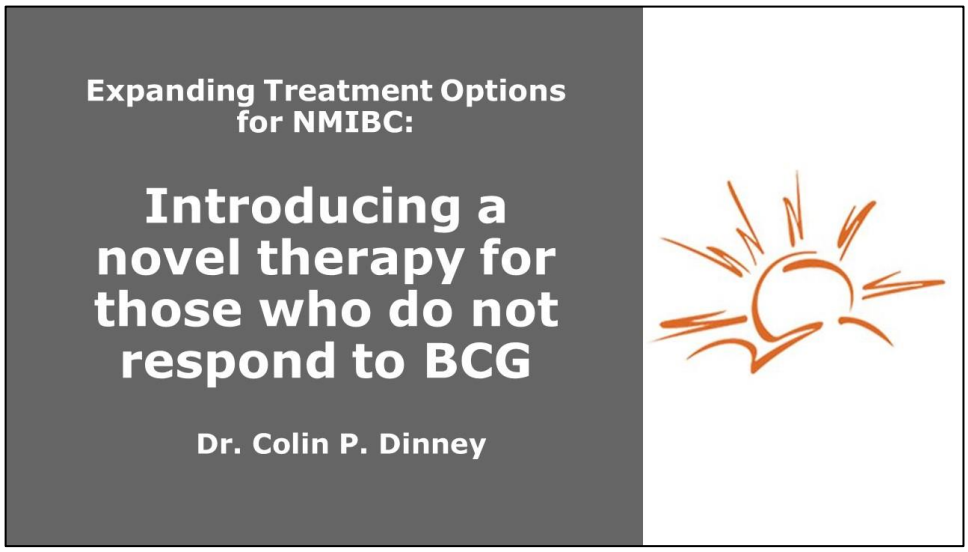

Stephanie Chisolm:

All of the people on this call have a much better perspective of the many steps and at the end how many years that you have been working to get this drug as a group collectively to the patients. And I think that it's really phenomenal because again, for patients who are non-muscle invasive, BCG had been the gold standard. There are few other options, and if that doesn't work, it's really challenging. So, this has been wonderful. I want to remind everybody, if you have questions, please drop them in the Q&A box and we will try to get to as many as we can.

I know that there was a question that was submitted that want to just know how do you get the drug. So, what I have is, I'm about to drop into the chat. There's a phone number for Ferring. That's the company that is doing this. They have what they call the Early Experience Program, and it's available mostly at the clinical trial sites and in other places around the country. So, if you want to know more, ask your doctor to find out because they have a website. But this is the phone number you can call, 888-FERRING, F-E-R-R-I-N-G. So, I dropped that in the chat so you can pull that up and make note of it.

Now, let's get to some of the questions. One question, are there specific mutations that Adstiladrin is more effective against? I know you mentioned CIS in the beginning, but are there other mutations that it seems to work well with?

Dr. Colin Dinney:

That's a very good question, and it's really something we're just starting to look at. We only have experience with the drug in high-grade disease, and high-grade disease is characterized by a specific set of mutations such as p53, RB. There's a mutation called TERT. There's other mutations like FGF receptor three and PIK3CA. Those other mutations tend to be found in earlier stage disease, which we have no experience. So, right now, it's the high-grade tumors that we know that we see responses in. And we haven't been able yet to distinguish which mutations are prone to predict sensitivity.

We have done some work though to identify potential biomarkers of response. We've identified that in patients whose tumors and bladders induce cytokines such as TRAIL or IL-6 have a better response. We started our first studies with a phase two study. The only robust genomic platform we had for urine was

microRNA, and there were about seven or eight microRNAs that changed, the expression changed significantly with treatment, but only one that seemed to be associated with response. And that's let-7f.

We've also found that there is one potential alteration, a mutation, it's a deletion, deletion of a gene called CDKN2A. And this gene is found at the same place in the chromosome as the interferon gene. So, the hypothesis is that these patients will have lost the interferon gene, and for them interferon treatment is gene replacement treatment. So, we are going to be looking at the phase three samples to see if we can corroborate what we found.

Stephanie Chisolm:

Yeah. That's another good segue to another question. Should patients consider a clinical trial?

Dr. Colin Dinney:

At this point in time, I think that there are some trials that are ongoing. I think that there are drugs that are approved. I think it would depend upon what's available right now. Generally, a patient should always consider a trial because it's been shown that the survival of patients that participate on clinical trials is superior to those of the patients that don't. They're going to get closer follow-up. They're going to get closer care and contact, and I think that that's all associated with an approved survival. We have a couple of drugs that are available now that are approved.

I think that Adstiladrin. I'm biased. You really can't ask me that, right? I'm biased. What I think is a positive, there's a document response as good as or better than whatever else has been tested to this point. And it's safe, and we didn't see patients progressing or dying from cancer who went on treatment. If you don't respond to it, you could always go out and try something else. But I do think it is a drug that has its place in the treatment of this disease.

Stephanie Chisolm:

Okay, great.

Dr. Colin Dinney:

But then, I'm biased. Okay?

Stephanie Chisolm:

We're talking also all clinical trials. There may be other clinical trials that somebody could be eligible for. So, we always try to remind people that clinical trials could be a treatment option and there's some real benefit to doing that. Not only will it change, no new drugs are approved without that clinical trial evidence, but it can expose you to something that might be more beneficial that's not currently available. So, they are out there and BCAN does have a clinical trials dashboard that lists all of the bladder cancer clinical trials in the United States that are open and recruiting patients.

Let me move on to some more questions because we have a lot of really good questions. Is papillary mixed grade non-muscle invasive in scope for this discussion or only high grade and or CIS? What about these mixed tumors?

Dr. Colin Dinney:

Right now, even though the approval was only for CIS, the FDA did encourage us to include patients that had high-grade Ta or T1 as well, and even by itself. You have to remember that the definition of BCG

unresponsive implies that all these tumors are high-grade, so they're not low-grade tumors. You could have a mixed tumor that's predominantly low-grade with some high-grade features. I guess they would potentially be candidates as well. There will be some studies that are going to be done, basically with low-grade tumors to see if it's effective or not. But right now, I think that the development has been in high-grade disease.

Stephanie Chisolm:

So, if this is not as frequent an installation as BCG, there's a question in here. Is Adstiladrin similar to BCG in that there might be a recommendation to rotate around to make sure it gets there, or is it just an installation and there's not as much of an issue with rotating and making sure you've reached all the nooks and crannies in somebody's bladder?

Dr. Colin Dinney:

Yeah, that's a good question too, but basically, you drain the bladder, the catheter, the bladder's collapsed. You put in, I think it could be 75 CCs at first then maybe 50 now. So, the bladder is all exposed to the drug. I don't think it's as important to have the patient roll around because there's such a strong bystander effect. And the fact is we drain the bladder so we know that the bladder is being exposed to it.

Stephanie Chisolm:

Okay.

Dr. Colin Dinney:

Also, the thing is that I think it would be hard to have someone roll around with it because also the Syn3 can be a little irritating, and you wouldn't ask someone, that would be cruel to ask them to roll around if they're having spasms from their bladder from the Syn3.

Stephanie Chisolm:

Yeah. And is there anything that you can do to help alleviate the spasms? Is there something that you can apply?

Dr. Colin Dinney:

We found in early trials, giving anticholinergics upfront was helpful. B&O suppositories were the best. They're not available right now, but they were the best. But now we use other drugs such as Levsin, those things. But yeah, we found that we made it more tolerable. Midway through phase one and phase two, we realized that we could improve the delivery by giving anticholinergic first to settle the bladder down, at least to some extent, and people could hold it longer.

Stephanie Chisolm:

Right. Well, here's a really, it's the question on everybody's mind. How soon after you start this process with Adstiladrin is a patient going to know that the therapy's effective? Is it usually right away? Do you have to do a couple of installations before you really see anything? Are there biomarkers or anything else that you can monitor to say, "Yeah, it's looking good, it's encouraging?"

Dr. Colin Dinney:

It's interesting. We looked at a lot of biomarkers. For instance, we looked at the interferon levels to see if interferon levels corresponded with response. The interferon was generating the urine. Turned out that it didn't because even in people who responded in those that didn't, the majority had levels at a certain level, which was 5000 units per mil. When you got above that, we were enriched for patients that were going to respond. So, those who induce high levels are responders. It's like anything else. We are looking at predictive biomarkers to see if they can correlate with response. So, we are doing that and we are collecting urine at sentinel moments during the course of treatment.

We found, for instance, that in our phase two trial, that if the person, if their bladder started producing a cytokine called IL-6, we can identify that by day four. And that patient was likely to have a response. I think moving forward, we're going to have these assays that we can do in real time, and they're likely going to be urine assays because it's a lot easier and you don't have to do a biopsy. And you can look at those urine assays and predict how that person could do. What goes hand in hand with that is developing combination therapies that are targeting resistance mechanisms. So, these are genes or pathways that pop up in people that don't respond.

A very good example. So, one of the consequences of, for instance, interferon treatment is upregulation of PD-L1 on the tumor cells. Now, PD-L1 is a biomarker that can lead to immune exhaustion because what it is, is the body's way of trying to prevent autoimmunity from the interferon. And that can be associated with resistance. What we've noted in preclinical studies is that combining the gene therapy with a checkpoint inhibitor such as pembrolizumab will actually improve the response and will treat those patients who are going to recur through that mechanism.

And I think we're trying to develop assays so we can analyze this in real time and see if we can predict early on who's likely to respond, who's likely not. That's just an example of a targetable alteration that comes up after treatment.

Stephanie Chisolm:

Yeah, I have a question about effectiveness as compared to... hang on one second, compares to gemcitabine and docetaxel.

Dr. Colin Dinney:

That's a very good question. I think docetaxel and gemcitabine have activity, but they haven't been tested at the same population. It's a mixed population of patients that would mostly be considered to be BCG exposed. So, they look like BCG unresponsive patients, but they, for the most part, don't fit the strict definition of BCG unresponsive disease so that their natural history is probably a little bit more favorable. But that combination does have activity, and I've used it when we don't have a protocol ongoing.

We've used it to treat these individuals as well who don't want to have their bladder, I mean whenever I see someone with BCG unresponsive disease, even though I've been involved in the development of a drug, I still recommend a radical cystectomy because from an oncologic perspective, it's the safest treatment.

Stephanie Chisolm:

That's a good point to make. Is Adstiladrin and this whole gene therapy similar to BCG that you might have a course, maybe you're on there for the year, but then you need maintenance? Is it lifelong, you're always going to have for the rest of your life quarterly treatments?

Dr. Colin Dinney:

Those are good questions. The real answer is I don't know, but basically, we treat them once every three months. Now in our trial, I mean, we were one of the first trials out of the blocks, and I was really conservative. I didn't want to risk somebody's cancer progressing and patients getting metastatic disease to be on a trial that I was promoting. So, if patients had a recurrence at three months, we took them off treatment. Subsequent trials have actually used the BCG definition of refractory, and actually will not declare defeat until it had gone six months. In that case, for us, it would be two treatments.

Because if you look at the trials that are ongoing, you can improve the response rate probably by another 25% by giving a second dose. So, I think today, if I had to redo it, I would give a second dose at three months for individuals who had recurrence, not if they progressed, had a recurrence, and then go from there. And we'd evaluate the person every three months after that.

Stephanie Chisolm:

Here's a question that came in after you were done, but if you could just reiterate what again is the definition of BCG unresponsive? How do you define that from a patient's perspective?

Dr. Colin Dinney:

Okay. There's three criteria. One is what's called BCG refractory. So, these are individuals who would receive optimal BCG. They would receive induction therapy, at least five of six induction courses, and then get at least two of three of the first maintenance. And if those individuals had persistent high-grade disease, then they would be considered to be BCG unresponsive. If you take another patient and they respond to BCG but then later recur, then those patients would also be considered to be BCG. They'd be the relapse. They'd formally been considered to be relapsed.

And then, because of the concern for progression for patients with T1 disease, it also includes individuals who had three months after induction therapy only, not allowing for maintenance, have persistent T1 disease or have progressed to T1 disease. So, those are the three criteria that identify BCG unresponsive disease today, and it's a strict criteria.

Stephanie Chisolm:

So, you still have to go through all the trouble of having BCG and seeing if it works and everything before you really could be eligible unless you enroll in one of the clinical trials that is moving you forward.

Dr. Colin Dinney:

That's correct, yeah. At this point, that's the indication for the drug. Obviously, there's going to be efforts to move the drug up higher in the disease state, but those efforts are being designed.

Stephanie Chisolm:

Remember to call 888-F-E-R-R-I-N-G and speak to the team at Ferring, and they can give you information about the Early Experience Program and tell you how to share with your doctor how they can get involved. And they are working on the manufacturing facility, so I think they're expecting.

It's not going to take too-too long to get up to full speed, but they do have this drug and they're making it available at most of those clinical trial sites. And there were quite a few of them. Let me see. Oh, will it be possible to have a treatment therapy with a combination of BCG and Adstiladrin? Is that something anybody's looking into?

Dr. Colin Dinney:

That's also a good idea. There's a lot of trials that combine BCG with something else, and BCG would be one of the attractive drugs to combine with Adstiladrin. They may overlap somewhat in their mechanisms of action, but it would be interesting in looking at that. There are other combinations that look promising as well. For instance, a combination with a checkpoint inhibitor that looks very, very promising. I think that would be something that I would think about in individuals who don't respond to Adstiladrin consider adding another drug onto it. You could consider adding it with chemotherapeutic agents. So, there's a lot of different combinations to think about.

So, once the manufacturing is up to speed, then we can start pursuing some of those interesting ideas.

Stephanie Chisolm:

Great. Here's another question for you. This comes from Canada. Are there trials going on in other countries that are using Adstiladrin?

Dr. Colin Dinney:

I believe that there is a trial ongoing in Japan, a trial of BCG unresponsive disease. I'm not aware of another trial that's ongoing right now. Again, I think that we have to make sure we have enough drug available to do these trials, and I think the trials will start opening up shortly once the manufacturing is up to speed.

Stephanie Chisolm:

I think that this is great. We still have a lot of really good questions. I'm just trying to filter through so I can make sure I hit on all the key points. Given the BCG shortage, many non-muscle invasive patients receiving other therapies like gemcitabine, docetaxel, what if they don't respond to those? Are they then eligible since they couldn't get BCG to be refractory in the first place?

Dr. Colin Dinney:

That's the same question that's plaguing us as well, right? Right now, letter of the law would say no. It is possible that when the drug is commercially available that practitioners could prescribe it assuming that the insurance will pay for it. But yeah, those are the critical questions for individuals who recur despite our standard upfront therapies. Right now they wouldn't be a candidate because it's a strict approval. People can be treated off-label. And so, I think that's possible.

Stephanie Chisolm:

So, the off-label availability's probably going to be a little bit more accessible once they're up to speed fully, because right now they're still doing that Early Experience Program where they have limited supply.

Dr. Colin Dinney:

Yeah.

Stephanie Chisolm:

Okay. All right. It's all good things to know. Somebody asked if you could explain again what the Syn3 component is in this.

Dr. Colin Dinney:

Okay. We thought that gene therapy was a slam dunk for bladder cancer because we had good exposure of the urethane, the tumor to whatever we put in the bladder. We found out that wasn't the case, and we found out that the barrier, the glycan barrier was preventing infection. So, there was a lot of work done to try to improve infection by altering the viruses, by doing other things. And one of the approaches was by using chemicals. And so, there was a chemical that they looked at, it was called Big CHAP, and this was worked done by Schering. They used Big CHAP as a detergent and they combined it with a gene and they administered it.

And they found out that it worked to a certain extent, but there was differences in... there was two companies, Big CHAPs they looked at. And one worked and one didn't. So, they looked at the one that worked, and this is ironic, and they actually found out that the Syn3 was actually a contaminant in the effect of a Big CHAP. And then, they had developed that. It's a detergent. And how it works, well, we don't really know for sure exactly how it works. We haven't looked at mechanism, but it alters the properties of the lining of the bladder to allow the virus to infect the bladder. So, probably disrupts the GAG layer somewhat.

Stephanie Chisolm:

Okay. Let's see. Is gene therapy an option if the patient is not eligible for BCG, maybe TA or recurrent disease? What about, again, going back to... you've already answered the question about comparing to non-BCG treatments, but if they're not eligible for that, maybe they have a reaction or something else?

Dr. Colin Dinney:

I think those individuals would be a candidate for treatment off-label. I think you can make a strong claim for that because they can't receive BCG. It hasn't been tested in the BCG intolerant population, but you would think that it actually might even be more effective because you're giving it early on, but we don't have the data. But I think that you could go for an off-label usage of it in that circumstance.

Stephanie Chisolm:

Here's a question. From what I've read, there appears to be a cohort of CIS patients, carcinoma in situ, maybe 15% to 20% who have very aggressive tumors with high rates of progression and metastasis. How do we determine if a patient is in this cohort, and if so, should they go directly to cystectomy bladder removal or consider one of these trials like this Adstiladrin trial?

Dr. Colin Dinney:

As I said, BCG unresponsive disease, I always recommend a radical cystectomy as the safest oncological approach, but I don't think that there's, I mean carcinoma in situ, we know the genetic alterations associated with them. And I don't think you can distinguish between one and the other. We know that carcinoma in situ that's associated with high-grade T1 disease tends to have a worse prognosis. So, in

that scenario, you might be a little more cautious and I would recommend a radical cystectomy for someone in that scenario. I don't think we have the knowledge of exactly what genetic alterations or mutations will make you unresponsive to the therapy.

Stephanie Chisolm:

Okey-doke. Well, I think we're coming up on time. I think we have time for one more question. Let's see. Would Adstiladrin be an option for someone who is unable to continue BCG due to severe inflammation but they haven't yet had a recurrence? Maybe they had to truncate their BCG.

Dr. Colin Dinney:

I would tend to watch that individual. This is not an infrequent event. Our clinical practices see this all the time. And we need to look closely at whether or not those individuals actually do pretty well because they've had such a robust inflammatory response that the tumors have been destroyed and it's been effective. So, my sense is that some of these people do pretty well and I would not want to treat them until we had evidence of a recurrence.

Stephanie Chisolm:

Yeah. Okay. Well, that's really good to know. There's great promise. There's more work to be done to really understand how this fits into the great schema of all non-muscle invasive treatments. But the nice thing is there are options, and that is something that we didn't have five years ago. We didn't have 15 years ago. We've had BCG as the standard of care for, what, 40 something years right now, and we're still dealing with the shortage.

I do want to say thank you, Dr. Dinney. This has been phenomenal.