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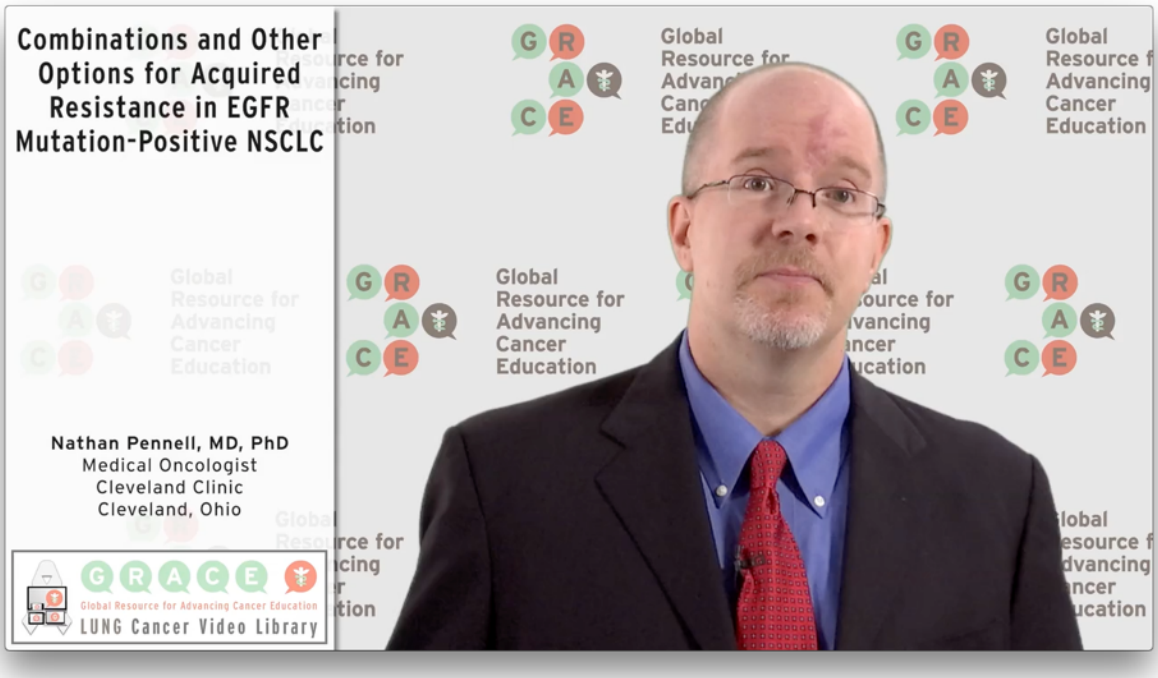
Combinations and Other Options for Acquired Resistance in EGFR Mutation-Positive NSCLC



TRANSCRIPT & FIGURES

On other videos in this series, we talked about next generation inhibitors for molecularly defined subgroups of patients who've developed acquired resistance. Now I want to talk about other options — if you don't have a clinical trial available, or if you've already tried a next generation inhibitor and it stopped working.

We know that for patients with EGFR mutation-positive lung cancer, or ALK-positive lung cancer, the targeted therapies with drugs like Tarceva or Xalkori are more effective than chemotherapy and are really the standard of care for these patients. But unfortunately, most patients go on to develop what's known as acquired resistance, where the cancer eventually begins to grow despite initially being controlled by the targeted therapy. While there are drugs being developed that are better inhibitors in that setting, they're not always available outside of a clinical trial, or perhaps not ideally suited for a particular patient's situation. So, what do you do in that setting?

There are a number of different options. The first thing to keep in mind is, not every patient who is developing acquired resistance needs to change what they're doing. Sometimes, if the cancer is beginning to grow, it can grow in a very slow, asymptomatic way. In other words, it's not causing symptoms, every time you do a scan it's a little bit bigger, but the patient feels fine, is not having a lot of side effects from the drugs — you can continue to watch these. This can be anxiety-provoking, but I've watched patients for six months, nine months, sometimes longer before we really need to make a change. In the same vein, we know that about 20% of patients who develop acquired resistance don't develop resistance everywhere in the body. Maybe only one or a couple of the tumors are growing, and if you biopsy those you

can see that new mutations and mechanisms of resistance can arise in individual tumors while the rest of the cancer remains under control.

To borrow a phrase from my friend Dr. Ross Camidge at the University of Colorado: don't overthink it — if one of the tumors is growing and all of the rest of them are the same, we can ablate the tumor that's growing, essentially eliminate that, and patients can stay on the drug that they're already on, sometimes, again, for six or nine months, sometimes longer, before resistance emerges elsewhere in the body.

The most commonly used mechanism for this is something called stereotactic body radiotherapy, or SBRT, which is a very effective way of using radiation to target individual tumors that tends to have very few side effects. Most patients, however, will eventually need to change the therapy that they're on.

So, if you can't stay on the drug any longer and you need to make a switch, one thing that many patients don't even consider is going to chemotherapy. We know now that, since patients are being tested for EGFR mutations and ALK gene fusions upfront, many of them never receive chemotherapy and they start on a targeted therapy, but chemotherapy can be very effective for patients with EGFR mutant lung cancer or ALK-positive lung cancer, and in fact, tends to work better on average than in people who don't have these mutations. I've had many patients who've had longer periods of disease control on chemotherapy than they had on the targeted therapies that everyone was so excited about. So, don't despair if your doctor suggests chemotherapy because it may be a good option for you.

There are other clinical trials available, we've got the immune therapies that are out there — just the same treatments that are available for other types of lung cancer. There is one other thing I want to mention, for EGFR mutation-positive patients, there is a second generation inhibitor called afatinib, or Gilotrif. Gilotrif by itself is not effective for acquired resistance in EGFR, but when you add it to a second EGFR inhibitor called Erbitux, or cetuximab, in a large phase IB trial, we know that about a third of patients will have a major response to that combination, regardless of why their cancer developed acquired resistance. Sometimes this can last, on average, seven or eight months; I've used this and actually seen pretty good responses. It can be a little bit tough — both drugs cause diarrhea and skin rash, which can be worse when given together, but these tend to be manageable for most people.

So, in 2015, if your cancer develops acquired resistance to a targeted therapy and there isn't a clinical trial available for one of the newer agents, don't despair. There still are a number of things that can be tried, from remaining on the drug, to ablating the limited number of spots that are progressing, to switching to chemotherapy or participating in another clinical trial.

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