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Interpreting Perioperative Trial Designs in Resectable NSCLC Research

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Bristol Myers Squibb. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here to help us interpret and compare key elements of perioperative clinical trial designs in non-small cell lung cancer are Drs. Laura Alder and Christine Bestvina. Dr. Alder is an Assistant Professor of Medicine at Duke University School of Medicine in Durham, North Carolina. Dr. Alder, welcome to the program.

Dr. Alder:
Hi, thank you so much. Very happy to be here today.

Dr. Turck:
And Dr. Bestvina is an Associate Professor of Medicine and the Associate Director for Clinical Operations for Thoracic Oncology at the University of Chicago Department of Medicine. Dr. Bestvina, it's great to have you with us as well.

Dr. Bestvina:
Thank you so much for inviting me and for the opportunity to talk with Dr. Alder.

Dr. Turck:
Well, let's hear from you first, Dr. Alder, and looking at the big picture here, when you're reviewing perioperative trials in resectable non-small cell lung cancer, what are the first design elements you assess to determine how clinically relevant the results might end up being?

Dr. Alder:
Yeah, thanks. That's a great question, especially since we have so many options in this early-line setting. So three things I look at are treatment sequencing, the endpoints, and the patient population of the trial. And that helps me to create a framework whenever I'm looking at any of these early-stage resectable non-small cell lung cancer trials.

So with treatment sequencing, I look to see if it's a neoadjuvant before surgery, an adjuvant only after surgery, or perioperative, which is both before and after surgery. This matters because we really get more information about what the immunotherapy is doing and where it's acting in the course of the patient's history.

The second thing is the endpoints. We have a lot of different endpoints with these resectable cases, including the pathological complete response versus a major pathological response, and then of course, event-free survival and overall survival. And we really want to look at these because we want to see if the overall survival is mature or not and because we have lots of different trials and there are different timelines in their course of presenting information.

And then, of course, the patient population is really important. The stage distribution can vary amongst some of these trials, including anywhere from stage I to stage IIIB, and it's important to note the mix of stage II versus III, the histology mix of squamous versus adenocarcinoma, PD-L1, and really looking at if EGFR and ALK were excluded, as in most of the trials, but just making sure that when we're looking at these trials, we really know who the patients were who were enrolled.

Dr. Turck:
Well, with that background in mind, let's zero in on the different key elements. Starting with treatment sequencing, Dr. Bestvina, how do

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differences between neoadjuvant, adjuvant, and combined approaches influence the way you interpret trial outcomes?

Dr. Bestvina:
Great question. And a lot of these trials have differences, not just in the agents that were used, but also in the endpoints that we use for these trial designs. And so neoadjuvant trials often rely on pathologic complete response or major pathologic response as early efficacy signals. And fortunately, we now have enough cumulative data across multiple clinical trials that we are confident that path CR and major pathologic response do correlate with long-term outcomes, but those are the primary outcomes in most of these trials.

Then we have adjuvant trials, which more frequently prioritize disease-free survival—or time without recurrence—or overall survival. These trials have much longer follow-up, so it takes a longer time for us to get data about the efficacy in the adjuvant setting.

And then lastly, we have our perioperative trials, or trials that look at interventions both before and after surgery. Certainly, these can be the most complicated trials to look at because we're never really sure what degree of the outcome is attributable to the neoadjuvant component versus the adjuvant component. But because we're typically trying to study both, we're looking more at disease-free survival and overall survival as the primary endpoints, though we do get that bonus information of path CR or major pathologic response at the time of surgery.

Dr. Turck:
And if we come back to you, Dr. Alder, and focus on other aspects of clinical trial design, what differences are most meaningful when comparing chemotherapy backbones and dosing strategies across studies, particularly when investigators incorporate immunotherapy?

Dr. Alder:
It's a great question and a really important thing to look at the trial design. We know there are different types of platinum agents. So one of the trials, KEYNOTE-671, mandated cisplatin-based doublets only—so cisplatin and pemetrexed for non-squamous and cisplatin and gemcitabine for squamous—while other trials like CheckMate 816, CheckMate 77T, and AEGEAN allowed both cisplatin and carboplatin options. So this can be important because there is some still measure of unknown about if the platinum agent does convey any significance. Most of the trials that we have are historical and did not incorporate immunotherapy.

The other thing is the partner agent. So taxane versus pemetrexed versus gemcitabine really affects both the efficacy and the tolerability. And so we really want to make sure that we have a good knowledge of what these patients received while on the trial. And nowadays, the NCCN guidelines usually list specific doublets for each checkpoint inhibitor based on the trial and based on which partners were used in that trial.

Another important thing to look at is the number of neoadjuvant cycles. This differs; CheckMate 816 used only three cycles over nine weeks, where most of the other perioperative use four cycles neoadjuvantly. And so we have to look at that when we're looking at pathological response, any delays in surgery, increased toxicity, and, of course, survival as well.

And then lastly, we want to look at the protocol just to see how flexible or rigid it was. A lot of times we're applying these clinical trials to our real-world patients, and they don't often fit into all the specifics of inclusion/exclusion of a clinical trial. So it's important to see how that inclusion/exclusion plays a role in the patients we're seeing every day in our clinic.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Drs. Laura Alder and Christine Bestvina about the key elements of perioperative trials in non-small cell lung cancer.

So, Dr. Bestvina, when you're interpreting endpoints like pathologic response, disease-free survival, and overall survival across different trials, which nuances tend to matter the most?

Dr. Bestvina:
Oftentimes, it's a composite of looking at all of these endpoints. For pathologic complete response and major pathologic response, when we were first using these in the lung cancer realm, we weren't really sure that this did correlate to outcomes. We were using some other breast cancer trials to try to make this parallel. Again, fortunately, due to the abundance of data across multiple different trials with multiple different immunotherapy agents, we now are pretty confident that there is that correlation between pathologic complete response and major pathologic response.

However, the gold standard, I would still say, is overall survival, and maybe the second gold standard or the silver standard is disease-free survival. Are we keeping these patients in a curative-intent setting? And so I think patients care more certainly about disease-free survival and overall survival and less about what their actual pathology looked like under the microscope.

Dr. Turck:

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Now, trial eligibility criteria can also vary quite a bit. So, Dr. Alder, would you tell us how disease stage, biomarker selection, surgical candidacy, and other factors shape the way we understand and apply these results in practice?

Dr. Alder:
Yeah, so what we've been discussing a bit is we know that the real-world can look differently, and there are a lot of different things that we assess when we're talking to the patient in front of us. And so disease stage is, of course, very important. We know that an earlier-stage patient—stage IIA versus IIIB—are going to have better outcomes no matter what. So sometimes it can be a bit harder to really show that incremental benefit of more cycles, more immunotherapy, neoadjuvant versus perioperative, etc. As I mentioned before too, we know that different trials enroll different percentages of stage II versus III patients. And so when we do look at these different trials, the old adage is you shouldn't do cross-trial comparisons, but a lot of us look that way anyhow to try and make sure that we give our patients the very best care. These are things we just have to be very aware of.

Another thing that you mentioned is biomarkers, so that includes PD-L1. It's one of the predictive biomarkers we have when looking at the benefit of immunotherapy. We see pretty much across the board that a higher PD-L1 expression does seem to correlate with greater pathological response rates and event-free survival across all trials. But we know that—just like in the metastatic setting—even low PD-L1 patients can see a lot of benefit. So we're still really trying to think about how we incorporate that into our decision-making, especially neoadjuvant versus perioperative, for example.

One thing that we know is important for any type of non-small cell lung cancer is genomic testing, so we really want to make sure that all of these early-stage patients get genomic testing, and we're really looking for EGFR and ALK specifically because we have treatments that could offer them a lot more benefit than checkpoint inhibitors, so we really want to make sure that's done as well.

And then one of the other things I like to highlight is surgical candidacy and then what is resectable? I think that question of whether it's resectable or not is still being defined, and it can vary depending on the center that you're at and the surgeon who's evaluating the patient. Some of that comes from what AJCC edition they used—7th, 8th, and now we're on the 9th. And then the N2 disease can vary between clinical trials, and for multistation or bulky involvement, we still don't always know the very best thing for some of these patients with N2 disease.

So just make sure that we keep a close eye on what our surgical colleagues think is resectable without any type of treatment and what was included in these specific clinical trials to make sure that we are offering surgery to the right patient population and not missing out on chemoradiation if that could be better than putting patients through a lot more that won't ultimately benefit them.

Dr. Turck:
And if we turn to you, Dr. Bestvina, for the final word, what practical considerations come into play when you translate findings into practice, especially concerning newer approaches like subcutaneous delivery?

Dr. Bestvina:
There's no question that there's a difference between the clinical trial population and our real-world population. I'm used to seeing people who would not have qualified for clinical trials—patients who have reduced kidney function who may not qualify for pemetrexed and patients who have decreased performance status and ECOG performance status of 2. And so understanding how these trials translate into the real world and how we can offer them new agents and some of these amazing advances that we've seen in the curative-intent setting, while also still being realistic about how these real-world populations may behave, I think is extremely important.

And then lastly, as subcutaneous immunotherapies become available and we start to use them for patients in that adjuvant setting, how do we modify our clinical practices? How do we modify our follow-up approaches so that patients are getting just as good care within this new model that may allow for virtual visits and subcutaneous injections at home? I think a lot still needs to be worked out here, but the important thing is that with all of these neoadjuvant, adjuvant, and perioperative approaches, we truly have moved the bar for our patients and are curing more patients.

Dr. Turck:
Well, with those considerations in mind, I want to thank my guests, Drs. Laura Alder and Christine Bestvina, for joining me to share their insights on how we can better understand perioperative clinical trial designs in non-small cell lung cancer. Dr. Alder, Dr. Bestvina, it was great speaking with you both today.

Dr. Alder:
Yeah, great speaking with you and Dr. Bestvina.

Dr. Bestvina:
Thank you so much for having both of us.

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