Crizotinib in ROS1-rearranged advanced non-small-cell lung cancer (NSCLC): updated results, including overall survival, from PROFILE 1001

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Background: In the ongoing phase I PROFILE 1001 study, crizotinib showed antitumor activity in patients with ROS1-rearranged advanced non-small-cell lung cancer (NSCLC). Here, we present updated antitumor activity, overall survival (OS) and safety data (additional 46.2 months follow-up) for patients with ROS1-rearranged advanced NSCLC from PROFILE 1001.

Patients and methods: ROS1 status was determined by FISH or reverse transcriptase–polymerase chain reaction. All patients received crizotinib at a starting dose of 250 mg twice daily.

Results: Fifty-three patients received crizotinib, with a median duration of treatment of 22.4 months. At data cut-off, treatment was ongoing in 12 patients (23%). The objective response rate (ORR) was 72% [95% confidence interval (CI), 58% to 83%], including six confirmed complete responses and 32 confirmed partial responses; 10 patients had stable disease. Responses were durable (median duration of response 24.7 months; 95% CI, 15.2–45.3). ORRs were consistent across different patient subgroups. Median progression-free survival was 19.3 months (95% CI, 15.2–39.1). A total of 26 deaths (49%) occurred (median follow-up period of 62.6 months), and of the remaining 27 patients (51%), 14 (26%) were in follow-up at data cut-off. Median OS was 51.4 months (95% CI, 29.3 to not reached) and survival probabilities at 12, 24, 36, and 48 months were 79%, 67%, 53%, and 51%, respectively. No correlation was observed between OS and specific ROS1 fusion partner. Treatment-related adverse events (TRAEs) were mainly grade 1 or 2, per CTCAE v3.0. There were no grade 3/4 TRAEs and no TRAEs associated with permanent discontinuation. No new safety signals were reported with long-term crizotinib treatment.

Conclusions: These findings serve as a new benchmark for OS in ROS1-rearranged advanced NSCLC, and continue to show the clinically meaningful benefit and safety of crizotinib in this molecular subgroup.

Trial Registration Number: ClinicalTrials.gov identifier NCT00585195

Key words: crizotinib, non-small-cell lung cancer, ROS1, overall survival

Introduction

ROS1 rearrangements occur in 1% to 2% of patients with non-small-cell lung cancer (NSCLC) [1, 2]. Chromosomal rearrangements activate ROS1 in NSCLC, resulting in the expression of ROS1 fusion kinases that promote cellular transformation [2, 3].

Crizotinib is an oral tyrosine kinase inhibitor (TKI) that targets the ALK, ROS1, and MET receptor tyrosine kinases [2, 4].
PROFILE 1001 (ClinicalTrials.gov identifier: NCT00585195) enrolled patients with advanced NSCLC harboring ROS1 rearrangements in a recommended phase II dose (RP2D) expansion cohort of the study between October 2010 and September 2013. Initial results from 50 patients enrolled showed an objective response rate (ORR) of 72%, with 3 complete responses (CR) and 33 partial responses (PR), median duration of response (DOR) of 17.6 months, and median progression-free survival (PFS) of 19.2 months [5]. These findings showed that targeting ROS1 was an effective treatment strategy in patients with ROS1-rearranged NSCLC. Crizotinib received approval in the United States and the European Union for the treatment of patients with ROS1-positive advanced NSCLC in March and August 2016, respectively, and is now approved for this indication in 70 countries worldwide.

Here, we report updated antitumor activity, overall survival (OS), and safety data (additional 46.2-month follow-up for a median of follow-up period of 62.6 months in total) from 53 patients with ROS1-rearranged advanced NSCLC to evaluate the long-term impact of crizotinib on this molecular subset of patients.

Study population and eligibility

Patients aged ≥18 years with locally advanced or metastatic, histologically confirmed NSCLC positive for ROS1 rearrangement were eligible for enrollment. Fifty-three patients were included in this analysis, including 50 patients in the ROS1-positive NSCLC expansion cohort [5] and 3 patients in an ALK-negative NSCLC cohort who were retrospectively determined to be positive for ROS1 rearrangement. Disease had to be measurable by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0 (or by RECIST v1.1 for the three patients in the ALK-negative NSCLC cohort). Patients were also required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1. Those with an ECOG PS of 2 could be enrolled into the study upon agreement between the investigator and sponsor.

Study design and treatment

Eligible patients were enrolled in an ongoing phase I, open-label study of crizotinib, which included an initial dose-escalation phase followed by an expansion phase in which the RP2D was evaluated in molecularly defined patient cohorts. We present updated data for this population (data cutoff: 30 June 2018).

The study design has been previously described [5]. The protocol was approved by institutional review boards or independent ethics committees at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent.

FISH or reverse transcriptase–polymerase chain reaction (RT-PCR) testing was carried out at local laboratories (all) or at a central laboratory (two patients in the ALK-negative NSCLC cohort). Patients were considered positive for ROS1 rearrangement by FISH if >15% of nuclei had evidence of gene rearrangement, as previously described [5]. Tumor tissue or nucleic acid was available in 30 patients to determine the ROS1 fusion partner (data analyzed and provided by Massachusetts General Hospital). Targeted next-generation sequencing (n = 27) and RT-PCR (n = 3) were used to detect ROS1 fusion transcripts, as described previously [5].

Crizotinib was to be administered orally at 250 mg twice daily in continuous 28-day cycles (or 21-day cycles for the three patients in the ALK-negative NSCLC cohort), until RECIST-defined disease progression or clinical deterioration, unacceptable toxicity effects, study withdrawal or death. Patients with RECIST-defined disease progression could continue crizotinib treatment at the investigator’s discretion and with approval from the sponsor.

Statistical analysis

All patients who received at least one dose of crizotinib were included in the analyses of PFS, OS, and safety. Response-evaluable patients were defined as all patients in the safety population who had an adequate baseline disease assessment and a minimum of one postbaseline disease assessment at least 6 weeks from the first dose or who withdrew from the study or had disease progression or death at any time during the study. Confidence intervals (CIs) for the ORR were estimated using the exact binomial method based on the F-distribution. Time-to-event data were analyzed using the Kaplan–Meier method to estimate median event times, with two-sided 95% CIs generated using the Brookmeyer–Crowley method. All analyses were carried out with SAS statistical software, v9.2 or later (SAS Institute, Inc., Cary, NC).

Results

Fifty-three patients with ROS1-rearranged advanced NSCLC were enrolled in a RP2D expansion phase of PROFILE 1001. Fifty-one of 53 patients (96%) were confirmed to have ROS1 rearrangements by FISH. The remaining two patients were confirmed to have ROS1 rearrangements by RT-PCR. Patient demographics and baseline disease characteristics are described in Table 1. Most patients (87%) had received at least one prior systemic treatment of advanced disease, and 23% of patients had received three or more prior treatments (Table 1).

Antitumor activity

Consistent with initial results of PROFILE 1001 [5], almost all evaluable patients had some degree of tumor shrinkage during the study (supplementary Figure S1, available at Annals of Oncology online). The ORR was 72% (95% CI, 58% to 83%),...
with 6 CR and 32 PR (Table 2). Responses were rapid with a median time to first tumor response of 7.9 weeks, corresponding to the approximate time of the first on-treatment tumor scan. Responses were also durable (median DOR 24.7 months; 95% CI, 15.2–45.3). ORRs were comparable across different subgroups defined by demographic and disease baseline characteristics (supplementary Table S1, available at Annals of Oncology online). At the time of data cutoff, 36 of 53 patients (68%) had experienced disease progression or had died. The median PFS was 19.3 months (95% CI, 15.2–39.1) (supplementary Figure S2, available at Annals of Oncology online).

A total of 26 (49%) deaths occurred (median follow-up period of 62.6 months); of the remaining 27 (51%) patients, 14 (26%) remained in follow-up at data cutoff. Median OS was 51.4 months [95% CI, 29.3 to not reached (NR)] (Figure 1 and Table 3), and the probabilities of survival at 6, 12, 24, 36, and 48 months were 91%, 79%, 67%, 53%, and 51%, respectively.

We previously identified the ROS1 fusion partner in the tumors of 30 patients enrolled in the ROS1 expansion cohort [5]. Among the 25 cases with detectable ROS1 rearrangements, we identified seven different fusion partners, including CD74 (in 11 tumors), EZR and SDC4 (each in 4 tumors), SLC34A2 (in 3 tumors), and LIMA1, MSN, and TPM3 (each in 1 tumor). We previously showed that the fusion partner does not appear to impact response rate or DOR with crizotinib [5]. To determine whether the fusion partner may impact survival, we evaluated OS according to ROS1 fusion partner. There was no apparent correlation between the specific ROS1 rearrangement and OS, with a wide range of survival durations seen within each class of ROS1 rearrangement (Figure 2). These findings suggest that crizotinib is active in ROS1-rearranged advanced NSCLC, regardless of the exact ROS1 fusion partner.

### Safety

At the time of data cutoff, 12 (23%) patients remained on treatment and 41 (77%) patients had permanently discontinued. Reasons for permanent treatment discontinuation included progressive disease (45%), withdrawal of consent (11%), clinical progression (15%), switch to commercially available crizotinib (4%), and death (2%). Median duration of treatment was 22.4 months (95% CI, 15.0–35.9) compared with 14.8 months (range, 0.5–41.9) reported previously [5]. All 53 patients experienced at least one treatment-related AE (TRAЕ). The majority of TRAEs were grade 1 or 2 in severity, and the most common
were vision disorder (87%), nausea (51%), edema (47%), diarrhea (45%), vomiting (38%), elevated transaminases (36%), and constipation (34%) (Table 4). The most common grade 3 TRAEs were hypophosphatemia (15%), neutropenia (9%), elevated transaminases (4%), and vomiting (4%). There were no grade 4 or 5 TRAEs. No TRAEs were associated with permanent discontinuation of treatment.

Discussion

The initial results of the PROFILE 1001 ROS1 expansion cohort established crizotinib as a standard therapy for ROS1-rearranged advanced NSCLC. In this updated analysis, after an additional >3-year follow-up, we have confirmed the marked efficacy of crizotinib in ROS1-rearranged advanced NSCLC and showed that crizotinib treatment is associated with prolonged survival, with a median OS of 51.4 months and an OS rate of 51% at 48 months.

In addition, our findings support the favorable safety profile of crizotinib, even with long-term treatment. No unexpected safety signals were identified in this updated analysis, and the safety profile was similar to previous reports in patients with ALK- or ROS1-rearranged NSCLC [5–7].

Overall, the efficacy of crizotinib in this updated analysis was highly consistent with our initial results on 50 patients with ROS1-rearranged advanced NSCLC [5]. In the original analysis after a median follow-up of 16.4 months, ORR was 72% (95% CI, 58% to 84%), and median PFS was 19.2 months (95% CI, 14.4 to NR), with 50% of patients still in follow-up for progression [5]. Similarly, in this updated analysis, after a median follow-up of 62.6 months, ORR and median PFS were nearly identical at 72% (95% CI, 58% to 83%) and 19.3 months (95% CI, 15.2–39.1), respectively, with 15% of patients still in follow-up for progression. Of note, DOR was longer in the updated analysis, with median DOR of 24.7 months (95% CI, 15.2–45.3), compared with 17.6 months in the initial study (95% CI, 14.5 to NR) [5].

To date, the clinical activity of crizotinib has been examined in two other prospective studies of ROS1-rearranged advanced NSCLC. In a larger phase II study of crizotinib conducted in East Asia, the ORR among 127 patients was 72% (95% CI, 63% to 79%), median PFS was 15.9 months (95% CI, 12.9–24.0), and median DOR was 19.7 months (95% CI, 14.1 to NR) [8], similar to the results of this updated analysis of PROFILE 1001. In a smaller phase II study conducted in France (AcSé), the ORR among 37 patients with ROS1-rearranged advanced NSCLC was also high at 68% (95% CI, 50% to 82%). While median PFS in this study was relatively short [5.5 months (95% CI, 4.6–9.1)], the follow-up period for PFS was not reported and the maturity of these data were not confirmed [9]. The variations in PFS among these three trials may be influenced by the relatively small trial populations. Baseline differences in the study populations may have also contributed to these variations; notably, 25% of patients in the AcSé trial had an ECOG PS of 2 [9].

This update to PROFILE 1001 reports for the first time mature survival data in ROS1-rearranged advanced NSCLC. In a larger phase II study of crizotinib conducted in East Asia, the ORR among 127 patients was 72% (95% CI, 63% to 79%), median PFS was 15.9 months (95% CI, 12.9–24.0), and median DOR was 19.7 months (95% CI, 14.1 to NR) [8], similar to the results of this updated analysis of PROFILE 1001. In a smaller phase II study conducted in France (AcSé), the ORR among 37 patients with ROS1-rearranged advanced NSCLC was also high at 68% (95% CI, 50% to 82%). While median PFS in this study was relatively short [5.5 months (95% CI, 4.6–9.1)], the follow-up period for PFS was not reported and the maturity of these data were not confirmed [9]. The variations in PFS among these three trials may be influenced by the relatively small trial populations. Baseline differences in the study populations may have also contributed to these variations; notably, 25% of patients in the AcSé trial had an ECOG PS of 2 [9].

This update to PROFILE 1001 reports for the first time mature survival data in ROS1-rearranged advanced NSCLC. In this mostly pretreated population of ROS1-positive patients, OS from the time of crizotinib initiation was remarkably prolonged with a median OS of 51.4 months; this was independent of the exact ROS1 rearrangement. The prolonged survival observed in this updated
analysis is reminiscent of that reported in the first-line study of crizotinib versus standard chemotherapy in ALK-rearranged advanced NSCLC (PROFILE 1014). Here, median OS was not reached in the crizotinib group (95% CI, 45.8 months to NR), but the probability of survival at 4 years was 56.6% [10], similar to the 51% rate seen in this updated analysis. Thus, in two distinct subtypes of advanced NSCLC—ALK-rearranged and ROS1-rearranged—crizotinib is associated with prolonged survival and median survival times exceed four years.

In addition to crizotinib, numerous other TKIs with ROS1 activity have been investigated in ROS1-rearranged advanced NSCLC. For example, the second-generation ALK inhibitor ceritinib was tested in 32 Korean patients with ROS1-rearranged NSCLC, of whom, 30 were crizotinib-naive. Similar to PROFILE 1001, ORR was 67% (95% CI, 48% to 81%) and median PFS was 19.3 months (95% CI, 1–37) in crizotinib-naive patients [11]. Of note, after a median follow-up of 14 months, median OS was only 24 months (95% CI, 5–43) in all patients, with a 12-month survival probability of 56%. The ROS1/NTRK/ALK inhibitor entrectinib has also demonstrated potent clinical activity in crizotinib-naive ROS1-rearranged NSCLC [12]. Among 53 ROS1-positive patients pooled from 3 separate trials of entrectinib, ORR was 77% (95% CI, 64% to 88%) and median PFS was 19.0 months (95% CI, 12.2–36.6). However, OS data from this pooled analysis are not yet mature. Other TKIs with promising clinical activity in ROS1-rearranged NSCLC include lorlatinib, repotrectinib, and DS-6051b [13–15]. While efficacy data with other ROS1 TKIs are still emerging, our findings show that treatment with crizotinib is associated with impressive OS in ROS1-rearranged advanced NSCLC.

In conclusion, this study provides a new benchmark for OS in patients with ROS1-rearranged advanced NSCLC and supports the continued use of crizotinib in the treatment of these patients.

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The studies were designed by the sponsor together with the members of the PROFILE 1001 steering committee. The sponsor collected the data for this analysis and analyzed them in conjunction with the authors, all of whom had full access to the data.

Disclosure

ATS has received fees for consulting/advisory board roles from Ariad/Takeda, Bayer, Blueprint Medicines, Chugai, Daiichi Sankyo, EMD Serono, Genentech, Ignyta, KSQ Therapeutics, Loxo, Natera, Novartis, Pfizer, Roche, Taiho, and TP Therapeutics, and honoraria from Foundation Medicine, Guardant, Novartis, Pfizer, and Roche, and ATS’s institution has received research funding from Ariad, Genentech/Roche, Ignyta, Novartis, Pfizer, and TP Therapeutics. GJR’s institution received funding from Pfizer for conduct of this research and his institution also receives research support from Novartis, Roche, and Takeda. GJR has been a compensated consultant for Genentech/Roche. Y-JB and JWC have received research funding from Pfizer to their institution. D-WK declares no conflict of interest. DRC has served on advisory boards for AbbVie, Ariad, Array, Celgene, Clovis, Eli Lilly, G1 Therapeutics (DSMB), Genoptix, Ignyta, Mersana Therapeutics, Novartis, Orion, Roche/Genentech, and Takeda, and has received research funding for investigator-initiated trials from Ariad and Takeda. BJS has received personal fees from AstraZeneca, BeiGene, Bristol-Myers Squibb, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Roche, Roche/Genentech, and Veristat (Biodiesix); grants from Pfizer; and non-financial support from Novartis, Pfizer, and Roche. MV-G has received fees for consulting and educational activities from Abbott Molecular. AJI has equity in ArcherDx and has been a compensated consultant for Pfizer. GIS has received research funding from Pfizer to the Dana-Farber Cancer Institute for the conduct of the study and has served on advisory boards for Eli Lilly, G1 Therapeutics, Merck/E MDR, Pfizer, Roche, and Vertex Pharmaceuticals. TU, SCW, and KDW are employees of and hold stock in Pfizer. SHIO has received fees for consulting/advisory boards from Pfizer and his institution has received research funding from Eli Lilly, Merck/EMD Serono, and Pfizer.

Data sharing: Upon request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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