Farletuzumab, a Humanized Monoclonal Antibody against Folate Receptor Alpha, 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 Martin D. Phillips,4 Charles Schweizer,4 Susan C. Weil,4 Steven M. Larson,2 and Lloyd J. Old5

1Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY; 2Department of Radiology, Nuclear Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, NY; 3Pulmonary Service, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College, New York, NY; 4Morphotek Inc., Exton, PA; and 5Ludwig Institute for Cancer Research, New York, NY, USA

Corresponding author

Jason A. Konner, M.D.
Department of Medicine
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10065
Tel: 212.639.8215
Fax: 212.717.3214
E-mail: gynbreast@mskcc.org

Running Title: Farletuzumab in EOC: Phase I Study

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**Statement of Translational Relevance:** Farletuzumab has demonstrated anti-tumor activity and favorable toxicity in preclinical evaluation. This phase I dose-escalation study was conducted to determine the safety of weekly intravenous farletuzumab and establish the maximum tolerated dose. We demonstrated that farletuzumab possesses an acceptable toxicity profile and, thus, may be a disease management option for heavily pre-treated patients with Epithelial Ovarian Cancer.
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ABSTRACT

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

Experimental Design: Patients with platinum-refractory or platinum-resistant EOC received farletuzumab (12.5-400 mg/m²) on days 1, 8, 15, and 22 of a 5-week cycle. Intra-patient dose escalation was not permitted. Dose-limiting toxicity (DLT) was defined by treatment-related Adverse Event (AE) ≥Grade 3 and the MTD was the highest dose at which ≤1 of 6 patients experienced a DLT. Disease progression was recorded using RECIST criteria and serum CA-125.

Results: Twenty-five heavily-pretreated patients were included in the safety, efficacy, and PK analyses. No DLTs or MTDs were encountered and dose escalation was continued to farletuzumab 400 mg/m². $C_{\text{max}}$ and AUC$_{0-24}$ increased in an approximately dose-proportional manner and a nuclear imaging substudy confirmed tumor targeting. There were no objective responses. SD by RECIST 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 IV infusion at doses of 12.5 to 400 mg/m² was generally safe and well-tolerated in the management of heavily pretreated patients with EOC.
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INTRODUCTION

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

Folate receptor alpha (FRα) is a membrane-bound protein with high affinity for binding and transporting physiologic levels of folate into cells (4). FRα expression is upregulated in a range of human cancer types, including ovarian, breast, brain, lung, and colorectal cancers (5,6). FRα is upregulated in approximately 90% of EOCs and correlates with stage and grade (7). Furthermore, overexpression confers a growth advantage in tumorigenic ovarian cells in vitro (8). Consequently, FRα 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 utilizing FRα-binding murine mAb, LK26, demonstrated highly restricted distribution of FRα in normal tissues, but widespread expression on tumor cells, including ovarian and renal tumors (6). The rationale for clinical evaluation of anti-FRα mAb therapy was further supported by in vivo activity of LK26 in a murine model of human ovarian cancer xenografts (9).
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Farletuzumab (MORAb-003; Morphotek Inc, Exton, PA, USA) is a humanized mAb immunoreactive with FRα. In vitro, farletuzumab inhibits FRα-dependent cell growth and mediates tumor cytotoxicity via complement-dependent cytotoxicity and antibody-dependent cytotoxicity (9). Additionally, there is evidence that farletuzumab reduces tumor growth via inhibition of FRα-mediated lyn kinase phosphorylation. Immunohistochemistry in human and primate tissues demonstrated identical binding and lack of cross-reactivity of farletuzumab with normal tissue (9). Preclinical evaluation demonstrated an absence of measurable toxicity in primates (9).

The current study, in patients with EOC, 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 intravenous (IV) infusions and establish the maximum tolerated dose (MTD) of farletuzumab in patients with platinum-resistant EOC. Secondary objectives included determination of serum and in vivo pharmacokinetics (PK) of farletuzumab, as well as detection of any human anti-human antibodies (HAHA). The study was performed at a single institution, Memorial Sloan-Kettering Cancer Center (MSKCC).

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**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 (NCI-CTC) Grade 1/2 hypersensitivity reactions (HSRs), but HSRs ≥Grade 3 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 HSRs.

At least 3 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/m². Patients with stable disease (SD) or better were permitted to continue treatment at the investigator’s discretion. Any treatment-related adverse event (TRAE) ≥Grade 3 constituted DLT. If DLT was observed within 5 weeks of initiating therapy, up to 6 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. Intra-patient dose escalation was not permitted. The MTD was defined as one dose level below which 2 or more of 6 patients experienced DLT.
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**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 ≥70%, life expectancy ≥3 months, and adequate hematologic, renal, pulmonary, and hepatic function were required. The protocol received Institutional Review Board approval at MSKCC 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 ≥500 mL. Patients with active serious systemic disease, including asthma or heart disease, were excluded. Chemotherapy, biologic therapy, or immunotherapy within 3 weeks before enrollment, or a history of immune or allergic reaction or documented HAHA were also exclusion criteria.

**Safety Analysis**

Safety data were recorded throughout the treatment period and for 2 weeks after the last dose. Potential TRAEs were monitored for 30 days following the final dose. AEs were graded using NCI-CTC version 3.0. Patients underwent complete physical exam and vital sign assessment before each treatment. Pulmonary function testing, chest X-ray, 12-lead ECG, and 24-hour urine

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testing were performed at screening and final visit. HAHA levels were determined at screening, on day 15, and final visit.

**Pharmacokinetic Analysis**

On days 1, 8, 15, and 22, blood samples for PK analysis were collected pre-infusion, mid-infusion, end of infusion, and 0.5, 1, 2, and 4 hours after infusion. Blood samples were also collected 24 hours after infusion on days 2 and 23. Additionally, 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 PK parameters (maximum observed serum concentration [C<sub>max</sub>], area under the serum concentration-time curve [AUCs], time of maximum serum concentration [t<sub>max</sub>], and terminal half-life [t<sub>1/2</sub>]) to assess the PK profile MORAb-003. Biodistribution of MORAb-003 was assessed via imaging.

**Radio-imaging substudy**
Consenting patients received 6-8 mCi $^{111}$In chelated with 5 mg DOTA-farletuzumab coadministered with cold antibody, and serial blood sampling was performed, and is further detailed in a prior publication (10).

**Efficacy Analysis**

Disease status characterized using RECIST criteria was noted and serum CA-125 measured at the screening and final visits. Computerized tomography (CT) 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 performed using SAS Version 9.1, under Windows 2000 operating system. PK parameters were derived using non-compartmental methods with WinNonlin Professional Version 5.2 (Pharsight Corp, Mountain View, CA).
RESULTS

Patients and Treatment Characteristics

A total of 25 patients received at least one IV infusion and were included in the safety, efficacy, and PK analyses. The median age was 56 years (44-79) and the median time since diagnosis was 59.9 months (10-200) (Table 1). Patients had received a median of 5 prior systemic cytotoxic chemotherapy regimens (2-18). Twenty-three patients received at least 4 doses of farletuzumab (days 1, 8, 15, and 22). The remaining 2 patients were withdrawn due to clinical disease progression, having received 3 and 2 doses of 12.5 and 400 mg/m², respectively. The patient in the 400 mg/m² dose group was replaced in the cohort. Of the 23 who completed the study, 3 received continued therapy. One received 12 doses of 400 mg/m². Two other patients who exhibited SD received 8 and 7 doses of 100 and 400 mg/m², respectively.

Toxicity

No DLTs were encountered and dose escalation was continued to 400 mg/m². A total of 153 AEs were reported by 25 patients; Grade 1/2 TRAEs (47 total) were observed in 20 patients (80.0%). There were no serious or severe (≥Grade 3) TRAEs and no treatment-related myelotoxicity or neurotoxicity. The most common TRAEs were HSRs (15 patients; 60%), fatigue (12 patients; 48%), and diarrhea (4 patients; 16%). There were no apparent dose-related trends in AE frequency or severity and no TRAEs required treatment discontinuation. Farletuzumab was not associated with clinically significant changes in cardiac, pulmonary, or renal function.
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A number of AEs are commonly associated with infusion of mAb therapies and were considered to be AEs of interest in the current study. A total of 53 AEs 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 \( \leq \) Grade 2, except Grade 3 fatigue reported by single patients in the 12.5 and 400 mg/m\(^2\) cohorts.

HSRs 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 HSRs were pyrexia (8 patients; 32%) and chills (5 patients; 20%). All but 3 HSRs 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 HSRs 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 cut-off point. The assay was sufficiently sensitive to detect 8 ng/ml of control positive antibody. Two patients demonstrated markedly increased HAHA levels; one at baseline (40 ng/mL), and one on day 15 (37 ng/mL). The patient with elevated HAHA at baseline experienced a Grade 1 HSR during the first infusion. Premedication
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Prevented HSR during subsequent infusions and all subsequent HAHA samples were negative. The positive value on day 15 for the second patient was an isolated finding. There was no apparent correlation between immunologic AEs and positive HAHA results, and patients with positive HAHA results did not demonstrate reduced recovery of administered dose or decreased $t_{1/2}$.

**Pharmacokinetics and Biodistribution**

Mean farletuzumab concentration-time profiles for the 7 dose levels at each weekly infusion are presented in Figure 1. Following the first infusion, the mean $C_{\text{max}}$ and $AUC_{0-24}$ values increased in an approximately dose-proportional manner for the 12.5 to 400 mg/m² dose levels, ranging from 6.88 to 287.1 $\mu$g/mL for $C_{\text{max}}$ and 70.4 to 4714.3 $\mu$g·hr/mL for $AUC_{0-24}$. 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 $\mu$g/mL across the range 12.5 to 400 mg/m².

The sampling scheme was not optimized for accurate determination of a long half-life, and resulted in difficulties observing a well-defined terminal phase to 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 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.
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Both $C_{\text{max}}$ and $AUC_{(0-24)}$ were plotted against the dose of MORAb-003 administered on a mg/kg basis for each subject for the first (Day 1) and fourth (Day 22) of the weekly infusions. These plots strongly suggest that the PK of MORAb-003 are linear up to the highest doses of approximately 10-12 mg/kg (representing the 400-mg/m$^2$ dose) evaluated in the current study.

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

**Anti-tumor Activity**

Nine (36%) patients had SD, 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 SD were approved by the investigator to receive farletuzumab for up to 3 total cycles, with mean decreases in target lesion size of 3% to 17% from baseline to end of cycle 1 noted (after 4 doses). Declines in CA-125 values were observed in 4 patients, with 1 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.
DISCUSSION

Preclinical data support the potential of farletuzumab in EOC, having demonstrated tumor-specific binding in immunohistochemical studies and the capacity to mediate several biological responses \textit{in vitro}. Farletuzumab inhibits FRα-dependent cell growth in a dose-dependent manner in FRα-overexpressing hamster cells (9), and farletuzumab-mediated inhibition of ovarian cancer cell growth \textit{in vitro} was associated with both antibody-dependent and complement-dependent cytotoxicity. A physical and functional association of FRα with the non-receptor (cytoplasmic) tyrosine kinase lyn has been demonstrated in coprecipitation assays in the IGROV1 ovarian carcinoma cell line (11). This association was inhibited by the murine antibody LK26. Additionally, farletuzumab was shown to inhibit the intracellular association of lyn kinase and FRα (9).

\textit{In vivo} activity for an anti-FRα 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 demonstrated a binding specificity nearly identical to humans; farletuzumab demonstrated 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/m². Furthermore, no TRAEs classified as serious or severe (≥Grade 3)
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were observed and there were no anaphylactoid reactions. Rare samples exhibited HAHA, but these did not correlate with AEs or alterations in PK profile. Immunohistochemistry demonstrated 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.

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

HSRs 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, in order to improve the patient experience, it would seem prudent to incorporate non-steroidal premedication in future studies with farletuzumab.

Systemic exposure to farletuzumab, as assessed by both \( C_{\text{max}} \) and \( \text{AUC}_{0-24} \), increased in an approximately dose-proportional manner across the dose range of 12.5 to 400 mg/m\(^2\), following both single and multiple weekly infusions. The sampling scheme employed in this
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study provided an estimation of the terminal $t_{1/2}$ of farletuzumab consistent with slow clearance of the drug. The PK of farletuzumab and the biodistribution of the radiolabeled antibody are consistent with other (radiolabeled) humanized/chimeric antibodies (14). While nonspecific binding is possible, prior data suggest that there is specific uptake of this antibody related to antigen binding and retention. Our prior 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 2 dose cannot be determined from this study. Tolerable doses at 400 mg/m² correspond roughly to a weight-based dosing of 10-12 mg/kg. In order to better correspond with standard dosing modalities of other monoclonal antibodies, phase 2 studies should consider dosing in the range of 2.5-10 mg/kg. This study indicates linear PK 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 CT 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 SD 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 demonstrate that farletuzumab possesses an acceptable toxicity profile, with expected PK. Ongoing studies of farletuzumab in patients with
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platinum-sensitive and platinum-resistant disease will further define the role of this agent in EOC.
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REFERENCES


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FIGURE LEGENDS

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

Some data from this study have previously been presented in poster format at the 42nd (June 2-6 2006; Atlanta, GE), 43rd (June 1-5 2007; Chicago, IL) and 44th (May 31-June 3 2008; Chicago, IL) American Society of Clinical Oncology annual meetings.

ACKNOWLEDGEMENTS

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Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Dose group (mg/m²)</th>
<th>Median age, years (range)</th>
<th>Karnofsky performance status, n (%)</th>
<th>Median time since diagnosis, months (range)</th>
<th>Tumor histology, n (%)</th>
<th>Median number of prior chemotherapy regimens (range)</th>
<th>Prior systemic chemotherapy (%)</th>
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<td>12.5 (n=3)</td>
<td>66 (60-68)</td>
<td>90% (0)</td>
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<td>Papillary serous 3/3  Adenocarcinoma 3/3  Clear cell/mucinous 0/0</td>
<td>11 (5-18)</td>
<td>Taxanes 3/3  Platinum 3/3  Gemcitabine 3/3  Topotecan 3/3  Doxorubicin 3/3  Vinorelbine 2/0</td>
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<td>5 (4-9)</td>
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<td>59.9 (10-200)</td>
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<td>5 (2-18)</td>
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<table>
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<th>62.5 (n=3)</th>
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*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 AE.
**Table 3.** Mean terminal farletuzumab $t_1/2$ values (hours) following each infusion. Number of samples presented in brackets.

<table>
<thead>
<tr>
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<th>Day 8</th>
<th>Day 15</th>
<th>Day 22</th>
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<td>121.9 [5]*</td>
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<td>113.6 [2]</td>
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*SD=35.8 hours
Figure 1

Mean (+SD) concentration-time profiles following infusion of farletuzumab on Days 1, 8, 5 and 22.

A) Infusion Day 1

B) Infusion Day 8
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Farletuzumab, a Humanized Monoclonal Antibody against Folate Receptor Alpha, in Epithelial Ovarian Cancer: A Phase I Study

Jason Konner, Katherine Bell-McGuinn, Paul J Sabbatini, et al.

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