Dr. Jennifer Taylor: We have plenty of time now to take questions. We're going to prioritize the questions that have been in the Q&A. I know there has been some discussion in the chat, which I'll try to look through and synthesize, but if you could please also transfer a question to the Q&A directly, we'll try to address some of those. One of the attendees did ask if each of you, "When you were getting BCG, was it always a complete dose?" This is definitely a big concern right now. We don't want to dwell on that issue necessarily, but just find out, each of you, if you knew you always got full dose BCG.

Doug Maclean: I did. Doug. I did.

Rick Oliver: I believe I did.

Lori Roscoe: I did not. I had multiple doses. About one and a half of my maintenance cycles were half doses.

Dr. Jennifer Taylor: This really did become an issue in 2019 and has continued since then related to production shortages worldwide. There are a lot of ongoing, active efforts to change the supply, but it's highly variable across centers, and sites, and regions of the country. There's really not a rhyme or a reason in some instances. What I will say is that BCAN, in conjunction with the American Urological Association and the Society of Urologic Oncology, created some guidance for clinicians, and you can reference that. It's readily available and pretty accessible in terms of easy to read, in terms of what is recommended.

Right now, there are some adjustments being recommended to prioritize full dose BCG for the highest risk patients, and then to use reduced dose BCG for maintenance therapy in those high risk patients. Then there's some other adjustments being made for intermediate risk patients. I would encourage you to access that. It's on the BCAN website and the AUA website. That is an ongoing thing that is being studied and monitored. There's been a great clinical trial that has just finished accruing that may give us some more answers and, potentially, another BCG strain available in the U.S., maybe within one to two years. I'm going to say one question was for Doug. "Did you have any side effects to gemcitabine and docetaxel so far?"

Doug Maclean: No, Jennifer. I thought about that when I was talking about it. I wanted to share that with people, that not everybody is as fortunate as I am. I virtually have no side effects at all. I tell my nurse that puts it in that if I don't set my timer on my phone, I would forget it was even in there, so I'm very fortunate I've had no side effects at all, and the drugs appear to be effective.

Dr. Jennifer Taylor: These two drugs are given back-to-back in the clinic, just like BCG or mitomycin. This is based on multiple centers that have done studies in patients with BCG unresponsive disease, like the condition we're talking about today. Someone did ask, "What is Keytruda?" I want to answer on behalf of that. It is pembrolizumab, and it is a systemic or intravenous immunotherapy drug that is given, typically in the U.S., by a medical oncologist. It is FDA approved now for just this entity, which is BCG unresponsive disease.

We are very grateful and happy to have more options that are not cystectomy, but it is still not something that is on the forefront of every urologist's knowledge base and toolkit, so I would say this is, again, bouncing back to the role for additional opinions. It's a complex conversation now to have with the patient with this disease state and talk about all these options. Keytruda, which is pembrolizumab. Cystectomy, which is still the gold standard sort of textbook answer. Then salvage intravesical doses of different agents like gemcitabine and docetaxel. Let's see.

Doug Maclean: Jennifer, just a quick question-Pembro is not generally recommended unless the disease has spread to other parts of your body. Is that correct?

Dr. Jennifer Taylor: Not true anymore. Originally, all of the drugs in that class, which are PD-1 and PD-L1 checkpoint inhibitors, there's a multiple of them that are available for advanced bladder cancer like you're speaking of, so metastatic bladder cancer, or bladder cancer that can't be removed surgically because it's advanced. That has been the original source of approvals for those drugs in bladder cancer, but within this year, well, 2020 I should say. Within the last year, pembrolizumab was studied in Europe and in the United States in non-muscle invasive bladder cancer, and is approved for non-muscle invasive bladder cancer that has not spread, that has come back after BCG. It does require for, say in my practice, for me to refer the patient to a medical oncologist for that discussion, to talk about the potential side effects and risks. Then I still monitor the patient with cystectomy, and so there's a lot of coordinating necessary at that point because we're no longer doing treatments in my clinic. It is a very viable option, and patients receive treatment up to 24 months, if there is response seen based on the checkups.

Another question just about the gemcitabine and docetaxel. It is given in a very similar schedule to induction BCG. First for six weeks, with weekly instillations, and then monthly. That is a similar schedule to treatment with mitomycin. Gemcitabine, or mitomycin, or this doublet we call it, with the two drugs can be used in that sort of schedule. Let's see. This was an important question. Do you guys have any pieces of advice, and I'll wait to answer myself, for a patient who doesn't have a spouse or close family for support, what can be sources for coping and dealing?

Doug Maclean: I would encourage them to reach out to the BCAN network. I wanted to talk to patients that had undergone various different treatment methods, and Stephanie was very kind to help me make connections to certain people. I found that incredibly helpful. You'll find that people quickly become friends when they're sharing personal stories about what you're about to consider undergoing. BCAN's fantastic. I have nothing but positive things to say, and I encourage you to utilize that resource.

Dr. Jennifer Taylor: I will put in a plug for the Survivor to Survivor, where survivors have been trained to be peer resources, so there is that. Then on the discussion board, Inspire, you can also ask a question and look for guidance, look for feedback, and look for input and like Doug said, potentially develop some friendships over the wavelengths.

Lori Roscoe: I would say another source of support that was very helpful to me was my home health nurse, who really gave me practical advice and a kick in the pants, when I needed one occasionally. Very practical advice, and just a lot of compassion and support, so I think you can ... There are wound care ostomy nurses at most cancer centers, and they can be extremely helpful. So can appliance representatives from different companies that manufacture appliances. They can be very helpful. They're not necessarily providing the same kind of emotional support but sometimes, what you need is to figure out, "What's going wrong with my appliance?" They can be very, very helpful too, so I would just add that there are multiple sources of support. Nobody will turn you away, believe me.

Dr. Jennifer Taylor: Technical, practical advice for managing the quality of life after this big surgery or even the quality of life when you're going through intravesical treatment is really important. There's no doubt that the ostomy nurses are wizards. They're magicians and brilliant. Those are great, great pearls. "Did either of the patients who went through cystectomy consider the other reconstructions such as neobladder or continent diversion?"

Rick Oliver: Yeah. I actually did. I looked at all three choices. I actually did a lot of research on three choices to ensure ... One of the biggest things is when you're looking at which one you want to pick, it's very important to make sure that the doctor you've selected for your particular one is well-versed in it. For me, being a man, and I'll just spit it out there. Being a man, I just did not feel comfortable if I would have had to catheterize myself. I would have had problems doing it. Neobladders aren't 100%, so there's 20, 25, I believe the number's 20, 25% that you can't empty it all the time. That was me, and plus my age. I'm relatively young, and so I thought that was a better choice for me.

Lori Roscoe: I considered all the options, and I agree with Rick. I couldn't face the catheterization process. Fortunately, my doctor knew me very well by this point, and he knew what an emotional and anxious patient I am. He said, "I can do anything that you want, and there are pros and cons to each. I'm not going to tell you what you should do." He said, "My goals for you would be the quickest, easiest reconstruction and the easiest to manage post-surgery."

I appreciated that because I needed his advice and input. I was really fortunate that he took my emotional state into account. There's a longer learning curve with neobladder and the Indiana pouch, and he said, "I don't see that as being in your best interest." He didn't say, "Oh, you have to do the ileal conduit." He was very honest with me. That really made a huge difference to me, that he was taking my whole self into account. That was very helpful.

Dr. Jennifer Taylor: Definitely. It's a very individualized decision. BCAN also has some handouts you can download and read that offer more descriptions of each of the diversion choices and some specific questions to ask. Maybe there are some selection factors that help us offer certain choices over others, but ultimately, it comes down to, do you understand the options? What's your goals? What's your expectation for your day-to-day? Again, quality of life is a big, big play in that.

Dr. Jennifer Taylor: Let's see. Someone asked about UTIs after BCG. I will say for men and women, interestingly, BCG itself will not cause urinary tract infections. There's some reports that BCG

actually treats bacterial infection that might be in the bladder, instead of antibiotics. Definitely, if any of you can speak to side effects you experienced with BCG, what those were like. Those side effects can feel like an ongoing, never ending infection, for some patients.

Lori Roscoe: I had, I think, a pretty rare side effect. I didn't have any bladder issues with BCG, inflammation or irritation. I think a relatively rare side effect is inflammation in your joints. I had arthritis in my hip and it was exacerbated, I don't know, 100 times by BCG. I think that's one of the reasons that the arthritis has accelerated to be as severe as it is, causing me to have that joint replaced so that I can get back to being as active as Doug and Rick are. I'm jealous, but I'll get there.

Dr. Jennifer Taylor: Wow. That is significant. Good luck with that upcoming surgery, for sure. Could any of you talk about what the variation was and how doctors were open to new, or different, or clinical trial kind of options? Do you find that they were, generally, willing or not willing to go for things that were less known or established?

Doug Maclean: I just feel tremendously lucky to have Dr. John Gore. As you've heard, he's partners in this study, the CISTO Study with Dr. Smith. John is just an amazing personality. He's just so positive. He's so thorough. He's on top of everything. I come to him with some crazy questions about new stuff I read about, and he's usually well aware of it, and talks to me about the pluses and minuses. I'm just tremendously lucky, and just feel I've got a partner for the rest of my life when it comes to these kind of questions and decisions. Yeah, he's a fantastic-

Dr. Jennifer Taylor: Wonderful guy. This is an interesting question. Someone asked about, "What defines BCG as failing?" I think that's been kind of a moving target for many years, and it had not been very well defined for a long time. All these clinical trials studying different treatment choices as second line and third line were using different definitions, but that has since changed. In 2016 and since, there have been a lot of FDA and urology organizations getting together to harmonize what these definitions are. Basically, you have to get adequate BCG first, which is BCG induction, five of the six, and at least one BCG maintenance, or another reinduction of BCG. That's kind of the initial BCG treatment that's considered adequate.

This individual talked about going several years without recurrence, so actually if you've been treated with BCG and had a long interval, at least 12 months of no BCG, and then cancer comes back, it may be reasonable to try to rechallenge with BCG and that doesn't fall in the same definition of BCG unresponsive. I hope that helps. There are some more outlines of BCG unresponsive definitions. There's also BCG intolerant, where you tried BCG, you had a lot of side effects. Even reducing the dose or trying medications to help with the side effects didn't work, so you're off BCG because it just was not able to be tolerated. There are some very specific individual questions about personal scenarios. I don't think it's the forum to go into individual questions, but there was a question about ... I think that, I don't know if all of these participants can tell us if they are on Inspire or available through BCAN as peer support.

Rick Oliver: I'm actually on Inspire. I don't want to say I go on there every day, but I do go on there regularly. That was one of the sources that I used after my surgery. As I said, I was reading a lot about that. Actually, that was actually where I found the University of Hawaii meditation clinical trial also. I'm on there. It's a super site, and I think, for the most part, people are really, really helpful. There's a few people on there, and when people come on with questions, they just answer them so well. Yeah, I do participate in that, amongst other things.

Lori Roscoe: I'm actually a newly trained BCAN Survivor to Survivor contact person. Nobody's called me yet. I would be happy to provide whatever support I might be able to.

Doug Maclean: I'm not on any of the formal networks myself either, but I am very happy to answer any questions people may have. I actually did it for a period of time following my prostate cancer surgery, which was really successful. I worked with several people diagnosed with prostate cancer for several years. It was the most rewarding experience I've ever had. Again, I would very much be willing to do that for anybody that wanted to reach out to me. I'm happy to give you any support I can.

Dr. Jennifer Taylor: Thanks to all of you for being willing to be there for others facing similar things. One question a little while ago did ask about, "What percentage of BCG treatment fails?" I would say that's really dependent on the initial factors that are part of your individual cancer. In general, BCG works in 50% of patients who receive it, initially. There are up to 50% of patients, depending on the initial stage and factors, that it may not be the right treatment or it may not be effective. This role for salvage treatment is still very real and very high need in all of our practices, for sure.

Someone asked, well, I think I put it in a written answer but, "Keytruda, pembrolizumab, does it cure or just delay cystectomy?" So far in the preliminary or early, which is short-term at this point, so far with that data, the response is that it controls the cancer, and there's no evidence of cancer. In non-muscle invasive bladder cancer, cure is hard but not seeing cancer on surveillance and how long you've been without any visible or detectable cancer is the goal. That's the outcome we're going for. Pembrolizumab is successful in doing that in a fraction of patients that are treated with it. That's in the 20 to 30% response range that's durable.

Doug Maclean: I just had a quick follow-up on that. There was some discussion, I believe, at one time about maybe considering pembro being instilled into the bladder. Do you have any comment on that?

Dr. Jennifer Taylor: There is a clinical trial of pembrolizumab with BCG, but if I understand, it's still given IV and BCG is given in the bladder, but I could be wrong on that. It's on clinicaltrials.gov.

As many of you have indicated in your own personal examples, this is a very complex condition, and lots of different moving factors. Speaking to your personal urologist and then seeking other opinions is definitely recommended. Somebody mentioned Blue Light in the questions in the chat. I think that that is as available as the clinics, so not every clinic everywhere has it. Do each of you know if you've had cystoscopies with Blue Light either in the OR or in the clinic, in the past?

Doug Maclean: My last biopsy, I believe, John used Blue Light, so I've had experience with it.

Rick Oliver: I actually had, when I went to UNC, I actually had Blue Light, but when I was at my urologist, as you said Jen, they did not have the Blue Light technology. They were only using the White Light, not the Blue Light. From all the research I've done, it does show a lot more.

Dr. Jennifer Taylor: It's very useful, particularly if you have carcinoma in situ. It has, historically, for less than a decade though, but it has been available in the U.S. for use in the operating room at the time of TURBT, but it is also newly available in the last year for use in the clinic. That available

technology is still small and growing. There's also narrow-band imaging that's available on another type of equipment that can also help distinguish some of these indeterminate, hard to decide. There's these couple of different enhanced cystoscopy techniques that are recommended and very useful.

Doug Maclean: One of the things I might ask you to comment on, because it took me a while to understand it, I mean years after I was first diagnosed. Can you explain to the patients the difference between a surgeon, a urologist surgeon, and then a medical oncologist? Just so they make that connection. You've referred to it in the context of pembro, and I think it would help if they understood the difference.

Dr. Jennifer Taylor: Absolutely. Thanks, Doug. We make it even more confusing when those of us who've done more specialized training also call ourselves urologic oncologists. Anyone with urologist or urology in their title does surgery, and they manage any of these diseases when they are surgically staged, or resectable, or need a biopsy. If there's systemic treatment needed, through an IV typically, that is done by a medical oncologist, who is a medicine trained doctor and then specialized in cancer and systemic treatment for cancer. Many of the ones we work with are specialized in genitourinary or urologic cancer, so a lot of terminology and labels, but there is definitely a distinction. For this type of disease, it's become more important to have that collaboration and teamwork to manage it.

Does any of you have any last pieces of advice or things on your outlook going forward now that you'd like to share?

I will touch quickly that someone did ask if radiation has a role in these circumstances, and as of right now, radiation does not have a place for non-muscle invasive bladder cancer, and particularly for carcinoma in situ. Generally, because it's this flat, hard to find kind of superficial cancer on the lining of the bladder, radiation has often not been very effective, even when patients have been given radiation. Say they had invasive cancer and got radiation. The CIS is potentially resistant to the radiation, but radiation is currently not a treatment choice for non-muscle invasive disease.

For Keytruda, for pembrolizumab to prevent recurrence, interesting. Only for someone who has disease that we're trying to control. It's not given for non-muscle invasive disease as any preventative type treatment, I guess. Hope that answered your question. Sorry. Like Morgan said, there are going to be some treatment webinars coming up, and you can also explore. There's already some recorded videos on BCAN's website to help you understand some of these pathways and ways that we think about bladder cancer as well. I'm so grateful for everyone's questions though. It has really helped us have even more conversation. Thanks to BCAN and thanks to CISTO. If you want more information, you can go to the BCAN website.