EPISODE 54: NEN Treatments: Focus on Cabozantinib
Dr. Namrata (Neena) Vijayvergia

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 today's guest, Dr Namrata (Neena) Vijayvergia, who is a medical oncologist and clinical trialist and physician leader known for bringing science, collaboration, and heart to the care of people with gastrointestinal and neuroendocrine cancers. We're really excited about today's topic because it really focuses on a topic that comes up constantly in our patient community: cabozantinib. Since its FDA approval in March 2025, we've received a steady stream of questions about this medication, and the topic comes up every single week in our virtual support group. Patients and caregivers alike want to know what to expect, how it works, what side effects are common, and how the treatment might impact day to day life.

So today, we're pleased to introduce our guest, Dr. Vijayvergia who's going to be speaking on the topic. As I mentioned, she's a leader in this field of both gastrointestinal and neuroendocrine cancers, and she serves as the Section Chief of Gastrointestinal Oncology at Fox Chase Cancer Center in Philadelphia and is an associate professor where she leads a wide research program spanning early-phase therapeutics, biomarker-driven strategies and patient-centered outcomes. Her work is supported by the NIH, NCCN, industry partners and multiple foundations. Dr Vijayvergia is a trusted voice in the field and a frequent speaker at major national and international medical meetings, including ASCO, NANETS, ESMO and SNMMI. All these to say that she's a leader in this field, and she also helps shape

national standards of care through her service on medical foundations and organizations such as ASCO, NCCN, ENETS, NCI and NANETS committees and guidelines panels. She chairs the NANETS scientific review committee and leads cooperative group efforts within ECOG-ACRIN. Behind her clinical and research leadership, Dr Vijayvergia is a dedicated mentor and advocate. She supports trainees and early career faculty through formal mentoring programs, advises patient advocacy organizations and champions community-focused efforts to make cancer care more inclusive and equitable, recognized through the ASCO leadership development program as one of the "40 under 40 in Cancer," she brings a strategic yet people first approach to advancing clinical trials, always guided by the belief that teamwork, curiosity and compassion can drive meaningful progress for patients and for teams who care for them.

In recognition of her impact, she received the 2025 NANETS Distinguished Clinician Award. Congratulations on that.

And I wanted to share a fun fact. She loves cooking, and that's her way to de-stress at home. She spends weekends preparing gourmet meals, which we would love to enjoy. And a second fun fact is, as a student and trainee, she had a second job as a TV show host. So she really should be hosting today's program. So welcome, Dr. Vijayvergia, we're really excited to have you.

Dr. Neena Vijayvergia 03:36
Thank you so much, Lisa. I feel like we should cut down some of that introduction. I'm not sure I'm deserving of everything, but it's all because of amazing people that have guided me through the years and to all my patients who have trusted me with their health, and I want to definitely do my best to take care of them. So, thank you for having me today.

Lisa Yen 03:53
Well, you've done an amazing job taking care of them in research, and you're creating ripples in this field. So, we're really grateful for all you do.

Dr. Neena Vijayvergia 4:02
Thank you.

Lisa Yen 04:03
Would you mind sharing a little bit about how you got into this field for those who don't know you?

Dr. Neena Vijayvergia 04:07
It's actually a very interesting story. I probably had seen two patients with neuroendocrine tumors through my entire residency or before that, that this was not something I was thinking that I'm going to be doing. But then, when I was in my fellowship, I worked with my mentor, Dr Paul Engstrom, who was the pretty big name in neuroendocrine field at the time, and he took me in a patient's room, and this patient had carcinoid syndrome, and he pressed on the patient's right upper quadrant area where the liver is, and then just touching that area, the patient just became all red like a beet. He was telling me that this is a difference between taking care of patients with other cancers and neuroendocrine tumors is that you're dealing with not just the tumor but also the secretory symptoms which make it so

fascinating. And that probably was my, you know, "aha moment" in my life. And obviously he mentored me very strongly, and I got the right opportunities. And there was so much happening in the neuroendocrine space at the time when I was introduced to this. So, I feel it's an act of God more than me choosing it. It chose me, and that's where I started. And then I was his trainee. At the end of my training, he's like, "I'm retiring. I want to give you my practice, if you learn more and we study hard." So, I was like, “All right, I'm going to do it.” And then that's where I am 10 years later.

Lisa Yen 05:24
We love that it chose you, and we need people like you who are so dedicated to this disease and helping people like us. So, what a story to show the impact of a patient.

Dr. Neena Vijayvergia 05:37
How their story of when they get flushed and they know when they're...it was just very fascinating to me at the time because I did not know much about it. But then as I went through and read about it, and that sort of became part of the mission too, that I'm just not dealing a tumor. I'm dealing with a lot of symptom burden tumors that come as a part of it, which just makes it more complex, but also more interesting for me.

Lisa Yen 06:00
Yeah, because it's not just about helping people live longer, but to feel better.

Dr. Neena Vijayvergia 06:06
Exactly. The symptom burden is so high with this disease that it takes a toll on you.

Lisa Yen 06:11
Yeah, well, we love that compassion and care that you have. And that leads into our topic. We're talking about Cabozantinib. And I've been really curious because I know that you've been doing a lot of work in this and you have your own project in this field.

Dr. Neena Vijayvergia 06:26
Well, I'll tell you the story of how I got involved with cabozantinib. So, Dr Chen, she's the PI for the study. She works with the Alliance Cooperative Group. I was a junior investigator, so, you know, I just started being an attending. And then they choose something called champions, which is basically from each cooperative group, they pick up somebody who's interested in that specialty to sort of work with the senior PI as a mentor to learn about how clinical trials are done. And that's how I got chosen to be part of the CABINET trial as a champion for ECOG. So, I opened the study at my institution. It was actually one of the very first studies that I opened at Fox Chase for patients and so I treated a lot of patients on the clinical trial at the time because we had a lot of patients we could offer this to. And I think one thing that really struck me during that whole phase was that I learned a whole lot about the trajectory of this disease, and the fact that what placebo control looks like in this setting, is it okay for six weeks if somebody is not getting a drug, and how to counsel patients about it, and how to help them through it, and how that made a change and a difference for today to get a drug that got approved. I'm so indebted the sacrifice a lot of the patients made to move the field forward by accepting a placebo control at the time.

And it was just so impressive to see, and I really feel that that brought me to the understanding of how important patients are. Yes, patients are required for clinical trials to be on the study, and they want it, but there's a much bigger commitment and a much bigger calling for them than just getting a drug on a study. That bigger calling of helping this disease in the community and helping 20 people or like 2000 or 200,000 people after them who are going to get benefit from it. And that led to the idea of, I need to do better and we need to do better at making sure that we get the right studies going so we're not wasting the effort our patients put in and also manage the side effects, so that we learn from what we learned on a clinical trial and then apply to the bigger population and not make the same mistakes again.

Lisa Yen 08:27
So well said. I mean the impact of the patient. Their gift.

Dr. Neena Vijayvergia 08:32
I think being a part of a study is a calling for them. It's not just a therapy for them. They're actually helping humanity.

Lisa Yen 08:38
Helping other NET patients and the field in general.

Dr. Neena Vijayvergia 08:42
Everybody, we learn more and we go forward. But yeah, so the CABINET study was this very nicely put together clinical trial, was vetted by so many experts and so many people in this field to do what we think is best for the patients at the time. So initially, it was for patients who had had one prior line of therapy and it was just everolimus at the time, and there was nothing else that was approved when the idea came about. But with the pace that drugs are moving and changing, they had to amend the protocol to allow patients to get PRRT or lutetium dotatate therapy as a part of it, and that showed how quickly we were adapting to how the field was changing, and then putting the right patients on the study and ultimately identifying what works.

So there was a pancreatic neuroendocrine tumor, **pancreatic cohort**. There was an **extrapancreatic cohort** on the study. And in the pancreatic cohort, these were just all patients with neuroendocrine tumors, so well differentiated neuroendocrine tumor patients of any grade. And then there were patients who were extrapancreatic cohort with these were neuroendocrine tumors of any site other than the pancreas. GI is the most common one. But they had lung in there, unknown sites, all the different areas, thymus, that was included in there. So, all these other patients from all the same grades, 1-2-3.

So, this study had a very wide eligibility because we want to be able to use it in all that wide populations. It's impossible to do a study for thymic NETs by itself, and this study included them. And that foresight came from all the experts and then patient information and the advocates that were involved in making those decisions that hey, these are all patients that should be included to allow a potential option for all of them. Rather than us thinking, hey, "This particular I don't have data. Or this particular disease, I don't have data." And you want everybody to benefit, not just one specific group.

So, I think that was a very inclusive study that included all sorts of patients, and then we saw the results.

Those cohorts were closed early because their treatment was better than placebo. It was way better than what we were doing, and as a result, we were able to offer these treatments to our patients sooner than when the full study was going to enroll. That's why there's people looking at study data every three months, every two months, and what they end up doing is making sure that everybody gets the benefit of the drug if it's working as soon as they find out. And that's what they did for this study, a very effective study that we were able to use for our patients.

Lisa Yen 11:10
Well, thank you for sharing all that backstory. I think that especially, at this point in time, people don't necessarily realize the years and years of dedication, hard work, blood, sweat and tears that have gone into it, and that how many people—people like you—so many people working so hard. So really appreciate that. I think for us, we've been following this trial. It was our first trial in our clinical trial guide. We've interviewed Jen Chan as the data was rolling out at the different conferences at ESMO, and then even talking about it after its FDA approval.

So, on the patient end, they're seeing this drug now. It's FDA approved. Their doctor is recommending it to them, so now they understand, okay, there's a backstory with this CABINET trial, and hopefully now with our conversation, we can help bring some more clarity and shed the light on the practical aspects of the treatment.

Let's start with “what is cabozantinib? Is it considered chemotherapy?”

Dr. Neena Vijayvergia
No.

Lisa Yen 12:04
Okay, let's talk about that, because that comes up right away.

Dr. Neena Vijayvergia 12:08
Cabozantinib is a oral medication. It's called a **tyrosine kinase inhibitor**, or a **small molecule TKI**. It's just a fancy word of saying it's a **targeted agent**. What it does is it goes and blocks off special proteins in the tumors which are signals for it to grow. Specifically to **VEG-F**, which is basically stimuli to form new blood vessels and the second is **MET**. These are two special proteins that stimulate cancer cell growth and this drug goes and blocks those receptors, so it cuts off the signal for those to grow. The simple way that what it's a novel mechanism. None of the other therapies that patients get until now are targeting this mechanism. So there's **sunitinib** for pancreas NET that's approved which has some similarities, but it doesn't have both. So, this is a very new mechanism that has not been targeted before, which provides a definitely a new option for our patient.

Lisa Yen 13:01

That's confusing, right? Because they think, "Okay, I'm taking a drug. It must be chemotherapy because it's cancer." But it's not. It's a targeted therapy, and you're saying it blocks blood flow from the path, VEG, V-E-G, dash, F and M, E, T, MET. So how does this differ from other targeted therapies, if there are any others?

Dr. Neena Vijayvergia 13:21
So, you may have heard the term **Afinitor or Everolimus**. That's one of the other drugs that is approved for neuroendocrine tumors. Cancer cells are smart. They grow by many different mechanisms. There's not just one specific one. And in neuroendocrine tumors, the two big pathways are this **VEG-F, the blood vessel formation pathway**, and the **mTOR pathway**, which is basically a signal one gets activated, stimulates the cancer cells to grow. And what Afinitor does, it blocks the mTOR pathway. And then cabozantinib blocks the VEG-F pathway. So, as a result, when you have patients that get one, the other pathway gets overactivated, and then ultimately you stop responding to that one treatment. So, then you bring the other one. It's like, you know, just trying to play a game of chess. You're blocking one area. They're going to start finding another area, and then you find a new target to block that area.

This is in comparison to chemo. What chemo does, chemo just goes and kills fast dividing cells. It does not distinguish between who these cells belong to. It just goes and kills fast dividing cells all through the body. Start from your hair. Diarrhea because of the GI tract being affected. Nausea and lowering of the blood counts. These are some chemo side effects which most targeted therapies don't have because they don't cause uncontrolled cell death.

Lisa Yen 14:35
That's so helpful to understand and to understand the difference, I think a little bit of a relief, right, to know that it's not going to cause hair loss. It's not causing all cells to be affected, but only certain ones that are targeted.

Dr. Neena Vijayvergia 14:46
It doesn't affect your immune system as negatively as other drugs do. You know there's nothing, it's 100% but chemo is a very strong thing that suppresses your immune system significantly, but these drugs do not cause that much of it.

Lisa Yen 14:59
So, when I think of targeted therapy, like, I'm in Los Angeles with all these little highways or big highways, right? I like to think of it like, Okay, I'm going to be taking the 405 or the 5 or the so it's blocking specific highways or paths.

Dr. Neena Vijayvergia 15:27
Absolutely. And then you block it. And at some point, they will get smart and start using the other strategy. And then that's why, at some point, whatever treatment we do stops working. So that's why we keep scanning people and everything, and when that happens, you bring a different target. That's why you need more than one target.

Lisa Yen 15:28
That's helpful to understand. There's different targets so each of these medications will help with different targets. So you were talking about the trial, and who it was for. Who is cabozantinib typically recommended for and when in someone's NET journey, do you consider starting it?

Dr. Neena Vijayvergia 15:45
How the study was done and how NCCN has recommended this drug is because it was tested in people who've had one line of therapy in addition to somatostatin analog. So for me, what it means is, if someone got a octreotide or the lanreotide shots as a frontline treatment. They started with that, then they got some sort of like, either PRRT or they got everolimus, like something after that is when cabozantinib comes in. Typically. It's usually a second line treatment, if you count the one treatment being the PRRT or the everolimus. Usually it's PRRT, liver-directed treatment, like any kind of treatments that you do systemically, and then you bring in the Cabozantinib after that. That's how FDA approves it. Having said that, there's always something to be said about changing it. According to phase two study of cabozantinib that was done, it was in patients who'd had no other treatment other than a somatostatin analog because nothing else was approved as well at that time. So, there is data that it can be used sooner, too. But currently, the recommendation, and what I tend to use is, most of my patients, it's after one other line of systemic treatment that I use it for, for the majority of my patients. Because oral agents, even though it is a targeted therapy, it will have some nuanced toxicities or side effects that we will talk about in a minute. But that's pretty much it.

Lisa Yen 17:06
I think there's always a little bit of concern and confusion around sequencing, but there's also concern if other treatments stopped working. Is this a last resort?

Dr. Neena Vijayvergia 17:16
I don't think so. I really do not think so. I probably think it is a third-line therapy. I actually use it before Afinitor for a lot of my patients. I don't think I can tell you that I have data to support that. There's an ongoing study comparing a drug similar to cabozantinib to everolimus and see which one's better, and maybe we'll find out one day. But it really doesn't matter. Most patients with neuroendocrine tumors end up getting all the different drugs. As you all know, this is a cancer in slow motion. It really is dependent on the toxicities and where the patient is in their journey at the time that we decide what's the best drug. So right, for example, I have a patient who recently had a blood clot in the leg. I don't think I'm going to give them Cabozantinib because of the toxicity profile. I recently actually had a patient who was struggling with diabetes. I'm not going to give them Afinitor.

So, the toxicity profile of the drugs helps us decide. We want to make sure we use the drug that is most effective and these, I would call equally effective oral agents, but we use them based on which fits the most for the patient at the time. If someone's hypertension is so out of control, I don't want to give them cabozantinib at the time. But mouth sores is a big issue with the everolimus so I want to be careful about that too. You pick between two choices based on the side effect profile, and it's a joint decision. And I really want to take the pressure off the patients. A lot of patients are very concerned about the idea like, "Which one should I do? Should I do this first or that first?" I tell my patients very frankly that most of them are going to get both these agents and it's which dose first or second, there is no data

that one going first makes the second one less effective or more effective. So what we need to focus on is what fits your lifestyle the most right now and affects you the least right now. So that we leave the one that's going to affect you more for the last.

Lisa Yen 19:10
Really back to that chess game of strategy.

Dr. Neena Vijayvergia 19:13
And it's a joint decision, and it's not the cookie cutter decision either. Everybody is different.

Lisa Yen 19:19
Yeah, it needs to be that open discussion, which is hard, because sometimes when we're uncertain, we just want someone like you to tell us exactly what to do.

That was really perfect, because I was just going to ask you, why might someone take cabozantinib instead of other treatments. So perhaps a follow up question is, does it limit future choices or burn any bridges?

Dr. Neena Vijayvergia 19:38
I don't think so. I have not had one patient had tried cabozantinib that precluded them from getting something in the future. Because most of the side effects are reversible, there's always one small, risky, serious side effects that can happen, but that can happen with any drug. All drugs have serious side effects. That's why we don't give it routinely to people. But I think ultimately, for cabozantinib, I have yet to find a real reason to say that "hey, you got this. I'm sorry I cannot give you any more treatment." That rarely ever happens. So, it's a good choice in that way.

Lisa Yen 20:13
That's really reassuring. So, speaking of side effects, what are the most common side effects?

Dr. Neena Vijayvergia 20:17
I'll tell you what I tell my patients in a very simple way, is that **VEGF is a protein that this drug targets, which is affecting blood vessels**. So most of the side effects that come from these drugs are related to your blood vessels. **Hypertension**, that's one of the most common side effect that comes with it. It's a good and a bad side effect. Hypertension is called a **silent disease** because it doesn't present with any symptoms, but it can cause problems. And hence, we have to look out for it. So it's important to know about this side effect. Monitor it closely. They give a kit that has a blood pressure monitor in that so I give my patients a blood pressure monitoring your kit and so that for the first month at least, you measure your blood pressure until you get to a stable dose. So that they can actually make sure that if you need to add a blood pressure medication to their regimen. Sometimes, rarely, I have to dose reduce for high blood pressure too. Most of the time, we could add a blood pressure medicine and control it. That's the most common side effect.

The second most common side effect is the **hand foot syndrome** and the **diarrhea**. The hand foot syndrome, it's like redness of the hands, and they become like hot and more dry and maybe peeling of

the skin. And it can be painful to some people. That would prevent you from doing your daily tasks or walking on your feet, and that can be very difficult to your quality of life. There are some mitigation strategies for the hand foot syndrome. Making sure you moisturize your hands very well. There are special creams. There's **Udder Cream**, which has high urea-based creams. **Udder Cream**, **Bag Balm**, **O'Keefe**. These are the different kinds of cream, and everybody uses a different one, and they work really well. Like I tell patients at nighttime, just apply those creams and put cotton gloves and cotton socks on and go to bed. And that actually helps prevent this. There's also some data for hand foot syndrome to apply **topical steroid ointments** or **topical diclofenac, which is like a Voltaren gel**. Think of it that way. Those can help control the symptoms. They all decrease the incidence of these. So we talk to our patients about all of these. I don't preemptively start the Voltaren and the steroid. I usually start with the ointments and just making sure we moisturize them very well. And then, even with the slightest hint, I ask them to start doing the steroid and the Voltaren too. And that has allowed me to keep it to grade one and look, just a little bit of symptom, just start of it, that it doesn't affect them too much.

The good part is, God forbid if that happens, if you get this painful, oh my god, I got blister in my hand, then stop it. That's the first thing I do, stop it. Let it heal up, and then you can restart it. It's always good to let it quiet down and then rebuild it, rather than, like trying to just reduce the dose, even when you have those symptoms. If there's only a little bit of thing, then you can always cut down on the dose. But it's not sure if you would cut down the dose anyways, but if it's enough that's bothering you, you got to stop it and then restart it and rechallenge at the same dose. But if it happens the second time, you know you have to reduce the dose.

Lisa Yen 23:09
You talk about the creams, I know that the company sends out a care package, if you go online and they include the Udderly smooth cream, which is really wonderful, and they send a little sample of that.

Dr. Neena Vijayvergia 23:20
It has 20% urea in it. They all have these very easily available and they actually, because it's a science behind this high urea content causes vasoconstriction in the hands that prevents that symptom. It's not just a voodoo.

Lisa Yen 23:32
That's really helpful to know. So, it really speaks to why it's helpful to understand how a drug works, because then you, as a patient caregiver, you can understand, then the side effects, and then how to prevent them.

Dr. Neena Vijayvergia 23:42
Absolutely. The third other side effect is **diarrhea** and **fatigu**e. So diarrhea is definitely, especially in our patients, because one of the major symptoms our patients have that it becomes a little tricky to manage, because you don't know if the diarrhea is worse because they're having more symptoms from the cancer, or is it worse because of the drug? It's a very dose dependent effect. You get diarrhea after the drug. You stop it, it gets better, and then it comes back again. You know it's the drug. So I tend to watch that very closely. Imodium, Lomotil, kinds of medications help with that diarrhea. It's different

than the carcinoid diarrhea, which you have different treatments for. This diarrhea really responds well to **anti-motility drugs like Lomotil and Imodium**, but also dose reductions and holds and breaks in between.

Lisa Yen 24:27
And how bad can the diarrhea and fatigue be?

Dr. Neena Vijayvergia 24:30
It's a range. There is a patient who would, for them, like they usually are at four bowel movements a day because of their disease, and now they've gone up to six. It's not too much for them. But then there are patients who were at three, and now there are ten. Every patient is a fingerprint. They just respond differently to every drug we give them. Most of the patients, it's…I haven't seen anybody get dehydrated from it, because I think neuroendocrine patients know how to manage diarrhea better than most other patients because of the nature of the disease. I don't think it's led to hospital admissions or anything like that, but definitely enough to be deterrent on quality of life. But they can all be managed. Dose reduction works. It's a very dose dependent effect, and we don't know what your dose is, because we don't have a great calculator for it. If you have it, you reduce the dose, and it's still effective at lower doses, and you can still continue therapy. You know, you don't have to suffer to get the benefit of the drug. You want to make sure you know that.

Lisa Yen 25:25
That's helpful, and we can go back and talk about dosing a little bit later. So you also mentioned the fatigue. People want to know, can I still do the things I do? Can I still work?

Dr. Neena Vijayvergia 25:35
I think the short answer to that question is yes. I think all our neuroendocrine patients specifically are very driven. I think work gives them joy. I think that's what I've seen for most of my patients. Doing this therapy can still let you do everything you want to do. If it is not, then the dose is not appropriate for you. Most patients who are at the right dosing are able to function without any problem.

Lisa Yen 25:58
What about any nausea or hoarse voice?

Dr. Neena Vijayvergia 26:01
And change in color of the hair. These are two big ones. Nausea, yes, I have seen clinically with some patients. It's just we have so many meds we're giving along with it. It's interesting, you know, I also use cabozantinib for liver cancer. I also see liver cancer a lot, and there, those patients don't have as much nausea with it. There, it actually affects their blood counts more than anything. You know, we also see them to some degree here, the platelet count can go down or your white blood cell count can go down. But usually it's limited. It doesn't go down very much, like grade one or two. To some degree they go down, but not enough that they'll be serious for you.

But the hoarseness of the voice is definitely a symptom that patients complain. These are very annoying side effects. These are things that affect daily life significantly, and that is one side effect that

I haven't seen being affected by the dose. You have it, you have it. Higher dose, lower dose. It's just some people get it and some don't. And it doesn't cause loss of hair, but it can cause graying of your hair.

Lisa Yen 27:01
Graying of your hair, wow. Well, helpful to know for people who have hair and really want to keep that looking nice. So you mentioned blood pressure, and I'll circle back to that, because this comes up frequently. Some people say, "Well, I'm already on blood pressure medications. Will I need to take more? Should I be concerned?" Or some people say, "I have low blood pressure? Will that be a concern?"

Dr. Neena Vijayvergia 27:20
Interestingly, I don't think there's correlation that people who have high blood pressure are at higher risk. That's not the case. But in general, the incidence of high blood pressure is very high with Cabozantinib. So as a result, most patients will have that problem. In someone's blood pressure is already high, they're on one med, they may need to add another medication to it. Patients who have low blood pressure, their blood pressure may go up a little bit. And if it goes up, it probably is going to go up to 13os, 140s, etc, which may or may not require medication, absolutely. But fortunately, if we do the monitoring closely, I see patients on day one, then I see them two weeks later, and then two weeks later. And then two weeks every two weeks is when I see patients for the first six weeks or so, just to make sure that all of these side effects are closely monitored and not affect my patient too much. So that we can get to the right dose which we can maintain them on a longer time, because I hope for them to be on this drug for a long time, which would mean they're tolerating and which would mean it's working.

Lisa Yen 28:23
Okay, that's helpful. So really need that close surveillance.

Dr. Neena Vijayvergia 28:27
It's an oral medicine. And sometimes people start oral medicines and say, "All right, we'll see you in three months with a scan, or in a month with it." I think you should see the doctors like every two weeks, at least in the beginning.

Lisa Yen 28:38
Okay. You were talking about side effects and how you go on and off. I think a common question really is, "Do these side effects tend to get worse over time? Or they stay pretty much the same?

Dr. Neena Vijayvergia 28:48
I've usually seen that these side effects don't even come in the first two weeks. Usually, most of these side effects come between the **two to the six-week timefram**e. You've been on it for two weeks. Then they start building up, and then probably peak around four to five weeks or so, by that time, we know it better, so we can dose reduce and then sort of taper them off. Fatigue is cumulative. Someone's been on the drug for a long time. Unfortunately, I wish I could develop a pill for that. It is just such a hard side effect to deal with. It affects quality of life so much. But the other side effects, like diarrhea,

hypertension and hand foot syndrome usually sort of taper like that's where their peak is, and then they just sort of taper into a plateau phase where they would be. But fatigue does build up over time. And that's why what I do is I give patients breaks from therapy. We do scans, six months of therapy, too much fatigue…all right, let's take a month break, and then we can restart.

Lisa Yen 29:43
And do the side effects ever go away? Or do they pretty much get to that peak and then stay at a steady state?

Dr. Neena Vijayvergia 29:49
Well, we are supposed to dose modify so if someone's having side effects that's bothering them too much, my job is to dose modify it so that these side effects go down to grade one or better for my patient, because it's not possible to live with these side effects forever.

Lisa Yen 30:06
Okay. So a lot of it is around the dosing of it. You touched on how it might affect blood counts, and I think that's a concern, especially for people who've had PRRT. Many people have. So can people who have lower blood counts because of PRRT, like chronically low platelets, other issues like lower kidney function, can they still get cabozantinib?

Dr. Neena Vijayvergia 30:27
Yes, may need a more closer monitoring and lower doses. So absolutely, I think we can try it. I have a patient whose platelet count was 70,000 and I tried cabozantinib for them. Instead of going at the full dose, we started at the 20 milligram dose and built it up. So that's how, because not everybody gets those. If this was chemo that we wanted to give we couldn't because we know everybody has low blood counts with chemo. Here it picks and chooses patients. We just don't know which one. And as I talked earlier, the level of reduction is limited. It's not that much. So, if someone's 70,000 platelet count goes down to 60 or 65, that's not a big change, and it might just do that. So that's why we have to, in that situation, I have them do blood work every week in the beginning, rather than every two weeks. So it can be given. That's the benefit of this oral drug. You can use it in a wide variety of patients because it can be given to patients whose PET scans don't light up and they don't have SSTR expression. That's a very important group where PRRT is not an option for them. Cabozantinib is. So that allows it to be used in a lot of different patients.

Lisa Yen 31:32
That's helpful, that it's an option for a wide range of people regardless of other issues that are going on, too.

So, before we go into dosing, what should patients watch out for or monitor while they're taking these? You mentioned blood pressure, for example. Should they be taking blood pressure a certain time of the day.

Dr. Neena Vijayvergia 31:50

So I definitely recommend my patients in the first months. I have a study where I'm doing this for my patients too. I give them like a log that they have to fill out their blood pressure at the same time every day. Doesn't have to be a specific time of the day. It has to be the similar time. It's not like by the hour dot. But if you do it in the mornings, get me for the mornings. If you do your blood pressures in the evenings, get me the evening readings for the two weeks that I will be in between you. And obviously I give them parameters to call me if your blood pressure goes over 180 over 110, you need to call me right away. Don't wait until my appointment comes. So, blood pressure is something that we definitely rely on patients to check and call us. Also, the hand foot syndrome, the diarrhea. If your number of your bowel movements you get is doubling than what your routine is, I need to hear about it so that we can act on it before it becomes a problem. Patients work hand in hand with us, trying to tell us so that we can act on it right away. Like hand foot syndrome, as I told you, once you start getting blister, you got to stop it. But you shouldn't do it by yourself. You should talk to your doctor, and then the doctors say, "All right, let's stop it, and then we'll regroup in a few days and then restart it once you're feeling better." You know, we have nurses. We have triage nurses, and most oncology providers have nurses who can talk to patients over the phone and guide them. I think the cabozantinib folks also have some support through their website to help people. These are different things that patients should use. And obviously, finding a problem early and taking care of it is better than waiting too long.

Lisa Yen 33:20
Yeah, that's very true. I mean, really, just keeping that log, blood pressure, other symptoms and being in close contact. What else, if anything should they monitor, like, are there certain other blood tests, organs, anything else that they should be watching?

Dr. Neena Vijayvergia 33:33
Definitely. In the beginning, cabozantinib is a drug that can irritate the liver. So, we definitely watch their liver functions. They wouldn't feel it. We want to catch things before they feel it. So typically, when they go to see their doctor every two weeks, they get their blood work done. Then if their liver functions are up, we may have them hold it. And then have them come back in two weeks, we'll start at the lower dose. Those kinds of things. But most of the time, the change in these liver function tests are not too much and are mostly reversible. So you know, yes, it's sounds scary. "Oh my God, my liver is irritated because of the drug." But usually we stop it and it gets better. So that's why another important thing is to monitor it closely. And these are all growing pains. They usually happen in the beginning. Once you start tolerating it after the six, eight weeks, it becomes better.

Lisa Yen 34:18
It's all about the dose. So, checking blood work, checking blood pressure, checking how I'm feeling, and logging all that and communicating. Is there anything else?

Dr. Neena Vijayvergia 34:27
A lot of patients talk to me about, what if I missed my dose? Because it's a daily medication, it's important to remember, take a medicine every day. I just tell my patients to skip it. If you've missed it and it's been more than eight hours since you skipped it, when you realize, just don't take the medicine that day.

Lisa Yen 34:42
Yeah, okay, I think we've had a big lead up to dosing. So, tell me what you know. I mean, you know a lot about dosing. You've been working hard in this area. What should patients know?

Dr. Neena Vijayvergia 34:52
The **recommended dosing for Cabozantinib is 60 milligrams**. And 60 milligram was the dose that was recommended on the CABINET trial. But even on the study, the **average dose that was given to the patients was close to 40 milligrams**. It was slightly less than 40 milligrams, actually. And that just showed us that even in my clinic when I put patients on that study, I had the same thing. I had to dose reduce everyone. That brought me to the idea, is this the right dose for our patients? It's not that they have to just do it for three months or one month. I hope that they can be on this treatment for a very long time. So, you want to make sure it's appropriately dosed and appropriately given.

There was this drug called Regorafenib, which we use for colon cancer. And this is not the same but a drug of the same class. There was this future study that came out of it that maybe it helps to start the drug at a lower dose and build up, rather than just start at the full dose and build down from that. It's called the **redose strategy**. So we wanted to do the same strategy for cabozantinib. Let's say that would allow us to maybe treat more patients and keep more patients on treatment. There'll be less drug discontinuations and less serious side effects, and patients will tolerate it better. So that's why we're doing this study. It's called **alternate dose cabozantinib**, and we have a study because there's one other disease tag that this drug is approved for, that's kidney cancer. So for both kidney cancer and for neuroendocrine, we have cohorts of these two groups where we have patients and we are starting the drug at **40 milligrams** instead of 60, with the goal to build up to 60 milligrams every two weeks if our patients can tolerate it. Because if someone can tolerate we want to get them to the highest dose. We just don't want to start at 40 and leave it at 40 if someone actually needs 60 milligram, because their metabolism is such.

So I think that's why it has strict criteria built in, like if their blood pressure didn't go up, if they didn't have any serious hand-foot syndrome, or their blood counts didn't go down or their liver function didn't go down. If everything's good, then we go up to a dose from 40 to 60. The drug comes in 20 milligram pills and 40 and 60. The only dose that are recommended is 60, 40, and 20. Those are the dose reductions that come in. But I'm like, What about 50? You're doing 60? Why couldn't I do 50 milligram? Why do I have to do 60? Or why from 40, why do you go down to 20? So what we devised in this study is we're doing 40 milligrams. If you're doing great, next time in two weeks, you go up to 40/60, which means one day you take 40, the other day you take 60, which is two pills one day, three pills [one day], with the ultimate goal to get to 60 milligram. But if you don't do well, even on the 40, you come down to a alternating 40/20, which evens after 30 milligram dosing. So if you take one pill or two pills just alternating, just to see that it would allow us to maintain the dose intensity, the doses that we want to get them, but still maintain the safety and the tolerability of the drug, which is hard. I'm grateful to all my patients who are part of the study. We're two thirds into accrual, so hopefully we'll be able to present the results next year.

Lisa Yen 37:48

That's really impressive to be accruing patients so fast. So let me see if I understand this correctly. So you start them at 40. If they're doing well, you might increase them to 60. But I think the question is really, what does the doing well mean? And if they're not doing well, is it okay then to stay at the lower dose?

Dr. Neena Vijayvergia 38:05
That's exactly what we're trying to find out. As you know, in the CABINET trial, most patients got the 40 milligram dose, and still, we see the benefit at the end. The study showed that patients with both pancreas and extrapancreatic NETs do better with cabozantinib, even though many patients got 40 milligram. That was the average dose they got. So we know that what's the right dose for the patient is determined by that patient, not by us, and those are determined by their side effects, etc. Yes, going up from 40 to increasing the dose is a very nuanced decision between the patient and the doctor because everyone will have some side effects. It's not a walk in the park. We cannot discount that fact. And is that side effect enough that it's affecting their quality of life or not? If it's not and they want to proceed and go ahead, increase the dosing, we discuss it, but we have to meet the certain criteria. Did their liver function not get bumped? Did their blood counts go down? Or make sure they don't get hand-foot syndrome, their diarrhea didn't get worse, and their blood pressure is okay. These are just some broad criteria. But also fatigue is there's no good measure of it, so it's patient telling us, “Hey, I'm feeling great on it.” No problems go up, so we'll go up.

Lisa Yen 39:11
I think that that's helpful, because sometimes patients feel like maybe, if I can endure this, maybe if I just suffer a little longer, I'll have more effect, so my tumors will shrink. But you're saying that you don't have to suffer, right? This is all customized, and it really needs to be customized.

Dr. Neena Vijayvergia 39:25
It's a marathon and not a sprint. So if you suffer, anybody can only suffer for a very small period of time. Your goal is to be on the treatment for a longer time. And the best way to assure that is to get on a dose that you can tolerate, that you actually can walk that far. I'm that way too. I'm getting a treatment. I don't want to tell my doctor about my side effect, they'll reduce the dose. I understand where that comes from, but then what ends up happening is, if we don't act early, you get very sick, and then we just have to take you off the drug completely. And we don't want that. That shouldn't be the case.

Lisa Yen 39:58
So really seeing it as a marathon. That's why it's so important to have that discussion. You mentioned 20 milligrams, so when would you do to 20 milligrams?

Dr. Neena Vijayvergia 40:06
Basically. I put everybody on my study, whoever is starting. So that's easy, but typically the first dose reduction is 40 and the second dose reduction is 20. If you start somebody at 40 and they do great, you go up, but if they don't do well, then you go down, and that's when the 20 milligram dose comes. So that's how most people, even if you look at the FDA package insert of how modification should be done. You start at 60, you have side effects. You go down 40 or more side effects. You go down to 20.

Lisa Yen 40:32
Do you ever start people at 20 and then go up?

Dr. Neena Vijayvergia 40:35
I have done that. It's a very case by case basis. I actually had a patient with PRRT associated thrombocytopenia, which I started at 20. Because the platelets for 70 so we started at 20 milligram, and then we build up. I have a patient who I'm giving 20 milligram for three weeks in a run, then a week off. I make it up. I don't want to say that to the patient, it's not approved or anything regimen, but you know, you work with your patient and whatever they can tolerate, if it's effective, you do it.

Lisa Yen 41:00
You know, when you speak of this, it makes me think of how you like cooking, and it's like really customizing a recipe.

Dr. Neena Vijayvergia 41:07
That's so true. The salt is always to taste. I don't want to trivialize what important discussion we're having, but everybody is different. And toxicity, nausea is awful for someone, but someone else it's fine. It's like when I was pregnant, I could swear I was dying every day from nausea. But there are people who don't have any, and they have the most beautiful pregnancy. So, everybody is so different than the next patient. Sometimes I really feel it's good to know from everyone, that allows you to understand everything, but don't be scared to try it because of someone else's experience. Because your experience may be very different than what someone else's has been.

Lisa Yen 41:44
Yeah, everyone's so different, and it's not possible to know what your own experience will be like until you try.

Dr. Neena Vijayvergia 41:51
And most side effects are reversible. That's the important thing.

Lisa Yen 41:54
That's a helpful thing with this drug, because you can just stop it and it goes away.

Dr. Neena Vijayvergia 41:58
No harm done. Stop it. You're fine, and we can go back to the drawing board.

Lisa Yen 42:02
Well, what if cabozantinib doesn't work for me?

Dr. Neena Vijayvergia 42:04
If not, then we go back to the drawing board and find something else. So yes, maybe the VEG-F pathways, right, in the beginning, we talked about the pathway that it blocked. Maybe that's a less traveled highway in your cancer. So then we go for Afinitor, that's the other drug that's a pathway. These are two that we know of. If not, then we have clinical trials. There's a lot of studies being done. I

don't want to even get into that part, because that would be another hour of our discussion, which is an exciting time. We will find something that works for you and go from there.

Lisa Yen 42:33
That's hopeful that there are other trials and other treatments as well. So, speaking of clinical trials, though, I've heard that there is a drug called **Zanza**, **Zanzalintinib, the STELLAR-311 trial**. What is that? And could you explain how it might fit into the treatment landscape?

Dr. Neena Vijayvergia 42:49
Sure. So **Zanzalintinib is a sister drug of Cabozantinib**. So it's similar, but it has a much shorter half-life, which means your body gets rid of it very quickly. You remember how we talked about that, if you have side effect, you stop the drug. And then when the body is flushed out the drug, your side effects will get better. And then we start again with the next one next one. With this drug, when the half-life is shorter, if you have any side effect, you stop it, the effect will reverse much faster. That's the idea. The idea being that it's a slightly better tolerated drug. They also say it maybe slightly more efficacious. We haven't seen any data to say that. That's the rationale for why it might be a better drug than cabozantinib.

The **STELLAR study is trying to compare Zanzalintinib to everolimus**. So we talked about the two big highways, the **mTOR highway** and the **VEGF highway**. We're going to see that blocking which one first actually is more efficacious than the other. Remember we talked about previously in sequencing that currently I don't know, and what I tell my patients is, there's no point belaboring this question of which one should I do first, because most people will get both during the course of their treatment. But once we have the data from the study and one of them is better than the other, then we will have an answer. And then we can probably tell patient this is what we should use first and then go to the other one.

So, it will be very important information that will add to our bucket. It will add another potential drug to our bucket, if it works out. But if that gets added, I don't know what will happen to cabozantinib because it's the similar drug. Would it take this away from our bucket? But I think if it is a better tolerated drug, we would love it, but there's so much more to come in that area that I don't think we should speculate about it now.

Lisa Yen 44:29
It is really exciting that there might be a better tolerated version. So who, I guess, and when should they consider Zanza versus Cabozantinib or other treatments?

Dr. Neena Vijayvergia 44:38
Zanza is only available on a clinical trial right now, so you wouldn't be able to get it without it. And I am biased, because I work at a Academic Cancer Center where I think clinical trials is the only way forward in this disease. So as a result, I would probably think that every patient, if you have the opportunity to go on the trial, should try to do that. Because that's the only way we will know and actually, you might be a little ahead of the game because no one else outside of the trial can get Zanzalintinib right now.

So that's a drug that you'll be able to get. So if it was open where I am, I would totally consider going on that clinical trial.

Lisa Yen 45:15
Sounds like if you're considering either of those two drugs, and also their exclusions. If you're considering either of those two, it might be the time to consider.

Dr. Neena Vijayvergia 45:24
Absolutely whenever that's the time, is the time to consider this study.

Lisa Yen 45:28
And if it's open. So just really asking your doctor about that. And what an opportunity, as we started the podcast talking about where we've seen your involvement in the CABINET trial and how we've now seen it come to fruition and now have this FDA approved drug. If people continue to invest, both patients, investigators continue to invest in this field by participating, how we can have more and more options.

Dr. Neena Vijayvergia 45:52
That is what our goal is. Our hope is that in future, this is what we will find. You'll have more drugs go from the phase of testing to actually getting approved, that we will not be required to tell a patient that, hey, I'm sorry we're out of standard options. Let's just look at random clinical trials. We don't want that, and unfortunately, we do it so more often than we would like to. So, I think this is definitely the next step.

Lisa Yen 46:14
Yeah, that's really exciting. I mean, we want to continue to move the field forward. So, I guess in closing, let's wrap up with one last question about cabozantinib, what practical tips or tricks of the trade do you share with your patients who may start this medication?

Dr. Neena Vijayvergia 46:30
I think the most important thing I tell my patients is that we start on a dose, but we need to find your dose, and it's a trial-and-error method, so please be patient in the first few weeks that we will have to find the right dose for them. And then the other is, we really want our patients to feel that they are able to contact us if they have a side effect, and that even though it is an oral agent, that there might be side effects and that they need to consider it as a anticancer therapy. Let's not bring it down to the level of oral medicine that we take for a lot of different reasons. Like, it's not an antibiotic, it's still an anti-cancer therapy so it has to be handled that way. Side effects need to be reported right away. And if you are not comfortable, you should talk to your doctor about any side effect that you're getting. Very important, I think, because early intervention can prevent serious complications.

Lisa Yen 47:22
Yeah, that open communication. I know, for me, the two things I always share with all my patients is, number one, go on the website and get the care kit. Because it has all of those things, like the creams

and something for nausea, lomotil, so you have it all already. And the second thing is ask to talk to the pharmacist.

Dr. Neena Vijayvergia 47:41
Yep, that helps so much. The pharmacist, the nurse, the triage nurse, the doctor, everybody like talking nutritionist so that you can, like, optimize your diet during this time. They're all very important things, just for the holistic care.

Lisa Yen 47:54
Yeah, and the more that you can learn about the disease, the more you can communicate, the better prepared you are for going into this and to have this conversation.

Dr. Neena Vijayvergia 48:02
This podcast and all the others from NCF.

Lisa Yen 48:04
We do have a podcast on the pharmacist as well, and that's really helpful. I know they were helpful for us. We didn't even know that there was oncology pharmacists who could help better understand new drugs.

So, I guess one last bonus question, as we close this episode, what's on the horizon in neuroendocrine cancer research or treatment that you're most excited about?

Dr. Neena Vijayvergia 48:22
Obviously, I think if you go through the tour of radioligand therapy, we're talking about PRRT, is it boosting up PRRT Alpha drugs? There's great enthusiasm. There's concern. There's, like, everything around all these new drugs, which is very interesting. The second is, you know, we just heard there was this new **SSTR-targeted antibody drug conjugate**. I know it seems a handful. It's basically chemotherapy that's directly targeted to the same protein that we use with our shots. I think these are new drugs that are coming down through the pike, which are hopefully going to shape the future for us patients.

Lisa Yen 48:57
Yeah, there's not only new treatments in the same categories of drugs we've been testing, but even new ways of targeting the cancer. Well, thank you so much for your time and all your dedication to this field, both as researcher and clinician. It's been really fascinating just learning from you, seeing your work and seeing what you're doing, and we really appreciate all you're doing on behalf of neuroendocrine cancer patients.

Dr. Neena Vijayvergia 49:20
And right back at you. I was telling you that in the beginning. All you do for our patients. You know, I've worked with you since I started, and it is just such a amazing resource for our patients that I think that you guys get blessings from a lot of people.

Lisa Yen 49:35
Well, it's a team effort. We're all in this together to move the field forward, as we were talking about.

For all our listeners, we hope today's conversation helps bring clarity and reassurance as you navigate whether cabozantinib may be part of your treatment journey. And as always, our goal is to empower you with practical, trustworthy information so you can make decisions and partnering with your care team, people like Dr Vijayvergia and feel supported every step of the way. Thank you for joining us, and please remember you're not alone. We're here for you.

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