FLAURA (Osimertinib in First Line) FINDINGS, EMERGING COMBOS ADVANCE EGFR+ NSCLC LANDSCAPE

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2017 marked a year of highlights across the non–small cell lung cancer (NSCLC) field, with clinical advancements in both targeted therapies and immunotherapy. Focusing on *EGFR*-positive patients, the treatment paradigm seemingly transformed overnight with the release of the phase III FLAURA findings.

The trial, which compared osimertinib (Tagrisso), a third-generation EGFR tyrosine kinase inhibitor (TKI), with standard first-generation EGFR TKIs erlotinib (Tarceva) or gefitinib (Iressa), demonstrated a statistically significant improvement in progression-free survival (PFS) with osimertinib in treatment-naïve *EGFR*-positive NSCLC patients.

Now the agent, which is currently approved in the second-line setting for patients who harbor the T790M resistance mutation, has been granted an FDA priority review for a first-line indication. With this news, experts are debating whether it will be more effective to administer osimertinib or

standard agents first, especially since resistance mechanisms that may develop from osimertinib treatment remain unknown.

In addition, combination regimens could be the next step for osimertinib, since its safety profile is more manageable than first- and second-generation agents.

Lecia V. Sequist, MD, associate professor of medicine at Harvard Medical School, the Mary B. Saltonstall Endowed Chair in Oncology at Massachusetts General Hospital, lectured on sequencing with *EGFR*-targeted agents in NSCLC at the 2017 *OncLive*® State of the Science Summit™ on Advanced Non–Small Cell Lung Cancer.

In an interview during the meeting, she reflected on the practice-changing osimertinib data, ongoing trials exploring combination regimens, and the hope that there might still be potential for immunotherapy in this patient subgroup.

OncLive: **You spoke on targeted therapies and EGFR sequencing. What are some key things to note in this space?**

Sequist: We saw some exciting data this year when it comes to *EGFR*-positive NSCLC with the FLAURA study, which was just recently presented at the 2017 ESMO Congress. In this randomized trial, they were looking at the third-generation T790M inhibitor osimertinib, which is usually given in the second-line setting after acquired resistance. In this trial, they were moving it up to the frontline setting and comparing it with standard of care—either erlotinib or gefitinib—and the trial showed that osimertinib has a much longer—almost double—median PFS, which was quite significant. In addition, this drug also has a much more tolerable safety profile.

The FDA has not approved osimertinib in the frontline setting yet, but it is approved in the second-line setting. Therefore, should we be giving it off-label as a frontline drug? Even if it does get approved, is that still the best strategy? We don't know about overall survival (OS) yet. In my lecture, I spoke about some of those issues with what we know about sequencing

and which drugs to give first. In some ways, it is still an open question. However, my take-home point is that…we have enough data to move osimertinib to the frontline setting.

How would a frontline approval of osimertinib move the field forward?

We are in the middle of the standard of care changing. The results were presented a little bit before an FDA approval, but I foresee, over the next few months, that it probably will get approved. Then, the standard-of-care will really change, and osimertinib is probably [going to be] the drug of choice for frontline *EGFR*-mutant NSCLC for newly diagnosed patients walking in the door. What we don't know much about yet is what types of resistance will emerge after osimertinib in the frontline setting. What are the options for those patients when it comes time for second-line treatment? That is something we are still learning about.

How does the safety profile of osimertinib compare with other EGFR inhibitors?

One of the big differences between osimertinib and other third-generation drugs, which are not yet approved, is that they have very little activity against *EGFR* wild-type. That is a distinction between the third-generation drugs and the drugs that came earlier—the first- and second-generation inhibitors—which had some degree of inhibition of *EGFR* wild-type. That is the *EGFR* allele that is found under healthy cells—like our skin cells and the lining of our gastrointestinal tract. The inhibition of that wild-type gives the rash and diarrhea that we typically associate with EGFR inhibitors. Osimertinib has much less rash and diarrhea than the older drugs that we are used to. Therefore, it really is much more tolerable for patients in my experience giving it.

What combinations are currently in development for *EGFR*-mutant NSCLC?

One of the unique benefits of the third-generation drugs having fewer adverse events is that the possibility of combining them with other drugs becomes even more feasible. There were many [toxicities] in the past

with drugs, such as erlotinib or afatinib (Gilotrif), in combination with other therapies.

However, moving forward, we are going to be watching new trials with third-generation drugs. You can potentially even combine 2 different EGFR drugs together much easier, and you can also combine EGFR drugs with other drugs, such as MET, JAK, or BRAF inhibitors. One of the next big waves of trials that we are going to see coming through are these combinations, either being done in the resistance setting or even in the frontline setting.

Once you determine that a patient has an *EGFR* mutation, how do you go about determining the best agent for them?

If we look back about 3 or 4 years ago, historically, there were a lot of academic discussions about whether there were subsets of *EGFR* mutations that fit better with one drug or another. I was giving a lot of lectures around that time saying that afatinib might be a better drug for exon 19 deletions, and erlotinib may be more suitable for L858R mutations because that is what the data were indicating at that time.

There was another study that came to completion last year called LUX-Lung 7, which directly compared afatinib and gefitinib in the frontline setting. In that study, there wasn't a lot of distinction either in the overall results for the whole study population. These drugs performed about the same in terms of PFS and OS. However, also, there was no real preference by subtype of mutation. It is still a little bit of an open question whether there is any particular preference for one drug or another based on mutation subtype.

What other main challenges exist in this patient population?

One thing that is obviously a very hot topic in oncology these days is immunotherapy. Immunotherapy has not been very active, unfortunately, in EGFR-mutant patients or other patients with driver mutations, such as *ALK, ROS1, RET, HER2,* and *MET.* None of these gene-driven cancers seem to respond well to at least the immunotherapies we have now, such as

PD-1/PD-L1 inhibitors. I am hoping that we, as a field, will be able to figure out better ways to harness the immune system against genetically defined cancers such as *EGFR*-mutant NSCLC. Perhaps it will be through combination therapy. Maybe it will be a totally different mechanism, like vaccine therapies. I'm not sure yet. However, there are lots of trials and interest in this area now.

Overall, what were the most significant advancements in lung cancer in 2017?

In targeted therapy, the FLAURA study and the ALEX study are the 2 big practice-changing studies of the year by moving osimertinib into the frontline setting for *EGFR*-mutant patients and moving alectinib [Alecensa] into the frontline setting for *ALK*-positive patients.

Perhaps the third biggest study of the year in lung cancer is cohort G of the KEYNOTE-021 trial, which looked at carboplatin/pemetrexed and pembrolizumab (Keytruda) in the frontline setting. Even though it was a small phase II study, it led to the FDA approval and has really generated a lot of heated debate about whether we should be using immunotherapy with chemotherapy or sequentially. There are strong opinions on both sides, so we are waiting for the phase III randomized study to guide us a bit more. However, itissuch a rapidlychangingfield.