Choosing the Right Treatment Option for the Right R/M HNSCC Patient: Should We Adhere to PFE for First-Line Therapy?

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Background: The landmark EXTREME trial established cisplatin, 5-fluorouracil and cetuximab (PFE) as first-line chemotherapy (1L-ChT) for recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). We were interested in outcome differences of R/M HNSCC in 1L-ChT and factors influencing outcome in certain subgroups, especially patients receiving PFE, and the value of PFE compared to other 1L-ChT regimens to provide real world evidence (RWE).

Methods: For this retrospective monocentric study, 124 R/M HNSCC patients without curative surgical or radiotherapy options receiving at least one cycle of 1L-ChT were eligible. We analyzed their outcome using Kaplan-Meier plot and Cox regression to identify predictors for prolonged survival.

Results: Subgroups benefiting significantly from PFE were patients suffering from an index HNSCC outside the oropharynx. The PFE regimen proved to be superior to all other 1L-ChT regimens in clinical routine. Significant outcome differences between PFE treatment within or outside controlled trials were not seen.

Conclusion: This retrospective analysis provides RWE for factors linked to improved outcome. Subgroup analyses highlight the lasting value of PFE among the growing spectrum of 1L-ChT. Importantly, fit smokers with high level alcohol consumption benefited from PFE; considering the patient’s lifestyle factors, PFE should not be ignored in decision-making.

Keywords: head and neck cancer, head and neck squamous cell carcinoma, palliative chemotherapy, first-line therapy, recurrent/metastatic head and neck squamous cell carcinoma, multivariate Cox proportional hazard regression, outcome research, p16+ oropharyngeal cancer

INTRODUCTION

Squamous cell carcinoma of the head and neck (HNSCC) is an entity with growing importance, in clinical but also in research settings. According to the EUROCASE-5 trial (1), there were 238,608 cases recorded from 1999 to 2007 in Europe. Five-years overall survival (OS) for all HNSCC entities was 42.2% (95% confidence interval, 95% CI: 41.5–42.9%), ranging from 25.5% for oropharynx to
61.1% for larynx cancer. At initial diagnosis of HNSCC, 54.0% of all HNSCC were classified as UICC IV due to regional or distant metastasis. According to the NCCN Guidelines for Head and Neck Cancer (2018) (2), curative therapy is considered appropriate until UICC IVB, whereas detection of distant metastasis (M1 defining stage IVB) means loss of curative treatment options advising switch to systemic treatment and palliative care (with the only exception of resectable solitary M1). The same applies to recurrent locally advanced HNSCC after radiotherapy without resectability. While there are certain therapy algorithms for HNSCC in curable stages, only a few approved options for first-line chemotherapy and other systemic first-line therapies (altogether summarized under the abbreviation 1L-ChT) are available in case of R/M HNSCC following the NCCN guidelines from 2018. Since publication of the landmark EXTREME trial (3), treatment with up to six cycles of cisplatin, 5-fluorouracil and cetuximab (PFE), became standard 1L-ChT in R/M HNSCC. After the KEYNOTE-048 trial (4), this standard was recommended being replaced by a stratified 1L-ChT according to programmed death ligand 1 (PD-L1) expression assessed by combined positivity score (CPS). According to immune histopathology, PFE remains a standard of care for patients with a CPS <1, whereas patients with a CPS ≥20 should be treated with pembrolizumab mono and patients with CPS ≥1 and <20 should receive cisplatin/5-fluorouracil/pembrolizumab (5).

Prior trials often used PFE as control arm (6–9), but new 1L-ChT options superior to PFE have not yet been identified or been established based on lower toxicity. In the course of precision medicine and decision-making for stratified therapy regimens leading to a more individualized or even personalized treatment, new therapy options became eligible for specific groups of patients as second-line therapy (2L-ChT) or 1L-ChT for patients not eligible for PFE (frail patients and/or insufficient kidney or liver function). We were interested in the outcome of PFE versus the other 1L-ChT and predictors for good outcome after PFE therapy and consequentially aimed on defining groups of patients that still benefit from PFE as part of a widened spectrum of therapy options.

MATERIALS AND METHODS

Study Population and Patient Samples

Eligible for the study were patients with pathological confirmed R/M HNSCC treated in the University Hospital Leipzig with data recorded in the Microsoft Access® tumor database (TDB) of the ENT department, comprising data of all patients diagnosed with a malignant disease since 1990, and data taken from the hospital’s electronic health records. Figure 1 shows the selection of patients for analyses according to the CONSORT recommendations. Among 346 R/M HNSCC patients presented to the multidisciplinary tumor board (MDTB; see below), 130 R/M HNSCC without curative treatment option were subjected to systemic therapy and received at least one cycle 1L-ChT. To prevent any inconsistency based on minor R/M HNSCC subgroups, patients with primary HNSCC localized in the nasopharynx (ICD10-C11), or nasal cavity (ICD-10-C30 and C31) were excluded from the present analyses resulting in a sample of 124 patients (Table 1). Pathological reports were available for all 124 patients. All resected specimen underwent pathological examination, and hematoxylin–eosin (HE) staining revealed squamous cell carcinoma histology. A sub-cohort of patients participated in a study approved by our Ethics Committee (votes 201-10-12072010 and 202-10-12072010).

Clinical Work-Up for R/M HNSCC

As recommended (2), clinical work-up for R/M HNSCC included clinical examination, ultrasound sonography, contrast-enhanced CT for head and neck and thorax, eventually PET-CT/PET-MRI, followed by a panendoscopy accompanied by taking biopsies before decision-making for treatment in the MDTB. Patient and tumor characteristics, diagnostic procedures, treatment and clinical follow-up were recorded in our Microsoft Access® tumor database (TDB) and OncoFlow® (10, 11).

CT and PET-CT Imaging

According to clinical guidelines, all patients received a head and neck and a CT scan of the chest during staging. In 2006, a PET-CT became available. An experienced board-certified nuclear-medicine physician and a radiologist analyzed PET-CTs. Sites of tumor involvement were identified visually by enhanced, non-physiologically [18F]-FDG uptake.

Decision-Making Process in the MDTB

The decision-making process in the MDTB followed ASCO and NCCN guidelines (2) and principles published earlier (10–13). Briefly, a radiologist and a nuclear medicine specialist presented all radiological imaging. The MDTB consisting of head and neck and maxillofacial surgeons, a pathologist, an oncologist, a radiation oncologist, and other clinical staff involved in the treatment of head and neck cancer patients discussed the results of diagnostic procedures. Considering the general health and comorbidity of the patient the pre-therapeutic MDTB regarding the guidelines (2) recommended the type of 1L-ChT according to inclusion criteria of open randomized controlled trials (RCTs) or according to fitness for current therapy standards, PFE or other 1L-ChT. For the subgroup of patients receiving 1L-ChT other than PFE, the most relevant RCTs were CeF CID (NCT02268695), RESGEX (NCT02052960) and ADVANTAGE (NCT00705016) (6–8).

Immunohistochemistry for P16 and HPV Genotyping

Before decision-making in MDTB and starting therapy, biopsies were taken under general anesthesia and underwent pathological examination. Pathological reports were available for all 124 patients. Besides hematoxylin–eosin (HE) staining, molecular analyses of p16 by immunohistochemistry utilizing the CI Nte c kit (Roche) were done in oropharynx squamous cell carcinomas (OPSCC) of RCT participants and performed in OPSCC routinely since 2013. Double-stained, p16-positive/Ki67-
positive cells or a cutoff level of ≥70% p16-positive OPSCC cells were considered p16+. DNA of p16+ OPSCC was extracted and analyzed for high-risk human papillomavirus utilizing the INNO-LiPA HPV Genotyping Extra kit (Innogenetics) as described earlier (14).

Statistical Analysis
Overall survival (OS) was the time from initial diagnosis of HNSCC to cancer-related (CRD) or non-cancer-related death (NCRD) censoring patients alive at the end of follow-up (data base lock: 08.02.2021). Survival after 1L-ChT (OS_{1L-ChT}) was the time from diagnosis that led to 1L-ChT until death by any cause, censoring patients alive at the end of follow-up or data base lock. We performed a statistical analysis in SPSS 25°. We used Chi-square tests, paired and heteroscedastic t-tests, receiver-operating characteristics (ROC) curves and Fisher’s exact test to investigate the association of clinical characteristics and the outcome of patients receiving PFE or other 1L-ChT. Kaplan-Meier cumulative survival plots and log-rank tests were used to investigate the impact of particular characteristics on OS_{1L-ChT}. We analyzed all parameters achieving P <0.2 in univariate models in multivariate Cox proportional hazard regression (MCR) models. After checking collinearity, independent predictors for the OS_{1L-ChT} have been identified in MCR applying the step-wise-forward method. For internal validation and to reduce over-optimism based on the effects of random sampling errors, we utilized bootstrapping (1,000 iterations). We considered P <0.05 being significant.
| Characteristics                          | Number of Patients (%) |
|-----------------------------------------|------------------------|
|                                           | Total | N = 124 | PFE | N = 77 | other 1L-ChT | N = 47 | P-value* |
| Age at initial diagnosis, years          |       |         |     |        |           |        |          |
| <50                                      | 29 (23.4) | 18 (20.8) | 13 (27.7) | 0.272 |
| 50–60                                    | 48 (38.7) | 35 (45.5) | 13 (27.7) |       |
| 60–70                                    | 40 (32.3) | 22 (28.6) | 18 (38.3) |       |
| >70                                      | 7 (5.6) | 4 (5.2) | 3 (6.4) |       |
| median (IQR)                             | 56.7 (50.2–63.7) | 56.6 (50.2–63.1) | 58.4 (49.4–64.1) | 0.592 |
| Age at 1L-ChT, years                     |       |         |     |        |           |        |          |
| <50                                      | 19 (15.3) | 11 (14.3) | 8 (17.0) | 0.199 |
| 50–59                                    | 50 (40.3) | 36 (46.8) | 14 (29.8) |       |
| 60–69                                    | 45 (36.3) | 26 (33.8) | 19 (40.4) |       |
| >70                                      | 10 (8.1) | 4 (5.2) | 6 (12.8) |       |
| median (IQR)                             | 58.8 (53.2–65.2) | 58.1 (53.1–65.5) | 61.0 (54.1–66.4) | 0.279 |
| ECOG                                     |       |         |     |        |           |        |          |
| 0–1                                      | 123 (99.2) | 77 (100.0) | 46 (97.9) | 0.199 |
| 2                                        | 1 (0.8) | 0 | 1 (2.1) |       |
| Sex                                      |       |         |     |        |           |        |          |
| Male                                     | 105 (84.7) | 67 (83.8) | 38 (80.9) | 0.355 |
| Female                                   | 19 (15.3) | 10 (13.0) | 9 (19.1) |       |
| Alcohol, status                          |       |         |     |        |           |        |          |
| Missing                                  | 7 (5.6) | 5 (6.5) | 2 (4.3) | 0.991 |
| Never                                    | 15 (12.1) | 9 (11.7) | 6 (12.8) |       |
| Former                                   | 13 (10.5) | 8 (10.4) | 5 (10.6) |       |
| Current                                  | 89 (71.8) | 55 (71.4) | 34 (72.3) |       |
| Alcohol, (g/d)                           |       |         |     |        |           |        |          |
| Missing                                  | 7 (5.6) | 5 (6.5) | 2 (4.3) | 0.999 |
| 0–30 g/d                                 | 15 (12.8) | 9 (11.7) | 6 (12.8) |       |
| >30 g/d                                  | 36 (30.8) | 22 (28.6) | 14 (29.8) |       |
| 30–60 g/d                                | 29 (24.8) | 18 (23.4) | 11 (23.4) |       |
| >60 g/d                                  | 37 (31.6) | 23 (29.9) | 14 (29.8) |       |
| Tobacco smoking, status                  |       |         |     |        |           |        |          |
| Missing                                  | 5 (4.0) | 4 (5.2) | 1 (2.1) | 0.490 |
| Never                                    | 13 (10.5) | 6 (7.8) | 7 (14.9) |       |
| Former                                   | 24 (19.4) | 15 (19.5) | 9 (19.1) |       |
| Current                                  | 82 (66.1) | 52 (67.5) | 30 (63.8) |       |
| Tobacco smoking history, pack years      |       |         |     |        |           |        |          |
| Missing                                  | 7 (5.6) | 4 (5.2) | 3 (6.4) | 0.489 |
| 0–30 psy                                 | 59 (47.6) | 35 (45.5) | 24 (51.1) |       |
| >30 psy                                  | 58 (48.4) | 38 (49.4) | 20 (40.5) |       |
| Localization                             |       |         |     |        |           |        |          |
| L-/HPSCC                                 | 31 (25.0) | 17 (22.1) | 14 (29.8) | 0.053 |
| OSCC                                     | 45 (36.3) | 23 (29.9) | 22 (46.8) |       |
| OPSCC                                    | 42 (33.9) | 32 (41.6) | 10 (21.3) |       |
| other                                    | 6 (4.6) | 5 (6.5) | 1 (2.1) |       |
| p16 status                               |       |         |     |        |           |        |          |
| p16 positive                             | 17 (13.7) | 13 (16.9) | 4 (8.5) | 0.188 |
| p16 negative                             | 107 (86.3) | 64 (83.1) | 43 (91.5) |       |
| HPV status                               |       |         |     |        |           |        |          |
| HPV positive                             | 15 (12.1) | 12 (15.6) | 3 (6.4) | 0.127 |
| HPV negative                             | 109 (87.9) | 65 (84.4) | 44 (93.6) |       |
| Initial UICC                              |       |         |     |        |           |        |          |
| Missing                                  | 1 (0.8) | 1 (1.3) | – | 0.227 |
| I                                        | 14 (11.3) | 7 (9.1) | 7 (14.9) |       |
| II                                       | 11 (8.9) | 4 (5.2) | 7 (14.9) |       |
| III                                      | 12 (9.7) | 6 (7.8) | 6 (12.8) |       |
| IVA                                      | 52 (41.9) | 33 (42.9) | 19 (40.4) |       |
| IVB                                      | 15 (12.1) | 12 (15.6) | 3 (6.4) |       |
| IVC                                      | 19 (15.3) | 14 (18.2) | 5 (10.6) |       |
| Duration of disease, months              |       |         |     |        |           |        |          |
| median (IQR)                             | 15.1 (7.2–33.1) | 10.7 (6.4–30.4) | 21.8 (9.8–37.3) | 0.186 |
| Extent of disease                        |       |         |     |        |           |        |          |
| LRR                                      | 39 (31.5) | 19 (24.7) | 20 (42.6) | 0.038 |
| MT                                       | 85 (68.5) | 58 (75.3) | 27 (57.4) |       |
| Previous treatments                      |       |         |     |        |           |        |          |
| None                                     | 10 (8.1) | 9 (11.7) | 1 (2.1) | 0.104 |
| One                                      | 66 (53.2) | 44 (57.1) | 22 (46.8) |       |
| Two                                      | 40 (32.3) | 19 (24.7) | 21 (44.7) |       |
| Three                                    | 6 (4.8) | 4 (5.2) | 2 (4.3) |       |
| Four                                     | 2 (1.6) | 1 (1.3) | 1 (2.1) |       |
| Type of prior treatment                  |       |         |     |        |           |        |          |
| No prior ChT                              | 56 (45.2) | 36 (46.8) | 20 (42.6) | 0.652 |
| • none                                   | 10 (17.9) | 9 (25.0) | 1 (5.0) |       |
| • PORT                                   | 28 (50.0) | 20 (55.6) | 8 (20.0) |       |
| • RT                                     | 8 (14.3) | 4 (11.1) | 4 (20.0) |       |

(Continued)
TABLE 1 | Continued

| Characteristics | Number of Patients (%) |
|-----------------|------------------------|
|                 | Total N = 124 | PFE N = 77 | other 1L-ChT N = 47 | P-value* |
| OP              | 10 (17.9)     | 3 (8.3)    | 7 (35.0)           |          |
| Prior ChT       | 68 (54.8)     | 41 (52.2)  | 27 (57.4)          |          |
| CRT             | 14 (20.6)     | 9 (22.0)   | 5 (18.5)           |          |
| PORCT           | 54 (79.4)     | 32 (78.0)  | 22 (81.5)          |          |

RCT enrollment

| Prior cisplatin | 1L trial | 2L trial | No | Yes |
|-----------------|----------|----------|----|-----|
| 56 (45.2)       | 43 (55.8)| 13 (27.7)|   |    |

Other therapies

| OS status | alive | NCRD | CRD |
|-----------|-------|------|-----|
| 3 (2.4)   | 2 (2.6)| 2 (2.6)| |

Further analysis:

- *P value from Pearson’s Chi-square (χ²) tests. PFE, Cisplatin/5-fluorouracil/cetuximab—EXTREME regimen; QR, Interquartile range; 1L-ChT, first-line chemotherapy; py, pack years; L-/HPSSC, laryngeal/hypopharyngeal squamous cell carcinoma; OS SCC, oral squamous cell carcinomas; OPSCC, oropharyngeal squamous cell carcinoma; UICC, tumor stages according to the Union International Contre le Cancer; LRR, locoregional recurrence; M1, distant metastasis; ChT, chemotherapy; PORT, postoperative radiation; RT, primary radiation; OP, surgical therapy; CRT, combined chemoradio-therapy; PORCT, postoperative chemoradio-therapy; RCT, randomized controlled trial; 1L trial, first-line controlled trial; 2L trial, second-line controlled trial; 2L-/3L-ChT, second-third-line chemotherapy; OS, Overall Survival; NCRD, Non-cancer-related death; CRD, cancer-related death.

P values from Pearson’s Chi-square tests < 0.05 are in bold.

RESULTS

Patients’ Characteristics

Of 124 R/M HNSCC patients, 77 received PFE (Table 1). The frequency of PFE was numerically higher in patients younger than 60 years (68.1% vs. 54.5%; X² = 2.4, P = 0.122). Other 1L-ChT regimens applied to 47 patients not receiving PFE were PFE plus docetaxel (TPFE; n = 15) according to the CeFCGID trial (6) and other cisplatin-based regimens (n = 21 in total, every subgroup n < 5); 11/47 patients received in 1L-ChT docetaxel plus cetuximab (n = 3) or a monotherapy with methotrexate (n = 1) or immunotherapy with either cetuximab (n = 3) or nivolumab (n = 4). ECOG performance status in subgroups receiving PFE or other 1L-ChT did not differ significantly (Table 1).

Patients’ Clinical Course Before and After 1L-ChT

The median time from the initial diagnosis of HNSCC to 1L-ChT was 15.1 months for the total cohort. There was no significant correlation between the time to 1L-ChT and the lifestyle-associated risk factors or patients’ age. Patients receiving surgery followed by postoperative radio-chemotherapy (PORCT; n = 52) had a prolonged median time from curative treatment to 1L-ChT of 30.6 months (95% CI: 21.5–40.2) compared to 10.4 months (95% CI: 0.3–20.4) of patients with other types of curative treatment (radiation, surgery, surgery followed by postoperative radiation; n = 62). Median time from initial diagnosis of HNSCC to death/lost to follow-up (OS) was 25.5 months; median time from start of 1L-ChT to death/lost to follow up (mOS1L-ChT) was 8.4 months; 21/124 (16.9%) died within 3 months after starting 1L-ChT (14.3% after PFE, 21.3% after other 1L-ChT regimen). Of 124 patients progressing after 1L-ChT, 27/124 (21.8%) were fit enough to receive either a 2L-ChT or further therapies, 21/77 (27.3%) after PFE, 6/47 (12.8%) after other cisplatin-based regimen. None of the patients treated without cisplatin-based 1L-ChT including all 1L-immunotherapies were fit enough for any 2L-ChT.

OS1L-ChT After PFE Compared to Other 1L-ChT Regimen

In Kaplan–Meier plots utilizing log-rank tests, a difference of 3 months in mOS1L-ChT was identified between patients being treated with PFE and those being treated with other 1L-ChT (mOS1L-ChT 95% CI): 9.8 months (8.1–11.5) vs. 6.8 months (3.9–9.7); P = 0.066; Figure 2A).

OS1L-ChT after PFE in RCT Versus Clinical Routine

In the group of patients not enrolled in first-line RCT (“real world patients”), a significant benefit from PFE was noticed [mOS1L-ChT (95%CI): 9.3 (3.3–15.3) months vs. 4.1 (1.8–6.4) months, P = 0.016; Figures 2B and 4]. In RCT, other 1L-ChT combined vs. PFE showed a similar OS [mOS1L-ChT (95%CI): 7.0 (3.0–11.0) months vs. 9.8 (8.7–11.9) months; P = 0.701; Figure 2C]. OS1L-ChT after PFE outside controlled trials [mOS1L-ChT (95%CI): 9.3 (3.3–11.3) months] was not significantly different from mOS1L-ChT in RCTs [9.8 (8.7–10.9) months; P = 0.728; Figure 2D]. Of seven long-term survivors within the subgroup of patients treated with PFE in clinical routine (Figure 2D), 4/7 were current drinkers, only 1/7 drank >30 g/d alcohol, and 5/7 were current smokers. The median age (56.9 years) was comparable to the median age in the total PFE subgroup (56.6 years, Table 1). Five of them (71.4%) had been treated with cisplatin prior to PFE, compared to 46.8% in the total PFE cohort (Table 1).
OS1L-ChT After Other 1L-ChT Regimen

In this subgroup, the enrollment in RCT was predictive for improved OS1L-ChT only in these 34 vs. 13 patients (mOS1L-ChT (95%CI): 9.3 (4.7–13.9) vs. 4.1 (1.8–6.4); P = 0.013). The small number of patients with other 1L-ChT (n = 47), however, did not allow to identify further predictors for OS1L-ChT in this subgroup.

Predictive Factors for OS1L-ChT After PFE

Kaplan–Meier plots showed the number of pretreatments to be important for therapy outcome in general. Patients initially diagnosed in the metastatic or very advanced stage or after two or more pretreatments had significantly shorter OS1L-ChT than those receiving 1L-ChT after one pretreatment (mOS1L-ChT (95% CI): 6.8 (4.2–9.4) vs. 9.9 (7.6–12.2) months; P = 0.038). Stratified by PFE vs. other 1L-ChT, there was still a statistical trend for this finding (Figure 4). Patients progressing after cisplatin-based ChT treated with PFE 1L-ChT had prolonged mOS1L-ChT (9.9 vs. 6.8 months; P = 0.082; Figure 4). Cisplatin-based ChT as part of multimodal pretreatment in the curative setting was equally predictive for OS1L-ChT in univariate Cox regression model.

Kaplan–Meier analysis linked outcome and age: the mOS1L-ChT in the age groups (a) ≤49 years (7.6 months, 95%CI: 0.2–15.0), (b) 50–59 years (9.3 months, 95%CI: 7.6–11.0), and (c) ≥60 years (6.8 months, 95%CI: 4.6–9.0) was insignificantly different (P = 0.192). Stratified by PFE vs. other 1L-ChT, the statistical trend proved to be true and revealed patients aged 50–59 years having the longest OS1L-ChT independent from the type of 1L-ChT applied (mOS1L-ChT (95%CI): 9.8 (7.7–11.9) after PFE vs. 8.2 (0.0–17.6) months after other 1L-ChT regimen; P = 0.560). There were only 11 vs. 8 patients aged ≤49 years, the mOS1L-ChT after PFE vs. other 1L-ChT was 10.3 (95%CI: 1.6–19.0) months vs. 3.3 (95%CI: 0.0–8.0) months (Δ 7.0 months; P = 0.754). However, there was a statistical trend in patients ≥60 years (30 vs. 25 patients) for improved mOS1L-ChT after PFE vs. other 1L-ChT of 7.5 (95%CI: 1.6–13.4) months vs. 6.4 (95%CI: 3.6–9.2) months (Δ 1.1 months; P = 0.082; Figure 4). Among PFE-treated patients, we did not see an inferior OS1L-ChT of patients older than 65 years compared to younger patients (21 vs. 56 patients; OS1L-ChT (95%CI): 9.9 (1.3–18.5) vs. 9.3 (6.9–11.7); P = 0.467). Even with a slightly different cut-off point of 60 years (30 vs. 47 patients then), we did not see a significant difference neither (OS1L-ChT (95%CI): 7.5 (1.6–13.4) vs. 9.9 (8.0–11.8); P = 0.974). However, the heterogeneity in response to PFE in older patients is demonstrated by the enlarged 95%CI.

Regarding different localizations of the primary site of the R/M HNSCC, a statistical trend for oropharyngeal cancer was found in Kaplan–Maier analyses (mOS1L-ChT (95%CI): 6.8 (2.9–10.7) months vs. 9.5 (6.6–12.4) months; P = 0.281; Figure 3A). Analyzing the PFE subgroup (n = 77), this difference was more than 3 months (OS1L-ChT (95%CI): 7.6 (2.5–12.7) vs. 10.7 (9.2–12.2); P = 0.097, Figure 3B). The p16-status was critical for OS1L-ChT: As p16-positive (p16+) OPSCC had mOS1L-ChT of 9.3 (95%CI: 4.6–14.0) months comparable with non-oropharyngeal cancer (9.5 (6.6–12.4) months; P = 0.784), p16-negative OPSCC had impaired...
mOS$_{1L-ChT}$ of 6.7 (95%CI: 2.9–10.5) months (Figure 3C). Stratified by type of 1L-ChT, we saw impaired mOS$_{1L-ChT}$ in p16-negative OPSCC patients even if PFE treated (Figure 3D). Considering HPV-driven OPSCC ($n = 15$ p16+ HR-HPV-DNA+ OPSCC out of $n = 17$ p16+ OPSCC) did not result in deviating measures but reduced differences due to enlarged 95% CI and increased $P$ values, besides use of sole p16-IHC in clinical routine.

Patients with index HNSCC outside the oropharynx had a significant benefit from PFE vs. other 1L-ChT regimens [mOS$_{1L-ChT}$ (95%CI): 10.7 (9.2–12.2) vs. 6.5 (3.8–9.2) months; $P = 0.043$; Δ 4.2 months; Figure 4]. Patients by the time of 1L-ChT

| Predictor | Characteristic | Male (%) | Events (%) | PFE–mOS$_{1L-ChT}$ (95%CI, months) | other 1L-ChT–mOS$_{1L-ChT}$ (95%CI, months) | $P$-value | ΔmOS$_{1L-ChT}$, results | $HR$ (95%CI) | $P$-value |
|-----------|----------------|----------|-------------|-----------------------------------|---------------------------------------------|-----------|-------------------------|------------|-----------|
| Sex       | Male           | 67 (67.0) | 65 (65.0)   | 5.3 (5.2–7.3)                     | 6.3 (5.3–9.2)                               | 0.132     | 3.9                     | 0.72 (0.49–1.03) | 0.335     |
| Tobacco smoking | 30 packyears | 38 (38.4) | 38 (38.4)   | 4.2 (3.0–6.4)                     | 6.3 (5.3–9.2)                               | 0.019     | 1.3                     | 0.62 (0.35–1.09) | 0.096     |
| Current smoker               | 67 (67.0) | 66 (66.0)   | 5.1 (3.6–7.6)                     | 6.3 (5.3–9.2)                               | 0.100     | 4.0                     | 0.72 (0.48–1.07) | 0.105     |
| Risk  | Risk  | 93 (93.0) | 93 (93.0)   | 9.1 (8.0–12.2)                    | 6.3 (5.3–9.2)                               | 0.130     | 5.1                     | 0.57 (0.47–0.69) | 0.002     |
| Tobacco and alcohol | 93 (93.0) | 93 (93.0)   | 9.1 (8.0–12.2)                    | 6.3 (5.3–9.2)                               | 0.130     | 5.1                     | 0.57 (0.47–0.69) | 0.002     |
| Alcohol consumption | Current consumption | 59 (59.6) | 58 (58.5)   | 5.0 (2.2–8.8)                      | 6.3 (5.3–9.2)                               | 0.179     | 3.9                     | 0.74 (0.41–1.35) | 0.102     |
| Localization | HNSCC outside Oropharynx | 45 (45.4) | 44 (44.1)   | 6.3 (5.3–9.2)                     | 6.3 (5.3–9.2)                               | 0.983     | 4.2                     | 0.05 (0.90–0.99) | 0.046     |
| p16+ OPSCC and HNSCC outside Oropharynx | 58 (58.5) | 57 (57.2)   | 5.0 (3.7–8.9)                      | 6.3 (5.3–9.2)                               | 0.099     | 4.3                     | 0.05 (0.43–0.99) | 0.041     |
| OSCC | OSCC | 23 (23.0) | 23 (23.0)   | 4.1 (1.3–12.1)                    | 6.3 (5.3–9.2)                               | 0.060     | 6.6                     | 0.36 (0.20–1.04) | 0.044     |
| Extent of disease | M1 | 58 (58.5) | 56 (56.2)   | 4.3 (3.8–5.3)                     | 6.3 (5.3–9.2)                               | 0.127     | 5.0                     | 0.70 (0.44–1.11) | 0.130     |
| Enrolment in 1L-ChT | Not enrolled | 43 (43.0) | 41 (41.3)   | 4.1 (3.6–4.6)                      | 6.3 (5.3–9.2)                               | 0.016     | 5.2                     | 0.45 (0.23–0.88) | 0.009     |
| Type of pretreatment | Platinum-based ChT | 36 (36.8) | 34 (34.4)   | 6.0 (3.0–13.8)                    | 6.3 (5.3–9.2)                               | 0.092     | 3.1                     | 0.62 (0.36–1.07) | 0.086     |
| Number of pretreatments | One pre-treatment | 44 (44.8) | 42 (42.9)   | 6.3 (4.3–11.7)                    | 6.3 (5.3–9.2)                               | 0.177     | 4.3                     | 0.70 (0.41–1.18) | 0.181     |
| Age by the time of 1L-ChT | ≥ 60 years | 30 (30.6) | 30 (30.0)   | 6.3 (5.6–13.4)                    | 6.3 (5.3–9.2)                               | 0.082     | 1.1                     | 0.60 (0.34–1.07) | 0.085     |

**FIGURE 3 |** Kaplan–Meier plots for cumulative overall survival (OS$_{1L-ChT}$) measured from diagnosis of incurable recurrent/metastatic head and neck squamous cell carcinoma (A, C) in the total cohort and (B, D) PFE treated patients. (A) OS$_{1L-ChT}$ for OPSCC vs. index HNSCC outside the oropharynx; (B) OS$_{1L-ChT}$ after PFE for OPSCC vs. HNSCC outside the oropharynx; (C) OS$_{1L-ChT}$ in p16-negative OPSCC vs. p16-positive OPSCC vs. HNSCC outside the oropharynx; (D) OS$_{1L-ChT}$ after PFE in p16-negative vs. p16-positive vs. HNSCC outside the oropharynx; $P$ values shown are from 2-sided log-rank tests.

**FIGURE 4 |** Subgroups of incurable recurrent/metastatic head and neck squamous cell carcinoma benefitting from PFE administered according to the EXTREME protocol by prolonged OS$_{1L-ChT}$, demonstrated by Kaplan–Meier estimates applying log-rank tests and univariate Cox proportional hazard regression. $P$ values of significant predictors <0.05 are in bold.
**FIGURE 5** | Individual outcome of 124 patients with incurable recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) receiving various first-line chemotherapy regimens are depicted according to overall survival measured from diagnosis of R/M HNSCC til death (OS1l-ChT). Patients are shown sorted stratified according to 1L-ChT, either EXTREME-regimen (PFE, red; \( n = 77 \)) or other 1L-ChT (blue; \( n = 47 \)) and treatment either within randomized controlled trial (RCT; shaded) or in clinical routine (‘real world setting’, full). Type of prior treatment in curative attempt is indicated in dark green (cisplatin-based chemo-radiation (CRT) or post-operative radio-chemotherapy (PORCT)) vs. light green (other or no pretreatment); time from initial diagnosis of HNSCC until diagnosis of incurable disease requiring 1L-ChT is shown in the left panel, OS1-ChT in the right panel according to the upper scale showing time in months. The horizontal lines indicate mOS1-ChT (95% confidence interval). Median and 95%CI of OS1l-ChT of PFE vs. other 1L-ChT in the total cohorts are shown in the lower rows. *censored: alive at last follow-up (\( n = 3 \)); 1, CeFiD (6); 2, ADVANTAGE (7); 3 RESGEX (8); 4, TPEExtreme (9); p16+, p16+ OPSCC.
diagnosed with distant metastasis (M1) demonstrated an improved benefit from PFE compared to patients with loco-regional recurrence (Figure 4). However, we performed sensitivity analyses and excluded all patients that were diagnosed already in a locally very advanced and metastatic stage without any curative option and therefore receiving 1L-ChT as first treatment (n = 10). Kaplan–Meier estimates showed a mOS1L-ChT after PFE vs. other 1L-ChT of 9.4 (95%CI: 7.8–10.9) months vs. 6.5 (95%CI: 4.1–9.2) months for the remaining 114 patients (P = 0.163). This compares well to the OS1L-ChT for the total cohort.

The lifestyle-factors tobacco and alcohol showed an impact on outcome (Figure 4). There were patients with both risk factors (current or former alcohol consumption and tobacco smoking; n = 93) and those without or solely one risk factor (n = 26; five patients without information). Both groups demonstrated a benefit from PFE, patients with two risk factors had an impaired mOS1L-ChT but showed a higher benefit from PFE in Kaplan–Meier estimates [mOS1L-ChT (95% CI); 9.3 (6.0–12.6) vs. 4.2 (2.7–5.7) months; P = 0.130; Figure 4]. We found a significant correlation of double-positive risk factor-anamnesis with two baseline characteristics: young patients (<60 years at 1L-ChT; Pearson’s r = 0.272; P = 0.003) and male patients (Pearson’s r = 0.288, P = 0.002) did more often belong to the group with both risk factors.

**Multivariate Cox Proportional Hazard Regression for Outcome**

The MCR model for OS in the total cohort achieving highest significance (X² = 21.7, P = 0.001) included five independent risk factors: the number of pretreatments and pack years smoking besides slightly lower median exposure to risk factors (22 pack years in 64.3% current smokers, as well as 64.3% current alcohol consumers; Table 1). Even the 12 RWE-PFE patients with OS1L-ChT above 95%CI OS1L-ChT in the CRT/PORCT and “other” subgroups (10.7 and 15.5 months, respectively) had a similar median age at the time of initial diagnosis of HNSCC (57.3 years) comparable to the total cohort of PFE patients (n = 77, 56.6 years). They were quite similar to the total PFE cohort respective to sex (17.9% female), type of prior treatment (50% cisplatin-based CRT/PORCT) and patients with OS1L-ChT above 95%CI OS1L-ChT in the CRT/PORCT as significant OS1L-ChT predictor we further stratified these groups by cisplatin-based CRT or PORCT vs. other pretreatments. The improved outcome of certain PFE-treated R/M HNSCC patients allowed further investigations in the subgroup surviving more than 11.3 months, the upper bound of 95%CI for mOS1L-ChT in PFE-treated patients. These 28 individuals had a median age (57.3 years) comparable to the total cohort of PFE patients (n = 77, 56.6 years). They were quite similar to the total PFE cohort respectively sex (17.9% female), type of prior treatment (50% cisplatin-based CRT/PORCT) besides slightly lower median exposure to risk factors (22 pack years in 64.3% current smokers, as well as 64.3% current alcohol consumers; Table 1). The number of pretreatments and pack years smoking besides slightly lower median exposure to risk factors (22 pack years in 64.3% current smokers, as well as 64.3% current alcohol consumers; Table 1).

| Predictor | Characteristic | n (%) | events (%) | HR (95% CI) | P-value | P-value bootstrapping |
|-----------|---------------|-------|------------|-------------|---------|----------------------|
| Number of pretreatments | One pretreatment | 66 (53.2) | 64 (96.7) | 0.582 (0.391–0.865) | 0.007 | 0.007 |
| Type of 1L-ChT | PFE | 77 (62.1) | 75 (97.4) | 0.720 (0.476–1.064) | 0.107 | 0.087 |
| Alcohol consumption | ≥ 60g/d | 37 (29.8) | 37 (100.0) | 1.470 (0.937–2.213) | 0.095 | 0.058 |
| Tobacco smoking | ≥ 30 packyears | 58 (46.8) | 58 (100.0) | 1.621 (1.041–2.451) | 0.027 | 0.027 |
| Localization and p16-status | p16-negative OPSCC | 25 (20.2) | 24 (96.0) | 1.425 (0.868–2.34) | 0.161 | 0.153 |

**FIGURE 6** | Predictors in multivariate Cox proportional hazard regression (HR) and 2-sided P-values from internal validation using bootstrapping applying 1,000 iterations. Significant independent predictors P < 0.005 are in bold. * Reference: 1L-ChT at initial diagnosis or ≥2 pretreatments; † Reference: other 1L-ChT regimen; ‡ Reference: <90 g/d; § Reference: <30 pack years; □ Reference: HNSCC outside oropharynx.
an independent predictor for improved OS\textsubscript{1L-ChT} in the total cohort, this might be causative involved in their prolonged OS\textsubscript{1L-ChT}. However, only 2/12 (16.7%) of RWE-PFE long-term survivors had a current alcohol consumption >30 g/d, pointing to the absent detrimental impact of maintained alcohol consumption on OS\textsubscript{1L-ChT} in most of RWE-PFE long-term survivors. Interestingly, smoking history and adhering to tobacco smoking may also play a role as only seven of these 12 long-term survivors (58.3%) were current smokers, and the median cumulative nicotine exposure was 25 pack years and somewhat lower compared to the total PFE cohort (Table 1). The proportion of p16+ OPSCC was higher in RCT; their OS\textsubscript{1L-ChT}, however, was not superior compared with R/M HNSCC localized outside the oropharynx (Figure 3C).

Identification of Long-Term Survivors in Other 1L-ChT Regimens
As enrollment in RCT was predictive for improved OS\textsubscript{1L-ChT} only in 34 vs. 13 patients (see OS\textsubscript{1L-ChT after other 1L-ChT regimen}) we were interested in long-term survivors in this subgroup. According to numbers in the right panel of Figure 5, PFE-based regimens containing an additional (investigational) drug, for instance docetaxel (TPFE) in the CeFCiD trial [labeled 1 (6)], cilengitide in the ADVANTAGE trial [labeled 2 (7)], or replaced cetuximab by glycosylation-modified cetuximab in the RESGEX trial [labeled 3 (9)], long-term survivors were only seen after PFE-based 1L-ChT. However, the outcome observed in such intensified PFE-based 1L-ChT did not improve outcome in general at least in our cohort as it is obvious that a huge heterogeneity exists in this regard.

DISCUSSION
According to several lines of evidence, our monocentric study comprises a sufficient number of R/M HNSCC receiving 1L-ChT to show outcome differences dependent on a number of well-defined covariates. The mOS\textsubscript{1L-ChT} in our sample is comparable to the survival times found in prior trials (6, 7, 15). Therefore, the subgroups with and without benefit from PFE identified in our study confirm the existence of certain subgroups already described (3). Uni- and multivariate analyses demonstrated that the number of pretreatments, consumption of alcohol and/or tobacco smoking as well as localization of the index cancer and patients’ age have a certain effect on OS\textsubscript{1L-ChT}. When treated with PFE in particular, predictive covariates are mostly the same. However, our study provides evidence that prior intensified treatments making use of cisplatin-based CRT and especially cisplatin-based PORCT do not negatively affect survival in PFE but rather improve OS\textsubscript{1L-ChT}. Indeed, prior cisplatin-based CRT or PORCT appeared to be an additional independent predictor for significant prolonged OS\textsubscript{1L-ChT}. These findings from multivariate Cox regression analyses may contribute to the ongoing discussion about a potential negative impact of treatment escalation in the curative setting on further therapies and the possibility to re-challenge R/M HNSCC with cisplatin when progressing after cisplatin-based curative treatment. As the median time from curative treatment with surgery followed by cisplatin-based PORCT to 1L-ChT (n = 52) was 30.6 months (95%CI: 21.5–40.2) and substantially longer (P = 0.005) compared to 10.6 months (95%CI: 5.0–16.3) of patients without prior treatment or other types of prior curative treatment, and these cisplatin-pretreated R/M HNSCC patients had the highest benefit from PFE, treatment escalation in presence of risk factors in the curative setting improves outcome and does not reduce OS\textsubscript{1L-ChT} if PFE is used. As, additionally, a 2L-ChT could be applied in a higher frequency after PFE as compared to other 1L-ChT, treatment escalation in the curative setting via cisplatin-based PORCT whenever high risk for relapse/recurrent disease (more than two disease-positive neck nodes, extracapsular extension of neck nodes, positive or narrow resection margins below 5 mm) is detected appears to be warranted.

Our results confirm OS data for PFE including subgroup analyses obtained in the landmark phase-III RCT EXTREME (3). Comparing outcome of PFE with PF, Vermorken et al. (3) showed in univariate models that patients ≥ 65 years demonstrate a minor benefit from PFE compared to younger patients. Our retrospective study comprises only 21 vs. 15 R/M HNSCC patients ≥65 years receiving PFE vs. other 1L-ChT regimen. We have not seen an inferiority of PFE in this subgroup compared to patients <65 years. By performing this analysis with a slightly different cut-off point of 60 years (30 vs. 15 patients), we found no evidence for an inferiority of PFE neither.

The recently published ELAN-FIT trial by Guigay et al. (16) showed a mOS\textsubscript{1L-ChT} of 14.7 months (95%CI: 11.0–18.2) after PFE for patients aged 70 and older and ECOG performance status 0 or 1. The impact of age and its influence on PFE efficacy and risk will be probably important in future trials. However, we found no evidence in our cohort for calendar age alone being the most relevant eligibility criterion for PFE, provided good general health (ECOG 0 or 1). PFE is only approved for ECOG 0 and 1 patient presenting, so the MDTB made the decision for either offering participation in a 1L-ChT RCT or 1L-ChT treatment in the routine setting only provided good general health as reflected by ECOG 0 or 1. Consequently, our sample mainly included “fit” patients in our retrospective trial to ensure comparability. As Guigay et al. (17) showed, “unfit” patients may be eligible for PFE or comparable regimens after a comprehensive geriatric assessment. By performing RCTs after a geriatric assessment, there could be more evidence about the impact of calendar age vs. biological age on treatment eligibility and potential benefit in older patients.

Referring to Guigay et al. (9), the TPEExtreme (TPE; docetaxel, cis- or carboplatin, cetuximab) 1L-ChT regimen is beneficial when followed by ICB in 2L-ChT. As retrospectively found, TPE outperformed PFE only in this treatment sequence. Due to our small sample of 124 patients collected over years and only two TPE patients unfit to receive 2L-ChT after recurrence, there are no such patients in our cohort.
Patients in the PFE subgroup had a longer mOS1L-ChT – independently on the following 2L-ChT— than patients treated with other 1L-ChT in our analysis. As all studies demonstrated the lasting value of PFE, we recommend—against the often suggested alternative use of TPE as unproblematic replacement for PFE to avoid potential dihydropyrimidine dehydrogenase (DPD) toxicity—rather DPD testing according to established guidelines (18) so that R/M HNSCC patients still can benefit from PFE. As only one RCT demonstrated an improved OS of R/M HNSCC in the minor subgroup of patients treated sequentially first with TPE followed by ICB over PFE followed by ICB in a retrospective analysis (17), it might be too soon to change 1L-ChT of R/M HNSCC in absence of a positive phase III RCT demonstrating superiority of TPE over PFE. Moreover, we were unable to see a benefit from TPE as only 2/124 patients received TPE, and both (indicated with four in Figure 5) had a rather impaired outcome below the mOS1L-ChT. Without replication of the findings by Guigay et al. (9) in such a phase-III RCT the TPEExtreme-ICB treatment sequence so far remains experimental at best.

Today, no published data for the efficacy of PFE for R/M HNSCC progressing under 1L-ICB are available. The question if patients failing on curative treatment involving ICB thereafter progressing and requiring 1L-ChT should preferentially be treated with PFE is not yet completely clear. However, we expect that PFE can benefit a substantial proportion of such R/M HNSCC.

Regarding the influence of HPV-status on OS1L-ChT, we have seen an impaired OS1L-ChT in patients suffering from a p16-negative OPSCC compared to patients with a p16+ OPSCC or index HNSCC outside the oropharynx. This is in line with former findings (19, 20). Based on the study by Mehr et al. (19) showing an improved OS in p16+/HPV+ R/M HNSCC patients, Vermorken et al. (20) performed a retrospective analysis of data from the EXTREME trial (3) and found a p16+ / HPV-prevalence and p16+/HPV-related OS1L-ChT similar to our findings. There is an ongoing discussion about the influence of HPV on survival in R/M HNSCC. In contrast to Mehr et al. and Vermorken et al., Szturz et al. (21) found in a meta-analysis of four prospective RCT that HPV-related (p16+ or HPV-DNA+) tumors rarely responded to EGFR-directed monotherapy, whereas improved response rates were only observed in HPV-negative cases. Since we did not observe detrimental effects by p16 positivity on OS1L-ChT no matter if EXTREME or other regimens were applied, but OS1L-ChT was strongly reduced in oropharyngeal R/M HNSCC and even further reduced in p16-negative cases, our study highlights the importance of further investigations in this field. The poorest OS1L-ChT in oropharyngeal R/M HNSCC could be linked to the proximity to essential cervical structures including arteries and their infiltration. Therefore, R/M HNSCC with rather reduced infiltrating growth patterns and without vascular infiltration may have prolonged OS1L-ChT independent from being HPV-related. Additionally, distance of the R/M HNSCC from vital vessels might prolong the time to life-threatening destruction of indispensable organs and critical bleeding events including arterial blowout leading to death.

During the time period analyzed in this retrospective study, therapy guidelines for R/M HNSCC have changed. Nowadays, and according to KEYNOTE-048 trial (4), immune checkpoint blockade (ICB) by pembrolizumab is declared new standard of care for patients with CPS >20 or ICB-PF combination for patients with CPS >1 to ≤20. According to KEYNOTE-048 investigators, PFE remains standard of care for CPS ≤1. Consequently, PFE may be 1L-ChT standard for this subgroup and 2L-ChT option for patients progressing after ICB. However, as we confirm data from the EXTREME trial (3), especially male patients, subgroups accumulating more lifestyle-associated risk factors, and those with their index HNSCC outside oropharynx still benefit the most from PFE. KEYNOTE-048 subgroup analyses (4) addressed this issue showing that patients <65 years and ≥65 years do not differ in benefit from pembrolizumab ± chemotherapy. There was no significant difference between never and former/current smokers. It may be interesting to conduct further analyses to see if there are any differences in OS depending on patients’ characteristics described here (Figure 5).

Unlike ICB in the KEYNOTE-048 trial, ICB with durvalumab (PD-L1 inhibitor) ± tremelimumab (CTLA-4-inhibitor) in the KESTREL phase III trial failed to meet the primary endpoint of improved OS compared to PFE. As AstraZeneca reported this result just recently [2021-02-05 (22)] and a peer-reviewed paper on KESTREL is still not published, it might be too soon to rank any ICB in general over PFE. At least, PFE should be considered standard for all 1L-ChT not belonging to the CPS >1 subgroup of R/M HNSCC patients.

Argiris et al. (23) showed an improved response rate and progression-free survival by adding the anti-VEGF antibody bevacizumab to chemotherapy. This may provide evidence for a benefit by targeted therapies other than EGFR- or PD-L1-inhibitors combined with PF. However, acute toxicity appeared to be increased if PF and bevacizumab were used in 1L-ChT, and the gain in OS compared to PF rather limited (18).

Discussing their KEYNOTE-048 results and referring to retrospective trials (24, 25), post-pembrolizumab sensitization of R/M HNSCC to a subsequent therapy with PFE was mentioned by Burtness et al. (4). This highlights the potential importance of 2L-PFE applied after 1L-ICB in the future. In the light of ICB applied within multimodal treatment regimen in the curative setting, e.g. during induction-chemotherapy for larynx-organ preservation or ICB as component of adjuvant therapies after curative resection and in postoperative maintenance, we are convinced that PFE will have a dominant role as 1L-ChT also in the future (26, 27). In context of earlier investigations highlighting improved outcome after increased utilization of PORCT in treatment of L/HSCC (23), prolonged OS1L-ChT through PFE after cisplatin-based PORCT may at least partially have contributed to the welcome impact of indication shift towards increased use of cisplatin-based PORCT according to Bernier and Cooper (12, 13) on heightened OS time (28).

In our study, 14.3% of the patients died within 3 months after starting PFE. These figures compare well to 17.1% found by Vermorken et al. (3). The majority of early deaths observed in
our cohort occurred outside RCTs (72.7% vs. 27.3% of all fatalities during PFE treatment). Treatment in clinical routine apart from adherence to the complete checklist of eligibility criteria as required to enter any of the RCT as well as survivorship bias may have potentially contributed to this situation. However, outcome in RCT vs. “real world” was not significantly different overall. Reproducibility of survival benefit of certain subgroups independent from RCT participation shows that RCT results are representative for the outcome achieved by PFE even in clinical routine. Subgroup analyses of the seven long-term survivors within the subgroup of RWE-PFE treated patients allude to the impact of risk factors on survival. Those seven patients barely drank alcohol but received PFE after cisplatin-based CRT/PORCT. The overall well-comparable or even slightly improved outcome in RWE compared to RCT PFECRT demonstrates an unprecedented situation. However, outcome in RCT vs. “real world” setting. Demonstrating again the high value of PFE in first-line chemotherapy, this effective treatment should not be replaced by treatments that failed to demonstrate superiority in RCT. PFE should hence remain standard for first-line chemotherapy at least in patients not belonging to the well-defined subgroups of recurrent/metastatic head and neck squamous cell carcinoma eligible for pembrolizumab or PF plus pembrolizumab according to KEYNOTE-048 (4).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Human Ethics Committee of the University Leipzig (votes 201-10-12072010 and 202-10-12072010). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conceptualization, GW. Data curation, KL, MP, TW, and GW. Formal analysis, KL and GW. Investigation, KL and GW. Methodology, GW. Project administration, GW. Resources, AD and GW. Validation, GW. Visualization, KL and GW. Writing – original draft, KL and GW. Supervision, SW, AD, VZ, and GW. Writing – review and editing, KL, MP, TW, SW, AD, VZ, and GW. All authors contributed to the article and approved the submitted version.

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CONCLUSIONS

This retrospective study highlights the lasting value of the triplet cisplatin, 5-fluoruracil, cetuximab (PFE) not only as comparator treatment within randomized controlled trials (RCT) but also—and independent on the age of R/M HNSCC patients—in clinical routine. Interestingly, we found no evidence for a negative impact of prior intensified treatments making use of primary or postoperative cisplatin-based chemo-radiotherapy on overall survival following first-line chemotherapy but rather improved outcome in this subgroup achieved by PFE independent from participation in RCT or applied in the “real world” setting. Demonstrating again the high value of PFE in first-line chemotherapy, this effective treatment should not be replaced by treatments that failed to demonstrate superiority in RCT. PFE should hence remain standard for first-line chemotherapy at least in patients not belonging to the well-defined subgroups of recurrent/metastatic head and neck squamous cell carcinoma eligible for pembrolizumab or PF plus pembrolizumab according to KEYNOTE-048 (4).
REFERENCES

1. Gatta G, Botti L, Sánchez MJ, Anderson LA, Pianannunzi D, Licitra L. Prognoses and Improvement for Head and Neck Cancers Diagnosed in Europe in Early 2000s: The EUROCARE-5 Population-Based Study. *Eur J Cancer* (2015) 51:2130–43. doi: 10.1016/j.ejca.2015.07.043

2. Colecas AD, Yom S, Pfister D, Spencer S, Adelstein D, Adkins D, et al. NCCN Guidelines Insights: Head and Neck Cancers, Version 1.2018. *J Natl Compr Canc Netw* (2018) 16:479–90. doi: 10.6004/jnccn.2018.0026

3. Vermaak JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, et al. Platinum-Based Chemotherapy Plus Cetuximab in Head and Neck Cancer. *N Engl J Med* (2008) 359:1116–27. doi: 10.1056/NEJMoa082656

4. Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, Castro G, et al. Cisplatin, 5-Fluorouracil, and Cetuximab (PFE) With or Without Cilengitide in Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (KEYNOTE-048): A Randomised, Open-Label, Phase 3 Study. *Lancet* (2019) 394:1915–28. doi: 10.1016/S0140-6736(19)32591-7

5. Pfister DG, Spencer S, Adelstein D, Adkins D, Anzai Y, Brizel DM, et al. Head and Neck Cancers, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* (2020) 18:873–98. doi: 10.6004/jnccn.2020.0031

6. Klinoglker H, Gauler T, Dietz A, Grünwald V, Stöhlmacher J, Knipping S, et al. Cetuximab, Fluorouracil and Cisplatin With or Without Docaetaxel for Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (CeFGD): An Open-Label Phase II Randomised Trial (AIO-IAG-KHT Trial 1108). *Eur J Cancer* (2019) 122:53–60. doi: 10.1016/j.ejca.2019.08.018

7. Vermaak JB, Peyrade F, Krauss J, Mesia R, Remenar E, Gauler TC, et al. Cisplatin, 5-Fluorouracil, and Cetuximab (PFE) With or Without Cilengitide in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck: Results of the Randomized Phase III ADVANTAGE Trial (Phase II Part). *Ann Oncol Off J Eur Soc Med Oncol* (2014) 25:682–8. doi: 10.1016/j.annonc.2014.06.003

8. Keilholz U, Kawecki A, Dietz A, Zurawski B, Schenker M, Kukiell-Budny B, et al. Efficacy and Safety of CetuxGEX in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck (RM-HNSCC): Results From the Randomized Phase II REGEX Study. *J Clin Oncol Off J Am Soc Clin Oncol* (2018) 36:59. doi: 10.1200/JCO.2018.36.5_suppl.59

9. Guigay J, Fayette J, Mesia R, Saada-Bouzid E, Lafond C, Geoffroy L, et al. TPExtreme Randomized Trial: Quality of Life (Qol) and Survival According to Second-Line Treatments in Patients With Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC). *J Clin Oncol Off J Am Soc Clin Oncol* (2020) 38:6507. doi: 10.1200/JCO.2020.38.15_suppl.6507

10. Meier J, Bohm A, Kielhorn A, Dietz A, Bohn S, Neumuth T. Design and Randomized Trial of Chemotherapy With or Without Bevacizumab in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck: Results From the Randomized Phase III EXTREME Trial. *Ann Oncol Off J Eur Soc Med Oncol* (2014) 25:801–7. doi: 10.1016/j.annonc.2013.11.015

11. Oeser A, Gaebel J, Dietz A, Wiegand S, Oeltze-Jafra S. Information Architecture for a Patient-Specific Dashboard in Head and Neck Tumor Therapy. *Int J Comput assisted Radiol Surg* (2014) 9:949–65. doi: 10.1007/s11548-014-0988-x

12. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Head and Neck non-Small Cell Carcinoma. *Carcinoma. Predictors of Impaired Survival in P16-Positive Oropharyngeal Squamous Cell* (2015) 51:2130–44. doi: 10.1056/NEJMoa1503264

13. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative Concurrent Radiotherapy and Chemotherapy for High-Risk Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* (2004) 350:1945–52. doi: 10.1056/NEJMoa0432641

14. Freitag J, Wald T, Kuhnt T, Gradistanac T, Kolb M, Dietz A, et al. Extracapsular Extension of Neck Nodes and Absence of Human Papillomavirus 16-DNA Are Predictors of Impaired Survival in P16-Positive Oropharyngeal Squamous Cell Carcinoma. *Cancer* (2020) 126:1856–72. doi: 10.1002/cncr.32667

15. Vermaak JB, Herbst RS, Leon X, Amellal N, Baselga J. Overview of the Efficacy of Cetuximab in Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck in Patients Who Previously Failed Platinum-Based Therapies. *Cancer* (2008) 112:2710–9. doi: 10.1002/cncr.23442