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ORIGINAL ARTICLE

A phase I escalating single-dose and weekly fixed-dose study of cetuximab pharmacokinetics in Japanese patients with solid tumors

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Abstract
Purpose Cetuximab is a therapeutic immunoglobulin G1 monoclonal antibody that recognizes the epidermal growth factor receptor (EGFR). This phase I dose-escalation study was designed to assess the safety and pharmacokinetics (PK) of cetuximab in Japanese patients with EGFR-expressing, advanced, solid tumors and also to look for evidence of antitumor efficacy.
Patients and methods Thirty patients were enrolled in the study; 29 with colorectal adenocarcinomas and one with an adenocarcinoma of the lung. Patients received an initial/weekly infusion of cetuximab at dose levels of 100/100 (dose level 1), 250/250 (dose level 2), 400/250 (dose level 3), 500/250 (dose level 4) or 400/250 (dose level 5) mg/m^2, for 7 or more weeks, with an interval between the initial and second infusion of 1 (dose level 5 representing the standard regimen) or 2 weeks (dose levels 1–4 of the non-standard regimens).
Results No dose-limiting toxicities (DLTs) were observed during the evaluation period. All patients had at least one adverse event (AE). The most common cetuximab-related AEs were skin toxicity (93% of patients), including acneiform dermatitis (83% of patients). Two patients experienced cetuximab-related grade 3 AEs of skin toxicity and diarrhea after DLT evaluation. C_{max} and $AUC_{0-\infty}$ after the initial infusion showed dose-proportional increases. Mean total body clearance (CL) values decreased with dose at the lower dose levels. At doses of $\geq$400 mg/m^2, CL values appeared to level off. Mean trough concentrations for dose level 5 were constant from week 4 (day 29) onward. Two patients (8%) achieved partial response (at 100/100 mg/m^2). The overall disease control rate (partial response + stable disease) was 58%.
Conclusion The current study demonstrated that cetuximab PK and safety profiles are similar between Japanese and non-Japanese patient populations. It would appear that

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the standard dose of an initial 2-h infusion of 400 mg/m^2 followed thereafter by weekly 1-h infusions of 250 mg/m^2 for non-Japanese patients is feasible for future clinical studies in Japanese patients.

Keywords Cetuximab · Japanese · EGFR · Safety · Pharmacokinetics · Colorectal

Introduction

Over recent years, the development of rationally selected targeted agents such as monoclonal antibodies and small molecule tyrosine kinase inhibitors has offered new possibilities in relation to improving the efficacy of the standard cytotoxic regimens used in the treatment of metastatic colorectal cancer (mCRC). The epidermal growth factor receptor (EGFR)-targeted immunoglobulin G1 monoclonal antibody cetuximab (Erbitux®) is one such targeted agent.

Cetuximab competitively inhibits the binding of endogenous EGFR ligands and thus prevents receptor dimerization and downstream signaling [1, 2]. Antibody-binding to the tumor cell may also result in a clinically-important antibody-dependent cell-mediated cytotoxicity reaction (ADCC) [3, 4]. Randomized mCRC studies in mainly Caucasian populations have shown that cetuximab, administered in accordance with the standard dosing regimen of an initial 2-h infusion of 400 mg/m^2 of body surface area (BSA) followed thereafter by weekly 1-h infusions of 250 mg/m^2, is effective as monotherapy [5, 6] or in combination with irinotecan [5, 7], following the failure of previous chemotherapy regimens. Furthermore, in the first-line setting, the phase III CRYSTAL study has shown that the addition of cetuximab to infusional 5-fluorouracil/folinic acid/irinotecan (FOLFIRI) significantly improves the response rate, progression-free survival (PFS) time and R0 resection rate in mCRC patients, compared with FOLFIRI alone [8]. Similarly, randomized studies have demonstrated the efficacy of cetuximab in combination with radiotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck (SCCHN) [9] and in combination with platinum-based therapy in the first-line treatment of recurrent and/or metastatic SCCHN [10].

Two recent studies in the US have explored the pharmacokinetics (PK) of single-dose administration of cetuximab in patients with solid tumors, with particular attention paid to the elimination phase [11, 12]. Both studies supported the saturation of EGFR binding at a clinically achievable dose level. A significant association was also noted between cetuximab clearance and both BSA and weight, supporting the use of these parameters in calculating individual cetuximab doses [12]. The primary objective of the current phase I study was to investigate the safety and tolerability of cetuximab in a population of Japanese patients with EGFR-expressing solid tumors. Secondary objectives were to evaluate the PK of cetuximab in Japanese patients the (mirroring the recent US PK analyses with an escalating single dose); expression of human antichimeric antibodies (HACA); the incidence of dose-limiting toxicity (DLT); and the antitumor efficacy of cetuximab.

Patients and methods

Patient eligibility

Only Japanese patients, aged between 20 and 74 years, with a histologically or cytologically confirmed advanced solid EGFR-expressing tumor, refractory to a standard therapy or for which no standard therapy existed, were eligible. They required an Eastern Cooperative Oncology Group performance status of 0–2; a life expectancy of at least 3 months after the start of study; adequate hematological (leukocyte count: $\geq$3,000 and <12,000 mm^{-3}; neutrophil count: $\geq$1,500 mm^{-3}; platelet count: $\geq$100,000 mm^{-3}; hemoglobin: $\geq$9 g/dL), hepatic (aspartate aminotransferase and alanine aminotransferase: $\leq$2.5 times the upper limit of the reference range; serum total bilirubin: $\leq$1.5 times the upper limit of the reference range), and renal (serum creatinine: $\leq$1.5 times the upper limit of the reference range) function. Patients were required to be available for hospitalization until day 22 of the study, to have no carry-over effect from prior therapy and to not have received treatment with blood transfusions, blood products or blood cell factors such as granulocyte colony stimulating factor during 2 weeks prior to enrollment. All patients gave their written informed consent prior to study entry.

Patients were excluded if they had: symptomatic brain metastasis, a previous history of cancerous meningitis, poorly controlled epileptic seizures or clinically significant mental or central nervous system disorders or if they had previously received monoclonal antibody therapy (including cetuximab). They were also ineligible if they had serious cardiac or cardiovascular disease, diabetes mellitus, hypertension, active infection or symptomatic blood coagulation disorder, acute pulmonary disorder, interstitial pneumonia, or pulmonary fibrosis; active, double cancers; a previous history of malignant tumors (other than non-melanoma skin cancer, uterine cervical carcinoma or gastrointestinal intramucosal carcinoma) with a sign of recurrence within the last 5 years; a large volume of pleural effusion or ascites or were positive for hepatitis B virus, hepatitis C virus or human immunodeficiency virus. Patients were also excluded if they required chronic treatment with systemic steroids; were pregnant or lactating; if they wished to have a child; or if they had an alcohol or drug

addiction or a previous history of drug allergy or anaphylactic symptoms.

Study design

This study was a two-center, phase I dose-escalation study of cetuximab in patients with advanced solid cancer. As this was the first such investigation in Japanese patients, a low dose level of 100 mg/m^2 as an initial dose and 100 mg/m^2 as a repeated weekly dose was selected to begin the study. All patients received 50 mg oral diphenhydramine hydrochloride (H1-antagonist) 30–60 min before each cetuximab infusion as a preventive measure in relation to infusion-related reactions. At first infusion, patients received 100 (dose level 1), 250 (dose level 2), 400 (dose level 3 or 5) or 500 (dose level 4) mg/m^2 of cetuximab as a 2-h intravenous infusion. Subsequent weekly 1-h infusions of 100 (dose level 1) or 250 (dose level 2–5) mg/m^2 of cetuximab began according to the schedule in Fig. 1 and continued to day 50, which was considered to be sufficient to assess cetuximab PK. For dose levels 1–4, patients had a 2-week interval between first and second infusion for the purposes of evaluation of single-dose PK. Patients in dose level 5 received cetuximab according to the standard 400/250 mg/m^2 schedule, with a 1-week interval between first and second infusions, curtailing the collection of single-dose PK at 7 days in this group.

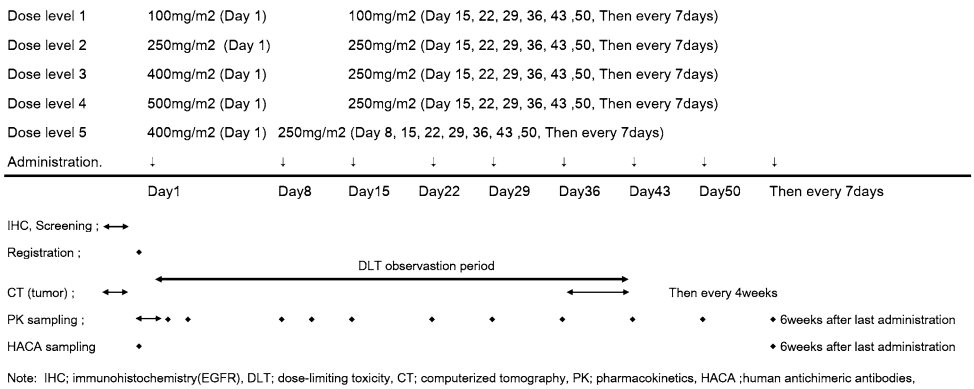
Six patients were assigned to each dose level 1–4, with the first cohort receiving cetuximab at the lowest dose level. If DLT was observed in ≥2 patients during the DLT evaluation period of 6 weeks from the first administration until 1 week after the fifth administration, no further patients were to be enrolled and this dose level was defined as the MTD. Otherwise, the dose was escalated to the next dose level (1–2, 2–3 or 3–4). If the MTD was not established at dose level 4, six patients received the standard 400/250 mg/m^2 regimen at dose level 5. DLT was defined as either: grade 4 or three incidences of grade 3 skin toxicity events, or the omission of three consecutive infusions due to grade 3 skin toxicity; adverse drug reactions ≥grade 3 (except for skin toxicity, electrolyte abnormality, anorexia, nausea, and alkaline phosphatase) or the development of acute pulmonary disease, interstitial pneumonia and other pulmonary symptoms. Infusion-related reactions were not regarded as DLTs as they were considered to be largely dose-independent. If progressive disease (PD) was not observed between the initial dose and fifth administration (or sixth administration for dose level 5), the study medication was to be continued as long as the patient gave consent, again after an observation period of 1 week. During the study period, the following drugs and therapies were not permitted; therapeutic modalities for malignant tumor, other antibody therapy, chemotherapy, hormonal therapy, immunological therapy, radiotherapy, hyperthermia and surgical therapy, and systemic steroids. The drugs and therapies used for symptomatic relief of concurrent diseases or complications were permitted before and during the study with minimal modification of dosage and mode of administration.

Study evaluations

Response was assessed in evaluable patients by the investigators according to RECIST guidelines [13] and had to be confirmed by a repeated consecutive assessment conducted a minimum of 28 days after the first assessment. Adverse events (AEs) were graded according to the National Cancer Institute—Common Toxicity Criteria version 2 (Japan Clinical Oncology Group—translation version). Safety variables assessed included; AEs, abnormal laboratory values and vital signs (blood pressure, heart rate, respiratory rate, body temperature, 12-lead electrocardiogram, chest X-ray).

Pharmacokinetic analysis

Blood samples (5 mL) were drawn prior to the first cetuximab infusion and at 1, 1:58, 2:30, 3, 4, 6, 8, 24, 48, 96, 168, 264 and 336 h (not 264 and 336 h for dose level 5) after the initiation of infusion. Subsequent samples were taken before cetuximab infusions on days 15 (dose level 5



Note: IHC; immunohistochemistry(EGFR), DLT; dose-limiting toxicity, CT; computerized tomography, PK; pharmacokinetics, HACA ;human antichimeric antibodies,

Fig. 1 Dosage and schedule of on-study cetuximab administration

only), 22, 29, 36, 43 and 50 and during the post-treatment observation period or at the time of withdrawal from the study. Cetuximab serum concentration data were generated using a validated sandwich enzyme-linked immunosorbent assay (ELISA) carried out by MDS PS Pharma Services Switzerland AG (Fehraltorf, Switzerland) essentially as described [14].

Results

Patients and demographics

EGFR expression was detected immunohistochemically in the tumor tissue of 43 of 47 screened patients (91%). Of these 43 patients, 30 fulfilled all the inclusion criteria and were enrolled in the study; all received at least one dose of the study drug. Summarized for all patients in Table 1, the demographic characteristics of the individual treatment groups were generally similar. There were no major differences between the dose levels with regard to medical history other than cancer. Twenty-nine patients were suffering from adenocarcinoma of the colon or rectum and the remaining patient had adenocarcinoma of the lung. The majority of patients had metastatic disease at study entry, and 8 (27%), 10 (33%) and 9 (30%) patients had 1, 2 and 3 organs involved, respectively. Most commonly involved organs were the lung in 22, liver in 20 and the lymph nodes in 15 patients. All patients had received previous chemotherapy or hormonal therapy; 29 had undergone surgery, 6 had received radiotherapy, and three had received other treatments. Similar percentages of patients received concomitant medication across dose levels, except for a higher incidence of the use of antihypertensive medications at dose levels 4 and 5.

Table 1 Patients characteristics

Characteristic	$N = 30$
Gender, *N* (%)	
Male	15 (50.0)
Female	15 (50.0)
Age (years)	
Median (min–max)	54 (36–73)
ECOG PS, *N* (%)	
0	20 (67.7)
1	9 (30.0)
2	1 (3.3)
Diagnosis, *N* (%)	
Colorectal cancer	29 (96.7)
NSCLC	1 (3.3)
Prior therapy, *N* (%)	
Chemotherapy	30 (100)
5-Fluorouracil	27
S-1	7
UFT	7
Irinotecan	28
Oxaliplatin	1
Radiotherapy	6 (20)

ECOG PS Eastern Cooperative Oncology Group performance status, *NSCLC* non-small cell lung cancer

Dose-limiting toxicity assessment

The safety population comprised all 30 patients, each of whom had received at least one dose of the study medication. Four patients did not complete the DLT evaluation period after withdrawing from treatment as a consequence of PD after one (one patient) or three infusions (three patients). DLT analyses were therefore performed on 26 evaluable patients (5 patients each at dose levels 2–5 and 6 patients at dose level 1). The median duration of treatment was 14.0 weeks and the median cumulative cetuximab dose was 2,450 mg/m^2. No DLT was reported during the evaluation period and consequently, the MTD was not reached even at the highest dose level. Eighteen patients continued treatment with cetuximab after completion of the preset weekly repeated treatment schedule (on day 50).

Adverse events

AEs and cetuximab-related AEs were reported in 30 (100%) and 29 (97%) patients, respectively. The most common AEs according to system organ class (SOC) distribution were skin and subcutaneous tissue disorders and investigations (both reported for 28/30, 93% of patients) followed by gastrointestinal disorders and general disorders and administration site conditions (both 26/28 patients, 87%).

The most common cetuximab-related AEs observed (summarized in Table 2) were acneiform dermatitis (83%), rash and skin reaction (both 47%), dry skin (40%), pruritus (33%), paronychia (37%), pyrexia (57%), diarrhea (33%) and fatigue and stomatitis (both 30%). Hypersensitivity reaction (HSR) was reported in only one patient at dose level 1. This patient experienced HSR twice: a grade 1 HSR on the day of the first cetuximab infusion and a grade 2 HSR on the second day after administration at week 6. Both reactions resolved. Pyrexia and headache appeared to more common at the higher dose levels and were mainly reported in a close temporal relationship with cetuximab infusion, suggesting that they may have been infusion-related events. Grade 3 or 4 AEs were reported in nine patients after DLT evaluation and in two cases, were considered to be

Table 2 Relevant common any grade and grade 3/4 cetuximab-related adverse events

Adverse event	Number of patients with any grade (grade 3/4)					Any grade total (%)	Grade 3/4 total (%)
	Dose level						
	1	2	3	4	5		
	Dose[a] (mg/m^2)						
	100/100 $N = 6$	250/250 $N = 6$	400/250 $N = 6$	500/250 $N = 6$	400/250 $N = 6$	$N = 30$	
Any adverse event	5 (1)	6	6	6 (1)	6	96.7	6.7
Acneiform dermatitis	5	6	4	5 (1)	5	83.3	3.3
Rash	3	2	5	2 (1)	2	46.7	3.3
Skin reaction	3	3	3	2	3	46.7	
Dry skin	1	2	1	4	4	40.0	
Pruritus	2	1	3	3 (1)	1	33.3	3.3
Paronychia	3			4	4	36.7	
Pyrexia		2	4	5	6	56.7	
Diarrhea	2 (1)	1	2	2	3	33.3	3.3
Fatigue	1	1	4	2	1	30.0	
Stomatitis	3	1	1	4		30.0	
Anorexia			2	4	2	26.7	
Nausea	1		2	3	1	23.3	
Vomiting		1	3	2	1	23.3	

[a] Dose; initial dose/weekly dose

cetuximab-related (grade 3 diarrhea, one patient at dose level 1; grade 3 acneiform dermatitis, pruritus and rash, one patient at dose level 4).

Although cetuximab-related AEs did not lead to discontinuation of cetuximab in any patient, the primary reason for discontinuation in two patients was an aggravation of disease symptoms. The weekly dose for one patient (dose level 4) was reduced from 250 to 200 mg/m^2 at the 38th week of administration due to grade 3 skin toxicity in accordance with the study protocol. There were no other dose reductions. One patient died within 30 days of the end of study treatment from an unrelated respiratory failure due to progressive lung metastases.

Pharmacokinetics

A full PK profile suitable for PK analysis following initial cetuximab infusion was available from all patients. Individual PK parameters after non-compartmental and compartmental analysis were in good agreement. In general, inter-patient variability in the cetuximab concentration values was not large. Cetuximab serum concentration time profiles are displayed in Fig. 2. Mean trough concentrations for dose level 5 were constant from week 4 (day 22) onwards (Fig. 3).

PK parameters, based on non-compartment analysis and data obtained at 2 weeks later (day 15) in dose level 1–4 and at a week later (day 8) in dose level 5, are shown in Table 3. Dose-proportional increases in mean C_{max} (range 49.0–396.7 μg/mL) were observed across the dose range of 100–500 mg/m². Moderate deviations from dose proportional increases were observed for $AUC_{0-\infty}$ (range 3,469–3,4817 μg/mL h), especially at the low doses. However, in general, maximum serum concentrations following infusion and the exposure to cetuximab as measured by $AUC_{0-\infty}$ are predictable for each dose used. Mean CL values decreased with dose at the lower dose levels. At doses of ≥400 mg/m^2, CL values appeared to level off. Mean terminal half-life ($t_{1/2}$) values increased from 54 to 111 h over the 100–500 mg/m^2 dose range. At the dose of 400 mg/m^2 (equivalent to the standard regimen), the mean $t_{1/2}$ values were 101 (dose level 3) and 106 h (dose level 5). Values for the volume of distribution at steady state (V_{ss}) were independent of dose and consistent with distribution of cetuximab in the theoretical vascular space.

Pre- and post-dose samples for the determination of HACA levels were available for 21 patients. The analytical results suggested that there had been no induction of such antibodies in these patients.

Efficacy

Six patients were excluded from the efficacy analysis, three because follow-up evaluation was not available (all

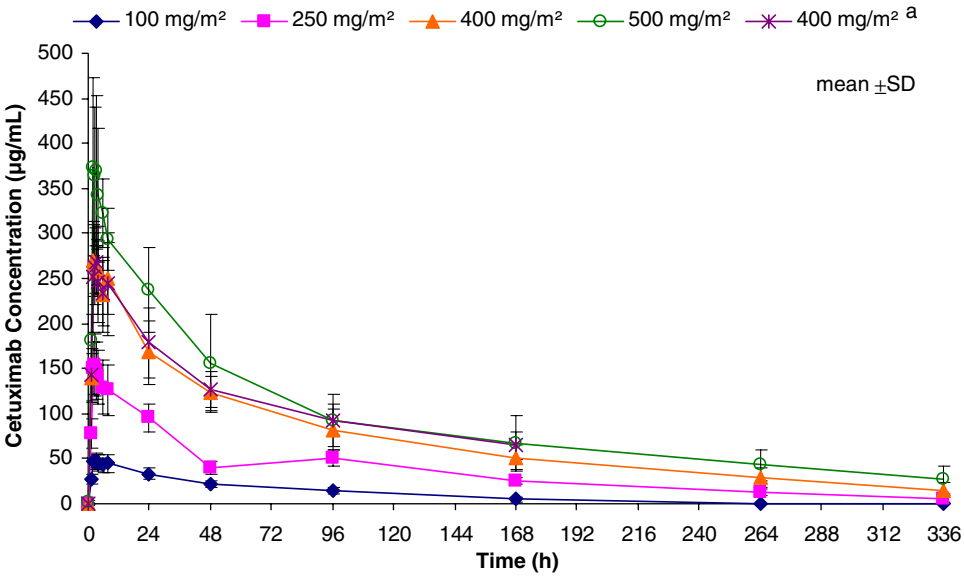


Fig. 2 Cetuximab serum concentration time profile

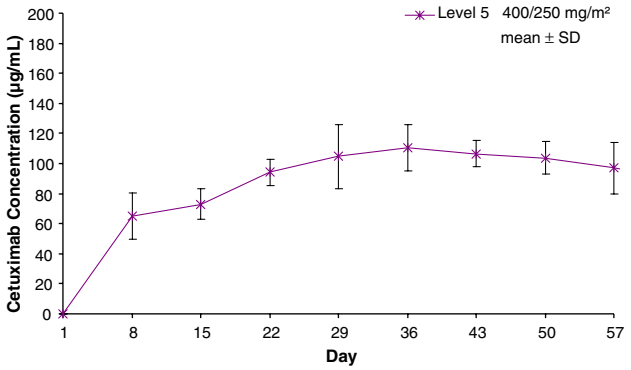


Fig. 3 Trough serum cetuximab concentrations (linear scale) after the 400 mg/m² initial dose and following weekly administrations of 250 mg/m² (dose level 5)

colorectal cancer), and three because the disease at baseline was not measurable (two colorectal cancer and one lung adenocarcinoma). Twenty-four patients were therefore evaluable for efficacy. Two patients treated at dose level 1 showed partial response, giving an overall response rate of 8.3% in the efficacy-evaluable population [95% confidence interval (CI): 1.0, 27.0]. Furthermore, 12 patients achieved stable disease (3, 3, 1, 3 and 2 patients at dose levels 1–5, respectively) to give an overall disease control rate of 58.3% (95% CI: 36.6, 77.9).

Discussion

Cetuximab has been shown to be effective and generally well tolerated in mixed but mainly Caucasian patient groups and the PK profile of this agent administered as a single dose of 20–500 mg/m^2 has been extensively characterized in a variety of separate studies in such populations [15]. Two recent studies have examined cetuximab single-dose PK in US patients with solid tumors using a similar

Table 3 Mean (standard deviation) pharmacokinetic parameters at day 15 (non-compartment analysis)

	Dose level (dose mg/m^2)				
	1 (100) $N = 6$	2 (250) $N = 6$	3 (400) $N = 6$	4 (500) $N = 6$	5 (400)[a] $N = 6$
C_{max} (µg/mL)	49.0 (8.5)	157.0 (31.9)	287.2 (37.9)	396.7 (83.6)	297.8 (30.5)
% CV	17	20	13	21	10
$AUC_{0-\infty}$ (µg/mL × h)	3,469 (583)	12,132 (2,300)	25,823 (6,525)	34,817 (11,498)	29,213 (6,431)
% CV	17	19	25	33	22
$t_{1/2}$ (h)	54 (17)	74 (12)	101 (31)	111 (19)	106 (24)
CL (L/h)	0.046 (0.007)	0.035 (0.009)	0.026 (0.009)	0.026 (0.013)	0.022 (0.005)
V_{ss} (L)	3.46 (0.59)	3.98 (0.78)	3.34 (0.48)	3.51 (0.56)	3.1 (0.5)

CV coefficient of variation, C_{max} maximum concentration, $AUC_{0-\infty}$ area under the concentration-time curve, $t_{1/2}$ terminal half-life, *CL* total body clearance, V_{ss} volume of distribution at steady state

[a] Dose level 5: pharmacokinetic parameters are based on concentration data measured up to timepoint 168 h (day 8) following the initial 400 mg/m^2 dose

dose-escalation protocol to that employed in the current study [11, 12]. Patients in both of these studies received either: 50, 100, 250, 400 or 500 mg/m^2 initial infusions, followed after a 3-week interval by weekly infusions of 250 mg/m^2. The similarity in schedules and type of patient included in these analyses allows a comparative evaluation of cetuximab PK and safety in the non-Japanese and Japanese patient groups. Mean C_{max} values were comparable for initial cetuximab dose levels of 100 and 250 mg/m² in the two populations. However, at the higher doses of 400 and 500 mg/m^2, C_{max} values were higher in the Japanese (287 and 397 μg/mL) compared with the non-Japanese populations 205/229 and 243/246 μg/mL, respectively). Likewise, mean $AUC_{0-\infty}$ values were comparable at the lower doses but higher in the Japanese compared with the non-Japanese patient groups at the 500 mg/m^2 dose level (34,817 vs. 30,870 and 24,740 μg/mL h).

However, the results of the current study confirm that the PK profile in Japanese patients is broadly similar to that obtained for non-Japanese patient groups. In particular, linear relationships for both mean C_{max} and $AUC_{0-\infty}$ with dose that were previously noted in the non-Japanese populations were also observed in the Japanese population, indicating that the exposure to cetuximab is predictable across the dose-range. Dose-dependent relationships were observed in the current study for $t_{1/2}$ and CL at lower doses, with the apparent leveling of CL seen at the higher doses mirroring the earlier studies in non-Japanese patients and supportive of receptor saturation at these doses. In addition, V_{ss} was independent of dose and consistent with a distribution of cetuximab in the theoretical vascular space, which is similarly consistent with the data from non-Japanese populations. The cetuximab mean trough concentrations following repeated weekly doses of 250 mg/m^2 (dose level 5) in the Japanese population were constant from fourth week (day 29) onwards and were in good agreement with previously reported pharmacologically active trough concentration values following the standard dosing regimen (equal to dose level 5) of cetuximab [16].

In relation to safety, cetuximab was generally well tolerated at all dose levels in Japanese patients and the MTD was not reached at the highest dose-level tested (500 mg/m^2 initial infusion followed by 250 mg/m^2 weekly). No specific toxicities were identified in Japanese patients compared with mainly Caucasian groups, and the incidence of cetuximab-related grade 3/4 AEs was low (2/30 patients) and as expected. The most common AEs at any grade according to SOC distribution were skin and subcutaneous tissue disorders, which were reported for 93% of patients. Acneiform dermatitis, which was noted in 83% of patients, was the most commonly occurring cetuximab-related AE. Although skin reactions are a class effect of EGFR-targeted agents, the level of incidence of this mainly mild adverse drug reaction in this study is in the upper range of what has been commonly reported for mixed but mainly Caucasian populations. A considerable number of studies in a range of cancer types including mCRC have noted a correlation between the incidence and severity of acne-like rash or skin reactions and efficacy [5, 8, 16–19]. The high level of skin toxicity noted in Japanese patients may therefore be a promising indicator for cetuximab efficacy in this population, a hypothesis that should be addressed in future clinical studies. The disease control rate of 58% achieved for cetuximab monotherapy in Japanese patients is encouraging in this context. On balance, the safety profile for all dose regimens in the current study was essentially consistent with the safety profile of cetuximab as described in the previous comparable studies in non-Japanese patient populations [11, 12].

In conclusion, the current study has demonstrated that cetuximab PK and safety profiles are similar between Japanese and non-Japanese patient populations. Given this assessment, it would appear that the standard dose of an initial 2-h infusion of 400 mg/m^2 followed thereafter by weekly 1-h infusions of 250 mg/m^2 is feasible for future clinical studies in Japanese patients.

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