Platinum-based chemotherapy plus cetuximab first-line for Asian patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: Results of an open-label, single-arm, multicenter trial

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Accepted 4 April 2014
Published online 17 September 2014 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23707

ABSTRACT: *Background.* The purpose of this study was to assess the efficacy, safety, and pharmacokinetics of cisplatin-based chemotherapy plus cetuximab as first-line treatment in Chinese and Korean patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN).

Methods. Patients ($n = 68$) received cetuximab weekly plus 3-week cycles of cisplatin/5-fluorouracil (5-FU) chemotherapy for up to 6 cycles. The primary endpoint was overall response rate.

Results. The overall response rate was 55.9%, including 2 complete responses (CRs). Median overall survival (OS) was 12.6 months and median progression-free survival (PFS) was 6.6 months. Grade 3/4 adverse events (AEs) were reported in 41 (60.3%) patients. The safety profile was in line with previous clinical experience. The pharmacokinetic profile was in line with that observed with cetuximab in white and Japanese patients.

Conclusion. The efficacy, safety, and pharmacokinetic findings from this study support the use of first-line platinum-based chemotherapy plus cetuximab in Chinese and Korean patients with recurrent and/or metastatic SCCHN (ClinicalTrials.gov NCT01177956). © 2014 The Authors Head & Neck Published by Wiley Periodicals, Inc. *Head Neck* **37:** 1081–1087, 2015

KEY WORDS: cetuximab, Chinese, EXTREME trial, head and neck cancer, recurrent and metastatic squamous cell carcinoma

INTRODUCTION

Cancers of the oral cavity, pharynx, and larynx account for approximately 4% of new cancer cases annually and are particularly prevalent in south and southeast Asian countries.[1] In China, the annual incidence of oral and pharyngeal cancers is estimated to be 2.95 per 100,000 of the population, and these cancers are associated with an annual mortality of 1.33 per 100,000.[2]

Approximately 40% of patients with squamous cell carcinoma of the head and neck (SCCHN) present with stage I or II disease and are treated with surgery or radiotherapy.[3] For the remaining 60% of patients who present with locally advanced disease, a combination of chemotherapy and radiotherapy is usually recommended.[4,5] Despite this treatment, disease will recur locally in the majority of patients and 20% to 30% of patients will develop distant metastases. Patients with recurrent and/or metastatic SCCHN not suitable for local therapy are usually offered chemotherapy as palliative treatment. Combinations of cisplatin and 5-fluorouracil (5-FU) or a taxane have commonly been used, delivering response rates of around 30% and median survival rates of 6 to 9 months.[6–12] In 2008, the phase III EXTREME trial demonstrated that the addition of the epidermal growth factor receptor-targeted

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Contract grant sponsor: The trial was sponsored by Merck KGaA, Darmstadt, Germany.

The preliminary results of this work were presented at the 4th International Conference on Innovative Approaches in Head and Neck Oncology held in Barcelona, Spain, February 7–9, 2013.

monoclonal antibody, cetuximab, to first-line platinum/5-FU chemotherapy significantly prolonged overall survival (OS) and progression-free survival (PFS) and improved the chance of a response compared with platinum-based chemotherapy alone in Western patients with recurrent and/or metastatic SCCHN.[13] The adverse event (AE) profile of platinum-based chemotherapy plus cetuximab was similar to that of platinum-based chemotherapy alone, although grade 3/4 skin rash, sepsis, and hypomagnesemia were more common with the addition of cetuximab.[13] This pivotal trial led to the regulatory approval of cetuximab for the first-line treatment of recurrent and/or metastatic SCCHN within the European Union in 2008 and in the United States in 2011.

In many countries, the standard treatment for recurrent and/or metastatic SCCHN is now platinum-based chemotherapy plus cetuximab,[5] as is recommended in National Comprehensive Cancer Network and EHNS-ESTRO-ESMO guidelines.[4,5] Based on the positive results of the clinical trials,[13,14] cetuximab was also approved for use in combination with platinum-based chemotherapy as the first-line treatment in patients with recurrent and/or metastatic SCCHN in Japan in 2012.[15] In China, however, the optimal therapeutic options for Chinese patients are unknown owing to the lack of data from rigorous randomized clinical trials, although the addition of cetuximab to platinum-based chemotherapy is suggested in the Chinese treatment guidelines.[16,17] The combination of cisplatin and 5-FU is generally the first choice of treatment regimen with cisplatin being given at a lower dose than commonly used in Western countries, because of the different treatment tolerability in Asian patients.[18,19]

Pharmacokinetic studies of cetuximab have generally been confined to predominantly white populations.[20,21] The pharmacokinetics of cetuximab in Japanese patients have been reported in a phase I trial, and the pharmacokinetic profile of cetuximab seemed to be similar to that seen in white patients.[22] The purpose of the present trial was to investigate the efficacy and safety results obtained with first-line cisplatin/5-FU chemotherapy plus cetuximab in Chinese and Korean patients with recurrent and/or metastatic SCCHN and to ascertain whether the results were similar to those reported for Western patients in the EXTREME trial.[13]

PATIENTS AND METHODS

Patients

The inclusion criteria for patients in this study were similar to those for the EXTREME trial. The main inclusion criteria were: in-patient at least 18 years old with histologically/cytologically confirmed recurrent and/or metastatic SCCHN unsuitable for local therapy with at least 1 measurable lesion (identified by CT scan or MRI); Karnofsky performance status (KPS) $\geq$80%; serum calcium within the normal range; and adequate hematologic, hepatic, and renal function.

Exclusion criteria included nasopharyngeal carcinoma, prior systemic chemotherapy (except as part of multimodal therapy completed >6 months before study entry), surgery or irradiation within 4 weeks of study entry, current or prior cardiac or pulmonary disease, high risk of uncontrolled arrhythmia or cardiac insufficiency, and active infection. All patients gave written informed consent to participate in the study.

Study design

This was an open-label, single-arm, multicenter study performed in China and South Korea (ClinicalTrials.gov NCT01177956). Treatments were similar to those in the EXTREME trial, except that patients received lower doses of cisplatin and 5-FU because of chemotherapy tolerability differences between Asian and white populations (in accordance with the treatment guidelines for Asian patients).[17]

The experimental regimen comprised cetuximab every 7 days (120-minute intravenous infusion of 400 mg/m^2 initial dose followed by 60-minute infusions of 250 mg/m^2/week) together with 3-week cycles of chemotherapy with cisplatin (60-minute intravenous infusion of 75 mg/m^2, day 1) and 5-FU (24-hour continuous infusion of 750 mg/m^2/day on days 1–5). Chemotherapy was continued for a maximum of 6 cycles, or until the occurrence of unacceptable toxicity or disease progression within this time period. Patients with unacceptable toxicity to one of the study drugs received the tolerated drugs until disease progression. Patients discontinuing treatment before disease progression remained on study. After 6 cycles of chemotherapy, patients who had at least stable disease received cetuximab monotherapy until disease progression or unacceptable toxicity.

Tumors were assessed for response every 6 weeks until disease progression, including in those patients who discontinued treatment before disease progression. Partial response (PR), complete response (CR), and progressive disease were confirmed with CT or MRI within 4 weeks. Patients were followed up for at least 30 days after the final tumor assessment visit (and before commencement of any subsequent anticancer therapy). After this, patients were then followed up for information on further anticancer treatment and survival every 3 months until death, loss to follow-up, or withdrawal of consent.

The study protocol and major amendments were approved by institutional review boards or independent ethics committees and health authorities, according to country-specific laws. The trial was conducted in accordance with the Declaration of Helsinki, as well as with the International Conference on Harmonization Note for Guidance on Good Clinical Practice.

Endpoints

The primary endpoint was the overall response rate (CR or PR) assessed by the investigator and their radiologist, according to modified World Health Organization criteria, and confirmed 28 days after the criteria were first met.

Secondary efficacy endpoints were OS (the time from first administration of trial treatment to death); PFS (time from the first administration of trial treatment to first observation of progressive disease [radiological or clinical, if radiological progressive disease was not available], or death because of any cause which occurred within 12 weeks from the last tumor assessment or the first

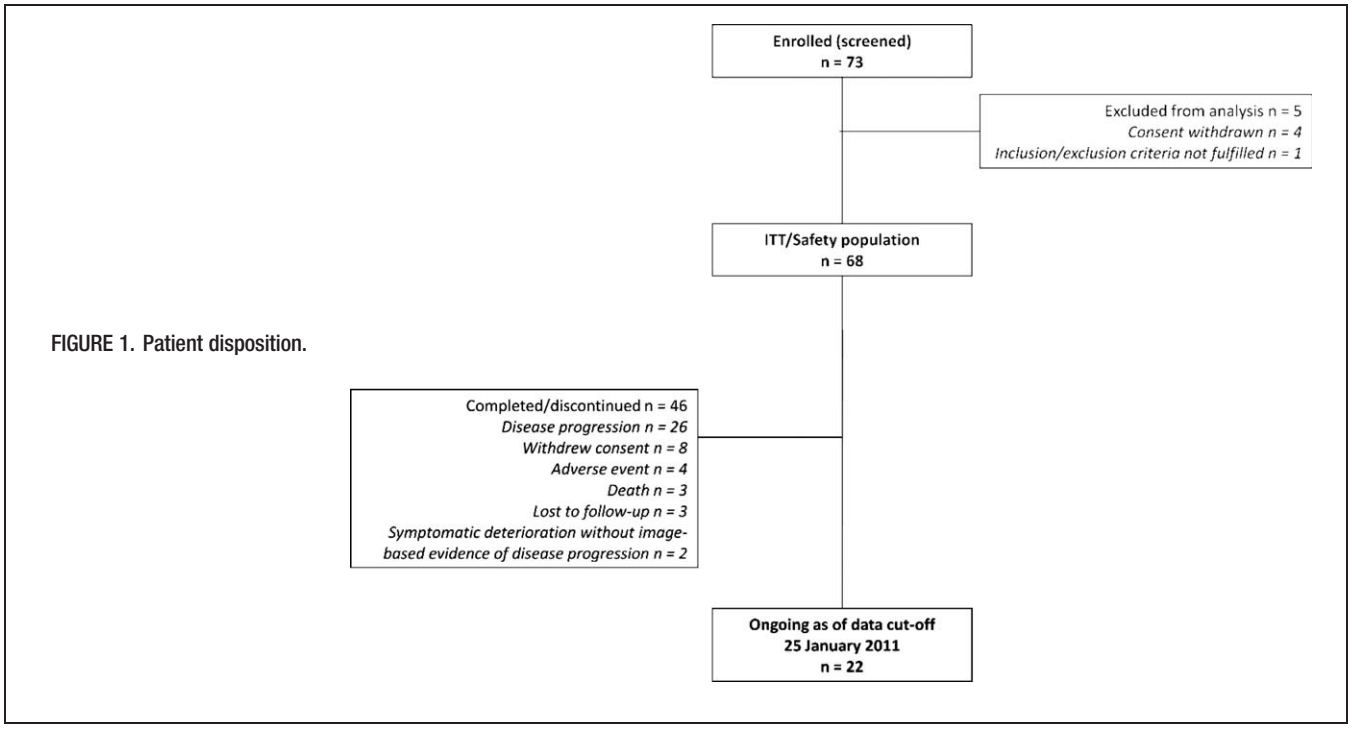

FIGURE 1. Patient disposition.

administration of trial treatment, whichever was later); time to progression (TTP; time from the first administration of trial treatment to progressive disease); and duration of response (time from the first assessment of CR or PR until the event defining PFS time).

AEs were coded using the Medical Dictionary for Regulatory Activities (version 13.0) and graded using the National Cancer Institute-Common Terminology Criteria for Adverse Events (version 3.0). AE categories of special interest (skin reactions, acne-like rash, cardiac events, and infusion-related reactions) were based on selected Medical Dictionary for Regulatory Activities preferred terms.

The pharmacokinetic profile of cetuximab was evaluated based on serum cetuximab concentrations in blood samples taken after the fourth dose of cetuximab (day 22). Evaluation of repeated weekly cetuximab administration was based on serum cetuximab concentrations in blood samples taken before infusion (trough levels). Cetuximab serum concentrations were analyzed using a validated enzyme-linked immunosorbent assay.

Statistics

Efficacy analyses were performed on the intent-to-treat/safety population (all patients who received at least 1 dose of cetuximab or chemotherapy). Continuous variables were summarized using descriptive statistics; qualitative variables were summarized by means of counts and percentages. Unless otherwise stated, the calculation of proportions included the missing category. No formal statistical tests were performed.

The study was designed as a bridging trial. The purpose of this study was to demonstrate that the efficacy and safety results obtained in the Asian population are similar to those obtained in the Western population, such as the pivotal EXTREME study. Thus, a small sample size of 65 patients and a single arm trial was planned.

Overall response rate was defined as the number of patients with a best overall response of CR or PR divided by the number of patients in the intent-to-treat population. The overall response rate for the intent-to-treat population is presented with 2-sided Clopper-Pearson 95% confidence intervals (CIs). Assuming an expected overall response rate of 35% in this population, the probability of observing an estimated response rate of at least 30% is 80% based on the binomial distribution. When the sample size is 65, a 2-sided 95% CI for the response rate using the large sample normal approximation will extend 0.116 from the observed proportion in both directions for an assumed proportion of 0.35.

For OS, patients who were still alive at the analysis cutoff date or were lost to follow-up were censored at the last recorded date they were known to be alive. The PFS time of patients who did not have objective evidence of progressive disease but died after 2 or more missed consecutive tumor assessments was censored on the date of last tumor assessment or first administration of trial treatment (whichever was earlier). For the time-to-event variables (PFS, OS, TTP, and duration of response), Kaplan–Meier estimates (product-limit estimates) for the intent-to-treat population are presented together with a summary of associated statistics, including the corresponding 2-sided 95% CIs. All statistical analyses were performed using SAS software, version 9.1.

The pharmacokinetic parameters of cetuximab after the fourth administration were calculated by non-compartmental standard methods using the software KINETICA, version 4.4.1.

RESULTS

Patient disposition

Between December 25, 2009, and September 17, 2010, 73 patients were enrolled at 13 centers in mainland China and 1 in South Korea. Of these patients, 5 did not receive any study treatment and were not included in the intent-to-treat population. In 4 patients, this was due to withdrawal of consent and 1 patient was withdrawn as they did not meet the inclusion criteria. Patient disposition is summarized in Figure 1. At the clinical cutoff date of November 15, 2012, all 68 patients had completed or discontinued the trial. Median follow-up time was 25.9 months.

Patient baseline characteristics

Patient baseline characteristics are summarized in Table 1. The majority of patients were men (72.1%), the median age was 55.7 years, and most patients were Chinese (92.6%) with 5 (7.4%) being Korean. The main primary tumor site was the oral cavity (38.2%) followed by the larynx (23.5%). Most patients (73.5%) had a KPS of $\geq$80.

Most patients (n = 62; 91.2%) had received prior therapy for cancer-related disease: 55 patients (80.9%) had received surgery, 43 patients (63.2%) had been treated with radiotherapy, 22 patients (32.4%) had received chemotherapy, and 5 patients (7.4%) had experienced other types of therapy. Of the 15 patients (22%) with metastatic disease, 9 had received prior treatment and 6 had not received any previous therapy for cancer-related disease.

Treatment exposure

The median duration of cetuximab treatment was 21.8 weeks (range, 1.0–125 weeks). After the first infusion, 29 patients (42.6%) received up to 18 cetuximab infusions, 6 (8.8%) received 19 to 21, and 33 (48.5%) received more than 22 infusions. The median cumulative dose was 5402.5 mg/m^2 (range, 398.8–31,375.6 mg/m^2) and 63 patients (92.6%) received cetuximab at a relative dose intensity of $\geq$80% (excluding the first dose). Relative dose intensity was calculated for patients receiving at least 2 cetuximab administrations (n = 65).

For cisplatin, the median duration of therapy was 18.0 weeks (range, 3.0–23.1 weeks). Forty patients (58.8%) had 6 infusions, 9 (13.2%) had 4 or 5, 13 (19.1%) had 2 or 3, and 6 (8.8%) had 1 infusion. The median cumulative dose of cisplatin was 405.1 mg/m^2 (range, 74.6–451.8 mg/m^2) and 49 patients (72.1%) received cisplatin at a relative dose intensity of $\geq$90%.

The median duration of 5-FU therapy was 18.0 weeks (range, 3.0–23.1 weeks). Thirty-eight patients (55.9%) had 6 infusions, 9 (13.2%) had 4 or 5, 13 (19.1%) had 2 or 3, and 8 (11.8%) had 1 infusion. The median cumulative dose of 5-FU was 19,703.9 mg/m^2 (range 3738.7–23,366.6 mg/m^2) and 46 (67.6%) received 5-FU at a relative dose intensity of $\geq$90%.

Post-study anticancer treatment was received by 33 patients. The most common types of treatment received were chemotherapy (n = 25) and radiotherapy (n = 12).

TABLE 1. Baseline patient and disease characteristics.

Characteristic	Intent-to-treat/safety population n = 68
Age, y	
Median (range)	55.7 (30–79)
<65, no. (%)	55 (80.9)
≥65, no. (%)	13 (19.1)
Sex, no. (%)	
Male	49 (72.1)
Female	19 (27.9)
Ethnic origin, no. (%)	
Asian (Chinese)	63 (92.6)
Asian (Korean)	5 (7.4)
KPS, no. (%)	
90	18 (26.5)
80	50 (73.5)
Disease duration (from initial diagnosis to informed consent), mo	
Median (range)*	14.3 (0−137.9)
Extent of disease, no. (%)	
Recurrent, not metastatic	31 (45.6)
Distant metastasis, not recurrent	15 (22.1)
Metastatic, including recurrent	22 (32.4)
Primary tumor site, no. (%)	
Oral cavity	26 (38.2)
Larynx	16 (23.5)
Hypopharynx	8 (11.8)
Oropharynx	7 (10.3)
Other†	11 (16.2)
Histology, no. (%)	
Well differentiated	23 (33.8)
Moderately differentiated	15 (22.1)
Poorly differentiated	14 (20.6)
None otherwise specified/unknown/missing	16 (23.5)
Previous treatment for SCCHN cancer-related disease, no. (%)‡	
Any	62 (91.2)
Radiotherapy	43 (63.2)
Chemotherapy	22 (32.4)
Surgery	55 (80.9)
Other	5 (7.4)

Abbreviations: KPS, Karnofsky Performance Scale; SCCHN, squamous cell carcinoma of the head and neck.

* Sixty-six patients (duration is missing for 2 patients with missing date of initial diagnosis/date of recurrence or metastasis).

† Paranasal sinuses (n = 3), non-classifiable (n = 8).

‡ Patients could have received more than 1 course of a particular therapy and more than 1 type of therapy, but were counted only once for a particular therapy, irrespective of the number of different courses received.

Efficacy

Tumor response results are shown in Table 2. The best overall response rate was 55.9% (95% CI, 43.3–67.9; Table 2), with 2 CRs and 36 PRs. A further 29.4% of patients had stable disease. Seven patients were not evaluable for tumor response: 6 had no on-study tumor assessment (death [n = 2], consent withdrawn [n = 3], lost to follow-up [n = 1]) and 1 patient had only 1 on-study tumor assessment. The median follow-up time was 25.9 months (95% CI, 25.8–29.7). At the clinical cutoff date, 82.4% of patients had experienced progressive disease or died within 12 weeks after the last tumor assessment. The median PFS was 6.6 months (95% CI, 5.1–7.7; see

TABLE 2. Tumor response results.

Efficacy parameter	No. of patients = 68
Response rate, no. (%)	
Overall response* rate	38 (55.9)
95% CI	43.3–67.9
CR	2 (2.9)
PR	36 (52.9)
Stable disease	20 (29.4)
Progressive disease	3 (4.4)
Not evaluable†	7 (10.3)
Duration of response, mo	
Median	6.1
95% CI	5.4–7.8

Abbreviations: CI, confidence interval; CR, complete response; PR, partial response.
* Overall response = CR + PR.
† No on-study tumor assessment ($n = 6$; death [$n = 2$], consent withdrawn [$n = 3$], lost to follow-up [$n = 1$]) and only 1 on-study tumor assessment ($n = 1$).

Figure 2) and the median TTP was 7.0 months (95% CI, 5.6–8.1). Fifty-six patients (82.4%) had died at the clinical cutoff date, and the median OS time was 12.6 months (95% CI, 9.1–15.0; see Figure 3). The 6-month OS rate based on 48 patients was 76.4%.

Safety

AEs were reported in 67 patients (98.5%). The most common AEs (>30% patients) were: leukopenia/white blood cell count decreased (47.1%), weight decreased (42.6%), nausea (39.7%), hypomagnesemia and neutropenia/neutrophil count decreased (both 38.2%), rash (35.3%), and hypokalemia and constipation (both 32.4%). Sixty-four patients (94.1%) had treatment-related AEs and 56 (82.4%) had cetuximab-related AEs. The most common cetuximab-related AEs were rash (35.3%), of which all but 1 instance were grade 1 or 2, hypomagnesemia (25.0%), acne (14.7%), pruritus (13.2%), and hypokalemia and dermatitis acneiform (11.8%, each).

Serious AEs were reported in 13 patients (19.1%): 6 patients (8.8%) had treatment (chemotherapy and/or cetuximab)-related and 6 patients (8.8%) had cetuximab-related AEs.

Grade 3/4 AEs were reported in 41 patients (60.3%; Table 3). The most common were neutropenia or neutrophil count decreased, hypokalemia, and leukopenia/white blood cell count decreased. Thirty patients (44.1%) had treatment-related grade 3/4 AEs. In 15 patients (22.1%), grade 3 ($n = 10$) and grade 4 ($n = 5$) AEs were considered to be related to cetuximab. The most common cetuximab-related grade 3/4 event was hypomagnesemia ($n = 5$).

For grade 3/4 AEs within the special interest categories, there was 1 case of grade 3 acne-like rash (no cases of grade 4), one grade 4 cardiac event (infarction/ischemia), and two reports of grade 3 anaphylaxis/allergy. Two treatment-related AEs, pneumonitis and microcytic anemia, led to death in 2 patients. Both AEs were assessed as being related to cetuximab and chemotherapy, although chemotherapy was considered to be the primary reason for the death because of microcytic anemia.

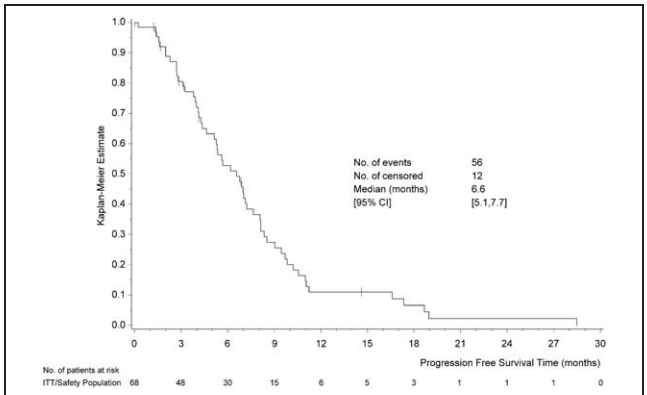

FIGURE 2. Kaplan–Meier estimate of progression-free survival (PFS).

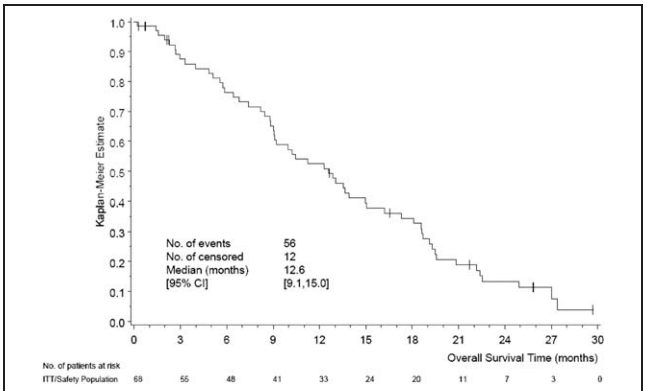

FIGURE 3. Kaplan–Meier estimate of overall survival (OS).

Pharmacokinetics

The pharmacokinetic analysis was conducted on a subgroup of 22 Chinese patients, selected before treatment initiation on the basis of time of entry into the study (generally the first patients entering the trial at each site).

TABLE 3. Grade 3–4 adverse events occurring in >2% of patients.

AE	No. of patients (%) (n = 68)
Any	41 (60.3)
Neutropenia or neutrophil count decreased	11 (16.2)
Hypokalemia	8 (11.8)
Leukopenia/WBC count decreased	6 (8.8)
Hypomagnesemia	5 (7.4)
Anemia/hemoglobin decreased	4 (5.9)
Hyponatremia	4 (5.9)
Thrombocytopenia/platelet count decreased	3 (4.4)
Diarrhea	2 (2.9)
Mouth ulceration	2 (2.9)
Stomatitis	2 (2.9)
Asthenia	2 (2.9)
Anaphylactic reaction	2 (2.9)
Hypocalcemia	2 (2.9)
Lung infection	2 (2.9)
Pneumonia	2 (2.9)

Abbreviations: AE, adverse events; WBC, white blood cell.

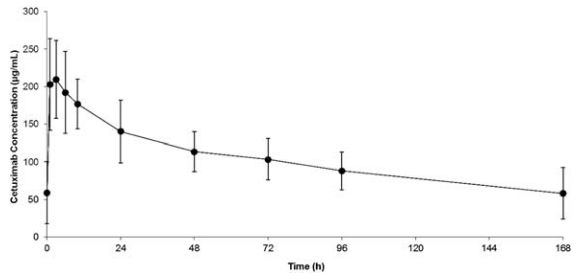

FIGURE 4. Mean cetuximab concentration-time profile after fourth infusion (day 22).

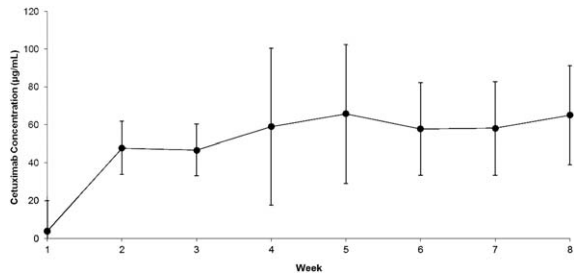

FIGURE 5. Mean serum cetuximab trough concentrations.

The mean cetuximab concentration-time profile after the fourth infusion (day 22) is shown in Figure 4. After the fourth dose (day 22), the mean C_{max} (observed maximum serum concentration) was 229 µg/mL (range, 170–343), the mean $t_{1/2}$ (apparent elimination half-life) was 114.8 hours (range, 52.8–363.8), and the mean area under the concentration-time curve$_{0-t}$ (up to the last time point in the dosing interval at which cetuximab shows concentrations above the lower limit of quantification) was 17121 µg/mL*h (range, 10,343–25,582). Clearance (CL_{ss}) was 0.024 L/h (range, 0.017–0.036) and the volume of distribution (V_{ss}) was 3.84 L (range, 1.94–9.73). After multiple dosing, mean cetuximab trough concentrations reached a level of approximately 60 µg/mL by week 4, and thereafter remained approximately constant (see Figure 5).

DISCUSSION

In this study of Chinese and Korean patients with recurrent and/or metastatic SCCHN, the combination of first-line cisplatin/5-FU chemotherapy and cetuximab was associated with a best overall response rate of 55.9%, a median OS of 12.6 months, and a median PFS of 6.6 months. These efficacy results are comparable to those achieved with platinum-based chemotherapy/cetuximab in the phase III EXTREME trial (overall response rate, 36%; OS, 10.1 months; and PFS, 5.6 months).[13] Although the 2 trials adopted similar eligibility criteria, treatment, and follow-up schedules, there remained some differences in terms of the composition of baseline characteristics and the dosing of the backbone chemotherapy, which may explain, in part, why key efficacy outcomes look numerically slightly better in the current trial. For example, in the current trial, 6 patients had not received previous treatment, which may, in part, account for the higher response rate compared with the EXTREME trial. It must also be noted that treatment of locally advanced SCCHN in Asia is generally based on surgical approaches and radiotherapy rather than chemotherapy. Therefore, the tumors of Asian patients in the recurrent/metastatic phase may be more chemosensitive than those of Western patients who are more likely to have received chemotherapy during the less advanced stages of their disease. In support of this, a higher proportion of patients in the EXTREME study did receive prior chemotherapy (40.5%) than in the present study (32.4%).

Argiris et al[23] analyzed combined data from 2 clinical trials in patients with recurrent and/or metastatic SCCHN treated with cisplatin-based combination chemotherapy in 2 randomized, phase III trials and suggested some unfavorable predictors for response and survival outcomes, including a primary tumor site other than oropharynx (or a primary tumor in the oral cavity or hypopharynx), prior radiation therapy, and well/moderate tumor cell differentiation. The EXTREME trial showed that the primary tumor site had a significant impact on the median OS ($p = .03$) and median PFS ($p = .02$) in favor of oral cavity. The patient population in this study was similar to that in the platinum-based chemotherapy plus cetuximab arm of the EXTREME study, with a few exceptions: in the present study, all patients had a KPS of $\geq$80, compared to 88% in the EXTREME study; in addition, there were fewer patients with oropharyngeal cancer as the primary tumor site in the present study compared to the EXTREME trial (10.3% vs 36%) but more with cancer of the oral cavity (38.2% vs 21%). Human papillomavirus (HPV) and p16 tumor status may also affect treatment response. A retrospective analysis of the EXTREME study suggests that patients with HPV+ or p16+ tumors treated with chemotherapy plus cetuximab seem to have a more favorable outcome than those with HPV- or p16- tumors.[24] However, HPV or p16 status was not analyzed in this study and more clinical evidence is required to confirm if any of the baseline characteristics of the patients were predictive values for efficacy outcomes. The subgroup results in the EXTREME trial and the prognostic factors identified by Argiris et al[23] should be interpreted cautiously.[13] It should also be mentioned that in the EXTREME trial approximately one third of patients were treated with carboplatin and two thirds of patients were treated with cisplatin as chemotherapy, whereas all the patients in the present trial received cisplatin. In a recent study of Japanese patients with recurrent and/or metastatic SCCHN treated with a combination of cisplatin and 5-FU plus cetuximab, an overall response rate of 36% was reported, equal to that observed for the chemotherapy plus cetuximab arm in the EXTREME trial. Of interest, the median PFS was shorter (4.1 months), whereas the median OS in the Japanese study was even longer (14.1 months).[14]

Compliance to treatment was very good in this trial with 92.6% of patients having received cetuximab at a relative dose intensity of $\geq$80% after the initial dose, which was similar to that in the EXTREME trial (84%) and the Japanese trial (88%).[13,14]

The safety findings in this study were in line with the AE profile expected for this treatment and there were no

unexpected safety findings in this Asian population. In general, the incidence of grade 3/4 AEs was lower in this study than in the platinum-based chemotherapy plus cetuximab arm of the EXTREME trial. This may be a result of the lower platinum dose administered to patients in this study or because of other reasons. Evaluation of AEs within the special interest categories, including acne-like rash and infusion-related reactions, also showed a lower incidence compared with those reported in the EXTREME trial. One case (1.5%) of grade 3 skin reactions (rash) and 2 cases (2.9%) of grade 3/4 infusion-related reactions (under the medical concept "allergy/anaphylaxis") were reported in this trial, whereas 9% of patients experienced grade 3/4 skin reactions and 6 cases (3%) of infusion-related reactions were reported in the EXTREME trial. The incidence of grade 3 skin reactions (1.5%) was also lower than that reported in the Japanese trial (15%).

The pharmacokinetic observations are of interest as they are the first assessment of cisplatin and 5-FU plus cetuximab in Chinese patients. The previously published pharmacokinetic analyses were carried out in mixed but predominantly white populations in patients with a variety of tumor types.[20] Since then, a population pharmacokinetic analysis based on data from 2 trials in patients with SCCHN has been published and the results were in line with the previous pharmacokinetic analyses for regulatory purposes.[21] A pharmacokinetic study of cetuximab in children and adolescents reported a similar profile to that obtained for adults.[25] A study of cetuximab pharmacokinetics in Japanese patients concluded that the pharmacokinetic profile in Japanese patients is broadly similar to that obtained for non-Japanese patient groups.[22] In the current study, the mean cetuximab concentration-time profile and derived pharmacokinetic parameters did not reveal any significant differences between Chinese and non-Chinese patients.

In conclusion, the efficacy, safety, and pharmacokinetic findings from this study support the use of first-line platinum-based chemotherapy plus cetuximab in Asian patients with recurrent and/or metastatic SCCHN.

Acknowledgments

The authors thank the contribution of Joyce Liu, of Merck Serono (Beijing) Pharmaceutical R&D, for her assistance in the preparation of this manuscript and for statistical evaluation of the trial results and thank Dr. Jianliang Yang, of Department of Medical Oncology, Cancer Institute/Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, 17 Panjiayuannanli, Chaoyang District, Beijing, China for his contributions to trial coordination. Cancer Communications & Consultancy, Cheshire, UK, provided medical writing services on the authors' behalf, funded by Merck KGaA.

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