A Phase 1 Study of Mapatumumab (Fully Human Monoclonal Antibody to TRAIL-R1) in Patients with Advanced Solid Malignancies

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Abstract

Purpose: Mapatumumab (TRM-1, HGS-ETR1) is a fully human agonistic monoclonal antibody that targets and activates tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) receptor 1 (death receptor 4). Mapatumumab functions like the natural receptor ligand, TRAIL, a tumor necrosis factor superfamily member that is an important mediator of apoptosis in cancer cell lines. Promising preclinical activity with mapatumumab has been observed.

Experimental Design: This phase I, open-label, dose-escalation study assessed the tolerability and toxicity profile of ≥2 doses of mapatumumab administered i.v. in patients with advanced solid tumors. Patients received mapatumumab every 28 days until progression or dose-limiting toxicity.

Results: There were escalation levels from 0.01 to 20.0 mg/kg. Forty-one patients, 27 female, with a median age of 55 years (range, 23-81) were entered into the study and received 143 courses. The most common diagnoses were colorectal (10 patients) and ovarian cancer (9 patients). Patients received a median of two cycles (range, 1-33). Mapatumumab was well tolerated. Adverse events considered at least possibly related to mapatumumab that occurred most frequently included fatigue (36.2%), hypotension (34.1%), nausea (29.3%), and pyrexia (12.2%). The majority of adverse events were grade 1 or 2. The maximum tolerated dose was not reached. Linear pharmacokinetics was observed for doses up to 0.3 mg/kg and for the 20 mg/kg level, whereas exposure at 3 and 10 mg/kg increased less than proportionally. No objective responses were observed, but 12 patients had stable disease for 1.9 to 29.4 months.

Conclusions: Mapatumumab is well tolerated and further evaluation of this TRAIL-R1 targeting agent is warranted.

The evolution of a cancer cell is dependent on six essential alterations including self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, limitless replicative potential, sustained angiogenesis, tissue invasion, and evasion of apoptosis (1). Similar to the cell division cycle, the pathways that lead to apoptosis are complex and consist of a fine homeostatic balance between cell death blockers and inducers (2). Because apoptosis is a physiologic death culminating in fragmentation of cells cleared by phagocytosis, inflammatory reaction or tissue scarring usually does not occur (2). Defects in apoptosis can prolong cellular lifespan and contribute to neoplastic cell expansion and can create a permissive environment for genetic instability that can contribute significantly to carcinogenesis. Apoptosis is triggered by two major pathways: the death receptor–induced extrinsic pathway and the mitochondrial–mediated intrinsic pathway, the latter is more typically activated by conventional chemotherapy (3). Both of these pathways lead to caspase activation and cleavage of cellular substrates.

The extrinsic pathway activates procaspase-8. Once activated, this initiator caspase can activate effector caspases, such as caspase-3, caspase-6, and caspase-7, which in turn cleave a variety of substrates to give rise to DNA degradation and characteristic morphologic changes (4). Recombinant members of the tumor necrosis factor family, including Fas ligand, tumor necrosis factor, and tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) can induce apoptosis in preclinical models (5). TRAIL was identified in 1995 and is a type II membrane protein that can be cleaved from the cell surface to form a soluble ligand capable of inducing apoptosis in a wide variety of cancer cell lines (6). TRAIL can bind to five

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different receptors, including four membrane-bound and one soluble receptor (7, 8). Two of these membrane receptors, TRAIL-R1 (death receptor 4) and TRAIL-R2 (death receptor 5) have a cytoplasmic death domain through which TRAIL can transmit its apoptotic signal by binding as a homotrimer. Interestingly, the apoptotic activity of TRAIL appears selective for cancer cell lines with minimal activity against normal cell types (6, 9–12).

Because of its purported role in inducing apoptosis in cancer cells while sparing normal cells, several TRAIL receptor agonists have recently entered the clinic (5, 13). Mapatumumab (TRM-1, HGS-ETR1) is a fully human monoclonal antibody that is agonistic to TRAIL-R1 with very high specificity and affinity (14). Mapatumumab was able to induce apoptosis in multiple tumor cell lines representing various tumor types. Treatment with various concentrations of mapatumumab resulted in a dose-dependent reduction of cell viability preceded by activation of caspase-3 and/or caspase-7 in most cell lines. Mapatumumab was also shown to enhance chemotherapeutic agent activity *in vitro* and reduced the growth of human tumors in xenograft models, including preestablished colon, lung, and kidney xenograft models. Although TRAIL-R1 cell surface expression was required for the cytotoxic activity of mapatumumab in preclinical models, TRAIL-R1 expression did not predict the level of sensitivity. Preclinically, mapatumumab was also found to have a desirable toxicity profile. Specifically, it did not readily bind normal tissues by flow cytometry or in a tissue-binding assay. Of three cell types that showed binding, only hepatocytes had any decreased viability to 80% to 90% of control cell values in response to mapatumumab.

Based on these promising preclinical observations, the current phase I study attempted to evaluate the safety and tolerability, immunogenicity, and pharmacokinetic profile in patients with advanced solid tumors.

Patients and Methods

Patient eligibility. Patients (18 years old) with malignant solid tumors refractory to conventional therapy or for whom no effective therapy exists were eligible. No restrictions were put on the number of previous chemotherapy regimens. Patients must have had completed any prior chemotherapy, immunotherapy, radiotherapy, or surgery at least 4 weeks before study entry and patients must have had recovered from the toxic effects from any prior therapy.

Patients had adequate performance status of European Cooperative Oncology Group 0 to 2, life expectancy of at least 12 weeks, normal bone marrow and organ function defined as absolute neutrophil count >1,500/μL, platelets >100,000/μL, total bilirubin ≤1.5 times the upper limit of normal, aspartate amino transferase and/or alanine amino transferase ≤2.5 times upper limit of normal, and creatinine ≤1.5 times upper limit of normal. Patients were excluded if they had known brain metastases; if they were positive for HIV or had active hepatitis; if they had a previous hematopoietic stem cell transplant; if they had greater than grade 1 neuropathy; a history of any infection requiring hospitalization or parenteral antibiotics within 2 weeks of study entry; if they had a myocardial infarction, cerebrovascular accident, or congestive heart failure within the last 6 months; if they received an investigational agent within 4 weeks of study entry; or if they had a serious medical condition. Pregnant or breast-feeding women were also excluded. Patients gave informed consent before they entered the study, which was approved by the local research ethics committees of both participating centers.

Therapy. Study treatment was administered i.v. on an outpatient basis. On the first day of each cycle, mapatumumab was infused over 30 min for concentrations up to and including 0.3 mg/kg and over 2 h for all greater concentrations. Because of the potential for infusion and hypersensitivity reaction, acetaminophen and diphenhydramine administered within 1 h before mapatumumab dosing was suggested as a possible premedication regimen. No routine antiemetic prophylaxis was ordered. The sponsor of the study, Human Genome Sciences, supplied mapatumumab. Cycle length was defined as 4 weeks or 28 days and treatment was continued until disease progression, dose-limiting toxicity (DLT), patient's refusal, or physician's decision.

Toxicity assessment and dose reductions. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria version 2. Dose adjustments because of toxicity were not planned. The treatment of a patient could be postponed for up to 2 weeks. A patient was discontinued from the study if the beginning of a given cycle was postponed due to toxicity for more than 2 weeks, unless approved by the Human Genome Sciences study medical monitor. Any patient who experienced a DLT was not permitted to receive any further dosing.

Assessment of response. Patients were evaluated for response every 8 weeks and responses were classified according to criteria proposed by the Response Evaluation Criteria in Solid Tumors Committee (15).

Plasma pharmacokinetic sampling. Blood specimens for plasma mapatumumab concentration measurement were collected selected time throughout the study. At each collection time, 7 mL blood was collected in an EDTA-coated Vacutainer tube. Each Vacutainer tube was then centrifuged at $\sim 1{,}500 \times g$ for 10 min at room temperature to separate the cells from the plasma. The plasma was then harvested and placed in cryovial tubes for storage and shipment. Plasma specimens were stored at -70°C.

Determination of plasma mapatumumab concentrations. Plasma samples were analyzed for mapatumumab by an ELISA that employed TRAIL-R1:FLAG for mapatumumab capture and a horseradish peroxidase–labeled anti-human λ antibody for mapatumumab detection. The signal was amplified by the addition of tetramethylbenzidine. The reaction was stopped with dilute acid before absorbance measurement at 450 nm (A_{450}). The assay had a lower limit of quantitation of 50 ng/mL using a four-variable fit for the standard curve. In each run, six positive controls and a negative control were included. The following criteria were used for acceptance of an analytical run: the standard curve composed of eight different concentrations must have a $r^2 \geq 0.98$, the A_{450} from the highest concentration must be ≥1.5, 4 of 6 positive controls must be detected within ±25% of the expected values, the A_{450} from the negative control must be ≤0.5, and the coefficient of variation for each point must be ≤25%.

Pharmacokinetic analyses. For pharmacokinetic analyses, patients were considered evaluable if they received at least one mapatumumab dose and had at least one measurable plasma mapatumumab concentration post-dose. Actual collection times and actual dose times relative to the first dose were used in the pharmacokinetic calculations. Plasma mapatumumab concentration-time profiles were analyzed for individual patients using compartmental analysis. Because each patient's concentration-time profile was multiphasic, two- and three-compartment models with first-order elimination from the central compartment were evaluated using WinNonlin (Enterprise 5.0.1, Pharsight). Weightings of 1, $1/p$, $1/p^{0.5}$, and $1/p^2$ (where p is the predicted value for the observation) were assessed for each model. For competing models with the same weighting scheme, the Akaike information criterion was used as the basis for model selection. For competing models with different weighting schemes, model selection was based on precision of the primary model variables (random sampling error, ≤100%), randomness of the residuals, and sum of squared residuals. Dose proportionality was assessed using a one-way ANOVA of log-transformed data at the $\alpha = 0.05$ significance level, with Bonferroni's multiple comparison for post-tests (GraphPad Prism, version 4.02, GraphPad Software). The pharmacokinetic results were inspected for possible effects of age, gender, race, physical characteristics (such as body surface area), renal function, hepatic function, study site, mapatumumab lot administered, and disease type/state (European

Cooperative Oncology Group score, tumor type, and baseline tumor size). The study was not prospectively designed to assess these factors as potential covariates. Their effect on the mapatumumab pharmacokinetic was assessed by visual inspection of graphical displays.

Detection of anti-mapatumumab antibodies. Anti-mapatumumab antibodies were detected using two ELISA formats. The first assay detected binding of serum anti-mapatumumab antibodies to mapatumumab antigen-binding fragment [F(ab) screening assay] and the second assay measured binding of serum anti-mapatumumab antibodies to mapatumumab (IgG screening assay). The sensitivity was directly dependent on pre-dose background signal for the F(ab) screening assay and was 10 and 100 μg/mL in serum specimens with low and high backgrounds, respectively. For the IgG screening assay, the sensitivity was 5 and 20 μg/mL for low and high backgrounds, respectively.

Statistical considerations. The primary objective of this study was to determine the maximum tolerated dose of mapatumumab and to determine the safety and tolerability of escalating doses of mapatumumab in patients with advanced cancer. Secondary objectives were to evaluate the immunogenicity and pharmacokinetic profile of mapatumumab and to assess for preliminary evidence of efficacy.

Two to 12 patients were to be treated at each dose level. The decision to escalate to the next dose level was based on observation of toxicity through 28 days following the second dose from at least 3 patients in the previous lower cohort. Each review was to be conducted by the Human Genome Sciences Review Committee. After review, the Human Genome Sciences Review Committee communicated its recommendation regarding dose escalation to the participating principal investigators. If one of the first 3 or 4 patients exhibited evidence of a DLT within 28 days after the second dose, additional patients were to be enrolled at the same dose level up to a total of 6 patients, and if none of these 3 additional patients experienced a DLT, dose escalation was allowed. The maximum tolerated dose of this drug combination was to be defined as the next lower dose level below the one in which >1 of 3 patients or ≥2 of 6 patients experience DLT. Three additional patients were entered at the maximum tolerated dose if only 3 patients were treated previously at that dose level. DLT needed to be considered possibly, probably, or definitely related to study agent within the first two cycles and was defined as follows: grade ≥4 hematologic event; grade ≥3 nonhematologic adverse event, except alopecia, nausea/vomiting, or fatigue; grade ≥3 vomiting in subjects who have received prophylaxis and treatment with an optimal antiemetic regimen; or grade ≥2 allergic reaction.

Results

Patients and treatment. Forty-one patients were accrued to the phase I study at two centers in Canada. Patients were enrolled into one of six dose levels, ranging from 0.01 to 20 mg/kg. Intrapatient dose escalation was not allowed. Patient characteristics are listed in Table 1. All patients had measurable disease. Twenty-seven patients were female and the median age was 55 years (range, 23-81). Most patients had a performance status of European Cooperative Oncology Group 0 or 1. As expected for most phase I studies, patients were quite heavily pretreated with a median of 3 regimens (range, 1-6). The most commonly seen primary tumor types were colorectal (10 patients) and ovary (9 patients).

A total of 143 cycles of mapatumumab were administered (Table 2). Patients received a median of 2 cycles (range, 1-33).

Toxicity. Treatment was generally very well tolerated and maximum tolerated dose was not reached. As detailed in Table 3, the most frequent adverse events experienced and felt to be possibly, probably, or definitely related to mapatumumab were fatigue (37%), hypotension (34%), nausea (29%), and fever (12%). Some of the more common events independent of relationship to study drug included constipation, anorexia, vomiting, abdominal pain, dyspnea, diarrhea, peripheral edema, dyspepsia, and weight loss.

The most severe toxicities potentially associated with mapatumumab included one episode of each of the following grade 3 events: hypertension, fatigue, thrombocytopenia, vomiting, and hypomagnesaemia. The patient with grade 3 thrombocytopenia also had progression of malignant neoplasm reported as potentially associated with mapatumumab. These events occurred at various dose levels and did not appear dose related.

Pharmacokinetics. All patients had measurable plasma mapatumumab concentrations following dosing. The mean pharmacokinetic variables are listed in Table 4. For the 0.01 mg/kg dose group, only three of the seven subjects had plasma mapatumumab concentrations that were measurable for a sufficient time after dose administration to allow reliable estimation of pharmacokinetic variables. For two other patients, one in the 0.03 mg/kg and one in the 10 mg/kg dose groups, reliable pharmacokinetic variables could not be determined.

The mean volumes of distribution for the central compartment (V_1) ranges from 35 to 64 mL/kg among the dose groups. The smallest mean V_1 is similar to the plasma volume (~42.8 mL/kg; ref. 16), whereas the largest mean V_1 is ~49% greater than the plasma volume. The steady-state volume of distribution (V_{ss}) ranges from 69 to 117 mL/kg across dose groups and is at least 73% greater than V_1 for each cohort. Overall, these results suggest that although distribution of mapatumumab may initially be restricted to a volume that is similar to or slightly greater than the plasma volume, it does subsequently distribute to tissues.

The disappearance of mapatumumab from serum is biphasic, with a mean initial phase elimination half-life ($t_{1/2,\alpha}$) of 0.7 to 1.4 days. The mean terminal phase elimination half-life ($t_{1/2,\beta}$) ranges from 14.2 to 28.4 days. Based on the average $t_{1/2,\beta}$ of 21.2 days, 90% of steady state would be attained 70 days after the first dose, that is, before the 4th every 28 days dose. The predicted accumulation factor at steady state is ~1.67 for every 28-day dosing regimen, given the average $t_{1/2,\beta}$ of 21.2 days.

The clearance (CL) of mapatumumab ranged from 2.5 to 5.6 mL/d/kg among the dose groups. These CL values are much smaller than the glomerular filtration rate (~2571 mL/d/kg; ref. 16), indicating that, as expected, there is virtually no renal clearance of this monoclonal antibody.

Results of one-way ANOVA on natural log-transformed compartmental pharmacokinetic variables are summarized in Table 4. Examination of the individual V_1, C_{max}/dose, and V_{ss} results showed that for each of those variables there is substantial overlap of individual results among dose groups. There were no other significant differences in pharmacokinetic variables among dose groups. In particular, it should be noted that no differences in mapatumumab elimination kinetics (CL and half-lives) were found. Overall, it is not possible to conclude that mapatumumab pharmacokinetic are linear across the dose range evaluated. Despite this, elimination of mapatumumab appears to be independent of dose.

Although this study was not prospectively designed to evaluate the potential effect of patient characteristics such as age, body size, sex, or race on mapatumumab pharmacokinetic,

Table 1. Baseline demographic characteristics

Characteristics	No. patients (n = 41)	Primary tumor type	No. patients (n = 41)
Sex		Lung	4
Male	14	Breast	3
Female	27	Cervical	5
Race		Prostate	2
White	37	Ovary	9
Asian	3	Colorectal	10
American Indian or Alaska Native	1	Head and neck	2
Age, y		Gastric	1
Median	55.0	Unknown	1
Range	23-81	Soft-tissue sarcoma	1
European Cooperative Oncology Group status		Endometrial	1
0	13	Neuroendocrine	1
1	23	Hepatocellular	1
2	5		
No. prior systemic regimens			
Median	3.0		
Range	1-6		

plots of the pharmacokinetic variables versus potential covariates were examined to ensure obvious relationships were not overlooked (data not shown). Overall, mapatumumab pharmacokinetic do not appear to be affected by the patients' demographics or disease characteristics.

Formation of anti-mapatumumab antibodies. There was no evidence of anti-mapatumumab antibodies detected in any of the 41 patients.

Response and survival. No objective responses were observed at any of the dose levels. Twelve patients (29.3%) through all dose levels experienced stable disease ranging from 1.9 to 29.4 months, with a median of duration of stable disease of 3.5 months. One patient who received mapatumumab for 33 cycles before discontinuing due to patient request had a diagnosis of metastatic borderline ovarian carcinoma that had been slowly progressive before entering into study. She tolerated treatment well and experienced no cumulative toxicity. Twenty-seven patients had a best response of progressive disease and seven patients experienced early death due to malignant disease. Two patients were not evaluable for response due to insufficient data. Median progression-free survival was 1.7 months, ranging from 0 to 29 months.

Discussion

This phase I study has shown that mapatumumab can be safely administered at doses up to 20 mg/kg in heavily pretreated patients with solid tumors. Dose escalation was not pursued after the 20 mg/kg dose level for pragmatic reasons and because preclinical data suggested that this dose approximated relevant biological concentrations for TRAIL-R1 trigger from preclinical models (14). Very little toxicity attributable to mapatumumab was encountered. Because one patient had experienced possible worsening of peripheral neuropathy early in the enrollment of another phase I study of mapatumumab (17), this trial excluded patients with grade $\geq$2 preexisting neuropathy. No further neurologic symptoms were observed and it therefore appears that mapatumumab has little toxic effects on peripheral neurons. Preclinical studies suggested that hepatocytes may be more sensitive than other types of cells to the proapoptotic effects of mapatumumab and elevations of AST and ALT, without elevations in bilirubin, were observed in some patients treated with 10 mg/kg in another phase I study (14, 17). Other researchers have also suggested that the myocardium may theoretically be at risk of damage through apoptosis (14, 18). However, no evidence of hepatotoxicity and no significant increases in transaminases attributed to mapatumumab were observed in this study. Similarly, there was no evidence of cardiotoxicity, including in the patient who received 33 cycles.

The $t_{1/2,\beta}$ of $\sim$21 days is consistent with that reported for other fully human antibodies, including what was observed for another phase I trial of mapatumumab, and can support dosing every 2 or 3 weeks (17). In animal studies, the terminal half-life

Table 2. Summary of extent of exposure to study agent by number of cycles by dose

No. cycles	0.01 mg/kg (n = 7)	0.03 mg/kg (n = 4)	0.3 mg/kg (n = 5)	3 mg/kg (n = 4)	10 mg/kg (n = 9)	20 mg/kg (n = 12)	Total (n = 41)
1	2	—	1	—	3	2	8
2	3	3	2	2	5	6	21
3	—	1	—	—	—	1	2
4	1	—	—	1	1	2	5
6	1	—	—	—	—	—	1
7	—	—	—	1	—	—	1
10	—	—	1	—	—	—	1
11	—	—	—	—	—	1	1
33	—	—	1	—	—	—	1

Table 3. Most frequent treatment-related (possibly, probably, or definitely related) adverse events (>10% of patients) by severity

Preferred term	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	All active (*n* = 41), *n* (%)
Fatigue	5 (12.2)	9 (22.0)	1 (2.4)	—	15 (36.6)
Hypotension	14 (34.1)	—	—	—	14 (34.1)
Nausea	12 (29.3)	—	—	—	12 (29.3)
Pyrexia	4 (9.8)	1 (2.4)	—	—	5 (12.2)

of mapatumumab in mice was 6.9 to 8.7 days (14). This is in contrast with the reported half-life of 3.6 minutes for the TRAIL ligand that binds both TRAIL-R1 and TRAIL-R2 (19). This large difference in elimination provides a distinct clinical pharmacologic profile versus TRAIL ligand in that prolonged and protracted dosing is not necessary to achieve continuous exposure. Mapatumumab elimination pharmacokinetics appears linear up to 20 mg/kg. In contrast, the mean volume of distribution for mapatumumab appears to be increased for the higher doses relative to the lower doses, although there is substantial overlap of the result for individual patients across dose levels.

Mapatumumab pharmacokinetics described for the current study is similar to those obtained in the previous phase I study (17). In both studies, plasma mapatumumab concentration-time profiles were multiphasic and best fit a two-compartment open model with first-order elimination from the central compartment, V_1 approximates the plasma volume, V_{ss} is ~70% larger than V_1, the initial and terminal phase half-lives were ~1 and 20 days, respectively, and CL ranged from 2.5 to 6.5 mL/kg/d. Although no objective responses were observed in this study, several patients experienced prolonged stable disease. One patient received 33 cycles of mapatumumab before coming off study per patient request. Although she had a diagnosis of borderline ovarian carcinoma, she had been experiencing slow progression before entering into study and it is conceivable that her disease may have been rendered static by mapatumumab. Although it is impossible to make definitive conclusions from one patient, the lack of cumulative toxicity despite very prolonged dosing suggests that mapatumumab may be safely administered for protracted periods. The effectiveness of single-agent mapatumumab has been evaluated in several phase II trials. In one study, 40 patients with relapsed or refractory non-Hodgkin's lymphoma received either 3 or 10 mg/kg every 21 days (20). One complete and two partial responses were observed, all in patients with follicular lymphoma. Another phase II study evaluated the role of mapatumumab at a dose of 10 mg/kg every 21 days in 32 patients with advanced non-small cell lung cancer (21). Stable disease was observed in 7 patients with a median duration of 2.8 months. A third study involving 38 patients with advanced colorectal cancer reported a best response of stable disease in 9 patients for a median of 2.6 months (22).

Based on preclinical data, it is expected that mapatumumab may exert its maximal effect when combined with other anticancer treatments such as chemotherapy, radiotherapy, or molecular targeted compounds. The binding of this agonist antibody or TRAIL to TRAIL-R1 has shown significant synergy when combined with chemotherapy or radiation (8, 10, 14, 23–29). Two phase Ib studies are currently ongoing in combination with full-dose cisplatin and gemcitabine and with full-dose paclitaxel and carboplatin (30, 31). When reported, these combinations had been well tolerated and pharmacokinetic analyses showed no signs of drug interaction. A randomized phase II trial of mapatumumab in combination with bortezomib in patients with relapsed/refractory multiple myeloma is also under way.

Table 4. Mean (SD) mapatumumab pharmacokinetics

Dose (mg/kg)	No. patients	C_{max} (μg/mL)	$AUC_{0-\infty}$ (μg h/mL)	$t_{1/2,\alpha}$ (d)	$t_{1/2,\beta}$ (d)	CL (mL/d/kg)	V_1 (mL/kg)	V_{ss} (mL/kg)
0.01	3	0.27 (0.03)	5.11 (3.12)	0.7 (0.4)	28.4 (23.4)	2.50 (1.42)	37.32 (3.88)	70.49 (20.81)
0.03	3	0.84 (0.06)	8.42 (1.58)	0.7 (0.1)	14.2 (4.3)	3.65 (0.71)	35.49 (2.58)	69.05 (14.51)
0.3	5	7.45 (0.62)	100.63 (34.01)	0.8 (0.3)	19.5 (9.8)	3.32 (1.29)	40.23 (3.31)	77.88 (22.89)
3	4	53.42 (13.86)	780.31 (276.13)	1.1 (1.1)	21.2 (9.5)	4.27 (1.66)	57.46 (13.44)	109.77 (16.13)
10	8	159.83 (30.98)	1981.72 (715.56)	1.4 (0.8)	16.4 (6.3)	5.63 (1.91)	63.85 (12.94)	110.64 (25.98)
20	12	405.10 (96.67)	5635.42 (2094.73)	1.4 (0.9)	27.3 (27.5)	4.24 (2.34)	51.08 (11.55)	116.83 (55.69)
	*P**	0.0002 †	0.0605	0.1411	0.7171	0.0605	0.0003 †	0.0370 ‡

Abbreviations: C_{max}, maximum plasma mapatumumab concentration; $AUC_{0-\infty}$, area under the plasma mapatumumab concentration-time curve to infinite time; $t_{1/2,\alpha}$, initial phase elimination half-life; $t_{1/2,\beta}$, terminal phase elimination half-life; CL, clearance; V_1, volume of distribution for the central compartment; V_{ss}, volume of distribution at steady state.

*From a one-way ANOVA of log-transformed values. C_{max} and $AUC_{0-\infty}$ were dose normalized before analysis.

†Significant difference between the 10 mg/kg group and the 0.01, 0.03, and 0.3 mg/kg groups; $P < 0.001$, Bonferroni's multiple comparison test.

‡No significant differences in any pairwise comparison; $P > 0.05$, Bonferroni's multiple comparison test.

In summary, mapatumumab has an excellent toxicity profile in patients with advanced solid malignancies. Although no objective responses were observed, several patients had prolonged stable disease. Because the best use of mapatumumab is likely to be in combination with other anticancer agents such as chemotherapy and targeted therapies, additional phase II studies involving mapatumumab in combination with other therapies are warranted.

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