CLINICS

READERS OPINION

Anaplastic lymphoma kinase gene rearrangement and non-small cell lung cancer management: a step forward in personalized therapy

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Dear Editor,

We greatly enjoyed reading the thought-provoking article by Lopes et al. in a recent issue of your esteemed journal (1). Interestingly, in recent years, data have emerged regarding a role for EML4 (echinoderm microtubule-associated protein-like 4)–ALK (anaplastic lymphoma kinase) in personalized treatment for advanced non-small-cell lung cancer (NSCLC) (2,3). EML4-ALK undergoes constitutive dimerization through the interaction between the coil-coil domains within the EML4 region of each monomer, thereby activating ALK and promoting oncogenic activity (4). EML4-ALK fusion, *EGFR*, and *KRAS* mutations are all mutually exclusive, implicating ALK rearrangement as a potential therapeutic target in *EGFR* wild-type and *KRAS* wild-type lung cancers (5). Nevertheless, Lopes' study (1) raises some interesting questions. Was patient selection for the study carried out appropriately? Did the study provide a representative sample of the Latin-American population, as described in the paper? Could immunohistochemistry be substituted for fluorescence in situ hybridization? Which technique is more appropriate for clinical practice? Should we perform this analysis in a specific subset of patients or in all advanced NSCLC patients? In addition, it is interesting to speculate whether EML4-ALK-targeted therapies may be relevant for clinicians, although patients positive for the *EML4–ALK* fusion protein frequently present at an advanced clinical stage, and their tumors demonstrate a solid adenocarcinoma pattern and signet ring cells (5). Furthermore, the presence of the EML4-ALK fusion oncoprotein is associated with nonsmokers or light smokers and is more frequent in younger patients (5). Thus, young, non-smoking patients and patients with adenocarcinoma tumor histology may indeed benefit from an EML4-ALK diagnostic test. Recently, the U.S. Food and Drug Administration approved crizotinib, which is a small-molecule inhibitor of the ALK tyrosine kinase, as a treatment for patients with locally advanced or metastatic NSCLC expressing the *EML4–ALK* fusion protein (2). The results were recently reported for a clinical trial in which 82 *ALK*-positive patients were evaluated for the therapeutic efficacy of crizotinib (6). The results were quite promising, demonstrating an overall response rate of 57% (46 partial responses and 1 complete response) and a 33% stable disease rate (27 patients) (2). Of the 82 patients, 63 (77%) continued to receive crizotinib at the time of data cut off, and the estimated probability of a 6-month progression-free survival was 72% (2). Thus, the refined understanding of the NSCLC molecular profile described over the last decade has proven to be an important tool to help medical oncologists develop new approaches for NSCLC treatment. Despite the small frequency of advanced NSCLC patients who present with EML4-ALK fusion (2.4 to 6.7%) (1), we believe that all patients in this setting should have the opportunity to receive such innovative therapies and approaches. However, further studies are warranted to establish the appropriate pharmaco-economic profiles.

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