Transcript Details

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Keeping Pace in Lung Cancer: Personalizing Treatment in NSCLC: Locally Advanced Disease (Stage IIIB/C)

Announcer:
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Dr. Socinski:
Hello, and welcome to this Keeping Pace in Lung Cancer education series. In recent years, the treatment landscape of locally advanced non-small cell lung cancer has changed dramatically. Consolidative immunotherapy after concurrent chemoradiation is now the new standard of care. Today we're going to discuss personalizing treatment for patients with locally advanced non-small cell lung cancer in this new landscape.

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

Dr. Higgins:
And I'm Dr. Kristin Higgins.

Dr. Socinski:
So, Kristin, can you start us off with an overview of the role of immune checkpoint inhibitors in locally advanced unresectable non-small cell lung cancer?

Dr. Higgins:
Sure, and I think before we discuss that, it's important just to lay the context and realize where we were at with best chemoradiation in stage III non-small cell lung cancer. We know from RTOG 0617 that the 5-year overall survival is 32% with radiation therapy and concurrent chemotherapy. This is, of course, relatively dismal knowing we can only cure about a third of patients. Patients would develop metastatic disease, and it would generally be very challenging to treat these patients. I think broadly speaking, as a field, we were really looking for the next step that could reduce distant metastatic disease and help our patients live longer.

There began to develop this excitement of adding immunotherapy after chemoradiation. We know that chemoradiation can prime the immune system, we can increase antigen release from the tumor, increase PD-L1 expression in the tumor and the tumor microenvironment, and perhaps by adding immunotherapy after chemoradiation, we could see synergies and then potentially improve clinical outcomes for our patients.

Dr. Socinski:
And so the approval of durvalumab in this setting really dramatically changed the treatment landscape in this setting. What data from the PACIFIC trial, really, in your opinion, contributed to this shift?

Dr. Higgins:

So the PACIFIC trial was really an exciting study. It was seminal in that it showed that we could improve overall survival by adding 12 months of immunotherapy given every 2 weeks after completion of concurrent chemoradiation.

I think it's important to first discuss the eligibility criteria for the PACIFIC study and understand how we can then apply immunotherapy to our patients. So first of all, this is a patient population that was relatively robust, an ECOG performance status of 0 or 1, patients that were eligible for curative-intent chemoradiation; they had to receive at least 2 cycles of concurrent chemotherapy. They completed their chemoradiation, and then were registered into the study after completion of chemoradiation, knowing that their scans had shown no evidence of disease progression. Also, importantly, they had to have resolution of high-grade toxicities. Patients then went on to receive immunotherapy every 2 weeks for 1 year.

I think the first important point is toxicity. Certainly, when we had less experience with immunotherapy, we were really worried about whether or not we would cause pneumonitis. As we know, pneumonitis is a toxicity from chemoradiation alone, about 7% of patients develop pneumonitis after chemoradiation, and people were worried, well, if we add durvalumab, will this become a toxicity that's just too difficult to manage? And the answer was no. High-grade pneumonitis was less than 5% in patients that received durvalumab. Really a manageable toxicity. So I think that's the first key thing.

And then of course, the second key thing is improvements in progression-free survival [PFS] and overall survival. If you look at the most recent update from the PACIFIC study, 5-year overall survival is 43%. That is markedly improved from that 32% that I mentioned with best chemoradiation. It's really, I think, powerful to be able to sit with our patients when we counsel them about chemoradiation and immunotherapy and tell them that we're getting close to curing almost half of our patients with this treatment paradigm.

Of course, I think it's important to note that we still have work to do. Progression-free survival at 5 years is only 33%. And I think that shows us that we've got to take this further. We've got to keep adding to the PACIFIC regimen to continue to cure more patients and really continue to move the needle for this group of patients for which no improvements had been seen for so many years.

Dr. Socinski:
Yeah, and just to make a point, Kristin, it wasn't for lack of trying in terms of phase 3 trials looking at different chemotherapy backbones, looking at dose escalation, looking at the integration of cetuximab and a few other things along the way. So the notable thing about PACIFIC is that this was really the first large phase 3 trial that changed the standard of care.

Dr. Higgins:
Absolutely. As a radiation oncologist, dose escalation was one of the things that we absolutely expected to improve overall survival. How could we not improve survival if we give 74 Gy compared with 60 Gy? And we were sorely mistaken.

Dr. Socinski:
Yeah. And I just want to kind of get your opinion on this because obviously, as you noted, the PACIFIC trial required patients to get through concurrent chemoradiotherapy to resolve all their toxicities and be randomized within 6 weeks of that. In your practice at Emory, what percentage of patients don't meet those criteria? I know in my experience that with proper management during concurrent chemoradiotherapy, we get the vast majority – I would say 90+% are able to get to the consolidative immunotherapy. But do you have a similar experience at Emory?

Dr. Higgins:
Yes, I would say the main reason that makes patients ineligible for immunotherapy is that they're not candidates for the chemoradiation part. I think for patients that are candidates for chemoradiation, we can get them through, we manage that esophagitis that's peaking at the end of treatment with IV fluids, we can get them to get that infusion of immunotherapy within 42 days. I agree with you; I think it's close to 90%.

But I do think there's an unmet need for those patients that are ECOG performance status 2 and not eligible for concurrent chemoradiation.

Dr. Socinski:
Yeah, I think this is a situation, as they say, an ounce of prevention is worth 2 ounces of cure, to manage patients appropriately during the concurrent, try to ameliorate the esophageal toxicity as best as one can. Of course, we rely on our radiation colleagues like you to kind of avoid as much of the esophagus as possible, although that's not always easy to do. But to try to make sure that you prospectively manage. Don't let the toxicities get the better of the patients so it erodes performance status or it takes too long to recover in these sorts of things. So I think those are tips for our listeners today, to be aggressive in the supportive care during the concurrent chemoradiotherapy so patients don't miss out on the opportunity. That window of 6 weeks, I think, is important. Do you ever go beyond the 6 weeks in offering or recommending this for patients?

Dr. Higgins:
You know, occasionally. Sometimes there's patient-driven factors. A patient might have a vacation or something that they really need to do. Or sometimes we'll have high-grade esophagitis that it just takes a longer time to resolve than what we expect. So if it's still within reason, then yes, we will occasionally go beyond that. You know, if it's somebody that's in the hospital for, you know, a prolonged period of time, if there's pneumonitis, those are the patients that we will generally forego immunotherapy if we're really not able to get that pneumonitis resolved.

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

There's a lot of excitement around clinical trials that are currently ongoing in now the locally advanced non-small cell lung cancer space. What should our audience know about some of the important trials that are currently ongoing?

Dr. Higgins:
Yeah, so I think the first major question is around the timing of immunotherapy. Potentially, is it better to give immunotherapy sooner at the outset of the concurrent chemoradiation? We do have some data looking at that approach. The KEYNOTE-799 trial is a non-randomized phase 2 trial that has been published. In this study, there's 2 cohorts, a squamous cohort and a non-squamous cohort, and patients received one cycle of chemotherapy and then received concurrent chemoradiation with pembrolizumab that then continued on for 1 year. The primary endpoint of this study was overall response rates. Both cohorts had overall response rates of greater than 70%. And the other endpoint was grade 3 or higher pneumonitis. And importantly, it was less than 10% in both arms. In the squamous cohort, we saw grade 3 and higher pneumonitis rates of 8% and 6.9% in the non-squamous cohort. So I think that those are manageable numbers. We certainly would expect some heightened pneumonitis if we're giving immunotherapy concurrent with chemoradiation.

The follow-up on this trial isn't long enough to really assess median overall survival. It hasn't been yet reached. However, the 2-year overall survival is really promising: 64% in the squamous cohort and 71.2% in the non-squamous cohort. So I'm excited about the concurrent approach.

There is a large phase 3 trial that's ongoing right now in the United States, an ECOG trial, EA5181. And this trial, I think, will really be the definitive trial that is assessing concurrent immunotherapy. This time durvalumab is given concurrently with chemoradiation and then continued on consolidatively. And this is compared directly to the PACIFIC regimen. And this is a large trial, over 500 patients. It's accruing quite well. I think we would expect to see it meet accrual, probably, potentially by the end of the year. And I think that the data out of EA5181 will really signal which way to go. Is it better to stick with just giving the durvalumab after chemoradiation? Or can we give it sooner, potentially give more patients the opportunity to benefit from immunotherapy? Is there more synergy? Those are all sort of important questions that are unanswered. So that'll be exciting data that will read out soon.

Dr. Socinski:
And what about immunotherapy combinations?

Dr. Higgins:
So yeah, and I think that's the other area that there's so much work going on, and there's so many trials that are ongoing that we'll see. There's a study called the KEYLYNK study, which is an industry-sponsored study that is kind of building on KEYNOTE-799. It's looking at that concurrent pembrolizumab and chemoradiation approach, but then it will add a PARP inhibitor with pembrolizumab in the consolidative setting after radiation is complete. And that trial is a phase 3 trial. It's randomized 1:1:1, so pembrolizumab plus or minus olaparib plus or minus placebo compared with, then, the PACIFIC regimen. I think that'll be an interesting study. There's certainly preclinical data showing that PARP inhibitors could be beneficial in patients that are receiving immunotherapy.

And there are other targets also. There is some interest in TIGIT as a target. There are multiple trials right now that are underway looking at anti-TIGIT along with immunotherapy. There's the KeyVibe trial, which, again, is that concurrent pembrolizumab plus or minus an anti-TIGIT molecule compared with the PACIFIC regimen. And there's also the SKYSCRAPER-03 trial, which is not looking at concurrent immunotherapy, it's just that PACIFIC backbone, and then it randomizes patients to atezolizumab plus tiragolumab compared with durvalumab. And these are all trials, again, adding to PD-L1 inhibitors or PD-1 inhibitors.

There's also another study I should mention, the PACIFIC-9 study. And this is a follow-up phase 3 trial from the COAST study that added oleclumab and monalizumab to durvalumab in the consolidative setting. And this study will be a phase 3 trial. It's enrolling currently.

And so we have a lot of different potential options for our patients. And it will be really interesting to see what these trials look like in terms of progression-free and overall survival. I really hope we can move the needle from that PFS of 33% at 5 years. That's not good enough. I think we've got to do better. You know, of course, toxicity will be important, too, because this patient population, they do have

side effects from their therapies. And they have, sometimes, side effects from things like smoking and heart disease and things like that. So I think the toxicity may drive how we interpret the results of all these different trials, because we'll really see a lot of different data coming out probably at the same time.

Dr. Socinski:
Yeah, this has been great. Obviously, PACIFIC was such an important trial. And now we're building on the observation shown there. And I completely agree with your sentiment about doing better with regard to both PFS as well as overall survival.

Well, Kristin, this has been a fascinating conversation. Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank you, Kristin, for joining me today. It was great speaking with you.

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

Dr. Higgins:
Thank you.

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