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Effect of re-treatment with gefitinib ('Iressa', ZD1839) after acquisition of resistance

A 70-year-old man with adenocarcinoma of the lung developed pulmonary metastases 7 months after middle and lower lobectomy of the right lung in October 1998. He received four courses of first-line chemotherapy with docetaxel/irinotecan from June to September 1999. The best response was stable disease and, after 6 months of treatment, there was evidence of progressive disease with increase in size and number of pulmonary metastases. Therefore, we recommended enrollment in a phase I study of gefitinib ('Iressa') [1], an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor.

The patient began to take gefitinib 700 mg/day in March 2000. Remarkable tumor regression was immediately achieved in April 2000 (Figure 1). This response lasted for 18 months. However, pulmonary metastases again developed (considered to be progressive disease), and gefitinib was discontinued in October 2001. The patient received a combination of nedaplatin, a second-generation platinum complex with high antitumor activity against non-small-cell lung cancer [2], and gemcitabine in November 2001. Significant tumor regression was achieved, and a total of six courses from November to April 2002 were administered. Pulmonary metastases progressed again and pulmonary effusion developed in August 2002. Although progressed, he had few symptoms, and was considered to have a performance status of 0. We planned to use a chemotherapy regimen that had not previously been used for this patient, but instead commenced re-treatment with gefitinib at the patient's request on September 3, 2002 (gefitinib 250 mg/day had by this time been approved for use in Japan). One month later, a significant response had been achieved (Figure 1).

This is an interesting case in which acquired resistance to gefitinib could be overcome. There are some possible explanations. First, resistance to gefitinib might naturally change over time, but there is no report of this so far. Secondly, because platinum-based cytotoxic chemotherapy was administered after the first treatment with gefitinib, the proportion of sensitive or resistant cells might have been modified. Thirdly, treatment with cytotoxic chemotherapy might produce genetic changes in EGFR or other unknown associated genes that regulate resistance to gefitinib. Saltz et al. reported that a combination of the EGFR inhibitor cetuximab (C225) and irinotecan produced a 22.5% partial response in patients with irinotecan-refractory colorectal cancer with high EGFR expression [3]. In contrast to that report, cytotoxic agents have the possibility of modifying resistance to cytostatic agents. Recently, two large phase III studies to compare concurrent use of conventional platinum-based chemotherapy (carboplatin/paclitaxel or cisplatin/gemcitabine) and gefitinib with conventional chemotherapy alone were reported [4, 5]. No differences in overall survival were found. These results suggested that gefitinib and chemotherapy may be targeting the same cells with the possibility of overlapping activity. If cytotoxic agents altered sensitivity to gefitinib by genetic modification, chemotherapy followed by gefitinib might be superior to concurrent use. Gefitinib is a very promising agent, but little knowledge is available concerning the types of cases for which gefitinib should be administered, or how gefitinib should be combined with conventional cytotoxic agents. Further investigations are needed to answer these questions.

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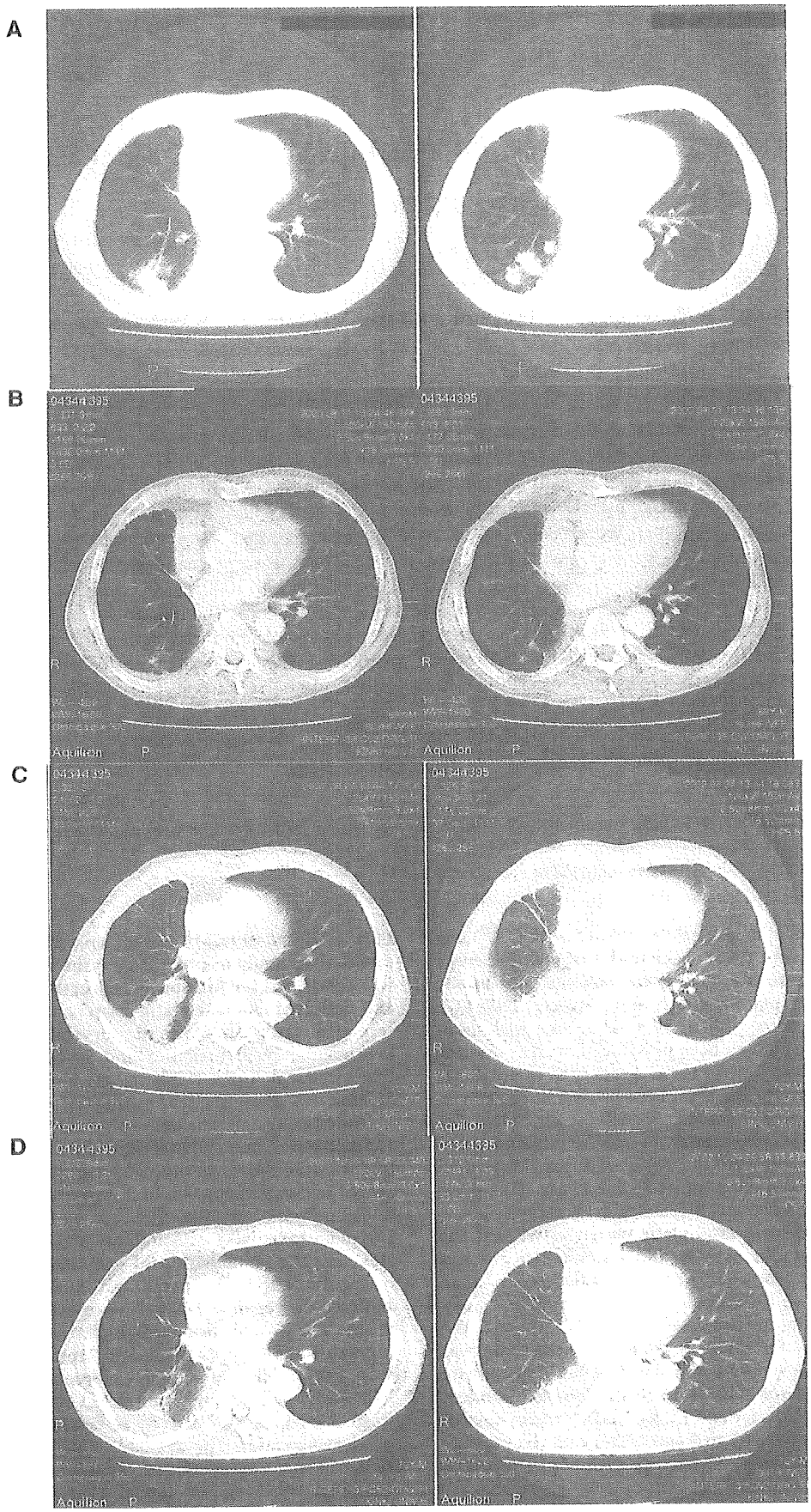

Figure 1. A 70-year-old man with adenocarcinoma of the lung. CT scan before treatment of gefitinib (**A**), after initiation of treatment (**B**), before re-treatment (**C**) and after initiation of re-treatment (**D**).

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Combination phase I study of nedaplatin and gemcitabine for advanced non-small-cell lung cancer

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To establish the toxicities and maximum tolerated dose (MTD) of nedaplatin with gemcitabine, and to observe their antitumour activity, we conducted a combination phase I study in advanced non-small-cell lung cancer (NSCLC). Patients received nedaplatin (60–100 mg m^{-2} given intravenously over 90 min) on day 1, and gemcitabine (800–1000 mg m^{-2} given intravenously over 30 min) on days 1, 8, every 3 weeks. In total, 20 patients with locally advanced or metastatic NSCLC who received no prior chemotherapy or one previous chemotherapy regimen were enrolled. The most frequent toxicities were neutropenia and thrombocytopenia; nonhaematological toxicities were generally mild. Three out of six patients experienced dose-limiting toxicities (neutropenia, thrombocytopenia and delayed anaemia) at dose level 4, 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine, which was regarded as the MTD. There were three partial responses, for an overall response rate of 16.7%. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. This combination is well tolerated and active for advanced NSCLC. The recommended dose is 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine. This combination chemotherapy warrants a phase II study and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as first-line chemotherapy for advanced NSCLC.

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Based on the results of a meta-analysis (Non-Small Cell Lung Cancer Collaborative Group, 1995), cisplatin-based chemotherapy is considered the best available therapy for patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC). Although several new agents with novel mechanisms and significant activity against NSCLC have been introduced, such as taxanes, gemcitabine and vinorelbine, any of these agents used in combination with a platinum agent provide equivalent survival improvement (Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). The prognosis of advanced NSCLC patients who receive cisplatin-based chemotherapy is still poor, and the renal and gastrointestinal toxicities caused by cisplatin often limit its clinical use. Therefore, development of different treatment strategies is necessary.

Nedaplatin is a second-generation platinum derivative that has shown equivalent antitumour activity and lower toxicity – less nausea, and lower nephrotoxicity and neurotoxicity – than cisplatin (Kameyama *et al*, 1990; Ota *et al*, 1992). A phase I study demonstrated the maximum tolerated dose (MTD) and the recommended dose (RD) for phase II studies of nedaplatin was 120 and 100 mg m^{-2}, respectively, and the dose-limiting toxicity (DLT) was thrombocytopenia (Ota *et al*, 1992). Two independent phase II studies of nedaplatin for NSCLC showed response rates of 14.7 and 20.5%, respectively, and 16.7 and 12.5% with the patients who had received chemotherapy previously (Fukuda *et al*, 1990; Furuse *et al*, 1992a). Based on these promising results, a randomised study of nedaplatin–vindesine *vs* cisplatin–vindesine was conducted for previously untreated NSCLC patients in Japan and indicated that nedaplatin-based chemotherapy yielded similar response rates and overall survival (Furuse *et al*, 1992b). Leucopenia, renal toxicities and gastrointestinal toxicities were more frequent in the cisplatin–vindesine arm, while thrombocytopenia was more frequent in the nedaplatin–vindesine arm.

Gemcitabine, an analogue of deoxycytidine, is a pyrimidine antimetabolite, that shows a reproducible response rates of >20% with a median survival time of 9 months, offering a quality of life benefit in comparison with best supportive care (Abratt *et al*, 1994; Anderson *et al*, 1994; Gatzemeier *et al*, 1996; Anderson *et al*, 2000). The main toxicity of gemcitabine is mild-to-moderate myelosuppression. The combination of gemcitabine and cisplatin showed synergistic effects in preclinical studies because gemcitabine inhibited the repair of DNA damage caused by cisplatin (Bergman *et al*, 1996), and achieved high response rates along with improvements in median survival time in clinical setting (Sandler *et al*, 2000; Schiller *et al*, 2002; Alberola *et al*, 2003).

Recently, carboplatin has attracted attention ahead of nedaplatin because it has similar activity to cisplatin with fewer nonhaematological toxicities. The available data suggest that carboplatin–paclitaxel or carboplatin–gemcitabine should be considered among standard regimen for advanced NSCLC (Kelly *et al*, 2001; Grigorescu *et al*, 2002; Rudd *et al*, 2002; Schiller *et al*, 2002).

It seems that nedaplatin has activity and toxicity profiles similar to those of carboplatin, although no randomised trial has not been done to allow direct comparison (Fukuda *et al*, 1990; Furuse *et al*,

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1992a; Ota *et al*, 1992). Moreover, Matsumoto *et al* (2001) demonstrated that the combination of nedaplatin and gemcitabine resulted in enhanced inhibition of tumour growth *in vivo* and the antitumour efficacy of the combination was superior to that of cisplatin–gemcitabine or carboplatin–gemcitabine. Based on the results of a preclinical study, we designed the present phase I study of the efficacy of the combination of nedaplatin and gemcitabine for advanced NSCLC. The purpose of this study was to establish the toxicities and MTD of this combination, to determine the RD for phase II studies, and to observe their antitumour activity.

PATIENTS AND METHODS

Patient eligibility

Patients with histologic or cytologic confirmation of locally advanced or metastatic NSCLC who received either no prior chemotherapy or one previous chemotherapy regimen were eligible. The eligibility criteria were as follows; (1) measurable lesions; (2) age $\leqslant 75$ years; (3) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1; (4) adequate organ function (a white blood count (WBC) $\geqslant 4000\,\mu l^{-1}$, a neutrophil count $\geqslant 2000\,\mu l^{-1}$, a platelet count $\geqslant 100\,000\,\mu l^{-1}$, a haemoglobin count $\geqslant 9.5\,g\,dl^{-1}$, serum total bilirubin $\leqslant 1.5\,mg\,dl^{-1}$, serum transaminase $\leqslant 2\times$ upper normal limits, a serum creatinine $\leqslant$ upper normal limits, blood urea nitrogen (BUN) $\leqslant 25\,mg\,dl^{-1}$, $PaO_2 \geqslant 60$ mmHg or $SpO_2 \geqslant 90\%$]; and (5) normal electrocardiogram (ECG). At least 4 weeks must have passed after the completion of previous therapy and the patients had to have recovered from the toxic effects of previous therapy. The exclusion criteria consisted of pulmonary fibrosis or interstitial pneumonitis with symptoms or apparent abnormalities on chest X-ray, massive pleural effusion or ascites, acute inflammation, pregnancy, lactation, symptomatic brain metastases, active concurrent malignancies, severe drug allergies, severe heart disease, cerebrovascular disease, uncontrollable diabetes mellitus or hypertension, severe infection, active peptic ulcer, ileus, paralysis intestinal, diarrhoea and jaundice. This study was performed at Kinki University School of Medicine and was approved by the Institutional Review Board. Written informed consent was obtained from all patients. This study was conducted in accordance with Declaration of Helsinki.

Pretreatment and follow-up studies

Prior to entry, a complete history was taken and physical examination including age, height, weight, performance status, histological diagnosis, tumour stage, contents of previous treatment and presence of a complication was performed. The pretreatment laboratory investigations included a complete blood cell count, differential WBC count, platelet count, serum electrolytes, total protein, albumin, total bilirubin, transaminase, alkaline phosphatase, lactate dehydrogenase, BUN, creatinine, creatinine clearance and urinalysis. After the initiation of therapy, a complete blood cell count with a differential WBC count was performed at least twice a week. Blood chemistry profiles and chest X-ray films were obtained weekly. The lesion measurements were performed during at least every second course. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 and tumour responses were assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Therasse *et al*, 2000). Time to progression was measured from the date of registration to the date of first progression or death from any cause. Survival time was also measured from the date of registration to the date of death or latest follow-up, and was calculated using the Kaplan–Meier method (Kaplan and Meier, 1958).

Drug administration and dose escalation

The treatment schedule included nedaplatin, diluted with 500 ml of normal saline, given intravenously over 90 min on day 1, and gemcitabine with 100 ml of normal saline, given intravenously over 30 min after the completion of nedaplatin infusion on days 1 and 8, every 3 weeks. All patients were allowed to receive antiemetics with dexamethasone and granisetron, and post-therapy hydration with 1000 ml of normal saline. Granulocyte colony-stimulating factor (G-CSF) prophylaxis was not administered. Doses of gemcitabine on day 8 were given if the WBC count was $>2000\,\mu l^{-1}$ and/or the platelet count was $>750\,000\,\mu l^{-1}$, and/or allergic reaction, fever, elevation of transaminase and pneumonitis were less than grade 2, and/or the other nonhaematological toxicities were less than grade 3. The subsequent courses were withheld until the toxic levels returned to those specified in the eligibility criteria. The doses of both drugs were decreased by one dose level if DLTs occurred. In the case of the initial dose level, the doses of nedaplatin and gemcitabine were reduced by 20 and $200\,mg\,m^{-2}$, respectively.

Dose escalations were performed as listed in Table 1. Intrapatient dose escalation was not allowed. At least three patients were treated at each dose level, and three additional patients were entered at the same dose level if DLT was observed in one of the first three patients. The MTD was defined as the dose level at which more than two of three patients, or three of six patients experienced DLT. The definition of DLT was as follows: (1) grade 4 leukopenia, (2) grade 4 neutropenia for more than 4 days, (3) thrombocytopenia $<20\,000\,\mu l^{-1}$, (4) grade 3 febrile neutropenia, (5) grade 3 nonhaematologic toxicity except for nausea/vomiting, (6) delay of administration of gemcitabine on day 8 over a week for toxicities.

RESULTS

Between August 2001 and February 2003, 20 patients were enrolled in this study. The total and the median number of courses were 56 and 3 (range 1–6), respectively. The patients' characteristics are shown in Table 2. The majority of patients had a PS of 1. There

Table 1 Dose-escalation schema

Dose level	Nedaplatin dose ($mg\,m^{-2}$)	Gemcitabine dose ($mg\,m^{-2}$)	No. of patients (courses)
1	60	800	3 (8)
2	80	800	3 (10)
3	80	1000	8 (18)
4	100	1000	6 (20)

Table 2 Patients' characteristics

No. of patients		20
Age, years	Median	63.5
	Range	36–74
Sex	Male/female	17/3
Performance status	0/1	5/15
Histology	Adeno/squamous	13/7
Stage	IIIB/IV	4/16
Prior therapy	None	5
	Surgery	5
	Radiation	6
	Chemotherapy	14
	CDDP-based	3
	CBDCA-based	4
	Nonplatinum	4
	UFT	2
	Gefitinin	1

were five previously untreated patients (level 3, two patients; level 4, three patients) and 15 (75%) previously treated patients. Of the previously treated patients, five had received prior surgery, five had prior radiotherapy, and 14 had prior chemotherapy. Seven had received platinum-based chemotherapy (cisplatin, three patients; carboplatin, four patients), and four a nonplatinum regimen. Responses to previous chemotherapy included partial response in five patients, stable disease in seven, progressive disease in one, and not evaluable in one. The median interval from previous treatment was 16 weeks (range 4–92.5 weeks). Out of 20 patients, 18 were assessable for toxicity and response. Two patients at level 3 were excluded from the toxicity and response evaluation because they had refused this study after registration.

Toxicities

The haematological and nonhaematological toxicities observed during the first course are shown in Tables 3 and 4, respectively. The most frequent toxicities observed in the first cycle were neutropenia and thrombocytopenia (Table 3). One-third of the patients had grade 3 thrombocytopenia, and one patient received a platelet transfusion during the first course. Three patients had grade 4 neutropenia for no longer than 4 days. The nadir for neutropenia and thrombocytopenia occurred on day 15 (median, range 5–18), and on day 15 (median, range 8–18), respectively. Nonhaematological toxicities generally were mild because none of the patients had experienced more than grade 3 in the first course (Table 4). The major toxicities following all courses are listed in Table 5. Grade 3 thrombocytopenia occurred in 16 out of 56 courses, and three patients received platelet transfusion (one patient at level 1, one at level 3 and one at level 4). However, no patient had haemorrhagic complications. The most frequent nonhaematological toxicities were elevation of transaminase activity, nausea and appetite loss, but all were mild. One previously untreated patient at level 3 experienced grade 3 pneumonitis after the fifth course, probably induced by this treatment, and the patient's condition improved after the administration of steroid. There was no treatment-related death. One of the 18 patients at level 4 underwent dose reduction after the first course due to neutropenia, and two patients at level 3 did not receive gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. Delays in the commencement of subsequent courses occurred in 11 courses, and the median length of the delay before starting the subsequent course was 21 days (21–35 days).

MTD and DLTs

At levels 1 and 2, none of the patients had developed a DLT. Haematological and nonhaematological toxicities were generally mild at these levels, although one patient had grade 3 thrombocytopenia at level 1. At level 3, two of six assessable patients had developed DLTs. Both could not receive their scheduled dose of gemcitabine on day 8 because they had neutropenia, thrombocytopenia and high transaminase activity. At level 4, three of six patients had developed DLTs. One patient received G-CSF for neutropenia, not lasting more than 4 days, which was considered as the DLT. Another patient required a platelet infusion because of thrombocytopenia $<20\,000\,\mu l^{-1}$. The third patient could not receive the second course due to the delayed anaemia, also considered as DLT. Therefore, dose level 4, 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine was regarded as the MTD. The recommended dose level for further phase II study was determined to be 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine (dose level 3 in this study).

Response and survival

There were three partial responses, for an overall response rate of 16.7%. As for squamous cell carcinoma, only one out of seven

Table 3 Haematological toxicity following first course of nedaplatin and gemcitabine

		WBC grade					ANC grade					plt grade					Hb grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	0	2	1	0	0	0	1	2	0	0	0	1	1	1	0	0	2	1	0	0
2	3	1	0	2	0	0	1	0	1	1	0	0	3	0	0	0	0	1	2	0	0
3	6	1	1	2	1	0	2	0	0	3	1	1	2	1	2	0	3	3	0	0	0
4	6	1	0	3	2	0	0	0	3	1	2	0	2	1	3	0	0	3	3	0	0

Table 4 Nonhaematological toxicity following first course of nedaplatin and gemcitabine

		Nausea grade					Vomiting grade					Fatigue grade					Transaminase grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	2	1	0	0	0	3	0	0	0	0
2	3	1	1	1	0	0	3	0	0	0	0	1	2	0	0	0	1	2	0	0	0
3	6	2	3	1	0	0	5	1	0	0	0	4	2	0	0	0	3	1	2	0	0
4	6	2	2	2	0	0	6	0	0	0	0	6	0	0	0	0	1	5	0	0	0

		Infection grade					Fever grade					Appetite loss grade					Constipation grade				
Dose level	No. of patients	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	3	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0	3	0	0	0	0
2	3	2	0	1	0	0	2	1	0	0	0	1	2	0	0	0	3	0	0	0	0
3	6	6	0	0	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0
4	6	4	0	2	0	0	6	0	0	0	0	2	4	0	0	0	4	2	0	0	0

Table 5 Toxicities following all courses of nedaplatin and gemcitabine (56)

	Grade			
	1	2	3	4
WBC	13	26	10	0
ANC	15	15	13	3
Hb	24	27	1	0
Plt	22	14	16	0
Nausea	17	4	0	0
Vomiting	6	0	0	0
Appetite loss	21	0	0	0
Fatigue	15	0	0	0
Constipation	6	7	0	0
Transaminase	27	5	0	0
Neuropathy	5	0	0	0
Pneumonitis	0	0	1	0
Fever	1	0	0	0
Infection	0	3	1	0

patients had a partial response. The median progression-free survival time was 5.1 months. The median survival time and 1-year survival rate were 9.1 months and 34.1%, respectively. Out of 15 patients who had received prior treatment, two (13.3%) achieved a partial response, and there was no clear relationship between responses to previous treatment and responses to this regimen. For previously treated patients, the median survival time and 1-year survival rate were 9.2 months and 40.3%, respectively. Among five previously untreated patients, one (20%) achieved a partial response and the median survival time and 1-year survival rate were 12.0 months and 50.0%, respectively.

DISCUSSION

Many recent randomised clinical trials have shown that the combinations of cisplatin with one of the new agents, such as gemcitabine, taxanes or vinorelbine, is the standard therapy for patients with locally advanced or metastatic NSCLC (Non-Small Cell Lung Cancer Collaborative Group, 1995; Kelly *et al*, 2001; Schiller *et al*, 2002; Fossella *et al*, 2003). As it is known that cisplatin strongly promotes nephrotoxicity, neurotoxicity and gastrointestinal toxicity, second-generation platinum-containing compounds including carboplatin have attracted attention. Based on several randomised trials that have shown that the combination of carboplatin with paclitaxel produces similar response rates and overall survival with a more favourable toxicity profile than the combination of cisplatin with new agents (Kelly *et al*, 2001; Scagliotti *et al*, 2002; Schiller *et al*, 2002), combined therapy of carboplatin and paclitaxel is considered to be a standard therapy. More recently, the combination of carboplatin with gemcitabine has become attractive as a therapy for advanced NSCLC. Some randomised studies have indicated that carboplatin-gemcitabine regimen offers equivalent median survival compared with cisplatin-gemcitabine or mitomycin-vinblastine-cisplatin /mitomycin-ifosfamide-cisplatin (Danson *et al*, 2003; Zatloukal *et al*, 2003), and results in significant improvements in overall survival over those for gemcitabine alone or the older cisplatin-containing regimens (Grigorescu *et al*, 2002; Rudd *et al*, 2002; Sederholm, 2002). However, neutropenia and thrombocytopenia were more common in carboplatin-gemcitabine regimens than others; thrombocytopenia was particularly common.

Like carboplatin, nedaplatin is also a second-generation platinum derivative that appears to have a similar mechanism and toxicity profile to carboplatin, although direct comparison has not been performed. Moreover, *in vivo* study suggested that nedaplatin-gemcitabine resulted in more enhanced inhibition of tumour growth than cisplatin-gemcitabine or carboplatin-gemcitabine. These results prompted us to investigate nedaplatin-based combinations and to conduct this phase I study.

With respect to toxicities, the most frequent toxicities were haematological toxicities, especially neutropenia and thrombocytopenia. Eight of 18 patients (44.4%) developed more than grade 3 neutropenia after the first courses, and after 16 out of 56 (28.6%) courses overall. On the other hand, six out of 16 patients (37.5%) developed grade 3 thrombocytopenia after the first courses, and after 16 out of 56 courses (37.5%) overall. However, patients required platelet transfusions during only three courses. In addition, one previously untreated patient developed drug-related pneumonitis, which improved with the administration of steroid, at level 3 after the fifth course.

Overall, the toxicities of the combination of nedaplatin with gemcitabine were generally mild and this combination chemotherapy is both well tolerated and active against advanced NSCLC.

The overall response rate of 16.7%, the median survival time of 9.1 months, and 1-year survival rate of 34.1% in this study were quite acceptable because most patients had been given prior chemotherapy. As evaluation of antitumour activity was not a primary objective, and our patient population was small and heterogeneous, we are unable to draw definitive conclusions about the activity of this regimen. Currently, it is still controversial whether novel platinum compounds such as carboplatin and nedaplatin could replace cisplatin for the treatment of advanced NSCLC. However, when not only antitumour activity but also palliation are the main goals of treatment, these new platinum compounds might play a useful role because of their favourable toxicity profile. Therefore, nedaplatin-gemcitabine warrants a phase II study, and further evaluation in prospective randomised trials with cisplatin- or carboplatin-based combinations as a first-line chemotherapy for advanced NSCLC in order to investigate whether nedaplatin could replace cisplatin or carboplatin.

In conclusion, the combination of nedaplatin with gemcitabine is well tolerated and active for advanced NSCLC. The MTD and recommended dose level are 100 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine and 80 mg m^{-2} nedaplatin with 1000 mg m^{-2} gemcitabine, respectively.

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Retrospective analysis of the predictive factors associated with the response and survival benefit of gefitinib in patients with advanced non-small-cell lung cancer

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Summary

Background: The purpose of the study was to identify the potential predictive features associated with the response and survival benefit of gefitinib administration. We have retrospectively reviewed data of all patients who received a single regimen of gefitinib in our institution from August 1998 until July 2003.

Methods: Overall 101 patients with non-small-cell lung cancer (NSCLC) who have received a single use of gefitinib were analyzed. Potential factors associated with the response of gefitinib included smoking index, gender, histology, performance status (PS), number of pre-treatments, age and stage. Univariate analysis was performed for these strata by Fisher's exact test and multivariate analysis was then performed using the logistic regression model.

Results: The overall response rate was 19.8%. Univariate analysis revealed that significant predictive factors were associated with the response for 'adenocarcinoma', 'female', 'good PS' (0–1) and 'non-smoker' categories. Multivariate analysis limited the predictive factors associated with the response for 'female' ($P = 0.0032$), 'good PS' ($P < 0.02$) and 'non-smoker' ($P = 0.0417$). In survival analyses, 'female' ($P < 0.005$), 'good PS' ($P < 0.0001$), and a low level of the smoking index ($P < 0.05$) indicated significantly prolonged survival. Response and survival data in elderly patients were equivalent to those in younger patients. Adverse events (AEs) were generally mild and were almost always skin reactions and diarrhea. Interstitial lung disease (ILD) occurred in 4% of the group under observation.

Conclusions: Gefitinib provided clinical benefit for the following factors 'female', 'good PS' and 'non-smoker'. A low smoking index is reported as a novel predictive prognostic factor following a single regimen of gefitinib.

Abbreviations: NSCLC, non-small-cell lung cancer; EGFR, epidermal growth factor receptor; IDEAL-1, Iressa dose evaluated advanced lung cancer-1; PS, performance status; NCI-CTC, National Cancer Institute-Common Toxicity Criteria; INTACT-1, Iressa NSCLC trial assessing combination treatment-1; INTACT-2, Iressa NSCLC trial assessing combination treatment-2

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1. Introduction

Patients with advanced non-small-cell lung cancer (NSCLC) have a poor prognosis with 1–5% 5-year survival rates [1]. A recent meta-analysis demonstrated that platinum-based combination chemotherapy is currently considered to be the most effective treatment for advanced NSCLC, and these have improved the median survival time (MST) by 2 months and caused a 10% increase in 1-year survival rates [2]. As platinum-based chemotherapy improves survival and quality of life in advanced NSCLC patients, most patients will receive second line chemotherapy. With recurrence or progression, docetaxel has been approved as a second line chemotherapy treatment due to demonstrated survival benefit compared with best supportive care (BSC) or vinorelbine/ifosfamide [3,4]. Currently, there is no proven effective chemotherapy for patients previously treated with platinum-based and docetaxel therapies.

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because many types of cancer cells express or overexpress EGFR (including NSCLC, renal cell carcinoma and breast cancer) [5,6]. EGFR overexpression has been reported as a poor prognostic factor in many types of human solid tumors including NSCLC in several studies [7–9]. Currently, monoclonal antibodies that bind to the extracellular domain of EGFR and intracellular tyrosine kinase inhibitors have been developed [10,11]. Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways implicated in the proliferation, angiogenesis, invasion, metastasis and survival of cancer cells [12,13]. Several phase I trials demonstrated safety and tolerability of gefitinib in pretreated patients with solid tumors, in which trials an 11% response rate was seen in 100 patients with heavily pretreated advanced NSCLC [14]. On the other hand, in Japan, a phase I trial demonstrated five responders out of a total of 31 patients who all had adenocarcinoma of the lung [12]. To confirm anti-tumour activity and the safety profile of gefitinib, an international phase II study (IDEAL-1) and United States trial (IDEAL-2) were conducted as a second or third line treatment in patients with advanced NSCLC [15,16]. Patients enrolled in these studies were randomized into two different doses, 250 and 500 mg/day. These trials demonstrated that toxicity was mild and showed an encouraging response rate with an RR of 18.4 and 11.8% of patients in the 250 mg arm, respectively, and an improvement in disease related symptoms and quality of life were observed. The IDEAL-1 study has also confirmed that there were statistically significant differences in efficacy for 'adenocarcinoma' and 'female' using multivariate analysis. Two large randomized phase III studies [17,18], which are standard chemotherapy (cisplatin/gemcitabine or carboplatin/paclitaxel) with or without gefitinib, failed to demonstrate a survival benefit for advanced NSCLC patients as a first line chemotherapy. Although the results of the phase III studies were negative, gefitinib is still considered a promising molecular targeted agent as a new generation treatment in patients with advanced NSCLC. Information on the clinical prognostic factors following a single regimen of gefitinib should be helpful in finding which patients are likely to receive benefit, and in the development of a future treatment. Although the previous phase II trial (IDEAL) showed that several predictive factors were associated with the response to gefitinib, the population was essentially biased towards the young, with good performance status (PS) and conserved, good organ functions.

In this study, to find factors associated with an objective response and survival benefit of gefitinib, we retrospectively analysed patients who received a single regimen of gefitinib at our institute.

2. Methods

All patients with stage IIIB or IV NSCLC, who received a single regimen of gefitinib from August 1998 until July 2003 at the Kinki University School of Medicine, Osaka, were retrospectively reviewed. We evaluated patients who participated in clinical trials (phase I trial, phase II trial; IDEAL-1), or phase II trial for investigating surrogate gene therapy, and in 53 patients who were administered the drug after marketing (including elderly or poor performance status patients). Patients who received gefitinib as part of a compassionate use program were excluded. All patients were checked for age, gender, histology, Eastern Cooperative Oncology Group (ECOG), PS, stage, pre-treatment regimen, number of prior regimen, and smoking status before treatment of gefitinib. Smoking status was evaluated by the Brinkmann index; number of cigarettes per day multiplied by number of years. We analyzed the response, overall survival rate and the adverse effects of gefitinib, and investigated predictive factors associated with response and prognosis. The response was assessed using physical examination, biochemical profile, chest X-ray, chest computed tomography (CT), head CT or magnetic resonance imaging (MRI) scan, abdominal echo-graphic or abdominal CT scan, bone scinti-graph, bronchoscope, and was evaluated according to the response eval-

uation criteria in solid tumor (RECIST) [19]. The severity of all the adverse events (AEs) that related to gefitinib administration was assessed by the NCPCTC (version 2.0) grading system. The predictive factors associated with the response that were analyzed in this study were age, gender, PS, histology, stage, number of prior regimen and smoking status. Variables were tested for any possible relationship with the response to gefitinib, at first by univariate analysis, and subsequently by the application of a multivariate model. Response rates were compared between strata using Fisher's exact test. Logistic regression models were used to explore observed differences and identify baseline factors that may independently predict for response rates. The survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. *P*-values less than 0.05 were considered significant.

3. Results

3.1. Patient profiles

From August 1998 until July 2003 at our institute, a total of 105 patients, who were already cytologically or histologically diagnosed as NSCLC, were treated by a single regimen of gefitinib. Patients received gefitinib until disease progression or intolerable toxicity. Of these, 101 patients were evaluated as suitable for analysis; four patients were excluded from analysis because they received gefitinib as part of a compassionate use program. As shown in Table 1, the 101 patients included: 2 patients who received gefitinib at a once daily dose of 50 mg; single patients who each received 100, 225, 400, 525 and 700 mg, respectively; 89 patients who received 250 mg; and 5 patients who received 500 mg. In the phase I trial, we used an intermittent administration schedule with 14 days continuous dosing followed by 14 days off.

Table 1 Patient characteristics

	Number of patient ($N = 101$)
Phase I	7
50 mg	2
100 mg	1
225 mg	1
400 mg	1
525 mg	1
700 mg	1
Phase II (IDEAL-1)	11
250 mg	6
500 mg	5
Phase II (gene expression) (250 mg)	30
Post marketing (250 mg)	53

Table 2 Patient characteristics ($N = 101$)

	Number of patients
Age (year)	
Median (range)	62 (31–84)
<69	74
≥70	27
Gender	
Male	64
Female	37
Performance status	
0	15
1	62
2	17
3	7
Tumor histology	
Adenocarcinoma	81
Squamous	18
Large-cell	2
Stage	
III	18
IV	83
Previous treatment	
No treatment	5
Failed 1 previous chemotherapy regimens	53
Failed 2 previous chemotherapy regimens	34
Failed 3 previous chemotherapy regimens	9
Smoking (smoker:never-smoker)	55:46
Index[a] 0:1–999:1000	46:32:23

[a] Index: number of cigarettes per day multiplied by number of years.

Patient characteristics are shown in Table 2. The median age was 62 years (ranging from 31–84) and 74 patients (73.3%) were less than 69 years old. 63.4% of the patients were male, 76.2% had performance status (ECOG) 0–1, 80.2% had adenocarcinoma of which 83.2% had stage IV disease. Fifty-three patients had received one prior regimen, 43 had more than two prior regimens and only five had previously been untreated. 54.5% of them were smokers, and the non-smokers were almost all female. This study included patients

Table 3 Overall objective response

	Number	%
Number of patients evaluated	101	
Complete response (CR)	1	1.0
Partial response (PR)	19	18.8
Stable disease (SD)	52	51.5
Progressive disease (PD)	25	24.8
Not evaluable	4	4.0
Response rate % (95% CI)	19.8 (12.0–27.6)	
Disease control rate[a] % (95% CI)	71.3 (62.5–80.1)	

[a] CR + PR + S.D.

who had failed several previous chemotherapy regimens, and patients with an ECOG PS score of 3.

3.2. Response to treatment

Table 3 shows an objective response observed in this study. Twenty responders were evaluated and the overall response rate was 19.8%. One patient achieved a complete response, 19 patients exhibited a partial response and 52 patients had stable disease, resulting in a disease control rate (objective responses plus stable disease) of 71.3%. When evaluated using patient characteristics, we determined the response rate detailed in Fig. 1. All patients that responded had adenocarcinoma of the lung as the histological subtype. In addition, for the factors 'female' and 'never-smoker', there were higher response rates than in 'male' and 'smoker' respectively, while RR was similar for age, stage and pre-treatment. The response rate of 'female' and 'never-smoker' were 37.8 and 32.6%, respectively. Using the Fisher's exact test, the predictive factors which were associated with a response were 'female' (37.8% versus 9.4%; $P = 0.0006$), 'adenocarcinoma' (24.7% versus 0%; $P = 0.0104$), 'good PS' (0–1) (26.0% versus 0%; $P = 0.0028$), and never-smoker (32.6% versus 9.1%; $P = 0.0025$). There were no significant differences for age, stage and pre-treatment (Table 4). A multivariate analysis was performed against the four significant predictive factors in univariate analysis (Table 5). Because the incidence of the female factor is very strongly correlated to the never-smoker factor, the statistical assay was rather unstable if the two factors were analyzed simultaneously. We then investigated two patterns of multivariate analysis. One analysis excluded smoking and the other excluded gender. If smoking status was extracted, then female and good performance status were statistically significant. If gender was extracted, then non-smoking and good performance were statistically significant. The odds of a response were over three times higher for patients with adenocarcinoma than for patients with other histologies, however, this is not considered to be statistically significant because the group in this study was of a small size and included a high percentage of adenocarcinoma.

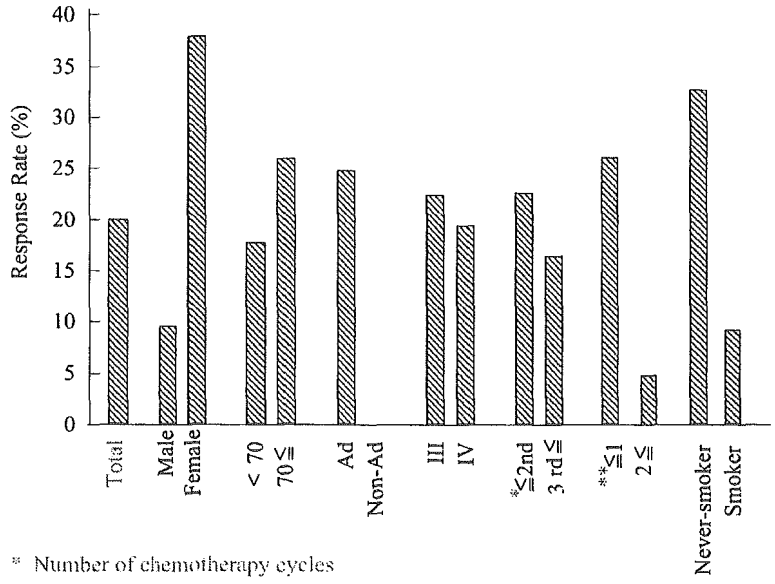

Fig. 1 Tumor response rate of the subgroups.

Table 4 Predictive factors associated with an objective response by univariate analysis

Parameter	*N*	Responder	RR (%)	*P*-value
Smoking index				
Non-smoker	55	15	32.6	
Smoker	46	5	9.1	0.0025
Gender				
Female	37	14	37.8	
Male	64	6	9.4	0.0006
Histology				
Adenocarcinoma	81	20	24.7	
Others	20	0	0.0	0.0104
PS				
0–1	77	20	26.0	
≥2	24	0	0.0	0.0028
Pre-treatment				
≤2 regimens	58	13	22.4	
≥3 regimens	43	7	16.3	N.S.
Age (years)				
≤70	74	13	17.6	
≥71	27	7	25.9	N.S.
Stage				
IIIB	18	4	22.2	
IV	83	16	19.3	N.S.

Abbreviations: N.S., not significant.

3.3. Toxicity

Drug-related AEs of all patients are shown in (Table 6). A total of 101 patients were evaluated for toxicity. The most frequent drug-related AEs were a rash, dry skin and diarrhea. Most of these AEs were mild (Grade 1 or Grade 2) and were controllable. Of all the drug-related AEs evaluated, Grade 3 or Grade 4 AEs were seen in less than 5%, and Grade 4 drug-related AEs were only pneumonitis. Grade 3 or 4 AEs required a treatment interruption, but recovered after discontinuation of gefitinib, except with pneumonitis. Four patients developed greater than Grade 3 pneumonitis requiring hospitalization. All patients had a fever and severe hypoxemia on admission. As soon as possible, all patients were administered steroid therapy. While two patients recovered with the steroid therapy, two patients died within 40 days after the administration of gefitinib. Hematological toxicities were not observed.

3.4. Survival

The median survival time of the patients who were 'good PS' (0 or 1) and 'poor PS' (2 or 3) was 353 and 97 days, respectively, and this difference was significant ($P = 0.0001$, log-rank test) (Fig. 2A). The MST of females was significantly longer than that of males (596 days versus 178 days, $P = 0.004$) (Fig. 2B). Furthermore, a low smoking index (<900) significantly prolonged survival (MST: 301 days versus 149 days, $P = 0.031$) (Fig. 2C). Age did not influence the survival benefit of the patients treated with gefitinib (Fig. 2D).

4. Discussion

Gefitinib is an orally active, selective EGFR tyrosine kinase inhibitor that blocks signal transduction pathways, and is one of the promising molecular targeted drugs used in the treatment of advanced NSCLC [16,17,20]. Although the large scale of the phase II study (IDEAL-1) [15] has already confirmed that there were statistically significant differences in efficacy for 'adenocarcinoma' and 'female' by multivariate analysis, the population was essentially biased towards young people with good performance status who had conserved, good organ functions. To clarify the predictive prognostic fac-

Table 5 Predictive factors associated with an objective response by multivariate analysis

Parameter	Odds ratio	95% CI	*P*-value
Extraction of smoking			
Gender (female vs. male)	0.163	0.040–0.585	0.0032
Performance status (1 vs. 2)	0.061	0.000–0.415	0.0018
Histology (Adeno[a] vs. others)	3.326	0.435–infinity	N.S.
Extraction of gender			
Non-smoking (non vs. ≥1)	0.297	0.063–0.959	0.0417
Performance status (1 vs. 2)	0.096	0.000–0.628	0.0101
Histology (Adeno vs. others)	4.385	0.588–infinity	N.S.

Abbreviations: N.S., not significant; CI, confidence interval.
[a] Adenocarcinoma.

Table 6 Patients with drug-related adverse events (NCI-CTC)

Adverse event	Number of patients ($N = 101$)				
	Grade 1	Grade 2	Grade 3	Grade 4/5	Total
Rash	33 (32.6%)	21 (20.8%)	3 (3.0%)	0	57 (56.4%)
Dry skin	24 (23.7%)	3 (3.0%)	0	0	27 (26.7%)
Pruritis	9 (9.0%)	7 (7.0%)	0	0	16 (16.0%)
Diarrhea	19 (18.8%)	4 (4.0%)	0	0	23 (22.8%)
Nausea	6 (6.0%)	1 (1.0%)	0	0	7 (7.0%)
Vomiting	3 (3.0%)	0	0	0	3 (3.0%)
Anorexia	7 (7.0%)	0	0	0	7 (7.0%)
ALT increased	5 (5.0%)	2 (2.0%)	5 (5.0%)	0	12(13.0%)
AST increased	8 (8.0%)	2 (2.0%)	3 (3.0%)	0	13 (13.0%)
Pneumonitis	0	0	2 (2.0%)	2[a] (2.0%)	4 (4.0%)

[a] Treatment-related death (Grade 5).

tors in a practical setting, we retrospectively analysed the patients who received a single regimen of gefitinib at our institute. Multivariate analysis demonstrated that the predictive factors which were associated with a response were 'female', 'good PS' and 'never-smoker'. In survival analyses, the factors 'female', 'good PS', and a low smoking index also significantly prolonged survival.

The mechanism by which these factors produced better prognosis has not been clarified.

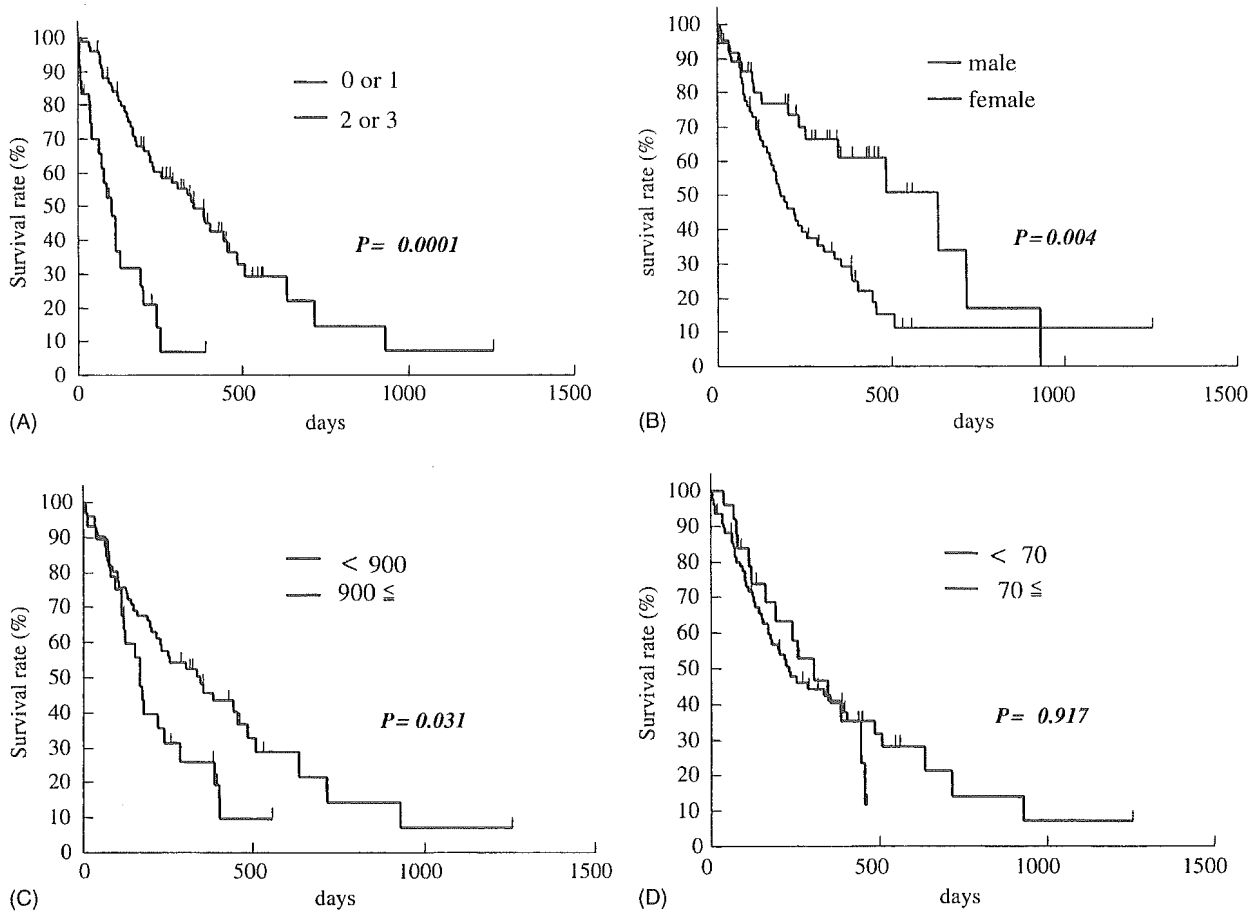

Fig. 2 A comparison of survival of: (A) PS 0, 1 vs. PS 2, 3; (B) gender: male vs. female; (C) smoking index: <900 vs. ≥900; and (D) age: <70 vs. ≥70.

Estrogen and progesterone may up-regulate EGFR in normal tissues [21], and activation of steroid hormones might impact on EGFR function in NSCLC [22]. Another explanation may be that the steroid hormone receptor might interact with EGFR and influence the response of an EGFR inhibitor.

Multivariate analysis in IDEAL-1 showed that PS was not a significant prognostic factor, however, the population of the study was restricted with regards to good PS. Although gefitinib was considered as an effector of symptom improvement in the phase II trial, the indication for patients with poor PS is controversial. Several authors described the case reports about the efficacy of gefitinib in NSCLC patients with poor PS [23,24] or with brain metastases [25]. Although 'good PS' were significant prognostic factor in this trial, gefitinib still might be a candidate drug for patients with poor PS, because of restriction of the use of other anti-cancer drug by their toxicities.

Elderly patients exhibited an equivalent response to young patients in this study. Recent data suggested, gefitinib is safe and well tolerated in elderly pretreated NSCLC patients [26]. A phase II study of gefitinib for elderly patients in NSCLC is needed.

A low smoking index was revealed as a predictive prognostic factor following a single regimen of gefitinib. Erlotinib is also administered orally and is a highly selective EGFR tyrosine kinase inhibitor [27] with a quinazolinamine-based structure similar to that of gefitinib. In the phase II study of erlotinib in NSCLC or bronchial alveolar carcinoma [28], a non-smoking history was also a prognostic factor. Chronic exposure to nicotine increases the expression level and phosphorylation status of EGFR and impairs its function [29]. Moreover, smoking produces overexpression of Her2/neu that binds to EGFR as a hetero-dimer in the tissue of normal bronchus. Expression of EGFR or Her2/neu or both in tissue samples by immunohistochemistry has not correlated in the response of gefitinib [30], however the different type of dimers formed between EGFR families might influence the response to gefitinib.

Four patients (4% of the patients) developed interstitial lung disease (ILD). Continuous smoking disrupted surfactant protein A or D [31,32], and the serum levels of the proteins were increased [33]. As 'smoking history' and 'male' are significant risk factors of ILD and also in treatment with gefitinib [34], a serum level of the surfactant protein A or D might be a predictive marker of ILD. Patients who are female and non-smokers are most likely to receive a high benefit and low risk with gefitinib treatment.

Although more basic biological research is needed to find the mechanism of action, we have found several predictive prognostic factors associated with the practical use of gefitinib. This is necessary clinical information which is important in order to set eligibility criteria for future clinical trials with gefitinib.

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TIMELINE

Gefitinib — a novel targeted approach to treating cancer

Roy S. Herbst, Masahiro Fukuoka and José Baselga

Abstract | Twenty years after the epidermal growth factor receptor (EGFR) was identified as a potential anticancer target, the EGFR inhibitor gefitinib (Iressa; AstraZeneca) has been approved for the treatment of patients with advanced non-small-cell lung cancer in many countries. Studies have indicated its potential for treating patients with other types of solid tumours. Investigation of gefitinib has not only increased our knowledge about the biology of EGFR signalling, but is contributing to our evolving understanding of which tumours are EGFR dependent.

Greater understanding of the molecular basis of cancer[1] is fostering the development of novel targeted strategies that inhibit specific cancer pathways and key molecules in tumour growth and progression. Such agents, for the most part, spare normal cells and have the potential to be well-tolerated therapies, which will enable patients with cancer to live longer and have an improved quality of life. Growth-factor signalling pathways have been a main focus of research for novel targeted anticancer agents because of their fundamental role in regulating key cellular functions including cell proliferation, differentiation, metastasis and survival. An important mediator of growth-factor signalling pathways is the epidermal growth factor receptor (EGFR) — a 170-kDa glycoprotein[2] that is expressed in most human tissues and is highly expressed in many human solid tumours. It is a member of the human epidermal growth factor receptor (HER) family, and in normal cells it is involved in mediating the signalling pathways related to cell growth and proliferation. Gefitinib (Iressa; AstraZeneca), an inhibitor of EGFR's tyrosine-kinase (EGFR-TK) activity, is the first targeted agent to be approved for the treatment of patients with advanced non-small-cell lung cancer (NSCLC).

The rationale for EGFR as a potential target for anticancer treatment was based on the work of several research groups. The breakthrough discovery of EGF in mice was made by Stanley Cohen in the early 1960s[3] (TIMELINE). EGF was one of the first growth factors to be isolated and its discovery opened up a research field that has been crucial to the development of both modern-day anticancer and other medical treatments. A decade after his pioneering contribution, Cohen isolated human EGF[4] and Harry Gregory reported the isolation of human urogastrone[5]. Gregory compared the amino-acid composition of the two polypeptides and concluded it was likely that both substances were one and the same[5]. However, another 10 years passed before Cohen cloned and isolated the EGFR[6] and the link between EGFR and the malignant transformation of cells was demonstrated[7]. Research has shown that transformation occurs by an autocrine mechanism, involving autostimulation of EGFR in cancer cells by ligands such as EGF or transforming growth factor-α (TGFα), which are produced by the cancer cells themselves. Other researchers have provided insight into the biochemical consequences of ligand binding to EGFR and suggested that binding stimulates activation of a cyclic-AMP-independent phosphorylation system through an inherent TK located within the receptor[8].

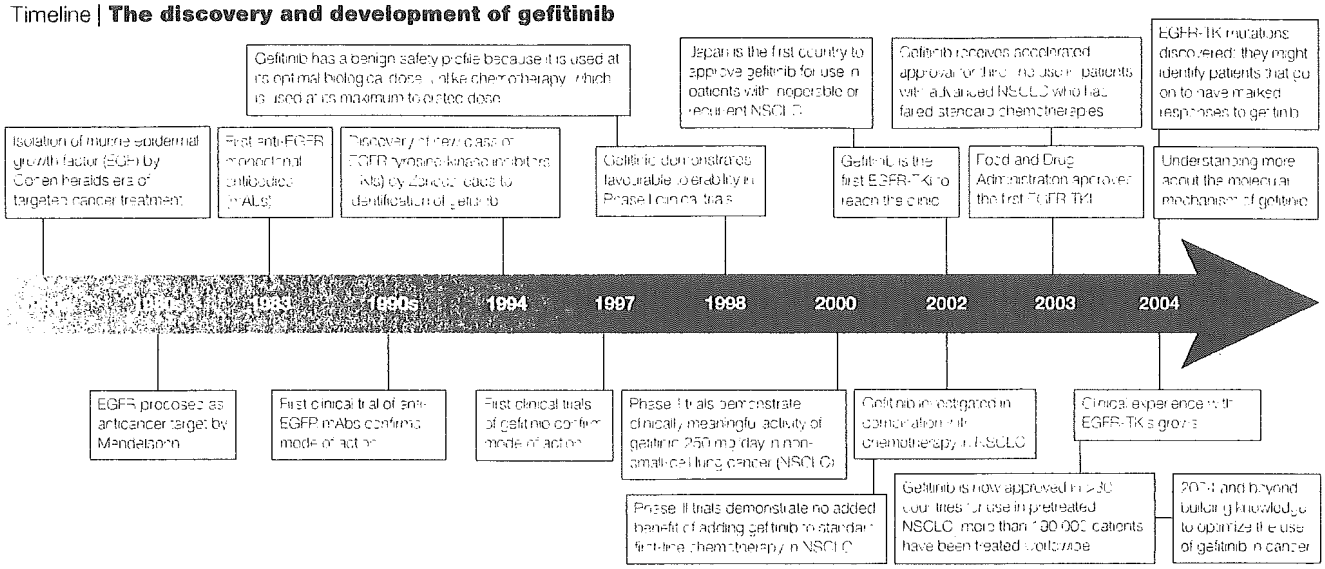
Additional compelling evidence for the role of EGFR in cancer pathogenesis came from reports that many human solid tumours express high levels of EGFR, which frequently correlates with poor prognosis[2,9]. Furthermore, many tumours that express EGFR also produce one or more EGFR ligand, which further supports the hypothesis that autocrine growth-stimulatory mechanisms are involved in EGFR-mediated tumorigenesis[10]. More recent studies have established the EGFR as an anticancer target. Research has shown that EGFR signalling not only increases cell proliferation, but also regulates a range of processes that are essential for tumour progression, including cell motility, cell adhesion, tumour invasion, cell survival and angiogenesis[11].

The magnitude of EGFR signalling is influenced by several cellular mechanisms. These include receptor mutations, heterodimerization with other members of the HER family, increased expression of autocrine ligands and alterations in molecules that control receptor signalling output. A schematic description of the EGFR pathway and its role in tumorigenesis is shown in FIG. 1.

EGFR-targeted therapies

In the early 1980s, Mendelsohn *et al.* proposed that agents designed to block EGFR signalling might be used to treat cancer (TIMELINE). Mendelsohn *et al.* produced two murine monoclonal antibodies (mAbs), 225 and 528, that targeted the EGFR-TK[11–15]. These antibodies inhibited activation of EGFR by competing with EGF or TGFα, binding with equal affinity, thus blocking activation of the receptor TK activity and its downstream signalling. These mAbs were the first anti-EGFR approaches to be developed (TIMELINE). It was anticipated that repeated administration of the mAb would be required to ensure sustained antitumour activity, and that the development of human

Timeline | **The discovery and development of gefitinib**



anti-mouse antibodies in patients would preclude the use of a murine antibody in the clinic; therefore a human:murine chimeric version of murine mAb 225 was developed. In addition, this mAb had superior binding characteristics and increased antitumour activity over mAbs 225 and 528 (REF. 16). This antibody, known as cetuximab (IMC-C225, Erbitux), has been approved for the treatment of patients with metastatic colorectal cancer (CRC) in the United States and Europe and is undergoing extensive clinical evaluation for the treatment of other cancers. During the 1980s and 1990s, other groups were investigating the potential of anti-EGFR mAbs in the treatment of cancers. In addition to the initial trials with mAb 225 (REF. 17) and mAb 528 (REF. 18), other studies with mAb 425 (REF. 19) and RG 83852 (REF. 20) were conducted.

The demonstration of the potential of EGFR-targeted therapies in the treatment of cancer has prompted the design of several other biological agents that block EGFR signalling. At present, there are more than 20 anti-EGFR agents in development and several are available for use in clinical practice or are at an advanced stage of clinical development (TABLE 1). These agents can be categorized into two main classes. One category comprises the small-molecule EGFR-TK inhibitors that compete with ATP binding to the TK domain of the receptor, which inhibits TK activity and subsequently blocks signal transduction from the EGFR. The other comprises mAbs that are directed at the extracellular portion of the EGFR, which competitively inhibit ligand binding to the receptor.

It is important to review the history of the development of gefitinib for several reasons. As one of the first anti-EGFR agents to enter clinical development, and as the first agent in its class to be approved for clinical use, the development of gefitinib is generating a large body of evidence that provides useful insight for the development of other agents of its class. Although the initial development of gefitinib has focused on its use in patients with NSCLC, investigation of gefitinib in several tumour types, including head and neck cancer, breast cancer and CRC, is ongoing. It has also been tested in combination with conventional chemotherapies in a range of settings, with important implications. Finally, the recent discovery of somatic EGFR-TK mutations in a subset of patients who respond to gefitinib and erlotinib[21–23] is building a greater understanding of the mechanism of action of the EGFR-TK inhibitors. However, many questions still remain, such as why some patients experience stable disease and symptom improvement with gefitinib therapy whereas others experience an objective response, and also how can we better define the use of this drug for patients with NSCLC and other solid tumours.

Characterization of gefitinib

Gefitinib is a novel, low-molecular-weight synthetic anilinoquinazoline — 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)-quinazoline. Its discovery was based on studies designed to characterize the catalytic mechanism of EGFR-TK inhibition and the finding that the 4-anilinoquinazoline class was a promising series of EGFR-TK inhibitors[24,25]. Of several candidate compounds synthesized and tested, gefitinib was identified to have the potential to be a clinically effective drug (TIMELINE). Assessments showed that gefitinib is a potent inhibitor of EGFR-TK activity and demonstrates high and sustained blood levels over 24-hour periods in bioassays[24]. Studies showed that gefitinib demonstrates high enzyme selectivity. Activity against other TKs, such as the structurally closely related HER-family EGFR-TK ERBB2, and the receptors for vascular endothelial cell growth factor (VEGF) FLT1 (also known as VEGFR1) and KDR (also known as VEGFR2) is minimal, as is activity against serine/threonine kinases[26]. Gefitinib inhibited the proliferation of several solid tumour cell lines *in vitro*, including ovarian, breast, colon, NSCLC and head and neck carcinomas, and provided a synergistic enhancement of the inhibitory action of single-agent cytotoxic drugs[27,28]. In addition, dose-dependent antitumour activity was seen in athymic nude mice bearing a range of xenografts[27,28].

Early clinical development

The safety and pharmacokinetics of gefitinib were evaluated in Phase I trials in healthy volunteers and in patients with a range of advanced, refractory, malignant tumours[29–33]. Compared with classical anticancer drug-development strategies, these early studies had two distinct characteristics. First, a large number of patients per dose level (50–1000 mg/day) were entered into these studies, and,

second, they incorporated pharmacodynamic end points to determine the effect of gefitinib on EGFR *in vivo* (BOX 1). Although the large trial populations fuelled some debate[34], they enabled the clinical activity of gefitinib to be studied in a range of tumour types, including NSCLC, and were important to the success of the biomarker programme.

As the basal layers of the epidermis express high levels of activated EGFR, skin biopsies (pre- and on-therapy) were incorporated into the studies to evaluate whether gefitinib could block EGFR activation and EGFR-dependent processes in patients[35]. At doses well below those producing unacceptable toxicity, gefitinib completely prevented EGFR phosphorylation, decreased mitogen-activated protein kinase activity, increased apoptosis and also increased levels of the cyclin-dependent kinase inhibitor p27 (also known as KIP1), which is believed to lead to G1 cell-cycle arrest. In addition, proliferation was reduced, as indicated by a decrease in the proliferation marker Ki67. Gefitinib was well tolerated and showed good bioavailability (60%)[29,33,36]. The most common adverse events reported in these trials were diarrhoea, nausea, rash/acne, vomiting and asthenia. Most of these were transient and mild in severity, according to National Cancer Institute Common Toxicity Criteria[37].

In patients with advanced refractory solid tumours, of whom most had NSCLC, responses were seen across the dose range tested[30–33]. No clear dose response relationship was observed, and pharmacodynamic and pharmacokinetic data showed that gefitinib doses of over 150 mg/day provided antitumour activity. These results highlight the fundamental differences in the dose–toxicity–activity relationships between chemotherapy and biologically targeted therapies. With chemotherapy agents, dose selection is a compromise between the antitumour activity of the agent and its dose-limiting toxicity. This is why these agents are used at their maximum tolerated dose (MTD) — the highest dose of an agent that can be tolerated by a patient. One of the complications of chemotherapy is that the MTD might be lower than the maximum effective dose — the dose that provides maximum cytotoxicity to the tumour and reduces tumour size. Because biologically targeted agents are usually active well below their MTD, they can be administered at their optimal biological dose (the dose that provides optimal efficacy and tolerability) and therefore provide a much-improved risk/benefit ratio, compared with chemotherapy[38].

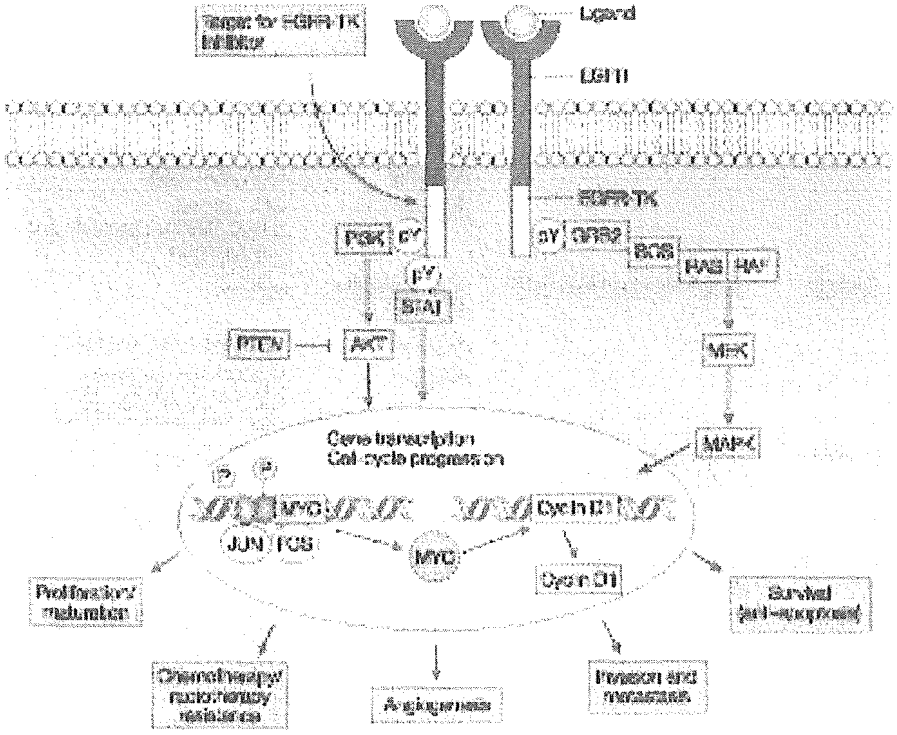


Figure 1 | **The epidermal growth factor receptor signalling pathway.** In response to ligand binding to its extracellular domain, the epidermal growth factor receptor (EGFR) forms homo- or heterodimeric complexes, with either another EGFR or another member of the HER family. This causes structural reorganization within the intracellular portion of the receptor, leading to activation of its kinase activity through autophosphorylation at a tyrosine residue (pY). This, in turn, leads to activation of a range of cell signalling pathways, including the recruitment of the adaptor proteins growth-factor-receptor-bound protein 2 (GRB2) and SOS, leading to activation of the small G proteins RAS and RAF, and signalling through mitogen-activated protein kinase (MAPK) kinase (MEK) and MAPK. EGFR activation also activates the kinase phosphatidylinositol 3-kinase (PI3K), which leads to AKT activation, along with the signal transducer and activator of transcription (STAT). Transduction of signals to the nucleus and the activation of gene transcription by factors such as MYC, JUN and FOS leads to the induction of several cellular responses that are required for normal cell growth, including proliferation, survival, differentiation, migration and adhesion. In some tumour cells, EGFR signalling is constitutively active, contributing to the upregulation of many processes that are essential for tumour growth (cell proliferation, survival, angiogenesis, invasion and metastasis)[85–87]. EGFR tyrosine kinase (TK) inhibitors (for example, gefitinib and erlotinib) are small molecules that inhibit ATP binding within the tyrosine-kinase domain of the EGFR, which completely inhibits EGFR autophosphorylation and consequently blocks signal transduction from activated EGFR. As a result, the key mechanisms of tumour growth (blue boxes) are inhibited. Figure modified with permission from REF. 88 © (2000) Adis International Limited.

Clinical development in NSCLC

Following the promising activity at a range of dose levels in patients with advanced NSCLC in Phase I studies, the clinical benefit of gefitinib monotherapy was studied further in this indication in two large, multicentre, Phase II trials. These studies named the Iressa Dose Evaluation in Advanced Lung cancer (IDEAL) 1 and IDEAL 2 (REFS 39,40) involved 210 and 216 participants, respectively. They compared the antitumour activity and safety of two doses of gefitinib, 250 and 500 mg/day, in patients with advanced NSCLC who had relapsed following previous treatment with platinum-based chemotherapy. A summary of results from both trials is shown in TABLE 2 (REFS 39–41).

Disease control. The IDEAL trials reported similar rates of disease control (response and stable disease) for the two doses: 42–54% of patients on the 250 mg/day dose and 36–51% of patients at the 500 mg/day dose. Compassionate use of gefitinib 250 mg/day in the Expanded Access Programme (EAP) in patients with late-stage NSCLC has supported the antitumour activity observed in the IDEAL trials[42]. This programme enrolled patients who either had experienced progression of their disease after chemotherapy or radiotherapy or were unsuitable for such therapies. Such patients were ineligible for gefitinib clinical studies and had no alternative treatment options.

Table 1 | **EGFR-targeted agents**

Anti-EGFR agent*	Drug type	Status	Tumour/cancer type
Gefitinib	Small-molecule EGFR-TKI	Launched, Phase III	NSCLC
		Phase III	Head and neck
		Phase II	CRC, breast, gastrointestinal, prostate and oesophageal
Erlotinib	Small-molecule EGFR-TKI	Pre-registration, Phase III	NSCLC
		Phase III	Pancreatic (trial completed)
		Phase II	Ovarian, head and neck, brain, lung (general), breast, renal, CRC, BAC and HCC
Lapatinib	Small-molecule EGFR-TKI/ERBB2-TKI	Phase III	Breast and renal
		Phase II	CRC, gastric bladder, head and neck, and NSCLC
Cetuximab	Extracellular EGFR mAb	Launched, Phase III	CRC
		Phase III	Pancreatic, head and neck, and NSCLC
		Phase II	NSCLC, breast, renal and prostate
Panitumumab	Extracellular EGFR mAb	Phase III	CRC and lung
		Phase II	NSCLC, renal and prostate

*Table lists agents that have completed or are currently in Phase III trials. BAC, bronchioloalveolar carcinoma; CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HCC, hepatocellular carcinoma; mAb, monoclonal antibody; NSCLC, non-small-cell lung cancer; TKI, tyrosine-kinase inhibitor.

A Phase III trial called BR21 compared the effects of erlotinib, another EGFR-TK inhibitor, with that of best supportive care (care that prevents or relieves the symptoms of disease or the side effects of treatment, but does not alter the course of the disease) in 731 patients with stage IIIB/IV NSCLC who had received one or two previous chemotherapy regimens[43]. The primary end point of this trial was overall survival, and secondary end points included progression-free survival, quality of life, response to treatment, and safety. This trial reported a disease control rate of 44% in patients on erlotinib versus less than 29% in patients in the placebo group.

Survival. In the IDEAL 1 and IDEAL 2 trials, the 1-year survival rates of pretreated patients with NSCLC who received 250 mg/day gefitinib were 35% and 27%, respectively. Their median duration of overall survival was 7.6 and 7.0 months, respectively[39,40]. Similarly, an analysis of 21,064 patients with locally advanced or metastatic NSCLC who had received gefitinib in the EAP reported a 1-year survival rate of 29.9%[44]. The data reported for gefitinib from both clinical trials and real-life usage compare favourably with the 1-year survival rate of 5.5% and median duration of overall survival of 4.0 months that has been reported in a retrospective analysis of NSCLC patients (n=43) receiving either third- or fourth-line chemotherapy[45].

Erlotinib-treated patients in the BR21 trial also experienced a 1-year survival rate of 31% and median duration of overall survival of 6.7 months[43]. A Phase III placebo-controlled study called Iressa Survival Evaluation in Lung cancer (ISEL), which includes about 1,600 patients with locally advanced or metastatic NSCLC, is underway to determine the effects of treatment with gefitinib 250 mg/day and best supportive care with best supportive care alone. This trial should provide further survival data for the EGFR-TK inhibitor class. The study has completed recruitment and results are expected soon.

Safety. The IDEAL trials showed that gefitinib was generally well tolerated at both 250 and 500 mg/day, and that the most common drug-related adverse events were mild diarrhoea and skin reactions. At both doses, most drug-related adverse events were reversible and caused few patients to discontinue treatment with gefitinib. As the 250 mg/day dose had a better tolerability profile than the 500 mg/day dose, albeit with similar efficacy, 250 mg/day was selected as the optimal biological dose of gefitinib for patients with pretreated advanced NSCLC. Tolerability data from the EAP support the favourable safety profile of gefitinib — in several large case series, most of the adverse drug reactions were mild diarrhoea and skin rash[46].

Recently, there have been reports that interstitial lung disease (ILD) developed in some patients during treatment with EGFR-TK inhibitors. In the IDEAL 1 trial, two Japanese patients who received 500 mg/day gefitinib experienced ILD-type events, but no such cases were reported in the IDEAL 2 trial[39,40]. Similarly, there has been a small number of reports of pulmonary toxicity with erlotinib[47,48]. With gefitinib treatment, the frequency of ILD seems to be higher in Japan (1.9–3% of patients) than in the rest of the world (0.3% of patients), including other South-East-Asian countries (0.3% of patients) (REF. 49, and B. Forsythe and K. Faulkner, personal communication). The mortality rate due to ILD is 0.7% for patients in Japan and 0.1% in the rest of the world (B. Forsythe and K. Faulkner, personal communication), which is approximately one-third of affected patients in each geographical group.

Box 1 | **How gefitinib modified clinical trial objectives**

As an epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitor, gefitinib was expected to reduce the proliferation rate of tumour cells, and thereby lead to disease stabilization rather than tumour regression (an objective response). By contrast, conventional chemotherapy aims to kill tumour cells, thereby producing an objective response. So to assess the full clinical potential of gefitinib as an anticancer agent, the Phase II clinical trials, in addition to measuring its significant antitumour activity, incorporated end points that were generally regarded as being of secondary importance in trials of cytotoxic agents, such as disease control (which incorporates objective response and stabilization of disease) and disease-related symptom improvement. These trials were the first to use the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy-Lung questionnaire to determine the effect of treatment on disease-related symptoms in patients with non-small-cell lung cancer. Similar new approaches to determining the activity of other targeted agents are now being considered by oncologists.