Weekly AUC2 Carboplatin is Inactive in Acquired Platinum Resistant Ovarian Cancer with or without Oral Phenoxodiol, a Sensitizer of Platinum Cytotoxicity: the phase III OVATURE multicenter randomized study

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Abstract

Purpose: Platinum resistant ovarian cancer (PROC) constitutes a therapeutic dilemma with limited efficacy from traditional cytotoxic agents. Based on prior data suggesting that scheduling alterations of platinum would increase activity, the aim of the present study was to assess the potential therapeutic benefit of phenoxodiol (PXD), a novel biomodulator shown to have chemoresistance reversing potential, when combined with weekly AUC2-carboplatin in PROC-patients.

Patients and Methods: A multicenter randomized double-blind placebo controlled phase-III-study was conducted to compare oral PXD plus AUC2-carboplatin (group 1) versus placebo plus AUC2-carboplatin (group 2) weekly in PROC-patients. The primary end point was progression-free-survival (PFS). Secondary objectives included overall survival (OS), response rates, duration of response and quality of life.

Results: A total of 142 patients were randomized. The groups were well balanced in terms of important baseline characteristics. The median PFS for group 1 was 15.4 weeks (95%CI=11.1-21.0) versus 20.1 weeks for group 2 (95%CI=13.1-33.4); p=0.3. The objective response rate and median survival in group 1 versus group 2 was 0% versus 1% and 38.3 weeks (95%CI=32.0-45.3) versus 45.7 weeks (95%CI=35.6-58.0), respectively. PXD appeared to be well tolerated. The main reason for dose modification in both groups was hematologic toxicity.

Discussion: Orally delivered PXD showed no evidence of clinical activity, when combined with weekly AUC2-carboplatin in PROC. In addition, weekly AUC2-carboplatin appeared to be inactive in a homogenously defined population of PROC. This has implications for the design of future studies.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the fifth leading cause of cancer death in females in the western countries and the most lethal gynecological malignancy.[1-3] While platinum-based chemotherapy results in high response rates ranging from 50-80%,[4] 70% of patients will relapse and eventually develop PROC with a corresponding adverse prognosis associated with this transition.[5-8]

The treatment of PROC utilizes non-platinum agents such as gemcitabine, pegylated liposomal liposomal doxorubicin, paclitaxel, vinorelbine and topotecan, however the development of resistance to platinum is associated with cross resistance to other drugs [7] resulting in very low response rates of 3-16%.[8] This acquired chemo-resistance represents one of the major hurdles to effective treatment of ovarian cancer and creates therapeutic dilemmas.

Reversal of chemotherapy resistance has been an attractive strategy in principle and much effort has been expended in trying to understand mechanisms of chemotherapy resistance.[24] Dose dense application of paclitaxel and cisplatin in phase II and randomized phase III trials showed a clear increase in overall response rates in relapsed PROC.[19-20,23,37]

Phenoxodiol (PXD) is a sterically-modified version of the naturally-occurring plant isoflavone, genistein. Pre-clinical studies suggest that exposure of human cancer cells to PXD results in up regulation of pro-apoptotic ceramide lipid levels with a concomitant

reduction in sphingosine-1-phosphate leading to AKT inhibition.[9-12] Two well described biological effects of PXD are mitotic arrest of tumour cells in the G1 phase of the cell cycle as a result of p53-independent upregulation of p21 Waf1/CIP1 and induction of apoptosis through inhibition of phosphorylation of the anti-apoptotic proteins, X-linked inhibitor of apoptosis (XIAP) and FLIPshort.[11]

PXD has shown both additive and synergistic interactions with chemotherapies including cisplatin, carboplatin, gemcitabine, paclitaxel, docetaxel and topotecan in a wide range of human cancer cells, including human ovarian cancer cells.[10,12-15] In a phase II study of intravenous PXD combined with either cisplatin or paclitaxel in PROC, stable disease rates of more than 55% and overall best response rates as high as 19% could be achieved with good tolerance.[16] No phase II efficacy studies were conducted with oral phenoxodiol prior to the initiation of OVATURE (Ovarian Tumor Response), however, phase I/II safety and pharmacokinetic studies with oral phenoxodiol suggested that the drug was immediately conjugated (glucuronidated) to an inactive metabolite and animal models demonstrated that this conjugation and inactivation was reversed within tumors, providing a tumor targeting strategy. This was the primary rationale to proceed with OVATURE (Clinicaltrials.gov identifier NCT00382811).[11,13,16-18]

Based on the promising phase II results in PROC, this trial was designed to confirm a clinically important interaction of PXD and carboplatin in this patient population.

PATIENTS and METHODS

Patients

PROC-patients with histologically-confirmed non-mucinous ovarian, fallopian tube, or primary peritoneal carcinoma of epithelial origin were eligible for the study if they fulfilled all of the following criteria: patients must have received at least one line of platinum based chemotherapy (cisplatin or carboplatin) for recurrence having responded to first line therapy previously; platinum resistant recurrence was defined as RECIST measurable disease relapse within 6 months of completing a second or subsequent course of platinum therapy at the time of enrollment, taken from the last day of platinum therapy. Measurable disease had to be ≥10 mm when measured by spiral CT and ≥20 mm when measured by conventional CT. Patients had an estimated survival of at least 3 months; a Karnofsky-Performance-Score (KPS)≥60; and biochemical/hematological function within the normal range.

The study was conducted in accordance with Good Clinical Practice (GCP) according to ICH guideline CPMP/ICH/135/95 and the Declaration of Helsinki (V11 Oct,2000) with notes of Clarification in 2002 (Washington) and 2004 (Tokyo).

Study Design

The primary objective of this study was to compare the effect of a treatment regime of (1) daily oral phenoxodiol in combination with weekly carboplatin, versus (2) daily oral

placebo in combination with weekly carboplatin on the progression free survival (PFS) in patients with PROC. Secondary objectives included comparisons of overall response rates (ORR) and duration of response (DOR), overall survival (OS), and quality of life (QoL). We also evaluated two additional endpoints: a) time to dose reduction due to toxicity in order to assess a postulated benefit of phenoxodiol to improve the tolerance to carboplatin and b) disease control rate, defined as any response achieved other than progressive disease (i.e., complete response, partial response, or stable disease).

Weekly carboplatin can be delivered as a single agent at an AUC not exceeding 2, although when given with weekly paclitaxel, the thromboprotective effect of paclitaxel allows an increase in weekly carboplatin. In this trial we were able to dissect the effects of schedule from those of dose in recurrent PROC, with carboplatin being given weekly at a non dose-dense AUC2, the maximum tolerated single agent dose. The patients groups and regimes are described in figure 1.

Treatment and Follow-up Procedures

Patients were randomized, 1:1, to either (1) PXD + carboplatin or (2) Placebo + carboplatin. Both PXD and the placebo were taken daily every 8-hours.

Carboplatin was given weekly over 1 hour at a dosage of AUC2. Although not validated for single agent platinum compounds, a change in regime from 3-weekly to weekly had been shown with taxanes[19,20] and also with the combination of carboplatin and taxol[34,48]

demonstrating tumor response in patients whose tumors have become resistant to a 3-weekly regime. Carboplatin dosing was based on the Calvert and, Cockroft-Gault formulae.

Phenoxodiol: PXD was administered orally, 400mg (2x200 mg capsules) every 8 hours continuously, unless body weight was >100kg where a 50% increase to 600mg (3x200 mg capsules) was used. PXD was taken on an empty stomach at least 30 min prior to eating. No toxicities or intolerances are known to be associated with the use of the oral dosage form of PXD, and therefore no precautions or preventative therapies were contemplated.

A treatment cycle was defined as 28 days (4 weeks). Treatment with both carboplatin and PXD or placebo was to be continued until disease progression, dose-limiting toxicity, or patient withdrawal. Dose adjustments or interruptions of carboplatin were undertaken based on toxicity using standard criteria for both drugs.

Patients were evaluated weekly for evidence of toxicity, including hematology and routine chemistry laboratory studies. Efficacy assessments, specifically computed tomography (CT) scanning, was performed every 8 weeks (2 cycles). In addition, CA125 levels were measured every 2 weeks. QoL instruments (FACT-O and FACT-BRM) were administered every 8 weeks (2 cycles).

Endpoints and Sample Size

Clinical response and progression were assessed according to the RECIST criteria[22] and based on the assessment determined by an independent Tumor Response Evaluation Committee (TREC) rather than the investigator. In addition, CA-125 response and progression was assessed according to the Rustin criteria. PFS (the primary endpoint) was measured from the day of randomization to the day of documented disease progression or death while OS was measured from the day of randomization to death. Stable disease was defined as any response between PR and DP.

Toxicity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3 (CTCAE v3).

Statistical Analysis

The study was originally designed to detect an improvement in median PFS from approximately 5 months in the control group to approximately 8 months in the experimental group, corresponding to a PFS hazard ratio of 0.625. Based on a projected recruitment duration of 36 months a sample size of 340 patients was planned. A single interim analysis was pre-specified at ~50% of the planned PFS events (~95/190), utilizing O'Brien-Fleming stopping boundaries at an alpha level of 0.005. The final analysis was planned at a two-sided alpha of 0.048. All efficacy analyses were conducted on all randomized patients (intention-to-treat population) while all toxicity analyses were

conducted on the safety population defined as all randomized patients who received at least one dose of protocol defined therapy. Patients who discontinued protocol defined therapy prior to disease progression or death were censored at 1) the last date of tumor evaluation for the PFS analysis and 2) the last date of known contact for the OS analysis.

Based on an observed recruitment velocity that was far below what was originally projected, an amended statistical analysis plan was developed. Recruitment was formally stopped on 14 April 2009. The amended statistical analysis plan specified removing the original planned interim analysis and replacing it with a new interim PFS analysis that was time specified (data cut off: 01 June 2009). It was projected that approximately 70% of the enrolled patients would have experienced a PFS event at this time point (~98 patients) and the alpha level for this new analysis was kept at 0.005, as per the original interim analysis plan. A revised final analysis was planned when all enrolled patients had either died, completed 18 months of follow-up, or had been lost to follow-up.

RESULTS

Patients

Between November 2006 and March 2009, 142 patients were randomized at 49 study sites in the OVATURE study; 72 patients to Placebo+Carboplatin and 70 to PXD+Carboplatin (Fig 1). At the time of the interim PFS analysis, 110 patients had

progressed or died without evidence of progression and 32 were censored (19 in the control group and 13 in the PDX group). At the time of the final OS analysis 118 patients had died and 24 were censored (13 in the control group and 11 in the PDX group). The median age was 57.5 years (range: 39-78) in the PXD/Carboplatin group and 59.0 years (range: 37-82) in the Placebo/Carboplatin group. Both arms were well balanced regarding important baseline characteristics, stratification factors, duration of study treatments, number of treatment cycles and other patient characteristics (Table 1). All patients in the study reported at least one comorbidity mainly in terms of gastrointestinal-, nervous system- or respiratory disorders. No significant differences in the comorbidities were noted between the two patients arms.

Withdrawals are summarized by subgroup in table 2. There were similar numbers of patients in each treatment group attending each visit and having evaluable tumor responses. The duration of study treatments and number of treatment cycles were similar between the two treatment groups and there were no obvious differences seen within any of the subgroups. Prior treatment and platinum-free interval were well balanced between the arms and are presented by cohort and overall in Table 3. All patients had received prior carboplatin or cisplatin.

Efficacy

RECIST outcomes

PFS, the primary study endpoint, was similar in the two groups, 20.1 weeks in the placebo group versus 15.5 weeks in the PDX group (HR=1.22, 95%CI 0.84-1.22, p=0.30). No differences between the treatment groups were noted for the secondary efficacy endpoints. OS was 45.7 weeks in the placebo group versus 38.3 weeks in the PDX group (HR=1.20, 95%CI 0.83-1.73, p=0.33. Exploratory analyses across a variety of pre-specified patient sub-groups did not identify a population that appeared to derive clinical benefit. The median time to progression for the PXD group was 15.4 weeks (95%CI = 11.1-21.0) and was 20.1 weeks for the placebo group (95%CI = 13.1-33.4). The median OS was also not statistically significantly different between the two groups with 38.3 weeks (95%CI=32.0- 45.3) in the PXD group compared with 45.7 weeks (95%CI=35.6-58.0) in the Placebo group (p=0.3). The hazard ratio was 1.2 (95% CI=0.83-1.73). Survival curves for OS and PFS are presented in figures 2 and 3.

Confirmed ORR was 1.4% in the placebo group versus 0% in the PDX group while stable disease was 52.8% and 51.4% respectively. A similar, non significant number of patients in each treatment group had stable disease (36 vs. 38; 51.4% vs. 52.8% for PXD and Placebo, respectively) in the ITT population. Overall response rates (ITT population) are presented in detail in table 4.

CA125 outcomes

When evaluating CA125 levels, there was no indication of a treatment effect in response as defined by a sustained fall of at least 50% in CA-125 for patients who had a valid baseline measure of CA125 in any of the subgroups. Also there was no indication of a treatment effect in progressive disease as defined by two consecutive values at least 7 days apart ≥2xULN in any of the subgroups.

No differences in quality of life or performance status were noticed between the two groups over the course of treatment.

Adverse events

Table 5 summarizes the dose modification in both arms of the trial. A total of 1362 AEs occurred post treatment in the phenoxodiol+carboplatin group and 1374 occurred in the placebo+carboplatin group. There were 518 AEs which were deemed possibly, probably or definitely related to the phenoxodiol+carboplatin combination and 472 to the placebo+carboplatin combination by the investigators. The majority of adverse events were mild (Grade 1) for both groups.

The most common adverse events in both groups were blood, lymphatic system and gastrointestinal disorders in terms of neutropenia, thrombocytopenia and diarrhea.

There were six serious adverse events which resulted in death and were largely the result of progressive disease. No treatment related grade 3 or 4 toxic changes were recorded in the liver or kidney function tests. Also no grade 3 or 4 disorders occurred in the musculoskeletal and connective tissue, nervous system, respiratory, thoracic and mediastinal system or any severe psychiatric deterioration in terms of lethargy or depression. Table 6 presents the most relevant treatment related toxicities.

DISCUSSION

This is a prospective randomized trial evaluating the efficacy of weekly carboplatin in combination with the oral sensitizer phenoxodiol in PROC. Even though weekly carboplatin had not been previously evaluated in PROC, it was considered justifiable based on data for other agents such as paclitaxel and cisplatin (and their combination). The development of weekly scheduling of platinum based drugs has a significant history. Accelerated weekly cisplatin schedules have demonstrated good efficacy in a variety of contexts, particularly as a component of primary chemoradiotherapy in cervical cancer in randomized phase III clinical trials with positive survival outcomes; furthermore, enhanced response rates of 25-60% especially for combinations with paclitaxel were observed in platinum resistant ovarian cancer.[23,34-40,48-51]

The impact of non-dose-dense -but nevertheless maximal tolerated dose- scheduling change to weekly single agent carboplatin AUC2 had not been previously evaluated in PROC, but from first principles might have been expected to have some activity.

In parallel, the understanding of mechanisms underlying clinical platinum resistance has expanded utilizing clinically appropriate translational models of intrapatient matched clinically sensitive and resistant cancer cell lines[41-43,47] and molecules such as VEGF, BRCA2, HDAC4, STAT3, AKT, and DNA-PK have become implicated in acquired platinum resistance.

This report summarizes the first clinical phase III trial, to our knowledge, to study the impact of fractionating the schedule of carboplatin in a single agent AUC2 weekly regime as a chemotherapeutic backbone in order to evaluate the impact of phenoxodiol, an chemo sensitizer with multiple postulated effects: pan protein tyrosine kinase inhibition, AKT inhibition and anti-angiogenesis in patients with PROC. Despite promising preclinical and early clinical results of PXD against epithelial cancers[27-33], and also promising data suggesting some impact from weekly-scheduled cisplatin and carboplatin delivering enhanced activity in PROC [19-21,23-25], this study could not demonstrate that phenoxodiol improved the outcome of patients with PROC receiving weekly AUC2 carboplatin. No significant difference was seen between the two arms of the study with respect to median PFS or OS, with a highly homogenous population of patients with acquired (not refractory) platinum resistance. The study was therefore

terminated appropriately at first interim analysis after enrollment of 142 out of 340 planned patients due to the absence of any difference between the arms.

Whilst it is understandable that a novel agent such as phenoxodiol could have shown no impact on the primary endpoint, the data within this study relating to the non-activity of weekly scheduled carboplatin AUC2 in PROC are striking and important since they have significant implications for the directions of clinical research in both PROC and also for the strategy surrounding scheduling and dose dense approaches in front line therapy in ovarian cancer.

Sharma et.al. reported their experience with dose dense carboplatin AUC3 and 70mg/m^2 paclitaxel weekly and demonstrated a 60%-RECIST response rate in platinum resistant/refractory ovarian cancer with an 8 month median PFS.[34] The authors noted the protective effect of paclitaxel against carboplatin-induced thrombocytopenia, which enabled an activity enhancement of carboplatin through dose increase without the associated toxicity.[24,44] Other investigators also confirmed that the weekly combination of carboplatin and paclitaxel in platinum refractory disease could achieve response rates ranging from 25% to 60%.45,46[48-51]

Although no pharmacokinetic data or intra-tumoral drug levels were obtained in OVATURE, the lack of discernible adverse events or anti-tumor activity raise suspicion that oral administration of phenoxodiol may have been less effective than the clearly active intravenous administration of the same agent. Regardless, these data do not support

further clinical development of oral phenoxodiol in human cancer and strongly indicate that weekly AUC2 carboplatin should not be considered for use in PROC either on its own or as a chemotherapeutic backbone for studies targeting platinum resistance reversal. The high priority area of understanding and applying therapeutic strategies that target the mechanisms of acquired platinum resistance in the context of the use of platinum based chemotherapy in PROC is an undiminished area of unmet need and is complementary and synergistic with other efforts to do the same with non-platinum chemotherapies. Future research should focus on translating our growing understanding of molecular mechanisms underlying platinum resistance and the identification of tumors that may be responsive to these approaches by better predictive biomarker signatures that may indicate those who would benefit from the reintroduction of platinum in combination with a molecular agent inhibition-targeting specific pathways that create platinum resistance.

In conclusion, this phase III study of weekly AUC2 carboplatin and placebo versus carboplatin plus PXD failed to demonstrate activity or survival benefit through an approach of weekly carboplatin scheduling and addition of PXD in a molecularly unselected but clinically homogenous population of patients with acquired platinum resistant ovarian cancer. Results of this study do not negate the strategy to molecularly target platinum resistance in the context of a platinum based chemotherapy backbone in

PROC but at the same time do not support future trials that would propose a fractionated carboplatin backbone to test reversal of PROC using molecularly targeted agents.

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Tables:

Table 1: Demographic, Clinical and Tumor Related Characteristics of 142 patients with platinum-resistant ovarian cancer relapse.

Parameter		**PXD + carbo** (n=70)	**Placebo + Carbo** (n=72)
Age (years)	Median (range)	57.5 (39-78)	59.0 (37-82)
Race n(%)	Caucasian	59 (41.5%)	62 (43.7%)
	Asian	4 (2.8%)	4 (2.8%)
	African American	3 (2.1%)	4 (2.8%)
	Hispanic	2 (1.4%)	0
	Other	2 (1.4%)	2 (1.4%)
Performance status	0/1	70%	72%
Primary site of malignancy	Ovary Fallopian tube Peritoneum	60 (85.7%) 1 (1.4%) 9 (12.9%)	64 (88.9%) 2 (2.8%) 6 (8.3%)
Histology	Serous Endometroid Clear cell Other	57 (81.4%) 7 (10%) 0 6 (8.6%)	53 (73.6%) 6 (8.3%) 5 (6.9%) 8 (11%)
Grade	1 2 3 4 unknown	1 (1.4%) 11 (5.7%) 44 (62.9%) 3 (4.3%) 11 (15.7%)	2 (2.8%) 10 (13.9%) 50 (69.4%) 1 (1.4%) 9 (12.5%)
Stage	I II IIIa-IIIb IIIc IV unknown	5 (7.2%) 3 (4.3%) 7 (10%) 38 (54.3%) 16 (22.9%) 1 (1.4%)	4 (5.6%) 2 (2.8%) 4 (5.6%) 50 (69.4%) 10 (13.9%) 2 (2.8%)
Number of Prior Platinum Treatments (per Patient)	1 2 3 >3 None reported	3 (4.3%) 29 (41.4%) 21 (20%) 16 (22.9%) 1 (1.4%)	2 (2.8%) 32 (44.4%) 14 (19.4%) 21 (29.2%) 3 (4.2%)
Platinum-Free Interval	Median (range)	3.5 (0-37)	2.6 (0-89)

(months)			

Table 2: Study Completion and Withdrawal (Safety/ITT population) in patients with platinum resistant ovarian cancer relapse treated with either carboplatin alone or carboplatin plus phenoxodiol.

	PXD + carbo (n=70)	**Placebo + carbo (n=72)**
Study completed		
Yes	70 (100%)	72 (100%)
No	0 (0%)	0 (0%)
Withdrawal reason		
Disease Progression	33 (47.1%)	33 (45.8%)
Confirmed Complete Response[a]	0 (0.0%)	0 (0.0%)
Unacceptable Toxicity	7 (10.0%)	16 (22.2%)
Investigator Decision	15 (21.4%)	11 (15.3%)
Patient's Request	9 (12.9%)	4 (5.6%)
Sponsor Decision	1 (1.4%)	1 (1.4%)
Other	5 (7.1%)	7 (9.7%)
Missing	0 (0.0%)	0 (0.0%)

Table 3: Prior Treatment of Disease by Dose Cohort (Safety/ITT Population)

	PXD + Carboplatin (N=70)	Placebo + Carboplatin (N=72)
Platinum-Free Interval (months) [b]		
N	69	69
Mean	4.7	4.2
Standard Deviation	6.79	10.48
Median	3.5	2.6
Minimum-Maximum	0 - 37	0 - 89

[a] Defined as treatment with either carboplatin or cisplatin.

[b] Defined as day of enrollment minus date of last day of most recent platinum therapy divided by 30.44 (365.25/12).

Table 4: Overall response rates (ITT population) in patients with platinum resistant ovarian cancer relapse treated with either carboplatin alone or carboplatin plus phenoxodiol.

Characteristics	PXD + Carboplatin (N=70)	Placebo + Carboplatin (N=72)
Best Target Tumor Response		
Complete Response [a]	0 (0.0%)	1 (1.4%)
Partial Response [a]	0 (0.0%)	0 (0.0%)
Stable Disease	36 (51.4%)	38 (52.8%)
Progressive Disease	27 (38.6%)	25 (34.7%)
No Post-Baseline Assessment	7 (10.0%)	8 (11.1%)
Overall Response Rate [b]	0.0%	1.4%
95% CI	(0.0%, 5.1%)	(0.0%, 7.5%)

Table 5: Reasons for Dose Modifications (Safety Population)

	PXD + Carboplatin (N=66)	Placebo + Carboplatin (N=71)
Total Number of PXD Dose Modifications [a]	100	61
Reason for PXD Dose Modification		
Hematologic Toxicity	44 (44.0%)	31 (50.8%)
Non-Hematologic Toxicity	14 (14.0%)	8 (13.1%)
Weight > 100kg	0 (0.0%)	0 (0.0%)
Other	33 (33.0%)	22 (36.1%)
Reason not stated in Data/CRF	9 (9.0%)	0 (0.0%)
Total Number of Carboplatin Dose Modifications [a]	224	198
Reason for Carboplatin Dose Modification		
Hematologic Toxicity	81 (36.2%)	59 (29.8%)
Non-Hematologic Toxicity	13 (5.8%)	13 (6.6%)
Other	52 (23.2%)	41 (20.7%)
Reason not stated in Data/CRF	78 (34.8%)	85 (42.9%)

[a] Dose modifications include dose delays and dose reductions.
The denominators are based on the total number of dose modifications

Table 6: Adverse Events Leading to Dose Reduction or Temporary Dose Withdrawal by System Organ Class and Preferred Term - (Safety Population) All Grades and ≥ Grade 3 Adverse Events by Group

	Maximum CTC Grading			
	ALL Grades Carboplatin + Placebo	ALL Grades PXD + Carboplatin	≥ Grade 3 Carboplatin + Placebo	≥ Grade 3 PXD + Carboplatin
Blood and lymphatic system disorders	17 (24%)	14 (15.1%)	8 (11.3%)	10 (15.1%)
Anaemia	3 (4.2%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Leukopenia	2 (2.8%)	2 (3.0%)	0 (0.0%)	0 (0.0%)
Neutropenia	9 (12.7%)	6 (9.1%)	6 (8.5%)	6 (9.1%)
Pancytopenia	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Thrombocytopenia	8 (11.2%)	10 (15.1%)	2 (2.8%)	6 (9.1%)
Gastrointestinal disorders	4 (5.6%)	9 (13.6%)	2 (2.8%)	4 (6.1%)
Abdominal pain	2 (2.8%)	1 (1.5%)	1 (1.4%)	0 (0.0%)
Diarrhoea	0 (0.0%)	5 (7.6%)	0 (0.0%)	1(1.5%)
Nausea	1 (1.4%)	2 (3.0%)	1 (1.4%)	0 (0.0%)

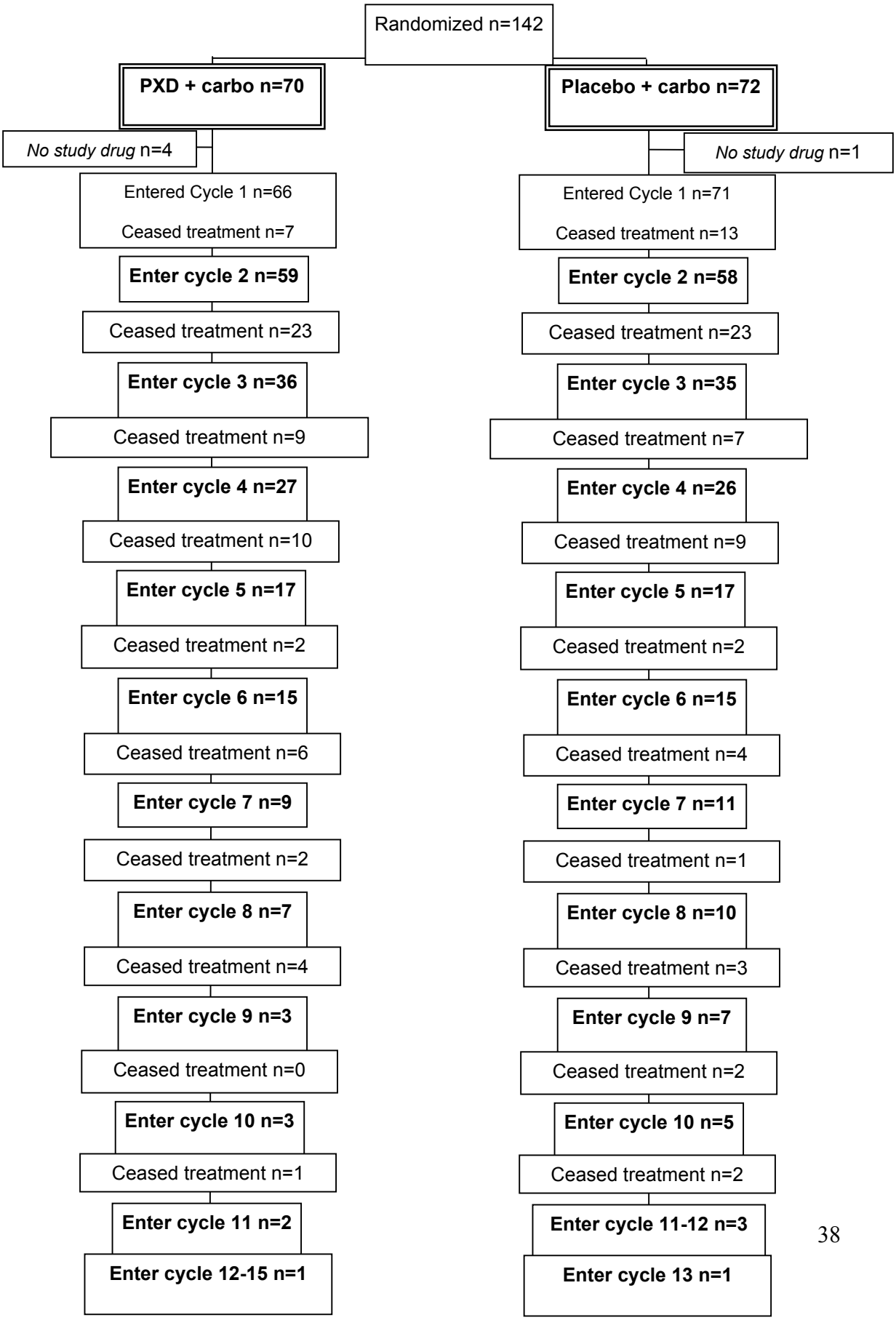
	Maximum CTC Grading			
	ALL Grades Carboplatin + Placebo	ALL Grades PXD + Carboplatin	≥ Grade 3 Carboplatin + Placebo	≥ Grade 3 PXD + Carboplatin
Vomiting	1 (1.4%)	3 (4.5%)	1 (1.4%)	2 (3.0%)
Dysgeusia	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Lethargy	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dyspnoea	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Figure Legends

Figure 1: CONSORT diagram:

Figure 2: Kaplan-Meier curves for progression free survival in patients with platinum resistant ovarian cancer relapse treated with either carboplatin alone or carboplatin plus phenoxodiol.

Figure 3: Kaplan-Meier curves for overall survival in patients with platinum resistant ovarian cancer relapse treated with either carboplatin alone or carboplatin plus phenoxodiol.


Randomized n=142
PXD + carbo n=70
Placebo + carbo n=72
No study drug n=4
No study drug n=1
Entered Cycle 1 n=66
Ceased treatment n=7
Entered Cycle 1 n=71
Ceased treatment n=13
Enter cycle 2 n=59
Enter cycle 2 n=58
Ceased treatment n=23
Ceased treatment n=23
Enter cycle 3 n=36
Enter cycle 3 n=35
Ceased treatment n=9
Ceased treatment n=7
Enter cycle 4 n=27
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Enter cycle 5 n=17
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Enter cycle 6 n=15
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Enter cycle 7 n=9
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Ceased treatment n=1
Enter cycle 8 n=7
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Enter cycle 10 n=5
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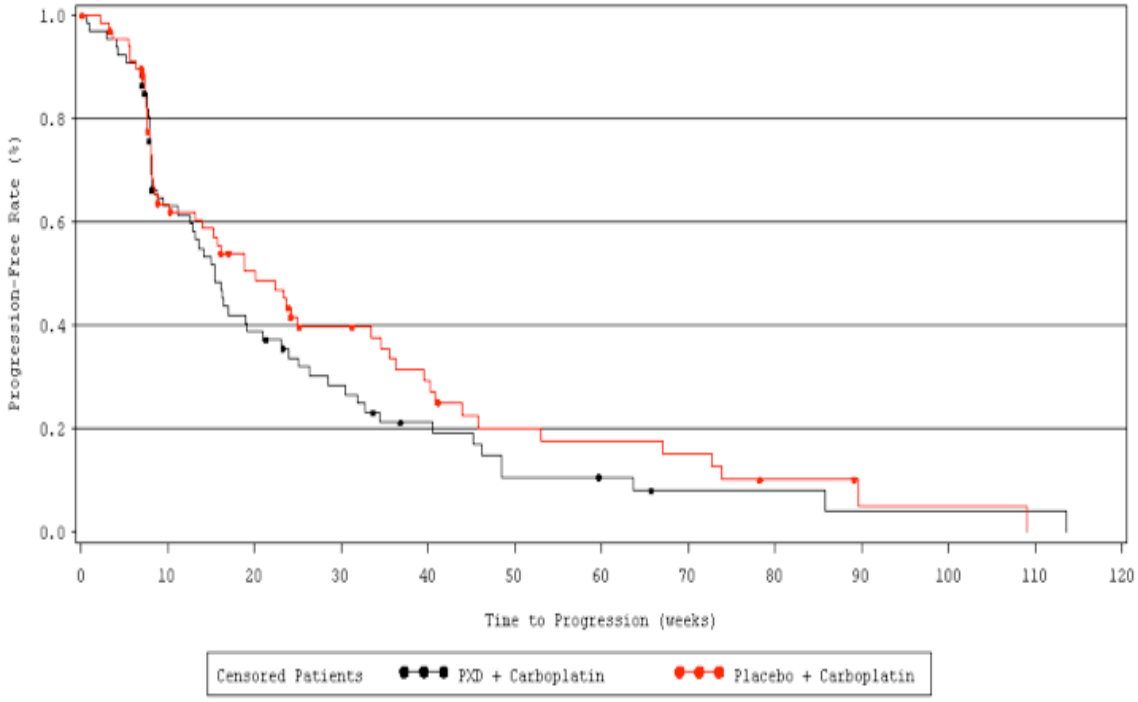
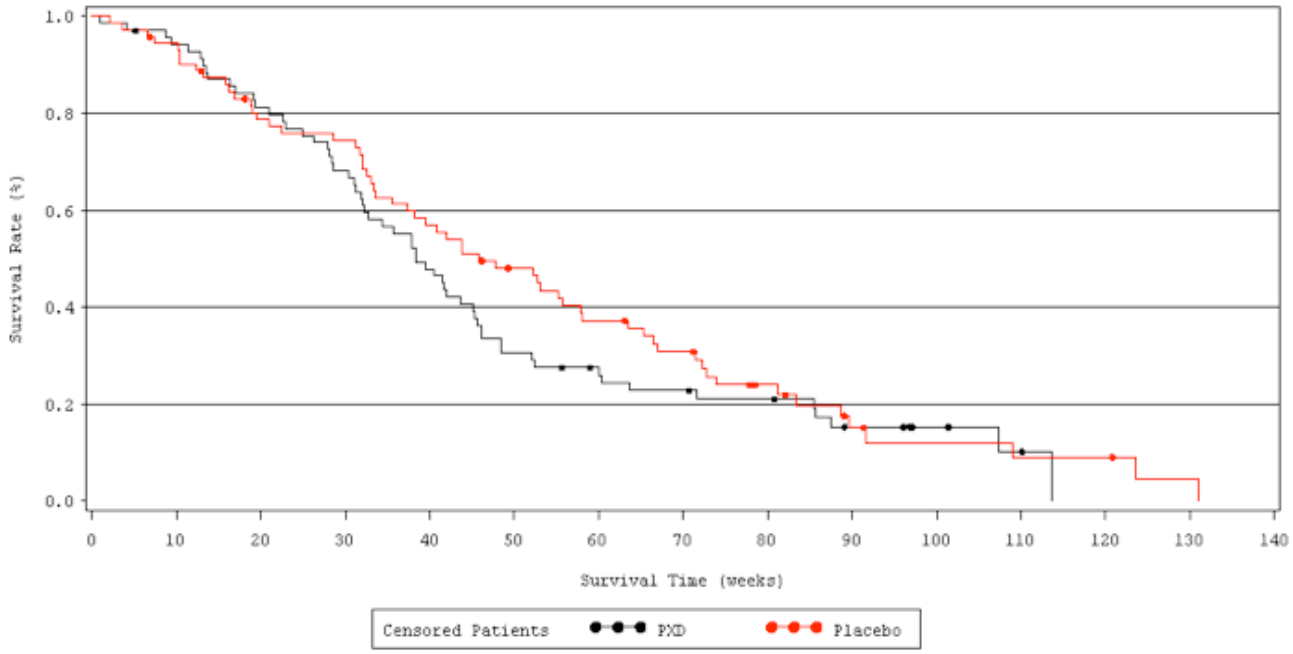
Enter cycle 12-15 n=1
Enter cycle 13 n=1

Figure 2



	PXD + Carboplatin (N=70)	Placebo + Carboplatin (N=72)
Number of Patients Who Progressed	34 (48.6%)	33 (45.8%)
Number of Patients Who Died with No Prior Progression	23 (32.9%)	20 (27.8%)
Number of Patients Who Were Censored	13 (18.6%)	19 (26.4%)

Figure 3: Kaplan-Meier curves for overall survival in patients with platinum resistant ovarian cancer relapse treated with either carboplatin alone or carboplatin plus phenoxodiol.



PXD + Carboplatin (N=70)

Placebo + Carboplatin (N=72)

Number of Patients Who Died	59 (84.3%)	59 (81.9%)
Number of Patients Who Were Censored	11 (15.7%)	13 (18.1%)