BCAN Patient WEBINAR SERIES

Clinical Trials: Muscle-Invasive Bladder Cancer

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Part II: Current Areas of Research

Presented by

***Seth P. Lerner, MD** is a Professor of Neurology at Baylor College of Medicine. He earned his medical degree from Baylor College of Medicine, completed a surgical internship at Virginia Mason Hospital in Seattle, and returned to Baylor for his residency training. He is Director of Urologic Oncology and the Multidisciplinary Bladder Cancer Program at Baylor. His clinical practice, education, and research activities are devoted to urologic oncology and particularly lower and upper tract urothelial cancer. His research interests include use of selective estrogen receptor modulators for treatment of bladder cancer, gene therapy, targeted molecular therapeutics, and outcomes of radical cystectomy and pelvic lymphadenectomy. Dr. Lerner has 22 years of experience as a clinical investigator for both NCI and industry funded clinical trials.*

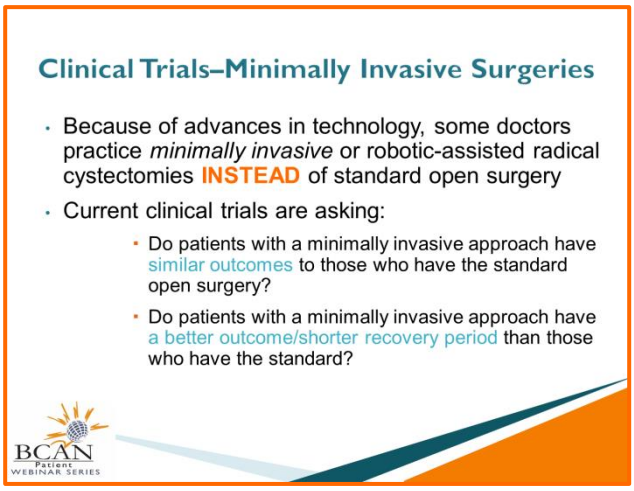
***James M. McKiernan, MD** is a professor and chair of the Department of Urology of the College of Physicians and Surgeons, and urologist-in-chief, at New York-Presbyterian/Columbia. Dr. McKiernan received his MD from Columbia University College of Physicians and Surgeons. He completed his training in urology and general surgery at NY-PH, followed by a urologic surgical oncology fellowship at Memorial Sloan-Kettering Cancer Center. Dr. McKiernan's clinical practice is focused in urologic oncology and particularly on surgical therapy in high-risk patients with bladder cancer. He has special expertise in organ preservation and reconstructive surgery to maximize quality of life. Dr. McKiernan is the principal investigator of the NIH-funded clinical trials program of experimental therapeutics in bladder cancer at NY-PH, which is investigating new agents for bladder preservation in patients whose cancer has recurred after standard therapy.*

Moderator: Let's talk a little bit about some of the current areas of research for muscle-invasive bladder cancer. I know you were just mentioning the issue about improving outcomes with surgery. Would you like to share more details about any of those trials that you know about that are going on—specifically for people who have a cystectomy or who try not to have a cystectomy?

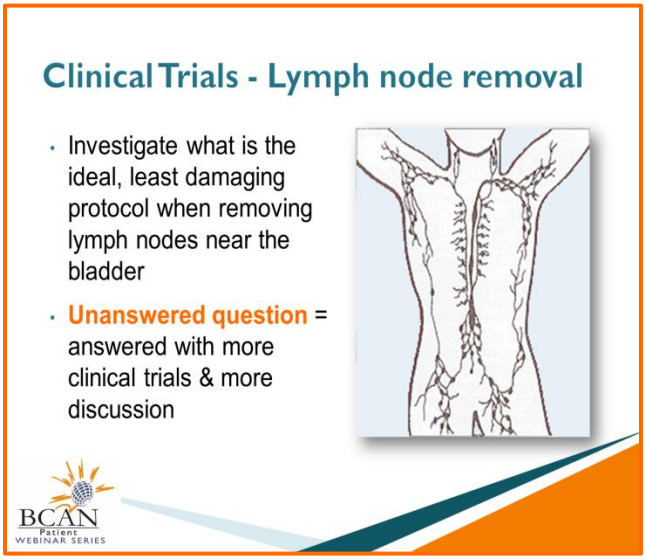
Dr. Seth Lerner: I think the big picture is that we are looking at everything from developing predictive algorithms for patients who might be at higher risk for complications, that maybe we should think about a non-surgical approach. We're looking at aspects of understanding a patient's nutritional status, an overall sense of physical well-being going into the operation, optimizing their nutritional status book before, during, and after the operation. This is in addition to a bladder removal operation. It's a bowel operation, because obviously we have to reroute the plumbing, and we always use a part of the intestine for that, so where we used to do these very aggressive cleansing of the bowel, we stopped doing that. It turns out patients do just as fine but have a much shorter period of time to recover bowel function.

You know, there's a drug that has come on the market a couple of years ago called **alvimopan.** It's been a game changer for our patients because it blocks what are called opioid receptors in the gut. We give narcotic medication for pain control, and that slows down the gut. This drug blocks that. The only reason we have this drug available for use in our patients is because a clinical trial was done where half the patients got the drug, half the patients didn't. So now we have an FDA approved drug to help our patients recover quicker. There's an example of some of the things that we do.

What is the role for minimally invasive surgical approach? Throughout time, this operation has been done through an incision, typically made either from high in the abdomen or below the belly button down to the pubic bone. We call that open surgery, and it has a very distinct set of advantages to it, but people have come along, and as minimally invasive surgery has become much more common, people have figured out how to do a radical cystectomy using minimally invasive or robotic-assisted techniques, but we don't know if that's as good, better, or worse in terms of the outcomes that matter after a radical cystectomy.

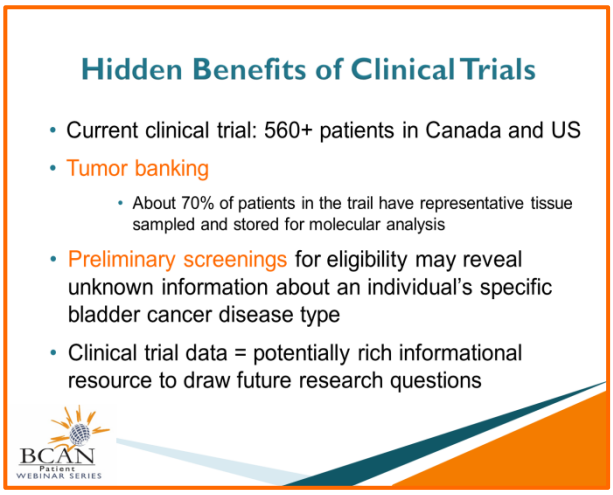


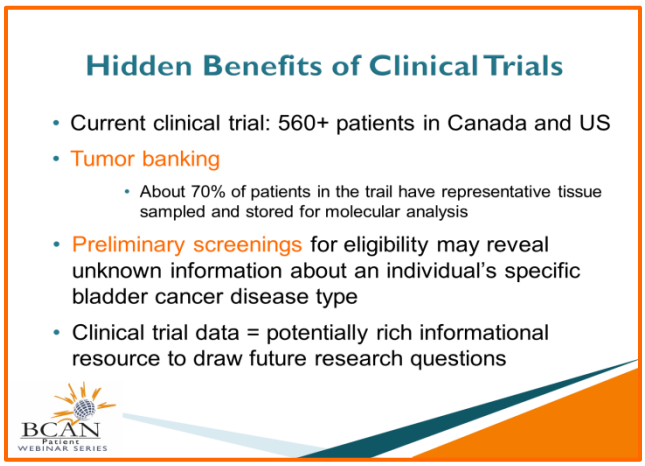
There are randomized clinical trials that have been done or recently completed asking a question about safety, about side effects, and we'll have results from clinical trials that will look at outcomes related to cancer, where half the patients get the traditional gold standard, if you will, open, and half the patients get a minimally invasive approach, and if the minimally invasive approach is shown to have similar outcomes to the open approach, then the question is **did the people do better? Did they recover quicker? Do they have shorter time to recover full function**, and we don't know the answer to that yet. This is why you do clinical trials, to try to ask and answer those questions.



Dr. James McKiernan: I agree. I would just add that Dr. Lerner is probably responsible for one of the more important clinical trials in surgical related issues that's gone on in the last five years in bladder cancer, and it actually has to do with not the bladder, but the lymph nodes around the bladder and what's the right form of operation to conduct to remove those lymph nodes. That really has been a question we've been wondering for years, and can't really be answered without a well-done clinical trial, because there's just too much bias associated with a lot of the information that's been available in the past. This is an aspect of the operation that doesn't even get talked about very often, but lymphadenectomy or removal of lymph nodes around the bladder.

Dr. Seth Lerner: Basically, any patient with a muscle invasive cancer that's having a cystectomy- I should say most patients- would be eligible for that clinical trial, and one of the gratifying things about this is we've enrolled now probably about 560 plus patients in Canada and the United States, and it's really one of the largest surgical trials in general, and certainly one of the largest in bladder cancer to ask and answer important questions. It's just an example of it's not a drug. The surgery that we think is better really, is it better, in fact?

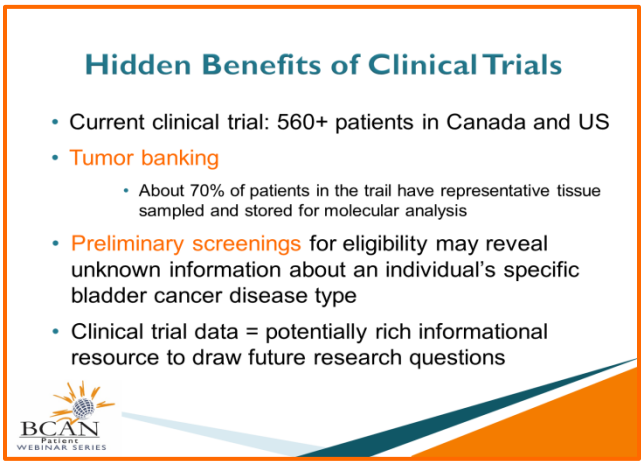




One of the nice things, one of the other hidden benefits of clinical trial participation is that in the context of a clinical trial, you have all of the clinical information, pathologic information for all the patients that went in the trial, but today, what we do is we also do what's called **tumor banking.** For about 70 percent of the patients in this trial, we will have representative tissue from their bladder tumor to do very sophisticated molecular analyses that we can ask questions about, about what I mentioned before, these molecular sub-types, but also relate them to outcomes.

When you have a completed clinical trial with all the clinical data, it becomes this amazingly rich resource to ask other important questions about biology that go along with the primary issue that we're trying to address in the clinical trial. There's a lot of hidden benefits beyond just the primary question that's being asked in the clinical trial.

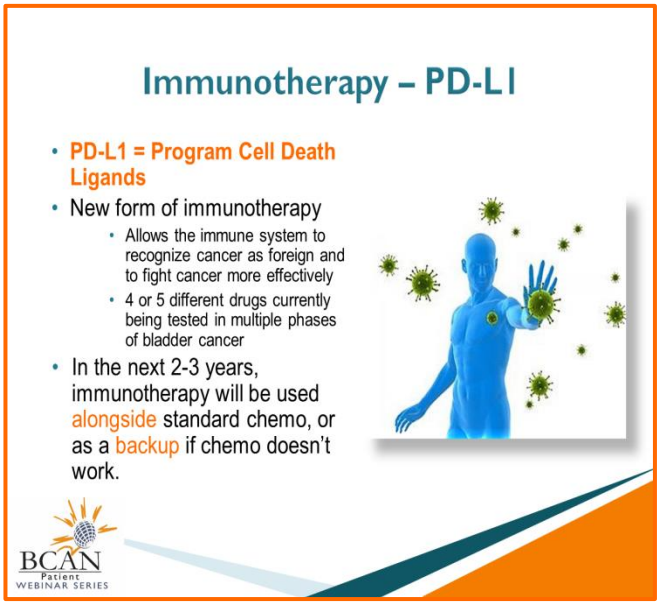
Dr. James McKiernan: I'd like to add to that, it's something that I've noticed that's even more subtle is that oftentimes, patients will seek information about a clinical trial, and let's say go to a center that's doing a clinical trial, and they may not be eligible for the trial. Maybe there's something about their condition that doesn't allow them into the trial, but the process of being reviewed and having your case reviewed for a clinical trial oftentimes will reveal information that was not known.



For instance, it may require a repeat cystoscopic surgery or a reanalysis of your biopsy results, or a repeat scan that may impact your care, even though you don't actually enter the trial. This is something we've been looking at very carefully. The process of seeking out a clinical trial and being evaluated as a patient may actually have some benefit to it. It's harder to measure, but it's a very interesting topic.

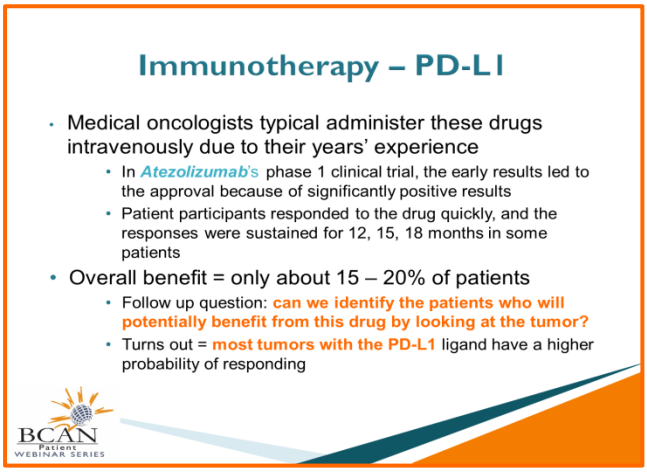
Moderator: Can you talk a little bit about what you know is going on in immunotherapy? We talked a little bit about ***Atezolizumab*** and that trial, but are there other trials in immunotherapy area, and how would they impact bladder cancer patients? What are they looking for in that trial?

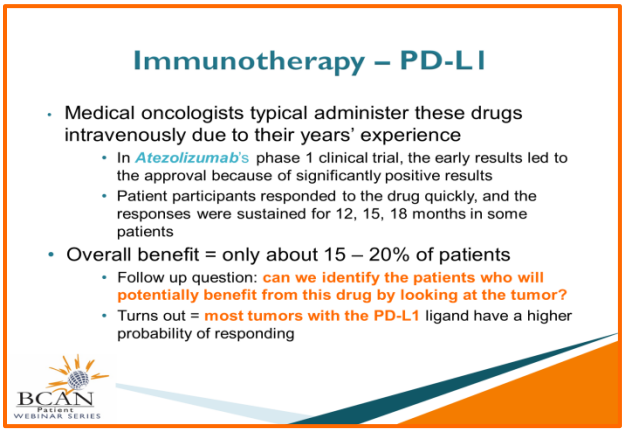
Dr. James McKiernan: The trial that was approved today is really a single agent in a category of agents that I think have been in the press quite a bit lately, and a lot of patients may have heard about them. Seth described them earlier. They're really drugs that target a pathway that allows the body's immune system to recognize or not recognize cancer as a foreign invader. There is what we call a **checkpoint** or a pathway that basically makes your cancer cells appear invisible to your immune system, and this new category of drugs, which have somewhat complex names and somewhat hard to pronounce names, are actually ways of turning off that checkpoint and making the cancer cells become more visible to the immune system.



The broad category is called **PD-L1 or program cell death ligand number 1, or program cell death inhibitors**. You'll hear that in the newspapers. Tomorrow morning, you'll probably pick up multiple newspapers and see that this drug was released. It's a member of that family. They are a new form of immune therapy. They're drugs, but they allow your immune system to recognize cancer as foreign, and really allow your immune system to fight cancer better. They're being tested. There's at least four or five of these agents made by multiple different pharmaceutical companies that are being tested really in all phases of bladder cancer, and you're going to see them come out more and more over the next two to three years, as either adjuncts to standard chemo, or as a backup plan if standard chemotherapy does not work.

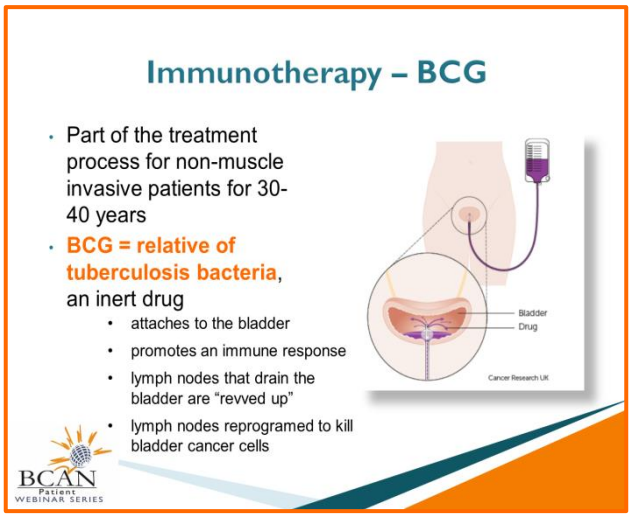
Dr. Seth Lerner: There's already a lot of experience with these drugs and other kinds of tumors, so one or more of these drugs is going to be approved for melanoma, for certain kinds of lung cancer, now for kidney cancer, and so what's really neat is the medical oncologists are typically the ones that give these drugs, because they're given intravenously, already have a lot of experience with it, and the early results that led to the approval for this particular checkpoint inhibitor showed astonishing results with just six to eight weeks of treatment.





Oftentimes, the people that responded to the drug responded very early, and those responses were sustained, in some cases for 12, 15, 18 months. Quite frankly, I don't think that we've seen a drug have that profound an effect when it works- that early and that sustained, with what I think most people would feel is a modest risk of side effects. Now, the overall benefit was really only accrued to about 15 to 20 percent of patients, and now the question is **can you identify who those patients are by looking at the tumor**, like Jim said, for expression of the PD-L1 ligand.

It turns out that, in tumors that express that, those patients tend to have a higher probability of responding, but you still see responses in the patients who don't have that ligand, so trying to understand the biomarkers that are associated with these dramatic responses is a very important part of the search.

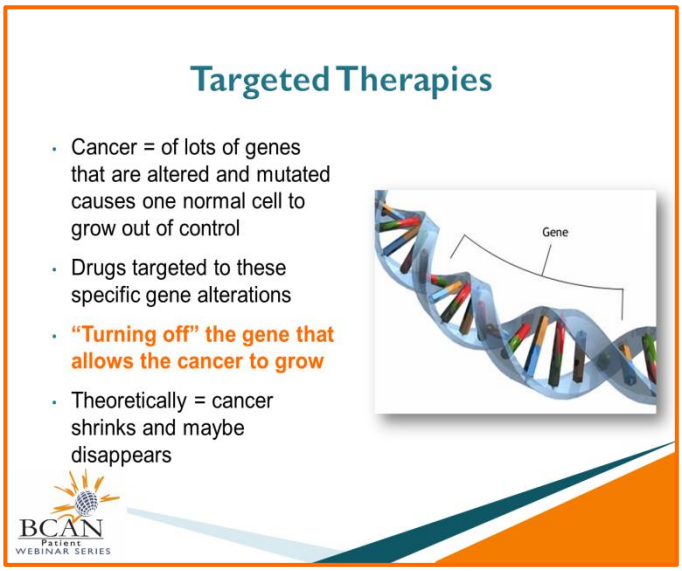


If you go to the earlier stages of non-muscle invasive disease, immunotherapy has been a part of how we treated patients for 30, 40 years, since the approval of BCG. **BCG** is a drug that's put inside the bladder. It's **a relative of the tuberculosis bacteria**, the bacteria are not quite inert, but they don't cause a systemic infection, but they attach to the bladder and then promote an immune response. The lymph nodes that drain the bladder get revved up because of the BCG vaccine and turn around and go kill the bladder cancer cells. Immunotherapy's really been a part of our treatment for a very long time, and so there's studies that are looking at drugs that mimic the effect of BCG.

I mentioned before about ways to improve the immune response from BCG. Now, what you're going to see is that checkpoint inhibitors combined with BCG to overcome some of the immune resistance that occurs inevitably with treatment. Immunotherapy is a big part of what we've been doing for a long time, and now we have this other piece to try to reactivate the immune system, if you will. Very exciting.

Moderator: It is an exciting thing to know that there's a lot going on in this particular area and, as you pointed out, there's still a lot more that we don't know about the benefits and how it works. Again, more reasons to be part of a clinical trial. We'll move on and talk a little bit about some of the targeted therapies that are being studied, particularly for muscle-invasive bladder cancer.

Dr. Seth Lerner: What is a targeted therapy? Probably the simplest example would be- and this kind of got everybody excited about bladder cancer, is the cancer is comprised of lots and lots of genes that are altered or mutated, and that's what causes the once normal cell to grow out of control, and essentially that's what cancer is. You can look at certain genetic alterations, and now there are drugs that are specifically targeted to those gene alterations. You have a target, and you have a drug that's specifically designed to go after that target, and if that gene is driving, if you will, a lot of the growth of the cancer, and you can target it and turn it off, then theoretically, the cancer will shrink or potentially disappear.

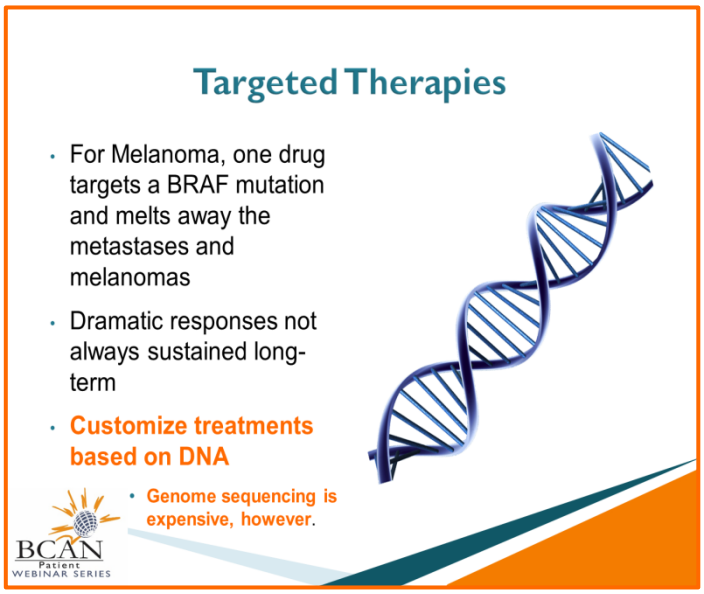


There's a wonderful story in melanoma about a drug that targets a BRAF mutation, and when the tumor expresses that BRAF mutation and you give the drug, the metasteases and the melanomas melt away. Again, you see these very dramatic responses to these targeted therapies. The challenge is that they're not always sustained long-term. There was a big splash made about two years ago because there was a drug called everolimus, which was approved for kidney cancer treatment, that was clinical trials of everolimus and patients with advanced bladder cancer.

As it turned out, it was a negative trial, in the sense that it didn't meet the efficacy bar that was set out, but there was one patient who had an extraordinary, dramatic, complete disappearance of all of her cancer, and it was sustained, I think for a year and half, two years. They went back, and they sequenced her tumor, and found out that the tumor was expressing this gene alteration in a gene mTOR, and that's exactly what everolimus targets.

You had this very dramatic example of an effective targeted therapy, and now there's many, many more examples of that. This is kind of where understanding the genetic alterations of a particular cancer may help us identify drugs to target an individual patient's tumor, so called personalized medicine.

Dr. James McKiernan: You imagine that each individual patient's cancer is perhaps similar appearing, but might actually have some pretty different underlying mechanisms of how it was created. Being able to look deeply into the DNA of the tumor or the protein of the tumor, which is actually the effector arm of how the cell works, and coming up with what's unique about any individual's tumor is really the cutting edge of where we are now, because there could be a thousand different treatments for bladder cancer patients, but as a doctor, we can't really figure out how to pick one and apply it to the right patients. Being able to customize therapies using targeted interventions is the next frontier.

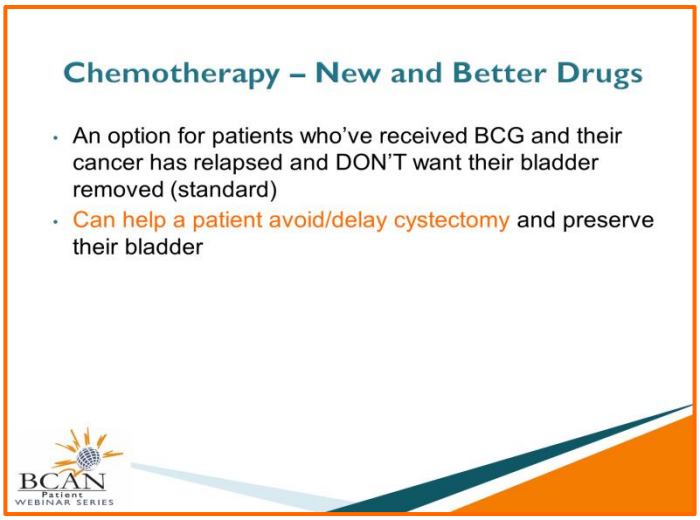


It's actually a fairly controversial one, **because it might be extremely expensive**, for instance. It might take a lot of time, and it may not be practical to do this on a large scale, but the ability to go to a center and have your entire genome sequenced to figure out exactly what's different about your cancer cells compared to everyone else's, and then sit down with a menu of options and say, "Well, these are the two standard drugs, but it doesn't look like either one of them would work for you, so we're going to try a new drug," is what's oftentimes referred to as **precision medicine, or personalized medicine**, and that can occur in a clinical trial, and may one day become the standard of care.

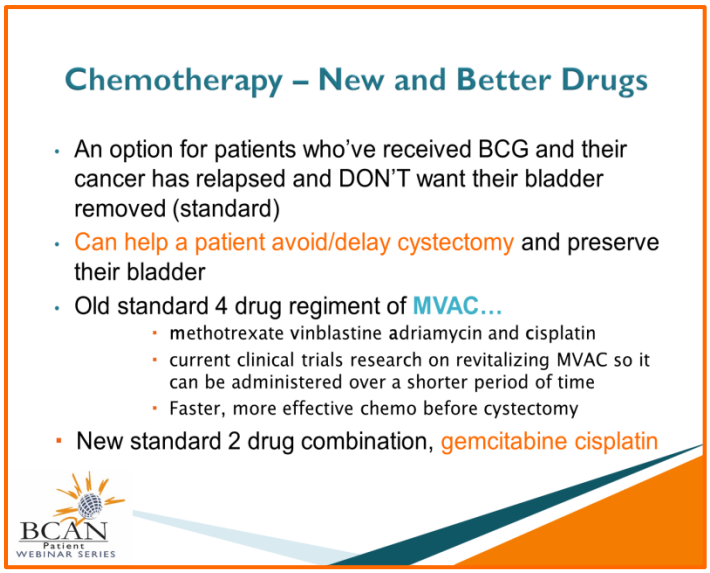
Moderator: Are there any new things that are out there being examined in the chemotherapy area, because we know that sometimes patients do get chemotherapy along with some other treatment?

Dr. Seth Lerner: Dr. McKiernan has spent a good part of his career developing new chemotherapy drugs for non-muscle invasive disease.

Dr. James McKiernan: In the setting of patients who've received BCG and the cancer has relapsed, one of the standard options is to remove the bladder. Oftentimes, patients don't want to necessarily do that for stage I cancer, so we've worked pretty hard, both in the laboratory, as well as in the clinic trying to figure out ways to target either targeted therapies or traditional chemotherapies, which are really chemical-based drugs that are not so specific, and put them into the bladder through clinical trials, both phase I and phase II clinical trials, and they've been relatively effective in certain situations.



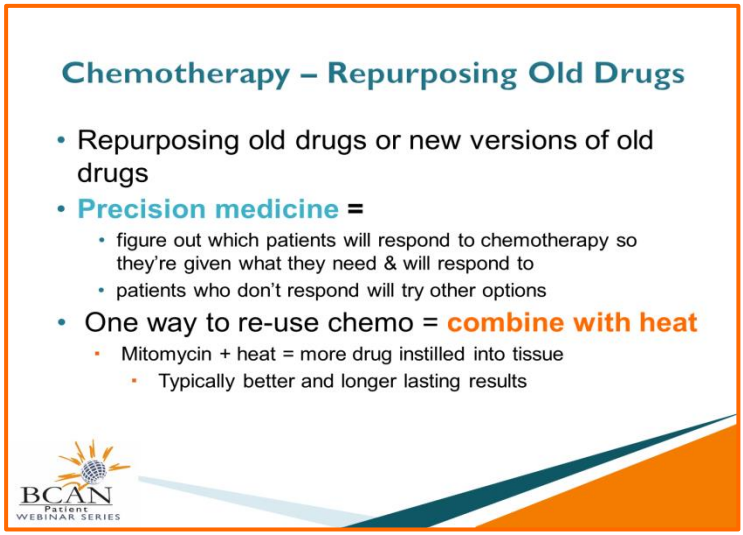
Again, that doesn't work for everyone, but oftentimes **can help a patient avoid cystectomy or delay cystectomy** until sometime in the distant future, and thereby preserve their bladder.
I think in muscle invasive cancers, the traditional chemotherapies over the past 20 years have moved from a standard four drug regimen of **MVAC,** which stands for methotrexate vinblastine adriamycin and cisplatin, to a two drug combination, which has been the backbone, really, for the past 15 years of all chemotherapies called **gemcitabine cisplatin.**



More recently, there's been a fair amount of clinical trial research on revitalizing the original formulation of MVAC, but in a way that it can be administered over a shorter time period, and it's oftentimes referred to as dose dense or accelerated MVAC, and this is now starting to see a resurgence around the United States and Europe, particularly for patients who are facing neoadjuvant chemotherapy, which means chemotherapy prior to bladder removal surgery, or cystectomy. This can actually allow the patient to get an equivalently effective dose of chemotherapy conducted over a shorter period of time and move on and have the surgery relatively quicker.

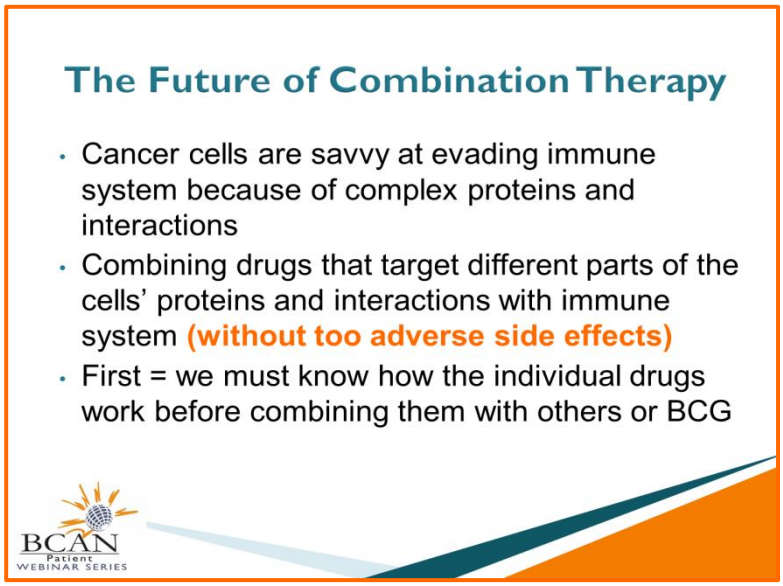
Dr. Seth Lerner: That's been a potential game changer, and also, patients tend to tolerate it a bit better. I think that what you're hearing about is sort of repurposing old drugs or new versions of old drugs, and, as I mentioned before, now- I like the term **precision medicine** that Jim mentioned, trying to figure out who are the patients that actually are going to respond to these chemotherapy drugs so that we're really just giving patients the drugs that they need and are most likely to respond to, and then taking patients for whom those drugs are not going to work, and trying different therapies or doing clinical trials, say for targeted agent.

I think that the field of non-muscle invasive bladder cancer, where we're instilling drugs in the bladder directly, you're seeing all kinds of research in terms of new kinds of treatments, not chemotherapy drugs per se that directly kill cancer cells, but drug delivery systems that can get a novel kind of treatment, say a gene therapy treatment, into the bladder cancer cells, using other ways to get a drug in there using various toxins to kill cancer cells. Again, another way of repurposing chemotherapy is to give it combined with heat. If you give, say, a drug like Mitomycin, which is a staple of chemotherapy delivered into the bladder.

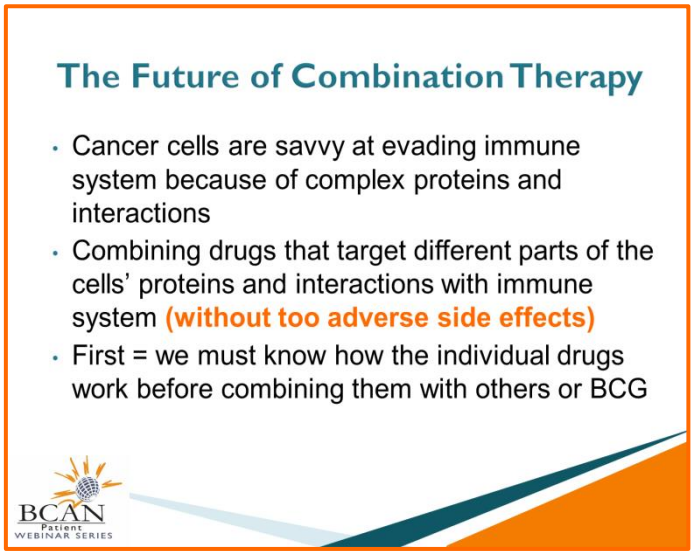


If you give it with heat, and there' a variety of different ways to heat up the bladder safely, you get more drug into the tissues, and more drug means typically better and potentially longer lasting results. There's a lot of really exciting stuff going on with chemotherapy, both old drugs and new drugs.

Moderator: Can you maybe summarize just one or two key takeaway points about clinical trials that are doing experiments in understanding combinations of therapy, just one or two brief points on that.



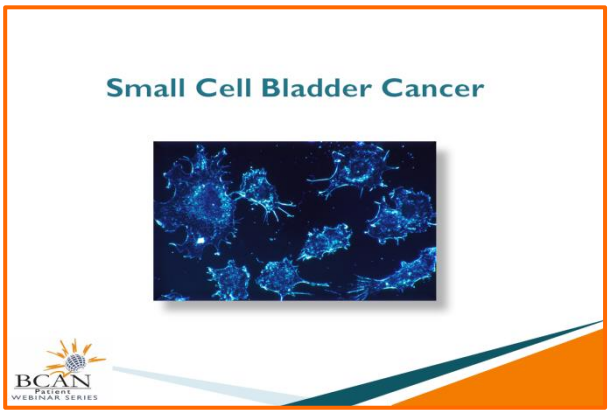
Dr. Seth Lerner: I guess one thing to think about, and I think Dr. McKiernan alluded to this earlier, we'll use the example of the new immunotherapy, these checkpoint inhibitors, so, right now, clinical trials are looking at one particular drug in this space. The future is going to be combining drugs that target different aspects of the immune regulatory system. It might be apparent that these cancer cells are pretty savvy at evading the immune system, and it's a very complex interaction of proteins that are expressed on the cancer cell and proteins that are expressed on the immune cell.

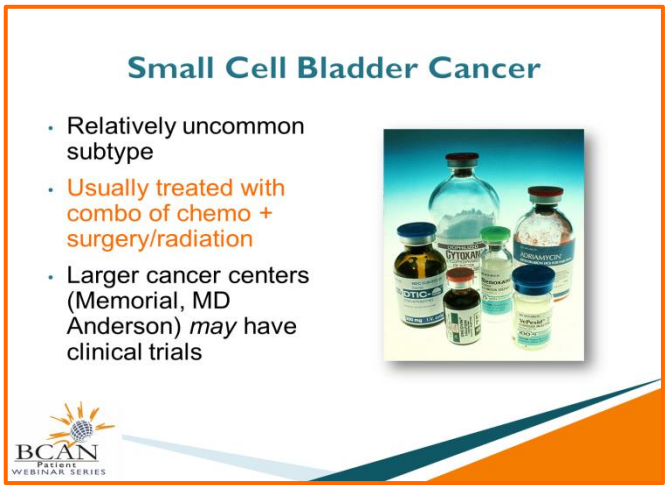


It's a very complex interaction, and targeting one of those, we see can work and be effective in some patients. But being able to target multiple parts of that pathway with different drugs as long as the side effects of the drugs don't become too much of a burden on the patient, so combination immune therapy has been tested already in organ sites like melanoma, and it's going to be happening in bladder cancer, but first, what we have to do is understand how these single drugs work, and then we can also combine single drugs with BCG to make the immune system work even better. Those are just two of a lot of examples of potential ways of combining treatments.

Moderator: I did have one question that came in. Do you know of any clinical trials that are specifically focused on small cell bladder cancer?

Dr. James McKiernan: I'll just say for the audience, small cell bladder cancer is a relatively uncommon subtype of bladder cancer, generally treated with a combination of chemotherapy and/or surgery and radiation. Because it's relatively uncommon, I don't know of a large trial that's going on right now to test any new agents.





Dr. Seth Lerner: There's a trial at MD Anderson that's asking a question about preventive brain irradiation because of the aggressive nature of small cell, there's a tendency for widespread to multiple organ sites. The more common type of small cell is seen in lung cancer, where spread to the brain is common, and they've sort of addressed this question of how to prevent that, so there is a trial at MD Anderson asking a question about brain irradiation.

People are trying different chemotherapy combinations, but as Dr. McKiernan mentioned, because it's a relatively uncommon tumor, you might see clinical trials at the large cancer centers like Memorial or MD Anderson, but most other sites are unable, because of the numbers. I will tell you one fascinating thing that will be coming up soon, and it's actually already been looked at by another group, is we're going to have a pretty good understanding of the molecular features of neuroendocrine tumors. I think that that, potentially, may lead to some work in the laboratory that potentially could lead to new treatments. That's a bit in the future, but very exciting for patients who happen to have this particular type of bladder cancer.