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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Assessing Advancements in Treatment Options for Small Cell Lung Cancer

Dr. Sands:
After more than a decade without any new approvals in small cell lung cancer, we've seen some exciting advances in the field. What those developments are and what they could mean, for patients and clinicians alike, is what we'll be exploring today.

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and joining me to discuss updates in small cell lung cancer is Dr. Taofeek Owonikoko, Professor and Vice Chair for Faculty Development in the Department of Hematology and Medical Oncology at Emory University School of Medicine. Dr. Owonikoko, welcome to the program.

Dr. Owonikoko:
Thank you, Dr. Sands. Happy to be here.

Dr. Sands:
I'm very excited to discuss this topic with you today, with all the new things going on, but let's start with first-line extensive stage disease, where we've seen multiple positive trials incorporating immunotherapy. Are you able to provide an overview, and what is your preferred regimen in the first-line setting of extensive stage small cell lung cancer?

Dr. Owonikoko:
Thanks for that question, and it's really exciting where we find ourselves these days, when it comes to treatment of small cell lung cancer. We've gone to a situation where we had only one option to where you can actually ask me about my preferred regimen. The studies about products this far, as we all recognize, are the studies of combination of immunotherapy and chemotherapy, and specifically we're talking about IMpower133 that combines atezolizumab with platinum doublet chemotherapy and shows that that regimen is superior to chemotherapy alone. We also have the CASPIAN trial. We have the arm of the trial that combined durvalumab with chemotherapy, outperformed chemotherapy alone. While the combination of pembrolizumab, as well as nivolumab with chemotherapy did not result in label indication at this point, we know that the trend from those trials, the KEYNOTE-604 and the ECOG-ACRIN 35161 were also this strategy in patients. For me, the combination of atezolizumab with chemotherapy or durvalumab with chemotherapy is equally important and useful for patients, and I tend to use one or the other, depending on specific concentrations that I have to the patient in front of me.

Dr. Sands:
So, just out of curiosity, then, what are some of those considerations, as far as whether you choose atezo or durva in the first-line setting with chemotherapy?

Dr. Owonikoko:
So there are a few basic concentrations that come into play, based on the design and the conduct of the trials. When I have a patient with brain metastasis that is asymptomatic, especially one that is very small, and does not require immediate use of radiation therapy, I'm more likely to go with the CASPIAN regimen of durvalumab with chemotherapy, because that trial allowed for patients with asymptomatic brain metastasis to come on this study. So that would be the one differentiating factor. The other factor would be whether or not I'm able to use carboplatin or cisplatin for the patient. The CASPIAN trial allowed for both agents to be used. The IMpower133 only used carboplatin, and we cannot just extrapolate and decide to use cisplatin. We know that majority of our patients with extensive-stage disease will tend to use carboplatin, but there are a few clinical concentrations that will make one consider cisplatin over carboplatin. One that comes readily to mind would be a patient with extensive marrow replacement, with cytopenias, where we perhaps would anticipate more hematologic cytotoxicity from carboplatin, and then you might elect to use cisplatin in that regard. For such a

patient, the available prospective then would be to use durvalumab along with cisplatin-based doublet chemotherapy.

Dr. Sands:
So, now we're gonna transition into second and beyond, because that's where things really get interesting. So, lurbinectedin was granted accelerated approval by the FDA, based on a single arm basket trial. But recent data from the randomized trial of doxorubicin and lurbinectedin was negative, compared to CAV versus topotecan, or at least was not a statistically significant difference, per the initial report we've gotten, although we still have details that we're waiting for. What do you see as the role for lurbinectedin right now, and what are you thinking looking forward?

Dr. Owonikoko:
The results of the ATLANTIS trial that compared lurbinectedin along with doxorubicin as a combination regimen, against topotecan or standard of care option in patients, was actually somewhat of a surprise, and to a great degree disappointing, because the approval for lurbinectedin, based on the single arm trial of single agent lurbinectedin, we were all hopeful that the time has finally come when we are going to have another approved standard option along with topotecan in this setting. While we don't have the full details yet as to the specific result for the trial, we are going by the information released by the study sponsor, saying that the study failed to meet its prespecified efficacy endpoint. So while this is a setback for the approval process for this compound, I think we still all have to wait for two things – one is the full details of the results of the trial, so that we get a better sense of why it failed to translate into a superior regimen over topotecan. More importantly for our patients would be the regulatory decision. What is the FDA going to do going forward? Are they going to allow them to keep the approval, so that still remains available for use for our patients, while demanding additional evidence of supported efficacy, or are they going to take away the accelerated approval that was granted before, which would then significantly limit the use of lurbinectedin to investigational settings only? Hopefully, we'll get some clarity with this in the next several months, and only then can we really start having practical strategies on how to access the drug and how best to use it.

Dr. Sands:
So with that in mind about lurbinectedin, Topotecan has really been the FDA approved option, and of course there are a lot of other treatments that are utilized off label. So what is your preference and practice? How do you utilize lurbinectedin along with Topotecan and other off label options?

Dr. Owonikoko:
My preference in terms of salvage therapy, I tend to go with paclitaxel, for several reasons. While this is not an FDA-approved drug, it has guideline recommendations through professional bodies such as NCCN, as in those by ASCO and ESMO, and other organizations like that, that we have several nonrandomized trials that showed the efficacy of this drug. It's already approved in other tumor types, with no side effect profile, and patients tend to tolerate it well, especially when given on the weekly schedule. The other agent that I started using in the last several months, based on the FDA approval, was lurbinectedin. With the results of the ATLANTIS trial, I have not changed my practice. I still consider lurbinectedin an option at this point, because the approval is still in place, and we have to remember the approval was not based on the ATLANTIS trial that is negative. The ATLANTIS trial was meant to provide additional support to the single arm trial that showed some signal of efficacy. So until we have some additional regulatory approval and decision, I think lurbinectedin will remain a part of our salvage therapy regimen going forward. One other drug that I tend to use, especially when I'm thinking of convenience for patients, is temozolomide. This is orally administered, and it doesn't require the patient to come in for weekly infusion as we do with paclitaxel. So these are some of the drugs I use.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking today with Dr. Taofeek Owonikoko about recent developments in small cell lung cancer. Now Dr. Owonikoko, in non-small cell lung cancer, of course, there is a whole bunch of discussion about biomarkers and targets and such. Within small cell lung cancer, are there any biomarkers? Is there anything being utilized right now?

Dr. Owonikoko:
Biomarkers are still quite investigational in small cell, unfortunately. We know that great effort has gone into testing whether or not PD-L1 expression would help identify patients for salvage immunotherapy treatment, with some signals suggesting increased response rate in PD-L1 positive patients. The challenge of PD-L1 is that overall expression rate is very, very low in small cell – less than 20% of patients would have PD-L1 expression. So it makes it difficult to even start asking the question of what degree of PD-L1 is likely to be predictive. But be that as it may, PD-L1 expression has been shown to correlate with improved response rates with pembrolizumab, for instance. Significant amounts of work and effort went into evaluating tumor mutation, in the CheckMate 032 trial, which initially showed possible impact with patients having high TMB and overall survival advantage of giving nivolumab and ipilimumab together, where almost 62% of those patients were alive at one year, which is unheard of in small cell – even in the front line setting. That is a very, very

high bar that we've not been able to see in unselected patient populations. The challenge with TMB is to date, all the prospective trials that looked at TMB as a potential predictor failed to show any significant association with TMB, and the challenge is it doesn't matter where you put the cut point. You always see benefit above and below that cut point, which then means that while you may have greater benefits with those with high TMB, you are likely to be denying potentially beneficial treatment to those with low TMB, because some of them would still benefit. So, this is quite investigational at this point, and I'm hopeful that down the road, we'll figure out how best to utilize TMB to select patients, especially for immunotherapy. Another area that we are focused on in the last year or two, is now the recognition that small cell lung cancer is not one and the same disease across patients – that we do have sub-types of small cell, even within this single rubric of small cell lung cancer. And this definition, or sub-typing, is based on the transcription of program that drives the growth of the cancer cells, for which we have now recognized four main subtypes, driven by ASCL1, NeuroD1, POU2F3, or YAP1. We don't yet have robust data to show any correlation between these subtypes, and the therapeutic strategies that we're using beats chemotherapy, or immunotherapy. And for some of the works that we recently published, as well as works by others, indicates to us that these subtypes of small cell, over time, would help guide us to select patients whereby we showed that the YAP1 subtype or small cell, has the tumor phenotype, which would suggest that that is probably a phenotype and subtype that is vulnerable to immunotherapy-based strategy. Efforts are still ongoing, but I'm very, very hopeful that in the next couple of years, we are going to find ourselves in the situation where we're able to use reproducible, simple and reliable biomarkers to select patients for therapeutic intervention.

Dr. Sands:
So, you've discussed a lot of what's going on, and for a disease without many approved options, it certainly has some nuances, and you really laid out a lot of those. Now going forward, we're in an exciting time with a number of new drugs in development, particularly within small cell lung cancer. Among these ongoing studies and drugs in development, what are you most excited about?

Dr. Owonikoko:
In small cell, we're getting to the point where the pharmaceutical industry is now paying attention. It's no longer that desert, where nobody wanted to invest their time, effort and res- drug, only to be shown to be ineffective by topotecan. There are a number of studies at advanced stages that I hope might give us newer options. One would be the liposomal Irinotecan trial, that is comparing these to topotecan in relapsed patients as second-line strategy. The study is almost fully accrued, is a global study, and will be very, very interesting to see the results of that trial in the next couple of years, once the overall survival data is in. The other strategy that looks promising – those strategies STARLITE and DLL3. So we know that DLL3 is a biomarker that is very prevalent in small cell. It has direct readout of transcription factor ASCL1 in small cell, and close to 80% of small cell lung cancer samples would have DLL3 expression of different intensity, and the earliest strategy looking at DLL3 as a target was the antibody drug conjugate with rovalpituzumab teserine, which unfortunately due to significant toxicity was not a successful strategy, so that drug is longer in development in small cell, but at least paved the way for our ability to target DLL3 for therapeutic strategy in small cell. Now we have the biospecific T-cell-engaging antibodies that also rely on the presence of DLL3 on small cell, with the benefit of also engaging with CD3 receptors on lymphocytes, and then serving as an anchor that brings the lymphocyte into the tumor microenvironment. The most advanced of these constructs is the compound from Amgen called AMG 757. This has actually enrolled significantly, and early efficacy data presented at the Citi meeting this year showed objective tumor response of around 20%, and stable disease in another 30% of patients, so, clinical benefit rate of somewhere between 50 and 60%. I think that is very, very encouraging for a strategy that's based on antibody therapy only. There is no chemotherapy involved. There is a similar compound being developed by Boehringer Ingelheim, that is already in clinical testing in Europe and very soon should be open to enrollment here in the U.S. So I see these strategies as paving the way for us, for using known biomarkers in small cell to drive therapeutic development.

Dr. Sands:
A lot going on in small cell lung cancer, and after a history of very few advances, this is certainly an exciting time. I look forward to talking to you in the future about some of these advances. I think the conversation in the next year or two is gonna be a different one, and that's exciting. But for now, I want to thank you, Dr. Owonikoko, for joining me to discuss some of these advances in small lung cancer. Absolutely wonderful having you on the program.

Dr. Owonikoko:
Thank you so much, Dr. Sands. A pleasure being here.

Dr. Sands:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit reachmd.com/projectoncology, where you can Be Part of the Knowledge. Thank you for listening.