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ORIGINAL ARTICLE

Efficacy and Safety of Rociletinib Versus Chemotherapy in Patients With *EGFR*-Mutated NSCLC: The Results of TIGER-3, a Phase 3 Randomized Study

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ABSTRACT

Introduction: The TIGER-3 (NCT02322281) study was initiated to compare the efficacy and safety of rociletinib, a third-generation EGFR tyrosine kinase inhibitor (TKI) that targets *EGFR* T790M and common *EGFR*-activating mutations, versus chemotherapy in patients with NSCLC who progressed on first- or second-generation EGFR TKIs.

Methods: Patients with advanced or metastatic *EGFR*-mutated NSCLC with disease progression on standard therapy (previous EGFR TKI and platinum-based chemotherapy) were randomized to oral rociletinib (500 or 625 mg twice daily) or single-agent chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel).

Results: Enrollment was halted when rociletinib development was discontinued in 2016. Of 149 enrolled patients, 75 were randomized to rociletinib (n = 53: 500 mg twice daily; n = 22: 625 mg twice daily) and 74 to chemotherapy. The median investigator-assessed progression-free survival (PFS) was 4.1 months (95% confidence interval [CI]: 2.6–5.4) in the rociletinib 500-mg group and 5.5 months (95% CI: 1.8–8.1) in the 625-mg group versus 2.5 months (95% CI: 1.4–2.9) in the chemotherapy group. An improved PFS was observed in patients with T790M-positive NSCLC treated with rociletinib (n = 25; 500 mg and 625 mg twice daily) versus chemotherapy (n = 20; 6.8 versus 2.7 mo; hazard ratio = 0.55, 95% CI: 0.28–1.07, $p = 0.074$). Grade 3 or higher hyperglycemia (24.0%), corrected QT prolongation (6.7%), diarrhea (2.7%), and vomiting (1.3%) were more frequent with rociletinib than chemotherapy (0%, 0%, 1.4%, and 0%, respectively).

Conclusions: Rociletinib had a more favorable median PFS versus chemotherapy but had higher rates of hyperglycemia and corrected QT prolongation in patients with advanced *EGFR*-mutated NSCLC who progressed on previous EGFR TKI. Incomplete enrollment prevented evaluation of the primary efficacy end point.

Keywords: EGFR tyrosine kinase inhibitor; Epidermal growth factor receptor mutations; Non–small cell lung cancer; Phase III randomized clinical trial; Rociletinib

Introduction

Activating *EGFR* mutations (exon 21 L858R and deletions in exon 19) have been detected in approximately 30% of patients of East Asian descent and 10% to 15% of patients of Northern or Western European descent with NSCLC.[1] Patients whose tumors carry these mutations typically have good responses to therapy with a first-generation (e.g., gefitinib, erlotinib) or second-generation (e.g., afatinib, dacomitinib) EGFR tyrosine kinase inhibitor (TKI) as assessed by progression-free survival (PFS).[2-4] However, after a median of 8 to 16 months of EGFR TKI therapy, the emergence of resistance, which is driven by a mutation in exon 20 (T790M, the "gatekeeper mutation") in 50% to 60% of cases, results in disease progression.[4-7] This led to the development of third-generation EGFR TKIs, including rociletinib and osimertinib, which added activity against T790M.

Rociletinib is a third-generation, orally-bioavailable, irreversible EGFR TKI that selectively targets common *EGFR*-activating mutations, such as L858R and deletions in exon 19, and the resistance T790M gatekeeper mutation with minimal activity toward wild-type *EGFR*.[8-10] In a phase 1 and 2 trial (TIGER-X, NCT01526928), rociletinib was investigated in patients with *EGFR*-mutated, T790M-positive, and T790M-negative NSCLC previously treated with a first- or second-generation EGFR TKI.[11] In the phase 1 portion of the study, 57 patients received a free-base formulation of rociletinib 150 to 900 mg twice daily. During the phase 2 portion, 548 patients received rociletinib (hydrogen bromide salt

formulation) at 500, 625, or 750 mg twice daily. In the final TIGER-X analysis that included 443 patients who received at least one dose of rociletinib (500, 625, or 750 mg twice daily) and had centrally confirmed T790M-positive tumors, the confirmed objective response rate (ORR) was 33.9%.[12] Across all three dosing groups, the most common treatment-emergent adverse events (AEs) included hyperglycemia, diarrhea, nausea, fatigue, and decreased appetite.

TIGER-3 (NCT02322281) was a phase 3 randomized trial initiated in 2014 to assess the efficacy and safety of rociletinib versus chemotherapy in patients with *EGFR*-mutated NSCLC who progressed on first- or second-generation EGFR TKIs. To be eligible for inclusion, patients in TIGER-3 had to have been previously treated with platinum-doublet chemotherapy.[13] No third-generation EGFR TKIs were available at the time of initiation of the trial; however, in 2016, osimertinib received approval from the U.S. Food and Drug Administration. The clinical development of rociletinib was halted in 2016 per sponsor decision. Here, we report the final results of TIGER-3.

Materials and Methods

Study Design

TIGER-3 was an international, phase 3, randomized, open-label study. Eligible patients were aged 18 years or older with metastatic or unresectable, locally advanced *EGFR*-mutated NSCLC (excluding exon 20 insertion–activating mutation) with radiological progression after at least one first- or second-generation EGFR TKI and one line of platinum-based doublet chemotherapy for advanced or metastatic NSCLC. Biopsy or surgical resection of either primary or metastatic tumor tissue within 60 days before study treatment was required for the central determination of T790M mutation status; however, results were not required before randomization. Central genotyping of the collected tissues was performed with the therascreen EGFR RGQ PCR Kit (Qiagen, Germantown, MD).[14] Patients who received previous treatment with rociletinib or other T790M-positive EGFR-specific medications (including osimertinib [AZD9291], olmutinib [HM61713], and TAS-121) were excluded. Patients with brain metastases were eligible if lesions were treated, asymptomatic, and stable. The full inclusion and exclusion criteria are listed in the Supplementary Data.

After screening, patients were randomized in a 1:1 ratio to receive oral rociletinib or investigator's choice of single-agent cytotoxic chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel). Initially, the starting dose of rociletinib was 625 mg twice daily, but after a protocol amendment, it was decreased to 500 mg twice daily in an effort to improve tolerability. Randomization was stratified on the presence of brain metastases (yes versus no), Eastern Cooperative Oncology Group performance status (0 versus 1), and region (East Asian versus non-East Asian).

Ethical Considerations

TIGER-3 was conducted in compliance with Good Clinical Practices, including the International Conference on Harmonization's Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines, the U.S. Food and Drug Administration regulatory requirements, and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, which was reviewed and approved by local ethics committees.

Treatments and Dosing

Depending on the protocol version in place at the time of study entry, patients were treated with rociletinib 625 or 500 mg twice daily in a 21-day continuous cycle. Two dose reduction steps were allowed for each patient (in decrements of 125 mg) for grade 3 or 4 hematologic and nonhematologic toxicities.

The investigators' choices of chemotherapy included any one of the following: (1) pemetrexed 500 mg/m^2 intravenously (IV) on day 1 of each 21-day cycle; (2) gemcitabine 1250 mg/m^2 IV on days 1 and 8 of each 21-day cycle; (3) docetaxel 75 mg/m^2 (60 mg/m^2 for East Asian patients) IV on day 1 of each 21-day cycle or 35 mg/m^2 IV weekly as part of a continuous 21-day cycle (d 1, 8, and 15 of each 21-d cycle); or (4) paclitaxel 80 mg/m^2 IV weekly as part of a continuous 21-day cycle (d 1, 8, and 15 of each 21-d cycle).

Patients were treated until radiographically confirmed disease progression, unacceptable toxicity, or other withdrawal criteria were met. Patients could choose to continue rociletinib therapy after radiographic progression if the patient provided consent and the investigator and sponsor approved. Patients who progressed while taking chemotherapy could cross over to receive rociletinib until disease progression, unacceptable toxicity, or other withdrawal criteria were met.

End Points

The primary end point was investigator-assessed PFS according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The PFS was calculated as one plus the number of days from the date of randomization to documented radiographic progression as

determined by the investigator, or death owing to any cause, whichever occurred first.

The planned secondary end points included ORR, duration of response (DOR), overall survival, and pharmacokinetics. ORR was defined as the proportion of patients with a confirmed complete response or confirmed partial response (PR) in the efficacy population. The DOR for a complete response or PR was measured from the date that a response (per RECIST) was first recorded until the first date that progressive disease (PD) was objectively documented. The overall survival, pharmacokinetics, and planned exploratory end points were not analyzed owing to the early termination of the study.

Efficacy and Safety Evaluations

Tumor scans were performed at screening, every 6 (±1) weeks until tumor progression or other withdrawal criteria were met, and at the end-of-treatment visit. Patients who discontinued rociletinib or chemotherapy without disease progression were scanned every 6 weeks until tumor progression occurred. Tumor assessments involved clinical examination and appropriate imaging (usually computed tomography scans of the chest and abdomen with appropriate slice thickness, per RECIST); other scans (magnetic resonance imaging and radiograph) were performed if necessary. Brain imaging (computed tomography or magnetic resonance imaging) was required at baseline; follow-up scans were conducted throughout the study for patients with brain lesions at enrollment. A central laboratory assessed the presence or absence of the T790M mutation in formalin-fixed paraffin-embedded tumor tissues. The details of additional planned evaluations are available in the Supplementary Data.

Safety evaluations included the following: (1) AEs; (2) clinical laboratory evaluations (hematology, serum chemistry, and urinalysis); (3) 12-lead electrocardiograms; (4) physical examination; (5) vital sign measurements; (6) body weight; (7) concomitant medications or procedures; and (8) Eastern Cooperative Oncology Group performance status. Patients were monitored for AEs from the first dose of rociletinib or chemotherapy until 28 days after the last dose of protocol-specified treatment. AEs were classified according to the U.S. National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[15] Safety assessments included the following: (1) study drug exposure AEs; (2) shift tables of changes in clinical laboratory parameters; (3) previous and concomitant hyperglycemia medications; (4) vital signs; (5) glucose elevations; and (6) changes in the corrected QT (QTc) interval.

Statistical Considerations

The target enrollment was 600 patients on the basis of a minimum anticipated treatment effect of a 4-month (chemotherapy) versus 6-month (rociletinib) median PFS in all patients. A total of 600 patients was predicted to result in 400 progression events, providing approximately 90% power to detect a hazard ratio [HR] of 0.70 at a two-sided 0.025 significance level.

The intention-to-treat population included all randomized patients. The efficacy and safety population included patients who had received at least one dose of rociletinib or single-agent cytotoxic chemotherapy. Kaplan-Meier methodology was used to summarize time-to-event variables.

The testing of primary and key secondary end points among the centrally confirmed T790M-positive and all randomized patients using an ordered, stepdown, multiple comparisons procedure was planned. Owing to the early termination of the study, this procedure was not undertaken. Stratified and unstratified log-rank tests and HRs were used to compare the PFS distributions among the rociletinib-treated (500 mg twice daily, 625 mg twice daily) and single-agent cytotoxic chemotherapy-treated patients in the efficacy population and according to centrally confirmed T790M mutation status. Investigator-assessed ORR was analyzed in the efficacy population and by T790M mutation status. DOR was analyzed in the efficacy population.

All analyses were conducted using Statistical Analysis System software (SAS Institute, Cary, NC) version 9.1 or higher.

Results

Patient Enrollment and Demographics

From May 2015 to May 2016, a total of 149 patients were enrolled in the TIGER-3 study at 53 sites in 10 countries (Australia, France, Germany, Italy, The Netherlands, Republic of Korea, Spain, Republic of China, United Kingdom, and the United States). Enrollment was halted when rociletinib development for patients with NSCLC was discontinued in 2016. However, patients who continued to derive clinical benefit from study treatment were allowed to remain in the study at the discretion of the investigator as part of an extension phase. Target enrollment was not achieved. Therefore, hypothesis testing as per protocol was not feasible; p values are provided for descriptive purposes only.

Of the 149 patients enrolled, 75 were randomized to rociletinib (n = 53: 500 mg twice daily; n = 22: 625 mg twice daily) and 74 to chemotherapy (Table 1). The treatment groups were generally well-balanced. In the combined rociletinib group (500-mg and 625-mg doses) and chemotherapy group, 25 (33.3%) and 20 (27.0%)

Table 1. Patient Demographics and Baseline Clinical Characteristics: ITT Population

Characteristic	Rociletinib			Chemotherapy (n = 74)
	500 mg Twice Daily (n = 53)	625 mg Twice Daily (n = 22)	Overall (n = 75)	
Age, y				
Median (min, max)	62.0 (37.0, 86.0)	63.5 (43.0, 90.0)	62.0 (37.0, 90.0)	62.5 (40.0, 85.0)
Female, n (%)	35 (66.0)	13 (59.1)	48 (64.0)	39 (52.7)
Region, n (%)				
North America	11 (20.8)	12 (54.5)	23 (30.7)	26 (35.1)
Europe	20 (37.7)	8 (36.4)	28 (37.3)	27 (36.5)
Asia	21 (39.6)	1 (4.5)	22 (29.3)	20 (27.0)
Other	1 (1.9)	1 (4.5)	2 (2.7)	1 (1.4)
Baseline ECOG PS, n (%)				
0	15 (28.3)	9 (40.9)	24 (32.0)	21 (28.4)
1	38 (71.7)	13 (59.1)	51 (68.0)	52 (70.3)
2	0	0	0	1 (1.4)
Smoking status, n (%)				
Current smoker	2 (3.8)	0	2 (2.7)	3 (4.1)
Former smoker	14 (26.4)	9 (40.9)	23 (30.7)	28 (37.8)
Never smoked	37 (69.8)	13 (59.1)	50 (66.7)	43 (58.1)
Time since NSCLC diagnosis, mo				
Median (min, max)	35.2 (8.8, 212.0)	39.4 (12.6, 69.0)	36.2 (8.8, 212.0)	29.5 (7.4, 105.3)
History of CNS metastases, n (%)	23 (43.4)	9 (40.9)	32 (42.7)	31 (41.9)
History of hyperglycemia, n (%)	8 (15.1)	4 (18.2)	12 (16.0)	8 (10.8)
No. of previous therapies				
Median (min, max)	3 (1, 8)	3 (2, 6)	3 (1, 8)	3 (0, 13)
T790M status by central test, n (%)				
Positive	16 (30.2)	9 (40.9)	25 (33.3)	20 (27.0)
Negative	26 (49.1)	10 (45.5)	36 (48.0)	42 (56.8)
Unknown	11 (20.8)	3 (13.6)	14 (18.7)	12 (16.2)
Activating *EGFR* mutations at randomization,[a] n (%)				
Exon 19 deletion	21 (39.6)	11 (50.0)	32 (42.7)	35 (47.3)
Exon 20 insertion[b]	1 (1.9)	2 (9.1)	3 (4.0)	1 (1.4)
L858R	18 (34.0)	6 (27.3)	24 (30.4)	29 (39.2)
G719X	1 (1.9)	0	1 (1.3)	3 (4.1)
L861Q	5 (9.4)	0	5 (6.7)	2 (2.7)
S768I	1 (1.9)	1 (4.5)	2 (2.7)	3 (4.1)
Other[c]	1 (1.9)	0	1 (1.3)	4 (5.4)

[a]Patients may be counted in more than one category.
[b]Patients with an exon 20 insertion were eligible for inclusion if they also had another activating *EGFR* mutation.
[c]Other activating mutations included E709A in the rociletinib 500-mg twice-daily group and E709A, E709G, G724S, and G729A in the chemotherapy group.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; max, maximum; min, minimum.

patients were T790M-positive, respectively; 36 (48.0%) and 42 (56.8%) were T790M-negative, and 14 (18.7%) and 12 (16.2%) had nonevaluable T790M status, respectively. A total of 148 patients received at least one dose of the study drug (75 patients in the rociletinib group and 73 patients in the chemotherapy group) and were included in the safety and efficacy populations. One patient discontinued owing to PD before receiving a single dose of chemotherapy. Of the patients assigned to chemotherapy, 39 (52.7%) crossed over to the rociletinib group at the time of progression.

Patient Disposition and Drug Exposure

The median duration of therapy was 4.2 months in the rociletinib 500-mg group, 4.2 months in the rociletinib 625-mg group, and 1.2 months in the chemotherapy group. Two patients (2.7%) were treated with chemotherapy for more than 12 months, whereas 15 patients (20.0%) received rociletinib for more than 12 months. Most patients in the combined rociletinib group (500-mg and 625-mg doses, 56 of 75; 74.7%) and chemotherapy group (49 of 74; 66.2%) discontinued the study drug owing to PD (Table 2).

Table 2. Reasons for Study Drug Discontinuation

Reason	Rociletinib			Chemotherapy (n = 74)[b]
	500 mg Twice Daily (n = 53)[a]	625 mg Twice Daily (n = 22)	Overall (n = 75)[a]	
Progressive disease	42 (79.2)	14 (63.6)	56 (74.7)	49 (66.2)
AE	3 (5.7)	4 (18.2)	7 (9.3)	6 (8.1)
Patient choice	1 (1.9)	1 (4.5)	2 (2.7)	6 (8.1)
Physician decision	2 (3.8)	0	2 (2.7)	5 (6.8)
Death (excluding disease progression)	3 (5.7)	3 (13.6)	6 (8.0)	3 (4.1)

[a]A total of 2 patients discontinued because of study termination.
[b]A total of 4 patients discontinued because of other reasons, and one patient had missing data.
AE, adverse event.

Efficacy

In the efficacy population (n = 148), the median investigator-assessed PFS was 4.1 months (95% CI: 2.8–5.5 mo) in the combined rociletinib group (500-mg and 625-mg doses) versus 2.5 months (95% CI: 1.4–2.9, HR = 0.60 [95% CI: 0.42–0.86], $p = 0.005$) in the chemotherapy group (Fig. 1*A*). The median PFS was 4.1 months (95% CI: 2.6–5.4) in the rociletinib 500-mg group and 5.5 months (95% CI: 1.8–8.1) in the rociletinib 625-mg group (Fig. 1*B*).

PFS was also analyzed according to T790M-mutation status for the rociletinib (pooled 500 mg and 625 mg) and chemotherapy groups. For the T790M-positive population, the median PFS was 6.8 months (95% CI: 3.8–12.2) in the rociletinib group versus 2.7 months (95% CI: 1.3–7.0, HR = 0.55 [95% CI: 0.28–1.07], $p = 0.074$) in the chemotherapy group (Fig. 1*C*). In the T790M-negative population, the median PFS was 4.1 months (95% CI: 2.5–4.6) in the rociletinib group versus 1.4 months (95% CI: 1.3–2.7, HR = 0.54 [95% CI: 0.32–0.88], $p = 0.012$) in

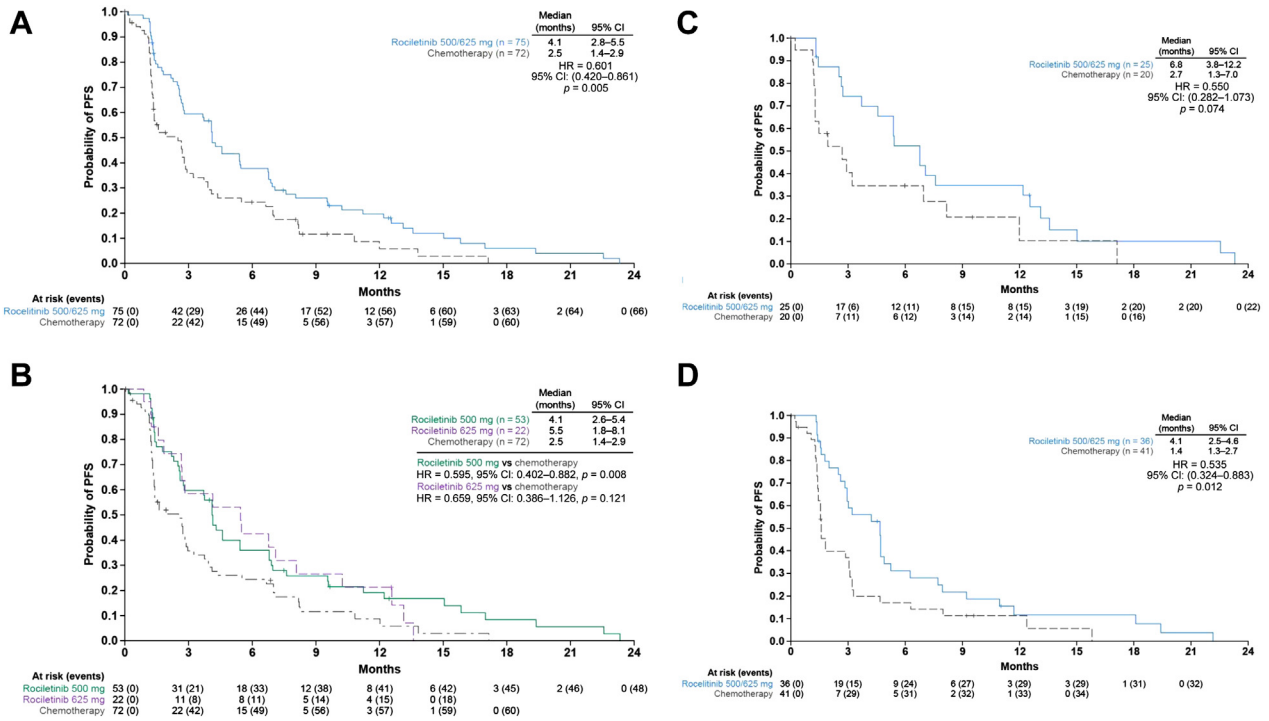

Figure 1. Investigator-assessed PFS. *(A)* Rociletinib (500 mg and 625 mg twice daily doses) versus chemotherapy (efficacy population, n = 148).[a] *(B)* Rociletinib 625 mg twice daily or 500 mg twice daily versus chemotherapy (efficacy population). *(C)* Rociletinib (500-mg and 625-mg twice-daily doses) versus chemotherapy in T790M-positive patients; and *(D)* Rociletinib (500-mg and 625-mg twice-daily doses) versus chemotherapy in T790M-negative patients. [a]One patient discontinued because of progressive disease before receiving a single dose of chemotherapy. One patient in the chemotherapy group was not followed up for PFS as the date of their death was not recorded. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Table 3. Response Rates in the Efficacy Population

	Overall[a]		T790M Mutation-Positive		T790M Mutation-Negative		T790 Mutation Unknown	
End Point	Rociletinib[b] (n = 75)	Chemotherapy (n = 73)	Rociletinib[b] (n = 25)	Chemotherapy (n = 20)	Rociletinib[b] (n = 36)	Chemotherapy (n = 41)	Rociletinib[b] (n = 14)	Chemotherapy (n = 12)
Confirmed ORR,[c] n (%) [95% CI]	13 (17.3) [9.6-27.8]	6 (8.2) [3.1-17.0]	9 (36.0) [18.0-57.5]	3 (15.0) [3.2-37.9]	3 (8.3) [1.8-22.5]	2 (4.9) [0.6-16.5]	1 (7.1) [0.2-33.9]	1 (8.3) [0.2-38.5]
Best overall confirmed response, n (%)								
CR	0	0	0	0	0	0	0	0
PR	13 (17.3)	6 (8.2)	9 (36.0)	3 (15.0)	3 (8.3)	2 (4.9)	1 (7.1)	1 (8.3)
SD	44 (58.7)	28 (38.4)	12 (48.0)	7 (35.0)	25 (69.4)	12 (29.3)	7 (50.0)	9 (75.0)
PD	11 (14.7)	31 (42.5)	3 (12.0)	8 (40.0)	4 (11.1)	21 (51.2)	4 (28.6)	2 (16.7)
NE	7 (9.3)	8 (11.0)	1 (4.0)	2 (10.0)	4 (11.1)	6 (14.6)	2 (14.3)	0
Median duration of response (95% CI), mo	11.0 (4.3-13.7)	6.8 (4.5-NA)	12.3 (2.5-22.1)	NA (4.5-NA)	5.5 (2.8-13.1)	NA (5.8-NA)	4.3[d]	6.8[d]

[a]Includes patients with unevaluable T790M mutation status.
[b]Rociletinib 500-mg twice daily and 625-mg twice-daily dosage groups were pooled for this analysis.
[c]Assessed according to RECIST.
[d]No 95% CI interval as n = 1.
CI, confidence interval; CR, complete response; NA, not assessable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Table 4. Most Common TEAEs

Event[a]	Rociletinib[b] (n = 75)		Chemotherapy (n = 73)	
	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)
Patients with ≥1 TEAE	74 (98.7)	49 (65.3)	71 (97.3)	42 (57.5)
Diarrhea	48 (64.0)	2 (2.7)	12 (16.4)	1 (1.4)
Hyperglycemia	44 (58.7)	18 (24.0)	6 (8.2)	0
Nausea	28 (37.3)	3 (4.0)	20 (27.4)	4 (5.5)
Fatigue	28 (37.3)	6 (8.0)	18 (24.7)	7 (9.6)
Decreased appetite	28 (37.3)	0	10 (13.7)	2 (2.7)
Cough	21 (28.0)	0	14 (19.2)	0
QTc prolongation	20 (26.7)	5 (6.7)	0	0
Vomiting	18 (24.0)	1 (1.3)	6 (8.2)	0
Anemia	9 (12.0)	2 (2.7)	18 (24.7)	2 (2.7)

[a]TEAEs of greater than or equal to 20% incidence in either group are illustrated, sorted by descending incidence in rociletinib-treated patients.
[b]Rociletinib 500-mg twice daily and 625-mg twice-daily dosage groups were pooled for this analysis.
QTc, corrected QT interval; TEAE, treatment-emergent adverse event.

the chemotherapy group (Fig. 1*D*). In the T790M-unknown subgroup, the median PFS was 2.3 months with rociletinib (95% CI: 1.2–9.6) versus 4.4 months with chemotherapy (95% CI: 1.4–7.1), (HR = 0.87 [95% CI: 0.36–2.11], $p = 0.759$; Supplementary Fig. 1). The Kaplan-Meier analyses of PFS in the individual rociletinib dose groups by T790M status are illustrated in the Supplementary Data (Supplementary Fig. 2*A–F*).

The investigator-assessed confirmed ORR was determined in the efficacy population. A confirmed ORR of 17.3% (95% CI: 9.6–27.8) was observed in the combined rociletinib group (500-mg + 625-mg doses) versus 8.2% (95% CI: 3.1–17.0) in the chemotherapy group (Table 3). All responses were PRs. Similar ORRs were seen for both doses of rociletinib: 17.0% (95% CI: 8.1–29.8) and 18.2% (95% CI: 5.2–40.3) for 500 mg and 625 mg, respectively.

Response data were also analyzed according to T790M mutation status. For the T790M-positive population, the ORR was 36.0% (95% CI: 18.0–57.5) in the rociletinib group and 15.0% (95% CI: 3.2–37.9) in the chemotherapy group. In the T790M-negative population, the ORR in the rociletinib group was 8.3% (95% CI: 1.8–22.5) versus 4.9% (95% CI: 0.6–16.5) in the chemotherapy group. In the small T790M-unknown subgroup, the ORR was 7.1% (95% CI: 0.2–33.9) for the combined rociletinib group versus 8.3% (95% CI: 0.2–38.5) for the chemotherapy group.

The median confirmed DOR was 11.0 months (95% CI: 4.3–13.7) in the rociletinib group versus 6.8 months (95% CI: 4.5–not assessable [NA]) in the chemotherapy group (HR = 0.91, 95% CI: 0.22–3.81, $p = 0.895$) (Table 3). For patients with T790M-positive tumors treated with rociletinib, the median DOR was 12.3 months (95% CI: 2.5–22.1) versus NA (95% CI: 4.5–NA) for chemotherapy-treated patients. For rociletinib-treated patients with T790M-negative tumors, the median DOR was 5.5 months (95% CI: 2.8–13.1) versus NA (95% CI: 5.8–NA) for patients treated with chemotherapy.

Adverse Events

Nearly all patients in the safety population (n = 148) experienced at least one treatment-emergent AE (TEAE) (74 of 75 [98.7%] in the combined rociletinib group; 71 of 73 [97.3%] in the chemotherapy group) (Table 4). A summary of TEAEs by rociletinib dose is illustrated in the Supplementary Table 1.

Grade 3 or higher TEAEs were reported by 49 of 75 (65.3%) rociletinib-treated patients and 42 of 73 (57.5%) chemotherapy-treated patients. The most frequently reported grade 3 or higher TEAE for rociletinib was hyperglycemia (18 of 75 [24.0%] versus 0 with chemotherapy); five of 75 (6.7%) rociletinib-treated patients experienced grade 3 or higher QTc prolongation versus none with chemotherapy. Neutropenia and neutrophil count decrease were the most common grade 3 or higher TEAEs in the chemotherapy group (both eight of 73 [11.0%]) and were observed more often in chemotherapy-treated patients than rociletinib-treated patients (both one of 75 [1.3%] in rociletinib-treated patients).

Five patients (6.7%) in the rociletinib group experienced a grade 4 TEAE. One patient each (1.3%) had lymphopenia, lymphocyte count decreased, and hypophosphatemia, all of which were assessed as not related to study drug; two patients (2.7%) had grade 4 hyperglycemia assessed as being related to study drug. Eleven patients (15.1%) in the chemotherapy group experienced at least one grade 4 TEAE (neutropenia: three of 73 [4.1%]; γ1 γ-glutamyltransferase increase: one of 73 [1.4%]; lymphocyte count decreased: one of 73 [1.4%]; neutrophil count decreased: four of 73 [5.5%]; aspiration: one of 73 [1.4%]; hypercalcaemia: one of 73 [1.4%]; white blood cell count decreased: one of 73 [1.4%]); the

events in eight patients (11.0%) were assessed as related to study drug.

Treatment interruption owing to a TEAE occurred in 37 of 75 patients (49.3%) in the combined rociletinib group and 19 of 73 (26.0%) in the chemotherapy group. Dose reduction owing to a TEAE occurred in 16 of 75 patients (21.3%) in the combined rociletinib group and 11 of 73 (15.1%) in the chemotherapy group (Supplementary Table 1). The most common TEAE leading to dose reduction was fatigue in the rociletinib group (6.7%) and neutropenia in the chemotherapy group (4.1%). Excluding disease progression, 12 of 75 patients (16.0%) in the combined rociletinib group and 11 of 73 (15.1%) in the chemotherapy group discontinued treatment owing to a TEAE, most often owing to diarrhea (4.0%) in rociletinib-treated patients and pleural effusion (2.7%) in chemotherapy-treated patients.

There were seven (9.3%) and two (2.7%) deaths owing to disease progression in the combined rociletinib group and chemotherapy group, respectively. Deaths because of a TEAE (excluding disease progression) were reported in six patients (8.0%) in the combined rociletinib group (two cases of pneumonia and one case each of cardiopulmonary arrest, dehydration, subdural hematoma, and sudden death) and one (1.4%) patient in the chemotherapy group (owing to an infection). The sudden death was the only TEAE considered by the investigator to be related to the study drug.

Other TEAEs of interest included pneumonitis and cataract. Four of 75 patients (5.3%) in the combined rociletinib group had pneumonitis versus none in the chemotherapy group. Cataract was reported in eight of 75 (10.7%) rociletinib-treated patients and one of 73 (1.4%) chemotherapy-treated patient. Three patients in the rociletinib group had grade 3 cataract, which were all considered to be related to the study drug.

Clinical Laboratory Assessments

Grade 3 or higher postbaseline glucose values (>250 mg/dL/13.9 mmol/liter) were observed in 17 of 75 (22.7%) of rociletinib-treated patients, five (6.7%) of whom had at least two incidences of grade 3 or higher postbaseline glucose levels. Hyperglycemia was managed with antihyperglycemic therapy and dose reductions. The frequencies of previous hyperglycemia medications in the safety population were 9.3% and 9.6% in the rociletinib and chemotherapy groups, respectively. After study treatment, 50.7% and 5.5% of patients in the rociletinib and chemotherapy groups, respectively, required hyperglycemia medication.

QTc Findings

QTc prolongation was observed in 20 of 75 (26.7%) of rociletinib-treated patients; five of 75 (6.7%) experienced a grade 3 QTc prolongation (prolonged QTc >500 msec [Common Terminology Criteria for Adverse Events version 4.03]) (Table 4). All events were assessed as related to the study drug. Nine rociletinib-treated patients (12.0%) experienced a QTc prolongation of greater than or equal to 501 msec using the Fridericia correction method. Of these, five patients (9.4%) were in the rociletinib 500 mg, and four (18.2%) were in the 625-mg group. One rociletinib-treated patient, who subsequently had a sudden death, experienced a serious QTc prolongation (559 ms) 2 weeks after the initiation of treatment, which was assessed as related to the study drug (as previously mentioned above). No patients in the chemotherapy group experienced QTc prolongation.

Discussion

The unmet need for novel therapies to treat patients with *EGFR*-mutated NSCLC, especially T790M-positive NSCLC, stimulated the discovery and clinical evaluation of rociletinib. Development of rociletinib for the treatment of patients with *EGFR*-mutant NSCLC who had been previously treated with an EGFR-targeted therapy and whose tumor carried the T790M mutation was halted in 2016 per sponsor decision. After this decision, regulatory submissions to the United States and European authorities were withdrawn. Beginning in late 2016, Clovis Oncology continued to provide rociletinib to patients who elected to continue receiving rociletinib therapy.

In the TIGER-3 study, a comparable number of patients in the rociletinib and chemotherapy groups experienced TEAEs; however, the types of TEAEs varied between the two groups. In the rociletinib group, we reported grade 3 or higher hyperglycemia and QTc prolongation—these TEAEs were not observed or reported in the chemotherapy group. In addition, grade 3 diarrhea and vomiting occurred at a higher rate in the rociletinib group. The incidence of pneumonitis (5.3%) in patients receiving rociletinib was higher than the reported incidence rate (1.3%–2.6%) in patients with advanced NSCLC who were treated with a first- (gefitinib) or second-generation (afatinib) EGFR TKI.[3,4] Discontinuation and dose reduction of study drug owing to TEAEs were more frequent in the rociletinib group than the chemotherapy group. One death in the rociletinib group was considered related to the study drug by the investigator; no drug-related deaths were reported in the chemotherapy group.

Treatment-related hyperglycemia is known to occur after the initiation of rociletinib treatment.[16] In humans, rociletinib has three major metabolites: M460, M502, and M544. M460 and M502 were found to exhibit inhibitory activity against the insulin growth factor receptor 1 and insulin receptor.[16] In the TIGER-3 study,

these metabolites also likely contributed to treatment-emergent hyperglycemia after initiation of rociletinib therapy.

Although the development of rociletinib was halted, other third-generation EGFR TKIs have been developed. In 2015, the third-generation EGFR TKI osimertinib was first approved for the treatment of patients with metastatic *EGFR* T790M-positive NSCLC who have progressed after treatment with a first-generation EGFR TKI,[17,18] based on the outcome of the phase 2 AURA study[19] and the phase 3 AURA3 study.[20] More recently, osimertinib was approved for first-line treatment of patients with *EGFR* mutation–positive NSCLC, on the basis of results from the phase 3 FLAURA study.[21-23]

Other third-generation EGFR TKIs in development include nazartinib[24] and lazertinib.[25,26] Nazartinib is being evaluated in combination with gefitinib in patients with recurrent or Stage IIIB to IV *EGFR*-mutated NSCLC. A dose-finding study of lazertinib is in progress among patients with *EGFR*-mutated advanced NSCLC.[26] Similar to rociletinib, the sponsors have halted the development of other EGFR TKIs. Although olmutinib is approved in South Korea for the treatment of patients with *EGFR* T790M mutation–positive lung cancer, it is not approved for other indications or in other territories, and its development was discontinued by Boehringer Ingelheim in 2016.[27] Other agents (including ASP8273 or PF-06747775) are no longer being developed for the treatment of patients with *EGFR*-mutated NSCLC.[28,29]

In the TIGER-3 study, although there was a trend toward improved PFS with rociletinib versus second-line chemotherapy in the T790M-positive and T790M-negative patient populations, early termination of the study precluded formal hypothesis testing of the primary end point. In patients who received rociletinib, 15 (20%) received treatment for more than 12 months. Nevertheless, rociletinib had unacceptable toxicities, including a higher incidence of hyperglycemia and QTc prolongation compared with chemotherapy. Whereas no conclusion can be drawn because of the early termination of the trial, rociletinib activity in patients with T790M-negative tumors could potentially be explained by the heterogeneity of the tumor cells or limitation in the sensitivity of the assay that detects T790M mutations. This brings into question whether these tumors were truly T790M negative. To our knowledge, TIGER-3 is the only randomized study that has compared second-line chemotherapy with an EGFR TKI after patients failed both a first- or second-generation EGFR TKI and platinum-based chemotherapy in an unselected patient population. In addition to osimertinib, we hope that novel agents will be developed to provide patients with *EGFR* mutation–positive advanced NSCLC with new treatment options that have a favorable benefit-risk profile in this setting.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2020.100114.

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