Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer


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Background: Anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) is highly responsive to crizotinib. To determine whether ALK-positive NSCLC is also sensitive to pemetrexed, we retrospectively evaluated progression-free survival (PFS) of ALK-positive versus ALK-negative patients who had been treated with pemetrexed-based chemotherapy for advanced NSCLC.

Patients and methods: We identified 121 patients with advanced, ALK-positive NSCLC in the USA, Australia, and Italy. For comparison, we evaluated 266 patients with advanced, ALK-negative, epidermal growth factor receptor (EGFR)-wild-type NSCLC, including 79 with KRAS mutations and 187 with wild-type KRAS (WT/WT/WT). We determined PFS on different pemetrexed regimens.

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Results: Among 70 ALK-positive patients treated with a platinum/pemetrexed regimen, the median PFS (mPFS) was 7.3 months (95% confidence interval (CI) 5.5–9.5). The mPFS of 51 ALK-positive patients treated with single-agent pemetrexed or nonplatinum/pemetrexed combinations was 5.5 months (2.8–9.0). For ALK-negative patients, PFS on all pemetrexed-based regimens was similar to that of ALK-positive patients, except in the specific setting of first-line platinum/pemetrexed where the mPFS was only 4.2 and 5.4 months in KRAS and WT/WT/WT patients, respectively. However, among patients with a never/light-smoking history (0–10 pack-year smoking history) treated with first-line platinum/pemetrexed, there was no difference in PFS between ALK-positive and ALK-negative patients.

Conclusions: PFS on pemetrexed or nonplatinum/pemetrexed combinations was similar in ALK-positive and ALK-negative patients. PFS on first-line platinum/pemetrexed may be prolonged in never/light-smoking patients regardless of ALK status.

Key words: ALK, lung cancer, pemetrexed

introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements define one of the newest molecular subsets of non-small-cell lung cancer (NSCLC) [1]. Detected in 3%–5% of NSCLC patients, ALK rearrangements are associated with distinct clinicopathologic features, including younger age at diagnosis, never-smoking history, and adenocarcinoma histology [2, 3]. ALK rearrangements are also associated with marked sensitivity to ALK tyrosine kinase (TK) inhibition. In an early phase study of crizotinib, a dual ALK/MET tyrosine kinase inhibitor (TKI), the objective response rate (ORR) was 56% and the median progression-free survival (mPFS) was 10 months in advanced, ALK-positive NSCLC [4, 5]. Based on its demonstrated efficacy and safety, crizotinib has recently become a standard therapy in several countries for patients with advanced, ALK-positive NSCLC.

However, at some point in the course of their disease, most patients with ALK-positive NSCLC will be treated with standard chemotherapeutic agents. Thus, establishing the efficacy of chemotherapeutic agents in this genetically defined subset of patients is clinically relevant. It has been previously shown that ALK-positive patients are as responsive to platinum combination chemotherapy as ALK-negative, epidermal growth factor receptor (EGFR)-wild-type patients, with ORRs ranging from 25% to 35% [2, 6], consistent with studies in unselected NSCLC populations. ALK-positive patients also respond poorly to EGFR TKI therapy, with a reported ORR of 0% and a shorter than expected median PFS (mPFS) of 1.4–1.6 months in several independent series [2, 6, 7].

Recently, two small retrospective studies have suggested that patients with ALK-positive NSCLC may be particularly responsive to pemetrexed chemotherapy [8, 9]. In one study, among 19 ALK-positive patients, who had received a variety of different pemetrexed-containing regimens as first-, second-, or fourth-line therapy, the mPFS was 9 months, exceeding that of 37 ALK/EGFR/KRAS-negative patients by 5 months [8]. Similarly, the second study reported that among 15 ALK-positive patients who had received single-agent pemetrexed in the second-line setting and beyond, the median time to progression (TTP) was 9.2 months; in contrast, the median TTP of 37 ALK-negative, EGFR-wild-type controls was only 2.9 months [9]. These findings have led to the notion that ALK rearrangement may serve as a predictive biomarker of enhanced pemetrexed sensitivity, and have raised the possibility that the efficacy of pemetrexed-based chemotherapy may be similar to that observed with crizotinib in clinical trials.

In the absence of randomized data, we have carried out a multicenter retrospective analysis of PFS in 121 ALK-positive patients treated with pemetrexed-based chemotherapy. To determine whether ALK rearrangement is associated with enhanced sensitivity to pemetrexed, we have also examined the PFS of 266 ALK-negative, EGFR-wild-type patients treated with similar pemetrexed-based regimens.

patients and methods

study populations

ALK-positive patients (N = 121) were seen at Massachusetts General Hospital (MGH) (n = 62), Memorial Sloan-Kettering Cancer Center (n = 30), Peter MacCallum Cancer Center (n = 14), Beth Israel Deaconess Medical Center (n = 9), and S. Luigi Gonzaga Hospital (n = 6). ALK-negative patients (N = 266) were seen at MGH and underwent genetic testing over the same time period (between December 2007 and August 2011). All patients had biopsy-proven advanced NSCLC, were negative for EGFR mutations, and had received a pemetrexed-containing regimen. This study was approved by the Institutional Review Board at each of the participating institutions.

data collection

Medical records were reviewed to extract data on clinicopathologic features and treatments. PFS was measured from the first day of pemetrexed until either radiologic/clinical disease progression or death. Patients without evidence of disease progression were censored at the date of last follow-up. Patients who started a different treatment in the absence of disease progression were censored at the date of last follow-up. The percentage of patients censored was 14%, 16%, and 11% for ALK, WT/WT, and KRAS, respectively. Data were updated as of November 2011.

tumor pathology and genetic analysis

Tumor histology was classified by pathologists at each institution using the standard World Health Organization criteria. ALK status was determined using the standard break-apart ALK FISH assay [2]. ALK-negative cases were tested for mutations in EGFR, KRAS, and other cancer-related genes using SNaPshot [10].

measurement of TS RNA levels in tumors

RNA was extracted from unstained sections and complementary DNA prepared according to standard protocols. Quantitative RT-PCR for
thymidylate synthase (TS) and β-actin were carried out as previously described [11, 12]. Control cases of resected ALK-negative, EGFR-wild-type NSCLC from an ongoing adjuvant study in Europe were also assessed to establish a median TS mRNA level.

**statistical analysis**

Fisher’s exact test and Wilcoxon rank-sum test were used to assess the association of genotype status with baseline characteristics. PFS was estimated by the Kaplan–Meier method, and the log-rank test was used to compare the difference between the groups. The data analysis was computed by StatXact 6.0 (Cytel Software, Cambridge, MA). All P values were based on a two-sided hypothesis.

**results**

**PFS outcomes in ALK-positive patients treated with pemetrexed-based chemotherapy**

We identified 121 ALK-positive patients who had received pemetrexed-based chemotherapy for advanced NSCLC. The clinicopathologic features of these ALK-positive patients are summarized in Table 1. Among the 121 ALK-positive patients, 70 had received pemetrexed in combination with a platinum agent, typically as first-line treatment. Supplementary Table S1, available at *Annals of Oncology* online, summarizes the platinum/pemetrexed regimens that were used. Of note, the majority of patients (81%) received four or more cycles of combination chemotherapy, and just over one-half of patients (53%) were continued on a maintenance regimen that included pemetrexed.

We first evaluated the PFS of the 70 ALK-positive patients treated with any platinum/pemetrexed combination regimen. The mPFS in this group was 7.3 months [95% confidence interval (CI) 5.5–9.5; Figure 1A]. There was no statistically significant difference in PFS between those patients who received at least two cycles of cisplatin and those who received carboplatin in combination with pemetrexed (median 5.9 versus 8.6 months, \(P = 0.361\); Supplementary Figure S1A, available at *Annals of Oncology* online). There was a trend toward improved PFS in patients who received bevacizumab, either as part of the platinum/pemetrexed combination or as part of a maintenance regimen; the mPFS was 9.5 months in patients who had received bevacizumab, compared with 5.5 months in patients who did not receive any bevacizumab; however, this difference was not statistically significant \(P = 0.087\); Supplementary Figure S1B, available at *Annals of Oncology* online).

We next examined PFS of the 51 ALK-positive patients treated with either single-agent pemetrexed or a variety of nonplatinum/pemetrexed combinations (Supplementary Table S2, available at *Annals of Oncology* online). The mPFS in this group was 5.5 months (95% CI 2.8–9.0; Figure 1C). In the subgroup of patients who received only single-agent pemetrexed in the second- or third-line setting \((n = 56)\), the mPFS was 8.5 months (95% CI 5.9–10.9; Figure 1B).

In contrast to previously published studies [8, 9], PFS with single-agent pemetrexed or nonplatinum/pemetrexed combinations

### Table 1

Clinicopathologic features of ALK-positive and ALK-negative patients treated with pemetrexed-based chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>ALK (N = 121)</th>
<th>Wild-type KRAS (WT/WT/WT) (N = 187)</th>
<th>KRAS (N = 79)</th>
<th>(P) value (ALK versus WT)</th>
<th>(P) value (ALK versus KRAS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>Median</td>
<td>52</td>
<td>62</td>
<td>64</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>Range</td>
<td>21–79</td>
<td>29–84</td>
<td>38–84</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>59 (49)</td>
<td>102 (55)</td>
<td>26 (33)</td>
<td>(P = 0.351)</td>
<td>(P = 0.029)</td>
</tr>
<tr>
<td>Female</td>
<td>62 (51)</td>
<td>85 (45)</td>
<td>53 (67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>100 (83)</td>
<td>163 (87)</td>
<td>74 (94)</td>
<td>(P = 0.166)</td>
<td>(P = 0.005)</td>
</tr>
<tr>
<td>Asian</td>
<td>10 (8)</td>
<td>7 (4)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (9)</td>
<td>12 (6)</td>
<td>3 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>88 (73)</td>
<td>47 (25)</td>
<td>0 (0)</td>
<td>(P &lt; 0.001)</td>
<td>(P &lt; 0.001)</td>
</tr>
<tr>
<td>(\leq 10) pack-years</td>
<td>20 (17)</td>
<td>24 (13)</td>
<td>8 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 pack-years</td>
<td>13 (11)</td>
<td>116 (62)</td>
<td>70 (89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>119 (98)</td>
<td>179 (96)</td>
<td>78 (99)</td>
<td>(P = 0.462)</td>
<td>(P = 1.000)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td></td>
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</tr>
<tr>
<td>Large cell</td>
<td>2 (2)</td>
<td>6 (3)</td>
<td>1 (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase. All ALK-negative patients are epidermal growth factor receptor (EGFR)-wild-type. WT/WT/WT denotes ALK-negative, EGFR-wild-type, KRAS-wild-type.

*a*Refers to the age at diagnosis of metastatic non-small-cell lung cancer. Age at diagnosis was not known for one ALK-positive patient.

*b*Ethnicity was not known for seven ALK-negative patients.

*c*Smoking history was not known for one ALK-negative patient.
does not appear to be markedly prolonged in ALK-positive NSCLC.

comparison of PFS in ALK-positive and ALK-negative patients treated with pemetrexed-based chemotherapy

Prospective studies have tested the efficacy of platinum/pemetrexed and single-agent pemetrexed in unselected NSCLC patients [13, 14]. Among patients with adenocarcinoma histology, the mPFS with first-line cisplatin/pemetrexed is 5.5 months, while the mPFS with second-line pemetrexed is 3.5 months [15]. As these patients were clinical trial participants treated prospectively with a defined pemetrexed regimen, they may not be directly comparable with the ALK-positive patients in this retrospective analysis. We therefore studied a control group of ALK-negative patients who had undergone genetic testing at the same time as the ALK-positive patients and had also received pemetrexed-based chemotherapy.

We identified 266 ALK-negative, EGFR-wild-type patients (referred to as WT/WT) as controls for the 121 ALK-positive patients. We further divided control WT/WT patients into two groups based on the KRAS mutation status: ALK-negative, KRAS-wild-type, EGFR-wild-type (designated WT/WT/WT) and ALK-negative, KRAS-mutant, EGFR-wild-type (designated KRAS). The clinicopathologic features of these patients are shown in Table 1, and treatment regimens are summarized in Supplementary Tables S1 and S2, available at Annals of Oncology online. As shown in Figure 2A, among patients receiving any platinum/pemetrexed combination in any setting, both ALK-negative groups showed a trend toward shorter PFS compared with the ALK-positive group, with a mPFS of 4.5 and 5.9 months in KRAS and WT/WT/WT patients, respectively. The differences in PFS between ALK-positive and ALK-negative patients were significant in the KRAS group (P = 0.042) but not in the WT/WT/WT group (P = 0.182). In the subset of patients who received the platinum/pemetrexed combination as front-line treatment, there was a statistically significant difference in PFS among the ALK-positive group (median 8.5 months), KRAS patients (median 4.1 months, P = 0.004) and WT/WT/WT patients (median 5.4 months, P = 0.018) (Figure 2B).

In contrast, in patients treated with pemetrexed either as a single agent or combined with a nonplatinum agent, PFS was similar across the three groups, with a mPFS of 5.5, 7.8, and 3.9 months in ALK-positive, KRAS, and WT/WT/WT patients, respectively (Figure 2C; P = 0.860 and P = 0.409, respectively). Furthermore, no statistically significant differences in PFS were observed in patients treated with single-agent pemetrexed in the second/third-line setting (Figure 2D; P = 0.606 and P = 0.787, respectively). Taken together, these results suggest that when compared with a large, ALK-negative comparator population, ALK-positive patients may have improved PFS with first-line platinum/pemetrexed-based chemotherapy, but have a similar PFS when treated with single-agent pemetrexed or nonplatinum/pemetrexed combinations.

Figure 1. Progression-free survival (PFS) of anaplastic lymphoma kinase (ALK)-positive patients treated with pemetrexed-based chemotherapy. (A) PFS on platinum/pemetrexed combinations. Patients received chemotherapy in the first- through fourth-line setting. (B) PFS on first-line platinum/pemetrexed combinations. (C) PFS on any nonplatinum/pemetrexed combinations or single-agent pemetrexed. Patients received chemotherapy in the first- through fifth-line setting. (D) PFS on single-agent pemetrexed. All patients received pemetrexed as their second- or third-line therapy.
PFS with pemetrexed chemotherapy in patients with similar demographics

In NSCLC, ALK rearrangement is associated with distinct clinicopathologic features that may influence response and survival outcomes with chemotherapy, including younger age and never/light-smoking status [2, 3]. To address whether the observed differences in PFS between ALK-positive and ALK-negative patients treated with pemetrexed chemotherapy could be confounded by differences in demographic features (Table 1), we examined the PFS of various subsets of patients. Among patients ≤65 years old treated with platinum/pemetrexed combinations, we observed a similar though nonsignificant trend toward longer PFS in ALK-positive patients compared with any group of ALK-negative patients; the mPFS was 8.1, 6.0, and 4.7 months in ALK, WT/WT/WT, and KRAS patients, respectively (Supplementary Figure S2A, available at Annals of Oncology online and data not shown). Similarly, there were no significant differences in PFS between ALK-positive and ALK-negative patients ≤65 years old treated with single-agent pemetrexed or nonplatinum/pemetrexed combinations (median 5.1 versus 4.4 months, respectively, \( P = 0.885 \); Supplementary Figure S2B, available at Annals of Oncology online).

We next examined the subset of patients with a never/light-smoking history (Table 1). As shown in Figure 3A, the PFS of never/light-smoking patients treated with any platinum/pemetrexed-based chemotherapy was remarkably similar in ALK-positive versus WT/WT patients (median 7.3 versus 7.5 months, \( P = 0.671 \)). Among those patients who received first-line platinum/pemetrexed chemotherapy, the mPFS was also similar (8.5 versus 7.4 months, \( P = 0.254 \); Figure 3B). Similarly, the PFS of never/light-smoking patients treated with single-agent pemetrexed or a nonplatinum/pemetrexed combination was nearly identical in ALK-positive versus WT/WT patients (median 5.5 versus 5.3 months, \( P = 0.941 \); Figure 3C). The mPFS in never/light smokers treated with only single-agent pemetrexed was 4.8 and 4.6 months in ALK-positive and WT/WT patients, respectively (\( P = 0.450 \); Figure 3D). Thus, relative to other never/light smokers, ALK-positive patients do not have a prolonged PFS on pemetrexed-based chemotherapy.

correlation of thymidylate synthase (TS) level with PFS on pemetrexed-based chemotherapy in ALK-positive NSCLC

TS is one of several key folate enzymes targeted by pemetrexed. Preclinical and clinical studies suggest that TS levels may be inversely correlated with pemetrexed sensitivity, with high levels of TS expression conferring decreased sensitivity to pemetrexed-based chemotherapy [12, 15, 16]. To begin to
address whether TS levels might be predictive of pemetrexed response in ALK-positive NSCLC, we determined TS transcript levels in a subset of ALK-positive cases. Ten of 12 assessable ALK-positive cases (83%) had lower TS levels \( (P = 0.039) \) than the median TS value established in unselected, resected lung adenocarcinomas. While ALK-positive patients with ‘low’ TS levels had variable survival on pemetrexed-based chemotherapy, the two ALK-positive patients with ‘high’ TS levels had the shortest PFS in the group (21 and 54 days, \( P = 0.091; \) Figure 4). Based on these results, we speculate that on average, TS levels may be lower in ALK-positive compared with ALK-negative NSCLC, and that differences in TS expression within the ALK-positive cohort may underlie differential responses to pemetrexed.

**Discussion**

We have carried out the largest retrospective analysis to date of ALK-positive and ALK-negative patients treated with pemetrexed-based chemotherapy. Our analysis demonstrates that compared with ALK-negative controls, ALK-positive patients do not have a longer PFS on pemetrexed-based chemotherapy, except in the setting of first-line platinum/pemetrexed combinations. Furthermore, within the subset of never/light-smoking patients, PFS on all pemetrexed regimens including first-line platinum/pemetrexed is remarkably similar between ALK-positive and ALK-negative patients. This finding suggests that smoking status, rather than ALK rearrangement *per se*, may be predictive of pemetrexed response.

These results differ significantly from those of two previously published retrospective studies [8, 9]. There are several potential reasons for the discordant findings. First, whereas our

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Progression-free survival (PFS) of never/light-smoking patients treated with pemetrexed-based chemotherapy. (A) PFS on platinum/pemetrexed combinations given as first-line therapy or beyond. (B) PFS on first-line platinum/pemetrexed combinations. (C) PFS on any nonplatinum/pemetrexed combinations or single-agent pemetrexed. (D) PFS on single-agent pemetrexed.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Correlation of tumor thymidylate synthase (TS) RNA levels with PFS of anaplastic lymphoma kinase (ALK)-positive patients treated with pemetrexed-based chemotherapy. TS RNA levels were compared with the median TS value of control cases of resected non-small-cell lung cancer (NSCLC).
study included 121 ALK-positive patients drawn from five different centers, both of the prior studies were small \((n < 20)\), single-institution series \([8, 9]\). These small cohorts may not be representative of the ALK-positive population at large, and with such small numbers, the survival outcomes can be significantly influenced by outliers with prolonged responses to chemotherapy and/or more indolent natural histories. Second, in both prior studies, PFS was determined in ALK-positive patients receiving pemetrexed after a variable number of prior treatments \((0–3 \text{ in one study, } 1–5 \text{ in the other study})\). In the former study, patients also received a variety of different pemetrexed-containing regimens \([8]\). Combined with a small sample size, this heterogeneity in patients and treatment regimens could complicate the interpretation of PFS. By analyzing a larger group of ALK-positive patients, subdivided based on the type of pemetrexed regimen and the line of treatment, we have shown that PFS differs depending on the pemetrexed regimen, with longer PFS evident only in the setting of first-line platinum/pemetrexed combinations. Of note, there was no difference in PFS between ALK-positive and ALK-negative patients treated with nonplatinum/pemetrexed combinations or with single-agent pemetrexed.

As with any retrospective analysis, our study has inherent limitations. One of the major limitations is that the study populations, particularly the ALK-positive cohort, may have been subject to sampling bias. Many ALK-positive patients were referred to our centers for genetic testing and/or enrollment in clinical trials of crizotinib. As clinical trial participants, these patients may not represent the average ALK-positive patient. A second major limitation with our study is that treatment regimens varied widely across both the ALK-positive and ALK-negative patients. Patients received different pemetrexed-containing regimens for variable numbers of cycles, and there was more use of cisplatin among ALK-positive compared with ALK-negative patients (Supplementary Table S1, available at Annals of Oncology online). Finally, as the vast majority of patients received pemetrexed-based chemotherapy off protocol, there was no central review of radiographs, no standardized schedule of tumor assessments, and minimal reporting of performance status. To try to minimize these limitations, we examined a control population of ALK-negative patients who had been screened over the same time frame and treated at the same institution as the majority of ALK-positive patients. These ALK-negative patients were treated with similar pemetrexed-containing regimens and were assessed in a similar manner as ALK-positive patients. Thus, the ALK-negative patients in our retrospective study represent a more valid comparator than unselected patients treated in prospective studies of pemetrexed-based chemotherapy.

Compared with ALK-negative patients, ALK-positive patients showed improved PFS with first-line platinum/pemetrexed combinations. However, among never/light smokers, PFS on first-line platinum/pemetrexed was similarly prolonged in ALK-positive and ALK-negative patients. This finding suggests that never/light-smoking status may be an important predictor of pemetrexed sensitivity. In support of this notion, in the phase III trial comparing front-line cisplatin/pemetrexed with cisplatin/gemcitabine, the median survival time was 15.9 months for never smokers and 10.0 months for former/current smokers treated with cisplatin/pemetrexed \([13]\). Interestingly, the median survival time was also 5 months longer in the never smokers compared with the former/current smokers on the cisplatin/gemcitabine arm \([13]\).

This observation raises the possibility that never-smoking status may be in general predictive of chemosensitivity. To date, the literature has been unclear on this question \([17, 18]\), but we speculate that smoking status may be predictive of chemotherapy response when the regimen consists of pemetrexed combined with platinum.

In this study, the mPFS of ALK-positive patients treated with any first-line platinum/pemetrexed combination was 8.5 months, approaching the 10-month mPFS of ALK-positive patients treated with crizotinib \([4, 5]\). While the similarity in mPFS could suggest that the efficacy is similar between platinum/pemetrexed chemotherapy and crizotinib, we believe that this inference is not valid. First, to date, all of the studies of pemetrexed-based chemotherapy in ALK-positive patients, including this one, are limited due to the retrospective nature of the analyses as well as the heterogeneity in patients and treatments. By contrast, PFS on crizotinib has been evaluated in a multicenter, prospective single-arm trial in which patients had to meet specific eligibility criteria for enrollment \([4]\). Second, 103 of 119 crizotinib-treated patients (86%) had received at least one prior line of chemotherapy \([5]\). The mPFS of ALK-positive patients treated with first-line crizotinib has not yet been reported. While the efficacy of EGFR TKIs does not seem to depend on the line of treatment \([19]\), it is possible that PFS on crizotinib could be significantly longer in the front-line setting. Finally, since the patients in this retrospective analysis were treated outside of clinical trials, the schedule of tumor assessments was nonstandard and likely less frequent than the assessments mandated in the trials of crizotinib. This difference in imaging frequency alone could lead to prolongation of the observed PFS \([20]\).

In summary, in this large multicenter retrospective study of ALK-positive NSCLC, we have shown that PFS with pemetrexed-based chemotherapy is shorter than that reported previously \([8, 9]\). While there may be improved efficacy with front-line platinum/pemetrexed in ALK-positive and other never/light-smoking patients, we believe that pemetrexed-based chemotherapy is unlikely to be equivalent to crizotinib therapy in terms of efficacy. This question will be directly addressed in two ongoing randomized phase III trials. In the first-line trial, the comparator is platinum/pemetrexed, while in the second-line trial, the comparator is either pemetrexed or docetaxel. The primary end-point in both the studies is PFS. In advanced, EGFR-mutant NSCLC, which has served as the paradigm of oncogene addiction in lung cancer, five randomized trials of first-line chemotherapy versus EGFR TKI have demonstrated the superiority of targeted therapy over standard chemotherapy, with significant differences in both the ORR and PFS \([21–25]\). Of note, none of the standard chemotherapy arms in these trials included pemetrexed. For ALK-positive patients, the results of randomized studies will be critical in establishing the role and timing of targeted therapy versus conventional chemotherapy in the management of advanced, ALK-positive NSCLC.
funding

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disclosure

ATS received consulting fees from Pfizer, Novartis, Chugai, Ariad, and Daiichi-Sankyo, and received research funding from Novartis and AstraZeneca. BJS received consulting fees from Pfizer and Lilly Oncology. DBC received consulting fees from Pfizer, Roche, and AstraZeneca. JAE received consulting fees from Novartis, Ariad, Chugai, and Sano福田-Aventis, and received research funding from Novartis and AstraZeneca. GJR received consulting fees from Abbott Molecular, Ariad, Chugai, and Foundation Medicine. GVS received consulting fees from Abbott Molecular, Ariad, Chugai, and Sano福田-Aventis and received research funding from Novartis and AstraZeneca. The remaining authors (AV, SN, MMK, MA, VM, and BY) have declared no conflicts of interest.

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