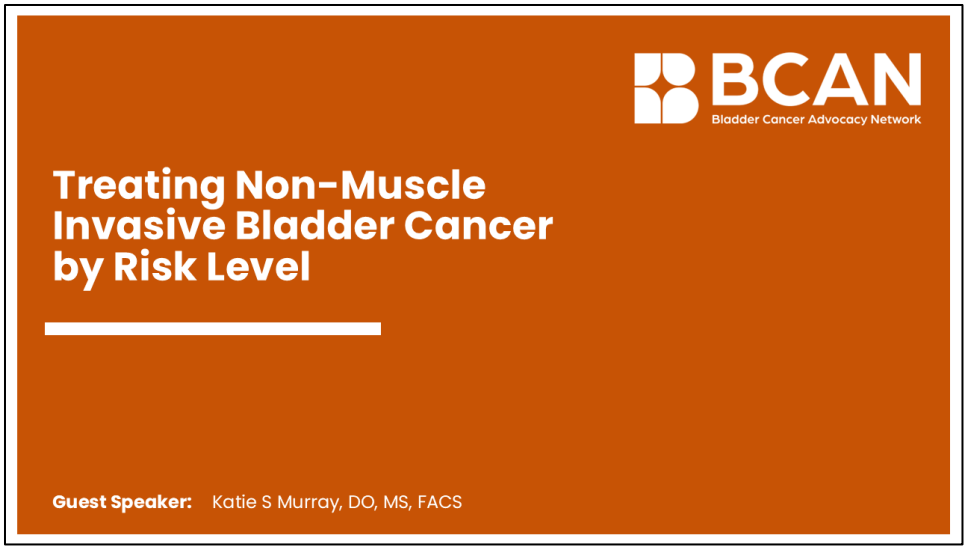
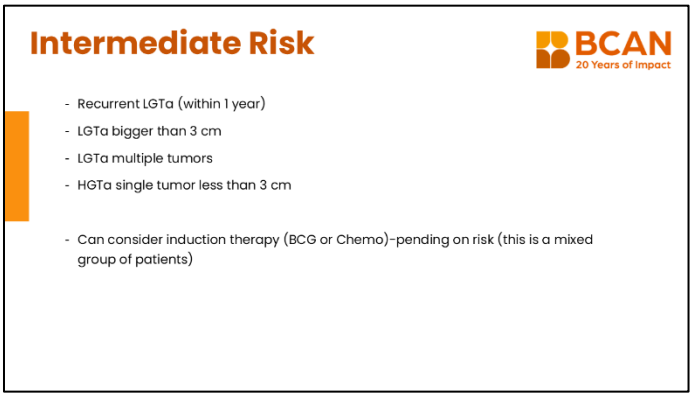


Dr. Katie Murray:



Now, reminder that I put in here, and this is where intermediate risk can be a little bit difficult or a little bit confusing, is that if you look here, the first three of this intermediate risk categorization are patients with low-grade tumors. The last one in the AUA guidelines really does include this mixed bag of patients with small first-time occurrence of high-grade TA tumors. Remember, the intermediate risk is a mixed bag. And so there might be a scenario where the patient falls in the intermediate risk categorization via AUA guidelines, but they had a high grade tumor, a tumor stage A, and that the recommendation may be for that patient because they had high grade disease to undergo induction BCG therapy. Very rarely, especially in today's world with the BCG shortage, are we utilizing BCG induction or maintenance on patients with these other categorizations of intermediate risk, i.e. these patients with low grade intermediate risk diseases, our first three bullet points here.

Dr. Katie Murray:

And so what I wanted to do in this presentation is really break it down group by group and talk about these risk stratifications and what have we done historically, what the options are, and then what we're looking at in today's world and it's 2026 in this really new exploding world of bladder cancer. For the first time, we do have an FDA approved agent for a subset of patients with intermediate risk non-muscle invasive bladder cancer. That newly approved agent is Intravesical Mitomycin Reverse Thermal Hydrogel technology, or known by the trade name of Zusduri. What is that? It's a once weekly installation for six weeks of a chemotherapeutic.

Now, interestingly, this does not have to be after a patient has a TURBT or a biopsy. It was FDA approved as a primary treatment for patients with recurrent low-grade TA disease. That first bullet point of what puts patients in an intermediate risk categorization, recurrent low-grade disease, if they have that cystoscopy in the office and recognize a recurrence, they could go to the operating room for a repeat TURBT or can use this Intravesical Mitomycin Hydrogel as a primary treatment induction course once a week for six weeks.

What were the results of the trial that got Zusduri approved by the FDA? And it was based upon complete response so a patient had this therapy after being considered in the intermediate risk categorization, and they had a follow-up cystoscopy at three months, and 78% of patients had a complete response, and so had no tumor remaining at three months. 79% of those patients remained free of recurrence at 12 months, and 70% of those patients were deemed free of tumor at a follow-up of two years. Now, if we remember back in our minds, the risk of recurrence over that four to five-year timeframe is around 50 to 60% for this patient population.

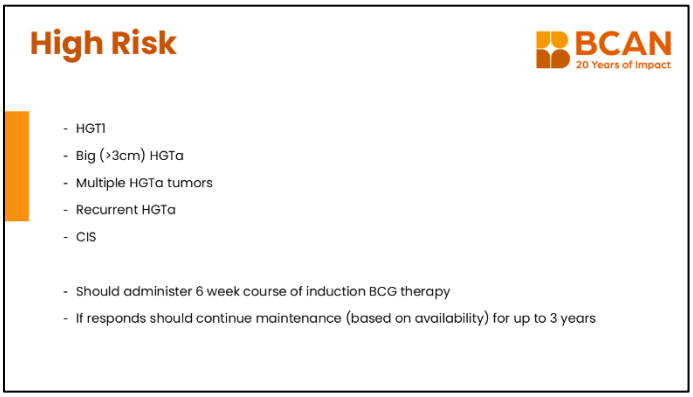
Dr. Katie Murray:

Whether patients we decide to proceed with a Zusduri treatment or another intravesical or ongoing surveillance, the important thing is that I tell my patients, "You're never free of me," meaning we get to be friends and we have to closely watch inside the bladder.

Intermediate risk is a little bit closer follow-up. And so these patients are seen with a cystoscopy in the office every three to six months for two years, every 6 to 12 months during year three and year four,

and then yearly thereafter. And then a reminder that anytime there's a recurrence, the clock resets. It goes back to square one. And then the other thing that's recommended for patients with intermediate risk or often considered recurrent low grade TA tumors that upper tract evaluation or evaluation on CT scan or MR urogram, looking at the kidneys and the ureters should be done every 12 to 24 months or every one to two years.

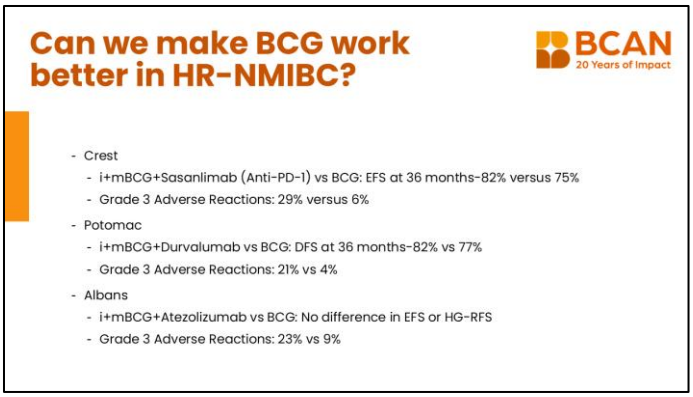
Dr. Katie Murray:



All right, let's really dive in here, time is flying, and really talk about high risk disease. There's a big chunk of people that fall into this high risk categorization, unfortunately, and it is where the mainstay of our BCG therapy and our ongoing new approvals for patients. In patients with high risk disease, who are these patients? Again, as a reminder, high grade tumor Stage I, big high grade tumor stage A tumors, patients with multiple high grade TA tumors, patients who have a recurrence of high grade tumor, and those patients with carcinoma in situ. Our guidelines say that you should administer a six-week course of induction BCG therapy for these patients. Now, if we remember back, this is a little bit of vocabulary, but in our intermediate risk categorization, it said clinician and patients could consider utilizing an induction course of chemo or BCG, but in high risk stratification in NMIBC, it is clinicians should administer six-week course of induction BCG therapy.

The original guidelines say when patients have a response or if it responds to intravesical BCG therapy, they should have continual ongoing maintenance therapy based upon the availability of BCG for up to three years. Now, as many of you out here recognize and have read about or your physicians have told you, we've been in an era where we've definitely had this crunch of availability of BCG therapy, and so many of our guidelines have actually kind of condensed that down and said in patients who respond well to induction course chemotherapy should have one year of maintenance therapy in follow-up.

Dr. Katie Murray:



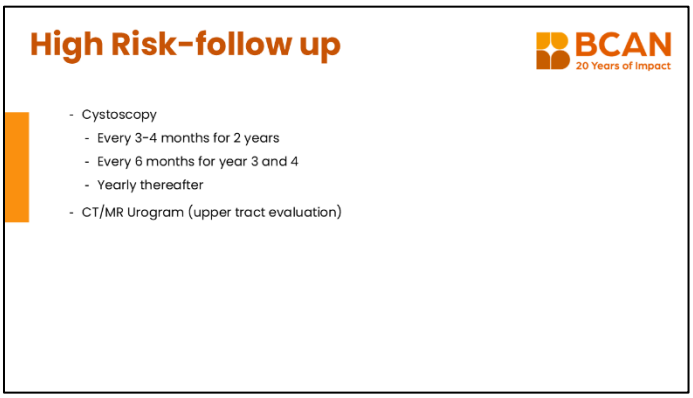
When we think about this, I think it's super important to look at new data and things that are coming out there. BCG, when it works, it can work quite well for patients. It's been the mainstay of high-grade non-muscle-invasive bladder cancer for many, many years.

And so what has happened over the past several years is we've asked ourselves the question, and patients have asked us this question, is BCG can work, but can we make it better? Can we make it better for high-risk patients for NMIBC? I have three trials listed here that have been hot in the news and recently of trying or attempting to do just that, make BCG better than what it already works. And so the first one is the Crest trial. It is a trial that basically, if you think about it in quick terms, it compared patients getting induction and one year of maintenance BCG plus Sasanlimab, which is a subcutaneous anti-PD-1 injection versus BCG therapy induction and maintenance on its own and followed these patients and out to 36 months.

They did see that there was an improvement in event-free survival, so recurrence-free survival or overall survival. 82% of patients who had this combination therapy had no recurrence versus 75% of patients had no events who had BCG induction and maintenance alone. Now, the other thing that's very important to recognize is obviously we see here that 7% difference, but when we think of any therapy and especially a new therapy, we have to say, "Okay, there's an advantage, but at what risk does that come at?" And so if we look at the grade three, which are the first serious adverse reactions, the adverse reaction of grade threes were 29% in those patients who had the addition of Sasanlimab versus 6%. I'm going to talk the same way through these remaining two trials.

The Potomac trial was induction in maintenance BCG plus Durvalumab versus BCG alone. Again, quite similar results at 36 months, 82% versus 77%, quite similar in our adverse reactions of 21% versus 4%. And then the last trial being the Albans trial, induction and maintenance BCG plus Atezolizumab or Tecentriq versus BCG induction and maintenance alone. And there was no difference in this trial in event-free survival or high grade recurrence-free survival. And we can see here the grade three adverse reactions in this population.

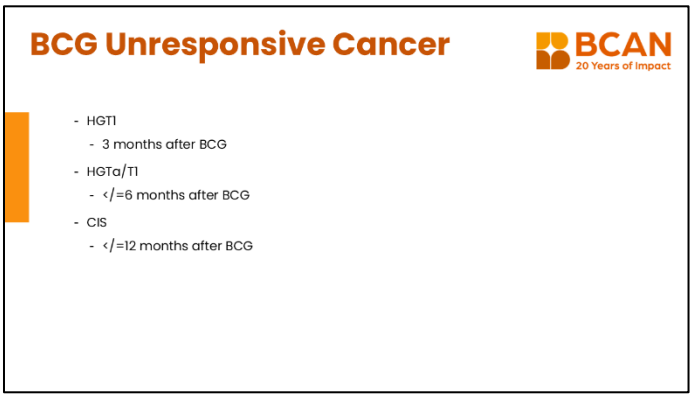
Dr. Katie Murray:



High risk we've kind of talked about and because of that risk of not just recurrence, but that risk of progression in this patient population, our surveillance protocol is a bit more stringent. And so patients who fall in that high risk categorization should have a cystoscopy every three to four months for two full years, and then every six months during year three and year four, and then yearly thereafter, and then a CT or MR urography every year to two years again in this patient population.

And so it's very common for patients to go through this.

Dr. Katie Murray:



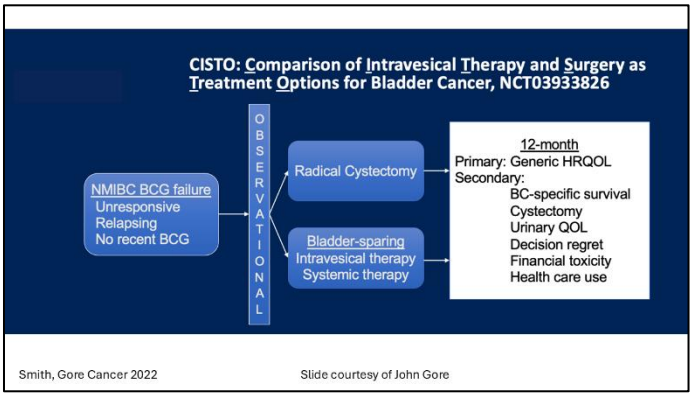
And a big thing that we talk about in today's world is BCG unresponsive disease. We just looked at these newer updated numbers from these trials that were comparing against induction and maintenance BCG for one year and saw that the risk of recurrence or the event-free survival of BCG alone was about 75 to 77%. But what does that tell us? That tells us that there are a group of people that BCG, that the cancer just does not respond to BCG. What does that mean? And so BCG unresponsive cancer has become really a term that we use often. And so patients may see in your clinical notes or in your chart, BCG unresponsive carcinoma in situ or BCG unresponsive non-muscle invasive bladder cancer. And so this is essentially these patients that have a recurrence of high grade T1 within three months after BCG, you can see here TA or T1 less than or equal to six months after the completion of BCG therapy, or carcinoma in situ less than equal to 12 months after BCG therapy.

Dr. Katie Murray:

What now? You've had BCG followed the guidelines. Unfortunately, we didn't fall in that categorization and BCG didn't work for my cancer. I tried really hard to... I wanted it to work. And so the first thing that your surgeon's going to talk to you about, a urologist is going to say, "I have a really good cure for that and it's guideline recommended. And that would be to do a radical cystectomy and take a person's bladder out."

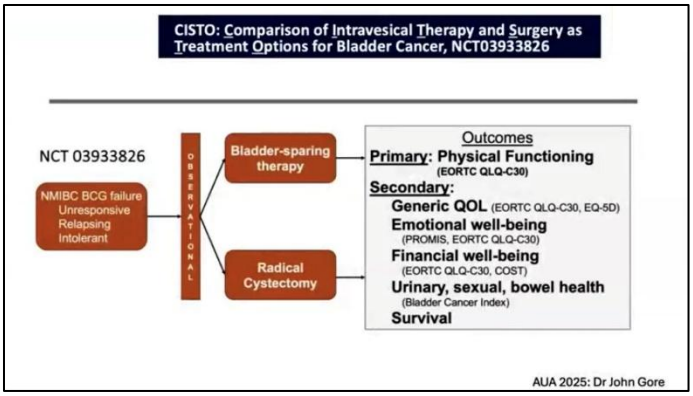
Dr. Katie Murray:

Of course, our patient centeredness says we're looking for something else and looking for something more. But essentially, I couldn't do this presentation without bringing up the impact of cystectomy versus these ongoing intravesical therapies in patients with BCG unresponsive disease, basically looking at patient reported outcomes in patients who have had their bladder removed versus their bladder staying intact



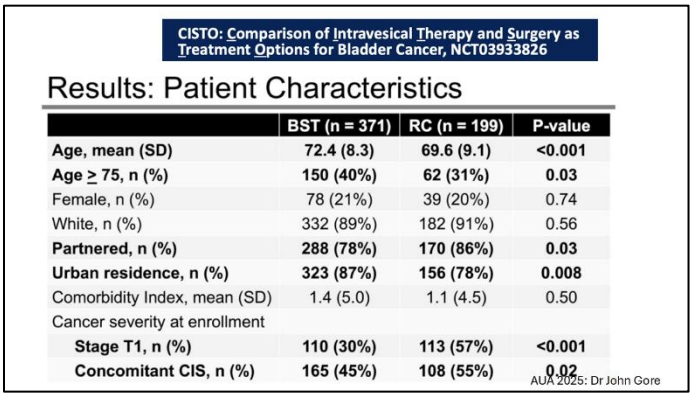
Dr. Katie Murray:

Called the CISTO trial as we see here.



Dr. Katie Murray:

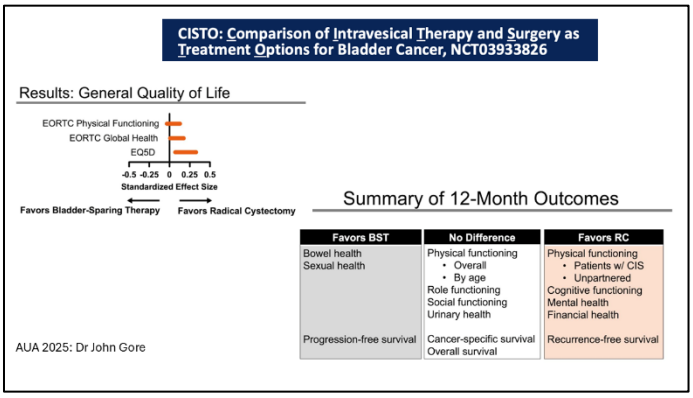
And what we did identify in this trial, which I think is important in looking at these group of patients with carcinoma and CIS is



	BST (n = 371)	RC (n = 199)	P-value
Age, mean (SD)	**72.4 (8.3)**	**69.6 (9.1)**	**<0.001**
Age ≥ 75, n (%)	**150 (40%)**	**62 (31%)**	**0.03**
Female, n (%)	78 (21%)	39 (20%)	0.74
White, n (%)	332 (89%)	182 (91%)	0.56
Partnered, n (%)	**288 (78%)**	**170 (86%)**	**0.03**
Urban residence, n (%)	**323 (87%)**	**156 (78%)**	**0.008**
Comorbidity Index, mean (SD)	1.4 (5.0)	1.1 (4.5)	0.50
Cancer severity at enrollment			
Stage T1, n (%)	**110 (30%)**	**113 (57%)**	**<0.001**
Concomitant CIS, n (%)	**165 (45%)**	**108 (55%)**	**0.02**

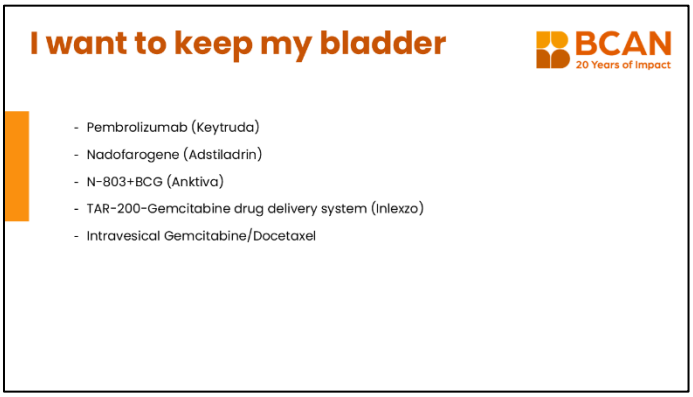
Dr. Katie Murray:

that quality of life, overall physical functioning and some things can favor radical cystectomy, bladder sparing, bowel health, sexual health, overall functioning, progression seat-free survival favored that bladder sparing. I throw that out there and then no difference in patients with overall physical functioning, physical functioning by age, urinary health, cancer-specific survival, or overall survival. Radical cystectomy is a very reasonable option and guideline-based for patients with BCG unresponsive cancer.



Dr. Katie Murray:

But what have we recognized over time is that our patients have come to us and said, "Okay, Dr. Murray, that is fine. I realize that that is a definitive way to remove my bladder, but I don't want that. I want to keep my bladder. What can I do to keep my bladder?" And so I have listed here, and we're going to spend a few minutes talking about each of these, and then I'm happy to, again, take questions towards the end, but quickly run through the agents for doing just that, keeping your bladder. Pembrolizumab, the first approved Nadofarogene, N-803 plus BCG, TAR-200, the Gemcitabine drug delivery device, those four options are all FDA approved, and



then retrospective studies of utilization of intravesical Gemcitabine-Docetaxel chemotherapies.

Dr. Katie Murray:

And so we see here these are going to be shared, so I'm not going to go through this because we're going to go through each of these a little bit fairly quickly individually, but we can see here these are all fairly new therapies. And so the long-term complete response is not here for all of the therapies, but something that I think is important and very patient-centered is that bottom line of looking on cystectomy-free rates. The incidence of patients being on these therapies and continuing to keep their bladder intact, which is what people desire.

Bladder Preserving Options Currently available

Outcomes	Pembrolizumab (FDA)	Nadofaragene firadenovec (FDA)	N-803+ BCG (FDA)	TAR-200 (FDA)	Gemcitabine/ Docetaxel	Gemcitabine Or MMC (Clinical Trials done!)
Mechanism of Action	PD-1	Adenovirus delivery of IFN alfa-2b gene	IL15-Superagonist	Direct cytotoxicity-sustained release	Direct cytotoxicity	Direct cytotoxicity
12 month CR CIS	19%	25%	45%	46%	67% (2yr 47%)	28%
12 month RFS papillary	44%	44%	55%	80% (9mo)	62% (2 yr 51%)	Approx 30-40%
Treatment Schedule	Q3 wk x 2 yrs (q6wks)	Q3mo x 4 yrs	Qwk x6, maintenance x3	Q3wks x 6 mo, then	Qwk x 6, then monthly x 2yr	Qwk x 6, then monthly x 1 yr
Long term CR	10% (5 yr)	5.8 (5 yrs)	?	?	?	?
G3-4 AEs	13%	4%	11%	13%	3.3%	5%
Cystectomy Free	63%	71%	87.5%	75%	75%	74%

*with help from Max Kates

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