



Ensartinib (X-396): what does it add for patients with ALK-rearranged NSCLC

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Comment on: Horn L, Infante JR, Reckamp KL, *et al.* Ensartinib (X-396) in ALK-Positive Non-Small Cell Lung Cancer: Results from a First-in-Human Phase I/II, Multicenter Study. *Clin Cancer Res* 2018;24:2771-9.

Submitted Oct 25, 2018. Accepted for publication Oct 26, 2018.

doi: 10.21037/cco.2018.10.12

View this article at: <http://dx.doi.org/10.21037/cco.2018.10.12>

Rearrangements of the anaplastic lymphoma kinase (*ALK*) gene were first identified in 2007 and occur in 3 to 5% of all patients with advanced non-small cell lung cancer (NSCLC) (1). Regardless of the fusion partners, these *ALK* rearrangements lead to oncogenic hyperactivation of cytoplasmic tyrosine kinase activity (2). Thus, small molecular tyrosine kinase inhibitors (TKIs) for the gain-of-function tyrosine kinase activity of rearranged *ALK* have been the focus of drug development strategy. In August of 2011, only 3 years after the clinical activity of crizotinib was first observed, it was granted accelerated U.S. Food and Drug Administration (FDA) approval as the first-in-class *ALK* TKI for treatment of patients with locally advanced or metastatic *ALK*-positive NSCLC, based on the objective response rate (ORR) of 50–61% and median response duration of 42–48 weeks (3). The most common adverse reactions ($\geq 25\%$) were vision disorder, nausea, diarrhea, vomiting, edema, and constipation. In November 2013, crizotinib received full FDA approval based on an improvement in median progression-free survival (mPFS) compared to second-line chemotherapy (7.7 *vs.* 3.0 months) in patients with metastatic *ALK*-positive NSCLC previously treated with one platinum-based chemotherapy regimen (4). Subsequently, first-line systemic therapy with crizotinib was shown to significantly improved mPFS (10.9 *vs.* 7.0 months) in patients with *ALK*-rearranged NSCLC compared to first line platinum-based, double-agent chemotherapy (5).

Patients with *ALK*-rearranged NSCLC commonly have

several characteristic clinicopathological features: the age of onset is usually 10–15 years younger than that of the average age NSCLC patient, most are either never or light smokers, and the majority of cases are adenocarcinomas. However, these clinicopathological features are not sufficient to identify patients with *ALK*-rearranged NSCLC. Concurrently approved with crizotinib in August 2011, the Vysis *ALK* Break-Apart FISH Probe Kit (Abbott Molecular, Inc.) became the first companion diagnostic for identifying *ALK*-rearranged NSCLC tumors. Currently, both the National Comprehensive Cancer Network (NCCN) and the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology (CAP/IASLC/AMP) Molecular Testing Guideline unanimously recommend testing for *ALK* rearrangement for adenocarcinoma and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade, gender, ethnicity, or smoking status (6,7). *Figure 1* summarizes the current algorithm for using companion diagnostics for initial identification of patients with *ALK*-rearranged NSCLC, and for subsequent assessment of resistance mechanisms for treatment decision. At initial diagnosis, diagnostics for identifying *ALK*-rearranged tumors include fluorescence in situ hybridization (FISH), immunohistochemistry (IHC), real-time polymerase chain reaction (RT-PCR) and next generation sequencing (NGS) (4,8,9) (*Figure 1*). Tumors are defined as *ALK* FISH-positive if at least 15% of cells show a split signal; a second

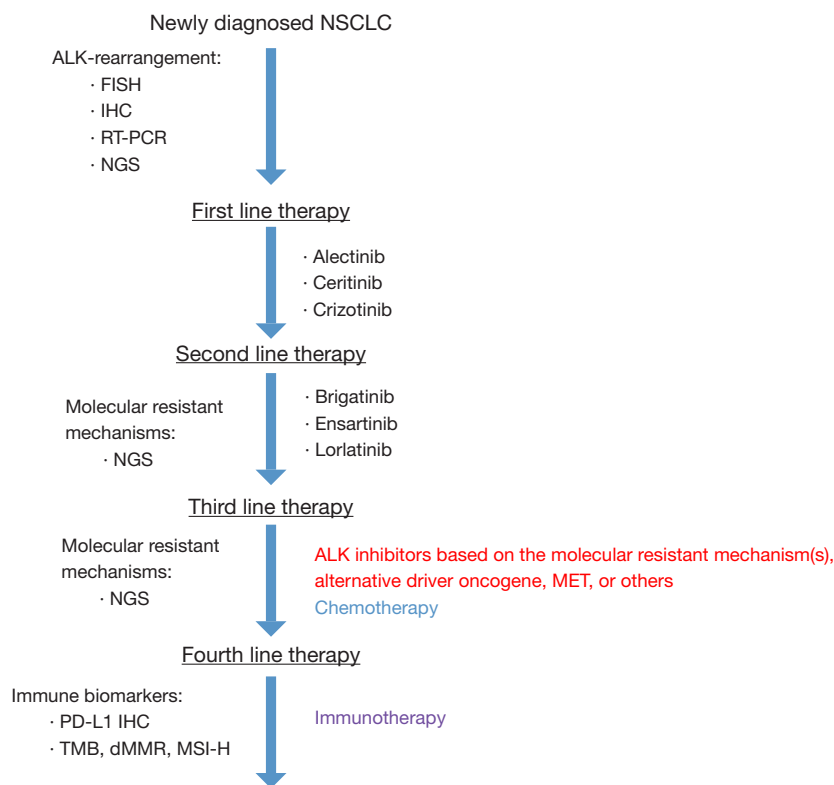


Figure 1 Diagnostics and treatment algorithm for *ALK*-rearranged NSCLC. Testing for *ALK* rearrangements by different diagnostics is recommended for patients initially diagnosed with adenocarcinoma and mixed lung cancers with an adenocarcinoma component, regardless of histologic grade or clinical characteristics. At tumor progression, NGS and immune biomarker assays are recommended to identify resistance mechanisms and select subsequent treatment strategies. FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; dMMR, deficient mismatch repair; MSI-H, microsatellite instability high; NGS, next generation sequencing; PD-1, Programmed death-1; RT-PCR, reverse transcription polymerase chain reaction; TMB, tumor mutation burden.

confirmatory test is required if the positive signal is between 10% and 15% (4). For the Ventana ALK (D5F3) CDx Assay, ALK IHC positivity requires the presence of strong granular cytoplasmic staining (3+) (8). More recently, NGS has been proven superior to both FISH and IHC for the sensitive detection of *ALK*-rearranged tumors, especially for those with rare *ALK* fusion variants and partners (9). For NSCLC patients who acquire resistance to an ALK inhibitor, NGS assessment of the molecular mechanism of resistance should inform the individualized treatment strategy and selection of an appropriate second- or third-generation ALK inhibitor. In cases where tumor tissue is insufficient for molecular testing, plasma circulating tumor DNA (ctDNA) from liquid biopsy is increasingly used as an alternative at initial diagnosis and at treatment resistance (7).

Despite drugs approved for *ALK*-rearranged NSCLC having exceptional ORR and mPFS, patients are not

cured. Almost all patients with *ALK*-rearranged NSCLC eventually develop acquired resistance to the ALK TKIs. Many strategies have been attempted to overcome primary and acquired resistance to ALK inhibitors (10). Two major unmet needs must be addressed to improve the treatment for *ALK*-rearranged NSCLC: (I) to delineate the distinct mechanisms underlying resistance to ALK TKIs so the treatment can be tailored to individual patients, and (II) to develop new ALK inhibitors or design effective combinational strategies with improved activity for both extracranial and intracranial metastases. Both ALK-dependent and independent mechanisms can contribute to the resistance mechanisms to ALK inhibitors, which include the presence of a second-site mutation in the *ALK*-rearranged gene (20–30% of cases), *ALK* amplification, *MET* proto-oncogene amplification, activation of bypass pathways, and histological transformation (10). Although

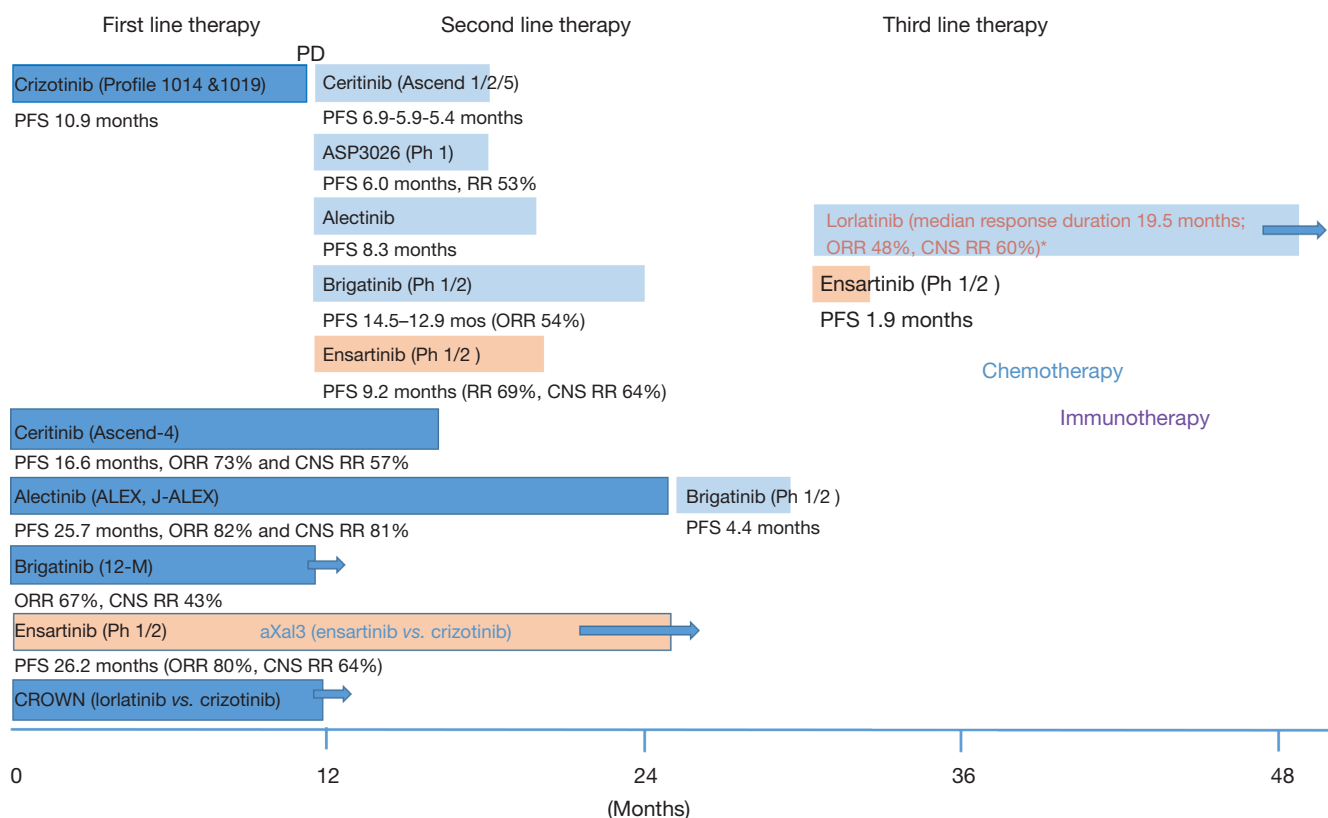


Figure 2 A summary for the current landscape for the treatment of *ALK*-rearranged NSCLC. The activity of ensartinib (beige color) in the phase I/II study is illustrated in the context of first-, second-, or third-line treatment after crizotinib alone or both crizotinib and at least one second generation *ALK* inhibitor. PD, progressive disease; Ph, phase; PFS, progression free survival; ORR, objective response rate; CNS RR, central nervous system response rate. Blue arrow, ongoing study. *US FDA accelerated approval on November 2, 2018.

different resistance mutations may confer variable responses to subsequent *ALK* inhibitor therapy, most second-generation *ALK* inhibitors, such as ceritinib (11), alectinib (12-14), ASP3026 (15), and brigatinib (16-18), have strong efficacy against both wild-type *ALK* gene amplification and secondary mutations in the *ALK* tyrosine kinase domain (such as the gatekeeper mutation L1196M) (15,19). Notably, third-generation *ALK* inhibitor lorlatinib (PF-06463922) has strong activity against the *ALK* G1202R mutation, which is a common cause of resistance against first- and second-generation *ALK* TKIs (20). However, the gain of L1198M mutation after lorlatinib treatment could resensitize *ALK*-rearranged NSCLC tumors to crizotinib (21). Patients with *ALK*-rearranged lung cancer are found to have a high incidence of brain metastasis at the initial diagnosis and after control of systemic disease with crizotinib (22). Disease progression in the central nervous system (CNS) is also common in patients receiving

crizotinib, probably due to its poor brain penetration (23).

Figure 2 summarizes the clinical activity of currently available *ALK* inhibitors. Compared to crizotinib, all second- and third-generation *ALK* inhibitors can overcome specific types of treatment resistance and have better CNS penetration, partially addressing the two unmet needs (24). These new-generation *ALK* TKIs vary in their sensitivity against wild-type and resistant mutations, the activity in the CNS, toxicity profile, and efficacy against drug targets other than *ALK* rearrangements. With the growing number of new-generation *ALK* inhibitors and their rising first-line use, further study is needed to determine the optimal sequence and potential combinations of *ALK* inhibitors.

Leora Horn and colleagues recently presented the results of the first-in-human phase I/II study evaluating the safety and efficacy of ensartinib (X-396) in patients with *ALK*-rearranged NSCLC (25). Ensartinib potently inhibited both wild-type *ALK* and all evaluated *ALK* variants (F1174,

C1156Y, L1196M, S1206R, T1151, and G1202R mutants) with *in vitro* IC₅₀s of <4 nM. Besides ALK, ensartinib also potently inhibits TPM3-TRKA, TRKC and GOPC-ROS1 with an IC₅₀ of <1 nM, and inhibits EphA2, EphA1, EphB1 and c-MET with an IC₅₀ of 1–10 nM. In this phase I/II study, ensartinib was generally well tolerated in the 97 patients tested (i.e., 37 patients in dose escalation and 60 patients in dose expansion cohorts). The majority (92%) of patients had NSCLC. In the dose escalation cohort, there were four patients with head and neck cancer, two with colorectal cancer, and one patient each with small cell lung and breast cancer. The median age was 56 (range: 21–83) years old. Eighty (82%) patients had received at least one prior systemic therapy for advanced disease, including chemotherapy or ALK TKIs, while 58 (60%) patients had ≥2 previous lines of therapy. Thirty-five (36%) patients had brain metastases at baseline. Treatment-related adverse effects (TRAEs) occurred in 83 (86%) patients. The most common TRAEs were rash (56%), nausea (36%), pruritus (28%), vomiting (26%), and fatigue (22%). The frequency and severity of nausea and vomiting were lessened when ensartinib was taken with food. Ensartinib has a different toxicity profile from the other second-generation ALK TKIs, with 23% of patients experiencing grade 3–4 toxicity (primarily rash and pruritus). The prevalence of dermatologic adverse events is consistent with the observation that the concentration of ensartinib was 9.0 times higher in the skin than in the plasma at 12 hours after a single dose of ensartinib. Fourteen patients (14%; 14/97) required at least one dose reduction and fifteen patients (15%; 15/97) required at least one dose interruption due to an ensartinib-related toxicity. The maximum tolerated dose was not reached. The recommended phase II dose was chosen as 225 mg based on the frequency of rash observed at 250 mg without improvement in activity.

Clinical activity was observed in 60 evaluable *ALK*-rearranged patients: the disease control rate was 81.7%, with the overall response rate (ORR) of 60% [95% confidence interval (CI), 47.4–71.4] and 13 (21.7%) patients achieving stable disease. mPFS was 9.2 months. In the *ALK*-rearranged NSCLC patients who received prior crizotinib only, the ORR was 69% and mPFS was 9.0 months. In those *ALK*-rearranged NSCLC patients who were ALK TKI-naïve, ORR was 80% and mPFS was 26.2 months. In patients that received prior crizotinib and a second-generation ALK TKI, the mPFS was 1.9 months (95% CI, 1.7–5.7). In addition, some degree of CNS response was noted, with responses in intracranial metastases in 64% of

cases. *Figure 2* summarizes the clinical efficacy of ensartinib in beige color in first-, second-, and third-line settings. These data suggest that ensartinib has comparable clinical activity to other second generation ALK TKIs.

There are several limitations to the current study. First, this is a single-arm, non-comparative, ongoing phase I/II trial. Cautions should be exercised in the interpretation of the available results. A randomized phase III study, eXalt3 (NCT02767804), comparing ensartinib to crizotinib in advanced ALK-positive, TKI-naïve NSCLC patients, was started in June 2016 and is currently ongoing. Second, further studies are needed to determine the resistance mechanisms to ensartinib and how to integrate its use in the current treatment landscape for patients with advanced *ALK*-rearranged NSCLC.

In conclusion, ensartinib is a unique, potent ALK inhibitor that has promising clinical activity and low toxicity in patients with *ALK*-rearranged NSCLC, most of whom had CNS metastases and had previous ALK-TKI treatment. Further study is needed to determine its role as either an initial or post-resistance therapy in *ALK*-rearranged NSCLC or other types of cancers.

Acknowledgments

Funding: This work was supported by “Novel Treatment Strategies for Adenocarcinomas” (UCD grant #49873) to T Li.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Li T, Ma W, Tian EC. Ensartinib (X-396): what does it add for patients with ALK-rearranged NSCLC. *Chin Clin Oncol* 2019;8(Suppl 1):S4. doi: 10.21037/cco.2018.10.12