Title

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Journal

Journal of Clinical Oncology, 40(9)

ISSN

0732-183X

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Publication Date

2022-03-20

DOI

10.1200/jco.21.02050

original reports

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

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abstract

PURPOSE This phase III randomized trial (NCT00954174) tested the null hypothesis that paclitaxel and carboplatin (PC) is inferior to paclitaxel and ifosfamide (PI) for treating uterine carcinosarcoma (UCS).

PATIENTS AND METHODS Adults with chemotherapy-naïve UCS or ovarian carcinosarcoma (OCS) were randomly assigned to PC or PI with 3-week cycles for 6-10 cycles. With 264 events in patients with UCS, the power for an overall survival (OS) hybrid noninferiority design was 80% for a null hazard ratio (HR) of 1.2 against a 13% greater death rate on PI with a type I error of 5% for a one-tailed test.

RESULTS The study enrolled 536 patients with UCS and 101 patients with OCS, with 449 and 90 eligible, respectively. Primary analysis was on patients with UCS, distributed as follows: 40% stage I, 6% stage II, 31% stage III, 15% stage IV, and 8% recurrent. Among eligible patients with UCS, PC was assigned to 228 and PI to 221. PC was not inferior to PI. The median OS was 37 versus 29 months (HR = 0.87; 90% CI, 0.70 to 1.075; $P < .01$ for noninferiority, $P > .1$ for superiority). The median progression-free survival was 16 versus 12 months (HR = 0.73; $P = < 0.01$ for noninferiority, $P < .01$ for superiority). Toxicities were similar, except that more patients in the PC arm had hematologic toxicity and more patients in the PI arm had confusion and genitourinary hemorrhage. Among 90 eligible patients with OCS, those in the PC arm had longer OS (30 *v* 25 months) and progression-free survival (15 *v* 10 months) than those in the PI arm, but with limited precision, these differences were not statistically significant.

CONCLUSION PC was not inferior to the active regimen PI and should be standard treatment for UCS.

J Clin Oncol 40:968-977. © 2022 by American Society of Clinical Oncology

INTRODUCTION

In 2021, an estimated 66,570 women in the United States will be diagnosed with uterine cancer and 21,410 will be diagnosed with ovarian cancer.[1] Within each of these diseases, the worst outcomes are among patients with the rarest forms: uterine carcinosarcoma (UCS) and ovarian carcinosarcoma (OCS). Although only 5% of uterine cancers are UCS,[2-5] this aggressive disease causes 15% of all uterine cancer deaths.[6] Similarly, between 1% and 4% of ovarian cancers are OCS, and patients with OCS have a shorter 5-year survival than those with other ovarian cancers (28.2% *v* 38.4%, $P < .001$).[7] In part, these poor outcomes are because these patients often present at a late stage. For example, more than half of patients with UCS present with regional or distant metastases,[2,8] and 5-year disease-free survival is shortest in those with the latest stage disease (stage I: 56%, stage II: 31%, stage III: 13%, and stage IV: 0%). Outcomes are often poor even in those diagnosed with early-stage UCS; more than 50% of such patients experience disease recurrence, leading to death.[9-11]

Standard treatment for patients with UCS and OCS is surgery (total hysterectomy or bilateral salpingo-oophorectomy), peritoneal washings, and retroperitoneal lymph node assessment.[10] Developing and testing treatments for these diseases has been hampered, as historically, UCS was treated with other sarcomas. However, recent evidence indicates that the carcinomatous components dictate tumor behavior,[8,12,13] and molecular studies demonstrated that the sarcomatous components are derived from the carcinomatous components through metaplastic transformation.[12,14,15] Thus, in 2009, the International Federation of Gynecology and Obstetrics (FIGO) mandated that UCS should be staged as an endometrial carcinoma.[16]

A 2013 Cochrane review of both published and unpublished data from the large phase III trials in UCS

ASSOCIATED CONTENT

See accompanying editorial on page 924

Appendix

Protocol

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

Accepted on November 18, 2022 and published at ascopubs.org/journal/jco on January 10, 2022: DOI https://doi.org/10.1200/JCO.21.02050

CONTEXT

Key Objective

The purpose of this study is to determine whether paclitaxel and carboplatin can be considered not inferior and potentially superior to paclitaxel and ifosfamide with regard to overall survival duration.

Knowledge Generated

Paclitaxel and carboplatin was not inferior with regard to overall survival and demonstrated improved progression-free survival when compared with paclitaxel and ifosfamide survival. Thus, paclitaxel and carboplatin should be standard treatment for uterine carcinosarcoma.

Relevance

These results establish a new standard therapy for patients with gynecologic carcinosarcomas.

(GOG-108, GOG-150, and GOG-161, n = 579) evaluated the efficacy of adjuvant radiotherapy, paclitaxel and ifosfamide (PI), cisplatin, ifosfamide, and mesna, or ifosfamide alone. The review concluded that patients in the PI and cisplatin, ifosfamide, and mesna arms had longer overall survival (OS) and progression-free survival (PFS) than those in the radiotherapy or ifosfamide-alone arms, but those in the cisplatin, ifosfamide, and mesna arm experienced greater toxicity than those in the PI or ifosfamide-alone arms. Thus, PI was established as the evidence-driven standard for treating UCS.[3,17-20] However, this regimen has three important limitations. First, it is difficult to administer, requiring 3 days of infusion. Second, it requires the use of growth factor support. Third, it is associated with a greater risk for central neurologic toxicity than other chemotherapy regimens, especially for older patients.

Paclitaxel and carboplatin (PC) has been a standard regimen for epithelial ovarian carcinoma since the late 1990s and became the standard for endometrial carcinomas with the results of GOG-209.[21] This regimen has been evaluated in small studies of patients with both OCS and UCS. For example, among 28 patients with OCS treated with PC, 16 (55%) had a complete response and six (23%) had a partial response, and the median OS for all patients was 27 months. Thus, PC was recommended for all stages of OCS.[22] GOG-0232 evaluated 55 patients with UCS treated with PC and found that 13% of patients had confirmed complete response and 41% had partial response. The total overall response rate was 54% (95% CI, 37 to 67), which compared favorably with earlier ifosfamide-based regimens for similar patients.[18,19]

Given the limitations of PI noted above, the efficacy of PC in ovarian carcinomas, and the findings of small studies evaluating PC in patients with OCS and UCS, PC could be a good alternative to PI. Here, we tested the null hypothesis that PC was inferior to PI for patients with all stages of UCS and OCS.

PATIENTS AND METHODS

Study Design and Patients

GOG-0261 (ClinicalTrials.gov identifier: NCT00954174) was an international, randomized, open-label, noninferiority phase III clinical trial. The study was designed to test the null hypothesis that survival among patients with UCS or OCS treated with PC is inferior to survival among patients treated with PI. The study population included adult women (18 years or older) with a Gynecologic Oncology Group (GOG) performance status of 0-2 with chemotherapy-naïve UCS or OCS of all stages or recurrent disease (prior radiation therapy allowed). The study was conducted after approval by both central and local institutional review boards, and investigators obtained written informed consent from each participant. Major protocol revisions include the following:

August 17, 2009: Open to accrual among patients with UCS; target accrual goal was 424 patients, with 264 events to be observed to trigger primary analysis.

June 10, 2010: Eligibility revised to include patients with OCS.

November 19, 2012: Eligibility revised to include patients with fallopian tube and peritoneal carcinosarcoma.

October 21, 2013: Eligibility revised to close accrual to patients with non-UCS and primary analysis restricted to patients with UCS at sponsor request. Revised target accrual goal because of high proportion of early-stage patients was 450 eligible patients with UCS and observation of 264 events, with 652 total enrollments. See Appendix 1 (online only) for additional inclusion and exclusion criteria; random assignment details; and interim analyses, analysis of safety, details of quality-of-life assessment, analyses, figures, CONSORT diagram of patient-reported outcomes, and trial oversight.

Study End Points and Assessments

The primary end point was OS, measured from date of random assignment to the date of death from any cause or, for living patients, date of last contact. Secondary end

points included PFS, adverse events (AEs), quality of life (QOL), and neurotoxicity scores. Treatment assignment was randomized with equal allocation between PI and PC after study registration. Stratification was defined by three factors: disease status or stage at entry (recurrent, clinical FIGO stage I or II, surgical FIGO stage I or II with or without pelvic nodal assessment, and surgical FIGO stage III or IV), tumor status at entry (measurable or nonmeasurable), and pelvic radiation history (any or none). The Common Terminology Criteria for Adverse Events v3.0 grading system was used.

Statistical Considerations

A one-tailed stratified log-rank test of inferiority (hazard ratio [HR] of 1.2 relative to the ifosfamide and paclitaxel arm) limiting type I error to 5% was planned for the primary analysis restricted to patients with UCS. With 264 events reported, the statistical power of this test is 80% to test the null hypothesis of noninferiority (HR 1.2) against the alternative of a true death rate on the ifosfamide and paclitaxel arm, which is 13% greater than the death rate associated with the carboplatin and paclitaxel arm.[23] This design has a 44% chance of concluding noninferiority if the true death rates for the arms were equal. A test of superiority (HR = 1 *v* HR < 1) was planned if the test of inferiority is rejected. A preplanned interim analysis of survival for efficacy (noninferiority) and futility (observed ratio of death hazards relative to the ifosfamide arm exceeds 1.2) was carried out using a nominal *P* value of .001 for stopping, with no correction to the *P* value for the final analysis.[24] The primary analysis and proportional hazards model used to estimate HRs were stratified by disease status, tumor status, and history of pelvic radiation. A forest plot of treatment HRs with CIs within covariate subgroups was planned. The final accrual goals were 450 eligible patients with UCS and 652 total enrollments.

Treatment Arms

PC. Paclitaxel (175 mg/m^2) intravenously (IV) over 3 hours plus carboplatin (area under the curve = 6) IV once on day 1 of each 3-week cycle for 6-10 cycles. The initial dose was reduced for paclitaxel (135 mg/m^2) and carboplatin (area under the curve = 5) both given once on day 1 of a 3-week cycle if the patient had previous whole pelvic radiotherapy and could be escalated if the patient tolerated the lower dose.

PI. Ifosfamide (1.6 g/m^2) IV daily days 1-3, IV and/or oral mesna plus paclitaxel (135 mg/m^2) by 3-hour infusion on once day 1, plus G-CSF support (filgrastim or pegfilgrastim) on days 4-6 of each 3-week cycle for 6-10 cycles. At each cycle, paclitaxel and ifosfamide dose could be increased or

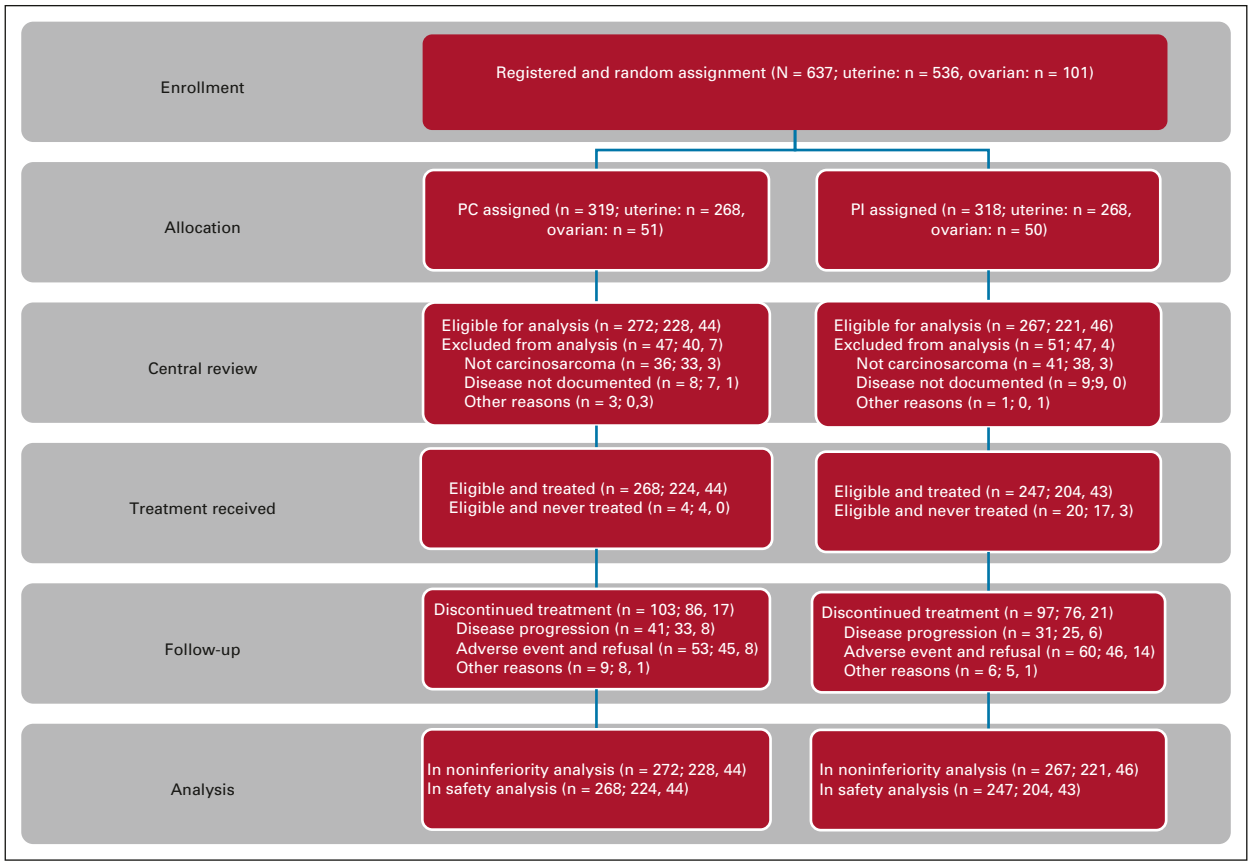

FIG 1. CONSORT diagram. PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide.

decreased if needed on the basis of cycle nadir counts. The initial dose was reduced to ifosfamide (1.2 g/m^2 once daily days 1-3) if the patient had previous whole pelvic radiotherapy.

RESULTS

Patient Characteristics and Treatment

The study accrued 637 women between August 17, 2009, and March 24, 2014, at 176 sites across the United States and Korea. As of February 18, 2019, the median follow-up time was 61 months. Ninety-eight patients deemed ineligible on central review were distributed equally across treatment arms as shown in the CONSORT diagram (Fig 1). Of all eligible patients enrolled, 24 (four in the PC arm and 20 in the PI arm) were never treated and 20 (12 in the PC arm and eight in the PI arm) withdrew consent to continuous follow-up. Of the 449 eligible patients enrolled with uterine primary disease (primary analysis cohort), 21 were never treated with protocol-assigned treatment (four in the PC arm and 17 in the PI arm). Reasons for coming off study treatment were balanced between treatment arms (Fig 1).

Select patient and tumor characteristics of the patients with UCS are shown in Table 1, and additional details are given in Appendix Table A1 (online only). For characteristics of the patients with OCS, see Appendix Table A2 (online only). Most participants were between the age 50 and 79 years and non-Hispanic or White and had a stage I or III uterine primary disease. More than 60% of patients completed all planned treatment, and the median time on treatment was 16 weeks from random assignment. Thirteen percent of participants discontinued treatment because of progression, 9% refused some or all treatment, and 13% discontinued treatment early because of AEs or death. Similar numbers of cycles of therapy were given to eligible patients in both regimens; 69% received four-six cycles of PC, and 70% received four-six cycles of PI. Major protocol violations occurred more commonly in the PI arm than in the PC arm (12% *v* 7%) and were often due to the

TABLE 1. Patient and Tumor Characteristic of the Uterine Carcinosarcoma Cohort

Characteristic	PC (n = 228), No. (%)	PI (n = 221), No. (%)	Total (N = 449), No. (%)
Age, years (median)	65	64	
BMI (median)	30.4	30.7	
Race			
White	150 (65.8)	133 (60.2)	283 (63.0)
Black or African American	66 (28.9)	72 (32.6)	138 (30.7)
Asian	9 (3.9)	9 (4.1)	18 (4.0)
Others or not specified	3 (1.3)	7 (3.2)	10 (2.2)
Performance status			
0	149 (65.4)	119 (53.8)	268 (59.7)
1	68 (29.8)	94 (42.5)	162 (36.1)
2	11 (4.8)	8 (3.6)	19 (4.2)
Ethnicity			
Hispanic or Latino	4 (1.8)	8 (3.6)	12 (2.7)
Non-Hispanic	215 (94.3)	206 (93.2)	421 (93.8)
Not specified	9 (3.9)	7 (3.2)	16 (3.6)
Disease status (as enrolled)			
Clinical or surgical stage I or II	105 (46.0)	101 (45.7)	206 (45.9)
Stage III or IV	109 (47.8)	106 (48.0)	215 (47.9)
Recurrent or persistent	14 (6.1)	14 (6.3)	28 (6.2)
Prior RT (as enrolled)			
No	197 (86.4)	189 (85.5)	386 (86.0)
Yes	31 (13.6)	32 (14.5)	63 (14.0)
Measurable disease (as enrolled)			
No	155 (68.0)	150 (67.9)	305 (67.9)
Yes	73 (32.0)	71 (32.1)	144 (32.1)

Abbreviations: BMI, body mass index; PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide; RT, radiation therapy.

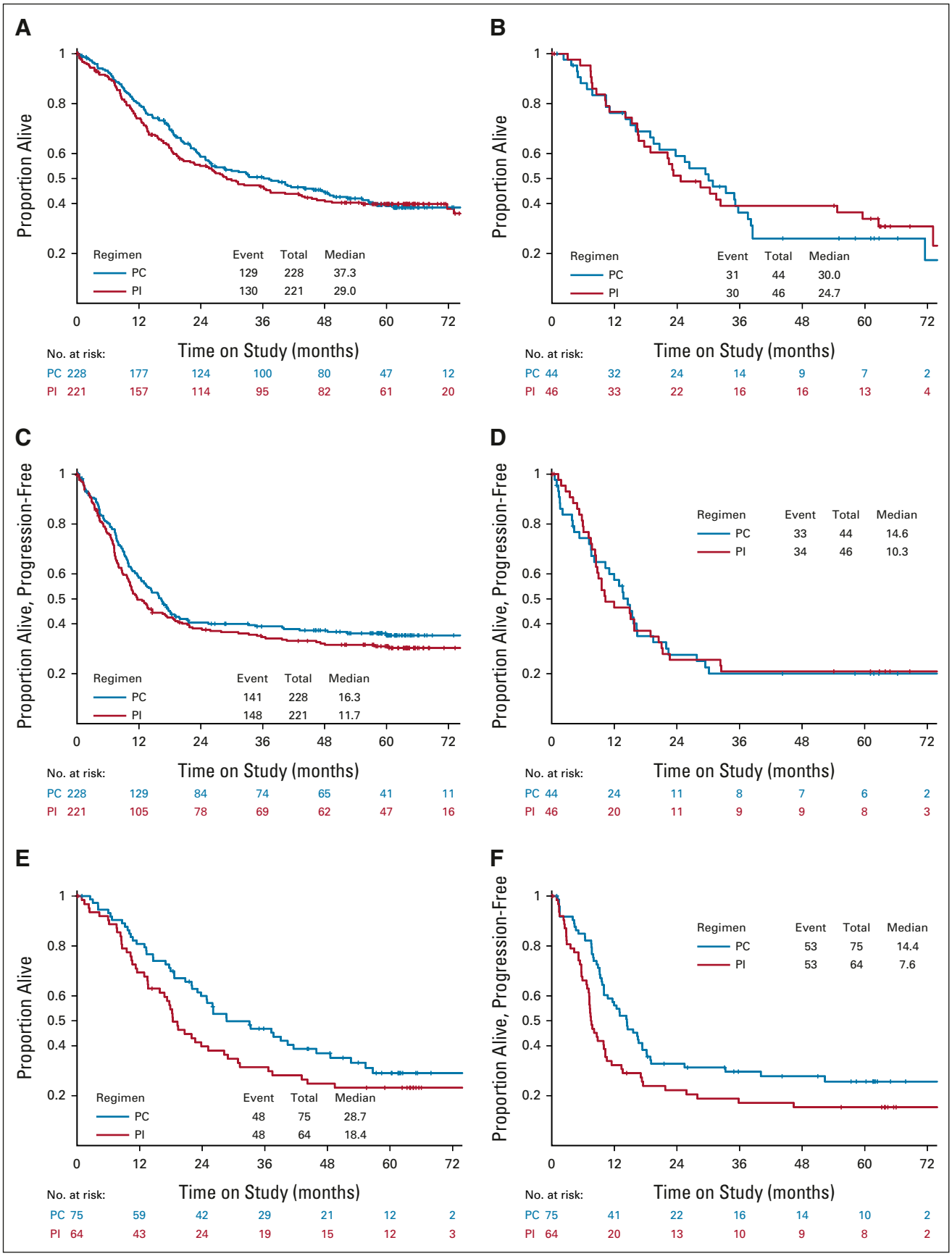

FIG 2. (continued on following page)

FIG 2. (Continued). (A) Survival by assigned treatment arms and for all eligible patients with UCS (HR = 0.87 PC relative to PI; 99% CI, 0.70 to 1.075). (B) Survival by assigned treatment arms for all eligible patients with OCS (HR = 1.15; 95% CI, 0.67 to 1.95). (C) PFS by assigned treatment arms for all eligible patients with UCS (16 *v* 12 months; HR = 0.735; 95% CI, 0.58 to 0.93; $P < .001$) considered both noninferior and statistically superior ($P < .01$). (D) PFS by assigned treatment arms for all eligible patients with OCS (HR = 1.01; 95% CI, 0.61 to 1.67). (E) OS for eligible patients with stage III UCS (HR = 0.82; 95% CI, 0.0.59 to 1.14). (F) PFS for eligible patients with stage III UCS (HR = 0.70; 95% CI, 0.0.51 to 0.96). HR, hazard ratio; OCS, ovarian carcinosarcoma; OS, overall survival; PC, paclitaxel and carboplatin; PFS, progression-free survival; PI, paclitaxel and ifosfamide; UCS, uterine carcinosarcoma. Paclitaxel and carboplatin is not inferior to paclitaxel and ifosfamide for gynecologic carcinosarcoma.

complex dosing adjustments required in response to nadir blood counts.

Efficacy

Among patients with UCS, the median OS was 37 months in the PC arm and 29 months in the PI arm (Fig 2A; adjusted hazard ratio [aHR] = 0.87; 90% CI, 0.70 to 1.075). The *P* value for the stratified test (< .01) rejects the null hypothesis of PC inferiority in favor of noninferiority. However, in a one-tailed test, the PC regimen was not statistically significantly superior to the PI regimen ($P = .14$). Results from restricting analysis to data from treated patients and from eligible treated patients were consistent with the intent-to-treat results (HR = 0.87 and 0.90, respectively).

Among patients with OCS, the median OS was 30 months in the PC arm and 25 months in the PI arm (aHR = 1.15; 95% CI, 0.67 to 1.95; Fig 2B); neither inferiority nor noninferiority were ruled out.

A total of 320 deaths (259 UCS and 61 OCS) were reported. The majority of deaths were attributed to disease. Two deaths in the PC arm were related to treatment.

Among patients with UCS, those in the PC arm had a longer median PFS than those in the PI arm (16 *v* 12 months; aHR = 0.735; 95% CI, 0.58 to 0.93; $P < .001$; Fig 2C). These data revealed that PC was both noninferior and superior to PI ($P < .01$). Among patients with OCS, although PFS in the two arms had similar results (aHR = 1.01; 95% CI, 0.61 to 1.67; Fig 2D), inferiority of PC could not be ruled out with the small sample size.

Forest plots of within-subgroup treatment effects on OS and PFS for the UCS and OCS cohorts are provided in Appendix Figures A1A-A1D (online only). There was no statistically significant evidence of heterogeneity among the factors analyzed. Among the stage III or IV subgroup of patients with UCS, those in the PC arm had longer OS (HR = 0.74; 95% CI, 0.54 to 1.01) and PFS (HR = 0.65; 95% CI, 0.48 to 0.88) than those in the PI arm, but the difference was only statistically significant for PFS. Among only patients with stage III UCS, unadjusted Kaplan-Meier plots reveal that those in the PC arm had longer OS and PFS than those in the PI arm, but the difference was only significant for PFS (Figs 2E and 2F).

We evaluated the impact of previous pelvic radiation therapy on outcomes in the patients with UCS. Among eligible patients, 13% of the entire cohort received previous radiation therapy, including 10% of patients with stage I, 15% of stage II, 13% of stage III, 4% of stage IV, and 45% of recurrent disease. Among patients with stage I-III UCS, 40 of 345 (11.5%) received radiation just before entry on trial. Because the protocol required that the starting doses of

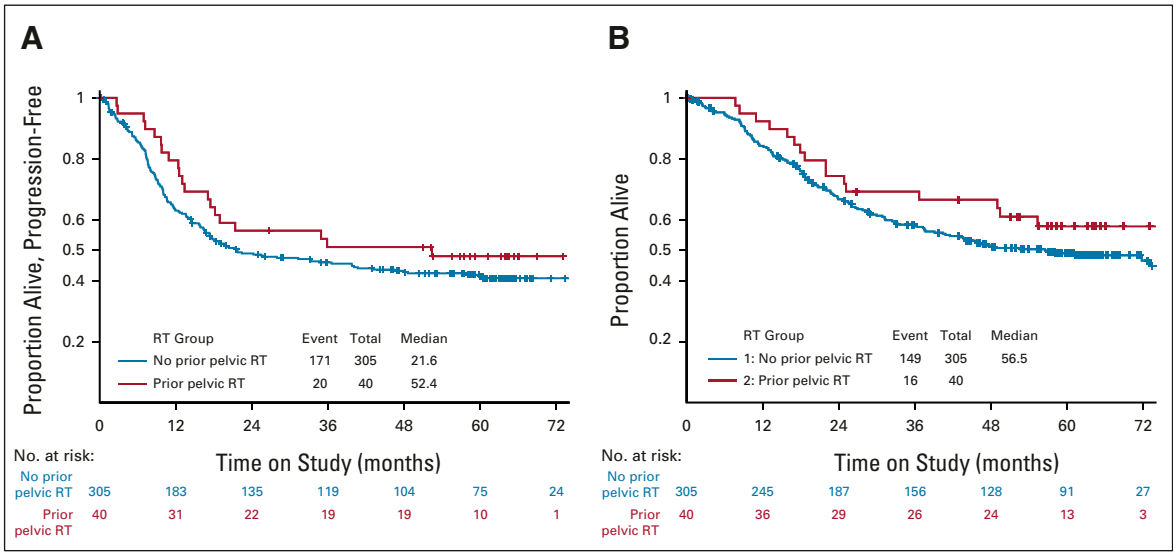

FIG 3. (A) PFS for prior pelvic RT and stage I-III patients and (B) OS for prior pelvic RT and stage I-III uterine patients (SAS system). OS, overall survival; PFS, progression-free survival; RT, radiation therapy.

TABLE 2. Summary of the Grade 3-4 AEs of Interest for the Patients With Uterine Carcinosarcoma (additional data included in Appendix Table A3)

System Organ Class or Term	PC (n = 224) Grade 3-4, No. (%)	PI (n = 204) Grade 3-4, No. (%)
Constitutional	11 (5)	13 (6)
Fatigue	9 (4)	13 (6)
Cardiac	13 (6)	9 (4)
Endocrine	0 (0)	0 (0)
GI	21 (9)	19 (9)
Genitourinary or renal	7 (3)	9 (4)
Hemorrhage	0 (0)	3 (1)
Hematologic	184 (82)	101 (50)
Infection	17 (8)	14 (7)
Lymphatics	2 (1)	0 (0)
Musculoskeletal	2 (1)	1 (0)
Metabolic	29 (13)	33 (16)
Neurologic	16 (7)	23 (11)
Pulmonary	6 (3)	7 (3)
Pain	17 (8)	14 (7)

Abbreviations: AE, adverse event; PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide.

chemotherapy are reduced for these patients in both arms, we conducted a post hoc evaluation of this group. PFS and OS were similar between those who did and did not receive previous radiation therapy (Figs 3A and 3B).

Toxicity

There were no apparent new safety signals with either regimen. Table 2 summarizes the grade 3-5 AE of interest for the patients with UCS (see additional Appendix Table A3, online only). More eligible, treated patients in the PC arm than in the PI arm had grade 3-5 hematologic toxicity (82% *v* 50%; $P < .01$), which was not unexpected given that growth factor support was required in the PI arm and only rarely used (n = 2) in the PC arm. Grade 3-5 neurologic AEs were reported in 12% and 7% of patients in the PI and PC arms, respectively ($P > .10$), despite trial eligibility requiring albumin of ≥ 3 g/dL.

QOL

Ninety-four percent of eligible patients completed the baseline assessment, with subsequent completion rates of 86% (cycle 3), 84% (cycle 6), and 74% (30 weeks after cycle 1; Appendix Fig A2 and Table A4, online only). The compliance rates at follow-up assessments were not significantly different ($P = .9$) between the two trial arms. Among patients with UCS, the patient-reported QOL (measured with the Trial Outcome Index of the Functional Assessment of Cancer Therapy—Endometrial [FACT-En TOI]) and the patient-reported neurotoxicity symptoms (measured with the Functional Assessment of Cancer Therapy with GOG-neurotoxicity subscale [FACT with GOG-Ntx subscale]) were not significantly different between those in the PC arm and those in the PI arm (Appendix Figs A3A and A3B, online only). Patients in both arms reported decreased QOL and increased neurotoxic symptoms during treatment.

DISCUSSION

This open-label, randomized, phase III therapeutic noninferiority clinical trial shows that PC is not inferior to PI in terms of OS and PFS and significantly increases PFS duration for patients with UCS. Findings were similar but not statistically significant in the smaller OCS cohort. Overall, the toxicity and patient-reported quality-of-life profiles were similar for the two drug regimens. These results establish that PC should be used as a standard regimen for patients with UCS and should be considered for treating patients with OCS. These findings are important because PC is easier to administer than is PI. Moreover, patients with UCS could be considered for inclusion in clinical trials for patients with the more common epithelial subtypes of uterine cancer treated with PC. Similarly, it may be reasonable to combine OCS patients with other epithelial subtypes in ovarian cancer trials.

Both UCS and OCS have significant racial and age disparities in risk and outcome. For example, UCS occurs up to three times more frequently in Black women than in White women, and this disparity appears to be increasing.[2,8,25,26] In addition, carcinosarcomas are most common in older women; the mean age at diagnosis is 68 years.[2,8] In part, this is because tamoxifen and previous radiation therapy are likely risk factors.[12,27-29] Predictors of recurrence and death for UCS and OCS include poorly differentiated epithelial or serous histology, rhabdomyosarcomatous components, advanced stage, Black race, older age, lymphovascular space invasion, and a history of cancer.[9,30-32] This study was sized to assess inferiority of PC to PI in subgroups defined by self-reported race or age.

We note several important differences in the two regimens investigated in the trial. First, PI requires a 3-day infusion, whereas PC can be delivered in 1 day. Second, PI requires growth factor support and has complex dosing requirements. Finally, PI likely costs considerably more than PC, although we did not assess cost in this study. In this study, patients in the PI arm were more likely than those in the PC arm to have central neurotoxicity, despite the eligibility requirement of serum albumin ≥ 3.0 g/dL. In other studies, between 5% and 20% of patients receiving ifosfamide have had central nervous system toxicity, including mild confusion, somnolence, seizure, coma, and death, although most events resolved with appropriate therapy.[33] Central nervous system toxicity has been a major deterrent to ifosfamide use in gynecologic malignancies and has hampered development of ifosfamide-containing drug combinations. Although paclitaxel causes predictable peripheral neurotoxicity, several clinical management options

can be used to decrease the risk of grade 3 or worse neurotoxicity. In this study, dose reductions and dose holds were used to manage peripheral neurotoxicity. Given that paclitaxel was included in both arms of the study, it is not surprising that no significant interarm differences were seen in quality-of-life assessments of neurotoxicity administered at four time points.

The utility of radiation for UCS, especially for early-stage UCS, is unclear. In this study, 13% of the entire cohort received previous pelvic radiation therapy, including 10% of stage I, 15% of stage II, 13% of stage III, 4% of stage IV, and 45% of recurrent disease patients. These rates are somewhat lower than older published data but may reflect recent trends in omitting radiation therapy for these patients in response to data from several studies. For example, GOG 150 noted no statistically significant difference in survival or recurrence rates among patients with UCS who received chemotherapy versus whole abdominal radiation.[17] In European Organisation for Research and Treatment of Cancer protocol 55874, which started in the 1980s and took 13 years to accrue, 91 of 224 patients had UCS. Among the patients with UCS, those in the pelvic radiotherapy arm had fewer local recurrences than those in the observation arm (24% *v* 47%) but no statistically significant differences in PFS or OS.[34] In both these trials, relapse tended to occur outside the radiated field or in areas with decreased dose of radiation, compelling many gynecologic oncologists to combine radiation and chemotherapy.

Our understanding of carcinosarcoma biology has improved recently. For example, we now know that expression of epithelial-mesenchymal transition–related genes and DNA methylation changes underly the sarcoma differentiation. In addition, like the more common endometrial carcinomas, UCSs can be classified into four molecular subtypes: polymerase epsilon (*POLE*)-mutated, microsatellite instability, copy number high, and copy number low. These molecular subtypes are linked with DNA repair deficiencies, potential therapeutic strategies, and multiple clinicopathologic features, including patient outcomes.[14,35] A predominance of copy number high subtype may explain the aggressive behavior and poor prognosis of UCS. Some differences are noted among the two major UCS molecular characterization studies. Although 81.3% of specimens in The Cancer Genome Atlas contained an epithelial component (serous or undifferentiated), 85% of specimens in the Japanese Foundation for Cancer Research were endometrioid. Thus, the histologic appearance of the epithelial component may be important to consider when evaluating treatment decisions. For example, de-escalating treatment of *POLE*-mutated tumors, using immunotherapy to treat mismatch repair–deficient tumors, and decreasing radiation and escalating chemotherapy to treat human epidermal growth factor receptor 2 (HER2)–positive tumors are options that can be explored in clinical trial designs.

A potentially important target in UCS is HER2 overexpression. Rottman et al found that 16% of 80 gynecologic carcinosarcoma specimens were HER2-positive, similar to the frequency of HER2 expression in endometrial serous carcinomas. Importantly, heterogeneity of HER2 protein expression was observed in 38% of HER2-positive tumors, and a lateral or basolateral membranous staining pattern was common.[36] In a randomized phase II trial, PC plus trastuzumab improved PFS and OS for patients with HER2-positive uterine serous carcinoma.[37,38] Future studies should assess the utility of this approach in patients with UCS, especially given our findings that PC is an effective therapy for these patients.

In conclusion, these results establish a new standard regimen–PC—for women with UCS of all stages and especially for stage III patients. Toxicity was as predicted and manageable. Identifying and targeting the molecular aberrations in these tumors should lead to further improvements in treatment.

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PRIOR PRESENTATION

Presented in part at ASCO annual meeting, Chicago, IL, June 1, 2019.

SUPPORT

Supported by National Cancer Institute grants to NRG Oncology SDMC (1 U10 CA180822), NCORP (UG1CA189867), NRG Operations (U10CA180868), and NRG Specimen Bank (U24CA186067). M.L.H. was supported in part by NIH with NCI Cancer Center Support Grant P30 CA008748.

CLINICAL TRIAL INFORMATION

NCT00954174

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.21.02050.

DATA SHARING STATEMENT

Within approximately 1 year of publication, deidentified data from this article will be available for data sharing proposals at the National Cancer Institute NCTN with NCORP data archive: https://nctn-data-archive.nci.nih.gov.

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ACKNOWLEDGMENT

NRG Oncology and Gynecologic Oncology Group member institutions participated in this study listed in Appendix 2 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase III Trial of Paclitaxel and Carboplatin Versus Paclitaxel and Ifosfamide in Patients With Carcinosarcoma of the Uterus or Ovary: An NRG Oncology Trial

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Patents, Royalties, Other Intellectual Property: Application No. PCT/US 2019/19465, Cannabis Based Therapeutic and Method of Use; Application No.: US Patent 0024098766, Compounds Cannabidiol and Flavanones, 63/047550 (July 1, 2020) 63/055458 (July 23, 2020), Title Country Status Filed Date Application No. Patent Ref. No. 199236-701611/EP, Title: Cannabis Based Therapeutic and Method of Use Country, European Patent Status: Published February 25, 2019, 19710540.6; Patent Ref. No. 199236-701691/PCT-BR, Title: Cannabis Based Therapeutic and Method of Use Country Brazil Status: Application February 25, 2019, 1120200170232; Patent Ref. No. 199236-701831/PCT-US, Title: Cannabis Based Therapeutic and Method of Use Country United States of America Status: Published February 25, 2019, 16/971,781; Patent Ref. No. 199236-701891/HK, Title: Cannabis Based Therapeutic and Method of Use Country Hong Kong Status: Published June 25, 2021, 62021033676.9; Patent Ref. No. Title Country Status Filed Date; Application No. Patent Ref. No. 199237-701601/PCT, Title: Compositions Comprising Cannabidiol and Flavanones Country: Patent Cooperation Treaty Status: Application July 1, 2021, PCT/US21/40115; Patent Ref. No. 199237-701691/BR, Title: Compositions Comprising Cannabidiol and Flavanones Country: Brazil Status: Application November 19, 2020, 1020200236644; Patent Ref. No. 199237-7019761/UY, Title: Compositions Comprising and Flavanones Country: Uruguay Status: Application November 20, 2020, 38965, John Wiley and Sons Editor 12th Edition Bonney's Gynaecological Surgery
Open Payments Link: https://openpaymentsdata.cms.gov/physician/8054, https://openpaymentsdata.cms.gov/physician/8054

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No other potential conflicts of interest were reported.

APPENDIX 1. ADDITIONAL STUDY DETAILS

Inclusion Criteria

1. Patients must have newly diagnosed stage I-IV, persistent or recurrent (including unstaged) uterine carcinosarcoma (UCS; malignant mixed mullerian tumor or with ovarian, fallopian tube, or peritoneal carcinosarcoma and an enrollment date before October 21, 2013; pathology confirmed by site or institutional pathologist before enrollment) and be chemotherapy-naïve as directed against their carcinosarcoma. Unstaged patients (patients who have not had hysterectomy or ovarian surgery) are eligible and should be included as unstaged if the only histologic (pathology) documentation of the disease is a biopsy or curettage of the uterus. If these patients have documented metastatic disease, it should be assigned the appropriate stage (III or IV).
2. Patients must have received prior adjuvant external beam radiation therapy and/or vaginal brachytherapy. Patients should be at least 4 weeks from the completion of external beam radiotherapy before beginning protocol chemotherapy. Patients do not need to be delayed if receiving vaginal brachytherapy only.
3. Patients must have a Gynecologic Oncology Group (GOG) performance status of 0, 1, or 2.
4. Patients must have recovered from effects of recent surgery, radiotherapy, or other therapies.
5. Patients must be free of active infection requiring antibiotics.
6. Any hormonal therapy directed at the malignant tumor must be discontinued at least 1 week before beginning protocol chemotherapy. Continuation of hormone replacement therapy is permitted.
7. Patients must have adequate:
   a. Bone marrow function: Platelet count $\geq$ 100,000/mcL and absolute neutrophil count $\geq$ 1,500/mcL, equivalent to CTCAE v3.0 grade 1.
   b. Renal function: creatinine $\leq 1.5 \times$ institutional upper limit normal (ULN), CTCAE v3.0 grade 1.
   c. Hepatic function: Bilirubin $\leq 1.5 \times$ ULN (CTCAE v3.0 grade 1). AST and alkaline phosphatase $\leq 2.5 \times$ ULN (CTCAE v3.0 grade 1). Serum albumin should be $\geq$ 3 g/dL.
   d. Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v3.0 grade 1.
8. Patients must have signed an approved informed consent and authorization permitting release of personal health information.
9. Patients of childbearing potential must have a negative serum pregnancy test before study entry and be practicing an effective form of contraception.
10. Patients must have measurable disease or nonmeasurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be >20 mm when measured by conventional techniques, including palpation, plain x-ray, computed tomography (CT), and magnetic resonance imaging, or $\geq$ 10 mm when measured by spiral CT. Patients with measurable disease must have at least one target lesion to be used to assess progression on this protocol as defined by RECIST. Tumors within a previously irradiated field will be designated as nontarget lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days after completion of radiation therapy.
11. Patients must be age 18 years or older.

Exclusion Criteria

1. Patients who have received prior cytotoxic chemotherapy for management of UCS or ovarian carcinosarcoma.
2. Patients with a history of other invasive malignancies or with a concomitant invasive malignancy, with the exception of nonmelanoma skin cancer, if there is any evidence of other malignancies being present within the past 5 years. Patients are also ineligible if their previous cancer treatment contraindicates this protocol therapy.
3. Patients for whom radiotherapy is planned after or during study chemotherapy before progression of cancer.
4. Patients with a known hypersensitivity to E. coli–derived drug preparations (pegfilgrastim and filgrastim).
5. Patients with a known hypersensitivity to mesna or other thiol compounds.
6. For enrollment before October 21, 2013, patients who are not biopsy-proven to have carcinosarcoma of the uterus, fallopian tube, peritoneum, or ovary. For enrollment after October 21, 2013, patients who are not biopsy-proven to have carcinosarcoma of the uterus.

Significant Revisions

Revision 2 June 10, 2010: Inclusion of patients with ovarian carcinosarcoma, switch to Oncology Patient Enrollment Network (OPEN) registration system, and clarification of isotope-dilution mass spectrometry versus non–isotope-dilution mass spectrometry dosing strategy.

Revision 8 November 19, 2012: Inclusion of patients with fallopian tube and peritoneal carcinosarcoma.

Revision 9 October 21, 2013: Accrual closed to patients with non-UCS at sponsor request. Revised target accrual goal was because of high proportion of early-stage patients.

Trial Design Additional Details

Additional materials collected. Formalin-fixed, paraffin-embedded tumor tissue and DNA extracted from whole blood were banked.

Additional details of registration and random assignment. Before June 10, 2010, patients were registered to this study and obtained random treatment assignment centrally at the GOG Statistical and Data Center. After June 10, 2010, patients were registered to this study through the OPEN and treatment random assignments were carried out centrally by the GOG or NRG Statistical and Data Center. Before registration, eligibility was reviewed via Fast Fact Sheet verification. The sequence of treatment assignments was concealed from institutions and patients until registration with verification of eligibility. A minimization procedure was used that tends to balance the treatment allocation equally within patient-level stratification factors. The original sample size was 364 eligible patients with UCS and 264 events, with 424 total enrollments. The revised accrual goal was based on eligible patients with UCS and events: 450 eligible patients with UCS and 264 events, with 652 total enrollments.

Originally, a pragmatic approach to the comparison of planned therapeutic regimens was to be carried out. All eligible enrolled patients were to be included in the primary analysis, regardless of the amount of study treatment received and regardless of primary tumor site (ie, uterine or ovarian), that is, the primary analysis will be an intention-to-treat analysis among eligible patients. The approach taken in redesigning this study was to leave the original study objectives intact and restrict the primary hypothesis test to include only eligible participants with UCS. Since the original study was opened to those with a diagnosis of UCS and they represented roughly 80% of the accrual, the accrual goal was set for hypothesis testing within this specific subgroup at 80% power.

Safety Analysis and Trial Oversight

The Data Monitoring Committee (DMC; also referred to as the Data Safety and Monitoring Board) reviewed study summary reports every 6 months and interim analyses as planned and provided recommendations to Group leadership. The Safety Review Committee (SRC)

reviewed accumulating summaries of adverse events (AEs) and serious adverse event reports on an ongoing basis (not efficacy results). This committee reviewed deaths in which study treatment might have been a contributing cause. SRC reporting to the DMC ended when NRG was formed in 2014. DMC safety reviews continued until the primary end point analysis occurred. A scheduled interim analysis was presented to the DMC in July 2014; no action was taken in response to this interim analysis.

AEs

The maximum grade over the entire course of therapy for any individual effect was used to summarize acute toxicity. The Kruskal-Wallis test corrected for ties was used to compare the maximum grade of acute adverse effects of therapy by treatment arms. The CTCAE v3.0 grading system was used (ie, scale from 0 for none to 5 for death). A significance level of 0.01 was set for each tested AE term or category. No correction for multiple testing was used since it is very important to identify moderate increases in the severity of toxicity at the risk of increasing the type I error. Since some of these toxicities are correlated, the overall type I error is less than that calculations would indicate when assuming complete independence. Toxicity was assumed to be independent of the primary site of disease.

Supplemental Results

Patient and Tumor Characteristics. Among the participants, 98 were deemed ineligible on central review. These patients are distributed equally across treatment arms. The reasons for ineligibility include the following: wrong cell type, n = 77; wrong or second primary, n = 4; or insufficient pathologic evidence, n = 17. This degree of ineligibility because of pathology is common for gynecologic carcinosarcoma on the basis of previous clinical trial experience. Of all eligible patients enrolled, 24 (four in the PC arm and 20 in the PI arm) were never treated and 20 (12 in the PC arm and eight in the PI arm) have withdrawn consent to continuous follow-up. There were 449 eligible patients enrolled with uterine primary disease, and 21 of these were never treated with protocol-assigned treatment (four in the PC arm and 17 in the PI arm).

Disease Outcome

Death attribution. There were two deaths attributed to treatment, both on the PC arm. One died from multiorgan failure thought to be sepsis related, and the other died from myelodysplastic syndrome 55 months after random assignment. The patient who died from Myelodysplatic syndrome received six cycles of treatment on study and was reported to have received retreatment with the same drugs at time of progression.

AEs. As of February 18, 2019, 515 eligible study participants have been reported to have initiated study treatment and are included in the AE tables. AEs are summarized across disease sites. Twenty-four eligible patients have refused or did not initiate study treatment and are not included in the AE summary tables. A grade 4 or higher AE has been reported in 136 versus 64 participants in the PC and PI arms, respectively. Nine grade 5 AEs were reported, six in the PC arm and three in the PI arm.

The frequency and severity were worse on the PI arm for the following AEs: hyperpigmentation, renal or genitourinary—other, hemorrhage, hemorrhage, GU—urinary NOS, alkaline phosphatase, proteinuria, confusion, and bone pain. However, the frequency and severity of blood or bone marrow (including leukocytes, platelets, and neutrophils) and hypomagnesemia AEs were worse on the PC arm (Appendix Table A3).

Quality of Life. The secondary patient-reported outcome (PRO) objectives were to compare patient-reported physical functioning or quality of life (QOL) measured with the Trial Outcome Index of the Functional Assessment of Cancer Therapy for endometrial cancer (FACT-En TOI) and neurotoxicity symptoms measured with the Functional Assessment of Cancer Therapy with GOG-neurotoxicity (FACT with GOG-Ntx) subscale between the two treatment groups. The FACT-En TOI is a scale for assessing general QOL of patients with endometrial cancer. It consists of three subscales: Physical Well-Being (seven items), Functional Well-Being (seven items), and Endometrium Cancer subscale (16 items). The FACT with GOG-Ntx subscale consists of 11 items and is designed to measure chemotherapy-induced peripheral neuropathy. Each item in the FACT-En TOI and the FACT with GOG-Ntx subscale was scored using a 5-point scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much). For the negative statements (or questions), reversal was performed before score calculation. According to the FACIT measurement system, a subscale score was the summation of the individual item scores if more than 50% of subscale items were answered. When unanswered items existed, a subscale score was prorated by multiplying the mean of the answered item scores with the number of items in the subscale. The total FACT-En TOI score is calculated as the sum of the subscale scores if more than 80% of the FACT-En TOI items provide valid answers and all the component subscales have valid scores. The total scores ranged between 0 and 120 for FACT-En TOI and between 0 and 44 for the FACT with GOG-Ntx subscale. A higher score indicates better QOL or less neurotoxic symptoms or concerns.

The Minimal Important Difference (MID) is 6 points for the FACT-En TOI and 3.3 points for the FACT with GOG-Ntx subscale (Yost and Eton[39]). QOL assessments were scheduled at: baseline, approximately week 6 (before cycle 3), week 15 (before cycle 6), week 30 after initiation of therapy. To ensure that the overall type I error is 0.05, the type I error for each of the two PRO end points was set at 0.025. All analyses were undertaken on the intention-to-treat and eligible population using SAS or STAT Software 9.4. The treatment difference in PROs was assessed with a linear mixed model adjusting for patient's pretreatment score, assigned treatment assignment, and age at enrollment. The assessment time points were treated as categorical since they are not equally spaced. The covariance matrix among the repeated PRO scores reported by the same patient is assumed to be unstructured. To reflect the observed covariance pattern of the PRO scores, the empirical variance was used in estimating the precision of parameter estimates. First, the interactions between assessment time points and treatment assignments were tested for the constant differential effects of treatments over time. If the interaction effect was not statistically significant, an overall treatment effect was estimated by a weighted average of estimates from each time point. If the testing for interaction was rejected, the treatment comparison was performed for each assessment time.

Every effort was made to avoid missing data, and the reasons for missing assessments were collected at each assessment time point and documented in the analysis. Assessment compliance was compared between assigned groups using generalized estimating equation methods.

Status of PRO Assessments

The status of PRO assessments of 449 eligible patients is presented in Appendix Figure A2. The completion rate was defined as the numbers of PRO assessments completed (with valid answers) as a proportion of those who were alive at each scheduled assessment time. Ninety-four percent of eligible patients completed the baseline assessment (Appendix Table A4). After the initiation of study treatment, the compliance dropped to 86% at cycle 3, 84% at cycle 6, and 74% at 30 weeks after cycle 1. The reasons for missing an assessment were documented and are presented in Appendix Table A4. The primary reasons for missing an assessment were administrative error and patient's withdrawal from study. Although more patients on PC completed baseline PRO assessment than those on PI (97% *v* 91%; chi-square test $P = .012$), a generalized estimating equation estimate suggested that the compliance rates of the follow-up assessments were not significantly different between the two randomized groups ($P = .9$).

Summary of the FACT-En TOI. At baseline, the FACT-En TOI scores were 96.2 and 97.5, respectively, as reported by patients assigned to PC and PI. After adjustment for patient's age and baseline

score, the fitted mixed model estimate suggested that the treatment differences in the FACT-En TOI score did not vary significantly over the assessment times ($P = .9$ for the interaction between assessment times and treatment groups). The estimated overall treatment difference (PC *v* PI) on average was 0.2 (97.5% CI, –2.6 to 2.9; $P = .9$).

Summary of the FACT with GOG-Ntx subscale. At baseline, the FACT with GOG-Ntx subscale scores were 40.2 and 41.0 as reported by patients assigned to PC and PI, respectively. After adjustment for patient's age at the enrollment and baseline Ntx subscale score, the fitted mixed model estimate suggested that the treatment differences in the FACT with GOG-Ntx subscale score did not vary significantly over the assessment times ($P = .9$ for the interaction between assessment times and treatment groups). The estimated overall treatment difference (PC *v* PI) was 0.15 (97.5% CI, –1.2 to 1.5; $P = .8$).

APPENDIX 2. NRG ONCOLOGY AND GYNECOLOGIC ONCOLOGY GROUP

The following NRG Oncology and Gynecologic Oncology Group member institutions participated in this study: University of Oklahoma Health Sciences Center, University of California Medical Center at Irvine-Orange Campus, Ohio State University Comprehensive Cancer Center, Duke University Health System, Washington University School of Medicine, Yale University, Georgia Center for Oncology Research and Education (CORE), Cooper Hospital University Medical Center, Women's Cancer Center of Nevada, Women and Infants Hospital, Metro-Minnesota CCOP, University of Mississippi Medical Center, Mayo Clinic Case Western Reserve University, Cancer Trials Support Unit, Seoul National University Hospital, University of Iowa Hospitals and Clinics, State University of New York Downstate Medical Center, Memorial Sloan Kettering Cancer Center, Saint Joseph's Hospital and Medical Center, University of Cincinnati, University of Alabama at Birmingham, Wayne State University and Karmanos Cancer Institute, University of North Carolina at Chapel Hill, University of Kentucky, Fox Chase Cancer Center, University of Chicago, Cleveland Clinic Foundation, Cancer Research for the Ozarks NCORP, Michigan Cancer Research Consortium Community Clinical Oncology Program, Walter Reed National Military Medical Center, Rush University Medical Center, Stony Brook University Medical Center, Carolinas Medical Center and Levine Cancer Institute, Mainline Health CCOP, Northwestern University, University of Texas Southwestern Medical Center, Wake Forest University Health Sciences, MD Anderson Cancer Center, Central Illinois CCOP, Delaware and Christiana Care CCOP, Wichita CCOP, The Hospital of Central Connecticut, Roswell Park Comprehensive Cancer Center, University of Colorado Cancer Center—Anschutz Cancer Pavilion, Indiana University Hospital and Melvin and Bren Simon Cancer Center, Aurora Women's Pavilion of Aurora West Allis Medical Center, Baystate Medical Center, Geisinger Medical Center, Virginia Commonwealth University, Colorado Cancer Research Program NCORP, Abington Memorial Hospital-asplundh Cancer Pavilion, University of Wisconsin Hospital and Clinics, UCSF-Mount Zion, Froedtert and the Medical College of Wisconsin, Upstate Carolina CCOP, Iowa-Wide Oncology Research Coalition NCORP, Fred Hutchinson Cancer Research Center, University of New Mexico, University of Texas-Galveston, Kalamazoo CCOP, Cancer Research Consortium of West Michigan NCORP, Greenville Health System Cancer Institute and Greenville CCOP, Florida Hospital Cancer Institute CCOP, University of California at Los Angeles Health System, Abramson Cancer Center of the University of Pennsylvania, Penn State Milton S. Hershey Medical Center, University of Massachusetts Memorial Health Care, Gynecologic Oncology of West Michigan PLLC, University of Kansas Medical Center, Kansas City CCOP, and Northern Indiana Cancer Research Consortium.

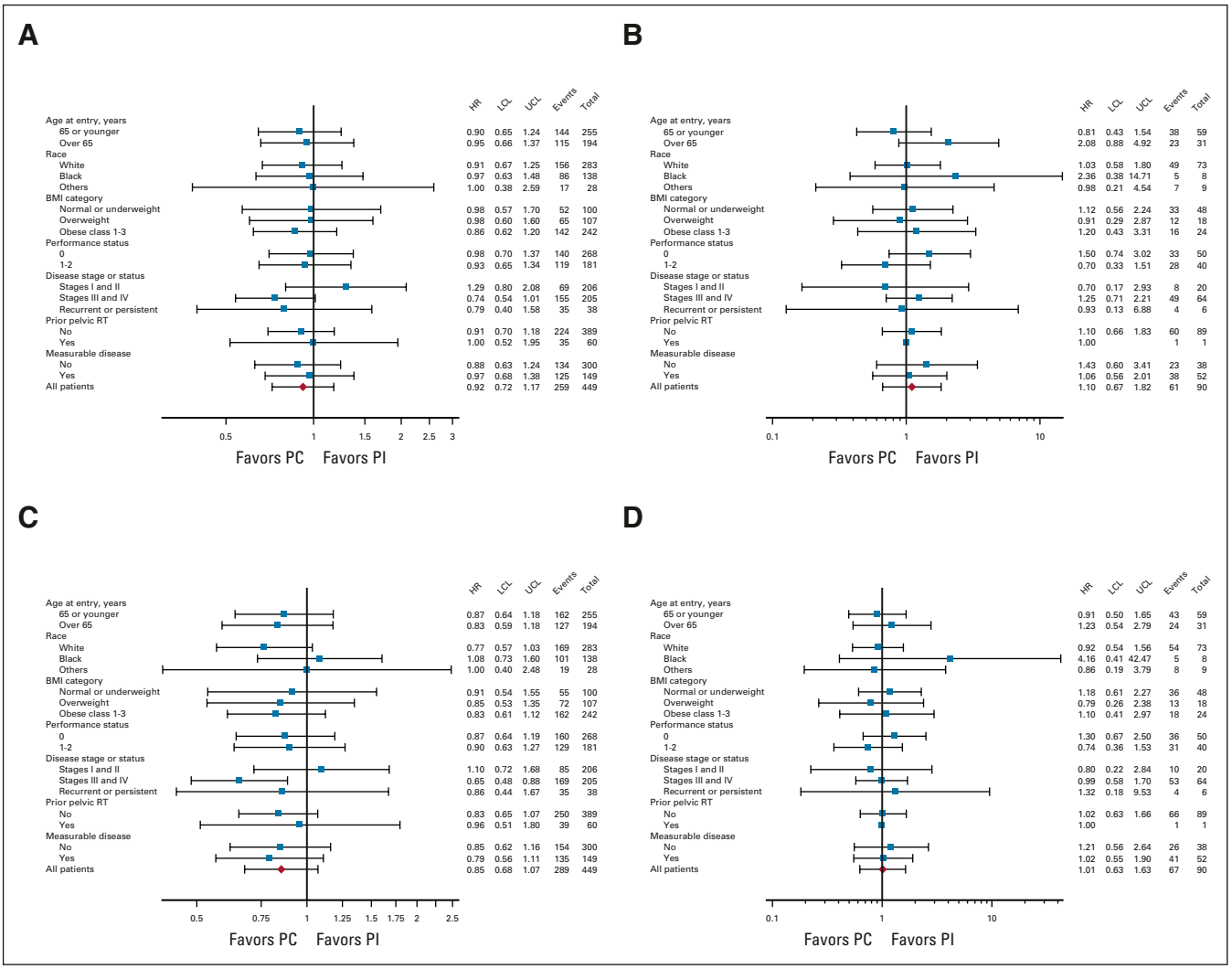

FIG A1. Forest plot of treatment effect on OS by subgroup of (A) all eligible patients with UCS and (B) all eligible patients with OCS. Forest plot of treatment effect on PFS by subgroup of (C) all eligible patients with UCS and (D) all eligible patients with OCS. BMI, body mass index; OCS, ovarian carcinosarcoma; OS, overall survival; PC, paclitaxel and carboplatin; PFS, progression-free survival; PI, paclitaxel and ifosfamide; RT, radiation therapy; UCS, uterine carcinosarcoma.

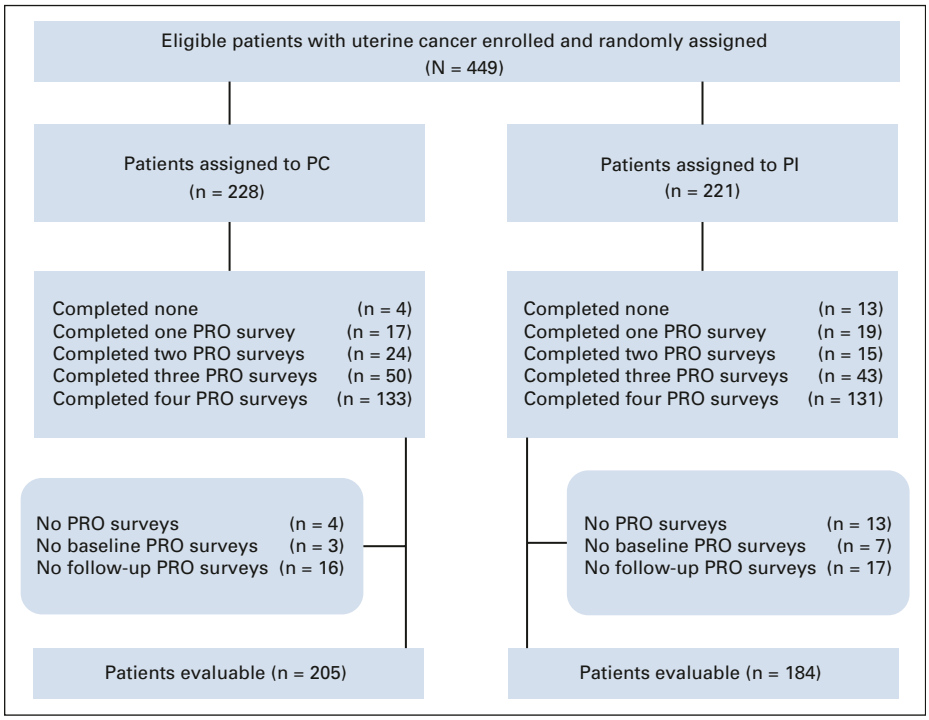

FIG A2. CONSORT diagram of PROs. PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide; PRO, patient-reported outcome.

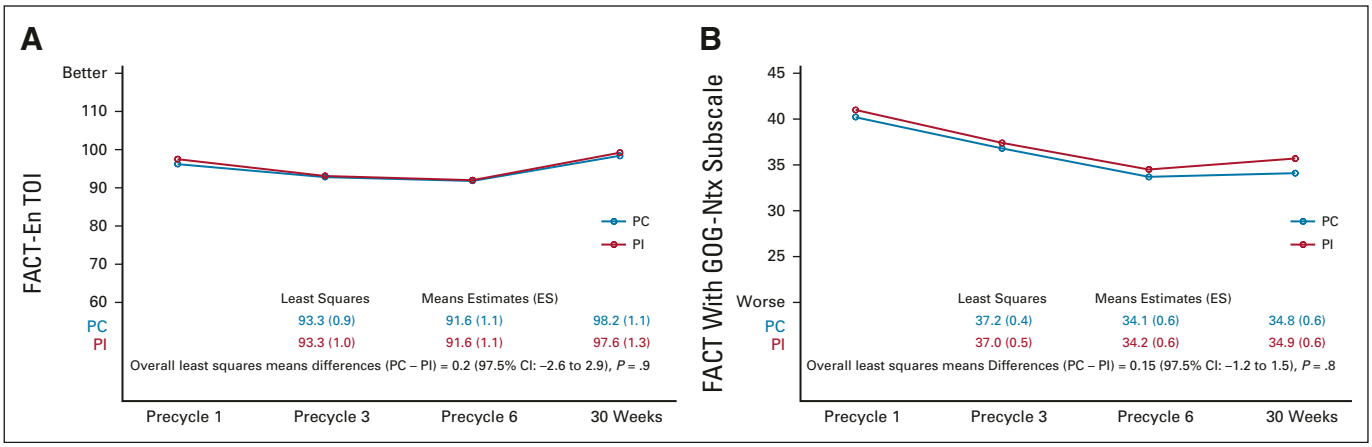

FIG A3. (A) Patient-reported FACT-En TOI scores by treatment arms. (B) Patient-reported FACT with GOG-Ntx subscale scores by treatment arms. FACT with GOG-Ntx, Functional Assessment of Cancer Therapy with GOG-neurotoxicity subscale; FACT-En TOI, Trial Outcome Index of the Functional Assessment of Cancer Therapy—Endometrial; PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide.

TABLE A1. Cycles of Treatment for All Eligible Enrolled Patients

Characteristic	Regimen		
	PC, No. (%)	PI, No. (%)	Total, No. (%)
No. of cycles			
0	4 (1.8)	17 (7.7)	21 (4.7)
1-3	44 (19.3)	33 (14.9)	77 (17.1)
4-6	160 (70.2)	159 (71.9)	319 (71.0)
7-10	20 (8.8)	12 (5.4)	32 (7.1)
Total	228 (50.8)	221 (49.2)	449 (100.0)

NOTE. Primary site = uterine carcinosarcoma.
Abbreviations: PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide.

TABLE A2. Patient and Tumor Characteristics and Cycles of Treatment for All Eligible Enrolled Patients

	Regimen		
Characteristic	**PC, No. (%)**	**PI, No. (%)**	**Total, No. (%)**
Age, years, median	62.5	60.5	
BMI, median	23.2	25.1	
Ethnicity			
Hispanic or Latino	2 (4.5)	3 (6.5)	5 (5.6)
Non-Hispanic	42 (95.5)	40 (87.0)	82 (91.1)
Not specified	0 (0)	3 (6.5)	3 (3.3)
Race			
White	37 (84.1)	36 (78.3)	73 (81.1)
Black or African American	4 (9.1)	4 (8.7)	8 (8.9)
Asian	2 (4.5)	4 (8.7)	6 (6.7)
Not specified	1 (2.3)	2 (4.3)	3 (3.3)
Performance status			
0	27 (61.4)	23 (50.0)	50 (55.6)
1	17 (38.6)	22 (47.8)	39 (43.3)
2	0 (0)	1 (2.2)	1 (1.1)
Disease status (as enrolled)			
Clinical or surgical stage I or II	9 (20.5)	14 (30.4)	23 (25.5)
Stage III or IV	35 (79.5)	31 (67.4)	66 (73.3)
Recurrent or persistent	0 (0)	1 (2.2)	1 (1.1)
Prior RT (as enrolled)			
No	43 (97.7)	46 (100.0)	89 (98.9)
Yes	1 (2.3)	0 (0)	1 (1.1)
Measurable disease (as enrolled)			
No	22 (50.0)	18 (39.1)	40 (44.4)
Yes	22 (50.0)	28 (60.9)	50 (55.6)
No. of cycles			
0	0 (0)	3 (6.5)	3 (3.3)
1-3	9 (20.5)	8 (17.4)	17 (18.9)
4-6	29 (65.9)	29 (63.0)	58 (64.4)
7-10	6 (13.6)	6 (13.0)	12 (13.3)
Total	44 (48.9)	46 (51.1)	90 (100.0)

NOTE. Primary site = ovarian carcinosarcoma.

Abbreviations: BMI, body mass index; PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide; RT, radiation therapy.

TABLE A3. AE Counts by Highest Grade With Statistically Significant Differences

	Treatment and/or AE Grade											
	Paclitaxel and Carboplatin						Ifosfamide and Paclitaxel					
System Organ Class or Term	0	1	2	3	4	5	0	1	2	3	4	5
Hyperpigmentation	267	1	0	0	0	0	234	13	0	0	0	0
Hemorrhage, GU—urinary NOS	267	0	1	0	0	0	233	12	2	0	0	0
Hypomagnesemia	199	57	12	0	0	0	229	17	1	0	0	0
Proteinuria	267	1	0	0	0	0	234	9	4	0	0	0
Renal or genitourinary—others	265	0	1	2	0	0	233	9	3	2	0	0
Hemorrhage or bleeding	248	18	1	1	0	0	206	35	3	3	0	0
Blood or bone marrow	6	9	32	93	128	0	10	33	81	67	56	0
Leukocytes	29	33	95	96	15	0	83	47	44	44	29	0
Platelets	90	110	41	20	7	0	110	102	21	12	2	0
Neutrophils	23	7	28	86	124	0	126	17	25	28	51	0
Alkaline phosphatase	245	23	0	0	0	0	197	47	2	1	0	0
Confusion	264	3	1	0	0	0	232	7	0	7	1	0
Pain: bone	248	9	9	2	0	0	202	29	14	2	0	0

Abbreviations: AE, adverse event; GU, genital urinary; NOS, not otherwise specified.

TABLE A4. QOL and PRO Assessment Completion

Assessment Time	PC (n = 228)	PI (n = 221)	Total (N = 449)
Precycle 1			
Death	0	1	1
Alive	228	220	448
Received and valid, No. (%)	221 (97)	201 (91)	422 (94)
Missed or invalid because of			
Illness	2	1	3
Administration error	1	4	5
Others	0	2	2
Insufficient answer	2	2	4
Withdrawal from study	2	10	12
Precycle 3			
Death	4	9	13
Alive	224	212	436
Received and valid, No. (%)	197 (88)	179 (84)	376 (86)
Missed or invalid because of			
Illness	1	2	3
Patient refusal	4	2	6
Administration error	6	6	12
Lost to follow-up	2	1	3
Others	1	5	6
Insufficient answer	3	1	4
Withdrawal from study	10	16	26
Precycle 6			
Death	11	15	26
Alive	217	206	423
Received and valid, No. (%)	182 (84)	172 (83)	354 (84)
Missed or invalid because of			
Illness	1	1	2
Patient refusal	4	2	6
Administration error	10	7	17
Lost to follow-up	1	0	1
Others	5	6	11
Insufficient answers	1	0	1
Withdrawal from study	13	18	31
30 weeks after cycle 1			
Death	27	23	50
Alive	201	198	399
Received and valid, No. (%)	147 (73)	150 (76)	297 (74)
Missed because of			
Illness	6	3	9
Patient refusal	4	2	6
Administration error	18	12	30
Lost to follow-up	3	2	5
Others	9	10	19
Insufficient answer	1	0	1
Withdrawal from study	13	19	32

Abbreviations: PC, paclitaxel and carboplatin; PI, paclitaxel and ifosfamide; PRO, patient-reported outcomes; QOL, quality of life.