## **SEASON TWO: Epsiode 31** Dr. Adam Brufsky shares findings from the recent San Antonio Breast Cancer Symposium and the important role of precision medicine

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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 back to the Precision Medicine Podcast. I'm Jerome Madison, Vice President at Trapelo, and today we have Dr. Adam Brufsky, Medical Director for The Women's Cancer Program at UPMC Hillman Cancer Center. That would be the University of Pittsburgh Medical Center. We asked Dr. Brufsky, who attended the San Antonio Breast Cancer Symposium, to come on and share his insights of how he believes precision medicine continues to make an impact on breast cancer care. Dr. Brufsky, thank you for being a guest on the podcast.

Dr. Brufsky: Thanks for having me.

Jerome Madison: So, to begin and orient some of our audience, some of our audience are avid researchers, followers of the news, and data in breast cancer, but certainly some are not. But, can you start by telling us what the San Antonio Breast Cancer Symposium is, and why this meeting is significant to breast cancer doctors?

Dr. Brufsky: Well, this meeting was founded over 30 years ago by a man named Chuck Coltman, who was director of one of the large cooperative groups, SWOG, the Southwest Oncology Group, to really have researchers from around the world discuss breast cancer topics. And it's been held in San Antonio ever since. I think this is the 37th or the 38th year. And basically, it really is a forum, unlike ASCO or any other large meetings where really, it's focused completely on breast cancer. And also, it turns out it used to be clinical and then, now the AACR got involved again. And so, really we see basic translational and clinical research presented, and it's really nice to get the interaction between all of us at this meeting. It's a large meeting. It's probably about, I think there's a lot of international attendants now, so over 10,000, 15,000 people come to it every year.

Jerome Madison: Wow. So, when you attended this year, what are some major topics that stood out to you, and we'll dive into each topic and what you thought was significant for people to know?

Dr. Brufsky: I mean I think that there's a number of things. I think the biggest abstracts are usually presented on the first day on Wednesday morning and that really had a lot to do with HER2-positive, both early stage and metastatic breast cancer. There's some very practice-changing research that was presented that morning. Other things that were presented were some interesting data on new topics in the use of circulating tumor cells, circulating DNA to prognosticate and to help guide therapy, both in the early stage setting of triple-negative breast cancer as well as actually in the metastatic setting and all kinds of breast cancer, both ER-positive, HER2-positive, as well as triple negative.

Another interesting thing to me that really stood out at this meeting was data that was presented from the Women's Health Initiative that we can get into, really suggesting that hormone replacement therapy with estrogen alone, not only does it not increase the incidence of breast cancer, it reduces the incidence of breast cancer, as well as improves survival for breast cancer. So that was a very interesting abstract presented by Rowan Chlebowski from Los Angeles. It was very interesting abstract. So we can talk about those three things, I think are three very important things that I think were discussed at San Antonio this year.

Jerome Madison: Well, you mentioned that the data findings from Enhertu were practice changing. What were those things that were practice changing, and what types of patients is this data going to impact?

Dr. Brufsky: The way this works is that the treatment of HER2-positive metastatic breast cancer and early stage breast cancer really has been one of the great successes of the last 20 years. In oncology in general, the development of anti-HER2 therapies like Trastuzumab and Pertuzumab and TDM-1, which is an antibody drug conjugate with Trastuzumab, really have changed the nature of practice. In fact, the vast majority of women now with HER2-positive metastatic breast cancer can live up to five years or more. In fact, there was data that was presented at the last ASCO meeting in 2019, where fully 37%, 40% of women, were still alive eight years after diagnosis of metastatic HER2-positive disease.

Jerome Madison: Wow.

Dr. Brufsky: And so, most of us right now, will give Trastuzumab, Pertuzumab, and Taxane as first-line therapy. Second-line therapy, they get Trastuzumab or TDM-1, the antibody drug conjugate. But the real issue is after that, what do we do? And the third-line treatment of HER2-positive metastatic breast cancer is really, in a large sense, up for grabs. I think a lot of us would just give chemotherapy and Trastuzumab, just go through five or six different chemos. But really what happens about 50% of the time is that women will develop brain metastases. And how do we treat those metastases? How do we prevent them, really has become a fairly intense area of research and focus. So, at last year's ASCO meeting to set the stage, HER2 tyrosine kinase, an oral drug called Neratinib was actually compared to another drug, an older drug called Lapatinib. In the setting, they're both given with Capecitabine, and actually Neratinib improved progression-free survival in these women by about two and a half months. It was about 25% was, about eight point eight months.

Overall survival was modestly improved, and I think what was most important in that trial, it was called NALA, was that the incidence of symptomatic brain metastases was reduced by about 10 to 15%. Now the problem with Neratinib is that it has a lot of diarrhea. Diarrhea can be tough to control, although I think we're doing a much better job with it now. We have a lot of strategies that have been tested, slow dose escalation of Neratinib can help with that.

But anyway, that set stage for this year's San Antonio. And there was another drug similar to Neratinib called Tucatinib, which is made by, well it was being developed by Seattle Genetics.

And the interesting thing about Tucatinib and how it's different than Neratinib is that Tucatinib binds the HER2 tyrosine kinase but not the HER1. That's the EGF receptor tyrosine kinase. And because of that, there's very little diarrhea, a lot less diarrhea, a lot less other side effects than Neratinib. And so, clearly it was a very interesting drug to develop. In their trial was women who were third-line and beyond with HER2-positive metastatic breast cancer were randomized to see Tucatinib, Trastuzumab, and Capecitabine, or Trastuzumab and Capecitabine, which is a known third-line therapy for metastatic breast cancer. And, in fact, what happened in this trial is that not only was progression-free survival significantly improved, but overall survival was significantly improved. It's very rare in metastatic breast cancer to see an overall survival benefit.

So what happened there is that additionally, they looked at women who had brain metastases at baseline (an MRI was required in everybody) and about half of the women had brain metastases. In fact, about 10% of women had brain metastases that were small enough and asymptomatic enough that they were not even treated with radiation or anything else. So in that group of women, with known brain metastases, they also had an improvement in progression-free and overall survival, which was quite dramatic. And so the improvements, in relative terms, were 50, 60%. It was really quite dramatic. And I think for this reason, this drug now is under review by the FDA, and we all expect it to be approved probably within the next four to six months.

Seattle Genetics is going to have an expanded access program, we hope, that at least has national scope in the US, so most people could potentially get this drug before approval. But we'll see what happens. So that's what's probably a very, very exciting abstract that was published in the Journal of Internal Medicine, I think that day or a day after. It was just like a few weeks ago.

So the other big thing in metastatic HER2-positive breast cancer is a drug called DS-8201. I forgot, I'll get to that in a minute, but it now has a name, Enhertu. But the bottom line is that, I'll call it DS-8201, and the idea behind this drug is that it's a Trastuzumab molecule. It's an antibody drug conjugate where the Trastuzumab molecule is bound to a derivative of a Topotecan.

So it's like a derivative of Exatecan. And this is a Topoisomerase inhibitor that really has been tried every so often in metastatic breast cancer, very active in colon cancer and some other cancers. But in breast, we really haven't used it that much. And it also, the interesting thing is the linker that links the drug to the antibody actually can be dissolved in the extracellular space. So what that means is that you can have what's called a bystander effect. So the drug is delivered, but the antibody doesn't have to get into the cell for the drug to be detached from the antibody and just leak into the cells that potentially don't endocytose the antibody. So, the bottom line is that, for a variety of reasons, and a lot of theoretical reasons that it could be better.

So the group is initially, let me think for a minute with what the group was that did it, but anyway, the bottom line is that what happened in this trial, oh, it was Daiichi antibody, and it's actually licensed by AstraZeneca. So the thing is that what happened in this initial trial, it was a phase two trial, it was not randomized. And women who had progressed through at least three anti-HER2 therapies in the metastatic setting, and almost everybody had had Trastuzumab, about 60% of them had Pertuzumab, I think almost all of them had the TDM one that is Trastuzumab emtansine antibody drug conjugate. We're giving DS-8201 every three weeks until progression. And in this trial, the median progression-free survival was over 16 to 18 months. The overall survival wasn't reached, and these were women who were heavily, heavily pre-treated, and six prior therapies was the mean number of therapies.

So, really to see this sort of result, and the response rate was 60, 70%, to see this sort of result is really, to us, suggesting that the natural history of the disease may be changed by the drug. And so we're all very excited about this. It got approved by the US FDA with accelerated approval based on this trial. Again, this was published in the Journal of Internal Medicine, I think a day or two after this presentation, and really this is now changed the natural history of the disease I think. Obviously insurance has to get on board, but it's going to be widely available now for women who have progressed through at least three anti-HER2 therapies, two or three. So it's going to be third-line and beyond, and probably will be the standard of care.

There are several randomized phase three trials of this drug that are currently ongoing. One is against TDM1 to determine what the second-line therapy for HER2-positive metastatic breast cancer will be. There's another one, a third-line therapy where they're comparing DS-8201 to Trastuzumab and Capecitabine. And then finally, it turns out there was activity in this drug in HER2 low, that is patients who have say HER2 one plus or two plus that ordinarily wouldn't receive Trastuzumab based therapy.

But there seems to be activity and response rate in phase one trials of about probably 40, 50% so there's actually a trial now in triple negative and ER-positive breast cancer in the third-line and beyond as well. Again, I think that this drug really could potentially be a real game changer in our business. The only problem is that there is interstitial lung disease. It's idiosyncratic, can occur at any time. Major symptoms, usually shortness of breath and cough, and I think that we're really trying to get people, once we started using this drug, to really monitor subjects very, very carefully to be sure that you detect this quickly, you put someone on steroids, you do a CT scan, you stop the drug.

And this occurs about probably, it can be fairly severe, in about 5 to 10% of women. In fact, the case fatality rate was about 2% in this trial from the interstitial lung disease. So on the one hand, it's fabulous in terms of efficacy, on the other, we're going to have to be very careful how we use it and how we monitor the women who are on it. So those are really the two big things. There's some other things we could talk about, but those are probably the two big things in the HER2-positive space that are very important that came out of San Antonio.

Jerome Madison: There's a tendency when we hear this news coming out of meetings like San Antonio breast or other meetings throughout the year to get really excited about it. But we know that there is some time before the data is published, the FDA might approve the therapy, and then the NCCN gets on board with putting it on their approved pathways, if you will. Do you or your patients experience any frustration behind that, and how do you view that?

Dr. Brufsky: Yeah, the bigger issue is insurance. It's the payers. I think in the case of DS-8201, I think it's really nice that the data's been published in a phase trial, it's widely accepted. The FDA gave it accelerated approval, obviously based on the fact that Daiichi is doing these randomized phase three trials. And I have no doubt in my mind that the NCCNc ommittee, I'm not part of the NCCN committee, I'm part of the Via oncology committee, it's a little bit different of a group, we probably will put it on our path via pathways in the next two or three months, and I bet you NCCN will as well. That's not going to be the issue. The issue is the payers, and we experienced with Pertuzumab, I think in 2015, 2014, Pertuzumab was approved in 2015. We had a delay of about three months before the payers got on board.

But I think Amgen is helping Daiichi out with this. Amgen licensed this drug from Daiichi and I think Amgen's, wide experience in dealing with payers I think will be very helpful as this drug continues to be developed and promulgated. In terms of Tucatinib, it's a little bit different. Seattle Genetics is a little bit smaller company. And as a result, we're going to have to see, they've applied, obviously, this is public information. They applied for NDA, new drug application, to the FDA, and I'm assuming it'll will be approved in the next six months if not sooner, but it's a little bit different. Seattle Genetics is a little bit smaller company. So it really depends on the company size, what resources they have, their connections to the payers, when these will be approved. And I think in the case of Tucatinib, they will have an expanded access program. So the hope is it'll be on a national scope that no one will have to go more than 150, 200 miles to get access to Tucatinib on expanded access. So that's the hope here for both of these drugs.

Jerome Madison: Great news for breast cancer patients all over the world there.

Dr. Brufsky: You bet.

Jerome Madison: You mentioned in the area of liquid biopsy, now we get a lot of requests from listeners and there's a lot of buzz around liquid biopsy. What were some of the news that came out at San Antonio that you thought were significant around liquid biopsy?

Dr. Brufsky: Sure. So let me start off by saying I've been involved in this field for a number of years, and we used to use circulating tumor cells a lot in the metastatic setting, because it appeared to predict results of CT scans by about a month. So if you had a lot of circulating tumor cells in your blood over five per seven point five CCs of blood, and you followed someone, they would have progression on their CT scan a month later. So the ECOG, large cooperative group, Eastern Oncology Cooperative Group, did a 500-patient phase three trial where women randomized to usual care or care guided by a circulating tumor cell biopsy. And so if the circulating tumor cells were over five at one month, their chemo was changed to their systemic therapy was changed to something else. And it turned out there was no difference in survival whether you did the CTC guided therapy or just didn't fit the standard of care therapy.

And so that gave everybody a lot of pause. It seemed to be exciting. But the problem is that, and the problem with all of these tests, liquid biopsies, et cetera, really the meat of the matter is, do we have any therapy that can affect the natural history if we detect the cancer earlier? That's what it comes down to. It's clear that all of these can detect the cancer earlier, but what can we do about it?

So let me go through the two big things over in San Antonio. There was two big things. One that shows the utility, and one that may show the utility. Well, we'll see what happens. The first one was something called plasma match, and it was a trial that was done in England. It was about a little under 1,000, 800 or 1,000 patients. And the idea was they would do circulating tumor DNA and they use the Guardant 360 assay, which I believe is about 100 genes that you test for on the blood.

And what they did is they look to see what kind of mutations came out from the cancer and the most common one, which is not surprising, was the mutation in the ester receptor. There was also a mutation in PI three kinase. There was also mutations in HER2, about 4.5%. Ester receptor was about 25%, I think pediatric kinase was about 25%. AKT, which is another mutation, was about 5%. And HER2 mutation, not amplification, a mutation in the tyrosine kinase domain of HER2 was a little under 5%, 4.7%. So if you had an ESR mutation, those would have been about 100 or something like that, were given high-dose Fulvestrant. Instead of getting it once a month, they're getting it every two weeks. And that didn't work. So the bottom line is that progression-free survival in that cohort was about two and a half months and really just no one responded.

I mean, 8% of patients had a minimal response. So that didn't seem to work. But what did seem to work was that if you had a HER2 mutation and they gave a drug Neratinib, that we had talked about before, which is a HER2 tyrosine kinase, the progression- free survival was about eight or nine months and the response rate was about 40% or something, 30, 40% so that had benefit.

The last thing, which is cool, was actually if you had a mutation to AKT, which I think was about 3 or 4% as I said before, and you've got an AKT inhibitor called Ipatasertib that you give with Fulvestrant. The progression free-survival of those women were about 10 and a half months, and I think the response rate is about 30, 40%.

So clearly we have a few mutations that are what we call actionable in the breast cancer space that a circulating tumor DNA test may help. Now, right now in the breast cancer, we're all doing it now, at least in HER2 and ER positive metastatic disease. And the main reason we're doing that is because Piqray, which is Alpelisib pediatric kindness inhibitor, which has been approved, needs to have a circulating pediatric kinase mutation to get approved. And so we're all doing this now, and what at least plasma match has done has showed us that you really could look at AKT mutations and treat them as well as HER2 mutations and treat them.

So I think that's good and that's helping us because now we have therapies that can affect the disease. So the other big thing that was done is that, and people have been trying to do this for a long time, there's a very nice abstract that came from University of Indiana, I think it was a lead organization where they looked at women who were undergoing adjuvant therapy or neoadjuvant therapy for triple negative breast cancer. And what they found, they did circulating tumor cells, and positive was over five, or they did circulating mutation. So they used the foundation circulating DNA assay. And if you had any mutation, you were considered positive. And again, it was a limited set of 70 or 100 mutations in the foundation assay. And what they found is that if you have circulating tumor cells or positive mutations in your blood or in your plasma, what they found is that your survival was worse than if you didn't have it.

And so, in fact, if you had both, your survival was obviously the worst of all three. You could have both are negative. That's the best survival. One is positive, it's intermediate. If both are positive, it was the worst survival. So the interesting thing there is we now have this. The question is what can we do with it? And there may be some interventions at least in the triple negative space, maybe a pediatric kinase inhibitor, an AKT inhibitor, immunotherapy, chemotherapy with Capecitabine. There are a lot of interventions we could try.

The issue is that we don't know right now, if you have these circulating tumor cells or circulating tumor DNA, we don't know if any of these interventions will actually affect the natural history once we did. That's the big question. That's a question we had certainly in tumor cells, five years ago in the metastatic setting. And I think it's still the question that's outstanding now in the adjuvant setting. We'll see, a lot of trials that are ongoing right now to try to figure out what to do with these patients that have the circulating DNA or the circulating tumor cell. So that's kind of interesting, and we'll see where that goes.

Jerome Madison: You've talked to us about HER2 positive patients and the continued innovation that we have there for those particular patients. And we talked about a liquid biopsy circulating tumor DNA, circulating tumor cells, which continues to be an area of investigation. But you mentioned at the top of this that something that you thought was really interesting was the news around hormone replacement. Tell us a little bit about that.

Dr. Brufsky: So this is something, the women's health initiative has been going, we've had lots of epidemiological data that has suggested that a hormone replacement in women can increase risk of breast cancer. I mean that's been known since 2002. All these big, the Harvard women's health study, all these hundreds of thousands of women, the nurses' health study, this epidemiological data suggested if you're on birth control pills, not birth control. If you're on hormone replacement, your risk of breast cancer is higher. And so we've really been advising women who develop breast cancer or who are at risk for developing breast cancer, which is just about all women at some point, to stay off hormone replacement, especially don't do it more than five years.

So this is actually a randomized trial from the women's health initiative. A huge study. I think it was 10, 15, 20,000, 30,000 women. A lot of patients. And what they did in this trial, if you had a hysterectomy, because they didn't want to induce uterine hyperplasia, if you had a hysterectomy, you were randomized to receive either nothing, estrogen-only hormone replacement, or estrogen and progestin hormone replacement. So it was a randomized, prospective study. And they presented the state a few years ago, showing that it looked like there was no increased risk of breast cancer in the estrogen-only hormone replacement. There was in the estrogen and progestin hormone replacement.

This is actually now a follow-up date. This was presented on Friday morning and really didn't get a lot of the traction I thought it was going to in the breast cancer community, as well as nationally. Maybe I just wasn't looking at it, but I was a little surprised. Because what they showed is that if you had it estrogen-only hormone replacement, not only was your risk of breast cancer reduced, but your survival from breast cancer if you got it, was improved. Now if you had an estrogen progestin combo, which a lot of women take, your breast cancer incidence was increased, and your survival, I think, was modestly decreased. So really what this is saying is that if women want to do estrogen replacement, this is implying it, I don't know if we're all going to do this yet as a community, but this implies if you want to give women hormone replacement now, it's okay to give them an estrogen-only pill.

And they probably should have some sort of, hopefully if they had a hysterectomy or something by then, so they don't get uterine hyperplasia, potentially uterine cancer from that. That's, from a big public health perspective, something that's really, I think, something that we are going to really think about now for the next couple of months before I decide what to make of it. Because this clearly could affect recommendations for hormone replacement in women. And I think something that women have been clearly interested in for many, many years. So, we'll see where that goes. That really struck me as another abstract that really deserves a lot of attention.

Jerome Madison: Wow. So you mentioned the San Antonio Breast Cancer Symposium, over 10,000 attendees, which I believe is the largest medical conference that focuses on a single tumor type in the world. We spoke to one of your colleagues about a few months ago, Dr. Erica Stringer-Reasor, Associate Professor of oncology at UAB, and she really walked us through a timeline of how breast cancer research has been the tip of the spear for precision medicine. Why do you think that breast cancer has really led in the precision medicine approach to treating tumors?

Dr. Brufsky: It's a good question. I think that for the longest time, I don't think we lead anymore, I'd have to say, unfortunately, and that's good because other tumors are that too, probably better than we are. I think that forever we had the first targeted therapy, which is estrogen or Tamoxifen, right? We had that first. We had the estrogen receptor, and we targeted it with Tamoxifen. We've done that for almost 50 years. Actually, probably more than 50 years now. We then had HER2, which is also probably in solid tumors, the first we'll target that people really could affect in natural history. And so that's why we've led for the longest time. But actually, I think lung cancer took over with the EGF receptor amplification and mutation with the ALC amplification.

And I think that there are other tumor types now, and now with tumor mutational burden, and all this immunotherapy in melanoma and other cancers, I think a lot of cancers are catching up or will have have exceeded breast cancer, especially in mutation detection. I think what's happening now, though, is breast cancer is going to catch up again. I told you at least, there's HER2 mutation, there's EGF, there's estrogen receptor mutation, there's AKT mutations, pediatric kinase mutations, all of which are clinically actionable. So now we have four mutations in breast that are clinically actionable that we didn't even consider three, four years ago. So I think in breast now, we're starting to catch up again in the precision medicine business.

And I didn't even talk about all the adjuvant assays we have. Things like Oncotype, Mammaprint, EndoPredict that allow us to prognosticate women and potentially have them avoid chemotherapy in the early-stage set. So we have a lot of really interesting stuff in breast cancer, and we have it in adjuvant, we still lead the adjuvant field. But I think we now have it in the metastatic field, we're catching up to other tumors like lung.

Jerome Madison: Dr. Adam Brufsky, Medical Director of the Women's Cancer Program at UPMC Hillman Cancer Center. For those out there who want to get in touch with you, Dr. Brufsky, are you active on Twitter or social media? How can they get in touch with you if they want to see you or have you speak?

Dr. Brufsky: I think that the best way to get hold of me, I do have a handle on Twitter, on BreastOncDoc, but I rarely use Twitter anymore. I tend to do email. You can email me. It's Brofskyam@upmc.edu.

Jerome Madison: And you can find that information on our landing page at precisionmedicinepodcast.com. Dr. Brufsky, this is a lot of information, really chock full of good bits for people, medical professionals and patients, so please come back and revisit this episode if you're out there listening to this. Dr. Brufsky, thank you for being a guest on the Precision Medicine podcast.

Dr. Brufsky: Thank you.

Karan Cushman: You've been listening to part one of our conversation with professor John Quackenbush, chair of the department of biostatistics at the Harvard T.H. Chan School of Public Health. Be sure to look out for part two where we'll continue our discussion on precision medicine beyond simple mutations. We hope you'll tune in.

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A person wearing a suit and tie smiling at the camera

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**About Our Guest: Adam Brusky, Ph.D.**

Adam Brufsky, MD, PhD, is professor of medicine at the University of Pittsburgh School of Medicine, PA. He serves as the associate division chief for the Division of Hematology/Oncology in the University of Pittsburgh School of Medicine, Department of Medicine. He is associate director for clinical investigation at the University of Pittsburgh Cancer Institute and co-director of the Comprehensive Breast Cancer Center Magee Women’s Hospital of the University of Pittsburgh Medical Center.

Dr Brufsky is board certified in internal medicine and medical oncology. He earned his medical degree and doctorate of philosophy from the University of Connecticut School of Medicine in Farmington. He then completed a residency in internal medicine at Brigham and Women’s Hospital/Harvard Medical School and a fellowship in medical oncology at Dana-Farber Cancer Institute, both located in Boston, MA.

Dr Brufsky is a member of several professional organizations, such as the American College of Physicians, the American Society of Clinical Oncology, and the American Association for Cancer Research. He has published over 250 abstracts, review articles, and research articles in leading journals such as the Journal of Clinical Oncology and the New England Journal of Medicine. He is currently an investigator on research grants funded by the National Institutes of Health, Susan G. Komen Foundation, and US Army-Breast Cancer Research Program.