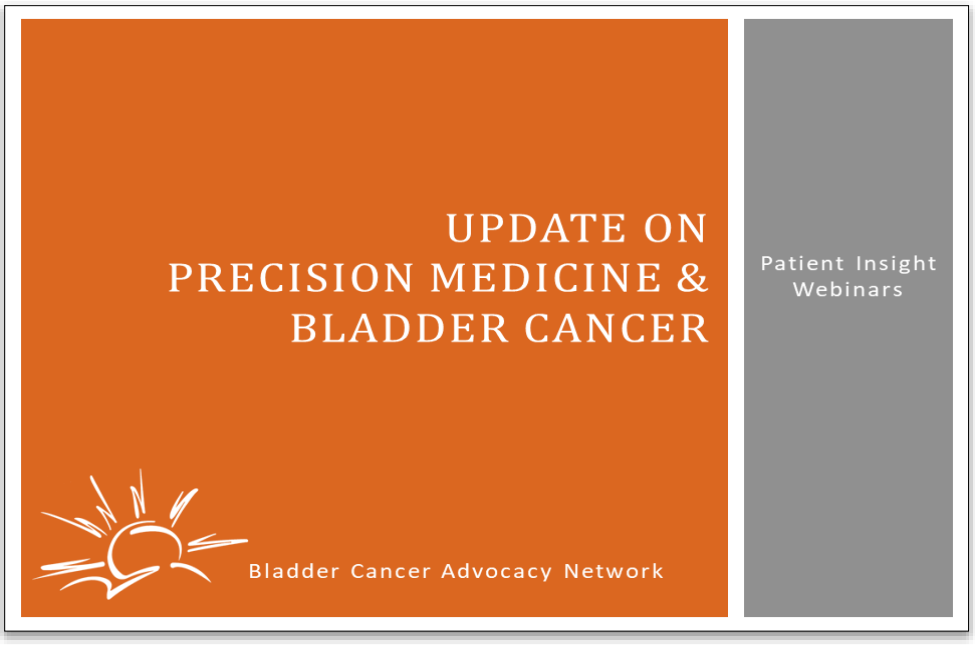
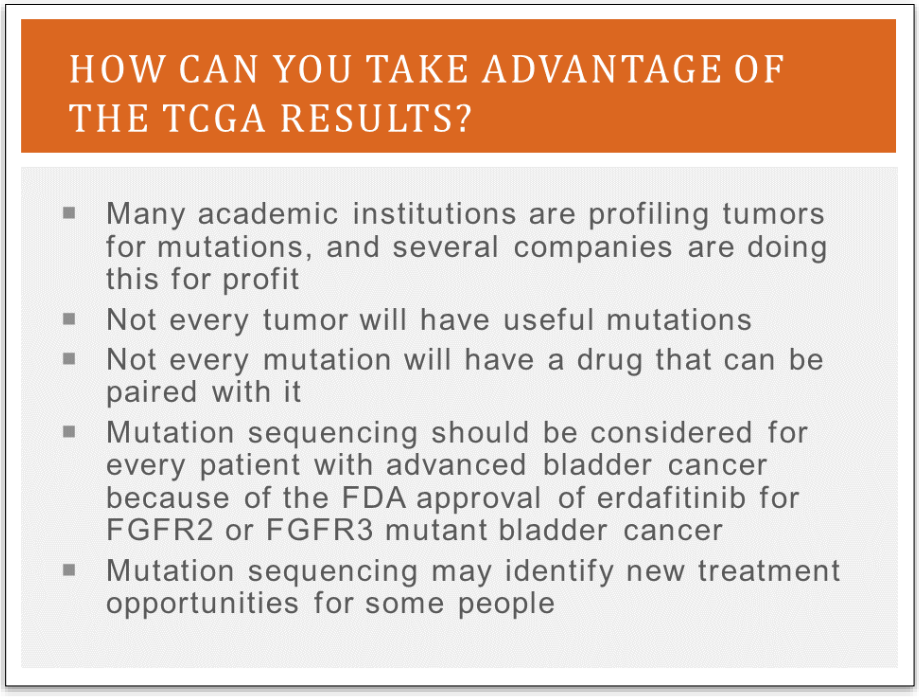


Dr. Gopa Iyer: Thank you. So thanks very much to BCAN, for the opportunity to sort of provide an update on Precision Medicine and Bladder Cancer, I'm really excited to share this virtual stage with my colleague, Dr. Lerner, and also provide those you on the call, hopefully, a sense of how we as clinicians try to apply the genetic information from work, from things like the bladder TCGA, which Dr. Lerner really pioneered and other sources, of genetic data into our daily care of patients who are diagnosed with bladder cancer. So this slide is titled, How Can You Take Advantage of The TCGA Results? And it's really a way to serve as sort of a launching path for the different applications of genetic data.



It lists some important points about genomics that apply to many types of cancer, including bladder cancer. So, as Dr. Lerner alluded to, we've seen a number of new therapies get approved for bladder cancer in the past five years, we've seen several immunotherapy drugs get approved. We've seen two drugs that we call antibody drug conjugates get approved in bladder cancer. And we're starting to see... We've also seen a targeted therapy now finally, that's got an FDA approved as well, which is really fantastic and exciting.

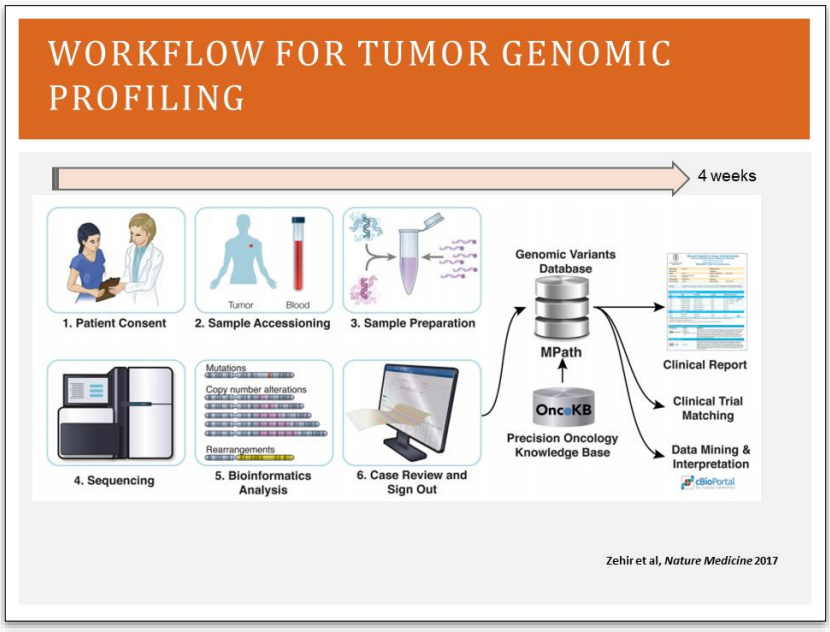
Dr. Gopa Iyer: But we also know that there are limits to how effective these treatments are and that unfortunately they don't work in every patient. So one of the really important things for us is to try to find out how can we better select those patients who are most likely to respond to a different treatment and not sort of waste valuable time in treating someone where their tumor is unlikely to respond to that treatment.

And one way to do this is through genetic sequencing, of DNA from a tumor. So this is really done to identify genetic alterations, which we call mutations that can be targeted by certain therapies. And these genetic mutations just as Dr. Lerner mentioned, are often referred to as actionable mutations, meaning, we can take action on them because there may be certain drugs out there to inhibit what those mutations are doing. And there are several companies that I'll offer genetic sequencing for tumors. And I'm sure in this audience, there's probably many of you who have actually had your tumor sent out maybe by your treating physician for genetic sequencing. And then there's many, institutions around the country that can actually do that genetic sequencing, as well. And if you're interested in doing that, definitely reach out to your physician who's caring for you because they can often help to coordinate sending that tumor tissue off for sequencing.

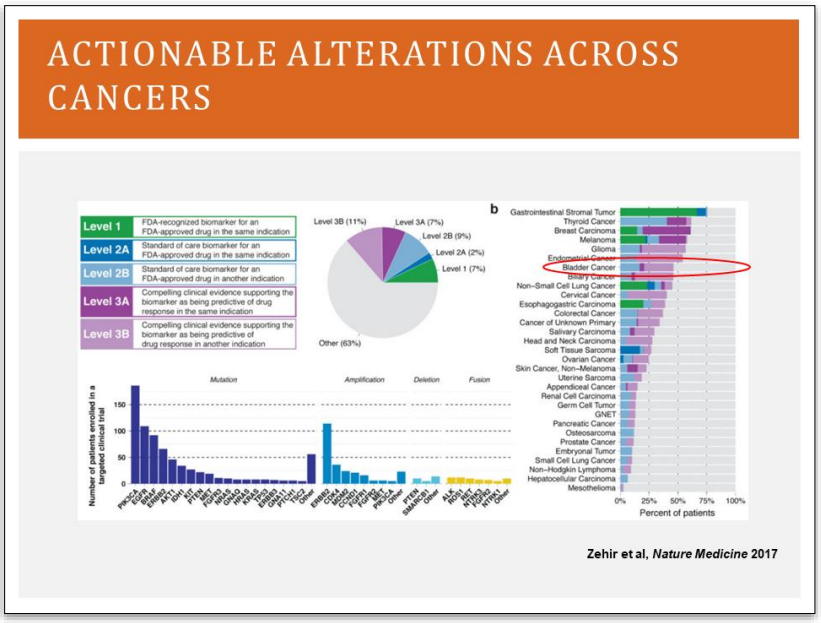
A couple of important points to keep in mind are when we look at this and we'll go over sort of genetic sequencing results in more detail, or that not every tumor will actually contain an actionable mutation. I think Dr. Lerner sort of showed this earlier as well, that, bladder cancer tends to contain a large number of mutations. We think part of the reason for that is because, it is what we call a carcinogen induced tumor, meaning that there may be environmental agents that cause it, and oftentimes those cancers have a lot of mutations within them. But the challenging part of that is that probably only a small number of those mutations are actually important for causing the cancer to grow, to divide, to spread. And there's also only a small number of those mutations that for which we have a drug that can be paired to it, to block what the mutations do.

Again, as I mentioned before, and I'll mention again, we do have a new drug, erdafitinib which was just FDA approved a few years ago. This was work that was pioneered, by Arlene Siefker-Radtke at MD Anderson and others. That is a drug that's specifically for patients whose bladder cancer contains mutations within FGFR2 or FGFR3, which were genes that, that Dr. Lerner mentioned before. And the drug was approved for patients with metastatic bladder cancer, but now it's being investigated in clinical trials, in patients who have earlier stages of FGFR3 mutant bladder cancer as well. And so because of this FDA approval, many of us now routinely offer genetic sequencing for patients with metastatic bladder cancer to pick up FGFR3 alterations and also other actionable alterations. So if we could go on to the next slide, please.

Dr. Gopa Iyer: Thank you. So this slide is an illustration of how, tumor genomic profiling is done. It's a little busy, but I was just going to go through some of these steps for you. Because I think it's important to kind of get a sense of how this is done. This is a workflow that we use at Memorial Sloan Kettering, but it's very similar to what many other institutions and companies are doing as well. So the initial step is that a patient with a diagnosis of bladder cancer has to sign a consent forms, giving permission for their tumor to be sequenced, that's very important. Following this the tumor is collected and oftentimes, we can do that using what we call archival tumor specimens. So if you've already had a biopsy or a surgery where a bladder tumor was removed, we can often use that. If that's not available, then the patient may need to undergo a new biopsy to sample a piece of tumor, somewhere in the body that we can send for sequencing. Most institutions store prior biopsy or surgery specimens for several years.



So, if a patient had a prior TUR or a bladder scraping procedure done, or maybe had their bladder removed, that tissue is often available for sequencing. And then the tissue goes through a processing step where the DNA is extracted from the tumor cells and it's sequenced using one of many different sequencing machines and following all this, all of that data that comes back, all of the different genetic mutations have to be reviewed and then classified based on whether the mutation is actionable or not. And so typically there are physicians trained in this process who perform that review and confirm the accuracy of the data. And then the results are usually uploaded, into a clinical report that's shared with the treating doctor, and the patient as well. And this report will indicate whether a given mutation is considered important for driving the cancer and whether there are drugs that target these mutations as well.



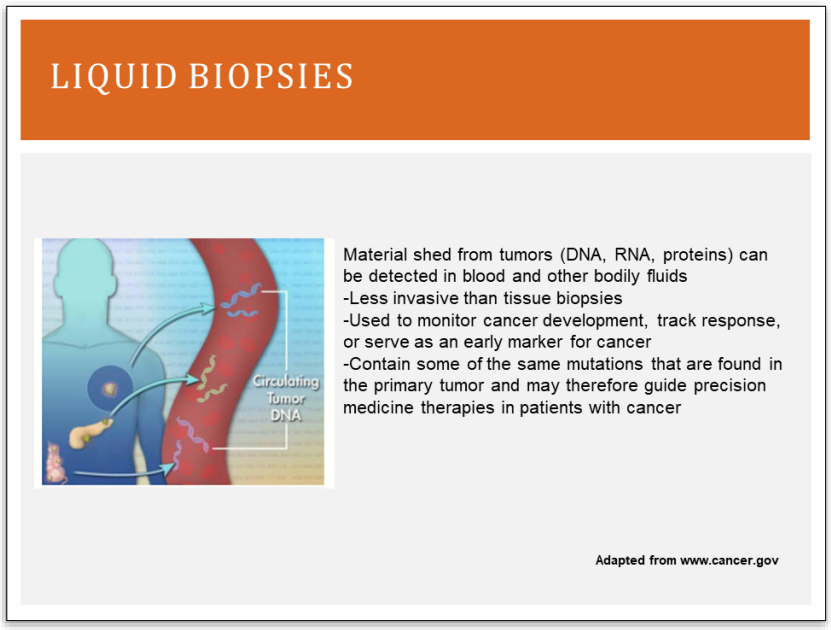
So we can move on to the next slide. I won't spend too much time on this, but basically, it shows the results of a large sequencing study that was performed, in over 10,000 tumors of all different types, they included bladder cancer as well. And it shows the different genetic mutations that are found and sort of shared across all of these cancers.

Dr. Gopa Iyer: What we found in what we call these pan-cancer analysis is that there are some key mutations that tend to be shared over and over again, across cancer types. And on the left, on the top there is sort of a chart that shows how to prioritize mutations, based on how much evidence there is to support their relevance in terms of driving cancer. And so that evidence can be from the literature from many different institutions where people are doing research on these mutations and coming up with sort of novel functions for these, for these specific mutations.

And these are evidence levels that were set up at MSK, but there's different evidence levels that are set up by many different institutions as well. For us, in green, there are level one mutation, means that there is an FDA approved drug available to target that mutation within that cancer type. And so an example, it's interesting. This was just published in 2017 and at that time, erdafitinib hadn't gotten FDA approved yet. So we actually didn't have any level one mutations in bladder cancer, but now we do, because all of those, FGFR3 mutations in bladder cancer, were considered level one alterations, because erdafitinib is approved. In the pie chart in the middle, really what we see is the distribution of all of the mutations that were identified across the 10,000 tumors by level of evidence.

And what you see is there's this big large gray area there, and that's about a little over 60% of all the mutations that were identified. What that me is that means is, those are all the mutations for which we simply don't know enough about their function, about their consequences, to be able to recommend a clinical trial. So I think it's important to keep that in mind that there's sort of a huge promise here with targeted therapy and we've come a long way just in the last five years, but there's clearly a long way to go still, because many of the mutations that we find, we're not sure what to do with in patients yet. And so it's a rapidly growing area of research as we try to understand the biology behind what they do. And ultimately from that biology, we can try to target them with new drugs.

So let's go on the next slide. So this is a slide that we actually just added this year and that's specifically talking about liquid biopsies, right? So this is something that's had a lot of interest, I think over the past few years, because really what it provides for us is a way to biopsy a tumor without actually having to do an invasive procedure. So we know that there's material, and typically this is DNA, RNA, or even proteins that are shed routinely from tumors. When tumors grow, while they make new cancer cells, they also old cancer cells die. And when they do, they sort of release this material into the blood, into the circulation and it can actually be detected in the blood, and other bodily fluids. It's actually really uniquely important for bladder cancer, because what we're finding is that sometimes we can even detect these types of mutations within urine, as well as blood.



Dr. Gopa Iyer: So in patients who have bladder cancer, we're very interested in collecting urine to see, are we able to detect the same mutations that we would detect from a TUR or a bladder scraping, or from a biopsy or a surgery within the urine or the blood. And it has a lot of uses. Right? And it's not quite prime time yet in bladder cancer, but it's getting there is what I would say. And so the big advantage, of course, of doing this is that you're sampling the blood for these mutations. So it's less invasive than tissue biopsies, but it can also... And it can be used to monitor in some cases development of cancer in patients. That's something that people are really excited about, can we use a blood test to detect if someone is already has cancer, but maybe it's such a low volume that we can't detect it on any scan?

It's also being used to track response to certain treatments. So an example of that would be that a patient who has an FGFR3 mutant bladder cancer who's on erdafitinib therapy, we might draw blood from them while they're on the treatment, to see, are the FGFR3 mutation levels going down as the treatment is working. And so it's a nice way for us to be able to track what's going on with the tumor. And can they serve as an early marker, for cancer. So in bladder cancer, that's especially important because many patients with bladder cancer undergo treatment followed by a surgery to remove their bladder, and then they're on surveillance after that. And so, we use scans basically to help us see if the cancer might come back or not, but now we might in the future be able to use a blood test as well, to be able to tell if mutations develop in the blood, that might be an early indicator, that the cancer is starting to come back again.

And the key about liquid biopsies that we're trying to validate is, are they an accurate reflection of what we would find if we sampled a primary tumor? And what we're finding is that in many cases, that is the case and work by actually a person that, that Dr. Lerner mentioned, Lars Dryskjot and others has actually shown that they do contain some of the very same mutations that are found in the primary tumor and the real way to leverage this is can we use liquid biopsies alone to guide precision medicine therapy in patients with cancer? A lot of the clinical trials that are coming out now of specific targeted therapies are allowing liquid biopsies to be done, in order to try to identify the mutations within that patient's tumor and as a potential eligibility for those trials.

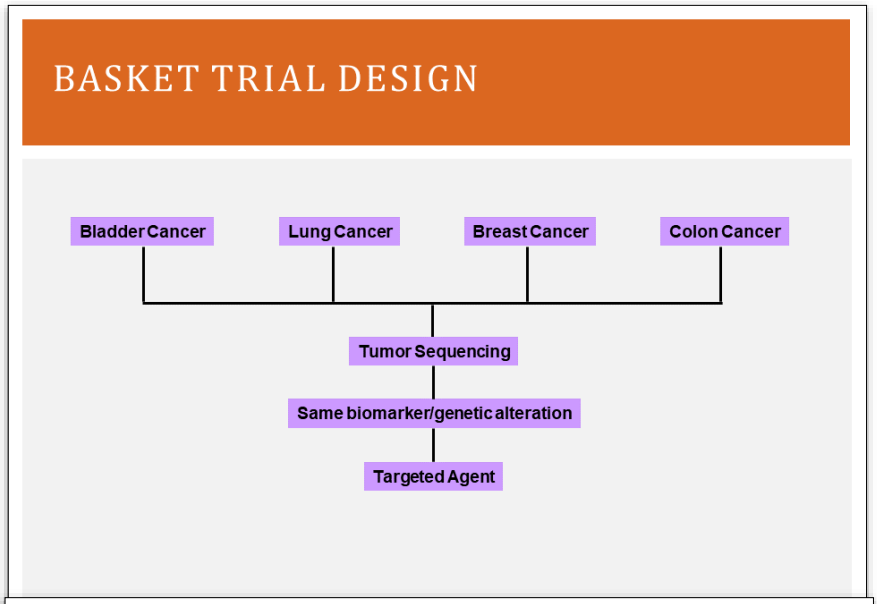
So it's a very exciting field, right now. So we can move on to the next slide, please. I wanted to just very quickly go over a couple of different trial designs that are, starting to become much more prominent. And these are typically trial designs that are used for trials that are testing targeted therapies. So a basket trial design, in this study patients with, basically any type of cancer, whether it's, bladder cancer or lung cancer, or breast cancer, et cetera, they all receive the same targeted therapy, based on the presence of a specific mutation within their tumor. So if the basket trial is testing an inhibitor of FGFR3, then basically any patient with an FGFR3 mutation, regardless of the tumor type is potentially eligible for this basket trial.

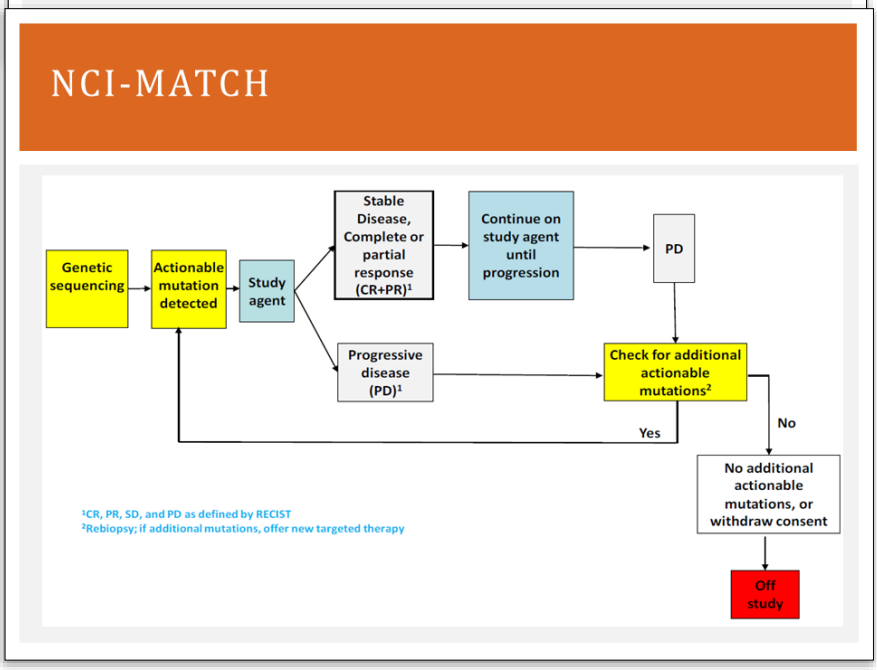
So they may have had their genetic sequencing done, by a company, by an academic institution, et cetera. And let's say that an FGFR three mutation was identified within their tumor. Well, then this trial might be something that they're eligible for. The advantage of this type of study is that we might identify certain cancer types that are extremely sensitive to this targeted therapy, which we might not have predicted, initially. So we can move to the next slide. So the umbrella trial design is something that's almost the opposite of that, it's basically a type of trial where patients with a single type of cancer

in this case, bladder cancer, are enrolled onto different types of treatment based upon the genetic seeing results from their tumor.

Dr. Gopa Iyer: So if their tumor, for example, has a specific mutation A then they would get targeted agent one, because that agent one is basically used to block whatever mutation A is doing. The other hand if they have mutation B, then they get targeted agent two instead. So the goal of this type of trial is to try to assess the effectiveness of a large number of targeted agents, and use genetic sequencing to identify the patients whose tumors have specific mutations that could benefit from it. There was a large bladder cancer, a large basket trial that was done, or I'm sorry, umbrella trial that was done in bladder cancer, which was the BISCAY trial, that matched patients with bladder cancer with specific treatments in this fashion as well.

So we know that this can be done successfully in bladder cancer and that's exciting. So we can move to the next slide. So one of the most sort of well known examples of a basket trial, is NCI-MATCH. And this was a study that was sponsored by the National Cancer Institute. And this was one of the first basket trials that was really performed, sort of nationwide. And the goal of this study was to really match patients with specific genetic alterations across cancer types, with certain inhibitors that block those alterations. There are many arms to the NCI-MATCH study that are testing basically many different drugs. The study has now completed accrual of patients. And actually, if we just go to the next slide, what we can see that's exciting is that there were 89 patients with bladder cancer who were screened for NCI-MATCH, and about a third of them, 36% of them were assigned to a specific treatment based on the genetics of their tumor.



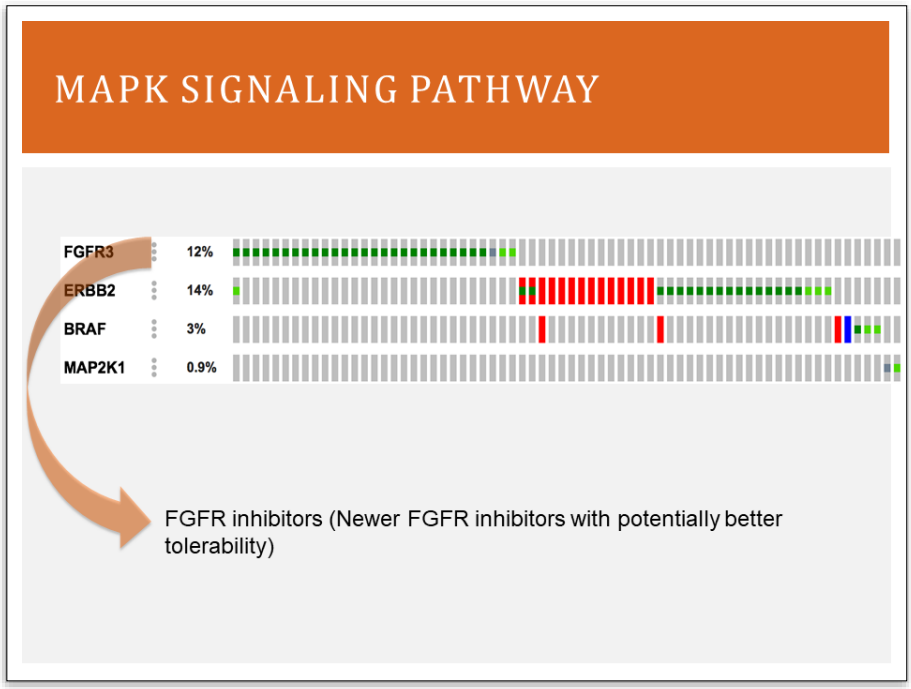


And just to put that in perspective, this trial was accepting patients who had any type of cancer. So patients who had much more common cancers like breast cancer, colorectal cancer, prostate cancer, et cetera, could have been potentially eligible for this study. And

what we found was that, when you look at 36%, that's actually quite high, that was a higher proportion than any other tumor type.

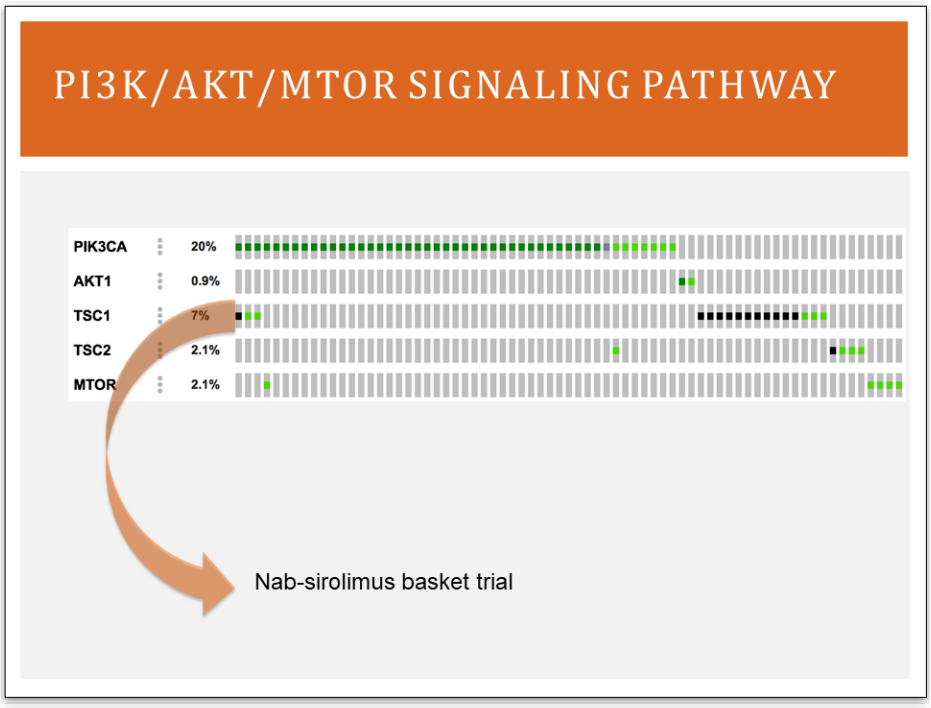
Dr. Gopa Iyer: And that's partly because bladder cancer has a lot of mutations and the chances are higher that there might be one for which we have a drug that's worth trying. So, in this slide right here, if we're just kind of drilling down into the sequencing data from the TCGA, each of the tiles here represents an individual patient with bladder cancer whose tumor underwent sequencing and the color coding based just shows the specific type of mutation that's list within the gene that's listed on the left.

And really the take home point of this slide in the next few slides is that there are several targets for which, small molecule inhibitors, or targeted therapies might be effective in bladder cancer. So, for example, we know that patients with bladder cancer have FGFR3 mutations and there's many trials right now are open, that are looking at FGFR inhibitors, that are actually different ones from erdafitinib which is already FDA approved. But the question is, can we improve on that drug with potentially better tolerability and better efficacy? We can move on to the next slide.

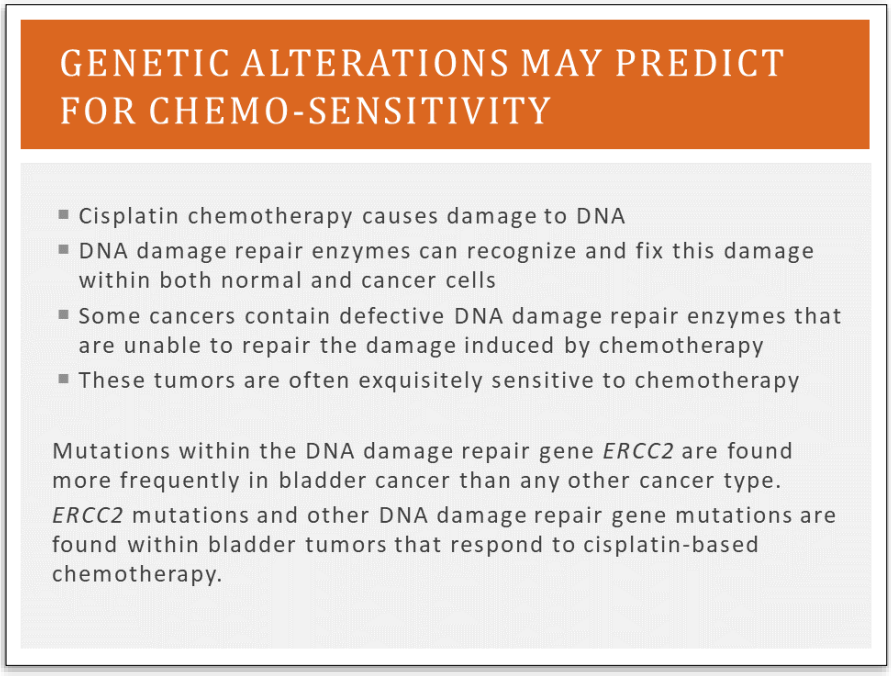


So then patients, for example, who have alterations with an ERBB2, which actually is a gene that encodes for HER2. And you might have heard that HER2 is a protein that's often, mutated or altered in breast cancer. So we think about HER2 positive breast cancer, but what we find is that actually bladder cancer has one of the highest mutation rates of HER2 of any cancer type. And so now there are many exciting HER2 targeted therapies that are in clinical trials, neratinib, afatinib are two of those, but there's also a few antibody drug conjugate therapies that are showing a lot of efficacy early on, including in bladder cancer that has HER2 alterations within it. So it'll be exciting to kind of see where this goes in terms of a research path. We can move on to the next slide.

Dr. Gopa Iyer: So, alterations within this pathway, the PI3-kinase/Akt/mTOR pathway, Dr. Lerner mention this as well in his talk, are ones that we're actively researching and trying to identify drugs that can target some of these alterations. There's one study of a drug called nab-sirolimus. It's a basket trial. So it's accepting patients with any type of cancer, including bladder cancer, whose tumors have mutations within this gene called TSC1, which is it in about eight to 10% of patients with bladder cancer. So those folks may potentially be eligible for this trial of nab-sirolimus. We can move on to the next slide. And then finally, bladder cancer has a significant number of alterations within genes that are involved in controlling cell division. And so there's a lot of trials that are trying to interfere with cell division, specifically that are inhibitors of cell division, that patients with bladder cancer whose tumors have these mutations might potentially be eligible for as well.



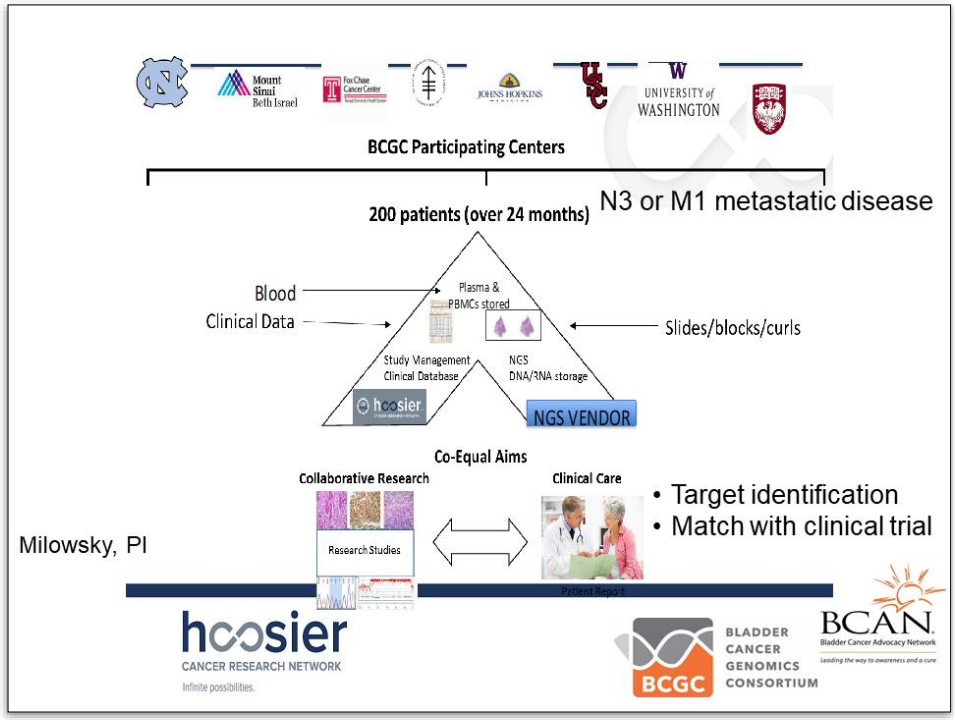
I would just point out that actually one of a great resource to try to identify these types of trials is the BCAN website, which does have a clinical dashboard that lists many trials that are relevant to bladder cancer. So we can move on to the next slide. So, something that Dr. Lerner alluded to and I'm going to actually wrap up, I think after this slide is, to talk about genetic alterations that may predict for a chemotherapy sensitivity. So one of the corner stones for treatment for bladder cancer, well, specifically for muscle invasive bladder cancer is to give a course of cisplatin-based chemotherapy followed by removal of the bladder. But we know that in some patients, about a third of patients that chemotherapy does a great job where their cancer is actually gone within the bladder, when they have their bladder removed. So the question is, do we need to take out the bladder in everybody who undergoes cisplatin-based chemotherapy?



And we don't know the answer to that yet. Right now the safe bet is to go ahead and do that surgery after chemotherapy. But what we have found from genetic sequencing data is that there are mutations within DNA damage repair or DDR genes that are actually involved in fixing damage to DNA within normal and cancer cells. Some cancers actually have defective DNA damage repair enzymes, and are unable to repair that damage induced by chemotherapy. And they tend to be exquisitely sensitive to chemotherapy. We don't know why they have these mutations, but we're trying to exploit them.

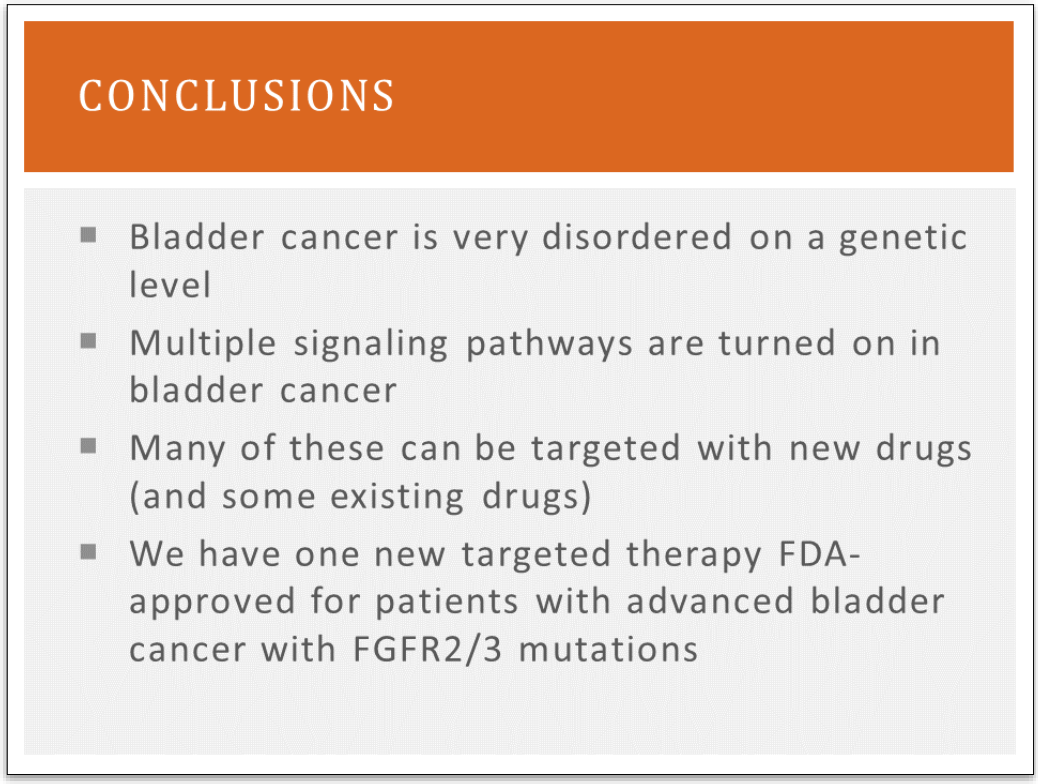
So mutations within DDR genes, such as a gene called ERCC2 are actually found more frequently in bladder cancer than any other cancer type. And so if we move to the next slide, there is actually a national clinical trial that's open right now through The Alliance for Clinical Trials in Oncology, that is testing whether the ability of these DNA damage response, gene alterations, to predict for sensitivity to chemotherapy and potentially to select some patients who might not have to go through a bladder surgery, who might be able to go with what we call bladder preservation. So in this trial patients who have muscle invasive bladder cancer undergo chemotherapy, and their tumor is sequenced at Memorial Sloan Kettering at the same time, if their cancer has these DDR gene mutations and they have a response to chemotherapy. So it's a very selective patient population, they may be eligible to spare themselves as surgery and undergo a bladder preservation approach, where we monitor closely for recurrence of their bladder cancer. If they don't have an alteration, then they go towards cystectomy or in some select cases, chemoradiation therapy.

Dr. Gopa Iyer: So we can move to the next slide. I didn't want to wrap up and without mentioning this. So this is something that BCAN has actually really spearheaded. And this is a study that has completed accrual, actually, but, yeah, it's hopefully going to be an area of a lot of research for us. So this is the UC Genome project, which is supported and led by BCAN. It's an effort involving multiple cancer centers. And the goal is really to perform tumor sequencing at no cost to patients with metastatic bladder cancer. This project is already enrolled 218 patients, which is a huge number with metastatic bladder cancer and their tumor tissue is undergone DNA and RNA sequencing.



The real reason I bring this up though, is that it's now all of that sequencing data is actually publicly available and it's going to be used as sort of a shared resource for scientific research for collaborations, and hopefully will serve as sort of a fruitful basis for designing novel treatments for patients with bladder cancer. It's really an unparalleled and precious resource for all of us who are doing research in the genomics of bladder cancer. So we can move to the next slide. So in conclusion, bladder cancer is very disordered, on a genetic level there are lots of mutations and other alterations, and there are multiple signaling pathways that are turned on in bladder cancer. Many of these can be targeted with new drugs and some existing drugs. And we finally have one new targeted therapy. That's FDA approved for patients with advanced bladder cancer with FGFR2 and three mutations.

Dr. Gopa Iyer: We can move to the next slide. So the TCGA findings offer sort of an immediate opportunity for us to be able to apply the genetic findings to the care of patients. But we do need carefully designed trials that are really enriched for patients who have specific alterations. So we hope that by enriching those trials for patients who, with specific genetic alterations within their tumor, that those are also going to be the patients who are most likely to benefit and this will lead to better treatments. So the TCGA project is an important step along the road to personalizing treatment for patients with bladder cancer. Thank you very much.



Stephanie Chisolm: Thank you so much, Dr. Iyer. This has been a phenomenal program, Dr. Lerner if you'll turn your back on, thank you. It's great to see you all here.