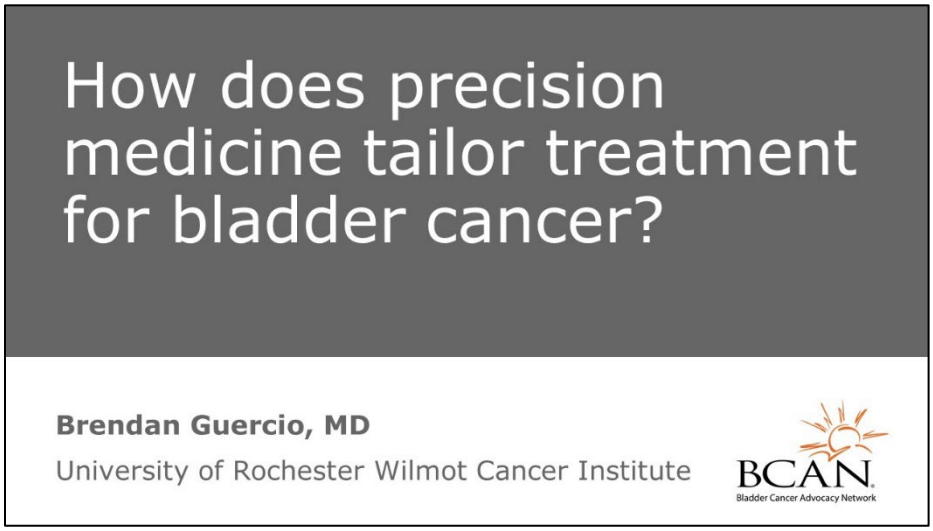
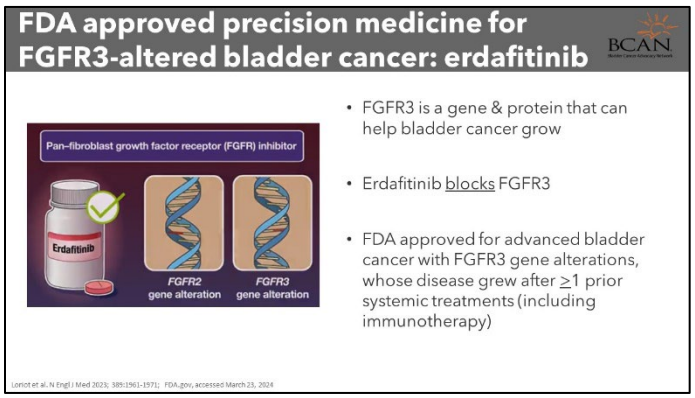


Dr. Brendan Guercio:



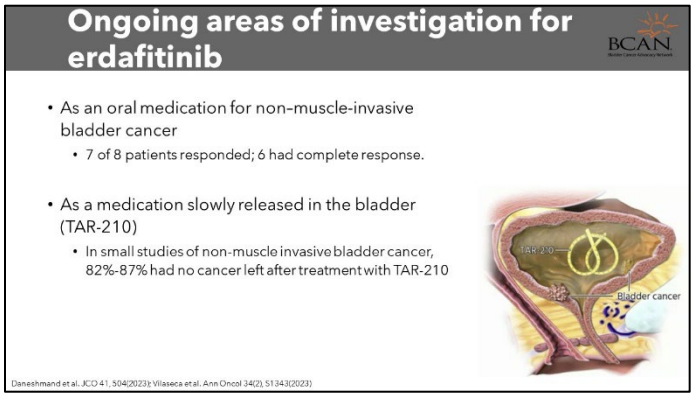
And FGFR3 stands for fibroblast growth factor receptor three. It's a gene and a protein that when mutated can actually help bladder cancer cells develop and grow faster than they should normally. And it actually has a treatment that's been approved by the FDA called Erdafitinib, where the brand name for it is Balversa.

But Erdafitinib blocks FGFR3 signaling, so that bladder cancer cells that are dependent on that protein can not grow. And this treatment based on Phase 3 randomized trials is now FDA approved for patients who have advanced or metastatic bladder cancer with those FGFR3 gene mutations, only in the case where patients have already had one or more type of systemic treatment for their bladder cancer before, usually including an immunotherapy because immunotherapy actually works even a little bit better than this type of treatment. But it is great that we have this type of treatment available because even though it's not a cure for folks with advanced bladder cancer, it is a good treatment option that can help patients live longer.

And even though Erdafitinib currently is only standard for folks with advanced bladder cancer, it is being actively studied in earlier stage bladder cancer now and has shown a lot of promise there, where FGFR3 alterations and the genes are even more common. Those FGFR3 alterations are present and maybe 20% of patients with advanced bladder cancer. But the frequency of those alterations can be much higher in early stage bladder cancer, which means Erdafitinib might play an even bigger role there. And when given as an oral medication for patients with

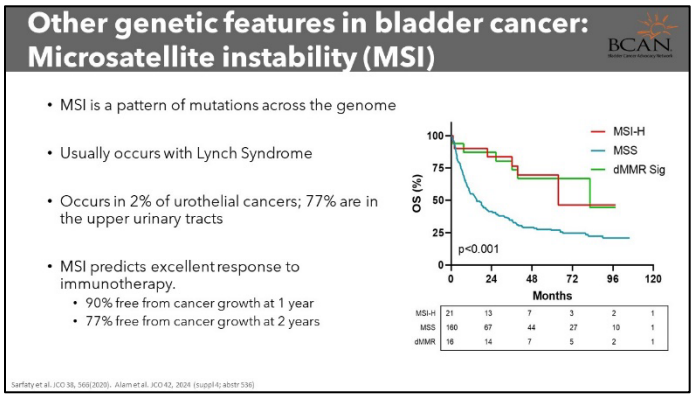
FGFR3 alterations for patients with non-muscle invasive bladder cancer, which are superficial early stage bladder cancers that are localized just to the bladder, in a small trial of eight patients, it was shown that seven of the eight actually responded well to the treatment, and six responded so well that they couldn't find any evidence of the cancer left in the bladder after treatment.

Dr. Brendan Guercio:



And one thing that's especially exciting is the use of Erdafitinib inside the bladder instead of an oral medication which helps reduce side effects. Basically, there's been a big push in bladder cancer treatment to develop this pretzel tool, which is the TAR-210 system, which can slowly release medications into the bladder over time while the pretzel sits in the bladder for three weeks at a time. And in small studies of non-muscle invasive bladder cancer, it looked like there were 82 to 87% of patients where the TAR-210 system slowly releasing Erdafitinib was able to get rid of all the bladder cancer. So these are still very early data, and these treatments are definitely not standard for non-muscle invasive bladder cancer yet. But there's a lot of excitement about them and we're hoping to see that future data shows that these trends are significant and improved treatment options for patients.

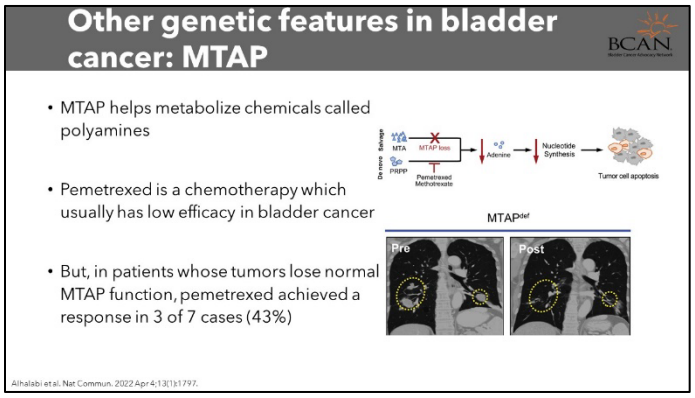
Dr. Brendan Guercio:



So what other genetic features besides FGFR3 are helpful for guiding precision for bladder cancer? Well, one that does occur in a subset of cases is called microsatellite instability, or often abbreviated as MSI. And microsatellite instability is interesting because it's not actually a mutation of a specific gene, but it's a pattern of mutations across the entire genome caused by defects in DNA repair. And it actually usually occurs in patients who have Lynch syndrome, that inherited syndrome that I mentioned earlier that makes it more likely to develop cancers. And so this microsatellite instability pattern in the genes of tumors can be found in about 2% of urothelial cancers like bladder cancer. It's actually a little bit more common in urothelial cancers that arise in the ureters and the kidneys, which often act a lot like bladder cancers.

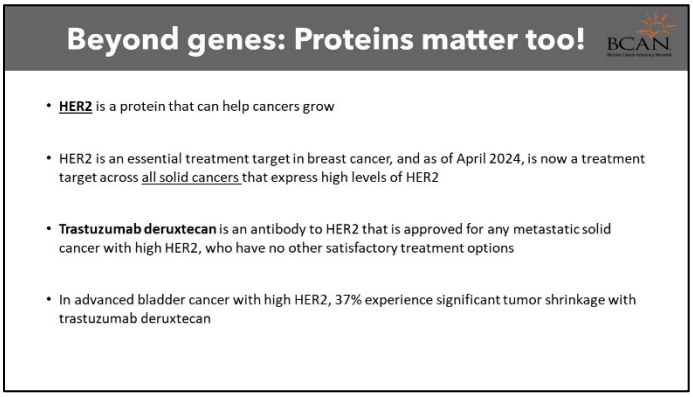
And the reason this is potentially important for patients is because if we detect microsatellite instability in the tumor, we found that those patients happen to respond particularly well to immunotherapy such that patients who have advanced bladder cancer and are treated with immunotherapy with microsatellite instability end up being free of any cancer growth at one year 90% of the time. So it's something that can potentially help physicians better tailor treatment to patients with advanced bladder cancer. It might be important to earlier stage cancers in the future.

Dr. Brendan Guercio:



Other genetic features in bladder cancer that could matter, one is called MTAP, which is an important gene and protein in the body that's involved in metabolizing chemicals called polyamines. And the reason the MTAP gene is important is because there's a type of chemotherapy that's standard for other cancers like lung cancer called Pematrexed, which unfortunately does not work very well in bladder cancer. But it turns out that when a bladder cancer has a mutation of the MTAP gene, it makes a bladder cancer much more sensitive to Pematrexed. For example, in a small study that was done at MD Anderson of seven patients with MTAP loss, they found that Pematrexed was able to cause significant shrinkage of the bladder cancer in about 40% of patients. So while this is not necessarily a good treatment for most patients with bladder cancer, if a patient has MTAP loss, it is potentially a good option after using other standard options like immunotherapy. And having more options to treat a cancer is always a good thing.

Dr. Brendan Guercio:



So I've been talking pretty much exclusively about genes and genetics and DNA so far, but not all precision medicine is limited to genes and genetics. It turns out that other features of cancer cells like proteins do matter to precision medicine too and tailoring treatment to a patient's cancer. And one of the protein targets that's important to know about is HER2 or human epidermal growth factor receptor 2, which is a protein that can, when it's overexpressed, help cancers grow faster than normal cells. And HER2 is already a very well-known and essential treatment target for breast cancer that's been used for many years. And in the past few years, it's become

an important target in other cancers too. And as of this past month, actually, there is now a HER2 targeted treatment that's approved for all solid advanced cancers if they have high levels of the HER2 protein on their cancer cells.

That treatment is called trastuzumab deruxtecan. It's an antibody to HER2. So it targets the HER2 protein on the cell surface, and it's gotten approval for any metastatic solid cancer with high levels of the HER2 protein if they have no other satisfactory treatment options at that point. So again, another good option if immunotherapy isn't working or traditional chemotherapies aren't working well for a patient with advanced bladder cancer. And in advanced bladder cancer, it's been shown in a prior study that if high HER2 levels are present, over a third of those patients will have a good amount of cancer shrinkage in response to this drug. So another good tool in our tool belt. And the HER2 protein is probably high in about 20% of patients with advanced bladder cancer, although the exact number varies from study to study, but definitely an important treatment option for some patients.

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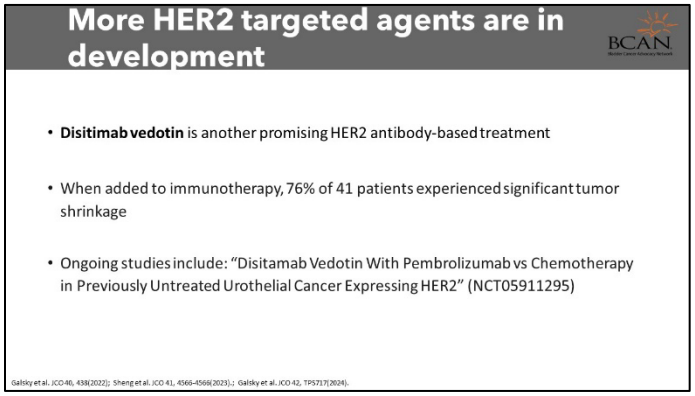
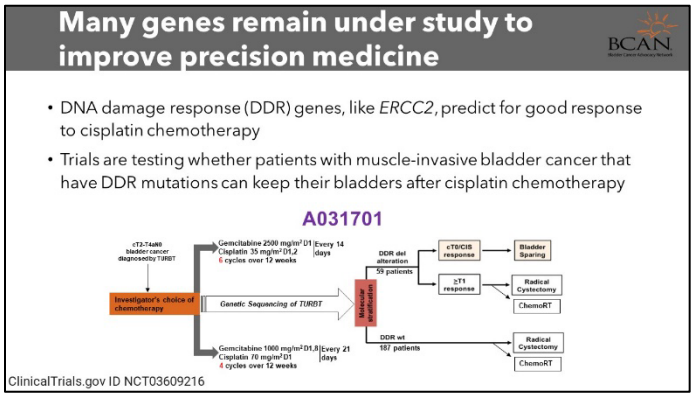


There are more HER2 targeted agents that are now in development specifically for bladder cancer and are developing a lot of excitement. One of those is a new medication called Disitamab vedotin, which actually was originally developed clinically in China but is now in clinical trials here in the US as well. It's also a HER2 antibody-based treatment that targets cells with high HER2. And in a study of 41 patients with advanced bladder cancer, when it was added to immunotherapy, 76% of patients had a good amount of tumor shrinkage in response to the treatment. And so there's now large Phase 3 trials that are going on to try and confirm whether or not this might be a good standard option for patients who are treated for bladder cancer in the future.

Dr. Brendan Guercio:



So what other reasons are there to do genetic testing? Well, outside of the potential standard treatment options that I discussed, it's also really important to help patients find clinical trials. There are many genes that are still under investigation to improve precision medicine for patients with bladder cancer. And the only way to know if a patient is eligible for those trials is through genetic testing. This is just an

example of one of the trials that's open across the nation at many different sites that's trying to make precision medicine better for bladder cancer. And it's focusing on mutations in a type of gene called DNA damage response genes, which when they're mutated actually predict for very good response to Cisplatin chemotherapy, where we know if we see those mutations present, those patients may have no cancer left in the bladder after they get Cisplatin because it works so well. And so this trial, which is being run through the Alliance Cooperative group under the National Cancer Institute is investigating whether patients with muscle invasive bladder cancer that have those mutations can maybe keep their bladders after Cisplatin chemotherapy instead of having their bladders removed by cystectomy if they have those mutations present.

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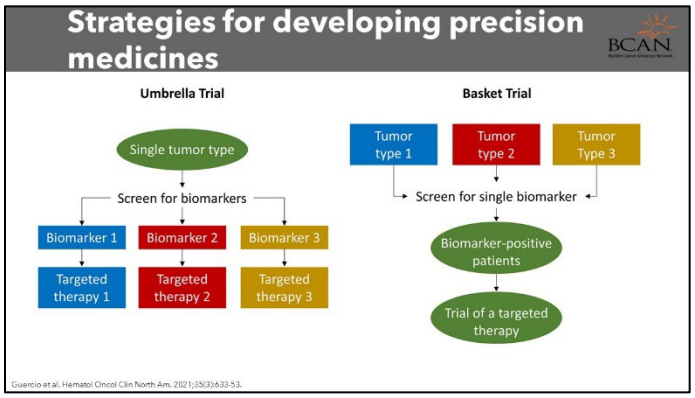


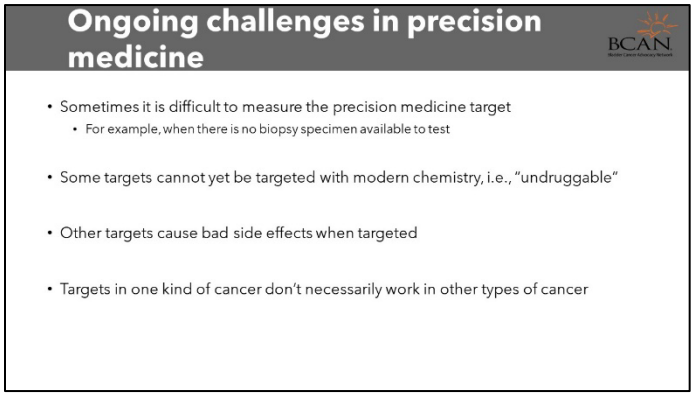
And there are many different strategies that are used in clinical trials for developing precision medicine. Some of them are kind of straightforward trials like the one that I just mentioned, but some of these trials are much more complicated. So for example, there are umbrella trials where there's a focus on a single type of cancer like bladder cancer, for example, and then those patients that enroll in that trial are screened for multiple different types of genetic features or biomarkers, and then each patient is given a specific targeted treatment, a specific precision medicine to target their specific biomarker or genetic feature to try and tailor the treatment to them and get the best efficacy possible.

And then there's also basket trials, which I like to make sure patients are aware of because these trials may not be specific to patients with bladder cancer, but they usually allow folks to enroll with a wide variety of cancer types and tumor types. They might enroll bladder cancer and lung cancer and breast cancer, for example. And as long as a patient has the biomarker that the trial is treating or the genetic feature that the trial is treating, then patients might be eligible or independent of the type of cancer they have for a targeted precision medicine therapy.

Dr. Brendan Guercio:

And so while precision medicine is really exciting and starting to increase the number of options that are available for our patients and improving patient outcomes, there are still a lot of challenges to developing precision medicines that researchers are working to overcome. For example, one of the difficulties that we often encounter in precision medicine is that it can be difficult to measure the target that you want to precisely hit. For example, as I mentioned earlier, sometimes there's no biopsy specimen available and there are some tests that can't be done without a piece of the tumor to do the test on. Luckily, as I mentioned, cell-free DNA tests

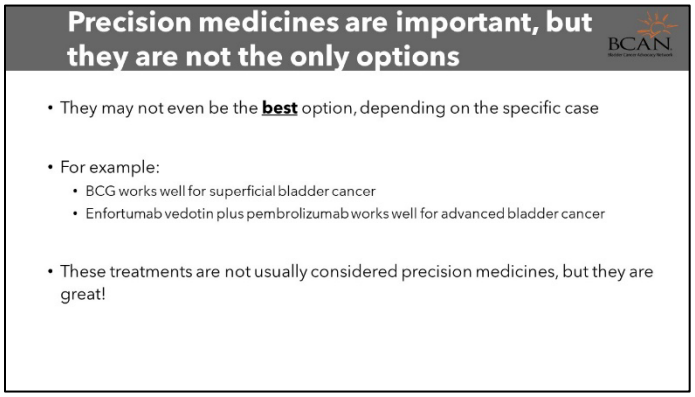
are starting to make that less and less of a problem, but it's still an issue depending on which kind of target you're trying to assess.



Then some targets, even though we know they're important to cancer cells, can't yet be targeted with modern chemistry. This is a category of targets that is often referred to as undruggable, because we just don't have the right kind of technology yet to block the targets in a safe way. Luckily, modern chemistry and medicinal chemistry is improving all the time. And so we certainly expect that the number of undruggable targets will decrease over time. And indeed in the recent years, it already has decreased such that some targets that were previously considered undruggable like a protein called KRAS, for example, is now considered a druggable target and has treatment options.

Another issue in developing precision medicines is side effects. So sometimes when precision medicines are used to hit a target, they are very well tolerated, but sometimes targets are important to both the cancer cell and the function of normal cells in the body. And so then that can make it harder to inhibit the cancer cell without causing bad side effects. So one of the things that researchers are always working on is figuring out ways to block a genetic feature or a target of a cancer cell without causing bad side effects, which can be difficult in certain situations. And then finally, another barrier to implementing precision medicine and oncology in general is that targets in one kind of cancer don't necessarily work in other types of cancer. For example, there's a gene and protein called PIK3CA, and that's a good target in breast cancer. And there have been some efforts to target that in bladder cancer, but they haven't really panned out yet. And so sometimes it takes extra work on the part of researchers to figure out which targets and which cancer are the best ones to use.

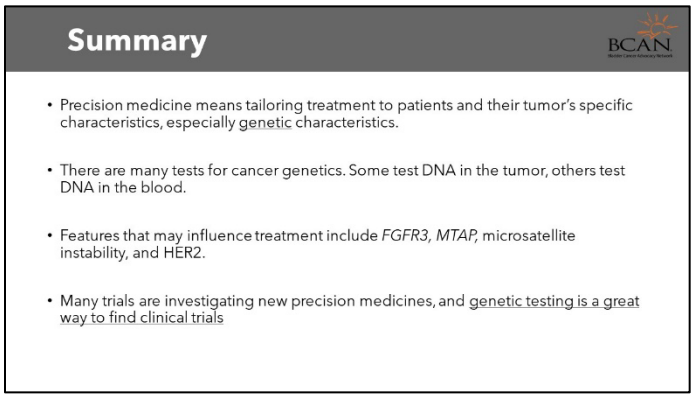
Dr. Brendan Guercio:



So another thing that I always want to make sure that folks are aware of is that precision medicines are important, but they are not the only options. And in certain situations, precision medicines aren't even the best option for a patient. For example, a lot of people on this webinar are probably already aware that BCG is a really good treatment for patients with early stage superficial bladder cancer, and for patients with advanced or metastatic bladder cancer, a really good treatment option is Enfortumab vedotin plus Pembrolizumab immunotherapy. And the reason I mentioned both of these is because

even though they're probably some of the best treatments we have for bladder cancer, neither of them are usually considered precision medicines because they work regardless, we think, of the genetic features of a patient's cancer. So if a physician recommends a treatment that isn't a precision medicine per se, that still may be okay and still may be the best treatment option depending on the situation.

Dr. Brendan Guercio:



So this is just a quick summary of some of the important points that I hope people take away from today. Precision medicine again means tailoring treatments to the individual patient and their individual tumor or cancer's characteristics, especially genetic characteristics. Although other features like proteins sometimes do matter too, there are many different types of tests that we use to guide precision medicines and to assess cancer genetics. A lot of those tests are tests that are looking at analyzing tumor DNA and tumor genes, although there are other growing tests that are really exciting that are looking at DNA in the blood that's shed by the cancer. And there are multiple features that can already be helpful in the treatment of especially advanced bladder cancer with precision medicines and those kinds of features that can help guide precision medicine for advanced bladder cancer include FGFR3, MTAP, which we talked about, the genetic pattern microsatellite instability and the protein HER2.

And there are still many trials that are working on making new precision medicines and better precision medicines for patients. And clinical trials are really important because that's really how we move the field forward to make things better for patient care and how we learn. And genetic testing is a great way to find these precision medicine clinical trials. In fact, some of the companies that do these genetic tests even include reports with the genetic testing that lists clinical trials that a gene might make a specific patient eligible for. So thank you very much for your time and attention. Really excited to talk to you today, and happy to use the time that we have left to hopefully answer any questions.