

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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ALK Inhibitors in Lung Cancer

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H&O What is the background on the anaplastic lymphoma kinase (ALK) fusion protein?

EH. ALK was originally described as a chimeric protein resulting from chromosomal rearrangement between chromosome 2 and 5 (2;5)(p23;q35) in anaplastic large cell lymphoma. This translocation generated the fusion protein NPM (nucleoplasmin)-ALK. ALK has the greatest sequence similarity to the insulin growth factor receptor (IGFR) subfamily. The oncogenic signaling pathway driven by NPM-ALK is thought to involve the PI3 kinase, RAS/MAPK, and JAK/STAT pathways. In addition, there have been other fusion partners of ALK in disease; TPM4-ALK in inflammatory myofibroblastic tumors and squamous cell carcinoma, CLTC-ALK in diffuse large B-cell lymphoma, and EML4-ALK in non-small cell lung cancer. Given the challenges that exist in treating patients with advanced lung cancer, the identification of the EML4-ALK fusion in 2007 has led to targeted therapeutic development of ALK inhibitors

H&O What are the clinical characteristics of lung cancer patients with EML4-ALK fusions?

EH A recently reported study by Shaw and colleagues analyzed the clinicopathologic characteristics of EML4-ALK-positive lung cancer patients. The researchers screened 141 patients and found that 13% were EML4-ALK mutant, 22% were EGFR mutant, and 65% were wild-type mutant for both ALK and EGFR. They also observed that the majority of EML4-ALK-positive patients had adenocarcinoma, were never/light smokers, more likely to be male, and were younger (median age, 52 years). This is of interest because it has been noted that patients

with an EGFR mutation tend to be nonsmokers, female, and Asian. So, unlike in EGFR mutants, in patients with EML4-ALK mutations, ethnicity does not appear to be a major contributing factor. The study also concluded that patients with an EML4-ALK mutation did not benefit from EGFR inhibitors. This is an important finding as it will help investigators to better design the next generation clinical trials

H&O Who is the ideal candidate for ALK inhibitors?

EH Identifying the ideal candidate for ALK inhibitors is a challenge, as the methods currently being used to identify the ALK fusion status are still being optimized. The presence of ALK fusions is being determined by immunohistochemistry, fluorescence-in-situ hybridization, and molecular genotyping. Hopefully, with additional testing and evolving technology, we will be better able to predict the type of patients that would benefit most from ALK inhibitors.

H&O Why is ALK an interesting cancer target?

EH ALK is an interesting target that will help us gain a better understanding of a subset of non-small cell lung cancer patients who do not respond to conventional therapies. In general, the discovery of fusion proteins enables us to approach drug development in a more rational manner. Developing inhibitors that target the ALK fusion protein is an important part of personalized cancer therapy. Although it is critical to increase the treatment armamentarium in a deadly disease such as lung cancer or anaplastic large cell lymphoma, it should be done with novel drugs that maximize benefit and minimize toxicity.

H&O What is some of the ongoing research with ALK inhibitors?

EH ALK is a challenging target; to date, PF-02341066 is one of the compounds being tested in a variety of clinical trials. PF-02341066 is an ATP-competitive small molecule inhibitor of cMET and ALK. The studies involving this compound are in various stages of clinical trials from phase I to phase III. In a phase I trial reported at American Society of Clinical Oncology 2009 meeting, Kwak and colleagues studied PF-02341066 and found that 53% of the patients with non-small cell lung cancer positive for EML4-ALK achieved an overall response while reporting manageable and reversible adverse events. A phase III trial studying the efficacy and safety of PF-02341066 versus chemotherapy (pemetrexed [Alimta, Eli Lilly] or docetaxel) in non-small cell lung cancer patients with the ALK gene is currently recruiting patients. Another phase I study of PF-02341066 in young patients with relapsed or refractory solid tumor or anaplastic large cell lymphoma is also actively recruiting in the pediatric population.

ALK is becoming a more visible target, and our next steps are to decipher the true mechanism of action and to develop clinical trials that will test novel compounds that are considered pure ALK inhibitors. Similarly, we also need to establish whether PF-02341066 is creating the response that we are seeing in lung cancer because of ALK or because of cMET inhibition or both. The ongoing clinical trials in various advanced solid tumor cancers, lung cancer, or anaplastic large cell lymphoma in both the adult and pediatric population will provide investigators a robust understanding of how to optimally design the next generation clinical studies.

H&O What are the future directions of research in this target?

EH I think eventually we will need to have a better, quicker, and consistent way to detect whether an individual cancer has ALK fusions. We are already moving in the right direction, with some studies looking to standardize

methodology and other studies proposing practical ways to detect ALK fusions such as in sputum. Although there is still a great deal to accomplish in this area, my hope is that we are as successful as the HER2/trastuzumab (Herceptin, Genentech) and BCR-Abl/imatinib (Gleevec, Novartis) combination.

Ongoing and future research should focus on determining how many patients really express ALK fusions and the cost of identifying and treating these patients. The economics of personalized healthcare is by no means a trivial issue. Whether ALK fusions will become part of standard testing conducted on all lung cancer patients or anaplastic large cell lymphoma patients requires a thoughtful approach. The frequency of EML4-ALK fusion is reported to be present in 3–7% of lung tumors, with potential for higher percentages in a more molecularly homogeneous subset of the non-small cell lung cancer patient population. At this time, the practical implication of identifying the presence of ALK fusions in cancer is to offer treatment with inhibitors that target this pathway. These treatment options, available only in clinical trials, should be encouraged and supported. Ongoing clinical trials that are evaluating the role of the ALK gene status will help guide next steps in drug development of this target.

Suggested Reading

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