Episode 22 – "What to Know about Pancreatic NETs" with Dr. Jennifer Chan
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Lisa Yen:

Welcome to the LACNETS podcast. I'm your host, Lisa Yen. I'm the LACNETS Director of Programs and Outreach, as well as a caregiver and advocate for my husband who is living with NET. In each podcast episode, we talk to a NET 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:
Welcome everyone to the LACNETS podcast. I'm really excited to introduce today's guest, Dr. Jennifer Chan. Let me just tell you a little bit about Dr. Chan.

Dr. Jennifer Chan is a medical oncologist and is the Clinical Director of the Gastrointestinal Cancer Center at Dana Farber Cancer Institute. She specializes in neuroendocrine tumors. Dr. Chan received her medical degree from Harvard Medical School in 2000. And she subsequently completed her residency in Internal Medicine at Brigham and Women's Hospital and her fellowship in medical oncology at Dana-Farber Cancer Institute.

In addition to her clinical practice, she lectures widely and has published several articles on treatment approaches for patients with pancreatic neuroendocrine or carcinoid tumors. She has also played a leading role in the development of novel neuroendocrine tumor therapies; She has served as the principal investigator of several Dana-Farber/Harvard Cancer Center clinical trials for patients with neuroendocrine tumors. She is currently the principal investigator of an exciting trial called the "CABINET trial" that studies the use of cabozantinib in advanced pancreatic neuroendocrine and carcinoid tumors.

Dr. Chan is a leader in the NET medical community and serves as the Treasurer on the Board of Directors of NANETS, the North American Neuroendocrine Tumor Society, the professional

medical society for NETs. She is the Finance Committee chair and was the past chair of the guidelines committee.

I'm really excited to have Dr. Chan here today. And I'd like to invite you to share a little bit about how you got involved in the neuroendocrine tumor community.

Dr. Jennifer Chan:
Thanks, Lisa, thanks for that really kind introduction. I'm really happy to be part of today's podcast, I have been treating patients with nets for gosh, almost close to 20 years. I started my fellowship at Dana Farber in 2003 and started as a GI oncologist in 2006. And pretty early on into my career, I started seeing patients with NET. At the time, there really weren't that many providers seeing patients with NET. And there really was a lot of unmet need for providers to care for patients with NETs for new treatments to be developed for patients with NET. So, it really for me was a really exciting time to be introduced to the field, to begin my career and to focus on a group of patients with very unique needs. It's been really a pleasure to care for people and to learn over the years about how to care for patients with NETs.

Lisa Yen:
Wow. So, you saw an unmet need, and you stepped up to meet it?

Dr. Jennifer Chan:
Yeah, I'd like to think of that way. It's been really amazing to see the field evolve over the years. And really, to see how we've come to where we are right now.

Lisa Yen:
I mean, that's really exciting that you were a witness to it, and you had your hand in it as well. Thank you for that. So, I'm really excited. I know that you've done a lot of work in these last two decades in pancreatic NET and continue to do quite a bit. And that's why we invited you here today. So, if you're ready, let's jump into the 10 questions.

Dr. Jennifer Chan:
Sure. Okay.

Lisa Yen:
The very first question, as you know, sometimes in a lot of the patient education conferences and meetings and programs, we tend to be lumpers. For the sake of efficiency for the sake of inclusivity, we try to have all our educational materials speak to everyone. And then, as you know, not everything applies to everyone, because everyone's individual and unique. And there's a need to speak to very specific types of NET. So, in this series, we're dividing them up to the different types of NETs. So today, we're talking about pancreatic NET, which is something that you're very familiar and very widely specialized in. And we have a wide range of patients who come to us.

So, the first question is really, especially for those who are just diagnosed, which we get many of all the time I think last week, I probably got five emails from people who are newly diagnosed with pancreatic NET. So, the first question is, what are pancreatic NET and where are they located?

Dr. Jennifer Chan:
So, maybe I'll take a step back to explain neuroendocrine cancers in general. Neuroendocrine cancers are a really diverse group of cancers that start in the neuroendocrine system. And I think it's really important to make a distinction between the well differentiated neuroendocrine tumors and the poorly differentiated neuroendocrine carcinomas.

The well differentiated neuroendocrine tumors have a very different biology and a very different natural history than the neuroendocrine carcinomas. The well differentiated neuroendocrine tumors most commonly start in the lung, the GI tract in the pancreas. And pancreas neuroendocrine tumors, they can begin anywhere in the pancreas. Sometimes they stay localized to the pancreas itself, and then sometimes they do have the ability to spread either to lymph nodes that are nearby or to other parts of the body, most commonly to the liver.

Lisa Yen:
Yeah, thank you for that overview. That's very helpful. So, the next question would be, “How are pancreatic nets found? And what are the symptoms of pancreatic NET?”

Dr. Jennifer Chan:
Pancreatic nets are often found incidentally. Patients may not have any symptoms at all, but a scan might pick up an abnormality in the pancreas. You know, for some radiologists, they can actually look at a mass involving the pancreas and suspect that it might be a neuroendocrine tumor. Sometimes patients who have larger tumors or cancers that might have spread may have symptoms that are just related to the actual physical presence of the cancer that might include abdominal discomfort. Some people might have nausea or vomiting or diarrhea.

And then one other thing that makes the neuroendocrine tumors very unique is their ability to make hormones. They make and secrete hormones. And there are some patients that might have symptoms that are not necessarily related to the actual presence of the mass or the cancer, but to the hormones. And some of those hormones might cause diarrhea. Some of those hormones might cause a lot of acid secretion that can cause ulcers and really severe heartburn. Some patients might have skin rash. So, there's a whole host of hormones that the pancreas neuro endocrine tumors can secrete. And maybe about 30% of patients have hormone-type symptoms related to what their pancreatic neuroendocrine tumors making and secreting.

Lisa Yen:

Yeah, so you kind of mentioned that there might be a physical discomfort. So, I'm wondering, you know, you and I might know where the pancreas is on the body, but for the lay people out there, where is it in the body and where might they feel the discomfort?

Dr. Jennifer Chan:
Yeah, that's a great question. So, the pancreas is a digestive organ. It serves two purposes. It has an endocrine function. It makes hormones like insulin. And then it has an exocrine function where it secretes enzymes that help with digestion. It's an organ that sits in the upper abdomen, kind of behind the stomach. So, it has a head, a body, and a tail. It's kind of like a fish-like structure where it has a head that's closer to the center of the abdomen, kind of the right side, so to speak of the abdomen. And then the tail part is towards the left side of your abdomen. So, there may be some symptoms in the upper abdomen. Some patients might have symptoms that they feel in their back, either because of the fact that the pancreas sits towards the back of the abdomen are there also are nerves that are near the pancreas that might be referred pain, where you might feel some symptoms in the back.

Lisa Yen:
Thanks for that, that gives a little bit better of a, kind of, anatomy overview. You talked about a lot of people are whether diagnosed incidentally. But in that stage of getting a diagnosis, a lot of times they're told by a doctor, “Oh, it could be pancreatic cancer” or that “maybe you have pancreatic cysts.” So, I'm wondering how is it different from pancreatic cysts, and how is it different from pancreatic cancer?

Dr. Jennifer Chan:
Yeah, that's also a really great question, Lisa. Pancreatic cysts. When we think about cysts, they are usually fluid filled cysts or structures in any organ, including the pancreas. And that's in contrast to pancreatic neuroendocrine tumors or pancreatic cancers that are usually solid. So that's one really important distinction. Is it cystic or fluid-filled, or is it a solid tumor? Most cysts are benign, some of the cysts may have an ability to become cancerous over time or especially as they develop solid components. But that's what I would consider as the main distinction between a cyst and a pancreatic neuroendocrine tumor or a pancreatic cancer.

The other really important distinction is between pancreatic neuroendocrine tumor and what we think of as pancreatic cancers. They are all malignancies, meaning they have the ability to grow abnormally, and also to spread. But the types of cells that are forming the cancer in the neuroendocrine tumor are different than in the most common form of pancreatic cancer, which is adenocarcinoma. So, because adenocarcinomas are much more common than pancreatic neuroendocrine tumors, many people think about adenocarcinoma when they think about pancreatic cancer. But the main differences are the type of cells that are forming the cancer. Neuroendocrine tumor versus adenocarcinoma, which is more of a glandular cancer that starts in the pancreatic ducts. They also are different in the way they behave. The pancreatic adenocarcinoma does tend to be more aggressive types of cancers. They also respond and are treated very differently than neuroendocrine tumors. So, I think that's also an important distinction, is just the biology of the cancer is different. The pace at which they grow, and

spread is different, and then also the way we treat them is also very different. So, I think whenever anybody says pancreatic cancer, it's important to make that distinction. Is it the usual type, the adenocarcinoma? Or is it neuroendocrine tumor?

Lisa Yen:
That's really helpful, and I think it's helpful to have the clarity that you just explained because whether someone is a patient or a caregiver or trying to explain it to a family member, you know, I'm sure that we all myself included come across that confusion quite a bit. So, thank you for clarifying. And what a relief right that it's not pancreatic adenocarcinoma.

Dr. Jennifer Chan:
Right.

Lisa Yen:
Yeah. So, you talked about how a lot of these pancreatic NETs are found incidentally, just by some other reason that they're being worked up. So, what types of labs and testing and scanning are done to find it, especially if someone doesn't have symptoms? And even when they start wondering what is this tumor to figure out if someone has pancreatic NET?

Dr. Jennifer Chan:
Right. So, you know, for the incidental tumors, sometimes a scan, whether it be a CAT scan, or an MRI has been done for some other reason. You know, oftentimes we think about anybody who goes to the emergency rooms with abdominal pain might end up with a CAT scan, that might show something in the pancreas. And these are very vascular tumors. The neuroendocrine tumors are very vascular. So, some radiologists may suspect that it's a neuroendocrine tumor. That can lead to other testing. MRI can be also characteristic for neuroendocrine tumors and then we sometimes will also if neuroendocrine tumor is highly suspected, get a dotatate PET CT scan, and I can explain a little bit more detail about dotatate PET CT scan, but that is an imaging test that is very specific for neuroendocrine tumors. Many of the well differentiated neuroendocrine tumors have on the surface of the cancer cell a receptor a hormone that's called somatostatin. The radiology team can use a nuclear medicine test to one, find out if it's neuroendocrine tumor and then if it is neuroendocrine tumor, where the neuroendocrine tumor is, by doing this dotatate PET CT scan where an analogue of that somatostatin hormone is linked to a radionuclide and then injected during the imaging procedure. So, it will light up so to speak, where there is neuroendocrine tumor. So, if you suspect that it's a neuroendocrine tumor, and the dotatate PET CT scan is done and lights up in that area that's very highly suspicious and almost diagnostic for neuroendocrine tumor.

But I think the most diagnostic test is ultimately a biopsy where that abnormal mass is biopsied. Oftentimes, it's done through radiology testing with a needle biopsy, a core biopsy that can get a sample of the abnormal tissue. And then under the microscope, the pathologist can look at the abnormal cells, tell that they're neuroendocrine. They sometimes will use certain stains that are also very classic for neuroendocrine tumors. Examples of these stains include chromogranin, and synaptophysin. And so that can also confirm that it's neuroendocrine. But,

you know, sometimes it's the imaging that is very suspicious for neuroendocrine tumors, but then ultimately, a biopsy is done to confirm that diagnosis. Some of the scans that are done often are CAT scans or MRIs, because these are imaging tests that can very clearly show you where the abnormalities are, where the cancer is, you can precisely kind of see and measure. But then as I mentioned to you the dotatate, PET CT scan is also helpful for staging neuroendocrine tumors and then telling us if that somatostatin receptor is present or not.

Lisa Yen:
Yeah, that's really helpful to have a better understanding of what scans and how the biopsy would be done. And I'm just wondering, also, you talked about all the different hormones that could be produced, does that need to be done for all people with pancreatic NET?

Dr. Jennifer Chan:
No, we don't have to do a wide panel of hormone testing for everybody with a pancreatic NET. We do hormone testing if there are any symptoms that are highly suggestive of a functional neuroendocrine tumor. And that's one term that you may hear, "**functional tumors**." And that really is a clinical diagnosis. So, we are evaluating whether there are any symptoms that might be related to hormone excess. Some of the common hormones that are made by pancreatic neuroendocrine tumors can include for instance, insulin. And in cases where we're suspecting that somebody's low blood sugar levels might be related to neuroendocrine tumor, we will do testing, looking at insulin levels and some of the other hormones that are associated with insulin. Some of the other neuroendocrine tumor syndromes include vasoactive intestinal peptide, this VIP hormone. So, if somebody has a very profound diarrhea and electrolyte abnormalities, we may check hormone levels from VIP in situations like that. But it's not typically helpful to have a whole blanket panel of hormones tested. So, we really rely on symptoms to guide us in that.

Lisa Yen:
Yeah, so symptoms guide and you also mentioned that a lot of these are found incidentally. So, I'm sure one question that comes up is, is there a way to detect it earlier? Is there a way to know, not just find it accidentally for some other reason that brings you to the ER?

Dr. Jennifer Chan:
We don't have any screening tools. You know, unlike colonoscopy where we're looking for polyps or early colon cancers or mammography. We don't have a really good screening test for neuroendocrine tumors at this point. Sometimes it is incidental diagnosis or symptoms. There are families where neuroendocrine tumors can develop because of inherited susceptibility. And I would say that probably is the exception to that screening, where if we know that there is an inherited susceptibility, we can work with genetic counselors to do screening for some tumors that might be associated with those inherited syndromes.

Lisa Yen:
Yeah there's so many nuances to this. And we're grateful that there are NET experts like you who kind of know which direction to pursue this right? And what labs and who else might need

to be screened. So, the next question is, what are some ways that pancreatic NETs differ from other types of NETs and what makes it unique?

Dr. Jennifer Chan:
So pancreatic NETs, I think one of the differences is location, because location often can influence symptoms. So, I think that's one thing to keep in mind. A lot of the symptoms that might be associated with pancreas neuroendocrine tumors are what we talked about previously, maybe some upper abdominal discomfort, maybe some impact on digestion and bowel movements. And that's going to be different than for instance, lung neuroendocrine tumors, where some of the symptoms are more respiratory, or even some of the GI small intestine neuroendocrine tumors even though they're all digestive, some of the symptoms are different.

The other thing that makes pancreas neuroendocrine tumor is different are the hormones that are secreted. You know, for instance, with the small intestine, particularly ileal neuroendocrine tumor is the hormones that are made are serotonin. Although in the serotonin can cause symptoms like diarrhea, and there's also flushing that's associated with that classic carcinoid syndrome that we see with the small bowel neuroendocrine tumors, the pancreas neuroendocrine tumors can secrete different hormones. We sometimes rarely can see serotonin secreted by pancreas neuroendocrine tumors. But if we're looking for functional neuroendocrine tumors that start in the pancreas, it's often the hormones like insulin, VIP, gastrin, which makes the high acid level. So hormones are different. And then also, there are some implications to primary site of tumor and how well treatments work. And I'd say one thing that is unique about pancreas neuroendocrine tumor is what makes it different from some of the GI, especially small bowel neuroendocrine tumors is the sensitivity to chemotherapy, particularly with temozolomide and capecitabine, which we will routinely use in pancreas neuroendocrine tumors, but not as commonly in the small bowel neuroendocrine tumors.

Lisa Yen:
Yeah, that's interesting, because a lot of times there's a blanket statement in the patient advocacy world, that chemotherapy is not really used for NETs, however, it is used more routinely with pancreatic NETs. So, I'm wondering what makes pancreatic NETs more sensitive to chemotherapy?

Dr. Jennifer Chan:
That's a really good question. I think those are things that we are still kind of on a very basic and translational level, trying to understand. You know, one thing that we have learned about, for instance, temozolomide, is that there may be some differences in the expression of a protein that's called MGMT in pancreas neuroendocrine tumors versus the small bowel neuroendocrine tumors. And this protein MGMT tries to repair some of the damage that chemotherapy does. So, if there is less expression or less of that protein around, the chemotherapy may work better. So, we have found, for instance, that some of the pancreas neuroendocrine tumors may be more deficient in that protein, that enzyme, so it's less able to repair some of that damage.

So that may be one of the clues, but we're still really actively trying to figure that out and to better understand how we might be able to predict which types of cancers will respond to what types of treatment.

Lisa Yen:
Wow, well, thanks for sharing that little insight. It's exciting to kind of have these little keys right to be able to work on and target. And thank you for your work. I can see you get excited when you talk about this. So, you're certainly passionate about research and finding these clues and some avenues to better treat neuroendocrine tumor.

Dr. Jennifer Chan:
Thanks.

Lisa Yen:
So, you know, one common question that often comes up when someone's newly diagnosed is, how do you decided the pancreatic NET can be surgically removed? And for you, when you're seeing these newly diagnosed patients? What type of surgeon would help make that determination?

Dr. Jennifer Chan:
You have so many great questions. This is a really good one. I think this really speaks to the importance of having a team of medical providers caring for patients with neuroendocrine tumors, because we all bring to the table different vantage points, different expertise. I think when it comes to questions about, can something be removed with surgery, that's where it's really important to consult with an experienced surgical oncologist who has training in dealing with pancreas and biliary tumors. When it comes to whether or not a pancreas neuroendocrine tumor can be resected, it's really all about location. And it's particularly the location of the tumor in relation to some of the major blood vessels that are in the area of the pancreas. Some of the major arteries, whether it be the superior mesenteric artery or the celiac artery, if those arteries are involved, it's very difficult to almost impossible to remove the tumor. And that's primarily for tumors that are located in the head of the pancreas where we have to make these really important decisions based on where the tumor is located in relation to blood vessels. Tumors that are in the tail of the pancreas are quite far away from the structure. So, the ability to remove them is perhaps less limited in the head. But again, really important to work with a radiology team and then also surgeons to make these decisions about resectability or not.

Lisa Yen:
Location, location, location

Dr. Jennifer Chan:
Right

Lisa Yen:
And when you talk about a certain what type of surgeon would you consult with?

Dr. Jennifer Chan:
We usually will consult with surgical oncologists at our center. At other centers that may be the hepatobiliary pancreas surgeons, because they have the most expertise in thinking about cancers in the case of surgical oncologist and then really the surgical approaches to treating cancers that are in that anatomic region.

Lisa Yen:
Yeah, thank you. It can be confusing for patients, right, which type of surgeons and also, how does having disease in the liver affect this whole realm of surgery and even what type of surgeon might they see?

Dr. Jennifer Chan:
So, when there is disease that has spread to the liver, it's also really important to think about whether there is a role for surgery. We know from a lot of different studies that have been done that even in the setting of spread to the liver, that there may be a role for resection of liver metastases to improve long term outcomes. It may not necessarily cure the cancer because there's a high chance that it may come back at some point in the future. But as we think about survival and living with the disease and setting the clock back, it's really important to have a surgeon who understands neuroendocrine tumors. Again, oftentimes, that's [the] surgical oncologist, and then surgeons who have training in removing liver metastases really thinking about your individual case and looking at the scans to determine whether there's a role for surgery and when that should be.

Lisa Yen:
Yeah, you've given a really helpful overview of the considerations for surgery. Let's shift to medical treatment, how are pancreatic NETs treated medically? And how would treatments be sequenced?

Dr. Jennifer Chan:
So, as we think about non-surgical approaches, I think it's important to think about other liver directed therapies. Oftentimes, these are done in conjunction with the interventional radiologists who can do embolization procedures to try to essentially inject into the liver articles that may have an ability to occlude the blood supply to tumor to directly treat the tumors that involve the liver. So even if surgery is not possible, there may still be a role for really going after disease that is primarily involving the liver. When we start to think about medical therapies, it's usually in patients where we don't necessarily see a role for surgery or liver-directed therapy, but we're trying to control disease progression or shrink disease with a medical approach.

There are a whole host of medical therapies that we use for pancreas neuroendocrine tumors, starting first with somatostatin analogs. As I mentioned a little bit earlier, one of the really distinguishing features of well differentiated neuroendocrine tumors is that they have high levels of the somatostatin receptor on the surface of the cancer cell. So, we can take advantage

of that not just for imaging purposes, but also for treatment approaches. And there are somatostatin analogues, octreotide and lanreotide are the ones that we use in clinical practice that can slow down growth of disease. So, for some patients where there might be a need to control growth, we often reach for somatostatin analogs. The other thing that this somatostatin analogues can do, their second property in addition to slowing down growth, is that they can reduce hormone secretion. So, they become very important for patients who have functional tumors where we're trying to control not just growth, but also hormone secretion. Because if we can control hormone secretion, then a lot of the symptoms that are related to hormone access can be improved. So that's the first category and often the category of medicines that we start with first.

There are some cases where we are looking for shrinkage, where we really want to achieve, not just slowing of growth, but really reduction in the amount of cancer that's there. As we think about the medical approaches to that we can often more commonly achieved that with chemotherapy for pancreas neuroendocrine tumors. And again, as I mentioned, into one of the regimens that we use to treat pancreas neuroendocrine tumors is this combination of temozolomide and capecitabine. Some people refer to that regimen as the **CAPTEM** regimen and these are oral chemotherapy medicines. We combine them and we know that that has a good chance of shrinking disease. The other class of medicines that we use also relies on the presence of the somatostatin receptor. And this is the category of **peptide receptor radionuclide therapy or PRRT**. So again, we're relying on this amount of statin receptor and our nuclear medicine colleagues will treat pancreas neuroendocrine tumors with a somatostatin analogue that is conjugated or linked to a radionuclide that can kill the neuroendocrine tumor cells.

And then that last class of medicines that we use, I think of as molecularly targeted therapies. So, we use medicines like sunitinib and everolimus to slow down growth of pancreas neuroendocrine tumors. Sunitinib falls into a class of medicines that is called a **tyrosine kinase inhibitor**. It works by blocking a whole host of receptors that are on the cancer cell, but one of the important receptors is involved in making new blood vessels. So, it's what we call an angiogenesis inhibitor. Angiogenesis is that process of making new blood vessels and we know that again, blood vessels are so important for growth and spread. And medicines like sunitinib can help to inhibit that process and also slow growth. Everolimus is what we call an **mTOR inhibitor**, it will block a pathway that's called the mTOR pathway that is involved in cell signaling for growth.

So these are all treatments that we have available. How to use them, how to sequence them, is very individualized and really, I think depends on the goals of therapy for each individual patient, meaning, are we trying to shrink something that might be large and causing symptoms? Or are we going for something that's going to slow disease progression, help hormone symptoms, or we just hope slow things down to keep things looking as they are for a long time?

Lisa Yen:

What an excellent overview of the four main categories. So, somatostatin analogs, and then on the other end, chemotherapy that are the pills, PRRT and targeted therapies.

Dr. Jennifer Chan:
Right.

Lisa Yen:
And as you said, it all depends on the goals of treatments.

Dr. Jennifer Chan:
Right, and also depends on the patient. And some of the medical conditions that patients might have that may make it more or less able to tolerate some of these medicines, all of these things very tumor related and patient related. So that's, again, why it's so important to think about individualized care.

Lisa Yen:
Yeah, individualizing, the care to put the patient at the center to weigh in all these different nuances of it with the patient's condition, their preferences and the goals of therapy. Well, thank you for that excellent overview of these medical treatments that are possible. So, you know, a lot of times in the educational meetings, all the NETs are lumped together. So, I'm wondering how do these treatments for pancreatic NET differ from other NETs?

Dr. Jennifer Chan:
There is a lot of commonality in the therapies that we use for all well differentiated NETs. For instance, for the GI NETs, we will use somatostatin analogues just like we use in pancreas neuroendocrine tumors. Although somatostatin analogs are not approved for lung neuroendocrine tumors, we've seen data that they're effective, especially if we know that lung neuroendocrine tumors have somatostatin receptor expression, we will use them. I think everolimus is also approved kind of across the board for GI, pancreas, and lung neuroendocrine tumors. Peptide receptor radionuclide therapy, specifically with lutetium 177 dotatate, is approved for both GI and pancreas neuroendocrine tumors. It's not yet approved for lung neuroendocrine tumors, although there are some studies that are ongoing to investigate that and, in some cases, we are able to think about using treatments off label.

I think where pancreas neuroendocrine tumor treatment is different from especially small intestine or other GI neuroendocrine tumors is our use of chemotherapy, particularly with CAPTEM. For some of the lung neuroendocrine tumors, we will also think about using chemotherapy, with CAPTEM and sometimes with some of the more aggressive lung neuroendocrine tumors that we're worried about, we'll even use platinum-based chemotherapy. But you know, I like to think of all of these treatments as similar across the board but with a little bit of nuance, as you think about different sites. And with pancreas neuroendocrine tumors, the nuances are he sensitivity to chemotherapy with CAPTEM. And the other thing to note is that across all neuroendocrine tumors for pancreas neuroendocrine tumors, this is the only site where sunitinib, that tyrosine kinase inhibitor, is approved. We're

doing a lot of investigation to see if there is activity of tyrosine kinase inhibitors in neuroendocrine tumors that start outside the pancreas, but as of right now the only one that is approved is sunitinib, and for pancreas neuroendocrine tumor.

Lisa Yen:
So, it sounds like there's more options for pancreatic neuroendocrine tumors than other types of NETs.

Dr. Jennifer Chan:
That's right. Yeah, I think of all of the different types of NETs. When you look at drug approvals, we see the most number in pancreas.

Lisa Yen:
Most number. It's more sensitive to chemotherapy. And it's interesting because all of the four different buckets of treatments you mentioned, they targeted different ways. They're really trying to kill or shrink the tumors using different mechanisms, which is really hopeful.

Dr. Jennifer Chan:
Yeah, definitely encouraging. And I think we're also optimistic as we learn more about the biology, we'll find new targets and hopefully add to, not just those four buckets, but have more options in each bucket.

Lisa Yen:
That's what we want. So, the next question is, you know, especially once someone is on some sort of treatment, how would you monitor pancreatic neuroendocrine tumors? What type of bloodwork or tests should be done and how often? And also, what's the best type of scan? You mentioned, the dotatate scan, the MRI and CT. What is the best type of scan?

Dr. Jennifer Chan:
I think if we think about specific situations, there are for instance, some patients who've been diagnosed with a pancreas neuroendocrine tumor, and maybe it's small, and people have decided that surgery might not be necessary, at least immediately. In cases like that, we often are going to be using CAT scans or MRI to look for growth. On the other hand, there may be some patients who've already had surgery and we're looking to see if there's any recurrence in the future. We do know that for many patients, we want to watch after surgery for at least up to 10 years. In situations like that, we also are relying on CAT scan and/or MRI to look for change. We don't always have to do a dotatate PET CT scan. Oftentimes that may have been done already before surgery. And if we know that everything has been removed, we will rely on CAT scan and our MRI, to look for change or regrowth. And hopefully that doesn't happen. But those are the things that we are going to be monitoring for. If we see anything on the CAT scan that looks like it might be growing, even if it's a little bit or if we see something that looks new, I think that's when we will typically integrate a dotatate PET CT scan to better characterize something that has been seen on either a CAT scan or MRI.

And then in the other situation that we commonly see, maybe patients who have metastatic or advanced disease where we are, again looking to see how well a treatment works, or looking to see if there is growth or spread in the future. And again, that's where I typically will still rely on CAT scan and MRI because those give us the best visualization of the tumor and we can kind of more precisely measure and follow for any size changes or development of new lesions. We also will at some point, integrate a dotatate PET CT scan, particularly if there's growth and we're looking for treatment options. And especially if we're trying to consider whether there might be a role for peptide receptor radionuclide therapy, we'll want to make sure that there is somatostatin receptor expression if we're going to be thinking along those lines of treatment.

There are some patients who might have disease that is in the bone or primarily in the bone. And that's again where CAT scan and MRI have that's probably one of the limitations even though we can work clearly see and measure things on a CAT scan or MRI, it's limited in their ability to follow things in the bone where the dotatate PET scan may have a leg up.

When it comes to blood markers, I think this is probably one of the most controversial areas om management of neuroendocrine tumor and to be honest with you where we see a lot of variability. I think what in the past had been done more commonly the now is routine measurement of a marker called **chromogranin**. But many people, including myself have really found that that chromogranin test when it's done as kind of a regular scheduled test, it really doesn't add a whole lot to care. It's not really that well validated or sensitive for picking up changes in disease that are important to act on. So, I've stopped routinely doing that. And many of the guidelines now also recommend not routinely checking chromogranin. For some patients who have hormone related symptoms, it can sometimes be helpful to follow not just symptoms, but also hormone levels to see if there are changes over time. But beyond you know hormone assessment, which can have some clinical implications, I don't usually do a whole lot of blood biomarker testing.

Lisa Yen:
Sounds like mainly you rely on scans.

Dr. Jennifer Chan:
Mainly rely on scans and symptoms. I think those two things often give me the most information for making decisions about how to care for people.

Lisa Yen:
Scans and symptoms. You mentioned a lot MRI or CT scan, how do you decide MRI versus CT scan?

Dr. Jennifer Chan:
So, they both provide good visualization of internal organs. MRI can be particularly helpful when we are following patients who have liver predominant disease, particularly when we do an MRI with a liver contrast agent that's called **Eovist**, we can very nicely see the liver metastases and follow for changes. I do also follow some patients who might have some

concerns about radiation exposure with MRI as part of their surveillance. But I think CAT scan and MRI, they both are good for looking at abdominal organs with liver MRI being particularly helpful when there's liver predominant disease.

Lisa Yen:
Thanks for that clarification. So, the last question, you know, we talked about the four different buckets of treatment options or surgery, liver-directed therapies, what clinical trials should we be aware of, or exciting new treatments that are in the pipeline for pancreatic NETs?

Dr. Jennifer Chan:
Yeah, thanks for asking that question. I think these are some of the things that we're all looking forward to seeing the results of these trials. We're all looking forward to expanding our treatment options for patients. There are some trials that are ongoing now that I think of as in the first line setting. As I mentioned to you, we often use somatostatin analogs as a first-line treatment. There is a trial that is being sponsored by a Swedish company called Camerus that's looking at a novel formulation of octreotide. It's called **CAM2029**. This is a drug that's been formulated to achieve higher exposure in the body higher levels compared to standard octreotide. And it's also something that patients can self-administer. So, we are participating at my center. And there are a few other centers in the US and internationally that are participating in this first-line trial. It's called the **Sorento trial**, that's looking at CAM2029 versus standard doses of octreotide LAR or lanreotide. Really looking to evaluate whether this is a more effective somatostatin analog by achieving higher bioavailability. We're looking forward to seeing how the patient experience is with something that can be self-administered, as opposed to something that requires monthly healthcare professional injections.

As we look at other trials that are beyond the first-line setting in patients who've had prior therapy, there are some trials that are ongoing that are looking to compare active agents to see whether we can prove that one treatment might be more effective than another there is a trial that's already been completed. This is a European trial called the **COMPETE trial**. So, the COMPETE trial was comparing PRRT with lutetium 177 edotreotide versus everolimus. And then in the US, we recently activated a clinical trial through the Alliance for Clinical Trials in Oncology Cooperative Group that's looking at lutetium 177 dotatate compared to CAPTEM. [**ComPareNET trial**] So, some of these trials that are looking at two activations will help us with treatment selection and potentially sequencing in the future.

There also are some really exciting novel PRRT trials that are looking at some of the Alpha PRRT agents which may have better activity compared to beta PRRT. So, there is a trial, this **ACTION-1 trial** that is going to be activated that will be comparing this Actinium 225 PRRT agent with standard therapy in patients who have had prior PRRT. So, we're looking forward to the results of those trials.

One trial that is very dear to my heart is the Alliance for Clinical Trials in Oncology for the **CABINET trial**, which is looking at **Cabozantinib**, which is a tyrosine kinase inhibitor. This particular trial is looking at the efficacy of cabozantinib compared to placebo in patients whose

cancer has progressed on prior therapies. And this is a group of patients who, for instance, may not have other active therapies available where the trial may represent an option. And hopefully, when the trial is complete, we'll be able to examine the efficacy of cabozantinib. And then know if this is something that may be active that we can add to the treatment landscape.

Lisa Yen:
Wow, you just named like half a dozen trials. So that's really exciting that there's so much going on. And I cannot even tell you how many patients are always asking, “How do we know how these trials are going like CABINET, the ACTION1? How do we know how they're going? Where is it open? How do we find out more about them?

Dr. Jennifer Chan:
So, I think these are great trials. And I'm glad for the work that you and other organizations are doing to spread the word. I think it's always for all patients really important to ask your physicians about whether a trial is right for you. I think that there are certain times when trials can become very important, either when a new treatment is necessary and usually that's when one treatment has stopped working or a new treatment needs to be started. Or if a treatment isn't so well tolerated and people are looking to switch treatment.

In terms of trying to understand what trials are available, I admit, and I think a lot of my colleagues also admit that it's very hard to keep track of things. And I think that's again, why we're grateful for the work that your organization is doing. And I know some of our colleagues, Josh Mailman, is trying to create a trial finder specifically for patients with neuroendocrine tumors. I think it's also important for us to keep everything updated in some of our search engines for us to be able to, in meetings, be able to highlight certain trials that we think are important and are ongoing, and even within our own institutions. We try to keep websites updated so that patients with neuroendocrine tumors who might be looking for something in the Boston area can know what's available.

Lisa Yen:
Yeah, that's exciting. It's exciting to have these trials open. And patients want to participate and also know how it's going. When would we know how the results are going, for example, with the CABINET trial?

Dr. Jennifer Chan:
We don't have any early results. As the study chair for the trial, I'm able to monitor accrual. But we won't probably have any results until our data safety monitoring board, which is looking at all the, you know, events that happen on the trial, as they come in, they will let me know. And usually then there's an announcement that's made. So, I think usually what we'll do is once a trial is open, we try to let people know if it's accepting new patients are not. But in terms of results, oftentimes, that usually comes at the direction of the data safety monitoring board. And for many of these trials, it can take several years from the start to be able to get results, especially for the larger randomized trials.

Lisa Yen:
Well, we're really grateful for your work on all these trials and the CABINET trial.
So, in closing, I'm wondering what words of hope would you like to share with the neuroendocrine tumor community?

Dr. Jennifer Chan:
Well, I'd like to share that there is a lot of progress that we have made in recent years. And I'm optimistic that that progress is going to continue. As I look back at what has happened, even over the last ten years, it has been really gratifying to see how much we've learned about the biology of the cancers and even just see the number of approved agents since 2010 increase by numbers. And I think as we look at some of the work that's ongoing, now, some of the new agents that are being investigated, we're hoping to be able to add to that. So, I think there is hope that we're going to be able to continue to optimize therapy, find newer therapies to help even understand how we can best utilize the treatments that we have available. A lot of that work is ongoing. And I think the other thing I'd like to say to the whole neuroendocrine tumor community is that, although in the past, this has been perceived as a rare disease and perhaps not as well studied, I think the fact is that there are a lot of patients who've either had this diagnosis or who are living well with this diagnosis. So, you're not alone. I think, LACNETS and other organizations, by bringing everybody together, to share what we know, to hear from one another, I think that's really quite empowering, and I think inspiring. So, it's definitely great to be connected and to stay involved. I'm looking forward to joining you in future meetings and sharing more about progress that is being made.

Lisa Yen:
We look forward to that too. Thank you for being part of empowering and inspiring our NET patient community and for sharing your passion, your dedication and hard work that is directly leading to new treatments and new advances for the field.

Dr. Jennifer Chan:
Thanks, Lisa. It's been great to join you today.

Lisa Yen:
We're grateful for you. Thank you so much.

Lisa Yen:
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