Molecular Cancer Therapeutics

Proof of Principle for Crizotinib in Anaplastic Lymphoma Kinase-Positive Malignancies Was Achieved in ALK-Positive Nonclinical Models

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Commentary on:
James G. Christensen, Helen Y. Zou, Maria E. Arango, Qiuhua Li, Joseph H. Lee, Scott R. McDonnell, Shinji Yamazaki, Gordon R. Alton, Barbara Mroczkowski, and Gerrit Los. **Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma.** Mol Cancer Ther 2007;6:3314–22.

Our 2007 MCT article "Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma" (1) highlights the antitumor mechanism and response of an experimental model of anaplastic large cell lymphoma (ALCL) to an experimental agent now known as crizotinib. Anaplastic large cell lymphoma is characterized by the expression of an oncogenic NPM-ALK fusion protein, believed to be a key oncogenic driver of this disease. The near complete inhibition of NPM-ALK activity in experimental ALCL was consistent with a robust inhibition of downstream signal transduction, induction of apoptosis, and a complete regression of ALCL *in vivo*. This was the first report that inhibition of ALK activity was associated with dramatic antitumor activity in ALK positive models and the first indicating that crizotinib is an inhibitor of ALK. This non-clinical proof of principle was also an initial catalyst to design clinical trials focusing on the enrollment of patients exhibiting genetic alterations of the targets of crizotinib including ALCL. Since the initial reports of ALK rearrangements in ALCL, there have also been reports of genetic alterations involving the ALK gene locus in other cancers including inversion events on chromosome 2 resulting in the expression of the EML4-ALK fusion oncogenes in lung adenocarcinoma and activating mutations in ALK in neuroblastoma. Initial reports of clinical activity of crizotinib in patients positive for genetic abnormalities involving the ALK gene locus have shown promise. In a recent Letter to the Editor in the New England Journal of Medicine (2), Drs. Gambacorti-Passerini and Messa report two ALCL patients positive for the NPM-ALK fusion treated with single agent crizotinib exhibited complete responses. In addition, in a brief report published by Butryinski et al. (3), crizotinib demonstrated tumor regression in a patient with inflammatory myofibroblastic tumor (IMT), a rare type of sarcoma in which ALK gene rearrangements are common. Finally, in Kwak et al. (4), crizotinib demonstrated a 57% response rate with in lung adenocarcinoma patients that tested positive for the EML4-ALK fusion event. Collectively, these clinical results indicate that ALK alterations are important genetic events in the pathogenesis of a subset of human cancers and that these cancers can be effectively treated with inhibitors of ALK activity. Clinical studies with crizotinib are ongoing and continue to evaluate the activity of crizotinib in ALK positive patient populations.

Disclosure of Potential Conflicts of Interest

J.G. Christensen is an employee and shareholder of Pfizer, Inc.

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