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Incorporation of Crizotinib into the NCCN Guidelines

The past 7 years have seen dramatic changes in our understanding of the pathogenesis and treatment of lung cancers. The clearest examples of these advances are erlotinib and gefitinib, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs). Both drugs were initially identified, developed, and eventually FDA-approved for treatment of all people with advanced non-small cell lung cancers (NSCLCs). Since 2004, however, it has become clear that the benefits of erlotinib and gefitinib in lung cancers are restricted to patients whose tumors harbor *EGFR* mutations. In the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for NSCLC, identification of *EGFR* mutations forms a critical initial decision point just after the determination of tumor histology (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). This early identification of *EGFR* mutations allows the choice of the best treatment beginning in the first-line. *EGFR* mutations and their ability to predict response to EGFR TKIs have clarified that some of the heterogeneity in treatment outcomes for NSCLCs can be explained by identifying molecular subsets of this disease defined by their hallmark “driver mutation.” Extending this paradigm, the newest molecularly defined entities of clinical significance are ALK-positive lung cancers driven by the EML4/ALK (echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase) fusion protein.

The EML4/ALK fusion protein in lung cancers was first identified in 2007 from experiments aimed at finding the causative molecular entity in a single patient with NSCLC.¹ Soda et al.¹ identified this fusion protein, the first in a human lung cancer, and verified that it could transform cells. Subsequent studies showed that these ALK fusion genes (which usually involve EML4 but can also be rearrangements with other genes) occur in approximately 3% to 5% of patients with advanced lung adenocarcinomas.^{2,3} ALK rearrangements rarely overlap with *EGFR* or *KRAS* mutations (< 5%). During the dose-escalation phase in the phase I trial of crizotinib, this drug led to marked tumor shrinkage in patients with ALK rearrangements.⁴ Based on this finding, a “molecularly enriched” cohort of 119 patients with ALK rearrangements were subsequently enrolled in this phase I trial. The overall response rate was 61%, with a median response duration of 12 months. Subsequently, a phase II trial involving patients with lung adenocarcinomas with ALK rearrangements showed similar outcomes in this second group of patients. This study included a total of 136 patients, with a radiographic response rate greater than 50%.⁵

Evaluated together, these studies led to the accelerated approval of crizotinib by the FDA in August 2011. Importantly, the FDA recognized the clinical heterogeneity of this molecularly defined patient population, leading to the label indication of “treatment of patients with locally advanced or metastatic non-small cell lung cancer that is ALK-positive....” This is a unique indication for a type of NSCLC, because the labels of most currently approved drugs describe patients by tumor histology or line of therapy, not by molecular marker.

Simultaneous with the approval of crizotinib, the FDA also approved the Vysis ALK Break Apart FISH (fluorescence in situ hybridization) probe kit to allow laboratories to identify patients with ALK rearrangements. This test uses probes to the 5' and 3' ends of ALK. When gene rearrangement occurs, the probes split, leading to separated signals. This test was an inclusion criteria for the phase II trial previously discussed⁵ and was used retrospectively on some patients in the phase I trial.⁴

Although this test was used to define the patient population likely to benefit from crizotinib, other tests may identify patients whose tumors depend on ALK expression and who are thus likely to benefit from crizotinib. These tests include

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reverse transcriptase polymerase chain reaction or other genomic tests, as well as immunohistochemistry with newer ALK antibodies. Current commercially available immunohistochemistry antibodies (often used for the characterization of anaplastic lymphoma) are usually not sufficiently sensitive to identify ALK-positive lung cancers because these tumors do not have the same intense staining seen in ALK-positive lymphomas. However, better antibodies are becoming available.

Some data regarding alternative ways to evaluate for ALK gene rearrangements were incorporated into the analysis of the phase I trial; however, further validation will be helpful to identify the most appropriate diagnostic test.⁴ The optimal test should be sensitive, specific, and reproducible in a spectrum of diagnostic laboratories, as seems to be the case so far with the Vysis ALK Break Apart FISH probe kit. However, as more molecular biomarkers become incorporated into lung cancer management, it will also become increasingly important for a given test to have the ability to be multiplexed with other molecular assays needed to optimally treat patients with lung cancer.

Following the approvals of crizotinib and the diagnostic test to identify ALK rearrangements, testing for ALK and the use of crizotinib were both included in the NCCN Guidelines for NSCLC. Critically, the NCCN Guidelines recommend ALK testing in all patients with recurrent or metastatic NSCLC (except those for whom the diagnosis of squamous cell carcinoma is certain based on sufficient tissue for morphologic evaluation and immunohistochemistry studies [TTF-1–negative and P63-positive]). Tumors with “pure” squamous histology are unlikely to have ALK rearrangements.^{6–9} ALK rearrangements have been noted in some tumors of adenosquamous histology.⁹

As with EGFR, the NCCN Guidelines recommend testing all specimens for ALK rearrangements at diagnosis. No clinical enrichment strategy exists for deciding which patients should be tested for ALK rearrangements or treated with crizotinib. All patients with adenocarcinomas, regardless of gender and smoking history, should undergo appropriate diagnostic testing for ALK and EGFR mutations. By placing this recommendation for ALK (and EGFR) testing at diagnosis, the NCCN Guidelines Panel sought to emphasize the importance of this molecular testing and to clearly illustrate that, when obtaining initial diagnostic material, clinicians must obtain sufficient material to allow for molecular testing to identify both EGFR mutations and ALK rearrangements.

The NCCN Guidelines recommendation for treatment with crizotinib is solely based on the results of ALK diagnostic testing. If a patient is found to have an ALK rearrangement (or tests positive using another test), treatment with crizotinib is recommended. The available data support the use of crizotinib in any line of therapy.^{4,5} Moreover, the relatively well-tolerated nature of crizotinib (severe toxicities such as neutropenia are rare) suggests that this drug would be a potential option for patients with poor performance status, provided evidence of an ALK rearrangement is found. The rapid development of crizotinib, with FDA approval obtained less than 4 years after the initial report of this transforming fusion gene, suggests that development and rapid approval of true targeted therapy is possible with appropriate drugs and diagnostic tests that identify patients who benefit.

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