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Redefining Non-Small Cell Lung Cancer Care: Updates in Targeted and Perioperative Therapy

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This program is produced in partnership with the American College of Chest Physicians and is sponsored by AstraZeneca. And now, here's your host, Dr. Gerard Silvestri.

Dr. Silvestri:
This is *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a pulmonologist and the Hillebrand Professor of Thoracic Oncology at the Medical University of South Carolina. Joining me today to discuss key updates in lung cancer care from the 2025 international conferences are Drs. Mariam Alexander and Jessica Donington.

Dr. Alexander is an Assistant Professor of Medical Oncology at the Medical University of South Carolina in Charleston. Dr. Alexander, welcome to the program.

Dr. Alexander:
Thanks, Gerard. It's great to be here.

Dr. Silvestri:
And Dr. Donington is a Professor in Surgery and Chief of the Section of Thoracic Surgery at the University of Chicago. Dr. Donington, it's great to have you here with us as well.

Dr. Donington:
Gerard, always a pleasure to chat with you about lung cancer. Thanks for inviting me.

Dr. Silvestri:
Now, we'll hear from Dr. Donington later on, but Dr. Alexander, I'd like to start with you to discuss updates on targeted therapies. FLAURA2 generated a lot of attention at ESMO and WCLC. Can you walk us through what this trial adds to the frontline management of EGFR-mutant non-small cell lung cancer?

Dr. Alexander:
Yes. Thanks, Gerard. So at World Lung 2025, we saw some updates in EGFR-mutated lung cancer. As a background, these are caused by mutations in this epidermal growth factor receptor. We were offering patients the third-generation tyrosine kinase inhibitor osimertinib, and that was based on the FLAURA trial, where osimertinib was compared to earlier-generation EGFR inhibitors. And there was significant benefit in both progression-free survival and overall survival with osimertinib, and we had more improved intracranial penetrance with this therapy. And this was our standard of care for several years.

So over the last two years, our frontline has significantly advanced. And we now have the overall survival results of the pivotal FLAURA2 trial where chemotherapy was added to osimertinib, and this regimen was compared to osimertinib alone. We saw that the overall survival was about 47.5 months compared to 37.6 months with osimertinib alone, with all subgroups benefiting, including those with CNS metastasis, making this a really new and improved standard of care. There were understandably more chemotherapy-associated toxicities with the combination, so we need to keep that in mind.

We also had updates on the other frontline EGFR trial, MARIPOSA, looking at amivantamab. So amivantamab is a bispecific inhibitor of both EGFR and another tyrosine kinase, MET. And upregulation of MET commonly acts as a resistance mechanism in EGFR-mutated lung cancer.

So amivantamab was combined with lazertinib, which is another third-generation EGFR inhibitor, and this combination of drugs was

compared to osimertinib. The overall survival data is not reached in the combination arm and about 36.7 months with osimertinib, making it about a year of benefit. And this benefit is looking very similar to the FLAURA2 survival. This regimen has slightly different side effects of rash, dermatitis, and venous thromboembolism.

So basically, our discussion with patients has gotten more complicated in the frontline setting, but with this overall survival data that was recently presented, we really want to make sure our patients have a chance to be on one of these two regimens, especially if they're young, have high-risk features, and want aggressive treatment. But these trials also raise questions on how to sequence treatment in the frontline setting as your second-line or later-line therapy very much depends on which of these two regimens you pick.

Dr. Silvestri:
So for me, that 47 months versus 37 months—we never saw that type of improvement in traditional chemotherapy. Now you're telling me that we should use osimertinib, which has been an amazing drug, in combination with chemotherapy. How do you have that conversation with a patient who sees that osimertinib is pretty good on its own? How does that conversation go?

Dr. Alexander:
So far, I actually have not had issues with patients wanting to be on more aggressive therapy. Patients with EGFR lung cancer have been more on the younger side, and the overall survival data really speaks for itself. With chemotherapy, you basically have four cycles of carboplatin and pemetrexed. And then after that, the carboplatin kind of goes away, and you just have pemetrexed alone. So I know it changes the game when patients have to come in for infusions every three weeks, but I haven't had issues with patients wanting to be more aggressive.

Right now, there's very few patients we are seeing in the frontline setting who are just on osimertinib alone. Even for some older patients with comorbidities, we've been able to get them through these combination regimens of either osi plus chemo or ami-laz.

Dr. Silvestri:
And how do you make the distinction between those two regimens?

Dr. Alexander:
That is a harder question, and there’s a lot of debate in the medical oncology community. I wish we had more risk factors, or who would benefit from what to decide. Right now, I am basing it a lot on toxicities and what patients would want to be on. So I have a long discussion on the side effects of these therapies, and then I make my recommendation based on what I think that they can handle, and then patients pick.

Dr. Silvestri:
Is there any need for a trial that randomizes to either of those types of regimens?

Dr. Alexander:
That would be amazing. I'm not sure if it would be easy to do that trial, but that would be an amazing option.

But one of the things that we are looking at in this space is any biomarkers that would drive us to doing one or the other. For example, amivantamab inhibits both EGFR and MET. So if patients have a high expression of MET, maybe they would benefit a little bit more from the ami-laz combination compared to the chemo-osi combination. We don't know the answers to these questions, but these are just hypotheses that are being looked at.

Dr. Silvestri:
Great. Thank you. And another standout trial was the ARROS-1 trial, which looked at next-generation TKI for ROS1 fusions. How does this agent compare to existing ROS1 inhibitors in terms of clinical utility?

Dr. Alexander:
So the ARROS- 1 trial was for patients with a very more rare type of alteration compared to EGFR, and this was ROS1 rearrangements. So over the years, we’ve had these multi-kinase tyrosine kinase inhibitors that showed benefit in this population, including crizotinib—less specific for ROS1 because they target multiple tyrosine kinases. Over the years, more optimized ROS1 inhibitors have been developed with very clever drug design. Our leading agent has been repotrectinib, and very recently we had an approval for a drug called taletrectinib.

So at World Lung, we had a presentation of the ARROS-1 clinical trial, which looked at another drug called zidesamtinib, which is very specific to targeting ROS1. It had an overall response rate of 89 percent and, more importantly, an intracranial response rate of 83 percent, including 67 percent with complete response in the brain.

So I am excited about this agent as patients who even have had prior specific ROS1 agents have had response to this drug up to 43 to

47 percent, which indicates that it has activity against some resistance mutations and mechanisms. I hope we have access to this therapy soon. Even though this is a very rare mutation, if a patient is currently identified with a ROS1 rearrangement and treated with these newer agents, it changes their prognosis considerably with disease control for many years.

I have a patient in clinic who came with significant ascites and pleural effusion and was actually recommended for hospice. We were able to get the ROS1 testing with circulating tumor DNA in less than seven days, and we started him on taletrectinib, and he's back at work. All his effusions are controlled without any further intervention. Hopefully he will respond for a long time, and if he progresses, hopefully we have approval of this other agent or few even better agents.

Dr. Silvestri:
Well, thank you so much for that. And I would just say for the pulmonology community, you have to test. Even though these are rare mutations, it's like hitting the home run ball if you test and you have those alterations for these drugs that are now taking patients out past five years. So thank you so much.

For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on *ReachMD*, I'm Dr. Gerard Silvestri and I'm speaking with Drs. Mariam Alexander and Jessica Donington about recent advances in lung cancer presented at the 2025 conferences.

So Dr. Donington, as we continue to explore how lung cancer care is evolving across disciplines, I'd like to bring you into the conversation to share the surgical perspective. If we look at the KEYNOTE-671 five-year follow-up data presented at ESMO, what stood out to you regarding long-term survival and the durability of perioperative immunotherapy in resectable non-small cell lung cancer?

Dr. Donington:
Five-year overall survival is really important in lung cancer. I think that's our gold standard of a cure. And seeing a significant survival benefit is really saying that we have a new gold standard for these patients. Whether it is neoadjuvant, as we saw in CheckMate 816, or peri-adjuvant, as we saw in the KEYNOTE trial, we see significant improvements in overall survival with these medications. We don't really see that in the adjuvant space. So it is really what has brought me to believe that this is a better approach for these patients with this class of medications.

I think it really has set a new standard of care. And 65 percent five-year overall survival for a stage three population is really impressive and meaningful. When I came through training, we used to think about 35 percent survival. This is really quite different.

Dr. Silvestri:
And just to make sure that our viewers understand, we're talking about giving preoperative, neoadjuvant chemoimmunotherapy followed by surgery if they turn out to be resectable and operable followed by more immunotherapy out back. You've seen a number of patients now going through this. How are they managing? Is the side effect profile reasonable enough? And how are most of your patients managing with that?

Dr. Donington:
So it is a lot of treatment. The one big difference between the neoadjuvant approach and the peri-adjuvant approach is that year of adjuvant therapy. It's only single-agent immunotherapy, so we do think that the toxicity is less. The time commitment is less, but it is still a trip in to see their oncologist and time in the infusion center once a month for another year.

They do have very nice quality-of-life data that came along with the KEYNOTE trial that showed quality of life is quite well preserved for these patients. This is a fairly well-tolerated therapy compared to other treatments for lung cancer.

Is there time toxicity? Is there a financial toxicity? Those things are quite real, and that's why there are some who really say that without strong evidence for benefit for the peri-adjuvant over the neoadjuvant, maybe everyone should just stop at surgery. I think there are populations where that might be true, but I think there are others who do continue to see a benefit from the addition of therapy after surgery, and that primarily seems to be those patients who don't reach path CR at resection, and possibly those patients with lower PD-L1. But those are still populations we're exploring.

Dr. Silvestri:
And to highlight that, I think there's another thing you're underselling in that you're a surgeon, which is I think robotic surgery and VATS surgery have led to much better quality of life and recovery. And we're seeing our patients go home in a day and a half after a robotic lobectomy and such.

And so I think while it is a lot of therapy, you get out to 65 percent five-year survival in these patients, we're talking about a game changer. And I wonder if it's not just that immunotherapy is better tolerated, but that we're getting better at surgery, and we're getting better at when to modify our chemotherapy approaches. We're just getting better at all parts of this.

Dr. Donington:
I think we're getting way better at all parts of this. I mean, it starts with patient selection. We are much better from the very beginning picking the correct therapy for the correct patient. The fact that this is no longer one size fits all, and everyone gets the same two drugs, is the first step in saying, "Oh my gosh, the right therapy for the right patient." We're much more sophisticated in who we pick for surgery. And I believe 100 percent that small incisions really make it much easier for patients to get to adjuvant therapy.

I think this is something we need to continue to push now that we have good drugs. As surgeons, we need to make sure our patients know that maybe the OR isn't the end of the treatment for their lung cancer, and we need to appropriately relay that message to them.

Dr. Silvestri:
And that brings us really to the second part of this, which is the MDT-BRIDGE trial. Can you recap some of the key findings about multidisciplinary decision-making in real-world practice?

Dr. Donington:
Yeah, so MDT-BRIDGE is a little bit of a game changer for surgeons. It's changing how we think about resectable stage three lung cancer. As surgeons, we always were taught that resectability—both technical and medical—is something that's determined up front. What this trial is showing, where patients get evaluated by the tumor board, get put on this trial if they're even close to being resectable, and then re-evaluated after 2 cycles, is that maybe the dramatic responses we're seeing will make more people more resectable.

So I will tell you my team has taken on this approach, but this approach is entirely dependent on a strong multidisciplinary team. You have to have everybody on board. You can't after two cycles ghost the patient, and no one knows what to do with them. You need your rad-onc, your med-onc, your pulmonary doctor, and everybody on board at the beginning and at that re-evaluation so that you're making the best decision for that patient. And there's no ball that is dropped. I can't stress that enough. This is not a way to just start and see what the surgeons say at the end; it is absolutely a team approach.

And we've been pretty happy. And lots of our patients who we put on this approach don't go to surgery, but we haven't left them without a plan if surgery is not where they go. And that means, like I said, having everybody on board in the beginning.

Dr. Silvestri:
And so the goal there is to take a certain population from what we would have normally deemed unresectable and, with the neoadjuvant approach, see if they're then resectable at the end of that. And that just provides us, I think, with more options for our patients. Is that sort of the thinking for this trial?

Dr. Donington:
Absolutely—that we're just offering more options for our patients. We really think that—we see it often that these drugs—you can see a pretty dramatic radiographic response pretty quickly. Two cycles is enough to see it. And once you see that, it can really change the extent of your resection and take someone who was borderline and bring them into the mix.

Also, I think we're also getting more sophisticated about thinking about surgery in stage three. For many places in this country, many institutions, with a hint of N2 disease, it was only chemoradiotherapy. I think now we're saying, "Oh, if this is something that can get an R0 resection, even if there's N2 disease, we should consider this approach." And I think this just goes along with that.

But I think this is so much about the team. And so much of lung cancer is not a one-man treatment anymore. Almost all of our stages, and especially stage three, require every person at the tumor board. And the impact of radiology, pathology, and pulmonary—it's never been more important than it is now.

Dr. Silvestri:
Sometimes it's really difficult up front for us, even radiographically, with great radiologists looking at this, to really distinguish what is truly resectable versus not. CT just can't always tell us where there's invasion, where there's other things. So it does give us this other pathway.

That's a great way to round out our discussion. And I want to thank my guests, Drs. Mariam Alexander and Jessica Donington, for joining me to share these exciting updates in lung cancer management.

Dr. Alexander, Dr. Donington, it was great having you both on the program.

Dr. Alexander:
Thanks, Gerard. It was great to be here.

Dr. Donington:
Yes, thank you, Gerard. A wonderful conversation.

Announcer:
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