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ZD0473 treatment in lung cancer: an overview of the clinical trial results

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Abstract

Three open-label, non-comparative, multicentre Phase II trials have examined the efficacy and tolerability of ZD0473 as first- and second-line therapy in non-small-cell lung cancer (NSCLC) patients and second-line therapy in small-cell lung cancer (SCLC) patients. Patients with second-line NSCLC or SCLC were evaluated as either platinum-sensitive or -resistant, based upon their time to relapse/progression after platinum-based therapy. First-line NSCLC patients ($n = 18$) received a total of 60 treatment cycles (median number per patient 2.5) whilst second-line NSCLC ($n = 50$) and SCLC ($n = 48$) patients both received a total of 127 treatment cycles (median number per patient 2.0). Grade 3/4 anaemia, neutropenia and thrombocytopenia was observed in: 38.8%, 22.2% and 27.7% of first-line NSCLC patients; 12.0%, 24.0% and 50% of second-line NSCLC patients; and 10.4%, 25.0% and 47.9% of second-line SCLC patients, respectively. The most common grade 3/4 non-haematological toxicities in all three trials were lethargy and dyspnoea. No clinically significant oto-, nephro- or neurotoxicity was observed. The first-line treatment of NSCLC produced an overall response rate (OR) of 6.3%. No OR was seen after second-line treatment of NSCLC, while ORs of 15.4% and 8.3% were seen in the platinum-resistant and -sensitive second-line SCLC patients, respectively.

Keywords: ZD0473; Lung cancer; NSCLC; SCLC; Platinum-resistant; Platinum-sensitive

1. Lung cancer epidemiology and treatment

Lung cancer is the leading cause of cancer death in most western European and North American countries. In 1999, lung cancer caused over 29,000 cancer deaths in England and Wales, accounting for 26% and 17% of all cancer deaths in men and women, respectively [1]. Similarly, in the USA it is estimated that there will be 154,900 lung cancer-related cancer deaths in 2002, accounting for approximately 28% of all cancer deaths [2]. The overall estimated 5-year survival rate for lung cancer varies between countries, but is generally very poor. For example, the 5-year survival rate in England and Wales was approximately 5% in 1999, while it is estimated that the 5-year survival rate will be 15% in the USA in 2002 [1,2].

Small-cell lung cancer (SCLC) represents approximately 20–25% of lung cancers and presents as metastatic disease in 60–70% of patients. Median survival for

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limited stage SCLC is 16–24 months, while for extensive disease it is 6–12 months, with the majority of patients dying within 2 years of diagnosis [3]. Non-small-cell lung cancer (NSCLC) represents approximately 75% of lung cancer cases. The median survival for patients with stage IIIa, IIIB or IV NSCLC, which represent 80% of NSCLC cases, is 8 months, and five-year survival for all stages of NSCLC is 16.1% [4,5].

Treatment can significantly improve outcome in some patients, particularly those with SCLC, where chemotherapy-containing regimens can produce at least a 4- to 5-fold improvement in median survival against metastatic disease, compared with supportive care alone [3]. Current chemotherapy options for SCLC mainly comprise etoposide/cisplatin or etoposide/carboplatin combinations [6]. NSCLC is more difficult to treat, with chemotherapy producing only objective partial responses or palliation at best [7]; only modest benefits are seen in survival. Current chemotherapy regimens for NSCLC tend to be platinum-based, with combinations of either cisplatin or carboplatin producing objective and subjective responses in patients with metastatic NSCLC [7], and a recent review demonstrated that cisplatin-based chemotherapy improved survival compared with best supportive care (1-year survival rates of 21–39% and 10%, respectively) [5].

However, although platinum-based therapies offer some benefits, platinum resistance is a common problem in lung cancer. This can be in the form of inherent resistance, as commonly seen in NSCLC, or acquired resistance, as seen in SCLC [8]. In both cases, resistance inevitably leads to relapse and shortened survival. There is therefore a need for new therapeutic approaches, which may overcome the problems of resistance and tolerability, and provide sustained benefits to patients.

2. ZD0473 and lung cancer

ZD0473 (*cis*-amminedichloro[2-methylpyridine]platinum[II]) is a new-generation platinum agent that has an extended spectrum of antitumour activity in a number of different cells and tumours, including lung cancer cells derived from clinical tumours [9], and human lung tumour xenografts [10]. In addition, ZD0473 overcomes platinum-resistance mechanisms *in vitro* [11]. Phase I studies showed some evidence of ZD0473 antitumour activity in a range of tumour types and demonstrated that ZD0473 has a manageable toxicity profile. The main toxicity at the recommended Phase II starting dose (120 mg/m^2) was myelosuppression [12].

Three Phase II trials were undertaken to assess the antitumour activity of ZD0473 monotherapy in lung cancer. ZD0473 was assessed as a first- and second-line therapy in advanced NSCLC, and as second-line therapy in advanced SCLC.

3. Phase II trials of ZD0473 in lung cancer

All three Phase II trials were open-label, non-comparative and multicentre. Patients with histologically or cytologically confirmed NSCLC or SCLC were recruited. Patients who had failed prior platinum-based therapy were eligible for the second-line trials. The remaining criteria were similar for the three trials, and included: age $\geq$18 years; life expectancy >12 weeks; World Health Organization performance status $\leq$2; absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L; haemoglobin $\geq$9 g/dL; creatinine clearance >60 ml/min; serum bilirubin $\leq 1.25 \times$ upper limit of the reference range (ULRR); aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) $<5 \times$ ULRR for the first-line NSCLC trial; and for the second-line trials, aminotransferases (ALT and AST) $<5 \times$ ULRR or $<2.5 \times$ ULRR in the presence or absence of liver metastases, respectively.

Exclusion criteria common to all three trials included: any evidence of severe or uncontrolled systemic disease; incomplete recovery from prior surgery; intracerebral metastases (unless diagnostic imaging demonstrated no peritumoural oedema or progression since the last scan, the patient did not require corticosteriods and was asymptomatic from the metastases). For the first-line NSCLC trial, other exclusion criteria included previous anticancer therapy for NSCLC (chemotherapy and/or radiotherapy), unless in an adjuvant setting. Exclusion criteria common to the two second-line trials included: systemic anticancer therapy in the past 2 weeks; extensive radiotherapy that included $\geq$30% of the bone marrow (for example the whole of the pelvis or half of the spine); and unresolved toxicity from prior anticancer therapy, apart from chronic non-haematological toxicities of $\leq$grade 2 (apart from alopecia).

Patients recruited to the SCLC second-line trial were evaluated as either platinum-resistant (cohort 1: relapsed or progressed $\leq$8 weeks following prior platinum-based therapy) or platinum-sensitive (cohort 2: relapsed or progressed >8 weeks following prior platinum-based therapy). Patients recruited to the NSCLC second-line trial were evaluated as either platinum-resistant (cohort 1: relapsed or progressed $\leq$12 weeks following prior platinum-based therapy) or platinum-sensitive (cohort 2: relapsed or progressed >12 weeks following prior platinum-based therapy).

4. Patients and treatment

In all three studies, the initial starting dose of ZD0473 was 120 mg/m^2 (1-h intravenous infusion on day 1, every 3 weeks). If ZD0473 was well tolerated, the dose could be escalated to 150 mg/m^2. After a safety review showing 120 mg/m^2 to be well tolerated, the starting dose was modified to 150 mg/m^2 every 3 weeks. Patients who did

not experience disease progression could receive up to 6 treatment cycles. A total of 116 patients were recruited on to the three studies (Table 1) and a total of 314 treatment cycles were given over the 3 trials (Table 2).

5. Tolerability in lung cancer

In the two NSCLC trials, clinical and laboratory assessments were made on days 1, 8, 15 and 22 of each treatment cycle, at treatment withdrawal and 30 days after the final dose. Where dose delay occurred, assessments were performed on days 29, 36 and 43. In the second-line SCLC trial, assessments were made on days 8 and 15 of each treatment cycle, with further assessments performed on days 22, 29, 36 and 43 if dose delay occurred. For all studies, adverse events were classified using the National Cancer Institute (NCI) Common Toxicity Criteria.

In all trials, the main toxicities were haematological (Table 3). It is interesting to note that a higher percentage of patients exhibited grade 3/4 anaemia in the first line NSCLC trial compared to the second-line NSCLC and SCLC trials (38.8% vs 12.0% and 10.4%, respectively). Lethargy and dyspnoea were common non-haematological grade 3/4 toxicities, occurring in >5% of patients in all three trials (Table 3). No clinically significant nephro-, neuro- or ototoxicity was observed in any of the trials. The predominant reason for withdrawal from ZD0473 therapy was disease progression, which occurred in 88.9% of first-line NSCLC patients and 82.0% and 77.1% of second-line NSCLC and SCLC patients, respectively. Other reasons for withdrawal included treatment-related adverse events and withdrawal of consent, which accounted for ≤10% of withdrawals in each trial. There were no drug-related deaths.

Table 1
Patient characteristics

	First-line trial	Second-line trials	
	NSCLC ($n = 18$)	NSCLC ($n = 50$)	SCLC ($n = 48$)
Age (years) median (range)	60.0 (31–72)	59.0 (38–77)	62.2 (38–80)
Sex			
male	16	25	29
female	2	25	19
Platinum			
-resistant	n/a	30	20
-sensitive	n/a	20	28
Metastatic disease			
yes	17	40	40
no	1	10	7
not recorded	0	0	1
Prior therapies[a]			
none	16	0	0
surgery	2	15	4
chemotherapy	0	50	48
immunotherapy/ hormone therapy	0	0	2
radiotherapy	0	27	29
other	0	4	0
not known	0	0	0
Performance status			
0	10	15	17
1	8	29	26
2	0	6	5

[a]Patients may have received >1 prior therapy; n/a, not applicable.

6. Activity of ZD0473 in lung cancer

The NCI Response Evaluation Criteria in Solid Tumors were used to assess tumour response. Assessments of antitumour activity were made in all three trials using objective measurements of tumour growth, and were performed before the first cycle of ZD0473 (at baseline), after treatment cycles 2, 4 and 6, at withdrawal, and at subsequent visits until disease progression occurred.

The first-line treatment of NSCLC produced an objective response (OR) in 6.3% (1/16) of patients (95% confidence intervals [CI] 0.2, 30.2). The best objective responses are detailed in Table 4. The median time to progression (TTP) was 89 days (95% CI 45, 126) and the median time to death (TTD) was 390 days (95% CI 93, 490) (Fig. 1); 58.9% of patients survived for >12 months after starting the trial therapy.

In the second-line treatment of NSCLC, ZD0473 failed to produce a complete or partial response in either cohort

Table 2
ZD0473 treatment details

	First-line trial	Second-line trials	
	NSCLC ($n = 18$)	NSCLC ($n = 50$)	SCLC ($n = 48$)
Total no. treatment cycles administered	60	127	127
Median no. treatment cycles per patient (range)	2.5 (1–6)	2.0 (1–9)	2.0 (1–6)
No. patients receiving ≥4 treatment cycles	8	10	13
No. patients (%)			
receiving 120 mg/m^2	3 (33.3)	9 (18.0)	10 (20.8)
receiving 120 mg/m^2 and escalating to 150 mg/m^2	6 (33.3)	9 (18.0)	5 (10.4)
starting on 150 mg/m^2	9 (50.0)	32 (64.0)	33 (68.8)
No. patients with cycles delayed due to unresolved toxicity	7 (38.9)	12 (24.0)	18 (37.5)
No. patients with dose reduced by >20%	2 (11.1)	8 (16.0)	13 (27.1)

Table 3
No. patients (%) treated with ZD0473 with grade 3/4 haematological and non-haematological toxicities (all cycles), irrespective of causality[a]

	No. patients (%)[b]		
	First-line trial	Second-line trials	
	NSCLC ($n = 18$)	NSCLC ($n = 50$)	SCLC ($n = 48$)
Haematological			
anaemia	7 (38.8)	6 (12.0)	5 (10.4)
neutropenia	4 (22.2)	12 (24.0)	12 (25.0)
thrombocytopenia	5 (27.7)	25 (50.0)	23 (47.9)
Non-haematological			
lethargy	2 (11.1)	6 (12.0)	3 (6.3)
dyspnoea	2 (11.1)	5 (10.0)	4 (8.3)
pneumonia	0 (0)	5 (10.0)	0 (0)
hyponatraemia	0 (0)	0 (0)	4 (8.3)
chest pain	0 (0)	3 (6.0)	0 (0)
dysphagia	0 (0)	3 (6.0)	0 (0)
infection	2 (11.1)	0 (0)	0 (0)
back pain	1 (5.6)	0 (0)	0 (0)
pain	1 (5.6)	0 (0)	0 (0)
anorexia	1 (5.6)	0 (0)	0 (0)
tachycardia	1 (5.6)	0 (0)	0 (0)
jaundice	1 (5.6)	0 (0)	0 (0)
alkaline phosphatase increased	1 (5.6)	0 (0)	0 (0)
SGPT increased	1 (5.6)	0 (0)	0 (0)
bronchitis	1 (5.6)	0 (0)	0 (0)
rhinitis	1 (5.6)	0 (0)	0 (0)

[a]Occurring in >5% of patients; [b]Patients may have experienced >1 grade 3/4 adverse event; SGPT, serum glutamic-pyruvic transaminase.

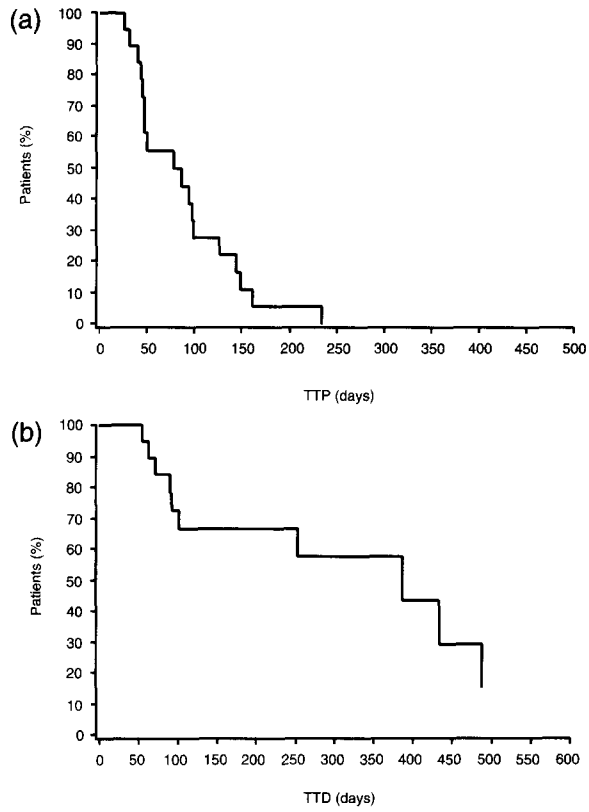

Fig. 1. Kaplan-Meier of (a) TTP and (b) TTD for ZD0473 as first-line therapy for NSCLC.

1 (platinum-resistant) or cohort 2 (platinum-sensitive) out of 19 and 28 evaluable patients, respectively (Table 4). The median TTP was 43.0 days (95% CI 38.0, 47.0) and 75.0 days (95% CI 43.0, 144.0) for cohorts 1 and 2, respectively, whilst the median TTD was also shorter in cohort 1 compared with that in cohort 2 (136 days; 95% CI 113.0, 203.0 versus 187 days; 95% CI 153, 335, respectively) (Fig. 2). Reflecting the TTD data, fewer patients remained alive 12 months after starting trial therapy in cohort 1 compared with cohort 2 (15.7% versus 22.0%, respectively).

For the second-line treatment of SCLC, the OR rate in cohort 1 (platinum-resistant) was similar to that in cohort 2 (platinum-sensitive) (15.4% [2/13]; 95% CI 1.9, 45.4 versus 8.3% [2/24]; 95% CI 1.0, 27.0, respectively). The best objective responses are detailed in Table 4. The median TTP in cohort 1 (42 days; 95% CI 40, 111) was shorter than that in cohort 2 (92 days; 95% CI 55, 107), and the median TTD for cohort 1 was 191 days (95% CI 115, 239) compared with 250 days (95% CI 141, 263) for cohort 2 (Fig. 3). No patients in cohort 1 remained alive 12 months after starting trial therapy, and only 16.4% of patients in cohort 2 survived beyond 12 months after initiating treatment.

Table 4
Best objective response to ZD0473 in the three ZD0473 lung cancer trials

	No. patients			
	Partial response	Stable disease	Disease progression	Symptomatic deterioration
First-line NSCLC ($n = 16$)	1	8	7	0
Second-line NSCLC				
cohort 1 ($n = 21$)	0	5	15	1
cohort 2 ($n = 18$)	0	9	9	0
Second-line SCLC				
cohort 1 ($n = 13$)	2	2	9	0
cohort 2 ($n = 24$)	2	14	7	1

7. Discussion

The studies reported here indicate that ZD0473 has a manageable tolerability profile when used either as first-line therapy for NSCLC or as second-line therapy for NSCLC and SCLC. Evidence of antitumour activity is seen in patients both as first-line therapy for advanced disease and as second-line therapy after failure of platinum-based first-line therapy. However, the antitumour activity of ZD0473 reported here in the two second-line trials, where patients were divided into platinum-resistant and -sensitive cohorts, suggests that ZD0473 is more active in the platinum-sensitive patients.

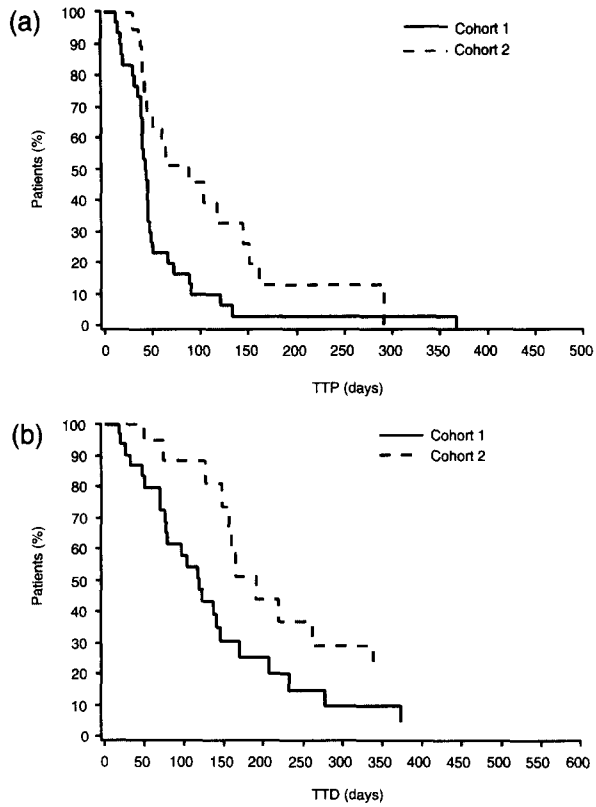

Fig. 2. Kaplan-Meier of (a) TTP and (b) TTD for ZD0473 as second-line therapy for NSCLC.

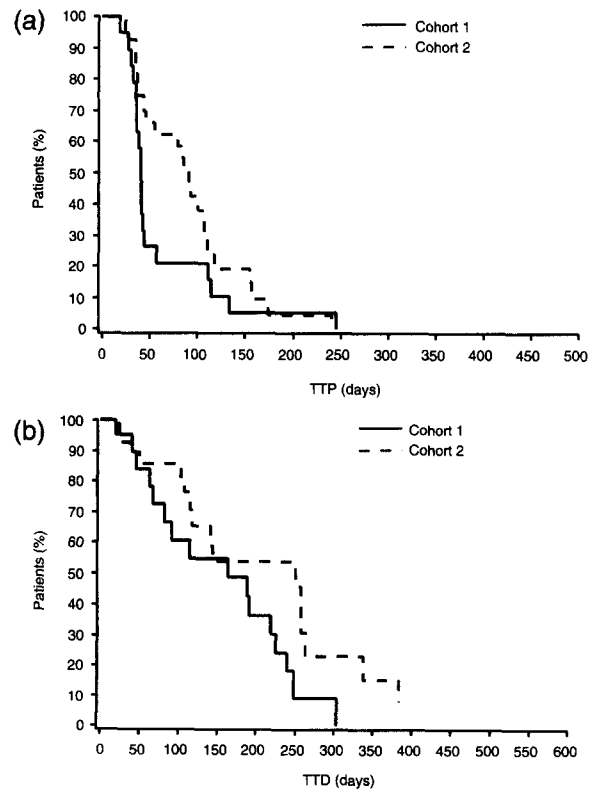

Fig. 3. Kaplan-Meier of (a) TTP and (b) TTD for ZD0473 as second-line therapy for SCLC.

The activity of first-line ZD0473 reported in the NSCLC patients can be compared with previously published data for cisplatin monotherapy. Cisplatin monotherapy has been previously shown to produce OR rates of 4–19% in the treatment of advanced NSCLC, progression-free survival times of 2.0–3.7 months and overall survival times of 6.0–7.6 months [13–15]. These data are broadly similar to the OR and survival data reported here for ZD0473 (6.7%).

A previously published trial of the paclitaxel analogue, docetaxel, as second-line therapy in NSCLC, reported ORs of 6.7% and 10.8% in patients treated with 75 mg/m^2 and 100 mg/m^2 docetaxel, respectively [16]. Similarly, docetaxel has been shown to improve TTP (median 10.6 weeks) and survival time (median 7.0 months) compared with best supportive care. In this study, ZD0473 did not produce a complete response or partial response in the second-line treatment of NSCLC, either in the platinum-resistant or -sensitive cohorts. In addition, the median TTP and TTD reported for ZD0473 were lower for the platinum-resistant patients compared with the published docetaxel data [17,18]. The platinum-sensitive patients treated with ZD0473 produced a broadly similar response to docetaxel in terms of TTP and TTD (approximately 12.4 weeks and 6.1 months, respectively).

Topotecan (1.5 mg/m^2/day for 5 days, every 3 weeks) is approved for use in platinum-sensitive patients with SCLC, and so a comparison can only be made with the platinum-sensitive ZD0473 patient cohorts. Second-line topotecan treatment has been shown to lead to an OR of 24% and a median TTP of 13.3 weeks in patients with recurrent SCLC [19].

In summary, the response rates seen with ZD0473 in the lung cancer trials reported here occurred at a lower rate than the response rates for the best of the corresponding standard therapies. However, ZD0473 did result in a similar OR, TTP and TTD to cisplatin.

8. Conclusions

Overall, ZD0473 has a manageable tolerability profile in first- and second-line NSCLC and second-line SCLC. Even though ORs were similar between the platinum-resistant and -sensitive patients, median TTP and TTD appeared longer for platinum-sensitive patients in both second-line trials. However, the response rates seen in these trials did not suggest that ZD0473 offered greater efficacy over existing agents in platinum-resistant patients.

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