JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2013;43(5)476–482
doi:10.1093/jjco/hyt030
Advance Access Publication 10 March 2013

Phase II Study of Cetuximab Plus Concomitant Boost Radiotherapy in Japanese Patients with Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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Received November 6, 2012; accepted February 11, 2013

Background: We investigated the tolerability of cetuximab plus radiotherapy in Japanese patients with untreated locally advanced squamous cell carcinoma of the head and neck.
Methods: Patients with epidermal growth factor receptor-expressing locally advanced squamous cell carcinoma of the head and neck received cetuximab (400 mg/m^2 initial dose then 250 mg/m^2 weekly) for 7 weeks plus concomitant boost radiotherapy (weeks 2–7: once daily [1.8 Gy] for 3.6 weeks, then twice daily [1.8 Gy morning and 1.5 Gy afternoon] for 2.4 weeks). The primary endpoint was treatment completion rate (the rate of treated patients completing $\geq$70% of the planned cetuximab dose and the full dose of radiotherapy within 2 weeks over the planned schedule).
Results: Twenty-two patients were evaluable. The treatment completion rate was 100% (95% confidence interval 85–100). The response rate 8 weeks post-radiotherapy was 82% (95% confidence interval 60–95). The most common grade 3/4 treatment-emergent adverse events were mucosal inflammation (73%); dermatitis (27%); and infection, radiation skin injury and stomatitis (23% each).
Conclusions: Cetuximab plus concomitant boost radiotherapy can be safely administered to Japanese patients with locally advanced squamous cell carcinoma of the head and neck. Tolerability and efficacy were in line with those reported in the Phase III Bonner trial in a Western population of patients with locally advanced squamous cell carcinoma of the head and neck.

Key words: cetuximab – concomitant boost – Japanese – locally advanced – radiotherapy – squamous cell carcinoma of the head and neck

INTRODUCTION

Globally, cancers of the lip, oral cavity, pharynx (other than nasopharynx) and larynx account for over 4% of all malignancies, with more than 500 000 new cases worldwide and 300 000 attributed deaths reported in 2008 (1). In Japan alone, in 2007, 7879 people died of head and neck cancer, representing 2.3% of all cancer deaths that year (2).

Patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (LASCCHN) have a number of treatment options available, depending on regulatory authority approvals. These options include concurrently administered chemoradiotherapy with or without surgery and the combination of the EGFR-targeting IgG1 monoclonal antibody cetuximab and radiotherapy (3,4). The use of cetuximab in combination with radiotherapy grew out of the finding that epidermal growth factor receptor (EGFR) is expressed by almost all SCCs of the head and neck (SCCHN) (5,6) and the observation from *in vivo* models that this combination enhanced tumor regression compared with radiation or cetuximab alone (7). Regulatory approval of the combination of cetuximab and radiotherapy in the USA and the EU was based on the results of the large Phase III trial conducted by Bonner et al. in centers in the USA and 14 other countries (8). This trial reported that the addition of cetuximab to once-daily, twice-daily or concomitant boost radiotherapy significantly improved overall survival, progression-free survival and locoregional control compared with radiotherapy alone in patients with LASCCHN. Survival benefits were maintained long term, with 5-year overall survival rates of 46% in the cetuximab plus radiotherapy arm and 36% in the radiotherapy alone arm (9).

It was notable that the addition of cetuximab to radiotherapy in the Bonner trial did not exacerbate the adverse events commonly associated with radiotherapy of the head and neck, including mucositis, xerostomia and dysphagia (8). Among grade $\geq$3 reactions, only acneiform rash and infusion reactions, both with a known association to cetuximab, occurred with a higher incidence in the cetuximab plus radiotherapy arm compared with the radiotherapy arm of the trial.

The Phase II study reported here was initiated to assess the tolerability and feasibility of administering cetuximab together with the concomitant boost radiotherapy regimen used in the Bonner trial to Japanese patients with newly diagnosed LASCCHN. The concomitant boost radiotherapy regimen was chosen because it was the most frequently used in the Bonner trial and the results from our trial would therefore be appropriate for comparison with those from the Bonner trial. Tumor response to treatment was also evaluated in this study.

PATIENTS AND METHODS

Patient Selection

The inclusion criteria used in this study closely followed those used in the Bonner trial to ensure that the patient, disease and treatment characteristics were similar in the two studies. Japanese patients with Stage III or IV (Union for International Cancer Control TNM classification) pathologically proven SCC of the oropharynx, hypopharynx or larynx confirmed by magnetic resonance imaging (MRI) and computed tomography (CT) and with tumor EGFR expression and an expected survival of at least 12 months were eligible for inclusion in the study. Tumor EGFR expression was determined at a single reference laboratory (SRL Medisearch, Inc., Tokyo, Japan) by immunohistochemistry on formalin-fixed or paraffin-embedded tumor tissue using the DAKO pharmDx kit (Glostrup, Denmark). The minimum criterion required to confirm EGFR expression was any intensity of membrane staining above-background level by at least one cell. Other main criteria were: at least bi-dimensionally measurable disease; age $\geq$20 years; Karnofsky performance status (KPS) $\geq$60; adequate bone marrow, kidney and liver function; no distant metastases; no prior chemotherapy within the last 3 years; no prior radiotherapy to the head and neck; and no prior treatment with cetuximab.

The study protocol was approved by institutional review boards and the trial was conducted in accordance with the protocol and with the ethical principles of the Declaration of Helsinki, as well as with 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. A quality assurance review of the data was conducted and an independent Radiation Therapy Quality Assurance Committee was set up to ensure compatibility of the type of radiotherapy used at each center with that defined in the protocol. All patients provided written informed consent and were also asked to provide informed consent for investigation of biomarkers other than EGFR in their tumor tissue.

Study Design and Treatment

This was an open-label, Phase II study conducted in patients with newly diagnosed LASCCHN across four centers in Japan. The primary endpoint of the study was tolerability, the main variable of which was treatment completion rate: the rate of patients who completed $\geq$70% of the cetuximab planned dose administration (in terms of relative dose intensity [RDI] of cetuximab) and the full dose of radiotherapy within 2 weeks over the planned schedule of $\leq$8 weeks. The RDI of cetuximab of $\geq$70% was estimated to be equivalent to no more than one missed dose of cetuximab, which, based on calculations on dose intensity data from the Bonner trial, was considered to be the minimum dose level required for cetuximab clinical activity. The selection of an RDI of $\geq$70% as a component of the treatment completion rate was therefore considered to represent tolerability at clinically effective doses. A secondary efficacy endpoint was the best

response 8 weeks after the completion of radiotherapy according to modified World Health Organization criteria as assessed by an independent review committee, the Efficacy and Safety Evaluation Committee (ESEC), and the investigators, using imaging. Tumor response at 8 weeks after completion of radiotherapy was to be confirmed at 12 weeks for the analysis of best tumor response. Determination of tumor *KRAS* mutation status was requested by the Pharmaceuticals and Medical Device Agency, Japan, in order to increase information on the incidence of this type of mutation among Japanese patients with LASCCHN, and response according to tumor *KRAS* mutation status was also assessed. Tumor DNA was screened for the presence of *KRAS* codon 12 and 13 mutations by pyrosequencing at a single laboratory (Biomarker Technologies, Merck Serono RBM, Ivrea, Italy) using a previously validated test (PyroMark KRAS kit; QIAGEN, Hilden, Germany).

All patients received a 7-week course of cetuximab plus concomitant boost radiotherapy. Cetuximab was administered at an initial dose of 400 mg/m^2 (over 120 min), with subsequent weekly doses of 250 mg/m^2 (over 60 min) as an intravenous infusion for 7 weeks of treatment, starting 1 week prior to radiotherapy. Radiotherapy treatment was determined using a 3D treatment planning system. Uninvolved nodal areas of the neck were treated with 54 Gy/30Fr. The primary tumor and gross nodal disease were treated with 72 Gy/42Fr. The irradiation schedule is shown in detail in Fig. 1.

On-study tumor response assessments were performed 8 and 12 weeks after completion of radiotherapy using MRI scanning of the neck and, at week 12, CT of the chest and abdomen. Where progressive disease (PD) was confirmed 8 weeks after completion of radiotherapy, imaging at 12 weeks was not performed. In cases where cetuximab therapy was discontinued before PD was confirmed, radiotherapy was to continue as planned, and assessments including imaging were to be performed at 8 and 12 weeks after completion of radiotherapy.

Treatment-emergent adverse events (TEAEs) (i.e. those events with an onset on or after the first dosing day of treatment and up until 60 days after the last treatment administration) were assessed weekly during treatment and at 4, 8 and 12 weeks after completion of radiotherapy. TEAEs were assessed by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0) and coded by the Medical Dictionary for Regulatory Activities (MedDRA version, 13.0): composite categories for the special adverse events skin reactions, acne-like rash and infusion-related reactions (IRRs), were based on MedDRA terms.

Statistical Considerations

All statistical analyses were performed on data recorded until the follow-up visit at week 12 after completion of the last radiotherapy dose for the last patient in the intention-to-treat (ITT)/safety population (defined as all patients receiving at least one dose of the study treatment). The clinical cut-off date was 11 June 2010.

Patients completing $\geq$70% of the cetuximab planned dose were those with a cetuximab RDI (from the second infusion onwards) $\geq$70%. Cetuximab RDI was calculated only for patients who received at least two doses of cetuximab. Patients receiving the full dose of radiotherapy within 2 weeks over the planned schedule were those receiving 42 fractions (thirty 1.8 Gy fractions [total dose 54.0 Gy] and twelve 1.5 Gy fractions [total dose 18.0 Gy]), at a total dose of 72.0 Gy and with a duration of exposure to radiotherapy of $\leq$56 days. The completion rate was defined as the proportion of patients who completed the planned cetuximab and radiotherapy schedules relative to the number of subjects in the ITT/safety population.

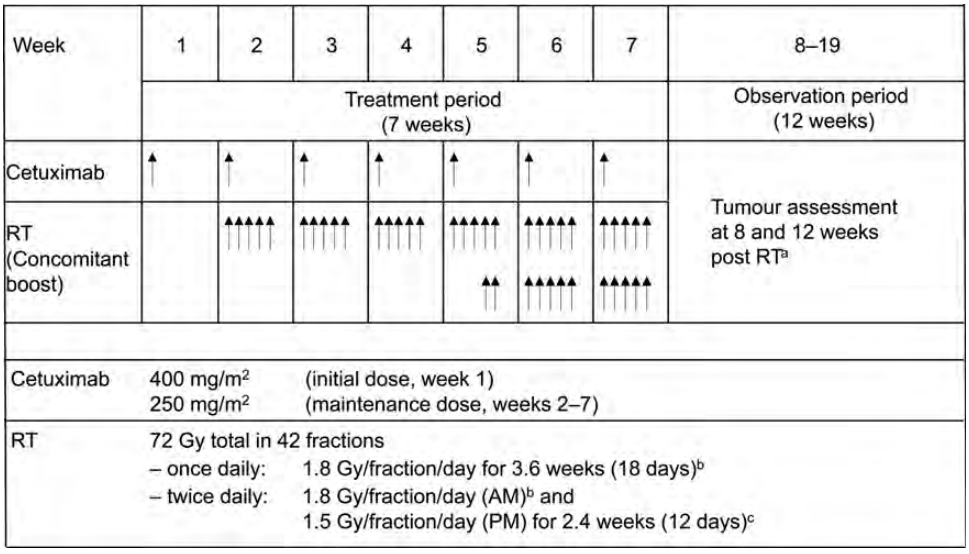

Figure 1. Schedule of irradiation treatment. [a]Imaging at week 12 (i.e. 4 weeks post-RT) was not to be performed for patients with progressive disease at week 8. [b]1.8 Gy/Fr (large field): The primary tumor, gross nodal area and uninvolved nodal area. [c]1.5 Gy/Fr (small field): The primary tumor and gross nodal area. Fr, fraction; Gy, Gray; RT, radiotherapy.

Descriptive statistics were used to summarize the data. A sample size of 20 patients was selected based on a completion rate of 94% reported for concomitant boost radiotherapy in the Bonner trial. The assumption was that at least 80% of the 20 patients would complete treatment, giving two-sided 95% confidence intervals of 68–99%, thereby encompassing the rate in the Bonner trial. The small sample size did not have any power to test statistical hypotheses but was considered to be sufficient for the evaluation of the tolerability (as primary endpoint), safety and efficacy in Japanese patients, in compliance with regulatory requirements. For completion and response rates, two-sided 95% confidence intervals (according to Clopper–Pearson) were calculated. All statistical analyses were performed using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.1.

RESULTS

Patient Characteristics

Between 6 March 2009 and 4 January 2010, 27 patients were enrolled. Five were ineligible for the study and therefore did not receive protocol-related treatment: due to investigator's decision, withdrawal of consent and interstitial lung disease ($n = 1$ patient each) and protocol-defined radiotherapy unable to be administered (because the required dose was out of the range of that defined by the protocol) ($n = 2$). Thus, 22 patients were enrolled and treated (ITT/safety population). Patient characteristics are summarized in Table 1. Most of the patients (95%) were male and 64% had a KPS of 100. The primary tumor sites were mainly the hypopharynx and larynx (36% each) and 45% of the patients had stage IV disease.

Table 1. Demographics and disease characteristics at baseline: ITT/safety population ($n = 22$)

Characteristic	
Age (years)	
Median	67
Range	(53–81)
Sex, *n* (%)	
Male	21 (95)
Female	1 (5)
Karnofsky performance status, *n* (%)	
100	14 (64)
90	8 (36)
Primary tumor site, *n* (%)	
Hypopharynx	8 (36)
Larynx	8 (36)
Oropharynx	6 (27)
Histology of squamous cell carcinoma, *n* (%)	
Well differentiated	5 (23)
Moderately differentiated	10 (45)
Poorly differentiated	3 (14)
Not known	4 (18)
TNM classification, *n* (%)	
T1–T2	9 (41)
T3–T4	13 (59)
N0	7 (32)
N+	15 (68)
UICC stage, *n* (%)	
Stage III	12 (55)
Stage IV	10 (45)

TNM, tumor node metastasis; UICC, Union for International Cancer Control.

Treatment Completion Rate

The treatment completion rate was 100% (95% CI 85–100) (Table 2). All 22 patients completed ≥70% of the cetuximab RDI and the full radiotherapy dose within 2 weeks over the planned schedule.

Treatment Exposure

One patient discontinued the study due to PD observed at 8 weeks after completion of treatment. The median duration of cetuximab treatment was 8 weeks, the median number of infusions administered was 8 and the median cumulative dose administered was 2169 mg/m^2 (Table 3). All but two patients (91%) received an RDI of ≥90%. The minimum observed cetuximab RDI was 80 to ≤90%. The dose of cetuximab was reduced in one patient, due to a TEAE (grade 3 dry skin). Most of the patients received cetuximab with fewer than 3 days delay in treatment, but two (9%) required cetuximab delays of 3–8 days (infection, $n = 1$; other reason, $n = 1$).

The median duration of radiotherapy was 44 days. All 22 patients received a total dose of 72.0 Gy radiotherapy divided into 42 fractions, i.e. 30 fractions of 1.8 Gy and 12 fractions of 1.5 Gy. The maximum radiotherapy delay which occurred in each patient is categorized as no delay or ≤5 days delay, 6–10 days delay, 11–15 days delay and ≥16 days delay. All patients were able to receive each fraction of radiotherapy with no or ≤5 days delay. In total, all patients completed their scheduled radiotherapy within ≤56 days, in accordance with the protocol-specified full radiotherapy dose criteria (Table 3).

Response Rate

According to the central review by the ESEC, the response rate 8 weeks after completion of radiotherapy was 82%, with a complete response rate of 41% (Table 4). The corresponding results based on the investigator assessment were 86 and 50%, respectively.

Table 2. Completion rate ($n = 22$)

Parameter	Patients, *n* (%)
Completion of ≥70% of cetuximab relative dose intensity	22 (100)
Completion of full dose of radiotherapy with a delay ≤2 weeks	22 (100)
Treatment completion rate [95% CI]	22 (100) [85–100]

CI, confidence interval.

Treatment completion rate and efficacy according to tumor *KRAS* mutation status

All 20 patients who underwent tumor *KRAS* mutation status testing had *KRAS* wild-type tumors. The completion rate among this group was 100% (95% CI 83–100). According to ESEC, 16 patients had a tumor response, giving a response rate of 80% (95% CI 56–94).

Safety

The most common TEAEs (≥50% patients) were mucosal inflammation (86%); dry mouth (77%); constipation, dry skin and dysgeusia (68% each); acne (64%); and dermatitis and pyrexia (50% each). Grade 3/4 TEAEs were reported in 21 (95%) patients. The most common (≥20% of patients) grade 3/4 TEAEs (Table 5) were mucosal inflammation (73%); dermatitis (27%); and infection, radiation skin injury and stomatitis (23% each). In terms of the special adverse events, all 22 patients experienced skin reactions and acne-like rash: three patients (14%) experienced a grade 3 reaction but there were no grade 4 TEAEs in these categories. There was one IRR (blood pressure increase, grade 1). No adverse events led to permanent discontinuation of either cetuximab or radiotherapy. No TEAE leading to death was reported.

DISCUSSION

In this study, we confirmed the feasibility of using a combination of cetuximab and concomitant boost radiotherapy for the treatment of Japanese patients with LASCCHN. The combination of cetuximab and concomitant boost radiotherapy has previously demonstrated efficacy benefits compared with concomitant boost radiotherapy alone in a subgroup of patients in the Phase III Bonner trial in a Western population. The characteristics of patients and their disease at baseline in the study reported here were generally similar to those observed in patients receiving cetuximab plus radiotherapy (once daily, twice daily and concomitant boost) in the Bonner trial, but with a few differences. In the present study, patients were slightly older versus those in the Bonner trial (8) (median age 67 versus 56 years), all had a good performance status (KPS ≥90, 100% versus 70%) and the proportion of patients with oropharynx as the primary tumor site was lower (27% versus 56%) whereas the proportion with primary hypopharyngeal tumors was higher (36% versus 17%). Patients with oropharyngeal tumors appeared to benefit particularly well from cetuximab plus radiotherapy in the Bonner trial (9).

Five patients enrolled to the trial were subsequently considered to be ineligible for protocol-defined treatment, and thus did not receive any study treatment. For two of these patients, the radiotherapy dose calculated to be required for effective treatment was outside the range specified by the

Table 3. Treatment exposure: ITT/safety population ($n = 22$)

Treatment	
Cetuximab	
Duration (weeks)	
Median	8
Range	7–9
Number of infusions	
Median	8
Range	7–9
Cumulative dose (mg/m^2)	
Median	2169
Range	1910–2415
Relative dose intensity,[a] *n* (%)	
≥90%	20 (91)
80 to <90%	2 (9)
Maximum dose delay, *n* (%)	
No delay or <3 days delay	20 (91)
3–8 days	2[b] (9)
Radiotherapy	
Duration[c] (days)	
Median	44
Range	40–52
Number of fractions	
Median	42
Range	42–42
Total dose administered (Gy)	
Median	72
Range	72–72
Maximum delay in each patient, [d] *n* (%)	
No delay or ≤5 days delay	22 (100)

[a]Relative dose intensity calculated only for patients who received at least two doses of cetuximab, with the initial cetuximab dose excluded from the calculation.
[b]One patient due to infection, one due to a reason other than an adverse event.
[c]Duration of radiotherapy exposure is defined as: the date of the last dose of radiotherapy − (date of the first dose of radiotherapy + 1).
[d]The maximum radiotherapy delay in each patient is categorized as follows: no delay or ≤5 days delay; 6–10 days delay; 11–15 days delay, and ≥16 days delay.

Table 4. Best response at 8 weeks after completion of radiotherapy: assessment by independent review committee and investigators: ITT/safety population ($n = 22$)

Response	Patients, *n* (%)	
	ESEC	Investigator
Complete response[a]	9 (41)	11 (50)
Partial response[a]	9 (41)	8 (36)
Stable disease	3 (14)	2 (9)
Progressive disease	1 (5)	1 (5)
Overall response rate [95% CI]	18 (82) [60–95]	19 (86) [65–97]

ESEC, Efficacy and Safety Evaluation Committee.
[a]Confirmed responses, whereby response at 8 weeks was confirmed at 12 weeks after the completion of radiotherapy.

Table 5. Most common grade 3/4 adverse events: ITT/safety population ($n = 22$)[a]

Adverse event	Patients, *n* (%)
Any	21 (95)
Mucosal inflammation	16 (73)
Dermatitis	6 (27)
Infection	5 (23)
Radiation skin injury	5 (23)
Stomatitis	5 (23)
Decreased appetite	4 (18)
Dysphagia	3 (14)
Lymphopenia	3 (14)
Pharyngeal inflammation	3 (14)
Diarrhoea	2 (9)
Dry skin	2 (9)
Pharyngitis	2 (9)

[a]Occurring in >1 patient.

protocol. For the other three patients, one was found to have interstitial lung disease (which was an exclusion criterion), one patient withdrew and the other was withdrawn at the decision of the investigator.

The completion rate of treatment was used as an indication of the tolerability of cetuximab plus radiotherapy in our study. The completion rate definition for cetuximab of ≥70% of the RDI represented no more than one missed dose of cetuximab, ensuring that tolerability was based on clinically effective levels of cetuximab. A treatment completion rate of 100% was reported, with all patients completing ≥70% of the cetuximab RDI and the full radiotherapy dose no later than 2 weeks after the planned end of treatment. The vast majority of patients received ≥90% of the cetuximab RDI and the lowest RDI was 80–90%. Only two patients required a cetuximab dose delay of more than 3 days. All patients were able to receive protocol-defined radiotherapy in combination with cetuximab.

The findings for treatment completion rate are in line with the data from the randomized Bonner trial, in which the treatment completion rate (according to the parameters defined in our study) of patients receiving cetuximab plus concomitant boost radiotherapy was 94% for patients receiving cetuximab in combination with radiotherapy (data on file, Merck KGaA). The results also compare favorably with data reported by Zenda et al. for the completion rate of cisplatin-based concurrent chemoradiotherapy in an exclusively Japanese population of patients with unresectable LASCCHN (10). In that study, in which patients received a 7-week course of radiotherapy (70 Gy at 2 Gy/day) combined with single-agent cisplatin (100 mg/m^2, days 1, 22 and 43), treatment completion was defined as administration of the planned dose of radiotherapy within 63 days and three courses of cisplatin no later than 14 days after the end of radiotherapy. The completion rate reported by Zenda et al. was 85%.

The adverse event profile in this study did not differ from that expected with the concomitant administration of cetuximab and radiotherapy for the treatment of LASCCHN. The overall incidence of grade 3 or 4 TEAEs in this study was similar to that seen in the cetuximab plus radiotherapy arm of the Bonner trial (95% versus 90%). The incidence of grade ≥3 mucosal inflammation was somewhat higher than that reported for mucositis in the cetuximab plus radiotherapy arm of the Bonner trial (73% versus 56%). This is probably due to the exclusive use of the concomitant boost radiotherapy regimen in our trial and the associated risk of an increase in mucositis severity with a concomitant boost compared with a once-daily regimen (11,12). Grade ≥3 acne-like rash, an adverse event associated with cetuximab, occurred with a similar incidence to acneiform rash in the cetuximab plus radiotherapy arm of the trial by Bonner et al. (14% versus 17%, respectively) (8).

In the study reported here, the response rate 8 weeks after completion of radiotherapy was 82% according to the independent review committee. This was in good agreement with the investigator-assessed analysis of response rate, which was 86%. It also compares well with the 74% response rate achieved after treatment with cetuximab plus radiotherapy in the Bonner trial (8). The finding that all of the 20 patients whose tumors were tested had *KRAS* wild-type disease supports data in the literature for the low incidence of *KRAS* mutations in SCCHN (13,14), including in an exclusively Japanese population (15). To our knowledge, this is the first time that *KRAS* mutation data have been obtained for LASCCHN from a prospective clinical trial.

Currently, concomitant chemoradiotherapy (16–18) and radiotherapy plus cetuximab (16,17) are accepted treatment approaches in a range of countries for patients with unresectable SCCHN. There are no trials directly comparing these two strategies, but a recently published quantitative analysis indirectly compared a meta-analysis of data from four randomized trials of cisplatin plus radiotherapy versus

radiotherapy alone and data from one meta-analysis with data from the Bonner et al. trial (19). The analysis indicated that cetuximab and cisplatin were equally effective when administered in combination with radiotherapy, in terms of locoregional control and overall survival in patients with LASCCHN. Given the estimated efficacy equivalence, the choice of whether to treat with concurrent chemoradiotherapy or with cetuximab plus radiotherapy should be based on the toxicity profiles of the two treatment approaches and which of them is considered by the treating physician to be the most suitable for the individual patient.

The study reported here demonstrated that the combination of cetuximab and concomitant boost radiotherapy was a feasible and well-tolerated approach for the treatment of Japanese patients with newly diagnosed LASCCHN. The tolerability of treatment, assessed using treatment completion rate as a surrogate measure, the safety and the antitumor activity observed, was similar to that reported in a pivotal Phase III randomized trial investigating the addition of cetuximab to radiotherapy in a Western population of patients with LASCCHN (8).

Acknowledgements

The authors acknowledge the valuable contributions of M. Tsukuda, Yokohama City University School of Medicine, Kanagawa, Japan, who is a coordinating investigator of the study, Y. Ariyoshi, Special Advisor (honorary director of Aichi Prefectural Cancer Center Aichi Hospital) Marumo Hospital, Chair of an Efficacy and Safety Evaluation Committee of the study and T. Seriu, Bristol-Myers Squibb, Japan, in reviewing the manuscript. The authors acknowledge the contribution of Jo Shrewsbury-Gee, Cancer Communications and Consultancy Ltd, Knutsford, Cheshire, who provided medical writing services on behalf of Merck KGaA.

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 is an employee of Merck KGaA. The other authors declare no conflict of interest.

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APPENDIX

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