Lung FAQ: What treatment should I receive now that my NSCLC with an EGFR mutation is progressing after responding for a year?

The response of cancers with a specific driver mutation, such as an EGFR mutation or ALK rearrangement, to a targeted inhibitor of that target, is often dramatic and long-lasting, but it is also almost always limited in duration, typically lasting several months or a few years. Beyond that point, we tend to see a subset of the cancer cells become resistant progress, perhaps manifested as one or several new lesions or growth of one area against a background of most of the remainder of the cancer still being well-controlled.

In other cases, the progression is more multifocal, sometimes very slow, and sometimes more rapid. What is the best treatment for patients whose cancer is now progression in this setting of “acquired resistance” after an initial good response to an EGFR tyrosine kinase inhibitor (TKI) or ALK inhibitor?

The short answer is that there is no consensus, so the best we can offer is a thoughtful perspective as someone with both experience in treating many such patients and a knowledge of the current data, which are limited. And in assessing an optimal treatment approach, I would contend that it really depends on the features of the particular case. Is this someone who demonstrated a very long response interval of at least 8-12 months, or a relatively short period before progression was demonstrated? Is the pattern of progression very limited, such as just one or a few lesions growing, or much more diffuse? Is the progression very indolent, such as just a few millimeters of change between scans done 2-3 months apart, or faster than that? And is the person with progression experiencing symptoms or not? And how we’ll are they tolerating the targeted therapy?

It’s worth noting that a minority of people with acquired resistance to an EGFR inhibitor (and likely also with an ALK rearrangement, though this hasn’t been reported specifically) will demonstrate faster progression once the EGFR inhibitor is discontinued, leading to a conclusion that “bad brakes are better than no brakes”...even though someone is experiencing progression, they may experience faster progression if someone discontinues that targeted
therapy than if they continue on it.

The key questions, then, are:

1) Should someone make a change at all?

2) If a new treatment is needed, what should it be?

3) If a new treatment is started, should the person discontinue the targeted therapy or continue it?

Tackling the first question, one point is that asymptomatic, slow progression need not necessitate a change in treatment. Many patients can continue to demonstrate slow progression and a disease burden far less than they started with prior to targeted therapy, so as long as patients are monitored with regular clinic visits and scans (I personally would do scans every 6-12 weeks or so, with clinic visits interspersed in between in some cases to ensure the person is still feeling well), I consider this not only appropriate but arguably optimal. You are very unlikely to burn bridges and stretch out the subsequent remaining treatment options over a longer period.

If there’s enough progression to warrant an intervention, what should it be? In those with progression in one lesion (e.g., a new lung or bone lesion, or progression in the brain only, with good disease control outside of the brain), some patients can do very well for months or even years with just a local therapy such as radiation or surgery directed to the progressing lesion and ongoing targeted therapy for the rest of the disease (no real change after the local treatment). This is particularly appealing for those with slow progression who are tolerating the targeted therapy well and progressing after a longer interval.

For those with more multifocal progression, initiation of a systemic therapy is warranted. While there are clinical trials directed towards reversing the resistance and focusing on continuing the targeted therapy as the main intervention, the most common approach is to start the best treatment that would be given as if the person didn’t have a driver mutation. In most cases of advanced NSCLC, that’s going to be a doublet chemotherapy with or without the anti-angiogenic agent Avastin (bevacizumab). There haven’t been meaningful studies to confirm this, but that is the recommendation that is pretty close to a consensus among experts, especially since most patients with acquired resistance have as good a performance status as they did before they started any treatment, if not better.

This leaves the question of whether to continue the targeted therapy with the new treatment, a question for which there is almost no real evidence. There are no prospective trials, though these are now being done. Though years ago I was not a fan of concurrent chemo and concurrent EGFR TKI therapy, that was in a setting of treating a broad range of patients, most of whom don’t have a driver mutation. In the setting of treating patients with a driver mutation associated with a very good response to that therapy, I believe that integrating a new chemotherapy-based treatment is appropriate and likely advisable for patients with slower progression of their disease, and who are tolerating that therapy well. It’s also still reasonable
to discontinue the targeted therapy and consider “re-treatment” with the targeted therapy after an interval off of it, as this is occasionally (though not frequently) associated with a response due to re-sensitization, or at least several months of non-progresison.

This is an area in which thoughtful oncologists might well have different recommendations, as there are few studies to guide our plans. Fortunately, this is an area of keen interest, and we can realistically hope to have more information in the next few years to help guide our recommendations.

For additional information:

Webinar on Acquired Resistance to EGFR TKIs, by Dr. Lecia Sequist, MGH

Acquired Resistance Case Discussion by Multiple Cancer Specialists

Local Therapy in Acquired Resistance

Ongoing Treatment Beyond Progression with Targeted Therapy

Retreating After Progression with Targeted Therapy