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Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin *vs* paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients

U Wagner*[,1], C Marth[2], R Largillier[3], J Kaern[4], C Brown[5], M Heywood[6], T Bonaventura[7], I Vergote[8], MC Piccirillo[9], R Fossati[10], V Gebski[5] and EP Lauraine[11]

[1]Department of Gynecology, Gynecologic Endocrinology and Oncology, University Hospital of Gießen and Marburg, Baldingerstrasse, 35043 Marburg, Germany; [2]Department of Obstetrics & Gynecology Medical University Innsbruck, Innsbruck, Austria; [3]Centre Azuréen de Cancérologie, Mougins, France; [4]Department of Gynecologic Oncology, The Norwegian Radium Hospital, Oslo, Norway; [5]NHMRC Clinical Trials Centre, Camperdown, New South Wales, Australia; [6]Department of Gyn Oncology, Gordon & Leslie Diamond Health Centre, Vancouver, British Columbia, Canada; [7]Department of Medical Oncology, Newcastle Mater Misericordia Hospital, Newcastle, NSW, Australia; [8]Department of Obstetrics and Gynaecology, University Hospital Leuven, Leuven Cancer Institute, Leuven, Belgium; [9]Clinical Trials Unit, National Cancer Institute of Napoli, Napoli, Italy; [10]Department of Oncology, Mario Negri Institute, Milan, Italy; [11]Department of Medical Oncology, Université Paris Descartes, AP-HP, Hôpitaux Universitaires Paris Centre, Paris, France

BACKGROUND: The CALYPSO phase III trial compared CD (carboplatin-pegylated liposomal doxorubicin (PLD)) with CP (carboplatin-paclitaxel) in patients with platinum-sensitive recurrent ovarian cancer (ROC). Overall survival (OS) data are now mature.

METHODS: Women with ROC relapsing >6 months after first- or second-line therapy were randomised to CD or CP for six cycles in this international, open-label, non-inferiority trial. The primary endpoint was progression-free survival. The OS analysis is presented here.

RESULTS: A total of 976 patients were randomised (467 to CD and 509 to CP). With a median follow-up of 49 months, no statistically significant difference was observed between arms in OS (hazard ratio = 0.99 (95% confidence interval 0.85, 1.16); log-rank $P = 0.94$). Median survival times were 30.7 months (CD) and 33.0 months (CP). No statistically significant difference in OS was observed between arms in predetermined subgroups according to age, body mass index, treatment-free interval, measurable disease, number of lines of prior chemotherapy, or performance status. Post-study cross-over was imbalanced between arms, with a greater proportion of patients randomised to CP receiving post-study PLD (68%) than patients randomised to CD receiving post-study paclitaxel (43%; $P < 0.001$).

CONCLUSION: Carboplatin-PLD led to delayed progression and similar OS compared with carboplatin-paclitaxel in platinum-sensitive ROC.

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In patients with recurrent ovarian cancer (ROC) that is platinum-sensitive (relapsing ⩾6 months following prior treatment), an analysis of International Collaborative Ovarian Neoplasm (ICON) and Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) phase III trials demonstrated improved overall survival (OS) with paclitaxel-carboplatin combination chemotherapy compared with carboplatin alone (hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.69–0.97; $P = 0.02$) (Parmar *et al*, 2003; Pfisterer *et al*, 2006). In a phase II trial of similar design, González-Martín *et al* (2005) also showed prolonged survival with paclitaxel-carboplatin (HR 0.31; 95% CI, 0.14, 0.68; $P = 0.0021$). However, this combination is accompanied by a significant toxicity, including peripheral neuropathy, neutropenia, and alopecia. Furthermore, additional survival improvement for this patient population remains an important goal, with a 2-year survival rate of 57% observed in the paclitaxel-carboplatin arm of the ICON/AGO-OVAR trials.

Pegylated liposomal doxorubicin (PLD) has been shown an active drug in platinum-sensitive ROC and has a better toxicity profile than paclitaxel. An earlier study evaluating PLD monotherapy *vs* topotecan demonstrated significantly improved progression-free survival (PFS) and OS in patients receiving PLD (Gordon *et al*, 2001, 2004). The survival benefit was more pronounced for patients with partially sensitive ROC (treatment-free interval (TFI) of >6 months and <12 months). In these patients, the HR for OS was 1.58 compared with 1.15 for those with

*Correspondence: Professor Dr U Wagner; E-mail: uwe.wagner@med.uni-marburg.de

This study was previously presented at the 2011 American Society of Clinical Oncology Annual Meeting: Marth C, Alexandre J, Hanker LC, *et al.* Pegylated liposomal doxorubicin and carboplatin (C-PLD) *versus* paclitaxel and carboplatin (C-P) in platinum-sensitive ovarian cancer (OC) patients (pts): Treatment at recurrence and overall survival (OS) final analysis from CALYPSO phase III GCIG trial. *J Clin Oncol* **29**: 2011 (suppl; abstr 5052).

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a TFI > 12 months (Gordon *et al*, 2004). The Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens et du sein (GINECO) has explored the combination of PLD and carboplatin in a phase II trial. The OS was 21 months in patients with partially platinum sensitive ROC and 36 months in fully sensitive ROC (Ferrero *et al*, 2007). Using the same regimen in a prospective, consecutive cohort, an OS of 30 months was observed in 32 partially sensitive patients and 54 months in 49 fully sensitive patients (Weber *et al*, 2009).

CALYPSO, a large international randomised Gynecologic Cancer Intergroup (GCIG) phase III trial, compared PLD plus carboplatin (CD) to paclitaxel plus carboplatin (CP) in 976 patients with platinum-sensitive ROC (Pujade-lauraine *et al*, 2010). The primary endpoint was the non-inferiority of CD relative to CP in PFS. Patients receiving CD experienced a statistically significant improvement in PFS compared with patients receiving CP (HR = 0.82 (95% CI, 0.72, 0.94); $P = 0.005$). Overall severe non-haematologic toxicity (28.4% *vs* 36.8%; $P = 0.001$) occurred less frequently in the CD arm, making this regimen an attractive option with a favourable therapeutic index for patients with platinum-sensitive ROC.

Overall survival data are now mature from CALYPSO. The current analysis investigates whether the observed PFS improvement translated into an OS benefit for patients receiving CD compared with CP for platinum-sensitive ROC.

PATIENTS AND METHODS

The patients, methods, and design of CALYPSO were previously reported (Pujade-Lauraine *et al*, 2010). Briefly, patients had ovarian cancer that recurred > 6 months after first- or second-line platinum-based chemotherapy and had received a taxane. Treatment consisted of carboplatin (C) AUC 5 plus PLD 30 mg m^{-2} (CD) on day 1 every 4 weeks or C AUC 5 plus paclitaxel (P) 175 mg m^{-2} (CP) on day 1 every 3 weeks. Patients received six cycles in the absence of disease progression or unacceptable toxicity, with additional cycles allowed for patients experiencing response or stable disease.

Randomisation and masking

CALYPSO was an international randomised, phase III, open-label, multicenter trial. Randomisation was performed in permuted blocks with stratification by measurable disease (yes *vs* no), TFI from last chemotherapy (6–12 *vs* > 12 months), and centre.

Statistical analysis

The study design was that of non-inferiority for PFS. The secondary endpoint was OS and analysed using a log-rank test. Exploratory analysis of baseline characteristics was performed with Cox regression and pre-specified subgroups were assessed for differing treatment effects.

RESULTS

A total of 976 patients were randomised between April 2005 and September 2007 (467 to CD and 509 to CP). Baseline patient and disease characteristics were balanced between arms (Table 1). The majority of patients had FIGO stage III/IV disease and had received only one line of prior treatment. Two-thirds of the patients had a TFI of > 12 months since prior chemotherapy. Further details of patient characteristics are reported elsewhere (Pujade-Lauraine *et al*, 2010).

In a prior analysis, PFS was statistically significantly prolonged in the CD arm (HR = 0.82 (95% CI, 0.72, 0.94); $P = 0.005$) based on a median follow-up of 22 months (Pujade-Lauraine *et al*, 2010). Median PFS times were 9.4 months in the CP arm and 11.3 months in the CD arm.

Table 1 Baseline characteristics

	CD ***n* = 466**	**CP** ***n* = 509**
	n (%)	
Median age, years	60.5	61.0
ECOG performance status[a]		
0	286 (61)	317 (62)
1	159 (34)	164 (32)
2	13 (3)	15 (3)
Primary disease site ovarian	415 (89)	451 (89)
Papillary/serous histology	334 (72)	366 (72)
Initial FIGO stage[a]		
I/II	52 (11)	59 (12)
III/IV	401 (86)	427 (84)
Number of previous therapy lines		
1	408 (88)	421 (83)
2	58 (12)	87 (17)
Prior taxane	462 (99)	500 (99)
Median interval since prior therapy		
6–12 months	162 (35)	182 (36)
> 12 months	304 (65)	326 (64)
Measurable disease		
Yes	281 (60)	321 (63)
No	185 (39)	188 (37)
Tumour size		
< 5 cm	377 (81)	419 (82)
⩾ 5 cm	89 (19)	90 (18)
Number of sites of recurrence		
1	217 (47)	245 (48)
> 1	249 (53)	264 (52)

Abbreviations: CD = carboplatin-pegylated liposomal doxorubicin; CP = carboplatin-paclitaxel; ECOG = Eastern Cooperative Oncology Group. [a]Missing values to attain 100%.

In this analysis, the median follow-up is 49 months (range 0–68 months) with a total of 663 deaths: 346 in the CP arm and 317 in the CD arm. The hazard ratio for CP : CD was 0.99 (95% CI, 0.85, 1.16), which was not statistically significant (log-rank $P = 0.94$; Figure 1). Median survival times were 30.7 months in the CD arm and 33.0 months in the CP arm.

Post-study therapy was received by 90% of patients in either arm of CALYPSO. The majority of patients (69%) received two or more lines (Table 2). Analysis of cross-over between the arms demonstrated an imbalance. The proportion of patients randomised to CP who received PLD as post-study therapy (68%) was higher than the proportion of patients randomised to CD who received paclitaxel as post-study therapy (43%; $P < 0.001$).

Factors that significantly correlate to survival were age, TFI, ECOG PS, residual disease, CA125, measurable disease, longest lesion size, and disease sites in univariate analyses. In multivariate analysis, TFI ⩾ 12 months, ECOG PS 0, CA125 < 100 U ml^{-1}, non-measurable disease, and one involved disease site remained significantly correlated to survival (Table 3).

For *a priori* subgroups age, body mass index, TFI, measurable disease, number of lines of prior chemotherapy, and ECOG performance status, univariate proportional hazards regression for treatment did not show any statistically significant effect (Table 4).

DISCUSSION

CALYPSO is the largest clinical trial in ROC, enroling 976 patients. Designed as a non-inferiority trial, CALYPSO demonstrated that

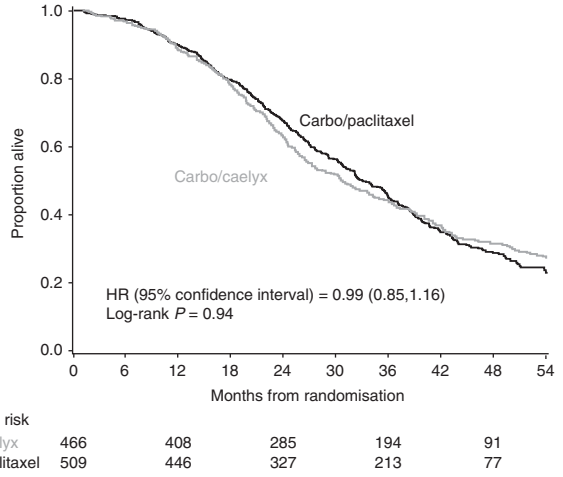

Figure 1 Overall survival in patients receiving carboplatin-paclitaxel or carboplatin-PLD for platinum-sensitive recurrent ovarian cancer. Abbreviation: PLD, pegylated liposomal doxorubicin.

Table 2 Number of post-study therapy lines and cross-overs

Treatment	Patients (%)
Number of lines	
0	10
1	21
2	25
3	21
4	13
5–11	10
2 or more lines	69
Cross-overs[a]	
CP arm	68
CD arm	43

Abbreviations: CD = carboplatin-pegylated liposomal doxorubicin; CP = carboplatin-paclitaxel. [a]$P < 0.001$ for comparison between arms.

Table 3 Multivariate cox regression model of overall survival ($N = 959$)

Factors	N	HR	95% CI	P-value
TFI, months				
6–12	342			
⩾12	617	0.50	0.43, 0.59	<0.001
ECOG PS				
0[a]	615			
⩾1	344	1.37	1.17, 1.60	<0.001
CA125, U ml^{-1}				
<100	316			
⩾100	643	1.78	1.49, 2.14	<0.001
Measurable disease/longest lesion, mm				
No	361			
⩽50	422	1.28	1.04, 1.57	0.02
>50	176	1.78	1.40, 2.26	<0.001
Involved disease sites				
1	453			
>1	506	1.26	1.05, 1.52	0.014

Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; TFI = treatment-free interval. [a]This category includes any unknown or not applicable values.

Table 4 Overall survival by treatment arm in pre-defined patient subgroups

	N		Univariate cox regression model			
	CD	CP	HR	95% CI	Subgroup P-value	Interaction P-value[a]
Age, years						
<70	395	423	0.98	0.83, 1.16	0.80	0.61
⩾70	71	86	1.10	0.76, 1.58	0.62	
BMI, kg m^{-2}						
<30	378	399	1.00	0.85, 1.19	0.98	0.74
⩾30	88	110	0.95	0.67, 1.35	0.76	
TFI, months						
6–12	161	183	1.01	0.80, 1.28	0.92	0.86
⩾12	305	326	0.99	0.81, 1.21	0.90	
Measurable disease						
No	137	138	0.88	0.65, 1.21	0.56	0.31
Yes	329	371	1.07	0.90, 1.27	0.47	
Number of prior lines						
1	408	418	0.99	0.84, 1.17	0.92	0.98
⩾2	58	88	0.97	0.65, 1.46	0.74	
ECOG PS						
0	295	329	0.99	0.81, 1.20	0.92	0.95
⩾1	171	180	0.99	0.78, 1.27	0.95	

Abbreviations: BMI = body mass index; CD = carboplatin-pegylated liposomal doxorubicin; CI = confidence interval; CP = carboplatin-paclitaxel; ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; TFI = treatment-free interval. [a]Interaction test is the *P*-value associated with the interaction term in the Cox regression model containing treatment effect, subgroup variable, and their interaction.

CD was not only non-inferior to CP in PFS but was also superior (HR = 0.82, $P = 0.005$) in patients with platinum-sensitive ROC. Furthermore, CD was associated with less carboplatin hypersensitivity, peripheral neuropathy, prolonged neutropenia, and alopecia. Toxicities observed more commonly with CD were mucositis, nausea and vomiting, and palmar-plantar erythrodysesthesia. These toxicities were generally low-grade, short-term, and manageable (Pujade-Lauraine *et al*, 2010; Joly *et al*, 2011). Taken together, CD emerged as a welcome option for treating platinum-sensitive ROC that exhibited a favourable therapeutic index.

Several analyses of CALYPSO have been undertaken (Gladieff *et al*, 2011; Joly *et al*, 2011; Kurtz *et al*, 2011; Lee *et al*, 2011). In the current analysis, OS of CD and CP were evaluated. In the overall population, OS was similar between arms (HR = 0.99; log-rank $P = 0.94$). Median survival was 30.7 months in the CD arm. Prior investigations of this regimen have shown median survival times of 25–39 months (Ferrero *et al*, 2007; Weber *et al*, 2009; Bafaloukos *et al*, 2010). Median survival in the CP arm was 33.0 months; historical data have shown 29 months (Parmar *et al*, 2003; Bafaloukos *et al*, 2010).

When analysed by patient subgroups according to age, BMI, TFI, measurable disease, number of prior therapy lines, and ECOG PS, no statistically significant differences emerged between treatment arms in any of the subgroups. Notable was the lack of difference between arms regardless of TFI. The HR for OS in the partially platinum-sensitive subgroup (TFI 6–12 months) was 1.01 (95% CI, 0.80, 1.28; $P = 0.92$), whereas the HR for OS in the sensitive subgroup (TFI > 12 months) was 0.99 (95% CI, 0.81, 1.21; $P = 0.90$). These results lie in contrast to the study of monotherapy

PLD *vs* topotecan, which showed a more pronounced survival benefit for PLD relative to topotecan in patients with partially platinum-sensitive disease (Gordon *et al*, 2004).

An imbalance in post-study therapy may have affected OS and mitigated the PFS benefit observed with CD. Post-study PLD was received by 68% of patients in the CP arm, while post-study paclitaxel was administered to 43% of patients in the CD arm ($P<0.001$).

The results of CALYPSO demonstrate that carboplatin-PLD offers an attractive option as compared with the standard of care, carboplatin-paclitaxel, for the treatment of platinum-sensitive ROC. Patients receiving carboplatin-PLD experienced delayed progression, similar survival, less carboplatin hypersensitivity, and less peripheral neuropathy, a toxicity associated with long-term sequelae, compared with patients receiving carboplatin-paclitaxel.

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Conflict of interest

The authors declare no conflict of interest.

Participant Institutions

AGO; AGO-Austria; GINECO; NSGO; Stat; NCI-CTG; ANZGOG; EORTC; MITO; MANGO; Stat; GINECO

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