Dr. Jack West, Swedish Cancer Institute, reviews trial evidence for the efficacy of rociletinib and osimertinib for EGFR acquired resistance not driven by a T790M mutation.

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Transcript

For patients who have an activating mutation in their cancer known as EGFR we have several very good first line treatment options to consider. There are three leading contenders as oral targeted therapies that block EGFR and tend to work very well for patients with an EGFR
mutation. These agents are known as Iressa (gefitinib), Tarceva (erlotinib), and Gilotrif (afatinib). These agents have a chance of shrinking the tumor in the range of 60% to 75% which is great, but unfortunately these responses do not last forever and on average, patients will develop progression of their cancer, so-called acquired resistance to this first line therapy, after something in the range of nine to 12 months — can be less, can be more.

The question is what to do when that occurs. Well, there are a couple of agents that have shown great promise and great activity, at least in the subset of patients who have a mutation, found at the time of this acquired resistance, that is known as T790M. And so we repeat a biopsy of an area of progressing cancer while patients are on and progressing on this first line EGFR inhibitor, and 50% or 60% will have this acquired resistance mutation known as T790M. For those patients, we standardly consider drugs like osimertinib and rociletinib, and I say standardly consider as if they’re commercially available, and they’re not yet, at this moment in late 2015, FDA approved but it is expected that both will be approved by the FDA based on their very good activity in the very near future, perhaps by the time you see this.

But these agents are best studied and have their greatest activity in the patients with a T790M mutation. So what about the patients who are still 40% or 50% of that population with progressing cancer on an EGFR inhibitor who don’t have a T790M mutation? It turns out that both of these agents have good activity, or at least some degree of activity, in patients who are T790M-negative. It doesn’t tend to be as long-lasting and the response rates tend to be lower, but the activity is certainly encouraging.
When you look at what’s called a waterfall plot that’s shown here of how patients respond, the bars going downward represent patients whose cancers have shrunk, and the ones that go upward are the ones whose cancers have progressed on a therapy. You can see that when we look at patients who received osimertinib, the AstraZeneca drug AZD9291, there is good activity in the majority of patients who receive this agent, even if they have no T790M mutation.
New Options for Acquired Resistance: Third Generation EGFR TKI Rociletinib

The same is true for rociletinib, the Clovis drug CO1686 — the waterfall plot shows that most of the bars do go down, and that a lot of patients receive a substantial benefit, even if they do not have T790M detected in their rebiopsied tumor.

So there are studies that are looking specifically at these agents in patients who are T790M-negative. A trial with rociletinib known as TIGER-3 is looking at patients who have received prior EGFR inhibitors like Iressa, Tarceva or Gilotrif, and have also received prior chemotherapy. These patients are then randomized to either receive rociletinib or a standard chemotherapy as a single agent, and there are several that your doctor can choose from. This trial will be looking at which patients do better depending on whether they get the targeted therapy or standard chemotherapy.

There is another trial being done with osimertinib in combination with an EGFR monoclonal antibody known as necitumumab, so a two drug combination being looked at in patients who are T790M-negative after progressing on a first line EGFR inhibitor. So both of these agents are being studied not just in patients with a T790M-positive cancer, but a T790M-negative cancer, and if you do have acquired resistance and are found to not have a T790M mutation,
you might want to look into information about these trials to see if one might be a good choice for you.

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