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Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209)

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abstract

PURPOSE Limitations of the paclitaxel-doxorubicin-cisplatin (TAP) regimen in the treatment of endometrial cancer include tolerability and cumbersome scheduling. The Gynecologic Oncology Group studied carboplatin plus paclitaxel (TC) as a noninferior alternative to TAP.

METHODS GOG0209 was a phase III, randomized, noninferiority, open-label trial. Inclusion criteria were stage III, stage IV, and recurrent endometrial cancers; performance status 0-2; and adequate renal, hepatic, and marrow function. Prior radiotherapy and/or hormonal therapy were permitted, but chemotherapy, including radiosensitization, was not. Patients were treated with doxorubicin 45 mg/m^2 and cisplatin 50 mg/m^2 (day 1), followed by paclitaxel 160 mg/m^2 (day 2) with granulocyte colony-stimulating factor or paclitaxel 175 mg/m^2 and carboplatin area under the curve 6 (day 1) every 21 days for seven cycles. The primary endpoint was overall survival (OS; modified intention to treat). Progression-free survival (PFS), health-related quality of life (HRQoL), and toxicity were secondary endpoints.

RESULTS From 2003 to 2009, 1,381 women were enrolled. Noninferiority of TC to TAP was concluded for OS (median, 37 *v* 41 months, respectively; hazard ratio [HR], 1.002; 90% CI, 0.9 to 1.12), and PFS (median, 13 *v* 14 months; HR, 1.032; 90% CI, 0.93 to 1.15). Neutropenic fever was reported in 7% of patients receiving TAP and 6% of those receiving TC. Grade $>$ 2 sensory neuropathy was recorded in 26% of patients receiving TAP and 20% receiving TC ($P = .40$). More grade $\geq$ 3 thrombocytopenia (23% *v* 12%), vomiting (7% *v* 4%), diarrhea (6% *v* 2%), and metabolic (14% *v* 8%) toxicities were reported with TAP. Neutropenia (52% *v* 80%) was more common with TC. Small HRQoL differences favored TC.

CONCLUSION With demonstrated noninferiority to TAP, TC is the global first-line standard for advanced endometrial cancer.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Although most patients with endometrial cancer have tumor confined to the uterus that is cured by hysterectomy with or without adjuvant therapy, advanced disease portends a grim prognosis. Interventions have focused on systemic therapy. Although hormonal therapy is less toxic and occasional long-term responses are reported, most studies demonstrate modest activity and relatively short progression-free survival (PFS).[1] Chemotherapy has typically produced better results.[2] Prior phase II trials by the Gynecologic Oncology Group (GOG) had demonstrated the activity of a number of single agents, including doxorubicin, cisplatin, and paclitaxel (TAP).[2] Subsequent phase III trials were directed at the identification and optimization of active drug combinations,[3-7] culminating in GOG0177, where the combination of TAP improved both PFS and overall survival (OS) over the previous standard of doxorubicin and cisplatin (AP).[7] To our knowledge, this was the first randomized trial in endometrial carcinoma to demonstrate a survival advantage for combination chemotherapy. Although TAP was the more active regimen, it was also more toxic, especially regarding neuropathy.[7] A regimen active in ovarian cancer, carboplatin and paclitaxel (TC), is more convenient, does not require growth factor support, and is well tolerated.[8] Phase II trials of TC suggested activity also in endometrial cancer.[9-11]

CONTEXT

Key Objective

Could the commonly used chemotherapy regimen of carboplatin and paclitaxel (TC) replace cisplatin, doxorubicin, and paclitaxel (TAP) as front-line therapy for advanced or recurrent endometrial cancer?

Knowledge Generated

TC is not inferior to TAP in terms of response, progression-free survival, and overall survival. Toxicity and quality of life measures favored TC.

Relevance

TC should be considered the first-line therapy for advanced or recurrent endometrial cancer. The tolerability of the TC regimen further suggests that it should serve as a suitable backbone for combination with targeted therapies in future trials.

Could doxorubicin be omitted and carboplatin substituted for cisplatin? The GOG launched this phase III trial, GOG0209 (ClinicalTrials.gov identifier: NCT00063999) to determine whether TC could replace TAP as first-line treatment in advanced or recurrent endometrial cancer based on noninferior efficacy and improved quality of life (QoL) or less toxicity.

METHODS

The specific trial objectives were to test the inferiority of TC chemotherapy to TAP with regard to survival, to assess treatment differences in the toxicity profile, specifically neurotoxicity and infection, and to compare TC with TAP in terms of patient-reported neurotoxicity and health-related quality of life (HRQoL).

Eligibility

Patients were required to have primary stage III, stage IV, or recurrent endometrial carcinoma with poor potential for cure by surgery and/or radiation therapy. Prior cytotoxic chemotherapy, including chemotherapy used for radiation sensitization, was not allowed. Treatment with radiation, hormones, or biologic agents must have been discontinued before enrollment. Adequate end-organ function and a GOG performance status of ≤ 2 was also required.

Treatment

The protocol was approved by the institutional review boards of participating centers (Appendix, online only), and patients provided written informed consent. One of two treatment regimens was randomly assigned to patients (Fig 1). Treatment sequences were as follows: regimen I (TAP)—day 1: doxorubicin 45 mg/m^2 followed immediately by cisplatin 50 mg/m^2; day 2: paclitaxel 160 mg/m^2 over 3 hours; day 3: filgrastim 5 mcg/kg/day for at least 10 days or pegfilgrastim 6 mg; or regimen II (TC)—day 1: paclitaxel 175 mg/m^2 over 3 hours followed by carboplatin dosed to an area under the curve (AUC) of 6.0. Sequences in both regimens were to be repeated every 21 days for up to seven cycles or unless disease progression or adverse effects necessitated discontinuation.

HRQoL Methods

HRQoL instruments were administered to patients before random assignment and 6, 15, and 26 weeks after starting study therapy. These included the Functional Assessment of Cancer Therapy (FACT) Physical Well-Being (PWB) Subscale, Functional Well-Being (FWB) Subscale, Endometrial Cancer Subscale (EnCS), and FACT/GOG-Neurotoxicity 4-item measure of sensory neuropathy (Ntx-4). Planned analyses included the summation of PWB and FWB (range, 0-56) and the Ntx-4 score (range, 0-16). The FACT-En Trial Outcome Index (TOI; PWB plus FWB plus EnCS; range, 0-120) was an exploratory HRQoL endpoint.

Patients Were Evaluated Weekly for Toxicity

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 2). After treatment, patients were seen quarterly for 2 years, semi-annually for 3 years, and then annually until death. Pelvic and abdominal computed tomography and chest x-ray were performed at specified intervals for 5 years.

Statistical Design

The primary null hypothesis to be tested from this open-label, randomized, phase III noninferiority trial was whether TC decreases survival time from study entry when compared with TAP. Sufficient precision in the estimate of the relative log hazard of death was planned to exclude clinically inferior values with a high degree of confidence. A hazard ratio (HR) of TC to TAP exceeding 1.20 was considered inferior. This threshold required observing at least 795 events assuming proportional hazards to provide 90% statistical power with type I error limited to 0.10 (one-tail test) at the final analysis.[12] Using a spending function, CIs were used to assess the relative log hazard rate at each of three planned analyses.[13-15] The analysis population was restricted to eligible patients, whether treated or not. Secondary outcomes included adverse events, PFS, and

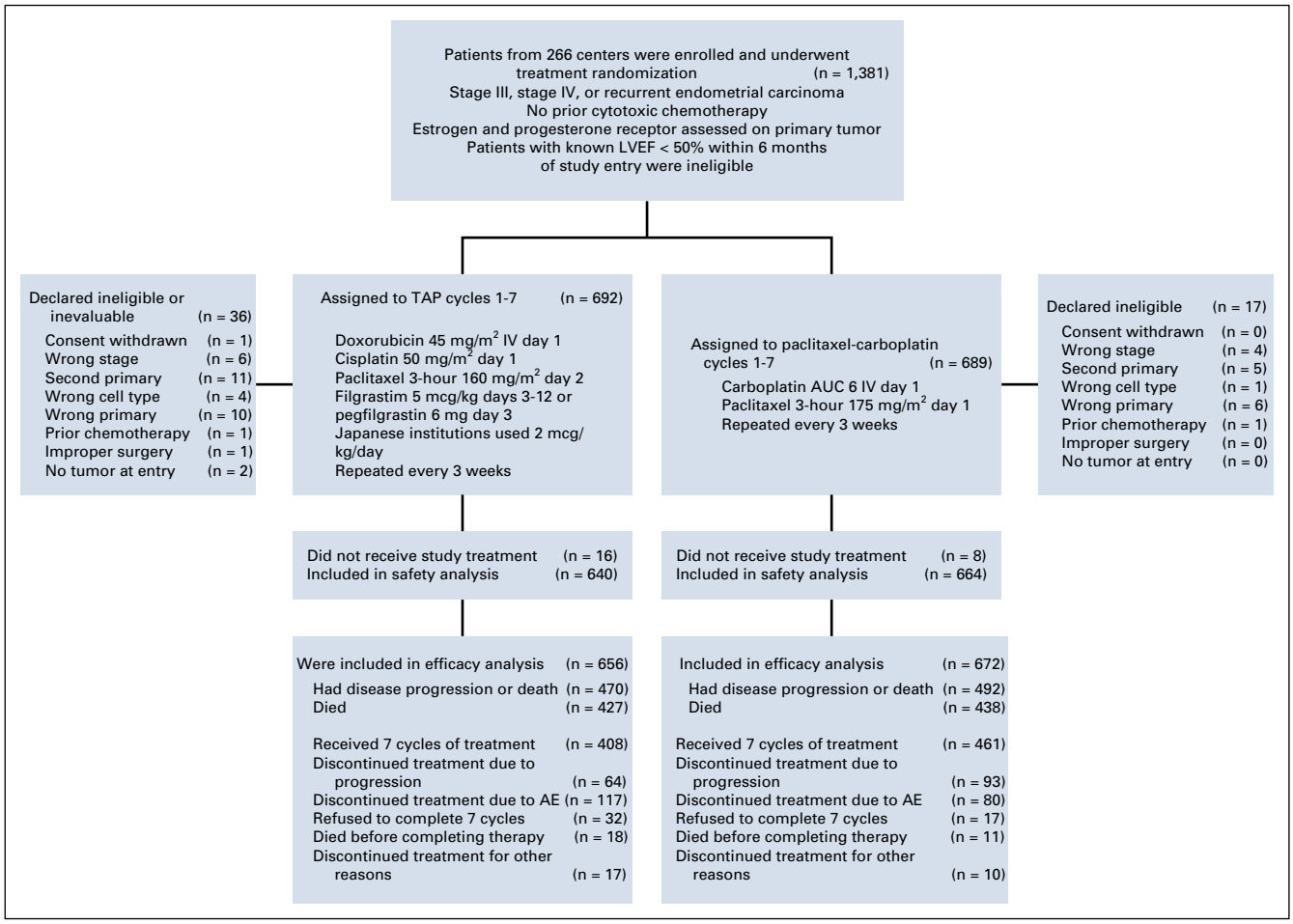

FIG 1. CONSORT diagram. AE, adverse event; AUC, area under the curve; IV, intravenous; LVEF, left ventricular ejection fraction; TAP, paclitaxel-doxorubicin-cisplatin.

HRQoL. In April 2006, eligibility was expanded from measurable only to include patients with International Federation of Gynecology and Obstetrics (FIGO) stage III, stage IV, and recurrent endometrial carcinoma who had not received prior chemotherapy. This change increased the accrual rate and decreased the risk of death, resulting in a sample size increase from 900 to 1,282 eligible patients. Performance status and disease status defined by measurable or recurrent disease status (before *v* after eligibility expansion) and use/no use of adjuvant radiation therapy just before entry were prespecified stratification factors for analysis. Two equally spaced interim analyses of survival outcomes were planned. The first interim analysis, reported in 2008, included 274 deaths among 956 eligible patients. Accrual was completed in April 2009. The second interim analysis, reported in July 2010, included 551 deaths. The early release of data was recommended at this second interim analysis. The results from the second interim analysis were presented as the main findings. At that time, all patients were off study treatment. Follow-up continued, and updated analyses of PFS and OS were planned after the data monitoring committee released the data and were considered ad hoc.

For QoL, the clinically meaningful differences were considered to be 3.5 points for the summation of PWB and FWB and 1.25 points for Ntx-4. Treatment differences were tested at a significance level of 2.5% (two-sided) for HRQoL and Ntx-4, respectively, to control type I error at 5%. With a sample size of 434 evaluable patients (217 patients per arm) there was 90% power to detect the clinically meaningful differences.[16] The HRQoL scores reported during and after treatment were compared and tested using a linear mixed effects model, adjusting for stratification level and pretreatment HRQoL score, assuming an unstructured covariance matrix. Treatment effect size was defined as the ratio of the treatment difference to the standard deviation of the baseline score in the reference group (TAP).

RESULTS

Between August 25, 2003 and April 20, 2009, 1,381 patients were enrolled in this study by 266 GOG member clinical sites. After central review that was blinded to

TABLE 1. Common Terminology Criteria for Adverse Events (version 2.0) Adverse Event Treatment Comparisons

	Regimen												
	TAP (n = 640)						TC (n = 664)						
	Grade						Grade						
Adverse Event Category or Term	0	1	2	3	4	5	0	1	2	3	4	5	Kruskal-Wallis Test *P*
Auditory	601	12	25	2	0	0	641	10	12	1	0	0	.024
Allergy	596	26	9	8	1	0	621	12	15	12	4	0	.855
2nd primary	631	0	0	0	9	0	645	0	0	0	19	0	.070
Coagulation	632	3	0	5	0	0	658	1	1	3	1	0	.547
Constitutional	532	72	33	3	0	0	581	56	25	2	0	0	.025
Fatigue	78	225	257	68	12	0	109	274	217	59	5	0	< .001
Fever, no neutropenia	625	11	4	0	0	0	650	8	6	0	0	0	.781
Cardiovascular	521	64	33	15	6	1	574	51	18	18	3	0	.013
Thrombosis/embolism	616	0	3	16	5	0	646	0	1	14	3	0	.289
Ventricular function	539	48	50	2	1	0	662	2	0	0	0	0	< .001
Dermatologic	531	82	25	2	0	0	574	79	11	0	0	0	.059
Alopecia	96	70	474	0	0	0	97	79	488	0	0	0	.877
Rash/desquamation	610	26	3	1	0	0	622	31	8	3	0	0	.186
Endocrine	610	19	9	2	0	0	634	23	7	0	0	0	.863
GI	298	176	116	46	4	0	339	199	91	31	4	0	.016
Nausea	143	278	160	59	0	0	266	276	85	37	0	0	< .001
Vomiting	326	148	120	39	6	1	459	123	59	22	1	0	< .001
Diarrhea	413	123	67	35	2	0	476	134	40	14	0	0	.001
Anorexia	471	90	68	11	0	0	532	92	32	8	0	0	.002
Stomatitis	495	91	46	8	0	0	594	52	17	1	0	0	< 001
Genitourinary/renal	596	29	11	2	1	1	608	36	14	4	1	1	.288
Creatinine	547	46	35	10	2	0	617	32	11	3	1	0	< .001
Hemorrhage	612	21	1	6	0	0	632	26	3	2	1	0	.712
Other hematologic	430	5	9	196	0	0	500	6	16	142	0	0	.001
Leukopenia	161	60	113	173	133	0	46	60	227	293	37	1	.101
Anemia	31	160	339	98	12	0	45	205	304	96	14	0	.017
Thrombocytopenia	177	215	102	125	21	0	247	243	95	70	8	1	< .001
Neutropenia	198	34	76	102	229	1	46	26	62	196	334	0	< .001
Hemolysis	639	0	1	0	0	0	662	0	0	2	0	0	.584
Hepatic	582	41	8	9	0	0	566	80	13	4	1	0	.002
Febrile neutropenia	596	0	0	32	11	1	628	0	0	35	1	0	.245
Infection w/o neutropenia	579	6	33	20	2	0	624	13	14	13	0	0	.015
Infection w/neutropenia	615	0	0	16	3	6	635	0	0	23	2	4	.694
Infection/fever	615	5	8	10	2	0	649	7	3	4	1	0	.081
Lymphatics	613	20	5	2	0	0	649	12	2	1	0	0	.045
Musculoskeletal	587	29	16	8	0	0	617	27	15	5	0	0	.405
Metabolic	360	136	54	64	26	0	422	145	46	46	5	0	.001
Neurologic	480	94	51	14	1	0	506	109	32	15	2	0	.474
Neuromotor	560	46	22	12	0	0	573	47	24	20	0	0	.475
Sensory neuropathy	197	276	127	40	0	0	191	343	86	42	2	0	.401

(continued on following page)

TABLE 1. Common Terminology Criteria for Adverse Events (version 2.0) Adverse Event Treatment Comparisons (continued)

	Regimen												
	TAP (n = 640)						TC (n = 664)						
	Grade						Grade						
Adverse Event Category or Term	0	1	2	3	4	5	0	1	2	3	4	5	Kruskal-Wallis Test *P*
Neurocranial	639	0	1	0	0	0	664	0	0	0	0	0	.308
Ocular/visual	567	26	44	2	1	0	618	12	33	1	0	0	.006
Pulmonary	528	21	67	16	6	2	563	18	70	11	2	0	.230
Pain	443	100	75	21	1	0	450	122	62	27	3	0	.691
Myalgia	436	107	88	9	0	0	408	157	79	20	0	0	.031
Arthralgia	445	111	77	7	0	0	431	145	70	18	0	0	.108
Sexual	634	6	0	0	0	0	654	6	4	0	0	0	.347

NOTE. No correction for multiple testing was used, because it is important to identify moderate increases in the severity of toxicity at the risk of increasing the type I error. Given the correlation between toxicities, the overall type I error is less than calculations would indicate when assuming complete independence.

Abbreviations: TAP, paclitaxel-doxorubicin-cisplatin; TC, carboplatin plus paclitaxel; w/, with; w/o, without.

outcome, 52 patients were deemed ineligible, and one withdrew consent just after randomization: 36 patients in the TAP arm and 17 in the TC arm (Fig 1). Twenty-eight patients declined all treatment: 20 in the TAP arm and eight in the TC arm. Patient and disease characteristics are shown in Appendix Table A1 (online only). With a median age at enrollment of 61 years, most patients had measurable or recurrent disease (61%), were non-Hispanic (86%), were White (78%), or had good performance status (64%). More than 50% had endometrioid tumors, and 77% had no prior pelvic radiation treatment (pRT). Characteristics appeared balanced between the treatment arms.

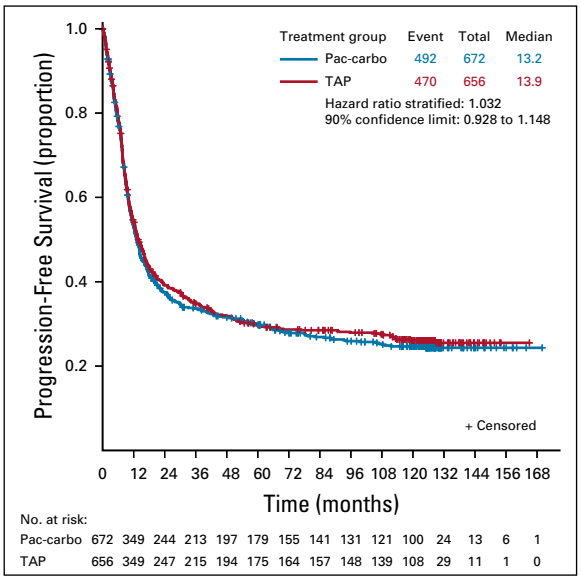

FIG 2. Updated progression-free survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

Adverse Events

The data safety monitoring board reported an increase in febrile neutropenia in patients receiving TC who had pRT. Beginning in February 2008, a one-level dose reduction to paclitaxel 135 mg/m^2 and carboplatin AUC 5 was implemented in the TC arm in patients with pRT. This change appeared to address the concern. Hospitalization decreased from 35% to 17% in patients with pRT enrolled after the amendment. Overall, no significant differences in toxicities were observed in this arm in regard to pRT (pRT, 7%; no pRT, 5%).

Chemotherapy was initiated by 1,282 patients; these patients were considered evaluable for toxicity (Fig 1). Neutropenic fever was reported in 7% of patients receiving TAP and 6% of those receiving TC (Table 1). Grade 2 and higher physician-graded sensory neuropathy was recorded in 26% of patients receiving TAP and 20% of those receiving TC ($P = .401$). The most common toxicities (grades 3-5; TAP *v* TC) were leukopenia (48% *v* 50%), neutropenia (52% *v* 80%), thrombocytopenia (23% *v* 12%), and other hematologic adverse events (31% *v* 21%). The TC arm was associated with significantly more frequent and severe neutropenia, hepatic events, and myalgia than the TAP arm ($P < .05$). The TAP arm was associated with significantly more frequent and severe auditory, constitutional, fatigue, cardiovascular, ventricular function, GI, nausea, vomiting, diarrhea, anorexia, stomatitis, creatinine, anemia, thrombocytopenia, other hematologic, infection without neutropenia, lymphatic, metabolic, and ocular/visual adverse events than the TC arm ($P < .05$). Study treatment was discontinued for toxicity in 18% of those in the TAP arm and 12% in the TC arm (Fig 1). Deaths during active treatment

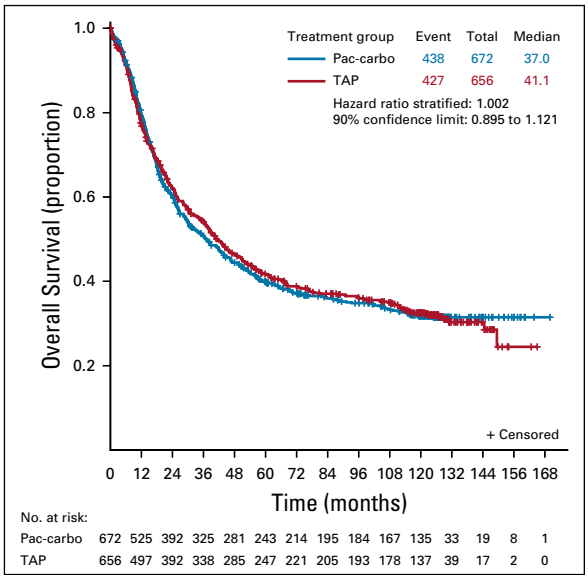

FIG 3. Updated overall survival time distribution by randomized treatment group. Carbo, carboplatin; pac, paclitaxel; TAP, paclitaxel-doxorubicin-cisplatin.

were reported in 3% of TAP-treated patients and 2% of TC-treated patients. Overall, the regimens were well tolerated, with 63% completing the planned seven cycles in the TAP arm, and 69% completing the TC arm (Fig 1). Second cancers were reported in 19 patients (3%) in the TC arm, including four diagnoses of acute myelogenous leukemia or myelodysplastic syndrome and nine (1%) in the TAP arm.

PFS and OS

At the second interim analysis, with a median follow-up of 28 months, the ratio of death hazards (HR) of TC relative to TAP estimated from a proportional hazards model stratified by the randomization stratification factors was 1.007, with a 90% upper confidence limit of 1.16 that excluded the inferiority region bounded at 1.2.[17] In this updated analysis, the median follow-up was 124 months. More than 65% of the patients have died, and 28% remain alive without evidence of cancer (Fig 1). The adjusted ratio of death hazards (HR) of TC relative to TAP was 1.002, with a 95% CI of 0.88 to 1.15. For progression, the HR of TC to TAP was 1.032, with a 90% CI of 0.93 to 1.15. Median PFS was 14 months in the TAP-treated patients and 13 months in the TC-treated patients (Fig 2). Median OS for the patients receiving TAP was 41 months and 37 months for patients receiving TC (Fig 3).

Crossover between regimens before disease progression was infrequent and not thought to affect outcome, and included three patients who crossed over from TAP to TC per protocol. Ten patients crossed over before disease progression, including seven patients from TAP to TC and three patients from TC to TAP. In patients with RECIST 1.0 measurable disease, the overall response rate for both treatment regimens was 52% with no significant advantage for either regimen in terms of response, stable disease, or increasing disease.

Subgroup analyses of the treatment effect on OS are summarized in Figure 4. A test of homogeneity of treatment effect across histologic groups and race/ethnicity groups was performed. The results of the exploratory analyses were consistent with heterogeneity in the treatment effect by histologic group, suggesting that TC may be superior to TAP among patients with grade 1 tumors. There was no statistically significant evidence of treatment effect heterogeneity across race/ethnicity subgroups. There was no significant difference in treatment outcome per treatment arm in regard to measurable versus nonmeasurable disease (Figs 4 and 5). Furthermore, there was no significant advantage for either treatment arm in regard to FIGO stage, age, pRT, grade, or hormone receptor status subgroups.

HRQoL Results

HRQoL was collected in the first 538 patients enrolled before March 26, 2007. Valid baseline and 6-, 15-, and 26-week QoL assessments were provided by 95%, 86%, 78%, and 69% of eligible patients, respectively. The generalized estimating equation estimates suggested no statistically significant differences between treatment arms in terms of the completion rates over time. A total of 474 patients provided valid baseline and at least one follow-up assessment and were included in the analysis. The mean HRQoL scores at each time point are displayed in Appendix Figure A1 (online only). The interaction effect between assessment time and treatment was statistically significant ($P = .013$). At 6 weeks, compared with the TAP group, the TC group reported better PWB plus FWB scores (2.1-point difference; 97.5% CI, 0.3 to approximately 3.9 points; $P = .009$; effect size, 0.19). There were no statistically significant differences between groups at 15 and 26 weeks. For the FACT-En TOI, the fitted estimate for the interaction effect between treatment and assessment time was not statistically significant ($P = .08$). After adjusting for the baseline score and stratification level, there remained no statistically significant difference in mean TOI score between the two groups (diff [TC − TAP] = 1.4 points; 97.5% CI, −0.93 to approximately 3.70 points; $P = .18$). For the FACT/GOG-Ntx subscale, the interaction effect between assessment time and treatment was statistically significant ($P < .001$). The TC group reported 1.4-point (97.5% CI, 0.4 to approximately 2.5 points; $P = .003$; effect size, 0.64) higher scores (fewer neurotoxic symptoms) in the Ntx-4 subscale at 26 weeks than those in the TAP group. There were no statistically significant differences between the groups at 6 and 15 weeks.

DISCUSSION

This trial sought to determine whether doxorubicin could be omitted and carboplatin substituted for cisplatin in the front-line therapy for advanced endometrial cancer. It

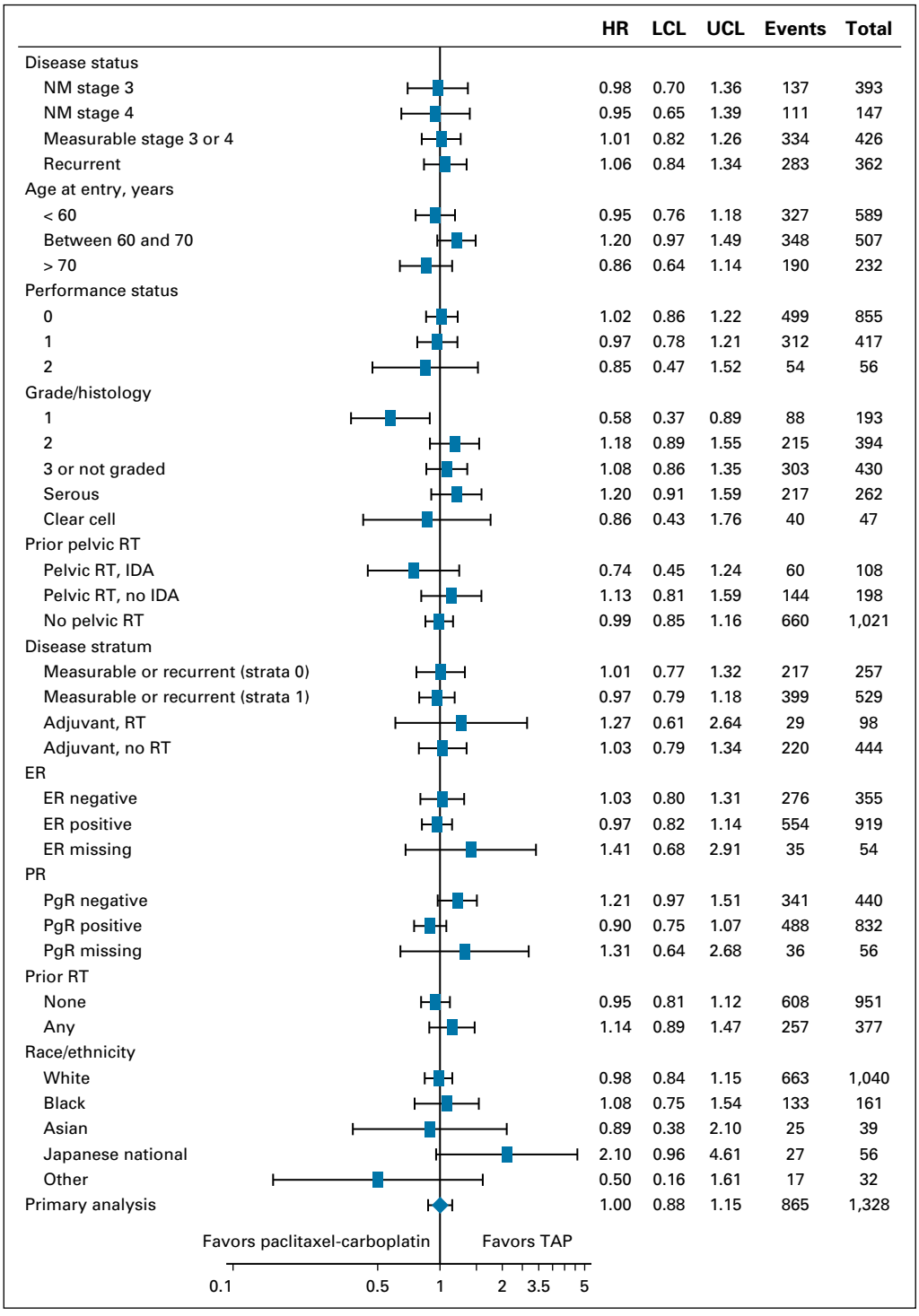

FIG 4. Overall survival treatment hazard ratio (HR) forest plots by subgroup. All estimates are based on a model stratified by disease group and performance status. The reference group is paclitaxel-doxorubicin-cisplatin (TAP). ER, estrogen receptor; HR, hazard ratio: IDA, initial dose adjustment; LCL, lower confidence limit; NM, nonmeasurable; PR, progesterone receptor; RT, radiotherapy; UCL, upper confidence limit.

shows that TC is not inferior to TAP in terms of OS and PFS. Overall, the toxicity and HRQoL profile favored TC. Therefore, TC appears to be an acceptable and less toxic alternative to TAP.

Before 2002, the control arm of GOG treatment trials of women with measurable stage III, stage IV, and recurrent endometrial cancer was cytotoxic chemotherapy using doxorubicin (60 mg/m^2) and cisplatin (50 mg/m^2; AP) for seven cycles.[5-7] This was based on several clinical observations. First, the results of whole abdominal radiotherapy in women with measurable disease has been disappointing, particularly in women with residual tumor size $>$ 2 cm.[18-20] Second, the results of GOG Protocols 0107, 0139, and 0163 suggested that AP is superior to single-agent doxorubicin therapy and not worse than the combination of doxorubicin and paclitaxel or circadian-

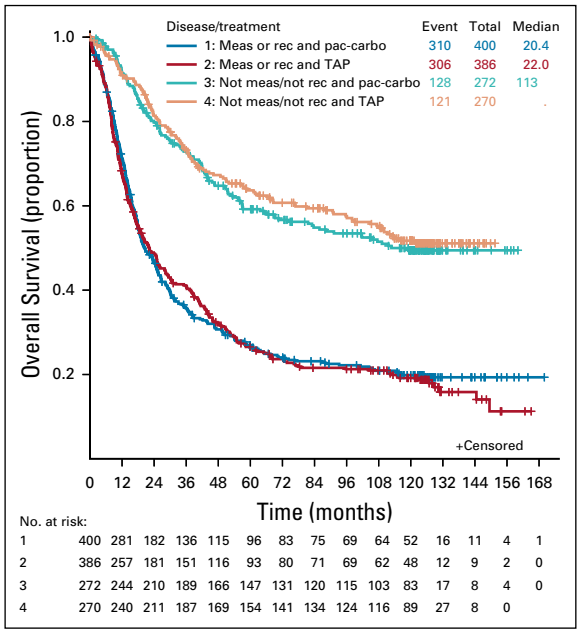

FIG 5. Updated survival time distribution by treatment group and measurable disease status. All estimates are based on a model stratified by disease group and performance status. Carbo, carboplatin; meas, measurable; pac, paclitaxel; rec, recurrent; TAP, paclitaxel-doxorubicin-cisplatin.

timed AP with respect to PFS and response and had a favorable toxicity profile.[3,5,6] Subsequently, GOG0177 compared AP with TAP and found that TAP increased the frequency of response (57% *v* 34%) and prolonged PFS (8 *v* 5 months) and OS (15 *v* 12 months).[7] This was the first trial to show a survival advantage for combination chemotherapy in patients with measurable advanced or recurrent endometrial cancer. For this reason, TAP was chosen to be the control arm in the current trial. Contemporaneously, TC was found to be tolerable and effective in ovarian cancer.[8] Although the regimen had not been tested in a phase III setting in patients with endometrial cancer, its efficacy had been evaluated in single-arm phase II studies with reported response rates of 45%-78%.[9-11]

Toxicity differences between TAP and TC were expected in this trial. Because the administration of TAP includes prophylactic granulocyte colony-stimulating factor, a difference in neutropenia was not anticipated. Interestingly, neutropenia (grade $>$ 2) was more often reported with TC (79%) than TAP (52%). Fortunately, neutropenic fever was infrequent with both TC (6%) and TAP (7%). Differences in neurotoxicity were anticipated with the expectation that TAP would be associated with more toxicity than TC. It was observed in GOG0177 that TAP is associated with more provider-reported and patient-reported neurotoxicity than AP therapy. However, major differences in provider-reported neurotoxicity were not noted when comparing paclitaxel plus cisplatin versus TC in previous GOG ovarian cancer trials.[8] Therefore, this was an important clinical question to ask in this trial. Indeed, at 26 weeks, patients who had received TAP reported more sensory neuropathy than those who received TC.

The main strength of this open-label, randomized, phase III, therapeutic noninferiority clinical trial was that it was well balanced and appropriately powered to answer the question. Did the study amendments limit the applicability of the conclusions? When originally opened, the trial allowed only measurable disease in chemotherapy-naïve patients. With the analysis of GOG0184, it was found that TAP was not superior to AP in patients with nonmeasurable, locally advanced disease after radiation therapy.[21] There was concern that the TAP versus TC results might not apply to nonmeasurable disease. Accordingly, eligibility was expanded to include stage III, stage IV, and recurrent cancer. The upper bound of the noninferiority margin chosen was an HR value of 1.2. For the original targeted population, this translates to ruling out a median survival of $\leq$ 12.75 months, assuming a median survival of 15.3 months for the TAP arm. For the patients in which the treatment is considered adjuvant, this HR translates to a decrease in OS at 5 years from 56% to 49%. With the data and safety monitoring committee notification of an unexpected higher rate of hospitalizations in the TC-treated patients, additional investigation revealed that most were associated with pRT. The consequent one-level dose reduction for patients with pRT taking TC appeared to alleviate the issue. This modified dosing has been successfully used in subsequent trials.[22] Although there might be concerns about study population heterogeneity, inspection of Figure 4 suggests no significant skewing of the results for pRT or nonmeasurable disease as well as multiple other parameters except for grade 1 tumors. At the time of study design, it was anticipated that most patients would experience recurrence during or soon after treatment. Thus, longer-term QoL follow-up was not specified. That information might have been especially interesting in the nonmeasurable patients for whom median survival is now $>$ 100 months (Fig 5).

In conclusion, this trial has shown that TC is not inferior to TAP with regard to efficacy. Given its more favorable toxicity profile and the small but potentially meaningful differences in HRQoL favoring TC, TC should be considered the first-line therapy for advanced or recurrent endometrial cancer. The tolerability of the TC regimen further suggests that it should serve as a suitable backbone for combination with targeted therapies in future trials.[23] This has been confirmed in subsequently initiated trials by the GOG and others.[22,24]

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Carlson MJ, Thiel KW, Leslie KK: Past, present, and future of hormonal therapy in recurrent endometrial cancer. Int J Womens Health 6:429-435, 2014
2. Miller DS, Randall ME, Filiaci V: Progress in endometrial cancer: Contributions of the former Gynecologic Oncology Group. Gynecol Oncol 157:312-322, 2020
3. Thigpen JT, Brady MF, Homesley HD, et al: Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: A gynecologic oncology group study. J Clin Oncol 22:3902-3908, 2004
4. van Wijk FH, Aapro MS, Bolis G, et al: Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: Definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol 14:441-448, 2003
5. Gallion HH, Brunetto VL, Cibull M, et al: Randomized phase III trial of standard timed doxorubicin plus cisplatin versus circadian timed doxorubicin plus cisplatin in stage III and IV or recurrent endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 21:3808-3813, 2003
6. Fleming GF, Filiaci VL, Bentley RC, et al: Phase III randomized trial of doxorubicin + cisplatin versus doxorubicin + 24-h paclitaxel + filgrastim in endometrial carcinoma: A Gynecologic Oncology Group study. Ann Oncol 15:1173-1178, 2004
7. Fleming GF, Brunetto VL, Cella D, et al: Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 22:2159-2166, 2004
8. Ozols RF, Bundy BN, Greer BE, et al: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 21:3194-3200, 2003
9. Price FV, Edwards RP, Kelley JL, et al: A trial of outpatient paclitaxel and carboplatin for advanced, recurrent, and histologic high-risk endometrial carcinoma: Preliminary report. Semin Oncol 24:S15-78-S15-82, 1997 (5, suppl 15)
10. Nakamura T, Onishi Y, Yamamoto F, et al: Evaluation of paclitaxel and carboplatin in patients with endometrial cancer [in Japanese]. Gan To Kagaku Ryoho 27: 257-262, 2000
11. Hoskins PJ, Swenerton KD, Pike JA, et al: Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: A phase II study. J Clin Oncol 19:4048-4053, 2001
12. Schoenfeld DA: Sample-size formula for the proportional-hazards regression model. Biometrics 39:499-503, 1983
13. Jennison C, Turnbull BW. One-sided sequential tests to establish equivalence between treatments with special reference to normal and binary responses. In *Multiple Comparisons, Selection, and Applications in Biometry* (Ed., F.M. Hoppe), New York: Marcel Dekker, 315-330, 1993
14. Lan KKG, DeMets DL: Discrete sequential boundaries for clinical trials. Biometrika 70:659-663, 1983

15. Kim K, DeMets DL: Design and analysis of group sequential tests based on the type I error spending rate function. Biometrika 74:149-154, 1987
16. Analysis of Longitudinal Data. Statistical Science Series, 13, Clarendon Press, Oxford, 1994.
17. Miller D, Filiaci V, Fleming G, et al: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 125:771, 2012
18. Potish RA, Twiggs LB, Adcock LL, et al: Role of whole abdominal radiation therapy in the management of endometrial cancer; prognostic importance of factors indicating peritoneal metastases. Gynecol Oncol 21:80-86, 1985
19. Greven KM, Curran WJ Jr, Whittington R, et al: Analysis of failure patterns in stage III endometrial carcinoma and therapeutic implications. Int J Radiat Oncol Biol Phys 17:35-39, 1989
20. Randall ME, Filiaci VL, Muss H, et al: Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. J Clin Oncol 24:36-44, 2006
21. Homesley HD, Filiaci V, Gibbons SK, et al: A randomized phase III trial in advanced endometrial carcinoma of surgery and volume directed radiation followed by cisplatin and doxorubicin with or without paclitaxel: A Gynecologic Oncology Group study. Gynecol Oncol 112:543-552, 2009
22. Aghajanian C, Filiaci V, Dizon DS, et al: A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol 150:274-281, 2018
23. Makker V, Green AK, Wenham RM, et al: New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract 4:19, 2017
24. Lorusso D, Ferrandina G, Colombo N, et al: Carboplatin-paclitaxel compared to carboplatin-paclitaxel-bevacizumab in advanced or recurrent endometrial cancer: MITO END-2 - A randomized phase II trial. Gynecol Oncol 155:406-412, 2019

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APPENDIX

The following Gynecologic Oncology Group member institutions participated in the primary treatment studies: Roswell Park Cancer Institute, University of Alabama at Birmingham, Duke University Medical Center, Abington Memorial Hospital, Walter Reed National Military Medical Center, Wayne State University, University of Minnesota Medical Center – Fairview, Mt. Sinai Medical Center, Northwestern University, University of Mississippi Medical Center, University of Colorado Cancer Center – Anschutz Cancer Pavilion, University of California at Los Angeles Health System, Fred Hutchinson Cancer Research Center, Abramson Cancer Center of the University of Pennsylvania, Penn State Milton S. Hershey Medical Center, University of Cincinnati, University of North Carolina at Chapel Hill, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center, Indiana University Hospital/Melvin and Bren Simon Cancer Center, Wake Forest University Health Sciences, University of California Medical Center at Irvine – Orange Campus, Massachusetts General Hospital, Rush University Medical Center, University of Pittsburgh, State University of New York Downstate Medical Center, University of Kentucky, University of New Mexico, Cleveland Clinic Foundation, Stony Brook University Medical Center, Washington University School of Medicine, Memorial Sloan Kettering Cancer Center, Cooper Hospital University Medical Center, Ohio State University Medical Center, MD Anderson Cancer Center, University of Massachusetts Memorial Health Care, Fox Chase Cancer Center, Women's Cancer Center of Nevada, University of Oklahoma Health Sciences Center, University of Virginia, University of Chicago, Mayo Clinic, Case Western Reserve University, Moffitt Cancer Center and Research Institute, Gynecologic Oncology Network/Brody School of Medicine, Fletcher Allen Health Care-Medical Center, Yale University, Saitama Medical University International Medical Center, University of Wisconsin Hospital and Clinics, Cancer Trials Support Unit, University of Texas – Galveston, Women and Infants Hospital, The Hospital of Central Connecticut, Georgia Core, New York University Langone Medical Center, Gynecologic Oncology of West Michigan PLLC, and Community Clinical Oncology Program.

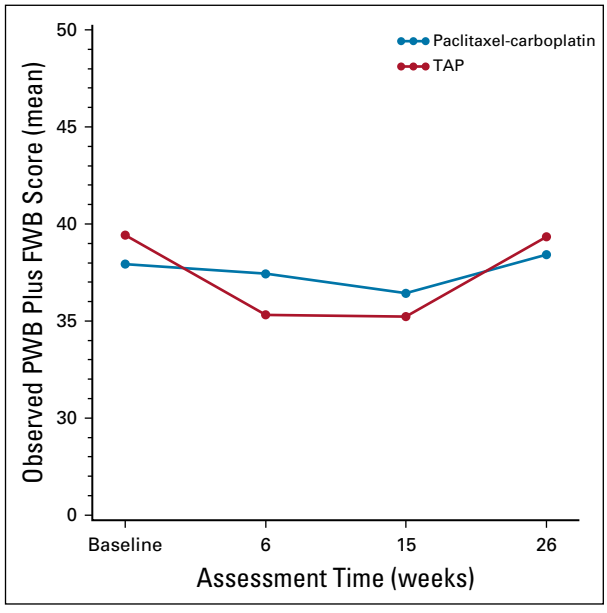

FIG A1. Observed Physical Well-Being (PWB) subscore plus Functional Well-Being (FWB) score by randomized treatment group. PAC, paclitaxel-doxorubicin-cisplatin.

TABLE A1. Patient and Tumor Characteristics for All Eligible Enrolled Patients

	Regimen					
	TAP		TC		Total	
Characteristic	No.	%	No.	%	No.	%
Age group, years						
20-29	2	0.3	3	0.4	5	0.4
30-39	17	2.6	16	2.4	33	2.5
40-49	66	10.1	71	10.6	137	10.3
50-59	195	29.7	219	32.6	414	31.2
60-69	261	39.8	246	36.6	507	38.2
70-79	97	14.8	108	16.1	205	15.4
80-89	18	2.7	9	1.3	27	2.0
Ethnicity						
Hispanic or Latino	21	3.2	34	5.1	55	4.1
Non-Hispanic	560	85.4	577	85.9	1137	85.6
Not reported	75	11.4	61	9.1	136	10.2
Race						
White	513	78.2	527	78.4	1040	78.3
Black/African American	76	11.6	84	12.5	160	12.0
Asian	54	8.2	41	6.1	95	7.2
American Indian/Alaskan Native	2	0.3	3	0.4	5	0.4
Native Hawaiian/Pacific Islander	2	0.3	5	0.7	7	0.5
Other	1	0.2	0	0.0	1	0.1
Not reported	8	1.2	12	1.8	20	1.5
Histology/grade						
Endometrioid/1	89	13.6	95	14.1	184	13.9
Endometrioid/2	161	24.5	184	27.4	345	26.0
Endometrioid/3	128	19.5	150	22.3	278	20.9
Serous	139	21.2	123	18.3	262	19.7
Clear cell	29	4.4	18	2.7	47	3.5
Mixed epithelial	57	8.7	62	9.2	119	9.0
Undifferentiated	19	2.9	8	1.2	27	2.0
Other	34	5.2	32	4.8	66	5.0
Stage						
III	274	41.8	280	41.7	554	41.7
IV	210	32.0	202	30.1	412	31.0
Recurrent/progression	172	26.2	190	28.3	362	27.3
Pelvic RT indicator						
No pelvic RT	515	78.5	507	75.4	1022	77.0
Pelvic RT	141	21.5	165	24.6	306	23.0
Measurable disease status						
Nonmeasurable	289	44.1	294	43.8	583	43.9
Measurable	367	55.9	378	56.3	745	56.1
Progesterone receptor status						
Missing	25	3.8	31	4.6	56	4.2

(continued on following page)

TABLE A1. Patient and Tumor Characteristics for All Eligible Enrolled Patients (continued)

	Regimen					
	TAP		TC		Total	
Characteristic	No.	%	No.	%	No.	%
Negative	235	35.8	205	30.5	440	33.1
Positive	396	60.4	436	64.9	832	62.7
Estrogen receptor status						
Missing	25	3.8	29	4.3	54	4.1
Negative	176	26.8	179	26.6	355	26.7
Positive	455	69.4	464	69.0	919	69.2
Total	656	49.4	672	50.6	1328	100.0

Abbreviations: RT, radiotherapy; TAP, paclitaxel-doxorubicin-cisplatin; TC, carboplatin plus paclitaxel.