



Expanding the portfolio of anaplastic lymphoma kinase inhibitors for anaplastic lymphoma kinase-rearranged lung cancers

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The discovery of molecular targets has led to a paradigm shift in the treatment of patients with lung cancer. Approximately 3% to 7% of the NSCLC patients harbor a rearrangement in the anaplastic lymphoma kinase (*ALK*) gene. The N-terminal portion of *EML4* inverts and fuses to the intracellular, tyrosine kinase domain-containing region of *ALK*, forming the most common *ALK* rearrangement (1). Other, rarer upstream fusion partners for *ALK* (e.g., *KIF5B* and *TFG*) have also been reported in non-small-cell lung cancers. There is substantial evidence that these alterations are events that are acquired early in tumorigenesis. *ALK* rearrangements are commonly found in patients who present with distinct clinicopathological features including younger age, never or former light smoking history, adenocarcinoma histology, and signet ring or acinar subtypes; there is no clear association with race and sex. Even though *ALK* rearrangement is more common in lung adenocarcinoma, and also identified in large cell carcinoma and NSCLC-NOS (not otherwise specified), testing for these fusions should be considered even in patients with squamous cell and mixed histologies, or those with small biopsy samples.

In November 2013, crizotinib, an oral small molecule targeting the *ALK*, *ROS1*, and *MET* tyrosine kinases, received full approval based on an improvement in progression-free survival (PFS) in patients with metastatic *ALK* fusion-positive NSCLC previously treated with one platinum-based chemotherapy regimen (2). Later, in the PROFILE 1,014 trial, crizotinib was shown to be superior to platinum doublet chemotherapy in treatment-

naïve patients with *ALK* fusion-positive NSCLC with a median PFS of 10.9 months (3). The most common adverse events associated with crizotinib were visual disorders, gastrointestinal complaints, and edema. Less common but higher-grade adverse events were elevated aminotransferases, neutropenia, and dyspnea. Interstitial lung disease was a serious and potentially fatal adverse event; however, it is very rare. Overall, crizotinib is tolerated well in the clinic and represented the standard of care for first-line therapy of patients with *ALK*-rearranged lung cancers.

Although advanced *ALK* fusion-positive NSCLC patients have a high initial response to crizotinib, they will ultimately relapse on therapy. Mechanisms of resistance to *ALK* inhibitors can be classified as on-target genomic alterations (*ALK* gene amplification or *ALK* resistance mutations) or off-target mechanisms of resistance (activation of alternative and bypass signaling including the *EGFR*, *MET*, *KRAS*, *KIT* and *IGF1R* pathways). The central nervous system is the first site of progression in approximately a quarter to half of patients receiving crizotinib, partly due to suboptimal CNS penetration. Ultimately, 60% of patients with *ALK* fusion-positive NSCLC will develop brain lesions during the course of their treatments, further highlighting the need for effective, CNS-penetrant therapies for these patients.

Shortly after the initial breakthrough of the identification of the clinical activity of crizotinib, several second generation *ALK* inhibitors demonstrated activity against crizotinib-refractory *ALK*-rearranged NSCLC. Importantly,

these tyrosine kinase inhibitors (alectinib and ceritinib) were active in patients both with and without acquired *ALK* resistance mutations detected in their cancers. This raised the question as to whether first-line crizotinib provided the most potent suppression of the *ALK* pathway. Alectinib and ceritinib displayed preclinical activity against crizotinib-resistance mutations, including both gatekeeper (*ALK* L1196M) and non-gatekeeper substitutions; however, activity against specific mutations varied by drug.

Ceritinib was associated with a post-crizotinib overall response rate (ORR) of 36% and a median PFS of 5.7 months (4), compared with a post-crizotinib ORR in 50% of patients and median PFS of 8.9 months for alectinib (5). From a safety perspective, ceritinib's most common adverse events are nausea, diarrhea, and vomiting, while alectinib's most common adverse events are constipation, fatigue, and peripheral edema; ceritinib was much less tolerable at full dosing in the clinic, however.

Brigatinib (AP26113) is a next-generation *ALK* inhibitor with distinct features. It has *in vitro* kinase activity against ROS1 with similar potency than *ALK*; lower potency against T790M-mutant EGFR, FTL3 and IGF-1R was also described. Brigatinib had 10-fold greater potency and a 10-fold broader therapeutic index than crizotinib *in vivo* against *ALK*. Thus, it represents a potent *ALK* inhibitor, with substantial activity against many more *ALK* secondary resistance mutations when compared to crizotinib, ceritinib, and alectinib, including improved *in vitro* activity against the *ALK* solvent front substitution G1202R (6).

During the clinical development of brigatinib, treatment-related pulmonary adverse events such as pneumonia, dyspnea, and hypoxia were of concern. A subset of these pulmonary events was observed to occur within 7 days of treatment initiation or reinitiation following a prolonged period of dose interruption, and was less frequent with lower starting doses. Most events were managed with dose interruption. The phase I dose-escalation phase of brigatinib identified a recommended phase two dose of 180 mg daily. To circumvent the pulmonary toxicity, phase II component of the study was divided into five histologically and molecularly defined cohorts where three oral once-daily regimens were assessed: 90, 180 and 180 mg with a 7-day lead-in at 90 mg daily. The latter cohort showed promising activity with acceptable safety; no pulmonary events were reported (7).

Kim and colleagues conducted a randomized phase II trial—the ALTA (*ALK* in Lung Cancer Trial of AP26113) trial—that included 222 patients who were randomized

to oral brigatinib 90 mg once daily (arm A) or 180 mg once daily following a 7-day lead-in at 90 mg once daily (arm B) (8). A higher ORR (54% *vs.* 42%) was observed in the latter, with a median follow-up of 8 months. Remarkably, an unprecedented PFS of more than a year was achieved in this *ALK* inhibitor-pretreated population: median PFS was 9.2 months (95% CI, 7.4–15.6) in arm A *vs.* 12.9 months (95% CI, 11.1 to not reached) in arm B. The 1-year probability of overall survival was 80% in arm B. 153 patients (69%) had brain metastasis at baseline and 44 patients had measurable intracranial disease. Among the patients with measurable disease, the intracranial ORR was 42% in arm A and 67% in arm B. Response rates were similar between all patients with measurable baseline brain metastases (treated and untreated) and those with active brain metastases (defined as brain metastases without prior radiotherapy or with investigator-assessed progression after prior radiotherapy).

The most common grade 3 or 4 treatment-related adverse events were hypertension (6%), increased blood creatine phosphokinase (9%), pneumonia (5%) and increased lipase (3%) in arm B. The pulmonary adverse events with early onset were managed with dose interruption and successful reintroduction of brigatinib in 6 of 14 patients, and one patient continued treatment with resolution of symptoms after dose reduction to 60 mg once daily without needing interruption. Older age and a shorter interval (less than 7 days) between the last crizotinib dose and the first brigatinib dose were significantly associated, in a multivariate analysis, with an increased frequency of pulmonary events.

Although the trial was not designed to compare arms statistically, efficacy outcomes favored the higher dose, most notably in relation to PFS and intracranial response. Besides establishing the right dose, ALTA trial demonstrated brigatinib substantial efficacy with high and durable response rates. Of note, one patient in arm B harbored a recalcitrant *ALK* G1202R mutation detected from tumor tissue at baseline, and had a confirmed partial response. Patients receiving brigatinib should be monitored for new or worsening respiratory symptoms, hypertension, bradycardia, visual symptoms, and elevations in amylase, lipase, blood glucose and creatine phosphokinase. In May of 2015, the U.S. Food and Drug Administration granted accelerated approval to brigatinib for the treatment of patients with metastatic *ALK* fusion-positive NSCLC who progressed on or were intolerant of crizotinib.

Beyond brigatinib, there is an ongoing debate regarding

the best second-line strategy after progression on crizotinib. There may be potential advantages of brigatinib and alectinib over ceritinib after crizotinib progression, including differences in PFS, intracranial activity, and a more favorable safety profile. In preclinical models, brigatinib had broader secondary *ALK* mutation coverage than ceritinib or alectinib. Importantly, 20% of patients treated with second-generation *ALK* inhibitors become resistant due to secondary *ALK* mutations, and about 50% of patients treated with second-generation *ALK* inhibitors become resistant due to secondary *ALK* mutations.

The treatment landscape of advanced *ALK*-rearranged NSCLC has quickly evolved based on the results of second-generation inhibitors tested in the first-line setting. In the global ASCEND-4 trial, ceritinib demonstrated a statistically significant improvement in PFS of versus pemetrexed-platinum chemotherapy including maintenance pemetrexed in untreated patients with *ALK*-rearranged NSCLC (9). Based on this data, in May of 2017, the FDA approved the expanded use of ceritinib to include first-line treatment; however, there were two main caveats including drug intolerance at full doses, as mentioned earlier, and the absence of an ideal comparator which should have been crizotinib.

The most awaited global ALEX trial has been recently published to set a turning point. With an outstanding hazard ratio for disease progression of 0.47 (95% CI, 0.34–0.65), alectinib was associated with longer PFS and lower toxicity than crizotinib and showed activity against CNS disease in patients with *ALK* fusion-positive treatment-naïve NSCLC. 18 patients (12%) in the alectinib group progressed intracranially, as compared with 68 patients (45%) in the crizotinib group (10). Alectinib is highly CNS penetrant and is not a substrate of P-glycoprotein efflux transporter. Earlier on, based as well on the J-ALEX study presented prior to ALEX (11), the FDA granted alectinib breakthrough therapy designation for the treatment of patients with advanced *ALK* fusion-positive NSCLC who have not received prior treatment with an *ALK* inhibitor.

In the first-line setting, brigatinib may, similar to alectinib and ceritinib, offer an increased duration of disease control compared to crizotinib, secondary to delaying the onset of resistance, and possibly improved intracranial disease control. A pivotal phase III study (ALTA-1L) is currently underway (NCT02737501) to investigate the activity of the drug in treatment-naïve patients. There are other *ALK* inhibitors in development such as entrectinib, lorlatinib, and TPX-0005. Lorlatinib is a third generation

ALK inhibitor which has also received breakthrough therapy designation for patients with previously treated with one or more *ALK* inhibitors. An ongoing phase 3 trial, CROWN (NCT03052608), is comparing lorlatinib to crizotinib in the first line setting. Like brigatinib, the drug has improved coverage of *ALK* resistance mutations, including *ALK* G1202R, compared to ceritinib and alectinib.

In conclusion, the algorithm for the treatment of *ALK*-rearranged NSCLC continues to change rapidly. Four inhibitors are already approved by one or more regulatory agencies, and data with both existing TKIs tested in new settings, and novel TKIs continue to emerge. The main doubt remains on how to best sequence TKIs, although data on first-line use of the later-generation *ALK* inhibitors such as alectinib will probably lead to a fundamental regulatory approval soon. To date, we know less about the mechanisms underlying the resistance to first-line alectinib, and this data should continue to be explored. One might foresee an increase in frequency of on-target resistance such as the G1202R substitution, or off-target resistance. Ultimately, the choice of next-generation *ALK* inhibitor will need to be individualized for each patient. A molecularly driven personalized approach will be of utmost importance with the use of more potent TKIs. Tissue biopsies or cfDNA analysis at baseline and at progression are poised to potentially provide information needed to choose the next best weapon from the current arsenal of *ALK* inhibitors at our disposal.

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appropriately investigated and resolved.

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