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Conversations
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Bladder Cancer: Personalized Medicine

Diane Zipursky-Quale: Welcome to Conversations About Bladder Cancer. I'm Diane Zipursky Quale, co-founder of the Bladder Cancer Advocacy Network. BCAN, as we like to call it. Today we're talking about exciting developments in cancer treatment for personalized medicine, as well as immunotherapy. We're very fortunate to have with us today 2 experts in bladder cancer to talk with us about these new developments, and what it means for the bladder cancer community.

With me today is Dr. Noah Hahn, a medical oncologist from Johns Hopkins in Baltimore, and Dr. Matt Milowsky, a medical oncologist from the University of North Carolina at Chapel Hill.

Welcome. Thanks so much for being here. It's great to have you guys.

Dr. Noah Hahn: Thanks for having us.

Dr. Matt Milowsky: Thanks for having us.

Diane Zipursky-Quale: Over the past several years, the terms 'personalized medicine' and 'precision medicine' have been used consistently in terms of cancer treatment. Is there a difference between these two terms, and what do they mean? What do these terms mean for bladder cancer patients? Matt?

Dr. Matt Milowsky: I think the fundamental background of medical oncology has been the use of chemotherapy in patients. That is across the spectrum of diseases in oncology. What has happened over the past several years is that we've developed an incredible fundamental understanding of the genetics of tumors. A better understanding of the patient or the host in terms of how the immune system works, within patients to potentially fight tumors. Using that type of information, we're able to develop a better understanding of how to actually personalize certain treatments toward those genetic alterations or events that occur within patients. Also, to harness the immune system with patients toward having an effect on the tumor.

Diane Zipursky-Quale: Noah, is there a difference between personalized medicine and precision medicine?

Dr. Noah Hahn: I would say, in my view, I don't tend to separate them. I think you'll hear different terms tossed around, whether it be 'personalized medicine', 'precision medicine', 'individualized therapeutics'. I think the basic concept behind them are very similar. We have focused a lot, in the last several years, on the genetics of the cancers, because we know a lot more about them now than we did before. I think the basic idea is trying to learn something about the individual patient's cancer at a basic level of its tumor biology in order to pick or

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select a more rational therapy for them. I think that underlies all of the terms that are used very frequently in the literature, and in the public lay press. We have different ways to do that, and I think it's an evolving field. We have some limitations, and some successes. I think we're going to continue to get better as we go forward.

Diane Zipursky-Quale: You both have used the term 'genetics', and I've heard the term 'genetics', and I've heard the term 'genomics'. Is there a difference between those two terms? Can you explain it to me?

Dr. Matt Milowsky: Sure. I mean, formally speaking, genetics is the study of individual genes. Historically, we were good at studying individual genes at that level in a person. Now, with the advent of new technologies such as next generation sequencing, we can study genomics in a major way. This is, basically, the ability to study thousands of genes in an individual, and understand the entire genetic landscape of that person's tumor, or that individual; to be able to use that information toward a better understanding of what treatments might be best for a particular person.

Diane Zipursky-Quale: I think most people, when they think about genetics, think about: "What have I been born with? Am I predisposed for Type 2 diabetes? Am I predisposed for ... " I'm trying to think of another disease that is inherited. Is that what you're looking at when you are examining the specific genetics of a patient's cancer?

Dr. Noah Hahn: I think it's both. We know that there are certain genes that predispose patients for certain types of cancers.

Diane Zipursky-Quale: Are there certain types of genes that predispose people for bladder cancer?

Dr. Noah Hahn: I would say not in the same way that we've seen with other diseases like breast and ovarian cancer. Some of that may be due to the fact that bladder cancer is heavily associated with smoking use. We have seen in other cancers like lung cancer, that once we've tackled the smoking exposure, that the disease may change over time, and there may be changes in the biology. For bladder cancer specifically, I don't think there is a single gene that, at least today, in 2016, that we can test for and advise patients what to do with it. When I think of genomics and genetics; I think Matt covered this very well: in terms of genetics, a lot of times we're thinking of single genes. There are diseases where there are single genes that cause them. Things like sickle cell, anemia, cystic fibrosis, where it is one gene that is altered that causes the disease.

When we talk about genomics its group of genes. It can be all of the genes; 20-30,000 that make up who we are, or it may be a smaller group; 10 to 15. In some ways, I think of it as ... genetics are the single color on a paintbrush, and genomics is when you put all of the colors together and then you see the picture. The individual gene, from a genomic standpoint, may not stand out, but when you put them all together, we're starting to see much clearer picture of what that cancer is and what's driving it.

Diane Zipursky-Quale: When we go back to the term, then, of 'personalized medicine', or 'precision' ... if you look at one patient's bladder tumor, and you look at another patient's bladder tumor, those genes and genomics might look very different?

Dr. Matt Milowsky: There's another distinction that's very important, which Noah alluded to, which is what we refer to as germ line genetics. Which are the genetics of the individual, and-

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Diane Zipursky-Quale: That you're born with?

Dr. Matt Milowsky: Correct.

Diane Zipursky-Quale: Are you born with your germ line?

Dr. Matt Milowsky: Correct. Then the other is the somatic, which is present in the tumor. Certainly, as we go from one person to the next person and look at their tumors, those somatic genetic events can be quite different although there are similarities that exist among individuals with similar tumors. That allows us to begin to think about the role of specific therapies that target specific genetic events that occur within those tumors.

On the other hand, the germ line, in other words, the "what you're born with" could also be helpful. They could be helpful in the context of telling us whether or not there's some predisposition to developing the disease. They also may play a role in a better understanding of whether or not someone may respond to a particular therapy. For example: an immune-based therapy. Both of those are pieces of the puzzle that will hopefully ultimately allow us to figure out what the best treatment is for a particular individual.

Dr. Noah Hahn: I think to build on that, I think it's the combination. There are certain genes that we're born with that may have very critical roles in how a cancer grows or responds to treatment.

Diane Zipursky-Quale: Genes that everybody's born with, or ... it differs for each individual?

Dr. Noah Hahn: It differs from one to another. It's what makes up who we are. Things like our eye color, our hair color, et cetera. The same applies to risk of cancer and subsequent therapies. If you think about it, the germ line, or what we're born with, that permeates all of us. It's in every cell of our body. In normal and cancer, to start with. Whereas the somatic mutations that Matt described, you can think of those as those are the acquired ones. The ones that happen later. That could be from exposure to radiation. It could be from diet. It could be from smoking; it could be from anything. There are germ line mutations that we are learning that are important for things like immune therapy.

For instance: there is a mutation in a process that helps us repair DNA breaks that happen all the time. There's a disease called Lynch Syndrome. We hear about that most often in colon cancer, but for the bladder and urothelial cancer community, it's also associated with Upper Tract Disease, the renal, pelvis, and the ureter. There's been some literature published in the last year that these patients tend to respond very well to immune therapy. That's a germ line mutation. I think we need to look at both. It may have a bigger impact in some patients versus others. I think what we're learning now as we're treating these patients, and as we're seeing the clinical trials starting to incorporate this, we're starting to see where we should take it. I don't think that we can say yet that we have that answer. I think most of us would agree, and Matt, definitely comment on this; that I think it's going to be very important to learn how to best position these therapies. I don't think we have a definite answer yet.

Diane Zipursky-Quale: What do we know about bladder cancer from a genomic, genetic, standpoint? What have we learned so far?

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Dr. Matt Milowsky: I think that there's been a tremendous amount learned, and it's incredibly exciting. The Cancer Genome Atlas experience, which is an NCI, or National Cancer Institute funded effort ... that's been done in multiple cancer, so now just bladder cancers. Has really defined the landscape of the genetics of bladder tumors, and has demonstrated to us that bladder cancer has many genetic events in it that are potentially targetable. It's upwards of 70%. What I mean by targetable is that there are therapies that are either available that is FDA approved, perhaps in other diseases, or in clinical trials, or in development that are potentially useful in targeting or hitting those specific genetic events within the tumor. That's been a very exciting development. Now, it's incumbent on us to actually study those therapies in patients to see if hitting that target has an effect on slowing the tumor.

Diane Zipursky-Quale: I've heard the term, whether or not these particular mutations are drivers, meaning, are they the ones you want to hit because those would impact the progression of the cancer? Is that correct?

Dr. Noah Hahn: When we think about a driver mutation, what we're implying is that that particular genetic mutation is one of the major alterations that's responsible for the growth and spread of the cancer. As Matt had said, from the TCGA project, that we've learned in the last couple of years: bladder cancer is one of the cancers that has one of the highest mutation rates per tumor than almost any other cancers. When we have a lot of mutations, what we don't know is, is an individual mutation the only one or two that are really responsible for driving the growth? Or, and I use this term sometimes, is it collateral damage? Is it just a chaotic progress that got hit in the way, and you have a drug that targets it, but maybe it's not driving the growth anymore. I think that defining what is a driver mutation and understanding that is the things that we're trying to do in the trials and research that we're doing right now.

I think many of us feel that in bladder cancer, because of the information that we've learned about the genetics of it in the mutations, that it may be only rare types that truly have a true single driver. We've seen that. We've seen that in some clinical trials that Matt's been involved in, as well, where there have been incredible responses to a single drug. I think it's on us as a research community to define: how do we identify those patients that might be candidates for maybe a single drug targeting a mutation approach? Versus: which patients, maybe they need to target a couple of mutations. Maybe they've got 3 or 4 mutations that have drugs that target them, and do we need to combine them?

The challenge with the combinations is then figuring out, can we safely do it? As you add more drugs, you do tend to see increased side effects.

Diane Zipursky-Quale: It's a really exciting time where we've learned a lot more about the genomics of bladder cancer; they're potential targets that can help improve the prognosis for bladder cancer patients. Can you explain what it means to have your tumor sequenced? What's involved in that in a very simply way, because I know it's somewhat complicated. Could you explain what it would mean to a patient?

Dr. Matt Milowsky: Sure. There's an effort that we're involved in that's referred to the UC Genome Project that speaks to this. In fact, this is spearheaded by BCAN, and the Bladder Cancer Genomics Consortium. The way this works is that a patient's tumor is taken and the tumor specimen is subjected to what is called next generation sequencing. That is the way in which the genomics of the tumor is analyzed.

Diane Zipursky-Quale: They take a piece of tissue, right, and put it in a machine, and it gets spun? Sort of?

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Dr. Matt Milowsky: Sort of.

Diane Zipursky-Quale: It's the way I like to think of it. It is way too complicated otherwise.

Dr. Matt Milowsky: I think that's the way we like to think about it.

Dr. Noah Hahn: Most of the time when we're talking about sequencing now for patients, it usually is a biopsy or their surgical sample that has already been obtained as part of their standard of care. When a patient has a procedure where they have tissue obtained, that tissue is stored. It's usually stored in wax block that's called paraffin. When we send it for sequencing, we usually talk with the patients ahead of time. We ask them why we're going to do this; we think it may be useful or give us more information about their tumor. They consent to that process. We don't do this without their permission. What that allows us to do is to tell the pathologist to go and get that block of tumor in the paraffin block and cut some sections. These are tiny, microscopic sections. Then we send it off for them to do the sequencing.

Diane Zipursky-Quale: Noah, I know Hopkins is also going to participate in the UC Genome Project. Matt, so you send the tissue off for sequencing, and then, what gets back to the patient and their doctor?

Dr. Matt Milowsky: With respect to the UC Genome Project, it's really got co-equal aims. What happens is that a personalized report of the results of the next generation sequencing comes back to the physician. The physician can review those specific genetic alterations that occur within that patient's tumor. What is also included in the report is a list of potential therapies that are available in the context of clinical trials for which that patient may be eligible to participate in.

Diane Zipursky-Quale: Just to be clear, too, this is not an all-comer study. Which bladder cancer patients are eligible to be part of this study?

Dr. Matt Milowsky: The way we started out in looking at this through our scientific review community in BCAN was to set out looking at patients with metastatic disease. The rationale behind that is because those patients are in need of therapies urgently, because we know at the moment we don't have a therapy that can eradicate the disease in the great majority of patients. That was our initial step in moving forward with this project.

Diane Zipursky-Quale: The other part of project too, though, is accumulating the research and the information?

Dr. Matt Milowsky: Right, and so that's the other great arm of this project. Again, really co-equal aims, where we are setting up a clinical database, and a bio repository. What that means is that we're storing tumor specimens, including DNA and RNA. The building blocks that defines the genes. As well as blood to ultimately be able to do research to understand more and more about bladder cancer.

Dr. Noah Hahn: I think the UC Genome Project is very important for the bladder cancer community, but even as example for other communities, as well, because when we look at genomics research, one of the things that's become very clear is that you need numbers in order to get some of these smaller groups of patients to become visible as a true separate biologically driven type of bladder cancer. We need numbers to do that, and I think this is a good example of being able to get the academic research community to come together about a cause that

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matter. It matters for everybody. This matters for the patients first and foremost, but it matters for the research community to be able to figure out, how do we help the patients in the next steps? This has been a large effort on both of your parts-

Diane Zipursky-Quale: Yes.

Dr. Noah Hahn: To get this going. I think all of us are excited to see it move forward.

Diane Zipursky-Quale: We're very excited about it, and to see the partnership and the collaboration that's gone into this and that's moving it forward, and we hope it's a foundation for a lot of additional efforts.

Changing subjects only slightly, in addition to precision medicine, the big excitement in cancer, and I'm happy to say now, in bladder cancer, is in immunotherapy. We just, a couple of weeks ago, had the first new treatment for bladder cancer in more than 30 years with Tecentriq™, also known as Atezolizumab. I'm showing off my ability to say that. For bladder cancer I believe it's a second-line therapy for advanced disease.

Noah, can you talk a little bit about what is immunotherapy, how does it work, and what does this mean for the bladder cancer community?

Dr. Noah Hahn: Immunotherapy itself is a very broad term. I think in general, the concept is to try to stimulate or harness our own immune system to recognize ... try to attack and kill a cancer, and then a third and crucial component is remember it; actually adapt. Many of us are familiar with immunotherapies in our day-to-day life, and a lot of people think of things like vaccines that we have for infectious diseases.

Diane Zipursky-Quale: In bladder cancer, BCG is an immunotherapy.

Dr. Noah Hahn: BCG has been used for 20-30 years. In reality, it was one of the first immunotherapies to show a benefit in any disease, and it's been part of the standard of care for decades. What we've seen in recent years, and what has led eventually to the atezolizumab approval, is we've learned a little bit more about what are the factors that inhibit the immune system from working normally. As a broad class, you'll hear the term 'immune checkpoints'. The ones that have gotten the most press and the most success in multiple cancers target a sort of lock-and-key mechanism called PD-1 and PD-L1. Atezolizumab is an antibody that targets the PD-L1 receptor. These targets, PD-1 and PD-L1, can be present on the tumor. They also can be present on the immune cells that are present around the tumor in lymph nodes trying to fight the cancer.

Again, in general terms, PD-1, PD-L1, are thought to be inhibitors of the natural immune response. They're there for a reason. When we have an insult, an infection, an injury, our immune systems turned on, and we don't want that to go too far. Then the body sort of up-regulates the PD-1, PD-L1. It's normally a nice-

Diane Zipursky-Quale: It up-regulates to stop the immune response at a certain level?

Dr. Noah Hahn: To hit the brakes on it, so to speak. Some of the diseases that are not cancer-related that are called autoimmune diseases, like rheumatoid arthritis, lupus, et cetera; those often are diseases where our own immune system has gone a little too far.

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Atezolizumab, by blocking that PD-L1 receptor, in some ways, takes the breaks off of the immune system, and allows the immune system to do what it normally is supposed to do, and actually recognize and fight the cancer. I think that's, in simple terms of where we're at, there are many other targets and ways to try to enhance our immune system to fight the cancer, many of which are under investigation, including the bladder cancer. I think what it's done for all of the cancer community is that what's different about this wave of immune therapies ... we have seen higher response rates of tumor shrinking. That's been encouraging. What has really gotten people excited is that there is a small group of patients that that response seems to be durable.

Diane Zipursky-Quale: Durable, you mean it lasts.

Dr. Noah Hahn: Lasting, yes. I say seems. I want to be cautious about that because we're in a little bit of a new era where we just don't have 5, 10 years of follow-up; particularly in bladder cancer. We're a little bit further in melanoma and other diseases. The simple fact is, we haven't seen that before. I think that has spurned a lot of hope, a lot of optimism. I think much of it, very justly so. I think our task is to learn who are those patients, and how do we move the bar a little higher? It's a very exciting time-

Diane Zipursky-Quale: Can we say to the patients and their families that are ... who are watching this, "Check out clinical trials"? "Anybody who has bladder cancer right now, and whatever stage it might be, you should talk to your doctor about potential clinical trials.

Dr. Matt Milowsky: The answer is that there are trials going on throughout the spectrum of bladder cancer, and I'm going to let Noah speak to this because Noah's really been a leader in this area, with respect to non-muscle invasive bladder cancer.

Dr. Noah Hahn: I think that's one of the most exciting things for patients that has happened in the last, I would say, 4 or 5 years for bladder cancer. We've talked about this: one of the missions in BCAN, that bladder cancer in some ways has been a little unrecognized or not gotten as much attention, both from drug development funding, et cetera. That's changed. There are now clinical trials across the entire spectrum, from metastatic, to patients who are going to cystectomy, to bladder sparing, to even the earlier stages in non-muscle invasive disease.

Non-muscle invasive disease, there is an intense amount of research going on in clinical trials looking at many different approaches.

Diane Zipursky-Quale: Including immunotherapy?

Dr. Noah Hahn: Including immunotherapy. Immunotherapy is one of them, both systemically administered, like the checkpoint inhibitors, but also agents that are intravesical, subcutaneous-

Diane Zipursky-Quale: Intravesical meaning just going directly into your bladder?

Dr. Noah Hahn: Yeah, meaning instilled into the bladder via catheter, typically by urologist. Then I would also add that, in non-muscle invasive disease, capitalizing on the genetics: there are agents that are targeting specific mutations that are common in non-muscle invasive bladder cancer like a receptor called FGFR3. There are also

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exciting delivery advances. Things like nanoparticles, which we've heard about. You can think about that as ways to package existing drugs so that they can penetrate and get into the caner better.

I think the message to patients, I would say, across all states, but including non-muscle invasive, is to definitely investigate your options, and discuss this with your physicians. Clinicaltrials.gov on the Web is sort of a clearing house that lists them. That can be confusing.

Diane Zipursky-Quale: There is also-

Dr. Noah Hahn: I was going to get there.

Diane Zipursky-Quale: (laughs) Got to make the plug!

Dr. Noah Hahn: …One of the things that I think is a little more user-friendly is through *BCAN*, there's *a clinical trials dashboard* and portal that will identify clinical trials that are relevant to your particular cancer, and also within a geographic area.

I think that ... I can't say every patient, although most of them do, but it's definitely not a situation where there's not options. I think, as someone involved in the research, bladder cancer; we all believe that progress and improvements are going to happen through clinical trials. We definitely encourage people to consider and potentially participate in them if they can. We have more trial options than we had before, and I think that overall is a very, very good thing for our patients and our community.

Diane Zipursky-Quale: Concluding this, with what we know from the bladder cancer genome and with what the advances we have through immunotherapy, what do you see the future looking like? It sounds optimistic, but ... what message would you want to give to our community about it?

Dr. Matt Milowsky: I think this is an absolutely revolutionary time in cancer medicine. There could not be a more exciting time to be a medical oncologist than now. That relates to all of these advances in the field. That being said, there's a lot more work to do. As Noah suggested, immunotherapy benefits patients. Figuring out who are more likely to benefit as compared to others who might be better suited with other types of therapies. Finding out how to combine agents, whether they be agents that target the genetics of tumors with immune-type therapies, or combinations of immune-type therapies. I mean, all of these things are happening. They're happening in real-time. Clinical trials are ongoing.

We need more patients to participate in clinical trials, and I can tell you that within the bladder cancer community ... in fact, I was recently on the phone with Noah not too long ago, related to this, because we speak to each other. We try to, if we don't have a trial where we are, discuss this with patients that a trial may be going on at another place that may offer a treatment that we happen not to have at our own institution.

I think everyone is trying to collaborate to come up with the best treatments, and to do the best research, and I think we're on our way.

Dr. Noah Hahn: I think, too, the ... as Matt said, we have a lot of work to do. I don't think that we can underestimate or sugarcoat that bladder cancer is a lethal disease, and we're having far too many people who

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are passing away from it. I think, for the first time ... there is genuine hope. Not only hope, but there are people in places and trials and options. I think the one message for patients that I think in bladder cancer has not been there consistently is: you are not alone, and there are people fighting for you that are thinking about this 24/7, and we finally have some options that are generating real results.

We do have a long way to go, but it's not a hopeless situation. I think that that is a dramatic change, even for those of us that have been in the field. That's been a very positive change.

Diane Zipursky-Quale: Well, I can say on behalf of the entire bladder cancer community, thank you both for your dedication, your motivation, and your compassion, and your drive to make this different. I can tell you, and certainly for me it's the most exciting and the most optimistic I've been in the 15 years that I've been engaged in the bladder cancer field. Thanks so much for all of your work, and thanks so much for joining me today.

A reminder to all of our viewers: for more information about clinical trials or any part of your bladder cancer journey, check us out. Check BCAN out on the Web at www.bcan.org. Thank you for joining us today.

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