

# Quality of Life of Patients with Head and Neck Cancer Receiving Cetuximab, Fluorouracil, Cisplatin Comparing to Cetuximab, Fluorouracil, Cisplatin, and Docetaxel within the CEFCD Trial

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## Keywords

Therapy intensification · Docetaxel · Head and neck cancer · Quality of life · Recurrent and metastatic

## Abstract

**Introduction:** CEFCD was a multicenter phase II study comparing the efficacy of cetuximab (C), 5-fluorouracil, and cisplatin with the same regimen adding docetaxel (D) in recurrent/metastatic head and neck cancer. The primary analysis

trial did not demonstrate survival benefit from therapy intensification in first-line recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN). The current analysis of the trial assessed the impact of treatment on quality of life (QoL). **Methods:** The European Organization for Research and Treatment of Cancer Quality of life Questionnaire QLQ-C30 and the tumor-specific module for head and neck cancer (QLQ-H&N35) were used to assess QoL at baseline (visit 1), after 2 (visit 3), 4 (visit 5), and 6 (visit 7) cycles of chemotherapy. **Results:** Of 180 patients included in this

study, 86 patients (47.8%) completed the questionnaires at baseline. Considering selected scores over treatment time, there was no difference in global QoL, dyspnea, swallowing, and speech between the treatment arms in the course. For fatigue, a significant increase from baseline to visit 3 ( $p = 0.02$ ), visit 5 ( $p = 0.002$ ), and to visit 7 ( $p = 0.003$ ) was observed for patients receiving D, cisplatin or carboplatin (P), 5-fluorouracil (F), and C. At the end of chemotherapy, the manifestation of fatigue was similar compared in the 2 treatment arms. **Discussion/Conclusion:** Therapy intensification not adversely affects selected scores of QoL of patients with recurrent and/or metastatic SCCHN. Nevertheless, fatigue seems to be pronounced in patients treated with D.

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## Introduction

For patients with recurrent squamous cell carcinoma of the head and neck (SCCHN) ineligible for locoregional curative treatment, prognosis remains poor. A median overall survival (OS) time of these patients remains around 10–14 months, which can be achieved with platinum (P)-based chemotherapy [1, 2]. For patients with a World Health Organization, performance status of  $\leq 1$  palliative P-based chemotherapy in combination with 5-fluorouracil (5-FU) and cetuximab (C) (EXTREME regimen) was considered the standard treatment option for more than a decade [3] before the checkpoint inhibitors were introduced. However, the survival remains disappointing, and only selected patients can be considered for this multiagent regimen. In this context and the known antitumor efficacy of taxanes in SCCHN, the CeFCiD study (trial registration CeFCiD 1108) evaluated whether the addition of docetaxel (D) to P, 5-FU and C (D-PFC) improved OS in first-line therapy. While the addition of D did not improve the progression-free survival (PFS) nor OS the incidence of grade 3 and 4 adverse events was similar. The results were for PFS: 6.3 months (95% CI: 5.2–7.3) versus 6.4 months (95% CI: 5.0–7.7) (HR 0.97, 95% CI: 0.72–1.32;  $p = 0.87$ ), and for OS: 8.9 months (95% CI: 7.6–10.0) versus 10.6 months (95% CI: 8.8–12.3) (HR 1.29, 95% CI: 0.95–1.175;  $p = 0.1$ ) [4]. Not only the efficacy of palliative treatment but also the associated toxicity and quality of life (QoL) issues are receiving increasing attention [5]. SCCHN and its treatment have an explicit impact on QoL [6, 7]. Not only the general QoL but also different important functions such as eating, swallowing, and speaking are negatively affected [8]. QoL is a major goal in the palliative treatment setting. Therefore, it was chosen as secondary objective of the CeFCiD study to compare the QoL of patients receiving D-PFC, or P, 5-FU, and C (PFC) for recurrent and/or metastatic SCCHN.

## Materials and Methods

### Study Design and Treatment

The CeFCiD study 1108 developed from the Arbeitsgemeinschaft internistischer Onkologen was a phase II randomized multicenter study. The protocol was approved by the independent Ethics Committees of each participating study center and also approved by the authorities in Germany. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Inclusion criteria were first-line recurrent and/or metastatic SCCHN, no local treatment options, performance status 0–1 according to the Eastern Cooperative Oncology Group (ECOG), and adequate renal, hepatic, and cardiac organ function. Patients were randomly assigned to receive D, cisplatin or carboplatin, 5-FU, and C (arm A: D-PFC) or cisplatin, 5-FU and C (arm B: PFC) [4]. Treatment was continued for a maximum of 6 cycles of chemotherapy. Patients who had at least a stable disease after 6 cycles received a C monotherapy every 2 weeks until disease progression or unacceptable toxicity. Randomization was stratified according to tumor recurrence (locally recurrent vs. metastatic) and ECOG (0 vs. 1). The primary objective was to assess the PFS. QoL was a secondary objective.

By evaluating QoL within the population, we addressed 2 questions: is there a difference in QoL for patients with recurrent or metastatic SCCHN in the course of treatment; and second: is there a difference in QoL between the 2 treatment arms at the end of treatment independent of number of cycles patients actually received.

### Measures

To measure the QoL, the validated Questionnaire from the European Organization for Research and Treatment (EORTC) (EORTC QLQ-C30, Version 3) [9] was used. This is a self-rating instrument to assess the QoL within 5 functional scales (physical role, emotional, cognitive, social, and functional scales), 3 multi-item symptom scales (pain, fatigue, and nausea/vomiting), and 6 single-item symptom scales (dyspnea, insomnia, appetite loss, diarrhea, obstipation, and financial difficulties). The core questionnaire was added through the tumor-specific module for head and neck cancer (EORTC QLQ-H&N35) [10], which assesses 18 symptoms and side effects of treatment for head and neck cancer patients, e.g., problems with teeth, sticky saliva and problems with eating, swallowing, or cough. According to an international phase III trial in head and neck cancer, conducted by the EORTC, results for fatigue scale as primary endpoint will be presented here [11]. Global QoL, dyspnea, swallowing, and speech problems were chosen as secondary endpoints. All results regarding QoL considering our 2 research questions as outlined above. Patients were scheduled to complete the questionnaires at randomization (baseline = visit 1), after 2 (visit 3), 4 (visit 5), and 6 cycles (visit 7) of chemotherapy. Cycles were repeated every 21 days.

### Statistical Analysis

Corresponding to the manual from the EORTC only those subscales were included, which have more than 50% of all items answered from the patients. At first, we estimated a raw score for each scale. This score was transformed to a linear scale ranging from 0 to 100. For global QoL scale and the functional scale higher scores correspond with higher functioning and thereby better QoL [9]. Whereas for symptom scales and single-item higher scores, correspond with more symptoms, high distress and impairment and indicates a worse QoL [10]. Following recommendation from the literature, a difference of 10 points on a scale from 0 to 100 is clinical meaningful [12, 13]. The level of compliance was computed for

**Table 1.** Baseline characteristics for patients completing QoL questionnaires

	All (N = 86)	Arm A (D-PFC) (N = 46)	Arm B (PFC) (N = 40)
Male, n (%)	72 (83.7)	39 (84.8)	33 (82.5)
Female, n (%)	14 (16.3)	7 (15.2)	7 (17.5)
Age, years, Median (min–max)	58 (42–76)	58 (43–74)	59 (42–76)
ECOG 0, n (%)	29 (33.7)	16 (34.8)	13 (32.5)
ECOG 1, n (%)	57 (66.3)	30 (65.2)	27 (67.5)
History of smoking, n (%)	70 (81.4)	36 (78.3)	34 (85.0)
History of alcohol, n (%)	22 (25.6)	12 (26.1)	10 (25.0)

SD, standard deviation; D, docetaxel; P, platinum; F, fluorouracil; C, cetuximab.

**Table 2.** Values of the QoL scales for arms of treatment to the different visits

	Visit 1 (baseline)		Visit 3		Visit 5		Visit 7	
	arm A (D-PFC)	arm B (PFC)	arm A (D-PFC)	arm B (PFC)	arm A (D-PFC)	arm B (PFC)	arm A (D-PFC)	arm B (PFC)
<i>Fatigue</i>								
Mean (SD)	47.22 (29.78)	49.03 (29.47)	58.44 (28.42)	51.56 (32.53)	65.28 (27.48)	49.67 (28.89)	55.56 (29.81)	52.53 (24.39)
N	46	40	27	25	16	17	6	11
<i>Global QoL</i>								
Mean (SD)	44.44 (24.68)	48.75 (20.81)	45.99 (19.25)	54.51 (21.84)	39.06 (18.69)	44.61 (23.19)	43.03 (24.65)	43.94 (24.18)
N	45	40	27	24	16	17	6	11
<i>Dyspnoe</i>								
Mean (SD)	29.71 (35.99)	30.77 (31.88)	23.46 (28.96)	33.33 (36.78)	35.71 (30.56)	41.67 (37.51)	22.22 (27.22)	36.36 (34.82)
N	46	39	27	24	14	16	6	11
<i>Swallow</i>								
Mean (SD)	43.30 (28.14)	49.17 (29.58)	44.55 (28.77)	48.91 (31.71)	38.02 (25.09)	55.39 (36.33)	26.39 (29.54)	47.73 (30.98)
N	46	37	27	23	16	17	6	11
<i>Speech</i>								
Mean (SD)	38.16 (28.94)	44.74 (30.97)	48.72 (33.42)	42.56 (35.08)	37.85 (27.76)	37.25 (32.32)	31.48 (33.27)	39.39 (33.10)
N	46	38	26	24	16	17	6	11

For analyses, we used imputations. SD, standard deviation; QoL, quality of life; D, docetaxel; P, platinum; F, fluorouracil; C, cetuximab.

baseline. Compliance was defined as the ratio of the total number of patients with at least one evaluable questionnaire over the total number of patients for whom a questionnaire was expected. Therefore, the number of forms received divided by the number of forms expected was calculated. Possible treatment effects on 5 scales of QoL, selected according to clinical relevance, (fatigue, global, dyspnea, swallow, and speech) were assessed by using linear mixed models with random intercept and treatment and time as fixed factors. Multiple imputation using available QoL measurements as predictors was applied for patients with at least a baseline measurement. Fifty imputation samples were used. The options “automatic” were chosen in SPSS which led for our data to FCS imputation as we did not have a monotone missingness pattern in the sense of Van Buuren ([14], p. 95). The analysis of interest refers to the treatment versus time interaction, global (4 df) and separately for pairwise of comparisons of 3 different time points (visit 3, 5, 7) to baseline. The same was done for the time end of therapy, regardless of the number of actually received chemotherapy cycles. The level of significance was 0.05 (two-sided), and no adjustment for multiple testing was performed. Analysis was calculated with SPSS release 23.

## Results

### Study Sample

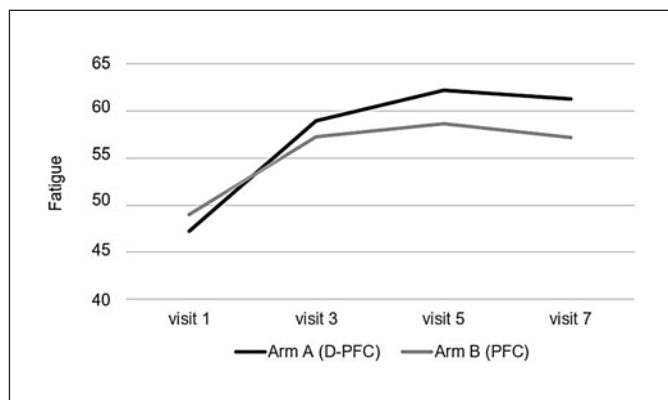
During August 2010 and September 2013, a total of 180 patients with the diagnosis of a head and neck cancer were recruited from 15 German study centers. Eighty-nine patients were randomized into arm A (D-PFC) and 91 into arm B (PFC). For more details, see Klinghammer et al. [4]. The compliance for the patients to return the QoL questionnaires at baseline was 47.8% ( $n = 86$ ). The baseline characteristics for patients completing the QoL questionnaires are shown in Table 1.

Dropout analyses showed no difference between patients who completed the questionnaires compared to those who did not complete the questionnaires in terms of gender ( $p = 0.953$ ), ECOG ( $p = 0.433$ ), history of smoking ( $p = 0.202$ ), history of alcohol ( $p = 0.397$ ), and ran-

domized arm of treatment ( $p = 0.299$ ). However, patients who completed the questionnaires were younger (58.41 years [standard deviation = 7.98] vs. 60.84 years [standard deviation = 8.34],  $p = 0.048$ ).

### QoL Over Time

At baseline, we found no difference between the treatment arms regarding fatigue, global QoL, dyspnea, swallowing, and speech. Table 2 shows the values of QoL scales. For none of the selected scales, any time versus treatment interaction was significant ( $p > 0.1$  for each comparison). Thus, no difference between treatment arms regarding QoL could be detected. Furthermore, for only one variable, a significant change over time was observed (fatigue, overall  $p = 0.012$ ). There was a significant increase from baseline to visit 3 (9.4 points,  $p = 0.02$ ), visit 5 (11.6 points,  $p = 0.002$ ), and visit 7 (12.8 points,  $p = 0.003$ ). Figure 1 shows the course of fatigue for both treatment arms over the time using imputed data.



**Fig. 1.** Mean scores for fatigue in both treatment arms over time.

For dyspnea ( $p = 0.094$ ), a trend to an increase was observed, for speech ( $p = 0.078$ ) a more complex pattern with increase at visit 3, decrease at visit 5 and a new increase at visit 7. However, no significant treatment effects were detectable for any of the scales.

### QoL at the End of Treatment

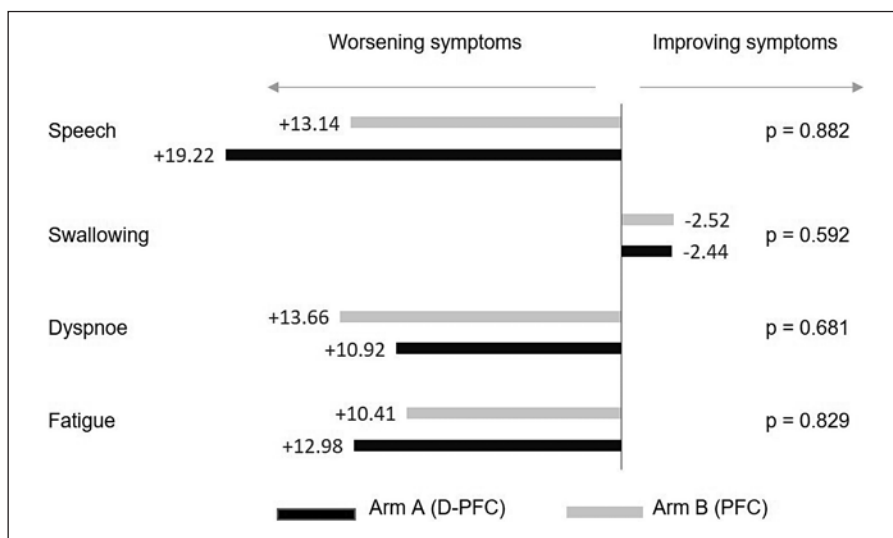
Only 24 patients fully completed the questionnaires until the end of the chemotherapy phase. Due to toxicity the number of chemotherapy cycles actually received, was between 1 and 6 cycles. At the end of chemotherapy treatment, 2 of these patients (8.3%) had an ECOG level of 0, 14 (58.3%) an ECOG level of 1, and 6 (25.0%) an ECOG level of 3, whereas this is unknown for 2 patients. For none of the selected scales, the time versus treatment interaction was significant ( $p > 0.1$ ). Figure 2 demonstrates the changes for the chosen scales from baseline to the end of chemotherapy within the 2 treatment arms.

## Discussion

This study was purposed to compare the course of 2 treatment regimens for patients with metastatic and recurrent HNSCC, receiving D-PFC, or PFC. The addition of D to the standard regimen was not superior in regard to survival and showed a higher level of toxicities as reported previously. Due to the fact, that D-PFC did not improve PFS and OS, QoL could be an important issue for the patients.

The compliance for the patients to return the questionnaires at baseline were unsatisfactory but in line with other studies. In the EXTREME trial [15] the compliance was less than 55% at all scheduled time points. We do not know how the QoL is for patients, who do not return their

**Fig. 2.** Mean changes for selected symptom scales from baseline to end of treatment score for arm A (D-PFC) and arm B (PFC).





questionnaires. It could be possible, that these patients have a poor QoL and/or are not able to fill out the questionnaires. The low adherence of patients reporting is a major limitation for QoL studies in palliative situations, especially in the field of head and neck cancer [16, 17]. The results concerning our first question, QoL over the treatment time, demonstrated that adding D does not negatively affect the QoL.

After 6 cycles of chemotherapy, there was no difference between the treatment arms regarding global QoL, dyspnea, swallowing, and speech problems. Speech and swallowing are demonstrated in other studies as very important for patients with head and neck cancer [18]. Within the CeFCiD trial, population fatigue was more pronounced during the course of treatment for those patients having received D. The increase in reported fatigue was particularly striking within the first cycles of chemotherapy. In the latter course, the level of reported fatigue was similar in both treatment arms, which might be due to the low compliance of patients that did not receive the planned 6 cycles.

Baseline scores for fatigue were found to be similar in both treatment arms, but higher than the reference score in patients with head and neck cancer [19]. Comparing our results of fatigue with the pivotal EXTREME-study the results were similar after 3 cycles of chemotherapy. There was no difference for the PFC arm in our study after 2 or 4 cycles (48.12 vs. 51.56 or 49.67) [15].

In the recently reported TPEx trial, 5-FU was substituted in the PFC regimen by D [20]. The level of reported fatigue of grade 3 or higher was 18% in the PFC arm versus 13% in the experimental arm containing D. So far there is no evidence that D is associated with an increase in fatigue over other chemotherapeutic agents. We therefore interpret the increase in fatigue in the D-PFC arm as a result of adding all agents.

The analysis for our second question, regarding QoL at the end of treatment, indicates similar results, independent of the number of cycles actually received. Considering fatigue at the end of chemotherapy patients in our study showed a high score for fatigue (60.29 respectively 59.44). These are higher compared with head and neck cancer patients in follow-up in the study by Krebber et al. [21] (48.58).

However, these results must be interpreted with caution due to varying instruments used to assess QoL. A systematic review of head and neck cancer QoL instruments reported that there is no gold standard questionnaire yet [17]. Nevertheless, the EORTC questionnaires show good psychometric properties and are used in many interventional studies. Furthermore, the results have to be classified against the background of the sample size and the rate of feedback.

The results of our study demonstrated that the addition of D-PFC did not result in different QoL compared to the traditional PFC regimen. This statement only applies to the population, which returned the questionnaires. D-PFC can therefore not be advocated as a feasible treatment option due to the reported toxicities in the whole population. Fortunately, with the introduction of checkpoint inhibitors into the treatment algorithm of head and neck cancer less toxic protocols are emerging with a significant improvement in QoL. Since for the majority of patients in the palliative setting, QoL is the primary goal of treatment thorough evaluation should be implemented in every clinical trial.

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### Statement of Ethics

Study approval statement: This study protocol was centrally reviewed and approved for all German study centers by the LAG-So Ethics Cie Berlin, approval number [ZS EK 10 310/09].

Consent to participate statement: Written informed consent was obtained from all individual participants included in the study.

### 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 consultant/advisory board member Astra Zeneca, Bristol-Myers Squibb, MSD, 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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## Author Contributions

The followings are the authors' contributions: study concepts: M.K. and U.K; study design: M.K. and U.K; data acquisition: K.K., M.K., and U.K; quality control of data and algorithms: K.K., U.G., M.K., and V.G; data analysis and interpretation: P.M., U.G., K.K., and U.K; statistical analysis: P.M., U.G., and K.K; manuscript preparation: U.G. and K.K; manuscript editing: all; manuscript review: all.

## Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## References

- 1 Peyrade F, Cupissol D, Geoffrois L, Rolland F, Borel C, Ciais C, et al. Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: review of the literature and proposal for management changes. *Oral Oncol.* 2013;49(6):482–91.
- 2 Price KA, Cohen EE. Current treatment options for metastatic head and neck cancer. *Curr Treat Options Oncol.* 2012;13(1):35–46.
- 3 Vermorken 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(11):1116–27.
- 4 Klinghammer K, Gauler T, Dietz A, Grünwald V, Stöhlmacher J, Knipping S, et al. 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). *Eur J Cancer.* 2019;122:53–60.
- 5 Goerling U, Stickel A. Quality of life in oncology. In: Goerling U, editor. *Recent results cancer research.* Springer; 2014. Vol. 197; p. 137–52.
- 6 Verdonck-de Leeuw IM, van Nieuwenhuizen A, Leemans CR. The value of quality-of-life questionnaires in head and neck cancer. *Curr Opin Otolaryngol Head Neck Surg.* 2012;20(2):142–7.
- 7 Harrington KJ, Ferris RL, Blumenschein G Jr, Colevas AD, Fayette J, Licitra L, et al. Nivolumab versus standard, single-agent therapy of investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck (CheckMate 141): health-related quality-of-life results from a randomised, phase 3 trial. *Lancet Oncol.* 2017;18(8):1104–15.
- 8 Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet.* 2008;371(9625):1695–709.
- 9 Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85:365–76.
- 10 Bjordal K, Hammerlid E, Ahlner-Elmqvist M, de Graeff A, Boysen M, Evensen JF, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer quality of life questionnaire-H&N35. *J Clin Oncol.* 1999;17(3):1008–19.
- 11 Bottomley A, Tridello G, Coens C, Rolland F, Tesselaar MET, Leemans CR, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results. *Cancer.* 2014;120(3):390–8.
- 12 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* 1998;16(1):139–44.
- 13 Cocks K, King MT, Velikova G, Fayes PM, Brown JM. Quality, interpretation and presentation of European Organisation for Research and Treatment of Cancer quality of life questionnaire core 30 data in randomised controlled trials. *Eur J Cancer.* 2008;44(13):1793–8.
- 14 van Buuren S. *Flexible imputation of missing data.* Boca Raton: CRC Press (Chapman & Hall); 2012.
- 15 Mesía R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, et al. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Ann Oncol.* 2010;21(10):1967–73.
- 16 Licitra L, Mesía R, Keilholz U. Individualised quality of life as a measure to guide treatment choices in squamous cell carcinoma of the head and neck. *Oral Oncol.* 2016;52:18–23.
- 17 Ojo B, Genden EM, Teng MS, Milbury K, Misiukiewicz KJ, Badr H. A systematic review of head and neck cancer quality of life assessment instruments. *Oral Oncol.* 2012;48(10):923–37.
- 18 Tschiesner U, Sabariego C, Linseisen E, Becker S, Stier-Jarmer M, Cieza A, et al. Priorities of head and neck cancer patients: a patient survey based on the brief ICF core set for HNC. *Eur Arch Otorhinolaryngol.* 2013;270(12):3133–42.
- 19 Scott N, Fayes P, Bottomley A. *EORTC QLQ-C30 reference value manual.* Brussels, Belgium: EORTC Quality of Life Group Publications; 2008.
- 20 Guigay J, Keilholz U, Mesia R, Vintonenko N, Bourhis J, Auperin A. TPEX extreme randomized trial: TPEX versus extreme regimen in 1st line recurrent/metastatic head and neck squamous cell carcinoma. *J Clin Oncol.* 2015;33(15\_Suppl):TPS6087.
- 21 Krebber AM, Jansen F, Cuijpers P, Leemans CR, Verdonck-de Leeuw IM. Screening for psychological distress in follow-up care to identify head and neck cancer patients with untreated distress. *Support Care Cancer.* 2016;24(6):2541–8.