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Role of Farletuzumab in Epithelial Ovarian Carcinoma

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Abstract

Epithelial ovarian cancer (EOC) is the most lethal of the gynecologic malignancies, largely due to the advanced stage at diagnosis in most patients. Standard treatment for EOC is surgical debulking followed by platinum-based chemotherapy. While the majority of ovarian cancer patients will respond to initial chemotherapy, most will ultimately relapse. The major focus of current clinical trials for treatment of recurrent ovarian cancer is the use of targeted biologic agents.

Folate receptor alpha (FR α) is upregulated in majority of EOC and correlated with tumor stage and grade. It is hypothesized that the presence of overexpressed FR α correlates with the propagation rate of the tumors. FR α is largely absent from normal tissue, making it an attractive therapeutic target. Farletuzumab (MORAb-003), a humanized monoclonal antibody against FR α , has shown antitumor activity in preclinical xenograft models. A Phase 1 dose escalation study did not demonstrate dose-limiting toxicities, or severe adverse effects. A phase 2 efficacy and safety study of farletuzumab with carboplatin and taxane in patients with platinum-sensitive EOC in first relapse, have shown an improved response rate and time to progression compared with historical controls. Recently, preliminary safety data from a phase 1 trial reported that the combination of farletuzumab, carboplatin and PLD has an acceptable safety profile in patients with platinum-sensitive EOC following first or second relapse.

Two randomized, double-blind, placebo-controlled Phase 3 studies with farletuzumab plus chemotherapy have been done. A trial of: farletuzumab with weekly paclitaxel in platinum-resistant EOC closed in December 2011 with full report pending. A second trial of farletuzumab with carboplatin and taxane in platinum-sensitive EOC in first relapse is slated to complete accrual in early 2012. Results from these trials will help define the role of farletuzumab in EOC.

Keywords

farletuzumab; epithelial ovarian cancer

INTRODUCTION

In the United States ovarian cancer is the second most frequent invasive malignancy of the female genital tract after cancers of the uterine corpus, with an estimated 21,880 cases annually. Approximately 75% of women with ovarian carcinoma present with stage III or IV disease and 13,850 women die each year from ovarian cancer, representing the most

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

common cause of death among women with gynecologic malignancies [1]. Epithelial ovarian cancers (EOC) account for nearly 90% of all ovarian malignancies

While the initial response rates to cytoreductive surgery and platinum based chemotherapy are good, the vast majority of women with advanced ovarian cancer relapse at a median of 11-65 months. Even patients who relapse late and respond completely to secondline therapy will have a second remission that is shorter than the first in more than 95% of cases [2]. Thus, developing agents that may achieve long-term disease stabilization may provide significant benefit for patients with recurrent EOC.

Folate, a basic component of cell metabolism and DNA synthesis and repair, is an essential vitamin required by both normal and tumor cells [3]. Folate receptors are glycosyl-phosphatidyl-inositol-linked membrane proteins of 38–40 kDa that preferentially bind to oxidized folates [4]. Three isoforms of folate receptors have been identified, and each of them has tissue-specific distribution and folate-binding potential [4]. The α -isoform is the most widely studied and has restricted expression in normal cells, but is highly-expressed in various non-mucinous tumors of epithelial origin, including ovarian carcinoma [5]. Folate receptor alpha (FR α) binds folic acid with high affinity and transports folate by receptor-mediated endocytosis. FR α is distinct from the bulk folate carrier and is not in the pathway of cellular metabolism of folic acid, a vitamin necessary for DNA synthesis and cellular homeostasis. FR is over expressed in virtually all EOC, including primary peritoneal and fallopian tube malignancies but largely absent from normal tissue making it attractive therapeutic target [6, 7]. The increasing levels of tissue α -FR were noted, when the tumor progressed from early to advanced stages [8]. Additionally, expression of FR is maintained in metastatic foci and recurrent tumors, and the degree of FR α expression has been associated with aggressiveness of tumor [9, 10]. Cells which express FR α have been shown to grow in presence of low folate concentrations [11], and have growth advantages *in vivo* and *in vitro* when compared with cells without FR α [12]. Furthermore, intracellular expression of singlechain antibodies (intrabody) to down-modulate membrane expression of FR α result in inhibition of cells growth [13]. Those data indicate that FR α overexpression may be associated with EOC cell proliferation, and by providing efficient blocking of FR α , cancer cells may be selectively inhibited without toxic effects on normal cells. Restricted distribution of FR α in normal tissues and its high expression in EOC, along with its putative role in tumor cell transformation, make this antigen a suitable target for antigen-specific, monoclonal antibody-based immunotherapy.

Farletuzumab is 145kDa a humanized immunoglobulin G (IgG1 κ) monoclonal antibody (mAb) produced in Chinese hamster ovary cells that targets humane FR α . Farletuzumab, initially identified as MORAb-003, was developed by Morphotek, Inc., from the optimization of the murine LK26 antibody using a whole cell genetic evolution platform [14]. After optimization MORAb-003 showed similar affinity to the original murine LK26 antibody, and a tissue binding profile consistent with distribution of FR α [10, 15].

PRECLINICAL DATA

Preclinical *in vitro* studies have shown that MORAb-003 was effective in inhibiting growth of cells that express FR α [16]. Farletuzumab has been shown to have immune anti-tumor activity via: the antibody-dependant fixation of complement factors and their induction of cell lysis (CDC), and antibody opsonization of tumor cells followed by the recruitment of immune killer cells which can illicit cell-mediated cytotoxicity (ADCC) [16]. Binding of farletuzumab to FR α can prevent phosphorylation of substrates specific for Lyn kinase [17], suppress proliferation of cells expressing FR α and tumor growth *in vivo* of FR α - expressing tumors in xenograft models and mediate FR α -positive tumor cell killing.

To explore the potential anti-tumor effect of FR targeting *in vivo*, murine LK26 antibody (precursor of farletuzumab) was employed to treat nude mice bearing SKOV3 ovarian tumor xenografts. Murine mAb was chosen assuming that effector functions in mouse are better mediated by a murine antibody rather than by its humanized version. Mice were treated with LK26 at 0.1mg/dose intravenously (IV) three times weekly for 4 weeks beginning on Day 1 after tumor cells inoculation. After 4 weeks, animals treated with LK26 had significant reduction (62%) of tumor growth compared to vehicle control ($p<0.05$) [16].

Immunohistochemistry studies determined almost identical binding of farletuzumab to tubular epithelium, epithelium of the fallopian tube, and duct epithelium of the pancreas in humans and cynomolgus monkey tissue, making cynomolgus monkeys a relevant model for human toxicology. MORAb-003 was administered to cynomolgus monkeys in non-clinical safety studies: dose escalating study, a high-dose tolerance study, a 28-day repeat dose study with a 28-day recovery period, and 24-week repeat dose study. There were no specific toxicities identified related to MORAb-003 up to a total dose of 136.8mg/kg over 28 days. The findings of a 24-week study were similar. As expected, splenomegaly was observed since hyperplasia of the lymphoid zone of the spleen is a known effect of injection of antigenic or immune stimulant due to foreign protein. The lack of toxicity was explained by the fact that normal tissues, unlike tumors, do not overexpress FR α . In monkey toxicology studies, MORAb was measurable in serum up to 4 weeks after the last infusion with a half-life of over 200 hours [16].

In murine xenografts bearing FR α -expressing ovarian tumors, MORAb-003 in combination with docetaxel demonstrated synergistic activity in reducing tumor growth [18].

With encouraging preclinical data, clinical trials with MORAb-003 were initiated. Results from a phase 1 dose escalation study of farletuzumab in platinum-resistant EOC patients (MORAb-003-001), and a phase 2 study of farletuzumab in combination with carboplatin and taxane in platinum-sensitive patients in first relapse (MORAb-003-002) have been reported recently [19, 20]. A phase 1 safety study of farletuzumab in combination with carboplatin and pegylated liposomal doxorubicin in patients with platinum-sensitive EOC (MORAb-003-005) is closed and preliminary safety data were reported [21]. At present, two Phase 3 trials with farletuzumab are ongoing: farletuzumab with weekly paclitaxel in platinum-resistant EOC (MORAb-003-003), and farletuzumab in combination with carboplatin and taxane in subjects with platinum-sensitive EOC in first relapse (MORAb-003-004).

CLINICAL DATA

MORAb-003-001

Results of single institution, Phase 1 dose escalation study in 25 heavily pretreated patients with platinum-resistant EOC were recently reported [19]. The median patient age was 56 years (44-79y), median time since diagnosis was 59.9 months (10-200 months), and patients received median of five previous cytotoxic chemotherapy regimens (2-18 regimens). Primary objective was to determine safety of farletuzumab and establish maximum tolerated dose (MTD). Secondary objective was to determine serum and *in vivo* pharmacokinetics of farletuzumab, as well as the detection of any human anti-human antibodies.

In this dose escalation study, 3 patients were dosed sequentially in dose cohorts 12.5, 25, 37.5, 62.5, 100, and 200 mg/m², and 7 patients at 400 mg/m². Drug was administered IV on days 1, 8, 15, and 22 of a five week cycle. Safety data were recorded throughout the treatment period and for 2 weeks after the last dose. Potential treatment-related adverse events (AEs) were monitored for 30 days following the last dose of farletuzumab. Most

patients (23 of 25) received at least four weekly doses of farletuzumab. The remaining two patients had clinical disease progression and were withdrawn from the trial. No dose-limiting toxicities were observed and the maximum tolerated dose was not encountered at a dose of 400mg/m² [19]. A total of 153 AEs were reported by 25 patients. Twenty patients (80.0%) experienced a total of 47 AEs, grade 1 or 2 that were considered related to administration of study drug. There were no serious or severe drug-related AEs (Grade >3) and no treatment related myelotoxicity or neurotoxicity observed. The most common treatment related AEs were hypersensitivity reactions (15 patients; 60%), fatigue (12 patients; 48%), and diarrhea (4 patients; 16%) [19].

Immunologic symptoms are commonly associated with administration of a monoclonal antibody. Those AEs that reflect immunologic symptoms were classified as adverse events of interest (AEIs) in this study. Among the 53 AEIs reported by 23 patients (92%), the most frequently reported were fatigue (16 patients; 64%), drug hypersensitivity (15 patients; 60%), headache (5 patients; 20%), and cough and exertional dyspnea (4 patients each; 16%). Drug hypersensitivity reactions that occurred no more than 2 days following a farletuzumab infusion were experienced by 15 (60%) of 25 patients, however all were mild (grade 1 or 2) and easily controlled with antipyretics and/or antihistamines. The most commonly reported drug hypersensitivity adverse events (DHAEs) were pyrexia (8 patients; 32%) and chills (5 patients; 20%). Other DHAEs reported were headache, acneiform dermatitis, infusion related reaction, and pruritus. 12 out of 15 hypersensitivity reactions were grade 1. Drug hypersensitivity reactions occurred following farletuzumab doses of 12.5 mg/m² (3 of 3 subjects), 62.5 mg/m² (2 of 3 subjects), 100 mg/m² (2 of 3 subjects), 200 mg/m² (2 of 3 subjects), and 400 mg/m² (6 of 7 subjects), and the majority of hypersensitivity reactions occurred during first infusion of the drug [19]. No subjects had treatment discontinued due to a drug-related AE or died during the study.

Human antihuman antibodies (HAHA) and pharmacokinetic (PK) analyses were performed. Most patients did not exhibit anti MORAb-003 antibodies at any point. Markedly increased levels of HAHA were observed in two patients (one at baseline and one on day 15). The patient with elevated HAHA at baseline experienced hypersensitivity reaction with first dose of farletuzumab. Premedication prevented hypersensitivity with subsequent infusions. The sampling scheme used in the study was not optimized for accurate determination of half-life, but provided an estimation of the terminal half-life of farletuzumab. The mean terminal half-life estimates from samples taken on day 22 ranged from 120 to 260 hours, consistent with slow clearance of the drug [19].

Although, efficacy was not an endpoint of the study, disease status was characterized using Response Evaluation Criteria in Solid Tumors (RECIST) criteria and serum cancer antigen 125 (CA-125) was measured at screening and final visit. Following 4 weeks of treatment, 9 patients (36%) demonstrated stable disease, and 15 patients had progression of disease based on RECIST. Three of the patients with stable disease were given farletuzumab as extended therapy, based on the response seen after 1 cycle for up to 3 cycles. Decline in CA-125 was observed in 4 patients [19].

Without MTD a precise recommendation of dose for phase 2 trial could not be determined. Tolerable dose of 400mg/m² established in the Phase 1 study of farletuzumab correspond to dosing of 10-12 mg/kg. In order to better correspond with standard dosing of other mAb, it was recommended that dosing for Phase 2 trial should be in range 2.5 to 10 mg/kg.

MORAb-003-002

An open-label, multicenter Phase 2 study was conducted in platinum sensitive EOC patients in first relapse in order to determine the efficacy of farletuzumab as a single agent or in

combination with platinum and taxane [20]. All patients had received treatment with a platinum and taxane regimen as frontline therapy. A total of 58 patients experiencing first platinum-sensitive EOC relapse occurring 6 to 18 months after completion of initial therapy were enrolled, and 54 of these 58 patients were considered evaluable for response.

Asymptomatic patients with rising CA-125 received single agent farletuzumab until disease progression. Symptomatic patients or those who progressed on single agent farletuzumab received combination of carboplatin, paclitaxel and farletuzumab. Patients received weekly doses of farletuzumab alone or with the chemotherapy. Chemotherapy was administered every 21 days for six cycles. This was followed by weekly farletuzumab maintenance until disease progression. The first six patients received farletuzumab at a dose of 37.5 mg/m², the second six patients received 67.5 mg/m² and the remainder of enrolled patients received 100 mg/m² (approximately 1 to 2.5 mg/kg). Normalization of CA-125, a biomarker used to assess disease progression and objective response rate was the primary endpoint of the study. In addition, the duration of each patients second response was compared to her own first response duration.

Of 54 evaluable patients, 28 were enrolled in single agent farletuzumab arm, and 25 of 28 patients completed at least 9 weeks of single agent treatment. Single agent farletuzumab decreased CA-125 in 2 out of 25 patients and stabilized CA-125 in an additional 8 patients. Eventually, 21 out of 28 patients initially treated with single agent continued on to combination therapy. Of 54 patients, 26 received combination therapy from the beginning of study. Including the 21 patients that initially received single agent farletuzumab, a total of 47 patients received combination therapy; 44 of them were evaluable for response. In 39 of the 44 evaluable patients (89%) CA-125 normalized after 6 cycles of combined therapy, and all went on maintenance weekly farletuzumab. Interestingly, 9 of 44 evaluable patients (21%) had second remission longer than their first remission. Out of 44 patients, 43 were available for response evaluation based on RECIST and Gynecologic Cancer Intergroup (GCIg) criteria. Complete response was found in 3 patients (7%), and partial response in 27 patients (63%), resulting in 70% overall response rate (ORR). Additionally, 23% of patients had stable disease, and only 7% had progression of disease. Unexpectedly high response rates were noticed among the subset of patients with a first progression-free interval of less than 12 months, and was comparable to response rates of patients with a first progression-free interval of longer than 12 months [20]. Results from this trial showed that farletuzumab with and after chemotherapy increases ORR and duration of second interval compared to historical outcomes.

Farletuzumab alone and in combination with standard chemotherapy therapy was generally well tolerated by most patients. About 40% of patients reported at least one DHAE, with pyrexia being the most common occurring in 17 patients (31%). The most frequent SAEs were febrile neutropenia, thrombocytopenia, abdominal pain, diarrhea, large intestinal obstruction, subileus, urosepsis, and hyperglycemia (2 patients; 3.7% each). No patients died during active treatment with MORAb-003. No additive toxicity was observed with prolonged use of farletuzumab, as single-agent or in combination with platinum-based chemotherapy [20].

MORAb 003-003

One of the more promising recent developments was the demonstration that single agent paclitaxel administered weekly can offer an overall response rate of about 21%, with a median duration of remission of 3 months, even in patients who have previously received taxane therapy [22]. Morphotek conducted a multinational, randomized, placebo-controlled trial of weekly paclitaxel with and without farletuzumab in platinum-resistant recurrent ovarian cancer patients. This study was designed to determine if farletuzumab in

combination with taxane chemotherapy improves progression-free and overall survival compared to taxane therapy alone in patients with platinum-resistant disease. This study closed in December 2011 when an interim analysis indicated that it was unlikely to produce a statistically significant difference in the two arms. We await a full report from this trial.

MORAb-003-004

This phase 3 randomized, double-blind, placebo-controlled, study was designed to assess the efficacy and safety of weekly farletuzumab in combination with carboplatin and taxane in patients with platinum-sensitive ovarian cancer in first relapse 6-24 months after completion of initial platinum regimen. Eligible patients are randomized to one of 3 arms: placebo plus carboplatin/taxane, farletuzumab at 1.25 mg/kg plus carboplatin/taxane, or farletuzumab at 2.5 mg/kg plus carboplatin/taxane. Completion of the planned 900 patients is expected in the first quarter of 2012. No interim efficacy results have been reported.

MORAb-003-005

Recently published results of the CALYPSO trial showed that pegylated liposomal doxorubicin (PLD) plus carboplatin was superior to combination of carboplatin and paclitaxel regarding progression free survival (11.3 vs 9.4 months; $P=0.005$) in platinum-sensitive relapsed ovarian cancer [23]. More myelo-suppression, mucositis and hand-foot syndrome was seen in patients treated with carboplatin/PLD, and more alopecia, neuropathy, and hypersensitivity/allergic reactions in patients treated with carboplatin/paclitaxel. Overall there were fewer drug-related adverse events and less early termination of therapy in the carboplatin/PLD arm. An open-label, multicenter, Phase 1 study was designed to assess the safety of weekly farletuzumab in combination with carboplatin and PLD in patients with platinum-sensitive ovarian cancer in first or second relapse.

Fifteen enrolled patients were treated with carboplatin/PLD given every 4 weeks along with weekly farletuzumab 2.5 mg/kg IV for 6 cycles, followed by maintenance phase farletuzumab until disease progression. Preliminary safety data have been recently reported [21]. As expected anemia, fatigue and hand-foot syndrome were the most common AEs and occurred in 14 (93%), 8 (53%), and 8 (53%) of patients respectively, and was consistent with toxicity profile of carboplatin/PLD regimen. No grade 4 or 5 toxicity was documented. No clinically significant changes in cardiac ejection fraction were noted. Preliminary data from this study support further investigation into the efficacy of this combination

SUMMARY

Treating patients with ovarian cancer is challenging, and despite the many advances in therapeutic options for this disease, there is a need for novel therapeutic agents that are both effective and well tolerated. Restricted distribution of FR α in normal tissues and its high expression in EOC, along with its putative role in tumor cell transformation, make this antigen a suitable target for antigen-specific, monoclonal antibody-based targeted therapy. Mono-clonal antibody farletuzumab, that targets FR α , has shown safety and efficacy in Phase 1 and 2 trials. While farletuzumab has modest effect as single agent, in combination with platinum-based regimen it has demonstrated increased response rates compared to historical controls. We eagerly await the outcomes from the randomized Phase III clinical trials to define the role of farletuzumab in treatment of epithelial ovarian carcinoma.

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