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Original Research

Durvalumab for recurrent or metastatic head and neck squamous cell carcinoma: Results from a single-arm, phase II study in patients with ≥25% tumour cell PD-L1 expression who have progressed on platinum-based chemotherapy☆

Dan P. Zandberg [a,*], Alain P. Algazi [b], Antonio Jimeno [c], James S. Good [d], Jérôme Fayette [e], Nathaniel Bouganim [f], Neal E. Ready [g], Paul M. Clement [h], Caroline Even [i], Raymond W. Jang [j], Stuart Wong [k], Ulrich Keilholz [l], Jill Gilbert [m], Moon Fenton [n], Irene Braña [o], Stephanie Henry [p], Eva Remenar [q], Zsuzsanna Papai [r], Lillian L. Siu [j], Anthony Jarkowski [s,1], Jon M. Armstrong [s], Kobby Asubonteng [s], Jean Fan [s], Giovanni Melillo [s], Ricard Mesía [t]

[a] *University of Pittsburgh Medical Center, Hillman Cancer Center, Pittsburgh, PA, USA*
[b] *University of California San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA*
[c] *Division of Medical Oncology, University of Colorado School of Medicine, Aurora, CO, USA*
[d] *Institute of Head and Neck Studies and Education, Queen Elizabeth Hospital, Birmingham, UK*
[e] *Clinical Oncology, Cancer Center Centre Léon Bérard, University of Lyon, Lyon, France*
[f] *Department of Oncology, McGill University Health Centre, Montréal, QC, Canada*
[g] *Duke University Medical Center, Durham, NC, USA*
[h] *Department of Oncology, Leuven Cancer Institute, KU Leuven, Belgium*
[i] *Department of Head and Neck Oncology, Institut Gustave Roussy, Villejuif, France*
[j] *Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*
[k] *Division of Hematology Oncology, Medical College of Wisconsin, Milwaukee, WI, USA*
[l] *Charité Comprehensive Cancer Center, Berlin, Germany*
[m] *Henry-Joyce Cancer Clinic, Nashville, TN, USA*
[n] *The West Cancer Center, University of Tennessee Health Science Center, Memphis, TN, USA*
[o] *Medical Oncology Department, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Universitat Autonoma de Barcelona, Barcelona, Spain*
[p] *Department of Oncology-Hematology, Radiotherapy, and Nuclear Medicine, CHU UCL Namur, Namur, Belgium*
[q] *National Institute of Oncology (Országos Onkológiai Intézet), Budapest, Hungary*

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* *Corresponding author:* Division of Hematology/Oncology, University of Pittsburgh Medical Center Hillman Cancer Center, UPMC Cancer Pavilion, 5150 Centre Avenue Room 552, Pittsburgh, PA 15232, USA.
E-mail address: zandbergdp@upmc.edu (D.P. Zandberg).

[1] Now Bristol-Myers Squibb.

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[r] State Health, Center Higatian Defanse Forses, Budapest, Hungary
[s] AstraZeneca, Gaithersburg, MD, USA
[t] Medical Oncology Department, Catalan Institute of Oncology, University of Barcelona, IDIBELL, Barcelona, Spain

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Abstract ***Background:*** Patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) progressing on platinum-based chemotherapy have poor prognoses and limited therapeutic options. Programmed cell death-1 (PD-1) and its ligand 1 (PD-L1) are frequently upregulated in HNSCC. The international, multi-institutional, single-arm, phase II HAWK study (NCT02207530) evaluated durvalumab monotherapy, an anti-PD-L1 monoclonal antibody, in PD-L1-high patients with platinum-refractory R/M HNSCC.
Patients and methods: Immunotherapy-naïve patients with confirmed PD-L1-high tumour cell expression (defined as patients with ≥25% of tumour cells expressing PD-L1 [TC ≥ 25%] using the VENTANA PD-L1 [SP263] Assay) received durvalumab 10 mg/kg intravenously every 2 weeks for up to 12 months. The primary end-point was objective response rate; secondary end-points included progression-free survival (PFS) and overall survival (OS).
Results: Among evaluable patients (n = 111), objective response rate was 16.2% (95% confidence interval [CI], 9.9–24.4); 29.4% (95% CI, 15.1–47.5) for human papillomavirus (HPV)-positive patients and 10.9% (95% CI, 4.5–21.3) for HPV-negative patients. Median PFS and OS for treated patients (n = 112) was 2.1 months (95% CI, 1.9–3.7) and 7.1 months (95% CI, 4.9–9.9); PFS and OS at 12 months were 14.6% (95% CI, 8.5–22.1) and 33.6% (95% CI, 24.8–42.7). Treatment-related adverse events were 57.1% (any grade) and 8.0% (grade ≥3); none led to death. At data cut-off, 24.1% of patients remained on treatment or in follow-up.
Conclusion: Durvalumab demonstrated antitumour activity with acceptable safety in PD-L1-high patients with R/M HNSCC, supporting its ongoing evaluation in phase III trials in first- and second-line settings. In an *ad hoc* analysis, HPV-positive patients had a numerically higher response rate and survival than HPV-negative patients.

1. Introduction

Recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) has poor prognosis and low survival rates [1]. Until recently, patients with progressive disease (PD) after first-line combination chemotherapy and cetuximab were treated with chemotherapeutic monotherapy, which yielded objective response rates (ORRs) of 4–13% [2–5].

HNSCC tumours often exhibit T-cell infiltration and can be antigenic due to high mutation burden or virally associated antigens, yet often escape immune elimination through inhibition of antitumour T-cell responses resulting from expression of checkpoint pathway components, such as programmed cell death-ligand 1 (PD-L1) [6,7]. Targeting the programmed cell death-1 (PD-1)/PD-L1 pathway has resulted in clinically meaningful activity and improved overall survival (OS) in patients with previously treated R/M HNSCC [8–12]. In 2016, 2 immuno-oncology agents targeting PD-1 were approved for patients with previously treated R/M HNSCC with PD on or after a platinum-based therapy [13,14].

Durvalumab is a selective, high-affinity, engineered human IgG1 monoclonal antibody (mAb) that blocks PD-L1 binding to PD-1 and CD80, allowing T-cells to recognise and kill tumour cells (TC). Durvalumab has shown antitumour activity in patients with HNSCC [15,16]. In a phase I/II study that included 62 patients with R/M HNSCC, ORR with durvalumab was 11% in all patients, 18% in 22 patients with high PD-L1 expression (TC ≥ 25%) and 8% in 37 patients with PD-L1-low/negative expression (TC < 25%) [16]. Encouraging 6- and 12-month OS rates of 62% and 42%, respectively, were observed in this pre-treated population [16].

In this report, we present the safety and efficacy of durvalumab from an international, multicentre study (NCT02207530) in patients with R/M HNSCC with PD-L1-high expression (TC ≥ 25%) after progression after only 1 platinum-containing regimen given in the R/M setting.

2. Methods

2.1. Study design

In this single-arm, phase II trial, eligible patients received 10 mg/kg durvalumab by intravenous infusion every 2 weeks for up to 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity or consent withdrawal. The primary endpoint was ORR using blinded independent central review (BICR) as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines. For a complete or partial response, radiographic confirmation was needed ≥4 weeks after first response. Secondary end-points were best objective response, duration of response, time to response, disease control rate, progression-free survival (PFS) and OS; safety and tolerability; and impact of treatment on symptoms and health-related quality of life (HRQoL) measures.

2.2. Patient population

Patients aged ≥18 years with histologically confirmed R/M HNSCC (oral cavity, oropharynx, larynx or hypopharynx) not amenable to therapy with curative intent (surgery or radiation therapy with or without chemotherapy/biologic therapy) and with PD-L1-high (TC ≥ 25%) expression were included. The PD-L1 TC ≥ 25% cut-off was chosen for its ability to discriminate between responders and non-responders in HNSCC [17,18]. Eligible patients had tumour progression or recurrence during or after treatment with only 1 platinum-based systemic regimen for R/M disease. Further eligibility criteria are provided in the Appendix.

All patients provided written informed consent, and any locally required authorisations were obtained from patient/legal representatives before any protocol-related procedures.

2.3. Study assessments

Tumour response was assessed by computed tomography or magnetic resonance imaging every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD. Tumour response (complete [CR], partial [PR], stable disease [SD] or PD) was based on BICR according to RECIST v1.1. Patients with CR, PR or SD at 12 months entered follow-up. Upon progression at any time, asymptomatic patients or those without functional decline were permitted to restart durvalumab for up to 12 further months.

PD-L1 expression levels of newly acquired or archival tumour tissues (<3 years old) were assessed by immunohistochemistry with the VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc., AZ).

Human papillomavirus (HPV) status was either collected from historical medical records or based on assessment according to local standard procedures and participating institutions' individual standards; status may have been measured by p16 immunohistochemistry, fluorescence *in situ* hybridisation or polymerase chain reaction.

Adverse events (AEs) were monitored every 2 weeks for the first 8 weeks and then every 4 weeks and graded according to National Cancer Institute CTCAE v4.03. Safety monitoring continued for ≤90 d post-last dose. Treatment-related AEs (TRAEs) of special interest (AESIs) were defined as AEs associated with potential inflammatory or immune-related events. A suspected immune-mediated AE (imAE) was identified and defined as an AESI that required the use of systemic steroids or other immunosuppressants, and/or, for specific endocrine events, endocrine therapy. All pneumonitis AEs were classified as suspected imAEs, regardless of concomitant steroid use. Patient-reported outcomes (PRO) assessments are presented in the Appendix.

2.4. Statistical methods

The primary objective assessment was based on all evaluable patients (evaluable analysis set), which included all treated patients who had baseline tumour assessments and measurable disease at baseline according to BICR and was set to determine whether the lower limit of the 95% confidence interval (CI) of ORR was >13%. Secondary efficacy variables were analysed based on evaluable analysis set and the full analysis set, which included all treated patients. Distributions of PFS and OS were estimated by Kaplan–Meier method.

Data underlying the findings described in this study may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

3. Results

3.1. Patient disposition and baseline characteristics

The data cut-off date was 31st March 2017, approximately 12 months after the last patient began treatment. Of 112 patients treated, 111 were evaluable for efficacy assessment; 1 patient did not have measurable disease at baseline according to BICR (Fig. A.1). At data cut-off, 21 patients (18.8%) had completed 12 months of treatment, and 27 (24.1%) remained on study on treatment or in follow-up. Ninety-one patients (81.3%) discontinued treatment: 69.6% due to PD, 7.1% due to AEs and 4.5% due to patient decision.

Demographic and disease characteristics of patients are shown in Table 1. Median age of patients was 60 years (range, 24–84 years), and 59.8% received prior cetuximab. Most patients were either current or former (n = 69; 61.6%) smokers. Among 99 patients evaluable

Table 1
Patient disposition and baseline characteristics.

Patient disposition	N
Patients screened, n[a]	158
Patients who failed screening, n	46
Patients receiving durvalumab, n (%)[b]	112 (100)
Evaluable patients, n[c]	111
Patients completing 12 months of treatment, n (%)	21 (18.8)
Patients who discontinued therapy, n (%)	91 (81.3)
Progression, n (%)	78 (69.6)
Baseline characteristics[b]	**N = 112**
Median age, years (range)	60 (24–84)
Male, n (%)	80 (71.4)
ECOG PS, n (%)[d]	
0	34 (30.4)
1	77 (68.8)
Classification at study enrolment, n (%)	
Locoregional recurrence	39 (34.8)
Metastatic disease[e]	73 (65.2)
Primary tumour location	
Oral cavity	47 (42.0)
Oropharynx	40 (35.7)
Larynx	15 (13.4)
Hypopharynx	9 (8.0)
Other	1 (0.9)
PD-L1 positive	112 (100)
Smoking/nicotine status, n	102
Current, n (%)	10 (8.9)
Former, n (%)	59 (52.7)
Never, n (%)	43 (38.4)
HPV/p16 status, n[f]	99
Positive, n (%)	34 (34.3)
Oropharynx	20 (58.8)
Oral cavity	7 (20.6)
Hypopharynx	2 (5.9)
Larynx	5 (14.7)
Negative, n (%)	65 (65.7)
Oropharynx	17 (26.2)
Oral cavity	33 (50.8)
Hypopharynx	6 (9.2)
Larynx	8 (12.3)
Other	1 (1.5)
Prior cetuximab, n (%)	67 (59.8)

ECOG PS, European Cooperative Oncology Group performance status; HPV, human papillomavirus; PD-L1, programmed cell death-ligand 1.
[a] Informed consent.
[b] Full analysis set, n = 112.
[c] One patient did not have measurable disease at baseline according to blinded independent central review.
[d] One missing evaluation.
[e] One patient had both locoregional recurrence and metastatic disease.
[f] HPV/p16 status was collected regardless of tumour site. Sites outside of oropharynx were tested.

for HPV/p16 status, 34 (34.3%) were positive and 65 (65.7%) were negative. Oropharynx was the primary site in most (59%) HPV-positive tumours.

3.2. Safety

Median duration of durvalumab treatment was 3.5 months (range, 0.3–12.2). Nine patients had TRAEs leading to dose interruptions of durvalumab. One patient discontinued treatment due to grade 4 pneumonitis, grade 3 hepatitis and grade 2 nephritis, all of which were considered related to durvalumab; this patient later died due to PD. There were no TRAEs leading to death. Most AEs were mild to moderate (grade 1 or 2). Altogether, 64 patients (57.1%) reported at least 1 TRAE (Table 2). Grade 3/4 TRAEs occurred in 9 patients, of which 2.7% had increased gamma-glutamyltransferase. AESIs occurred in 39 patients: skin related (15.1%), endocrine related (12.5%), renal/hepatic related (10.7%),

Table 2
Treatment-related adverse events.[a]

Treatment-related adverse events	Durvalumab (N = 112)
	n (%)
Any treatment-related AE	64 (57.1)
Treatment-related AEs leading to death	0 (0)
Treatment-related AEs leading to discontinuation	1 (0.9)
Treatment-related AEs occurring in >5% of patients	
Nausea	11 (9.8)
Fatigue	11 (9.8)
Hypothyroidism	10 (8.9)
Asthenia	9 (8.0)
Pruritus	7 (6.3)
Diarrhoea	6 (5.4)
Decreased appetite	6 (5.4)
Grade 3/4 treatment-related AEs	9 (8.0)
Gamma-glutamyltransferase increased	3 (2.7)
Tumour pain	1 (0.9)
Dehydration	1 (0.9)
Hypokalaemia	1 (0.9)
Hypophosphatemia	1 (0.9)
Pneumonitis	1 (0.9)
Hepatitis	1 (0.9)
Chest pain	1 (0.9)
Alanine aminotransferase increased	1 (0.9)
Aspartate aminotransferase increased	1 (0.9)
Blood bilirubin increased	1 (0.9)
Treatment-related AEs of special interest	39 (34.8)
Skin related	
Rash	9 (8.0)
Dermatitis	8 (7.1)
Endocrine related	
Hypothyroidism	11 (9.8)
Hyperthyroidism	3 (2.7)
Renal/hepatic related	
Select hepatic events	9 (8.0)
Select renal events	3 (2.7)
Gastrointestinal related	
Diarrhoea	6 (5.4)
Lung related	
Pneumonitis	4 (3.6)
Other rare/miscellaneous	3 (2.7)

AE, adverse event.
[a] As assessed by investigator.

gastrointestinal related (5.4%), lung related (3.6%) or other (2.7%) (Table 2). imAEs were observed in 18 patients treated with durvalumab; the majority were grade 1/2 (hypothyroidism [11 patients], select hepatic events and hyperthyroidism [2 each], diarrhoea, select renal events and rash [1 each]). Four patients had pneumonitis, 1 of which was grade ≥3.

3.3. Efficacy

Eighteen patients treated with durvalumab had a response (ORR, 16.2%; 95% CI, 9.9–24.4) (Table 3), including 1 CR (0.9%) and 17 PR (15.3%). Three patients (2.7%) had an unconfirmed CR/PR. Disease control rate (CR + PR + SD) at 24 weeks was 23.4%, and 58 patients (52.3%) had PD during the first 12 months of treatment. Median time to response was 2.0 months (range, 1.6–9.2). At data cut-off, median duration of response was estimated to be 10.3 months and 10 of 18 patients (55.6%) had ongoing responses. Decreases in size of target lesions occurred in 40.5% of all patients (Fig. A.2). ORR was consistent across most subgroups evaluated, with the exception of HPV status.

In an exploratory analysis testing HPV/p16 at all anatomical sites (i.e. not limited to oropharynx), ORR among 34 patients with HPV-positive tumours was 29.4% (95% CI, 15.1–47.5) and 10.8% (95% CI, 4.4–20.9) among 65 patients with HPV-negative tumours (Table 3). Among patients with HPV-positive tumours, ORR with durvalumab was 30% (95% CI, 11.9–54.3) for oropharyngeal primary site and 28.6% (95% CI, 8.4–58.1) for non-oropharyngeal site. Among patients with HPV-negative cancer, ORR was 11.8% (95% CI, 1.5–36.4) for oropharyngeal site and 10.4% (95% CI, 3.5–22.7) for non-oropharyngeal site (Table 3).

Table 3
Best objective response rate with durvalumab treatment.

Best objective response	Durvalumab (N = 111)
ORR, n (%)	**18 (16.2)**
95% CI	9.9–24.4
Complete response	1 (0.9)
Partial response	17 (15.3)
Stable disease	7 (6.3)
Unconfirmed complete/partial response	3 (2.7)
Progressive disease	58 (52.3)
Median time to response, months (range)	2.0 (1.6–9.2)
Median duration of response, months	10.3
ORR by HPV/p16 status, n (%)	
HPV positive (n = 34)	10 (29.4)
95% CI	15.1–47.5
Oropharynx (n = 20)	6 (30.0)
Non-oropharynx (n = 14)	4 (28.6)
Oral cavity (n = 7)	1 (14.3)
Larynx (n = 5)	2 (40.0)
Hypopharynx (n = 2)	1 (50.0)
HPV negative (n = 65)	7 (10.8)
95% CI	4.4–20.9
Oropharynx (n = 17)	2 (11.8)
Non-oropharynx (n = 48)	5 (10.4)
Oral cavity (n = 33)	3 (9.1)
Hypopharynx (n = 6)	1 (16.7)
Larynx (n = 8)	1 (12.5)
Other (n = 1)	0 (0)

CI, confidence interval; HPV, human papillomavirus; ORR, objective response rate.

Kaplan–Meier estimate of median PFS was 2.1 months (95% CI, 1.9–3.7) (Fig. 1A). PFS at 6, 12 and 18 months was 25.5% (95% CI, 17.6–34.1), 14.6% (95% CI, 8.5–22.1) and 8.7% (95% CI, 2.7–19.2), respectively. Median PFS in patients with HPV-positive and HPV-negative tumours was 3.6 months (95% CI, 1.9–5.6) versus 1.8 months (95% CI, 1.6–2.0), respectively.

At median follow-up of 6.1 months (range, 0.2–24.3), median OS was 7.1 months (95% CI, 4.9–9.9) (Fig. 1B). OS at 12 and 18 months was 33.6% (95% CI, 24.8–42.7) and 23.0% (95% CI, 14.3–32.9), respectively. At data cut-off, 27 patients (24.1%) remained on study treatment or in follow-up without progression. Kaplan–Meier estimate of median OS in patients with HPV-positive and HPV-negative tumours was 10.2 months (95% CI, 7.2–16.3) versus 5.0 months (95% CI, 3.4–8.4), respectively (Fig. 1C).

3.4. Patient-reported outcomes in symptoms and HRQoL

Based on the European Organisation for Research and Treatment of Cancer (EORTC) 30-item core QoL questionnaire (QLQ-C30), PROs were improved over baseline for several measures (Fig. 2A). Clinically meaningful improvements, defined as an increase in baseline score of ≥10 at 2 consecutive assessments ≥14 d apart, were observed for global health status/QoL (13.5%; 95% CI, 8.1–21.8), physical functioning (17.1%; 95% CI, 10.1–27.6) and fatigue (21.3%; 95% CI, 14.1–31.0) (Table A.1). To note, increased scores on the global health status and functioning scales indicate better health status/function. Median time to deterioration was 3.7 months for global health status/QoL, 5.0 months for physical functioning and 1.8 months for fatigue.

Head and neck cancer–specific symptoms evaluated using the EORTC QoL questionnaire head and neck cancer module (QLQ-H&N35) (Fig. 2B) showed clinically meaningful improvements, defined as a decrease in baseline score of ≥10 at 2 consecutive assessments ≥14 d apart, for mouth pain (24.6%; 95% CI, 16.0–36.0), swallowing (19.4%; 95% CI, 11.4–30.9), taste and smell (34.3%; 95% CI, 24.1–46.3) and speech (28.4%; 95% CI, 19.7–39.0) (Table A.2). To note, decreased scores on symptom scales represent symptom improvement. Median time to deterioration was 4.6 months for mouth pain, 4.9 months for swallowing, 4.9 months for taste and smell and 2.7 months for speech.

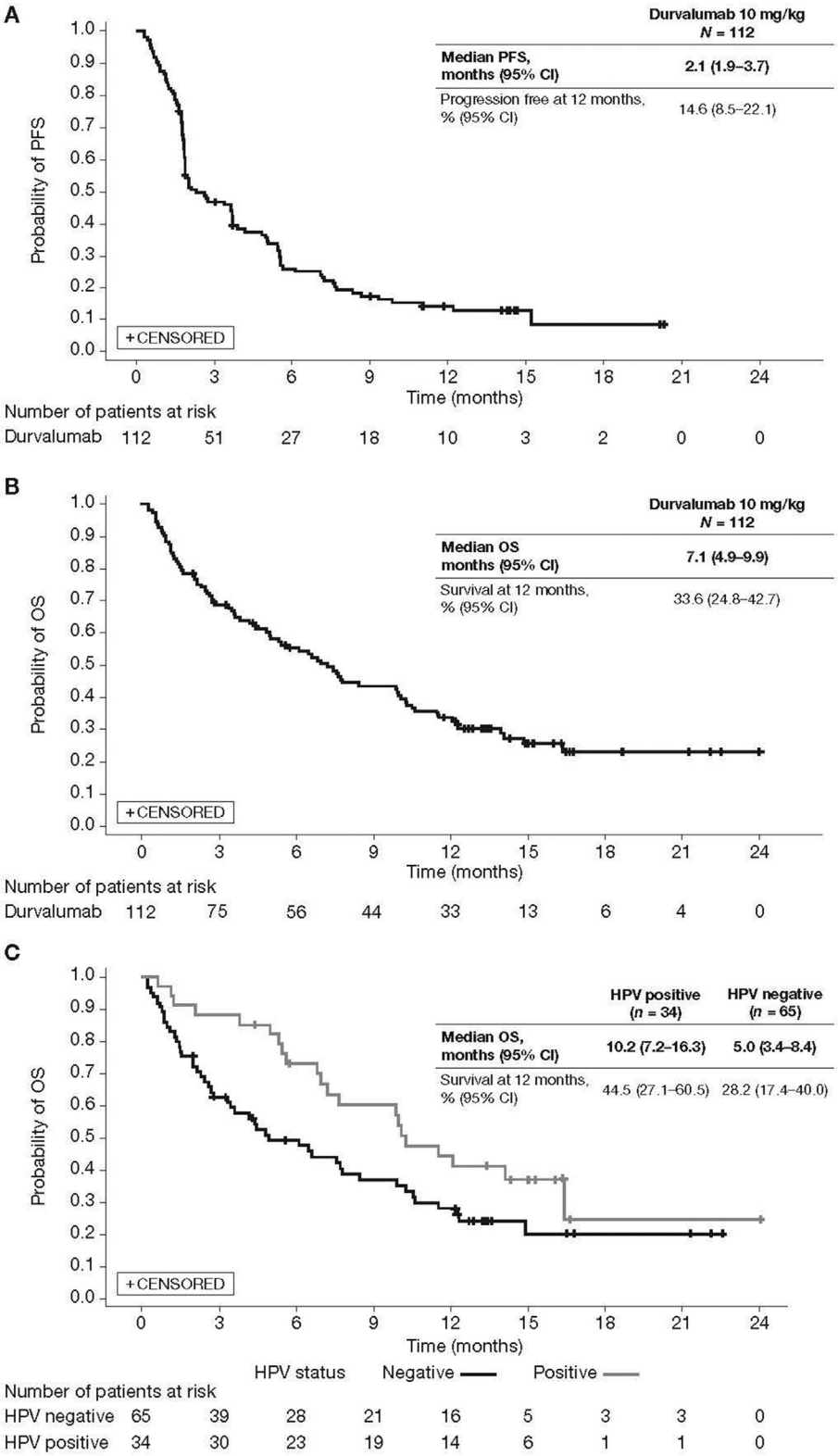

Fig. 1. Kaplan–Meier estimates of PFS (A) and OS (B). Exploratory analysis of Kaplan–Meier estimates of OS by HPV status (C). HPV status was unknown for 13 patients (full analysis set; N = 112). CI, confidence interval; HPV, human papillomavirus; OS, overall survival; PFS, progression-free survival.

4. Discussion

4.1. Conclusions

Durvalumab demonstrated clinically meaningful anti-tumour activity in patients with HNSCC with PD-L1-high expression (TC $\geq$ 25%) who had progressed after first-line platinum-based therapy in the R/M setting. ORR was 16.2% (95% CI, 9.9–24.4), with over half of patients (55.6%) maintaining their response at data cut-off. A median OS of 7.1 months was observed, with approximately one-third (33.6%) of patients surviving $\geq$1 year. In an *ad hoc* analysis, HPV-positive patients with HPV-positive tumours had a numerically higher ORR and OS than patients with HPV-negative tumours.

Durvalumab exhibited a manageable safety profile, consistent with previous reports [16,19]. While most patients (57.1%) reported at least 1 TRAE, most were grade 1/2, with grade 3/4 TRAEs occurring in 8.0% of patients. There were no deaths due to TRAEs, and only 1 patient discontinued durvalumab because of a TRAE.

Finally, improvements in PROs measured by both EORTC QLQ-C30 and QLQ-H&N35 scales were observed with durvalumab treatment, suggesting improved QoL for patients.

4.2. Discussion

To our knowledge, this is the first large prospective study evaluating an anti-PD-L1 mAb in patients with R/M HNSCC. While direct comparison to CHECKMATE 141 or KEYNOTE-040 phase III studies is limited based on differences in study design and inclusion criteria, including PD-L1 expression, it is important to note that, despite an ORR of 13.3% (95% CI, 9.3–18.3) in CHECKMATE 141, nivolumab improved OS compared with standard-of-care therapy (hazard ratio, 0.70; 97.73% CI, 0.51–0.96, $p = 0.01$) [10,12]. This is similar to other second-line trials in advanced

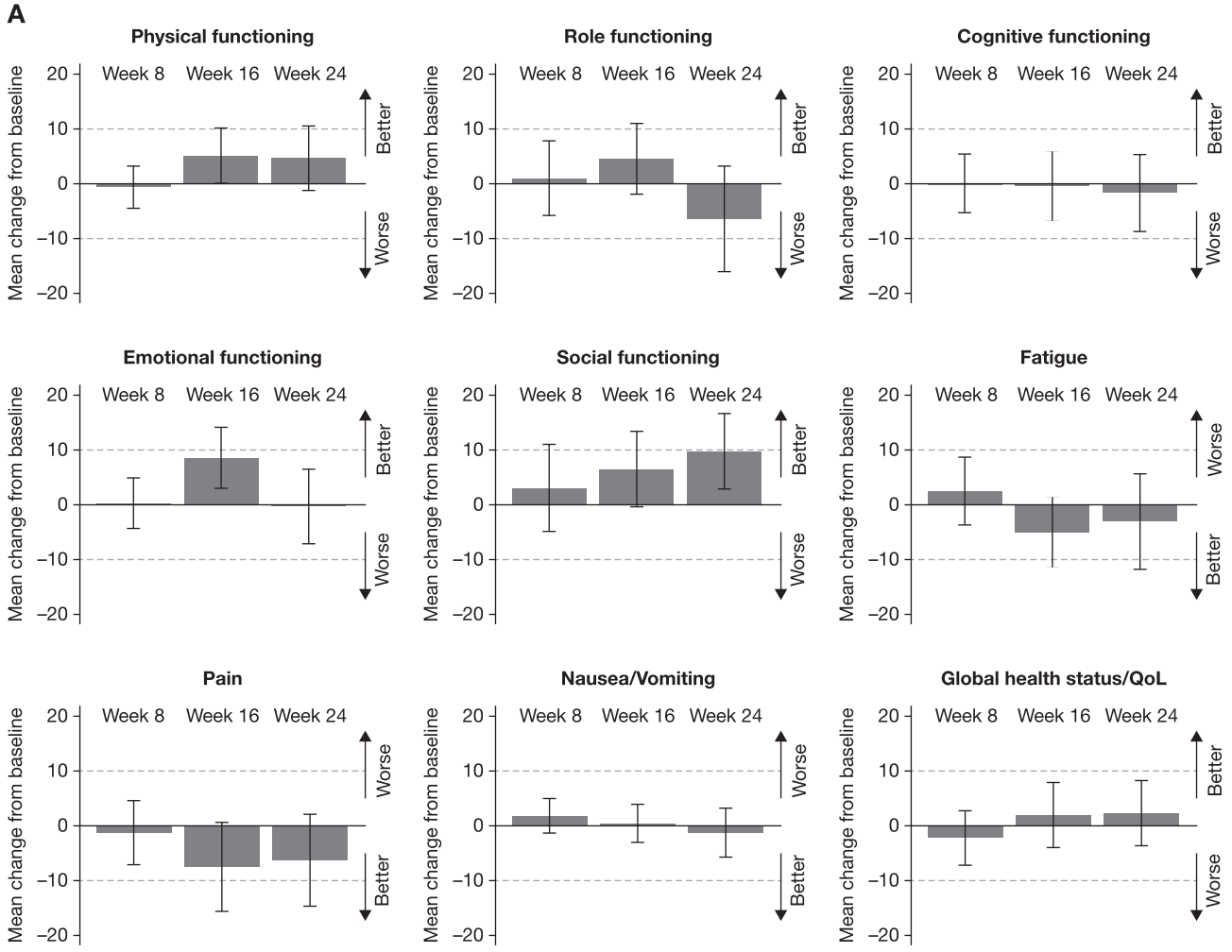

Fig. 2. Patient-reported outcomes assessed by EORTC QLQ-C30 v3 (full analysis set; N = 112) (A) and EORTC QLQ-H&N35 (full analysis set; N = 112) (B). Error bars represent 95% CI for the mean change from baseline. CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, 30-item core QoL questionnaire; QLQ-H&N35, QoL questionnaire head and neck cancer module; QoL, quality of life.

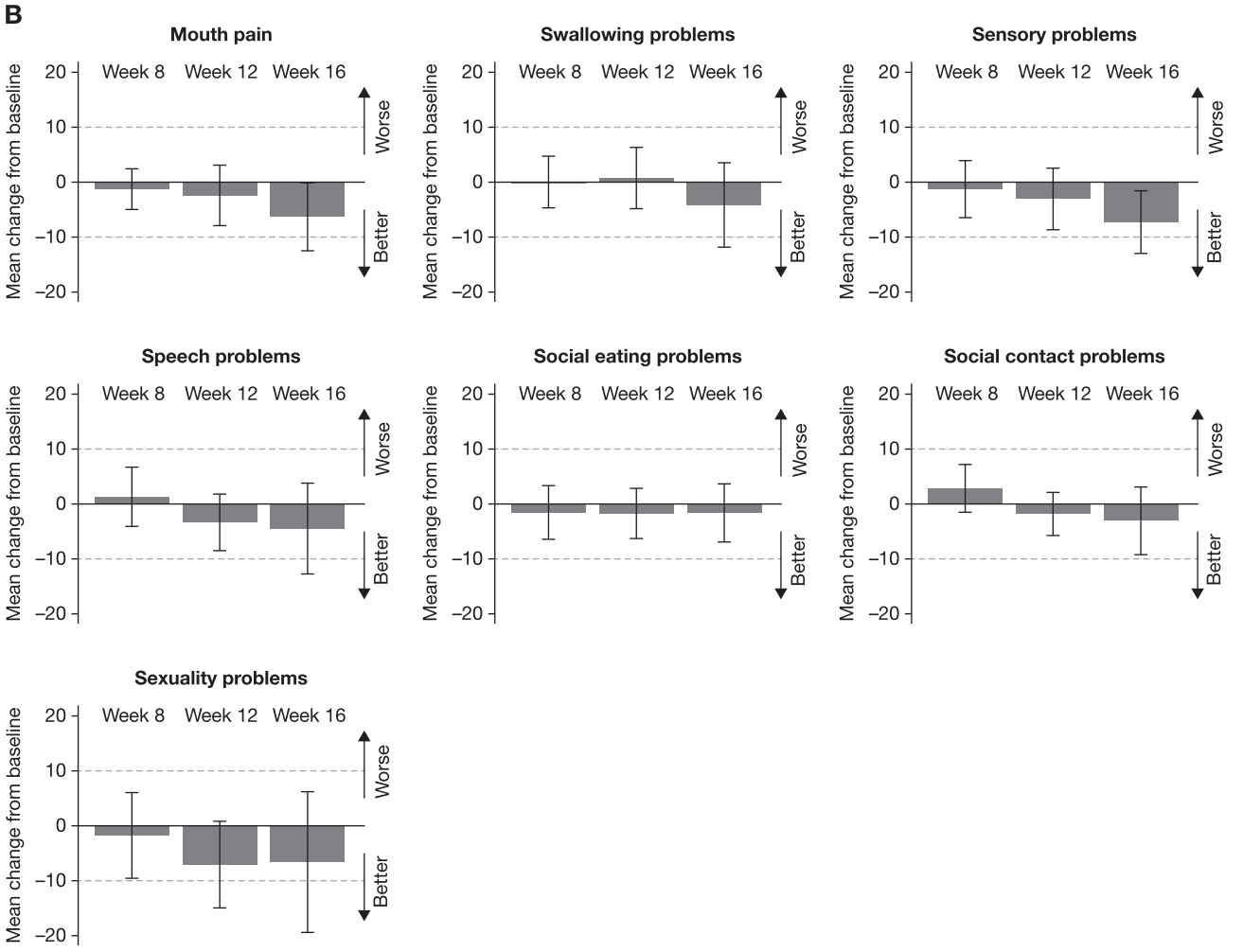

Fig. 2. (*continued*).

solid tumours, including bladder cancer, where, despite low response rates, treatment with single-agent anti-PD-1 or PD-L1 mAbs led to significant OS improvement compared with traditional chemotherapy [19]. The statistical threshold of 95% CI for ORR was set at >13% in this study. Although the lower limit for ORR was only 9.9%, promising OS was observed with durvalumab in this platinum-pre-treated patient population.

The *ad hoc* exploratory analysis showed that among this PD-L1-high cohort, patients with HPV/p16-positive tumours (all tumour locations) treated with durvalumab experienced higher response rates and longer survival than patients with HPV-negative tumours. Conflicting results have been observed as to whether patients with HPV-positive tumours have improved efficacy with blockade of the PD-1/PD-L1 pathway [9–11]; however, it is important to consider both PD-L1 expression and HPV status together, given PD-L1 expression can be predictive of efficacy. While analysis of KEYNOTE-055 with pembrolizumab showed similar ORR by HPV status, this analysis included both PD-L1-negative and PD-L1-positive patients [9]. Similar to our results, patients with HPV-positive tumours had higher ORR and longer OS in KEYNOTE-012, where all patients were PD-L1 positive (TC $\geq$ 1%) [9,11]. In an exploratory subgroup analysis of PD-L1-negative patients treated with nivolumab in CHECKMATE 141, patients with HPV-positive tumours had median OS of 10 months versus 7.1 months for those with HPV-negative tumours [10]. It is possible that virally associated tumour antigenicity in combination with intratumoural inflammation is predictive of response. Further research is needed to determine whether HPV is independently associated with improved treatment outcomes with anti-PD-1 or anti-PD-L1 mAbs.

In this study, non-oropharyngeal cancer patients were included in the exploratory analysis of HPV status. Interestingly, while HPV does not have a consistent or established role in oncogenesis or prognosis of non-oropharyngeal sites, the response rate of non-oropharyngeal HPV-positive tumours was similar to that of oropharyngeal HPV-positive tumours. Together, all patients with HPV-positive tumours still had doubled median OS compared with HPV-negative tumours.

Reasons for this remain unclear, and further analysis is needed to determine whether HPV was biologically relevant in these non-oropharyngeal patients, or whether the presence of HPV in non-oropharyngeal primary tumours has any immunologic effect that might lead to better efficacy.

Finally, HNSCC patients in whom toxicity from disease and treatment can often lead to long-term impairment, disability and handicap, showed improvements in HRQoL assessments. The impact of durvalumab versus standard-of-care chemotherapy on patient QoL will be assessed in 2 randomised phase III trials [20,21].

This study has 2 design features that warrant careful interpretation of its results. First, as a non-randomised single-arm study, it lacks a standard-of-care control arm. Second, the patient population had only PD-L1-high-expressing tumours, compared with earlier studies of patients with tumours of PD-L1-high and PD-L1-low/negative status; the absence of PD-L1-low/negative tumours allowed focused analysis on this particular subgroup of patients that may be more likely to respond to anti-PD-L1 mAb therapy. A companion phase II study, CONDOR, has assessed responses to durvalumab monotherapy in a PD-L1-low/negative HNSCC population (NCT02319044) [22]. The variety of technologies, assays and cut-off algorithms used to determine PD-L1 expression make comparisons across different trials challenging. Another limitation is that HPV status was determined by different methods at the discretion of each participating site.

Overall, encouraging efficacy was observed with single-agent durvalumab in PD-L1-high R/M HNSCC patients, most of whom had failed cetuximab in addition to platinum-based chemotherapy. Currently, 2 ongoing phase III trials (EAGLE NCT02369874; KESTREL NCT02551159) will evaluate durvalumab with or without tremelimumab in patients in the first- and second-line settings for R/M HNSCC [20,21].

Author contributions

DZ, A Jarkowski, GM, JA and LS provided study concepts. DZ, A Jarkowski, GM, JA, KA, NR, JF and JFan designed the study. PC, AJ, UK, SW, AA, JG, LS, MF, NB, NR, RJ, SH, ZSP, JF and JGilbert helped in data acquisition. JA, KA and JFan assisted in quality control of data and algorithms. PC, AJ, UK, SW, DZ, A Jarkowski, AA, GM, JA, JG, KA, LS, MF, NB, NR, RJ, SH, ZSP, JF, JGilbert and JFan took part in data analysis and interpretation. JA and KA helped in statistical analysis. PC, SW, DZ, A Jarkowski, AA, GM, JA, KA, LS, NB, NR, ZSP and JF contributed to manuscript preparation. AJ, UK, SW, DZ, A Jarkowski, AA, GM, JA, JG, KA, LS, MF, NB, NR, RJ, SH, ZSP, JF, JGilbert and JFan involved in manuscript editing. AJ, PC, UK, SW, DZ, A Jarkowski, AA, GM, JA, JG, KA, LS, MF, NB, NR, RJ, SH, ZSP, JF, JGilbert and JFan reviewed the manuscript.

Conflict of interest statement

Dan P. Zandberg: Research Funding: AstraZeneca/MedImmune (Inst), Bristol-Myers Squibb (Inst), Gliknik (Inst), MacroGenics (Inst), Merck (Inst).

Alain P. Algazi: **Consulting or Advisory Role:** Array Pharmaceuticals. **Research Funding:** Aceria (Inst), AstraZeneca/MedImmune (Inst), Bristol-Myers Squibb (Inst), Genentech (Inst), Incyte (Inst), Merck (Inst), Novartis (Inst), OncoSec (Inst).

Antonio Jimeno: **Consulting or Advisory Role:** AstraZeneca. **Research Funding:** AstraZeneca/MedImmune (Inst).

James S. Good: **Honoraria:** Bristol-Myers Squibb, BTG, Eisai, Merck, Sirtex. **Consulting or Advisory Role:** GenesisCare UK. **Research Funding:** AstraZeneca. **Travel, Accommodations, Expenses:** BTG, GenesisCare UK, Sirtex.

Jérôme Fayette: **Honoraria:** AstraZeneca, Bristol-Myers Squibb, Merck. **Consulting or Advisory Role:** Bristol-Myers Squibb. **Travel, Accommodations, Expenses:** AstraZeneca, Bristol-Myers Squibb.

Nathaniel Bouganim: No relationship to disclose.

Neal E. Ready: **Consulting or Advisory Role:** AbbVie, AstraZeneca, Bristol-Myers Squibb, Celgene, Merck.

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Caroline Even: **Consulting or Advisory Role:** AstraZeneca, Bristol-Myers Squibb, Innate Pharma, Merck Serono, MSD. **Travel, Accommodations, Expenses:** Merck Serono.

Raymond W. Jang: **Honoraria:** Ipsen. **Research Funding:** AstraZeneca (Inst), Boston Biomedical (Inst), Bristol-Myers Squibb (Inst), Lilly (Inst), Merck (Inst), Novartis (Inst).

Stuart Wong: No relationship to disclose.

Ulrich Keilholz: **Honoraria:** Amgen, AstraZeneca, Bristol-Myers Squibb, GSK, Merck, Pfizer. **Consulting or Advisory Role:** AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer. **Speakers' Bureau:** Amgen, AstraZeneca, Bristol-Myers Squibb, Merck, Pfizer. **Research Funding:** AstraZeneca, Merck, Pfizer. **Travel, Accommodations, Expenses:** AstraZeneca, Bristol-Myers Squibb, Merck.

Jill Gilbert: **Honoraria:** TRM Oncology. **Consulting or Advisory Role:** AstraZeneca, TRM Oncology. **Research Funding:** AstraZeneca (Inst), Bristol-Myers Squibb (Inst), Merck (Inst), Pfizer (Inst). **Travel, Accommodations, Expenses:** TRM Oncology.

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Jon M. Armstrong: **Employment and Stock or Other Ownership:** AstraZeneca.

Kobby Asubonteng: **Employment and Stock or Other Ownership:** AstraZeneca.

Giovanni Melillo: **Employment and Stock or Other Ownership:** AstraZeneca.

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Appendix A. Supplementary data

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