PERGAMON

European Journal of Cancer Vol. 38 Suppl. 8 (2002) S7–S12

European Journal of Cancer

www.ejconline.com

Results of ZD0473 in platinum-pretreated ovarian cancer: analysis according to platinum free interval

M.E. Gore[a,*], R.J. Atkinson[b], H. Thomas[c], H. Cure[d], D. Rischin[e], P. Beale[f], P. Bougnoux[g], L. Dirix[h] and W.M. Smit[i]

[a]*Medical Oncology, Royal Marsden Hospital NHS Trust, London, UK*
[b]*Department of Oncology, Belfast City Hospital, Belfast, N. Ireland*
[c]*The Royal Surrey Hospital, Guildford, UK*
[d]*CAC Jean Perrin, Clermont Ferrand, France*
[e]*Peter McCallum Cancer Institute, St Andrews Place, East Melbourne, Australia*
[f]*Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia*
[g]*CHU Hospital Bretonneau, Tours, France*
[h]*Oncologisch Centrum, Oosterveldlaan, Wilrijk, Belgium*
[i]*Medisch Spectrum Twente, Enschede, the Netherlands*

Abstract

Resistance to platinum-containing regimens can develop in many women with ovarian cancer and may lead to relapse in >80% of patients. ZD0473 is a new-generation platinum agent that, in preclinical studies, shows evidence of antitumour activity and overcomes platinum-resistance mechanisms. This Phase II trial has evaluated the efficacy and tolerability of ZD0473 in second-line ovarian cancer patients. Patients received ZD0473 120 mg/m^2 (1-h iv infusion, day 1 q 3-weeks); the starting dose was increased to 150 mg/m^2 after a safety review. We report here on results when patients are divided into four cohorts depending upon whether they were considered platinum-resistant or -sensitive. Patients were placed into one of 3 cohorts if they were platinum resistant (relapsed/progressed ≤26 weeks after completion of prior platinum-based chemotherapy) or cohort 4 if this period was >26 weeks (sensitive). Ninety-four patients were recruited to the trial (59 resistant, 35 sensitive; median age 58 [range 27–75] years; 86 with performance status [PS] ≤1). Forty-nine patients received a starting dose of 120 mg/m^2, of which 15 escalated to 150 mg/m^2, and 45 received a starting dose of 150 mg/m^2. Overall, the median number of treatment cycles received was 3 (range 1–8). Grade 3/4 thrombocytopenia was the most common haematological adverse event occurring in 62% of patients overall. Grade 3/4 lethargy, vomiting and nausea were the most common non-haematological toxicities. No clinically significant oto-, nephro- or neurotoxicity was observed. Overall response rates for all platinum-resistant and -sensitive patients were 8.3% and 32.4%, respectively. Stable disease occurred in 17 resistant and 15 sensitive patients.

Keywords: Ovarian cancer; ZD0473; Monotherapy; Platinum resistance

1. Platinum resistance in ovarian cancer

Resistance to platinum-containing regimens can develop and this can lead to relapse in >80% of ovarian cancer patients [1]. Three different mechanisms may cause this resistance: (1) decreased drug accumulation; (2) increased intracellular drug inactivation; and (3) prevention of cell death following platinum–DNA binding [2,3].

Following relapse, the likelihood of a response to platinum-containing chemotherapy increases with the length of time since the patient's previous treatment of this type

* Tel.: +44-0207-808-2198; Fax: +44-207-808-2475.
E-mail address: martin.gore@rmh.nthames.nhs.uk (M.E. Gore).

0959-8049/02/$ – see front matter

[4,5]. However, patients relapsing within 6 months of their previous therapy are considered to be platinum-resistant [6].

Clearly, the development of novel agents that provide activity in relapsed, platinum-resistant ovarian cancer patients is very important [7].

2. ZD0473

ZD0473 (*cis*-amminedichloro[2-methylpyridine]platinum[II]) is a new platinum agent that has been rationally designed to overcome the mechanisms of platinum resistance. Data from preclinical studies demonstrated that ZD0473 has an extended spectrum of antitumour activity in a number of different cell and tumour types, including a panel of 11 ovarian cancer cell lines [2] and ovarian cancer cells derived from clinical tumours [8]. Holford et al. [2] have also reported that ZD0473 retained its activity against three platinum-resistant ovarian cell lines that represented the main mechanisms of cisplatin resistance [2]. ZD0473 also exhibits antitumour activity against six out of seven human ovarian cancer xenografts, including those with cisplatin resistance [9,10].

Phase I studies provided evidence for the anti-tumour activity of ZD0473 in the clinical setting, including a partial response (PR) in a patient with recurrent ovarian carcinoma. Stable or improved disease was also observed in five other patients with a variety of tumours, including two patients with ovarian cancer [11]. Phase I studies demonstrated that ZD0473 had a manageable toxicity profile, with the main toxicity being myelosuppression [11] and that the recommended starting dose for Phase II studies was 120 mg/m^2.

Amongst Phase II trials was a study to determine the antitumour activity of ZD0473 monotherapy in patients with ovarian cancer who had relapsed after first-line, platinum-based chemotherapy. The results from this study are described in this paper.

3. ZD0473 Phase II trial in patients with ovarian cancer

As noted earlier, this was a Phase II, open-label, non-comparative, multicentre study in women with histologically or cytologically confirmed measurable ovarian cancer who had previously failed one prior platinum-based chemotherapy regimen. Patients were recruited from centres across Europe, South Africa and Australia.

Patients were screened to establish eligibility. Patient inclusion criteria were: women aged $\geq$18 years with a histologically or cytologically confirmed diagnosis of ovarian cancer who had failed first-line, platinum-based chemotherapy; life expectancy of $\geq$12 weeks; progressive or relapsing disease; and WHO performance status $\leq$2; absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L and haemoglobin $\geq$9 g/dL; creatinine clearance $\geq$60 mL/min; serum bilirubin $\leq$1.25 $\times$ upper limit of reference range (ULRR) and alanine/aspartate aminotransferase (ALT/AST) $<5 \times$ ULRR. All patients provided informed, written consent prior to study entry.

Patients were divided into four cohorts (Fig. 1), with cohorts 1–3 considered to be platinum-resistant and cohort 4 considered to be platinum-sensitive.

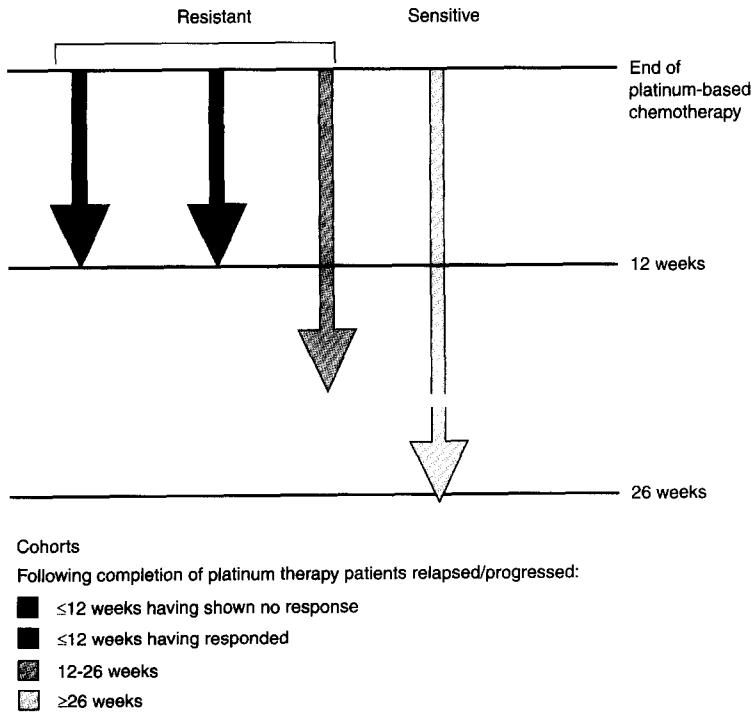

Fig. 1. Patient cohorts.

Table 1
Patient demographics

	No. patients ($n = 94$)
Median age, years (range)	58 (27–75)
No. patients per cohort	
cohort 1	11
cohort 2	19
cohort 3	29
cohort 4	35
WHO performance status	
0	50
1	36
2	8
Creatinine clearance (mL/min)	
<60	14
60–79	37
≥80	43
Metastatic disease	
yes	74
no	20
Prior therapies, *n* (%)	
none	0 (0)
surgery	88 (93.6)
chemotherapy	94 (100.0)
immunotherapy/hormonal therapy	2 (2.1)
radiotherapy	2 (2.1)
other	2 (2.1)

Initially, a starting dose of 120 mg/m^2 ZD0473 (1-hour iv infusion) was administered to patients on Day 1 of a 3-week cycle. This dose was escalated to 150 mg/m^2 in the absence of major toxicity. Following a safety review showing that 120 mg/m^2 was well tolerated, the starting dose was modified to 150 mg/m^2, which was also administered at 3-week cycles.

Patients who did not experience disease progression could receive up to six treatment cycles. Biochemical and haematological parameters were measured on Days 1, 8, 15 and 22 of each treatment cycle, at treatment withdrawal, and 30 days after the last dose. In cases of dose delay, these measurements were also performed on Days 29, 36 and 43. After the first treatment cycle (and prior to subsequent cycles), the following criteria had to be met before further treatment was given: ANC $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; serum creatinine $\leq 1.25 \times$ ULRR; bilirubin $\leq 1.25 \times$ ULRR; and resolution of any non-haematological toxicity to <grade 2. If these re-treatment criteria were not met by Day 28, the dose of ZD0473 was reduced in all subsequent cycles. Patients not meeting the criteria by Day 43 were withdrawn from the study.

Adverse events occurring during each cycle and up to 30 days after the last dose of ZD0473 were classified using the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Revised NCI response evaluation criteria in solid tumours (RECIST) criteria were used to determine tumour response after treatment cycles 2, 4 and 6, at treatment withdrawal, and at subsequent visits until disease progression.

Table 3
Percentage of patients with grade 3/4 haematological toxicity (worse grade per patient)

	ZD0473 dose (mg/m^2)			
	120 ($n = 34$)	120/150 ($n = 15$)	150 ($n = 45$)	total ($n = 94$)
Thrombocytopenia	38	60	80	62
Neutropenia	32	20	47	37
Anaemia	29	53	33	35

4. Results

A total of 94 patients were recruited into the study and the demographics of patients in cohorts 1–4 are shown in Table 1.

A total of 49 patients received a starting dose of 120 mg/m^2, of whom 15 patients were subsequently escalated to 150 mg/m^2 as the initial starting dose was well tolerated. A total of 45 patients received a starting dose of 150 mg/m^2 (Table 2).

4.1. Tolerability of ZD0473 in ovarian cancer

Grade 3/4 haematological toxicities included thrombocytopenia, neutropenia and anaemia (Table 3). Further details relating to the tolerability profile of ZD0473 in ovarian cancer can be found in the accompanying primary manuscript [12].

Table 2
ZD0473 treatment received

	ZD0473 dose (mg/m^2)			
	120 ($n = 34$)	120/150 ($n = 15$)	150 ($n = 45$)	total ($n = 94$)
Total no. cycles	104	67	166	337
Median no. cycles (range)	2 (1–8)	6 (2–6)	3 (1–8)	3 (1–8)
No. patients receiving ≥4 cycles	13	10	21	44
No. patients with cycles delayed due to toxicity	10	6	25	41
No. patients with dose reduced >20%	6	8	21	35

Table 4
Activity of ZD0473

Cohort	No. patients ($n = 82$)				
	evaluable	complete response	partial response	stable disease	disease progression
1	8	0	0	2	6
2	13	0	1	4	8[a]
3	27	3	0	11	13
4	34	5	6	15	8[a]

[a]Includes 1 patient with symptomatic deterioration.

4.2. Activity of ZD0473 in ovarian cancer

Activity data were available for 82 patients (48 platinum-resistant, 34 platinum-sensitive) and some antitumour activity was observed in cohorts 2, 3 and 4 (Table 4). Activity was minimal in patients who responded to prior platinum therapy but relapsed within 3 months (cohort 2), with only 1 PR. However, three complete responses (CR) were seen in cohort 3 (patients who had relapsed 3–6 months from prior platinum therapy) and patients who had relapsed >6 months from prior platinum therapy (cohort 4) were associated with encouraging antitumour activity (5 CR, 6 PR). There was no antitumour activity in patients who did not respond to previous platinum therapy and progressed within 3 months of treatment (cohort 1) [Table 4].

Overall, there was minimal antitumour activity in patients who were platinum-resistant. The majority of responses amongst platinum-resistant patients were observed in patients who had relapsed 3–6 months after ending prior platinum therapy (cohort 3). In contrast, antitumour responses were most frequently observed in platinum-sensitive patients (cohort 4).

The time to progression (TTP) for cohorts 1–3 (platinum-resistant) and cohort 4 (platinum-sensitive) is shown in Fig. 2. The overall response rate for the platinum-resistant patients was 8.3% (95% CI 2.3, 20.0) in comparison with 32.4% (95% CI 17.4, 50.5) for the platinum-sensitive patients. TTP for the platinum-resistant and -sensitive groups was 57 (95% CI 49, 92) and 180 (95% CI 98, 299) days, respectively.

The time to death (TTD) for cohorts 1–3 and cohort 4 is shown in Fig. 3. The overall TTD for the platinum-resistant patients was 242 (95% CI 194, 560) days with 39.3% of patients surviving at 1 year. In contrast, the overall TTD for the platinum-sensitive patients was 402 (95% CI 309, 480) days with 55.4% of patients surviving at 1 year.

5. Discussion

The present study provides evidence that ZD0473 has a manageable tolerability profile when administered as second-line chemotherapy for ovarian cancer. Furthermore, ZD0473 does show some activity in the second-line therapy of ovarian cancer in patients who have relapsed after prior platinum chemotherapy. This activity is particularly apparent in those patients who are platinum-sensitive.

Studies have previously shown that the use of cisplatin or carboplatin as second-line therapy in patients who are platinum-sensitive produces a response rate of at least 30% [4,13–15], which is comparable with the response rate in the ZD0473-treated, platinum-sensitive patients (32.4%) reported in this study. Previously published TTP data shows longer median TTP for cisplatin-treated patients who are platinum-sensitive (approximately 46 weeks) [14] than the TTP for ZD0473 reported in this study (24–25 weeks).

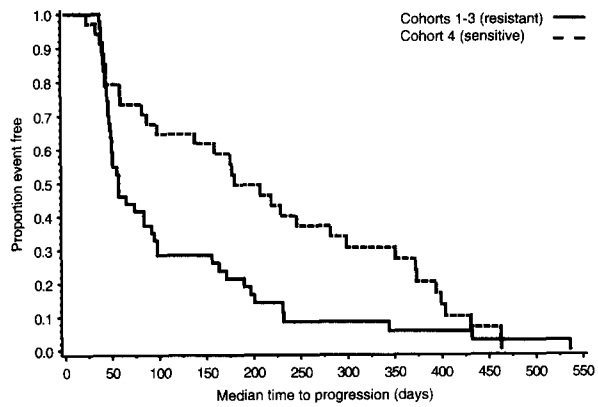

Fig. 2. Median time to progression (Kaplan–Meier).

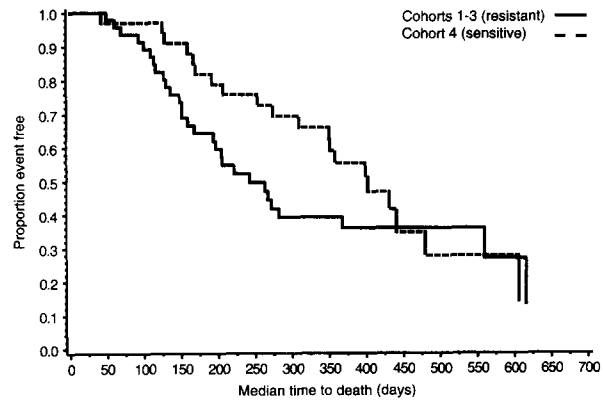

Fig. 3. Median time to death (Kaplan–Meier).

ZD0473 appears to possess similar activity to standard platinum agents when used as second-line therapy in ovarian cancer patients who are platinum-sensitive. To identify whether ZD0473 offers any therapeutic advantages to patients classified as platinum-resistant, the results can be compared with other studies in relapsed/resistant ovarian cancer patient populations. Paclitaxel, topotecan and liposomal doxorubicin monotherapy are standard treatment options in platinum-resistant patients [16] and these treatments offer useful comparisons with which to assess the activity of ZD0473.

Higher response rates have been reported in patients with platinum-resistant ovarian cancer with paclitaxel or liposomal doxorubicin. Response rates of 30–48% have been reported in paclitaxel-treated platinum-resistant ovarian cancer [17–19] that are superior to the response rate of 8.3% in the present study. Liposomal doxorubicin has also shown response rates of 12–26% in platinum-refractory ovarian cancer [20,21]. Topotecan has been shown to produce overall response rates of 6–13% in platinum-resistant ovarian cancer [21,22], which is similar to the response rate of 8.3% reported in the present study.

Clinical studies have indicated that the median TTP in platinum-resistant patients is approximately similar for the clinically approved monotherapy agents paclitaxel, topotecan and liposomal doxorubicin, with none reporting TTP equivalent to those seen in retreated platinum-sensitive patients [14]. In platinum-resistant patients, paclitaxel has been shown to produce median TTPs of 14 and 17 weeks [19,22], liposomal doxorubicin 16 weeks [21] and topotecan 14 and 23 weeks [21,22].

Other chemotherapeutic agents, such as oral etoposide [23] and vinorelbine [24] are currently being investigated in platinum-resistant ovarian cancer and have produced reasonable response rates (27% and 21%, respectively). However, it should be highlighted that these response rates were achieved with significant dose-limiting haematological toxicity, while in comparison ZD0473 has manageable tolerability and minimal dose-limiting adverse events.

Studies are currently ongoing with other new platinum agents such as oxaliplatin [7].

6. Conclusions

In conclusion, the results of the present study indicate that while ZD0473 is effective in overcoming preclinical models of platinum resistance, major resistance mechanisms remain in the clinical setting that limit the activity of ZD0473 in platinum-resistant patients. However, ZD0473 may offer some benefits in terms of tolerability over existing platinums and may therefore be a possible alternative.

Final data are almost complete from ZD0473 combination studies, including studies evaluating ZD0473 in combination with paclitaxel [25] and liposomal doxorubicin [26]. Interestingly, some antitumour activity (CR and PR) has been reported in the latter trial that included patients with refractory ovarian cancer.

Acknowledgements

The authors wish to thank: T. Bauknecht (Universitatsfrauenklinik, Bonn, Germany); A. Bols (Ocologische Centrum, Brugge, Belgium); A. Chevalier-Place (Centre Oscar Lambret, Lille, France); F. Daniel (Derriford Hospital, Plymouth, UK); A. du Bois (Dr Horst Schmidt Kiniken, Wiesbaden, Germany); B. Filleul (Hôpital de Jolimont, Haine St Paul, Belgium); D. Guthrie (Derbyshire Royal Infirmary, Derby, UK); D. Hacking (Durban Oncology Centre; Mayville, South Africa); P. Harnett (Westmead Hospital, Westmead, Australia and Nepan Hospital Pennith, Kingswood, Australia); A. Hong (Royal Devon and Exeter Hospital, Exeter, UK); A.H. Honkoop (Isala Klinieken, Zwolle, the Netherlands); F. Joly (Centre Francois Baclesse, Caen, France); E. Joosens (Dienst Oncologie-Hematologie, Antwerpen, Belgium); J. Kerger (Clinique St Elisabeth, Namur, Belgium); F. Kridelka (CHR La Citadelle, Liège, Belgium); D. Parkin (Aberdeen Royal Infirmary, Aberdeen, UK); B. Smit (Tygerberg Hospital, Tygerberg, South Africa); R. Soeters (Vincent Palloti Hospital, Capre Town, South Africa); W.W. Ten Bokkel Huinick (Antoine van Leeuwenhoek Ziekenhuis, Amsterdam, The Netherlands); I. Vergote (Dienst Gynaecologische Oncologie, Leuven, Belgium); D. Vorobiof (Sandton Oncology Clinic, Sandton, South Africa).

References

[1] Conte PF, Cianci C, Tanganelli L, Gadducci A. Ovarian cancer: optimal therapy in relapsed disease. *Ann Oncol* 2000, **11**, 145–150.
[2] Holford J, Sharp SY, Murrer BA, Abrams M, Kelland LR. In vitro circumvention of cisplatin resistance by the novel sterically hindered platinum complex AMD473. *Br J Cancer* 1998, **77**, 366–373.
[3] Akiyama S-I, Chen Z-S, Sumizawa T, Furukawa T. Resistance to cisplatin. *Anticancer Drug Design* 1999, **8**, 143–151.
[4] Gore ME, Fryatt I, Wiltshaw E, Dawson T. Treatment of relapsed carcinoma of the ovary with cisplatin or carboplatin following initial treatment with these compounds. *Gynecol Oncol* 1990, **36**, 207–211.
[5] Markman M, Rothman R, Hakes T, *et al.* Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991, **9**, 389–393.
[6] Ozols RF. Update of the NCCN ovarian cancer guidelines. *Oncology* 1997, **11**, 95–105.
[7] Piccart MJ, Lamb H, Vermorken JB. Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. *Ann Oncol* 2001, **12**, 1195–1203.
[8] Medina-Gundrum L, Gomez L, Cerna C, *et al.* ZD0473 exhibits marked *in vitro* antitumour activity in human tumour specimens. *Eur J Cancer* 2001, **37**, 454 (abstr).
[9] Raynaud FI, Boxall FE, Goddard PM, *et al.* cis-Amminedichloro(2-methylpyridine)platinum(II) (AMD473), a novel sterically hindered platinum complex: in vivo activity, toxicol-

ogy, and pharmacokinetics in mice. *Clin Cancer Res* 1997, **3**, 2063–2074.

[10] Akiyama Y, Kusaba H, Kanzawa F, Tamura T, Saijo N, Nishio K. Overcoming cisplatin-resistance by ZD0473 (*cis*-amminedichloro[2-methylpyridine]platinum[II]) in human lung cancer cells. Poster presented at the 2nd International Lung Cancer Conference, Hawaii, July 18–21, 2001.

[11] Kelland L, Judson I, Koehler M, Stephens T, Roberts D. Preclinical and clinical overview of the novel platinum complex, ZD0473 (*cis*-amminedichloro [2-methylpyridine] platinum [II]). *Lung Cancer* 2000, **70**, 227 (abstr).

[12] Gore ME, Atkinson RJ, Thomas H, *et al.* A phase II trial of ZD0473 in platinum-pretreated ovarian cancer. *Eur J Cancer* 2002, In Press.

[13] Canetta R, Bragman K, Smaldone L, Rozencweig M. Carboplatin: current status and future prospects. *Cancer Treat Rev* 1988, **15** (Suppl B), 17–32.

[14] Gershenson DM, Kavanagh JJ, Copeland LJ, Stringer CA, Morris M. Re-treatment of patients with recurrent epithelial ovarian cancer with cisplatin-based chemotherapy. *Obstet Gynecol* 1989, **73**, 798–802.

[15] Kjorstad K, Harris A, Bertelsen K, *et al.* A multicentre phase II study of carboplatin in advanced ovarian carcinoma: final report. *Ann Oncol* 1992, **3**, 217–222.

[16] National Cancer Institute PDQ Statement. Ovarian epithelial cancer (PDQ): treatment – health professionals. January 2002.

[17] McGuire WP, Rowinsky EK, Rosenshein NB, *et al.* Taxol: a unique antineoplastic agent with significant activity in advanced ovarian neoplasms. *Ann Intern Med* 1989, **111**, 273–279.

[18] Kohn EC, Sarosy G, Bicher A, *et al.* Dose-intensive taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. *J Natl Cancer Inst* 1994, **86**, 18–24.

[19] Thigpen JT, Blessing JA, Ball H, Hummel SJ, Barrett RJ. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum based chemotherapy: a Gynaecologic Oncology Group study. *J Clin Oncol* 1994, **12**, 1748–1753.

[20] Muggia FM, Hainsworth JD, Jeffers S, *et al.* Phase II study of liposomal doxorubicin in refractory ovarian cancer: antitumour activity and toxicity modification by liposomal encapsulation. *J Clin Oncol* 1997, **15**, 987–993.

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

[22] ten Bokkel Huinink W, Gore M, Carmichael J, *et al.* Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997, **15**, 2183–2193.

[23] Rose PG, Blessing JA, Mayer AR, Homesley HD. Prolonged oral etoposide as second-line therapy for platinum-resistant and platinum-sensitive ovarian carcinoma: a Gynaecologic Oncology Group study. *J Clin Oncol* 1998, **16**, 405–410.

[24] Bajetta E, Leo AD, Biganzoli L, *et al.* Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: activity in platinum resistant disease. *J Clin Oncol* 1996, **14**, 2546–2551.

[25] Gatzemeier U, Twelves C, Anthoney DA, Pentheroudakis G, Groth G, Cosaert J. A phase I dose-escalation study of ZD0473 combined with paclitaxel in refractory solid malignancies. *Eur J Cancer* 2001, **37**, 264 (abstr).

[26] Dizon DS, Maluf F, Aghajanian C, *et al.* Phase I study of ZD0473 and liposomal doxorubicin in advanced refractory solid tumour malignancies. *Eur J Cancer* 2001, **37**, 273 (abstr).