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Final report on serial phase II trials of all-intraperitoneal chemotherapy with or without bevacizumab for women with newly diagnosed, optimally cytoreduced carcinoma of Müllerian origin

C.N. Krasner [a,*], C. Castro [b], R.T. Penson [b], M. Roche [c], U.A. Matulonis [a], M.A. Morgan [d], C. Drescher [e], D.K. Armstrong [f], J.K. Wolfe [g], H. Lee [b], J.G. Supko [b], M. Seiden [h], M.J. Birrer [i], D.S. Dizon [j]

[a] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States of America
[b] Department of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, United States of America
[c] Blueprint Bio, Cambridge, MA, United States of America
[d] Division of Gynecologic Oncology, University of Pennsylvania, Philadelphia, PA, United States of America
[e] Translational Research Program, Division of Gynecologic Oncology, Fred Hutchinson Cancer Center, Seattle, WA, United States of America
[f] Department of Medical Oncology, Johns Hopkins University Medical Center, Baltimore, MD, United States of America
[g] Community Health, Indianapolis, IN, United States of America
[h] US Oncology, United States of America
[i] Department of Medical Oncology, University of Alabama, Birmingham, AL, United States of America
[j] Department of Medical Oncology, Rhode Island Hospital, United States of America

HIGHLIGHTS

- Weekly administered IP carboplatin and IP paclitaxel is tolerable
- Peak plasma concentration of free platinum was approximately 40% lower when carboplatin was given IP compared to IV.
- Addition of bevacizumab resulted in higher toxicity.

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ABSTRACT

Background. Intraperitoneal (IP) chemotherapy can improve outcomes for women with optimally cytoreduced epithelial ovarian cancer but toxicities are a concern. We conducted 2 phase 2 trials of an IV/IP regimen using carboplatin and paclitaxel without (Trial A) and with bevacizumab (Trial B).

Methods. Both trials consisted of carboplatin AUC 6 day 1, and paclitaxel 60 mg/m^2 on days 1,8, 15 of a 21-day cycle; in Trial B, patients received IV bevacizumab 15 mg/kg every cycle starting cycle 2. Chemotherapy was administered IV for cycle 1 and then IP for all subsequent cycles. Primary objectives included safety and tolerability, pathologic CR rate (Trial A), and the rate of completion of IP cycles of therapy (Trial B). Progression-free (PFS), overall survival (OS), and pharmacokinetic analysis were secondary endpoints.

Results. 81 patients were treated on both trials (n = 40 and 41 in trials A and B, respectively). Median age for trials A and B was 59 (range, 36–76) and 55 (range, 19–69) years, respectively. 68% and 85% of patients, respectively for A and B, completed at least 4 cycles of treatment in both trials. Treatment with bevacizumab resulted in higher rates of grade 3 fatigue (37 versus 33%) and grade 3–4 diarrhea (22 versus 8%). Median PFS was 23.5 (95% CI 16.2–35.3) and 25 (95%CI 16.4–42.7) months, respectively; median OS was 68 (95%CI 49.5-NR) and 79.7 (95% CI 59.0–79.7) months, respectively for Trial A and B.

Conclusions. Weekly administered IP carboplatin and IP paclitaxel is tolerable and safe with similar activity with and without concommittant bevacizumab in these 2 trials.

* Corresponding author at: Division of Gynecologic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, United States of America.
E-mail addresses: Carolyn_krasner@dfci.harvard.edu (C.N. Krasner), mroche2@blueprintmedicines.com (M. Roche), Mark.Morgan@uphs.upenn.edu (M.A. Morgan), cdresche@fredhutch.org (C. Drescher), armstde@jhmi.edu (D.K. Armstrong), JWolf4@ecommunity.com (J.K. Wolfe), Michael.seiden@mckesson.com (M. Seiden), mbirrer@uab.edu (M.J. Birrer), don.dizon@lifespan.org (D.S. Dizon).

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1. Introduction

Epithelial ovarian cancer is the second most common malignancy of the gynecologic tract, yet is the most lethal of these malignancies [1]. For most patients, treatment consists of surgical cytoreduction followed by adjuvant platinum- and taxane-based chemotherapy. There are multiple accepted treatment options for patients who have undergone an optimal cytoreduction, including the use of intravenous (IV) chemotherapy administered weekly [2–4] or every 3 weeks [5], the combined administration using IV and intraperitoneal (IP) therapy [8], and IV platinum-based combination chemotherapy plus the angiogenesis inhibitor, bevacizumab [6,7].

The concept of regional drug delivery in the treatment of ovarian cancer was first proposed by Dedrick, to maximize drug delivery to the prevalent sites of residual tumor [9]. High concentrations of drugs can be achieved and maintained for prolonged periods of time within the IP cavity. In addition, capillary uptake of the drug from the peritoneal cavity allows therapeutic concentrations to be achieved systemically. Available evidence suggests that patients undergoing IP therapy are more likely to first recur outside the abdominal cavity, suggesting effective peritoneal control [10].

A meta-analysis confirmed that for women with advanced ovarian cancer who undergo an optimal cytoreduction to <1 cm of residual disease postoperatively, there is a survival advantage when IP therapy is incorporated in to the upfront treatment of optimally cytoreduced ovarian cancer [8]. The most commonly used regimen in the US comes from the seminal Gynecologic Oncology Group 172 trial (GOG 172), which utilized IV paclitaxel 135 mg/m^2 over 24 h on day 1, IP cisplatin 100 mg/m^2 on day 2, and IP paclitaxel 60 mg/m^2 on day 8 every 21 days [11]. However, utilization of this regimen has become limited. Wright and colleagues reported this finding in a study of the National Comprehensive Cancer Network [12]. Between 2003 and 2006 there was an increase in the use of IP chemotherapy from 0 to 33%, which peaked in 2007–2008 to 50%. However, since then there was a decline with 43% use between 2009 and 2012. In addition, Wright reported that of those receiving IP therapy, only 29% received treatment as described in GOG 172, with 43% of patients treated with a modified IP regimen.

The first-line treatment of ovarian cancer has moved beyond IP treatment as well. Today, the angiogenesis inhibitor, bevacizumab, is now United States Food and Drug Administration (FDA) approved with standard IV carboplatin and paclitaxel as upfront treatment for women with newly diagnosed ovarian cancer based on the improvement in progression free survival (PFS) seen in GOG 218. While this therapeutic approach does not improve OS as compared to non-bevacizumab regimens, the prolongation of first remission was felt to supportive of approval [4,6,7]. The preliminary results of GOG 252, a 3-arm randomized trial comparing 2 IP-containing regimens (GOG 172 using a modified cisplatin dose from 100 to 75 mg/m2 given IP on day 2 or the incorporation of IP carboplatin to weekly IV paclitaxel) to IV carboplatin and paclitaxel as given in GOG 262, where patients in all 3 arms received bevacizumab, did not demonstrate a difference in clinical outcomes among the 3 treatment arms [13].

Despite the evolution of treatment paradigms for the first-line treatment of ovarian cancer, interest in IP chemotherapy for ovarian cancer still persists, particularly in view of the OS advantages seen in phase 3 trials (in absence of bevacizumab). Hence, we were interested in evaluating an all IP administered regimen, either alone or in combination with bevacizumab to assess feasibility, tolerability and efficacy. Here we report the efficacy and toxicity of 2 such trials performed at our center. In the first (Trial A), we evaluated the feasibility of a novel regimen utilizing carboplatin on day 1 with weekly paclitaxel on days 1,8, and 15, with all treatments administered IP starting at cycle 2. In the second trial (Trial B), we evaluated this same IP chemotherapy regimen in combination with bevacizumab delivered intravenously. The primary objectives were determining the safety and tolerability of the regimens (A and B) and determining pathologic CR rate (Trial A). Secondary objectives included PFS, OS, and PK evaluation of both regimens.

2. Methods

2.1. Patients

Eligible patients had advanced epithelial ovarian cancer, peritoneal cancer or fallopian tube cancer who achieved an optimal cytoreduction to ≤1 cm of residual disease; resection to no gross residual disease (R0) was not required or specified as part of eligibility. All histological subtypes, including carcinosarcoma, were allowed to enroll. Patients with colostomy or ileostomy or evidence of significant intra-abdominal adhesions were excluded. All patients had to be candidates for and willing to undergo IP therapy. All patients were over the age of 18 and were required to have an Eastern Cooperative Oncology Group performance status of ≤2. Adequate hematologic, renal, and hepatic function were required. All patients gave written informed consent. The study was reviewed and approved by the institutional review board of the involved hospitals and was monitored by the Dana-Farber/Harvard Cancer Center Data Safety Monitoring Committee. These trials were registered with clinicaltrials.gov (Trial A, NCT00181701; Trial B, NCT00652119). Although all patients with stage IV disease were excluded in Trial A, women with stage IV disease on the basis of a malignant pleural effusion alone were allowed to enroll in Trial B.

2.2. Study treatment

Patients with newly diagnosed ovarian cancer were consented in either the pre- or post-operative period following surgical cytoreduction, which allowed for placement of the IP port as part of the initial surgery or at a later date during a second surgical procedure. A Bard IV port (BardPort® Single-Lumen Implanted IV Port (Bard Access Systems)) as per institutional standard was used and typically anchored on the lower right ribcage and tunneled.

The chemotherapy regimen consisted of a total of 6 cycles of therapy, with each cycle running over 21 days (Fig. 1). Patients underwent a history and physical exam weekly during the study. A complete blood count was performed weekly; chemistries and CA-125 levels were drawn prior to day 1 of each cycle. In both trials, patients received IV treatment in cycle 1, consisting of carboplatin AUC 6 on day 1 and paclitaxel 60 mg/m^2 on days 1, 8, and 15. Patients were pre-treated with oral dexamethasone (20 mg) the night before and morning of each paclitaxel infusion. In addition, patients were premedicated with IV cimetidine, IV diphenhydramine, and IV dexamethasone prior to paclitaxel infusion. Standard antiemetics consisting of ondansetron and lorazepam were administered prior to carboplatin. For cycles 2 through 6, all patients received IP carboplatin AUC 6 and IP paclitaxel 60 mg/m^2 on days 1, 8, 15. Oral dexamethasone premedication was mandated prior to each planned paclitaxel infusion, although patients who completed the first 2 cycles without a hypersensitivity reaction were allowed to taper it off for subsequent cycles. The same IV premedications and antiemetics used for the IV cycle were continued for subsequent treatments. In Trial B, patients also received IV bevacizumab (15 mg/kg) on day 1 starting at cycle 2 through 6. Maintenance bevacizumab after chemotherapy was not given. Following IP infusion of chemotherapy, patients were administered 500–1000 mL of normal saline IP warmed to room temperature as tolerated. Patients were also instructed to change positions every 10–15 min following IP infusion to ensure adequate drug distribution.

2.3. Dose modifications and adjustments

The dose modification and adjustment plans for both trials were similar. Decisions on treatment were based on complete blood counts obtained within 24 h of planned treatment. An absolute neutrophil

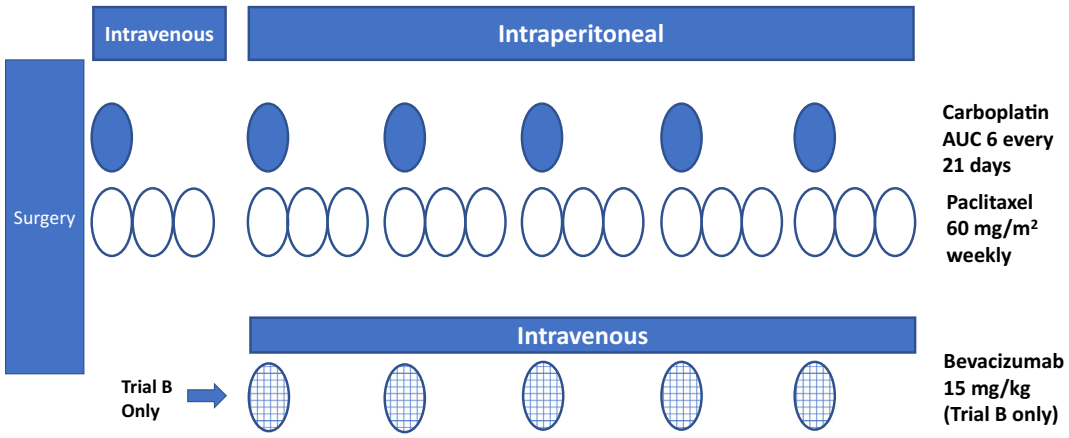

Fig. 1. Schema for the 2 clinical trials. Both trial A and B used IV carboplatin and IV weekly paclitaxel for cycle 1; both studies tested IP carboplatin and IP weekly paclitaxel for cycles 2 through 6. Trial B added IV bevacizumab 15 mg/kg from cycles 2 through 6.

count (ANC) ≥1000 cells/mL and platelet count ≥100,000 were required prior to day 1 of each cycle. For patients with an ANC 800–999 both paclitaxel and carboplatin were reduced for subsequent cycles to 50 mg/m^2 and AUC 5, respectively. If the platelet count was 80–99,000 on day 1, carboplatin alone was dose reduced to AUC 5. If ANC <800 or platelets <80,000, chemotherapy was held for up to 1 week. If hematologic blood counts recovered, treatment proceeded at reduced doses. Once dose reduced, re-escalation was not permitted.

For treatment with single agent paclitaxel on days 8 and 15, ANC ≥1000 cells/mL and platelet count ≥100,000 were required within 24 h of planned treatment. If ANC 750–999 and/or platelet count 80–99,000, paclitaxel was dose reduced to 50 mg/m^2. If ANC <750 and/or platelet count was <80,000, that dose of paclitaxel was not administered. No missed doses were made up in subsequent cycles. Patients who did not recover hematologic counts by 21 days were given 14 additional days for hematologic recovery, after which they were removed from study treatment. For patients who experienced neutropenic fever, treatment resumed only after clinical recovery. For subsequent cycles, patients were placed on filgrastim. Dose adjustments for abdominal pain were made based on the worst intra-cycle toxicity reported. Two dose-level reductions for both paclitaxel and carboplatin were allowed in this protocol: dose level −1 consisted of paclitaxel 50 mg/m^2 and/or carboplatin AUC 5; dose level −2 consisted of paclitaxel 40 mg/m^2 and/or carboplatin AUC 4. Pain >grade 1 on day of treatment dictated a treatment hold, which was allowed for up to 14 days. Any pain that did not resolve within 35 days prompted treatment discontinuation. In addition, patients who experienced recurrent episodes of grade 3 pain despite dose reductions were discontinued from treatment. Any patient experiencing grade 4 pain despite maximal management were removed from study treatment. If pain occurred within the first seven days of a cycle, both carboplatin and paclitaxel were dose-reduced for subsequent treatments. If pain occurred on days 8 to 21, dose reduction of paclitaxel was required.

There were no reductions in the dose of bevacizumab in Trial B. However, if a toxicity occurred that required holding of bevacizumab, chemotherapy could still be administered if all other retreatment criteria were met. Following resolution of toxicities, bevacizumab was restarted without any dose reductions. All toxicities related or possibly related to bevacizumab were managed according to standard medical practice. Bevacizumab was permanently discontinued if any of the following events occurred: toxicity lasting 6 weeks or longer; grade 4 hypertension; grade 2 or greater pulmonary or central nervous system hemorrhage; any arterial thromboembolic event; grade 4 congestive heart failure; grade 4 proteinuria (nephrotic syndrome); any wound dehiscence requiring surgical or medical treatment; and any grade 4 toxicity that was at least possibly related to bevacizumab.

2.4. Pharmacokinetics

Blood samples were collected during cycles 1, 2, and 6 shortly before dosing and at the following times relative to the beginning of the paclitaxel infusion: 0.25, 0.50, 1.0, 1.2, 1.5, 2.0, 2.5, 3, 4, 6, 8, 24, and 48 h. The samples designated for collection at 1.0 h and 2.0 h were drawn several minutes before the end of the paclitaxel and carboplatin infusions, respectively. At each time point, blood (5 mL) was drawn from a peripheral vein in the arm not used for infusing the drugs into a collection tube with freeze-dried sodium heparin. The blood was centrifuged (1300 *g*, 4 °C, 10 min) to afford plasma which was stored at −70 °C. The concentration of paclitaxel in plasma was determined by isocratic reversed-phase high performance liquid chromatography with mass spectrometric detection and the concentration of free platinum in plasma ultrafiltrate was measured by flameless atomic absorption spectrometry, as previously reported [16,17]. Plasma concentration-time curves were analyzed by standard noncompartmental methods using WinNonlin Professional 5.0 software (Pharsight Corp., Cary, NC). The duration of time that the concentration of paclitaxel in plasma exceeded 50 nM was determined by logarithmic-linear interpolation of the plasma concentration-time data. Mean values of the pharmacokinetic variables for each cycle of therapy were calculated as the geometric mean of the individual patient values and the standard deviation estimated by the Jacknife method [18,19]. Mean pharmacokinetic parameters for different cycles of therapy were statistically compared using the two-tailed *t*-test after logarithmic transformation of the data, with $P < 0.05$ considered to be significantly different.

2.5. Response definitions

A clinical complete response (cCR) was defined as a normal post-treatment CA-125 value without imaging evidence suspicious for intraperitoneal or distant metastases. In addition, any non-measurable disease (i.e., ascites or pleural effusion) should be absent, and the physical exam (including pelvic examination) had to be within normal limits. Of note, imaging evidence of lymphocysts or non-specific findings of omental or pleural thickening were not considered as evidence of disease if the clinical exam and remainder of scan were normal and the CA-125 value was within normal limits.

A partial response (PR) was characterized as a reduction in the sum of 2 perpendicular diameters of any lesion by >50%. There had to be no imaging evidence of disease progression and no evidence of non-measurable disease (i.e., ascites and pleural effusion).

Microscopic positive second look laparotomy was defined as the absence of tumor on physical exam, chest x-ray and a normal laparotomy-

directed inspection of the peritoneal cavity. Patients with positive washings and/or biopsies consistent with malignancy were considered to have a microscopic positive second look procedure. For patients who enrolled without evidence of measurable disease, the CA-125 value was used to determine response based on Rustin criteria [14].

2.6. Statistical plan

2.6.1. Trial A

In order to determine the efficacy of this protocol regimen, the main endpoints are defined as the proportion of patients with a negative second-look laparotomy (pCR) and determining the safety and tolerability of the regimen. Patients who signed informed consent but were not ultimately optimally cytoreduced, those with stage IV disease, those who withdrew from study treatment for reasons unrelated to disease progression, and those who were candidates for SLL but did not undergo this procedure for whatever reason, were excluded from the denominator for efficacy (pCR rate). We defined criterion for efficacy in this group as a 70% pCR rate, while 45% or less was considered not promising to be worthy of subsequent evaluation. With enrollment of 40 patients, the probability of observing 24 or more patients who achieved a pCR is 93.7% when the true rate is 70% whereas it is <4% if the true rate was 45%. Therefore, if at least 24 patients had a pCR, we could sufficiently exclude the true rate of 45% and deem this regimen to be potentially efficacious. To account for a potential dropout rate of 15% (for reasons unrelated to the protocol), this study was designed to enroll 46 women with an anticipated yield of 40 evaluable patients.

2.6.2. Trial B

Given the preliminary efficacy data achieved in Trial A, Trial B was performed to determine the tolerability and feasibility of the IP paclitaxel and carboplatin with IV Bevacizumab. Given this endpoint, we adopted the proportion of the patients who complete the entire course as the primary analysis endpoint. The preliminary analysis of Trial A demonstrated that 68% of patients treated on the all-IP regimen of carboplatin and paclitaxel were able to complete therapy. Therefore, we estimated that at least 60% of the patients treated in Trial B would complete the entire regimen. With 40 evaluable subjects and if there are at least 24 patients completing planned therapy, then the lower bound of a 95% confidence interval of the true completion rate (i.e., a poor rate to be ruled out) will be at most 45%.

3. Results

3.1. Patients

A total of 89 patients were enrolled to these trials (43 in Trial A and 46 in Trial B). Of these, 3 patients in each trial received 1 cycle of IV chemotherapy and subsequently withdrew from the study and 2 patients in Trial B were never treated. Hence, 40 and 41 patients, respectively, are included in this report as evaluable patients. The median age of patients was similar (Trial A, 59 [range, 36–76]; Trial B, 55 [range, 19–69]). All had an excellent performance status (PS) on entry, though more patients were recorded as a PS of 0 on Trial B (56 versus 45%). Most patients on these trials had stage III disease; 3 patients on Trial A and 1 patient on Trial B had stage II and IV disease, respectively. Table 1A summarizes the key characteristics of all patients that were eligible and participated in these trials.

Table 1A
Patient demographics and tumor characteristics.

Demographics and tumor characteristics	Trial A (n = 40) no. (%)	Trial B (n = 43) no. (%)
Age median (Range)	59 (36–76)	55 (19–69)
Performance status		
0	18 (45)	23 (56)
1	22 (55)	18 (44)
Grade		
1	1 (3)	3 (7)
2	3 (8)	4 (10)
3	34 (85)	32 (83)
Unknown	2 (5)	2 (5)
Stage		
II	3 (8)	0
A	0	
B	1 (33)	
C	1 (33)	
Not specified	1 (33)	
III	37 (93)	36 (88)
A	1 (3)	3 (7)
B	4 (11)	4 (10)
C	29 (78)	29 (76)
Not specified	3 (8)	
IV	0	1 (2)
Unknown	0	4 (10)
Disease		
Ovary	30 (75)	30 (76)
Primary peritoneal	7 (18)	5 (12)
Fallopian tube	3 (8)	4 (12)
Not specified	0	2 (5)

3.2. Toxicity

The completion rates to 6 cycles was higher in Trial B (85% versus 68% in Trial A, Table 1B). In addition, more patients on Trial B completed 4 or more cycles (95% versus 86%). Among those patients completing all 6 cycles of chemotherapy in Trial A, grade 3 and 4 adverse events were uncommon and consisted of neutropenia (23%), thrombocytopenia (8%), metabolic complications (8%), abdominal pain (5%), fatigue (5%), infection (5%), and diarrhea. More serious toxicities were recorded in Trial B, with higher rates of thrombocytopenia (12%), abdominal pain (9%), fatigue (13%), and diarrhea (5%). Grade 2 proteinuria and grade 2 hypertension were encountered in 5 and 7% of patients, respectively. Of note, no patients in this study experienced complete alopecia and neuropathy was generally mild with only 1 patient (3%) treated on Trial B reporting grade 2 toxicity. The toxicity results are summarized in Table 2. No deaths occurred on study.

3.3. Pathologic complete response rates: Trial A

No patients experienced disease progression on treatment. All patients with cCR were eligible for second look (SL) procedure assuming no surgical contraindications. Surgical exploration should be performed not <21 days after the final cycle of chemotherapy and not >8 weeks after the last dose of chemotherapy was administered. Laparoscopic evaluation of the peritoneal cavity was acceptable as a second-look procedure if histologically confirmed persistent disease can be seen and biopsied through the laparoscope. If no disease is seen, then exploratory laparotomy was mandatory. Of the 40 evaluable patients, 26 (65%) met criteria for a cCR, all of whom underwent a second look procedure (Table 3). Of these patients, 19 (66%), 4 (14%), and 2 (7%) had a pCR, mSL+, and evidence of gross disease, respectively. Of note, 1 patient

Table 1B
Summary of cycles[a] completed.

Number of Cycles Completed*	Trial A N = 40 n (%)	Trial B N = 41 n (%)
2	6 (15)	1 (2)
3	0	1 (2)
4	4 (10)	2 (5)
5	3 (8)	2 (5)
6	27 (68)	35 (85)

Patients receiving only 1 cycle (IV) of treatment alone were excluded from the study.
[a] One cycle consists of a dose of carboplatin on day 1, followed by paclitaxel on days 8 and 15 for an entire cycle of 21 days (for specific doses see study treatment section). In Trial B, patients received bevacizumab starting at cycle 2.

Table 2
Frequency of grade 2, 3 or 4 adverse events[a].

Event	Grade 2 (%)		Grade 3 (%)		Grade 4 (%)	
	Trial A (n = 40)	Trial B (n = 41)	Trial A (n = 40)	Trial B (n = 41)	Trial A (n = 40)	Trial B (n = 41)
Neutropenia[b]	1 (3)	8 (20)	6 (15)	2 (5)	3 (8)	2 (5)
Thrombocytopenia	10 (25)	5 (12)	3 (8)	4 (10)	0	1 (2)
Anemia	8 (20)	13 (32)	1 (3)	2 (5)	0	0
Neuropathy	1 (3)	1 (2)	0	0	0	0
Abdominal pain	12 (29)	12 (26)	2 (5)	3 (7)	0	1 (2)
Metabolic[c]	4 (10)	10 (24)	2 (5)	3 (7)	1 (3)	0
Fatigue	13 (33)	17 (37)	2 (5)	6 (13)	0	0
Infection	7 (18)	3 (7)	2 (5)	0	0	1 (2)
Alopecia	0	3 (7)	0	0	0	0
GI event						
Constipation	10 (25)	10 (24)	3 (8)	0	0	0
Diarhhea	3 (8)	7 (17)	0	2 (5)	0	0
Obstruction	1 (3)	1 (2)	0	1 (2)	0	0
Other						
Proteinuria		2 (5)		0		0
Hypertension		3 (7)		0		0

[a] These adverse events occurred during all cycles [1–6].
[b] WBC < 1000.
[c] Creatinine, Dehydration, Hypocalcemia, Hypokalemia, Hypomagnesemia, Hyponatremia.

had no evidence of disease at SL, but no biopsies were taken and thus was not evaluable for pCR.

3.4. Pharmacokinetics: Trial A

Mean values of selected pharmacokinetic parameters for paclitaxel and free (ultrafilterable) platinum are presented in Supplementary Table and Fig. 3. There were no statistically significant differences between the mean pharmacokinetic parameters for the initial (cycle 2) and final (cycle 6) doses of either drug when IP administered. Plasma concentration-time data that was amenable to pharmacokinetic analysis was obtained for 40 patients receiving the initial dose of paclitaxel as a 60 min IV infusion, for 37 patients treated with the initial IP dose in cycle 2, and for 25 patients receiving the final IP dose in cycle 6 (Fig. 3). The mean ± SD of the maximum concentration (C_{max}) of paclitaxel in plasma achieved at the end of the 60 min IV infusion was 2100 ± 747 nM. When the same dose was given IP the C_{max} was approximately 30-times lower, with mean values of 69 ± 26 nM for the patients treated in cycle 2 and 60 ± 20 nM in cycle 6. The mean systemic bioavailability for IP paclitaxel was 49 ± 19% in cycle 2 and 44 ± 15% in cycle 6. The duration of exposure to paclitaxel at concentrations >50 nM, which has been associated with the pharmacologic effects of the drug, was similar for both routes of administration. The average times that paclitaxel concentration in plasma exceeded 50 nM were 8.8 ± 3.5 h for IV dosing, 9.6 ± 8.0 h for the initial IP dose, and 7.3 ± 6.4 h for the final IP dose. Paclitaxel C_{max} was below 50 nM following IP administration in 22% of the patients in cycle 2 and 24% of the patients in cycle 6.

Pharmacokinetic data for free platinum was also available for 41 patients receiving the initial dose of carboplatin by IV infusion, for 32 patients treated with the initial IP dose in cycle 2, and for 26 patients receiving the final IP dose in cycle 6. The peak concentration of free platinum in plasma was approximately 40% lower when carboplatin was given IP in cycle 2 (77 ± 21 μM) and cycle 6 (72 ± 20 μM) as compared to IV infusion (121 ± 30 μM), both statistically significant at $p < 0.05$. The systemic availability of free platinum was effectively 100% for IP administration.

Table 3
Efficacy: second look operation (Trial A).

	No. (%)
Second look operation	
Yes	26 (65)
Microscopic	4 (14)
Gross disease	2 (7)
PCR[a]	19 (66)
No visible disease[b]	1 (3)
No	13 (33)

[a] Pathological Complete Response.
[b] Second Look Operation performed, but no biopsy taken.

3.5. Efficacy

PFS and OS for both trials are shown in Fig. 2a and b, respectively. Similar PFS outcomes were noted in Trial A and Trial B (median, 23.5 [95%CI 16.2–35.3] versus 25 months [95%CI 16.4–42.7]), respectively. In addition, OS was also similar, median 79.7 (95%CI 59.0–79.7) versus 68 months (95%CI 49.5-NR).

4. Discussion

We report 2 sequential single arm phase II trials that utilized an all IP regimen of carboplatin and dose-dense paclitaxel, without and with bevacizumab. Our findings show that both regimens are tolerable and efficacious, and these 2 studies are an investigation into possible ways to ameliorate toxicity and produce a better tolerated regimen. The efficacy analysis serves to be hypothesis-generating, and these results cannot be acted upon without further confirmatory randomized studies. While direct comparison between these trials is not appropriate it is noted that the survival of patients in both trials is roughly similar as seen in other trials, most notably GOG 252 [13].

The median PFS in both studies is similar to PFS obtained in GOG 172 (median PFS, 24 months) [11]. In addition, we obtained a similar approximation of OS without and with bevacizumab, which is also in line with larger phase III trials that have consistently shown a lack of an overall survival advantage when bevacizumab is combined with chemotherapy [6,15]. However, it is interesting that an all IP chemotherapy regimen appeared to be more tolerable with less neuropathy reported and no events of complete alopecia. While cross trial comparisons are not methodologically ideal, it is curious that our median OS is longer than what was reported in either the seminal Gynecologic Oncology Group 218 (GOG 218) or the International Collaboration on Ovarian Neoplasms 7 (ICON7) trials, where the median OS with bevacizumab was 39 and 45.5 months, respectively [6,7]. Both GOG 218 and ICON7 included maintenance bevacizumab, which was not used in Trial B reported here. This difference is potentially explained by the selection of patients for IP therapy in our trials as compared to those patients enrolled in GOG 218 and ICON7. Unfortunately, when our trials were

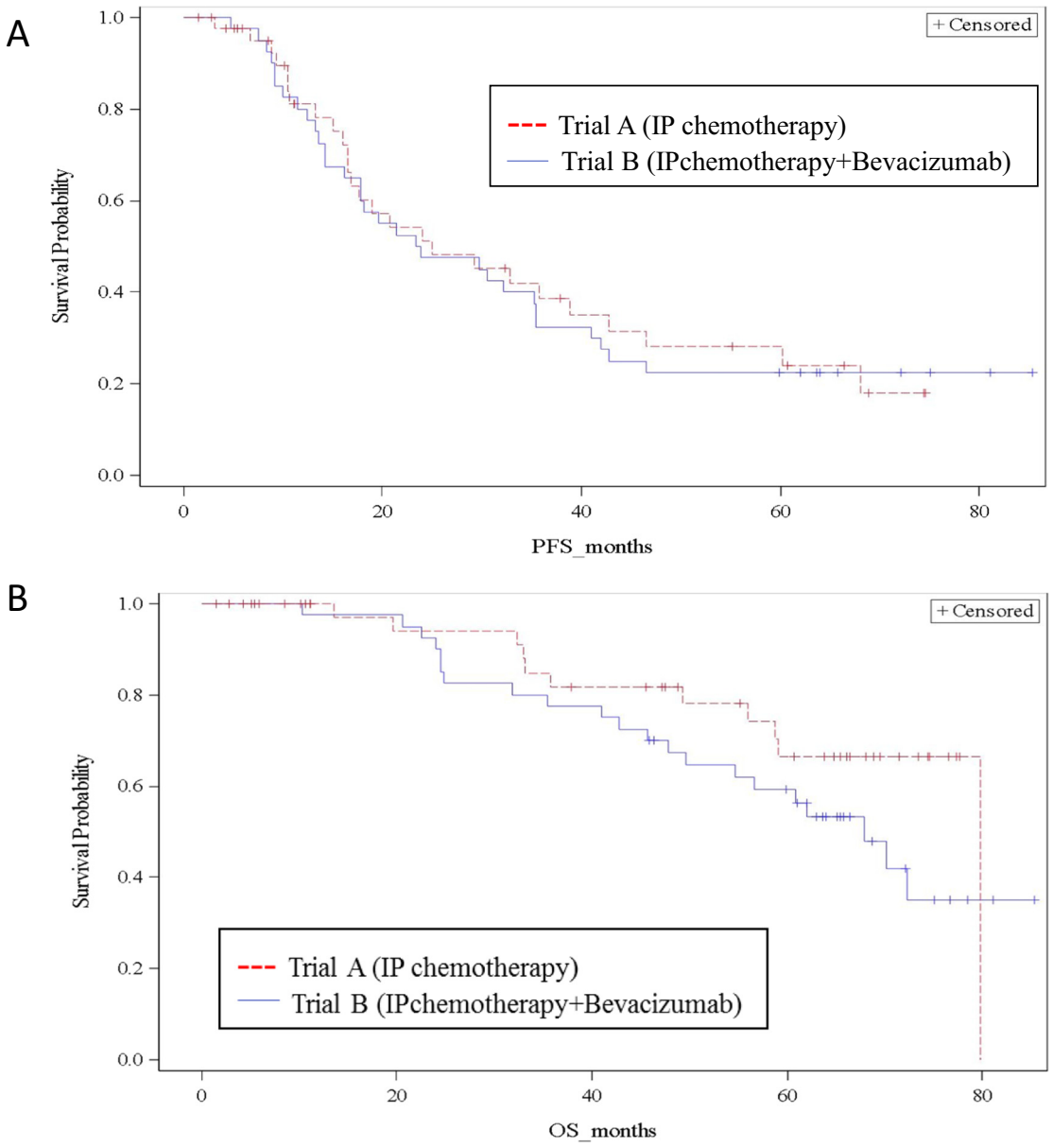

Fig. 2. A represents the Progression free survival (PFS). B shows the overall survival of patients enrolled in Trial A and Trial B. Trial A is represented by the red dotted line and Trial B is represented by the solid blue line.

designed, the stratification of patients who underwent an optimal cytoreduction was not stratified by residual disease (eg, R0 versus <1 cm), and these data were not captured.

Our PK data support a duration of exposure above a threshold as the key to paclitaxel efficacy while the lower peak concentration possibly resulting in less neurotoxicity and alopecia. While not possible to say with certainty, the PK data also suggests that adhesions which may form at the time of or following surgery appear not to impair systemic absorption of paclitaxel.

So, where do these data fit in the current treatment paradigms in ovarian cancer? This is unclear. The first results of GOG 252, was reported at the 2016 Annual Meeting for Women's Cancers by Walker and colleagues [13]. In this trial, over 1500 women with predominantly stage III and serous carcinomas were randomly assigned to 1 of 3 chemotherapy regimens: IV carboplatin plus IV weekly paclitaxel; IV weekly paclitaxel plus IP carboplatin; or IV paclitaxel on day 1, IP cisplatin on day 2, and IP paclitaxel on day 8. Bevacizumab was administered to all patients during chemotherapy (beginning at cycle 2) and then continuing after chemotherapy for up to 22 cycles. As reported, there was no difference in PFS across the trial with a median PFS of 27, 29, and 28 months, respectively. OS was not reported as sufficient survival events had not yet occurred at time of PFS disclosure. While our trials are similar in that one arm included IP carboplatin, we do not believe these trials inform the question we posed at the start of this project due to the use of bevacizumab during chemotherapy and then as maintenance, and the fact that IP paclitaxel administration on a weekly basis was not included as part of any of the regimens on GOG 252.

In summary, IP carboplatin and IP weekly paclitaxel is relatively well tolerated with a high completion rate, and promising efficacy with far less toxicity than is generally recorded with standard IV/IP treatment. There also do not appear to be any notable changes in outcomes nor efficacy noted with or without the addition of bevacizumab. Although the future of IP therapy in ovarian cancer is controversial in the era of molecular therapies, these data support the feasibility of an all-IP therapeutic regimen that should be considered for inclusion in future randomized trials. In addition, for patients with pre-existing neuropathy or who might consider refusing chemotherapy for fear of alopecia

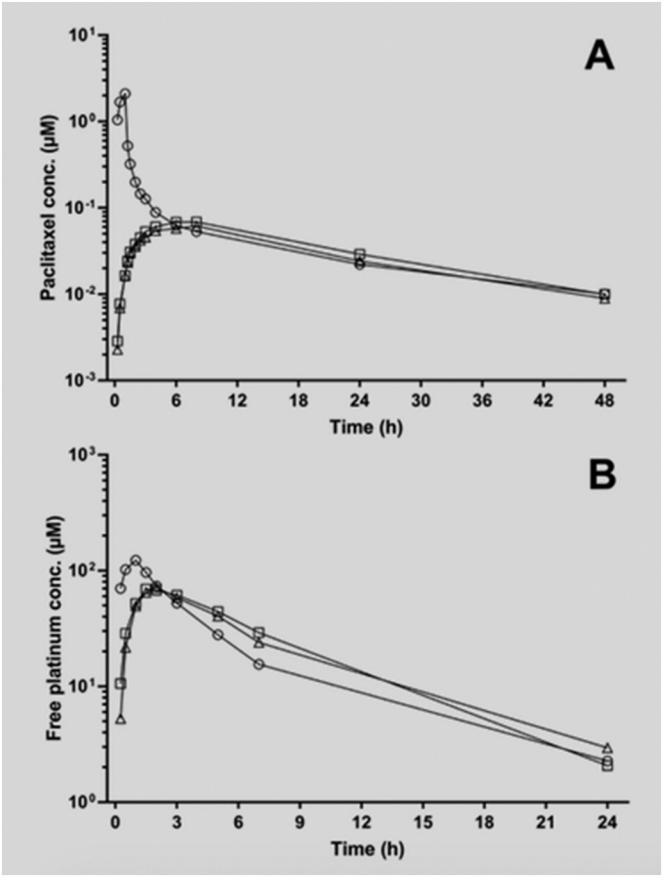

Fig. 3. A: Mean plasma concentration-time profiles for paclitaxel 60 mg/m^2 given as an i.v. infusion in cycle 1 (○) and by the i.p. route in cycle 2 (□) and cycle 6 (Δ). B: Mean free platinum plasma concentration-time profiles for carboplatin given as an i.v. infusion in cycle 1 (○) and by the i.p. route in cycle 2 (□) and cycle 6 (Δ).

these regimens might be considered an acceptable alternative to more conventional treatment regimens. If the cooperative groups and treating oncologists deem IP therapy worthy of further study, given that GOG172 continues with the best OS reported in an upfront trial, and acknowledging that the many new agents currently being investigated in upfront and maintenance settings may make the paradigm of upfront platinum-doublet obsolete, a randomized trial with a standard arm of IP/IV therapy per GOG 172 and an experimental arm of an all-IP regimen may answer the questions of relative tolerability and possible non-inferiority of using the IP-only approach.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.02.004.

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Conflict of interest statement

The following authors acknowledge no conflicts of interest: Krasner, Castro, Penson, Roche, Morgan, Drescher, Armstrong, Wolfe, Lee, Supko, Birrer, Dizon.

The following authors acknowledge conflicts of interest as detailed:

UA Matulonis: Astra Zeneca, Myriad Genetics, Clovis, Merck, Eli Lilly, Mersana, Geneos, Fuji Film, 2× Oncology, Cerulean, Immunogen.

M Seiden: McKesson/US Oncology, GRAIL.

Author contribution

Study conception and design: Krasner, Seiden.

Acquisition of data: Krasner, Penson, Roche, Morgan, Drescher, Armstrong, Wolfe, Matulonis.

Analysis and interpretation of data: Supko, Lee, Castro, Birrer, Dizon, Matulonis, Krasner.

Drafting of manuscript: Supko, Castro, Birrer, Dizon, Matulonis, Krasner.

Critical revision: Lee, Matulonis.

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