm ( $n = 14$ ; HR 0.85, 95% CI 0.31-2.34,

$P = 0.75$ ). In the group with negative post-CCRT PD-L1 expression ( $n = 23$ ), the median DFS was 15.8 months in the durvalumab arm ( $n = 12$ ) and NR in the placebo arm



**Figure 3.** Kaplan–Meier curves of (A) disease-free survival (DFS) and (B) overall survival of the durvalumab and placebo arms in the pathologic complete response (ypCR) group, and those of (C) DFS and (D) overall survival of the durvalumab and placebo arms in the non-ypCR group. CI, confidence interval; DFS, disease-free survival; HR, hazards ratio.

( $n = 11$ ; HR 1.42, 95% CI 0.45-4.50,  $P = 0.55$ ). The interaction  $P$  value between post-CCRT PD-L1 status and adjuvant durvalumab therapy for DFS was 0.54 (Figure 4A).

In the group with positive post-CCRT PD-L1 expression, the median overall survival was NR in both the durvalumab and placebo arms, with 36-month overall survival rates of 94% and 64%, respectively (HR 0.42, 95% CI 0.10-1.76,  $P = 0.22$ ). In the group with negative PD-L1 post-CCRT, the median overall survival was 21.8 months in the durvalumab arm and NR in the placebo arm, with 36-month overall survival rates of 42% and 55%, respectively (HR 1.53, 95% CI 0.48-4.83,  $P = 0.47$ ). The interaction  $P$  value between the post-CCRT PD-L1 status and adjuvant durvalumab therapy for overall survival was 0.18 (Figure 4B).

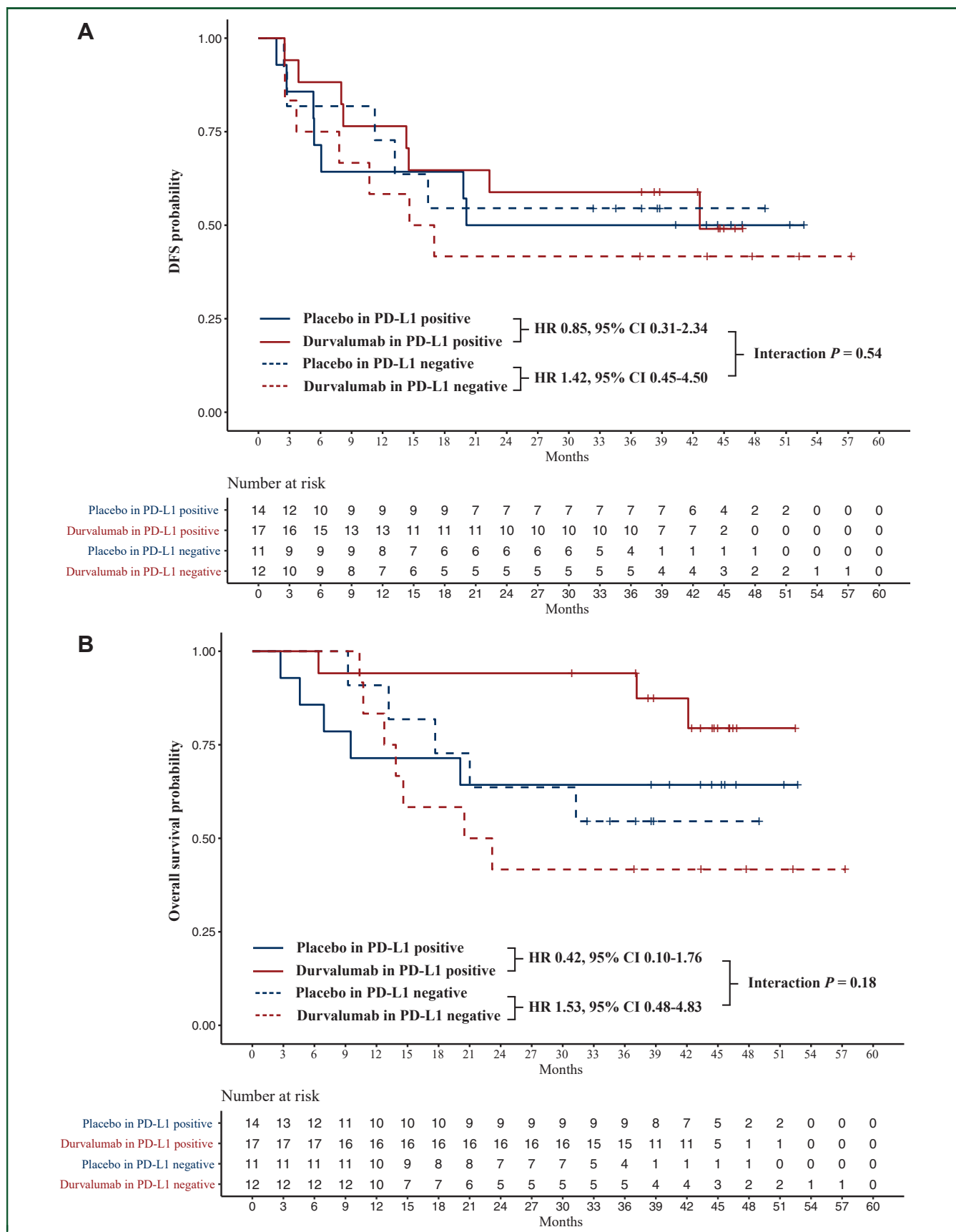
**Safety profile**

In the durvalumab arm, 26 patients (58%) experienced treatment-related adverse events, with 51% ( $n = 23$ ) presenting with grade 1 or 2 events. In the placebo arm, 13 patients (32%) experienced treatment-related adverse events, of which the majority were grade 1 and 2 events,

except for one patient with grade 5 pneumonitis (Table 2). A detailed list of all adverse events is provided in Supplementary Table S1, available at <https://doi.org/10.1016/j.esmooop.2022.100385>.

During the study period, emergency unblinding was required in two patients who developed serious adverse events that were presumably related to the study drug. The first patient who needed the unblinding presented with grade 3 pneumonitis and was receiving durvalumab. The second patient presented with grade 4 pneumonitis and was unblinded immediately after admission to the intensive care unit. This patient was assigned to the placebo arm; therefore pneumonitis was interpreted as an acute respiratory distress syndrome caused by aspiration pneumonia. Despite intensive care, the patient died of respiratory failure. This was the only treatment-related death observed in this study.

Three patients from the durvalumab arm discontinued treatment permanently owing to drug-related adverse events (two developed grade 3 and 2 pneumonitis and one developed grade 3 fatigue and grade 2 anorexia). In the placebo arm, the sole patient who discontinued treatment developed pneumonitis, as mentioned previously.



**Figure 4. Kaplan—Meier curves of (A) disease-free survival and (B) overall survival of the durvalumab and placebo arms stratified according to PD-L1 expression status on surgical samples after neoadjuvant chemoradiotherapy.**

CI, confidence interval; DFS, disease-free survival; HR, hazards ratio; programmed death-ligand 1.

Table 2. Treatment-related adverse events

Adverse event	Durvalumab related (n = 45)		Placebo related (n = 41)	
	Group	Group	Group	Group
	1 or 2, n (%)	≥3, n (%)	1 or 2, n (%)	≥3, n (%)
Hypothyroidism	18 (40)	0 (0)	4 (10)	0 (0)
Skin rash	4 (9)	0 (0)	2 (5)	0 (0)
Hyperthyroidism	4 (9)	0 (0)	1 (2)	0 (0)
Urticaria	3 (7)	0 (0)	0 (0)	0 (0)
Hyperglycemia	2 (4)	0 (0)	1 (2)	0 (0)
Arthralgia	2 (4)	0 (0)	1 (2)	0 (0)
Pneumonitis	2 (4)	1 (2)	0 (0)	1 (2)
Fatigue	1 (2)	1 (2)	2 (5)	0 (0)
Anorexia	1 (2)	0 (0)	1 (2)	0 (0)
Oral stomatitis	1 (2)	0 (0)	1 (2)	0 (0)
Diarrhea	0 (0)	0 (0)	3 (7)	0 (0)
Fever	0 (0)	0 (0)	1 (2)	0 (0)
Nausea	0 (0)	0 (0)	1 (2)	0 (0)
Hepatitis	0 (0)	0 (0)	1 (2)	0 (0)
Adrenal insufficiency	0 (0)	1 (2)	0 (0)	0 (0)
Bowel perforation	0 (0)	1 (2)	0 (0)	0 (0)

## DISCUSSION

Our study failed to demonstrate a survival benefit of adjuvant durvalumab therapy in patients with ESCC who underwent surgery and neoadjuvant CCRT. This result was unexpected because the recently published CheckMate 577 trial reported a significant benefit of immunotherapy in patients with esophageal cancer. In patients with ESCC or EAC who underwent surgery after neoadjuvant CCRT, adjuvant therapy with nivolumab led to a significant improvement in DFS compared with the placebo (median DFS 22.4 versus 11.0 months, HR 0.69, 95% CI 0.56-0.86).<sup>15</sup> Furthermore, subgroup analysis of the CheckMate 577 population revealed that the benefit in DFS was greater in patients with ESCC (median DFS: 29.7 versus 11.0 months, HR 0.61) than in those with EAC (median DFS: 19.4 versus 11.1 months, HR 0.75).

In addition to differences in eligible histologic types (ESCC only versus ESCC and EAC) and study drugs (durvalumab versus nivolumab), several differences between our study and the CheckMate 577 study may account for the disparate results. First, our study was a single-center phase II study, while the CheckMate 577 trial was a global phase III study that included a significantly larger population ( $n = 794$ ). Second, the CheckMate 577 trial excluded patients who were free from residual cancer after neoadjuvant CCRT (ypCR patients).

Besides the independently better prognosis of the ypCR subgroup compared with the non-ypCR subgroup, there was a slight difference in the survival benefit of adjuvant durvalumab between the two subgroups. The durvalumab arm was associated with insignificantly inferior survival outcomes to the placebo arm in the ypCR group, while it showed comparable or insignificantly superior survival in the non-ypCR group (Figure 3). This phenomenon can be explained by that patients who achieved ypCR after CCRT were less likely to have residual tumor after operation than those with non-ypCR and, accordingly, have less chance of benefiting from adjuvant durvalumab therapy.

Several studies have suggested the predictive role of PD-L1 expression for PD-1/PD-L1 inhibitor therapy in patients with recurrent or metastatic esophageal cancer.<sup>8-10,16</sup> In addition, PD-L1 status is dynamic and changes with chemotherapy or radiotherapy.<sup>17,18</sup> Therefore in trials investigating the efficacy of adjuvant immunotherapy after neoadjuvant CCRT, it is crucial to decide which specimens should be used to evaluate the predictive role of PD-L1 expression. On comparative analysis, we found that CCRT significantly changed PD-L1 expression. There was a change in PD-L1 tumor proportion score after CCRT in 73% (35 out of 48) of paired pre- and post-CCRT samples, and PD-L1 positivity or negativity was also changed in 44% (21 out of 48). According to pre-CCRT PD-L1 status, there was no difference in DFS or overall survival between the two study arms. However, post-CCRT PD-L1 status appeared useful to differentiate overall survival outcomes between the two study arms (Figure 4B), although the interaction  $P$  value between post-CCRT PD-L1 status and adjuvant durvalumab for overall survival was not statistically significant, probably due to the small sample size. Regarding DFS, the utility of post-CCRT PD-L1 expression was weaker, although there was still a tendency favoring its predictive role (Figure 4A). The role of post-CCRT PD-L1 status was different in the CheckMate 577 subgroup analysis<sup>15</sup>: the effect of nivolumab on DFS was similar in the PD-L1 tumor proportion score positive (HR 0.75) and negative groups (HR 0.73). However, *post hoc* analyses according to PD-L1 CPS in the CheckMate 577 showed that patients with higher (CPS  $\geq 5$ ) PD-L1-expressing tumors benefited more from adjuvant nivolumab (median DFS 29.4 versus 10.2 months, HR 0.62, 95% CI 0.46-0.83) than those with lower or negative (CPS  $< 5$ ) PD-L1-expressing tumors (median DFS 16.3 versus 11.1 months, HR 0.89, 95% CI 0.65-1.22). Although this disparity might be in part attributed to the use of a different PD-L1 antibody (28-8 pharmDX) in the CheckMate 577 study, the predictive role of post-CCRT PD-L1 expression remains to be evaluated in further studies including overall survival analysis of CheckMate 577.

In this study, the use of adjuvant durvalumab was overall safe; events were comparable to those of other durvalumab monotherapy studies.<sup>12</sup> Only three patients required permanent discontinuation of the study drug due to adverse events, most of which resolved well.

In conclusion, the current placebo-controlled, double-blind, randomized phase II study failed to meet the primary endpoint, possibly owing to the small sample size and the outperformance of the control arm. However, we obtained invaluable information for further study design. First, adjuvant durvalumab therapy following neoadjuvant CCRT and surgery seems to be safe. Second, post-CCRT PD-L1 status could help predict the survival of patients who receive adjuvant PD-1/PD-L1 inhibitors. Third, because patients with ypCR exhibit a good prognosis and are less likely to benefit from adjuvant durvalumab, caution should be exercised when including this population in future studies investigating adjuvant immunotherapy. We cautiously anticipate that the role of adjuvant ICIs, including durvalumab, in



patients with esophageal cancer will be validated in further large-scale studies.

## ACKNOWLEDGEMENTS

None.

## FUNDING

This work was supported by AstraZeneca (no grant number) by providing durvalumab and funds for this study. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## DISCLOSURE

The authors have declared no competing interests.

## DATA SHARING

The data that support the findings of this study are available on request from the corresponding author.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice Guidelines. The protocol was approved by the Samsung Medical Center Institutional Review Board and all patients provided written informed consent before enrollment.

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