A review of phase II studies of ZD9331 treatment for relapsed or refractory solid tumours

John Hainsworth[a], Ignace Vergote[b] and Jacques Janssens[c]

Background **Non-small cell lung cancer (NSCLC), ovarian and breast cancers, especially in advanced stages, are difficult to treat using chemotherapy, and novel treatments are required to improve the outcome for the large numbers of patients who relapse after receiving the most effective first- and second-line treatments currently available. This paper reviews the results from three trials of ZD9331, a novel, direct-acting antifolate, in patients with relapsed or refractory solid tumours.**

Patients and methods **Patients with relapsed or refractory NSCLC, ovarian or breast cancer were included in these three open-label, multicentre trials. All three trials included an i.v. arm of ZD9331 at a dose of 130 mg/m^2; the ovarian study also included a 65 mg/m^2 i.v. treatment arm and the breast cancer trial included a 3 mg oral treatment arm. Patients received ZD9331 as a 30-min i.v. infusion once weekly for 2 weeks followed by 1 week without treatment (3-week cycle). Oral ZD9331 was given once daily for 28 consecutive days and repeated every 6 weeks.**

Results **One hundred and eighty-nine patients were included in the three trials (NSCLC: $n = 46$; ovarian: $n = 80$; breast: $n = 63$). Neutropenia (45–59%), asthenia (25–42%) and nausea (41–59%) were amongst the most common adverse events observed in all three trials; however, in the oral treatment group of the breast cancer trial anaemia (58%) and increased alanine aminotransferase (45%) or aspartate aminotransferase (39%) were also frequent. There were no objective responses seen in the NSCLC trial; 20 of 46 patients (43.5%) experienced a best overall response of stable disease. Objective response rates (ORRs) in the ovarian trial were 2.5% (one patient) and 10% (four patients) in the 65 and 130 mg/m^2 treatment arms, respectively. In the breast cancer trial ORRs were 9.7% (three patients) and 12.5% (four patients) in the oral and i.v. groups, respectively.**

Conclusions **ZD9331 has a manageable toxicity profile, and shows some evidence of activity in patients with relapsed or refractory NSCLC, ovarian and breast cancer.**
***Anti-Cancer Drugs* 14 (suppl 1):S13–S19 © 2003 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2003, **14 (suppl 1)**:S13–S19

Keywords: breast cancer, non-small cell lung cancer, ovarian cancer, treatment-refractory, ZD9331

[a]Sarah Cannon Cancer Center, Nashville, TN, USA, [b]Gynaecologic Oncology, University Hospital Leuven, Gasthuisberg, Belgium and [c]Department of Oncology, Limburg Oncological Center, Salvator Ziekenhuis, Hasselt, Belgium.

Correspondence to J. Hainsworth, Sarah Cannon Cancer Center, 250 25th Avenue North, Suite 110, Nashville, TN 37203, USA.
Tel: +1 615 986 4300; fax: +1 615 342 1745;
e-mail: jhainsworth@tnonc.com

Introduction

Epidemiology of non-small cell lung cancer (NSCLC), ovarian and breast cancers

Lung cancer is the leading cause of cancer death in most Western European and North American countries. It has been estimated that there will be 154 900 lung cancer-related deaths in the USA in 2002, accounting for approximately 28% of all cancer deaths [1,2]. The latest published statistics from Europe show that, with an estimated 377 000 cases, lung cancer was the most common cancer in 1995 and also the most common cause of cancer death that year (330 000) [3]. NSCLC represents approximately 75% of lung cancer cases.

Ovarian cancer is the fifth most common cause of cancer deaths and the leading cause of death from gynaecological cancers among women in the USA [2]. The estimated number of new ovarian cancer cases in the USA in 2002 is 23 300, with approximately 13 900 deaths [2]. There were an estimated 58 000 new cases of ovarian cancer in Europe in 1995, ranking the disease as the seventh most common cancer and the fifth most common cause of cancer death in European women [3].

Breast cancer is the commonest cancer in women, with a lifetime risk of up to 10% in the Western World. It is also the second leading cause of cancer death in Caucasian women in the USA. The American Cancer Society estimates that there will be about 205 000 new cases of invasive breast cancer (stages I–IV) diagnosed in the USA in 2002 and approximately 40 000 deaths [2]. Breast cancer is also the most common cancer in European women (with an estimated 321 000 cases in 1995), accounting for over a quarter of all new female cancers. There were approximately 124 000 deaths from breast cancer in Europe during this period (17% of all female cancer deaths) making it the most common cause of cancer death in women [3].

0959-4973

The need for new treatments for NSCLC, ovarian and breast cancers

NSCLC, ovarian and breast cancers, especially in advanced stages, are difficult to treat, with most chemotherapeutic regimens resulting in only partial responses (PRs) or palliation at best. Platinum-based therapies may offer some benefits in NSCLC and ovarian cancer. The development of platinum resistance, however, is a known problem with this type of treatment [4] and can lead to relapse for many patients, as is the case in more than 80% of ovarian cancer patients treated with platinum-containing regimens [5]. Therefore, novel treatments are needed in order to improve the outcome for the large numbers of patients with NSCLC, ovarian or breast cancer who relapse even after receiving the most effective first- and second-line treatments currently available, including platinum-based regimens.

ZD9331 in the treatment of solid tumours

ZD9331 is a novel, direct-acting, cytotoxic antifolate developed for the treatment of solid malignant tumours. It is a highly specific thymidylate synthase inhibitor that is actively transported into cells via the reduced folate carrier (RFC). The RFC is believed to be overexpressed in certain tumour cells, including, breast, ovarian and lung cancers, thus potentially allowing ZD9331 to selectively target tumour cells over their normal tissue counterparts [6]. In contrast to some other folate analogues, ZD9331 does not require polyglutamation by folylglutamyl synthetase to become active.

In preclinical studies, ZD9331 has demonstrated activity in a range of human tumour cell lines including breast, ovarian and lung tumours, suggesting that it could offer the prospect of broad-spectrum antitumour activity in the clinic [7].

Phase I studies demonstrated that ZD9331 had encouraging activity against a range of solid tumours [8–11]. This paper will review the main efficacy and tolerability data from three phase II trials of ZD9331 in the treatment of patients with relapsed or refractory NSCLC, ovarian or breast cancers.

Methods

Study design

All three phase II trials were open-label, non-comparative and multicentre.

Patients

Inclusion criteria

Patients with histologically or cytologically confirmed NSCLC, ovarian or breast cancer were recruited into these phase II trials. Other criteria included: aged ≥18 years, life expectancy >12 weeks, measurable disease (more than one measurable lesion) and written informed consent.

For the NSCLC trial, additional inclusion criteria included recurrent disease (failure after response [complete response (CR), partial response (PR) or stable disease (SD)] to first-line chemotherapy regimen) and a Karnofsky performance status ≥70.

Additional inclusion criteria in the ovarian cancer trial included refractory or recurrent disease following platinum plus paclitaxel combination treatment, platinum-resistance (refractory or relapsed within 6 months of last platinum therapy) and a WHO performance status of 0 or 1. Patients with primary peritoneal cancer or cancer of the fallopian tube were also permitted.

For the breast cancer trial additional inclusion criteria included breast tumours refractory to first- or second-line cytotoxic chemotherapy (defined as tumour progression during or since completion of therapy) and a WHO performance status of 0 or 1.

Exclusion criteria

Exclusion criteria common to all three trials included: inadequate bone marrow reserve (absolute neutrophil count $<1.5 \times 10^9$/l, platelets $<100 \times 10^9$/l), inadequate liver function or kidney function [serum bilirubin ≥1.25 × upper limit of reference range [(LRR), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 × ULRR if no demonstrable liver metastases or >5 × ULRR in the presence of liver metastases, creatinine clearance <60 ml/min and albumin level below the lower limit of reference range), severe or uncontrolled systemic disease, concomitant use of folic acid in any form within last 24 h, incomplete recovery from prior surgery and other malignancies known to be active within the last 5 years.

Patients who had received other cancer therapy within the previous 4 weeks were excluded from the ovarian and breast cancer trials, and patients with haemoglobin <9 g/dl were excluded from the breast cancer trial. For the ovarian cancer trial, patients with any metastasis to the central nervous system were also excluded. The ovarian study also included a ZD9331 plus topotecan combination treatment arm and therefore previous treatment with topotecan was not permitted. The combination treatment arm of this study will be discussed elsewhere in this supplement.

Treatment

All three trials included an i.v. ZD9331 dose of 130 mg/m^2. The ovarian cancer study also included a 65 mg/m^2 i.v. treatment arm and the breast cancer trial a 3 mg oral treatment arm (Table 1).

ZD9331 was given as a 30-min i.v. infusion once weekly for 2 weeks (days 1 and 8) followed by 1 week without treatment (days 15–21) (3-week cycle). Oral ZD9331 was

Table 1 Summary of the phase II ZD9331 monotherapy study designs

Patient group	Clinical criteria	Treatment regimen	Cycle of treatment
Relapsed NSCLC	Relapsed after a CR or PR or after a period of SD following treatment with one previous regimen of chemotherapy	130 mg/m^2 i.v.	30-min infusion on days 1 and 8 of a 3-week cycle
Platinum-resistant/refractory ovarian cancer	PD during previous platinum therapy or relapsed within 6 months of last platinum therapy	65 or 130 mg/m^2 i.v.	30-min infusion on days 1 and 8 of a 3-week cycle
Refractory/relapsed breast cancer	Tumour progression during or since first- or second-line cytotoxic chemotherapy	130 mg/m^2 i.v. or 3 mg oral	30-min infusion on days 1 and 8 of a 3-week cycle Once daily for 28 consecutive days, repeated every 6 weeks

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression.

given once daily for 28 consecutive days and repeated every 6 weeks. For patients receiving oral ZD9331 there had to be a minimum of 14 days between the last dose of one cycle and the first of the next cycle.

In all three trials, ZD9331 doses were modified for individual patients according to the toxicity seen in the previous cycle. The maximum and minimum doses allowed were 125 and 50% of the initial doses, respectively. There was no dose escalation for patients receiving oral ZD9331. Patients could continue with treatment until a withdrawal criterion [e.g. disease progression (PD)] was met and there was no limit to the maximum number of cycles permitted in these trials.

Tolerability and efficacy assessments

The intent-to-treat (ITT) population was used for analysis of tolerability and efficacy in each trial. The ITT population comprised all patients who received one or more doses of trial therapy. Adverse events (AEs) and laboratory parameters were monitored continuously throughout the trials and classed according to National Cancer Institute Common Toxicity Criteria (NCI-CTC). NCI Response Evaluation Criteria in Solid Tumours (RECIST) definitions were used to determine patients' best overall objective tumour response and the objective tumour response rate.

Results

Patients

Patient baseline characteristics are summarised in Table 2.

One hundred and eighty-nine patients were included in the three trials. Forty-six patients were included in the NSCLC trial. In the monotherapy arm of the ovarian cancer trial, 40 patients received 65 mg/m^2 ZD9331 and 40 patients received 130 mg/m^2 ZD9331. Thirty-one patients received oral ZD9331 and 32 patients received i.v. ZD9331 in the breast cancer trial.

All patients in the NSCLC, ovarian cancer and breast cancer trials had previously received chemotherapy (including adjuvant or neoadjuvant chemotherapy). Most of the patients (46 of 63, 73.0%) in the breast cancer trial had also received previous hormonal therapy (44 of 46) or immunotherapy (2 of 46). Only one patient in the ovarian cancer trial had previously received radiotherapy treatment compared with 22 of 46 patients (47.8%) in the NSCLC trial and 47 of 63 patients (74.6%) in the breast cancer trial. Most of the patients were receiving ZD9331 as second- (NSCLC, 87.0%; ovarian cancer, 45.0%; breast cancer, 50.8%) or third-line chemotherapy (NSCLC, 13.0%; ovarian cancer, 43.8%; breast cancer, 38.1%).

In total, 37 patients (80.4%) were withdrawn from the NSCLC trial, 74 patients (92.5%) from the ovarian cancer trial (37 from each monotherapy arm) and 50 patients (79.4%) from the breast cancer trial (25 patients from each treatment group) at the time of the analyses.

In all three trials, the most common reason for withdrawal from treatment was PD [NSCLC, 27 patients (58.7%); ovarian cancer, 55 patients (68.8%); breast cancer, 37 patients (58.7%)]. Nine patients (19.6%) in the NSCLC trial, six patients (7.5%) from the ovarian cancer trial and eight patients (12.7%) from the breast cancer trial were withdrawn from treatment because of AEs. Other reasons for withdrawal from treatment included protocol non-compliance (one patient), withdrawal of informed consent (nine patients) and withdrawal at the investigator's discretion (nine patients).

There were nine deaths during the three trials, six as a result of cancer and three as a result of AEs that were considered by the investigator to be treatment-related (NSCLC, two patients; breast cancer, one patient).

Treatment

In the NSCLC trial, the mean number of cycles of ZD9331 received was 3.5 (range 1–10, 1 cycle = 3 weeks) with 159 cycles administered in total. A total of 308 cycles of treatment were administered in the ovarian cancer trial (65 mg/m^2, 148 cycles; 130 mg/m^2, 160 cycles). Patients in the 65 mg/m^2 ZD9331 group received a mean of 3.7 cycles (range 1–13; 1 cycle = 3 weeks) and those in the 130 mg/m^2 ZD9331 group received a mean of

Table 2 ZD9331 phase II trials: baseline characteristics

	NSCLC	Ovarian cancer		Breast cancer	
	130 mg/m^2 (i.v.)	65 mg/m^2 (i.v.)	130 mg/m^2 (i.v.)	3 mg (oral)	130 mg/m^2 (i.v.)
Patients (*n*)	46	40	40	31	32
Age (years)					
mean (SD)	59.2 (10.2)	55.8 (10.1)	57.8 (11.3)	56.7 (9.2)	57.8 (12.2)
range	28–74	31–79	40–83	39–73	29–77
Sex [*n* (%)]					
male	28 (60.9)	–	–	–	–
female	18 (39.1)	40 (100.0)	40 (100.0)	31 (100.0)	32 (100.0)
Performance status [*n* (%)]					
Karnofsky		NA	NA	NA	NA
70	3 (6.5)				
80	16 (34.8)				
90	13 (28.3)				
100	14 (30.4)				
WHO	NA				
0		24 (60.0)	23 (57.5)	20 (64.5)	17 (53.1)
1		16 (40.0)	17 (42.5)	11 (35.5)	15 (46.9)
Previous cancer therapy [*n* (%)]					
chemotherapy[a]	46 (100.0)[b]	40 (100.0)[c]	40 (100.0)[c]	30 (96.8)[d]	30 (93.8)[d]
1 previous course	40 (87.0)	20 (50.0)	16 (40.0)	19 (61.3)	13 (40.6)
2 previous courses	6 (13.0)	16 (40.0)	19 (47.5)	10 (32.3)	14 (43.8)
3 previous courses	0 (0.0)	4 (10.0)	4 (10.0)	0 (0.0)	2 (6.3)
4 previous courses	0 (0.0)	0 (0.0)	1 (2.5)	1 (3.2)	1 (3.1)
immuno/hormonal therapy	–	–	–	24 (77.4)	22 (68.8)
radiotherapy	2 (47.8)	0 (0.0)	1 (2.5)	25 (80.6)	22 (68.8)
surgery	14 (30.4)	38 (95.0)	40 (100.0)	29 (93.5)	29 (90.6)
other therapy	2 (4.3)	0 (0.0)	0 (0.0)	1 (3.2)	0 (0.0)

[a]Not including adjuvant or neoadjuvant chemotherapy.
[b]All patients relapsed following previous chemotherapy.
[c]Twenty-three patients refractory and 57 patients relapsed following previous platinum/paclitaxel chemotherapy.
[d]Fifteen patients refractory and 45 patients relapsed following previous chemotherapy.
NA: not assessed in this particular study.

4.0 cycles (range 1–8; 1 cycle = 3 weeks). In the breast cancer trial 223 cycles were administered in total (oral ZD9331, 79 cycles; i.v. ZD9331, 144 cycles). The mean number of cycles of oral ZD9331 received per patient was 2.5 (range 1–6, 1 cycle = 6 weeks) and patients in the i.v. ZD9331 group received a mean of 4.5 cycles (range 1–12, 1 cycle = 3 weeks).

Tolerability

NSCLC trial

In the NSCLC trial the most common AEs were neutropenia (24 patients, 52.2%), asthenia (19 patients, 41.3%) and nausea (19 patients, 41.3%). Twenty-three patients (50%) experienced a haematological AE of grade 3 or 4. The most commonly occurring grade 3 or 4 events (Table 3) were neutropenia [grade 3, four patients (8.7%); grade 4, six patients (13.0%)], thrombocytopenia [grade 3, four patients (8.7%); grade 4, three patients (6.5%)] and anaemia [grade 3, three patients (6.5%); grade 4, one patient (2.2%)]. Twenty-five patients (54.3%) experienced a non-haematological AE with a worst grade of 3 or 4, the most common being asthenia [grade 3, five patients (10.9%)], nausea [grade 3, five patients (10.9%)] and vomiting (grade 3, three patients [6.5%); grade 4, one patient (2.2%)].

Nine patients (19.6%) were withdrawn from the trial as a result of AEs (Table 4). The AEs that led to withdrawal in more than one patient were neutropenia (three patients, 6.5%), thrombocytopenia (two patients, 4.3%) and sepsis (two patients, 4.3%).

Two patients died as a result of treatment-related sepsis, neutropenia and thrombocytopenia.

Table 3 Grade 3 and 4 haematological and non-haematological AEs occurring in two or more patients by worst CTC grade

	NSCLC	Ovarian cancer		Breast cancer	
AE [*n* (%)][a]	130 mg/m^2 (i.v.) (*n* = 46)	65 mg/m^2 (i.v.) (*n* = 40)	130 mg/m^2 (i.v.) (*n* = 40)	3 mg (oral) (*n* = 31)	130 mg/m^2 (i.v.) (*n* = 32)
Haematological					
anaemia	4 (8.7)	2 (5.0)	3 (7.5)	4 (12.9)	2 (6.3)
neutropenia	10 (21.7)	9 (22.5)	8 (20.0)	–	11 (34.4)
thrombocytopenia	7 (15.2)	4 (10.0)	2 (5.0)	4 (12.9)	4 (12.5)
leucopenia	–	4 (10.0)	3 (7.5)	–	5 (15.6)
Non-haematological					
abdominal pain	2 (4.3)	2 (5.0)	–	–	–
anorexia	2 (4.3)	–	–	–	–
asthenia	5 (10.9)	5 (12.5)	2 (5.0)	–	–
diarrhoea	2 (4.3)	–	2 (5.0)	–	3 (9.4)
dyspnoea	3 (6.5)	2 (5.0)	–	–	–
hyponatraemia	–	2 (5.0)	–	–	–
ileus	–	2 (5.0)	–	–	–
nausea	5 (10.9)	3 (7.5)	–	–	2 (6.3)
AST increase	–	–	–	7 (22.6)	–
ALT increase	–	2 (5.0)	2 (5.0)	9 (29.0)	–
vomiting	4 (8.7)	2 (5.0)	3 (7.5)	–	2 (6.3)

[a]A patient may have had more than one CTC graded AE; a patient was only counted once at the worst CTC grade in each CTC category.
A '–' indicates grade 3/4 AEs occurring in one patient or less.

Table 4 AEs leading to withdrawal from treatment

Patient[a]	NSCLC ($n = 46$)	Patient[a]	Ovarian cancer ($n = 80$)	Patient[a]	Breast cancer ($n = 63$)
1	fever, neutropenia, thrombocytopenia, sepsis	1	bilirubinaemia	1	rash
2	neuropathy	2	pulmonary embolism	2	anaemia
3	febrile neutropenia	3	asthenia, dyspnoea, hypoxia	3	diarrhoea, epistaxis, fever, melaena, nausea, neutropenia, rash, thrombocytopenia, vomiting
4	skin disorder	4	asthenia, malaise, nausea, vomiting	4	abdominal pain, nausea
5	diarrhoea	5	diarrhoea, dehydration	5	neutropenia
6	neutropenia, stomatitis	6	asthenia, stomatitis	6	anaemia, dehydration, hypotension, pancytopenia, thrombocytopenia
7	haemoptysis			7	aphasia, brain oedema, confusion, CNS neoplasia, syncope
8	asthenia, neutropenia thrombocytopenia, sepsis			8	increased creatinine levels, neutropenia, thrombocytopenia, sepsis
9	rash				

[a]Patients withdrawn due to AEs.

Ovarian cancer trial

In the ovarian cancer trial, the most commonly experienced AEs occurring in the 65 mg/m^2 ZD9331 group were neutropenia (18 patients, 45.0%), nausea (17 patients, 42.5%) and asthenia (17 patients, 42.5%). Patients receiving 130 mg/m^2 ZD9331 most frequently experienced neutropenia (19 patients, 47.5%), nausea (18 patients, 45.0%) and vomiting (17 patients, 42.5%). Ten patients (25.0%) in the 130 mg/m^2 group experienced asthenia.

In the 65 mg/m^2 ZD9331 treatment group, the most frequent grade 3 or 4 AEs (Table 3) were neutropenia [grade 3, seven patients (17.5%); grade 4, two patients (5.0%)], asthenia [grade 3, 5 patients (12.5%)], thrombocytopenia [grade 3, three patients (7.5%); grade 4, one patient (2.5%)] and leucopenia [grade 3, three patients (7.5%); grade 4, one patient (2.5%)]. Neutropenia [grade 3, 5 patients (12.5%); grade 4, three patients (7.5%)], leucopenia [grade 3, three patients (7.5%)] and vomiting [grade 3, three patients (7.5%)] were the most frequent grade 3 or 4 AEs occurring in the 130 mg/m^2 ZD9331 group.

Six patients were withdrawn from treatment as a result of AEs (Table 4). The only AE leading to withdrawal in more than one patient was asthenia (one patient at 65 mg/m^2; two patients at 130 mg/m^2). There were no treatment-related deaths during the trial.

Breast cancer trial

In the breast cancer trial the most common AEs in the oral ZD9331 group were anaemia (18 patients, 58.1%), nausea (15 patients, 48.4%), increased ALT (14 patients, 45.2%) and AST (12 patients, 38.7%). Neutropenia occurred in six patients (19.4%) in the oral group. Patients receiving i.v. ZD9331 most frequently experienced nausea (19 patients, 59.4%), neutropenia (19 patients, 59.4%), asthenia (12 patients, 37.5%) and vomiting (12 patients, 37.5%). Increased ALT or AST were each experienced by five patients (15.6%) receiving i.v. ZD9331.

The most common grade 3 or 4 AEs (Table 3) in the oral therapy arm of the breast cancer trial were increased AST and ALT [grade 3, seven patients (22.6%) and nine patients (29.0%), respectively], anaemia [grade 3, four patients (12.9%)] and thrombocytopenia [grade 3, two patients (6.5%); grade 4, two patients (6.5%)]. Patients receiving i.v. ZD9331 therapy most commonly experienced neutropenia [grade 3, 5 patients (15.6%); grade 4, six patients (18.8%)], leucopenia [grade 3, four patients (12.5%); grade 4, one patient (3.1%)] and thrombocytopenia [grade 3, two patients (6.3%); grade 4, two patients (6.3%)].

Eight patients in the breast cancer trial were withdrawn as a result of AEs (two patients in the oral treatment arm and six patients in the i.v. treatment arm) (Table 4). The events that led to withdrawal in more than one patient were neutropenia (three patients), thrombocytopenia (three patients), anaemia (two patients), skin rash (two patients) and nausea (two patients).

One patient, a 76 year-old diabetic in the i.v. therapy treatment group, died during the trial (on day 12 of treatment). The AEs leading to death (which were considered to be treatment-related) were grade 3 neutropenia, grade 4 sepsis (secondary to neutropenia) and grade 4 thrombocytopenia. The patient had a baseline creatinine clearance of 29.8 ml/min and haemoglobin of 8.4 g/dl, which were violations of the entry criteria.

Efficacy

NSCLC trial

There were no objective tumour responses in the NSCLC trial. Twenty patients (43.5%) had a best overall response of SD that was maintained for 5 or more cycles of therapy in four patients (Table 5). Median time to progression was 63 days in the ITT population.

Ovarian cancer trial

In the ovarian cancer trial, the objective tumour response rate was 2.5% [95% confidence interval (CI): 0.1, 13.2%] in the group receiving 65 mg/m^2 ZD9331 and 10.0%

Table 5 Best overall response to ZD9331 treatment: ITT population

	NSCLC	Ovarian cancer		Breast cancer	
Response [*n* (%)]	130 mg/m^2 (i.v.) (*n* = 46)	65 mg/m^2 (i.v.) (*n* = 40)	130 mg/m^2 (i.v.) (*n* = 40)	3 mg (oral) (*n* = 31)	130 mg/m^2 (i.v.) (*n* = 32)
Best overall response					
CR	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.2)	1 (3.1)
PR	0 (0.0)	1 (2.5)	4 (10.0)	2 (6.5)	3 (9.4)
SD	20 (43.5)	17 (42.5)	14 (35.0)	18 (58.1)	15 (46.9)
PD	22 (47.8)	21 (52.5)	19 (47.5)	9 (29.0)	11 (34.4)
SYD	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
NR	2 (4.3)	1 (2.5)	3 (7.5)	1 (3.2)	1 (3.1)
Objective response					
CR or PR	0 (0.0)	1 (2.5)	4 (10.0)	3 (9.7)	4 (12.5)
Disease control					
CR, PR or SD	20 (43.5)	18 (45.0)	18 (45.0)	21 (67.7)	19 (59.4)

CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; SYD, symptomatic deterioration; NR, not recorded.

(95% CI: 2.8, 23.7%) in the 130 mg/m^2 ZD9331 group. Five patients (6.3%) had a PR (65 mg/m^2 ZD9331, one patient; 130 mg/m^2 ZD9331, four patients). Of these five partial responders, three patients (65 mg/m^2 ZD9331, one patient; 130 mg/m^2 ZD9331, two patients) were receiving ZD9331 as second-line chemotherapy, two of whom had relapsed within 6 months of the previous treatment and one who was refractory to first-line treatment. Both of the remaining partial responders were receiving ZD9331 as third-line chemotherapy (both 130 mg/m^2 ZD9331; one patient relapsed and one patient refractory). Seventeen patients (42.5%) in the 65 mg/m^2 ZD9331 group had a best overall response of SD, eight of these for four or more cycles. Fourteen patients (35.0%) in the 130 mg/m^2 ZD9331 group experienced SD, eight of these for four or more cycles. In the ITT population, the median time to progression was 63 days for patients treated with 65 mg/m^2 ZD9331 and 58 days for patients treated with 130 mg/m^2 ZD9331.

Breast cancer trial

The objective response rates in the breast cancer trial (ITT population) were 9.7% (95% CI: 2.0, 25.8%) in the oral ZD9331 group and 12.5% (95%, CI: 3.5, 29.0%) in the i.v. ZD9331 group. Two patients (3.2%) had a best overall response of CR (oral ZD9331, one patient; i.v. ZD9331, one patient) and five patients (7.9%) had a best overall response of PR (oral ZD9331, two patients; i.v. ZD9331, three patients). One of the patients who experienced a CR was receiving i.v. ZD9331 as first-line chemotherapy (not including previous adjuvant chemotherapy) and the other patient was receiving oral ZD9331 as second-line chemotherapy, having relapsed since first-line treatment. Of those patients who had a PR, three patients (oral ZD9331, two patients; i.v. ZD9331, one patient) were receiving ZD9331 as second-line chemotherapy (two patients relapsed and one patient refractory to previous chemotherapy). The two remaining partial responders (both in the i.v. ZD9331 group) were receiving ZD9331 as third-line chemotherapy having relapsed following previous treatment. Eighteen patients (58.1%) receiving oral ZD9331 had a best overall response of SD, eight of these for 3 or more cycles (1 cycle = 6 weeks). Fifteen patients (46.9%) receiving i.v. ZD9331 had a best overall response of SD, eight of these for five or more cycles (1 cycle = 3 weeks). In the ITT population, median time to progression was 106 days for patients treated with oral ZD9331 and 120 days for patients treated with i.v. ZD9331.

Discussion

No objective responses were observed in patients with NSCLC, although ZD9331 did show some evidence of activity with nearly 50% of patients experiencing disease stabilisation. Although response rates in relapsed or refractory NSCLC are generally low, these data appear inferior to results reported with docetaxel for previously treated NSCLC. In a study evaluating docetaxel monotherapy in patients with advanced NSCLC who had previously failed platinum-containing chemotherapy, the response rate was 10.8% [12]. Another study of docetaxel in a similar group of patients resulted in a response rate of 7.1% [13].

Although there was no formal comparison between treatment doses in the ovarian cancer trial, a numerically higher rate of objective tumour response was observed in patients in the 130 mg/m^2 treatment arm compared with those receiving the 65 mg/m^2 dose (10.0 versus 2.5%, respectively), suggesting a possible dose-related response. In another study in heavily pretreated patients with ovarian cancer, treatment with 130 mg/m^2 ZD9331 resulted in an overall response rate of 7% [14]. Furthermore, a CR was observed in the same study in a patient receiving ZD9331 as her eighth line of treatment.

There are a variety of other available single-agent treatment options for patients with relapsed or refractory ovarian cancer that offer comparable or superior efficacy. These include doxorubicin, gemcitabine, etoposide, paclitaxel and topotecan, the latter demonstrating objective response rates ranging from 13 to 33% [15–17]. The standard second-line treatment in most countries is now liposomal doxorubicin. As all these single-agent drugs, including ZD9331, have disparate mechanisms of action and are valuable alternatives to platinum-based therapies for second-line treatment, attention is now being focused on their use in combination in an effort to further improve survival. One treatment arm of the ovarian cancer study discussed here included the combination of ZD9331 plus topotecan and these data are reported elsewhere in this supplement.

In the breast cancer trial response, rates for ZD9331 were similar for both oral and i.v. therapy. One patient in each treatment arm experienced CR (3.1 and 3.2%,

respectively) and five patients (7.9%) experienced PR (oral ZD9331, two patients; i.v. ZD9331, three patients). Comparative results from similar studies involving monotherapy in patients with metastatic breast cancer who have progressed following first-line chemotherapy are limited. For example, one recent study reported response rates of 54 and 38% for second- and third-line docetaxel monotherapy in patients with metastatic breast cancer [18]. Other options for this patient group include sequential use of single agents or combination chemotherapy.

Intravenous ZD9331 was associated with more grade 3 or 4 AEs than oral administration in the breast cancer trial. The most notable difference was the development of neutropenia in 11 patients (grade 4, six patients) and leucopenia in five patients (grade 4, one patient) in the i.v. group, whilst there were no grade 3 or 4 occurrences of neutropenia or leucopenia in the oral treatment group.

In general, ZD9331 treatment showed a manageable toxicity profile for an anticancer therapy. AEs, particularly the most common ones, myelosuppression and gastrointestinal symptoms, were consistent with its safety profile of the drug or the underlying disease.

Conclusions

Overall, ZD9331 has a manageable toxicity profile at the applied dose levels and shows some evidence of activity in patients with NSCLC, ovarian and breast cancer. However, response rates do not appear to offer substantial improvement over existing alternative single-agent treatment options, particularly in NSCLC and breast cancer. Nevertheless, ZD9331 remains a useful therapeutic tool for the palliative treatment of advanced cancer patients, supplementing the options available to oncologists who are considering monotherapy, and offers a different mode of action.

Acknowledgements

The authors would like to thank the following investigators for their involvement in these trials: *Austria:* H. Samonigg, G. Steger; *Belgium*: D. Becquart, V. Cocquyt, J. De Gréve; *Czech Republic:* I. Bustova, A. Dorr, R. Kalabova, M. Kùta, L. Rob, V. Stáhalová, B. Svoboda, P. Ventruba; *Germany:* K. Becker, K. Hoeffken, D. Kieback, M. Kindler, K. Kittel, U. Kleeberg, O. Ortmann, W. Schmidt, P. Schmidt-Rhode, H. Sommer, D. Wallwiener; *Israel:* A. Amit, R. Catane, A. Fishman, J. Korach, F. Kovner, O. Lavie, A. Shani; *Italy:* S. Barni, R. Labianca, C. Lacono, G. Mustacchi, S. Siena; *Poland*: E. Filipczyk-Cisarz, J. Markowska, M. Pawlicki, A. Roszak, I. Rzepka-Gorska, B. Utracka-Hutka, M. Wojtukiewicz, J. Zielinski; *Spain:* J. Alés, J. Casinello, C. Mendiola, M. Martin; *Sweden*: P. Rosenberg; *UK:* M. Adams, D. Cameron, S. Chan, J. Green, P. Harper, A. Jones, D. Parkin, T. Perren, C. Poole, D. Rea; *USA:* J. Barter, D. Blayney, R. Boothby, P. Braly, R. Butler, R. Castillo, D. Fleming, J. Hajdenberg, A. Hano, E. Hernandez, R. Holloway, M.-S. Kao, H. Katzen, P. Kennedy, S. Kuross, J. Michalak, W. Nahhas, H. Nguyen, R. Patel, D. Pinelli, J. Rader, M. Rarick, T. Rocereto, M. Rose, B. Tranum, L. VanLe, T. Weisberg, C. Whitney, S. Williamson, I. Wiznitzer.

References

1 Jemal A, Thomas A, Murrary T, Thun M. Cancer Statistics, 2002. *CA Cancer J Clin* 2002; **52**:23–47.
2 American Cancer Society. *Cancer Facts and Figures 2002.* http://www.cancer.org.
3 Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 2002; **38**:99–166.
4 Giaccone G. Clinical perspectives on platinum resistance. *Drugs* 2000; **59 (suppl 4)**:9–17.
5 Conte PF, Cianci C, Tanganelli L, *et al.* Ovarian cancer: optimal chemotherapy in relapsed disease. *Ann Oncol* 2000; **11 (suppl 3)**:145–150.
6 Sirotnak FM. Obligate genetic expression in tumor cells of a fetal membrane property mediating 'folate' transport: biological significance and implications for improved therapy of human cancer. *Cancer Res* 1985; **45**: 3992–4000.
7 Jackman AL, Kimbell R, Brunton L, *et al.* Activity of ZD1694 and ZD9331 in human colon and ovarian tumour cell lines. *Proc Am Ass Cancer Res* 1996; **37**:382.
8 Bertucci D, Smith R, Mani S, *et al.* A fixed dose phase I study of ZD9331, a novel non-polyglutamated inhibitor of thymidylate synthase in patients with refractory cancer. *Eur J Cancer* 1999; **35**:S286.
9 Plummer R, Rees C, Judson I, *et al.* Phase I trial of ZD9331 in adult patients with refractory solid malignancies administered by 30-min infusion on days 1 and 8 with the cycle repeated every 3 weeks. *Eur J Cancer* 1999; **35**:S285.
10 Rees C, Beale P, Trigo J, *et al.* Phase I trial of ZD9331, a non-polyglutamatable thymidylate synthase (TS) inhibitor given as a 5-day continuous infusion. *Proc Am Soc Clin Oncol* 1999; **18**:657.
11 Trigo J, Rees C, Beale P, *et al.* Phase I trial of ZD9331, a non-polyglutamatable thymidylate synthase inhibitor given as a 5-day continuous infusion every 3 weeks. *Eur J Cancer* 1999; **35**:S286.
12 Fossella FV, DeVore R, Kerr RN, *et al.* Randomized phase II trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000; **18**:2354–2362.
13 Shepherd FA, Dancey J, Ramlau R, *et al.* Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; **18**:2095–2103.
14 Rader J, Clarke-Pearson D, Moore M, *et al.* Phase II trial of ZD9331 as third-line therapy for patients with ovarian carcinoma. *Ann Oncol* 2000; **11 (suppl 4)**:83 (abstr 368).
15 Bookman MA, Malmstrom H, Bolis G, *et al.* Topotecan for the treatment of advanced epithelial ovarian cancer: an open-label phase II study in patients treated after prior chemotherapy that contained cisplatin or carboplatin and paclitaxel. *J Clin Oncol* 1998; **16**:334–352.
16 Hoskins P, Eisenhauer E, Beare S, *et al.* Randomized phase II study of two schedules of topotecan in previously treated patients with ovarian cancer: a National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol* 1998; **16**:2233–2237.
17 McGuire WP, Blessing JA, Bookman MA, Lentz SS, 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* 2000; **18**:1062–1067.
18 Brodowicz T, Koestler WJ, Tomek S, *et al.* Monotherapy with docetaxel in second- or third-line treatment of anthracycline-resistance metastatic breast cancer. *Anti-Cancer Drugs* 2000; **11**:149–153.