Cancer Therapy: Clinical

Mapatumumab, a Fully Human Agonistic Monoclonal Antibody That Targets TRAIL-R1, in Combination with Gemcitabine and Cisplatin: a Phase I Study

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Abstract

Purpose: To evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of mapatumumab, a fully human monoclonal antibody targeting tumor necrosis factor–related apoptosis–inducing ligand receptor 1 (TRAIL-R1), in combination with gemcitabine and cisplatin.

Experimental Design: Patients with advanced solid tumors received gemcitabine 1,250 mg/m^2 i.v. on days 1 and 8 and cisplatin 80 mg/m^2 i.v. on day 1 of each 21-day cycle. Escalating mapatumumab doses were administered i.v. every 21 days. Toxicity was evaluated and pharmacokinetic analysis of plasma mapatumumab, gemcitabine, 2-difluoro-2-deoxyuridine, and unbound and total platinum was done. TRAIL-R1 tumor expression was determined immunohistochemically.

Results: Forty-nine patients received mapatumumab (1 mg/kg, $n = 4$; 3 mg/kg, $n = 7$; 10 mg/kg, $n = 12$; 20 mg/kg, $n = 13$; or 30 mg/kg, $n = 13$). A median of six cycles (range, 1-48) was administered. The adverse events most commonly observed reflect the toxicity profile of gemcitabine and cisplatin. Dose-limiting toxicities were seen in 3 of 12 patients at 10 mg/kg, consisting of grade 3 transaminitis, neutropenic fever, and grade 4 thrombocytopenia. At 20 mg/kg, 2 of 12 patients had dose-limiting toxicities, including grade 4 thrombocytopenia and grade 4 fatigue. The maximum tolerated dose was not reached. Pharmacokinetic interactions have not been observed. Twelve patients had a partial response, and 25 patients showed stable disease with a median duration of 6 months.

Conclusions: Mapatumumab in combination with gemcitabine and cisplatin is safe and well tolerated at doses up to 30 mg/kg. Further studies on this combination are warranted. (Clin Cancer Res 2009;15(17):5584–90)

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The tumor necrosis factor–related apoptosis–inducing ligand (TRAIL) pathway is an attractive target for antitumor therapy because the activation of death receptors (DR) on the cell surface results in stimulation of the intracellular signaling routes leading to apoptosis. The naturally occurring ligand TRAIL is a member of the tumor necrosis factor superfamily that can bind to five different receptors, including TRAIL receptors 1 (TRAIL-R1; DR4) and 2 (TRAIL-R2; DR5), through which TRAIL transmits its apoptotic signal (1, 2). For yet unknown reasons, TRAIL, in preclinical models, selectively induces apoptosis in tumor cells without toxic effects on normal cells.

Mapatumumab (TRM-1, ETR1) is a fully human immunoglobulin G1 λ agonistic monoclonal antibody to TRAIL-R1 competing with TRAIL for binding to TRAIL-R1. Single agent mapatumumab induces apoptosis in a range of cancer cell lines and inhibits tumor growth in various human tumor mouse xenograft models (3). Expression of TRAIL-R1 is frequently observed in human tumors, including pancreatic, ovarian, colorectal, gastric, uterine, lung, and breast carcinomas (4).

In two phase I studies in patients with solid tumors, single-agent mapatumumab was well tolerated, and adverse events were generally mild to moderate in severity (5, 6). The maximum tolerated dose in these studies was not reached with 10 mg/kg every 14 days (6) and 20 mg/kg every 28 days (5). Pharmacokinetic results showed a mean terminal elimination half-life of 18 to 21 days. In addition, in phase II studies with mapatumumab in patients with non–small cell lung carcinoma, colorectal cancer, and non-Hodgkin's lymphoma, a similar toxicity profile was observed (7–9). In the non–small cell lung carcinoma and colorectal cancer studies, stable disease was the best observed response in 30% of the patients. Three patients with follicular lymphoma experienced a tumor response.

Combination therapy may synergistically enhance antitumor activity because mapatumumab induces apoptosis through the extrinsic pathway, whereas chemotherapy results in cell death by activating the intrinsic pathway. Accordingly, the addition of mapatumumab to gemcitabine or cisplatin resulted in increased cytotoxicity in various human tumor cell lines. Furthermore, in a human non–small cell lung carcinoma (H460) xenograft model, combining cisplatin and mapatumumab showed increased tumor growth inhibition compared with either agent alone (10). We therefore did a phase I study to evaluate the safety and tolerability of escalating doses of mapatumumab in combination with gemcitabine and cisplatin in patients with solid tumors. Secondary objectives were to determine plasma mapatumumab concentrations, to assess the influence of mapatumumab on plasma gemcitabine and cisplatin pharmacokinetics, to evaluate disease response, and to assess TRAIL-R1 expression in tumors of participating patients.

Patients and Methods

Eligibility criteria. Eligible for the study were patients with a histologically or cytologically confirmed advanced solid malignancy for whom no standard therapy options were available or for whom the combination of gemcitabine and cisplatin was considered an appropriate treatment. Additional eligibility criteria included age ≥18 y; Eastern Cooperative Oncology Group performance status 0 or 1; estimated life expectancy ≥3 mo; adequate bone marrow and renal function; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 fold upper limit of normal; no previous chemotherapy, immunotherapy, radiotherapy, or hormonal therapy within 3 wk; no treatment with monoclonal antibodies within previous 3 wk (murine or chimeric) or 8 wk (human or humanized); and no investigational agents within 4 wk. Specific exclusion criteria included known positive HIV status; known chronic or acute viral hepatitis; clinical signs of brain metastases; hearing loss requiring the use of a hearing aid; neuropathy grade ≥ 2; and myocardial infarction, cerebrovascular accident, or ≥ New York Heart Association class III congestive heart failure within 6 mo before study entry.

The study was approved by the local ethics committees and the competent regulatory authorities. All patients provided written informed consent.

Study design. A cycle was defined as 21 d. Mapatumumab was administered at escalating dose levels (1, 3, 10, 20, and 30 mg/kg). At each dose level, three to four patients were enrolled initially. Patients were considered to be evaluable for toxicity if they had completed one full cycle. Dose escalation decisions were made based on the safety assessments of all patients in the dose cohort using the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0. Dose escalation was considered if <33% of the patients experienced dose-limiting toxicity (DLT). If one of three to four patients experienced a DLT, the dose level was expanded to a total of six evaluable patients. If a DLT was observed in two or more of six patients in a cohort, the maximum tolerated dose was exceeded. To further characterize safety at a certain dose level, up to 12 additional patients could be included.

By the initial DLT criteria, electrolyte disturbances secondary to inadequate antiemetic therapy and chemotherapy-induced transient liver enzyme elevations were considered dose limiting. The protocol was amended after inclusion of the fifth patient in the 10-mg/kg cohort to consider only those events as DLTs that were at least possibly related to mapatumumab or to its interaction with gemcitabine and/or cisplatin. DLTs were thereafter defined as grade 4 neutropenia lasting >7 d, febrile neutropenia, grade 4 thrombocytopenia; and grade 3 or 4 non-hematologic adverse events, with the following qualifications: grade ≥3 transaminase elevations that did not resolve to grade ≤1 before cycle 2, grade ≥3 nausea and vomiting despite optimal antiemetic treatment, persistent grade ≥2 neuropathy, serum creatinine twice or more than the upper limit of normal, and grade 4 fatigue. Electrolyte disturbances due to inadequately treated vomiting were not considered dose-limiting if this had resolved before cycle 2. All DLTs described in this article are DLTs according to the amended protocol.

Patients could receive a maximum of six chemotherapy cycles. Thereafter, in the absence of disease progression, mapatumumab monotherapy could be continued. Patients were withdrawn from the study in case of disease progression, unacceptable toxicity, or refusal of treatment.

Drug administration. Mapatumumab (Human Genome Sciences, Inc.) was administered i.v. in 250 mL 0.9% saline over 2 h on day 2 of cycle 1 and on day 1 of cycles 2 to 6 after gemcitabine and cisplatin administration.

Gemcitabine (Eli Lilly) 1,250 mg/m^2 was administered i.v. over 30 min on days 1 and 8 of each cycle. Cisplatin (Pharmachemie) 80 mg/m^2 in 1,000 mL of 0.9% saline was infused i.v. over 3 h following gemcitabine on day 1 of each cycle.

No dose modifications were allowed for mapatumumab. Chemotherapy doses were reduced for severe side effects considered to be at least possibly related to chemotherapy or for the patient's safety in the opinion of the investigator. At the beginning of each cycle, the absolute neutrophil count had to be ≥1,500/μL and platelets ≥ 100,000/μL. Treatment could be delayed up to 2 wk for hematologic recovery. Chemotherapy doses were reduced when treatment was delayed for >1 wk. The day 8 gemcitabine was omitted in case of absolute neutrophil count < 1,000/μL and platelets < 75,000/μL.

Pretreatment and follow-up studies. Before therapy, a complete medical history, physical examination, electrocardiography, chest X-ray, laboratory evaluations (including blood chemistry, hematology, and urinalysis), and CT scan or MRI for disease assessment were done. Vital

Table 1. Patient characteristics

Characteristic	No. of patients (n = 49)
Age	
Median	53
Range	34-72
Sex	
Male	32
Female	17
ECOG performance status	
0	18
1	31
Previous treatment	
Systemic*	14
Surgery	29
Radiotherapy	8
Tumor types	
Pancreatic cancer	19
(A)CUP	9
Esophageal cancer	4
NSCLC	3
Cholangiocarcinoma	3
Melanoma	2
SCLC	2
Bladder cancer	1
Carcinoid	1
Gallbladder	1
Gastric	1
Head-neck	1
Renal	1
Thymus	1

Abbreviations: (A)CUP, (adeno)carcinoma of unknown primary; NSCLC, non–small cell lung carcinoma; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.
*Includes chemotherapy, immunotherapy, and hormonal therapy.

signs were taken before administration of the study agents, every 30 min during mapatumumab administration, and 1, 2, 3, and 4 h following completion of mapatumumab. Patients were evaluated for toxicity and laboratory values before the start of every cycle; on days 5 ± 1, 8, 11 ± 1, and 15 of each cycle; and on days 2 and 3 of cycle 1. Response was assessed after every two cycles by Response Evaluation Criteria in Solid Tumors (11). If patients continued on mapatumumab monotherapy, tumor evaluations were done every three cycles.

Pharmacokinetics and immunogenicity. Serial blood samples for plasma gemcitabine, cisplatin, and mapatumumab concentration measurements were collected before dosing and over a 26-h period following the start of the infusion of the respective agents in cycles 1 and 2. In addition, mapatumumab samples were collected on day 15 of cycle 2, days 1 and 15 of cycle 4 and 6, days 15 and 29 of the final cycle, and during mapatumumab monotherapy before dosing every third cycle. Serum samples for immunogenicity were also collected before each cycle to determine plasma mapatumumab concentrations and antimapatumumab antibodies (6).

Plasma concentrations of gemcitabine and its inactive metabolite 2-difluoro-2-deoxyuridine were measured using a validated high performance liquid chromatography with diode array detection, and analysis of unbound platinum and total platinum were done using an atomic absorption spectrophotometer (12). To determine pharmacokinetic parameters, plasma concentrations of gemcitabine, 2-difluoro-2-deoxyuridine, and cisplatin-derived unbound and total platinum were subjected to noncompartmental analysis with WinNonlin Enterprise, version 5.0.1 (Pharsight Corporation) using nominal dose and actual times postdose according to standard methods (13). Differences in pharmacokinetic parameters between cycle 1 (before mapatumumab treatment) and cycle 2 (with mapatumumab treatment) were assessed

by a 95% confidence interval for each cohort. Plasma mapatumumab concentration results were compared with a predicted range of concentrations based on phase 1 study results in subjects with solid tumors who received mapatumumab as a monotherapy (5, 6).

Immunohistochemical staining of tumor tissue. Three-micrometer thick archival tumor tissue sections from patients were cut from paraffin blocks and deparaffinized in xylene. Slides were immunohistochemically stained for TRAIL-R1 (14). Thereafter, slides were reviewed by light microscopy and scored by two investigators (C.N.A.M. Oldenhuis, not blinded for clinical outcome; J. Bart, blinded for clinical outcome). Intensity of TRAIL-R1 staining was scored in four categories (no, low, moderate, and strong).

Results

General. Patient characteristics are shown in Table 1. From November 2004 to January 31, 2009, 49 patients received a total of 209 cycles of combination treatment (median, 5; range, 1-6). In addition, 15 patients received 124 cycles of mapatumumab monotherapy (median, 6; range, 2-4 d). The number of patients treated at each dose level is shown in Table 2. At 20 mg/kg, one patient experienced a cerebrovascular accident on day 5 of cycle 1, most likely related to cisplatin. In the 30 mg/kg cohort, one patient experienced an epileptic seizure due to previous unknown brain metastases and went off study on day 8 of the first cycle. Both patients were replaced because the toxicity data for cycle 1 were incomplete.

Toxicity. The most frequent chemotherapy-related and/or mapatumumab-related adverse events are listed in Table 3. Nausea and vomiting were frequently observed. These are well-known side effects of cisplatin and gemcitabine and were therefore considered most likely caused by the chemotherapy. Hematologic toxicity, including thrombocytopenia, neutropenia, and anemia, were considered to be most likely related to cisplatin and gemcitabine, although anemia may also have been cancer related. Hematologic toxicity caused treatment delays, dose reductions, and/or omissions of day 8 gemcitabine at all mapatumumab dose levels. The dose intensity of cisplatin and gemcitabine was maintained at the highest dose level of mapatumumab (Supplementary Table S1).

Grade 3 or 4 elevations of transaminases was observed in eight patients (16%). Three of these were reported as adverse events at least probably related to gemcitabine; one of the three was also considered possibly related to cisplatin and mapatumumab.

Table 2. Mapatumumab dose levels and DLTs as a function of dose

Dose level (mg/kg)	No. of patients	Median no. of cycles (range)	No. of patients with DLT
1	4	6 (3-12)	0
3	7	6 (3-18)	0
10	12	6 (1-21)	3
20	13	4 (1-48)*	2
30	13	5 (1-15)	0

*One patient is ongoing and received 48 cycles as of January 31, 2009.

Table 3. Number of patients with study drug–related adverse events by the Medical Dictionary for Regulatory Activities preferred term and maximum toxicity grade occurring in ≥10% of all patients (*n* = 49)

Adverse event	Mild		Moderate		Severe		Life threatening		All active	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Nausea	20	40.8	22	44.9	4	8.2	0		46	93.9
Vomiting	18	36.7	18	36.7	3	6.1	0		39	79.6
Fatigue	10	20.4	22	44.9	4	8.2	1	2.0	37	75.5
Thrombocytopenia	2	4.1	5	10.2	12	24.5	7	14.3	26	53.1
Neutropenia	0		4	8.2	12	24.5	9	18.4	25	51.0
Tinnitus	10	20.4	12	24.5	1	2.0	0		23	46.9
Anemia	0		17	34.7	4	8.2	0		21	42.9
Leukopenia	0		6	12.2	11	22.4	3	6.1	20	40.8
Alopecia	10	20.4	8	16.3	0		0		18	36.7
Peripheral sensory neuropathy	12	24.5	3	6.1	0		0		15	30.6
Diarrhea	7	14.3	4	8.2	1	2.0	0		12	24.5
Dysgeusia	8	16.3	2	4.1	0		0		10	20.4
Anorexia	9	18.4	0		0		0		9	18.4
Stomatitis	9	18.4	0		0		0		9	18.4
Hypomagnesemia	4	8.2	3	6.1	1	2.0	0		8	16.3
Hypokalemia	3	6.1	0		2	4.1	0		5	10.2
Paresthesia	4	8.2	1	2.0	0		0		5	10.2

NOTE: Possibly, probably, or definitely related to gemcitabine, cisplatin, and/or mapatumumab.

DLT. In the 1- and 3-mg/kg cohort, no DLTs occurred. At 10 mg/kg, one patient experienced a grade 3 ALT elevation. However, this patient had an elevated ALT > 2.5 times upper limit of normal at baseline (88 U/L; upper limit of normal, 30 U/L) and therefore did not meet the inclusion criteria. The grade 3 ALT elevation was regarded as probably related to gemcitabine and possibly related to mapatumumab. The 10-mg/kg cohort after expansion to six patients showed no additional DLTs. During expansion of the 10-mg/kg cohort, two additional patients experienced a DLT. One patient developed neutropenic fever; the other had grade 3 ALT and AST elevations and grade 4 thrombocytopenia. Thus, 3 of 12 patients experienced a DLT at 10 mg/kg (Table 2).

In the 20-mg/kg cohort, DLTs were observed in 2 of 12 evaluable patients. One patient had a grade 4 fatigue, and one patient had grade 4 thrombocytopenia.

No DLTs occurred in the 30-mg/kg cohort.

Pharmacokinetics. Individual subject's plasma mapatumumab concentrations for each cohort of this study, along with predicted concentrations based on phase I pharmacokinetic study results, are illustrated in Fig. 1. There was substantial overlap between the observed concentrations and the predicted concentration ranges at all dose levels.

The mean (±SD) plasma gemcitabine, 2-difluoro-2-deoxyuridine, and unbound platinum and total platinum concentration-time profiles pooled from all cohorts are shown in Fig. 2. For each compound, concentrations for the first treatment cycle are virtually superimposable or within 1 SD of the respective mean for the second treatment cycle.

Mean (with 95% confidence interval) exposure in cycles 1 and 2, as measured by Area Under the Curve C_0, $AUC_{0-6\ h}$, or AUC_{last} for gemcitabine, 2-difluoro-2-deoxyuridine, and cisplatin-derived unbound platinum are summarized by cohort in Supplementary Table S2. The 95% confidence interval for each compound in cycle 2 overlapped the 95% confidence interval in cycle 1 within and across each cohort. Exposure for each agent was fairly constant within a cohort and maintained its consistency across cohorts.

Antimapatumumab antibodies. One previously untreated patient in the 10-mg/kg cohort tested positive for antimapatumumab antibodies at day 29 of cycle 2. All mapatumumab plasma values observed for this subject were within the predicted concentration range.

Tumor response. Figure 3 shows reduction of target lesions in 26 of the 37 patients in whom target lesions were present. Confirmed partial responses were observed in 12 of the 49 patients. Stable disease after two cycles was seen in 25 patients. Median duration of stable diseases and of partial responses was 6 months (range, 1-33).

TRAIL-R1 expression. Tumor tissue was available in 35 patients. All tumors showed at least low cytoplasmic TRAIL-R1 expression in most tumor cells. Staining intensity seemed not to be associated with tumor response (Supplementary Table S3).

Discussion

This paper is the first full report on combining chemotherapy with a TRAIL-receptor targeting agent. In this study, mapatumumab was combined with gemcitabine and cisplatin. This combination is safe and well tolerated. The side effects observed reflects the toxicity profile of the chemotherapeutic agents. There were no pharmacokinetic interactions observed between the study drugs. Partial responses as well as prolonged stable diseases were seen.

TRAIL-R1 is known to be expressed by human hepatocytes, and therefore, liver functions were closely monitored in this study (15). We observed transient and reversible grade 3 ALT and/or AST elevations in eight patients. Single-agent gemcitabine

is known to induce transient grade 3 to 4 transaminase elevations in up to 25% of the patients (16–18). Nevertheless, a relation with mapatumumab cannot be completely ruled out. In a phase I study with single-agent mapatumumab, two patients at the highest dose level of 10 mg/kg every 14 days experienced DLTs consisting of grade 3 bilirubin and transaminase elevations that were considered to be probably related to mapatumumab (6). Other patients treated at 10 mg/kg experienced mild or moderate liver enzyme elevations, likely also partially related to liver metastases. However, in another phase I study with single agent mapatumumab, there was no evidence of hepatotoxicity (5).

Hematologic side effects in this study included neutropenia and thrombocytopenia. Grade 3 and 4 neutropenia was observed in 43% of the patients, with one patient experiencing neutropenic fever. Grade 3 and 4 thrombocytopenia occurred in 39% of the patients. These side effects as well as the nausea and vomiting experienced by most patients were considered to be related to cisplatin and gemcitabine and occurred in a frequency that is common for this combination (19, 20). Other nonhematologic adverse events included fatigue, tinnitus, and alopecia and were mainly mild to moderate in severity.
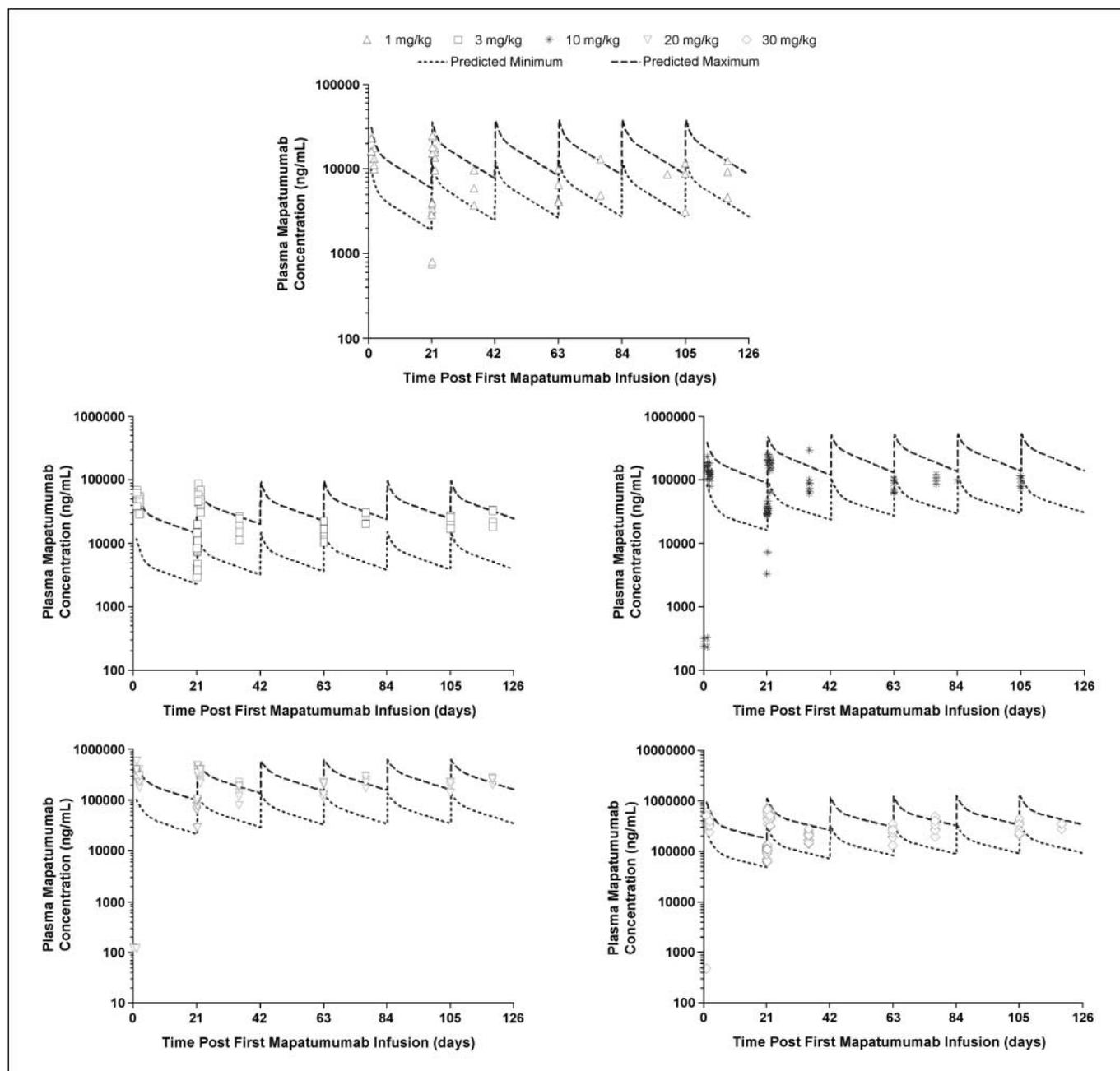

Fig. 1. Plasma mapatumumab concentrations observed for individual subjects following 1, 3, 10, 20, or 30 mg/kg mapatumumab IV infusion doses given 21 d apart, with the expected minimum to maximum concentration range based on phase I study results.
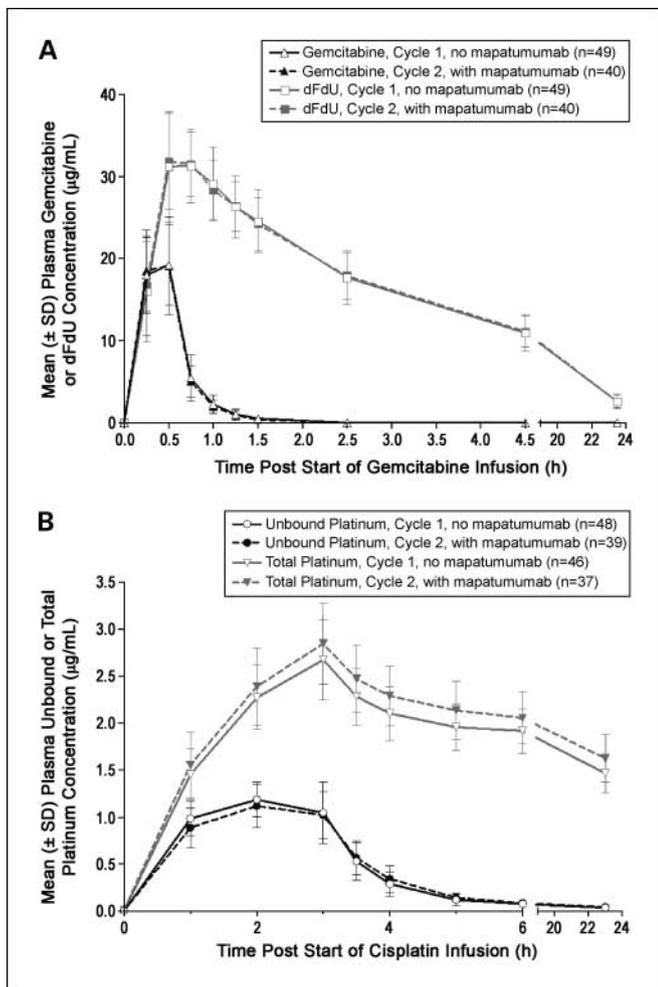
Fig. 2. *A,* mean (±SD) plasma gemcitabine and 2-difluoro-2-deoxyuridine (dFdU) concentrations following 1,250 mg/m² i.v. gemcitabine doses administered as 30-min infusion every 21 d (available data are presented for all cohorts combined). *B,* mean (±SD) plasma unbound and total platinum concentrations following 80 mg/m² i.v. cisplatin doses administered as 3-h infusion every 21 d (available data are presented for all cohorts combined).

Side effects did not influence the total amount of cisplatin and gemcitabine administered at the various dose levels of mapatumumab. As a result, the dose intensity of cisplatin and gemcitabine was maintained throughout all mapatumumab dose levels explored.

The difficulty of assessing toxicity in studies evaluating a combination of various agents lies in the attribution of side effects. In the current study, toxicity may have been the result of either one of the three drugs or of the combination of chemotherapy and mapatumumab. This dilemma is exemplified by the protocol amendments we had to make with regard to the DLT criteria. According to the initial criteria, 4 of 12 patients experienced a DLT at the 10-mg/kg dose level. One of these patients experienced a grade 3 hypokalemia due to cisplatin-induced vomiting; this is common and was unlikely to have been potentiated by mapatumumab. The protocol was amended during the third cohort to consider only events related to mapatumumab or its interaction with gemcitabine and/or cisplatin as DLTs. According to the initial DLT criteria, none of the patients at 1 mg/kg and two of seven

patients at 3 mg/kg experienced DLTs. These two patients had liver enzyme elevations unrelated to mapatumumab, and one also experienced hyponatremia due to cisplatin-induced vomiting. Further dose escalation to 20 mg/kg was pursued without major toxicities, and at the highest tested dose level of 30 mg/kg, no DLTs occurred.

Plasma mapatumumab concentrations were in agreement with the predicted exposure based on the previous phase I studies, rendering it unlikely that coadministration of mapatumumab with gemcitabine and cisplatin has a meaningful impact on mapatumumab exposure (5, 6). Furthermore, coadministration of mapatumumab did not affect exposure to gemcitabine, 2-difluoro-2-deoxyuridine, or cisplatin.

In this study, doses up to 30 mg/kg are evaluated, wherein the maximum dose given in the single-agent phase I studies was 20 mg/kg (5). We considered the evaluation of 30 mg/kg safe because administration of mapatumumab seemed to be well tolerated at dose levels up to and including 20 mg/kg in the (ongoing) phase I and II studies at that moment. In addition, the plasma mapatumumab concentrations in the subjects who received 20 mg/kg mapatumumab were consistent with the predicted exposures, and gemcitabine and cisplatin did not affect the mapatumumab plasma values.

Biological agents are often active at doses below the maximum tolerated dose, and the highest dose tested in clinical studies may exceed the effective dose by far. With lower mapatumumab doses, maximum receptor occupation may have been reached already. In addition, there were no apparent differences in mapatumumab plasma concentrations between patients treated at 20 mg/kg compared with those receiving 30 mg/kg mapatumumab (Fig. 1). Consequently, doses >30 mg/kg mapatumumab are unlikely to yield higher plasma concentrations. However, in the absence of studies that determine the optimal biological dose, we recommend 30 mg/kg mapatumumab every 3 weeks for randomized studies evaluating the efficacy of gemcitabine, cisplatin, and mapatumumab.

Most tumors in the present study did express TRAIL-R1. No association was found between baseline TRAIL-R1 expression and tumor response. It would be interesting to study TRAIL-R1 expression during therapy in relation to response because mapatumumab combined with cisplatin resulted in synergistic antitumor effects *in vivo,* possibly because of TRAIL-R1 up-regulation by chemotherapy (21). In addition, it is not likely that TRAIL-R1 expression solely is predictive of response to mapatumumab-containing therapy because several downstream factors in the
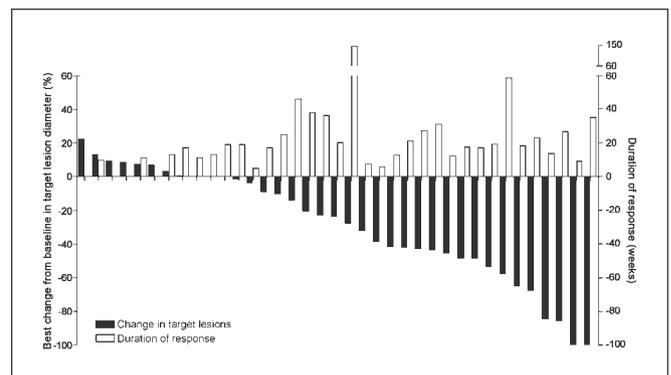

Fig. 3. Maximum percent change in target lesions from baseline (*black bars*) and duration of response (*transparent bars*) per patient.

TRAIL signaling pathway can affect the apoptotic response (22). This also points to the interest of combining mapatumumab with chemotherapy because, presumably, optimal antitumor efficacy will be achieved by targeting more than one pathway (23). Moreover, the simultaneous engagement of the intrinsic and extrinsic apoptotic pathways may result in the prevention of resistance to either drug. This is important because recently evidence has emerged that, in TRAIL-resistant cells, activation of the TRAIL receptors can lead to activation of nuclear factor-κB, which subsequently mediates proliferation, invasion, and metastasis (24–26). To prevent such detrimental effects of TRAIL pathway directed therapy, the development of resistance to TRAIL receptor activating agents should be avoided. In tumor cell lines, treatment with chemotherapy results in sensitization to TRAIL-mediated apoptosis, even in TRAIL resistant cell lines (27, 28).

In this study, 26 of the 37 patients with measurable disease showed a decrease in tumor lesions, and 12 patients achieved a partial response (Fig. 3). These response numbers are interesting compared with a historical overview of response rates in oncology phase I trials, including combination therapy studies (29). Moreover, stable disease was achieved in 51% of the patients and was markedly prolonged in a subset of patients, including several with tumor types that in general are marginally respon-sive to standard chemotherapy regimens such as biliary tract cancer and pancreatic cancer. However, the value of these findings is of course limited by the non randomized nature of the study. Furthermore, no patients were previously treated with gemcitabine and cisplatin. It is therefore difficult to assess the contribution of mapatumumab to the efficacy of this combination.

In conclusion, mapatumumab can be safely administered in combination with gemcitabine and cisplatin in doses up to 30 mg/kg. The pharmacokinetics of gemcitabine and cisplatin are not influenced by mapatumumab and vice versa. Responses and durable stable disease were seen across dose levels and in high numbers. Therefore, further studies in a randomized setting that explore the efficacy of this combination are warranted.

Disclosure of Potential Conflicts of Interest

Acknowledgments

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Correction

Correction: Mapatumumab, a Fully Human Agonistic Monoclonal Antibody That Targets TRAIL-R1, in Combination with Gemcitabine and Cisplatin: A Phase I Study

In this article (Clin Cancer Res 2009;15:5584–90), which published in the September 1, 2009, issue of *Clinical Cancer Research* (1), in the Results section, General subsection, the third sentence should read, as follows: In addition, 15 patients received 124 cycles of mapatumumab monotherapy (median, 6; range, 2-48). Also, in the Results section, Pharmacokinetics subsection, first sentence of the last paragraph should read, as follows: Mean (with 95% confidence interval) exposure in cycles 1 and 2, as measured by Area Under the Curve C_0, $AUC_{0-\infty}$, or AUC_{last} for gemcitabine, 2-difluoro-2-deoxyuridine, and cisplatin-derived unbound platinum is summarized by cohort in Supplementary Table S2.

Reference

1. Mom CH, Verweij J, Oldenhuis CNAM, et al. Mapatumumab, a fully human agonistic monoclonal antibody that targets TRAIL-R1, in combination with gemcitabine and cisplatin: a phase I study. Clin Cancer Res 2009;15:5584–90.

Clinical Cancer Research

Mapatumumab, a Fully Human Agonistic Monoclonal Antibody That Targets TRAIL-R1, in Combination with Gemcitabine and Cisplatin: a Phase I Study

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