Third Generation EGFR TKIs for Acquired Resistance

Dr. Nathan Pennell, Cleveland Clinic, discusses the concept of acquired resistance and new agents designed to address it, including Rociletinib and Merelitinib.

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Transcript

So I'd like to talk now about third generation, or mutation-specific inhibitors for epidermal growth factor receptor mutation-positive lung cancer. We know that for EGFR mutation-positive lung cancer, targeted therapy with drugs like Tarceva, Iressa, or Gilotrif are the standard of

care based on trials showing they're better than chemotherapy for improving tumor responses and the time to progression of cancer for many patients, and they can be very effective and sometimes last a long time.

Unfortunately, the majority of patients will eventually go on to develop something called acquired resistance, where the cancer begins to grow despite continued treatment with the drug that worked so well, sometimes for a long time. Something has changed in the cancer that has caused it to be resistant to the drug. When we biopsy these tumors that are progressing, what we find for EGFR mutant patients is that about 50-60% of these tumors have a new mutation, something called T790m, in exon 20. The original mutation is still there, but now it has a new mutation and this has caused the cancer to no longer respond to the Tarceva or the Gilotrif.

The good news is, there's a whole new class of drugs available that have been specifically designed for this type of cancer, the T790m-positive cancer. These are called mutation-specific inhibitors because they inhibit only the mutant EGFR, and not the normal wild type EGFR that's spread throughout the rest of your body. So, they tend not to have the same side effects that drugs like Tarceva or Gilotrif would have. They have less of the acne-like rash, less diarrhea; they do have different side effects. For example, one of the best known drugs is called Rociletinib, formerly CO-1686, and while it doesn't have a rash or much diarrhea, it can raise blood sugar similar to type 2 diabetes which usually can be managed in the same way with oral drugs. The other well known drug is called AZD-9291, and one or both of these drugs is likely to be approved within the next year for T790m-positive EGFR mutant lung cancer.

Both of these have had large trials that have been presented showing that between 50% and 70% of patients with the T790m mutation will have a major response, and the vast majority of patients will have disease control, with a median time, average time, somewhere in the 8-10 month range before progression — some patients significantly longer. These are really nice options for patients who have this specific type of cancer.

Unfortunately, patients will need to have a new biopsy of their cancer at the time of developing acquired resistance, although they are trying to develop blood tests which are hopefully going to eventually replace needing a new procedure to biopsy your cancer. In 2015, for patients who develop acquired resistance, I would recommend a biopsy of the progressing cancer, and if they have T790m, enroll them on one of the clinical trials with either Rociletinib, AZD-9291, or one of the many other third generation EGFR inhibitors that are farther back in development.