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Clinical Trial

Cetuximab, fluorouracil and cisplatin with or without docetaxel for patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (CeFCiD): an open-label phase II randomised trial (AIO/IAG-KHT trial 1108)

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Abbreviations: CR, complete response; CTC, common toxicity criteria; CT, computed tomography; DPFC, docetaxel, platinum, fluorouracil, cetuximab; EGFR, epidermal growth factor receptor; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTP, time to progression; KPS, karnofsky performance score; MRI, magnetic resonance imaging; OS, overall survival; PFC, platinum, fluorouracil, cetuximab; RECIST, response evaluation criteria in solid tumours; SCCHN, squamous cell carcinoma of the head and neck.

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Abstract ***Background:*** The combination of cisplatin, 5-fluorouracil (5-FU) and cetuximab (PFC) is the reference first-line treatment for recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). We analysed whether treatment intensification by the addition of docetaxel to PFC improved efficacy in R/M SCCHN.
Methods: A total of 180 patients with R/M SCCHN (1:1) were assigned to receive either cisplatin (40 mg/m^2), docetaxel (40 mg/m^2) and 5-FU (2000 mg/m^2) at days 1 and 8 and cetuximab (400/250 mg/m^2) at days 1, 8 and 15 (DPFC) or standard cisplatin (100 mg/m^2) at day 1, 5-FU (1000 mg/m^2) at days 1–4 and cetuximab (400/250 mg/m^2) at days 1, 8 and 15 (PFC). Chemotherapy was repeated every 21 days and continued for a maximum of 6 cycles in absence of disease progression or limiting toxicity, followed by cetuximab maintenance (500 mg/m^2 every 2 weeks). The primary end-point was progression-free survival (PFS).
Results: A preplanned interim analysis for toxicity after 20 patients/arm revealed excessive grade 3 and 4 gastrointestinal (65%) and infectious toxicities (35%) in arm A, which led to dose reduction of cisplatin to 30 mg/m^2 and 5-FU to 1000 mg/m^2 for subsequent patients. With a median follow-up of 2 years, grade 4 toxicities were 21.3% vs. 30.8% for DPFC and PFC, respectively. More treatment-related deaths occurred with DPFC vs. PFC, with 11.2% and 6.6%, respectively. For DPFC and PFC, the median PFS was 6.3 vs. 6.4 months (hazard ratio [HR] = 0.97, p = 0.87), the median overall survival was 8.9 vs. 10.6 months (HR = 1.29 p = 0.1) and response rates were 38.2% vs. 31.9% (p = 0.9), respectively.
Conclusions: DPFC failed to improve efficacy in R/M SCCHN. On the contrary, a high toxicity and mortality rate was detected in both arms, which underscores the vulnerability of patients with R/M SCCHN, and research on the need for further optimisation of the front-line chemotherapy backbone is ongoing.

1. Introduction

Patients with recurrent and/or metastatic (R/M) squamous cell cancer of the head and neck (SCCHN) have a poor prognosis and few efficacious treatment options. Cetuximab in combination with platinum and 5-fluorouracil (5-FU) (PFC regimen) remained the standard of care in the first-line treatment of these patients for almost a decade, based on a randomised trial [1]. The objective response rate achieved was 36%, median progression-free survival (PFS) was 5.6 months and median overall survival (OS) was 10.1 months, clearly indicating a medical need to further improve clinical outcome in R/M SCCHN.

In locoregional disease, intensification of the induction chemotherapy by addition of docetaxel (T) to the cisplatin/5-FU (PF) doublet was associated with an OS benefit in two trials, indicating that docetaxel combinations may further improve clinical activity in R/M SCCHN [2,3] The dose of cisplatin and 5-FU was reduced in the DPF triplet in contrast to the PF doublet, and with this reduction, the toxicity of the TPF triplet was even lower compared with the PF doublet. Preclinical data further suggested a synergistic effect of taxanes and cetuximab [4], which in fact was mirrored by phase II trial data [5–7]. In the recurrent metastatic setting, small non-randomised phase II trials demonstrated a comparable efficacy of the chemotherapeutic triplet of a taxane, 5-FU and platinum but without cetuximab [8,9]. Based on these data, we asked the research question whether the addition of docetaxel to the established doublet chemotherapy backbone may further improve efficacy of the PFC regimen in R/M SCCHN in a randomised trial.

The CeFCiD trial reported here was designed to evaluate whether efficacy of treatment could be improved in R/M SCCHN by introduction of docetaxel to the chemotherapy backbone. The CeFCiD study is a randomised phase II study evaluating the combination of cetuximab, 5-FU, cisplatin and docetaxel as first-line treatment of R/M SCCHN with the standard-of-care

EXTREME regimen with cisplatin, 5-FU and cetuximab as the comparator (Fig. 1).

2. Patients and methods

Patients with R/M SCCHN without prior palliative medical treatment for R/M disease were eligible for enrolment if they met the following selection criteria. Human papilloma virus (HPV) status was not mandated for study participation. The key inclusion criteria were as follows: age ≥18 years; histologically confirmed diagnosis of R/M SCCHN not suitable for local therapy; ≥ 1 lesion measurable by computed tomography (CT) or magnetic resonance imaging (MRI); and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1. The key exclusion criteria were as follows: prior systemic treatment with cetuximab and docetaxel therapy during the preceding 6 months; surgery or irradiation within 4 weeks before study entry; and documented or symptomatic brain or leptomeningeal metastasis. All patients provided written informed consent before enrolment. The study was approved by the institutional ethics committees of all participating institutions before patient enrolment. The trial was performed within the head and neck cancer group of the AIO (German medical oncology society) together with the IAG-KHT (German Cancer Society—interdisciplinary head and neck cancer working group) and registered under the accession number CeFCiD 1108.

2.1. Study design

This was a prospective, open-label, randomised, multicenter phase II study (15 centres). It was conducted in Germany in accordance with the Good Clinical Practice guidelines and the latest version of the Declaration of Helsinki. The competent authorities and ethics committees approved the study protocol in August 2010 and an amendment of the study protocol in October 2012. The primary end-point was median PFS, defined as the time from randomisation to first radiologically confirmed progressive disease (PD) or death due to any cause. The secondary end-points were the best overall response (ORR), OS, toxicity and quality of life.

2.2. Treatment

Patients were randomly assigned (1:1) to one of the two groups according to a bloc randomisation schema. Randomisation was stratified according to study centres and the interval between primary treatment and recurrence/metastasis (0–2, 2–6, 6–12, and >12 months). Patients in the DPFC group (arm A) received 40 mg/m^2 of intravenous (i.v.) docetaxel at days 1 and 8, 40 mg/m^2 of i.v. cisplatin at days 1 and 8, 2000 mg/m^2 of i.v. 5-FU at days 1 and 8 plus i.v. cetuximab at days 1, 8 and 15 (400 mg/m^2 at day 1 of cycle 1 and 250 mg/m^2 weekly on subsequent administrations) of a 3-week cycle. Owing to excessive toxicity, DPFC was modified to 40 mg/m^2 of i.v. docetaxel at days 1 and 8, 30 mg/m^2 of i.v. cisplatin at days 1 and 8 and 1000 mg/m^2 of i.v. 5-FU at days 1 and 8, with no change in the dose or regimen for cetuximab. Patients in the standard group (arm B; PFC) received 100 mg/m^2 of i.v. cisplatin at day 1 and continuous i.v. infusion of 1000 mg/m^2/day 5-FU at days 1–4 plus i.v. cetuximab at days 1, 8 and 15 (400 mg/m^2 at day 1 of cycle 1 and 250 mg/m^2 weekly on subsequent administrations). Cycles were repeated every 21 days for a maximum of 6 cycles with chemotherapy. Treatment with cetuximab was continued as maintenance therapy with an i.v. dose of 500 mg/m^2 every 2 weeks after chemotherapy discontinuation in both arms until disease progression or the appearance of unacceptable toxicity. Protocol-specified dose modifications and interruptions of study drugs were specified in case of toxicity.

2.3. Assessments

Tumour responses were assessed by CT or MRI at baseline and then every 6 weeks during chemotherapy treatment. During maintenance treatment with cetuximab and during follow-up, tumour responses were assessed every 3 months. Response Evaluation Criteria in Solid Tumours 1.1 criteria were used for response evaluation by the investigators. After disease progression, survival status and any further anticancer treatments were documented at follow-up visits every 3 months. Toxicity was scaled based on common toxicity criteria version 4.0. Two interim analyses for toxicities were planned after 20 and 40 patients per arm, respectively. The safety profile was

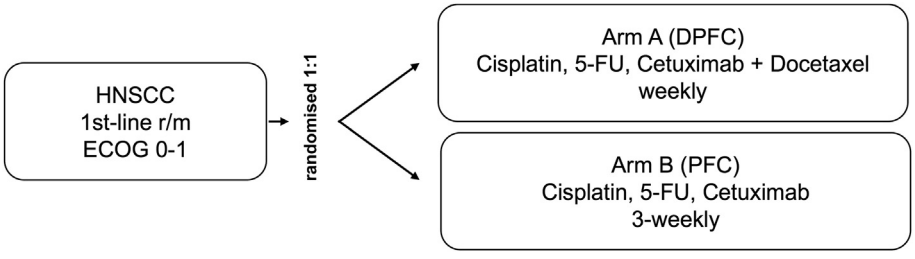

Fig. 1. Study design. HNSCC = head and neck squamous cell carcinoma; DPFC = docetaxel, platinum, fluorouracil, cetuximab; ECOG = Eastern Cooperative Oncology Group; 5-FU = 5-fluorouracil.

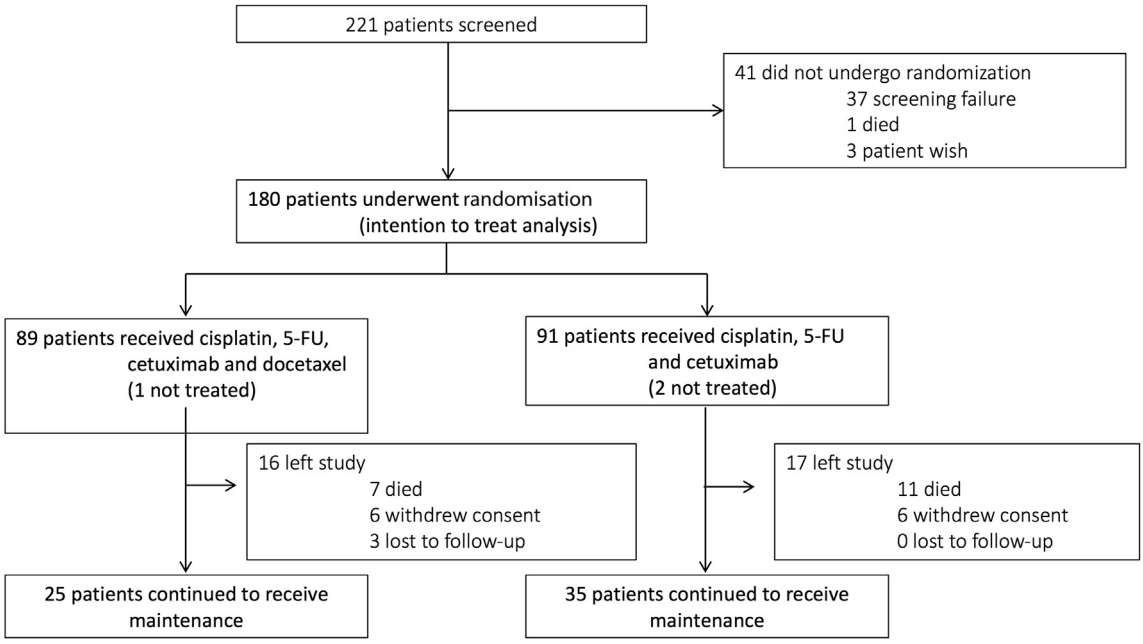

Fig. 2. Trial profile. 5-FU = 5-fluorouracil.

assessed based on adverse events (AEs), laboratory parameters, vital signs and physical examinations on a regular basis as defined in the protocol.

2.4. Statistical analysis

The primary end-point PFS per investigator read and the secondary end-point OS were analysed using Kaplan–Meier methodology. The goal of the primary end-point was to describe the median PFS. From the literature, the median PFS was expected to be 5.6 months with standard treatment. Considering a PFS of 5.6 months (HO) versus 8.6 months (H1) at most 77 evaluable patients in each study arm was required (alpha: 0.05, power: 90%, 2-sided test). Assuming a dropout rate of 15% of the recruited patients, a total of 90 patients should be enrolled. A Cox proportional hazards model was used to calculate hazard ratio (HR) and 95% confidence intervals (CIs). Further secondary analyses were summarised using descriptive statistics. Efficacy was assessed in the intention-to-treat population, which included all the patients who had undergone randomisation. Safety was assessed in the as-treated population, which included all patients who had undergone randomisation and received at least one dose of the assigned combination therapy.

3. Results

3.1. Patient characteristics

In total, 180 patients were accrued between August 2010 and September 2013 from 15 centres in Germany and randomly assigned to treatment arms (Fig. 2). Three patients did not start the intended treatment owing to acute symptomatic deterioration or non-compliance. A total of 177 patients received ≥1 treatment dose. A total of 110 patients (66%) discontinued owing to PD (n = 30; 27%), AE (n = 32; 29%), death (n = 18; 16%) or other reasons, which concluded in withdrawal of consent, patient wish, protocol violation or loss of follow-up (n = 30; 27%). A total of 5 (3%) patients remained on study treatment at the data cutoff. Patient characteristics are summarised in Table 1: the median age was 59.7 years, the patients were predominantly

Table 1
Patient demographics and baseline characteristics.

	All n = 180 (%)	Arm A (DPFC) n = 89 (%)	Arm B (PFC) n = 91 (%)
Gender			
Female	29 (16.1)	15 (16.9)	14 (15.4)
Male	151 (83.9)	74 (83.1)	77 (84.6)
Age, years (median)	59.7	59.2	60.1
Primary site			
Oral cavity	36 (20)	17 (19.1)	19 (20.9)
Oropharynx	52 (28.9)	24 (27)	28 (30.7)
Hypopharynx	37 (20.6)	20 (22.5)	17 (18.9)
Larynx	34 (18.9)	17 (19.1)	17 (18.9)
Nasopharynx	6 (3.3)	5 (5.6)	1 (1)
Other	15 (8.3)	6 (6.7)	9 (9.9)
ECOG performance status			
0	66 (36.6)	34 (38.2)	32 (35.2)
1	114 (63.4)	55 (61.8)	59 (64.8)
History			
Smoking	139 (77.2)	68 (76.4)	71 (78)
Alcohol	50 (27.7)	23 (25.8)	27 (29.7)

ECOG = Eastern Cooperative Oncology Group; DPFC = docetaxel, platinum, fluorouracil, cetuximab

Table 2
Drug-related adverse events (grade III/IV).

Event	Arm A (before amendment)	Arm A (after amendment)	Arm B (before amendment)	Arm B (after amendment)	Arm A (total)	Arm B (total)
	N = 23 (%)	N = 19 (%)	N = 19 (%)	N = 21 (%)	N = 42 (%)	N = 40 (%)
	Number of patients (%)					
Any event	11 (48)	13 (68)	11 (58)	5 (24)	24 (57)	16 (40)
Haematotoxicity	11 (48)	6 (32)	14 (74)	9 (43)	17 (40)	23 (58)
Fatigue	7 (30)	4 (21)	2 (11)	3 (14)	11 (26)	5 (13)
Mucositis	4 (17)	4 (21)	0	3 (14)	8 (19)	3 (8)
Diarrhoea	5 (22)	3 (16)	1 (5)	0	8 (19)	1 (3)
Vomiting	5 (22)	3 (16)	1 (5)	1 (5)	8 (19)	2 (5)
Infections	5 (22)	2 (11)	3 (16)	0	7 (17)	3 (8)
Rash	3 (13)	1 (5)	3 (16)	2 (10)	4 (10)	5 (13)
Asthenia	3 (13)	1 (5)	0	0	4 (10)	0
Febrile neutropenia	3 (13)	0	2 (11)	2 (10)	3 (7)	4 (10)
Hypomagnesaemia	1 (4)	2 (11)	2 (11)	1 (5)	3 (7)	3 (8)
Anorexia	3 (13)	0	1 (5)	0	3 (7)	1 (3)
Allergic reaction	1 (4)	1 (5)	1 (5)	0	2 (5)	1 (3)
Renal failure	0	2 (11)	1 (5)	2 (10)	2 (5)	3 (8)
Hypokalemia	2 (9)	0	2 (11)	2 (10)	2 (5)	4 (10)
Colon perforation	0	2 (11)	0	0	2 (5)	0
Colitis	1 (4)	0	1 (5)	0	1 (2)	1 (3)
Sepsis	1 (4)	0	1 (5)	0	1 (2)	1 (3)
Hyponatraemia	1 (4)	0	1 (5)	1 (5)	1 (2)	2 (5)

males (83.9%) and most had an ECOG performance status of 1 (63.4%). Seventy-seven percent of the patients were smokers, 28% reported regular use of alcohol and 52 patients (28.9%) had oropharynx carcinomas.

3.2. Treatment administration

During the study treatment, a total of 323 cycles were administered (median, four cycles/patient) for DPFC and 331 cycles for PFC (median, four cycles/patient). The dose intensity calculation demonstrated moderate tolerance of the treatment, with only 24% of the patients receiving the planned six cycles of chemotherapy in both arms. The cetuximab dose intensity was >80%. Twenty-five patients with disease control (31%) with DPFC and 35 patients (38%) with PFC were able to start the maintenance phase. During this phase, the median relative dose intensity of cetuximab was close to 100%. The median duration of the maintenance phase was 2.9 months. One patient was treated with cetuximab during maintenance for >24 months.

3.3. Toxicity

At the time of the primary interim analysis (n = 40, with 20 patients per arm) on September 2012, grade 3 and 4 toxicities reported in the experimental arm were higher than expected. In the experimental arm, >90% of patients experienced grade 3 and 4 AEs, most commonly (65%) gastrointestinal AEs with mucositis (17%), vomiting (22%), diarrhoea (22%) and colitis (4%) with additional AEs related to infections (22%) and febrile neutropenia (13%). Therefore, dose reductions of cisplatin from 40 to 30 mg/m^2 and 5-FU from 2000 to 1000 mg/m^2 were made. After this amendment with dose reductions in the docetaxel group, no clinically meaningful safety differences were noted between treatment arms. This was confirmed by a secondary interim analysis for toxicity with 40 patients per arm. Because collection of acute toxicities was rapid, the trial accrual was not stopped during the four-week waiting interval for the results of the second interim analysis. Treatment-related deaths during or within 30 days after treatment potentially occurred in 11.2% of patients for DPFC vs 6.6% of patients for PFC; the reported causes of treatment-related deaths were infection (n = 9), general disorder (n = 3) and bleeding complications (n = 4), as shown in Table 2 and Table S1. Of the total 16 treatment-related deaths, 10 occurred before the first interim analysis (63%).

3.4. Survival

The primary end-point PFS was not significantly different between the treatment groups. The median PFS was 6.3 months (95% CI = 5.2–7.3) in the experimental group and 6.4 months (95% CI = 5.0–7.7) in the control group (HR = 0.97, 95% CI = 0.72–1.32; p = 0.87, Fig. 3). At the time of analysis, 76 patients (85%) in the docetaxel group and 74 patients (81%) in the control group had progressed or died. The median OS was 8.9 months (95% CI = 7.6–10) in the experimental group and 10.6 months (95% CI = 8.8–12.3) in the control group (HR = 1.29, 95% CI = 0.95–1.75; p = 0.1), as shown in Fig. 4. The median follow-up was

6.3 months for treatment group A and 9.5 months for treatment group B.

3.5. Response to treatment

Objective responses were similar between treatment groups. The objective response rate (complete response [CR] and partial response [PR]) was 38.2% (n = 34) in the experimental arm and 31.9% (n = 29) in the standard arm ($p = 0.9$). In each treatment arm, 5 patients had a CR. Disease control rates (CR, PR and stable disease) were 71.9% and 68.2%, respectively (Table 3).

4. Discussion

In this randomised phase II study of patients with R/M SCCHN, addition of docetaxel to cisplatin, 5-FU and cetuximab (DPFC) did not improve PFS compared with the standard PFC regimen alone. Therefore, the primary end-point was not met. The safety profile of the experimental arm with additional docetaxel resulted in unexpected high toxicities and mandated dose reductions of the DPFC regimen. In the total study population and after the substantial amendment with dose reductions of cisplatin and 5-FU for the DPFC regimen, toxicities in both treatment arms were comparable and as expected. PFS in the experimental arm was slightly higher than that previously reported in the trial by Vermorken et al [1,10,11], but not different compared with the control arm, indicating that intensification of the chemotherapy backbone does not add clinical benefit and increases the toxicity. Some differences in the study population limit the comparability to the EXTREME trial. Within the reference trial, patients with an early relapse within 6 months were excluded. These patients were eligible for the CeFCiD trial, and although the total number was less (n = 14) with similar distribution between the arms (arm A, 8 vs. arm B, 6), it remains a limitation. Furthermore, in the CeFCiD trial, nasopharyngeal, sinonasal, lip and nasal carcinomas were permitted. These localisations were excluded in the EXTREME trial for differential biology and response to chemotherapy compared with oral and pharyngeal cancers. In total, this accounts for 11% (n = 21) of the study population, which needs to be respected in comparing the two trials. The high mortality rate in both arms in this study indicates that patients with R/M SCCHN are vulnerable, and multidrug regimens expose patients to an increased risk of toxicity and mortality. Recent studies have therefore focused on the optimisation of the chemotherapy backbone to fit patients' needs. In this context, the TPEx study evaluated docetaxel combined with cisplatin and cetuximab in the first-line setting and reported an encouraging clinical activity (PFS = 6.2 months; OS = 14.0 months; ORR = 51.9%) [12]. This observation has led to the development of the TPExtreme study, which tested the combination of docetaxel, cisplatin and cetuximab against PFC in a phase II trial.

However, more recently, a randomised phase II study indicated that further de-escalation to a cisplatin and

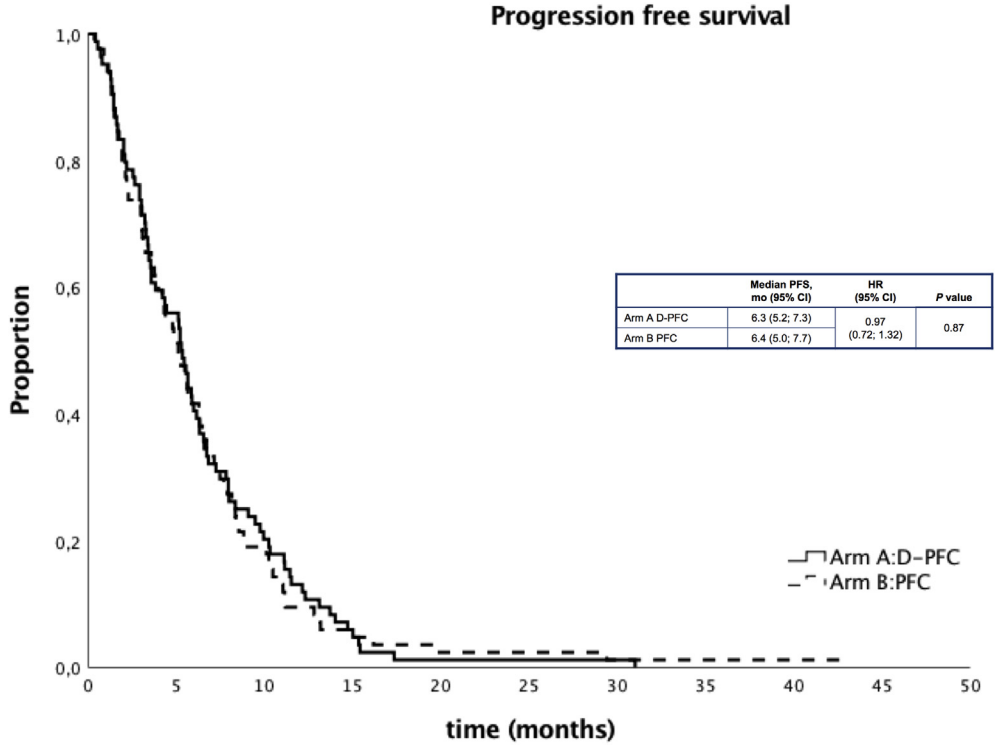

Fig. 3. Kaplan–Meier graph for progression-free survival. PFS = progression-free survival; CI = confidence interval; DPFC = docetaxel, platinum, fluorouracil, cetuximab.

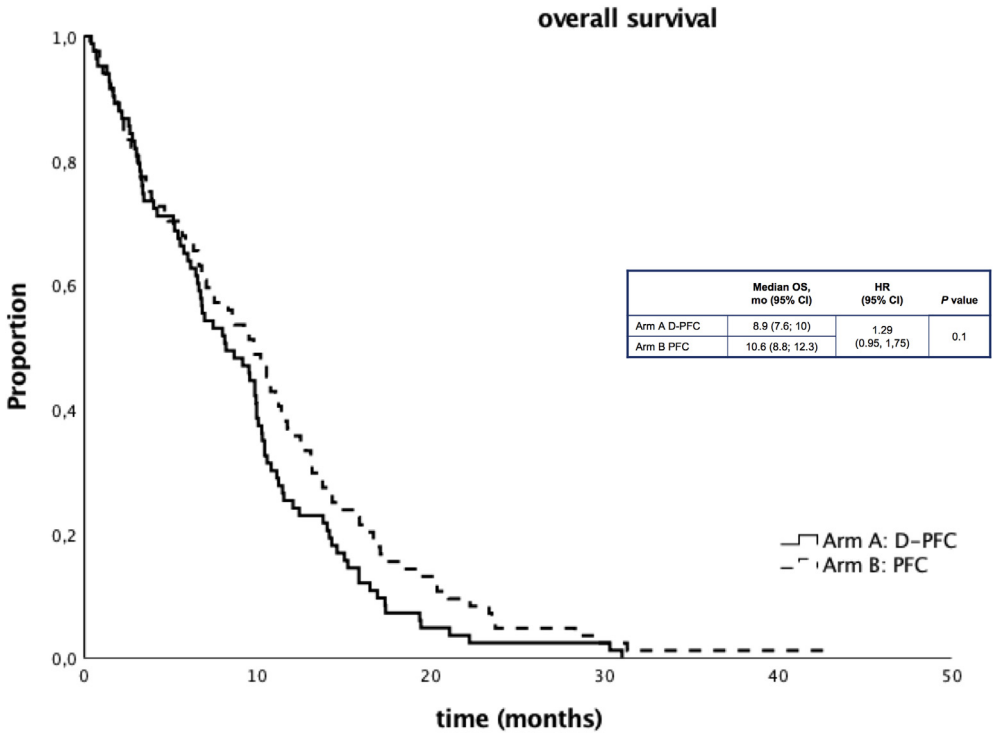

Fig. 4. Kaplan–Meier graph for overall survival. PFS = progression-free survival; CI = confidence interval; DPFC = docetaxel, platinum, fluorouracil, cetuximab.

Table 3
Response to treatment.

Response	Arm A, DPFC (n = 89)	Arm B, PFC (n = 91)	
Complete response	5 (5.6%)	5 (5.5%)	
Partial response	29 (32.6%)	24 (26.4%)	
Stable disease	30 (33.7%)	33 (36.3%)	
Progressive disease	15 (16.9%)	16 (17.6%)	
Not assessable	10 (11.2%)	13 (14.3%)	
Objective response rate	**34 (38.2%)**	**29 (31.9%)**	***p* = 0.9**
Disease control rate	**64 (71.9%)**	**62 (68.2%)**	

DPFC = docetaxel, platinum, fluorouracil, cetuximab.

cetuximab doublet may exert comparable efficacy compared with the combination of paclitaxel, cisplatin and cetuximab, which merits further exploration [13].

The median OS (10.6 months) and the proportion of patients who had an overall response (38.2%) in the cisplatin, 5-FU and cetuximab plus docetaxel arm in our study were similar to historical data, especially to the EXTREME study (median OS = 10.1 months and response in 36% of patients), indicating that intensification of chemotherapy is not warranted in R/M SCCHN [1].

There are several potential explanations for the failure of the experimental treatment to improve outcomes. Most likely, the addition of the fourth substance and also dose splitting reduced the relative dose intensity for cisplatin and thus precluded a significant improvement in the response rate that could have potentially contributed to improvement in PFS. Overall, addition of docetaxel to first-line cisplatin, 5-FU and cetuximab in patients with R/M SCCHN provided no benefit compared with the PFC standard regimen alone. Current studies especially the randomised TPExtreme trial comparing cisplatin, docetaxel and cetuximab with PFC will help to understand the role of taxanes in combination with cetuximab in the first-line setting (ClinicalTrial.gov no. NCT02268695), which will also be of high relevance for the design of future trials combining chemotherapy with immune checkpoint inhibitors.

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Conflict of interest statement

K.K. has been a consultant/advisory board member for Merck KGaA, Darmstadt, Germany, and Bristol-Myers Squibb. V.G. has been a consultant/advisory board member for AstraZeneca, Bristol-Myers Squibb, MSD and Merck KGaA, Darmstadt, Germany, and received research funding from Pfizer, Bristol-Myers Squibb and MSD. O.G.-L. has been a consultant for Merck KGaA, Darmstadt, Germany. G.M. has received

honoraria for lectures from Merck KGaA, Darmstadt, Germany, and Bristol-Myers Squibb. U.K. has been a consultant/advisory board member for Merck KGaA, Darmstadt, Germany. All remaining authors have declared no conflicts of interest. Merck KGaA, Darmstadt, Germany, reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.018.

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