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Global treatment patterns and outcomes among patients with recurrent and/or metastatic head and neck squamous cell carcinoma: Results of the GLANCE H&N study

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ABSTRACT

Objectives: Given a lack of universally-accepted standard-of-care treatment for patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC), study objectives were to assess treatment utilization and survival outcomes for R/M HNSCC in the real-world setting.

Materials and methods: A multi-site retrospective chart review was conducted in Europe (Germany, United Kingdom, Italy, Spain), Asia Pacific (Australia, South Korea, Taiwan), and Latin/North America (Brazil and Canada) to identify patients who initiated first-line systemic therapy for R/M HNSCC between January 2011 and December 2013. Patients were followed through December 2015 to collect clinical characteristics, treatment and survival data.

Results: Among 733 R/M HNSCC patients across 71 sites, median age was 60 years (inter-quartile range 54–67), 84% male, and 70% Eastern Cooperative Oncology Group performance status 0–1; 32% had oral cavity and 30% oropharyngeal cancers. The most common first-line regimen across all countries consisted of platinum-based combinations (73%), including platinum + 5-fluorouracil (5-FU) (26%), cetuximab + platinum ± 5-FU (22%), or taxane + platinum ± 5-FU (16%). However, use of different platinum-based combinations varied

Abbreviations: 5-FU, fluorouracil; CI, confidence interval; ECOG, Eastern cooperative oncology group; e-CRF, electronic case report form; EORTC, European Organization for Research and Treatment of Cancer; HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; HR, hazard ratio; I-O, immune-oncology; IQR, inter-quartile range; KM, Kaplan-Meier; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death ligand; R/M, recurrent or metastatic; rwOS, real-world OS; UK, United Kingdom

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[1] A complete list of investigators who participated in the GLANCE H&N STUDY is provided in the web appendix (Supplementary Table 7).

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substantially; administration of cetuximab + platinum ± 5-FU was frequent in Italy (81%), Germany (46%) and Spain (38%), whereas use in other countries was limited. Median follow-up was 22.6 months (95% confidence interval [CI]: 21.5–24.6 months). Median real-world overall survival was only 8.0 months (95% CI: 7.0–8.0), with one-year survival reaching only 30.9% (95% CI: 27.5–34.3).

Conclusion: Systemic therapies used in clinical practice for patients with R/M HNSCC vary substantially across countries. Prognosis remains poor in this patient population, highlighting the need for newer, more efficacious treatments.

Introduction

Head and neck cancers encompass a range of tumours arising in the oral cavity, pharynx, larynx, salivary glands, nasal cavity and paranasal sinuses [1]. Head and neck squamous cell carcinoma (HNSCC) is the predominant histological type, which includes cancers of the oropharynx, larynx, hypopharynx and lip/oral cavity. HNSCC is the 7th leading cause of cancer-related mortality: an estimated 705,781 new cases and 358,144 deaths were attributable to HNSCC globally in 2018 [2]. Whereas newly diagnosed distant metastatic HNSCC (Stage IVc) is uncommon (3.5% of newly diagnosed HNSCC), 58% of patients with HNSCC initially present with locoregionally advanced disease (stage III–IVb) [3,4].

A significant proportion of patients initially diagnosed with locoregionally advanced HNSCC develop disease recurrence, in 30% to 45% within the first year following multi-modal treatment consisting of surgery and/or chemoradiation [5]. Patients with recurrent and/or metastatic (R/M) HNSCC present a therapeutic challenge [6,7]. Despite available chemotherapeutic and targeted therapies, the prognosis of patients with R/M HNSCC is poor. Historically, first-line treatment of R/M HNSCC consisted of platinum-based chemotherapy (cisplatin or carboplatin) in combination with 5-fluorouracil (5-FU) or a taxane (docetaxel or paclitaxel). These platinum-based combination regimens resulted in median overall survival (OS) ranging from 5.0 to 8.7 months across trials [8,9]. Most recent evidence from prospective clinical trial data reported an improvement in the median OS to 10.1 months for the targeted systemic therapy cetuximab combined with platinum-based chemotherapy, and thereby defined a new standard of care in first-line treatment of R/M HNSCC according to clinical guidelines [6,7,10]. However, in some countries, the use of cetuximab in combination with platinum-based therapy may be limited due to toxicity concerns or regulatory and reimbursement restrictions, potentially resulting in different standard treatment patterns across various regional settings [11,12].

Treatment choice remains heterogeneous for patients whose disease has progressed following first-line platinum-based therapy. Historically, evidence remained limited and single-agent chemotherapy or cetuximab were considered standards of care [6,7]. Clinical guidelines in Spain have recently highlighted the clinical benefits of weekly paclitaxel plus cetuximab for patients who have progressed on or are intolerant of platinum-based therapy [13]. More recently, studies of programmed cell death protein 1 (PD-1) inhibitors, nivolumab and pembrolizumab, reported improved OS after platinum-failure and represent preferred choices in guidelines, where available [7].

Given a lack of universally accepted standard-of-care treatment for patients with R/M HNSCC, there are limited data describing how R/M HNSCC is treated in clinical practice [14–17]. Furthermore, there is a paucity of data focused on survival outcomes with current use of systemic therapies for R/M HNSCC outside of the clinical trial setting to help identify unmet needs in this population.

To this end, the Global Longitudinal Assessment of Treatment Outcomes in Squamous Cell Carcinoma of the Head and Neck (GLANCE H&N) chart review study was designed to explore treatment patterns and OS outcomes in patients with R/M HNSCC who received systemic therapy.

Methods

Study design and data collection

The GLANCE H&N retrospective observational study was conducted at 71 sites in nine countries across Europe (Germany, United Kingdom, Spain, Italy), Asia Pacific (Taiwan, South Korea, Australia), and Latin/North America (Brazil and Canada) (Fig. 1). The study protocol was approved by relevant national and local regulatory authorities.

Adult patients with R/M HNSCC who initiated first-line systemic

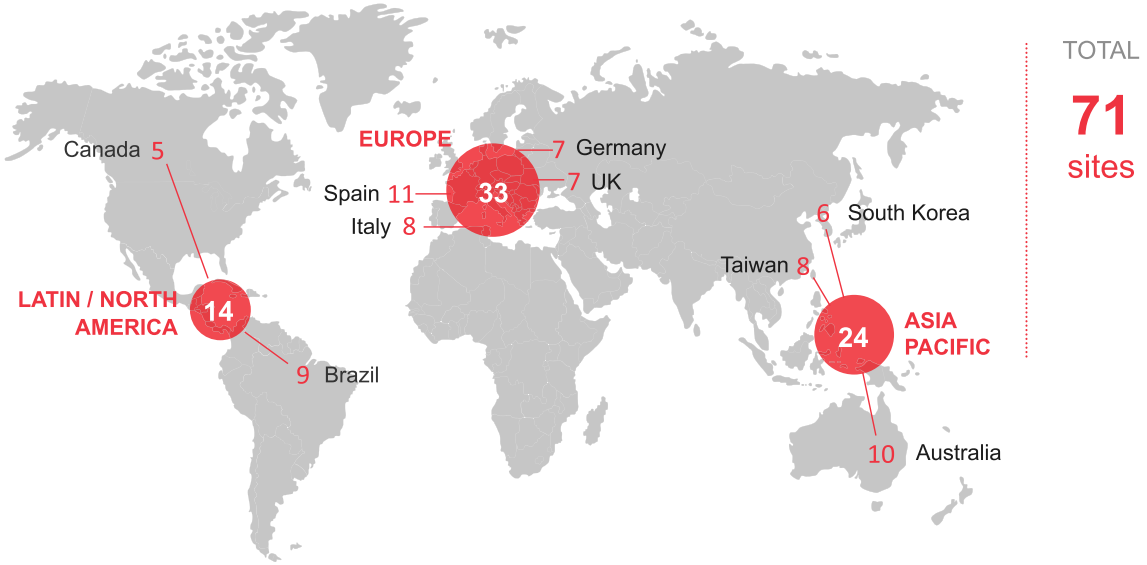

Fig. 1. Scope of the GLANCE H&N study. UK: United Kingdom.

therapy for the treatment of R/M HNSCC (defined as the index date) between the January 1, 2012 and June 30, 2013 eligibility period were identified (Fig. 2). For sites in Germany, Australia and Canada the eligibility period was extended to January 1, 2011 through December 31, 2013 to increase patient enrolment. Patients were followed from the index date through December 31, 2015 to collect data on clinical characteristics, treatment patterns and survival outcomes. Initial diagnosis and treatment information were collected during the background period prior to the index date.

Anonymized data were gathered by study investigators and site staff through manual chart review into an electronic case report form (e-CRF). Additional details on the study design and data collection procedures are provided in the Supplementary Table 1.

Patient population

Adult patients were eligible for inclusion if they had a histopathological or cytological diagnosis of HNSCC involving the lip/oral cavity, oropharynx, hypopharynx or larynx, and initiated first-line systemic therapy for the treatment of locoregional recurrent HNSCC (including second primary tumour and primary tumour relapse) with or without distant metastases, distant metastatic recurrent HNSCC or newly diagnosed metastatic HNSCC (stage IVc). Patients could be included if they participated in a clinical trial at any line of treatment. Patients were excluded if they had: cutaneous squamous cell carcinoma involving the lip; cancers involving the nasopharynx, nasal cavity, paranasal sinuses, salivary glands or thyroid; received locoregional treatment (radiation or surgery) with curative intent in the context of relapsed/metastatic disease; and had not received any systemic therapy for the treatment of R/M HNSCC.

Subgroup analyses were conducted for platinum-progressed R/M HNSCC patients, defined as patients who had experienced disease progression after prior treatment with a platinum-containing regimen for the treatment of R/M HNSCC or in the locoregionally advanced disease setting. Treatment regimens for the next line of therapy for patients with platinum progressed R/M HNSCC were defined based on the setting of prior platinum-based therapy exposure:

(1) For patients who received a platinum-based therapy for the treatment of R/M HNSCC and who had no prior platinum-based therapy or whose last date of platinum-based therapy in the locally advanced HNSCC setting occurred $>$ 6 months prior to the index date, the next line of systemic therapy for R/M HNSCC was reported.
(2) For patients whose last date of platinum-based therapy in the locally advanced HNSCC setting occurred $\leq$ 6 months prior to the index date, the first-line systemic therapy for R/M HNSCC was defined from the index date.

Study outcomes

Primary endpoints included systemic treatment patterns and treatment duration according to line of therapy among patients with R/M HNSCC in the overall and platinum-progressed populations. Treatment duration was defined as the time (in months) between the first and last administration across all agents within each regimen. Secondary endpoints included OS in the overall and platinum-progressed populations. OS according to country and according to common treatment regimens were descriptively presented. OS was defined from the date of first-line systemic therapy until death from any cause; patients still alive at the end of follow-up were censored as of December 31, 2015.

Statistical analysis

Descriptive statistics were reported for demographic, clinical and treatment characteristics. OS analyses were performed using the Kaplan-Meier (KM) product limit method; no imputation was made for missing variables. KM curves and median real-world OS (rwOS) were reported in months, and survival rates at landmark time points (e.g., 6 and 12 months) were reported. Log-rank tests were conducted to compare rwOS across countries and common treatment regimens.

A multivariate Cox proportional hazard model was constructed to identify prognostic factors for OS with first-line therapy. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated and reported in Forest plots. The model covariate list included the following patient characteristics: age, gender, history of smoking, alcohol consumption, comorbidities, tumour location, TNM disease stage at diagnosis, disease status at index date, performance status at index date/Eastern Cooperative Oncology Group (ECOG) criteria, first-line treatment regimens and prior therapies, including radiotherapy, surgery and systemic therapy.

Analyses were performed using SAS V-9.3 (SAS Institute, Cary, NC, USA).

Results

Patient demographics

The study population included 733 patients from 71 sites (Table 1; Fig. 1). Median age was 60 years (inter-quartile range [IQR] 54–67), 84.4% were male, and 76.7% were current/former smokers (Table 1; Supplementary Table 2). Patient demographics were largely consistent across countries except for smoking status and alcohol use as risk factors for HNSCC: a higher proportion of patients were current/former

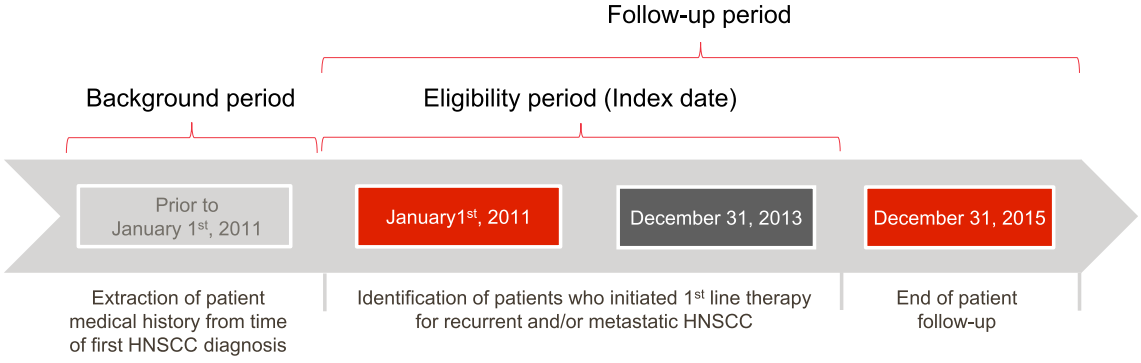

Fig. 2. Design of the GLANCE H&N study. Investigators in the UK, Italy and Spain (Europe), Taiwan and South Korea (Asia-Pacific) and Brazil (Latin/North America) enrolled patients diagnosed between January 1, 2012 and December 31, 2013 (eligibility period). For investigators in Germany (Europe), Australia (Asia-Pacific) and Canada (Latin/North America) this period was extended to January 1, 2011 through December 31, 2013 to increase patient enrolment. HNSCC: head and neck squamous cell carcinoma; UK: United Kingdom.

Table 1
Demographic and clinical characteristics of patients with R/M HNSCC, overall and by country.

Characteristic	Overall (N = 733)	Europe				Asia Pacific			Latin/North America	
		Germany (N = 102)	UK (N = 95)	Spain (N = 88)	Italy (N = 69)	Taiwan (N = 111)	South Korea (N = 76)	Australia (N = 53)	Brazil (N = 98)	Canada (N = 41)
Gender, n (%)										
Male	619 (84.4)	90 (88.2)	71 (74.7)	74 (84.1)	58 (84.1)	106 (95.5)	57 (75.0)	46 (86.8)	85 (86.7)	32 (78.0)
Age at Index date										
Median (IQR), years	60.0 (54.0–67.0)	61.0 (55.0–68)	60.0 (54.0–67.0)	60.0 (54.0–67.0)	60.0 (54.0–67.0)	60.0 (54.0–67.0)	60.0 (54.0–67.0)	62.0 (55.0–67.0)	59.0 (55.0–66.5)	61.0 (55.0–67.0)
Tumour location, n (%)										
Lip/oral cavity	236 (32.2)	14 (13.7)	30 (31.6)	22 (25.0)	24 (34.8)	68 (61.3)	33 (43.4)	11 (20.8)	24 (24.5)	10 (24.4)
Oropharynx	221 (30.2)	33 (32.4)	41 (43.2)	25 (28.4)	12 (17.4)	15 (13.5)	11 (14.5)	25 (47.2)	38 (38.8)	21 (51.2)
Larynx	137 (18.7)	21 (20.6)	16 (16.8)	25 (28.4)	22 (31.9)	2 (1.8)	15 (19.7)	12 (22.6)	18 (18.4)	6 (14.6)
Hypopharynx	98 (13.4)	28 (27.5)	8 (8.4)	11 (12.5)	8 (11.6)	22 (19.8)	10 (13.2)	1 (1.9)	7 (7.1)	3 (7.3)
Other[a]	41 (5.6)	6 (5.9)	0 (0)	5 (5.7)	3 (4.3)	4 (3.6)	7 (9.2)	4 (7.5)	11 (11.2)	1 (2.4)
Disease status at Index date, n (%)										
Recurrent/Progressed	590 (80.5)	79 (77.5)	77 (81.0)	73 (83.0)	57 (82.6)	90 (81.1)	63 (82.9)	44 (83.0)	71 (72.4)	36 (87.8)
Locoregional recurrent disease, no distant metastases	263 (35.9)	20 (19.6)	44 (46.3)	34 (38.6)	13 (18.8)	59 (53.2)	17 (22.4)	28 (52.8)	41 (41.8)	7 (17.1)
Locoregional recurrent disease, distant metastases	168 (22.9)	21 (20.6)	17 (17.9)	16 (18.2)	16 (23.2)	25 (22.5)	28 (36.8)	10 (18.9)	16 (16.3)	19 (46.3)
Distant metastatic recurrent disease	106 (14.5)	30 (29.4)	13 (13.7)	15 (17.0)	10 (14.5)	6 (5.4)	18 (23.7)	4 (7.5)	4 (4.1)	6 (14.6)
Progression of residual local or distant disease	53 (7.2)	8 (7.8)	3 (3.2)	8 (9.1)	18 (26.1)	0 (0)	0 (0)	2 (3.8)	10 (10.2)	4 (9.8)
Newly diagnosed metastatic disease (stage IVc)	143 (19.5)	23 (22.5)	18 (19.0)	15 (17.0)	12 (17.4)	21 (18.9)	13 (17.1)	9 (17.0)	27 (27.6)	5 (12.2)
ECOG PS at Index date, n (%)										
0–1	515 (70.2)	60 (58.8)	82 (86.3)	64 (72.7)	36 (52.2)	78 (70.3)	61 (80.3)	41 (77.3)	71 (72.4)	22 (53.6)
2	109 (14.9)	29 (28.4)	7 (7.4)	11 (12.5)	3 (4.3)	21 (18.9)	6 (7.9)	9 (17.0)	16 (16.3)	7 (17.1)
3–4	25 (3.4)	8 (7.8)	0 (0)	0 (0)	1 (1.4)	7 (6.3)	1 (1.3)	1 (1.9)	5 (5.1)	2 (5.0)
Unknown	84 (11.4)	5 (4.9)	6 (6.3)	13 (14.8)	29 (42.0)	5 (4.5)	8 (10.5)	2 (3.8)	6 (6.1)	10 (24.4)
Systemic therapy prior to Index date, n (%)										
Yes	337 (46.0)	44 (43.1)	39 (41.1)	41 (46.6)	34 (49.3)	57 (51.4)	32 (42.1)	25 (47.2)	44 (44.9)	21 (51.2)
Prior Platinum	304 (90.2)	37 (84.1)	36 (92.3)	35 (85.4)	33 (97.1)	52 (91.2)	31 (96.9)	19 (76.0)	43 (97.7)	18 (85.7)
Platinum ≤ 6 months prior to Index date	102 (33.6)	10 (27.0)	7 (19.4)	8 (22.9)	9 (27.3)	32 (61.5)	9 (29.0)	6 (31.6)	17 (39.5)	4 (22.2)
Unknown	150 (20.5)	23 (22.5)	18 (18.9)	14 (15.9)	12 (17.4)	25 (22.5)	13 (17.1)	9 (17.0)	30 (30.6)	6 (14.6)

ECOG: Eastern Cooperative Oncology Group; HNSCC: head and neck squamous cell carcinoma; IQR: interquartile range; PS: performance status; R/M: recurrent and/or metastatic; UK: United Kingdom.

[a] Includes other and ill-defined sites in lip, oral cavity and pharynx.

smokers in Spain, Taiwan, Australia, Brazil, and Canada (82.8–87.5%), and heavy alcohol use was reported in UK, Spain, Taiwan and Australia (28.8–45.5%) (Supplementary Table 2). Among patients with cancer of the oropharynx (N = 221), only 25.3% were tested for human papillomavirus (HPV) infection (N = 56) based on P16 staining, and 15.8% tested positive for HPV infection (N = 35) (Supplementary Table 2).

Table 2
First-line treatment patterns for patients with R/M HNSCC, overall and by country.

Systemic therapy	Overall (N = 733)	Europe				Asia Pacific			Latin/North America	
		Germany (N = 102)	UK (N = 95)	Spain (N = 88)	Italy (N = 69)	Taiwan (N = 111)	South Korea (N = 76)	Australia (N = 53)	Brazil (N = 98)	Canada (N = 41)
Any combination, n (%)	**575 (78.4)**	**86 (84.3)**	**93 (97.9)**	**72 (81.8)**	**67 (97.1)**	**92 (82.9)**	**59 (77.6)**	**34 (64.2)**	**48 (49.0)**	**24 (58.5)**
Platinum-based combination	535 (73.0)	78 (76.5)	93 (97.9)	51 (58.0)	67 (97.1)	87 (78.4)	59 (77.6)	34 (64.2)	47 (48.0)	19 (46.3)
Platinum + 5-FU	193 (26.3)	4 (3.9)	67 (70.5)	8 (9.1)	1 (1.4)	40 (36.0)	41 (53.9)	24 (45.3)	5 (5.1)	3 (7.3)
Cetuximab + platinum ± 5-FU	159 (21.7)	47 (46.1)	13 (13.7)	33 (37.5)	56 (81.2)	0 (0)	0 (0)	0 (0)	4 (4.1)	6 (14.6)
Taxane + platinum ± 5-FU	119 (16.2)	11 (10.8)	13 (13.7)	10 (11.4)	5 (7.2)	10 (9.0)	17 (22.4)	6 (11.3)	38 (38.8)	9 (22.0)
Cetuximab + platinum + taxane ± 5-FU	18 (2.4)	16 (15.7)	0 (0)	0 (0)	2 (2.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other platinum	46 (6.3)	0 (0)	0 (0)	0 (0)	3 (4.3)	37 (33.3)	1 (1.3)	4 (7.5)	0 (0)	1 (2.4)
Non-platinum combination	40 (5.4)	8 (7.8)	0 (0)	21 (23.9)	0 (0)	5 (4.5)	0 (0)	0 (0)	1 (1.0)	5 (12.2)
Cetuximab + taxane	27 (3.7)	6 (5.9)	0 (0)	20 (22.7)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.0)	0 (0)
Other non-platinum	13 (1.8)	2 (2.0)	0 (0)	1 (1.1)	0 (0)	5 (4.5)	0 (0)	0 (0)	0 (0)	5 (12.2)
Any monotherapy, n (%)	**147 (20.1)**	**16 (15.7)**	**2 (2.1)**	**16 (18.2)**	**2 (2.9)**	**19 (17.1)**	**12 (15.8)**	**18 (34.0)**	**46 (47.0)**	**16 (39.1)**
Platinum	52 (7.1)	0 (0)	1 (1.1)	4 (4.5)	0 (0)	14 (12.6)	1 (1.3)	5 (9.4)	23 (23.5)	4 (9.8)
Taxane	36 (4.9)	6 (5.9)	0 (0)	4 (4.5)	1 (1.4)	0 (0)	4 (5.3)	0 (0)	18 (18.4)	3 (7.3)
Methotrexate	28 (3.8)	0 (0)	0 (0)	5 (5.7)	0 (0)	1 (0.9)	0 (0)	11 (20.8)	3 (3.1)	8 (19.5)
Cetuximab	22 (3.0)	10 (9.8)	1 (1.1)	3 (3.4)	0 (0)	1 (0.9)	2 (2.6)	2 (3.8)	2 (2.0)	1 (2.4)
Other	9 (1.2)	0 (0)	0 (0)	0 (0)	1 (1.4)	3 (2.7)	5 (6.6)	0 (0)	0 (0)	0 (0)
Clinical trial, n (%)	**11 (1.5)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**5 (6.6)**	**1 (1.9)**	**4 (4.0)**	**1 (2.4)**

5-FU: fluorouracil; HNSCC: head and neck squamous cell carcinoma; R/M: recurrent and/or metastatic; UK: United Kingdom.

HNSCC clinical characteristics

The most common primary tumour sites were the lip/oral cavity (32.2%) or the oropharynx (30.2%), although primary tumour location varied across countries/regions (Table 1). Oropharyngeal cancers were more common in Latin/North America (51.2% Canada; 38.8% Brazil), Australia (47.2%) and Northern Europe (43.2% UK; 32.4% Germany). Oral cavity cancers were more common in the Asia-Pacific region (61.3% Taiwan; 43.4% South Korea).

The majority of patients had recurrent/progressive disease at the index date (80.5%), of whom over one-third had distant metastases (37.4%); 19.5% were newly diagnosed metastatic; no notable differences were observed across countries (Table 1). Most patients (70.2%) had good performance status (ECOG 0–1), although a lower proportion of patients with good performance status were seen in Canada, Germany, and Italy (52.2–58.8%).

Systemic therapy was administered to 46.0% of patients prior to the index date, among which platinum-based chemotherapy was the most common (90.2%). Only Australia had a notably lower proportion of patients with prior platinum-based chemotherapy (76.0%). Approximately one-third of patients who received platinum-based therapy received their last dose ≤ 6 months prior to index date.

Treatment patterns in R/M HNSCC

The most common first-line systemic therapy regimens consisted of platinum-based combinations (73.0%) across all countries, including platinum + 5-FU (26.3%), cetuximab + platinum ± 5-FU (21.7%), or taxane + platinum ± 5-FU (16.2%; Table 2). However, use of different platinum-based combinations varied substantially across countries; administration of cetuximab + platinum ± 5-FU was frequent in Italy (81.2%), Germany (46.1%), and Spain (37.5%), whereas the use of cetuximab + platinum ± 5-FU was limited in other countries. Platinum with 5-FU was the most common first-line regimen in the UK (70.5%) and in Asia-Pacific countries (36.0–53.9%), whereas taxane + platinum ± 5-FU was most frequent in Brazil (38.8%) and Canada (22.0%). Monotherapy was frequently used in the first-line setting in Brazil (47.0%), Canada (39.1%) and Australia (34.0%), but accounted for first-line treatment in only 20.1% of patients overall.

Following first-line systemic therapy, 39.4% of patients underwent second-line therapy (N = 289), with estimates ranging 23.2%–54.5% across countries (Supplementary Fig. 1). Monotherapy was the most common second-line treatment overall (54.3%) among which a taxane (23.5%) or methotrexate (11.8%) were most common (Table 3). Re-treatment with platinum-based combinations was also common in certain countries (29.1% overall), particularly in Taiwan (54.3%), UK (45.4%) and Germany (36.4%), whereas in Italy (82.1%), Brazil (75.7%) and Australia (75.0%) monotherapy was the predominate approach. In Spain, cetuximab + taxane combination was more commonly used (31.3%) as an alternative to platinum-based combinations in the second-line setting. Following second-line therapy, very few patients received third-line (12.7%) and fourth-line therapy (4.1%), although patient numbers were too small to definitively examine trends (Supplementary Fig. 1).

Among the full cohort of 733 patients, 380 patients (51.8%) had progressed on platinum-based therapy and received additional systemic therapy (Supplementary Table 3). Re-treatment with platinum-based combinations was common across all countries (46.0%), and 38.4% of patients received monotherapy, primarily consisting of taxane (17.4%), methotrexate (6.8%), or cetuximab (5.7%). Utilization of monotherapies and re-treatment with platinum-based combinations differed greatly across countries. Re-treatment with platinum-based combinations was very common in Taiwan (71.2%) and UK (70.6%), and least common in Spain where cetuximab + taxane combination was more commonly used (38.8%). Monotherapies were most commonly administered in Australia (65.2%) and Brazil (60.4%), and among the monotherapies administered, taxanes were generally used across most countries.

Treatment duration in R/M HNSCC

Median treatment duration was 2.0 months (IQR 1.0–4.0 months) across all first-line systemic therapies administered (Supplementary Table 4). Median treatment duration was longest for cetuximab + platinum ± 5-FU after taking cetuximab maintenance therapy into account (3.0 months; IQR 2.0–5.0 months) and was similar for platinum + 5-FU (2.0 months; IQR 1.0–3.9 months) and taxane + platinum ± 5-FU (2.0 months; IQR 1.0–3.0 months). Median treatment duration was 2.0 months for patients who received second-line therapy (IQR 1.0–3.0; Supplementary Table 5).

Median treatment duration for patients who progressed on platinum-based therapy and received additional systemic therapy was 2.0 months (IQR 1.0–3.9 months) (Supplementary Table 6).

Table 3
Second-line treatment patterns for patients with R/M HNSCC, overall and by country.

Systemic therapy	Overall (N = 289)	Europe				Asia Pacific			Latin/North America	
		Germany (N = 44)	UK (N = 22)	Spain (N = 48)	Italy (N = 28)	Taiwan (N = 35)	South Korea (N = 41)	Australia (N = 20)	Brazil (N = 37)	Canada (N = 14)
Any combination, n (%)	**116 (40.2)**	**23 (52.3)**	**10 (45.4)**	**25 (52.1)**	**5 (17.9)**	**23 (65.7)**	**10 (24.4)**	**5(25.0)**	**9 (24.3)**	**6 (42.9)**
Platinum-based combination	84 (29.1)	16 (36.4)	10 (45.4)	10 (20.8)	1 (3.6)	19 (54.3)	10 (24.4)	5 (25.0)	9 (24.3)	4 (28.6)
Platinum + 5-FU	24 (8.3)	0 (0)	3 (13.6)	5 (10.4)	0 (0)	8 (22.8)	3 (7.3)	3 (15.0)	2 (5.4)	0 (0)
Cetuximab + platinum ± 5-FU	25 (8.6)	13 (29.5)	0 (0)	3 (6.2)	1 (3.6)	1 (2.9)	3 (7.3)	1 (5.0)	1 (2.7)	2 (14.3)
Taxane + platinum ± 5-FU	25 (8.6)	3 (6.8)	5 (22.7)	1 (2.1)	0 (0)	4 (11.4)	4 (9.8)	0 (0)	6 (16.2)	2 (14.3)
Other platinum	10 (3.5)	0 (0)	2 (9.1)	1 (2.1)	0 (0)	6 (17.4)	0 (0)	1 (5.0)	0 (0)	0 (0)
Non-platinum combination	32 (11.1)	7 (15.9)	0 (0)	15 (31.3)	4 (14.3)	4 (11.4)	0 (0)	0 (0)	0 (0)	2 (14.3)
Cetuximab + taxane	23 (8.0)	7 (15.9)	0 (0)	15 (31.3)	1 (3.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other non-platinum	9 (3.1)	0 (0)	0 (0)	0 (0)	3 (10.7)	4 (11.4)	0 (0)	0 (0)	0 (0)	2 (14.3)
Any monotherapy, n (%)	**157 (54.3)**	**21 (47.7)**	**8 (36.4)**	**22 (45.8)**	**23 (82.1)**	**12 (34.3)**	**21 (51.2)**	**15 (75.0)**	**28 (75.7)**	**7 (50.0)**
Platinum	17 (5.9)	1 (2.3)	3 (13.6)	3 (6.3)	2 (7.1)	5 (14.3)	0 (0)	0 (0)	2 (5.4)	1 (7.1)
Taxane	68 (23.5)	10 (22.7)	3 (13.6)	7 (14.6)	15 (53.6)	3 (8.6)	14 (34.1)	6 (30.0)	6 (16.2)	4 (28.6)
Methotrexate	34 (11.8)	4 (9.1)	0 (0)	5 (10.4)	0 (0)	2 (5.7)	0 (0)	7 (35.0)	16 (43.2)	0 (0)
Cetuximab	15 (5.2)	2 (4.5)	2 (9.1)	3 (6.3)	0 (0)	0 (0)	5 (12.2)	2 (10.0)	0 (0)	1 (7.1)
Other	23 (8.0)	4 (9.1)	0 (0)	4 (8.3)	6 (21.4)	2 (5.7)	2 (4.9)	0 (0)	4 (10.8)	1 (7.1)
Clinical trial, n (%)	**16 (5.5)**	**0 (0)**	**4 (18.2)**	**1 (2.1)**	**0 (0)**	**0 (0)**	**10 (24.4)**	**0 (0)**	**0 (0)**	**1 (7.1)**

5-FU: fluorouracil; HNSCC: head and neck squamous cell carcinoma; R/M: recurrent and/or metastatic; UK: United Kingdom.

Overall survival in R/M HNSCC

Median follow-up duration was 22.6 months (95% CI: 21.5–24.6 months). The median rwOS for R/M HNSCC patients who initiated first-line systemic therapy was 8.0 months (95% CI: 7.0–8.0), with one-year survival reaching only 30.9% (95% CI: 27.5–34.3%) (Table 4). Some variation in median rwOS was observed across countries, ranging from 6.0 months (95% CI: 4.9–12.0) to 10.5 months (95% CI: 8.0–14.0), but the confidence intervals consistently overlapped suggesting no notable country-specific differences. Result of the log-rank test did suggest a difference in OS across countries (log-rank test p = 7e-07); however, these results should be interpreted with care given the low patient numbers in certain countries at later time points. Median rwOS for the most common first-line platinum-based regimens were similar: median rwOS was 8.0 months (95% CI: 7.0–9.0) for platinum + 5-FU, 8.0 months (95% CI: 7.0–10.0) for cetuximab + platinum ± 5-FU, and 7.1 months (95% CI: 6.0–9.0) for taxane plus platinum ± 5-FU (Fig. 3; log-rank test p = 0.2). In the subgroup of patients who progressed on platinum therapy (n = 361), median rwOS was 6.0 months (95% CI: 5.0–7.0), and one-year survival rate reached only 22.3% (95% CI: 18.0%–26.7%; Supplementary Table 6). Median rwOS for the most common regimens used in the subgroup of patients who progressed on platinum therapy were similar: median rwOS was 6.0 months (95% CI: 5.0–7.9) for platinum-based combinations, 4.0 months (95% CI: 3.0–6.0) for taxane monotherapy, and 6.0 months (95% CI: 5.0–8.0) for other monotherapies (Supplementary Fig 2; log- rank test p = 0.1).

Results of the multivariate Cox proportional hazards regression to identify factors that were prognostic of OS for the overall population are presented in Supplementary Fig. 3. As expected, a high ECOG performance status score (2 or 3–4) was an independent predictor of worse survival outcomes (ECOG 2: HR 1.42, 95% CI: 1.12–1.8; ECOG 3–4: HR 4.6, 95% CI: 2.99–7.08). There was no significant influence of type of platinum-based first-line treatment regimen on OS, confirming the trends observed in the unadjusted KM OS curves. Additional patient demographic characteristics did not appear to be prognostic of OS. In addition, no notable differences in OS were observed according to disease stage at diagnosis and disease status at the index date.

Discussion

The GLANCE H&N was a multisite, retrospective observational study that examined the treatment patterns and outcomes of patients with R/M HNSCC in oncology practices across nine regionally representative countries in Europe, Asia Pacific and Latin/North America. Consistent with prior studies and trials in R/M HNSCC [14,18], the study population was predominately male (84%), with median age of 60 years and a higher proportion of patients with good performance status (70% ECOG 0–1), confirming the generalizability of the study population. Only 25% of patients with cancer of the oropharynx were tested for HPV infection, which may not be surprising as the study eligibility period (2011–2013) largely predates the recent awareness of HPV infection as a major risk factor for HNSCC [19].

Overall, the results of the study identified that platinum-based combination regimens were most widely used as first-line therapy (73%), and monotherapies were most frequently used in the second-line setting (54%). However, the use of systemic therapies for patients with R/M HNSCC varied substantially across countries. Among platinum-based combinations utilized in the first-line setting, administration of cetuximab in combination with platinum-based therapy was frequent in Italy, Germany and Spain, but was seldom used in other countries despite regulatory approval of this regimen in most countries (excluding Canada), and consistent designation as preferred treatment option by global clinical guidelines (EXTREME regimen: cetuximab + platinum + 5-FU) [6,7,20]. Potential reasons for low utilization of cetuximab in combination with platinum-based therapy may be due to toxicity concerns or regulatory and reimbursement restrictions [11,12].

Treatment patterns in the UK and Germany are largely consistent with prior publications, which have identified predominate use of platinum in combination with 5-FU in the UK and cetuximab in combination with platinum in Germany [14,15]. Among Asia-Pacific countries in this study, taxanes in combination with platinum were most frequent. A study from the United States similarly highlighted higher use of taxanes and platinum combination and infrequent use of cetuximab and platinum combinations [16]. Among studies examining second-line treatment patterns, results also confirm predominate use of taxanes and methotrexate monotherapies as seen in this study [14]. As an exception, use of cetuximab in combination with a taxane was common in Spain, as currently recommended by local clinical guidelines [13].

Median rwOS with first-line therapy in the study population was only 8.0 months, with one-year survival reaching only 30.9%. Despite differences in treatment patterns, OS was similar across countries and

Table 4
Overall survival[a] for patients who initiated first-line systemic therapy for R/M HNSCC, overall and by country.

Overall Survival		Overall (N = 722)	Europe				Asia Pacific			Latin/North America	
			Germany (N = 102)	UK (N = 95)	Spain (N = 88)	Italy (N = 69)	Taiwan (N = 111)	South Korea (N = 71)	Australia (N = 52)	Brazil (N = 94)	Canada (N = 40)
Median (95% CI)[b]		8.0 (7.0–8.0)	7.0 (6.0–8.0)	7.0 (5.0–8.0)	10.5 (8.0–14.0)	7.0 (6.0–8.0)	9.0 (6.0–11.0)	9.0 (7.9–11.0)	7.0 (6.0–12.0)	10.0 (8.0–13.0)	6.0 (4.9–12.0)
Rate, % (95% CI)[b]											
6 months	n	441	60	50	60	40	65	48	33	63	22
		61.1 (57.5–64.7)	58.8 (49.2–68.4)	52.6 (42.6–62.6)	68.2 (58.5–77.9)	58.0 (46.3–69.7)	58.6 (49.4–67.8)	67.6 (56.7–78.5)	63.5 (50.4–76.6)	67.0 (57.5–76.5)	55.0 (39.6–70.4)
12 months	n	223	28	16	37	14	43	19	17	38	11
		30.9 (27.5–34.3)	27.5 (18.8–36.2)	16.8 (9.3–24.3)	42.0 (31.7–52.3)	20.3 (10.8–29.8)	38.7 (29.6–47.8)	26.8 (16.5–37.1)	32.7 (20.0–45.4)	40.4 (30.5–50.3)	27.5 (13.7–41.3)
2 years	n	104	8	2	21	3	26	9	9	20	6
		14.4 (11.8–17.0)	7.8 (2.6–13.0)	2.1 (0.0–5.0)	23.9 (15.0–32.8)	4.3 (0.0–9.1)	23.4 (15.5–31.3)	12.7 (4.9–20.5)	17.3 (7.0–27.6)	21.3 (13.0–29.6)	15.0 (3.9–26.1)
3 years	n	49	2	0	9	1	17	3	4	11	2
		6.8 (5.0–8.6)	2.0 (0.0–4.8)	0 (NA)	10.2 (3.9–16.5)	1.4 (0.0–4.2)	15.3 (8.6–22.0)	4.2 (0.0–8.2)	7.7 (0.4–15.0)	11.7 (5.2–18.2)	5.0 (0.0–11.0)

95% CI: confidence interval; HNSCC: head and neck squamous cell carcinoma; NA: not applicable; R/M: recurrent and/or metastatic; UK: United Kingdom.
[a] Overall survival analyses exclude patients who participated in clinical trials.
[b] log rank test p = 7e-07.

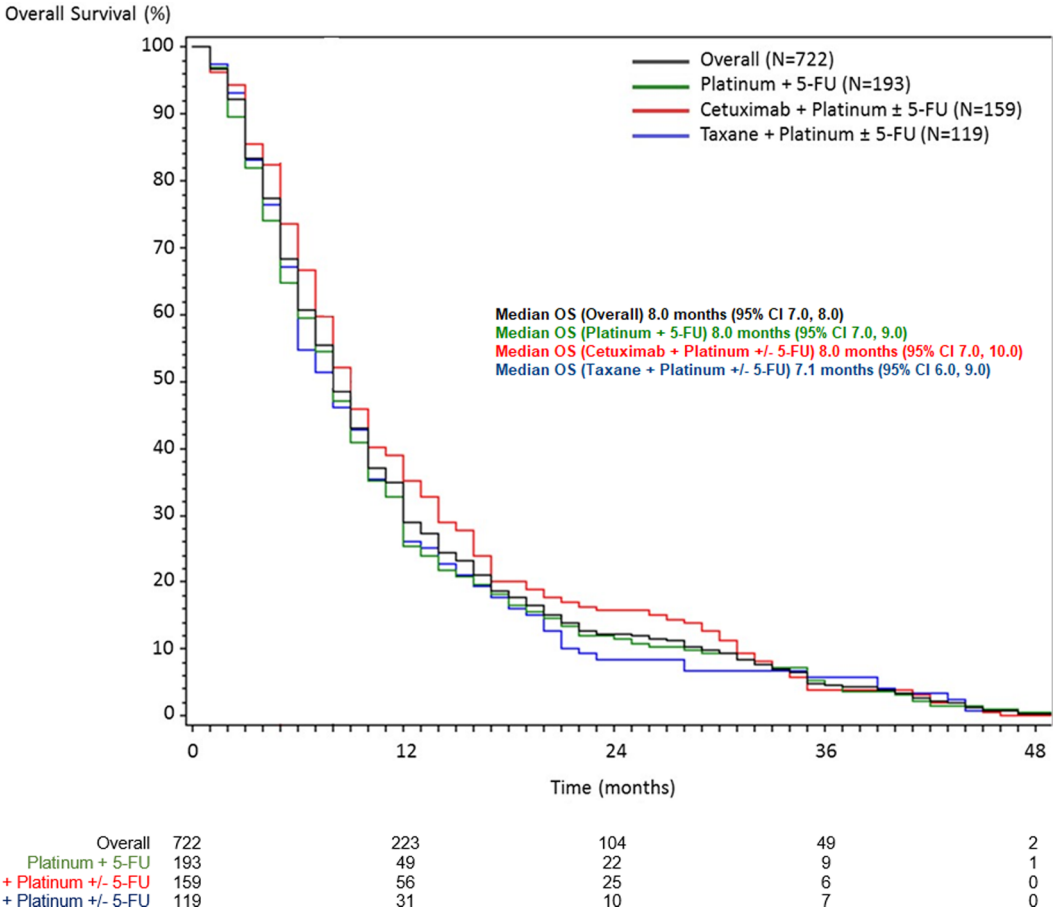

Fig. 3. Kaplan–Meier curves of overall survival for patients who initiated first-line systemic therapy for R/M HNSCC, overall and by most common regimens. Overall difference between groups: Log-rank test p = 0.2. Overall survival analyses excluded patients who participated in clinical trials. 5-FU: fluorouracil; 95% CI: 95% confidence interval; excl: excluding; OS: overall survival; R/M HNSCC: recurrent and/or metastatic head and neck squamous cell carcinoma.

among the main systemic therapies administered. As expected, a high ECOG performance status score (2 or 3–4) was an independent predictor of worse survival outcomes; otherwise, no notable differences in OS were observed according to patient demographics or disease characteristics such as recurrent versus distant metastatic disease status. These OS results are largely consistent with previous analyses from clinical trials and observational studies and underscore the medical need for novel therapies in R/M HNSCC [14]. Currently, there is a lack of head-to-head clinical trial comparisons of OS across commonly used platinum-based regimens, but trial results have indicated median OS ranging from 10.1 to 11.6 months with cetuximab and platinum combinations [10,18] as compared with median OS ranging from 6.8 to 8.1 months with taxane and platinum combinations [8,9,21,22].

Overall, the results of this study highlight that patients with R/M HNSCC had poor prognosis with use of available therapies during the study period. More recent trials of immune-oncology (I-O) therapies in R/M HNSCC patients who have progressed after platinum-based therapy have demonstrated clinically meaningful improvements in OS. In the CheckMate 141 trial, nivolumab demonstrated a 32% reduction in risk of death compared with investigator's choice therapy (HR: 0.68, 95% CI: 0.54– 0.86) [23]. In the KEYNOTE-40 trial, pembrolizumab was associated with a 20% reduction in risk of death over investigator's choice chemotherapy in patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy (HR: 0.80, 95% CI: 0.65–0.98) [24].

In the first-line R/M HNSCC setting, the Phase 3 KEYNOTE-048 trial demonstrated that pembrolizumab in combination with chemotherapy and as monotherapy in patients with programmed death-ligand 1 (PD-L1) biomarker expression significantly improved OS compared to standard treatment with cetuximab in combination with platinum-based chemotherapy. At the second interim analysis, pembrolizumab monotherapy improved OS versus standard treatment in patients whose tumours expressed PD-L1 with Combined Positive Score (CPS) ≥ 20 (HR: 0.61, 95% CI: 0.45–0.83) and in patients with CPS ≥ 1 (HR: 0.78, 95% CI: 0.64–0.96) [25]. Pembrolizumab in combination with chemotherapy improved OS versus standard treatment (HR: 0.77, 95% CI: 0.63–0.93) at the second interim analysis and in the CPS ≥ 20 population (HR: 0.60, 95% CI: 0.45–0.82) and CPS ≥ 1 population (HR: 0.65, 95% CI: 0.53–0.80) at the final analysis. Additional phase III trials of I-O therapies for the first-line treatment of R/M HNSCC are on-going, including the CheckMate 651 trial of nivolumab in combination with ipilimumab (NCT02741570) [26], and the KESTREL trial of durvalumab monotherapy and in combination with tremelimumab (NCT02551159) [27].

Limitations of this study include the retrospective nature of this chart review and potential for documentation bias if there were errors/omissions in patient medical records. However, these limitations should be balanced against the study's strengths, including the large sample of participating sites and representation from multiple countries. Nevertheless, the predominance of larger oncology practices that participated in this study may limit generalizability of the study findings with smaller clinical practices within each country. In addition, results among the countries participating in this study may not be representative of regional treatment practice among countries not included in this study. The study period predates the introduction of I-O therapies and the recent awareness of HPV infection as a major risk

factor for HNSCC. Future research should explore real-world treatment patterns after the introduction of I-O therapies, as well as prognostic factors of survival outcomes such as ECOG performance status, HPV status, and PD-L1 status, in patients with R/M HNSCC. As new therapeutic advancements emerge, the results of this study will continue to provide valuable historical benchmark information to inform the evolution of survival outcomes of patients with R/M HNSCC treated with systemic therapies in clinical practice.

Conclusions

Choice of systemic therapies for patients with R/M HNSCC varies substantially across countries in routine clinical practice. Prognosis remains poor with limited therapeutic options, underscoring the need for newer, more efficacious treatments. Despite differences in treatment patterns, OS is similar across countries and among main systemic therapies administered. Future research should explore the evolution of treatment patterns and survival outcomes in real-world practice after the recent clinical development of I-O therapies for the treatment of R/M HNSCC.

Declaration of Competing Interest

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Appendix A. Supplementary material

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