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Clinical Cancer Research

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A Phase I Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG_1 Monoclonal Antibody Directed Against EGFR in Patients with Advanced Solid Malignancies

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Abstract

Purpose: This study aimed to determine a maximum tolerated dose (MTD) and recommended dose for disease-directed studies of necitumumab (IMC-11F8), a fully human IgG_1 monoclonal antibody directed at the epidermal growth factor receptor, and to characterize the safety profile, pharmacokinetics, preliminary antitumor activity, and immunogenicity of necitumumab.

Experimental Design: Patients with advanced solid malignancies were treated with 100 to 1,000 mg (flat dosing) necitumumab followed by a 2-week pharmacokinetics sampling period, before beginning 6-week cycles of therapy.

Results: Sixty patients received necitumumab weekly (29 patients) or every other week (31 patients). Two patients receiving 1,000 mg every 2 weeks experienced dose-limiting toxicities (DLT; grade 3 headache), accompanied by grade 3 nausea and vomiting in one patient. Occurring hours after the initial dose, these DLTs established 800 mg as the MTD. Mild dose-related skin toxicity was the most common drug-related toxicity (80%). One patient in each arm experienced grade 3 acneform rash, which responded to oral antibiotics and topical therapy. Toxicity was similar on both schedules. Necitumumab exhibited saturable elimination and nonlinear pharmacokinetics. At 800 mg (both arms), its half-life was approximately 7 days. All patients treated with ≥600 mg necitumumab achieved target trough concentrations (≥40 μg/mL). Antibodies against necitumumab were not detected. Partial response and stable disease were experienced by 2 and 16 patients, respectively.

Conclusion: Well tolerated, necitumumab is associated with preliminary evidence of antitumor activity, and achieves biologically relevant concentrations throughout the dosing period. The recommended dose of necitumumab for further clinical development is 800 mg (flat dose) weekly or every 2 weeks based on the clinical setting. *Clin Cancer Res; 16(6); 1915–23. ©2010 AACR.*

Activation of the epidermal growth factor receptor (EGFR), a member of the EGFR subfamily of type I receptor tyrosine kinases, has been implicated in the pathogenesis of many human malignancies (1–4). The binding of EGFR ligands to the EGFR, including the epidermal growth factor, transforming growth factor-α, amphiregulin, and betacellulin, influences cellular proliferation, apoptosis, differentiation, and metastasis via a number of critical signaling cascades such as the reticular activating system/mitogen activated protein kinase, phospholipase C-γ, phosphatidylinositol 3-kinase/protein kinase B, and the signal transducer and activator of transcription 3 pathways (1–3).

Both EGFR expression and EGFR-mediated activation of downstream signaling pathways are related to poor outcome in many types of cancer (5–10). Furthermore, several tumor types, particularly colorectal, head and neck, and lung cancers, coexpress the EGFR and its ligands, indicating a potential for autocrine activation of the receptor; coexpression of EGFR and its ligands has also been identified as a poor prognostic indicator (11–15). Both monoclonal antibody (mAb) and small molecule therapeutics targeting the EGFR have shown to be efficacious as monotherapy and in combination regimens.

Necitumumab (IMC-11F8; ImClone Systems) is a fully human immunoglobulin G, subclass 1 (IgG_1) mAb targeting the EGFR, designed with specific characteristics in an effort to maximize its therapeutic index in the clinic. Following the identification of a fully human fragment

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Findings from this study were previously presented at the 2006 Annual Meeting of the American Society of Clinical Oncology (Abstract #3024), and at the 2007 AACR-NCI-EORTC Annual Meeting (Abstract B52).

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Translational Relevance

In this first-in-man study, necitumumab is a fully human IgG_1 monoclonal antibody to the epidermal growth factor receptor (EGFR) that was designed to integrate structural and clinical features so that its therapeutic index would be more favorable than other EGFR-targeting monoclonal antibodies. Necitumumab was shown to be well tolerated, with evidence of antitumor activity at doses capable of producing therapeutically relevant trough concentrations throughout the dosing period. On the basis of the preclinical attributes of necitumumab, as well as the favorable safety and pharmacokinetic profiles shown in this phase I pharmacologic study, necitumumab is undergoing phase II and III clinical evaluations in multiple oncologic indications worldwide.

antigen binding targeting the EGFR from a phage display library, necitumumab was engineered to bind to the EGFR with high affinity (Kd = 0.32 nmol/L) and block the binding of relevant EGFR ligands (IC_{50} = 1-2 nmol/L; ref. 16). Necitumumab neutralizes ligand-induced EGFR phosphorylation (IC_{50} = 1.5-3 nmol/L; ref. 16) and downstream signaling in multiple tumor cell lines, and inhibits proliferation of EGFR-dependent DiFi tumor cells (IC_{50} = 0.8-1.0 nmol/L; ref. 16). In addition, as a fully human IgG_1 construct, treatment with necitumumab would be expected to result in a decreased potential for hypersensitivity and increased potential to mediate efficient antibody-dependent cellular cytotoxicity by human peripheral blood mononuclear cells to EGFR-expressing cancer cells. Necitumumab has shown significant antitumor activity in multiple established human xenograft tumor models, and augments the antitumor effects of irinotecan and oxaliplatin in a panel of colorectal cancer models (16). The antitumor effects of necitumumab in preclinical studies were either comparable with or superior to those observed with cetuximab (16).

The primary objective of this first-in-man trial was to determine a maximum tolerated dose (MTD) and a dose to recommend for subsequent disease-directed studies. Secondary objectives included characterization of the safety profile, pharmacokinetics, and immunogenicity of necitumumab, and a preliminary assessment of its antitumor activity in patients with advanced solid malignancies.

Patients and Methods

Study design. Patients were randomized into one of two arms. Following randomization, patients in both arms received one necitumumab infusion at their assigned cohort dose level (see Table 1), followed by a 2-wk treatment-free "rest" period to enable pharmacokinetic sampling before beginning repetitive 6-week cycles of therapy. In arm A, patients received necitumumab once a week, whereas necitumumab was administered once every 2 wk to patients in arm B. The starting dose in cohort 1 of each arm was 100 mg; the dose escalation schemes along with actual enrollment into each cohort are summarized in Table 1. Necitumumab was administered as a flat (unit) dose based on a population pharmacokinetic analysis of the anti-EGFR antibody cetuximab, which indicated that body weight and height (determinants of body surface area) were not significant covariates of clearance (17).

A treatment cohort was considered complete when three patients completed the initial pharmacokinetic sampling period and the first 6-wk treatment cycle without experiencing a dose-limiting toxicity (DLT), which was defined as any grade 3 or 4 major organ toxicity that was at least possibly related to necitumumab. Once a given cohort was completed, dose escalation to the next cohort was to occur. However, if one patient in a cohort experienced a DLT during the first cycle, three additional patients were to be enrolled in that cohort; if no additional patient in the same cohort experienced a DLT, dose escalation was to proceed. If a second patient in the same cohort experienced a DLT, dose escalation was not to occur, and the preceding dose level was to be considered the MTD for that arm. Therefore, the MTD was defined as the dose preceding the dose level at which at least two patients experienced a DLT. Once the MTD was identified, additional patients were to be enrolled at the MTD. If no DLTs were observed during the first cycle in any cohort, then three additional patients each (to a total of six patients per cohort) were to be enrolled in cohorts 5 (800 mg) and 6 (1,000 mg), which were projected *a priori* to be relevant human doses of necitumumab.

All patients were evaluated for tumor response according to Response Evaluation Criteria in Solid Tumors guidelines (18). Following the initial 6-wk treatment cycle, patients continued to receive additional cycles of therapy at the same dose and schedule as long as there was no disease progression or intolerable toxicity.

Patients. Eligible patients were ≥18 y old, with solid malignancies that were refractory to standard treatment or for which standard treatment was not available. Participants were required to have measurable or nonmeasurable, evaluable disease, Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2, a life expectancy of ≥3 mo, and adequate hematopoietic (absolute neutrophil count ≥1,500/μL; hemoglobin >9 g/L; platelet count ≥100,000/μL), hepatic [alkaline phosphatase ≤5.0 × the upper limit of normal (ULN), bilirubin ≤1.5 × the ULN, and aspartate aminotransferase /alanine aminotransferase ≤2.5 × the ULN or ≤5 × the ULN in the presence of liver metastases), and renal functions (serum creatinine within normal limits). Key exclusion criteria included concurrent uncontrolled disease or additional malignancy (other than basal cell carcinoma or cervical carcinoma *in situ*), newly diagnosed or symptomatic brain metastases, prior EGFR-targeted therapy, or pregnancy. All patients were

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required to provide written informed consent consistent with applicable local and institutional guidelines.

Evaluation procedures. Pretreatment evaluations were done within 14 d prior to treatment. Evaluation procedures done pretreatment and every 2 wk during treatment included a medical history with an assessment of adverse events, physical examination, laboratory testing (chemistry, coagulation, and hematology studies and urinalysis), and determination of ECOG PS. Pregnancy testing was done on women of childbearing potential pretreatment and every 6 wk thereafter.

To assess tumor status, computed tomography or magnetic resonance imaging was done within 2 wk prior to necitumumab treatment in the first cycle (unless previous imaging had been done during or within 2 wk prior to the beginning of the 2-wk pharmacokinetic sampling period), after the first two treatment cycles (6 and 12 wk after the first dose of necitumumab in the first cycle), and at least every 12 wk thereafter.

Pharmacokinetic and immunogenicity analyses. For all patients enrolled in the study, extensive pharmacokinetic sampling was done following necitumumab administration during the first and final infusion of the initial 6-wk treatment cycle. Thereafter, 5- to 10-mL pharmacokinetic samples were obtained prior to and 1 h after the completion of the final necitumumab infusion of each cycle, as well as 45 d after the last dose was administered. For each necitumumab sampling time point, a 5- to 10-mL blood sample was collected and allowed to coagulate at room temperature for 30 to 60 min. After centrifugation, the serum supernatant was collected and stored at -20°C to -80°C until analysis. A validated Biacore 3000-based instrument method was used to determine serum concentrations of necitumumab. Briefly, soluble EGFR was covalently coupled to certified CM5 sensor chips (GE Healthcare Life Sciences). Prior to analysis, serum necitumumab samples were diluted 100-fold with Hepes Buffered Saline (HBS-EP) Biacore running buffer. Necitumumab samples were injected at 20 μL/min in HBS-EP and quantitated by comparing the resulting Biacore plasmon resonance signal with that obtained from a standard necitumumab preparation. Necitumumab calibration curves were linear in the undiluted concentration range of 11.72 to 1,500 ng/mL. The lower limit of quantification for the undiluted necitumumab sample was 11.72 ng/mL. A necitumumab concentration of 40 μg/mL at steady state was selected *a priori* as biologically relevant and represents the lowest concentration that exhibited antitumor activity in preclinical xenograft models. Serum trough concentrations of necitumumab achieved at the MTD and recommended phase II dose are expected to result in levels that meet or exceed this target with an acceptable safety profile.

Serum blood samples used to evaluate formation of antibodies against necitumumab were obtained prior to the initial infusion of the pharmacokinetic sampling period and prior to the final dose in each treatment cycle. Antibodies against necitumumab were determined using a double antigen radiometric assay. Briefly, necitumumab was immobilized onto polystyrene beads, which were then incubated with serum samples. Any anti-necitumumab (drug) antibodies (ADA) present in the sample bound to the beads to form an ADA:necitumumab complex. ^{125}I-labeled necitumumab was used as a tracer to identify bound ADA, which was reported in ng/mL of bound ^{125}I-labeled necitumumab. The cut point for a positive sample was 6 ng/mL of bound ^{125}I-labeled necitumumab. A patient was considered to have a positive response if the patient's postbaseline anti-necitumumab level was more than twice the baseline value for at least two consecutive determinations, or if the positive determination was for the final time point sampled. Patients with a baseline anti-necitumumab level >6 μg/mL were considered nonevaluable for an anti-necitumumab response.

Noncompartmental pharmacokinetic analysis and mathematical modeling were done using WinNonlin 5.1 (Pharsight). An ANOVA of necitumumab clearance as a function of dose and weight was done using the "Fit Model" platform of JMP 6.0.

Results

Patient disposition and maximum tolerated dose. Sixty enrolled patients, whose relevant demographic and disease characteristics are shown in Table 2, received at least one dose of necitumumab, including 29 patients in arm A

Table 1. Necitumumab dose escalation scheme

Cohort	Necitumumab dose	Arm A (weekly)		Arm B (every 2 wk)	
		Number of patients	Median number of infusions (range)	Number of patients	Median number of infusions (range)
1	100 mg	4	7 (2-7)	3	4 (4-4)
2	200 mg	3	18 (7-74)	4	4 (3-21)
3	400 mg	3	13 (7-36)	3	4 (4-18)
4	600 mg	3	7 (7-19)	5	5 (1-14)
5	800 mg	7	7 (1-48)	7	4 (2-7)
6	1000 mg	9	6 (1-37)	9	3 (1-7)

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(weekly schedule) and 31 patients in arm B (every-2-weeks schedule).

Fifty-five (91.7%) patients discontinued treatment due to disease progression. Two patients withdrew consent, and three patients (two in arm A, one in arm B) discontinued treatment due to an adverse event, including one DLT. Two patients (one in each arm) discontinued treatment due to an adverse event, one due to a grade 4 cerebrovascular accident and one due to a grade 2 left pneumothorax; neither event was related to necitumumab.

No DLTs were observed in cohorts 1 to 5 (100 to 800 mg) of either arm, or in cohort 6 (1,000-mg dose level) of arm A. However, two patients in cohort 6 of arm B (necitumumab at 1,000 mg every 2 weeks) experienced necitumumab-related adverse events that were considered DLTs. The first, a 70-year-old man with prostate cancer, experienced grade 3 headache, nausea, and vomiting, as well as grade 1 fever, immediately after his first treatment. All toxicities resolved completely within 6 days of onset. However, the patient was discontinued from the study as a result of these events. The second patient also developed a grade 3 headache associated with a grade 1 fever 6 hours after completing his first necitumumab infusion, with grade 1 nausea and vomiting developing over the next 5 hours. Because the constellation of these grade 3 adverse events, consisting of headache, nausea, and vomiting, was considered to be at least possibly related to necitumumab, these events were classified as dose limiting. Therefore, necitumumab was reintroduced with a dose reduction from 1,000 to 800 mg, with no recurrence of these events. Because both DLTs occurred in the immediate posttreatment period after a first dose of necitumumab, they were felt to be related to dose and not schedule; therefore, the previous dose level, 800 mg, was defined as the MTD for both schedules.

Table 2. Relevant patient characteristics

	Arm A (*n* = 29)	Arm B (*n* = 31)
Age (y)		
Mean	59.3	58.6
Median	60.0	59.0
Range	39-76	37-71
Gender		
Female	11 (37.9%)	14 (45.2%)
Male	18 (62.1%)	17 (54.8%)
ECOG PS		
0	9 (31.0%)	8 (25.8%)
1	19 (65.5%)	19 (61.3%)
2	1 (3.4%)	4 (12.9%)
Prior disease-related therapy		
Chemotherapy	25 (86.2%)	29 (93.5%)
Hormonal therapy	3 (10.3%)	2 (6.5%)
Immunotherapy	5 (17.2%)	2 (6.5%)
Radiotherapy	11 (37.9%)	13 (41.9%)
Investigational agent	5 (17.2%)	12 (38.7%)
Surgery	28 (96.6%)	28 (90.3%)
Cancer type		
Colorectal	8 (27.6%)	14 (45.2%)
Esophageal	1 (3.4%)	2 (6.5%)
Ovarian	1 (3.4%)	1 (3.2%)
Lung (non–small cell)	1 (3.4%)	3 (9.7%)
Pancreatic	3 (10.3%)	1 (3.2%)
Prostate	3 (10.3%)	2 (6.5%)
Renal	5 (17.2%)	3 (9.7%)
Stomach/Esophageal	1 (3.4%)	2 (6.5%)
Other	6 (20.7%)	3 (9.7%)

Adverse events. Patients in arm A received a median of 7 infusions (range, 1 to 74) of necitumumab, spanning a median of 8 weeks (range, 2 to 83), whereas patients in arm B received a median of 4 infusions (range, 1 to 21), spanning a median of 8 weeks (range, 2 to 40). The median relative dose intensity, measured over the entire dosing period for all patients, was 100% for both arms (means, 98.1% and 97.3% for arms A and B, respectively). A single patient in arm B (every-2-weeks dosing) received a dose reduction from 1,000 to 800 mg.

Overall, necitumumab treatment was well tolerated for both weekly and every-2-weeks schedules. The most common drug-related adverse event was skin toxicity, which was experienced by 80% of patients in both arms combined (79.3% in arm A; 80.6% in arm B). Specifically, the most common dermatologic toxicities included acneform rashes (65.5%), dry skin (41.4%), and skin fissures (34.5%) in arm A, and acneform rashes (64.5%), pruritus (22.6%), and dry skin (19.4%) in arm B. Necitumumab-related skin toxicity was cumulative and generally mild (grade 1) in severity.

Two patients experienced grade 3 acneform rashes. The first was documented on study day 152 in a patient receiving necitumumab at the 400-mg once-per-week dose level. The severity of the rash decreased to grade 1 concurrent with treatment with oral antibiotics and topical therapy, without either treatment delay or omission. The second experienced a grade 3 acneform rash on study day 26 following treatment with necitumumab 600 mg every 2 weeks. The severity of the rash decreased to grade 2 concurrent with treatment with oral antibiotics and topical therapy. Despite a brief necitumumab treatment delay of 7 days, treatment ensued in the patient who had a chronic grade 2 rash during treatment, which eventually resolved after discontinuation of necitumumab.

Table 3 summarizes adverse events related to necitumumab, affecting >20% of patients in either arm or of worst grade ≥3. The most common adverse events related to necitumumab, which were predominately grade 1 or 2 in severity, included headache (42% of patients), nausea (33% of patients), and vomiting (20% of patients). Only 10 (16.7%) patients experienced adverse events of at least grade 3 severity.

Except for headache (previously discussed), neither the severity nor frequency of adverse events related to

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Table 3. Adverse events related to necitumumab

Adverse event*	All grades	Arm A (n = 29)		Arm B (n = 31)		
		Study day	Grade ≥3†	All grades	Study day	Grade ≥3†
Acne	16 (55.2%)	152	1 (3.4%)	10 (32.3%)	26	1 (3.2%)
Acneform dermatitis	3 (10.3%)		0	11 (35.5%)		0
Anemia	1 (3.4%)		0	3 (9.7%)	50	1 (3.2%)
Blood magnesium decreased	1 (3.4%)		0	1 (3.2%)	101	1 (3.2%)
	1 (3.4%)		0	1 (3.2%)	11	1 (3.2%)
Diarrhea	12 (41.4%)		0	6 (19.4%)		0
Dry skin	7 (24.1%)	36, 43	2 (6.9%)	9 (29.0%)	23, 70	2 (6.5%)
Fatigue	10 (34.5%)		0	15 (48.4%)	1, 1	2 (6.5%)
Headache	0		0	1 (3.2%)	56	1 (3.2%)
Hypokalemia	9 (31.0%)		0	11 (35.5%)	2	1 (3.2%)
Nausea	3 (10.3%)		0	7 (22.6%)		0
Pruritus	6 (20.7%)		0	13 (41.9%)		0
Pyrexia	10 (34.5%)		0	3 (9.7%)		0
Skin fissures	6 (20.7%)		0	6 (19.4%)	2	1 (3.2%)
Vomiting						

*Most common and most severe adverse events (all events of worst grade ≥ 3 or affecting at least 20% of patients in either arm).
†Worst grade per patient.

necitumumab seemed to be clearly dose dependent. Similarly, skin toxicity related to necitumumab occurred with approximately similar frequencies across all dose groups. The incidences of dry skin, acneform dermatitis, and skin fissures seemed to increase slightly at dose levels >600 mg; however, the differences were modest, and the small number of patients involved precludes meaningful interpretation.

No hypersensitivity or infusion reactions were observed.

Table 4. Summary of necitumumab pharmacokinetic parameters following weekly dosing (arm A)

	Necitumumab pharmacokinetic parameter values following the first dose of cycle 1 (mean ± SD)					
Dose (/wk)	100 mg	200 mg	400 mg	600 mg	800 mg	1,000 mg
No of patients	4	3	3	3	7	8
Half-life (h)	67.7 ± 9.58	63.1 ± 21.9	99.1 ± 28.3	131 ± 94.1	125 ± 43.4	175 ± 99.0
Clearance (mL/h)	53.2 ± 9.67	45.8 ± 10.9	29.4 ± 13.2	20.3 ± 10.4	12.9 ± 4.15	13.9 ± 7.72
C_{max} (μg/mL)	32.3 ± 10.3	72.7 ± 8.02	222 ± 99.6	293 ± 64.9	509 ± 100	637.0 ± 215
C_{min} (μg/mL) [#]	2.50 ± 0.717 [2]	6.67 ± 4.73	29.7 ± 14.6	56.7 ± 25.0	163 ± 90.1	202.6 ± 197.7
$AUC_{0\text{-inf}}$ (h × μg/mL)	1,932 ± 379.4	4,559 ± 1,196	15,967 ± 8,055	38,151 ± 25,673	67,821 ± 21,322	104,932 ± 78,301
	Necitumumab pharmacokinetic parameter values following the last dose of cycle 1 (mean ± SD)					
Dose (/wk)	**100 mg**	**200 mg**	**400 mg**	**600 mg**	**800 mg**	**1,000 mg**
No of patients	3	3	3	3	3	5
Half-life (h)	70.8 ± 30.4	154 ± 74.0	132 ± 82.5	142 ± 95.8	149 ± 57.60	1,710 ± 1,754
Clearance (mL/h)	40.2 ± 20.8	14.2 ± 7.83	8.18 ± 1.74	10.8 ± 8.36	5.88 ± 3.64	1.45 ± 1.14
C_{max} (μg/mL)	40.0 ± 13.9	120.0 ± 21.0	307 ± 159	687 ± 272	955 ± 126	962 ± 266
C_{min} (μg/mL) [#]	4.00 ± NA [1]	40.0 ± 11.3 [2]	112 ± 51.6 [2]	255 ± 188 [2]	397 ± 135 [3]	836 ± 281 [5]
$AUC_{0\text{-inf}}$ (h × μg/mL)	3,081 ± 1,799	16,927 ± 7,890	50,286 ± 9,764	100,537 ± 97,024	170,699 ± 86,604	2,020,514 ± 2,646,845

Abbreviations: NA, not applicable; [#], number of patients, if different from above.

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Pharmacokinetics. In preclinical xenograft studies, concentrations of ≥40 μg/mL were achieved at the lower doses associated with antitumor activity as previously described; therefore, pharmacokinetic analyses were directed toward identifying doses capable of achieving these trough concentrations ≥40 μg/mL for subsequent disease-directed studies.

Tables 4 and 5 present pharmacokinetic parameters from a noncompartmental analysis of the necitumumab concentration versus time data. In both arms A and B, the mean necitumumab clearance decreased in a less-than-dose-proportional manner with dose escalation from 100 to 1,000 mg. Mean clearance for 600/800 mg of necitumumab (cycle 1) was 20/13 mL/h and 11/6 mL/h (arm A), and 19/15 mL/h and 7/10 mL/h (arm B) after the first and last infusion, respectively. In addition, maximum serum concentration (C_{max}) and area under the concentration versus time curve extrapolated from time 0 to infinity ($AUC_{0\text{-}inf}$) values increased disproportionately to necitumumab. This nonlinear pharmacokinetic behavior suggests a saturable clearance mechanism (s) in the dose range studied (100-1,000 mg). Necitumumab mean clearance was independent of patient body weight. This suggests that administration of a nonweight normalized flat dose of necitumumab is appropriate (data not shown).

Target trough concentrations (≥40 μg/mL) were achieved in all patients treated with necitumumab doses of 600 mg on both once weekly and every-2-weeks schedules. Necitumumab concentration-versus-time profiles are presented in Fig. 1. Following necitumumab weekly dosing at 600/800 mg, the mean trough concentrations at 168 hours after the first and final infusions of cycle 1 were 57/163 μg/mL and 255/397 μg/mL, respectively. Because the last pharmacokinetic sampling time point following the final infusion of arm B was 168 hours, the minimum serum concentration (C_{min}) at 336 hours for each subject was predicted by mathematical modeling. Following necitumumab every-2-weeks dosing at the 600- and 800-mg dose levels, the mean predicted trough concentrations at 336 hours after the first and final infusion of cycle 1 were 10/49 μg/mL and 78/83 μg/mL, respectively.

For cycle 2 onward, the mean serum trough concentrations of necitumumab at 600/800 mg were 105 μg/mL (n = 1)/514 μg/mL (n = 2), respectively in arm A, and 107 μg/mL (n = 2)/76 μg/mL (n = 2), respectively in arm B. This suggests that maintenance of trough concentrations above target concentrations (≥40 μg/mL) was achieved throughout the treatment period.

No anti-necitumumab antibodies were identified in any patient.

Antitumor activity. A total of 23 of 29 patients in arm A and 24 of 31 patients in arm B were considered evaluable for response. Two patients experienced confirmed partial responses. The first was observed in a 53-year-old woman with metastatic melanoma who experienced disease progression while receiving dacarbazine chemotherapy prior to enrollment, initially documented after 3.3 months of necitumumab treatment at the 200-mg dose level (arm

Table 5. Summary of necitumumab pharmacokinetic parameters following every-2-weeks dosing (arm B)

	Necitumumab pharmacokinetic parameter values following the first dose of cycle 1 (mean ± SD)					
Dose (every 2 wks)	**100 mg**	**200 mg**	**400 mg**	**600 mg***	**800 mg**	**1,000 mg**
No of patients	3	4	3	4	7	9
Half-life (h)	60.2 ± 22.4	59.7 ± 5.70	83.9 ± 35.6	102 ± 54.0	121 ± 20.6	137 ± 48.5
Clearance (mL/h)	58.9 ± 9.67	46.8 ± 10.9	24.7 ± 13.2	19.1 ± 4.85	14.5 ± 4.17	11.8 ± 4.56
C_{max} (μg/mL)	38.3 ± 14.1	75.8 ± 18.3	179 ± 6.03	479 ± 179	506 ± 168	724 ± 128
C_{min} (μg/mL) [#]	2.00 ± NA [1]	BLQ ± NA	10.0 ± 7.90	10.0 ± 2.82 [2]	49.0 ± 24.2	75.1 ± 37.5
$AUC_{0\text{-}inf}$ (h × μg/mL)	1,707 ± 156.8	5,077 ± 2,314	16,972 ± 4,724	29,468 ± 5,571	59,071 ± 16,571	95,434 ± 32,451
	Necitumumab pharmacokinetic parameter values following the last dose of cycle 1 (mean ± SD)					
Dose (every 2 wks)	**100 mg**	**200 mg**	**400 mg**	**600 mg**	**800 mg**	**1,000 mg**
No of patients	3	3	3	3	6	4
Half-life (h)	30.6 ± 12.9	60.8 ± 34.1	122 ± 58.6	283 ± 179	131 ± 42.0	149 ± 69.4
Clearance (mL/h)	89.8 ± 31.8	47.8 ± 21.2	22.6 ± 18.2	6.99 ± 4.71	10.4 ± 3.43	6.90 ± 1.81
C_{max} (μg/mL)	33.0 ± 7.00	88.7 ± 23.2	173 ± 72.5	382 ± 205	669 ± 234	885 ± 78.5
Predicted† C_{min} (μg/mL) [#]	BLQ ± NA	1.2 ± NA [1]	16.9 ± 15.2	78.0 ± 56.5 [2]	83.0 ± 85.5	203 ± 141
$AUC_{0\text{-}inf}$ (h × μg/mL)	1,245 ± 553.7	4,723 ± 1,854	25,112 ± 13,978	110,653 ± 56,065	87,329 ± 38,572	153,136 ± 41,405

*One subject excluded from the analysis due to extremely high concentrations post 48 h (reasons unknown).
†Data predicted for each subject by mathematical modeling.

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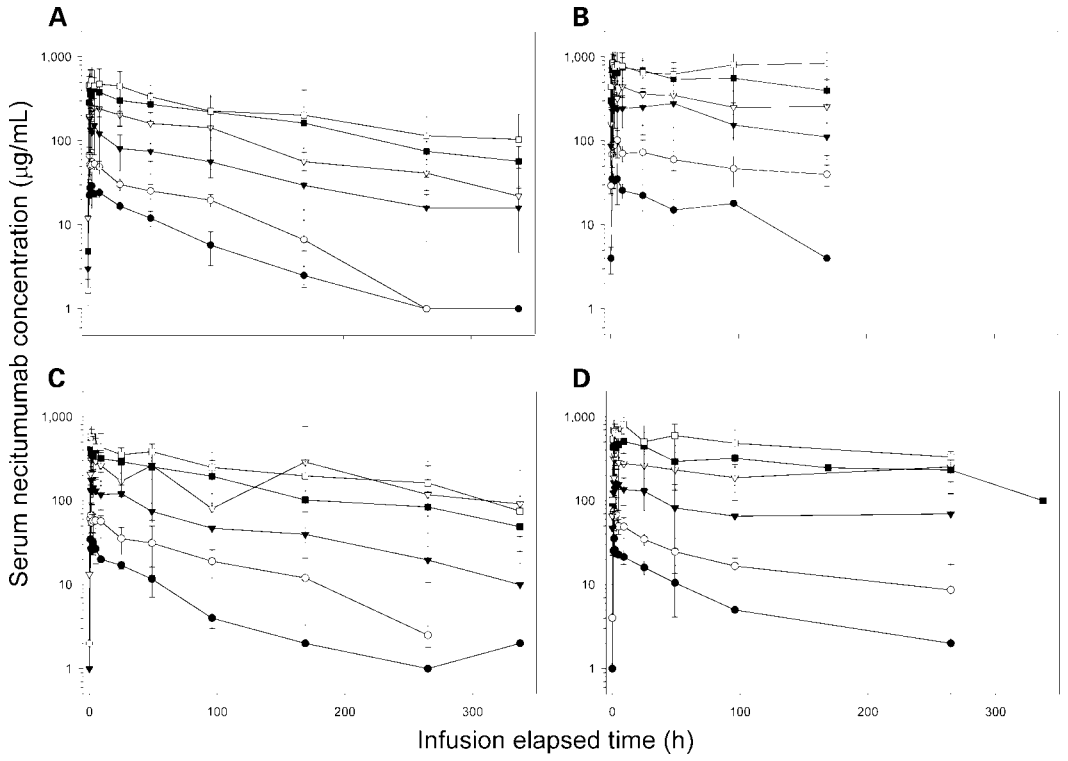

Fig. 1. Necitumumab concentration versus time profiles. The concentration versus time profiles for the first (A) and final (B) infusions of cycle 1, arm A, and for the first (C) and final (D) infusions of cycle 1, arm B, for the 100-mg (●), 200-mg (○), 400-mg (▼), 600-mg (▽), 800-mg (■), and 1,000-mg (□) necitumumab dose groups. Each symbol, mean ± SD of the patients assayed in each dose group.

A), and lasted 15.6 months. The patient received a total of 13 cycles of therapy (75 doses), with progression-free survival and overall survival times of 19 and 23 months, respectively. The second partial response was experienced by a 65-year-old male with metastatic colorectal cancer and documented following 2.8 months of treatment with necitumumab at the 400-mg dose level (arm B). The patient had received multiple prior chemotherapy regimens consisting of 5-fluorouracil, leucovorin, and oxaliplatin, as well as pemetrexed, with a best previous response of stable disease. The duration of response with necitumumab was 5.6 months. The patient received approximately six cycles of therapy (17 doses) before developing progressive disease; progression-free survival and overall survival times were 8.4 and 14.9 months, respectively.

A best overall response of stable disease was observed in 16 patients (8 in each arm). Stable disease was most commonly observed in patients with colorectal cancer, with a best overall response of stable disease in 8 (36.4%) of 22 patients, including 3 of 5 patients treated in the 800-mg cohort of arm B. Seventeen (28%) patients remained alive and progression free for ≥3 months (9 in arm A and 8 in arm B) and 9 (15%) for ≥6 months. Four patients experienced progression-free survival for ≥9 months.

Discussion

Necitumumab has been designed to integrate its features so the therapeutic index is more favorable than other EGFR-targeting mAbs. To accomplish this, necitumumab was designed to bind to a specific epitope on the EGFR to maximize blockade of all relevant stimulatory ligands (1–3). In a wide variety of well-established human tumor xenografts, necitumumab, both as monotherapy and combination therapy, has produced anticancer activity that is at least comparable with cetuximab, and is superior in several models (16). Additionally, as a fully human IgG_1 construct, necitumumab would not be expected to produce major hypersensitivity reactions (in contrast to mAb constructs that comprise immunogenic murine protein constituents). However, necitumumab would be expected to confer incremental antitumor activity via antibody-dependent cellular cytotoxicity, as shown in an *ex vivo* assay (16). Based on a retrospective analysis of the pharmacokinetic behavior of the chimeric EGFR-targeting mAb cetuximab, and especially because necitumumab is a fully human IgG_1 construct, it was also projected that the pharmacokinetic behavior of necitumumab would support its administration as a flat (unit) dose on an every-2-weeks schedule.

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In this first-in-man phase I study, treatment with necitumumab at 1,000 mg resulted in two nearly identical DLTs, consisting of grade 3 headache associated with nausea, vomiting, and fever. Both the qualitative aspects and temporal onset of these toxicities (i.e., immediately following the administration of necitumumab) suggest that they were not related to the principal EGFR-targeting mechanism of necitumumab, but were more likely nonspecific manifestations of the administration of relatively high doses of biological proteins. Although both events occurred in patients receiving necitumumab on the weekly schedule, the fact that they occurred immediately posttreatment indicated that the toxicities were dose related. Thus, the dose of necitumumab was not escalated above 1,000 mg on either administration schedule. Additionally, although there were some differences in the number of toxicities between the two schedules, there were no qualitative or significant quantitative differences in adverse events associated with weekly and every-2-weeks dosing schedules.

In contrast to the apparently nonspecific nature of the dose-limiting events in the present study, the most common adverse effect felt to be related to necitumumab, dermatologic toxicity, was indeed mechanism related. Dermatologic manifestations, which were similar to those noted with most small-molecule tyrosine kinase inhibitors and other mAbs targeting the EGFR, included acneform rashes, pruritus, skin fissures, and dry skin. Although skin toxicity related to necitumumab seemed to be dose related and cumulative, it was generally mild in severity and rarely resulted in treatment delay exceeding seven days – only two patients experienced skin toxicity of grade 3 severity. The cumulative nature of EGFR-related skin toxicity renders it difficult to fully characterize its overall frequency, severity, and tolerance in the phase I setting, because toxicity is not often evaluated in a sufficient number of patients treated over a protracted period in any specific disease setting. Nonetheless, preliminary data from a phase II study of necitumumab combined with mFOLFOX6 chemotherapy in patients with colorectal cancer in the first-line metastatic setting further support this preliminary evidence that skin toxicity related to necitumumab is not preclusive, even when administered with mFOLFOX6 (19, 20). Other toxicities related to necitumumab, including nausea, vomiting, and headache, were manageable and generally of modest frequency and mild to modest severity. Of further note, hypersensitivity was not observed and anti-necitumumab antibodies were not detected.

In addition to the toxicity data, various aspects of the pharmacokinetic behavior of necitumumab support the selection of its MTD, 800 mg, on an every-2-weeks schedule for subsequent disease-directed evaluations. First, the minimal target necitumumab trough concentration level (≥40 μg/mL) was achieved in all patients treated with necitumumab doses of ≥600 mg on both once-weekly and every-2-weeks schedules. For example, in patients treated with necitumumab 800 mg every 2 weeks, concentrations at trough (14 days posttreatment and immediately prior to the next treatment) averaged 78 and 83 μg/mL, respectively, after the first and final dose of cycle 1. In essence, mean serum necitumumab concentrations exceeded biologically relevant target concentrations by ≥2-fold throughout the entire treatment period. Furthermore, the pharmacokinetic behavior within the dosing range studied was nonlinear and saturable. This behavior suggests a situation of "limiting returns" with increasing dose because binding sites are saturated. Finally, a necitumumab flat (unit) dose of 800 mg (every 2 weeks) represents 1.4 and 3.9 times the recommended initial (400 mg/m^2) and maintenance dose (250 mg/m^2) of cetuximab on a weekly schedule for 2 weeks, respectively, for a patient with a body surface area of 1.7 m^2. Because cetuximab and necitumumab have similar molecular weights and EGFR binding affinities, these relative values suggest that the 800-mg dose of necitumumab provides sufficient "breathing room" over that achieved with cetuximab at an efficacious dose.

Dosing anticancer agents based on body surface area or body weight has become almost reflexive: it is often universally adopted from the very outset of a drug's development, despite a lack of evidence in many circumstances that drug clearance is dependent on these parameters (21–24). Necitumumab clearance, albeit dose dependent, behaved independently of body weight, indicating that administration of a flat (unit) dose is appropriate for administering necitumumab.

Based on the toxicologic and pharmacologic results of the present study, a necitumumab dose of 800 mg on either a weekly or an every-2-weeks schedule is recommended for disease-directed evaluations, with the selection of schedule dependent on the clinical situation and scheduling of the concomitant chemotherapy regimen. Preliminary evidence of objective antitumor activity further supports the biological relevance of necitumumab in the dosing range evaluated in the present study. Nevertheless, although necitumumab possesses many structural, functional, and pharmacologic characteristics that might be considered more advantageous relative to currently available EGFR-targeting mAbs, its incremental advantage in the clinic can only be elucidated by carrying out disease-directed clinical evaluations in appropriate patient populations, perhaps guided by the results of molecular correlates of response, as shown in recent clinical trials of other EGFR-targeted therapeutics.

Disclosure of Potential Conflicts of Interest

Youssoufian, Rowinsky, Fox, Dontabhaktuni, Katz, and Zhu: employees of ImClone Systems; E. Voest, consultant, ImClone Systems Corp.

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Clinical Cancer Research

Correction

Correction: A Phase I Pharmacologic Study of Necitumumab (IMC-11F8), a Fully Human IgG_1 Monoclonal Antibody Directed against EGFR in Patients with Advanced Solid Malignancies

In this article (Clin Cancer Res 2010;16;1915–27), which was published in the March 15, 2010 issue of *Clinical Cancer Research* (1), Table 3 was incorrectly formatted. The correct table appears below:

Table 3. Adverse events related to necitumumab

Adverse event*	Arm A (*n* = 29)			Arm B (*n* = 31)		
	All grades	Study day	Grade ≥3†	All grades	Study day	Grade ≥3†
Acne	16 (55.2%)	152	1 (3.4%)	10 (32.3%)	26	1 (3.2%)
Acneform dermatitis	3 (10.3%)		0	11 (35.5%)		0
Anemia	1 (3.4%)		0	3 (9.7%)	50	1 (3.2%)
Blood magnesium decreased	1 (3.4%)		0	1 (3.2%)	101	1 (3.2%)
Diarrhea	1 (3.4%)		0	1 (3.2%)	11	1 (3.2%)
Dry skin	12 (41.4%)		0	6 (19.4%)		0
Fatigue	7 (24.1%)	36, 43	2 (6.9%)	9 (29.0%)	23, 70	2 (6.5%)
Headache	10 (34.5%)		0	15 (48.4%)	1, 1	2 (6.5%)
Hypokalemia	0		0	1 (3.2%)	56	1 (3.2%)
Nausea	9 (31.0%)		0	11 (35.5%)	2	1 (3.2%)
Pruritus	3 (10.3%)		0	7 (22.6%)		0
Pyrexia	6 (20.7%)		0	13 (41.9%)		0
Skin fissures	10 (34.5%)		0	3 (9.7%)		0
Vomiting	6 (20.7%)		0	6 (19.4%)	2	1 (3.2%)

*Most common and most severe adverse events (all events of worst grade ≥3 or affecting at least 20% of patients in either arm).
†Worst grade per patient.

Also, on page 1,922, the last sentence should read, "For example, in patients treated with necitumumab 800 mg every 2 weeks, trough concentrations (14 days posttreatment and immediately prior to the next treatment) averaged 83 μg/mL after the final dose of cycle 1," not "between 78 and 83 μg/mL, respectively, after the first and final dose of cycle 1."

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