JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(5)524–531
doi:10.1093/jjco/hyt034
Advance Access Publication 10 March 2013

Platinum-based Chemotherapy Plus Cetuximab for the First-line Treatment of Japanese Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck: Results of a Phase II Trial

Takayuki Yoshino[1,*], Yasuhisa Hasegawa[2], Shunji Takahashi[3], Nobuya Monden[4], Akihiro Homma[5], Kenji Okami[6], Yusuke Onozawa[7], Masato Fujii[8], Takahide Taguchi[9], Barbara de Blas[10], Frank Beier[10] and Makoto Tahara[1]

[1]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, [2]Department of Head and Neck Surgery, Aichi Cancer Center Hospital and Research Institute, Aichi, [3]Department of Medical Oncology and Hematology, Japanese Foundation for Cancer Research, Tokyo, [4]Department of Head and Neck Surgery, National Hospital Organization, Shikoku Cancer Center, Ehime, [5]Department of Otolaryngology, Hokkaido University Hospital, Hokkaido, [6]Department of Otolaryngology, Tokai University Hospital, Kanagawa, [7]Division of Clinical Oncology, Shizuoka Cancer Center, Shizuoka, [8]Department of Otorhinolaryngology, National Hospital Organization, Tokyo Medical Center, Tokyo, [9]Department of Otolaryngology, Yokohama City University Hospital, Kanagawa, Japan and [10]Merck KGaA, Darmstadt, Germany

For reprints and all correspondence: Takayuki Yoshino, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: tyoshino@east.ncc.go.jp

Received November 15, 2012; accepted February 12, 2013

Objective: To assess the efficacy and safety of cetuximab in combination with cisplatin and 5-fluorouracil for first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.

Methods: In this open-label, single-arm, multicenter, Phase II study conducted in Japan, patients with confirmed recurrent and/or metastatic squamous cell carcinoma of the head and neck received weekly cetuximab (week 1, 400 mg/m^2; subsequent weeks, 250 mg/m^2) plus a maximum of six three-weekly cycles of cisplatin (100 mg/m^2, day 1) and 5-fluorouracil (1000 mg/m^2/day, 24-h infusion, days 1–4). The primary endpoint was the best overall response assessed by an independent review committee according to the modified World Health Organization criteria.

Results: In total, 33 patients received treatment. The most frequent primary tumor site was the hypopharynx (42%), and most patients had metastatic disease (85%). The best overall response rate as assessed by the independent review committee was 36% (95% confidence interval: 20, 55) and was significantly greater ($P = 0.002$) than the protocol-specified threshold of 15% at the one-sided 5% level. The disease control rate was 88%. The median progression-free survival and overall survival were 4.1 and 14.1 months, respectively. There were no unexpected safety concerns. Grade 3 or 4 adverse events were experienced by nearly all patients (32, 97%). No adverse events were fatal.

Conclusions: The demonstrated efficacy and safety of cetuximab in combination with cisplatin and 5-fluorouracil for the first-line treatment of Japanese patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck justify the further use of this combination treatment in this patient population (ClinicalTrials.gov number, NCT00971932).

Key words: cetuximab – chemotherapy – head and neck – squamous cell carcinoma – Phase II trial

INTRODUCTION

Cancer of the head and neck [oral cavity, pharynx (excluding nasopharynx) and larynx] is estimated to represent around 4% of cancers, globally (1). In Japan in 2006, there were 16 351 patients (12 577 males and 3774 females) with oral/pharyngeal or laryngeal cancer, accounting for 2.5% of all cancer cases (2). A total of 7528 deaths due to oral/pharyngeal or laryngeal cancer occurred in Japan in 2009, representing 2.2% of annual cancer deaths (3). Tumors in Japanese patients are most frequently located in the oral cavity (36% of patients), larynx (25%), hypopharynx (16%) and oropharynx (12%); other sites are the nasal cavity/paranasal sinus (7%) and nasopharynx (4%) (4).

Epidermal growth factor receptor (EGFR) is frequently expressed in squamous cell carcinoma of the head and neck (SCCHN) (5–7). Cetuximab (Erbitux®, Merck KGaA, Darmstadt, Germany) is an EGFR-targeting monoclonal antibody which is widely used in the treatment of SCCHN in countries outside Japan.

In the Phase III EXTREME trial, conducted in Europe in patients with recurrent and/or metastatic SCCHN (R/M SCCHN), the addition of cetuximab to platinum/5-fluorouracil (5-FU) in the first-line setting significantly improved overall survival (OS), progression-free survival (PFS) and best overall response rate (ORR) compared with platinum/5-FU alone (8). The median OS time was 7.4 months in the chemotherapy-alone group compared with 10.1 months in the group that received chemotherapy plus cetuximab [hazard ratio for death, 0.80; 95% confidence interval (CI): 0.64, 0.99; $P = 0.04$]. The addition of cetuximab to chemotherapy also prolonged the median PFS time (from 3.3 to 5.6 months; hazard ratio for progression, 0.54, 95% CI: 0.43, 0.67; $P < 0.001$) and increased the best ORR (from 20 to 36%; odds ratio 2.33, 95% CI: 1.50, 3.60, $P < 0.001$). The use of cetuximab plus platinum/5-FU for the first-line treatment of R/M SCCHN is now recommended by a group of European cancer societies (9) and the USA-based National Comprehensive Cancer Network (NCCN) Practice Guidelines (10).

In Japan, cetuximab has not yet been approved for use in head and neck cancers. In other respects, however, the treatment options for R/M SCCHN are not substantially different from those in Europe and the USA. Cisplatin is the mainstay of treatment, and the combination of cisplatin and 5-FU is the most frequently used chemotherapy regimen (11). The dose of cisplatin used in combination with 5-FU at an interval of 3 or 4 weeks is commonly lower in Japan (cisplatin 75–100 mg/m^2 on day 1 plus 5-FU 600–1000 mg/m^2/day for 4–5 days) than in many Western countries (11,12), in keeping with observations from the treatment of different types of cancer, including head and neck cancers, that Japanese patients are generally not able to tolerate the doses of chemotherapy approved for use in Western patients (13,14). However, others have reported that the incidence of high-grade toxicity associated with standard doses of chemotherapy used in Western patients is not substantially higher in Japanese patients (15,16).

The use of cetuximab in combination with radiotherapy for patients with locally advanced SCCHN showed significant benefits over radiotherapy alone in a Phase III trial in Western patients (17), and the efficacy and safety of cetuximab plus radiotherapy has since been demonstrated in a Phase II trial in Japanese patients (18).

The primary objective of the current trial was to assess the antitumor activity of cetuximab when given in combination with cisplatin and 5-FU for the first-line treatment of R/M SCCHN in Japanese patients. Of note, cisplatin was used at a dose of 100 mg/m^2 in line with the dose used in the EXTREME trial. Secondary objectives included the assessment of safety, pharmacokinetic (PK) parameters, biomarkers, pharmacogenomics and the immunogenicity of cetuximab in Japanese patients. This paper reports the efficacy, safety and PK results.

PATIENTS AND METHODS

Patient eligibility criteria and treatment regimens were consistent with those used in the EXTREME trial (8).

Patient Selection

Japanese adults with histologically or cytologically confirmed R/M SCCHN, unsuitable for local therapy, with at least one bidimensionally measurable [computed tomography (CT) scan or magnetic resonance imaging (MRI)] lesion and confirmed expression of EGFR by immunohistochemistry (IHC) were eligible for entry to the trial. The exclusion criteria included nasopharyngeal carcinoma, prior systemic chemotherapy (except as part of multimodal therapy completed >6 months before the trial entry), surgery or irradiation within 4 weeks of trial entry, current or prior cardiac or pulmonary disease, high risk of uncontrolled arrhythmia or cardiac insufficiency and active infection. A written informed consent was provided by all patients taking part in the trial, and additional consent was provided by those also taking part in PK and biomarker analyses.

Trial Design

This was an open-label, single-arm, multicenter, Phase II trial conducted in Japan. Patients received weekly cetuximab (week 1, 400 mg/m^2; subsequent weeks, 250 mg/m^2) plus three-weekly cycles of cisplatin (100 mg/m^2, day 1) and 5-FU (1000 mg/m^2/day, 24-h infusion, day 1–4). Patients could switch to carboplatin (AUC5 on day 1 of each cycle) in the event of non-hematologic toxicities to cisplatin. All drugs were administered by intravenous infusion. Chemotherapy was continued for up to six cycles, or until unacceptable toxicity or progressive disease (PD). Patients received cetuximab until PD or unacceptable toxicity.

Response was assessed every 6 weeks until PD occurred, including in those patients who discontinued treatment before PD. Partial response (PR), complete response (CR) and PD were confirmed with CT or MRI within 4 weeks. Adverse events (AEs) were recorded from the start of treatment until the end of treatment (EOT) visit (30 days after the last trial treatment, or immediately prior to the initiation of any subsequent anticancer treatment). After the EOT visit, patients were followed up every 3 months until death, loss to follow-up or withdrawal of consent.

A PK investigation was carried out in patients enrolled at centers with PK sampling facilities. Blood samples were taken at the following times: days 1, 8 and 15, immediately before and after cetuximab infusion; day 22, directly before and at several time points (up to 168 h) after cetuximab infusion; days 36, 43 and 50, directly before the cetuximab infusion. Serum prepared from each blood sample was divided into two aliquots and stored at -20°C. Samples were analyzed by Celerion, Zurich, Switzerland, for concentrations of cetuximab using a validated enzyme-linked immunosorbent assay (ELISA). PK analysis was monitored and conducted under the supervision of the Institute of Drug Metabolism and Pharmacokinetics, Merck KGaA, Grafing, Germany. The PK parameters of cetuximab after the fourth dose (day 22) were calculated according to the standard non-compartmental methods using the PK software program KINETICA™, version 4.1.1.

Tumor EGFR expression was assessed by SRL medisearch, Tokyo, Japan, using the EGFR pharmDx™ kit (Dako Denmark A/S, Glostrup, Denmark) on archived tumor material or a biopsied specimen collected at the screening visit. EGFR-positive staining was defined as any IHC staining of tumor cell membranes above the background level, whether complete or incomplete circumferential staining. The tumor *KRAS* mutation status was assessed by Merck Serono Ivrea, Colleretto Giacosa (Turin), Italy, by pyrosequencing using the PyroMark Q24 system (developed by QIAGEN Manchester Ltd, Manchester, UK).

The trial protocol was approved by the institutional review boards of each center, and the trial was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (GCP) (ICH Topic E6, 1996), the Japanese ministerial ordinance on GCP, the standard stipulated in Articles 14–3 and 80–2 of the Japanese Pharmaceutical Affairs Law, and applicable regulatory requirements.

Endpoints

The primary endpoint was the best overall response (CR or PR) assessed by an independent review committee (IRC) according to the modified World Health Organization (WHO) criteria. The ORR was the proportion of patients with a CR or a PR. The best overall response according to Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.0) criteria was also assessed by the IRC as a secondary efficacy endpoint (19). Other secondary efficacy endpoints were: disease control rate (CR plus PR plus stable disease); duration of response (in patients achieving a CR or PR); time-to-treatment failure (PD assessed by the investigator, discontinuation of treatment due to PD or due to an AE, start of any new anticancer therapy or withdrawal of consent or death within 60 days of the last tumor assessment or first administration of trial treatment); PFS (time from the first administration of trial treatment to the first observation of PD, or death due to any cause when death occurred within 60 days of the last tumor assessment) and OS.

Adverse events were assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE version 3.0). AEs considered to be of special interest in patients receiving cetuximab and based on Medical Dictionary for Regulatory Activities (MedDRA) preferred terms were also investigated: skin reactions and acne-like rash, infusion-related reactions (IRRs) and cardiac events.

Statistics

In the EXTREME trial, patients treated with chemotherapy plus cetuximab achieved a best ORR of 36% (95% CI: 29, 42) compared with 20% (95% CI: 15, 25) for those receiving chemotherapy alone (8). The lower confidence limit in the chemotherapy arm (15%) was considered to be the reference value for this trial, and an exact one-sided test (significance level $\alpha = 5\%$) was used to test the null hypothesis that the response rate was $<15\%$. Assuming a response rate of 35% (similar to that in the EXTREME trial), a patient sample size of 31 was required to achieve a power of $>80\%$.

Efficacy analyses were performed on the intention-to-treat (ITT)/safety population (all patients who received at least one dose of trial medication). 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 and CIs were calculated as two-sided with a confidence probability of 95%.

All analyses were performed using SAS® Software version 9.1.

RESULTS

Patient Disposition

In total, 46 patients were enrolled at nine centers in Japan between 22 July 2009 and 3 September 2010. Of these patients, 35 were eligible for the trial and 33 were treated (ITT/safety population). Two patients were not treated due to worsening condition ($n = 1$) and creatinine clearance of <60 ml/min ($n = 1$). At the data cutoff of 14 December 2011, one patient remained on treatment.

Patient Baseline Characteristics

Patients were predominantly male (30, 91%), with good Karnofsky performance status (31, 94% had KPS 90–100), and mainly metastatic (including recurrent) cancer (28, 85%, Table 1). Almost one-third of patients were 65 years or older. All patients had EGFR-positive tumors. The most frequent primary tumor location was the hypopharynx. In one-third of patients ($n = 11$), tumors were reported as non-classifiable, but were specified as tongue ($n = 8$), and maxillary, hard palate and mandibular tumors ($n = 1$, each).

Most patients (30, 91%) had received prior therapy for cancer-related disease: surgery (28, 85%), radiotherapy (11, 33%), chemotherapy (11, 33%) and other types of therapy (10, 30%).

Table 1. Baseline patient and disease characteristics

Characteristic	($n = 33$)
Age (years)	
Median (range, years)	61 (31–71)
<65, *n* (%)	23 (70)
≥65, *n* (%)	10 (30)
Sex, *n* (%)	
Male	30 (91)
Female	3 (9)
Karnofsky performance status, *n* (%)	
100	17 (52)
90	14 (42)
80	2 (6)
Disease duration (from initial diagnosis to informed consent) (months), median (range)	14.3 (0–79)
Frequency of the extent of disease, *n* (%)	
Recurrent, not metastatic	5 (15)
Metastatic, including recurrent	28 (85)
Location of primary tumor, *n* (%)	
Hypopharynx	14 (42)
Larynx[a]	5 (15)
Oropharynx	3 (9)
Non-classifiable[b]	11 (33)
Histology	
Well differentiated	4 (12)
Moderately differentiated	13 (39)
Poorly differentiated	4 (12)
None otherwise specified/unknown/missing	12 (36)
Stage according to UICC at diagnosis, *n* (%)	
Stage I	3 (9)
Stage II	2 (6)
Stage III	4 (12)
Stage IV	24 (73)

UICC, Union for International Cancer Control.
[a]The tumor in one patient was 'non-classifiable' but was specified as 'larynx' and was therefore analyzed as such.
[b]The location of the primary tumor was non-classifiable, but was specified as tongue ($n = 8$), and maxillary, hard palate and mandibular ($n = 1$, each).

Treatment Exposure

All 33 patients received at least one dose of cetuximab, and 29 (88%) patients received cetuximab at a relative dose intensity (RDI) of ≥80%. The median duration of cetuximab treatment was 19 (range 1−98) weeks, the median number of infusions was 18 (range 1–91) and the median cumulative dose was 4650 (range 166–16 877) mg/m^2. In total, 21 (64%) patients received at least one dose of cetuximab monotherapy.

Thirty-two patients (97%) received at least one dose of cisplatin. The median duration of therapy was 11.3 (range 3–23) weeks, and the median cumulative dose was 300 (range 100–600) mg/m^2. RDI was ≥80% in 21 (66%) patients. Seven (21%) patients received two or more doses of carboplatin. The median duration of therapy was 12 (range 6–18) weeks, and the median cumulative dose was 1264 (range 676–2257) mg. Most patients, 32 (97%), received at least one dose of 5-FU. The median duration of therapy was 18.5 (range 3–23) weeks, and the median cumulative dose was 20 000 (range 4000–24 000) mg/m^2. RDI was ≥80% in 19 (59%) patients.

Twenty-seven (82%) patients received post-trial anticancer therapy, comprising chemotherapy (23, 70%), radiotherapy (9, 27%), surgery (2, 6%), immunotherapy (1, 3%) and/or other forms of treatment (2, 6%).

Table 2. Tumor response results

	Response rates, $n = 33$	
Characteristic, *n* (%)	Modified WHO criteria[a]	RECIST criteria[a]
ORR	12 (36)[b]	15 (45)
[95% CI][c]	[20, 55]	[28, 64]
Best overall response		
CR	1 (3)	1 (3)
PR	11 (33)	14 (42)
SD	17 (52)	14 (42)
PD	1 (3)	1 (3)
Not evaluable	3 (9)	3 (9)

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; WHO, World Health Organization.
[a]Assessed by an Independent Review Committee.
[b]$P = 0.002$ vs. the protocol-specified 15% threshold.
[c]Two-sided Clopper–Pearson.

Efficacy

The best ORR assessed by the IRC according to the modified WHO criteria (primary endpoint) was 36% (95% CI: 20, 55) (Table 2), with a CR in one patient. The ORR was significantly greater than the protocol-specified threshold of 15% ($P = 0.002$). The best ORR assessed by the IRC according to RECIST was 45%, with a CR in one patient (Table 2): three patients with stable disease (SD) according to modified WHO criteria were considered to have a PR according to RECIST.

The median PFS was 4.1 (95% CI: 4.0, 5.5) months (Fig. 1a). The PFS rate was 70% (95% CI: 53, 86) at 3 months and 23% (95% CI: 7, 39) at 6 months. The median OS was 14.1 (95% CI: 10.2, 15.4) months (Fig. 1b). At last follow-up, 24 patients had died due to PD. The OS rates at 3, 6, 9 and 12 months were 100, 85 (95% CI: 73, 97), 67 (95% CI: 51, 83) and 61% (95% CI: 44, 77), respectively. The disease control rate was 88%. The median duration of response (first assessment of CR or PR until PD) was 2.8 (95% CI: 2.8, 5.5), with a median time-to-treatment failure of 4.2 (95% CI: 4.1, 5.6) months.

Safety

The most common AEs reported were decreased appetite (91%), leukopenia (85%), hypomagnesemia (82%), neutropenia (82%) and stomatitis (79%). Grade 3–4 AEs were reported in 32 (97%) patients, and grade 4 events were reported in 21 (64%) patients. Treatment-related grade 3–4 AEs were reported in 32 (97%) patients. Cetuximab-related grade 3–4 AEs were experienced by 20 (61%) patients, and the most frequent of these ($\geq$10% patients) were diarrhea,

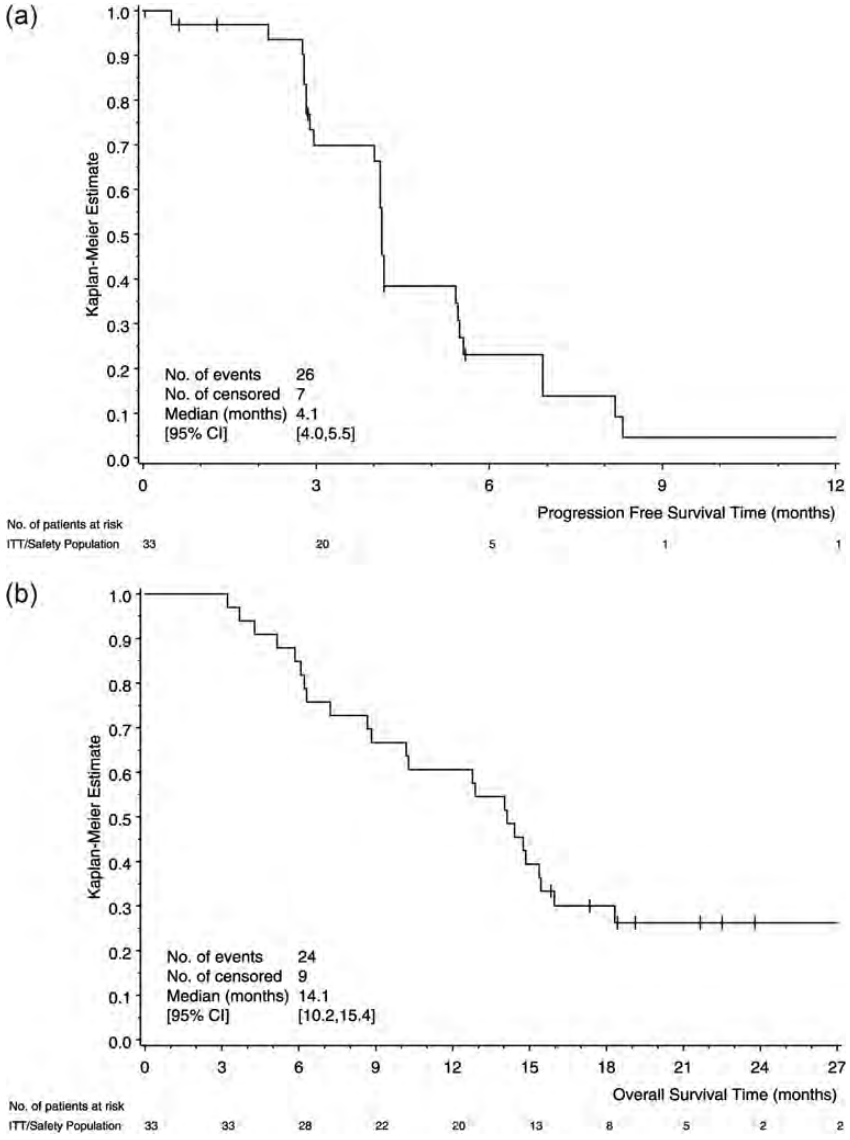

Figure 1. Kaplan–Meier estimates of (a) progression-free survival and (b) overall survival. CI, confidence interval.

hypomagnesemia and neutropenia, each occurring in four (12%) patients. The most common grade 3–4 AEs reported (total and cetuximab-related) are displayed in Table 3.

Among AEs considered to be of special interest, skin reactions and acne-like rash were each reported in 32 (97%) patients. Grade 3 skin reactions were reported in five (15%) patients, and grade 3 acne-like rash in four (12%) patients. There were no grade 4 events. Only two patients experienced an IRR: hot flush (grade 1) and chills and tremor (grade 3); each resolved within the same day. There were seven cardiac events: six grade 1 and one grade 2 event.

Twelve patients experienced serious AEs (SAEs), nine of which were related to treatment: diarrhea, dysphagia, staphylococcal sepsis, septic shock, syncope, intracardiac mass, esophageal fistula, increased C-reactive protein, dehydration, hypercreatininemia and decreased appetite. No AEs were fatal.

Eighteen (55%) patients permanently discontinued either cetuximab or chemotherapy as a result of AEs. The most frequent AEs (occurring in >5% of patients) leading to permanent discontinuation of chemotherapy were toxic nephropathy and neutropenia (three patients, 9% each), and thrombocytopenia (two patients, 6%). Four (12%) patients had AEs leading to permanent discontinuation of cetuximab (hypomagnesemia, IRR, esophageal fistula and septic shock, each in one patient).

Table 3. Most common grade 3–4 adverse events

AE, *n* (%)	All *n* = 33	Cetuximab-related *n* = 33
Any	32 (97)	20 (61)
Neutropenia	21 (64)	4 (12)
Leukopenia	17 (52)	2 (6)
Anemia/hemoglobin decreased	11 (33)	3 (9)
Decreased appetite	7 (21)	0
Lymphopenia	6 (18)	1 (3)
Thrombocytopenia	6 (18)	1 (3)
Diarrhea	5 (15)	4 (12)
Hypomagnesemia	5 (15)	4 (12)
Fatigue	4 (12)	0
Hypokalemia	4 (12)	1 (3)
Hyponatremia	3 (9)	1 (3)
Nausea	3 (9)	0
Syncope	3 (9)	2 (6)
Dermatitis acneiform	2 (6)	2 (6)
Hyperkalemia	2 (6)	2 (6)

Pharmacokinetics

Cetuximab PK parameters were investigated in 12 patients with available samples. All serum cetuximab concentrations after dosing on day 22 were above the lower limit of quantification (0.25 μg/ml) of the bioanalytical assay (Fig. 2). The mean trough concentrations of cetuximab reached around 70 μg/ml after day 36 (Fig. 3). The mean concentration time profile and derived PK parameters were in good agreement with those described previously in Japanese patients receiving cetuximab monotherapy (20).

Tumor *Kras* Mutation Status

Twenty-one patients gave consent for further tumor biomarker testing. Of these, 15 had tumor samples that were evaluable. All 15 patients had *KRAS* wild-type tumors.

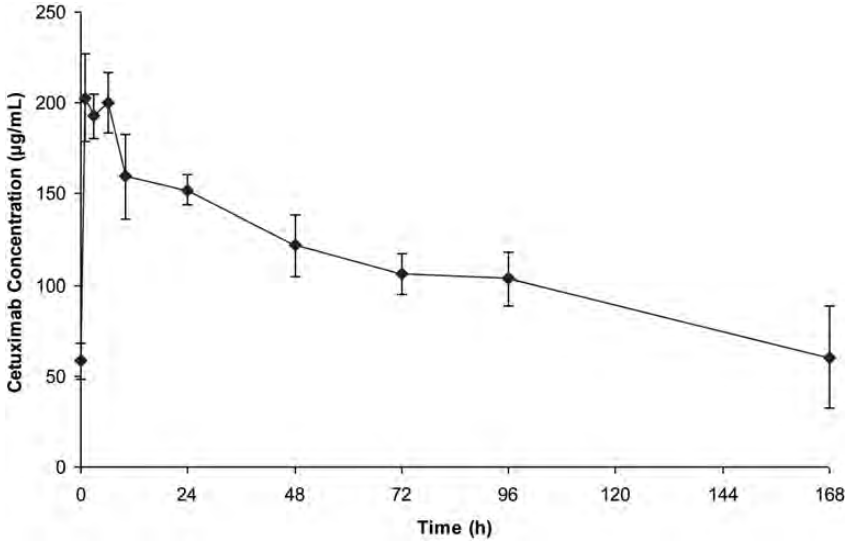

Figure 2. Serum cetuximab concentrations after a dose of 250 mg/m^2 on day 22. Linear plot. Points are mean ± standard deviation.

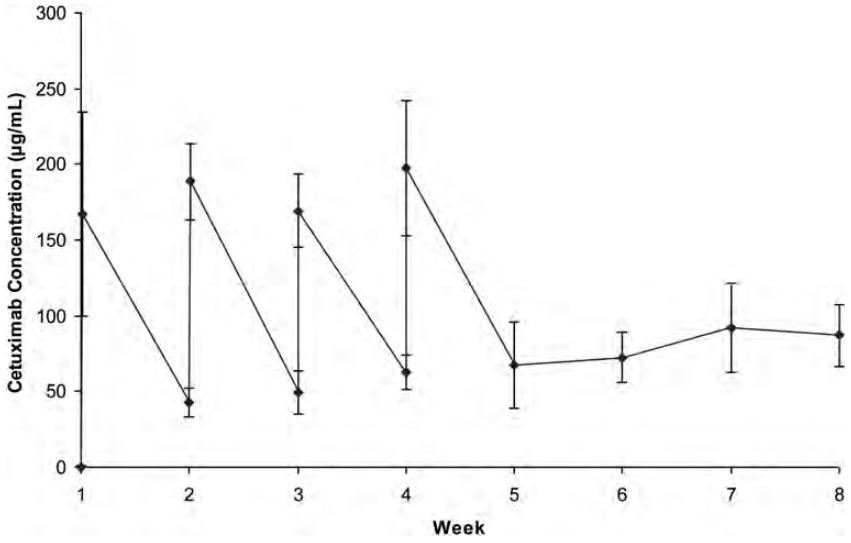

Figure 3. Serum cetuximab peak and trough concentrations.

DISCUSSION

Data from this open-label, multicenter, Phase II trial demonstrated that the combination of platinum-based chemotherapy with cisplatin administered at a dose of 100 mg/m^2, and cetuximab as the first-line treatment for R/M SCCHN was effective and well tolerated in Japanese patients. Furthermore, the efficacy and safety results obtained in the present trial were similar to those obtained in the Phase III EXTREME trial in a Western population (8).

The best ORR achieved (36% assessed by IRC according to modified WHO criteria) was significantly higher than the protocol-specified 15% at the one-sided 5% level, thereby meeting the primary endpoint of the trial. The ORR was equal to that observed for the chemotherapy plus cetuximab arm in the reference EXTREME trial (36%) (8).

The secondary endpoints further supported the efficacy of the combination of chemotherapy and cetuximab in this Japanese patient population. The median OS (14.1 months) was longer than that reported for the platinum/5-FU/cetuximab arm of the EXTREME trial (10.1 months) (8). This may be due to the small number of patients in our trial. In addition, an influence on OS of post-trial anticancer treatment cannot be discounted. The number of patients who received anticancer treatment after the completion of the present trial was higher than in the platinum/5-FU/cetuximab arm of the EXTREME trial [27 patients (82%) vs. 91 patients (41%)]. The apparently shorter median PFS in this trial, compared with the EXTREME trial, is probably due to the small population size. However, given that the 95% CIs of the median PFS in the two trials are overlapping, it may be suggested that the PFS in our trial is similar to that in the platinum/5-FU/cetuximab arm of the EXTREME trial.

In colorectal cancer, the benefits of cetuximab are restricted to patients with *KRAS* wt tumors (21,22). All patients in this trial whose tumors were tested for *KRAS* mutation status had *KRAS* wt tumors, as would be expected, given the low rate of *KRAS* mutations reported previously in head and neck cancers (23–25).

The efficacy reported here is particularly encouraging, given that the patient population in the present trial was older than that in the chemotherapy plus cetuximab arm of the EXTREME trial (30% $\geq$65 years compared with 18%) and had characteristics indicative of a poorer prognosis, including a higher proportion of patients with recurrent and metastatic primary tumors (85 vs. 47%) and localization of the primary tumor in the hypopharynx (42 vs. 13%). It is also notable that this efficacy was achieved despite dose modifications in platinum therapy made for the management of adverse events, which led to patient exposure to platinum being lower than in the EXTREME trial. For example, 89% of patients in the chemotherapy plus cetuximab arm of the EXTREME trial received $\geq$80% of RDI of cisplatin compared with 66% of patients in this trial.

The AEs observed in this trial are consistent with the underlying disease, administration of chemotherapy and the known safety profile of cetuximab. No new safety findings were identified in this trial. The overall safety profile observed in the present trial was also similar to that observed in the chemotherapy plus cetuximab arm in the EXTREME trial (8), and it is notable that no AEs had a fatal outcome. However, the incidence of a number of grade 3–4 AEs was higher compared with the EXTREME trial, notably neutropenia, leukopenia, decreased appetite (anorexia) and hypomagnesemia. This might be explained by the poor tolerability of cytotoxic chemotherapy reported for Japanese patients that has been documented previously (13). However, it may also reflect the poorer prognosis of the patient population in the present trial, as discussed briefly in the previous paragraph. The AEs concerned were mostly those known to be chemotherapy related and were manageable by dose adjustments or switches from cisplatin to carboplatin.

In conclusion, the demonstrated efficacy of platinum-based chemotherapy plus cetuximab in Japanese patients with R/M SCCHN, together with a predictable safety profile and PK, justifies the further use of this combination treatment in this patient population.

Acknowledgements

The authors acknowledge the contribution of Jo Shrewsbury-Gee and Neil Fisher, who provided medical writing services on their behalf funded by Merck KGaA. The authors are fully responsible for the content and editorial decisions involved in the production of this manuscript.

Funding

This work was supported by Merck Serono Co, Ltd, Tokyo, Japan, an affiliate of Merck KGaA, Darmstadt, Germany.

Conflict of interest statement

Takayuki Yoshino received honoraria from Chugai, Takeda, Bristol-Myers Squibb, Yakult and Merck Serono, a research grant from Bayer, Taiho, Daiichi-Sankyo and ImClone and consulting fees from Takeda. Makoto Tahara received consulting fees from Merck Serono. Barbara de Blas and Frank Beier are employees of Merck KGaA, Darmstadt, Germany. The other authors declare no conflicts of interest.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
2. Sofue T, Miki W, Matsuda T, Marugame T. *Monitoring of Cancer Incidence in Japan (MCIJ 2006)* Tokyo, Japan: Center for Cancer Control and Information Service, National Cancer Center.
3. Cancer mortality (1958–2009). Center for Cancer Control and Information Services, National Cancer Center. http://ganjoho.jp/data/professional/statistics/odjrh3000000hwsa-att/cancer_mortality(1958–2009).xls. (23 May 2011, date accessed).
4. *Clinical Oncology Update-Essentials for the Medical Oncologist*. 2nd edn. Japanese Society of Medical Oncology. Tokyo, Japan: Nankodo 2009.
5. Christensen ME, Therkildsen MH, Hansen BL, Albeck H, Hansen GN, Bretlau P. Epidermal growth factor receptor expression on oral mucosa dysplastic epithelia and squamous cell carcinomas. *Eur Arch* 1992;249:243–7.
6. Fujii S, Uryu H, Akashi K, et al. Clinical significance of KRAS gene mutation and epidermal growth factor receptor expression in Japanese patients with squamous cell carcinoma of the larynx, oropharynx and hypopharynx. *Int J Clin Oncol* 2012 [epub 24 March 2012 ahead of print].
7. Rubin Grandis J, Melhem MF, Barnes EL, Tweardy DJ. Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer* 1996;78:1284–92.
8. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–27.
9. Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010;21:v184–6.
10. NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers National Comprehensive Cancer Network, Inc. http://www.nccn.org.
11. Head and Neck Cancer In: *Residents of internal medicine of National Cancer Center. Resident manual for clinical practice on cancer*. 5th edn. Tokyo, Japan: IGAKU-SHOIN Ltd 2010;275–86.
12. Skeel RT, Furue H, Tsukagoshi S. Head and Neck Cancer. In: *Cancer chemotherapy handbook*. 6th edn. Tokyo, Japan: Medical Science International Co., Ltd 2009;177–93.
13. O'Donnell PH, Dolan ME. Cancer pharmacoethnicity: ethnic differences in susceptibility to the effects of chemotherapy. *Clin Cancer Res* 2009;15:4806–14.
14. Watanabe A, Taniguchi M, Sasaki S. Induction chemotherapy with docetaxel, cisplatin, fluorouracil and l-leucovorin for locally advanced head and neck cancers: a modified regimen for Japanese patients. *Anticancer Drugs* 2003;14:801–7.
15. Kiyota N, Tahara M, Okano S, et al. Phase II feasibility trial of adjuvant chemoradiotherapy with 3-weekly cisplatin for Japanese patients with post-operative high-risk squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 2012;42:927–33.
16. Zenda S, Onozawa Y, Tahara M, et al. Feasibility study of single agent cisplatin and concurrent radiotherapy in Japanese patients with squamous cell carcinoma of the head and neck: preliminary results. *Jpn J Clin Oncol* 2007;37:725–9.
17. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;354:567–78.
18. Fujii M, Yoshino T, Onozawa Y, et al. Phase II study of cetuximab with concomitant-boost radiotherapy (RT) in Japanese patients with locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN). *Eur J Cancer* 2011;47 (Suppl 1):S564–5 (Abstract 8570).
19. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–16.
20. Shirao K, Yoshino T, Boku N, et al. A phase I escalating single-dose and weekly fixed-dose study of cetuximab pharmacokinetics in Japanese patients with solid tumors. *Cancer Chemother Pharmacol* 2009;64:557–64.
21. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;27:663–71.
22. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408–17.
23. Anderson JA, Irish JC, Ngan BY. Prevalence of RAS oncogene mutation in head and neck carcinomas. *J Otolaryngol* 1992;21:321–6.
24. Rathcke IO, Gottschlich S, Gorogh T, Lippert BM, Werner JA. Incidence of point mutations in Ki-ras codon 12 and 13 in squamous epithelial carcinomas of the head-neck region. *Laryngorhinootologie* 1996;75:465–70.
25. Yarbrough WG, Shores C, Witsell DL, Weissler MC, Fidler ME, Gilmer TM. Ras mutations and expression in head and neck squamous cell carcinomas. *Laryngoscope* 1994;104:1337–47.

APPENDIX

In addition to the authors listed on the first page, the following authors also contributed equally to this study:

Tetsuo Akimoto: Department of Radiation Oncology and Particle Therapy, National Cancer Center Hospital East, Chiba, Japan.
Naoyuki Kohno: Department of Otorhinolaryngology/Head and Neck, Kyorin University Hospital, Tokyo, Japan.
Hiroya Ojiri: Department of Radiology, Jikei University School of Medicine, Tokyo, Japan.