ORIGINAL ARTICLE

Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Non–small-cell lung cancer (NSCLC) with a mutation in the gene encoding epidermal growth factor receptor (*EGFR*) is sensitive to approved EGFR inhibitors, but resistance develops, mediated by the T790M *EGFR* mutation in most cases. Rociletinib (CO-1686) is an EGFR inhibitor active in preclinical models of *EGFR*-mutated NSCLC with or without T790M.

METHODS

In this phase 1–2 study, we administered rociletinib to patients with *EGFR*-mutated NSCLC who had disease progression during previous treatment with an existing EGFR inhibitor. In the expansion (phase 2) part of the study, patients with T790M-positive disease received rociletinib at a dose of 500 mg twice daily, 625 mg twice daily, or 750 mg twice daily. Key objectives were assessment of safety, side-effect profile, pharmacokinetics, and preliminary antitumor activity of rociletinib. Tumor biopsies to identify T790M were performed during screening. Treatment was administered in continuous 21-day cycles.

RESULTS

A total of 130 patients were enrolled. The first 57 patients to be enrolled received the free-base form of rociletinib (150 mg once daily to 900 mg twice daily). The remaining patients received the hydrogen bromide salt (HBr) form (500 mg twice daily to 1000 mg twice daily). A maximum tolerated dose (the highest dose associated with a rate of dose-limiting toxic effects of less than 33%) was not identified. The only common dose-limiting adverse event was hyperglycemia. In an efficacy analysis that included patients who received free-base rociletinib at a dose of 900 mg twice daily or the HBr form at any dose, the objective response rate among the 46 patients with T790M-positive disease who could be evaluated was 59% (95% confidence interval [CI], 45 to 73), and the rate among the 17 patients with T790M-negative disease who could be evaluated was 29% (95% CI, 8 to 51).

CONCLUSIONS

Rociletinib was active in patients with *EGFR*-mutated NSCLC associated with the T790M resistance mutation. (Funded by Clovis Oncology; ClinicalTrials.gov number, NCT01526928.)

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Increasingly, treatment decisions for patients with non–small-cell lung cancer (NSCLC) are based on the driver mutation rather than the histologic subtype, when such mutations are present. Mutations in the gene encoding epidermal growth factor receptor (*EGFR*) are among the most common oncogenic mutations in lung adenocarcinoma and are present in approximately 10 to 15% of Western patients and 30 to 35% of Asian patients.[1] At the time of diagnosis, approximately 90% of *EGFR*-mutation–positive patients have one of two activating mutations, an in-frame deletion in exon 19 or an L858R point mutation in exon 21.[1] The first-generation and second-generation EGFR tyrosine kinase inhibitors gefitinib, erlotinib, and afatinib are highly active against cancers with these mutations, with objective response rates of 50 to 70%.[2-4] However, acquired resistance develops after a median of 9 to 13 months[2-4] and is most commonly due to the *EGFR* T790M mutation, present in approximately 50 to 60% of resistant cases.[5,6] There are no approved therapies that specifically target T790M, so cytotoxic chemotherapy is typically used. The median survival is less than 2 years after the emergence of T790M.[6]

Rociletinib (CO-1686; Clovis Oncology) is a small-molecule, orally available, mutant-selective covalent inhibitor of commonly mutated forms of EGFR, including exon 19 deletions, L858R, and T790M, but not exon 20 insertions. Preclinical studies have confirmed that rociletinib has minimal activity against wild-type EGFR.[7] In contrast, currently approved EGFR tyrosine kinase inhibitors result in substantial inhibition of nonmutant EGFR, leading to rash and diarrhea as their two most common and dose-limiting side effects. In xenograft models with *EGFR*-activating mutations alone or combined with T790M resistance mutations, rociletinib resulted in durable tumor shrinkage,[7] which was most marked when plasma concentrations were maintained at more than 200 ng per milliliter across the dosing interval. Therefore, we performed a phase 1–2 study of rociletinib in patients with *EGFR*-mutated NSCLC with acquired resistance to first-generation or second-generation EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib, or afatinib.

Methods

Study Design

This was a phase 1–2 dose-finding study of rociletinib in patients with advanced *EGFR*-mutated NSCLC who had disease progression during previous treatment with a first-generation or second-generation EGFR tyrosine kinase inhibitor. Continuation of the existing inhibitor was allowed until 3 days before initiation of rociletinib. Additional eligibility criteria included an age of 18 years or older, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a scale of 0 to 5, with 0 indicating no symptoms and 1 indicating mild symptoms), and adequate organ function. All patients were required to undergo tumor biopsy during screening for central assessment of *EGFR* mutation status. In phase 1, enrollment was not restricted to T790M-positive patients, but in phase 2, confirmation of T790M-positive status by central testing was required before study entry.

Two forms of rociletinib were developed. The study was initiated with the free-base form, which was available first. The hydrogen bromide salt (HBr) was designed to improve the pharmacokinetic profile and was introduced into the study later, during dose escalation. Both forms contain the same active moiety. Patients received oral rociletinib one, two, or three times daily, in 21-day continuous cycles, until disease progression according to the Response Evaluation Criteria in Solid Tumors, version 1.1 (see Table S4 in the Supplementary Appendix, available with the full text of this article at NEJM.org), unacceptable toxic effects, or withdrawal of consent occurred. At each dose level, dose-limiting toxic effects (for definition, see the protocol, available at NEJM.org) were assessed during the first cycle (21 days), with the frequency of dose-limiting toxic effects guiding the dose-escalation steps (see below). Intrapatient dose escalation was allowed to dose levels at which at least three patients had been treated without dose-limiting toxic effects. Restaging scans were performed every 2 cycles until the end of cycle 6 and every 3 cycles thereafter. Treatment beyond progression was permitted if the investigator believed the patient was still benefiting.

The study consisted of two parts, the phase 1 dose-escalation part (complete), followed by the phase 2 expansion part to assess efficacy at 500 mg twice daily, 625 mg twice daily, and 750 mg twice daily (ongoing). The data set described in this report comprises data from 130 patients in phase 1 or phase 2 who have follow-up data through at least the cycle 2 restaging scan or who discontinued treatment before the end of cycle 2.

The primary objectives of phase 1 were to assess the safety, side-effect profile, and pharmacokinetic characteristics of rociletinib. Secondary end points included assessment of the objective response rate, duration of response (defined as the time from first observation of response until disease progression), progression-free survival (defined as the time from the first dose until progression or death), and quality of life as assessed with the Dermatology Life Quality Index,[8] the European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire for patients with lung cancer (QLQ-LC13),[9] and the EORTC quality-of-life core questionnaire (QLQ-C30).[10] In phase 2, the primary end points were response rate and duration of response. With the exception of pharmacokinetics, all secondary and exploratory end points were the same as in phase 1.

For central genotyping of tumors, *EGFR* mutation status was measured with the use of allele-specific polymerase-chain-reaction assays (cobas, Roche Molecular Systems, or Therascreen, Qiagen). DNA was isolated from formalin-fixed, paraffin-embedded tumor tissue obtained within 60 days before the initiation of rociletinib.

STUDY OVERSIGHT

This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonisation. The protocol was approved by the local human investigations committee at each site. Written informed consent was obtained from all patients. The study was designed by study investigators together with the sponsor (Clovis Oncology). The sponsor collected the data and analyzed them in conjunction with the authors. The first author and employees of the sponsor wrote the first draft of the manuscript. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and analyses reported and for the fidelity of the study to the protocol. No one who is not an author contributed to writing the manuscript.

STATISTICAL ANALYSIS

The initial cohorts followed a 3+3 design for dose escalation. In this design, groups of 3 patients are treated and evaluated for toxic effects. If there are no toxic effects, 3 different patients are treated at an increased dose. However, if 1 patient has a dose-limiting toxic effect, 3 more patients are enrolled at the same dose. If at least 2 of 6 patients have a dose-limiting toxic effect, dose escalation stops. The protocol was amended after the dose level of 900 mg twice daily of the free-base form to incorporate a continual reassessment model algorithm, in order to increase flexibility in dose selection. In each case, the aim was to identify the maximum tolerated dose of rociletinib, defined as the highest dose associated with a rate of dose-limiting toxic effects of less than 33%. Dose escalation was to continue until the maximum tolerated dose was defined but could be stopped earlier on the basis of emerging preclinical and clinical data.

Safety and efficacy data are summarized for all patients who received at least one dose of rociletinib. Pharmacokinetic analyses were performed only in the dose-escalation cohorts. The data-cutoff date was June 18, 2014.

RESULTS

PATIENT CHARACTERISTICS

A total of 130 patients were enrolled between March 2012 and April 2014 at 10 centers in the United States, France, and Australia. Demographic characteristics were typical of patients with *EGFR*-mutated NSCLC (Table 1). Per the study protocol, all had received at least one previous line of EGFR tyrosine kinase inhibitor therapy, most frequently erlotinib. The median number of prior treatments was four, and 72% of the patients were taking an EGFR inhibitor at the time of consent. A total of 50% (65 of 130 patients) had three or more sites of metastatic disease, and 44% (57 of 130 patients) had a history of brain metastases. Tumor biopsy was a mandatory screening procedure in both phases of the study, and T790M positivity had to be confirmed before enrollment in the phase 2 portion. Among the 172 patients screened for the phase 2 portion of the

Table 1. Baseline Characteristics of the Patients.

Characteristic	Any Dose of Rociletinib (N=130)	Free Base		Hydrogen Bromide Salt			
		<900 mg Twice Daily (N=38)	900 mg Twice Daily (N=19)	500 mg Twice Daily (N=17)	625 mg Twice Daily (N=16)	750 mg Twice Daily (N=34)	1000 mg Twice Daily (N=6)
Median age — yr	60.0	61.5	59.0	55.0	52.5	62.0	64.5
Female sex — no. (%)	100 (77)	31 (82)	15 (79)	12 (71)	13 (81)	24 (71)	5 (83)
Asian race — no. (%)*	19 (15)	6 (16)	4 (21)	0	3 (19)	5 (15)	1 (17)
ECOG performance-status score of 0 — no. (%)†	35 (27)	11 (29)	3 (16)	5 (29)	3 (19)	10 (29)	3 (50)
History of brain metastases — no. (%)	57 (44)	20 (53)	6 (32)	10 (59)	8 (50)	10 (29)	3 (50)
≥3 Metastatic sites — no. (%)	65 (50)	19 (50)	8 (42)	11 (65)	9 (56)	15 (44)	3 (50)
History of diabetes or impaired glucose tolerance — no. (%)	12 (9)	5 (13)	2 (11)	1 (6)	1 (6)	3 (9)	0
Previous lines of therapy — median	4	4	4	3	4	3	4
Previous EGFR inhibitor ongoing at study consent — no. (%)	94 (72)	20 (53)	14 (74)	15 (88)	12 (75)	29 (85)	4 (67)
Previous lines of therapy containing an EGFR inhibitor — median	2	2	2	1	2	1	2
Previous use of erlotinib — no. (%)	120 (92)	35 (92)	19 (100)	15 (88)	14 (88)	32 (94)	5 (83)
Previous use of gefitinib — no. (%)	13 (10)	5 (13)	2 (11)	2 (12)	2 (12)	1 (3)	1 (17)
Previous use of afatinib — no. (%)	23 (18)	4 (11)	5 (26)	2 (12)	2 (12)	6 (18)	4 (67)
Initial activating EGFR mutation — no. (%)							
Del19	74 (57)	22 (58)	12 (63)	8 (47)	9 (56)	18 (53)	5 (83)
L858R	42 (32)	14 (37)	6 (32)	5 (29)	4 (25)	12 (35)	1 (17)
Other	11 (8)	2 (5)	1 (5)	3 (18)	2 (12)	3 (9)	0
Unknown	3 (2)	0	0	1 (6)	1 (6)	1 (3)	0
T790M status by central testing — no. (%)							
Positive	74 (57)	23 (61)	9 (47)	7 (41)	9 (56)	22 (65)	4 (67)
Negative	23 (18)	5 (13)	3 (16)	2 (12)	6 (38)	7 (21)	0
Unknown	33 (25)	10 (26)	7 (37)	8 (47)	1 (6)	5 (15)	2 (33)

* Race was determined by the treating physician.
† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability.

Table 2. Best Response, Objective Response, and Disease Control.*

Variable	Any Dose of Rociletinib	Free Base, 900 mg Twice Daily	Hydrogen Bromide Salt			
			500 mg Twice Daily	625 mg Twice Daily	750 mg Twice Daily	1000 mg Twice Daily
			number/total number (percent)			
Patients with centrally confirmed T790M-positive tumors						
Best response						
Partial response	27/46 (59)	6/8 (75)	3/6 (50)	5/9 (56)	10/19 (53)	3/4 (75)
Stable disease	16/46 (35)	2/8 (25)	2/6 (33)	2/9 (22)	9/19 (47)	1/4 (25)
Progressive disease	3/46 (7)	0/8	1/6 (17)	2/9 (22)	0/19	0/4
Objective response	27/46 (59)	6/8 (75)	3/6 (50)	5/9 (56)	10/19 (53)	3/4 (75)
Disease control	43/46 (93)	8/8 (100)	5/6 (83)	7/9 (78)	19/19 (100)	4/4 (100)
Patients with centrally confirmed T790M-negative tumors						
Best response						
Partial response	5/17 (29)	0/2	0/2	2/6 (33)	3/7 (43)	NA
Stable disease	5/17 (29)	2/2 (100)	0/2	0/6	3/7 (43)	
Progressive disease	7/17 (41)	0/2	2/2 (100)	4/6 (67)	1/7 (14)	
Objective response	5/17 (29)	0/2	0/2	2/6 (33)	3/7 (43)	NA
Disease control	10/17 (59)	2/2 (100)	0/2	2/6 (33)	6/7 (86)	

* Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Objective response was defined as a complete response or a partial response. Disease control was defined as a complete response, a partial response, or stable disease for more than 6 weeks. Six patients (five with T790M-positive tumors and one with a T790M-negative tumor) could not be evaluated according to RECIST.

study at the time of this analysis, genotyping was possible for 148 (86%), and 78 (53%) were found to harbor T790M. The majority of testing failures resulted from insufficient tumor tissue in the biopsy sample.

The starting dose of free-base rociletinib was 150 mg once daily. Regimens involving administration one, two, or three times daily were studied. The highest dose of free-base rociletinib administered was 900 mg twice daily. The starting dose of the HBr form was 500 mg twice daily, and the highest dose administered was 1000 mg twice daily. The maximum tolerated dose was not reached according to the protocol definition, because all doses studied had a cycle 1 rate of dose-limiting toxic effects of less than 33%.

EFFICACY

Objective responses were consistently observed at a dose of 900 mg twice daily of the free-base form and all doses of the HBr form (hereafter referred to as therapeutic doses). Among 38 patients who received the free-base form at a dose of less than 900 mg twice daily, 1 partial response and some minor tumor shrinkage and sustained disease control were observed. All remaining efficacy results are reported for the 92 patients who received therapeutic doses.

The response rate among 46 patients with centrally confirmed T790M-positive tumors was 59% (95% confidence interval [CI], 45 to 73), and the disease-control rate (the proportion of patients with a complete or partial response or stable disease) was 93% (43 of 46 patients) (Table 2 and Fig. 1A). Response rates were similar between patients with deletion 19 or L858R *EGFR* mutations (Table S1 in the Supplementary Appendix). The median follow-up was 10.5 weeks (range, 0.1 to 53.9). The estimated median progression-free survival at the time of the current analysis was

13.1 months (95% CI, 5.4 to 13.1), with data on 82% of the patients censored (Fig. S1 in the Supplementary Appendix).

Among 17 patients whose tumors were T790M-negative by central testing, the response rate was 29% (95% CI, 8 to 51), and the disease-control rate was 59% (10 of 17 patients) (Table 2 and Fig. 1B). In this group, the median progression-free survival was 5.6 months (95% CI, 1.3 to not reached). Of the 17 patients, 12 had been taking an EGFR inhibitor as the therapy immediately before taking rociletinib, and 4 of these had a partial response. Among 20 patients whose tumors were not assessable for T790M at the central laboratory, the response rate was 15% (3 of 20 patients).

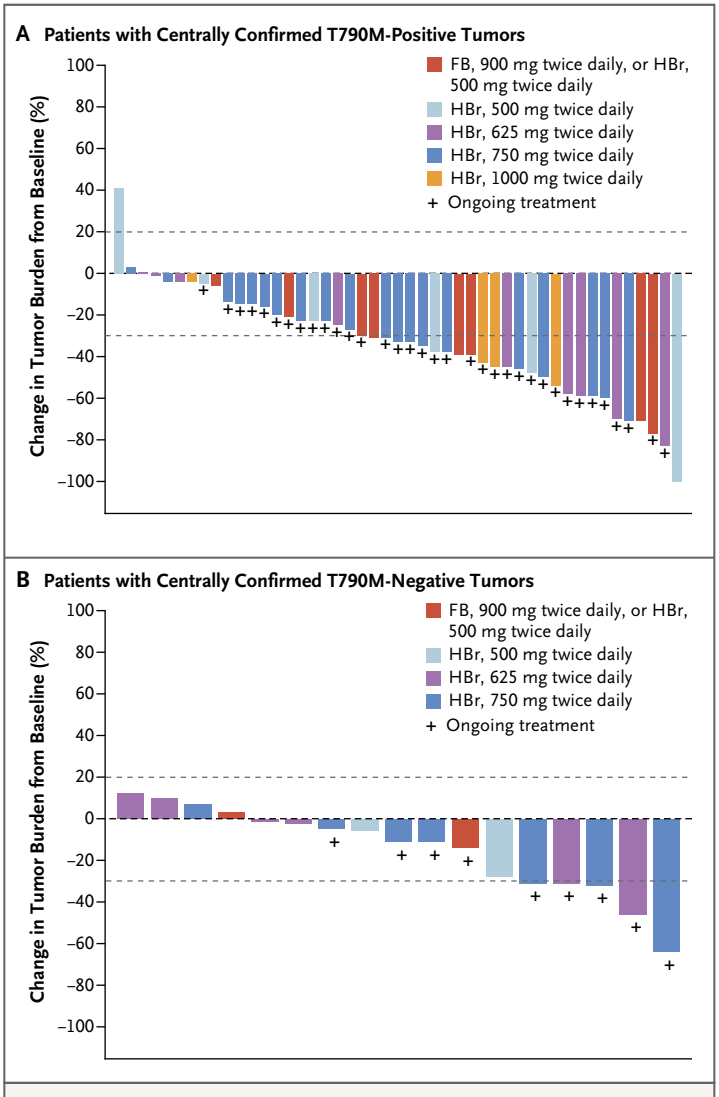

Figure 1. Best Response to Rociletinib.

Each bar represents an individual patient, and the amplitude and direction of the bar represent the percent change in tumor burden during treatment as compared with baseline. Tumor burden was measured as the sum of the longest diameters of the target lesions, according to the Response Evaluation Criteria in Solid Tumors, version 1.1. The dashed line at 20% represents the boundary for determination of progressive disease, and the dashed line at –30% represents the boundary for determination of partial response. FB denotes free base, and HBr hydrogen bromide salt.

SAFETY

Treatment-related adverse events were generally infrequent and mild (Tables 3 and 4). The predominant grade 3 adverse event was hyperglycemia, occurring in 20 of the 92 patients (22%) who received therapeutic doses. Hyperglycemia was most often managed with dose reduction, an oral hypoglycemic agent (typically metformin), or both, and did not result in rociletinib discontinuation in any patient; 35 of the 92 patients (38%) received glucose-lowering therapy to treat hyperglycemia. Grade 3 prolongation of the QT interval corrected for heart rate caused no symptoms and was managed in all cases by dose reduction; no ventricular arrhythmias were reported. Acneiform rash was not observed, though a single patient had a grade 1 maculopapular rash. Grade 1 or 2 diarrhea was noted in 20% of the patients, with no reports of diarrhea of grade 3 or higher. Dose reduction occurred in 44 of the 92 patients (48%) who received therapeutic doses.

PHARMACOKINETICS

Pharmacokinetic analyses showed that exposure to the HBr form of rociletinib (the form being used in all ongoing and future development) increased with dose in the range studied, 500 mg twice daily to 1000 mg twice daily. Rociletinib was absorbed rapidly, with an elimination half-life of 2 to 4 hours (Table S3 in the Supplementary Appendix). The increase in the maximal plasma concentration was proportional to the dose administered. In healthy volunteers, food increased absorption of the HBr form of rociletinib as compared with fasting administration (data not shown). At therapeutic doses, plasma concentrations of rociletinib were sustained in the predicted efficacious range for an average of 22 hours daily.

DISCUSSION

We found that treatment with rociletinib — an EGFR inhibitor selective for mutated *EGFR*, including the T790M resistance mutation — results

Table 3. Treatment-Related Adverse Events, According to Dose Level.*

Event	Any Dose of Rociletinib (N=130)	Free Base		Hydrogen Bromide Salt				Therapeutic Dose (N=92)†
		<900 mg Twice Daily (N=38)	900 mg Twice Daily (N=19)	500 mg Twice Daily (N=17)	625 mg Twice Daily (N=16)	750 mg Twice Daily (N=34)	1000 mg Twice Daily (N=6)	
		number (percent)						
Hyperglycemia‡	47 (36)	4 (11)	6 (32)	10 (59)	10 (62)	13 (38)	4 (67)	43 (47)
Nausea	40 (31)	8 (21)	6 (32)	5 (29)	7 (44)	11 (32)	3 (50)	32 (35)
Fatigue	31 (24)	9 (24)	6 (32)	5 (29)	3 (19)	7 (21)	1 (17)	22 (24)
Diarrhea	26 (20)	6 (16)	6 (32)	4 (24)	4 (25)	4 (12)	2 (33)	20 (22)
Decreased appetite	19 (15)	1 (3)	6 (32)	4 (24)	3 (19)	3 (9)	2 (33)	18 (20)
Vomiting	18 (14)	5 (13)	2 (11)	2 (12)	4 (25)	5 (15)	0	13 (14)
Muscle spasms	13 (10)	3 (8)	4 (21)	3 (18)	0	3 (9)	0	10 (11)

* Shown are events of any grade that occurred in at least 10% of the patients.
† Therapeutic doses of rociletinib were 900 mg twice daily of the free-base form and 500 mg twice daily, 625 mg twice daily, 750 mg twice daily, and 1000 mg twice daily of the hydrogen bromide salt form.
‡ Hyperglycemia includes the combined terms of increased blood glucose level, glucose intolerance, impaired glucose tolerance, and hyperglycemia.

in sustained tumor responses in patients with *EGFR*-mutated NSCLC who had disease progression while taking currently available EGFR inhibitors. The response rate of 59% and prolonged disease control among some T790M-positive patients are encouraging, particularly because there are no approved therapies that specifically target T790M, although several other molecules are in development.[11] The antitumor activity of rociletinib was observed regardless of initial activating mutation and in a trial population of heavily pretreated patients (median number of previous therapies, 4). A maximum tolerated dose was not defined in the phase 1 portion.

Previous approaches to address T790M-driven resistance to EGFR tyrosine kinase inhibitors have had only modest success. Second-generation EGFR inhibitors such as afatinib, dacomitinib and neratinib, which are covalent inhibitors of HER family kinases (including EGFR), inhibit T790M in vitro, but clinical data suggest that toxic effects (rash and diarrhea) probably mediated by inhibition of nonmutant EGFR prevented T790M-inhibitory plasma concentrations from being reached.[12-14] For example, studies of afatinib monotherapy showed a response rate of less than 10% among patients with acquired resistance to erlotinib or gefitinib, with a progression-free survival of approximately 4 months.[13,15] The most successful therapy to date for acquired resistance has been a combination of daily afatinib and the EGFR monoclonal antibody cetuximab every other week, with a response rate of 30% and a median progression-free survival of 4.7 months.[16] However, this combination is associated with substantial skin and gastrointestinal toxic effects, which may limit its use. Existing data for cytotoxic chemotherapy in patients with acquired resistance to EGFR inhibitors suggest that benefits are also of relatively short duration, with studies showing a median progression-free survival of 4.0 to 5.5 months.[17,18]

In contrast, T790M-positive patients treated with rociletinib in our study had a sustained clinical benefit. A response rate of 59% with prolonged disease control was noted. Although the best responses were observed among those with T790M-positive cancers, rociletinib showed some antitumor activity in patients without a documented T790M mutation. This issue is complex, because the ability to document a T790M mutation relies on several factors: whether T790M is biologically present in any of the tumor cells, none of the cells, or only a portion of the cells; the accuracy of the biopsy approach in sampling the true biologic characteristics of the tissue; and the sensitivity of the genotyping platform to detect the mutation in the biopsy material.[19]

Nevertheless, in our study, those who were T790M-negative on the central assay had a response rate of 29% (5 of the 17 patients) and a median progression-free survival of 5.6 months. Some of this activity may have been due to biologic presence of T790M that was not detected, and some of the clinical benefit may have been due to other factors, including activity of the drug against other resistance mechanisms and subpopulations of the tumor cells that maintain sensitivity to EGFR inhibitors without resistance mechanisms (i.e., T790M heterogeneity). A retreatment effect seems unlikely given that 12 of the 17 T790M-negative patients, and 80% of the T790M-negative patients who had a response, had been taking an EGFR inhibitor immediately before rociletinib. Although a retreatment effect must be considered when assessing new treatments for acquired resistance among patients whose tumors harbor EGFR mutations,[20] in this study 72% of patients overall and 70% of T790M-positive patients who had a response were also taking an EGFR inhibitor immediately before study therapy, findings that minimize this concern in our study.

Table 4. Treatment-Related Adverse Events in the 92 Patients Receiving Therapeutic Doses of Rociletinib, According to Event Grade.*

Event	Any Grade	Grade 1	Grade 2	Grade 3
	number (percent)			
Hyperglycemia†	43 (47)	14 (15)	9 (10)	20 (22)
Nausea	32 (35)	16 (17)	14 (15)	2 (2)
Fatigue	22 (24)	9 (10)	9 (10)	4 (4)
Diarrhea	20 (22)	16 (17)	4 (4)	0
Decreased appetite	18 (20)	10 (11)	7 (8)	1 (1)
Vomiting	13 (14)	9 (10)	2 (2)	2 (2)
QTc prolongation	11 (12)	3 (3)	3 (3)	5 (5)
Muscle spasms	10 (11)	9 (10)	0	1 (1)

* Shown are events that occurred in at least 10% of the patients. Therapeutic doses of rociletinib were 900 mg twice daily of the free-base form and 500 mg twice daily, 625 mg twice daily, 750 mg twice daily, and 1000 mg twice daily of the hydrogen bromide salt form. Events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events. One patient had a treatment-related grade 4 event (hypokalemia), and there were no treatment-related grade 5 events. QTc denotes QT interval corrected for heart rate.

† Hyperglycemia includes the combined terms of increased blood glucose level, glucose intolerance, impaired glucose tolerance, and hyperglycemia.

Rociletinib did not cause the syndrome of rash, stomatitis, and paronychia that is associated with inhibition of nonmutant EGFR, which suggests that the mutation-specific selectivity observed in preclinical testing was also present in patients. The most common grade 3 toxic effect associated with rociletinib was hyperglycemia. Most hyperglycemia events were successfully managed with dose reduction, oral hyperglycemic therapy (most commonly metformin), or both, and no hyperglycemia events led to rociletinib discontinuation. The study included some patients with preexisting diabetes, who were treated uneventfully, and such patients have not been excluded from ongoing studies. The remainder of the observed adverse effects were primarily mild upper and lower gastrointestinal events, which may have been compounded by the presence of hyperglycemia and the need for metformin in some patients. In fact, many of the common adverse effects occurred more frequently in patients who also had hyperglycemia than in those who did not (Table S2 in the Supplementary Appendix). We speculate that hyperglycemia (or potentially hyperinsulinemia) may have played a causative role, although we cannot rule out a more direct relationship with drug exposure. Appropriate glucose control (random plasma glucose level, <200 mg per deciliter) was often noted to lead to resolution of symptom clusters in patients with hyperglycemia. Because of the short half-life of rociletinib, dose reduction or temporary discontinuation of treatment resulted in swift resolution of adverse effects, without sustained clinical sequelae.

Ongoing preclinical studies suggest that hyperglycemia is caused by a rociletinib metabolite rather than by the parent molecule. This metabolite inhibits the type I insulin-like growth factor receptor (IGF-IR) and, to a lesser extent, insulin receptor kinases in biochemical and cellular studies and induces hyperglycemia in an oral glucose-tolerance test in rodents. Activation of the IGF-IR pathway is a proposed resistance mechanism for EGFR inhibition,[21,22] although the contribution of the IGF-IR inhibitory effect of rociletinib to its antitumor activity is currently unknown.

The main limitation of our study is the relatively small number of patients who have been treated with rociletinib to date. Larger studies are ongoing, though previous results of treating NSCLCs defined by a driver mutation with corresponding tyrosine kinase inhibitors suggest that strong and early activity as we have seen with

rociletinib will translate into a sustained benefit in larger populations.[2,23-25]

In summary, rociletinib was associated with tumor responses and sustained disease control among patients with heavily pretreated *EGFR*-mutated NSCLC from the United States, Europe, and Australia in whom the T790M resistance mutation has developed.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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