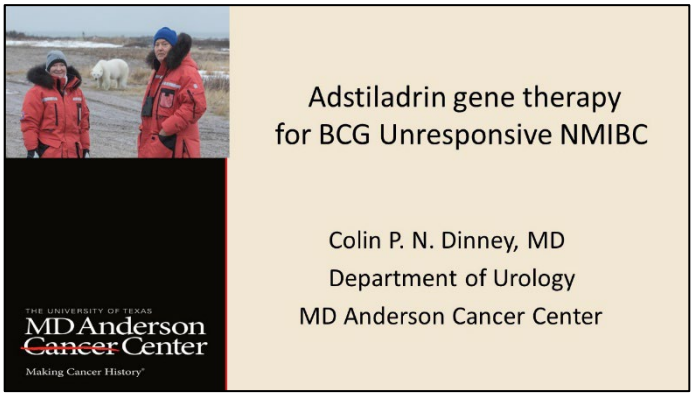
Stephanie Chisolm:

Welcome to Expanding Treatment Options for Non-muscle Invasive Bladder Cancer: Introducing a novel therapy for those who do not respond to BCG.''

Stephanie Chisolm:



Bacillus Calmette-Guérin has long been the gold standard for treating non-muscle invasive bladder cancer, and for those whose tumors don't respond to BCG, which is the standard of care, there's a newly approved gene therapy that may provide a valuable alternative to bladder removal surgery.

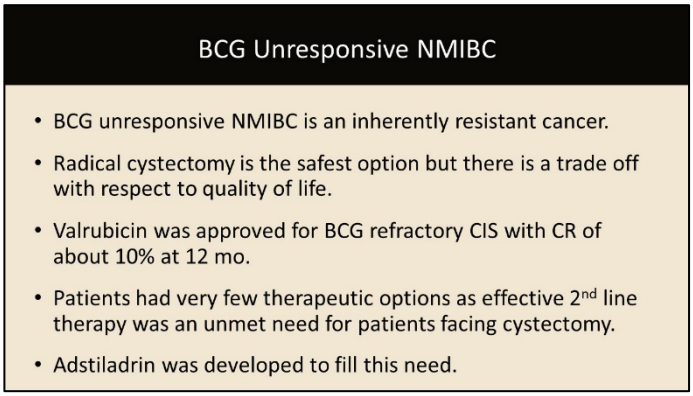
This new treatment, a gene therapy, was recently approved by the FDA, and BCAN is delighted to welcome the chairman of the Department of Urology at MD Anderson Cancer Center in Houston, Dr. Colin Dinney, a longtime member of BCAN Scientific Advisory Board and a globally recognized expert in treating bladder cancer. Dr. Dinney was the principal investigator on the clinical trials that led to this approval, and he's going to talk about this new adenovirus vector-based gene therapy and show you how it works, how it's administered, and who would benefit from the latest treatment options for non-muscle invasive bladder cancer.

Welcome, Dr. Dinney. It's a pleasure to have you here.

Dr. Colin Dinney:

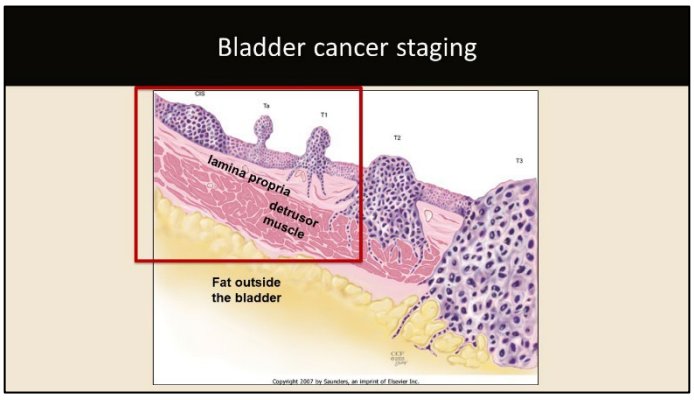
Thanks, Stephanie, and thank you for inviting me to speak on the development of Adstiladrin for what's now known as BCG unresponsive disease.

Dr. Colin Dinney:



So, I'm going to start, I mean, we're talking about BCG unresponsive non-muscle invasive bladder cancer, which really is an inherently resistant cancer. From a cancer perspective, a radical cystectomy is the safest option, but we all know there's a tradeoff with respect to quality of life. Historically, valrubicin was approved for what's known as BCG refractory carcinoma in situ, carcinoma in situ that was not treated by this, do not respond to BCG, with a complete response rate though of only about 10% at 12 months. Up until recently, patients had very few therapeutic options as effective second-line therapy was an unmet need for patients facing cystectomy. And Adstiladrin was developed to fill this need.

Dr. Colin Dinney:

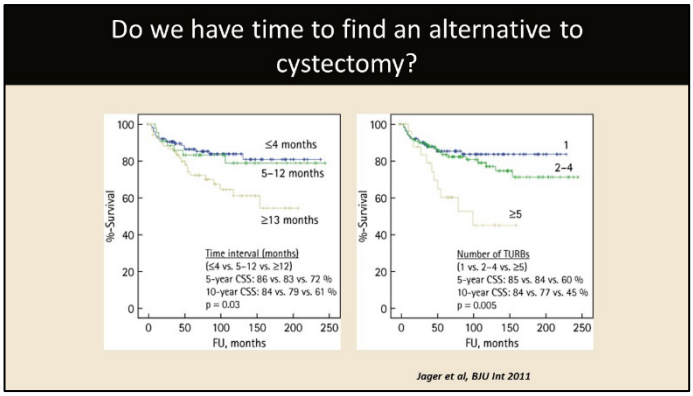


When talking about non-muscle invasive bladder cancer, what are we talking about? We're talking about cancers that are confined to the urothelium and the lamina propria. So, this is the bladder. This is the bladder lumen. The tumors we're talking about are the high-grade Ta lesions. These are lesions that are confined to the urothelium, and under the urothelium is the lamina propria. We're talking about carcinoma in situ, which is a high-grade intraepithelial neoplasm. It's confined to the urothelium, but it's high-grade. It can invade and it can metastasize.

And also includes these tumors, these are T1 tumors, and these tumors invade into what is called the lamina propria. That's the tissue between the lining and the deep muscle. And it's a misnomer to consider these to be superficial tumors, but you can see that these tumors look very much like a tumor that's invading the muscle. The only difference is they haven't gone as far. So, it's very, very important that when the urologist resects these tumors that they get adequate tissue depth and they get into the muscle and get all the way around it prior to starting any treatment.

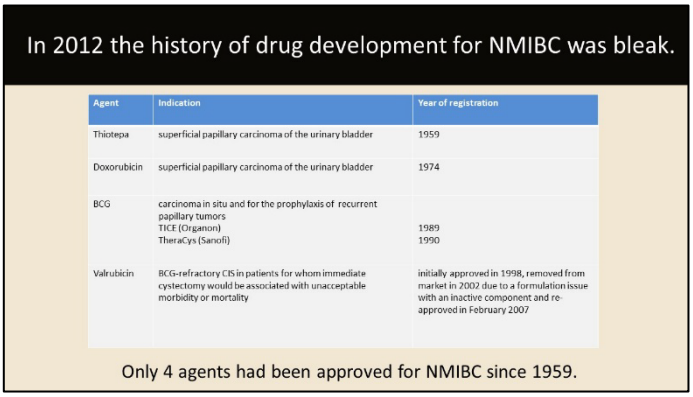
Dr. Colin Dinney:

I guess the first question you have to answer is, if BCG isn't working, do we have time to find an alternative to cystectomies? Well, this is a recent paper that says we do, we have about 12 months until the survival of patients who don't respond to therapy gets worse. And that corresponds to about five TURBTs.



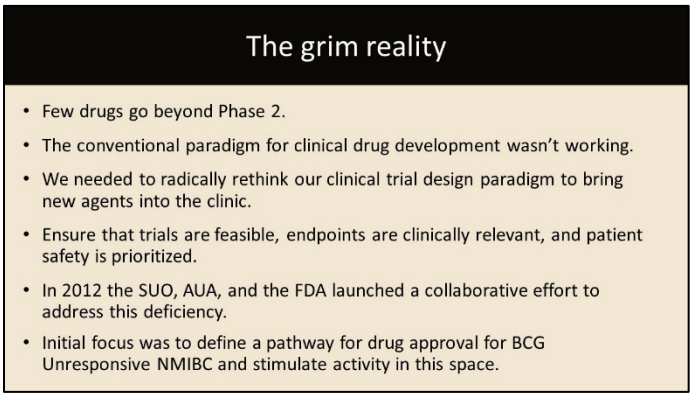
Dr. Colin Dinney:

Now, I'm going to take it back to 2012 where the story began, and if you look back in 2012, the history of drug development for non-muscle invasive bladder cancer was bleak. Only four agents had been approved for the treatment of non-muscle invasive bladder cancer since 1959. And only one of those drugs, a BCG was being used currently.



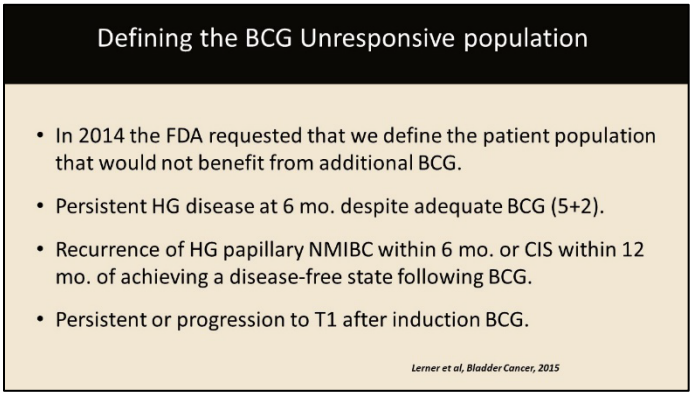
Dr. Colin Dinney:

So, the grim reality was that very few drugs went beyond early-stage trials as the conventional paradigm for clinical drug development just wasn't working. So, we recognized we needed to radically rethink our clinical trial design if we wanted to bring new agents into the clinic for our patients. We had to ensure that trials would be feasible so they could be finished, but the endpoints were clinically relevant, so we would've analyzed the drugs properly and foremost, that patient safety was prioritized. So, in 2012, the SUO, the AUA, and the FDA launched a collaborative effort to address this deficiency. And the initial focus was to define a pathway for drug approval for what we now call BCG unresponsive non-muscle invasive bladder cancer to stimulate drug development in this space.



Dr. Colin Dinney:

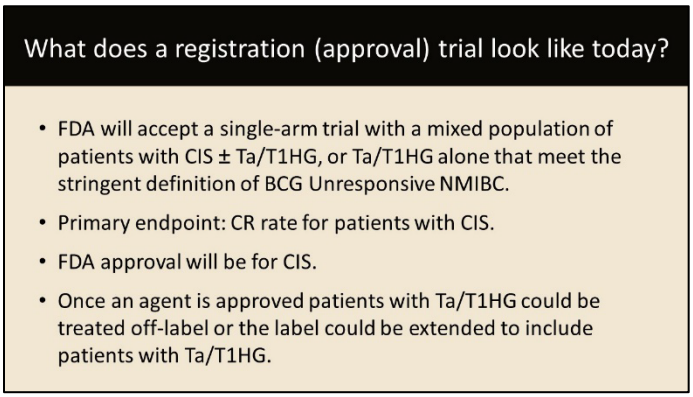
Now, back in 2014, the FDA approached a group of us and asked us to identify the patient population that would not benefit from additional BCG, and those were patients who had persistent high-grade disease after adequate BCG being defined as having induction BCG plus first maintenance.



It also included patients who initially responded to BCG but then recurred a high-grade papillary disease and individuals who had persistent or progression to T1 disease. That's that minimally invasive tumor. So, we thought they were especially aggressive subtype.

Dr. Colin Dinney:

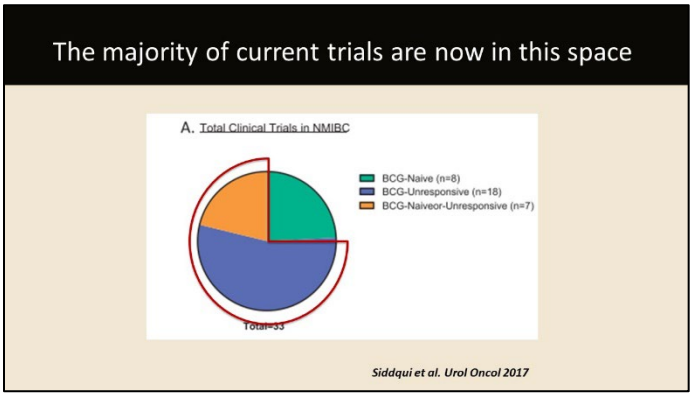
So, what does a registration or approval trial look like today? Well, the FDA will accept a single-arm trial. We don't have to do a randomized trial in this disease space because it was not feasible and there really isn't an acceptable comparator for a trial.



This is a trial of a mixed population of patients who have carcinoma in situ with or without high-grade Ta or T1 or patients with high-grade Ta and T1 disease only, providing that they meet the stringent definition of BCG unresponsive disease. Now, the FDA has made it clear that the primary endpoint will be the complete response rate for patients with carcinoma in situ, and that the approval will be for carcinoma in situ. Now, once an agent is approved, patients who have Ta and T1 high-grade only could be treated off-label or perhaps the label could be extended to include them, although that hasn't happened yet.

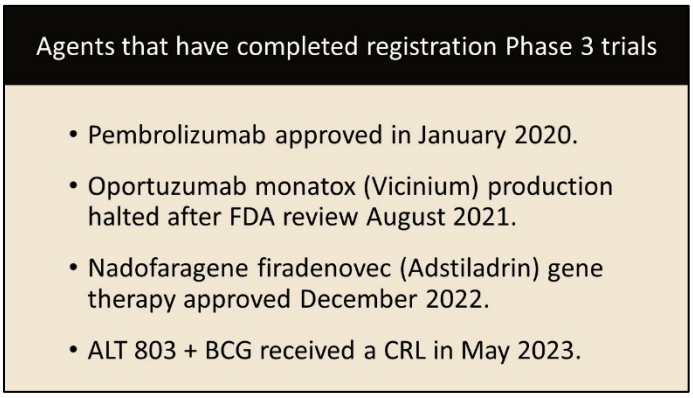
Dr. Colin Dinney:

Now these efforts have been successful because today the vast majority of clinical trials for patients with non-muscle invasive bladder cancer include patients with BCG unresponsive disease.



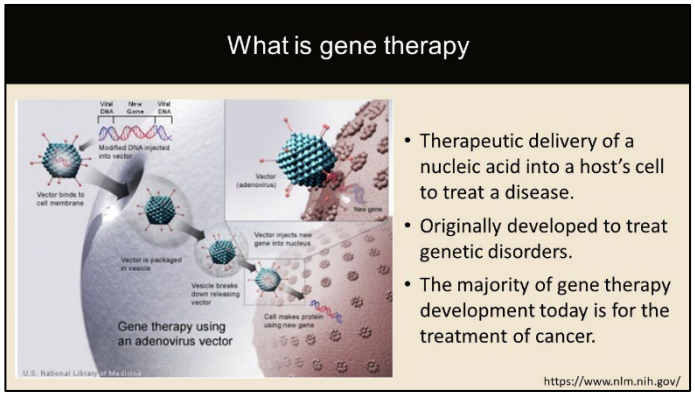
Dr. Colin Dinney:

Now, these are the agents that recently have completed registration phase three trials. Pembrolizumab was approved in January 2020. Another drug, Oportuzumab Monatox or Vicinium went to the FDA panel in August of 2021. But issues came up and the production of this drug has been halted. The drug we're talking about today, Adstiladrin was approved by the FDA in December of 2022. And recently, the combination of ALT 803 and BCG went to the FDA but it was not approved. And right now the company is addressing FDA issues.



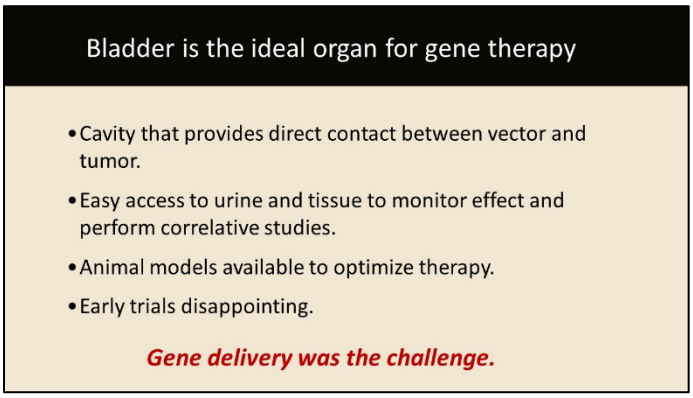
Dr. Colin Dinney:

So, what is gene therapy? So, gene therapy really is the delivery of a nucleic acid that's the building block of your DNA into a host's cell to treat a disease. Now, gene therapy was originally developed to treat genetic disorders, but today the majority of gene therapy development is for the treatment of cancer.



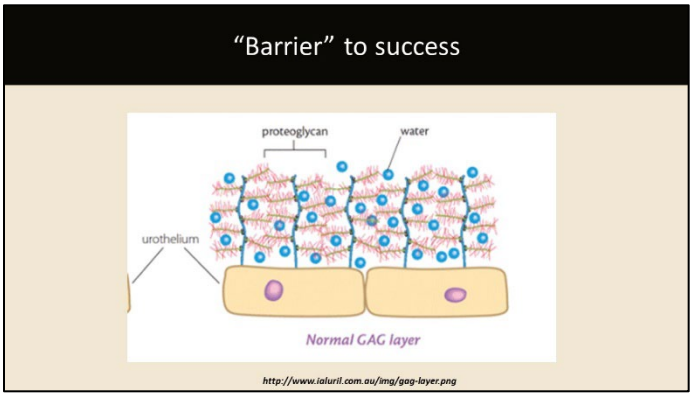
Dr. Colin Dinney:

And if you think about it, the bladder is an ideal organ for gene therapy. It's a cavity that allows for direct contact between the vector. The vector is the agent that carries the gene. In our case, it's adenovirus, and the tumor. We have relatively easy access to urine and tissue to monitor the effects of therapy and to perform correlative studies that might link some biomarker expression to response. We have models available to optimize therapy, but despite the relative advantages of developing gene therapy for bladder cancer, the early trials were disappointing because gene delivery was a real challenge.



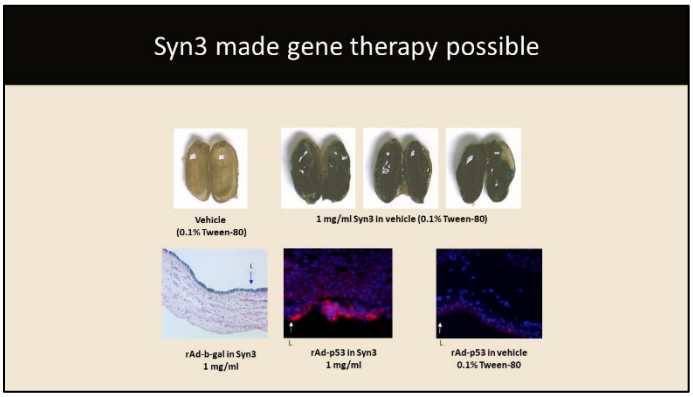
Dr. Colin Dinney:

So, the barrier to success was the GAG layer, a glycan layer that lines the urothelium. It's designed to prevent infections of the bladder by bacteria and viruses, and that was the barrier to effective gene transfer across the urothelium.



Dr. Colin Dinney:

So, we were very fortunate. Early on we worked with a company called Canji. They were the gene therapy subsidiary of Schering, and they identified this drug. They discovered this drug called Syn3. It's a detergent which made gene therapy possible. So, I'm showing you some early work that they did.

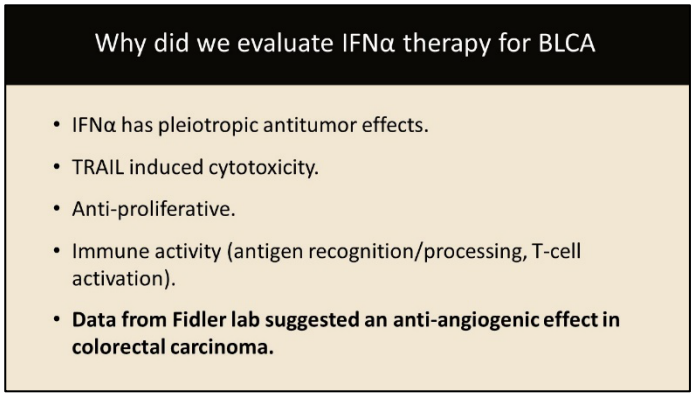


What they did was they took adenovirus containing a gene, not the interferon gene, but a gene called beta-galactosidase. If that gene is expressed by the bladder, if they can effectively transfer that gene to the bladder, it turns the bladder blue. And you can see here that when they administered that vector with the gene, with Syn3, they turned all the bladders blue. Without Syn3, there was no gene transfer. So, Syn3 made all the difference. Syn3 allowed for this gene to be transferred.

This is another experiment they did. They delivered another gene in adenovirus. This was the p53 gene, which you may have heard of. And then, they took sections, and this is with Syn3 and without Syn3. Then they took sections from that bladder and they stained them with immunofluorescent antibodies to p53. So, you can see with Syn3, you're seeing lots of fluorescence of the cells indicating the expression of p53, not so when they didn't use it. So, Syn3 was the difference-maker and it was the game-changer for us in developing gene therapy.

Dr. Colin Dinney:

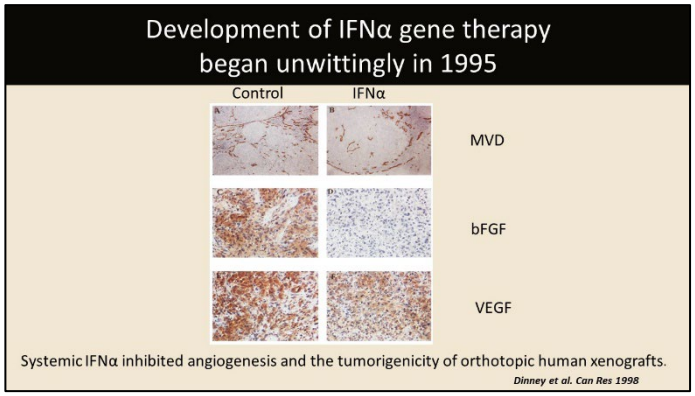
You might ask why did we evaluate interferon alpha gene therapy for bladder cancer. Well, I mean, interferon alpha has pleiotropic antitumor activity. It can kill cells directly through releasing an agent called TRAIL. It's anti-proliferative. That means it stops cancer cells from dividing. And recently there's a lot of interest in its immune activities involved in antigen recognition and processing, leading to activation of T-cells that could kill the tumor cells and NK cells and macrophages. But that's not why we started developing interferon gene therapy.



It actually started because data from Josh Fidler's lab, he was my mentor at MD Anderson when I started. This was at the era when anti-angiogenesis therapy was in vogue, and the data from his laboratory suggests that interferon alpha had an anti-angiogenic effect in colorectal cancer. So, essentially, they were saying that interferon could actually choke off the tumor's blood supply because the tumors grow by inducing a blood supply that feeds them nutrients and allows them to grow. If you can stop that, you can theoretically stop the tumor from growing. So, that's how the development of this began.

Dr. Colin Dinney:

I was studying interferon as an anti-angiogenic agent using a model that we developed for metastatic bladder cancer and seeing if interferon would inhibit angiogenesis, inhibit tumor growth. So, this is histochemical staining for a protein called basic FGF, which promotes blood vessel formation. And you can see with interferon, we're not seeing any expression of the protein. In the control we're seeing strong expression. When we counted blood vessels, we also saw that they went down. So, what we found was that systemic interferon, inhibited angiogenesis and the growth of these bladder tumors.



Dr. Colin Dinney:

So, the next series of experiments we asked, does the schedule of interferon influence the response. So, we treated these tumors, these mice with these human tumors with a constant weekly dose of interferon, 70,000 units a week, either once a week bolus of 70,000, 35,000 units twice a week or 10,000 units daily. And we found that the daily interferon was more effective at inhibiting tumor growth.

Does the schedule of IFNα influence response?

IFN-α Therapy	Tumor weight (mg) Median	Range
Control	376	130 - 434
IFN-α 10,000 U Daily	**54***	**24 - 36**
IFN-α 35,000 U Bi-weekly	247	108 - 387
IFN-α 70,000 U Once per week	240	84 - 427

*p< 0.05

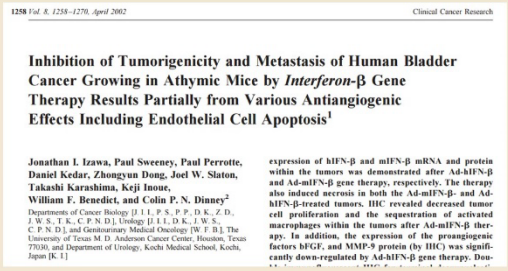
Daily IFNα more effective against this IFN resistant cell line.

Slaton et al, Clin Can Res 1999

Dr. Colin Dinney:

We asked ourselves, how can you deliver continuous low-dose interferon alpha? And the answer to that question led us to interferon gene therapy. And this is actually the first work that was published by my group where we showed that interferon gene therapy could inhibit tumor growth by inhibiting angiogenesis. We published this in 2002, 20 years before the drug was approved.

How can you deliver continuous low dose IFNα?



1258 *Vol. 8, 1258–1270, April 2002* Clinical Cancer Research

Inhibition of Tumorigenicity and Metastasis of Human Bladder Cancer Growing in Athymic Mice by *Interferon*-β Gene Therapy Results Partially from Various Antiangiogenic Effects Including Endothelial Cell Apoptosis[1]

Jonathan I. Izawa, Paul Sweeney, Paul Perrotte, Daniel Kedar, Zhongyun Dong, Joel W. Slaton, Takashi Karashima, Keji Inoue, William F. Benedict, and Colin P. N. Dinney[2]

Departments of Cancer Biology [J. I. I., P. S., P. P., D. K., Z. D., J. W. S., T. K., C. P. N. D.], Urology [J. I. I., D. K., J. W. S., C. P. N. D.], and Genitourinary Medical Oncology [W. F. B.], The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, and Department of Urology, Kochi Medical School, Kochi, Japan [K. I.]

expression of hIFN-β and mIFN-β mRNA and protein within the tumors was demonstrated after Ad-hIFN-β and Ad-mIFN-β gene therapy, respectively. The therapy also induced necrosis in both the Ad-mIFN-β- and Ad-hIFN-β-treated tumors. IHC revealed decreased tumor cell proliferation and the sequestration of activated macrophages within the tumors after Ad-mIFN-β therapy. In addition, the expression of the proangiogenic factors bFGF, and MMP-9 protein (by IHC) was significantly down-regulated by Ad-hIFN-β gene therapy. Dou-

The answer led us to interferon gene therapy.

Dr. Colin Dinney:

So, based upon that work, we hypothesized that this potentially could be a new drug for treating patients with non-muscle invasive bladder cancer. We knew that the intravesical interferon protein was largely ineffective because there was insufficient exposure of the tumor to the interferon due to the transient availability after installation. So, this recombinant ad interferon with Syn3 was developed to overcome this limitation.

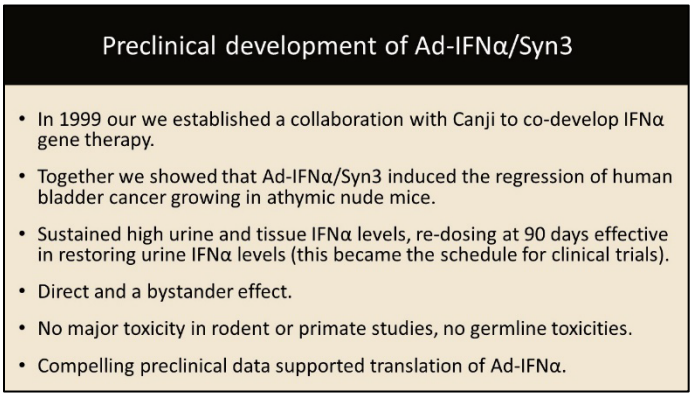
Developing intravesical IFNα gene therapy

- We hypothesized that intravesical IFNα gene therapy represented a novel paradigm for the treatment of NMIBC.
- Intravesical IFNα protein was ineffective due to insufficient exposure due to transient IFNα availability after bladder instillation.
- rAd-IFNα/Syn3 was developed to overcome this limitation.
- Essentially the bladder becomes a bioreactor that produces high, sustained IFNα levels in the bladder and urine.
- Collaborated with Canji who provided Syn3 and Ad-IFNα vectors.

So, when you infect the bladder, essentially the bladder becomes a bioreactor that produces high sustained levels of interferon that you could measure in the bladder and the urine. So, we collaborated with Canji back in the late '90s because they had Syn3 and they had vectors that we could use in our experiments.

Dr. Colin Dinney:

So, together starting in 1999, we co-developed interferon alpha gene therapy. Together we showed that ad interferon with Syn3 could inhibit the growth of human bladder cancer growing in mice, and this was accompanied by sustained high levels of interferon in the urine and the tissues.

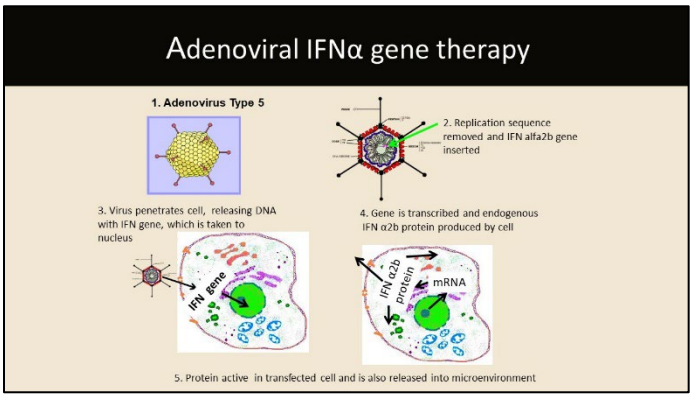


We didn't think that one dose would be sufficient. So, we did some experiments to see about the timing of re-dosing, and we found that we had to wait out to 90 days to re-dose these animals in order to restore urine interferon alpha levels in the urine. And this is how the schedule for the drug was developed. It came directly from this experiment, and that's why the schedule for Adstiladrin is one intravesical therapy every 90 days or every three months. We also found that it had both a direct effect and a bystander effect. And a bystander effect is the effect of killing a tumor cell that isn't been infected by the virus.

Now, it's virtually impossible to infect every single cell in the bladder with the viral treatment. However, we're very fortunate that interferon has a very rich bystander effect that's mediated through its anti-angiogenic effect through TRAIL that's released into the urine and can kill neighboring cells, and also by its role in signaling immune system. We did not see any major toxicity in any preclinical studies, no germline toxicities. And so, the data suggested and supported the translation of this work in the lab into the clinic.

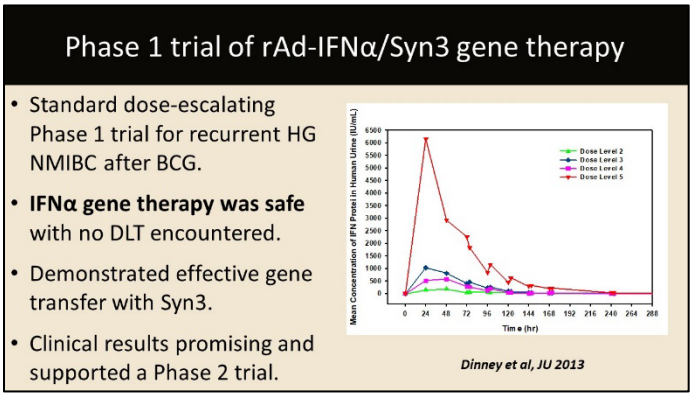
Dr. Colin Dinney:

So, this is the vector we're using. It's an adenovirus type five. It's a first generation adenovirus. We construct it so that it has the interferon alfa, it expresses the interferon alfa gene in its DNA. We then would instill this vector with a Syn3 into the bladder. The virus will penetrate a cell, either a normal cell or a cancer cell and releasing its DNA with interferon gene, which is taken up into the nucleus. The gene is then transcribed in the nucleus, and the protein is translated in the cytoplasm of the cell within the cell and released intracellularly, which can kill that cell or into the microenvironment.



Dr. Colin Dinney:

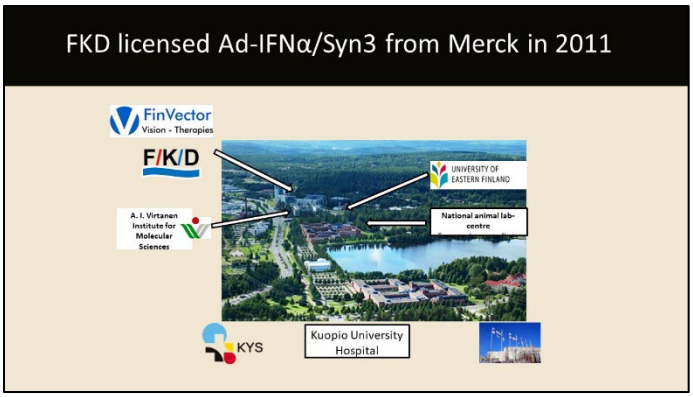
And so, using that vector, that drug, we did a phase one study.



This was sponsored by Schering, and this was a standard dose-escalating phase one trial for recurrent high-grade non-muscle invasive bladder cancer after BCG. We had not yet coined the term BCG unresponsive disease. What we found in this phase one study was that interferon alpha gene therapy was safe. We did not encounter any dose-limiting toxicity, and we were able to demonstrate effective gene transfer by measuring interferon levels in the urine. So, we were able to actually infect the bladder and have the bladder produce interferon. Now, while this was a phase one study, the clinical results were promising and together everything supported a phase two trial.

Dr. Colin Dinney:

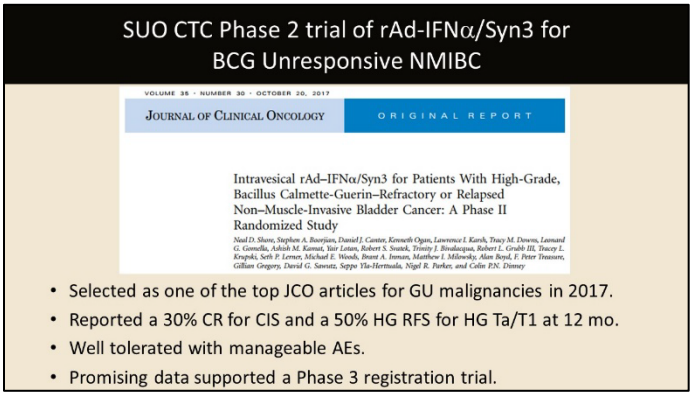
Now there have been a lot of bumps in the road along the development of this drug. And at that point in time, Schering was brought up by Merck. Merck had other priorities and put the product on the shelf. And it sat on the shelf for about a year and a half to two years until FKD, a small gene therapy company in Finland licensed the product from Merck in 2011, after the CEO talked to me about the drug. At around the same time, the SUO, the Society of Urological Oncology, formed the SUO's Clinical Trials Consortium (CTC). I was the founding president of that organization and I was the lead of the bladder committee.



And our goal was to develop trials for urologists to get involved in clinical research. So, we needed a clinical trial to jumpstart the SUO-CTC. FKD needed a clinical trials group to run their phase two trial. And so, I negotiated with them such that the SUO-CTC would be the exclusive site for their phase two trial.

Dr. Colin Dinney:

And we conducted a phase two trial, the SUO-CTC, and we reported a 30% complete response rate for CIS and a 50% high-grade recurrence-free survival for high grade Ta and T1 at 12 months. And this 30% CR rate is about threefold higher than was reported with valrubicin.



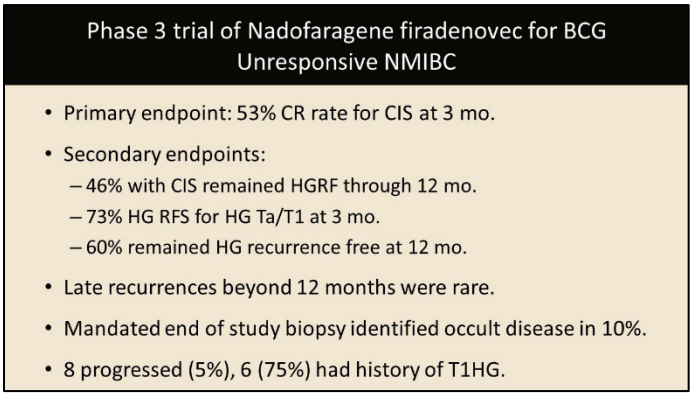
We also found that the drug was well tolerated with manageable adverse events. And in fact, we published this in a high impact journal, the Journal of Clinical Oncology. And in fact, this article was selected as one of the top JCU articles for GU malignancies in 2011. And the promising data supported a phase three registration trial.

Dr. Colin Dinney:

So, this is the phase three trial of Adstiladrin. This is the trial that led to the approval by the FDA.

Dr. Colin Dinney:

And we reported as a primary endpoint, a 53% complete response rate for carcinoma in situ at three months. And in those patients with carcinoma in situ who achieved a CR, about half those patients maintained that high grade recurrence-free survival through 12 months. They didn't recur through the 12-month period. For patients with high grade Ta or T1 disease, 73% were high grade recurrence-free at three months, and 60% maintained that status at 12 months.



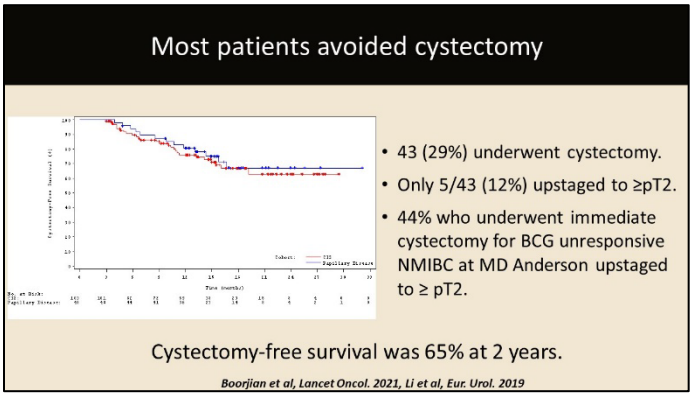
And that was important because late recurrences beyond 12 months were very rare. And so, recurrence-free survival was fairly stable after that point. Now, our study differed from most of them in the same

space that we're in. We had a mandated end-of-study biopsy and we found occult disease in 10% of the patients who underwent the biopsy. These have been patients that we would've considered to have had been disease-free based on clinical grounds, cystoscopy and the results of cytology. So, we found disease in 10%.

Now, of the patients on our trial, eight patients are 5% progressed. That's not a high level. No patients died from bladder cancer. But of the eight patients that progressed, six of the eight or 75% had a history of T1 high grade. And now again, that's the lesion that's minimally invasive, and in fact, it's notoriously understaged. So, it's likely that some of the patients who came on the trial had occult muscle-invasive disease at the time that they were treated, and they actually did not progress, but they had the disease when they started.

Dr. Colin Dinney:

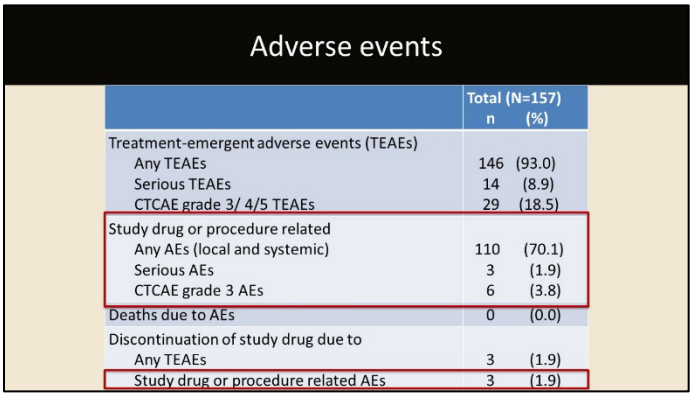
Now of course, the other goal of the study is to avoid a radical cystectomy. Forty-three patients or 29% ultimately underwent cystectomy. And the cystectomy-free survival was 65% at two years. If you looked at those patients who underwent cystectomy on this trial, only five of 43 or 12% upstaged to having muscle-invasive disease or greater. So, I think that points to the high quality of the study and then the investigators on the trial. Because we looked at our patients who were referred to MD Anderson. So, they came to MD Anderson with BCG unresponsive disease for a radical cystectomy.



And when we did the radical cystectomy, we found that 44% were upstaged to pT2 at cystectomy. So, you can see the high quality of the investigators that did this trial because the risk of progression was much lower.

Dr. Colin Dinney:

Now, there were adverse events secondary to the treatment, and study drug, the Adstiladrin, or procedure-related adverse events occurred to about 70% of our patients. The procedure-related events are related to the catheterization. That's the procedure.

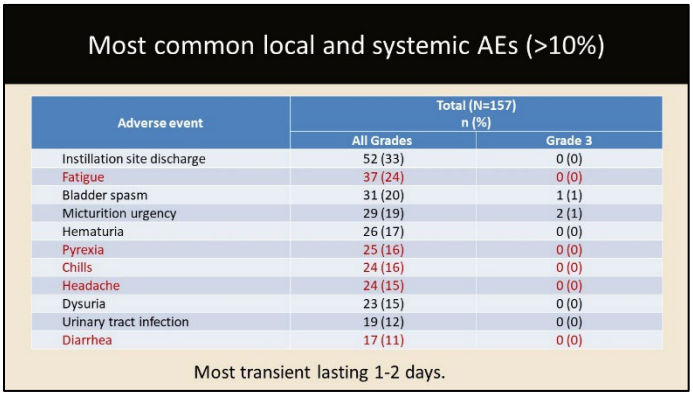


	Total (N=157) n	(%)
Treatment-emergent adverse events (TEAEs)		
Any TEAEs	146	(93.0)
Serious TEAEs	14	(8.9)
CTCAE grade 3/ 4/5 TEAEs	29	(18.5)
Study drug or procedure related		
Any AEs (local and systemic)	110	(70.1)
Serious AEs	3	(1.9)
CTCAE grade 3 AEs	6	(3.8)
Deaths due to AEs	0	(0.0)
Discontinuation of study drug due to		
Any TEAEs	3	(1.9)
Study drug or procedure related AEs	3	(1.9)

Fortunately, most of the adverse events were minor. Only three patients or 2% had a serious adverse event, and no patients died from an adverse event secondary to the drug or procedure. And in fact, only three patients or 2% discontinued the study drug secondary to a treatment related adverse event. So, that's pretty good. That speaks to the tolerability of the agent.

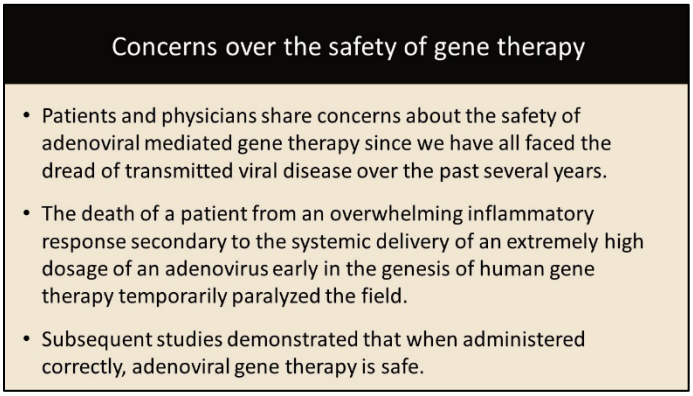
Dr. Colin Dinney:

Now, here are the most common local and systemic adverse events that were seen at least 10% of the patients on the trial. In dark, you can see the local symptoms. Majority were bladder spasms were common, or urinary urgency, blood in the urine, painful urination, urinary tract infection. We also saw systemic side effects such as fatigue, fever, chills, headache, or diarrhea. And these are likely related to the exposure to the low-dose interferon. But luckily, most of these adverse events were transient, lasting only one to two days.



Dr. Colin Dinney:

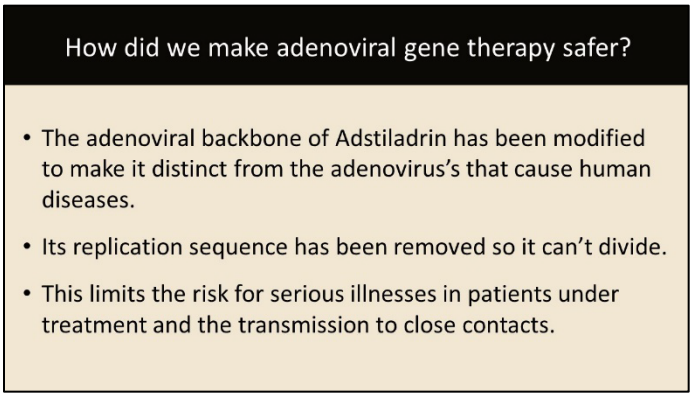
Now, there are other concerns that you might have about gene therapy, especially when we think about the last couple of years we've gone through. Patients and physicians alike share concerns about the safety of adenoviral gene therapy after living through the consequences of transmitted viral disease over the past several years. And there was an unfortunate death of a patient from an overwhelming inflammatory response secondary to the delivery of an extremely high dose of the adenovirus early on. And this temporarily paralyzed the field. I mean, this was an inappropriate treatment. The patient, a young man died from complications from the therapy. So, gene therapy really stopped for a while.



Subsequent studies, including our own, demonstrated that when administered correctly the therapy is safe. We don't say you're not at risk for an overwhelming inflammatory response. It's much safer than you would think.

Dr. Colin Dinney:

Now why is that? Well, also, the adenoviral backbone of Adstiladrin has been changed to make it distinct from the adenoviruses that cause human disease. So, the part of the gene, the virus's gene that controls replication has been removed so the virus can't divide. The virus will infect the bladder, release the interferon, and then the virus is gone. And what does this do? Well, this limits the risk for severe illnesses for patients under treatment and also transmission to close contact, to their close contacts.



Dr. Colin Dinney:

And there's another theoretical concern, and this is the risk for insertional mutagenesis and a secondary malignancy falling incorporation of viral DNA into the patient's DNA. Some viruses inserted into your own DNA and they can cause a problem.

How did we make adenoviral gene therapy safer?
• Also minimizes the risk for viral gene insertional mutagenesis and the development of a secondary malignancy. • Adstiladrin is delivered directly into the bladder and no measurable viral interferon-α DNA has been detected in the circulation. • Indicates that there is limited transmission of the virus outside the bladder. • No risk for germline transmission.

A good example of that is the AIDS virus. It is a lentivirus that becomes incorporated into the host's DNA and causes serious problems. Now, our virus is not incorporated into the host's DNA. So, this is not a problem. And in fact, we really didn't even measure any viral DNA in the circulation after intravesical therapy because there's limited transmission of the virus outside the bladder. So, the virus is not getting outside the bladder. There's also no risk for germline transmission. You couldn't transfer the virus to, say, an offspring. That doesn't happen as well.

Dr. Colin Dinney:

Another concern would be that patients who might have a cold or a flu might have natural antibodies in their circulation that could neutralize the adenovirus and make the gene therapy less effective. Now, this concern has not been borne out by clinical experience. And in fact, we've found that generating higher titers of systemic antiviral antibodies actually predicts for a favorable clinical response. So, patients who have more antibodies in their circulation have a better response to the adenoviral gene therapy, likely because they have a more profound immune response to the therapy and an inflammatory response.

Concerns about gene therapy
• A final concern is the risk for an immune reaction or an unpredictable off-target effect. • Patients who have a cold or flu might have natural antibodies in their circulation that could neutralize the adenovirus, rendering viral gene therapy less effective. • This concern has not been borne out by clinical experience. • The induction of systemic anti-adenoviral antibodies actually predicted for a favorable clinical response (Mitra).

Dr. Colin Dinney:

So, just to summarize, we found that on the phase three trial that, acceptable safety and tolerability of Adstiladrin. As I mentioned, most adverse events were transient, lasting one to two days. We only had one grade four adverse event, which was secondary to a urinary tract infection, no grade five drug or procedure-related events. And so, no patients died from an adverse event related to the drug. Fourteen patients or 9% had a total of 26 serious adverse events, but only

Phase 3 trial of Nadofaragene firadenovec
• Acceptable safety and tolerability. • Most AE were transient (1-2 days). • One Grade 4 and no Grade 5 drug/procedure related AE's. • 14 (9%) patients had a total of 26 serious adverse events. • Only 3 drug or procedure related SAEs (2%). • Syncope related to drug, sepsis, and hematuria related to procedure.

three of those were drug or procedure related for 2%. And the adverse events that were considered serious, one patient fainted after getting the drug.

And I'm not even really sure this is an adverse event related to the drug, but it was quoted that way by the site PI. Therefore, that's how it's recorded. One patient developed sepsis and that was the patient that had the grade four adverse event and one patient had blood in their urine secondary to the catheterization.

Dr. Colin Dinney:

As I mentioned, three patients or 2% stopped treatment because of a treatment-related adverse event. Two of these were bladder spasms and one patient had this benign proliferative bladder growth. It wasn't the cancer, but they came off the trial. We don't see any of the immune-related adverse events that characterize drugs like pembrolizumab.

Phase 3 trial of Nadofaragene firadenovec for BCG Unresponsive NMIBC

- 3 (2%) stopped treatment because of treatment related adverse events: 2 bladder spasms, one benign bladder growth.
- No pattern of immune-related adverse events.
- No treatment-related or deaths from bladder cancer.
- Convenient dosing schedule with only one intravesical treatment/q3 months.
- **Nadofaragene firadenovec provides a favourable benefit-risk profile for patients facing cystectomy.**

As I said, no treatment-related deaths or even deaths from bladder cancer. And I think one of the more favorable aspects to this drug is this convenient dosing schedule. Patients only need one intravesical therapy every three months. So, based on this, we concluded that Adstiladrin does provide a favorable benefit-risk profile for patients facing cystectomy.

Dr. Colin Dinney:

How does Adstiladrin compare to the other drug that has been recently approved for this indication? That's pembrolizumab. So, the trials were quite different. So, the Adstiladrin trial, all of the patients were from the US because it was a US-based trial. The pembrolizumab trial was an international trial, and 35% of the patients only were from the US. If you look at the three-month complete response rate for CIS, we reported it to be 53%, where pembro was 41%. But if you looked at the US population, it was only 31%.

Head-to-head: Adstiladrin vs. Pembrolizumab

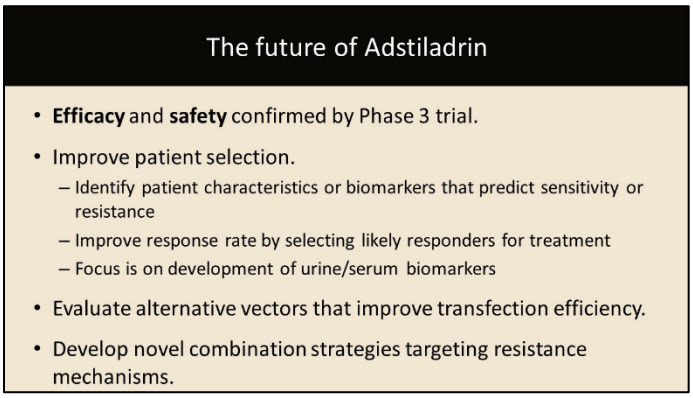
	Adstiladrin	Pembrolizumab
US population	100%	35%
3 mo. CR (CIS)	53%	41% (31% in US population)
12 mo. CR (CIS)	24% (with biopsy) 27% (without)	19% (without)
12 mo. CR in US population	24%	13% (estimated)
Treatment related G3-4 AE	5% SAE (2%)	13% SAE (8%)
Mode of administration	Intravesical	Intravenous
Treatment intensity	Q3 mo. x 4 years	Q3 wk x 2 years
Administered by	Urologist	Medical Oncologist

The patients that really benefited from pembro were patients that were treated in Asia, in Korea, and in Japan where they have a different definition of BCG unresponsive disease. Some of these patients may not have been considered to be BCG unresponsive in a US population. If you look at the 12-month complete response rate for patients with CIS, we reported 24% with a biopsy, 27% without a biopsy. And for pembrolizumab is 19% without a biopsy. If you look at the 12-month complete response rate in the US population, well, it's the same. It was 24% in our trial because everybody was from the US.

And for pembrolizumab, if you estimate it based upon the CR rate at three months and the durability data, it comes out to be about 13%, and that's not much better than valrubicin. And there's a price to pay for that. You can see that the treatment-related adverse events, grade three and four are 5% with Adstiladrin, 13% with pembro. And serious adverse events, 2% versus 8%. Furthermore, the schedule is a benefit, one intravesical therapy every three months, and it is administered by an urologist who's very aware of how to manage this disease.

Dr. Colin Dinney:

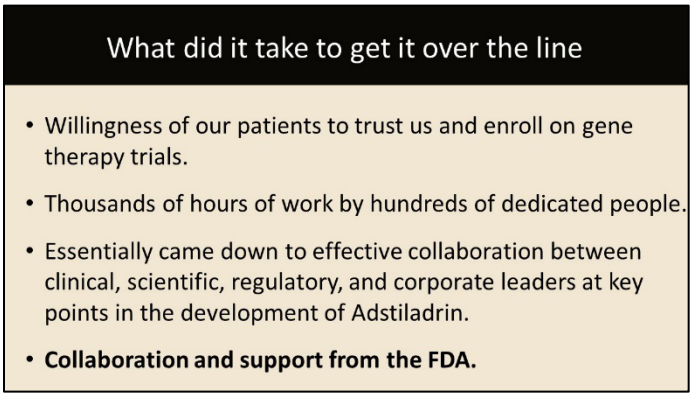
So, just to summarize then, the efficacy and safety of Adstiladrin was confirmed by the phase three trial. We're very pleased with the results to date. We do feel we can do better. And how are we going to do that? We're going to do that, first of all, by improving patient selection. So, either by identifying patient characteristics or biomarkers that predict sensitivity resistance and how will that improve response rates? It'll improve response rate because we'll select patients that are likely to respond to treatment.



And our focus is on the development of urine and serum biomarkers so we can avoid a biopsy. We're also looking at alternative vectors, so other viruses or non-viral vectors that might improve the delivery of the gene and doing so might improve the response. And we're very interested in developing novel combination strategies, targeting resistance mechanisms through Adstiladrin.

Dr. Colin Dinney:

So, finally, what did it take to get us over the line? Well, really, it took the willingness of our patients to trust us and enroll in these gene therapy trials. It took thousands of hours of work by hundreds of dedicated people, and essentially came down to an effective collaboration between clinical, scientific, regulatory, and corporate leaders at key points in the development of this drug. And of course, we could have done this with the collaboration and the support of the FDA.



Dr. Colin Dinney:

Thank you for your attention and I'd be happy to answer any questions.