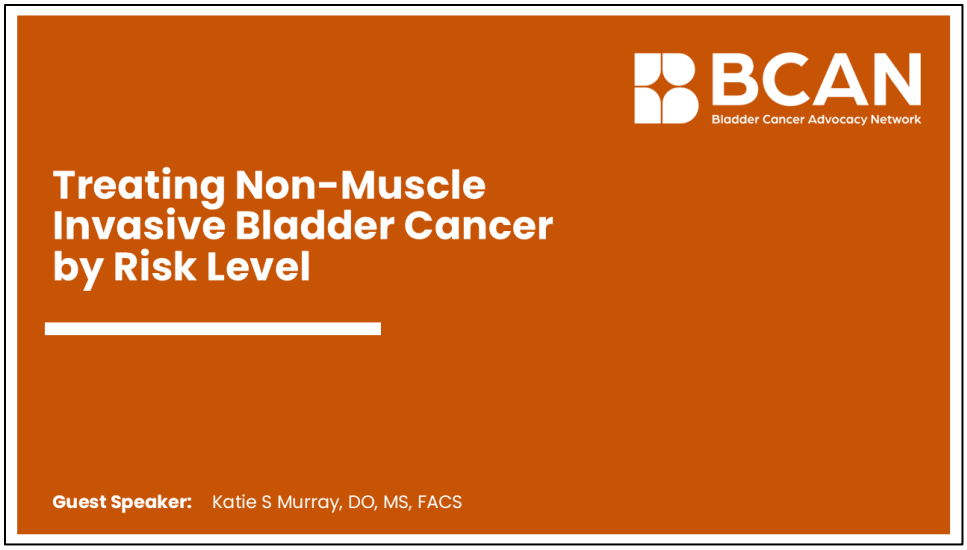

Patricia Rios:

So there's a question in the chat about the EAU risk stratification. Could you talk about what that is and if they vary at all, and what are your thoughts around the EAU guidelines?

Dr. Katie Murray:

Yeah. I think that's an excellent question. Obviously, we have limited time, and so we didn't go into that, but it's a discussion that we have in the urology world all the time. And so one of the most important things, I think, at least in my mind, one difference in the EAU guidelines is that all patients with high grade tumor fall in a high risk categorization. And that's a little bit different than the AUA where we have those first time small high grade TA tumors that fall in that intermediate risk categorization. That's one big difference. And then the other thing that I think is important to recognize in the EAU guidelines is they do substratify the high risk population into a very high risk population. And so that can be patients who have a variant histology. A traditional bladder cancer is urothelial cell carcinoma, but they may have a component of another type.

And sometimes we start talking about cell types, we talk about squamous cell carcinoma, we can talk about a micropapillary variant and some of these other variant histologies. And really that is based upon our worry and our risk of progression of disease in that patient population. It's a group of patients that we might worry a bit more and might fall on the higher side of that risk of progression from that. That also accounts, if you think about the AUA guidelines, you've noticed in many of these follow-ups and these surveillances, it gives a little bit of wiggle room. It might say for the first year or the first two years, the cystoscopy is every three to six months, or in the high risk it was every three to four months. And so it allows a little bit for that wiggle room and that patient physician discussion of what that is, meaning if you have a variant histology, we might watch you a little bit make sure we do that every three

months instead of the every four months from that situation. They're very similar with a few minute differences.

Patricia Rios:

Great. Thank you for explaining that. Cystoscopies continue to be sort of the gold standard and patients are wondering, are there any sort of replacements for that, especially for follow-up, particularly as it relates to urine biomarkers? Any thoughts on that?

Dr. Katie Murray:

Yeah, so it seems like a dream world, and that the answer to that should be magically yes. Urine is such a great way, and it's so easy to attain in our clinic. Unfortunately, at present time, there's many biomarkers in exploration, and there's some companies out there, and your physician may actually even utilize some in practice, but a majority of times they're still being utilized all in adjunct to cystoscopy. Nothing has had enough sensitivity and specificity to say, "You don't have to have a cystoscopy anymore, and we trust this urine-based test to say, yes, you have a recurrence, or no, you don't have a recurrence." A majority of them in today's world all use as adjunct. I would like to say that that's my future dream world, is that I don't have to do all these surveillance cystoscopies, but the evidence just isn't there yet.

Patricia Rios:

Thank you. I think that's a hope and dream for all of us.

Dr. Katie Murray:

That's right.

Patricia Rios:

Speaking of test, we have a question relating to the MRI urogram versus the CT urogram. Is one more sensitive than the other?

Dr. Katie Murray:

Yeah. No, I think as long as you're getting one of those scans, and part of it becomes a little bit of your own institution or your own practice, because there are differences in CT machines and MR machines across different practices and how sensitive or specific that they might be or how well they can image. Probably more important than saying which one you're going to get is really staying consistent, meaning if you've done CT scans, continuing that CT scan so we can always compare back to the past is more important than one being better than another.

Patricia Rios:

That's helpful. Okay. Now related to BCG and the shortages, how do you select how or which patients will get versus something else?

Dr. Katie Murray:

Yeah, so I think that's a huge challenge. And I've talked to so many of my friends in how we do this. And I think it is where we just talked about the European guidelines versus the AUA guidelines, and it does give this ultimate even higher risk. And so my real goal is to be able to get induction BCG in every single patient who falls in that high risk categorization and I think that's the highest risk of recurrence and the highest risk of progression. And then the evidence for the ongoing maintenance therapy is not quite as strong as the induction therapy. Getting that induction in has been prioritized at our practice over the ongoing maintenance, which is also why that maintenance schedule has been kind of condensed down to that one-year timeframe in many, many practices from that standpoint.

But I didn't even have time tonight and I thought about doing it, but talking about trials that are going head-to-head against BCG that are not based upon BCG. I talked about the three trials that combined a PD therapy along with BCG, but for example, the ongoing or the now closed, but waiting for results of the BRIDGE trial, which is comparing BCG to an intravesical chemotherapy such as intravesical Gemcitabine-Docetaxel to say, "If we don't have BCG, which has been the standard forever, can we use an intravesical chemotherapy and are the results as good or could they be better?"

Patricia Rios:

That kind of goes well with the second question then. I don't know if the information is available. There is a question about GemDoce as a second-line therapy compared to the newly approved second-line treatments that you mentioned, particularly for intermediate risk. Do we have any information about that?

Dr. Katie Murray:

Yeah, so it's really comparing a little bit of apples and oranges. And so what we don't have in any of these trials is we don't have any evidence where we said, "Okay, we took all of these patients and we said, 'You get this one, you get this one and you get this one.'" And we're not supposed to say, "Okay, we did this trial and this was the results of this drug, this was the results of this one, this was the results of this one," and try to pick what's best. The simple answer is no, we don't have that answer, but we're humans, and so it's hard for us to not look at those numbers. The one thing that often gets brought up about intravesical Gemcitabine-Docetaxel, which is widely utilized across the United States, especially in academic urology practices as a second line to BCG therapy is it's been tried and true.

We've used intravesical chemotherapies for quite some time after BCG therapy, but all of the results with intravesical or majority of the results we have with intravesical chemotherapy is based upon our own experiences and reporting on that retrospectively, meaning treating a bunch of patients and then looking back and seeing what the results have been of that GemDoce. Again, I mentioned already once, but the BRIDGE trial is a very exciting trial that we'll read out, but not until another year or so, but it compared patients new bladder cancer,

high-grade disease either got intravesical chemotherapy with the GemDoce or intravesical BCG therapy. We're really excited about that as a urology community.

Patricia Rios:

Yes, we'll be excited to hear what those results say.

Dr. Katie Murray:

Yes.

Patricia Rios:

There was a question about biomarkers earlier on, but do you mind explaining what biomarkers are? What are they looking for? Is it the tumor itself, the urine, the blood? What is, I guess, the biomarkers?

Dr. Katie Murray:

Sure. I think a biomarker, if you think about it in traditional terms, essentially a biomarker is looking for a cancer, and that can be in any way, shape, or form. And so if we think about it technically, you might say our cystoscopy is a biomarker. Now this is getting really technical because it's trying to marker out the cancer and say yes or no, there is a cancer. When we identify or we find something, and what we're looking for in a biomarker is for that biomarker to, if it's positive to say, there is definitely a cancer in this person, if I test a urine biomarker and it's positive, then it says, "Katie, there is a cancer there and you have to find it." If that biomarker is negative, that I would have complete confidence saying, "You do not have cancer. The chances of that are extremely low." That's essentially what a biomarker is trying to do.

Patricia Rios:

Great, thank you. There was questions about CIS, C-I-S, and whether the new treatment options that you share, how do they respond to CIS type tumors?

Dr. Katie Murray:

Yeah, so interestingly, and like I said, there's so short of time, but all of the FDA approved agents, so that would include the Pembrolizumab, Nadofarogene, N-803 plus BCG, and Inlexzo are all very specifically delineated out by the FDA that these are FDA approved for BCG unresponsive carcinoma in situ tumors with or without concomitant papillary disease. The numbers that you look at across the board in that table are those carcinoma in situ population.

Patricia Rios:

Thank you. And so there seems to be a lot of questions in the chat related to GemDoce treatment, and so questions around efficacy, surveillance, cystoscopies. Could you provide

more information around that treatment option, particularly as it relates to, I guess, the intermediate risk?

Dr. Katie Murray:

Okay. The important thing, the one thing I will say, and this kind of came up a question, I think I saw it somewhere else in the chat as well, is the reminder that irrelevant of what your schedule is and what therapy you're undergoing, if that's BCG or GemDoce or any other of these newer approved FDA agents, that follow-up pattern of the follow-up cystoscopies, CT scans, MR urograms does not change. I often explain it to people is you may be getting your intravesical chemotherapy on this timeline, but you also have this other kind of calendar going of how often you need to have your cystoscopy. Intravesical GemDoce is the retrospective data essentially that is inclusive of an induction course of the two chemotherapies together into the bladder. That's a six-week induction course, and assuming a complete response, patients would go on a maintenance course of GemDoce, and that's one single installation in the bladder every single month for 11 additional doses, so for 11 months. And so while that's happening, so they get six doses and then monthly maintenance.

And then a reminder, you're getting that monthly maintenance, but you're also seeing your urologist and not just the nurses or MAs in clinic, and you're getting a cystoscopy every three to four months per the guidelines. There's kind of two things happening at once. You're getting your therapy and you're getting your surveillance. They may not always coincide on the same day.

Patricia Rios:

Thank you. Gosh, we have so many questions. I'm looking at the clock.

Dr. Katie Murray:

I know. I'm going through as well. I'm like, "Oh my goodness." Okay.

Patricia Rios:

Thank you, Dr. Murray. Okay. Let's take this one around full dose for BCG versus half a dose. Is there a difference?

Dr. Katie Murray:

Yep. I don't have any prospective data that's ever proven to say full dose versus half and third doses. What we believe is the BCG elicits an immune response. And so eliciting that immune response and having that ongoing dosage with the maintenance BCG is really what's upmost important. And so based upon that science and the fact that we do have a shortage and we're trying to get as much BCG to have that ongoing response in patients as possible, many practices are doing half dosing or I should say split dosing in using one vial. And instead of doing the whole entire dose into a single patient, that might be split and using half of the dose. And so half dosing or even quarter dosing, one third dosing in the maintenance regimen that is not very much utilized in the induction course because that induction priming

with the immune system with BCG is really the mainstay, that once a week for six weeks, full dose.

Patricia Rios:

Thank you. Well, I'm looking at the time end, so what I want to offer is to our listeners today. Thank you so much for joining us. You have such great questions. And what we'll try to do is gather these questions and invite Dr. Murray back for another presentation or part two, and we can continue to build that presentation around these questions. What I will say is that also related to, I think there were a lot of questions about when this new plant Merck is opening, so that hopefully will address some of the BCG shortages. And so continue to stay updated with BCAN. We are in communication and we'll share any updates as we receive them.

With that, Dr. Murray, what I would like to ask, I mean, there was so much information, very rich content today. What would be the takeaway message that you want our listeners to leave with today?

Dr. Katie Murray:

Yeah. Yeah, thanks so much for having me. And I think really it gets very confusing of realizing that risk stratification and why one person might be getting one thing and somebody else is getting something else, but really understanding and trying to ask your provider the question, "What is my risk stratification?" And that's important for you to know because it tells you your risk of recurrent disease, it tells you your risk of this disease progressing. And then based on those two numbers determines how aggressive you need to be in the treatments that you give and how aggressive you need to be in making sure that you have that follow-up surveillance with those cystoscopies, so with the urologist. I think it's okay. Ask your surgeon, what is the risk stratification? Because they may not just come out and blanketly say it as simply as, "As you fall in intermediate risk so because of that, I'm going to do this." They might just say, "You need BCG or I'm going to do this therapy." And I think it's okay to ask those questions.

Patricia Rios:

That is an excellent takeaway. Well, thank you so much, Dr. Murray, for joining us today and for the comprehensive presentation. We hope to have you back real soon.

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