Moving more potent and less toxic options to the frontline in the management of advanced lung cancer

Xiuning Le, Deepa Rangachari, Daniel B. Costa

Division of Hematology/Oncology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, US

Correspondence to: Daniel B. Costa, MD, PhD. 330 Brookline Avenue – Shapiro 9, Boston MA 02115, USA. Email: dbcosta@bidmc.harvard.edu.

Introduction

The most common primary lung cancers can be divided into small cell lung cancer and non-small cell lung cancer (NSCLC)—the latter compromised predominantly of adenocarcinoma and squamous cell carcinoma histologies.

In the last fifteen years, somatic genomic analysis of NSCLC has identified critical driver oncogenes in a subset of these tumors (1). In turn, the identification and delineation of these oncogenic events has led to the successful development of nearly ten different oral targeted therapies now approved for use in routine clinical practice for advanced NSCLCs (2-6). These are directed against: mutations in the epidermal growth factor receptor (*EGFR*) (7-10), anaplastic lymphoma kinase (*ALK*) (11-14) gene rearrangements, ROS proto-oncogene 1 (*ROS1*) (15) gene rearrangements, and B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) mutations (16) (*Figure 1*). These well vetted targeted therapies have demonstrated superior and more durable clinical outcomes and quality of life in patients with genotype-defined advanced NSCLC, as compared to the efficacy and toxicity profiles associated with cytotoxic chemotherapies in this disease. Ongoing research also shows promising potential for use of kinase inhibitors for other putative driver mutations in NSCLC (17).

Immunotherapy can also be efficacious in solid tumors with high somatic mutational burden, including NSCLC (18-20). The most promising examples include multiple anti-programmed cell death protein 1 (PD-1)/anti-programmed death-ligand 1 (PD-L1) immune checkpoint inhibitors. Both types of immune checkpoint inhibitors have been demonstrated in rigorous, phase III studies to improve objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) in certain patients with advanced NSCLC when compared to standard cytotoxic chemotherapy (18,21,22). Anti-PD-1/PD-L1 antibodies are now used as both first and second line therapies for advanced NSCLC, depending on the tumor's PD-L1 tumor proportion score (TPS) as assessed by immunohistochemistry (IHC) (*Figure 1*).

Thus, the initial evaluation and management of advanced NSCLC and use of biomarkers for therapeutic stratification has evolved substantially over the past decade plus and with progressive and important improvements in clinical outcomes and quality of life for patients living with this disease. In our own cancer center, we adhere to the diagnostic and treatment pathway described in *Figure 1* for advanced NSCLCs. This scheme incorporates evolving worldwide drug approval patterns and evidence-/guideline-based treatment strategies (23).

ALK and the development of the first approved ALK inhibitor crizotinib

The *ALK* gene is located on chromosome 2p in humans (24). The first *ALK* rearrangements identified in NSCLC were small inversions within chromosome 2p leading to the

Histology	Biomarkers	First line therapy	Second line therapy	Third line therapy
Squamous cell carcinoma	PD-L1 IHC (22C3 clone) → TPS≥50%	Pembrolizumab	Platinum-based doublet chemotherapy +/- necitimumab	Docetaxel +/- ramucirumab Afatinib Best supportive care
	→ TPS<50%	Platinum-based doublet chemotherapy +/- necitimumab	Pembrolizumab (PD-L1>1%) Nivolumab Atezolizumab	Docetaxel +/- ramucirumab Afatinib Best supportive care
Adenocarcinoma	*EGFR mut.* →	Erlotinib/gefitinib/afatinib	Osimertinib (EGFR-T790M)	Chemotherapy or anti-PD-1/PD-L1
	ALK rearr. →	Crizotinib/alectinib/ceritinib	Alectinib/ceritinib/brigatinib	
	ROS1 rearr. →	Crizotinib	Chemo. or anti-PD-1/PD-L1	or anti-PD-1/PD-L1
	BRAF-V600E →	Dabrafenib + trametinib	Chemo. or anti-PD-1/PD-L1	Best supportive care
	PD-L1 IHC (22C3 clone) → TPS ≥50%	Pembrolizumab or Platinum-pemetrexed + pembrolizumab	Platinum-pemetrexed +/- bevacizumab Docetaxel +/-ramucirumab	Docetaxel+/-ramucirumab Best supportive care
	→ TPS <50%	Platinum-pemetrexed or Platinum-pemetrexed + pembrolizumab	Pembrolizumab (PD-L1>1%) Nivolumab Atezolizumab Docetaxel+/-ramucirumab	Docetaxel+/-ramucirumab Best supportive care

Figure 1 Schema of management of advanced non-small-cell lung cancer (NSCLC) based on histology, tumor biomarkers and line of therapy. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1; TPS, tumor proportion score; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; IHC, immunohistochemistry.

formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK*. These fusion translocations were noted to be oncogenic in preclinical models (5,25,26). By 2007, *ALK* rearrangements were established as *bona fide* oncogenic drivers in NSCLC and potential targets for development of tyrosine kinase inhibitors (TKIs).

Crizotinib (formerly PF-02341066, Pfizer, New York, USA) is a small molecule TKI that was originally developed to target MET proto-oncogene, receptor tyrosine kinase (MET) prior to the discovery of *ALK* rearrangements in NSCLC (27). It is now known to be multi-targeted TKI, with efficacy against *MET*, *ALK*, and *ROS1* kinase domains (28). The first-in-human clinical trial of crizotinib commenced before the seminal report of *ALK*-rearranged NSCLC and allowed the first glimpse of activity in patients whose tumors harbor *ALK* rearrangements. This clinical trial (NCT00585195, also known as PROFILE_1001) established crizotinib at a dose of 250 mg orally twice daily for the treatment of *ALK*-rearranged NSCLC. Crizotinib has adequate tolerability in most patients, with nausea, diarrhea, and mild visual disturbance as the most common adverse events. Impressively, in the initial 82 patients with

ALK rearrangements treated in this study, the reported ORR was 57% (11,29). Based on rapid and sustained responses, crizotinib received accelerated approval for advanced *ALK*-rearranged NSCLC in August 2011. By 2013, a randomized trial (PROFILE_1007, NCT00932893) in the second line setting established improved ORR and PFS in this subset of patients receiving crizotinib as compared to cytotoxic chemotherapy (30). PROFILE_1014 (NCT01154140) subsequently established crizotinib as the standard of care for first line palliative therapy in *ALK*-rearranged advanced NSCLC. In this trial, 343 patients were randomized to receive crizotinib or conventional platinum doublet chemotherapy in the first line setting (31). ORR and PFS were superior for crizotinib *vs.* platinum doublet, with a median PFS of 10.9 *vs.* 7.0 months, respectively. These results have firmly established the use of crizotinib as first line therapy for TKI-naïve advanced *ALK*-rearranged NSCLC since 2014.

Acquired resistance to crizotinib and development of next generation ALK inhibitors

Despite the significant clinical success with crizotinib in

the advanced disease setting, acquired resistance occurs almost inevitably within the initial year of use. Our cancer center's own longitudinal cohort established that <10% of cases reach three or more years of crizotinib monotherapy without the identification of tumor progression (32). The two most common mechanisms that lead to disease progression in crizotinib-treated tumors include: (I) re-activation of ALK signaling by acquired secondary mutations in the *ALK* kinase domain or (II) pharmacokinetic escape - usually manifested as central nervous system (CNS) disease progression (33-37). To address these clinical challenges, a variety of potent ALK TKIs are under development. To date, three next generation ALK inhibitors—ceritinib, brigatinib, and alectinib—have gained regulatory approval (*Figure 1*).

Ceritinib (formerly LDK378, Novartis, Basel, Switzerland) was developed as a TKI with preclinical activity against ALK and ROS1 fusion proteins (12,38-40). Ceritinib is about 10 times as potent as crizotinib and is able to inhibit many crizotinib-resistant ALK mutants, including the gatekeeper ALK-L1196M mutant (38). The phase I clinical trial of ceritinib (ASCEND, NCT01283516) highlighted that gastrointestinal adverse events (nausea, diarrhea, and vomiting) established the maximum tolerated dose (MTD) (12). Nevertheless, the efficacy of ceritinib was established with an ORR of 56% in previously treated patients and 62% in TKI-naïve *ALK*-rearranged advanced NSCLCs (12). Most importantly, responses were seen in tumors that harbored *ALK* mutations (such as L1196M, 1151Tins, S1206Y and G1269A), lacked known mechanisms of resistance to crizotinib, and in those patients with brain metastases (12,41,42). Ceritinib received regulatory approval for use in crizotinib-resistant or intolerant patients in 2014.

Brigatinib (formerly AP26113, Ariad/Takeda, Deerfield, USA) is another potent ALK TKI with a broader spectrum of activity against ALK kinase domain mutants. Clinical data from the brigatinib phase II ALTA clinical trial (NCT02094573) showed ORRs of 45% and 54% for doses of 90 and 180 mg daily, respectively (14). The most noticeable adverse event associated with brigatinib is early pulmonary toxicity. Subsequent study schema have therefore incorporated a dose escalation phase with a starting dose of 90 mg orally daily for 7 days, then increasing to 180 mg daily. Outside of pulmonary concerns, the drug is otherwise well tolerated and with serious gastrointestinal side effects and headaches occurring in a minority of cases (14). Brigatinib received regulatory approval for use in crizotinib-resistant or intolerant patients in 2017.

Alectinib (formerly CH5424802, Roche/Chugai, Basel, Switzerland/Tokyo, Japan) is a selective ALK inhibitor. Similar to other next generation ALK TKIs, it has greater potency and higher CNS penetration than crizotinib and is active against ALK fusion proteins with ALK kinase domain mutants (13,43). In the initial Japanese phase I/II study (AF-001JP), alectinib was highly active (44). The drug was extremely well tolerated with minimal serious adverse events. Constipation, fatigue and peripheral edema were the most common adverse events. These findings led to the approval of alectinib in Japan in July 2014. Worldwide, alectinib is prescribed at 600 mg twice daily and was approved in 2015 following results from two single-arm phase-II trials [global NP28673 (NCT01801111) and the North American NP28761 (NCT01871805) studies] in patients with disease progression on or intolerance to crizotinib. These studies confirmed ORRs of approximately 50% or higher for systemic and intracranial sites of tumor burden (13,45).

J-ALEX and ALEX clinical trials confirm superiority of alectinib when compared to crizotinib

Given the promising efficacy and tolerability of alectinib in the AF-001JP study, a phase III trial (J-ALEX, JapicCTI-132316) was designed to directly compare the efficacy and safety of alectinib 300 mg twice daily versus crizotinib 250 mg twice daily in Japanese patients with advanced *ALK*-rearranged NSCLC (46). Between November 2013 and August 2015, 207 patients were enrolled and randomly assigned to receive alectinib (n=103) or crizotinib (n=104). At the second planned interim analysis, alectinib met the trials primary endpoint of superiority in PFS [hazard ratio (HR) of 0.34 (99.7% CI: 0.17–0.71), P<0.0001]. After about 12 months of follow-up in each of the treatment groups, median PFS had not yet been reached with alectinib (95% CI: 20.3 to not reached) and was 10.2 months (95% CI: 8.2–12.0 months) with crizotinib. Furthermore, alectinib showed better tolerability with less serious adverse events and less frequent dose interruptions as compared to crizotinib.

J-ALEX's data was further supported by the multi-center international ALEX trial (NCT02075840), comparing alectinib 600 mg twice daily versus crizotinib 250 mg twice daily in TKI-naïve, *ALK*-rearranged advanced NSCLC (47). Again, the median PFS (primary outcome) with alectinib was not reached (95% CI: 17.7 months to not reached) as compared with 11.1 months (95% CI: 9.1–13.1 months)
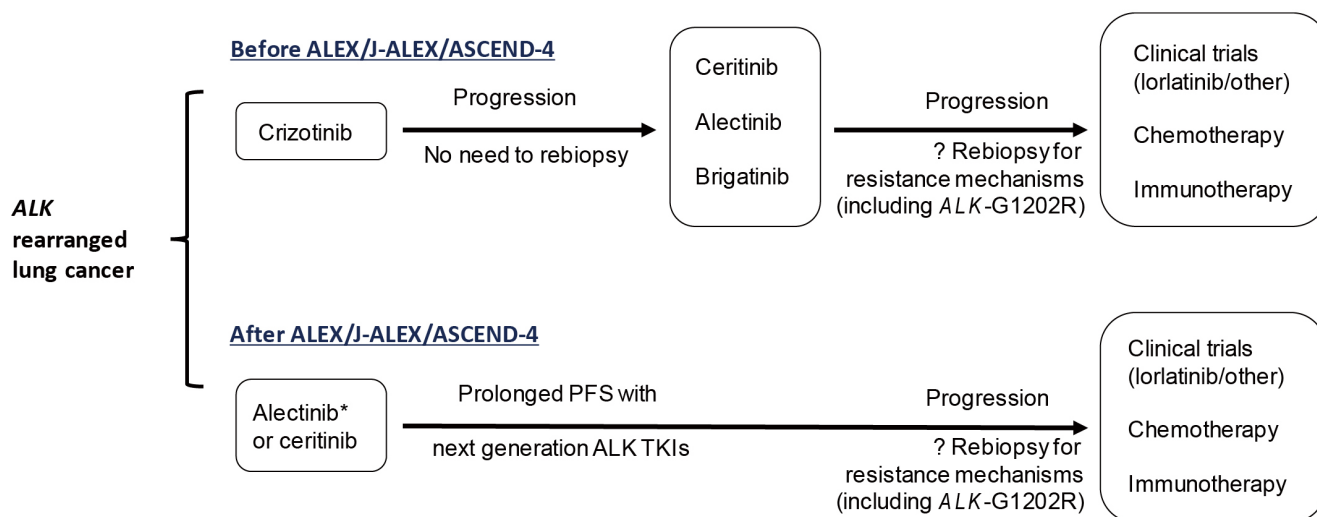
Figure 2 Management of advanced ALK rearranged lung cancer before and after the J-ALEX, ALEX and ASCEND-4 trials. *, for countries and areas that alectinib is not approved or available, crizotinib or ceritinib are still the recommended first line treatment.

with crizotinib (HR of 0.47 95% CI: 0.34–0.65; P<0.001). These two studies were the first trials to compare head-to-head the efficacy and safety of a next generation ALK inhibitor to crizotinib (46,47). The trials convincingly show that alectinib is superior in prolonging median PFS with lesser toxicity than crizotinib. Although with relatively short follow up, the OS of first line alectinib to date remains non-inferior to crizotinib (46,47).

Given the significant impact of intracranial disease burden on the long-term outcomes of patients with *ALK*-rearranged advanced NSCLC, it is important to note that both trials evaluated alectinib's efficacy in patients with CNS metastases. The J-ALEX trial had a pre-planned exploratory analysis of cumulative incidence of CNS disease with competing events of death, CNS progression, and non-CNS progression. The results indicate that alectinib reduced the risk of progression in both non-CNS and CNS lesions compared with crizotinib (46). For the ALEX trial, an independent analysis conducted solely for assessment of CNS disease showed that the time to CNS progression was significantly longer with alectinib than with crizotinib (cause-specific HR of 0.16, 95% CI: 0.10–0.28). The rate of events (CNS progression) was only 12% with alectinib *vs.* 45% with crizotinib during the duration of follow-up (47). The intracranial ORR in the alectinib group was also higher than in the crizotinib group, thus establishing alectinib as an ALK TKI with superior ability to control existing and delay subsequent intracranial disease, something that

crizotinib had been previously shown to do when compared to platinum-based chemotherapy (34,47,48).

Prolonged durations of PFS in the TKI-naïve setting have also been reported with the use of ceritinib within the ASCEND-4 trial (NCT01828099, ceritinib versus platinum doublet) (42). Median PFS was 16.6 months (95% CI: 12.6–27.2 months) with ceritinib at a starting dose of 750 mg daily. Common dose-limiting toxicities include: diarrhea (85% of cases), nausea (69% of cases), and vomiting (66% cases). Ceritinib gained additional approval for first line use in *ALK* rearranged advanced NSCLC in 2017.

Ongoing trials, future directions and conclusions

Outcomes from the pivotal J-ALEX and ALEX trials have revamped the paradigm for first line management of advanced *ALK*-rearranged NSCLCs. In moving more potent next generation ALK TKIs to the frontline setting, superior clinical efficacy—particularly with regards to intracranial disease—along with improved tolerability have been hallmarks of the continued advancement and drug development in this subset of advanced lung cancers (*Figure 2*). In parallel to these developments in the *ALK*-directed arena, outcomes from the ongoing FL-AURA trial (NCT02296125) comparing the 3rd generation EGFR TKI osimertinib to the 1st generation EGFR TKIs erlotinib and gefitinib in the first line setting may well change the benchmark for initial management of *EGFR*-mutated

NSCLC, as well. This trial has completed accrual, and results are awaited later this year.

The main limitation of next generation ALK TKIs (alectinib, ceritinib, brigatinib, and other ALK TKIs) is the inevitable development of acquired resistance—particularly through selection of clones with *ALK* kinase domain mutations (49). More than half of alectinib- and ceritinib-resistant tumors develop the *ALK*-G1202R mutation which confers a high degree of cross-resistance to all other approved ALK TKIs (37,49). However, recent investigation of the more potent TKI lorlatinib and other in-development ALK inhibitors suggest that this resistance profile may be overcome (49,50). The completed phase I/II clinical trial of lorlatinib (NCT01970865) is undergoing evaluation by regulatory agencies, and the drug may be soon approved for patients following failure of one or more prior ALK TKIs (51). Another ongoing trial is evaluating lorlatinib *vs.* crizotinib in the TKI-naive first line setting (NCT03052608). It is possible that with early use of more potent ALK inhibitors (i.e., lorlatinib), patterns of ALK TKI resistance may become dominated by bypass pathway upregulation rather than ALK kinase domain resistance mutations (49). Therefore, combination strategies may be required to prevent or overcome this type of resistance (33,37,52).

ALK-rearranged lung cancer has been exemplary in the field of targeted cancer therapy in many ways. In the span of 4 years between 2007 and 2011, *EML4-ALK* went from a just discovered driver oncogene in NSCLC to a readily actionable target with approval of crizotinib, a highly effective and tolerable therapy. Next, evolution in the understanding of ALK-dependent and pharmacokinetic mechanisms of resistance to crizotinib have paved the way for the clinical development of next generation ALK TKIs ceritinib [2014], alectinib [2015], and brigatinib [2017]. Most recently, the J-ALEX and ALEX trials have established that the more potent, less toxic next generation ALK TKI alectinib should now supersede crizotinib as the evidence-based standard for first line palliative therapy in TKI-naïve, advanced *ALK*-rearranged NSCLC (*Figure 2*) in countries that grant regulatory approval for this indication.

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Footnote

Conflicts of Interest: DB Costa has received consulting fees

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