Hyperthermic Intraperitoneal Chemotherapy in Platinum-Sensitive Recurrent Ovarian Cancer: A Randomized Trial on Survival Evaluation (HORSE; MITO-18)

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ABSTRACT

PURPOSE To investigate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to secondary cytoreductive surgery (SCS) without neoadjuvant chemotherapy has a benefit on progression-free survival (PFS), as opposed to SCS alone in patients with platinum-sensitive recurrent epithelial ovarian cancer (platinum-free interval, >6 months).

METHODS This was a multicenter randomized phase III study. Random assignment was performed at the time of surgery in cases with residual tumor ≤0.25 cm. HIPEC with cisplatin (CDDP) 75 mg/m² for 60 minutes at 41.5°C was administered at the end of surgery in the experimental arm. Both groups received postoperative platinum-based chemotherapy. The primary end point was PFS. The safety profile and postrecurrence survival (PRS) were the secondary end points.

RESULTS A total of 167 patients underwent random assignment, 82 patients to SCS plus HIPEC (experimental arm) and 85 to SCS alone (control arm). The median follow-up was 83 months (IQR, 64-102). The median PFS was 23 months (95% CI, 17 to 29) in the group that underwent surgery alone and 25 months (95% CI, 18 to 32) in the group that underwent cytoreductive surgery with HIPEC. The probability of PRS at 5 years was 61.6% (95% CI, 50.8 to 72.4) in the SCS group and 75.9% (95% CI, 66.5 to 85.3) in the SCS plus HIPEC group. The incidence of postoperative adverse events of any grade was similar between the two groups.

CONCLUSION The addition of HIPEC to complete or nearly complete primary SCS did not confer a benefit in terms of PFS in patients with platinum-sensitive peritoneal recurrence.

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Despite the efforts made in recent decades to improve the efficacy of different therapeutic strategies, including advanced surgical procedures and maintenance treatment,[1-5] up to 70% of patients with ovarian cancer (OC) experience recurrence after primary treatment, and their survival outcome remains poor.[6]

International guidelines list secondary cytoreductive surgery (SCS) as an option for adequate management of platinum-sensitive patients with recurrent OC.[7] Nonetheless, its beneficial impact on survival outcomes compared with systemic therapy alone remains controversial, and only recently data from a few randomized controlled trials have been presented.[8-10]

A recent meta-analysis has shown SCS as superior to systemic therapy alone in terms of progression-free survival (PFS). The survival benefits are particularly observed for complete surgical resection. However, the impact on overall survival (OS) in the general population remains to be proven.[11,12]

van Driel et al[13] showed that patients affected by advanced epithelial OC, treated with neoadjuvant chemotherapy (NACT), followed by interval debulking surgery (IDS) with hyperthermic intraperitoneal chemotherapy (HIPEC) have longer recurrence-free survival and OS than surgery alone and no additional risks in terms of side effects. Thanks to these data, the use of HIPEC at IDS is considered a therapeutic option in National Comprehensive Cancer Network guidelines.[7]

CONTEXT

Key Objective

To demonstrate whether the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) to secondary cytoreductive surgery (SCS) without neoadjuvant chemotherapy (NACT) has a benefit in terms of progression-free survival (PFS) in patients with platinum-sensitive recurrent ovarian cancer (OC).

Knowledge Generated

HIPEC during SCS, without NACT, seems not to prolong PFS with respect to SCS alone, in patients with recurrent ovarian cancer (ROC) with favorable prognostic factors (initial power 80%, conditional power 10%). HIPEC is not associated with increased postoperative morbidity.

Relevance *(G. Fleming)*

HIPEC should not be used in women with platinum sensitive recurrent OC undergoing SCS without neoadjuvant therapy.*

*Relevance section written by *JCO* Associate Editor Gini Fleming, MD.

Although the rationale for delivering heated antiblastic drugs intraperitoneally at the time of surgery has been known for a long time,[14–17] to our knowledge, this is the only randomized controlled trial (RCT) showing a clear survival benefit of HIPEC in a specific subgroup of patients with OC. Other trials investigating the role of HIPEC in patients with OC have been performed (ClinicalTrials.gov identifiers: NCT03448354, NCT03842982, NCT01628380, NCT02124421, NCT01376752), but few data are available right now.

Here, we present the results of a randomized, open-label, phase III controlled trial of SCS with or without HIPEC in patients with platinum-sensitive recurrent OC.

METHODS

The trial was designed by an executive committee within the Multicenter Italian Trials in Ovarian cancer and gynecologic malignancies (MITO) group and conducted in eight hospitals in Italy at which medical personnel had experience in cytoreductive surgery and HIPEC. Each Institutional Ethical Committee approved the trial protocol. The trial was registered on ClinicalTrials.gov (identifier: NCT01539785; Eudract number: 2012-002872-15) and follows the ethical principles outlined by the Declaration of Helsinki. All patients gave written informed consent before starting the study.

Data were collected, and analyses were performed by an Independent Data Monitoring Committee (IDMC) at Fondazione Policlinico A. Gemelli Clinical Trial Center.

Patients

Eligible patients had a primary platinum-sensitive (platinum-free interval [PFI], ≥6 months) recurrence from epithelial ovarian, fallopian tube or peritoneal cancer and were referred for SCS because of disease in the abdominal cavity, with or without extraperitoneal spread, considered completely resectable during surgery. None of the patients received chemotherapy before SCS. Chances of complete resection were assessed by imaging revision with a dedicated radiologist and staging laparoscopy.

Eligibility criteria also included age between 18 and 70 years, Eastern Cooperative Oncology Group performance status <2, normal blood count, and adequate renal, heart, and liver function. Patients with ascites, with recurrences other than primary or with an estimated life expectancy of <4 weeks were excluded.

Trial Design

HORSE is an open-label, multicenter, randomized phase III study aiming to assess the efficacy and safety of SCS with HIPEC (experimental, arm B) compared with SCS alone (control, arm A). The CONSORT diagram of the trial is reported in Figure 1. Random assignment took place centrally at the time of surgery in cases in which complete cytoreduction, defined as no visible residual disease (CC-0) or with residual disease <0.25 cm (CC-1), was achieved. HIPEC was administered at the end of surgery with the closed technique (Appendix 1, online only). All patients, regardless of the treatment received, underwent adjuvant chemotherapy. The trial's minimum follow-up period was 24 months from SCS. Computed tomography of the chest, abdomen, and pelvis was performed at 1, 6, 12, 18, and 24 months after treatment and every 6 months until disease recurrence. Serum cancer antigen 125 (CA-125) levels were monitored every 3 months. If the patient had clinical progression or if she had an increase of CA 125 twice over the threshold, an extra imaging assessment was required. No participation in other clinical trials was allowed for any patients until the primary end point (secondary recurrence) occurred. BRCA status was retrieved for 131 patients (78%).

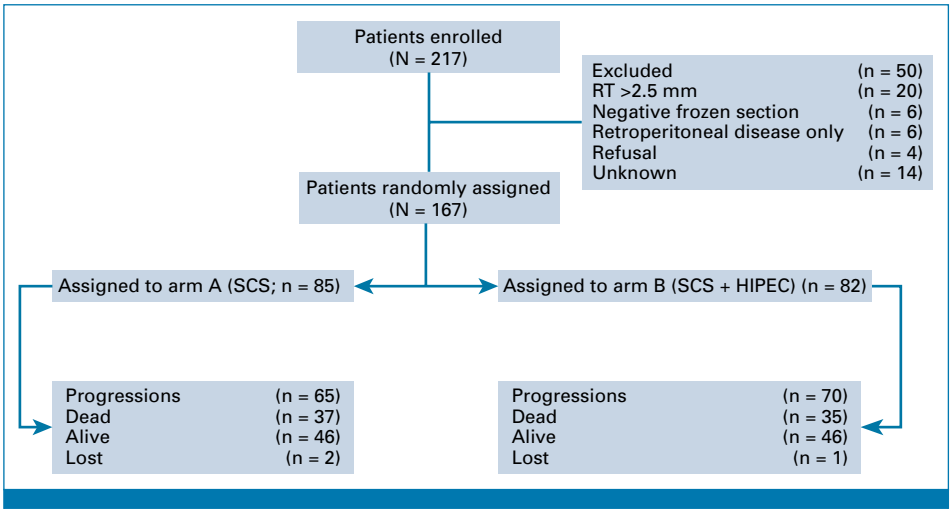

FIG 1. Flow chart of the study. HIPEC, hyperthermic intraperitoneal chemotherapy; RT, residual tumor; SCS, secondary cytoreductive surgery.

End Points

The primary end point of the study was PFS, which was defined as the time from random assignment to secondary recurrence or progression or death from any cause, whichever occurred first. Disease progression was defined according to RECIST version 1.1 or based on an increase from baseline in the CA 125 level, whichever was met first, as recommended by the Gynecologic Cancer InterGroup.[18,19]

Secondary end points included postrecurrence survival (PRS), which was defined as the time from random assignment to death from any cause, pattern of relapse at the time of secondary recurrence, safety, and time to adjuvant treatment.

Data on PFS and PRS were censored at the date of the last contact (either physical or virtual) for patients with no evidence of disease.

The complexity of surgical procedures was graded according to the surgical complexity score.[20] The severity of perioperative complications was graded on a 1-5 scale according to the Memorial Sloan Kettering Cancer Center Surgical Secondary Events Grading System.[21] Complications were registered 30 days (early) and 6 months (late) after surgery. Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events v4.0.[22]

Statistical Analysis

We determined that 144 events (disease recurrence, disease progression, or death) would provide the trial with 80% power to detect an increase in median secondary PFS from 18 months to 24 months, with a hazard ratio (HR) of 0.66, in the surgery plus HIPEC group than in the surgery group, at an overall α-error (one-tailed) of .05. A sample of 158 patients (79 per arm) increased for dropout to 167 was then considered.

A prespecified interim analysis was performed after 40 patients to assess the safety of the study. Based on CIs, if more than two G4-G5 early complications were observed in one arm, the trial would have been stopped.

Baseline surgical and postoperative characteristics were presented as absolute count and percentages (%) for categorical variables and as median and IQR for continuous variables. χ^2 and Mann-Whitney U tests were used to detect statistical differences according to the treatment arm, if appropriate. Median follow-up was calculated according to the reverse Kaplan-Meier technique. PFS and PRS curves were estimated by the Kaplan-Meier product limit method and compared by using the log-rank test. Cox proportional hazards models were used to estimate HRs and their 95% CIs. Efficacy analyses were performed according to the intention-to-treat principle: all randomly assigned patients were included regardless of whether they received all planned procedures or could be evaluated.

All estimates were presented with two-sided 95% CIs, and differences were considered significant at a level of $P < .05$. IBM SPSS for Windows statistical software program version 21.0 was used (Armonk, NY) and R software v.4.1.2.

Early Closure of the Study

At the time of cutoff date (December 31, 2023), 139 PFS events (135 recurrences and four deaths) were observed. We decided to perform this analysis because the event rate markedly decreased, and the conditional power to refuse the null hypothesis was 10%. We also simulated two scenarios with the remaining alive and without recurrence patients all relapsing at the same moment in arm A or, alternatively, in

arm B, and no differences between the two arms were observed.

We asked an IDMC to review our results (Appendix 2). We held two meetings (March 2023 and January 2024). After the second meeting, the IDMC advised to proceed to the primary analysis and study publication.

RESULTS

Patients

Between September 2012 and January 2019, 217 patients were enrolled at eight different centers in Italy. A total of 167 patients were randomly assigned after SCS. Eighty-two patients received HIPEC (arm B, experimental arm), and 85 did not (arm A, control arm; Fig 1). All patients had confirmation of recurrence both at the frozen section and final histology. Demographic and baseline are reported in Table 1. BRCA status is known in 131 of 167 patients (78.4%). Of them, 57 women carried BRCA 1 and 2 pathogenic variants (43.5%).

Efficacy

At the time of cutoff date (December 31, 2023), after a median follow-up of 83 months (IQR, 64-102), 135 of the 167 patients (80.8%) had a recurrence and 72 (43.1%) died for any cause.

In the intention-to-treat analysis, 69 of the 85 patients (81.2%) in the surgery group and 70 of the 82 patients (85.4%) in the surgery plus HIPEC group had an event of disease recurrence or death (B *v* A; HR, 1.02 [95% CI, 0.73 to 1.42]; $P = .91$; Fig 2A). The median PFS was 23 months (95% CI, 17 to 29) in the group that underwent surgery alone and 25 months (95% CI, 18 to 32) in the group that underwent surgery with HIPEC. The probability of PFS at 2 years was 47.3% in the surgery group (95% CI, 36.5 to 58.1) and 51.1% in the surgery plus HIPEC group (95% CI, 40.3 to 61.9).

The median PRS was 101 months in arm A (95% CI, 51 to 151) and 91.0 months in arm B (95% CI, 79 to 103; $P = .40$).

No statistically significant difference in the pattern of distribution of the secondary recurrence was observed (Appendix Table A1).

A total of 37 of the 85 (43.5%) patients in the surgery group and 35 of the 82 patients (42.7%) in the surgery plus HIPEC group died (B *v* A; HR, 0.86 [95% CI, 0.54 to 1.37]). The probability of PRS at 5 years was 61.6% (95% CI, 50.8 to 72.4) in the surgery group and 75.9% (95% CI, 66.5 to 85.3) in the surgery plus HIPEC group (Fig 2B). A lower HR for PFS in histologies other than serous (HR, 0.29 [95% CI, 0.11 to 0.75]), in favor of HIPEC, was reported (Fig 3), leading to a significant interaction ($P = .004$).

TABLE 1. Demographic and Baseline Disease Characteristics

Clinical Characteristic	Arm A: SCS (n = 85)	Arm B: SCS + HIPEC (n = 82)
Age, years, median (IQR)	55 (49-61)	55 (49-62)
BMI, No. (%)		
<25	30 (35.3)	36 (43.9)
≥25	41 (48.2)	37 (45.1)
Unknown	14 (16.5)	9 (11.0)
BRCA status, No. (%)		
Wild type	40 (47.1)	34 (41.5)
BRCA1	17 (20.0)	22 (26.8)
BRCA2	5 (5.9)	12 (14.6)
BRCA1/2	1 (1.2)	0
Unknown	22 (25.9)	14 (17.1)
Primary treatment, No. (%)		
PDS	69 (81.2)	69 (84.1)
NACT	16 (18.8)	13 (15.9)
RT at PDS/IDS, No. (%)		
Absent	76 (89.4)	75 (91.5)
≤1 cm	2 (2.4)	0
>1 cm	4 (4.7)	4 (4.9)
Unknown	3 (3.5)	3 (3.6)
Histology, No. (%)		
Serous	75 (88.2)	65 (79.3)
Endometrioid	2 (2.4)	5 (6.1)
Indifferentiated	5 (5.9)	5 (6.1)
Clear cell	1 (1.2)	4 (4.9)
Mixed	1 (1.2)	1 (1.2)
Unknown	1 (1.2)	2 (2.4)
Grading, No. (%)		
G1-2	7 (7.2)	6 (7.3)
G3	76 (89.4)	74 (90.3)
Unknown	2 (2.4)	2 (2.4)
Stage, No. (%)		
I-II	18 (21.1)	14 (17.1)
III-IV	65 (76.5)	67 (81.7)
Unknown	2 (2.4)	1 (1.2)
Platinum-free interval, months, median (IQR)	17 (11-30)	20 (12-32)
Type of relapse, No. (%)		
Intraperitoneal only	53 (62.4)	50 (61.0)
Intraperitoneal and extraperitoneal	32 (37.6)	32 (39.0)

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; IDS, interval debulking surgery; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; RT, residual tumor; SCS, secondary cytoreductive surgery.

Safety

Surgical and postoperative details are shown in Tables 2 and 3. Overall, 40 patients (23.9%) developed at least one early postoperative event of any grade, and two (1.2%) required

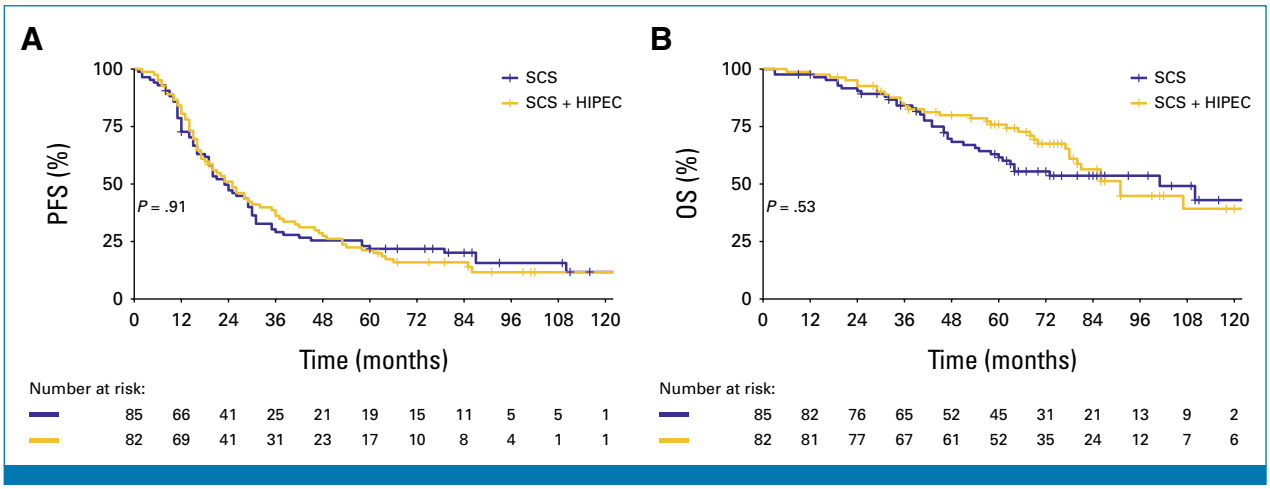

FIG 2. (A) PFS and (B) postrecurrence survival in the ITT population. HIPEC, hyperthermic intraperitoneal chemotherapy; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; SCS, secondary cytoreductive surgery.

reinterventions (one volvulus and one wound suture, one in each arm). No difference between the two groups was noted. In particular, grade 3 or 4 adverse events were reported in six patients (7.1%) in the surgery group and 10 patients (12.2%) in the surgery plus HIPEC group (P = .26). No deaths within 30 and 90 days from surgery were observed in both groups. Late postoperative complications were observed in seven patients (8.2%) in arm A and five patients (6.1%) in arm B (P = .83).

Adjuvant Therapy

A total of 135 (80.8%) patients received the planned six cycles of adjuvant chemotherapy, and 159 (95.2%) women had at least three cycles (78 in arm A and 81 in arm B), with no differences between the groups (Table 3). Grade 3 or grade 4 toxicities caused four delays in chemotherapy administration (two in arm A and two in arm B) and 16 chemotherapy dose reductions (eight in arm A and eight in arm B). Twelve patients in the surgery arm and 12 in the surgery plus HIPEC arm had maintenance treatment after random assignment, either with bevacizumab or poly adenosine diphosphate ribose polymerase inhibitors (Appendix Table A2).

DISCUSSION

In this prospective, randomized, multicenter, phase III clinical trial on the addition of HIPEC to complete or optimal

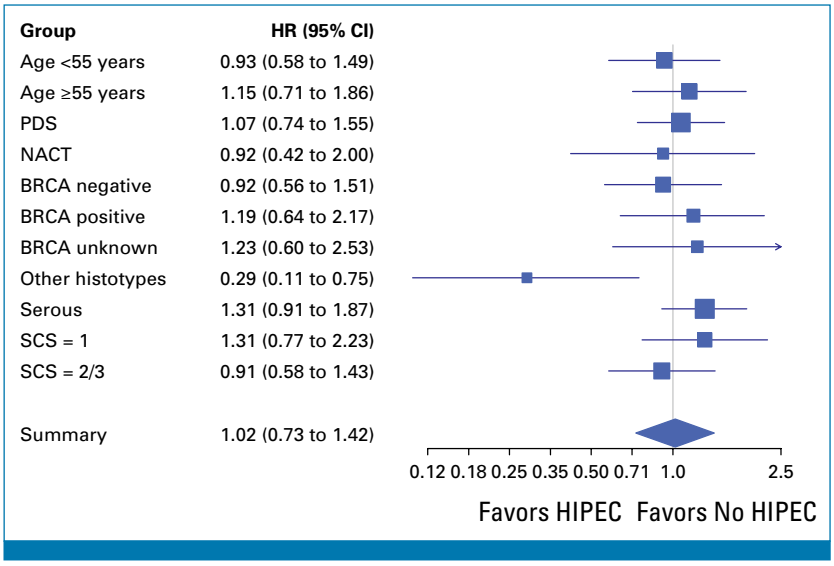

FIG 3. Forest plot for progression-free survival in the ITT population. HRs and their 95% CIs are reported for each subgroup with the dimension of squares related their size. HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; PDS, primary debulking surgery; SCS, secondary cytoreductive surgery.

TABLE 2. Surgical Treatment Characteristics

Surgical Characteristic	Arm A: SCS	Arm B: SCS + HIPEC	*P*
All patients, No.	85	82	
Surgical complexity score,[19] No. (%)			.10
1	33 (38.8)	45 (54.9)	
2	40 (47.1)	30 (36.6)	
3	12 (14.1)	7 (8.5)	
Bowel resections, No. (%)	38 (44.7)	25 (30.4)	.06
Oostomies,[a] No. (%)	15 (39.5)	7 (28.0)	.08
Operative time, minutes, median (IQR)	305 (235-384)	450 (363-526)	<.0001
RT at SCS, No. (%)			.43
Absent (CC-0)	82 (96.5)	77 (93.9)	
≤2.5 mm (CC-1)	3 (3.5)	5 (6.1)	
EBL, mL, median (IQR)	100 (50-300)	150 (50-250)	.35
Patients with blood transfusions, No. (%)			.86
No	74 (87.1)	72 (87.8)	
Yes	9 (10.6)	9 (11.0)	
Unknown	2 (2.4)	1 (1.2)	
Hospital stay, days, median (IQR)	7 (5-9)	8 (5-13)	.07

Abbreviations: CC, complete cytoreduction; EBL, estimated blood loss; HIPEC, hyperthermic intraperitoneal chemotherapy; RT, residual tumor; SCS, secondary cytoreductive surgery.
[a]Calculated on patients with bowel resection.

(residual tumor [RT] <0.25 cm) SCS in women with resectable, platinum-sensitive, recurrent OC, we found that primary SCS plus HIPEC did not result in longer PFS than primary SCS alone.

The median PFS was exceptionally long in both groups, reaching 24 months. This value is longer than expected, especially considering that only a small rate of women (14.4%) received maintenance treatment.

We found two possible explanations for the primary end point failure. The first one lies in the selection of extremely platinum-sensitive patients (median PFI, 18 months). The second explanation lies in the selection of patients at the time of surgery. Indeed, the vast majority of the patients in the study population (95%) achieved complete gross resection, with the remaining 5% having RT <0.25 cm, at the price of a simple/intermediate complexity of surgery in most of the cases (87% Surgical Complexity Score 1-2).

It is conceivable that these two inclusion criteria may be responsible for better PFS even in patients without HIPEC, thus making the study planned difference in median PFS unmeasurable.

These patient and tumor characteristics may also explain the differences in PFS compared with GOG213, DESKTOP-III, and SOC-1 trials. In these trials, the complete gross resection rate was 64%, 72.5%, and 76.5%, respectively, with a median PFS after the recurrence of around 18 months in the entire surgical arm and 19-21 months for the completely resected cases.[8-10]

The similar frequency and patterns of recurrence between treatment groups also support the lack of efficacy of platinum-based HIPEC in increasing local control, in the absence of significant intraperitoneal diffusion at the time of primary recurrence.

The high rate of BRCA mutations we found in the HORSE population (43.5%) represents another selection of patients with more favorable outcomes, which may also explain the negative results of the trial. Indeed, our data are in line with those presented by Koole et al,[23] regarding the absent effect of HIPEC on recurrence-free survival and OS in BRCAm tumors.

In conclusion, with the abovementioned limitations, no subgroups of women were found to benefit from the addition of HIPEC in terms of PFS, except for histotypes other than serous (Fig 3).

A very similar phase II randomized study was published in patients with platinum-sensitive recurrent OC receiving primary SCS with or without HIPEC. The authors showed that no treatment arm was able to reach the predefined number of 17 patients disease free at 24 months, thus concluding that HIPEC did not result in superior clinical outcomes than SCS only, in this setting of patients.[24]

This is not the case in the OVHIPEC-1 trial involving patients with prognostically unfavorable stage III OC who were all ineligible for primary cytoreduction owing to extensive abdominal disease.[13] Complete gross resection after NACT was achieved in around 70% of the cases versus 95.2% in the

TABLE 3. Adverse Events From Random Assignment to 6 Weeks After Completion of Last Cycle of Chemotherapy

	Arm A: SCS (n = 85[a])		Arm B: SCS + HIPEC (n = 82[a])	
Surgery-Related Adverse Event	All, No. (%)	G3-G4, No. (%)	All, No. (%)	G3-G4, No. (%)
Patients with at least one early complication	18 (21.2)	6 (7.1)	22 (26.8)	10 (12.2)
SSI	2	0	2	2
Urinary tract infection	2	0	2	0
Sepsis	1	0	1	0
Fever	3	0	1	0
Pancreatic leak	1	0	0	0
Pulmonary embolism	0	0	1	0
Pleural effusion	7	5	7	5
Pneumothorax	0	0	1	1
Bowel (sub)occlusion	2	1	1	0
Vomiting	2	0	0	0
Lymphocyst	0	0	1	1
Acute kidney injury[b]	0	0	4	0
Anemia	5	0	6	1
Ipokalemia	0	0	2	0
Atrial fibrillation	1	0	0	0
Patients with at least one late complication	7 (8.2)	4 (4.7)	5 (6.1)	3 (3.6)
Acute coronary syndrome	1	1	0	0
Bronchopneumonia	2	0	0	0
Sepsis	0	0	1	0
Laparocele	2	2	0	0
Lymphocyst	1	0	0	0
Vesico-vaginal fistula	1	1	0	0
CKI	0	0	1	0
Bowel (sub)occlusion	1	0	3	3

	Arm A: SCS (n = 72)		Arm B: SCS + HIPEC (n = 79)	
Chemotherapy-Related Adverse Event (CTCAE v4)	All, No. (%)	G3-G4, No. (%)	All, No. (%)	G3-G4, No. (%)
Patients with at least one complication	54 (75.0)	25 (34.7)	58 (73.4)	23 (29.1)
At least one hematological adverse event	45 (62.5)	22 (30.6)	43 (54.4)	20 (25.3)
Anemia	2 (2.7)	1 (1.3)	8 (10.1)	2 (2.5)
Platelet count decreased	11 (15.2)	6 (8.3)	10 (12.6)	6 (7.5)
WBC decreased	12 (16.6)	3 (4.1)	10 (12.6)	2 (2.5)
Neutropenia	20 (27.7)	12 (16.6)	15 (18.9)	10 (12.6)
At least one nonhematological adverse event	42 (58.3)	3 (4.2)	52 (65.8)	8 (10.1)
Mucositis	4 (5.5)	1 (1.3)	4 (5)	0
Fatigue	7 (9.7)	0	14 (17.7)	2 (2.5)
Nausea	13 (18)	0	16 (20.2)	2 (2.5)
Vomiting	2 (2.7)	0	6 (7.6)	1 (1.2)
Arthralgia	2 (2.7)	0	0	0
Constipation	2 (2.7)	0	1 (1.2)	0
Diarrhea	3 (4.1)	1 (1.3)	1 (1.2)	1 (1.2)
Alanine/AST increased	2 (2.7)	1 (1.3)	2 (2.5)	1 (1.2)

(continued on following page)

TABLE 3. Adverse Events From Random Assignment to 6 Weeks After Completion of Last Cycle of Chemotherapy (continued)

	Arm A: SCS (n = 72)		Arm B: SCS + HIPEC (n = 79)	
Chemotherapy-Related Adverse Event (CTCAE v4)	All, No. (%)	G3-G4, No. (%)	All, No. (%)	G3-G4, No. (%)
Chemotherapy allergy	2 (2.7)	0	1 (1.2)	0
Fever	0	0	1 (1.2)	1 (1.2)
Other	5 (6.9)	0	6 (7.6)	0

Abbreviations: CKI, chronic kidney impairment; CTCAE, Common Terminology Criteria for Adverse Events; HIPEC, hyperthermic intraperitoneal chemotherapy; SCS, secondary cytoreductive surgery; SSI, surgical site infection.
[a]One patient may have more than one complication.
[b]Three grade 1, one grade 2. Among them, one patient developed grade 1 chronic kidney disease.

HORSE trial. The lower dose of cisplatinum and the shorter timing of exposure, although within the recommended ranges, may also explain the lack of efficacy of HIPEC in this study compared with the OVHIPEC-1 trial. In addition, the Korean study (ClinicalTrials.gov identifier: NCT01091636) included a heterogeneous population of patients with stage III and IV advanced OC receiving HIPEC with 75 mg/m^2 of cisplatinum either at the time of primary cytoreductive surgery or after NACT.[25] Very recently, the CHIPOR trial[26] has been presented, showing significantly improved OS and peritoneal PFS of women with first platinum-sensitive relapse of epithelial ovarian cancer treated with second-line platinum-based chemotherapy followed by SCS and HIPEC.

The 30- and 90-day mortality rate was 0 in each group, and only two reinterventions were needed for postoperative complications (1.2%), all in arm A. These proportions are similar to those reported by the GOG213, DESKTOP III, and SOC-1 trials during SCS without HIPEC.[8-10] This finding supports the concept that appropriate patient selection for SCS is a cornerstone in the management of recurrent disease and that HIPEC does not increase postoperative morbidity.

Our study has some limitations. At the time of the trial design, no survival data were available from randomized trials in platinum-sensitive recurrent patients treated with cytoreductive surgery alone or with maintenance. The 6-month increase in PFS that we postulated in SCS plus HIPEC group was probably an overestimate. In addition, the probability of survival at 5 years was very high, since patients in the study received substantial systemic chemotherapy and targeted therapies that might have increased PRS. Finally, although not all events postulated in the study design were registered (139 of 144), the impact of the early termination was negligible on the power of this study.

However, the HORSE trial has its strength in the selection of a very homogeneous population, who was followed up for at least 24 months from random assignment in 91% of the cases.

In conclusion, we observed no additional benefit in PFS in patients with platinum-sensitive recurrent OC, treated with SCS plus platinum-based HIPEC compared with complete SCS alone. No extra toxicity related to HIPEC was reported.

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SUPPORT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Hyperthermic Intraperitoneal Chemotherapy in Platinum-Sensitive Recurrent Ovarian Cancer: A Randomized Trial on Survival Evaluation (HORSE; MITO-18)

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APPENDIX 1. HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY ADMINISTRATION

Hyperthermic intraperitoneal chemotherapy was administered at the end of surgery with the closed technique. In brief, the abdomen was filled with saline that circulated continuously with the use of a roller pump through a heat exchanger. An intra-abdominal temperature of 41.5°C was maintained. Once the target temperature was reached, perfusion with cisplatin (CDDP) 75 mg/m^2 at a flow rate of 1 L per minute was then initiated and maintained for 60 minutes. Urine production was maintained at a minimum of 1 mL per kilogram per hour during hyperthermic perfusion and for 3 hours after surgery. We did not use sodium thiosulfate as part of nephroprotection in the protocol. During hospitalization, patients' renal function was monitored by serum creatinine measurement in the first 3 postoperative days.

APPENDIX 2. INDEPENDENT DATA MONITORING COMMITTEE

Members of the Independent Data Monitoring Committee (IDMC) were Dr Gennaro Daniele, Medical Oncologist at Fondazione Policlinico Gemelli IRCCS, Rome; Prof Dr Gabe Sonke, Medical Oncologist and Epidemiologist at Netherlands Cancer Institute, Amsterdam; Dr Willemien van Driel, Gynecologist at Netherlands Cancer Institute, Amsterdam; Dr Oliver Zivanovic, Gynecologist at Memorial Sloan Kettering Cancer Center, New York; and Heidelberg University Hospital, Germany. In deciding to proceed to the primary analysis and study publication, the IDMC considered the following points:

1. In 11 months, between the two meetings, only one progression-free survival (PFS) event occurred to a patient.
2. The curve of events on time had reached a plateau (Appendix Fig A1).
3. The numbers of BRCA1-2 patients and those on treatment with PARP inhibitors are well balanced between the arms.
4. The difference between the two treatments in terms of both PFS and overall survival is not modifiable in any clinically relevant manner by the five events required for the formal analysis.

The importance of giving a contribution to the debate on the role of hyperthermic intraperitoneal chemotherapy suggested sharing our results.

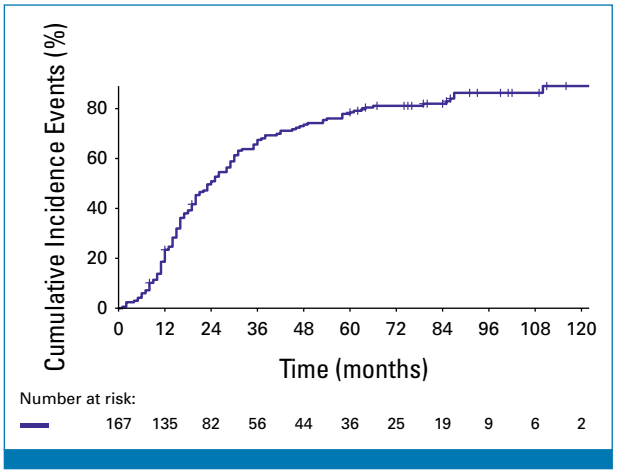

FIG A1. Cumulative incidence events' rate during the follow-up.

TABLE A1. Pattern of Recurrence

Relapse	Arm A: SCS, No. (%)	Arm B: SCS + HIPEC, No. (%)
All patients	85	82
All	65 (76.5)	70 (85.4)
Intraperitoneal	25 (38.5)	24 (34.3)
Intraperitoneal and extraperitoneal	9 (13.8)	11 (15.7)
Extraperitoneal	30 (46.2)	33 (47.1)
Unknown	1 (1.5)	2 (2.9)

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; SCS, secondary cytoreductive surgery.

TABLE A2. Chemotherapy Regimens

Chemotherapy Detail	Arm A: SCS	Arm B: SCS + HIPEC	*P*
All patients, No.	85	82	
Time to start chemotherapy, days, median (IQR)	46 (36-53)	43 (36-52)	.95
Chemotherapy regimen, No.			
Carboplatin-paclitaxel	12	16	
Carboplatin-gemcitabine	33	30	
Carboplatin-docetaxel	21	28	
Carboplatin	3	3	
Gemcitabine	4	1	
Cisplatin-gemcitabine	1	1	
Missing	11	3	
Maintenance treatment, No.			
Bevacizumab	9	10	
PARPi	3	2	
Olaparib	1	1	
Niraparib	2	1	

Abbreviations: HIPEC, hyperthermic intraperitoneal chemotherapy; PARPi, poly adenosine diphosphate ribose polymerase inhibitors; SCS, secondary cytoreductive surgery.