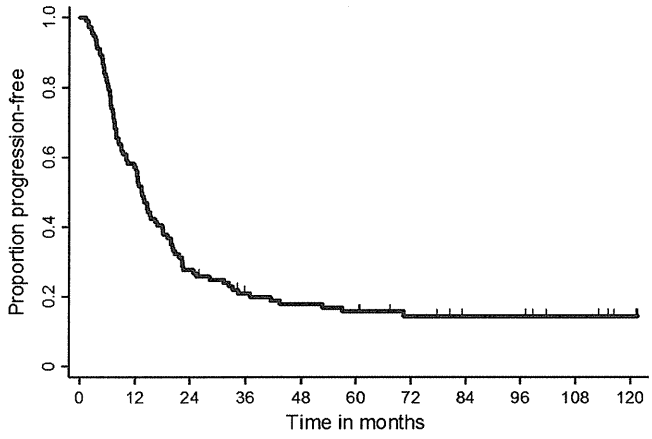

Fig. 1. Progression-free survival (n = 111). The median progression-free survival is 13.5 months (95% confidence interval [CI] 10.1–16.7).

months and 30.0 (24.5–38.8) months, respectively (Fig. 2). There was no significant difference in survival results between subgroups; patients with or without docetaxel consolidation and patients with or without gefitinib.

Pattern of relapse. Relapses were noted in 91 (82%) of 111 patients. Initial relapse sites were local alone in 39 (42%) patients, regional alone in 5 (5%), and distant alone in 38 (41%), including 17 (18%) patients with brain metastases as a sole recurrence site. Brain metastases were detected in 19 (21%) patients and were the most frequent sites of distant metastases. Brain metastases were detected within 3 years of initial treatment, and the last brain relapse was observed after 33 months of follow-up (Table 2). Three (3%) patients experienced adrenal metastases as a first relapse site.

Late toxicities. Grade 1, 2, 3, and 5 late pulmonary toxicities were observed in 18 (16%), 15 (13%), 3 (3%), and 4 (4%) patients, respectively. Seventy-two (64%) patients did not experience late pulmonary toxicities (Table 3). Four cases of grade 5 pulmonary toxicity developed at 4.4, 5.9, 9.4, and 9.6 months, respectively, after the treatment started. Late esophageal toxicities were observed in three patients (one grade 1 and two grade 3).

Causes of death in long-term survivors. There were 67 (60%) patients that survived 24 months or more from the initial treatment. Among them, five patients died because of reasons other than lung cancer. One patient was diagnosed as having pharyngeal cancer at the point of 35 months and died 4 months later. Other than malignancies, community-acquired pneumonia (one patient at 43 months), sudden death due to unknown etiology (two patients at 41 and 42 months) and suicide (one patient at 29 months) were reported, respectively.

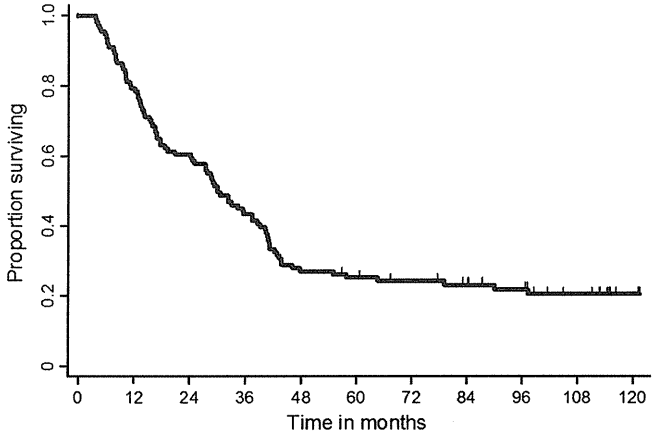

Fig. 2. Overall survival (n = 111). The median overall survival is 30.0 months (95% confidence interval [CI] 24.3–38.6).

Table 2. Sites of initial relapse

Site of recurrences	Number of relapses			
	<1 year	1–3 years	>3 years	Total (%)
Local	16	21	2	39 (42)
Distant	23	12	3	38 (41)
Distant without brain	12	4	3	19 (21)
Distant including brain	1	1	0	2 (2)
Brain only	10	7	0	17 (18)
Regional	3	2	0	5 (5)
Others (L/D/R)†	3	5	1	9 (10)
Unknown	–	–	–	2 (2)

†Others includes 2 Local+Regional relapses, 6 Local+Distant relapses, and 1 Local+Regional+Distant relapse.

Table 3. Late pulmonary toxicities§

Toxicity grades	Clinical trial		Total (%)
	Phase I trial†	DTX consolidation‡	
Without late toxicity	10	62	72 (64)
Grade 1	4	14	18 (16)
Grade 2	3	12	15 (13)
Grade 3	1	2	3 (3)
Grade 4	0	0	0
Grade 5¶	0	4	4 (4)

†The phase I study of concurrent thoracic radiotherapy with cisplatin plus vinorelbine. ‡The docetaxel consolidation therapy following concurrent chemoradiotherapy study. §Late toxicities were defined as those that occurred or persisted 90 days after completion of radiotherapy. ¶The Grade 5 pulmonary toxicities developed at 4.4, 5.9, 9.4, and 9.6 months after the treatment started.

Predictive factors for survival. The associations between overall survival and patients' characteristics (age [in 10-year increments], sex, body weight loss [$\leq$5.0% *vs* $\geq$5.1%], histology [squamous cell carcinoma versus non-squamous cell carcinoma], T factor [T1/2 *vs* T3/4], N factor [N0-2 *vs* N 3], and stage [IIIA *vs* IIIB]) were also examined using Cox regression analysis. Age was significantly associated with survival (hazard ratio [HR] 1.34, 95% CI 1.02–1.75, Table 4).

Discussion

Concurrent chemoradiotherapy has been established as a standard treatment for patients with unresectable locally advanced NSCLC. The long-term feasibility and efficacy of vinorelbine and cisplatin chemotherapy with concurrent thoracic radiotherapy were investigated. The 3-, 5-, and 7-year overall survival rates (95% CI) were 43.2% (33.9–52.2), 25.2% (17.6–33.5), and 23.1% (15.7–31.4), respectively. Older age was associated with poor survival on multivariate analysis (HR 1.34, 95% CI 1.02–1.75).

Two phase III trial examined the efficacy and safety of newer generation cytotoxic agents in concurrent chemoradiotherapy for patients with locally advanced NSCLC.[13,14] The 5-year survival rates (around 20%) were comparable to cur-

Table 4. Cox proportional hazard model for assessment of overall survival

Factors	Hazard ratio	95% CI	*P* value
Age			
10-year increment	1		
	1.34	1.02–1.75	0.03
Sex			
Female	1		
Male	1.23	0.69–2.31	0.46
Body Weight Loss			
<5.0%	1		
>5.1%	1.19	0.69–2.11	0.51
Histology			
Non-squamous	1		
Squamous	1.31	0.80–2.19	0.28
T factor			
T1/2	1		
T3/4	0.91	0.53–1.61	0.77
N factor			
N 0–2	1		
N 3	1.05	0.55–2.08	0.85
Stage			
IIIA	1		
IIIB	0.97	0.52–1.83	0.93

rent analysis. To date, the present report (median survival time 30 months and 7-year overall survival rate 23.1%) is one of the longest observation periods after concurrent chemoradiotherapy using third-generation agents for locally advanced NSCLC. Recently, Tokuda *et al.*[15] reported a favorable long-term survival data (median survival time 2.1 years and 5-year survival rate 31%) of concurrent thoracic radiotherapy with docetaxel and cisplatin in a phase II trial conducted by Okayama Lung Cancer Study Group (OLCSG). It seems that the result of these analyses were about twice better than that of the previous long-term report of chemoradiotherapy with former generation agents by Ohe *et al.*[6] (median survival time 16.1 months and 7-year overall survival rate 12.0%) and others.[16]

Of the 91 patients with relapses, 85 (93%) experienced recurrence within 3 years after initial treatment. Local relapses (37 patients, 41%) and distant relapses (35 patients, 38%) were equally frequent. After 3 years of follow-up, two local, three distant (without brain), and one mixed-site recurrence was observed. Considering the proportion of local recurrence was similar to the OLCSG 0007 trial, a better strategy to control local relapse is a key to improving survival in locally advanced NSCLC.[13] To gain a better local control, the radiation therapy oncology group (RTOG) conducted a phase III trial (RTOG 0617) to examine a higher dose (74 Gy) of radiotherapy with concurrent chemotherapy. However, the experimental arms of higher radiotherapy were terminated early because of survival futility.[17] We recently reported early termination of a multicenter phase II trial of high-dose thoracic radiotherapy (72 Gy) because of slow accrual and pulmonary toxicities.[18] Based on these results, development of another strategy such as surgery followed by induction therapy might offer a better local control in selected patients.[19] On the other hand, 11 of 20 brain relapses as a first recurrence were found within a year of initial treatment. Several authors reported that brain metastases were frequent early in the course after the initial treatment of stage III NSCLC.[20,21] According to our findings and previous reports, intensive brain surveys might be indicated for such patients no longer than 3 years from initial chemoradiotherapy.

The frequency and control of late toxicities, especially lung injury, have been emphasized along with the improvement of survival by concurrent chemoradiotherapy in stage III NSCLC. In the present analysis, four patients (4%) in the docetaxel consolidation trial experienced grade 5 pulmonary toxicities 4.4–9.6 months from initial treatments. On the other hand, life-threatening pulmonary toxicities were not reported in phase I trial. (Table 3) This difference in the frequency of severe pulmonary toxicities might be related to consolidation docetaxel because the dose of cisplatin (80 mg/m^2), vinorelbine (20 mg/m^2) and thoracic radiotherapy (60 Gy) were the same in these two trials except for five patients who received 25 mg/m^2 of vinorelbine in the phase I trial.[7,8] A relatively higher frequency of pulmonary complications was also reported in the experimental arm of the previous phase III trial that examined docetaxel as a consolidation therapy after concurrent chemoradiotherapy.[22,23] Although a note of caution might be indicated with docetaxel, the present result suggests that severe pulmonary toxicities were rare after 10 months from concurrent chemoradiotherapy.

According to recent trials, about half of Japanese patients with locally advanced lung cancer survive more than 2 years after concurrent chemoradiotherapy.[13,14] In those who survived more than 2 years, mortalities due to second primary malignancies and etiologies other than lung cancer were reported by several authors.[15,24] Five patients (4.5%) died without recurrence of lung cancer and whose causes of death were as follows: second primary malignancy (pharyngeal cancer, one patient), community-acquired pneumonia (one patient), sudden death due to unknown etiology (two patients) and suicide (one patient), respectively. With an even greater proportion of patients cured by modern therapies including combined modality treatments, it would be increasingly important to consider and evaluate an appropriate care and monitoring for survivors.

In the present analysis, older age was significantly associated with poor survival (HR 1.34, 95% CI 1.02–1.75) after adjusting for sex, degree of weight loss, histology, T factor, N factor, and stage. In the previous literature on concurrent chemoradiotherapy with cisplatin and vinorelbine, age ($\geq$70 years) was marginally associated with poor survival (HR 1.79, 95% CI 0.94–3.39).[25] Several investigators reported higher incidences of adverse events in elderly patients with locally advanced NSCLC, even though they had a similar survival benefit.[26–28] Furthermore, better clinical outcomes were reported in elderly patients (>70 years) by thoracic radiotherapy rather than chemoradiotherapy with a similar regimen for younger patients.[29,30] Based on these reports, it is necessary to develop an optimal treatment strategy, especially to find the best chemotherapy regimen combined with thoracic radiotherapy, for elderly patients with stage III NSCLC.

This study had several limitations. First, the proportion of patients with stage IIIA disease was relatively high compared to previous phase III trials, which might have a favorable effect on overall survival.[13,14] Second, the population included in this analysis was relatively younger than those reported by Segawa *et al.*[13] and had better prognosis than real world patients. As discussed in this article, younger age might be a better prognostic factor in concurrent chemoradiotherapy (Table 3). The third limitation is potential selection bias in a highly selected population suitable for early phase clinical trials. To enable to follow clinical and prognostic information with the least missing data, however, we selected the patients that participated in the current phase I and feasibility trial of docetaxel consolidation.

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In conclusion, approximately 15% of patients with unresectable stage III NSCLC could be cured with chemoradiotherapy without severe late toxicities after 10 months of follow-up. Although based on the data from a highly selected population participated in phase I and phase II trial, this analysis would strengthen and confirm the previous reports concerning concurrent chemoradiotherapy with third generation cytotoxic agents.

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Disclosure Statement

The authors have no conflict of interest.

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REVIEW

Molecularly targeted approaches herald a new era of non-small-cell lung cancer treatment

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Abstract: The discovery of activating mutations in the epidermal growth-factor receptor (*EGFR*) gene in 2004 opened a new era of personalized treatment for non-small-cell lung cancer (NSCLC). *EGFR* mutations are associated with a high sensitivity to EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib. Treatment with these agents in *EGFR*-mutant NSCLC patients results in dramatically high response rates and prolonged progression-free survival compared with conventional standard chemotherapy. Subsequently, echinoderm microtubule-associated protein-like 4 (*EML4*)–anaplastic lymphoma kinase (*ALK*), a novel driver oncogene, has been found in 2007. Crizotinib, the first clinically available ALK tyrosine kinase inhibitor, appeared more effective compared with standard chemotherapy in NSCLC patients harboring *EML4-ALK*. The identification of *EGFR* mutations and *ALK* rearrangement in NSCLC has further accelerated the shift to personalized treatment based on the appropriate patient selection according to detailed molecular genetic characterization. This review summarizes these genetic biomarker-based approaches to NSCLC, which allow the instigation of individualized therapy to provide the desired clinical outcome.

Keywords: non-small-cell lung cancer, epidermal growth factor receptor, *ALK* rearrangement, gefitinib, erlotinib, crizotinib

Introduction

Non-small-cell lung cancer (NSCLC) has a poor prognosis and remains the leading cause of death related to cancer worldwide.[1] For most individuals with advanced, metastatic NSCLC, cytotoxic chemotherapy is the mainstay of treatment on the basis of the associated moderate improvement in survival and quality of life.[2,3] However, the outcome of chemotherapy in such patients has reached a plateau in terms of overall response rate (25%–35%) and overall survival (OS; 8–10 months).[4] This poor outcome, even for patients with advanced NSCLC who respond to such chemotherapy, has motivated a search for new therapeutic approaches.

Recent years have seen rapid progress in the development of new treatment strategies for advanced NSCLC, in particular the introduction of molecularly targeted therapies and appropriate patient selection. First, the most important change has been customization of treatment according to patient selection based on the genetic profile of the tumor. Small-molecule tyrosine kinase inhibitors (TKIs) that target the epidermal growth-factor receptor (EGFR), such as gefitinib and erlotinib, are especially effective in the treatment of NSCLC patients who harbor activating *EGFR* mutations. In addition, TKIs that target the receptor tyrosine kinase anaplastic lymphoma kinase (ALK) have a high response rate and markedly prolong OS in NSCLC

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patients positive for *ALK* rearrangement. The identification of *EGFR* mutations and *ALK* rearrangement in individuals with NSCLC has thus accelerated the shift to personalized treatment for this condition. Second, recent studies have demonstrated the efficacy of monoclonal antibodies, such as bevacizumab, in combination with first-line platinum-based chemotherapy in advanced non-squamous NSCLC. Third, the introduction of pemetrexed has revealed differences in OS based on histological subtype of NSCLC, with the efficacy of pemetrexed being superior to that of gemcitabine in combination with cisplatin in individuals with non-squamous NSCLC (especially adenocarcinoma), and the opposite being true for those with squamous cell carcinoma. Together, these developments show that treatment for NSCLC is evolving toward a more personalized approach based on histological subtype or the molecular or genetic profile of the tumor. This review summarizes new treatment approaches to NSCLC, focusing on the development of molecularly targeted agents, including EGFR-TKIs and ALK-TKIs, both of which are key agents for personalized (genetic information-based) therapies in individuals with this condition.

EGFR-TKIs

In 2004, three groups in the US reported the landmark findings that a subset of NSCLC patients harbor activating mutations of *EGFR*,[5–7] and those tumors positive for such mutations are highly sensitive to EGFR-TKIs, such as gefitinib and erlotinib. Indeed, most NSCLC patients who experienced a marked response to EGFR-TKIs were found to harbor *EGFR* mutations. *EGFR* mutations are present predominantly in women, never-smokers, individuals with adenocarcinoma, and those of East Asian ethnicity.[8–11] It has now been demonstrated definitively that the efficacy of EGFR-TKIs is largely dependent on the presence of an *EGFR* mutation in the tumor.

The role of EGFR-TKI treatment for NSCLC positive for *EGFR* mutations

Subsequent to the discovery of *EGFR* mutations in a subset of NSCLC patients in the relatively small studies published in 2004, several prospective single-arm studies showed significant efficacy of EGFR-TKIs, with a high response rate of 55%–91%, in such patients.[8,12–18] Our group analyzed individual patient data from seven prospective phase II trials of gefitinib monotherapy in Japan, including a total 148 *EGFR* mutation-positive patients.[19] The Iressa (gefitinib) Combined Analysis of Mutation Positives (I-CAMP) study showed that the overall response rate for gefitinib was 76.4%. With a median follow-up of 20.7 months, the patients treated with gefitinib showed a highly favorable progression-free survival (PFS) of 9.7 months and OS of 24.3 months. Erlotinib yielded similar results, with a median survival time of more than 2 years, in a large prospective study of the Spanish Lung Cancer Group performed with 217 *EGFR* mutation-positive NSCLC patients.[8] A pooled analysis of five additional trials also showed that *EGFR* mutations are a better indicator of clinical outcome in NSCLC patients than are such clinical predictors as sex, tumor histology, smoking status, and ethnicity.[20] These data suggested that there is no major ethnic difference in the pronounced clinical effects of EGFR-TKI treatment in *EGFR* mutation-positive patients, even though the *EGFR* mutation rate differs markedly between East Asian and Western countries, with a lower frequency in the latter.

Taken together, evidence thus supports a key role for EGFR-TKIs as a new and highly effective treatment option for NSCLC patients who harbor activating *EGFR* mutations. The clinical application of these findings, however, raises important issues with regard to molecular analysis of the tumor before initiation of treatment, drug selection, and treatment sequence.

The need for molecular analysis prior to treatment with EGFR-TKIs

Two pivotal phase III trials compared gefitinib with standard platinum chemotherapy in the first-line setting for individuals with advanced NSCLC.[21,22] The patients enrolled in these trials were selected according to clinical characteristics associated with a high prevalence of activating *EGFR* mutations. The largest of these phase III trials, the Iressa pan-Asia Study (IPASS),[22] assigned 1217 East Asian never-smokers (or former light smokers) with previously untreated lung adenocarcinoma to either gefitinib or carboplatin plus paclitaxel. First-line gefitinib treatment yielded a significantly higher overall response rate and longer PFS, the primary end point of the study, compared with chemotherapy. However, the PFS curves crossed at ~6 months after the start of treatment, favoring the chemotherapy group during the initial 6 months and gefitinib thereafter, indicating that the beneficial effect of gefitinib on PFS might be limited to those patients who harbored activating *EGFR* mutations. A total of 683 (56%) tumor samples were obtained from the patients enrolled in this study for exploratory biomarker analysis.[23] *EGFR* mutational status was evaluated in 437 patients, of whom 261 (60%) were found to harbor an activating mutation. In comparison with chemotherapy, gefitinib treatment improved PFS in

patients with *EGFR* mutations, whereas it was inferior to chemotherapy in those without such mutations (Table 1).[22] Even in a patient population selected on the basis of a clinical characteristic associated with a favorable outcome of EGFR-TKI treatment, heterogeneity was clearly apparent between the patients with or without *EGFR* mutations. On the other hand, there was no difference in OS between the two treatment groups for *EGFR* mutation-positive patients in the overall analysis (Table 1).

The First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung (First-SIGNAL),[21] a smaller Asian trial, obtained results similar to those of the IPASS trial. The eligibility criteria for this study were also similar to those of the IPASS trial. A total of 313 Korean never-smokers with adenocarcinoma were randomized to first-line treatment with either gefitinib or gemcitabine and cisplatin. Overall, OS and PFS did not differ significantly between the two groups. Among 96 patients (31%) whose tumors were analyzed for *EGFR* mutations, 42 individuals (44%) were positive for such mutations (Table 1). As in the IPASS study, gefitinib prolonged PFS in *EGFR* mutation-positive patients, although the difference between the two treatment arms was not statistically significant. However, PFS in the *EGFR* mutation-negative patients was worsened by gefitinib compared with chemotherapy. In this study, there was a higher response rate to gefitinib in the mutation-negative population compared with that observed in the IPASS study, which together with the lack of a significant difference in PFS between gefitinib and chemotherapy in the mutation-positive population was due to a higher false-negative rate for *EGFR* mutations that resulted from non-centralized testing. The remarkable finding from both these trials, however, was that patient selection based on clinical characteristics alone was insufficient to predict accurately the benefit of EGFR-TKI treatment,[24] indicating that molecular analysis of *EGFR* mutational status is mandatory prior to treatment.

EGFR-TKIs in the first-line setting for *EGFR* mutation-positive patients with advanced NSCLC

The results of the IPASS study indicated that EGFR-TKIs have promising efficacy for individualized treatment of advanced NSCLC positive for *EGFR* mutations. We conducted a randomized phase III trial (WJTOG3405) that compared gefitinib with platinum-based chemotherapy (cisplatin plus docetaxel) in the first-line setting for 172 patients with advanced NSCLC positive for *EGFR* mutations.[25] This study met the primary end point in that PFS was found to be significantly longer in the gefitinib group than in the chemotherapy group (hazard ratio 0.489, 95% confidence interval 0.37–0.71; $P < 0.0001$). It did not,

Table 1 Results of phase III trials comparing epidermal growth-factor receptor (EGFR)-tyrosine kinase inhibitors with chemotherapy as first-line treatment in non-small-cell lung cancer patients with *EGFR* mutations

Authors	Trial	Regimens	Patients	Method to detect *EGFR* mutation	ORR (%)	PFS		OS	
						Months	HR (95% CI)	Months	HR (95% CI)
Mok et al,[22]	IPASS	Gefitinib	132	SARMS	71.2	9.5	0.48	21.6	1.00
Fukuoka et al[23]		CBDCA plus PAC	129		47.3	6.3	(0.34–0.67) $P < 0.001$	21.9	(0.76–1.33) $P = 0.990$
Han et al[21]	First-SIGNAL	Gefitinib	26	Direct	84.6	8.0	0.54	27.2	1.043
		CDDP plus GEM	16	sequencing	37.5	6.3	(0.269–1.100) $P = 0.086$	25.6	(0.498–2.182) –
Mitsudomi et al[25,26]	WJTOG3405	Gefitinib	86	Various	62.1	9.6	0.520	38.8	1.185
		CDDP plus DOC	86	methods	32.1	6.6	(0.378–0.715) $P < 0.001$	35.5	(0.767–1.829) $P = 0.443$
Maemondo et al[27]	NEJ002	Gefitinib	114	PNA-LNA	73.7	10.8	0.322	27.7	0.887
Inoue et al[28]		CBDCA plus PAC	114	PCR clamp	30.7	5.4	(0.236–0.438) $P < 0.001$	26.6	(0.634–1.241) $P = 0.483$
Zhou et al[30]	OPTIMAL	Erlotinib	82	Direct	83.0	13.1	0.16	22.7	1.04
		CBDCA plus GEM	72	sequencing	36.0	4.6	(0.10–0.26) $P < 0.0001$	28.8	(0.69–1.58) $P = 0.691$
Rosell et al[32]	EUROTAC	Erlotinib	86	Various	64.0	9.7	0.37	19.3	1.04
		CDDP-based	87	methods	15.0	5.2	(0.25–0.54) $P < 0.0001$	19.5	(0.65–1.68) $P = 0.870$

Abbreviations: CBDCA, carboplatin; PAC, paclitaxel; CDDP, cisplatin; GEM, gemcitabine; DOC, docetaxel; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; SARMS, Scorpion amplification-refractory mutation system; PNA-LNA PCR, peptide nucleic acid-locked nucleic acid polymerase chain reaction.

however, reveal a statistically significant improvement in OS in the gefitinib group. Updated OS analysis of the study showed that the median OS of patients who received gefitinib was 35.5 months, which did not differ significantly from the value of 38.8 months for those who received standard chemotherapy (hazard ratio 1.185, 95% confidence interval 0.767–1.829; $P = 0.443$)[26] (Table 1). Similar findings on the superiority of EGFR-TKIs were obtained in another Japanese phase III study (NEJ002),[27] in which 228 NSCLC patients with *EGFR* mutations were assigned to gefitinib or to carboplatin and paclitaxel. The recent updated analysis for this study again demonstrated no significant difference in OS between the two groups. Whereas the median PFS for the gefitinib group was 10.8 months compared with 5.4 months for the chemotherapy group (hazard ratio 0.322, 95% confidence interval 0.236–0.438; $P < 0.001$), the median OS for gefitinib and for chemotherapy was 27.7 and 26.6 months, respectively.[28] When survival curves are virtually identical for different groups in a randomized trial for advanced NSCLC, an improvement in quality of life or cancer-related symptoms becomes an important issue. Whereas the WJTOG3405 trial did not provide data on quality of life, the NEJ002 study found that quality of life was maintained for a longer time in patients receiving gefitinib than in those receiving standard systemic chemotherapy.[29] Several other phase III trials have also shown that EGFR-TKIs improve quality of life compared with chemotherapy.[21,22,30,31] Superiority of erlotinib over platinum-based chemotherapy in terms of overall response rate and PFS but not OS has also been demonstrated in phase III trials[30,32] (Table 1).

None of the phase III trials that have compared EGFR-TKIs with standard platinum-based chemotherapy in patients with *EGFR* mutations has revealed a benefit in terms of OS. Failure to translate an extended PFS into an obvious survival benefit in these studies is accounted for by a high frequency of crossover treatment with EGFR-TKIs after disease progression in the chemotherapy group. However, this finding does not mean that EGFR-TKIs have little value in the first-line setting. In clinical practice, not all patients with *EGFR* mutations who receive standard chemotherapy in the first-line setting will be suitable for subsequent treatment with EGFR-TKIs, as a result of a rapid deterioration of their general condition and performance status due to disease progression. The chance to administer EGFR-TKIs in such patients would thus be missed. Subset analysis of the NEJ002 trial recently showed that the impact of platinum-based chemotherapy on OS was not greater than that of gefitinib in NSCLC patients with *EGFR* mutations.[28] The median OS of patients who were treated with gefitinib in any line but who did not receive platinum-based chemotherapy was more than 2 years, which is an improvement compared with historical data obtained when EGFR-TKIs were not available.[33] EGFR-TKIs are thus now globally recognized as important drugs and the standard first-line treatment for advanced NSCLC patients with *EGFR* mutations.

Resistance to EGFR-TKIs

Most NSCLC patients who harbor activating *EGFR* mutations, including deletions in exon 19 or the point mutation L858R in exon 21, experience an initial marked response to the EGFR-TKIs gefitinib or erlotinib. However, almost all such individuals eventually develop acquired resistance to these drugs within 1 year. In addition, 20%–30% of NSCLC patients with *EGFR* mutations do not show an initial response to EGFR-TKIs.[22,25,27] Therapeutic strategies to overcome EGFR-TKI resistance in NSCLC patients with *EGFR* mutations have been developed on the basis of the biological mechanisms of such resistance, which include a T790M secondary mutation in *EGFR* as well as amplification of the gene for the receptor tyrosine kinase MET, which serves as the receptor for hepatocyte growth factor.

T790M secondary *EGFR* mutation as a mechanism of EGFR-TKI resistance

A secondary point mutation of *EGFR* that results in the substitution of methionine for threonine at amino acid position 790 (T790M) was the first identified mechanism of acquired EGFR-TKI resistance in NSCLC patients.[34,35] About 50%–70% of NSCLC patients who develop acquired resistance to EGFR-TKIs have been found to harbor the T790M secondary mutation, with the mutation not being present in tumor specimens obtained before EGFR-TKI treatment.[36,37] The T790M mutation has also been detected, however, in a small proportion of NSCLC patients who have not yet received any treatment.[38] Several highly sensitive methods, compared with direct sequencing, have recently been developed to detect a low frequency of T790M in genetically heterogeneous clinical specimens. These methods include polymerase chain reaction (PCR) invader,[39] peptide nucleic acid-locked nucleic acid PCR clamp,[40] and Cycleave PCR assays.[37] The Scorpion amplification-refractory mutation system assay identified T790M in circulating tumor cells of NSCLC patients before EGFR-TKI treatment.[41] Matrix-assisted laser desorption ionization–time of flight mass spectrometry detected T790M in 25.2% of TKI-naive NSCLC patients who harbored activating *EGFR* mutations.[42]

The presence of the T790M mutation in NSCLC patients before treatment was found to be associated with a significantly shorter PFS after initiation of EGFR-TKI treatment.[41,42] These observations thus suggest that T790M contributes not only to acquired resistance to EGFR-TKIs but also to intrinsic resistance to these drugs.

Similar to mutations in *BCR-ABL* (T315I)[43] or in *KIT* (T670I)[44] that underlie resistance to imatinib, T790M is thought to interfere with the binding of EGFR-TKIs at the adenosine triphosphate-binding cleft of EGFR.[34,35,45] On the other hand, the affinity of this cleft for adenosine triphosphate is increased by T790M.[46] Treatment with irreversible EGFR-TKIs such as afatinib (BIBW2992)[47] and dacomitinib (PF00299804)[48,49] is thought to be a potential approach to overcome the resistance conferred by T790M (Figure 1A). Although recent preclinical studies have demonstrated only limited activity of irreversible EGFR-TKIs alone in NSCLC cells positive for T790M,[50,51] such studies have shown that combinations of these drugs with other agents – such as afatinib combined with cetuximab (a monoclonal antibody to EGFR)[52] or with PI-103 (an inhibitor of signaling by phosphoinositide 3-kinase and mammalian target of rapamycin)[50] – are more promising as a treatment option to overcome resistance conferred by T790M. In addition, treatment with heat-shock protein 90 inhibitors such as 17-DMAG is also thought to be a potential approach to counter the effect of T790M.[53] Furthermore, WZ4002, which selectively inhibits the activity of EGFR harboring activating mutations and T790M, has been identified as a candidate for translation to the clinic.[54]

MET amplification and other mechanisms of EGFR-TKI resistance

MET amplification was identified as a mechanism of gefitinib resistance in 22% of NSCLC patients with acquired resistance to this drug.[55] Both MET and EGFR signaling were found to activate phosphoinositide 3-kinase via ErbB3 (also known as HER3) in gefitinib-resistant NSCLC cells positive for *MET* amplification.[55] The combination of gefitinib and the MET inhibitor PHA665752 was thus required to block survival signaling in these cells (Figure 1B).[55] In the clinical setting, a phase I/II trial of the MET-TKI crizotinib in combination with erlotinib is ongoing in patients with NSCLC (NCT00965731). The results of the phase I portion of a

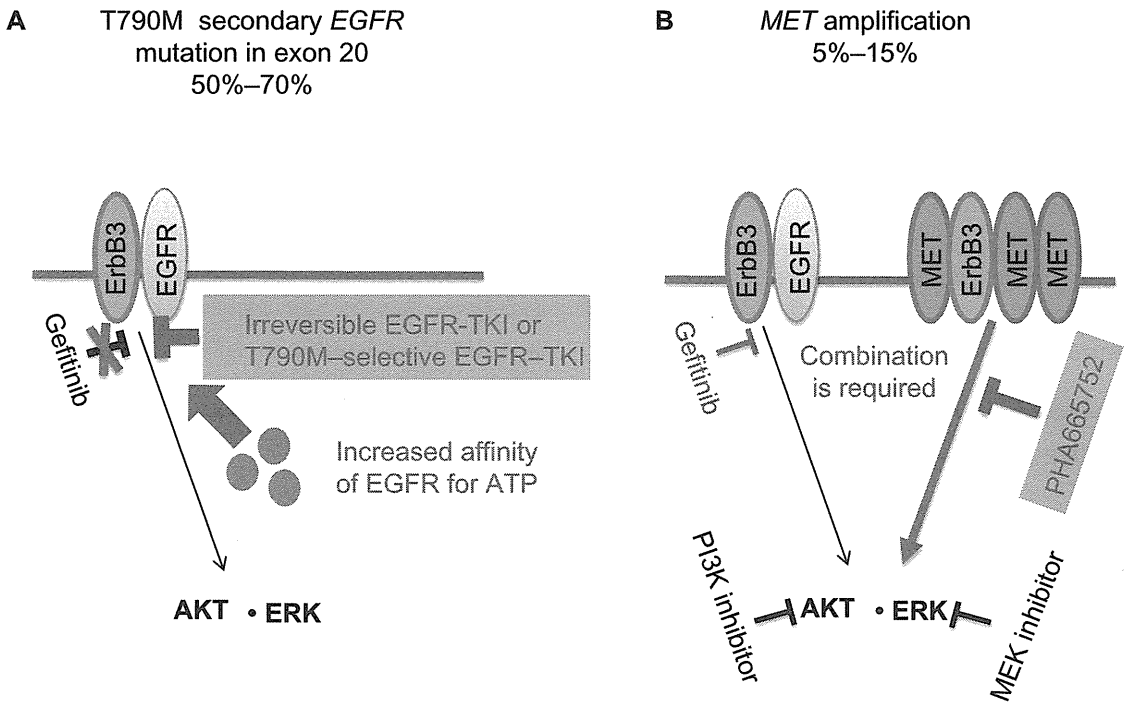

Figure 1 (**A** and **B**) Strategies to overcome acquired epidermal growth-factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) resistance in non-small-cell lung cancer (NSCLC). (**A**) The T790M secondary mutation in exon 20 of *EGFR* is present in 50%–70% of NSCLC patients who acquire resistance to EGFR-TKIs, such as gefitinib or erlotinib. In such patients, gefitinib is not able to compete with adenosine triphosphate (ATP) for binding to the ATP-binding cleft of EGFR because of an increased affinity of this site for ATP. Treatment with irreversible EGFR-TKIs or EGFR-TKIs selective for EGFR harboring T790M is thus thought to represent a potential approach to overcome the resistance conferred by this mutation. (**B**) Amplification of *MET* is apparent in 5%–15% of NSCLC patients who acquire EGFR-TKI resistance. In this situation, MET signaling through ErbB3 (HER3) is activated in addition to EGFR signaling, with the result that both gefitinib and a MET inhibitor (such as PHA665752) are necessary to overcome the resistance conferred by *MET* amplification. The combination of inhibitors that block molecules that function downstream of both EGFR and MET, such as a phosphoinositide 3-kinase (PI3K) inhibitor combined with an MEK (ERK kinase) inhibitor, might also be an alternative approach to overcome the resistance induced by *MET* amplification.

phase I/II dose-finding study for crizotinib were reported at the 2012 Annual Meeting of the European Society for Medical Oncology.[56] This study allowed recruitment of NSCLC patients who had received prior EGFR-TKI therapy. Of the 25 enrolled patients, two showed a partial response and eight had stable disease. Although few studies have addressed other therapies to overcome resistance conferred by *MET* amplification, dasatinib, an inhibitor of the non-receptor tyrosine kinase Src, effectively inhibited the growth of gefitinib-resistant NSCLC cells positive for *EGFR* mutation and *MET* amplification, with this approach being based on the observation that Src acts downstream of both EGFR and MET in these cells.[57] Another preclinical study suggested that combination of gefitinib with the oral fluoropyrimidine derivative S-1 is a potential therapy to overcome acquired resistance due to *MET* amplification.[58]

Several other possible mechanisms of acquired resistance to EGFR-TKIs – including upregulation of insulin-like growth-factor 1 receptor signaling,[59–61] loss of the phosphatase PTEN,[62,63] small-cell transformation,[64–66] and overexpression of hepatocyte growth factor[67] – have been described. However, the mechanism of acquired EGFR-TKI resistance in ~30% of NSCLC patients remains unclear. Recent studies have implicated epithelial–mesenchymal transition (EMT) as a possible mechanism of acquired EGFR-TKI resistance in NSCLC cell lines.[68,69] Furthermore, tumor cells having undergone EMT were detected in a subset of NSCLC patients who developed EGFR-TKI resistance.[70,71] Although histone deacetylase inhibitors may help overcome EMT-related resistance to EGFR-TKIs in NSCLC,[69] further studies are required to provide a better understanding of the role of EMT in such resistance and to identify novel therapeutic strategies to overcome it.

ALK inhibitors

Role of the *EML4-ALK* fusion gene in NSCLC

The *ALK* gene undergoes transforming rearrangements that generate fusion genes in several human hematologic and solid malignancies.[72,73] The partner genes in such fusions with *ALK* include *NPM*, *TPM3*, and *CLTC*. In 2007, Soda et al[74] identified a new *ALK* rearrangement that results from an inversion within chromosome 2p and generates a transforming fusion of *ALK* with the echinoderm microtubule-associated protein-like 4 gene (*EML4*) in NSCLC. Several in-frame fusion variants of *EML4-ALK* have been found to be generated as a result of diversity in the breakpoint–fusion point of *EML4*, and other rare non-*EML4* fusion partners of *ALK*, including *KIF5B* and *TFG*, have since been identified in NSCLC.[75–77]

The reported incidence of *EML4-ALK* has varied among studies as a result of different procedures adopted for detection of the fusion gene.[78] The prevalence of *ALK* rearrangement as detected either by reverse transcription and PCR analysis or by fluorescence in situ hybridization (FISH) is relatively low (in the order of 3%–5%), however, in unselected patients with NSCLC.[78] *ALK* status as determined by FISH, which is regarded as the global standard for detection of *ALK* rearrangement, is currently considered the key predictive marker for treatment of NSCLC patients with an ALK-TKI.[79] Indeed, positive identification of *EML4-ALK* by FISH was associated with a high sensitivity to a small-molecule inhibitor of ALK tyrosine kinase activity in a clinical trial.[79] Although *EML4-ALK* is present in only a small proportion of unselected NSCLC patients, the clinical characteristics of NSCLC patients harboring *EML4-ALK* are highly similar to those of such patients who harbor activating *EGFR* mutations.[76,79,80] Both types of gene alteration are thus found most frequently in patients with adenocarcinoma and in those who are never- or light smokers. Individuals with *EML4-ALK* also tend to be younger than unselected NSCLC patients. With rare exceptions, the presence of *EML4-ALK* appears to be mutually exclusive with that of *EGFR* or *KRAS* mutations.[81] Furthermore, whereas *EGFR* mutations are present more frequently in East Asian populations than in Caucasians, no ethnic differences in the frequency of *EML4-ALK* among NSCLC patients have been reported. With regard to its associated pathological features, *EML4-ALK* tends to be found in lung adenocarcinoma with a mucinous cribriform pattern and signet-ring cells,[82–84] although it has also been detected in other pathological subtypes of NSCLC and other types of cancer, including breast and colorectal tumors.[85,86]

Crizotinib

Whereas several ALK inhibitors have already been introduced into clinical trials, crizotinib was the first ALK-TKI to be so evaluated. Crizotinib was initially designed as an inhibitor of MET and is thus also known as a dual inhibitor of both ALK and MET kinases.[87,88] A phase I trial revealed marked therapeutic efficacy of crizotinib in patients with NSCLC positive for *EML4-ALK* (Table 2), with an overall response rate of 60.8% and a disease control rate of up to 90%.[79,89] Crizotinib was thus approved as a therapeutic drug for certain patients with NSCLC positive for *EML4-ALK* by the US Food and Drug Administration.

Table 2 Clinical trials of crizotinib treatment for advanced non-small-cell lung cancer positive for anaplastic lymphoma kinase rearrangement

Phase	Regimens	Patients	ORR (%)	PFS (months)	OS (months)	References
I	Crizotinib	149	60.8	9.7	Not achieved	79,89
II	Crizotinib	261	59.8	8.1	Not achieved	91
III	Crizotinib	172	65.7	7.7	20.3	90
	Docetaxel	72	6.9	2.6	22.8	
	Pemetrexed	99	29.3	4.2		

Abbreviations: PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

These remarkable findings of crizotinib activity led to two subsequent phase III clinical trials of this drug. The Profile 1007 trial, a global, randomized phase III study with a primary end point of PFS, was designed to compare crizotinib with pemetrexed or docetaxel chemotherapy in patients with advanced NSCLC positive for *EML4-ALK* in the second-line setting.[90] Patients treated with docetaxel or pemetrexed who developed progressive disease were allowed to receive crizotinib in a companion phase II trial (Profile 1005) that was designed to enroll *EML4-ALK*-positive NSCLC patients who were not eligible for Profile 1007.[91] The purpose of the phase II study was to evaluate crizotinib in terms of efficacy and safety through analysis of adverse events. The second phase III trial, Profile 1014, is ongoing and compares crizotinib with cisplatin/carboplatin and pemetrexed as a first-line treatment for patients with advanced NSCLC harboring *EML4-ALK* as detected by FISH (NCT01154140). The primary end point of this trial is also PFS, as was the case for EGFR-TKI trials, because of a high potential for crossover treatment. The Profile 1007 trial showed that crizotinib significantly prolonged PFS and had a higher overall response rate in comparison with standard single-agent chemotherapy (Table 2). However, no statistically significant difference in OS was observed between crizotinib and chemotherapy as a result of the anticipated high level of crossover, although the interim analysis of OS was premature. Furthermore, the improvement in both lung cancer-related symptoms and quality of life relative to baseline observed with crizotinib was significantly greater than that achieved with chemotherapy. These findings thus demonstrated an efficacy for crizotinib in patients with *ALK* rearrangement-positive NSCLC similar to that for EGFR-TKIs in those with *EGFR* mutation-positive NSCLC. These thus established crizotinib treatment as the standard of care for previously treated patients with advanced NSCLC harboring *EML4-ALK*.

Other ALK inhibitors

As of March 2013, at least five additional distinct inhibitors of ALK were undergoing evaluation in early clinical trials worldwide (Table 3). CH5424802 is a potent, selective inhibitor of ALK that was found to show preferential antitumor activity for *ALK* rearrangement-positive cancer cells, such as *EML4-ALK*-positive NSCLC cells and *NPM-ALK*-positive anaplastic large-cell lymphoma cells, in a preclinical study.[92] This agent also potently inhibits the activity of ALK containing the L1196M "gatekeeper mutation," which confers clinical resistance to ALK inhibitors. A phase I trial revealed that CH5424802 had marked efficacy and was well tolerated in patients with *ALK* rearrangement-positive NSCLC.[93] Preliminary results of a phase II trial have also been presented.[94] As of March 2012, 34 patients with *ALK* rearrangement-positive NSCLC previously untreated with ALK inhibitors had been enrolled and received CH5424802 at 300 mg twice daily until the development of progressive disease or unacceptable toxicity. Most of the patients were never-smokers with good performance status and had previously received extensive chemotherapy. Of the first 15 patients receiving this agent, one individual achieved a complete response and ten individuals showed a partial response, yielding a response rate of 73.3%. Most treatment-related adverse events were of grade 1. No dose reductions were necessary, although two cases of grade 3 neutropenia occurred. With regard to eye disorders, which are frequently observed with crizotinib, only one case of grade 1 was described.

LDK378 is another potent and selective small-molecule ALK inhibitor (median inhibitory concentration of 0.00015 μM) that does not inhibit MET. A phase I trial has

Table 3 Anaplastic lymphoma kinase (ALK) inhibitors in early clinical development for treatment of *ALK* rearrangement-positive non-small-cell lung cancer

Inhibitor	Phase	Company	References
CH5424802	II	Chugai	93,94
LDK378	I	Novartis	95
ASP3026	I	Astellas Pharma	100
AP26113	I/II	Ariad	98
X396	I	Xcovery	99

been initiated to determine the maximum tolerated dose and safety profile of this agent in patients with solid tumors positive for genetic alterations of *ALK*, including gene rearrangement.[95] Patients previously untreated with ALK inhibitors or those with disease relapse after previous treatment with such an inhibitor are eligible for enrollment in the trial. As of August 2012, 79 *ALK* rearrangement-positive NSCLC patients, including 56 who had received prior crizotinib treatment, were enrolled and had been administered LDK378 in a dose range of 50–750 mg/day. At doses of ≥400 mg, steady-state concentrations of the drug in plasma exceeded efficacious levels determined in vivo. Among 59 evaluable NSCLC patients, there were 24 responses, yielding a response rate of 40.7%. Among 45 patients with *ALK* rearrangement-positive NSCLC who had experienced progression following crizotinib treatment and received LDK378 at ≥400 mg/day, preliminary responses were apparent in 21 patients (46.7%). Dose-limiting toxicity occurred at doses of ≥400 mg/day and included diarrhea, nausea, vomiting, dehydration, and elevation of alanine aminotransferase levels. The maximum tolerated dose was 750 mg/day. These preliminary results suggest that LDK378 may prove effective for the treatment of patients with *ALK* rearrangement-positive NSCLC who develop acquired resistance to crizotinib. Two phase II trials of LDK378 at a dose of 750 mg/day are ongoing for *ALK* rearrangement-positive NSCLC patients previously treated either with crizotinib or with standard chemotherapy.

AP26113 is a synthetic and highly selective small-molecule inhibitor designed to target ALK. It is actually a dual inhibitor for both ALK and EGFR with activating mutations, whereas it does not inhibit wild-type EGFR. Furthermore, it potently inhibits TKI-resistant forms of these kinases harboring gatekeeper mutations (L1196M in ALK and T790M in EGFR).[96,97] As of September 2012, 15 patients with advanced malignancies, including eleven individuals with NSCLC, had been enrolled in a phase I/II trial of AP26113.[98] The NSCLC patients included four with *ALK* rearrangement-positive tumors that developed resistance to prior crizotinib treatment. All patients received AP26113 at doses of 30–120 mg/day. All four *ALK* rearrangement-positive NSCLC patients showed partial responses, with one patient treated at a dose of 60 mg and the other three at 90 mg. The efficacy and safety of this agent were evaluated at a dose of 120 mg. Neither dose-limiting toxicities nor treatment-related serious adverse events were observed, with the most common adverse events being fatigue and nausea. The results of the phase I portion of the trial thus indicate that AP26113 is effective with acceptable toxicity, and they suggest it may have potential for the treatment of patients with *ALK* rearrangement-positive NSCLC who have experienced disease progression while receiving crizotinib. The phase II portion will evaluate the efficacy and safety of AP26113 in several cohorts.

Phase I clinical trials of the remaining two ALK-specific agents – X-396[99] and ASP3026[100] – have been initiated in patients with *ALK* rearrangement-positive advanced solid tumors and NSCLC, respectively.

Conclusion

Over the course of the last several years, the introduction of molecularly targeted agents such as gefitinib, erlotinib, and crizotinib has resulted in marked changes in treatment approaches to NSCLC. The introduction of these agents into the clinic has followed the identification of genetic changes that give rise to NSCLC and has been accompanied by appropriate patient selection. Such drugs are expensive, however, and their use is limited to subsets of patients in whom the target has undergone activating changes and become an "essential growth driver" for the cancer. Personalized therapy is based on the notion that appropriate patient selection according to detailed molecular genetic characterization will allow the instigation of individualized therapy to provide the desired clinical outcome. Treatment of NSCLC will thus come to rely more and more on a genetic biomarker-based approach to prolong survival. The advent of next-generation technologies for genetic characterization of each patient will be important to facilitate further development of individualized treatment of NSCLC with molecularly targeted agents.

Disclosure

The authors report no conflicts of interest in this work.

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Original Article

Phase 2 Study of S-1 and Carboplatin Plus Bevacizumab Followed by Maintenance S-1 and Bevacizumab for Chemotherapy-Naive Patients With Advanced Nonsquamous Non–Small Cell Lung Cancer

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BACKGROUND: A previous phase 3 trial demonstrated noninferiority in terms of overall survival for combined S-1 (an oral fluoropyrimidine) and carboplatin compared with combined paclitaxel and carboplatin as first-line treatment for advanced non-small cell lung cancer (NSCLC). In the current study, the authors evaluated the efficacy and safety of combined S-1, carboplatin, and bevacizumab followed by maintenance with S-1 and bevacizumab in chemotherapy-naive patients with advanced nonsquamous NSCLC. **METHODS:** Patients received carboplatin (area under the concentration-time curve, 5 mg mL^{-1} per minute) and bevacizumab (15 mg/kg) on day 1 plus oral S-1 (80 mg/m^2 per day) on days 1 through 14 every 21 days for up to 6 cycles. For patients without disease progression, S-1 and bevacizumab were continued until disease progression or unacceptable toxicity developed. **RESULTS:** Forty-eight patients were enrolled in the phase 2 study; of these, 35 patients (72.9%) completed at least 4 cycles. Most toxicities of grade ≥3 were hematologic, and no increase in relative incidence associated with maintenance with S-1 and bevacizumab was observed. The objective response rate was 54.2% (95% confidence interval, 39.2%-68.6%), and the median progression-free survival was 6.8 months (95% confidence interval, 4.3-8.2 months). **CONCLUSIONS:** The regimen of combined S-1, carboplatin, and bevacizumab followed by maintenance with S-1 and bevacizumab was active and feasible as first-line treatment for advanced nonsquamous NSCLC. ***Cancer*** **2013;119:2275-81.**

KEYWORDS: bevacizumab; carboplatin; chemotherapy; maintenance; non-small cell lung cancer; S-1.

INTRODUCTION

Lung cancer is the leading cause of death related to cancer worldwide, with non–small cell lung cancer (NSCLC) accounting for 85% of lung cancer cases.[1] For individuals with advanced or metastatic NSCLC, platinum-based chemotherapy is the mainstay of first-line treatment[2,3] on the basis of the moderate improvement in survival and quality of life it affords compared with best supportive care alone.[4]

A phase 3 study, the Eastern Cooperative Oncology Group (ECOG) E4599 trial, demonstrated that bevacizumab, a humanized monoclonal antibody specific for vascular endothelial growth factor,[5] given with paclitaxel and carboplatin resulted in significant improvements in the overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) compared with paclitaxel and carboplatin alone in individuals with advanced nonsquamous NSCLC.[6] A Japanese phase 2 study also indicated that bevacizumab in combination with paclitaxel and carboplatin improved the ORR and PFS compared with paclitaxel and carboplatin alone.[7] In a confirmatory phase 3 study (the Avastin in Lung [AVAiL] trial), the addition of bevacizumab to cisplatin and gemcitabine resulted in a significant improvements in the ORR and PFS.[8,9] These observations provide a rationale for combining bevacizumab with platinum-doublet chemotherapy in individuals with advanced nonsquamous NSCLC.

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S-1 (TS-1; Taiho Pharmaceutical Company Ltd., Tokyo, Japan) is an oral fluoropyrimidine agent that consists of tegafur (a prodrug of 5-fluorouracil), 5-chloro-2,4-dihydroxypyridine, and potassium oxonate.[10] It has demonstrated activity and acceptable tolerability in phase 2 studies of patients with advanced NSCLC.[11] Our previous phase 3 study demonstrated the noninferiority in terms of OS as well as a favorable toxicity profile for S-1 and carboplatin compared with standard paclitaxel-carboplatin as first-line treatment for patients with advanced NSCLC.[12] Thus, our results indicated that the combination of S-1 and carboplatin is a valid option for the first-line treatment of such patients.

In addition to the enhanced efficacy of cytotoxic chemotherapy observed with bevacizumab, preclinical studies indicate that the combination of bevacizumab with 5-fluorouracil derivatives results in increased antitumor activity.[13,14] Therefore, we have now performed a multicenter phase 2 study to evaluate the efficacy and safety of S-1 and carboplatin in combination with bevacizumab followed by maintenance therapy with S-1 and bevacizumab alone in chemotherapy-naive patients with advanced nonsquamous NSCLC.

MATERIALS AND METHODS

Eligibility

Eligible patients were required be aged ≥20 years and to have histologically or cytologically confirmed stage IIIB or IV nonsquamous NSCLC (diagnosed according to the seventh edition of the International Union Against Cancer cancer staging manual) or recurrence of this condition after surgery. The patients also were required to have measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1); adequate hematologic, hepatic, and renal function; an ECOG performance status of 0 or 1; and no tumor invasion into the trachea, main bronchi, or major vessels. Exclusion criteria included hemoptysis (>2.5 mL of red blood per episode), radiologic evidence of tumor invasion or tumor abutting of major blood vessels, evidence of a brain metastasis >1 cm, current or recent use of full-dose anticoagulants, medically uncontrolled hypertension or a history of thrombotic or hemorrhagic disorders, interstitial pneumonia recognized on a chest x-ray, supporting radiation therapy occupying the pulmonary region in the 3 months before enrollment, and major surgery within 28 days before enrollment. The study was performed according to good clinical practices and ethical principles outlined in the Declaration of Helsinki. The study protocol was approved by the institutional review board at each participating center, and all patients signed written informed consent forms before enrollment. The trial has been registered under University Medical Hospital Information Network (UMIN) Clinical Trials Registry Identifier UMIN 000003698.

Study Design and Treatment

The study was designed as a prospective, multicenter, single-arm phase 2 trial of first-line combination therapy with S-1, carboplatin, and bevacizumab followed by continuous maintenance therapy with S-1 and bevacizumab. The primary endpoint was treatment efficacy measured as the ORR in patients who received at least 1 course of the initial combination therapy. OS, PFS, the disease control ratio, and adverse events also were evaluated as secondary endpoints.

Patients received S-1 orally at a dose of 80 mg/m^2 per day on days 1 through 14 as well as carboplatin at a dose calculated to produce an area under the concentration-time curve of 5 mg mL^{-1} per minute and bevacizumab at a dose of 15 mg/kg as an intravenous infusion on day 1. The combination therapy was repeated every 21 days for up to 4 to 6 cycles unless there was evidence of disease progression or intolerance of the study treatment. After 4 to 6 cycles of treatment with S-1, carboplatin, and bevacizumab, patients who attained a complete response (CR), a partial response (PR), or stable disease (SD) continued to receive cycles of maintenance therapy with S-1 and bevacizumab every 21 days until they had evidence of disease progression or developed unacceptable toxicity. Administration of S-1 during the maintenance phase was interrupted if patients developed grade 4 neutropenia, a platelet count <50,000/μL, a serum creatinine concentration ≥1.5 mg/dL, a serum total bilirubin concentration ≥2.0 mg/dL, a putative infection with fever of at least 38°C, or severe diarrhea or stomatitis (grade 2 or higher). Treatment with S-1 and bevacizumab was resumed if the neutrophil count was ≥1500/μL, the platelet count was ≥100,000/μL, the serum total bilirubin concentration was <1.5 mg/dL, there was no infection with fever of at least 38°C, and diarrhea or stomatitis was grade 1 or lower.

Subsequent cycles of treatment were withheld until the following criteria were satisfied: neutrophil count, ≥1500/μL; platelet count, ≥100,000/μL; performance status, 0 to 2; serum total bilirubin concentration, ≤1.5 mg/dL; weight loss, grade 2 or lower abnormal electrolytes, peripheral nerve damage, and hepatotoxicity (based on aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels); grade 3 or lower

hypertension; grade 2 or lower proteinuria; grade 0 hemoptysis or bleeding; and no infection with fever of at least 38°C. The study therapy was stopped if grade 2 or higher hemoptysis developed or if bleeding persisted after treatment of hemorrhage. Patients also were to be removed from the study if the next treatment cycle had not started within 42 days of the previous dosing as a result of toxicity.

Baseline and Treatment Assessments

Baseline evaluations included medical history, physical examination, electrocardiogram, ECOG performance status, and laboratory analyses. Computed tomography (CT) scans of the chest and abdomen, magnetic resonance imaging (MRI) studies of the brain, and bone scintigraphy or positron emission tomography (PET)-CT studies were performed for tumor assessment within 28 days of initiation of the study treatment. CT scans of the chest and abdomen were repeated every 2 cycles, brain MRI studies were repeated every 3 months or on the appearance of any neurologic symptoms, and bone scintigraphy or PET-CT studies were performed every 6 months or on the appearance of any bone-related symptoms. All treatment responses were defined according to RECIST version 1.1. If a patient had a documented a CR or a PR, then the respective response had to be confirmed 4 weeks later. A patient was considered to have SD if their response was confirmed and sustained for at least 6 weeks. PFS was calculated from the date of enrollment to the date of confirmation of progressive disease or the date of death from any cause. PFS from the start of maintenance therapy was calculated by subtracting the period of the initial combination therapy from overall PFS. OS was calculated from the date of initial treatment to the date of death from any cause. For patients with unknown death status, OS was censored at the last date the patient was known to be alive. Patients were assessed for toxicity according version 4.0 of the National Cancer Institute Common Toxicity Criteria.

Statistical Analysis

We assumed that an ORR of 50% for the study regimen in eligible patients would indicate potential usefulness, whereas an ORR of 30% would be the lower limit of interest. On the basis of these assumptions, our study was designed to have a power of 80% and a 1-sided level of type I error of 0.05, resulting in a requirement for 45 patients. A Simon 2-stage design (MiniMax) was adopted. Nineteen patients were to be initially assessed for response, and if more than 6 patients manifested a PR or a CR, then 26 additional patients would be added to the assessment. Efficacy and safety analyses were planned for patients who received at least 1 cycle of the treatment. PFS and OS were analyzed using the Kaplan-Meier method to estimate the median points with 95% confidence intervals (CIs).

RESULTS

Patient Characteristics

Between April 2010 and October 2011, a total of 48 patients with recurrent or newly diagnosed, advanced nonsquamous NSCLC were enrolled at 3 participating centers. The baseline characteristics of all assigned patients are provided in Table 1. The median age for the treated patients was 65.5 years (range, 35-77 years), 33 patients (68.8%) were men, 42 patients (87.5%) had adenocarcinoma histology, 40 patients (83.3%) had stage IV disease, and 16 patients (33.3%) were never-smokers. Epidermal growth factor receptor mutation status was evaluated in 42 patients (87.5%), and 4 individuals had activating mutations identified.

Treatment Delivery

Patient disposition is illustrated in Figure 1. Overall, 35 patients (72.9%) completed at least 4 cycles of S-1 and carboplatin combined with bevacizumab, and 29 patients (60.4%) were shifted to subsequent maintenance therapy with S-1 and bevacizumab and received a median of 4 cycles (range, 1-18 cycles). In the initial combination phase, 13 of 48 patients (27.1%) experienced dose

TABLE 1. Baseline Characteristics of the Study Patients, n = 48

Characteristic	No. of Patients (%)
Age: Median [range], y	65.5 [35-77]
Sex	
Men	33 (68.8)
Women	15 (31.3)
ECOG PS	
0	15 (31.3)
1	33 (68.8)
Disease stage	
IIIB	3 (6.3)
IV	40 (83.3)
Recurrence	5 (10.4)
Histology	
Adenocarcinoma	42 (87.5)
Large cell carcinoma	1 (2.1)
Others	5 (10.4)
Smoking status	
Never-smoker	16 (33.3)
Former or current smoker	32 (66.7)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status.

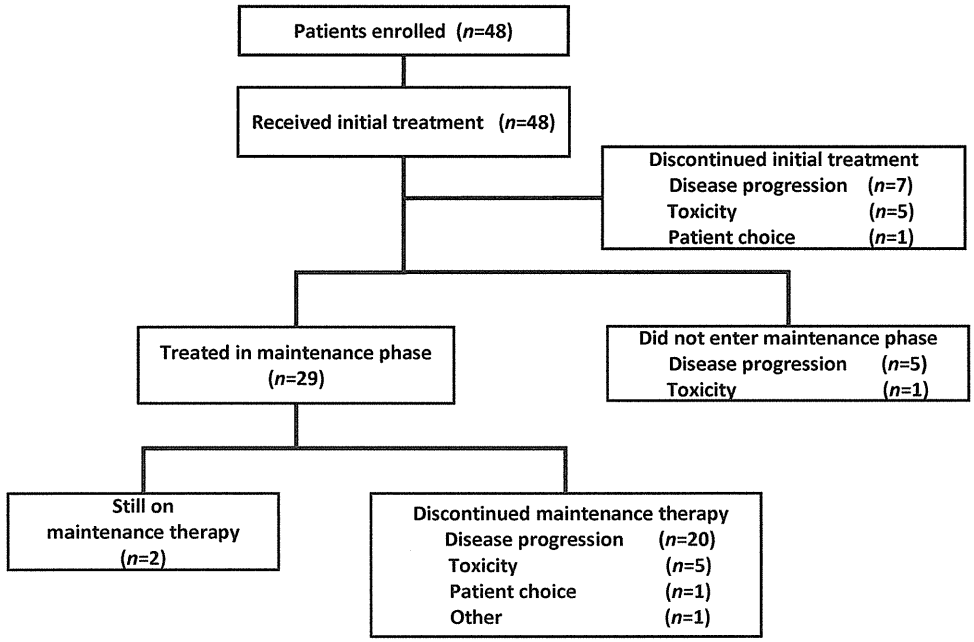

Figure 1. This is a Consolidated Standards of Reporting Trials (CONSORT) diagram for the current study.

TABLE 2. Treatment Outcomes for the Study Patients,, n = 48

Outcome	No. of Patients (%)
Complete response	0 (0)
Partial response	26 (54.2)
Stable disease	11 (22.9)
Progressive disease	11 (22.9)
Overall response rate [95% CI], %	54.2 [39.2-68.6]
Disease control rate [95% CI], %	77.1 [67.2-88]

Abbreviations: CI, confidence interval.

reductions, and 34 patients (70.8%) experienced a treatment delay because of adverse events, mostly related to myelosuppression. Among the 29 patients who received maintenance therapy with S-1 and bevacizumab, 2 individuals (6.9%) underwent a dose reduction, and 20 individuals (69%) had a treatment delay.

Efficacy

Forty-eight patients were deemed eligible for evaluation of treatment response. Twenty-six patients attained a PR, and no patients attained a CR, yielding an ORR of 54.2% (95% CI, 39.2%-68.6%) (Table 2). Eleven patients (22.9%) had SD, yielding a disease control ratio (CR + PR + SD) of 77.1% (95% CI, 67.2%-88%). Eleven patients (22.9%) had progressive disease as their best response. At a median follow-up of 13.9 months (range, 2.0-27.5 months), the median PFS was 6.8 months (95% CI, 4.3-8.2 months) (Fig. 2), and the median OS was 22.8 months (lower limit of 95% CI, 13.1 months). Thirty-seven patients (77.1%) received subsequent chemotherapy regimens as poststudy treatment.

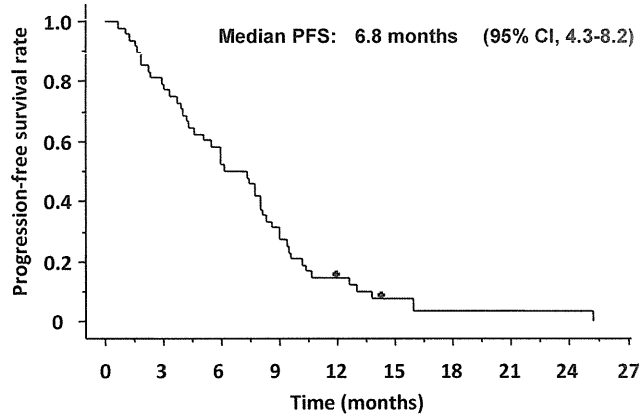

Figure 2. This Kaplan-Meier curve illustrates progression-free survival (PFS). CI indicates confidence interval.

Safety Analysis

All 48 patients who received the study treatment were deemed eligible for safety analysis. The major adverse events for each treatment phase (initial and maintenance phases) are listed in Table 3. During treatment with the combination of S-1, carboplatin, and bevacizumab, grade

TABLE 3. Incidence of Adverse Events in the Study Patients

	No. of Patients (%)					
	Initial Treatment Phase, n = 48			Maintenance Phase, n = 29		
Adverse Event	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic AEs						
Leukopenia	43 (89.6)	4 (8.3)	0 (0)	17 (58.6)	0 (0)	0 (0)
Neutropenia	44 (91.7)	12 (25)	3 (6.3)	16 (55.2)	4 (13.8)	0 (0)
Anemia	37 (77.1)	2 (4.2)	3 (6.3)	25 (86.2)	1 (3.4)	0 (0)
Thrombocytopenia	43 (89.6)	5 (10.4)	3 (6.3)	11 (37.9)	0 (0)	0 (0)
Nonhematologic AEs						
Fatigue	36 (75)	1 (2.1)	0 (0)	14 (48.3)	0 (0)	0 (0)
Appetite loss	31 (64.6)	3 (6.3)	0 (0)	12 (41.4)	0 (0)	0 (0)
Proteinuria	25 (52.1)	0 (0)	0 (0)	9 (31)	2 (6.9)	0 (0)
Nausea	21 (43.8)	0 (0)	0 (0)	9 (31)	0 (0)	0 (0)
Mucositis	17 (35.4)	0 (0)	0 (0)	9 (31)	1 (3.4)	0 (0)
Hypertension	14 (29.2)	4 (8.3)	0 (0)	5 (17.2)	0 (0)	0 (0)
Diarrhea	11 (22.9)	3 (6.3)	0 (0)	4 (13.8)	1 (3.4)	0 (0)
Hemoptysis	6 (12.5)	0 (0)	0 (0)	1 (3.4)	0 (0)	0 (0)
Intestinal perforation	2 (4.2)	0 (0)	1 (1.1)	1 (3.4)	0 (0)	0 (0)
Interstitial pneumonia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AEs, adverse events.

3 and higher hematologic toxicities included neutropenia (31.3%), thrombocytopenia (16.7%), anemia (10.5%), and leukopenia (8.3%). Among the 29 patients who continued with S-1 plus bevacizumab during the maintenance phase, 4 patients (13.8%) had grade 3 neutropenia, and 1 patient (3.4%) had grade 3 anemia during the period. Most nonhematologic adverse events were of mild to moderate intensity (grade 1 or 2); those that were grade 3 or higher during the initial phase of the study treatment included hypertension (8.3%), appetite loss (6.3%), diarrhea (6.3%), fatigue (2.1%), and intestinal perforation (2.1%); whereas those during the maintenance phase included proteinuria (6.9%), mucositis (3.4%), and diarrhea (3.4%). There were no clinically relevant bleeding events during either treatment phase for any patient, and there were no treatment-related deaths.

DISCUSSION

This multicenter phase 2 study is the first to evaluate the efficacy and safety of a new regimen, S-1 and carboplatin combined with bevacizumab followed by maintenance S-1 and bevacizumab, for first-line treatment of patients with advanced nonsquamous NSCLC. We observed that the combination was active, with an ORR of 54.2% (95% CI, 39.2%-68.6%), which met the primary objective of the study. At a median follow-up of 13.9 months, the median PFS was 6.8 months, and the median OS was 22.8 months. Our previous phase 3 study demonstrated that the combination of S-1 and carboplatin was not inferior relative to a standard paclitaxel-carboplatin regimen in terms of OS for chemotherapy-naive patients with advanced NSCLC.[12] The ORR for S-1 and carboplatin, however, was significantly lower than that for paclitaxel-carboplatin (20.4% vs 29%; $P = .019$). This difference in ORR also was apparent for patients who had nonsquamous NSCLC (18.8% vs 27.6%; $P = .027$).[15] It is believed that bevacizumab is targets the tumor vasculature, reducing interstitial pressure and increasing vessel permeability, thereby resulting in enhanced tumor sensitivity to cytotoxic chemotherapy.[16,17] Although there are limitations to comparisons of results among different studies, the ORR (54.2%) obtained in the current trial is indicative of increased antitumor activity of S-1 and carboplatin with the addition of bevacizumab.

Our trial also indicates a favorable toxicity profile for the study treatment. All toxicities were manageable with symptomatic treatment and dose reduction or interruption. In our previous phase 3 study, the combination of S-1 and carboplatin was associated with significantly lower rates of neutropenia, leukopenia, and febrile neutropenia compared with paclitaxel and carboplatin.[12] Consistent with these results, most patients enrolled in the current study had only mild hematologic toxicities, and no cases of febrile neutropenia occurred. Thus, no obvious exacerbation of chemotherapy-induced myelosuppression by the addition of bevacizumab to S-1 and carboplatin was apparent. There also was no increase in the relative incidence of hematologic toxicities associated with maintenance therapy with S-1 and bevacizumab. With regard to nonhematologic toxicities, there were no grade 3 or 4

toxicities encountered in >10% of patients throughout the study treatment. Mild or moderate fatigue and gastrointestinal adverse effects were the most frequent nonhematologic toxicities, consistent with findings from previous studies with combined S-1 and carboplatin.[12] Hypertension and proteinuria have been associated with bevacizumab administration[6,8] and also were observed in the current study. Two patients experienced grade 3 proteinuria in the maintenance period; however, both cases were fully reversible without dose reduction or cessation of treatment. Because clinically significant (grade ≥3) hemoptysis was observed in 0.9% to 1.9% of patients who received bevacizumab in the ECOG E4599 and AVAiL trials,[6,8] the lack of fatal bleeding events and treatment-related deaths in the current study also is noteworthy. Patients with brain metastases have been excluded from most clinical trials of bevacizumab for fear of intracranial hemorrhage.[6,8] However, recent data suggest that the risk of developing intracranial hemorrhage is independent of bevacizumab therapy in patients with NSCLC who have brain metastases.[18] Conversely, another study suggested that intracranial hemorrhage is more likely to become clinically symptomatic in larger (>2 cm) brain metastases.[19] On the basis of these data, patients with brain metastases that measured <1 cm were eligible for the current study. Indeed, 2 patients who had asymptomatic, small (<1 cm) brain metastases were enrolled in the study, but no intracranial hemorrhage was observed.

Bevacizumab is used in the maintenance setting for patients with advanced nonsquamous NSCLC on the basis of the results from the ECOG E4599 and AVAiL trials, in which bevacizumab monotherapy after induction therapy with bevacizumab plus platinum doublets was administered until patients developed disease progression.[6,8] More recently, a large phase 3 trial (PARAMOUNT) demonstrated that maintenance therapy with pemetrexed after induction therapy with pemetrexed and cisplatin resulted in a significant improvement in PFS and OS.[20] Furthermore, an ongoing ECOG phase 3 trial is comparing bevacizumab alone, pemetrexed alone, and the pemetrexed-bevacizumab combination for maintenance therapy after initial therapy with paclitaxel, carboplatin, and bevacizumab (National Clinical Trials identifier NCT01107626). Thus, extensive efforts are under way to examine the effects of the combination of bevacizumab and chemotherapy during the maintenance phase of treatment for advanced nonsquamous NSCLC. On the basis of the low level of toxicity accumulation for S-1,[21] we explored the efficacy and feasibility of continued maintenance therapy with S-1 and bevacizumab in the current study. The favorable tolerability profile of maintenance with S-1 and bevacizumab after induction therapy with S-1, carboplatin, and bevacizumab is reflected in out observation that 60% of patients were able to continue on S-1 and bevacizumab for a median of 4 cycles (range, 1-18 cycles). Among the 29 patients who received maintenance therapy with S-1 and bevacizumab, the median PFS of 8.2 months (95% CI, 7.4-9.6 months) from the beginning of induction treatment is encouraging and compares favorably with that of 6.9 months reported in the PARAMOUNT study for maintenance with pemetrexed monotherapy. Despite the limitations to comparisons of results from different studies, these data may stimulate further interest in the clinically relevant efficacy of maintenance therapy with S-1 and bevacizumab.

In conclusion, here, we have presented results from the first phase 2 study of combined S-1, carboplatin, and bevacizumab followed by maintenance therapy with S-1 and bevacizumab. Although our study was not randomized, the promising efficacy and favorable toxicity profile of the study treatment justify further development of regimens that contain S-1 and bevacizumab. A large randomized phase 3 trial comparing single-agent S-1 with docetaxel in previously treated patients with advanced NSCLC in Asian countries is currently under way (JPRN-JapicCTI-101155). We believe that further randomized trials are warranted comparing S-1, carboplatin, and bevacizumab with the current standard of care (paclitaxel, carboplatin, and bevacizumab) in previously untreated patients with advanced nonsquamous NSCLC.

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