FIRST- AND SECOND-LINE TREATMENT PATTERNS IN RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK: A CHART REVIEW STUDY IN THREE COUNTRIES

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Background and Objectives

Squamous cell carcinoma of the head and neck (SCCHN) is a heterogeneous group of upper aerodigestive tract malignancies.

When diagnosed in early stages, SCCHN is highly curable with surgery and/or radiation therapy[1]. However, 10% to 20% of patients with early-stage disease develop recurrence. In patients diagnosed initially with more advanced disease, approximately 50% recur and/or become metastatic. The prognosis is poor in locally advanced and metastatic disease, with limited treatment options and a median survival time of less than 1 year.[2]

The ERBITUX in first-line Treatment of REcurrent or MEtastatic head and neck cancer (EXTREME) regimen was standard of care in many countries as first-line (1L) treatment prior to availability of immunotherapies for 1L treatment. EXTREME is a platinum-based regimen combined with 5-fluorouracil and cetuximab, followed by maintenance cetuximab. EXTREME has the best demonstrated median overall survival (OS) in patients with recurrent/metastatic (R/M) disease, however, OS is a median of only 10 months. [3] In 2017, nivolumab, a monoclonal programmed death-1 (PD-1) antibody, was approved in Europe for the treatment of patients recurrent/metastatic SCCHN with disease progression on or after a platinum-based therapy. [4]

The overall strategic objective of the current study was to describe the real-world treatment landscape and unmet need of patients with recurrent or metastatic SCCHN in 3 countries. This retrospective chart review study was conducted in France (FR), Germany (DE), and the United Kingdom (UK) to describe demographics, clinical characteristics, first (1L) and second line (2L) treatment patterns for patients with R/M SCCHN of the head and neck in the real-world setting.

Methods

- This real-world study was conducted retrospectively via chart review
- Physicians/institutions were recruited from a national database in each country, with physicians acting as study investigators
- Data was collected on each patient from their index data via medical record review for up to 24 months
- The study examined patients newly diagnosed with R/M SCCHN between 01-June-2017 and 01-June-2018. For the purposes of this study, R/M SCCHN is defined as locoregional recurrence (recurrence in the same region of the body), metastatic recurrence, or newly diagnosed metastatic disease. Included criteria were the following:
  1. Adults 18 years or older
  2. Diagnosis of histologically confirmed R/M SCCHN, from any of the following primary sites only: oral cavity, oropharynx, hypopharynx, and larynx between 01-Jun-2017 and 31-June-2018.
  3. Prescribed 1L treatment for R/M SCCHN
  4. Treatment history available for medical chart abstraction from the date of diagnosis until death or the end of the study in living patients
  5. Have available for review one month of follow-up data post initiation of 1L R/M SCCHN therapy
  6. Informed consent form (ICF) signature/collection of living patients, if required by country regulation and local ethics committees
- Patients were excluded from if they met any of the following criteria:
  1. Were enrolled in a cancer treatment-related clinical trial since the diagnosis of R/M SCCHN
  2. Recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary site, squamous cell carcinoma that originated from the skin and salivary gland, or non-squamous histology (e.g., mucosal melanoma)
- Analyses were descriptive in nature. Treatment characteristics were reported descriptively to understand treatment selection. Categorical measures such as agents (mono and combination therapy) prescribed for 1L, and in subsequent therapy lines were described using proportions. Continuous measures including dose, duration of therapy were reported as either mean (SD), and/or median, and range.

Results

- Twenty-four oncologists contributed data on 101 R/M SCCHN patients (FR: N = 35, DE: N = 31, and UK: N = 35)
- Patients were a mean (SD) age of 63 (9) years, and 83% were current or former tobacco users
- 72.3% had documented HPV testing, of which 49% were positive and most (69.3%) were regular consumers of alcohol

Table 1. Demographics

	FR n = 35	DE n = 31	UK n = 35	Total N = 101
Age at R/M diagnosis				
Median (range)	60 (36, 82)	67 (47, 81)	63 (43, 83)	63 (36, 83)
Primary Health Insurance, n (%)				
National/public insurance	35 (100.0)	31 (100.0)	35 (100.0)	101 (100.0)
Private insurance	0 (0)	0 (0)	0 (0)	0 (0)
Patient- out-of-pocket	0 (0)	0 (0)	0 (0)	0 (0)
Tobacco use, n (%)	33 (94.3)	30 (96.8)	21 (60.0)	84 (83.2)
Current	14 (42.4)	21 (70.0)	7 (33.3)	42 (50.0)
Former	19 (57.6)	9 (30.0)	14 (66.7)	42 (50.0)
Alcohol use, n (%)	26 (74.3)	20 (64.5)	24 (68.6)	70 (69.3)
Human papilloma virus tested, n (%)	22 (62.9)	29 (93.5)	22 (62.9)	73 (72.3)
Positive	8 (36.4)	16(55.2)	12 (54.5)	36 (49.3)
Negative	14 (63.6)	13 (44.8)	10 (45.5)	37 (50.7)

- Most patients (>80%) were stage IVc at the time of R/M SCCHN diagnosis
- At 1L treatment initiation, 66% were platinum naïve/de novo, and 18% were platinum sensitive, with the remainder platinum ineligible/refractory.
- Only 25% of patients were tested for PD-L1 expression prior to 1L therapy initiation. Of these 77% had scores > 1%
- Most patients (75%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Patients were followed a median of 29.7 weeks after R/M diagnosis to determine treatments administered (Table 2)

Table 2. Disease characteristics at R/M SCCHN diagnosis

	FR n = 35	DE n = 31	UK n = 35	Total N = 101
Duration of follow-up (weeks) since diagnosis, median (range)	33.7 (7, 43.0)	24.3 (3.7, 40.6)	26.7 (2, 42.0)	29.7 (2, 43.0)
Primary site, n (%)				
Oral cavity	5 (14.3)	3 (9.7)	9 (25.7)	17 (16.8)
Oropharynx	22 (62.9)	12 (38.7)	18 (51.4)	52 (51.5)
Hypopharynx	4 (11.4)	13 (41.9)	6 (17.1)	23 (22.8)
Larynx	4 (11.4)	3 (9.7)	2 (5.7)	9 (8.9)
AJCC stage at R/M diagnosis, n (%)				
II	1 (2.9)	0 (0.0)	0 (0.0)	1 (1.0)
III	3 (8.6)	0 (0.0)	1 (2.9)	4 (4.0)
IVa	3 (8.6)	1 (3.2)	8 (22.9)	12 (11.9)
IVb	1 (2.9)	1 (3.2)	1 (2.9)	3 (3.0)
IVc	27 (77.1)	29 (93.5)	25 (71.4)	81 (80.2)
Metastases at R/M diagnosis, n (%)	28 (80.0)	29 (93.5)	25 (71.4)	82 (81.2)
Site(s) of metastasis				
Lymph nodes	14 (50.0)	22 (75.9)	9 (36.0)	45 (54.9)
Distant skin	1 (3.6)	1 (3.4)	1 (4.0)	3 (3.7)
Lung	28 (100.0)	26 (89.7)	21 (84.0)	75 (91.5)
Bone	7 (25.0)	8 (27.6)	7 (28.0)	22 (26.8)
Liver	3 (10.7)	4 (13.8)	0 (0.0)	7 (8.5)
ECOG performance status at R/M diagnosis, n (%)				
0	3 (8.6)	2 (6.5)	3 (8.6)	8 (7.9)
1	21 (60.0)	17 (54.8)	30 (85.7)	68 (67.3)
2	11 (31.4)	10 (32.3)	1 (2.9)	22 (21.8)
3	0 (0.0)	2 (6.5)	0 (0.0)	2 (2.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	1(2.9)	1 (1.0)
First diagnosed early stage	11 (31.4)	6 (19.4)	29 (82.9)	46 (45.5)
Received platinum prior to R/M disease, n (%)	8 (72.7)	5 (83.3%)	16 (55.2)	29 (63.0)
Physician determined platinum exposure status, n (%)				
Platinum naïve or de novo metastatic	25 (71.4)	24 (77.4)	18 (51.4)	67 (66.3)
Platinum Sensitive	7 (20.0)	19 (3.2)	10 (28.6)	18 (17.8)
Platinum Refractory	2 (5.7)	3 (9.7)	6 (17.1)	11 (10.9)
Platinum ineligible	1 (2.9)	3 (9.7)	1 (2.9)	5 (5.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PD-L1 tested, n (%)	2 (5.7)	13 (41.9)	11 (31.4)	26 (25.7)
Negative	1 (50.0)	4 (30.8)	1 (9.1)	6 (23.1)
Positive, n (%)	1 (50.0)	9 (69.2)	10 (90.9)	20 (76.9)
Combined positive score, median (range)	-	22 (20, 50)	-	25 (20, 50)
Tumor proportion score, median (range)	-	50 (5, 55)	30 (5,75)	30 (5,75)

- Systemic therapy was initiated within 4 weeks of initial diagnosis and was administered for a median of 21 weeks
- In the 1L therapy, an EXTREME regimen (Cetuximab + Cisplatin or Carboplatin + 5-Fluorouracil) was administered to 38% of the total
- 41% received other platinum-based therapy with/without a taxane, 11% received nivolumab as a single agent, 9% received other cetuximab-based therapy, and 1% received pembrolizumab
- Radiotherapy was also administered in the first line in 15% of patients

Table 3. First line therapy for R/M SCCHN

	FR n = 35	DE n = 31	UK n = 35	Total N = 101
Time (weeks) to therapy initiation, median (range)	4 (0,105)	2 (0, 12)	5 (1, 110)	4 (0, 110)
Duration of therapy (weeks) median (range)	28 (0,144)	21 (4, 109)	17 (1, 38)	21 (1, 144)
Regimen, n (%)				
EXTREME (Cetuximab+Cisplatin+5-Fluorouracil), n (%)	14 (40.0)	14 (45.2)	0 (0.0)	28 (27.7)
Cycles, median (range)	6 (6,39)	6 (6, 6)	-	6 (6, 39)
EXTREME (Cetuximab+Carboplatin+5-Fluorouracil), n (%)	8 (22.9)	3 (9.7)	0 (0.0)	11 (10.9)
Cycles, median (range)	7.5 (6,24)	6 (4, 6)	-	6 (4, 24)
Other doublet, triplet, single agent therapies, n (%)				
Platinum + Taxane	6 (17.1)	2 (6.5)	10 (28.6)	18 (17.8)
Platinum+5FU	3 (8.6)	0 (0.0)	13 (37.1)	16 (15.8)
Nivolumab	1 (2.9)	4 (12.9)	6 (17.1)	11 (10.9)
Platinum + Cetuximab + Capecitabine	0 (0.0)	5 (16.1)	0 (0.0)	5 (5.0)
Platinum + Capecitabine	0 (0.0)	0 (0.0)	5 (14.3)	5 (5.0)
Platinum monotherapy	0 (0.0)	0 (0.0)	1 (2.9)	1 (1.0)
Taxane monotherapy	0 (0.0)	1 (3.2)	0 (0.0)	1 (1.0)
Cetuximab monotherapy	1 (2.9)	0 (0.0)	0 (0.0)	1 (1.0)
Platinum + Taxane + 5FU	1 (2.9)	0 (0.0)	0 (0.0)	1 (1.0)
Cetuximab + Taxane	0 (0.0)	1 (3.2)	0 (0.0)	1 (1.0)
Platinum + Taxane + Cetuximab	1 (2.9)	0 (0.0)	0 (0.0)	1 (1.0)
Pembrolizumab	0 (0.0)	1 (3.2)	0 (0.0)	1 (1.0)

- Of 1L treated patients, 63% proceeded on to a second line of therapy (2L)
- In 2L, there was a large uptake of immunotherapy, with 78% of 2L treated patients receiving nivolumab and 3% receiving pembrolizumab (Table 4).

Table 4. Second line therapy for R/M SCCHN

	FR n = 35	DE n = `31	UK n = 35	Total N = 101
Received a 2L, n (%)	27 (77.1)	22 (70.1)	15 (42.9)	64 (63.3)
ECOG performance status at therapy initiation, n (%)				
0	0 (0.0)	2 (9.1)	0 (0.0)	2 (3.3)
1	17 (70.8)	3 (13.6)	15 (100)	35 (57.4)
2	9 (33.3)	14 (63.6)	0 (0.0)	23 (35.9)
3	1 (4.2)	3 (13.6)	0 (0.0)	4 (6.6)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Regimen, n (%)				
Nivolumab	22 (81.5)	15 (68.2)	13 (86.7)	50 (78.1)
Paclitaxel	2 (7.4)	0 (0.0)	0 (0.0)	2 (3.1)
Docetaxel	0 (0.0)	2 (9.1)	0 (0.0)	2 (3.1)
Methotrexate	2 (7.2)	0 (0.0)	0 (0.0)	2 (3.1)
Pembrolizumab	0 (0.0)	2 (9.1)	0 (0.0)	2 (3.1)
Carboplatin + Capecitabine	0 (0.0)	0 (0.0)	1 (6.7)	1 (1.6)
Carboplatin + Cetuximab + Paclitaxel	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.6)
Carboplatin	0 (0.0)	0 (0.0)	1 (6.7)	1 (1.6)
Cetuximab	1 (3.7)	0 (0.0)	0 (0.0)	1 (1.6)
Cetuximab + Paclitaxel	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.6)
Nimotuzumab	0 (0.0)	1 (4.5)	0 (0.0)	1 (1.6)

- Only 13% of the total cohort received a third line of therapy (3L)
- In 3L, immunotherapy continued to be the most frequently utilized therapy with 35.7% receiving nivolumab (Table 5)

Table 5. Third line therapy for R/M SCCHN

	FR n = 35	DE n = 31	UK n = 35	Total N = 101
Received a 3L, n (%)	6 (17.1)	6 (19.4)	2 (5.7)	14 (13.8)
ECOG performance status at therapy initiation, n (%)				
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	2 (33.3)	4 (66.7)	2 (100.0)	4 (28.6)
2	4 (66.7)	2 (33.3)	0 (0.0)	8 (57.1)
3	0 (0.0)	2 (33.3)	0 (0.0)	2 (14.3)
Regimen, n (%)				
Nivolumab	2 (33.3)	2 (33.3)	1 (50.0)	5 (35.7)
Paclitaxel	2 (33.3)	1 (16.7)	0 (0.0)	3 (21.4)
Carboplatin + Capecitabine	0 (0.0)	0 (0.0)	1 (50.0)	1 (7.1)
Carboplatin	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)
Carboplatin + Cetuximab + Paclitaxel	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)
Gemcitabine	0 (0.0)	1 (16.7)	0 (0.0)	1 (7.1)
Methotrexate	1 (16.7)	0 (0.0)	0 (0.0)	1 (7.1)
Vinorelbine	1 (16.7)	0 (0.0)	0 (0.0)	1 (7.1)

Limitations

- Treatment patterns represent only the practices of physicians who have agreed to participate, and may vary from non-responding physicians
- Study results are generalizable only to the R/M SCCHN patients who were diagnosed during the study period, so extrapolation to other R/M SCCHN diagnosis periods will be limited
- Limitations to retrospective chart review research include incomplete or missing documentation in patient charts

Conclusions

- During this time, platinum-based chemotherapy – primarily EXTREME regimens, accounted for the majority of 1L R/M SCCHN treatment in each country studied
- There was some early uptake of immunotherapy as 1L treatment, primarily nivolumab, in 11% of patients
- In line with the approval of nivolumab for use in the post-platinum setting, immunotherapies demonstrated high uptake in both the second and third lines of therapy, however few patients progressed to 3L therapy during the timeframe of this study

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