Efficacy of Platinum/Pemetrexed Combination Chemotherapy in ALK-Positive NSCLC Refractory to Second-Generation ALK Inhibitors

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Introduction: The current standard initial therapy for advanced ALK receptor tyrosine kinase (ALK)-positive NSCLC is a second-generation ALK tyrosine kinase inhibitor (TKI) such as alectinib. The optimal next-line therapy after failure of a second-generation ALK TKI remains to be established; however, standard options include the third-generation ALK TKI lorlatinib or platinum/pemetrexed-based chemotherapy. The efficacy of platinum/pemetrexed-based chemotherapy has not been evaluated in cases that are refractory to second-generation TKIs.

Methods: This was a retrospective study performed at three institutions. Patients were eligible if they had advanced ALK-positive NSCLC refractory to one or more second-generation ALK TKI(s) and had received platinum/pemetrexed-based chemotherapy.

Results: Among 58 patients eligible for this study, 37 had scans evaluable for response with measurable disease at baseline. The confirmed objective response rate to platinum/pemetrexed-based chemotherapy was 29.7% (11 of 37 patients; 95% confidence interval [CI]: 15.9% – 47.0%), with median duration of response of 6.4 months (95% CI: 1.6 months – not reached). The median progression-free survival for the entire cohort was 4.3 months (95% CI: 2.9 – 5.8 months). Progression-free survival was longer in patients who received platinum/pemetrexed in combination with an ALK TKI compared to those who received platinum/pemetrexed alone (6.8 months vs. 3.2 months, respectively; hazard ratio = 0.33; p = 0.025).

Conclusions: Platinum/pemetrexed-based chemotherapy shows modest efficacy in ALK-positive NSCLC after failure of...
second-generation ALK TKIs. The activity may be higher if administered with an ALK TKI, suggesting a potential role for continued ALK inhibition.

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Keywords: Chemotherapy; Efficacy; ALK; NSCLC

Introduction
Tyrosine kinase inhibitors (TKIs) targeting ALK receptor tyrosine kinase (ALK) are highly effective against ALK-rearranged (i.e., ALK-positive) NSCLC.1 Recently, second-generation ALK TKIs have replaced crizotinib as the standard-of-care initial therapy for patients with newly diagnosed advanced ALK-positive NSCLC.2-6 Ceritinib and alectinib are both approved by the United States Food and Drug Administration (FDA) for this indication on the basis of the ASCEND-4 and global ALEX trials, respectively.6,7 Most recently, first-line brigatinib showed superior progression-free survival (PFS) compared to crizotinib (ALTA-1L), and may also receive regulatory approval in this setting.6 Despite the initial clinical benefit from second-generation ALK inhibitors, almost all patients ultimately develop resistance and experience disease relapse.

Optimal treatment options for patients following disease progression on second-generation ALK TKIs remain to be determined. Lorlatinib, a third-generation ALK inhibitor, represents one standard option in the United States and Japan. In a phase II study, lorlatinib was associated with a confirmed objective response rate (ORR) of 40% and median PFS of 6.9 months among 139 patients who had received one or more second-generation ALK TKIs.7-9 Based on these results, lorlatinib was granted FDA approval for second- or third-line treatment of ALK-positive NSCLC, including for patients who had failed alectinib or ceritinib as their initial ALK TKI. Lorlatinib showed significantly greater efficacy among patients with baseline ALK resistance mutations compared to those without ALK resistance mutations.8 Therefore, additional treatment options are needed for patients following progression on second-generation ALK inhibitors, particularly for those without ALK resistance mutations. Other potential options after the failure of a second-generation ALK TKI include alternative second-generation ALK TKI(s)—such as ceritinib or brigatinib following the failure of alectinib—selected based on the knowledge of ALK resistance mutation status. Both ceritinib and brigatinib have been evaluated in small numbers of patients following failure of at least one second-generation ALK inhibitor (such as alectinib), and have shown ORRs ranging from 17% to 50%.9-13 Most patients with advanced ALK-positive NSCLC will receive chemotherapy at some point during their disease course, especially once available TKI options are exhausted. In two separate phase III trials, PROFILE 1014 and ASCEND-4, platinum (PT)/pemetrexed (pem) chemotherapy showed efficacy in newly diagnosed patients with advanced ALK-positive NSCLC, with a median PFS of 7.0 and 8.1 months, respectively.2,14 Similarly, in one retrospective analysis, first-line PT/pem-based chemotherapy was associated with a median PFS of 8.5 months.15 However, there is little to no data on the efficacy of PT/pem chemotherapy in patients once they have progressed on ALK inhibitors, including second-generation ALK TKI(s).

Here we performed a multicenter retrospective analysis to determine the efficacy of PT/pem-based combination chemotherapy in patients with advanced ALK-positive NSCLC refractory to at least one second-generation ALK TKI.

Materials and Methods
Study Population
Patients were identified at three participating institutions: Massachusetts General Hospital (n = 37), Memorial Sloan Kettering Cancer Center (n = 13), and University of California–Irvine (n = 8). Patients were eligible if they had been diagnosed with advanced NSCLC with an ALK rearrangement identified by local molecular profiling (e.g., fluorescent in situ hybridization, immunohistochemistry, DNA-based next-generation sequencing [NGS], or targeted RNA sequencing). Patients had to have previously received at least one second-generation ALK inhibitor with disease progression, and subsequently received PT/pem-based combination chemotherapy. PT/pem could have been administered with bevacizumab, programmed cell death 1 (PD-1) or programmed cell death ligand 1 checkpoint inhibitor, and/or an ALK TKI. Prior adjuvant or neoadjuvant chemotherapy was allowed. Up to two cycles of prior PT-based chemotherapy were allowed, if given before the ALK testing result became available with no evidence of disease progression. Treatment with the third-generation ALK TKI lorlatinib before PT/pem-based chemotherapy was not permitted. This study was approved by the institutional review board at each participating institution.

Data Collection
Medical records were reviewed to extract relevant clinical and pathologic data. Overall and intracranial responses to therapy were determined retrospectively using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 based on investigator assessment,
with measurable extracranial or intracranial tumor lesions defined per the RECIST version 1.1 criteria (i.e., at least 10 mm in size, or if lymph node, then at least 15 mm in short axis).\textsuperscript{16} Previously irradiated tumor lesions were not measurable unless there had been unequivocal progression in those lesions.\textsuperscript{16} PFS was defined as the time from the start of PT/pem-based chemotherapy to first clinical/radiographic progression or death. Patients without documented disease progression were censored at their last follow-up. For those patients without scans available for objective tumor response review, PFS was determined by review of medical records. Duration of response was calculated from the date of the first documented response to the date of disease progression, or censored at last follow-up if no progression occurred. All data were updated as of February 15, 2019.

**Results**

**Patient Characteristics**

We identified 58 patients with advanced ALK-positive NSCLC eligible for this study. Baseline characteristics are summarized in Table 1. The median age at diagnosis of advanced disease was 50 years (range, 22–75 years), the majority of patients (74%) were never smokers, and all patients had adenocarcinoma histology. The chemotherapy regimens included (Supplemental Table 1): PT/pem (32 of 58 patients, 55%), PT/pem/bevacizumab (7 of 58 patients, 12%), PT/pem/PD-1 inhibitor (4 of 58 patients, 7%), PT/pem with ALK TKI (8 of 58 patients, 14%), PT/pem/bevacizumab with TKI (6 of 58 patients, 10%), and PT/pem/PD-1 inhibitor with TKI (1 of 58 patients, 2%). At the time of starting PT/pem chemotherapy, 31 (53%) patients had known metastases in the central nervous system (CNS), 5 of whom (9%) had leptomeningeal disease.

Most patients (88%) had received at least two prior ALK TKIs. Thirty-three patients (57%) received prior crizotinib followed by a second-generation ALK TKI (ceritinib, alectinib, or brigatinib) (Supplemental Table 2). Twelve patients (21%) received three or more prior ALK TKIs; in all of these cases, crizotinib was followed by two or three second-generation ALK inhibitors. Most (55 patients; 95%) received PT/pem-based chemotherapy as the immediate next line of therapy following a second-generation ALK inhibitor. Three patients received intervening investigational therapies with AUY922 (n = 1), an AKT inhibitor (n = 1), and an ALK TKI combined with an MEK inhibitor (n = 1), respectively. All patients had disease progression on the immediate preceding therapy (extracranial only: 39 patients, 67%; CNS only: 4 patients, 7%; CNS and extracranial: 14 patients, 24%; and pattern unknown: 1 patient, 2%). The median duration between the time of progression on the last ALK TKI and the initiation of PT/pem chemotherapy was 24 days (range, 3 – 559 days). The median duration on the immediately preceding ALK TKI was 6.2 months (range, 1.5 – 36.9 months).

Six patients received prior neoadjuvant or adjuvant PT-based chemotherapy. Additionally, five patients received one to two cycles of prior PT-based chemotherapy at diagnosis before their ALK testing results became available and switched therapies without evidence of disease progression on chemotherapy (Table 1). Among 10 of 11 patients with prior exposure to chemotherapy, the median interval between the last dose of prior chemotherapy and the start of PT/pem-based chemotherapy for advanced disease was 22.7 months (range, 10.0 – 88.1 months); the remaining 1 patient started PT/pem-based chemotherapy at a
minimum of 38.7 months after the prior chemotherapy, but the exact time interval could not be determined.

**Efficacy of PT/pem-Based Chemotherapy**

Median follow-up was 11 months. Forty patients in the cohort had scans available for radiology review and were evaluable for objective tumor response. The remaining 18 patients did not have scans available for response review (Supplemental Fig. 1). Of 40 patients with evaluable scans, 37 had measurable disease at baseline (Fig. 1). Confirmed partial responses (PRs) were observed in 11 patients, with an ORR of 29.7% (95% CI: 15.9% – 47.0%). Thirteen patients had stable disease as the best tumor response, 2 of which were unconfirmed PRs. The remaining 13 patients had progressive disease. Three additional patients with evaluable scans had nonmeasurable disease at baseline, of whom two had non-complete response/non-progressive disease and one had complete response. Among 19 patients with measurable and/or nonmeasurable CNS disease at baseline who had scans evaluable for CNS objective responses, the CNS ORR was 15.8% (95% CI: 3.4% – 39.6%). Three of 19 patients had measurable CNS lesions at baseline, and of these, 1 had CNS PR.

The median duration of response among 11 patients who had confirmed PRs was 6.4 months (95% CI: 1.6 months – not reached), with two ongoing responses at data cutoff (Fig. 2). The median overall PFS on PT/pem-based chemotherapy for the entire cohort was 4.3 months (95% CI: 2.9 – 5.8 months) (Fig. 3A). The risk of intracranial progression at 1 year was 30% (95% CI: 18% – 44%), whereas the median was not reached.

In the subgroup of patients who received PT/pem plus bevacizumab (n = 7), there was a modest trend towards improved PFS compared to those who received PT/pem only (n = 32) (median PFS: 4.6 months vs. 3.2 months; HR = 0.40). However, the difference was not strictly statistically significant (p = 0.062) due to low power (Supplemental Fig. 2). Among the five patients who received PT/pem plus a PD-1 inhibitor (of whom one received PT/pem plus PD-1 inhibitor together with brigatinib), the median PFS was 4.7 months (95% CI: 1.0 month – not reached). Four of these patients were evaluable for tumor response; of these, one had PR, one had stable disease, and two had progressive disease as best response.

**Continuation of an ALK TKI With Chemotherapy**

A total of 15 patients in the cohort received a PT/pem-based chemotherapy regimen in combination with an ALK TKI (Supplemental Table 1). Nine patients (60%) continued on the same immediate preceding second-generation ALK TKI (alectinib, n = 7; brigatinib, n = 2) when they started chemotherapy (Supplemental Table 3). Of the remaining six patients, two went on PT/pem plus alectinib, which they had previously received though not as the immediate preceding TKI. Three patients went back to crizotinib, which they had...
previously received. The remaining one patient went on crizotinib for the first time, after having received prior brigatinib and ceritinib.

We observed that the receipt of any PT/pem-based combination chemotherapy plus an ALK TKI (n = 15) was associated with a significant increase in PFS compared to PT/pem-based chemotherapy alone (n = 43) (median PFS: 7.7 months vs. 3.6 months; HR = 0.31; p = 0.002). Baseline characteristics of patients who received the chemotherapy combination regimen with versus without ALK TKI were overall comparable (Supplemental Table 4). This PFS difference was also seen when comparing those who received PT/pem (without bevacizumab or anti–PD-1/programmed cell death ligand 1 agent) plus an ALK TKI (n = 8) versus PT/pem only (n = 32), with a median PFS of 6.8 months versus 3.2 months, respectively (HR = 0.33; p = 0.025) (Fig. 3B). The ORR was numerically higher for those with baseline measurable disease receiving PT/pem plus ALK TKI versus PT/pem alone (3 of 5 patients [60%] vs. 4 of 21 patients [19%]), but this difference did not reach strict statistical significance (p = 0.101) due to low power.

When the baseline characteristics of patients who received PT/pem with an ALK TKI (n = 8) were compared to those of patients who received PT/pem alone without an ALK TKI (n = 32), they were found to be largely comparable without statistically significant differences (Supplemental Table 5). A higher percentage of patients who received PT/pem with an ALK TKI (7 of 8 patients [88%]) had known history of brain metastases at the time of starting therapy compared to those who received PT/pem alone without an ALK TKI (15 of 28 patients [54%]) (p = 0.115). Nevertheless, the incidence of CNS disease progression on PT/pem was similar for those who received it together with an ALK TKI (28% at 1 year) versus without an ALK TKI (38% at 1 year) (p = 0.598).
Efﬁcacy According to Baseline ALK Mutation Status

Twenty-three patients (40%) had undergone a repeat biopsy following disease progression on the immediately preceding second-generation ALK inhibitor. On the basis of tumor (n = 19) or plasma (n = 4) genotyping, 12 patients (52%) had a detectable ALK resistance mutation, whereas 11 patients (48%) did not (Supplemental Fig. 3A). Among these patients, the median PFS on PT/pem-based chemotherapy was 4.1 months and 3.6 months for those with and without ALK mutations, respectively (HR = 1.02; p = 0.966) (Supplemental Fig. 3B). Among patients with measurable baseline disease, objectives responses were observed in 14.3% (1 of 7 patients) and 37.5% (3 of 8 patients) for those with and without ALK mutations, respectively (p = 0.569).

Discussion

The current standard first-line therapy in advanced ALK-positive NSCLC is a second-generation ALK inhibitor such as alectinib. PFS with first-line alectinib signiﬁcantly exceeds that of crizotinib, with median PFS of first-line alectinib reaching 34.8 months based on an updated analysis of the phase III global ALEX trial.2,4,20 Despite these impressive results, acquired TKI resistance remains a major challenge. For patients experiencing disease relapse on alectinib or other second-generation ALK inhibitors, the optimal next-line therapy remains to be established.

Here we evaluated the efﬁcacy of PT/pem-based chemotherapy in patients with advanced ALK-positive NSCLC refractory to second-generation ALK TKI(s). We found that PT/pem-based chemotherapy showed modest clinical activity in this setting, with an ORR of 29.7% and median PFS of 4.3 months. Although the response rate is overall comparable to what has been reported in prior phase III trials of treatment-naive ALK-positive patients, the median PFS is shorter than the 7.0 to 8.1 months previously observed in treatment-naive patients.2,14 This ﬁnding suggests that ALK-positive tumors may be less sensitive to chemotherapy once they have become resistant to ALK TKI(s). In advanced EGFR-mutant NSCLC, a similarly short median PFS of 4.4 months (95% CI: 4.2 – 5.6 months) with PT/pem was reported among patients resistant to earlier-generation EGFR TKIs due to an EGFR T790M mutation.21 It is not yet known whether prior — in many cases, sequential — TKI therapies could enhance genomic instability and tumor heterogeneity leading to diminished sensitivity to cytotoxic chemotherapy. Additionally, in at least a subset of tumors, prior treatment with TKIs could contribute to chemotherapy (or overall drug) resistance by promoting epithelial to mesenchymal transition.22,23

These ﬁndings should be interpreted in the context of emerging efﬁcacy data with next-generation ALK TKIs in patients who are refractory to prior second-generation ALK inhibitor(s). The second-generation inhibitors ceritinib and brigatinib have been evaluated in small numbers of patients who have failed prior alectinib or other second-generation ALK inhibitor(s), and have shown some activity with a median PFS ranging 3.7 to 6.4 months.10-13 Certain tumors harboring alectinib-resistant but ceritinib- or brigatinib-sensitive ALK mutations may have more favorable responses to these latter second-generation ALK inhibitors, although this remains to be validated in larger studies.11,24 The third-generation ALK TKI lorlatinib has demonstrated
overall as well as intracranial efficacy in patients who failed one or more prior second-generation ALK inhibitors, and has received FDA approval for second- or third-line treatment of advanced ALK-positive NSCLC. Whereas the efficacy was significantly greater for patients with baseline ALK mutations compared to those without ALK mutations (median PFS: 11.0 months vs. 4.0 months; ORR = 69% vs. 31%, respectively), reflecting the continued ALK dependency of the tumors harboring ALK mutations, lorlatinib did show modest clinical activity in the ALK mutation-negative, second-generation TKI-refractory patients. This activity appears comparable to that seen with PT/pem-based chemotherapy among ALK mutation-negative patients in our study (lorlatinib: ORR = 31%, median PFS = 4.0 months; PT/pem-based chemotherapy: ORR = 37.5%, median PFS = 3.6 months). However, it must be emphasized that our study was a small retrospective study and not a trial designed to directly compare the efficacy of PT/pem-based chemotherapy versus lorlatinib in this clinical context.

Ultimately, when evaluating next-line treatment options for patients progressing on a second-generation ALK inhibitor, clinicians must consider various parameters including baseline ALK-resistance mutation status, CNS disease burden, co-morbidities, and drug tolerability, in addition to patient preference and access to/eligibility for clinical trials. In general, for patients relapsing on a second-generation ALK inhibitor and known to have a secondary ALK resistance mutation, lorlatinib may be preferable to PT/pem-based chemotherapy based on the demonstrated efficacy of lorlatinib in these patients. For patients relapsing on a second-generation ALK inhibitor with tumor genotyping showing no ALK mutation, either lorlatinib or PT/pem-based chemotherapy could be considered at this time, in the absence of prospective trial data directly comparing lorlatinib versus chemotherapy.

In this study cohort, those patients receiving PT/pem with an ALK TKI had a significantly longer PFS compared to those receiving PT/pem alone. This finding contradicts prior results in advanced EGFR-mutant NSCLC. In the phase III IMPRESS trial, EGFR-mutant NSCLC patients with progression on gefitinib were randomized to cisplatin/pem with gefitinib versus placebo, and no significant PFS difference was observed between the treatment arms. All patients in the IMPRESS trial had previously received gefitinib only, a first-generation EGFR inhibitor, without additional lines of therapy. Whether the same conclusion would be reached in the context of next-generation TKIs (such as osimertinib or alectinib) — which have improved CNS activity and can suppress or delay the emergence of CNS metastases —, or following multiple prior sequential TKIs, is unknown. Our study included patients who had received at least one prior second-generation ALK inhibitor, with the majority having received two or more prior ALK TKIs. Given the small and retrospective nature of our study and the variety of ALK TKIs that were administered in combination with PT/pem chemotherapy, further investigation is needed to better address whether concurrent administration of an ALK TKI with chemotherapy may improve outcomes compared to chemotherapy alone.

Our study had a number of limitations, several of which are inherent in any retrospective study. First, as aforementioned, the study included a small number of patients. Because all participating centers were tertiary academic institutions, patients may not be representative of the general ALK-positive population. Second, patients received a range of PT/pem-based regimens, including regimens with or without bevacizumab, PD-1 inhibitor, or an ALK TKI. The decision of the treating physician to administer PT/pem in combination with bevacizumab, PD-1 inhibitor, or an ALK TKI may have been influenced by multiple factors, including the patient’s performance status, extent of CNS and extracranial disease, tumor genotyping results, smoking history, and/or the degree of response to and tolerability of prior ALK TKIs. These confounders, in turn, could have affected the PFS comparisons performed herein. Similarly, the exact ALK TKIs the patients previously received were variable, although all were required to have received at least one prior second-generation ALK TKI. Third, because this was a retrospective analysis, there was no standardized schedule for tumor assessments, and imaging was not subjected to centralized review, both of which may have impacted the PFS and ORR outcomes. Finally, because crizotinib was the standard initial therapy for advanced ALK-positive NSCLC until recently, majority of the patients in this study received prior crizotinib followed by next-generation ALK TKI(s). The efficacy of PT/pem-based chemotherapy may in theory be different among patients who receive prior second-generation ALK inhibitors without preceding crizotinib.

In summary, our findings suggest limited efficacy of PT/pem-based chemotherapy in advanced ALK-positive NSCLC after failure of a second-generation ALK inhibitor. Efficacy may be higher in patients who receive chemotherapy in combination with an ALK TKI, suggesting a potential role for ongoing ALK inhibition. This study underscores the need to develop more effective therapeutic strategies for ALK-positive NSCLC patients progressing on next-generation ALK inhibitors.
Acknowledgments
This work was supported by a grant from the National Cancer Institute (R01CA164273, to A.T.S.), by Be a Piece of the Solution, and by the Targeting a Cure for Lung Cancer Research Fund at Massachusetts General Hospital, and additionally by the National Cancer Institute (T32 CA009207, P30 CA008748) and the Lung Cancer Research Foundation.

Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the Journal of Thoracic Oncology at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.10.014.

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