A Randomized Phase 2 Study of Erlotinib Alone and in Combination with Bortezomib in Previously Treated Advanced Non-small Cell Lung Cancer

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Introduction: This phase 2 study was conducted to determine the efficacy and safety of erlotinib alone and with bortezomib in patients with non-small cell lung cancer (NSCLC).

Methods: Patients with histologically or cytologically confirmed relapsed or refractory stage IIIb/IV NSCLC were randomized (1:1; stratified by baseline histology, smoking history, sex) to receive erlotinib 150 mg/d alone (arm A; $n = 25$) or in combination with bortezomib 1.6 mg/m^2, days 1 and 8 (arm B; $n = 25$) in 21-day cycles. Responses were assessed using Response Evaluation Criteria in Solid Tumors. Tumor samples were evaluated for mutations predicting response. Six additional patients received the combination in a prior dose deescalation stage and were included in safety analyses.

Results: Response rates were 16% in arm A and 9% in arm B; disease control rates were 52 and 45%, respectively. The study was halted at the planned interim analysis due to insufficient clinical activity in arm B. Median progression-free survival and overall survival were 2.7 and 7.3 months in arm A, and 1.3 and 8.5 months in arm B. Six-month survival rates were 56.0% in both arms; 12-month rates were 40 and 30% in arms A and B, respectively. Response rate to erlotinib±bortezomib was significantly higher in patients with epidermal growth factor receptor mutations (50 versus 9% for wild type). The most common treatment-related grade ≥3 adverse event was skin rash (three patients in each treatment group).

Conclusion: Insufficient activity was seen with erlotinib plus bortezomib in patients with relapsed/refractory advanced NSCLC to warrant a phase 3 study of the combination.

Key Words: Advanced non-small cell lung cancer, Bortezomib, Erlotinib, Phase 2.

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Lung cancer is the leading cause of cancer-related mortality in the United States. In 2007, there were an estimated 213,380 new cases, with the disease accounting for nearly one third of all cancer deaths.[1,2] Non-small cell lung cancer (NSCLC) represents approximately 85% of lung cancers.[1] Most patients with NSCLC present with locally advanced or metastatic disease, for which potentially curative therapy is not available.[1–3] Treatment options include chemotherapy with or without radiation and supportive care. Standard first-line chemotherapy for fit patients with advanced NSCLC comprises platinum-based doublet therapy, typically resulting in median overall survival (OS) of 8 to 11 months.[4] Addition of bevacizumab, a targeted monoclonal antibody against vascular endothelial growth factor (VEGF), to paclitaxel-carboplatin improves both response and survival in a select subgroup of patients with NSCLC.[5]

The benefits of second-line therapy in NSCLC have been defined within the past decade.[6] The chemotherapeutic

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agents docetaxel[7,8] and pemetrexed,[9] along with erlotinib[10] and gefitinib,[11] oral agents that inhibit the epidermal growth factor receptor (EGFR) tyrosine kinase (TK; EGFR TKIs), are approved as single agents in this setting.[6,12,13] Erlotinib gave a 9% response rate in patients with NSCLC who had received at least one prior therapy and demonstrated a significant progression-free survival (PFS) advantage (2.2 versus 1.8 months, $p < 0.001$) and OS advantage (6.7 versus 4.7 months, $p < 0.001$) versus placebo[10]; promising results with erlotinib have also been reported in highly selected groups of previously untreated patients.[14–18] However, there was no significant survival advantage in a large placebo-controlled study of gefitinib in patients with previously treated NSCLC.[11] Gefitinib was subsequently withdrawn in the United States and Europe but is still used elsewhere, particularly in Asia because of a demonstrated survival advantage in patients of Asian origin.[11] Recently, third-line therapy has also been shown to be of benefit in NSCLC.[10] Erlotinib is currently the only agent approved in this setting in North America and Europe, although gefitinib is used elsewhere, notably Asia.

Given the limited management options for previously treated NSCLC and the need to improve outcomes, investigation of novel treatment combinations is warranted. Bortezomib is a proteasome inhibitor that affects multiple signaling pathways relevant to NSCLC.[19–22] Preclinical studies have shown bortezomib to have activity in NSCLC cell lines, both alone[20,23–27] and in combination with other agents.[19,25,28–30] Bortezomib has demonstrated modest activity in clinical studies in advanced NSCLC as a single agent[31–33]; additionally, combination studies with docetaxel,[32,34] gemcitabine,[35] gemcitabine and carboplatin,[36,37] and gemcitabine and cisplatin[38] have shown that it can be combined with acceptable toxicity. Anecdotal evidence suggests bortezomib may be active in bronchioloalveolar carcinoma,[39] a subset of NSCLC in which erlotinib also is active.[40]

Erlotinib and bortezomib may have complementary effects, with erlotinib blocking EGFR TK activity[13] and bortezomib causing increased degradation of activated EGFR by 26S proteasome inhibition[21,22] (and consequent reduction in antiapoptotic and proliferative signals generated by activated EGFR). Preclinical studies of erlotinib plus bortezomib showed that the combination had synergistic antitumor activity against the H460 NSCLC cell line (unpublished data, Millennium Pharmaceuticals, Inc., Cambridge, MA). The combination also showed more activity in H358 bronchoalveolar cells than either agent alone; however, in other NSCLC cell lines tested in the same study, the combination was neither additive nor synergistic.[41] Based on the results of these preclinical and early clinical studies, the aims of this trial were to determine the efficacy and safety of erlotinib alone or erlotinib plus bortezomib in patients with relapsed or refractory, locally advanced or metastatic NSCLC.

METHODS

Patients

Patients aged ≥18 years with histologically or cytologically confirmed, relapsed or refractory locally advanced (stage IIIb), or metastatic (stage IV) NSCLC were eligible for the study. Patients were required to have measurable disease by RECIST,[42] life expectancy >3 months, and Eastern Cooperative Oncology Group performance status ≤1. Patients must have received one prior line of conventional cytotoxic chemotherapy for stage IIIb or stage IV NSCLC (excluding adjuvant or neoadjuvant chemotherapy) and required documented progressive disease (PD) during or since their last prior therapy. All patients provided written informed consent.

Patients were ineligible if they had received previous treatment with bortezomib, an anti-EGFR antibody or anti-EGFR-TKI (such as erlotinib, gefitinib, or cetuximab), or if they had undergone chemotherapy, radiation therapy, monoclonal antibody therapy, or major surgery within 4 weeks before enrollment. Those with preexisting interstitial lung disease, grade ≥2 peripheral neuropathy (by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 3.0), grade >1 diarrhea or vomiting (irrespective of antidiarrheal and/or antiemetic therapy), or inadequate organ function were excluded.

Study Design

This two-part, randomized, noncomparative, multicenter, open-label, phase 2 study of erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) alone and erlotinib plus bortezomib (ELCADE, Millennium Pharmaceuticals, Inc., Cambridge, MA; and Johnson & Johnson Pharmaceutical Research and Development LLC, Raritan, NJ) was conducted at 19 sites in the United States and Canada from August 2005 to July 2007. Patients received treatment in 21-day cycles; in both parts of the study, erlotinib was administered at 150 mg/d orally, the approved dose in NSCLC, and bortezomib was administered intravenously on days 1 and 8, at least 60 minutes after erlotinib. Study treatment continued until PD or until another termination criterion was met, including unacceptable toxicity, consent withdrawal, loss to follow-up, death, major protocol violation, or noncompliance. The protocol was approved by an independent ethics committee/institutional review board at participating centers, in accordance with the Declaration of Helsinki.

The objective of part 1 of the study was to determine the maximum tolerated dose (MTD) of bortezomib in combination with erlotinib, defined as the dose level at which no more than one of at least six patients experienced predefined dose-limiting toxicity (DLT) after completion of the first cycle of therapy. A dose deescalation scheme was used, with planned bortezomib doses of 1.6, 1.3, and 1.0 mg/m^2 (based on the MTD of 1.6 mg/m^2 in a phase 1 trial in patients with advanced solid tumors).[43] Six patients were enrolled at the initial dose of 1.6 mg/m^2. No DLTs were reported; this dose was identified as the MTD and used for part 2.

In part 2, patients were randomized (1:1) to receive erlotinib alone (arm A) or erlotinib plus bortezomib 1.6 mg/m^2 (arm B). Neither patients nor physicians were blinded regarding treatment assignment. Randomization was stratified by baseline histology (adenocarcinoma versus other), smoking history (smoking versus nonsmoking), and gender (male versus female), to balance for factors associated with a greater likelihood of response to erlotinib (female gender, never smokers, adenocarcinoma histology).[10–13] Erlotinib

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Erlotinib Alone Arm A (ITT), (n = 25)	Erlotinib Plus Bortezomib Arm B (ITT), (n = 25)	Erlotinib Plus Bortezomib Safety, (n = 31)
Age, yr			
Median	64	62	62
Range	45–82	36–81	36–81
Sex, *n* (%)			
Female	12 (48)	14 (56)	15 (48)
Male	13 (52)	11 (44)	16 (52)
Race, *n* (%)			
White	20 (80)	21 (84)	26 (84)
Black	3 (12)	1 (4)	2 (6)
Asian/Pacific Islander	2 (8)	1 (4)	1 (3)
Other	0	2 (8)	2 (6)
ECOG performance status, *n* (%)			
0	7 (28)	7 (29)	8 (27)
1	18 (72)	16 (67)	21 (70)
3	0	1 (4)	1 (3)
Unknown	0	1	1
Time from initial diagnosis to randomization, mo	n = 23	n = 24	n = 24
Median	10.3	8.9	8.9
Range	5–37	2–34	2–34
Histologic classification, *n* (%)			
Adenocarcinoma	14 (56)	14 (56)	16 (52)
Squamous cell carcinoma	7 (28)	7 (28)	10 (32)
Pure bronchioloalveolar carcinoma	0	1 (4)	1 (3)
Large cell carcinoma	1 (4)	0	0
Other	3 (12)	3 (12)	4 (13)
TNM stage, *n* (%)			
Stage IIIb	3 (12)	4 (16)	7 (23)
Stage IV	22 (88)	21 (84)	24 (77)
History of smoking (ever smoked), *n* (%)			
Yes	20 (80)	21 (84)	27 (87)
No	5 (20)	4 (16)	4 (13)
No. of prior lines of therapy, *n* (%)			
0	3 (12)	1 (4)	1 (3)
1	21 (84)	19 (76)	24 (77)
2 or more	1 (4)	5 (20)	6 (19)
Prior platinum-based therapy, *n* (%)	19 (76)	22 (88)	28 (90)
Prior single-agent therapy, *n* (%)	2 (8)	2 (8)	2 (6)

ECOG, Eastern Cooperative Oncology Group; ITT, intent to treat.

and/or bortezomib doses were withheld or reduced as necessary according to predefined criteria. If required, the erlotinib dose was reduced in 50-mg intervals; up to three dose reductions were allowed for bortezomib ($1.6 \rightarrow 1.3 \rightarrow 1.0 \rightarrow 0.7$ mg/m^2). Supportive care medications permitted included antiemetics, loperamide for diarrhea, colony-stimulating factors, antiinflammatory drugs, bisphosphonates, and topical or oral treatments for rash. Treatment with cytotoxic chemotherapeutic agents, and other monoclonal antibodies or investigational agents was prohibited.

Efficacy, Safety, and Other Measurements

The primary end point was tumor response rate (complete response + partial response using RECIST[42]) in the intent to treat (ITT) population. In part 2, disease assessment was performed by investigators every 6 weeks until PD. Secondary end points included disease control rate (complete response + partial response + stable disease), time to progression (TTP), PFS, OS, 6-month and 12-month survival rates, and safety and tolerability. Adverse events (AEs) were assessed throughout treatment and for 30 days after last dose of study treatment and were graded using NCI CTCAE 3.0.

An additional objective was the evaluation of banked tumor tissue for *EGFR* and v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status and correlation with response. DNA was prepared from 100-μm sections of whole blocks or tissue scraped off and pooled from

2 to 3 glass slides. Profiling for *KRAS* mutations was performed using polymerase chain reaction (PCR)/ligase detection reaction.[44] *EGFR* mutation detection was performed using PCR/ligase detection reaction[44] and capillary electrophoresis,[45] plus fluorescent PCR using primers flanking the hotspot for insertions/deletions in exon 19.

Statistical Methods

This was a noncomparative study; there was no formal statistical comparison between treatment arms. Based on Simon's two-stage optimal design, a sample size of 80 patients (40 per arm) was determined. This would provide 80% power to reject the null hypothesis response rate of 9% at a significance level of $\alpha = 0.15$ when the true response rate was 20%. To ensure that at least 80 patients (40 per arm) enrolled in part 2 were evaluable for response in the final analysis, it was planned to enroll approximately 100 patients overall (part 1 and part 2). An interim analysis of objective tumor response for arm B was planned, to provide the option to discontinue the study early should the combination not demonstrate sufficient effectiveness (fewer than two objective responses in the first 19 response-evaluable patients who had the opportunity to complete a minimum of four cycles of therapy).

The ITT population included all randomized patients (part 2) who received at least one dose of treatment. This population was intended to be used for all efficacy analyses. Response and disease control rates were calculated with two-sided 95% confidence intervals. TTP, PFS, and OS were analyzed using Kaplan-Meier estimates. The safety population included all patients enrolled in part 1 and part 2 who received at least one dose of treatment. Safety data including treatment-emergent AEs (those that occurred or worsened from baseline during treatment or within 30 days after the last dose), treatment-related AEs, and serious AEs were tabulated.

TABLE 2. Best Response to Treatment (ITT Population)

Response	Arm A Erlotinib Alone ($n = 25$)	Arm B Erlotinib Plus Bortezomib ($n = 22$)[a]
Overall response (CR + PR), *n* (%)	4 (16)	2 (9)
95% CI (%)	4.5–36.1	1.1–29.2
Disease control (CR + PR + SD), *n* (%)	13 (52)	10 (45)
95% CI (%)	31.3–72.2	24.4–67.8
Complete response (CR), *n* (%)	1 (4)	0
Partial response (PR), *n* (%)	3 (12)	2 (9)
Stable disease (SD), *n* (%)	9 (36)	8 (36)
Progressive disease (PD), *n* (%)	11 (44)	11 (50)
Inevaluable, *n* (%)	1 (4)	1 (5)

[a] Response data missing for three patients in arm B. Only one of the first 19 response-evaluable patients achieved a response.

RESULTS

Patient Demographics and Disposition

Between August 2005 and June 2006, the study enrolled 57 patients; six were treated at the bortezomib 1.6 mg/m^2 dose level in part 1, and 51 were randomized to erlotinib (arm A; $n = 25$) or erlotinib plus bortezomib (arm B; $n = 26$) in part 2. One patient randomized to arm B provided informed consent but was withdrawn 4 days after randomization because of PD and did not receive study treatment; therefore, 50 patients were included in the ITT population and 56 in the safety population (see Supplementary Figure 1, Supplemental Digital Content 1, Available at: http://links.lww.com/A1283). Baseline demographics and clinical characteristics were comparable between treatment groups and between arms in part 2 (Table 1). In arm A, patients received erlotinib for a mean of 17.5 weeks; mean total dose was 17.1 g, with mean relative dose intensity of 92%. In the combination treatment group (arm B plus part 1 patients), patients received erlotinib for a mean of 11.1 weeks; mean total dose was only 10.4 g, although mean relative dose intensity was 97%. Patients received bortezomib for a mean of 9.4 weeks; mean total dose was 10.9 mg/m^2, and mean relative dose intensity was 93%. Erlotinib and bortezomib exposure was similar between patients in part 1

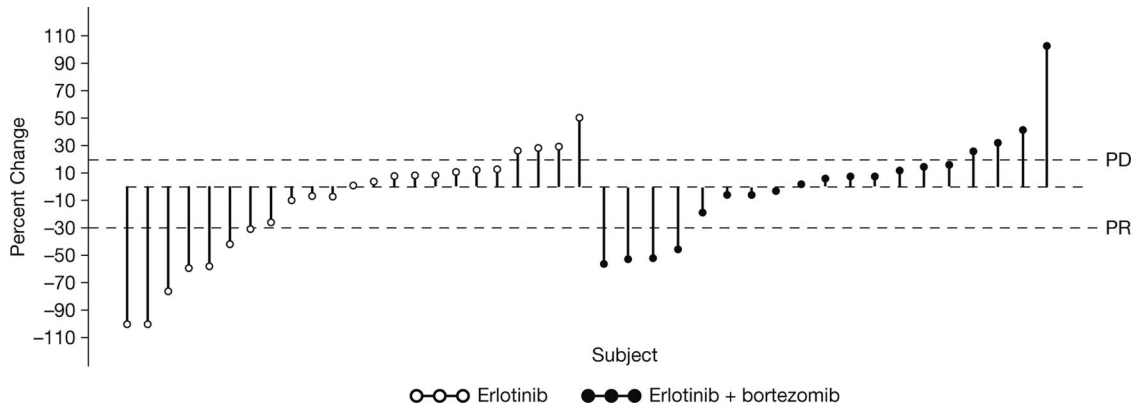


FIGURE 1. Best percent change in tumor size in target lesions in patients in arm A (erlotinib alone) and arm B (erlotinib plus bortezomib). In arm A, the patient represented by the second line from the left achieved complete response by RECIST, and the patients represented by the first, fourth, and fifth lines from the left achieved partial response by RECIST. In arm B, the patients represented by the first and third lines from the left achieved partial response by RECIST.

and part 2. Patients completed a median of two treatment cycles of bortezomib in part 2 (range 1–18).

Response and Survival

The response rate was 16% in arm A and 9% in arm B; disease control rates were 52 and 45%, respectively (Table 2). Individual patient responses in terms of best percentage tumor reduction in target lesions are shown in Figure 1. Per protocol, enrollment was halted as of September 22, 2006 because of insufficient clinical activity in arm B.

Kaplan-Meier distribution curves of TTP, PFS, and OS are presented in Figure 2. Median TTP was 2.7 months in arm A and 1.5 months in arm B; median PFS was 2.7 months and 1.3 months, respectively. Intensity of skin rash correlated with PFS, although this correlation was not significant ($p = 0.17$); median PFS was 2.8 months versus 1.3 months for patients with grade 2/3 versus grade 0/1 skin rash. After median follow-up of 14 months, median OS was 7.3 months in arm A and 8.5 months in arm B. The 6-month survival rate was 56% in both treatment arms; 12-month survival rates were 40 and 30% in arm A and arm B, respectively.

Biomarker Analyses

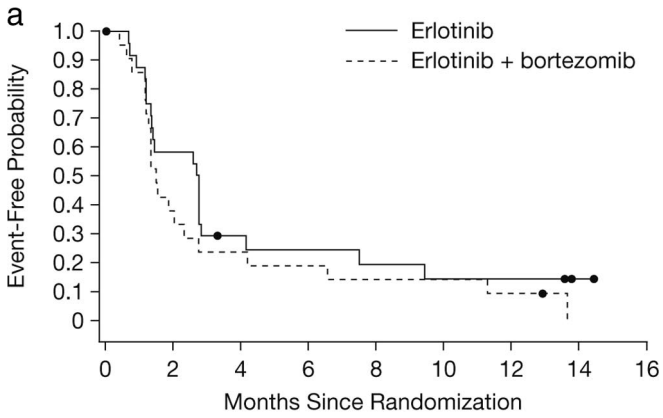
Sufficient tumor tissue samples for biomarker analysis were obtained from 32 patients; 31 were evaluable for *KRAS* mutations and 29 for *EGFR* mutations. *KRAS* mutations were observed in 11/31 (35%) evaluable samples and *EGFR* mutations in 6/29 (21%) evaluable samples. Frequencies of *KRAS* and *EGFR* mutations in arm A were 35 (6/17) and 27% (4/15), respectively, and in arm B, 36 (5/14) and 14% (2/14), respectively. Responses according to *KRAS* and *EGFR* mutation status are shown in Table 3. There was no significant correlation between TTP or PFS and *KRAS* mutation status, either overall or within treatment arms (data not shown). Median TTP (13.6 months versus 2.0 months) and PFS (4.3 months versus 1.5 months) were longer in patients with tumors with an *EGFR* mutation versus those with *EGFR* wild-type tumors, although differences were not significant. Similar trends were observed within treatment arms (data not shown).

Safety

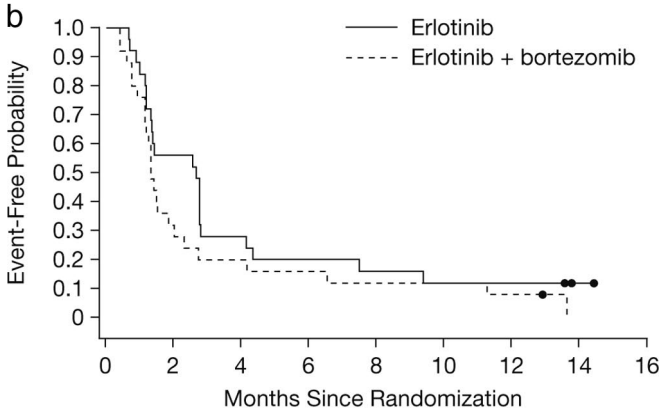
The majority of patients in each treatment group experienced at least one AE (Table 4). The most commonly reported AEs were acneiform rash (88% of patients receiving erlotinib, 74% of patients receiving erlotinib plus bortezomib), diarrhea (72%, 48%), and fatigue (60%, 42%). Incidences of grade ≥3 AEs and treatment-related grade ≥3 AEs are summarized in Table 4. The most common treatment-related grade ≥3 AE was skin rash (rash or dermatitis acneiform), reported by three patients receiving erlotinib alone (12%) and three patients receiving erlotinib plus bortezomib (10%). Only one serious AE, of pneumonia, in a patient receiving erlotinib plus bortezomib in part 2, was considered treatment related; this was the only treatment-related AE leading to death during the study.

DISCUSSION

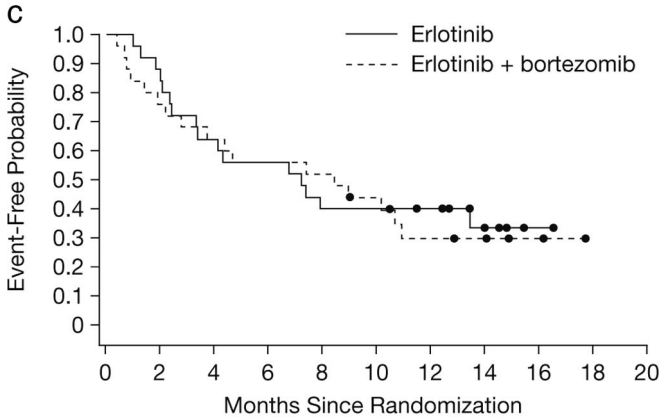
Bortezomib and erlotinib both have demonstrated single-agent activity in previously treated advanced NSCLC[10,32]



	N	PD, n	Median TTP, months
Erlotinib alone	25	20	2.7
Erlotinib + bortezomib	25	20	1.5



	N	PD or Death, n	Median PFS, months
Erlotinib alone	25	22	2.7
Erlotinib + bortezomib	25	24	1.3



	N	Deaths, n	Median OS, months
Erlotinib alone	25	16	7.3
Erlotinib + bortezomib	25	17	8.5

FIGURE 2. Kaplan-Meier plots for (a) time to progression (TTP), (b) progression-free survival (PFS), and (c) overall survival (OS) (intent to treat [ITT] population).

TABLE 3. Response to Treatment According to *KRAS* and *EGFR* Mutation Status in all Evaluable Patients and by Treatment Arm

Responses, *n*/*N* (%)	*KRAS* Mutation Status			*EGFR* Mutation Status		
	All (*n* = 31)	Arm A (*n* = 17)	Arm B (*n* = 14)	All (*n* = 29)	Arm A (*n* = 15)	Arm B (*n* = 14)
Mutation	2/11 (18%)	2/6[a] (33%)	0/5 (0%)	3/6 (50%)	2/4 (50%)	1/2 (50%)
Wild type	4/20 (20%)	2/11 (18%)	2/9 (22%)	2/23 (9%)	2/11 (18%)	0/12 (0%)
p	1.0	0.58	0.51	0.046	0.52	0.014

[a] Both responding patients also had *EGFR* mutations.
EGFR, epidermal growth factor receptor; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog.

TABLE 4. Summary of Treatment-Emergent AEs and On-Study Deaths (Safety Population)

	Erlotinib Alone (*n* = 25)	Erlotinib Plus Bortezomib (*n* = 31)
Any AE, *n* (%)	25 (100)	30 (97)
Any treatment-related AE, *n* (%)	23 (92)	28 (90)
Any grade ≥3 AE, *n* (%)	15 (60)	18 (58)
Any treatment-related grade ≥3 AE, *n* (%)	4 (16)	7 (23)
Treatment-related grade 3 AEs		
Rash or dermatitis acneiform	3 (12)	3 (10)
Diarrhea NOS	0	1 (3)
Nausea/vomiting NOS	0	1 (3)
Paraesthesia	1 (4)	0
Peripheral neuropathy aggravated	0	1 (3)
Hypokalemia	0	1 (3)
Any SAE	10 (40)	12 (39)
Any treatment-related SAE	0	1 (3)[a]
AE leading to discontinuation	6 (24)	5 (16)
AE leading to dose reduction	5 (20)	6 (19)
AE leading to dose interruption	3 (12)	11 (35)
Deaths within 30 d of last dose of study drug	6 (24)	7 (23)
Deaths due to treatment-related AEs	0	1 (3)[a]

AE, adverse event; NOS, not otherwise specified; SAE, serious adverse event.
[a] One patient with grade 5 pneumonia.

and may have complementary mechanisms of action.[13,21,22] Preclinical data suggested that the combination of erlotinib and bortezomib may have greater antitumor activity than either agent alone (unpublished data, Millennium Pharmaceuticals).[41] However, despite this, the results of this randomized phase 2 study in patients with relapsed or refractory NSCLC did not indicate a response or survival benefit when bortezomib was added to erlotinib. The response rate was 16% with erlotinib alone, and 9% with erlotinib plus bortezomib, which is not different from the reported 9% response rate for single-agent erlotinib in patients with previously treated NSCLC.[10] Median TTP and PFS were both 2.7 months in arm A, and 1.5 months and 1.3 months, respectively, in arm B; median OS was 7.3 months for erlotinib alone and 8.5 months for erlotinib plus bortezomib. Therefore, the study was halted at the planned interim analysis due to insufficient clinical activity with the combination treatment. It is not clear why erlotinib plus bortezomib in the clinical setting failed to reflect the additive activity demonstrated in preclinical studies; it is possible that preexposure to erlotinib may abrogate the activity of bortezomib due to disruption of the cell cycle at different phases.[41]

Both treatment regimens were fairly well tolerated during the study; AEs were consistent with the known safety profiles of erlotinib and bortezomib.[10,32] The rates of grade 3 AEs previously reported as DLTs in phase 1 studies of bortezomib in solid tumors,[31,43] including diarrhea, hypotension, and peripheral neuropathy, were limited in arm B, because of the lower dose and/or dose intensity of bortezomib used in this study compared with those at which the DLTs typically occurred, as well as the limited duration of treatment. There was no notable additional toxicity with the combination of erlotinib and bortezomib. The most common treatment-related grade 3 AE was skin rash, reported by three patients in each treatment group. Skin rash is a common AE in clinical trials with EGFR-targeted agents such as erlotinib.[13,46] In this study, the severity of skin rash correlated positively with PFS in the ITT population. A previous analysis of two large phase 2 studies of erlotinib in NSCLC and pancreatic cancer also showed a strong correlation between occurrence of rash and survival, with longer PFS and disease control correlated with increasing rash severity.[47] Thus, rash may be a surrogate marker of clinical benefit with erlotinib, although the mechanism underlying its development remains unclear.[46]

This study found no significant correlation between presence of *KRAS* mutations and response rate, TTP, or PFS, although *KRAS* mutation has previously been identified as a predictor of resistance to EGFR-TKI therapy in NSCLC.[48] In contrast, a significantly higher response rate was seen in patients with tumors with an *EGFR* mutation versus those with *EGFR* wild-type tumors. Notably, the two patients with *KRAS* mutations who responded also had *EGFR* mutations, a rare finding as these mutations have been shown in most but not all studies to be mutually exclusive. The presence of *EGFR* mutations seems to be a potential indicator of increased responsiveness to erlotinib.[13,49,50] *EGFR* mutations also seem to be associated with longer survival overall in NSCLC, compared with wild-type *EGFR*, although to date, randomized trial data have not confirmed that they predict a

differentially greater survival benefit from EGFR-TKI therapy.[49–52] In this study, patients with *EGFR* mutations demonstrated longer TTP and PFS than those with wild-type *EGFR*. Although it is not yet clear whether EGFR protein expression predicts response or differential survival benefit in response to EGFR-TKI therapy,[49,52–54] studies have demonstrated a significant survival benefit with EGFR-TKI therapy versus placebo in EGFR-positive patients but no significant benefit for EGFR-negative patients.[49,52] Moreover, high *EGFR* gene copy number by fluorescence in situ hybridization has been shown to be predictive of a differentially greater survival benefit from erlotinib[50] and gefitinib.[52] No analyses of EGFR protein expression or *EGFR* gene copy number were conducted in this study.

There is a clear need for therapies that increase response and survival rates in advanced NSCLC. Given the multilevel cross-stimulation between pathways involved in cancer cell survival and replication, combining targeted therapies to block multiple signaling pathways may provide additional antitumor activity.[55] Several targeted combinations for first-line therapy or subsequent-line therapy are being explored in advanced NSCLC. Erlotinib is being investigated in combination with the VEGF monoclonal antibody bevacizumab, the multitargeted antifolate agent pemetrexed, sorafenib (a potent Raf-1 inhibitor that is also active against VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor), and the mammalian target of rapamycin inhibitor everolimus.[13] Clinical trials in advanced NSCLC are also exploring the use of bortezomib in combination with other targeted agents including pemetrexed and bevacizumab (with carboplatin).

In conclusion, this study did not show a benefit with the combination of erlotinib and bortezomib in patients with previously treated advanced NSCLC. Thus, a phase 3 study of this combination in this patient population is not supported. Nevertheless, combining erlotinib with other active targeted agents remains a potentially promising strategy in this setting. This study shows the value of performing randomized phase 2 trials of novel combinations in advanced NSCLC; this approach is recommended before large phase 3 trials are initiated.

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