# Phase II multicentre trial of ZD9331 monotherapy as first-line treatment for gastric cancer

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*Background* **ZD9331 is a novel, direct-acting and specific inhibitor of thymidylate synthase that has shown clinical activity and manageable tolerability in solid tumours. This phase II trial was designed to determine the antitumour activity and tolerability of ZD9331 given as a first-line therapy to patients with advanced gastric cancer.**

*Patients and methods* **Eligible patients who were chemonaïve with histologically or cytologically proven gastric cancer entered an open-label, multicentre, two-stage trial. Initially, patients were dosed at 130 mg/m$^2$ (Regimen 1); however, following a protocol amendment, the starting dose was reduced to 65 mg/m$^2$ (Regimen 2). Patients received ZD9331 as a 30-min i.v. infusion once weekly for 2 weeks followed by 1 week without treatment (3-week cycle).**

*Results* **Twenty-nine patients with advanced, relapsed or inoperable gastric cancer were recruited from 11 centres across Europe. Five patients (17.2%), all from Regimen 2, showed a partial response and 16 patients (55.2%) had a best response of disease stabilisation. Most patients (72.4%) had a best response of disease control with median time to progression being 98 days. ZD9331 had manageable toxicity with the most frequently reported adverse events being neutropenia (62%) and diarrhoea (38%).**

*Conclusions* **ZD9331, as a first-line treatment for patients with advanced gastric cancer, demonstrated clinical activity and manageable toxicity. *Anti-Cancer Drugs* 14 (suppl 1):S7–S12 © 2003 Lippincott Williams & Wilkins.**

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## Introduction

Gastric cancer is the second most common cause of cancer-related mortality worldwide [1]. Although the number of deaths from gastric cancer has decreased in the USA since the 1960s, the incidence is still high in other countries, such as Japan, China, Korea, Eastern Europe and Latin America [2]. In 2001, an estimated 21 700 new cases of gastric cancer were diagnosed, with 12 800 people dying from the disease in the USA [3]. The high mortality rate associated with gastric cancer is due to patients typically having no symptoms in the early stages of the disease when it may be surgically curable. As a consequence, at the time of presentation the disease is often locally advanced or metastatic [4]. Furthermore, the primary site for most gastric cancers has changed over the past few decades, from the distal to the proximal stomach, the latter of which is associated with a poorer prognosis [4].

### Treatment options

The current treatment options available for advanced gastric cancer are limited and far from satisfactory with overall survival rates being poor. The 5-year survival rate is 50% in the early stages of the disease (stage I), although this drops significantly in the advanced stages of the disease to 13 and 3% at stage III and IV, respectively [2]. At present, the only potential curative treatment for gastric cancer is surgery, which yields good results in early disease. However, gastric cancer is usually diagnosed at an advanced stage, where curative-intent surgery is inapplicable. Palliative resections may be of some benefit, but are associated with significant operative morbidity and mortality [2].

Radiotherapy is not considered appropriate due to the low radiosensitivity of adenocarcinoma (the most common type of gastric cancer) and the radiation intolerance of the intestine [2], and for these reasons it has not been fully investigated in gastric cancer. However, in some patient groups the use of radiation, in combination with chemotherapy, is being investigated in the neoadjuvant and adjuvant settings [5,6].

Gastric cancer is relatively chemosensitive and chemotherapy may offer benefits to patients in terms of either a reduction in tumour-related symptoms or increased survival [7]. At present, the use of chemotherapy for the treatment of advanced gastric cancer is still controversial. Combinations of commonly used chemotherapeutic agents, including mitomycin C, doxorubicin, 5-fluorouracil (5-FU) and cisplatin, have demonstrated good response rates (20–40%) with median

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survival times of between 6 and 12 months [2,7]. However, combination therapy has a higher toxicity than single-drug treatment [2]. Studies with single chemotherapy agents have generally shown only modest effects in advanced gastric cancer [7], with agents such as mitomycin C being used as a second-line treatment [8]. Therefore, single-drug treatment may represent a suitable approach in patients who would not tolerate a combination of drugs.

### ZD9331 as a first-line treatment

Thymidylate synthase (TS) is the rate-limiting enzyme in the biosynthesis of DNA, catalysing the methylation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate, an essential precursor for DNA synthesis [9]. Since thymidine nucleotides are used exclusively for DNA synthesis, TS is an important target for anticancer chemotherapy.

ZD9331 is a novel, direct-acting and specific inhibitor of TS. It is actively transported into cells by the reduced folate carrier protein, which is believed to be overexpressed in certain tumour cells and may offer antitumour selectivity [10]. Unlike other TS inhibitors, ZD9331 does not require polyglutamation by the enzyme, folylpolyglutamate synthetase (FPGS), to become active [11] and, therefore, is not affected by the FPGS/hydrolase status of tumours, i.e. ZD9331 may have better activity against tumour cells with a poor ability to polyglutamate antifolates [12]. Phase I trials have shown ZD9331 to have clinical activity and a manageable toxicity profile in a variety of solid tumours including gastric cancer [13–15]. Therefore, ZD9331 was considered a suitable candidate for further exploratory phase II studies in gastric carcinoma, for which no effective medical therapy currently exists.

The purpose of this phase II trial was to evaluate the efficacy and tolerability of ZD9331 as first-line monotherapy in patients with gastric cancer who had not received prior therapy. The doses of ZD9331 used in this phase II trial were based on the results of phase I trials [14,15].

## Patients and methods

### Study design

This was a phase II, open-label, two-stage, multicentre trial. Stage 1 covered the recruitment period for the first 20 patients and was used to assess the tolerability of ZD9331, together with its antitumour activity. Stage 2 covered subsequent recruitment and allowed a final assessment of the activity and tolerability profile of ZD9331 and patient quality of life (QoL). Follow up continued for at least 6 weeks.

### Patients

Eligible patients had histologically or cytologically confirmed gastric cancer and were chemonaïve (prior adjuvant chemotherapy was also not permitted). Patients were required to have advanced, relapsed or inoperable disease with a life expectancy of >12 weeks, be aged ≥18 years and have a baseline WHO performance status of 0 or 1.

Exclusion criteria for this trial included a neutrophil count of $<1.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l, total bilirubin ≥1.25 × upper limit of reference range (ULRR), creatinine clearance of <60 ml/min, current intestinal obstruction, pregnancy or breast feeding, other malignancies known to be active within the past 5 years (other than squamous cell or basal cell carcinoma of the skin or *in situ* carcinoma of the cervix) and extensive radiotherapy. No other systemic anticancer therapy was permitted during the trial. The prophylactic use of antiemetics [5-hydroxytryptamine $(HT)_3$ antagonists] was recommended at all cycles, and supportive care measures and symptomatic treatment was permitted. The study was conducted according to the principles of Good Clinical Practice and according to the Declaration of Helsinki (1996). The local ethics committees approved the trial and informed consent was obtained from each patient.

### Treatment

Patients received ZD9331 as a 30-min i.v. infusion once weekly for 2 weeks followed by 1 week without treatment (3-week cycle). Initially patients were treated with a dose of 130 mg/m$^2$ (Regimen 1); however, following a protocol amendment, the starting dose was modified to 65 mg/m$^2$ (Regimen 2).

*Regimen 1*: Ten patients [intent to treat (ITT) population] were administered 130 mg/m$^2$ ZD9331 on days 1 and 8. The per-protocol (PP) population comprised nine patients. The ITT population consisted of all patients who received one or more doses of trial therapy, while the PP population consisted of all patients who received one or more doses of trial therapy and who had not significantly violated or deviated from the protocol. Dose reductions due to treatment-related toxicity were carried out on an individual basis to a minimum of 65 mg/m$^2$. In the absence of toxicity, dose escalations to a maximum of 162.5 mg/m$^2$ were allowed.

*Regimen 2*: Twenty-four patients (ITT population) were administered 65 mg/m$^2$ ZD9331 on days 1 and 8 of cycle 1. The PP population comprised 20 patients. Dose escalation to 100 mg/m$^2$ at cycle 2 and 130 mg/m$^2$ at cycle 3 was permitted if, after each cycle, there were no toxicities that exceeded National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 2, and if albumin levels had not decreased from the baseline (visit 1) assessment.

### Efficacy assessments

The primary efficacy endpoint was the antitumour activity of ZD9331 treatment. Tumour response was assessed by

measurement of target lesions based on the National Cancer Institute Response Evaluation Criteria in Solid Tumours (NCI-RECIST). Responses were assessed at screening, after every 2 cycles of treatment and on withdrawal of treatment. Repeat evaluations were obtained at least 4 weeks following an apparent attainment of either a partial response (PR) or complete response (CR).

Secondary efficacy endpoints included median time to progression, disease control and patient QoL. Baseline QoL was measured within 1 week prior to the initiation of treatment and on day 1 of every second cycle until withdrawal using the Functional Assessment of Cancer Therapy—General (FACT-G) questionnaire [16]. Blood samples were taken on a weekly basis for assessment of laboratory parameters. PP analysis was used for all reported efficacy results except the Kaplan-Meier plots.

### Tolerability assessments

Tolerability was assessed using the NCI-CTC grading system. Haematological and biochemical abnormalities, urinalysis, vital signs, 12-lead electrocardiograms (ECGs), and WHO performance status were assessed routinely throughout the study. Adverse event (AE) data was collected prior to each cycle of ZD9331 treatment. Before the initiation of each treatment cycle, patients were reassessed to confirm that they had adequate haematological (neutrophils $\geq 1.5 \times 10^9$/l and platelets $\geq 75 \times 10^9$/l), renal [creatinine clearance ≥60 ml/min (Cockcroft–Gault formula)] and hepatic function (total bilirubin $< 1.25 \times$ ULRR and albumin ≥ baseline albumin value). ITT analysis was used for all reported safety results.

## Results

### Patients

The ITT population consisted of 34 patients with advanced, relapsed or inoperable gastric cancer. Patients were recruited from 11 centres across Europe over a period of 6 months, between October 2000 and March 2001. The PP population comprised of 29 patients. Patients' characteristics at baseline are listed in Table 1. At the time of analysis, the majority of patients ($n = 26$; 77%; ITT population) had been withdrawn from treatment; of those, most were withdrawn due to disease progression (PD) ($n = 21$; 62%), the remaining were withdrawn due to AEs ($n = 4$; 12%) and at the discretion of the investigator ($n = 1$; 3%).

**Table 1 Patients' characteristics at baseline (ITT population)**

| | Regimen 1 ($n = 10$) | Regimen 2 ($n = 24$) | All patients ($n = 34$) |
|---|---|---|---|
| Age [mean ± SD (years)] | 57.9 ± 7.7 | 60.3 ± 11.1 | 59.6 ± 10.2 |
| Range (years) | 49–71 | 26–76 | 26–76 |
| Sex [*n* (%)] | | | |
| male | 5 (50) | 13 (54) | 18 (53) |
| female | 5 (50) | 11 (46) | 16 (47) |
| Previous cancer treatment [*n* (%)] | | | |
| none | 5 (50) | 9 (37) | 14 (41) |
| radiotherapy | 0 (0) | 0 (0) | 0 (0) |
| surgery | 5 (50) | 15 (63) | 20 (59) |
| other | 0 (0) | 0 (0) | 0 (0) |
| Tumour stage [*n* (%)] | | | |
| stage Ib | 0 (0) | 1 (4) | 1 (3) |
| stage II | 0 (0) | 1 (4) | 1 (3) |
| stage IIIa | 0 (0) | 1 (4) | 1 (3) |
| stage IIIb | 0 (0) | 1 (4) | 1 (3) |
| stage IV | 10 (100) | 17 (71) | 27 (79) |
| not assessable | 0 (0) | 3 (13) | 3 (9) |
| Primary tumour location [*n* (%)][a] | | | |
| distal third of stomach | 2 (20) | 10 (42) | 12 (35) |
| pars media | 3 (30) | 8 (33) | 11 (32) |
| proximal third of stomach | 5 (50) | 6 (25) | 11 (32) |
| cardia (superior stomach orifice) | 0 (0) | 1 (4) | 1 (3) |
| distal oesophagus | 1 (10) | 0 (0) | 1 (3) |
| terminal oesophagus | 1 (10) | 0 (0) | 1 (3) |
| WHO performance score [*n* (%)] | | | |
| 0 (normal activity) | 3 (30) | 6 (25) | 9 (27) |
| 1 (restricted activity) | 7 (70) | 18 (75) | 25 (73) |
| Locally advanced disease [*n* (%)] | | | |
| yes | 9 (90) | 21 (87.5) | 30 (88) |
| no | 1 (10) | 3 (12.5) | 4 (12) |

[a]Patients may have had more than one primary tumour location.

### Treatment

In total, the 34 patients received 151 cycles of therapy (ITT population). The median number of cycles of ZD9331 treatment was 4.0 cycles/patient (Regimen 1, 3.5 cycles, range 1–9 cycles; Regimen 2, 4.5 cycles, range 1–11 cycles).

In Regimen 1 (starting dose of 130 mg/m$^2$), seven of 10 patients (70%) had a dose delay, reduction or omission due to toxicity. Two patients had reductions to 65 mg/m$^2$ and four patients had a day 8 dose omission in cycle 1. Three patients received a dose increase, one of which was to 162 mg/m$^2$.

In Regimen 2 (starting dose of 65 mg/m$^2$), 14 of 24 patients (58%) had a dose increase; 10 patients (42%) had an increase to 130 mg/m$^2$ and one patient had their dose further increased to 162.5 mg/m$^2$. Fourteen patients (58%) had a dose delay, reduction or omission due to toxicity; three patients (13%) had a day 8 dose omission in cycle 1, one patient had a dose decrease to 32.5 mg/m$^2$ (which was a protocol deviation) and three patients (13%) had dose omissions which were not a result of toxicity.

### Efficacy

*Objective tumour response*

The objective tumour response rate in the PP population was 17.2% (Table 2). Five patients, all from Regimen 2, experienced PRs. Overall objective tumour response rates were 0% and 25% for Regimens 1 and 2, respectively. Sixteen patients (55.2%) showed disease stabilisation [five patients from Regimen 1 (55.6%) and 11 patients from Regimen 2 (55.0%)]. No CRs were reported during the trial.

*Progression status, time to progression and disease control*

By the time data cut-off was reached, gastric cancer had progressed in 72.4% of patients ($n = 21$; 100% and 60%

**Table 2 Best overall objective tumour responses (PP population) for Regimen 1, Regimen 2 and all patients**

| | Regimen 1 ($n = 9$) | Regimen 2 ($n = 20$) | All patients ($n = 29$) |
|---|---|---|---|
| Best overall objective tumour response [*n* (%)][a] | | | |
| CR | 0 (0) | 0 (0) | 0 (0) |
| PR | 0 (0) | 5 (25) | 5 (17) |
| SD | 5 (56) | 11 (55) | 16 (55) |
| PD | 3 (33) | 2 (10) | 5 (17) |
| SYD | 0 (0) | 1 (5) | 1 (4) |
| NR | 1 (11) | 1 (5) | 2 (7) |
| Objective tumour response [*n* (%)] | | | |
| CR or PR | 0 (0) | 5 (25) | 5 (17) |

[a]Determined programmatically based on NCI-RECIST. CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; SYD, symptomatic deterioration; NR, not recorded.

for Regimens 1 and 2, respectively). The median time to progression (Fig. 1; ITT population) for both regimens was 98 days (88 and 104 days for Regimens 1 and 2, respectively). The estimated median duration of survival at 6 months after the last dose of ZD9331 was 384 days (Fig. 2; ITT population). The disease control rate was 72.4% ($n = 21$), which included five patients (55.6%) in Regimen 1 and 16 patients (80.0%) in Regimen 2.

*Quality of life (QoL)*

Overall, patient QoL showed a small improvement over baseline during therapy; however, by the time of withdrawal this was already beginning to deteriorate. Three of the individual domain scores (physical, emotional and functional) showed a similar pattern, while social/family well-being showed no improvement, with a worsening at withdrawal.

### Tolerability

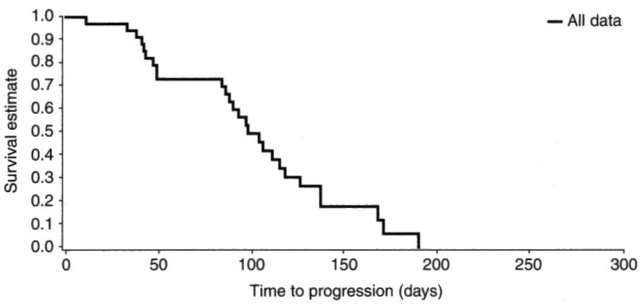
The majority of patients ($n = 32$; 94%) in the ITT population reported at least one AE during the trial. Twenty-six patients (77%) reported AEs considered by the investigator to be treatment-related. Overall, the most frequently reported AEs were neutropenia (62%), diarrhoea (38%), anaemia (35%) and abdominal pain (32%).

Three patients (9%) died during the trial. One patient died from cancer and two patients died as a result of AEs; one (who received Regimen 1) from fever, leucopenia, dehydration and diarrhoea (considered treatment-related), and one (who received Regimen 2) from haematemesis and hypovolaemia (not considered treatment-related).

All CTC grade 3/4 AEs are shown in Table 3. Nine patients (27%) reported AEs that were considered serious because they prolonged or resulted in hospitalisation. Four patients (12%) were withdrawn from the trial due to AEs (Regimen 1, $n = 1$, 10%; Regimen 2, $n = 3$, 13%).

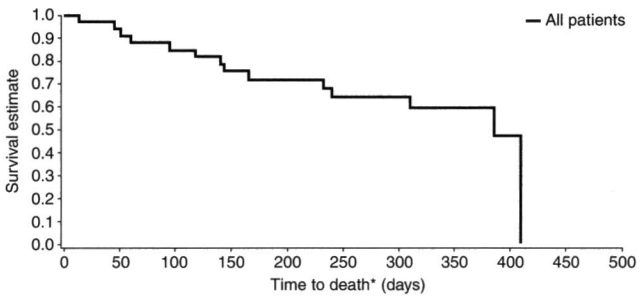
At withdrawal, the WHO performance status showed 50% of patients had normal or restricted activity. There were no clinically significant changes in vital signs, urinalysis or ECG data in either the ITT or PP population.

**Fig. 1**




Kaplan-Meier plot for time to progression for the ITT population.

**Fig. 2**




Kaplan-Meier plot for time to death for the ITT population. *Survival status assessed 6 months after last dose of study medication.

## Discussion

Patients with advanced gastric cancer generally have a poor prognosis and the management of these patients remains a significant clinical problem. ZD9331 is a non-polyglutamatable inhibitor of TS that has shown clinical activity and manageable toxicity in a variety of solid tumours, including gastric cancer [13–15]. This phase II study evaluated the efficacy and tolerability of ZD9331 as a first-line, single-agent treatment of advanced gastric cancer and showed a consistent level of clinical activity accompanied by manageable toxicity.

In this study, treatment with ZD9331 gave an overall objective tumour response rate of 17.2%, which is similar to that seen with other single-agent treatment options, such as cisplatin [7] and docetaxel [17]. This rate, when compared with combination therapies containing 5-FU and/or cisplatin (20–40% response rate), was at the lower end of the spectrum [7]. However, due to protocol amendments Regimen 2 was adopted for the majority of patients, giving an overall objective tumour response rate of 25%; a rate that was higher than the majority of single-agent chemotherapy treatments and also in line with combination therapy responses [7]. Most single chemotherapy agents do not reach the maximum response rates seen with combination therapy, but they do have the benefit of being

**Table 3 Number of patients with CTC grade 3/4 AEs (all cycles, all events; ITT analysis)[a]**

| | Regimen 1 ($n = 10$) | Regimen 2 ($n = 24$) | All patients ($n = 34$) |
|---|---|---|---|
| Haematological | | | |
| neutropenia | 2 | 11 | 13 |
| anaemia | 1 | 2 | 3 |
| leucopenia | 1 | 2 | 3 |
| febrile neutropenia | 1 | 1 | 2 |
| thrombocytopenia | 1 | 1 | 2 |
| Non-haematological | | | |
| hypokalaemia | 2 | 2 | 4 |
| diarrhoea | 1 | 2 | 3 |
| abdominal pain | 1 | 1 | 2 |
| dysphagia | 1 | 1 | 2 |
| ALT (SGPT) increased | 1 | 1 | 2 |
| haematemesis | 0 | 2 | 2 |
| asthenia | 0 | 1 | 1 |
| constipation | 0 | 1 | 1 |
| dehydration | 0 | 1 | 1 |
| fever | 0 | 1 | 1 |
| hyperglycaemia | 0 | 1 | 1 |
| melaena | 0 | 1 | 1 |
| AST (SGOT) increased | 1 | 0 | 1 |
| tachycardia | 1 | 0 | 1 |
| urinary tract infection | 0 | 1 | 1 |
| vomiting | 1 | 0 | 1 |

[a]Individual patients may have had more than one AE.
ALT: alkaline phosphatase; SGPT: serum glutamic pyruvic transaminase; AST: aspartate aminotransferase; SGOT: serum glutamic oxaloacetic transaminase.

less toxic [7], and may, therefore, provide a better QoL for patients during the advanced stages of the disease.

The majority of patients (72.4%) in this study had a best response of disease control (i.e. PR or disease stabilisation). No CRs were observed, which was expected since most patients in this trial had stage IV primary tumours, nodes and metastases at entry. It is well established that once a patient develops metastases, a CR is very rare [7]. By completion of the trial, the majority of patients showed PD, with median time to progression for all patients being 98 days. All patients in Regimen 1 had PD by the end of the trial. This was probably because patients from Regimen 1 were recruited into the trial at an earlier stage and therefore more likely to have progressed by the time of data cut-off (i.e. the period of assessment was longer for Regimen 1). The estimated median duration of survival at 6 months after the last dose of ZD9331 was 384 days, which is longer than most chemotherapy agents (single or in combination) for patients with advanced gastric cancer [7]. One study, although conducted over a decade ago, showed 5-FU treatment alone to have similar survival rates to those obtained with combination therapies [18], suggesting that combination therapies, which are generally more toxic, may not provide any greater benefit than single chemotherapy agents in survival rates.

FACT-G did appear to be sensitive enough to detect differences in QoL between disease states and was therefore a suitable questionnaire for use in this study. However, it was not possible to draw firm conclusions on patient QoL as this was a non-comparative study and only a small number of patients were involved.

ZD9331 showed a manageable toxicity profile in this group of patients, which may reflect the fact that ZD9331 does not interfere with the process of RNA synthesis [9] AEs were consistent with the known safety profile of ZD9331 and the underlying disease. The most frequently observed severe AE (CTC grade 3/4) was neutropenia, which is commonly associated with conventional chemotherapy treatment. The incidence of AEs, treatment-related AEs, and serious AEs were similar with both Regimens. There was one treatment-related death in Regimen 1 and none in Regimen 2. No clinically significant changes in patient vital signs, urinalysis or ECG data were observed. However, an overall decline in WHO performance was evident, which reflected PD during the trial.

## Conclusions

ZD9331 demonstrated clinical activity and manageable toxicity as a first-line treatment for patients with advanced gastric cancer, with the majority of withdrawals due to PD. The overall response rate observed in this study was similar to those reported with other cytotoxic agents used as monotherapy in gastric cancer. ZD9331 may represent a valuable alternative single-agent palliative treatment option for patients with advanced gastric cancer and further studies of ZD9331 monotherapy and/or combination therapies may be warranted.

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