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Evolving Strategies in Resectable NSCLC: Insights from ASCO and ASTRO 2025

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:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Gerard Silvestri, a Pulmonologist and the Hillenbrand Professor of Thoracic Oncology at the Medical University of South Carolina. Today we're diving into updates from major medical meetings ASCO and ASTRO 2025, which are reshaping how we treat resectable non-small cell lung cancer. Joining me are Drs. Mariam Alexander, Anurag Singh, 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 for having me, Gerard.

Dr. Silvestri:
Also joining us is Dr. Singh, who's the Director of Radiation Research, Director of Head and Neck and Lymphoma Radiation Services, and the Associate Dean of Graduate Medical Education in Radiation Medicine at Roswell Park Comprehensive Cancer Center in Buffalo, New York.

Dr. Singh, thanks for being here.

Dr. Singh:
Thank you, Gerard.

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:
Thanks for having me. Excited for the conversation.

Dr. Silvestri:
To start us off, Dr. Donington, is chemoimmunotherapy a good idea for every resectable patient that does not have an actionable alteration?

Dr. Donington:
Yes, I absolutely believe that we have had multiple trials that have demonstrated to us that chemoimmunotherapy improves survival in stage 2 and 3 lung cancer. And I do think that everyone who doesn't have a targetable mutation should be considered for this. It doesn't mean everybody gets it; there are patients who have contraindications to these medications. But I do believe it should be a discussion for everyone.

I am definitely more in favor of the neoadjuvant and peri-adjuvant approaches for patients with stage 2 and 3. I think that really has to do with how these medications work. This is not chemotherapy; these are medications which induce the patient's own immune system to better kill the tumor. And I think we've seen evidence in melanoma and translational work in lung cancer that shows we build better armies of T-cell clones if the tumor is in place. And that's really what's making the difference in survival—teaching our immune systems how to recognize the tumor and go find micro-metastatic disease and eliminate it before it can cause problems in the patient.

Are there challenges to this? Yes. Is it something that we're still learning how to do well—how to make sure we get all our information upfront and how to safely get patients through these treatment strategies? Absolutely. But I think that this is really where treatment for stage 2 and stage 3 is going, and we have to learn how to do it. And there's a lot that's made about attrition—that maybe 20 percent of patients in the trials who started down this approach didn't make it to surgery. I think we have to talk about how we get better at that. And a lot of that is patient selection. But I do think that this is a change in how we treat patients—a change in mindset both for patients and providers—that we have to work through.

Dr. Silvestri:
I'm just going to ask a quick follow-up question to that. What proportion of your patients who start on that neoadjuvant journey don't get surgery? And if there are things that there are barriers to, what percentage would you like to see that be? What is it now, and where do you think it could go with more knowledge and practice?

Dr. Donington:
I definitely think that my practice has matured over time. I participated in many of these trials, so I've been doing neoadjuvant chemoimmunotherapy for greater than 10 years now. And you're right—in the beginning, our numbers were higher. We were more apprehensive; there's no doubt about it.

I would say my number now probably got super low—probably in the range of five percent for a while because we started to recognize that mix of what makes someone unresectable. I think in this population, it has a lot more to do with performance status than what surgeons normally think about. You're right—if someone looks okay and if their PFTs are good, that's one thing. But you give them three cycles of chemo and they don't look good anymore. And I think we've all gotten better in my practice of recognizing who that is.

As of late, the number is getting bigger again. And I think that's a good thing. And that's because we are now going for the more marginal patients because we've seen such dramatic responses with chemoimmunotherapy. We are starting to ask the question: "Can I make someone who today is unresectable, possibly resectable?" That means we have to take risks and say, "This patient might not make it to surgery," and I have to have a little bit of, I always say, a pivot point or an off-ramp and something else to offer them.

But I think that we've had that number down as low as five percent, and now it's sneaking up because we will take a person who's currently unresectable and see what happens, especially if they have high PD-L1 and we're expecting maybe a dramatic response.

Dr. Silvestri:
Dr. Singh, what stood out most to you from ASCO and ASTRO this year regarding our approach to treating patients with resectable non-small cell lung cancer?

Dr. Singh:
One study that really stood out was a SWOG/NRG study that looked at adding atezolizumab before and after stereotactic body radiation therapy for early-stage lung cancer. And what they found is that SBRT, done after three cycles of atezolizumab, followed by five cycles of atezolizumab, did not meaningfully improve any endpoint. And so it gives us pause when we're considering how to incorporate immunotherapy with radiation therapy, and it's probably very important how the timing goes.

So we know from PACIFIC that durvalumab given after chemoradiation significantly improves outcomes. But from PACIFIC-2, we know that that same durvalumab given before, during, and after chemoradiation does not improve outcomes. So I think that we are starting to understand that the way we time and interpolate these therapies with radiation has a significant impact on the outcomes.

Dr. Silvestri:
Thank you, Dr. Singh.

Now, Dr. Alexander, if we zero in on the updates from ASCO, we've seen growing enthusiasm for neoadjuvant chemoimmunotherapy in patients with stage 2 or 3 resectable disease. So, how do you have those patients incorporated into your practice? And what factors guide your patient selection?

Dr. Alexander:
Thanks, Gerard. So the final analysis of the overall survival for the CheckMate-816 study was reported at ASCO 2025. To remind

everybody, this study randomized patients with resectable stage 1B to 3A non-small cell lung cancer to three cycles of neoadjuvant chemo immunotherapy, and the immunotherapy here was nivolumab. The final overall survival favored neoadjuvant chemoimmunotherapy with a hazard ratio of 0.72, with 65.4 percent of patients alive at five years compared to 55 percent with chemo alone. And if you look specifically at those who had the pathological complete response, five-year overall survival was 95.3 percent compared to 55.7 percent who did not. When they look at the PD-L1, that also played a role. In the PD-L1-high subgroup, there was greater benefit than in the PD-L1-low.

In another study, called CheckMate-717, where adjuvant immunotherapy after surgery was offered in addition to the same regimen as CheckMate-816 in the neoadjuvant setting, there was benefit seen for event-free survival. In this study, they found that the event-free survival benefit was more clear in patients who had that pathological complete response.

So if patients have not received chemoimmunotherapy, we have the IMpower-010 and PULSE trial, which led to the approval of one year of adjuvant immunotherapy after surgery and chemotherapy. In the IMpower-010 trial, the overall survival showed a better benefit in patients with stage 2 to 3A and PD-L1 score greater than one percent.

So all this is to say that in real world, my preference would be neoadjuvant chemoimmunotherapy, either based on CheckMate-816 or CheckMate-717, or Keynote-671, where the immunotherapy was pembrolizumab and the more offered to patients with the higher stages—stage 2 to 3A. However, if patients have not received it upfront and they have a higher stage, I would offer adjuvant chemoimmunotherapy, especially if the PD-L1 is positive. We have to consider the proportion. There was about 17 percent of patients who did not make it to surgery. So we really need to make sure we're picking the right surgical candidates here as well.

I want to talk about molecular testing here. So patients with EGFR- and ALK-mutated lung cancer were excluded from these discussions of immunotherapy because we have approvals for great drugs, such as osimertinib and alectinib, in the adjuvant setting based on the ADAURA and ALINA trials, with both trials showing tremendous benefit to adding these oral therapies after surgery.

Another update at ASCO 2025 is that there was a study called NeoADAURA, where patients were randomized to receive neoadjuvant osimertinib with chemotherapy, osimertinib alone, or chemotherapy alone before surgery. And in this trial, they used major pathologic response as the primary endpoint.

And they found that the major pathologic response was 25 percent when osimertinib was added compared to chemo alone. However, the pathological complete response was only four percent with osimertinib alone and nine percent with osimertinib and chemo. And you want to compare that to the neoadjuvant chemoimmunotherapy trial where the PATH-C had already been in the order of 24 percent or higher.

So I do feel like much work is required before neoadjuvant targeted therapy becomes a standard of care compared to adjuvant targeted therapy.

Dr. Silvestri:
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, Anurag Singh and Jessica Donington, about key updates from ASCO and ASTRO that are informing our approach to treating non-small cell lung cancer.

So, Dr. Singh, let's now shift over to updates from ASTRO. What did we learn that could reshape how we approach postoperative radiation therapy, especially in stage 2 or 3 patients?

Dr. Singh:
So, thank you for the question, Gerard. We actually are presenting an abstract at ASTRO that deals with a single institution study of a single fraction of postoperative radiation therapy. So a patient comes in and has N2 disease or not quite an R0 resection, so positive surgical margins, etcetera. And they got a single-arm study of 10 to 16 gray radiation therapy. The outcomes were good. They were very similar to the Lung ART trial.

Now, the Lung ART trial tried to use our newer radiation techniques—3D conformal radiation and a little bit of IMRT—in the postoperative setting and limit the volume some. In doing that, they were able to limit the toxicity, but they were not able to show any overall survival difference. But the issue still arises—if you have positive margins and you have N2 disease, there is older data that suggests the postoperative radiation is still important. So, in our multidisciplinary clinics, the surgeons often will come and say, “Look, I'm very worried about this patient. Either the tumor came really close to the staple line or there was N2 disease, and I'm worried about a mediastinal recurrence.”

So this may be a new opportunity in a very non-toxic manner to give patients radiation and potentially benefits akin to what was seen in terms of local regional control without any of the toxicity, which may make the radiation therapy more palatable in the postoperative

setting.

Dr. Silvestri:
Great. Thank you. And staying with you for just a moment, what do you think about stage 1 disease in the evolving landscape, especially among medically inoperable patients or those who prefer nonsurgical options?

Dr. Singh:
It is an open question about which we have equipoise. There's an ongoing trial that's being run through the VA called the VALOR study where patients with stage 1 disease are being randomized as we speak to either surgery or stereotactic ablative body radiation—SABR, otherwise known as SBRT. And so I think it is an open question. The studies that we have looked at in the past have been too small and have not accrued. VALOR appears to be accruing well, and so we hope that we will have a final answer to that question. And until then, we have equipoise for the question overall.

Dr. Silvestri:
As we approach the end of the program, Dr. Donington, I have one last question for you. How have the new findings presented at ASCO and ASTRO changed how you approach multidisciplinary collaboration and tumor board planning?

Dr. Donington:
I think it's impacted our tumor boards and how we think about it, just because the data comes so fast now. Everything changes it feels like every six months, and so it has really increased the need for collaboration amongst my team. The interpretation of the data—I don't want to say it's all over the map, but we get excited every six months because everything is so exciting.

I think the really exciting data from CheckMate-816—the fact that cure rates are so high even without the adjuvant therapy—has just refueled that conversation about who needs adjuvant after neoadjuvant and who doesn't. I do believe that the PORT work is really exciting—another question that I feel like has never been fully answered, despite having randomized trials.

But I think it's just this reminder, and I think the PORT trial does a really good job of saying that nothing's one-size-fits-all anymore. Everything is very personalized to where this patient is and what this individual patient needs, and you just can't compare all patients with N2-positive disease because not only does each patient's disease differ, but techniques for delivery of radiation are also so different every year and so much more refined from one year to the next.

Dr. Silvestri:
I couldn't agree with you more.

And as those final comments bring us to the end of today's discussion, I want to thank my guests, Drs. Mariam Alexander, Anurag Singh, and Jessica Donington, for joining me to share key updates from ASCO and ASTRO.

Dr. Alexander, Dr. Singh, Dr. Donington, thanks so much for being here.

Dr. Donington:
Thanks for having me, Gerard. It was a great discussion.

Dr. Singh:
Thank you, Gerard.

Dr. Alexander:
Thank you, Gerard. Really fun. Thank you so much.

Announcer:
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