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Updates in Limited-Stage Small Cell Lung Cancer (LS-SCLC)

Announcer:
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Dr. Liu:
Welcome to CME on ReachMD. I'm Dr. Stephen Liu and here with me today to discuss therapeutic advances in limited-stage small cell lung cancer, Dr. Joshua Sabari and Dr. Susan Scott. Josh, can you begin by walking us through some of the data regarding the integration of immunotherapy into the care of this patient population?

Dr. Sabari:
So Steve, first off, thanks for having me. This is the ADRIATIC study. It is a practice-changing study, really to assess whether adjuvant therapy with durvalumab, a PD-L1 inhibitor, would prolong survival among patients with limited-stage small cell lung cancer.

So patients enrolled had limited-stage disease, stage I to III, good performance status, 0 or 1. And remember they hadn't progressed on prior concurrent chemotherapy and radiation. We did allow for PCI prior to randomization here. This is a large study, 730 patients randomized to three arms, the treatment arm being durvalumab, the control arm here being placebo. Primary endpoint here, overall survival, as well as progression-free survival.

And Dr. Liu, the data was quite impressive, and as I mentioned, practice-changing. So median overall survival for those patients who received concurrent chemotherapy and radiation, which previously was the standard of care, now followed by durvalumab on this trial, was 55.9 months, compared to those who received placebo at only 33.4 months.

This is something that I'm doing in my clinical practice. There was a slight increase in adverse events, but when you look at grade 3 or 4 treatment-related adverse events, very similar in the durvalumab-treated arm versus the placebo arm. So really an exciting trial, an exciting data set, something that I think has penetrated the clinic for all patients.

Dr. Liu:
Yeah, completely agree. Some key points there, durvalumab 2-year duration, little different from what we see in some of the later-stage settings and other clinical trials. Also that point you made is very important. We're including people after completion of chemoradiation, so sort of a selective patient population. That absolute difference in median survival, I think, breathtaking. Hazard ratio of 0.73, certainly meeting our criteria for significance. Actually, very similar to what we see in CASPIAN, what we've seen in IMpower133, showing that we can just make a bigger absolute difference in earlier stages. We want to catch these earlier.

It's not the only study looking at immunotherapy in limited-stage small cell lung cancer. And Susan, how do these data from ADRIATIC compare to that of NRG-LU005?

Dr. Scott:
Yeah. So the NRG-LU005 study is similarly adding immunotherapy to our current concurrent chemoradiation backbone with platinum

chemo. But there's a few key differences in the study design. This study randomized patients after their first cycle of platinum etoposide chemotherapy. They were then randomized to concurrent chemoradiation with or without atezolizumab every 3 weeks. So as opposed to the ADRIATIC study where durvalumab was started after the completion of chemoradiation, LU005 looked at concurrent immunotherapy with the chemoradiation.

So this also had some differences in inclusion criteria. They included patients with a ECOG performance status of 2, which was different. And then they also continued the atezolizumab only for 12 months after chemoradiation, which was a year shorter than ADRIATIC. They stratified by cisplatin versus carboplatin, daily versus BID, and the lower performance status 0–1 versus 2. The main primary endpoint was overall survival. Secondary endpoints were progression-free survival, overall response rate, and PCI was recommended but not required in this study.

And then we want to talk about the outcome. So there was, unfortunately, no difference in the overall survival with or without atezolizumab. So this is a bit surprising given the stark improvement we saw with durvalumab. There was no difference in progression-free survival, no difference in distant metastasis- free survival, or the overall response rate. Pneumonitis is, of course, a concern, as Josh mentioned, with immunotherapy and radiation given together or around the same time. There was a higher rate of grade 3 or 4 pneumonitis at 5.6% with the atezo compared to 3.1% in the non-atezo arm.

But overall, I think the headline here is that there was no benefit. And the implication here is that we're not using concurrent checkpoint inhibitor with chemoradiation, but that this is something we're incorporating after. Now, why these are so different is something I'm not sure about. Is it the timing? Is it the duration? Is it the inclusion criteria? Probably all of the above. But right now we have the ADRIATIC regimen.

Dr. Liu:
Yeah, I think that at first a little bit of a head-scratcher if taken in isolation, but coming on the heels of PACIFIC-2 where we saw durvalumab profound benefit in non-small cell lung cancer after chemoradiation, when given with chemoradiation—granted, different patient population because you don't have that selection criteria of people that make it through chemo-rads, so it's a different patient population, but no benefit at all, not even a hint of benefit compared to placebo in PACIFIC-2, really suggests that giving concurrent chemoradiation to your lymph node beds with a PD-L1 inhibitor probably not just the best strategy going forward.

Josh, looking back on these data, how have these studies impacted our clinical practice?

Dr. Sabari:
Yeah. So first off, disappointed to see the NRG study being negative but completely agree. When we look at non-small cell lung cancer, the strategy of concurrent use with IO and radiation therapy has not been successful. So the ADRIATIC study is the clear leader, in my mind. It's what I use now in my clinical practice, limited-stage patients, good performance status, I will get concurrent chemotherapy and radiation followed by consolidation durvalumab.

And remember, this is sort of out of the playbook that we've seen in non-small cell lung cancer as well with the PACIFIC trial. Patients tolerate this therapy well, we have a lot of experience with PD-L1 inhibitors in this setting.

Dr. Liu:
As we know, ADRIATIC, durvalumab 2 years after chemoradiation for limited-stage small cell lung cancer approved by the US FDA, December 4, 2024. Susan, what other research avenues do you find most promising in this area?

Dr. Scott:
Yeah. So we know that chemoradiation has excellent local control, but small cell lung cancer is a systemic disease. So to me, optimizing systemic therapy is paramount.

I'm interested to see the outcomes of DeLLphi-306, which is using tarlatamab maintenance. And maybe bringing other novel therapies like ADCs or bi and trispecific antibodies and others. But most importantly, we need precision in small cell lung cancer. You need to use molecular biomarkers to identify the patients most likely to benefit from each of these therapies, and I hope we have more options to come.

Dr. Liu:
Yeah. Well said. Well, this has been a great discussion. Unfortunately, our time is up, so thanks for listening.

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