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A Supplement to

COMMUNITY ONCOLOGY

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Farletuzumab (MORAb-003) in platinum-sensitive ovarian cancer patients experiencing a first relapse

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As for many solid tumors, major advances in the treatment of ovarian cancer are more likely to be made through the introduction of novel targeted approaches rather than by manipulating cytotoxic chemotherapy regimens. Farletuzumab is a monoclonal antibody that binds to and blocks the function of folate receptor alpha, which is expressed in at least 90% of ovarian cancer patients. In platinum-sensitive patients experiencing the first relapse of their disease, farletuzumab enhances CA-125 responses as well as tumor response, as determined by RECIST criteria, compared with historic controls. Farletuzumab therefore represents a promising candidate for evaluation in phase III trials. The FAR-131 study is a multicenter, double-blind, randomized, placebo-controlled trial examining the safety and efficacy of two dose levels of farletuzumab in combination with carboplatin and a taxane in patients with platinum-sensitive ovarian cancer in first relapse. The primary endpoint is progression-free survival; the effects of this combination on overall survival, CA-125 response, duration of second remission, and quality of life are among the secondary objectives of this study.

Ovarian cancer is the ninth most common cancer and ranks fifth among all causes of cancer death in women in the United States. The lifetime risk of developing invasive ovarian cancer is about 1 in 71, and a woman's chances of dying from it are 1 in 95.[1] There are no established means of preventing or screening for ovarian cancer. As a result, over 70% of patients will have advanced disease at the time of diagnosis.

Advanced ovarian cancer is highly sensitive to chemotherapy. Response rates of 70%–80% are observed when platinum-containing agents and taxanes are used as first-line treatment. Unfortunately, the majority of patients relapse. Those who respond well to initial chemotherapy and develop a recurrence 6 months or more after treatment are more likely to be platinum-sensitive and have an increased response to retreatment with a platinum-containing regimen. The longer the relapse-free interval, the greater the chance of responding to second-line therapy. Unfortunately, recurrent disease, while treatable, is not curable. Thus, long-term disease stabilization is an

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Commun Oncol 2010;7(suppl 1):1–4

Resources

- FAR-Trials: www.far-trials.com
- Coalition of Cancer Cooperative Groups: www.CancerTrialsHelp.org
- National Cancer Institute: www.cancer.gov/clinicaltrials
- National Ovarian Cancer Coalition: www.ovarian.org/clinical_trials.php
- Ovarian Cancer National Alliance: www.ovariancancer.org/clinical-trials

important goal in recurrent ovarian cancer. There is a clear need for novel approaches to achieve this. Monoclonal antibody therapy represents such a promising new approach.

What is farletuzumab?

Farletuzumab (MORAb-003) is a humanized monoclonal antibody to folate receptor alpha (FRA). FRA is overexpressed in at least 90% of epithelial ovarian cancers, including primary peritoneal and fallopian tube malignancies. The degree of FRA expression correlates with the malignant potential of the cancer, and overexpression confers growth advantages to tumorigenic cells in vitro.

Farletuzumab inhibits phosphorylation of proteins by the Lyn kinase (a member of the src family of kinases) and inhibits the growth of FRA-expressing cells under low-folate conditions. Xenograft studies have shown a synergistic effect when farletuzumab is combined with taxanes, and the combination is effective against cells with either high or low FRA expression.[2]

Early clinical data

In a dose-finding study of 25 platinum-resistant patients with advanced epithelial ovarian cancer,[3] patients received weekly infusions of farletuzumab at 12.5, 25, 37.5, 62.5, 100, 200, or 400 mg/m^2. No dose-limiting toxicities or drug-related serious or severe adverse events or trends were observed.

Twenty patients (80%) reported a total of 47 adverse events that were considered related to study treatment. The majority of these adverse events were grade 1, and there were no drug-related grade 3, 4, or 5 toxicities. Adverse events of interest in the study included drug hypersensitivity (16 grade 1; 3 grade 2), fatigue (11 grade 1; 5 grade 2), dyspnea upon exertion (7 grade 1), headache and cough (each 4 grade 1). No patients discontinued treatment due to a drug-related adverse event or died during the study.

Disease stabilization was observed in seven patients, along with a reduction in serum CA-125 levels in four patients, after one cycle (4 weeks) of treatment with farletuzumab. Three patients in this trial received a tracer dose of ^{111}In-labeled farletuzumab, and significant tumor uptake was observed on SPECT-CT and planar imaging.

Based on these encouraging data, Armstrong and colleagues conducted an exploratory phase II study of farletuzumab among platinum-sensitive patients with epithelial ovarian cancer who experienced their first relapse after an initial remission of 6–18 months. Preliminary results from this study were presented at the 2009 Joint European Cancer Organization (ECCO) and European Society for Medical Oncology (ESMO) Congress in Berlin.[4]

The study aimed to determine the efficacy of farletuzumab as a single agent or in combination with a platinum/taxane regimen. Patients who had an elevated CA-125 serum level without clinical symptoms received single-agent farletuzumab until disease progression occurred. Those who experienced symptomatic relapse or disease progression on single-agent farletuzumab were then retreated with a platinum/taxane regimen plus farletuzumab for six cycles. Those who attained a complete or partial response on farletuzumab continued on single-agent farletuzumab for maintenance.

Farletuzumab was dosed at 100 mg/m^2 weekly in both arms of the study. Patients in the combination arm also received carboplatin (AUC 5–6) plus paclitaxel (175 mg/m^2) or docetaxel (Taxotere; 75 mg/m^2) every 21 days. Endpoints were CA-125 response, duration of second response compared with first response, tumor response as determined by RECIST (Response Evaluation Criteria in Solid Tumors) criteria, and safety.

The study enrolled 58 patients with platinum-sensitive recurrent disease who had received carboplatin and a taxane first-line. The mean age of the patients was 63 years, mean length of first progression-free interval (measured from beginning of initial chemotherapy to recurrence) was 15.5 months (range, 6.3–29.7 months), and duration of remission (measured from completion of initial chemotherapy to study registration) was 6–12 months (31.5%), 12–18 months (37.0%), or 18+ months (31.5%).

Of the 58 patients enrolled, 54 were eligible for the study; 28 entered the single-agent arm and 26 entered the combination arm. Of the 28 single-agent patients, 25 completed at least 9 weeks of treatment with farletuzumab, and 6 remained on the single agent for 16–32 weeks. CA-125 responses at week 7 (day 43) for patients receiving 9 weeks or more of treatment with farletuzumab were as follows: 1 decreased > 75%; 1 decreased > 50%; 3 decreased > 25%; 13 unchanged; 6 increased; 1 untested.

For the six patients who remained on treatment for 16–32 weeks, CA-125 responses decreased in three and were unchanged in three. Seven of the 28 patients receiving single-agent farletuzumab stopped treatment, and 21 crossed over to the combination.

Altogether, 47 patients ultimately received the combination therapy, and 44 were evaluable for response to treatment with the carboplatin/taxane regimen plus farletuzumab. Of these patients, 39 (88.6%) achieved normal CA-125 levels. Nine (20.5%) had a second progression-free inter-

val that was longer than their first remission. Of the 39 responders, 4 are still on study with ongoing responses. Five of the 44 evaluable patients in the combination arm (11.4%) did not experience a reduction in their serum CA-125 levels to normal levels, but 3 of these 5 achieved a CA-125 response by Rustin criteria.

By RECIST criteria, the objective response rate to combination therapy was 69.8%, with stable disease seen in an additional 23.2%, yielding a clinical benefit rate of 93.0%. The median progression-free interval for the total group was 13 months. Disease stabilization was achieved in 38.5% on farletuzumab as a single agent.

Farletuzumab alone and in combination was well tolerated. Infusion reactions were infrequent and were limited to grades 1 and 2 that were well controlled by antipyretics and antihistamines. No additional toxicity was observed by combining farletuzumab with platinum/taxane chemotherapy. Five serious adverse events were observed in three patients, including wound dehiscence, sub-ileus (incomplete intestinal obstruction), peripheral occlusive disease, cytokine release syndrome, and embolectomy. Eight grade 3 events occurred in five patients receiving single-agent farletuzumab, including headache, abdominal complaints as part of progression, peripheral occlusive disease, bronchitis, and Herpes zoster infection. Among the 26 patients receiving combination therapy, eight grade 3 events occurred in four patients, including diarrhea and neutropenia.

Rationale for a phase III study

Initial response rates are high among patients with advanced ovarian cancer to first-line platinum-containing doublets after surgical resection, but this success is typically followed by relapse in most patients. There is clearly an unmet need for treatments that are effective in the recurrent ovarian cancer setting—especially when they offer patients a disease progression-free interval that is at least as long as their first remission.

TABLE 1

Key eligibility criteria for Morphotek study FAR-131

Inclusion criteria

- 18 years of age or older
- Histologically or cytologically confirmed diagnosis of non-mucinous epithelial ovarian cancer (including primary peritoneal and fallopian tube malignancies)
- Previously treated with surgery and first-line platinum and taxane-based chemotherapy (prior intraperitoneal therapy permissible)
- In first relapse after a remission of ≥ 6 and ≤ 24 months from first-line platinum/taxane-based chemotherapy, as defined by the presence of measurable disease on CT or MRI
- Candidate for repeat carboplatin/taxane therapy
- Life expectancy of ≥ 6 months, as estimated by the investigator
- Other significant medical conditions well controlled and stable for at least 30 days prior to study day 1
- Karnofsky performance status ≥ 70%
- Sensory and motor neuropathy ≤ CTCAE grade 1

Exclusion criteria

- Lack of response to first-line platinum-based therapy or first relapse < 6 months or > 24 months from last treatment with platinum-based chemotherapy
- Treatment with other ovarian cancer therapy following relapse
- Central nervous system tumor involvement
- Evidence of other active invasive malignancy requiring treatment in the past 5 years
- Allergic reaction to prior monoclonal antibody therapy or documented HAHA response
- Previous treatment with farletuzumab
- Clinical contraindications to use of a taxane

CT = computed tomography; MRI = magnetic resonance imaging; CTCAE = Common Terminology Criteria for Adverse Events; HAHA = human anti-human antibody

In a 2004 report of 176 women with recurrent ovarian cancer, Markman et al[5] showed that retreatment with a platinum-based regimen yielded CA-125 responses in 59%, ranging from 33% in patients who relapsed less than 12 months after initial treatment to 75% in those with relapsed 18 months or later.

Only 3% of secondary responses were of longer duration than the prior response to first-line therapy in a specific patient. In contrast, in the phase II farletuzumab study, normalization of CA-125 levels was observed in 88% of patients, and 20% experienced a progression-free interval at least as long as their first one.[4]

Farletuzumab has the potential to be an effective and safe agent, either alone or in combination with chemotherapy, with little toxicity observed in phase I and II trials. Results of a phase II study indicated the drug in combination with conventional platinum/taxane chemotherapy can achieve a second remission and prolong a second response to chemotherapy. A large randomized phase III trial is necessary to further confirm these encouraging results. If positive, data from this study may lead to the addition of this novel targeted agent in relapsed platinum-sensitive ovarian cancer.

How will this study be conducted?

FAR-131 is a multicenter, double-blind, randomized, parallel-group study of two dose levels of farletuzumab in combination with carboplatin and a taxane. The study, which is currently recruiting patients, aims to enroll approximately 900 patients from 300 sites in North America, Europe, South America, Australia/New

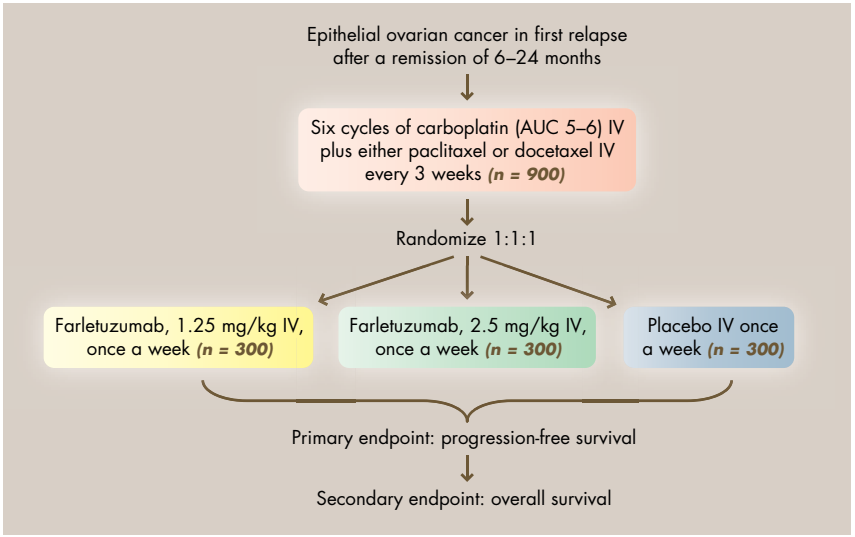

FIGURE 1 Treatment schema of Morphotek study FAR-131

Zealand, and Asia. The key eligibility criteria are shown in Table 1.

Enrolled patients will be entered into three parallel groups (farletuzumab 1.25 mg/kg, farletuzumab 2.5 mg/kg, or placebo) in a 1:1:1 ratio. Randomization will be stratified by (1) length of first remission (6 to less than 12 months, 12 to less than 18 months, or 18–24 months), (2) route of administration for first-line therapy (intraperitoneal vs intravenous), (3) planned taxane therapy (paclitaxel vs docetaxel), and (4) geographic region (North America and Western Europe vs other participating countries).

Patients will receive standard therapy for relapsed platinum-sensitive disease, consisting of six cycles of carboplatin (AUC 5–6) IV and either paclitaxel or docetaxel IV every 3 weeks (Figure 1). Patients may discontinue study treatment for intolerable toxicity or disease progression. To attain a more complete response, additional cycles of chemotherapy may be given at the judgment of the investigator. In addition, patients will be randomized to weekly IV infusions of farletuzumab, 1.25 mg/kg or 2.5 mg/kg, or placebo. If chemotherapy is discontinued for reasons other than progression, the patient may continue on single-agent farletuzumab or placebo until disease progression.

Following completion of carboplatin/taxane therapy, maintenance treatment with weekly single-agent farletuzumab or placebo will continue in 3-week cycles until disease progression. The study duration will be 65 months, including 12–17 months of treatment and follow-up for assessment of survival. The primary analysis for progression-free survival is event-driven and is expected to be conducted after at least 13 months of follow-up.

Secondary objectives of this study include assessment of the safety or tolerability of weekly doses of 1.25 or 2.5 mg/kg of farletuzumab in combination with carboplatin/taxane chemotherapy and the effects of farletuzumab on overall survival, CA-125–defined progression-free survival and serologic response (Rustin criteria), length of second remission versus that of first remission, tumor response (RECIST criteria), patient quality of life, and resource utilization. Subanalyses of the study data will assess the effects of concomitant chemotherapy on farletuzumab pharmacokinetics and examine genomic DNA, serum, and archived tumor tissue to identify molecular markers as a surrogate for immunotherapy response.

Enrolling patients

Community oncologists are encouraged to enroll patients in this study. They can obtain more information by reviewing a description of the trial on the National Institute of Health's clinical trials Web site, www.ClinicalTrials.gov (ClinicalTrials.gov identifier NCT00849667) or contacting the study sponsor, Susan Weil, MD, FACP, Morphotek, Inc., 210 Welsh Poor Road, Exton, PA 19341; telephone: 610-423-6182; e-mail: weil@morphotek.com. A complete list of study locations is available at www.ClinicalTrials.gov.[6]

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Conflicts of interest: Dr. Armstrong has provided consultative services for Morphotek, the sponsor of this study. The Johns Hopkins Kimmel Cancer Center received research support from Morphotek, the sponsor of this study.