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Phase 3 randomised study of canfosfamide (Telcyta®, TLK286) versus pegylated liposomal doxorubicin or topotecan as third-line therapy in patients with platinum-refractory or -resistant ovarian cancer

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ARTICLE INFO

Article history:
Received 22 March 2009
Accepted 7 May 2009
Available online 8 June 2009

Keywords:
Canfosfamide
Glutathione S-transferase
Platinum refractory or resistant
Epithelial ovarian cancer
Prodrug

ABSTRACT

Rationale: Canfosfamide HCl (CAN) is a glutathione analogue prodrug that is activated by glutathione S-transferase P1-1 and induces apoptosis. CAN is synergistic *in vitro* with carboplatin, paclitaxel and anthracyclines.

Methods: Patients with platinum-refractory or -resistant ovarian cancer (OC) who had progressed on second-line therapy with pegylated liposomal doxorubicin (PLD) or topotecan (TOPO), were randomised between CAN 1000 mg/m^2 IV q 3 weeks or to either PLD 50 mg/m^2 IV q 4 weeks or TOPO 1.5 mg/m^2 IV d1-5 q 3 weeks.

Results: About 461 patients were randomised after stratification for ECOG performance status, prior therapy, and bulky (>5 cm) disease. Groups were well balanced. In the control arm 58% and 42% were treated with PLD and TOPO, respectively. CAN was well tolerated with the most common grade 3–4 toxicities of 5% anaemia, 4% neutropaenia (no febrile neutropaenia), 4% thrombocytopaenia, and 7% vomiting. Progression-free survival (PFS) and overall survival (OS) were significantly higher in the control arm ($p < 0.001$ and $p < 0.01$, respectively). In a subgroup analysis PFS and OS tended to be higher with PLD than with TOPO.

Conclusion: CAN was well tolerated. This is the first randomised study showing an increased OS with third-line therapy. This might have important consequences for other recurrent OC trials.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.05.016

1. Introduction

Ovarian cancer is the second most common gynaecological malignancy in the United States of America and Europe.[1–3] In 2008, an estimated 21,650 new cases of ovarian cancer will be diagnosed, resulting in approximately 15,310 deaths.[1] Five-year survival for advanced-stage disease is showing modest improvement, particularly among women who have had optimal cytoreductive surgery and front-line combination chemotherapy but the majority of patients will still ultimately die of the disease.[4,5] The current standard of therapy in the initial treatment of ovarian cancer is debulking surgery, followed by carboplatin and paclitaxel chemotherapy and most patients with advanced disease will receive second- and third-line therapy. The platinum-free interval (PFI) [defined as the time from completion of platinum-based chemotherapy to the time of documented tumour progression] influences the choice of second-line therapy and is of prognostic importance for the ongoing course of the disease.[6]

Recurrent ovarian cancer can be differentiated into four groups: Platinum refractory, primary platinum resistant, platinum sensitive and secondary platinum resistant.

Approximately 25–30% of patients who develop persistent or recurrent ovarian cancer have platinum-refractory or primary platinum-resistant disease. However, eventually all patients will become refractory or resistant to platinum after reiterative therapy with platinum-based regimens (secondary platinum-resistant disease). Treatment options are limited for patients who experience progressive or persistent disease during initial platinum-based therapy (platinum refractory) or relapse of disease after a PFI of less than 6 months (primary platinum resistant) and typically involve single-agent non-platinum therapy. Most patients with platinum-refractory or primary platinum-resistant ovarian cancer experience rapidly progressive disease. Non-platinum and non-taxane chemotherapy options used in this setting include: topotecan (TOPO), gemcitabine, yondelis and pegylated liposomal doxorubicin (PLD).[7]

Considerations in the choice of second- and third-line chemotherapy include assessment of efficacy, cumulative toxicities and the optimal sequencing of available agents. Doxorubicin HCl liposome injection (Caelyx® or Doxil®) and TOPO HCl for injection (Hycamtin®) are approved by the Food and Drug Administration and European Medicines Agency for use in patients with ovarian cancer whose disease has progressed or recurred after platinum-based chemotherapy. A confirmatory Phase 3 randomised trial in second-line therapy compared PLD to TOPO in 474 patients (combined platinum-resistant and platinum-sensitive disease). In this trial, there was no clinical or statistical difference between TOPO and PLD in the platinum-refractory or -resistant subpopulation in objective response rate (ORR) [6.5% versus 12.3%], time to tumour progression (TTP) [9.1 weeks versus 12 weeks] and overall survival (OS) [36 weeks versus 41 weeks], respectively.[8,9] Interestingly, a long-term survival advantage was seen, in favour of PLD, in the platinum-sensitive sub-group.[9] A recent randomised Phase 3 trial of gemcitabine compared with PLD in patients with platinum-resistant ovarian cancer reported equivalency with the two agents.[10] The median PFS was 3.6 months for gemcitabine versus 3.1 months for PLD. The ORR was 6.1% versus 8.3% in the subset of patients with measurable disease, and overall ORR was 9.2% versus 11.7%, respectively, inclusive of both measurable and non-measurable disease. The PLD group experienced more hand-foot syndrome and mucositis while the gemcitabine group experienced significantly more constipation, nausea, vomiting, fatigue and neutropaenia.

Various chemotherapy combinations reported in the literature have not yet demonstrated improvement in efficacy in randomised trials for the treatment of platinum-refractory or -resistant ovarian cancer, although promising approaches such as weekly treatment with carboplatin/paclitaxel are being actively studied.[11] Based on the evidence-based literature studies, the available second-line agents have a similar antitumour activity with a median PFS of 9.1 weeks for PLD, 12 weeks for TOPO[9] and 3.6 months for gemcitabine versus 3.1 months for PLD.[10] Therefore, decisions regarding the current treatment options are often guided by consideration for drug toxicities.

In a Phase 2 study of single-agent canfosfamide in a heavily pretreated, platinum-refractory or -resistant ovarian cancer population, treatment was well tolerated with fatigue, nausea and anaemia as the most commonly observed adverse events (AEs) with no evidence of cumulative toxicity.[12] Durable objective tumour responses by the Response Evaluation Criteria in Solid Tumours (RECIST) were reported. In the search for effective third-line therapies of platinum-refractory or -resistant epithelial ovarian cancer, drugs such as canfosfamide, which have the potential to treat chemotherapy-resistant disease, were considered a possible therapeutic option.

Canfosfamide is a glutathione analogue prodrug that is activated by the enzyme glutathione s-transferase P1-1 (GST P1–1), which is overexpressed in many types of cancers.[13,14] Following activation, the apoptotic activity of canfosfamide is mediated through the stress response pathway, resulting in the induction of cellular apoptosis. Human cancer cells exposed to canfosfamide demonstrate activation of mitogen-activated protein (MAP) kinase MKK4, p38 kinase, jun-N-terminal kinase (JNK) and caspase 3.[15] The cytotoxic activity of canfosfamide has been demonstrated *in vitro* and *in vivo* against a variety of human cancer cell lines, including ovarian cancer cells (OVCAR3).[16]

Hitherto, studies have demonstrated that the sequence of administration of currently approved second-line therapeutic agents such as PLD or TOPO does not have a significant impact on PFS or OS of patients with platinum-refractory or -resistant epithelial ovarian cancer.[8,9,17] A Phase 3 randomised multinational study was undertaken to demonstrate superiority in improving OS and PFS with canfosfamide versus PLD or TOPO in this heavily pretreated, platinum-refractory or -resistant patient population. The ASSIST-1 trial was registered at www.clinicaltrials.gov (NCT00057720). The results of this multinational study are reported here.

2. Patients and methods

2.1. Eligibility

Patients with histologically or cytologically confirmed advanced epithelial ovarian, fallopian tube or peritoneal carcinoma, considered platinum refractory or resistant, who failed 1 second-line therapy with either PLD or TOPO were eligible. Inclusion criteria included age $\geqslant$18 years, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and adequate haematopoietic, hepatic and renal function. No prior treatment with more than 1 second-line chemotherapy regimen of PLD or TOPO was permitted. Patients were excluded with a history of bone marrow transplantation, a history of prior malignancy (with the exception of curatively treated carcinoma *in situ* of cervix, stage 1 endometrial cancer, basal cell or squamous cell skin cancer) and clinically significant cardiac disease, hypercalcaemia or a systemic infection.

This study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice standards. Approval of the protocol was obtained from each of the local Institutional Review Boards/Ethics Review Committees for all participating institutions and Ministries of Health for all participating countries. All patients provided written informed consent prior to participation in the study.

2.2. Study design and treatment

This multinational, study enrolled 461 patients randomised to an active control treatment arm or the canfosfamide treatment arm. The choice of treatment (PLD or TOPO) for patients randomised to the active control arm was based on the prior failed second-line therapy. Stratification was based upon the prognostic variables of prior second-line therapy (PLD or TOPO), bulky disease [present or absent (defined as presence of a tumour $\geqslant$5 cm)] and ECOG PS (0, 1 versus 2). Patients randomised to the canfosfamide treatment arm received canfosfamide at 1000 mg/m^2 as a 30-minute constant rate infusion on day 1 of a 21-day cycle. In the active control arm, patients received PLD at 50 mg/m^2 as a 1-hour constant rate infusion on day 1 of a 28-day treatment cycle or TOPO at 1.5 mg/m^2 administered as a 30-minute infusion on days 1–5 of a 21-day cycle. Growth factor support was allowed per institutional guidelines in patients with Grade 4 neutropaenia (absolute neutrophil count [ANC] $\leqslant$ 500/mm^3) or febrile neutropaenia. Patients with a partial response or stable disease continued treatment until documented disease progression or an unacceptable toxicity.

The primary end-point of the study was to demonstrate superiority in OS with canfosfamide versus the active control with PLD or TOPO. Secondary end-points were the assessment of safety and progression-free survival (PFS). Other analyses included the comparison of ORR in each treatment group. An independent data monitoring committee met regularly for oversight of study conduct and assurance of safety of the study participants.

2.3. Pre-treatment and follow-up assessments

Screening evaluation included complete medical history, physical examination including vital signs, ECOG PS, ECG, chest X-ray and radiological determination of baseline tumour measurements of all areas of metastatic disease. Pre-treatment laboratory evaluation included complete blood count (CBC) with differential and platelet count, serum chemistries, CA-125 tumour marker and urinalysis. On day 1 of each subsequent treatment cycle, a physical examination, ECOG PS, vital signs and laboratory assessments (CBC with differential, platelet count and serum chemistries) were obtained, use of concomitant medication(s) was documented, and AEs were assessed. Radiographic imaging (spiral/helical CT scan, chest X-ray or MRI scan) was required to assess tumour response for every 8 weeks. All patients who discontinued study treatment were followed for survival.

Baseline tumour measurements were obtained by spiral/helical CT scan or MRI scan within 21 days of randomisation and repeated every 8 weeks while on study. If an objective response was documented, a radiographic evaluation was to be performed within 4–6 weeks to confirm response. Assessment of response was evaluated according to RECIST.[18] Levels of tumour marker CA-125 were determined within 7 days of randomisation, every 8 weeks thereafter and at the end of study treatment follow-up.

2.4. Statistical analysis

An estimated sample size of 440 patients (220 patients in each treatment arm) was determined to detect a 28.6% reduction in the relative risk of death, corresponding to an approximate 40% increase in median survival in the canfosfamide-treated arm, based on a two-sided log-rank test with a 0.05 level of significance and a power of 90%. The sample size estimation was based on the assumption of a median survival of 6 months in the active control arm and of 8.4 months in the canfosfamide-treated arm.

Efficacy analyses were conducted in the intent-to-treat (ITT) population. The primary analysis for this study was to compare the OS as the primary efficacy end-point between the treatment arms. The PFS was the secondary efficacy end-point. The supportive analyses included ORR and safety. Overall survival and PFS were estimated by the Kaplan–Meier method and compared using the unstratified log-rank test between the canfosfamide-treated arm and the active control arm. The hazard ratio and 95% confidence intervals (CIs) were obtained from the Cox regression model with treatment as the only covariate in the model. The ORRs were calculated as rates with the exact binomial 95% CI provided by treatment arms. The ORR between treatment arms was compared using Fisher's exact test.

Patient demographics and ovarian cancer disease characteristics, dosing information and AEs were evaluated using descriptive statistics in terms of count and percentage for categorical variables and sample size, mean, median and range for continuous variables.

All patients who received any amount of study drug(s) were included in the safety population. Treatment-emergent

AEs related to study treatments were summarised descriptively by preferred term, system organ class, treatment arm and the National Cancer Institute Common Terminology Criteria version 2.0 toxicity grade.

3. Results

3.1. Patient characteristics

A total of 461 patients (232 in the canfosfamide treatment arm and 229 in the active control arm) were enrolled in the study and treated at 112 sites in North America, 44 sites in Europe, 26 sites in South America and 6 sites in South Africa between June 2, 2003, and August 30, 2006. The first patient was randomised in June, 2003 and the last patient in January, 2005. Baseline patient demographics and ovarian cancer disease characteristics are summarised in Table 1.

The treatment arms were well balanced for ECOG PS, prior second-line therapy and presence or absence of bulky disease. The majority of patients had an ECOG PS of 0 or 1 (90.9%). A higher percentage of patients withdrew from the active control arm as compared to the canfosfamide treatment arm (24% versus 11%, respectively) due to investigator's decision or voluntary withdrawal. This may have contributed to bias in the study. Disease progression was the most common reason from the withdrawal of both treatment arms (60% in canfosfamide treatment arm and 49% in the active control arm).

3.2. Drug exposure

The mean and median numbers of cycles/patient were similar among the 3 agents. Patients in the canfosfamide treatment arm received a median of 3 cycles/patient (range 1–33) as compared to a median of 4 cycles/patient (range 1–32) with PLD and median of 5 cycles/patient (range 1–21) for those patients receiving TOPO. The median duration of treatment was longer on the active control arm (125 days for PLD and 121 days for TOPO) than on the canfosfamide arm [65 days] (Table 2). The number of treatment cycles with dose delays, interruptions or reductions is summarised in Table 2. The majority of dose reductions required on the canfosfamide treatment arm were due to haematologic AEs whereas both haematologic and non-haematologic AEs resulted in dose reductions on the active control arm with PLD or TOPO.

3.3. Efficacy

The ITT population comprised all 461 patients (232 on the canfosfamide-treated arm and 229 on the control-treated arm) enrolled in the study.

Table 1 – Patient demographics and baseline ovarian cancer disease characteristics

	Canfosfamide treatment arm (*N* = 232)	Active control treatment arm (*N* = 229)
Age (Years)		
Median (range)	60 (26–85)	60 (30–82)
ECOG performance status	*n* (%)	*n* (%)
0 or 1	211 (91)	208 (91)
2	21 (9)	21 (9)
Race		
White, non-hispanic	203 (88)	197 (86)
Black, non-hispanic	7 (3)	11 (5)
Asian	12 (5)	4 (2)
Hispanic	8 (3)	12 (5)
Other	2 (1)	5 (2)
Primary site of disease		
Ovary	203 (88)	201 (88)
Peritoneal	23 (10)	27 (12)
Fallopian tube	6 (3)	1 (<1)
FIGO stage at primary diagnosis		
I–IIIB	43 (19)	53 (23)
IIIC	130 (56)	136 (59)
IV	50 (22)	32 (14)
Unknown	9 (4)	8 (4)
Baseline platinum status		
Platinum refractory	94 (41)	35 (15)
Platinum resistant	101 (44)	108 (47)
Secondary platinum resistant	1 (<1)	5 (2)
Bulky disease		
Present	136 (59)	138 (60)
Absent	96 (41)	91 (40)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; Bulky disease, defined as having at least one tumour $\geqslant$5 cm.

Table 2 – Study treatment administration

	CAN	PLD	TOPO
	N = 231	N = 130	N = 87
Total # of cycles administered	1052	699	469
Median # of days treatment duration (range)	65 (21–764)	125 (28–918)	121 (23–515)
Median # of cycles per patient (range)	3 (1–33)	4 (1–32)	5 (1–21)
Median # of dose delays, interruptions or reductions (range)	2 (1–9)	2 (1–9)	2 (1–9)
With dose delays	128 (12.2)	107 (15.3)	128 (27.3)
With dose interruptions	7 (0.7)	20 (2.9)	37 (7.9)
With dose reductions	28 (2.7)	46 (6.6)	37 (7.9)

CAN, canfosfamide; PLD, pegylated liposomal doxorubicin; TOPO, topotecan.

For the ITT population, the median survival was 8.5 months (95% CI 6.8–9.9) with canfosfamide and 13.5 months (95% CI 11.0–16.0) with PLD or TOPO [p = <0.01, HR = 1.71] (Fig. 1). The median survival observed with PLD was 14.2 months (95% CI, 12.6–17.6) and 10.8 months (95% CI, 9.1–16.0) with TOPO [p = 0.1695, HR = 0.81] (Fig. 2). Median PFS for patients treated with canfosfamide was 2.3 months (95% CI 2.1–2.7) as compared to 4.3 months (95% CI, 3.9–5.3) [p < 0.01, HR = 1.59] with the PLD or TOPO control (Fig. 3).

The ORR in the ITT population for canfosfamide was 4.3% (95% CI, 2.1–7.8) and 10.9% (95% CI, 7.2–15.7) for the active control arm. For patients with an objective tumour response, the duration of response was similar for both the treatment arms, 22.5 weeks (95% CI, 17.0–32.9) for the canfosfamide arm and 23.4 weeks (95% CI, 14.0–42.1) for the active control arm (p = 0.5189).

3.4. *Safety*

Treatment-emergent AEs were similar on each arm. Canfosfamide was generally well tolerated with infrequent haematologic and non-haematologic AEs reported in this heavily pre-treated population (Table 3). Haematologic AEs were seen more frequently in the control arm with PLD or TOPO. Febrile neutropaenia was observed at 4.6% in the control arm with PLD or TOPO as compared to none in the canfosfamide arm. Non-haematologic AEs of nausea, vomiting and fatigue were similar in each arm; however, as expected, the incidence of stomatitis and hand-foot syndrome was seen more frequently with PLD in the active control arm at 10.8% and 10%, respectively (Table 4).

Grade 4 toxicities were observed more frequently in the active control arm with PLD or TOPO (21.2%) as compared to the canfosfamide treatment arm (2.6%). The Fisher exact test for Grade 4 AEs indicated a statistically significant difference in favour of the canfosfamide treatment arm (p = 0.013).

4. Discussion

To the best of our knowledge, this is the largest randomised Phase 3 study assessing the third-line treatment of platinum-refractory or -resistant ovarian cancer. In the current

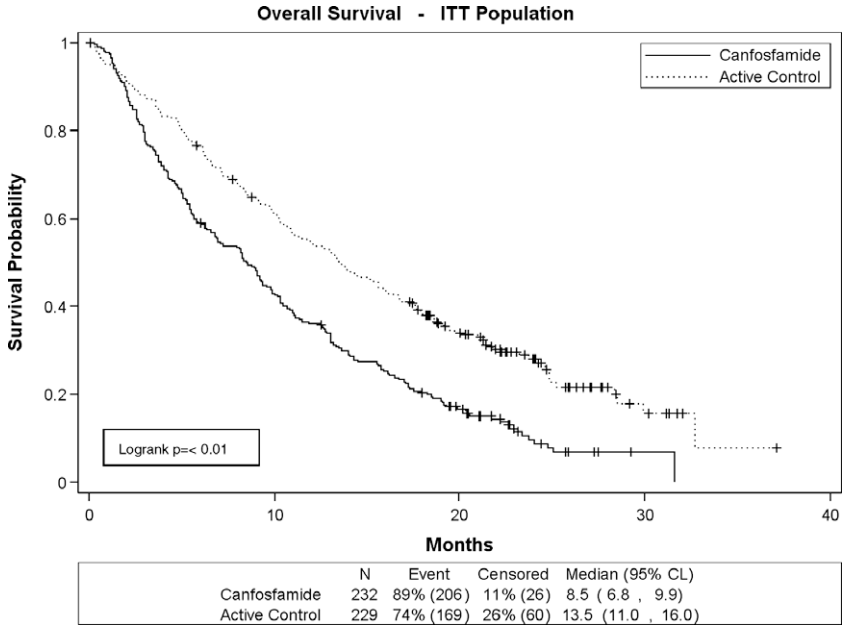

Fig. 1 – Overall survival for patients in the ITT population treated with canfosfamide versus active control (PLD or TOPO) study treatments.

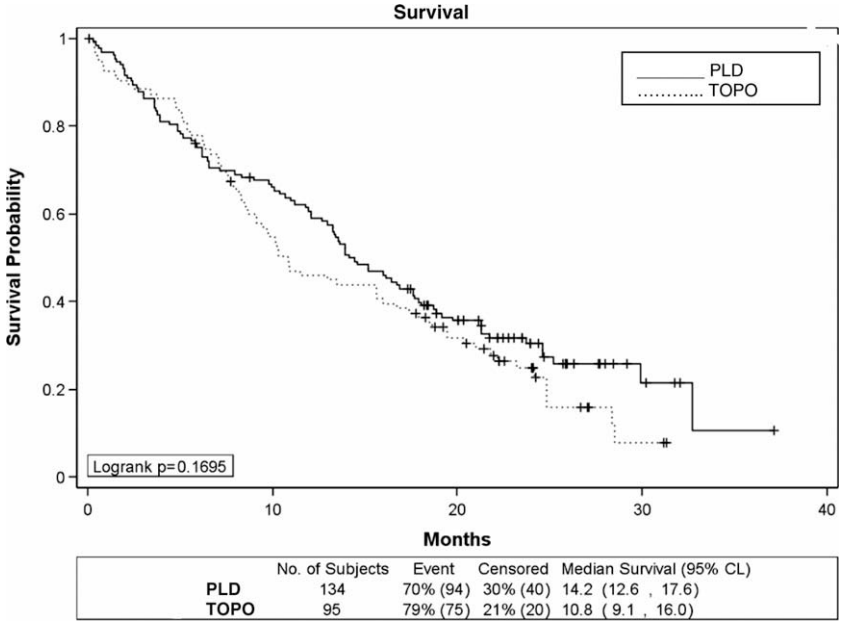

Fig. 2 – Survival for patients treated with active control (PLD or TOPO) study treatments.

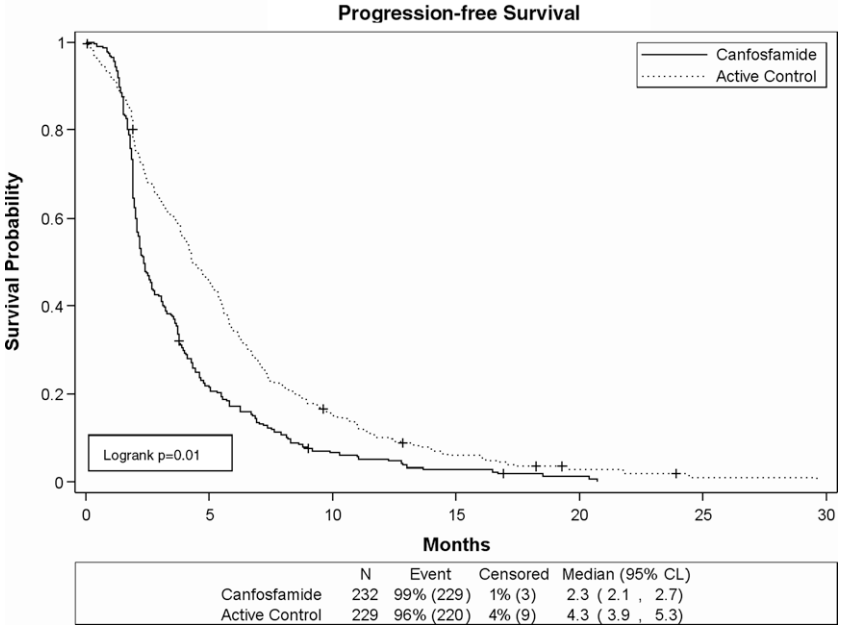

Fig. 3 – Progression-free survival for patients treated with canfosfamide versus active control (PLD or TOPO) study treatments.

trial, single-agent canfosfamide did not meet the primary end-point of superiority in improving OS or PFS as compared to the active control with PLD or TOPO.[19]

The survival data generated in the study were unexpected for several reasons. The first is that the two control arm drugs (PLD and TOPO) produced different survival results (14.2 months versus 10.8 months, respectively), which per evidence-based literature should have been similar in platinum-resistant OC.[8,9] Overall survival of patients treated with PLD in this study exceeded the expected based on the data from the published literature on second-line platinum-refractory or -resistant disease and tended to be superior to TOPO.[2,20–22] No known prognostic or predictive factors accounted for this difference. In addition, studies have demonstrated that the sequence of administration of these agents does not have a significant impact on PFS or OS.[17,18] The significant difference in survival between the study arms was also surprising since the usual correlates with increased survival such as median and mean number of cycles/patient of study treatments, were similar among the three agents, the response rates were low and similar, and duration of responses was similar with all three agents. The likeliest explanation may well lie in the post-study treatment with available anti-cancer agents, which occurred overall in 60% of patients (median 1, range 1–8). Further

Table 3 – Haematologic and non-haematologic adverse events related to canfosfamide for injection in >10% of patients

Adverse event (preferred term)	Canfosfamide treatment arm NCI-CTC (V.2.0) maximum toxicity grade				
	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	Total *n* (%)
Haematologic					
Anaemia	13 (5.6)	24 (10.4)	11 (4.8)	1 (0.4)	49 (21.2)
Neutropaenia	12 (5.2)	14 (6.1)	9 (3.9)	1 (0.4)	36 (15.6)
Thrombocytopaenia	5 (2.2)	11 (4.8)	7 (3.0)	2 (0.9)	25 (10.8)
Non-haematologic					
Nausea	57 (24.7)	40 (17.3)	20 (8.7)	0	117 (50.6)
Fatigue	27 (11.7)	45 (19.5)	14 (6.1)	0	86 (37.2)
Vomiting	35 (15.2)	25 (10.8)	16 (6.9)	1 (0.4)	77 (33.3)
Constipation	22 (9.5)	14 (6.1)	1 (0.4)	0	37 (16.0)
Anorexia	17 (7.4)	6 (2.6)	5 (2.2)	0	28 (12.1)
Diarrhoea	16 (6.9)	7 (3.0)	4 (1.7)	0	27 (11.7)
Abdominal pain	10 (4.3)	11 (4.8)	2 (0.9)	0	23 (10.0)

NCI-CTC, National Cancer Institute-Common Toxicity Criteria.

Table 4 – Haematologic grade 3 or 4 adverse events in any patient and non-haematologic adverse events occurring in ⩾5% of patients 'possibly related', 'probably related' or 'related' to canfosfamide as compared to PLD or TOPO

Adverse event	Active control arm					
	CAN *N* = 130		PLD *N* = 87		TOPO *N* = 130	
	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Haematologic						
Anaemia	11 (4.8)	1 (0.4)	7 (5.4)	3 (2.3)	16 (18.4)	4 (4.6)
Neutropaenia	9 (3.9)	1 (0.4%)	7 (5.4)	5 (3.8)	12 (13.8)	27 (31.0)
Thrombocytopaenia	7 (3.0)	2 (0.9%)	3 (2.3)	1 (0.8)	17 (19.5)	2 (2.3)
Leukopaenia	1 (0.4)	0	2 (1.5)	0	3 (3.4)	2 (2.3)
Febrile neutropaenia	0	0	1 (0.8)	1 (0.8)	9 (10.3)	2 (2.3)
Haematotoxicity	0	0	1 (0.8)	0	–	–
Pancytopaenia	0	0	0	0	1 (1.1)	0
Bone marrow failure	0	0	0	0	0	2 (2.3)
Lymphopaenia	3 (1.3)	0	1 (0.8)	0	–	–
Non-haematologic						
Nausea	20 (8.7)	0	7 (5.4)	0	6 (6.9)	0
Vomiting	16 (6.9)	1 (0.4%)	10 (7.7)	0	5 (5.7)	0
Fatigue	14 (6.1)	0	8 (6.2)	0	5 (5.7)	2 (2.3)
Stomatitis	0	0	11 (8.5)	3 (2.3)	0	0
Palmar-plantar erythrodysesthesia	0	0	13 (10.0)	0	–	–

CAN, canfosfamide; PLD, pegylated liposomal doxorubicin; TOPO, topotecan.

chemotherapy (with agents such as carboplatin) is widely known to be easier to administer following failure of PLD than failure of TOPO, probably due to differences in bone marrow reserve.

The survival analysis may also have been confounded by the cancer biology heterogeneity in third-line therapy patients potentially leading to variations in the activation or metabolism of canfosfamide in this population.

Canfosfamide has been shown to be non-cross resistant with platinums, taxanes and anthracyclines, and synergistic with these agents.[16,23–27] The non-overlapping toxicity profile of canfosfamide with standard chemotherapy agents and synergism with other cytotoxic drugs suggest that canfosfamide would best be further studied in trials with combination regimens. It is indeed clear from the mechanism of action, preclinical laboratory data and multiple Phase 2 studies of canfosfamide in combination with platinums, taxanes and anthracyclines, that canfosfamide works better in combination than as a single agent.[23,25,27–32] In addition, the mechanism of targeted activation of canfosfamide suggests that biological factors may predict activity and these warrant further exploration. A Phase 3 randomised study is in progress to evaluate the combination of canfosfamide and PLD versus PLD alone as second-line therapy of platinum-refractory or -resistant OC, a more homogeneous population of less heavily pretreated ovarian cancer, and the study incorporates relevant biomarker assays.

This was the first large randomised study in third-line therapy of platinum-refractory or -resistant OC. The study

demonstrated that active treatment with available agents in the third-line therapy setting may improve survival outcome significantly. This might have important consequences for future recurrent OC disease trials. Canfosfamide is not active enough as a single agent in this setting but further studies in combination with platinums, taxanes and anthracyclines are warranted.

Conflict of interest statement

Ignace Vergote declares no conflict with regard to the work described in this manuscript. Neil Finkler declares no conflict of interest. Jose del Campo declares no conflict of interest. Daniel Matei has consulted with Bayer, Genentech and Glaxo Smith Kline (GSK) and declares no conflict with regard to the work described in this manuscript. Stan Kaye declares no conflict of interest. Jan Vermorken declares no conflict of interest. Andreas du Bois has received research support from Glaxo Smith Kline (GSK) and declares no conflict with regard to the work described in this manuscript. James Hunter declares no conflict of interest. John Kavanagh declares no conflict of interest. Lisa Meng, Marsha Jones and Gail Brown are employees of Telik, Inc.

Role of funding sources

This work was supported by Telik, Inc., Palo Alto, CA, USA.

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