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ORIGINAL REPORT

Abagovomab As Maintenance Therapy in Patients With Epithelial Ovarian Cancer: A Phase III Trial of the AGO OVAR, COGI, GINECO, and GEICO—The MIMOSA Study

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ABSTRACT

Purpose
To determine whether abagovomab maintenance therapy prolongs recurrence-free (RFS) and overall survival (OS) in patients with ovarian cancer in first clinical remission.

Patients and Methods
Patients with International Federation of Gynecology and Obstetrics stage III to IV ovarian cancer in complete clinical remission after primary surgery and platinum- and taxane-based chemotherapy were randomly assigned at a ratio of 2:1 in a phase III, double-blind, placebo-controlled, multicenter study. Abagovomab 2 mg or placebo was administered as 1-mL suspension once every 2 weeks for 6 weeks (induction phase) and then once every 4 weeks (maintenance phase) until recurrence or up to 21 months after random assignment of the last patient. The primary end point was RFS; secondary end points were OS and immunologic response.

Results
Characteristics of the 888 patients included: mean age, 56.3 years; Eastern Cooperative Oncology Group performance status, ≤ 1 in > 99% of patients; serous papillary subtype, 81.5%; stage III, 85.9%; and cancer antigen 125 ≤ 35U/mL after third cycle, 80.9%. Mean exposure to study treatment (± standard deviation) was 449.7 ± 333.08 days. Hazard ratio (HR) of RFS for the treatment group using tumor size categorization (≤ 1 cm, > 1 cm) was 1.099 (95% CI, 0.919 to 1.315; $P = .301$). HR of OS using tumor size categorization (≤ 1 cm, > 1 cm) was 1.150 (95% CI, 0.872 to 1.518; $P = .322$). The most frequently reported type of adverse event was an injection site reaction in 445 patients (50.2%), followed by injection site erythema and fatigue in 227 (25.6%) and 212 patients (23.9%), respectively. By the final visit, median anti–anti-idiotypic antibody level was 493,000.0 ng/mL, indicating a robust response.

Conclusion
Abagovomab administered as repeated monthly injections is safe and induces a measurable immune response. Administration as maintenance therapy for patients with ovarian cancer in first remission does not prolong RFS or OS.

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INTRODUCTION

Ovarian cancer remains the leading cause of mortality among women with gynecologic malignancies. Many patients have achieved complete clinical remission at the conclusion of primary treatment with surgical debulking and platinum- and taxane-based chemotherapy. Recurrence is common and characterized by subsequently shorter intervals of response until uniform chemotherapy resistance develops.[1] To improve the clinical outcome of patients with advanced ovarian cancer, maintenance therapy for patients in remission might be beneficial.

No randomized phase III maintenance or consolidation study has shown a statistically significant improvement in overall survival (OS) for those with ovarian cancer in first remission. Examples of negative randomized approaches applied in remission

include both subcutaneous and intraperitoneal (IP) interferon alfa,[2,3] high-dose chemotherapy,[4] continued intravenous carboplatin versus whole-abdominal radiation therapy,[5] chemotherapy versus observation versus whole-abdominal radiation therapy,[6] IP radioactive phosphorus (phosphorus-32),[7] non–cross-resistant chemotherapy,[8,9] IP therapy with an yttrium-90–labeled HMFG1 murine monoclonal antibody,[10] and oregovomab, a monoclonal antibody that targets cancer antigen 125 (CA-125).[11] Extended paclitaxel use prolonged progression-free survival but not OS.[12]

There is evidence supporting a role for the immune system in ovarian cancer surveillance. With regard to potential targets, CA-125 is a cell-surface, high–molecular weight mucin (MUC16) expressed by > 80% of nonmucinous epithelial ovarian cancers, and changes in its value are closely associated with disease recurrence and progression.[13-16] MUC16 expression has been directly correlated with platinum resistance and tumor invasiveness.[17,18] Two major obstacles have hampered the development of CA-125–directed immunotherapy. First, these peptides are self-antigens, which are tolerated by the host, and attempts at vaccination with irradiated autologous or allogeneic tumor cells or tumor lysates have not produced meaningful immune responses.[19,20] Second, the successful cloning of CA-125, categorizing it as a complex mucin (MUC16), occurred only recently, leading to its recognition as a massive transmembrane glycoprotein with > 60 repeat domains and an amino terminus.[21] Although understanding the structure has made the development of directly targeted synthetic immunogenic constructs possible, work is necessary to understand which parts of the larger structure need to be included in a vaccine approach, because size prohibits immunization with the entire construct.[22]

Abagovomab is an anti-idiotypic antibody produced by a mouse hybridoma and generated against OC125. The murine monoclonal antibody recognizes the tumor-associated antigen CA-125. The induction of a specific immune response (both humoral and cellular) was confirmed in preclinical studies, and a phase I/II trial with 119 patients showed an association between prolonged survival in patients with ovarian cancer who demonstrated an anti–anti-idiotypic antibody (Ab3) response to vaccination (68%) versus those who did not (23.4 *v* 4.9 months). No significant adverse events were noted.[16,23] Subsequent phase I studies confirmed safety and efficacy of the subcutaneous route and suggested that longer vaccination sequences produced more robust immune responses.[16,24] These data provided the rationale for the phase III randomized trial reported here.

PATIENTS AND METHODS

Eligibility Criteria

Patients were accrued at multiple institutions from December 2006 to February 2009. Eligible patients had a history of histologically and serologically CA-125–confirmed diagnosis (CA-125 > 35 U/mL) of stage III to IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients underwent debulking surgery and six to eight cycles of standard taxane- and platinum-based treatment, resulting in a complete clinical response. Complete clinical response was defined as normal physical examination, computed tomography scan and chest radiograph without definite evidence of disease, and serum CA-125 within normal laboratory range. Patients were enrolled within 12 weeks of last chemotherapy treatment. Adequate hematologic, renal, and hepatic function were required to include absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelets $\geq 75 \times 10^9$/L; hemoglobin $\geq$ 9.9 g/dL; serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN); bilirubin $\leq 1.5 \times$ ULN; and AST, ALT, and alkaline phosphatase $\leq 2.5 \times$ ULN. Patients with known autoimmune disease requiring treatment with immunosuppressive agents were excluded. Prior vaccine or monoclonal antibody treatment was not allowed.

Study Design

The study was a randomized, double-blind, placebo-controlled, multicenter trial of abagovomab maintenance therapy versus placebo in patients with epithelial ovarian, primary peritoneal, or fallopian tube cancer in first complete clinical remission. Registration and random assignment in a 2:1

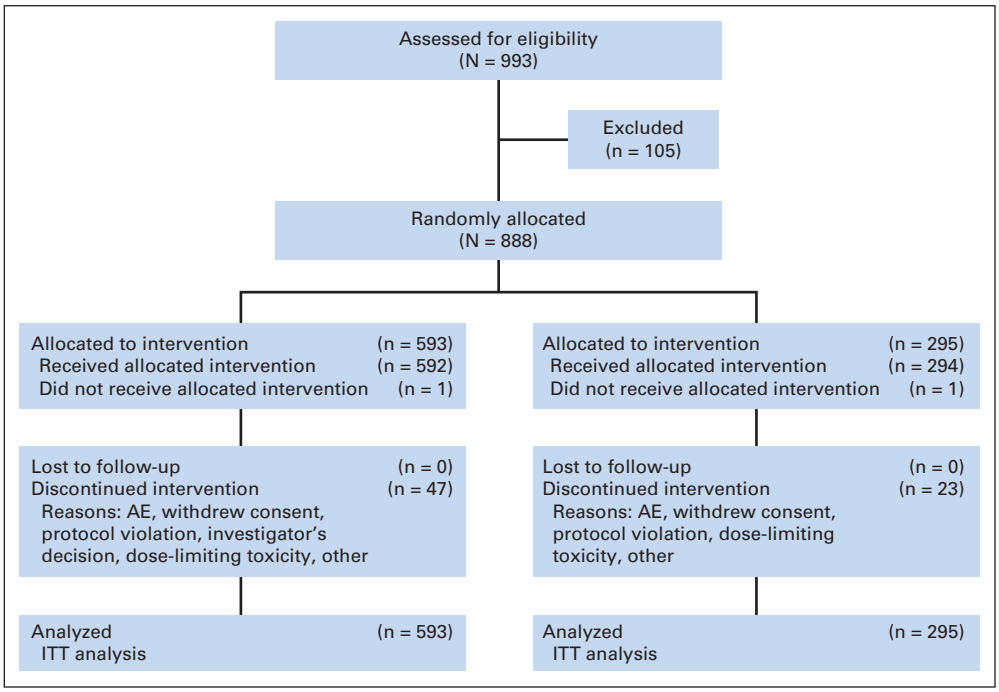

Fig 1. CONSORT diagram. AE, adverse event; ITT, intention to treat.

fashion favoring abagovomab was centralized. Predetermined strata included International Federation of Gynecology and Obstetrics (FIGO) stage (III *v* IV), tumor size after debulking surgery (residual tumor ≤ 1 or > 1 cm), and serum CA-125 after first three cycles of chemotherapy (≤ 35 or > 35 U/mL). The primary study end point was recurrence-free survival (RFS) at the end of double-blind observation. Secondary end points included OS; safety; and immunologic parameters, including human antimouse antibody (HAMA), Ab3, Ab1′, and serum CA-125 (blinded during study). The double-blind observation period extended from random assignment of the first patient to 24 months after random assignment of the last patient. The open survival follow-up period started at the end of the double-blind observation period for a planned additional 5 years. Abagovomab was administered subcutaneously in a 1-mL suspension once every 2 weeks for three injections (induction phase) and then once every 4 weeks for up to 21 months after random assignment of the last patient (maintenance phase). A steering committee, independent radiology review panel, and data and safety monitoring board were established for study management.

Dose Modifications

Dose modification was not permitted. Patients were to be removed for dose-limiting toxicity using Common Terminology Criteria for Adverse Events version 3.0 criteria defined by grade 2 allergic reaction, grade ≥ 2 autoimmune reaction, grade ≥ 3 hematologic or nonhematologic toxicity including fever, or grade 3 injection site reaction.

Baseline and Treatment Assessments

Radiologic tests were performed within 28 days of study entry. Medical history, laboratory tests, urinalysis, and ECG were performed within 14 days. Interval assessments included physical examination, concomitant medication assessment, hematologic and serum chemistries, and immune assessments at weeks 4 and 10 and then every 12 weeks. Serum CA-125 (kept blinded) and computed tomography imaging were obtained at week 10 and then every 12 weeks in both arms. RECIST version 1.0 was used to assess for disease progression. Central radiology review was provided. Adverse events and survival status were monitored throughout the observation period.

Statistical Methods

The planned study population was 870 patients (580 to receive abagovomab, 290 to receive placebo). The expected RFS for the placebo arm was 18 months, and the expected number of recurrence events was 535 (338 in abagovomab arm, 197 in placebo arm). The study was powered to detect a hazard ratio (HR) between abagovomab and placebo of 1.33 (leading to an approximate benefit of abagovomab over placebo of 6 months). Significance level (α) = 5% (two sided), and the expected dropout rate was 10%. The primary analysis for RFS was run on progression-free survival as assessed by the central radiology review committee. A Cox proportional hazards model was used for the primary analysis, which had treatment as a major covariate, adjusted only for the predefined prognostic stratification factors (ie, FIGO stage, tumor size after debulking, and CA-125 level after first three cycles of chemotherapy). Kaplan-Meier estimation analysis was used to support the results seen in the Cox regression model. Safety parameters were descriptively analyzed using Common Terminology Criteria for Adverse Events version 3.0 descriptors. The following subgroups were also analyzed for effect on the primary end point: tumor size after debulking (residual tumor ≤ 1 or > 1 cm), FIGO stage (III *v* IV), and serum CA-125 level after the first three cycles of chemotherapy (≤ 35 or > 35 U/mL). For the immunologic parameters Ab3 and HAMA, descriptive statistics by time point (ie, baseline, week 10, and week 22) were performed for FIGO stage, tumor size after debulking, and CA-125 level after the first three cycles of chemotherapy.

RESULTS

Patient Characteristics

Patient flow is outlined in the CONSORT diagram (Fig 1). Patient characteristics, which were similar for both groups, are listed in Table 1. Overall mean age (± standard deviation [SD]) was 56.3 ± 10.53 years. At week 0, 78.8% of patients had Eastern Cooperative Oncology Group performance status of 0, and 20.9% had performance status of 1. Of the total population, the majority (82%) had stage III disease and had serous histology (81.5%), followed by endometrioid histology (6.7%). All patients received surgical debulking and platinum- and taxane-based primary therapy for six to eight cycles. The mean time from primary surgery to random assignment (± SD) was 192 ± 43 days. Most patients (80.1%) were debulked to < 1 cm, and 47.7% had no visible residual disease at the conclusion of primary surgery. There were no observed differences between treatment groups regarding tumor size after debulking surgery. The majority of patients (80.9%) experienced reduction in CA-125 to ≤ 35 U/mL after three cycles of primary therapy. There were no observed differences between treatment groups regarding serum CA-125 level after the first three cycles of chemotherapy.

Table 1. Patient Demographics and Clinical Characteristics

Characteristic	Abagovomab (n = 593) No.	%	Placebo (n = 295) No.	%
Age, years				
Mean	56.3		56.0	
SD	10.57		10.47	
Ethnicity				
Hispanic or Latino	121	20.4	66	22.4
Non-Hispanic or non-Latino	471	79.6	229	77.6
Race				
White	582	98.1	291	98.6
Black or African American	3	0.5	3	1.0
Hawaiian or Pacific Islander	1	0.2	0	0
Asian	2	0.3	1	0.3
Other	5	0.8	0	0
FIGO stage				
III	513	86.6	252	85.7
IV	80	13.5	42	14.3
Tumor size after debulking, cm				
≤ 1	479	80.8	232	78.6
0	285	48.1	139	47.1
> 0 to ≤ 1	194	32.7	93	31.5
> 1	114	19.2	63	21.4
Serum CA-125 after three cycles, U/mL				
≤ 35	479	80.8	239	81.3
> 35	114	19.2	55	18.7
Histology				
Serous	481	81.5	245	83.1
Endometrioid	38	6.4	21	7.1
Mucinous	6	1.0	3	1.0
Other	65	11.1	26	8.9

Abbreviation: CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

Dose Administration

All patients (100%) completed the screening visit. At week 10 (end of induction and start of maintenance phase), 825 patients (92.9%) had completed the visit. Patients received all doses in the induction phase, and compliance was approximately 70% during the maintenance phase. Mean exposure to study treatment (± SD) was 449.7 ± 333.08 days for the overall study population, with no differences observed between treatment groups (450.6 ± 335.49 days in abagovomab group; 447.9 ± 328.73

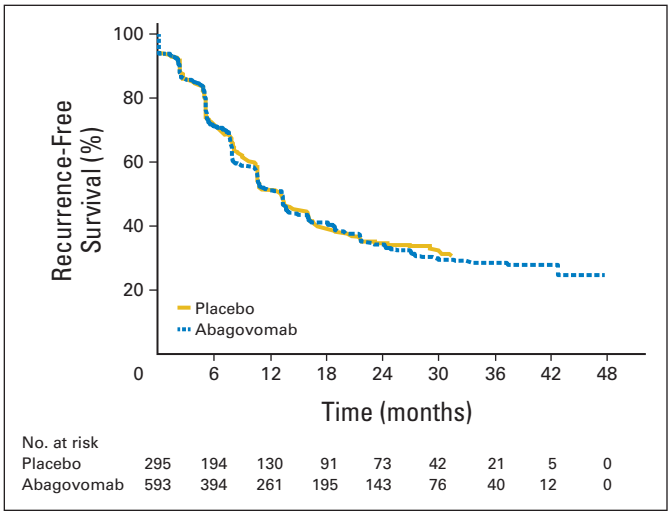

Fig 2. Primary end point: recurrence-free survival distribution against time.

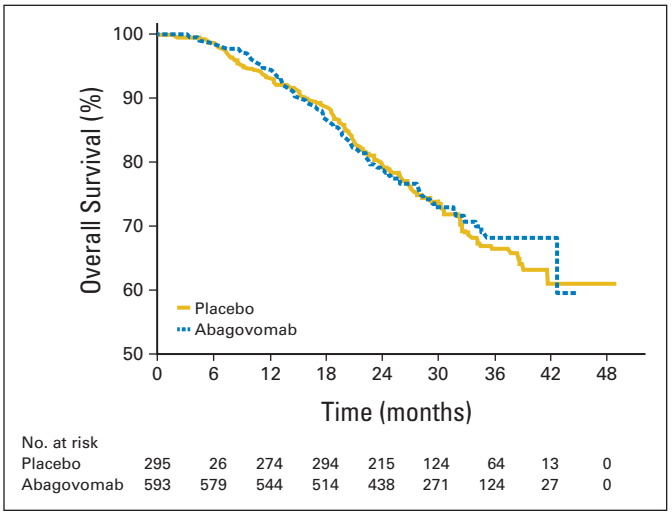

Fig 3. Secondary end point: overall survival distribution against time.

days in placebo group). For the abagovomab arm, median (quartile one to quartile three) exposure was 351.0 days (range, 160.5 to 702.5 days), whereas for the placebo arm, it was 377 days (range, 157.0 to 686.0 days).

Mean exposure (± SD) was longer among patients with residual tumor size ≤ 1 cm (468.7 ± 336.27 days) versus patients with residual tumor size > 1 cm (373.2 ± 309.16 days), among patients with baseline FIGO stage III (470.4 ± 338.0 days) versus baseline FIGO stage IV (319.8 ± 266.91 days), and among patients with CA-125 ≤ 35 U/mL after the first three cycles of chemotherapy (489.8 ± 336.18 days) versus CA-125 > 35 U/mL (280.7 ± 260.13 days).

Efficacy

At the end of double-blind observation period, 554 recurrence events had been observed in total (374 in abagovomab arm; 180 in placebo arm). HR of RFS was 1.099 (95% CI, 0.919 to 1.315; $P = .301$). This showed no statistical difference in risk of recurrence between the abagovomab-treated and placebo groups.

Figure 2 shows the survival distribution against time for RFS. The results of this confirmatory analysis support those seen in the primary Cox regression model. The median estimated time to recurrence was similar between both treatment groups (abagovomab group: 403 days; 95% CI, 323 to 414; placebo group: 402 days; 95% CI, 323 to 487).

At the end of the double-blind observation period, 251 patients had died (171 in abagovomab arm; 80 in placebo arm). HR of OS for the treatment group was 1.150 (95% CI, 0.872 to 1.518; $P = .322$). This showed no statistical difference in the risk of death between patients receiving abagovomab versus placebo. OS rate at 2 years was 80% in both arms, with SE equal to 1.71 and 2.43 for abagovomab and placebo, respectively. Figure 3 shows the survival distribution against time for OS. No statistically significant difference was observed in the survival curves ($P = .607$).

Primary Immune Response Parameters

Response parameters are listed in Table 2. Median Ab3 level was set to 0 (ie, below predefined limit of quantification) at baseline in both treatment groups. In the placebo group, median Ab3 level remained at 0 ng/mL, whereas in the abagovomab-treated group, it increased during the course of study. At week 10 (end of induction/start of maintenance phase), median Ab3 level was 63,550.0 ng/mL, and at week 22, median Ab3 level was 335,500.0 ng/mL. By the final study visit, median Ab3 level was 493,000.0 ng/mL.

Median HAMA level was set to 0 (ie, below predefined limit of quantification) at baseline in both treatment groups. In the placebo group, median HAMA level remained at 0 ng/mL, whereas in the abagovomab-treated group, it increased during the course of study. At week 10 (end of induction/start of maintenance phase), median HAMA level was 326.0 ng/mL, and at week 22, median HAMA level was 6380.0 ng/mL. By the final study visit, median HAMA level was 11,300.0 ng/mL.

Analyses by FIGO stage, tumor debulking status, and CA-125 level after the first three cycles of chemotherapy did not reveal any differences in the subgroups regarding the time course of median Ab3 level (data not shown).

Secondary Immune Response Parameters

The secondary immune response parameters will be reported separately.

Adverse Events

In the total study population, 564 patients (95.3%) in the abagovomab group and 278 patients (94.6%) in the placebo group experienced an adverse event (Tables 3 and 4). The proportions of patients experiencing treatment-related adverse events, serious adverse events, treatment-related serious adverse events, and adverse events leading to permanent withdrawal from study medication were similar between the abagovomab- and placebo-treated groups. The most frequently reported adverse event was an injection site reaction, reported in 443 patients (50%), characterized overall by localized erythema. Fatigue was reported in 170 patients (19.1%). For the majority of patients, the most severe adverse events were grade 1 (n = 212; 23.9%) or 2 (n = 423; 47.7%). A total of 182 patients (20.5%) experienced grade 3 adverse events, with 115 (19.4%) in the abagovomab group and 67 (22.8%) in the placebo group. The number of grade 4 adverse events was small, with 12 (2.0%) in the abagovomab group and five (1.7%) in the placebo group. Overall, 213 patients (24.0%) experienced a serious

Table 2. Immune Response Parameters (Ab3, HAMA) at Week 10, Week 22, and Final Study Visit in Overall ITT Population

	Abagovomab (n = 593)		Placebo (n = 295)		Total (N = 888)	
Parameter	Actual Value	Change From Baseline	Actual Value	Change From Baseline	Actual Value	Change From Baseline
Ab3, ng/mL						
Baseline						
No.	576		288		864	
Mean	893.5		985.0		924.0	
SD	7,585.82		5,613.77		6,987.36	
Median	0.0		0.0		0.0	
Q1 to Q3	0 to 0		0 to 0		0 to 0	
Week 10						
No.	538	532	269	263	807	795
Mean	89,952.1	89,230.7	1,128.9	500.4	60,344.4	59,877.1
SD	91,321.64	92,190.47	6,588.91	4,141.14	85,592.98	86,224.51
Median	63,550.0	63,150.0	0.0	0.0	31,400.0	30,700.0
Q1 to Q3	31,400.0 to 115,500.0	30,100.0 to 115,500.0	0 to 0	0 to 0	0 to 88,000.0	0 to 88,000.0
Week 22						
No.	472	460	234	228	706	688
Mean	404,625.5	407,134.7	1,245.3	533.3	270,927.2	272,388.9
SD	271,569.40	273,703.11	6,433.85	4,396.22	292,219.18	294,520.64
Median	335,500.0	339,000.0	0.0	0.0	225,500.0	227,000.0
Q1 to Q3	224,000.0 to 536,500.0	225,500.0 to 540,000.0	0 to 0	0 to 0	0 to 455,000.0	0 to 457,500.0
Final study visit						
No.	449	441	230	224	679	665
Mean	595,209.8	596,580.7	3,950.5	2,936.4	394,930.5	396,616.3
SD	469,647.94	470,366.17	33,697.04	33,040.60	473,866.07	475,199.78
Median	493,000.0	493,000.0	0.0	0.0	256,000.0	258,000.0
Q1 to Q3	258,000.0 to 794,000.0	258,000.0 to 798,000.0	0.0	0.0	0 to 627,000.0	0 to 625,400.0
HAMA, ng/mL						
Baseline						
No.	576		288		864	
Mean	13.730		4.712		10.724	
SD	117.7044		28.4410		97.5600	
Median	0.000		0.000		0.000	
Q1 to Q3	0 to 0		0 to 0		0 to 0	
Week 10						
No.	538	532	269	263	807	795
Mean	832.904	822.022	6.800	1.602	557.536	550.613
SD	1,523.2716	1,522.1293	35.2562	38.6689	1,303.1505	1,303.5092
Median	326.000	322.500	0.000	0.000	110.000	106.000
Q1 to Q3	101.0 to 824.0	95.9 to 818.0	0 to 0	0 to 0	0 to 548.0	0 to 537.0
Week 22						
No.	472	460	234	228	706	688
Mean	9,844.807	9,833.055	13.795	8.922	6,586.370	6,577.383
SD	13,721.0703	13,779.9604	95.4973	100.9670	12,133.7797	12,177.3228
Median	6,380.000	6,415.000	0.000	0.000	2,795.000	2,760.000
Q1 to Q3	2,760.0 to 11,850.0	2,745.0 to 11,850.0	0 to 0	0 to 0	0 to 8,370.0	0 to 8,465.0
Final study visit						
No.	449	441	230	224	679	665
Mean	21,990.183	22,028.887	633.039	645.449	14,755.804	14,826.045
SD	40,079.0892	40,272.9965	7,038.0481	7,131.7401	34,357.8623	34,556.3083
Median	11,300.000	11,300.000	0.000	0.000	2,840.000	2,950.000
Q1 to Q3	295.0 to 26,100.0	295.0 to 26,100.0	0 to 0	0 to 0	0 to 16,500.0	0 to 16,600.0

NOTE. Baseline value is defined as last measurement taken before first administration of study drug. Values specified as below limit of quantification were set to 0 in summary tables.

Abbreviations: Ab3, anti–anti-idiotypic antibody; HAMA, human antimouse antibody; Q, quartile; SD, standard deviation.

adverse event, the most commonly attributed cause of which was recurrent ovarian cancer (11.5% of patients).

DISCUSSION

Despite the association between Ab3 production and OS seen in the previous phase I/II trial evaluating abagovomab in patients with advanced ovarian cancer, no benefit with regard to RFS or OS was seen in this large international randomized phase III study evaluating abagovomab for patients in first clinical remission. The patient characteristics evaluated here were typical for patients with ovarian cancer. A majority were optimally debulked, and the requirement for complete clinical remission provided a good patient group for the evaluation of an immunotherapeutic approach. The study used

Table 3. Summary of Treatment-Emergent AEs

AE	Abagovomab		Placebo	
	No.	%	No.	%
Treatment-emergent AE	564	95.3	278	94.6
Grade 3 AE	115	19.4	67	22.8
Grade 4 AE	12	2.0	5	1.7
Treatment-emergent related AE	507	85.6	246	83.7
SAE	141	23.8	72	24.5
Treatment-related SAE	12	2.0	3	1.0
SAE leading to withdrawal of study drug	93	15.7	57	19.4

Abbreviations: AE, adverse event; SAE, serious adverse event.

central randomization, and both patients and investigators were blinded to treatment arms and serum CA-125 values. The time to RFS was adjudicated by a central radiology review committee and was as expected for the patient groups. Study compliance was good overall, and the treatment was well tolerated. In addition to the lack of benefit in the overall intention-to-treat population, no benefit was seen in those characterized by the planned subgroups based on FIGO stage, size of residual tumor, or normalization of CA-125 after three cycles of primary chemotherapy.

Vaccination with abagovomab resulted in a robust Ab3 response. The lack of benefit seen in this study despite its immunogenicity is in contrast to that seen in the phase II study, in which a strong association was seen between antibody response and OS (23.5 *v* 4.9 months; $P > .001$).[25] This illustrates the importance of phase III randomized trials in drawing any conclusions regarding efficacy for maintenance approaches. This finding may indicate that in the phase II study, antibody production was a biomarker for improved outcome in that patients who were able to generate such a response despite disease status had longer survival. The proactive induction of the antibody response using abagovomab did not show similar results. The high percentage of immune responders with regard to Ab3 in this study does not permit a comparison between those who produced antibodies and those who did not.

The lack of a RFS or OS benefit with abagovomab parallels the data recently reported with oregovomab, which is a murine monoclonal antibody specific for CA-125. It similarly had strong phase II supporting data, but no benefit was seen in a randomized phase III trial.[26] Although neither antibody-directed approach showed a survival improvement, much interest remains in considering CA-125 (MUC16) as one viable target for future studies with other effectors. MUC16 is overexpressed on most epithelial ovarian cancer cells with its cleaved and released domain (CA-125) as well as a retained domain (MUC-CD). Because it is otherwise expressed at low levels in other tissue sites, and preclinical data support its modulation of ovarian tumor growth and invasiveness, it is ideally suited for targeting. Recent studies have shown that T cells, for example, modified to express a chimeric antigen receptor (4H11) specific to the MUC-CD of MUC16 can lyse human ovarian cancer cells in vitro and have shown tumor kill in orthotopic xenotransplant tumor models.[27] Ovarian cancer is a markedly immunogenic tumor, and there is significant evidence that the presence of both antibody and T-cell effectors correlate with outcome.[28,29] Recent data in renal cell cancer suggest that multiple tumor-associated peptide targets have a positive clinical effect.[30] Exploring multiple targets simultaneously in addition to CA-125 (MUC16) for immunotherapy, exploiting other effectors, and combining these approaches with immunomodulatory efforts directed toward CTLA4 or PDL1 remain reasonable approaches to try and improve outcome for patients with ovarian cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Table 4. AEs by Maximum Relationship Related to Study Medication Occurring in ≥ 5% Patients

System Organ Class	Abagovomab (n = 592)						Placebo (n = 294)					
	Possible		Probable		Certain		Possible		Probable		Certain	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Abdomen pain	38	6.4	3	0.5	4	0.7	6	2.0	4	1.4	3	1.0
Diarrhea	38	6.4	5	0.8	9	1.5	8	2.7	4	1.4	2	0.7
Nausea	43	7.3	12	2.0	4	0.7	14	4.8	3	1.0	11	3.7
Fatigue	89	15.0	22	3.7	12	2.0	33	11.2	10	3.4	4	1.4
Injection site reaction	13	2.2	48	8.1	246	41.6	5	1.7	25	8.5	106	36.1
Arthralgia	52	8.8	17	2.9	13	2.2	25	8.5	8	2.7	8	2.7
Myalgia	25	4.2	8	1.4	5	0.8	18	6.1	5	1.7	7	2.4
Headache	37	6.3	3	0.5	7	1.2	10	3.4	9	3.1	2	0.7

Abbreviation: AE, adverse event.

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