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A Chat with "Cancer Discovery" at ESMO

Announcer:
You're listening to a special focus on breast cancer from *Advances in Women's Health,* sponsored by Lilly.

Dr. Birnholz:
Coming to you from the European Society for Medical Oncology's Annual Congress in Barcelona, Spain, this is ReachMD. I'm Dr. Matt Birnholz, and I have the pleasure of joining I-Mei Siu, who's the editor for Cancer Discovery, which is a publication journal for the American Association for Cancer Research based in Philadelphia. I-Mei, welcome to you.

Dr. Siu:
Well, thank you, Matt. I'm glad to be here. Thank you for asking me to speak with you. A very exciting time here at ESMO, yeah?

Dr. Birnholz:
Well, thank you for having me and for hosting me in your beautiful booth. It's great to be right here and to be able to speak to you about this really exciting conference.

We're exploring novel directions in breast cancer research discovery and treatment. As the editor for Cancer Discovery, can you tell me a little bit about what brought you and your organization to ESMO and maybe a little bit about the journal in general?

Dr. Siu:
Sure. Well, first of all, we're a team of PhD scientists who are editors at Cancer Discovery. And Cancer Discovery is a journal that strives to publish a range of articles from very basic science to clinical trials, science-driven clinical trials, which provide the most novel advances in the field, and we basically strive to attract a wide range of readers that was. But basically what we're trying to do is give people a broad—a breadth of scope in reading about cancer research because cancer research comprises a huge number of disciplines, and this gives basic scientists, for instance, a chance to look at the clinical science, what's going on in the clinical field and vice versa, so basically, we editors at Cancer Discovery really want to publish the most interesting, thought-provoking, novel advances in the field in general.

Dr. Birnholz:
I have to say, I mean, you've chosen your key words very wisely because you had me at cancer and discovery.

Dr. Birnholz:
I think many of our audience are instantly tuned in to trying to find out what's the latest and the greatest, what's the most novel directions for new types of diagnostic procedures or diagnostic approaches or treatment advances, completely novel directions, not simply looking to tack on to what we already know, which itself is very, very valuable, but we're looking for whole new directions, whole different ways of thinking about cancer.

Dr. Siu:
Sure. Yeah, we try to do that by providing—by publishing papers that we think are providing that are not only providing new evidence of, say, resistance mechanisms or basic biology, of providing insights into the biology of cancer, but also that are hypothesis-generating so that people can follow up. And our ultimate goal, of course, as Cancer Discovery might attest to—the name Cancer Discovery might attest to—is to ultimately try to benefit the patients, so that's what everybody is trying to do, but we want to provide a way forward to translate the findings that basic scientists provide, and we're hoping that some of our publications… And some of them have, which we're very excited about. We published scientific, hypothesis-driven clinical trials that now have led to great patient benefit and big clinical efforts, so we're very humbled that we can be a part of that process.

Dr. Birnholz:
That's great. And I have to say, that excitement is infectious. I feel revved up ready to hit this conference with renewed energy based on having talked to you for a few minutes. But let's get right into that conference. You've been touring the floors, getting a sense of some of the updates out there, areas that have sort of been turning your head and having the eyes perk open. Within the breast cancer arena, what have you seen that sparked your interest or that seemed like interesting areas that Cancer Discovery might pursue?

Dr. Siu:
Well, I think it's interesting. It seems to be a big question in the field as to for instance, I attended a CDK4/6 inhibitor session, and it seems to be a big question in the field as to what the actual markers are for response to CDK4/6 inhibition and also how to stratify patients for this treatment, because, I mean, it seems that oncologists are trying to avoid unnecessary toxicity, and really the best way to do that is to stratify patients. So, what are the molecular or pathologic determinants that would determine whether or not a patient receives therapy?

And similarly, in the immuno-oncology realm for, say, anti-PD-1 therapy, how do you stratify—how do you define response even? Is it a standard assay to quantify PD-L1 expression? How do you even do like the very... And it appears to me at least—not speaking as a clinician, of course, but from what I've gleaned from the talks—it seems like there are some even very more fundamental questions as to how to even define positivity. So it seems like there is a lot of discussion, and it seems that these clinicians are working together to determine these things. For instance, I heard a talk about the working group, the ESMO working group, for determining—basically just sending out the guidelines for determining response to precision—how to perform precision medicine in general, but basically, how do you define molecular determinants, how do you define... And it's just very interesting that they had to even standardize terminology. So, I mean, it feels like this field is in general so rapidly growing that there's almost a need to stop and make sure that everybody is on the same page.

Dr. Birnholz:
Yeah. Do we all know what we're talking about? And I completely agree with you. We hear the term biomarkers, and it seems like that term is getting defined in multiple ways based on what biomarkers they are actually looking for. And even when they have a biomarker such as saying, "Oh, we're investigating PD-L1, anti- PD-L1," understanding the biomarkers, how to apply that and what the biomarker actually means for patients with certain subtypes of cancer it's not entirely known because the data isn't out there yet.

Dr. Siu:
Right, yeah, exactly. And there are so many different trials, and it's a lot of data to try to analyze and integrate, and it's been very helpful, actually, as somebody with a basic science research background, to go to some of these poster discussions run by the clinicians where you have a discussant summarizing and analyzing a couple of presentations, and then when they put it into context of the whole field, you realize just how much data must be absorbed and analyzed to try to reconcile the different results—seemingly different results—you're getting, because every trial is run so differently, or even if you think they're not run differently, you have different patient cohorts depending what country you're from, what city you're from. There are just so many different confounding factors it seems that there seems to be some kind of need to standardize. And I'm just speaking as a basic scientist, but it appears that there needs—there's a push to try to standardize how analyses are done, how markers are defined, in order to better be able to compare these different clinical results.

Dr. Birnholz:
Well, it seems like there is a powerful role emerging for basic scientists such as yourself, both in the role of trying to elucidate the meanings in a way, walking it back a little bit and for us to understand who and what we're talking about with regards to breast cancer biomarkers, therapeutics, etc, but also in the communications area, which is where you're in this wonderfully hybridized role. As I look at some of the new studies out there or some of the late-breaking data, I'm given more confidence by the idea of where basic science needs to re-enter the picture given the completely opposite diametric results that I'm hearing. For instance, the role of PARP inhibitors for triple-negative breast cancer, on one end there are studies and people have spoken who have said we have some really great indicators here that PARP inhibitors and other small molecules such as CDK4/6 inhibitors could be just about ready to hit the primetime for neoadjuvant treatment for breast cancer patients.

On the other side, there are these keynotes that come out that say, hmm, you know, we're really not seeing great results at all for a number of things, for immunotherapies to other things for triple-negative breast cancer. And so, whether those 2 are actually riding along the same direction or if they are completely opposed, I'm not entirely sure, because I don't entirely know what they mean by the biomarkers, and they don't entirely know because the patient subpopulations are different.

As you said, the confounders are all over the place. There are different regions, locations where these studies are being done.And so,

how do we walk this back and investigate this from a basic science standpoint?

Dr. Siu:
Well, I think that it's actually really nice that the EACR, the European Association for Cancer Research, is also co-sponsoring this Congress with ESMO because you see a strong basic science presence here. As Joseph Saponaro said in his initial address, that it's important that we understand what the underlying biology is and how that also helps you better understand the heterogeneous nature of these tumors, so these are very-Breast cancers and cancers in general are quite heterogeneous, so when you for instance, going back to the PD-L1 as a biomarker issue, one thing that somebody—one speaker pointed out was one possible confounder is that maybe it's a matter of where you're sampling to look for PD-L1 expression. Maybe that's why it fails sometimes, and then maybe that's why it works sometimes, because it's a matter. It's just a purely technical issue of where you're sampling and how do you best. Ask where do you best assess for- what region of the tumor or which area of metastasis do you-which organ of metastasis do you sample to look for PD-L1 expression? It was suggested in the case of breast cancer that maybe you should look at the peripheral lymph nodes, the adjacent lymph nodes and not in. I don't quite remember what the other regions were, but they specifically pointed out like it's better to go to like a regional lymph node as opposed to, say, a lung or something for breast cancer.

It's interesting. But, I mean, I think it's going to come down to a partnership between basic and clinical science to unravel, to elucidate the mechanisms driving—to identify the biomarkers that are going to ultimately help the clinicians stratify their patients for therapy. And the CDK4/6… As I mentioned before, the CDK4/6 inhibitor story was very interesting just because it's interesting that the things that you would think should be a marker response like RB or something are not, and it's unclear why that's not, and maybe it's not just a 1 marker, maybe it's a set of markers that have to... Maybe it's a signature of some kind. Maybe it's a signature plus a pathologic change. It's unclear, but definitely there needs to be more basic research efforts into those issues.

Dr. Birnholz:
And it's funny that you mentioned that there are a number of experts in this field who are entirely in your camp for thinking that that is the next stage of development of evolution for breast cancer research and treatment. One of them in particular that I had the chance to speak to spoke to the idea of developing what he called an immunogram that would take into account not just 1 biomarker, not just 1 signature, but several upwards of 15, 20, maybe 30 different biomarkers hailing from many different areas that you wouldn't even. I think from my case standpoint being a little bit removed would not think to even associate with breast cancer development. But it goes to your point. We need to walk it back, expand our understanding of the biology of this disease to truly elucidate what predictive biomarkers are going to lead to better treatment selection, better prognostic indicators for our patients.

Dr. Siu:
Yes. Oh, I agree, absolutely. Yes, I mean, it sounds like everybody is coalescing around that, around that thought, but it's just a daunting amount of data to try to sort through and separate, basically trying to separate the wheat from the chaff, right?—what's noise and what's real, and I think that's when basic science is very crucial to churning all that data and then showing it preclinically before these things get tested in the clinic, because as they pointed out—as somebody pointed out at one of the talks, to run all the clinical trials that you would need to to test, say, all the different immuno-oncology combinations, it would take millions of patients and hundreds of years, and that's just not possible, so the more we can. The more basic scientists can eliminate and narrow down the possibilities, the better it would be for the patients.

Dr. Birnholz:
Well, I think the challenge that you have just spelled out also perfectly articulated the challenge, the daunting proposition of being an editor for a publication devoted to cancer discovery separating the wheat from the chaff and being able to glean through lots of data to find out what is going to be the most impactful. With that kind of segue, I'd love to... I guess my last question to you, looking ahead with Cancer Discovery and the work that you're doing there, how do you look to do that, to help position the best information possible out there in this area for your readership?

Dr. Siu:
Well, I would like to say that it's not that we don't. We see a lot of very good papers. It's just that the way our editorial process is, we know that a lot of the papers that we don't ultimately take—and I don't know if this should go into the interview—but a lot of the papers that we don't take are worthy of being published. We're not saying that at all. It's just that we're a high-impact journal and we really are striving to publish very novel science, and so what we want to do is try to help push that, really push the leading—be part of that leading edge of scientific research, providing new paradigms, whether it's basic biology or translational or even clinical, new ways of thinking, and we're really looking for that a-ha kind of—like that's a very... Or even, oh, that's a really cool study kind of. Those are the kinds of reactions that we have when we read papers that we think that would be great for—we hope we can publish this, and we think our readers would really like this, and our readers have said, "Oh, we like this range, the breadth that you have in the journal," so we don't

want to be all basic or all clinical. I mean, we want to provide people with that whole breadth of experience in cancer biology, so we want people to be excited about the whole process. Right?

Dr. Birnholz:
Well, you've definitely turned the corner for me. You've got me on board. I'm excited to see the advanced—the next publications that come out given the onus, the drive that Cancer Discovery is about. You definitely have one admirer. I've already heard others coming around the booth and saying the same, so thank you for your time.

Dr. Siu:
Thanks, Matt. Thank you for talking to me.

Dr. Birnholz:
I've been speaking with Dr. I-Mei Siu, the editor of Cancer Discovery from the American Association for Cancer Research. I-Mei, a pleasure as always. I hope to talk to you again.

Dr. Siu:
Thank you, pleasure as well.

Dr. Birnholz:
For access to this and other episodes, visit ReachMD.com where you can join the conversation and Be Part of the Knowledge. I'm Dr. Matt Birnholz. For ReachMD, thanks again.

Announcer:
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