Highlighting Clinical Trials | Non-Muscle Invasive Bladder Cancer

Part IV: Questions & Answers

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BCAN Patient WEBINAR SERIES

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Rick: What I'm going to do in this section is I'm going to pose a question, and the questions are basically myths or common perceptions about clinical trials. We're going to work together through some of these myths, and debunk some of these myths.

Question 1: **Dr. Svatek, aren't clinical trials just for people who have run out of options?**

Dr. Svatek: I think people that are designing the trials, clinical investigators, we are definitely motivated to provide trials for people that have run out of options. You will see a large number, especially in the area of cancer, you'll see a large number of trials in the second line, where patients have, let's say, failed a prior therapy. We do see a large number of these things, because we're motivated to have options. I mean, that's true, but the answer is no. There are certainly a lot of trials out there available for people who have plenty of options, but are maybe interested in seeking an alternative option; or the options that are available, it's not quite clear what's the right move to do. One good trial is to take two perfectly practiced options, and compare them in a trial to find out which one is actually better for the patients.

Question 2: **Will I receive what's called a placebo, which many people would think of as a sugar pill, or saline solution, or something else that really doesn't do anything? Will I receive a placebo in a clinical trial?**

Dr. Singh: That's a very important question which put patients in kind of a corner. They may feel that they have a cancer, they're dealing with a cancer situation, and then they're being offered a placebo, or a sugar pill, or a saline; which is technically not an effective drug for their cancer. That happens in clinical

trials which are in very late-stage of development, where we are looking for drugs in disease setting where there is no standard of care. Where we don't know if giving any treatment is of any benefit.

Then we want to conduct a clinical trial looking at a new medication, where the regulatory authority, which is the FDA, may ask us to have a control arm where the patient is not receiving any treatment - since we don't have a standard of treatment in that stage or in disease setting- and/or may ask us to offer a patient placebo. Although, more and more new trials are coming without having placebo; because we feel it is unethical to bring in a patient to give a saline infusion, whereas the other group is getting a real medication. But sometimes, in combination clinical trials ... I'll give you an example.

There is a new medication like immunotherapy. We know already chemotherapy works for bladder cancer, and we want to see if adding immunotherapy to chemotherapy will improve the efficacy of chemotherapy. To test that kind of hypothesis, the clinical trial design will require us to have half of the patients to receive chemotherapy only, and half of the patients will receive chemotherapy and the immunotherapy combined with it. Now, to remove a bias of the treating physician, who is deciding if the treatment is working or not, we may make the treating physician blind to the drug which the patient is receiving.

How we do that is supply a bag to the investigator site, and just label it as drug. The treating physician may not know whether they are administering immunotherapy or they are administering a placebo. Such an experiment, once it concludes, will give us a true picture of how many patients did really benefit from the immunotherapy and/or if they had any additional toxicities due to immunotherapy and not the placebo.

There are certain designs where, yes, we need placebo. Again, that is more so in advanced stage trials, not in early phase trials. Like the trials we showed you today, there is no placebo. Everybody is receiving treatment medication. It depends on the disease setting and the stage of development of the drug. I hope I answered that question.

Question 3: **Can I select the treatment I prefer from the choices being tested in the trial?**

Dr. Svatek: This is a great question, and I think it's an important one that a lot of, not a lot, but some patients are kind of surprised when I explain that we can't choose a certain arm in a trial. There are clinical studies, where they're set up in such a way that the patient is allowed to choose. There's these certain trials, for example, where the choice of the patient is actually the meaningful end point and the meaningful data element that we're trying to collect. We actually want to know what patients choose, and that's incorporated into the design of the study; so, there are some interesting trial designs where that is allowed.

In many trial designs in cancer research, we utilize something called randomization. With randomization, patients are not allowed to choose, and doctors are not allowed to choose. It's so important that the randomization be done in such a way as to limit any type of influence by the doctor or the patient onto which arm the patient is randomized to. Why do we take such efforts to do that?

Generally, when we're looking at a clinical trial, we're trying to ask a question. Is Drug A better than Drug B? If the doctor, the treating clinician, or the patient have some reason for thinking that Drug A may be better, or that there's some thought that this particular patient might be better served with Drug A; then they may, either consciously or unconsciously, try to shuffle certain patients into one arm, and different patients into another arm. That's called bias. The effect of that is at the end of the study, and all these resources are put into it, if end of the study we won't be able to know whether Drug A is better than Drug B, because we kind of selected certain patients for certain groups. The gold standard is not only to have the selection of which arm the patient goes to be randomized; but also in some cases, as Dr. Singh was explaining, we blind the investigator. We may sometimes even blind to patient to which arm they're randomized to.

The bottom line is that it provides for unbiased separation of any pre-conceived notions of which arm would be better, unbiased distribution of patients across the study. That, ultimately, gives us a better answer with using fewer resources and optimizing the efficiency of a clinical trial. Great question.

Question 4: **It is how do I find a clinical trial for me?**

Dr. Singh: In bladder cancer context, BCAN is the biggest resource. They list all clinical trials on their website, and they keep updating that. In general, for any cancer patient, or for, in fact, any other disease setting; clinicaltrials.gov website offers you the most comprehensive resource of clinical trials, which are open here in the US and abroad. All you need to do is just put in the disease setting which you are looking for, and then you can click on trials which are recruiting right now. You can then click on the trial and look for where the trial is open, and you can easily call the phone number listed on that page to find more about the trial and how you can be enrolled on that trial.

What I usually tell my patients is that if they are interested in some trials, they can go there, explore them, and bring in what they think is interesting to them; and I can help them decide what trial might be better for them, if they are going to travel for that regular clinical trial. Obviously, each cancer center has a certain number of trials which are open. For example, like Mayo Clinic here in Arizona, in bladder cancer we have four or five clinical trials open. We cannot open hundreds of trials because of the limited resources, and also, we have to assign resources to other tumor types. Different centers will have different trials. Some trials may be better for you, in your particular disease setting, and your physician can help you guide which trial might be appropriate.

Question 5: **My physician has not offered or did not offer a clinical trial. What should I do?**

Dr. Svatek: The first thing is that I want to assure you, or reassure you, that it doesn't necessarily mean that the clinician ... What I want to make sure is that we shouldn't link the offering of clinical trials, necessarily, to whether or not you're getting good care or not. There are some clinicians that may not be able to open a specific trial, because they have competing other trials. Or they may be in an environment which doesn't have the resources for them to open a specific trial. That's one thing.

You could start by just asking your physician, "Are there any trials ..." You know, call them back or talk to them there at that meeting, "Are there any trials available for me? Do you have any open, or do you

know where I might find some?" If they don't have any open, and you find an opportunity through the BCAN website, or you find an opportunity through clinicaltrials.gov; what's really nice about these sites is that they have contact people that you can actually ... They provide an email, and oftentimes a phone number for you to email them, contact them, and ask them. Is this trial currently available? I live in South Texas, where's the closest place I could be enrolled in a trial? It does take a little bit of initiative, from the patient's perspective, to identify some of them when they're not open; but you can ask your physician, "Can you look and see if there are any trials available for someone like me? Can you make a recommendation of where I might could go?" Look on the BCAN website as well.

Question 6: Can I say no to or during a clinical trial?

Dr. Singh: This is a very important question in terms of rights of patients during clinical investigation. As a patient, you have full right to be on a trial, since these trials are done through NCI directed effort. Many of these clinical trials are done through NCI directed effort, and the federal money involved, and you are a taxpayer; so, you have a right to explore these trials and be on a trial. As long as you meet eligibility, you can go on a clinical trial; but at the same time, you have the right to refuse a clinical trial.

If your physician is asking you to be enrolled on a clinical trial, and it doesn't meet your conscious. You feel that going on a trial is not something that you would like to be, you can always say no; and it should not hurt your relationship with your physician in any way or form. So much so that every clinical trial has a consent form, which clearly describes that during the conduct of the clinical trial -including from the day one when you sign the consent form, to even up to a year or whatsoever time you are on a trial- at any time point, you can state that you wish not to be on that trial any more. You don't even have to give a reason for not being on a trial. The physician and your relationship should not be impacted by that decision.

We see that all the time on clinical trials where patients, due to professional needs, family needs, they have to move from one place to the other. As I said before, clinical trials may not accept you moving out and going to a different center on a clinical investigation. At that situation, you have to go off the trial. You're right is most important, either you want to go on a trial, or come off the trial. That can happen any time, and will not affect your relationship with your physician.

Question 7: I don't live near a major city. Are there clinical trials for me?

Dr. Svatek: Well, there may be. Certainly, one of the challenges with being enrolled in a clinical trial is the key information that needs to be gathered is usually what happens after the treatment. For example, in bladder cancer, if we're studying a certain drug or a certain type of approach, then we want to follow the patients very closely to see if the tumor comes back; because we're hoping that it doesn't. That often requires repeated evaluations, as would be for standard of practice; but the repeated evaluations need to be at the same site. Now, there are exceptions to that, and there are certain trials and situations where you could have your urologist, that you're used to seeing, perform the standard routine follow-up. The results of which could be just mailed to the major site.

A couple of options. A) There are lots of people that participate in trials that are not in a major city. There may be urologists or clinicians in a smaller city that are participating and have active practices with trials. It's possible that you may have an opportunity right at home. B) There may be a possibility for commuting to a major city for the initial steps, and then getting some of the subsequent stuff done nearby. C) You never really know, depending on the situation, how many visits the patient will require. One important question to ask if you're considering going on a trial is: What is the follow-up period? What's going to be required of me afterward? How many visits are required, and are they standard visits, or are these actually new visits that I wouldn't have to do under the standard circumstances?

Question 8: If I participate, what costs will I pay?

Dr. Singh: Again, a very important question with the cancer care, especially with the rising costs, and the insurance complicated scenario, which is happening at the national level. This should be a very important part of the discussion, which the patient needs to have with the treating physician. Usually, the cancer centers who are offering clinical trials, they will have a person assigned who would review, with your insurance, the visits and the treatments which are part of the clinical trial, if they are covered. If they are not covered, then what would be the cost or whatever copay would be to you, if you go through the standard treatment on the clinical trial? That is very important for you to know up front, since you will be liable for that cost.

Many insurance providers would refuse patients to go on a clinical trial, because they may feel that certain tests which are being offered on the trial are not standard of care and the research, or the clinical trial, should pay for that. In certain circumstances, if it's a pharmaceutical driven trial, or even an NCI driven trial; there could be an extra test which the trial is asking, and they usually try to budget that in and pay the site for that test, so that the patient doesn't incur. Unfortunately, many times the insurance providers may refuse to accept the costs involved in the clinical trial, and that may come to the patient. It's very important that you should address that when you're signing consent. Before that, you should ask them to run the estimates with the insurance company and give you an idea of what it would be for you to be on a clinical trial.

Question 9: Tell me about the additional research beyond the treatment portion of the trial.

Dr. Svatek: Often, and especially nowadays as technology is improving, there are often additional components of research embedded in a trial. For example, we're conducting this current trial studying two different BCG strains. Embedded in that study, we're also asking a very important question. We think that we have a biomarker that could distinguish responders from non-responders. We think that this biomarker will be able to help us identify patients who are unlikely to respond to BCG early on, before waiting for the tumor to relapse. Part of the benefit of this trial is that we're going to be able to validate this biomarker, and potentially have this available for patients in practice. There's a whole kind of other objective of trying to validate or develop biomarkers in the context of the trial.

I wanted to get back to one other thing that we haven't really touched upon, that I want to make sure I say it. One of my things is when patients are asking me about clinical trials, and often a question is, "Well, what are the benefits to me? What are the potential benefits, and what are the risks?" I think

that we should at least acknowledge that the risks are very clear. We don't know if this treatment may work. It is a trial, and so there could be some drugs that are not effective. There could also be some untoward effects, or unpleasant, serious sometimes, side effects of therapy that can happen with new agents; but there are a lot of benefits.

Those benefits could be access to drugs that normally wouldn't be available to patients. There is treatment that may be more effective than the standard approach. One of the unappreciated benefits is the close observation, and advice, and medical care you receive; because you have a research team involved with your care. There's additional people checking your studies, checking your laboratory tests, reviewing your chart; so, there are some definite benefits from that. Studies have shown that people that participate in clinical trials tend to have better outcomes for standard of care monitoring. Then, of course, there's certainly the chance to participate actively in the role of your own care through trial research; and the potential benefits in helping other patients afterward. That's kind of the one thing that I just wanted to make sure I get across.

Rick, do you have any other questions?

Rick: No, no. I just want to let everybody know there is an article that I co-wrote with one of my counterparts at SWOG, which remember is one of the National Cancer Institute's virtual teams. It was structured to speak to clinicians like Dr. Svatek and Dr. Singh, and talk about some things that are important in terms of designing clinical trials.

Stephanie, do we have any other questions coming in through the chat window or another source?

Stephanie: We do actually have two questions, and hopefully we'll be able to get through them.

Question 10: For non-muscle invasive bladder cancer, what would be the optimal time to apply for a trial? This individual is a T1 high-grade, currently having BCG plus interferon. If they want to join, should they wait until after their three-month cysto, or should they do it now?

Dr. Singh: Essentially from a patient's perspective, if the BCG and interferon therapy which they have already received, if it works for you and your cancer is not seen in your bladder any more, then you don't need any clinical trial. All you need is maintenance to help you with the same strategy and follow-up. BCG is a very good medication, and that's why Dr. Svatek's trial is looking to explore more BCG options; so that we can provide that therapy to patients, especially in situations of shortage. But then, the clinical trial which we are conducting, which is looking at BCG unresponsive disease, then the patient has to receive full treatment, and then repeat cystoscopy should confirm that the treatment is not working; and then, they can go on to the clinical trial.

I hope that the medication which they are receiving will work for them, and they may not need the clinical trial. You have to remember, as Dr. Svatek pointed out, the clinical trials, there's risks that you are taking of side effects. Number two, what if the medicine doesn't work, and the disease progressed to more muscle invasive disease. That disease setting may require more aggressive treatments with chemotherapy. This comes at a price, which the patient and physician will have a discussion over risks

and benefits. At the same time, these are the clinical trials, and hundreds and thousands of patients have gone on clinical trials; so now we have all these new treatment options. Your support is appreciated, but at the same time, that decision has to be well-informed decision, and a discussion between a patient and physician for the right time to go on a trial.

Dr. Svatek: I just wanted to add just a comment on that. In terms of timing, I think it's never too soon or too early to discuss a trial. For example, for Dr. Singh's trial, I've had several patients who have come to me, that may, or may not have had a relapse of disease despite BCG. They're not quite eligible for that trial yet, but we at least had the opportunity to talk about the trial, to show them the consent form, to go over it. The earlier, the better is the bottom line.

The other thing I will say is you may not be eligible for any therapeutic trials right now, but there could be a biomarker trial, and there are some surveillance studies. Basically, trying to identify biomarkers that could help identify tumors that relapse, that you may be eligible for right now; even though you don't necessarily need a therapeutic trial.

Question 11: **With the new molecular classification of bladder cancer, including neuronal subgroups being the most aggressive tumor with no response to chemotherapy treatment, could BCG help these patients? In the future, is it possible to imagine personalized medicine for bladder cancer treatment according to genomics for information about the tumor? Are there trials that are being done in the non-muscle invasive space? There are some being done in the muscle-invasive or metastatic phase, but are there any trials being done specifically to non-muscle invasive and genomics?**

Dr. Svatek: Hi, so there are. This is rapidly evolving, and this changes from year to year. We've learned so much about bladder cancer, and there's so much more exciting things that we learn. For example, there's a lot of evidence that FGFR3, a specific genetic mutation, is prevalent in bladder cancer; particularly in the non-muscle invasive bladder tumors. There's a development of a drug that specifically targets FGFR3. A trial design that is currently, either being implemented or soon to be implemented, is identifying patients that have this specific mutation. Superficial bladder cancer, non-muscle invasive, but they have an FGFR3 mutation; and then, enrolling them in a trial of an FGFR3 agent. That's an example, but there are others like that that are in the queue in terms of being developed.

Dr. Singh: Just to add a point to it. It's an excellent point regarding the neuronal type of bladder subtype, molecular subtype. Since you know about these subtypes, you probably also know that it's a rare entity and an aggressive type of bladder cancer. Most of these patients, they are found in the later stages of T2 or muscle invasive disease setting, where then they end up receiving chemotherapy. Since, considering their rarity, it is difficult to conduct large-scale trials in that space; because each hospital may see one patient or a provider may see one patient in a year. In high-volume centers like MD Anderson or Mayo Clinic, we may end up seeing more, five or ten patients a year; but again, clinical trials require a lot of patients, so we don't have a specific trial for neuronal subtype at this point in a non-muscle invasive disease setting.

Then at the same time, there are many trials which are looking for bladder cancer treatment based on the genomic markers which are coming up. As Dr. Svatek pointed to, the FGFR data was presented

recently at [inaudible 01:03:57] also regarding the early results on FGFR and bladder cancer. Definitely, the field is moving forward in a very promising direction.

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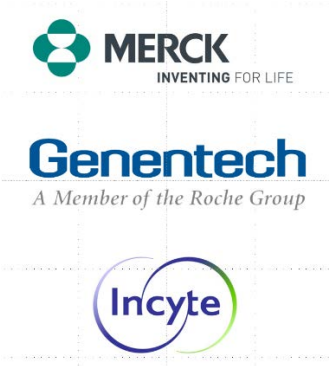

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