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TRANSCRIPT FOR VIDEO #1: RESEARCH (PART 2)—
WITH DR. MICHAEL BIRRER
Interview, Massachusetts General Hospital
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Produced by The GCS Project

(DR—Diane Redington, CRNP; MB—Michael Birrer, MD;)

Slide: **Patient/Advocate, Diane Redington, and Dr. Michael Birrer discuss the results of the research to date and where the research is headed**

DR: Is there any other ongoing research related to GCS or MMMT anywhere else in the world?

MB: So**,** historically, these tumors have sort of been the… the molecular analysis of these tumors has sort of been left to the more common tumors from the same organ. So, carcinosarcoma of the ovary has been treated clinically, as you know, and from a molecular standpoint, assumed to be the same as, what I will call "run of the mill" ovarian cancer. We know that's *absolutely* not true. So, it has been a neglected area. There are not a lot of centers specifically dedicated to doing the research like this project. I will mention, out of respect, Dr. Santin at Yale has had an interest in carcinosarcomas and has recently published one quite interesting paper showing some initial molecular analysis. So, there's scattering of labs but not a lot, and I think that **this project will be far out in front of anything being done anywhere in the world.**

DR: Do you anticipate any clinical trials in the pipeline for 2017?

MB: So, that's a really great question. ***The good news is that because of the molecular analysis, because of just a general appreciation for the natural history of the disease, it is now well recognized that it is a unique disease.*** So, that has prompted cooperative groups like Energy and institutions like National Cancer Institute to start to think about carcinosarcoma-specific trials. It's been discussed. I've been present at those discussions, and I think you're going to see at least one or not two carcinosarcoma-specific trials in 2017.

DR: Do you think… What's the role of the immunotherapies that are emerging relative to this research and potential therapies down the road?

MB: Well, as you know, immunotherapy's a hot topic and has shown some spectacular responses in other tumors. The early data for ovarian cancer has not been overwhelming. But again, I think a lot of that is not applicable to carcinosarcoma, because it's a different tumor. *And there's some early molecular data to suggest that the targets for immunotherapy, like PDL-1 and PD1, are present in the tumor.* So I think it's a good candidate. And there's the type of trial where if you really want to do it and do it right, you need to have multiple centers across the United States dedicated to carcinosarcoma and a well-written trial that's open at all those sites.

DR: And how do we make that happen?

MB: *Well, it takes motivated investigators,* which I think we are. It takes a *network of dedicated clinician researchers*, which I think we have. Certainly, I know the sites throughout the United States who would be willing to do this. ***And then finally, as you know, what drives everything is financial resources.*** Now, if we could get a pharmaceutical company interested, then that would be the ideal source. The complaint usually is that it's a small market and we've got bigger things to do. But that can be addressed. ***If the science behind it is really strong, you can get companies interested.***

DR: What about the immunotherapies like the vaccine trials? Does that have any relevance here? Like the antibody drug conjugate therapies? Are any of those on the horizon?

MB: **So, I'm most enthusiastic about the immunotherapy trials using immune checkpoint inhibitors [e.g., PDL-1],** which I've just discussed. I think vaccines are more problematic for a couple of reasons. First of all, I don't think the targets for the vaccines have been well characterized. Some of the work we're doing may be able to do that. What you're looking for are proteins that come from the genes that have been mutated—they've been changed. They make good vaccine targets. So we need to do some work on that. Second concern about vaccines is I think most of us believe they're helpful in very small volume disease. They kind of "clean up"—they mop up what's left. So for recurrent tumors, they'd be a little more challenging. But certainly still a worthy area of research.

And then there's **Adoptive T-cell experiments. These are the CAR T-cells [Chimeric Antigen Receptor T-cell].** That's a really exciting area. Led to some spectacular responses in ALL [acute lymphoblastic leukemia], for instance.

DR: Is that where you are creating the antigen using the tumor to create an antigen?

MB: Well, ….that would be autologous T-cell transfer where you're priming the T-cell —the patient's own T-cells—and then putting them back in. **CAR T-cells are actually engineered T-cells**. They're being engineered to a protein that's on the surface of the tumor. And that's where the challenge is. **We need to find those for carcinosarcoma.**

You notice the common theme, which is—***a lot of this in the clinic leads back to getting the science right, which is why this project is so important. Because it should deliver a lot of those endpoints.*** *Cell surface markers, mutational peptides.* These are all important things to lead to clinical trials.

DR: Well, women will want to know, "What can I do to help?" They'll donate money; they'll donate tissue. What else can we do to support this research and find a cure?

MB: Well, I think the first two you mention are important. **This is a resource-dependent process.** There's no issue about that. I think material and tissue is very important, and that is not only primary tissue but recurrent tissue. *We need to know what the evolution of the molecular events are in this tumor.* Don't know that yet.

I think what you've done with this project and with the website is equally important. Uncommon tumor. So, every woman felt she was by herself. Now you've begun to create a network and a place where people can and patients can talk about this. That's going to be incredibly important. So, let's say tomorrow, the science leads me to a clinical trial possibility. **I need a mechanism by which we can spread the word on that. And so, the website and what you're doing is so important for that.**

But let's say we can't get a company involved or we can't get the NCI, National Cancer Institute, interested. We need a group of ladies who are motivated to make that happen. Because there's nothing more convincing than motivated ladies.

DR: Show up at Genentech.

MB: It works. Been there; done that.

DR: Yes, it worked with Herceptin and breast cancer.

MB: Absolutely. ***What I would see and the timeline I would see it in, would be that in a year—at most a year and a half—we have mapped out the molecular origins of this tumor.*** **When I mean "this tumor," I mean *carcinosarcomas coming from either organ and potentially any differences between these two*.** We will have a set of biomarkers that would be at least prognostic, meaning which patient is at highest risk for recurring and which is not, because we think there's a spectrum there. So this would be important for stratifying patients. *We'd have the molecular data to potentially design trials.* And then I really would like to get into the chromatin remodeling issue, because I think there's an important element within this tumor from that angle, and those trials—those drugs—are now in Phase 1. They're not in Phase 2. So we would be perfectly positioned in about a year and a half—maybe earlier—to begin to design a couple of trials and run with it.

DR: That sounds kind of breakthrough. That sounds like new science, breakthrough science.

MB: That's right.

DR: So that could really impact other cancers as well.

MB: Absolutely. So, I will tell you ... you could guess what another tumor is that has chromatin abnormalities. It's soft tissue sarcomas. And that may be why carcinosarcoma shares that. I don't know. *But the exciting part would be where we would we be 1½ to 2 years from now. That women who suffer this disease will not be alone, and they will have a portfolio—a smorgasbord of scientifically sound clinical trials—to either chase this tumor away or at least hold it at bay.* Rather than just pulling off random drugs from the shelf, we'll have that, and I think that's important.

DR: It seems like there's broad variation in terms of treatment, knowledge base, innovation. Women who are out there in the hinterlands don't have access to the knowledge base to be able to even access clinical trials if….

Well, let me ask you this. Are there any clinical trials available for women with carcinosarcoma now that women who are kind of along that continuum of disease might help them?

MB: Well, as you know, the answer at least in this country is really nothing that's specific to carcinosarcoma. You were able to identify one across the pond, so to speak. And that's, unfortunately, the state of the science right now. I'm anticipating that changing. I think the only way you can drive it, though, is with the scientific rationale.

I mean, how many times do ladies with this tumor hear that sort of dreaded comment like, "Well, this is a rare tumor, so we have to extrapolate from [other cancers]"? Those days need to disappear.

DR: The "R" word—"Rare." Exactly. Absolutely. Well, we're a bunch of motivated ladies, so we just need to know what to do. And I think your direction and help and working with us has just made me feel so optimistic and positive about… . **I think we're going to make history.**

MB: Good. I like that.

DR: That's our challenge.

MB: That's the plan.

DR: That's what we're going to do.