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ORIGINAL REPORT

Phase III Trial of Carboplatin Plus Paclitaxel With or Without Gemcitabine in First-Line Treatment of Epithelial Ovarian Cancer

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
One attempt to improve long-term survival in patients with advanced ovarian cancer was thought to be the addition of more non–cross-resistant drugs to platinum-paclitaxel combination regimens. Gemcitabine was among the candidates for a third drug.

Patients and Methods
We performed a prospective, randomized, phase III, intergroup trial to compare carboplatin plus paclitaxel (TC; area under the curve [AUC] 5 and 175 mg/m^2, respectively) with the same combination and additional gemcitabine 800 mg/m^2 on days 1 and 8 (TCG) in previously untreated patients with advanced epithelial ovarian cancer. TC was administered intravenously (IV) on day 1 every 21 days for a planned minimum of six courses. Gemcitabine was administered by IV on days 1 and 8 of each cycle in the TCG arm.

Results
Between 2002 and 2004, 1,742 patients were randomly assigned; 882 and 860 patients received TC and TCG, respectively. Grades 3 to 4 hematologic toxicity and fatigue occurred more frequently in the TCG arm. Accordingly, quality-of-life analysis during chemotherapy showed a disadvantage in the TCG arm. Although objective response was slightly higher in the TCG arm, this did not translate into improved progression-free survival (PFS) or overall survival (OS). Median PFS was 17.8 months for the TCG arm and 19.3 months for the TC arm (hazard ratio [HR], 1.18; 95% CI, 1.06 to 1.32; $P = .0044$). Median OS was 49.5 for the TCG arm and 51.5 months for the TC arm (HR, 1.05; 95% CI, 0.91 to 1.20; $P = .5106$).

Conclusion
The addition of gemcitabine to carboplatin plus paclitaxel increased treatment burden, reduced PFS time, and did not improve OS in patients with advanced epithelial ovarian cancer. Therefore, we recommend no additional clinical use of TCG in this population.

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INTRODUCTION

Since two large studies reported superiority of platinum with paclitaxel compared with the older combination of platinum with alkylating agents,[1,2] this combination has been widely adopted as standard first-line treatment for advanced ovarian cancer. Several attempts have been made to optimize this cisplatin-based regimen, and two randomized trials have demonstrated that carboplatin can substitute for cisplatin without loss of efficacy but superior tolerance and quality of life.[3,4] Among other options, one method for achieving additional progress in the first-line treatment of advanced ovarian cancer might be the addition of a non–cross-resistant drug to platinum and paclitaxel. Gemcitabine was among the candidates to be evaluated as a third drug, because it fulfilled the following prerequisites: it has shown activity as a single agent in relapsed ovarian cancer comparable to the standard liposomal doxorubicin in two randomized trials[5,6]; it has shown activity and could be combined with platinum in so-called platinum-sensitive recurrent ovarian cancer,[7,8] and this combination has proven higher efficacy than carboplatin as a single agent in this population[9]; and it could be added as third drug to platinum-taxane combinations, which thus would allow comparison of the triple-drug regimen

without compromising therapy by withholding a standard drug.[10-12] Consequently, the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) had developed a triple-drug regimen that combines carboplatin plus paclitaxel with gemcitabine (TCG) for additional evaluation.[13] Under the auspices of the Gynecologic Cancer Intergroup (GCIG), the AGO-OVAR together with the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) and the Nordic Society of Gynecologic Oncology (NSGO) performed a prospective, randomized, phase III study to compare TCG with carboplatin plus paclitaxel (TC) in ovarian cancer. Some results of this trial have already been presented at the 45th Annual Meeting of the American Society of Clinical Oncology in 2009,[14] and the final results are reported here.

PATIENTS AND METHODS

The study was carried out in accordance with good clinical practice guidelines, national laws, and the Declaration of Helsinki. Local ethics committee of each center approved the study. All patients provided written informed consent.

Patients with histologically confirmed International Federation of Gynecology and Obstetrics (FIGO)[15] stages I to IV ovarian cancer who had undergone up-front debulking surgery within 6 weeks before random assignment were eligible. All patients had to be at least 18 years of age and were required to have adequate hematologic, renal, and hepatic function, which were defined as follows: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ cells/L, platelets $\geq 100 \times 10^9$ cells/L, and serum creatinine and bilirubin $\leq 1.25 \times$ upper normal limit. Patients were excluded if they had ovarian tumors with low malignant potential; an Eastern Cooperative Oncology Group (ECOG) performance status of greater than 2; an estimated glomerular filtration rate (GFR) less than 50 mL/min; other malignancies, previous chemotherapy, immunotherapy, or radiotherapy; severe neuropathy; cardiac arrhythmias; or congestive heart failure.

Patients were stratified according to residual tumor size and FIGO stage. Stratum 1 contained patients with FIGO I to IIA disease, stratum 2 contained those with FIGO IIB to IIIC disease and residual tumor up to 1 cm, and stratum 3 contained patients with residual tumor larger than 1 cm or with FIGO IV disease. Within each stratum, random assignment lists for each study center were prepared by using permuted blocks of randomly varying size. Patients were stratified (ie, strata S1 to S3) and were randomly assigned by the respective office of the study group. All centers were regularly monitored by trained field monitors, and these checks included review of the surgeon's and pathologist's reports and 100% data source verification.

Patients were randomly assigned to receive carboplatin plus paclitaxel (ie, TC arm) or the same combination added by gemcitabine (ie, TCG arm). The TC arm consisted of paclitaxel 175 mg/m^2 administered intravenously (IV) over 3 hours followed by carboplatin (area under the curve [AUC] 5) administered by IV over 30 to 60 minutes both on day 1 of a 3-week schedule. Patients in the TCG arm received gemcitabine 800 mg/m^2 IV over 30 to 60 minutes on days 1 and 8. The carboplatin dose was calculated according to Calvert.[16] GFR was estimated by using the Jelliffe formula.[17] Regardless of calculated doses, the maximal absolute dose was limited to 385 mg for paclitaxel, 800 mg for carboplatin, and 1,600 mg for gemcitabine. Dose reductions were allowed depending on hematologic or nonhematologic toxicity, as follows: carboplatin AUC 4 (level –1/level –2); paclitaxel 150 mg/m^2 (level –1) or 135 mg/m^2 (level –2); and omission of gemcitabine on day 8 (level –1). Any subsequent treatment cycle was delayed when the patient ANC was less than 1.5×10^9 cells/L or when the platelet count was less than 100×10^9 cells/L. Primary prophylaxis with colony-stimulating factors (ie, granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]) was not allowed; however, supportive G-CSF/GM-CSF treatment could be initiated at the discretion of the investigator. All patients received established antiallergic and antiemetic premedication. Patients with disease progression during therapy went off protocol for treatment. Patients who achieved partial remission after six cycles could receive additional cycles on their physicians' discretion.

Adverse events and toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NIC-CTC).[18] Toxicities were recorded continuously; blood chemistry parameters were measured before each treatment cycle and weekly thereafter. Quality of life was evaluated by using global health status/quality-of-life score of the European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-C30, version 3.0)[19] and the specific module for ovarian cancer (OV-28,

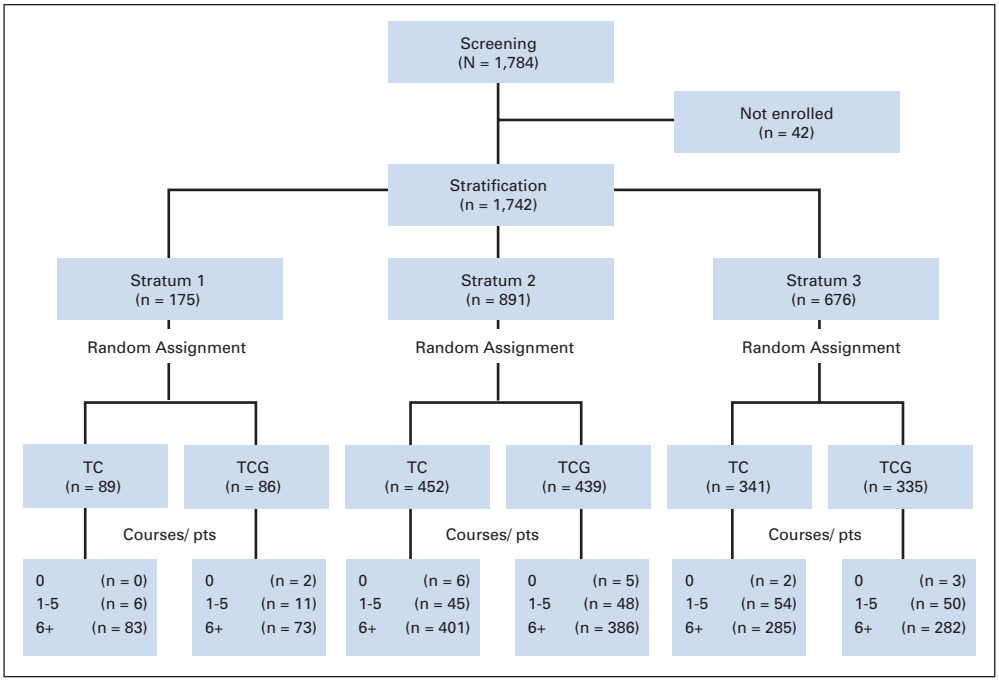

Fig 1. CONSORT diagram. Stratum 1, International Federation of Gynecology and Obstetrics (FIGO) stage I-IIA; stratum 2, FIGO stage IIB-IIIC and residual tumor ≤ 10 mm; stratum 3, FIGO stage IIB-IIIC and residual tumor > 10 mm or FIGO IV. TC, carboplatin plus paclitaxel; TCG, TC plus gemcitabine.

version 1.0).[20] Patients assessed their own health-related quality of life at baseline, after the third treatment cycle, after the last treatment cycle, and 3 months after cessation of treatment. Quality-of-life responses were evaluated according to the EORTC guidelines.[21] Tumor measurements were made before each cycle by physical examination, before every third cycle by imaging methods in patients with measurable or evaluable disease, and after the last cycle. The same tumor assessment methods that were employed for baseline measurement were used for each repeat evaluation. Tumor response was graded according to Response Evaluation Criteria in Solid Tumors (RECIST).[22] Follow-up visits were scheduled every 3 months in the first 2 years after cessation of treatment and every 6 months thereafter, for a total follow-up time of 5 years.

The primary end point was overall survival (OS), defined as the time from random assignment to death as a result of any cause. Secondary end points were progression-free survival (PFS), response to treatment, toxicity, and quality of life. Toxicities were evaluated per course and per patient (worst score over all courses).

Time-to-event data were analyzed by using the Kaplan-Meier method, and the (stratified) log-rank test was used to compare the distributions between groups. In addition, hazard ratios (HRs) with 95% CIs were estimated by using the Cox proportional hazards model. Response rates were estimated by using the method of Blyth-Still-Casella and were compared by using exact methods for stratified testing, including the Zelens exact test. The global health score of the QLQ-C30 as well as its difference from baseline were used as summary measures of the quality-of-life analysis and were compared by using the Wilcoxon-Mann-Whitney test.

According to protocol, confirmatory analysis encompassed hierarchically testing differences in OS between treatment arms (ie, two-sided stratified tests) within all strata at a type I error level of 5%. An HR of 9/11 = 0.818, which corresponds to an increased median survival of 8 months, was postulated as a clinically meaningful difference to be detected with a power of 80%. This required at least 783 observed deaths and provided a power of at least 50% for an HR of 6/7 = 0.857. An optimized group sequential design with two interim analyses after observation of 407 and 604 deaths, spending cumulative type I error rate of 0.00796 and 0.01838, respectively, and the final analysis after observation of 801 deaths were fixed in the protocol for S2 and S3 (ie, both strata together). On the basis of the OS of patients treated with TC in AGO-GINECO study OVAR-5,[23] the number of patients needed was calculated.[24] Assuming that 13% of patients belong to S1, and compensating for a lost-to-follow-up rate of 10%, recruitment of 1,716 patients was planned.

Table 1. Baseline Patient Demographic and Clinical Characteristics

Characteristic	Treatment Arm					
	TC		TCG		Overall	
	No.	%	No.	%	No.	%
No. of patients	882	50.6	860	49.4	1,742	100.0
Age in years						
Median	60		59		60	
Range	23-82		20-80		20-82	
FIGO stage						
IA	12	1.4	13	1.5	25	1.4
IB	3	0.3	1	0.1	4	0.2
IC	61	6.9	57	6.6	118	6.8
IIA	19	2.2	19	2.2	38	2.2
IIB	26	2.9	31	3.6	57	3.3
IIC	38	4.3	37	4.3	75	4.3
IIIA	29	3.3	33	3.8	62	3.6
IIIB	67	7.6	58	6.8	125	7.2
IIIC	484	54.9	470	54.7	954	54.8
IV	143	16.2	140	16.3	283	16.3
Unknown	0		1		1	
Postoperative residual tumor size, cm						
≤ 1	569	70.9	542	69.2	1,111	70.1
> 1	234	29.1	241	30.8	475	29.9
Unknown	79		77		156	
Histology						
Serous/papillary	650	73.7	646	75.1	1,296	74.4
Mucinous/clear cell	40	4.5	40	4.7	80	4.6
Other	192	21.8	174	20.2	366	21.0
Histologic grading						
G1	90	10.7	57	6.9	147	8.8
G2	244	29.1	278	33.7	522	31.4
G3	505	60.2	491	59.4	996	59.8
Unknown	43		34		77	
ECOG performance status						
0	372	42.2	373	43.4	745	42.8
1	434	49.3	421	49.0	855	49.1
2	75	8.5	66	7.7	141	8.1
Unknown	1		0		1	

Abbreviations: TC, paclitaxel/carboplatin treatment; TCG, paclitaxel/carboplatin/gemcitabine treatment; FIGO, International Federation of Gynecology and Obstetrics; ECOG, Eastern Cooperative Oncology Group.

To cope with deviations from the prespecified numbers of observed deaths or other uncertainties, a use function[25] was set up by reoptimization, and the method for a redesign[26] was fixed as predefined in the protocol. Each of the two confirmatory interim analyses after 430 and 620 observed deaths in S2 and S3 neither induced a stop nor induced a redesign. Therefore, the calculated values of the local type I error level for the final analysis after observation of 817 deaths in all strata and 805 deaths in S2 and S3 were 0.04389 and 0.04391, respectively.

Efficacy analyses were primarily performed according to intention-to-treat (ITT) protocol and included all randomly assigned patients. Sensitivity analyses were additionally performed on a per-protocol (PP) basis and used clean data after monitoring. PP analyses excluded ineligible patients and corrected with regards to stratification (ie, strata P1 to P3).

Analyses were performed with SAS, version 9.1 (SAS Institute, Cary, NC) and StatXact of Cytel Studio, version 6.2.0 (Cytel Studio; Cytel Corporation, Cambridge, MA). Two-sided *P* values quantified results of confirmatory or descriptive tests.

RESULTS

Between 2002 and 2004, 1,784 patients were screened. Of these, 42 patients (2.4%) were not enrolled because of low GFR, incorrect histology, other malignancies, or surgery more than 6 weeks before study entry. Of the remaining 1,742 patients, 175 patients fulfilled the criteria for stratum 1; 891, for stratum 2; and 676, for stratum 3 (Fig 1). Overall, 882 patients were randomly assigned to TC, and 860 were randomly assigned to TCG. The treatment arms were well balanced (Table 1).

Overall, 5,268 cycles were administered in the TC arm, and 5,129 cycles were administered in the TCG arm. Most patients received at least six treatment cycles: 87.2% in the TC arm and 86.2% in the TCG arm; 139 of the patients in the TC arm (15.8%)

Table 2. Grading of Toxicities and Supportive Therapy by Treatment Arm

		% of Patients According to NCI-CTC Grade by Treatment Arm												
		TC						TCG						
Toxicity	Set	No. of Patients	0	1	2	3	4	No. of Patients	0	1	2	3	4	*P**
Auditory	P	866	92.5	5.2	1.5	0.7	0.1	840	92.9	4.2	1.9	0.8	0.2	.5773
Allergic reaction	P	869	66.4	22.2	7.5	2.8	1.2	841	68.5	19.7	7.9	3.1	0.8	.9939
Edema	P	865	78.2	16.8	4.5	0.5	0.1	839	73.8	19.0	6.0	1.2	0.1	.1175
Alopecia	P	859	2.6	3.6	93.8	—	—	827	4.0	3.1	92.9	—	—	.4330
Constipation	P	865	47.5	27.3	20.7	3.8	0.7	841	48.5	23.9	21.0	4.8	1.8	.0672
Diarrhea	P	865	73.6	16.4	6.7	3.0	0.2	841	67.3	19.3	10.1	3.0	0.4	.9173
Nausea	P	865	36.9	42.2	17.7	3.2	—	841	33.7	40.4	21.6	4.3	—	.2579
Emesis	P	865	67.3	20.2	9.5	2.8	0.2	840	60.2	22.5	13.6	3.1	0.6	.4344
Stomatitis/mucositis	P	865	76.9	18.3	4.2	0.5	0.1	840	70.6	21.2	7.6	0.4	0.2	.9669
Infections	P	866	79.5	7.6	9.6	3.2	0.1	840	75.8	9.6	9.9	3.8	0.8	.1724
Neuropathy motor	P	865	80.4	13.0	4.5	2.1	0.1	840	81.1	11.1	4.9	2.9	0.1	.3139
Neuropathy sensory	P	865	28.1	39.7	25.8	6.0	0.5	840	28.1	38.2	26.3	6.6	0.8	.4655
Vertigo	P	865	88.1	8.9	2.8	0.2	0.0	840	85.7	10.4	3.1	0.8	0.0	.0824
Arthralgia	P	865	52.1	26.0	17.1	4.7	0.0	840	51.1	29.0	15.8	3.6	0.5	.4871
Pain, other	P	865	31.6	32.1	27.1	8.8	0.5	842	29.9	35.0	26.6	7.4	1.1	.5515
Creatinine	P	872	94.0	5.2	0.2	0.2	0.3	848	95.5	4.1	0.4	0.0	0.0	.0271
Fatigue	P	865	28.6	35.6	28.8	6.2	0.8	840	23.3	36.8	29.4	8.8	1.7	.0125
Hemoglobin	C	5,168	28.5	54.8	15.7	1.0	0.1	5,067	11.2	45.2	38.7	4.2	0.8	< .001
Hemoglobin	P	873	9.1	50.3	36.3	4.0	0.3	848	2.2	18.9	61.1	15.0	2.8	< .001
Platelets	C	5,168	78.4	18.8	1.8	1.0	0.1	5,068	44.9	32.2	11.5	10.8	0.6	< .001
Platelets	P	873	52.6	36.9	5.8	4.4	0.3	848	13.4	28.3	22.5	32.0	3.8	< .001
Leukocytes	C	5,168	29.0	28.8	32.9	8.9	0.4	5,067	14.9	18.6	38.2	26.1	2.2	< .001
Leukocytes	P	873	9.2	18.4	44.3	25.9	2.2	848	2.9	4.0	22.9	59.8	10.4	< .001
Neutrophils	C	4,905	33.4	14.0	20.3	21.8	10.5	4,882	22.4	11.2	21.2	28.2	17.0	< .001
Neutrophils	P	860	12.1	9.0	16.9	32.9	29.2	842	5.8	2.9	9.9	29.5	52.0	< .001
Febrile neutropenia	C	5,115	99.6	—	—	0.3	0.1	5,003	98.8	—	—	1.1	0.1	< .001
Febrile neutropenia	P	866	97.7	—	—	2.0	0.3	840	93.5	—	—	6.0	0.6	< .001
Transfusion of blood products	C	5,268	97.7			2.3		5,129	90.7			9.3		< .001
Transfusion of blood products	P	874	90.0			10.0		850	67.5			32.5		< .001
Supportive care EPO	C	5,268	94.4			5.6		5,129	87.7			12.3		< .001
Supportive care EPO	P	874	88.4			11.6		850	73.3			26.7		< .001
Supportive care G-CSF/GM-CSF	C	5,268	94.7			5.4		5,129	87.4			12.6		< .001
Supportive care G-CSF/GM-CSF	P	874	87.2			12.8		850	72.0			28.0		< .001
Supportive care antibiotics	C	5,268	96.8			3.2		5,129	94.7			5.3		< .001
Supportive care antibiotics	P	874	85.9			14.1		850	78.4			21.6		< .001

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; TC, paclitaxel/carboplatin treatment; TCG, paclitaxel/carboplatin/gemcitabine treatment; C, grade of all courses; P, maximum grade over all courses within a patient; EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.

*Stratified Cochran-Mantel-Haenszel test for differences in the proportions of courses or patients with grades 3 or 4 toxicity or use of supportive care (yes *v* no), respectively.

and 136 of the patients in the TCG arm (15.8%) received more than six treatment cycles.

Treatment delays of ≥ 7 days occurred more frequently in the TCG arm than the TC arm (11.6% *v* 7.5%; $P < .001$). Overall, 204 (11.8%) of 1,742 patients received at least one dose reduction within courses 1 to 6. Again, there was a significant difference between the treatment arms: 8.7% in the TC arm versus 15.1% in the TCG arm ($P < .001$). The mean carboplatin doses per patient were AUC 4.99 and 4.98 in the TC and TCG arms, respectively. The corresponding mean paclitaxel doses were 172.3 mg/m^2 and 172.6 mg/m^2, respectively. The achieved mean gemcitabine doses were 774.8 mg/m^2 and 511.6 mg/m^2 on day 1 and 8. Actual dose intensity on day 1 was greater than 93% of planned dose in both arms, whereas gemcitabine dose intensity on day 8 decreased to 84.5%.

Grades 3 to 4 hematologic toxicities occurred significantly more frequently in the TCG arm and included hemoglobin, leukocytes, neutrophils, and platelets (Table 2). Furthermore, grades 3 to 4 febrile neutropenia occurred more frequently in the TCG arm, and TCG treated patients received more packed red blood cells, antibiotics, and supportive care with erythropoietin, G-CSF, or GM-CSF (Table 2). All grades 3 to 4 nonhematologic toxicities systematically asked for that occurred in > 1% of patients are displayed in Table 2. Only fatigue occurred significantly more frequent in the TCG arm.

Quality of life was primarily analyzed with respect to change of the global health status. Five hundred twenty-six patients in the TC arm and 519 patients in the TCG arm qualified for this analysis. The distribution of the score values at baseline was comparable in both treatment arms (Fig 2). In both groups, an improvement was observed over time. The addition of gemcitabine to TC showed a delaying impact on improvement of the global health status ($P < .05$ after the third cycle). However, we did not observe any significant differences after completion of chemotherapy.

The median follow-up was 49 months in both groups. Altogether, 102 patients (5.9%) were lost to follow-up, including 69 (4%) before disease progression. A total of 1,246 patients (71.5%) developed progressive disease or recurrence, and 817 patients (46.9%) died within the observation period.

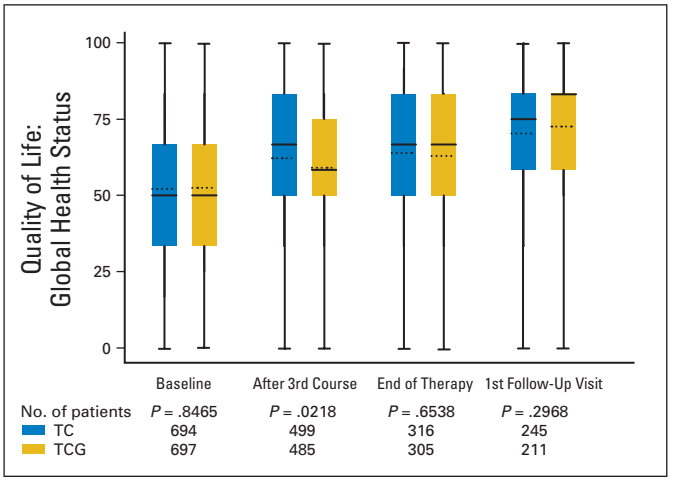

Fig 2. Global quality of life by treatment in all patients according to European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30, version 3.0). Whisker plots indicate maximums and minimums; dotted line indicates mean; solid line indicates median; box indicates interquartile region. TC, carboplatin plus paclitaxel; TCG, TC plus gemcitabine.

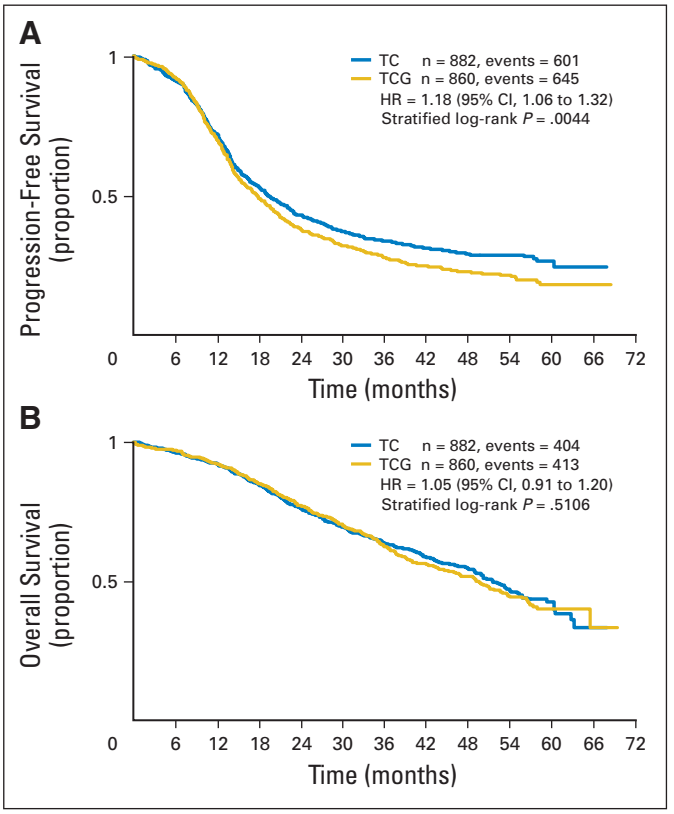

Fig 3. Kaplan-Meier estimates of progression-free survival and overall survival in all randomly assigned patients by treatment. TC, carboplatin plus paclitaxel; TCG, TC plus gemcitabine; HR, hazard ratio.

Only 400 patients (23.0%) had measurable disease at study entry. Of those, tumor response could be assessed in 356 patients (89.0%). Objective response favored the experimental arm and was observed in 86.2% of 174 patients compared with 77.5% of 182 patients in the TC arm ($P = .0303$; Appendix Table A1, online only). This advantage did not translate into superior PFS. In contrast, PFS was superior in the standard arm. This difference was statistically notable; however, differences in median PFS were less than 2 months—19.3 and 17.8 months in the TC and TCG arm, respectively ($P < .01$; Fig 3); a comparable difference in favor of TC was observed in strata 2 and 3 only—17.1 and 15.9 months in the respective arms ($P < .01$; Fig 4). PFS differences of about 1 to 2 months translated into a 2-month difference of median survival, which was 51.5 and 49.5 months for all patients after TC and TCG, respectively. However, this was not statistically significant ($P = .5106$; Fig 3). Observed differences of median survival in strata 2 and 3 in TC and TCG arms were 48.9 and 45.8 months, respectively ($P = .6653$; Fig 4).

Corresponding details for all strata and in the PP populations are shown in Appendix Table A2 (online only). The survival data in stratum 1 suggest an advantage for the standard therapy; however, survival events were rare in this subgroup, and only 12 patients had died so far (Fig 5). An exploratory analysis of HRs for survival on the basis of participating study groups or on established prognostic factors like FIGO stage (I or II *v* III *v* IV), residual tumor (microscopic *v* 1 to 10 mm *v* > 1 cm), and histologic type (serous *v* mucinous/clear cell *v* other) failed to disclose any evidence of a benefit from addition of gemcitabine to TC in any subgroup. Overall, the experimental arm

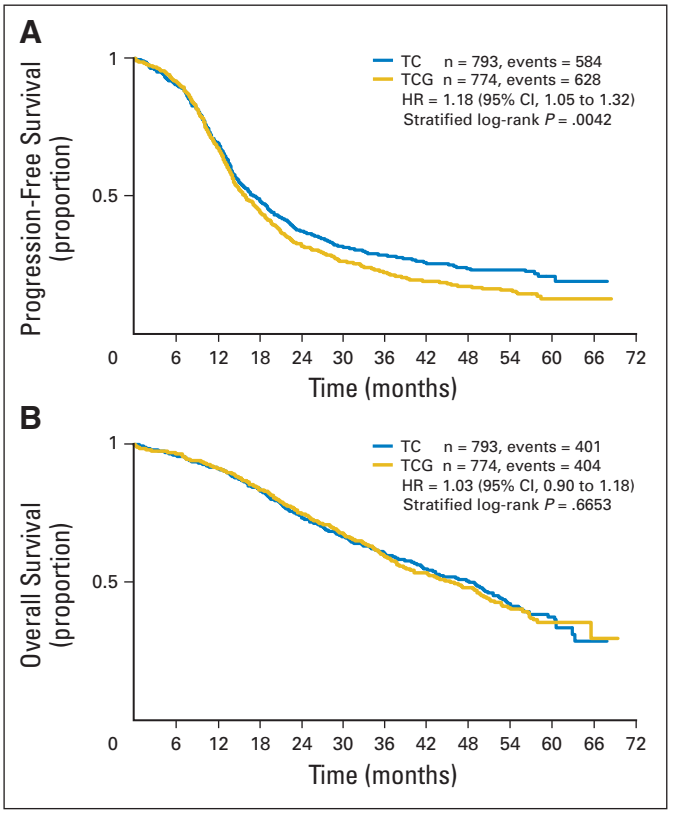

Fig 4. Kaplan-Meier estimates of progression-free survival and overall survival in all randomly assigned patients by treatment within strata 2 and 3. TC, carboplatin plus paclitaxel; TCG, TC plus gemcitabine; HR, hazard ratio.

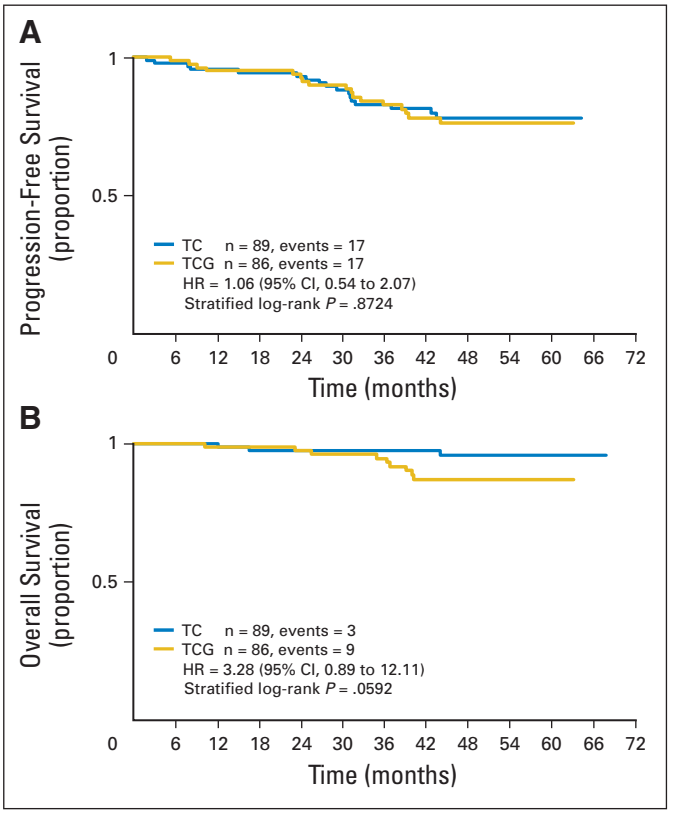

Fig 5. Kaplan-Meier estimates of progression-free survival and overall survival in all randomly assigned patients by treatment within stratum 1. TC, carboplatin plus paclitaxel; TCG, TC plus gemcitabine; HR, hazard ratio.

TCG could not demonstrate the postulated survival benefit. Moreover, a negative trend was observed regarding the primary end point. Furthermore, secondary end point analyses rather showed a potential disadvantage of adding gemcitabine to TC regarding OS in early ovarian cancer (stratum 1); PFS in advanced disease (strata 2 and 3); and hematological toxicity, fatigue, and some aspects of global quality of life.

DISCUSSION

Despite the progress that had been achieved by the incorporation of platinum and taxanes into first-line treatment of ovarian cancer, long-term survival rates are still disappointing, and improving efficacy of chemotherapy is still a major issue. The addition of presumed non–cross-resistant cytostatic drugs to a platinum-taxane backbone was the most popular approach and has dominated clinical study scenarios over the last decade. More than 10,000 patients have been enrolled onto intergroup trials that evaluated anthracylines, topotecan, and gemcitabine incorporated either in triple-drug regimens, within sequential doublets, or as sequential single-agent therapy.[23,27-31] These trials showed unanimously that addition of the third drug did not provide any relevant benefit regarding OS or PFS but was commonly associated with more toxicities and treatment burden. We observed an inferior outcome in the experimental arm in patients with minimal residual tumor when treated with the triple-drug regimen compared with standard TC. The reason for the observed disadvantage remains unclear and was obviously not caused by less-intensive treatment with carboplatin and paclitaxel. Theoretically, the addition of an additional drug, such as cytokines as well, could have implications on immune suppression, which could potentially impact outcome.[32,33] This could theoretically explain the negative trend in OS, especially in low-volume disease, as observed here. Although all efforts of adding a third cytostatic to TC have shown disadvantages rather than any benefit, this did not lead to a change of strategies within the GCIG network. The next generation of trials, which are already completed or still ongoing, followed the same design of adding a third drug either sequentially or concomitantly to TC. Again, experimental drugs were mainly selected on the basis of noncomparative phase II data. The only difference between both generations of trials is that the latter evaluate so-called targeted third drugs (eg, bevacizumab, erlotinib, pazopanib, vargatef). This strategic continuity is based on the assumption that the model did not fail but that the wrong selection of the experimental drug led to serial negative results.[34] However, even promising phase II study results do not necessarily imply that adding the new drug to platinum-taxane combination therapy acts additively or even synergistically, and later phase III results are sometimes disappointing.[35] This deficiency may be based on the dilemma of an only empiric definition of platinum sensitivity. A population selected mainly by treatment-free interval will contain tumors resistant to any conventional chemotherapy (including the new drug), tumors responding to platinum and/or taxanes again, and some not responding to platinum-taxane combinations but to the new drug. The later success of a new drug as combination partner with standard therapy may significantly depend on the composition of the phase II cohort, and

much more effort should be spent on predictive models. In this context, both selection of patient populations and selection of end points must be reconsidered. Most phase II studies chose objective response as a primary end point. However, objective response is only a surrogate end point and might not predict later effect on PFS or OS. In this study, TCG showed a significantly increased response rate but an inferior PFS and a negative trend in OS. At first sight, response and PFS data may look contradictory. However, response is only measured in a small subgroup of patients with rather bulky disease, and the addition of the third drug might help to increase the speed and amount of response of principally chemotherapy-sensitive tumor clones. The disappointing results regarding PFS and OS are more related to regrowth of nonsensitive tumor masses, which obviously were not reduced by the addition of the third drug.

A more promising approach for selecting drugs for additional evaluation could be the use of different end points, like time to treatment failure, in relation to prior recurrence-free interval. In this case, the patient provides an internal control of the impact of a new therapy on individual tumor growth.[36] Utilization of tumor kinetics observed in phase II studies for prediction of survival gain achievable in phase III settings may be another approach.[37] The most promising model has already been established in breast and lung cancer and is based on identification of therapeutic targets: sex steroid and *HER2/neu* receptors in breast cancer or epidermal growth factor receptor mutations in lung cancer.[38,39] Unfortunately, no comparably useful targets have been identified yet in ovarian cancer.

Lessons to be learned from the last generation of intergroup trials may be that common efforts should be focused on development of more reliable selection strategies. The recent large international intergroup trials may provide a good opportunity both for sharing databases for methodologic research and for using already collected tumor material for additional translational research.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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