Editorial

Crizotinib as first line therapy for advanced *ALK*-positive non-small cell lung cancers

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The field of targeted therapeutic development has been propelled forward by remarkable advances in the understanding of driver mutations, particularly in non-small cell lung cancer (NSCLC). Our initial understanding of the importance of driver mutations developed from the discovery of somatic oncogenic epidermal growth factor receptor (EGFR) mutations, which sensitize tumors to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib (1), erlotinib (2), and afatinib (3). Anaplastic lymphoma kinase (*ALK*) gene rearrangements act as a distinct oncogenic driver in about 4% of NSCLC tumors (4). Testing of metastatic NSCLC adenocarcinomas to determine if they are "*ALK*-positive" has become the standard of care, because these tumors respond well to *ALK* inhibitors such as crizotinib, an orally available TKI. Crizotinib induced remarkable responses in patients with *ALK* positive NSCLCs in phase I and II trials (5), and appeared to improve survival of these patients in a retrospective analysis (6). A second line phase III study subsequently showed that crizotinib was superior to both pemetrexed and docetaxel as standard chemotherapy (7).

In the PROFILE 1014 trial published by Solomon *et al*. (8), the investigators examined the effect of crizotinib compared with standard platinum-based doublet chemotherapy as first line treatment in patients with advanced *ALK*-positive NSCLC. A total of 343 patients with untreated advanced *ALK*-positive non-squamous NSCLC were randomized to receive either crizotinib at 250 mg BID or intravenous (IV) chemotherapy with either cisplatin (75 mg/m^2) or carboplatin (AUC 5 to 6) plus pemetrexed (500 mg/m^2) every three weeks for up to six cycles. Of note, no pemetrexed maintenance therapy was administered. Patients randomized to the chemotherapy group had the opportunity to crossover to crizotinib upon progression, and patients randomized to the crizotinib group were allowed to continue on crizotinib upon progression if deemed by investigators that they may still derive benefit from continuation. The primary endpoint was progression free survival (PFS), with secondary endpoints including objective response rate, overall survival, safety, and patient-reported outcomes. The enrolled population consisted of mostly younger patients (median age 52-54), 62-65% non-smokers, and adenocarcinoma histology, and approximately a quarter of patients on each arm had previously treated brain metastases.

The study achieved its primary endpoint, demonstrating a significant improvement in PFS in the crizotinib arm compared to the standard chemotherapy arm [median, 10.9 *vs*. 7.0 months; hazard ratio (HR) for progression or death with crizotinib =0.45; 95% confidence interval (CI): 0.35 to 0.60; P<0.001]. The objective response rates were 74% for crizotinib and 45% for chemotherapy (P<0.001), with disease control rates of 95% for the crizotinib arm and 88% for the chemotherapy arm. There was no statistically significant difference for overall survival, although the median overall survival was not reached in either group (HR for death with crizotinib =0.82; 95% CI: 0.54-1.26; P=0.36). The probability of 1-year survival was 84% (95% CI: 77-89%) in the crizotinib arm and 79% (95% CI: 71-84%) in the chemotherapy arm. Of note, 70% of the patients in the chemotherapy group crossed over to the crizotinib arm.

The treatments were in general well tolerated, and there was overall good treatment exposure. The median duration of treatment was 10.9 months for crizotinib, and

4.1 months (median of six cycles of chemotherapy started) for the chemotherapy group. Most adverse events in the two treatment groups were grade 1 or 2, with vision disorders, diarrhea, and edema being the most common adverse events in the crizotinib arm, and fatigue, nausea, vomiting, and decreased appetite in the chemotherapy arm. In addition, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in global quality of life when compared to standard chemotherapy.

The results of the PROFILE 1014 study establish crizotinib as a standard frontline therapy for patients with advanced *ALK*-positive NSCLC, based on the superior response rate and improved progression free survival compared to standard chemotherapy. One criticism of this study is that continuation maintenance pemetrexed was not part of the study design, because the overall survival benefit of the PARAMOUNT study (9) was reported after the study was underway. Inclusion of maintenance pemetrexed may have equalized the PFS differential, but also may have improved the overall survival of both groups, which was not different presumably due to crossover either on trial or through treatment with crizotinib or other ALK inhibitors post-study. Even without maintenance pemetrexed, the median overall survivals for both arms were not reached but appear to exceed 20 months, which is numerically better than historical rates in any other first line trials of unselected patients with advanced NSCLC and suggests that the sequential use of both therapies helps patients survive longer overall. Practically speaking, patients with advanced *ALK*-positive NSCLC should receive both crizotinib and chemotherapies during their course of care. Because a primary goal of treatment in metastatic setting is to improve disease related symptoms, the superior response rates, longer duration of response and improvement in quality of life over chemotherapy justify the routine use of crizotinib prior to chemotherapy.

In clinical practice, the selection of initial therapy is likely to depend heavily on available diagnostic information, patient condition including disease burden and underlying comorbidities, and anticipated tolerance of side effects. Since it takes time to obtain ALK testing results and drug, often 2-4 additional weeks from the initial pathological diagnosis of cancer, the decision to delay chemotherapy waiting for a positive result should factor in pre-test probability of a positive *ALK* result, which is more likely in patients with no smoking history and adenocarcinoma histology. Another point for practice is that *ALK* positive patients with existing brain metastasis should generally receive crizotinib following radiotherapy, because it has reduced efficacy in the central nervous system. Indeed, the brain is also a common site of relapse for patients on crizotinib, and our practice is increasingly to perform routine CNS surveillance for these patients (10).

The ongoing development of second generation ALK inhibitors may eventually impact the frontline use of crizotinib. Ceritinib has been shown to be highly active in either crizotinib-pretreated or -naïve population, with median PFS 18.4 months in ALK inhibitor-naïve and 6.9 months in ALK inhibitor-pretreated patients, and is FDA approved for patients who have failed crizotinib (11). Though separate studies, it is interesting that the median PFS for frontline ceritinib alone is numerically equal to the 17.8 months interval calculated by adding the PFS from the Solomon study to the PFS from the ALK pretreated study. Another second generation ALK inhibitor, alectinib, shows promising results from phase 1/2 studies, with objective response rates of 93.5% and the 12-month PFS rate of 83% in patients who are pre-treated with chemotherapy but ALK TKI-naïve (12), and 55% in patients who are resistant or intolerant of crizotinib (13). It has already been approved in Japan, and FDA granted breakthrough-therapy designation for alectinib for *ALK*-positive advanced NSCLCs that have progressed on crizotinib. While initial approval may be for crizotinib refractory patients, the question of whether alectinib is superior as a first-line therapy is being directly tested in the ALEX trial, a randomized, phase III study comparing alectinib with crizotinib in treatment-naive *ALK*-positive advanced NSCLC patients (NCT02075840). Ultimately it may be the balance between length of predicted efficacy and the side effect profile of these drugs that helps with the initial selection of ALK-directed therapies. For decades, chemotherapy has remained the standard of care for advanced NSCLC. It is exciting to see the emergence of highly effective kinase inhibitors allowing postponement of cytotoxic chemotherapy to third line for patients with *ALK*-positive NSCLC, helping advanced lung cancer become an increasingly controllable disease.

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Footnote

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