THE LACNETS PODCAST

"Top 10 Highlights of the 2022 NANETS Symposium"
With Dr. Will Pegna
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Lisa Yen:

Welcome to the LACNETS Podcast. I'm your host, Lisa Yen. I'm the LACNETS, Director of Programs & 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 as medical advice. Please discuss your questions and concerns with your physician.

Thank you so much for joining us for today's episode of The LACNETS Podcast. I'm excited to introduce today's guest, Dr. Guillaume Pegna, also known as Dr. Will Pegna. Dr. Pegna is a medical oncologist at the Oregon Health and Science University, or OHSU in Portland, Oregon.

Dr. Pegna specializes in the care of adults with gastrointestinal cancers and neuroendocrine tumors, or NETs. And he also has experience in managing the more rare neuroendocrine tumors pheochromocytomas, paragangliomas and adrenal cortical cancers.

Dr. Pegna is actively involved in clinical trials and clinical research to improve survival and quality of life for cancer patients. And to better understand the biology of these diseases. Dr. Pegna finds it rewarding to help patients understand their disease, providing treatment options based on each individual patient, and supporting them through their treatment journeys.

I've learned that Dr. Pegna grew up on the East Coast, in upstate New York, in a French speaking family. And so that's where his name comes from, Dr. Guillaume, or Will, the English translation of his name. And you spent your life mostly on the East Coast before moving out to Portland.

So Dr. Pegna, you did your undergrad studies at Stony Brook University and went on to attend the University of North Carolina School of Medicine, and completed your internal medicine at

University of North Carolina and hematology oncology, followed by a fellowship in hematology oncology, at the National Institute of Health where you trained under LACNETS friend and medical advisory council member Dr. Jaydi Del Rivero, who is well known to us in the neuroendocrine tumor community, and here at LACNETS.

So, I had the pleasure of meeting Dr. Pegna, in person in Portland this summer, and we sat down for several hours to discuss gaps and issues in neuroendocrine tumor patient care and neuroendocrine tumor patient advocacy. And I felt like we could have kept talking for hours and hours. So, I'm really happy to welcome you Dr. Pegna, it's really good to have you. And before we dive into our topic for today, I'll just invite you to tell us a little bit about yourself and how you became interested in the neuroendocrine tumor population.

Dr. Will Pegna:

Absolutely. Thank you so much, Lisa. And really the whole LACNETS team for inviting me to join today. It was really great to see you in person, see everyone in person really, after so many years of COVID. But yes, to introduce myself to some of the viewers, who I haven't had the chance to meet yet. My name is Guillaume Pegna, I typically go by Will, which, of course can be a lot easier to say. And I have the pleasure of taking care of neuroendocrine tumor patients here at OHSU in Portland. And so, my role is as the medical oncology lead of our multidisciplinary team so I'm very lucky to have the chance to work with other team members, including doctors, Rod Pommier, Erik Mittra, Nadine Mallak, really many more people. Just a great team here in Portland.

As you mentioned, I am an East Coast transplant here, having previously been at the NIH and UNC for med school and residency. But in terms of my interest in neuroendocrine tumors, I always have to credit my amazing mentor and friend, Dr. Jaydi Del Rivero, who's really the one who introduced me to this world as a fellow.

So many things have drawn me to taking care of neuroendocrine tumor patients from a research and a clinical side, but really, when it comes down to it, what I really find motivation in, and what's pushed me towards dedicating my career to neuroendocrine tumor patients, are the patients who are living with neuroendocrine tumors.

And as most anyone who would be listening to this podcast knows, it's a journey, it's full of ups and downs. It's incredibly exciting because so much has changed in recent years. And it's really fun to be a part of such a quickly evolving landscape. But each patient, each disease is so unique. And oftentimes you're managing this with patients for years and years and years. And through the ups and the downs. It's really kind of a special relationship that you get to build with neuroendocrine tumor patients. And that's really, when it comes down to it, with what has drawn me and kept me in the field of neuroendocrine tumors here. So, but I could keep going on, but I know we have a lot to talk about today.

Lisa Yen:

Well, it really warms our hearts, that you're interested in the population that you have a passion for it. And we have to credit Dr. Del Rivero for connecting the two of us. So, it's been so fun to get to know you. And as you mentioned, we got to connect in person again after Portland recently at the 2022, NANETS Symposium in Washington, DC.

And because the mission of the NANETS focuses on educating medical professionals and events are not open to patients. You and I may know many people in the NET patient community often want to hear about the research or updates discussed at the symposium. So, to that end, we decided that it would be great to have a podcast episode on the Top 10 of NANETS.

As we talked about, there were a lot of great things in the symposium. So, as we count down, we're gonna count down from 10 to one, let's start with number 10.

Dr. Will Pegna:

I guess I have to throw in a couple of caveats as we do our countdown. For one, to start narrowing down to 10 pieces from the symposium. It was really actually quite difficult. There was a lot of great content. And I think, if anyone were to say, "No, I disagree, it's these 10 completely different things that were presented." I just have to back up and say, "Yes, you're probably right. These are really interesting as well."

So, one caveat is narrowing it to 10 is very difficult. Also, this list doesn't include many of the great symposium presentations, including the co-presentations that were ongoing, including SMMI, SIO, which was interventional radiology, mainly because these were co-occurring with other events at the same time. And try as I might, and as much as I would have wanted to, being at all of the different presentations at the same time is impossible.

And the last caveat is, we had a fantastic keynote address by, Dr. Aldo Scarpa. And a great Year-in-Review by our President-elect, Dr. Pam Kunz. I'm not including these within the list of the presentations, but really some great information and some fantastic ongoing research and directions, as we're moving forward.

But to get started at number 10, I think the first presentation here was the one given by Dr. Lindsay Hunter out of the Huntsman Cancer Institute in Utah. Looking at circulating tumor DNA, or ctDNA, detection using a personalized tumor informed assay in metastatic, well-differentiated neuroendocrine tumor patients.

Lisa Yen:

Yeah, that one was really interesting. And as we know, we could use more markers. So, tell us a little bit more about what that is.

Dr. Will Pegna:

Yeah, so the ctDNA, or circulating tumor DNA, this is something that's been talked about a lot more in the blood cancer and colorectal world, and there's really a good reason is that it's really

revolutionized the way that we approach these cancers, both in terms of which patients need treatment because their tumor's still around, as well as in figuring out which patients may not need to be exposed to the toxicity of treatment and can be spared. And so, looking for tumor markers in neuroendocrine tumors would be of profound importance moving forward as well. Now, this is to say that this is one of the first studies that's actually looked at ctDNA in neuroendocrine tumors. And it's a study that looked at 15 patient's, ctDNA levels who had neuroendocrine tumors. What was surprising is that it was actually only detectable in 60% of patients. And those patients tended to be those with really bulky or metastatic disease. So, it's surprising in that how few patients actually have this circulating marker.

Lisa Yen:

Yeah, it's a small cohort, and very few patients have this marker.

Dr. Will Pegna:

You're absolutely right. It's a small cohort, but I think it's really important technology. And these assays are new. We know that and sensitivity or the actual ability to detect tumor DNA in the blood is something that's being worked on. So, I think its role in, in kind of response monitoring or surveillance of neuroendocrine tumors is still being developed. But it will be interesting to see this kind of moving forward in the future.

Lisa Yen:

Yeah, that's exciting. So, you think that this might have some promise for us?

Dr. Will Pegna:

Yeah, potentially a think there's, again, the sensitivity of this test and perhaps, combined with other tests, as a way of kind of monitoring disease, it would be important but still work to be done.

Lisa Yen:

Yeah, still work to be done. And that's kind of the take home. And you know, just so the audience can hear what was the takeaway from that talk in terms of where, where will they be going next?

Dr. Will Pegna:

So, the disease groups in which this was primarily seen, where patients had circulating tumor DNA, were patients with bulky tumor disease, and also patients with carcinoid syndrome. So, I think it's trying to figure out why it is that these low levels may be seen in certain patients or undetectable levels in certain patients, and trying to figure out what are the ways to kind of close the gap. Because having a useful tumor marker like this would be really helpful in the future.

Lisa Yen:

Yeah, so understanding more about those gaps and maybe make a better assay from it. Well, this is very interesting in the way that you explained it, it makes a lot of sense. So, we got number 10. We ready to move onto number nine?

Dr. Will Pegna:

Yeah, I think we can go to number nine. And so, for number nine, we have a presentation by an early career investigator, Dr. Mehran Taherian with the Department of Pathology at University of Texas, MD Anderson Cancer Center, who presented, "High-grade Pancreatic Neuroendocrine Neoplasms: Interobserver Diagnostic Accuracy and Relationship with Clinicopathological and Molecular Characteristics." It's a mouthful.

Lisa Yen:

It is a mouthful. So, Dr. Pegna, we're going to have to have you interpret what that mouthful was.

Dr. Will Pegna:

Before jumping into it, I'll say there was nearly a full day of early career presentations. And that's just the oral abstracts. There were poster presentations, really some fantastic presentations on both sides. And one of the great things to see as the NET world continues to grow and attract fantastic talent, which is really exciting to see. But to jump into this specific study that Dr. Taherian did, so Grade 3 neuroendocrine tumors and neuroendocrine carcinomas are two diseases that can be really difficult to differentiate.

And really, the way that we do it, per guidelines, is we look at the pathology to help differentiate. Is there necrosis that would favor a carcinoma? Is there still kind of the cellular architecture that would favor neuroendocrine tumors, but there's absolutely a subjective component to this. And so, what he wanted to do is see just how much of a subjective component there is. And so, he looked at 32 cases of Grade 3 NETs and neuroendocrine carcinomas and had eight dedicated pathologists look at the slides for each patient, kind of in retrospect, when we thought we knew their diagnosis afterwards, and try to see how often they actually agreed with one diagnosis or the other.

Lisa Yen:

Wow, that sounds fascinating. And what was the results?

Dr. Will Pegna:

Yeah, so sort of surprisingly, the interobserver, or how often the pathologist actually agreed with the diagnosis was only really, fair. With a majority of pathologists, or five-out-of-eight, only in agreement on about 90% of the cases. Now, this makes you think, but then, when they

provided some clinical information to the pathologist, including the Ki 67 index, the PET scan results, their mutational status, then all of a sudden, kind of the diagnosis that was given, correlated much more closely with how patients actually did. So, what to me this sort of tells us is that the current diagnostic criteria that we really tunnel in on pathologic criteria, just like neuroendocrine tumors, perhaps we really need to be improving our accuracy by being a little bit more multi-dimensional and multidisciplinary. And working to define is this a Grade 3 NET based on not only what we see in Pathology, but what the patient is experiencing and what the other kind of imaging and all the other characteristics that kind of come together to a diagnosis.

Lisa Yen:

Okay, so if I'm understanding this correctly, when they just look at the pathology, 90% of them are in agreement. It really takes looking at everything else.

Dr. Will Pegna:

Well, it's 90% of cases, a majority of the pathologists agreed. Not to say that all the pathologists agreed, but I mean, that means that in 10% of the cases, there was just no agreement in terms of a majority of the pathologists. So quite a high number.

Lisa Yen:

Yeah, 10% where they don't agree and that can really make a difference in someone's care. So, what's the takeaway from this?

Dr. Will Pegna:

Yeah, so I think that takeaway is that, just like the treatment and the management is evolving, I think that diagnosis is also in the process of evolving as we get more information. As we start learning about some of the mutational patterns that we see in these different disease types. This is a little bit of a sneak peek to another presentation that we had. But I think the big takeaway for me is that even when it comes down to the diagnosis, it has to be a team effort in diagnosing these Grade 3 NETs vs. neuroendocrine carcinomas.

Lisa Yen:

Yeah, I'm glad that they brought attention to this because Grade 3 NET vs. NEC deserves the attention and there's been so much change in this field even defining on that there's a Grade 3 NET.

Dr. Will Pegna:

They behave very differently and kind of how we approach the treatment is very different, so.

Lisa Yen:

Yeah, how you approach treatment is different. So, it's really fundamental that we get the diagnosis correct.

Dr. Will Pegna:

Completely agree yeah.

Lisa Yen:

Yeah. Okay. So takeaway is multidisciplinary approach in this.

Dr. Will Pegna:

Yes.

Lisa Yen:

Very interesting. Thanks for sharing this one. And what about number eight?

Dr. Will Pegna:

Number eight. So, this is a one by a regular star within the NANETS conferences, and this is Dr. Chauhan, at the University of Kentucky Markey Cancer Center, who gave the talk, "How to Define PRRT Refractory and the Role of PRRT Repeat." So, when I'm talking about PRRT, of course, this is Lutathera therapies directed at the somatostatin receptor.

Lisa Yen:

Yeah, I'm glad you brought this one up. I also thought this is very interesting. And Dr. Aman Chauhan is a friend to the neuroendocrine patient community, as he's often invited to speak at many patient events as well. And he's been doing a lot of studies in the PRRT world. So, tell us a little bit about this study.

Dr. Will Pegna:

Yeah, the background is, as many people have been discussing recently, is the first FDA approved PRRT or peptide receptor radionuclide therapy, also called radionuclide ligand. There's all sorts of mixtures here. But the first one approved for any disease was Lutathera therapy for neuroendocrine tumor patients based on the NETTER-1 studies.

And so that was back in 2018. Now, some patients can benefit from Lutathera treatment for years. But given that it's been now a half decade, since we started giving this treatment, it only makes sense that now we're starting to approach the question of well, we have these patients who benefited so much from Lutathera, but now the benefit seems to be dissipating. Can we do it again? And that's just not a question that we have a great answer to right now.

Lisa Yen:

Yeah, and that's something that patients care about, because, you know, once they've had it once, they wonder can they have it again? So what did the study show?

Dr. Will Pegna:

So, Dr. Chauhan went over some retrospective analyses that have been done nationally, internationally, that generally point in the direction that yes, patients can benefit from retreatment with Lutathera if they've benefited at first. But what I think is kind of the most exciting thing that he described as actually, we're going to look to answer this question with a clinical trial. And so, he announced a phase two clinical trial. It's a collaboration between SWOG and CCTG, randomized phase two clinical trial comparing retreatment of patients who previously had 12 plus months of benefit from treatment of Lutathera vs. what we otherwise are doing based on current guidelines, which is treating them with everolimus, for instance. So, this has been a question that has been asked, we may finally be getting answers in the next few years, which is really exciting.

Lisa Yen:

It is exciting. It's really reassuring that the retrospective study does show that it's safe. And it's exciting to have a new trial, because of course, we know that new trials lead to approvals. And so hopefully, we know that there's science behind this. And we might be able to get approvals or even more treatment. And that's such a relief, right to know that there are more options out there.

Dr. Will Pegna:

Yeah, absolutely agree.

Lisa Yen:

Yeah. And if you might share, what is the name of the new trial?

Dr. Will Pegna:

So, it is the "RETREAT Trial," very, very well named.

Lisa Yen:

RETREAT Trial. So that is something that the community can look out for.

Dr. Will Pegna:

I don't think it's on clinical trials.gov yet. I think it's kind of in the early planning stages, but I'm sure we'll be hearing a lot more about it once we get some more news.

Lisa Yen:

So, you're kind of giving everyone a teaser to this trial that's opening up soon. And it's reassuring, right that the other arm to it is the standard of care. So, it's not just getting a high dose octreotide like NETTER-1 was.

Dr. Will Pegna:

I completely agree.

Lisa Yen:

Yeah, so that's exciting. So not only was number eight, an exciting study, but an announcement of a new trial. Wow!

Dr. Will Pegna:

Yes.

Lisa Yen:

If that's number eight, I wonder what you have in store for us for some of the other top 10s.

Dr. Will Pegna:

We have – well, many good ones to go here so.

Lisa Yen:

I'm curious, what's number seven?

Dr. Will Pegna:

So, number seven, I will be honest, I cheated a little bit here because I'm actually combining two talks on a similar subject. So, this is a little bit how I got around narrowing it down to 10 talks. So, the two talks are, one a very entertaining talk that was given by Dr. Jaume Capdevila, "Novel TKIs for GEP NETs." And then a review and meta-analysis of the "Efficacy and Toxicity of Tyrosine Kinase Inhibitors in neuroendocrine tumors by Dr. Satya Das.

Lisa Yen:

Yeah, so TKIs. And if you could just explain what TKIs are before diving into number seven.

Dr. Will Pegna:

So TKIs are really a large class of medications. They are targeted therapies, and specifically, the full name, receptor tyrosine kinase inhibitors, explains a little bit how they act. They go within the tumor cell, and they actually block these proteins or kinases that then have signaling cascades that help with blood vessel formation, tumor growth. And these are drugs that we know have a role in neuroendocrine tumor, specifically pancreas neuroendocrine tumors,

where we've had one sunitinib around for a number of years now for pancreas neuroendocrine tumors.

Lisa Yen:

Yeah, so sunitinib, you mentioned is one of them. So, what else did you discover from this number seven where you're putting two talks together.

Dr. Will Pegna:

So, starting with Dr. Das's review of these. He looked at 17 studies of eight different tyrosine kinase inhibitors. So, it's a good number—sunitinib, lenvatinib, cabozantinib, axitinib, I mean, all the "ibs" that you can imagine here, and kind of putting them all together. And looking at the objective response rate of these treatments. What he found was that, as expected, the response rates to treatment with these and all these trials were higher in pancreas neuroendocrine tumors, that was just about 20%. But there's actually a signal, though small, but present in non-pancreatic neuroendocrine tumors, just south of 10%.

With really the expected side effects of these medications, hypertension, some issues with GI disturbance and otherwise. But, even though there's a great diversity of these agents, we only have one currently approved and really only one on the horizon. And Dr. Capdevia did a great analysis of these TKIs, in a way that's a little bit of an interesting, but a cautionary tale, in the development of treatments for neuroendocrine tumors.

So, for clinical trial design reasons, we have sunitinib that was approved a decade ago, we have lenvatinib that showed really promising activity but is a little bit stuck in that phase two trial that was published back in 2021, probably won't be moving much more forward and development past that. We have surufatinib that was developed and analyzed in China in a large phase three clinical trial, which unfortunately, was found to not really apply to European and American patients and thus surufatinib will likely not be progressing, unless the company decides to have a large phase three clinical trial here in the US, as well as some others.

Now there's one exception and kind of cause for hope here, and that's cabozantinib with the "CABINET Trial" that's opening nationally. So again, this is a trial that's looking at cabozantinib. And not just pancreas neuroendocrine tumors, but really all neuroendocrine tumors. And I think there's a lot of hope that this may add a treatment option in the future for both pancreas and non-pancreas neuroendocrine tumors.

Lisa Yen:

Yeah, we like that. We like the possibility of new treatments. And so, the takeaway is some caution for research scientists, research physicians to look at this…

Dr. Will Pegna:

We have to be very, very thoughtful, and what we're hoping to get in the information on the clinical trials, because if we don't answer the right question and the right patients, then it can be disappointing.

Lisa Yen:

Yeah. And what's the takeaway for patients? What makes this important for them?

Dr. Will Pegna:

I think one of the takeaways, for one I would say the CABINET Trial is open nearly, I think in every state, or if not every state, then most every state it's available nearby. And it's really a critical piece of information moving forward, that we'll be gathering. But I think for patients, I mean, one, it's important in understanding what the side effects of these medications are that they're very real just because it's a pill, that you can be surprised by how many side effects just a pill can give. When we first kind of went down the path of the TKI is this is a very outside-the-box treatment option, there's going to be more in the future. They're still in the phases of development, but I'm hoping that when we get the results from the Cabozantinib Trial, that we'll have another treatment option here.

Lisa Yen:

Yeah. So there's the category of drugs to be keeping our eyes on the TKIs, or the "ibs," and much work to be done in this area and something that patients can get excited about, whether volunteering to enroll in the trial, if it's something for them, or just being supportive of this.

Dr. Will Pegna:

Absolutely.

Lisa Yen:

Okay. Well, thanks for sharing that. I think it's a category of drugs that may not always come up in the discussions for patients. It's good to hear about all the work being done in this area.

Dr. Will Pegna:

Absolutely.

Lisa Yen:

Okay, so what about number six? I'm curious what number six would be for you?

Dr. Will Pegna:

Yes. So, number six is a presentation by Dr. Nancy Joseph, out at UCSF titled, "TP53 Mutation Portends a Worse Overall Survival in Patients with Advanced Grade 3, Well-Differentiated Neuroendocrine Tumors.

So, this is harking back a little bit to number nine that I gave a teaser to you earlier.

Lisa Yen:

So, tell us a little bit about this one.

Dr. Will Pegna:

Yeah. So again, Grade 3 NETs, neuroendocrine carcinomas, these are difficult categories, both pathologically differentiating, figuring out how we're going to treat patients because we have to base it on really sometimes a tiny little sample of tumor. And the treatments are quite different between the two.

So, what Dr. Joseph did is she looked back retrospectively at 134 patients with High Grade metastatic neuroendocrine neoplasms, who had genetic sequencing done of their tumors and looked at the classification of these three tumors pathologically as Grade 3 neuroendocrine tumors, ambiguous, or neuroendocrine carcinomas and then looked at their survival moving forward.

Lisa Yen:

Wow. Again, I'm glad that someone was looking at High Grade. And what did she find?

Dr. Will Pegna:

So, what's surprising, and I thinking part a reflection of a relatively small number of patients, but that if you just went based on the, this classification of Grade 3 NET ambiguous or neuroendocrine carcinoma, the survival time between the three groups were not statistically different. They kind of all sort of hovered in the 15-to-20-month range, however, when she looked at those patients who had a specific mutation, and that's the tumor suppressor protein, TP53, I think it was the protein of the year, 15 years ago, or something. So very important tumor suppressor. But, if you looked at those patients who did not have a mutation vs. those who did have a mutation and TP53, there, the survival difference, kind of across the three groups was very statistically significant, 25 months vs. six months. So really separating into two very specific groups.

Lisa Yen:

Wow, 25 months vs. six months. That's a huge difference.

Dr. Will Pegna:

Yeah, the kind of big take home point to me is there's been years of debate of do we do genetic analysis on next generation sequencing and neuroendocrine tumors, you can still debate it for Grade 1 and Grade 2s. I think there's still some work being done in that regards. But this ends the debate for Grade 3s and neuroendocrine carcinoma. And so, this is a very valuable piece of

information, if this mutation is here versus if it's not present. This is just tells me we need to know that information on every one of these patients.

Lisa Yen:

Yeah, that's a really good point. And what a strong take home message that next generation sequencing really must be done for Grade 3s. It could literally mean months, or years…

Dr. Will Pegna:

Yeah.

Lisa Yen:

…or someone's survival. Wow, what a good point. Dr. Pegna, I'm glad that you brought that one up. And anything else that we can take away from that particular study?

Dr. Will Pegna:

So, there was some other parts of that study, but I think from other presentations that were given that maybe there's a role for next generation sequencing in Grade 1 and Grade 2s. For prognostic and predictive significance, certain mutations seem to be predictive of better responses to keep sight of being in temozolomide chemotherapy for pancreas neuroendocrine tumors for instance. That was another one of our early career presentations. So more to come in this field.

Lisa Yen:

Yeah, well, so exciting and we look forward to hearing more. And as you said, it's exciting to see all the early career people that are doing work in this area. So, it's even more than just the people we saw presenting on the main stage.

Dr. Will Pegna:

Yeah.

Lisa Yen:

Okay. Well, so we're now halfway through. So, number five, what was your midpoint number five?

Dr. Will Pegna:

Yeah. So, number five. This was an oral presentation by Taymeyah Al-Toubah from the Moffitt Cancer Institute. So, she was also the only presenter to have not one, but two abstracts selected, for oral presentations. Also, the inaugural distinguished APP Award winner, so really doing some great things. This first study that she presented were the results of a really interesting phase two, study looking at the combination of the oral TKI, tyrosine kinase inhibitor

medication, Lenvatinib with the immune checkpoint inhibitor, immunotherapy Pembrolizumab. Pembrolizumab has really revolutionized the treatment of so many cancers, but we haven't really seen a role in neuroendocrine tumors yet.

Lisa Yen:

I'm glad you brought this one up, because a lot of people do wonder about immunotherapy, and this one in particular is an interesting one, because it combines what you mentioned with TKI with immunotherapy.

Dr. Will Pegna:

Yeah, and so neuroendocrine tumors outside of the High Grade and the carcinomas are generally thought to be rather immunologically silent. And within this context of these cold, immune tumors, immunotherapy has really been disappointing thus far for the treatment of neuroendocrine tumors. Just haven't seen some of the results that we've seen in other tumors. But in multiple other cancers, there's been a synergy that's been found between tyrosine kinase inhibitors, with immunotherapy that when combined, it turns these immunologically cold tumors into tumors that may respond to immunotherapy. Now, to kind of throw some cold water on it, unfortunately, the results in the 20 patients treated with the combination, there wasn't enough activity seen to support further pursuit of this combination. It was a negative study.

Lisa Yen:

Oh, that's such a bummer. So then why Dr. Pegna, would you bring up a negative study?

Dr. Will Pegna:

Yes. Yes, I'm happy that you would ask, so for one, negative results are still results. And it's really important that this information be provided. And oftentimes, there's kind of a publication bias or presentation bias, because people want to give positive and uplifting results. But we need to know what doesn't work too, and it's not just to say that this is done, and we're not progressing this path, but also suggesting to us, maybe we need to take another path forward and look at other potential paths. And this actually brings us to our next presentation here, which is the perfect segue.

Lisa Yen:

Oh, yeah. Okay, tell us now. I'm excited with that little teaser!

Dr. Will Pegna:

Yeah. And so, this was a presentation out of the basic and translational science side of things. So, this was the development of a novel anti-somatostatin receptor bispecific T-cell engager

like, molecule for the treatment of neuroendocrine tumors by Dr. Eleanora Pelle at the Moffitt Cancer Institute.

Lisa Yen:

Wow. Moffitt's doing some great things. And why do you bring this one up?

Dr. Will Pegna:

Yeah, so just as I mentioned, immune checkpoint inhibitors, having thus far been disappointing, this is a really fascinating and different take on immunotherapy for neuroendocrine tumor. So, a bispecific T-cell engager, to try to explain a little bit of how it works. Whereas the immune checkpoint inhibitors like Pembrolizumab, they bind to your T-cells, and they try to rev up your T-cells to really kind of be awake and active and attack tumor cells, if they recognize them. This works very differently. So, this molecule actually binds to the somatostatin receptor. But on the same molecule, it also binds to the T-cell. So, what you're actually doing is you're using a connector that is physically approaching a T-cell to the cancer cell. So, you're not just hoping that you're going to get the T-cell excited to attack the tumor cell, you're kind of forcing them to get together in close proximity.

Lisa Yen:

Wow. So it's like a magnet to bring them together.

Dr. Will Pegna:

It is. Absolutely.

Lisa Yen:

And what excites you most about this?

Dr. Pegna:

Yeah. So, this is just, just like a was mentioning previously. It's not that immunotherapy is not a path forward and neuroendocrine tumors. It's just we need to explore, just like everything else with neuroendocrine tumors out-of-the-box thinking. And I think this is a great example. Now this is a very early preclinical study. But what was demonstrated was that by kind of treating with this by specific T-cell engager, you actually triggered an immune reaction in that T-cell that was brought close to the tumor cell.

So, the T-cell, the immune cell knows that there's something's wrong there. And this just opens a different avenue, perhaps combining this with immune checkpoint inhibitors in the future, perhaps. I mean, there's just a lot of questions that are answered. So, where we hit a dead end, in one way, it's actually just we're revealing all the other paths forward as well.

Lisa Yen:

Ah, that's a good way to put it. Yeah. So, you know, it's not completely a closed door. There are just other avenues to explore, and this is one avenue that's new and being created and explored here.

Dr. Will Pegna:

Yeah.

Lisa Yen:

So why should this matter to patients?

Dr. Will Pegna:

What I would say is, with neuroendocrine tumors, so much has changed in the last 10 years. We went from having the somatostatin analogs, then Lutathera, which was really a totally new treatment, unlike anything that had been seen before. This is also a very outside-the-box approach to treating cancer. It's been used in certain hematologic malignancies. But I think there is progress, even though sometimes it seems like maybe we're hitting a slow patch potentially, there are things that are coming down the pipeline that are wildly different. And neuroendocrine tumors have really proven to be a good testing ground for things that then are used for many other cancers. That PSMA, the Lutathera equivalent for prostate cancer is the prime example for this. It's really, PRRT proved its worth in neuroendocrine tumors. And now it's kind of branching out. And I think this is just another treatment, or potential treatment, that can be developed further in the future. And so, as we're treating the disease, as we're keeping disease under control, these researchers are developing really fantastic potential treatments for the future as well.

Lisa Yen:

So, the hope is really, that there are people thinking outside of the box, and really working hard on our behalf. Well, so now we're down to the top three Dr. Pegna, what would you say is number three?

Dr. Will Pegna:

Yeah, so number three is we're actually staying in Florida, this is Dr. Taymeyah Al-Toubah's second presentation. The title of this one was the, Risk of Myelodysplastic Syndrome and Acute Leukemia with Sequential Capecitabine/Temozolomide and Lutathera treatment. This one is a little bit scary. It's not the good or the exciting news that we always like to share. But it is, I think, just as important, if not, in some ways, more important than looking at new treatments. We need to really consider the safety of the treatments that we have, and really always keep thinking, are we doing the best thing for our patients? Because that's the whole goal of all of this in the end?

Lisa Yen:

Yeah, that's such a good point. And so, before you talk about what the results were, could you just also define what the MDS and also the drugs that you mentioned capecitabine and temozolomide?

Dr. Will Pegna:

Absolutely. So, of course we have Lutathera that we've already talked about, PRRT. Then we also have capecitabine and temozolomide. So, this is a combination chemotherapy. Really, a lot of amazing work has been done by Dr. Kunz, her team, looking especially in pancreatic neuroendocrine tumors, it's really a well-tolerated chemotherapy combination that results in impressive tumor shrinkage, especially compared to essentially every other treatment that we have.

It can shrink tumors, it can control disease for a long time, so really an effective treatment. But what we're coming across now, is that for both capecitabine and temozolomide and Lutathera, we always counsel patients that there's a low, but not impossible risk, of developing a second cancer in the future, or, more specifically a blood disorder or a blood cancer. So, the most common of these are MDS, myelodysplastic syndrome. So, this is a disorder it's in some ways pre-cancerous to developing into a cancer disorder where your bone marrow has real difficulty creating new white blood cells, red blood cells, platelets and when it goes into kind of an uncontrollable growth, that becomes leukemia.

And so, what we usually counsel patients is that for Lutathera, the risk is probably in the one-to-50 to one-in-100 patients. Capecitabine and temozolomide, specifically the temozolomide component, it's also on the lower side, probably in the low single digits range as well. So, we know there's these risks, but the benefits because these treatments work so well is clearly there. But what Taymeyah did here, is she looked back at 462 patients who had received treatment with both Capecitabine and temozolomide and Lutathera and looked at the proportion of patients who developed MDS or leukemias.

Lisa Yen:

Yeah. And for those patients too, just to clarify, did they receive it at the same time? Or like, what's the time period they received them?

Dr. Will Pegna:

So typically, sequentially, one after the other.

Lisa Yen:

Yeah, so not together at the same time. They were prescribed capecitabine and temozolomide in the past, and then eventually got PRRT? Or vice versa.

Dr. Will Pegna:

Typically, yes.

Lisa Yen:

Okay. And what did the results show?

Dr. Will Pegna:

Yeah, so results were eye opening. Up to 10% of the patients that she looked retrospectively develop MDS or acute leukemia. So that's a very different number than 1% or 2%, that we usually talk for each of those separately, it's surprisingly higher. Now, this is a relatively small analysis. It's retrospective. So, there's room for error, there's room for kind of observer bias, this could be a higher number. But it makes us think how we approach treatment. It makes us think, okay, which between the two, is a patient likely to benefit from the most and for the longest?

How can we try to, if we need to pick one, what can we do to try to put as much distance until the next treatment? We definitely want to be very hesitant about combining these treatments. And then the question also comes up of what avenues of development are coming that would push us towards sort of going one line or the other?

Lisa Yen:

Yeah, really good points and thoughts. So, I mean, this is really new information, right? Ten percent is quite a big difference from the single digits.

Dr. Will Pegna:

Yeah, I want to say this sounds, like scary. But again, this is still a small minority of patients. This is a retrospective analysis. So, we don't know with certainty that it's quite this high, but it's just good safety information for us to consider.

Lisa Yen:

Yeah, something to consider. So, what does this mean to patients? What do patients need to know about this?

Dr. Will Pegna:

Yeah, so this, I think, empowers patients. This is data that when we talk about the risks of these treatments, and when we start thinking about the long game, because in neuroendocrine tumors, you always have to think two or three steps ahead. This empowers your decision making and the shared decision making that you have with your doctor of, okay, if we use this treatment now, then what is the next one going to look like? If we treat with Lutathera now, then are we going to look to avoid chemotherapy? So, are we going to go more towards some other targeted agents? It's information, it is empowering, even if it's not always positive?

Lisa Yen:

Yeah, it's helpful to know this. And this is something that comes up in the patient community, right, in terms of sequencing and playing the long game together.

Dr. Will Pegna:

Yeah.

Lisa Yen:

Okay. So, something we can have a discussion about with our doctors. Where do you see this going from here?

Dr. Will Pegna:

So, I think for one, having some larger datasets to either confirm or refute this will be helpful. And there are a lot of patients that have been treated with this combination. So, I do look forward to more information coming out. Now, there are some different treatments specifically in the PRRT world that are coming that will have different side effect profiles, that will have to be considered just the same. And I think these are sort of safety endpoints that when we're talking about designing clinical trials, when we're talking about planning treatments, that we'll be working on more moving forward and looking forward prospectively.

Lisa Yen:

Yeah. So, it helps us all to ask big questions, harder questions, have these discussions, and be empowered to make intelligent decisions, and being aware of safety risks.

Dr. Will Pegna:

And for many patients, it may still be even if there's a risk, that 10% risk, if we feel pretty certain that one treatment is going to really provide some benefit over the short, medium and long term, it may still be that the benefit outweighs the risk. But we need to know what that risk is so that we can make an informed decision together.

Lisa Yen:

That's a really good point. And that informed decision, is together. I love that. Thank you for that. So now we're down to the top two. So, Dr. Pegna what is number two on your list?

Dr. Will Pegna:

Yes. So, number two, I cheated again here and had two studies. But these are in many ways related, and I think critically important components in the research field of NETs. The first is, "Transcriptomic Influences of Racial Disparities in Black Patients with Pancreatic Neuroendocrine Tumors," by Brendon Herring at the University of Alabama, Birmingham. And

the second is, “Variants of Unknown Significance are More Common in Non-Caucasian Patients with Neuroendocrine Neoplasms,” by Farhana Moon from UCSF.

Lisa Yen:

Yeah, I'm glad you brought these two up. And of course, Brendon Herring did win an award for this one. So, what makes you bring these two studies up?

Dr. Will Pegna:

Yeah. So, these two studies approach a topic that's really important. And that's really racial disparities and the information that we have in, not just neuroendocrine tumors, but in cancer treatment as a whole. Now, we know that there are racial disparities and outcomes, cancer outcomes, neuroendocrine tumors included.

We know that there are racial disparities, in really disease behavior, how people's disease manifests itself, across the different ethnicities, different races. Yet, most of our clinical trial data tends to be collected from certain populations, and then that information is generalized to the entire population.

And so, these are two studies that kind of call this into a little bit of question. And so, for one Dr. Herring’s studies knowing that there are differences in outcomes with black vs. white neuroendocrine tumor patients, with black patients more frequently having metastatic disease from smaller tumors, than white patients. He and his team undertook the analysis of messenger RNA or kind of the genetic information that passes from the DNA into the actual proteins. And he compared it in 14 and 16 grade and sex-matched primary pancreas neuroendocrine tumor patients self-identified as black and white respectively.

And what he found was that the actual pathways, within the tumor, were actually different. Whereas pathways related to blood vessel development, cell migration, key elements in metastatic development were more common and black patient’s pathways that were related to immune response were actually downregulated in by patients.

So, this indicates that there actually is like a difference in disease biology that we need to consider. When we do our clinical trials, we need to make sure that we're representative of the population. If we're going to generalize these treatments and these recommendations and these guidelines to populations. We want to make sure that our clinical trials are representative of populations.

Lisa Yen:

Wow, such a good point, right, we need to study the treatment…

Dr. Will Pegna:

Yeah.

Lisa Yen:

…in the population that they need to receive.

Dr. Will Pegna:

And the second part to that is Dr. Moon's study where she looked at germline genetic profiles. So, this is looking at mutations not within the tumor itself, but in patients' bodies, DNA, in Caucasian vs. non-Caucasian patients.

So oftentimes, there's the possibility of an underlying genetic syndrome being responsible for neuroendocrine tumors. And when we do these germline genetic tests, we get both: yes, no, the presence of known harmful mutations, or non-harmful mutations. But then we sometimes get these mutations where we just don't have the data to say if these are harmful or not. And these are called variants of unknown significance, or VUS mutations.

And so, what she found was that these VUS mutations were much, much more likely to be found in non-white population. So, 65% of non-white populations had these VUS mutations. Whereas it was actually only 40% in white populations. So again, this is telling us, we have a lot more data and our clinical trial research has been not generalizable to the populations that we're looking to treat. And this is important in addressing the needs of all of our patients, regardless of race, ethnicity, etc.

Lisa Yen:

Yeah, what a good point. So, Dr. Pegna, what can we do about this?

Dr. Will Pegna:

Yeah. So, I think one of the reasons I really wanted to highlight these two studies is actually echoing our President-elect, Dr. Kunz, who really, pointedly has this as one of the priorities for neuroendocrine tumor research moving forward. And that is equity in research. So, this is for us as researchers as clinical trial designs, and as we gather information, thinking about equity. Including equity in our clinical trial designs and how we approach treating patients and thinking that maybe some of the data that we have doesn't apply to all patients. And so, we need to be, have a little bit of an open mind and looking at what we see in the treatments that we have.

Lisa Yen:

Wow, yeah. So, equity is, you know, we think about it in terms of access to doctors and treatments. And as researchers, as you're thinking of the work being done, the groundwork to even provide those treatments, it's important to have diversity and representation in clinical trial design and in the enrollment as well.

Dr. Will Pegna:

Completely agree. Yes.

Lisa Yen:

So how can we help with that?

Dr. Will Pegna:

Yeah, I think patient advocacy and kind of reaching out to patients, regardless of community, regardless of where they live, or everything, and helping provide access to clinical trials, and equitable health access, and opportunities. All of this is just so important in improving the outcomes for everybody. And really, it's we grow by improving the diversity, but it also improving the diversity of our knowledge, because we find out more about diseases when we're not just considering a specific subtype. But we're looking at these across the spectrum of how these develop.

Lisa Yen:

Yeah. And you know, this is a big task to take on. Really, definitely, it takes all of us.

Dr. Will Pegna:

It's huge.

Lisa Yen:

Yeah, well, thank you for bringing this up. And for this discussion, it really speaks to us and something that is near and dear to our heart and our mission as well.

So last, but not least, what is number one on your list?

Dr. Will Pegna:

So, number one, I think some of the most exciting data to come out of this year's symposium was some really important research presented by Dr. Delpassand and that's the early data on the alpha emitters. I think this is some of the information that everyone wants to hear, of course, because this is one of the newest and hottest things coming through the neuroendocrine tumor world.

Lisa Yen:

Yeah, it's so exciting. And what did you hear him say?

Dr. Will Pegna:

So, to give a little bit of background on the alpha emitters, so these fall under the category of PRRT, or radioligand therapies. These are very similar to Lutathera, but where the Lutathera is targeted to the somatostatin receptor and releases electrons, or doses of radiation on the tumor, these alpha emitters release huge particles that are 60 to 80 times more energetic directly onto the tumors.

And there's kind of an added benefit that because these, these, I don't know, I would compare this from a bowling ball to a marble. So, because these bowling balls are so big, they don't travel even a tenth of the distance. So, we think that potentially not only do they have more anti-cancer effect, but they may have less side effects, because the fact that they travel less distance. So, there's currently two alpha emitters being studied. Both of them are in phase one clinical trials, but they'll hopefully soon be in phase three. These are Lead 212 and Actinium 225. And the studies that Dr. Delpassand presented, these are early phase one, but the results are really, truly impressive. And if they bear out, they could really be game changer in somatostatin positive neuroendocrine tumors.

Lisa Yen:

Wow, we like to hear that, "game changers." And you and I saw the images and I know the listeners can't see what we saw. So, would you maybe describe what you saw?

Dr. Will Pegna:

Yeah, so it was presented in two groups, patients who have never seen PRRT, or Lutathera, and those who have. So, who are being, in essence, retreated with PRRT. In both groups, thankfully, the treatment was well tolerated –no clinically significant blood count kidney liver toxicity, all the things that we usually worry about. And again, this is focused on the Lead 212 Alpha emitter, but in that first group, the PRRT naive group, who have never seen Lutathera radiologic responses or shrinkage of the tumor by 30% or more, were seen in 10-out-of-12 patients and the other two patients had stable disease.

Lisa Yen:

Wow, that's impressive.

Dr. Will Pegna:

Yes, so more than 80%, which is a number that is completely unheard of when we talk about treatments for neuroendocrine tumors.

Lisa Yen:

So, all of them had a response 10-out-of-12, the tumor shrank and the other two had stable disease.

Dr. Will Pegna:

Yes. And so that 10-out-of-12 had really significant shrinkage that passes really strict parameters for calling it a response. But the other two patients, or disease at a minimum, did not grow significantly during treatment.

Lisa Yen:

Which is important. I mean, that's a lot of times what we hope for with Lutathera.

Dr. Will Pegna:

Absolutely. And so that was the data in patients who had never gotten Lutathera, but he also looked at patients, which is many patients who have received Lutathera already, and what was really also very impressive in the second group, six out of 10 patients had these responses and actually there was one of these patients who had a complete response, or really radiographic resolution of their tumor. Again, all the rest of the patients had at least stable disease.

Lisa Yen:

Wow, a complete response, you mentioned?

Dr. Will Pegna:

Yes.

Lisa Yen:

So that means all the tumors disappear.

Dr. Will Pegna:

Yeah, it's the Holy Grail of oncology is getting these complete responses. Now, there's the important caveat, this is phase one. Phase one oftentimes can look better than things look like, but, you know, if it was half as good as this, if it was even a quarter as good as this, I think we'd still be really excited. So, this was some really exciting work. And I'm looking forward to some more results in the future.

Lisa Yen:

Wow. So, this is like, you know, *the* most exciting thing—doctors are excited, patients are excited. So, what's our takeaway from this?

Dr. Will Pegna:

So, the takeaway is, good things are coming. I think, like I mentioned, the phase three components are going to be openings for both agents. I think it's planned for both of them in 2023. So, these treatments are coming. They seem to be safe; they seem to be tolerated. And it's going to be another tool in our arsenal in taking care of patients living with neuroendocrine tumors.

Lisa Yen:

Yeah, wow. Well, you've mentioned several tools today in the top 10, and then several other different developments. So, as we're closing, I'm just wondering, what's your overall closing

thoughts? Or what words of hope would you like to offer the neuroendocrine tumor community?

Dr. Will Pegna:

Yeah, so this was a really exciting conference, I feel like what we saw at the NANETS 2022 Symposium is not just excitement in terms of new treatment, but also the beginnings of clarity, and plans to clarify the treatments that we already have, how to use them. Which is something that's been missing.

So, there was a lot of excitement, a lot of information from this year. Some of it is exciting, some of it can be scary, but it's all very important information that we have, and that we're gathering. So, this is something that I've told so many of my patients is if you look at the last 10 years, the changes that we've had the number and how well the treatments that we have worked for neuroendocrine tumors. If you look at the last five years, I think the next five years, the next 10 years, are going to be even more impressive. I would venture to say the next three years are going to be even more impressive.

So, when we talk about treatments, and we're looking at your scans, and we're saying, "we've got stable disease and things are controlled," we are kicking the can down the road, but we're kicking the can down the road for good reason. We have a lot coming down the road. And we're, we're really looking forward to taking this journey with our patients.

Lisa Yen:

Oh, wow, that is really encouraging really hopeful. You know, this is personal to me. So just to hear you say that is really hopeful and encouraging again. I really felt like you captured the information from the conference, from the symposium, really well, the gems of it. And most importantly, the spirit of it. The energy and the spirit that we, the two of us, got to experience really that hope and that energy, that buzz and excitement that there is more good things coming. So, thank you so much for sharing that.

Dr. Will Pegna:

Absolutely. My pleasure. And it was really a, a great environment. And we're already looking forward to next year. So...

Lisa Yen:

Yes, we look forward to next year too, and hopefully, more developments to come that we can share with the neuroendocrine cancer community.

Dr. Will Pegna:

Absolutely.

Lisa Yen:

Well, thank you again for joining us today, and we look forward to seeing you in person sometime soon.

Dr. Will Pegna:

Thank you, Lisa.

Lisa Yen:

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