EPISODE 48: NEN TREATMENTS: FOCUS ON DLL3 with Dr. Rohit Thummalapalli

Lisa Yen 00:00

Welcome to the Neuroendocrine Cancer Foundation podcast. I'm your host Lisa Yen. I'm the Director of Programs & Outreach, as well as a caregiver and advocate for my husband who is living with neuroendocrine cancer. In each podcast episode, we talk to an expert who answers your top 10 questions. This podcast is for educational purposes only and does not constitute medical advice. Please discuss your questions and concerns with your physician.

Lisa Yen 00:31
Welcome to today's episode of the Neuroendocrine Cancer Foundation podcast. I'm really excited to introduce our guest for today, Dr. Rohit Thummalapalli. Dr. Thummalapalli is a gastrointestinal medical oncologist and assistant attending physician at Memorial Sloan Kettering Cancer Center, specializing in clinical care and research in patients with neuroendocrine and billary tract cancers. Originally from Florida, Dr, Thummalapalli completed medical training at Harvard and Johns Hopkins before arriving at Memorial Sloan Kettering as a medical oncology fellow in 2021 and started on faculty in 2024.

Dr. Thummalapalli was awarded a 2024 NANETS clinical investigator scholarship for his research in this area of DLL3 for neuroendocrine cancers. Thanks to this prestigious award and honor, NANETS supported Dr. Thummalapalli's research titled "A pilot study of DLL3-directed immuno-PET imaging for patients with gastroenteropancreatic neuroendocrine neoplasms. I'm really excited to have Dr. Thummalapalli here today to talk about his work.

And I wanted to share a fun fact: Dr. Thummalapalli grew up in Miami, Florida, and he is a big time South Florida sports fan. He's currently celebrating the Florida Panthers Stanley Cup title. So, congratulations on your team's win. I'm glad you can celebrate that. And we're really glad to have you here. Thank you for joining us today.

Dr. Rohit Thummalapalli 01:56

Thanks so much, Lisa. It's really nice. It's really nice to be in touch with you all, and happy to come on the podcast.

Lisa Yen 02:02
We're really grateful for your work. And as we get started, I'd love to hear a little bit about how you got involved in the neuroendocrine cancer community.

Dr. Rohit Thummalapalli 02:10
Yeah. I mean, I think you had mentioned a bit in the introduction. I started my medical oncology training here Memorial Sloan Kettering a few years ago. And actually, I come to neuroendocrine from the lung cancer field. I actually did more of my initial training in lung cancer and have some exposure to small cell lung cancer. And as you might be aware, a lot of the DLL3-targeted therapies was originally born in small cell lung cancer. And so over the last year or so in GI oncology, we've been focused on seeing what we can bring from the lung cancer space into neuroendocrine GI oncology. And so DLL3 targeting is sort of natural fit.

Lisa Yen 02:48
A natural fit. And we've had the inside scoop that you're very knowledgeable and have excellent bedside manner and explain this topic clearly in a patient-friendly way. So, we're excited to talk to you today about what you've been working on in this field. So, if you're ready, we'll just get started with questions.

Dr. Rohit Thummalapalli 03:04
Yeah, that sounds great.

Lisa Yen 03:06
So, this topic in general, DLL3. I think, first of all, we need to take a step back, and this question comes up every single program we do, every single educational conference or webinar. What is immunotherapy and how does it work?

Dr. Rohit Thummalapalli 03:18
Yeah, so big question. **Immunotherapy** is generally a method of treating cancer, trying to use the body's immune system to fight the cancer. And so, when we think about immunotherapy, that's really a large bucket of classes of therapies. And probably the most common immunotherapy we've thought about for cancer treatment has been our **PD1, PDL1 immune checkpoint inhibitor therapies**. So, these have really revolutionized care for many patients with other cancers--melanoma, lung cancer, kidney cancer, et cetera.

There's been a little bit less progress for immune checkpoint inhibitor therapies for patients with neuroendocrine cancers, but now we're starting to learn that there may be an opportunity for next generation, novel, specific immunotherapies targeting specific cell surface proteins that may be found in neuroendocrine cancer tumor cells, and so our goal is to understand whether there's opportunity for new immune-based therapies to target patients with neuroendocrine cancers.

Lisa Yen 04:21
Yeah, this topic has gotten a lot of press in mainstream media, and it's always something of curiosity to the patient community. So, what is DLL3 then, and how does this work in the context of neuroendocrine cancer?

Dr. Rohit Thummalapalli 04:34
So **DLL3** is a protein that is commonly found on the cell surface in multiple different **high grade neuroendocrine cancer** types. And so, as I mentioned before, the observations really were born out of **small cell lung cancer**, one

of our more common high grade neuroendocrine cancers, where decades of work has shown that a majority of patients with small cell lung cancer express this protein, DLL3, on the cell surface. And there have actually been many efforts trying to target DLL3 in small cell lung cancer that have actually gone back for quite a few years now. So far, up until the last few years, had been unsuccessful, but now we have developed novel immunotherapies and also other classes of therapies targeting DLL3 in small cell lung cancer. And now we're trying to understand, you know, is this target other cancers as well, possibly some of our extrapulmonary neuroendocrine cancers. And then, of course, my interest specifically is in gastrointestinal neuroendocrine cancers as well.

Lisa Yen 05:36
Okay, so it sounds like immunotherapy is a big bucket, and DLL3 is one type of immunotherapy. And you also mentioned PD-1 and immune checkpoint inhibitors. So, how's DLL3 targeted therapy similar to or different than other types of immunotherapy?

Dr. Rohit Thummalapalli 05:52
I would say when we think about targeting DLL3, they're actually probably some of the therapies that are most developed right now are **DLL3-targeted immune therapies**, the **T-cell engagers**. Some examples are **tarlatamab**, **obrixtamig**. Those are probably most along in development.

But I will say, taking a step back, there are actually a number of **non-immunotherapy based treatments** that are also being developed against DLL3, and these include some of radioligand therapies targeting DLL3, similar to lutetium dotatate, antibody drug conjugate therapies, CAR T cells. So, when I think about DLL3 targeting, I actually don't look just at the immunotherapies. I'm actually interested to see how many different classes of therapies might be applicable for patients with neuroendocrine cancers.

Focusing on the immunotherapies, though, if you compare DLL3 T-cell therapies compared to checkpoint inhibitors, there are similarities and differences. I think both are meant to try to wake up the immune system and activate a patient's own T-cells to fight the cancer. I would say immune checkpoint inhibitor PD-1 based therapies are a bit more nonspecific, and they're trying to wake up the body's immune system to fight nonspecific cancer proteins that are found in tumor cells, whereas DLL3 targeted T cell engagers specifically try to recruit in T-cells to target DLL3 on tumor cells. And so, a little bit of different approach, but along the same principles.

Lisa Yen 07:24
So, this is really interesting, that you're interested in DLL3 as a whole, and that there's more use to it than just immunotherapy. So, we'll circle back to that. Also, you mentioned that this is similar, but different. Is there evidence that one works better than the other in terms of the types of immunotherapy, DLL3 versus the other?

Dr. Rohit Thummalapalli 07:42
No, I don't think so. I mean, unfortunately or fortunately, we are quite early in our journey of understanding how DLL3 targeted therapies work and how effective they are in comparison or in addition to standard checkpoint inhibitor immunotherapies. We've ever actually had a study comparing DLL3 immune-based therapies to our standard immune checkpoint inhibitor therapies. I think there's a reason to believe that they may work together in combination, but unfortunately, most of the data right now we have are small studies that look at the effectiveness of DLL3 immunotherapies on their own. We haven't yet compared them to immunotherapies, at least yet.

What we do know, at least in the randomized setting, is now also from small cell lung cancer, where recently the DLL3 T-cell therapy, **tarlatumab**, was compared against basically later line chemotherapy in small cell lung cancer, and it appears to be superior. And so, that's certainly an exciting advance of small cell lung cancer, but we don't know how that stacks up against immunotherapy.

Lisa Yen 08:46
Okay, so there's promise, and still needs to be work done in this area. And probably for many people in the audience, if they've heard of DLL3, we're thinking immunotherapy. So, tell me about what else you're thinking in terms of DLL3 and how it might be used.

Dr. Rohit Thummalapalli 09:01
Yeah, I think that's what's exciting about moving from what I would call DLL3's initial home in small cell lung cancer to other cancers in that small cell lung cancer is a disease where we know immune checkpoint inhibitors work. We know there could be an opportunity for immune based therapies. And so, there's been a lot of efforts focused on that.

But when we think about patients with gastrointestinal neuroendocrine cancers, we don't always use immunotherapy in these diseases. We often use other treatments, like chemotherapies or radioligand theranostic therapies like lutetium dotatate. There are multiple companies and academic groups working on development of *other* DLL3-targeted therapies, **antibody drug conjugates** or **radioligand therapies**. And I think there's a lot to be learned to understand whether the best DLL3 therapy for gastrointestinal neuroendocrine cancer patient, is that an immune therapy, or is that a different class of therapy? I think we're still we're still trying to learn that, and those studies are still very early, or may not have even opened yet, and so I think there's a lot to be learned.

Lisa Yen 09:59
Yeah, a lot to be learned. I want to take a step back, because you've mentioned that this is based on work on small cell lung cancer, and if you could explain a little bit why that is? And then you're talking about applying this to GI and pancreas. So, there's probably people in the audience who are like, I have GI and pancreas. What does this have to do with lung cancer?

Dr. Rohit Thummalapalli 10:17
I'll take a step back. When we think about our gastrointestinal and pancreatic neuroendocrine cancers, we often lump them into different groups. Our **well-differentiated neuroendocrine tumor**s and our **poorly differentiated neuroendocrine carcinomas, or PD-NECs**. When we think about. DLL3 targeting, the tumor types in which we extrapolate most from our small cell lung cancer treatment paradigms are the patients with poorly differentiated neuroendocrine carcinomas. And so, we generally extrapolate from small cell lung cancer data, thinking about first line etoposide and carboplatin chemotherapy, extrapolating from the small cell lung cancer literature. But when we think about our well-differentiated neuroendocrine tumors, these are a completely different tumor type, and so, really should be thought of differently.

And so, I will say a lot of the energy towards DLL3 targeting in gastrointestinal neuroendocrine cancers has really focused, at least to this point, on the poorly differentiated neuroendocrine carcinoma space, because that is the space in which therapeutically we've borrowed most from our small cell lung cancer treatment approaches. And I think we're starting to understand that DLL3 expression may not be limited just to the poorly differentiated space and may also be found in a high grade well-differentiated tumors as well.

Lisa Yen 11:32

Okay, so you said a lot there. And actually, that's where it was going next in terms of when is DLL3 used in neuroendocrine cancer? So traditionally, the thought has been in higher grade, poorly differentiated, but now there's maybe some thought that it could also be used in some well differentiated neuroendocrine cancers?

Dr. Rohit Thummalapalli 11:49
Yeah, exactly. I think this is all kind of recent data that myself and some colleagues in Memorial Sloan Kettering are working on. But I'll say in the past few years, there's been a much greater appreciation that patients with extrapulmonary poorly differentiated neuroendocrine carcinomas, including in the gastrointestinal system, there's been more of an appreciation that likely a high fraction of these patients might express DLL3 as a target. Estimates ranging from **60 to 80%** or so. And so, a lot of the early clinical trials moving beyond small cell lung cancer have focused on the gastrointestinal poorly-differentiated neuroendocrine carcinoma population.

But what we're starting to learn is that, and this is something we presented at ASCO back in June, there's probably a fraction of the high-grade well-differentiated neuroendocrine tumors, mostly pancreatic neuroendocrine tumors, that may also express DLL3.

And so, this is, I would consider it, a wide open research question: **Can DLL3 targeted therapies also be efficacious in the high-grade, well-differentiated NET population?** I think that is something that we're also very interested in understanding, and whether that'll be the same therapy as a patient with also lung cancer, or even a different class of therapies, I think is an open question.

Lisa Yen 13:05
Just to clarify a couple of terms, you said extrapulmonary. When you say extrapulmonary, you mean outside the lungs?

Dr. Rohit Thummalapalli 13:11
Exactly. So, when I talk about extrapulmonary neuroendocrine carcinomas, that really can be GI, but also genitourinary, so bladder and prostate. Gynecologic, so cervical, ovarian, et cetera.

Lisa Yen 13:24
What about those people who have neuroendocrine in the lungs? How might this be an option, if it is at all?

Dr. Rohit Thummalapalli 13:31
When we think about our lung neuroendocrine tumors, we think about **small cell lung cancer as our poorly differentiated tumors**. But then we also think about our **lung NETs, typical and atypical lung NETs**. There is some emerging data that also lung NETs, most of them probably express DLL3 two. And this is not my area of focus, but there are some clinical trials that are ongoing looking at evaluating DLL3-targeted therapies for the atypical pulmonary or lung NET population too. And I think that's certainly a valid area of research.

Lisa Yen 14:01
Lung neuroendocrine is definitely a special area and needs to be included as well.

And you also mentioned that some of your work is suggesting high grade, well differentiated pancreatic neuroendocrine. Could you define that? Does that mean grade 3?

Dr. Rohit Thummalapalli 14:14
Grade 3, that's exactly right. So, I think we've been able to look at our institutional tissue bank over the past few years, and this is a that we presented recently. At least in our data set, most patients with low or intermediate

grades, a grade 1 or grade 2, pancreatic neuroendocrine tumors do *not* express DLL3. However, we've appreciated that approximately **40%** or so of patients with **high grade or grade 3 PNETs** do express DLL3 to varying degrees. And so, whether this can be translated into a therapeutic opportunity remains uncertain. But I think certainly promising. An observation that needs to be followed up on in subsequent therapeutic studies.

Lisa Yen 14:54
40%. That's a large amount.

Dr. Rohit Thummalapalli 14:58
Yeah, it is. I think the question is, how much target do you need for a treatment to be effective? And I think that is a bit of a million-dollar question. There's more expression of DLL3 in our poorly differentiated neuroendocrine carcinomas. The average poorly differentiated NEC tumor seems to have more DLL3 expression than the average high grade NET tumor. But just how much antigen you need for a treatment to work is totally uncertain. So, I think if there is a population and the right drug that can be efficacious with a lower amount of antigen, that could be very promising for the high-grade NET population.

Lisa Yen 15:34
Yeah, the amount of expression. That's actually something we can circle back to, because I have follow up questions on that. But before we get to that, how does someone even know if this is a potential treatment option for them, and at what point in their journey would they consider this?

Dr. Rohit Thummalapalli 15:47
That's a great question. I think this question is rapidly evolving. I would say, up until the last one year or so, most of the clinical trials for DLL3 targeted therapies have really focused on patients with advanced disease, metastatic disease, who have previously received prior systemic therapy, our chemotherapy-refractory so on and so forth. And the FDA approval for tarlatamab in small cell lung cancer is now for patients who have previously received at least one line of chemotherapy.

But there has been a lot of effort recently to try to move up DLL3 therapies earlier in the course of care. And so, now there are clinical trials ongoing in small cell lung cancer exploring DLL3 T-cell engager therapy plus chemotherapy in the first line setting for patients who have not received treatment. And it looks like some of these clinical trials are now going to be extended to patients with gastrointestinal neuroendocrine cancers, under the idea that perhaps hitting the tumor hard with multiple modalities of therapy might lead to better outcomes.

So, I think it's mixed. I think most clinical trials right now continue to focus on patients who've been previously treated. But I think very reasonably, there's interest in trying to see if this can be moved earlier in the natural history of the disease.

Lisa Yen 17:04
Yeah, it's a rapidly evolving field, and we look forward to hearing more of the data. So, you mentioned a couple times that there are clinical trials in this area. Is this something that's only available in clinical trials, or is this something is this something that's now widely available?

Dr. Rohit Thummalapalli 17:16
I would say we have it approved for tarlatumab in small cell lung cancer now. So that is something that's certainly commercially available. In talking to some of my colleagues around the country, some clinicians and some institutions have been able to be successful at gaining compassionate use access to tarlatumab for our

non-small cell lung cancer neuroendocrine carcinomas, extrapulmonary NECs, including GI cancers. And so that is an approach that I have seen potentially be an option.

That being said, the majority of these therapies continue to be squarely in clinical trials. That's where they are right now. And I think certainly a lot of interest in expanding and fleshing out these patient populations.

Lisa Yen 17:55
Yeah, and if a patient's interested in it, what do they ask their physician for in terms of the clinical trials? Or search on the clinical trials.gov? How do they know what DLL3 trials might be something that they can access?

Dr. Rohit Thummalapalli 18:09
Neuroendocrine cancer is a generally small field, and so you know, a lot of the experts in the neuroendocrine oncology field generally are well connected. And so, I think being at a referral center that specialized in neuroendocrine oncology can be important. I think we call them zebras. It's not always that every oncologist may be aware of the clinical trial landscape for these rare cancers. And so, I think certainly being at a referral center with providers who see neuroendocrine cancer patients frequently is a good start. But yeah, certainly clinicaltrials.gov is certainly a resource that can be useful.

The first question is, probably the most simple question is, a patient can ask their doctor, "**Does my tumor express DLL3 protein**?" And I think many centers around the country are now offering DLL3 testing. Variably so, because up until now, we have not had a clear need to test for patients routinely seen in the clinic. But now, with these clinical trials starting to open more broadly, there is more and more rationale to test and to understand whether someone could be a good candidate.

Lisa Yen 19:09
That's a perfect segue to my next series of questions around testing. So, tell me a little bit more about this testing. How does someone find out if their tumors express DLL3 receptors?

Dr. Rohit Thummalapalli 19:18
Yeah, it's a great question. There's a simple answer and there's a complicated answer. I think the simple answer is that many pathology labs at institutions throughout the country now offer DLL3 protein testing through **IHC or immunohistochemistry**. And so, that is certainly a test that can be done.

Now the question is, what do you do with the information? Because not every clinical trial in this space requires confirmation of DLL3 expression. That's one issue. The second issue is, we don't always know how much DLL3 protein expression is needed for a patient to respond. And so, that answer is a little bit medicine specific. But I think the first thing to think about is testing the tumor for DLL3 protein. That's the simplest answer.

Lisa Yen 20:03
And is that testing done through a tissue sample, blood work, imaging or something else?

Dr. Rohit Thummalapalli 20:08
Right now, tissue sample. I think the most straightforward test right now is either an old or perhaps even a new biopsy to test for DLL3 protein on a tissue sample is the most straightforward approach. My colleagues at Memorial Sloan Kettering are working on a novel PET imaging approach, looking specifically at DLL3 PET imaging, which certainly can potentially be an option to help understand for patients who may have variable expression across tumor sites. But I will say this is still investigational and has not yet been used for selection of patients in clinical trials.

Lisa Yen 20:42
And you mentioned that the jury's out in terms of the amount of DLL3 expression required. So is there a minimum level of DLL3 expression that's required to receive the treatment?

Dr. Rohit Thummalapalli 20:53
Yes and no. I think, for example, in small cell lung cancer, the tarlatumab trials have not been requiring confirmation of DLL3 expression. Just because in small cell lung cancer, the literature says that most patients upward 70-80% express the target. And so those trials were not designed to require confirmation of DLL3 expression. Moving to **obrixtamig, DLL3 T-cell engager study** --this was recently presented at ASCO--their study in the extrapulmonary NEC population required at least 1% of patients with DLL3 expression needed to be confirmed to come on to study. And so, ultimately, what the exact amount of protein needed for a drug to work or for the next clinical trial, for their inclusion criteria remains an undecided question. Something that we'll continue to learn as we learn more about this field.

Lisa Yen 21:42
Okay. So, it's something that we still have to look at, and then under the clinical trials inclusion criteria, we'd have to look at that.

Dr. Rohit Thummalapalli 21:49
Exactly.

Lisa Yen 21:50
If someone's getting their DLL3 testing done by tissue, would that level of DL three expression vary by institution? Like so, if they send their biopsy tissue off to one institution versus the other, would that test result come back different?

Dr. Rohit Thummalapalli 22:05
It's a great question. It certainly could. I think, fortunately or unfortunately, the way we assess tumors by pathology is by doing biopsies or assessing a tumor that had a procedure. Maybe a surgery, maybe a biopsy, so on and so forth. But we don't necessarily know that every tumor in one's body is the same, right? And so there certainly can be **heterogeneity** or differences between different tumor samples in the individual patient.

And so, if the same sample is assessed by two different pathology labs, the hope is that you would see **concordance**, because most of us are using the same antibody. But there is certainly possibility that, depending on the timing of the tissue sample or even where the tissue sample was collected, either primary tumor or metastasis, for example, it is possible it could be different. And I think another open question, we're learning how different can this be an individual patient across different lines of treatment? I think these are also open questions.

Lisa Yen 23:04
It's interesting to think that there's heterogeneity in the expression, similar to how maybe all the tumors have different ki-67, that also with the DLL3 expression, it could vary.

Dr. Rohit Thummalapalli 23:14
I think that's exactly right. I think we have not proven this, so I'm venturing a bit, but we have shown from our pancreatic NET database so far that most low grade, intermediate grade--grade one, grade two-- tumors do not express the target. However, many grade three tumors express the target. And as we know, at least in the well

differentiated NET space, you can certainly get heterogeneity across different sites of disease. And so, whether that will be true for patients for DLL3 expression is an open question. But I think there is certainly reason to believe that within a single patient, DLL3 expression may be heterogeneous. And so, this is where we're excited about this functional PET imaging approach to see if we can really capture that heterogeneity in individual patients and see who might be the best candidate for targeted therapy.

Lisa Yen 23:58
We talked a lot about this expression. I think the most important question is, what does this mean for patients? Does the level of the DLL3 expression predict how well someone's going to respond to treatment?

Dr. Rohit Thummalapalli 24:10
I think the prediction is that it should. But we don't have a ton of data to support that. I would say the only data we have so far is from the recent ASCO data for obrixtamig. The obrixtamig data that was presented so far at ASCO has suggested that patients require at least **50%** of tumor cells to express DLL3 to have a chance to respond for a long duration of time to that drug. Now, it's still early data and that's still dose escalation data, and there are larger studies that are being planned to look at this. But so far, at least with that drug, the suggestion is that higher levels matter.

Now we don't know if for other therapies, if you need that level of expression, I'll draw from other cancer types, for example, breast cancer, gastroesophageal tumors, we see a lot of HER-2 targeted therapies, where we've always thought that need a lot of HER-2 to respond to some of these drugs. But now, in breast cancer for example, we have an approval for HER-2 therapy in patients with HER-2 low disease. And so, is there a possibility that a novel agent targeting DLL3 out there can be effective requiring less expression of the target? I think that's something we're all awaiting, and if that's the case, that would be certainly promising for patients. So, it's a long-winded answer, saying I think it probably matters, but how much it matters is still uncertain.

Lisa Yen 25:28
Well, thanks for explaining that, and that's helpful to know. That this expression, there's a reason we're testing it, that it may matter. It's likely to matter.

You've already mentioned that you thought the expression could vary from tumor to tumor. What about over time? Can tumors gain or lose expression?

Dr. Rohit Thummalapalli 25:45
It's a really good question. That is something that we've been trying to look at in our institutional database so far. It's sort of preliminary data, but we're still putting that together, trying to look at that to see if DLL3 levels can vary over time. The thought is that they could, but we have not proven that yet. But I think it's a totally valid question, and I think something that we will continue to look into going forward.

Lisa Yen 26:08
And we look forward to hearing your research on that. What about following treatment, do you measure the DLL3 expression following treatment?

Dr. Rohit Thummalapalli 26:15
Great question. So, you know, as the clinical trials have been written so far, generally, what's been mandated is an understanding of what DLL3 levels are prior to start of treatment. But I think a natural open question is, what's going on in the tumor in the patients with tumors who do not respond to treatment? And or if a patient's tumor responds to treatment and ultimately grows afterward, what's going on in those tumors? And so, I think

another open question, is it possible that patient who receives a DLL3 therapy and then the cancer initially responds and does well and then ultimately grows, has that tumor changed? Is DLL3 expression levels the same? Is it higher? Is it lower? Is it lost? I think all of those questions are open questions. I think really important, because, as I mentioned, we have a lot of different classes of therapies that are being developed, and so can this be an observation that allows for a different DLL3-targeted therapy, if a patient received a previous targeted therapy? Or even, could it be something where that could allow repeat treatment? We think about for PRRT for lutetium dotatate, we often give a few cycles of PRRT and then follow our patients and watch for tumor regrowth. But if the tumor does regrow, we often think about repeating PRRT for patients who have a preserved dotatate PET avidity. And so, could that be the same idea for DLL3? We have no idea, but I think that's something that's very important to look at.

Lisa Yen 27:43
Yeah, there's a lot of unanswered questions. And you mentioned that you're doing this DLL3 PET imaging. How do you think that will play in with the tumor testing that you're mentioning. Will that replace it? Will it enhance it? How will this work in with testing for DLL3 expression?

Dr. Rohit Thummalapalli 28:00
I think it's certainly unlike that it would replace it because logistically, it's a much more resource intensive test. Instead of just doing a protein test on one slide, this is a whole functional imaging approach requiring a patient to come in to get the PET tracer, to get a whole full body scan, a radiologist to review, so on and so forth. And so, it's probably more of a resource intensive approach. And right now, it's not widespread, ready for commercial use. And so, I don't anticipate it to replace protein testing anytime soon, but I do think it can certainly complement or inform or add to tumor protein testing for a couple of reasons. One is it's possible that different tumor sites within an individual patient may have different levels of expression. So, if, for example, a patient had a pancreatic primary tumor that had surgery a few years ago and ultimately they developed a liver metastasis, for example, and the previous primary tumor did not express DLL3, that doesn't necessarily mean their liver metastasis may or may not. And so, the idea of using a real-time imaging approach to look to see what's going on in the tumor right now could be very important. And also, gets back to your earlier question, it is possible that these levels change over time. And so, we don't want to be doing biopsies every month or every year on patients. Oftentimes, if we have tissue from an old biopsy or an old surgery, we often use that for testing. But how applicable is that for a patient walking into your clinic today? It may or may not 100% capture what's going on right now. And so, I certainly think that a real-time imaging assessment could be something to complement protein testing.

Lisa Yen 29:35
Yeah, and from a patient standpoint, as you said, it's not necessarily practical to biopsy multiple times. And how much preferable it would be to have an image versus the needle stuck in.

Dr. Rohit Thummalapalli 29:44
That's exactly what we're thinking.

Lisa Yen 29:46
Well, we'll be curious to hear what your research shows. So, you mentioned that there's been results released from a recent ASCO article. How effective is DLL3 targeted therapy in neuroendocrine cancers?

Dr. Rohit Thummalapalli 29:59
So far, I think probably the two molecules that have probably the most clinical data that's been released so far include **tarlatamab in small cell lung cancer** and then **obrixtamig in our small cell lung cancer and**

extrapulmonary NECs. And so, I would say both of these molecules certainly have the potential to shrink the disease, stabilize disease with really promising durations of response as well. And so, we look at the obrixtamig data in their DLL3 high population. They estimated approximately 40 percent of patients had significant disease shrinkage with the average or median amount of time patients responded to therapy upwards of eight months. And so, I think this is certainly promising for poorly differentiated NECs, which can be really aggressive tumor types but often very difficult to treat with chemotherapies after first line chemotherapy. And so, I think definitely promising signal, but certainly room to work on as well. And I think whether that activity would be the same or perhaps even higher other tumor types remains uncertain.

Lisa Yen 31:01
Yeah, you mentioned 40% shrinkage, that is hopefully patients want to be within that 40%. And could you go back to like, what is the goal of the treatment? Sometimes people say, “Okay, well, if I put you on this medication, our goal is just to stop the growth.” But what's the goal of treatment with DLL3? Is it to shrink? Is it to stabilize the tumors, or is it for symptom relief?

Dr. Rohit Thummalapalli 31:21
I would say all three. I think those are not mutually exclusive. I think in the best case scenario, we want to shrink the disease significantly and hopefully make patients feel better. I mean, that's always the bottom line. We want to make patients live longer and feel better while they're doing so and so I think it has the potential to do all three. I think at the least, we want to find a treatment option that least stabilizes disease for patients who have had their disease grow despite other standard therapies, but certainly in the best-case scenario, we want to develop therapies that shrink disease and make patients feel better and hopefully live longer. Those are studies that we're now starting to see if DLL3 therapies compared to standard therapies can help patients live longer. But I think the hope is that we'll find some effectiveness here.

Lisa Yen 32:05
Live longer and feel better. That's important.

Dr. Rohit Thummalapalli 32:07
Absolutely.

Lisa Yen 32:09
You mentioned the recent study gave eight months of efficacy, that it worked for eight months. I mean, from a patient standpoint, it doesn't feel like very long. How long is it expected to work? And could it be longer than that? I think we all want longer.

Dr. Rohit Thummalapalli 32:23
Absolutely, we all want longer, and patients deserve longer. And I think what I will say is this is an initial signal from a first study looking at, is there any potential for this therapy in this class of cancers? And so, I certainly think there is a lot of potential to improve upon this. I think whether DLL3 therapies can be combined with other therapies to help them work longer, whether we can understand how tumors evolve and how patients ultimately develop progression on these therapies, and if we can leverage that to make them work better. I certainly think these are all things we're working on. Because you're right. Absolutely. We want to improve that response rate. We want to improve that duration of response, and we want to help patients live longer and live better. And so, I think it's a good first start, but absolutely, a lot of room for improvement. I will say that eight months estimate is really in the poorly differentiated NEC population. We don't know if this duration of disease control may be better in patients with a disease with a longer natural history, say, pancreatic neuroendocrine

tumors, well-differentiated tumors. Is it possible that this or a different agent may be more effective and may work for longer? I think that's certainly possible. And I think that's something, again, we want to evaluate.

Lisa Yen 33:33
Thank you. I was going to ask you to put in perspective, in terms of all of research, where people might fall in that average of the eight months, if they know they're going to be on the shorter end of it, if it could be longer than that? And how this patient population might differ from the individual who's not in a clinical trial, how they would know that this could work for them?

Dr. Rohit Thummalapalli 33:52
It's a tough question. Unfortunately, beyond just the amount of DLL3 in the tumor, we don't have great predictive markers yet. I think that is, again, something that we're thinking about, that we want to learn. I think there's a lot of biology that we have not learned about why patients respond or don't respond to these DLL3 immunotherapies. And then why a patient may or may not respond to another DLL3 therapy, radioligand, antibody drug conjugate, so on and so forth. And so, I think we're always looking for new biomarkers to see if we can predict if someone might be above the median, kind of in that curve, or god-forbid, below the median. We're just not there yet. But I think that's definitely one of our tasks to figure that out.

Lisa Yen 34:36
Yeah, we need that biomarker so we can predict response. And on the flip side, how do you measure response to DLL3 treatment?

Dr. Rohit Thummalapalli 34:44
Generally, in clinical trials, we confirm that a patient has what we call "measurable disease," based on a CT scan or a PET scan. And we usually identify a number of so called "target lesions" that we track with clinical trial based therapies. And so, generally, it's a matter of CT imaging or PET imaging every so often. Every six weeks to three months, looking at the size of those tumors as we go in time with more cycles of treatment. And then, of course, probably more importantly, is how the patient's feeling. I think we see our patients in clinic, we get a sense for how they're feeling. You check their blood work, a combination of seeing patients in clinic, seeing how they're feeling, and then also imaging on regular assessments, is what we use to track the efficacy of the treatments.

Lisa Yen 35:24
Since we don't have that reliable biomarker, really it's relying on imaging and then also how people feel.

Dr. Rohit Thummalapalli 35:30
I think the high DLL3 level may, at least for this drug, may suggest that a patient could respond, but doesn't guarantee it. And the same as vice versa, even if someone has a lower level, it doesn't mean they won't respond. And so, I think despite what an initial DLL3 level is, it's still very important to watch patients closely and monitor them through treatment.

Lisa Yen 35:52
Do [you] then retest the DLL3 level of expression to see if they've responded to treatment? Or do you rely mostly on the imaging?

Dr. Rohit Thummalapalli 35:59
We haven't done that yet. I think we're relying more on the imaging and the clinical assessment.

Lisa Yen 36:04
Okay, so back to imaging, as with many treatments. You mentioned that, and you've touched on that you hope that DLL3 might be combined with other therapies? Could you talk a little bit more about that?

Dr. Rohit Thummalapalli 36:14
Yeah, absolutely. I think I'll go back to small cell lung cancer, because that is where most of these therapies, at least, have started. And so, in the small cell lung cancer field, there's now an effort to understand whether DLL3 immune-therapies can pair or can be added to frontline chemotherapy with etoposide and carboplatin, or platinum-based chemotherapy. And so, I would say, from a combination therapy perspective, a lot of the energy has been put towards seeing how well it may combine with chemotherapy.

On the flip side, I think if we're talking about immune-based therapies, I think a natural question is, "Can DLL3 immune-based therapies be combined with our traditional immunotherapies, our PD1, PDL1 check-inhibitors?" I think there is probably a hypothesis that a patient who does not respond to a T-cell based therapy, that may happen because their T-cells are so-called exhausted or essentially don't work as well as a patient with a healthy set of T-cells. And so, there is a thought that potentially adding an immune checkpoint inhibitor could be a strategy to augment the efficacy of an immune-based therapy. And so, that is also something we're certainly thinking about.

I think one thing that we have thought about this is still very early and kind of an “out there” concept, is we have a number of DLL3-targeted therapies in different classes now: radioligands, antibody drug conjugates, immune-therapies. Can they be used together? I think that's a very “out there” idea and needs to be investigated very carefully, especially from a safety perspective. But that also could be something we could be thinking about in the next few years.

Lisa Yen 37:50
I love that you and others are dreaming big on our behalf, to try to find treatments, not just to shrink the disease, but maybe, hopefully someday, to cure. And that's really encouraging and hopeful for me and others in this community.

So, I know you see patients as a clinician, so when you're seeing them in a clinic, how do you decide when to offer DLL3 for someone with neuroendocrine cancer?

Dr. Rohit Thummalapalli 38:15
It's a great question. I'll only speak about my practice because I will say that this is a rapidly evolving and honestly, it's a very nascent field. And so, I think if you ask 10 different neuroendocrine specialists, you might get 10 different answers, and that's not wrong. If anything, my answer might be wrong. But how I have approached testing has been focused on patients who have been exposed to more standard therapies. And so generally, I have focused testing more on patients who have received more of our standard therapies for advanced disease.

So, for example, for our poorly differentiated GEP-NECs, generally patients who have previously received frontline chemotherapy, we generally have been offering testing to see if they might be eligible for a clinical trial looking at DLL3 therapies to be given after chemotherapy. That's where we have focused a lot of our energy so far.

Our recent observation that some of our G3 well differentiated PNETs expressed to target has now prompted testing in these patients. But also, generally, we focus more on patients who have received many prior therapies. As we know, we have a lot of effective therapies for pancreatic NETs. We have lutetium dotatate,

cabozantinib, capecitabine temodar, other chemotherapies. Of course, somatostatin analogs. And so, we're blessed with having a number of active therapies for PNETs. And so, because this is such an early field, generally been focused on patients who have received many of our standard therapies before thinking about testing for DLL3. It's still quite early to be thinking about these therapies in patients who have not received our standard therapies, because we know they can be very effective for a long period of time.

Lisa Yen 39:51
So, for both of those buckets, the poorly differentiated neuroendocrine carcinomas and the well differentiated grade three pancreatic neuroendocrine tumors, you're looking at people who have already gotten multiple therapies, or standard therapies.

Dr. Rohit Thummalapalli 40:05
Generally so far, yes, but the landscape of clinical trials is changing. So now, it looks like, at least in the PD NEC space, it looks like there is an interest in moving some of these therapies earlier for patients who have not been treated with standard therapy, newly diagnosed patients.

And so, I do think our practice will change. If there is a new study that opens that is looking at a DLL3 therapy at initial diagnosis, then certainly. I think we certainly would adapt our practice and start testing earlier too.

Lisa Yen 40:34
Okay, so for poorly differentiated neuroendocrine carcinoma, definitely something to think about. Possibly earlier.

Dr. Rohit Thummalapalli 40:39
Definitely.

Lisa Yen 40:40
And a lot of patients are concerned about burning bridges. So, what factors or prior treatments might make someone ineligible for DLL3 therapy?

Dr. Rohit Thummalapalli 40:49
That's a great question. It depends on how the clinical trials have been written, and this is another sort of evolving question. Some of the early clinical trials of DLL3 therapies have excluded patients who have received a different DLL3 therapy. That is also changing. This is something that we presented at ASCO that it's quite premature, but it's just a proof of concept. At least in our experience, not every patient who receives a DLL3 therapy loses the target after prior exposure, implying that there may not be rationale to exclude patients from these studies who have received a previous DLL3-targeted therapy. And so, every clinical trial is different. I would say some clinical trials are requiring no prior DLL3 therapies, but some trials are more inclusive. I think there's no right answer. I think every treatment is different. And the groups leading each trial know the drugs really well, know the patients really well, and so they've been designed very carefully. But it's a mixed bag right now. I would say I think it's a promising class of therapies. And I think if we are thinking about clinical trials and the patient's eligible, I don't know if I would be concerned about not doing one DLL3 opportunity in favor of another one, because it's quite early in the process right now. And so, I think if there's an opportunity, and it sounds like a reasonable choice, I would encourage a patient to consider enrolling.

Lisa Yen 42:10
What about other immunotherapies, like immune checkpoint inhibitors, do they need to be concerned about doing those?

Dr. Rohit Thummalapalli 42:17
No, not at all. I think I'll speak in the poorly differentiated GI space, checkpoint inhibitors are not necessarily standard of care to be added to frontline chemotherapy, but many of us do. And there is an ongoing SWOG study looking at chemotherapy plus minus immunotherapy for patients with newly diagnosed gastrointestinal, pancreatic NECs. And so, it's certainly reasonable to consider adding a checkpoint inhibitor to frontline treatment, and those generally are not exclusion criteria for DLL3 trials. And so, that's not something I'd be concerned about.

Lisa Yen 42:50
What about other medical conditions? Are there any comorbidities or medical conditions that might exclude patients?

Dr. Rohit Thummalapalli 42:57
I mean, generally, when we think about clinical trials, many of these clinical trials are early in development, phase one and early phase two studies. And many of these agents were still trying to understand the safety and tolerability of these drugs. And so oftentimes, with these clinical trials, the inclusion criteria can be strict. And so, if a patient has severe medical conditions or significant changes in baseline bloodwork, for example, that may lead to the possibility of an increased risk of toxicity from the drug, then that's a patient that it may not be safe to do a clinical trial of the DLL3 immune or other targeted therapy.

I will say that there has been a big push among clinical investigators to make trials as inclusive as possible. I mean, that's something I'm very passionate about, and I think we do that as much as we can. But at some point, we are still often trying to figure out how safe is this drug? And so, there are some hard lines that unfortunately cannot be crossed in terms of other severe medical conditions, another primary cancer, for example. Those are often things that make it difficult to enroll in clinical trials.

Lisa Yen 44:03
And what about their functional status? I mean, sometimes people go to clinical trials as a last resort, but they're not feeling well. Their mobility, eating is really poor. How does that factor in?

Dr. Rohit Thummalapalli 44:16
Any clinical investigator who is thinking about offering a clinical trial, an early phase clinical trial for a patient has to make an assessment of whether it's the right fit for them. And so generally, we use **performance status** or **functional status** as sort of our way to determine whether a patient is a good fit or not. Oftentimes, for patients who are highly symptomatic from disease and if they're just not feeling well and have lost more of their mobility and really not able to do their activities of daily living, we often think that the risks of a clinical trial may be more than the benefit. And so, oftentimes, shared decision-making between the provider and the patient. It's not always the best idea to expose a patient to a clinical trial like these where there could be significant side effects that could make the patient feel worse. We would never want that. It's always a very tricky decision. I think we always try to advocate for our patients as best as we can. But there are times in which we'll have tough discussions with our patients, and together, we'll decide that maybe a trial really isn't the best thing right now.

Lisa Yen 45:16
Yeah, hard decisions. And on the other end of the spectrum, could receiving DLL3 exclude a patient from a non-DLL3 clinical trial or other treatments that are out there?

Dr. Rohit Thummalapalli 45:26

It's a really good question. It's a complicated question. I think it depends on the type of therapy. My broad answer is no. Generally, these are quite specific treatments, and so, you haven't come across a lot of exclusion criteria for non-DLL3 therapies. I think one exception might be for **antibody drug conjugates [ADC]**, where antibody drug conjugates are medicines that combine an antibody against a protein conjugated to a chemotherapy. And so many different types of antibody drug conjugates carry a similar chemotherapy. And so, theoretically, if one received a DLL3 antibody drug conjugate, they perhaps could be excluded from a future ADC for a different target that had the same chemotherapy attached to it. That's possible, but I'm not sure if I've seen that yet in my practice. I don't think I would be too worried about that as an issue.

Lisa Yen 46:20
Okay, thank you for that. So, I know you're counseling patients often. How do you counsel patients who are considering DLL3? What do they need to know about? Say, how the treatment's given possible side effects, what's known or unknown about long term safety?

Dr. Rohit Thummalapalli 46:34
I think it depends on the drug. I would say focusing on the immune therapies, some of these therapies can often, especially for the early phase clinical trial setting, it can be intensive in terms of the amount of close monitoring that has to be done at least at the beginning of a clinical trial of an immunotherapy or T-cell engager therapy. Many of these patients actually require being admitted to the hospital for the first one or two cycles for close monitoring, because these therapies can lead to something called **cytokine release syndrome** that can lead to essentially heavy inflammation in the body that needs to be watched closely.

Ultimately, our goal is to bring these treatments out of the hospital into the clinic to be given regularly over a period of every two to three weeks in the clinic. But it's not always the case, and I think especially for new clinical trials of new agents, there often can be a need for close monitoring, sometimes as frequently as once a week. And so, it certainly can be a burden for patients who are thinking about new therapies.

Lisa Yen 47:29
Very intensive. A lot of work. Sounds like possibly high risk, high reward?

Dr. Rohit Thummalapalli 47:34
Certainly, I would say reasonable risk. I think, you know, we obviously feel strongly about the promise of the therapies, but certainly any new therapy involves risk. In general, we've been excited about the field, and we've been thinking that the potential benefits of therapy outweigh risks, but it's always an individualized decision. But certainly, there can be risks for severe side effects that need to be watched closely.

Lisa Yen 47:55
And what about the long-term safety? What do we know about that so far?

Dr. Rohit Thummalapalli 47:59
Not a lot. We're still learning that. We don't have a lot of experience in terms of long term follow up of patients receiving these T-cell engager therapies. And we have almost no experience with long term follow up for patients receiving other DLL3 therapies. And so, I think that's a very open question. What I will say is that, as a clinical investigator, it's our responsibility to follow patients, both in the short term and the long term. We rely on our patients for most up to date reporting of symptoms, and we often follow these patients for many years even after completion of therapy to look for these long-term, delayed potential side effects. So far, we haven't seen much. But again, that's limited by our short duration of follow up so far with these patients.

Lisa Yen 48:41
You mentioned people need to be in the hospital. So why do they need to be in the hospital? And what kind of side effects are they experiencing?

Dr. Rohit Thummalapalli 48:49
The two main class of side effects from DLL3-based T cell engagers are related to overactivation of the immune system, and so there's sort of two buckets of side effects. One is a syndrome called **CRS**, **cytokine release syndrome**. Essentially, the idea is, when you're giving a treatment that activates the body's immune system or T-cells, you can often lead to a significant increase in the activity of T-cells in the body, which can essentially mimic a patient going into so called sepsis or being sick. And so, when the T-cells in the body are active, they can secrete cytokines. They can increase many symptoms: fevers, lower blood pressure, things like that. And so, it often requires close monitoring IV fluids, antibiotics to make sure the patient doesn't have an infection, so on, so forth. And so, that is a side effect that can require close monitoring with the first few cycles of treatment.

The second is a side effect called **ICANS**, which is essentially n**eurotoxicity**. Some of these immune cell therapies can actually lead to temporary effects in the central nervous system, can lead to confusion and neurologic side effects that need to be watched very closely. Often very, very treatable with steroids and immunosuppression, other types of immunosuppression. But certainly needs to be watched carefully.

Lisa Yen 50:09
Yeah, and when you talk about watching for all these symptoms and monitoring and treating the cytokine release syndrome and the potential neurological symptoms, how long are these potential side effects lasting?

Dr. Rohit Thummalapalli 50:19
Each side effect profile can be different. Generally, the severe immune-related side effects tend to appear early. And so that's why many of these T-cell engager trials require the first two treatments to be given in the hospital. And we often require **ramp up dosing**, where patients are treated with a small dose. If they do well, they're treated with a higher dose. If they do well, they're treated with a target dose. Generally, the severe side effects are experienced early, within the first few weeks. And this is why, generally, many of the clinical trials are requiring hospitalization for the early cycles but are okay with moving the treatments to the clinic in later cycles.

So generally, I would say over the first few weeks. But that's not always the case. Sometimes we do see delayed cytokine release syndrome. We do see delayed neurotoxicity. We can see lower organs of blood counts and things like that, that can appear later in the course. We're generally more comfortable with managing those in the clinic. But that's not always the case, and sometimes, unfortunately, we do have to send patients to the hospital, even if they're receiving the treatment in the clinic.

Lisa Yen 51:21
When they're receiving the treatment in the hospital, how long are they in the hospital? And how many cycles do you give?

Dr. Rohit Thummalapalli 51:26
A lot of this is clinical trial specific. Generally, the first couple of cycles, two to three, are done in the hospital. Generally, the period of monitoring can be somewhere between one and three days for each cycle of treatment. Subsequently, after that, I would say most patients are able to receive it in the clinic alone, where they wouldn't need to be monitored beyond the time of the infusion.

Lisa Yen 51:48

And are people able to work and do normal activities?

Dr. Rohit Thummalapalli 51:53
That's the goal, right? The goal of therapy is not just to shrink the disease. The goal of therapy is to shrink the disease and have the patient feel well and maintain their autonomy and try to be as active and as functional and as productive as they normally could be. And so, that's always our goal, to try to allow patients to be as active and working as possible. Now, it's not always achievable. If there are side effects that pop up that require intensive monitoring or treatment, then that may be something that is not achievable for that patient. But in general, especially as we move into the clinic, the goal is to develop therapies that can allow for patients to remain functional and be working and do all the things they want to do, at home, and between home and the clinic.

Lisa Yen 52:35
That's a key goal to maintain the quality of life.

Dr. Rohit Thummalapalli 52:38
Yeah, absolutely.

Lisa Yen 52:39
Well, we'll end with this last question. There are many questions that you mentioned are unanswered. So, what are the key questions you hope to answer about DLL3, say, in the next year? And then what about in the next three to five years?

Dr. Rohit Thummalapalli 52:51
I think there's two big buckets. I think, are there other patient populations that can benefit from these therapies? And if so, which therapies? And so I had mentioned that, can we move beyond small cell lung cancer into gastrointestinal neuroendocrine carcinomas? PD NECs? And then can we move from PD NECs into well-differentiated neuroendocrine tumors? We know that our well-differentiated neuroendocrine tumors are much more common in our clinical practice. So, is there a subset of patients that can benefit? And who are those patients? And how do we predict? I think that's one bucket of questions I think is very important and also dependent on the type of therapy that we think about.

And I think the second big bucket is, how do we make these drugs work better? We talked about the early data from some of the T-cell therapy showed that many patients can have disease shrinkage, and many patients can have a period of disease control. But it's not perfect, and I think we always want to do better. And so, understanding how tumors evolve with these therapies, how they may develop resistance, how we can make a therapy work better and last for a longer amount of time. And those are key goals, and I think that will take a lot of collaboration between clinicians, clinical investigators and also really basic scientists. Immunologists and basic investigators who can really try to look at the biology of response to these therapies to try to see if we can engineer sort of a next generation or a next version that can hopefully work better.

Lisa Yen 54:13
Takes teamwork. It takes an army.

Dr. Rohit Thummalapalli 54:15
Absolutely.

Lisa Yen 54:16

This has been really informative, and while there are still many unanswered questions, I think what is really encouraging, what is really hopeful for me, is that there are people like you who are putting a lot of thought into this and intention and research. And at least I'll speak for myself, it's hopeful to know that there are people who are dedicated to this work, who are working so hard on our behalf, to fight for us, to explore and put work into new therapies that will help us and our loved ones live longer and live better. And I really, really appreciate all your work in this area.

Dr. Rohit Thummalapalli 54:53
I really appreciate it. It was really great to meet you and talk to you, and I'm looking forward to keeping in touch going forward.

Lisa Yen 54:58
Thank you so much. You really bring hope by your dedication and hard work. And we look forward to hearing more about what you're doing in this area. And just thank you. Thank you for all you do on behalf of the neuroendocrine cancer community.

Dr. Rohit Thummalapalli 55:11
Thanks so much. Really appreciate it.

Lisa Yen 55:14
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