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ORIGINAL REPORT

Phase III Trial of Intraperitoneal Therapy With Yttrium-90–Labeled HMFG1 Murine Monoclonal Antibody in Patients With Epithelial Ovarian Cancer After a Surgically Defined Complete Remission

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ABSTRACT

Purpose
This was a multinational, open-label, randomized phase III trial comparing yttrium-90–labeled murine HMFG1 (^{90}Y-muHMFG1) plus standard treatment versus standard treatment alone in patients with epithelial ovarian cancer (EOC) who had attained a complete clinical remission after cytoreductive surgery and platinum-based chemotherapy.

Patients and Methods
In total, 844 International Federation of Gynecology and Obstetrics stage Ic to IV patients were initially screened, of whom 447 patients with a negative second-look laparoscopy (SLL) were randomly assigned to receive either a single dose of ^{90}Y-muHMFG1 plus standard treatment (224 patients) or standard treatment alone (223 patients). Patients in the active treatment arm received a single intraperitoneal dose of 25 mg of ^{90}Y-muHMFG1 (target dose 666 MBq/m^2). The primary end point was length of survival; secondary end points included time to relapse and safety. The study had an 80% power to detect a 15% change in survival.

Results
After a median follow-up of 3.5 years (range, 1 to 6 years), 70 patients had died in the active treatment arm compared with 61 patients in the control arm. Cox proportional hazards analysis of survival demonstrated no difference between treatment arms. In the study drug arm, 104 patients experienced relapse compared with 98 patients in the standard treatment arm. No difference in time to relapse was observed between the two study arms. Active therapy was associated with occasional grade 3 or 4 thrombocytopenia and neutropenia and grade 1 or 2 GI symptoms, abdominal discomfort, arthralgia, and myalgia.

Conclusion
A single IP administration of ^{90}Y-muHMFG1 to patients with EOC who had a negative SLL after primary therapy did not extend survival or time to relapse.

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death among women in the United States and Northern and Western Europe.[1] Despite high response rates to cytoreductive surgery followed by platinum-based chemotherapy, the relapse rate is high, and consequently, for patients with advanced disease, the 5-year survival rate is approximately 25% to 35%.[2,3] Because the site of disease recurrence is usually within the peritoneal cavity, intraperitoneal (IP) consolidation strategies offer the possibility of focusing therapy to the site of residual disease while minimizing systemic toxicities.[4,5]

The HMFG1 murine monoclonal antibody is directed at a specific epitope of the *MUC1* gene product, which is a large, heavily glycosylated mucin expressed on the apical surface of the majority of secretory epithelial cells.[6] *MUC1* is an attractive target for immunotherapy because it is overexpressed in 90% of adenocarcinomas, including cancers of the ovary, breast, and pancreas, and is antigenically distinct from normal tissue mucin as a result of underglycosylation or aberrant glycosylation of this protein in cancerous tissue.[7] The extracellular portion of the MUC1 protein mainly consists of a variable number of highly conserved 20 amino acid repeats. In malignancy, the complex carbohydrate

side chains are truncated, leading to exposure of cryptic epitopes within these amino acid repeats.[8,9]

The radiolabeled monoclonal antibody HMFG1 has been previously used to successfully image lesions in patients with primary and metastatic ovarian cancer.[10] However, the absolute amount of antibody reaching the target was not considered to be high enough for effective targeting of radioactivity.[11] This led to the concept of applying radiolabeled antibodies regionally (ie, IP or intrapleurally) for the treatment of regionally confined tumors such as ovarian cancer.

In a nonrandomized, extended, phase I/II trial, patients with EOC were treated with a radiolabeled HMFG1 antibody, yttrium-90–labeled murine HMFG1 (^{90}Y-muHMFG1), administered once IP after surgical debulking and chemotherapy.[12] The primary results of that study[13] as well as an update[14] demonstrated prolonged disease-free survival in a small cohort of patients who had received the therapy after achieving a complete remission with conventional primary chemotherapy. On the basis of the results of the phase I/II study, the Study of Monoclonal Antibody Radioimmunotherapy was initiated. The primary aim of this large phase III trial was to evaluate whether the delivery of a single dose of IP ^{90}Y-muHMFG1 prolonged survival. Secondary study end points included an analysis of relapse and safety of ^{90}Y-muHMFG1 after surgery and platinum-based chemotherapy.

PATIENTS AND METHODS

Between February 1998 and January 2003, 844 patients were initially screened, of whom 702 met primary eligibility criteria and were enrolled after written informed consent was provided. The study, which involved 74 centers in 17 countries, was sponsored by Antisoma Ltd (London, United Kingdom) and approved by the appropriate scientific and ethical authorities and was conducted in compliance with Good Clinical Practice and the standards of the Declaration of Helsinki.

Eligibility Criteria

Patients who were entered onto this randomized, open-label, phase III study had to fulfill the following criteria: histologically proven EOC (all histology was reviewed before random assignment by a central pathology review committee: G. Stamp and G. Spiegel), International Federation of Gynecology and Obstetrics (FIGO) stage $\geq$ Ic, and complete clinical response, as assessed by physical examination, computed tomography (CT) scan, and CA-125. All patients were required to have received a platinum-based chemotherapy regimen and to have undergone an attempt at surgical cytoreduction. At the time of primary screening, patients had to be 18 years old or older, have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and a life expectancy of more than 3 months. At baseline, patients had to have adequate hematologic (leukocyte count $\geq 3 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin $\geq$ 10 g/dL), renal (serum creatinine $\leq$ 177 μmol/L or 20 mg/L), and liver function (ALT and AST not higher than 2$\times$ the upper limit of normal). In addition, the final eligibility criteria included a macroscopically negative second-look laparoscopy (SLL) that was to be performed in those patients who met primary eligibility criteria between 4 and 8 weeks after the delivery of their final cycle of chemotherapy.

Patients were excluded from entering the study if they had known metastases at the time of the SLL or had prior/concomitant malignancy, other than basal cell carcinoma of the skin. Patients with extensive IP adhesions that would prevent dispersal of study medication in less than three quadrants were excluded. This was assessed both at the time of laparoscopy and then by CT scan or isotope diffusion scan. Patients who had previous exposure to a murine antibody, were positive for human antimurine antibodies (HAMA) at a level of greater than 50 ng/mL (HAMA Elisa; Roche Diagnostics, Basel, Switzerland), or had a tumor that proved to be MUC1 negative at central pathology review were excluded. Patients participating in other trials involving investigative consolidation or intensification strategies were also excluded, as were patients with recurrent disease.

Study Medication

The murine HMFG1 anti-MUC1 monoclonal antibody was manufactured by BioInvent (Lund, Sweden) in accordance with the standards of Good Manufacturing Practice. The murine HMFG1 antibody is an intact immunoglobulin G1. The investigational product comprised the following two components: 20 mg of muHMFG1 and 5 mg of immunoconjugate (muHMFG1 antibody linked to the chelating agent p-isothiocyanatobenzyldiethylenetriaminepentaacetic acid), as described previously.[15] Immediately before administration, the immunoconjugate, muHMFG1–p-isothiocyanatobenzyldiethylenetriaminepentaacetic acid was radiolabeled with yttrium-90, a radioactive beta-emitting metal. Thin-layer chromatography was conducted to ensure a minimum of 95% radiolabeling efficacy.

Study Procedures

Patients were randomly assigned (1:1) to receive either ^{90}Y-muHMFG1 plus standard care or standard care only. After random assignment but before administration of study medication, patients had to undergo an SLL to confirm the absence of macroscopic disease. Patients with visible disease at SLL were excluded from the study. Patients without visible residual disease who were assigned to active therapy received a single IP infusion of ^{90}Y-muHMFG1 25 mg to provide a planned dose of 666 MBq/m^2 (18 mCi/m^2) of body-surface area and not exceeding 1,110 MBq (30 mCi) in total. During the first hour after administration of study medication, the patient was moved frequently to ensure adequate dispersal of medication.

Institutions were permitted to deliver other standard consolidation therapies after the study per written institutional guidelines, which were defined before study initiation. In all cases, the standard consolidation therapy was delivered to patients in both treatment groups. Institutions choosing consolidation strategies that were potentially myelotoxic were not permitted to initiate such therapies within 4 weeks of study medication.

Patients who received ^{90}Y-muHMFG1 were observed weekly for the first 6 weeks and at week 8 and month 3, whereas patients who received standard care were observed at weeks 1, 4, and 8 and month 3. Thereafter, follow-up for all patients occurred at 3-month intervals for 36 months and then at 6-month intervals until study completion.

Assessments conducted during the study included clinical tumor evaluation, laboratory assessments (hematology, biochemistry, CA-125, and HAMA levels), ultrasound, CT or magnetic resonance imaging scan (when relapse was suspected and at least once per year), Eastern Cooperative Oncology Group performance status, and assessments of adverse events.

Efficacy Parameters

The primary efficacy end point was overall survival. For patients who died during the study, survival was measured as the number of days between the SLL and death from any cause. Survival times for all other patients were censored at the end of the trial (March 8, 2004) or when the patient was withdrawn from the study, whichever occurred first.

Secondary efficacy end points included an analysis of time to relapse. Time to relapse was defined as the time from laparoscopy to clinical presence of disease or time of death, if death occurred without a prior diagnosis of relapse. The clinical presence of disease had to be supported by independent assessment, using radiologic, histologic, or cytologic evidence.

Safety Parameters

Safety was assessed by the collection of adverse events, toxicity (evaluated, recorded, and graded using the National Cancer Institute Common Toxicity Criteria), and laboratory data. Adverse events were collected for up to 3 months after the SLL; severe adverse events were collected throughout the study. Severe adverse events were defined as any event that resulted in death, was life threatening, required hospitalization or prolongation of existing hospitalization, or resulted in persistent or significant disability/incapacity. Safety was independently monitored on a regular basis during the study by an independent Data and Safety Monitoring Board.

Statistical Methods

This study had an 80% power to detect a 15% difference in survival times between the two study arms. The study design was event driven, and patients were observed until at least 116 deaths had occurred. All statistical tests were performed at the 0.05 level of significance, unless specifically stated, and were two sided. A single hypothesis test, comparing treatment groups with respect to all-cause mortality, was confirmatory, with a difference between the treatments being asserted if the observed significance level was less than 0.05. The intent-to-treat population was the primary population. A single interim analysis evaluating primary outcomes was performed after 87 deaths and was presented to the independent Data and Safety Monitoring Board.

Time to event variables were estimated using the Kaplan-Meier method. Differences between treatments with respect to time to event variables were assessed using either the log-rank test or Cox model regression when it was necessary to consider the impact of covariates. Analysis of survival times was performed using a Cox model regression with the inclusion of the following two binary covariates: initial FIGO stage at diagnosis ($\leq$ II $v \geq$ III) and the extent of residual disease after cytoreductive surgery (no residual disease v presence of residual disease).

RESULTS

Patient Characteristics

In total, 844 patients consented and initiated screening. Of these, 142 patients were excluded as a result of ineligible histologic diagnosis at review or for logistic reasons, and 702 patients were randomly assigned (345 were assigned to active treatment and 357 were assigned to standard care). After random assignment, 133 patients were excluded as a result of reasons listed in Table 1, 122 patients were found to have residual disease at SLL. The remaining 447 patients constituted the intent-to-treat analysis group (224 patients in the active treatment group and 223 in the standard care group). The median duration of follow-up was 1,042 days. In total, 296 patients completed the study (145 patients in the active treatment group and 151 in the standard care group), 131 patients died (70 patients in the active group and 61 in the standard care group), eight patients withdrew consent (two patients in the active group and six patients in the standard care group), seven patients were withdrawn for other reasons (four patients in the active treatment group and three in the standard care group), and five patients were lost to follow-up (three patients in the active treatment group and two in the standard care group).

Baseline patient demographics and disease characteristics are listed in Table 2. Overall, patient characteristics at baseline were well balanced between the two treatment arms, although there was a higher proportion of patients in the ^{90}Y-muHMFG1 arm with residual disease after their primary surgery compared with the standard care arm (44.2% v 35.9%, respectively). As part of the random assignment process, residual disease was included as a covariate in the analysis. The median age of patients in the active treatment and standard care arms was 54.5 and 53.7 years, respectively. The majority of patients were FIGO stage III or greater at baseline (72.3% in the ^{90}Y-muHMFG1 arm and 69.5% in the standard care arm). The most common histologic tumor subtype in both arms was serous (64.1% in the ^{90}Y-muHMFG1 arm and 57.5% in the standard care arm). Fifty-seven percent of patients in the ^{90}Y-muHMFG1 arm and 55.7% of patients in the standard care arm had poorly differentiated tumor types.

During the follow-up period, 58.0% of patients in the ^{90}Y-muHMFG1 group and 55.6% of patients in the standard care group

Table 1. Screening Failures: Reasons Why Patients Were Excluded From the Study After Second-Look Laparoscopy Was Performed (ie, before the random assignment code was broken)

Reason	Experimental Arm (No.)	Standard Arm (No.)	Total (No.)
HAMA positive	6	17	23
Histology failure on review	6	9	15
Residual disease on CT or biopsy	6	4	10
Raised CA-125	3	4	7
Medical problems	5	3	8
Myelosuppression	3	4	7
Patient withdrawal	3	6	9
Doctor/sponsor withdrawal	1	3	4
Adhesions at laparoscopy	17	14	31
Laparoscopic complications	4	2	6
Poor distribution on imaging study	6	0	6
Other	1	6	7
Total	61	72	133

Abbreviations: HAMA, human antimurine antibodies; CT, computed tomography.

Table 2. Patient Demographics and Disease Characteristics

Demographic/Characteristic	% of Patients	
	^{90}Y-muHMFG1	Standard Care
Age, years		
Median	54.5	53.7
Range	21-76	23-79
ECOG performance status		
0	77.6	75.0
1-2	22.4	25.0
FIGO stage		
Ic	14.3	16.1
IIa	2.2	4.0
IIb	3.6	2.2
IIc	7.6	8.1
III	66.1	64.1
IV	6.3	5.4
Histology		
Serous	64.1	57.5
Mucinous	2.3	6.3
Endometrioid	25.0	22.6
Clear cell	10.0	12.2
Malignant Brenner	0.5	0.5
Undifferentiated	4.5	5.0
Other	2.3	3.2
MUC1-stained cells		
$\leq$ 60%	18.4	23.6
$>$ 60%	81.6	76.4
Prior taxane	92.4	93.3
Residual disease after surgery		
Yes	44.2	35.9
No	47.8	55.2
Unknown	8.0	9.0
Microscopic disease at SLL		
Yes	9.8	10.3
No	90.2	89.7

Abbreviations: ^{90}Y-muHMFG1, yttrium-90-labeled muHMFG1; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; SLL, second-look laparoscopy.

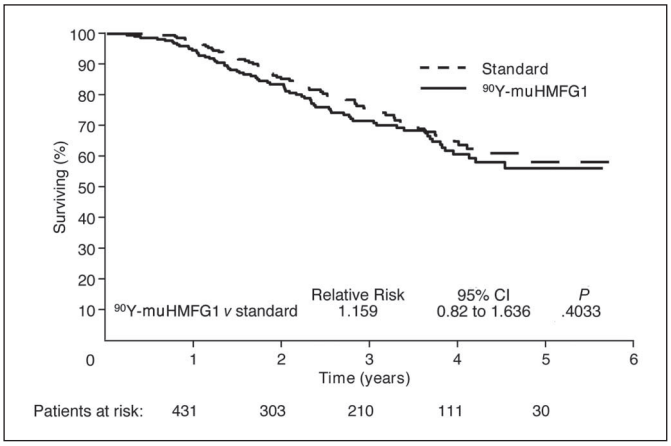

Fig 1. Kaplan-Meier curve of survival (intent-to-treat population). ^{90}Y-muHMFG1, yttrium-90–labeled murine HMFG1.

received chemotherapy. Within 100 days of laparoscopy, 12.5% of patients in the ^{90}Y-muHMFG1 group and 19.7% in the standard care group received chemotherapy. The most commonly used second-line chemotherapeutic regimens were platinum/taxane/other (31.5% in the ^{90}Y-muHMFG1 arm and 36.3% in the standard care arm) and platinum/other (23.8% in the ^{90}Y-muHMFG1 arm and 23.4% on the standard care arm).

Efficacy

The primary efficacy end point was length of survival. A Kaplan-Meier plot of survival times is shown in Figure 1. Cox proportional hazards model analysis of survival showed no significant difference in survival times between the ^{90}Y-muHMFG1 arm and the standard care arm, with a relative risk of death of 1.159 ($P = .4033$). During the study, 70 patients (31.3%) died on the ^{90}Y-muHMFG1 arm, and 61 (27.4%) died on the standard care arm. An exploratory analysis of subgroups failed to identify a subgroup that benefited from ^{90}Y-muHMFG1 treatment compared with the standard care arm. Subgroup analyses comprised FIGO stage, presence or absence of microscopic disease at SLL, presence or absence of residual disease after primary surgery, histology (serous or other), number of MUC1-stained cells ($\leq 60\%$ or $> 60\%$), intensity of stained cells, level of differentiation (well/moderate or poor), age (≤ 55 or > 55 years), and location (United States or non–United States).

A multivariate analysis was performed to look at the impact of baseline disease characteristics on survival for the entire study population (Table 3). The relative risk of death was significantly greater for patients with a FIGO stage of $\geq$ III at baseline compared with patients with a FIGO stage of $\leq$ II (relative risk = 2.733; $P = .0003$). Patients with microscopic disease at the time of the SLL had a significantly higher relative risk of death compared with patients without microscopic disease (relative risk = 1.81; $P = .0125$).

Figure 2 is a Kaplan-Meier plot of time to relapse. There was no statistically significant difference between the ^{90}Y-muHMFG1 arm and the standard care arm with respect to time to relapse (relative risk = 0.904; $P = .4764$). There were 104 relapses (46.4%) on the ^{90}Y-muHMFG1 arm and 98 relapses (43.9%) on the standard care arm. Multivariate analysis looking at the impact of baseline characteristics on relapse demonstrated that patients whose disease was FIGO stage III or greater at baseline were at significantly greater risk of relapse than patients whose disease was FIGO stage II or less (relative risk = 3.126; $P < .0001$; Table 4). Additionally, patients with residual disease after primary surgery were at significantly greater risk of relapse than patients without residual disease (relative risk = 1.432; $P = .0241$).

Mean CA-125 levels after laparoscopy initially increased for the experimental arm compared with the standard care arm; however, by month 3, CA-125 levels were similar in both treatment arms. There was no statistically significant difference in the time to serologic relapse in the ^{90}Y-muHMFG1 arm compared with the standard care arm, with a relative risk of serologic relapse of 0.83 ($P = .3140$). Multivariate analysis of the effect of baseline factors on serologic relapse showed also that the relative risk of serologic relapse was significantly greater for patients with FIGO stage III or greater disease at baseline compared with patients with FIGO stage II or less disease (relative risk = 4.427; $P < .0001$). Similarly, patients with residual disease after primary surgery had a significantly greater risk of serologic relapse than patients without residual disease (relative risk = 1.535; $P = .0381$).

Safety

Adverse events were collected during the first 90 days of the study. The most common clinical adverse events are listed in Table 5. The most common events associated with ^{90}Y-muHMFG1 treatment were nausea, fatigue, arthralgia, myalgia, abdominal pain, rash, vomiting, and diarrhea. These events were predominantly mild to moderate in severity and were transient.

Hematologic toxicities were more common in the ^{90}Y-muHMFG1 arm compared with the standard care arm, with the peak incidence occurring approximately 6 weeks after study medication administration (Table 6). By week 8, more than 80% of patients who received ^{90}Y-muHMFG1 had at least one hematologic toxicity, and 26% of patients had National Cancer Institute grade 3 or 4 hematologic toxicities. Thrombocytopenia was the most common hematologic

Table 3. Disease, Treatment, and Patient Characteristics Evaluated for an Association With Disease Recurrence: Cox Regression Analysis of Time to Death (intent-to-treat population)

Characteristic	Relative Risk	95% CI	Z	*P*
^{90}Y-muHMFG1 *v* standard care	1.159	0.82 to 1.636	0.835	.4034
FIGO stage $\geq$ III *v* $\leq$ II	2.733	1.58 to 4.727	3.598	.0003
Residual disease, yes *v* no	1.305	0.879 to 1.938	1.321	.1866
Residual disease, not known *v* no	1.899	1.045 to 3.452	2.105	.0353
Microscopic disease at SLL, no *v* yes	0.551	0.345 to 0.879	−2.499	.0125

Abbreviations: ^{90}Y-muHMFG1, yttrium-90-labeled muHMFG1; FIGO, International Federation of Gynecology and Obstetrics; SLL, second-look laparoscopy.

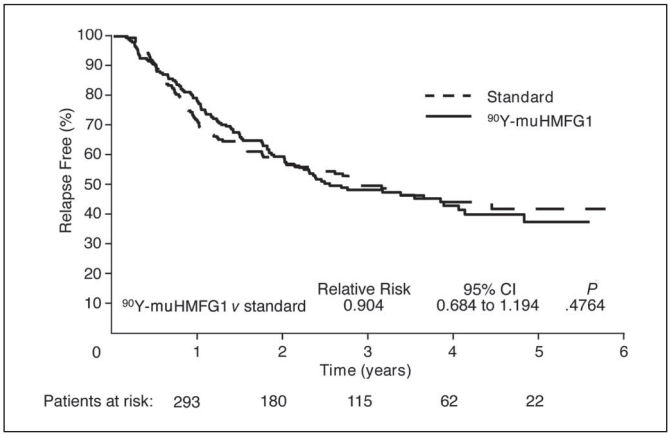

Fig 2. Kaplan-Meier curve of time to relapse (intent-to-treat population). ^{90}Y-muHMFG1, yttrium-90–labeled murine HMFG1.

toxicity associated with ^{90}Y-muHMFG1 and was recorded for 24.3% of patients. Serious adverse events were balanced between the two arms, and most were attributed to complications of recurrent disease.

DISCUSSION

Although more radical surgical technologies exist and better chemotherapeutic regimens have significantly improved the interval between diagnosis and death, the overall survival rate for advanced cancer of the ovary has not changed significantly over the last 25 years. A single IP administration of ^{90}Y-muHMFG1 murine monoclonal antibody did not prolong survival in patients with a negative SLL after surgical debulking and platinum-based chemotherapy. Moreover, the proportion of patients with tumor recurrence and the time to relapse were similar in the two treatment arms. No subgroup of patients could be identified for whom IP radiolabeled antibody conferred an advantage compared with standard care. At the time of analysis, the study was adequately powered to detect a 15% difference in survival, if such a difference existed. The group randomly assigned to ^{90}Y-muHMFG1 did not show an increase in severe adverse events. Baseline factors found to have a detrimental effect on mortality were higher FIGO stage, presence of residual disease after primary surgery, presence of microscopic disease at SLL, and poorly differentiated tumor types.

This is the largest prospective and randomized trial evaluating a novel therapeutic strategy in women with no evidence of macroscopic disease at SLL after primary platinum-based therapy. Prior studies using IP platinum, oral hexamethylmelamine, or even high-dose chemotherapy with autologous bone marrow or stem-cell rescue have also explored consolidation or intensification strategies.[16] All of these trials have demonstrated that these therapies are feasible in selected patient populations, with encouraging disease-free survival in phase II studies. For example, administration of 6 months of oral hexamethylmelamine to a group of women in a clinical complete response led to a 28-month disease-free survival.[17] Administration of IP platinum to a group of women with a negative second-look laparotomy was also associated with a long disease-free period.[18] All of these trials were single armed and, hence, cannot exclude selection bias. The recently reported Southwest Oncology Group/Gynecologic Oncology Group study was a randomized comparison of short-course (3-month) paclitaxel versus a year of paclitaxel consolidation. This study demonstrated a significant prolongation in disease-free survival, but its design did not allow demonstration of a survival advantage.[19] A report of a randomized trial evaluating consolidation therapy in women who had a response to primary platinum-based therapy demonstrated that consolidating topotecan offered no advantage to immediate chemotherapy.[20] In the majority of these studies, response was clinically defined instead of surgically determined.

Why did this study fail to demonstrate an effect on disease-free or overall survival? In retrospect, dose and pharmacokinetics, as well as biologic factors, may have reduced the likelihood of success. The dose of the radionuclide may have been insufficient. In previous studies, we attempted to estimate the microdosimetry to the peritoneal surface after IP administration of radiolabeled antibodies such as HMFG1. It was found that, when using iodine-131 as the radiolabel, the dose of radiation from a single administration of radiolabeled antibody was sufficiently high to sterilize macroscopic epithelial tumors, such as ovarian cancer, in only a few patients.[21] Therefore, the isotope was changed from iodine-131 to yttrium-90 with the expectation that dosimetry would be more favorable.[22] It is conceivable that substitution of yttrium with lutetium or rhenium would have further improved efficacy, but these radionuclides were not in clinical use at the time of study initiation. Although 80% of the antibody was unlabeled, previous studies had supported this mixture to optimize pharmacokinetics.[15] Finally, in contrast to previous studies, our patients all had microscopic residual disease at most, which may theoretically have hampered sufficient or appropriate binding.

Pharmacokinetics were not performed in this study, and it is possible that there was limited systemic exposure to the intact radioimmunoconjugate. From previous studies, it was known that approximately 20% of the injected dose could enter the systemic circulation within 48 hours from the time of administration. There is growing evidence that EOC is a systemic disease, and although the bulk of this tumor resides within the peritoneal cavity, tumor

Table 4. Disease, Treatment, and Patient Characteristics Evaluated for an Association With Disease Recurrence: Cox Regression Analysis of Time to Relapse (intent-to-treat population)

Characteristic	Relative Risk	95% CI	Z	*P*
^{90}Y-muHMFG1 *v* standard care	0.904	0.685 to 1.194	−0.71	.4776
FIGO stage ≥ III *v* ≤ II	3.126	2.054 to 4.758	5.319	.0000
Residual disease, yes *v* no	1.432	1.048 to 1.957	2.255	.0241
Residual disease, not known *v* no	1.331	0.779 to 2.273	1.047	.2950

Abbreviations: ^{90}Y-muHMFG1, yttrium-90-labeled muHMFG1; FIGO, International Federation of Gynecology and Obstetrics.

cells can frequently be detected in retroperitoneal lymph nodes, bone marrow, and blood at the time of diagnosis. Limited extraperitoneal exposure with this agent may be a contributory factor to the failure of the current approach.

Limited radiation dose to the tumor from a single administration of ^{90}Y-muHMFG1 may be the most important reason why this approach failed. This may be overcome by repeat doses of radiolabeled antibody preferably using a nonimmunogenic protein, such as human or humanized antibody, administered concurrently with, rather than after, chemotherapy, as was done in this study. It has recently been shown by several investigators that one can obtain a cooperative effect when radiolabeled antibodies are combined with chemotherapy.[23] Several issues precluded such a study design, including concerns about cumulative hematologic toxicity and logistic challenges of repetitive administration of IP radiolabeled antibody and the development of HAMA. This latter issue may not be a significant limitation with IP administration because the IP-administered antibody enters the systemic circulation slowly.

Biologic issues may have also limited the trial's chance for success, including the submesothelial location of tumor metastases that may have shielded the *MUC1* antigen expression from the IP cavity, thus avoiding interaction with the antimucin antibody. It is also possible that nests of residual small-volume disease include clusters of cells that lack the appropriate mucin epitope. However, the beta radiation emitted from the yttrium-90 isotope should be able to reach and irradiate clusters of antigen-negative tumor cells that are present a few millimeters away from the tumor-bound radiolabeled antibody. It is possible that delivery of this therapy immediately postoperatively or further from primary therapy may have provided more optimal physiologic or immunologic conditions for success.

Another potentially confounding variable was the use of additional consolidation strategies in both the active and control populations. The publication of the Southwest Oncology Group/Gynecologic Oncology Group paclitaxel consolidation study, as well as institutional and/or investigator biases about the potential value of consolidation, required the incorporation of such treatment at the discretion of the lead investigators. The use of consolidation was to be defined by the institution's lead investigator at the time the trial was opened, and both the control and active treatment arms were to receive this therapy. Most institutions did not incorporate consolidation strategies, whereas other institutions did incorporate paclitaxel or other therapies. Within 100 days of laparoscopy, 19.7% of patients randomly assigned to standard care received chemotherapy, which, in view of the timing, should be regarded as consolidation therapy, compared with 12.5% of patients assigned to the ^{90}Y-muHMFG1 arm. It is possible that the unbalanced delivery of consolidation therapy may have altered the study outcome or, alternatively, that such therapies abrogated the potential benefit of what might be considered an IP immunotherapy.

Table 6. National Cancer Institute Grade 3 or 4 Hematologic Toxicity at Weeks 0, 4, 6, and 8 and Month 6 for the Experimental Arm

	Platelets		Neutrophils	
	Grade ≥ 3		Grade ≥ 3	
Time	No. of Patients	%	No. of Patients	%
Week 0	0	0	0	0
Week 4	9	4.3	0	0
Week 6	51	24.3	1	0.5
Week 8	27	12.9	1	0.5
Month 6	5	2.4	0	0

Despite the lack of therapeutic efficacy, this study has provided the largest prospectively collected database of patients with a negative SLL and is, therefore, a valuable resource for studying patients with EOC who respond well to primary therapy. For example, the database can be used to study the impact of various prognostic factors in this patient population, predictors of negative SLL, safety of SLL in this patient population, and patterns of relapse in both the treated and untreated population. Such analyses, although not part of the primary study design, are currently being undertaken.

This study constitutes the largest prospective series of laparoscopy after primary treatment for ovarian cancer. In a comparative but small (20 patients) study of SLL versus second-look laparotomy, Clough et al[24] were unable to perform a complete IP investigation in 59% of laparoscopies compared with 5% of laparotomies. Our study refutes these results and indicates that laparoscopy is a safe and adequate procedure in patients who have undergone extensive primary surgical as well as cytostatic treatment. Specifically, our findings confirm that, after chemotherapy, adhesions usually do not hamper IP administration. Moreover, chemotherapy might even diminish adhesion formation.[25]

Table 5. Common Adverse Events by National Cancer Institute Grade

	^{90}Y-muHMFG1 (n = 224)						Standard Care (n = 223)					
	Mild		Moderate		Severe		Mild		Moderate		Severe	
Adverse Event	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Nausea	60	27	28	13	6	3	29	13	14	6	3	1
Fatigue	49	22	27	12	2	< 1	28	13	18	8	1	< 1
Arthralgia	46	21	22	10	6	3	24	11	17	8	0	0
Myalgia	35	16	20	9	4	2	9	4	6	3	0	0
Abdominal pain	37	17	19	8	5	2	21	9	16	7	7	3
Rash	29	13	10	4	1	< 1	6	3	5	2	2	< 1
Diarrhea	24	11	13	6	0	0	12	5	6	3	2	< 1
Vomiting	23	10	16	7	2	< 1	14	6	5	2	2	< 1

Abbreviation: ^{90}Y-muHMFG1, yttrium-90-labeled muHMFG1.

This study reaffirms the need for randomized trials in this clinical setting. Strategies to target and eliminate small-volume residual disease at the conclusion of primary chemotherapy remain a high priority in this disease. New targeted therapies, immunotherapies, and chemotherapeutic agents with novel mechanisms of action may offer benefit and should be considered for testing in a similar setting. Hopefully, information gleaned from the conduct of this study will aid in the execution of those trials.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. 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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