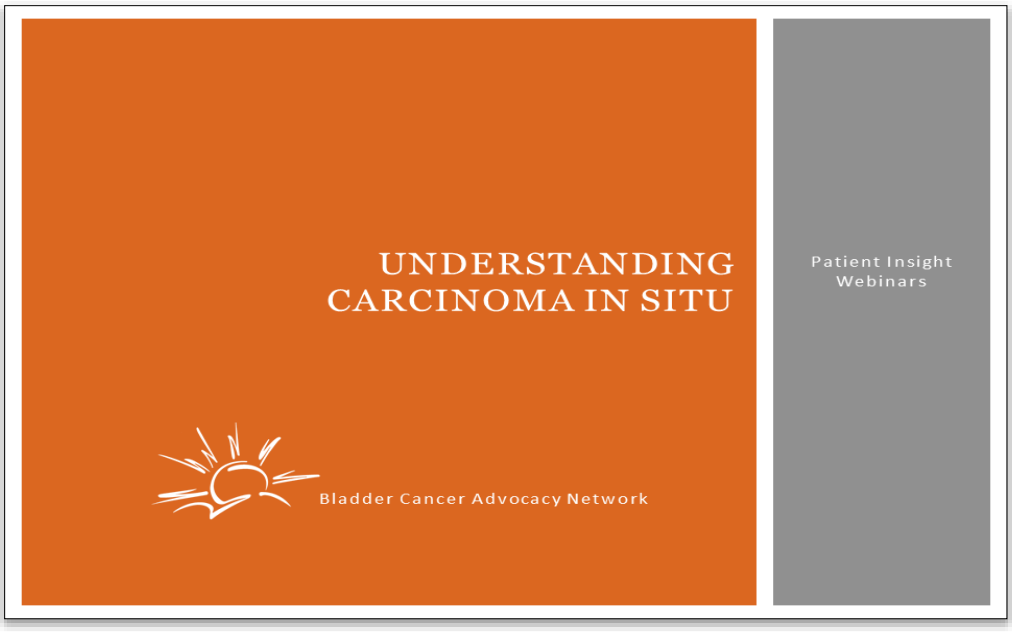
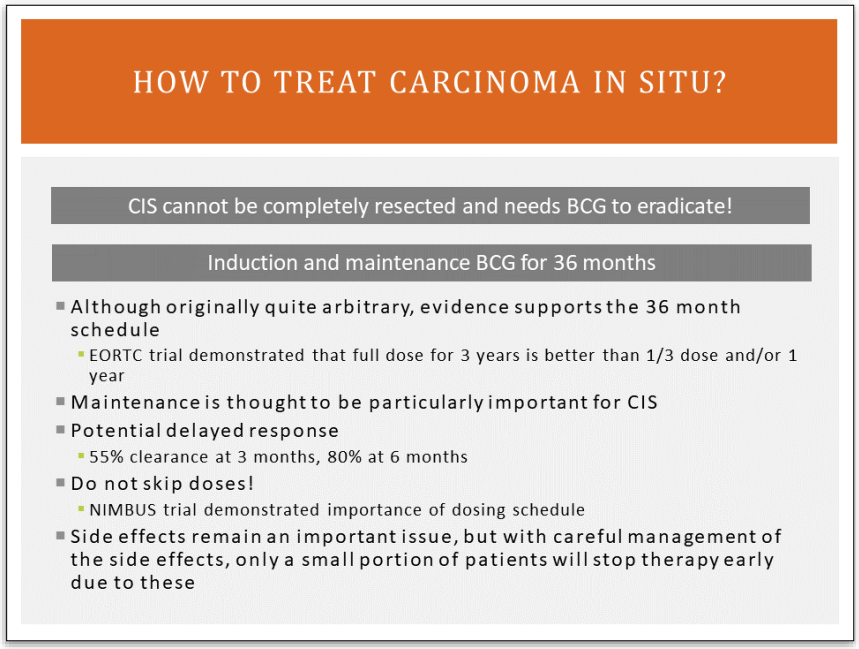


Dr. Peter Black:

Great. I would take this pathology report that Hikmat has provided and sit down with the patient and say, "Okay, how are we going to treat this carcinoma in situ?" It's pure carcinoma in situ. There's nothing else there. One thing to highlight again is that we cannot count on having completely resected this. An 87-year-old patient with a lot of medical problems who maybe had a papillary tumor where we're confident we resected it all, we could consider of course doing that here. We can also consider doing nothing, but there, we would have some confidence that we may have resected it all, whereas here we would not have that confidence.



The standard of care for a patient like this is to give intravesical BCG treatment for the full three-year course. So six induction courses, and then the maintenance therapy up to 36 months. And although this 36-month schedule seems rather arbitrary, and it was initially arbitrary, there's actually very good evidence to support its use. There's a European trial, for example, that compared three years versus one year and a full dose versus a third dose, and it showed that the full three years, full dose has the best outcomes. That wasn't specific to carcinoma in situ, but we think that maintenance is maybe even more important to carcinoma in situ because we can't resect it all.

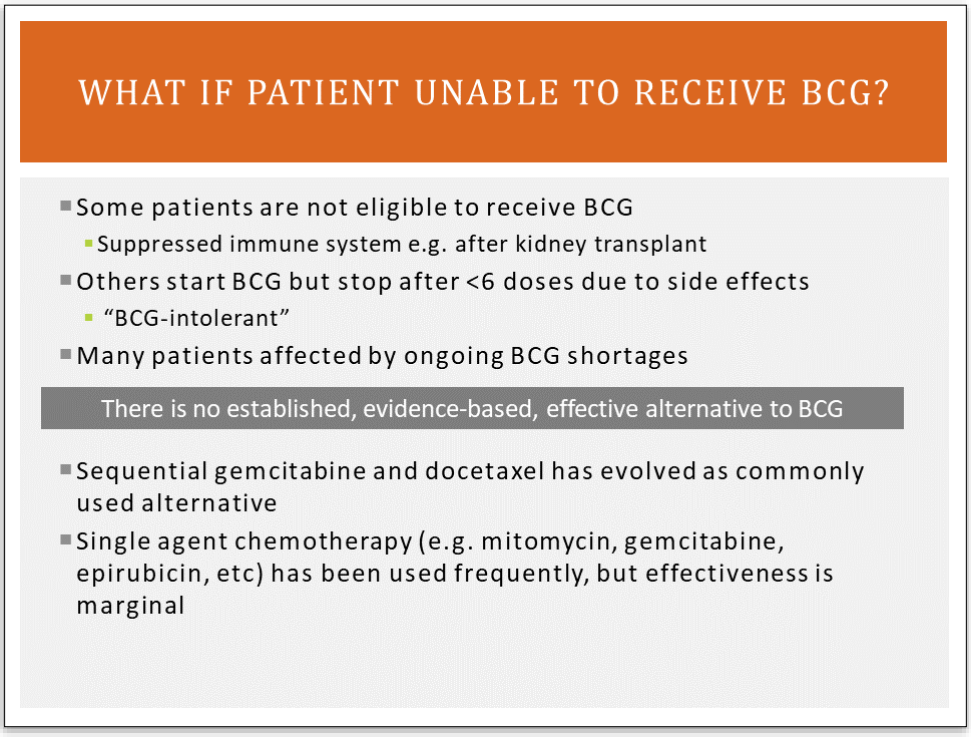
Really interesting with carcinoma in situ is that we often or we can see a delayed response. The early, biggest trial that showed us that we need to do maintenance therapy, some patients had maintenance

and some didn't, and we saw that at three months after just the first six induction doses of BCG, 55% of patients had cleared the carcinoma in situ from their bladder. But at six months, it was up to 80% if the patients got maintenance therapy. So we see that there's a good 25% of patients who are having response beyond the first three months, so it's critically important to wait for those first six months.

Dr. Peter Black:

It's important not to skip doses. So in an era of BCG shortage, we tend to reduce the dose or shorten the maintenance if we have to. We think that longer is better, up to three years, but the differences are fairly small, but there's a trial published now two years ago that tried to reduce the number of doses, the Nimbus trial, and it showed a dramatic difference in efficacy. So we really need to stick to the schedule, but if we have to, we can reduce the dose or shorten maintenance.

Side effects of course are important with BCG. It represents an important burden on patients. It can cause a lot of local bladder symptoms. It can cause patients to have low-grade temperatures, just generally feel lousy, but we are able to manage those symptoms and I would say the stakes are high. It's about preserving the bladder and avoiding removal, and so most patients are motivated to be compliant and the rate of stopping because the side effects I think is relatively low, even though it's something that we certainly worry about. Next slide.

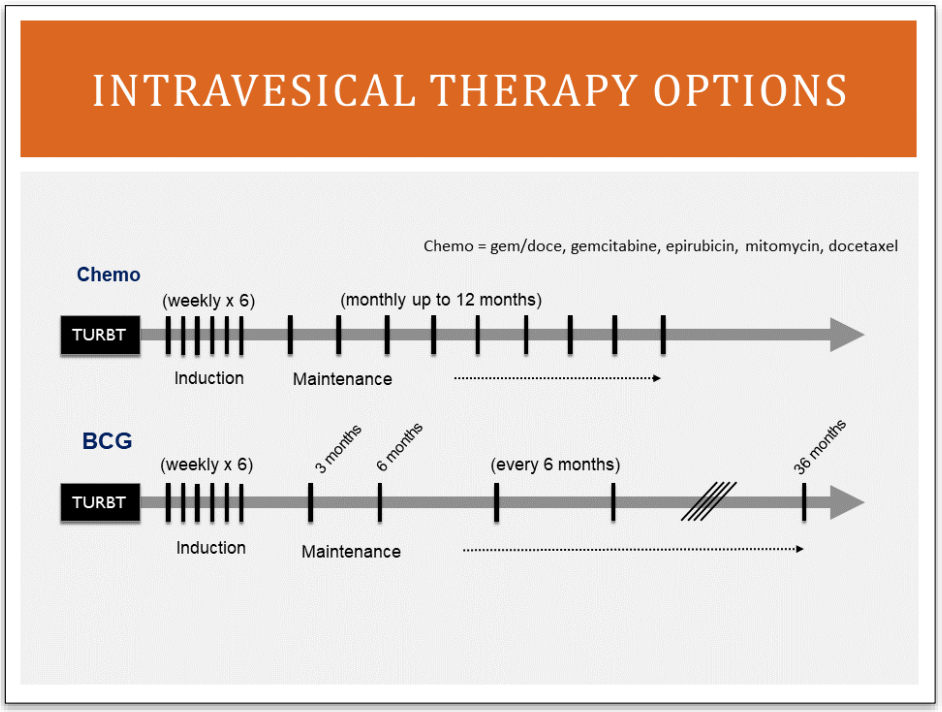


So, what if a patient cannot get BCG? So, a patient with carcinoma in situ of the bladder, this could be a patient, for example, who's had a kidney transplant. And so the patient is on immunosuppressive medications that would make BCG a little bit dangerous, but also unlikely to work since it's dependent on a functioning immune system, Other patients, so-called BCG intolerance patients or their disease is BCG intolerant, they have to stop before they get the full induction course, and they can't have any additional BCG. I had a patient, for example, recently who developed a joint inflammation that was triggered by the BCG and we couldn't give more BCG because we would trigger the same again. And so for these patients, and of course, there's a BCG shortage, so maybe in the last few years, the most common reason not to get BCG is because it hasn't been available.

Dr. Peter Black:

Regardless of the cause, there's no established evidence-based effective alternative to BCG. And this is a big unmet need in the care of bladder cancer patients. And it's not just carcinoma in situ it's also high-grade Ta and T1 tumors. There's no really well-defined alternative. I'd say one thing that has sort of

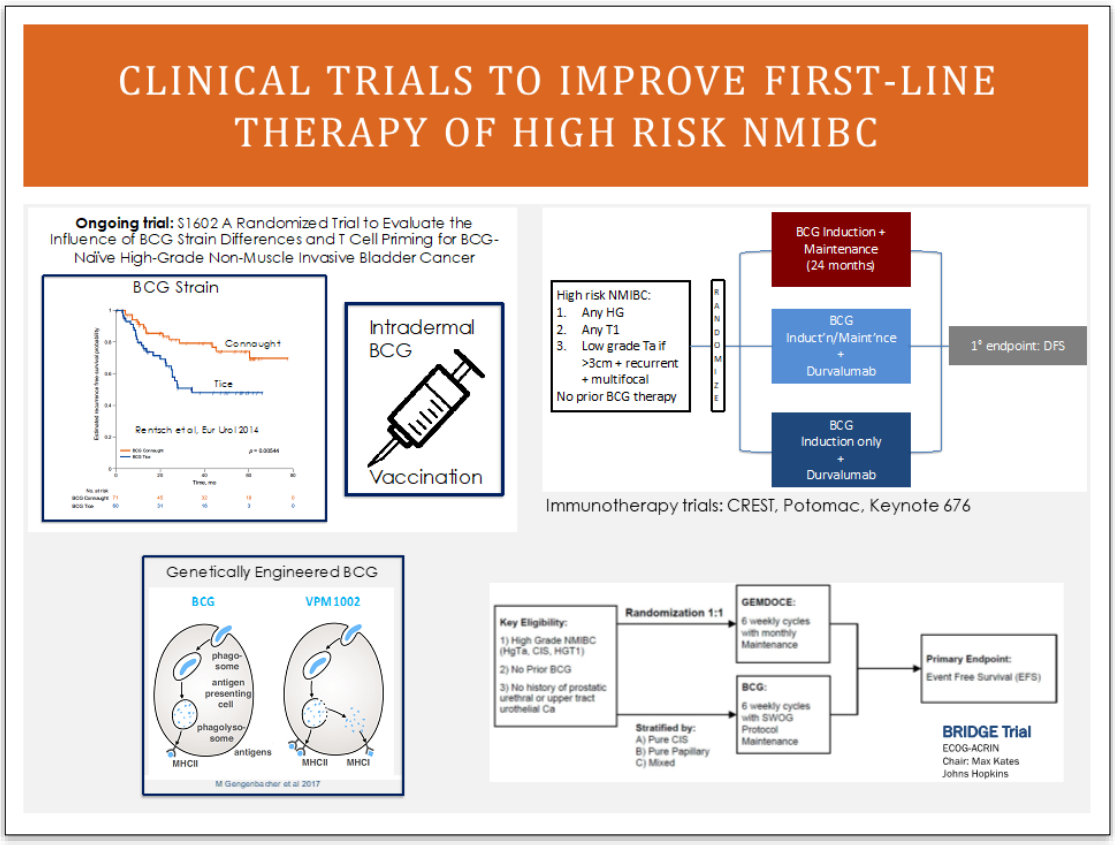
evolved over the past few years is that this combination of gemcitabine and docetaxel, where on the same day, the patient gets gemcitabine and then docetaxel has evolved as a commonly used alternative, and there's now a big trial that is going to evaluate how it compares to BCG. Otherwise, what you'll find in a lot of places around Canada and the US is that a single dose of chemotherapy is used, but it's really not a single dose, a single agent, so either mitomycin or gemcitabine, but it's not really effective. It does not compare to BCG. Next slide.



Dr. Peter Black:

This just reiterates what many of you are probably familiar with. At the top, you can see the intravesical chemotherapy, which is given once a week for six weeks and then monthly up to a year. And that can be either the combination that I talked about or one of the single drugs, or the bottom BCG, which is given once a week for six weeks, and then at intervals, it's given in three doses. So once a week for three weeks, at three months, six months and every six months up to 36 months. So a total of 27 doses in 36 months. Next slide.

And there's a lot going on in this field. And I put this as a busy slide, but I just want to highlight some of the different clinical trials are going on just so you can see that there really is some optimism that we can improve things in the next several years. In the top left-hand corner, there's a curve that just shows that there are differences in disease control, depending on the strain of BCG that's used. So BCG was founded, I can't even remember how many years ago, but about a hundred years ago, and it has evolved so there are different strains in different parts of the world, and they may trigger a different immune response. So there are differences there.



Dr. Peter Black:

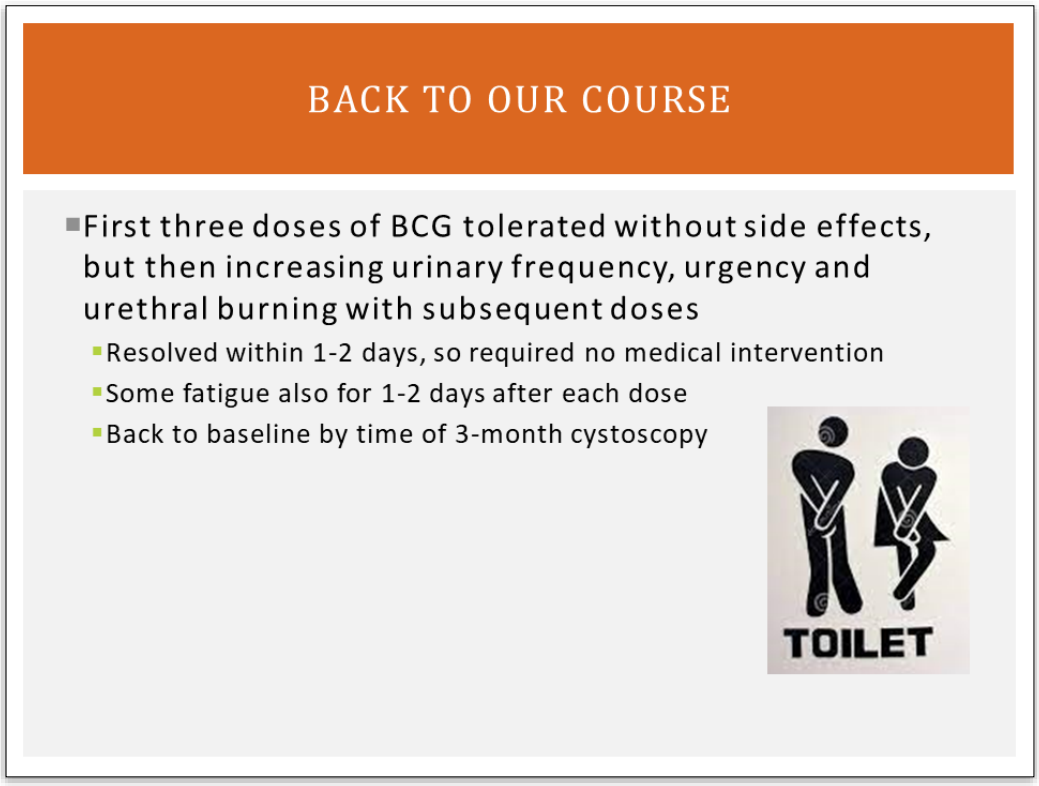
A large trial has been completed in the United States, what's called 1602, that compares a strain from Japan, the Tokyo strain, with the usual strain used in North America, the TICE strain. So we're eagerly awaiting those results. What that trial also did is that it gave patients in one arm of the trial a BCG vaccination, so an injection under the skin that would hopefully enhance the immune response to the BCG that was subsequently put in the bladder. And so we'll have results within a couple of years to show us if that helps. Importantly, it may also allow us to then have a second strain, the Tokyo strain, on the market to get over some of the shortages.

On the top right-hand side is a trial that... they're actually three trials that look essentially identical, where patients with high-risk disease, non-muscle invasive disease are randomized to get either just the usual BCG or BCG plus immunotherapy, and that BCG can be either a limited BCG or the full dose. And that's also exciting to see if we can improve upon the effects of BCG with immunotherapy, which has had such a positive impact in more advanced bladder cancer.

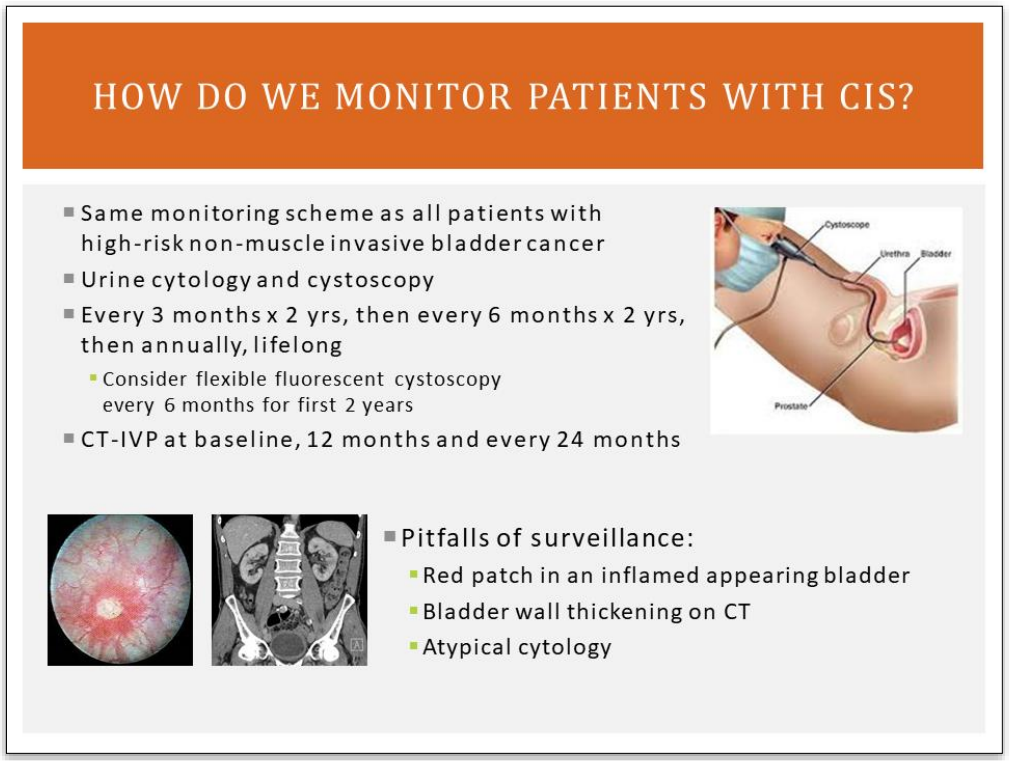
On the bottom left, I've shown an example of genetically engineered BCG where you take the actual bacteria and you modify them so they're expressing different proteins. This is one example where the BCG is made to express a toxin from a different type of bacteria, listeria, which enhances the immune response and decreases the toxicity. And so that's in clinical trial, and then the bottom right is just a trial that compares the gemcitabine and docetaxel to the BCG, which I alluded to on the prior slide. That trial, again, that's being led by Max Cates at John's Hopkins, and it's called the Bridge trial. So we're looking forward to getting that one started soon. Next slide.

Dr. Peter Black:

Our patient, our 87-year-old gentleman, started with BCG and he had the first three doses really without too much side effects at all, but what typically happens is after dose number four, five, and six, you get increasing symptoms, things like urinary frequency, burning with urination, urgency, and that's sort of increased. And it's usually resolved within a couple of days of a dose. There are medications that we can give to help with this. This patient didn't require any. He felt very tired for a couple of days after BCG. I think we sometimes, as the treating physician, sometimes forget sort of the general, full-body response that some patients have, but that also recovered within a couple of days. And when he came back to his office for his cystoscopy three months after his diagnosis, so about six weeks or four weeks after his last dose of BCG, he was already feeling back to baseline. Next slide.



And so how do we monitor a patient like this who's getting BCG therapy? Well, it's the same for carcinoma in situ as it is for a high-grade Ta or T1 tumor, so the other non-muscle invasive bladder cancers, and the standard regimen I think is almost universal, meaning it's done in multiple different countries around the world, is that we do a urine cytology and the cytoscopy where we look inside of the camera, we do that every three months for the first two years, then every six months for the subsequent two years, and then annually. And the recommendation is to do it lifelong, or as long as the patient can be motivated to come back for follow up. This implies, of course, that there's not a recurrence. If there's a recurrence, then we have to recalibrate and figure out a new plan.



I put in a bullet point there about the use of the fluorescent cystoscopy, so flexible fluorescent cystoscopy at the time of surveillance. And again, it's not available in most centers. There is a consensus document that some experts in the US put out recommending that it could be done every six months for the first two years in patients at high risk for recurrence. I would say that's not written in stone. Different urologists will do it differently, so just bear that in mind. And then we always have to remember that the kidneys are at risk, and so we get a CAT scan, a CTIVP of the kidneys and ureters at baseline, as we had already in this patient, but also a month later and then often every two years. Again, not written in stone. Different people will do it differently.

Dr. Peter Black:

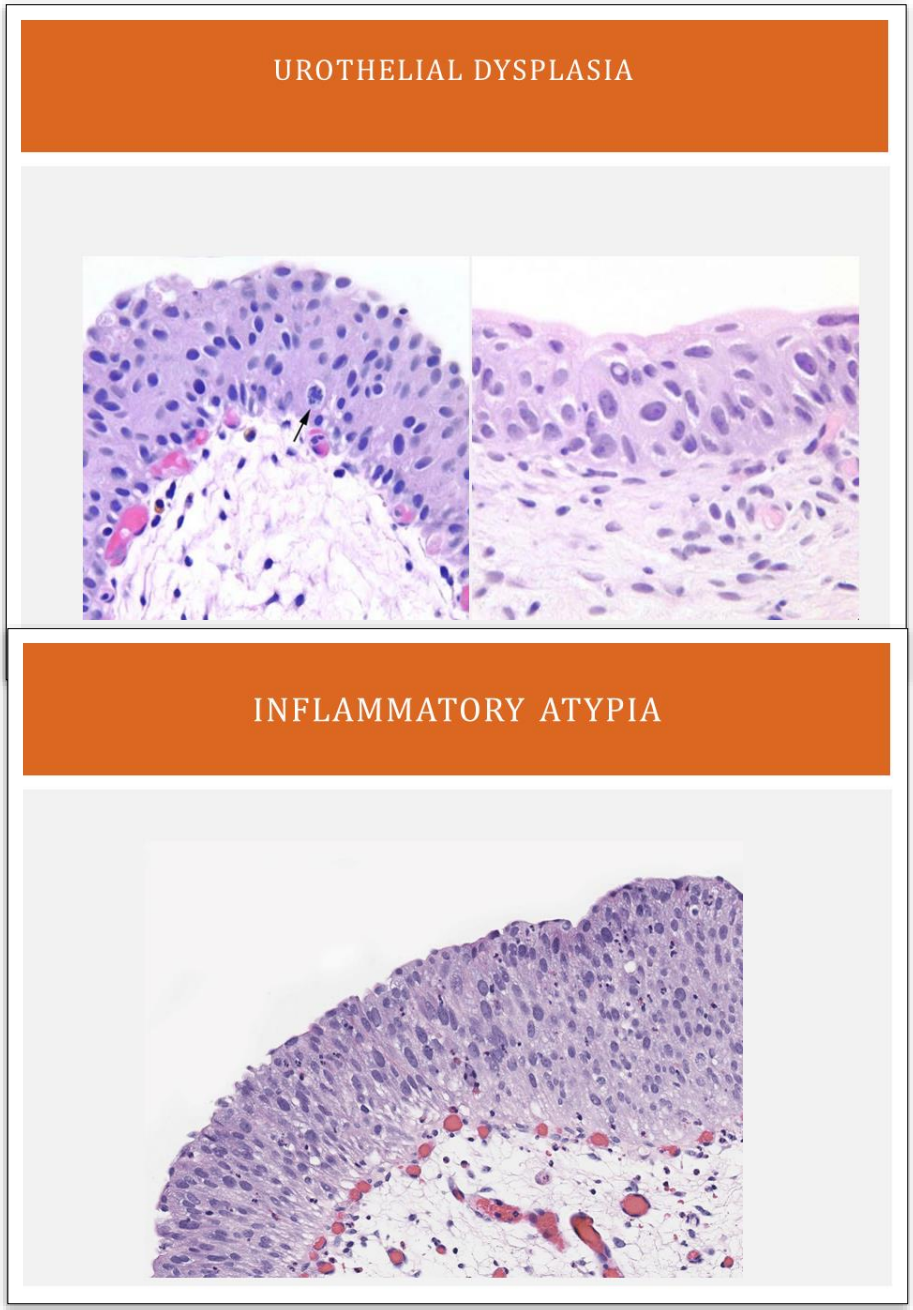
What makes the surveillance of carcinoma in situ particularly difficult is that once you've started BCG, once the patient's started BCG, there will often be red patches in the bladder that are due to inflammation from the BCG or from the prior biopsy and prior procedures, and so it can be very difficult just based on inspection alone to decide if there's something concerning or not. If we do a CAT scan, the bladder wall is often thickened, and as I have a picture there of a CAT scan in the middle, and the bladder wall is severely thickened, but this is a nonspecific finding. It's very, very common that bladder cancer patients have a thickened bladder wall just from all the procedures and treatments they've had, and it doesn't really mean very much.

And then the third part is the cytology, which as we said, is so important for the patient with carcinoma in situ, but once we've started with all these treatments and BCG, we often get atypical cytology because of inflammation. And so if we have a patient with a somewhat inflamed-looking bladder, but

maybe it's carcinoma in situ and an atypical cytology, but maybe it's cancer cells, it can be very difficult to figure out exactly what to do. And so Hikmat is going to take us back to the atypical cytology.

Dr. Hikmat Al-Ahmadie:

So, most of the times, the diagnosis is actually straightforward. You get a tissue from the procedure, you are able to tell it's benign or malignant straightforward. There are occasional times when that diagnosis not very straightforward. There are these situations which are challenging to all of us because they provide a level of uncertainty, because you look at the slides in the microscope and you will see some atypical features as I show you on these two examples here, but then it's not atypical enough, at least not up to the level of what we see in textbooks, to make it a straightforward diagnosis of cancer.



These are these cases where you may leave the word atypia. Some people use the word dysplasia, in a way acknowledging that I see something that is not completely normal, but it's not to the level of calling it urothelial carcinoma in situ. May not necessarily be very helpful, but at least it is helpful in the sense to alert the patient and the physician that this may be worth observing a little bit more closely, or just do something extra to make sure that it's either benign or malignant. So this is the word atypia or dysplasia. The next slide.

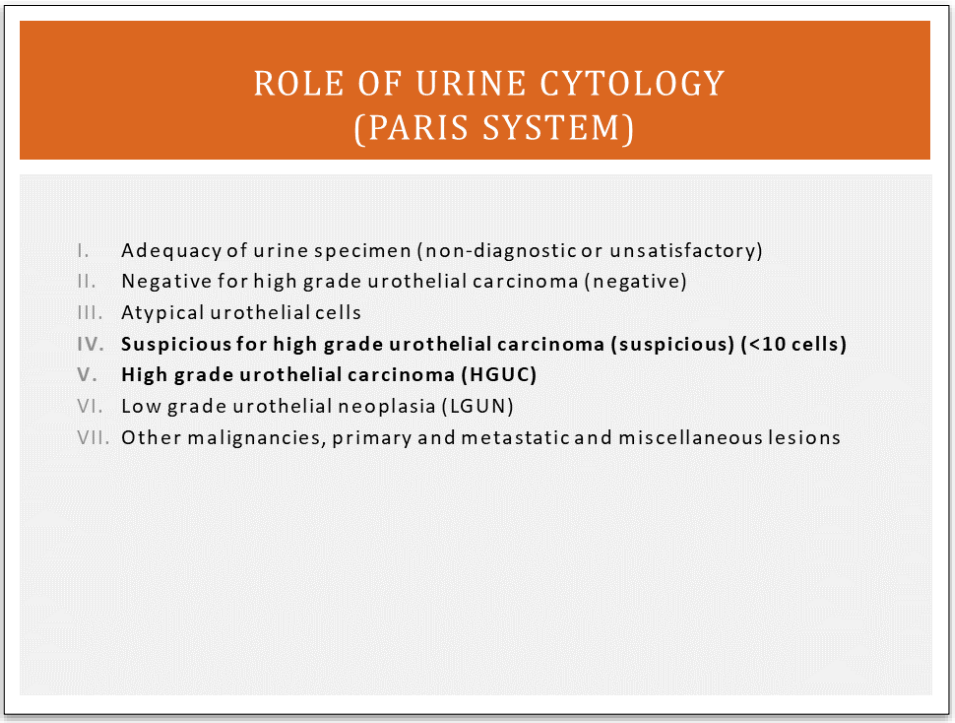
Dr. Hikmat Al-Ahmadie:

Another thing that can happen, especially after treatment or after a first procedure, like if you do a repeat biopsy, the urothelium is very sensitive to injury, so it can react very quickly and you could see a lot of changes that are related to inflammation. As you can see in this example, the urothelium is very thickened and the cells have variations in size and shape, difference in the intensity. These are all vary atypical features, but at the same time, the borders of the nuclear are very smooth and makes you wonder if this is really a severe or markedly a reactive process. And that can be supported by the presence of some inflammatory cells. All

these small dark dots in the the urothelium here, these are all inflammatory cells. So this atypia can in part be explained by an inflammatory process, but not necessarily be always the case, because you can have carcinoma in situ and inflammation, and that can compound the process.

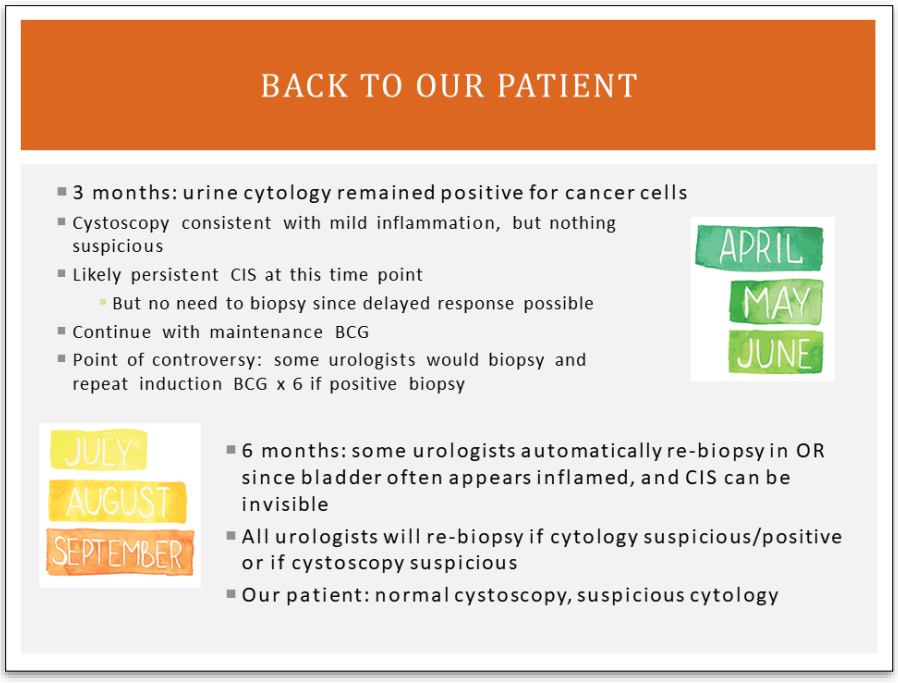
Dr. Hikmat Al-Ahmadie:

These are the challenging cases, and if you go to the next slide, having these features in mind when you're looking at the histology section under the microscope, we always keep in mind how that might look with the urine cytology, and we try to always make the correlation between the pathologist and the cytopathologist, and again, we follow the system, the Paris System, just to try to categorize the atypical features that we see into one of these entities. The action should be based on mostly categories four and five, when there's high level of suspicious for urothelial carcinoma high-grade, but then all the other categories can trigger some other downstream processes or steps to clarify or be certain that you're dealing with a benign or a malignant process. Next.



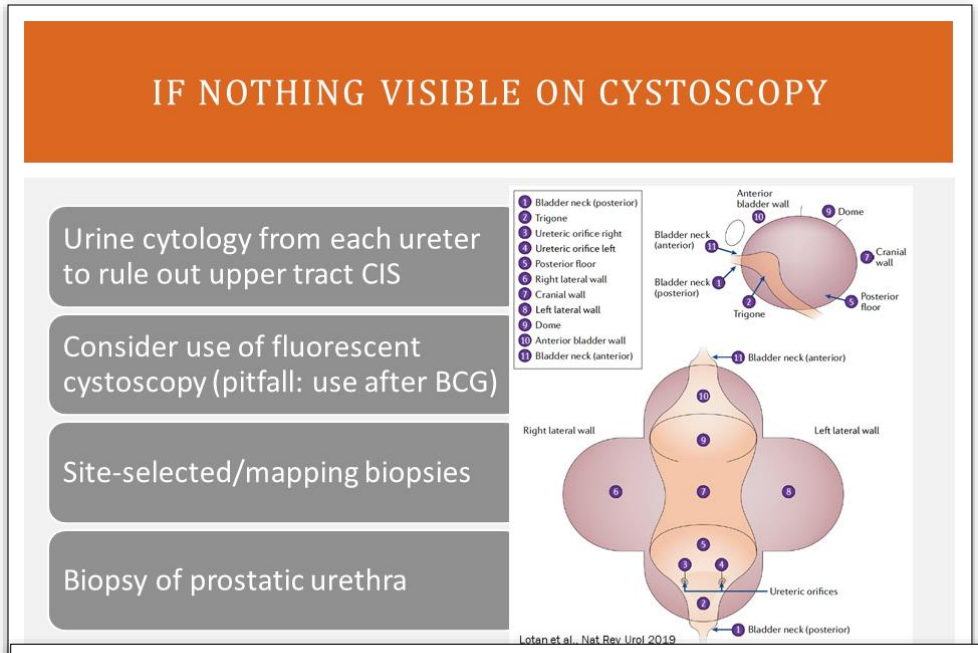
Dr. Peter Black:

Terrific. I would say from a urologist perspective that the atypical cytology is something that we generally don't get too excited about. I noticed also that I'm talking too much, so I'm going to try and accelerate here so we have time at the end for some questions, but if we come back to our patient, so he completed the induction BCG over six weeks. His cytology has remained positive, so there's still cancer cells in his cytology, in his urine. The cystoscopy, there's some inflammation, but nothing suspicious for invasive tumor or anything really concerning. So we expect based on the cytology, the patient actually still has persistent carcinoma in situ at this point, but you'll remember that I said that a good proportion of patients can still respond between the three-month and six-month time point. So a lot of urologists at this point would say, "Okay, let's just maintain the course. We'll continue with maintenance BCG and we'll reevaluate at six months." Some urologists would re-biopsy to make sure what's there. If the biopsy's positive for carcinoma in situ, they'd actually do another round of induction BCG, so a few more doses. A little bit of differences in practice patterns there.

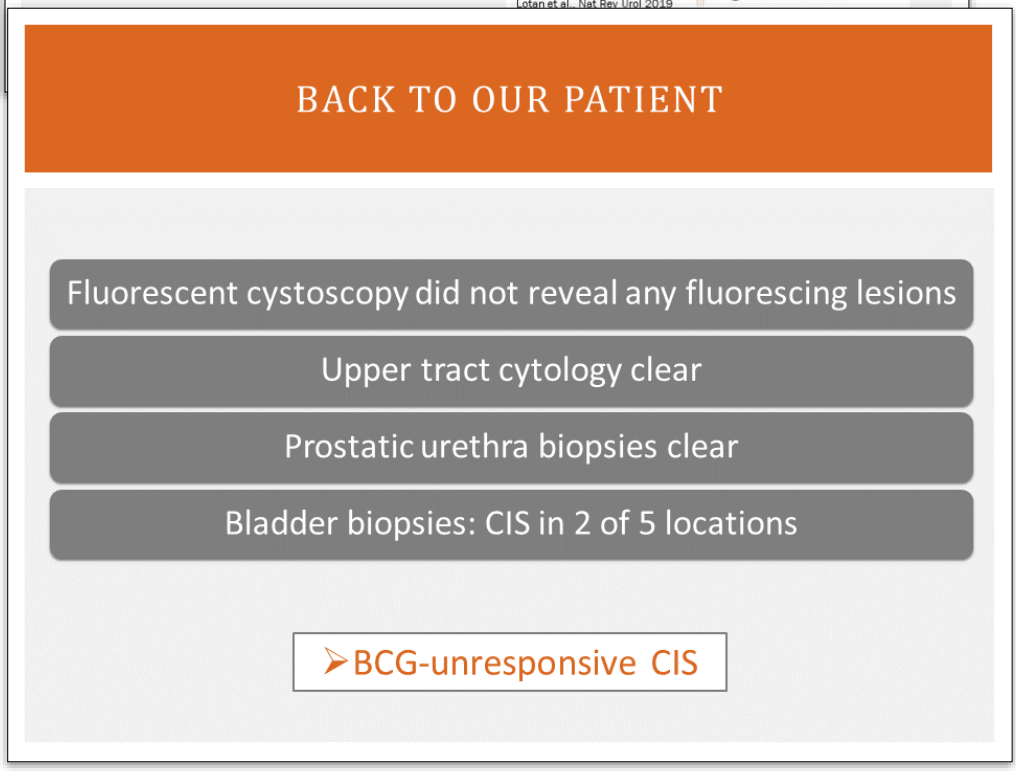


Since I was treating this patient, he had had three more doses of the maintenance BCG and then at six months, what I do is an automatic re-biopsy. Because of these issues with red patches and atypical cytology, it can be very difficult to discern. In some patients it's completely invisible, so the safest way is to go back to the operating room and do a biopsy, but not everybody does that. Our patient had a normal cystoscopy and a suspicious cytology at six months. Next slide.

And so if you don't see anything, you again would get urine from the upper tracts to make sure it's not kidneys. We always have to be thinking about that. We like to do the fluorescent cystoscopy, but we have to be careful because there's a high rate of what we call false positives after BCG. BCG can cause inflammation and the inflammatory lesions can also light up, so there's some caveats there. Otherwise, we do what we call site-selected or mapping biopsies, and the picture on the right is just supposed to be a diagram of the bladder where you can go to different regions specifically: the right wall, the left wall, the front wall, the back wall, and we always include the prostatic urethra in men. Next slide.

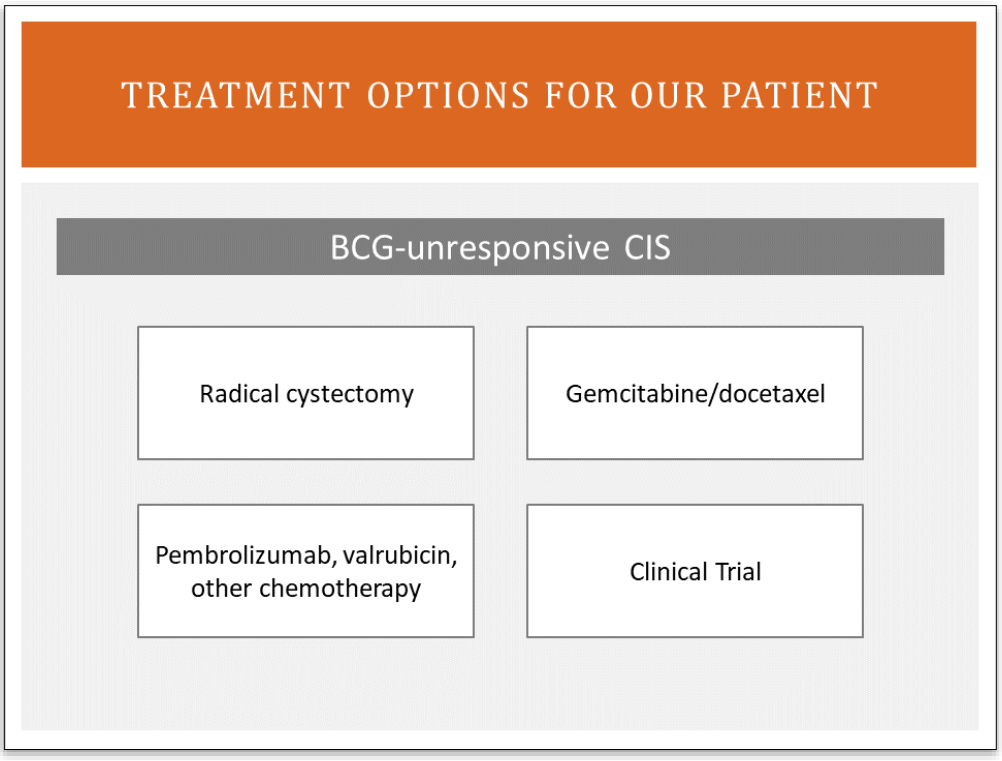


And so our patient on the fluorescent cystoscopy, we didn't actually see anything, so it didn't add any value in this case. The cytology from the right ureter and the left ureter was clear. The prostatic urethra biopsies were clear. And the only thing we found was carcinoma in situ in two out of five of the site-directed biopsies. So this is kind of a typical thing that we might find. Not everything is going to light up on fluorescent cystoscopy, but this patient now has carcinoma in situ despite induction and the first round of maintenance BCG, and he meets criteria for what we call BCG-unresponsive carcinoma in situ. Next slide.

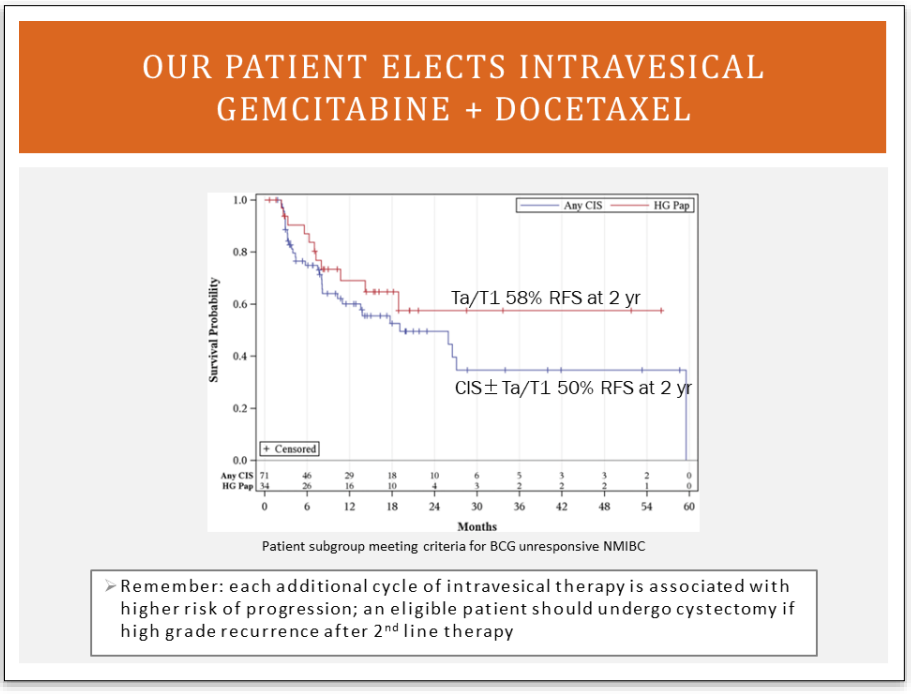


Dr. Peter Black:

I'm actually going to skip over this one. Next slide, just for the sake of time. For our patient with BCG-unresponsive carcinoma in situ, there are a couple different options. First of all, the standard of care, according to the guidelines, is a radical cystectomy and replacement of the bladder with bowel, so an ileal conduit or neobladder, whatever it might be. Of course this patient is really not medically fit for a cystectomy. What has evolved, as I've also alluded to as sort of the standard second line treatment after BCG in the US and Canada is this combination of gemcitabine and docetaxel. And so that would be probably the most common thing that this patient would get around the country at this point in time.



There are some other alternatives. So pembrolizumab is an intravenous immunotherapy that is approved for patients like this, but the efficacy is relatively marginal and it has increased toxicity because it is an intravenous drug and it does trigger some specific immune-related side effects. Valrubicin is a chemotherapy. It doesn't work very well. It's not used widely and the other chemotherapies don't work very well either as a second line treatment. And if we can, of course, we like to get patients in clinical trials, because there are a lot of exciting new drugs being tested and some them are looking very promising. Next slide.

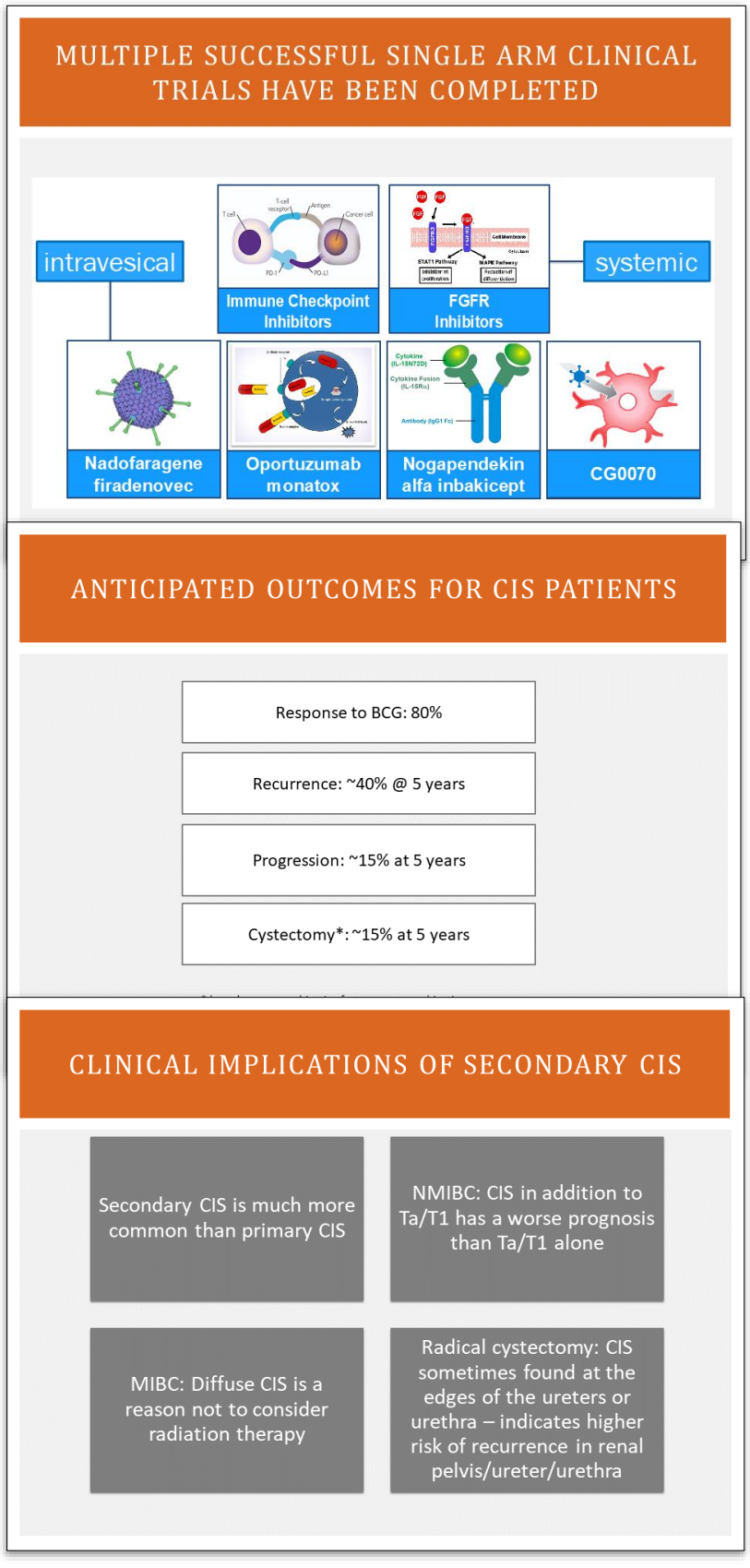


Dr. Peter Black:

This is just an example of what we would expect with gemcitabine and docetaxel. The bottom line, the purple line is for patients like our patient with carcinoma in situ. There's a 50% chance of being without recurrence at

two years. And you say, "Well that's not great, 50%," but it is better than anything we've had up to now, although this is retrospective data. Next slide, please.

Next slide. I'm just going to skip over some of this just because the time is getting ahead of us, here. This slide just shows you some of the exciting new drugs that are in clinical trials or that have been tested and hopefully will be approved soon. The names are horrible, we'll have to get past that, but a lot of really unique mechanisms of action, virus therapies, antibody drug conjugates, lots of exciting things happening in this space. Next slide.



So if we think of the anticipated outcomes for a patient like this, I told you that the response, specifically for carcinoma in situ, and some of this is estimates. We don't know it very precisely, but the response to BCG is about 80%. The likelihood of recurrence, however, within five years is about 40% and the likelihood of progression to muscle-invasive bladder cancer, even with optimal therapy is about 15%, and approximately that proportion will also undergo cystectomy, although there's a lot of subjectivity into that decision on when to do a cystectomy. Some urologists and some patients will want it done sooner versus later. Next slide.

Dr. Peter Black:

And I think this is my second to last slide. We've focused really on carcinoma in situ by itself, but carcinoma in situ in combination with another tumor is actually much more common. Carcinoma in situ plus other non-muscle invasive tumors, I said at the beginning that it's a worse prognosis than those other tumors alone. Carcinoma in situ with muscle-invasive bladder cancer might be a reason not to consider radiation because we would consider it a diffuse disease with a higher risk of recurrence. And then carcinoma in situ is also something we

find frequently at the time of bladder removal, radical cystectomy, where you can have carcinoma in situ sometimes in the ureters or the urethra that we remove at the time of surgery. Sometimes it's even carcinoma in situ right at that edge, at the margin of what is removed, and that indicates a higher risk of recurrence. Carcinoma in situ comes up in different scenarios with different implications.