original reports

Secondary Cytoreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study

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abstract

PURPOSE The purpose of this phase II study was to evaluate hyperthermic intraperitoneal chemotherapy (HIPEC) with carboplatin for recurrent ovarian cancer during secondary cytoreductive surgery.

MATERIALS AND METHODS Patients were intraoperatively randomly assigned to carboplatin HIPEC (800 mg/m^2 for 90 minutes) or no HIPEC, followed by five or six cycles of postoperative IV carboplatin-based chemotherapy, respectively. Based on a binomial single-stage pick-the-winner design, an arm was considered winner if ≥ 17 of 49 patients were without disease progression at 24 months post-surgery. Secondary objectives included postoperative toxicity and HIPEC pharmacokinetics.

RESULTS Of 98 patients, 49 (50%) received HIPEC. Complete gross resection was achieved in 82% of the HIPEC patients and 94% of the standard-arm patients. Bowel resection was performed in 37% of patients in the HIPEC arm compared with 65% in the standard ($P = .008$). There was no perioperative mortality and no difference in use of ostomies, length of stay, or postoperative toxicity. At 24 months, eight patients (16.3%; 1-sided 90% CI, 9.7 to 100) were without progression or death in the HIPEC arm and 12 (24.5%; 1-sided 90% CI, 16.5 to 100) in the standard arm. With a medium follow-up of 39.5 months, 82 patients progressed and 37 died. The median progression-free survival in the HIPEC and standard arms were 12.3 and 15.7 months, respectively (hazard ratio, 1.54; 95% CI, 1 to 2.37; $P = .05$). There was no significant difference in median overall survival (52.5 *v* 59.7 months, respectively; hazard ratio, 1.39; 95% CI, 0.73 to 2.67; $P = .31$). These analyses were exploratory.

CONCLUSION HIPEC with carboplatin was well tolerated but did not result in superior clinical outcomes. This study does not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer.

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INTRODUCTION

In 2021, an estimated 21,410 women will be diagnosed with ovarian cancer in the United States, and approximately 13,770 women will die from this disease.[1] Peritoneal metastases are characteristic of ovarian cancer, and recurrence after initial response is almost inevitable. Intraperitoneal (IP) chemotherapy with cisplatin and paclitaxel after primary cytoreductive surgery resulted in improved progression-free survival (PFS) and overall survival (OS) compared with intravenous (IV) chemotherapy in patients with optimally resected stage III ovarian cancer.[2,3] Despite the survival benefit, IP treatment remains underused in comprehensive cancer centers secondary to toxicity and the difficulty of administering IP therapy.[4] Furthermore, in the recent GOG252 study, two postoperative IP-containing regimens with cisplatin or carboplatin did not result in improved outcomes compared with IV treatment alone when combined with bevacizumab.[5] Quality of life during chemotherapy was statistically worse in the IP cisplatin arm. Hyperthermic intraperitoneal chemotherapy (HIPEC) differs from postoperative IP chemotherapy as it is a single administration delivered intraperitoneally in a hyperthermic state upon completion of cytoreduction. Hyperthermia has direct cytotoxic effect and enhances tumor penetration and DNA-adduct formation of platinum compounds.[6-9] HIPEC with cisplatin at

ASSOCIATED CONTENT

Appendix

Protocol

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

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CONTEXT

Key Objective

Is the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) with carboplatin during secondary cytoreductive surgery beneficial in the treatment of recurrent ovarian cancer?

Knowledge Generated

The median progression-free survival was 12.3 months for patients who received HIPEC during secondary cytoreduction and 15.7 months for those who did not receive HIPEC ($P = .05$). Median overall survival was 52.5 months and 59.7 months, respectively ($P = .31$).

Relevance

The findings of this phase II study do not support the use of HIPEC with carboplatin during secondary cytoreductive surgery for platinum-sensitive recurrent ovarian cancer.

100 mg/m^2 has been shown to be safe and cost effective and results in superior PFS and OS in patients with stage III ovarian cancer undergoing interval debulking surgery after neoadjuvant chemotherapy.[10,11] Another recent study suggested a survival benefit with HIPEC at the time of primary cytoreductive surgery.[12] The role of HIPEC at secondary cytoreductive surgery for recurrent ovarian cancer is not established.

Outcomes with recurrent ovarian cancer depend on various factors, such as time from last treatment with platinum-based chemotherapy, mutational status (eg, *BRCA*), residual disease at the time of surgery, and general performance status.[13-17] Multiple retrospective but few prospective studies have evaluated HIPEC in patients with platinum-sensitive ovarian cancer.[18-21] Because of concerns of cisplatin-induced grade 3 and 4 adverse events (AEs) seen in IP-containing studies, carboplatin has emerged as an alternative drug, with potentially less treatment-related toxicities when administered intraperitoneally.[2,5,6,8,22,23] The aim of this phase II study was to evaluate the efficacy of HIPEC with carboplatin at 800 mg/m^2 in patients undergoing secondary cytoreduction for first recurrence of platinum-sensitive ovarian cancer.

MATERIALS AND METHODS

This is an investigator-initiated, multicenter, open-label, randomized phase II study in patients with platinum-sensitive epithelial ovarian cancer undergoing secondary cytoreduction. The study was approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center (MSKCC #12-275) and registered at (ClinicalTrials.gov identifier: NCT01767675; Protocol, online only). Potentially eligible patients were identified and consented at outpatient gynecologic oncology practices.

End Points

The primary objective was proportion of patients without evidence of disease progression at 24 months following secondary cytoreduction in the two arms—one with and one without HIPEC with carboplatin, followed by standard carboplatin-based postoperative IV chemotherapy. Secondary end points included 30-day postoperative morbidity, ability to complete assigned postoperative chemotherapy, pharmacokinetics, and OS. Data were censored at the date of last clinical assessment for patients alive and without disease progression. Disease progression was assessed using RECIST version 1.1.[24] OS, defined as the time from random assignment to death from any cause, was a secondary end point.

Eligibility Criteria

Eligible patients were 21 years of age or older with first recurrence of high-grade epithelial ovarian cancer confirmed radiographically 6-30 months after completion of first-line platinum-based chemotherapy and deemed resectable based on our previously reported selection criteria for secondary cytoreduction.[15,25] No prior chemotherapy or surgery for recurrent epithelial ovarian cancer was allowed. Other key eligibility criteria included a Karnofsky performance score of $\geq$ 70%, and adequate bone marrow, coagulation, renal, and hepatic function. Patients were ineligible if they had pre-existing neuropathy (National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0) grade $>$ 1; known platinum allergy; low-grade serous or borderline histology; and other serious disabling conditions that would contraindicate secondary cytoreductive surgery.

Study Design

After informed consent, patients were taken to the operating room for planned secondary cytoreduction. Random assignment occurred intraoperatively, after the surgeon confirmed resectability to $\leq$ 0.5 cm residual disease. Patients were stratified by platinum-free interval (6-12 months *v* $>$ 12-30 months) and number of disease sites (single *v* multiple). Patients with $>$ 0.5 cm residual disease were not randomly assigned and replaced. Carboplatin was administered as HIPEC at 800 mg/m^2 for 90 minutes at 41°C-43°C. The dose selected was based on studies using carboplatin as IP or HIPEC in patients with ovarian

carcinoma.[5,26-28] Patients received five additional cycles of postoperative IV carboplatin-based chemotherapy in the HIPEC arm and six in the standard arm (carboplatin and paclitaxel or carboplatin and gemcitabine or carboplatin and liposomal doxorubicin, at the treating physician's discretion). Maintenance treatment (bevacizumab, poly-adenosine diphosphate-ribose polymerase inhibition, or endocrine therapy) was not permitted.

Treatment

Secondary cytoreductive surgery was performed as per institutional standards. All patients randomly assigned to HIPEC received intraoperative IV antiemetics, including a serotonin 5-HT3 receptor antagonist, a neurokinin 1 antagonist, and dexamethasone before initiation of HIPEC. After surgical cytoreduction via laparotomy, percutaneous inflow and outflow catheters and IP temperature probes were placed. The skin was closed temporarily. The catheters were connected to the perfusion system (ThermoChemTM HT-1000 System, IN, PA), and 3,000 mL of normal saline was heated to 41°C-43°C and circulated through the abdomen. Subsequently, carboplatin was added to the perfusate. HIPEC was administered for 90 minutes, during which the perfusion rate, perfusion volume, and inflow and outflow temperatures were monitored and adjusted, if necessary. After completion of perfusion, the perfusate was drained and the abdomen was opened and irrigated with 3,000 mL of normal saline. Fascia and skin were closed in standard fashion. Postoperatively, all patients were observed and transferred to the floor as per standard institutional guidelines.

Pharmacokinetics and Pharmacodynamics

In 15 consecutive patients randomly assigned to HIPEC, peritoneal samples were collected at 0, 5, 10, 15, 30, 45, 60, 75, and 90 minutes of HIPEC. Blood samples were collected at 0, 15, 30, 45, 60, 75, and 90 minutes, and at 3, 6, 12, 18, 24, 48, and 72 hours. Ultrafiltrable carboplatin was separated from plasma by using the CentrisartVR ultrafiltration system (Sartorius AG, Göttingen, Germany). Platinum concentrations were measured by flameless atomic absorption spectrometry, as previously described.[29] Platinum pharmacokinetics were assessed using a standard noncompartmental approach with estimation of the area under the concentration-time curve (AUC) by use of the trapezoidal rule.

Safety Assessment

Safety analyses included 30-day surgical morbidity and mortality and treatment-related AEs according to the Memorial Sloan Kettering Cancer Center surgical complication grading system.[30,31] All patients underwent a baseline assessment within 28 days before surgery. After secondary cytoreduction, patients were assessed daily during hospitalization. After hospital discharge toxicities, AEs, hematology, and chemistries were tracked systematically. Patients were followed during standard postoperative IV platinum-based chemotherapy.

Disease Assessment

Postoperative chest and abdominopelvic computed tomography or magnetic resonance imaging was to be completed after secondary cytoreduction during a 28-day window. Disease was also assessed with imaging every 6 months for 2 years or if there was an unplanned imaging for suspected recurrence. CA-125 levels were measured every 3 months after secondary cytoreduction for 2 years but were not used to assess response or progression. Progression was determined by RECIST version 1.1. After 2 years, institutional standard follow-up guidelines were followed. The study radiologist who reviewed all scans was blinded to the treatment arm.

Statistical Considerations

We chose a pick-the-winner design by using a single-stage design in a phase II randomized trial to determine the winner arm. Each arm was powered to show an improvement over a historical control estimate of 24-month PFS rate of 25.5%.[15,32] Each arm used the null hypothesis of 24-month PFS rate of 25.5% and an alternative hypothesis of 40%. With a type I error rate of 10% and type II error rate of 20%, a target accrual of 49 patients per arm was planned. Based on an exact binomial single-stage design, each regimen was considered efficacious if at least 17 of 49 patients were progression-free at 24 months. Early stopping rules were incorporated to halt the study if the overall rate of major postoperative complications was twice the acceptable rate ($> 50\%$) following accrual of the first 20 patients and again after the first 49 patients. Secondary objectives included OS, postoperative complication rates, and completion rates of IV standard platinum-based chemotherapy in both arms. The primary objective of PFS rate at 24 months was reported as well as its exact one-sided 90% CI for each arm separately assuming binomial proportions. All except two patients had 24 months of follow-up. Both patients were in the standard arm with a follow-up of 22 months. Patients with < 24 months of follow-up were considered failures. The study was not powered for a head-to-head comparison of the two arms as in a phase III trial; each arm was compared to a historical control estimate.

Patient characteristics and other clinical factors were compared between the two arms using the Fisher exact test for categorical variables and Wilcoxon-rank sum test for continuous variables. Grade ≥ 3 postoperational AEs were summarized using descriptive statistics. PFS was calculated from the date of random assignment to the date of progression, death, or last clinical assessment, whichever occurred first. OS was calculated from the date of random assignment to the date of death or last follow-up. Survival was calculated using the Kaplan-Meier method. Log-rank test and Wald test based on the Cox proportional hazards

(PH) model were used to obtain *P* values for categorical variables or continuous variables in the univariate setting. Multivariate PFS and OS models were built by using variables that were univariately significant ($P < .05$). The effect of HIPEC on survival among certain clinical factors' strata was modeled in a Cox PH model with the treatment arm, the clinical factor, and the interaction term. The hazard ratio (HR) of HIPEC versus no HIPEC for specific subgroups is presented in a forest plot. These analyses were exploratory; the study was not powered to detect interaction effects.

RESULTS

A total of 117 patients were consented from February 2014-November 2019 (Fig 1, CONSORT diagram). Of these patients, 99 were randomly assigned to secondary cytoreduction followed by six cycles or secondary cytoreduction with HIPEC with carboplatin at 800 mg/m^2 followed by five cycles of IV carboplatin-based chemotherapy. Five patients withdrew or were found ineligible before planned surgery. Thirteen patients were not randomly assigned because of intraoperative findings (11 because of extent of disease, one because of extensive adhesions, and one because of absence of any evidence of disease). One patient was excluded from the study because of initiation of maintenance treatment before progression of disease.

Demographic and clinical characteristics and specific intraoperative characteristics are presented in Table 1. Most variables were balanced between the groups. The median platinum-free interval for the entire cohort before study enrollment was 16 months; 69% had a platinum-free interval of 12-30 months. A complete gross resection (CGR) was achieved in 40 patients (82%) in the HIPEC arm and 46 (94%) in the standard arm ($P = .12$). Bowel resections were performed in 50 patients (51%). Significantly fewer patients in the HIPEC arm underwent a bowel resection. As expected, the median operative time was significantly longer in patients randomly assigned to HIPEC (474 minutes *v* 292 minutes; $P < .001$).

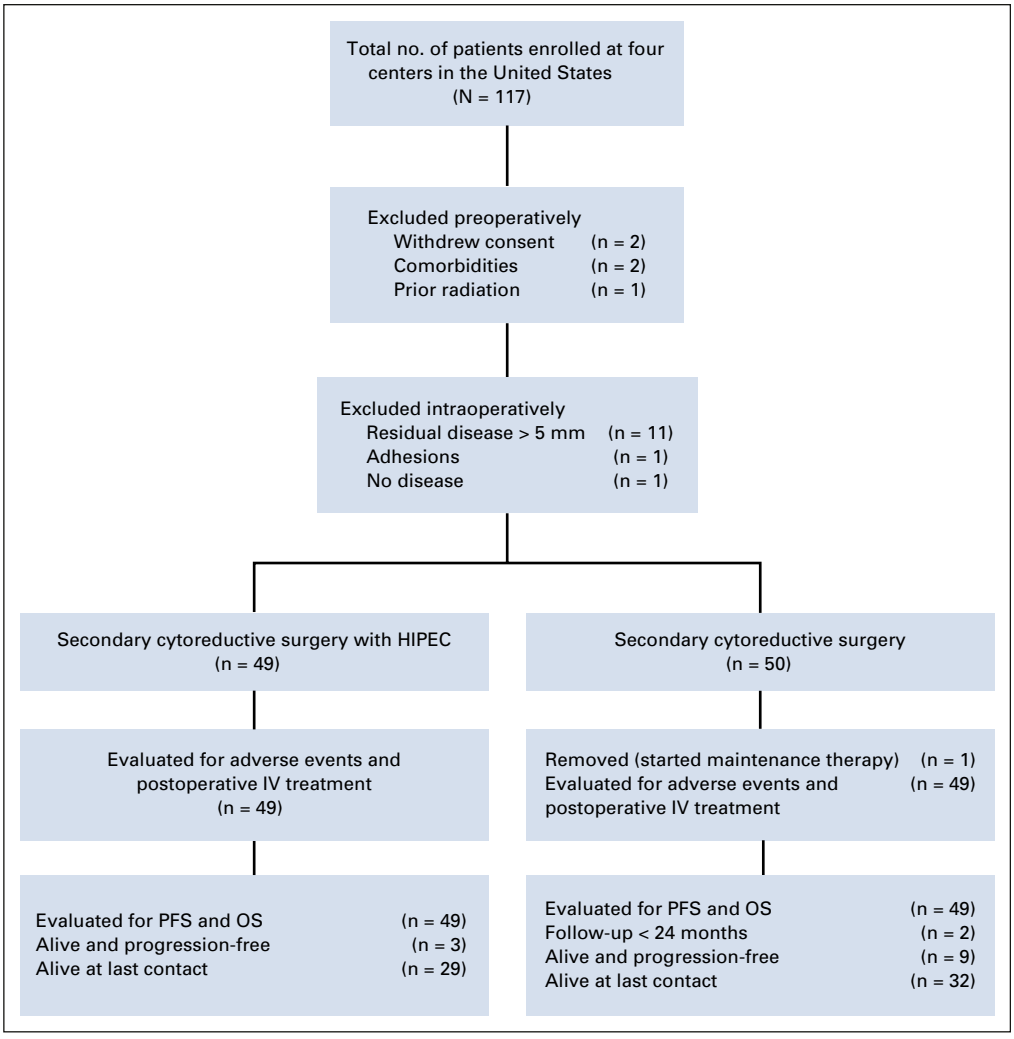

FIG 1. CONSORT diagram. HIPEC, hyperthermic intraperitoneal chemotherapy; IV, intravenous; OS, overall survival; PFS, progression-free survival.

TABLE 1. Demographic and Clinical Characteristics

Variable	HIPEC Arm (n = 49)	Standard Arm (n = 49)	*P*
Age, median, years (range)	59 (39-74)	58 (33-78)	.4
High-grade serous histology, No. (%)	47 (96)	48 (98)	> .9
Multiple sites of disease preoperatively, No. (%)	43 (88)	42 (86)	> .9
Platinum-free interval > 12 months, No. (%)	34 (69)	34 (69)	> .9
Median platinum-free interval, months (range)	16 (6-30.5)	17 (6-30)	.45
BRCA mutation, No. (%)	10 (20)	11 (22)	> .9
Operative time, minutes, (range)	475 (235-813)	296 (83-678)	< .001
Estimated blood loss, mL, (range)	402 (30-1,550)	340 (50-1,550)	.2
Bowel resection, No. (%)	18 (37)	32 (65)	.008
Complete gross resection, No. (%)	40 (82)	46 (94)	.12
≥ Grade 3 complications, No. (%)	12 (24)	10 (20)	.81
Length of inpatient stay, days, (range)	6 (1-26)	5 (2-22)	.05
Postoperative chemotherapy regimen, No. (%)			
Carboplatin and liposomal doxorubicin	35 (71)	39 (80)	
Carboplatin and gemcitabine	13 (27)	8 (16)	
Carboplatin and paclitaxel	0 (0)	2 (4)	
Other	1 (2)	0 (0)	
Completed assigned postoperative platinum-based chemotherapy, No. (%)	46 (94)	46 (94)	

Abbreviation: HIPEC, hyperthermic intraperitoneal chemotherapy.

Platinum pharmacokinetics after carboplatin administered as HIPEC are shown in Figure 2. Figure 2A depicts the first 24 hours and Figure 2B the first 6 hours post HIPEC. The extrapolated time = 0 platinum concentration of 204 μg/mL corresponded with the 242 μg/mL theoretical starting concentration of the infusate based on the 800 mg/m^2 carboplatin dose, typical body surface area, and the 3 L infusate volume (800 mg/m^2·1.73 m^2·(195/371)/3 L). Plasma platinum increased during the perfusion procedure and appeared to reach a steady state toward the end of the perfusion. The geometric mean (geometric standard deviation) maximum ultrafiltrable platinum concentrations in the peritoneum and plasma were 140 (1.28) μg/mL and 16.7 (1.24) μg/mL, respectively, with a peritoneum-to-plasma ratio of 8.47 (Appendix Table A1, online only). Corresponding platinum AUC values in the peritoneum and plasma were 174 (1.37) μg·h/mL and 97.5 (1.34) μg·h/mL, respectively, with a peritoneum-to-plasma ratio of 1.77. Post-treatment tumor tissue (1 cm^3) was available from three patients and yielded a geometric mean (geometric standard deviation) platinum tissue concentration of 3.38 (1.62) μg/g. The majority of peritoneal and all of plasma total platinum exposure was accounted for by the respective ultrafiltrable portions.

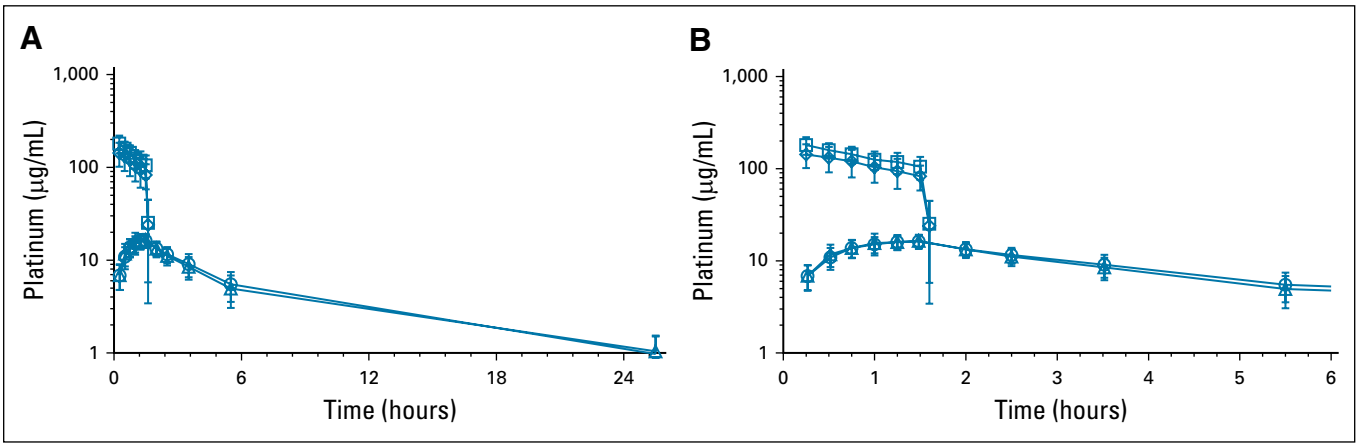

FIG 2. HIPEC carboplatin pharmacokinetics at (A) 24 hours and (B) 6 hours post HIPEC with carboplatin. HIPEC, hyperthermic intraperitoneal chemotherapy.

No 30-day mortality was observed. There was no difference in 30-day morbidity (Table 2); 12 patients (24%) in the HIPEC arm and 10 (20%) in the standard arm experienced a grade ≥ 3 AE ($P = .81$). The toxicity rate was 45% (9 patients) in the first 20 patients and 35% (17 patients) in the first 49 patients. The stopping threshold of > 50% toxicity rate was not observed. Overall, 92 patients (94%) completed all assigned postoperative IV chemotherapy treatment, with no difference between groups. The most common postoperative chemotherapy regimen used was carboplatin and liposomal doxorubicin in 74 patients (76%). The median time from surgery to initiation of postoperative IV chemotherapy was 32 days (18-91 days), without difference between arms.

The last follow-up date was February 15, 2021. At that time, 82 patients had progressed and 37 had died. At 24 months, eight patients (16.3%; 1-sided 90% CI, 9.7 to 100) in the HIPEC arm and 12 (24.5%; 1-sided 90% CI, 16.5 to 100) in the standard arm were without progression or death. The median follow-up for the 14 progression-free survivors was 52.8 months (range, 51.4-88.9 months). The median follow-up for the 61 survivors was 39.5 months (range, 19.8-88.9 months). The median PFS and OS for the entire cohort were 14.3 months (95% CI, 12 to 16) and 55.2 months (95% CI, 50.3 to 78), respectively. The median PFS and OS for patients who achieved a CGR were 15.1 and 59.7 months, respectively. Survival curves are shown in Figures 3A and 3B. Patients randomly assigned to HIPEC had a median PFS of 12.3 months, compared with 15.7 months for patients randomly assigned to the standard arm (HR, 1.54; 95% CI, 1 to 2.37). Patients randomly assigned to HIPEC had a median OS of 52.5 months, compared with 59.7 months for patients randomly assigned to the standard arm (HR, 1.39; 95% CI, 0.73 to 2.67). Univariate analysis and multivariate analysis for PFS and OS are shown in Tables 3 and 4. Single-site disease was independently associated with improved PFS, whereas CGR was independently associated with OS. In a post-hoc blinded radiologic review of all recurrences, the two groups did not demonstrate differences in pattern of recurrence (Appendix Table A2, online only). An unplanned Cox PH model for PFS and OS was created to evaluate the effect of HIPEC on other patient variables (Appendix Figs A1 and A2, online only). In this analysis, patients with a long preceding platinum-free interval and patients with a known deleterious *BRCA* mutation appeared to have no PFS benefit with HIPEC.

TABLE 2. Complications (30-Day Mortality)

Adverse Event	All, N = 98 (%)	HIPEC Arm, n = 49 (%)	Standard Arm, n = 49 (%)
Abdominal infection	2 (2)	2 (4.1)	0 (0)
Anemia	15 (15.3)	7 (14.3)	8 (16.3)
Ascites	1 (1)	0 (0)	1 (2)
Colitis	1 (1)	1 (2)	0 (0)
Colonic obstruction	1 (1)	1 (2)	0 (0)
Deep vein thrombosis	1 (1)	1 (2)	0 (0)
Diarrhea	1 (1)	1 (2)	0 (0)
Fever	1 (1)	0 (0)	1 (2)
Hemorrhage	1 (1)	1 (2)	0 (0)
Ileus	3 (3.1)	2 (4.1)	1 (2)
Intraoperative ureteral injury	2 (2)	1 (2)	1 (2)
Lung infection	1 (1)	0 (0)	1 (2)
Nausea	1 (1)	1 (2)	0 (0)
Noninfected intra-abdominal or thoracic fluid collection	3 (3.1)	1 (2)	2 (4.1)
Pancreatic fistula	1 (1)	1 (2)	0 (0)
Platelet count decreased	1 (1)	1 (2)	0 (0)
Pleural effusion	3 (3.1)	1 (2)	2 (4.1)
Sepsis	1 (1)	1 (2)	0 (0)
Urinary tract infection	4 (4.1)	4 (8.2)	0 (0)
Vascular access complication	1 (1)	1 (2)	0 (0)
Wound infection	2 (2)	0 (0)	2 (4.1)

Abbreviation: HIPEC, hyperthermic intraperitoneal chemotherapy.

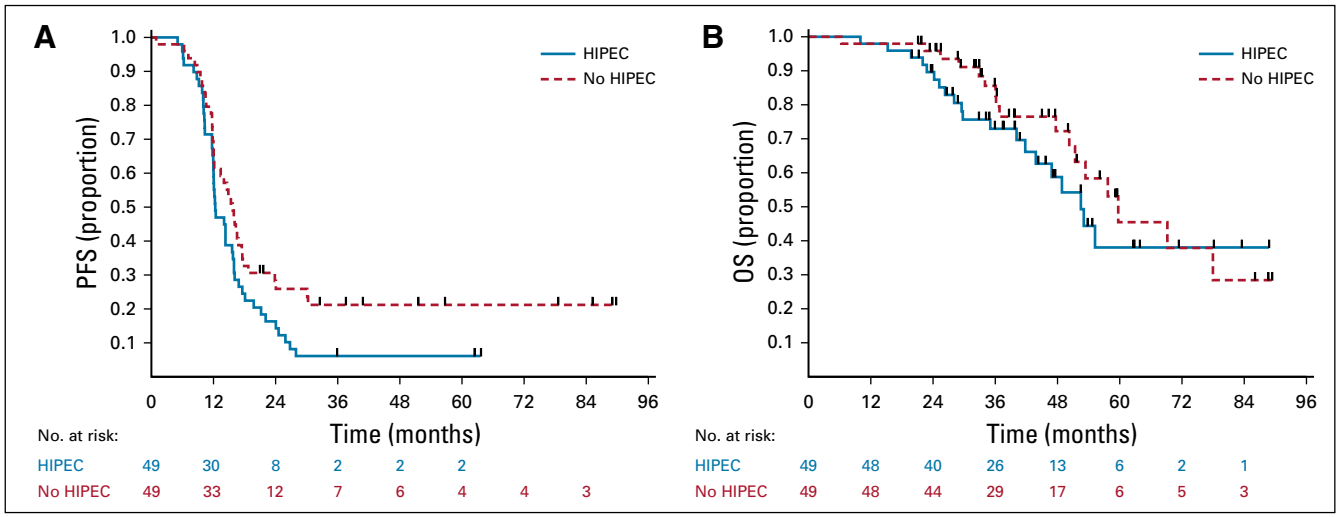

FIG 3. (A) PFS by treatment arm. Kaplan-Meier survival plots of PFS. (B) OS by treatment arm. Kaplan-Meier survival plots of OS. HIPEC, hyperthermic intraperitoneal chemotherapy; OS, overall survival; PFS, progression-free survival.

DISCUSSION

This randomized, multicenter phase II study evaluated the safety and efficacy of HIPEC with carboplatin in patients undergoing secondary cytoreduction for platinum-sensitive recurrent ovarian cancer. Carboplatin administered as HIPEC was well tolerated. No perioperative mortality or increased perioperative morbidity or toxicity was observed with HIPEC. A winner was not determined because no treatment arm achieved our prespecified end point of 17 disease-free patients at 24 months. This prespecified end point was based on a retrospective analysis of select patients undergoing secondary cytoreduction at our center.[15] Secondary cytoreductive surgery with 800 mg/m^2 carboplatin HIPEC followed by five cycles of IV carboplatin-based chemotherapy was not superior to surgery without HIPEC followed by six cycles of IV carboplatin-based chemotherapy. Further evaluation of this regimen is not warranted at this time.

Our trial design does not permit direct arm-to-arm comparison. The comparisons of survival estimates and subgroup analyses are hypothesis-generating and should be interpreted with caution. The secondary post-hoc analyses, however, support the primary conclusion. Furthermore, at the time of study design, carboplatin HIPEC was chosen because of concerns of cisplatin-induced nephrotoxicity.[8] The dose of 800 mg/m^2 was based on previous studies in patients with ovarian cancer. In a phase I study, the recommended dose of carboplatin used as HIPEC was 1,000 mg/m^2, with dose-limiting toxicity observed at 1,200 mg/m^2.[27] In GOG252, carboplatin was administered intraperitoneally at a dose of AUC 6, in a volume of up to 2 L, without retrieval of infusate.[5] The dose of carboplatin at AUC 6 corresponds to approximately 400 mg/m^2, depending on kidney function.[33] Peritoneal exposure was 174 μg·h/mL ultrafiltrable platinum, which corresponds to a conventional ultrafiltrable carboplatin AUC of 5.5 mg·min/L. Similarly, the plasma exposure corresponds to an ultrafiltrable carboplatin AUC of 3.1 mg·min/L. However, the latter plasma exposure is possibly not biologically active. Although after IV carboplatin dosing, ultrafiltrable platinum corresponds to free and still biologically active carboplatin,[34] the same may not be true of plasma ultrafiltrable platinum after peritoneal cavity dosing. Since total plasma platinum is accounted for by ultrafiltrable platinum, especially at the late 24-hour time point, this suggests that plasma platinum, although having low molecular weight and being ultrafiltrable, is no longer capable of reaction and consequently is inactive. If the ultrafiltrable (low-molecular-weight) platinum had been reactive, total platinum should have exceeded ultrafiltrable platinum at the late time point, the difference being the reaction product of reactive platinum and macromolecules such as albumin.[35] Therefore, the 1.77-fold AUC ratio of peritoneum to plasma is likely a large underestimate of the true exposure advantage to reactive platinum that IP administration conveys. The tumor platinum tissue concentration of 3.38 (1.62) μg/g compared relatively favorable to the approximately 0.7 μg/g observed in preclinical rat models.[8,36] Furthermore, carboplatin exposure was truncated because the carboplatin perfusate was removed immediately following HIPEC. It is unclear if a higher carboplatin dose, leaving the carboplatin in the peritoneum, or the use of cisplatin would have resulted in superior outcomes.

Furthermore, patients randomly assigned to no HIPEC received one additional cycle of standard postoperative IV chemotherapy. When the study was designed, the intraoperative administration of carboplatin was counted toward the first of six cycles of chemotherapy to avoid an overestimate of the HIPEC effect.

TABLE 3. PFS as Time to Event (N = 98)—Univariate Analysis and Multivariate Analysis (N = 84)

		Univariate Analysis PFS (N = 98)					Multivariate PFS (N = 98; Events = 84)		
Variable	No.	Progression or Death	Median PFS (two-sided 95% CI)	24-Month PFS (%; two-sided 95% CI)	HR (95% CI)	Log-rank *P*	HR	95% CI	*P*
All	98	84	14.3 (12 to 16)	22.3 (14.6 to 31)					
Arm									
HIPEC	49	46	12.3 (11.9 to 15.6)	16.3 (7.6 to 27.9)	1.54 (1 to 2.37)	.049	1.49	0.96 to 2.32	.076
Standard	49	38	15.7 (12 to 17.5)	28.3 (16.5 to 41.3)	1		Reference		
Age at surgery, years									
< 65	72	62	14.3 (12 to 15.8)	20.5 (12 to 30.5)	1	.518			
≥ 65	26	22	14.7 (12 to 18.7)	26.9 (11.9 to 44.5)	0.85 (0.52 to 1.39)				
Platinum-free interval, months									
≤ 12	30	28	13.7 (11.7 to 15.4)	13.3 (4.2 to 27.8)	1	.133			
> 12	68	56	15.7 (12 to 16.5)	26.3 (16.5 to 37.2)	0.71 (0.45 to 1.12)				
Sites of disease									
Single	13	6	NR	61.5 (30.8 to 81.8)	1	< .001	3.82	1.63 to 8.91	.002
Multiple	85	78	14 (12 to 15.7)	16.1 (9.2 to 24.8)	3.94 (1.7 to 9.16)		Reference		
BRCA status									
Wild-type or VUS or unknown	77	68	12.3 (12 to 15.6)	19.1 (11.2 to 28.7)	1	.074			
Deleterious	21	16	16.5 (13.4 to 24)	33.3 (14.9 to 53.1)	0.61 (0.35 to 1.06)				
Residual disease									
Complete gross resection	86	72	15.1 (12.1 to 16.1)	25.4 (16.7 to 34.9)	1	.028	1.54	0.81 to 2.91	.19
Minimal residual disease	12	12	12 (10.1 to 14.3)	NR	1.99 (1.06 to 3.72)		Reference		

NOTE. *P* value is obtained by applying log-rank test.

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; NR, not reached; PFS, progression-free survival; VUS, variant of unknown significance.

Although stratification was not necessary in this noncomparative randomized phase II trial, differences in prognostic factors between arms should be considered when interpreting the survival estimates. We did not stratify for residual disease after surgery, which is a strong prognostic factor. Although not statistically significant, 40 patients (82%) achieved a CGR in the HIPEC arm compared with 46 (94%) in the standard arm, favoring the standard arm. Patients were randomly assigned after cytoreduction to < 0.5-cm residual disease. Despite protocol-specific intraoperative random assignment, bowel resections were performed less frequently in the HIPEC arm. Morbidity concerns possibly resulted in an underuse of bowel resections in the HIPEC arm. In patients randomly assigned to HIPEC, surgeons potentially accepted minimal residual disease when a CGR was achievable with a bowel resection. Future head-to-head comparison studies should stratify by residual status to reduce bias following intraoperative random assignment. We did not, however, observe a higher rate of ostomies in the HIPEC arm. This was observed in a previous randomized trial, which could also be a result of intraoperative bias.[10]

The obvious negative aspect of intraoperative random assignment is the longer operative time. The logistical challenges of this clinical trial with preparation of the drug, transportation to the operative room, and the setup of the perfusion machine after random assignment and the HIPEC on average resulted in a 3-hour longer procedure, likely significantly overestimating the additional time needed for HIPEC in a nonexperimental setting.

Although no maintenance treatment was approved for patients with platinum-sensitive recurrent ovarian cancer at the time of study design, the FDA granted approval to both bevacizumab and polyadenosine diphosphate-ribose

TABLE 4. OS as Time to Event (N = 98)—Univariate Analysis and Multivariate Analysis (N = 84)

		Univariate Analysis OS (N = 98)					Multivariate OS (N = 98; Events = 84)		
Variable	No.	Death	Median OS (two-sided 95% CI)	24-Month OS (%; two-sided 95% CI)	HR (95% CI)	Log-rank *P*	HR	95% CI	*P*
All	98	37	55.2 (50.3 to 78)	92.7 (85.4 to 96.5)					
Arm									
HIPEC	49	20	52.5 (41.8 to NE)	89.6 (76.8 to 95.5)	1.39 (0.73 to 2.67)	.313	1.33	0.69 to 2.56	.39
Standard	49	17	59.7 (50.3 to NE)	95.8 (84.3 to 98.9)	1		Reference		
Age at surgery, years									
< 65	72	27	57.7 (50.3 to NE)	92.9 (83.7 to 97)	1	.803			
≥ 65	26	10	52.5 (40.1 to NE)	92.3 (72.6 to 98)	1.1 (0.53 to 2.27)				
Platinum-free interval, months									
≤ 12	30	15	50.3 (29.7 to 78)	89.9 (71.8 to 96.6)	1	.056			
> 12	68	22	57.7 (52.5 to NE)	94 (84.8 to 97.7)	0.53 (0.28 to 1.03)				
Sites of disease									
Single	13	2	NR	100 (100 to 100)	1	.082			
Multiple	85	35	53.4 (48.8 to 69.2)	91.6 (83.2 to 95.9)	3.31 (0.79 to 13.81)				
BRCA status									
Wild-type or VUS or unknown	77	29	55.2 (48.8 to 78)	92.1 (83.3 to 96.4)	1	.487			
Deleterious	21	8	59.7 (41.8 to NE)	95 (69.5 to 99.3)	0.76 (0.35 to 1.66)				
Residual disease									
Complete gross resection	86	29	59.7 (51.4 to NE)	94.1 (86.5 to 97.5)	1	.007	2.77	1.24 to 6.17	.013
Minimal residual disease	12	8	40.1 (22.8 to 52.5)	81.8 (44.7 to 95.1)	2.84 (1.28 to 6.31)		Reference		

NOTE. *P* value is obtained by applying log-rank test.

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival; VUS, variant of unknown significance.

polymerase inhibitors while the study was ongoing.[37-40] To avoid potential treatment imbalance between arms, we did not permit the use of any maintenance treatment. This was carefully discussed with the patients during the informed consent process. Furthermore, patients with a platinum-free interval of > 30 months were ineligible, resulting in a median platinum-free interval of 16 months, which is substantially shorter than what was reported in recent studies evaluating the role of secondary cytoreduction in patients with platinum-sensitive ovarian cancer.[13,41] In addition, a bowel resection was necessary in 51% of patients as part of cytoreductive surgery. This is significantly more than reported in GOG213 (28%), suggesting that patients enrolled in this trial had higher disease burden. The omission of maintenance treatment, the shorter platinum-free interval, and the inclusion of higher-risk patients explains the shorter median PFS in our study. Despite this, the OS was comparable to GOG213, suggesting that maintenance strategies were successfully administered in later lines of therapy.

Secondary cytoreduction and HIPEC with carboplatin was well tolerated but did not result in superior outcomes compared with standard of care as estimated by a historical control estimate. Our study does not support the use of HIPEC with carboplatin at 800 mg/m^2 during secondary cytoreduction. Further studies are needed to address how to best incorporate HIPEC with optimization of the intraoperative random assignment process to minimize surgeon bias as well as careful consideration for relevant stratification factors, such as residual disease and *BRCA* status.

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CLINICAL TRIAL INFORMATION

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, et al: Cancer statistics, 2021. CA Cancer J Clin 71:7-33, 2021
2. Armstrong DK, Bundy B, Wenzel L, et al: Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 354:34-43, 2006
3. Tewari D, Java JJ, Salani R, et al: Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: A Gynecologic Oncology Group study. J Clin Oncol 33:1460-1466, 2015
4. Wright AA, Cronin A, Milne DE, et al: Use and effectiveness of intraperitoneal chemotherapy for treatment of ovarian cancer. J Clin Oncol 33:2841-2847, 2015
5. Walker JL, Brady MF, Wenzel L, et al: Randomized trial of intravenous versus intraperitoneal chemotherapy plus bevacizumab in advanced ovarian carcinoma: An NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol 37:1380-1390, 2019
6. Zivanovic O, Abramian A, Kullmann M, et al: HIPEC ROC I: a phase I study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer. Int J Cancer 136:699-708, 2015
7. Los G, van Vugt MJ, den Engelse L, et al: Effects of temperature on the interaction of cisplatin and carboplatin with cellular DNA. Biochem Pharmacol 46: 1229-1237, 1993
8. Los G, van Vugt MJ, Pinedo HM: Response of peritoneal solid tumours after intraperitoneal chemohyperthermia treatment with cisplatin or carboplatin. Br J Cancer 69:235-241, 1994
9. Los G, Verdegaal E, Noteborn HPJM, et al: Cellular pharmacokinetics of carboplatin and cisplatin in relation to their cytotoxic action. Biochem Pharmacol 42: 357-363, 1991
10. van Driel WJ, Koole SN, Sikorska K, et al: Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 378:230-240, 2018
11. Koole SN, van Lieshout C, van Driel WJ, et al: Cost effectiveness of interval cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in stage III ovarian cancer on the basis of a randomized phase III trial. J Clin Oncol 37:2041-2050, 2019
12. Lei Z, Wang Y, Wong J, et al: Evaluation of cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy for stage III epithelial ovarian cancer. JAMA Netw Open 3:e2013940, 2020
13. Coleman RL, Spirtos NM, Enserro D, et al: Secondary surgical cytoreduction for recurrent ovarian cancer. N Engl J Med 381:1929-1939, 2019
14. Bristow RE, Puri I, Chi DS: Cytoreductive surgery for recurrent ovarian cancer: A meta-analysis. Gynecol Oncol 112:265-274, 2009
15. Chi DS, McCaughty K, Diaz JP, et al: Guidelines and selection criteria for secondary cytoreductive surgery in patients with recurrent, platinum-sensitive epithelial ovarian carcinoma. Cancer 106:1933-1939, 2006
16. Harter P, du Bois A, Hahmann M, et al: Surgery in recurrent ovarian cancer: The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol 13:1702-1710, 2006
17. Harter P, Hahmann M, Leuck HJ, et al: Surgery for recurrent ovarian cancer: Role of peritoneal carcinomatosis: Exploratory analysis of the DESKTOP I trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis. Ann Surg Oncol 16:1324-1330, 2009
18. Spiliotis J, Halkia E, Lianos E, et al: Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: A prospective randomized phase III study. Ann Surg Oncol 22:1570-1575, 2015

19. Konigsrainer I, Beckert S, Becker S, et al: Cytoreductive surgery and HIPEC in peritoneal recurrent ovarian cancer: Experience and lessons learned. Langenbecks Arch Surg 396:1077-1081, 2011
20. Fagotti A, Costantini B, Petrillo M, et al: Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: A case-control study on survival in patients with two year follow-up. Gynecol Oncol 127:502-505, 2012
21. Bakrin N, Cotte E, Golfier F, et al: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advanced ovarian carcinoma: A multicenter, prospective study of 246 patients. Ann Surg Oncol 19:4052-4058, 2012
22. Gould N, Sill MW, Mannel RS, et al: A phase I study with an expanded cohort to assess feasibility of intravenous docetaxel, intraperitoneal carboplatin and intraperitoneal paclitaxel in patients with previously untreated ovarian, fallopian tube or primary peritoneal carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 127:506-510, 2012
23. Morgan MA, Sill MW, Fujiwara K, et al: A phase I study with an expanded cohort to assess the feasibility of intraperitoneal carboplatin and intravenous paclitaxel in untreated ovarian, fallopian tube, and primary peritoneal carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 121:264-268, 2011
24. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
25. Cowan RA, Eriksson AGZ, Jaber SM, et al: A comparative analysis of prediction models for complete gross resection in secondary cytoreductive surgery for ovarian cancer. Gynecol Oncol 145:230-235, 2017
26. Steller MA, Egorin MJ, Trimble EL, et al: A pilot phase I trial of continuous hyperthermic peritoneal perfusion with high-dose carboplatin as primary treatment of patients with small-volume residual ovarian cancer. Cancer Chemother Pharmacol 43:106-114, 1999
27. Lentz SS, Miller BE, Kucera GL, et al: Intraperitoneal hyperthermic chemotherapy using carboplatin: a phase I analysis in ovarian carcinoma. Gynecol Oncol 106:207-210, 2007
28. Argenta PA, Sueblinvong T, Geller MA, et al: Hyperthermic intraperitoneal chemotherapy with carboplatin for optimally-cytoreduced, recurrent, platinum-sensitive ovarian carcinoma: A pilot study. Gynecol Oncol 129:81-85, 2013
29. Joshi A, Guo J, Holleran JL, et al: Evaluation of the pharmacokinetic drug-drug interaction potential of iohexol, a renal filtration marker. Cancer Chemother Pharmacol 86:535-545, 2020
30. Strong VE, Selby LV, Sovel M, et al: Development and assessment of Memorial Sloan Kettering Cancer Center's Surgical Secondary Events grading system. Ann Surg Oncol 22:1061-1067, 2015
31. Grobmyer SR, Pieracci FM, Allen PJ, et al: Defining morbidity after pancreaticoduodenectomy: Use of a prospective complication grading system. J Am Coll Surg 204:356-364, 2007
32. Simon R, Wittes RE, Ellenberg SS: Randomized phase II clinical trials. Cancer Treat Rep 69:1375-1381, 1985
33. Bookman MA, McGuire WP, Kilpatrick D, et al: Carboplatin and paclitaxel in ovarian carcinoma: a phase I study of the Gynecologic Oncology Group. J Clin Oncol 14:1895-1902, 1996
34. Harland SJ, Newell DR, Siddik ZH, et al: Pharmacokinetics of cis-diammine-1,1-cyclobutane dicarboxylate platinum(II) in patients with normal and impaired renal function. Cancer Res 44:1693-1697, 1984
35. Eads JR, Beumer JH, Negrea L, et al: A pharmacokinetic analysis of cisplatin and 5-fluorouracil in a patient with esophageal cancer on peritoneal dialysis. Cancer Chemother Pharmacol 77:333-338, 2016
36. Los G, Smals OA, van Vugt MJ, et al: A rationale for carboplatin treatment and abdominal hyperthermia in cancers restricted to the peritoneal cavity. Cancer Res 52:1252-1258, 1992
37. Aghajanian C, Blank SV, Goff BA, et al: OCEANS: A randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. J Clin Oncol 30:2039-2045, 2012
38. Mirza MR, Monk BJ, Herrstedt J, et al: Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 375:2154-2164, 2016
39. Pujade-Lauraine E, Ledermann JA, Selle F, et al: Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 18:1274-1284, 2017
40. Coleman RL, Brady MF, Herzog TJ, et al: Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 18: 779-791, 2017
41. Shi T, Zhu J, Feng Y, et al: Secondary cytoreduction followed by chemotherapy versus chemotherapy alone in platinum-sensitive relapsed ovarian cancer (SOC-1): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 22:439-449, 2021

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Secondary Cytoreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study

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APPENDIX

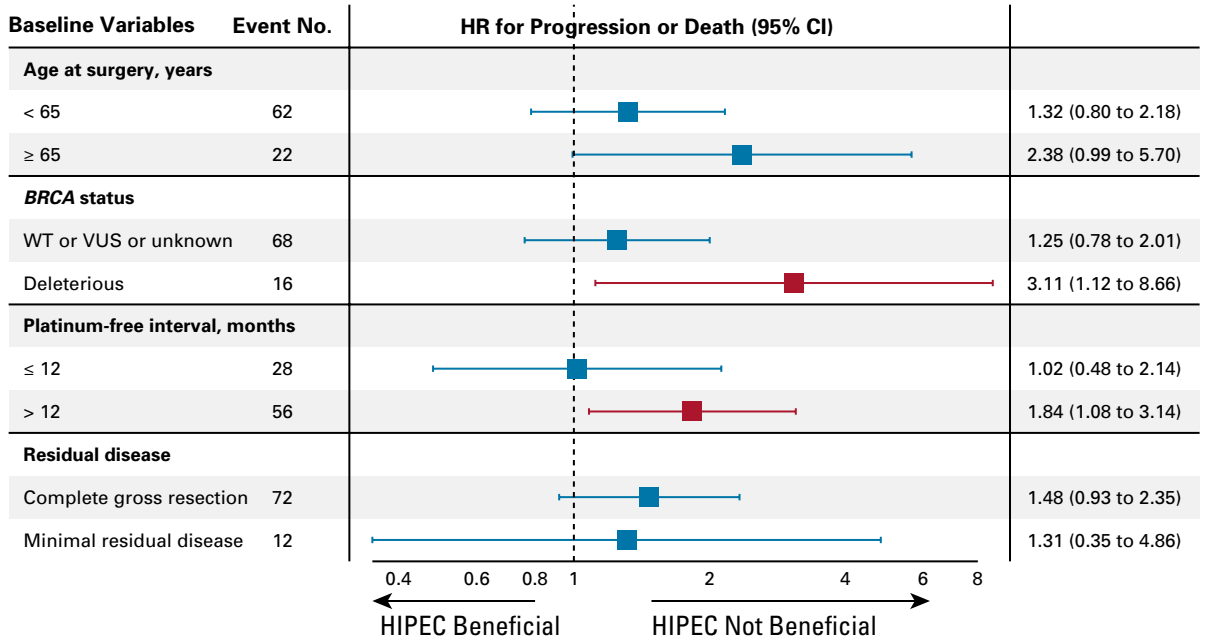

FIG A1. Forest plot for baseline variables and HR for progression or death. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; VUS, variant of unknown significance; WT, wild type.

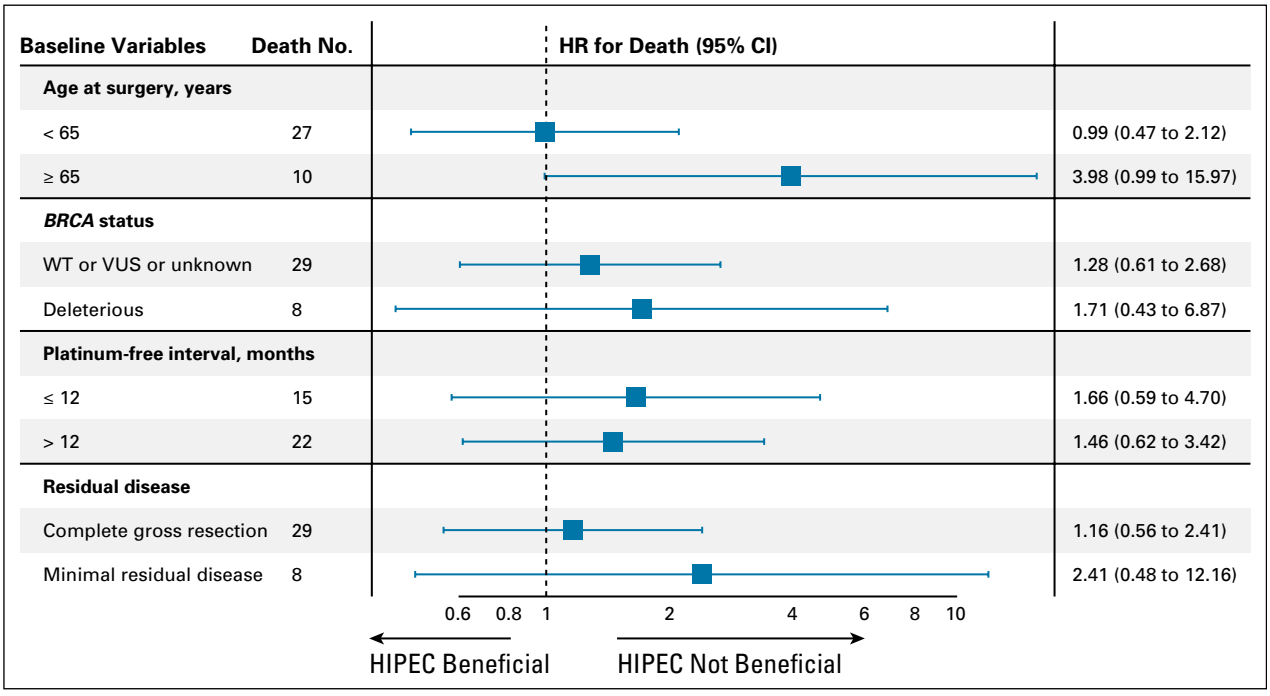

FIG A2. Forest plot for baseline variables and HR for death. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; VUS, variant of unknown significance; WT, wild type.

TABLE A1. Geomean (SD) Pharmacokinetic Parameters of Plasma and Peritoneal Perfusate Total and UF or Free Platinum

Parameter	C_{max} (μg/mL)	AUC_{0-t} (μg h/mL)	T_{max} (h)	$T_{1/2}$ (h)
Peritoneal fluid				
Total platinum	178 (1.23)	221 (1.26)	0.25 (1.11)	—
UF platinum	140 (1.28)	174 (1.37)	0.27 (1.31)	—
% UF/total	79.3 (1.18)	79.9 (1.18)	—	
Plasma				
Total platinum	16.4 (1.20)	101 (1.33)	1.4 (1.1)	7.4 (1.5)
UF platinum	16.7 (1.24)	97.5 (1.34)	1.3 (1.2)	8.4 (1.5)
% UF/total	102 (1.11)	96.8 (1.14)	—	—
UF platinum peritoneal/plasma	8.47 (1.42)	1.77 (1.54)	—	—

NOTE. AUC_{0-t} defined as $AUC_{0-25.5h}$ for plasma and AUC_{0-last} for peritoneal fluid. % UF/total for plasma C_{last} was 116% (1.77). Peritoneal fluid total platinum at time 0 (C_0) was 204 (1.26) μg/mL. An AUC of 174 and 97.5 μg h/mL platinum correspond to a carboplatin equivalent AUC of 5.5 and 3.1 mg min/L, respectively.

Abbreviations: AUC, area under the curve; SD, standard deviation; UF, ultrafiltrable.

TABLE A2. Pattern of Recurrence

	All[a]	HIPEC Arm	Standard Arm
Site of Recurrence	N = 82 (%)	n = 45 (%)	n = 37 (%)
Peritoneum	64 (80)	35 (80)	29 (81)
Lymphadenopathy	42 (52)	23 (52)	19 (53)
Pleura	4 (5.0)	2 (4.5)	2 (5.6)
Others	10 (12)	5 (11)	5 (14)

Abbreviation: HIPEC, hyperthermic intraperitoneal chemotherapy.

[a]Two patients died without recurrence.