Published OnlineFirst October 29, 2010; DOI: 10.1158/1078-0432.CCR-10-2275

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Clinical Trial of the Chimeric Anti-Mesothelin Monoclonal Antibody MORAb-009 in Patients with Mesothelin-Expressing Cancers

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Abstract

Purpose: MORAb-009 is a chimeric monoclonal antibody that targets mesothelin, a tumor differentiation antigen overexpressed in pancreatic cancer, ovarian cancer, mesothelioma, and other malignancies. We conducted a phase I clinical trial of MORAb-009 in patients with advanced mesothelin-expressing cancers to determine its safety, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD).

Methods: Cohorts consisting of 3 to 6 subjects each received MORAb-009 intravenously on days 1, 8, 15, and 22 at progressively increasing doses ranging from 12.5 to 400 mg/m^2. Disease evaluation with computed tomography occurred on day 35. Subjects with responding or stable disease could receive additional cycles of MORAb-009.

Results: A total of 24 subjects were treated including 13 mesothelioma, 7 pancreatic cancer, and 4 ovarian cancer patients. The median number of MORAb-009 infusions was 4 (range 1–24 infusions). At the 400 mg/m^2 dose level, 2 subjects experienced DLT (grade 4 transaminitis and a grade 3 serum sickness). Thus, although there were other contributing causes of these adverse events, 200 mg/m^2 was considered the MTD. Other adverse events at least possibly related to MORAb-009 included 7 drug hypersensitivity events (all grade 1 or 2) and a thromboembolic event (grade 4). Eleven subjects had stable disease. There was a dose-dependent increase in serum MORAb-009 concentration.

Conclusion: MORAb-009 is well tolerated and the MTD when administered weekly is conservatively set at 200 mg/m^2. In this group of previously treated patients, 11 subjects had stable disease. Phase II studies of MORAb-009 in different mesothelin-expressing cancers are ongoing. *Clin Cancer Res; 16(24); 6132–8. ©2010 AACR.*

Introduction

MORAb-009 is a high-affinity monoclonal antibody targeting the cell surface glycoprotein mesothelin (1). Normal mesothelin expression in human tissues is limited to the mesothelial cells lining the pleura, peritoneum, and pericardium (2, 3). However, it is highly expressed in many common epithelial cancers. Mesothelin expression by immunohistochemistry is present in approximately 100% of epithelial malignant mesotheliomas and ductal pancreatic adenocarcinomas, 67% to 100% of ovarian cancers and 41% to 53% of lung adenocarcinomas (4–8). In addition, mesothelin is expressed to varying degrees by other tumors including cervical, head and neck, gastric, and esophageal carcinomas (9). This differential expression of mesothelin makes it an attractive target for cancer therapy.

The normal biological function of mesothelin is not known. Homozygous mesothelin knockout mice were phenotypically wild type and developed normally to adulthood (10). However, recent studies have shown that mesothelin binds to the cell surface mucin CA-125/MUC16, which is commonly used as a marker to follow patients with ovarian cancer (11–13). Binding of tumor associated CA-125 to mesothelin on normal mesothelial cells lining the pleura or peritoneum can lead to heterotypic cell adhesion and tumor metastasis within the pleural and peritoneal cavities.

Small amounts of cell bound mesothelin are shed into the serum in patients with mesothelioma and ovarian cancer and may be a useful biomarker to follow these patients (14–16). In addition, ongoing clinical studies suggest that mesothelin is a potentially important target for the treatment of mesothelin-expressing tumors (17). The first anti-mesothelin agent to enter clinical trials was SS1P, a recombinant immunotoxin consisting of an anti-mesothelin Fv linked to a truncated *Pseudomonas* exotoxin

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doi: 10.1158/1078-0432.CCR-10-2275

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Translational Relevance

Mesothelin is a tumor differentiation antigen that is highly expressed in many epithelial cancers with limited expression in normal human tissues. MORAb-009 is a chimeric monoclonal antibody to mesothelin that in preclinical studies shows antitumor activity against mesothelin-expressing cell lines and xenografts in nude mice. This report summarizes the results of the phase I clinical trial of MORAb-009 to determine its safety and maximum tolerated dose in patients with advanced mesothelin-expressing cancers. Currently, phase II clinical trials of MORAb-009 with chemotherapy are ongoing in different tumor types.

(18). In phase I clinical studies, SS1P was shown to be safe and some minor responses were observed in patients with previously treated mesothelin-expressing cancers (19, 20). Currently, a clinical trial is evaluating SS1P in combination with chemotherapy for the treatment of patients with malignant mesothelioma. In a clinical trial of tumor cell vaccination for the treatment of pancreatic cancer using granulocyte macrophage colony stimulating factor–transduced pancreatic cancer cell lines, 3 of 14 subjects developed a postvaccination delayed-type hypersensitivity response that correlated with improved survival. In all 3 cases, the subjects developed a CD8+ T-cell response to mesothelin (21, 22).

MORAb-009 is a chimeric IgG1/k antibody that was generated by fusing the genes encoding the anti-mesothelin Fv (SS1 scFv) in frame with human IgG1 and kappa constant regions (1). *In vitro*, MORAb-009 elicits antibody-dependent cellular cytotoxicity (ADCC) against mesothelin-expressing tumor cell lines. In addition, MORAb-009 inhibits heterotypic cell adhesion of mesothelin-positive tumor cells to CA-125–expressing tumor cells. In tumor xenograft studies combination treatment with MORAb-009 plus chemotherapy led to a greater reduction in the growth of mesothelin-expressing tumors than either MORAb-009 or chemotherapy alone (1). On the basis of these preclinical studies and safety in monkey toxicology studies, we initiated a phase I clinical trial of MORAb-009 in patients with treatment refractory mesothelin-expressing solid tumors.

Patients and Methods

Patients

Patients ages 18 years or more with a histologically confirmed diagnosis of mesothelioma, pancreatic adenocarcinoma, or mesothelin-positive ovarian or non–small cell lung cancer were eligible for this study. Because nearly 100% of epithelial mesotheliomas and pancreatic carcinomas express mesothelin, immunohistochemical confirmation of mesothelin positivity in these cancers was not required. However, for patients with ovarian cancer and non–small cell lung cancer, mesothelin expression assayed by immunohistochemistry using archival tumor tissue was required prior to study entry. Mesothelin positivity was defined as 2+ or greater staining of tumor cells on a scale of 0 to 4+ staining. Tumor mesothelin expression was evaluated using the commercially available anti-mesothelin antibody 5B2 (Novocastra). Eligible patients had to have progressed on at least 1 standard chemotherapy regimen prior to enrolling on study. Patients with pancreatic cancer were required to have received gemcitabine as part of prior therapy and patients with ovarian cancer had to be platinum refractory or resistant to be eligible. Other eligibility criteria included a life expectancy of 3 months or more; Eastern Cooperative Oncology Group (ECOG) performance score of 0 to 2; adequate bone marrow, hepatic, and renal function [absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelet count $\geq 100 \times 10^9$/L; hemoglobin ≥ 9 g/dL; serum aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase $\leq 5 \times$ upper limit of normal; serum bilirubin ≤ 2.0 mg/dL; serum creatinine ≤ 2.0 mg/dL] determined 2 weeks or less before starting therapy. In addition, patients were required to have measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) or evaluable by clinical signs/symptoms (e.g., ascites, pleural effusion, or lesions of less than 2 cm) supported by radiologic, or pathologic studies conducted within 4 weeks of study entry. Patients with coexisting malignancies requiring active treatment, central nervous system involvement, active hepatitis, HIV, or systemic bacterial or fungal infections were excluded.

Study design

This was a multicenter, open-label, phase I dose-escalation study designed to evaluate the safety and maximum tolerated dose (MTD) of MORAb-009. The subjects were enrolled in 6 dose cohorts of 3 to 6 subjects each. Three subjects were to be treated at the starting dose level and if no dose-limiting toxicity (DLT) was noted in these subjects then they were treated at the next higher dose level. If 1 out of 3 subjects developed a DLT, then additional subjects were to be treated at that dose level for a maximum of 6 subjects. Of 6 subjects, if 1 or less had DLT, then escalation to the next higher dose level could proceed. If 2 of 6 subjects had a DLT then the MTD had been exceeded. DLT assessment for dose escalation was done at the end of 6 weeks from the first dose of MORAb-009.

MORAb-009 was given as 4 weekly infusions on days 1, 8, 15, and 22 followed by 2 weeks off. Subjects without evidence of disease progression or significant adverse events could continue treatment for subsequent cycles. MORAb-009 was given as a continuous infusion initially at 1 mg/min. After 30 minutes, if no grade 2 or greater infusion reactions were encountered, the rate was increased by 2 mg/min increments, up to a total of 5 mg/min. No premedications were given to subjects prior to antibody therapy. However, if subjects developed allergic reactions then premedication for subsequent infusions was permitted.

Assessments

Baseline tumor imaging was done within 4 weeks of starting therapy, after the first cycle, and every odd cycle

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thereafter. Tumor response was measured using RECIST criteria. Baseline screening also included a complete medical history and physical examination, ECOG performance status, chest X-ray, electrocardiogram, as well as complete blood count, serum chemistries, and tumor markers, where appropriate.

Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (CTC), version 3.0. Subjects were evaluated for toxicity at every scheduled visit. A DLT was defined as any grade 3, 4, or 5 hematologic or nonhematologic toxicity that was definitely, probably, or possibly related to the administration of MORAb-009. Infusion-related toxicities that could be treated or controlled to grade 2 or less by maximal medical management were not considered a DLT. Allergic reactions (other than isolated drug fever) of grade 3 or greater, which were determined to be definitely, probably, or possibly related to MORAb-009 were considered DLTs, irrespective of whether they were controlled by medical management. Subjects with pretreatment grade 2 liver function abnormalities that progressed to grade 3 during the study were not considered a DLT if in the opinion of the treating physician this was related to disease progression.

Pharmacokinetics

Serial blood samples to determine MORAb-009 concentration were collected on days 1, 8, 15, and 22 at the following time points: prior to infusion, 15 minutes after beginning infusion (for infusions longer than 30 minutes, approximately halfway through the infusion), end of infusion, and 30 minutes, 1 hour, 2 hours, and 4 hours after completion of drug infusion. In addition, on days 1 and 22 samples were also collected 24 hours after completion of the infusion. A single sample for pharmacokinetic analysis was collected on day 35. Serum concentrations of MORAb-009 were measured to determine standard pharmacokinetic parameters including maximum observed serum concentration (C_{max}), area under the concentration curve (AUC), time of maximum serum concentration (t_{max}), and terminal half-life ($t_{1/2}$). Noncompartmental analysis was performed on the concentration–time profiles following the 4 weekly infusions using the WinNonlin Professional Edition version 5.0 (Pharsight Corporation).

Human anti-chimeric antibody detection

Blood samples for human anti-chimeric antibody (HACA) analysis were collected at baseline, on day 15, and at the final/early termination visit. Blood sampling was performed prior to the start of MORAb-009 infusion. Examination for the presence of HACA was performed by Huntingdon Life Sciences, Inc.

Statistical analysis

The sample size for this study was based on the traditional "3 + 3" dose-escalation design used in phase I oncology trials. The MTD was determined on the basis of the appearance of DLTs at a given dose level during dose escalation following a modified Fibonacci series beginning at 12.5 mg/m^2. Summary statistics (*n*, mean, SD, median, minimum, and maximum) were derived within each MORAb-009 dose group for continuous data and the number and percentage of subjects in each category were provided for categorical data. Baseline values for safety and efficacy parameters were selected as the last nonmissing observation before the administration of the first dose of MORAb-009. Actual and percent change from baseline was derived by subtracting postbaseline values from the baseline value. All statistical calculations were performed using the Statistical Analysis System (SAS) Version 8.0 (SAS Institute).

Results

Patient characteristics

From June 2006 to November 2007, a total of 24 patients were enrolled in the study and received at least 1 infusion of MORAb-009 (median 4 infusions, range 1–24 infusions). Demographics are summarized in Table 1. All patients had received prior chemotherapy, and most of them had mesothelioma and were ECOG performance status 1.

Phase I dose escalation

All subjects who received any study treatment were included in the safety and pharmacokinetic analyses. The subjects were treated at 6 different dose levels of MORAb-009 (Table 2). Because no DLTs were observed in 3 subjects each treated at doses of 12.5 mg/m^2, 25 mg/m^2, and 50 mg/m^2, the MORAb-009 dose was escalated to 100 mg/m^2. One out of the first 3 subjects treated at this dose level had a DLT, a deep venous thrombosis, and pulmonary embolism that were detected at the time of restaging after cycle 1 of MORAb-009. Although this adverse event was felt to be most likely due to the subjects underlying mesothelioma, relationship to study drug could not be ruled out and it was conservatively considered to be a DLT. Thus, this dose level was expanded to a total of 6 subjects. Without any further

Table 1. Subject demographics

Characteristics	Subjects (*n* = 24)
Median age, years	60
Range	48–80
ECOG performance status	
0	7
1	15
2	2
Diagnosis	
Mesothelioma	13
Pancreatic cancer	7
Ovarian cancer	4
Prior treatments	
Chemotherapy	24
Radiation therapy	10
Immunotherapy	2

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Table 2. Number of subjects treated at different MORAb-009 dose levels

	MORAb-009 dose level (mg/m^2)					
	12.5	25	50	100	200	400
Mesothelioma	1	3	1	4	1	3
Pancreatic cancer	2	-	1	1	1	2
Ovarian cancer	-	-	1	1	1	1

DLT in the expanded 100 mg/m^2 cohort, the MORAb-009 dose was escalated to 200 mg/m^2. As no DLTs were noted at this dose level, 6 subjects were treated per protocol at the next and highest dose level of MORAb-009, 400 mg/m^2.

Two DLTs were noted at the 400 mg/m^2 dose level. One was in a 51-year-old male with peritoneal mesothelioma who had a transient grade 4 elevation of ALT and AST the day after the first infusion of MORAb-009. The subject had a history of Crohn's disease and extensive colon resection with prior unexplained episodes of transient grade 2 to 3 ALT/AST elevation and whose ALT/AST were within normal limits before receiving MORAb-009. Grade 4 transaminitis was noted in this subject 24 hours after MORAb-009 infusion. He had also engaged in strenuous exercise. The ALT and AST decreased to grade 3 by day 3, grade 2 by day 12, and resolved to within normal limits by day 27. Because this elevation of liver enzymes was noted in temporal association with the MOARAb-009 infusion, it was considered a DLT even though the subject had a history of prior elevation of liver enzymes. Thus, the subject was taken off study and no further drug was administered.

Another subject treated at the 400 mg/m^2 was a 55-year-old female with peritoneal mesothelioma who developed serum sickness the day after the second infusion of MORAb-009, characterized by grade 1 fever, pain, and arthralgias. These symptoms resolved with supportive care that included administration of systemic steroids. This subject had been previously treated with 2 monoclonal antibody-based treatments including 1 immediately preceding MORAb-009 therapy and retrospective analysis of her serum showed that she was positive for HACA prior to receiving the first infusion of MORAb-009. The presence of HACA may have contributed to her developing serum sickness. However, the serum sickness in this patient was considered a DLT and the subject was withdrawn from study.

Safety

Treatment with MORAb-009 was generally well tolerated. Adverse events that were possibly, probably, or definitively related to MORAb-009 are listed in Table 3. There were 7 drug hypersensitivity adverse events (DHAE) including 1 allergic reaction, 4 infusion reactions, and 2 episodes of flushing that occurred in 7 subjects (29.2%) within 48 hours of MORAb-009 infusion. All were grade 1 or 2. Three subjects experienced a DHAE at the first infusion, 3 subjects experienced a DHAE at the second infusion and 1 subject experienced a DHAE at infusion 4. No subject discontinued treatment because of a DHAE. The serum sickness hypersensitivity event described earlier in the text was considered a grade 3 toxicity and the subject was taken off study. As described earlier, 1 subject had a DLT (deep venous thrombosis/pulmonary embolism) at the 100 mg/m^2 dose level and 2 subjects had DLTs (grade 4 transaminitis and serum sickness) at the 400 mg/m^2 dose level. Four subjects did not receive all 4 scheduled weekly infusions of MORAb-009; 3 due to adverse events and 1 because of disease progression. In the patients who received more than 1 cycle of MORAb-009 there was no pleuritis or pericarditis (due to targeting of mesothelin normally expressed on pleura or pericardium) or any other unexpected toxicity.

Pharmacokinetics

The pharmacokinetic data are summarized in Table 4. The duration of drug infusion increased as the MORAb-009 dose increased. Therefore, the relationship between dose and C_{max} could not be determined accurately because of the confounding effect of infusion duration on C_{max}. Following the first infusion of MORAb-009, the mean C_{max} values generally increased as the dose increased. Mean C_{max} values increased from 7 μg/mL for the 12.5 mg/m^2 dose level to 244 μg/mL for the 400 mg/m^2 dose level. The mean day 1 $AUC_{(0-168)}$ values also increased as dose increased, ranging from 296 μg·h/mL at the 12.5 mg/m^2 dose level to 21,528 μg·h/mL at the 400 mg/m^2 dose level. Half-life values were estimated over the 1-week period following infusion 1. There was no significant increase in $t_{1/2}$ with increasing MORAb-009 dose on day 1.

Following the fourth of the weekly infusions of MORAb-009 the day 22 mean C_{max} values increased in an approximately dose-related manner and ranged from 5 μg/mL for the 12.5 mg/m^2 dose level to 521 μg/mL for the 400 mg/m^2 dose level. The mean day 22 $AUC_{(0-168)}$ values also increased as MORAb-009 dose increased, ranging from 783 to 72,656 μg·h/mL across the 12.5 to 400 mg/m^2 dose range. For day 22, there appeared to be an increase in $t_{1/2}$ with increasing dose, particularly for doses greater than 12.5 mg/m^2 where mean $t_{1/2}$ value was 78 hours. Half-life values for the 50, 200, and 400 mg/m^2 doses were 247, 235, and 244 hours, respectively, indicating approximately a 10-day terminal half-life, which is typical for chimeric antibodies. The exception was the

Published OnlineFirst October 29, 2010; DOI: 10.1158/1078-0432.CCR-10-2275

Table 3. Number of adverse events that were possibly, probably, or definitively related to MORAb-009 at different dose levels[a]

Adverse events	MORAb-009 dose level (mg/m^2)					
	12.5	25	50	100	200	400
Abdominal pain						1
Anemia				1		
Chills					1	
Deep venous thrombosis/pulmonary embolism				1[d,e]		
Dizziness						1
DHAEs[b]	1	3		1		2
Dysgeusia	1					
Dyspepsia					1	
Fatigue						2
Headache						1
Hypotension						1
Liver function test elevation[c]						1[d,e]
Nausea						1
Serum sickness						1[d,f]
Vomiting						1

[a]All adverse events were grade 1, 2 (CTC version 3.0) except as indicated.
[b]DHAEs includes subjects who developed acute infusion reaction/cytokine release syndrome, flushing or allergic reaction during or following MORAb-009 infusion.
[c]Includes increased alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and serum bilirubin
[d]DLT
[e]Grade 4
[f]Grade 3

mean $t_{1/2}$ value for the 100 mg/m^2 dose, which was 68 hours. Figure 1 shows the mean serum MORAb-009 concentration level at different time points following the fourth infusion of MORAb-009 on day 22.

Human anti-chimeric antibodies

Seven subjects had at least 1 positive HACA value at some point during the study. This included 3 patients who had baseline HACA prior to MORAb-009 infusion and 4 patients who developed HACA after at least 1 dose of MORAb-009. Of the 7 subjects with positive HACA values, 3 experienced no DHAEs whereas the other 4 experienced a DHAE during the study.

Efficacy

Of the 24 subjects treated on this study, 20 were evaluable for response as they completed at least 1 cycle of MORAb-009. No complete or partial responses were noted.

Table 4. MORAb-009 pharmacokinetics[a]

MORAb-009 (mg/m^2)	Mean C_{max} (μg/mL)		Mean $AUC_{(0–168)}$ (μg·h/mL)		Mean $t_{1/2}$ (h)	
	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22
12.5	7	5	296	783	58	78
25	43	[b]	600	[b]	37	[b]
50	24	38	1,903	4,971	91	247
100	53	77	4,165	6,713	82	68
200	119	187	10,424	22,570	93	236
400	244	521	21,528	72,656	96	244

[a]Pharmacokinetic values after the first (day 1) and fourth (day 22) dose of MORAb-009.
[b]Data not available because only 1 out of 3 patients treated at this dose level had blood drawn for C1D22 pharmacokinetic analysis.

Published OnlineFirst October 29, 2010; DOI: 10.1158/1078-0432.CCR-10-2275

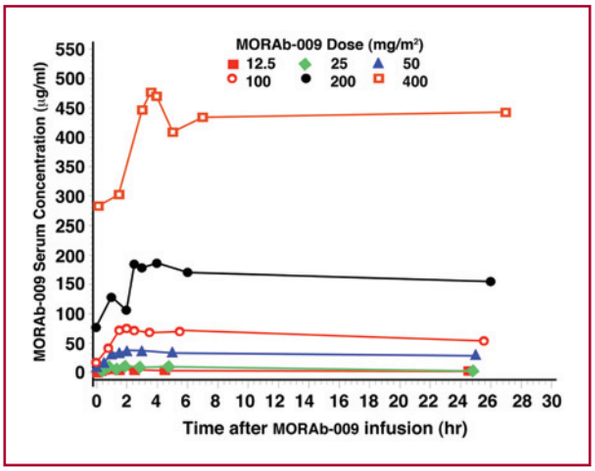

Fig. 1. Mean serum MORAb-009 concentration at different time points following MORAb-009 infusion on cycle 1, day 22.

Eleven subjects had stable disease as best response and 9 subjects had progressive disease. Seven subjects with stable disease received more than 1 cycle of treatment. This included a subject with pancreatic cancer who had progressed on prior gemcitabine and had stable disease for 6 months while on MORAb-009.

Discussion

The results of this phase I clinical trial in patients with mesothelin-expressing advanced solid tumors show that MORAb-009 is well tolerated by patients with a low incidence of immunogenicity. The single-agent MTD with weekly administration is 200 mg/m^2. MORAb-009 blood levels increased in a dose-dependent fashion. Although there were no objective responses, disease stabilization was observed in several heavily pretreated patients.

The rationale for the MORAb-009 dosing schedule chosen for this phase I trial was partly based on pharmacokinetic analysis of a good laboratory practice (GLP) study conducted in cynomolgus monkeys. In this GLP study, monkeys received MORAb-009 twice per week for 7 doses over 23 days at 2 different dose levels (2 mg/kg per dose and 15 mg/kg per dose). Pharmacokinetic analysis showed a dose-dependent increase in MORAb-009 AUC and C_{max} and its half-life was estimated to be between 11.9 and 14.2 days. On the basis of these pharmacokinetic data a weekly infusion schedule was selected. A "2-week-off" treatment was chosen as a precaution for any unanticipated cumulative toxicity from MORAb-009 such as pleuritis or pericarditis.

The most common adverse event noted in this clinical trial was drug hypersensitivity consisting of infusion reaction/cytokine release syndrome and allergic reactions. All of these reactions were CTC grade 1 or grade 2 with the exception of grade 3 serum sickness in 1 subject, who had been previously treated with 2 different antibody-based therapies. These infusion reactions were easily managed by decreasing the infusion rate of MORAb-009 and administering antihistamines and acetaminophen. Of note, subjects did not receive premedications prior to the MORAb-009 infusion. However, if any subject developed infusion reaction, they then received premedications with antihistamines and acetaminophen for subsequent infusions of MORAb-009. The MTD was determined as 200 mg/m^2. At 400 mg/m^2, 2 serious adverse events were observed, which were most likely related to comorbidities in the 2 subjects, but were conservatively termed related and thus considered DLTs. However, it is likely that patients may be able to tolerate MORAb-009 at doses higher than 200 mg/m^2, which may be reassessed in future studies. Given the frequency of drug hypersensitivity noted in this phase I clinical trial; subjects being treated on phase II studies of MORAb-009 receive acetaminophen and antihistamines prior to any infusion of MORAb-009.

The systemic exposure of MORAb-009, as assessed by $AUC_{(0-168)}$, increased in a dose-related manner over the 12.5- to 400-mg/m^2 dose range following both single and multiple weekly infusions. Half-life did not appear to change as a function of dose on day 1, but it did appear to increase as a function of dose on day 22. A gradual increase in $t_{1/2}$ with increasing dose was not apparent, possibly because of the small number of subjects in each dose group and because of variability in the $t_{1/2}$ estimates. The $t_{1/2}$ values are likely underestimates of the actual $t_{1/2}$ values because of the relatively short period of time over which they were estimated and the lack of data between the 24 and 168 hour time points. The mean C_{max} of MORAb-009 at the MTD (200 mg/m^2) is significantly higher than the concentration of MORAb-009 required for ADCC against mesothelin-expressing cell lines or to inhibit the mesothelin CA-125 interaction *in vitro* (1).

A subset of mesothelioma patients treated on this phase I clinical trial had serial CA-125 measurements done during the course of their treatment, because CA-125 levels are commonly elevated in patients with mesothelioma and can be used to follow their response to therapy (23, 24). These included 4 subjects with pleural mesothelioma and 4 with peritoneal mesothelioma. Treatment with MORAb-009 led to a marked increase in serum CA-125 levels in these subjects including those whose serum CA-125 levels were within normal levels before receiving MORAb-009 (25). This increase in serum CA-125 was not because of disease progression, because the CA-125 decreased to baseline values once MORAb-009 treatment was stopped. It appears likely that the increase in serum CA-125 concentration level is due to MORAb-009 inhibiting the binding of tumor shed CA-125 to mesothelin that is present on mesothelial cells that line the pleura and peritoneum. These results suggest that MORAb-009 can potentially inhibit the interaction between mesothelin and CA-125 and therefore inhibit heterotypic adhesion and intracavitary metastasis in patients with mesothelioma and ovarian cancer. In addition, serum CA-125 will not be a useful marker to follow for response in patients with ovarian cancer being treated with MORAb-009 because it may increase CA-125 irrespective of tumor response.

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Preclinical studies have shown that the antitumor activity of MORAb-009 against mesothelin-expressing tumor xenografts is enhanced when it is administered in combination with chemotherapy (1). Thus, a multi-institutional randomized double-blind placebo-controlled phase II clinical trial of MORAb-009 for the treatment of pancreatic cancer was initiated (ClinicalTrials.gov NCT00570713). In this study patients with newly diagnosed pancreatic cancer are treated with MORAb-009 plus gemcitabine or placebo plus gemcitabine with overall survival as the primary endpoint. In addition, an open-label multicenter phase II clinical trial of MORAb-009 plus pemetrexed and cisplatin has just opened for the treatment of malignant pleural mesothelioma with progression-free survival as the primary end point is ongoing (ClinicalTrials.gov NCT00738582). Given the favorable safety profile of MORAb-009, additional exploration in other mesothelin-expressing cancers is warranted.

Disclosure of Potential Conflicts of Interest

R.H., S.J.C., I.P., E.S., R.J.K., and D.L. claim no conflict of interest. M.P., C. S., and S.W. are employees of Morphotek Inc. IP is a coinventor on patents describing antibodies to mesothelin that are owned by the NIH and licensed to Morphotek Inc.

Grant Support

This research was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research, and in part by Morphotek, Inc., under a Cooperative Research and Development Agreement with National Cancer Institute.

Received 08/24/2010; revised 10/14/2010; accepted 10/18/2010; published OnlineFirst 10/29/2010.

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Published OnlineFirst October 29, 2010; DOI: 10.1158/1078-0432.CCR-10-2275

Clinical Cancer Research

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Clin Cancer Res 2010;16:6132-6138. Published OnlineFirst October 29, 2010.