BCAN
Bladder Cancer Advocacy Network

Treating Non-Muscle Invasive Bladder Cancer by Risk Level

Guest Speaker: Katie S Murray, DO, MS, FACS

Dr. Katie Murray:

Let's quickly start here. Pembrolizumab is PD-1. It's the first FDA-approved agent, but not highly utilized due to adverse reactions and a low complete response with around 19% complete response compared to other agents. That five-year data shows about 10% complete response at five years. And there definitely can be some benefits of this in that it isn't systemic IV therapy, so it doesn't require a patient to hold their bladder if there's any issues with catheterizations or specific reasons that make giving therapies in the bladder more difficult. Pembrolizumab could be an option for patients.

Pembrolizumab

- First agent approved, but not agent used first line
  - Low CR @ 12 month, responders are durable
  - 5 Yr data: 10% CR
- Benefit is that given IV →poorly functional bladder

Outcomes	Pembrolizumab (FDA)
Mechanism of Action	PD-1
12 month CR CIS	19%
12 month RFS papillary	44%
Treatment Schedule	Q3 wk x 2 yrs (q6wks)
Long term CR	10% (5 yr)
G3-4 AEs	13%
Cystectomy Free	63%

Dr. Katie Murray:

How about Nadofarogene? Nadofarogene firadenovac is a non-replicating recombinant adenoviral vector that copies this interferon alpha-2B gene into the cancer cells. It's the second agent that was approved for BCG unresponsive carcinoma in situ. It's very tolerable. It's given once every three months to an intact bladder, of

Nadofaragene

- Second agent approved
- Very tolerable, given q3 months 1 hr (patient friendly)
- Higher CR at 1 year, but like others attrition

Outcomes	Nadofaragene firadenovec (FDA)
Mechanism of Action	Adenovirus delivery of IFN alfa-2b gene
12 month CR CIS	25%
12 month RFS papillary	44%
Treatment Schedule	Q3mo x 4, + more
Long term CR	5.8 (5 yrs)
G3-4 AEs	4%
Cystectomy Free	71%

course. Patients must hold that in their bladder. It does have a higher complete response at one year at about 25 to 44% for CIS versus papillary disease, but it has attrition just like these other patients, but at five years, over 71% of patients have their bladder intact still on the inside of their body.

Dr. Katie Murray:

N-803 is the third agent that's approved or third agent that was approved by the FDA that has even a higher complete response rate at one year with a bit less attrition. There's some goods and bads here.

And that is good, is extremely familiar to urology clinics because it is co-administered along with BCG and urology clinics are quite familiar and patients are familiar with the dosing regimen and schedule of BCG and have extensive experience with that. But the downside of that is that it has to be given along with BCG. And we do live in an era where sometimes the attaining BCG can be complicated for patients or for practices in general in being able to do that.

Nogapendekin alfa inbakicept-pmln

- Third agent approved
- Even higher CR at 1 year, less attrition
- Co-administered with BCG
  - Urology clinics have extensive experience
  - Impacted by shortage

Kaplan Meier (KM) Duration of Complete Response (n=77)

12 MONTH
24 MONTH
36 MONTH
45 MONTH

Time After First CR (Months)

Duration of response showing probability of duration 12, 24, 36, and 45 months.

Outcomes	N-803+ BCG (FDA)
Mechanism of Action	IL15-Superagonist
12 month CR CIS	45% (66%)
12 month RFS papillary	55%
Treatment Schedule	Qwk x6, maintenance x3
Long term CR	??- responders durable
G3-4 AEs	11%
Cystectomy Free	87.5%

Dr. Katie Murray:

With the fourth then approved agent by the FDA, the most recently approved in the last four or five months is TAR-200 or Inlexzo. And basically it's the fourth approved agent, has a high complete response rate, has some durability, but like many of the others, it has some attrition and continues to wane over time. They do have a randomized controlled trial that's completed for papillary disease. A big advantage of this is that patients, this is administered. It is a chemotherapy, it's administered in a urology office, so it's quite familiar from a side effect profile to urologists, but it doesn't require any compounding or chemotherapeutics, but it is a device that's inserted into the bladder. It's a drug eluding "pretzel," as you can see here, the size of that a little bit bigger than the size of a quarter, maybe a half dollar size here in the United States that we would be familiar with.

TAR- 200

- 4th agent approved
- High CR, durable but like other wanes with time
- RCT completed for papillary disease
- Urology clinic based, no compounding

CR Rate From Treatment Initiation	Observed Overall CR Rate, % (n/N)
12 months[a]	45.9 (39/85)

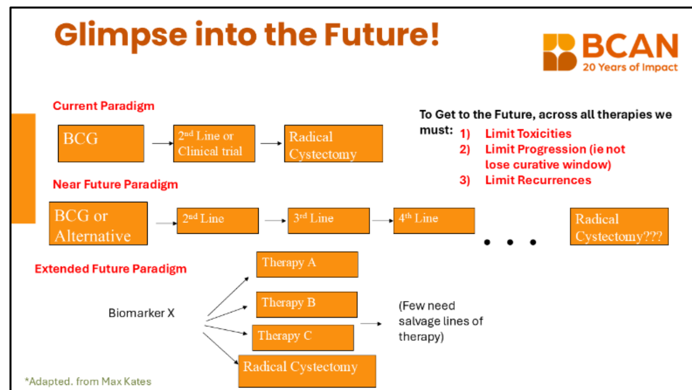
	KM Estimated Overall CR Rate, % (95% CI)
12 months	52.4 (40.7-62.8)
24 months	44.7 (33.1-55.7)

- Rapid onset of response: median time to onset, 2.8 months (range, 2.1-8.3)
- 95.7% (67 of 70) CRs achieved at the first (3 month) disease assessment

Outcomes	TAR-200 (FDA)
Mechanism of Action	Direct cytotoxicity-sustained release
12 month CR CIS	46%
12 month RFS papillary	80% (9mo)
Treatment Schedule	Q3wks x 6 mo, then q 3 mo x 6
Long term CR	?
G3-4 AEs	13%
Cystectomy Free	75%

And it is a device that goes in the bladder. It is not permanent. It has to be removed every three weeks. That is a removal of the device with a cystoscopy and a replacement of the device with a catheter every three weeks for six months, and then every three months for an additional six doses, about a 13% grade three or grade four adverse reaction.

Dr. Katie Murray:



And so when we think about this, time flies and there's so many things to talk about and so much excitement, but I think what's really important for us to recognize as urologists and for you all out there to recognize as patients and caregivers and people that are dealing with loved ones and family members with bladder cancer is that we have options now. We're doing the very best that we can at present time, but essentially in today's world, our current paradigm is BCG. And if that does not work for the cancer or the cancer outsmarts it, we move on to second line or third line therapies in clinical trial, and then a patient has to go on to radical cystectomy.

What do we hope for in the future or what is our near future paradigm as we look at these new agents that's been approved, that we utilize BCG or BCG, some alternative to BCG, essentially a frontline therapy, whether that be BCG or an intravesical chemotherapy. And if the cancer doesn't respond to that, we have options for second line, potentially third line and fourth line therapies, and really kind of kick that can down the road of requiring a radical cystectomy. Now, what's extremely important for me to bring up here is that I just listed out four agents that have been FDA approved in the last five years for BCG unresponsive non-muscle invasive bladder cancer. But questions that we don't know is how well these agents might work before or after one another, how they would be potentially sequenced in different patients, which one should come first or which one should come second.

And we never want to lose that window of opportunity for cure, meaning part of the reason we do all of the aggressive things we do for patients with high-risk disease is because of that risk of recurrence in 60% of people, but also because there is that risk of progression of over up to 10, 20, in some reports, even up to 30 or 40% of patients have progression of disease with high-risk disease. And we do not want to be doing therapies inside the bladder and lose an opportunity to cure someone of bladder cancer and miss that opportunity to do that because we're trying to spare the bladder. Finding that fine line between sequencing these newly approved therapies and learning how to sequence them for different patients is our new future paradigm. I think this is what many of us are using in today's practice because we do have more than one option now in BCG unresponsive disease.

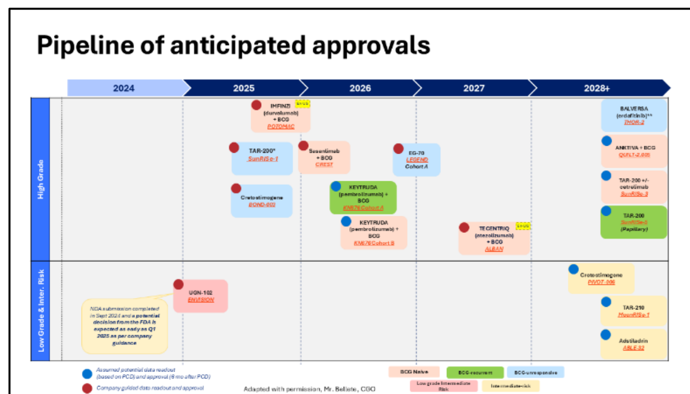
But really to get to these futures, like I said, we have to limit toxicities, we have to not lose that curative window, limit progression, and then really limit recurrence at the same time. What's our real hope and desire when we look at this is this extended future paradigm, I'll give thanks to Max for providing this slide, but is that we might be able to predict what patient is going to respond most appropriately to an intravesical immunotherapy such as BCG or may need BCG plus an additional immunotherapy as in the BCG-naive setting or patients that may respond better to one of these antiviral immunotherapies or an intravesical chemotherapy.

We might be able to say, "Okay, the patient in front of me right now, we have a biomarker that predicts you should have therapy A, B, C or D, or these therapies are not going to be beneficial and we should think about doing an early cystectomy or removing the bladder." And then the desire is that that really reduces our risk of recurrences and our need for these ongoing salvage therapies, that there's a different personalized medicine therapy for each of our patients.

This is not even come close to approaching everything that we want to approach for or get to here as we think about non-muscle invasive bladder cancer, but I hope this really kind of laid a baseline as to why when you're in your friend group and you're out to dinner and you have friends with bladder cancer, why one person might get an intravesical chemotherapy and somebody else might end up with an intravesical BCG therapy or an induction and maintenance and ongoing therapies.

Dr. Katie Murray:

And so this is not by any means conclusive, but it's really just an idea of kind of looking ahead of how many new things are coming out, really looking at this personalized therapy and what we can do



Dr. Katie Murray:

next over the years to come for patients with non-muscle invasive bladder cancer, because that's what we owe to you guys.

Thank You
Questions?
Next Topics?

BCAN
Bladder Cancer Advocacy Network

SPONSORS: