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ORIGINAL REPORT

A Randomized, Double-Blind, Placebo-Controlled, Phase III Study to Assess Efficacy and Safety of Weekly Farletuzumab in Combination With Carboplatin and Taxane in Patients With Ovarian Cancer in First Platinum-Sensitive Relapse

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ABSTRACT

Purpose

Farletuzumab is a humanized monoclonal antibody that binds to folate receptor-α, which is highly expressed in ovarian carcinoma and largely absent from normal tissue. Farletuzumab was investigated in a double-blind, randomized phase III study in platinum-sensitive ovarian cancer.

Patients and Methods

Eligible patients had first recurrent ovarian cancer 6-24 months following completion of platinum-taxane chemotherapy. All patients received carboplatin plus paclitaxel or docetaxel (for six cycles combined with randomly assigned test products in a 1:1:1 ratio: farletuzumab 1.25 mg/kg, farletuzumab 2.5 mg/kg, or placebo). The single-agent test product was continued weekly until disease progression. The primary end point was progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors. Additional analyses not outlined in the original protocol were prespecified in the final statistical analysis plan, including a subgroup analysis by baseline CA-125 and farletuzumab exposure levels.

Results

A total of 1,100 women were randomly assigned to treatment dose or placebo. PFS from the primary analysis was 9.0, 9.5, and 9.7 months for the placebo, farletuzumab 1.25 mg/kg, and farletuzumab 2.5 mg/kg groups, respectively. Neither farletuzumab group was statistically different from the placebo group (hazard ratio [HR], 0.99 [95% CI, 0.81 to 1.21] and 0.86 [95% CI, 0.70 to 1.06] for farletuzumab 1.25 mg/kg and 2.5 mg/kg group *v* placebo, respectively). In the prespecified subgroup, baseline CA-125 levels not more than three times the upper limit of normal (ULN) correlated with longer PFS (HR, 0.49; $P = .0028$) and overall survival (OS) (HR, 0.44; $P = .0108$) for farletuzumab 2.5 mg/kg versus placebo. Subgroup analysis of farletuzumab exposure above the median, regardless of dose, showed significantly better PFS versus placebo. The most common adverse events were those associated with chemotherapy.

Conclusion

Neither farletuzumab dose met the study's primary PFS end point. Prespecified subgroup analyses demonstrated that patients with CA-125 levels not more than three times the ULN and patients with higher farletuzumab exposure showed superior PFS and OS compared with placebo.

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INTRODUCTION

Ovarian cancer is the leading cause of death among women with gynecologic malignancies, with initial disease presentation often at advanced stages. In 2012, there were an estimated 239,000 new cases of ovarian cancer worldwide, leading to > 140,000 deaths.[1] Farletuzumab is a humanized monoclonal antibody to folate receptor α (FRA), which is expressed in 80% to 100% of epithelial ovarian cancers (EOCs), including primary peritoneal and fallopian tube cancers but is largely absent from normal tissue.[2-4] The expression of FRA is known to relate to the malignant potential of the cancer.[5] The mechanism of action of farletuzumab uses, in part, immune effector activity. This includes both

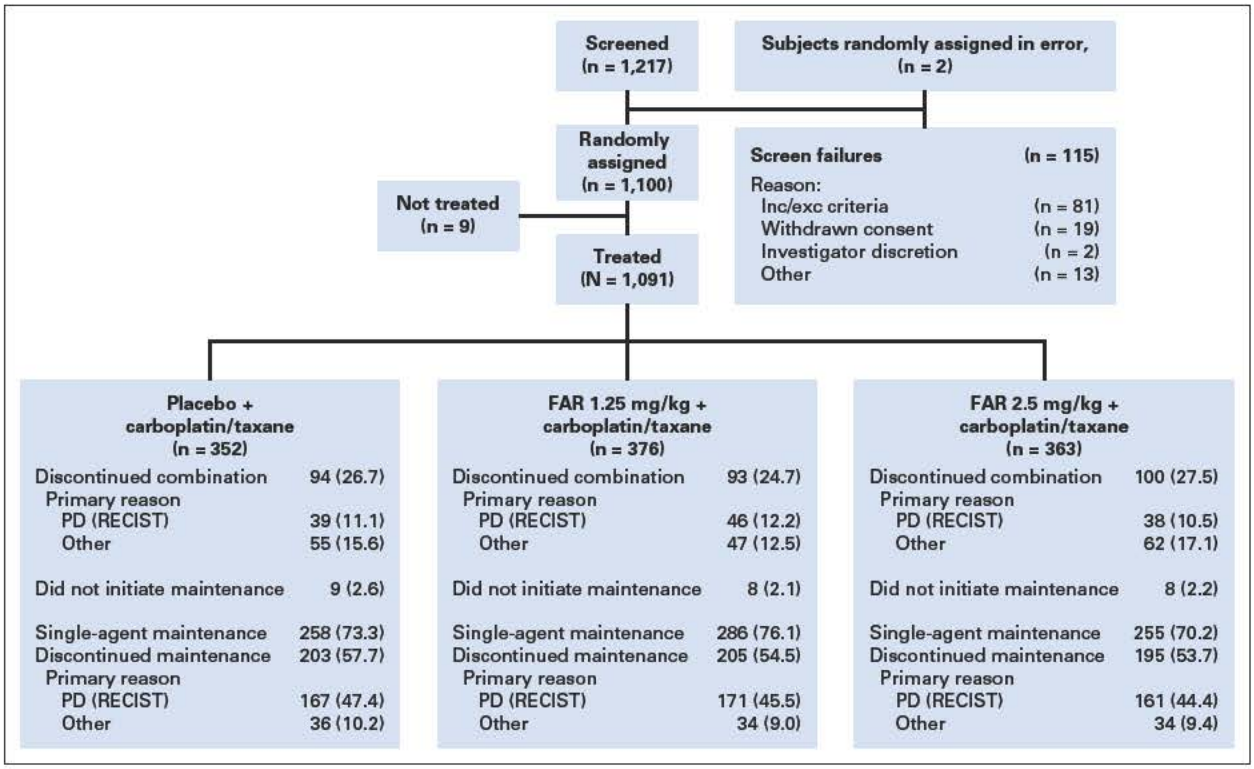

Fig 1. Study disposition. Data in figure tables given as No. (%) unless otherwise indicated. FAR, farletuzumab; Inc, inclusion; Exc, exclusion; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors.

antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity mediated immune based antitumor activity. Farletuzumab has demonstrated potent antitumor activity in preclinical xenograft models of ovarian cancer, both as a single agent and synergistically with chemotherapeutic agents.[6,7]

In a multisite, open label, phase II study in relapsed EOC, farletuzumab had an acceptable safety and pharmacokinetic profile across multiple doses, both as a single agent and in combination with carboplatin/taxane.[8] The collective findings of high response rates (both serologically and radiographically

Table 1. Patient Characteristics

Parameter	No. (%) of Patients			
	Placebo + Carboplatin/ Taxane (n = 364)	FAR 1.25 mg/kg + Carboplatin/ Taxane (n = 370)	FAR 2.5 mg/kg + Carboplatin/ Taxane (n = 366)	Total FAR (N = 736)
Median age (range), years	59.0 (30 84)	58.0 (29 89)	58.0 (35 83)	58.0 (29 89)
Karnofsky performance status				
100	173 (47.5)	174 (47.0)	184 (50.3)	358 (48.6)
90	134 (36.8)	139 (37.6)	132 (36.1)	271 (36.8)
80	46 (12.6)	50 (13.5)	38 (10.4)	88 (12.0)
70	11 (3.0)	7 (1.9)	12 (3.3)	19 (2.6)
First remission length, months				
6 to <12	194 (53.3)	196 (53.0)	193 (52.7)	389 (52.9)
12 to <18	108 (29.7)	112 (30.3)	111 (30.3)	223 (30.3)
18 24	62 (17.0)	62 (16.8)	62 (16.9)	124 (16.8)
Route of administration for first line therapy				
Intraperitoneal	26 (7.1)	28 (7.6)	26 (7.1)	54 (7.3)
Intravenous	338 (92.9)	342 (92.4)	340 (92.9)	682 (92.7)
Geographic region				
North America and Western Europe	183 (50.3)	186 (50.3)	185 (50.5)	371 (50.4)
Other participating countries	181 (49.7)	184 (49.7)	181 (49.5)	365 (49.6)
Planned taxane therapy				
Paclitaxel	294 (80.8)	298 (80.5)	296 (80.9)	594 (80.7)
Docetaxel	70 (19.2)	72 (19.5)	70 (19.1)	142 (19.3)

NOTE: Data are given as No. (%) unless otherwise indicated.
Abbreviation: FAR, farletuzumab.

assessed), the second response durations exceeding the first in > 20% of patients, and the absence of additional toxicity in this phase II trial suggested that farletuzumab in combination with chemotherapy may be an important treatment advance for patients with platinum sensitive, recurrent ovarian cancer.

The serum biomarker CA 125 has been used extensively in ovarian cancer to assess treatment response and recurrence. The sensitivity of CA 125 in the detection of recurrence is approximately 90%, and low CA 125 levels are hypothesized to be associated with lower volume of residual disease.[9,10] Baseline CA 125 levels have been used previously in ovarian trials as a stratification factor to assess the prognostic and predictive significance.[11,12] CA 125 (also known as MUC16) is implicated in the inhibition of target cell killing via ADCC by suppressing natural killer cell function, thereby reducing the efficacy of immunotherapeutic antibodies.[13,14] Therefore, higher levels of CA 125 may disrupt the ability of farletuzumab to elicit an immune response, thereby lowering its anti FRA mediated tumor killing potential.

The primary objective of this global, randomized, double blind, placebo controlled phase III study (MORAb 003 004) described here was to compare the effect of combination carboplatin and taxane with either farletuzumab or placebo on progression free survival (PFS), as determined by protocol specific modified Response Evaluation Criteria in Solid Tumors version 1.0[15] (RECIST), in patients with EOC in a platinum sensitive first relapse.

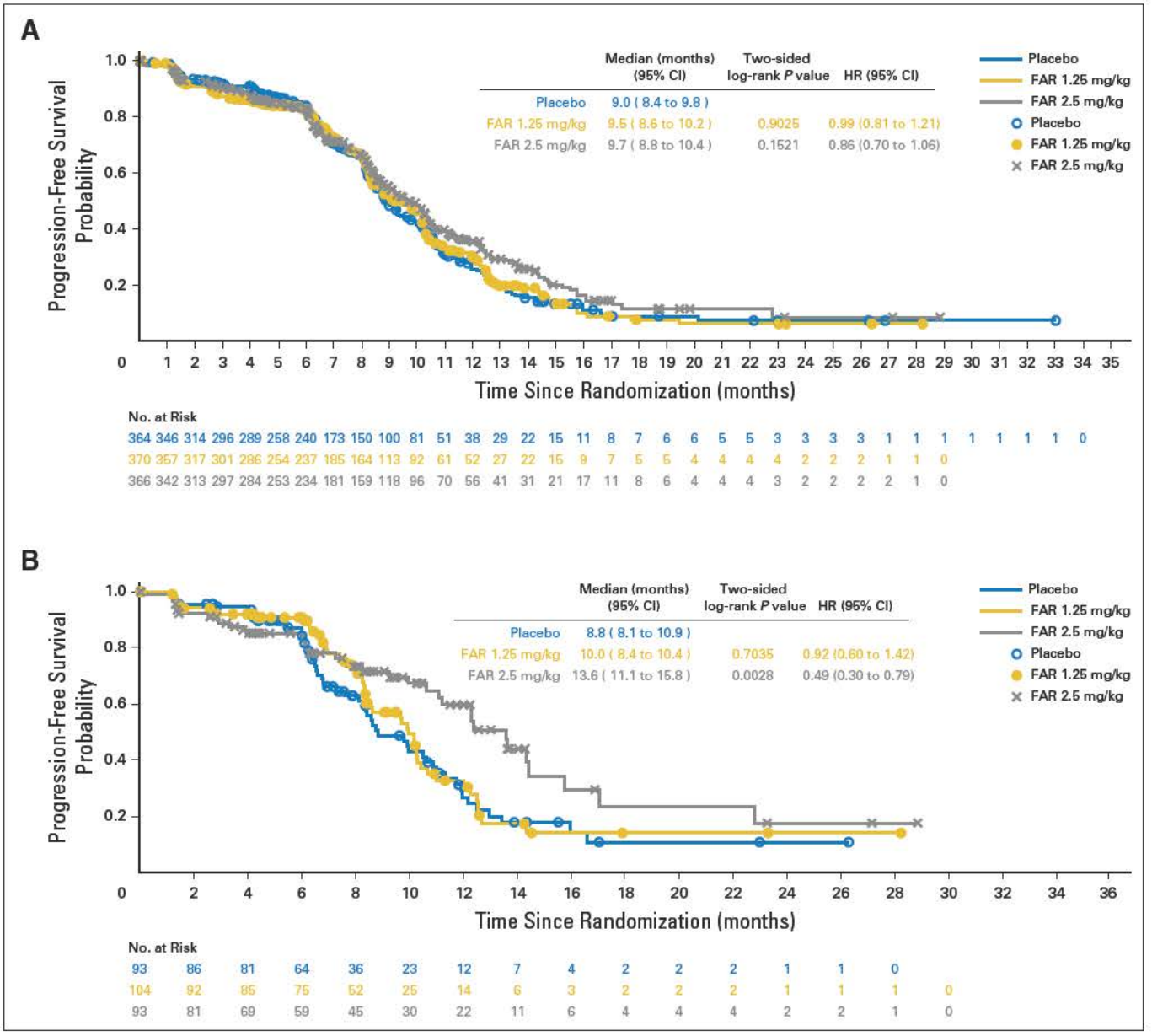

Fig 2. Progression free survival in the (A) overall population and (B) subgroup with CA 125 levels not more than three times the upper limit of normal. CI, confidence interval; FAR, farletuzumab; HR, hazard ratio.

PATIENTS AND METHODS

Patient Population

A total of 1,100 women with nonmucinous EOC who had relapsed 6 to 24 months after initial surgery and platinum/taxane chemotherapy were enrolled at 274 sites in North America (n = 73), Europe (n = 104), the Asia Pacific region (n = 43), Latin America (n = 24), and Japan (n = 30). Patients were required to have measurable disease and a Karnofsky performance score of 70% or higher. Patients were randomized in a 1:1:1 ratio to chemotherapy plus either farletuzumab 1.25 mg/kg, farletuzumab 2.5 mg/kg, or placebo.

Study Design and Methods

All patients were diagnosed with first relapsed platinum sensitive ovarian cancer, defined as response to first line platinum based therapy with relapse occurring at least 6 months after the last dose of platinum. Patients received standard therapy consisting of six cycles with carboplatin (target area under the curve [AUC], 5 to 6) administered intravenously (IV) and the investigator's choice of taxane (paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2) IV every 3 weeks. Patients were randomly assigned to receive weekly farletuzumab 1.25 mg/kg, farletuzumab 2.5 mg/kg, or placebo during the combination therapy, followed by single agent test product maintenance therapy once weekly until disease progression based on modified RECIST (Fig 1). Randomization was stratified by length of first remission (i.e., 6 to < 12 months, 12 to < 18 months, and 18 to 24 months), route of first line therapy administration (intraperitoneal *v* IV), planned taxane therapy (paclitaxel *v* docetaxel), and geographic region (North American and Western Europe *v* other participating countries).[16]

Efficacy was assessed by computed tomography or magnetic resonance imaging using the protocol specific modified RECIST version 1.0 performed every 6 weeks during combination therapy and every 9 weeks during single agent maintenance therapy. Analysis was by independent review; clinical decision making was based on investigator assessment. The primary end point was PFS based on independent assessment; a key secondary end point was overall survival (OS).

Standard safety assessments were used during the study, including assessment of adverse events (AEs) by National Cancer Institute Common Terminology Criteria for Adverse Events, laboratory parameters, and physical examinations. Blood samples for measurement of farletuzumab serum levels were collected every 3 weeks during chemotherapy cycles and every 9 weeks during maintenance.

All protocol and informed consent documentation received institutional review board approval in accordance with the Declaration of Helsinki. Each patient received detailed study information and provided written informed consent before any study specific screening.

Statistical Analysis

Sample size considerations were based on the primary PFS end point and a target hazard ratio (HR; farletuzumab:placebo) of 0.70, equivalent to a 43% improvement in PFS. The primary analysis occurred when both comparisons (high or low dose farletuzumab *v* placebo) had at least 391 PFS events. The targeted number of 391 events for each pairwise treatment to control comparison was derived on the basis of a log rank test at the pairwise one sided 0.0125 significance level, which accounts for multiplicity, with 90% power for an HR of 0.70. Approximately 1,080 patients (360 in each treatment arm) were planned to be randomly assigned to achieve the specified number of events. All *P* values presented in this report are two sided.

Additional analyses not outlined in the original protocol were prespecified in the final statistical analysis plan approved before data unblinding for primary analysis compliant with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 standards, which included a subgroup exploratory analysis by baseline CA 125 level. As a potential measure of disease burden, Kaplan Meier curves were generated to present PFS and OS for patients whose baseline serum CA 125 levels were not more than three times the upper limit of normal (ULN) versus CA 125 levels higher than three times the ULN. Stratified log rank tests were used to compare PFS and OS among treatment arms. A stratified proportional hazard (Cox) model was applied to calculate HR for PFS and OS comparing farletuzumab to placebo.

A separate population based pharmacokinetic/pharmacodynamic analysis plan was also planned and finalized before study unblinding using population based modeling to evaluate farletuzumab pharmacokinetics (PK) and serum exposure efficacy relationships. A two compartment PK model with linear elimination from the central compartment for farletuzumab serum concentration data was applied to calculate PK parameters including average AUC and minimum

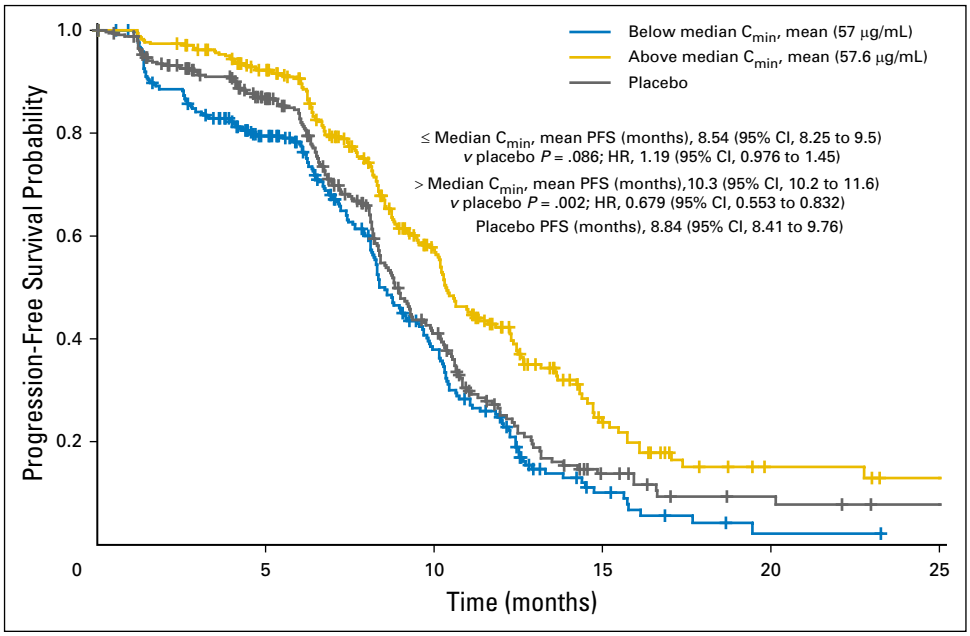

Fig 3. PFS by minimum serum concentrations of farletuzumab. CI, confidence interval; C_{min}, minimum concentration; HR, hazard ratio; PFS, progression free survival.

concentration, with Kaplan Meier plots generated to examine calculated PK exposure parameters with efficacy.

RESULTS

Patient Characteristics and Disposition

A total of 1,100 women were randomly assigned, with 1,091 receiving at least one dose of study drug during the combination therapy phase (361 received placebo, 367 received farletuzumab 1.25 mg/kg, and 363 received farletuzumab 2.5 mg/kg). Overall, 294 patients (26.9%) discontinued treatment during combination therapy, with almost half of all treatment discontinuations due to progressive disease, either by radiologic assessment (42.9%) or by clinical assessment (2.7%). Other primary reasons for discontinuation from combination therapy were nonfatal adverse events (AEs; 15.0%), patient's choice (12.6%), withdrawn consent (10.5%), investigator discretion (5.8%), and fatal AE (5.4%). An equal proportion of patients initiated single agent maintenance among the three arms (69.7% to 71.9%), and reasons for discontinuation were well balanced across the three arms in both combination and single agent maintenance phases. Nine patients assigned to the placebo group received one or more infusions of farletuzumab (dose unknown) in error and were arbitrarily counted in the farletuzumab 1.25 mg/kg group in the Safety Population (Fig 1).

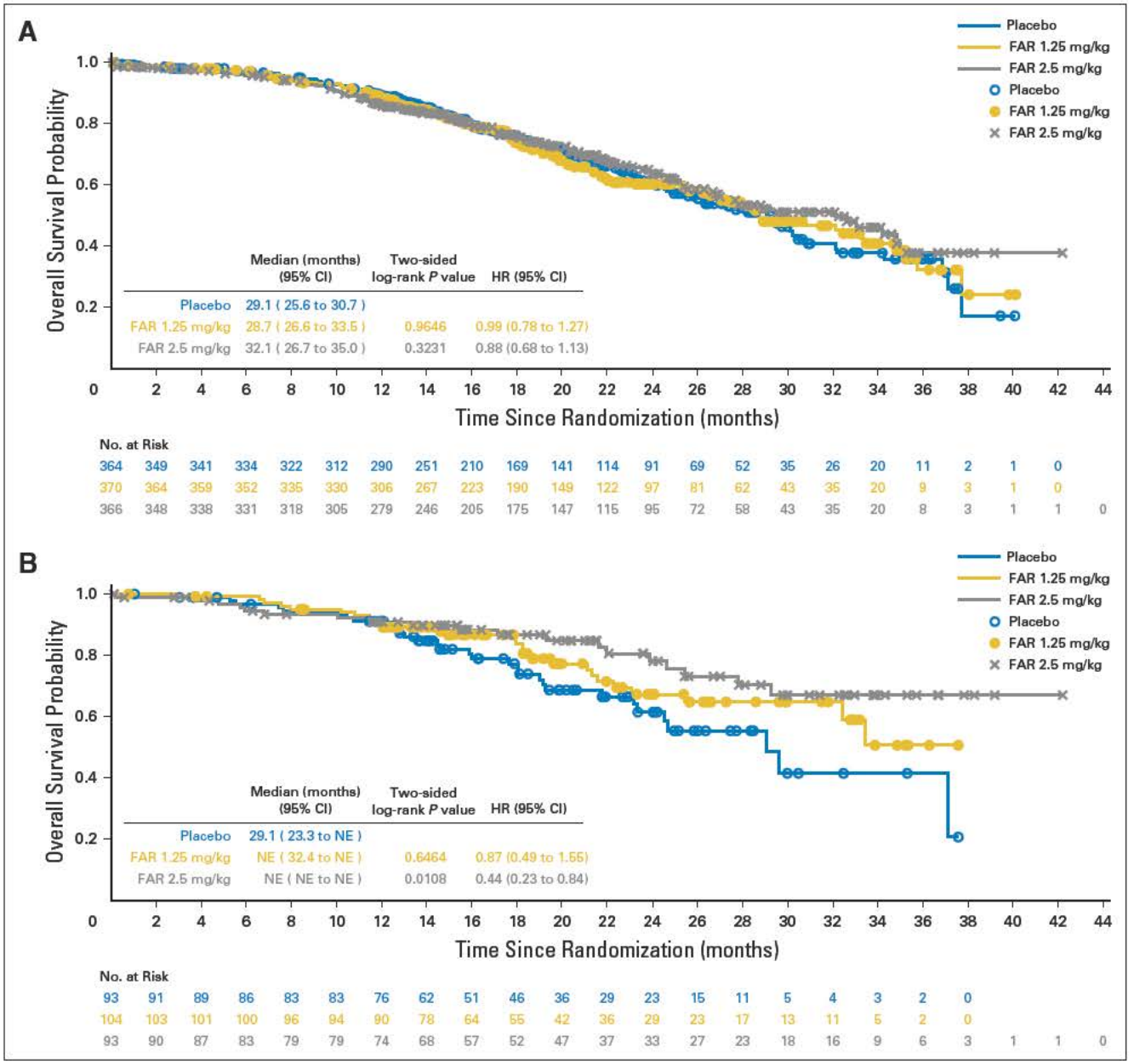

Fig 4. Overall survival in the (A) overall population and (B) subgroup with CA125 levels not more than three times the upper limit of normal. CI, confidence interval; FAR, farletuzumab; HR, hazard ratio; NE, not estimable.

Table 2. Treatment Emergent Adverse Events (Frequency, ≥25%)

MedDRA Preferred Term*	No. (%) of Patients							
	Placebo + Carboplatin/ Taxane (n = 352)		FAR 1.25 mg/kg + Carboplatin/Taxane (n = 376)†		FAR 2.5 mg/kg + Carboplatin/Taxane (n = 363)		Total FAR (N = 739)	
Neutropenia	672	181 (51.4)	665	220 (58.5)	626	190 (52.3)	1,291	410 (55.5)
Alopecia	207	202 (57.4)	225	221 (58.8)	186	184 (50.7)	411	405 (54.8)
Nausea	466	191 (54.3)	491	218 (58.0)	397	186 (51.2)	888	404 (54.7)
Fatigue	325	151 (42.9)	322	173 (46.0)	209	136 (37.5)	531	309 (41.8)
Anemia	207	126 (35.8)	232	145 (38.6)	281	158 (43.5)	513	303 (41.0)
Diarrhea	271	128 (36.4)	255	137 (36.4)	214	130 (35.8)	469	267 (36.1)
Thrombocytopenia	244	102 (29.0)	365	130 (34.6)	304	122 (33.6)	669	252 (34.1)
Vomiting	222	107 (30.4)	235	132 (35.1)	174	113 (31.1)	409	245 (33.2)
Constipation	158	103 (29.3)	170	121 (32.2)	165	107 (29.5)	335	228 (30.9)
Abdominal pain	156	95 (27.0)	164	109 (29.0)	132	91 (25.1)	296	200 (27.1)
Decreased appetite	167	70 (19.9)	195	95 (25.3)	138	75 (20.7)	333	170 (23.0)
Peripheral sensory neuropathy	121	90 (25.6)	138	89 (23.7)	117	71 (19.6)	255	160 (21.7)

Abbreviations: FAR, farletuzumab; MedDRA, Medical Dictionary for Drug Regulatory Activities.
*Adverse events were coded using MedDRA version 14.1.
†Nine patients who were randomized to placebo but received farletuzumab in error are counted in the FAR 1.25 mg/kg + carboplatin/taxane treatment group.

The study population enrolled was evenly distributed between investigative sites in North America and Western Europe (50.4%) and other participating countries (49.6%). Most patients received their first line therapy via IV administration (92.7%) and received paclitaxel as taxane therapy in combination with carboplatin (80.7%). Length of first remission was 6 to < 12 months for 53.0% of patients, 12 to < 18 months for 30.1% of patients, and 18 to 24 months for 16.9% of patients (Table 1).

Efficacy

In the primary analysis, median PFS in the intention to treat (ITT) population based on independent review was 9.0, 9.5, and 9.7 months in the placebo, farletuzumab 1.25 mg/kg, and farletuzumab 2.5 mg/kg groups, respectively. Neither farletuzumab group had a statistically significant difference in PFS from the placebo group (HR, 0.99 [95% CI, 0.81 to 1.21] and HR, 0.86 [95% CI, 0.70 to 1.06] for the 1.25 and the 2.5 mg/kg groups *v* placebo, respectively) (Fig 2A). In the subgroup exploratory analyses pre specified in the statistical analysis plan, baseline serum CA 125 levels not more than three times ULN correlated with longer PFS (median, 13.6 *v* 8.8 months; HR, 0.49; $P = .0028$) in the farletuzumab 2.5 mg/kg group compared with placebo (Fig 2B). In a stratified Cox model, the interaction P values were .0368 or .7031 for the interaction between 2.5 mg/kg or 1.25 mg/kg and CA 125 level not more than three times the ULN, respectively. The HR for the interaction of 2.5 mg/kg and CA 125 not more than three times the ULN was 0.57 (95% CI, 0.36 to 0.88).

In the exposure PFS analysis, PFS in patients with average minimum serum concentrations of farletuzumab above median levels (> 57.6 μg/mL) showed a significant relationship with PFS in comparison with placebo (HR=0.679; 95% CI, 0.553 to 0.832; $P = .002$) (Fig 3). Similarly, there was a significant relationship with PFS when assessing farletuzumab AUC levels above the median relative to placebo (HR, 0.77; 95% CI, 0.628 to 0.943; $P = 0.012$) (Fig 4).

Table 3. Grade 3 or 4 Treatment Emergent Adverse Events

MedDRA Preferred Term*	No. (%) of Patients							
	Placebo + Carboplatin/ Taxane (n = 352)		FAR 1.25 mg/kg + Carboplatin/ Taxane (n = 376)†		FAR 2.5 mg/kg + Carboplatin/ Taxane (n = 363)		Total FAR (N = 739)	
Neutropenia	449	145 (41.2)	431	167 (44.4)	379	139 (38.3)	810	306 (41.4)
Thrombocytopenia	41	28 (8.0)	86	49 (13.0)	70	42 (11.6)	156	91 (12.3)
Leukopenia	117	48 (13.6)	99	44 (11.7)	74	36 (9.9)	173	80 (10.8)
Anemia	43	35 (9.9)	51	38 (10.1)	50	37 (10.2)	101	75 (10.1)
Febrile neutropenia	18	17 (4.8)	20	18 (4.8)	31	27 (7.4)	51	45 (6.1)
Fatigue	11	10 (2.8)	17	15 (4.0)	20	17 (4.7)	37	32 (4.3)
Hypokalemia	11	10 (2.8)	17	14 (3.7)	18	15 (4.1)	35	29 (3.9)
Drug hypersensitivity	11	9 (2.6)	15	14 (3.7)	18	14 (3.9)	33	28 (3.8)
Abdominal pain	14	9 (2.6)	20	17 (4.5)	10	9 (2.5)	30	26 (3.5)
Vomiting	11	8 (2.3)	16	15 (4.0)	12	10 (2.8)	28	25 (3.4)

Abbreviations: FAR, farletuzumab; MedDRA, Medical Dictionary for Drug Regulatory Activities.
*Adverse events were coded using MedDRA version 14.1.
†Nine patients who were randomized to placebo but received farletuzumab in error are counted in the FAR 1.25 mg/kg + carboplatin/taxane treatment group.

In the final analysis for OS, median OS in the ITT population was 29.1 months (placebo), 28.7 months (farletuzumab 1.25 mg/kg), and 32.1 months (farletuzumab 2.5 mg/kg) (Fig 4A). Neither farletuzumab group was statistically different from the placebo group (HR, 0.99 and 0.88 for farletuzumab 1.25 mg/kg group and farletuzumab 2.5 mg/kg group *v* placebo, respectively). Approximately two thirds of patients in each treatment group were censored, mostly because they were still alive at the time of study closure (53% to 57%). Baseline CA 125 levels of not more than three times the ULN correlated with longer OS (median not estimable *v* 29.1 months; HR, 0.44; $P = .0108$) in the farletuzumab 2.5 mg/kg group compared with placebo (Fig 4B).

Safety

The overall safety profile was comparable across all three treatment groups, with no new safety signals identified in this study population. The most common AEs reported were those known to be associated with the study chemotherapy drugs, specifically alopecia, nausea, neutropenia, fatigue, thrombocytopenia, and neuropathy (Table 2). Anemia was reported by a larger percentage of patients in the farletuzumab 2.5 mg/kg group (42.1%) compared with the placebo (34.9%) or the farletuzumab 1.25 mg/kg group (37.0%). Other individual treatment emergent AEs, regardless of frequency and including grade ≥ 3 reports (Table 3), were reported in a similar percentage of patients across the three treatment groups.

During single agent maintenance therapy, eight patients (3.2%) in the placebo group reported serious test product related AEs compared with four patients (1.5%) who received farletuzumab 1.25 mg/kg and six (2.4%) of those who received farletuzumab 2.5 mg/kg. Similarly, the percentages of patients with grade 3 or higher AEs while on single agent maintenance were 17.9%, 17.6%, and 16.5%, respectively.

DISCUSSION

Despite a high initial response rate to first line platinum doublet chemotherapy following surgical resection of EOC, there is also a high rate of relapse and, therefore, an ongoing unmet medical need for improved treatment outcome.[16] To our knowledge, this global phase III study of farletuzumab for the treatment of platinum sensitive EOC represents the largest randomized study in this population reported to date.

Although neither farletuzumab dose met the study's primary PFS end point in the ITT population, prespecified subgroup analyses identified patients who may potentially benefit from farletuzumab. Patients with lower CA 125 levels at baseline did show improvement in both PFS and OS at the 2.5 mg/kg dose. Despite these subgroup results not being a confirmatory statistical analysis according to ICH E9 guidelines, the observations warrant additional preclinical and clinical investigation to more clearly explain such a potential clinical effect and the biologic mechanisms of CA 125 being involved in the functioning of natural killer cells and in the efficacy of farletuzumab. Higher CA 125 levels may directly inhibit the immune response of farletuzumab mediated ADCC by suppressing natural killer cell function; therefore, patients with lower CA 125 levels may exhibit a stronger farletuzumab mediated immune response.

In the phase II study 003 002, the observed PK profile indicated patients obtained adequate farletuzumab serum concentration levels for clinical activity, with some long term responding patients reaching high accumulation levels even at lower doses of 0.67 2.5 mg/kg. In this phase III study, patients treated at the 2.5 mg/kg dose generally had better outcomes than those treated at the lower dose of 1.25 mg/kg. Importantly, the results of this pharmacokinetic/pharmacodynamic population based analysis indicated that patients with higher serum farletuzumab exposure levels were associated with superior PFS compared with placebo. These findings suggest that some patients may not accumulate adequate antibody levels to produce the intended pharmacologic effect. In the initial phase 1 study, doses up to 400 mg/m^2 (approximately equivalent to 10 mg/kg weekly) were tested in a dose escalation monotherapy study, with no observed dose limiting toxicity or maximum tolerated dose.[17] In the absence of dose limiting toxicities, testing a higher dosing regimen to elicit a stronger exposure benefit effect is warranted.

The most commonly reported AEs across treatment arms were those known to be associated with the study chemotherapy agents. The addition of farletuzumab to the standard carboplatin/taxane regimen did not seem to increase toxicity. Furthermore, with single agent therapy, the placebo group had a higher rate of test product related serious AEs than did either farletuzumab dose group. Given this safety profile, a higher dose of farletuzumab should likely be possible without undue intolerance by the patient.

Based on the results of this phase III study, a follow on study in patients with platinum sensitive EOC who have low CA 125 levels is planned using a modified farletuzumab dosing regimen.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

A Randomized, Double Blind, Placebo Controlled, Phase III Study to Assess Efficacy and Safety of Weekly Farletuzumab in Combination With Carboplatin and Taxane in Patients With Ovarian Cancer in First Platinum Sensitive Relapse

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