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ORIGINAL ARTICLE

Durvalumab with or without tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma: EAGLE, a randomized, open-label phase III study

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Background: Targeting the programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) axis has demonstrated clinical benefit in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). Combining immunotherapies targeting PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) has shown evidence of additive activity in several tumor types. This phase III study evaluated the efficacy of durvalumab (an anti-PD-L1 monoclonal antibody) or durvalumab plus tremelimumab (an anti-CTLA-4 monoclonal antibody) versus standard of care (SoC) in R/M HNSCC patients.

Patients and methods: Patients were randomly assigned to receive 1 : 1 : 1 durvalumab (10 mg/kg every 2 weeks [q2w]), durvalumab plus tremelimumab (durvalumab 20 mg/kg q4w plus tremelimumab 1 mg/kg q4w × 4, then durvalumab 10 mg/kg q2w), or SoC (cetuximab, a taxane, methotrexate, or a fluoropyrimidine). The primary end points were overall survival (OS) for durvalumab versus SoC, and OS for durvalumab plus tremelimumab versus SoC. Secondary end points included progression-free survival (PFS), objective response rate, and duration of response.

Results: Patients were randomly assigned to receive durvalumab ($n = 240$), durvalumab plus tremelimumab ($n = 247$), or SoC ($n = 249$). No statistically significant improvements in OS were observed for durvalumab versus SoC [hazard ratio (HR): 0.88; 95% confidence interval (CI): 0.72−1.08; $P = 0.20$] or durvalumab plus tremelimumab versus SoC (HR: 1.04; 95% CI: 0.85−1.26; $P = 0.76$). The 12-month survival rates (95% CI) were 37.0% (30.9−43.1), 30.4% (24.7−36.3), and 30.5% (24.7−36.4) for durvalumab, durvalumab plus tremelimumab, and SoC, respectively. Treatment-related adverse events (trAEs) were consistent with previous reports. The most common trAEs (any grade) were hypothyroidism for durvalumab and durvalumab plus tremelimumab (11.4% and 12.2%, respectively), and anemia (17.5%) for SoC. Grade ≥3 trAE rates were 10.1%, 16.3%, and 24.2% for durvalumab, durvalumab plus tremelimumab, and SoC, respectively.

Conclusion: There were no statistically significant differences in OS for durvalumab or durvalumab plus tremelimumab versus SoC. However, higher survival rates at 12 to 24 months and response rates demonstrate clinical activity for durvalumab.

Trial registration: ClinicalTrials.gov: NCT02369874.

Key words: durvalumab, head and neck squamous cell carcinoma, immunotherapy, metastatic, randomized clinical trial, tremelimumab

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INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is among the 10 most common cancers worldwide, with increasing incidence.[1] Approximately 10% of patients with HNSCC will be diagnosed with metastatic disease, and even when treated early, around half will have disease recurrence.[2,3] The platinum-based doublet chemotherapy with cetuximab regimen has been the most widely-used therapy and considered standard of care (SoC) since it was proven effective in 2007 for recurrent/metastatic (R/M) HNSCC in the first-line setting.[3,4] However, patients typically progress even after aggressive first-line therapy, and, until recently, the available options (e.g. cetuximab, methotrexate, and taxanes) have delivered limited survival benefits.[3]

Durvalumab is an immunotherapeutic agent that blocks the interaction between programmed cell death ligand 1 (PD-L1) and its receptors.[5] Durvalumab demonstrated encouraging response rates and duration of response (DoR) with a manageable safety profile in patients with HNSCC.[6] Although monotherapy agents that block the programmed cell death protein 1 (PD-1)/PD-L1 axis have shown clinical activity, immunotherapy combinations have the potential to improve upon monotherapy activity.[7–9] Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-L1/PD-1 pathways have largely non-redundant roles, suggesting that blockade of both could have additive or synergistic effects.[10] Indeed, the combination of durvalumab and tremelimumab, an anti-CTLA-4 monoclonal antibody, was explored based on improved efficacy over monotherapy in other solid tumor types.[7] This observation, in addition to the activity demonstrated by durvalumab in earlier R/M HNSCC studies, served as the rationale to evaluate durvalumab and tremelimumab in patients with R/M HNSCC. Several studies, including the EAGLE study, were initiated to evaluate combination immunotherapy regimens in various patient groups.[11,12] The EAGLE study was the first phase III study to investigate durvalumab and tremelimumab in patients with R/M HNSCC who had progressed after platinum-based therapy.

During the conduct of the EAGLE study, anti-PD-1 monoclonal antibodies were approved for use for R/M HNSCC progression following a platinum-based regimen. Treatment with these immunotherapies resulted in a median overall survival (OS) of 7.5—8.4 months.[13,14] These immunotherapies are now recommended for second-line treatment as monotherapies for patients with R/M HNSCC.[3,13,14] More recently, immunotherapy alone or in combination with platinum-based chemotherapy has shown improvements in OS in the first-line setting, underscoring the clinical utility of immunotherapy in HNSCC.[15]

Here, we report the results of the randomized phase III EAGLE trial evaluating durvalumab and durvalumab plus tremelimumab versus SoC therapies in patients with R/M HNSCC who have progressed following a platinum-containing regimen.

METHODS

Study design and conduct

The study was conducted at 156 sites globally in accordance with ethical principles originating from the Declaration of Helsinki and consistent with International Conference on

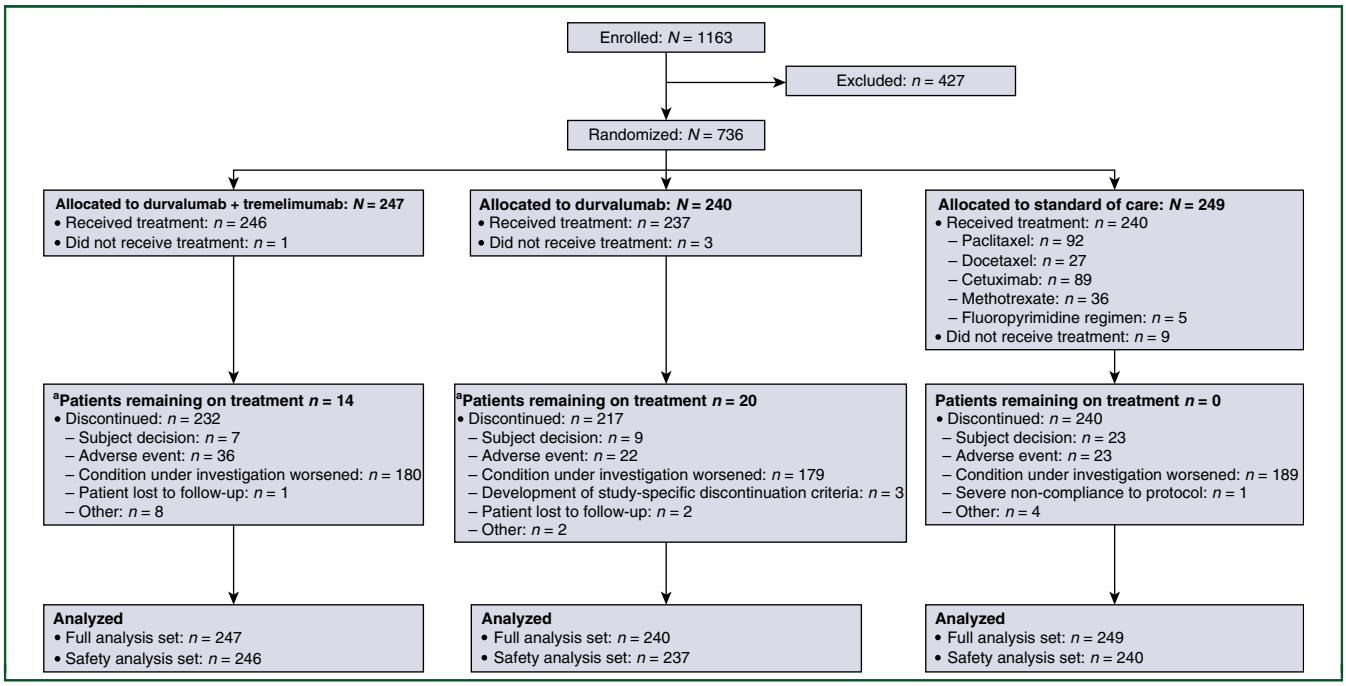

Figure 1. CONSORT diagram.
[a] As of 10 September 2018.

Table 1. Baseline demographics and clinical characteristics in the full analysis set

	Durvalumab ($n = 240$)	Durvalumab + tremelimumab ($n = 247$)	Standard of care ($n = 249$)
Median age, years (range)	59.0 (24–84)	61.0 (23–81)	61.0 (22–82)
Male, *n* (%)	202 (84.2)	209 (84.6)	207 (83.1)
Race, *n* (%)	$n = 238$	$n = 242$	$n = 240$
White	198 (83.2)	204 (84.3)	189 (78.8)
Asian	35 (14.7)	33 (13.6)	45 (18.8)
Other (including black or African American)	5 (2.1)	5 (2.0)	6 (2.4)
Ethnicity, *n* (%)			
Hispanic or Latino	15 (6.3)	16 (6.6)	13 (5.4)
Nicotine use, *n* (%)			
Current smoker	41 (17.1)	45 (18.2)	56 (22.5)
Former smoker	153 (63.8)	146 (59.1)	140 (56.2)
Never	46 (19.2)	56 (22.7)	53 (21.3)
Other nicotine use[a]	3 (1.3)	0	2 (0.8)
Primary tumor location, *n* (%)			
Oral cavity	64 (26.7)	65 (26.3)	61 (24.5)
Oropharynx	92 (38.3)	91 (36.8)	91 (36.5)
Hypopharynx	41 (17.1)	51 (20.6)	37 (14.9)
Larynx	37 (15.4)	33 (13.4)	45 (18.1)
Other	6 (2.5)	7 (2.8)	15 (6.0)
Time from last platinum therapy, *n* (%)	$n = 227$	$n = 234$	$n = 237$
≤6 months	185 (81.5)	195 (83.3)	208 (87.8)
>6 months	42 (18.5)	39 (16.7)	29 (12.2)
ECOG PS, *n* (%)			
0	62 (25.8)	64 (25.9)	79 (31.7)
1	178 (74.2)	183 (74.1)	170 (68.3)
Median number of prior treatments (range)	1.0 (1–4)	1.0 (1–4)	1.0 (1–4)
Tumor location/HPV status, *n* (%)	$n = 240$	$n = 246$	$n = 249$
OPC/positive	30 (12.5)	30 (12.2)	31 (12.4)
OPC/negative	60 (25.0)	58 (23.6)	60 (24.1)
Non-OPC/any HPV	150 (62.5)	158 (64.2)	158 (63.5)
PD-L1 status, *n* (%)			
TC ≥ 25%	68 (28.3)	72 (29.1)	72 (28.9)
TC < 25%	172 (71.7)	175 (70.9)	177 (71.1)
Disease extent at baseline, *n* (%)			
Local/regional recurrence ± distant metastases	221 (92.1)	224 (90.7)	214 (85.9)
Distant metastases only	19 (7.9)	23 (9.3)	35 (14.1)

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HPV, human papilloma virus; OPC, oropharyngeal cancer; PD-L1, programmed death ligand 1; TC, tumor cell.

[a] Including chewing tobacco/oral snuff/sublingual nicotine.

Harmonisation and Good Clinical Practice guidelines, applicable regulatory requirements, and sponsor's policy on Bioethics and Human Biological Samples. Written informed consent from participants was obtained before performing any protocol-related procedures.

Randomization was stratified according to PD-L1 expression, tumor location/human papilloma virus (HPV) status, and smoking status. PD-L1 expression was centrally assessed using the VENTANA (Ventana Medical Systems, Inc., Tuscon, AZ) PD-L1 (SP263) Assay, using a cut-off of ≥25% tumor cells (TC ≥ 25%) with membrane staining for PD-L1 at any intensity.[16] HPV was assessed according to local standard procedures, including immunohistochemistry, FISH or polymerase chain reaction.

Patients were randomly assigned to receive 1 : 1 : 1 durvalumab [10 mg/kg every 2 weeks (q2w)], durvalumab plus tremelimumab [durvalumab 20 mg/kg every 4 weeks (q4w) plus tremelimumab 1 mg/kg q4w up to four doses, followed by durvalumab 10 mg/kg q2w], or investigator's choice of a single-agent SoC therapy. Each SoC agent (cetuximab, docetaxel, paclitaxel, methotrexate, 5-fluorouracil, TS-1, or capecitabine) was dosed and administered according to local regulations. Treatment continued until confirmed disease progression, initiation of alternative therapy, or unacceptable toxicity.

Recruitment was voluntarily suspended to investigate a potential increase in bleeding events identified by the independent data monitoring committee (IDMC), and sites were notified on 21 September 2016. After a comprehensive evaluation, no causal link between study treatment and bleeding events was established and the IDMC recommended study continuation. Recruitment resumed on 1 December 2016.

Patients

Eligible patients were aged ≥18 years, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and histological or cytological confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx not amenable to curative therapy who had progression or recurrence during or after only one systemic treatment regimen containing a platinum agent, or progressed within 6 months of the last dose of platinum administered as part of multimodal therapy of curative intent.

Outcomes measurements

The dual primary end points were OS for durvalumab versus SoC and OS for durvalumab plus tremelimumab versus SoC. Secondary objectives included 12-, 18-, and 24-month OS rates as well as progression-free survival (PFS), objective response rate (ORR), DoR (using investigator assessments according to RECIST version 1.1), and safety.

The sample size was selected to provide approximately 90% power to demonstrate statistical significance at an overall 2.5% level (two-sided, allowing for one interim analysis) if the assumed true treatment effect is a hazard ratio (HR) of 0.69 for comparison of either durvalumab or durvalumab plus tremelimumab versus SoC. The intent-to-treat population (defined as all randomized patients) was used for efficacy outcome analyses, which were conducted using a log-rank test stratified by randomization factors, and a stratified Cox proportional hazards model to estimate treatment effect. Medians were derived using the Kaplan–Meier method. Safety data were analyzed using the safety analysis set (defined as all patients receiving ≥1 doses of study treatment). Adverse events (AEs) were monitored and graded by investigators according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. Safety data were periodically reviewed by the IDMC.

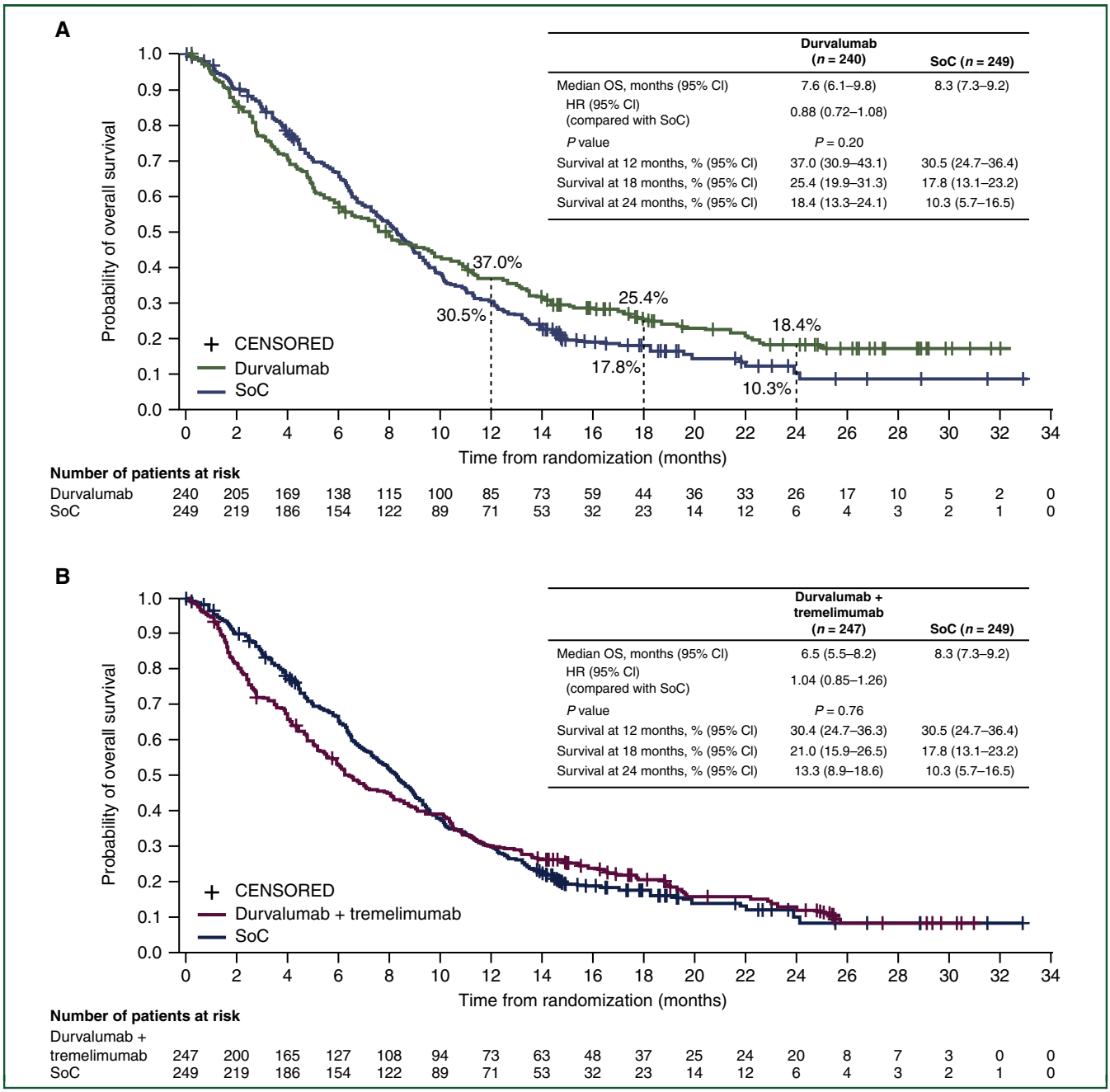

Figure 2. Analyses of planned endpoints in the full analysis set.
(A) Kaplan–Meier plot of median OS for durvalumab versus SoC. (B) Kaplan–Meier plot of median OS for durvalumab plus tremelimumab versus SoC. (C) Kaplan–Meier plot of duration of response for patients who responded to durvalumab versus SoC. (D) Kaplan–Meier plot of duration of response for patients who responded to durvalumab plus tremelimumab versus SoC.
CI, confidence interval; DoR, duration of response; SoC, standard of care.

RESULTS

Patient disposition and baseline characteristics

Between 5 November 2015 and 21 July 2017, 736 patients were randomly assigned to receive either durvalumab ($n = 240$), durvalumab plus tremelimumab ($n = 247$), or SoC chemotherapy ($n = 249$; Figure 1). Paclitaxel (36.9%) and cetuximab (35.7%) were the most frequent choices for SoC (Figure 1).

Patient demographics and characteristics were representative of the intended patient population and most were balanced across treatment groups (Table 1). However, there were more patients in the SoC arm with ECOG PS of 0 and a higher percentage of patients in the SoC arm had only distant metastases (no locoregional recurrence) at baseline. The median age for all patients was 60.0 years, 84.0% were male, 82.1% were white, and 15.7% were Asian. At baseline, 28.8% of tumor samples had PD-L1 expression of TC $\geq$ 25%.

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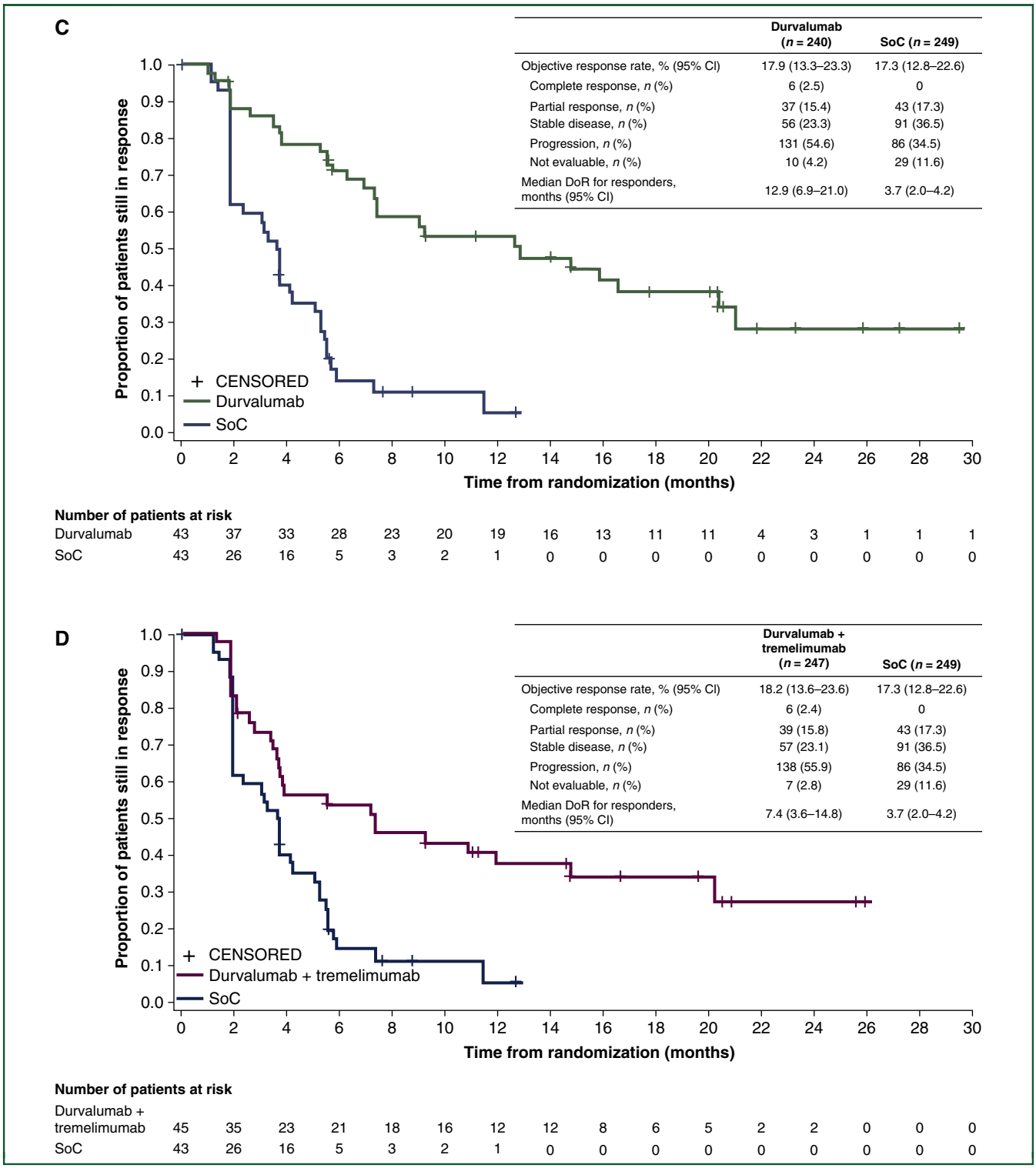

	Durvalumab (*n* = 240)	SoC (*n* = 249)
Objective response rate, % (95% CI)	17.9 (13.3–23.3)	17.3 (12.8–22.6)
Complete response, *n* (%)	6 (2.5)	0
Partial response, *n* (%)	37 (15.4)	43 (17.3)
Stable disease, *n* (%)	56 (23.3)	91 (36.5)
Progression, *n* (%)	131 (54.6)	86 (34.5)
Not evaluable, *n* (%)	10 (4.2)	29 (11.6)
Median DoR for responders, months (95% CI)	12.9 (6.9–21.0)	3.7 (2.0–4.2)

	Durvalumab + tremelimumab (*n* = 247)	SoC (*n* = 249)
Objective response rate, % (95% CI)	18.2 (13.6–23.6)	17.3 (12.8–22.6)
Complete response, *n* (%)	6 (2.4)	0
Partial response, *n* (%)	39 (15.8)	43 (17.3)
Stable disease, *n* (%)	57 (23.1)	91 (36.5)
Progression, *n* (%)	138 (55.9)	86 (34.5)
Not evaluable, *n* (%)	7 (2.8)	29 (11.6)
Median DoR for responders, months (95% CI)	7.4 (3.6–14.8)	3.7 (2.0–4.2)

Figure 2. Continued.

Of the patients with oropharyngeal cancer ($n = 269$), 91 were HPV-positive (12.4%). The majority of patients were former (59.6%) or current (19.3%) smokers.

Efficacy

Data cut-off was 10 September 2018. The median duration of follow-up was 7.6, 6.3, and 7.8 months for durvalumab, durvalumab plus tremelimumab, and SoC, respectively. No statistically significant difference in OS was observed for durvalumab versus SoC [HR = 0.88; 95% confidence interval (CI): 0.72−1.08; $P = 0.20$] or for durvalumab plus tremelimumab versus SoC (HR = 1.04; 95% CI: 0.85−1.26; $P = 0.76$) (Figure 2A and B). Treatment effect was analyzed in several subgroups (Supplementary Figure S1, available at

Annals of Oncology online). The 12-month survival rate was higher for durvalumab [37.0% (95% CI: 30.9—43.1)] compared with SoC [30.5% (95% CI: 24.7—36.4)] and similar differences were seen at 18 and 24 months (Figure 2A). There were numerically higher survival rates for durvalumab plus tremelimumab at 18 and 24 months (Figure 2B).

In patients with tumors having PD-L1 expression of TC $\geq$ 25%, median OS was 9.8 months (95% CI: 4.3—14.1) for durvalumab, 4.8 months (95% CI: 3.3—6.4) for durvalumab plus tremelimumab, and 9.0 months (95% CI: 6.8—11.0) for SoC. Median OS was 7.6 months (95% CI: 6.2—9.5) for durvalumab, 7.8 months (95% CI: 5.9—10.3) for durvalumab plus tremelimumab, and 8.0 months (95% CI: 6.7—8.9) for SoC for patients with tumors expressing TC $<$ 25%. Evaluating a PD-L1 expression cut-off of TC $\geq$1%, OS for both durvalumab and durvalumab plus tremelimumab did not differentiate from SoC. However, in the small population of patients in the $<$1% TC group, OS was longer for durvalumab than SoC. There was no difference for durvalumab plus tremelimumab versus SoC in the $<$1% TC group (Supplementary Figure S1, available at *Annals of Oncology* online).

There was no difference in PFS for durvalumab versus SoC (HR = 1.02; 95% CI: 0.84—1.25; P = 0.75) or for durvalumab plus tremelimumab versus SoC (HR = 1.09; 95% CI: 0.90—1.33; P = 0.54). Median PFS was 2.1 months (95% CI: 1.9—3.0) for the durvalumab arm, 2.0 months (95% CI: 1.9—2.3) for durvalumab plus tremelimumab, and 3.7 months (95% CI: 3.1—3.7) for SoC.

ORR (95% CI) was 17.9% (13.3—23.4) for durvalumab, 18.2% (13.6—23.6) for durvalumab plus tremelimumab, and 17.3% (12.8—22.5) for SoC (Figure 2C and D). The only complete responses were observed in the immunotherapy arms (n = 6, durvalumab; n = 6, durvalumab plus tremelimumab). Median DoR (95% CI) was longer for durvalumab and durvalumab plus tremelimumab versus SoC; 12.9 months (6.9—21.0), 7.4 months (3.6—14.8), and 3.7 months (2.0—4.2), respectively (Figure 2 C and D). The median time to response (range) was 3.7 months (1.9—11.4) for durvalumab, 2.1 months (1.5—9.1) for durvalumab plus tremelimumab, and 1.6 months (1.3—20.3) for SoC.

As the ORR was higher than expected, and notably, because the median OS for SoC was unexpectedly long considering historical values and more recent reports, *post hoc* analyses were conducted to understand the performance of the SoC arm. As noted, there were imbalances in ECOG PS and patients with only distant metastatic disease at baseline. A multivariate analysis confirmed that these were prognostic, and when the primary stratified Cox model was adjusted for these characteristics, the HR was 0.81 (95% CI: 0.66—1.00) for durvalumab compared with SoC (Supplementary Table S1, available at *Annals of Oncology* online). Another *post hoc* analysis evaluated the impact of subsequent therapy on OS in the SoC arm, and showed that 263 (35.7%) patients from all arms received subsequent therapy after discontinuation. Overall, the median OS of patients receiving subsequent immunotherapy was 18.3 months (95% CI: 14.7—22.9), which was longer than the median OS for patients who received other subsequent anticancer therapies [n = 207, 10.8 months (95% CI: 10.1—12.3)]. Notably, more patients from the SoC arm received subsequent immunotherapy (n = 38, 15%) than those in the durvalumab (n = 5, 2.1%) or durvalumab plus tremelimumab arms (n = 13, 5.3%).

Safety

The median duration of exposure was approximately 3 months for each arm (Supplementary Table S2, available at *Annals of Oncology* online). Treatment-related AEs (trAEs) of any grade occurred in 57.4% in the durvalumab arm, 61.0% in the durvalumab plus tremelimumab arm, and 82.1% in the SoC arm (Table 2). Grade $\geq$3 trAEs occurred in 24 patients (10.1%) receiving durvalumab, 40 patients (16.3%) receiving durvalumab plus tremelimumab, and 58 patients (24.2%) receiving SoC. Discontinuation attributed to trAEs occurred in nine patients (3.8%) in the durvalumab arm, 10 (4.1%) in the durvalumab plus tremelimumab arm, and 10 (4.2%) in the SoC arm (Supplementary Table S3, available at *Annals of Oncology* online). Any bleeding-related trAEs were rare (Supplementary information, available at *Annals of Oncology* online). Death attributed to trAEs occurred in four patients in the durvalumab arm, two in the durvalumab plus tremelimumab arm, and none in the SoC arm.

DISCUSSION AND CONCLUSIONS

The study results did not demonstrate a statistically significant survival benefit for immunotherapy over single-agent SoC as second-line treatment of patients with R/M HNSCC. Combining durvalumab with tremelimumab did not show improvement over durvalumab activity, though it should be noted that the EAGLE study was not designed for comparison between durvalumab and durvalumab plus tremelimumab arms.

Despite the apparent lack of benefit over SoC, durvalumab clinical activity was in line with other checkpoint blockade agents in this setting.[13,14] Although cross-trial comparisons should be approached with caution, median OS for durvalumab (7.6 months) was similar to median OS for nivolumab (7.5 months) and pembrolizumab (8.4 months) in comparable patient populations. Likewise, 12-month survival rates for all three were similar (durvalumab, 37.0%; nivolumab, 36.0%; pembrolizumab, 37.0%).[13,14] Additionally, within the context of the EAGLE study, there were examples of activity in favor of durvalumab, including complete responders and longer DoR versus SoC, suggesting that the benefit from durvalumab was more durable than from SoC. There also seems to be a survival benefit favoring durvalumab, with 12-, 18-, and 24-month survival rates being numerically higher in the durvalumab arm versus the SoC arm.

This study was characterized by an unexpectedly high OS for the SoC arm with a median of 8.3 months. This outcome was higher than median OS values for SoC arms reported in similar studies with PD-1 inhibitors (5.1—6.9 months).[13,14] Several potential contributing factors were identified. One

Table 2. Incidence of trAEs (≥5% for any grade, ≥2% for grade 3–4 in any arm) in the safety analysis set

	Durvalumab (n = 237)		Durvalumab + tremelimumab (n = 246)		Standard of care (n = 240)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Patients with any trAE, *n* (%)	**136 (57.4)**	**24 (10.1)**	**150 (61.0)**	**40 (16.3)**	**197 (82.1)**	**58 (24.2)**
Alopecia	0	0	0	0	28 (11.7)	0
Anemia	12 (5.1)	0	20 (8.1)	4 (1.6)	42 (17.5)	11 (4.6)
Asthenia	15 (6.3)	1 (0.4)	20 (8.1)	5 (2.0)	32 (13.3)	2 (0.8)
Decreased appetite	12 (5.1)	0	14 (5.7)	2 (0.8)	28 (11.7)	3 (1.3)
Dermatitis acneiform	2 (0.8)	0	2 (0.8)	0	16 (6.7)	0
Diarrhea	14 (5.9)	0	20 (8.1)	2 (0.8)	17 (7.1)	3 (1.3)
Elevated ALT	7 (3.0)	1 (0.4)	10 (4.1)	0	14 (5.8)	1 (0.4)
Elevated GGT	8 (3.4)	1 (0.4)	10 (4.1)	2 (0.8)	12 (5.0)	1 (0.4)
Fatigue	16 (6.8)	2 (0.8)	18 (7.3)	3 (1.1)	26 (10.8)	2 (0.8)
Hypothyroidism	27 (11.4)	0	30 (12.2)	0	0	0
Leukopenia	2 (0.8)	0	9 (3.7)	0	12 (5.0)	4 (1.7)
Mucosal inflammation	0	0	1 (0.4)	0	12 (5.0)	1 (0.4)
Nausea	12 (5.1)	1 (0.4)	10 (4.1)	0	33 (13.8)	0
Neuropathy peripheral	3 (1.3)	1 (0.4)	3 (1.2)	0	20 (8.3)	2 (0.8)
Neutropenia	3 (1.3)	0	11 (4.5)	1 (0.4)	31 (12.9)	12 (5.0)
Pruritus	8 (3.4)	0	20 (8.1)	0	6 (2.5)	0
Rash	15 (6.3)	0	11 (4.5)	0	33 (13.8)	0
Stomatitis	4 (1.7)	1 (0.4)	3 (1.2)	0	23 (9.6)	0
Thrombocytopenia	5 (2.1)	1 (0.4)	11 (4.5)	2 (0.8)	16 (6.7)	1 (0.4)

ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; trAEs, treatment-related adverse events.

factor, and a key difference between EAGLE and other studies, is that both paclitaxel and docetaxel were used as choices for SoC in this study, while only docetaxel was allowed in other studies. A comparison of paclitaxel and docetaxel activity within the SoC arm of the EAGLE study showed a nominal HR of 0.69 (95% CI: 0.44–1.13) in favor of paclitaxel. Notably, more patients were treated with paclitaxel than docetaxel. Another factor that commonly affects assessment of OS is subsequent therapy. A *post hoc* analysis showed that patients who received an immunotherapy agent after discontinuation of treatment in the EAGLE study had longer OS. A higher percentage of patients from the SoC arm went on to receive subsequent immunotherapy. Lastly, imbalances were noted in clinical characteristics between the randomized groups, specifically ECOG PS and patients with metastatic disease only (as opposed to loco-regional disease with or without metastatic disease) at baseline. Other imbalances were evaluated, but none impacted OS and, indeed, both characteristics have been reported to have a meaningful prognostic impact on OS in other studies involving patients with R/M HNSCC.[17,18] These factors may have confounded the results by creating a larger proportion of patients with a more favorable prognosis in the SoC arm and a multivariate analysis adjusting for these imbalanced factors showed that the estimated treatment effect improved in favor of immunotherapy when accounting for that imbalance. Collectively, choice of SoC therapy, subsequent therapy, and imbalances in clinical characteristics provide a possible explanation for the longer-than-expected OS of the SoC arm.

It is worth noting that a recently published systematic analysis by the US Food and Drug Administration identified a trend in disproportionately high early mortality rates in studies evaluating anti-PD-1 and anti-PD-L1 agents against active control arms where authors describe a crossing of Kaplan–Meier OS curves.[19] This phenomenon was also observed in the EAGLE study where a higher percentage of patients in the immunotherapy arms died within the first 3 months from randomization. Conversely, higher survival rates for durvalumab indicates that patients who live beyond the initial treatment period may be those most likely to receive benefit. It is therefore critical to develop a means to identify patients at risk of early death, which could guide treatment decisions by identifying patients who are optimal candidates for single-agent immunotherapy.

The safety profile for durvalumab was consistent with prior data.[11,12] The durvalumab plus tremelimumab arm was likewise consistent with other studies evaluating this regimen, though grade 3–4 trAEs and the discontinuation rate were slightly higher than with durvalumab alone.[7,11] Following a voluntary recruitment pause initiated to investigate bleeding AEs, no association between durvalumab or durvalumab plus tremelimumab and bleeding-related AEs was found and recruitment was resumed.

In conclusion, although durvalumab showed antitumor activity and durvalumab and durvalumab plus tremelimumab did prove to be tolerable, the primary objectives of the study were not met. Further biomarker evaluations are underway in an attempt to understand the clinical activity of immune checkpoint inhibition in this setting.

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