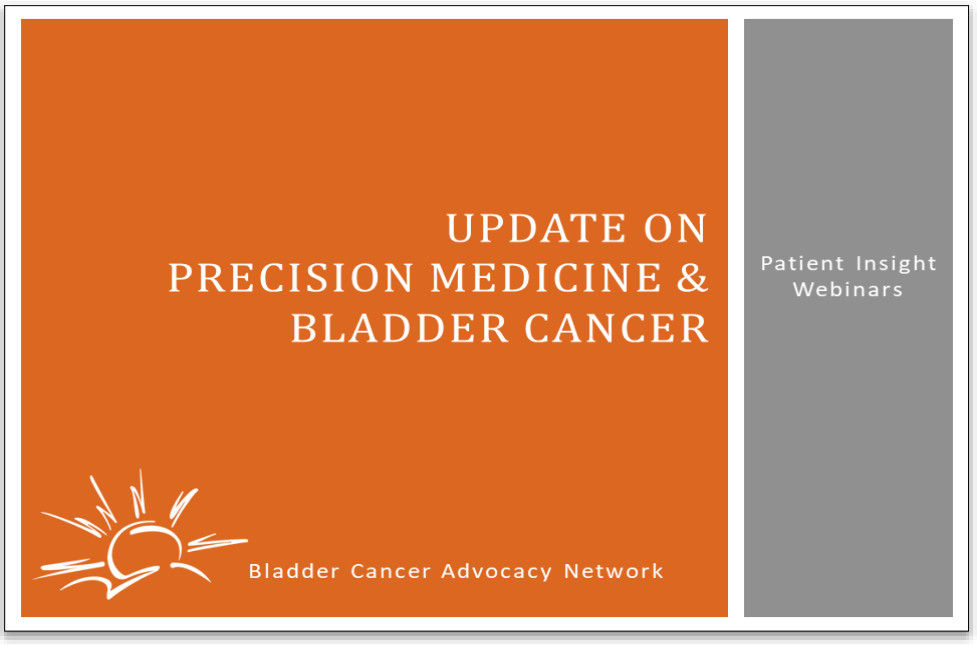


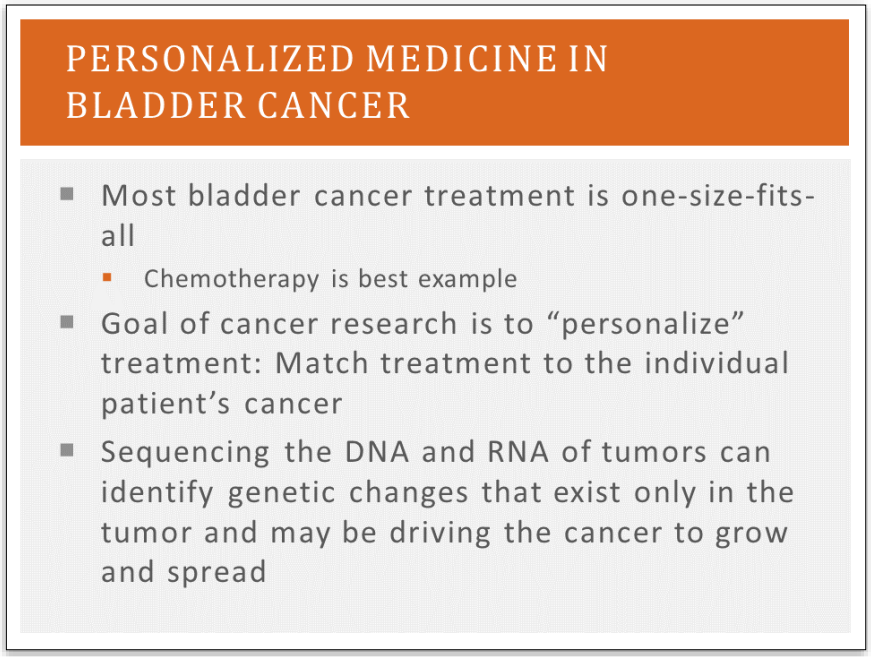
Stephanie Chisolm: Personalized or precision medicine has advanced greatly in the past few years. And we actually did this program four years ago, and I know that everything has advanced. Today, medical decisions, practices and interventions can now be tailored to individual patients more than they ever were before.

We're very excited to have Dr. Seth Lerner, the professor of urology who holds the Beth and David Swalm Chair in Urologic Oncology at Baylor College of Medicine in Texas. He's been involved in the National Cancer Institute's, Bladder Cancer Task Force and the bladder cancer disease working group for The Cancer Genome Atlas. Dr. Lerner also is on the board of directors for The Bladder Cancer Advocacy Network. And it's always an honor and a pleasure to have you with us, Dr. Lerner. So thank you.

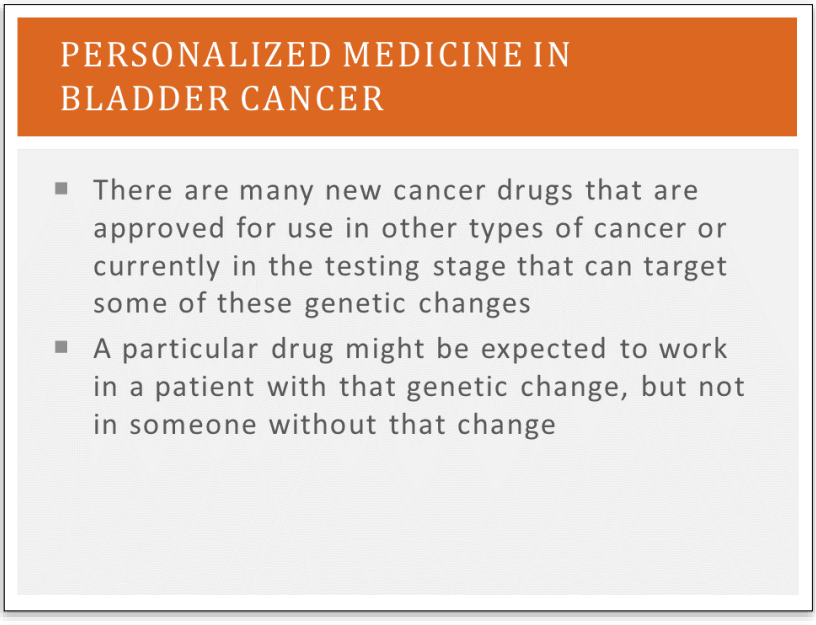
And then Dr. Gopa Iyer is a medical oncologist for Memorial Sloan Kettering Cancer Center in New York. Dr. Iyer specializes in research and treatments of patients with genetic urinary malignancies, and he has a special interest in understanding the genetic basis for bladder cancer. He's very involved with Memorial Sloan Kettering Bladder Cancer Oncogenome Project. It's just a multidisciplinary effort to discover key genetic abnormalities that drive the disease. And I think you're going to be pretty excited about what you're going to hear today. So Dr. Lerner, if you'd like to take over the screen, I'm going to stop touching my mouse and you can do that. Okey doke.

Dr. Seth Lerner: All right. Thank you very much. Stephanie, thank you, BCAN for putting on this seminar and really excited to have everybody with us today, and especially to get to do this with my buddy Gopa Iyer, who I'm a big fan and I watched his work, from, since he was a fellow. So he and I did

this as Stephanie said a few years ago and the world's changed, for the better. And we'll try to give you a snapshot of that and, I guess fair warning, there'll be some technical stuff, but we'll try to, explain it along the way, don't be put off by that. And hopefully we'll put all this in context for you over the next, 30, 40 minutes. So, just as by way of background, so the current, or sort of evolving standard of care has been chemotherapy for patients with metastatic bladder cancer.



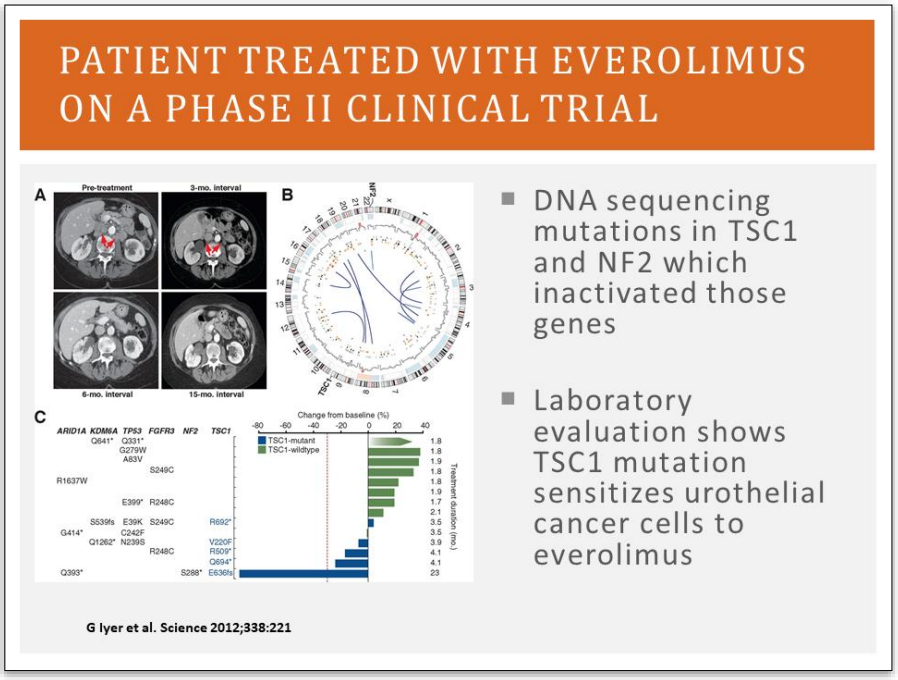
Dr. Seth Lerner: So that's when it spreads outside the bladder lymph nodes, lung, liver and bone would be the most common. And despite, a reasonable response rate, when you look at two years, after the initiation of treatment, unfortunately all, but about 10 to 15%, maybe 20% on a good day have succumbed to their disease. Huge problem, we're making progress, you'll hear about that, today and though, sort of the new combinations of chemotherapy, new chemotherapy agents have really not made a dent, and you're going to hear about sort of the promise and some of the early deliverables on precision, medicine. And I think that, probably many of you in the audience are unfortunately all too well acquainted with the side effects of chemotherapy and the sometimes profound impact or negative impact on quality of life. So let's see, here we go.



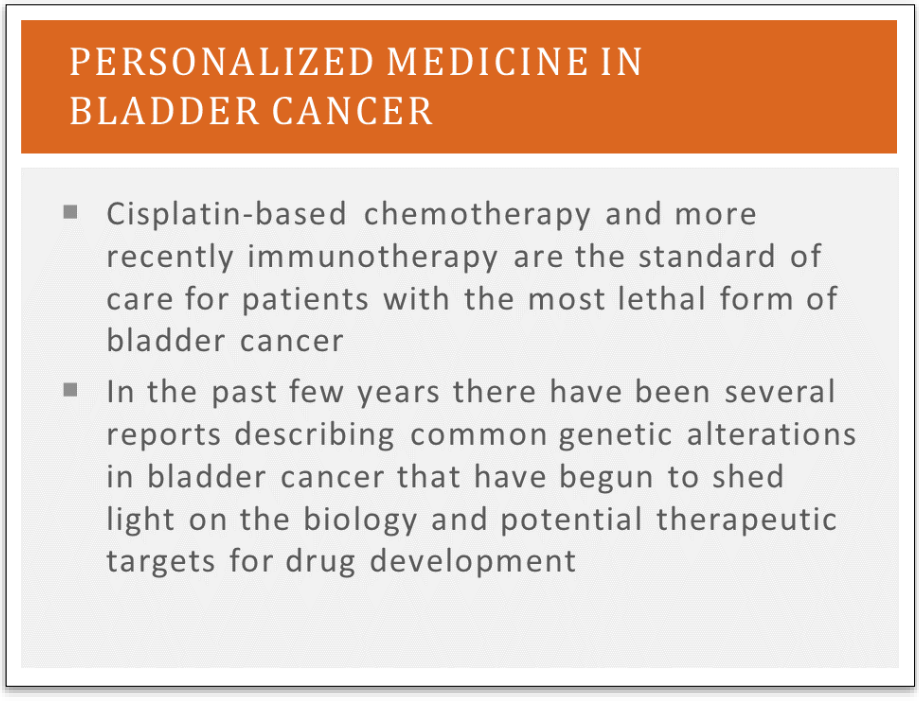
Okay. So, until recently, and again, we're going to try to walk you through this, treatment for bladder cancer, both, when it's spread outside the bladder or when it's muscle invasive and we're incorporating say chemotherapy with surgery chemotherapy with radiation, it's still one size fits all. So we're in a way kind of treating patients as if they're all alike. And of course they aren't, and their cancer is all alike and of course that's not the case, and you're going to hear about that, shortly. So the goal of really any treatment for any organ site cancer is to personalize it. And what that means to us and hopefully means to you, right treatment, right patient and it's based upon the patient's individual characteristics, and particularly the genomics, or the genomic alterations associated with their tumor. And now as you'll hear, sequencing DNA in the RNA, and now even the protein of an individual's tumor, it's no longer sort of magical thinking.

Dr. Seth Lerner: You can get this in a multiple of different laboratories, oftentimes turn around within two to three weeks, depending upon what you're really aiming for. And so the era of precision medicine is here, we can take advantage of all of that. Let's see, here we go. And, you're going to hear about a lot of new, exciting, drugs that have been approved, for bladder cancer, that target some of these genetic changes. And, I think the idea is that you'll hear about a specific one, I'll tell you an example of one that Dr. Iyer was really the first to sort of, to strike the first blow, so to speak, where if you have a drug that targets a specific genetic alteration, and that sort of drug gene target relationship is well established, you can oftentimes have a dramatic and lasting effect on the individual's cancer.

So here it is. So this really was the first salvage, and I'm going to just point out that this was published now almost 10 years ago. And this came out of a trial that, Matt Milowsky was running, when he was at Memorial Sloan Kettering. Matt has now been at University of North Carolina, and for quite some time. But now what you see up here in the top left is a patient with spread of the cancer. These are all in large lymph nodes in what we call the retroperitoneum, we're looking at the kidneys here. And, this individual is being treated with a drug called Everolimus, which targets a specific pathway we'll call mTOR. And, it was unselected, the trial by all measure was actually a negative trial, but this patient was what we call an unusual or exceptional responder.

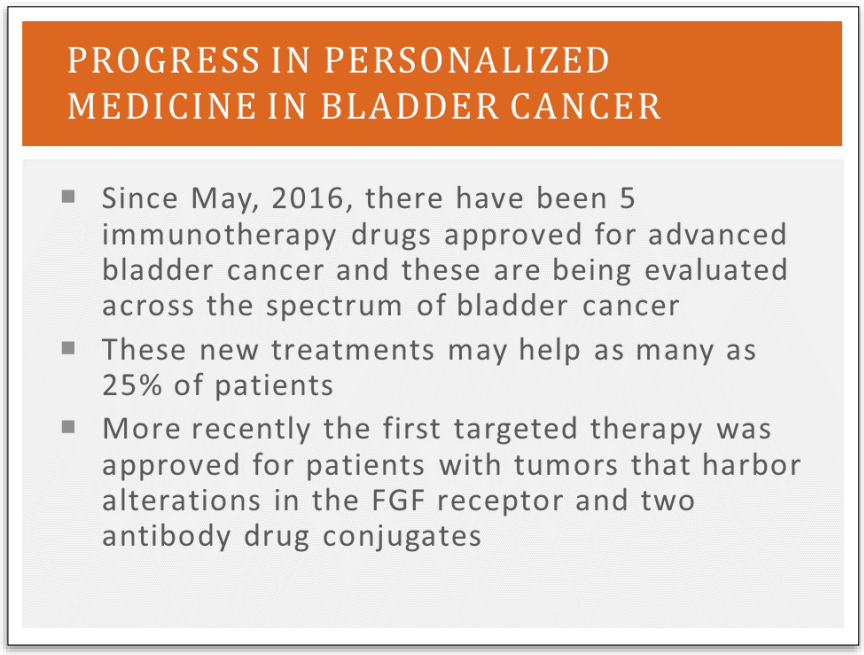


And what you see here even 15 months later, is that there's no evidence of disease and Gopa I know that you know how this patient did. And, well, that's not the point of the story. The point of the story is target relationship and an amazing response. So they went back and they sequenced the person's tumor and found that in fact, they had an alteration in this pathway, and therefore, that's why this drug worked. And, all right, so

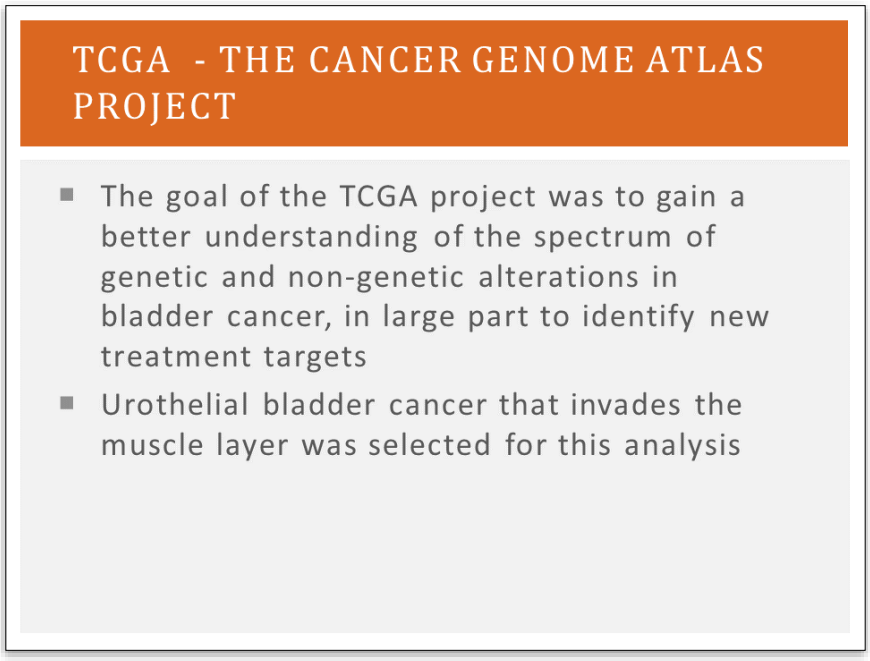


you'll hear a lot more examples on larger scale with this.

Dr. Seth Lerner: So, you're going to hear now about immunotherapy and combining chemotherapy with immunotherapy, and some of the advances that we've seen with that. And, we'll, talk to you a little bit about the biology and the therapeutic implications of that. So, since May of 2016, just a little over five years ago, and let me just give you a little bit of context that prior to that, what happened? We're going... Yeah, prior to that, the last approved drug for any stage of bladder cancer was 1998.

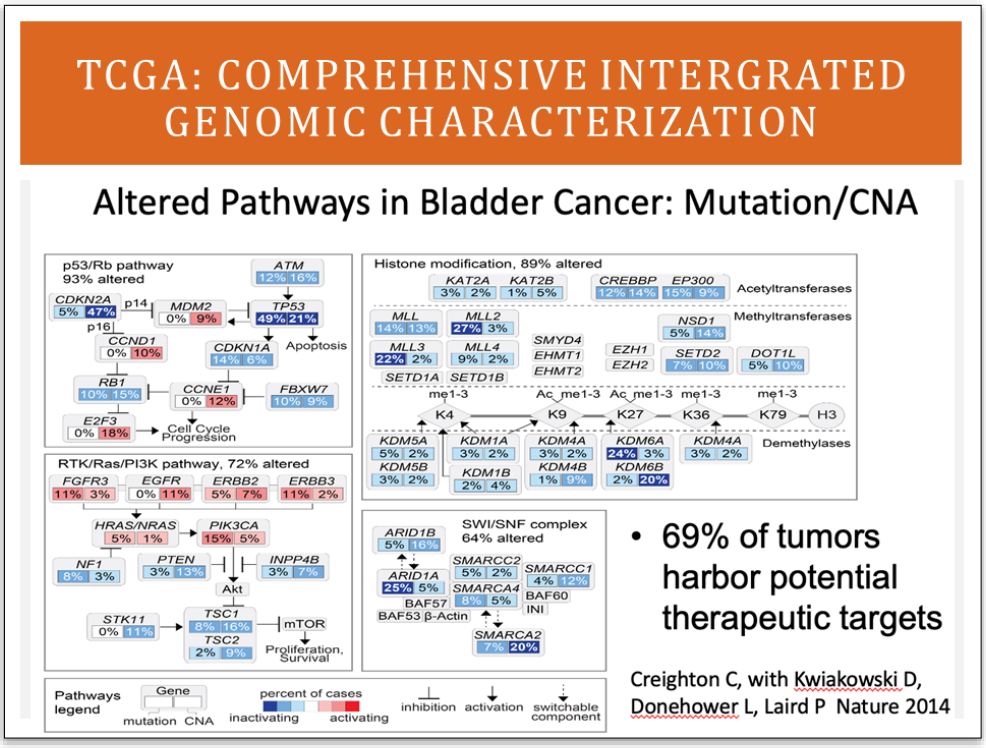


So kind of a desert of drug approvals. And those five were immunotherapy drugs they got approved in fairly rapid succession based upon, in many cases, phase two trials, the results looked so good that they got what's called accelerated approval from the FDA so that they could get to patients as quickly as possible. And if you pay attention to the news, you're obviously aware of some of the perceived benefits of immunotherapy. However, overall only about a quarter of the patients seem to benefit from it. And you can begin to identify what those patients look like by some of the changes in the immunologic profile of their tumor. And you can measure this in the bloodstream as well. And you'll hear a little bit more about that. And now we actually have also, the first targeted therapy approved in this case targeting the fibroblast growth factor receptor. And there is now a number of drugs out the market, only one of them is approved for this purpose. And that too, has been a game changer for patients that often have not responded to chemotherapy or immunotherapy.

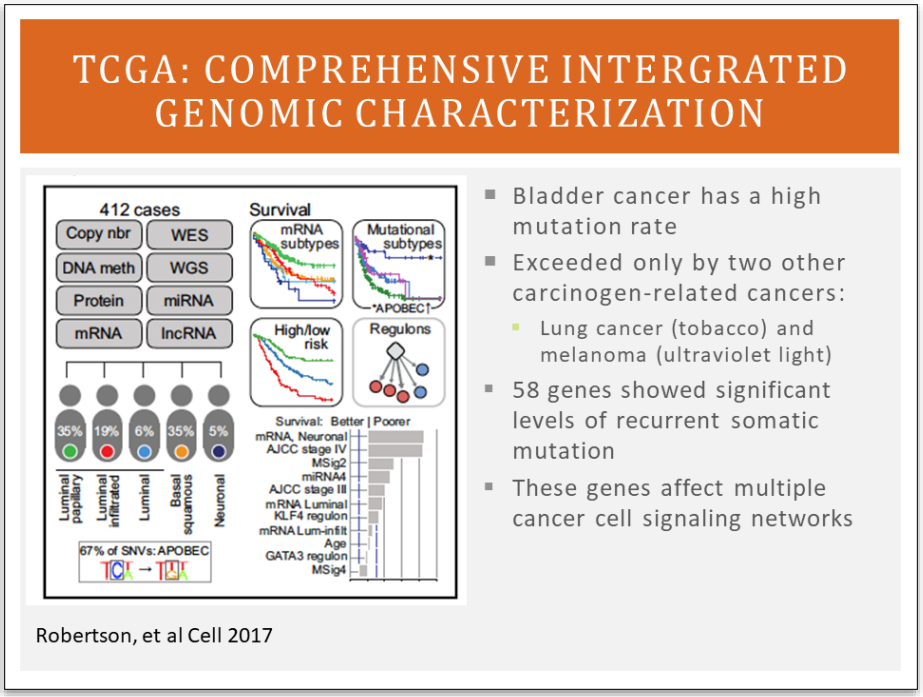


So, by way of introduction, I would just want to talk briefly about The Cancer Genome Atlas Project, this was started by the National Cancer Institute, well, over a decade, probably about 15 years ago. And the idea was, if you think about it was a human genome project for what turned out to be 33 cancers, 26 common, seven rare. And we were very fortunate that one of them was muscle invasive cancer. And the idea was to look at the entire genome of the cancer, DNA, RNA protein, and everything in between, and do what's called an integrated genomic analysis.

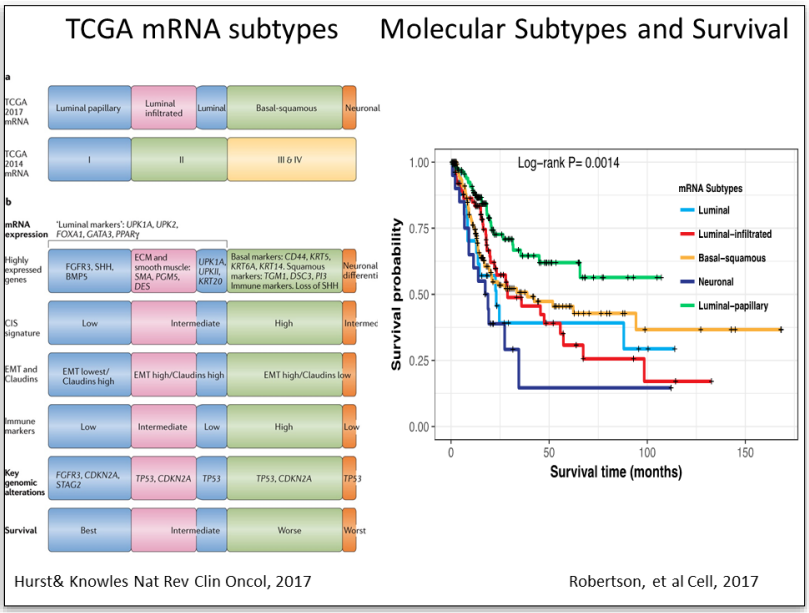
And in this case, urothelial cancer, muscle invasive cancer, which obviously is well, and which is the most serious and lethal form of the disease. And I was fortunate enough to co-chair that project with John Weinstein who's an absolute world class computational biologist at MD Anderson. And then we brought in David Kwiakowski from the Dana-Farber who happens to be a medical oncologist, who's a lung specialist, but he had a lot of interest in bladder and a tremendous amount of expertise. And so David helped us lead that as well. So don't worry about this image, but the take home message is what I've got right here. There were a number of questions that were submitted ahead of time back, I'm not sure why this is doing this.



So, what we looked at, and this was actually the work of Chad Creighton and others, and this was something that we published with the first iteration of The Cancer Genome Atlas Project. This was after 131 tumors only, all identified in the top left cell cycle regulation. This RTK/Ras/PI3 kinase pathway, three quarters of the tumors had alterations. These are things that sort of drive cell growth and duplication and proliferation. And then, this histone modification in this complex down here, sort of dictate how the DNA is organized if you will. But the take home message was roughly about two thirds of the patients had what we call potentially actionable

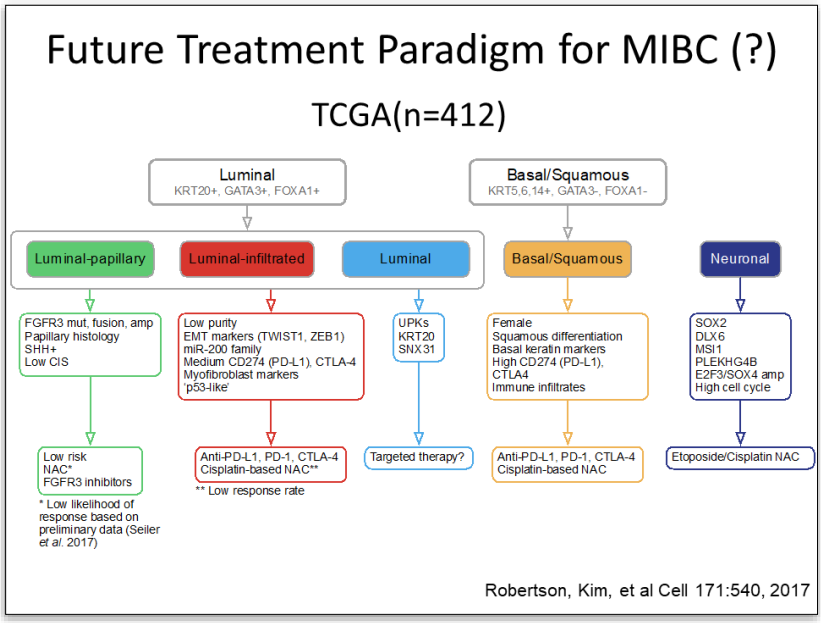


mutations. In other words, there were alterations in one or more of these genes that... And there were drugs out there that targeted that.



Dr. Seth Lerner: So this was really, for hope in at least muscle invasive bladder cancer. So let me just throw this up. And then, subsequent to that, we tripled a number of tumors that we analyzed just over 400, published another paper a couple of years ago. And I'll tell you some of the highlights about that, but one of the things is that bladder cancer looks a lot like lung cancer and melanoma with this very high mutation rate, that generates a lot of targets, but also might explain why, oftentimes it's resistant to chemotherapy and sort of grows out of control no matter what we do. And we also identified a number of, in this case, 58 genes or gene alterations that maybe had not been described specifically in bladder cancer. We knew a lot about it in other tumors and it's affecting multiple different pathways.

So one of the challenges in personalized medicine is... And oftentimes you see this in other organ sites where you see all of these targets, and you go, okay, we got a drug that's going to target this, patient responds, it lasts for maybe six months, nine months, 12 months, everybody's excited and then comes back. And it comes back because there's lots of other things going on that might allow it to say, escape the immune system, or overcome this drug target relationship. Okay. So one of the things I want to talk about is on the RNA side. So DNA encodes RNA, encodes proteins, and it's really proteins where all the action is. But these mRNA subtypes, and M is for messenger RNA, have been described by a number of different groups looking at that. And that's fantastic for the field because you've got everybody sort of thinking about this and these subtypes, tell us a lot about the biology of the cancer.

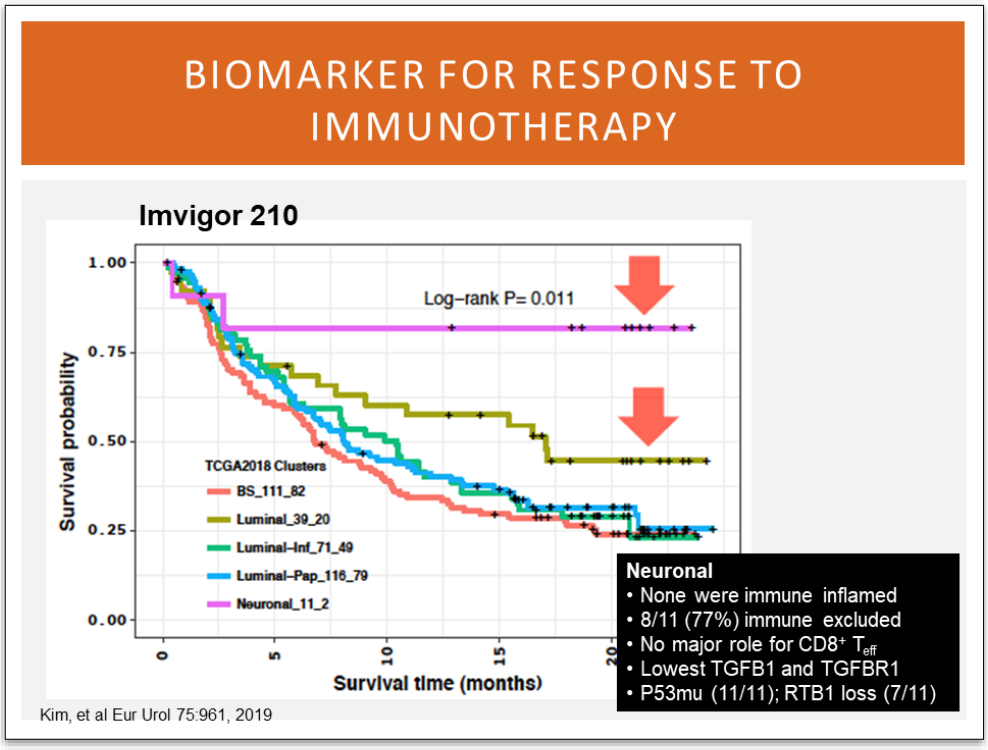


And one of the things that we learned and many others have shown this is that these subtypes are associated with the probability of survival. And you have this green line, luminal-papillary, which looks a lot like non-invasive cancer on the surface, even though it's muscle invasive has the best prognosis. And then you have these other subtypes, basal, squamous, neuronal, I'll show you an example of neuronal in just a second. And this was

really one of the early, sort of signals that these subtypes are now out only describing a different but a unique biology, but also perhaps dictating the long-term outcome.

Dr. Seth Lerner: And so, we proposed, in this paper, and this is a hypothesis, what does that mean? It doesn't mean that this is proven, it just suggests and that we now know on a single patient we can characterize a particular subtype and then potentially do subtype directed therapy.

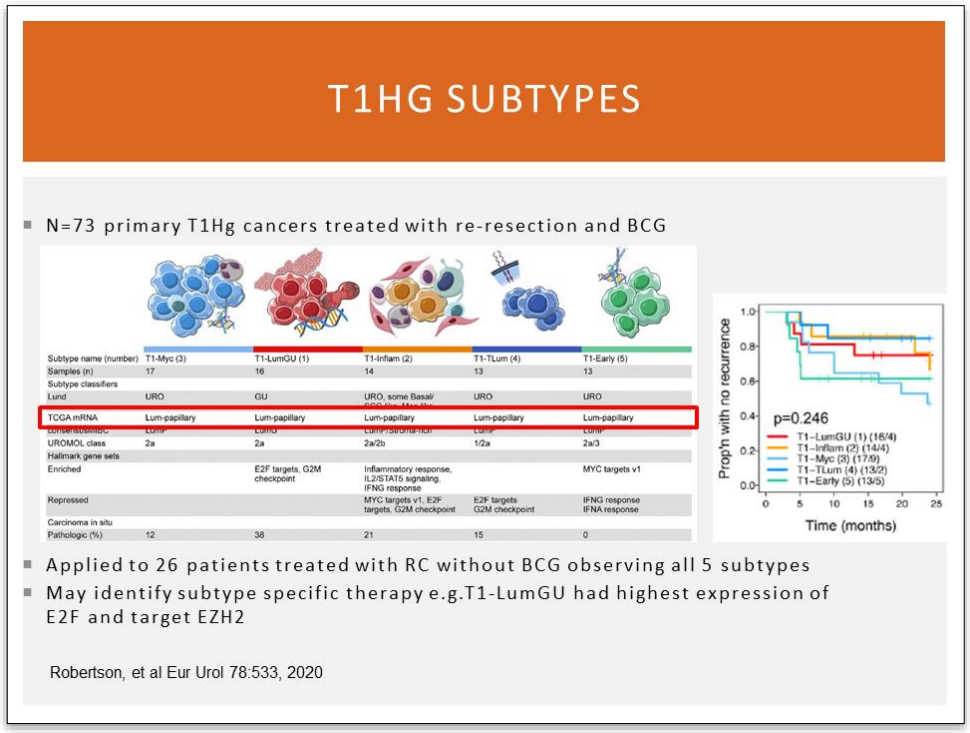
And that's a clinical trial that we're working on and trying to get approved. These luminal-papillary tumors appear to be lower risk for spread of the cancer. They happen to be enriched with this FGFR3 mutation. So maybe they're good to target that. Maybe they don't need NAC or neoadjuvant chemotherapy. We know that the basal/squamous tumors over here in the orange are, they tend to respond a bit better, the cisplatin-based chemotherapy, they also respond pretty well to the immunotherapy agents. These neuronal tumors I'll show you in a second maybe primed to respond to immunotherapy. And then these tumors over here are enriched and in immune infiltrated. So they may be better to respond to immunotherapy. And you'll hear about other potential biomarkers that may prime an individual's tumor to respond to a specific therapy.



Well, one of the things that we and others have done this is, in the TCGA was, in order to be able to apply this on an individual patient or in a personalized way, have to have what's called a single patient classifier. This was developed by Jaegil Kim, who was part of our group, was published a couple of years ago. And one of the things that Jaegil did was apply this to, one of the early immunotherapy trials in advanced disease. This happens to be the IMvigor 210, which was a phase two and phase three trial, using atezolizumab. And I do have to say upfront that I have a number of consulting relationships with several of the companies, including Genentech who's funding two trials of our research, just so you understand those potential conflicts of interest. But what Jaegil showed was that in these neuronal tumors, which have such an awful outcome, they had the best response to atezolizumab, suggesting that maybe the neuronal subtype for one reason or another is prime to respond to immunotherapy.

And if you look in this black box, it has many of the features that we look for, that might make it more sensitive to immunotherapy. So, in the next two slides, and I've got three more slides, I want to talk just

a little bit about non-muscle invasive disease, because the world is catching up. There've been a ton of work done in muscle invasive.



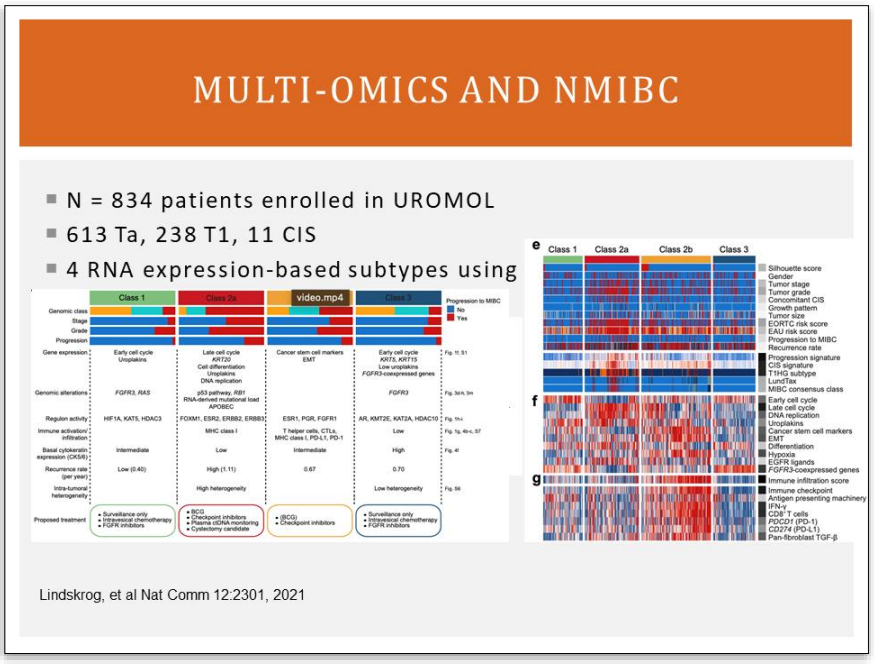
Dr. Seth Lerner: That's everything that I've been showing you. And this is a really neat paper by, Josh Meeks, who's a colleague of ours, a urologic oncologist, brilliant physician scientist at, University of Northwestern. And he teamed up with Gordon Robertson, who was one of the lead bioinformatics people on the TCGA group. And he decided to study T1 high-grade cancer. So, I'm not sure why that's going automatically, but that's fine. And so Josh had a group of patients with high grade tumors, previously untreated standard of care resection got BCG, and they took the tumors before treatment and sequenced their tumors. And that determined that there were five molecular subtypes.

And some of these are very different than what we see in muscle invasive cancer, except the interesting thing is they're all luminal-papillary. So within this luminal-papillary group, which had a favorable prognosis in muscle invasive disease, they found five different subtypes characterized by whether or not they were immune infiltrated, they had this... Meek is a cancer oncogene, whether they're inflamed and over here on the right, even though this is not statistically significant, it's probably a numbers game, but you see that there's differences in outcome, in terms of risk of recurrence. And then you went into the laboratory and tested one particular relationship with this, E2F transcription factor that can be targeted by drugs that target this EZH2 and show that it works.

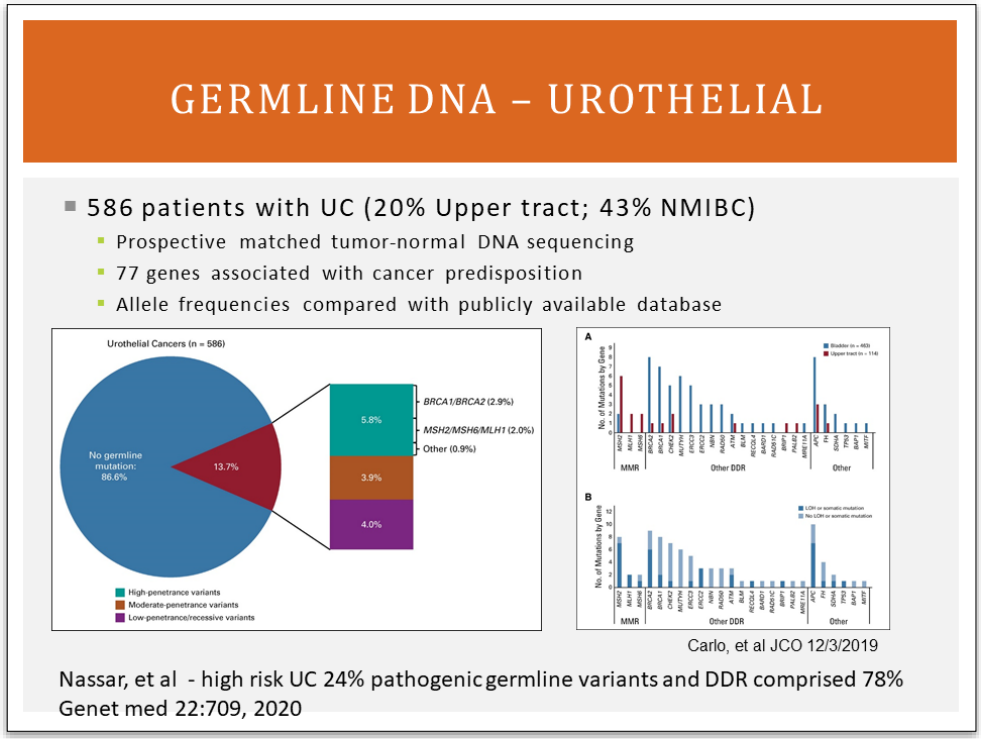
So a proposal or a hypothesis that there might be a targeted therapy opportunity for patients with this high-grade T1 cancer, which, this audience may be aware, it has a much higher risk of progression to a muscle-invasive cancer and that what is what we consider high risk non muscle-invasive disease.

Dr. Seth Lerner: So another group that's been working in this and for quite a long time is Lars Lindskrog, who's a colleague of ours from in Denmark, I'll just throw all this up here. And so they just published a very exciting paper and a high impact journal. And Lars has, helped put together this group UROMOL. It's a European group, which has been building this very rich clinical and pathologic database of tumors, You can see it's all non-muscle invasive disease. And so they've been using the same RNA expression based subtyping and expanding on some work that they published several years ago.

Again, you see that in this case, progression free survival, recurrence free survival, and you can see the association with, outcome there. But the wise investigators that they are, they also proposed a so-called subtype directed therapy. And you can see the different treatment proposals that they've got here, based upon these expressions subtypes for non-muscle invasive disease. So I think that the efforts from this group and I would be remiss by, if I didn't acknowledge some of the really nice work that's also been done by Memorial Sloan Kettering. And maybe you'll hear a little bit more about that. And so the last thing I want to talk about is, germline alterations. And again, kind of a shout out to the Memorial group, they've been very early adopters of lines of research, as well as Cornell and others.



And so what does this mean? So, germline is essentially the normal DNA that's in all of our cells, and you can measure this in white blood cells. And so, The audience may be most familiar with, breast cancer susceptibility genes. So BRCA1, BRCA2, that confer an increased risk of breast cancer in the offspring of carriers. And we didn't really think that this was a major issue for patients with bladder cancer, but that's changed, we've learned a lot about it in the prostate cancer world, and now what we're seeing in urothelial cancer, and this is a study that was published two years ago, a large number of patients, you can see that 20% had upper urinary tract tumors about, 43% were non-muscle invasive disease. And they looked at the DNA in these normal white blood cells and found 14% of the subjects had one or more germline alteration.



Dr. Seth Lerner: Here's our friend, the breast cancer susceptibility genes. These genes here are associated with Lynch syndrome and patients with Lynch syndrome they're, you may be more familiar with colon cancer, which is the predominant tumor that they get, but they're also at higher risk for getting particularly upper tract tumors. We do see some bladder cancer in those patients. And then, there was another paper that was published just more recently, which suggests... Whoops. Bear with my other finger, ooh, you lost the last thing I had. So there was another study that I was going to show, that suggests that this number is actually quite a bit higher, maybe is high as a fifth or a quarter. And you'll hear from Dr. Iyer I about DNA damage repair genes, which made up about 75% in that group.

And if you have a DNA damage repair gene alteration, you are likely to respond to cisplatin-based chemotherapy, for instance, maybe also immunotherapy. And those are big players in this disease that you're going to hear about in the second part of the talk. So, I hope I haven't, confused you too much, but the take home message is that we know a lot about the biology of these cancers, and we know a lot about an individual patient's biology based upon some of the work that I've shown you. And you're going to hear in the second half of this webinar, how that's beginning to be translated into the clinic, towards a more personalized medicine approach. And so, I'm going to turn it over to Dr. Iyer. And I'm going to pass sit back to Stephanie and then Gopa, I think you can pick it up.