in the previous studies[2–4]. Our presented study supports that relatively high dose administration of CBDCA with initiation of HD 1 hour after drug injection would be an alternative strategy for patients with HD -dependent renal insufficiency.

Etoposide is active against various types of malignant tumors, but its membrane permeability in HD remains unclear. The AUC range for etoposide in 13 patients with normal renal function treated with this drug at a dose of 100 mg/m^2 was previously shown to be 2291 to 6832 minutes μg/ml (Ref. [11]). The present patient was treated with etoposide at 50 mg/m^2 on days 1 and 3, with HD being initiated 2 hours after completion of the drug injection. The AUC of etoposide was 3612 to 4401 minutes μg/ ml, values that are within the range achieved in patients with normal renal function. Indeed, the combination chemotherapy in the proband induced a tumor response that persisted for at least 8 months. Administration of etoposide at 100 mg/m^2 on days 1, 3, and 5 in combination with cisplatin at 80 mg/m^2 was shown to be acceptable in 4 lung cancer patients with renal dysfunction.[12] In the previous study, HD was performed soon after drug administration, resulting in an AUC for etoposide of 4800 to 6204 minutes μg/ml. Data from the previous studies and our present patient thus indicate that etoposide can be administered safely in HD patients.

The present case shows that CBDCA and etoposide chemotherapy combined with HD resulted in AUCs for these drugs within the therapeutic range in a SCLC patient with chronic renal failure. Although further studies are needed, our findings suggest that this regimen of combination chemotherapy can be administered to lung cancer patients with renal insufficiency.

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Prognostic Significance of Thin-Section CT Scan Findings in Small-Sized Lung Adenocarcinoma*

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Objectives: **The purpose of this study is to evaluate the prognostic importance of thin-section (TS) CT scan findings in small-sized lung adenocarcinomas.**

Patients and methods: **We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral lung adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. By using TS-CT scan images, tumors were defined as air-containing types if the maximum diameter of tumor opacity on mediastinal window images was less than or equal to half of that seen on lung window images, and as a solid-density type if the maximum diameter on the mediastinal window images was more than half of that on lung window images. We compared TS-CT scan findings to pathologic findings (*ie*, lymph node metastasis, pleural invasion, vessel invasion, and lymphatic invasion) and prognosis. The following prognostic factors were analyzed by χ^2 test and Cox proportional hazard model: age; gender; tumor size; pathologic stage; TS-CT scan findings; histologic subtypes defined by Noguchi et al (*ie*, Noguchi type); pleural involvement; lymphatic invasion; and vascular invasion.**

Results: **No pathologic invasive findings or recurrence were found in patients with air-containing-type tumors. Pathologic invasive findings and recurrence were found in 10 to 30% of patients with solid-density-type tumors. The air-containing type tumors seen on TS-CT scans and Noguchi type A or B tumors were demonstrated as prognostic factors for good outcome by χ^2 test ($p < 0.001$). Multivariate analyses revealed lymphatic permeation as a significant prognostic factor.**

Conclusion: **The TS-CT scan findings were important predictive factors for postsurgical outcome in patients with lung adenocarcinoma.** ***(CHEST 2008; 133:441–447)***

Key words: bronchioloalveolar cell carcinoma; ground-glass opacity; limited surgery; noninvasive cancer

Abbreviations: BAC = bronchioloalveolar cell carcinoma; GGO = ground-glass opacity; HU = Hounsfield units; TS = thin section

The number of patients with small-sized lung carcinoma has been increasing due to the routine clinical use of CT scanning and the increasing use of helical CT scan screening for lung cancer. Adenocarcinoma is the most common histologic type of lung cancer in those cases. The population of lung adenocarcinoma is heterogeneous, and many subtypes of adenocarcinoma have been advocated.[1,2] For example, Noguchi et al[1] classified small-sized lung adenocarcinoma into six subtypes based on tumor growth patterns. In this study, a type A or B tumor was localized bronchioloalveolar cell carcinoma (BAC), which showed no lymph node metastasis, rare vascular and pleural invasion, and excellent prognosis (5-year survival rate, 100%). A type C tumor was BAC with foci of active fibroblast proliferation, and showed pathologic invasive findings, and poor prognosis (5-year survival rate, 74.8%). A type D, E, or F tumor was adenocarcinoma without BAC and showed worst prognosis (5-year survival rate, 52.4%). Although these pathologic characteristics are useful as prognostic indicators, the results are defined only after surgery. If we have techniques by which we know the biological behavior of the tumor

and prognosis before treatment, they may be useful for planning therapy.

Many investigators reported that preoperative CT scan findings were related to the pathologic features and prognosis after resection of the tumor. The ratio of ground-glass opacity (GGO), defined as a hazy increase in lung attenuation without obscuring the underlying vascular marking on the CT scan, was associated with the histologic type of the tumor and survival. One of the purposes of these studies was to determine noninvasive carcinoma, defined as a tumor without lymph node metastasis, pleural invasion, vascular invasion, and lymphatic invasion by using thin-section (TS) CT scan images. However, there are few articles accurately determining noninvasive carcinoma by TS-CT scan images. If we determine a diagnosis of noninvasive carcinoma using CT scan images, they are useful for deciding on the surgical procedure to be used, especially lesser resection. This study was carried out to determine whether TS-CT scan findings were good indicators of noninvasive carcinoma of the lung, and also to clarify whether TS-CT scan findings were related to the prognosis.

Materials and Methods

We reviewed TS-CT scan findings and pathologic specimens from 359 consecutive patients who underwent surgical resection for peripheral adenocarcinomas ≤ 20 mm in diameter during the period from July 1997 to May 2006. All patients underwent physical examination, chest roentgenography, CT scan of the chest and abdomen, bone scintigraphy, and MRI of the brain for the staging and evaluation of resectability before the operation. The patients with disease of clinical stage IIB or less underwent surgery. We also surgically treated the patients with clinical N2 disease without evidence of mediastinal lymph node metastasis proven by mediastinoscopy. This study was approved by our institutional review board after confirmation of informed consent by the patients for us to review their records and images. Chest CT scan images were obtained by a commercially available scanner (X-Vigor/Real or Aquilion M/16 CT scanner; Toshiba Medical Systems; Tokyo, Japan). Conventional CT scan images were obtained serially from the thoracic inlet to the lung bases at 120 kV peak spacing, 512 × 512 pixel resolution, and 1-s scanning time. TS images targeted to the tumor were obtained serially at 120 kVp and 200 mA, with 2-mm section thickness, pitch 1, section spacing of 1 to 2 mm, 512 × 512 pixel resolution, and 1-s scanning time, using a high-spatial-reconstruction algorithm with a 20-cm field of view. These images were printed as photographs on each sheet of films using a mediastinal window level setting (level, 40 Hounsfield units [HU]; width, 400 HU) and a pulmonary window level setting (level, −600 HU; width, 1,600 HU).

While contrast medium (60 mL) was infused IV during imaging, lesion sites were translocated in a helical scan mode with a CT scan table speed of 2 mm/s; TS-CT scan images were obtained at one breath hold (120 kVp; 200 mA). The time interval between CT scan examination and subsequent surgery was ≤ 2 weeks in all patients. All CT scan images were reviewed by four thoracic oncologists who were not informed of the pathologic findings. They obtained the maximum dimension of the tumor using a pulmonary window level setting and the maximum dimension of the tumor using a mediastinal window level setting from the TS-CT scan images.

Tumors were defined as air-containing types if the ratio of the maximum dimension of the tumor using a mediastinal window level setting to the maximum dimension of the tumor using a pulmonary window level setting was ≤ 50%, and were defined as solid-density types if it was > 50%. Examples of CT scan images of the two groups are shown in Figures 1 and 2.

Each pattern based on TS-CT scan images was evaluated in terms of pathologic findings and survival outcome. We evaluated pathologic stage (TNM system), pleural involvement, vascular invasion, and lymphatic invasion. In addition, pathologic subtypes defined by Noguchi et al[1] (called hereafter *Noguchi type*) were evaluated.

The statistical significance of the difference between the incidence of relapse and TS-CT scan findings or Noguchi type was assessed by χ^2 tests. Relapse-free survival was calculated by the Kaplan-Meier method. Log-rank tests were used to compare the Kaplan-Meier curves. The Cox proportional hazards model was applied for multivariate analysis. Significance was defined as $p < 0.05$.

Results

Patient and tumor characteristics are listed in Table 1. There were 60 cases in which the largest diameter of the lesion was ≤ 10 mm, 130 cases in which it was 11 to 15 mm, and 169 cases in which it was 16 to 20 mm. There were 152 patients with air-containing-type tumors, and 207 patients with solid-density-type tumors. Table 2 shows the relationship between TS-CT scan findings and pathologic findings. No patients with air-containing-type tumors had lymph node metastasis, pleural involvement, vascular invasion, or lymphatic permeation. Among patients with solid-density-type tumors, 23 (11%) had lymph node metastasis, 45 (22%) had pleural involvement, 69 (33%) had vascular invasion, and 41 (20%) had lymphatic permeation. Table 3 shows the relationship between TS-CT scan findings and

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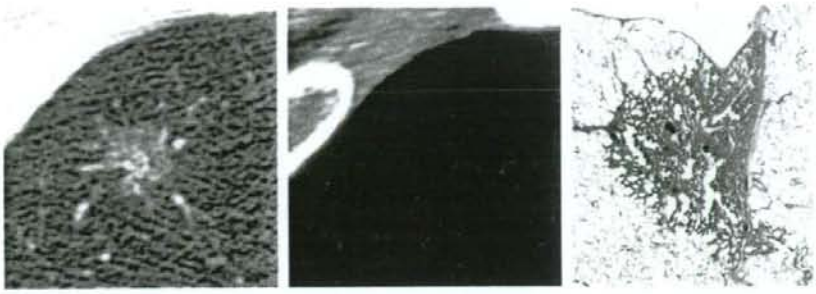

FIGURE 1. TS-CT scan findings of an air-containing-type tumor (diameter, 13 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows BAC (hematoxylin-eosin, original × 6).

pathologic stage. All patients with air-containing-type tumors had pathologic stage IA disease. In contrast, 39 patients (19%) with solid-density-type tumors had pathologic stage IB or greater disease. Table 5 shows the relationship between TS-CT scan findings and Noguchi type tumors. Among 152 patients with air-containing-type tumors, 79 patients received lobectomy, while 73 underwent limited resections (*ie*, segmentectomy or wedge resection) because of their small size (median tumor diameter, 11 mm). Among 207 patients with solid-density-type tumors, 3 patients underwent pneumonectomy and 155 underwent lobectomy, while 49 underwent limited resections because of their being elderly or having pulmonary hypofunction.

Table 2 shows the relationship between TS-CT scan findings and cancer relapse after surgery. No postoperative cancer relapse was seen in patients with air-containing-type tumors; in contrast, relapse was found in 31 patients (15%) with solid-density-type tumors. The relapse-free survival of 207 patients for whom ≥ 3 years have passed since surgery is shown in Figure 3. Patients with air-containing-type tumors had a 100% 5-year relapse-free survival rate, which was significantly better than that for patients with solid-density-type tumors ($p < 0.001$).

We assessed prognostic factors in 207 patients for whom ≥ 3 years had passed since undergoing surgery. Table 5 shows the relationship between cancer relapse and TS-CT scan findings or Noguchi type. No cancer relapse was seen patients with air-containing-type tumors or patients with Noguchi type A or B tumors. The presence of both air-containing-type and Noguchi type A or B tumors were demonstrated as significant prognostic factors for good outcome by χ^2 tests ($p < 0.001$). The reason for using χ^2 tests but not Cox proportional hazards models to analyze the prognostic factors for TS-CT scan findings and Noguchi type tumors was due to the difficulty in conducting a statistical analysis at the time of no relapse event in the patient group with air-containing-type tumors or Noguchi type A or B tumors. Then, a multivariate analysis with a Cox pro-

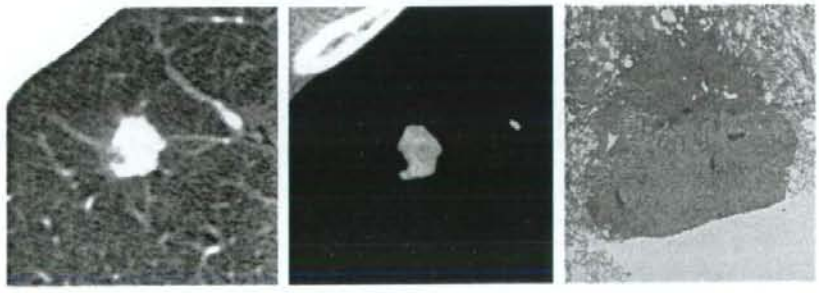

FIGURE 2. TS-CT scan findings for a solid-density-type tumor (diameter, 14 mm) on lung window setting images (*left*, *a*) and on mediastinal window setting images (*center*, *b*). The histologic specimen (*right*, *c*) shows poorly differentiated adenocarcinoma (hematoxylin-eosin, original × 6).

Table 1—*Patient and Tumor Characteristics

Variables	Values
Patients, No.	359
Age, yr	29–86 (65)
Gender, No.	
Male	159
Female	200
Tumor size, mm	5–20 (15)
Noguchi type tumor, No.	
Type A	52
Type B	75
Type C	162
Type D	39
Type E	5
Type F	25
TS-CT scan findings, No.	
Air-containing-type tumor	152
Solid-density-type tumor	207

*Values are given as range (median) or No.

portional hazard model was performed in 116 patients without air-containing type tumors or Noguchi type A or B tumors. The results showed that lymphatic permeation was a significant prognostic factor (Table 6).

Discussion

In patients with small-sized lung adenocarcinomas, several authors[1,2] have shown that pathologic characteristics are correlated with prognosis. Noguchi et al[1] have used tumor growth patterns to classify small-sized adenocarcinomas into six subtypes (*ie*, types A to F). Small, localized BACs (*ie*, types A and B) have not yet metastasized to lymph nodes or invaded vessels or pleura, and are associated with an excellent prognosis (5-year survival rate, 100%). Localized BAC with central fibrosis formation (*ie*, type C) is thought to be advanced carcinoma, which progresses from type A or B and is associated with a poorer prognosis than before (5-year survival rate, 74.8%). The prognosis for patients with nonreplacement-type adenocarcinomas (*ie*, types D, E, or F) is worse than that for patients with replacement-type adenocarcinomas (*ie*, types A, B, and C) [5-year survival rate, 52.4%]. Suzuki et al[3] showed that the size of the central fibrosis was a prognostic factor among peripheral lung adenocarcinomas that were ≤ 3.0 cm in size. In this study, the patients with adenocarcinoma having central fibrosis ≤ 5 mm in the maximum dimension had a 5-year survival rate of 100%, whereas the other patients had a 5-year survival rate of 70%. Higashiyama et al[4] showed that the component area of BAC was correlated with postoperative survival in patients with small peripheral adenocarcinomas ≤ 2.0 cm in diameter. Patients with adenocarcinoma having a BAC component comprising < 50% of the tumor tissue showed a significantly poorer prognosis than those with ≥ 50%.

In TS-CT scan images, consolidation areas represent mostly the foci of fibrosis or tumors of a solid growth pattern, whereas GGO areas reflect areas of a growth pattern of tumor cells replacing alveolar lining cells such as BAC. Because the fibrotic foci increase with the progression of the tumor, and because these areas and advanced adenocarcinomas with a solid growth pattern demonstrate consolidation areas on CT scans, it is suggested that the percentage of the consolidation or GGO areas relative to the tumor is a prognostic indicator. Many investigators[5–22] have reported on the correlation among TS-CT scan findings, pathologic findings, and prognosis. These studies have shown that GGO ratios were very much associated with BAC ratios and had favorable prognostic factors. However, the methods used to calculate the percentage of GGO areas (*ie*, GGO ratio) differ in different articles. Besides, we have few articles that have accurately determined the presence of noninvasive carcinoma, which was defined as a tumor without lymph node

Table 2—*Relationship Between TS-CT Findings and Both Pathologic Findings and Recurrence*

	TS-CT Scan Findings	
Pathologic Findings	Air-Containing-Type Tumors (n = 152)	Solid-Density-Type Tumors (n = 207)
Lymph node metastasis	0	23
Pleural involvement	0	45
Lymphatic permeation	0	41
Vascular invasion	0	69
Recurrence	0	31

Table 3—*Relationship Between TS-CT Findings and Pathologic Stage*

	Pathologic Stage					
TS-CT Scan Findings	IA	IB	IIA	IIB	IIIA	IIIB
Air-containing-type tumor	152	0	0	0	0	0
Solid-density-type tumor	167	16	5	3	15	1

Table 4—*Relationship Between TS-CT Findings and Noguchi Type*

	Noguchi Type					
TS-CT Scan Findings	A	B	C	D	E	F
Air-containing-type tumor	49	53	49	0	0	1
Solid-density-type tumor	3	22	113	39	5	24

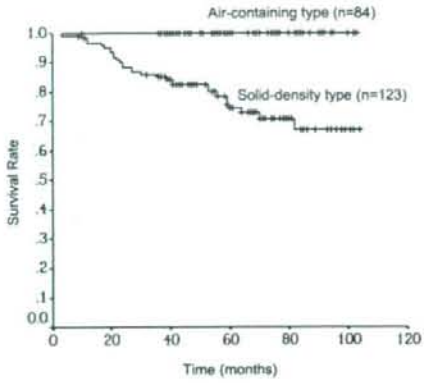

FIGURE 3. Relapse-free survival curves in patients with air-containing-type tumors and solid-density-type tumors.

metastasis, pleural invasion, vascular invasion, and lymphatic invasion, by TS-CT scan images. The parameters used to calculate the GGO ratio that have previously been reported are as follows: a GGO/tumor area ratio[5–10]; a consolidation/tumor dimension ratio[11–14]; a GGO/tumor volume ratio[15]; an area ratio of tumor on mediastinal window to that on the lung window[16,17]; a product of the dimension ratio of the tumor on the mediastinal window to that on lung window[18–20]; and a maximum dimension of tumor on the mediastinal window.[21] Matsuguma et al[8] reported on the relation between the proportion of the GGO and both clinicopathologic characteristics and tumor recurrence in patients with clinical T1N0M0 adenocarcinoma. In this study, the patients with a GGO ratio of ≥ 50% seen on high-resolution CT scans had neither lymph node metastasis nor lymphatic invasion and were alive without cancer recurrence. Ohde et al[12] reported the relation between the proportion of consolidation to GGO and pathologic invasive findings in patients with lung adenocarcinomas ≤ 3.0 cm. They showed that all tumors in which the ratio of the greatest diameter of consolidation to that of the tumor was ≤ 50% had neither lymph node metastasis nor vessel invasion and 5-year survival rate of 95.7%. Although only one cancer relapse was seen in tumors with a ratio of the greatest diameter of consolidation to that of the tumor of ≤ 50% in the study by Ohde et al[12]; the methods used to calculate the GGO ratio in these two studies[8,12] may be useful in defining noninvasive cancer. On the other hand, several investigators[16–20] used not only lung window images but also mediastinal window images to classify the tumors on TS-CT scan images. Kondo et al[16] used a ratio of the tumor area on the mediastinal window images to that on lung window images in patients with pulmonary adenocarcinoma of ≤ 2.0 cm, and showed that the tumors with a ratio of ≤ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse. Okada et al[18] and Shimizu et al[20] used the tumor shadow disappearance rate, which was determined from the product of the maximum dimension of the tumor and the largest dimension perpendicular to the maximum axis on both pulmonary and mediastinal window images on TS-CT scan, as previously described by Takamochi et al.[22] They showed that the tumors with a tumor shadow disappearance rate of ≥ 50% had no lymph node metastasis, rare vascular invasion, and no cancer relapse in patients with lung adenocarcinomas ≤ 2.0 cm in diameter. However, the methods used to classify the tumors in these studies with both pulmonary and mediastinal window images could not completely discriminate the tumor without invasive findings (*ie*, vascular, lymphatic, and pleural involvement) from the other. In contrast, the present study showed that the air-containing-type tumor did not have lymph node metastasis, pleural involvement, vessel invasion, or lymphatic permeation, and did not recur after resection. These results suggest that the air-containing-type tumor should be defined as a noninvasive cancer.

Table 5—*Relationship Between Recurrence and Both TS-CT Findings and Noguchi Type Tumor in 207 Patients for Whom 3 Years or More Have Passed Since Surgery*

TS-CT Scan Findings	Recurrence		p Value
	No	Yes	
Tumors			0.000
Air-containing type	84	0	
Solid-density type	93	30	
Noguchi type tumor			0.000
Type A or B	66	0	
Type C, D, E, or F	111	30	

The GGO area is sometimes neither clear nor objective. We sometimes experienced cases in which the border of consolidation and the GGO shadow on the TS-CT scan was unclear, and it was difficult or impossible to measure this size accurately. To select noninvasive cancer more simply and more objectively, we measured the maximum dimensions of tumors on both the lung and mediastinal windows. Our classification has the advantage of simplicity and objectiveness. We have only to compare the greatest dimension of the tumor on lung window images with that on mediastinal images of the TS-CT scan.

Although a number of prognostic indicators have been proposed such as TNM staging, tumor differentiation, molecular expression, and vascular inva-

Table 6—*Multivariate Analysis of Relapse-Free Survival*

Variables	Hazard Ratio	95% Confidence Interval	p Value
Age	0.968	0.923–1.014	0.170
Gender (male vs female)	2.372	0.986–5.707	0.054
Tumor size	1.062	0.947–1.192	0.305
Pathologic stage (≥ II vs I)	1.795	0.598–5.389	0.297
Noguchi type tumor (type D, E, or F vs type C)	2.169	0.842–5.586	0.109
Pleural involvement (positive vs negative)	2.181	0.951–5.001	0.066
Lymphatic permeation (positive vs negative)	2.819	1.094–7.265	0.032
Vascular invasion (positive vs negative)	0.864	0.289–2.588	0.795
Operation mode (lobectomy vs wedge resection)	0.453	0.188–1.094	0.079

sion, the final results are defined only after surgery. As yet, no definite preoperative indicators have been discovered for the postoperative outcome of patients with adenocarcinomas. This study showed that preoperative TS-CT scan findings had prognostic importance. The air-containing-type tumor defined in this study showed no cancer relapse and was revealed as an independent prognostic factor for relapse-free survival. The identification of prognostic variables, especially before the operation is important to decide on the operative procedure and adjuvant therapy. Although lobectomy and pneumonectomy with systemic mediastinal lymphadenectomy is the standard surgical treatment for non-small cell lung cancer, if noninvasive lung cancers are distinguishable on CT scans, limited surgery can be indicated before the operation. Since patients with the air-containing-type tumor showed neither pathologic invasion nor relapse after surgery, we think it is reasonable that we can treat patients with lesser resection for tumors of this type. Treating patients with limited resection leads to a reduction in operative complications and the maintenance of pulmonary function. The number of both elderly patients with lung cancer and patients with a second lung cancer has been increasing. Lesser invasive techniques such as limited resection and stereotactic radiotherapy will play an important role in the future. Studies[23,24] have shown the results of the attempt to apply limited surgery for small lung tumors ≤ 2.0 cm in diameter, in which a small number of local relapses was seen in patients who underwent limited resections. Our study also showed that 11% of solid-density-type tumors had lymph node metastasis. We think that it is not the size of the tumor but the findings of the CT scan of the tumor that is a good indicator for determining whether to use limited resection. Nakata et al[25] reported the results of limited resection of pure GGO selected by the CT scan, in which no cancer relapse was seen in 33 patients who underwent limited resection. In the selection of a candidate for limited surgery, it is important to select patients with noninvasive cancers that not only have high specificity but also high sensitivity. In our study, among 162 patients with Noguchi type C tumor, which is thought to be advanced carcinoma, 49 patients had air-containing-type tumors (Table 4). This result means that our classification using TS-CT scans can preoperatively determine the presence of type C tumors without invasive findings. A prospective study is needed to clarify whether patients with air-containing-type tumors defined preoperatively on TS-CT scan images are candidates for limited surgery. In conclusion, the presence of air-containing-type tumors in patients with peripheral adenocarcinomas < 2.0 cm in diameter means noninvasive cancer and that such patients are candidates for limited surgery.

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EXPERT REVIEWS

Gefitinib for the treatment of non-small-cell lung cancer

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Gefitinib is an orally bioavailable, EGF receptor tyrosine kinase inhibitor and was the first targeted drug to be approved for non-small-cell lung cancer (NSCLC). Identification of objective tumor regressions with gefitinib in NSCLC patients has resulted in intense, worldwide clinical and basic research directed toward finding the optimal use of gefitinib in NSCLC. A recent large international Phase III study (IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere [INTEREST]) comparing gefitinib and docetaxel in unselected pretreated patients showed equivalent survival with better tolerability and quality of life. In addition, a Phase III study (WJTOG0203) evaluating gefitinib as sequential therapy after platinum-doublet chemotherapy showed the improved progression-free survival time. Furthermore, a large-scale randomized study (IRESSA Pan-Asia study [IPASS]) comparing gefitinib monotherapy with carboplatin/paclitaxel for previously untreated patients with adenocarcinoma who were never- or light-smokers showed an improved progression-free survival time in the gefitinib arm. A smaller Phase III study of pretreated Japanese patients (V-15-32) also demonstrated no difference in overall survival compared with docetaxel, with a statistically greater overall response rate. Somatic mutations in the *EGFR* gene, the target of gefitinib, were associated with dramatic and durable regressions in patients with NSCLC. Currently, investigators are trying to determine the optimal approach to select patients for treatment with gefitinib. This article aims to briefly summarize the profile of gefitinib, *EGFR* mutations, landmark trials with gefitinib and, also, ongoing trials that may herald an era of individualized therapy in at least some NSCLC patients.

KEYWORDS: EGF receptor • *EGFR* gene mutation • gefitinib • non-small-cell lung cancer • tyrosine kinase inhibitor

Lung cancer is the most common cause of cancer deaths worldwide. Lung cancer is divided into two morphological types: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). SCLC is a distinct clinicopathological entity with a highly aggressive clinical course and neuroendocrine properties. Patients with SCLC are generally more sensitive to a variety of cytotoxic drugs and radiation therapy compared with NSCLC patients. NSCLC, which is less sensitive to chemotherapeutic agents, accounts for over 80% of all lung cancers and NSCLC can be further subdivided by histological type into adenocarcinoma, squamous-cell carcinoma, large-cell carcinoma and others. Adenocarcinoma is the predominant histological subtype and is increasing among patients with lung cancer. Among adenocarcinoma bronchioloalveolar carcinoma is a well-differentiated subtype originating in the peripheral lung that spreads through the airways.

Currently, platinum-based combination chemotherapy regimens, including several active new chemotherapeutic agents, comprise the standard option for patients with advanced NSCLC and good performance status. However, various combinations of drugs have similar efficacy, producing objective response rates of 30–40%, a median survival time of 8–10 months and 1-year survival rates of 30–40% [1–3]. These results remain unsatisfactory and new modalities of treatment are urgently awaited. Recently, novel molecular-targeted strategies that block cancer progression pathways have been suggested as a more cancer cell-specific treatment to control cancer and are considered an exciting therapeutic approach for treating NSCLC [4]. The development of agents that target the EGF receptor (EGFR) signal transduction pathways have provided a class of novel targeted therapeutic agents with improved side-effect profiles compared with conventional chemotherapeutic agents. EGFR is a promising target for anticancer therapy because it is expressed in a variety of tumors, including NSCLC [5]. Furthermore, high levels of EGFR expression have been associated with a poor prognosis in lung cancer patients in several studies.

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EGFR-targeted cancer therapies are being developed currently, and gefitinib (IRESSA®; AstraZeneca, Wilmington, DE, USA) is an orally active, selective EGFR tyrosine kinase inhibitor (TKI) that blocks signal transduction pathways implicated in the proliferation and survival of cancer cells.

Overview of the market

Lung cancer frequently presents at an advanced and biologically aggressive stage, resulting in poor prognosis. Surgery, chemotherapy and radiation have been generally unsatisfactory, especially in the treatment of advanced disease, and new strategies based on better understanding of the biology are clearly needed to improve the treatment efficacy of this fatal disease. The development of agents that target EGFR signal transduction pathways have provided a class of novel targeted therapeutic agents. Different approaches to inhibiting EGFR have resulted in a number of EGFR-targeted agents in clinical development, including small-molecule EGFR TKIs and monoclonal antibodies. The role of cetuximab (Erbitux®), a monoclonal antibody directed at the extracellular domain of the EGFR, and of gefitinib and erlotinib (Tarceva®; OSI Pharmaceuticals, NY, USA), oral, low-molecular-weight ATP-competitive inhibitors of the EGFR's tyrosine kinase domain is under investigation. Anti-EGFR monoclonal antibodies have demonstrated activity in the therapy of advanced colorectal carcinoma [6] and in a variety of epithelial tumor types, including head and neck cancer and NSCLC. A large Phase III study has found that targeted therapy with cetuximab, combined with platinum-based chemotherapy, improves survival outcome as a first-line treatment for patients with advanced NSCLC (overall survival [OS]: 11.3 months vs 10.1 months; $p = 0.044$) [7]. Erlotinib is another TKI with slightly different pharmacologic characteristics from gefitinib. Similar to gefitinib, erlotinib is a potent inhibitor of EGFR autophosphorylation, with a concentration that inhibits 50% in the nanomolar range *in vitro*. Erlotinib is the only EGFR TKI approved based on demonstrating improved survival versus placebo, which was observed in patients with advanced NSCLC who had been treated previously with chemotherapy. The randomized study (BR.21 study) brought erlotinib to registration by the US FDA on November 19, 2004, for the treatment of second- and third-line advanced NSCLC [8]. Other EGFR TKIs are currently under investigation in Phase I/II trials, many of which have differing selectivities for the various members of the human EGFR family. In the near future, gefitinib and erlotinib may face competition from EGFR-specific TKIs, such as EKB-569 (Wyeth, Maidenhead, UK) and CL-387785 (Calbiochem, CA, USA), and EGFR-family TKIs, such as BIBW-2992 (Boehringer Ingelheim, Berkshire, UK), HKI-272 (Wyeth), PKI-166 (Novartis), GW-572016 (GlaxoSmithKline, NC, USA), CI-1033 (Pfizer, MI, USA) and PF-00299804 (Pfizer). The VEGF pathway forms another target for cancer treatment, because the growth of solid tumor is angiogenesis dependent. VEGF and EGF exert their biological effects directly or indirectly on tumor growth and metastasis/invasion, as well as on tumor angiogenesis. The biological effects by VEGF and EGF are mediated through activation of their specific downstream signaling, but both factors also share common downstream signaling pathways. There is, thus, the potential for improved therapeutic efficacy by the combination of both EGF/EGFR-targeting and VEGF/VEGF receptor-targeting drugs, although they have a different side-effect profile. It may also face competition later on from multitargeted TKIs, such as ZD6474 (AstraZeneca), AEE-788 (Novartis) and XL647 (Exelixis Inc., San Francisco, CA, USA). Karaman *et al.* have reported small-molecule kinase interaction maps, which provide a useful graphic overview of how compounds interact with the kinome [9].

Gefitinib: an EGFR TKI

Gefitinib is the first molecularly targeted agent to be registered for advanced NSCLC. In Phase II clinical trials, the selective and orally active EGFR TKI gefitinib produced objective tumor responses and symptom improvement in patients with NSCLC who had previously received chemotherapy (response rates of 12–18% and symptom improvement rates of 40–44% in IRESSA Dose Evaluation in Advanced Lung Cancer [IDEAL]-1 and -2) [10,11]. Partial clinical responses to gefitinib have been observed most frequently in women, never-smokers and patients with adenocarcinomas. The IRESSA Survival Evaluation in Lung Cancer (ISEL) study also showed a survival benefit for gefitinib over placebo in Asian patients and never-smokers [12]. Thus, gefitinib clinical trials have shown that higher response rates and longer survival are associated with specific patient characteristics. Using conventional doublet chemotherapy simultaneously with gefitinib or erlotinib in unselected first-line patients does not increase survival [13–16], but the results of a recent Phase III study showed that gefitinib improves progression-free survival (PFS) as sequential therapy after platinum-doublet chemotherapy [17]. The Phase III IRESSA NSCLC Trial Evaluating Response and Survival Against Taxotere (INTEREST) and V-15-32 studies comparing gefitinib and docetaxel in unselected pretreated patients showed no difference in OS, suggesting that gefitinib and docetaxel were equally effective as the second-line therapy [18,19]. In addition, the Phase III IRESSA Pan-Asia study (IPASS) comparing gefitinib monotherapy with carboplatin/paclitaxel showed an improved PFS time in the gefitinib arm [20]. On the other hand, molecular studies have revealed that EGFR-activating mutations and high *EGFR* gene copy number are frequently found in patients who have the best outcomes with EGFR TKIs [21–27]. Currently, investigators are trying to determine the optimal approach to selecting patients for treatment with EGFR TKIs. Gefitinib is the first class of oral targeted therapies to produce such responses in advanced NSCLC and the most studied agent in clinical trials.

Chemistry

Gefitinib, 4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline (ZD1839, IRESSA; Figure 1), is an orally active, low-molecular-weight (447 kDa) quinazolin derivative

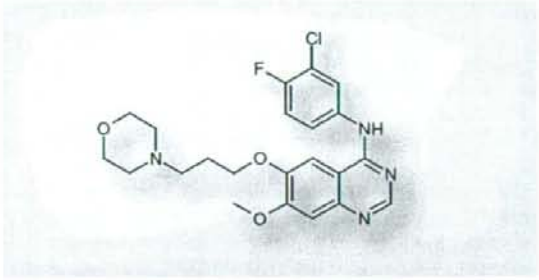

Figure 1. Gefitinib.

with a molecular formula $C_{22}H_{24}ClFN_4O_3$ that specifically inhibits the activation of EGFR tyrosine kinase through competitive binding of the ATP-binding domain of the receptor.

It is readily soluble at pH1 and highly insoluble above pH7. Gefitinib is very stable at room temperature with a proven shelf-life of 36 months [28].

Pharmacodynamics

Gefitinib selectively inhibits the activation of EGFR tyrosine kinase through competitive binding of the ATP-binding domain of the receptor. Selectivity was demonstrated versus HER2 and the VEGF tyrosine kinases, kinase insert domain receptor and Flt-1, with at least a 100-fold difference in IC_{50} for EGFR compared with other tyrosine kinases. Similarly, gefitinib did not inhibit the activity of the serine threonine kinases raf, MEK-1 and ERK-2 (MAPK) [29]. In the Phase I trials, the maximum tolerated dosage was 700 mg/day, although dosages as low as 150 mg/day provided plasma concentrations sufficient for pharmacological activity, evidence of targeted biological effect and anti-tumor activity [30–33]. An analysis of pharmacodynamics marker levels in the skin also provided evidence that sufficient gefitinib was reaching the skin and inhibiting EGFR signaling at 150 mg/day [34]. Additionally, objective tumor responses observed across a dosage range of 150–1000 mg/day indicated that these dosages resulted in target inhibition in tumors. Two large Phase II trials (IDEAL-1 and -2) evaluated 250- and 500-mg/day dosages of gefitinib in patients with advanced NSCLC. As predicted from the Phase I trials, dosages of more than 250 mg/day provided no additional efficacy benefit, whereas adverse effects increased in a dose-dependent manner. Consequently, the recommended dose of gefitinib in NSCLC is 250 mg/day [10,11]. Pharmacodynamic studies indicate that gefitinib blocks cell cycle progression in the G_1 phase by upregulating $p27^{Kip1}$, a cell cycle inhibitor, and downregulating c-fos, a transcriptional activator that is prominent in EGFR-mediated signaling [35]. Elevated levels of $p27^{Kip1}$ block cell cycle progression in the G_1 phase of growth. This sustains the hypophosphorylated state of the *Rb* gene product, which is necessary to keep cells from progressing in the cell cycle [36]. The inhibition of tumor growth seen with gefitinib is also accompanied by decreases in VEGF, basic FGF and TGF-α, all potent inducers of tumor angiogenesis [37]. Thus, gefitinib may also inhibit tumor growth by interfering with angiogenesis. These observations suggest that by inhibiting the EGFR tyrosine kinase, gefitinib treatment alters expression levels of key molecules in tumor cells that are important for stimulating proliferation, cell cycle progression, tumor angiogenesis, metastasis and inhibition of apoptosis. Gefitinib treatment can also cause apoptosis to occur *in vitro*, the frequency of which correlates with the cell line sensitivity to the drug and provides a link with the tumor shrinkage reported clinically [38].

Pharmacokinetics & metabolism

The pharmacokinetic profile revealed that gefitinib is orally bioavailable and suitable for once-daily dosing in cancer patients. In healthy volunteer studies, gefitinib was absorbed moderately slowly, reaching C_{max} 3–7 h after administration. The elimination half-life of 28 h suggests that once-daily oral administration is appropriate [34]. In the initial Phase I studies of gefitinib, sequential skin biopsies were performed prior to and after 4 weeks of therapy [34]. The skin was selected as the target tissue due to its easy access and the established role of the EGFR in renewal of the dermis. Inhibition of EGFR phosphorylation and EGFR-dependent downstream processes was detected at dosages of 150 mg/day, well below the maximal tolerable dosage (MTD) of 700 mg/day. In a clinical study (BCIRG 103), gefitinib (250 mg) was administered orally to breast cancer patients for at least 14 days [39]. Gefitinib concentrations in each tumor sample (mean: 7.5 µg/g) were substantially higher (mean: 42-fold) than the corresponding plasma sample (mean: 0.18 µg/ml). Haura *et al.* conducted a pilot Phase II study of a 28-day preoperative course of gefitinib 250 mg orally, followed by surgical resection for patients with stage IA to selected IIIA NSCLC [40]. Tumor penetration of gefitinib was assessed in surgically resected tumor samples along with plasma assessment on day 28. Day 28 plasma concentrations of gefitinib averaged 531 ± 344 nM (range: 65–1211 nM) while tumor concentrations of gefitinib averaged 33,108 ± 44,312 nM (range: 74–134,669 nM). These results also demonstrate that NSCLC tumor penetration of gefitinib is high, as its tumor concentrations were much higher than concentrations found in plasma.

Gefitinib is metabolized extensively by expressed cytochrome P450 (CYP)3A4, producing a similar range of metabolites to liver microsomes, while CYP3A5 produced a range of metabolites, similar to CYP3A4 but to a much lower degree [41,42]. By contrast, CYP2D6 catalyzed rapid and extensive metabolism of gefitinib to desmethyl-gefitinib (M523595). While formation of M523595 was CYP2D6 mediated, the overall metabolism of gefitinib was dependent primarily on CYP3A4. Quantitatively, the most important routes of gefitinib metabolism were mediated primarily by CYP3A4, while CYP3A5 and CYP2D6 were minor contributors. The wide variability in CYP3A4 activity in human liver is probably a significant factor in the interindividual variability observed in gefitinib pharmacokinetics. Gefitinib has interactions with CYP3A4 inducers, or CYP3A4 enzyme inhibitors or substrate of CYP2D6 (gefitinib inhibits CYP2D6 activity) or H2 blockers. Pharmacokinetic studies have shown that the bioavailability of gefitinib is unaffected by food intake to any clinically significant extent [43].

Clinical efficacy

Several challenges were encountered in designing the clinical trials of gefitinib, because this agent was expected to be cytostatic rather than cytotoxic. These challenges included a scarcity of precedents, the way in which 'biological activity' was defined, the integration of outcomes across multiple tumor types in Phase I trials, the relationship between biological activity and clinical outcome, and unknown pharamakokinetic and pharmacodynamic relationships. Initially, clinical trials of gefitinib were performed principally in unselected patient populations with NSCLC. However, recent results indicate that different patients derive different degrees of clinical benefit from treatment with gefitinib. The identification of the patients who are most likely to derive clinical benefit from gefitinib is of paramount importance.

Phase I

As biologically targeted agents are expected to provide clinical benefits that are not predicted by surrogate end points of toxicity to normal replicating tissue, new Phase I trials have been designed to determine the optimum biological dose for use in further studies. Initial Phase I trials performed in healthy volunteers showed that oral administration of gefitinib given once on day 1 (50, 100, 250 or 500 mg) or daily for 14 days (100 mg/day) was feasible [44]. Four multicenter Phase I trials then evaluated the safety profile of gefitinib (50–1000 mg/day) in more than 250 patients with a wide range of solid tumors that were known to express EGFR, although baseline EGFR expression levels were not determined [30–32,45]. Adverse events (AEs) occurred at dosages of 50 mg/day, with the most commonly reported AEs being mild-to-moderate acne-like rash, diarrhea, nausea, anorexia, vomiting and asthenia. The frequency of AEs, such as skin rash and diarrhea, increased with dose, and the MTD was identified as 700 mg/day. Clinical benefit was not dose-related, whereas the most common AEs (skin rash and acne) increased with gefitinib dose. In addition, pharmacokinetic studies indicated that plasma levels of gefitinib over this dose range were sufficient for effective EGFR inhibition. Although the lowest dose at which objective tumor responses were observed was 150 mg/day, there was potential for individuals receiving this dose to have subtherapeutic exposure as a result of interpatient variability in pharmacokinetics. Accordingly, the slightly higher dosage of 250 mg/day was chosen. The second dosage chosen was 500 mg/day, which was the highest dosage that was well tolerated by most patients on a daily dosing schedule. Both dosages were significantly lower than the MTD, unlike conventional dosage selection for chemotherapy agents, which would use the MTD.

Phase II

Large-scale dose-evaluation study

Two large, dose-randomized, double-blind, parallel-group, multicenter Phase II trials (IDEAL-1 and -2) independently evaluated the activity of gefitinib 250 and 500 mg/day in 425 patients with advanced NSCLC [10,11]. These trials allowed a more detailed evaluation of the doses selected from the Phase I trials and included symptom improvement as an additional end point. In IDEAL-1, conducted mainly in Europe and Japan, patients with one or two prior chemotherapy regimens, including a platinum compound, were randomly assigned to receive gefitinib at 250 or 500 mg/day. Response rate approached 20% and was similar in both arms, and symptom improvement was 40%, which was higher in patients who had an objective response. Adverse effects were, in general, well tolerated, but were more severe with the 500-mg dose. In IDEAL-2, the study was performed in 30 centers in the USA. In total, 221 patients were randomly assigned to receive either gefitinib 250 or 500 mg daily. A total of 126 patients (58%) had three or more regimens in the past and 65% had histology of adenocarcinoma. Symptoms of NSCLC improved in 43% of patients receiving gefitinib 250 mg and in 35% of those receiving 500 mg. There was no significant difference in response rate or survival between the two doses. There was a good correlation between clinical response and symptomatic improvement. However, the gefitinib 500-mg dose was more toxic as it induced more acne-like rash and diarrhea. In conclusion, gefitinib was well tolerated at 250 mg/day and it induced anti-tumor activity in approximately 10% of patients. These results are impressive compared with chemotherapy, which induces far more adverse effects and, probably, even a lower level of activity.

Gefitinib as first-line treatment

In East Asia, Phase II trials of gefitinib as first-line therapy have demonstrated good response rates of 30% compared with those in patients of non-East Asian origin (<10%) [46–51]. In a prospective Phase II trial of chemotherapy-naive patients with advanced NSCLC conducted in Japan, 40 patients treated with first-line gefitinib were evaluated for response. Partial response was seen in 12 (30%) patients [47]. Response to gefitinib in studies of non-Asian patients have been shown to be much lower than in studies of Asian patients. In a study in the USA, response rate among 70 patients with advanced NSCLC and poor performance status (2 or 3) was 4% [50]. In Germany, response rate among 58 patients with inoperable advanced NSCLC and good performance status (0–2) was 5% [49]. Results from IRESSA in NSCLC versus Vinorelbine Investigation in the Elderly (INVITE) reported no statistical difference between gefitinib and chemotherapy first-line for median PFS rates (2.7 vs 2.9 months, respectively) or overall response rates (3.1 vs 5.1%, respectively) [52,53]. Iressa NSCLC Trial Evaluating Poor Performance Patients (INSTEP) reported a response rate of 6% and a trend toward improved efficacy end points with gefitinib first-line compared with placebo, with similar improvements in quality of life and symptoms in Western patients with poor performance status [54]. See Table 1 for a detailed list.

Gefitinib therapy in selected patients

Table 2 lists several reports on gefitinib sensitivity in selected patients [55–66]. In 2004, several investigators reported that somatic mutations in the gene for the EGFR [21–23], the targets

Table 1. Phase II studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Gefitinib in the second- and third-line treatment of advanced NSCLC							
Fukuoka *et al.* (IDEAL-1)	Gefitinib 250 mg daily	103	18.4	2.7	7.6*	Randomized Phase II trial conducted mainly in Europe and Japan	[10]
	Gefitinib 500 mg daily	105	19.0	2.8	8.0		
Kris *et al.* (IDEAL-2)	Gefitinib 250 mg daily	102	12.0	NA	7.0**	Randomized Phase II trial conducted in the USA	[11]
	Gefitinib 500 mg daily	114	9.0		6.0		
Gefitinib in the first-line treatment of patients with NSCLC							
Goss *et al.* (INSTEP)	Gefitinib	100	6.0			Randomized Phase II trial in patients with poor performance status; modest benefit seen with gefitinib	[54]
	Placebo	101	1.0				
Crino *et al.* (INVITE)	Gefitinib	97	3.1	2.7		Randomized Phase II trial in elderly patients; similar efficacy observed	[52]
	Vinorelbine	99	5.1	2.9			
Niho *et al.*	Gefitinib 250 mg	40	30.0	NA	13.9		[47]
Lin *et al.*	Gefitinib 250 mg	53	32.1	3.2	9.4		[46]
Suzuki *et al.*	Gefitinib 250 mg	34	26.5		14.1		[48]
Reck *et al.*	Gefitinib 250 mg	58	5.0	1.6	6.7		[49]
Spigel *et al.*	Gefitinib 250 mg	70	4.0	3.7	6.3	Patients with poor performance status	[50]
Swinson *et al.*	Gefitinib 250 mg	41	10.0	1	2.7	Patients unsuitable for chemotherapy	[51]
Gefitinib compared with docetaxel in the second-line treatment of advanced NSCLC							
Cufer *et al.* (SIGN)	Gefitinib 250 mg	68	13.2	3.0	7.5***	Open label,randomized Phase II study; fewer drug-related side effects with gefitinib	[114]
	Docetaxel 75 mg/m²	73	13.7	3.4	7.1		

*p = NS.
**p = 0.40.
***p = 0.88.
HR: Hazard ratio; IDEAL: IRESSA Dose Evaluation in Advanced Lung Cancer; INVITE: Iressa in NSCLC versus Vinorelbine Investigation in the Elderly; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; PFS: Progression-free survival.

of gefitinib, were associated with dramatic and durable regressions with gefitinib in patients with NSCLC. To confirm the encouraging but retrospective results of early studies, multiple groups undertook prospective Phase II trials of gefitinib in patients found to have an *EGFR* mutation on screening. To date, at least nine studies have been reported [55–63]. Collectively, these showed that nearly 80% of patients whose tumors had either exon 19 deletions or L858R mutations had radiographic responses to gefitinib, although responses varied between different trials. The combined analysis of seven prospective trials conducted in Japan, which examined the efficacy and safety of gefitinib monotherapy for NSCLC with *EGFR* mutations, has been reported. In this study, Morita *et al.* updated OS and PFS data for the combined survival analysis and examined prognostic factors for OS and PFS (I-CAMP study) [67]. A total of 148 patients were combined from the seven trials and median OS and PFS of 24.3 months and 9.7 months weer reported, respectively. The combined response rate was 76.4%, and only 6% of the patients had progressive disease. They concluded that gefitinib produces significant anti-tumor activity and prolonged survival in this selected NSCLC population. A prospective Phase II study has also demonstrated that gene copy number assessed by fluorescent *in situ* hybridization (FISH) [25] may predict clinical outcome in TKI-treated NSCLC patients. In advanced bronchioloalveolar carcinoma, a distinct subtype of adenocarcinoma, gefitinib was clinically active in both chemotherapy-naive and pretreated patients [65,66].

Phase III

Gefitinib in combination with chemotherapy

The IRESSA NSCLC Trial Assessing Combination Treatment (INTACT)-1 and -2 studies were large randomized studies of two dosages of gefitinib (250 or 500 mg/day), or placebo, in combination with two different chemotherapy regimens [13,14]. INTACT-1 used cisplatin and gemcitabine (cisplatin 80 mg/m² on day 1 and gemcitabine 1250 mg/m² on days 1 and 8 every

Table 2. Phase II studies of gefitinib in selected patients.

Author	Selection	Patients (n)	Response rate (%)	TTP/PFS (months)	MST (months)	1-year survival (%)	Ref.
EGFR selected							
Inoue *et al.*	Mutation	16	75	9.7	NR	NR	[55]
Sutani *et al.*	Mutation	27	78	9.4	15.4	NR	[56]
Asahina *et al.*	Mutation	16	75	8.9	NR	88	[57]
Sunaga *et al.*	Mutation	19	84	13	NR	NR	[58]
Yoshida *et al.*	Mutation	21	90	7.7	NR	NR	[59]
Tamura *et al.*	Mutation	28	75	11.5	NR	79	[60]
Sugio *et al.*	Mutation	16	50	8.8	15.4	NR	[61]
Sequist *et al.* (iTARGET)	Mutation*	31	55	9.2	17.5	73	[62]
Yang *et al.*	Mutation‡	43	84	8.9	24		[63]
	Mutation§	12	16	2.1	6.7		
Cappuzzo *et al.* (ONCOBELL)	FISH	42	48	6.4	NR	64	[25]
Never-smokers							
Lee *et al.*		72	55	5.5	19.7	76	[64]
Cappuzzo *et al.*	Never smoker or FISH)	42	48	6.4	NR	64	[25]
Bronchioloalveolar carcinoma							
West *et al.*		101	17	4	13	51	[65]
Cadranel *et al.*		88	13	2.9	13.3	55	[66]

*EGFR mutations were primarily exon 19 deletions (53%) and L858R (26%), although 21% of mutation-positive cases had less-common subtypes, including exon 20 insertions, T790M/L858R, G719A and L861Q.
‡Del 19 or L858R.
§Other mutations.
EGFR: EGF receptor; MST: Median survival time; NR: Not reported; PFS: Progression-free survival time; TTP: Time to progression.

3 weeks), whereas INTACT-2 used carboplatin and paclitaxel (carboplatin given at AUC of 6 and paclitaxel at 225 mg/m^2 in 3-h infusions every 3 weeks). Chemotherapy was administered for up to six cycles and gefitinib or placebo were continued in nonprogressing patients until progression. A total of 1093 and 1037 patients were entered, respectively, in the two studies in less than 1 year of accrual. These two large randomized studies failed to demonstrate a survival increase with the addition of gefitinib to standard chemotherapy in first-line treatment of advanced NSCLC. A subset analysis of patients with adenocarcinoma who received 90 days of chemotherapy or more in the INTACT-2 study demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect. In general, treatment was well tolerated and the toxicity of chemotherapy did not overlap with gefitinib treatment, which made the studies feasible. However, as expected, gefitinib 500 mg was associated with a higher degree of toxicity, as observed in the IDEAL studies, which led to more dose reductions and treatment interruptions. In none of these studies were patients selected based on EGFR expression or any other marker of efficacy, and this lack of patient selection may have caused the lack of positive outcome. In addition, the antagonistic effect of EGFR TKIs may also halt cells in the G_1 phase of their cycle and, therefore, render them insensitive to chemotherapy. Interestingly, however, the time-to-progression curves and survival curves suggest that maintenance EGFR inhibition may be helpful after termination of chemotherapy. These considerations would suggest that sequential therapies are the best approach to this disease for front-line therapy.

The Southwest Oncology Group trial, SWOG0023, was designed to deliver gefitinib after completion of chemoradiotherapy and consolidation chemotherapy, avoiding a potentially negative interaction with chemotherapy. In this randomized, placebo-controlled trial in unresectable stage III NSCLC, gefitinib maintenance therapy failed to show a survival advantage in an unplanned interim analysis; the inferior survival observed in the gefitinib arm raises the possibility of a deleterious effect [68]. The reasons for this result remain unclear. Recently,

Hida *et al.* reported the results of a randomized Phase III trial (WJTOG0203), which evaluated whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in advanced NSCLC (stage IIIb/IV) [17]. In this study, sequential gefitinib following dual platinum-based induction therapy improved PFS (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.57–0.80; $p < 0.001$), with a trend toward improved overall survival ($p = 0.10$). Furthermore, a prespecified subset analysis showed that gefitinib significantly increased overall survival for patients with adenocarcinoma (n = 467; HR: 0.79; 95% CI: 0.65–0.98; $p = 0.03$) and for smokers (n = 410; HR: 0.79; 95% CI: 0.64–0.98; $p = 0.03$). However, gefitinib failed to show a significant survival advantage in patients with nonadenocarcinoma. These results demonstrate a possible clinical benefit for sequential therapy of gefitinib, especially in adenocarcinoma histology. Regarding the maintenance effects, although no benefit with concurrent EGFR TKI was seen in response rate, PFS or OS in the INTACT 2 and Tarceva responses in conjunction with paclitaxel and carboplatin (TRIBUTE) trials, landmark analyses of them favored patients receiving single-agent TKI maintenance therapy after completion of chemotherapy (Table 3) [14,15].

Gefitinib versus best supportive care

In the ISEL study, 1692 patients from 28 countries (not including Japan) were randomized to receive gefitinib 250 mg/day versus placebo [12]. Approximately 20% of the patients included in the study were Asians. Among the subjects, 1129 were assigned to the gefitinib group and 563 to the placebo group. Although the response rate was similar to that observed with erlotinib in BR.21 [8], in the ISEL study, gefitinib failed to prolong survival in comparison with placebo in the overall population. As for the differences in the ISEL and BR.21 patient populations, 90% of the patients in ISEL were chemorefractory, while patients in BR.21 were not required to be refractory to their previous treatment [8,12]. Median survival was 5.6 months for gefitinib and 5.1 months for placebo ($p = 0.08$; HR: 0.89; 95% CI: 0.77–1.02). Among the 812 patients with adenocarcinoma, median survival times were 6.3 and 5.4 months, respectively ($p = 0.09$; HR: 0.84; 0.49–0.92). However, gefitinib prolonged survival in never-smokers (median survival time [MST]: 8.9 vs 6.1 months; $p = 0.012$) as well as in Asian patients (MST: 9.5 vs 5.5 months; $p = 0.01$) in preplanned subset analyses. Based on these results, the FDA limits the indication of gefitinib to cancer patients who are currently benefiting or have previously benefited from gefitinib treatment or are enrolled in clinical trials as of June 2005.

Gefitinib versus chemotherapy in pretreated advanced NSCLC

Recently, the results of two large Phase III studies were reported (INTEREST and V-15-32). The INTEREST trial compared gefitinib with docetaxel as the second- or third-line therapy in 1466 advanced NSCLC patients with prior treatment of platinum-based chemotherapy [18,69]. Noninferiority of gefitinib in OS was demonstrated (MST: 7.6 vs 8.0 months; HR: 1.020; 95% CI: 0.905–1.150). The one point that should be highlighted in this study is that all of the predictors of efficacy identified in the gefitinib versus placebo studies, including adenocarcinoma, women, Asian and never-smoker, disappear in the comparison with the docetaxel group. The results suggest that these clinical characteristics may be efficacy predictors for docetaxel as well as gefitinib. Gefitinib and docetaxel were equally effective as the second-line therapy for advanced NSCLC patients but gefitinib resulted in an improved quality of life and less toxicity compared with docetaxel. Recently, Douillard *et al.* reported that OS was equally improved with both gefitinib or docetaxel treatments in *EGFR* mutation positive patients compared with *EGFR* mutation-negative patients [69]. On the other hand, PFS was longer with gefitinib than docetaxel in mutation-positive patients [69]. In the V-15-32 trial, however, noninferiority of gefitinib was not demonstrated [19]. The V-15-32 trial, almost identical to the INTEREST trial comparing gefitinib with docetaxel, was a comparative study of 489 patients that was conducted in Japan. The response rate in the gefitinib group was approximately twice as high as in the docetaxel group, but it was impossible to demonstrate noninferiority in OS of gefitinib compared with docetaxel. The survival rate at an early stage, such as less than 1 year, and the CI for therapeutic effects indicated that docetaxel was better than gefitinib. While noninferiority in OS between gefitinib and docetaxel was not demonstrated according to predefined criteria, there was no statistically significant difference in survival between the two arms. This discrepancy in survival between the INTEREST and V-15-32 could be attributable to the smaller patient numbers and imbalances in poststudy treatments in the V-15-32 trial (36% in the gefitinib vs 53% in the docetaxel arm had switched over to the opposite treatment after discontinuation of the study treatment). These two studies established the fact that gefitinib is better tolerated than docetaxel with less toxicities and better quality of life. Recently, Lee *et al.* reported the results of randomized Phase III study (Iressa as Second line Therapy in Advanced NSCLC-Korea [ISTANA]) conducted in Korea [70]. They concluded that PFS was longer with gefitinib compared with docetaxel ($p = 0.04$).

Gefitinib versus chemotherapy as first-line therapy in NSCLC

The result of IPASS has been reported [20]. This large-scale randomized study, which compared gefitinib monotherapy with carboplatin/paclitaxel for previously untreated patients with adenocarcinoma who were never- or light-smokers, was started in April 2004. The results showed improved PFS time in the gefitinib arm; however, the HR was constant over time, initially favoring the carboplatin/paclitaxel arm and later favoring the gefitinib arm, indicating the possibility of gefitinib as the first-line therapy in selected patients. Results of this pivotal trial might establish the role of gefitinib as the first-line therapy in selected patients with advanced NSCLC (Table 3).

Randomized trials currently in progress

At present, the West Japan Oncology Group is conducting a multicenter clinical trial (WJTOG3405) that targets progressive/recurrent lung cancer patients with *EGFR* gene mutations

Table 3. Phase III studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Chemotherapy with gefitinib in the first-line treatment of non-small-cell lung cancer							
Giaccone (INTACT-1)	Gem/cis + gefitinib 250 mg	365	51.2	5.8	9.9	Phase III negative trial, corresponding with the TALENT trial	[13]
	Gem/cis + gefitinib 500 mg	365	50.3 (p = NS)	5.5 (p = 0.76)	9.9 (p = 0.46)		
	Gem/cis + placebo	363	47.2	6.0	10.9		
Herbst (INTACT-2)	Pac/carbo + gefitinib 250 mg	345	30.4	5.3	9.8	Phase III negative trial, corresponding with the TRIBUTE trial	[14]
	Pac/carbo + gefitinib 500 mg	347	30.0 (p = NS)	4.6 (p = 0.06)	8.7 (p = 0.64)	Subset analysis of patients with adenocarcinoma who received 90 days' chemotherapy demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect	
	Pac/carbo + placebo	345	28.7	5	9.9		
Kelly (SWOG 0023)	Gefitinib	118	NA	8.3 (p = 0.17)	23 (p = 0.01)	Phase III trial of maintenance therapy after definitive chemoradiation in stage III NSCLC	[68]
	Placebo	125		11.7	35		
Hida (WJTOG0203)	Chemotherapy + gefitinib 250 mg	300	34.2	4.6 (p < 0.001)	13.68 (p = 0.10)	Phase III trial of sequential therapy Superior overall survival time with adenocarcinoma histology in the gefitinib arm (p = 0.03)	[17]
	Chemotherapy alone	298	29.3	4.2	12.89		
Gefitinib versus BSC in the treatment of advanced non-small-cell lung cancer							
Thacher (ISEL)	Gefitinib	1129	8.0 (p < 0.0001)	3.0* (p = 0.0006)	5.6 (p = 0.09)	Survival advantage seen in nonsmoking and Asian patients; MST, p = 0.03 by Cox's analysis	[12]
	Placebo	563	1.0	2.6*	5.1		
Gefitinib compared with chemotherapy in the treatment of advanced non-small-cell lung cancer							
Douillard (INTEREST)	Gefitinib 250 mg	733	9.10 (p = 0.33)	2.2 (p = 0.47)	7.6 (HR: 1.04)	Effect seen across subgroups: favorable toxicity profile with gefitinib; noninferiority of gefitinib demonstrated	[18]
	Docetaxel 75 mg/m²	733	7.6	2.7	8.0		
Maruyama (V-15-32)	Gefitinib 250 mg	245	22.5 (p = 0.009)	2.0 (p = 0.34)	11.5 (p = 0.33)	Favorable toxicity profile with gefitinib; noninferiority of gefitinib not demonstrated	[19]
	Docetaxel 60 mg/m²	244	12.8	2.0	14.0		

*Time to treatment failure.
*Preliminary (37% maturity).
BSC: Best supportive care; Carbo: Carboplatin; Cis: Cisplatin; EGFR: EGF receptor; Gem: Gemcitabine; HR: Hazard ratio; INTACT: IRESSA NSCLC Trial Assessing Combination Treatment; INTEREST: IRESSA Non-Small-Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere; IPASS: IRESSA Pan-Asia study; ISTANA: Iressa as Second line Therapy in Advanced Non-Small Cell Lung Cancer-Korea; ISEL: IRESSA® Survival Evaluation in Lung Cancer; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall respone rate; Pac: Paclitaxel; PFS: Progression-free survival; SWOG: Southwest Oncology Group.

Table 3. Phase III studies of gefitinib.

Author/study	Treatment arms	Number	ORR (%)	PFS (months)	MST (months)	Comments	Ref.
Gefitinib compared with chemotherapy in the treatment of advanced non-small-cell lung cancer							
Lee (ISTANA)	Gefitinib 250 mg	82	28.1 ($p = 0.0007$)	3.3 ($p = 0.04$)	N/A	Second-line chemotherapy previously received platinum-based chemotherapy; PFS was longer with gefitinib arm ($p = 0.04$)	[70]
	Docetaxel 75 mg/m²	79	7.6	3.4	N/A		
Mok (IPASS)	Gefitinib 250 mg	606	43.0 ($p = 0.0001$)	5.7 ($p < 0.0001$)	18.6*	Open-labeled, randomized, Phase III previously untreated patients with adenocarcinoma who are never- or light-smokers; improved PFS in the gefitinib arm; PFS favoured pac/carbo initially and then gefitinib, potentially driven by different outcomes according to EGFR mutation status	[20]
	Pac/carbo	606	32.2	5.8	17.3*		

*Time to treatment failure.
*Preliminary (37% maturity).
BSC: Best supportive care; Carbo: Carboplatin; Cis: Cisplatin; EGFR: EGF receptor; Gem: Gemcitabine; HR: Hazard ratio; INTACT: IRESSA NSCLC Trial Assessing Combination Treatment; INTEREST: IRESSA Non-Small-Cell Lung Cancer Trial Evaluating Response and Survival Against Taxotere; IPASS: IRESSA Pan-Asia study; ISTANA: Iressa as Second line Therapy in Advanced Non-Small Cell Lung Cancer-Korea; ISEL: IRESSA® Survival Evaluation in Lung Cancer; MST: Median survival time; NA: Not available; NS: Not significant; NSCLC: Non-small-cell lung cancer; ORR: Overall response rate; Pac: Paclitaxel; PFS: Progression-free survival; SWOG: Southwest Oncology Group.

assigned randomly to a standard treatment (cisplatin plus docetaxel) or a gefitinib-treatment group. It uses PFS as a primary end point. In addition, the North-East Japan Gefitinib Study Group is carrying out a similar clinical trial that targets stage IIIB/IV lung cancer patients assigned randomly into a carboplatin plus paclitaxel treatment or a gefitinib-treatment group and that also uses PFS as a primary end point. The European Organization for Research and Treatment of Cancer are currently testing a Phase III trial of gefitinib or placebo following first-line chemotherapy (EORTC08021) (Table 4).

EGFR in NSCLC

Clinical trial data suggested that gefitinib was more efficacious in patients who were never smokers, female or had adenocarcinoma histology. Since a different 'targeted therapy' (e.g., trastuzumab) was known to be most effective in patients whose tumors had high levels of expression of that drug's target (HER2), an important question was whether responses to gefitinib correlated with levels of EGFR expression [71]. However, analyses of specimens from gefitinib-sensitive and -refractory tumors using immunohistochemistry (IHC) showed no relationship between tumor sensitivity and EGFR expression levels [72–74]. Negative findings regarding the predictive value of EGFR protein expression using IHC in gefitinib-treated patients raised considerable doubt about the role of IHC techniques in patient selection. Recently, Hirsch *et al.* have demonstrated that EGFR immunostaining with the Dako PharmDx kit according to the percentage of cells with positive staining appears to better predict for survival outcome with gefitinib than Zymed antibody according to staining index [75]. With the discovery of EGFR-activating mutations in tumors from most patients who had EGFR TKI-induced tumor responses, skepticism was soon replaced by enthusiasm for molecular profile research in patients treated with EGFR TKIs. There is increasing evidence that EGFR mutations and high *EGFR* gene copy number are associated with higher response rates and longer survival in patients receiving EGFR TKI therapy.

EGFR mutations

In previous studies that investigated the relationship between *EGFR* gene mutations and sensitivity to EGFR TKIs, objective responses were seen in more than 60% of lung cancer patients, with *EGFR* gene mutations receiving EGFR TKI treatment, whereas objective response was seen in only 10% of patients with no mutations (Table 5) [24,76–80]. The response rate of gefitinib of Western NSCLC patients is approximately 10%, much lower than the response rate 20–30% of East Asian patients. This discrepancy may be due to the EGFR mutations [21]. With mutant *EGFR*, the gefitinib response rate of East Asian patients is approximately 60–80%, but goes down to 0–30% in East Asian patients without mutant *EGFR* [60,81]. *EGFR* mutations are mainly present in the first four exons of the gene encoding the tyrosine kinase domain. Approximately 90% of the EGFR mutations are either small deletions encompassing five amino acids from codons 746 through 750 (ELREA) or missense

mutations resulting in leucine to arginine at codon 858 (L858R) [82]. There are over 20 variant types of deletion, for example, larger deletion, deletion plus point mutation and deletion plus insertion. Approximately 3% of the mutations occur at codon 719, resulting in the substitution of glycine to cysteine, alanine or serine (G719X). Furthermore, approximately 3% are in-frame insertion mutations in exon 20. These four types of mutations seldom occur simultaneously. There are many rare point mutations, some of which occur with L858R. Sensitivity of cancers to EGFR TKI was found to be more than 70% in patients with exon 19 and exon 21 mutations. Variations in response rate may arise from different classes of EGFR mutations. Patients with an exon 19 deletion or L858R showed high response rates of 81 and 71%, respectively. By contrast, only approximately 50% of the patients with G719X responded to EGFR TKIs. There have been few reports on insertion mutations associated with clinical effects of EGFR TKIs (Figure 2) [25,59,83–86]. Many investigators have reported that patients with EGFR mutations have a significantly longer survival than those with wild-type EGFR when treated with EGFR-TKIs. However, this point is still controversial because some investigators indicated that patients with EGFR mutations survived for a longer period than those without EGFR mutations even when treated by chemotherapy [87,88].

Table 4. Randomized trials with gefitinib currently in progress.

Study	Population	Treatment arm	Primary end point
WJTOG3405	First-line chemotherapy with EGFR gene mutation	Gefitinib vs cisplatin + docetaxel	PFS
NEJGSG	First-line chemotherapy with EGFR gene mutation	Gefitinib vs carboplatin + paclitaxel	PFS
NCIC BR.19	First-line maintenance after complete resection of stage I-IIIA NSCLC ± adjuvant chemotherapy	Gefitinib vs placebo	OS
EORTC08021	First-line maintenance for advanced NSCLC in patients without disease progression after chemotherapy	Gefitinib vs placebo	OS

EGFR: EGF receptor; NCIC: National Cancer Institute of Canada; NEJGSG: North-East Japan Gefitinib Study Group; NSCLC: Non-small-cell lung cancer; OS: Overall survival; PFS: Progression-free survival; WJTOG: West Japan Thoracic Oncology Group.

EGFR secondary mutations & resistance against EGFR TKIs

Another major issue is that nearly all patients who respond initially to EGFR TKIs later develop drug resistance (Figure 3). The effective period of EGFR TKI varies from 2–4 months to more than 2 years. It has been reported that, in some patients with such acquired resistance, in addition to the original deletion and L858R mutations that elevate sensitivity to EGFR TKIs, an extra secondary mutation occurs with the threonine at codon 790 being changed to a methionine (T790M) [89]. Tumors with T790M are highly resistant to reversible TKIs, such as gefitinib or erlotinib. However, the T790M mutant kinase remains sensitive to irreversible inhibitors, including CL-387,785, EKB-569, and HKI-272 [89–93]. Although the substitution in EGFR with a bulky methionine has been thought to cause resistance by steric interference with binding of TKIs, including gefitinib and erlotinib, Yun *et al.* have reported that the T790M mutation is a 'generic' resistance mutation that will reduce the potency of any ATP-competitive kinase inhibitor (T790M substitution confers resistance by increasing the affinity for ATP) and that irreversible inhibitors overcome this resistance simply through covalent binding, not as a result of an alternative binding mode [94]. Recently, Engelman *et al.* reported that amplification of the *MET* gene is another mechanism of acquired resistance to EGFR TKIs [95,96]. With the use of a 1000-times resistant cell line, HCC827GR, established by exposing it to increasing concentrations of gefitinib, the authors found that phosphorylated forms of MET, ERBB3 and EGFR remain after gefitinib treatment and that the *MET* gene is amplified. Inhibition of *MET* signaling restored the cells' sensitivity to gefitinib. *MET* amplification was also detected in four of 18 (22%) clinical specimens

Table 5. *EGFR* mutations versus wild-type *EGFR* related to response rate, progression-free survival and overall survival in patients treated with gefitinib.

Study	Patients (n)	Mutation (%)	Response rate (mutation/wild-type; %)	PFS (mutation/ wild-type; months)	OS (mutation/ wild-type; months)	Ref.
Cappuzzo *et al.*	89	19	54/5	9.9/2.6	20.4/8.4	[24]
Cortez-Funes *et al.*	83	12	60/9	12.3/3.6	13.0/4.9	[76]
Han *et al.*	90	19	65/14	21.7/1.8	30.5/6.6	[77]
Takano *et al.*	66	59	82/11	12.6/1.7	20.4/6.9	[78]
Mitsudomi *et al.*	59	56	83/10			[79]
Taron *et al.*	68	25	94/13		–/9.9	[80]

OS: Overall survival; PFS: Progression-free survival.

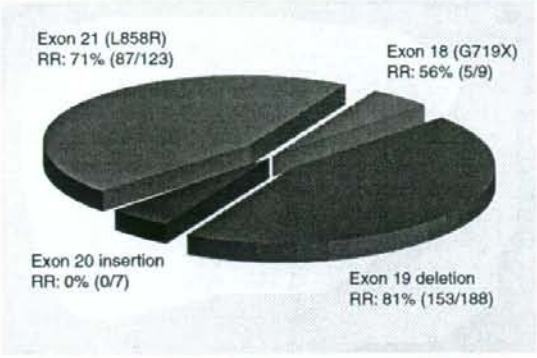

Figure 2. Distribution of EGF receptor mutations and response rates to EGF receptor tyrosine kinase inhibitors.
RR: Response rate.

from patients who had developed resistance to EGFR TKIs. In some specimens, *MET* amplification can occur concurrently with T790M.

EGFR mutation & amplification

There is increasing evidence that *EGFR* mutations and high *EGFR* gene copy number are associated with higher response rates to TKIs and longer survival. Both mutation and amplification of EGFR in lung cancers have been reported in association with clinical responses to TKIs. The *EGFR* locus can undergo both mutation and amplification. Yatabe *et al.* examined the topographical distribution of amplification in three microdissected portions each of 48 individual lung cancers with confirmed mutations [97]. Gene amplification was found in 11 lung cancers. Strikingly, nine of the cancers showed heterogeneous distribution, and amplification was associated with higher histologic grade or invasive growth. They also examined 17 precursor lesions and 21 *in situ* lung adenocarcinomas and found that only one *in situ* carcinoma harbored gene amplification. Taken together, their results show that mutation occurs early in the development of lung adenocarcinoma, and that amplification may be acquired in association with tumor progression. In general, tumors with EGFR mutations tend to have gene amplification. Mutation and amplification are probably both important in determining EGFR 0TKI sensitivity. The FISH scoring system, generated by the Colorado group, stratifies results into six groups by number of copies of the *EGFR* gene and frequency of tumor cells in the sample. These groups include disomy, low trisomy, high trisomy, low polysomy, high polysomy and gene amplification, with high polysomy or gene amplification being considered FISH positive [98,99]. However, the role of high polysomy is unclear.

KRAS mutation

Activating mutation of the *KRAS* gene was one of the earliest discoveries of genetic alterations in lung cancer known as a poor prognostic indicator. It was reported that the occurrence of *EGFR* and *KRAS* mutations are strictly mutually exclusive [100,101]. This finding can be explained by the fact that the KRAS–MAPK pathway is one of the downstream signaling pathways of EGFR. *KRAS* mutations predominantly occur in Caucasian patients with a history of smoking. Pao *et al.* reported that lung cancers with *KRAS* mutations are resistant to EGFR TKIs [102].

Postmarketing surveillance

It was shown that erlotinib, another EGFR TKI, extended the median survival time in the BR.21 trial [8]. In the BR.21 study, patients with NSCLC, after failure of first- or second-line chemotherapy, were randomized to receive erlotinib 150 mg/day or placebo (2:1, respectively). Statistically significant differences were observed for OS (6.7 vs 4.7 months; HR: 0.70; $p < 0.001$) and PFS (2.2 vs 1.8 months; HR: 0.61; $p < 0.001$) in favor of erlotinib. These results led to regulatory approval of erlotinib for NSCLC refractory to chemotherapy. However, gefitinib failed to prolong survival in comparison with placebo in the overall population in the ISEL study, possibly due to the refractory, difficult-to-treat nature of the population [12]. Based on the lack of improvement in survival in response to gefitinib, the FDA has restricted the labeling of gefitinib. Both gefitinib and erlotinib are currently available and are used to treat patients with advanced or metastatic NSCLC in the second- or third-line setting or, sometimes, in the first-line setting for selected patients. Most patients treated with these agents, however, had progressive disease even after showing an initial dramatic response. Among the mechanism of acquired resistance to EGFR TKIs, T790M secondary mutation or amplification of the *MET* oncogene was reported frequently [89,95,96]. However, other secondary mutations have also been reported. Of note, unlike T790M secondary mutation, some mutations, such as E884K or L747S mutations, may result in different sensitivities to gefitinib and erlotinib, resulting in different tumor responses to these two agents. Choong *et al.* reported a case of erlotinib-refractory adenocarcinoma with leptomeningeal metastases that had a L858R+ E884K somatic mutation of the *EGFR* [103]. Gefitinib responded to erlotinib-refractory lung cancer, showing a differential response between erlotinib and gefitinib that was mediated by the *EGFR* mutation E884K. On the other hand, Costa *et al.* reported a case of differential response to erlotinib in *EGFR*-mutated lung cancers with acquired resistance to gefitinib carrying the L747S secondary mutation [104]. Therefore, although half of patients could overcome the resistant T790M secondary mutation by empirical use of irreversible new EGFR TKIs [90], identification of the mechanism of acquired resistance in each patient could guide the proper use of these two different EGFR TKIs.

Safety & tolerability

Compared with conventional chemotherapeutic agents, gefitinib produces relatively few severe side effects, such as hematotoxicity. Gefitinib is generally well tolerated, even in elderly patients or patients with poor performance status. The principal side effects of gefitinib are skin rash, acniform changes of the skin, diarrhea, nausea, vomiting and anorexia. Diarrhea was actually the dose-limiting toxicity in Phase I studies. Most toxicities

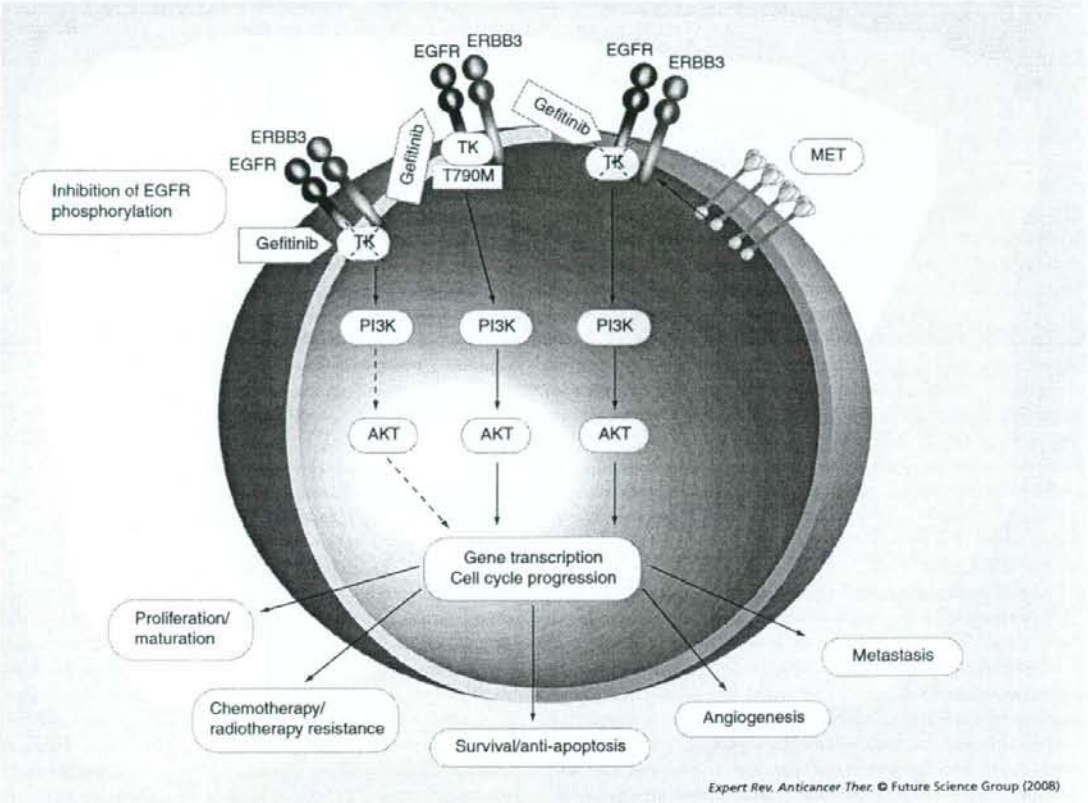

Figure 3. Mechanism of action of gefitinib signal-transduction blockage through EGFR TK and mechanisms of acquired resistance to gefitinib. When gefitinib is administered, EGFR TK is specifically inhibited and the survival signal is blocked leading to apoptosis of cancer cells. When a secondary threonine-to-methionine mutation at codon 790 of the *EGFR* gene (T790M) is acquired, T790M prevents gefitinib from binding EGFR TK. Alternatively, when *MET* is activated by amplification, ERBB3 is phosphorylated by *MET*. Even when EGFR TK is inhibited by gefitinib, activation of the PI3K/AKT pathway is maintained through ERBB3 phosphorylation [113]. EGFR: EGF receptor; TK: Tyrosine kinase.

are common toxicity criteria grade 1 or 2. Interstitial lung disease has been observed in patients receiving gefitinib [105,106]. Worldwide, the incidence of interstitial lung disease is approximately 1% (2% in the Japanese postmarketing experience and ~0.3% in a US expanded-access program), with approximately a third of the cases being fatal. Retrospective studies on the incidence of interstitial lung disease (ILD) and prospective studies involving 3000 subjects were conducted in Japan. The risk factors of ILD have been identified as male gender, prior history of smoking and pre-existing ILD. In addition, a case–cohort study that involved the identification of cohorts among patients receiving treatment for NSCLC to determine their relative risks was conducted [107]. For this study, 4423 subjects were included in the analysis as a cohort. Among them, 122 patients were identified with ILD. The results suggest that, regardless of patients' background, administration of gefitinib carries a 3.23-fold risk of ILD compared with conventional chemotherapeutic agents. The risk factors for ILD incidence do not apply to women, adenocarcinoma patients or nonsmokers – patient groups who are more likely to benefit from gefitinib treatment. In clinical practice, it may be possible to use such risk factors as a reference for selecting appropriate patients for gefitinib treatment to reduce the incidence of ILD. Interestingly, the issue of ILD in patients with NSCLC, after gefitinib or other treatments, appears to be a problem largely limited to Japan. From the AstraZeneca Global Drug Safety Database, the reporting rate of ILD-type events in patients receiving treatment with gefitinib was only 0.23% worldwide, excluding Japan, based on more than 275,000 patients worldwide estimated to have been exposed to gefitinib. Even for neighboring countries, the pattern differs from Japan: the rate for East Asian countries, including Korea and Taiwan, but excluding Japan, was 0.17%.