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ORIGINAL REPORT

Phase II Clinical Trial of Chemotherapy-Naïve Patients ≥ 70 Years of Age Treated With Erlotinib for Advanced Non–Small-Cell Lung Cancer

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ABSTRACT

Purpose
This is a phase II, multicenter, open-label study of chemotherapy-naïve patients with non–small-cell lung cancer (NSCLC) and age ≥ 70 years who were treated with erlotinib and evaluated to determine the median, 1-year, and 2-year survival. The secondary end points include radiographic response rate, time to progression (TTP), toxicity, and symptom improvement.

Patients and Methods
Eligible patients with NSCLC were treated with erlotinib 150 mg/d until disease progression or significant toxicity. Tumor response was assessed every 8 weeks by computed tomography scan using Response Evaluation Criteria in Solid Tumors. Tumor samples were analyzed for the presence of somatic mutations in *EGFR* and *KRAS*.

Results
Eighty eligible patients initiated erlotinib therapy between March 2003 and May 2005. There were eight partial responses (10%), and an additional 33 patients (41%) had stable disease for 2 months or longer. The median TTP was 3.5 months (95% CI, 2.0 to 5.5 months). The median survival time was 10.9 months (95% CI, 7.8 to 14.6 months). The 1- and 2- year survival rates were 46% and 19%, respectively. The most common toxicities were acneiform rash (79%) and diarrhea (69%). Four patients developed interstitial lung disease of grade 3 or higher, with one treatment-related death. *EGFR* mutations were detected in nine of 43 patients studied. The presence of an *EGFR* mutation was strongly correlated with disease control, prolonged TTP, and survival.

Conclusion
Erlotinib monotherapy is active and relatively well tolerated in chemotherapy-naïve elderly patients with advanced NSCLC. Erlotinib merits consideration for further investigation as a first-line therapeutic option in elderly patients.

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INTRODUCTION

Patients older than 70 years of age derive a clinical benefit from systemic chemotherapy.[1-3] Yet, elderly patients are less likely than younger patients to receive chemotherapy or be included in clinical trials.[4-8] Concern for treatment-related toxicities may be partly responsible for this disparity. Combination chemotherapy causes increased hematologic and neuropsychiatric toxicity in older patients. Moreover, greater than 90% of elderly patients experience a grade ≥ 3 toxicity when treated with a platinum-based doublet.[3] Availability of an effective, less toxic therapy might help extend potentially beneficial treatment to a greater proportion of older patients.

Given the manageable toxicity and demonstrated efficacy of erlotinib in patients experiencing treatment failure with one to two prior regimens,[9] we conducted a phase II study of erlotinib in chemotherapy-naïve elderly patients (age ≥ 70 years) with stage IIIB or IV non–small-cell lung cancer (NSCLC). As part of the trial, pretreatment tissue was collected for future correlative science analyses. When it was discovered that *EGFR* mutations were associated with sensitivity to gefitinib and erlotinib[10-12] and that *KRAS* mutations were associated with resistance to these agents,[13,14] specimens were then analyzed for these mutations. This allowed investigators to correlate mutation status with clinical outcomes in patients not yet exposed to other chemotherapy regimens.

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PATIENTS AND METHODS

Patient Selection

Eligible patients were ≥ 70 years of age with histologically or cytologically confirmed stage IIIB/IV NSCLC. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status of 0 to 2; WBC ≥ 3,000/μL; hemoglobin ≥ 9.0 g/dL; platelet count ≥ 100,000/μL; total bilirubin ≤ 1.5 mg/dL; AST ≤ 2.0× institutional upper limit of normal; creatinine ≤ 1.5 mg/dL; measurable or assessable lesions as defined by Response Evaluation Criteria in Solid Tumors; and life expectancy more than 8 weeks. Patients with stable brain metastases after surgical resection and/or cranial irradiation were eligible. Exclusion criteria included prior chemotherapy or treatment with any ErbB1- or ErbB2-targeted agent; major surgery or radiation therapy within the last 21 days; any malignancy within the last 5 years (excluding nonmelanoma skin cancers or definitively treated cervical cancer); any active gastrointestinal disorder that alters motility or absorption; and severe and unstable medical comorbidities.

Study Procedures and Treatment

The study was approved by the Dana-Farber/Partners Cancer Care institutional review board. All patients gave written, informed consent. Baseline assessment included a history and physical examination, standard laboratory studies, ECG, computed tomography (CT) of the chest and abdomen, head CT or magnetic resonance imaging, and quality-of-life (QOL) assessment using the patient scale of the Lung Cancer Symptom Scale.[15] Lung cancer histology was classified using the 1999 WHO classification system.[16]

Patients were treated with erlotinib 150 mg daily without interruption until disease progression, severe or intolerable toxicity, or withdrawal of consent. Compliance was checked after each 28-day cycle with a treatment diary. At the start of each cycle, patients underwent assessment of performance status, adverse events, and QOL; physical examination; and laboratory studies. Tumor assessment by CT was evaluated after every two cycles of therapy. Toxicity was graded by the National Cancer Institute Common Toxicity Criteria, version 2.0.[17] Treatment interruptions up to 14 days were allowed. For toxicities ≥ grade 3, patients were restarted on a reduced dose (100 mg/d) if symptoms improved to ≤ grade 2 within 14 days. A second dose reduction to 50 mg/d was allowed, if necessary.

Statistical Analysis

This single-arm, open-label, phase II study recruited 82 patients in two centers. In this two-stage trial, continuation past the first stage was based on a response rate ≥ 10% among the first 29 patients enrolled. The primary end point of the study was median survival. Secondary end points included clinical response rate, time to progression (TTP), toxicity, QOL, and correlation of *EGFR* and *KRAS* mutations with clinical outcomes.

Study size was based on a statistical model that estimated that a cohort of 60 erlotinib-treated patients achieving a median survival of 37 weeks would provide sufficient power to warrant a phase III trial comparing erlotinib with vinorelbine.[18] After the discovery of activating mutations in tumor *EGFR*,[10,11] the planned study size was expanded to 80 patients to increase the number of tumor samples available for *EGFR* and *KRAS* mutation analyses.

Best clinical response to treatment with erlotinib was determined using Response Evaluation Criteria in Solid Tumors.[19] TTP and survival were calculated from the date of enrollment to the date of progression or death, respectively. Outcomes were censored if an end point was not reached by the time of last follow-up or if a patient was lost to follow-up. TTP and survival were estimated using the Kaplan-Meier method.[20] Univariate analyses of TTP and survival used the log-rank test to examine effects of baseline clinical factors, *EGFR* mutation status, and treatment-related rash. Proportional hazards models were fitted to TTP and overall survival data to assess the effects of mutational status and clinical characteristics.[21] Statistical analyses were performed using SAS, version 9.1 (SAS Institute Inc, Cary, NC).

Symptom Response and Quality-of-Life Analysis

Symptoms and global QOL were assessed using the nine-item, visual analog patient scale of the Lung Cancer Symptom Scale. Results on symptom prevalence, response, and QOL changes will be reported separately.

EGFR and KRAS Mutation Analysis

Written consent for tissue banking and correlative studies was obtained. Tumor specimens (frozen or paraffin embedded) were collected from previous diagnostic or surgical procedures. No specific requirements were prospectively mandated for the type of tumor specimen. The primary correlative science analysis was determination of the presence of *EGFR* and *KRAS* mutations.

For patients with sufficient tissue for direct DNA sequencing, tumor cells were isolated by microdissection. Exons 18 through 24 of the *EGFR* and exons 2 and 3 of *KRAS* were amplified and sequenced according to previously described methods.[10,11,22] For tumor samples deemed inadequate by a molecular pathologist for direct sequencing based on a high percentage of normal cells (< 50% tumor cells), mutation analysis was performed with the WAVE-HS (Transgenomic Inc, Omaha, NE) platform using previously published methods.[23] All detected mutations were confirmed by repeat analysis.

RESULTS

Patients

Eighty-two patients were enrolled between March 2003 and May 2005; 80 were eligible for treatment. Table 1 lists the baseline patient

Table 1. Baseline Patient Characteristics

Characteristic	No. of Patients	%
Patients enrolled	82	
Patients eligible	80	
Sex		
Male	40	50
Female	40	50
Age, years		
Median	75	
Range	70-91	
Race/ethnicity		
White	76	95
Black	3	4
Asian/Pacific Islander	1	1
ECOG performance status		
0	13	16
1	59	74
2	8	10
Stage at enrollment		
IIIB	12	15
IV	68	85
Histology		
Adenocarcinoma, non-BAC	41	51
Adenocarcinoma with BAC features	6	8
BAC	4	5
Squamous cell carcinoma	7	9
Other NSCLC	22	28
Smoking status		
Never	8	10
Former	67	84
Current	5	6
Prior therapy		
Surgery only	13	16
Radiation only	12	15
Both	9	11
Neither	46	58

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BAC, bronchioloalveolar carcinoma; NSCLC, non–small-cell lung cancer.

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and disease characteristics. Two patients were deemed ineligible before receiving erlotinib therapy; one was found to have only early-stage disease, whereas a second had concurrent lymphoma.

Toxic Effects

Table 2 lists the treatment-related adverse effects by grade. The most frequent adverse effects were rash (79%) and diarrhea (69%). In general, toxicities were mild (grade 1 to 2) and easily managed.

Fifteen patients experienced treatment-related toxicities ≥ grade 3. Thirteen patients required dose reduction to 100 mg/d for treatment-related toxicity (eight patients with rash, two with hand-foot syndrome, one with mucositis, one with eye dryness and irritation, and one with diarrhea). Twelve patients were removed from the protocol because of erlotinib-related toxicity (three patients with interstitial lung disease [ILD], three with dehydration, three with diarrhea, one with hemoptysis, one with rash, and one with anorexia). There were four patients with possible ILD, with one treatment-related death. Of three patients with major bleeding (two with gastrointestinal bleeds and one with hemoptysis), two patients had concomitantly received erlotinib and warfarin and had elevations in their prothrombin time, with international normalized ratios of more than 10.

There were several notable events believed to be unrelated to erlotinib. These were primarily vascular (three cerebrovascular accidents and one myocardial infarction) and occurred in patients with pre-existing risk factors for these conditions; two stroke patients had high-grade stenosis of the internal carotid artery on magnetic resonance angiography, and another patient had atrial fibrillation and mitral regurgitation. The myocardial infarction patient had known coronary artery disease, hypertension, and hyperlipidemia. There was also a case of melanoma occurring in a patient with a prior history of suspicious skin lesions and dermatologic care that predated administration of erlotinib.

Response

There were eight partial responses (PR) among the eighty patients treated (response rate, 10%). Thirty-three patients (41%) achieved stable disease (SD), whereas 28 patients (35%) had progressive disease as their best clinical response. The overall disease control rate (PR + SD) was 51%. Eleven patients were removed from study before being evaluated for response; five patients had toxicity (two had diarrhea, one had rash, one had dehydration, and one had hemoptysis), three had exacerbation of pre-existing medical conditions (one had coronary artery disease, one had stroke, and one had chronic obstructive pulmonary disease), two withdrew consent before restaging scans, and one was lost to follow-up.

TTP and Survival

All 80 treated patients were assessable for TTP and survival, with minimum potential follow-up of 7 months and median potential follow-up of 23 months. At the time of analysis, there were 57 deaths, 22 patients confirmed alive, and one patient lost to follow-up. Of the surviving patients, only seven remain progression free on therapy with erlotinib (range, 7.3 to 31.8 months). Median TTP was 3.5 months (95% CI, 2.0 to 5.5 months; Fig 1A). One-year progression-free rate was 20%. Median survival time was

Table 2. Treatment-Related Adverse Effects

	Toxicity Grade									
	1		2		3		4		5	
Toxicity	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Rash	27	34	31	39	5	6	—	—	—	—
Diarrhea	42	53	9	11	4	5	—	—	—	—
Dry skin	24	30	9	11	—	—	—	—	—	—
Anorexia	14	18	4	5	1	1	—	—	—	—
Fatigue	9	11	7	9	—	—	—	—	—	—
Nausea	11	14	2	3	2	3	—	—	—	—
Elevated bilirubin	12	15	3	4	—	—	—	—	—	—
Elevated hepatic transaminases	11	14	3	4	1	1	—	—	—	—
Alopecia	11	14	3	4	—	—	—	—	—	—
Nail changes/pain	11	14	1	1	—	—	—	—	—	—
Mucositis	5	6	5	6	1	1	—	—	—	—
Ocular dryness or irritation	6	8	2	3	2	3	—	—	—	—
Dehydration	2	3	4	5	3	4	—	—	—	—
Elevated creatinine	3	4	3	4	—	—	1	1	—	—
Hypokalemia	4	5	—	—	2	3	—	—	—	—
Hand-foot skin reaction	2	3	1	1	2	3	—	—	—	—
Interstitial lung disease	—	—	—	—	3	4	—	—	1	1
Elevated PT and/or PTT	—	—	1	1	2	3	—	—	—	—
Hyperkalemia	2	3	—	—	1	1	—	—	—	—
Hypomagnesemia	1	1	—	—	1	1	—	—	—	—
GI bleeding	1	1	—	—	1	1	1	1	—	—
Hemoptysis	—	—	—	—	—	—	1	1	—	—
Hypophosphatemia	—	—	—	—	1	1	—	—	—	—

Abbreviations: PT, prothrombin time; PTT, partial thromboplastin time; GI, gastrointestinal.

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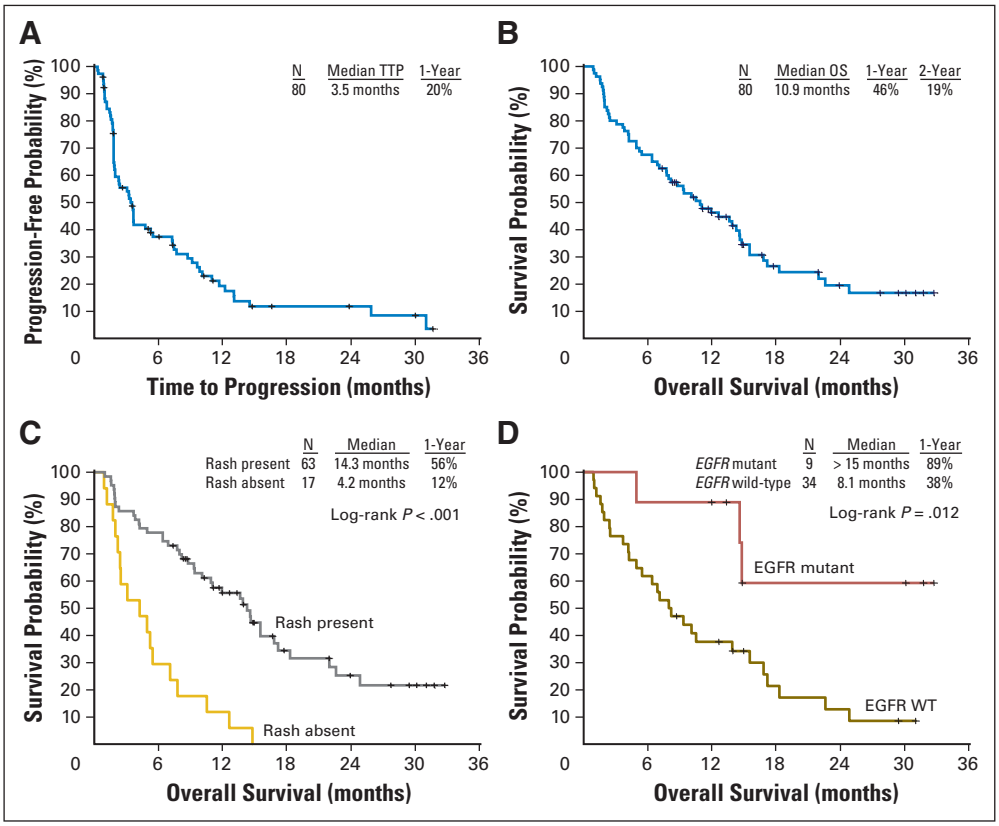

Fig 1. (A) Overall time to progression (TTP). (B) Overall survival (OS). (C) Survival by the presence or absence of treatment-related rash. (D) Survival by *EGFR* mutation status. WT, wild type.

10.9 months (95% CI, 7.8 to 14.6 months; Fig 1B). The 1- and 2-year survival rates were 46% and 19%, respectively.

Multivariate analysis showed treatment-related rash was correlated with prolonged TTP and survival (Table 3, Fig 1C). Smoking history and weight loss at presentation were predictors of shorter survival, and each was associated with a more than five-fold increase in the hazard ratio.

EGFR *and* KRAS *Mutations*

Tumor samples from 43 patients were analyzed for *EGFR* mutation status. Of 37 untested patients, four samples could not be obtained from outside hospitals, seven patients had not signed specific consent for *EGFR* testing, and 26 tumor samples were deemed inadequate for testing. Thirty-four samples were analyzed by direct DNA sequencing, whereas nine samples were evaluated using WAVE-HS. *EGFR* mutations were detected in nine patients (Tables 4 and 5). The only clinical characteristic correlated with the presence of an *EGFR* mutation was a smoking history of less than 15 pack-years ($P = .006$).

Presence of an *EGFR* mutation was marginally associated with clinical response in this trial ($P = .054$). However, *EGFR* mutation status closely correlated with disease control; all patients harboring an *EGFR* mutation achieved either a PR or SD ($P < .01$). The presence of an *EGFR* mutation was also associated with prolonged TTP and survival (Fig 1D). In multivariate analysis, the presence of an *EGFR*

Table 3. Multivariate Analysis of Progression and Survival

Characteristic	Progression			Overall Survival		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Treatment-related rash	0.27	0.11 to 0.65	.003	0.10	0.04 to 0.30	< .001
EGFR mutation present	0.26	0.09 to 0.78	.017	0.20	0.05 to 0.83	.027
Female sex	0.73	0.33 to 1.60	.432	0.41	0.17 to 1.02	.055
BAC pathology	0.60	0.19 to 1.86	.377	0.46	0.13 to 1.66	.236
Good baseline performance status, ECOG PS 0-1	1.05	0.24 to 4.65	.947	1.07	0.23 to 4.97	.929
Age ≥ 80 years	1.00	0.39 to 2.57	.997	1.67	0.64 to 4.34	.291
Weight loss at presentation	1.73	0.67 to 4.43	.257	5.22	1.70 to 15.99	.004
Any history of smoking	1.95	0.50 to 7.61	.335	5.36	1.19 to 24.26	.029

Abbreviations: BAC, bronchioloalveolar carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status.

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Table 4. Characteristics and Outcomes of Patients With *EGFR* Mutations

Age (years)	Sex	*EGFR* Mutation	Method of *EGFR* Analysis	Smoking Status	Histology	Response	TTP (months)	Survival (months)
74	F	Exon 19 deletion	Direct sequencing	Former	Adeno	SD	31	32.6+
76	F	Exon 19 deletion	Direct sequencing	Never	Adeno	PR	31.7+	31.7+
70	M	Exon 19 deletion	Direct sequencing	Former	Adeno with BAC features	PR	30+	30+
78	F	L858R	Direct sequencing	Former	Adeno	PR	9.7	13.3+
78	F	L858R	Direct sequencing	Never	Adeno	SD	13	14.7
75	F	L858R	WAVE-HS	Former	NSCLC	SD	3.7	12+
73	M	L858R	WAVE-HS	Former	Squamous cell carcinoma	SD	3.4	4.9
72	M	L858R	WAVE-HS	Former	Adeno	SD	10	14.6
73	F	L861Q, exon 19 deletion	WAVE-HS	Former	Adeno with BAC features	SD	14.8+	14.8+

Abbreviations: TTP, time to progression; F, female; Adeno, adenocarcinoma; SD, stable disease; PR, partial response; M, male; BAC, bronchioloalveolar carcinoma; NSCLC, non–small-cell lung cancer.

mutation was associated with a nearly four-fold reduction in the hazard ratio of both of these clinical outcomes (Table 3).

Tissue samples from 41 patients were analyzed for *KRAS* mutations (32 by direct DNA sequencing and nine by WAVE-HS). *KRAS* mutations were detected in six patients (five by direct sequencing and one by WAVE-HS). All six patients had a history of tobacco use (five former smokers and one current smoker), with an average of 52 pack-years smoked (range, 30 to 78 pack-years). There were no clinical responses in this group (Table 5). Although median time on study was only 2.5 months for this subset, median survival time for these six patients was 15.5 months (95% CI, 4.2 to 16.8 months). No patients had both *KRAS* and *EGFR* mutations.

Statistical Modeling

A previously published statistical model estimates the expected probability that a phase II regimen would yield a significant result in a subsequent phase III trial; regimens with an expected power of more than 55% were likely to be good candidates for phase III testing.[18] With a 19-week survival difference between erlotinib in the current trial and vinorelbine in the Elderly Lung Cancer Vinorelbine Italian Study[1] (47 weeks *v* 28 weeks, respectively), the statistical model predicts a power of 97%.

Table 5. Clinical Response by *EGFR* and *KRAS* Mutation Status

Mutation Status and Best Response	No. of Patients		
	Mutant	Wild Type	Total
EGFR			
PR	3	2	5
SD	6	15	21
PD	0	11	11
NA	0	6	6
Total	9	34	43
KRAS			
PR	0	5	5
SD	3	17	20
PD	1	9	10
NA	2	4	6
Total	6	35	41

Abbreviations: PR, partial response; SD, stable disease; PD, progressive disease; NA, not assessable.

Second-Line Chemotherapy

Thirty-five patients received second-line chemotherapy (carboplatin plus paclitaxel, n = 6; carboplatin plus gemcitabine, n = 4; vinorelbine monotherapy, n = 19; pemetrexed monotherapy, n = 3; gefitinib monotherapy, n = 1; or erlotinib rechallenge, n = 2). Altogether, two patients partially responded to second-line vinorelbine, with no responses among patients receiving other regimens. Overall response rate to second-line chemotherapy was 6%.

DISCUSSION

Treatment with erlotinib previously demonstrated a clear survival benefit compared with best supportive care (6.7 *v* 4.7 months, respectively; $P < .001$) in patients with advanced NSCLC treated with one to two prior chemotherapy regimens.[9] Moreover, this benefit seemed to extend across clinical subgroups, including older age, male sex, and nonadenocarcinoma histology.

In the present study, erlotinib was administered to 80 unselected, previously untreated NSCLC patients older than age 70 years. A median survival time of 10.9 months (47 weeks) compares favorably with the survival times achieved in elderly patients receiving vinorelbine (6.5 to 8.5 months),[1,2] paclitaxel (5.5 months),[24] and cisplatin-based combination therapy (8.0 to 8.5 months).[3,24]

One potential limitation in interpreting survival data from this trial is that 64% of patients had adenocarcinoma (including bronchioloalveolar carcinoma). Earlier studies suggested a higher response rate and higher likelihood of somatic *EGFR* mutations in patients with adenocarcinoma.[9,25,26] Although the protocol did not specifically recruit by tumor histology, a selection bias on the part of treating physicians may partly account for the increased prevalence of adenocarcinoma among enrolled patients in our trial compared with other trials of elderly patients with NSCLC (34% to 36%).[1,2] However, in multivariate analysis, tumor histology was not associated with improved survival in this trial.

Conversely, because planned treatment on this trial did not include chemotherapy, patients with better performance status may

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have chosen or been recommended doublet chemotherapy, which might introduce a negative selection bias. A less fit population might account for adverse events both related and unrelated to erlotinib treatment, as well as for the low number of patients receiving second-line treatment.

Regarding treatment-related adverse effects, there were four patients with suspected ILD (5%), with one death. One of the four patients was of Asian ethnicity, and none had received prior chemotherapy or chest radiotherapy. Although the rate of ILD in this trial was less than the 12% incidence seen in a recent Japanese phase II study,[27] it is higher than the rate of less than 1% seen in each arm of the BR.21 trial.[9] However, it was unclear in at least one patient whether radiographic findings represented ILD or lymphangitic spread of a tumor that was progressing systemically.

The toxicity of erlotinib in this population compares favorably with other studies performed in patients with NSCLC older than age 70 years. Fifteen patients (19%) in this study developed at least one toxicity of grade ≥ 3 compared with more than 25% of elderly patients in studies with vinorelbine,[2] 73% in studies with paclitaxel,[24] and 90% to 95% in studies with platinum-based combination therapy.[3,24] The relative tolerability of erlotinib in patients older than age 70 years may represent an important first-line option in this undertreated population.[4-8]

Given their age and concomitant comorbidities, patients on the current trial were expected to have a higher incidence of adverse effects than younger patients receiving erlotinib. Not surprisingly, 12% of patients in this study required toxicity-related discontinuation compared with 5% of patients in the erlotinib arm of the BR.21 trial, whose median age was only 62 years.[9] The percentage of patients requiring dose reduction as a result of treatment-related adverse effects in this trial was similar to that seen in the erlotinib arm of the BR.21 trial (16% *v* 19%, respectively).[9]

The 51% disease control rate (PR + SD) in this trial is very similar to the rate found in both the BR.21 trial (45%)[9] and a European trial of first-line erlotinib in unselected patients with advanced NSCLC (53%).[28] In the current trial, the presence of an *EGFR* mutation was the only pretreatment factor studied that was independently correlated to disease control, TTP, and survival in multivariate analysis. For a trial that did not mandate the collection of tumor tissue as a criterion for enrollment, it is noteworthy that tumor tissue was obtained and analyzed for *EGFR* mutations in more than half of the eligible patients (54%).

There are important limitations to *EGFR* mutation testing as a method to select patients for treatment. First, nearly half of the patients in this trial lacked adequate tissue for such testing; however, these patients did not differ significantly in baseline characteristics (age, sex, performance status, smoking history, tumor histology, or development of a treatment-related rash) from those patients with assessable tissue. Second, response and prolonged SD were found in patients with wild-type *EGFR*; 12 patients with confirmed wild-type *EGFR* status were alive for more than 1 year, with two of these patients showing PRs to therapy. Although not studied in this trial, combined analysis of *EGFR* mutation status, *EGFR* copy number, and EGFR immunochemistry may provide a more comprehensive means of appropriate patient selection.[29,30] Third, it remains unclear whether presence of an *EGFR* mutation is truly predictive of erlotinib treatment benefit or merely prognostic of prolonged survival. In the TRIBUTE and BR.21 trials, patients with *EGFR* mutations seemed to do better regardless of treatment regimen.[13,31] In contrast, *EGFR* mutations were a negative prognostic marker in a large series of resected NSCLC patients.[32] In either case, the predictive utility of *EGFR* mutations may ultimately depend on specific genotypes. Two recently published studies showed an association between prolonged survival for patients with exon 19 deletions compared with L858R point mutations.[33,34]

Treatment-related rash was independently correlated with disease control, prolonged TTP, and survival. The survival of patients according to rash status (14.3 months for patients with rash and 4.2 months for patients without rash) mirrors the difference noted in a recent first-line trial of gefitinib (survival time of 16 months with rash and 5 months without rash).[35] It is unknown whether development of treatment-related rash is a reflection of differences in immunocompetence, pharmacokinetics, or some other factor. Also remarkable were the poor outcomes seen in current smokers; median TTP and survival time in the five patients who were still smoking at the time of enrollment were only 1.2 months and 1.5 months, respectively. Nonetheless, although four current smokers survived for less than 5 months, the fifth had prolonged SD and remains on therapy after nearly 17 months.

The lack of clinical response with EGFR tyrosine kinase inhibitors (TKIs) in patients with *KRAS* mutations has been previously described.[13,14] In the current study, patients with a *KRAS* mutation had no clinical responses and a median TTP of only 2.5 months. Although the negative impact of *KRAS* mutations may be partly confounded by smoking history (in this study, all six patients with *KRAS* mutations were current or former smokers, with a mean of 53 pack-years), the collective evidence suggests that patients with *KRAS* mutations do not benefit from therapy with an EGFR TKI.

In summary, erlotinib represents a first-line treatment option worthy of further consideration for elderly patients with advanced NSCLC. A median survival time of 10.9 months in patients older than age 70 years exceeded our predetermined statistical end point. Erlotinib was generally well tolerated, with fewer high-grade toxicities than seen in other trials of systemic chemotherapy in this population. Vigilance for and treatment of ILD is required in this more vulnerable group. As with any treatment regimen, the preselection of patients who will ultimately benefit requires further investigation. Ongoing prospective trials with EGFR TKIs in clinically and pathologically defined subsets of patients will hopefully add to our understanding of the mechanism of action and appropriate patient selection for erlotinib and related agents.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Temel, Amgen; Matthew Meyerson, Genentech, Novartis **Testimony:** N/A **Other:** Thomas J. Lynch, Genzyme (patent for EGFR testing); Matthew Meyerson, Genzyme (patent for EGFR testing); Bruce E. Johnson, Genzyme (patent on EGFR testing); Pasi A. Jänne, Genentech (unrestricted funding), Genzyme (patent for EGFR testing)

AUTHOR CONTRIBUTIONS

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