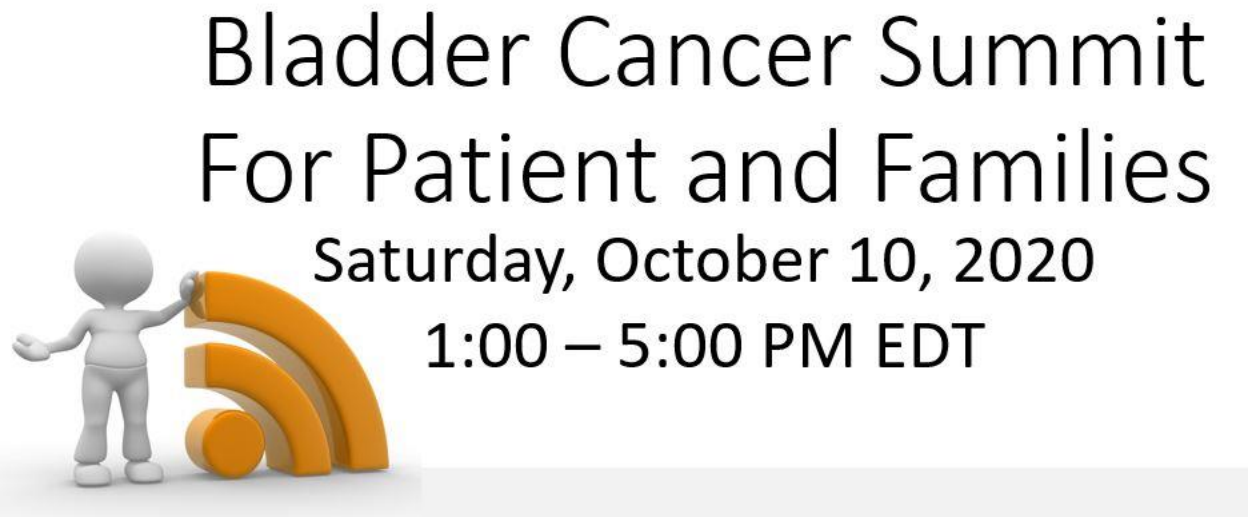



## PART 4: Bladder Cancer – New Developments and New Treatments

**Stephanie Chisolm:** The next panel is going to be chaired by Dr. Gary Steinberg. And let me go back to this. And so, Gary Steinberg is a professor and the director of the Goldstein Bladder Cancer Program at NYU. And he is joined by an international panel: Dr. Max Kates, who is at Johns Hopkins; Dr. Molly Ingersoll, who is a PhD at the Institute Pasteur in France; Dr. Kala Sridhar, who is up in Toronto at Princess Margaret Cancer Center; and Dr. Josh Meeks at the Feinberg School of Medicine in Chicago. So thank you all for doing this. I'm going to turn off my sharing screen, and that way we can just see you all talking..

**Dr. Gary Steinberg:** Thank you. Let's get started. That was a great talk, and we're going to probably expound and expand on a number of the things that were in the great talk that was just given. We're really going to want to try to focus on some of the innovation that we're seeing. You know, bladder cancer is sure seeing an explosion of what we call translational research, or in the old days we used to call it a bench to the bedside. But what we're seeing is research being done by a variety of physicians, medical oncologists, scientists, radiation oncologists, pathologists, and radiologists, who are actually doing research that is relevant to humans. When I was a resident, and this is a generation ago, we were doing a lot of animal studies. And we're still doing animal studies, but we're very rapidly bringing the knowledge we're learning from these animal studies to patients, and to improve patient care.

One of the areas that has really exploded in the last five, ten years, is the area of non-muscle invasive bladder cancer. Non-muscle invasive bladder cancer. And that's the stage where about 75% of the patients initially present. And I'm going to ask Dr. Max Kates and Dr. Joshua Meeks, two young, outstanding, urologic oncologists, who are truly leading the field. Not only are they providing outstanding clinical care, but they're also actively involved in the bench, using a number of different experimental techniques, finding out new information, and bringing that rapidly to the patient. So I'm going to start with Max. And Max, why don't you give us a little background of what you're looking at in the laboratory and how you're translating that to patients.

**Dr. Max Kates:** Sure. Thank you, Gary. That sounds great. I think maybe I'll focus on some of the work that we've done with chemotherapy, because I know that some of the others have a lot of experience with immunotherapy. So, chemotherapy given into the bladder for non-muscle invasive bladder cancer is perhaps one of the oldest remedies for early stage bladder cancer. It was started giving in at least the '70s, if not earlier. And some of the most important trials were in the early '80s. And some of them panned out. Actually, one of the first chemotherapies that's FDA approved is valrubicin for non-muscle invasive bladder cancer. Some of you may have gotten that therapy. It's not given too, too often anymore. But, one of the problems when you give chemotherapy, which is meant to be given into the vein systemically, is that when you give it into the bladder, over 99% of it is immediately urinated out.

And so, one of the things that my lab did in conjunction with, actually, a nanoengineer group at Hopkins, is we started looking at, "How can we improve uptake of chemotherapy into the bladder?" And we were not alone. Over the last five to ten years, there have been many different ways that groups have tried to do this. And what's really cool is, in the last few years, they've reached late phase trials. So, I don't have a mouse, but just kind of going from the bottom, the bladder neck, all the way around, there's various modalities, including gels. So getting these chemotherapies in gel form, that when they're at room temperature, they're liquid, but when they get into the bladder, they form these gels. And so it acts like a depot release of chemo. There's a drug for upper tract urothelial cancer that just got FDA approved for that, UroGen MitoGel,  what we used to say and is getting actively looked at for low grade bladder cancers.

There are other types of releasive chemotherapies.  like, I explain it like the NuvaRing for birth control, where it's not giving birth control, it's delivering chemo in the bladder. So this is what this product Taris is doing. This is at the center of your screen. And some of the other work, a lot of it out of Europe, is heating the chemotherapy. And what that does is it increases the permeability in the bladder, so the bladder can easily absorb the chemotherapy. So, what's really cool is that these have all been done in the lab. My lab has been looking at cisplatin and docetaxel, two chemotherapies to get into the bladder. But all of these modalities have really sort of revolutionized the capability of the standard chemotherapy. So really, what is old is now becoming new again, and we're seeing FDA approvals in these spaces. So, as Gary said, there's direct translation from bench to bedside, and we're really starting to see that. So I'll just stop there, and we can get into more of this. But I want to expand.

**Dr. Gary Steinberg:** That's great. So Josh, you've been doing a tremendous amount of work looking at the genes that cause bladder cancer, and that are involved in bladder cancer. Can you tell us a little bit about where we are in terms of the genetics of non-muscle invasive bladder cancer? As you know, the TCGA and BCAN was actively involved in identifying the genomic variability and abnormalities in muscle-invasive bladder cancer, but you've done a very nice job looking at non-muscle invasive bladder cancer. Can you expound a little bit on how you see that fitting into what Max has talked about, and new treatment for non-muscle invasive bladder cancer?

**Dr. Josh Meeks:** Well, thank you Gary, and thank you Stephanie, for the chance to be involved today. I think, really building off of what Max has described as far as all the new possibilities for therapy, we've kind of approached non-muscle invasive bladder cancer as a one size fits all.

You know, if you have high-risk disease, you get BCG. But we know, again, for example, for T1 patients, almost a third of them are not going to respond to BCG and 15% will have progression on BCG. So, if we knew that ahead of time, we could save a long amount of therapy in which, potentially, we have better

options to give patients. And again, as Max has shown us, there's a lot more coming down the road, and a lot of exciting opportunities to potentially treat patients better. So really, our work is trying to figure out, again, who's going to respond to different therapies, and if you're not going to respond to the standard of care, then our hope is that we can do some kind of tests to figure out what other therapy you would respond to.

And we're trying to use our patients' tumors as an example to really look at that. And the only way that can be done is by looking at large data sets of patients to figure out, again, who's going to respond and who's going to not respond. And what we find is that there's not one, "If you have this gene, then you will," or "If you don't have this gene, then you won't respond." It's actually a very complicated system. But again, if you can start putting patients or their tumors into different bins, then we have a better sense, potentially, about how to better treat people. And again, to skip those general steps and go right to, "This is the best therapy for you." So, I really think that's one of the things that I'm the most excited about, is pairing our new therapies with a better understanding of this cancer, so that we can do more precision-based therapies for our patients, again, limiting toxicity and getting right to hopefully curing people.

**Dr. Gary Steinberg:** Josh and Max, what do you think about the IV immunotherapies that we're looking at for non-muscle invasive bladder cancer? How does that all fit in?

**Dr. Josh Meeks:** Well, I would say that I'm excited that we have more options. Again, prior to this, really the best advance we had was your work with Valstar (Valrubicin) so we have more options for patients. And clearly, there's a group of patients that respond. We definitely see long-term, at a year, there's a 20 to 25% response rate for pembrolizumab, for example. But the question is, "Who are those folks?" And you'd love to identify them. So to me, that really is a great example of Keynote 57 is a success, but what else can we learn from that? From a biomarker perspective, it's unlikely to be the same things that we see in the metastatic setting. Even PD-L1, which we think was the biomarker, right now we know that's not the case, and certainly not going to be the case for carcinoma in situ.

So I think they play an important role. Personally. I recommend those therapies for a few patients. Usually, those folks who have a hard time making it to our institution in Chicago. Right? So getting into the city is not easy. Right now, it's dose, potentially, every six weeks. So that's certainly an option for folks, again, and a quarter are going to respond. Additionally, other folks can't hold different therapies in their bladder. So all the things that Max showed, you have to often be able to hold those. If you can't do that, then pembrolizumab is a great option for patients. And the third, I'd say, is people who have tumors, potentially in the upper tract, that BCG can't get up there. We don't have anything right now for high grade, upper tract, for example, in someone with a solitary kidney. So again, those are sort of the three populations. But again, Gary, I talk to every patient about it, and it's a decision that, individually, people make together. And we kind of go down that road and see if that works for them.

**Dr. Gary Steinberg:** Max, you did a very nice study looking at why patients may not respond to BCG, what patients may respond to checkpoint inhibitors. Can you talk to us a little bit about that study? I believe it's been published in the last couple of months.

**Dr. Max Kates:** Sure. Yeah. So one of the critical questions I've been working on, Josh and Gary, all of us have been working on, is trying to understand, number one, who are those patients who may not

respond well to BCG? And just as importantly, what are the scientific sort of mechanisms of not responding to BCG? And what we found is that, for a portion of patients, one of the mechanisms of resistance to BCG appears to be through the PD-L1 pathway. First of all, I completely agree with everything Josh just said about how he discusses this with his patients. But, one thing I would say is I think that the way I interpret it is that immunotherapy, immune checkpoint therapy is a home run for the patients that it works for. It's probably a single for us as a whole. But, one of the things that's exciting for us is it will be a scaffold for us to figure out, can we use that to combine with some of these other drugs that are coming down the pike? And that's also what its FDA approval has allowed for. So that's how I would respond to that.

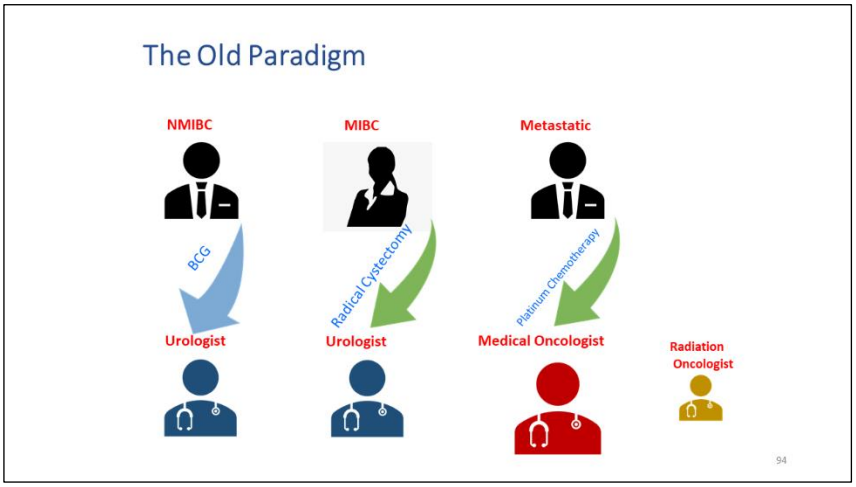
**Dr. Gary Steinberg:** Great. Kala, let's kind of change directions a little bit. Let's start talking a little bit about muscle-invasive bladder cancer, and more importantly, what are we doing today for preserving the bladder?

**Dr. Kala Sridhar:** Okay, perfect. So, I think that there's been a lot of progress in the state of muscle-invasive bladder cancer. So, this is really cancer that's invading into the muscular wall. We know that this is both a local disease, but also a systemic disease. So it's really important to combine both systemic treatments, as well as local treatments. So one of the things that there's been a lot of focus on for years and years is this concept of having a cystectomy, so patients having their bladder taken out with some lymph nodes removed, as well. That's always been seen as the gold standard. And, for patients who can't have that, the alternative has typically been bladder-sparing trimodality therapy, and it's called trimodality because it a TURBT. So, maximally removing the tumor as much as you can, followed by a combination of chemotherapy and radiation, where the chemo is working to make the radiation work better, essentially. So that's called trimodality or bladder-sparing. And typically, that was reserved for people who are not surgical candidates. But we're starting to see a very significant shift in who is wanting bladder-sparing. Many patients don't want to lose their bladder. And so we're seeing this shift where younger, fitter, healthier patients are actually opting for bladder-sparing under certain caveats. You know, there are certain criteria that the radiation oncologist and the urologist together talk to our patients about it in a very multidisciplinary way to say, "You are, or you're not a great candidate for this approach." But that's probably one of the biggest things. And then the other thing I'll add to that is, we've typically given neoadjuvant chemotherapy before cystectomy. Now it raises the question, "Should we also be doing that before bladder sparing, if we think of it as a systemic disease?"

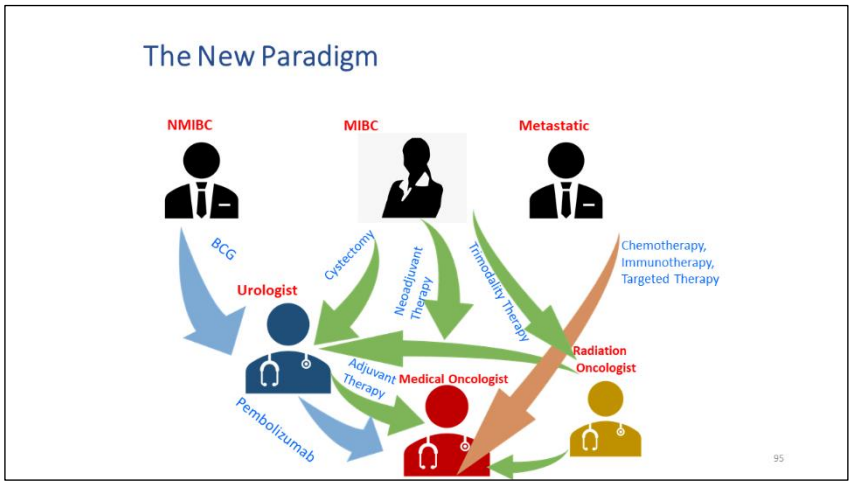
**Dr. Gary Steinberg:** Josh and Max, are patients asking for bladder preservation? And how do you approach it?

**Dr. Josh Meeks:** Yeah, I would tell you that we offer it to patients just along with cystectomy. We talk at that initial discussion about, "These are your options." And certainly, I think we put that on the table just with, again, radical cystectomy. And there's benefits of each approach, and every patient kind of makes their own decision. I would say that I agree that it's not a therapy for people who are unfit for cystectomy. Certainly I think it has a role there, but I've certainly had folks in their 30s and 40s who've elected for that, and done very well.

**Dr. Max Kates:** Josh is doing such a great job without visual aids, but I'm going to ask Stephanie to pull up the visual aid of the different doctors, the old and new paradigm, because I think that this drives home something we're kind of assuming, but talking about under the surface, which is that Gary first asked us about systemic therapy for non-muscle invasive disease. Now we're talking about radiation for muscle-invasive disease. And just so everybody looking understands, the way we used to treat this is the old paradigm was you'd see a urologist, basically, if you had non-muscle invasive disease. If you had muscle-invasive disease, maybe you'd see a urologist and an oncologist, if you were sending them for chemotherapy, which not everybody did a while back. And the radiation oncologist was sort of off in the corner.



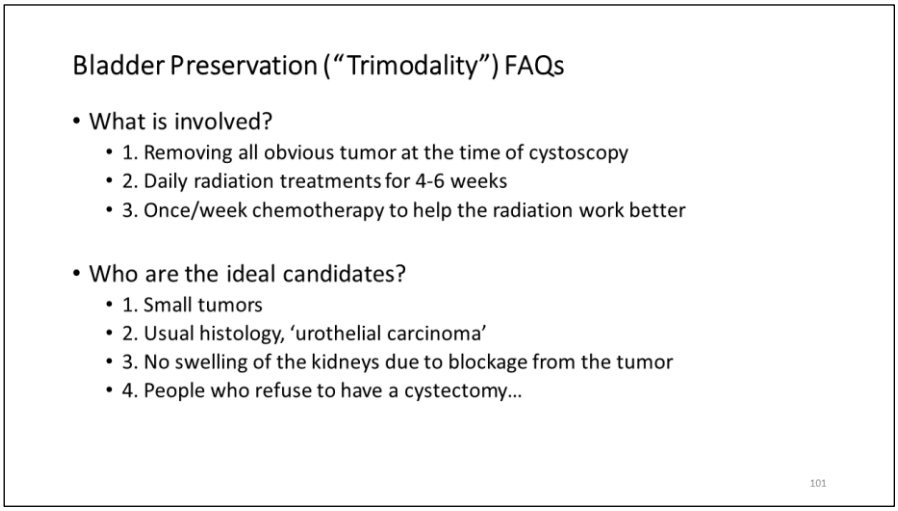

This is a very confusing slide. And that's the point, because now we're talking about giving systemic agents, often with our medical oncologist for early stage disease. For muscle-invasive disease, all of these patients should be meeting, in my opinion, with a medical oncologist to have discussions, not just a urologist. And radiation oncologists are often involved, and at some centers they're seeing every patient, as well, with muscle-invasive disease. And so, the care of the vast majority of patients is multidisciplinary now. And I would completely agree. I think that there is not one approach that's right for everybody. And so, every patient's a little bit different, and part of our job is to counsel patients about reasonable expectations, and risks and benefits of every option.




**Dr. Josh Meeks:** I've always been struck by sort of this data that half of people with muscle-invasive cancer don't get treatment. And, I think as surgeons, we have to take responsibility for that, that it was cystectomy or not. So, I think we've tried to fill that gap. And again, I think what's driven a lot of that quite honestly, especially in our guideline meetings, is patient advocacy. So, we're listening, and I think we're trying to do a better job of addressing every patient, and trying to do the best we can.

**Dr. Gary Steinberg:** Can we put up Kala's slides? Kala developed a very nice slide set for everybody. Let's see if we can put that up, and Kayla can kind of take us through some of those slides.

**Dr. Kala Sridhar:** So, I'll kind of walk us through this really quickly. So muscle-invasive disease, as I said, two options for local treatment, radical cystectomy, or, potentially, bladder preservation. I kind of explained how that was done, a TURBT followed by daily radiation for four to six weeks, and once per week, a little bit of chemotherapy, just to make the radiation work better. And, I think it's important that the pros and cons of each option, as we sort of discussed already, be really discussed with your doctor. Really know what you're getting, why you're getting it, and what the positives of each approach might be. If you do have bladder-sparing, it's really, really critical that you have close follow-up, because if the disease were to come back locally in the bladder, then the next step is usually salvage cystectomy. So it's important that the follow-up is accurate.




What is involved? So, we start by removing all the obvious tumor at the time of cystoscopy, daily radiation, and once per week chemotherapy.

And who are the ideal candidates? Those with small tumors, usual histology, so urothelial carcinoma, either pure or variant, but not the pure variants. We have very little data in that group. No swelling of the kidneys because of blockage from the tumor, and really, people who refuse to have a cystectomy. And I think, we alluded to this earlier, that if someone is adamant that they're not going to have a cystectomy, I would rather have them do something along the lines of bladder sparing than nothing at all.

**Dr. Gary Steinberg:** Let's stop a little bit. Let's talk about, and I know Molly's going to have a lot of information, but we're changing paradigms, and patients come to see us and say, "Oh, I really don't want chemotherapy." Is immunotherapy a substitute? And how are we using immunotherapy in the muscle-invasive bladder cancer prior to metastatic disease?

**Dr. Kala Sridhar:** Yeah, I was just going to say, it's a really, really great question. So immunotherapy, we know, is a way of helping the body to better recognize the cancer, and it is approved in more advanced metastatic disease. In the setting of muscle-invasive disease, we have a couple of trials that have reported. Two single-arm trials, ABACUS and PURE, if you're wanting to know the names, that really looked at giving immunotherapy upfront. So, two to three cycles of immunotherapy. The patient populations were slightly different. One was a cisplatin-eligible, and one was cisplatin-ineligible. And the response rates were encouraging, somewhere in the range of about 40% or so with pathological down staging, which means there's still some residual non-muscle invasive tumor sitting probably at around 50%. And it seems that in the PD-L1 positive population, they do a little bit better. These are, I caution you, single arm trials, so I don't think they're completely practice-changing just yet. We really need the randomized trials. That's in the neoadjuvant setting.

In the adjuvant setting, it's a little bit murky, because we have one trial that looked at giving patients PD-L1 or PD-1 inhibitors after surgery and after neoadjuvant chemotherapy and didn't show a benefit. But

then we also have a press release saying that, "Maybe there is a benefit." So we have to wait to see where things are for the moment.

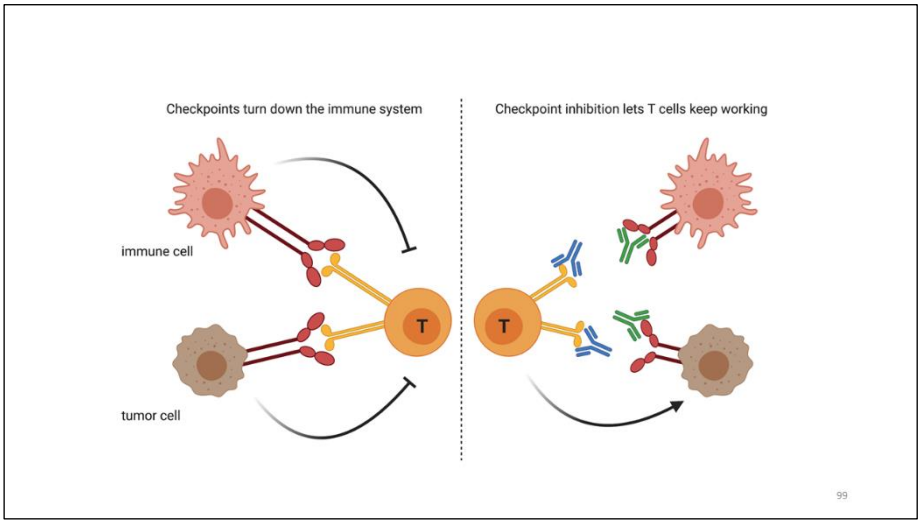
**Dr. Josh Meeks:** Again, I think the data is still out there. We've had two major 1,000 patient trials that have just read out in the last year, showing that adding chemotherapy and immunotherapy probably doesn't give you the boost that we would hope it would. But there is some signal that, maybe in the earlier setting, there is a benefit. And again, many of us have trials open to sort of test that question of, "If you add immunotherapy to neoadjuvant chemotherapy, can you improve the response?" So I think that the question is still an important one, and still not answered. I think we all would agree, though, one of the benefits of immunotherapy is, if you a responder there's some durability there. And so, I think really, the question is trying to figure out who's going to respond, because again, if you respond it seems to be a durable response.

**Dr. Max Kates:** Yeah. I would echo that. I'm cautiously hopeful about this press release that was just referred to two weeks ago is about nivolumab being given after surgery. And one of the challenges as a surgeon is, when we give people neoadjuvant chemotherapy, so chemotherapy before surgery, and then we remove bladders and there's still a fair amount of disease left. To have that conversation with a patient that, right now, the standard of care is getting CT scans periodically. And so, I'm very hopeful as a surgeon, that will continue to be positive moving forward, because to be able to offer immunotherapy in that setting of there still being residual cancer after the bladder is removed. And the bladder is very hopeful to me. So I'm looking forward to getting more data.

**Dr. Kala Sridhar:** I just want to also reiterate for everybody that neoadjuvant chemotherapy with platinum-based chemotherapy remains the standard of care in the neoadjuvant setting. We know patients who have a complete pathological response, that leads to improved overall survival. That is the standard of care. You should be asking your doctor, "Can I have some chemotherapy before surgery?"

**Dr. Gary Steinberg:** Molly, we've been talking a lot about immunotherapy, and if we can put up Molly's slides so that we can have Molly explain to everybody what immunotherapy, what immunology is, and why are we talking about it as it relates to cancer?

**Dr. Molly Ingersoll:** think this is a slide that I made just to try to demonstrate why we want to employ immunotherapies. The idea here is, if you look on the left side, essentially what happens is in a normal immune response in the body, you'll have an immune cell and it'll interact with a T cell. Eventually what needs to happen is the immune response needs to be turned off. We can't have a constant immune response in our body. This is a natural interaction. These interactions are mediated by molecules called checkpoint



molecules. Checkpoints essentially, they'll turn down the immune response. That's what this arrow with a flat line means, that this is a way to turn off the immune system.

But it turns out that tumor cells also will express some of these checkpoint molecules, and when they do this, they can turn off the T cells that we need to fight against the tumor. The idea here is immunotherapy essentially targets these checkpoint molecules.

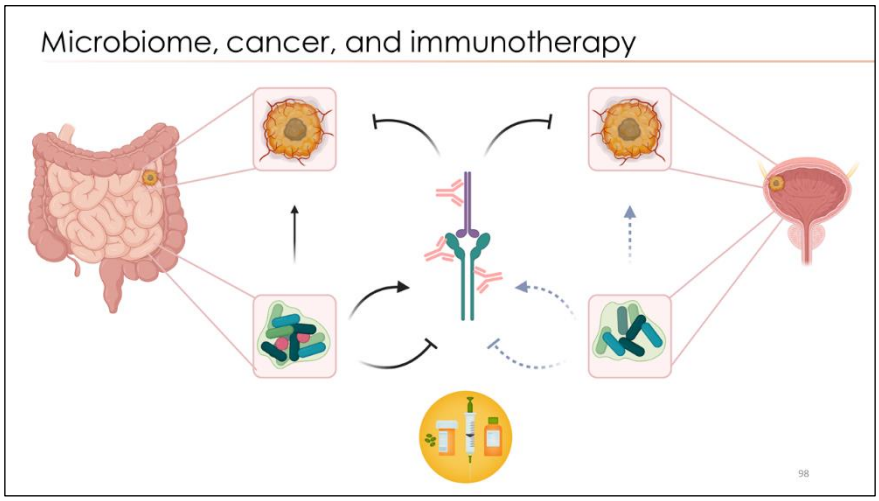
What you can see on the right side is these antibodies, which are here in blue or in green, what they do is they actually get between these molecules, and essentially what they're doing is they're cutting off the communication. What this does is this allows the T cells to keep working because they're not getting the signal that says, "Turn off, you're finished." So the T cell can keep working.

I think what is really interesting and what we're starting to see now, and Josh and Max referred to these trials, is changing the timing of immunotherapy such that it's coming earlier. What this does is it's really keeping the immune system turned on at a time when you have agents like chemotherapy that are killing the tumor cells.

Now, we have these immune cells that will recognize these dead tumor cells, and instead of turning off the T cells, they're going to keep them on, they're going to tell them what cells to target. When you add in checkpoint inhibition, these antibodies, the T cell can keep working.

**Dr. Gary Steinberg:** But Molly, again, we're talking about a lot of the innovative work that you've done. Tell us about what the microbiome is. I think it's a word that people are reading about and hearing about. How does the microbiome have anything to do with cancer?

**Dr. Molly Ingersoll:** With cancer? That's a much bigger question. That's definitely something that my lab and my team are working on, but many scientists are working on it, and many clinicians as well. Maybe if we go to the slide before. What I can start to tell you about, again, is if you look on the left side... You hear a lot about the microbiome. What does the microbiome mean? The microbiome essentially refers to all of the different microbe, that can be bacteria, but it also can be viruses or fungi, that live in and on our body. The largest population of the microbiome they live in, that's in the gut.




A lot of what we know about the microbiome and its interaction with cancer and its interaction with immunotherapies come from studies that look at the gut and also cancers that are related to the gut.

Essentially what I'm trying to illustrate here is, you may have a tumor in the gut and you'll have all of these different microbes. You'll have, like I said, bacteria or viruses, and essentially what happens is these microbes can interact with the tumor directly. In some cases, they can actually provide signals that help the tumors to grow. In some cases, they may inhibit that tumor growth. We don't understand exactly why these relationships happen or which types of microbes will inhibit or promote tumor growth.

In addition, we know for instance that some of these microbes will actually go and live inside of the tumors and this is because the tumors can provide nutrients for them. First we have that first level of interaction where the microbes may be directly interacting with the tumor cells, but we also know that the microbes can interact with immunotherapy agents.

What's really quite interesting is three different clinical studies that were done at three different sites, all found that there was some microbes, or a mix of microbes essentially, could be found in some patients that respond to checkpoint inhibition or immunotherapy, and certain patients did not respond.

What I think is really interesting about these three studies is they didn't find the same microbes, they didn't find the same mix of microbes. Essentially what that means is we do know that the microbiome in general can have an influence on the success of immunotherapy, but we still don't entirely understand what that mix is. Essentially it means there's not one single type of bacteria, for example, that is specifically good or specifically bad. But I think future studies will help us understand what that mix is and what are these important interactions.

I think one of the other important things to understand is while we know that the microbes that live in the gut can influence a tumor directly or can influence how well checkpoint inhibition or immunotherapy works, we don't have a really good idea yet whether these interactions also occur in the bladder. That's what I'm trying to illustrate on the right side.

Essentially, the bladder also has a microbiome, it's less complex and we know less about it. We don't know, for instance, if this microbiome interacts directly with tumors in the bladder, we don't know for instance, if this microbiome can interact with immunotherapy or with chemotherapies, or really with anything that's put into the bladder. We don't actually know for instance, and I don't have an arrow even to illustrate this, but we don't know if the microbiome that exists in the gut can interact or impact therapies that are specifically in the bladder.

We suspect that all of these different interactions may be occurring, there are a lot of ongoing studies right now. But I think this is an important aspect to take in when we start thinking about new future therapy approaches.

**Dr. Gary Steinberg:** Molly, what about antibiotics? How do they affect all of this and the microbes in cancer?

**Dr. Molly Ingersoll:** Certainly. Those three studies that I referred to, at least one of them demonstrated that antibiotics could impact how well a patient would respond to immunotherapy. In general, it's antibiotics tend to be limited before immunotherapy, certainly before BCG therapy, for instance. I would say that we don't know enough to know with any certitude what types of antibiotics

may have a positive impact or a negative impact or really no impact. I think that's going to be a future area of study.

**Dr. Gary Steinberg:** We talk about immunotherapy, we're talking about the microbiome, how does the genetics of bladder cancer, or the genome, interact with the immunology of cancer, with the microbiome? Or these separate?

**Dr. Josh Meeks:** Boy, that's a really important question, Gary. I just don't think we have the answer now. I'd love to hear other people's thoughts on that, but I do tend to think that one of the things that really determines how we respond to BCG is less to do with the tumor and potentially more to do with the patient, their age, their immune system, how well it works or not.

Then again, I'd love Molly's thoughts on how well the microbiome fits in with that, because I just don't think we know. I know people are looking at that, certainly at University of Chicago. That's one of the questions that's being investigated, but I don't think we really know at this point.

**Dr. Molly Ingersoll:** I would absolutely agree. I think that we can consider three global concepts that impact how we'll respond to a therapy or to a vaccine or to any sorts of treatment. The first is genetics. Certainly our genetic makeup will determine how strong our immune response is, for example.

The second is likely microbiome, but because of the complexity of the microbiome and the fact that microbiome communities are different in different places in the body, those things are really challenging.

The third I think is environment. We know that certainly what you've been exposed to in the past shapes your immune response. Trying to dissect all of these different aspects of how well you will respond to a disease or to a therapy is incredibly complicated, but I've seen some amazing studies coming out, so I know that that work is moving forward. Our understanding is getting better.

**Dr. Josh Meeks:** Can I ask you what about antibiotics? I know there was some concern about how antibiotics is changing our flora and could potentially affect our response. Any thoughts or any data coming up that you've seen or heard for bladder cancer?

**Dr. Molly Ingersoll:** With respect to antibiotics, I haven't personally seen anything that I think is truly definitive. Different types of antibiotics will eliminate different types of microbes, but typically big classes of them, so it's not with any sort of precision. I think because we haven't really performed enough studies to directly target different types of microbes in different places, I think it's really hard to say exactly how this impacts response to therapy.

**Dr. Kala Sridhar:** Molly, I was just going to say, I think there's also a question on the chat about probiotics and what do we think about things like kombucha, if I said that right.

**Dr. Molly Ingersoll:** I haven't seen any very good clinical trials that directly support a strong benefit, but also I haven't seen anything that have suggested that there's any sort of detriment into this.

I think the best advice would be talk to a physician when you make a decision like this and to ask them what they think how that will impact your health in general.

**Dr. Kala Sridhar:** I think that's fair. I think that's true of all alternative treatments. I always tell my patients to be cautious, because when we're adjusting treatments based on side effects or what have you, we don't know if it's a side effect from the treatment, a side effect from the alternative treatment, or some combination of both.

So think it's really critical, especially as we're evaluating new drugs. For example, the new checkpoint inhibitors, they can affect the liver function. So can some of the alternative treatments. I think we have to be really careful how we navigate that.

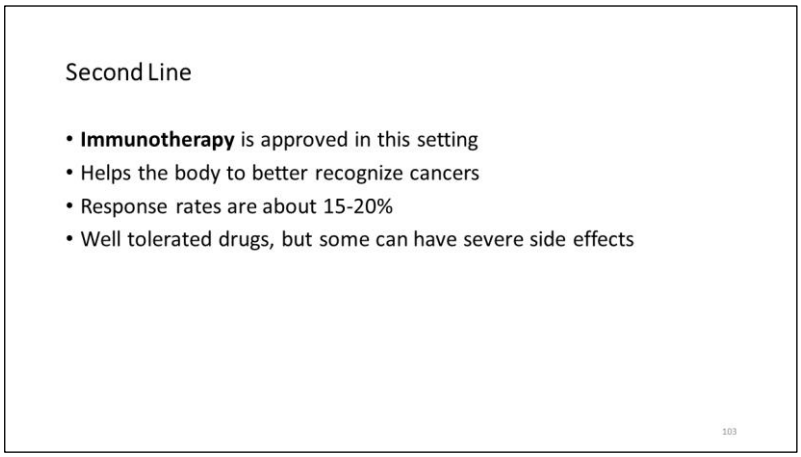
**Dr. Molly Ingersoll:** You pick up a great point. We know that some of these immunotherapies will actually have detrimental impact on the gut. We know that that arises because of changes in the microbiome, especially when you're trying to, I think, I guess, trying to ameliorate those types of adverse events, certainly you would want to be as informed as possible.

**Dr. Gary Steinberg:** Kala, can you show us your slides? Let's talk about the newer things in metastatic bladder cancer. We've had a number of reports and new drug trials that are really game changing in metastatic bladder cancer.

**Dr. Kala Sridhar:** Okay. Standard first-line treatment for metastatic disease remains chemotherapy. I know a lot of patients aren't keen on chemotherapy, but it is still the most effective drug that we have.

In the frontline setting standard chemotherapy is where we go, gemcitabine-cisplatin is commonly used. We don't tend to use a lot of MVAC which is another four-drug regimen, but GemCis is a pretty reasonable drug.

Of course there are some patients who can't get it because of their renal function or that type of thing. But I think we've gotten actually pretty good at giving chemotherapy. Maybe one of the biggest advances we've made in oncology are actually all the supportive care therapies to help people get through. It's not like maybe 30, 40 years ago. People can go to work while they're on chemotherapy. I think those are important messages to keep in mind.



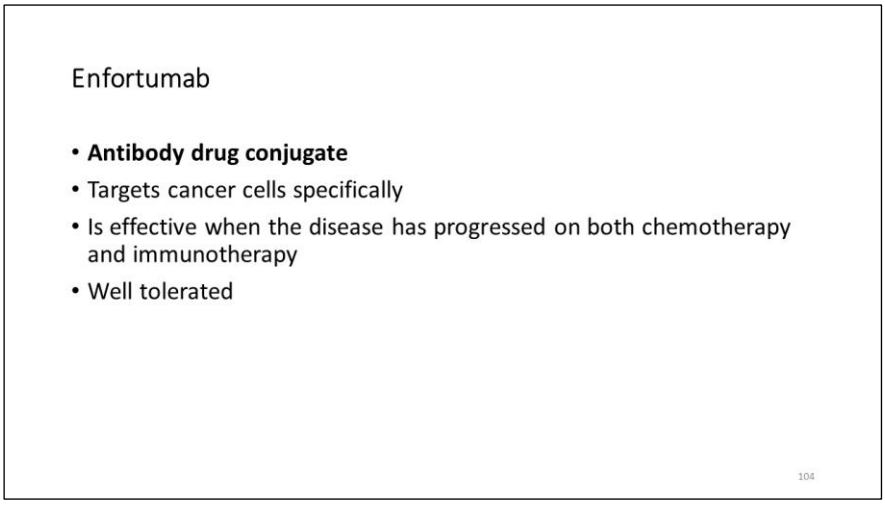

In the second line setting immunotherapy, the new checkpoint inhibitors, there's a number of them, which all probably have similar efficacy. The one that many places is approved is pembrolizumab, and it really helps the body to better recognize and attack the cancers.

As mentioned earlier, only about 15-20% of patients will respond. This is a really critical thing to keep in mind. People are very excited about

immunotherapy and I understand that, but at the same time, it doesn't work in everybody. They are well-tolerated drugs, but they sometimes can have very severe side effects, so you really need a multidisciplinary team of people, including you as a patient, to be watchful of symptoms, things like shortness of breath, cough, and some non-specific diarrhea. These things are really important to be aware of and report to your doctor.

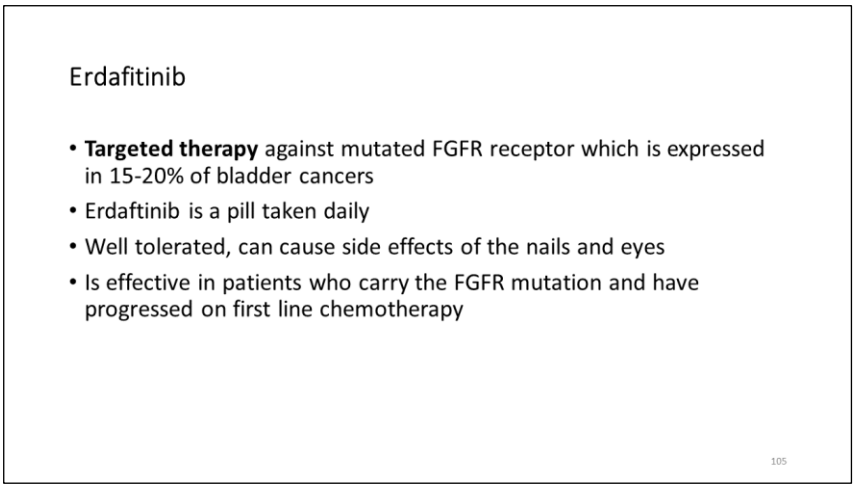
Although we have treatments for this disease, none of these treatments are yet considered curative, meaning we're not able to get rid of this disease completely and for forever just yet. But there's a lot of excitement, a lot of new drugs, and a lot of these drugs have come because of patients who are willing to participate in clinical trials. We really can't thank patients enough for walking this road of drug development.

I'll just highlight a few of them really quickly. Enfortumab, this is an antibody drug conjugate, meaning that it's like a payload example where you have an antibody that targets something in the tumor. You have a little linker and then the chemotherapy coming along. It's bringing the chemotherapy along to the site of the cancer and it tends to target fairly specifically. This drug has shown to be effective when the disease has progressed on both chemotherapy and immunotherapy.




Maybe, as mentioned earlier, they're studying it in earlier and earlier stages of the disease. It is FDA approved, but for places, for us in Canada for example, we don't have access to it. We're really trying to push forward in terms of clinical trials. Next slide, please.

Another type of treatment that it's one of the first targeted therapies that we have in bladder cancer, and really what it is is some of the cancers have certain mutations and mutations in something called fibroblast growth factor occurs in about 15-20% of patients who have bladder cancer. Erdafitinib, and this FGFR is like a signal, it tells the cell to grow. If you can actually block the signal, you may be able to block the growth of the cell.




Erdafitinib is a pill that actually targets the FGFR receptor. Of course, if you don't have the receptor, this treatment won't work. This is a fairly well tolerated treatment but can cause some unusual side effects in the nails and the eyes, and so important to talk to your doctor about that. It is, as mentioned, effective in patients who carry the FGFR mutation.

There's been a lot of talk about mutations are there in the cancer, but one of the things that we need to understand a bit better, which are driver mutations. I picture a car with 20 different steering wheels, and they're all different mutations. You don't really know which steering wheel, or which two or three steering wheels, are necessarily driving that car. You could block the steering wheel on the left, but maybe it really has no role at all in driving the cancer. That's an area of active research. Next slide.

That just gives you a little window into where we're going with some of the newer treatments. We're also looking at some combination treatments, like combining chemotherapy and immunotherapy. I think we mentioned earlier, two trials were showing that combination may not be the way to go. Probably the most exciting just published in the New England Journal was a study that said, if you give chemotherapy upfront, four to six cycles of chemotherapy, then you're able to maintain that response with a drug called Avelumab. That's probably one of the biggest advances by far that we've seen in bladder cancer over the last 30 years. That's super, super exciting.

I think that's FDA approved very rapidly in the US. We're waiting still in Canada, but this concept is definitely an important one. I'll stop there.

**Stephanie Chisolm:** What about any new combinations that you see being promising on the horizon. Is that basically it, because you didn't come through very clearly unfortunately.

**Dr. Max Kates**: Kala just gave us this amazing talk about all of the new drugs that are being developed in the metastatic disease space. One of the really interesting things that we're starting to learn is that in patients who are not responsive to BCG, not responsive to our main therapies for non-muscle invasive bladder cancer, they may be responsive to some of these systemic therapies. That's what pembrolizumab has addressed.

I just would like to ask you, as a medical oncologist, what do you think is that balance when we take drugs that are for metastatic disease that have a little bit more toxicity, patients are willing to, and I'd love to hear patient's perspectives on this at some point too, that have more toxicity because it is more advanced disease and we start taking them towards earlier stage disease, the balance of the risk/benefit changes a little bit, and how we talk to patients about that risk/benefit changes a little bit. Just would love to hear your perspective.

**Dr. Kala Sridhar:** I think it's a great question. I think one of the things that we're now having to deal with, which is actually a good problem to deal with, is this number of treatments that have shown to be active in this disease, which is new and super exciting. That's point one.

Point two, I think that what we're seeing and what's particularly interesting is drugs like Enfortumab, maybe to some lesser extent Erdafitinib. I don't have as much experience with Erdafitinib, but Enfortumab is actually a very well tolerated drug. I think as we build the experience in the advanced setting, but beyond that also build the experience in patients who are not candidates for trials, because I think there's a subtlety there where patients who are getting on trials tend to be younger, fitter, healthier. The question is, as we move this into the general population, are we seeing any red flags? Is there any concerns?

Once we've done that, or paralleled with that, I think we can now see these drugs moving into the earlier settings with perhaps a little bit less risk. But I think it's always important to discuss with patients

the benefits, the risks. Being involved in a trial is always voluntary. Going on the trial is voluntary, coming off the trial is voluntary, and we want something that's going to work. We're never going to put someone on a trial if it's not working, or they're having toxicity we'll be the first to want to take them off.

But I think it's going to be very interesting too, that as these drugs move earlier, what do we do in later stage disease? What do we do in first-line metastatic disease, if they've already had all these new drugs in the earlier setting? I think it's a great question and we'll really have to watch and see how things play out.

**Dr. Gary Steinberg:** Great. Can we now open it up to see if there's any questions from the audience?

**Stephanie Chisolm:** Yes, actually we do have some questions. There was a question for Dr. Meeks. Is anyone working on compound genetic variants of uncertain significance, for example, MSH-6 and MET, then using that information as determined for treatment options.

**Dr. Josh Meeks:** I think more and more we're sequencing tumors earlier and earlier. The problem is, we haven't had that information. Unfortunately, I think you could argue that we probably don't have that information in the advanced space where many patients we know would benefit from getting their tumor sequenced. I tend to think, again, we're not there yet. But you see more and more precision trials coming out. There's going to be better opportunities for better precision based medicine for bladder cancer.

**Stephanie Chisolm:** Great. Thank you. Here's another question. A patient has T1 high-grade and the doctor at the Cleveland Clinic recommended initial BCG, but does not have maintenance. They never discussed any type of chemo options. When they talked they said they would do maintenance if there wasn't a shortage, but he doesn't want to recommend it. Is it time to see a new doctor to get somebody who might be interested in pursuing something more aggressive like more chemo? Any of you can answer that one.

**Dr. Max Kates:** I would say that basically, if you have a good relationship with the doctor that's treating you, and the Cleveland Clinic is an amazing place, you should stick to that relationship. I never say it's wrong to get a second opinion if you want other views. Sometimes urologists, especially around non-muscle invasive bladder cancer, or like, what we used to say, two rabbis, three opinions. Sometimes it can be like that.

But no, in all seriousness, for a while we weren't able to give maintenance therapy. I suspect that because of the BCG shortage, for a while we weren't able to give maintenance BCG therapy for even high-grade T1 disease. That's how I would answer. Josh, how would you answer that question?

**Dr. Josh Meeks:** This is all BCG shortage related. Guidance from the AUA and the SUO suggest to prioritize high-risk patients and that after induction, if you don't have BCG, you should probably cut the dose to a third and a half dose. Honestly, it puts us as providers into a very challenging position of having to have that discussion with patients, that we just don't have the therapy, or enough of the therapy that could benefit them.

I tell folks, obviously having full dose BCG is better. If you can't do that, then the hazard ratios or the data on reduced dose is actually pretty almost close to being as good as full dose. Additionally, many patients don't need full dose. We often over-treat patients anyway. That's one thing.

But then if people want to go after a year, I tend to switch them to either chemotherapy with one or two chemotherapies, depending on what they feel like. But again, I've had people do maintenance gemcitabine-docetaxel, for example. Again, I think this is, as you said Max, this is a discussion to have with your physician as far as what you'd like and what you can offer and what makes sense.

**Dr. Max Kates:** We've had a lot of these discussions around maintenance recently because of COVID, because more maintenance we give the more exposures our patients are receiving. It's a very strange time with the BCG shortage and the pandemic. I think that each approach should probably be tailored.

**Stephanie Chisolm:** Here's another question. Would the new drug, Nadofaragene firadenovec, be a game changer in trimodal therapies? Any of you can answer that one. When it gets approved.

**Dr. Max Kates:** I'll answer that question because I think it's getting at a really exciting thing, which is traditionally when we think of trimodal therapy as systemic agents, radiation, and a radical transurethral resection, but we know that patients undergoing a trimodal therapy have local recurrences in their bladder, oftentimes are non-muscle invasive. Groups are starting to look at how can we avoid these local recurrences on trimodal therapy.

I think Adstiladrin (Nadofaragene firadenovec) is not the only drug that could be used in that way, but it's just a different approach. We may be thinking about it as quad modal therapy , trying to reduce local reoccurances.

**Stephanie Chisolm:** Can the microbiome enhance the effect of Keytruda or any of the other immunotherapies? I think you covered that mainly, but if you want to just expound on that just a little tiny bit.

**Dr. Molly Ingersoll:** I can speak from understanding the studies that have been put out, but I'm curious if anyone has any practical experience. What we can say is with more traditional immunotherapy with checkpoint blockade, there are aspects of the microbiome. We know we can manipulate the microbiome using antibiotics, or just look at what the content is of the microbiome in patients who respond, who don't respond, and we can say there is a relationship.

But I think that we aren't at a place where we can very specifically say these microbes are beneficial, or these microbes are interfering with these therapies. But I think we have a little bit more information. We know that certain chemotherapy agents are actually broken down by some of the microbes that are in the gut. That's something that we need to keep in mind, certainly. And by we, I mean the physicians on the panel, not me. But I just think we just don't have enough information yet to definitively say yes or no.

**Dr. Kala Sridhar:** I would completely agree with that. I think it's still early. I think it's very exciting.

And I would completely agree with that. I think it's still early. I think it's very exciting, the research, but if someone has an infection, we need to treat that infection. So patients should not avoid antibiotics because of immunotherapy not working, I think that's a really significant risk. So the microbiome is still in its infancy. There's a lot of great, amazing research going on, but we're not yet there to put that into clinical practice.

**Stephanie Chisolm:** We have time for just a couple more questions. In a patient who initially responds to immunotherapy for metastatic disease, but had to be taken off due to serious immune-related side effects. Can immunotherapy be resumed after successful treatment for the side effects? Is that something that's an option?

**Dr. Kala Sridhar:** Yeah, that's a great question. There's a lot of heterogeneity in how this is managed, cause it really depends on how you define serious.

So there's some of the toxicities that we would really not want to re challenge cause there's real risk associated with those toxicities. Other toxicities, once we've got them under control sometimes with a tapering dose of steroids and things are stable. And if someone's having a response to the treatment, we may think about re challenge, but it's really handled case-by-case basis. It's important again to talk to your doctor about what are the risks of doing it? What are the risks of not doing it? And with some new treatments coming down the line, is there an opportunity to maybe change to a different treatment?

**Stephanie Chisolm:** Okay, great. All right. I think we have time for one last question. Is gemcitabine better alternative to BCG for a Ta low grade tumor?

**Dr. Max Kates:** I'll answer that one. Yeah. So I think that the AUA has actually come out during the BCG shortage and were not typically giving BCG for low grade tumors, what would be called intermediate risk if they recur. And data out of Europe has essentially shown that chemotherapy, intra vesical chemotherapy like gemcitabine or combination intra vesical chemotherapy is more than adequate for those recurrent low-grade tumors.

**Stephanie Chisolm:** Well thank you all so very much. Molly, you are coming in from France and Kayla from Canada and Max you're in Baltimore right up the road from where I am. And then obviously Josh out there from Chicago and Gary from New York. It has been a phenomenal, phenomenal panel. We'll have that up on our website. I want to express deep gratitude because this has been fabulous. So thank you all so much.