Editorial

Clinical development and approval of second generation ALK inhibitors for *ALK* rearranged lung cancer

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Lung cancers are heterogeneous tumors often characterized by mutations in oncogenes and tumor suppressor genes. Anaplastic lymphoma kinase (*ALK*) genomic aberrations were first identified in non-small cell lung cancer (NSCLC) in 2007 (1). We now know that a substantial fraction (approximately 5%) of all NSCLCs harbor rearrangements between *ALK* and fusion partners (such as *EML4*, *TFG*, *KIF5B*, *KLC1* among others). Although ALK is not an important signal for untransformed lung epithelial cells (hence the low to undetectable expression of ALK in normal lung tissues), deranged ALK signaling is a main driver of *ALK* rearranged NSCLC (2) and inhibition of ALK is often accompanied by deactivation of intracellular proliferation cascades with induction of apoptosis. The latter susceptibility has been exploited as a therapeutic target in NSCLC with the successful development of ALK inhibitors.

The "oldest" tyrosine kinase inhibitor (TKI) to enter the clinical domain against *ALK* rearranged NSCLC was crizotinib [Pfizer, Inc, New York, NY (USA)]; a multitargeted TKI with preclinical activity against ALK, hepatocyte growth factor receptor (MET) and c-ros oncogene 1 (ROS1). The original 2010 publication of the phase I clinical trial of crizotinib (at a recommended starting dose of 250 mg twice daily) already demonstrated impressive anti-tumor activity of this TKI in *ALK* rearranged NSCLC: a response rate (RR) that surpassed 55%, median progression-free survival (PFS) that exceed 8 months and prolonged overall survival (OS) times for heavily-pretreated patients (3). Near-identical results were demonstrated in the confirmatory phase II trial (PROFILE 1005). The second line randomized phase III trial (PROFILE 1007, which compared crizotinib to docetaxel or pemetrexed), reported in 2013, unequivocally confirmed that crizotinib led to improved outcomes when compared to standard cytotoxic chemotherapies in RR (65% versus 20%), PFS (7.7 versus 3.0 months) and quality of life parameters (4). The combined results of crizotinib's development program led to the Food and Drug Administration (FDA) approval of crizotinib for metastatic NSCLCs that are positive for *ALK* rearrangements; initially by accelerated approval on August 26th 2011 with subsequent regular approval on November 20th 2013.

The advances brought forth by crizotinib not only validated ALK as an important target for NSCLC but also highlighted some of the limitations of this first generation ALK TKI. Acquired resistance to crizotinib therapy can come about through multiple biological mechanisms (2): (I) kinase ALK mutations—including L1196M (the gatekeeper position of ALK), 1151Tins, C1156Y, F1174L, and G1202R among others—that shift inhibitory curves and have been identified in over a third of crizotinib-resistant tumors; (II) activation of other oncogenes [such as the epidermal growth factor receptor (EGFR)] that create bypass signaling cascades; and (II) pharmacokinetic fallacies of the drug [either due to its achievable systemic levels or poor central nervous system (CNS) penetration]. These limitations have spawned the development of "second generation" ALK TKIs that were designed to have more potent activity against ALK and ALK kinase mutants in the context of *ALK* rearranged NSCLC. The most advanced second generation ALK TKIs that recently have graduated clinical development include ceritinib and alectinib.

Ceritinib, previously known as LDK378 (Novartis Pharmaceuticals), was developed as an oral ATP-competitive

multitargeted TKI with activity against ALK and ROS1 (2). In preclinical models, ceritinib was more than 10 times as potent as the first generation ALK TKI crizotinib and was able to inhibit a great majority of cells with *ALK* crizotinib-resistant mutations (2,5). The first-in-human phase I clinical trial of ceritinib was published in 2014 and focused exclusively on patients with *ALK* rearranged NSCLC (5). In this trial, the presence of *ALK* rearrangements was determined using the FDA-approved Vysis *ALK* break-apart fluorescence in-situ hybridization (FISH) probe (Abbott Molecular, Inc.) used in the PROFILE crizotinib trials. Out of the initial 130 cancer patients treated with ceritinib, 68% had received prior crizotinib therapy and therefore the trial was mostly targeted for a cohort of *ALK* rearranged NSCLCs with acquired resistance to crizotinib (5). The maximum tolerated dose (MTD) of ceritinib was achieved at a dose of 750 mg daily, which led to significant nausea, diarrhea and vomiting; and a majority (62%) of patients required at least one dose reduction (5). The efficacy of ceritinib was astounding with an overall RR of 56% and PFS of 6.9 months among patients previously treated with crizotinib; and RR of 62% and PFS of 10.4 months for crizotinib-naïve *ALK* rearranged NSCLCs (5). Responses were seen in tumors that harbored *ALK* mutations (such as L1196M, 1151Tins, S1206Y and G1269A) and in brain metastases (5). Based on the aforementioned trial, on April 29th 2014 the FDA granted accelerated approval for ceritinib for the treatment of patients with *ALK* rearranged metastatic NSCLC with disease progression on crizotinib or who are intolerant to crizotinib; validating continued ALK inhibition as a clinical strategy for *ALK* rearranged tumors. The other second generation ALK TKI with proven efficacy in *ALK* rearranged NSCLC is alectinib (formerly CH5424802, Roche/Chugai Pharmaceutical Co. Ltd.); an ALK TKI without activity against ROS1 or MET (6). The initial phase I-II trial of the compound found that the MTD was 300 mg twice daily in Japanese patients with *ALK* rearranged NSCLC, and 93.5% of the 46 patients receiving this dose achieved an objective response (6) with responses seen in brain metastases. The Japanese ministry of health approved alectinib for the treatment advanced *ALK* rearranged NSCLC on July 4th 2014 and the drug has been granted breakthrough therapy designation by the FDA as European/American trials in patients who failed crizotinib mature.

The fast-paced development of precision therapies for *ALK* rearranged NSCLC has culminated with the approval of multiple ALK inhibitors within the last 5 years. Second generation ALK TKIs (ceritinib and alectinib) may add significant palliative benefits to patients who have progressed on crizotinib; and they are now undergoing head-to-head comparison in the first line treatment of ALK TKI-naïve NSCLCs. However, both first and second generation ALK TKIs as monotherapies are unable to provide lasting control for *ALK* rearranged tumors. For ceritinib, emerging data shows that *ALK*-G1202R and F1174V/C are ceritinib-resistant mutations found in re-biopsy specimens (7) and the median PFS for most patients does not exceed 7 months (5,7). It is likely that further *ALK* mutations, oncogene bypass signaling and pharmacokinetic escape in sanctuary sites (such as the CNS) will be responsible for acquired resistance to crizotinib, ceritinib and alectinib when given in sequence. To truly maximize precision therapies against *ALK* rearranged NSCLC, the academic and pharmaceutical enterprises will need to develop even more potent ALK TKIs (such is the case of PF-06463922 that was designed as a potent ALK/ROS1 TKI with increased CNS penetration) and design clinical trials combining ALK-targeted with other (different TKIs, cytotoxic agents or immunomodulators) therapies.

ALK rearranged NSCLC has come a long way in the in the last decade; from and unknown entity to now the most successful example of precision therapies for epithelial cancers. Most patients with a new diagnosis of advanced *ALK* rearranged NSCLC in 2014 can expect to receive multiple lines of ALK TKIs and can anticipate a median OS that exceeds 2 years. In addition, some of the current ALK TKIs are multitargeted and can also benefit tumors driven by ROS1 rearrangements or *MET* amplification (2). The next decade of research milestones for *ALK* rearranged tumors will need to address current unmet clinical needs; which include: the role of ALK TKIs in the management of earlier stages (I-III) of NSCLC, the need for improved management of CNS disease and the requisite for treatment strategies that can delay or overcome acquired resistance to first and second generation ALK inhibitors.

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