



## ORIGINAL ARTICLE

# Evaluation of pharmacokinetics and safety of cetuximab with cisplatin/carboplatin in patients with advanced solid tumor: Result from phase II studies

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## Abstract

The pharmacokinetics and potential drug–drug interactions between cetuximab and cisplatin or carboplatin from two studies (JXBA and JXBB) were evaluated. These studies were multicenter, open-label phase II trials designed to evaluate the drug–drug interactions between cetuximab (400 mg m<sup>-2</sup> initial dose) and cisplatin (JXBA; 100 mg m<sup>-2</sup>) or carboplatin (JXBB; area under the curve [AUC] = 5 mg × min mL<sup>-1</sup>) with or without 5-fluorouracil (5FU) in patients with advanced solid tumors. Concentrations of cetuximab, cisplatin and carboplatin were determined using analytical methods. The safety and tolerability of cetuximab in combination with cisplatin or carboplatin was also determined in all treated patients. The JXBA study showed that cetuximab serum concentrations were similar when cetuximab was administered alone or in combination with cisplatin. The C<sub>max</sub>, t<sub>max</sub> and overall AUC for the cetuximab group (194 µg mL<sup>-1</sup>, 2.0 hour, 14 900 µg × h mL<sup>-1</sup>) and the cetuximab and cisplatin combination group (192 µg mL<sup>-1</sup>, 1.99 hour, 16 300 µg × h mL<sup>-1</sup>) were similar. The JXBB study showed that mean cetuximab serum concentrations were similar when cetuximab was administered alone or in combination with carboplatin. The C<sub>max</sub>, t<sub>max</sub> and overall AUC for the cetuximab group (199 µg mL<sup>-1</sup>, 1.15 hour, 17 200 µg × h mL<sup>-1</sup>) and the cetuximab and carboplatin combination group (199 µg mL<sup>-1</sup>, 3.17 h, 16 800 µg × h mL<sup>-1</sup>) were similar. Both studies showed that the safety profile was consistent with known side effects of cetuximab, platinum-based therapies and 5-FU. There was no clinically relevant change in cetuximab pharmacokinetics when it was administered in combination with cisplatin or carboplatin.

## KEYWORDS

carboplatin, cetuximab, cisplatin, pharmacokinetics, solid tumor

**Abbreviations:** 5FU, 5-fluorouracil; 5-FU, 5-fluorouracil; AUC, area under the curve; EGFR, Epidermal growth factor receptor; SCCHN, squamous cell carcinoma of the head and neck.

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## 1 | INTRODUCTION

Epidermal growth factor receptor (EGFR) is an established therapeutic target in various solid malignancies including squamous cell carcinoma of the head and neck (SCCHN) and colon carcinoma.<sup>1,2</sup> Cetuximab, an immunoglobulin G1 chimeric human/murine monoclonal antibody, specifically binds to the EGFR with high affinity. The proposed mechanisms of its anticancer activity include inhibition of receptor activation by natural ligands, endocytosis of the receptor and activation of antibody-dependent cell-mediated cytotoxicity through the activation of macrophages and natural killer cells.<sup>3</sup> Cetuximab has been evaluated in the treatment of recurrent or metastatic SCCHN as monotherapy and in combination with platinum-containing regimen.<sup>4-6</sup> The addition of cetuximab to platinum-containing regimen has shown a significant increase in response rate. Currently, cetuximab in combination with cisplatin or carboplatin plus 5-fluorouracil (5-FU) is an accepted standard of care in first-line recurrent/metastatic SCCHN.<sup>7-11</sup>

We evaluated the pharmacokinetics and potential drug-drug interactions between cetuximab and cisplatin or carboplatin. Here we report results from two phase II pharmacokinetic studies, one evaluated pharmacokinetics of cetuximab and cisplatin (JXBA study), and the second evaluated pharmacokinetics of cetuximab and carboplatin (JXBB study). The studies were conducted in response to a postmarketing request by the US Food and Drug Administration to further characterize the pharmacokinetics of cetuximab with cisplatin/carboplatin when these two agents were coadministered and to investigate any potential for drug-drug interactions. The main rationale for this request was that the US Food and Drug Administration determined that the analysis of spontaneous post-marketing adverse events (AEs) reported was not sufficient to evaluate the known serious risks of infusion reactions, cardiopulmonary arrest, pulmonary toxicity and dermatologic toxicity caused by drug exposures when administered at recommended dose and schedule. Few AEs were also reported to adequately identify unexpected serious risks from drug-drug interactions between cetuximab and cisplatin or cetuximab and carboplatin. The JXBA and JXBB studies were conducted to address these issues.

## 2 | METHODS

### 2.1 | Study design

JXBA (NCT01099358) and JXBB (NCT01063075) studies were multicenter, open-label phase II trials designed to evaluate the drug-drug interactions between cetuximab and cisplatin (JXBA) or carboplatin (JXBB) with or without 5-FU in patients with advanced solid tumors. The JXBA study was conducted at six centers in the USA and Canada whereas the JXBB study was conducted at seven centers in these two countries. Institutional review boards at all participating institutions approved the study protocol(s). All patients gave written informed consent. These studies were conducted according to good clinical practice, and the Declaration of Helsinki and its amendments.

Both studies were amended to address ongoing patient recruitment and retention challenges, including providing investigators the

flexibility to enroll patients with any advanced solid tumor histology. In the original randomized, two-arm design the effect of cetuximab on the pharmacokinetic parameters of cisplatin or carboplatin was studied in one arm (group A), while the effect of cisplatin or carboplatin on the pharmacokinetic parameters of cetuximab was investigated in the other arm (group B). This design had ongoing patient recruitment and retention challenges and was therefore discontinued. Instead, a single-arm study design was introduced and patients were enrolled in group C. In both JXBA and JXBB studies, patients in group C received up to six cycles of combination therapy. Thereafter, treatment with cetuximab monotherapy was permitted until there was evidence of progressive disease, unacceptable toxicity or another withdrawal criterion was met. Due to challenges, patient enrollment in group C was discontinued and enrollment in group D was initiated. Patients in group D, received one cycle of cetuximab in combination with cisplatin with or without 5-FU (JXBA study), or one cycle of cetuximab in combination with carboplatin with or without 5-FU (JXBB study). The treatment schedule was designed to investigate the influence of cetuximab on the single-dose pharmacokinetics of the platinum compounds. In both the studies, the main inclusion criteria were that patients (male and female) should be 18 years or older with histologically or cytologically confirmed advanced solid tumors and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

### 2.2 | Study objectives

The primary objectives of the studies were to investigate the pharmacokinetics of cetuximab in combination with cisplatin (JXBA) or carboplatin (JXBB) in patients with advanced solid tumors and to assess the potential for drug-drug interactions. The secondary objective was to assess the safety of cetuximab in combination with cisplatin or carboplatin, with or without 5-FU.

### 2.3 | Dosage

For group C, the duration of cycle 1 was for 4 weeks and of cycles 2-6 was for 3 weeks. Cisplatin ( $100 \text{ mg m}^{-2}$ ) or carboplatin area under the curve (AUC)  $5 \text{ mg} \times \text{min mL}^{-1}$  was administered over 60 minutes on day 1 of cycles 1-6. Patients received an intravenous infusion of cetuximab ( $400 \text{ mg m}^{-2}$  initial dose, over 120 minutes) on day 8 of cycle 1 followed by subsequent weekly doses of  $250 \text{ mg m}^{-2}$  (over 60 minutes) Optional 5-FU ( $1000 \text{ mg m}^{-2} \text{ d}^{-1}$ ) was administered on day 1 through day 4 (96 hour continuous infusion) for each cycle of chemotherapy. Patients in group C who completed six cycles of the combination chemotherapy continued to receive cetuximab monotherapy in the absence of progression of disease, unacceptable toxicity or until another withdrawal criterion.

Patients in group D received one cycle of combination therapy with cycle length defined as 1 week for the purpose of the primary objectives of investigating the pharmacokinetics of cetuximab in combination with cisplatin in patients with advanced solid tumors and to assess the potential for drug-drug interactions between cetuximab and cisplatin. On day 1 of cycle 1, group D patients

received an intravenous infusion of cetuximab (400 mg m<sup>-2</sup> initial dose) followed by cisplatin (100 mg m<sup>-2</sup>) or carboplatin AUC 5 mg × min mL<sup>-2</sup>. The 5-FU (1000 mg m<sup>-2</sup> d<sup>-1</sup>) was an optional treatment administered on day 1 through day 4. Infusion durations for all drugs were the same as noted for Group C above. Patients in group D who completed one cycle of combination chemotherapy were permitted continued access to cetuximab in the absence of progression, unacceptable toxicity or until another withdrawal criterion.

## 2.4 | Bioanalytical methods

Concentrations of cetuximab, cisplatin and carboplatin were determined using validated analytical methods. In both the studies, the serum samples obtained were analyzed for cetuximab using a validated enzyme-linked immunosorbent assay at ICON Laboratory Services, Inc (Whitesboro, NY, USA). The lower limit of quantification was 0.100 µg mL<sup>-1</sup> and the upper limit of quantification was 6.400 µg mL<sup>-1</sup>. Samples above the limit of quantification were diluted to yield results within the calibrated range. Plasma samples obtained during both studies were analyzed for total and free platinum using a validated inductively coupled mass spectrometry method at Maxxam Analytics International Corporation (Burnaby, British Columbia, Canada). Free platinum was determined in protein-precipitated human plasma. The lower limit of quantification for both free and total platinum was 0.050 µg mL<sup>-1</sup> and the upper limit of quantification was 2.000 µg mL<sup>-1</sup>. Samples above the limit of quantification were diluted to yield results within the calibrated range.

## 2.5 | Pharmacokinetic analyses

In both studies, pharmacokinetic analyses were conducted for those patients who received the study drug and had evaluable concentration data suitable for noncompartmental analysis. Blood for the pharmacokinetic analyses was drawn on day 1 of cycle 1 immediately prior to cisplatin/carboplatin infusion and then 1, 1.5, 2, 3, 5, 8, 24, and 72 hours after the start of the cisplatin infusion. Pharmacokinetic parameters estimates were calculated using Phoenix WinNonlin 6.4. The AUC for cetuximab and total cisplatin or carboplatin was calculated by a combination of the linear and logarithmic trapezoidal methods.

## 2.6 | Safety

All patients who received any quantity of study drug were evaluated for safety and toxicity. The safety and tolerability of cetuximab was determined by reported AEs, physical examinations, vital signs and laboratory assessments.

## 3 | RESULTS

### 3.1 | Patient characteristics

Table 1 summarizes patient demographics and baseline characteristics of patients included in both the studies. In the JXBA study,

**TABLE 1** Summary of patient demographics and other baseline disease characteristics

Parameter	JXBA study (N = 44)	JXBB study (N = 34)
Gender, n (%)		
Male	25 (56.8)	26 (76.5)
Female	19 (43.2)	8 (23.5)
Age, mean (SD)	56.6 (11.29)	58.2 (12.88)
Age group, n (%)		
Age < 65	33 (75.0)	19 (55.9)
Age ≥ 65	11 (25.0)	15 (44.1)
ECOG performance status, n (%)		
0	13 (29.5)	6 (17.6)
1	30 (68.2)	23 (67.6)
2	1 (2.3)	5 (14.7)
Pathological diagnosis, n (%)		
Squamous cell carcinoma	26 (59.1)	21 (61.8)
Non-squamous cell carcinoma	18 (40.9)	13 (38.2)
Disease state at diagnosis, n (%)		
Nonmetastatic (M0)	23 (52.3)	20 (58.8)
Metastatic (M1)	10 (22.7)	6 (17.6)
Unknown	11 (25.0)	8 (23.5)
Tumor grade, n (%)		
Grade cannot be assessed (GX)	1 (2.3)	0
Well-differentiated (G1)	1 (2.3)	1 (2.9)
Moderately differentiated (G2)	15 (34.1)	12 (35.3)
Poorly differentiated (G3-4)	19 (43.2)	10 (29.4)
Unknown	8 (18.2)	11 (32.4)
Prior therapy <sup>a</sup> , n (%)		
Surgery	29 (65.9)	17 (50.0)
Radiotherapy	37 (84.1)	21 (61.8)

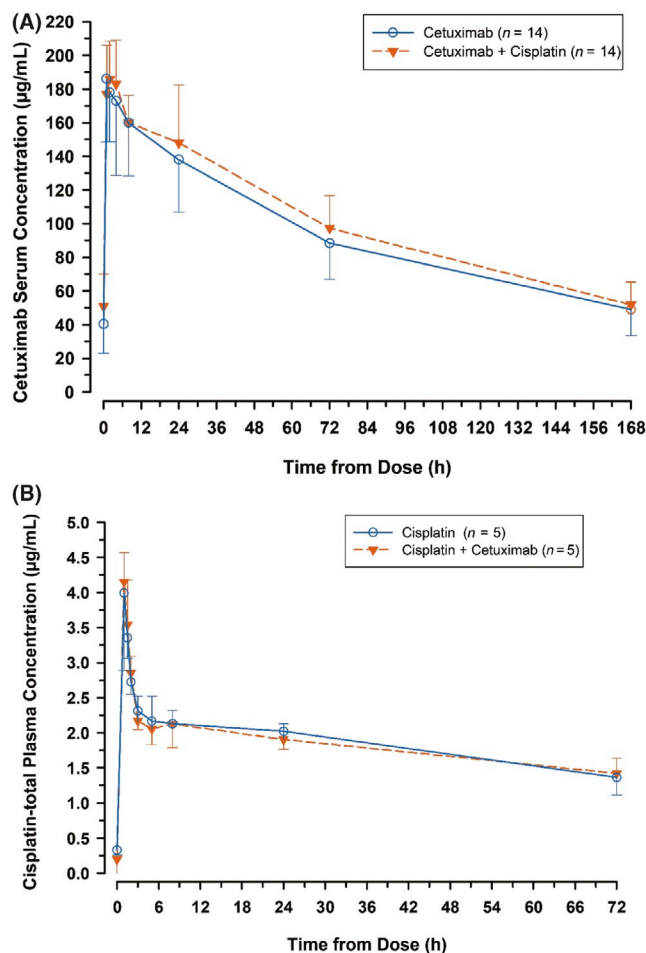
Abbreviations: ECOG, Eastern Cooperative Oncology Group; G, grade; N, all treated population size; n, number of patients in the specified category; SD, standard deviation.

<sup>a</sup>Patients may/may not have received more than one prior therapy.

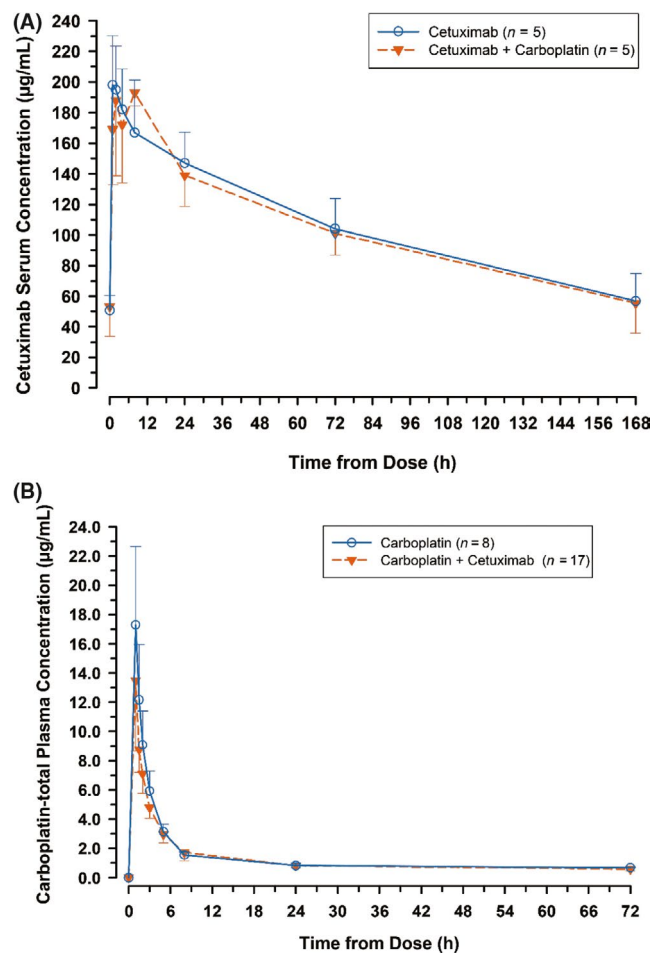
44 patients were treated; of which, 56.8% (n = 25) were men and 43.2% (n = 19) were women. Over half of the patients (68.2%) had a baseline ECOG performance status score of 1. In the JXBB study, 34 patients were treated; of which, 76.5% (n = 26) were men and 23.5% (n = 8) were women; 67.6% of patients had a baseline ECOG performance status score of 1.

### 3.2 | Pharmacokinetic evaluation

In the study JXBA, cetuximab pharmacokinetic parameters were compared when cetuximab was administered alone and in combination with cisplatin. There were 14 patients with cetuximab



**FIGURE 1** (A) Mean cetuximab concentration-time profile after administration of a  $250 \text{ mg m}^{-2}$  cetuximab infusion alone or in combination with a  $100 \text{ mg m}^{-2}$  cisplatin infusion in patients with cancer. (B) Mean cisplatin concentration-time profiles after administration of a  $100 \text{ mg m}^{-2}$  cisplatin infusion alone or in combination with  $250 \text{ mg m}^{-2}$  infusion of cetuximab in patients with cancer



**FIGURE 2** (A) Mean cetuximab concentration-time profile after administration of a  $250 \text{ mg m}^{-2}$  cetuximab infusion alone or in combination with an AUC 5 of carboplatin in patients with cancer. (B) Mean carboplatin concentration-time profile after administration of an AUC 5 carboplatin infusion alone or in combination with  $250 \text{ mg m}^{-2}$  infusion of cetuximab in patients with cancer

**TABLE 2** Geometric means and confidence intervals of total cisplatin pharmacokinetic parameters following  $400 \text{ mg/m}^2$  intravenous infusion of cetuximab in Study JXBA

Parameter	N	Treatment	Geometric mean (90% CI)	Ratio of geometric means (90% CI) (cisplatin + cetuximab) versus cisplatin
$AUC_{(0-t_{\text{last}})}$ ( $\mu\text{g} \times \text{h mL}^{-1}$ )	13	Cisplatin	126.3 (108.2, 147.5)	1.036 (0.893, 1.201)
	22	Cisplatin + cetuximab	130.9 (121.4, 141.1)	
$AUC_{(0-\infty)}$ ( $\mu\text{g} \times \text{h mL}^{-1}$ )	13	Cisplatin	339.5 (306.3, 376.4)	1.030 (0.857, 1.239)
	22	Cisplatin + cetuximab	349.9 (306.9, 398.9)	
$C_{\text{max}}$ ( $\mu\text{g mL}^{-1}$ )	13	Cisplatin	4.00 (3.77, 4.26)	1.054 (0.968, 1.147)
	22	Cisplatin + cetuximab	4.22 (3.99, 4.46)	

$AUC_{(0-\infty)}$ , area under the concentration versus time curve from zero to infinity;  $AUC_{(0-t_{\text{last}})}$ , area under the plasma concentration versus time curve from time zero to time  $t$ ; where  $t$  is the last time point with a measurable concentration;  $C_{\text{max}}$ , maximum observed drug concentration; N, number of patients used in the pharmacokinetic analysis.

concentration-time data representing profiles with a sufficient number of pharmacokinetic samples with a reference (cetuximab) and a test (cetuximab + cisplatin) profile. Cetuximab serum concentrations

were similar when cetuximab was administered alone or in combination with cisplatin (Figure 1A). The  $C_{\text{max}}$ ,  $t_{\text{max}}$  and overall AUC for the cetuximab group ( $194 \mu\text{g mL}^{-1}$ , 2.0 h,  $14\,900 \mu\text{g} \times \text{h mL}^{-1}$ ) and

the cetuximab and cisplatin combination group ( $192 \mu\text{g mL}^{-1}$ , 1.99 h,  $16\,300 \mu\text{g} \times \text{h mL}^{-1}$ ) were similar. The 90% CIs for cetuximab  $C_{\text{max}}$  and AUC were within 0.80-1.25.

The effect of cetuximab on cisplatin pharmacokinetics was evaluated when cisplatin was administered alone or in combination with cetuximab. Cisplatin analysis was based on total cisplatin concentration (both unbound and bound platinum) and data showed that mean total cisplatin concentrations were similar when cisplatin was administered with or without cetuximab (Figure 1B). The  $C_{\text{max}}$ ,  $t_{\text{max}}$  and overall AUC for the cisplatin group ( $4.08 \mu\text{g mL}^{-1}$ , 1.02 h,  $132 \mu\text{g} \times \text{h mL}^{-1}$ ) and the cisplatin and cetuximab combination group ( $4.22 \mu\text{g mL}^{-1}$ , 1.05 h,  $126 \mu\text{g} \times \text{h mL}^{-1}$ ) were similar. Table 2 shows the geometric means, their ratios, and 90% CIs for total cisplatin when cisplatin was administered alone and when cisplatin was administered with cetuximab. The 90% CIs for  $C_{\text{max}}$  and AUC were within the no-effect boundary of 0.80-1.25, thus indicating no clinically relevant change in total cisplatin exposures when cisplatin was administered with  $250 \text{ mg m}^{-2}$  cetuximab.

In the JXBB study, cetuximab pharmacokinetic parameters were compared when cetuximab was administered alone and in combination with carboplatin. Mean cetuximab serum concentrations were similar when cetuximab was administered alone or in combination with carboplatin (Figure 2A). The  $C_{\text{max}}$ ,  $t_{\text{max}}$  and overall AUC for the cetuximab group ( $199 \mu\text{g mL}^{-1}$ , 1.15 h,  $17\,200 \mu\text{g} \times \text{h mL}^{-1}$ ) and the cetuximab and carboplatin combination group ( $199 \mu\text{g mL}^{-1}$ , 3.17 h,  $16\,800 \mu\text{g} \times \text{h mL}^{-1}$ ) were similar.

The effect of cetuximab on carboplatin pharmacokinetics was evaluated when carboplatin was administered with and without co-administration of cetuximab. Carboplatin analysis was based on total

platinum (both the unbound and bound in plasma). Data showed that there was no clinically relevant change in total carboplatin exposures when carboplatin was coadministered with cetuximab (Figure 2B). The  $C_{\text{max}}$  and  $t_{\text{max}}$  for the carboplatin group was  $16.9 \mu\text{g mL}^{-1}$ , 1.04 h, respectively and for the carboplatin and cetuximab combination group was  $11.9 \mu\text{g mL}^{-1}$ , 1.07 h, respectively. The 90% CIs for  $\text{AUC}_{(0-72)}$  and  $\text{AUC}_{(0-\text{tlast})}$  were within the boundary of 0.909-1.21 and the ratios of  $\text{AUC}_{(0-72)}$  and  $\text{AUC}_{(0-\text{tlast})}$  were within the percentage change (range: 50%-125%) in exposures occurring in clinical practice as a result of recommended dose modifications. Due to the limited number of patients ( $n = 5$ ) completing both the cetuximab and cetuximab + carboplatin periods of the study (Groups B and C), a formal statistical comparison of cetuximab data was not performed to determine the effect of carboplatin on cetuximab  $C_{\text{max}}$  and overall exposure (AUCs).

Table 3 shows the cetuximab pharmacokinetic parameters estimates from both JXBA and JXBB studies. These parameters further demonstrate that the  $C_{\text{max}}$ ,  $t_{\text{max}}$  and overall exposure to cetuximab were similar between the two treatments.

## 4 | SAFETY

In the JXBA study, 95.5% ( $n = 42$ ) of patients discontinued the study. The reasons for discontinuation were AEs (43.2%), progressive disease per Response Evaluation Criteria In Solid Tumors (RECIST) 36.4%, withdrawal of consent without further follow-up (4.5%) and other (11.4%); other reasons included doctor's decision, mutual decision between principal investigator and patient due to mildly progressive disease that

**TABLE 3** Pharmacokinetic parameters of cetuximab from JXBA and JXBB studies

Parameter	Geometric mean (CV%)			
	JXBA study		JXBB study	
	Cetuximab	Cetuximab + cisplatin	Cetuximab	Cetuximab + carboplatin
N	14	14	5	5
$C_{\text{max,ss}}$ ( $\mu\text{g mL}^{-1}$ )	194 (20.6)	192 (12.8)	199 (10.3)	199 (13.8)
$t_{\text{max,ss}}$ <sup>a</sup> (h)	2.0 (1.0-4.05)	1.99 (1.0-4.18)	1.15 (1.02-7.83)	3.17 (2.0-4.07)
$\text{AUC}_{(0-\text{tlast})}$ ( $\mu\text{g} \times \text{h mL}^{-1}$ )	14 900 (25.0)	16 300 (25.6)	17 200 (15.7)	16 800 (19.1)
$\text{AUC}_{\tau,\text{ss}}$ ( $\mu\text{g} \times \text{h mL}^{-1}$ )	15 000 (25.7)	16 200 (22.5)	17 200 (15.8)	16 700 (18.5)
$C_{\text{av,ss}}$ ( $\mu\text{g mL}^{-1}$ )	89.1 (25.7)	96.6 (22.5)	102 (15.8)	99.2 (18.5)
CL ( $\text{L h}^{-1}$ )	0.0304 (24.2)	0.0277 (23.2)	0.0253 (26.3)	0.0259 (31.3)
$V_{\text{ss}}$ (L)	4.30 (21.1)	3.81 (25.4)	3.88 (29.5)	3.68 (36.1)
$t_{1/2}$ <sup>b</sup> (h)	99.9 (76.4-137)	96.1 (71.7-155)	108 (87.9-136)	100 (75.0-136)

AUC, area under the concentration versus time curve;  $\text{AUC}_{\tau,\text{ss}}$ , area under the concentration versus time curve during one dosing interval at steady state, where the dosing interval  $\tau = 168$  hours;  $\text{AUC}_{(0-\text{tlast})}$ , area under the plasma concentration versus time curve from time zero to time  $t$ , where  $t$  is the last time point with a measurable concentration;  $C_{\text{av,ss}}$ , average drug concentration under steady state conditions during multiple dosing; CL, total body clearance of drug calculated after intravenous administration;  $C_{\text{max,ss}}$ , maximum observed drug concentration at steady state; CV, coefficient of variation; N, number of patients used in the pharmacokinetic analysis;  $t_{1/2}$ , apparent terminal elimination half-life;  $t_{\text{max,ss}}$ , time of maximum observed drug concentration at steady state;  $V_{\text{ss}}$ , volume of distribution at steady state following intravenous administration.

<sup>a</sup>Median (range).

<sup>b</sup>Geometric mean (range).



**TABLE 4** Adverse events and treatment-emergent adverse events (occurring in  $\geq 5\%$  of patient population) resulting in dose delay or modification during study or within 30 days of last dose in studies JXBA and JXBB

System organ class	JXBA study (N = 44)	JXBB study (N = 34)
	n (%)	n (%)
Patients with $\geq 1$ AE/TEAE	19 (43.2)	18 (52.9)
Blood and lymphatic disorders	7 (15.9)	4 (11.8)
Neutropenia	6 (13.6)	2 (5.9)
Febrile neutropenia	3 (6.8)	–
Thrombocytopenia	–	3 (8.8)
Ear and labyrinth disorders	3 (6.8)	–
Tinnitus	3 (6.8)	–
Gastrointestinal disorders	3 (6.8)	2 (5.9)
Stomatitis	1 (2.3)	2 (5.9)
General disorders and administration site conditions	4 (9.1)	6 (17.6)
Mucosal inflammation	4 (9.1)	4 (11.8)
Infections and infestations	–	2 (5.9)
Upper respiratory tract infections	–	2 (5.9)
Hematological assessment	11 (25.0)	9 (26.5)
Platelet count decreased	–	5 (14.7)
Neutrophil count decreased	7 (15.9)	3 (8.8)
WBC count decreased	2 (4.5)	–
Metabolism and nutrition disorders	5 (11.4)	3 (8.8)
Dehydration	3 (6.8)	3 (8.8)
Skin and subcutaneous tissue disorders	1 (2.3)	3 (8.8)
Palmar-plantar erythrodysesthesia syndrome	–	2 (5.9)

N, all treated population size; n, number of patients with at least one AE/TEAE in that category; WBC, white blood cell.

may not have met RECIST criteria, disease progression per magnetic resonance imaging, progressive disease with rising tumor marker and more pain and patient entered hospice).

In the JXBA study, 52.3% (n = 23) of patients experienced at least one serious adverse event (SAE) of which 11.4% (n = 5) were related to cetuximab. The cetuximab-related SAEs were grade 4 anaphylactic reaction, grade 4 pancytopenia, grade 3 and grade 2 hypomagnesemia (one event each) and grade 3 pneumonia.

All 44 patients experienced at least one AE (or treatment-emergent adverse event [TEAE]) and 40 patients (90.9%) experienced at least one cetuximab-related AE. In total, 43.2% (n = 19) of patients had AEs/TEAEs that resulted in a dose delay/modification (Table 4). There was no death during the study duration but three patients died within 30 days of the last dose of study drug (one patient from group B and two patients from group C).

A total of 34 (100.0%) patients discontinued the JXBB study. The reasons for discontinuation were AE (8.8%), progressive disease per

RECIST (55.9%), progressive disease (symptomatic deterioration; 14.7%), withdrawal of consent with further follow-up (5.9%) and without further follow-up (2.9%) and other (11.8%; other reasons included patient wished to discontinue therapy, patient was non-compliant with study protocol rules, principal investigator chose to stop treatment as he felt there were no further benefits to be had by continuing study treatment and patient completed study therapy).

In the JXBB study, 50.0% (n = 17) of patients experienced at least one SAE and 2.9% (n = 1) patient had an SAE related to cetuximab. The cetuximab-related SAE was grade 3 pneumonia. All patients experienced at least one AE/TEAE; 91.2% (n = 31) of patients experienced at least one cetuximab-related AE. In all, 52.9% (n = 18) of patients had AEs/TEAEs that resulted in a dose delay/modification (Table 4). There was no death during the study duration but three patients (all from group D) died within 30 days of the last dose of study drug.

## 5 | DISCUSSION

These studies (JXBA and JXBB) were conducted to further characterize the pharmacokinetics of cetuximab and cisplatin (JXBA) or carboplatin (JXBB) when the two agents were coadministered and to investigate the potential for drug-drug interactions. In both the studies, two-way drug interaction was investigated.

In the JXBA study, cetuximab pharmacokinetics parameters were compared when cetuximab was administered alone and in combination with cisplatin. The 90% CIs for cetuximab  $C_{\max}$  and AUC were within 0.80-1.25, which is a very conservative no-effect range typically applied to demonstrate bioequivalence of dosage formulations. Thus, no clinically relevant change in cetuximab exposures occurred when cetuximab was administered with 100 mg m<sup>-2</sup> cisplatin. These results are consistent with results reported from a phase I/II study of cetuximab in combination with cisplatin or carboplatin and 5-FU<sup>8</sup> and a randomized phase II study of cetuximab plus cisplatin/vinorelbine compared with cisplatin/vinorelbine alone.<sup>11</sup> The effect of cetuximab on cisplatin pharmacokinetics was also evaluated when cisplatin was administered alone and in combination with cetuximab. The 90% CIs for  $C_{\max}$  and AUC were within the no-effect boundary of 0.80-1.25, thus indicating no clinically relevant change in total cisplatin exposures when cisplatin was administered with 250 mg m<sup>-2</sup> cetuximab.

In the JXBB study, data showed that the mean AUC<sub>(0-72)</sub> and AUC<sub>(0-tlast)</sub> of total carboplatin were approximately 1%-9% greater when carboplatin was administered in combination with cetuximab compared to when administered without cetuximab. The 90% CIs were within the boundary of 0.909-1.21. The ratios of AUC<sub>(0-72)</sub> and AUC<sub>(0-tlast)</sub> were well within the percentage change (range: 50%-125%) in exposures occurring in clinical practice as a result of recommended dose modifications. Thus, no clinically relevant change in total carboplatin exposures occurred when carboplatin was coadministered with cetuximab.

No formal comparison of cisplatin and carboplatin pharmacokinetics was performed. The rationale for this decision was based on

the fact that many such comparisons have been published since carboplatin's introduction into human clinical trials in the 1980's. This study was designed to investigate potential PK interactions between either platinum complex and cetuximab, but was neither designed nor powered for comparison between the two platinum. Although the JXBA and JXBB trials had essentially identical eligibility criteria, several considerations preclude such comparison, including: patients were not randomized between the two trials, both studies were not open in parallel at all sites, and some sites contributed relatively more enrollment to one of the trials. Taken together, these factors weighed against either a prespecified or post hoc comparison of their pharmacokinetics.

Safety was the secondary objective of both studies. The safety profiles observed in the JXBA and JXBB studies were consistent with the known side effects of cetuximab, platinum-based therapies and 5-FU. No new safety signals were observed. In the JXBA study, all patients experienced at least one AE and 23 patients experienced at least one SAE. Of the patients who experienced SAEs, five patients had SAEs related to cetuximab. Similarly, in the JXBB study, all patients experienced at least one AE and 17 patients experienced at least one SAE. Of the patients who experienced SAEs, one patient had SAEs related to cetuximab.

To conclude, in the JXBA and JXBB studies, no evidence of drug-drug interaction between cetuximab and either cisplatin or carboplatin was observed. No new safety signals were observed in either study. These findings provide further evidence that cetuximab can safely be given in combination with cisplatin or carboplatin, allowing clinicians to more confidently administer such regimens to patients who could potentially benefit.

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## CONFLICT OF INTEREST

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## AUTHOR CONTRIBUTIONS

RPP, DNH, KB and SC helped in the study preparation (including study design), conduct of study and interpretation of data. KS, EC, JTB and SH were responsible for interpretation of data. All authors

were involved in the writing and review of the manuscript and approved the final version.

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