Introduction

Stephanie Chisolm: Thank you again for joining us for Treatment Talks live bladder cancer video chat from the Bladder Cancer Advocacy Network. The immune system detects and protects the body from anything it perceives as foreign. However, cancers found ways over the years to evade our immune system, and cancer immunotherapy is designed to help our immune system to recognize those cells and to reactivate the specific immune cells that help target and attack them.

While BCG has been around for decades and works as an immunotherapy, there are now a number of new immune checkpoint inhibitors targeting the PDL1 receptor pathway that have been approved by the FDA for people with types of bladder cancer known as locally advanced or metastatic carcinoma. That's the focus of today's program.

We're delighted to have a leading expert with us today from the University of Chicago. I'm going to introduce Dr. O'Donnell. He is a specialist in genitourinary malignancies, including prostate, kidney, testicular. But he really does specialize in bladder cancer.

Dr. O'Donnell is a well-published researcher with training in pharmacology and pharmacogenomics, the study of the genetic trait that cause differences between patient and drug response and side effects. I know some of that comes into play as we're talking about these immune therapies.

And so, we're also joined by two of Dr. O'Donnell's patients, Lynn Sperling and Andrew Kunz, who I will introduce a little bit later on. Dr. O'Donnell, I'm going to turn it over to you. We know that immunotherapy is not a new therapy, but now it's being used in many different ways. What do you think we should know about immune therapy today?

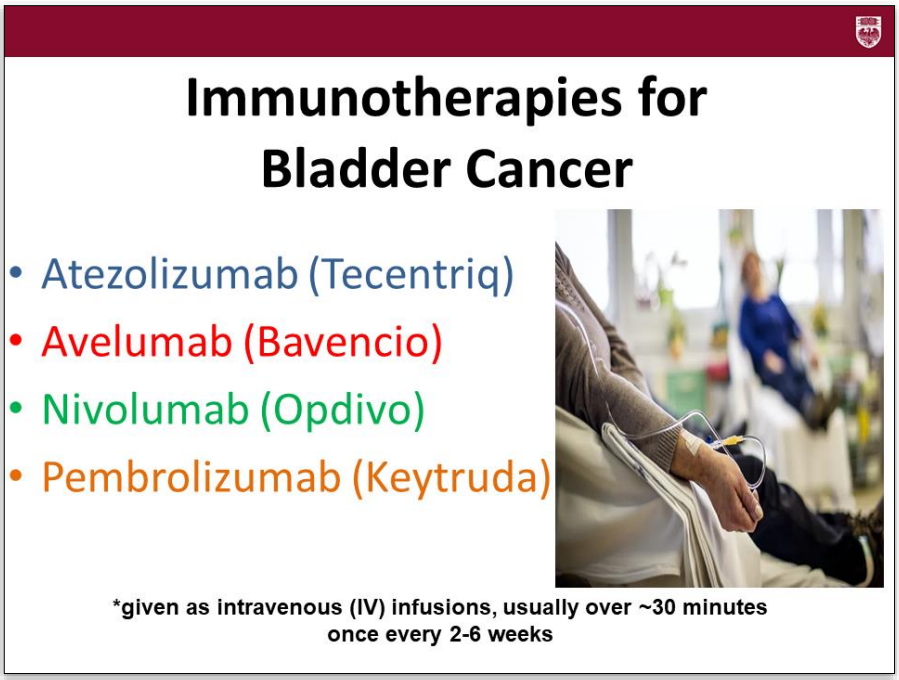
Dr. Peter O'Donnell: Thank you, Stephanie. It's really my pleasure to be here today. I see my charge as setting the stage for really the highlight of this hour, which is hearing from two people that I've had the privilege of getting to know over many years and really are the ones that are going through and have gone through treatments like this, Miss Sperling and Mr. Kunz. So I'll set the stage and then we'll move to that portion of the program.

What is Immunotherapy?

Dr. Peter O'Donnell: All right. So I first thought I'd say that let's get the groundwork of the terminology when we're talking about immunotherapy. Some people refer to these treatments as immunotherapy, some you might hear the words immune therapy, some you might hear the word immune checkpoint inhibitor. For our purposes today, they all mean the same thing. These are drugs that modulate or alter a patient's own immune system to fight cancer. Next slide.

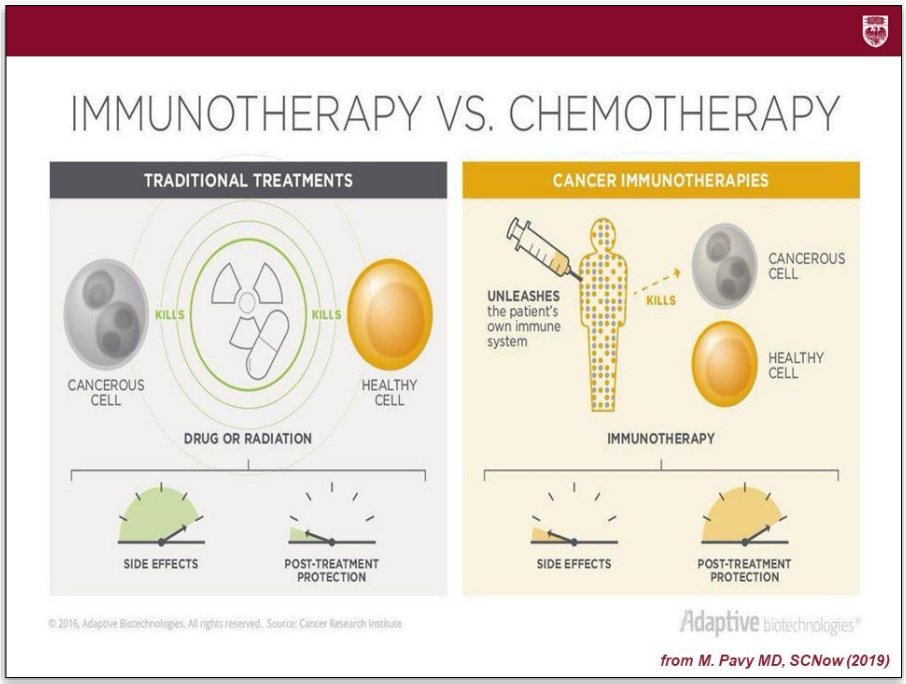
There are four drugs that are approved for use against bladder cancer that are immunotherapy agents, and I listed those on the slide here. I've listed both the common name or the generic name of these drugs and then the brand name. You might hear your doctor or your treatment provider refer to either.

Dr. Peter O'Donnell: The four drugs are atezolizumab, avelumab, nivolumab, and pembrolizmab. All four of these drugs are immunotherapies. They're all given as intravenous treatments, IV treatments. They are administered over a portion of about 30 minutes' time. The schedule can be anywhere from as often as every two weeks needing to get these fusions to as less frequent as every six weeks, depending on which specific drug your physician has chosen and which schedule for that drug they have chosen.



Dr. Peter O'Donnell:

I want to start here before we talk more about these drugs in depth, with a brief portion of a video that I actually recorded with BCAN's help. We're going to watch about a minute of this to understand how immunotherapies actually work in the body. (Please visit https://www.youtube.com/watch?v=SnfFkrsGDOA to watch the video.)



So I'm going to say some of that another way, because I know that was quick, to understand how immunotherapies work. I think one of the best ways to really put it into context is to describe how immunotherapies are different from traditional chemotherapy treatments, which I think many patients are often familiar with or at least had family members or friends that might have been treated with chemotherapy.

So on the left, we're looking at a representation of how chemotherapies work. Here they're showing that the chemotherapy drug has toxic effects on any cell that it comes into contact with, that being a cancer cell on the left or a healthy cell, any healthy cell in your body.

One of the hallmarks that we think about with chemotherapy is that the side effect profile is often difficult or harsh, as is shown on the lower part of the left-hand part of the slide. Then we traditionally don't think about chemotherapies as having longer lasting effects. That is the post-treatment protection is often of short duration.

So chemotherapies traditionally work while they're being given about, but the effect will typically stop after the chemotherapy has to be stopped. What typically happens in almost every patient is that we have to stop chemotherapy at some point because the effects on the healthy tissues accumulate, the side effects accumulate, where we have to pause or stop chemotherapy at some point in almost every patient.

Now contrasted against immunotherapies on the right, where, as we're seeing here, the immunotherapies unleash the patient's own immune system to find and kill cancer cells. And so, they're actually acting on the patient's own healthy immune cells to use those cells to the body's advantage.

And so, we think, for immunotherapy, unlike chemotherapy, that typically these drugs have a much lower side effect profile, that they're very tolerable in a large majority of patients who received immunotherapies. A clear advantage to these types of drugs.

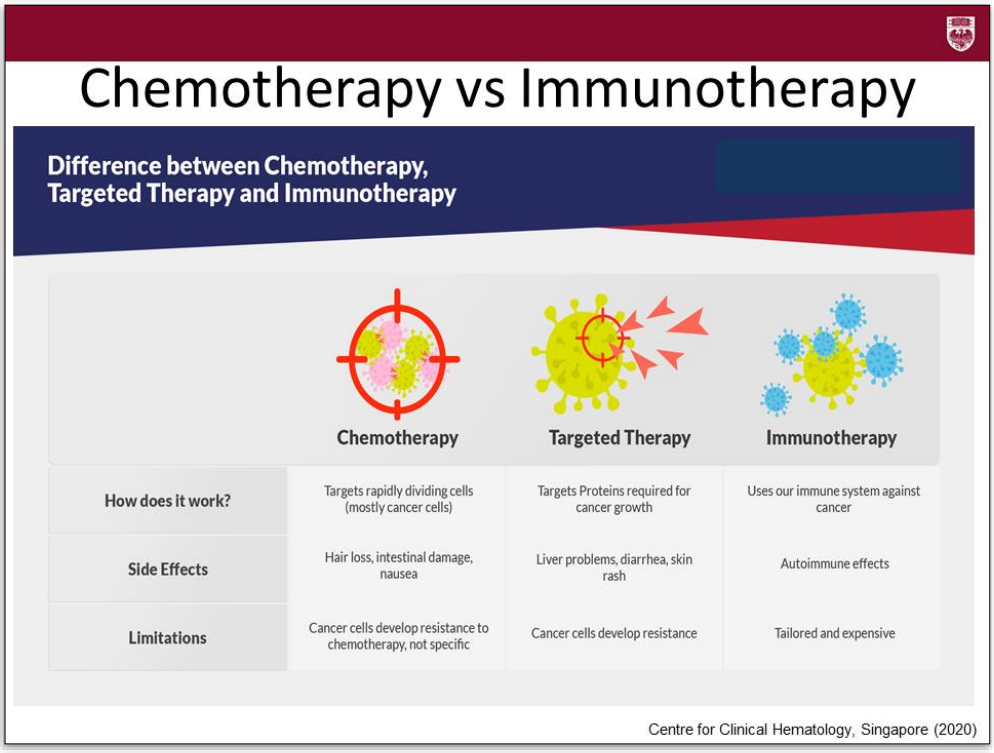
Dr. Peter O'Donnell:

We also have this very interesting effect of immunotherapies, that even in patients who stop immunotherapies, who are not actively continuing to receive those ongoing infusions, we can see that in a number of patients, there will be a post-treatment protection effect. That's believed to occur because we think that these drugs can actually train the person's own immune system to recognize those cancer cells, and that even when we withdraw the immunotherapy, and immune system remains trained and has a memory to learn how to keep those cancer cells at bay. Next slide.

The last thing I'll do, to put this into context, is to try to compare and contrast a third type of therapy that you might have heard of, and that is targeted therapies, which are on the middle part of the slide. So now we're thinking about differences between chemotherapy, targeted therapies, and immunotherapies. There are some targeted therapies that are approved for bladder cancer treatment. We don't have time today to focus on those.

Dr. Peter O'Donnell:

But if we look at this slide, how do they work? Again, chemotherapy generally targets any rapidly dividing cell in the body. Hopefully has preferential effects against cancer cells, but also clearly damages normal cells in our body. Targeted therapies try to find a specific target on the surface of a cancer cell to then destroy that specific cancer cell because it has the target. Immunotherapies, as we've said, use our own immune system to stimulate the immune cells to identify and treat the cancer, kill the cancer cells.



Side effects. Again, with chemotherapy, people generally know, have lots of different effects that are difficult for patients to tolerate, including hair loss, gastrointestinal effects like diarrhea and nausea, and many other effects on the body's own immune system, for example, where the bone marrow can be damaged by chemotherapies.

Targeted therapies can have specific problems related to the specific target. Those can sometimes include liver problems, diarrhea, skin rashes. Again, we won't have time to focus on those today.

For immunotherapy, what we'll talk about at the end of this session is that really the side effect that we worry about. Again, it's infrequent in most patients, but that is if the immune system gets revved up too much. If we overactivate the immune system, our own immune cells can start to attack itself. That is

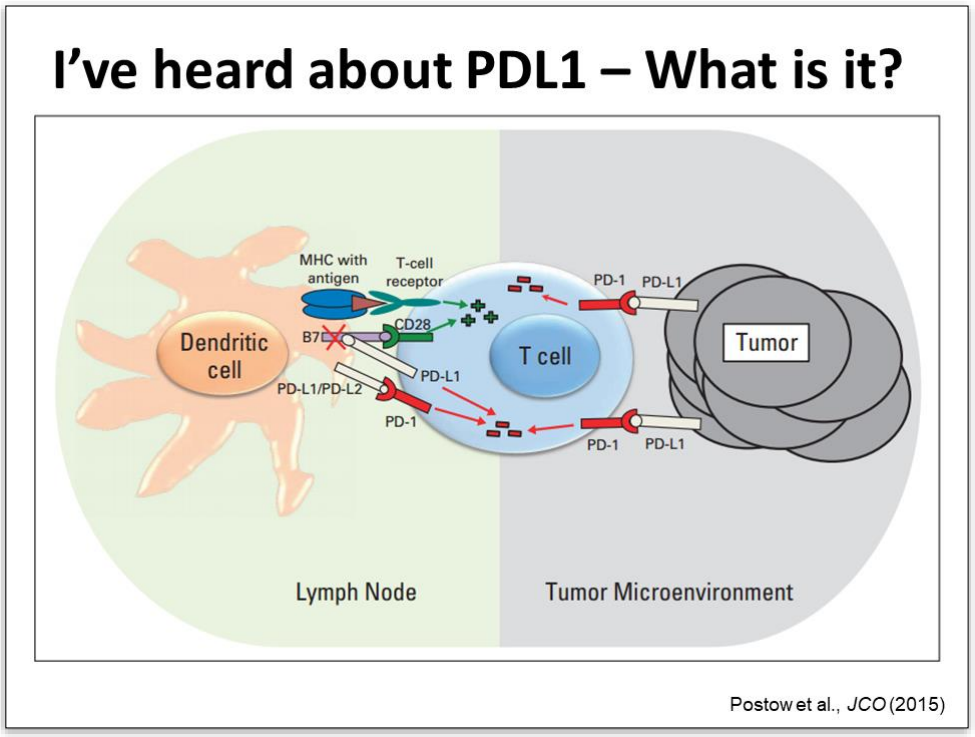
they can attack normal tissues in our body like an autoimmune reaction, which many patients are familiar with.

Dr. Peter O'Donnell:

The limitations of each of these. For chemotherapy, well, cancer cells can develop a resistance to chemotherapy, which means that they can start to grow even when the chemotherapy is being given. As I already mentioned, there's a limitation to the amount of chemotherapy that a person can tolerate in their lifetime because of the damage to normal tissues.

For targeted therapy, we also see cancer cells developing resistance. For immunotherapy, resistance can happen, but perhaps is less likely, especially in patients where immunotherapies are working. It's tailored because it's using the body's own immune system. One downside is that these therapies are still very expensive to give.

You might say, "Well, I've heard about PDL1. What's that?" So how are we talking about immunotherapies without talking about PDL1? And so, I'll draw a connection to something that we saw in the video, which is that protein that's expressed on the surface of tumor cells. It's actually being shown on this slide.

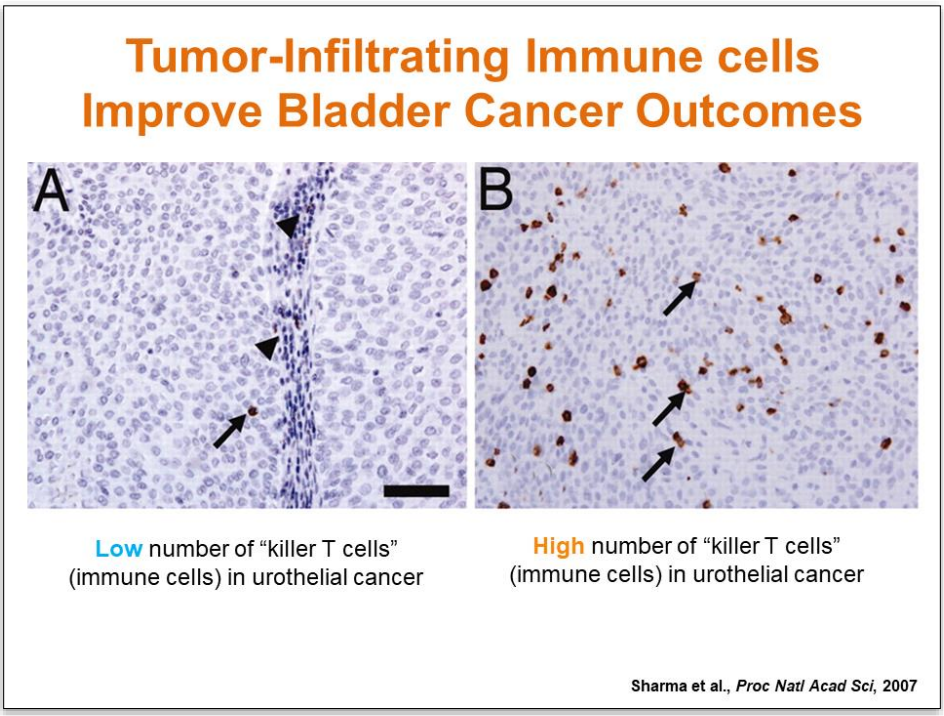


If you look at the right, where we're seeing a collection of tumor cells, they're expressing that protein, which is actually called PDL1. It's a protein that some tumors can express on the surface. That expression of PDL1 engages a receptor on the T-cell, which is the immune fighting cell. That T-cell then engages with the PDL1, and that's what causes the T-cell to be turned off. It's what allows the tumor to hide, as we talked about in the video, so that that T-cell, that immune system can't actually see the tumor any longer and can't activate to kill the tumor cell.

So PDL1 ends up being important. It's important in bladder cancer treatment. We don't always have to test for PDL1 when we're thinking about using immunotherapies. But in general, if your tumor is expressing PDL1, or if the cells around the tumor are expressing PDL1, there's a higher likelihood that immunotherapies will work for you.

They still can work in patients without PDL1, and your physician doesn't always need to test for this before they use immunotherapies. There are certain specific scenarios where your physician may need to test for PDL1 before they can prescribe immunotherapy. But in general, we're able to prescribe immunotherapies regardless of PDL1 status in bladder cancer.

Dr. Peter O'Donnell: The last thing I'll say about this idea of immune-fighting cells getting activated is that we actually know that in a person with bladder cancer, if those immune cells can be turned on, can be revved up, and actually infiltrate into the tumor. So wherever that tumor might be in your body, whether it's in the bladder itself or if your tumor has, unfortunately, metastasized or spread somewhere else in the body, and if we did a biopsy of that tissue and took a sample, on the left-hand side, I'm showing a slide of bladder cancer under the microscope where you don't see many immune-fighting cells infiltrating into that tumor.



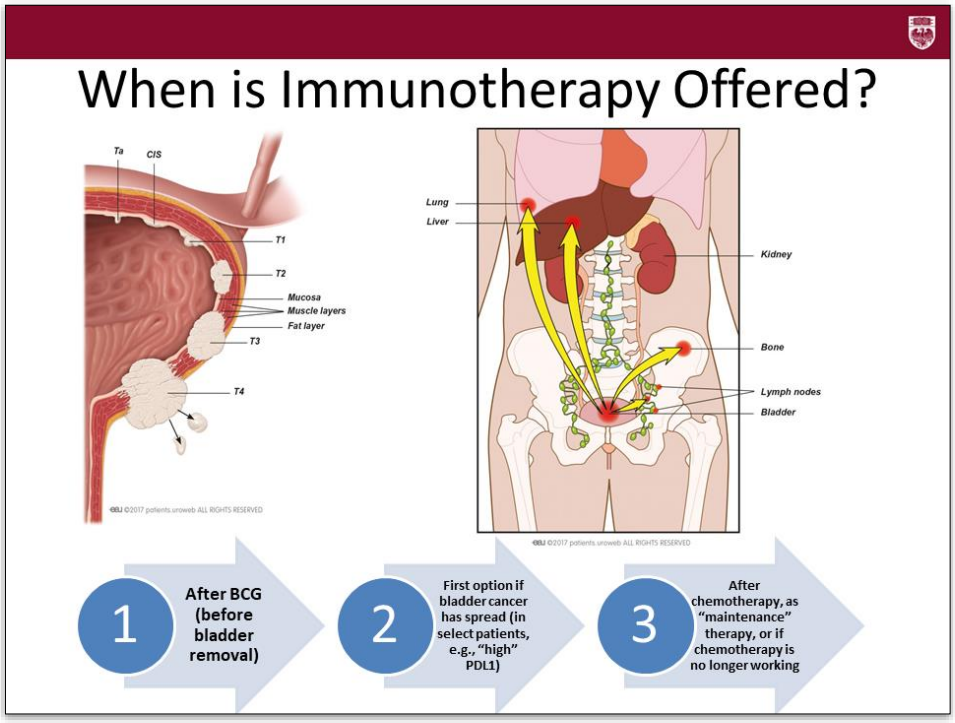
The immune cells on this slide would be brown, staining brown. You could see maybe just one or two of those cells infiltrating into this patient's cancer. We call that a low number of immune cells, sometimes called killer T-cells. Low number on the left.

On the right, we see a large number of these brown staining cells, which are the immune-fighting cells, infiltrating into the bladder cancer sample. What's been shown in many instances, in elegant work, is that if your cancer has infiltration of these immune-fighting cells, your outcomes are much likely to be better from a bladder cancer standpoint. You're likely to respond to immunotherapies better and you're likely to live longer.

Dr. Peter O'Donnell:

The last thing I'll say is where do we think about using immunotherapies? Maybe this will be a great topic for the question and answer portion, is thinking about, well, when would your doctor actually think about using an immunotherapy?

There's three main settings right now in 2021 where immunotherapies have a role for the treatment of bladder cancer according to FDA approvals. The first treatment setting is one that patients may not know as much about. It's more recent. It's happened only in the last couple of years.



That is actually for patients after BCG treatment, before the bladder has actually needed to be removed, specifically patients, as I'm showing on the left-hand part of this slide, that have tumors that earlier. They're not as far advanced. You can see some of those tumors are described T2 or T3 or T4. These are more advanced tumors that have invaded into at least the muscle or in deeper layers of the bladder.

Those patients right now, we don't think about using immunotherapies. Those patients need their bladder removed and they probably need chemotherapy as well.

For patients that have lower stage disease, you can see on this slide T1 or CIS, which means carcinoma in situ. If you have those features, you may be eligible to think about using immunotherapy, a drug specifically called pembrolizmab, which I mentioned at the beginning, one of the four immune therapies that's approved.

Pembrolizmab may be an option for you if BCG is no longer working. It may allow us to decrease that tumor, keep it from coming back in the bladder, and delay the need for your bladder being removed.

That's a less common instance of how we use immunotherapies, at least right now. More commonly, we use these immunotherapies when, unfortunately, the cancer has already spread outside the bladder, as I'm showing on the diagram on the right. Many patients know that bladder cancer can spread basically anywhere in the body. Common locations where bladder cancer can spread is in the lymph nodes, into the liver, into the lung, even into the bone.

Dr. Peter O'Donnell: And so, there are options where if your cancer has spread, to use immunotherapy as the first treatment that you would receive for metastatic bladder cancer. In specific instances, we will think about using immunotherapies as the first-line treatment if, for example, a patient cannot tolerate traditional chemotherapy.

Chemotherapy is usually the first choice for most oncologists if you have metastatic bladder cancer, but a small portion of patients might be able to be spared chemotherapy altogether and receive immunotherapy as the frontline treatment. Those patients, again, they have some reason why they can't receive chemotherapy, and those patients need to have high PDL1 status, as we talked about earlier.

The more common reason is the third one that I'm listing on the slide at the far right, which is that if you've already had metastatic spread of your bladder cancer, you receive that frontline chemotherapy. There's now a role for using immunotherapy after chemotherapy in one of two different ways.

One is that your doctor can go ahead and, as soon as you're done with that initial chemotherapy, transition you or switch you straight into what we call maintenance immunotherapy. This is something that's new over just the past year in bladder cancer. A large study was published in the past year that showed the patients who come off of their frontline chemotherapy and go straight into a maintenance immunotherapy approach live longer than patients who just get chemotherapy alone and then are followed.

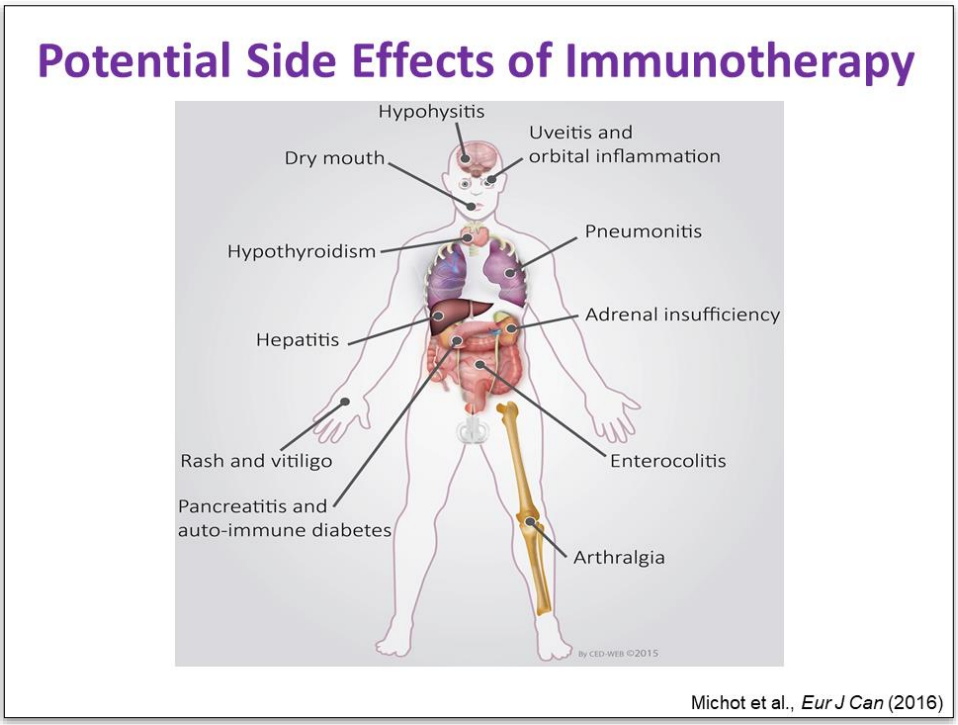
So the idea of maintenance immunotherapy, which has specific evidence around the drug avelumab, which I mentioned earlier, is now becoming adopted widely in the treatment of bladder cancer. So if you haven't heard about this, you should ask your doctor about whether there's a role for maintenance immunotherapy for you.

The last option, as is said in item number three on this slide, is that some patients will go through frontline chemotherapy and then they would choose to be followed, that is to watch their cancer after the initial chemotherapy has worked.

Typically, doctors will adopt a period of regular scans that will be done every three to six months. Then if one of those scans should, unfortunately, show that your cancer is growing again, we don't typically go back to the chemotherapy. That's when we would go to immunotherapy as a second-line treatment after chemotherapy has stopped working. These are very common instances where immunotherapies are given.

Dr. Peter O'Donnell:

This is my second to the last slide, which is that we do have to acknowledge that just like any therapy A and medicine, any medicine that you would take certainly can have side effects. I already said that compared to chemotherapy, immunotherapies are much more well-tolerated in general for bladder cancer patients.



I tell my patients that probably about nine out of 10 patients that get immunotherapy are going to feel generally well. They're going to actually say, "Doc, I see the bag hanging up there, but I don't feel like I have any side effects from the therapy."

One out of 10 patients will have a more serious reaction in the body to the immunotherapy, and that is sometimes what we call an -itis. You can see that a lot of the words ending on this slide end in I-T-I-S, which means an inflammation of a specific organ in the body.

The most common inflammation that we see is on the skin, which is the patients can get a rash or itching or discoloration of areas of the skin. These are the most common type of immune-related side effect. Most patients, these are minimal and tolerable and can be treated with even topical treatments.

In other instances where we see more severe reactions against the immunotherapy, this gets to what I was saying earlier about an autoimmune-like reaction, where your body's immune system has revved up so much that now your own immune system is attacking a critical organ. It can attack the lungs, the liver, the gut, even the heart or the nervous system. These are serious events, and these patients often need to be hospitalized for high-dose steroids to calm down the immune response.

The good news is that, in many cases, that inflammation, that -itis, can be reversed with the use of steroids. The question really is then whether a patient can ever go back to immunotherapy if your body has had one of these very high stimulation of the immune system adverse events. That's a discussion that you would have with your doctor.

But again, in general, compared to chemotherapy, I can tell you that my patients would choose immunotherapy every day of the week from a side effect profile. Next slide, please.

Dr. Peter O'Donnell: So in summary, immune therapies have really revolutionized the treatment of bladder cancer. All of these immunotherapies were approved within the last five years. And so, we've seen a dramatic change in how we can approach the treatment of bladder cancer and a huge increase in the number of tools that physicians have to combat this terrible disease.

These therapies have clearly increased patients' chances for survival, even patients with metastatic disease. They work differently than chemotherapy, they're generally well-tolerated, and they are options in multiple different settings of bladder cancer. So I'm going to stop here.