OV21/PETROC: A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer

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Abstract

Purpose

The purpose of this multistage, adaptively, designed randomized phase II study was to evaluate the role of intraperitoneal (IP) chemotherapy following neoadjuvant chemotherapy (NACT) and optimal debulking surgery in women with epithelial ovarian cancer (EOC).

Patients and Methods

We performed a multicentre, 2 stage, phase II trial. Eligible patients with stage IIB-IVA EOC treated with platinum-based intravenous (IV) NACT followed by optimal (<1cm) debulking surgery were randomized to one of 3 treatment arms: 1) IV carboplatin/paclitaxel; 2) IP cisplatin plus IV/IP paclitaxel, or 3) IP carboplatin plus IV/IP paclitaxel. The primary endpoint was 9 month progressive disease rate (PD9). Secondary endpoints included progression free survival (PFS), overall survival (OS), toxicity and quality of life (QOL).

Results

Between 2009 and 2015, 275 patients were randomized. IP cisplatin containing arm did not progress beyond the first stage of the study after failing to meet the pre-set superiority rule. The final analysis compared IV carboplatin/ paclitaxel (n=101) to IP carboplatin, IV/IP paclitaxel (n=102). The intention to treat PD9 was lower in the IP carboplatin arm compared to the IV carboplatin arm: 24.5% (95% CI 16.2%-32.9%) vs. 38.6% (95% CI 29.1%- 48.1%) p=0.065. The study was underpowered to detect differences in PFS: HR PFS 0.82 (95% CI 0.57 - 1.17); p=0.27 and OS HR 0.80 (95% CI

0.47-1.35) p=0.40. The IP carboplatin based regimen was well tolerated with no reduction in QOL or increase in toxicity compared to IV administration alone.

Conclusion

In women with stage IIIC or IVA EOC treated with NACT and optimal debulking surgery, IP carboplatin based chemotherapy is well tolerated and associated with an improved PD9 compared to IV carboplatin based chemotherapy. clinicaltrials.gov, NCT01622543

Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic malignancy in the developed world with the majority of women presenting with stage III/IV disease[1]. The peritoneal cavity is the principal site of disease and intraperitoneal (IP) chemotherapy has been investigated as a means of increasing the dose intensity delivered to the tumor[2]. At the time OV21/PETROC was conceived, three randomized clinical trials (RCTs) and a meta-analysis had demonstrated improved survival for women with stage III EOC who received a combination of intravenous (IV) and IP chemotherapy following optimal, primary debulking surgery[3-5]. An update of the most recent of these trials, GOG 172, confirmed a continued benefit for women who had received the experimental arm[6]. IP/IV chemotherapy, however, remains controversial[7,8]. Debate has centred on the impact of drug scheduling on the IP benefits and concerns over the toxicity of IP cisplatin, used in the positive studies, compared to IV carboplatin[9].

The use of neoadjuvant chemotherapy (NACT) prior to a definitive debulking attempt is increasingly used in advanced EOC[10,11] based on two RCTs which demonstrated non-inferiority and lower peri-operative morbidity compared to primary surgery followed by chemotherapy[12,13]. None of the IP/IV RCTs included patients who had undergone optimal debulking surgery following NACT.

OV21/PETROC investigated the hypothesis that women undergoing NACT followed by optimal debulking surgery would benefit from IV/IP chemotherapy.

Patients and Methods

Patients

Patients were eligible if they had histologically confirmed EOC, primary peritoneal or fallopian tube carcinoma, were FIGO[14] stage IIB-IVA (pleural effusion only) at initial diagnosis, had undergone 3 or 4 cycles of platinum based NACT followed (within 6 weeks) by optimal (≤1cm) debulking surgery and had an ECOG performance status of 0-2. Exclusion criteria included: mucinous or borderline histology, extensive intra-abdominal adhesions, bowel obstruction or unresolved > grade 2 peripheral neuropathy.

Trial Design

OV21/PETROC was a Gynecologic Cancer Intergroup (GCIG) study developed by the Canadian Clinical Trials Group (CCTG) in collaboration with the National Cancer Research Institute (UK) and was approved by institutional ethics boards of participating institutions. OV21/PETROC was a randomized multistage study. The initial stage of the study was designed to "pick the winner" of two IP chemotherapy regimens to carry forward into a two-arm (IV vs. IP) phase III comparison with progression free survival (PFS) as the primary outcome. However, due to poor accrual and following Independent Data Monitoring Committee review, the design was subsequently amended to an expanded two-arm phase II study using the primary outcome measure of PD9, defined as the proportion of patients with disease progression or death due to any cause occurring within 9 months of randomization (Figure 1).

Protocol Therapy

Randomization was permitted intraoperatively or within 6 weeks of debulking surgery using a central, web-based minimization procedure with the following stratification factors: Cooperative Group, reason for NACT (unresectable disease vs. other), residual disease (macroscopic vs. microscopic), and timing of IP catheter placement

(intraoperatively or post-operatively by interventional radiology) (see IR - Appendix protocol for details).

Protocol chemotherapy was administered every 21 days for 3 cycles. Stage I patients were randomized 1:1:1 to Arm 1: paclitaxel 135 mg/m^2 IV and carboplatin area under the curve (AUC) 5/6 IV on day 1 with paclitaxel 60 mg/m^2 IV on day 8; Arm 2: paclitaxel 135 mg/m^2 IV and cisplatin 75 mg/m^2 IP on day 1, with paclitaxel 60 mg/m^2 IP on day 8; or Arm 3: paclitaxel 135 mg/m^2 IV and carboplatin AUC 5/6 IP day 1, with paclitaxel 60 mg/m^2 IP on day 8. Subsequent to stage I, patients were randomized 1:1 to the IV arm (Arm 1) and the remaining IP arm. Carboplatin dosing was AUC 5 if a measured glomerular filtration rate (GFR) was available and AUC 6 if an estimated GFR was used. Doses were adjusted for grade 3 adverse events (AEs) (≥ grade 2 for neurotoxicity); while grade 4 AEs or ≥ grade 3 neurotoxicity led to drug discontinuation. Patients not tolerating IP chemotherapy were offered institutional standard IV chemotherapy.

Assessments and Outcome Measures

The primary endpoint for the study was PD9 rate. Disease progression was defined using RECIST V1.1 and/or GCIG CA125 criteria[15,16]. Secondary endpoints included PFS, OS, feasibility, safety and quality of life (QOL) assessed using questionnaires EORTC QLQ-C30[17], EORTC QLQ-OV28[18,19] and FACT/GOG-Ntx[20]. AEs were coded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Physical examination, biochemistry and CA125 were assessed on day 1 of each cycle and complete blood count on days1, 8 and 15. Imaging studies were done at the

end of treatment; every 6 months for 2 years and then as clinically indicated. Patients were reviewed (physical examination, CA125) post treatment at 6 weeks, every 3 months for 2 years, every 6 months years 2-4 then annually until death. QOL instruments were collected at 3, 6 and 12 months then annually.

Statistical Methods

First Stage

After the first 50 patients randomized to each arm had a minimum 9-month follow-up, an independent Data Safety Monitoring Committee (DSMC) reviewed PD9, compliance, and safety to determine if the trial should continue to the second stage. An IP arm would be considered as futile to continue if its PD9 was 5% or greater than that of the IV arm, which had an expected PD9 of 40% (based on results of a previous front-line randomized study[21] adjusted for the randomization timing in OV21/PETROC after NACT). If neither IP arm met criteria for futility, the arm with lower PD9 would be selected for the second stage unless ≥ 29 patients failed to complete that IP treatment due to toxicity.

Second Stage

A sample size of 200 in the second stage, including patients accrued in Stage I, permitted detection of a 19% difference in PD9 between Arms 1 (assumed to be 40%) and the selected IP arm (Arm 3) with 80% power at two-sided 0.05 level. This absolute difference was considered relevant based PD9 data extrapolated from GOG172[4]. The final analysis of both intention to treat (ITT- as randomized) and per protocol (eligible, received at least one dose of protocol treatment, not lost to follow-up or consent withdrawal) populations was performed once all patients had 9-month follow-up. A

stratified Cochran-Mantel-Haenszel (CMH) test adjusting for stratification factors at randomization was the primary method used to compare PD9 between the two treatment arms. Odds ratio and associated 95% confidence interval were obtained from stratified logistical regression models. PFS and OS were summarized using Kaplan-Meier plots and compared using the stratified log rank test. Estimates of the relative treatment differences were obtained from hazard ratios (HRs) and 95% CIs from stratified Cox regression models.

Analyses of QOL data using previously described methodology[22,23], were restricted to patients who had a baseline and at least one assessment on study. Chi-square test was used to compare the distributions of response categories between arms.

Safety was evaluated in patients who received at least one dose of protocol therapy.

Results

Patients and Protocol Treatment Received

Between September 2009 and May 2015, 275 patients were randomized: 101 in Arm 1(IV alone), 72 in Arm 2 (IP cisplatin based regimen) and 102 in Arm 3 (IP carboplatin based regimen). 254 patients received at least one dose of protocol therapy (Figure 1). 72 patients were accrued to Arm 2 since accrual was not halted while awaiting Stage I outcomes.

Baseline characteristics by treatment arm are presented in Table 1. The three groups were well balanced and the median time from diagnosis to randomization was 3 months. The majority of participants (72.8 %) underwent intraoperative randomization.

Most patients (88% Arm 1, 72% Arm 2, and 76% Arm 3) were able to complete three cycles of chemotherapy. Seven IP patients crossed over to IV chemotherapy (3 in Arm 2 and 4 in Arm 3).

Efficacy

First Stage

Stage 1 analysis included 51 patients on each arm. The PD9 at this time was 37.3% on Arm 1, 45.1% on Arm 2, and 27.5% on Arm 3. As per the statistical plan, Arm 2 accrual was discontinued. Follow-up was maintained on all patients until the final analysis.

Second Stage

A total of 203 patients were enrolled in Arms 1 and 3. As shown in Table 2, for the ITT population, the PD9 was 38.6% (95% CI 29.1 to 48.1) in Arm 1 (IV), and 24.5% (95% CI 16.2 to 32.9) in Arm 3 (IP carboplatin), p = 0.065. For the per protocol population analysis, the PD9 was 42.2%, (95% CI 31.9 to 53.1) Arm 1 and 23.3%, (95% CI 15.1 to 33.4) Arm 3, p= 0.03.

At the time of data cut off (February 28, 2016) the median follow-up was 33 months. The median PFS was 11.3 months in Arm 1 and 12.5 months in Arm 3 (Figure 2) with a hazard ratio of 0.82 95% CI (0.57 to 1.17). The 2-year OS was 74.4% in Arm 1, and 80.6% in Arm 3 (Figure 3), HR 0.80, 95% CI (0.47 to 1.35) (Figure 3).

Adverse Events

Severe treatment related (≥ grade 3) AEs during protocol therapy occurred in 23% of patients in Arm 1, 22% in Arm 2, and 16% Arm 3 (p=NS, details in Supplemental Table

1). The most common severe AEs (≥ 5% in at least one treatment arms) were febrile neutropenia (Arm 1: 5.3%, Arm 2: 1.5%, Arm 3: 1.1%) and abdominal pain (Arm 1: 1.1%, Arm 2: 6.0%, Arm 3: 1.1%). Catheter-related complications, obstruction being the most common, led to treatment discontinuation in 8 (11.9%) patients in Arm 2 and 7 (7.6%) in Arm 3.

Quality of Life

Compliance with QOL assessment was 87% at baseline and 80% at 6 months across arms. No statistically significant difference between arms was found on any scale. In particular, no differences were seen in peripheral neuropathy or gastrointestinal symptoms scales at baseline or in follow-up between all arms. Significant improvements in gastrointestinal functioning over time were seen in all arms (see detailed QOL response by treatment arm in Supplemental Figure 1).

Discussion

OV21/PETROC was designed to answer two clinically important questions: The role of IP/IV chemotherapy in the NACT patient population and to provide RCT data on an IP carboplatin-based regimen. The study demonstrates that IP/IV chemotherapy is safe and well tolerated in this patient population with no detriment to QOL. Whilst delivery of IP/IV chemotherapy was associated with an 17.7% improvement in the PD9 (ITT) (18.9% improvement, per protocol treatment), similar to that extrapolated from GOG 172[4], the trial is underpowered to draw firm conclusions about PFS and OS. OV21/PETROC provides data for discussion with patients around the use of IP carboplatin based regimens which have, in some cases, been adopted in the community without RCT data[8].

OV21/PETROC had a novel, adaptive, 2 stage design. The PD9, post randomization, endpoint was selected as a surrogate measure of efficacy to allow for a seamless transition into the second stage of the trial. To avoid the criticism levelled at previous studies the regimens included in the trial were balanced for both schedule and dose of paclitaxel and carboplatin[9]. As a result, the IV reference arm (with day 8 paclitaxel) was not a previously reported, standard of care. However, the observed PD9 of 42.2% is reassuringly consistent with the (40%) rate observed for the IV arm in our previous study[21]. At the end of the first stage of this trial, Arm 2 (IP cisplatin) was discontinued due to lack of efficacy compared to the IV regimen. The prior positive, frontline IP RCTs investigated regimens containing IP cisplatin 100 mg/m^2 [3-5]. Our use of a lower dose (cisplatin 75 mg/m^2) was based on concerns over toxicity at 100mg/m^2 and this may have impacted efficacy. These data plus the initial findings of GOG 252, that also show no benefit for IP cisplatin at 75mg/m^2 [24], do not support using 75mg/m^2 cisplatin IP in practice.

A major limitation of OV21/PETROC was the revision of the statistical design for the second stage of the trial. The independent DSMC were asked to make a recommendation, based on the study's potential to provide clinically useful information, to either stop the trial or to continue with a limited expansion into the 2-arm stage. Whilst acknowledging that PD9 represented an unconventional endpoint, the DSMC recommended amending the protocol. In addition, the comparison of IP and IV carboplatin based regimens provides additional data on QOL and toxicity. Further data on the upfront use of IP carboplatin (alone) is awaited from the JGOG iPocc study and survival analysis of GOG 252 which also investigated an IP carboplatin arm[24].

Placing the OV21/PETROC data in the context of other NACT studies is challenging given that study entry/randomization was at the time of debulking surgery. However, in over 80% of cases the decision to select NACT was inoperable disease with over 90% having stage IIIC-IV disease. This aligns with entry requirements for other NACT studies[12,13]. Median OS (from randomization) observed in OV21/PETROC (microscopic and < 1cm) was 38.1 months in the IV arm and 59.3 months for the IP/IV arm. Making a conservative presumption of 10 weeks from date of first pre-operative chemotherapy to randomization (3 cycles of chemotherapy and median 4-week time interval to surgery in OV21/PETROC) that would translate into an OS from diagnosis of 40.6 months in the IV arm and 61.8 months in the IP/IV arm. Whilst the comparison is crude, the IV arm of OV21/PETROC does appear to be performing in a similar range to the other NACT studies. The IP arm is certainly no worse than the IV arm and, had the study been completed as originally intended, raises the intriguing possibility that it may have been better.

Interpretation of the clinical relevance of OV21/PETROC is limited by the lack of power to detect changes in PFS and OS. IP chemotherapy remains controversial. OV21/PETROC does, however, provide RCT data both to support the use of IP carboplatin, and to inform clinicians and patients when making choices about subsequent therapy following NACT and optimal debulking surgery. Correlative studies are planned to identify potential predictive biomarkers and inform the design of future clinical trials.

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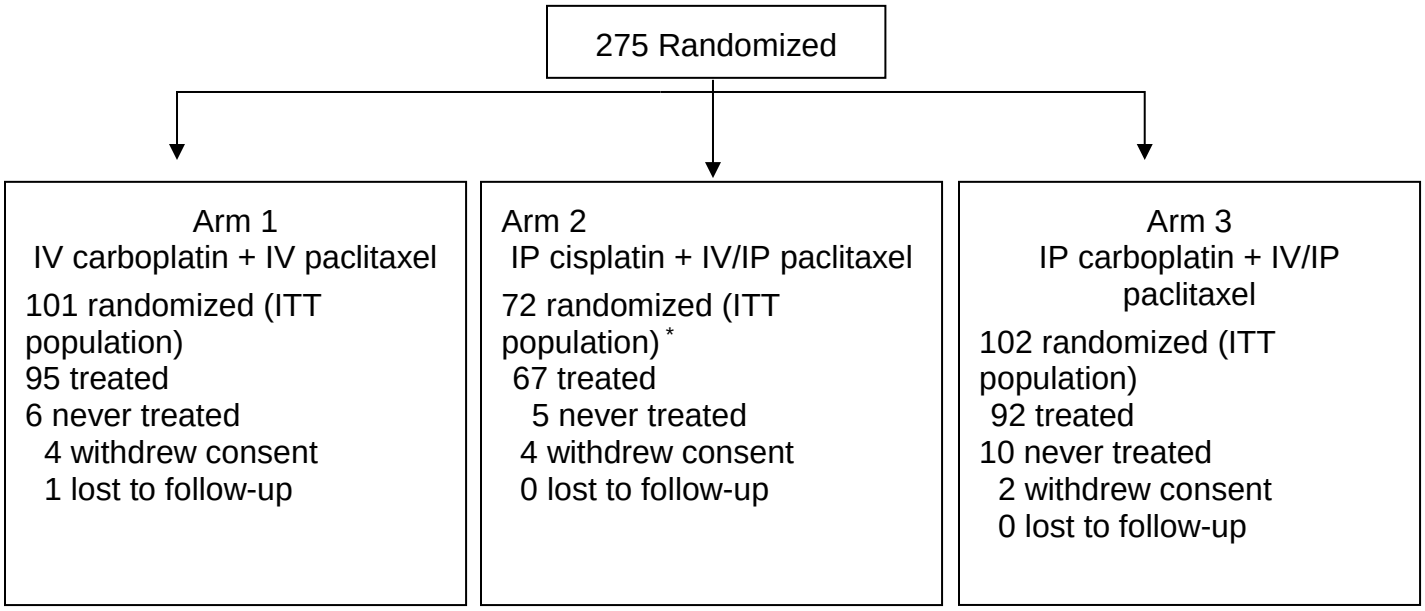
Figure Legends

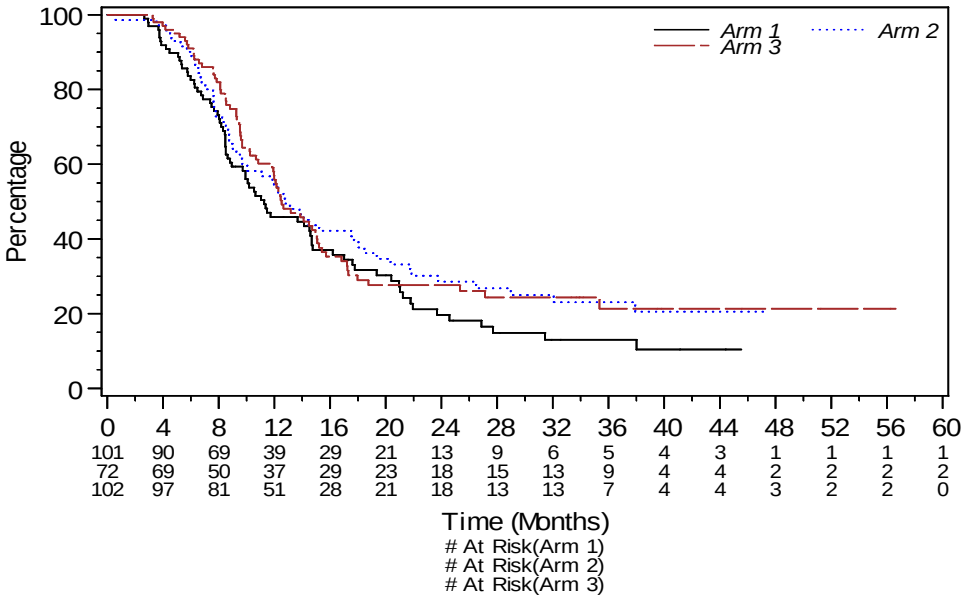
Figure 1: OV21/PETROC Flow Diagram

Figure 2: PFS Arm 1: IV carboplatin + IV paclitaxel; Arm 2: IP cisplatin + IV/IP paclitaxel; Arm 3: IP carboplatin + IV/IP paclitaxel

Figure 3: Overall Survival - Arm 1: IV carboplatin + IV paclitaxel; Arm 2: IP cisplatin + IV/IP paclitaxel; Arm 3: IP carboplatin + IV/IP paclitaxel

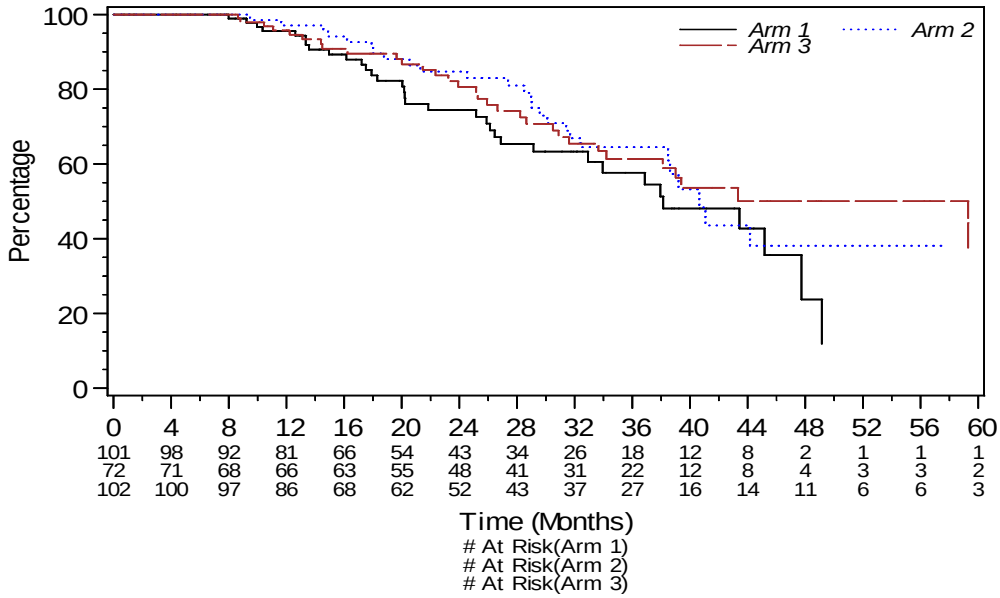
Figure 1: OV21/PETROC Flow Diagram





(a)

Figure 2: PFS Arm 1: IV carboplatin + IV paclitaxel; Arm 2: IP cisplatin + IV/IP paclitaxel; Arm 3: IP carboplatin + IV/IP paclitaxel



(b)

Figure 3: Overall Survival - Arm 1: IV carboplatin + IV paclitaxel; Arm 2: IP cisplatin + IV/IP paclitaxel; Arm 3: IP carboplatin + IV/IP paclitaxel

Table 1: Characteristics of Patients and Treatments

	Arm 1 (N=101) IV carboplatin + IV paclitaxel	Arm 2 (N=72) IP cisplatin + IV/IP paclitaxel	Arm 3 (N=102) IP carboplatin + IV/IP paclitaxel	Total (N=275)
Age				
Median (range), years	62 (33-83)	61 (29-78)	62 (40-82)	62 (29-83)
≤ 65	65 (64.4)	52 (72.2)	71 (69.6)	188 (68.4)
> 65	36 (35.6)	20 (27.8)	31 (30.4)	87 (31.6)
Race or ethnic group				
White	92 (91.1)	67 (93.1)	95 (93.1)	254 (92.4)
Black or African American	1 (1.0)	1 (1.4)	1 (1.0)	3 (1.1)
Asian	5 (5.0)	1 (1.4)	4 (3.9)	10 (3.6)
Other	3 (3.0)	3 (4.2)	2 (2.0)	8 (2.9)
ECOG performance status				
0	46 (45.5)	41 (56.9)	49 (48.0)	136 (49.5)
1	53 (52.5)	29 (40.3)	47 (46.1)	129 (46.9)
2	2 (2.0)	2 (2.8)	6 (5.9)	10 (3.6)
Primary site				
Ovary	75 (74.3)	55 (76.4)	73 (71.6)	203 (73.8)
Peritoneal	17 (16.8)	16 (22.2)	20 (19.6)	53 (19.3)
Fallopian tube	6 (5.9)	1 (1.4)	7 (6.9)	14 (5.1)
Other or unknown	3 (3.0)	0 (0.0)	2 (2.0)	5 (1.0)
Histologic type				
Serous adenocarcinoma	95 (94.1)	69 (95.8)	95 (93.1)	259 (94.2)
Adenocarcinoma, unspecified	3 (3.0)	2 (2.8)	3 (2.9)	8 (2.9)
Other or unknown	3 (3.0)	1 (1.4)	4 (3.9)	8 (2.9)
Histologic grade				
Poorly differentiated or undifferentiated (III)	91 (90.1)	65 (90.3)	96 (94.1)	252 (91.6)
Intermediate differentiation (II)	3 (3.0)	5 (6.9)	3 (2.9)	11 (4.0)
Unknown	7 (6.9)	2 (2.8)	3 (2.9)	12 (4.4)
Months from histologic diagnosis to randomization				
Median (range)	3.0 (0-4.7)	2.8 (0-5.9)	3.2 (0-5.3)	3.0 (0-5.9)
Stage at initial diagnosis				
IIB	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.4)
IIC	0 (0.0)	1 (1.4)	1 (1.0)	2 (0.7)
IIIB	6 (5.9)	0 (0.0)	6 (5.9)	12 (4.4)
IIIC	82 (81.2)	61 (84.7)	82 (80.4)	225 (81.8)
Iva	12 (11.9)	10 (13.9)	13 (12.7)	35 (12.7)
Reason for NACT before debulking surgery				
Unresectable disease	85 (84.2)	61 (84.7)	84 (82.4)	230 (83.6)
Other	16 (15.8)	11 (15.3)	18 (17.6)	45 (16.4)
Delayed interval debulking surgery				
Weeks from NACT last cycle to surgery				
Median (range)	4.1 (2.4-6.9)	4.1 (1.6-6.3)	4.0 (1.7-6.1)	4.1 (1.6-6.9)
Presence of disease at end of surgery	40 (39.6)	30 (41.7)	37 (36.3)	107 (38.9)
Days from surgery to randomization				
0 (peroperative)	78 (77.2)	58 (80.6)	78 (76.5)	214 (72.8)
1-7	4 (4.0)	0 (0.0)	1 (1.0)	5 (1.8)
8-14	1 (1.0)	1 (1.4)	2 (2.0)	4 (1.5)
≥ 15	18 (17.8)	13 (18.1)	21 (10.6)	52 (18.9)
Days from surgery to day 1 of cycle 1				
Median (range)	28 (5-50)	32 (7-56)	32 (7-51)	31 (5-56)

Data are number (percentage) unless otherwise specified
IP=intraperitoneal; IV=intravenous; NA- not applicable; NACT=neoadjuvant chemotherapy

Table 2: Progression Events (ITT analysis)

	Arm 1 (N=101) IV carboplatin + IV paclitaxel		Arm 2 (N=72) IP cisplatin + IV/IP paclitaxel		Arm 3 (N=102) IP carboplatin + IV/IP paclitaxel		Crude differences in cumulative incidence of PD9
	N	**% (95%CI)**	**N**	**% (95%CI)**	**N**	**% (95%CI)**	**% (95%CI)**
Progression or death at or before Month 9	39	38.6 (29.1- 48.1)	25	34.7 (23.7- 5.7)	25	24.5 (16.2 -32.9)	
Arm 1 versus Arm 3							14.1 (1.5-26.7)
Arm 2 versus Arm 3							10.2 (-3.6-24.0)
Time of event							
First relapse/Progression on treatment	0		1		0		
Objective progression only	0		0		0		
CA125 progression only	0		0		0		
Both objective and CA125 progressions	0		1		0		
First relapse/Progression during follow-up	39		24		24		
Objective progression only	17		5		7		
CA125 progression only	0		0		0		
Both objective and CA125 progressions	22		19		17		
Death (without relapse/progression)	0		0		1		

IP=intraperitoneal; IV=intravenous

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Appendix – See attached NCIC CTG OV.21 Protocol