Pegylated Liposomal Doxorubicin and Carboplatin in Late-relapsing Ovarian Cancer: A GINECO Group Phase II Trial

BÉATRICE WEBER[1], ALAIN LORTHOLARY[2], FRANÇOISE MAYER[3], HUGUES BOURGEOIS[4], HUBERT ORFEUVRE[5], MARTIN COMBE[6], CHRISTIAN PLATINI[7], JACQUES CRETIN[8], DANIÈLE FRIC[9], DÉSIRÉ PARAISO[10] and ERIC PUJADE-LAURAINE[11]

Departments of Medical Oncology: [1]Centre Alexis Vautrin, Vandoeuvre-les-Nancy; [2]Centre Catherine de Sienne, Nantes; [3]Centre Georges-François Leclerc, Dijon; [4]Centre Jean Bernard, Le Mans; [5]Centre Hospitalier Fleyriat, Bourg-en-Bresse; [6]Centre Hospitalier Général, Le Mans; [7]Hôpital Notre-Dame de Bon Secours; Metz, [8]Clinique Valdegour, Nîmes; [9]Clinique du Mail, Grenoble; [10]Centre Hospitalier Général, Montargis; [11]Hôpital Hôtel-Dieu; and Université Paris Descartes (AP-HP), Paris, France

Abstract. *Background: The GINECO group previously demonstrated that pegylated liposomal doxorubicin (PLD)-carboplatin combination was an effective and well-tolerated treatment for advanced ovarian cancer (AOC) patients in late relapse. The purpose of the present analysis was to confirm these results in a prospective cohort of late-relapsing AOC patients. Patients and Methods: Eighty-one consecutive patients received PLD 30 mg/m^2, followed by carboplatin (area under the curve) 5 mg min/ml, every 28 days for 6 courses or until progression. Results: The objective response (OR) rate was 65.4% . The median progression-free survival (PFS) and overall survival (OS) were 13.6 months and 38.9 months, respectively. Haematological toxicities were more common than non-haematological toxicities. Non-hematologic adverse reactions were moderate and grade 3 palmar-plantar erythrodysesthesia was limited to one patient. No cardiotoxicity was observed and no toxic death occurred. Conclusion: These data support the clinical efficacy and tolerability of PLD in combination with carboplatin as second-line therapy for AOC patients in late relapse.*

Although being the fifth most prevalent female cancer, ovarian cancer remains the leading cause of death among gynaecological malignancies (1). Because early-stage ovarian cancer is generally asymptomatic, most women (70% -75%) present with stage III/IV disease (2). While approximately 85% of patients respond to surgery and first-line chemotherapy, 50% to 75% of patients with advanced ovarian cancer (AOC) experience recurrent disease (3).

In these patients, the choice of a second-line treatment is generally based on the length of the therapy-free interval (TFI) defined as the time from the date of the last platinum-based chemotherapy cycle until the date of disease progression. In patients with partially platinum-sensitive recurrent disease (TFI between 6 and 12 months), rechallenge with a platinum-based chemotherapy is an option (4-6). Some studies have suggested that the use of non-platinum compounds, as a single-agent or in combination, may also be of benefit in these partially platinum-sensitive patients (7-9). However, re-treatment with a platinum-based combination remains the standard of care for patients with disease that relapses beyond twelve months after completion of an initial platinum- and paclitaxel-based regimen. In five trials involving patients considered as sensitive to platinum-containing chemotherapy, a further platinum-based polychemotherapy significantly improved the progression-free survival (PFS) in four trials, and the overall survival (OS) in three trials when compared with single-agent chemotherapy using carboplatin or paclitaxel (10-14). Out of the three randomized trials reporting an improvement in OS with a platinum-based combination, two compared the combination of carboplatin and paclitaxel to carboplatin alone. This led to the opinion that re-treatment with carboplatin and paclitaxel should be considered in patients with platinum-sensitive disease and a TFI beyond twelve months.

A limitation of platinum-taxane therapy in women with AOC in late relapse rests in the wide use of this combination

Correspondence to: Pr. Eric Pujade-Lauraine, Département d'Oncologie Médicale, Hôpital Hôtel-Dieu, 1 place du Parvis Notre-Dame, 75004 Paris, France. Tel: +33 142348028, Fax: +33 142348110, e-mail: epujade@arcagy.org

Key Words: Advanced ovarian cancer, late relapse, pegylated liposomal doxorubicin, carboplatin, platinum-sensitive.

in first-line therapy, leading to adverse events such as neurotoxicity and alopecia (11-18). Patients may be at risk of more severe neurological events in the event of re-treatment with a taxane. The need for effective, convenient and well-tolerated therapies for patients with AOC has led researchers to continually refine chemotherapeutic regimens in an effort to balance efficacy with safety and tolerability. The substitution of paclitaxel by gemcitabine in carboplatin-based chemotherapy allowed a lower rate of alopecia and neurotoxicity (12). Although the gemcitabine-carboplatin combination led to a higher rate of myelotoxicity and had the drawback of frequent infusions. The combination of gemcitabine with carboplatin significantly increased PFS compared to carboplatin as a single-agent, without improvement in OS. There is thus an obvious need for other platinum-based regimens in platinum-sensitive recurrent ovarian cancer patients in late relapse. Pegylated liposomal doxorubicin (PLD) is an attractive drug to combine with platinum in place of paclitaxel as it induces a very low rate of alopecia and neurotoxicity (19, 20). In addition, patients with platinum-sensitive recurrent disease treated with PLD as a single-agent had a longer OS than those treated with topotecan or gemcitabine (21, 22).

We have previously demonstrated in a large phase II study of 104 platinum-sensitive patients that PLD 30 mg/m^2 followed by carboplatin at area under the curve (AUC) of 5 mg min/ml every 28 days, was well tolerated (23). This combination was found to be effective with a 63% objective response (OR) and a median survival time of 32 months. The purpose of the present phase II trial was to confirm these encouraging results in a cohort of consecutive AOC patients in late relapse similarly treated and registered in the GINECO data centre.

Patients and Methods

Study population. Consecutive patients with ovarian adenocarcinoma and disease progression occurring at least 6 months after the end of a first or second-line chemotherapy were registered at the GINECO data centre, as part of a cohort study of patients in late relapse treated with PLD and carboplatin. The protocol was submitted to the Ethics Committee/Institutional Review Board and the study was conducted according to the Declaration of Helsinki and European Good Clinical Practice requirements.

The eligibility criteria for participating in this cohort study were similar to those described in the previous phase II trial (23). Prior treatment with one or two lines of chemotherapy, of which one included a platinum salt and a taxane, was required. The patients were required to have measurable lesions and/or a carbohydrate antigen (CA) 125 level ≥40 IU/ml, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and adequate organ functions. Treatment consisted of PLD 30 mg/m^2 infused over one hour, followed by carboplatin at AUC 5 mg min/ml infused over 30 minutes (maximum dose of 800 mg in patients with a creatinine clearance >135 ml/min). The treatment was repeated every 28 days. At baseline, an assessment of left ventricular ejection fraction (LVEF) measured at rest by radioisotopic or ultrasonographic methods was mandatory. The clinical assessment and laboratory tests, including CA 125 levels, were repeated before each cycle.

The data collected included demographics and baseline characteristics, compliance to chemotherapy, haematological and non-haematological adverse events, response to chemotherapy, and survival parameters (time to tumour progression, death).

Efficacy assessment. The response was assessed by clinical and radiological (chest X-ray, CT-scan) evaluations every two cycles. In the patients achieving an OR, a confirmatory assessment was recommended at least 4 weeks after the first examination. The patients with at least one measurable lesion were evaluated for response according to the standard World Health Organization (WHO) efficacy criteria. Non-measurable lesions were categorized as evaluable or not evaluable. In the patients with measurable disease, a clinical complete response (CR) was defined as the complete disappearance of all signs of measurable or evaluable disease with CA 125 level normalization for at least 4 weeks. A partial response (PR) was defined as per the WHO efficacy criteria. The patients who showed neither a CR nor a PR were considered non-responders. The patients with non-measurable disease and CA 125 levels ≥40 IU/ml were evaluated according to the Gynecologic Cancer InterGroup (GCIG) criteria (24). A serological response was achieved if there was at least a 50% reduction in the CA 125 levels compared to the pretreatment sample. The response had to be confirmed and maintained for at least 28 days. The serological response was considered as complete (*i.e.*, serological CR) when the CA 125 level was normalized for at least 28 days. Patients were not eligible if they had no measurable disease and a baseline CA 125 level <40 IU/ml.

The PFS was calculated from the first day of treatment until the date of progression or death from any cause. Progression was defined as an increase of 25% or more in existing lesions, and/or the appearance of new lesions, and/or serological progression according to the GCIG criteria. The OS was calculated from the first day of treatment until death.

Safety assessment. Safety was evaluated during each cycle. Using National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, the highest grade of toxicity encountered during treatment was recorded before each cycle and during follow-up. Follow-up visits were planned every 3 months for 2 years, then every 6 months for 5 years or until death. All the patients receiving at least one cycle of treatment were assessable for toxicity.

Statistical analysis. The primary end-point was OR and secondary end-points were compliance to chemotherapy, incidence of adverse events and survival.

To summarize the results, the qualitative data were presented as a percentage of the sample size and the quantitative data were described using mean, median, standard deviation and range. The Chi-square test was used to compare proportions, replaced by Fisher exact test if the expected frequency in any one of the cells of the contingency table was less than 5. Ordinal variables were compared using analysis of variance or Kruskal-Wallis test in the absence of variance equal terms, confirmed by a Bartlett test.

The relapse-free and alive patients were censored at the date of their last known contact. The PFS and OS rates were calculated by the Kaplan-Meier method.

Table I. *Patient demographics*.

Characteristics	Number of patients	Percentage
Assessable patients	81	
Age, years median (range)	62 (31-80)	
Histology		
Serous papillary	61	75
Endometrioid	6	8
Other	14	17
Histological grade		
1	8	10
2	22	27
3	24	30
Unknown	27	33
Number of previous CT regimens		
1	62	76
2	19	24
Treatment-free interval		
<6 months	0	0
6 to 12 months	32	40
≥12 months	49	60
Response to previous platinum-taxane regimen		
Complete	70	87
Clinical partial	6	7
None	5	6
ECOG performance status		
0	41	51
1	36	44
2	4	5
Ascites	25	31
Type of lesions		
Measurable	43	53
Non-measurable and CA 125≥40 IU/ml	36	44
Not evaluable	2	3
Number of disease sites		
1	49	61
>1	32	39

CT, Chemotherapy; ECOG, Eastern Cooperative Oncology Group.

Results

Patient and treatment characteristics. From March 2001 to October 2003, 81 consecutive patients participating in this cohort study were registered in the GINECO data centre. The baseline characteristics are summarized in Table I.

The patients received a median of 6 cycles of chemotherapy (range, 1 to 10), and 28 (35%) received more than 6 cycles. The median doses of PLD and carboplatin were 97% and 98.4% of the planned doses, respectively. Dose reduction and course delay, due mainly to delays in haematological recovery, were observed in 29.6% and 50.7% of the patients, and 6.7% and 14.7% of the cycles, respectively.

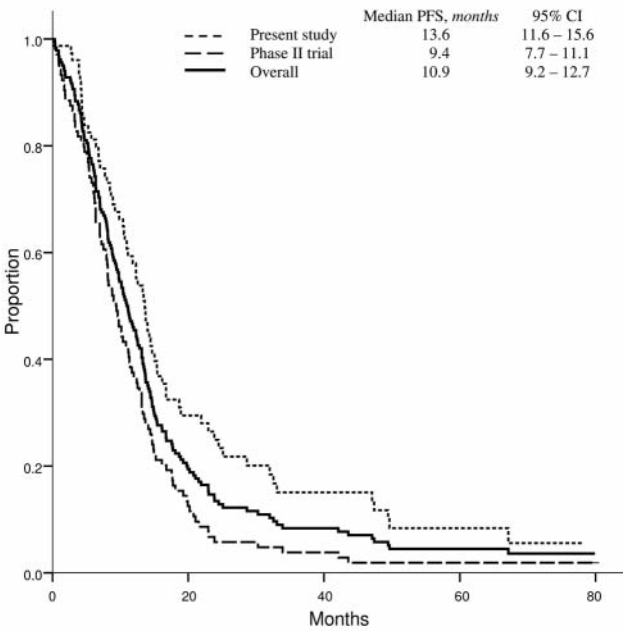

Figure 1. *Progression-free survival: data from previous (23) and present trials and pooled data*.

Table II. *Response rates, median progression-free and overall survival according to the therapy-free interval*.

Response, n (%)	
Complete response	32 (39.5)
Partial response	21 (25.9)
Overall response	53 (65.4)
Stable disease	18 (22.2)
Progressive disease	5 (6.2)
Not evaluable	5 (6.2)
Median PFS, months	
Overall	13.6
TFI<12 months	9.8
TFI≥12 months	14.4
Median OS, months	
Overall	38.9
TFI<12 months	30.0
TFI≥12 months	54.0

PFS, Progression-free survival; OS, overall survival; TFI, therapy-free interval.

Efficacy. The intent-to-treat efficacy analysis was based on 81 patients, including five patients not assessable for response. The OR rate was 65.4% (Table II). The median PFS was 13.6 months (95% confidence interval [CI], 11.6 to 15.6 months) (Figure 1). The median OS was 38.9 months (95% CI, 26.7 to 51.2 months) (Figure 2). The median PFS and OS according to the TFI are summarized in Table II.

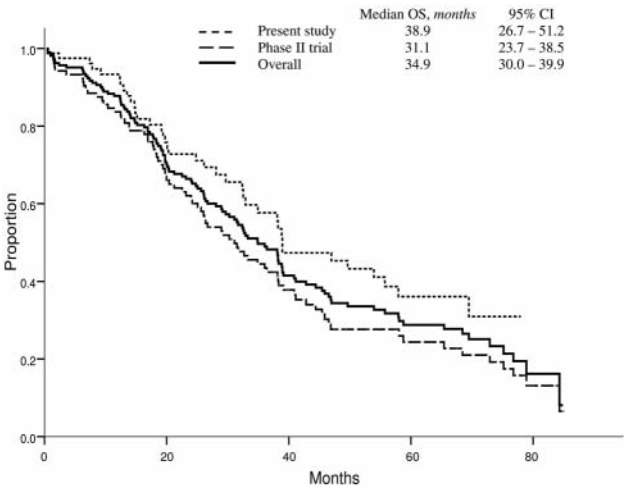

Figure 2. *Overall survival: data from previous (23) and present trials and pooled data.*

Safety. Haematological toxicity was more common than non-haematological toxicity (Table III). Grade 3-4 neutropenia was observed in 55% of the patients with a low incidence of febrile neutropenia (3%) and infection (4%). Grade 3-4 thrombocytopenia occurred in 29%. Granulocyte-colony stimulating factor (G-CSF), red blood cells or platelets were required in 24.7%, 9.9% and 8.6% of patients, respectively. The non-haematological adverse reactions were primarily of low-grade. Toxicity consisted mainly of moderate asthenia, nausea-vomiting, stomatitis and palmar-plantar erythrodysesthesia (PPE). Grade 2 alopecia was observed in only 16% of the patients and the occurrence of grade 3 PPE was limited to one patient. No clinical evidence of cardiotoxicity was observed and no toxic death occurred.

Table III. *Haematological and non-haematological toxicities experienced per patient.*

Toxicities	Grade 2, n (%)	Grade 3-4, n (%)
Haematological toxicity		
Leucopenia		24 (30)
Neutropenia		45 (55)
Anaemia		11 (13)
Thrombocytopenia		24 (29)
Febrile neutropenia		2 (3)
Infection		3 (4)
Non-haematological toxicity		
Nausea-vomiting	24 (29)	4 (5)
Stomatitis	20 (25)	0 (0)
Constipation	10 (12)	0 (0)
Diarrhoea	4 (5)	2 (3)
PPE	13 (16)	1 (1)
Alopecia	13 (16)	0 (0)
Asthenia	30 (37)	4 (5)
Neuropathy	5 (9)	0 (0)
Hypersensitivity	1 (1)	0 (0)
Cardiac toxicity		
Heart failure	0 (0)	0 (0)
Arrhythmia	2 (2)	1 (1)

PPE, Palmar-plantar erythrodysesthesia.

Discussion

This analysis confirmed our previous results regarding the clinical efficacy and tolerability of PLD-carboplatin combination in AOC patients in late relapse (23). The present series of patients was selected by the same investigators as the previous phase II study, according to identical eligibility criteria, and served as a confirmatory set. The patients were treated according to the same chemotherapy regimen and the efficacy assessments were the same in both studies.

Of note, the ORs were similar in both the first phase II study (23) and this present analysis (62.5% *versus* 65.4%), the median PFS (9.4 *versus* 13.6 months) and the median OS (31.1 *versus* 38.9 months) were longer in the present set of patients (Figures 1 and 2). In this study, the longer survival times were independent of the TFI length. Several hypotheses could explain the better outcome in the present study. The patients' characteristics were slightly better than in the previous phase II trial. A significantly higher proportion of the patients had received only one previous chemotherapy regimen (76% *versus* 60%, p=0.038), and were thus treated earlier in the course of their disease. Although not significant, the patients of the present study had a trend to a higher rate of CR after first-line therapy (87% *versus* 74%) and a higher rate of TFI ≥12 months (60% *versus* 53%).

In addition to their better prognostic profile, the patients treated in this series received a greater number of chemotherapy cycles than in the initial phase II study (35% *versus* 26% of patients having received more than 6 cycles). The longer treatment exposure in this confirmatory set of patients may reflect the increased experience of the investigators with the carboplatin-PLD combination and their wish to deliver chemotherapy until progression or significant toxicity. It might be assumed that the higher number of cycles delivered in this series might have not only influenced the patient outcome, but also the toxicity, explaining a slightly higher incidence of some non-haematological toxicity such as moderate stomatitis or PPE.

The results of the combined data from the 185 treated patients in both studies are very similar to the experience from other authors with the same combination. The median PFS and OS of 11.1 and 34.9 months were close to those reported by the German AGO group and South African investigators in

platinum-sensitive patients treated with higher doses of PLD (40 and 50 mg/m^2, respectively) (25,26). In patients with partially platinum-sensitive disease (TFI: 6 to 12 months) treated with the same regimen as the present study, a multicenter Canadian study reported a median PFS of 8.8 months, identical to our findings in this subgroup, and impressive for this challenging patient population (27). The potential interest of the PLD-carboplatin combination in late relapse AOC patients is further supported by the recent results of the Southwest Oncology Group (SWOG) 0200 randomized phase III trial, which compared PLD 30 mg/m^2 plus carboplatin AUC5 to carboplatin AUC5 alone (28). The efficacy results showed a significant improvement with the combination in terms of median PFS and OS. Grade 3-4 haematological toxicity was more frequent in the PLD-carboplatin arm, but the rate of grade 3 PPE was low. Interestingly, no patients in the PLD-carboplatin arm experienced grade 3-4 allergic reactions compared to 16% in the carboplatin alone arm.

Overall, the PLD-carboplatin combination results seem to be similar to those reported with the paclitaxel-carboplatin regimen of the ICON4 study (PFS=12 months; OS=29 months) (10). The Hellenic Cooperative Oncology Group (HeCOG) conducted a randomised phase II trial comparing PLD (45 mg/m^2)-carboplatin (AUC 5) with paclitaxel-carboplatin in 189 patients with ovarian cancer in late relapse (TFI≥6 months) (29). No significant difference was observed between arms in terms of OR, PFS, or OS. Discontinuations related to toxicity were higher with paclitaxel-carboplatin. Severe thrombo-cytopenia was more frequent in the PLD-carboplatin arm, whereas severe neurotoxicity and alopecia were more frequent in the paclitaxel-carboplatin arm. These results have prompted the GCIG to initiate a randomised phase III trial (CALYPSO) comparing PLD (30 mg/m^2)-carboplatin (AUC5) with paclitaxel-carboplatin in terms of PFS. This study has fully accrued a total of 976 patients with recurrent ovarian cancer relapsing beyond 6 months after first- or second-line platinum-based therapy. Premature discontinuations of therapy due to toxicity and treatment-related adverse events appeared to be more frequent in the paclitaxel-carboplatin arm (30).

Our findings confirm the efficacy and safety of the PLD-carboplatin combination previously reported (23) in a prospective cohort of late-relapsing AOC patients. Although final efficacy data of CALYPSO trial are awaited, these results suggest that PLD-carboplatin is an acceptable alternative to paclitaxel-carboplatin in the setting of platinum-sensitive recurrent ovarian cancer.

Acknowledgements

We thank all the investigators of the GINECO Group who participated in the study: Maria Rios (Vandoeuvre-lès-Nancy), Marie-Christine Kaminsky (Vandoeuvre-lès-Nancy), Dominique Spaeth (Vandoeuvre-lès-Nancy), Sophie Abadie-Lacourtoisie (Angers), Rémy Delva (Angers), Rémy Largillier (Mougins), Pierre Fargeot (Dijon), Laure Chauvenet (Paris), Alain Serre (Alès), Geneviève Netter-Pinon (Corbeil-Essonnes), Isabelle Méchin (Chambéry), Xavier Froger (Chambéry), Karim Yakendji (Créteil), Gilles Freyer (Lyon), Jocelyne Provençal (Annecy), Patrick Bouffette (Neuilly-sur-Seine) and Christine Abraham (Le Chesnay).

We thank Nathalie Lefur and Nicolas Gane for the data management. The statistical analysis was supported by grants from Schering-Plough, France. Isabelle Chapelle-Marcillac provided editorial assistance in the preparation of the manuscript.

References

1 Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T *et al*: Cancer statistics, 2008. CA Cancer J Clin *58*: 71-96, 2008.

2 Memarzadeh S and Berek JS: Advances in the management of epithelial ovarian cancer. J Reprod Med *46*: 621-630, 2001.

3 Ozols RF: Update on the management of ovarian cancer. Cancer J *2(suppl 1)*: S22-S30, 2002.

4 Gershenson DM, Kavanagh JJ, Copeland LJ, Stringer CA, Morris M and Wharton JT: Re-treatment of patients with recurrent epithelial ovarian cancer with cisplatin-based chemotherapy. Obstet Gynecol *73*: 798-802, 1989.

5 Gore ME, Fryatt I, Wiltshaw E and Dawson T: Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. Gynecol Oncol *36*: 207-211, 1990.

6 Markman M, Rothman R, Hakes T, Reichman B, Hoskins W, Rubin S *et al*: Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. J Clin Oncol *9*: 389-393, 1991.

7 McGuire WP, Blessing JA, Bookman MA, Lentz SS and Dunton CJ: Topotecan has substantial antitumor activity as first-line salvage therapy in platinum-sensitive epithelial ovarian carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol *18*: 1062-1067, 2000.

8 Eisenhauer EA, Vermorken JB and van Glabbeke M: Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients. Ann Oncol *8*: 963-968, 1997.

9 Monk BJ, Herzog T, Kaye S, Krasner CN, Vermorken J, Muggia F *et al*: A randomized phase III study of trabectedin with pegylated liposomal doxorubicin (PLD) *versus* PLD in relapsed, recurrent ovarian cancer (OC). Ann Oncol *19(Suppl 8)*: viii1–viii4, 2008.

10 Parmar MK, Ledermann JA, Colombo N, du Bois A, Delaloye JF, Kristensen GB *et al*: Paclitaxel plus platinum-based chemotherapy *versus* conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial. Lancet *361*: 2099-2106, 2003.

11 Cantu MG, Buda A, Parma G, Rossi R, Floriani I, Bonazzi C *et al*: Randomized controlled trial of single-agent paclitaxel *versus* cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. J Clin Oncol *20*: 1232-1237, 2002.

12 Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ *et al*: Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. J Clin Oncol *24*: 4699-4707, 2006.

13 Bolis G, Scarfone G, Giardina G, Villa A, Mangili G, Melpignano M *et al*: Carboplatin alone *vs*. carboplatin plus epidoxorubicin as second-line therapy for cisplatin- or carboplatin-sensitive ovarian cancer. Gynecol Oncol *81*: 3-9, 2001.

14 McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY *et al*: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med *334*: 1-6, 1996.

15 Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA *et al*: Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol *21*: 3194-3200, 2003.

16 du Bois A, Lück HJ, Meier W, Adams HP, Möbus V, Costa S *et al*: A randomized clinical trial of cisplatin/paclitaxel *versus* carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst *95*: 1320-1329, 2003.

17 du Bois A, Quinn M, Thigpen T, Vermorken J, Avall-Lundqvist E, Bookman M *et al*: 2004 consensus statements on the management of ovarian cancer: final document of the 3rd International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (GCIG OCCC 2004). Ann Oncol *16(Suppl 8)*: viii7- viii12, 2005.

18 Guastalla JP, Pujade-Lauraine E, Weber B, Curé H, Orfeuvre H, Mousseau M *et al*: Efficacy and safety of the paclitaxel and carboplatin combination in patients with previously treated advanced ovarian carcinoma. A multicenter GINECO (Group d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) phase II study. Ann Oncol *9*: 37-43, 1998.

19 Martin FJ: Pegylated liposomal doxorubicin: scientific rationale and preclinical pharmacology. Oncology *11(Suppl 11)*: 11-20, 1997.

20 O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A *et al*: Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX™/Doxil®) *versus* conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol *15*: 440-449, 2004.

21 Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME and Lacave AJ: Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin *versus* topotecan. J Clin Oncol *19*: 3312-3322, 2001.

22 Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A *et al*: Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol *26*: 890-896, 2008.

23 Ferrero JM, Weber B, Geay JF, Lepille D, Orfeuvre H, Combe M *et al*: Second-line chemotherapy with pegylated liposomal doxorubicin and carboplatin is highly effective in patients with advanced ovarian cancer in late relapse: a GINECO phase II trial. Ann Oncol *18*: 263-268, 2007.

24 Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK *et al*: Re: new guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). Gynecologic Cancer Intergroup. J Natl Cancer Inst *92*: 1534-1535, 2000.

25 du Bois A, Pfisterer J, Burchardi N, Loibl S, Huober J, Wimberger P *et al*: Combination therapy with pegylated liposomal doxorubicin and carboplatin in gynecologic malignancies: a prospective phase II study of the Arbeitsgemeinschaft Gynäekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and Kommission Uterus (AGO-K-Ut). Gynecol Oncol *107*: 518-525, 2007.

26 Rapoport BL, Vorobiof DA, Slabber C, Cohen G, Alberts AS and Hlophe HS: Phase II study of combination therapy with pegylated liposomal doxorubicin (PLD) and carboplatin in patients (pts) with relapsed, platinum sensitive and platinum semi-sensitive ovarian cancer. J Clin Oncol *26(Suppl)*: 5555 (abstr), 2008.

27 Power P, Stuart G, Oza A *et al*: Efficacy of pegylated liposomal doxorubicin (PLD) plus carboplatin in patients with partially sensitive relapsing advanced ovarian cancers. Int J Gynecol Cancer *16(Suppl 3)*: 194 (abstr), 2006.

28 Alberts DS, Liu PY, Wilczynski SP, Clouser MC, Lopez AM, Michelin DP *et al*: Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin *versus* carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). Gynecol Oncol *108*: 90-94, 2008.

29 Linardou H, Bafaloukos D, Bamlas A *et al*: A randomized phase II study of carboplatin plus liposomal doxorubicin (CLD) *vs*. carboplatin plus paclitaxel (CP) in potentially platinum sensitive ovarian cancer patients. A Hellenic Cooperative Oncology Group study. Eur J Cancer *5(Suppl)*: 5003 (abstr), 2007.

30 Åvall-Lundqvist E, Wimberger P, Gladieff L, Gebski V, Huober JB, Floquet A *et al*: Pegylated liposomal doxorubicin (PLD)-carboplatin (C) (C-D) *vs*. paclitaxel-carboplatin (C-P) in relapsing sensitive ovarian cancer (OC): A 500-patient interim safety analysis of the CALYPSO GCIG Intergroup phase III study. J Clin Oncol *26(Suppl)*: 5565 (abstr), 2008.

Received April 16, 2009
Revised August 7, 2009
Accepted September 1, 2009