Question and Answer

Stephanie Chisolm: Okay, that's really helpful. I want to go to some of the questions that have been submitted. I'm going to start with this one because there's been all sorts of things on the news these days about people with immune-compromised systems, because they're on immune therapies, not necessarily showing any benefit from the COVID vaccine. **So the question is do immune therapies degrade or negatively impact the COVID-19 vaccine efficacy? If so, what precautions do you recommend?**

Dr. Peter O'Donnell: Yeah, great question here. So I haven't seen any data in bladder cancer that suggests that the COVID vaccine is less effective if you're getting immunotherapy.

There was some data, especially out of New York, during the earlier parts of the pandemic, that some patients who were on immunotherapy treatments, that they were having worse outcomes if they contracted COVID, that those patients were actually doing worse, which almost seems counterintuitive.

If you're on a drug that's stimulating your immune system, you'd think, well, maybe I'd be able to fight off COVID better. But actually it seems like those patients were getting really strong inflammatory responses and having complications in the lungs because of the over-inflammation in the lungs.

With respect to the vaccine now, I'm counseling all of my patients, certainly cancer patients but all patients, to go ahead and get the COVID vaccine. What we've done for patients that are on immunotherapy is that if the patient's been on immunotherapy for a long time, we'd go ahead and just get the COVID vaccine. If a patient's thinking about just starting an immunotherapy or a chemotherapy, we've tried to separate the timing of those by at least a couple of weeks. But I don't know of a data that the vaccines do not work. I have not seen that.

Stephanie Chisolm: Okay. I think we're just now beginning to really start looking at all of these things. So I'm sure that there's going to be evolutions of our knowledge and articles that come out that are demonstrating whether this is an issue or if you need to have an extra booster or whatever. So I think that there's a lot of TBD, to be determined, when it comes to understanding the vaccine since it's so new and then how does this impact us with immunotherapy. So thank you. That's a great thing, great

question to have answered. I have a couple other questions that I will ask. **What do you think about beta-glucan, glucan with immunotherapy, Dr. O'Donnell?**

Dr. Peter O'Donnell: Yeah. This is one that not a lot of my patients have asked about. I know that beta-glucans are being explored for the treatment of lots of different types of cancers as a way to boost immune responses. But they're not proven yet. They still have an experimental role in cancer treatment. I haven't had personal experience with using them. I don't know if Mr. Kunz or Miss Sperling have used other supplements or nutrients to try to boost immune responses.

Ms. Lynn Sperling: No.

Mr. Andrew Kunz: No.

Stephanie Chisolm: Which leads to another question: **is there anything that patients and their families could do to enhance this immune response, whether it's diet or exercise or anything else that they should be paying attention to as they're going through the treatment?**

Dr. Peter O'Donnell: Yeah, I don't know. Mr. Kunz or Miss Sperling, do you want to comment on that? Because that's something I think we have talked about at various points, the things you're doing in your own lifestyle. Then maybe I can chime in as well. Patients ask this all the time. "Now what can I do, doc? Is there anything else I can do?" Are there things that you feel helped both of you?

Mr. Andrew Kunz: Well, I like to walk and walk, about three and a half miles a day. When it's nice, I'll play golf once a week. So I do just regular living, I guess, is the only way to put it. It's not holding me back in any way. Lynn?

Ms. Lynn Sperling: Yeah. I go to an exercise class three times a week. It's a sitting exercise. It's called sit and get fit. I think a positive mental attitude too, being social, being with friends is also very helpful.

Dr. Peter O'Donnell: I love that. I'm a big proponent of the idea of some form of exercise, because I think there's clearly data that exercise improves immune responses in general, even in the absence of immunotherapy. So I think it's healthy for the immune system in general. I love the mind-body comment there, Miss Sperling, because there's a lot of data actually around that, that positive influences in your life can actually have positive outcomes.

Stephanie Chisolm: Yeah, attitude is everything. I do believe that. Attitude determines your altitude in many cases. I think that that really does apply here. But it's not always the case because there are plenty of people that have real issues.

Stephanie Chisolm: So if you have immunotherapy and it causes your immune system to overreact, Dr. O'Donnell, can you explain how the steroids help quiet things down? Do you gradually start back? Do you start back with a lower dose? How do you fix that problem and still maintain the benefit of the immunotherapy?

Dr. Peter O'Donnell: Right. So this is where you're really going to need to rely on your doctor, understanding what severity of the inflammatory response are we seeing? Some small degree of inflammatory response, like Mr. Kunz talked about a little bit of itching that he has, I actually tell my patients it's probably a good thing. It tells me the immune therapy's doing something in your body. It's activating, that you're getting a little bit of a response. As long as you can still function and it's tolerable, then we wouldn't do anything differently. That would be what we call the least severe form of an inflammatory response. A second grade of it would be where now it's starting to cause you to be a little bit limited in what you would be able to do. For example, a rash that's covering a good portion of your body, where now it's requiring more intense treatment than a large amount of cream over your areas of skin, where it's limiting your ability to walk because of skin folds being rubbed against.

That's where we start to say, all right, now this is becoming a little more severe and we're going to probably pause that immune therapy, meaning we're going to withhold the drug for a while, give some topical treatments to the skin there, and maybe even a short course of an oral steroid, a steroid pill like prednisone.

Dr. Peter O'Donnell: Then beyond that are what we call the higher grades, the more severe. We call them grade three and four immune events. These are ones where the patient has clearly had organ dysfunction. For example, a patient has severe diarrhea because the gut has become so inflamed, or is having shortness of breath, or lowered oxygen saturation because the lungs have been inflamed. These would be instances where your doctor should hospitalize you immediately, and you're going to get high dose IV steroids through the vein, a drug like prednisone or a similar drug through the vein, to calm down that immune response.

Typically, doctors will need to use that high-dose steroids for at least 48 hours in the hospital. Usually within that first 48 hours, we see patients dramatically improving. The diarrhea will quickly reverse, the skin rash will quickly improve, the breathing will improve. And so, all of those are the metrics that your doctor is looking for.

Then what they will often transition you to is then an oral pill of steroids that often has to be tapered over a period of at least a month. So they'll discharge you from the hospital, you go on an oral steroid, and that steroid dose will be slowly lowered over the course of a month or six weeks until the steroid can be taken off.

Then the real question is once that steroid comes off, is your body going to re-inflame? Is the immune system going to reactivate? I talked a little bit about the idea of your immune system getting a memory to it. And so, it can have a memory around these side effects as well.

And so, sometimes when we stop the steroids, the immune effect that you were having flares right back up. That's troublesome because then we have to put a patient back on steroids, and many patients know that steroids for long-term are not fun to take. They can cause patients to have swelling. The face will puff up. You get very hungry and people will gain weight. You can retain fluid. There's lots of side effects of long-term steroids.

And so, that's the problem when we get these severe immune adverse effects. Really your doctor then has a real tough question about whether they could ever go back to immune therapy.

One little trick that I have done, and I'm a believer in this, is that if you're patient gets a severe immune related adverse event and then improves, and you have a discussion where that cancer is then growing again one day and your patient says, "Doc, I want to fight. I want to do everything I can," and you have no other options, I'm willing in those cases to consider going back to the immune therapy. But that's when I switch it.

We have for drugs that are out there on the market. I definitely wouldn't give the same one again. I'd switch it to a different type in hopes that that inflammatory reaction doesn't come back in the same way.

I know somebody was asking a question too, Stephanie, about lowering the dose of the immune therapy. Generally, that's not helpful. With chemos, we will reduce the dose and the side effects usually improve. With immunotherapies, we don't see that.

Stephanie Chisolm: Okay, that's great. Well, I remember in your talk, you had that really lovely slide that, to me, was very encouraging, where you're showing the difference between the killer cells going after the tumors with those immune therapy.So that leads me to another question that came in. **To what extent is the presence of immune cell infiltrates in the tumor biopsy of predictive value?** Do they even check the tumor to see if those killer cells are activating? How do they know ... Unless they actually see tumor shrinkage, that it's starting to work, that you should continue on this therapy. How do they know that?

Dr. Peter O'Donnell: Yeah, right. So in most cases, we don't do a follow-up biopsy. It's not that we start the immune therapy and then we do a biopsy and try to see if those immune cells have infiltrated. The slides that I showed you there have been from research experiments where this has been looked at to show that it actually correlates, that the infiltration of these immune-fighting cells is actually correlated with the patients who do better.

But in a regular practice, that's a lot to put on a patient to say we're going to do a biopsy just to see if those immune cells have infiltrated. Usually you can tell, like you said, Stephanie, by doing that scan. If the scan shows that the cancer is shrinking, now we know that probably those immune cells are getting in there. One thing that we're thinking about for the future, though, is what we do if a patient doesn't seem to be responding to the immunotherapy? It probably tells us those immune cells aren't getting in there. Is there a way to try to do something else to those immune cells and really kick those immune cells, those killer cells to get in there?

That's where the field is probably moving, the idea of these double immune therapies, where maybe in a given patient, for whatever reason, they're not responding to one immunotherapy, but that second one might help those cells to get in there. We're learning about that. We're also learning that there's actually different types of bladder cancer, that patients probably are familiar with that, and that there are now tests where we can categorize a patient's tumor into ones that are likely to have the immune cells that it'll infiltrate, that might already have been immune cells that are sitting in there and they just need to be turned on, or cancers that don't have any immune cells. We call them immune deserts. For whatever reason, that cancer just cannot find immune cells in it. And so, those are tests that your doctor could do nowadays, although they're not done in routine clinical practice.

Stephanie Chisolm: Okay. You mentioned, Dr. O'Donnell, that BCG that was given to patients with non-muscle invasive disease, who didn't respond to the BCG could possibly get pembrolizmab. Is that something that's given intravesically like BCG and do you have to be in a clinical trial, or is that something that you can just get off-label perhaps?

Dr. Peter O'Donnell: This is on-label. This is an FDA-approved indication for pembrolizmab, the Keytruda drug, now, as of the past couple of years now. So it's more recent, and I'm actually seeing that not a lot of the patients are aware, but even doctors are still slowly recognizing that this is an option.

So it's exactly what you said, Stephanie. The patient that whether cancer hasn't yet invaded into the muscle layer of the bladder, they've been through BCG, and technically those patients also have that CIS component, that carcinoma in situ, feature of their bladder cancer, those patients are eligible to get pembrolizmab on-label as a way to try to prevent further deep progression of that bladder cancer.

In my own practice, I've used it rarely. It's just we're having trouble finding a lot of patients that fit that very specific label indication right now for pembrolizmab. But a lot of us wonder if we're going to start using immune therapies earlier and earlier in the disease course. That's one example. Why wait until you get metastatic disease to use immunotherapy? Could we use it earlier? Could we use it around the time of your bladder being removed or, in this case, as you're saying, even earlier before it's invaded the muscle?

Stephanie Chisolm: Right. So now, as a medical oncologist, you're used to using chemotherapy. **So if a patient benefits from chemotherapy, is the recommendation moving towards all patients going to some kind of maintenance with**

immunotherapy? Is that where we're really heading, just make sure once we get it knocked down that it stays down? Is that what we're looking at?

Dr. Peter O'Donnell: Yes, that's become the new standard where I think almost all patients are really offered that now, this idea of maintenance. I mean in Mr. Kunz's case, we're doing exactly that. We're doing a maintenance immunotherapy approach where we're going to probably do this indefinitely. If it's not broke, why fix it, that kind of idea.

Stephanie Chisolm: Right. If, for whatever reason, then, if immunotherapy no longer is effective, if it's not getting that response, then you've got the targeted therapies as yet another option. So there are still arrows in the quiver, but you don't necessarily focus just on the immunotherapy because there are still other options. So, for instance, in Lynn's case, if her cancer were to come back and she didn't respond to immunotherapy the next time, there would be other options.

Dr. Peter O'Donnell: Yeah. **What you're just asking about, Stephanie, I see that in the chat, that someone's asking about that, this idea of waiting for the cancer to return.** We're moving away from that in bladder cancer now, just over the past year, this idea of going straight from chemo and going to that maintenance immunotherapy.

Stephanie Chisolm: Kind of like with your car. You don't necessarily wait for it to breakdown before you get it fixed. You do routine maintenance to just make sure it keeps running smoothly, I guess, in that case.

Lynn, this is a question for you. **There is a question, do you still have your bladder and were there tumors that were high-grade tumors?** Somebody is receiving BCG and they're in an 18-month trial. They want to know do you think immunotherapy is something they should consider? So, Lynn, if you'd talk a little bit about your experience and then Dr. O'Donnell, as the expert, could weigh in on that.

Ms. Lynn Sperling: I still have my bladder. I originally had some surgery to remove the cancerous growth in my bladder, and it had escaped to the lymph system. That's why they were treating me with chemo, and that's how I got referred to Dr. O'Donnell. But, yes, I do still have my bladder.

Stephanie Chisolm: Well, does immunotherapy have an effect on tumor still in the bladder?

Dr. Peter O'Donnell: I mean that's what I was talking about before where we're seeing immunotherapies have an effect on even tumors that haven't innervated the muscle. We're wondering whether immunotherapies will have an effect on tumors that are muscle-invasive. I think one of the questions is around that. If you have a muscle-invasive tumor, is there a role for immunotherapy there?

That's still under exploration, but there's been a couple of trials now published that show that even patients with tumor invading the muscle might have very nice responses to immunotherapy. Not everybody, but some portion of the patients are having a response to that immunotherapy.

And so, the idea is that maybe we can use immunotherapy either before we take that patient to bladder surgery to shrink down the tumor and try to eradicate any microscopic cells that have escaped, or one study that just came out this year, which was really exciting to all of us in the bladder community, is for a patient that's gone through bladder surgery and yet they have high-risk features, that that bladder had

tumor that was maybe farther invaded than we hoped, those kind of patients are at high risk for that cancer coming back because the cancer cells had an ability to perhaps spread where the surgeon can't even see that they've escaped beyond the surgical field. Those patients now might be candidates in the near future for using immunotherapy as a preventative to prevent the cancer from coming back.

So it goes to that whole topic we were talking about, preventative maintenance or maintenance immunotherapy. If your cancer's already spread and you've been through chemo, we'll now do a maintenance immunotherapy. In the near future, I believe we might be thinking about immunotherapy post-surgery to prevent the cancer from coming back. It's still unproven, though.

Stephanie Chisolm: I know that you're involved in many research trials. Do you see that there might be something five or 10 years down the road where perhaps immunotherapy would be used as a first line in muscle-invasive disease in lieu of getting your bladder removed? Do you think that that's something that we're just trying to understand if that's a benefit? Where are we going in that direction?

Dr. Peter O'Donnell: Maybe. I want to be careful answering that one because patients need to be clear that if your cancer has invaded into the muscle, the gold standard, the standard of care, is that that bladder needs to be removed to save your life. And so, we really get into dangerous ground thinking about trying to spare the bladder there in those patients, because I've seen too many times where patients delayed having their bladder removed and they die of bladder cancer.

So maybe. Maybe we'll be using immunotherapies along with bladder removal. I know that there's one question in the Q&A about combining this with radiation treatments. Some patients who opt to try to keep their bladder will use radiation treatment, treating the bladder cancer in its place without removal of the bladder. That is an option in some patients even for when it's invaded into the muscle. And so, there's actually studies going on now to say can we combine immunotherapy with radiation to have even better outcomes for saving the bladder in place?

Stephanie Chisolm: Right. What you were mentioning before was a little bit more like neoadjuvant chemotherapy. I always use the analogy that's like putting the evil genie back in the bottle before you take the bottle and throw it away. It's what happens with removing your bladder. You want to make sure everything gets into that bottle and then you take it out.

I think it's really relevant because a small portion of our patient community has what's known upper tract disease, where their cancer is not necessarily directly in their bladder, but perhaps up in the ureters or even in the renal pelvis of their kidneys. Is immunotherapy being used in that case at all? Have you seen any benefit for those patients?

Dr. Peter O'Donnell: It's being studied there. Although patients who have upper tract urothelial cancer, the type of cancer is actually the same. Urothelial cancer, it can start anywhere along the urinary tract. I saw one question asking about urethral tumors. That's the very end of the urinary tract. That can be urothelial cancer. The bladder, of course, is urothelial cancer. Then the ureter, which is the tube connecting the bladder up to the kidney, that's urothelial cancer. Even the first portion of the kidney itself, what we call the renal pelvis, is actually urinary cells. And so, anywhere along that whole tract is where urothelial cancers can form.

And so, we end up treating the urothelial cancer wherever it forms along that tract in a very similar way. If it spreads, if it metastasizes from an upper tract urothelial cancer, immunotherapy certainly have a role.

The last thing I'll say about upper tract cancers is that we're learning that they do have some differences from bladder cancer, and that is much more likely that a patient might have a genetic syndrome that predisposed them to getting an upper tract cancer. Lynch syndrome, for example, is a genetic syndrome that maybe some people have heard of. It's commonly known to cause colon cancers and endometrial cancers, but it's now more recently been shown to be associated with urothelial cancers of the upper tract. So your doctor should be thinking about whether maybe you have Lynch syndrome if you develop an upper tract urothelial cancer.

The other genetic aspect that we definitely realize nowadays is that you're much more likely to have one of these mutations in a specific gene we call FGFR, which has a targeted drug that's now FDA-approved. We didn't get to talk too much about targeted therapies. But if you have an upper tract urothelial cancer, your doctor should be thinking about these genetic aspects.

Stephanie Chisolm: Okay. A good question that's in here relating to starting chemotherapy. It's necessarily related to immunotherapy. **How long do you go on chemotherapy before you say, "I give up on this. It's not really working for you. Let's go to immunotherapy"?**

Dr. Peter O'Donnell: I feel like I'm talking so much. Miss Sperling, do you remember how we made that decision with you? I'm putting you on the spot a little.

Ms. Lynn Sperling: Six rounds. That's when the oncologist said I had some choice to make. And so, it was three weeks on, one week off, and that there were six of those before they decided that I could talk to you about immunotherapy.

Stephanie Chisolm: Six months then? If there were three weeks on and a week off, or two weeks off, it's like six months before you could really be considering or should be considering, because we still know that chemotherapy is still the gold standard. It's still what's recommended first. That's the first line in many cases, right?

Dr. Peter O'Donnell: Right, for most patients. Miss Sperling is exactly right. Generally, the rule of thumb is that you don't go beyond around six rounds of the chemo. After six rounds, the side effects really just accumulate. Very difficult for a patient to tolerate beyond six rounds. And we really don't see a lot of bang for the buck after six rounds of chemo. The effect is usually completely gained at that point. I tell my patients, "We're going to try to plan for somewhere between four and six rounds of the chemo. I'd like to get you through four, if we can, at a minimum. Then we'll see how you're feeling and we'll play it by ear. After four, we'll see how you feel, if we can go to number five. Then we'll see if we can get to number six." But if you have to stop, I tell my patients don't feel bad if you have to stop after four rounds of chemo, and then we can switch to the immunotherapy maintenance like we talked about.

Stephanie Chisolm:

Okay. So this is a very specific question, you may not have the answer, but how do you tell if symptoms are a side effect or possibly a cancer recurrence, such as genital ulcers that would be down in that area? **How do you discern that that would be perhaps a side effect or is it a recurrence of your cancer?**

Dr. Peter O'Donnell: Yeah, that's a real tough one because I rely really on what was the presenting symptoms with that patient when they were found that they had cancer in the first place. I do get a little nervous if the patient now is starting to have a similar symptom as when their cancer was first found. That really sticks with me. I've had many patients that say, "You know what, doc? I'm developing a symptom that I ... It was exactly like when my urologist first found the cancer." That is something that I would pay attention to and probably think about re-scanning that patient to see what's going on. Immune-related side effects like rash, they're usually more generalized and not specific to just one area of the body.

Stephanie Chisolm:

So, Dr. O'Donnell ... And, Andrew, you're still on the immunotherapy ... **is there an upper limit to how many years you should be on this treatment? Are there things you should watch out for longterm?**

Mr. Andrew Kunz: I'm feeling fine. Each month before I go in, I have my blood tests and doc goes over it. They don't mix the chemicals until he approves that I'm good for that treatment. So I don't have a problem with it because I know that I'm being watched closely each month.

Dr. Peter O'Donnell: Yeah, I'll say that there really isn't an upper bound. Some of the trials have proposed stopping the immunotherapy after two years. It's a bit arbitrary. There's not a lot of evidence around that. Miss Sperling, I think in your case, it's what we did. So there are some data that suggests you could stop after two years if you've had a really nice response. But in other cases, a lot of my patients I counseled that we're going to do this indefinitely, as long as you're not having side effects from it, because I've, unfortunately, had a number of patients where when we do stop, the cancer then starts coming back.

Ms. Lynn Sperling: I was just wanting to add that I actually had full knee replacement after I stopped the immunotherapy, and it went fine, with the doctor's permission and everything. I had been putting it off and putting it off. But that went very well. So I now have two new knees.

Dr. Peter O'Donnell: Miss Sperling, I remember, in your case, one of the reasons that we ended up deciding to stop the immunotherapy was you did have some sort of chronic fatigue that we thought was related to the immunotherapy. I think that did get better after we stopped.

Ms. Lynn Sperling: A little bit.

Dr. Peter O'Donnell: So these are the kind of things we raise, Stephanie.

Stephanie Chisolm: So what others things should people be aware of if they're going into their third year of immunotherapy? What are some of the things that maybe they should consider having checked? Is there something metabolic that they should be aware, something that they should be telling their doctor? Because they might not think to tell them about something that doesn't seem like an immune response problem.

Dr. Peter O'Donnell: Yeah. I mean, of course, we're checking blood work before every infusion. We still do that. No matter how many years you've been on it, we're checking blood work to make sure there's no inflammation of the liver, to make sure the kidney function is okay.

But actually, in general, if a patient is going to have one of these one out of 10 severe side effects from immunotherapy, it typically happens in the first six months. Not every time, but almost all the time. If you're going to have one of these severe effects, it's going to happen earlier on. I do not generally see patients that are three years out getting out-of-the-blue new side effects from immunotherapy. It just doesn't happen.

Stephanie Chisolm: That's just good to know. Well, we're coming towards the end of our program. I think you covered most of the other questions. There's a question in here about is there a difference between the side effects or the effects of Keytruda and avelumab, and which one might have more side effects. **But how do you as a clinician pick ... Because you can prescribe all of the different approved treatments. How do you decide which one each patient should go on?**

Dr. Peter O'Donnell: Yeah, it's a really tough question and it gets a little bit technical on the answer. I will say that we think maybe some of these four immunotherapies have small differences in their side effect profile, whereas some patients might be less likely to get, for example, the lung reaction with certain of the drugs compared to others. But, in general, they probably are all about the same.

One that has stood out and probably gets the most common use is pembrolizmab, the Keytruda drug, because that drug has had a definitive trial in patients with metastatic disease that showed that it really elongated the survival for patients, where some of the other drugs haven't shown that. The avelumab drug has shown that survival benefit as a maintenance, like we talked about.

So most of the time, if your doctor's thinking about that maintenance strategy right after chemotherapy going into a maintenance immunotherapy, avelumab has the best evidence. For patients that have been through chemo and they adopted that wait and see and then the cancer came back, pembrolizmab has the best evidence.

I think oncologists always want to use the drug that has the best evidence around it for a given treatment setting. So that's probably how we end up picking.

Stephanie Chisolm:

Yeah. I think this has been an incredibly useful program. I'd like to thank you, Lynn and Andrew, for sharing your stories and your experiences. Dr. O'Donnell, as always, you're amazing. We appreciate your sharing all this information.

BCAN would like to thank our
Treatment Talk sponsors

for their support.

BCAN
Bladder Cancer Advocacy Network