Clinical Cancer Research

Farletuzumab, a Humanized Monoclonal Antibody against Folate Receptor α, in Epithelial Ovarian Cancer: a Phase I Study

Jason A. Konner[1], Katherine M. Bell-McGuinn[1], Paul Sabbatini[1], Martee L. Hensley[1], William P. Tew[1], Neeta Pandit-Taskar[2], Nicholas Vander Els[3,4], Martin D. Phillips[6], Charles Schweizer[6], Susan C. Weil[6], Steven M. Larson[2], and Lloyd J. Old[5]

Abstract

Purpose: Folate receptor α expression is highly restricted in normal adult tissues but upregulated in a wide range of human cancer types, including epithelial ovarian cancer. Farletuzumab, a humanized monoclonal antibody against folate receptor α, has shown antitumor activity and favorable toxicity in preclinical evaluation. This phase I, dose-escalation study was conducted to determine the safety of weekly i.v. farletuzumab and establish the maximum tolerated dose (MTD).

Experimental Design: Patients with platinum-refractory or platinum-resistant epithelial ovarian cancer received farletuzumab (12.5-400 mg/m^2) on days 1, 8, 15, and 22 of a 5-week cycle. Intrapatient dose escalation was not permitted. Dose-limiting toxicity (DLT) was defined by treatment-related adverse event of grade 3 or higher, and the MTD was the highest dose at which one or none of six patients experienced a DLT. Disease progression was recorded using Response Evaluation Criteria in Solid Tumors criteria and serum CA-125.

Results: Twenty-five heavily pretreated patients were included in the safety, efficacy, and pharmacokinetic analyses. No DLTs or MTDs were encountered, and dose escalation was continued to farletuzumab 400 mg/m^2. C_{max} and $AUC_{0\text{-}24}$ (area under the serum concentration-time curve) increased in an approximately dose-proportional manner, and a nuclear imaging substudy confirmed tumor targeting. There were no objective responses. Stable disease by Response Evaluation Criteria in Solid Tumors was observed in nine (36%) patients and CA-125 reduction in four. Three patients received continued therapy and completed a total of up to three cycles.

Conclusions: In this phase I study, farletuzumab administered as an i.v. infusion at doses of 12.5 to 400 mg/m^2 was generally safe and well tolerated in the management of heavily pretreated patients with epithelial ovarian cancer. *Clin Cancer Res; 16(21); 5288–95. ©2010 AACR.*

Epithelial ovarian cancer is the eighth most common cancer and fifth most common cause of cancer deaths among women in the United States (1). First-line, platinum-based chemotherapy achieves clinical remission in most patients with debulked epithelial ovarian cancer (2), but the disease will recur in most. The 5-year survival rate is ~45% (3). Therapies with additional clinical benefits are needed.

Folate receptor α is a membrane-bound protein with high affinity for binding and transporting physiologic levels of folate into cells (4). Folate receptor α expression is upregulated in a range of human cancer types, including ovarian, breast, brain, lung, and colorectal cancers (5, 6). Folate receptor α is upregulated in ~90% of epithelial ovarian cancers and correlates with stage and grade (7). Furthermore, overexpression confers a growth advantage in tumorigenic ovarian cells *in vitro* (8). Consequently, folate receptor α has been identified as a potential therapeutic target.

Monoclonal antibody (mAb) therapy may allow tumor targeting and may enhance immune response to effect tumor kill. Immunohistochemical studies using a folate receptor α-binding murine mAb, LK26, showed highly restricted distribution of folate receptor α in normal tissues but widespread expression on tumor cells, including ovarian and renal tumors (6). The rationale for clinical

Authors' Affiliations: [1]Department of Medicine; [2]Department of Radiology, Nuclear Medicine Service; [3]Pulmonary Service, Memorial Sloan-Kettering Cancer Center; [4]Weill Cornell Medical College; [5]Ludwig Institute for Cancer Research, New York, New York; and [6]Morphotek, Inc., Exton, Pennsylvania

Note: Presented in part at the 42nd (June 2-6, 2006, Atlanta, GA), 43rd (June 1-5, 2007, Chicago, IL), and 44th (May 31-June 3, 2008, Chicago, IL) American Society of Clinical Oncology annual meetings.

Corresponding Author: Jason A. Konner, Department of Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Phone: 212-639-8215; Fax: 212-717-3214; E-mail: konnerj@mskcc.org.

doi: 10.1158/1078-0432.CCR-10-0700

Translational Relevance

Farletuzumab has shown antitumor activity and favorable toxicity in preclinical evaluation. This phase I, dose-escalation study was conducted to determine the safety of weekly i.v. farletuzumab and establish the maximum tolerated dose. We showed that farletuzumab possesses an acceptable toxicity profile and thus may be a disease management option for heavily pretreated patients with epithelial ovarian cancer.

evaluation of anti-folate receptor α mAb therapy was further supported by *in vivo* activity of LK26 in a murine model of human ovarian cancer xenografts (9).

Farletuzumab (MORAb-003; Morphotek, Inc.) is a humanized mAb immunoreactive with folate receptor α. *In vitro*, farletuzumab inhibits folate receptor α-dependent cell growth and mediates tumor cytotoxicity through complement-dependent cytotoxicity and antibody-dependent cytotoxicity (9). In addition, there is evidence that farletuzumab reduces tumor growth through inhibition of folate receptor α-mediated lyn kinase phosphorylation. Immunohistochemistry in human and primate tissues showed identical binding and lack of cross-reactivity of farletuzumab with normal tissue (9). Preclinical evaluation showed an absence of measurable toxicity in primates (9).

The current study on patients with epithelial ovarian cancer is the first clinical study with farletuzumab.

Materials and Methods

Trial objectives

This open-label, dose-escalation study was conducted to determine the safety of multiple i.v. infusions and establish the maximum tolerated dose (MTD) of farletuzumab in patients with platinum-resistant epithelial ovarian cancer. Secondary objectives included determination of serum and *in vivo* pharmacokinetics of farletuzumab, as well as the detection of any human anti-human antibodies. The study was done at a single institution, Memorial Sloan-Kettering Cancer Center.

Drug administration

Farletuzumab was supplied in solution in PBS with 0.01% Tween and administered as a continuous infusion commenced at 1 mg/min and advanced to 5 mg/min as tolerated. Infusion interruption and/or rate reduction and supportive medication were used to manage National Cancer Institute Common Toxicity Criteria grade 1/2 hypersensitivity reactions, but hypersensitivity reactions of grade 3 or higher required treatment discontinuation. Premedication was not given before the first infusion. Premedication with acetaminophen and antihistamines was administered before subsequent infusions in patients experiencing infusion-related hypersensitivity reactions.

At least three patients were enrolled into each sequential cohort and received farletuzumab on days 1, 8, 15, and 22 of a 5-week cycle. Dose escalation followed a modified Fibonacci sequence incorporating the following dose levels: 12.5, 25, 37.5, 62.5, 100, 200, and 400 mg/m^2. Patients with stable disease or better were permitted to continue treatment at the investigator's discretion. Any treatment-related adverse event of grade 3 or higher constituted dose-limiting toxicity (DLT). If DLT was observed within 5 weeks of initiating therapy, up to six patients were to be entered at that dose level. Dose escalation was permitted only after all patients in the cohort had completed the 4 weekly infusions plus 2 weeks' follow-up. Intrapatient dose escalation was not permitted. The MTD was defined as one dose level below which two or more of six patients experienced DLT.

Patient eligibility

Patients were ≥18 years of age with histologically confirmed epithelial ovarian, fallopian, or primary peritoneal carcinoma, and measurable disease evaluable by Response Evaluation Criteria in Solid Tumors (RECIST) or clinical signs/symptoms and an elevated CA-125. Eligible patients must have experienced disease progression within 6 months of last platinum therapy. A Karnofsky performance status of ≥70%, life expectancy of ≥3 months, and adequate hematologic, renal, pulmonary, and hepatic function were required. The protocol received Institutional Review Board approval at Memorial Sloan-Kettering Cancer Center, and all patients were required to provide written informed consent.

Patients were ineligible if they had central nervous system tumor involvement, evidence of other active malignancy, or ascites of ≥500 mL. Patients with active serious systemic disease, including asthma or heart disease, were excluded. Chemotherapy, biological therapy, or immunotherapy within 3 weeks before enrollment, or a history of immune or allergic reaction or documented human anti-human antibodies were also exclusion criteria.

Safety analysis

Safety data were recorded throughout the treatment period and for 2 weeks after the last dose. Potential treatment-related adverse events were monitored for 30 days following the final dose. Adverse events were graded using National Cancer Institute Common Toxicity Criteria version 3.0. Patients underwent complete physical exam and vital sign assessment before each treatment. Pulmonary function testing, chest X-ray, 12-lead electrocardiogram, and 24-hour urine testing were done at screening and final visit. Human anti-human antibody levels were determined at screening, on day 15, and on the final visit.

Pharmacokinetic analysis

On days 1, 8, 15, and 22, blood samples for pharmacokinetic analysis were collected preinfusion, midinfusion, at the end of infusion, and at 0.5, 1, 2, and 4 hours after infusion. Blood samples were also collected

Table 1. Patient demographics

	Dose group (mg/m^2)							
	12.5 (*n* = 3)	25.0 (*n* = 3)	37.5 (*n* = 3)	62.5 (*n* = 3)	100 (*n* = 3)	200 (*n* = 3)	400 (*n* = 7)	Total (*n* = 25)
Median age, years (range)	66 (60-68)	54 (52-61)	51 (47-55)	70 (51-72)	59 (44-79)	61 (54-62)	54 (49-62)	56 (44-79)
Karnofsky performance status, *n* (%)								
90%	0	1	2	2	3	2	5	15 (60)
80%	3	2	1	1	0	1	2	10 (40)
Median time since diagnosis, months (range)	84.7 (75-146)	59.9 (14-69)	93.1 (15-200)	41.9 (40-45)	59.2 (30-114)	62.8 (38-126)	55.2 (10-119)	59.9 (10-200)
Tumor histology, *n* (%)								
Papillary serous	3	3	1	3	2	3	6	21 (84)
Adenocarcinoma	0	0	2	0	1	0	1	4 (16)
Clear cell/mucinous	0	0	0	0	0	0	0	0
Median number of previous chemotherapy regimens (range)	11 (5-18)	3 (2-8)	5 (3-9)	4 (4-5)	7 (6-13)	8 (4-9)	5 (4-9)	5 (2-18)
Previous systemic chemotherapy (%)								
Taxanes	3	3	3	3	3	2	7	25 (100)
Platinum	3	3	3	3	3	3	7	25 (100)
Gemcitabine	3	1	3	3	3	3	6	22 (88)
Topotecan	3	0	1	2	2	3	1	12 (48)
Doxorubicin	3	1	2	3	3	3	6	21 (84)
Vinorelbine	2	0	1	1	2	0	0	6 (24)

24 hours after infusion on days 2 and 23. In addition, a single sample was collected on day 35. Plasma farletuzumab concentrations were determined by enzyme-linked immunosorbent assay.

Plasma concentrations of MORAb-003 were measured to determine standard pharmacokinetic parameters (maximum observed serum concentration, C_{max}; area under the serum concentration-time curve, AUC; time of maximum serum concentration, t_{max}; and terminal half-life, $t_{1/2}$) to assess the pharmacokinetic profile MORAb-003. Biodistribution of MORAb-003 was assessed through imaging.

Radioimaging substudy

Consenting patients received 6 to 8 mCi ^{111}In chelated with 5 mg 1,4,7,10-tetra-azacylododecane (DOTA)-farletuzumab coadministered with cold antibody, and serial blood sampling was done and is further detailed in a previous publication (10).

Table 2. Number (%) of patients experiencing drug hypersensitivity adverse events (all grade 1 adverse events)

	Dose group (mg/m^2)							
	12.5 (*n* = 3)	25.0 (*n* = 3)	37.5 (*n* = 3)	62.5 (*n* = 3)	100 (*n* = 3)	200 (*n* = 3)	400 (*n* = 7)	Total (*n* = 25)
Total events*	3	0	0	2	2	2	6	15
Pyrexia	2[†]	0	0	0	1	2[†]	3	8
Chills	0	0	0	1	0	1	3	5
Headache	0	0	0	0	1	0	1	2
Acneiform dermatitis	1	0	0	0	0	0	0	1
Infusion-related reaction	0	0	0	0	1	0	0	1
Pruritus	0	0	0	1	0	0	0	1

*Preferred terms (i.e., pyrexia, chills etc.) occurring on the same day or the day after a farletuzumab infusion are counted as one occurrence at "Total events" level.

[†]Includes one patient with grade 2 adverse event.

Efficacy analysis

Disease status characterized using RECIST criteria was noted and serum CA-125 measured at the screening and final visits. Computerized tomography was preferred for lesion evaluation, but magnetic resonance imaging or clinical evidence of progression were also acceptable.

Accrual time and statistical analysis

Accrual spanned from June 2005 to June 2007, and the data analysis extended to November 2007. All statistical analyses, summaries, and listings were done using SAS Version 9.1, under Windows 2000 operating system. Pharmacokinetic parameters were derived using noncompartmental methods with WinNonlin Professional Version 5.2 (Pharsight Corp.).

Results

Patients and treatment characteristics

A total of 25 patients received at least one i.v. infusion and were included in the safety, efficacy, and pharmacokinetic analyses. The median age was 56 years (44-79 y), and the median time since diagnosis was 59.9 months (10-200 mo; Table 1). Patients had received a median of five previous systemic cytotoxic chemotherapy regimens (2-18 regimens). Twenty-three patients received at least four doses of farletuzumab (days 1, 8, 15, and 22). The remaining two patients were withdrawn because of clinical disease progression, having received three and two doses of 12.5 and 400 mg/m^2, respectively. The patient in the 400 mg/m^2-dose group was replaced in the cohort. Of the 23 who completed the study, three received continued therapy. One received 12 doses of 400 mg/m^2. Two other patients who exhibited stable disease received eight and seven doses of 100 and 400 mg/m^2, respectively.

Toxicity

No DLTs were encountered, and dose escalation was continued to 400 mg/m^2. A total of 153 adverse events were reported by 25 patients; grade 1/2 treatment-related adverse events (total, 47) were observed in 20 patients (80.0%). There were no serious or severe (grade, ≥3) treatment-related adverse events and no treatment-related myelotoxicity or neurotoxicity. The most common treatment-related adverse events were hypersensitivity reactions (15 patients; 60%), fatigue (12 patients; 48%), and diarrhea (4 patients; 16%). There were no apparent dose-related trends in adverse event frequency or severity and no treatment-related adverse events required treatment discontinuation. Farletuzumab was not associated with clinically significant changes in cardiac, pulmonary, or renal function.

A number of adverse events are commonly associated with infusion of mAb therapies and were considered to be adverse events of interest in the current study. A total of 53 adverse events of interest were reported by 23 patients (92%), the most common of which were fatigue (16 patients; 64%), drug hypersensitivity (15 patients; 60%), headache (5 patients; 20%), and cough and exertional dyspnea (4 patients each; 16%). All were grade 2 or lower, except grade 3 fatigue reported by single patients in the 12.5 and 400 mg/m^2 cohorts.

Hypersensitivity reactions occurring during or following farletuzumab infusion were experienced by 15 (60%) of the 25 patients (Table 2) and readily resolved following acetaminophen and diphenhydramine. The most common hypersensitivity reactions were pyrexia (8 patients; 32%) and chills (5 patients; 20%). All but three hypersensitivity reactions were grade 1. One patient treated at 200 mg/m^2 experienced grade 2 pyrexia during the first infusion, and one patient (with pre-existing Sjögren's syndrome) treated at 12.5 mg/m^2 experienced grade 2 pyrexia during the first infusion, with recurrence during the third infusion despite prophylaxis with acetaminophen and ranitidine. All other hypersensitivity reactions occurred during the first infusion, with the exception of another patient treated at 12.5 mg/m^2, who developed grade 1 acneiform dermatitis at the third infusion and was treated with celecoxib.

Most patients did not exhibit anti–MORAb-003 antibodies at any point, and many of the positive results were close to the assay cutoff point. The assay was sufficiently sensitive to detect 8 ng/mL of control positive antibody. Two patients showed markedly increased human anti-human antibody levels: one at baseline (40 ng/mL) and one on day 15 (37 ng/mL). The patient with elevated human anti-human antibodies at baseline experienced grade 1 hypersensitivity reaction during the first infusion. Premedication prevented hypersensitivity reaction during subsequent infusions, and all subsequent human anti-human antibody samples were negative. The positive value on day 15 for the second patient was an isolated finding. There was no apparent correlation between immunologic adverse events and positive human anti-human antibody results, and patients with positive human anti-human antibody results did not show reduced recovery of administered dose or decreased $t_{1/2}$.

Pharmacokinetics and biodistribution

Mean farletuzumab concentration-time profiles for the seven dose levels at each weekly infusion are presented in Fig. 1. Following the first infusion, the mean C_{max} and $AUC_{0\text{-}24}$ values increased in an approximately dose-proportional manner for the 12.5 to 400 mg/m^2 dose levels, ranging from 6.88 to 287.1 μg/mL for C_{max} and 70.4 to 4,714.3 μg·h/mL for $AUC_{0\text{-}24}$. The mean farletuzumab plasma concentration at the end of the respective infusions also increased in a dose-proportional manner and ranged from 4.70 to 239.3 μg/mL across the range 12.5 to 400 mg/m^2.

The sampling scheme was not optimized for accurate determination of a long half-life and resulted in difficulties observing a well-defined terminal phase in many of the concentration-time profiles. Where estimated, the mean terminal farletuzumab $t_{1/2}$ values are shown in Table 3. The estimated day 22 $t_{1/2}$ values were typically

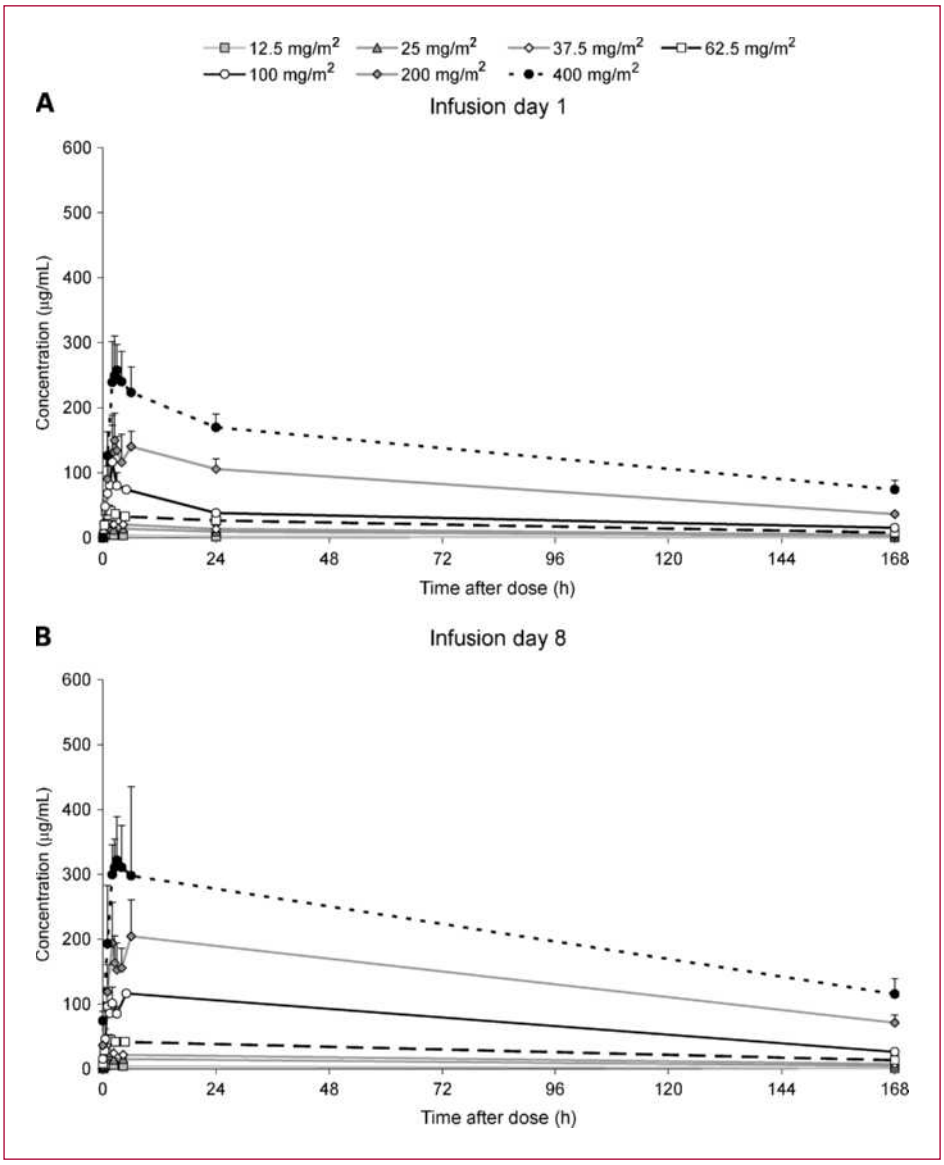

Fig. 1. Mean concentration time profiles following infusion of farletuzumab on days 1, 8, 15, and 22.

higher than the corresponding day 1 estimates across the dose range. Following multiple weekly infusions, the $t_{1/2}$ estimates ranged from 121 to 260 hours, indicating a slow clearance of farletuzumab.

C_{max} and $AUC_{0\text{-}24}$ were plotted against the dose of MORAb-003 administered on a milligram-per-kilogram basis for each subject for the first (day 1) and fourth (day 22) of the weekly infusions. These plots strongly suggest that the pharmacokinetics of MORAb-003 are linear up to the highest doses of ~10 to 12 mg/kg (representing the 400 mg/m^2 dose) evaluated in the current study.

A nuclear imaging substudy supported tumor targeting, and results are reported in a separate manuscript (10). On average, ^{111}In–DOTA–MORAb-003 plasma levels were 46 ± 8 % injected dose/L at the end of infusion, decreasing to 16 ± 2 %ID/L by 5 days postinjection. Maximum lesion uptake was typically observed at 5 days postadministration. Half-life, as measured by the radiolabeled antibody, was similar to that seen with the cold antibody (10).

Antitumor activity

Nine (36%) patients had stable disease, and the remaining 15 patients had progression as the best response according to RECIST. One patient was not evaluable by RECIST. Three of the patients with stable disease were approved by the investigator to receive farletuzumab for up to three total cycles, with mean decreases in target lesion size of 3% to 17% from

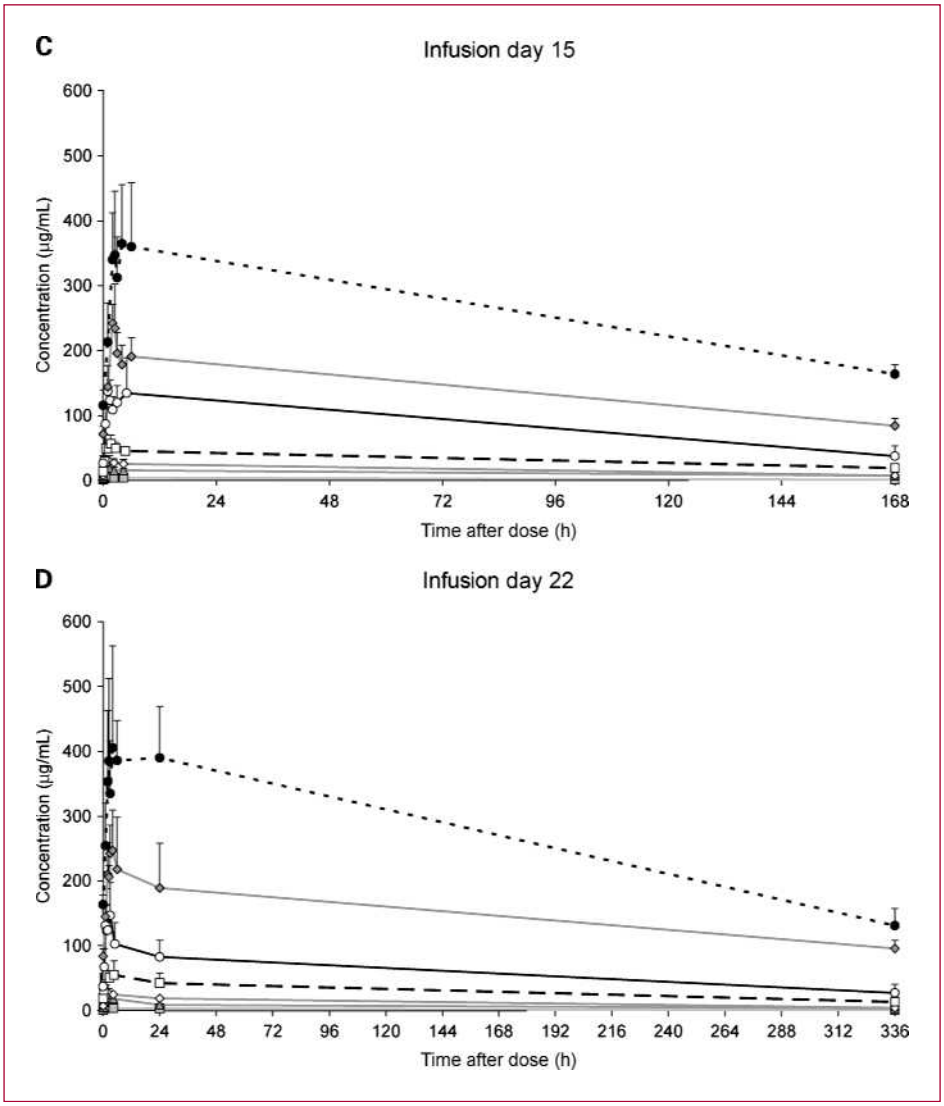

Fig. 1. *Continued.*

baseline to end of cycle 1 noted (after four doses). Declines in CA-125 values were observed in four patients, with one patient, treated for 12 doses in the 400 mg/m^2 cohort, showing a 43% decrease in CA-125, a progressive decline over the first 3 months from 317 to 167. Changes in target lesion size from baseline to final visit were, in general, temporally and directionally associated with changes in CA-125 value.

Table 3. Mean terminal farletuzumab $t_{1/2}$ values (hours) following each infusion

	Dose group (mg/m^2)						
	12.5 (*n* = 3)	25.0 (*n* = 3)	37.5 (*n* = 3)	62.5 (*n* = 3)	100 (*n* = 3)	200 (*n* = 3)	400 (*n* = 7)
Day 1	56.2 [3]	76.3 [3]	77.0 [2]	79.5 [3]	—	97.1 [3]	121.9 [5]*
Day 8	81.8 [1]	86.3 [2]	108.6 [2]	100.2 [3]	92.3 [1]	131.4 [1]	137.3 [1]
Day 15	46.2 [1]	135.1 [3]	90.3 [3]	117.9 [1]	84.1 [1]	135.9 [3]	113.6 [2]
Day 22	120.9 [1]	146.4 [1]	131.9 [2]	135.3 [2]	174.8 [3]	—	260.0 [3]

NOTE: Number of samples are presented in brackets.
*SD = 35.8 hours.

Discussion

Preclinical data support the potential of farletuzumab in epithelial ovarian cancer, having shown tumor-specific binding in immunohistochemical studies and the capacity to mediate several biological responses *in vitro*. Farletuzumab inhibits folate receptor α-dependent cell growth in a dose-dependent manner in folate receptor α-overexpressing hamster cells (9), and farletuzumab-mediated inhibition of ovarian cancer cell growth *in vitro* was associated with antibody-dependent and complement-dependent cytotoxicities. A physical and functional association of folate receptor α with the nonreceptor (cytoplasmic) tyrosine kinase lyn has been shown in coprecipitation assays in the IGROV1 ovarian carcinoma cell line (11). This association was inhibited by the murine antibody LK26. In addition, farletuzumab was shown to inhibit the intracellular association of lyn kinase and folate receptor α (9).

In vivo activity for an anti-folate receptor α strategy was supported by tumor growth inhibition observed with LK26 in a murine model of human ovarian cancer xenografts (9). The female cynomolgus monkey was selected for toxicology studies because it showed a binding specificity nearly identical to humans; farletuzumab showed an absence of measurable toxicity, including monkey anti-human antibody IgG, in this animal model.

In the current study, farletuzumab was generally safe and well tolerated, with no DLT observed up to 400 mg/m^2. Furthermore, no treatment-related adverse events classified as serious or severe (grade, ≥3) were observed and there were no anaphylactoid reactions. Rare samples exhibited human anti-human antibodies, but these did not correlate with adverse events or alterations in pharmacokinetic profile. Immunohistochemistry showed moderate cross- reactivity of farletuzumab with cryosections of lung and kidney tissues; however, despite rigorous evaluation of renal and pulmonary toxicity in the current study, no clinically significant findings were observed.

Folate receptor α is a glycosylphosphatidyl inositol-linked protein that functions as a high affinity folate transporter (12). Folate receptor α is overexpressed in a variety of tumors, including ~90% of ovarian cancers (7). The selective upregulation of folate receptor α on tumor compared with normal tissue suggests folate receptor α as a therapeutic target in epithelial ovarian cancer. Given the high frequency of folate receptor α overexpression in epithelial ovarian cancer, it was not necessary to select patients on the basis of tumor folate receptor α expression for this phase I study. This strategy was further supported by folate receptor α overexpression in recurrent and synchronous metastatic disease consistent with the primary tumor (13).

Hypersensitivity reactions were observed in 15 of 25 patients in the current study; however all were mild (grade, 1 or 2) and easily controlled with antipyretics and/or antihistamines. Nevertheless, to improve the patient experience, it would seem prudent to incorporate nonsteroidal premedication in future studies with farletuzumab.

Systemic exposure to farletuzumab, as assessed by C_{max} and $AUC_{0\text{-}24}$, increased in an approximately dose-proportional manner across the dose range of 12.5 to 400 mg/m^2, following single and multiple weekly infusions. The sampling scheme used in this study provided an estimation of the terminal $t_{1/2}$ of farletuzumab consistent with slow clearance of the drug. The pharmacokinetics of farletuzumab and the biodistribution of the radiolabeled antibody are consistent with other (radiolabeled) humanized/chimeric antibodies (14). While nonspecific binding is possible, previous data suggest that there is specific uptake of this antibody related to antigen binding and retention. Our previous publication using this antibody in animal studies also tested and verified optimal radiolabeling and immunoreactivity of the radiolabeled antibody (10). Animal and *in vitro* data suggested specific uptake and retention in cells of this antibody.

Without MTD or reliable PD marker, a precise recommended phase II dose cannot be determined from this study. Tolerable doses at 400 mg/m^2 correspond roughly to a weight-based dosing of 10 to 12 mg/kg. To better correspond with standard dosing modalities of other mAbs, phase II studies should consider dosing in the range of 2.5 to 10 mg/kg. This study indicates that linear pharmacokinetics is maintained in this range.

An efficacy analysis was not an endpoint of this study. In addition, with only 6 weeks between baseline and endpoint computerized tomographic scans, there was limited opportunity to evaluate progression. It was noted that, after 4 weeks of treatment with farletuzumab, more than one third of patients had radiologically stable disease and that there was a decrease from baseline to final CA-125 level in four patients. Efficacy assessments of farletuzumab are awaited in ongoing phase II trials.

In conclusion, the results of this study show that farletuzumab possesses an acceptable toxicity profile, with expected pharmacokinetics. Ongoing studies on farletuzumab in patients with platinum-sensitive and platinum-resistant disease will further define the role of this agent in epithelial ovarian cancer.

Disclosure of Potential Conflicts of Interest

M.L. Hensley is a consultant/advisory board member of Morphotek, Inc. S.M. Larson is consultant of Amgen, an advisor of Cougar Biotech and Perceptive Informatics, a scientific committee member of ImaginAb, and a scientific advisor of Millenium.

Acknowledgments

We thank Tracy McNally, PhD, and Mary Gaskarth, PhD (Complete Medical Communications), for the assistance in drafting this manuscript; the participating patients for their invaluable contribution; and Peter Smith-Jones (Memorial Sloan-Kettering Cancer Center) for the technical expertise with the radiolabeling studies.

Grant Support

Eisai, Inc.; Morphotek, Inc., a subsidiary of Eisai Corporation of North America; and grants from the Ludwig Center for Cancer Immunotherapy, Sloan-Kettering Institute, and PO1CA033049 (S.M. Larson and N. Pandit-Taskar).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received 03/18/2010; revised 06/02/2010; accepted 06/29/2010; published OnlineFirst 09/20/2010.

References

1. Jemal A, Siegal R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–49.
2. Bukowski RM, Ozols RF, Markman M. The management of recurrent ovarian cancer. Semin Oncol 2007;34:S1–15.
3. Ozols RF. Systemic therapy for ovarian cancer: current status and new treatments. Semin Oncol 2006;33:S3–11.
4. Kelemen LE. The role of folate receptor α in cancer development, progression and treatment: cause, consequence or innocent bystander? Int J Cancer 2006;119:243–50.
5. Ross JF, Chaudhuri PK, Ratnam M. Differential regulation of folate receptor isoforms in normal and malignant tissues *in vivo* and in established cell lines. Physiologic and clinical implications. Cancer 1994;73:2432–43.
6. Garin-Chesa P, Campbell I, Saigo PE, et al. Trophoblast and ovarian cancer antigen LK26. Sensitivity and specificity in immunopathology and molecular identification as a folate-binding protein. Am J Pathol 1993;142:557–67.
7. Toffoli G, Cernigoi C, Russo A, et al. Overexpression of folate binding protein in ovarian cancers. Int J Cancer 1997;74:193–8.
8. Bottero F, Tomassetti A, Canevari S, et al. Gene transfection and expression of the ovarian carcinoma marker folate binding protein on NIH/3T3 cells increases cell growth *in vitro* and *in vivo*. Cancer Res 1993;53:5791–6.
9. Ebel W, Routhier EL, Foley B, et al. Preclinical evaluation of MORAb-003, a humanized monoclonal antibody antagonizing folate receptor-α. Cancer Immun 2007;7:6.
10. Smith-Jones PM, Pandit-Taskar N, Cao W, et al. Preclinical radioimmunotargeting of folate receptor α using the monoclonal antibody conjugate DOTA-MORAb-003. Nucl Med Biol 2008;35:343–51.
11. Miotti S, Bagnoli M, Tomassetti A, et al. Interaction of folate receptor with signaling molecules lyn and G(α)(i-3) in detergent-resistant complexes from the ovary carcinoma cell line IGROV1. J Cell Sci 2000; 113:349–57.
12. Leamon CP, Low PS. Delivery of macromolecules into living cells: a method that exploits folate receptor endocytosis. Proc Natl Acad Sci U S A 1991;88:5572–6.
13. Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor α as a tumor target in epithelial ovarian cancer. Gynecol Oncol 2008;108:619–26.
14. Lear JL, Kasliwal RK, Feyerabend AJ, et al. Improved tumor imaging with radiolabeled monoclonal antibodies by plasma clearance of unbound antibody with anti-antibody column. Radiology 1991;179: 509–12.