Growth of Targeted Therapy Requires More Nuanced Treatment Considerations in NSCLC

November 11, 2020
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D. Ross Camidge, MD, PhD discusses the role of targeted therapy and how it is rapidly expanding in the treatment paradigm of patients with non–small cell lung cancer.

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The role of targeted therapy is rapidly expanding in the treatment paradigm of patients with non–small cell lung cancer (NSCLC), said D. Ross Camidge, MD, PhD, who added that among multiple therapeutic options for common aberrations, such as *ALK, ROS1, BRAF,* and *MET*, treatment selection should be based on more than just genetics.

“Molecular heterogeneity in NSCLC is here to stay,” said Camidge. “We are now getting into a situation where first-line choices for some targeted therapies have entered the field of luxury oncology where we have choices with similar or equivalent efficacies. Perhaps we are going to have to start making [treatment] choices based on toxicity, convenience, tolerability, drug-drug interactions, and cost.”

In an interview with *OncLive®* during the 2020 Institutional Perspectives in Cancer webinar on lung cancer, Camidge, professor of medicine-medical oncology at the University of Colorado (UC) School of Medicine and director of the Thoracic Oncology and Clinical Research Programs at the UC Hospital Cancer Center, discussed the current state of targeted therapy in NSCLC and factors to consider before ordering next-generation sequencing (NGS).

***OncLive®*: How have frontline treatment decisions become more complex over the past 3 years?**

Camidge: The big question in the field of advanced NSCLC is: What do we start with? Once upon a time, life was easy. There was crizotinib [Xalkori], which is a first-generation ALK inhibitor. We know [crizotinib] is more effective and better tolerated than chemotherapy.

Then, within the last 3 years, ceritinib [Zykadia] was licensed in the first-line setting. Ceritinib is probably better than crizotinib, but it was never compared head-to-head. However, [ceritinib] is poorly tolerated, so it is not that much better [than crizotinib].

The field really started to change when alectinib [Alecensa] was licensed in the first-line setting, and then very rapidly [afterward,] brigatinib [Alunbrig] was licensed. In 2020, we've seen updates on an experimental drug called ensartinib, which is not yet licensed, and lorlatinib [Lorbrena], which is licensed as later-line therapy.

How are you navigating treatment selection for *ALK*-positive patients among these available agents?

Even though alectinib and brigatinib look very different—brigatinib being much more effective than alectinib—in the post-crizotinib setting, [the agents] look almost identical in terms of end points.

In the post-crizotinib setting, ensartinib looks very similar to alectinib. The eXalt3 study [showed] that ensartinib looks exactly the same as brigatinib and alectinib vs crizotinib in the first-line setting. Therefore, [ensartinib] is not going to shake anything up.

However, during the 2020 ESMO Virtual Congress, we saw the CROWN study of lorlatinib, a third-generation ALK inhibitor, vs crizotinib. We knew that [lorlatinib] was going to beat crizotinib, simply because any next-generation drug will beat crizotinib. However, how much [lorlatinib] appeared to beat crizotinib was a big surprise. All of these other drugs looked very similar, yet the hazard ratio [HR] was 0.28. The other [HRs with other later-generation ALK TKIs] are all around 0.48, 0.49, and 0.47. This seemed like there was something else going on [with lorlatinib].

In that case, should lorlatinib be given to all patients with *ALK*-positive NSCLC?

If you view the [lorlatinib] data in isolation, [that is] your first thought, but we need to think about it in 2 ways. What is going on and what are we going to do about it?

In terms of what is going on, if we look at the HRs among patients with baseline brain metastases, lorlatinib doesn't look any different from brigatinib or alectinib. [They are all] good in the brain. What was surprising was how much better lorlatinib appeared to be over crizotinib in those patients without baseline brain metastases. That is what is driving this reduction in the HR that seems like [lorlatinib] is best in class; 70% of patients in the study, even close to 80%, don't have baseline brain metastases. Yet, in the CROWN study, the HR is 0.32.

Therefore, what do we do about that? We know that [lorlatinib] is incredibly good at getting into the brain, probably the best of all the ALK inhibitors. We also know it probably has the broadest spectrum of mutation coverage. The

only thing that lorlatinib is hitting that, for example, brigatinib isn't is the *ALK* G1202R mutation. However, *ALK* G1202R mutations are pretty rare post-crizotinib. Is that really the reason why the HR suddenly dropped by 0.2? I don't know.

Even in the setting of brain metastases where lorlatinib, brigatinib, and alectinib have similar HRs, maybe differences can manifest in patients without baseline brain metastases when the blood–brain barrier is intact. Maybe we are seeing enhanced protection of those [patients] who do not have baseline brain metastases where lorlatinib is good enough for getting across an intact blood brain barrier. Is that what is [causing] the drop?

Therefore, do we suddenly give lorlatinib to everybody? Do we say, if the HR is lower, it is a no-brainer? Well, the issue is that lorlatinib is not a particularly well-tolerated drug. We know that 70% to 80% of patients are going to have to go on statins or triglyceride-lowering agents. As many as 50% of patients will have higher cognitive function impairment that can be mood, memory, thinking, and speech alterations. [These toxicities were observed] at low levels, but there is also the concern that like "chemo brain," they are not well captured in these studies. We feel a little hypocritical in complaining about something that we can't prove is there, but when we talk to patients, [these toxicities] can be a big deal. There may even be a cumulative effect.

Perhaps the other reason is that although a longer progression-free survival [(PFS) gives us] time before we have to make another treatment decision, what we are going to do next if we have used lorlatinib? Across multiple studies, *ALK*[-positive NSCLC] has been shown to be a forgiving disease with many patients [in terms of] living years. It is not just about who has the longest initial PFS. Instead, perhaps it is about giving patients the longest time without financial or physical toxicity. I don't know if lorlatinib is the [drug] to start with.

[In my practice], I am going to start patients on alectinib, but I am going re-biopsy patients who progress to make a rationale choice of where to go next.

What targeted options are available for patients with *ROS1*-positive disease?

ROS1 is a gene rearrangement. It is not quite as common as *ALK*, but accounts for about 2% of NSCLC, particularly nonsquamous NSCLC. Crizotinib has been licensed; it is a very good drug. Entrectinib [Rozlytrek] is also licensed, but what is the difference? [The agents] have slightly different [safety] profiles, but entrectinib can get into the brain while crizotinib cannot.

[Between these 2 drugs, some people are inclined to say], that if a patient has brain metastases, they should get entrectinib and if they don't, they should get crizotinib. In trying to narrow down treatment choices, some say why not just give entrectinib to everybody. Certainly, if patients tolerate entrectinib, that seems like a reasonable choice.

When patients progress on crizotinib or entrectinib in the body, we have to then think about next-line options. Some ALK inhibitors are also ROS1 inhibitors, but not all of them. That is a rookie mistake to put a patient on an ALK inhibitor, assuming it is also a ROS1 inhibitor. Also, we have to recognize that mechanisms of resistance in the body can turn ROS1 signaling back on; however, that is relatively rare. The most common [on-target resistance mutation] is called *ROS1* G2032R, and the only drug that has shown activity is called repotrectinib [TPX-0005], which is experimental. Lorlatinib, which has some activity against some *ROS1*mutations, does not work on *ROS1* G2032R. Additionally, the activity of [lorlatinib] in the post-crizotinib or post-entrectinib setting is modest.

Again, it comes back to the idea that these drugs aren't going to work in everybody. They work in some patients. The more we know about

mechanisms of resistance, the more we can make rationale choices. Of course, the elephant in the room is: What happens when it is not an on-target resistance mechanism? What acquired resistance mechanisms are second drivers? These are starting to be discovered. Big surprise, it is the usual suspects that can drive other cancers. People have started to look at *RET* rearrangements and *MET* amplifications. That is the next work in progress.

What other genetic alterations are found in NSCLC, and what targeted options are available to treat patients who harbor these specific aberrations?

There are a number of oncogene-addicted subtypes of NSCLC. We have made tremendous progress in the fact that multiple drugs have been licensed as first-line options. For example, in *RET* gene rearrangements, 2 different drugs are licensed: selpercatinib [Retevmo] and pralsetinib [Gavreto]. We don't know that there is any real difference between the 2 agents in terms of efficacy, but there may be subtle differences in toxicity.

We know that *NTRK* rearrangements, which are incredibly rare, can occur in NSCLC and other subtypes of lung cancer. Two drugs are also licensed in this space: entrectinib and larotrectinib [Vitrakvi].

In *BRAF* V600E mutations, we have dabrafenib [Tafinlar] and trametinib [Mekinist]. Other BRAF/MEK combinations are licensed in melanoma, although they are not yet licensed in lung cancer. Given that these [therapies] do not appear to be different, we have entered this phase of luxury oncology, where we get to base which drug we give first on something more than just efficacy. We can look at toxicity, which can vary between individuals, convenience, drug-drug interactions, the potential for combinations, and cost. These [factors] never used to matter in oncology. It will start to feel more like choosing which blood pressure medications [to give].

Of course, with this group of agents that have been licensed relatively recently, we wonder what the mechanisms of acquired resistance are. When will we have a new drug for each of those specific subtypes? Those are works in progress.

Finally, *MET* exon 14 (*MET*ex14) mutations are targetable in NSCLC. Could you highlight the emergence of capmatinib (Tabrecta) and any potential targeted options coming down the pike for this population of patients?

Some are licensed and some may not have a license structure, meaning there is no one telling us we have to test for this. however, if a patient has [another targetable alteration], it would transform their treatment journey.

For example, *MET* can be activated a number of different ways. *MET*ex14 skipping mutations occur in about 4% of lung cancer, and there is a licensed drug [that targets *MET*ex14 mutations]. Using capmatinib can produce response rates of 40% to 50%. That is lower than we have seen with many of these other driver oncogenes, which raises the issue of what is going on in that *MET*ex14-mutated group.

Tepotinib is licensed in Japan and will probably get licensed in the USA, but there is going to be some drilling down in terms of who is included in the [tepotinib-]sensitive population.

However, that is not the only way *MET* can be turned on as an oncogene. *MET* fusions have also been described and are incredibly responsive to MET inhibitors. *MET* fusions have a higher level of *MET*amplification, which is often missed by some NGS assays and is more accurately picked up by fluorescence in situ hybridization. [*MET* fusions] can also define a subpopulation that is sensitive to MET inhibition.

What else is important to know that could change the course of treatment for a patient?

Things like *NRG1* fusions, which are rare, can be picked up by some broad NGS panels. There are treatments in clinical trials leading to long-lived

responses with HER3-directed antibodies. *EGFR* exon20 insertions now have targeted drugs showing activity, such as with TKIs like TAK-788.

Additionally, [agents targeting] *HER2* exon20 [*HER2*ex20] insertion mutations—not *HER2* amplifications—are showing activity with some TKIs and antibody-drug conjugates [ADCs]. The classic [*HER2*ex20 insertion mutation] is called YVMA because of the 4 amino acids that are inserted. It seems that if [the cell] happens to be addicted to the targeted oncogene, [the cell] can't shed it as a means of acquiring resistance. It may also enrich for certain biology, which is sensitive to some of these toxins. For example, [fam-]trastuzumab deruxtecan[-nxki; Enhertu], which is an ADC directed against HER2, has around a 60% response rate. If there is a *HER2* mutation, [trastuzumab deruxtecan] is quite incredible. This is going to change the future.

Among these targeted options, could you speak to the importance of molecular testing in NSCLC and what nuances should be considered before a genomic assay is ordered?

With all of these different molecular subtypes of NSCLC, figuring out the right kind of molecular testing is a new challenge. Community practitioners should begin to understand what they are ordering because NGS is a technique, not a uniform product. It is important to know that whoever is doing the molecular testing has all of the FDA-approved abnormalities included within it. However, you should if [testing] is based on a DNA or RNA-based extraction, or both.

Why does that matter? Well, the starting material can influence sensitivity. For example, a *MET*ex14 skipping mutation can be picked up by a DNA-based NGS assay. However, using an RNA-based NGS assay will double the detection rate. That is important because if I use the DNA assay, I won't know that I missed 2 other cases in the intervening time.

If you are still checking boxes to try to remember what to order, that is yesterday's paradigm. If you are ordering more than 4 individual [tests], you are wasting money. Health economic analyses suggest that once you get past 4 [tests], ordering an NGS panel is the way to go.

Finally, start thinking about when a blood-based test vs a tissue-based test is useful. Blood-based testing is incredibly convenient and often has a rapid turn-around time. However, those same questions that we are asking about NGS panels in tissue also apply in the blood. What are we picking up? What is the basis for what we may miss? It is also important to understand the significance of a negative result, particularly for blood-based assays. Not finding something doesn't mean that it is not there; it just means that you can't find it. It may be because it is below the limit of detection. Time and time again, I hear about somebody with an *EGFR* mutation [that wasn't present] on blood-based testing whose cancer is progressing. Is it a different cancer now? The answer is "no". Just because you can't find it in the blood, doesn't mean it is not there.