Karen Jagoda: Welcome to the empoweredpatientpodcast.com show. I'm Karen Jagoda and my guest today is Dr. Edith Perez. She's the chief medical officer at Bolt Biotherapeutics. That's boltbio.com. Edith is a renowned oncologist and cancer researcher. The topic today is treatments for HER2 cancers and what Bolt is doing to change the current outcomes. Welcome to the show today, Edith. I really appreciate you taking a few minutes to be with us.

Dr. Edith Perez: It's a pleasure to be with you and for listeners to join us today.

Karen Jagoda: Thank you. Tell us a little bit about what HER2 cancers are and why they are harder to treat.

Dr. Edith Perez: Essentially, the HER2 protein comes from the HER2 gene, and it's one of the markers that is sometimes over expressed in many cancers, particularly in breast cancer and gastric or stomach cancer, although it can also be overexpressed or amplified in other cancers. But again, the two tumor types that are most prevalent in terms of having HER2 positivity are breast and gastric. Approximately 15 to 20% of all breast cancers are what we call HER2-positive and approximately 5 to 10% of gastric cancers are HER2-positive.

Dr. Edith Perez: You may ask, "What is it? Why is it that these tumors tend to be more aggressive or more difficult to treat?" Well, this pathway, the HER2 pathway, is associated with increased cell growth and risk for developing metastasis, so these tumors tend to be rather aggressive. On the other hand, it is very good that anti-HER2 treatments started to be developed actually back in the 1990s, with first approvals occurring in 1998.

Dr. Edith Perez: There's a lot to the story that your listeners, I'm sure, are very interested in learning about, and I can share that very good treatments have been developed so far. However, there's much more work that remains to be done, and that's where we at Bolt Biotherapeutics come in.

Karen Jagoda: Tell us what the current challenges are for patients with HER2 cancers, and particularly with respect to the resistance to checkpoint inhibitors.

Dr. Edith Perez: The checkpoint inhibitors work in a different pathway compared to the HER2 pathway. HER2-positive tumors have extra expression of the HER2 protein in the tumor cell or they may have extra copies of the HER2 gene. The medicines that are currently used to target HER2 are pretty specific for that pathway. These are medications that some people may know of, including, trastuzumab, neratinib amongst others.

Dr. Edith Perez: The checkpoint inhibitors modulate the immune system in a totally different way, so a different pathway, and what happens in cancers is that the immune

system tries to kill the cancers but at the same time, the immune system is pretty smart and it tries to control itself.

Dr. Edith Perez: The immune system creates breaks for each activity, and that's where the checkpoint inhibitors come in because they release some of the breaks that exist in the immune system so that the immune system can kill cancers. But again, there are many different pathways associated with cancer and cancer treatment, so HER2 and the checkpoint inhibitor pathways are very distinct from each other.

Dr. Edith Perez: However, we at Bolt feel that there are ways that we can actually combine both understanding the biology of cancer and understanding the biology of the immune system to develop strategies that actually allow us to harmonize them into one treatment for patients. We're very excited about this strategy.

Karen Jagoda: That's your Boltbody platform, and I noticed on your website you described it... Your platform is generating systemic immunological memory. Tell us a little bit more about what that Boltbody platform's enabling you to do.

Dr. Edith Perez: We at Bolt are evaluating a new platform for the treatment of patients with cancer. Specifically, we developed a treatment that combines the antitumor activity of cancer drugs called monoclonal antibodies along with localized stimulation of the immune system. In more detail, the innovative approach is called immune stimulating antibody conjugates. Experiments in pre-clinical models, have shown marked antitumor activity and even cures in some of the animal models-mice.

Dr. Edith Perez: In addition to the initial response or killing of tumors in pre-clinical models, we also elicit the so-called immunological memory that you alluded to, which means that if we have the mice that have been cured with our treatment and then we can reinject the mice with the same type of tumors they originally had at the beginning, these tumors don't grow, which means that we have essentially taught the immune system to reject the regrowth of these cancers. And that's what we call immunological memory. You can imagine how enthusiastic we are about taking this approach that we've seen over and over and over in preclinical models into the human setting because that's where we really want to have a big impact.

Karen Jagoda: Just to drive home the point about the recurrence of these cancers, these HER2 cancers are prone to recurrence, aren't they?

Dr. Edith Perez: Yes, because they are really aggressive tumors. Even if we manage them with the classic surgery, radiation therapy, chemotherapy, they recur. And even with the existing anti-HER2 therapies, many of these patients develop cancer recurrence. We need to continue our focus to develop strategies to take great

science from the laboratory into clinical trials and, we hope, to available drugs that will help patients.

Karen Jagoda: You're working with immune stimulating antibody conjugates, ISACs. Can you tell us how they improve outcomes from current cancer treatments?

Dr. Edith Perez: Yeah, very good. It's just an outstanding question, and one we thought of for quite a while. There are many different ways to treat cancer. A class of drugs that are very efficacious for many cancers is called monoclonal antibodies, and there are many examples of monoclonal antibodies in the marketplace which have already had a major impact on patient's lives.

Dr. Edith Perez: What the monoclonal antibodies do is that they target abnormal proteins or proteins that are expressed in excess in cancer cells. It happens that HER2 is one of those proteins so there are monoclonal antibodies that have been developed to target HER2.

Dr. Edith Perez: We're actually leveraging the use of an anti-HER2 monoclonal antibody as part of our strategy, but we're actually combining that monoclonal antibody with a way to stimulate the immune system at the local place where the HER2-positive cancer cells are located.

Dr. Edith Perez: Essentially, what we have here in our first ISAC, which sometimes we call Boltbody is the monoclonal antibody against HER2, trastuzumab biosimilar, connected to a proprietary molecule that stimulates the immune system. This is a way to stimulate the immune cells at the local level.

Dr. Edith Perez: In other words, when we inject this medication intravenously, the medication essentially has the monoclonal antibody that will attach to the cancer cell that expresses that abnormal HER2 protein. But along with this molecule, we're bringing a direct stimulator of the immune system so we can activate the immune system exactly at the place where the cancer is located. This makes complete sense from the scientific standpoint. It makes complete sense from the biological standpoint. We've shown that it works in preclinical models, and that's why we are very happy that we've been able to start our first in human clinical trial.

Karen Jagoda: Tell us about how tumors are either cold or hot and what these ISACs have to do with that.

Dr. Edith Perez: Okay. Very good. They call them hot tumors refer to the expression of lymphocytes, which are part of the immune system. Essentially, cold tumors have very few visible lymphocytes, a type of white cell, when we look under the microscope, whereas hot tumors tend to have a lot of these lymphocytes. What has been shown over the last several years is that hot tumors, these tumors that

have already a lot of immune cells within the area of the cancer, tend to be more sensitive to some of the existing immune modulating drugs such as the checkpoint inhibitors.

Dr. Edith Perez: But then the cold tumors tend not to respond very well. One of the things that we are trying to do with our strategy at Bolt is actually to help wake up the immune system because we're taking these Boltbodies or these immune stimulating antibody conjugates that get into the tumor area then they stimulate the immune system right there. Thus, we anticipate that we will be able to make some of these cold tumors essentially become hot because we're stimulating the immune system right at the place with where the cancer is located.

Dr. Edith Perez: This is a revolutionary strategy that we hope will be tolerable and efficacious in patients with cancer. The conduct of our ongoing clinical trial is a major step towards this goal.

Karen Jagoda: I just have to ask a rather naive question. Are you changing the tumor or are you just making the immune cells think that the tumor is hot?

Dr. Edith Perez: We are actually stimulating the immune system so that the immune system can be better at recognizing the cancer and ultimately help destroy the cancer cells.

Karen Jagoda: Thank you. Can you tell us a little bit more about the clinical trials that you have going on with your first drug?

Dr. Edith Perez: We started what we call a phase one trial in which we are evaluating safety... In other words, tolerability... and understanding if we can establish the correlations of the mechanism of action of our compound with what happens in the blood specimens of patients. Ultimately, this trial will also allow us to start getting some evidence of efficacy. We already have a plan for 14 treatment clinics or academic centers where patients can access participating in our clinical trial and are considering expanding the trial in the United States as well as abroad so that patients who are potentially eligible can participate in what we call the novel era of combining this novel strategy, targeting tumor abnormalities with stimulating the immune system.

Karen Jagoda: Thank you for defining that age that we've entered here. Before I let you go, I just wanted to ask you a little bit about your background and why you're so excited to be working at Bolt.

Dr. Edith Perez: I must say, I grew up with a great family in Puerto Rico and then eventually advanced my career training in Puerto Rico, California, then I went to Mayo Clinic initially in Rochester, Minnesota and then Jacksonville Florida. I've been honored to be involved in basic laboratory research and clinical research nationally and globally for the last 20 years.

Dr. Edith Perez: I also had the opportunity to work at Genentech from 2015 to 2018, where I focused on team work, internal and external collaborations, developing therapeutic strategies for patients and, also the critical importance of access of medicines to patients. And I think this comes the full circle. I think Bolt is the right a place for me to leverage all I've learned and help take science into the reality to help patients with cancer. I'm very fortunate to be working as part of a great team anchored on great science and collaboration. But I tell you, our focus is ultimately to be able to really have a major impact on patient's lives.

Karen Jagoda: Thanks to my guest today, Dr. Edith Perez, chief medical officer at Bolt Biotherapeutics. That's boltbio.com. Follow them on Twitter @BoltBio. I'm Karen Jagoda, and you've been listening to the empoweredpatientpodcast.com show. Follow me on Twitter @KarenJagoda, like us on Facebook at Empowered Patient Radio. Thanks for listening and we'll see you next time.

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