



CAP Lung Cancer Medical Writers' Circle

EML4-ALK: Newly Discovered Mutation Brings New Insights and New Potential Treatment

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Just a little more than two years ago, researchers in Japan identified a new mutation in a few lung cancer tumors ([ref here](#)). It involved the fusion of the EML4 gene with the ALK gene, both found on chromosome 2, but normally separated from each other. These researchers looked at a broader population of Japanese patients and found that this mutation was present in a small minority of non-small cell lung cancer (NSCLC) tumors, all with adenocarcinomas and generally with a history of either never-smoking or smoking in the remote past ([ref here](#)). You may know that this description of Asian never-smokers with an adenocarcinoma sounds very similar to the group of patients who are most likely to have a different mutation, of the epidermal growth factor receptor (EGFR), which is associated with a high probability of a dramatic and prolonged response to EGFR inhibitors like Tarceva (erlotinib) or Iressa (gefitinib). But not all of the patients with this clinical profile have the EGFR mutation, and in fact many of these same patients have an EML4-ALK mutation. Thus far, there hasn't been a patient identified who has both.

Identifying a potential explanation for why someone with little or no exposure to mutation-inducing tobacco or other chemicals is not inherently helpful unless you have a potential fix for the problem, and fortunately a new oral investigational agent being studied, with the not-very-catchy name PF-02341066 (a new marketing name will invariably follow) has been given in early studies to patients with an identified EML4-ALK mutation. This work began just within the last 18 months ago, and the first presentation of results from a few dozen generally heavily pretreated patients was presented at the large American Society for Clinical Oncology (ASCO) meeting in late May/early June of 2009 ([ref here](#)). There, Dr. Eunice Kwak from Massachusetts General Hospital presented work on this very early experience, reporting that not only were about half of the patients responding, but many were showing dramatic and long-lasting responses. This new treatment was also generally quite well tolerated, with some patients experiencing irritation of the liver, as well as some mild to moderate nausea in a minority of patients, but no prohibitive side effect challenges.

Not surprisingly, this work has led to rapid further study of the mutation and this agent. Similar to the Japanese experience, the North American population has a low incidence of this mutation, in the 4-5% range, and it has been concentrated in patients with little or no smoking history and an adenocarcinoma and who don't have an EGFR mutation ([ref here](#)). If patients with these characteristics are screened for the EML4-ALK mutation, the yield is in the range of 30%, making it much less of a fishing expedition with a low yield. At the same time, the ongoing work from the early



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trial with PF-02341066 has shown a response range in the 60% range and several patients continuing to respond a year later, some patients with a very dramatic response to treatment:



(Courtesy of Dr. Alice Shaw)

This has led to two larger trials that are being activated as a pair in many centers around the US and even elsewhere in the world, although only patients with an identified EML4-ALK mutation, which can be tested on tumor tissue only through participating sites, may enroll. One study is a phase III trial in which patients with metastatic NSCLC who have received one line of prior chemotherapy (and potentially also Tarceva, based on the presumption that this agent is likely quite ineffective in these patients) are randomized to receive either Alimta (pemetrexed) or PF-02341066; patients who received Alimta as a first line therapy are randomized to Taxotere (docetaxel) or the investigational agent. For patients who are randomized to standard chemo and then progress, they are eligible for the companion single agent phase II trial in which everyone receives PF-02341066. This trial is also available for patients with the EML4-ALK inhibitor who are not eligible for the larger phase III randomized trial.

Of course, as encouraging as the early results are, they apply to only a minority of the lung cancer population. But this effort has been a sign of hope for many of us in the field, not to mention the patients who stand to be the beneficiaries of this line of research. We're seeing patients benefit today from a story that only began in 2007, a very short interval to have lab research translate to real responses in the cancer clinic. For the few who have the mutation, we're able to offer an oral, generally well-tolerated therapy that appears to significantly shrink cancers more than half of the time in patients who have already progressed on several lines of prior therapy, and these re-



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sponses may last a year or longer (we don't know how long yet, since we're still watching some of the patients who were the first recipients of PF-02341066). And even though the clear majority of lung cancer patients don't have the EML4-ALK mutation, it's one more important piece of the puzzle.

We can only learn how to better address more genetically complex lung cancers after we make meaningful headway against the more genetically simple cancers. And we can all benefit from the encouragement of seeing us chip away at the dismal statistics for lung cancer.

This work is so new that many oncologists may not be aware of this exciting target yet. Patients who have many of the predictive characteristics of having an EML4-ALK mutation – those with an adenocarcinoma, little or no smoking history, and also typically younger than average patients with lung cancer – are encouraged to begin a conversation about this possibility with their oncologist or another member of their medical team. Additional information about the agent and the activated clinical trials are available by calling 1-877-369-9753 or checking at PfizerCancerTrials@emergingmed.com.

Refs:

As per hyperlinks in text

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Dr. Jack West is a medical oncologist and Medical Director of the Thoracic Oncology Program at the Swedish Cancer Institute in Seattle, Washington. He also serves as President of the medical education website OncTalk, LLC and the Global Resource for Advancing Cancer Education (GRACE).

Dr. West received an M. Phil. in Experimental Biology from Cambridge University on a Fulbright Scholarship before returning to the US to undertake his medical training at Harvard Medical School in Boston, where he earned his MD magna cum laude and conducted research as a Howard Hughes Medical Student Fellow. He stayed in Boston for his internship and residency in internal medicine at Brigham and Women's Hospital, then moved to Seattle, Washington for his fellowship in medical oncology at the Fred Hutchinson Cancer Research Center/University of Washington. He moved to the Swedish Cancer Institute in Seattle in late 2002, where he directs the medical oncology component of thoracic oncology program. In 2007, he was named one of the Best Doctors in Seattle by his regional medical colleagues.

Dr. West maintains a strong clinical research focus on lung cancer; he currently serves as the principal investigator on several clinical trials of chemotherapy and novel agents and has authored numerous peer-reviewed as well as invited publications. He has been actively involved with the SWOG Lung Cancer Committee on multiple recent and ongoing protocols, and he leads several investigator-initiated trials at his own institution. In addition to his work in lung cancer, he maintains a significant interest in clinical research in prostate cancer and genitourinary oncology.