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ORIGINAL ARTICLE

Durvalumab with or without tremelimumab versus the EXTREME regimen as first-line treatment for recurrent or metastatic squamous cell carcinoma of the head and neck: KESTREL, a randomized, open-label, phase III study

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Background: Patients with recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC) have a poor prognosis. The phase III KESTREL study evaluated the efficacy of durvalumab [programmed death-ligand 1 (PD-L1) antibody] with or without tremelimumab [cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibody], versus the EXTREME regimen in patients with R/M HNSCC.

Patients and methods: Patients with HNSCC who had not received prior systemic treatment for R/M disease were randomized (2 : 1 : 1) to receive durvalumab 1500 mg every 4 weeks (Q4W) plus tremelimumab 75 mg Q4W (up to four doses), durvalumab monotherapy 1500 mg Q4W, or the EXTREME regimen (platinum, 5-fluorouracil, and cetuximab) until disease progression. Durvalumab efficacy, with or without tremelimumab, versus the EXTREME regimen in patients with PD-L1-high tumors and in all randomized patients was assessed. Safety was also assessed.

Results: Durvalumab and durvalumab plus tremelimumab were not superior to EXTREME for overall survival (OS) in patients with PD-L1-high expression [median, 10.9 and 11.2 versus 10.9 months, respectively; hazard ratio (HR) = 0.96; 95% confidence interval (CI) 0.69-1.32; $P = 0.787$ and HR = 1.05; 95% CI 0.80-1.39, respectively]. Durvalumab and durvalumab plus tremelimumab prolonged duration of response versus EXTREME (49.3% and 48.1% versus 9.8% of patients remaining in response at 12 months), correlating with long-term OS for responding patients; however, median progression-free survival was longer with EXTREME (2.8 and 2.8 versus 5.4 months). Exploratory analyses suggested that subsequent immunotherapy use by 24.3% of patients in the EXTREME regimen arm contributed to the similar OS outcomes between arms. Grade 3/4 treatment-related adverse events (TRAEs) for durvalumab, durvalumab plus tremelimumab, and EXTREME were 8.9%, 19.1%, and 53.1%, respectively.

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Conclusions: In patients with PD-L1-high expression, OS was comparable between durvalumab and the EXTREME regimen. Durvalumab alone, and with tremelimumab, demonstrated durable responses and reduced TRAEs versus the EXTREME regimen in R/M HNSCC.

Key words: durvalumab, tremelimumab, head and neck squamous cell carcinoma, immune checkpoint inhibition, programmed death-ligand 1, phase III study

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide; HNSCC is increasingly prevalent and the frequency of new cases is anticipated to reach 1.08 million annually by 2030.[1] Recurrent/metastatic (R/M) HNSCC has a poor prognosis and limited treatment options.[2] Before recent approvals of anti-programmed cell death protein 1 (anti-PD-1) immunotherapies,[3-5] the EXTREME regimen (NCT00122460) was the standard of care (SoC) for R/M HNSCC consisting of triplet therapy with cetuximab, a recombinant human/mouse chimeric monoclonal antibody against the epidermal growth factor receptor, 5-fluorouracil (5-FU), and either carboplatin or cisplatin chemotherapy.[6,7] This regimen conferred a median overall survival (OS) of 10.1 months in patients with R/M HNSCC, but was also associated with considerable toxicity. Eighty-two percent of patients in the EXTREME study experienced a grade 3 or 4 adverse event (AE) and 20% discontinued therapy due to AEs, suggesting a need for better-tolerated and more effective treatment options.[7] Immunotherapies are beginning to address this unmet need.[8]

HNSCC is an immunogenic-type cancer due to high mutational burden and/or expression of viral elements, namely human papillomavirus (HPV) genes.[9] HNSCC may evade antitumor immunity via multiple mechanisms, including frequent up-regulation of immune checkpoint molecules such as PD-1, programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).[10] The anti-PD-1 antibodies, pembrolizumab and nivolumab, are approved by the United States Food and Drug Administration and European Medicines Agency as single agents for the second-line treatment of R/M HNSCC.[3-5,11-13] Pembrolizumab is also approved as first-line treatment, with or without chemotherapy, in adults with tumors expressing PD-L1.[11-13] Durvalumab is an anti-PD-L1 antibody that has demonstrated clinical activity and manageable safety in multiple tumor types, including as a monotherapy in HNSCC.[14,15] Tremelimumab is an anti-CTLA-4 antibody with a well-established safety profile.[15-17] Recently, durvalumab plus tremelimumab demonstrated an improved OS benefit compared with sorafenib in patients with unresectable advanced hepatocellular carcinoma (HCC) in the phase III HIMALAYA trial (NCT03298451),[18] and durvalumab plus tremelimumab in combination with chemotherapy demonstrated an improved OS benefit compared with chemotherapy in patients with metastatic non-small-cell lung carcinoma in the phase III POSEIDON trial (NCT03164616).[19]

Herein, we report the results of the phase III KESTREL randomized, open-label, multicenter, global study of durvalumab alone or in combination with tremelimumab versus the EXTREME regimen as first-line treatment of R/M HNSCC.

METHODS

Study design and conduct

KESTREL (ClinicalTrials.gov: NCT02551159) was a phase III randomized, open-label, multicenter, global study. The study was conducted at 197 sites in 23 countries in accordance with ethical principles originating from the Declaration of Helsinki and consistent with International Conference on Harmonisation and Good Clinical Practice guidelines, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples. Written informed consent from participants was obtained before carrying out any protocol-related procedures. Patients were randomized in a 2 : 1 : 1 ratio to receive durvalumab plus tremelimumab [concurrent durvalumab 1500 mg every 4 weeks (Q4W) and tremelimumab 75 mg Q4W for a maximum of four doses], durvalumab monotherapy (1500 mg Q4W), or the EXTREME regimen (cisplatin 100 mg/m^2 of body surface area or carboplatin at an area under the curve of 5 mg/ml/min on day 1, at the discretion of the investigator, and 5-FU 1000 mg/m^2/day on days 1 through 4 of every 3-week cycle, as well as cetuximab 400 mg/m^2 on day 1, followed by 250 mg/m^2 Q1W). Patients received treatment until confirmed disease progression (PD), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or until any other treatment discontinuation criterion was met. However, patients could be treated beyond progression if, in the opinion of the investigator, they continued to receive benefit. Randomization was stratified according to tumor cell (TC) PD-L1 expression ($\geq$25% versus $<$25%,[20,21]), tumor location [oropharyngeal (OPC) or non-OPC], and smoking history ($>$10 or $\leq$10 pack-years). Patients with OPC were further stratified by HPV status (positive or negative). A voluntary recruitment pause was initiated to investigate bleeding-related AEs between 20 September 2016 and 11 November 2016. No association between durvalumab or durvalumab plus tremelimumab and bleeding-related AEs was found, and recruitment was resumed.

Patients

Eligible patients were aged $\geq$18 years with histologically or cytologically confirmed R/M HNSCC (oral cavity, oropharynx, hypopharynx, or larynx) not amenable to local curative

therapy with surgery or radiation. Patients were eligible if they had not received prior systemic therapy for R/M disease, unless it was given as part of multimodal treatment for locally advanced or recurrent disease, and recurrence had occurred >6 months from the last platinum dose.

Study assessments

The primary objective of the KESTREL study was to assess the OS of durvalumab monotherapy compared with the EXTREME regimen in patients with R/M HNSCC whose tumors express high PD-L1 [PD-L1 TC ≥50% or immune cells (IC) ≥25%, as defined previously[22] and described in the protocol]. This was an amendment from the previous primary objective of OS for durvalumab plus tremelimumab versus the EXTREME regimen in patients with R/M HNSCC. The amendment was based on results from the phase III EAGLE study,[17] which found a longer OS with durvalumab monotherapy in patients with PD-L1 TC expression of ≥25% versus <25% and collective data from the EAGLE and CONDOR studies in R/M HNSCC,[16,17] which for R/M HNSCC did not support earlier data in solid tumors and HCC showing improved clinical activity from adding tremelimumab (anti-CTLA-4) to durvalumab.[23]

Secondary objectives included the following: (i) assessment of the efficacy of durvalumab monotherapy versus the EXTREME regimen in all randomized patients (all-comers); and (ii) assessment of the efficacy of durvalumab plus tremelimumab combination therapy versus the EXTREME regimen in both patients with PD-L1-high tumors and in all randomized patients (all-comers). Efficacy was assessed in terms of OS; progression-free survival (PFS); best objective response; objective response rate [ORR, defined as the number (percentage) of patients with at least one assessment of complete or partial response]; duration of response (DoR); and proportion of patients alive at 12, 18, and 24 months after randomization. Investigator assessments for response were carried out according to RECIST version 1.1 criteria.[24] Safety and tolerability of durvalumab monotherapy, durvalumab plus tremelimumab, and the EXTREME regimen were also assessed. Outcome measures were assessed in both the population of patients with PD-L1-high expression (TC ≥50% or IC ≥25%) and all randomized patients.

PD-L1 expression was assessed by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay on freshly obtained or archival (<3 years), formalin-fixed, paraffin-embedded tissue samples. PD-L1 high (TC ≥50% or IC ≥25%) was defined as either ≥50% of TCs or ≥25% of ICs staining for PD-L1 at any intensity if >1% of the tumor area contained ICs or ≥50% of TCs or 100% of ICs staining for PD-L1 at any intensity if 1% of the tumor area contained ICs. PD-L1 low was defined as not meeting any of the criteria for PD-L1 high.[22]

Tumor assessments were carried out on computed tomography and magnetic resonance imaging scans with intravenous contrast. Objective tumor assessments were carried out every 6 weeks for the first 24 weeks, then every 8 weeks thereafter (relative to the date of randomization) until treatment discontinuation due to disease progression or toxicity. Patients were followed every 3 months for survival after confirmed disease progression. Patients with OPC required a known HPV status before randomization; HPV status was assessed according to local standard, or centrally using a p16 immunohistochemical assay.

Safety and tolerability were assessed in terms of AEs, deaths, laboratory data, vital signs, electrocardiograms, and exposure for all treated patients. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.[25] AEs considered causally related to treatment (TRAEs) were determined by the reporting investigator.

Statistical analyses

The primary analysis of OS for durvalumab monotherapy versus the EXTREME regimen in patients with PD-L1-high expression (TC ≥50% or IC ≥25%) was carried out when ∼147 deaths occurred in ∼172 patients (85% maturity) across the durvalumab monotherapy and the EXTREME regimen treatment arms in patients with PD-L1-high expression, assuming that 45% of the patients randomized were within this population. Assuming the true average OS hazard ratio (HR) for durvalumab monotherapy versus the EXTREME regimen in patients with PD-L1-high expression is 0.59, the trial would have ∼90% power to demonstrate statistical significance at the 5% level (using a two-sided test) for the primary analysis, with the smallest treatment difference that could be statistically significant being an average HR of 0.72. OS was estimated using the Kaplan–Meier method. Because superiority was not met for the primary analysis, no formal statistical testing was completed for secondary endpoints in the multiple testing procedure.

The stratified log-rank test and Cox proportional hazards model were used for analysis of primary and secondary endpoints, stratified by PD-L1 status (TC ≥25% or TC <25%), tumor location, and smoking history. The full analysis set included all randomized patients.

RESULTS

Patient disposition and baseline characteristics

A total of 1084 patients were enrolled between Q4 of 2015 and Q2 of 2017. Of these, 823 patients were randomized to receive either durvalumab monotherapy ($n = 204$), durvalumab plus tremelimumab ($n = 413$), or the EXTREME regimen ($n = 206$). Of the randomized patients, 46.5% ($n = 383$) had tumors characterized as PD-L1-high (TC ≥50% or IC ≥25%). Of the 806 patients who received treatment, 32 were receiving ongoing treatment at the data cut-off date (6 July 2020), and 774 had discontinued treatment (Figure 1).

Patient demographics and baseline characteristics, including PD-L1 status as defined at stratification (TC ≥25% or TC <25%), were well balanced across the treatment groups for patients with PD-L1-high expression (TC ≥50% or IC ≥25%) and all randomized patients, with the one

exception being apparent variation in primary tumor location between patients with PD-L1-high expression in the durvalumab and the EXTREME regimen arms (Table 1). Of 823 total randomized patients: 100 patients (12.2%) were in North America; 495 patients (60.1%) were in Europe; and 228 patients (27.7%) were in the rest of the world (RoW).

Efficacy results

At final analysis, median OS and survival rates over time were similar for durvalumab and the EXTREME regimen in patients with PD-L1-high expression, with median OS [95% confidence interval (CI)] of 10.9 (9.0-14.3) months for durvalumab versus 10.9 (8.3-13.4) months for the EXTREME regimen and 24-month OS rate (95% CI) of 27.6% (19.2-36.6) versus 26.4% (17.8-35.7), respectively (Figure 2A). Durvalumab was not superior to the EXTREME regimen for OS in patients with R/M HNSCC with tumors characterized by high PD-L1 expression (HR = 0.96; 95% CI 0.69-1.32; $P = 0.787$; Figure 2A) nor in all randomized patients (HR = 1.03; 95% CI 0.83-1.27; Figure 2B). Durvalumab plus tremelimumab was not superior to the EXTREME regimen for OS in patients with R/M HNSCC with tumors characterized by high PD-L1 expression (HR = 1.05; 95% CI 0.80-1.39; Figure 2A) nor in all randomized patients (HR = 1.04; 95% CI 0.87-1.25; Figure 2B). Median OS and 12-, 18-, and 24-month OS rates were similar across durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms in patients with PD-L1-high expression and all randomized patients (Figure 2A and B). None of the patient or tumor characteristics assessed had a statistically significant impact on OS with durvalumab versus the EXTREME regimen (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2022.12.008).

Median PFS was longer with the EXTREME regimen compared with the durvalumab or durvalumab plus

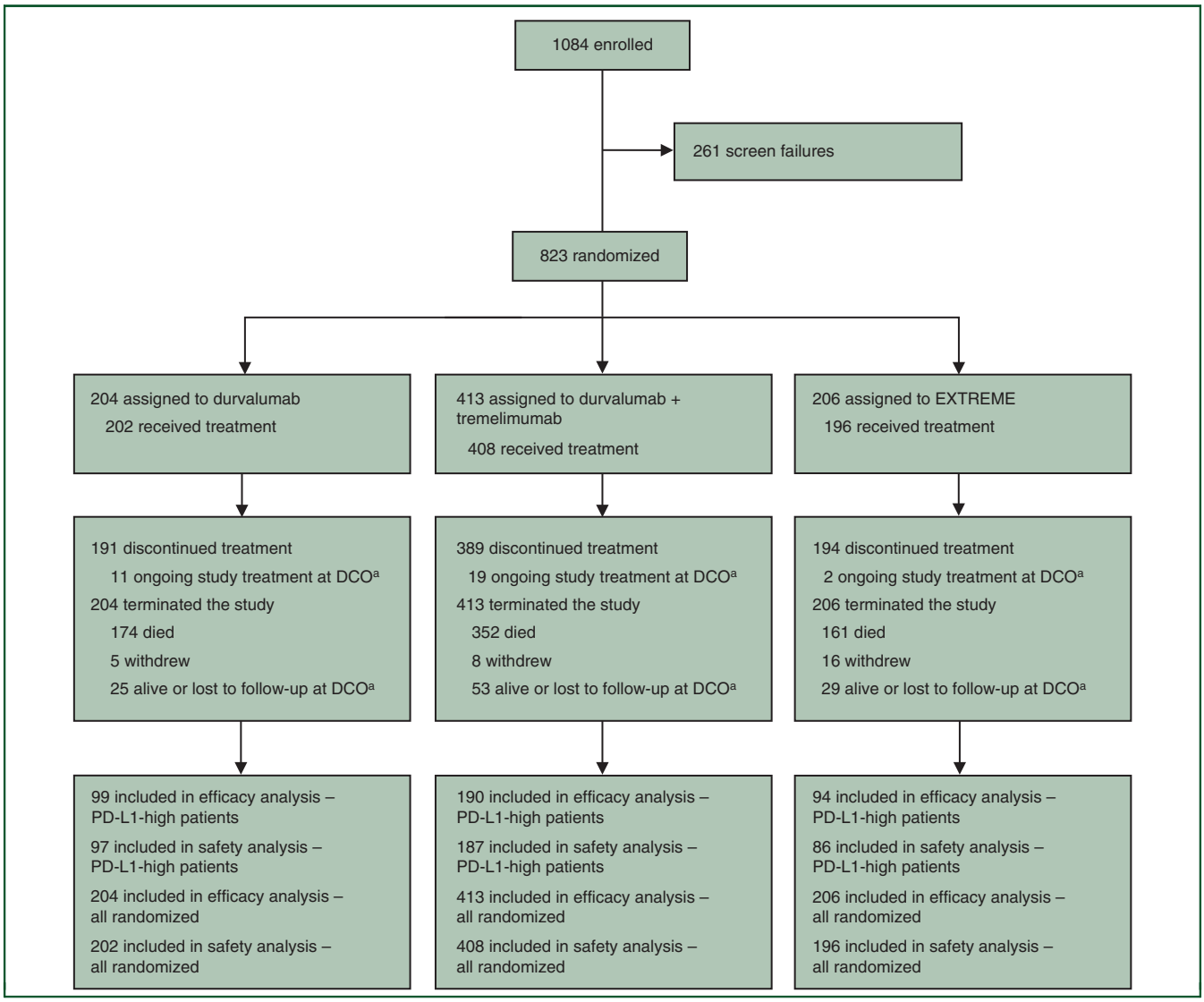


Figure 1. CONSORT patient flow diagram. DCO, data cut-off; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; IC, immune cell; PD-L1, programmed death-ligand 1; PD-L1-high, TC ≥50% or IC ≥25%; TC, tumor cell. [a]Date of DCO was 06 July 2020. Patients ongoing study treatment at the time of DCO were included in efficacy and safety analyses.

Table 1. Patient demographics and baseline characteristics in patients with PD-L1-high expression and all randomized patients

	Durvalumab		Durvalumab plus tremelimumab		EXTREME	
	PD-L1-high[a] ($n = 99$)	All randomized patients ($n = 204$)	PD-L1-high[a] ($n = 190$)	All randomized patients ($n = 413$)	PD-L1-high[a] ($n = 94$)	All randomized patients ($n = 206$)
Median age, (range) years	62.0 (32-89)	62.0 (26-89)	61.0 (25-86)	61.0 (25-87)	61.0 (43-84)	61.0 (22-84)
Sex, *n* (%)						
Female	17 (17.2)	29 (14.2)	35 (18.4)	73 (17.7)	15 (16.0)	32 (15.5)
Male	82 (82.8)	175 (85.8)	155 (81.6)	340 (82.3)	79 (84.0)	174 (84.5)
Race, *n* (%)						
White	66 (66.7)	145 (71.1)	130 (68.4)	298 (72.3)	66 (70.2)	160 (77.7)
Black or African American	1 (1.0)	3 (1.5)	1 (0.5)	5 (1.2)	2 (2.1)	2 (1.0)
Asian	30 (30.3)	54 (26.5)	59 (31.1)	109 (26.5)	25 (26.6)	42 (20.4)
Other	2 (2.0)	2 (1.0)	0 (0)	0 (0)	1 (1.1)	2 (1.0)
Region of enrollment						
North America	11 (11.1)	19 (9.3)	27 (14.2)	53 (12.8)	14 (14.9)	28 (13.6)
Europe	56 (56.6)	128 (62.7)	99 (52.1)	238 (57.6)	51 (54.3)	129 (62.6)
Rest of the world	32 (32.3)	57 (27.9)	64 (33.7)	122 (29.5)	29 (30.9)	49 (23.8)
ECOG PS, *n* (%)						
0	35 (35.4)	80 (39.2)	71 (37.4)	153 (37.0)	39 (41.5)	75 (36.4)
1	64 (64.6)	124 (60.8)	118 (62.1)	259 (62.7)	55 (58.5)	131 (63.6)
Current or former smoker,[b] *n* (%)	78 (78.8)	168 (82.4)	151 (79.5)	336 (81.4)	75 (79.8)	165 (80.1)
Primary tumor location, *n* (%)						
Oral cavity	33 (33.3)	63 (30.9)	71 (37.4)	130 (31.5)	28 (29.8)	55 (26.7)
Oropharynx	34 (34.3)	65 (31.9)	64 (33.7)	145 (35.1)	35 (37.2)	72 (35.0)
Hypopharynx	17 (17.2)	32 (15.7)	27 (14.2)	55 (13.3)	12 (12.8)	28 (13.6)
Larynx	15 (15.2)	44 (21.6)	28 (14.7)	83 (20.1)	19 (20.2)	51 (24.8)
HPV status (OPC only), *n* (%)						
Positive	18 (18.2)	32 (15.7)	34 (17.9)	62 (15.0)	15 (16.0)	30 (14.6)
Negative	16 (16.2)	31 (15.2)	29 (15.3)	79 (19.1)	19 (20.2)	39 (18.9)
Disease status, *n* (%)						
Metastatic	60 (60.6)	131 (64.2)	127 (66.8)	291 (70.5)	59 (62.8)	138 (67.0)
Recurrent only	38 (38.4)	72 (35.3)	60 (31.6)	114 (27.6)	35 (37.2)	65 (31.6)
Tumor PD-L1 expression, *n* (%)						
≥25% TCs	51 (51.5)	63 (30.9)	92 (48.4)	128 (31.0)	50 (53.2)	65 (31.6)
<25% TCs	48 (48.5)	141 (69.1)	98 (51.6)	285 (69.0)	44 (46.8)	141 (68.4)
Chemotherapy treatment regimen, *n* (%)						
Cisplatin	N/A	N/A	N/A	N/A	28 (29.8)	60 (29.1)
Carboplatin	N/A	N/A	N/A	N/A	52 (55.3)	114 (55.3)
Switched from cisplatin to carboplatin	N/A	N/A	N/A	N/A	5 (5.3)	18 (8.7)
5-fluorouracil	N/A	N/A	N/A	N/A	86 (91.5)	195 (94.7)

ECOG, Eastern Cooperative Oncology Group; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; HPV, human papillomavirus; IC, immune cell; N/A, not available; OPC, oropharyngeal cancer; PD-L1, programmed death-ligand 1; PS, performance status; TC, tumor cell.
[a]PD-L1-high, TC ≥50% or IC ≥25%.
[b]Does not include chewing tobacco, oral snuff, and sublingual nicotine.

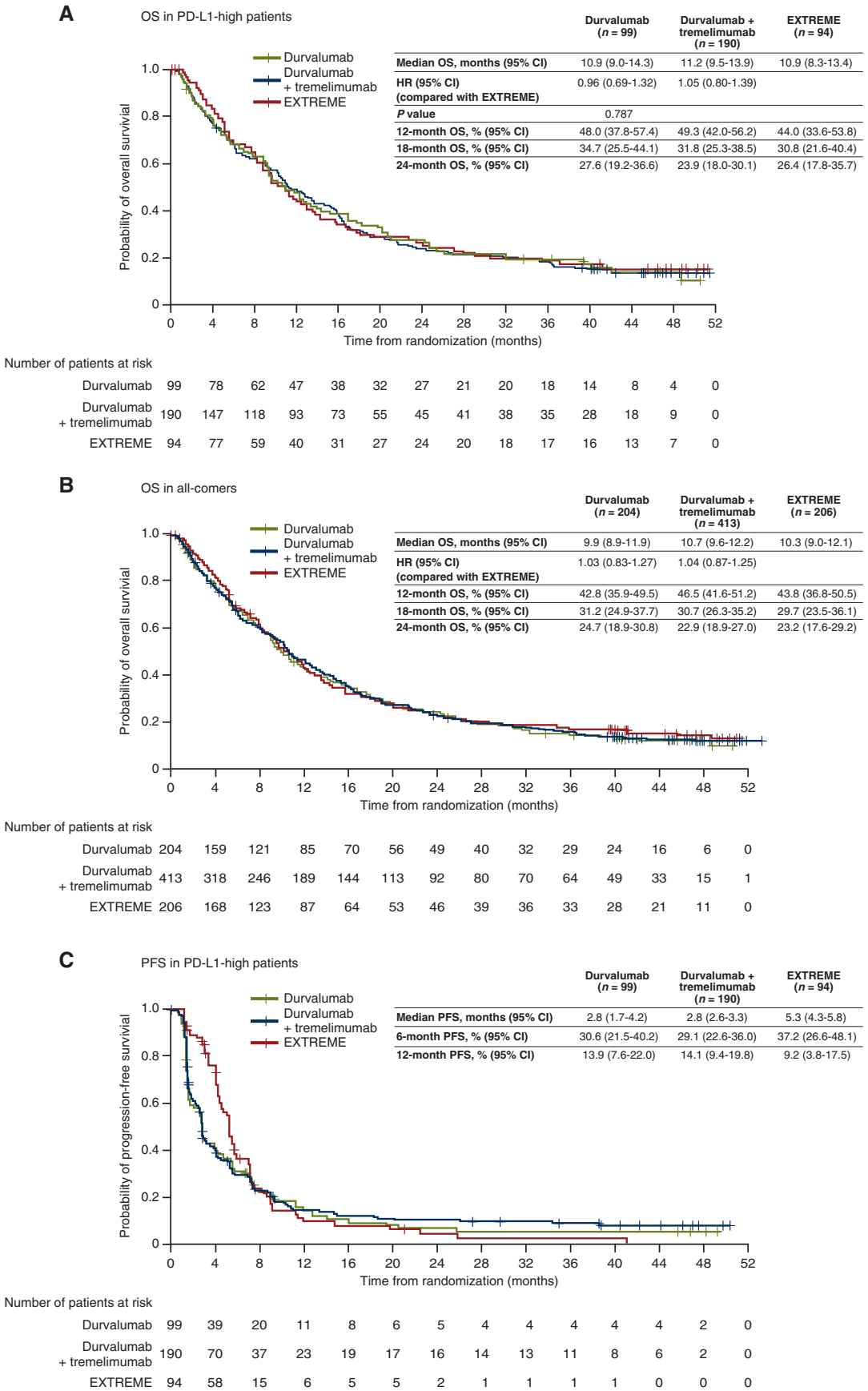
tremelimumab arms in patients with PD-L1-high expression and all randomized patients (Figure 2C and D). However, the 12-month PFS rate was higher in patients with PD-L1-high expression treated with durvalumab (13.9%; 95% CI 7.6% to 22.0%) or durvalumab plus tremelimumab (14.1%; 95% CI 9.4% to 19.8%) compared with the EXTREME regimen (9.2%; 95% CI 3.8% to 17.5%; Figure 2C and D).

ORR was greater with the EXTREME regimen compared with durvalumab alone or durvalumab plus tremelimumab, in both patients with PD-L1-high expression (50.0%, 16.2%, and 25.3%, respectively) and all randomized patients (49.0%, 17.2%, and 21.8%, respectively; Table 2). Among patients who achieved a response, median DoR and the percentage of patients remaining in response at 12 months were both higher with durvalumab alone, and with durvalumab plus tremelimumab, compared with the EXTREME regimen, both in patients with PD-L1-high expression and all randomized patients (Table 2).

In an exploratory analysis of patients who experienced a partial response, median OS (95% CI) was more than three times longer for patients with PD-L1-high expression who experienced a partial response to durvalumab [48.5 (21.0-N/A) months] compared with those who experienced a partial response to the EXTREME regimen [13.4 (8.8-22.7) months; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2022.12.008].

Subsequent immunotherapy in the EXTREME regimen group

Subsequent treatment was received by 53.9%, 40.4%, and 65.0% of patients included in the durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms, respectively (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2022.12.008). Those receiving subsequent immunotherapy included 6.4%, 3.4%,



	Durvalumab (*n* = 99)	Durvalumab + tremelimumab (*n* = 190)	EXTREME (*n* = 94)
Median OS, months (95% CI)	10.9 (9.0-14.3)	11.2 (9.5-13.9)	10.9 (8.3-13.4)
HR (95% CI) (compared with EXTREME)	0.96 (0.69-1.32)	1.05 (0.80-1.39)	
***P* value**	0.787		
12-month OS, % (95% CI)	48.0 (37.8-57.4)	49.3 (42.0-56.2)	44.0 (33.6-53.8)
18-month OS, % (95% CI)	34.7 (25.5-44.1)	31.8 (25.3-38.5)	30.8 (21.6-40.4)
24-month OS, % (95% CI)	27.6 (19.2-36.6)	23.9 (18.0-30.1)	26.4 (17.8-35.7)

	Durvalumab (*n* = 204)	Durvalumab + tremelimumab (*n* = 413)	EXTREME (*n* = 206)
Median OS, months (95% CI)	9.9 (8.9-11.9)	10.7 (9.6-12.2)	10.3 (9.0-12.1)
HR (95% CI) (compared with EXTREME)	1.03 (0.83-1.27)	1.04 (0.87-1.25)	
12-month OS, % (95% CI)	42.8 (35.9-49.5)	46.5 (41.6-51.2)	43.8 (36.8-50.5)
18-month OS, % (95% CI)	31.2 (24.9-37.7)	30.7 (26.3-35.2)	29.7 (23.5-36.1)
24-month OS, % (95% CI)	24.7 (18.9-30.8)	22.9 (18.9-27.0)	23.2 (17.6-29.2)

	Durvalumab (*n* = 99)	Durvalumab + tremelimumab (*n* = 190)	EXTREME (*n* = 94)
Median PFS, months (95% CI)	2.8 (1.7-4.2)	2.8 (2.6-3.3)	5.3 (4.3-5.8)
6-month PFS, % (95% CI)	30.6 (21.5-40.2)	29.1 (22.6-36.0)	37.2 (26.6-48.1)
12-month PFS, % (95% CI)	13.9 (7.6-22.0)	14.1 (9.4-19.8)	9.2 (3.8-17.5)

Figure 2. Analysis of OS and PFS in patients with PD-L1-high expression and all randomized patients. (A) OS in patients with PD-L1-high expression (TC ≥50% or IC ≥25%), (B) OS in all randomized patients, (C) PFS in patients with PD-L1-high expression (TC ≥50% or IC ≥25%), and (D) PFS in all randomized patients.
CI, confidence interval; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; HR, hazard ratio; IC, immune cell; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TC, tumor cell.

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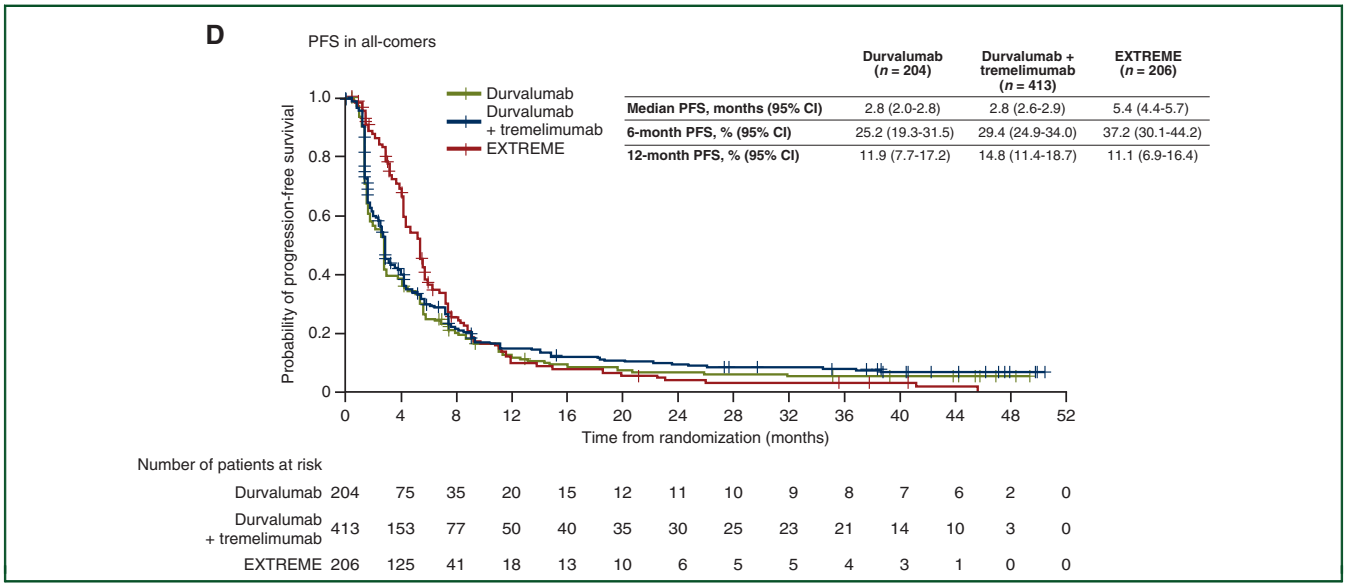

	Durvalumab (n = 204)	Durvalumab + tremelimumab (n = 413)	EXTREME (n = 206)
Median PFS, months (95% CI)	2.8 (2.0-2.8)	2.8 (2.6-2.9)	5.4 (4.4-5.7)
6-month PFS, % (95% CI)	25.2 (19.3-31.5)	29.4 (24.9-34.0)	37.2 (30.1-44.2)
12-month PFS, % (95% CI)	11.9 (7.7-17.2)	14.8 (11.4-18.7)	11.1 (6.9-16.4)

Figure 2. Continued.

and 24.3% of all randomized patients in the durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms, respectively. Therefore, 11.8%, 8.4%, and 37.3% of patients receiving subsequent therapy received immunotherapy as part of their care in the durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms. For patients who received subsequent therapy, there was a numerical (but not significant) difference in OS between patients with PD-L1-high expression (TC $\geq$50% or IC $\geq$25%) compared with patients with PD-L1-low expression (TC $<$50% and IC $<$25%) in any arm (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.12.008). In patients who did not receive subsequent immunotherapy, survival was numerically lower with the EXTREME regimen than with durvalumab or durvalumab plus tremelimumab (Supplementary Figure S3, available at https://doi.org/10.1016/j.annonc.2022.12.008). Due to the known activity of immunotherapy in the second-line setting,[5,26] and the high proportion of patients in the EXTREME treatment arm who went on to receive immunotherapy, the impact on OS of subsequent immunotherapy following study discontinuation was explored.

Median OS in the EXTREME regimen arm was longer for patients who received subsequent immunotherapy in the population of patients with PD-L1-high expression and in all randomized patients (35.6 months; 95% CI 15.6 months-N/A, and 22.4 months; 95% CI 15.6-37.2 months, respectively) compared with those who received subsequent therapy that did not contain an immunotherapy agent (14.3 months; 95% CI 11.1-24.0 months, and 12.4 months; 95% CI 10.9-15.8 months, respectively), or who received no subsequent therapy (5.6 months; 95% CI 4.5-8.0 months, and 5.6 months; 95% CI 4.7-7.7 months, respectively, Figure 3).

Table 2. Response to treatment in patients with PD-L1-high expression and all randomized patients

	Durvalumab		Durvalumab plus tremelimumab		EXTREME	
	PD-L1-high[a] (n = 99)	All randomized patients (n = 204)	PD-L1-high[a] (n = 190)	All randomized patients (n = 413)	PD-L1-high[a] (n = 94)	All randomized patients (n = 206)
Best objective response						
Complete response, n (%)	0	3 (1.5)	10 (5.3)	16 (3.9)	3 (3.2)	4 (1.9)
Partial response, n (%)	16 (16.2)	32 (15.7)	38 (20.0)	74 (17.9)	44 (46.8)	97 (47.1)
Stable disease $\geq$5 weeks, n (%)	38 (38.4)	73 (35.8)	61 (32.1)	148 (35.8)	27 (28.7)	59 (28.6)
Progression, n (%)	40 (40.4)	88 (43.1)	73 (38.4)	161 (39.0)	9 (9.6)	28 (13.6)
Not assessable, n (%)	5 (5.1)	8 (3.9)	8 (4.2)	14 (3.4)	11 (11.7)	18 (8.7)
Objective response rate, n (%)	16 (16.2)	35 (17.2)	48 (25.3)	90 (21.8)	47 (50.0)	101 (49.0)
Median DoR, months (95% CI)	12.3 (5.6-NC)	11.9 (4.6-17.8)	6.5 (4.5-16.1)	9.2 (6.0-19.6)	4.2 (3.0-5.7)	4.2 (3.7-4.5)
Percentage remaining in response at 12 months, %	55.6	49.3	42.6	48.1	9.7	9.8

CI, confidence interval; DoR, duration of response; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; IC, immune cell; NC, not calculated; PD-L1, programmed death-ligand 1; TC, tumor cell.
[a]PD-L1-high, TC $\geq$50% or IC $\geq$25%.

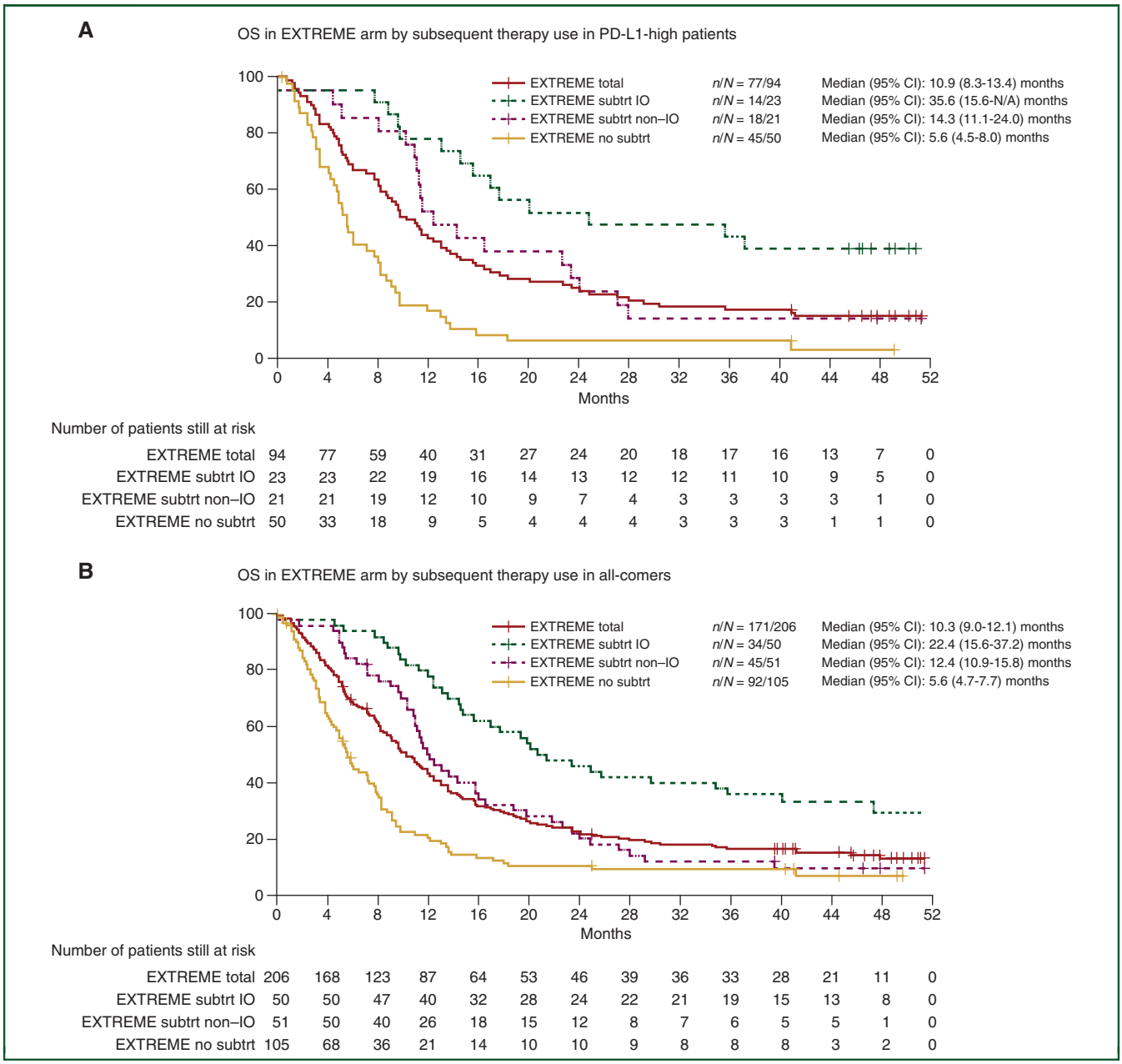

Figure 3. OS in the EXTREME regimen arm by subsequent therapy use. (A) OS in the EXTREME regimen arm by subsequent therapy use in patients with PD-L1-high expression (TC ≥50% or IC ≥25%) and (B) OS in the EXTREME regimen arm by subsequent therapy use in all randomized patients.
CI, confidence interval; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; HR, hazard ratio; IC, immune cell; IO, immunotherapy; N/A, not available; OS, overall survival; PD-L1, programmed death-ligand 1; subtrt, subsequent treatment; TC, tumor cell.

Post hoc analyses revealed that a higher proportion of patients recruited to the EXTREME regimen arm were in North America and Europe than the RoW (76.2% versus 23.8%), where there was better access to second-line immunotherapy compared with the RoW. Of all randomized patients treated with the EXTREME regimen, the median OS was numerically longer in patients recruited in North America (12.0 months; 95% CI 8.3-15.6 months) and Europe (12.4 months; 95% CI 9.6-15.7 months), compared with the RoW (9.0 months; 95% CI 6.0-10.7 months; Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2022.12.008). The HR for North America and Europe versus RoW showed a similar trend (HR = 1.30; 95% CI 0.90-1.82). Median OS with EXTREME was longer pre-pause versus post-pause (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2022.12.008).

For patients with PD-L1-high expression, there was a slight numerical improvement in OS with durvalumab with or without tremelimumab compared with the EXTREME regimen after adjusting for subsequent immunotherapy in the EXTREME regimen group (Supplementary Appendix and Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2022.12.008).

Table 3. Summary of safety data in patients with PD-L1-high expression and all randomized patients

	Durvalumab		Durvalumab plus tremelimumab		EXTREME	
	PD-L1-high[a] ($n = 97$)	All randomized patients ($n = 202$)	PD-L1-high[a] ($n = 187$)	All randomized patients ($n = 408$)	PD-L1-high[a] ($n = 86$)	All randomized patients ($n = 196$)
Any-grade AEs, *n* (%)	91 (93.8)	185 (91.6)	173 (92.5)	381 (93.4)	86 (100)	195 (99.5)
Grade 3/4 AEs, *n* (%)	39 (40.2)	80 (39.6)	83 (44.4)	190 (46.6)	60 (69.8)	135 (68.9)
Any-grade TRAEs, *n* (%)	50 (51.5)	92 (45.5)	112 (59.9)	246 (60.3)	83 (96.5)	184 (93.9)
Grade 3/4 TRAEs, *n* (%)	7 (7.2)	18 (8.9)	38 (20.3)	78 (19.1)	45 (52.3)	104 (53.1)
Any-grade AESI, *n* (%)	39 (40.2)	71 (35.1)	93 (49.7)	187 (45.8)	57 (66.3)	126 (64.3)
Grade 3/4 AESI, *n* (%)	4 (4.1)	6 (3.0)	24 (12.8)	32 (7.8)	5 (5.8)	12 (6.1)
Any-grade imAE, *n* (%)	8 (8.2)	18 (8.9)	51 (27.3)	85 (20.8)	2 (2.3)	10 (5.1)
Grade 3/4 imAE, *n* (%)	5 (5.2)	8 (4.0)	22 (11.8)	29 (7.1)	2 (2.3)	4 (2.0)
TRAEs leading to discontinuation of study treatment,[b] *n* (%)	2 (2.1)	5 (2.5)	17 (9.1)	28 (6.9)	19 (22.1)	46 (23.5)
Treatment-related deaths, *n* (%)	1 (1.0)	1 (0.5)[c]	3 (1.6)	8 (2.0)[d]	2 (2.3)	2 (1.0)[e]

AE, adverse event; AESI, adverse event of special interest; EXTREME, cetuximab, 5-fluorouracil, and either carboplatin or cisplatin; IC, immune cell; imAE, immune-mediated adverse event; PD-L1, programmed death-ligand 1; TC, tumor cell; TRAE, treatment-related adverse event.

[a]PD-L1-high, TC ≥50% or IC ≥25%.

[b]TRAEs leading to discontinuation of study treatment included infections and infestations, tumor hemorrhage, blood and lymphatic system disorders, immune system disorders, endocrine disorders, anxiety, nervous system disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, hepatobiliary disorders, skin and subcutaneous tissue disorders, musculoskeletal and connective-tissue disorders, renal and urinary disorders, general disorders and administration site conditions, investigations (e.g. aspartate aminotransferase increased), and injury, poisoning and procedural complications.

[c]Cause of death unknown.

[d]Two patients each died of tumor hemorrhage and pneumonitis, and one patient each died of hemorrhage, interstitial lung disease, laryngeal edema, and sudden death.

[e]One patient each died of sepsis and pneumonia aspiration.

Safety

The median duration of treatment exposure in each treatment arm is shown in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2022.12.008. Safety data for patients with PD-L1-high expression and all randomized patients in the durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment groups are summarized in Table 3. Among all randomized patients, TRAEs of grade 3 or 4 occurred in 8.9% of patients in the durvalumab arm, 19.1% in the durvalumab plus tremelimumab arm, and 53.1% in the EXTREME regimen arm. Serious TRAEs were reported in 7.4%, 14.5%, and 23.5% of patients in each arm, respectively. In all randomized patients, TRAEs leading to treatment discontinuation occurred in 2.5%, 6.9%, and 23.5% of patients in each arm, respectively. One, eight, and two treatment-related deaths occurred in the durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen arms, respectively. The most common (>13%) AEs (treatment-related or not) in the immunotherapy treatment arms included fatigue, diarrhea, hypothyroidism, anemia, and constipation. In the durvalumab monotherapy, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms, 2.0%, 4.7%, and 0.5% of patients, respectively, discontinued treatment due to immune-mediated adverse events (imAEs) and 4.5%, 14.5%, and 4.6% of patients recovered, respectively. Nine patients (2.2%) in the durvalumab plus tremelimumab arm and three (1.5%) in the EXTREME regimen arm developed colitis, and two patients (0.5%) in the durvalumab plus tremelimumab arm developed type 1 diabetes.

Hemorrhage. Similar proportions of patients reported hemorrhage Standardized MedDRA Query (SMQ) AEs in the durvalumab monotherapy, durvalumab plus tremelimumab, and the EXTREME regimen arms (17.3%, 16.2%, and 14.8% of patients, respectively). A review of bleeding-related AEs was conducted in response to a finding identified by the independent data-monitoring committee on 12 September 2016 of a 'signal of (more than expected) bleeding complications'. As a result of this recommendation, new patient enrollment was suspended. A comprehensive analysis by the sponsor with available data from across the durvalumab HNSCC clinical program was carried out, and no increased risk of bleeding-related AEs was found at that time. Upon review of the safety analysis, the independent data-monitoring committee agreed that enrollment could resume without a protocol amendment. Analyses of hemorrhage SMQ AEs reported during the KESTREL study have been conducted in order to confirm the previous finding. There was no meaningful difference in severity or seriousness of hemorrhage SMQ AEs across the treatment arms. The type and severity of events were consistent with the established safety profiles of durvalumab monotherapy, durvalumab plus tremelimumab, or the EXTREME regimen.[15-17]

DISCUSSION

The KESTREL study showed that durvalumab was not superior to the EXTREME regimen for OS as a first-line treatment for patients with R/M HNSCC with tumors characterized by high PD-L1 expression (TC ≥50% or IC ≥25%). OS was similar across durvalumab, durvalumab plus tremelimumab, and the EXTREME regimen treatment arms in patients with PD-L1-high expression and in all randomized patients. The median PFS was longer with the EXTREME regimen compared with immunotherapy. However, a higher 12-month PFS rate was observed with durvalumab and durvalumab plus tremelimumab compared with the EXTREME regimen in patients with PD-L1-high expression. A previous phase III study (KEYNOTE-048) also demonstrated

a longer median PFS with the EXTREME regimen compared with pembrolizumab (5.0 versus 3.4 months), but lower, corresponding 12-month PFS rates of 12% and 23%, respectively, in the population of patients with PD-L1-high expression [combined positive score (CPS) $\geq$20].[27]

In this study, patients who experienced a partial response had a markedly longer DoR after immunotherapy than after the EXTREME regimen. This correlated with a longer median OS in responding patients receiving immunotherapy compared with those who responded to the EXTREME regimen. Similar trends were observed in the KEYNOTE-048 and CheckMate-651 studies, where pembrolizumab or nivolumab plus ipilimumab, respectively, drove long-term responses compared with cetuximab combination therapies.[27,28] Overall, these data suggest that compared with immunotherapy, more patients may achieve response to cetuximab plus chemotherapy; however, such responses are usually not durable. Those patients who respond to immunotherapy are more likely to experience durable benefit, with improved OS compared with the EXTREME regimen or cetuximab plus chemotherapy. It is important to note that the proportion of patients that did not respond to therapy (best response progressive disease) treated with a single agent, durvalumab in KESTREL and pembrolizumab in KEYNOTE-048, regardless of PD-L1 status is comparable, with 43% and 41%, respectively. In patients with PD-L1-high expression, this proportion remains similar in KESTREL (40%) while in KEYNOTE-048 it decreases to 32%. When chemotherapy was added to pembrolizumab for patients with PD-L1-high expression in KEYNOTE-048, the proportion of patients with a best response of PD reduced to 15%, highlighting the clear benefit of chemotherapy in this setting.

Median OS for the EXTREME arm in KESTREL (10.3 months) was comparable with the EXTREME arm of the original EXTREME study (10.1 months). However, noting that access to immunotherapy varied by geographic region during the conduct of the KESTREL study, OS in the EXTREME regimen arm for patients located in North America and Europe (76.2% of patients in all regions) was numerically longer than expected based on historical data (median OS was 12.0 and 12.4 months, respectively[7]). This may be attributable in part to the use of subsequent immunotherapy, given the high proportion of patients in the EXTREME regimen arm (24.3%) who received subsequent immunotherapy and the known positive impact of immunotherapy on OS in the second- or later-line setting,[5] which was not available at the time of the EXTREME study. This is consistent with the CheckMate-651 study, which had a higher rate of subsequent immunotherapy use in the EXTREME regimen arm and did not find any statistical improvement in OS with nivolumab plus ipilimumab versus the EXTREME regimen, either in patients with PD-L1-high expression or in the overall population.[28] Furthermore, better-than-expected OS was observed in patients receiving SoC in the KEYNOTE-040 study; *post hoc* exploratory analysis strongly suggested that subsequent immunotherapy influenced outcomes in the SoC group and confounded the OS analysis.[11]

In KESTREL, the performance of the EXTREME regimen treatment group may have been impacted by geographic differences in the patient population, coupled with changes in the treatment paradigm for R/M HNSCC that occurred during the conduct of the trial. In particular, approvals of pembrolizumab and nivolumab for second-line use and guideline updates meant that immunotherapy use became the new SoC.[29] Indeed, improved outcomes were observed in North America and Europe compared to the RoW, likely due to ready access to immunotherapy after patients discontinued study treatment in the KESTREL study. The phase III KEYNOTE-048 study, which demonstrated improved OS with PD-1 inhibition versus the EXTREME regimen in R/M HNSCC, included a lower proportion of patients from North America and Europe in the EXTREME regimen arm compared with the KESTREL study (55% versus 76%)[27] and the biggest difference in OS for PD-1 inhibition versus the EXTREME regimen was in R/M HNSCC patients recruited in RoW [OS HR of 0.41, 0.94 and 0.73 in patients with PD-L1-high expression (CPS $\geq$20) for pembrolizumab versus cetuximab plus chemotherapy from RoW, North America, and Europe, respectively]. As OS with the EXTREME regimen is likely to be higher in countries with better access to immunotherapies for subsequent treatment, this supports the hypothesis that high recruitment in North America and Europe may have contributed to KESTREL not meeting its primary objective.

Furthermore, using the study pause to define early versus late recruitment revealed that more patients received subsequent immunotherapy before the study pause compared with after (29.3% versus 11.9%). There appears to be an improvement in OS with durvalumab post-pause versus pre-pause; however, we have been unable to explain this possible discrepancy. Early recruitment was predominantly in North America and Europe and was associated with numerically longer OS for the EXTREME regimen arm versus late recruitment, which included more patients in the RoW. Moreover, the median OS of the EXTREME regimen in the post-pause phase (8.1 months; 95% CI 5.1-9.4 months) was also lower than the historical control (10.1 months; 95% CI 8.6-11.2 months).[7] These collective data correlate with the overall regional subgroup analysis results and support the hypothesis that access to subsequent immunotherapy and other regional variations in patient care may have contributed to the observed EXTREME regimen performance in this study.

Subsequent immunotherapy following the EXTREME regimen improved OS. This is consistent with the phase III KEYNOTE-040 and CheckMate-141 studies which indicated that subsequent treatment with immunotherapy (pembrolizumab and nivolumab, respectively) following disease progression on or after a platinum-containing chemotherapy improved OS.[11,30] Subsequent treatment with immunotherapy following a cetuximab-containing chemotherapy regimen has also been shown to improve OS.[31,32] Therefore, the EXTREME regimen may be an appropriate choice of first-line therapy for those patients with a high tumor burden and life-threatening disease, followed by

checkpoint inhibition upon disease progression or following disease stabilization. Nevertheless, immunotherapy is a standard first-line treatment option for R/M HNSCC, either in combination with platinum and 5-FU chemotherapy or as a single agent for patients whose tumors express PD-L1.[29]

The safety and tolerability profiles for durvalumab as a monotherapy and in combination with tremelimumab were consistent with previous studies,[15-17] with no new safety signals identified. The rate of TRAEs, including grade 3 and 4 TRAEs, and those leading to treatment discontinuation, were higher with the EXTREME regimen than with durvalumab or durvalumab plus tremelimumab in patients with PD-L1-high expression and all randomized patients. Most imAEs were categorized as grade 1 or 2, and were generally manageable with appropriate medical management. Overall, durvalumab alone or in combination with tremelimumab appeared to be well tolerated and demonstrated a manageable safety profile. As has also been demonstrated in previous studies, the toxicities associated with the EXTREME regimen are substantial,[7] and novel, less-toxic treatment options such as immune checkpoint inhibitors may have the potential to be part of chemotherapy-sparing options for patients with R/M HNSCC.

This study has some limitations: the open-label design meant that there was no blinding to treatment. Study pause, especially during change to SoC in the second line, may have impacted patient and physician expectations and behaviors during study. Lastly, the population size for the primary analysis was defined retrospectively and was therefore not prospectively sized or randomized.

In conclusion, although the primary objective of the KESTREL study was not met, chemotherapy-sparing approaches of durvalumab monotherapy and durvalumab in combination with tremelimumab demonstrated comparable OS with the EXTREME regimen, durable responses, and were tolerable in patients with R/M HNSCC who had not received prior systemic therapy for R/M disease. The high proportion of patients receiving subsequent immunotherapy in the EXTREME regimen arm may have contributed to the KESTREL study not meeting its primary objective.

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