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**FROM HER VANTAGE POINT** at Rutgers Cancer Institute of New Jersey, Janice Mehnert, MD, has had a front-row seat to the immuno-oncology revolution. Mehnert returned to her alma mater in 2007, and since 2014, she has headed Rutgers' Phase I/ Developmental Therapeutics Program; she is also head of the melanoma research team. Her work on the KEYNOTE-028 trial



MEHNERT

has produced important results in multiple cancers, including neuroendocrine tumors, thyroid cancer, small cell lung cancer, and, recently, advanced ovarian cancer.<sup>1-4</sup>

Mehnert has shared how, as a native of the Jersey Shore, she is especially attuned to the risks for her patients with melanoma.<sup>5</sup> Early on, she studied the use of ipilimumab (Yervoy) in patients who were excluded from clinical trials; in 2013, she was the senior

author on case studies of 2 patients who received the treatment while living with hepatitis B and C, respectively.<sup>6</sup>

Her findings are broad and sometimes unexpected. In 2014, she achieved a spectacular result in a 53-year-old woman with endometrial cancer whose disease had returned after aggressive chemotherapy. Mehnert treated her with pembrolizumab (Keytruda) and saw what she called a "rapid and durable response."<sup>7</sup> But the question remained: How did this happen?

The Rutgers Cancer Institute's Precision Medicine team found more than 30 mutations in the patient's tissue samples, and the answer turned out to be polymerase epsilon, or POLE, seen in 10% of endometrial cancers. As described in the *Journal of Clinical Investigation*,<sup>8</sup> their analysis showed that POLE mutation was associated with both a high mutation burden—already seen in the tissue—and an elevated expression of immune checkpoint genes, increasing the chances that checkpoint inhibitors would produce a response. Thus, Mehnert's use of pembrolizumab had uncovered a solution for not just 1 patient but possibly other women with the same mutation.

By contrast, Mehnert said in an interview that much of the science will involve the patients who *don't* respond to the programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. Who are they, and what can be done for them? Identifying these patients and finding treatments for them calls for more work with biomarkers, a topic Mehnert has written about extensively.<sup>9,10</sup>

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## INTERVIEW

# Rutgers' Janice Mehnert, MD, on Biomarkers, Being Inclusive in Clinical Trials, and Taking Time to Weigh the Options

Mary Caffrey

## CONTINUED FROM COVER

She is also a leading voice on the need to enroll patients with comorbidities in clinical trials<sup>11,12</sup> and the importance of ensuring that patients understand their options. In 2018, she took part in one of the field's most challenging discussions—when to stop therapy—as part of a task force of the Society for Immunotherapy of Cancer, which addressed this issue when it updated guidelines for the treatment of cutaneous melanoma.<sup>13</sup>

Mehnert visited *Evidence-Based Oncology™ (EBO)* for a discussion of current topics in immuno-oncology and how issues of payer coverage affect patients. (This interview is edited for clarity).

## EBO: As you lead phase 1 studies, what treatment developments excite you the most?

**MEHNERT:** We're in a bit of a lull for therapies that I'm enormously excited about, and that's an honest answer. But that's because the development of the checkpoint inhibitors has just been revolutionary. We are now in an era where we're trying to figure out resistance—especially PD-1 resistance. We have a lot of trials open for patients who are resistant to PD-1 inhibition; I don't know that we have the right strategy just yet.

We've got to pay attention to the end points that we're choosing as we write those trials; otherwise, we could end up in a place where we have many promising phase 1 agents that look good in small studies, but when we get to a larger study, the benefit doesn't pan out. We have to be very rigorous in how we design and test those strategies. And we must be true to ourselves with the patients we select. It has always been a challenge to enroll patients in clinical trials who will be representative of the patients we will treat in the real world. There are many reasons for that, safety being first and foremost. Nonetheless, as you get more comfortable with new agents, it's time to be more inclusive with the population that you treat. That's something we will need to do as we move new agents into development.

## EBO: You've written about the importance of biomarkers and about the need for multiple biomarkers. Are you seeing progress in this area?

**MEHNERT:** I think we're seeing a dedicated effort toward the sophisticated quality collection of tissue specimens. I think we are still rather far away from the holy grail of having a test we can run prospectively, that will tell us when we meet a patient what type of therapy to use. But certainly, the importance of having those assessments is noted by the immunotherapy community.

The problem, as I've written, is that the immune microenvironment is very dynamic, and having 1 assessment that captures everything that is relevant is rather challenging—and may be out of reach. But certainly, it's a topic of hot research, and the value of it is very much recognized. I think that we're working on it, but I think we are [a way off] from having hard tests we can order in clinical practice.

## EBO: There have been many studies in the literature about the microbiome and the potential here, both in diagnostic and therapeutic strategies in immunotherapy. How important is this area, in your opinion?

**MEHNERT:** It's important to understand the relevance. [Last fall]

I attended the Society for Melanoma Research meeting in Manchester, England, and Drs Jennifer Wargo and Jennifer McQuade [both of The University of Texas MD Anderson Cancer Center] gave excellent talks in this area.

I think of the immune system in 3 parts. They're not separate; they're integrated:

- There's the tumor and its genomic factors and genomic presence.
- We also have the tumor microenvironment that the tumor sits in and interacts with.
- There are host-specific factors, and that's where the microbiome comes into play.

Certainly, understanding the relevance of how an individual microbiome may be applicable to the response to immunotherapy and the development of the cancer is mind-boggling, but it's a very important topic, and we're going to be hearing a lot about it as we move forward.

## EBO: For some patients, the trade-off with immunotherapy has been toxicity. What is the role of education in connecting the rest of the healthcare team in recognizing side effects?

**MEHNERT:** I think we have a lot of work to do here, especially just with educating our medical peers. Even though we've been using immunotherapy in cancer care for melanoma since 2011—before that, actually, but 2011 was ipilimumab's approval<sup>14</sup>—we are still very far away from when a patient presents in the emergency [department] and their oncologist is not present or notified, that the physician-led healthcare team knows what to do.

Education in this area is still of prime importance. What we must understand is that with first-generation therapy like ipilimumab, the toxicity profile is similar but different—if you can have that—to nivolumab. ... For a classic example, I'll give you colitis.<sup>15</sup> I've seen several cases of colitis presenting with just pain and constipation. It's not very dramatic bloody diarrhea that we may have seen before with other checkpoint inhibitors, so educated oncologists may not pick that up—I've pointed it out to colleagues. So, we're learning more how to manage these treatment effects, and we must keep spreading the word and teaching our primary and specialty care colleagues, our nurses, our physician assistants—the entire healthcare team.

## EBO: How are we doing in developing treatment strategies than can reduce side effects?

**MEHNERT:** In terms of managing the side effects once we recognize them, I think we're much better in that arena. There are times where side effects, even if we're doing everything right, may escalate and be life-threatening no matter what we do. But I do think once we recognize side effects, we can put a treatment paradigm in place.

I also want to see more education on the patient side. I am blessed—I have excellent nurses and nurse practitioners who spend a lot of time in the patient education arena. And yet, even the patients who are very motivated will go home and convince themselves that the diarrhea that's been going on for 10 days is the Chinese food they had 2 weeks ago. Some of it is not recognizing that something's going on. Some it may be fear: "Oh gee, if I report this, I'm not going to get treated." There are a lot of ways we can work on emboldening the patient to tell us things that are



### MEHNERT

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going on so that we can recognize these things as soon as we need to. I do think that overall, there's obviously a broad need for this kind of education; since immunotherapy is being used for almost every kind of disease type now.

**EBO: Is there a role for biomarkers in identifying the patients who are most likely to have side effects, or in identifying the type of side effects they might have?**

**MEHNERT:** So, “absolutely” is the answer—there's a role for it. Getting to that role and finding a streamlined and applicable approach for every patient who walks into the exam room is something we're still far away from.

[It would be valuable] to be able to tell treatmentwise, prognosticationwise, to have a test that would tell me who should get 2 drugs versus 1 drug. But once I've decided that I need to give 2 drugs, which generally generates a higher response rate but also has more toxicity, then to know who's going to be the person that sails through this and who's going to be the person that hits a lot of bumps in the road—that would be an enormously valuable test to have.

**EBO: You've written about the importance of including patients with comorbidities in clinical trials. What can be done to promote this?**

**MEHNERT:** The reason clinical trials are so stringent in the beginning is because there's a duty to your patient and there's a duty to the study. Obviously, you've got to keep the patient safe. If the patient has no cardiovascular or kidney or liver reserve to withstand a side effect, and they sustain a side effect that they can't recover from, you've done nobody any good. The flip side is when patients are enrolled in clinical trials, and there are a lot of side effects that are maybe not related to the medication but are related their disease, sometimes it's very difficult to tease that out. If you enroll patients with too many medical problems and there are lots of side effects reported, you don't know if it is the disease or the drug causing it, so you can't properly study the drug. So, there's a lot of very good reasons to have strict eligibility criteria for clinical trials.

But once you get into an arena where you have a reasonable handle on the safety profile of the medication—and you're starting to see it approved in multiple places—that's the time to say, “OK, do I really need to have this perfectly measured kidney function to enroll this patient? Do I really need to exclude somebody who has a history of hepatitis C, perfect liver function, and a tiny, tiny viral load that's detectable in blood work? Do I need to exclude that patient that had a very small brain metastasis that was treated and stable?” I think the answer to many of these questions is no. I think we can be more inclusive, and there's a task force developed by the American Society of Clinical Oncology that has addressed these questions in a larger forum.<sup>15</sup> Hopefully, we'll start to see some change.

Certainly, in melanoma we've seen change in the brain metastasis space. We've had a paper in the *New England Journal of Medicine* looking at immunotherapy in patients who'd had brain lesions written by my colleague Dr Hussein Tawbi.<sup>16</sup> We

have had trials ongoing with targeted therapy for a number of years now. Certainly, we are recognizing that this is not a population we should exclude from clinical trials. We've addressed the fact that patients have extracranial disease, and the intracranial disease remains such an Achilles' heel. We have to continue studying that area.

**EBO: How have you seen payer coverage evolve during the time you have treated patients with immunotherapy?**

**MEHNERT:** I will say that payer coverage for patients where the label may not be 100% approved has been more generous than what I have seen in the past, and I believe that is somewhat encouraging. There's nothing worse than having a drug that you know is going to be approved any minute—that could really make a difference in a patient's life—and not be able to get that drug to the patient because the paperwork just isn't done yet. And we were in that situation with pembrolizumab. We did an expanded access protocol [which allows patients to take investigational drugs under an FDA guidance] ...and even in that window before that [protocol] opened, we were seeing patients that really could have benefited.

But when it's too frequently available off-label, it means that patients aren't enrolled in trials and we don't get rigorous data. So, there's a sweet spot in there we need to hit.... I do think it's been fairly generous; however, I still say it's very difficult to give patients financial advice about treatment, because there's no way to be able to tell people what their cost of care is going to be up front. A lot of it is very vague, and that is very, very challenging to people who are just trying to hold it all together during diagnosis and treatment of their cancer.

When you think about how life changing a diagnosis of cancer is... It is just so stressful just to be able to maintain any sense of normalcy. People want to work. They want to be able to do things and maintain a normal life. And yet a lot of times, the financial piece is just as devastating as the clinical piece of this.

**EBO: If you could recommend 1 thing to a patient newly diagnosed with cancer, what would it be?**

**MEHNERT:** It's important for patients to understand that when you're planning your cancer care, make sure that [while] you're a participant in this journey, and you're as comfortable as possible in this journey. [It is] more important than getting your diagnosis and getting your infusion 2 weeks later, which every patient always wants—when a patient hears “You have cancer” and needs systemic treatment, the next question is always “Well, when am I going to get started?”

But if I could impress something on patients that it's much more important—for the most part—to take that time to educate yourself about the disease, get a good education, get an expert opinion, seek out a clinical trial consultation—that's critical. It's quite a few cases where it's a true emergency to initiate therapy. Seeking multiple opinions, seeking expert consultations, and seeking trial offerings is really empowering to patients. If I were to have a dream policy change,

such a consult would be something that would be mandatory for every patient who has a diagnosis of cancer. Especially with immunotherapy—we wouldn't be here if it wasn't for clinical research. And understanding that now we're just going to improve upon the existing advancements, but we still need to have those expert consultations and those expert collaborations—I think patients should know that. ♦

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