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(866) 423-7849

Exploring Treatment Strategies in epNEC: The Emerging Role of DLL3

Announcer:

You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. Here's your host, Dr. Charles Turck.

Dr. Turck:

This is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and today I'm joined by Dr. Jason Starr, who's an oncologist in Jacksonville, Florida. Together, we'll be exploring the role of DLL3 targeting in the evolving treatment landscape for extrapulmonary neuroendocrine carcinoma, or epNEC for short.

Dr. Starr, thanks for being here today.

Dr. Starr:

Thanks for having me. Great to be here.

Dr. Turck:

Well, to start us off, Dr. Starr, when you look at the current state of epNEC care, where are we making progress, and where do the biggest unmet needs remain?

Dr. Starr:

For epNEC, or extrapulmonary neuroendocrine carcinoma, we've been pretty stagnant for decades. We have extrapolated from our colleagues in thoracic oncology with what we call lung neuroendocrine carcinoma, or small cell or large cell, and we view platinum-based therapies with etoposide and very little evolution from there. In this era of biomarkers and immunotherapy, we're starting to make some inroads, but patients deserve better therapies than we've had for the last few decades. I'm starting to see the first few hints of that.

Dr. Turck:

Now, DLL3 has emerged as a major focus of research in neuroendocrine carcinoma. For clinicians who may not be familiar with DLL3, would you explain what makes it such a compelling target in epNEC and how it compares with other approaches that have been explored in this disease?

Dr. Starr:

The reason why this became of interest in epNEC is there is a high expression of this protein in neuroendocrine carcinoma. For example, what we call gastroenteropancreatic neuroendocrine carcinoma, which is a category of epNEC, has about 70 percent expression. That's a pretty high expression. Now, again, extrapolating from our colleagues in thoracic oncology, it was first studied in the small cell lung cancer space—tarlatamab, which is an FDA-approved therapy. It's targeting DLL3. It's a bispecific antibody, which also engages CD3, which is on T-cells, so it's a T-cell engager.

And we saw positive data in that space, and that has now become part of the treatment armamentarium. In the epNEC space, we said, "All right, well, let's explore this protein." And that's where things have been moving with DLL3.

But I think, again, the excitement that I've recently experienced with the progression of therapies and the evolution of the science—I think we're seeing the first few hints of the fruits of that labor.

Dr. Turck:

And before we get into specific therapies, when should DLL3 be a part of the workup for a patient with epNEC, and what stands in the way of that happening consistently in practice?

Dr. Starr:

So DLL3 is tested with immunohistochemistry in the pathology lab. And with any new biomarker, there is a learning curve. What constitutes positive? And do you have the reliable antibody to do the stain? So there's always going to be growing pains.

I always parallel this to Claudin 18.2, a new biomarker. It's now become standard of care in gastroesophageal cancer, but it took a while for this to be incorporated in terms of doing the IHC as standard of care. A lot of the labs around the country don't have DLL3 readily available. And further, in small cell lung cancer, you don't need to do DLL3 testing to give the patient that therapy. So it's not even a biomarker-driven therapy; it's just that there's a high expression, so you assume it's there.

So it is going to take some time for labs to get comfortable with the DLL3 stain, and then we're going to have to establish cutoffs for what's positive and what's negative.

Dr. Turck:

Now, as DLL3-targeted development expands, what approaches are emerging for patients with high DLL3 expression compared with broader DLL3-positive populations, and where are there still uncertainties in the current evidence base?

Dr. Starr:

The data that I would quote was presented at ASCO 2025 by Dr. Capdevilla, and it's an agent referred to as obixtamig. And they looked at patients in terms of that cutoff of DLL3, and you would imagine if an antibody binds to the antigen, and if the antigen receptor is more rich and more dense, that therapy may work better.

Sure enough, in this phase one study, they looked at 200 patients, and they did a cutoff of 50 percent. So if there was at least 50 percent staining of DLL3 or higher in the tumor, that was considered DLL3 high, and if it was less than 50 percent, it was DLL3 low. And sure enough, when they looked at the responses, it was very striking. The patients who had DLL3 high had a much higher benefit from obixtamig than the DLL3-low group. So we don't know if that's the optimal way to assess which patients are going to benefit from the therapy, but this was at least an indicator.

Dr. Turck:

For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Jason Starr about emerging targeted approaches for patients with extrapulmonary neuroendocrine carcinoma or epNEC.

So Dr. Starr, DLL3-targeted therapies are also being evaluated across settings, including earlier-line combination strategies. What do the current data support, and what still needs to be established?

Dr. Starr:

Based on that phase one data that I had mentioned, they have further evaluated the obixtamig in a bigger study setting using that DLL3-high cutoff. And we're awaiting that data to see efficacy, essentially. But also, with the DLL3, once you find an antigen, you can exploit that antigen in a number of different ways—antibody-drug conjugates, where you tag a chemotherapy to the antibody. We talked about T-cell engagers. There's probably some development of adoptive T-cell therapy or CAR T therapy. So there's a lot of different mechanistic ways to go after DLL3.

But I think that in epNEC in particular, the DAREON-5 study looking at obixtamig is probably going to give us the first indications of whether or not this DLL3-high group is the group that really benefits and establish that there needs to be a cutoff. Because again, to date, there is no cutoff for DLL3 in patients who are candidates in the small cell lung cancer group. So I think that study will give us a lot of information. And we maybe can talk a little bit about another study for patients who have progressed on platinum etoposide. We're also going to look at patients in the frontline setting, so with chemotherapy, with that same agent.

Dr. Turck:

Well, to that, as you look across the current clinical trial landscape in epNEC, what do ongoing studies reveal about where the field may be headed?

Dr. Starr:

I think the DLL3 is probably the most exciting area of investigation—and to that point, the DLL3 antibody-drug conjugates—but epNEC tends to be not focused on. So that's why I said the obixtamig is really an area of focus for epNEC. So I think we're going to get some good data in terms of in that group because it's a very heterogeneous group typically, right? You have patients with sometimes lung mixed in. You have patients with gynecologic neuroendocrine carcinoma. So it's hard to make conclusions sometimes because historically we've looked at immunotherapy—so nivolumab and ipilimumab. And at first, we got a signal that maybe it does something, but in clinical practice, it really hasn't panned out.

There's a trial called the SWOG S2012 study looking at carboplatin etoposide and atezolizumab. And this is, again, an extrapolation from the small cell group where the same study was done and was positive, albeit modestly positive. So that's another trial that's going on in the epNEC space to see if we should add immunotherapy to the frontline chemotherapy backbone, and then should we continue the immunotherapy? So that's another aspect of that study.

But I think, generally speaking, most of the momentum is DLL3 in different iterations of, like I said, a bispecific T-cell engager like obixtamig or tarlatamab, and then the antibody-drug conjugate, and then probably further behind, CAR T-type therapies.

Dr. Turck:

Now, given how aggressive epNEC can be, when should clinical trial consideration become part of the treatment conversation, and what does the referral process actually look like in practice, particularly with timing being so important?

Dr. Starr:

These are typically aggressive cancers. Sometimes patients don't have the luxury of traveling to a tertiary care center, and sometimes oncologists don't have the luxury of waiting and seeing what clinical trials are available. So treatment initiation is always a consideration, in terms of how fast you need to get the therapy started, and how sick is the patient? And what's the burden of disease? Is there any organ dysfunction? So that all has to be taken into consideration if somebody's waiting to see a specialist to be considered for a clinical trial. Now, this frontline obixtamig trial does allow for a "cycle of chemotherapy." And that SWOG S2012 trial also allows for a cycle of chemotherapy. So I think the clinical trials are being built understanding that most patients need treatment, right away. Get that first treatment in, and then maybe start doing the clinical trial search. But it can be difficult with the timing, not to mention if you're doing a biomarker study, you have to send the tissue off and then get the DLL3 testing done. And so that can take some time as well.

So it's challenging for these patients to get on trials for those reasons.

Dr. Turck:

Now, to bring this all together, Dr. Starr, as clinicians work to build treatment plans for patients with epNEC, what are the most important considerations they should keep in mind, particularly around integrating emerging DLL3-targeted options and identifying patients who may be appropriate for a clinical trial referral?

Dr. Starr:

Yeah, I think awareness—awareness of what trials are out there, where the field is moving, and in the community, what centers around you have trials, and having a good relationship with those physicians or doing a clinicaltrials.gov search. There's a lot of AI types of programs also that can do some clinical trial searching. But I think it's awareness that these trials exist and time can be of the essence. I can't advocate for doing DLL3 testing at this time as a standard of care because again, there's not an FDA-approved therapy that uses DLL3 in terms of biomarker-driven treatment. Tarlatamab, like I mentioned, doesn't do that. It doesn't need DLL3 testing. But as this data evolves, my hope is that this therapy ends up being beneficial in terms of efficacy and safety, and then the DLL3 story is important.

Now, I would advocate for all physicians taking care of these patients to do next-generation sequencing, so genomic testing, on all these patients because there's a multitude of targets that we can find. Unfortunately, a lot of them are not targetable. Most commonly, you'll find retinoblastoma mutations and P53 mutations. But once in a while, you can get lucky and hit a needle in a haystack.

Dr. Turck:

Well, with those key considerations in mind, I want to thank my guest, Dr. Jason Starr, for joining me to explore the future of extrapulmonary neuroendocrine carcinoma care and emerging evidence on DLL3-targeted treatments.

Dr. Starr, it was great having you on the program.

Dr. Starr:

Thank you for having me. I enjoyed it.

Announcer:

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