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Novel Therapies in Extensive-Stage Small Cell Lung Cancer (ES-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 novel approaches for extensive-stage small cell lung cancer are Dr. Joshua Sabari and Dr. Susan Scott.

Susan, can you start us off with a brief overview of current standard of care approaches for this group?

Dr. Scott:
Yep. So for extensive-stage small cell, we have two kind of backbone regimens that combine platinum etoposide chemotherapy with an immune checkpoint inhibitor. We have the CASPIAN regimen, which adds durvalumab, and the IMpower133 regimen, which adds atezolizumab. Both of these studies demonstrated an overall survival benefit with the addition of the immunotherapy to the chemo backbone. Both had about a 2-month improvement in the median overall survival. This is likely driven by a subset of patients with durable responses. In the CASPIAN study, there was a three times increase in the overall survival at 3 years, from about 6% to 18%. So these are our standard of care options right now.

The IMforte trial is really noteworthy, as it's the first phase 3 trial to show both progression-free and overall survival improvement with frontline maintenance therapy. Stephen, could you tell us more about this study, given your involvement?

Dr. Liu:
This was a randomized phase 3 trial for patients with extensive-stage small cell lung cancer. All received four cycles of standard carboplatinum, etoposide, and atezolizumab. After the fourth cycle of induction, those patients who had not progressed and still had a performance status of 0 to 1 were then randomized to standard atezolizumab maintenance every 3 weeks or maintenance atezolizumab plus lurbinectedin 3.2 mg/m^2 with primary GCSF prophylaxis. Now, what we saw was giving lurbinectedin in that maintenance setting improved progression-free survival from 2.1 months with atezolizumab to 5.4 months with lurbinectedin and atezo. Remember, those absolute numbers are in the maintenance setting, so you have to add the 3.2 months of induction therapy to sort of compare to other studies. But that PFS benefit is pretty profound. Hazard ratio 0.54. The 6-month PFS rate 19%, up to 41%. So an improvement in PFS. But it comes at an increase in toxicity. The rate of grade 3–4 treatment-related adverse events, about 25% with lurbinectedin and atezo compared to about 6 or 7% with atezolizumab alone.

Now, an increase in PFS and increase in toxicity is what we expect with any maintenance regimen that's active. The real question: does this translate to an improvement in overall survival? And here, it did. The addition of lurbinectedin increased overall survival from 10.6 months to 13.2. Again, adding the 3.2 months of induction. The OS hazard ratio 0.73. So an improvement in survival by giving lurbinectedin early. And while it does increase toxicity, if you look at the rate of discontinuation—stopping drug due to adverse event—

only 6% with lurbinectedin compared to 3% with atezolizumab. So I think a tolerated regimen that translated into people living longer.

Unfortunately, even with this approach, while survival is longer and improved, most patients still do relapse and are in need of other therapy. And so if we look at pure second-line treatment, what about tarlatamab? Josh, can you tell us a little bit more about tarlatamab and what's been seen in recent clinical trials?

Dr. Sabari:
Yeah. So tarlatamab is an interesting therapy. It's a BiTE, or a bispecific T cell engager. It targets both you know DLL3, which is commonly overexpressed in neuroendocrine cancers including small cell, really not expressed in normal tissues in the body. And it also targets the CD3, the T cell engager. So really interesting, novel mechanism.

So Delphi 304 is the confirmatory phase 3 study. this is a randomized controlled trial in the second-line setting of tarlatamab, The CD3, DLL3 BiTE, versus chemotherapy alone in patients with extensive-stage small cell lung cancer who had prior chemo and PD-1 or PD-L1 therapy. We did stratify by what prior therapy they received, prior PD-1 or PD-L1. We also looked at chemotherapy-free intervals, whether they had brain metastasis.

Primary endpoint here, overall survival, as well as progression-free survival. Stephen, this is one of the most exciting sort of data I've seen in the small cell lung cancer space in quite some time. A dramatic improvement in overall survival, median for tarlatamab, 13.6 months versus chemotherapy alone at 8.3 months. And remember, we've seen very sort of meager improvements in progression-free survival. And I think this study is the same, right? Progression-free survival for tarlatamab 4.2 months versus chemotherapy at 3.7 months. But really, we're seeing those patients who do respond are obtaining durable responses, something that has been elusive in the small cell lung cancer space. At what cost? So there is dramatic increase in toxicity with this agent versus standard of care. And important to sort of state that the control arm is dealer's choice here. Standard of care could be topotecan, it could be lurbinectedin, or other agents used in clinical practice.

So we're seeing high rates of CRS, or cytokine release syndrome, generally occurring 13 to 14 hours after the first infusion, Cycle 1, Day 1. Most patients you know or all patients really on this trial are admitted and observed for 24 hours. We're also seeing ICANS or neurological toxicity related to the immune activation with these therapies. We have a lot of experience with these agents and we feel comfortable managing them, but if you're starting them for the first time, really important to look at how to administer them, what to look out for, using early steroids, for example, as well as IL-6, anti–IL-6 inhibitors, tocilizumab, if needed.

So this is an exciting study, Steve. DeLLphi- 304 really affirmed tarlatamab as a new standard of care in patients who were previously treated with small cell lung cancer.

Dr. Liu:
Yeah. Completely agree. Really a practice-affirming study. That OS hazard ratio of 0.6 is something we can't argue about. So where available in patients that are eligible, this clearly becomes our preferred second-line option, and we'll see how this space continues to evolve.

Susan, how are you using this drug in practice today? Do you agree that this is sort of our preferred second-line option off study?

Dr. Scott:
It is. Yeah, I think I'm definitely using tarlatamab before lurbinectedin for my patient post-platinum now. I'm interested to see if we start to use maintenance lurbinectedin, how that might change. But for right now, it maintains its place as my kind of go-to post-platinum, usually second-line therapy.

Dr. Liu:
Yeah, I would completely agree. And I should mention that the maintenance lurbinectedin doesn't preclude use of tarlatamab in that second-line setting. So really, we want our patients to benefit from all of these agents.

And it's nice to see a lot of other drugs being developed in this space. We have a lot of antibody-drug conjugates targeting B7-H3, targeting DLL3, targeting SEZ6. For example, ABBV-706 is an antibody-drug conjugate with topoisomerase I payload that targets SEZ6, highly expressed in small cell, has shown very promising response rates. We have a number of B7-H3 ADCs, including ifinatamab deruxtecan, YL-201. We have new agents targeting DLL3 that we're seeing about. There are a lot of unique proteins that serve as pretty good targets for ADCs, and they do seem to be topo I sensitive.

Susan, do you think antibody-drug conjugates are eventually going to play a role in the evolving treatment landscape of extensive-stage small cell lung cancer?

Dr. Scott:

I hope so. And I'm hopeful that early activity is really encouraging. I'm looking forward to more biomarker-directed studies. I like the use of SEZ6 and DLL3 as kind of targets for some of these ADCs. And I'm hopeful that we'll kind of refine these approaches and get some really powerful agents to help our patients.

Dr. Liu:

Yeah, we're always in the need for new agents. And it also appears we're beginning to see a shift towards some targeted therapies in this setting too. Joshua, are there other approaches or clinical trials that you're excited about for patients with extensive-stage small cell lung?

Dr. Sabari:
I mean, we saw updated data on a TrITE, a trispecific T cell engager. I mean, we're trying to target DLL3. So we talked about bispecifics engaging the immune system. We also talked about ADCs in this space, and we just mentioned the SEZ6 as well. So this is an exciting time, because in small cell lung cancer, where we only had these tumor suppressor loss—RB1, p53, very difficult to target in the clinic, we're now starting to see unique biomarkers emerge where we're actually seeing sort of the gains from all of our work in the lab.

So this is a really exciting time.

Dr. Liu:
Joshua, Susan, great insights to wrap up a brief discussion. Thanks for listening.

Announcer:
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