



Clinical Trials: Muscle-Invasive Bladder Cancer

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Part I

Presented by



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James M. McKiernan, MD is a professor and chair of the Department of Urology of the College of Physicians and Surgeons, and urologist-in-chief, at New York-Presbyterian/Columbia. Dr. McKiernan received his MD from Columbia University College of Physicians and Surgeons. He completed his training in urology and general surgery at NY-PH, followed by a urologic surgical oncology fellowship at Memorial Sloan-Kettering Cancer Center. Dr. McKiernan's clinical practice is focused in urologic oncology and particularly on surgical therapy in high-risk patients with bladder cancer. He has special expertise in organ preservation and reconstructive surgery to maximize quality of life. Dr. McKiernan is the principal investigator of the NIH-funded clinical trials program of experimental therapeutics in bladder cancer at NY-PH, which is investigating new agents for bladder preservation in patients whose cancer has recurred after standard therapy.

Moderator: People don't always know the benefit of the clinical trial and it's really interesting to know that there are over 150 bladder cancer clinical trials that are open and recruiting patients in the United States. If anyone were looking for a clinical trial, you can find them on our website on our clinical trials dashboard. Or you can go to www.clinicaltrials.gov and search there. There are a lot of different interesting trails I'm going to highlight but I want to be specific to muscle invasive bladder cancer. One of the things I just would like to point out before we start the doctors on some of these different aspects of clinical trials is that, no treatments would exist without clinical trials today. Clinical trials do a lot to ensure that drugs are effective and drugs and treatment are effective and they are also safe for patients.

What is a Clinical Trial?

All bladder cancer treatments are a result of clinical trials. There are currently > 150 bladder cancer studies are actively recruiting patients in the US.



Phase I Clinical Trials

- Is it safe for humans?
- Typically for patients without a standard treatment available for them (previous therapy unsuccessful)
- Experimental drug that may or may not work
- Smaller groups of patient participants (15-25)



Dr. Seth Lerner: Let's take the example of this drug that just got approved. It's a drug made by Genentech, as *Atezolizumab*. It targets the immune system. It helps boost the immune system to fight cancer cells. It's really an incredible breakthrough. How did we get to this point? Say a company develops a drug in the laboratory. The first thing that they have to do is to find out if it's safe to give to humans. That's what a **phase one** trial is. It's typically small trials. They are usually in a case like this done say for patients who may have gone through standard therapy and say their cancer has come back and there is no standard treatment for them. They might look for an experimental therapy.

A **phase one** trial gives them access to a drug without honestly any expectation or knowledge of whether the drug will work or not. Phase one is really, is it safe to give to humans? Oftentimes they will start with a very low dose and go up to a high dose and then back-off once they hit the ceiling to balancing those side effects or toxicity. Once the drug is determined to be safe, then they'll do what's called a **phase two** study. That's really the first point in time where you're taking the dose that we know to be safe, and asking the question of does it work? These are going to be larger trials.

Phase 2 Clinical Trials

- Once drug is determined to be safe
- Trials of different dosages to determine what dose is the most safe and effective
- Making sure the drug actually works
- Larger groups (50+)



Large phase one trails would be 80 patients and above, but a lot of times we're treating only about 15 to 25 patients because you can get a signal, does it work or not, on a smaller group of patients. Sometimes we'll do what's called a **randomized phase two** where we'll try two different doses, where we think that maybe giving a bit higher dose is going to be effective but we're not sure what it's going to do in terms of side effects. Once we establish the best dose with that's safe and effective. Now we determine that the drug works, then we go into a phase three trail where the new drug is compared to a standard therapy.



Phase 3 Clinical Trials

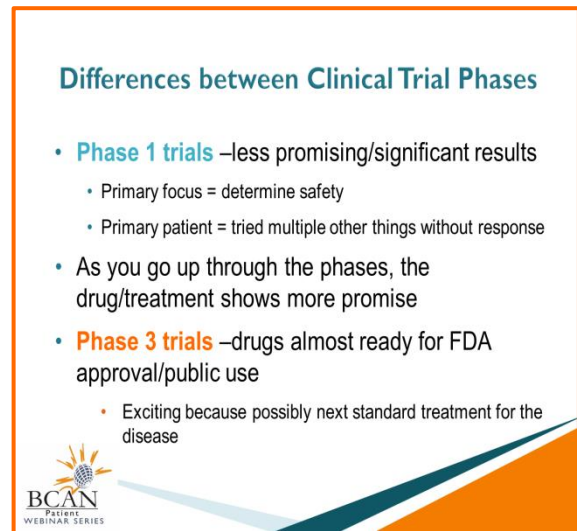
- Drug is determined to work → compare with standard therapy
- Randomized phase 3 clinical trials
 - One group gets experimental drug, the other gets standard of care
- If new treatment is as good, has less side effects, or is better → taken to the FDA for review

BCAN Patient Webinar Series

Let's say that for bladder cancer we've got an established treatment that we know how it works, we've been using it for a long time and we want to compare the new drug to the standard drug. We have an experimental one with the new drug, we have a standard therapy. These are what are called **randomized phase three** clinical trials. If the new drug is shown to be maybe as good but less side effects or better, then you can take that information to the Food and Drug Administration and request a new drug application. The FDA reviews it and gives up a thumbs up or a thumbs down.

In the case of this drug, Atezolizumab, it was fast-tracked because the results were much better than anything we have seen. Patient population does not have any standard therapy available to them and so this was a breakthrough. As Stephanie mentioned this is the first new drug that's been approved for any stage of bladder cancer since 1998. Jim what else do you think?

Dr. James McKiernan: I agree, 100%. I think most patients don't necessarily understand the difference between these different phases of trails. In general as Steph pointed out, the patient who would be investigating or interested in a **phase one trail is a patient who has perhaps tried multiple other things and really has not had a response.** These trails have less in the way of a promise of guarantee or promise of response but they are more testing the safety of the drug to look for the side effect profile. Oftentimes the patient will look at that from their own perspective and say, "That's more a risky trail". That's a trail where there might not be as much reward for the patient but there is a lot learned about how the drug is tolerated.



Differences between Clinical Trial Phases

- **Phase 1 trials** –less promising/significant results
 - Primary focus = determine safety
 - Primary patient = tried multiple other things without response
- As you go up through the phases, the drug/treatment shows more promise
- **Phase 3 trials** –drugs almost ready for FDA approval/public use
 - Exciting because possibly next standard treatment for the disease

BCAN Patient Webinar Series

As you go up through the phases, the drug is showing some promise. Maybe some other drugs in the arena have fallen off to the side and as you get into **phase three trails**, these are drugs that are almost ready for prime time and might very well be the next standard treatment. They are ones that patients are getting more excited about, doctors are excited about. Those trails and those trails tend to draw a lot more attention. They are the ones that potentially lead to new FDA approvals.

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Atezolizumab Clinical Trial Design

- Atezolizumab trial was not a comparison trial
 - Single arm
 - No randomization
 - Used patient's history (historical controls) as comparison
 - No placebo arm



The drug that was approved today was just breaking news but interestingly this drug was tested in a trial that was not a comparison trial. It was a single arm trial where patients were given the drug. There was no randomization. Normally when the FDA asks for a new drug the information for a new drug prior to approval, they ask for a randomized phase three trial. In this particular setting because the patients had failed in the standard treatment, chemotherapy with platinum there were very few options for them.

The trial design was unique, that the patients were enrolled and their responses were recorded but there was no comparison group and they were using the historical controls as the comparisons. There was no placebo arm, if you will or no sugar pill. In a randomized trial like a phase three trial, most often there is an established treatment. Let's say for instance in bladder cancer. Muscle invasive bladder cancer may be a drug like Jim cider bean and platinum; two commonly used chemotherapy agents. The question is, is the new drug better than that?

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Typical Randomized Phase Three Trials

- Established standard treatment vs new drug
- Patients divided 50/50 and randomly assigned between the two treatment plans



A randomized trial would then allocate either 50/50 patient to either one of those treatments. It would not be up to the patients or the doctor to choose. Let's say half the patients in the trail would get the 'standard' treatment. The other half would get the new treatment. The new treatment could be a completely new drug or it could be the old drug plus a new drug, so the standard of care plus for instance a new therapy added to it to determine if that new therapy would give you a differential benefit and outcome. Most commonly you don't see placebo control trails when there is a standard of care because it's unethical. One group of patients in a cancer trail is rarely going to be treated with nothing. They are going to be received in the treatment that would normally be given outside of the clinical trial.

Dr. Seth Lerner: I just wanted to add that sometimes in both arms of a randomized trial we're testing the standard therapy alone versus the standard therapy plus additional therapy. We'll talk about some examples of that but that was actually how platinum-based neo chemotherapy became a standard of care. It was chemotherapy plus a radical cystectomy to remove the bladder for muscle invasive cancer versus just the surgery alone. The surgery would be the standard therapy. Everybody in both arms got the standard therapy and this phase of surgery and then have to face the chemotherapy.

Typical Randomized Phase Three Trials

- Sometimes in **BOTH** arms we test the standard therapy alone vs the standard therapy + new therapy.
- Platinum-based chemotherapy became the standard through a randomized clinical trial
 - One arm: chemotherapy + radical cystectomy (bladder removal)
 - Other arm: radical cystectomy surgery alone
 - **BOTH** arms got standard = surgery
- Give chemo to patients who will respond well, and give alternative to those who don't.



That's what we refer to as an add-on design where everybody is going to get a standard of care and then half the patients get the experimental therapy or in this case this is actually a question about this chemotherapy. Some trials too we're not asking is the treatment better than the other. Now in the clinical trial that we're doing, we're trying to ask a question about is there a molecular bio-marker that's associated with response to chemotherapy. In that case, we have a randomized trial where patients are getting two standard types of chemotherapy and really the question we're asking is can we develop predictive bio-markers that are associated with response? Instead of treating 100% of patients knowing that only about 40 to 50% are actually going to be deriving any benefit, asking a question about can we know who those patients are so we give the chemotherapy to the patients who are really going to do well with it and try something else with the patients who we don't think are going to do well with it.

Dr. James McKiernan: Obviously from an individual patient perspective, you do want to look at a clinical trial and decide in a somewhat of selfish way what is in for me. It's important to understand that clinical trials are the way we move the field forward so the entire community of bladder cancer patients benefit from clinical trials, but if you're facing a clinical trial and you're asking about it, you do want to know, how will I benefit. Will my cancer be cured because of this? Will I have a better outcome because of this? Some of the examples on the slide right now in the beginning are things that Dr. Learner was just mentioning such as biomarkers.

Pros & Cons of Clinical Trials for MIBC

Many important questions:

- Biomarkers
 - Predictive and prognostic
- Tumor genomics
- Optimal surgery
- Integrating chemotherapy and radiation



Results not promised/guaranteed

Quality of life issues



Potential Benefits = Potential Risks

- How will I benefit?
- **Low risk** associated with trials trying to discover biomarkers for cancer
- **Slightly higher risk** when interventions like chemo, radiation, and surgery if not well-tested
- **Equipoise** = balance between benefits & risks



In general there is very little harm to participate in a trial which is trying to discover a new tissue or blood or urinary marker for cancer. There is not going to be much of a risk associated with that. Potentially you may benefit from it. When you start to talk about intervention trials like chemo, radiation and surgery, if those interventions are not well tested then potentially there is risk. There is a term in clinical trials that frequently comes up when we're training new doctors how to participate in a clinical trial. It's called equipoise which basically is a fancy word that means 'reaching an equal balance between risks and benefits.'

If there is a clinical trial where you get the option of having surgery versus surgery plus chemo, the doctor should be able to discuss the trial with you and say look, both of these options are reasonable, they both have some upsides and some downsides and the risk and benefit on both sides, as far as we can tell, is roughly equal. We don't know whether the chemo, for instance will help you or not. If we knew it, we wouldn't have to do the research study to find out. There may be some downsides but there may be some upsides

Always Ask Questions!

- If presented the option of having surgery vs surgery + chemo, ask your doctor about potential upsides and downsides of your participation in either group
- But ultimately, **uncertainty is inevitable**
 - If we knew that a treatment worked, we wouldn't have to do this research to find out.



Always Ask Questions!

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It's fairly rare where it's clear that one group in a trial is going to benefit a lot more than the other because then doing the study would be considered relatively unethical. You wouldn't want to conduct that kind of research, so you do want to ask questions about the upsides and downsides of each individual trial and try to get as much information as you can, usually over one or two counselling sessions before you make a decision about going into a trial or not. There should be relatively equal risks and benefits.

Moderator: That's a really good point. Keep in mind as participants that nothing is promised or guaranteed, that if you take a certain treatment it's going to have a definite impact. It's all part of that learning, gathering information to really determine; what is the best approach to take for all this.

Safety = #1 Priority

- You are **NOT** a "guinea pig"
 - Just a lack of confidence/trust that your best interests aren't protected
- Your safety, rights and ability to control your destiny **ARE** protected



Dr. James McKiernan: For sure. The most common question that we often get before enrolling a patient in clinical trials is well doctor one, I don't want to be a 'Guinea pig'. That term comes up a lot. It sounds like you're going to do some kind of experiment and there may be a lack of confidence or trust and that maybe their best interests aren't going to be protected. I think it's very important to recognize that today in the modern clinical trial healthcare system there is an enormous amount of effort to protect patient's individual safety, rights and ability to control their own destiny.

It's very, very rare that anyone entering a clinical trial isn't actually going to get improved overall healthcare when compared to the general population. I know some patients don't believe that, but it's actually true. The system that takes care of you when you are in a trial is actually quite a bit different than the system that takes care of patients in routine healthcare environment.

Moderator: That includes things like regular monitoring. Do they typically in many trials do more of that, keeping an eye on all of these bio-markers and things that are going on with the patient? Are they going to get more screening done? Is that what you typically see in most trials?

Extensive and Frequent Screenings

- Safety and toxicity monitoring → do no harm
- Expect extra check-ups to ensure patient safety



Dr. James McKiernan Yes, always. It's an exhaustive amount of both safety and toxicity style monitoring because the ultimate goal in a clinical trial is to do no harm. You hope to benefit patients and you also hope to learn that there is a new treatment that will benefit more patients but you have to protect against downside harm. I oftentimes find patients are shocked how much extra check-ups there are instituted once they enter a trial. Sometimes they actually don't want to be checked that much.

For instance they might say well normally we would

do a CAT scan every six months, but because you are in the trial, we have to get one every three months just to be extra safe and make sure that nothing else is happening. Patients say, "Well I never used to do it that way. Why would you check me that much? Why do I have to have blood-work on Monday and Wednesday? I usually only get the blood-work on Monday." There is a lot of extra safety checks that are installed into clinical trials designed to protect patients.

Moderator: I have another question that is related to another topic. Right now looking at the quality of life, I think from that perspective because if they are looking at the impact of a new treatment, they are also trying to determine perhaps what some of the potential side effects are that they should be looking at. Would there be a lot more interest in the how the drug or the new treatment whether what that happens to be is impacting the quality of life as well? Is that an issue that you see often in trials?

Dr. James McKiernan: Yes, absolutely and particularly in muscle invasive bladder cancer research when the quality of life impacts cystectomy for instance is so well known to be significant. Any study that involves monitoring or treating patients with muscle invasive bladder cancer today almost has a built-in questionnaire regarding quality of life. If you look through the NCI clinicaltrials.gov site now, I think there are about 85 trials listed for muscular bladder cancer. Many of them, at least a third of them involve issues attempting to preserve someone's bladder. For instance using chemotherapy and radiation instead of surgery, using chemotherapy and the bio-marker. All of these are designed to try to improve patient's quality of life by minimizing the risk of surgery or improving their outcomes after surgery.

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Many important questions:

- Biomarkers
 - Predictive and prognostic
- Tumor genomics
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Side Effects & Impact on Quality of Life from new drug/treatment

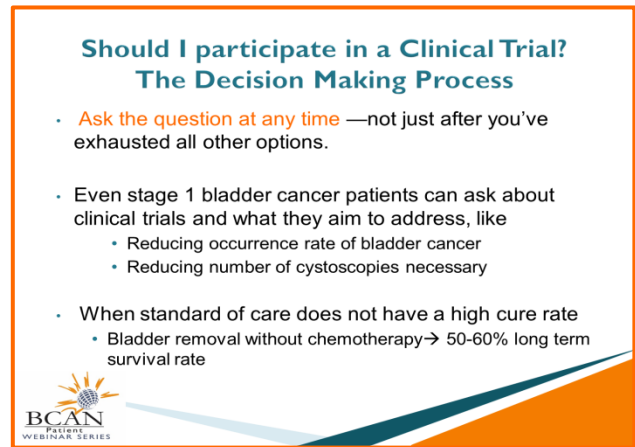
- Muscle-Invasive bladder cancer → cystectomies impact the quality of life
- Studies involving monitoring or treating patients who have muscle invasive bladder cancer have a built-in questionnaire regarding quality of life.
- A third of the 85 trials listed on clinicaltrials.gov for this type of bladder cancer are designed to improve patient's quality of life by preserving their bladder through alternative treatments.



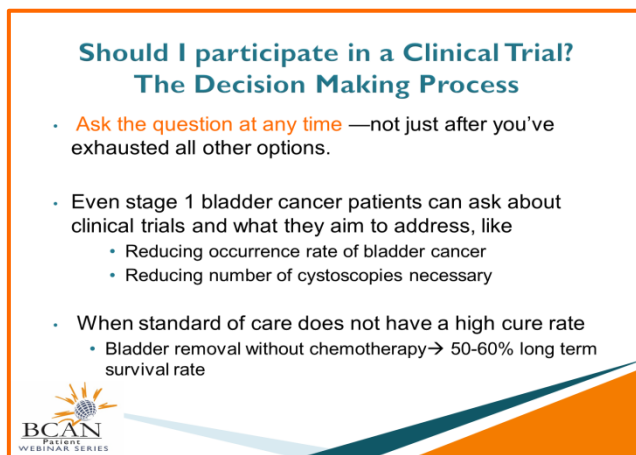


Moderator: Talk a little bit about how do patients decide, should I participate in a clinical trial or if someone being seen in a community setting and not a major academic institution, how does she bring up the subject with their healthcare provider whether it's a neurologist or medical oncologist? How can we find out about whether or not they should or could be part of the clinical trial?

Dr. James McKiernan: That's a great question. Oftentimes, I think people feel as though the only time that they should ask that question is when they have exhausted all their other options. A typical old fashioned approach to clinical trials, "Well, we've tried everything we had for you. Unfortunately it didn't work, so you'd better go seek treatment in a clinical trial." That is one avenue to enter into the world of clinical trials, but today that's not the only avenue. Even in a newly diagnosed patient with stage one bladder cancer, the question is very appropriate to ask.



It might be something for instance to reduce the occurrence rate of bladder cancer. It might be a new treatment that could decrease the number of cystoscopies that the patient has to have. Patients should feel comfortable asking those questions at almost any point in the treatment continuum for bladder cancer even prior to muscle invasive disease or even after the muscle invasive disease, if it happens. If the feedback that they are getting is discouraging or the doctor says oh we don't do that or we don't recommend that they should feel free to on the BCAN site or ask more questions because it's never the wrong question to ask.



Deciding to do it in my mind, is one, if you don't like the standard options that you're hearing. If someone says, "Unfortunately right now we don't have any good treatments left for you." That's it an obvious sign that you should start to look around for new treatments that might not be approved by the FDA yet.

Also if there is a situation in which the standard of care appears to not result in a not very high cure rate. Dr. Learner earlier mentioned that the original oncology group trial looking at chemotherapy plus cystectomy was conducted as



randomized trial. At that time bladder removal alone which is still done today frequently without chemotherapy was associated with between a 50 to 60% long-term survival rate.

The major driver to investigate that treatment was that we just weren't satisfied with that kind of a cure rate. If a patient hears that the outcome that is expected is not what they hoped for then they should start to say "Hey, how can I improve that? I don't want 65% chance of being cured. I want a 95% chance. What else do you have Doctor?" Really press us, the healthcare system to try to either come up with new clinical trials or if there is one out there help them find it.

Dr. Seth Lerner: That's a good point, Jim. I think it's safe to say that over the next couple of years there will be probably multiple clinical trials for virtually every disease staking bladder cancer that we take care of. We're not just asking questions about new drugs or new types of surgery. We're asking questions about maybe a simple urine test that can predict someone's risk of having a tumor that may not be able to be detected right now or a higher risk of developing a tumor in the next 12 to 24 months. We're asking questions about how to make current treatments better.

Current and Future Clinical Trials

- **BCG (tuberculosis vaccine)** = best drug available for non muscle-invasive bladder cancer...
- ...but **high risk** of recurrence and developing worse degree of cancer
 - Big study in the fall focusing on making BCG work better



Current and Future Clinical Trials

- Focus on improving major operations like radical cystectomy by making them...
 - **Better**
 - **Quicker**
 - **With lower complication rates.**



There'll be a big treatment starting in the fall asking about the best drug that we have for noninvasive muscle bladder cancer as a vaccine called BCG. BCG is a terrific drug, but it's associated with still too high of a risk of recurrence or developing a worse cancer in the future so we're asking a very simple question about an intervention that can make BGC work better. There's a lot of opportunities. I think Jim put it quite well is you should always ask your doctors "am I eligible for a clinical trial? Are you working on any new treatments? Is there a way to make the treatments you recommended for me better? Is there a way can I participate in the trial to ask a question about understanding better my risk of recurrence?"

Another way of improving current treatment is getting people through major operations like a radical cystectomy, better, quicker faster with lower complication rates. It's a huge area where we're researching right now.

Moderator: This has been a wonderful overview of whether or not people should get involved in clinical trials. I hope that everyone is at least thinking more about it as a potential option or something they would like to learn more about.