

# LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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## Emerging Gene Mutation Targets in Lung Cancer



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**H&O** How common are mutations in *EGFR*, *ALK*, and *ROS1* in lung cancer, and how does identifying these alterations affect treatment?

**BJ** We routinely test for mutations in *EGFR* and rearrangements in *ALK* in nonsquamous non–small cell lung cancer (NSCLC), as stated in guidelines from the National Comprehensive Cancer Network (NCCN). This is important to do because *EGFR* mutations predict response to erlotinib (Tarceva, Genentech/Astellas), gefitinib (Iressa, AstraZeneca), and afatinib (Gilotrif, Boehringer Ingelheim), and *ALK* rearrangements predict response to crizotinib (Xalkori, Pfizer) and ceritinib (Zykadia, Novartis). Although crizotinib does not have an indication from the US Food and Drug Administration (FDA) for use in patients with *ROS1* rearrangements, oncologists generally want to get patients with *ROS1* rearrangement on crizotinib or on an investigational agent. The NCCN's guidelines say that we should consider testing for *ROS1* rearrangements, and we generally do so.

Mutations in *EGFR* and rearrangements in *ALK* and *ROS1* are all much more common in lung adenocarcinoma than in squamous cell carcinoma or small cell lung cancer. They are also much more common in nonsmokers and light smokers than in heavy smokers. In addition, patients with *ALK* or *ROS1* rearrangements tend to be younger than patients without these alterations. *EGFR* mutations typically occur in 10% to 15% of patients with NSCLC who are of Western European ancestry, and in 30% to 40% of those with NSCLC who are of Asian ancestry—specifically those from China, Korea, Taiwan, and Japan.

One advantage of afatinib is that it improved overall survival compared with chemotherapy among patients with *EGFR* exon 19 mutations in an analysis of LUX-Lung 3 and LUX-Lung 6 (Afatinib Versus Cisplatin-Based Chemotherapy for *EGFR* Mutation-Positive Lung Adenocarcinoma). By contrast, erlotinib and gefitinib have been shown to increase only progression-free survival compared with chemotherapy in patients with *EGFR* mutations.

Among patients who had *ALK* rearrangements, progression-free survival was 4 months longer with crizotinib than with chemotherapy as first-line therapy, according to a study published in the *New England Journal of Medicine* in 2014 by Solomon and colleagues. This study also found a trend toward improved survival with crizotinib, but the data were immature because most patients were still alive. Among patients with *ROS1* rearrangements, a single-arm study published in the *New England Journal of Medicine* in 2014 by Shaw and colleagues found that progression-free survival was 19 months with crizotinib, which is dramatically better than what we typically see with chemotherapy.

**H&O** How common are *BRAF* mutations in lung cancer, and what is their potential role in treatment?

**BJ** Most of the work on *BRAF* mutations has been done in melanoma. The majority of patients with melanoma have mutations in *BRAF*, and in most of these patients the mutation is located in V600E. Both dabrafenib (Tafinlar, Novartis) and vemurafenib (Zelboraf, Genentech/Daiichi

Sankyo) are FDA-approved to treat patients with melanoma who have *BRAF* V600E mutations.

*BRAF* mutations occur in approximately 2% of patients with lung cancer, and about half of those patients have the mutation located in V600. The response rate to dabrafenib or vemurafenib among patients with lung cancer who have a V600 *BRAF* mutation is approximately 30% to 35%. In a basket study by David Hyman and colleagues that was published in the *New England Journal of Medicine* in 2015, the response rate to vemurafenib among the 20 patients with NSCLC was 42%, and median progression-free survival was 7.3 months.

In another study, a combination of dabrafenib and the MEK inhibitor trametinib (Mekinist, Novartis) was shown to produce response rates in excess of 60%, with a response duration that is yet to be determined. I presented these results at the 2015 annual meeting of the American Society of Clinical Oncology (ASCO); David Planchard is listed as the first author on the abstract.

### H&O What are some of the other mutations in lung cancer that may become targets for treatment?

**BJ** A number of attempts have been made to target *MET*, using both antibodies and tyrosine kinase inhibitors that inhibit *MET*. *MET* amplification of 2- to 5-fold, which is considered low-level amplification, is present in approximately 4% of lung cancers. *MET* amplification of 5-fold or greater, which is considered high-level amplification, is present in approximately 1% of lung cancers. As such, *MET* positivity is relatively rare in lung cancer.

In a trial that was presented at the 2014 ASCO annual meeting by Ross Camidge, 1 of 6 patients with low-level amplification had a response to crizotinib monotherapy, and 3 of 6 patients with high-level amplification had a response. So we can see that the degree of amplification appears to be important in determining how well these patients respond to crizotinib.

Regarding agents to target *MET* in patients with evidence of *MET* overexpression documented by immunohistochemistry, the antibody onartuzumab (MetMab) looked promising in the randomized phase 2 *MET*Lung trial of onartuzumab/erlotinib vs erlotinib alone in late-stage NSCLC, but it failed in the phase 3 trial. David Spigel was the presenting author of this study at the ASCO annual meeting in 2014.

Efforts also have been made to target exon 14 skip mutations in *MET*, which are present in approximately 3% to 4% of lung cancers. Crizotinib appears to have antitumor activity in these patients. The researchers in the original crizotinib study identified a cohort of patients with exon 14 mutations. My colleague Mark Awad has a paper in press in which he identifies the frequency of

exon 14 skip mutations and our ability to target them. There is also a case report with David Barbie as the senior author and Russell Jenkins as the first author that has been published in *Clinical Lung Cancer* showing a response to crizotinib in a patient with an exon 14 skip mutation. We think this is pretty promising.

### H&O Do the exon 14 skip mutations overlap with *MET* amplification?

**BJ** The skip mutations overlap with *MET* amplification approximately 20% of the time. About 20% of the skip mutations also have *MET* amplification.

### H&O How common are *RET* fusions, and what is their potential role in treatment?

**BJ** *RET* fusions also occur in 1% or 2% of patients with lung cancer. We are not as good at targeting this oncogenic driver as we are with the previous drivers we have discussed. The drugs directed against *RET* are not very potent or specific, and so far the therapeutic results have not been as encouraging.

Alexander Drilon presented results at the 2015 ASCO annual meeting of a study of patients with *RET* fusions in which 5 of 20 patients responded to cabozantinib (Cometriq, Exelixis), and the response duration was relatively short. So there was some effect, but not as dramatic as we see with the agents targeting *ALK* or *ROS1* rearrangements. We probably need a more specific drug than cabozantinib for patients with *RET* fusions.

### H&O What other mutations are emerging as possible targets in lung cancer?

**BJ** Researchers are working on agents that target *NTRK1* fusions, which affect approximately 1% to 2% of people with lung cancer. We are very early in our research aimed at this oncogenic driver. Robert Doebele from the University of Colorado is one of the researchers who has examined these mutations. In 2015, he reported on a patient with sarcoma and an *NTRK1* fusion who responded to LOXO-101.

### H&O Could describe your work with the Lung Cancer Mutation Consortium, and explain why this project was undertaken?

**BJ** Paul Bunn and I discussed this idea during the 2008 meeting of the American Association for Cancer Research after learning that grants for multicenter research would be made available through the American Recovery and Reinvestment Act of 2009. Paul led the effort to put the grant together and was our principal investigator.

Our proposal was to test 1000 patients with carcinoma for a series of 10 genomic changes. We had several reasons for wanting to do this. First, we wanted to determine the true frequency of these mutations. Second, we wanted to find out how many people would be eligible for targeted treatment. Third, we wanted to see what the outcomes would be with targeted treatment. Finally, we wanted to find out how patients would fare who had more than 1 of these mutations.

One of the things we learned is that multiple fluorescence in situ hybridization tests require a fair amount of tissue; somewhere between 5 and 10 slides are needed to carry out all the tests. We simply did not have enough tumor tissue for testing in one-third of the patients. As a result, we needed to begin with approximately 1500 patients in order to do the sequencing on 1000 patients, and we obtained information on all 10 genes in 733 patients.

Another thing we learned is that, as we had suspected, people generally had only 1 of those 10 genes activated by mutation, amplification, or translocation. Just 2% of the patients had more than 1 mutation. Approximately half of the 733 patients had an oncogenic driver, and of those, half were able to receive targeted treatment. We found that overall survival was more than 1 year longer in people who received targeted treatment than in those who were not eligible for targeted treatment. The survival advantage persisted even when patients with a mutation in *EGFR* or a rearrangement in *ALK* were taken out of the equation. We published our results in 2014 in the *Journal of the American Medical Association*, with Mark Kris as the first author.

Our results do not prove that conducting this sequencing and giving targeted treatments will make

people live longer, but our findings are consistent with this hypothesis. That was very encouraging to see.

Another encouraging effect of our study is that it helped prompt industry to begin developing drugs to treat tumors with rare genotypes.

## Suggested Readings

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