TREATMENT TALKS

What you need to know about intravesical therapy to treat bladder cancer

BCAN
Bladder Cancer Advocacy Network

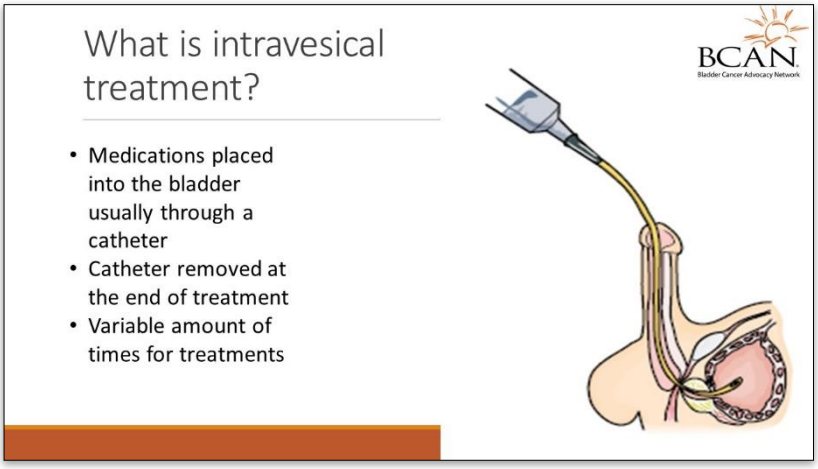
Leading the way to awareness and a cure

Stephanie Chisolm: My name is Stephanie Chisolm and I'm the Director of Education and Research with the Bladder Cancer Advocacy Network.We know there's certain types of bladder tumors are hard to remove using surgical procedures like a TURBT, particularly flat tumors like carcinoma in situ. Some tumors are also likely to recur after an initial resection. In these cases, medications that destroy the cancer cells can be placed directly into the bladder, which is what we call intravesical therapy.

Meet Our Presenters:

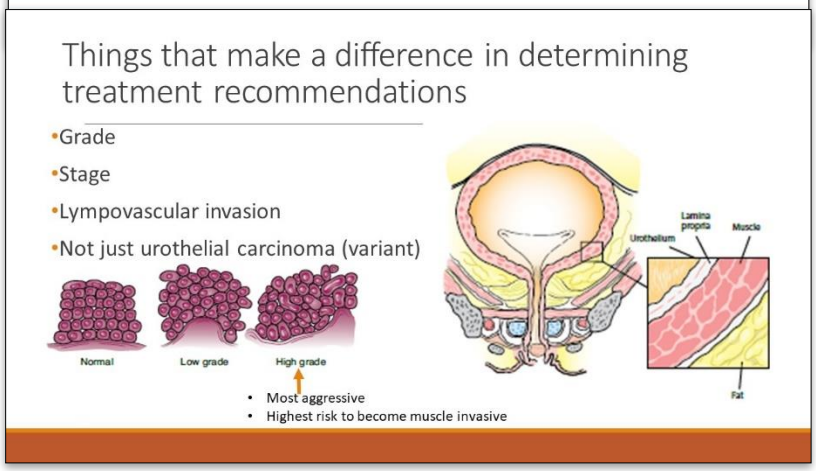
Dr. Janet Kukreja: Dr. Kukreja is a urology specialist in Aurora, Colorado. She has over 11 years experience in the medical field. She graduated from the University of Kansas School of Medicine medical school in 2010. She's very passionate about offering advanced technology and care to patients with neurologic cancers. She is joined by her patients, **Judy Walker** and **Jay Powers.**

Dr. Janet Kukreja: Well, thank you for that wonderful introduction while we're getting that settled. All right. So I'm going to spend about 15, 20 minutes doing an overview of intravesical treatments. So we're going to talk about what non-muscle invasive bladder cancer is, what the FDA approved medications are for non-muscle invasive bladder cancer, questions to discuss with your provider, future intravesical treatments.



So, as Stephanie alluded to, intravesical treatment is medication that's placed through the urethra using a catheter. So you can see here in this diagram, this is the catheter going in. This is the bladder here and then this is the treatment going in. All of these treatments, usually the catheter

comes out at the end of the treatment. And each treatment has its own variable amounts of time that the liquid needs to be in the bladder for it to work.



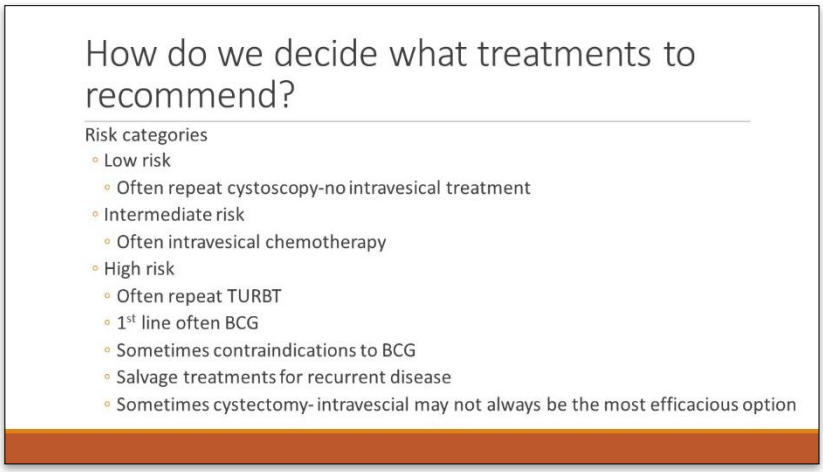
Dr. Janet Kukreja: So how do we decide what treatment to offer and recommend? So there's a few things that go into bladder cancer treatment. So important thing that you might hear your urologist talk about, and that you should know about your bladder cancer is what grade it is. So there's two grades, so we have low-grade and high-grade.

The low-grade is one that just grows into the bladder, but doesn't really have the ability to grow through the bladder wall. Whereas the high-grade is most aggressive and has the ability to grow through the bladder wall and become muscle invasive.

The stage is how far the tumor has spread into the bladder wall. So you may have a high-grade tumor that's just in the urothelium, or the lining of the bladder. And that's usually a stage A. If it then goes into the lamina propria, which is this little thin layer over here, underneath the urothelium, that's a stage one. And then the stage two is when it gets into the muscle here. And that's not the subject of this talk. And usually we don't use intravesical treatment for that.

So how do we decide what to recommend? So with that grade and stage, we develop risk categories. So the low risk ones, we actually usually don't recommend any intravesical treatments, we usually just do a cystoscopy at three months. And then usually once a year after that, as long as it's the first time. Then if it recurs quickly, or there's multiple spots of the low-grade cancer, we call that intermediate risk. There's all other things that make intermediate risk. Often that's intravesical chemotherapy. Usually, we don't use a BCG for that.

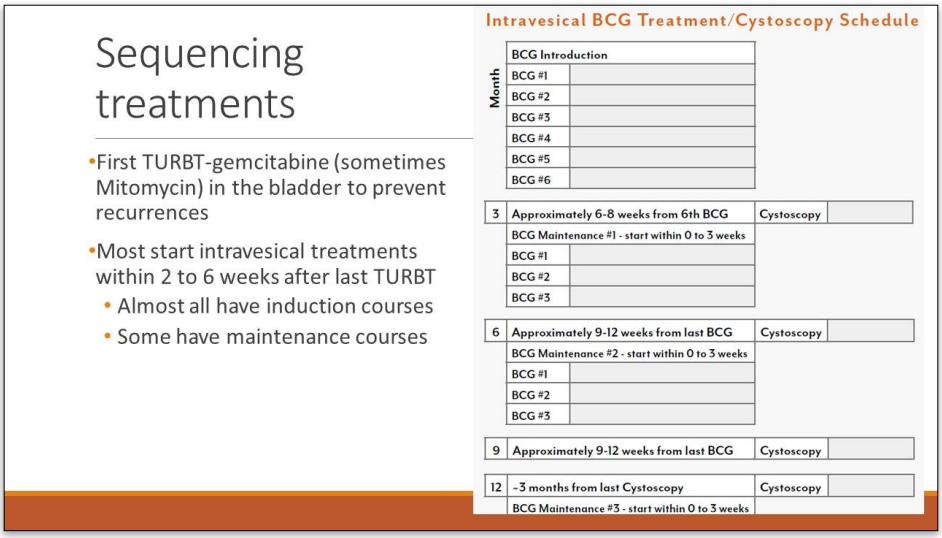
Dr. Janet Kukreja: Then we talk about the highest risks, and that includes the carcinoma in situ. So anything that's a high-grade tumor, that's a larger tumor, multiple high-grade tumors or recurrence within a year of initial diagnosis, those all fall in this high risk category. Oftentimes part of standard of care that your provider will recommend is a repeat TURBT before you start intravesical therapy.



First line for these high risk tumors is often BCG, and we're going to talk more about BCG. There are definitely some contraindications to it. And then after the BCG, if that does not work, there are salvage treatments for recurrent disease. Now keep in mind, there are some times where intravesical therapy might not be the answer. So there are some times where a provider may recommend cystectomy at some point down the line or upfront.

So intravesical therapy is usually just part of the treatment plan. You still need routine cystoscopies, often urine cytology or other urine biomarkers are used and then CT scans as well.

So, sequencing treatments, so most providers offer some sort of chemotherapy in the bladder initially. So it is an intravesical treatment right after they do the initial TURBT or bladder tumor resection in the operating room. Then after that, most of the intravesical treatments will start about two to six weeks after TURBT. So if you need a second TURBT it's usually two to six weeks after that, to let the bladder heal a little bit.

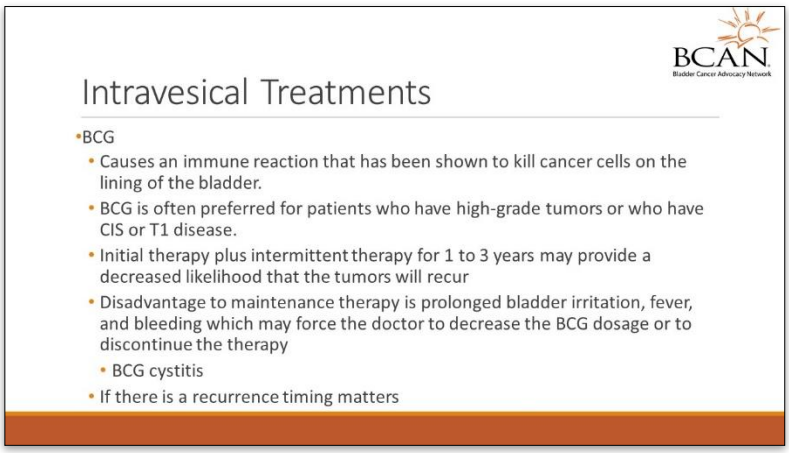


Almost all the intravesical therapies that I'm going to talk about have what we call an induction course and then a maintenance course. So over here on this side of the screen, you'll see we have an induction course and this is just an example of BCG therapy. So the induction course is usually six treatments, so once a week for six weeks. And then at three months, it goes once a week for three weeks, and then that repeats itself.

Dr. Janet Kukreja: So some of the intravesical treatments we're going to talk about, so I'm going to talk about BCG, and then some chemotherapy options. Gemcitabine, mitomycin and then some combination chemotherapy options.

So let's start with BCG. So BCG, I think is probably the most popular for the high risk disease. What BCG does is it goes into the bladder and actually causes an immune reaction in the bladder cells and systemically. So it activates the immune system to attack the cancer cells. This is actually one of the original immunotherapy. So we'll talk a little bit later about immunotherapy that goes to the IV. But in the bladder, this is the original immunotherapy.

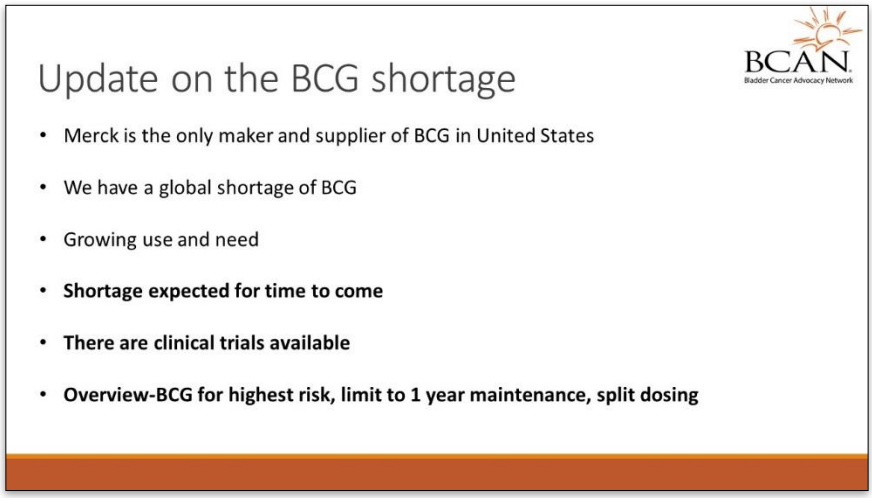
So, the side effects of BCG profile are a little bit different than the chemotherapy side effects because it does activate the immune system. Anytime we activate the immune system we do see often low-grade fevers. Most of the time this resolves on its own. Occasionally, there's a high-grade fever. Occasionally, there's what we call BCG cystitis where the bladder has a severe reaction to the BCG.



But most of the time, by far the most of the time it's lower urinary tract symptoms that patients experience. So increased urinary frequency, some burning when you pee, that type of stuff.

Dr. Janet Kukreja: So this is the induction and maintenance course, and a lot of questions that were submitted before the program were about what happened if BCG fails treating the bladder cancer? And the bottom line is it all about when it recurs, how much occurs and the provider's interpretation of what's going on in the bladder.

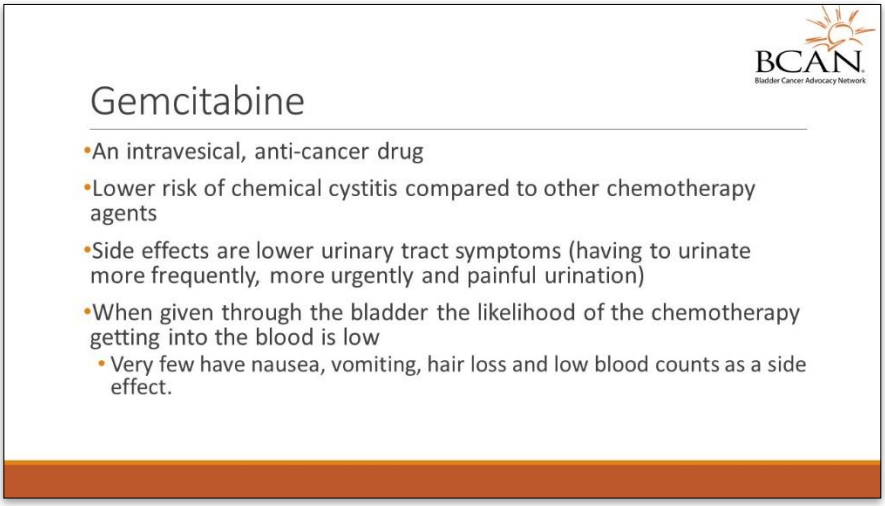
So a little bit on the BCG shortage. So there's actually a great resource on the BCAN website about the BCG shortage. Why do we have the BCG shortage? So Merck is the only maker in the United States for BCG. There's very high standards for when they create a batch of the BCG. And so if the BCG fails any of those quality checks as they go along, that batch fails, and it takes several months to make one batch.



In general, we have a global shortage of BCG. There's growing use and need. We are working on currently getting other BCGs approved in the United States, but they have to be quality BCGs. And so they are being studied in randomized controlled trials to bring them in eventually, but the shortage is expected for time to come. Merck announced within the last year that they are planning on increasing their BCG production. But it takes a lot of time to build these factories to make the BCG.

There are clinical trials available if BCG is not available to you. And there's been a lot of modifications in BCG usage recommendation with the help of the Bladder Cancer Advocacy Network, with the American Urological Association and Society of Urologic Oncology, all have said, "We need to focus our BCG on those that are at the highest risk." Right now maintenance is usually limited to one year. And for those that do have BCG, a lot of people are doing split dosing. And this is all to try and conserve BCG so that anybody that needs it can hopefully get it.

So the next thing I'm going to talk about is gemcitabine. So this is an intravesical treatment that is an anti-cancer drug. So, traditionally, this was a drug that was administered through veins, but we use it directly in the bladder to treat bladder cancer. This medication often is used right after the transurethral resection of the bladder tumor. However, it can be used later on down the line.

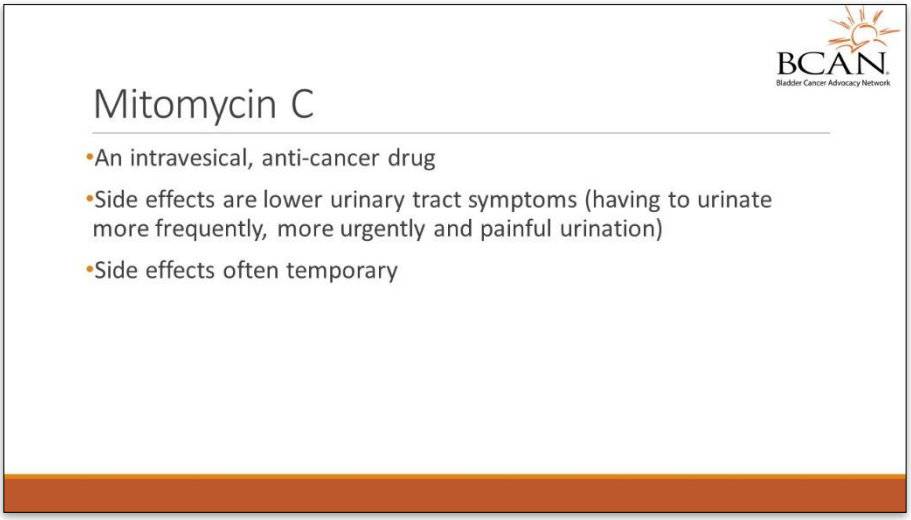


So some people are using it in the maintenance setting if they don't have BCG for maintenance, and

then some people are also just using it for recurrence after BCG. And if no BCG is available, a lot of people are using the gemcitabine because there's usually easy access to it.

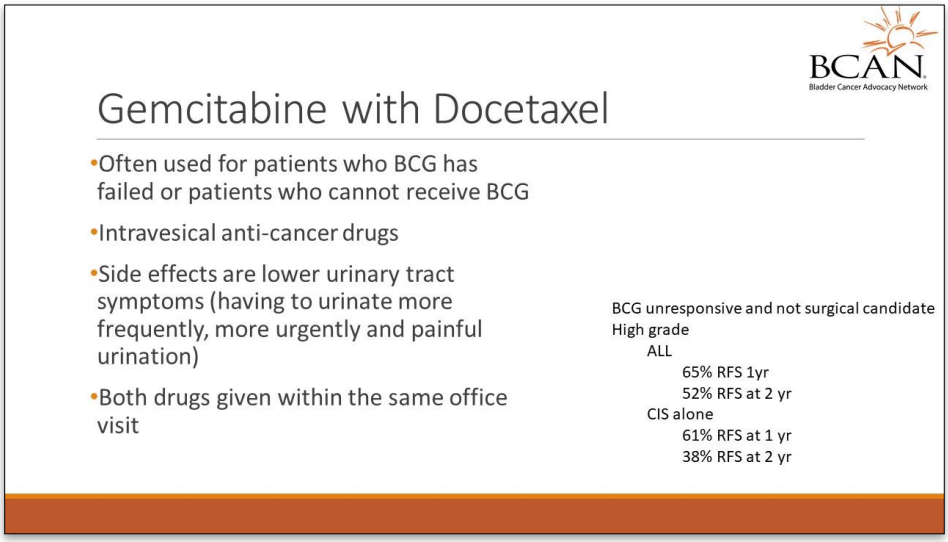
Dr. Janet Kukreja: The side effects are very similar. Lower urinary tract symptoms, urinating more frequently, more urgently and painful urination. This medication has the lowest risk of causing these severe cystitis. The severe cystitis you can see with BCG, one of the other drugs that I'm going to talk about in a second, and it can really cause chronic problems with the bladder. But again, those are rare. When this is given, even though it's a medication that can get into the veins, for the most part it doesn't. So very few patients have nausea, vomiting, hair loss or a low blood counts as side effects of this medication.

The next medication we'll talk about is also an anti-cancer drug called mitomycin-C. This one has more severe lower urinary tract symptoms and is a little bit more harsh on the bladder. The side effects are often temporary, but occasionally, this is one of those ones that can cause that severe bladder reaction.

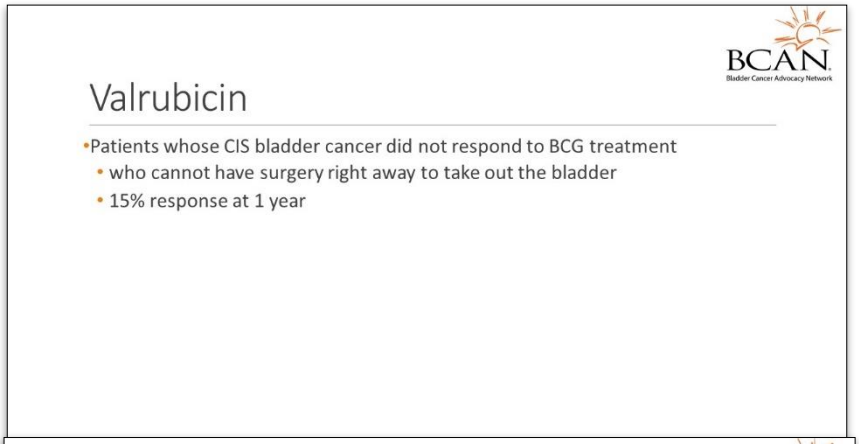


There have been studies of this mitomycin-C being heated and it does appear that it's more effective when it's heated. However, that severe cystitis reaction is much more likely in these patients that have the heated mitomycin-C. So about 40% of people that get the heated mitomycin-C have somewhat of a reaction and about over 10% are actually quite severe reactions.

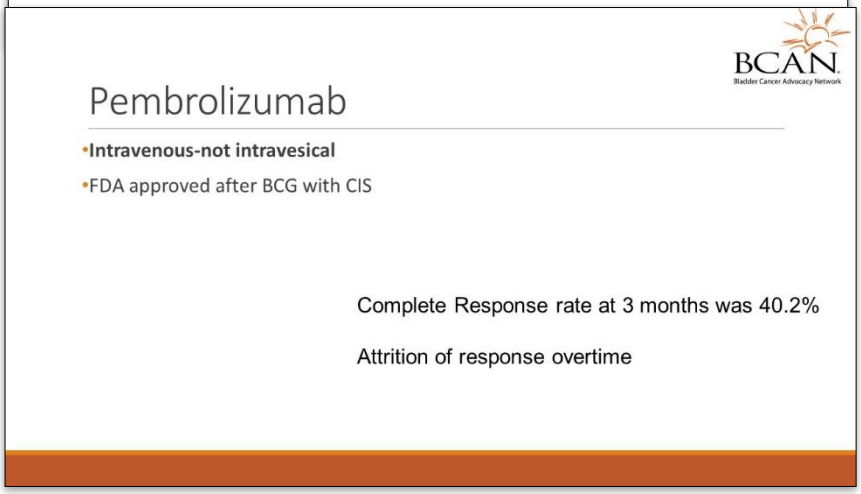
So a combination that we have begun using and is pretty common across the country right now is gemcitabine with docetaxel. So this is that medication, the gemcitabine and the docetaxel is also an anti-cancer drug, using this really in patients where BCG has failed, or patients who cannot receive BCG for multiple reasons. Some of those reasons, some people that have transplants can't receive BCG, if they're on certain medications or have certain autoimmune diseases, often we recommend not doing BCG.



Dr. Janet Kukreja: This has the same side effects gemcitabine, docetaxel. The lower urinary tract side effects, often we can give some medications to help change the acid-base balance of the urine and can decrease the side effects of these. We give both of these drugs in the same office visit, so it's the same six week induction. The maintenance is a little bit different. Often we'll do once a month of one to two years after the induction.



So valrubicin. This is a medication that is used really in patients who had carcinoma in situ in their bladder that didn't respond to BCG. And really we reserve this for patients that can't have surgery. And I would say it's an available drug right now. I'm going to show you a chart in a few minutes, it's not a super effective drug, though. But it is one that has FDA approval for bladder cancer treatment.



Pembrolizumab, this is actually not an intravesical treatment. And I think one of the important things when you talk with your provider, knowing what intravesical treatments that are out there are very important. But also knowing when an intravesical treatment is not the answer is also important.

So this is FDA approved for that carcinoma in situ that we talked about after BCG treatments. The side effects of this are autoimmune side effects. So this pembrolizumab does the same thing that BCG does, it actually activates your immune system. But this is given through the vein. So it activates your immune system quite broadly, to fight the cancer cells, and it's used in a lot of different settings for cancer right now. But it can over activate your immune system and your immune system can attack your colon, your lungs, your liver, all sorts of things. And so this requires usually very strict monitoring.

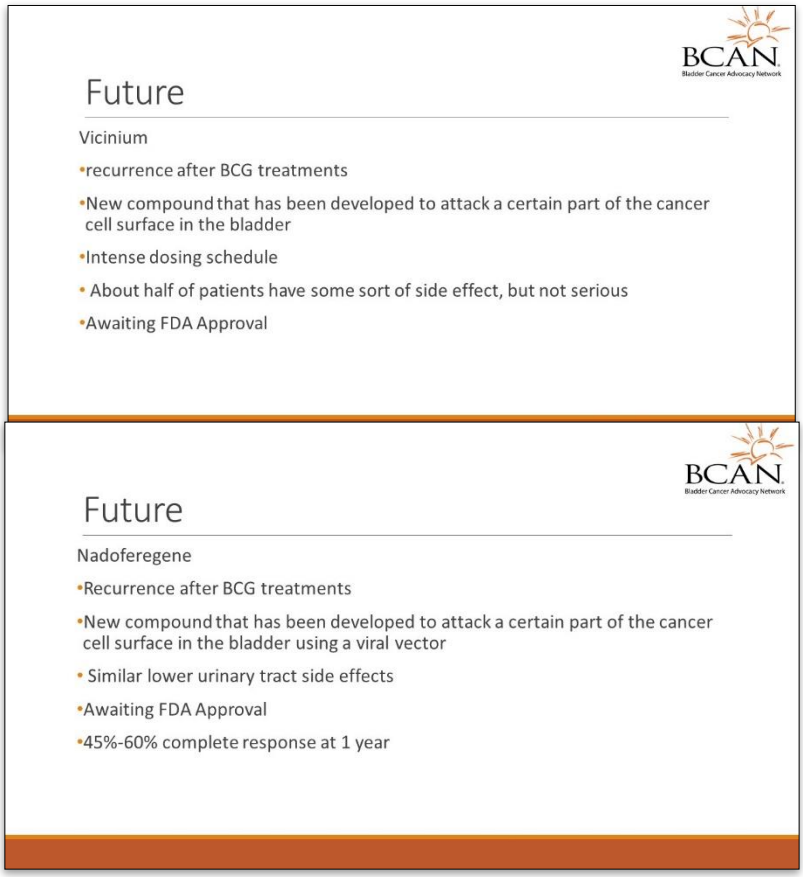
So BCG maintenance is our most effective that we have. So BCG plus maintenance, is the most effective that we have. So, at three months we take a look in the bladder, about 80% of people will not have a tumor. At two years, about 60% of people will not have a tumor. Now if you have a tumor recurrence often we can consider what we call BCG reinduction. So that means we just start that BCG process all the way over. And that has about a 35% chance of us taking a look within that two years of not seeing another tumor. BCG for people that respond initially don't have at three months, don't have a tumor at two years, the rate at five years is about 40%.

So we look in the bladder for five years and of 10 patients, six patients will have a recurrence but four will not have a recurrence.

Dr. Janet Kukreja: And then valrubicin, only 7% of patients, so seven out of 100 have no tumor recurrence by two years. So since we have these other things available, often I recommend these other things.

So the pembrolizumab, the one that we talked about is actually not in the bladder. That's 40% will not have a tumor at three months and 20% will not have a tumor at two years. And now these ones they're not FDA approved, but these are chemotherapy drugs that we really rely on clinical trials rather than FDA approval. So mitomycin-C that has pretty promising response rate, so 60% at three months don't have a tumor and 40% at two years don't have a tumor.

Gemcitabine is a little bit lower, but when we combine that gemcitabine to docetaxel, numbers are a little bit better. Vicinium and nadoferegene, I'm going to talk about in a minute. Those are both treatments that have FDA approval pending for non-muscle invasive bladder cancer. So the vicinium has pretty good three months chance of not having a tumor in the bladder, so 40% chance no tumor in the bladder. But that drops off it at two years with a 15% chance.



And then nadofaragene, you'll hear this called a bunch of different names, but I'm just going to call it nadofaragene. At three months, about half of patients do not have a tumor in the bladder. And then two years, about a quarter of patients do really well. The numbers are still pending on this. This is some of what we call phase three trials. So like the end stage trials before FDA approval are still pending. So these numbers could certainly improve and from what we hear we expect them to see higher rates of not having bladder cancer recurrence.

So future, so we had the BCG-PRIME trial and this trial just closed last month. And this is the one that we looked at a strain of BCG from Tokyo, and are hoping that this will be something that we can bring into the United States to treat bladder cancer and decrease that BCG shortage.

Vicinium, so this is used for recurrence after BCG treatments. This is a new compound that's been developed and it attacks certain parts of the cancer cells surface in the bladder. It has an intense dosing schedule. So it's twice a week for six weeks, and then, or for 12 weeks, and once a week for another 12 weeks. And then it's like every other week for three years. So it's a lot of visits to the urologist. But, it does have some efficacy. And the side effects are not serious, most patients do pretty well with it.

And then the second one, nadoferegene, this is also used for recurrence after BCG treatment. It's a compound that attacks part of the cancer cell surface using a viral vector. And it has the similar lower urinary tract side effects. And I think most of us are anxiously awaiting the FDA approval for this.