Profile of farletuzumab and its potential in the treatment of solid tumors

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Abstract: Folate receptor (FR) α expression in normal tissues is restricted to a subpopulation of epithelial cells. In contrast, FRα is overexpressed in epithelial ovarian cancer (EOC) and non-small-cell lung carcinoma. Therefore, FRα is considered a promising therapeutic target for EOC and non-small-cell lung carcinoma. Farletuzumab (MORAb-003) is a humanized monoclonal antibody of immunoglobulin G subtype 1 kappa, targeting human FRα. To date, Phase I/II clinical trials have clearly demonstrated the feasibility and safety of farletuzumab as a treatment option against solid tumors. However, in Phase III clinical trial that was conducted to verify the combined effect of paclitaxel–carboplatin combination therapy and farletuzumab for patients with recurrent EOC, improvement in progression-free survival was not statistically significant. This result might be owing to the fact that the eligibility criteria for these studies did not include FRα expression. The significance of FRα as a predictive/prognostic biomarker remains unclear. In addition, there is currently no established biomarker to predict the response and toxicities among patients receiving farletuzumab therapy. Furthermore, the primary mechanism of action of farletuzumab has not yet been identified. Therefore, further research to identify the mechanism of farletuzumab in tumor suppression is necessary to clarify the full potential of this chemotherapeutic agent.

Keywords: immunoglobulin G subtype 1 kappa, folate receptor α, monoclonal antibody, targeted therapy, epithelial ovarian cancer, non-small-cell lung carcinoma

Introduction

DNA synthesis in cancer cells is highly dependent on folate, whereas folate receptor (FR) α expression in normal tissues is restricted to a subpopulation of epithelial cells. In contrast, FRα is overexpressed in nearly 90% of epithelial non-mucinous ovarian cancers and has been correlated with tumor stage and grade, chemotherapeutic response, and treatment outcome. In addition, FRα expression is retained in recurrent tumors and metastatic lesions. Among lung cancers, FRα expression is increased in non-small-cell lung carcinoma (NSCLC) and is higher in adenocarcinomas than in squamous cell carcinomas. Hence, FRα is considered a promising therapeutic target for epithelial ovarian cancer (EOC) and NSCLC.

Farletuzumab (MORAb-003), a humanized monoclonal antibody of immunoglobulin G subtype 1 kappa that targets human FRα, was derived by optimizing the FRα-binding murine antibody LK26, which has high affinity for FRα. A profile of farletuzumab is summarized in Table 1. Farletuzumab is considered to induce immune-dependent cell death, although no underlying mechanism has yet been clarified. Farletuzumab has shown efficacy in both preclinical and clinical studies as a single agent and in combination chemotherapy with minimal drug-specific toxicity. However, no improvement in progression-free survival (PFS) was observed in Phase III clinical
trials that were conducted to verify the combined effect of cytotoxic drugs and farletuzumab. This result might be because the eligibility criteria for these study did not include FRα expression. Hence, there is a need for appropriate patient selection based on predictive biomarkers to clarify the potential of FRα expression in the clinical setting. In this review, we describe preclinical and clinical data related to farletuzumab and update recent findings.

**Preclinical data on farletuzumab**

An in vitro study found that farletuzumab did not inhibit binding of folic acid and antifolates to FRα and that it had no significant effect on cell growth or folate uptake via FRα. The proposed mechanism of farletuzumab-induced cell toxicity shown in Figure 1 suggests that farletuzumab inhibits FRα-dependent cell growth in a dose-dependent manner and exhibits tumor cytotoxicity through complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity. Farletuzumab has also been shown to inhibit the interaction between cytoplasmic tyrosine kinase Lyn and

**Table 1** Profile of farletuzumab

| Development code | MORAb-003 |
|------------------|-----------|
| Target           | Folate receptor α |
| Drug class       | Humanized monoclonal antibody |
| Molecular weight | 145 kDa |
| Immunoglobulin (Ig) | IgG1/κ |
| Mechanism        | Antibody-dependent cellular cytotoxicity |
|                   | Complement-dependent cytotoxicity |
|                   | Inhibition of interaction between FRα and Lyn kinase |
|                   | Induces cell death associated with autophagy |
| Administration   | Intravenous injection |
| Recommended dose | 2.5–10 mg/kg |
| Cmax             | 6.88–287.1 μg/mL |
| Half-life        | 121–260 hours (estimated) |
| Common adverse events | |
| Hypersensitivity reactions | 60% |
| Pyrexia          | 32% |
| Chills           | 20% |
| Headache         | 8% |
| Fatigue          | 48% |
| Diarrhea         | 16% |

**Notes:** All events were grade 1 or 2.

**Abbreviations:** FRα, folate receptor α; Cmax, peak plasma concentration of a drug after administration.

**Figure 1** Schema of the mechanism of farletuzumab-induced cell toxicity.

**Notes:** Farletuzumab mediates tumor cytotoxicity through ADCC and CDC. Farletuzumab was also shown to inhibit the intracellular association of Lyn kinase and folate receptor α, thereby reducing the growth advantage of these cells. Furthermore, farletuzumab inhibited tumor growth via induction of autophagy-associated cell death.

**Abbreviations:** ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity.
membrane-signaling complexes; this results in a reduction in the growth of these cells. 

A recent preclinical study, which found that farletuzumab inhibited tumor growth via induction of autophagy-associated cell death, demonstrated this inhibitory effect in three-dimensional in vitro models and showed that farletuzumab reduced tumor cell proliferation but had no significant effect on apoptosis, suggesting that blockade of FRα by farletuzumab induced sustained autophagy and suppressed cell proliferation.

Clinical data on ovarian cancer

Among gynecological malignancies, EOC is the most difficult to cure. Although >80% of patients respond to paclitaxel–carboplatin combination therapy, most will relapse. Because the prognosis of advanced EOC remains poor, new agents are urgently needed to improve treatment outcome. Toward this goal, farletuzumab is currently among the most promising drugs for EOC, as evidenced in several clinical trials.

Phase I studies

MORAb-003-001 (NCT00428766)

In this Phase I dose-escalation study, farletuzumab was intravenously administered to 25 patients with platinum-refractory or platinum-resistant EOC to assess the safety of weekly administration of 12.5–400 mg/m² on days 1, 8, 15, and 22 and to determine the maximum tolerated dose. Drug efficacy was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) and by monitoring serum cancer antigen (CA) 125 levels and evaluating pharmacokinetics of the drug. Because there was no dose-limiting toxicity, which is defined by the occurrence of grade ≥3 treatment-related adverse events (AEs), maximum tolerated dose was not determined. Therefore, a recommended dosage was not determined in this study. Given that 400 mg/m² substantially corresponds to a weight-based dosing of 10–12 mg/kg, a dosage of 2.5–10 mg/kg was adopted in a Phase II clinical trial.

Although AEs were generally mild, grade 1/2 treatment-related AEs were observed in 20 patients (80.0%); however, there were no severe (grade ≥3) treatment-related AEs. The most common treatment-related AEs and drug hypersensitivity AEs are shown in Table 1. Drug hypersensitivity reactions were mild and managed with antipyretics and/or antihistamines. Efficacy was assessed at 4 weeks after cessation of treatment. No objective responses were observed. Of the 24 surviving patients who were included in this trial, stable disease was observed in nine (36%) and disease progression was observed in 15 (60%), while decreased CA125 levels were observed in four (17%). A population pharmacokinetic analysis revealed that body weight was the only investigated covariate, which explained inter-patient variability in disease clearance and central volume of distribution.

MORAb-003-005 (NCT01004380)

This Phase I study evaluated the safety of combination therapy with farletuzumab, carboplatin, and pegylated liposomal doxorubicin (PLD) in subjects with platinum-sensitive EOC. In this study, 15 patients who relapsed after >6 months after the completion of first- or second-line platinum-based chemotherapy were enrolled. All patients received six cycles of carboplatin (area under the curve [AUC] of 5–6) and PLD (30 mg/m²) on day 1 of every 4-week combination treatment cycle. The patients also received weekly intravenous injections of farletuzumab at 2.5 mg/kg. Following the completion of carboplatin/PLD/farletuzumab therapy, maintenance treatment with 7.5 mg/kg farletuzumab was administered triweekly until disease progression. Among this cohort, there were no severe AEs, although anemia was observed in 14 (93%) patients; moreover, fatigue and hand–foot syndrome were observed in eight patients (53%). No increase in the incidence of side effects associated with the combination of farletuzumab and cytotoxic drugs was observed. Further clinical trials on the efficacy of this regimen are expected.

NCT01049061

This Phase I study assessed the safety and tolerability of farletuzumab among Japanese patients with solid tumors that express FRα. Pharmacokinetic profiles were also examined. Sixteen patients (14 with EOC and two with gastric cancer) were enrolled in this study. Farletuzumab (50, 100, 200, and 400 mg/m²) was intravenously administered weekly until tumor progression. No dose-limiting toxicity was observed among the study participants, and there were no severe AEs. Grade 1/2 infusion-related reactions were observed in 15 (93.8%) patients, and decreased CA125 levels were observed in seven (43.8%). Furthermore, nausea and appetite loss were observed in five (31.3%) patients, respectively. Pharmacokinetic profiles in this study were similar to those in previous reports. Together, these results suggest that farletuzumab is also well tolerated by Japanese patients.

Phase II studies

MORAb-003-002 (NCT00318370)

This Phase II study evaluated the efficacy of farletuzumab treatment alone and in combination with chemotherapy,
which consists of taxane and platinum, in patients with platinum-sensitive relapsed EOC. For six cycles over a 21-day interval, 54 evaluable patients received weekly farletuzumab alone or in combination with chemotherapy, followed by weekly doses of farletuzumab maintenance until disease progression. The primary end points were normalization of CA125 levels and overall response rate. A serologic response (change in CA125) was defined using the modified Gynecologic Cancer Intergroup (GCIG) criteria. Furthermore, the interval of secondary responses was compared with the duration of the first response.

Of the 54 patients enrolled in this study, 47 (87%) received combination chemotherapy. In 38 (70%) patients, CA125 levels normalized after six cycles of combination therapy. Forty-three (80%) patients were evaluated based on RECIST. In these patients, the overall response rate was 70% (complete response, 7%; partial response, 63%). Notably, a second remission that was longer than their first remission was observed in nine (21%) of 44 evaluable patients. Furthermore, the response rate was high among patients with a first progression-free interval of <12 months. The results of this study suggested that farletuzumab combined with standard chemotherapy improves the response rate and progression-free interval in platinum-sensitive EOC patients.

**MORAb-003-011 (NCT02289950)**

This Phase II global, multicenter, double-blind, randomized, placebo-controlled study is underway to assess the safety and efficacy of farletuzumab in platinum-sensitive subjects in their first relapse with high-grade serous EOC and low CA125 levels. In this trial involving a target enrollment of 210 patients, weekly farletuzumab at a dosage of 5 mg/kg is being compared with a placebo in combination with chemotherapy (carboplatin + paclitaxel or carboplatin + PLD). The primary end point is PFS based on RECIST, and secondary endpoints are overall survival (OS), length of first vs second platinum-free interval, and tumor response.

**Phase III studies**

**MORAb-003-003 (NCT00738699)**

This Phase III randomized, placebo-controlled trial assessed the efficacy and safety of farletuzumab in combination with weekly paclitaxel in patients with platinum-resistant recurrent or refractory EOC (Table 2) to determine whether paclitaxel is more efficacious when administered alone or in combination with farletuzumab. The primary end point was 2-year PFS. This study was terminated early after recruiting 417 patients because the study did not meet the prespecified criteria for continuation following interim futility analysis.

**MORAb-003-004 (NCT00849667)**

This Phase III randomized, double-blind, placebo-controlled trial compared the efficacy and safety of six cycles of carboplatin and taxane (paclitaxel or docetaxel) with and without weekly farletuzumab in patients with a first platinum-sensitive relapse of EOC (Table 2). A total of 1,100 women were randomized to the following three arms: 1.25 mg/kg farletuzumab plus combination therapy, 2.5 mg/kg farletuzumab plus combination therapy, 2.5 mg/kg farletuzumab plus combination therapy, and Placebo plus taxane/CBDCA. The primary end point was 2-year PFS. This study was terminated early after recruiting 417 patients because the study did not meet the prespecified criteria for continuation following interim futility analysis.

**Table 2 Characteristics of Phase III trial of farletuzumab for non-mucinous ovarian cancer including primary peritoneal or fallopian tube malignancies**

| Identifier | NCT00738699 | NCT00849667 |
|------------|-------------|-------------|
| Confirmation of FR | None | None |
| Patient group | Platinum-resistant, a relapse or refractory | Platinum-sensitive, b first relapse |
| Age: >18 years | Age: >18 years |
| Pretreated with debulking surgery and at least one line platinum-based chemotherapy | Pretreated with debulking surgery and first-line platinum- and taxane-based chemotherapy |
| Measurable disease or elevated CA125 (2×ULN) | Measurable disease |
| Enrollment | 412 | 1,100 |
| Interventions | Arm 1: 2.5 mg/kg farletuzumab plus PTX | Arm 1: 1.25 mg/kg farletuzumab plus taxane/CBDCA |
| Arm 2: Placebo plus PTX | Arm 2: 2.5 mg/kg farletuzumab plus taxane/CBDCA |
| Arm 3: Placebo plus taxane/CBDCA | Arm 3: Placebo plus taxane/CBDCA |
| Primary end point | PFS, OS | PFS |
| Results summary | This study was terminated due to the study not meeting the prespecified criteria | No statistical difference |

**Notes:** aRelapse occurs within 6 months after most recent platinum-based chemotherapy. bRelapse occurs between ≥6 and <24 months from the last platinum-based chemotherapy.

**Abbreviations:** FR, folate receptor; CA, cancer antigen; ULN, upper limit of normal; PTX, paclitaxel; CBDCA, carboplatin; PFS, progression-free survival; OS, overall survival.
Farletuzumab in the treatment of solid tumors

Clinic data on lung cancer

Lung cancer is a leading cause of cancer-related death worldwide.\textsuperscript{29,30} NSCLC constitutes \textasciitilde 85\% of lung cancers, and the median OS of patients with untreated advanced NSCLC is \textasciitilde 6 months. Furthermore, the 1-year OS rate is 10\% at best.\textsuperscript{31} Thus, effective treatment for these patients is urgently needed.

A meta-analysis to verify the effectiveness of cytotoxic chemotherapy containing cisplatin for advanced NSCLC showed that platinum-based chemotherapy reduced the risk of mortality in these patients and improved symptom control and quality of life.\textsuperscript{32} However, the effect of chemotherapy remains insufficient. In recent years, targeted therapies using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and anaplastic lymphoma kinase (ALK) inhibitors have continued to attract attention. For example, the EGFR tyrosine kinase inhibitor gefitinib prolonged PFS in patients with NSCLC having \textit{EGFR} mutations as compared with paclitaxel–carboplatin combination therapy.\textsuperscript{33} However, \textit{EFGR} mutations and translocations involving ALK only occur in 13\% and 5\% of patients with NSCLC, respectively.\textsuperscript{34} Thus, an alternative therapeutic target is essential for improving the prognosis of patients with advanced NSCLC.

Similar to ovarian cancer, FR\alpha expression is relatively higher in NSCLC tissues than in normal lung tissue. In addition, expression of FR\alpha in lung adenocarcinoma is higher than that in squamous cell carcinoma.\textsuperscript{5,35,36} Furthermore, some studies have revealed that \textit{FOLR1} expression is also relatively higher in lung adenocarcinoma.\textsuperscript{37–39} These characteristics have become the rationale for developing a targeted therapy that is efficacious against NSCLC with mild AEs. Therefore, farletuzumab is expected to be a new treatment option against NSCLC.

Based on the aforementioned preclinical data and safety profile of farletuzumab in combination with carboplatin–taxane doublet against EOC, a Phase II study involving patients with metastatic adenocarcinoma of the lung with FR\alpha-expressing tumors was conducted.\textsuperscript{NCT01218516}

This Phase II, double-blind, placebo-controlled study evaluated the efficacy of farletuzumab in patients with FR\alpha-positive metastatic adenocarcinoma of the lung. Importantly, in all patients, FR\alpha expression of resected tumors was confirmed by immunohistochemistry using an antihuman FR monoclonal antibody. The primary end point was PFS, and the secondary end point was OS. Farletuzumab at a dose of 7.5 mg/kg was combined with a platinum-containing doublet in chemonaive patients. The following platinum-based regimens were allowed: carboplatin (AUC of 6) and paclitaxel (200 mg/m\textsuperscript{2}), carboplatin (AUC of 5) and pemetrexed (500 mg/m\textsuperscript{2}), and cisplatin (75 mg/m\textsuperscript{2}) and pemetrexed (500 mg/m\textsuperscript{2}). Four to six cycles of combination chemotherapy were administered on a triweekly schedule. Patients who achieve objective tumor shrinkage after combination therapy will receive maintenance therapy with a placebo or 7.5 mg/kg of farletuzumab every 3 weeks until documented disease progression. The target enrollment of a total of 130 patients has already been reached. However, the results of this study were not available at the time that this manuscript was submitted for publication. Therefore, at present, the clinical evidence is insufficient to establish the efficacy of farletuzumab for the treatment of NSCLC.

Discussion

Past clinical trials revealed that farletuzumab exhibited certain antitumor effects with slight side effects, as described earlier. However, the effectiveness of farletuzumab alone for cancer treatment remains insufficient. To realize the actual potential of farletuzumab, appropriate patient selection based on appropriate biomarkers and combination therapy with other agents is important (Figure 2).

Selecting appropriate patients through biomarker screening will facilitate the improvement of patient outcomes and decrease the degree of toxicity.\textsuperscript{40} We already confirmed FR\alpha expression of malignant tumors in the clinical setting.\textsuperscript{5,42} However, the significance of FR\alpha as a predictive/prognostic biomarker remains unclear,\textsuperscript{2} and the primary mechanism of action of farletuzumab has not yet been identified. The mechanisms of antitumor effects of monoclonal antibody therapy are believed to involve direct tumor targeting and indirect...
effects by enhancing immune responses. Farletuzumab exhibits tumor cytotoxicity mediated by antibody-dependent cellular cytotoxicity and CDC rather than blocking FRα-mediated folate transport. A recent in vitro study showed that farletuzumab enhanced type 2 cell death of tumor cells due to late-stage autophagy. Hence, this mechanism may be considered the primary action of farletuzumab. However, the effectiveness of farletuzumab to increase autophagy of tumor cells is unpredictable. In other words, there is currently no biomarker to predict the effectiveness of treatment. Therefore, further studies are needed to identify the underlying mechanisms involved in the antitumor effects of farletuzumab.

Proliferation of cancer cells is not necessarily dependent on a single pathway. When cancer cells are exposed to an anticancer agent, they acquire resistance through a variety of bypass pathways. In lung cancer, interactions between FRα expression and other molecular characteristics including EGFR mutation and ALK rearrangement, which are targets for treatment of lung cancer, are unclear. Hence, additional research to further elucidate the molecular biological mechanisms of the folate-related pathway is necessary. Bronte et al suggested that combination therapy, consisting of farletuzumab and pemetrexed, may have a synergic effect because both drugs target the folate pathway. However, worsening of AEs remains a concern. From the viewpoint of side effects, anticancer drugs, targeting molecules that are not associated with the folate pathway, for use in combination with farletuzumab are preferred. To this end, the combined effect of docetaxel and farletuzumab was confirmed in a recent in vitro study. Based on these outcomes, future clinical applications for treating EOC and NSCLC are expected.

**Conclusion**

Phase I/II clinical trials clearly demonstrated the feasibility and safety of farletuzumab as a treatment option against solid tumors. In contrast, a Phase III clinical trial that was conducted to verify the effect of paclitaxel–carboplatin therapy combined with farletuzumab for patients with recurrent EOC found that improvement in PFS was not statistically significant, which might be due to the fact that the eligibility criteria for this study did not include FRα expression. The significance of FRα as a predictive/prognostic biomarker remains unclear. In addition, at present, there is no biomarker to predict the response and toxicities of patients treated with farletuzumab. Furthermore, the primary mechanism of action of farletuzumab has not yet been identified. Therefore, further research to discern the underlying mechanism of farletuzumab in tumor suppression is necessary to clarify the full potential of this chemotherapeutic agent.

**Disclosure**

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