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Clinical Benefit From Pemetrexed Before and After Crizotinib Exposure and From Crizotinib Before and After Pemetrexed Exposure in Patients With Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer

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Abstract

Retrospective analyses suggest enhanced sensitivity to pemetrexed in crizotinib-naïve anaplastic lymphoma kinase-positive (ALK+) non–small-cell lung cancer (NSCLC). We report the results of a retrospective analysis of ALK+ patients exposed to crizotinib and pemetrexed to determine if any clinical cross-resistance exists. Progression-free survival (PFS) results for ALK+ patients administered pemetrexed followed by crizotinib (PEM-CRIZ) and ALK+ patients first treated with crizotinib and then pemetrexed (CRIZ-PEM) are reported.

Background—Crizotinib produces high response rates and prolonged PFS in ALK+ NSCLC. Retrospective analyses suggest enhanced sensitivity to pemetrexed in crizotinib naïve ALK+ NSCLC. Cross-resistance between crizotinib and pemetrexed has not been previously investigated.

Patients and Methods—Patients with stage IV ALK+ NSCLC treated with PEM-CRIZ, or CRIZ-PEM were identified. Overall PFS and PFS excluding central nervous system events (eCNS) were compared.

Results—Objective response rates in evaluable patients were 66% (PEM-CRIZ) and 75% (CRIZ-PEM) for pemetrexed and 84% (CRIZ-PEM) and 66% (PEM-CRIZ) for crizotinib. For PEM-CRIZ (n = 29), median PFS and eCNS PFS were both 6 months with pemetrexed, and 10 and 14.5 months, respectively, with crizotinib. For CRIZ-PEM (n = 9), median PFS and eCNS PFS were 4.5 and 3 months, respectively, with pemetrexed, and 8.5 and 7.5 months, respectively,

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with crizotinib. There was a statistically significant increase in the risk of an overall PFS event with pemetrexed when administered after crizotinib ($P = .0277$; hazard ratio [HR], 2.5898; 95% confidence interval [CI], 1.1100–6.0424), but differences in the risk of an eCNS PFS event were not significant ($P = 0.4913$; HR, 1.3521; 95% CI, 0.5727–3.1920). Neither overall nor eCNS PFS for patients while taking crizotinib was associated with a sequence effect relative to pemetrexed.

Conclusion—Crizotinib and pemetrexed are active drugs in ALK+ NSCLC. PFS benefit appeared higher with crizotinib than with pemetrexed. PFS benefit from pemetrexed was less after crizotinib compared with before crizotinib, however, this difference was only statistically significant for overall and not eCNS PFS. Pemetrexed exposure did not seem to affect crizotinib outcomes.

Keywords

ALK; Crizotinib; Lung cancer; NSCLC; Pemetrexed

Introduction

The discovery of anaplastic lymphoma kinase (*ALK*) gene fusions as oncogenic drivers in non–small-cell lung cancer (NSCLC)¹ and the early promise of crizotinib in this population led to the accelerated FDA approval of this agent in *ALK*-positive (ALK+) NSCLC.^{2,3} The PROFILE 1007 randomized phase III study demonstrated that progression-free survival (PFS) with crizotinib is superior to a composite control arm of 2 standard second-line chemotherapies (docetaxel or pemetrexed) in ALK+ NSCLC.⁴ Yet many questions remain regarding the natural history of ALK+ NSCLC beyond its sensitivity to crizotinib, in particular with regard to its sensitivity to different standard cytotoxic chemotherapies.

Pemetrexed is a multitarget antifolate with activity against several key enzymes involved in nucleotide synthesis including thymidylate synthase (TS), dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/inosine mono-phosphate cyclohydrolase (ATIC).^{5,6} *ALK* rearrangements have largely been reported among lung cancers with adenocarcinoma histology and, when only considering lung adenocarcinomas, pemetrexed monotherapy has been associated with a median PFS of 3.5 months and an objective response rate (ORR) of 12.5%.^{7–9} However, in a small retrospective series we previously demonstrated significantly longer PFS values from pemetrexed-based treatment regimens (monotherapy or combination therapy) in ALK+ crizotinib-naïve tumors compared with an *ALK*-negative, epidermal growth factor receptor (*EGFR*) Kirsten rat sarcoma viral oncogene homolog (*KRAS*) wild type group.¹⁰ These observations were later replicated by others, who also showed a significant increase in the ORR to pemetrexed in ALK+ NSCLC compared with *EGFR* mutant and *ALK*-negative/*EGFR* wild type control groups.¹¹

In contrast, ALK+ patients appear to show no such differential sensitivity to platinum-based regimens that do not contain pemetrexed.¹² Consistent with what might be a specific pemetrexed effect with regard to cytotoxic sensitivity, in PROFILE 1007 the response rate to pemetrexed was 29% compared with 7% with docetaxel, and the PFS with pemetrexed was 4.2 months compared with 2.6 months with docetaxel.⁴ Although the underlying

biology behind the differential response to pemetrexed in ALK+ NSCLC remains under investigation, evidence from other ALK+ diseases suggests that aspects of ALK biology and pemetrexed's mechanism of action might converge at key points in nucleotide biosynthesis.^{13–16}

What is currently not clear is whether these data offer any insights into optimal treatment paradigms for ALK+ NSCLC when pemetrexed and crizotinib are used sequentially as different lines of therapy. Because ALK inhibition and antifolate agents might affect a common intracellular pathway, a potential concern arises—that clinical resistance to pemetrexed therapy might confer resistance to crizotinib and vice versa.^{14,16} Within PROFILE 1007, and all of the published retrospective studies, all of the ALK+ pemetrexed-treated patients were crizotinib-naïve and their outcomes from subsequent crizotinib use were not reported.^{4,10,11} Similarly, considering that acquired resistance to crizotinib has been noted to develop after 7 to 10 months of therapy, and multiple different mechanisms of acquired resistance have now been described, it is unknown whether pemetrexed-based regimens will show equally high activity in ALK+ NSCLC when treatment with crizotinib fails.^{3,4,7,17} Here we explore the potential for cross-resistance between these 2 drugs by investigating correlations between the clinical benefit (PFS and ORR) of sequential pemetrexed and crizotinib using 2 separate patient cohorts: a stage IV ALK+ NSCLC cohort given crizotinib after progression while taking pemetrexed (PEM-CRIZ), and another stage IV ALK+ NSCLC cohort given pemetrexed after progression while taking crizotinib (CRIZ-PEM).

Patients and Methods

Patients

Patient data were obtained from our updated Colorado Molecular Correlates (CMOCO) database, from the Karmanos Cancer Institute (Detroit, MI), and the Peter MacCallum Cancer Center (Melbourne, Australia). Tumor biopsies from NSCLC patients were tested for *ALK* gene rearrangements using fluorescence in situ hybridization (FISH) using the Vysis *ALK* break-apart probe set (Abbott Laboratories, Abbott Park, IL) as described previously.^{18,19} Briefly, a tumor sample was considered ALK+ if more than 15% of tumor cells displayed split red and green *ALK probe* signals or single red (residual 3' *ALK probe*) signals. All patients with stage IV NSCLC (Tumor, Nodes, Metastases, 7th edition) tested within the CMOCO laboratory from October 2008 until June 2012 were reviewed for: (1) *ALK* positivity using FISH; (2) treatment of their advanced disease with either monotherapy or combination therapy with pemetrexed; and (3) treatment with crizotinib.²⁰ Similar methods were used for a retrospective trial at the University of Colorado, resulting in overlap of some patient data.¹⁰ ALK+ patients were identified at Karmanos and Peter MacCallum through registers of patients treated with crizotinib in clinical trials and notes examined for previous or subsequent pemetrexed exposure. Patients receiving pemetrexed as standard of care or within the context of a clinical trial were included for analysis. Crizotinib was given within a clinical trial setting in all cases.^{2–4} No minimum exposure to pemetrexed or crizotinib was mandated. Therapy line calculations for each cohort excluded monotherapy with tyrosine kinase inhibitors (TKIs) other than crizotinib (eg, erlotinib). Data

were collected using retrospective scan and chart review. Patients were classified as “never/light” smokers if they smoked less than 10 pack-years or as ‘smokers’ if they smoked greater than or equal to 10 pack-years in their lifetime. The context of pemetrexed therapy including line of therapy, combination (with platinum or nonplatinum agents) vs. monotherapy was collected, as was line of therapy for crizotinib. Patients were categorized into 2 separate groups according to sequence of systemic therapies: pemetrexed before crizotinib (PEM-CRIZ) or crizotinib before pemetrexed (CRIZ-PEM). PFS while taking pemetrexed and crizotinib was documented for each patient, rounded to the nearest half month, taken from time of first dose for each therapy until documented clinical or radiographic progression or death from any cause. Interval systemic imaging (computed tomography [CT] or positron emission tomography/CT) for patients while they were taking pemetrexed was obtained at the physician’s discretion, and interval imaging for patients while they were taking crizotinib was obtained per trial protocols.²⁻⁴ Central nervous system (CNS) imaging at baseline and while taking treatment for pemetrexed was performed at physician’s discretion. CNS imaging at baseline for crizotinib was mandated in some but not all studies, but could also be performed at the physician’s discretion. CNS imaging during treatment with crizotinib was similarly mandated in some but not all studies, but only for those with known CNS disease at baseline. However, CNS imaging during treatment could also be performed at the physician’s discretion.²⁻⁴ Considering that CNS-only progression could reflect a failure of CNS penetration rather than true drug resistance, overall PFS (counting progression in any site), and PFS excluding CNS-only progression events (extra-CNS; eCNS) PFS (provided there was neither escalation nor change in systemic therapy at the time) were collected separately for pemetrexed and crizotinib.²¹ Patients with CNS progression with otherwise excellent systemic control of their disease were offered appropriate local CNS treatment such as stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT), and continuation of the systemic agent.²² Patients who were alive but had not progressed at the time of analysis were noted and censored within the analysis. Best objective responses per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were assessed in patients with measurable disease and available imaging from both study cohorts.²³

Statistical Analysis

Descriptive statistics were calculated on ALK+ patients with previous pemetrexed and crizotinib exposure. Separate Kaplan–Meier curves were generated for overall and eCNS PFS for patients while taking pemetrexed and crizotinib. The difference in PFS benefit between PEM-CRIZ and CRIZ-PEM cohorts was analyzed using matched-pair survival analysis within a Cox proportional hazards regression model.²⁴

Results

Anaplastic Lymphoma Kinase-Positive Patients Sequentially Treated With Pemetrexed and Crizotinib

From October 2008 until June 2012, we identified 19 patients at the University of Colorado Cancer Center and 10 patients at Karmonos Cancer Center with ALK+ stage IV NSCLC that had undergone treatment with pemetrexed for their metastatic disease and then subsequent

treatment with crizotinib after progression (PEM-CRIZ cohort). We also identified 5 patients at the University of Colorado Cancer Center and 4 patients at Peter MacCallum Cancer Center that had undergone treatment with crizotinib and then subsequent treatment with pemetrexed (CRIZ-PEM cohort). The details of these patients are listed in Table 1. Systemic imaging during pemetrexed treatment occurred with a median interval of 7 weeks. Systemic imaging during crizotinib treatment occurred every 6 to 8 weeks per trial protocols. Beyond crizotinib, no other ALK-specific TKI therapy was used during the interval studied. Treatment details for the PEM-CRIZ and CRIZ-PEM cohorts are listed in Table 2. In 22 of 29 (76%) PEM-CRIZ cases and 9 of 9 (100%) CRIZ-PEM cases, the 2 therapies proceeded without additional intervening therapies (excluding other non-crizotinib TKIs). Forty-eight percent (14/29) of the PEM-CRIZ and 11% (1/9) of the CRIZ-PEM cohort were chemotherapy-naïve at the time of the first cycle of pemetrexed. Pemetrexed was given as combination therapy with a platinum-based chemotherapy agent or in the context of a clinical trial with other agents in 65% (19/29) of PEM-CRIZ patients and 33% (3/9) of CRIZ-PEM patients. Pemetrexed was administered as a single agent in 34% (10/29) of PEM-CRIZ patients and 66% (6/9) of CRIZ-PEM patients (Table 2). All patients receiving platinum and nonplatinum combination therapy with pemetrexed in both patient cohorts were given single-agent maintenance pemetrexed after discontinuation of the other agent(s) until unacceptable toxicity or disease progression. Patients were evaluated for CNS disease in 84% (n = 32) of patients before pemetrexed exposure and 92% (n = 35) of patients before crizotinib exposure, with CNS disease noted in 39% (n = 15) of patients before they were given pemetrexed, and in 37% (n = 14) of patients before they were given crizotinib. Progression events (including CNS and eCNS and events occurring after initial CNS progression) for both cohorts are detailed in Table 3.

All patients in both cohorts with CNS progression while taking pemetrexed or crizotinib who had controlled systemic disease continued on the same systemic therapy after control of their CNS disease with local radiation therapy in the form of SRS or WBRT. ORR data on crizotinib was obtained for 19 of 29 (66%) evaluable patients in the PEM-CRIZ cohort and 5 of 9 (56%) of the CRIZ-PEM patients (Table 4). Similarly, ORR for pemetrexed was available for 31% (9/29) of the PEM-CRIZ and 44% (4/9) of the CRIZ-PEM cohort, with 33% (3/9) of the PEM-CRIZ and 100% (4/4) of CRIZ-PEM receiving pemetrexed monotherapy. Statistical analysis of ORR data was not conducted because of the small sizes of the subgroups involved.

Progression-Free Survival Data

Kaplan–Meier plots of PFS for PEM-CRIZ and CRIZ-PEM cohorts during pemetrexed therapy are depicted in Figure 1, with separate plots generated for overall and eCNS PFS. The median overall PFS for pemetrexed was 6 months (range, 0.5–34.5 months) vs. 3 months (range, 0.5–13 months), and the median eCNS PFS was 6 months (range, 0.5–34.5 months) vs. 4.5 months (range, 0.5 to > 13 months) in the PEM-CRIZ vs. CRIZ-PEM cohorts, respectively. Figure 2 depicts PFS of the same cohorts of patients taking crizotinib. The median overall PFS while taking crizotinib was 10 months (range, 0.5–27.5 months) vs. 7.5 months (range, 2–20.5 months) and the median eCNS PFS was 14.5 months (range, 0.5–31 months) vs. 8.5 months (range, 2–29 months) in the PEM-CRIZ vs. CRIZ-PEM

cohorts, respectively. Systemic progression while taking pemetrexed and crizotinib for individual patients in both cohorts is represented as sequential bars in the graph in Figure 3. Median overall PFS was statistically similar across all patients regardless of whether pemetrexed was given as monotherapy or as combination therapy (5.5 vs. 4.5 months, respectively; $P = .7956$; hazard ratio [HR], 1.092; 95% confidence interval [CI], 0.563–2.114) as was eCNS PFS for pemetrexed monotherapy and combination therapy (6.5 vs. 4.5 months, respectively; $P = .6446$; HR, 1.172; 95% CI, 0.596–2.305).

Patients were significantly more likely to have an overall PFS event while taking pemetrexed when this therapy was sequenced after crizotinib (CRIZ-PEM) as opposed to before crizotinib (PEM-CRIZ) ($P = .0277$; HR, 2.5898; 95% CI, 1.1100–6.0424). Although there was a modest trend toward patients being more likely to have an eCNS PFS event while taking pemetrexed when this therapy was sequenced after crizotinib (CRIZ-PEM) as opposed to when it was sequenced before crizotinib (PEM-CRIZ), this was not significant ($P = .493$; HR, 1.3521; 95% CI, 0.5727–3.1920). Patients had a modest trend toward a higher risk of an overall PFS event while taking crizotinib when this drug was sequenced before pemetrexed (CRIZ-PEM) as opposed to after pemetrexed (PEM-CRIZ), but this was not statistically significant ($P = .4223$; HR, 1.3633; 95% CI, 0.6395–2.9067). There was a similar modest trend toward patients being more likely to have an eCNS PFS event while taking crizotinib when this therapy was sequenced before pemetrexed (CRIZ-PEM) as opposed to after pemetrexed (PEM-CRIZ), but this was also not statistically significant ($P = .3345$; HR, 1.4077; CI, 0.7029–2.8189). Considering that most of our patients were still alive at the time of data assessment, with 83% (24/29) of PEM-CRIZ and 78% (7/9) of CRIZ-PEM patients alive at the time of analysis, no estimates of median overall survival were made.

Discussion

Our retrospective study, including data from 3 separate sites and on patients treated with pemetrexed monotherapy and combination therapy, continues to reinforce previous findings that stage IV ALK+ NSCLC demonstrates enhanced sensitivity to pemetrexed, with a longer overall PFS and a higher response rate (6 months and 60%, respectively, in the pre-crizotinib cohort) compared with either unselected NSCLC or adenocarcinoma patients treated within the original pemetrexed monotherapy and platinum combination therapy registration trials.^{8–11} Although there was a statistically significant increase in overall PFS events when pemetrexed was sequenced after crizotinib (CRIZ-PEM) as opposed to before (PEM-CRIZ), this retrospective analysis remains hypothesis-generating only and would require validation in larger prospective trials. The high ORR and median PFS of each drug in our analysis, regardless of sequence, reinforce that both crizotinib and pemetrexed appear to be highly effective agents in ALK+ NSCLC. To illustrate, in the largest retrospective series to date, using information on previous therapies from the PROFILE 1005 crizotinib study, 141 ALK+ patients who received single-agent pemetrexed in the second-line setting were noted to have a median time to progression while taking pemetrexed of 5.4 months, which also appeared to be longer compared with a historical second-line matched control group.²⁵ Although the response rate to pemetrexed in our study appeared even higher than in previous studies, the PFS with pemetrexed we recorded and the PFS in the retrospective

analysis of PROFILE 1005 did appear more modest than the median PFS or time to progression (TTP) values of approximately 9 months that have been previously reported.^{10,11,25} Consistent with this, the PFS in pemetrexed-treated patients in the prospective randomized PROFILE 1007 was only 4.2 months, compared with 7.7 months for patients taking crizotinib.⁴

One potential explanation for the difference between these smaller and larger series is that there appears to be a variation in responsiveness to pemetrexed in ALK+ NSCLC. This is strongly suggested by the shape of the pemetrexed PFS curve in the PROFILE 1007 study, in which there is a rapid drop-off consistent with the existence of a pemetrexed-insensitive population, followed by a leveling off of the curve such that it parallels the crizotinib curve, including the equivalent demonstration of a pronounced tail of nonprogressors even after many months of therapy.^{4,10,11,25} Whether the ‘pemetrexed sensitive’ sub-type of ALK+ NSCLC which, by chance, might have dominated in the initial smaller series reflects additional molecular context that remains dependent on the tumor’s *ALK* status or is only indirectly associated with *ALK* positivity remains unknown. To illustrate these 2 hypotheses, some data suggest that *ALK* signaling might directly affect aspects of nucleotide synthesis through phosphorylation of *ATIC*; a bifunctional enzyme involved in nucleotide synthesis, which could, affect pemetrexed sensitivity depending on the status of the other known targets of pemetrexed in individual tumors.^{6,10,14,16} Alternatively, *ALK* might only be functioning as a surrogate marker for some other sensitivity factor that occurs in ALK+ disease more commonly than in other molecular subtypes of NSCLC. For example, low TS levels, which might have no direct relationship to *ALK* signaling, have been reported to broadly predict for sensitivity to pemetrexed within several large NSCLC series and have now been reported to be lower on average in ALK+ NSCLC compared with ALK-negative cases.^{9,15,26} Shaw et al. have also recently suggested that smoking status could also be an important determinant of pemetrexed sensitivity and that the beneficial effects of pemetrexed are a reflection of the lower smoking status associated with ALK+ NSCLC compared with other forms of NSCLC.²⁷

One additional way of assessing whether activity of different agents involve overlapping cellular processes is to explore whether clinical cross-resistance occurs to one agent after progression while taking the other. Resistance to pemetrexed might occur via several known mechanisms, such as increased expression of TS or adenosine triphosphate binding cassette drug efflux pumps.²⁸ Similarly, multiple different molecular mechanisms of resistance to crizotinib have recently been described, at least half of which are predicted to reinstitute *ALK* signaling in the presence of crizotinib through the development of either new mutations within the *ALK* kinase domain and/or increases in the copy number of the rearranged gene relative to baseline.^{7,29,30} With regard to exposure to pemetrexed affecting crizotinib sensitivity in our study, not only was there no statistically significant effect of pemetrexed on either overall or eCNS PFS benefit from crizotinib, the statistically nonsignificant trends favored giving crizotinib after pemetrexed as opposed to before. Considering that this goes directly against the notion of cross-resistance it is therefore hard to ascribe the minor differences in crizotinib PFS before and after pemetrexed to anything other than chance effects within a relatively small study. In contrast, there was a statistically

significant effect of crizotinib exposure on benefit from pemetrexed when overall PFS was considered (HR, 2.5898; $P = .0277$; 95% CI, 1.1100– 6.0424), suggesting that pemetrexed is less effective when given after crizotinib. However, this did not remain significant when eCNS PFS was considered which would be expected to be a more accurate reflection of the true benefit of the drug on the cancer because it excludes CNS progression events (see later in text).

In addition to changes in the dominant biology of the cancer, inadequate penetration of drugs across the blood–brain barrier has also been proposed as a distinct mechanism of acquired resistance to drugs when the sites of progression include the CNS.⁷ Consistent with this, eCNS PFS for both drugs was usually longer than overall PFS in our study, illustrating that neither crizotinib nor pemetrexed might have equivalent activity on disease in the CNS compared with other organ sites. The absolute differences in the two end points in our observational study were more pronounced during crizotinib treatment. This might reflect differences in blood–brain penetration between crizotinib and pemetrexed, with the CNS more likely to act as a sanctuary site of disease during crizotinib treatment.^{21,30,31}

Our study had several limitations. The overall size of the analyzed populations was small and the study was conducted retrospectively. Therefore, all end points are potentially subject to bias. Tables 1 and 2 make clear, within this nonrandomized study, that there were imbalances in the cohorts in several variables that could have affected PFS outcomes, most notably in the baseline incidence of known brain metastases and whether pemetrexed was used as monotherapy or as part of a platinum doublet.

Conclusion

PFS benefit from pemetrexed was less after crizotinib compared with before crizotinib, however, this difference was only statistically significant for overall and not eCNS PFS. A larger prospective series is required, adjusting for relevant confounding effects, ideally with some rebiopsy-based information on the specific mechanisms of resistance expressed by the patient's tumor.

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Clinical Practice Points

- Crizotinib is associated with high response rates and prolonged PFS in ALK+ NSCLC.^{2–4,16}
- Crizotinib-naïve ALK+ NSCLC also demonstrates higher PFS/TTP and ORR compared with pemetrexed in retrospective analyses than wild type *EGFR*/*KRAS* and/or *EGFR* mutant controls, and higher response rates and PFS compared with docetaxel in ALK+ NSCLC in prospective analyses.^{4,10,11}
- Optimal treatment paradigms for ALK+ NSCLC when pemetrexed and crizotinib are used sequentially are unknown. It is unknown whether pemetrexed-based regimens will show high activity in ALK+ NSCLC when treatment with crizotinib fails.
- Twenty-nine ALK+ patients treated with pemetrexed then crizotinib (PEM-CRIZ), and 9 patients treated with crizotinib then pemetrexed (CRIZ-PEM) were evaluated.
- In evaluable patients the ORRs were 60% (n = 6 out of 9) and 75% (n = 3 out of 4) with pemetrexed before and after crizotinib treatment, respectively, and 66% (n = 2 out of 3) and 84% (n = 16 out of 19) with crizotinib treatment before and after pemetrexed, respectively.
- Overall PFS was 7.5 to 10 months with crizotinib and 3 to 6 months with pemetrexed. Patients were significantly more likely to have overall progression/death while taking pemetrexed in the CRIZ-PEM cohorts as opposed to the PEM-CRIZ cohort ($P = .0277$; HR, 2.5898; 95% CI, 1.1100–46.0424), however this did not remain significant when only eCNS PFS events were considered. Pemetrexed exposure did not appear to affect crizotinib outcomes.
- Both agents are associated with high activity in ALK+ NSCLC according to ORR, but PFS was consistently longer with crizotinib than with pemetrexed.
- There was no clear evidence of cross-resistance between the agents.

Figure 1.

Kaplan—Meier Curves for PEM-CRIZ (n = 29) and CRIZ-PEM (n = 9) Cohorts During Pemetrexed Therapy. (A) Overall PFS During the Pemetrexed Portion of Therapy Depicting a Statistically Significant Increase in Overall PFS Events in the CRIZ-PEM Cohort ($P = .0277$; HR 2.5898; 95% CI, 1.1100–6.0424). (B) Extra-CNS PFS During the Pemetrexed Portion of Therapy Depicting a Trend Toward Increased eCNS PFS Events in the CRIZ-PEM Cohort That was not Statistically Significant ($P = .493$; HR, 1.3521; 95% CI, 0.5727–3.1920). Median PFS (Rounded to the Half Month) and Range is Provided for Each Cohort Abbreviations: CNS = central nervous system; eCNS = extra-CNS; HR = hazard ratio; PFS = progression-free survival.

Figure 2.

Kaplan–Meier Curves for PEM-CRIZ ($n = 29$) and CRIZ-PEM ($n = 9$) Cohorts During Crizotinib Therapy. (A) Overall PFS During the Crizotinib Portion of Therapy Depicting a Trend Toward Increased Overall PFS Events in the CRIZ-PEM Cohort That was not Statistically Significant ($P = .4223$; HR 1.3633; 95% CI, 0.6395–2.9067). (B) Extra-CNS PFS During the Crizotinib Portion of Therapy Depicting a Trend Toward Increased eCNS PFS Events in the CRIZ-PEM Cohort That was not Statistically Significant ($P = .3345$; HR, 1.4077; 95% CI, 0.7029–2.8189). Median PFS (Rounded to the Half Month) and Range is Provided for Each Cohort

Abbreviations: CNS = central nervous system; eCNS = extra-CNS; HR = hazard ratio; PFS = progression-free survival.

Figure 3. Serial eCNS PFS for Individual Patients in the PEM-CRIZ and CRIZ-PEM Cohorts. (A) Overlapping bar Graph Depicting Serial eCNS PFS for Individual Patients Receiving Pemetrexed Then Crizotinib (PEM-CRIZ Cohort). (B) Overlapping bar Graph Depicting Serial eCNS PFS for Individual Patients Receiving Crizotinib Then Pemetrexed (CRIZ-PEM Cohort). ^y Indicates Patients who Have not yet Progressed in any Site With Final Data Censored; ^z Indicates Patients With CNS Progression, who Continue Taking Therapy With Systemic Control; and * Indicates Patients in our Series who Died Before Disease Progression

Abbreviations: CNS = central nervous system; eCNS = extra-CNS; PFS = progression-free survival.

Table 1

Patient Characteristics

Characteristic	Group	
	PEM-CRIZ	CRIZ-PEM
Total	n = 29	n = 9
Histology, n (%)		
Adenocarcinoma	28 (97)	9 (100)
Poorly differentiated carcinoma	1 (3)	0
Smoking History, n (%)		
Never/light	25 (86)	9 (100)
Current/former	4 (14)	0 (0)
Sex, n (%)		
Male	18 (62)	4 (44)
Female	11 (38)	5
Median age pemetrexed therapy, years (range)	51 (22–70)	60 (35–64)
Median age crizotinib therapy, years (range)	52 (23–71)	59 (35–64)
Median therapy line pemetrexed^a	Second	Third
Median therapy line crizotinib^a	Third	Second
Known CNS disease before starting pemetrexed, n (%)	10 (34)	5 (55)
Known CNS disease before starting crizotinib, n (%)	13 (45)	1 (11)

Abbreviation: CNS = central nervous system.

^aLine of therapy excluding previous targeted therapy (eg erlotinib), except crizotinib.

Table 2

Treatment Cohorts

Cohort Characteristic	Patients in Cohort, n (%)
No Intervening Nonstudy Therapies	
PEM-CRIZ	22/29 (76)
CRIZ-PEM	9/9 (100)
First-Line Therapy	
Pemetrexed: PEM-CRIZ	13/29 (45)
Crizotinib: CRIZ-PEM	1/9 (11)
Second-Line Therapy	
Pemetrexed: PEM-CRIZ	9/29 (31)
Crizotinib: CRIZ-PEM	1/9 (11)
Pemetrexed Monotherapy	
PEM-CRIZ	10/29 (34)
CRIZ-PEM	6/9 (66)
Pemetrexed Combination Therapy^a	
PEM-CRIZ	19/29 (66)
CRIZ-PEM	3/9 (33)

^aCombination with platinum or in the context of a clinical trial with another agent(s).

Table 3

Initial Progression Events

Progression Event	Pemetrexed: PEM-CRIZ (n = 29)	Crizotinib: CRIZ-PEM (n = 9)	Crizotinib: PEM-CRIZ (n = 29)	Pemetrexed: CRIZ-PEM (n = 9)
CNS Progression	1 (3)	2 (22)	10 (34) ^a	2 (22) ^b
Systemic Progression	27 (93)	7 (78)	12 (62)	5 (55)
Simultaneous Progression				
Systemic and CNS	1 (3)	0 (0)	2 (7)	0 (0)
Death	c	c	0 (0)	1 (11)
Censored (No Progression Event)	c	c	5 (17)	1 (11)

Data are presented as n (%).

Abbreviations: CNS = central nervous system; eCNS =extra-CNS.

^a Subsequent eCNS progression events in this cohort: 6 (21%) systemic, 3 (10%) death, 1 (3%) censored.

^b Extra-CNS progression events in this cohort: 1 (11%) systemic, 1 (11%) censored.

^c All patients, by definition of the dual therapy cohort, proceeded to additional therapy after systemic progression without censoring/death.

Table 4

Best Response Data (Evaluable Patients) According to RECIST 1.1 criteria^a

Patient Cohort	CR	PR	SD	PD	ORR
PEM-CRIZ: Pemtrexed (n = 9)	1 (11)	5 (55)	2 (22)	1 (11)	6 (66)
PEM-CRIZ: Crizotinib (n = 19)	1 (5)	15 (79)	3 (16)	0 (0)	16 (84)
CRIZ-PEM: Pemtrexed (n = 4)	1 (25)	2 (50)	0 (0)	1 (25)	3 (75)
CRIZ-PEM: Crizotinib (n = 3)	0 (0)	2 (66)	1 (33)	0 (0)	2 (66)

Data are presented as n (%).

Abbreviations: ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

^aData not analyzed statistically because of small sample sizes.