Transcript Details

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Keeping Pace in Lung Cancer: Personalizing Treatment in NSCLC: Early-Stage Disease (Stage I-IIIa)

Announcer:
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Dr. Socinski:
Hello, and welcome to this Keeping Pace in Lung Cancer education series. In recent years, the treatment of early-stage non-small cell lung cancer has undergone considerable change. We now have new treatment options and modalities, including the use of immunotherapy. Today we're going to discuss personalizing treatment for patients with early-stage non-small cell lung cancer.

This is CME on ReachMD, and I'm Dr. Mark Socinski.

Dr. Forde:
And I'm Dr. Patrick Forde.

Dr. Socinski:
So, Patrick, let's start off. Can you just review for us the recent NCCN guideline updates in early-stage non-small cell lung cancer?

Dr. Forde:
Sure, Mark. It's been a busy couple of years in terms of NCCN for early-stage disease, after a very fallow period for many years. First of all, we've had the approval and the incorporation in the guidelines of adjuvant osimertinib, and recent data – very recent press release suggesting there's an overall survival benefit from adjuvant osimertinib for those patients with classical sensitizing EGFR mutations. And the current guideline recommends adjuvant osimertinib after adjuvant chemotherapy for patients with stage IB to IIIA non-small cell lung cancer, which has been fully resected. We've also seen updates in the use of immunotherapy. First of all, we had the approval and incorporation of adjuvant atezolizumab for resected stage II and IIIA non-small cell lung cancer, including consideration for IB after adjuvant chemotherapy, and that's for PD-L1 1% or above disease. And most recently, we've had the PEARLS trial which suggested a benefit for adjuvant pembrolizumab, which was agnostic of PD-L1 status, and that has also been incorporated as a 2A recommendation in the guidelines for fully resected, stage IB to IIIA non-small cell lung cancer. So several updates.

Dr. Socinski:
Yeah, so that obviously creates a number of options for treating early-stage disease, from monotherapy to chemoimmunotherapy, even to immunotherapy combinations. I wonder if you could give us an overview of the key clinical data, for specifically neoadjuvant therapy in early-stage disease.

Dr. Forde:
Sure, well, so one interesting thing in the guidelines is that they now recommend evaluation of all patients with clinical stage IB, II, or

IIIA disease for potential neoadjuvant systemic therapy, and that's a new update as well. That's largely building on the CheckMate 816 trial, which was published last year in *The New England Journal of Medicine*. And this was a trial where patients were randomized with stage IB to IIIA disease – randomized either to a control arm of neoadjuvant platinum doublet chemotherapy for 3 cycles or the investigational arm which was 3 cycles of chemotherapy with nivolumab. Surgery was planned to take place within 6 weeks after the last dose of treatment, and postoperatively there was no mandate of systemic therapy. And in that trial there was initially a report of pathological complete response showing a significant improvement with the addition of nivolumab. And last year, we saw that there was a significant improvement also in event-free survival, which is the term we use in the neoadjuvant setting similar to disease-free survival in the adjuvant setting. And that showed, really, that those patients who received nivolumab with chemotherapy had a longer event-free survival by about 1 year. They had very similar toxicity between the 2 arms and no real addition of toxicity when nivolumab was added to chemotherapy in the neoadjuvant setting. And the surgical outcomes appeared good, perhaps even better in the nivolumab plus chemotherapy arm. So that led to the incorporation of the neoadjuvant paradigm in the NCCN guidelines.

More recently we've had press releases on 2 other large, phase 3 neoadjuvant trials. That's the AEGEAN trial which looked at neoadjuvant chemo plus durvalumab followed by 1 year of adjuvant durvalumab. A press release has suggested that it's positive both for pathologic complete response and for event-free survival. And most recently we've also had a press release on the KEYNOTE-671 trial, which was neoadjuvant chemo plus pembrolizumab followed by adjuvant pembrolizumab in the postoperative setting. And that is also reportedly positive for the event-free survival endpoint. So we should see those reports very soon. They're not yet in the guidelines, obviously, and I think people will be looking at that question of what does neoadjuvant alone do, and do you need an adjuvant portion of anti-PD-1 or PD-L1?

There are several other earlier phase trials which have looked promising, NADIM I and II, in particular, 2 studies conducted in Spain, phase 2 trials. Patients received neoadjuvant carboplatin/taxol and nivolumab followed by adjuvant nivolumab. Very promising results in both trials, particularly on NADIM II, which suggested a hazard ratio for overall survival of 0.4. I know it was a phase 2 trial, but I think adds to the support for the neoadjuvant paradigm.

We're also awaiting results from 2 other trials which have completed accrual. That's CheckMate 77T, which was neoadjuvant chemo/nivolumab followed by adjuvant nivolumab, and IMpower030, which was neoadjuvant chemotherapy plus atezolizumab followed by adjuvant atezolizumab. And those, I expect to report out in the next couple of years. Finally, there's been a lot of interest in monotherapy, anti-PD-1 or PD-L1 alone, and we've conducted some of those trials. And most recently, we're starting to see combination immunotherapy, so the NEOSTAR 2 trial reported in *Nature Medicine*, and this was looking at platinum doublet chemo plus ipilimumab and nivolumab. And that trial for that combination showed a very high pathological complete response, and you could envisage we're now probably going to move into a scenario where people are giving novel agents in the neoadjuvant setting, trying to drive up that pathological complete response rate, and eventually, hopefully, lead to prolonged survival and moving novel agents more quickly from advanced disease to earlier-stage disease.

Dr. Socinski:
Yeah, Patrick, although the major pathologic response or complete pathologic response seems like a very good surrogate endpoint, we'd like to have proof of concept that this goes from an event-free survival advantage to an overall survival advantage. You mentioned early on, we are, I guess, beginning to see that in the ADAURA trial with further follow-up.

But certainly, all of these trials raise a number of different questions, which you've covered quite nicely. I wonder if you could just kind of give me your thought about the issue of induction chemoimmunotherapy versus immuno-monotherapy.

Dr. Forde:
Yeah, so we're limited to a degree in that the phase 3 data we have available at the moment is really on a neoadjuvant chemoimmunotherapy. We don't have randomized, phase 3 data for monotherapy. But some of the phase 1 and phase 2 data we have in the neoadjuvant setting for single-agent PD-1 or PD-L1, is actually fairly encouraging. So you see lower complete path response rates – maybe in the region of 10%, with single-agent PD-1 or PD-L1 – but also very low rates of toxicity compared to, say, a platinum doublet. And I think perhaps in the future, we may see larger trials looking at monotherapy, perhaps even for lower-risk patients, where you don't necessarily want to expose them to chemotherapy, but their risk is not zero of relapse, and situations where perhaps exposing them to a PD-1 or PD-L1 in the neoadjuvant setting would have a lower risk. At the moment, though, I don't generally administer single-agent PD-1 or PD-L1 outside of a clinical trial in the neoadjuvant setting simply because we don't really have robust, randomized data showing showing it's the best strategy. But in the future, I could envisage it becoming something we look at in more detail.

Dr. Socinski:
Yeah, sure, and it would be nice to have some biomarker information on what patients might be best served with monotherapy versus combination therapy.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Mark Socinski, and here with me today is Dr. Patrick Forde. We're discussing personalizing treatment in early-stage non-small cell lung cancer.

Let's let's transition here, because I think the vast majority of patients come to medical oncology after surgical resection, so it kind of transitions to the adjuvant setting, and I just want to get your thoughts about the role of adjuvant immunotherapy. You've mentioned the IMpower010 trial, and the PEARLS trial previously, but what are some of the strategies, key outcomes that influence your decision-making in the adjuvant setting?

Dr. Forde:
Yeah, I think it's a very good point, Mark. For years the vast majority of patients have gotten adjuvant therapy for non-small cell lung cancer, not neoadjuvant, perhaps the only exception being clinical stage IIIA with N2 disease, where neoadjuvant was usually preferred. But I think going into the results of these adjuvant trials, they've been something of a mixed bag so far, with the immunotherapy in particular. So we have results from Impower010, which looked at adjuvant atezolizumab for 1 year after adjuvant cisplatin-based chemotherapy. What that study showed, really, was that there was a very significant benefit in terms of disease-free survival for those patients with high PD-L1 tumors, 50% or above. The primary analysis which led to approval was in the 1% or above population, so the FDA approval was in 1% or above. But when you look at the breakdown, it's really that high PD-L1 group derives most of the benefit. And I think for patients who've had surgery and they're coming to our clinics for consideration for adjuvant chemotherapy or systemic therapy, if they have high PD-L1 non-small cell lung cancer and fit the stage groups, I think that's a very good choice for them. So in the 1-49 group, I think it's more of a discussion in terms of the risks and benefits, potentially. And there isn't really a role for adjuvant atezolizumab in the PD-L1-negative group, at least from the results of the trial so far.

The other trial which recently reported out and led to an approval of adjuvant pembrolizumab was the KEYNOTE-091 or PEARLS trial. And what this trial did, really, it had coprimary endpoints of disease-free survival in the overall population, irrespective of PD-L1, and in the PD-L1-high population of 50% and above. And it was somewhat counterintuitive, but the overall population was positive for disease-free survival by the terms of the statistics, but not, so far, in the PD-L1-high group, which is not what you would expect and is kind of different than what we saw in the IMpower010.

Nevertheless, the FDA have approved adjuvant pembrolizumab for patients with stage IB to IIIA non-small cell lung cancer in the setting where they've received adjuvant chemotherapy, and it's approved irrespective of PD-L1 status. So I think that kind of adds complexity in the adjuvant setting.

I think at the moment, the strongest data in the PD-L1-high is with atezolizumab, and I think what PEARLS or KEYNOTE-091 does for us is it brings that discussion to our clinic, where we will talk to patients about adjuvant pembrolizumab who have lower PD-L1 levels or even PD-L1 negative, and discuss the pros and cons of 1 year of adjuvant immunotherapy for those patients to try and reduce the risk as much as possible of relapse of their cancer.

There's a few other studies we're waiting for results on. The ANVIL trial, conducted here in the US, was adjuvant nivolumab, and the BR.31 trial, which was conducted in Canada and Europe with adjuvant durvalumab. And both of those studies are not yet reported out results.

There have been attempts to look at a ctDNA-based strategy or liquid biopsies. So, for example, taking a blood sample/plasma sample after surgery for lung cancer and trying to look for evidence of persistent ctDNA and then trying to pick out that group of patients who are highest risk. Now that study in particular, the MERMAID group of trials, they have actually stopped early because of some challenges in terms of using a tumor-informed assay which requires whole exome sequencing of the resected tumor and turning around that test quickly. But I think lots of people are looking at other strategies as well, like methylomics and other approaches that might allow us to maximize our benefit from adjuvant therapy.

So, Mark, what are your thoughts on all of these trials and what we should do for our patients in the adjuvant setting?

Dr. Socinski:
It's gotten more complex and certainly a little bit of confusion thrown in there with the observations that are quite different in 010 versus PEARLS in the high expressers, so. But I do agree with you. It does open up the option for the PD-L1-negative population.

So, Patrick, I also wanted comments on some patient selection considerations when you're trying to decide neoadjuvant, adjuvant, these sorts of things.

Dr. Forde:
Sure. If the patient is referred for consideration of neoadjuvant, one of the first questions I consider is whether this is a patient fit enough to have chemotherapy, because our current neoadjuvant approach is chemo plus immunotherapy. If they are, then I'll go through the

pros and cons of that. I think stage IIIA disease is probably where there's the strongest benefit for neoadjuvant therapy. And then the patients we see in the adjuvant setting, again, where the toxicity is there and there's a relatively modest though true benefit in overall survival, and I think we'll have to apply that as well with adjuvant immunotherapy, keeping in mind that we don't yet have overall survival data there. And we will have to keep that in mind in talking to our patients.

Dr. Socinski:
Well, Patrick, this certainly has been a fascinating conversation. That's all the time we have today. I certainly want to thank our audience for listening in and thank you Dr. Forde, for joining me. It was great speaking with you today.

And be sure to tune in to our other episodes in Keeping Pace series for additional discussions on non-small cell lung cancer. Thank you very much.

Dr. Forde:
Thanks, Mark.

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