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

Investigating DLL3-Targeted Immunotherapy: The Potential of T Cells to Fight SCLC

Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Investigating DLL3-Targeted Immunotherapy: The Potential of T Cells to Fight Small Cell Lung Cancer,” is sponsored by Amgen.

Here’s your host, Dr. Jennifer Caudle.

Dr. Caudle:
Small cell lung cancer is an aggressive cancer associated with rapid growth and early metastasis.[1] In 2023, it's estimated there will be approximately 30,000 new cases of small cell lung cancer in the US alone.[2] Small cell lung cancer can either be limited-stage or extensive-stage disease based on if the cancer has spread and where, with approximately two-thirds of patients having extensive-stage disease at diagnosis.[1] How are emerging modalities like T-cell engagers being investigated for this disease? This is Project Oncology on ReachMD, and I'm your host, Dr. Jennifer Caudle.

And joining me to discuss the potential of investigational T-cell engagers and delta-like ligand 3 as a target in small cell lung cancer is Dr. Taofeek Owonikoko.

Dr. Owonikoko is the Chief of the Division of Hematology/Oncology at the UPMC Hillman Cancer Center, and in the Department of Medicine. Dr. Owonikoko also serves as Associate Director for Translational Research and Co-Leader of the Cancer Therapeutics Program at Hillman. He holds the Stanley M. Marks OHA Endowed Chair in Hematology/Oncology Leadership.

Dr. Owonikoko, welcome to the program!

Dr. Owonikoko:
Thank you, Dr Caudle. I'm really excited to be here and to discuss this topic with you.

Dr. Caudle:
To start us off, Dr Owonikoko, what can you tell us about the current state for patients with small cell lung cancer?

Dr. Owonikoko:
Yeah, thank you. You know, as you rightly alluded to in your introduction there, small cell lung cancer remains a very, very challenging disease, devastating disease for a majority of our patients, primarily because majority of these patients will be diagnosed at the more advanced, incurable stage.[1] And while the disease can be very, very sensitive to the initial treatment, oftentimes chemotherapy alone or along with other modalities, such as radiation and immunotherapy, a majority of our patients would eventually progress.[3]

And if you look at historical data and even more recent data from clinical trials, the 5-year relative survival for patients with extensive-stage disease, small cell lung cancer, hasn’t changed much, over the past three decades. That number is somewhere around 5 to 10%.[4] We are beginning to make some progress, the median survival right now, in aggregate is somewhere around 13 months for patients treated with chemotherapy and immunotherapy, which is modest but significant, compared to the median overall survival of 10 months if you only treat patients with chemotherapy alone.[5,6]

The other challenge that we face with this disease, is that we currently do not have actionable driver alterations that we can go after

with, therapeutic targeted agents, or even validated biomarkers that can help us segregate patients into different subgroups, and then treat them accordingly.[1] But I'm very hopeful that this state of affairs will change for small cell lung cancer with ongoing work in this space by us as well as many others around the world.[3]

Dr. Caudle:
So given the significant unmet need in these patients, how is the research evolving?

Dr. Owonikoko:
There has been a lot of research in this space, it's just that advances have been very few and far between.[1] We do have now more recently in the last 5 years, evidence that the addition of immunotherapy, specifically agents targeting the PD-1 signaling axis, when combined with chemotherapy, resulted in better outcomes for patients.[3] Only about 20 to 25% of those patients treated with immunotherapy and chemotherapy will actually make it out to 2 or 3 years out from the initial diagnosis.[7] So that is still a lot of patients that we are leaving behind with what we will consider to be the current standard-of-care.[3,7]

Additionally, about 35% of patients diagnosed with small cell in the limited-stage setting, we've not made any real progress for more than 20 years, since the introduction of combined chemotherapy and radiation.[1,3] But I think where the greatest unmet need resides is actually in the second line and beyond, where we do not have very easy-to-tolerate options. So I would say currently beyond the second line, there is really no standard-of-care for any of our patients.[1,3,8]

Dr. Caudle:
You know with that in mind, let's discuss the role of cytotoxic T cells in fighting cancer. Dr. Owonikoko, can you tell us more about this?

Dr. Owonikoko:
Yeah, I think it's important to emphasize the – the role of the immune system in cancer development and cancer progression, not just in small cell lung cancer or lung cancer, but in oncology as a whole.[9] You know, we've always talked about cancer being a genetic disease, but I also think we should think of cancer as being an immunologic disease. It's a failure of the body's immune system that allows the cancer to develop, establish, and grow.[1,10] Because ordinarily, when the body senses that there is something abnormal with a cell, that cell is recognized as foreign or abnormal, and then the immune cells are recruited to identify those cells and get rid of them.[9]

And one way by which this happens is through the recognition by T cell, of MHC class I protein on the surface of the abnormal cells, in this case the tumor cells. So the binding of the T cells to the tumor cells through recognition of the MHC class I presented abnormal protein, leads to the destruction of those tumor cells.[9] But it is important to know that tumors can often evade immune detection by downregulating MHC I, and through an immunosuppressive tumor microenvironment.[10]

Additionally, when we think about small cell, specifically, you know, works that have been done looking at tissue samples from patients with small cell, we know that the vast majority of these tumors actually tend to be immunologically cold, meaning you do not have any infiltrate of immune cells into the tumor immune microenvironment.[11] So that you have a double whammy problem where it's not just that the immune cells are not able to recognize the cancer cells and get rid of them, there appears to be some barrier created either by the tumor, by the tumor stroma, or the combination of both to exclude the immune cells from getting into the tumor microenvironment and being able to get rid of the tumor.[12] So being able to turn small cell lung cancer, which in about 80% of cases will be a cold tumor, into a hot tumor, that you can actually mobilize the immune cells into that environment.[13]

Dr. Caudle:
That's very interesting. So can you tell us about T-cell engagers as a novel modality under investigation in small cell lung cancer?

Dr. Owonikoko:
Yeah, so there are many novel approaches; T-cell–engaging antibody being one of them. And this has been actively investigated in small cell.[3,14]

This is a modality that is designed to direct the patient own T cells to target a specific tumor-associated antigen on tumor cells, without relying on the normal T-cell recognition of the MHC I presentation of the antigen.[10]

And once the T-cell–engaging molecules bind to the tumor-associated antigen on the tumor cells, and at the same time able to bind to CD3 on T cells, you have then the creation of an immunological synapse, that leads to the activation of the T cells.[10,15] The activation of those T cells now leads to what we expect to happen with activated T cells with creation of perforin pores in the tumor cell membrane. This allows for cytolytic granzymes being released, and the induction of apoptosis, and death of the tumor cell.[15] At the same time, the tumor cell death will also activate more cells to proliferate, leading to expansion of T cell beyond the initial T cell that was to present into

the environment to potentially facilitate additional T-cell–dependent killing.[15]

Dr. Caudle:
Thank you. Now how are BiTE® molecules designed?

Dr. Owonikoko:
BiTE® refers to bispecific T-cell–engaging molecules, which consists of 2 single chain variable fragment domains designed to bind the cell surface antigen on tumor cells, and at the same time recognize CD3 on T cells.[10] Some of these have also been engineered specifically to silence their Fc domain so that they do not get destroyed, and then they can stay in circulation for an extended period of time. So they have what we call the extended half-life.[16]

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD, sponsored by Amgen. I'm your host, Dr. Jennifer Caudle, and today I'm speaking with Dr. Owonikoko about the prospects of investigational T-cell engagers in small cell lung cancer.

So, Dr. Owonikoko, let's turn our attention now to delta-like ligand 3, or DLL3 for short. Can you tell us a little bit more about this potential target for T-cell engagers?

Dr. Owonikoko:
Oh, sure. You know, DLL3, still a lot is unknown about the biological function of this protein.

But what we do know is that it's an inhibitory protein that is involved in Notch signaling. And that is the pathway, the notch pathway is - that's known to be involved in embryonic development, as well as neuroendocrine cell differentiation.[1] You know, typically in healthy cells, DLL3 is typically found located within the Golgi apparatus and the cytoplasmic vesicles. They're rarely expressed on the surface of the cell.[17] But in high-grade neuroendocrine tumors, such as small cell lung cancer, we find aberrant expression of DLL3 on the surface of the cell, therefore making these a potential target for therapeutic development.[1]

Dr. Caudle:
And how prevalent is DLL3 expression among patients with small cell lung cancer?

Dr. Owonikoko:
That's a very good question. A lot of work has been done, and I think the most impressive is a large multicenter study of about 1,050 patients, with small cell lung cancer, where 85% of the samples tested using immunohistochemistry showed the presence of DLL3 on the surface of the cells. Specifically, these tests rely on the surface expression of at least 25% of the tumor cells are to be positive.[18]

And, one thing to know – to note, however, is that in this study, DLL3 was considered present if the tumor cells showed punctate and/or diffuse cytoplasmic and/or partial circumferential membranous staining. So it's not just surface expression alone but also cytoplasmic staining that was considered positive.[18] When you look at this overall prevalence of about 83% or 85% positivity actually was consistent across disease stage; it did not matter whether it was limited-stage or extensive-stage disease. The proportion of cells expressing DLL3 was consistent.[18] And also, it did not seem to change, whether you're looking at patient newly diagnosed or those who have gone through different lines of therapy.[18]

So with such a high expression on the surface of small cell lung cancer and the minimal expression on normal cells, DLL3 will seem to be a very appropriate and exciting target for investigational T-cell–engaging therapeutic strategy.[1,17]

Dr. Caudle:
To close out our talk today, Dr. Owonikoko, do you have any parting thoughts on the potential of DLL3 and investigational T-cell engager immunotherapy in small cell lung cancer?

Dr. Owonikoko:
Yeah, thank you. I think it's important to emphasize that, you know, small cell lung cancer remains an aggressive disease despite some of the progress we've made. There is still need for additional novel approaches that can improve outcomes for our patients.[1] T-cell–engaging technology are currently being investigated in small cell lung cancer. And these are designed to direct cytotoxic T cells to target and kill the tumor cells.[14] There is room for investigational T-cell engagers that are directly targeting DLL3 as an option for these patients going forward.[1,17]

Dr. Caudle:

Thank you, and as that brings us to the end of today's program, I'd like to thank you, Dr. Owonikoko, for the great insight and information. It was a pleasure speaking with you today!

Dr. Owonikoko:
Thank you, Dr. Caudle. It was great being here.

Announcer:
This medical industry feature was sponsored by Amgen. If you missed any part of this discussion, visit ReachMD.com/industry-feature. This is ReachMD. Be Part of the Knowledge.

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