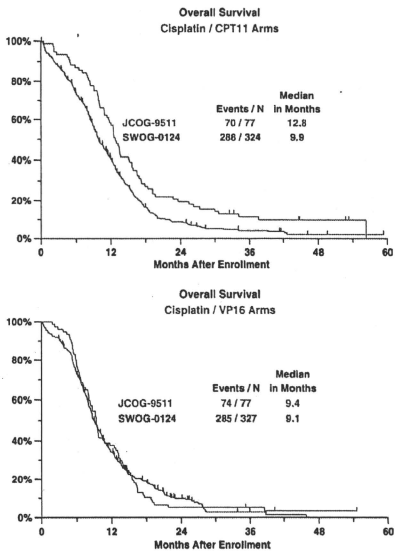

Figure 1. (*Top*) Overall survival analysis by trial is shown for the cisplatin and irinotecan (CPT-11) treatment arm. (*Bottom*) Overall survival analysis is shown for the cisplatin and etoposide (VP16) treatment arm. JCOG-9511 indicates Japan Clinical Oncology Group 9511 trial; SWOG-0124, Southwest Oncology Group 0124 trial.

between patient populations. Although a preliminary pharmacogenomic analysis of specimens from 0124 patients was performed to investigate some of these irinotecan-related genes, no specimens were available from the older 9511 trial for similar pharmacogenomic investigations. Hence, no direct comparison of relevant genotypes between trials is possible. However, insights on this issue can be derived from prior common arm joint collaborations between Southwest Oncology Group and Japanese investigators wherein patients with advanced nonsmall cell lung cancer were enrolled in Southwest Oncology Group and Japanese trials onto a common arm of paclitaxel and carboplatin.[11] In that experience, genes relevant to chemotherapy metabolism and transport were analyzed in both American and Japanese populations. Significant differences in toxicity, efficacy, and allelic distribution for genes involved in paclitaxel disposition or DNA repair were observed between Japanese and US patients, supporting the hypothesis that pharmacogenomics may in part be responsible for outcome divergence among patient populations. This may also partly explain the toxicity differences seen between the Japanese and North American populations, wherein Japanese patients apparently had increased hematologic toxicity (neutropenia, leucopenia, and anemia) in both treatment arms when compared with North Americans.

In addition, there appears to be some differences in the delivered DI in the cisplatin/irinotecan arms of both trials (as reported in the published papers). Specifically, more 9511 patients achieved a higher DI for both irinotecan and cisplatin as compared with 0124 patients. Enhanced DI for 9511 patients may potentially explain the differences in toxicity and efficacy between the trials. A more detailed and expansive analysis of dose delivery using individual patient data is required, but is beyond the scope of this article. Finally, it must be noted that other trials comparing similar chemotherapy regimens in SCLC have previously been published.[12,13] Some of us (P.N.L., R.N., and D.R.G.) have previously discussed these trials in the context of 0124 and 9511 in a recent editorial.[14] We refer readers to that editorial for additional details.

In conclusion, etoposide/cisplatin remains the reference treatment standard in North America. In Japan, cisplatin/irinotecan remains a standard treatment option. Significant differences in patient demographics, toxicity, and efficacy exist between Japanese and North American SCLC patients receiving identical treatment. These results, relevant in the current era of clinical trials globalization, warrant 1) consideration of differential patient characteristics and outcomes among patients receiving identical therapy, 2) utilization of the common arm model in prospective trials, and 3) inclusion of pharmacogenomic correlates in cancer trials where ethnic/racial differences in drug disposition are expected.

CONFLICT OF INTEREST DISCLOSURES

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INTERNAL MEDICINE

□ REVIEW ARTICLE □

Recent Development of Molecular-Targeted Drugs in Lung Cancer

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Abstract

Numerous molecular target drugs have been introduced for the treatment of advanced malignancies. In the treatment of lung cancer, epidermoid growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) demonstrate striking antitumor activity in selected EGFR mutation positive patients. Patient selection by biomarker is extremely important to obtain successful results. The anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, shows a markedly increased response rate, progression free survival of advanced non-squamous cell lung cancer when combined with cytotoxic drugs. The classification of lung cancer is rapidly changing based on the advances in molecular biology. Here, the recent development of new molecular target drugs against lung cancer is thoroughly reviewed in addition to EGFR-TKIs and bevacizumab with special emphasis on the clinical application.

Key words: molecular target drugs, lung cancer, EGFR-TKI, VEGF, angiogenesis

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Introduction

In recent years, the understanding of cancer at the molecular level has progressed, and numerous genes and proteins which play important roles in the growth, invasion and metastasis of tumors have been identified. Furthermore, by setting these genes and proteins as the targets, small molecular weight drugs called signal transduction inhibitors (e.g., tyrosine kinase inhibitors), monoclonal antibodies, etc., have been developed for the treatment of cancer(s). Numerous molecular-targeted drugs have been developed, including epidermal growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) antibodies, etc, have also been developed for the treatment of non-small cell lung cancer (NSCLC), and a number of clinical studies on these new drugs have been conducted towards the goal of their clinical application.

1. Treatment targeted at EGFR

EGFR is a transmembrane-type receptor protein composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. When a growth factor binds to this receptor, a dimer is formed and the downstream signal transduction system is activated, resulting in cancer cell proliferation, metastasis, vascularization and apotosis, etc (1-3).

Excessive EGFR expression has been reported to be detected in 32-81% of all cases of NSCLC (4-6). Two therapeutic strategies designed to inhibit the EGFR signal transduction system have been developed. One is to use EGFR tyrosine kinase inhibitors (EGFR-TKIs) which are low molecular weight compounds that bind to the ATP-binding site of intracellular tyrosine kinase, inhibiting the self-phosphorylation of EGFR. The other strategy is to use monoclonal antibodies that bind specifically to the extracellular domain of EGFR, thereby inhibiting ligand binding to EGFR.

1) EGFR tyrosine kinase inhibitors

a. Gefitinib

The results of randomized phase II clinical studies of gefitinib in previously treated cases of NSCLC were reported in 2002. In the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL)-1 study, carried out primarily in Europe and Japan, the response rate was 18.4% in the 250 mg/day

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group and 19.0% in the 500 mg/day group (7). Also in IDEAL-2, carried out in the USA, the response rates were almost the same between the 250 mg/day group (11.8%) and the 500 mg/day group (8.8%), and there was no difference in the survival period between the two dose groups (8). Toxicity was lower in the 250 mg/day group than in the 500 mg/day group, and the dose level of 250 mg/day was adopted as the recommended dose level. In a subgroup analysis, the response rate was significantly higher in females, patients with adenocarcinoma, and Japanese patients. On the basis of these results, the Japanese regulatory authority approved the use of gefitinib in 2002, earlier than in other countries around the world.

The Iressa Survival Evaluation in Advanced Lung Cancer (ISEL) was a large-scale phase III clinical study in which 1,692 previously treated patients with NSCLC were randomly allocated to the gefitinib and the placebo group. The results revealed that the response rate was significantly higher in the gefitinib group than in the placebo group (8% vs. 1%, p<0.0001). Of the primary endpoints, the median survival time (MST) and one-year survival rate were 5.1 months and 21%, respectively, in the placebo group and 5.6 months and 27% in the gefitinib group, respectively, with no significant difference between the two groups (p=0.087) (9). In the subgroup analysis, however, gefitinib was shown to extend the survival in non-smokers (MST: 8.9 months vs. 6.1 months, p=0.012) and Asian patients (MST: 9.5 months vs. 5.5 months, p=0.01). A randomized phase III clinical study (V-15-32) aimed at confirming the non-inferiority of gefitinib to docetaxel (DOC) was carried out in Japan, involving 490 previously treated patients with NSCLC. The response rate was significantly higher in the gefitinib group (22.5%) than in the DOC group (12.8%) (p=0.009). The median progression-free survival (mPFS) was 2.0 months in both groups. The MST (a primary endpoint) was 14.0 and 11.5 months in the two groups, respectively. The hazard ratio (HR) was 1.12 (95% confidence interval [CI]: 0.89-1.40). Thus, the study did not demonstrate non-inferiority of gefitinib to DOC (10). In addition, a report was published of a randomized phase III clinical study (INTEREST) carried out in 24 countries (Europe, USA and Asia), comparing gefitinib with DOC in 1,433 previously treated patients with NSCLC. In that study, the response rate did not differ significantly between the gefitinib group (9.1%) and the DOC group (7.6%) (p=0.33), and there was no significant difference in the mPFS either between the gefitinib group (2.2 months) and the DOC group (2.7 months) (p=0.47). In the analysis of the overall survival period, the primary endpoint, the HR was 1.020 (95%CI: 0.905-1.150) and did not exceed the preset upper limit (1.154), thus endorsing the non-inferiority of gefitinib to DOC (11). In the evaluation of toxicity, the gefitinib group most frequently developed skin eruptions and diarrhea, while the DOC group most frequently developed decreased blood neutrophil count, myasthenia, and alopecia. In 2008, interesting results were reported from a phase III clinical study (Iressa Pan Asia Study: IPASS) comparing gefitinib therapy with carboplatin (CBDCA) + paclitaxel (PTX) therapy, each administered as the initial therapy (to be described in detail later) (12). Furthermore, a randomized phase III clinical study (WJTOG 0203) was carried out in Japan, comparing platinum-based chemotherapy (3-6 cycles) with platinum-based chemotherapy (3 cycles) + sequential gefitinib therapy in 598 previously untreated patients with NSCLC. In that study, mPFS was significantly longer in the sequential therapy group (4.60 months) than in the platinum-based chemotherapy alone group (4.27 months) (p<0.001), while the overall survival period (a primary endpoint) did not differ significantly between the two groups (MST: 12.89 months vs. 13.68 months, p=0.10). In a subset analysis, the overall survival period of adenocarcinoma patients was extended by the sequential therapy (MST: 14.33 months vs. 15.42 months, p=0.03) (13). In a randomized phase II clinical study in which 97 previously untreated patients with NSCLC were divided into two groups, one group receiving oral gefitinib therapy after 4 cycles of CBDCA + PTX therapy until exacerbation of the condition and the other receiving oral gefitinib therapy (until exacerbation of the condition) followed by 4 subsequent cycles of CBDCA + PTX therapy, the overall survival period (a primary endpoint) differed little between the two groups (MST: 18.8 months vs. 17.2 months) (14).

b. Erlotinib

In a phase II clinical study of erlotinib monotherapy involving 57 previously treated patients of NSCLC showing positive immunostaining of the tumor cells for EGFR, the response rate was 12.3% and the MST was 8.4 months (5). In this study, the results suggested that the overall survival period was probably correlated with the incidence and severity of skin eruptions (15).

In sharp contrast to the findings of the above-mentioned studies on gefitinib were the results obtained in a phase III clinical study comparing erlotinib with BSC. In this phase III comparative study (BR.21) carried out by the National Cancer Institute of Canada Clinical Trial Group (NCIC), 731 previously treated patients with NSCLC were allocated randomly to the erlotinib group and the placebo group at a ratio of 2:1. In analysis of the primary endpoints, erlotinib was significantly superior in terms of both the overall survival (MST: 6.7 months in the erlotinib group vs. 4.7 months in the placebo group, p<0.001) and the progression-free survival (2.2 months in the erlotinib group vs. 1.8 months in the placebo group, p<0.001) (16). On the basis of the results of this study, erlotinib was adopted as one of the standard therapies for previously treated cases of NSCLC. Following publication of the results of this study, erlotinib was approved in 2004 in the USA and in 2007 in Japan. Regarding the discrepancy of the results between ISEL and BR.21, the influence of pharmacological differences has been pointed out; such as the difference in the dose level (erlotinib dose level equal to the MTD and gefitinib dose level equivalent to about 1/3 of the MTD) and the difference in the affinity for EGFR (17). In addition, a phase IV clini-

Table 1. Phase II Study of EGFR- TKI in EGFR Mutation (+) Patients

	n	EGFR-TKI	RR (%)	mPFS (M)	MST (M)
Morita S (I-CAMP)	148	gefitinib	76.4	9.7	24.3
Sirera R	193	erlotinib	70.8	12.0	22.0
Sequist LV	34	gefitinib	55	9.2	17.5

EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

RR: Response Rate

mPFS: median Progression-Free Survival

MST : Median Survival Time

M: Month

cal study (TRUST) was carried out on erlotinib monotherapy for NSLCLC. In an analysis of the interim results of this study covering 6,809 patients, the response rate was 13% and mPFS was 3.5 months, close to the results obtained in the BR.21 study (18). At a meeting of ASCO in 2009, the results of a phase III clinical study (SATURN) comparing maintenance erlotinib therapy with placebo were reported, demonstrating the superiority of erlotinib in terms of the PFS as a primary endpoint (19). At present, clinical studies such as a phase III clinical study of erlotinib with chemotherapy of pemetrexed (PEM) or DOC as secondary chemotherapy and a phase III clinical study (RADIANT) comparing erlotinib with placebo as postoperative adjuvant therapy are ongoing. Interesting results from these studies are expected.

2) Predictors of responses to EGFR-TKI

EGFR gene mutations are reported as the most important factor predictive of the responses of NSCLC to EGFR-TKI (20-22). More than forty mutations of the EGFR gene in exon 18-21 of the tyrosine kinase domain have been reported. Among others, deletion of 5 amino acids in exon 19 and the L858R point mutation of exon 21 are reported to account for more than 80% of all mutations of the EGFR gene (3, 23). EGFR gene mutations have also been reported to be correlated with clinical factors associated with a high sensitivity to EGFR-TKI, such as adenocarcinoma, female gender, non-smoker and Asian race (20, 24, 25). In addition, the results of a phase II clinical study of EGFR-TKI in patients carrying EGFR gene mutations have been reported (Table 1) (26-28). In 2008, the results of an integrated analysis of the results of 7 Japanese phase II clinical studies of gefitinib (I-CAMP) were reported. In that analysis, EGFR-TKI therapy yielded excellent outcomes in 148 patients carrying gene mutations, with a response rate of 76.4%, mPFS of 9.7 months, and MST of 24.3 months (26). The responses of the gene mutation-positive cases to this therapy were also favorable in other studies, suggesting that the presence of EGFR gene mutation serves not only as a predictor of the response to treatment, but also as a prognostic factor (29).

There are also reports on the usefulness of the number of EGFR gene copies, evaluated by fluorescence *in situ* hybridization (FISH), as a predictor of the response to treatment (30-32). In an evaluation of patients registered with the BR.21 study, amplification of gene copies was significantly correlated with the response rate to erlotinib, whereas the presence of gene mutation was not correlated with the response rate (33). In a similar analysis of cases registered with the ISEL study, patients with gene copy amplification tended to have a longer survival period following gefitinib therapy, although the difference was not statistically significant (p=0.07). In that analysis, it was not possible to evaluate the correlation of the presence of gene mutations with survival, because the number of gene mutation-positive cases was not sufficiently large (34). In Western countries, the number of gene copies is often used as a predictor of response to treatment, because the frequency of gene mutations is low.

KRAS gene mutation is seen in 20-40% of cases of NSCLC and has been reported to serve as a predictor of a poor response to EGFR-TKI and chemotherapy (35, 36) but to date there is not sufficient evidence.

3) EGFR-TKI as a means of primary treatment

a. EGFR-TKI monotherapy

The results of a phase II clinical study on gefitinib conducted on previously untreated patients with NSCLC in National Cancer Center Hospital East have been reported. Of the 40 patients eligible for the study, 40% were female, 75% had adenocarcinoma and 20% were non-smokers. The response rate was 30%, MST was 13.9 months, and the one-year survival rate was 55%. However, death from acute lung disorders as an adverse event occurred in 10% of all patients (37). EGFR-TKI monotherapy also did not yield promising results in other phase II studies which did not incorporate careful patient selection (38). In addition, the results of phase II studies of the efficacy of initial treatment with EGFR-TKIs incorporating patient selection have also been reported. In a phase II study of gefitinib in 36 non-smokers with adenocarcinoma, the response rate was as high as 69%. The mPFS was 8.3 months and the estimated one-year survival rate was 73%, representing more favorable results as compared to the results of previously reported studies on standard chemotherapy (39). Furthermore, a phase II study on gefinitib as the initial chemotherapy was carried

Table 2. Randomized Controlled Trial of EGFR-TKI vs Platinum Doublet in EGFR Mutation(+) Patients

Trial	n	EGFR-TKI	Chemotherapy	Primary Endpoint	Results
NEJ002	320	gefitinib	CBDCA + PTX	PFS	Positive
WJOG3405	200	gefitinib	CDDP + DOC	PFS	Positive
EURTAC	146	erlotinib	platinum-doublet *	PFS	On going
ML20981	150	erlotinib	CBDCA + GEM	PFS	On going

*GEM + CDDP, DOC + CDDP, GEM + CBDCA, DOC + CBDCA

EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

PFS: Progression-Free Survival

CBDCA: Carboplatin

PTX: Paclitaxel

CDDP: Cisplatin

DOC: Docetaxel

GEM: Gemcitabine

out in Japan, in 30 patients with NSCLC satisfying one of the following requirements: 1) EGFR gene mutation-positive elderly patients; and 2) patients with poor performance status (PS) who were not candidates for standard chemotherapy. In that study, the outcome was excellent, with a response rate of 66% and MST of 17.8 months, and number of treatment-associated deaths was zero (40).

A phase III study (Iressa Pan Asia Study: IPASS) was carried out in 10 East Asian countries including Japan to compare gefitinib therapy with carboplatin (CBDCA) + paclitaxel (PTX) therapy as the first-line treatment in patients with clinical factors (adenocarcinoma; non-smoker or light smoker) possibly associated with a high sensitivity to EGFR-TKIs. In this study, 1,217 patients were allocated randomly into two groups, and the response rate was significantly higher in the gefitinib group (43.0%) than in the CBDCA + PTX group (32.2%) (p=0.0001). In the analysis of the PFS (the primary endpoint), the HR was 0.741 (95% CI: 0.651-0.845, p<0.0001) and the outcome was significantly better in the gefitinib group. However, since the survival curves for the two groups crossed each other, the interpretation of the data was controversial. When the patients of this study were divided according to the presence/absence of EGFR gene mutation, the crossing of the survival curves disappeared, and the PFS was significantly longer in the gene mutation-positive group. Data on the patient overall survival in this study have not yet been reported because they are still premature (12). At present, four phase III studies comparing EGFR-TKIs with standard chemotherapy in EGFR gene mutation-positive patients are under way and preliminary results of two studies have been reported (Table 2) (41, 42). EGFR-TKIs are now viewed as useful alternatives for first-line chemotherapy in EGFR gene mutation-positive patients with NSCLC, although they have not been demonstrated to be superior to platinum-based therapy in overall survival.

b. Combined EGFR-TKI + chemotherapy

In regard to studies conducted to evaluate the significance of combining EGFR-TKI with chemotherapy, the Iressa NSCLC Trial Assessing Combination Therapy (INTACT)-1 (43) and INTACT-2 (44) have been carried out using gefitinib as the EGFR-TKI. These studies, however, failed to endorse the significance of administering gefitinib in combination with chemotherapy. Similarly, phase III studies of erlotinib administered in combination with chemotherapy have been carried out, however, no enhancement of the efficacy with the use of erlotinib in combination with chemotherapy was demonstrated in either the Tarceva Lung Cancer Investigation (TALENT) study (45) or the Tarceva Responses in Conjunction with Taxol and Carboplatin (TRIBUTE) study (46) (Table 3). However, subgroup analysis of the data from the TRIBUTE study revealed a significant extension of the survival period in non-smokers following the addition of erlotinib to the chemotherapeutic regimen (MST: 22.5 months vs. 10.1 months, p=0.01). Therefore, it would seem valuable to conduct similar studies on appropriately selected patients for further evaluation.

4) Toxicity of EGFR-TKIs

The major toxicities of EGFR-TKIs are skin disorders (eruption, dry skin, pruritus, etc.), diarrhea, and liver dysfunction. Interstitial lung disease (ILD) is a toxicity that needs the greatest attention. The incidence of this adverse reaction is reported to be about 3.5-5% and some of the risk factors for its onset are advanced age, male gender, poor PS, positive smoking history and the presence of underlying interstitial disease (47, 48). When EGFR-TKIs are used, it is essential to take into account the risk of onset of ILD.

5) Second-generation EGFR-TKIs

Recurrence of disease occasionally takes place within about 12 months after successful treatment with EGFR-TKIs (gefitinib, erlotinib, etc.) even in gene mutation-positive cases (49). This has been explained by the development of tumor resistance to EGFR-TKIs through the development of secondary EGFR gene mutations such as mutation of T790

Table 3. Randomized Phase III Trial of Platinum Doublet ± EGFR-TKI

Trials	n		Response Rat (%)	TTP (M)	MST (M)	p Value
INTACT-1	1,093	GP + gefitinib (500mg)	49.7	5.5	9.9	NS
		GP + gefitinib (250mg)	50.3	5.8	9.9	
		GP + placebo	44.8	6.0	10.9	
INTACT-2	1,037	PC + gefitinib (500mg)	30.0	4.6	8.7	NS
		PC + gefitinib (250mg)	30.4	5.3	9.8	
		PC + placebo	28.7	5.0	9.9	
TRIBUTE	1,059	PC + erlotinib (150mg)	21.5	5.1	10.6	NS
		PC + placebo	19.3	4.9	10.5	
TALENT	1,172	GP + erlotinib (150mg)	31.5	5.9	10.8	NS
		GP + placebo	29.9	6.2	11.0	

GP : GEM + CDDP, PC : PTX + CBDCA

EGFR-TKI: Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor

TTP: Time To Progression

MST: Median Survival Time

M: Month

NS: Not Significant

GEM: Gemcitabine

CDDP: Cisplatin

PTX: Paclitaxel

CBDCA: Carboplatin

M (50, 51). For the treatment of such resistant cases, an irreversible EGFR inhibitor has been developed and clinical trials are now under way (52).

6) Anti-EGFR antibodies

Antibodies directed against EGFR that are used for therapy include cetuximab (a chimeric IgG1 antibody), matuzumab (a humanized IgG1 antibody), panitumumab (a completely humanized IgG2 antibody), etc. Clinical trials of these agents are now under way in patients with various cancers.

a. Cetuximab

A phase II clinical study of cetuximab monotherapy in previously treated cases of NSCLC yielded a response rate of 4.5%. Toxicity was mild, but skin eruptions were seen in about 90% of all patients (grade 3/4 in 6.1%) (53).

A randomized phase II clinical study designed to evaluate the effects of the addition of cetuximab to CDDP + vinorelbine (VNR) therapy in 86 previously treated cases of NSCLC has been reported. The response rate, mPFS and MST were 35%, 5.0 months and 8.3 months, respectively, in the CDDP + VNR + cetuximab group, while they are 28%, 4.6 months and 7.3 months, respectively, in the CDDP + VNR group (54). In another randomized phase II clinical study (SWOG 0342) comparing a synchronous combined therapy (4 cycles of CBDCA + PTX therapy and simultaneously started cetuximab therapy for one-year) with a sequential combined therapy group (start of cetuximab therapy after completion of 4 cycles of CBDCA + PTX therapy), the response rate tended to be higher in the synchronous combined therapy group (34% vs. 31%), while a PFS of 4 months and MST of 11 months was obtained in both groups (55).

A randomized phase III clinical study (BMS 099) was carried out to compare CBDCA + taxane (PTX or DOC) therapy with CBDCA + taxane + cetuximab therapy in 676 previously untreated patients with NSCLC. The response rate was 17.2% in the CBDCA + taxane group and 25.7% in the CBDCA + taxane + cetuximab group, while no significant difference was noted in the primary endpoint, that is, PFS between the two groups (4.24 months vs. 4.40 months, p=0.2358) (56). Furthermore, a randomized phase III clinical study (FLEX) was carried out to compare CDDP + VNR therapy with CDDP + VNR + cetuximab therapy in 1,125 previously untreated patients with NSCLC showing positive EGFR expression. The response rate was significantly higher in the CDDP + VNR + cetuximab group (36%) than in the CDDP + VNR group (29%) (p=0.010). No significant difference in the PFS was observed between the two groups (mPFS: 4.8 months in both groups), however, the MST (a primary endpoint) was extended in the group additionally receiving cetuximab (10.1 months vs. 11.3 months, p=0.044) (57). In a subgroup analysis in the same study, the survival of Asian patients was poorer in the CDDP + VNR + cetuximab group (20.4 months vs. 17.6 months), probably because of the influence of EGFR-TKIs used for second-line and subsequent treatment.

Higher efficacy was obtained when cetuximab, an anti-EGFR antibody, was used in combination with chemotherapy than when it was used alone, unlike the findings ob-

Table 4. Clinical Trials of Cetuximab

Investigator	No of cases	Regimen	Response Rate (%)	PFS (M)	MST (M)	IHC
Rosell	44	CDDP + VNR	28	4.2	7.0	+
	43	CDDP + VNR + C225	35	4.8	8.3	+
Butts	66	Plat + GEM	18	4.2	9.3	—
	65	Plat + GEM + C225	28	5.1	12.0	—
Herbst	106	CBDCA + PTX + C225	34	4.0	11.0	—
	117	CBDCA + PTX⇒C225	31	4.0	11.0	—
Lynch	338	CBDCA + taxane	17	4.2	—	—
	338	CBDCA + taxane + C225	26	4.4	—	—
Pirker	568	CDDP + VNR	29	4.8	10.1	+
	557	CDDP + VNR + C225	36	4.8	11.3	+

PFS: Progression-Free Survival
MST: Median Survival Time
IHC : Immunohistochemistry
M : Month
CDDP: Cisplatin
PTX: Paclitaxel

tained for EGFR-TKIs (Table 4). A phase III clinical study designed to evaluate the effects of the addition of cetuximab to second-line chemotherapy (PEM or DOC) is now underway (58).

2. Anti-VEGF antibodies

1) Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is not only involved in neovascularization, but also enhances the vascular permeability (59). Bevacizumab binds to VEGF to inhibit the binding of VEGF to VEGF-R, thereby also inhibiting vascularization. In addition, this drug reduces the interstitial pressure within tumor cells through normalizing tumor vessels, possibly leading to improved delivery of cytotoxic anticancer agents to tumor cells and manifestation of synergistic effects when this antibody is used in combination with chemotherapy (60).

The Eastern Cooperative Oncology Group (EOCG) carried out a randomized phase II clinical study to compare three groups of patients with advanced or recurrent NSCLC, i.e., the CBDCA + PTX (CP) therapy group (control arm), the CBDCA + PTX + bevacizumab 7.5 mg/kg group (CPB 7.5 group) and the CBDCA + PTX + bevacizumab 15 mg/kg group (CPB 15 group). The primary endpoint of progression-free survival was significantly longer in the CPB 15 group:* p=0.023 (control vs. CPB 7.5 group vs. CPB 15 group: 4.2 months* vs. 4.3 months vs. 7.4 months*), and the best response rate (18.8% vs. 28.1% vs. 31.5%) and overall survival (14.9 months vs. 11.6 months vs. 17.7 months) were also obtained in the CPB 15 group (61). However, severe hemoptysis was seen in 6 patients (9%) and 4 patients died following combined use of bevacizumab with chemotherapy. Squamous cell carcinoma, presence of tumor necrosis and a central location of the tumor were identified as the factors associated with severe hemoptysis. In a subsequent randomized phase III clinical study (ECOG 4599) designed to compare CBDCA + PTX (CP group) with CBDCA + PTX + bevacizumab 15 mg/kg (CPB group), patients with squamous cell carcinoma and patients who had hemoptysis or brain metastasis were excluded from the subject population to reduce the incidence of severe adverse events. In this study, significantly better outcomes were obtained in the CPB group in terms of the response rate (15% vs. 35%, p<0.001), PFS (mPFS: 4.5 months vs. 6.2 months, p<0.001) and overall survival (MST: 10.3 months vs. 12.3 months, p=0.003) (62). This was the first study to demonstrate prolongation of the survival period in patients with NSCLC following administration of a molecule-targeted drug in combination with chemotherapy. On the basis of the results of this study, CPB therapy was adopted by ECOG as the new standard therapy for non-squamous cell carcinoma. However, despite exclusion of patients who were at a high risk for hemoptysis from the subject population, the incidence of grade 3 or more severe bleeding was still significantly higher in the CPB group (0.7% vs. 4.4%, p<0.001) and 7 patients from the CPB group died of bleeding (5 deaths from hemoptysis and 2 deaths from gastrointestinal bleeding). The non-hematological toxicities (grade 3/4) observed at a high incidence were hypertension (5.6%), proteinuria (4.2%), malaise (5.1%), and dyspnea (5.6%).

The results of a randomized phase III clinical study (AVAiL) in which 1,043 patients with NSCLC (excluding squamous cell carcinoma) with no prior history of chemotherapy were divided into three treatment groups, i.e., the GEM + CDDP therapy group (GC group), GEM + CDDP +

bevacizumab 7.5 mg/kg therapy group (GCB 7.5 mg/kg group), and the GEM + CDDP + bevacizumab 15 mg/kg therapy group (GCB 15 mg/kg group). The primary endpoint, PFS, was extended significantly by the addition of bevacizumab to the therapy (mPFS: 6.2 months vs. 6.8 months vs. 6.6 months, p=0.0003*) and the response rate was also higher in the GCB groups (20.1% vs. 34.1% vs. 30.4%) (63). However, the MST did not differ significantly between any two of the three groups (13.1 months vs. 13.6 months vs. 13.4 months, p=0.42*) (*comparison between the GC group and GCB 7.5 mg/kg group) (64). The absence of significant inter-group differences in the overall survival period despite the finding of significant inter-group differences in the PFS was considered to be attributable to the chemotherapy administered for the second/subsequent-line treatment. During the ASCO meeting in 2009, the results of a randomized phase II clinical study in Japanese patients were reported. This study, which was designed to evaluate the safety and efficacy of two regimens (CPB vs. CP), similar to the evaluation in ECOG 4599, revealed favorable outcomes of CPB (65).

In addition, a study to evaluate the safety of initial treatment with a combination of standard chemotherapy and bevacizumab (7.5 or 15 mg/kg) was carried out (SAiL study) in 2,240 patients with advanced NSCLC. The incidence of severe adverse events associated with bevacizumab was 23.5%, however, the incidence of grade 3-5 bleeding in the central nervous system was 0.4% and that of hypertension was 0.7%. Thus, the therapy could be administered relatively safely (66).

A randomized phase II clinical study was carried out in patients with recurrent or therapy-resistant NSCLC (other than squamous cell carcinoma) allocated to one of the three following treatment arms, Arm 1: chemotherapy (DOC or pemetrexed [PEM]) + placebo, Arm 2: chemotherapy (DOC or PEM) + bevacizumab, and Arm 3: erlotinib + bevacizumab. The response rate, mPFS and MST were 12.2%, 3.0 months and 8.6 months, respectively, in Arm 1, 12.5%, 4.8 months and 12.6 months, respectively, in Arm 2, and 17.9%, 4.4 months and 13.7 months, respectively, in Arm 3. Thus, the regimens containing bevacizumab tended to yield better outcomes. The incidence of severe toxicities was the lowest in the erlotinib + bevacizumab group (67). On the basis of these results, a randomized phase III clinical study (BETA Lung) was carried out, comparing erlotinib + placebo therapy (E+P group) with erlotinib + bevacizumab therapy (E+B group) in 636 patients with recurrent NSCLC. The response rate (6.2% vs. 12.6%, p=0.006) and PFS (mPFS: 1.7 months vs. 3.4 months, p<0.0001) were significantly better in the E+B group, while the overall survival period (MST: 9.2 months vs. 9.3 months, p=0.7583) did not differ significantly between the two groups. As for the reason why the significant inter-group difference in the PFS was not reflected in the overall survival period, it was pointed out that tertiary treatment had been administered to 60% or more of all patients in each group and quaternary and subsequent treatment had also been administered in a considerable number of the patients. In the analysis of toxicity, the incidence of skin eruptions and thrombosis was higher in the E+B group, but it did not differ from the previously reported rate (68).

At the ASCO meeting in 2009, the results of a phase III clinical study (ATLAS) designed to compare bevacizumab monotherapy with bevacizumab doublet + erlotinib therapy, both administered as maintenance therapy after platinum + bevacizumab therapy in previously untreated cases of NSCLC (other than squamous cell carcinoma), were reported. In terms of the primary endpoint of PFS, the results in the combined therapy were superior to those in the monotherapy group (69). Some of the studies now under way include a phase III clinical study (ECOG 1505) designed to evaluate the effect of addition of bevacizumab to postoperative adjuvant therapy in completely resected cases of NSCLC and a phase III clinical study (SABRE-L) designed to evaluate the effect of the addition of sunitinib to CBDCA + PTX + bevacizumab therapy administered as initial chemotherapy.

3. VEGFR tyrosine kinase inhibitors

1) Vandetanib (ZD6474)

Vandetanib is a multi-targeted tyrosine kinase inhibitor capable of inhibiting both VEGFR and EGFR at the same time. In a randomized phase II clinical study comparing DOC monotherapy with DOC + vandetanib therapy (100 or 300 mg/day) in previously treated cases of NSCLC, significant prolongation of the PFS was observed in the combined treatment group given vandetanib (100 mg/day) (mPFS: 12 weeks in the DOC monotherapy group vs. 18.7 weeks in the DOC + vandetanib 100 mg/day group, p=0.037, one-tailed; vs. 17.0 weeks in the DOC + vandetanib 300 mg/day group, p=0.231, one-tailed) (70). On the basis of these results, a phase III clinical study (ZODIAC) comparing DOC + placebo therapy with DOC + vandetanib (100 mg/day) therapy was carried out, and a significant difference in the PFS (primary endpoint) between the two groups was reported during the ASCO meeting in 2009 (71). In a phase II study comparing vandetanib with gefitinib, the PFS (primary endpoint) was significantly longer in the vandetanib group (11.0 weeks vs. 8.1 weeks, p=0.025) (72). In an early phase II dose-determination study conducted in Japan, in which the drug was administered at three dose levels (100, 200 and 300 mg/day), the response rates in the three dosage groups were 17.6%, 5.6% and 16.7%, respectively (73). In a randomized phase II clinical study comparing CBDCA + PTX therapy (PC group) with CBDCA + PTX + vandetanib therapy (VPC group), with both administered as the initial chemotherapy, the response rate and mPFS were 25% and 23 weeks, in the PC group, and 32% and 24 weeks, respectively, in the VPC group (74).

During the meeting of ASCO in 2009, the results of a phase III clinical study (ZEAL) comparing vandetanib with

erlotinib administered as the second-line chemotherapy (75) and a phase III clinical study of PEM ± vandetanib were reported. Neither of these studies revealed superiority of vandetanib over the reference drug in terms of the PFS (primary endpoint) (76). A phase III clinical study (ZEPHYR) comparing this drug with placebo in patients with NSCLC treated previously with EGFR inhibitors also showed negative results.

2) Sorafenib

Sorafenib serves as a tyrosine kinase inhibitor for Raf-kinase, VEGFR-2, VEGFR-3, PDGFR-B, Flt-3 and c-kit (77). A phase II clinical study of sorafenib monotherapy in previously untreated cases of NSCLC was started, but it was discontinued when only 25 cases had been registered, because of the poor responses (78). In this study, the response rate, mPFS and MST were 12%, 2.9 months and 8.8 months, respectively. A phase II clinical study of sorafenib monotherapy was also performed in 52 cases of recurrent NSCLC, which yielded tumor reduction in 29% of all cases, and the mPFS and MST of 11.9 weeks and 29.3 weeks, respectively. As grade 3 or more severe toxicities, the hand-foot syndrome (10%) and hypertension (4%) were noted (79). A randomized phase II clinical study was carried out in 83 patients with NSCLC with a history of having received two or more regimens of chemotherapy before. These 83 patients were initially treated with sorafenib and later with either with placebo (placebo group) or sorafenib (continued sorafenib therapy group). The percentage of patients rated as showing SD or a better outcome at 2 months (primary endpoint) was 19% in the placebo group and 47% in the continued sorafenib therapy group, indicating the significantly better outcome in the continued sorafenib therapy group (p=0.01). Significant difference in the PFS was also found (mPFS: 2.0 months vs. 3.6 months, p=0.009), however, there was no significant difference in the overall survival between the two groups (MST: 9.0 months vs. 11.9 months, p=0.18) (80).

In addition, a phase III clinical study (ESCAPE) comparing PTX + CBDCA + placebo therapy with PTX + CBDCA + sorafenib therapy in 926 previously untreated cases of NSCLC was carried out, which yielded no significant inter-group difference in the response rate (23% vs. 25%), PFS (mPFS: 4.8 months vs. 4.8 months, p=0.92) or overall survival (MST: 10.6 months vs. 10.7 months, p=0.93) between the two treatment groups (81). At present, a phase III clinical study designed to evaluate the effect of addition of sorafenib to GEM + CDDP therapy is underway.

3) Sunitinib

Sunitinib is a multi-targeted tyrosine kinase inhibitor for VEGFR-1, -2 and -3, PDGFR-α and -β, KIT, RET, CSF-1R and Flt-3. A phase II clinical study of sunitinib 50 mg/day (oral treatment for 4 weeks, followed by drug cessation for 2 weeks) was carried out in 63 previously treated cases of NSCLC. In this study, 22% of all patients required dose reduction. The major toxicities observed were malaise, myalgia, nausea and hypertension. The response rate, median time to progression (mTTP) and MST were 11.1%, 12.0 weeks and 23.4 weeks, respectively (82). On the basis of these results, a phase II clinical study was conducted to evaluate the effect of daily treatment with sunitinib (37.5 mg/day) in 47 previously treated cases of NSCLC. In this study, dose reduction was needed in 29.8% of all the patients. The response rate, mPFS and MST were 2.1%, 12.3 weeks and 37.1 weeks, respectively. These results suggest that this drug may be a promising agent for the treatment of recurrent NSCLC. The major toxicities were malaise, dyspnea and hypertension. Grade 3/4 hemoptysis was noted in 2% of all the patients (83).

In addition, several clinical studies designed to evaluate the efficacy of sunitinib combined with other therapies (chemotherapy including platinum preparations, single chemotherapy or EGFR-TKI) have been carried out. A phase III clinical study comparing erlotinib monotherapy with erlotinib + sunitinib therapy in previously treated cases of NSCLC is now underway (84).

4) Cediranib (AZD2171)

Cediranib is a tyrosine kinase inhibitor for VEGFR. A randomized double-blind phase II/III study (BR.24) was carried out, comparing CBDCA + PTX + cediranib therapy with CBDCA + PTX + placebo therapy in patients with advanced NSCLC. In this study, 150 patients were allocated to the CBDCA + PTX + placebo group (CPP group) or the CBDCA + PTX + cediranib 30 mg/day group (CPC group). The response rate was significantly higher in the CPC group (38%) than in the CPP group (16%) (p<0.001), but the PFS did not differ significantly between the two groups (mPFS: 5.0 months vs. 5.6 months, p=0.13). In the analysis of toxicity, the incidence of diarrhea, dehydration, mucositis, hand-foot syndrome, hypertension and decreased blood neutrophil count was higher in the CPC group. A clinical study on cediranib administered at a lower dose level (20 mg) is now planned (85).

4. Other molecule-targeted drugs

1) Bexarotene

Retinoids play an important role in the growth, division and differentiation of cells and the activation of cell apoptosis. Bexarotene is considered to exert antitumor activity through its selective actions on the retinoid X receptor (86).

A phase I/II clinical study on bexarotene combined with VNR + CDDP as the initial chemotherapy for NSCLC was carried out. In this study, the maximum-tolerated dose (MTD) was 400 mg/m^2/day. In the phase II trial, the response rate and MST were 25% and 14 months, respectively (87). In a phase II clinical study of bexarotene + GEM + CBDCA in 47 previously untreated cases of NSCLC, the response rate, MST and one-year survival rate were 25%, 12.7 months and 53%, respectively. In the analy-

sis of toxicity in the same study, all of the adverse reactions other than hypertriglyceridemia were tolerable (88). On the basis of these results, two randomized phase III studies were carried out in previously untreated cases of NSCLC to evaluate the effect of the addition of bexarotene to platinum-based chemotherapy. In one of these studies (SPIRIT I), 623 patients were allocated to either the VNR + CDDP group (VP group) or the VNR + CDDP + bexarotene group (VPB group). The response rate was significantly higher in the VP group (24.4% vs. 16.7%, p=0.0224), and the VP group also tended to have a better outcome in terms of the PFS (mPFS: 5.0 months vs. 4.3 months, p=0.095) and overall survival (MST: 9.9 months vs. 8.7 months, p=0.3). In the analysis of toxicity, the incidences of hypertriglyceridemia and hypothyroidism were higher in the group treated with bexarotene (89). In a second study (SPIRIT II), 612 patients were allocated to either the CBDCA + PTX group (CP group) or the CBDCA + PTX + bexarotene group (CPB group). The outcomes tended to be better in the CP group, in terms of the response rate (23.5% vs. 19.3%, p=0.24), PFS (mPFS: 4.9 months vs. 4.1 months, p=0.061) and the overall survival (MST: 9.2 months vs. 8.5 months, p=0.2) (90). Neither of the two studies demonstrated that the use of bexarotene in combination with platinum-based chemotherapy augmented the effects of platinum-based chemotherapy.

2) Figitumumab (CP-751,871)

Figitumumab is a completely humanized IgG2 type monoclonal antibody directed against insulin-like growth factor I (IGF-I) receptor. A randomized phase II clinical study was carried out comparing CBDCA + PTX therapy (TC group) with figitumumab + CBDCA + PTX therapy (TCI group) in 150 previously untreated cases of advanced NSCLC. The response rate was 41% in the TC group and 54% in the TCI group. The response rate was higher among patients with squamous cell carcinoma (46% vs. 78%), suggesting that the addition of anti-IGF-IR antibody is likely effective in patients with squamous cell carcinoma (91). In the analysis of toxicity, the incidences of hyperglycemia and dehydration were higher in the TCI group. Figitumumab may thus be a promising agent for the treatment of squamous cell carcinoma of the lung.

A randomized phase III clinical study comparing TC with TCI in previously untreated cases of NSCLC and a randomized phase III clinical study comparing figitumumab therapy with erlotinib + figitumumab therapy for recurrent NSCLC are now underway. There are also ongoing clinical studies on several other products of anti-IGF-IR antibody, such as R 1507, and the results of these studies are awaited.

3) ASA404

ASA404 is an agent causing vascular destruction and has been reported to induce irreversible tumor vessel destruction, hemorrhagic necrosis at the center of the tumor, and the production of cytokines. This drug is considered to induce tumor necrosis through its actions on existing blood vessels rather than on the newly formed blood vessels (92-95). Its target molecules remain unidentified. A randomized phase II clinical study was carried out in 76 previously untreated cases of advanced NSCLC, comparing ASA404 + CBDCA + PTX therapy (ASA404-CP group) with CBDCA +PTX therapy (CP group). The outcomes were better in the ASA404-CP group in terms of the response rate (31% vs. 22%), mTTP (5.4 months vs. 4.4 months) and MST (14.0 vs. 8.8 months). In the analysis of toxicity, no differences were noted between the two groups (95). On the basis of these results, a randomized phase III clinical study is now underway.

Conclusion

In recent years, the development of molecular-targeted drugs has progressed remarkably, and numerous clinical studies have been carried out on molecular-targeted drugs for the treatment of NSCLC. In this paper, the results obtained to date have been presented, focusing on drugs for which phase III clinical studies have been carried out. In parallel with clinical studies, studies exploring biomarkers have also been carried out. It is essential to develop biomarkers to serve as predictors of the responses to treatment with molecular-targeted drugs, like EGFR gene mutations serving as a predictor of the response to EGFR tyrosine kinase inhibitors. The outcomes of NSCLC treatment will improve if the appropriate therapeutic strategies are applied to appropriately selected patients on the basis of clinical factors (histological type, etc.) and biomarkers found in the tumor tissues and serum.

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Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial

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Summary

Background Vandetanib is a once-daily oral inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and rearranged during transfection (RET) tyrosine kinases. In a randomised phase 2 study in patients with previously treated non-small-cell lung cancer (NSCLC), adding vandetanib 100 mg to docetaxel significantly improved progression-free survival (PFS) compared with docetaxel alone, including a longer PFS in women. These results supported investigation of the combination in this larger, definitive phase 3 trial (ZODIAC).

Methods Between May, 2006, and April, 2008, patients with locally advanced or metastatic (stage IIIB–IV) NSCLC after progression following first-line chemotherapy were randomly assigned 1:1 through a third-party interactive voice system to receive vandetanib (100 mg/day) plus docetaxel (75 mg/m^2 intravenously every 21 days; maximum six cycles) or placebo plus docetaxel. The primary objective was comparison of PFS between the two groups in the intention-to-treat population. Women were a coprimary analysis population. This study has been completed and is registered with ClinicalTrials.gov, number NCT00312377.

Findings 1391 patients received vandetanib plus docetaxel (n=694 [197 women]) or placebo plus docetaxel (n=697 [224 women]). Vandetanib plus docetaxel led to a significant improvement in PFS versus placebo plus docetaxel (hazard ratio [HR] 0·79, 97·58% CI 0·70–0·90; p<0·0001); median PFS was 4·0 months in the vandetanib group versus 3·2 months in placebo group. A similar improvement in PFS with vandetanib plus docetaxel versus placebo plus docetaxel was seen in women (HR 0·79, 0·62–1·00, p=0·024); median PFS was 4·6 months in the vandetanib group versus 4·2 months in the placebo group. Among grade 3 or higher adverse events, rash (63/689 [9%] *vs* 7/690 [1%]), neutropenia (199/689 [29%] *vs* 164/690 [24%]), leukopenia (99/689 [14%] *vs* 77/690 [11%]), and febrile neutropenia (61/689 [9%] *vs* 48/690 [7%]) were more common with vandetanib plus docetaxel than with placebo plus docetaxel. The most common serious adverse event was febrile neutropenia (46/689 [7%] in the vandetanib group *vs* 38/690 [6%] in the placebo group).

Interpretation The addition of vandetanib to docetaxel provides a significant improvement in PFS in patients with advanced NSCLC after progression following first-line therapy.

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Introduction

Non-small-cell lung cancer (NSCLC) is a major cause of cancer-related death and most patients are diagnosed with NSCLC at an advanced stage of disease.[1,2] Many patients initially achieve clinical remission or disease stabilisation with first-line therapy, but nearly all experience disease progression and eventually die from advanced NSCLC. Several drugs are approved as second-line treatments for advanced NSCLC, including docetaxel,[3,4] pemetrexed,[5] erlotinib,[6] and gefitinib;[7] however, none have been shown to be better in this setting. One strategy to improve efficacy and alleviate symptom burden, without increasing toxicity, is to combine chemotherapeutics with drugs that selectively target signalling pathways associated with lung-cancer progression.

Vandetanib (AstraZeneca, Macclesfield, UK) is a once-daily oral anticancer drug that targets vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) signalling.[8,9] Vandetanib is also a potent inhibitor of rearranged during transfection (RET) tyrosine kinase, an important growth driver in some thyroid cancers[10] and possibly other cancers.[11] Simultaneous targeting of VEGFR and EGFR with vandetanib is supported by evidence from clinically relevant xenograft models of human NSCLC,[12] which showed that vandetanib could abrogate primary and acquired resistance to EGFR tyrosine-kinase inhibitors (TKIs). In some of these preclinical models, resistance to EGFR inhibitors was associated with increased expression of tumour-derived and host-derived VEGF. Both the VEGFR and EGFR signalling pathways are established therapeutic targets in patients with advanced NSCLC: bevacizumab, an anti-VEGF monoclonal antibody, prolonged survival when added to paclitaxel and carboplatin in previously untreated non-squamous advanced NSCLC[13] (bevacizumab is not indicated in patients with squamous histology because of

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the risk of life-threatening haemoptysis), and the EGFR inhibitors gefitinib and erlotinib have shown single-agent activity in previously treated advanced NSCLC.[6,7]

Phase 2 assessment of vandetanib has shown antitumour activity in advanced, previously treated NSCLC[14,15] and in hereditary medullary thyroid cancer.[16] In patients with previously treated NSCLC, vandetanib 100 mg/day plus docetaxel improved progression-free survival (PFS; hazard ratio [HR] 0·64) and objective response rate (ORR) versus docetaxel alone.[14] Additionally, exploratory subgroup analyses showed a greater PFS benefit in women (HR 0·31) than in men (HR 0·87) with vandetanib 100 mg plus docetaxel versus docetaxel alone. The trial also showed that vandetanib 100 mg plus docetaxel resulted in a longer PFS and was better tolerated than vandetanib 300 mg plus docetaxel.[14] Overall, these phase 2 results provided the rationale for further assessment of vandetanib 100 mg/day plus docetaxel in the randomised, placebo-controlled, phase 3 study (Zactima in cOmbination with Docetaxel In non-smAll cell lung Cancer [ZODIAC]) reported here.

Methods

Study design and patients

ZODIAC was a multinational, randomised, double-blind, phase 3 study of vandetanib plus docetaxel (Sanofi-Aventis, Paris, France) versus placebo plus docetaxel in patients with locally advanced or metastatic NCSLC after progression following platinum-based first-line chemotherapy. The recent approval and increasing use of pemetrexed as first-line therapy in NSCLC suggest a continuing role for docetaxel as second-line therapy.

Eligibility criteria included age 18 years or older; histological or cytological confirmation of locally advanced or metastatic stage IIIB–IV NSCLC after failure of first-line platinum-based therapy; WHO performance status of 0 or 1; measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST); no previous therapy with docetaxel or a VEGFR TKI; and adequate cardiac, haematopoietic, hepatic, and renal function. Patients with squamous-cell histology were eligible, and brain metastases were permitted if treated at least 4 weeks before study entry and clinically stable without steroids for 10 days. Previous treatment with bevacizumab or paclitaxel was also permitted.

The trial was approved by the institutional review boards or ethical committees at each centre, and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca Bioethics policy. All patients provided written informed consent.

Randomisation and masking

A standard computerised randomisation scheme was used to randomly assign treatment to patients (1:1). Randomisation numbers were allocated to centres in balanced blocks. The block size was such that the randomisation scheme was effectively stratified by centre. Eligible patients were randomised strictly sequentially. After a patient was screened for eligibility, the investigator contacted the centralised registration/randomisation centre (CR/RC) by telephone and an interactive voice response system (IVRS) was used to assign a unique randomisation code to each patient and allocate blinded randomised therapy. Medication was labelled using a unique material pack code linked to the randomisation scheme, and was assigned by the CR/RC to be dispensed to each patient at each visit. The active and placebo tablets were identical and were presented in the same packaging. Each patient's randomisation code break was available to the local investigator through the IVRS. The treatment code was to be broken only in medical emergencies; otherwise, codes were not broken for the planned analyses until all decisions on the evaluability of data from each patient had been made and documented. This masking was maintained for AstraZeneca personnel responsible for analysis and interpretation of results at the study's conclusion.

Procedures

Patients were randomly assigned to receive docetaxel (75 mg/m^2 in a 1-h intravenous infusion every 3 weeks; maximum six cycles) in combination with vandetanib (100 mg/day orally) or placebo until disease progression, unacceptable toxicity, or withdrawal of consent. Consistent with Japanese prescribing information, the docetaxel dose in Japan was 60 mg/m^2.

The primary objective was to assess whether vandetanib plus docetaxel prolonged PFS compared with placebo plus docetaxel. PFS was selected as the primary endpoint to provide a direct measurement of the effect of study treatment on the tumour, since, unlike overall survival, PFS is not potentially confounded by the use of post-progression therapies. Secondary endpoints included assessments of overall survival, ORR (complete+partial responses), disease control rate (complete+partial responses+stable disease ≥6 weeks), time to deterioration of disease-related symptoms, and safety.

Objective tumour response was assessed radiologically by the local investigators according to RECIST 1.0, with assessments done at baseline and every 6 weeks until progression. There was no independent blinded review of radiological assessments, which is consistent with other studies using PFS as the primary endpoint.[17,18] Although the absence of independent radiological assessment is a potential limitation of the study, it was considered sufficient that the study was double-blind and randomised, and the common side-effects predicted for the drug combination (rash and diarrhoea) are similar to those seen with docetaxel alone.

PFS was defined as the time from randomisation to the earliest occurrence of disease progression or death from any cause, provided death was within 3 months of the last evaluable assessment. Patients who had not progressed or died at the time of statistical analysis were censored at the time of their latest evaluable RECIST assessment. Although PFS is often defined as the time from

randomisation to progression (or death by any cause in the absence of progression), a 3-month limit was adopted for the Food and Drug Administration (FDA)-reviewed study protocol, to minimise artificial prolongation of PFS.

Overall survival was calculated from the date of randomisation to the date of death by any cause; patients who had not died at the time of analysis were censored at the time they were last known to be alive. An unplanned overall survival update was also done in accordance with a request from the FDA, and the results of this analysis are reported for completeness. No efficacy endpoints other than survival were updated at this time.

Symptoms were assessed using the seven-item Lung Cancer Subscale (LCS) derived from the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire that has been previously validated in patients with lung cancer.[19] The FACT-L questionnaire was given to patients at baseline and every 3 weeks thereafter, until 30 days after progression or discontinuation of treatment. The LCS consists of three items relating to breathing or dyspnoea and one item each relating to cough, weight loss, appetite, and cognition. Each item is rated on a five-point scale (0 [worst] to 4 [best]), with a total score ranging from 0 (most symptomatic) to 28 (asymptomatic). Deterioration was predefined as an adverse change of three points or more from baseline, with no improvement in the next 21 days, which has been shown to be a clinically meaningful change in patients with advanced NSCLC.[20] Time to deterioration of symptoms (TDS) was the interval from date of randomisation to first assessment of symptom deterioration (as defined above). If deterioration was not observed at the time of analysis, TDS was censored at the time of the last evaluable LCS assessment.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE 3.0). Prespecified groups of preferred terms were identified as being of interest, based on pharmacological class or previous studies with vandetanib. Scheduled 12-lead ECGs were done during screening, at 1, 3, 6, and 12 weeks after starting randomised treatment and every 3 months thereafter, and at the end of study. The QTc interval was assessed centrally, and prolongation was defined as previously described.[16] Management of adverse events generally consisted of dose interruption followed by dose reduction as necessary.

Statistical analysis

The study had two coprimary analysis populations: all randomised patients (intention-to-treat [ITT]) and all randomised female patients. The conventional 5% significance level was therefore adjusted to 2·5% for all analyses, and further adjusted to 2·42% for PFS and 2·48% for overall survival to allow a single interim analysis. p values are two-sided. The study was designed to have greater than 90% power to detect a 25% prolongation of PFS (HR <0·80). Assuming a median PFS of 3 months for docetaxel alone, a sample size of 1380 patients was estimated to achieve 1176 progression events, with accrual over 19 months and a minimum follow-up of 3 months.

PFS, overall survival, and TDS were analysed using the log-rank test (unadjusted model with treatment factor only). A secondary analysis of PFS and overall survival was done using Cox's proportional-hazards regression model that allowed for the effect of treatment and included terms for tumour stage, number of organs involved, previous bevacizumab failures, histology, smoking history, sex, ethnic origin, and plasma and tumour biomarker status. The ORR and disease control rate were analysed using logistical regression. Patients were stratified only by centre.

Patients of east Asian origin have previously been shown to derive differential benefit from anti-EGFR treatment.[21] Interaction tests were therefore done before the main study analyses to determine if the treatment effect in Japan or China differed from that in all other countries. The interaction test was done for PFS and overall survival at a two-sided, 10% significance level. All statistical analyses were done using SAS version 9.1. This study is registered with ClinicalTrials.gov, number NCT00312377.

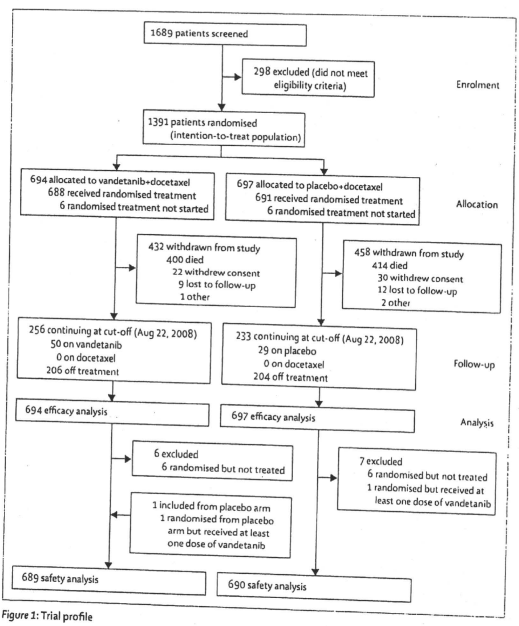

Figure 1: Trial profile

Role of the funding source

The corresponding author designed the trial in collaboration with the study sponsor, and the steering committee met nine times during the trial to supervise the conduct of the study. The sponsor provided funding and organisational support, collected the data, and undertook the analyses. The report was written by the senior investigators, who had unrestricted access to the study data and gave assurance for the accuracy and completeness of the reported analyses. The corresponding author had final responsibility for the decision to submit for publication.

	Vandetanib+docetaxel (n=694)	Placebo+docetaxel (n=697)
Age (years; median and range)	59 (28–82)	59 (20–82)
Sex		
Male	497 (72%)	473 (68%)
Female	197 (28%)	224 (32%)
Ethnic origin		
Caucasian	410 (59%)	417 (60%)
East Asian	259 (37%)	252 (36%)
Other	25 (4%)	28 (4%)
Smoking history*		
Smoker	536† (77%)	524 (75%)
Current smoker	259 (37%)	242 (35%)
Former smoker	276 (40%)	282 (40%)
Non-smoker	158 (23%)	173 (25%)
WHO performance status		
0	250 (36%)	238 (34%)
1	436 (63%)	451 (65%)
Other‡	8 (1%)	8 (1%)
Histology		
Adenocarcinoma	412 (59%)	417 (60%)
Squamous	184 (27%)	160 (23%)
Other§	98 (14%)	120 (17%)
Stage of disease¶		
Stage IIIb	95 (14%)	106 (15%)
Stage IV	598 (86%)	590 (85%)
Brain metastases	65 (9%)	80 (11%)
Previous chemotherapy		
Platinum compound	660 (95%)	664 (95%)
Pyrimidine analogue	308 (44%)	314 (45%)
Taxane	216 (31%)	209 (30%)
Vinca alkaloid or analogue	124 (18%)	122 (18%)
Best response to first-line chemotherapy		
Complete response	14 (2%)	13 (2%)
Partial response	217 (31%)	216 (31%)
Stable disease	252 (36%)	260 (37%)
Progressive disease	168 (24%)	170 (24%)
Non-evaluable	16 (2%)	15 (2%)
Not applicable or not recorded	27 (4%)	23 (3%)
Prior bevacizumab	20 (3%)	24 (3%)

ITT=intention-to-treat. Data are n (%), unless stated otherwise. *Smoker: includes ex-smoker (stopped smoking ≥365 days), occasional smoker (<1 tobacco product per day), and habitual smoker (≥1 tobacco product per day). Non-smoker: patients who have smoked ≤20 g of tobacco in lifetime. †One smoker in the vandetanib group had status "unknown". ‡WHO performance status 2 at entry: six (vandetanib) and two (placebo). Not recorded: two (vandetanib) and six (placebo). §Includes adenosquamous carcinoma, large-cell carcinoma, and non-small-cell lung cancer not further classified. ¶Not recorded for one patient in each group.

Table 1: **Patient demographics and baseline characteristics in the ITT population (all randomised patients)**

Results

Between May, 2006, and April, 2008, 1391 patients recruited from 198 centres in 25 countries were randomly assigned to receive vandetanib plus docetaxel (n=694) or placebo plus docetaxel (n=697; figure 1). Patient characteristics and baseline demographics were similar in both treatment groups (table 1). At data cut-off (Aug 22, 2008), 1205 patients (87%) had progressed, 814 (59%) had died, and the median potential duration of follow-up was 12·8 months. The median number of docetaxel cycles in each group was four (range 1–6). The total median duration of exposure to vandetanib or placebo was 12·1 weeks (range 0·1–103·9) and 13·0 weeks (range 0·1–84·9), respectively. Dose intensity of docetaxel was not compromised by the addition of vandetanib, with a median of 98·1% of the planned dose being received in the vandetanib group versus 98·4% in the placebo group. The numbers and types of subsequent anticancer therapies were well balanced between groups, with 51% (351) patients in the vandetanib group and 55% (387) in the placebo group receiving at least one post-progression therapy. Before the main study analyses, formal assessment of whether treatment effects (PFS and overall survival) in Japan or China differed from all other countries did not show significant qualitative interaction—ie, no evidence of treatment effects in opposite directions. The main study analyses therefore included patients from Japan and China.

Patients randomly assigned to receive vandetanib plus docetaxel showed a significant improvement in PFS versus those randomly assigned to receive placebo plus docetaxel for the overall population (HR 0·79, 97·58% CI 0·70–0·90; p<0·0001; figure 2A); median PFS was 4·0 months in the vandetanib group versus 3·2 months in the placebo group. At 6 months, 28% of patients in the vandetanib group and 22% in the placebo group were progression-free. A similar improvement in PFS with vandetanib plus docetaxel versus placebo plus docetaxel was observed in women (HR 0·79, 0·62–1·00; p=0·024); median PFS was 4·6 months in the vandetanib group versus 4·2 months in the placebo group.

The addition of vandetanib to docetaxel also resulted in a significant improvement in ORR (17% [120 patients] *vs* 10% [71 patients], p=0·0001): all were partial responses in the vandetanib group, with six complete responses and 65 partial responses in the placebo group. The disease control rate was comparable in both groups: 60% (413 patients) with vandetanib plus docetaxel versus 55% (380 patients) with placebo plus docetaxel (p=0·06). At data cut-off for PFS analysis (814/1391 [59%] of patients dead), there was no significant difference between treatment groups for the secondary endpoint of overall survival (HR 0·91, 97·52% CI 0·78–1·07; p=0·196; figure 2B); similar results were observed in women (HR 0·96, 0·71–1·30; p=0·759). The proportion of patients alive at 1 year was 44·7% in the vandetanib group versus 41·2% in the placebo

group. The results of preplanned exploratory subgroup analyses for PFS and overall survival were generally consistent with the results seen in all patients, including those with squamous-cell histology (figure 3).

Overall compliance with the FACT-L questionnaire, calculated as patients with a baseline evaluable assessment and at least one follow-up evaluable assessment, was 72% (503 patients) in the vandetanib group and 74% (515 patients) in the placebo group. TDS was delayed in the vandetanib group compared with in the placebo group (HR 0·77, 97·5% CI 0·65–0·92; p=0·0008; FACT-L LCS; figure 4). Median TDS was 3·5 months in the vandetanib group versus 2·7 months in the placebo group. At 6 months, 34% (234 of 694) of patients in the vandetanib group and 26% (181 of 697) in the placebo group had not experienced deterioration of symptoms.

At the time of overall survival follow-up analysis (September, 2009), 1075 patients had died: 538 (78%) in the vandetanib group and 537 (77%) in the placebo group. There was no significant difference in overall survival (HR 0·95, 95% CI 0·84–1·07; p=0·371); median overall survival was 10·3 months in the vandetanib group and 9·9 months in the placebo group. The overall survival subgroup results were consistent with those from the August data cut-off (data not shown).

Adverse events (all grades) occurring more frequently in the vandetanib group included diarrhoea, rash, and neutropenia (table 2). Nausea, vomiting, and anaemia occurred less frequently in the vandetanib group (table 2). Protocol-defined QTc prolongation occurred in 1·9% (13/689) of patients receiving vandetanib (*vs* none in the placebo group); all events were asymptomatic and resolved with dose interruption, reduction, or discontinuation. Overall, 22·2% (153/689) of patients in the vandetanib group and 11·0% (76/690) in the placebo group had an adverse event that led to discontinuation of vandetanib or placebo. The proportion of patients requiring dose interruption or reduction of vandetanib or placebo was higher in the vandetanib group (23% [157/689]) than in the placebo group (14% [97/690]). The incidence of hypertension was 6% (41/689; 35 grade 1 or 2, six grade 3) with vandetanib plus docetaxel and 2% (12/690; 11 grade 1 or 2, one grade 3) with placebo plus docetaxel. The incidence of haemorrhage was 17% (116/689) in the vandetanib group versus 16% (112/690) in the placebo group; the incidence of venous thrombotic or embolic events was 2% (14/689) in the vandetanib group versus 4% (27/690) in the placebo group. The incidence of haemoptysis was 6% (40/689) in the vandetanib group versus 7% (50/690) in the placebo group, with one fatal case in each group.

Among grade 3 or higher adverse events, rash, neutropenia, leukopenia, and febrile neutropenia occurred more frequently in the vandetanib group than in the docetaxel group (table 2). More patients required dose interruption or reduction in the vandetanib group than in the placebo group (23% [157/689] *vs* 14% [97/690]), which was mainly due to the higher incidence of rash leading to dose interruption or reduction (11% [73/689] *vs* 1% [5/690]). Serious adverse events leading to death occurred in 42 of 689 (6%) of patients in the vandetanib group and 38 of 690 (6%) in the placebo group. The most common serious adverse event was febrile neutropenia (7% [46/689] in the vandetanib group and 6% [38/690] in the placebo group). Consistent with the natural history for patients with lung cancer, the most commonly reported serious adverse events that led to death in either group were pneumonia (n=11), respiratory failure (n=10), and dyspnoea (n=5). Three deaths were attributed to interstitial lung disease, including two patients from Japan. All three patients had received vandetanib plus docetaxel. There were two deaths from skin reactions in the vandetanib group (Stevens–Johnson syndrome and toxic skin eruption), compared with none in the placebo group.

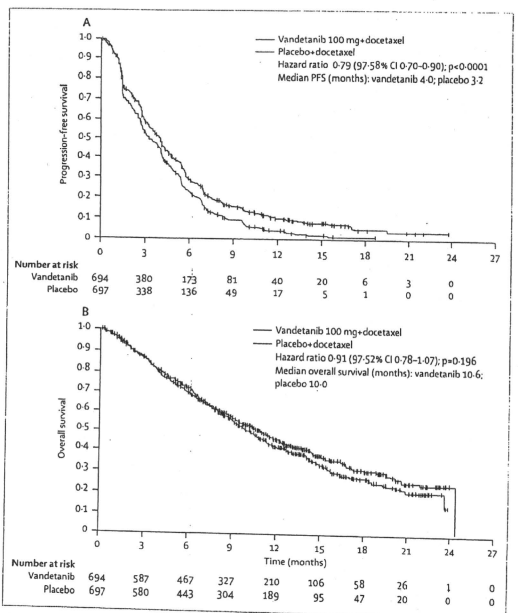

Figure 2: Kaplan-Meier estimates of progression-free survival (A) and overall survival (B) in the intention-to-treat population (all randomised patients)

Discussion

In this randomised, double-blind, international phase 3 study, vandetanib in combination with docetaxel significantly prolonged the time to disease progression,

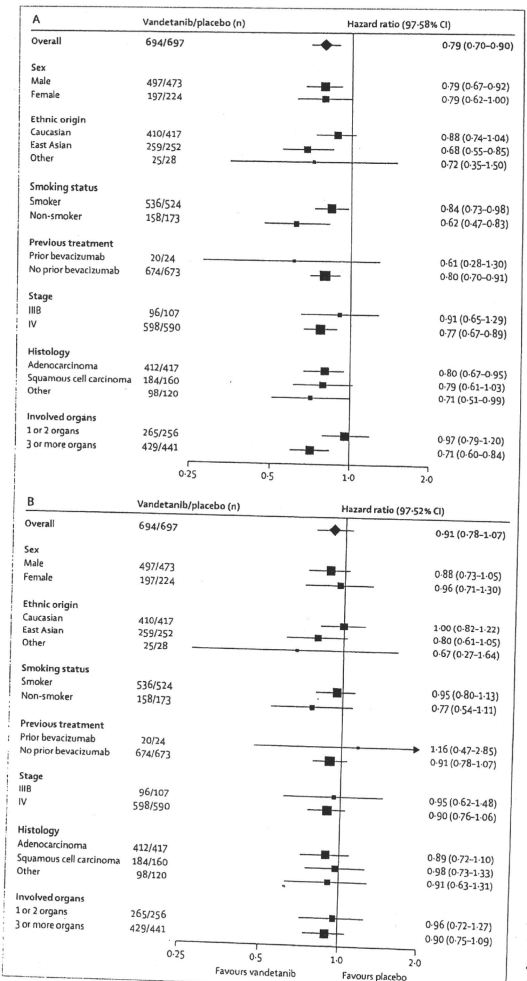

Figure 3: Hazard ratios for progression-free survival (A) and overall survival (B) by patient and clinical characteristics in the intention-to-treat population (all randomised patients)
Analyses were done using a log-rank test with treatment as the only factor.

compared with placebo plus docetaxel, for patients with advanced metastatic NSCLC in the second-line setting. Patients in the vandetanib plus docetaxel group also had a higher ORR and longer time to deterioration in lung-cancer symptoms than did those in the placebo group.

The study was representative of the patient population receiving second-line treatment for NSCLC, and docetaxel exposure (median four cycles) was generally consistent with standard clinical practice and with previous second-line trials of the drug at 75 mg/m².[1–5] However, in the present study, the median overall survival of 10 months for patients receiving placebo plus docetaxel is longer than that reported in the earlier studies (range 5·7–7·9 months). This difference might be explained by differences in the availability or use of first-line and post-progression therapies, as well as general improvements in standards of care over time. Unknown differences in the baseline characteristics of patients in the present study might also be a factor.

It is unclear why the PFS advantage for patients receiving vandetanib did not translate into an improvement in overall survival. However, differences between treatment groups in the use of, and response to, post-progression therapies might have confounded the overall survival outcome. About 50% of patients received post-progression therapy; although the number of patients and type of therapy received was balanced across groups, it cannot be excluded that differences in response to post-progression therapy could have contributed to the results.

Despite the absence of an overall benefit with vandetanib plus docetaxel, the longer PFS in the group that received this combination, relative to those who received placebo plus docetaxel, was associated with a significant delay in time to deterioration of common lung-cancer symptoms; the magnitude of benefit (in terms of HR and median prolongation) favouring vandetanib plus docetaxel was very similar for PFS and TDS. This improvement in symptom relief experienced by patients receiving vandetanib raises the possibility that patients with advanced NSCLC can live with fewer symptoms (and therefore fewer interventions) for a longer period of time. Since progressive disease is generally associated with a worsening in disease-related symptoms, the results of the present study suggest that slowing disease progression also slowed symptom progression, leading to an important palliative benefit. The lower rate of treatment-related toxic effects with vandetanib, such as nausea, vomiting, and anaemia, might also be a factor, although it is not clear how a decrease in these effects relates to delay in the time to worsening of lung-cancer symptoms measured by the LCS. Symptoms measured by the LCS correlate with PFS and ORR, as shown in three phase 3 studies of gefitinib (ISEL, INTEREST, and IPASS).[7,10,21] Previous studies[10,12] have shown that an increase of 2–3 points represents an improvement in symptoms and a decrease of 2–3 points represents a deterioration of symptoms. Cella and