

Transcript Details

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www.reachmd.com
info@reachmd.com
(866) 423-7849

Investigating Unanswered Questions in ALK+ mNSCLC Care

Announcer:

You're listening to *Project Oncology* on ReachMD. On this episode, Dr. Alice Shaw will discuss unanswered questions in ALK-positive metastatic non-small cell lung cancer and how ongoing research could address them. She's the Chair of the Department of Medical Oncology at Dana-Farber Cancer Institute and a Professor of Medicine at Harvard Medical School. Let's hear from Dr. Shaw now.

Dr. Shaw:

I would say that, even with the dramatic improvements that we've seen for this type of lung cancer, there are so many important questions to address to really ensure that all of our patients can achieve long-term and highly durable responses, live chronically with their disease, or potentially be cured of their disease.

So why do some patients derive so much less benefit from frontline targeted therapies than others? Even with first-line lorlatinib, about 20 percent of patients progress within the first year, and we call those patients rapid progressors. And for these patients, the treatment options are really limited and not that effective, so I really regard this as a really critical, unanswered question.

And in the seven-year follow-up of the CROWN trial, we specifically looked at these early progressors. We compared their baseline circulating tumor DNA with that of patients who were long-term responders, so still responding to first-line lorlatinib at seven years. And interestingly, we did find some differences, including a higher tumor mutational burden at baseline in the rapid progressors, and also a higher incidence of co-occurring TP53 mutations.

But I actually think we need to go much deeper into the biology of these early progressors so that we can develop rational or mechanistically informed treatment strategies. For example, if we had a gene signature or some type of expression signature that could accurately predict patients who are at high risk of relapse on first-line lorlatinib, perhaps those patients would still start first-line lorlatinib, but then undergo some form of intensification of treatment through addition of another therapy, such as another targeted therapy or chemotherapy.

Another unanswered question in the field I would highlight relates to what we refer to as MRD, or minimal residual disease. And I would say even with our most potent targeted therapies, we don't think that we can really eliminate every last cancer cell. Not uncommonly, we still see on scans a residual lesion at the primary site or at a metastatic site after the initial TKI treatment, and that's what we're referring to as this MRD state. And we really believe that MRD comprises what we call drug-tolerant persisters. So these are cancer cells that are somehow able to lie dormant and persist. And then, with time, they acquire additional genetic and non-genetic alterations that now allow them to become full-fledged resistant cells. And so we really regard these drug-tolerant persisters as the reservoirs, or the seeds of eventual resistance.

Now, there's incredible amounts of work ongoing in the lab and the clinic to better understand these drug-tolerant persisters, and the hope is to try to exploit specific vulnerabilities in these persisters so that we can selectively target and eradicate them. And then that could hopefully delay or maybe even prevent resistance altogether. And there are a number of strategies now aimed at MRD, and these are being tested in the clinic or will soon be tested in the clinic.

As an example, many of us in the field routinely consider what we call local consolidation therapy. That's typically radiation or surgery to address residual disease, so this MRD state after the initial TKI treatment. And we actually already have clinical trial data supporting this approach, but we do need larger randomized studies to really establish this as a standard option. But local consolidation therapy has limitations as well, because we can really only radiate or resect what we can see. And so, in some cases, I would say probably quite a few cases, we're missing microscopic residual disease. And so several other strategies are being explored for MRD, the most exciting of

which I think are immune-based approaches. So as an example, Roberto Chiarle at Boston Children's Hospital and Dana-Farber, and Mark Awad, now at Sloan Kettering, have developed an ALK mRNA vaccine, which will be tested in ALK-positive patients who've achieved MRD after first-line lorlatinib to see if boosting the endogenous immune response against ALK can eradicate residual disease.

Announcer:

That was Dr. Alice Shaw discussing how ongoing research is addressing unanswered questions in ALK-positive metastatic non-small cell lung cancer. To access this and other episodes in this series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!