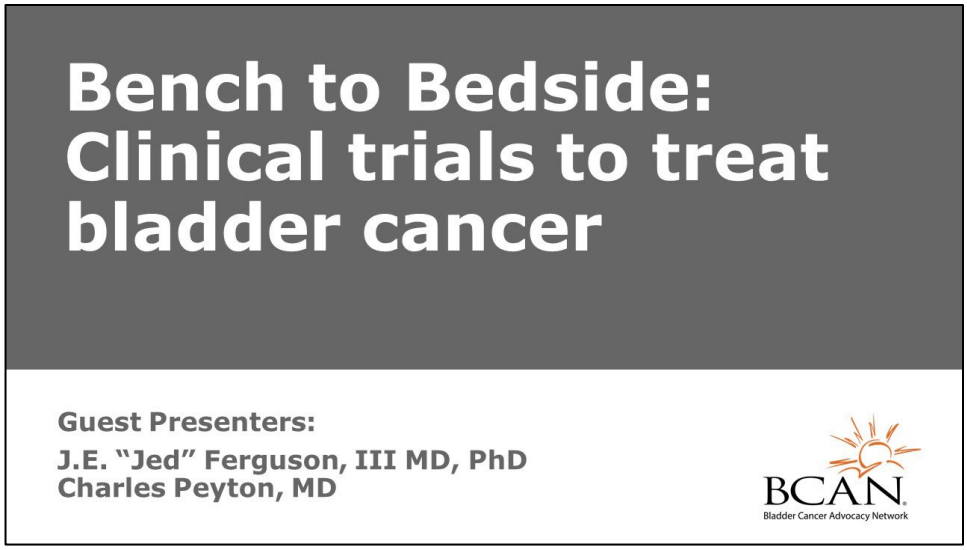
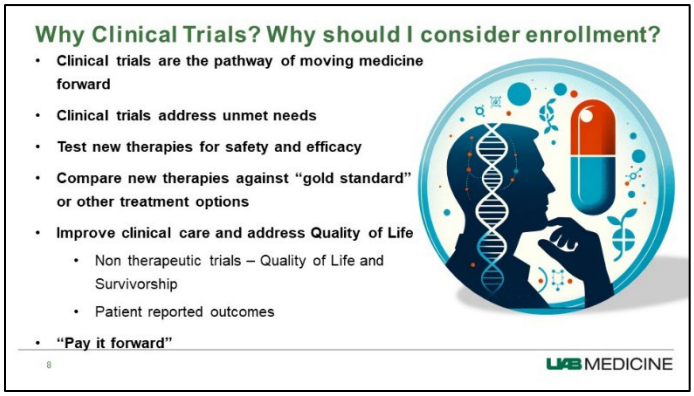


Dr. Charles Peyton:

Yeah, thanks so much, everyone. Thanks for inviting us to talk. My name is Chas Peyton. I'm a urologic oncologist just like Jed and do a lot of bladder cancer as well. I'm going to give you kind of the more clinical spiel of this. He's very much a surgeon scientist and does both sides of the equation. I do more of the clinical side than anything else.

Dr. Charles Peyton:

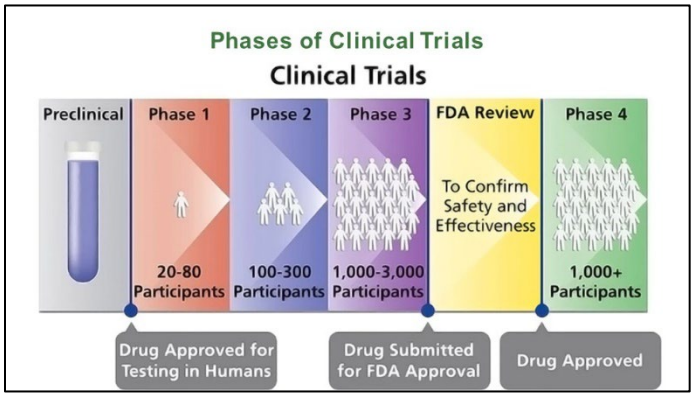


I'm going to talk to you more about the kind of nuts and bolts of what clinical trials are. So Jed gives you the kind of ideas of what happens in the lab and how we develop some of these things. And then what happens once they get to clinic? How does that work? First question that many of you as patients may have been asked by some of your providers is, why should I enroll in a clinical trial? Well, really, clinical trials are the pathway that we actually move this medicine that we develop in labs to clinical practice, which clearly has a lot of red tape around it and regulations that we have to abide by to make sure things are safe and effective.

Clinical trials can address unmet needs in patients. They're usually specified in the areas where we don't have good success rates. We have multiple areas in bladder cancer where our success rates need improvement. And they're used to test new therapies for safety and efficacy, which is the most important thing. Additionally, we can use clinical trials to compare new therapies against what's considered gold standard or other treatment options as well.

Another reason that clinical trials exist is not necessarily just therapeutics, but also trials to address quality of life in practices that we do so need to know that for muscle invasive bladder cancer, one thing that's standard practice is removing your bladder, which has a lot of quality of life implications and clinical trials allows us in a way an avenue to study those implications and what that means to patients in terms of survivorship and how they do long-term. Patient-reported outcomes is a critical component of clinical trials. It's always incorporated. Then, of course, obviously it's devastating to be diagnosed with something like bladder cancer, but if you can find a silver lining in anything, participating in clinical trials can give you the opportunity to pay it forward to those folks that are not yet diagnosed and may be in the future. So you can go to the next slide please.

This is important in understanding how clinical trials work. So there's different phases of clinical trials. So the preclinical investigational studies and work that's done for years and years and years is exactly what Jed was just telling you about. That takes decades, on the order of decades for some medications and some therapies. Then the drug is approved for testing in humans through a variety of regulatory pathways. And phase 1 studies are really where things start. Phase 1 studies are very low numbers, very few institutions and sometimes they are single investigator studies that are very limited and very tightly regulated because these are new drugs, new therapies, new things that we believe we know how they're going to interact in humans, but we really don't know. We don't know until they're tested.



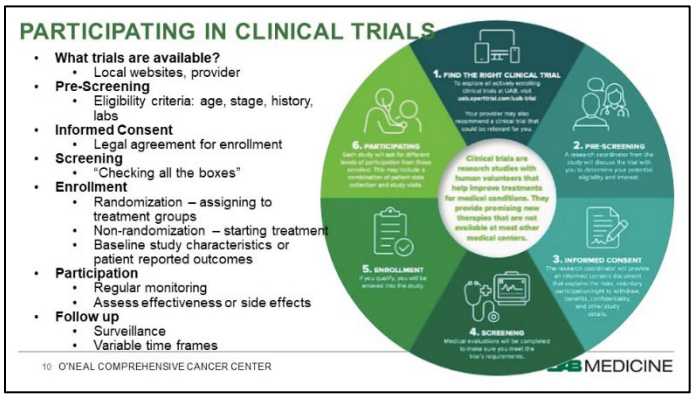
Dr. Charles Peyton:

The risks are can be a little bit more dramatic in some of these patients, but the opportunities are there, too. So those are very limited studies that are done very closely and it's just the drug that you're talking. There's no comparison on them. You're just looking at safety. It's essentially safety and effectiveness. So looking at the safety of the medicine and what the effective dose or regimen is to get the patients to the appropriate biologic availability of that medication or that drug to make sure it's effective to see it works.

Phase 2 studies includes a lot more patients and it's more focused on safety as well but more efficacy. How well does this work in the general population amongst a lot of patients? Then the next step is phase 3 is large rollout studies. We've proven that this is safe. Now we really want to know more about the efficacy and more of this secondary end points on how it impacts other measures, not just cancer cure or cancer treatment, more quality life, symptomatology, various other things.

So once a new treatment has gone through a phase three study, they can be submitted to the FDA to get reviewed and confirmed for safety and effectiveness and the FDA may or may not approve it for whatever it is applied for. The study may prove that it's effective for one component of cancer treatment but not another, and it's up to the FDA to review an enormous amount of data that's collected in phase 3 studies to decide whether or not it's appropriate to approve it. And then phase

4 studies are really beyond drug approval, and that's more like comparing one drug to the other, seeing what's even better once we get beyond the approval of these drugs. Next slide please.



Dr. Charles Peyton:

So participating in clinical trials. This is a slide from UAB where we have this posted on the website. The first thing you have to know is what trials are available, and this can be found from your local provider and websites. I have a link right there in the middle of that wheel. It says Find the Right Trial, and you can click on the link and be linked right to a bunch of studies at UAB to investigate what's available. Then if you know a trial is available, and it may not be available where you are getting treated, but there may be one in the area. And if you ask your provider who is taking care of you to investigate it, if they don't have that opportunity, others may if you have the means to travel there. And then there's a pre-screen eligibility where we see if you're eligible by the general criteria, which is age, stage, history, and various labs.

And if that pre-screening checks out, meaning that you meet all the criteria to enroll in the study. Then you do an legal informed consent. Informed consent process is something we do every day in the hospital for various things. But in clinical trials, it is a true mountain of paperwork sometimes. A lot of times patients are a little burdened by the amount of stuff they're handed to sign. A lot of that is necessary for protection of both the patient and the institution and the various folks and stakeholders involved. But it is a lot. It's a lot to throw a 90 page document in a patient and expect them to read it, understand it, and sign it. This requires kind of a little bit of handholding and understanding and explaining what's what. So a lot of times, it's a lot of trust that the folks that are telling you to enroll in this really know what they're talking about. And for the most part, people do. They wouldn't be offering you the study if they didn't believe in it, aren't thinking it was important.

And then it goes to the real screening criteria. So once you sign an informed consent, then we have to get even deeper into the criteria for screening, meaning all those labs we got were just age-appropriate labs and stage. But now we have to get... In certain studies, you'll have to get pathologic confirmation of the diagnosis from a centralized pathology that's sponsoring the study. You may have to get labs drawn at a certain place where they can regulate the lab draws and various other detailed screening things that allows us to check all the boxes to make sure that the clinical trial you're enrolling to, that everything is standardized. When you have medicines in the pre-clinical setting in an controlled lab, you're able to control all the variables that you're testing.

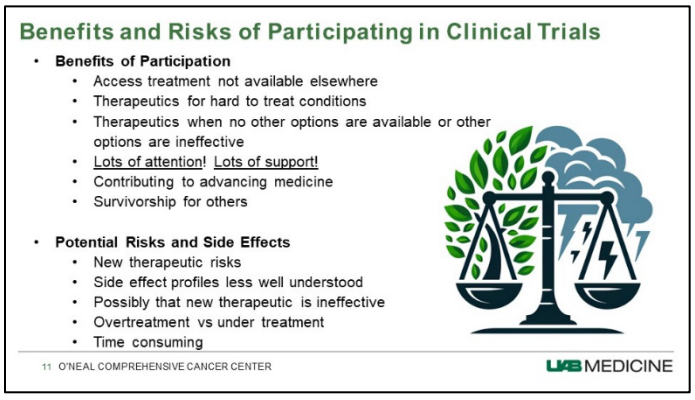
In trials, it's much more challenging because you're enrolling multiple people throughout the entire nation and maybe lab practices aren't necessarily standard across the board, so there has to be some way to standardize those things to control for all the differences amongst institutions. That can be quite a challenge and one of the headaches of doing trials like this. Then enrollment. You get enrolled into the study and some studies are randomized, some are not. Randomization means

you're assigned to one treatment group or the other. And sometimes the patient will know what treatment they're getting. Sometimes they won't. Sometimes the provider will know what treatment they're getting and sometimes they won't. So double-blinded means that the patient doesn't know what they're getting. Neither does the provider. Or single-blinded, the patient doesn't know, but the provider does.

Blinding a study is really important in reducing our biases of what's going to happen when we report the results. If I don't know if you're getting drug X or a placebo, I'm less likely to monitor you or think about you or presume that something is going on that may not actually be going on if I really don't know what medicine you got, right? Some trials that's available and you can do that, but it can't be done in all trials. And bladder cancer has a particular area where it's hard to do that, particularly when you're doing surgery. You can't randomize somebody to get surgery and not know that they didn't get surgery or certain medicines that go in the bladder that have clear side effects and whatnot.

So non-randomized studies, you're just testing a medicine or testing something else that just you observe over time. And a lot of this you have baseline study characteristics and patient-reported outcomes that you have to address. So then as you participate in the study, you have regular monitoring and you assess the effectiveness and the side effects of these medications or whatever intervention is ongoing. Participation is a lot more paperwork, a lot more appointments than probably you would get otherwise. But that's part of the benefit of enrolling into study is that you get a lot of attention, sometimes more attention than you want.

In terms of follow-up, there's a standardized surveillance. Surveillance has a lot of variability amongst providers sometimes even though there's guideline-dependent surveillance. For something to be standardized, we have to make it the same for everyone. And the follow-up times can be variable. So next slide please.



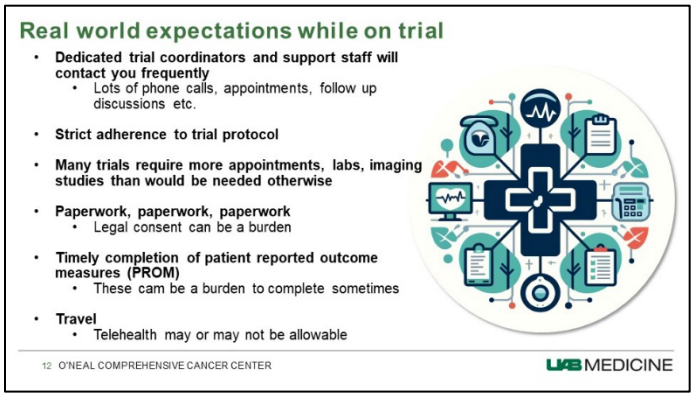
Dr. Charles Peyton:

Again, what are the benefits of participating in a clinical trial? Well, the benefits of participating are access to treatments that aren't necessarily available elsewhere, meeting an unmet need that we don't have, and therapeutics for hard-to-treat conditions that have failed multiple other treatments. And therapeutics where no other options are available like that unmet need I was talking about. Again, lots of attention, lots of support. When you're on a clinical trial, typically you'll get contact information from a coordinator and you'll have their work phone. Ours, at least, there's a direct line to that person. If you're not on a trial and you try to call your physician, everyone knows the headache that you get when you answer a nurse. Then they give you this person, then they give you this person. Eventually, you just leave a message and 72 hours later, then finally somebody gets back to you on what your question is.

Well, when you're on a trial, you get a direct line, usually. Not all of them, but usually you'll get a direct line to somebody who has a direct answer waiting for you. And that's because you're important and you'll get a lot of support and there's a lot of money invested in these trials that provides that. You can contribute to advancing medicine. And there's survivorship benefits obviously.

So what are the risks and side effects? Well, sometimes they're new medicines. We don't know exactly how risky again they're going to be. Although we think they're safe or else they wouldn't be in trial. Side effect profiles are less well understood, and there's a possibility that if the medicine that we put you on is ineffective. There's certain space in kidney cancer that we deal with right now that we've had countless trials in the adjuvant space for high-risk kidney cancer that have been negative. And it's been incredibly frustrating to put these patients on medicines that have side effects and they really haven't helped. But that can happen. That's part of trials.

And then we also wrestle with overtreatment in some of these studies and undertreatment. And then they can be time-consuming both for the patient and their support family around them because there's a lot of appointments, a lot of phone calls, a lot of visits. So next slide.

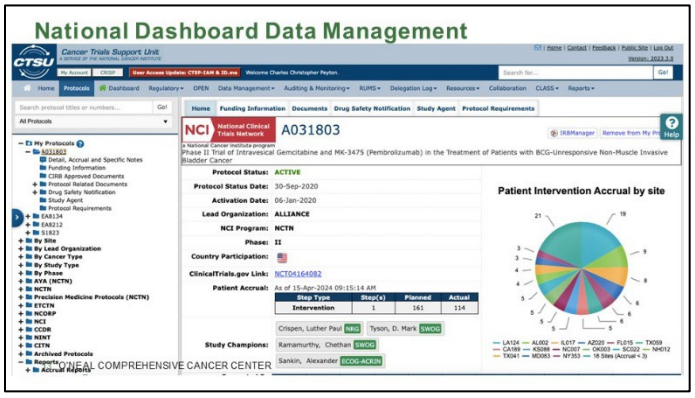


Dr. Charles Peyton:

What are the real-world expectations, why you would put on a trial? Again, I just mentioned the dedicated coordinator and support staff, lots of phone calls and appointments and discussions. We have to be strict about the adherence to the protocol. That's hard because in real-world medicine outside of a trial, there's flexibility. We say you need the surveillance study in three months. We give you a pretty flexible window with that. On trial, we've got to get that surveillance study done in three months within a seven-day window or else the data may not be allowed to be captured going forward for that date because it will get flagged or dinged or whatnot. Then many of your trials require more appointments, labs, imaging, and studies that would've been used otherwise. They're all basically standard of care, but sometimes we would go up and above the labs that you would need, particularly when you're having an investigational medicine or trying to understand what it does.

Paperwork. Tons of paperwork. Legal consent can be a burden like I talked... The other thing is I haven't talked too much about is that a lot of these studies also include patient-reported outcomes, which are surveillance questionnaires. They can be kind of a burden to complete sometimes. But the benefit is we're learning more about what these medicines and what these treatments do and the side effects and quality of life implications of these medicines when you complete those. But they also kind of make the patient have a little bit more introspection and understanding of what's actually going on with them and be able to better describe their symptomatologies.

Travel. If you're at an institution that has a study and it's far away, that can be a problem for some patients. And telehealth is still reasonably new since Covid, but it may or may not be allowable for various studies. Next slide please.



Dr. Charles Peyton:

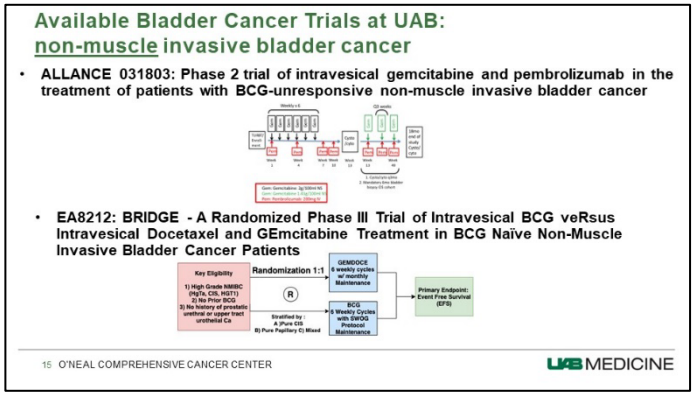
What does it look like on my end when I'm enrolling patients? This is a study that I have open at UAB, and I can go on this website right here and I can see exactly what studies are available. These are all nationally listed. This is a co-op study through Alliance, which is a big group that UAB and various big institutions are a part of that we can get these studies through our regulatory system pretty quickly because they're run through these mega co-op groups. When I look in here, I can see exactly who the study champions are, who I need to call if there's a problem, and then I can see the accruals down on the right hand corner. This study, for instance, we're looking at patient accruals. UAB is the green one that has the nine next to it. So we put nine patients on this study, which is good. That means we're getting people enrolled. We're the second highest enroller for this study in the nation. That 21 is not one institution. That's a bunch of institutions.

Anyway. So this is kind of what we see on our end and monitoring these because these are big studies usually that are done through multiple institutions with a big enrollment criteria. You can't get it all done in one place. You never can. So you have to have a diverse population throughout the nation. Next slide.

Dr. Charles Peyton:

So this is finding clinical trial opportunities. You got to talk to your treating provider, ask for a specialist if you don't have one, if you're just seeing a general urologist in the community. Sometimes they're not going to know necessarily about trials if they're not as interested in bladder cancer as Jed and I are. So you may want to say, "Hey, I'm interested in learning more about trials. Is there any places around here where I can have an opportunity for that?" You can go on this website. You can go on NCI and find out trials. But even better than that is clinicaltrial.gov. That's the easiest place to find trial opportunities. The website is a little hard to navigate when you're a patient, but with a little bit of clicking around, you can

probably figure it out. BCAN is another obviously great support network for trials, and then there's local support groups you can go by as well. Next slide.

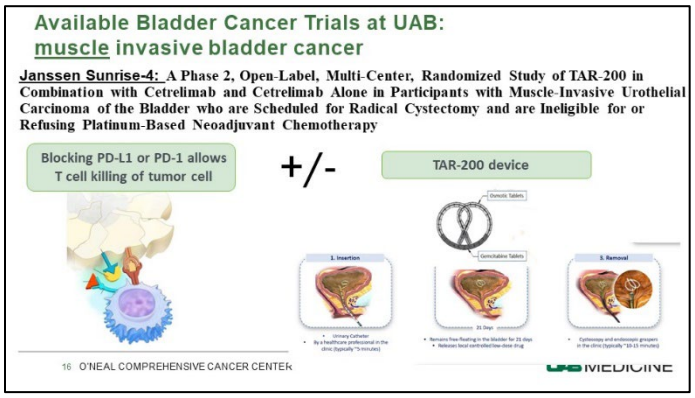


Dr. Charles Peyton:

Then just briefly, I'm going to go over just as an example... We're a typical big academic institution. What are the trials that we have open at UAB? I'll just tell you for bladder cancer. This is the Alliance trial. This is for non-muscle invasive bladder cancer. It is a phase 2 trial of intravascular gemcitabine plus Keytruda, which is a medicine made by Merck. It's a systemic infusion, so it's both local treatment with chemotherapy and then systemic treatment with immunotherapy. That's for BCG unresponsive non-muscle invasive bladder cancer. So that's one.

And then we have another non-muscle invasive bladder cancer trial. So let me just talk. So the unmet need in that first trial is that these are a specific group of patients that don't respond to BCG and they're the highest risk of disease progression to muscle invasive disease. So that's the niche of where this trial is fitting in. There's a lot of trials in this space. This is one that's been enrolling reasonably well, will hopefully conclude within the next year in terms of enrollment.

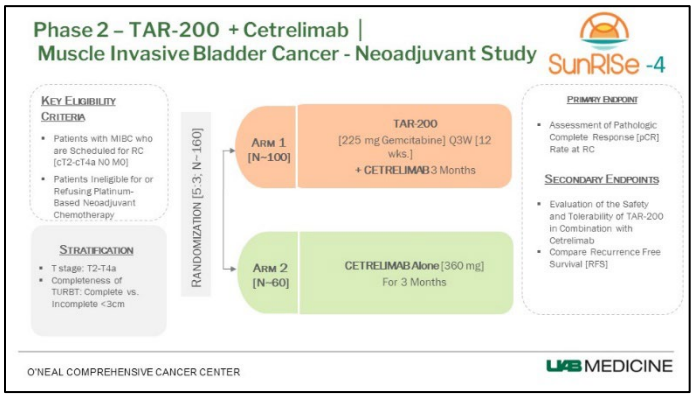
Then we have the BRIDGE study, which is also meeting another unmet need. Many of you as bladder cancer patients, you've heard about the BCG shortage that we are always suffering from in the community. This is asking the question of, well, can't we use something other than BCG? Let's see, we've been using BCG for 40, 50 years. This is a great trial. This is going to be really helpful for patients. One of the most helpful trials I can think of. Basically we're just randomizing... We have the data now to support the upfront intravesical use, in the bladder use of two different chemotherapies in the bladder may be as effective as upfront BCG. This is basically comparing the two upfront. You see this is a phase 3, whereas the phase 2 is above just one medicine, no comparator arm. This is a phase 3 where we're comparing two drugs to each other. Next slide please.



Dr. Charles Peyton:

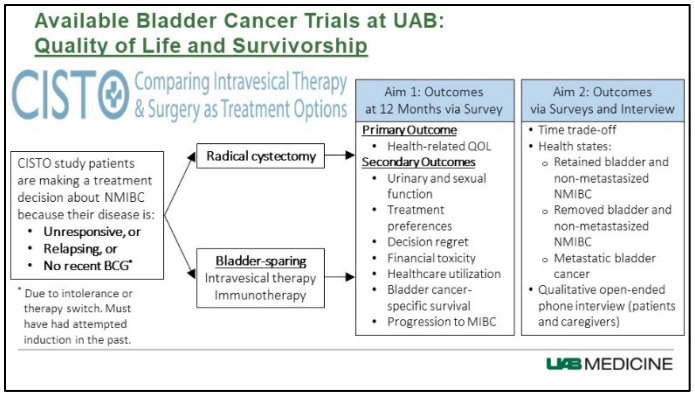
And then finally, this is a more advanced... This is an industry sponsored trial we have at UAB, which is looking at a really revolutionary, very interesting way of delivering medicine. And it's from Janssen. And basically this is for muscle invasive bladder cancer. We're giving you neoadjuvant therapy or therapy before bladder removal surgery. And it's using cetrelimab, which is an immunotherapy medicine that's basically... To describe it easily, it's Janssen's version of pembrolizumab, which is the other medicine I was just mentioning. It is a PD-1, PD-L1 inhibitor that causes your own body to kind of fight the tumor. Then we know that that would work in neoadjuvant therapy.

So the trial is randomizing patients to getting or not getting this device called the TAR-200, which is this little device down here. It looks like a pretzel. It's inserted into the bladder, and as opposed to just giving an intravascular dose of medicine that's liquid that you pee out, which is how we usually do it, this medicine elutes the drug through this little device in the bladder as you make urine and it stays in there for two to three weeks. Then we take it out and put a new one in. This is a very revolutionary type of delivery of medicine that we know is effective, but we're trying to evaluate whether or not this is effective in patients with muscle-invasive disease. The trial has been out and it's been proven to work in non-muscle-invasive disease. Now we're seeing how effective it is in the muscle-invasive setting of this trial. So you can go to the next slide, please.



Dr. Charles Peyton:

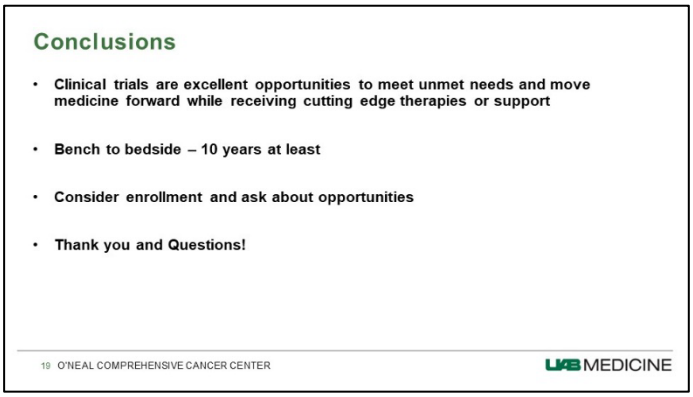
This is what the trial is just showing you and how it's randomized. There's two arms. Some of the patients are going to get the cetrelimab plus the device in the lower arms. Some people will just get the immunotherapy alone. That's classic of how you're organizing a clinical trial comparing one treatment to another. Then there's primary and secondary endpoints. The primary endpoint being assessment of pathologic complete response and secondary endpoints being tolerability and recurrence-free survival. You can go to the next slide, please.



Dr. Charles Peyton:

And then lastly, not all clinical trials investigate medicine. So this is a trial that we opened at UAB that's now closed. It's nationally been enrolled and BCAN has been completely involved with this from day one and it's called the CISTO trial. It is comparing intramuscular therapies to surgery treatment options and basically is a quality of life study. So people in this finite group of patients that I mentioned earlier where they're BCG unresponsive disease, they have the option of trying... The best option for cure is removing your bladder. Most patients don't want that done, so there's other bladder-sparing methods with various different intravascular medicines to try. This study was basically looking at the quality of life assessments of what went into that choice first of why that patient chose to not have a cystectomy or to have a cystectomy upfront, and then how they did over a long period of time in terms of health-related quality of life, urinary, sexual function, treatment preferences, decision regret, financial toxicity, you name it. This was a quality of life trial that was looking at how patients responded to their treatments.

This is just as important as all these medicines that I've been talking about the whole time because if we don't know how patients respond to standard of care or treatments or what's the importance of their quality of life long term, then we really don't really know how well we're treating them. So a very important other concept in trial literature. The next slide.



Dr. Charles Peyton:

So in conclusion, we'll wrap up here, your clinical trials, they're great opportunities to meet unmet needs and move medicine forward while receiving some cutting edge therapies and support. Bench to beside, 10 years minimum. Wouldn't you say, Jed? At least. And then consider enrollment and ask for opportunities locally. And with that, thank you and we're happy to answer some questions and open this up for discussion.