

A phase I study of the humanized monoclonal anti-epidermal growth factor receptor (EGFR) antibody EMD 72000 (matuzumab) in combination with paclitaxel in patients with EGFR-positive advanced non-small-cell lung cancer (NSCLC)

C. Kollmannsberger^{1,2}, M. Schittenhelm¹, F. Honecker¹, J. Tillner³, D. Weber³, K. Oechsle¹, L. Kanz¹ & C. Bokemeyer^{1,4*}

¹Department of Hematology/Oncology, University of Tuebingen, 72076 Tuebingen, Germany; ²Division of Medical Oncology, British Columbia Cancer Agency - Vancouver Cancer Center, Vancouver, Canada; ³Merck KGaA, Darmstadt; ⁴Department of Oncology, Hematology, Bone Marrow Transplantation, University Medical Center Hamburg-Eppendorf, Germany

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Background: Epidermal growth factor receptor (EGFR) is overexpressed in 80%–90% of non-small-cell lung cancer (NSCLC). Matuzumab, a humanized immunoglobulin G₁ (IgG₁) anti-EGFR monoclonal antibody, blocks activation of EGFR. Paclitaxel and EGFR inhibitors have additive antitumour effects *in vitro*. This phase I study assessed the tolerability, pharmacokinetics and efficacy of the combination of matuzumab and paclitaxel in patients with advanced NSCLC.

Materials and methods: Eighteen chemotherapy-naïve ($n = 9$) or pretreated ($n = 9$) patients with stage IIIB or IV EGFR-positive NSCLC received weekly doses of matuzumab (100, 200, 400 or 800 mg) followed by paclitaxel 175 mg/m² every 3 weeks. Toxicity was evaluated weekly and pharmacokinetics were measured during cycles 1 and 2.

Results: The maximum planned matuzumab dose of 800 mg was achieved without reaching the maximum tolerated dose. Grade 4 neutropenia occurred in one of three patients at 800 mg but resolved within 1 week; five additional patients treated with 800 mg had no dose-limiting toxicity (DLT). Grade 1/2 acneiform skin rash in 14 patients was the most frequent matuzumab-related side-effect. There were no higher-grade adverse events. Grade 2 toxicities included pruritus ($n = 2$), bronchospasm ($n = 1$), fissures ($n = 1$), abdominal pain ($n = 1$) and hot flushes ($n = 1$). Paclitaxel was discontinued in four patients due to allergic reactions. Coadministration of paclitaxel did not alter matuzumab pharmacokinetics. Responses occurred in four of 18 patients and included one complete response.

Conclusions: Matuzumab doses up to 800 mg weekly with paclitaxel 175 mg/m² every 3 weeks are well tolerated, with no apparent drug interactions and with evidence of antitumor activity.

Key words: EMD 72000, matuzumab, lung cancer, paclitaxel, phase I

introduction

Patients with inoperable advanced or metastatic non-small-cell lung cancer (NSCLC) possess a poor prognosis, with 5-year survival rates being less than 5% following combination chemotherapy [1]. The development of new treatment strategies for these patients remains an important objective of clinical research. The new treatments, which include molecularly targeted therapy directed at the epidermal growth factor receptors (EGFRs), have been tested in several cancer types, including advanced NSCLC. The EGFR pathway appears to

contribute to a number of processes important to cancer development and progression, including cell proliferation, apoptosis, angiogenesis and metastatic spread [2, 3]. The presence of the EGFR is typical for several epithelial malignancies, and in approximately 80%–90% of patients with NSCLC an overexpression of EGFR can be found within the tumors [4]. Receptor tyrosine kinases not only serve as therapeutic targets but may also offer prognostic information for the clinical course of the subject and may be involved in the development of chemotherapy resistance [2, 5]. For example, results of *in vitro* experiments suggest a relationship between the overexpression of EGFR and HER2-*neu* and a resistance to cisplatin and paclitaxel [6, 7]. In addition, amplification and overexpression of either HER2-*neu* or EGFR are correlated with an unfavorable outcome in patients with metastatic breast, ovarian, esophageal and lung cancers [8–10]. Inhibition of the

*Correspondence to: Dr C. Bokemeyer, Department of Oncology/Hematology, Bone Marrow Transplantation, University Medical Center Hamburg Eppendorf, Martinistraße 52, 20246 Hamburg, Germany. Tel: +49-40-42803-2960; Fax: +49-40-42803-8054; E-mail: c.bokemeyer@uke.uni-hamburg.de

EGFR pathway has enhanced the antitumor activity of paclitaxel in EGFR-positive cell lines [11, 12].

Different strategies have been developed to target the EGFR. Receptor activation can be blocked by monoclonal antibodies such as cetuximab, which binds to the extracellular domain of EGFR. In contrast, small-molecule tyrosine kinase inhibitors, such as gefitinib or erlotinib, selectively and competitively inhibit receptor tyrosine kinase activity by blocking the adenosine triphosphate binding site within the tyrosine kinase domain [13–15]. Four studies of small molecule tyrosine kinase inhibitors combined with chemotherapy performed in an unselected NSCLC patient population have been reported negative. No randomized study using monoclonal antibodies has yet been reported. Antibodies appear to differ from small molecules with regards to pharmacokinetic and pharmacodynamic characteristics, but also in their mechanism of action [16, 17]. Whether the now known EGFR mutations, which appear to predict for the majority of responses to small molecule TK inhibitors, play a similar critical role for the efficacy of EGFR monoclonal antibodies is unknown [18, 19]. More research on EGFR monoclonal antibodies in NSCLC is therefore warranted.

Matuzumab is a novel humanized monoclonal antibody of the immunoglobulin G₁ (IgG₁) subclass that binds selectively to the EGFR and inhibits ligand-mediated activation. In contrast to the chimeric antibody cetuximab, the humanized antibody matuzumab has a prolonged half-life of 6–8 days. Matuzumab as a humanized antibody does not induce auto-antibodies, which is a known problem with chimeric or murine antibodies [20]. Substantial antitumor activity of matuzumab has been observed in non-clinical xenograft models [21, 22]. Besides blocking ligand-binding and subsequently inhibiting signal transduction, matuzumab has shown in these models the ability to attract immunocompetent cells by antibody-dependent cellular cytotoxicity (ADCC), which might contribute to its antitumor activity [23]. Paclitaxel, administered as single-agent therapy or in combination regimens, is one of the most active drugs for the treatment of advanced NSCLC [24–26]. In preclinical xenograft and cell line models, the combination of paclitaxel plus EGFR inhibitors has shown enhanced efficacy compared with either drug given as a single agent (data on file) and matuzumab has demonstrated activity in paclitaxel resistant xenograft models [21]. Additive effects have also been demonstrated for the combination of gemcitabine with matuzumab in pancreatic cancer nude mouse models [22].

Therefore, in this phase I study we investigated the maximum tolerated dose (MTD), safety and tolerability, as well as the pharmacokinetic profile of matuzumab plus paclitaxel, in patients with both chemotherapy-naïve and pretreated advanced NSCLC. In addition, preliminary data on antitumor activity were collected.

materials and methods

Inclusion criteria were as follows: age ≥ 18 years, histologically confirmed NSCLC stage IIIB or IV, measurable disease either by computed tomography (CT) or magnetic resonance imaging (MRI), immunohistochemical evidence of EGFR expression in tumor tissue (as defined in the next section),

predicted life expectancy > 3 months, Karnofsky performance status $\geq 60\%$, no chemotherapy or radiotherapy within 4 weeks before the first infusion of matuzumab and paclitaxel, adequate baseline organ functions [creatinine level $< 1.5 \times$ upper limit of normal (ULN); bilirubin level $< 2 \times$ ULN, alanine aminotransferase/aspartate aminotransferase (ALT/AST) $< 5 \times$ ULN], adequate bone marrow function (white blood count $> 3000/\mu\text{l}$; platelet count $> 100\,000/\mu\text{l}$; hemoglobin level > 9 mg/dl), no severe uncontrolled comorbidities, and signed informed consent. The study was approved by the Ethics Committees of the University of Tuebingen and was carried out according to the Declaration of Helsinki and good clinical practice guidelines. The subject's informed consent was obtained prior to any study-related activities.

EGFR expression

For the analysis of EGFR expression, tumor material was obtained from the initial tumor resection or biopsy that had yielded the primary diagnosis. EGFR expression was determined in representative paraffin-embedded tumor blocks using the binding of a specific monoclonal anti-EGFR antibody (Clone E30; Merck KGaA, Darmstadt, Germany). Slides were pretreated using 0.07% Pronase E (Sigma Nr. P5147; Sigma Chemical Co, St Louis, MO) for 13 min. The primary antibody was diluted 1:25 in Tris-buffered saline (pH 7.62) and incubated overnight at 4°C. Visualization was performed using the ChemMateEnVision Detection Kit (AP, Mouse, code No. K5005; DakoCytomation, Hamburg, Germany) and with neufuchsin (Merck KGaA) as the chromogen. Tumors were considered positive if any membrane staining was observed in at least 10% or more of tumor cells. EGFR expression was defined by immunohistochemistry as follows: score 1+, faint or barely perceptible partial staining of the membrane; score 2+, weak to moderate complete membrane staining or strong partial staining of the membrane; and score 3+, strong complete membrane staining in at least 10% of tumor cells. Only patients with EGFR-positive tumors were enrolled in the study. All immunohistochemical investigations were centrally performed and reviewed. Only the reference pathologist (Prof Stoerckel, Wuppertal, Germany) was allowed to determine whether EGFR positivity fulfilled the inclusion criteria for this study.

pretreatment evaluation and follow-up

Pretreatment evaluation consisted of a medical history, physical examination, complete blood count (CBC), serum chemistry, urine analysis, electrocardiogram (ECG), echocardiogram, and chest X-ray study. All sites of measurable disease were documented by CT scans. During study treatment, subject monitoring included the assessment of clinical toxicities, CBC, serum chemistry and physical examination before each weekly matuzumab administration. The target lesion(s) were measured by CT scans every 6 weeks. Responses had to be confirmed at 4-week intervals. A chest X-ray study or CT scan and ECG were repeated at the end of treatment. During the follow-up period, patients were evaluated every 2 months until disease progression was documented.

treatment and dose-escalation plan

The study was subdivided into two parts. The first 6-week period was designated as phase A, to determine the MTD and pharmacokinetic parameters. In phase B, from week 7 onwards, matuzumab plus paclitaxel treatment was continued until disease progression or occurrence of unacceptable toxicity. Paclitaxel was given at a dose of 175 mg/m² over 3 h on day 1 of a 3-week cycle. Premedication for paclitaxel included dexamethason 20 mg i.v., diphenhydramine 50 mg and ranitidine 300 mg i.v. Matuzumab was administered as a 1-h i.v. infusion once weekly without premedication in 250 ml of 0.9% (wt/vol) normal saline solution. On day 1 of the 3-week cycle, matuzumab was given prior to paclitaxel, with a 1-h time interval from the end of infusion to the start of paclitaxel administration. Matuzumab was supplied by Merck KGaA, Germany, as

a lyophilisate of 200 mg/vial. The starting dose was 100 mg (absolute dose) of matuzumab per week (dose level 1) with no loading dose. Doses were escalated to dose levels 2–4 using 200, 400 and 800 mg (absolute doses) per week. No intrasubject dose escalation was allowed. At each dose level, three patients were initially enrolled. If none of the patients experienced a dose-limiting toxicity (DLT) during the first 6 weeks of treatment, the next cohort of three patients was treated at the subsequent dose level. If one of three patients experienced DLT at a given dose level, an additional three patients were enrolled at the same dose level. If two or more patients at one dose level experienced any DLT, three additional patients were enrolled at the next lower dose level. The MTD was defined as the dose level at which no more than one of six patients had experienced a DLT. Treatment was given on an outpatient basis.

evaluation of toxicities and response

Toxicities were evaluated weekly and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Assessment of DLT was limited to the first two treatment cycles (phase A). A DLT was defined as follows: non-hematologic toxicities exceeding grade 2 (with the exception of alopecia, nausea, vomiting and skin reactions); NCI-CTC grade 4 nausea, vomiting, or skin reactions; neutropenia grade 4 or grade 3 associated with complications (e.g. neutropenic fever); thrombocytopenia NCI-CTC grade 4; and toxicity-related discontinuation of treatment for more than 1 week during the first two treatment cycles. Tumor response was assessed by CT or MRI of the target lesion(s) and non-target lesion(s) every 6 weeks and defined according to RECIST [27]. All radiologic assessment was performed by two study-assigned radiologists at the Department of Radiology at Tuebingen University.

pharmacokinetics

For pharmacokinetic analysis of matuzumab, blood samples of 5 ml were drawn before and 1, 2, 5, 48 and 96 h after the start of the first infusion in cycles 1 and 2. Samples were allowed to clot and then centrifuged. Serum was collected and stored at -20°C . Serum concentrations of matuzumab were determined using a validated sandwich enzyme-linked immunosorbent assay with a lower limit of quantification of 0.5 $\mu\text{g/ml}$. The pharmacokinetic parameters of matuzumab in cycles 1 and 2 were calculated independently according to non-compartmental methods using the pharmacokinetic software program Kinetica™, version 4.0 (InnaPhase Corp, Philadelphia, PA). The following parameters were determined: maximum serum concentration (C_{max}), time to reach C_{max} (t_{max}), elimination half-life ($t_{1/2}$), area under the serum concentration-versus-time curve from zero to the last detectable serum concentration (AUC_{0-t}), area under the serum concentration-versus-time curve until infinity ($\text{AUC}_{0-\infty}$), volume of distribution during terminal phase (V_z), total-body clearance of drug from serum (CL) and mean residence time (MRT). C_{max} and t_{max} were taken directly from the plasma concentration curve. λ_z (where λ_z is the elimination rate constant) was determined from the terminal slope of the log-transformed plasma concentration curve using linear regression on terminal data points of the curve; $t_{1/2}$ was calculated by using $0.693/\lambda_z$. AUC_{0-t} was determined using the log linear trapezoidal rule, and $\text{AUC}_{0-\infty}$ was derived from the following formula: $\text{AUC}_{0-t} + Ct/\lambda_z$, where Ct is the last measurable concentration. For calculation of V_z , CL and MRT, the following equations were used: $\text{dose}/(\text{AUC}_{0-\infty} \cdot \lambda_z)$ for V_z ; $\text{dose}/\text{AUC}_{0-\infty}$ for CL and $(\text{AUMC}_{0-\infty}/\text{AUC}_{0-\infty}) - T/2$ for MRT, where AUMC is the area under the moment curve, and $T/2$ is half of the infusion time. Concentrations below the lower limit of quantification (i.e. below the last quantifiable data point) were denoted as zero for the purpose of calculating the AUC. Pharmacokinetic results were presented descriptively only; no statistical tests were performed with pharmacokinetic parameters. Paclitaxel concentrations were not determined.

results

From July 2001 to August 2003, 33 patients were registered for this study at the University of Tuebingen Medical Center, Tuebingen, Germany and tumor tissue was investigated for EGFR expression. Immunohistochemical analysis of EGFR expression on tumor tissue was positive in all patients (100%) with adequate tumor material available for testing. Of these 33 patients, 18 (13 male and five female) received matuzumab plus paclitaxel at four different dose levels (Table 1); 15 patients were not enrolled and did not receive matuzumab. Reasons for not enrolling in the study included the following: eight patients withdrew their informed consent or received another treatment between signing the informed consent and receiving the results of EGFR testing; the histological diagnosis was reassessed in one patient; chemotherapy was administered within 4 weeks prior to the start of the study in one patient; two patients were diagnosed with brain metastases; one patient had an uncontrolled infection with deteriorating performance status; one patient had inadequate liver function; and one patient had an insufficient amount of tumor tissue available for EGFR testing. The demographics of the treated patients are listed in Table 2.

Median age was 63 (29–76) years. Of the 18 patients, 14 had a histological diagnosis of adenocarcinoma and four had a diagnosis of squamous cell carcinoma of the lung. Nine patients (50%) had been pretreated with a median of one chemotherapy regimen (range 0–3 regimens) and six patients (33%) had previously received radiation therapy to either the primary tumor region or sites of symptomatic metastases. Prior single agent chemotherapy included vinorelbine (two patients), gemcitabine (three patients), trofosamide (one patient) and oral etoposide (one patient). Prior combination chemotherapy included carboplatin/paclitaxel (two patients),

Table 1. Dose escalation regimen of matuzumab

	Dose level			
	1	2	3	4
Applied dose, mg (absolute)	100	200	400	800
No. of patients treated ($n = 18$)	3	3	4	8

Table 2. Patient characteristics

Number of patients	18
Median age	63 (29–76) years
Gender (male/female)	13 (72%)/5 (28%)
Smoking history	
Non-smoker	3 (17%)
Smoker	15 (83%)
Tumor stage (IIIB/IV)	1 (6%)/17 (94%)
Histology (adenocarcinoma/ squamous cell carcinoma)	14 (78%)/4 (22%)
Prior treatment	
None	3 (17%)
Chemotherapy	9 (50%)
Radiotherapy	6 (33%)

cisplatin/gemcitabine (one patient), carboplatin/vinorelbine (three patients) and carboplatin/etoposide (one patient). The maximum planned dose of 800 mg given once weekly was achieved without reaching the MTD. At the first three dose levels, 10 patients were treated without a DLT. At the fourth dose level, 800 mg once weekly, a DLT of grade 4 neutropenia occurred in one of the three patients and resolved within 1 week without complication. Five additional patients were enrolled at dose level 4 to assess further the safety of the combination of paclitaxel with matuzumab at a dose of 800 mg once weekly. No further DLTs were observed among these patients.

A total of 103 cycles of matuzumab were administered with a median of three (range 1–23) cycles per patient. Maximum treatment duration was 74+ weeks in one patient and 58+ weeks in a second patient. During the infusions three patients developed grade 3/4 dyspnea, which was considered an allergic reaction to paclitaxel. Paclitaxel was discontinued due to allergic reactions in four patients. These patients continued on matuzumab single-agent therapy. The most frequent matuzumab-related side effect was grade 1/2 acneiform skin rash in 14 patients. One patient developed grade 2 bronchospasm related to matuzumab. This patient continued on study and with glucocorticoid premedication received additional doses of matuzumab without recurrence of the event. Other grade 2 matuzumab-related events (there were no other grade 3/4 adverse events) included pruritus ($n = 2$), fissures ($n = 1$), abdominal pain ($n = 1$), and hot flushes ($n = 1$) (Table 3).

pharmacokinetic analysis

Eighteen patients were assessable for pharmacokinetic analyses, and the results are listed in Table 4. Peak serum concentrations were generally achieved within 1–4 h after the start of the infusion. Mean values for C_{max} for weekly doses between 100 and 800 mg ranged from 33.5 to 248.6 $\mu\text{g/ml}$ and from 35.0 to

422.3 $\mu\text{g/ml}$ in cycles 1 and 2, respectively. The range of mean $AUC_{0-\infty}$ was 2131–32 299 $\mu\text{g/ml} \cdot \text{h}$ and 2974–75 042 $\mu\text{g/ml} \cdot \text{h}$ in cycles 1 and 2, respectively. The increase of C_{max} and $AUC_{0-\infty}$ was dose proportional in week 1 within the tested dose range (Table 4). The terminal elimination $t_{1/2}$ was not constant for the four dose groups in both cycles. Mean $t_{1/2}$ increased from 38.7 h at 100 mg to 137.6 h at 800 mg in cycle 1. Values for $t_{1/2}$ were slightly higher in cycle 2 than in cycle 1 (see Table 4).

The sampling period (168 h) was short in relation to the observed $t_{1/2}$, and accordingly, the extrapolated part of the $AUC_{0-\infty}$ exceeded the 20% margin in all dose groups in cycle 2 and the two highest dose groups in cycle 1. The mean values for V_z were small and dose independent (see Table 4). Drug accumulation was more pronounced at higher doses.

antitumor activity

Although tumor response was not a primary end point of this study, all patients received at least two cycles of the combination of paclitaxel plus weekly matuzumab and were therefore evaluable for antitumor activity. Of 18 patients, three achieved a partial response and one a complete response (overall response rate 22%; 95% CI 2.6% to 41.8%) All but one of these patients were untreated prior to study entry. The patient with the complete response had been diagnosed with a metastatic squamous cell carcinoma of the left upper lobe. After two cycles, his chest CT scan showed no evidence of disease (Figure 1). This patient has had an ongoing complete remission and has received matuzumab as a single agent for 8 months following 7 months of receiving matuzumab together with paclitaxel. One of the patients achieving a partial remission had been pretreated with two different chemotherapy regimens. All responding patients were smokers. An additional six patients (33.3%; 95% CI 11.1% to 55.6%) showed a stabilization of their formerly progressive disease, including one patient with a minor response. Duration of disease stabilization in these patients lasted from 2.5 to

Table 3. Matuzumab-related adverse events per dose level (DL) after multiple administrations, graded according to NCI-CTC version 2.0

	No. of patients												Total adverse events
	DL 1: 100 mg			DL 2: 200 mg			DL 3: 400 mg			DL 4: 800 mg			
	<i>n</i> = 3			<i>n</i> = 3			<i>n</i> = 4			<i>n</i> = 8			
	NCI-CTC grade			NCI-CTC grade			NCI-CTC grade			NCI-CTC grade			
Side-effects	1	2	3	1	2	3	1	2	3	1	2	3	
Acneiform rash	2	1	0	1	0	0	2	0	0	4	4	0	14 (78.0%)
Abdominal pain	0	1	0	0	0	0	0	0	0	0	0	0	1 (5.5%)
Mucositis/oral fissures	1	0	0	0	0	0	0	0	0	1	0	0	2 (11.1%)
Hot flushes	0	1	0	0	0	0	0	0	0	0	0	0	1 (5.5%)
Palpitations	1	0	0	0	0	0	0	0	0	0	0	0	1 (5.5%)
Flushing	1	0	0	2	0	0	1	0	0	1	0	0	5 (27.7%)
Diarrhea	0	0	0	0	0	0	1	0	0	1	0	0	2 (11.1%)
Bronchospasm	0	0	0	0	0	0	0	1	0	0	0	0	1 (5.5%)
Pruritus	0	0	0	0	0	0	0	0	0	1	2	0	3 (16.6%)
Fissures hands + feet	0	0	0	0	0	0	0	0	0	1	1	0	2 (11.1%)
Mouth dryness	0	0	0	0	0	0	0	0	0	1	0	0	1 (5.5%)
Dry skin	0	0	0	0	0	0	0	0	0	1	0	0	1 (5.5%)
Dysesthesia (parasternal)	0	0	0	0	0	0	0	0	0	1	0	0	1 (5.5%)

Only matuzumab-related toxicities, no grade 3 or 4 toxicities. Paclitaxel-related toxicities are not listed in this table.
NCI-CTC, National Cancer Institute Common Toxicity Criteria.

Table 4. Pharmacokinetic Results

	Dose, mg	C _{max} , µg/ml	t _{max} , h	AUC _{0–t} , µg/ml·h	AUC _{extra} , µg/ml·h	AUC _{0–∞} , µg/ml·h	%AUC _{extra} , %	t _{1/2} , h	MRT, h	CL, l/h	V _z , l
Cycle 1 (week 1)											
Mean	100	33.5	3.7	1764	367	2131	17.4	38.7	56.9	0.048	2.7
SD (n = 3)		4.7	2.3	400	95	421	4.3	6.0	7.8	0.010	0.7
Mean	200	71.8	1.3	4355	800	5155	12.6	55.4	82.7	0.049	3.6
SD (n = 3)		25.2	0.6	2484	905	3385	6.8	15.1	19.4	0.024	1.3
Mean	400	109.4	2.3	8497	5477	13 974	39.2	131.1	182.9	0.029	5.5
SD (n = 4)		19.3	1.9	1407	1098	1669	6.5	28.1	35.8	0.004	1.3
Mean	800	248.6	2.8	18 943	13 356	32 299	40.7	137.6	192.3	0.025	5.0
SD (n = 8)		38.1	1.9	2443	3860	5328	7.2	29.8	36.7	0.005	1.0
Cycle 2 (week 4)											
Mean	100	35.0	2.7	2335	640	2974	21.6	60.6	89.4	0.034	3.0
SD (n = 3)		3.4	2.1	626	440	525	16.0	14.3	18.4	0.006	0.6
Mean	200	99.6	2.3	8232	3752	11 983	26.8	89.5	130.4	0.021	2.4
SD (n = 3)		35.1	2.3	3925	3797	7705	10.9	28.0	41.5	0.010	0.7
Mean	400	149.9	1.8	14 369	11 520	23 009	31.9	110.9	137.7	0.035	3.0
SD (n = 4)		40.0	0.5	7952	9853	17 386	24.1	65.0	89.4	0.036	1.3
Mean	800	422.3	2.0	39 371	35 671	75 042	46.0	142.2	207.9	0.012	2.2
SD (n = 8)		79.8	1.3	9380	14 530	23 233	6.5	37.0	54.2	0.005	0.3

AUC_{0–t}, area under the serum concentration-versus-time curve from zero to the last detectable serum level; AUC_{0–∞}, AUC from zero to infinity; AUC_{extra} extrapolated part of AUC; C_{max}, maximum serum concentration; CL, total-body clearance of drug from serum; MRT, mean residence time; SD, standard deviation of the mean; t_{1/2}, half-life; t_{max}, time to reach C_{max}; V_z, volume of distribution during terminal phase.

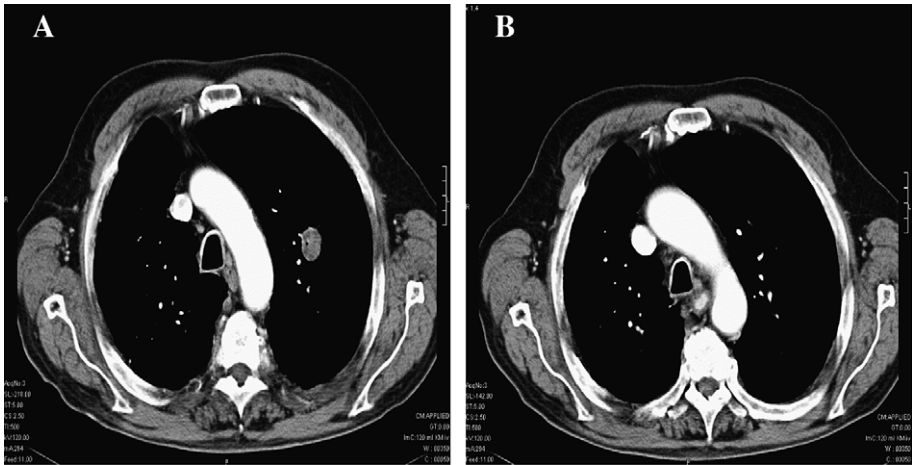


Figure 1. CT scan (A) prior to and (B) after receiving two cycles of paclitaxel and matuzumab.

6 months. Two of the responding patients received matuzumab for more than 12 months.

discussion

This phase I study demonstrated that the humanized monoclonal anti-EGFR antibody matuzumab administered intravenously at doses up to 800 mg weekly is generally well tolerated when combined with paclitaxel given at the standard dose of 175 mg/m² every 3 weeks. The MTD of matuzumab in combination with paclitaxel was not reached in this study, with only one DLT occurring at the 800-mg dose level. Since paclitaxel at 175 mg/m² every 3 weeks is known to be associated with a 25%–30% risk of inducing an NCI-CTC grade 4

neutropenia, it is likely that the observed DLT of grade 4 neutropenia was paclitaxel related. This is supported by the outcome of a study with matuzumab monotherapy in which the MTD was found to be 1600 mg weekly [20]. The same study demonstrated no differences in the pharmacodynamic effects for doses between 800 mg and 1600 mg of matuzumab, indicating that 800 mg, as used as the highest dose level in our study, is a biologically active dose with a significant abrogation of downstream signaling [20].

As in other studies investigating monoclonal anti-EGFR antibodies, the most commonly reported adverse event for the combination tested here was a mild acneiform rash, which occurred in almost all patients. This type of skin toxicity has been described as the most common side-effect of both

monoclonal anti-EGFR antibodies and low molecular-weight tyrosine kinase inhibitors targeting EGFR [28]. Diarrhea was mild and only rarely observed in our study. A higher rate of severe diarrhea has been reported following treatment with low molecular-weight EGFR tyrosine kinase inhibitors, such as gefitinib [29].

The rate of allergic reactions to paclitaxel appeared slightly elevated compared with data in the literature, but it is unclear whether this was related to a drug interaction between paclitaxel and matuzumab or a chance occurrence. Drug interactions involving paclitaxel are common because paclitaxel is metabolized via cytochrome P450 isoenzymes [30]. However, there is no evidence that matuzumab affects cellular cytochromes, and it would therefore not be expected to alter the metabolism of drugs metabolized by cytochrome P450 isoenzymes. If pharmacokinetic data from this study are compared with results of single-agent matuzumab studies, the pharmacokinetic profile of matuzumab does not appear to be altered in the presence of paclitaxel, suggesting that the matuzumab dose does not need to be adjusted when these drugs are coadministered. Similar data were reported for the combination of trastuzumab (a monoclonal HER2-*neu* antibody) and paclitaxel, and no new or unexpected toxicities were observed [31].

The pharmacokinetic analyses showed that the increase of AUC and $C_{\max}$ was dose-proportional for matuzumab over the range of 100–800 mg weekly, indicating linear pharmacokinetics in this dose range. In contrast, the terminal elimination $t_{1/2}$ was not constant and increased with dose, but it seemed to level between 400 and 800 mg. Varying $t_{1/2}$ values at lower dose ranges is a typical characteristic for anti-EGFR monoclonal antibodies. Results of several recently performed studies with matuzumab monotherapy reveal that $t_{1/2}$ increases at lower doses (50–400 mg weekly doses) but finally levels off at doses above 400 mg [20]. So far, there is no explanation for these contradictory results for AUC (indicating linear pharmacokinetics) and $t_{1/2}$ (indicating non-linear pharmacokinetics). The extrapolated part of the total AUC increased with dose, which is evidence of an insufficient sampling interval. Extended sampling may lead to somewhat different AUC values which do not increase in proportion with dose. Results of this trial correlate well with results of previous studies. AUC_{0-t} after the first infusion calculated for doses of 400 and 800-mg matuzumab monotherapy were 10 414 and 21 471 $\mu\text{g}\cdot\text{h}/\text{ml}$ [20]. In addition, $t_{1/2}$ values obtained from this study and matuzumab monotherapy studies do not differ substantially. There is no indication that matuzumab pharmacokinetics were altered by co-administration of paclitaxel, with evidence of accumulation at doses above 400 mg weekly.

Chemotherapy treatment for NSCLC patients provides only a modest survival benefit. The response rate of 22% plus 33% disease stabilization achieved with the combination of matuzumab plus paclitaxel is an encouraging result in this study, particularly since half of the patients had been pretreated with chemotherapy. One of our patients achieved a durable complete remission, which is seen only rarely after cytotoxic chemotherapy. He continued receiving matuzumab therapy for 15 months without any signs of cumulative toxicity. From cycle

7 onwards, he received matuzumab alone to avoid cumulative paclitaxel toxicity and has not yet had disease progression.

Evidence of antitumor activity was also reported in another phase I study using escalating doses of matuzumab as a single agent [20]. In that phase I study, no clear dose–response relationship was observed for antitumor activity (i.e. results similar to those seen in our study). Vanhoefer et al. [20] demonstrated similar pharmacodynamic effects in skin biopsies for matuzumab at doses between 800 and 1600 mg, suggesting that the maximal inhibition of EGFR in skin may be achieved at doses below the level of 2000 mg, which resulted in DLT in two of three patients. In contrast to cytotoxic therapy, in which the MTD is close to the dose of choice, increasing data based on pharmacodynamic, pharmacokinetic and clinical data suggest that for matuzumab, antitumor activity may be seen at doses below the MTD. Preliminary pharmacodynamic and pharmacokinetic data from a phase I study investigating matuzumab as a single agent in advanced cancer with administration of 1200 mg matuzumab weekly, every 2 weeks and every 3 weeks suggest that 1200 mg given every 3 weeks is feasible and a potential target effective dose (TED) [32]. This new dosing schedule for matuzumab is currently being explored in NSCLC patients in combination with paclitaxel.

In conclusion, the combination of matuzumab and paclitaxel is associated with acceptable toxicity and should be explored further in patients with NSCLC.

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