Update on Precision Medicine & Bladder Cancer

Part II: Developments in Targeted Therapy

February 28, 2018

BCAN Patient WEBINAR SERIES

Presented by:

Dr. Gopa Iyer *is a medical oncologist from Memorial Sloan Kettering Cancer Center who specializes in research in and the treatment of patients with genitourinary malignancies, including bladder, prostate, kidney, and testes. He has a special interest in understanding the genetic basis for bladder cancer, and he is a member of Memorial Sloan Kettering's Bladder Cancer Oncogenome Project, a multidisciplinary effort to discover the key genetic abnormalities that drive this disease.*

Dr. Iyer: I'm really thrilled to be able to discuss how we can take the findings that Seth and others have generated from the bladder TCGA and apply this now to the care of patients with bladder cancer. That's really what this slide is showing here. How can you as a patient take advantage of TCGA results?

While chemotherapy, as we know, can be very active in bladder cancer that has spread or metastasized, it rarely works for as long as we would like it to. Many academic institutions are now profiling tumors in order to identify specific mutations that are present within them, to see if maybe there are actually drugs, what we call targeted therapies, that can block the effects of those mutations. These are called actionable mutations or actionable alterations. There are lots of companies that are now also offering sequencing for profit, as well.

HOW CAN YOU TAKE ADVANTAGE OF THE TCGA RESULTS?

- While chemotherapy can be very active in bladder cancer that has spread, it rarely works for as long as we would like it to
- Many academic institutions are profiling tumors for mutations, and there are many companies are doing this for profit
- Not every tumor will have useful mutations
- Not every mutation will have a drug that can be paired with it
- Mutation sequencing may identify new treatment opportunities for some people

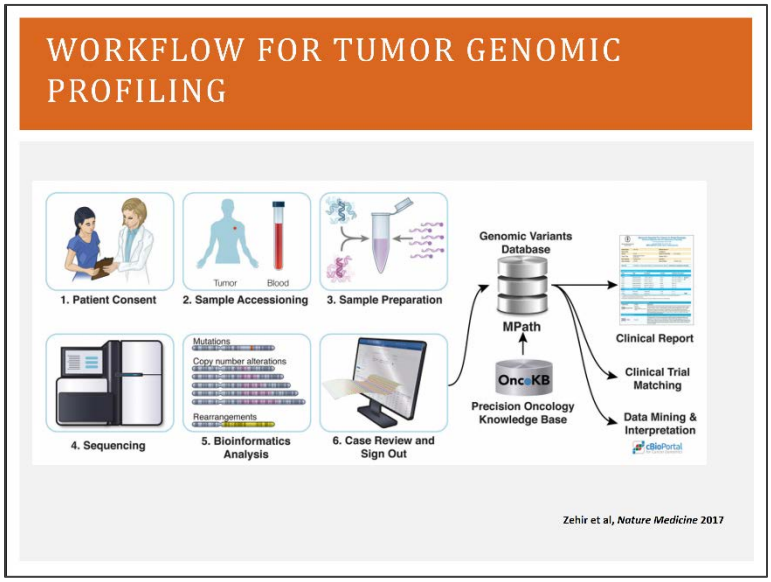
*Disclaimer-> this is not yet standard for bladder cancer

A couple of important points are that not every tumor will actually have a useful or actionable mutation within it. We oftentimes find a large number of mutations within a tumor, and as Seth had mentioned, bladder cancer is one of those cancers where there tend to be a large burden or number of mutations present. Not all of those are actually relevant for how the cancer grows and divides, and not all of those

mutations will actually have a drug that can be paired with it. Mutation sequencing, though, does definitely have the opportunity to identify new treatment options for some patients. It is important to keep in mind that right now there are no FDA-approved targeted therapies for bladder cancer, so this is not yet a standard of care for bladder cancer. What that means for patients is that their access to these drugs will come primarily through clinical trials.

I'm going to talk about that a little bit more now in the next slide. This is an illustration of the typical workflow for doing tumor genomic profiling. We use this at Memorial Sloan Kettering Cancer Center, and it's very similar to what other academic institutions and what some for-profit companies are doing, as well. Just to walk you through this, initially a patient, for example a patient with bladder cancer, consents to having their tumor sequenced.

Once that's done, if a tumor sample is not available, the patient may undergo a biopsy. That's sample accessioning, step number two, in order to collect the tissue. Sometimes, especially in bladder cancer, where surgery to remove the bladder and to remove the tumor is a mainstay of treatment, we oftentimes already have tumor tissue stored and available for genetic sequencing, so the patient doesn't always have to go through a biopsy to obtain that tissue.



Then there's a sample preparation step, where the DNA is extracted from the tumor cells, and then it's sequenced using one of several different sequencing platforms. These vary depending upon the institution that's performing the sequencing. We actually get quite a lot of sequencing data from each of these individual tumors. There are many, many mutations, sometimes over hundreds to thousands of mutations that can be identified in a given tumor. The goal then is actually to analyze this data using what we call bioinformatics algorithms in order to identify these mutations and other changes that may occur within the tumor DNA, and then actually to be able to divide these into ones that are actually important for the biology of the tumor and also important from a clinical trials standpoint. At our institution, and at many others, there are physicians who actually review these mutations initially to confirm the accuracy of the data. That's really what step six is.

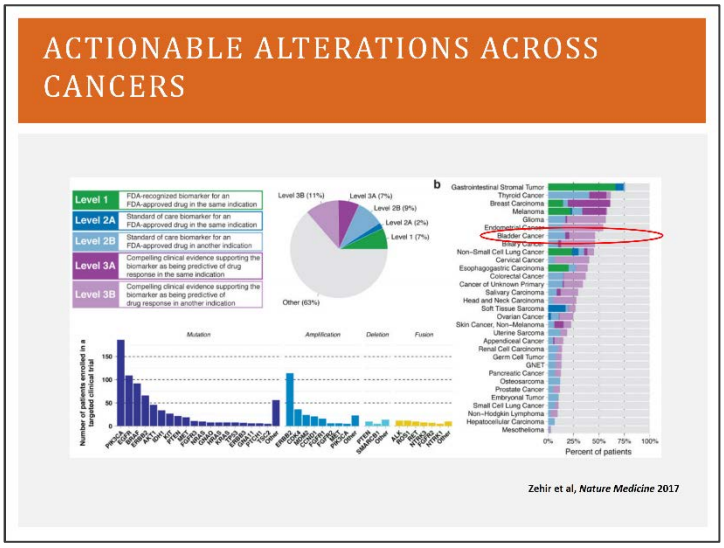
Once that's done, all of this genetic sequencing data can actually be placed into a large database, where it can be housed. From here, a clinical report is generated. This is a report that's actually given to patients as well as their treating physician. The report usually has a list of the genes that are mutated, the specific mutations that were identified within those genes, and also recommendations about possible clinical trials that the patient may be eligible for that they could be paired with based upon the

specific mutations that were identified. This is where the clinical trial matching step can really take place. We store typically all the genetic mutations and information from patients in an anonymized database, and this can also be used for research purposes, as well.

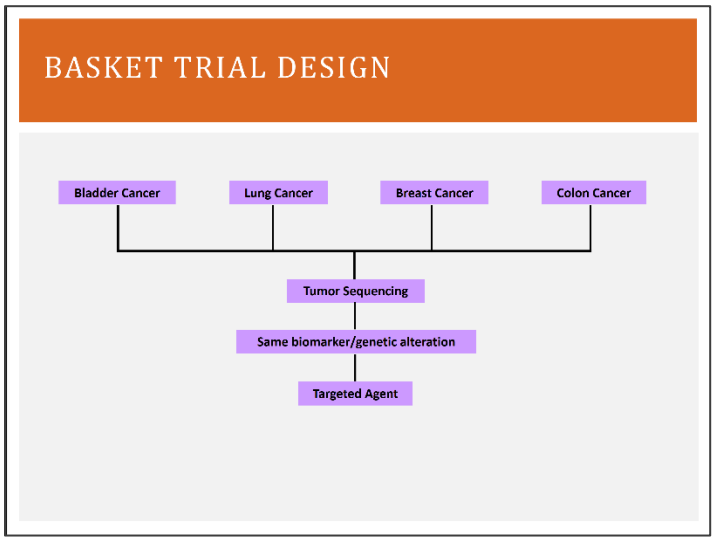
This is a busy slide, and I'm just going to walk you through it. It's basically there to give you a sense of how useful this mutation analysis is for us and for patients who have bladder cancer. This slide is actually showing the different genes that are mutated across cancers, not just bladder cancer but a lot of different cancers, from a cohort of around 10,000 tumors. What happens is that you can actually categorize these mutations into different levels of evidence.

That's really what the chart all the way on the left over here is showing. Each level actually corresponds to whether there's a drug that's available that might inhibit the effects of that mutation. For example, a level one mutation is one where there's actually an FDA-recognized drug already available to treat that mutation, and the mutation itself is also an FDA-recognized biomarker, meaning that it's known that when that mutation is present, that a specific drug will probably work to try to block the effects of that mutation and try to basically kill that cancer cell that carries that mutation. One example of a level one drug would be something like Tarceva, for example, for EGFR-mutant lung cancer. When we go down to a level three mutation, though, that means that there's clinical data from individual patients, maybe, that that mutation could predict for response to a drug, but there's no actual FDA-approved drug for that mutation within that specific cancer type.

In the pie chart on the middle, what that's really showing is that most mutations that we identify across cancers fall in what's called an other category. About 63% of them do. What that means is that we're still learning about the biology of these mutations, and we don't yet have a drug that blocks the effect of that mutation. It might be in development, or they may still be being tested in the laboratory, but there's not something that's ready yet for use or testing in humans yet.



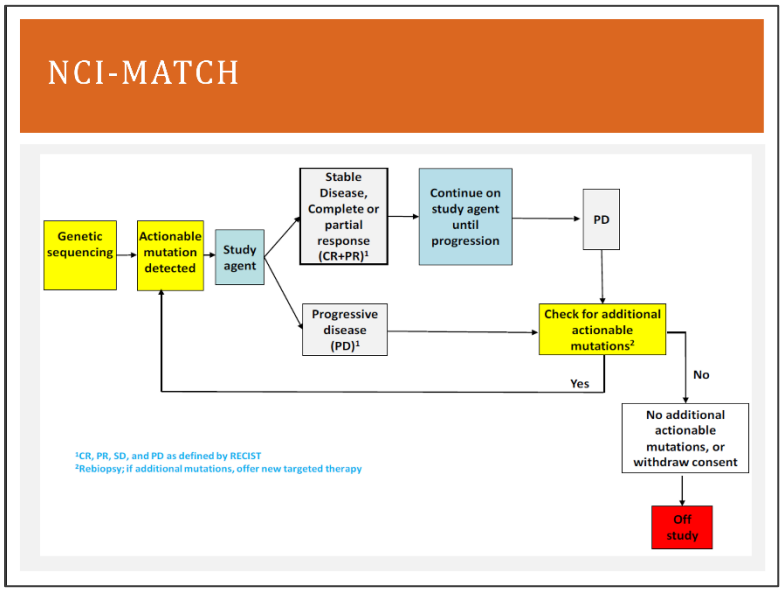
If we look at the bar chart on the right, what we see is that in bladder cancer, many actually of those mutations are found within that gray area, where we don't quite yet know what the biology of them are. However, there are a good number that fall, a little less than 50%, that actually fall within other levels of evidence. Most of the levels of evidence, mutations are actually level two or level three for bladder cancer. That means that there aren't any FDA-approved drugs specifically for that mutation in bladder cancer, but there are drugs that are being tested in clinical trials. This is important because patients who have these types of level two and level three mutations may be eligible for clinical trials that test drugs that are targeting these mutations.



If we go to the next slide, I wanted to just show you a schematic for what we call a basket trial. These types of clinical trials are actually becoming more and more common, mainly because of all the information that's been generated from TCGA and other sequencing efforts. In the past, and actually still now to a certain extent, trials were designed of specific ... that were testing specific drugs for a specific cancer type. There were specific drugs tested in bladder cancer, specific drugs tested in lung cancer, or breast cancer. Now, though, these basket trials are changing that. They're testing a drug for a specific mutation. It doesn't matter what type of cancer a patient may have. As long as their cancer has that mutation, they might be eligible for a basket trial of that drug.

In this schematic of the basket trial, patients with any cancer type, bladder cancer, lung cancer, breast cancer, colon cancer, and other cancer types, undergo tumor genetic sequencing and are found to have a specific genetic alteration, for which there's a drug that's being tested. They're all put into the same so-called basket, where they all get the same drug because they have that shared mutation. This is actually one avenue by which many patients with bladder cancer might be able to get onto these types of clinical trials and have access to drugs that are being tested.

One of the best examples of a basket trial is actually the NCI-MATCH study. It's sponsored through the National Cancer Institute, and the goal actually of this study is to match patients who have specific genetic alterations across cancer types with specific clinical trials of drugs that are blocking the effects of those mutations. For example, bladder cancer patients certainly might be eligible for one of the drugs that's being tested in the MATCH trial if their tumor has a relevant mutation.

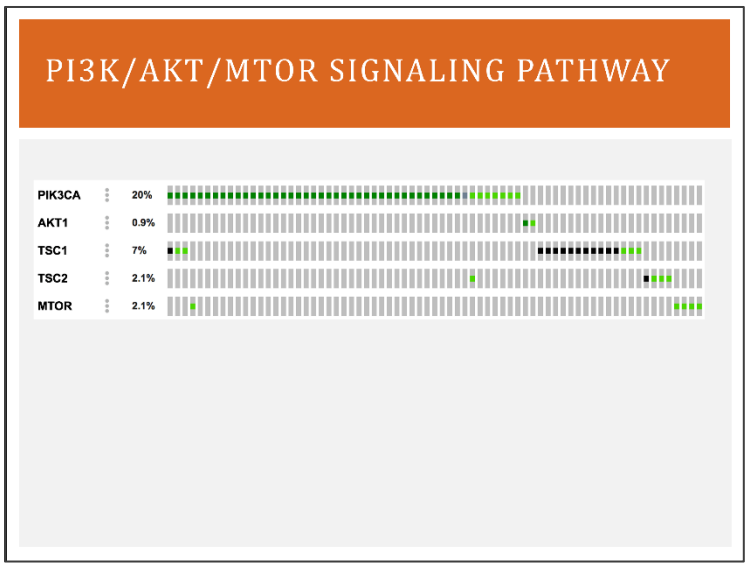


The way that this study works is that patients will undergo genetic sequencing of their tumor tissue, and if an actionable mutation is detected, then they'll be matched up to a specific study drug. They'll receive that drug and continue on it as long as they're having some sort of response to the drug. That can be

either what we call stabilization of their disease, where the disease stops growing or spreading to other parts of the body, but also if they have responses, where the tumor actually shrinks or goes away. They'll actually continue on that drug until there's evidence of progression again.

One special step with this study that's actually very nice is that if their cancer does progress again, they might be able to undergo another biopsy, for example, of one of the growing tumors that they have, and have it sent for sequencing. If there is another actionable mutation present, then they might actually be eligible then for another drug that's being tested within the NCI-MATCH study. There are many arms to the NCI-MATCH study testing many different drugs, so that possibility is there. If there aren't any specific mutations that are identified, or if the tumor starts to grow again, then they'll come off of the study.

The NCI-MATCH actually expects that about one in about four to five patients will actually have a mutation that can be matched to a specific drug. Of course, what that means is that there's probably about three to four patients who will have mutations present but there isn't a drug available yet that can block the effects of that mutation.



Going back to something that Seth had mentioned about how there are different signaling pathways in bladder cancer, I wanted to just go over a couple of the other signaling pathways that are found in this disease, and for which there are active clinical trials that are accruing patients who have mutations within these signaling pathways. One of the most frequently altered pathways across all types of cancer is the PI3-kinase/AKT/mTOR signaling pathway. There are actually multiple components to this pathway, multiple genes that are involved within this pathway, that can be mutated or altered. When that happens, oftentimes that causes the cancer cell to grow and divide uncontrollably. PI3-kinase itself is mutated in about 20% of bladder cancers, and there are large efforts at many drug companies that are ongoing to target this pathway.

What this schematic is showing is actually that each of these tiles represents an individual patient with muscle-invasive bladder cancer whose tumor was sequenced. The color coding just represents that there is a specific type of mutation within the gene that's listed on the left. All of these patients, their tumors were sequenced, and they had mutations within PIK3CA, which is the gene that encodes for PI3-kinase. What's interesting is that there's actually a clinical trial ... There's been multiple clinical trials, but one that I wanted to mention of a drug called GDC 0032 that's actually a PI3-kinase inhibitor, and this is being tested in a basket trial. This is actually for patients who have mutations in PIK3CA. Again, it could be patients who have lots of different cancer types, who have other cancer types other than bladder

cancer, but also bladder cancer patients. If they have a mutation within this gene, then this is a potential therapeutic option for them.

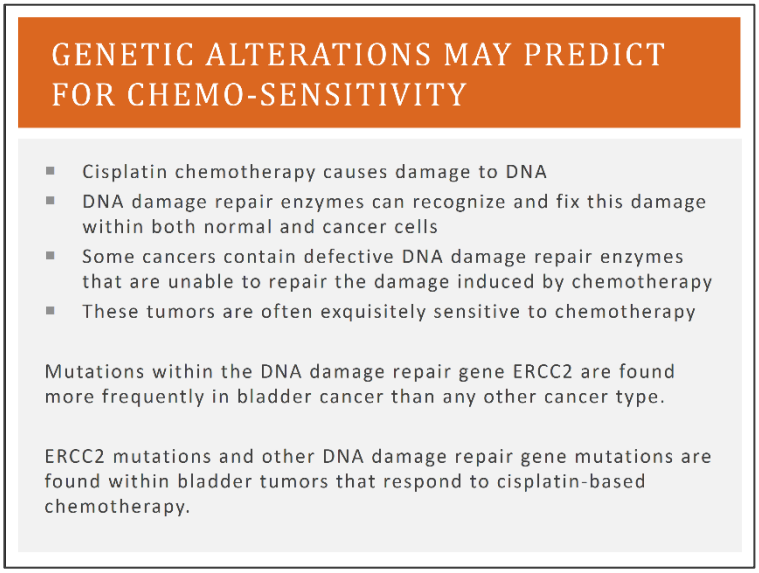
Another example of a component of this pathway that's mutated in about 7 to 8% of bladder cancers is TSC1, which had Seth had mentioned on an earlier slide. When TSC1 is mutated, oftentimes that causes the cancer cell to grow and divide uncontrollably. There's actually a clinical trial, also a basket study, of the mTOR inhibitor everolimus in patients who have TSC1 or TSC2 altered tumors. That includes patients who have bladder cancer as well.

Going back to the signaling pathway that Seth had mentioned, which includes HER2 and FGFR3, as he had mentioned, there are actually a number of clinical trials now testing FGFR inhibitors. I've just listed a couple of these, Debio, BGJ398, but there's also many others that are now being investigated in more detail in both basket studies across cancer types but also in bladder-specific studies as well. Just to emphasize once again what Seth had said, FGFR3 alterations are thought to be actually potentially drivers of bladder cancer growth and spread outside of the bladder, and so if we can come up with drugs that can actually inhibit what these FGFR3 mutations are doing, this has the potential to be quite effective in patients with bladder cancer.

Again, as he mentioned also, there are a number of studies that are now investigating HER2 inhibitors as well in bladder cancer. These are a couple of the drugs that have been tested so far, neratinib, afitinib, but there's also others as well that are being looked at in different clinical trials.

Another growth area or signaling area that's often altered across cancers but also in bladder cancer are the signals that are involved in regulating cell division. There are lots of proteins that can instruct a cancer cell as to when it should divide into two cancer cells or when it should not divide. The cell division pathway actually has a number of different components. Many of them are actually turned on abnormally in bladder cancer, and actually probably most bladder cancers have some part of this pathway turned on. That's something that's come out of the data analysis of the TCGA in bladder cancer. In breast cancer, there's actually a drug that can block one of these components called palbociclib that's shown significant promise. This drug is being tested in bladder cancer, and other drugs are also being looked at to see if they might also be effective in stopping cell division within bladder cancer.

We've talked a lot about these genetic alterations and how they might be targeted by specific drugs, but what we are also finding that's kind of exciting in bladder cancer is that some of these mutations can also predict whether a person might be very sensitive to chemotherapy as well, which is still

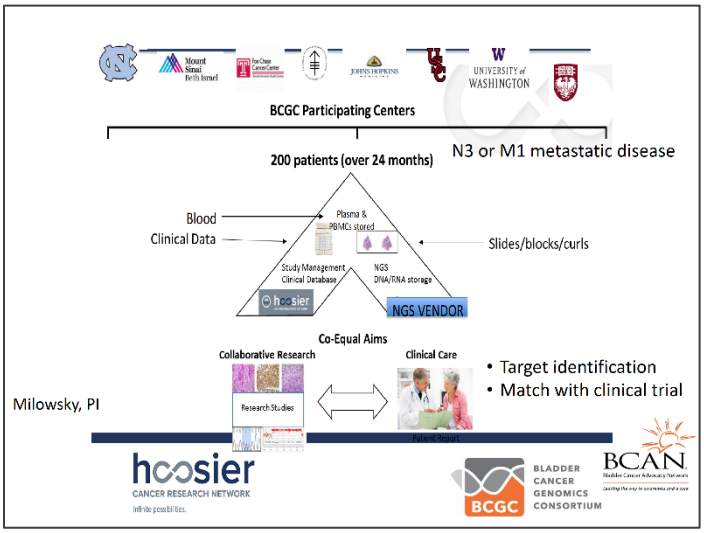


used quite frequently in bladder cancer patients. We know that cisplatin chemotherapy actually causes damage to DNA, and there are DNA damage repair enzymes that can actually see this damage and fix it. That can happen both within normal cells in our body but also within tumor cells or cancer cells. What's interesting is that some cancers have a problem with the DNA damage repair enzyme machinery within them. We don't know why that happens, but we do see it. When that happens, these cancers are actually unable to repair the damage caused by chemotherapy, and many of these tumors are very sensitive, exquisitely sensitive, to chemotherapy.

What's been found is that there are mutations within a specific DNA damage repair gene called ERCC2. These mutations are found more frequently in bladder cancer than any other cancer type. ERCC2 mutations and other DNA damage repair gene mutations are found in bladder tumors that respond to cisplatin-based chemotherapy. In the next several months, we're actually hoping to open up a clinical trial for patients who have mutations within these DNA damage response genes. Those patients who have muscle-invasive bladder cancer know that one of the mainstays of treatment for that disease is to undergo a course of chemotherapy, and then to follow that up with surgery to remove the bladder.

In this clinical trial, the plan is actually to do tumor sequencing of the tumors from patients who have muscle-invasive bladder cancer. All of these patients will still undergo chemotherapy, but if they have a DDR or DNA damage response gene mutation within their tumor, and they have a very good response to chemotherapy, then they might be eligible for what we call bladder preservation, where they don't have to go through removing the entire bladder, but could actually be monitored carefully with cystoscopies and scans. If their tumor, on the other hand, does not have a DNA damage response gene mutation, then they would move forward with the standard of care, which is removal of the bladder.

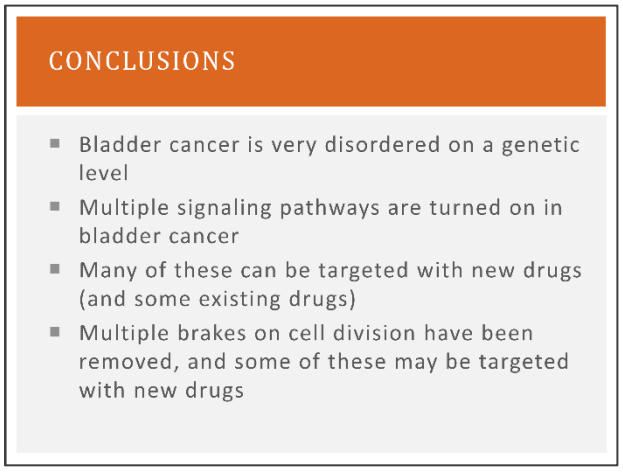
This is an example of where the genetic sequencing that's being done through TCGA and other institutions and efforts might actually also help us not just to match patients for clinical trials of targeted therapies, but might actually be helpful in being able to predict whether someone is going to have a really nice response to chemotherapy or not, and therefore we may also be able to impact how we treat those patients on a routine basis.



One other trial that I wanted to mention that's very exciting is actually one that's being supported and funded through the Bladder Cancer Advocacy Network, BCAN, as well as the Bladder Cancer Research Consortium. This is a trial in which patients who have metastatic bladder cancer, so much more advanced bladder cancer than the muscle-invasive disease that was sequenced in the TCGA, will actually have their tumor tissue sequenced at a commercial lab. The idea is that actually after the sequencing is completed, they will actually have a report sent back to them and to their

treating oncologist with a list of the different mutations that were identified within their bladder cancer, and whether or not some of these mutations might match with a clinical trial.

There is another aim to this study, which is actually also to generate a lot of data, mainly sequencing data from these patient tumors, so that we can better understand the biology of how these mutations drive bladder cancer formation and spread. That will hopefully also help us as clinicians and researchers to come up with better tools and better treatments for patients with bladder cancer.



In conclusion, we know that bladder cancer is very disordered on a genetic level, with lots of mutations present within any given bladder tumor, and that there are multiple signaling pathways that are turned on within bladder cancer. Many of these can actually be targeted with new drugs, and also some existing drugs, in the context of clinical trials. Multiple brakes on cell division, for example, have been removed in bladder tumors, and some of these may also be targeted with new drugs. TCGA, actually, the findings from there offer an immediate opportunity, because we can now analyze this data and try to match patients up for clinical trials as well based upon this information.

We still need to design very carefully these trials of targeted therapy, because we would probably ... The way for these trials to be successful will be to enrich them for patients who have specific genetic alterations. We hope that enriching those trials for patients who are most likely to benefit will lead to better treatments for them. The TCGA bladder project is really a fundamental and important step along the road to personalized treatment to a specific patient's tumor.

BCAN would like to thank our sponsors

MERCK INVENTING FOR LIFE

Genentech
A Member of the Roche Group

Incyte

EMD SERONO

Pfizer

for their support.