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A randomized phase III trial in patients with recurrent platinum sensitive ovarian cancer comparing efficacy and safety of paclitaxel micellar and Cremophor EL-paclitaxel

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HIGHLIGHTS

- Paclitaxel micellar is a Cremophor-EL-free formulation devoid of EtOH and human and animal products.
- Paclitaxel micellar can be administered at a dose of 250 mg/m^2 during a 1 h intravenous infusion without premedication.
- In combination with carboplatin, paclitaxel micellar is non-inferior to Cr-EL paclitaxel in the studied population.
- In the population of patients with a first relapse there is a tendency favouring paclitaxel micellar in terms of PFS.

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ABSTRACT

Objective. Paclitaxel micellar was developed to avoid Cremophor-EL (Cr-EL) associated dose limiting toxicity and to allow a shorter infusion time. The efficacy and safety of paclitaxel micellar (+carboplatin) was compared to Cr-EL paclitaxel (+carboplatin) in recurrent platinum-sensitive ovarian, fallopian tube or peritoneal carcinoma.

Methods. This was a multicentre, open-label, randomized phase III trial. Adult patients with recurrent disease was assigned to six 3-week cycles of paclitaxel micellar (250 mg/m^2) administered as 1-h infusion or Cr-EL paclitaxel (175 mg/m^2) as 3-h infusion. Both arms received carboplatin (AUC 5–6). Primary objective was non-inferiority for progression free survival (PFS) using computed tomography scans. Overall survival (OS) was included as secondary endpoint.

Results. Between 2009 and 2013, 789 patients were randomized to receive experimental ($N = 397$) or control ($N = 392$) treatment. PFS for paclitaxel micellar was non-inferior to Cr-EL paclitaxel with a hazard ratio of 0.86 (95% CI: 0.72;1.03) in the per protocol population (PP), favouring paclitaxel micellar (non-inferiority margin was 1.2). Non-inferiority of OS was shown in the PP population with a hazard ratio of 0.95 (95% CI: 0.78; 1.16), favouring paclitaxel micellar (non-inferiority margin was 1.185). The most common adverse event was neutropenia (grade ≥ 3); 245 patients (79%) for paclitaxel micellar vs 213 patients (66%) for Cr-EL paclitaxel. The frequency of peripheral sensory neuropathy (any grade) was similar between the arms; 16% for paclitaxel micellar and 20% for Cr-EL paclitaxel.

Conclusion. Paclitaxel micellar (+ carboplatin) is non-inferior to Cr-EL paclitaxel (+ carboplatin) in terms of PFS and OS in the studied population. It provides a treatment option of a higher paclitaxel dose with a shorter infusion time without mandatory premedication.

Trial registration number. 2008–002668-32 (EudraCT), NCT00989131 (ClinicalTrials.gov)

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1. Introduction

Ovarian cancer is often diagnosed at an advanced stage and is the most common cause of gynaecological cancer-associated death [1]. Despite treatment including surgery and cytotoxic chemotherapy, approximately 70% of the ovarian cancer will relapse in the first 3 years [2]. In general, recent guidelines for the treatment of ovarian cancer [2–4] recommend platinum-based combinations (e.g. with paclitaxel, gemcitabine, pegylated liposomal doxorubicin) for platinum-sensitive recurrent disease, especially in first relapses. Platinum-sensitivity is currently defined as the length of the disease-free interval being ≥6 months. Alternative treatments for this intractable disease including nucleoside analogues and monoclonal anti-vascular endothelial growth factor (VEGF) antibodies [5,6] in various combinations have been tested in attempts to improve long term survival. Interestingly, maintenance monotherapy with poly ADP ribose polymerase (PARP) inhibitors have significantly improved progression free survival (PFS) as well as quality of life and possibly overall survival (OS) in patients with platinum-sensitive ovarian cancer [7–9].

A Cremophor EL (Cr-EL)-free formulation of paclitaxel was developed using isoforms of retinoic acid derivates as micellar forming excipients to make paclitaxel water soluble (paclitaxel micellar). The lack of Cr-EL will allow a shorter infusion time and attenuate pre-medication which may provide an attractive candidate for further studies in combination with immunotherapy [10] as well as health-economy advantages [11]. The maximum tolerable dose for paclitaxel micellar as monotherapy was defined in a previous dose-finding study to be 250 mg/m^2 [12]. The aim of the present study was to compare the efficacy and safety of paclitaxel micellar with Cr-EL formulated paclitaxel (Cr-El paclitaxel), both in combination with carboplatin, with the intention to provide women with recurrent platinum-sensitive epithelial ovarian cancer a Cr-EL-free formulation with possibly a better safety profile. The primary objective in the study was to show non-inferiority of paclitaxel micellar and Cr-EL paclitaxel in terms of PFS. Secondary objectives were to show non-inferiority in terms of OS and to assess the safety of paclitaxel micellar. An initial objective was also to demonstrate superiority with regards to hypersensitivity reactions (HSRs) but this was changed to be a descriptive presentation due to low rates in both arms. Paclitaxel micellar has received market authorization in the European Union (2018) for treatment of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer in combination with carboplatin in first relapse. It has also received market authorization in Russia (2015), and Kazakhstan (2017).

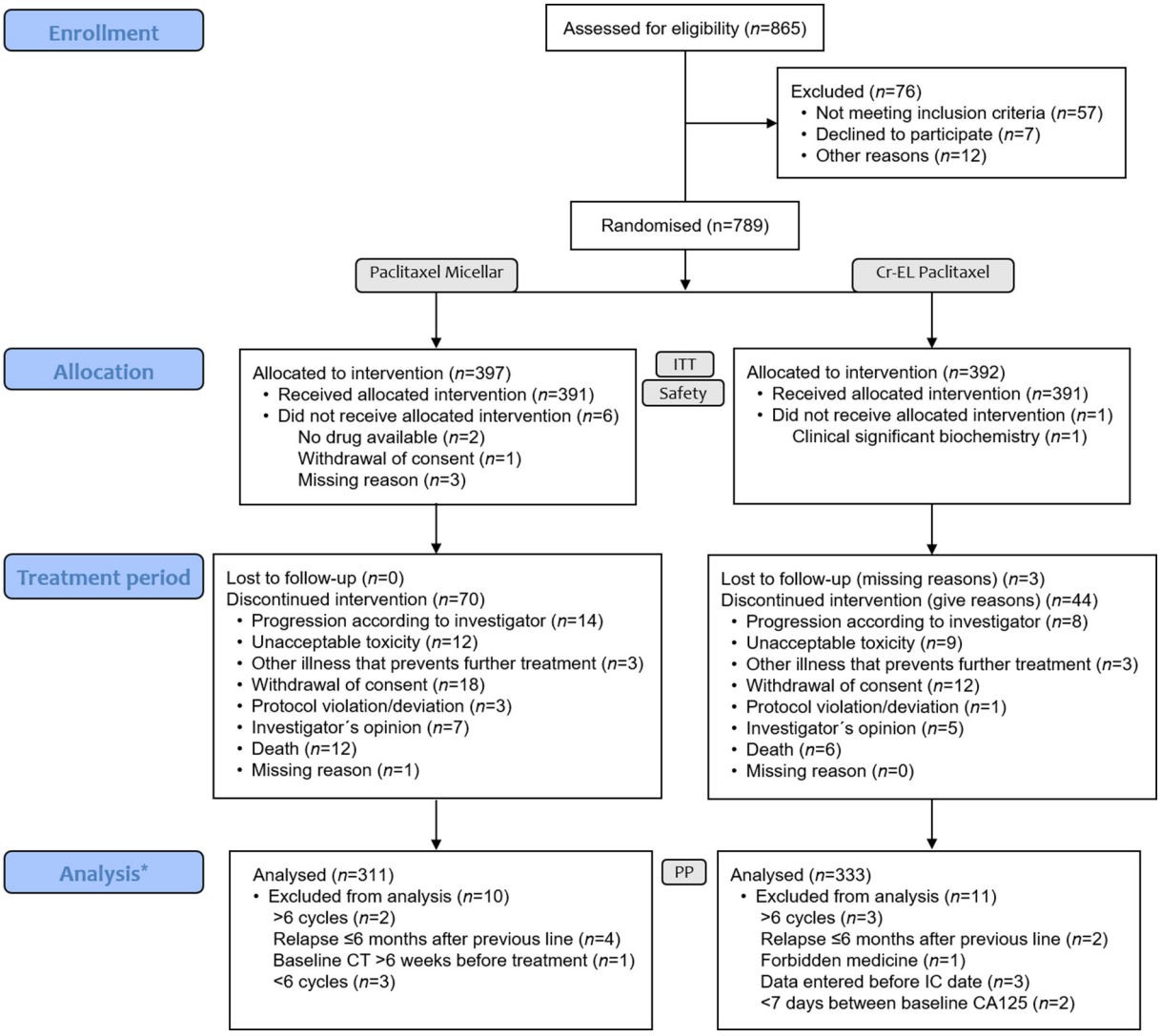

Fig. 1. CONSORT diagram showing the patient disposition where 865 patients were screened and 789 randomly assigned to receive paclitaxel micellar in combination with carboplatin or Cr-EL paclitaxel in combination with carboplatin. n, number of patients; ITT, intention-to-treat population; Safety, safety population; PP, per protocol population; IC, informed consent. * Last death during the follow-up period was captured in October 2015.

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2. Patients and methods

2.1. Patient eligibility

This was an open-label, parallel, randomized, phase III study conducted at 81 sites in 12 EU countries as well as Belarus, Russia, Serbia and Ukraine. Adult patients with confirmed epithelial ovarian cancer, primary peritoneal or fallopian tube cancer were eligible if they had; relapsed >6 months after end of first or second line treatment including platinum-based therapy; cancer antigen (CA) 125 value of >2× upper limit of normal (ULN); Eastern Cooperative Oncology Group (ECOG) performance score ≤2; and life-expectancy >12 weeks. Other inclusion criteria were adequate bone marrow, kidney and liver function. Patients were excluded if they had; peripheral neuropathy ≥2; surgical procedure 4 weeks before the measurement of CA 125; received hormonal, immuno-, or radiotherapy with 4 weeks of start of study treatment; bowel obstruction or tumours of other origin. Independent ethics committees at the sites approved the study protocol and all subsequent amendments. The study was conducted in accordance with the Declaration of Helsinki, and Good Clinical Practice.

2.2. Treatment plan

The patients received either experimental treatment: paclitaxel micellar 250 mg/m^2 administered as 1-h intravenous infusion followed by carboplatin 5–6 AUC, or control treatment: Cr-EL paclitaxel 175 mg/m^2 as 3-h intravenous infusion followed by carboplatin 5–6 AUC. Treatment was given in 6 cycles with 3 weeks in-between in both study arms. Patients in the control group received pre-medication according to local summary of product characteristics for Cr-EL paclitaxel. Pre-medication was not mandatory before paclitaxel micellar but could be given in preparation for the carboplatin infusion. Randomization was web-based in a 1:1 ratio with minimisation software and stratification was based on CA 125 values (< 250 U/L or ≥ 250 U/L) and relapse (first or second). Due to differences in appearances of the two treatments, infusion times and requirements for pre-medication, neither patients nor clinicians were blinded. The treatment period lasted from day of first dose until 22 days after the sixth dose. During the follow-up period, the patients were followed monthly with start at six months after first dose until progression or when leaving the study. Dose delays or reductions were made if unacceptable toxicity occurred. One dose reduction to 135 mg/m^2 was allowed for Cr-EL paclitaxel, and two dose reductions to 200 mg/m^2 and then 175 mg/m^2 were allowed for paclitaxel micellar. Computer tomography (CT) scans were performed within 6 weeks before start of first treatment (cycle 1), after cycles 3 and 6, and when the patient left the study to confirm progression. In a protocol amendment, the CT schedule during the follow-up period changed to include CT scans every 3rd month until end of study visit. 34% of the patients in each arm followed this amendment.

2.3. Safety assessments

All adverse events (AEs) were reported between first day of treatment and when the patient left the study. The severity was graded using Common Terminology Criteria for Adverse Events (CTCAE) v 3.0 [13]. All AEs were assessed by the investigator whether it was a HSR or not and if so, graded according to the British Columbia Cancer Agency (BCCA) summary.

2.4. Efficacy assessments

The primary endpoint, PFS, was defined as the time from randomization to progression or death of any cause. Tumour response was assessed using CT scans and evaluated centrally by an independent image review committee according to response evaluation criteria in solid tumours (RECIST) 1.0 [14].

OS was defined as the time between date of randomization and date of death. During the follow-up period (from November 2013 until August 2016), information of death was collected on a special form. Patients with no date of death, because they were still alive or it was not possible to obtain a date, were censored at last date of contact.

2.5. Quality of life

Quality of life was assessed among patients included in Russia, Sweden, Denmark and Finland using the 5 dimensions of EQ-5D and EORTC Quality of Life Questionnaire – Ovarian Cancer Module (QLQ-OV28) questionnaires. Assessments were done pre-treatment, at cycle 2/day 8, cycle 4/day 8, cycle 6/day 8, month 8, 10 and end of study. The analyses of summary scores were performed according to the EuroQoL [15] and EORTC [16] manuals, respectively.

2.6. Statistical design and monitoring

All statistical analyses were performed using SAS version 9.1.3. The intention-to-treat (ITT) population included all randomized patients, the per protocol (PP) population included all patients receiving 6 cycles

Table 1
Demographic and baseline characteristics (ITT population).

	Paclitaxel micellar (N = 397)	Cr-EL paclitaxel (N = 392)
Age (years)	56 ± 9 (26–81)	56 ± 9 (27–81)
Ethnicity		
White/Caucasian	396 (100%)	392 (100%)
Other	1 (0%)	0 (0%)
Body weight (kg)	76 ± 15 (43–125)	75 ± 15 (44–123)
Body surface area (m^2)	1.8 ± 0.2 (1.4–2.4)	1.8 ± 0.2 (1.4–2.2)
ECOG status		
0	202 (51%)	203 (52%)
1	181 (46%)	182 (46%)
2	14 (4%)	7 (2%)
Diagnosis		
Epithelial ovarian cancer	386 (97%)	369 (94%)
Fallopian tube cancer	7 (2%)	13 (3%)
Primary peritoneal cancer	4 (1%)	10 (3%)
Initial tumour stage (FIGO classification)		
Stage I	39 (10%)	36 (9%)
Stage II	43 (11%)	39 (10%)
Stage III	257 (65%)	251 (64%)
Stage IV	58 (15%)	65 (17%)
Histologic cell type at diagnosis		
Serous adenocarcinoma	258 (65%)	267 (68%)
Endometrioid adenocarcinoma	29 (7%)	28 (7%)
Mucinous adenocarcinoma	6 (2%)	8 (2%)
Undifferentiated carcinoma	6 (2%)	8 (2%)
Clear cell adenocarcinoma	3 (1%)	7 (2%)
Squamous carcinoma	1 (<1%)	0 (0%)
Mixed epithelial carcinoma	3 (1%)	9 (2%)
Malignant Brenner tumour	4 (1%)	0 (0%)
Adenocarcinoma, not specified	24 (6%)	18 (5%)
Other	45 (11%)	35 (9%)
Relapse		
First relapse	301 (76%)	298 (76%)
Second relapse	96 (24%)	94 (24%)
Platinum-free interval[a]		
6–12 months	159 (40%)	169 (43%)
12–24 months	121 (30%)	132 (34%)
>24 months	110 (28%)	90 (23%)
Prior cancer therapy		
Chemotherapy including platinum	396 (100%)	392 (100%)
Surgery	366 (92%)	359 (92%)
Hormone therapy	4 (1%)	3 (1%)
Radiotherapy	24 (6%)	22 (6%)

Numerical data are presented as mean ± sd (min–max) and categorical data as N (%).
[a] Period between end date of last platinum-containing chemotherapy and start of study drug administration.

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Table 2
Number of patients with pre-medication by treatment arm and relationship to paclitaxel or carboplatin.

	Paclitaxel micellar ($N = 391$)			Cr-EL paclitaxel ($N = 391$)		
	Overall	Paclitaxel	Carboplatin	Overall	Paclitaxel	Carboplatin
Antiemetics and antinauseants	341 (87%)	30 (8%)	316 (81%)	359 (92%)	149 (38%)	245 (63%)
Corticosteroids for systemic use	170 (43%)	23 (6%)	154 (39%)	387 (99%)	380 (97%)	58 (15%)
Antihistamines for systemic use	75 (19%)	15 (4%)	62 (16%)	333 (85%)	332 (85%)	37 (9%)
Drugs for acid related disorders	18 (5%)	9 (2%)	9 (2%)	350 (90%)	350 (90%)	4 (1%)

of treatment without major protocol violation, and the safety population included all treated patients. In the efficacy analysis, time to event parameters was analysed with the log-rank test stratified by CA 125 values and relapse. Kaplan-Meier plots were estimated. Additionally, a Cox proportional hazards model including the stratification factors and treatment were fitted to estimate the hazard ratio between the two treatment arms and its 95% confidence interval. The non-inferiority margin was set to equal to 1.2 for PFS and 1.185 for OS based on a meta-analysis on two available studies chosen because they best mirrored the design of the present study [17,18]. The trial was aimed at showing non-inferiority, however a claim of superiority could be made if the test rejected the null hypothesis of no treatment difference in favour of the experimental treatment.

3. Results

3.1. Patient characteristics

Between Jan 21, 2009 and Nov 7, 2013, 865 patients were screened, and 789 patients were randomized to receive experimental treatment ($N = 397$) or control treatment ($N = 392$) (Fig. 1). The baseline characteristics were balanced between the two arms (Table 1). In the paclitaxel micellar group, 77% of the patients progressed or died during the study compared to 81% in the Cr-EL paclitaxel group. Twelve patients in the paclitaxel micellar arm died during the treatment period and ten of these were associated with a fatal AE and two out of these were assessed by the investigator to be related to treatment (Table S1). Six

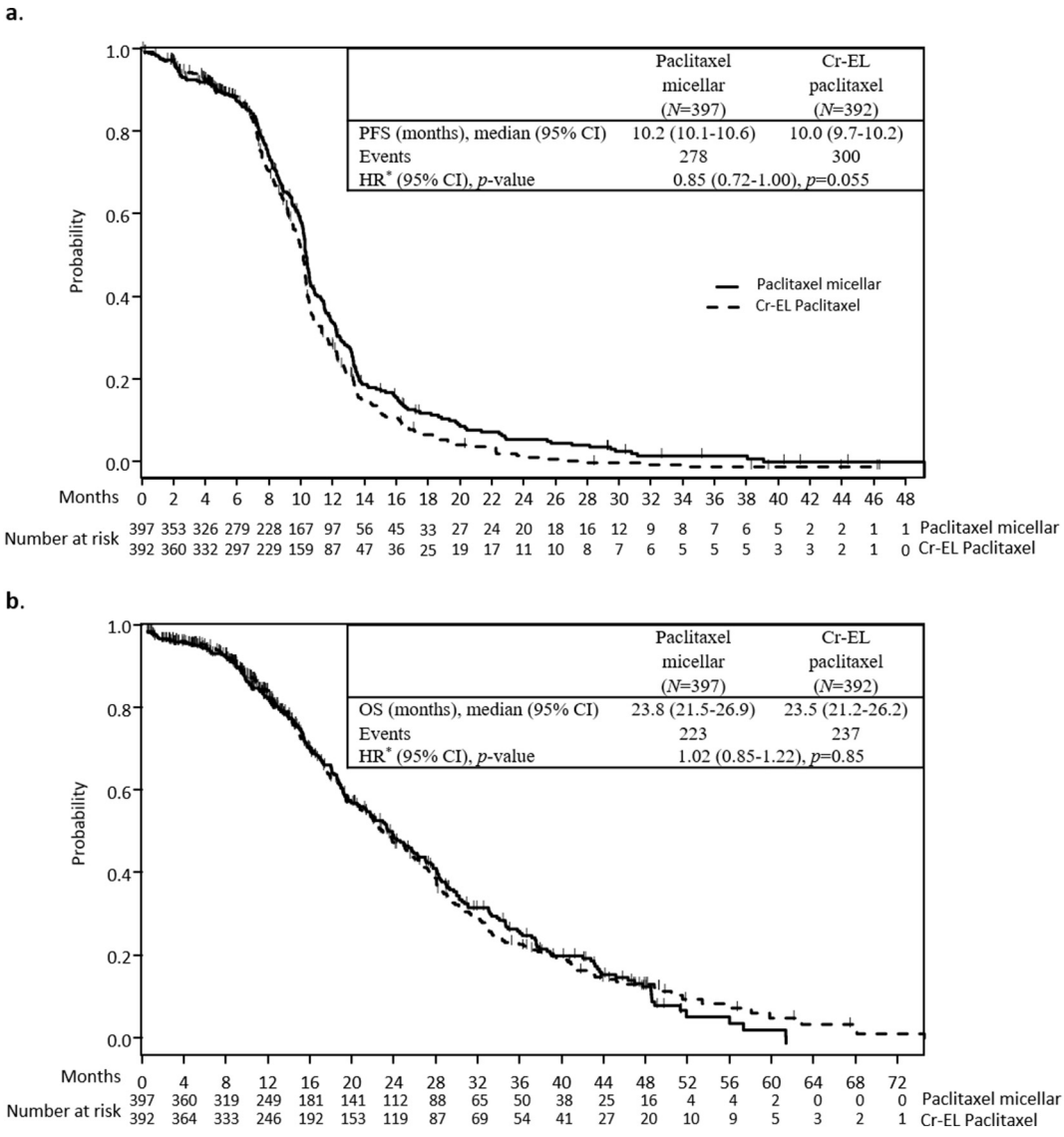

Fig. 2. Kaplan Meier curves of PFS (a.) and OS (b.) in the intention to treat (ITT) population. *The arms have been stratified for CA 125 and relapse. HR, hazard ratio; CI, confidence interval.

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patients died in the Cr-EL paclitaxel arm and five of these events were associated with a fatal AE and three were assessed by the investigator to be related to treatment (Table S2).

3.2. Pre-medication

Most patients in both arms received antiemetics either before the paclitaxel or the carboplatin infusions (87% in the paclitaxel micellar arm and 92% in the Cr-EL paclitaxel arm), see Table 2. It was a distinct difference in use of corticosteroids, antihistamines and proton pump inhibitors between the treatment arms. Whereas almost all patients received these pre-medications (85–99%) in the Cr-EL paclitaxel arm, 43% of the patients in the paclitaxel micellar arm received corticosteroids either before the paclitaxel or the carboplatin infusions, 19% received antihistamines and 5% received proton pump inhibitors (Table 2).

3.3. Efficacy

3.3.1. Progression free survival

PFS for the paclitaxel micellar group was determined to be non-inferior to the Cr-EL paclitaxel group; the hazard ratio was 0.86 (95% CI: 0.72;1.03) in the PP population (Fig. S1a and Fig. 3a) and 0.85 (95% CI: 0.72;1.00) in the ITT population (Fig. 2a and Fig 3a). The upper limit of the one sided 97.5% CI was thus well below the criteria of non-inferiority, 1.2. The median PFS were 10.3 (95% CI: 10.1;10.7) months for paclitaxel micellar and 10.1 (95% CI: 9.9;10.2) months for Cr-EL paclitaxel. The results are supported by a sub-group analysis only including patients with CT scans regularly performed every third month commencing at month seven, where median time to event was slightly higher in the paclitaxel micellar arm; 12.2 (95% CI: 10.3;13.2) months for paclitaxel micellar ($N = 120$) and 10.2 (95% CI: 10.1;11.1) months for Cr-EL paclitaxel ($N = 123$) with a hazard ratio of 0.76 (95% CI: 0.56;1.03) in the PP population. Median time to event in the ITT population was 12.0 (95% CI: 10.2;13.1) months for paclitaxel micellar ($N = 133$) and 10.2 (95% CI: 10.0;10.3) months for Cr-EL paclitaxel (N = 133) with a hazard ratio of 0.74 (95% CI: 0.55;0.99) (Table S3). The results are also supported by a CA125 sensitivity analysis for PFS based on CT scans according to RECIST (Table S3).

3.3.2. Overall survival

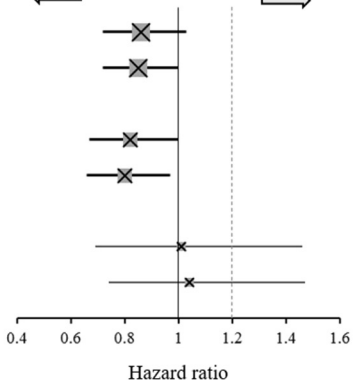
Non-inferiority was also shown for OS in the PP population; hazard ratio of 0.95 (95% CI: 0.78;1.16). Median OS time in the PP population was 25.7 months in the paclitaxel micellar arm and 24.8 months in the Cr-EL paclitaxel arm (Fig. S1b and Fig. 3b). Median survival time in the ITT population was similar between the arms (Fig. 2b) but non-inferiority could not be established (hazard ratio: 1.02 (95% CI: 0.85;1.22)) (Fig. 2b and Fig. 3b).

3.3.3. Efficacy in first and second relapses

A sub-group analysis was performed to estimate treatment effects in first and second relapse (Fig. 3). The overall effects were confirmed in

a.

	N (all)	Paclitaxel micellar n	events	Median PFS (months)	Cr-EL paclitaxel n	events	Median PFS (months)	HR* (95% CI)
All patients								
PP	644	311	239	10.3	333	270	10.1	0.86 (0.72-1.03)
ITT	789	397	278	10.2	392	300	10.0	0.85 (0.72-1.00)
First relapse								
PP	497	240	180	10.3	257	209	10.1	0.82 (0.67-1.00)
ITT	599	301	208	10.3	298	231	10.0	0.80 (0.66-0.97)
Second relapse								
PP	147	71	59	9.9	76	61	10.1	1.01 (0.69-1.46)
ITT	190	96	70	9.9	94	69	10.1	1.04 (0.74-1.47)



b.

	N (all)	Paclitaxel micellar n	events	Median OS (months)	Cr-EL paclitaxel n	events	Median OS (months)	HR* (95% CI)
All patients								
PP	644	311	179	25.7	333	206	24.8	0.95 (0.78-1.16)
ITT	789	397	223	23.8	392	237	23.5	1.02 (0.85-1.22)
First relapse								
PP	497	240	139	26.1	257	162	23.6	0.92 (0.73-1.16)
ITT	599	301	172	24.7	298	186	23.4	0.98 (0.79-1.21)
Second relapse								
PP	147	71	40	23.2	76	44	24.8	1.07 (0.68-1.68)
ITT	190	96	51	19.1	94	51	23.8	1.18 (0.79-1.75)

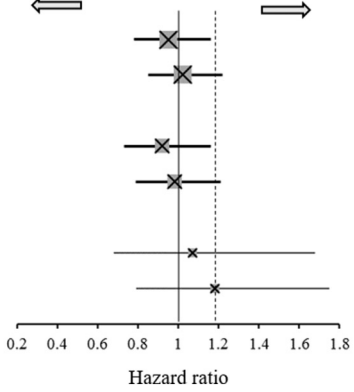


Fig. 3. Forest plot per relapse for (a.) progression free survival (PFS) and (b.) overall survival (OS) in the per-protocol (PP) and (ITT) population. * The arms have been stratified for CA 125 and relapse. Dashed line indicates non-inferiority margin. HR, hazard ratio; CI, confidence interval.

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patients with first relapse but not in the small subpopulation with second relapse. The hazard ratio of 0.80 (95% CI: 0.66;0.97) suggest a significant benefit of paclitaxel micellar for PFS in patients with first relapse (Fig. 3a).

3.4. Adverse events

90% of the patients in the paclitaxel micellar arm experienced at least one AE and 40% had at least one SAE during the treatment period. In the Cr-EL arm, 87% of the patients had at least one AE and 26% had a SAE. 60% of the patients treated with paclitaxel micellar and 46% of the patients treated with Cr-EL paclitaxel had at least one dose delay (Tables S4 and S5). At least one dose reduction was noted in 18% of the patients in the paclitaxel micellar arm (mainly at 200 mg/m^2) and 12% in the Cr-EL paclitaxel arm (at 135 mg/m^2). The most common reason for dose-reductions and dose-delays was haematological toxicity. There were numerically higher frequencies of AEs reported in the paclitaxel micellar arm compared to the Cr-EL arm and the most common events ≥ CTCAE grade 3 was haematological AEs, mainly neutropenia, in both arms (Table 3). For non-haematological AEs, alopecia and nausea were reported as the most common events (any grade) in both arms. The classification of an adverse event as HSR was based on the investigator's judgement and the frequency of paclitaxel-related hypersensitivity reactions was similar in both groups (5% of the patients receiving paclitaxel micellar and 7% of the patients receiving Cr-EL paclitaxel), whereas a higher frequency of carboplatin-related hypersensitivity reactions was observed in the group receiving paclitaxel micellar (12% vs 7%). As a result of the combined treatment, delayed reactions related to paclitaxel cannot be excluded. The overall frequency of HSR was similar in both arms; 15% and 13% for paclitaxel micellar and Cr-EL, respectively. Infusion site reactions were experienced by 12% in the paclitaxel micellar arm and 1% in the control arm. The infusion site reactions observed constituted mainly of low grade (CTCAE grade 1 or 2) events including pain but also phlebitis, discolouration, redness, oedema and rash. A lower proportion of patients with at least one peripheral sensory neuropathy (any grade) was reported in the paclitaxel micellar arm (16%) compared to the Cr-EL paclitaxel arm (20%) (Table 3). Number of patients with at least one neuropathy (neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy or polyneuropathy in malignant disease) were 112 (29%) and 124 (32%) in the paclitaxel micellar and the Cr-EL paclitaxel arms, respectively. Use of granulocyte colony stimulating factor (G-CSF) was permitted in case of life-threatening condition requiring its use or as prophylactic due to neutropenic fever or delays caused by neutropenia. 35% of the patients in the paclitaxel micellar group and 30% of the patients in the Cr-EL paclitaxel group received G-CSF to treat neutropenia. The median number of cycles with administration of G-CSF was 3 in both groups.

3.5. Adverse event profile by relapse

The toxicity profile in first and in second relapse patients followed the same trend as in the entire population (Table 4). Neutropenia as a SAE showed a difference between the two treatment arms also in first relapse patients (Table 4). The relative daily dose of paclitaxel micellar was slightly higher in second relapse patients (96% of the dose was received) than in the first relapse patients (91%) or the entire population (91%). In general, the toxicity profile was not worse in second relapse compared to first relapse patients in the paclitaxel micellar arm.

3.6. Quality of life

Quality of life data at pre-treatment were available for 184 patients (98%) randomized to the paclitaxel micellar arm and 174 patients (98%) randomized to the Cr-EL arm at sites in Russia, Sweden, Denmark and Finland. Data at end of study were available for 136 patients (72%) in the paclitaxel micellar arm and 122 patients (69%) in the Cr-EL arm. There were no marked differences in quality of life assessed by EQ-5D. Summary scores for EQ VAS were as follows; 66.9 ± 16.9 (paclitaxel micellar), 68.6 ± 17.8 (Cr-EL paclitaxel) at pre-treatment, 64.6 ± 17.8 (paclitaxel micellar), 67.9 ± 17.3 (Cr-EL paclitaxel) at cycle 6/day 8, and 63.6 ± 18.3 (paclitaxel micellar), 63.8 ± 17.6 (Cr-EL paclitaxel) at end of study. There were no major differences noted between the two treatment groups for any of the QLQ-OV28 scales (i.e. abdominal/gastrointestinal, peripheral neuropathy, hormonal, body image, attitude to disease/treatment, chemotherapy side effects, other single items) either (data not shown).

4. Discussion

The present study shows that paclitaxel micellar (+carboplatin) is non-inferior to Cr-EL paclitaxel (+carboplatin) in terms of PFS and OS. The results in the subgroup of patients with first relapse are consistent with the results in the overall population and in addition, there was an indication of PFS benefit for paclitaxel micellar (Fig. 3a). It is a commonly observed pattern and expected that the efficacy of treatment may decrease with disease relapses. Statistical non-inferiority could not be shown in the smaller subpopulation with second relapse (n = 71 and n = 76, respectively). Hanker et al. 2012 [19] reported that for second relapse patients (including both platinum sensitive and resistant patients) receiving any kind of treatment or no treatment, the median PFS was 6.4 (5.9–7.0) months and the median OS was 11.3 (10.4–12.9) months. The present study suggests a median PFS of 3.5 month longer and a median OS of 11 months longer for second relapse patients. A meta-analysis suggests that treatment of up to four relapses may improve PFS and OS [19].

There were numerically higher frequencies of AEs, mainly connected to bone-marrow suppression in the paclitaxel micellar arm. However, all were considered uncomplicated and did not translate into relevant

Table 3
Most common adverse events (>10% in any arm).

	Paclitaxel micellar (N = 391)		Cr-EL paclitaxel (N = 391)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Haematological adverse events				
Anaemia[a]	381 (98%)	92 (24%)	372 (96%)	55 (14%)
Thrombocytopenia[a]	361 (93%)	69 (18%)	341 (88%)	38 (10%)
Leukopenia[a]	383 (98%)	208 (53%)	371 (96%)	130 (34%)
Neutropenia[b]	302 (97%)	245 (79%)	308 (96%)	213 (66%)
Non-haematological adverse events				
Abdominal pain	42 (11%)	2 (0.5%)	32 (8%)	3 (0.8%)
Diarrhoea	66 (17%)	5 (1.3%)	36 (9%)	1 (0.3%)
Nausea	162 (41%)	4 (1.0%)	155 (40%)	0 (%)
Vomiting	95 (24%)	5 (1.3%)	59 (15%)	3 (0.8%)
Asthenia	101 (26%)	5 (1.3%)	97 (25%)	4 (1.0%)
Fatigue	52 (13%)	6 (1.5%)	46 (12%)	6 (1.5%)
Anorexia	44 (11%)	1 (0.3%)	44 (11%)	1 (0.3%)
Arthralgia	79 (20%)	1 (0.3%)	76 (19%)	1 (0.3%)
Myalgia	42 (11%)	1 (0.3%)	51 (13%)	1 (0.3%)
Neuropathy peripheral	42 (11%)	0 (0%)	41 (10%)	0 (0%)
Peripheral sensory neuropathy	61 (16%)	1 (0.3%)	77 (20%)	0 (0%)
Alopecia	183 (47%)	0 (0%)	183 (47%)	0 (0%)

Adverse events are graded according to NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events).
[a] N = 390 (paclitaxel micellar) and N = 386 (Cr-EL paclitaxel).
[b] Grade 3 and above according to lab values.

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Table 4
Patients (%) experiencing at least one event of the most common adverse events by relapse.

	Entire population		First relapse		Second relapse	
	Paclitaxel micellar ($N = 391$)	Cr-EL paclitaxel ($N = 391$)	Paclitaxel micellar ($N = 297$)	Cr-EL paclitaxel ($N = 297$)	Paclitaxel micellar ($N = 94$)	Cr-EL paclitaxel ($N = 94$)
Any adverse event	90%	87%	91%	87%	89%	89%
Any serious adverse event (SAE)	40%	26%	40%	23%	39%	35%
Haematological adverse events as SAE						
Anaemia	4%	3%	4%	3%	9%	4%
Thrombocytopenia	2%	2%	3%	3%	4%	5%
Leukopenia	5%	2%	6%	2%	5%	3%
Neutropenia	28%	19%	31%	18%	24%	27%
Non-haematological adverse events						
Abdominal pain	11%	8%	10%	9%	12%	4%
Diarrhoea	17%	9%	17%	10%	17%	6%
Nausea	41%	40%	45%	40%	31%	38%
Vomiting	24%	15%	26%	15%	19%	15%
Asthenia	26%	25%	27%	27%	22%	17%
Fatigue	13%	12%	13%	12%	14%	12%
Anorexia	11%	11%	12%	11%	10%	11%
Arthralgia	20%	19%	21%	21%	19%	15%
Myalgia	11%	13%	11%	14%	11%	9%
Neuropathy peripheral	11%	10%	11%	11%	9%	9%
Peripheral sensory neuropathy	16%	20%	16%	21%	14%	15%
Alopecia	47%	47%	51%	48%	34%	43%

clinical consequences such as febrile neutropenia or more infections. 60% of the patients treated with paclitaxel micellar had at least one dose delayed though, mainly due to haematological toxicity. This could potentially affect the efficacy results, but a subgroup analysis showed no indication that delaying the dose would affect the PFS efficacy (Table S4). Neutropenia was by far the most common event in the study and importantly, the data observed for paclitaxel micellar and Cr-EL paclitaxel (neutropenia grade 3 and 4) were in agreement with an incidence prediction based on a Cr-EL paclitaxel model for neutropenia [20]. This model suggests that the dose-neutropenia relationship for paclitaxel is not linear, but follows a sigmoidal curve, and hence an increase in dose is not directly proportional with an increase in toxicity. In terms of non-haematological toxicities, the trial failed to meet its initial stated objective of demonstrating superiority of the paclitaxel micellar arm in terms of HSRs, most likely because of the premedication of corticosteroids, antihistamines and H2-antagonists in the Cr-EL paclitaxel group. It was initially thought that patients treated with Cr-EL paclitaxel would experience HSR despite pre-medication, but this was not the case and fewer HSRs than expected were observed during trial conduct. The peripheral infusion site reactions observed following paclitaxel micellar are most likely connected to the novel excipient. However, the risk for these events to occur is probably reduced by using a central venous catheter for drug administration.

A major concern with paclitaxel therapies is the dose-limiting peripheral neurotoxicity. Paclitaxel-related neuropathy has been reported to depend on several factors such as cumulative dose and duration of therapy [21] and a higher dose is related to higher incidence of sensory neuropathy [22,23]. Cr-EL has also been associated with peripheral neuropathy [24] and thereby both paclitaxel and Cr-EL can contribute to neuropathies. Importantly, a similar or even a somewhat lower proportion of patients with peripheral neuropathies was seen in the paclitaxel micellar arm despite the higher dose.

Even though the study showed that the efficacy goals were reached for the studied populations, there is a concern that patients who progress after two consecutive therapy regimens have a diminished likelihood of benefitting from additional therapy [25]. 42% of the patients in the first relapse group and 65% in the second relapse group in the paclitaxel micellar arm had previously been exposed to taxanes and the corresponding number of patients in the Cr-EL paclitaxel arm is similar with 50% in the first and 62% in second relapse group. Interestingly, the toxicity profile in second-relapse patients in this study was not worse compared to the population of patients with first relapse only, supporting platinum and paclitaxel as a treatment option for these patients.

As mentioned, the development of a Cr-EL-free option has allowed a shorter infusion time without requirement of premedication. These improvements may provide health-economy advantages similar to the lower costs identified in a cost-effectiveness analysis performed in the Italian hospital system for nab-paclitaxel, with regard to infusion time and pre-medication, compared to conventional paclitaxel [11].

The use of PARP-inhibitors has recently provided an additional maintenance treatment option for patients with partial or complete response in order to prolong the period of disease control and delay progression [26].

In conclusion, paclitaxel micellar provides a Cr-EL-free formulation that can be administered at a high dose without mandatory premedication. More myelosuppression was reported during treatment with paclitaxel micellar but peripheral neuropathies were not more frequent despite the higher dose. In combination with carboplatin, paclitaxel micellar is non-inferior to Cr-EL paclitaxel in treatment of first and second relapse of platinum-sensitive ovarian, fallopian tube or peritoneal carcinoma, with a tendency favouring paclitaxel micellar in terms of PFS.

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Author contribution

IgnaceVergote: Conceptualization, Methodology, Investigation. Nina Heldring: Writing-original draft, Project administration, Funding acquisition, Visualization. Helena Bjermo: Writing- original draft, Project administration, Funding acquisition, Visualization. Kjell Bergfeldt: Methodology, Writing-Review and Editing. Ann Franquet: Data curation, Formal analysis, Validation, Writing-Review and Editing. Marc

Buyse: Formal analysis, Validation, Writing-Review and Editing. Alla Lisyanskaya: Investigation, Writing-Review and Editing. Arija Brize: Investigation, Writing-Review and Editing.

Declaration of competing interest

N. Heldring and H. Bjermo are full time employees at Oasmia Pharmaceutical AB.

I. Vergote, A.S. Lisyanskaya and A. Brize were investigators in the clinical trial. M. Buyse has stock and ownership to disclose in IDDI. K. Bergfeldt was a salaried consultant at Oasmia Pharmaceutical AB. The remaining author has declared no conflict of interest.

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Table S1. Deaths associated with fatal AE's in the paclitaxel micellar arm

Patient	Investigator assessment	SOC	PT coded in study	Comment
1	Not related	Nervous system disorders	Coma, status epilepticus	Autopsy concluding disease progression
2	Not related	Renal and urinary disorders	Azotaemia	-
		Metabolism and nutrition disorders	Hyperglycaemic hyperosmolar nonketotic syndrome	
3	Not related	Gastrointestinal disorders	Intestinal functional disorder	Disease progression, no autopsy performed
4	Not related	Respiratory, thoracic and mediastinal disorders	Respiratory failure	-
5	Related	General disorders and administration site conditions	Multiorgan failure	Autopsy concluding final stage of cancer.
		Blood and lymphatic system disorders	Pancytopenia	Pancytopenia is related and multi-organ failure not related
6	Related	Blood and lymphatic system disorders	Febrile neutropenia	Autopsy concluding hepatorenal insufficiency caused death
7	Not related	Blood and lymphatic system disorders	Disseminated intravascular coagulation	Autopsy concluding disease progression
		Neoplasms benign, malignant and unspecified	Paraneoplastic syndrome	
8	Not related	Vascular disorders	Embolism	-
9	Not related	Respiratory, thoracic and mediastinal disorders	Pulmonary artery thrombosis	-
10	Not related	General disorders and administration site conditions	Death	-

SOC, System Organ Classe; PT, Preferred Term

Table S2. Deaths associated with fatal AE's in the Cr-EL paclitaxel arm

Patient	Investigator assessment	SOC	PT coded in study	Comment
1	Related	Blood and lymphatic system disorders	Thrombocytopenia	-
		Infections and infestations	Sepsis	
2	Related	General disorders and administration site conditions	Sudden death	-
3	Related	Hepatobiliary disorders	Cholecystitis chronic	-
4	Not related	Cardiac disorders	Cardiac failure acute	-
5	Not related	Neoplasms benign, malignant and unspecified	Malignant ascites	Disease progression

SOC, System Organ Classe; PT, Preferred Term

Table S3. Sensitivity analyses for progression free survival in months based on CT according to RECIST 1.0

	Paclitaxel micellar (*N*=391)			Cr-EL paclitaxel (*N*=391)			Hazard ratio
	n	events	Median (95% CI)	n	events	Median (95% CI)	(95% CI)
CA125 sensitivity analysis							
Per Protocol	311	268	10.1 (9.9-10.3)	333	290	10.1 (9.7-10.1)	0.89 (0.75-1.05)*
Intention-to-treat	397	309	10.1 (9.8-10.2)	392	324	9.8 (9.3-10.1)	0.87 (0.74-1.02)*
Patients with CT every 3rd month during follow up							
Per Protocol	120	86	12.2 (10.3-13.2)	123	94	10.2 (10.1-11.1)	0.76 (0.56-1.03)*
Intention-to-treat	133	88	12.0 (10.2-13.1)	133	102	10.2 (10.0-10.3)	0.74 (0.55-0.99)*

*Non-inferiority was shown.

Table S4. Progression free survival in months based on CT according to RECIST 1.0 for patients having or not having serous adenocarcinoma or patients with dose delay

	Paclitaxel micellar (*N*=391)			Cr-EL paclitaxel (*N*=391)			Hazard ratio
	n	events	Median (95% CI)	n	events	Median (95% CI)	(95% CI)
Patients with serous adenocarcinoma at diagnosis							
Per Protocol	202	153	10.2 (10.0-11.2)	231	188	10.1 (9.9-10.2)	0.85 (0.68-1.05)*
Intention-to-treat	258	177	10.1 (10.0-10.7)	267	208	10.1 (9.7-10.2)	0.85 (0.69-1.04)*

Patients not having serous adenocarcinoma at diagnosis							
Per Protocol	109	86	10.3 (10.0-11.1)	102	82	10.2 (9.3-10.7)	0.85 (0.62-1.16)*
Intention-to-treat	139	101	10.3 (9.9-11.1)	125	92	9.8 (9.8-10.4)	0.81 (0.60-1.08)*
Patients with at least one dose delay							
Per Protocol	202	159	10.3 (10.1-11.1)	168	138	10.2 (9.8-10.6)	0.90 (0.71-1.14)*
Intention-to-treat	236	177	10.3 (10.1-11.1)	180	144	10.1 (9.7-10.5)	0.89 (0.71-1.11)*

*Non-inferiority was shown.

Table S5. Overall survival in months for patients having or not having serous adenocarcinoma or patients with dose delay related to chemotherapy complications

	Paclitaxel micellar (*N*=391)			Cr-EL paclitaxel (*N*=391)			Hazard ratio (95% CI)
	n	events	Median (95% CI)	n	events	Median (95% CI)	
Patients with serous adenocarcinoma at diagnosis							
Per Protocol	202	108	26.8 (22.9-29.1)	231	231	22.7 (20.4-26.7)	0.85 (0.66-1.09)*
Intention-to-treat	258	137	23.8 (21.5-27.5)	267	165	22.5 (20.3-26.3)	0.96 (0.76-1.20)
Patients not having serous adenocarcinoma at diagnosis							
Per Protocol	109	71	25.2 (20.2-28.4)	102	60	26.2 (22.3-31.6)	1.14 (0.80-1.63)
Intention-to-treat	139	86	23.8 (19.1-28.4)	125	72	25.2 (20.5-29.4)	1.13 (0.82-1.57)

Patients with dose delay related to chemotherapy complications							
Per Protocol	146	96	24.8 (19.1-28.4)	124	78	27.1 (23.3-29.4)	1.32 (0.97-1.80)
Intention-to-treat	170	108	23.8 (18.9-27.9)	134	82	27.1 (23.5-29.4)	1.42 (1.06-1.91)

*Non-inferiority was shown.