

What's the Deal with Carcinoma in Situ (CIS) and Why Does It Matter?

Guest Speaker:

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Dr. Eugene Pietzak:

And so the standard first line treatment is BCG, which is a live but attenuated bacteria. It's microbacterium bovis, it's been used for 50 years now since 1976, and it does remain the most effective first line treatment for carcinoma in situ. And the success rates with that are somewhere between 60 to 80%, and that certainly increases when maintenance BCG is given. And it does require frequent monitoring.

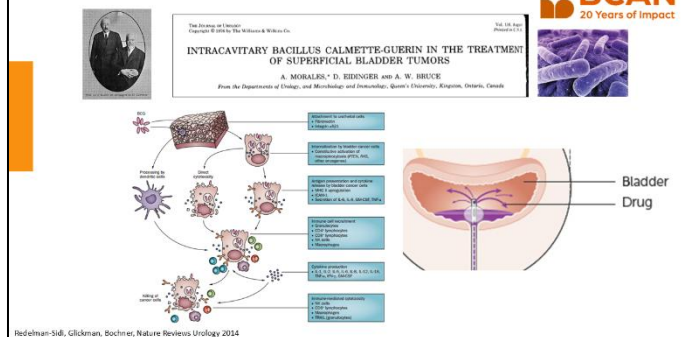
Dr. Eugene Pietzak:

I won't kind of belabor this but this is the original publication from 1976, and this is some nice cartoons of how this bacteria gets preferentially taken up by carcinoma cells like carcinoma in situ, and then allows the body's immune system to recognize the cancer as being foreign and starts to attack it. And it gets instilled in, as I mentioned, it is literally a bacteria. So the symptoms

Standard First-Line Treatment: BCG

- **BCG is an immune-based therapy:**
 - A weakened bacterium placed into the bladder
 - Activates the immune system to attack cancer cells
- Remains the most effective treatment for CIS
- Success rates: ~60–80% will have a durable response
 - Maintenance therapy reduces recurrence risk

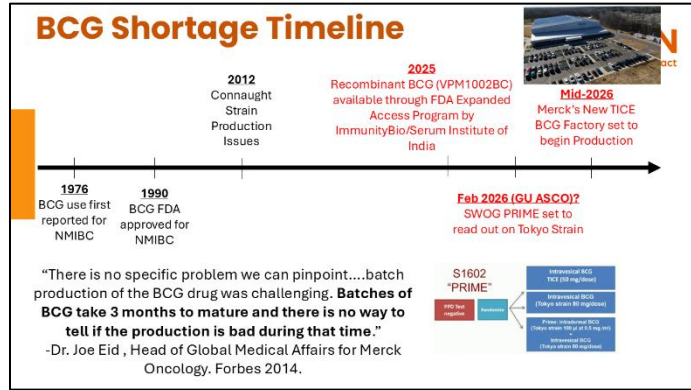
BCG is the Original Cancer Immunotherapy



of it that, many of you may have experienced, are very much like mild urinary tract infections with urinary urgency, frequency, burning with urination, et cetera.

Dr. Eugene Pietzak:

Many of you are probably also aware that there is a BCG shortage, and this is kind of the timeline. I won't kind of belabor this too much but there is what appears to be light at the end of the tunnel after well over a decade of dealing with the shortage. There is this new factory that is supposed to be completed by Merck, hopefully within the next six months or so, and that's supposed to hopefully resolve the BCG shortage and it'll become more available. And this is just some details as to why the manufacturing of BCG has been so challenging.



Dr. Eugene Pietzak:

So when BCG does not work as the first line option, historically radical cystectomy was really the only effective treatment option. And to be forthright with you, it still remains the only definitively curative option for BCG unresponsive carcinoma in situ, but there's been major advantages and there are numerous potential available options at this point.

When BCG Does Not Work **BCAN** 20 Years of Impact

- BCG-unresponsive CIS:
 - Cancer persists or returns despite adequate BCG
- Higher risk of progression
- Historically limited options
- This has driven major research advances

Dr. Eugene Pietzak:

I won't go through each one at this point in time because the way these drugs have been FDA approved, it's all through single arm, non-randomized trials, and it is impossible, and I think often misleading, for people to try to make head-to-head direct comparisons across these trials. But with this designation of BCG unresponsive carcinoma and situ, which we won't go into there's not enough time, there has been an increasing number of

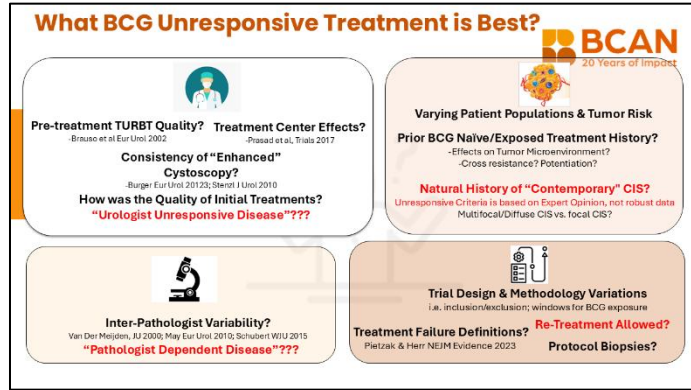
Current Treatment options for BCG Unresponsive CIS **BCAN** 20 Years of Impact

- FDA Approved Single Arm Trials**
 - Pembrolizumab
 - Nadofaragene firadenovec
 - Nogapendekin alfa inbakicept (IL-15) + BCG
 - TAR-200 (intravesical Gemcitabine Pretzel)
 - [Valrubicin, FDA approved 1999 for BCG refractory CIS]
- Off label "Real World"**
 - Gemcitabine (+/- Docetaxel)
 - "Optimized" Mitomycin
 - Re-Treatment with BCG (in select elect patients)

available treatments, and there will be, I think, several more that will be options. And there's also several chemotherapy options as well that are put into the bladder that are used off-label in the so called real world, and then carefully selected individuals re-treatment with BCG may be a very viable option.

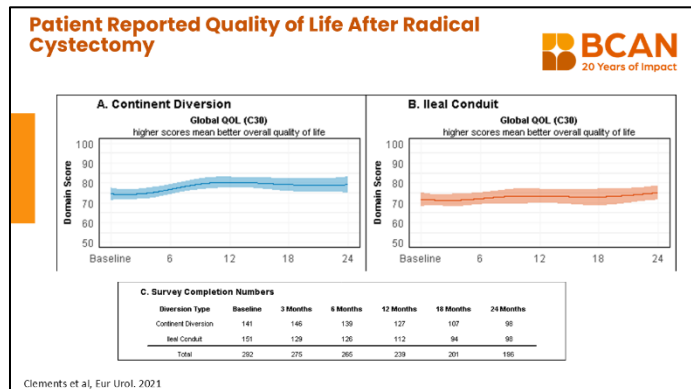
Dr. Eugene Pietzak:

So to the point that I was kind of making with BCG unresponsive treatments, which one is best for an individual patient, I personally think it's nearly impossible to figure that out, and that's because of all the reasons I was just talking about. It is difficult to identify, there's various different quality metrics for TURBT that's questionable about how these single arm, non-randomized trials could have been conducted. And as was just eloquently highlighted, it also depends on who the pathologists are, and there's different pathologists across these different trials. There's different patients who are being enrolled in these trials, they would have got different treatments and a different amount of carcinoma in situ, and I think that all matters. And there's also substantial variation in the clinical trials, and what was treatment failure in one trial may not have been considered treatment failure in another. Some allowed re-treatment, some mandated biopsies versus others. So again, it's just emphasizing that there are treatment options available, but it's hard to say which treatment is better than another.



Dr. Eugene Pietzak:

And I just put this up as well because we now have all these newer treatments for BCG unresponsive CIS, and generally I feel that most patients, it's safe to try at least one or two lines of therapy, but I think we also should not ignore the fact that radical cystectomy is a potentially definitively curative option for patients who are able to undergo it and willing to. And almost regardless of the urinary diversion option, we do see that patients do bounce back and do have very good quality of life, patient reported outcomes after cystectomy, after that initial period of time.



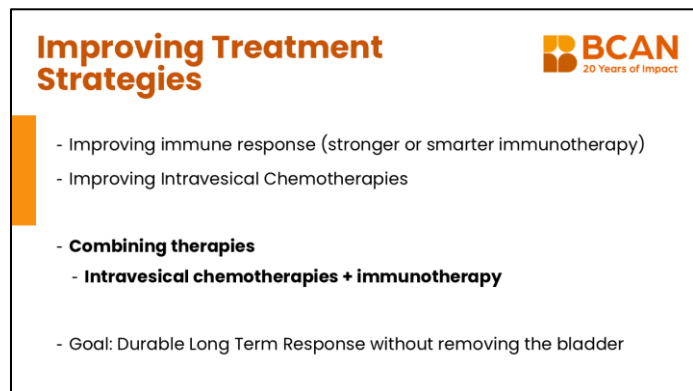
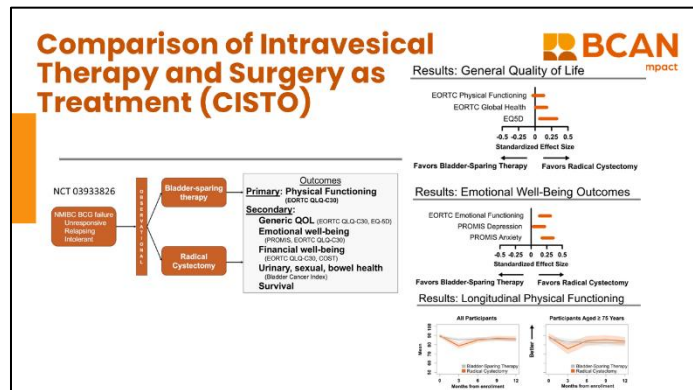
Dr. Eugene Pietzak:

And I think just highlighting this is a BCAN involved initiative by Angie Smith and John Gore, the CISTO study, that was a non-randomized comparison between individuals with BCG unresponsive disease, BCG failure, choosing between bladder sparing therapy and radical cystectomy.

And I think not surprising to us at MSK, but I think what was pretty surprising to others was that the quality of life for a lot of people ends up being better for those that undergo radical cystectomy for various different reasons, and I think this is a good discussion point that people should be aware of. But what I always emphasize with my patients at least is it does take two to three months at least to recover from the surgery, with the expectation that hopefully they'll be able to put things behind them and move on. But I do believe that a lot of patients with non-invasive recurrences, it is reasonably safe for most patients to try a couple lines of therapy.

Dr. Eugene Pietzak:

So moving forward there's now efforts to try to improve treatment strategies because although we now have some FDA approved treatments, without going too much into it, very few of them are actually durable and most of the results we're only seeing is about 12 months to less than two years essentially. And so unfortunately recurrences are still continuing, so we need better treatments for sure. And so some of them are focused at immunotherapies to improve the immune response, some of them are focused at improving chemotherapy delivery and combinations. What I personally think is most interesting are combining both chemotherapies and immunotherapies as well, especially with BCG, with the goal of developing durable, long-term responses without the need for surgical removal of bladder, without the need for cystectomy.




Dr. Eugene Pietzak:

So just highlighting one of them, and just selfishly, because I'm the principal investigator for this national trial, but also because a lot of the preliminary data was supported from BCAN and kind of highlighting that the effort, and the research initiatives, and the funding from BCAN really can make an impact. And also a lot of the BCAN patient advocates, who hopefully are on this call, did provide feedback on this trial that I found incredibly helpful. So if anyone ever on this call has the opportunity to do that, it is very helpful for clinical trialists like myself to hear from you about what is something you like or don't like about a trial to make it so it's very patient centric, really. So this is just the GAIN study, which is combining intravesical gemcitabine with BCG for individuals who have previously been treated with BCG but their cancer came back, and the current standard of care is re-treatment with BCG alone. And so that's just one example of a trial that's up and coming.

Dr. Eugene Pietzak:

Other research efforts are also on finding better ways to detect and monitor carcinoma in situ, and a lot of these are more and more focused on urine. So urine-based molecular tests are coming forward with the idea that maybe we could avoid potentially doing as many cystoscopies, as many biopsies, and potentially detect and better personalize the frequency of surveillance systems.

Example of Intravesical Chemotherapy + Immunotherapy being tested in Trials



THE GAIN TRIAL: Gemcitabine Alternating with Intravesical BCG randomized against BCG alone for patients with recurrent "BCG-exposed" high grade NMIBC (ALLIANCE A032303/NCT07000084)

Eligibility Criteria:
Inclusion: Recurrent High Grade NMIBC after 2 or more courses of prior BCG exposure
Exclusion: BCG unresponsive disease, contraindication to BCG, concurrent UTI/BC

Study Design:
Randomized, Phase III, Open-label, Parallel-group, Superiority Trial

Interventions:
Group 1: Intravesical Gemcitabine 200 mg (100 mg BID) + Intravesical BCG (120 mg) every 2 weeks
Group 2: Intravesical BCG (120 mg) every 2 weeks

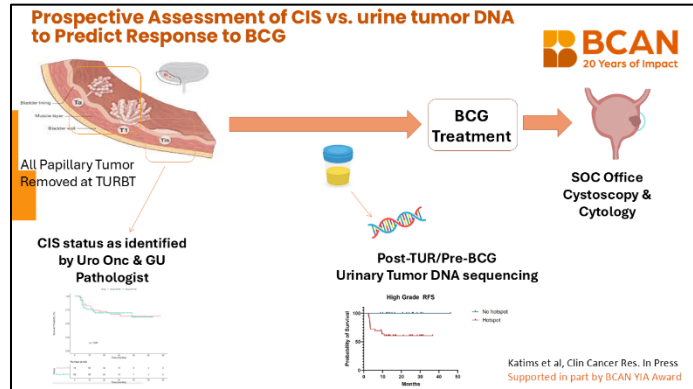
Primary Endpoints: High Grade Recurrence-Free Survival
Secondary Endpoints: 6-month complete response rate (CR), Progression-free survival (PFS), Patient Reported Outcomes

Study Duration: 12 weeks (with maintenance + Week 25)

Assessments: Progress at Week 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, 108, 114, 120, 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, 216, 222, 228, 234, 240, 246, 252, 258, 264, 270, 276, 282, 288, 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, 528, 534, 540, 546, 552, 558, 564, 570, 576, 582, 588, 594, 600, 606, 612, 618, 624, 630, 636, 642, 648, 654, 660, 666, 672, 678, 684, 690, 696, 702, 708, 714, 720, 726, 732, 738, 744, 750, 756, 762, 768, 774, 780, 786, 792, 798, 804, 810, 816, 822, 828, 834, 840, 846, 852, 858, 864, 870, 876, 882, 888, 894, 900, 906, 912, 918, 924, 930, 936, 942, 948, 954, 960, 966, 972, 978, 984, 990, 996, 1002, 1008, 1014, 1020, 1026, 1032, 1038, 1044, 1050, 1056, 1062, 1068, 1074, 1080, 1086, 1092, 1098, 1104, 1110, 1116, 1122, 1128, 1134, 1140, 1146, 1152, 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Dr. Eugene Pietzak:

This is another example of work that our group is doing that was supported, again in part by BCAN, the Young Investigator Award that I had previously won. And so this is looking at carcinoma in situ identified by the urologic oncologist, as well as the genital urinary pathologist. And this is what's called the Kaplan-Meier curve, just very quickly, 100% of people cancer-free, 0% of people cancer-free, and then just followed over time. And as you could hopefully see, the red bar is no carcinoma in situ, the blue bar is yes carcinoma in situ, and what you could see is like these curves are relatively overlapping.



So at least in this group of individuals who are receiving BCG for the first line, we did not see the standard carcinoma in situ biopsy and identification being able to say this individual is more likely to recur after BCG or not. But what we did is we collected urine samples after the TURBT but before their BCG, where it would be thought that this would be residual carcinoma in situ cells. And what this Kaplan-Meier curve demonstrates is that if there are no detectable mutations that were seen in the urine, essentially none of these patients, and I think there was about 20 something or so patients, none of these patients recurred over time. Where if there was detectable mutations, presumably from carcinoma in situ, we saw that nearly 50% of patients recurred almost within the first year. So this is an area that our group's interested in and many others as well, but we are really all trying to do a better job of detecting carcinoma in situ and monitoring the response.

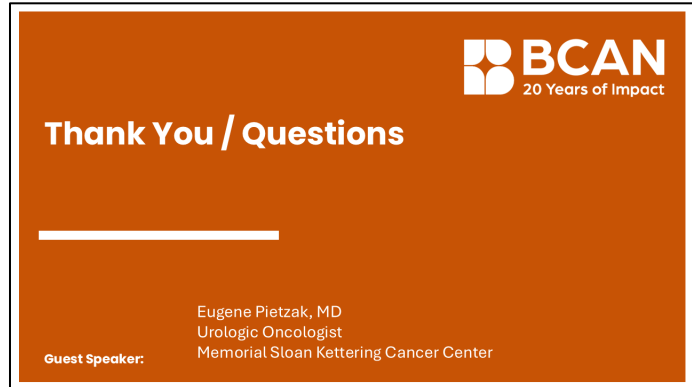
Dr. Eugene Pietzak:

And so just with my final slide, CIS is difficult to see and identify, it does often require some degree of expertise to identify and to make sure it's treated properly. BCG is still, in my opinion, and guidelines, et cetera, the most effective first line option. But when we start to get into the second line options that's where it becomes more individualized. And there are many bladder preserving options that now exist for BCG unresponsive CIS, and that patients should ask about these available options, including clinical trials. And it is all about shared decision making in this situation and figuring out what's best for each individual patient, and this is improving. And then I'm very excited about the role for urinary biomarkers in this space.

- CIS is difficult to see but often biologically aggressive
- Diagnosis and treatment require expertise
- BCG remains the most effective first line treatment option for CIS
- Many bladder-preserving options now exist if BCG fails
 - Patients should ask about available options, including trials
 - Treatment choice is individualized
 - Knowledge empowers shared decision-making
 - Research is rapidly improving outcomes
- Ongoing surveillance remains critical
 - Urine biomarkers may improve detection and monitoring

Dr. Eugene Pietzak:

So with that, I thank everyone for their time and attention.



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Thank You / Questions

Guest Speaker: Eugene Pietzak, MD
Urologic Oncologist
Memorial Sloan Kettering Cancer Center



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