**SEASON TWO: Episode 39**

Breast Cancer Specialist Dr. Mark Moasser Discusses Overcoming Barriers to Clinical Trial Access

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Karan Cushman: Welcome to season two of the Precision Medicine Podcast sponsored by Trapelo. This is the podcast where experts come to discuss the problems oncologists, reference labs, and payers face as precision medicine grows and consider solutions for advancing the quality of patient-centered cancer care. Be sure to subscribe at precisionmedicinepodcast.com to get the latest episodes delivered straight to your inbox.

Jerome Madison: Welcome to the Precision Medicine Podcast. I'm Jerome Madison, and today we have Dr. Mark Moasser, Professor of Medicine at the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco. Dr. Moasser, thank you for joining us on the podcast.

Dr. Mark Moasser: Pleasure to be here.

Jerome Madison: I've read many bios that describe you as a physician scientist, can you tell us about your oncology training and why you chose this path in medicine?

Dr. Mark Moasser: Sure. I trained in the Northeast; Penn, Tufts, Cornell, spent a lot of years in New York. My training was in a hybrid path, both clinical training, learning how to manage patients, take care of patients, fellowship in oncology, learning how to take care of cancer patients, as well as a scientific training, post-doctoral training, in the laboratory learning how to do laboratory research, ask scientific questions, and make scientific discoveries. That's what's called a physician scientist; learn two related sets of tools and techniques, and you go into an academic career where not only do you deliver care to patients with cancer, but you also try to push the frontiers, try to make the treatments better, try to discover new mechanisms, new types of treatments, and that's the career of a physician scientist.

Dr. Mark Moasser: Cancer training was at Memorial Sloan Kettering in New York, and then about 16 years ago I came to San Francisco to UCSF. The environment here is extremely conducive to cancer research and to science in general, and there's an incredible community of scientists here to facilitate this kind of research. Cancer research requires a lot of collaborations, people from different areas of science working together. It can't be done just in one focused area, and so here we have a critical mass of a lot of people from different fields of science that work together, and that's why I'm here.

Jerome Madison: Did you have a mentor along the path of your training that really influenced you to hone in on building a translational lab or going in that direction?

Dr. Mark Moasser: Yeah. Well, mentorship in academia is always very important, especially in the early parts of your career is when a mentor is critical, and my mentor was a doctor called Larry Norton in New York. He's a breast cancer specialist and is very supportive of science, and he's the one who was a key mentor in my early years.

Jerome Madison: You mentioned there at UCFS you have a translational lab, it's called the Moasser Lab, and the HER2 oncogene has been one of your long-term research focuses, and at this year's virtual ASCO meeting Dr. Nancy Lin at the Dana-Farber Cancer Center presented findings from the HER2CLIMB trial, which has also been subsequently published in JCO. This trial demonstrated tucatinib in combination with trastuzumab and capecitabine to be the first to improve overall survival in HER2 positive patients with brain metastasis. How important is this for breast cancer patients?

Dr. Mark Moasser: It's important, it's important for a couple of reasons. As you mentioned, I work in the area of HER2 and my research program has to do with HER2. My own research program has more to do with the fundamentals of this oncogene, how it functions and what are the challenges in targeting it, but there's different dimensions to the research in the area of HER2. One of the areas is pharmacology and then this recent to tucatinib study, or the drug tucatinib itself, is an advance in the realm of pharmacology.

Dr. Mark Moasser: There are a number of drugs that have been developed over the past 20 years to target this HER2 oncogene and these cancer cells through various mechanisms, and one of the shortcomings of all of these drugs has been that they don't enter the area of the brain. Our brain has a protective capacity, it won't let drugs inside it, and that's because the brain is very sensitive and needs to protect itself from toxins and molecules and drugs. One of the challenges of cancer therapy is if the cancer enters the brain, it's much harder for us to treat it because our drugs don't get in there. However, drugs can be modified to get through the barrier and get into the brain, and so tucatinib is advanced in this route.

Dr. Mark Moasser: There have been other small molecule HER2 inhibitors in the past that don't get into the brain that well, this one is advanced because it does get into the brain. It's one of the first ones that does get into the brain very well, and this is particularly relevant to HER2 positive breast cancer patients because that's one of the areas where this cancer hones into, likes to go to, and it's one of the major causes of mortality in patients with advanced HER2 positive breast cancer. This is a big deal in the realm of pharmacology, a drug that can get across this barrier and get into the brain. It'll make a big impact.

Jerome Madison: Yeah. Some of the findings in the outcomes that she talked about is the improved intercranial response, as you mentioned, the mechanism of such, the reduced risk of central system progression, and reduced risk of death by nearly 50% for patients in this particular study. I guess the question is, and it's described as a small molecule, TKI, what is this small molecule, TKI? What have we learned from precision medicine that led to developing these particular agents?

Dr. Mark Moasser: The research in this area of HER2 has been going on since the late 1980s when HER2 was discovered. It was one of the earliest oncogenes discovered, the oncogene being a gene that becomes abnormal in a cell and makes it malignant, makes it cancerous, and this is one of the principle drivers of this disease, the abnormal function of this gene and its protein product. A central paradigm of modern oncology is to treat these cancers by developing a drug that very specifically inhibits that bad oncogene or oncoprotein, and that's what precision medicine is all about. That's what targeted therapy is all about. And now, there are different types in the realm of drug development, smart drug development, there are different categories.

Dr. Mark Moasser: There are drugs that on the molecular size they're very, very big, and they can't be taken orally; they have to be administered intravenously because the GI tract will destroy them. And then, there are other drugs that are very small, and they can be taken orally, they'll make it through the GI tract and get absorbed. They fit into certain pockets within this HER2 protein, and it's because of their small size. They're called small molecules, and their design is so exquisite that of all the proteins in the body, they almost selectively go into this hole, this pocket, in this protein called HER2.

Dr. Mark Moasser: This is the basic concept of targeted therapy or precision medicine, designing a drug that specifically attacks the protein that you have in mind that is a driver of this cancer. There've been a number of targeted drugs for HER2 developed of all categories. There are large molecule antibody drugs that are given intravenously, you mentioned trastuzumab, that's one of them, and there are several small molecules that have been developed over the years that taken orally, they're pills. Tucatinib that you mentioned is the latest one of those.

Jerome Madison: Yeah. You've had your finger on the pulse of early-phase clinical trials for quite some time, and in fact we became aware of you through Laura Holmes Haddad, which was one of your patients who you helped enroll into a PARP inhibitor trial almost or equal to years ago, which she said saved her life as a young mother of two toddlers. As you know, she's now a published author, a speaker, patient advocate working to influence healthcare policy for greater access to clinical trials in precision medicine, and fortunately we're honored that she's been a guest on the Precision Medicine Podcast.

Jerome Madison: For those listening, full disclosure, both Laura Holmes Haddad and Dr. Moasser know this, so they gave us permission to talk about this, but the trial that she participated in back then, I believe it ultimately didn't reach its objective endpoints, but she, in that trial, was a super responder, and since that time there have been over 100 trials involving PARP inhibitors in different cancer types. As a researcher, can you share your perspective on treating cancer based on the tissue of origin versus treating patients based on biological expression of their tumor? Is this within reach?

Dr. Mark Moasser: Yes, this is within reach, this is what we're doing now, but it's an evolving field. This is the cutting edge of cancer therapy, and it's a rapidly evolving field, not only in our fundamental understandings and our scientific understandings, but in drug development, newer and newer drugs, better and better drugs, and better and better diagnostics trying to identify what the abnormalities are in cancers. Laura was right at the cutting edge, she's a pioneer, she's a true champion in her own right. She developed cancer at a time when we were only beginning to understand what the scientific basis for this cancer was, that an abnormal gene that gets defective in some breast cancers is inherited and causes breast cancer at a young age.

Dr. Mark Moasser: We were beginning to understand: How can we treat these cancers better? And there were some initial suggestions from the scientific literature that this new class of drugs can particularly treat this cancer very well because of the defect that these cancers have in DNA replication. It was based on those very early ideas that we enrolled Laura in one of these early clinical trials. These drugs were just beginning to be tested in clinical studies, and it turned out very well for her. At that time we didn't have any proof of this, but it was just a scientific hypothesis. Now, years later, this is well established, about four of these drugs are already FDA-approved and used commonly. She was at the very cutting edge of this in her time, but this is the paradigm for precision medicine basically.

Dr. Mark Moasser: These days we're doing a lot of newer and newer diagnostics when a patient develops breast cancer or any other type of cancer. We take a piece of that tumor or a biopsy or from the surgical resection, we subjected to some very cutting-edge, extensive testing—genetic testing—that looks at a whole bunch of genes, 500 or so cancer genes inside the cell, to see what has become deranged. What are the driving genes in this cancer? There's a lot of information now about how to treat particular genetic abnormalities in cancer cells, and this is rapidly evolving, rapidly expanding. Not only the diagnostics, the drugs, and it's a changing world.

Jerome Madison: Yeah. In your lab, can you tell us more about your team and what the priorities are? You've been engaged in, as you mentioned, in this particular space for quite a while, but what are some of the priorities that you see that your lab is working on?

Dr. Mark Moasser: Our lab works on some oncogenes in particular HER2, which you mentioned, and our focus is more on the long term rather than the short term. There are new drugs being developed for HER2, and you mentioned some of them, these are incremental progress. They're better than the ones before, the patients benefit from them, but the principal challenge, the holy grail of cancer therapy is if we can eradicate the cancer, if we can make it go away and never come back. Right now patients with advanced breast cancer in whom the cancer has spread to other areas of the body, we have drugs, we have treatments, we can prolong life, but, ultimately, we can't save that life unfortunately.

Dr. Mark Moasser: The long-term vision of myself and our research program and many others is to bring about something—a type of treatment that can eradicate this cancer that can cure somebody from advanced stage. That will be a watershed event in the history of medicine, but it still remains kind of a holy grail. Our focus is on the best, and I'm interested in this oncogene HER2 because we've learned so much about it. I think this is one of the subtypes of cancer that were closest to actual eradication, to actual cure from advanced stage, and so I want to be part of the effort to take this to the finish lines.

Dr. Mark Moasser: This involves deeper understanding of how this functions, how does this HER2 receptor function, who are its talking partners, how does it engage with them? The drugs we have that target it, they work, but they work only for a duration of time. How can we make them work better? Why is it that they only work for a certain duration? We're asking the questions that are the key questions to take us to that finish line. They won't give return in short term, but they hopefully give return in the long term, so we ask these fundamental questions in our research program.

Jerome Madison: Yeah. As a researcher, what are your perspectives around treating cancer patients based on the tissue of origin versus treating patients based on the biological expression of their tumor?

Dr. Mark Moasser: Yeah. Well, this is definitely an evolving field. More and more we're moving towards treating a patient based on the biology of that cancer, and the way we define that is by looking at the genes. What genes are abnormal, and what are the precision, targeted-type of therapies that we can apply for the treatment of that patient? This involves progress along several lines. This a complex landscape, not only the diagnostics are improving day by day, we didn't have this before where we can test all the genes in the cancer, now we have it.

Dr. Mark Moasser: There is more and more ways of testing the genes, not only the gene structure, the sequence, but the gene expression, the epigenetics of it, the proteins, some of these require biopsies. Biopsies are sometimes difficult to get when its internal organs, now tests are being developed that can detect it in the blood stream, genes that broke off from the cancer and are floating in the bloodstream at low levels. These can now be detected, and this avoids the need for the biopsy.

Dr. Mark Moasser: The diagnostics are rapidly improving; the drugs are rapidly improving. We're getting better and better drugs, more selective, safer, more effective. The other thing though is that precision targeting is not a one-time thing. You realize that when you treat cancer with a precision target, with a very effective drug, it works for a while, and then the cancer learns to evade it. It develops resistance, then once we understand this, second-generation drugs are made. We go after it with a second-generation drug, then after a while the cancer learns to evade that as well. Then you come up with third-generation drugs, et cetera, and then it just continues.

Dr. Mark Moasser: Precision medicine is going after a moving target, it's kind of like a chess game. We make a move, the cancer makes a move, we hope to come up with the checkmate eventually, but it's a back and forth, and it's a moving target. The field is evolving rapidly, the drugs are evolving, the diagnostics are evolving, the computational algorithms are evolving, these are very important as well, and ultimately we try to not only treat the cancer, but try to stop its evolution of developing resistance and evading us, and hopefully to get to the finish line and eradicate it.

Dr. Mark Moasser: There are newer challenges that are emerging in the field, one is heterogeneity. Sometimes the cancer is not just one biology, one gene, it has five flavors and you have to treat them differently. This is another challenge, and sometimes we have to go after it with different drugs. Two different drugs, three different drugs, and so this is the evolving landscape of precision targeting. It's definitely the wave of the future. It is complex, but we have to meet this complexity head on.

Jerome Madison: Yeah. I've heard it said in the past that precision medicine is enabling physicians to treat cancer as a chronic disease. Do you agree with that?

Dr. Mark Moasser: Yes, people say that a lot, and they say that because advanced cancer used to kill patients quicker, now we can slow this process down. So yes, it is turning it into a chronic disease. I hope that eventually we can turn the chronic disease into a cure.

Jerome Madison: I think it's worth noting…that we mention Laura. It's Laura and her team of supporters that had to do their own research in order to find you and the work that you were doing in your lab. As we look at the landscape of clinical trials, we see that 85% of patients are treated in the community, and only less than 5% of patients participate in clinical trials. What are some of the challenges that you have at an academic center attracting patients from the community to participate in clinical trials?

Dr. Mark Moasser: Yeah, you're right. I wish there was many more patients participating in clinical trials, research would move along much faster. The challenges are on several fronts. Most of them are logistic challenges. The big challenge is the financial aspect, the insurer coverage aspect. A lot of patients in this area are in HMOs, and they're locked into their insurance coverage; they can only go to certain hospitals and doctors, and so they don't have access to us. If they come to our university tertiary care center for treatment, they have to pay it all out of pocket, so there's locked in barriers to this.

Dr. Mark Moasser: Second challenge, another challenge is incentive challenges for the private practitioners. Most of oncology cancer care is administered in the community by oncologists in their private practices and in their community hospitals, and they need to survive. They need to see patients, they need to have income, and they don't want to give patients away. When they refer a patient to a tertiary care center, oftentimes then they've lost that patient, so they don't have an incentive to refer a patient. There's also information or educational challenges. Many of the doctors in local communities, they don't know what's going on at the cutting edge. They don't know that there may be something really interesting or exciting happening in this field for this particular type of patient, and so there's informational challenges as well.

Dr. Mark Moasser: These are many of the challenges, and we have to help break down some of these barriers, and each one has its own approaches. As far as the HMOs and being locked into your own coverage, maybe legislation can help with that, break down some of those barriers. Patients should have rights to get treatments on clinical trials. As far as the incentives for private practitioners, private oncologists, to refer patients, there's some efforts going on here.

Dr. Mark Moasser: We're trying to bring them under our umbrella, perhaps call them our affiliates. This has advantages for them. They can advertise themselves, brand themselves as satellites of our university. But, on the other hand, they have an obligation to help us enroll in accruals. This is some of the ways we're approaching that. As far as the educational challenges, more outreach, more webinars, more conference presentations, podcasts, et cetera, and hopefully to reach both the patients and the doctors getting treatment in the community to want to seek or refer to tertiary care centers for clinical studies.

Jerome Madison: Well, it does come down to raising awareness. For those who are out there listening, Dr. Moasser, who would like to get in touch with you for collaboration, speaking, or for patients who may want to come see you, what's the best way for them to reach out and connect with you?

Dr. Mark Moasser: I haven't been doing much social media as a physician. Some doctors do, but the best way to reach me is contact my practice at the hospital at the UCSF Medical Center, and I'll reach back. I have publications in the literature, patients can respond to the publications. There are online mechanisms to do that as well, and perhaps I should increase my social media presence.

Jerome Madison: You know, Dr. Moasser, one of the things that I find about our guests that come on the podcast is your work is fascinating, and your dedication to the science is phenomenal, but many of our guests are just as fascinating outside of the clinic or the laboratory, and I understand you are a musician. Tell us about that.

Dr. Mark Moasser: Yeah. I trained all my life in music, studied music in college. In med school and residency I was in Conservatory in night school. Music has been a passion of mine, and to have a different dimension in your life, a different language, different set of eyes, puts everything into so much more perspective. I don't get time to play piano so much these days, but I attend a lot of concerts. I go to music festivals all the time. Unfortunately, this summer's European music festivals have all been canceled most of them, but this is a big passion of mine, and it helps illuminate. It gives you a perspective on life, on humanity that you wouldn't otherwise. It's important to have different dimensions in your life.

Jerome Madison: Yeah. On your way to the lab are you listening to classic, jazz, or are you rocking out?

Dr. Mark Moasser: My background and training is all in classic.

Jerome Madison: Awesome, thanks for sharing that with us.

Dr. Mark Moasser: Absolutely.

Jerome Madison: Well, we appreciate your efforts, Dr. Mark Moasser, Professor of Medicine at the Helen Diller Family Comprehensive Cancer Center. Now Dr. Moasser, you're living in San Francisco now, but you trained in the Northeast. What's colder, winter in the Northeast or summer in San Francisco?

Dr. Mark Moasser: I know it does get close, yeah. San Francisco is generally moderate, the climate here is moderate all year round. The southern Californians think this is cold, but you come from the northeast, and it's a joke. I would have to say it's pretty moderate here all year round.

Jerome Madison: Good stuff. Well, keep doing great things, and we appreciate you for being a guest on the Precision Medicine Podcast.

Dr. Mark Moasser: It's my pleasure. Thank you for having me.



**About Our Guest**

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Dr. Moasser is a physician-scientist at the University of California, San Francisco.

He earned his B.A. from the University of Pennsylvania and his M.D. from Tufts University School of Medicine. He then completed his residency training at The New York Hospital – Cornell Medical Center followed by a Medical Oncology Fellowship at Memorial Sloan-Kettering Cancer Center. After serving a few years on the faculty at Memorial Sloan-Kettering, he moved to UCSF where he has been for the past ten years. He is currently Professor of Medicine at UCSF and member of the Breast Oncology Program, co-chair of the Early Phase Investigational Therapeutics Program, and co-chair of the Molecular Tumor Board of the Helen Diller Family Comprehensive Cancer Center at UCSF.

Dr. Moasser sees and treats patients with breast cancer and directs a laboratory research program focused on tyrosine kinase signaling in human cancers with a particular interest in the HER and SRC families of oncogenes. He is most interested in understanding the complexities and mechanisms of resistance undermining the first generation of targeted therapies with the intent to lay the foundations for highly effective, targeted therapy of oncogene-driven cancers. His research spans a wide spectrum of activities from basic mechanisms of signaling and biochemistry to preclinical models to early-phase clinical trials. He is an investigator of the National Institutes of Health and a recipient of research awards from Susan Komen for the Cure, The California Breast Cancer Research Program, the American Association for Cancer Research, the Breast Cancer Research Foundation, and numerous other funding agencies. Dr. Moasser is a member of the American Society for Clinical Investigation and frequent reviewer for scientific and clinical journals as well as funding agencies.