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VOLUME 36 · NUMBER 20 · JULY 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

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Published at jco.org on March 27, 2018.

Clinical trial information: NCT01367002.

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0732-183X/18/3620w-2044w/$20.00

ABSTRACT

Purpose
Uterine serous carcinoma is a rare, aggressive variant of endometrial cancer. Trastuzumab is a humanized monoclonal antibody that targets human epidermal growth factor receptor 2 (HER2)/neu, a receptor overexpressed in 30% of uterine serous carcinoma. This multicenter, randomized phase II trial compared carboplatin-paclitaxel with and without trastuzumab in patients with advanced or recurrent uterine serous carcinoma who overexpress HER2/neu.

Methods
Eligible patients had primary stage III or IV or recurrent HER2/neu-positive disease. Participants were randomly assigned to receive carboplatin-paclitaxel (control arm) for six cycles with or without intravenous trastuzumab (experimental arm) until progression or unacceptable toxicity. The primary end point was progression-free survival, which was assessed for differences between treatment arms via one-sided log-rank tests.

Results
From August 2011 to March 2017, 61 patients were randomly assigned. Forty progression-free survival–related events occurred among 58 evaluable participants. Among all patients, median progression-free survival was 8.0 months (control) versus 12.6 months (experimental; $P = .005$; hazard ratio [HR], 0.44; 90% CI, 0.26 to 0.76). Similarly, median progression-free survival was 9.3 (control) versus 17.9 (experimental) months among 41 patients with stage III or IV disease undergoing primary treatment ($P = .013$; HR, 0.40; 90% CI, 0.20 to 0.80) and 6.0 (control) versus 9.2 months (experimental), respectively, among 17 patients with recurrent disease ($P = .003$; HR, 0.14; 90% CI, 0.04 to 0.53). Toxicity was not different between treatment arms, and no unexpected safety signals emerged.

Conclusion
Addition of trastuzumab to carboplatin-paclitaxel was well tolerated and increased progression-free survival. These encouraging results deserve further investigation to determine their impact on overall survival in patients with advanced or recurrent uterine serous carcinoma who overexpress HER2/neu.

J Clin Oncol 36:2044-2051. © 2018 by American Society of Clinical Oncology

Endometrial cancer is the most common gynecologic malignancy in the United States. In 2016, there were 60,050 cases and 10,470 deaths.[1] Uterine serous carcinoma (USC) is an aggressive variant first described in 1972.[2] Although only 3% to 10% of all cases, USC accounts for a disproportionately high number of endometrial cancer deaths (39%).[3] As many as 37% to 70% of women diagnosed with this subtype have extrauterine spread at diagnosis,[4-6] contributing to poor outcomes compared with women with the more prevalent endometrioid endometrial adenocarcinoma.[7-10] Five-year survival for women with USC is approximately 41%, compared with 75% among women with grade 3 endometrioid tumors ($P = .01$),[11] and recurrences are difficult to salvage.[12]

In part because of its rarity, optimal management of USC is controversial and understudied. USC is typically treated with hysterectomy and

ASSOCIATED CONTENT

Appendix
DOI: https://doi.org/10.1200/JCO.2017.76.5966

Data Supplements
DOI: https://doi.org/10.1200/JCO.2017.76.5966

DOI: https://doi.org/10.1200/JCO.2017.76.5966

surgical staging followed by platinum plus taxane combination chemotherapy.[13-15] Existing evidence supports the benefit of chemotherapy for treatment of USC, even in early-stage disease.[12-15] Response rates to carboplatin-paclitaxel among patients with previously untreated advanced-stage disease may be as low as 60%, and ≤ 50% among those with recurrent disease.[16]

USC is molecularly distinct to endometrioid carcinoma.[17,18] The mutational profile of USC consists of alterations in *TP53* and dysregulation of *HER2/neu*, in contrast to endometrioid cancers, which demonstrate aberrant *PTEN*.[18] Human epidermal growth factor receptor 2 (HER2)/neu provides critical signaling for cancer cell growth, survival, and proliferation, and its overexpression occurs in 14% to 80% of USC.[19-27] These estimates vary widely because of a lack of standardized algorithms for interpretation and scoring of HER2 immunostains in endometrial cancer.

Trastuzumab is a humanized monoclonal antibody against HER2/neu. It was first approved by the Food and Drug Administration in 1998 for first-line treatment of metastatic breast cancer with overexpression of HER2/neu either in combination with paclitaxel or as a single agent in women who have received one or more chemotherapy regimens. It has since been approved in combination with capecitabine and fluorouracil for HER2/neu-overexpressing gastric adenocarcinomas. In GOG-181B,[28] the Gynecologic Oncology Group examined trastuzumab as a single agent in women with advanced/recurrent endometrial carcinoma. The study failed to reach target accrual, and trastuzumab was deemed inactive in HER2-overexpressing endometrial carcinoma. However, the final analysis of GOG 181B was flawed, in that 47% of the study participants treated with trastuzumab ultimately did not have tumoral HER2/neu gene amplification. In addition, there was no limit on prior lines of chemotherapy, so much of the cohort had bulky, measurable, and heavily pretreated recurrent disease.[29]

On the basis of biologic plausibility, encouraging case reports,[30-32] and extensive experience with trastuzumab as a chemotherapeutic adjunct in multiple other disease sites, we constructed a randomized phase II trial to quantify the benefit conferred by addition of trastuzumab to carboplatin-paclitaxel among women with USC whose tumors overexpress HER2/neu, in both the primary setting for advanced disease and pretreated/recurrent disease.

METHODS

Study Design and Conduct

This was an investigator-initiated, randomized phase II study among 11 participating academic institutions within the United States. The study was approved by a local Human Investigations Committee and in accordance with the precepts established by the Declaration of Helsinki. Participants were randomly assigned 1:1 by the lead study institution using minimization[33] to balance the treatment arms for study site, disease status (advanced-stage primary *v* recurrent USC), and residual tumor after primary surgical cytoreduction within the advanced-stage cohort. Participants were scheduled to receive intravenous carboplatin area under the curve 5 and paclitaxel 175 mg/m^2 over 3 hours every 21 days with or without trastuzumab at 8 mg/kg for the first dose and 6 mg/kg in subsequent cycles until disease progression or prohibitive toxicity (Fig 1). Study drug was supplied by Genentech (South San Francisco, CA). This study was registered with the National Institutes of Health (ClinicalTrials.gov identifier: NCT01367002). There were no significant changes to eligibility criteria or trial methodology after commencement.

The trial was designed to accrue 100 participants at a rate of five per month for 20 months. Interim analysis for futility was scheduled on observing 26 recurrences, progressions, or deaths and final analysis on observing 85 events. Power calculations assumed that median progression-free survival (PFS) would be 6 months on the carboplatin-paclitaxel arm and 10.5 months on the carboplatin-paclitaxel-trastuzumab arm, equivalent to a hazard ratio (HR) of 0.57 with trastuzumab addition. For the final efficacy analysis, we planned to compare the carboplatin-paclitaxel-trastuzumab arm to the carboplatin-paclitaxel arm for the expected increase in PFS by means of the log-rank test, conducted using a one-sided α of 0.10. Under this plan, 85 recurrence/progression/death events gave the study 90% power to detect HR of 0.57 with carboplatin-paclitaxel-trastuzumab versus carboplatin-paclitaxel. Power was adjusted for the interim futility analysis using the O'Brien-Fleming spending function to allocate type II error. We expected to observe the 26th recurrence/progression/death event at 12.9 months and the 85th recurrence/progression/death event at 33.6 months. The first participant was enrolled in August 2011, after which the accrual rate was slower than planned, and observed PFS exceeded original expectations. Because of this, the interim futility analysis was not triggered until March 2016, when 47 participants were enrolled; its results indicated that the trial should continue to enroll. Nonetheless, in March 2017, after enrolling a total of 61 participants, the study was closed to further enrollment because of slow accrual and long PFS. Final efficacy analysis commenced in August 2017, when the last enrolled participant completed her assigned treatment.

Eligibility

All patients were ≥ 18 years old and had primary advanced (International Federation of Gynecology and Obstetrics 2009 stage III or IV)[34] or recurrent (any previous stage) HER2/neu-positive USC as defined by an immunohistochemistry score of 3+, or 2+ with gene amplification confirmed by fluorescence in situ hybridization (FISH).[35] HER2/neu-positive status was determined using paraffin-embedded tumor tissue from either primary surgery or recurrent disease. Scoring was performed according to guidelines set forth by the 2007 ASCO/College of American Pathologists (ASCO-CAP) for breast cancer.[36] Specimens were centrally reviewed for HER2/neu-positivity and confirmed to contain ≥ 10% USC by two gynecologic pathologists. Patients may have undergone optimal or suboptimal primary cytoreductive surgery. Patients were enrolled within 8 weeks after surgery or diagnosis of recurrence. Patients were required to exhibit Eastern Cooperative Oncology Group[37] performance status of 0 to 2, adequate bone marrow function, renal function, and hepatic function. All patients diagnosed with recurrence were required to have measurable disease, defined as one or more target lesions per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[38] Tumors within a previously irradiated field were designated as nontarget lesions unless progression was documented or a biopsy was obtained to confirm persistence at least 90 days after completion of radiation. A treatment-free interval of > 6 months from last carboplatin-paclitaxel was required. Patients with recurrent disease may not have received more than three prior chemotherapies. Patients with recurrent disease who achieved a response with an acceptable level of toxicity were permitted to continue treatment with their assigned chemotherapy regimen beyond six cycles after discussion with the study chair. Patients who had received prior doxorubicin or its liposomal encapsulated preparation may not have had ≥ 320 mg/m^2 total dose and must have demonstrated a normal left ventricular ejection fraction (ie, ≥ 45%). Granulocyte colony-stimulating factors or erythropoietin were allowed only in the event of persistent neutropenia or anemia. Detailed inclusion criteria and the schemata for treatment modification are provided in the full protocol (Data Supplement).

End Points

The primary study end point was PFS, defined as length of time from random assignment to disease recurrence, disease progression, or death for any reason. Secondary objectives included objective response rate, overall survival (OS), and safety of trastuzumab in patients with USC. Response and disease progression were defined by RECIST 1.1.[38] Common

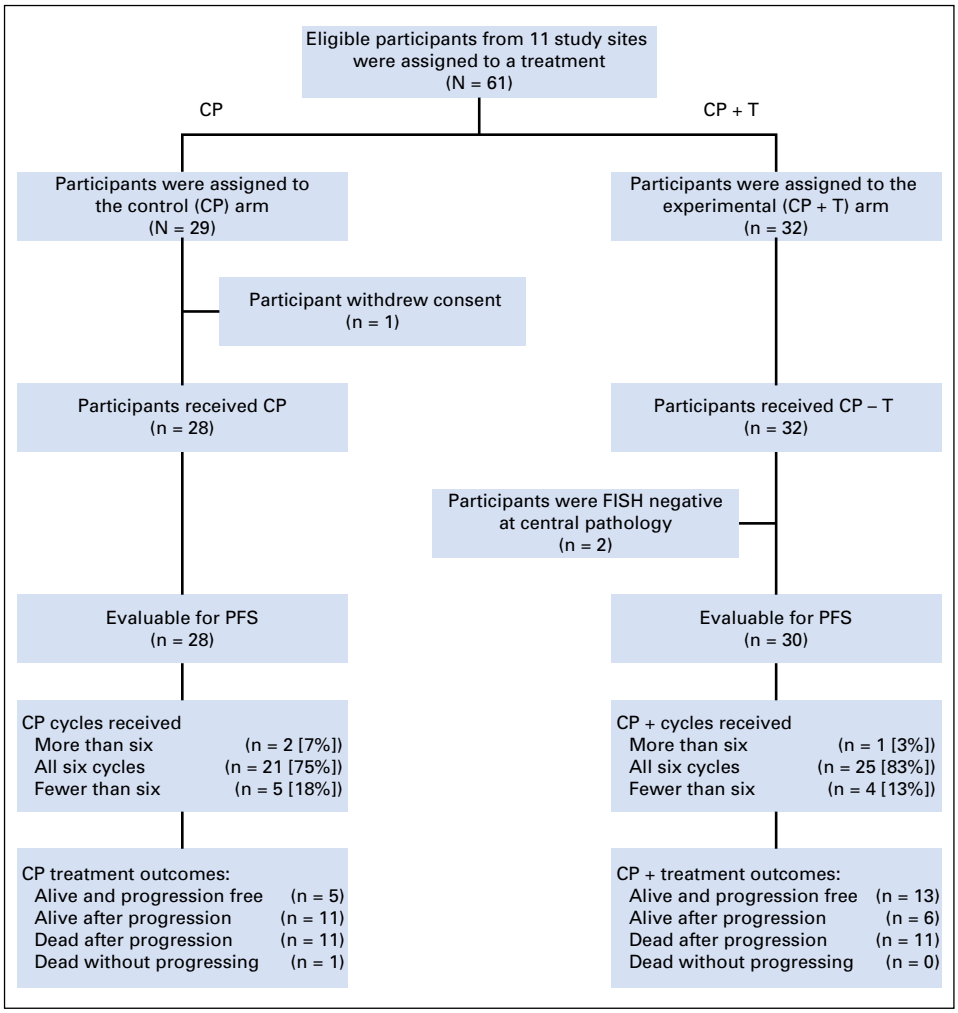

Fig 1. CONSORT diagram. CP, carboplatin-paclitaxel; CP + T, carboplatin-paclitaxel plus trastuzumab; FISH, fluorescence in situ hybridization; PFS, progression-free survival.

Terminology Criteria for Adverse Events (CTCAE) version 4.0 was used to describe adverse events.[39] Computed tomography of the chest, abdomen, and pelvis were performed every 3 months or more frequently in cases of clinical suspicion for progression.

Statistical Analyses

Patient characteristics, objective response rate, and occurrence of high-grade adverse events were examined for differences between treatment arms using two-sided Fisher's exact and Wilcoxon rank sum tests at $\alpha = 0.05$. PFS was visualized as Kaplan-Meier curves both overall and stratified by disease status and assessed for improvement with trastuzumab using one-sided log rank tests. For the primary efficacy analysis, the log rank test used a one-sided $\alpha = 0.10$ significance level, as originally specified in the study's protocol. All other log rank tests used one-sided $\alpha = 0.05$ significance levels. Every assessment was accompanied by a Cox regression HR with two-sided 90% CI.

RESULTS

Patients

Between August 2011 and January 2017, 61 participants were enrolled (Fig 1). Three were excluded due to withdrawal of consent (n = 1) or failure to confirm HER2 positivity by FISH after 2+ immunohistochemistry (n = 2) by central review, leaving 58 (28 carboplatin-paclitaxel in the control arm and 30 carboplatin-paclitaxel-trastuzumab in the experimental arm) evaluable for response to treatment. Patient and disease characteristics are listed in Table 1. Forty-one participants (71%) had advanced-stage disease; 17 participants (29%) had recurrent disease. Of those with advanced-stage disease, 22 (54%) received primary radiation, and only five (12%) had gross residual disease after primary cytoreductive surgery. Of the participants with recurrent disease, the median number of prior lines was one (range, zero to two) and was identical between treatment arms. In addition, the treatment arms did not differ significantly by race, ethnicity, study site, or disease status (advanced *v* recurrent disease) or by radiation or cytoreductive surgery status among participants with advanced-stage disease. Participants in the experimental arm were younger (median, 67 years; interquartile range, 64-69) compared with the control arm (median, 73 years; interquartile range, 68-78; $P = .006$).

Treatment

The 28 participants in the control arm and 30 participants in the experimental arm completed a total of 156 (range, one to eight) and 178 (range, four to nine) cycles of carboplatin-paclitaxel, respectively. Participants in the experimental arm received

Table 1. Patient and Disease Characteristics

Characteristic	Control Arm		Experimental Arm		Both Arms	
	No.	%	No.	%	No.	%
All patients	(n = 28)		(n = 30)		(n = 58)	
Age,* years						
Median	73		67		69	
Quartiles	68-78		64-69		65-73	
Range	45-88		57-85		45-88	
Race						
White	17	61	20	67	37	64
Black or African American	8	29	10	33	18	31
Asian	1	4	0	0	1	2
American Indian/Alaska native	1	4	0	0	1	2
Unknown	1	4	0	0	1	2
Ethnicity						
Hispanic or Latino	1	4	3	10	4	7
Non-Hispanic or Latino	26	93	26	87	52	90
Unknown	1	4	1	3	2	3
Disease status						
Advanced	20	71	21	70	41	71
Recurrent	8	29	9	30	17	29
Study site						
Duke University Medical Center	3	11	3	10	6	10
Greater Baltimore Medical Center	3	11	3	10	6	10
Jersey Shore University Medical Center	0	0	1	3	1	2
John Muir Medical Center	1	4	2	7	3	5
Montefiore Medical Center	1	4	2	7	3	5
Penrose–St Francis Medical Center	3	11	1	3	4	7
Ohio State–Wexner Medical Center	3	11	3	10	6	10
University of Arizona Cancer Center	3	11	2	7	5	9
University of Maryland	1	4	2	7	3	5
Walter Reed National Military Medical Center	1	4	1	3	2	3
Yale University	9	32	10	33	19	33
Advanced-disease subgroup	(n = 20)		(n = 21)		(n = 41)	
FIGO stage						
Stage IIIA	3	15	1	5	4	10
Stage IIIB	0	0	1	5	1	2
Stage IIIC1	5	25	3	14	8	20
Stage IIIC2	4	20	6	29	10	24
Stage IV	2	10	4	19	6	15
Stage IVB	6	30	6	29	12	29
Primary radiation						
No	9	45	10	48	19	46
Yes	11	55	11	52	22	54
Residual disease						
No	17	85	19	90	36	88
Yes	3	15	2	10	5	12
Recurrent-disease subgroup	(n = 8)		(n = 9)		(n = 17)	
Prior lines						
0	1	13	2	22	3	18
1	6	75	5	56	11	65
2	1	13	2	22	3	18

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.
*Median age was significantly lower in the experimental arm ($P = .006$). All other characteristics were not significantly different between treatment arms.

a total of 519 cycles of trastuzumab (median, 15; range, 5 to 53). In all, 23 participants (82%) in the control arm completed six or more cycles of carboplatin-paclitaxel. In the experimental arm, 26 participants (87%) completed six or more paclitaxel cycles, and 28 participants (93%) completed six or more carboplatin cycles.

Primary End Point: PFS

At time of analysis, the 58 response-evaluable participants experienced 40 PFS-related events (39 progressions, one fatal thromboembolism) during 854.0 months (median, 10.0 months) of follow-up. Among those who remained alive and progression free, five were in the control arm, and 13 were in the experimental arm. Overall, median PFS was 8.0 months in patients in the control arm and 12.6 months in patients in the experimental arm ($P = .005$; HR, 0.44; 90% CI, 0.26 to 0.76; Fig 2A).

After subgrouping participants by disease status (ie, advanced stage or recurrent), median PFS was 9.3 (control arm) versus 17.9 (experimental arm) months in patients with stage III and IV disease undergoing primary treatment ($P = .013$; HR, 0.40; 90% CI, 0.20 to 0.80; Fig 2B), and 6.0 (control arm) versus 9.2 (experimental arm) months in patients with recurrent disease ($P = .003$; HR, 0.14; 90% CI, 0.05 to 0.54; Fig 2C).

The 2009 refinements in International Federation of Gynecology and Obstetrics staging nomenclature for uterine cancer more accurately predict survival among patients with stage III disease relative to previous staging schemes, with a clear disadvantage for women with nodal involvement, particularly para-aortic.[40,41] In a subset analysis that excluded stage IIIA or IIIB disease, trastuzumab continued to show benefit in women with the worst prognoses (Appendix Fig A1).

Secondary End Points: Overall Response, Safety, OS

Among patients with recurrent disease, best RECIST responses to treatment were as follows: two patients (25%) with complete responses (CRs), four patients (50%) with partial responses (PRs), one patient (12.5%) with stable disease (SD), and one patient (12.5%) with progressive disease (PD) in the control arm, compared with one patient (11%) with CR, three patients (33%) with PR, five patients (56%) with SD, and zero patients (0%) with PD in the experimental arm. Clinical benefit thus reached 87.5% in the control arm and 100% in the experimental arm (P = .47), with objective response (CR + PR) rates of 75% and 44%, respectively (P = .33).

Sixty patients were evaluable for toxicity; 57 of them had one or more CTCAE events during treatment. Table 2 counts all high-grade toxicities (CTCAE grade ≥ 3) that occurred in one or more patients; none differed significantly between treatment arms. Hypertension displayed the largest treatment-arm difference (a 5:0 split; P = .055), but the five events in question, all grade 3, were scored by investigators as unrelated (n = 2), unlikely (n = 2), and possible (n = 1) for relatedness to study drug. One patient in the experimental arm experienced a grade 3 decrease in left

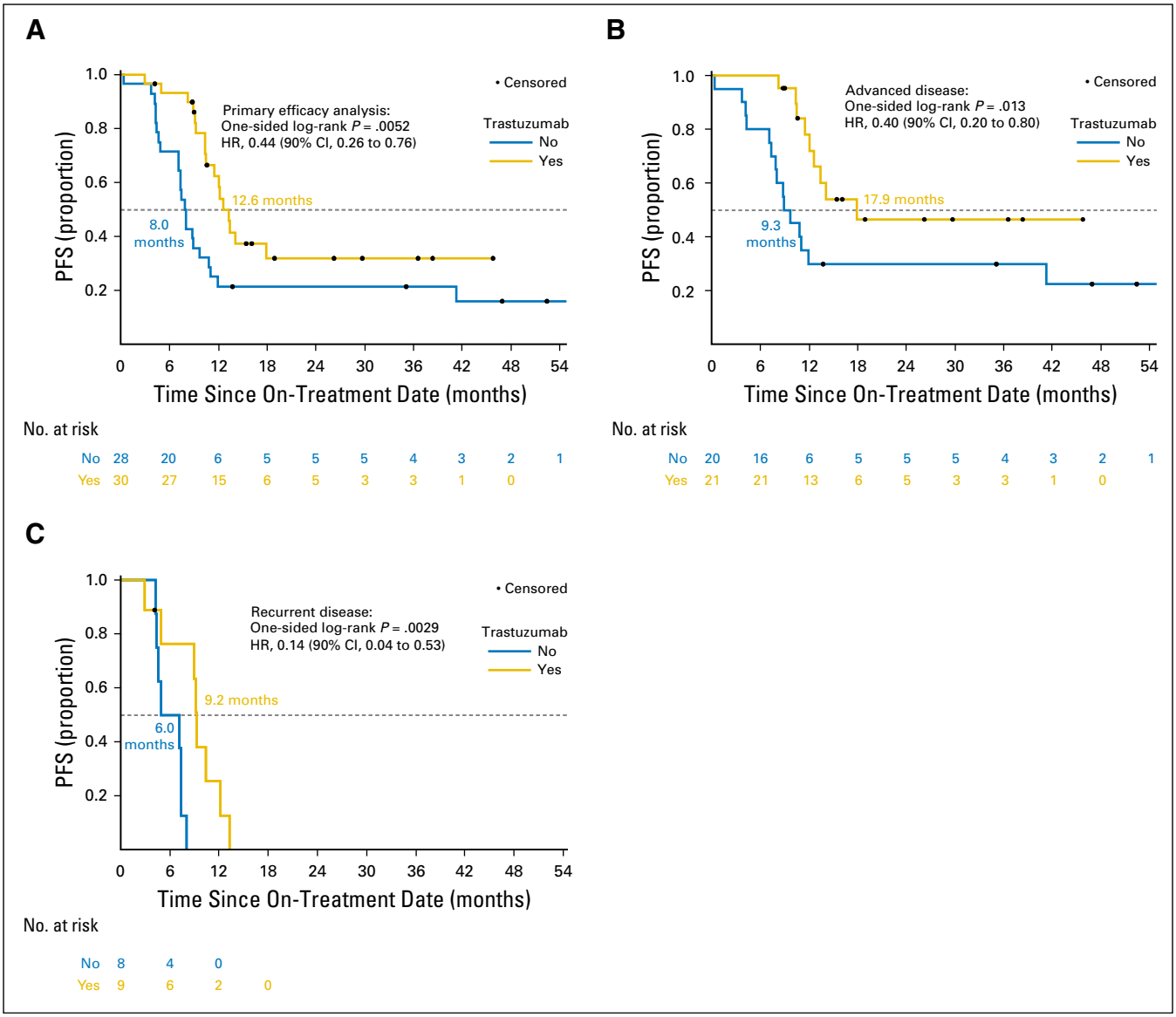

Fig 2. Progression-free survival (PFS). (A) Median progression-free survival was improved by 4.6 months in patients (n = 58) who received trastuzumab with carboplatin-paclitaxel (12.6 months) compared with those who received carboplatin-paclitaxel alone (8.0 months; P = .005; hazard ratio [HR], 0.44; 90% CI, 0.26 to 0.76). (B) The addition of trastuzumab benefitted patients (n = 41) with advanced disease in the primary treatment setting (17.9 *v* 9.3 months; HR, 0.40; 90% CI, 0.20 to 0.80; P = .013). (C) The addition of trastuzumab also benefitted patients (n = 17) with recurrent disease after zero, one, or two lines of prior chemotherapy (9.2 *v* 6.0 months; HR, 0.14; 90% CI, 0.05 to 0.54; P = .003). In total, there were 40 progression events; among those who remained alive and progression free, five were in the control arm and 13 were in the experimental arm.

ventricular ejection fraction. The fatal thromboembolism occurred in a patient randomly assigned to the control arm. Event-level toxicities by system and patient-level toxicities by frequency of treatment occurrence are shown fully in the Data Supplement.

Twenty-three deaths were observed among the 58 participants during 1,156.8 total months (median, 15.4 months) of follow-up, indicating that current data are not yet mature. Preliminary analysis showed that among 41 participants with advanced USC (14 deaths), we observed a 59% mortality reduction in the trastuzumab arm (HR, 0.41; 90% CI, 0.16 to 1.03), but the improvement fell short of statistical significance ($P = .0503$). Similarly, among 17 participants with recurrent USC (nine deaths), we observed a 68% mortality reduction in the trastuzumab arm (HR, 0.32; 90% CI, 0.07 to 1.46; $P = .097$). Finally, in the sensitivity analysis, we excluded five participants with stage IIIA or IIIB disease and re-examined the effect of trastuzumab in the advanced-stage setting. Among 36 patients with stage IIIC or IV disease (14 deaths), we observed a 66% mortality reduction in the trastuzumab arm (HR, 0.34; 90% CI, 0.14 to 0.86; $P = .023$). The preliminary analysis of OS thus suggests that the greatest benefit of trastuzumab may be in the up-front setting in those with the most advanced disease. A more robust analysis of the effect of trastuzumab effect on OS will be conducted once deaths reach 30.

DISCUSSION

In this study, we demonstrate that addition of trastuzumab to carboplatin-paclitaxel in HER2/neu-positive USC results in a 56% decrease in risk of progression relative to carboplatin-paclitaxel alone and increases PFS by 4.6 months, with benefit both in first-line adjuvant therapy for advanced-stage disease and in the recurrent setting. A preliminary analysis of OS suggests similar

Table 2. Number of Participants Who Experienced a High-Grade Adverse Event During Treatment, Overall and by Treatment Arm

	Control Arm (n = 28)		Experimental Arm (n = 32)		Both Arms (n = 60)	
Official CTCAE Toxicity Term	No.	%	No.	%	No.	%
Neutrophil count decreased	5	18	4	13	9	15
Anemia	2	7	6	19	8	13
Blood and lymphatic system disorders—other (neutropenia)	1	4	5	16	6	10
Hypertension*	0	0	5	16	5	8
Hyperglycemia	1	4	3	9	4	7
WBC decreased	1	4	3	9	4	7
Diarrhea, colitis, and enterocolitis	1	4	3	9	4	7
Thromboembolic event	2	7	1	3	3	5
Abdominal pain	0	0	2	6	2	3
Dehydration	1	4	1	3	2	3
Febrile neutropenia	1	4	1	3	2	3
Hyponatremia	2	7	0	0	2	3
Hypoxia	0	0	2	6	2	3
Small intestinal obstruction	1	4	1	3	2	3
Acute kidney injury	1	4	0	0	1	2
Aspiration	0	0	1	3	1	2
Bone pain	0	0	1	3	1	2
Cognitive disturbance	0	0	1	3	1	2
Constipation	0	0	1	3	1	2
Creatinine increased	1	4	0	0	1	2
Dyspnea	0	0	1	3	1	2
Fatigue	0	0	1	3	1	2
Gastroparesis	1	4	0	0	1	2
Hematuria	0	0	1	3	1	2
Hypokalemia	0	0	1	3	1	2
Left ventricular systolic dysfunction	0	0	1	3	1	2
Lymphocyte count decreased	0	0	1	3	1	2
Peripheral sensory neuropathy	1	4	0	0	1	2
Platelet count decreased	0	0	1	3	1	2
Pleural effusion	1	4	0	0	1	2
Psychiatric disorders—other (depressed consciousness level)	1	4	0	0	1	2
Renal and urinary disorders—other (urinary tract infection)	1	4	0	0	1	2
Respiratory, thoracic and mediastinal disorders—other (upper respiratory infection)	0	0	1	3	1	2
Sepsis	0	0	1	3	1	2
Urinary tract infection	1	4	0	0	1	2
Vomiting	0	0	1	3	1	2
Wound infection	1	4	0	0	1	2
Total	27		51		78	

NOTE. Data indicate No. and percentage of participants who experienced the high-grade adverse event. High grade means maximum grade of 3, 4, or 5. Terms followed by free-text event descriptions in parentheses when the toxicity term ends in other.
Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.
*No significant toxicity differences were observed between treatment arms, not even for hypertension.

trends, with the most clinical benefit from trastuzumab observed in the up-front treatment setting in those with stage IIIC or IV disease. The combination is well tolerated and may be associated with exceptional PFS in some patients, including two who received ≥ 50 cycles of trastuzumab. We have also herein demonstrated for uterine cancer that HER2/Neu overexpression defined as 3+ by immunohistochemistry or 2+ with confirmatory FISH reliably identifies a target population for whom clinical benefit can be achieved with this therapy. Although our study failed to achieve planned enrollment because of slow accrual and long PFS, to our knowledge this is the first prospective study in endometrial cancer targeting USC exclusively and the largest randomized report to date to describe the activity of trastuzumab in HER2-overexpressing USC. Our findings contribute to a growing body of literature, including preliminary data from the phase IIa My Pathway trial in HER2-overexpressing solid tumors (ClinicalTrials.gov identifier: NCT02091141), to support site-agnostic drug approval, in which molecular biologic characteristics may prevail over tissue of origin alone.[42]

Our study encompasses limitations that may add imprecision to our estimates. First, although minimization was used as a method of ensuring balance between groups (Table 1), patients in the control arm were older (median, 73 years) than those in the experimental arm (median, 66 years; $P = .006$). Although this may have biased outcomes in favor of the experimental arm, several studies have shown that age is not an independent prognostic factor for recurrence in patients with comparably staged and treated endometrial cancer.[43] Second, given the absence of validated biomarkers or other means of assessing progression, a scan interval of 3 months during maintenance therapy may have overestimated progression-free intervals compared with a study design that incorporates more frequent assessments; however, it would have done so equally in both arms. Third, the study was not placebo controlled and imaging was not centrally reviewed; notably, only radiologists with expertise in RECIST criteria reviewed the images at each site. Fourth, our study closed before enrolling all participants. Although an interim futility analysis indicated benefit of the trastuzumab arm, enrollment was slower than anticipated because of the rarity of the tumor type, the long PFS, and a lower-than-expected number of women with HER2-positive tumors. Fifth, the ASCO-CAP breast cancer guidelines for HER2 testing were updated midtrial in 2013; our study team opted to maintain uniformity in testing by using the 2007 testing guidelines throughout the trial duration. In support of such an approach, a recent ancillary study of three Breast Cancer International Research Group studies, published in *Journal of Clinical Oncology*, showed no difference between the original US Food and Drug Administration–approved criteria for HER2 gene amplification and the current ASCO-CAP guidelines for correlation with survival outcomes. Thus, there may not be a demonstrable advantage to using the current ASCO-CAP guidelines.[44] Finally, these data are immature, and final OS estimates are eagerly awaited. We anticipate that OS may be tainted by crossover to the experimental arm, leading to underestimation of benefit from trastuzumab. Nevertheless, preliminary analysis favors the trastuzumab arm in patients with the most advanced (stage IIIC or IV) disease. Of note, improvement in PFS is increasingly believed to be an appropriate primary end point in oncology, and one that was met in the current study.

In summary, novel therapeutic strategies must be developed for USC. Outcomes for women with this malignancy remain dismal.[16] Our study demonstrates that the addition of trastuzumab to carboplatin-paclitaxel improves PFS by 4.6 months in women with advanced-stage or recurrent USC and achieves a meaningful clinical benefit rate without increasing toxicity. The greatest benefit may be observed when trastuzumab is used with carboplatin-paclitaxel in the up-front setting and in those with stage IIIC or IV disease. These encouraging results deserve further investigation to determine their impact on overall survival in patients with advanced or recurrent USC who overexpress HER2/neu. We await the analysis of more mature survival data to inform next steps in studying this targeted therapeutic approach.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Support

Study drug was supplied by Genentech-Roche (South San Francisco, CA).

Prior Presentation

Presented at the International Gynecologic Cancer Society 16th Biennial Meeting, Lisbon, Portugal, October 29-31, 2016.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor 2/neu

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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Research Funding: AbbVie (Inst), Amgen (Inst), Astellas Pharma (Inst), Astex Pharmaceuticals (Inst), AstraZeneca (Inst), Boehringer Ingelheim (Inst), Bristol-Myers Squibb (Inst), Eisai (Inst), Endocyte (Inst), Exelixis (Inst), Incyte (Inst), Merck (Inst), PharmaMar (Inst), Prima BioMed (Inst), Genentech (Inst), Tesaro (Inst)

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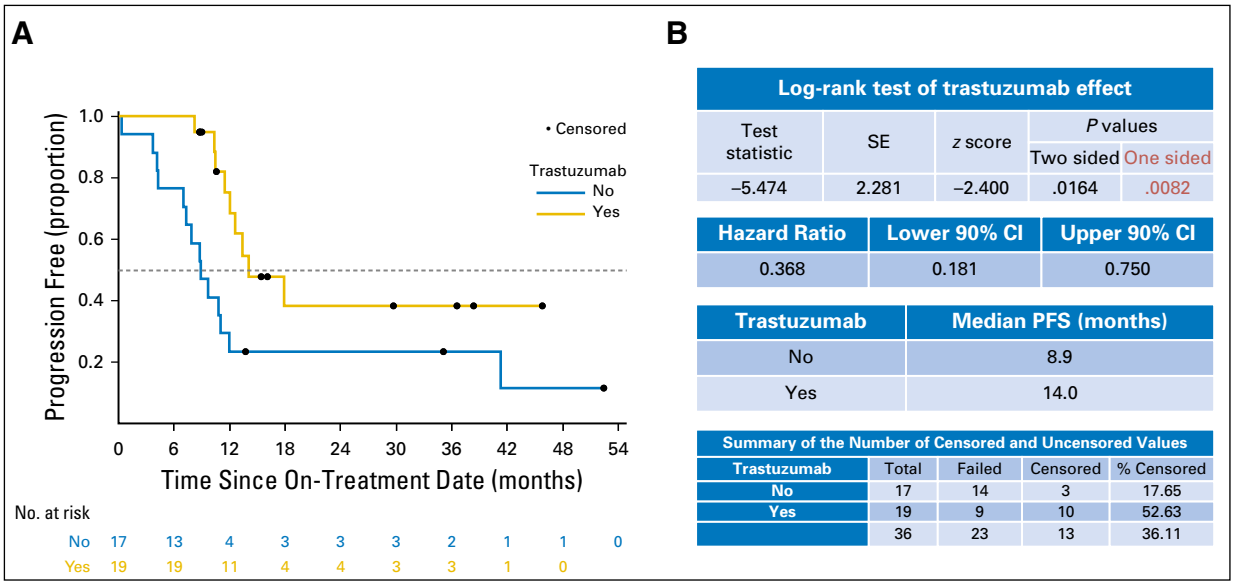
Appendix



Log-rank test of trastuzumab effect				
Test statistic	SE	*z* score	*P* values	
			Two sided	One sided
–5.474	2.281	–2.400	.0164	.0082

Hazard Ratio	Lower 90% CI	Upper 90% CI
0.368	0.181	0.750

Trastuzumab	Median PFS (months)
No	8.9
Yes	14.0

Summary of the Number of Censored and Uncensored Values				
Trastuzumab	Total	Failed	Censored	% Censored
No	17	14	3	17.65
Yes	19	9	10	52.63
	36	23	13	36.11

Fig A1. Progression-free survival among patients with advanced-stage disease, excluding stage IIIA and IIIB disease. Addition of trastuzumab to carboplatin-paclitaxel continued to show benefit in women with the poorest prognosis (14.0 *v* 8.9 months; hazard ratio, 0.368; 90% CI, 0.181 to 0.750; *P* = .0084).