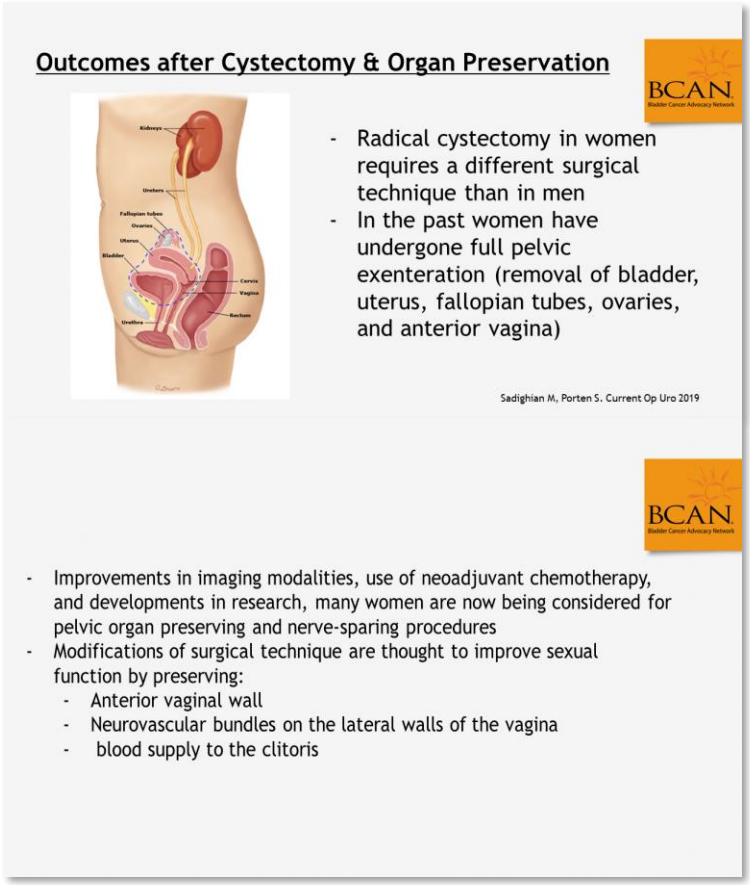
Treatment Differences for Women with Bladder Cancer

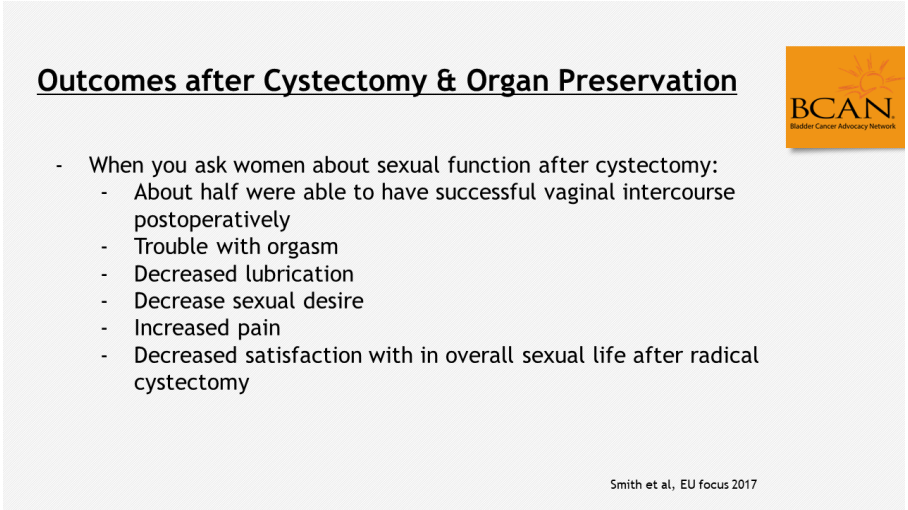


Sima: Moving toward treatment of bladder cancer and women, a radical cystectomy in women requires a different surgical technique than in men. And in the past, women have undergone a full pelvic exoneration. So what that means is in the picture on the left, there's a blue dotted line that is drawn around the bladder, uterus, fallopian tubes, ovaries, as well as part of the vagina. And so in the past, because of fear of leaving cancer behind or there being a positive margin, when women had a curative surgery for bladder cancer, all of these things came out. And so that's a pretty big procedure and operation and a pretty big thing to go through from a quality of life standpoint.

So the great thing is, is that recent improvements in imaging modalities like MRI, using things like neoadjuvant chemotherapy and Jeannie will talk a little bit about that. And developments in research. And that really is research both with our OB/GYN colleagues as well as within our own neurologic oncology colleagues saying that, "Hey, do we actually have to really remove all of these things if we are better able to tell that the ovaries are not invaded, the anterior vagina is not invaded."

In that now most people are paying attention to pelvic organ preservation and nerve sparing procedures in this aspect because those organs, it can be pretty important into things that affect women's quality of life, such as sexual function. And so modifications of our surgical technique are thought to improve sexual function by preserving the anterior vaginal wall.

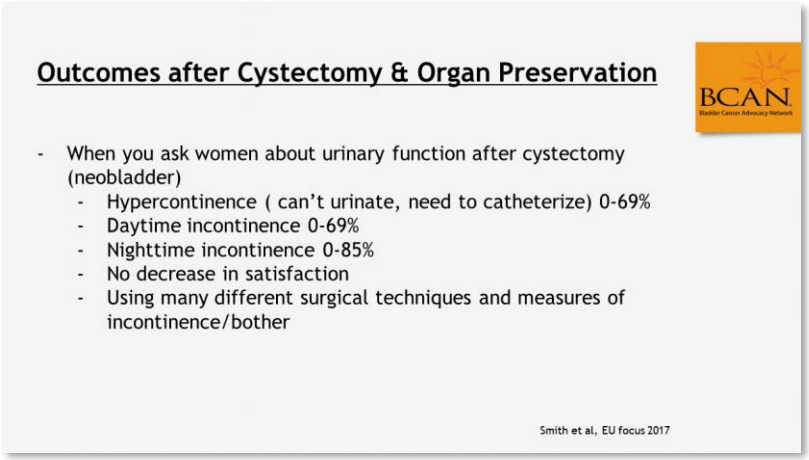
So you don't really need to take that vaginal wall behind the bladder. The neurovascular bundles on the lateral walls of the vagina, we know that a lot of the innervation of the vagina in terms of sensation and providing adequate lubrication runs on the lateral size. And if we don't have to dissect in that area because the tumor is confined or has been



shrunk by chemotherapy, then maybe we don't need to disturb those nerves at all.

We also know by removing the urethra that we have to be very careful to the blood supply to the clitoris, which is how most women or some women orgasm and enjoy sexual activity. And so we know that blood supply runs on the side of the urethra. And so if you do need to take the urethra for cancer control, you can be extra careful not to devascularize the clitoris in the process. And so all of these things are becoming a lot more widely known and accepted.

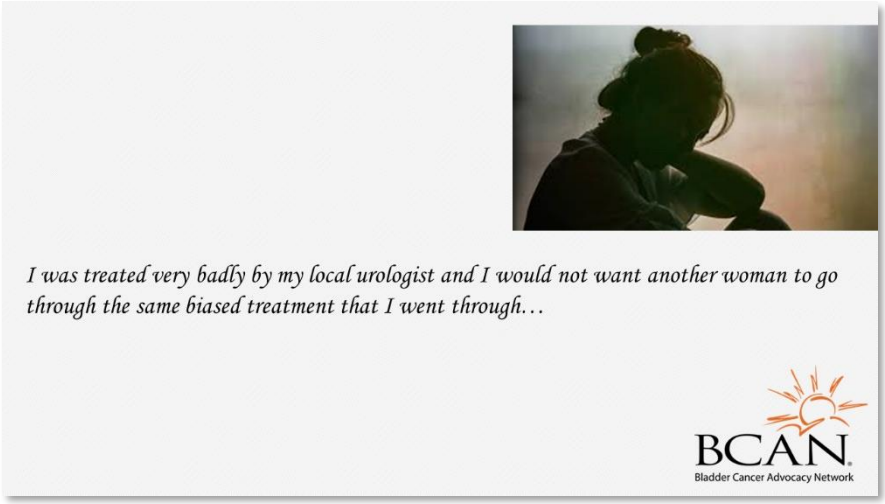
And so why does it matter if we take organ's, if you happen to be older and in menopause, a lot of people say, "No, you don't need your uterus, you don't need your ovaries. Maybe you don't need that part of the vagina." But when you actually ask women about their sexual function after cystectomy, only about half were able to successfully have vaginal intercourse. Many had trouble with orgasm, many had decreased lubrication, many had a decrease in desire. A lot of women had increased pain and overall there was a decreased satisfaction with sexual life after radical cystectomy. So it does matter. These things do matter and they do deserve study.



I put this slide in because as urologists we tend to be very focused on urinary function. And we saw almost a similar story with men and prostatectomy for prostate cancer, that everybody's focus was on continence and urinary function, and sexual function was left by the wayside in terms of counseling and how important it is to patient's quality of life. And our colleagues and also us as urologic oncologists who do prostate cancer to made an intentional change on how we ask patients and counsel patients on these things and how we try to do as much as we can to preserve that function to help men after prostatectomy.

So hopefully webinars like this and awareness is going to spur the same change in terms of looking at sexual function after cystectomy, similar to urinary function. So when you ask women about urinary function after cystectomy, most of this is in women with neobladders. We do see a higher rate of hypercontinence.

Women do need to catheterize more after the surgery, meaning they can't empty their bladder. Even though we've taken out their native bladder and stitched and a new one in its place made of bell, they're unable to empty. We do see definite rates of daytime and nighttime incontinence that range widely based on how people report these. But we don't see a decrease in satisfaction. And this is across using many different surgical techniques and measure of incontinence. And when you look at studies that delve into this, it's because there was a discussion around this that people knew what to expect and new strategies to figure out how to manage these things after you undergo a big surgery like that. So I wanted to put this slide in as a contrast between what we're seeing with sexual function and urinary function and also as a focus of, of something we're trying to improve along with our patients.

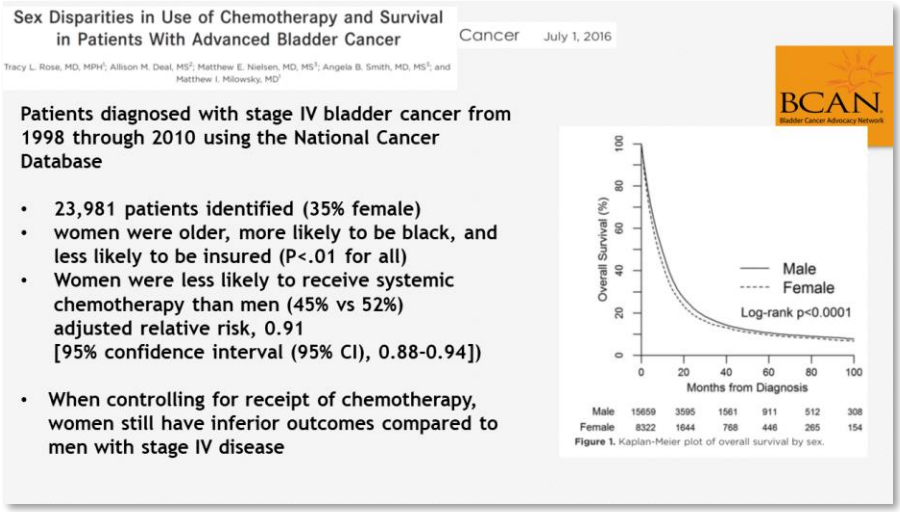


And so this is what we really want to avoid with awareness in treating women with bladder cancer. This type of a statement, and this came again from our breakout session at BCAN in talking with a lot of different patients and doing a survey and seeing what their experience and what their thoughts were. We as physicians, we want to improve this. We want no patient to feel like they had a bias to treatment based on something they can't control like their gender.

And so that's part of why we're doing these webinars and we're passionate. Both Jeannie and I are very passionate about this issue. So I'm going to pass it back over to Jeannie to talk about a little bit more in terms of treatments, mainly systemic treatments in patients with bladder cancer and looking at it from that lens and gender.

Jeannie: Thanks Sima. So I would say that there's some data on surgery and surgical outcomes in women compared to men with bladder cancer. I would say there's much less data on understanding differences between chemotherapy and other therapies. And so this next section is going to be somewhat sparse, but I think is the best that we have. So just talking about what is therapy for bladder cancer. We introduced that earlier.

So for patients with locally advanced bladder cancer where assuming you may send a patient to your medical oncologists that you work with in the multidisciplinary setting for neoadjuvant or preoperative chemotherapy. What are we talking about? So we're talking about one of two different regimens, both containing a drug called cisplatin. Cisplatin is the most active chemotherapy that we know of today in 2019 December for bladder cancer.



We use it both in the locally advanced setting as well as in the metastatic setting and just flatten based chemotherapy has been our standard of care for 30 years. So when we talk about quote unquote chemotherapy, that's what we're talking about. Other cisplatin, in one of two regimens, cisplatin gemcitabine or cisplatin incorporated into a four drug regimen called MVAC. About 50% of all patients who walk into my clinic are not candidates versus flatten based chemotherapy.

Now as we mentioned earlier, the patients who get bladder cancer tend to be older. We do see some young patients, which is striking, but they tend to be older in their 60's, 70's, 80's. The average age of bladder cancer in the United States is 73 years old or the women tend to be a little bit older. So most 73 year olds are not the fittest although we have plenty of patients who are lot fitter than maybe you or I are. But oftentimes there's what we call comorbid diseases. Cisplatin is a drug that is metabolized by as well as potentially toxic to the kidneys.

In the beginning when we showed an anatomy slide, where we demonstrated that the ureters that carry urine from the kidneys feed into the bladder. And unfortunately sometimes those ureters can get blocked and that can change kidney function for the worst and that can limit somebody's ability to get frontline chemotherapy. We look at something called performance status or functional status, which are get up and go, what is your daily routine? Patients who work full time are able to be caretakers for others tend to do much better on chemotherapy than those who spend more than half of their day in bed or in chair or are so symptomatic from their disease that they're unable to readily come into clinic.

We know that Cisplatin based chemotherapy can affect hearing and so patients with baseline hearing loss might not be the best candidates for treatment. Cisplatin can also cause numbness and tingling in the fingers and toes as well as be potentially unsafe for patients with port cardiac functions. There's a lot that goes into a baseline assessment for the use of chemotherapy. If someone is not a candidate for Cisplatin based chemotherapy, we can give an alternative chemotherapy called carboplatin, but in general it's not felt to be as effective.

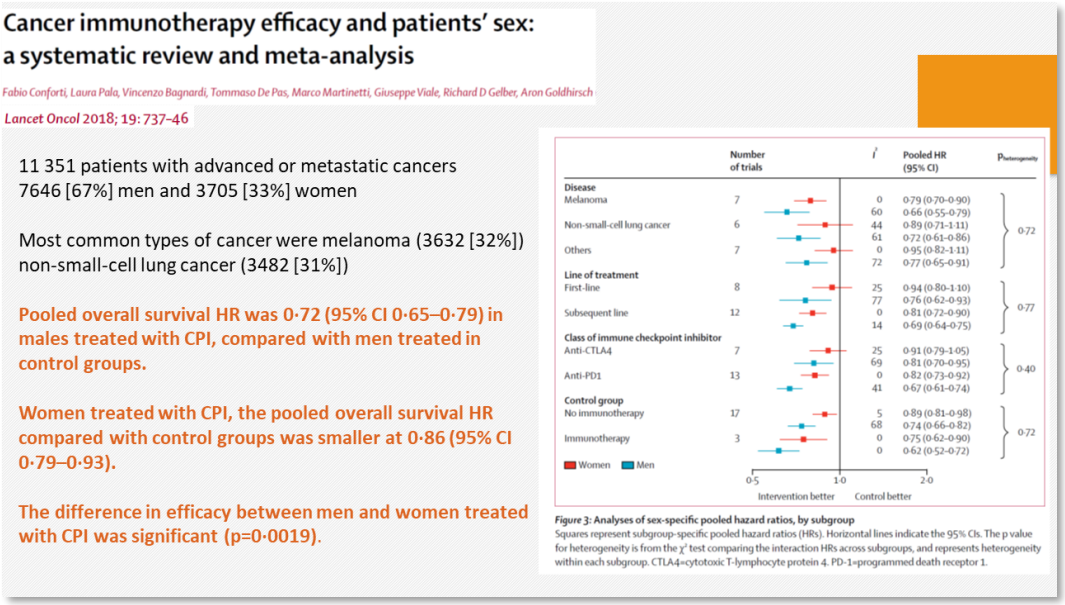
So this study is looking at sex disparities in the use of chemotherapy and survival in patients with advanced bladder cancer. It's published in 2016 and at that point, platinum based chemotherapy is the only thing FDA approved for bladder cancer. The BCAN team, I'm sure, has other webinars that you can either go to or look back at some of the exciting new treatments we have for bladder cancer like immunotherapy and targeted therapy as well as other therapies coming down the line.

But in 2016 chemotherapy was the only thing that we had and in fact this study was looking at patients treated a decade before that, between 1998 and 2010. This was a large study looking at over 20 almost 24,000 patients. Women tend to be older and we know that they're older at the time of bladder cancer diagnosis. They were more likely to be non Caucasians and less likely to be insured in this database and they were also less likely to receive systemic chemotherapy than men.

Is it because they were potentially sicker? Well maybe if they were a little bit older, that might be the case. If they had a locally advanced disease and had blockage of their kidneys that could not be unblocked by urologists like Dr. Porten or through interventional techniques, then maybe they weren't going to be a good candidate for chemotherapy or potentially the doctor that was sitting in front of them just felt that maybe they weren't going to do as well.

We don't know exactly why those choices were made, but we do know that when the investigators in the study controlled for the receipt of chemotherapy you mean that they only looked at the patients who got chemotherapy were intended to do worse. So does that mean they had more toxicity from chemotherapy, they didn't get as much, or the cancer just was not as responsive to chemotherapy? It's not entirely clear, but this is one of the only studies that really breaks this down. So I think it's important to look at and to potentially continue to think about as we move forward with other kinds of therapies in bladder cancer.

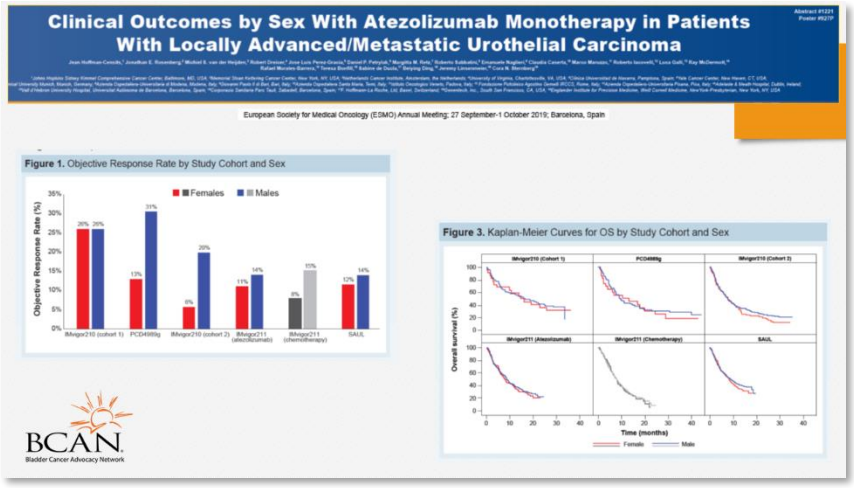
So as I mentioned before immunotherapies now FDA approved for bladder cancer, there's been five immunotherapies approved since 2017, which is great. We have two agents that we can use for patients that have locally advanced unresectable tumors or metastatic disease if they are not good chemotherapy candidates. So those patients that I mentioned that are very frail or have poor renal function, there are two drugs that we can use or if patients do get upfront chemotherapy and the cancer unfortunately continues to move or progress, we could use all five, not all at once, but potentially in sequence.



So this was a study looking at the effect of immunotherapy. This is not done in bladder cancer, but this was the effective immunotherapy and how effective it was across different cancers. The majority had either melanoma or non-small cell lung cancer. And then look at the difference in outcomes between men and women. Just thinking that maybe this is an interesting thing to see and compare to historical benchmarks on how men or women, how their tumors responded to chemotherapy historically.

When using immunotherapy instead of chemotherapy it seemed like the effect of immunotherapy was stronger in men compared to women. So this was an interesting study that came out. It didn't say anything about bladder cancer, but this is what we call a hypothesis generating study. Really interesting. And I think a lot of us wanted to know more.

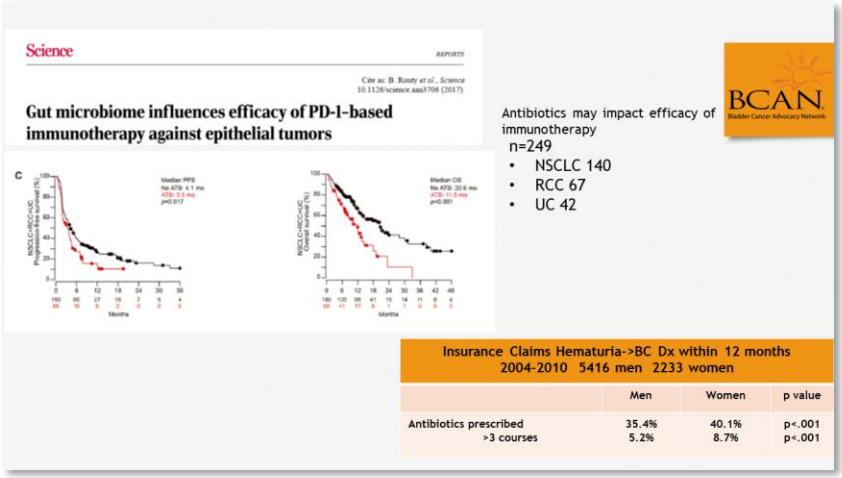
And so this is actually a study that our group did looking at outcome by sex, men or women, with just one drug, and was men that has been tested in multiple different clinical trials and using just the drug alone in patients with locally advanced or metastatic bladder cancer. So on the left hand panel, women are either in red or gray. The gray is a large randomized trial. And men are in blue or light gray again, in a large randomized trial.



And what we saw across different studies. Every one of these paired panels here is a different clinical trial that we saw for trial women tended to have a lower response rate, meaning a lower shrinkage rate of their tumors compared to men, but our gold standard is looking at overall survival and that's on the right. And those curves are called Kaplan-Meier curves and essentially they look like they're overlapping.

They're not splitting too much. You can almost not tell if there's a difference between the two for the most part in these trials. And what that tells us is that despite maybe the scans not looking as impressive for women compared to men on that the overall survival didn't seem to be very different. Again, this is a retrospective meaning looking back at time, but gives us a little bit of a hint in terms of efficacy with immunotherapy, which is a really powerful tool that we have in our toolbox for patients with metastatic bladder cancer as well as many other diseases.

So this is an interesting study and got a lot of press when it was first put out now two years ago, believe it or not, in 2017. And for a long time I think patients asked us about what they ate and how that contributed to outcomes in cancer. And I think in general we knew very little about that, potentially still do. But what this study is looking at is something called the microbiome and particularly the gut microbiome. So in our bodies we have living ecosystems of bacteria that normally exist on our skin, in our mouths, throughout our entire gastrointestinal system, in women in the vagina. And for a long time these ecosystems were felt to be relatively inert. We knew that if they were shown off by antibiotics, patients are at increased risk of an infection called C difficile.

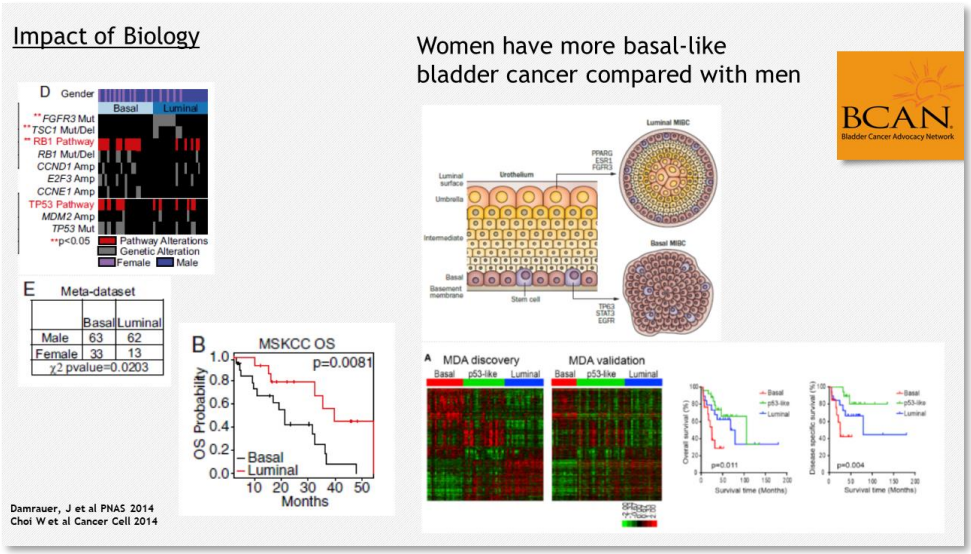


So we knew that in some ways they were important. But this was one of the first studies to show that potentially those ecosystems may have an impact on how patients responded to certain kinds of therapies. And so when some of us saw these data, looking at the difference in the black and the red, and again these are Kaplan-Meier curves, looking at a group of patients who had non-small cell lung cancer, kidney cancer as well as urothelial cancer.

The black, which is a better survival per both on the left and on the right were patients who are not treated with antibiotics. Compared to patients treated with antibiotics there seem to be a detrimental effect on cancer survival if you got antibiotics. So that is pretty profound. And other studies have been done since, some even looking at changing the microbiome and effect on cancer.

So these are complicated things to look at and to measure. But I think one thing hits home for us. Just thinking about prior to patients coming into either my office or Sima's office and it may be for months or years before, we know that women have a higher exposure to antibiotics. Does that affect the way that their cancer may progress? Does that affect the way that their cancer may respond to either chemotherapy, immunotherapy, other drugs? I think the answer is we don't quite know, but it's something that we think is important to think about and to look into and may play into some of that tumor biology that may be different between men and women. And this is just referring us back to an earlier slide reminding us that women are exposed to more antibiotics compared to men prior to the diagnosis of bladder cancer.

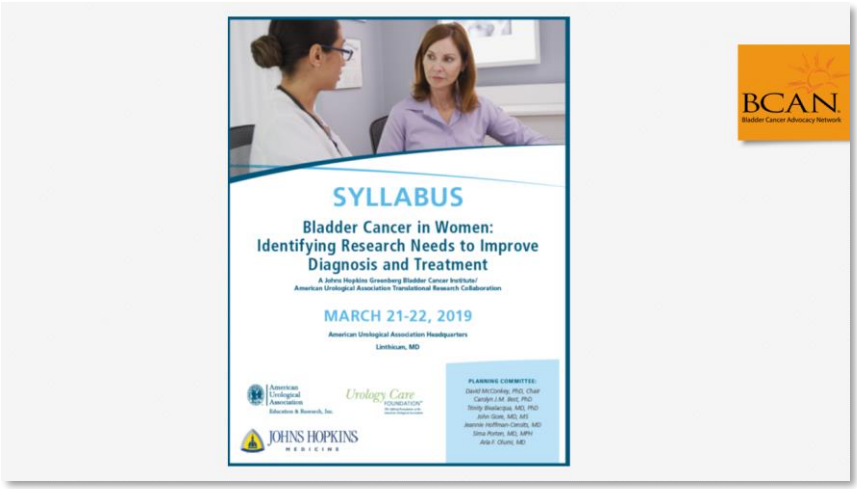
So one of the things and one of the I think exciting topics in bladder cancer that's happened over the last couple of years is that from a clinical standpoint, we've always known that bladder cancer is more than one disease. Patients with metastatic disease, sometimes localized disease, some have disease in multiple different sites, some do well on chemotherapy, some don't.



So I always felt like that there are different kinds of subtypes of bladder cancer. And what we've learned from a lot of our colleagues in the basic science realm in bladder cancers at indeed what we clinically felt is playing out at the microscopic level. So this is a summary slide of data that's been generated from multiple different groups across the country and actually across the world looking at muscle invasive bladder cancer and starting from a biological standpoint to understand what are the differences, why do some tumors evolve in a certain way.

What are some of the microscopic changes or mutations that we see in some cancers versus others? And how does this then play into response to therapy? So we know that these cancers can be, in general, broken up to five different subgroups and there may be more coming. So one is the luminal papillary, one is infiltrated when it's called luminol. Another is called basal squamous, where it seems like of all the subtypes there may be more women that have this subtype. And then neuroma.

So this just tells us a little bit about what we see in the biology. So we know that there's different changes or mutations such as RB, P53, FGFR3 that are present in some versus other subtypes. And that the luminal versus basal subtypes are really actually derived from where the tumor starts within the bladder itself. So the bladder is a big muscular balloon. The basal cells are the ones that are interacting more with what's called the stroma, the patient membrane and that can invade into muscle, whereas the luminal surface, that's a surface that actually hits the urine, that's the inside part of the bladder wall. And so we think that tumors can develop in the cell in these different areas, and that biologically they may behave differently and they may respond differently to chemotherapy. Next slide.



So earlier this year, I think Sima and I are really proud of this, which is the first ever academic meeting about bladder cancer in women. Identifying research needs to improve diagnosis and treatment. We partnered with the American Urologic Association and Urology Care Foundation. There were many of us who have interest in this field who came together to share

ideas and develop research collaborations and BCAN like always was a big part of this collaboration and this effort. I think one of the very special parts about that meeting, which is always a part of every BCAN meeting, is that patient voices were at the forefront and heard and we had five different women come and speak to us about their experience with the diagnosis and management of their bladder cancer, which again typically framework for this meeting.

Sima: Look at the differences between women and men and we go through all of those slide headings that we had. You can see that with women, the time to diagnosis is more, who present with hematuria. The time being referred around to non-urologist is greater, less completeness of evaluation, a greater stage at presentation, potentially less intense therapy given, maybe a decrease in response to some of these therapies that we give, and maybe a greater presentation with potential more hormone effects.

Differentiating factors in Bladder Cancer Between W:M	Women	Men
Symptoms at presentation	hematuria	hematuria
Time to diagnosis	↑↑	—
Non-urology referrals	↑↑	—
Completeness of evaluation	↓	—
Stage at presentation	↑	—
Therapy	↓	—
Response to therapy	↓	—
Age at presentation/hormone effects	↑	—
Tumor biology	More Basal	More luminal

And then how Jeannie summarized it at the end is that potentially a different tumor biology at the heart of the cancer. So it gets back to our ying yang of many of these fall in the realm of what our social determinants of health are and the others fall in the realm of actual tumor biology. And that's what really interplays in making how bladder cancer looks in women from all aspects much different then men.

And so this also fills in all of the bubbles in these realms as well. And I'm not going to spend too much time on this slide because I think both Jeannie and I would love to take some questions. And our goal is for improved outcomes and values. We really want to thank everyone for joining us for this webinar and helping us continue the energy and the passion behind this topic so that we can move things forward.