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Released: 08/01/2025
Valid until: 08/01/2026
Time needed to complete: 15 Minutes

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# Chairperson's Perspective: Optimizing Perioperative Therapy in Early-Stage NSCLC: A Multidisciplinary Approach

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**Dr. Wakelee:**
Hi, I'm Heather Wakelee, Chief of the Division of Oncology at Stanford University, and Deputy Director of the Stanford Cancer Institute, and today I'm going to be talking about optimizing perioperative therapy in early-stage non–small cell lung cancer, a multidisciplinary approach.

We'll first talk about neoadjuvant immune checkpoint inhibitors, or ICI, adjuvant ICI, and then perioperative. And kind of thinking about, what do these approaches add to each other and what variables are important.

So, first, neoadjuvant. We only have one big trial that looked at just neoadjuvant, but let's kind of talk about these theoretical benefits of neoadjuvant. The main one being, if you give the immune checkpoint inhibitor while the tumor is still there, a lot more opportunity to find the right new antigens to go after. And so that's sort of the main theoretical reason. You're going to get that stronger response because there's more tumor to see and attack.

So this is that trial I mentioned, the CheckMate 816. This trial enrolled patients who had theoretically resectable stage 1B (but that was a small percentage), 2, and 3A non–small cell lung cancer. Most patients ended up having stage 3A (two-thirds). You can see in that box up at the top, here, about half the patients had some PD-L1 expression on their tumor. And remember, patients with a known EGFR mutation, or ALK translocation, were excluded.

And then, the patients were randomized to get chemotherapy by itself for 3 cycles or that same chemo with the addition of nivolumab. Surgery was done within 6 weeks, and then they had the option of getting additional chemotherapy/radiation. But no immune therapy afterwards.

We just saw the 5-year survival results at ASCO 2025 by Patrick Ford, and you see a nice robust separation of the curves. Hazard ratio of 0.68, here. Really, really nice. And this, again, this is event-free survival.

When we look at the event-free survival by path CR, you can see that those who had a path CR, top, looking great. Those who did not, you're still getting about a third of patients having that long-term outcome, but that means two-thirds of patients had recurrences.

So what does that mean for overall survival? Here, we see that data. Remember, that event-free survival hazard ratio, 0.68, overall

survival 0.72. We see these curves separating by the first year and a half, 18 months, continuing to stay separated. There's about a 10% overall survival difference in the end.

This, however, varies quite a bit by stage as well as by, especially by PD-L1 level. When we look at the stage, the 1Bs and 2s here, the stage 3As here, you can see higher stage, more benefit. This is for overall survival.

And then, when we look at PD-L1, when you look at those with less than 1%, that hazard ratio is 0.89. Less clear benefit. And then, as you get into the higher levels, either 1 to 49 or greater than 50, we see the highest benefit in that greater than 50% PD-L1 expression level for the tumor.

So putting that neoadjuvant data together and thinking about it, benefits and harms. There were only three cycles of treatment. Every patient got immune checkpoint inhibitor and chemo. PD-L1 level looked really important. Patients with driver mutations were excluded. Stage: We see more benefit in stage 3 but still some of those earlier stages. And we now have a definitive overall survival benefit with that hazard ratio of 0.72.

What about pure adjuvant? So what about patients where they only get the immune checkpoint inhibitor after they've had that surgery? And we have three trials.

This is the IMpower010 trial. When we look at who went on it, we're seeing about 50% of patients stage 2, 40% stage 3, so slightly different patient population. Again, about half have some PD-L1 expression. Patients with known driver mutations were allowed, but it's only about 15%. And this was the design. Patients had surgery. They then got chemotherapy, and then they were randomized to get immune therapy or not. So a different group of people than those who were theoretically able to get their surgery and got their immune checkpoint inhibitor and chemo and went to surgery. These patients had already been through surgery, been through chemo, and then got randomized. And the study also had a complex hierarchical statistical design.

But on the left side here, we see these results with 5 years of follow up with patients who had a tumor PD-L1 expression of at least 1%, stage 2 to 3A. We see that these curves actually separate very early and stay separated. This is the disease-free survival. Most of that in the patients with high PD-L1 expression, just like in the pure neoadjuvant.

When we look at overall survival, we also see these curves separating. We can't really call anything statistical. I didn't show it on this slide, but most of this benefit is in those with the high PD-L1 expression.

Alright. So what about the other trials? Well, there it gets a bit more complicated. When we look at the PEARLS trial or KEYNOTE-091, nice robust disease-free survival benefit, hazard ratio of 0.76. PD-L1 level didn't matter, which was a bit odd because it's mattered in every other trial that used the pembrolizumab.

And then, we had the most recent trial, the BR.31, with durvalumab. And here, the trial was absolutely, completely negative, even in those with the highest PD-L1 expression. So you have one trial that was sort of positive regardless of PD-L1 expression, one trial that was very positive with high PD-L1 expression, and one trial that was totally negative in the adjuvant setting.

So, when we think about adjuvant, everyone gets surgery, with this disease-free survival endpoint. Driver mutations are known because you've already had surgery or the tumor is out. The path CR, MPR, MRD seem somewhat relevant, but you don't really know how to look for MRD. The assays aren't sensitive enough. I'll come to that more a little bit later. And the PD-L1 results are totally confusing across the trials.

So then, what if we put it all together? That perioperative immune checkpoint inhibitor where you're doing neoadjuvant and adjuvant. We've had 5 trials reported out. This is one of them, the AEGEAN trial. They all have a very similar design, so I just put one design up. Here, patients have, again, theoretically resectable disease. Most of the trials excluded EGFR and ALK known driver mutations. Not every trial, but most of them did. And then, patients in general are randomized to get chemo or chemo plus immune checkpoint inhibitor, then go to surgery, and then, if they're on the immune checkpoint inhibitor arm, they continue that for up to a year. And if they were on the placebo arm, they continue the placebo for up for a year. So that's kind of how these were designed. And when we look at the results so far, event-free survival in all of these trials has been positive. It's been very similarly positive with event-free survival hazard ratios around 0.68, 0.7, around that range.

I'll just remind everybody, event-free survival is different than disease-free survival, right? Disease-free survival, the cancer is already out. Theoretically, disease-free. We're watching it. Event-free survival means we're enrolling these patients before their surgery, and they haven't had an event that would prevent them from getting surgery or any evidence of recurrence or progression. So it's slightly different. But okay.

So 3 trials; similar results. Two more trials. These were done in Asia. Very, very similar results. All positive event-free survival.

And the KEYNOTE-671 is the only one of these trials where we have definitive overall survival. This is with a shorter follow-up than we needed for the CheckMate 816 neoadjuvant-only overall survival. But here, robust overall survival and a hazard ratio that's very, very similar to what we saw in the CheckMate 816.

So, with perioperative, we have 5 trials, consistent event-free survival benefit, overall survival proven in KEYNOTE-671. PD-L1, I didn't really show you, but it was super important in all of the trials. Driver mutations were excluded. Benefit not really seen, even when they were included. Stage, benefit across stages. And this path CR, all of that's important. Again, I didn't, in the interest of time, go through all of the details, but we do see that same trend. But more therapy, more toxicity, increased costs because of more therapy, and 20% of patients don't go to surgery.

So each of these trials, pure adjuvant or perioperative, and all of them, about 20% of patients not getting to surgery. And this reinforces: Whatever you do first, you get. Whatever you do second, you probably will get. If we look at the trials that were neoadjuvant studies and kind of look at, of those, who ended up getting adjuvant treatment, not everybody. So it's sort of, whatever you do first, you definitely get.

Okay. So key questions. How do we decide whether to go with neoadjuvant, adjuvant, or perioperative? Well, we need multidisciplinary tumor board discussions. Everybody should have their case discussed by Med-Onc, Rad-Onc, and thoracic surgery with radiology and pathology weighing in, and pulmonary, before you do anything. If you can't, if you don't have the mechanism to do that, you want to at least have everybody kind of weighing in through e-mail or some other discussion. Again, all HIPAA compliant, of course.

And then there's some clear advantages to neoadjuvant and perioperative, like we talked about before. Getting that immune checkpoint inhibitor in early, so you get those most robust responses. But keeping in mind, if you go with surgery first, you definitely get surgery. That's the right plan for some patients. And if you start with surgery, some patients aren't going to get that immune checkpoint inhibitor, which is really important, especially if they have high PD-L1 expression.

Okay. And we've got to know the PD-L1 expression and you've got to know at least EGFR and ALK before making your decisions.

So what about immune-related adverse events in management? How do those impact surgery? Well, I show this slide to demonstrate. An immune-related adverse event can happen to any organ, and it can happen at any time. We're specifically, really seeing a lot with endocrine though. Thyroid, pituitary, seeing a lot of skin issues, potentially diarrhea. But anything can happen. Any change in symptoms, think about this event. Usually, you're going to hold your immune checkpoint inhibitor. You want to have a very high suspicion. You want to make sure your patients know if they end up in a different emergency room, to mention that they're on that drug. You got to think about other things that can mimic that. And then, usually it's immunosuppression with steroids. If that doesn't work, other things can be escalated.

This is a great paper from 2018. A lot of this hasn't changed much since then, so I encourage people to look at that. And then, trying to think about when do you start back again? Well, for endocrine, you hold, but you can usually restart if you can correct it. The ‘permanently discontinues’ have to do with the more severe adverse events such as myocarditis, encephalitis, ocular toxicities. All of these things can happen. But basically, it's good to have your multidisciplinary discussion with disease experts for those different organs and trying to decide what makes sense.

Alright. What about CT DNA? I always talk about this because I think it's really going to be helpful in the future for helping us determine who is done after just surgery alone. Remember, we cure people with surgery alone. Who is done after that neoadjuvant and surgery? Is it just CT DNA? Is that going to help us enough? Is it those with path CR? Is that enough? What about those patients who have minimal residual disease, less than 10% viable tumor? Maybe this will help us determine who actually can be done.

So this is a couple of different early studies. One was from Stanford, so I like to talk about that one. This is with our CAPP-SEQ. And you can see patients had their treatment with definitive treatment for early-stage and then we did CT DNA. If we didn't find it, no recurrence. If we did, rapid recurrence. So this sort of set the benchmark in 2017. Another group, very similar results published in 2017, that went on to become the Signatera assay.

So CheckMate 816, CT DNA clearance was seen. Again, this is our neoadjuvant study with nivolumab. If you had clearance, it was far more likely if you got the nivolumab arm. And when we look at overall survival, those with clearance, very high rates of long-term survival. Without clearance, much lower.

AEGEAN trial. Again, this was the perioperative with durvalumab. We see that they did multiple time-points of blood draw. One of them was for patients who had gotten their neoadjuvant and gotten their surgery.

They did a landmark time-point after they've had that, and those who did not have any evidence of CT DNA, those with MRD negative, whether they were on the durvalumab or placebo arm, did much better. And those where any evidence of CT DNA was found had recurrences.

So let's put this all together with a case. Sixty-one-year-old patient. He's got some hypertension, hyperlipidemia, he's smoked for a long time, started early. He presents to his primary care doctor with some blood sputum and some fevers. Gets an X-ray that doesn't look good, and then had the CT scan, which looks very concerning.

So, in addition to biopsying that primary mass, after tumor board, they talk about doing an endobronchial ultrasound to look at lymph nodes and also to have enough tissue to send for PD-L1, EGFR, and ALK. Most people agree, some of the surgeons are saying they should go straight to surgery, but his PD-L1 is 40%. EGFR and ALK are negative, but he did have some lymph nodes.

So neoadjuvant treatment has started. He has 3 cycles chemo and immune therapy. Starts to feel really tired. TSH is checked; it's high. T4 is low. They check for ACTH and cortisol levels. Important, because you want to make sure you're not dealing with more than just thyroid dysfunction in the endocrine system. Started on thyroid replacement, starts to feel better. Goes to surgery. He still has some viable residual tumor, but it's much improved from where it was at the beginning. And so then the question is, do you continue additional treatment or not? He didn't have a major pathological response, but it was good. What if he'd had a path CR? Would you give adjuvant treatment? So just some thoughts.

So questions from our case. Who determines resectability? Do we have to wait for overall survival data to mature before we make decisions? Which biomarkers are ready? What about CT DNA? I don't think it's quite there, but getting there. If immune-related adverse events develop, how do you decide when to go to surgery? Do patients with a path CR need adjuvant, and what is the sentiment about potential for subcutaneous immune checkpoint inhibitors? A lot of excitement about that.

So, in conclusion, whether you give neoadjuvant, adjuvant, or perioperative, they're all reasonable approaches for certain patients. Multidisciplinary tumor board discussions are critical. Testing for EGFR, ALK, PD-L1 is critical. If you do find EGFR and ALK, we've got great data for adjuvant now in both of those settings, and neoadjuvant with the NeoADAURA. For Stage 3, chemo immune therapy up-front, critical. Stage 1 and 2, maybe some can go to surgery.

We need to keep working on our biomarkers. The additional benefit of adjuvant after neoadjuvant is likely, but we need to do trials to look at those contribution of components. I think CT DNA is going to be critical, and we need new drugs to keep moving forward.

But it's very exciting times. So thank you very much.

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