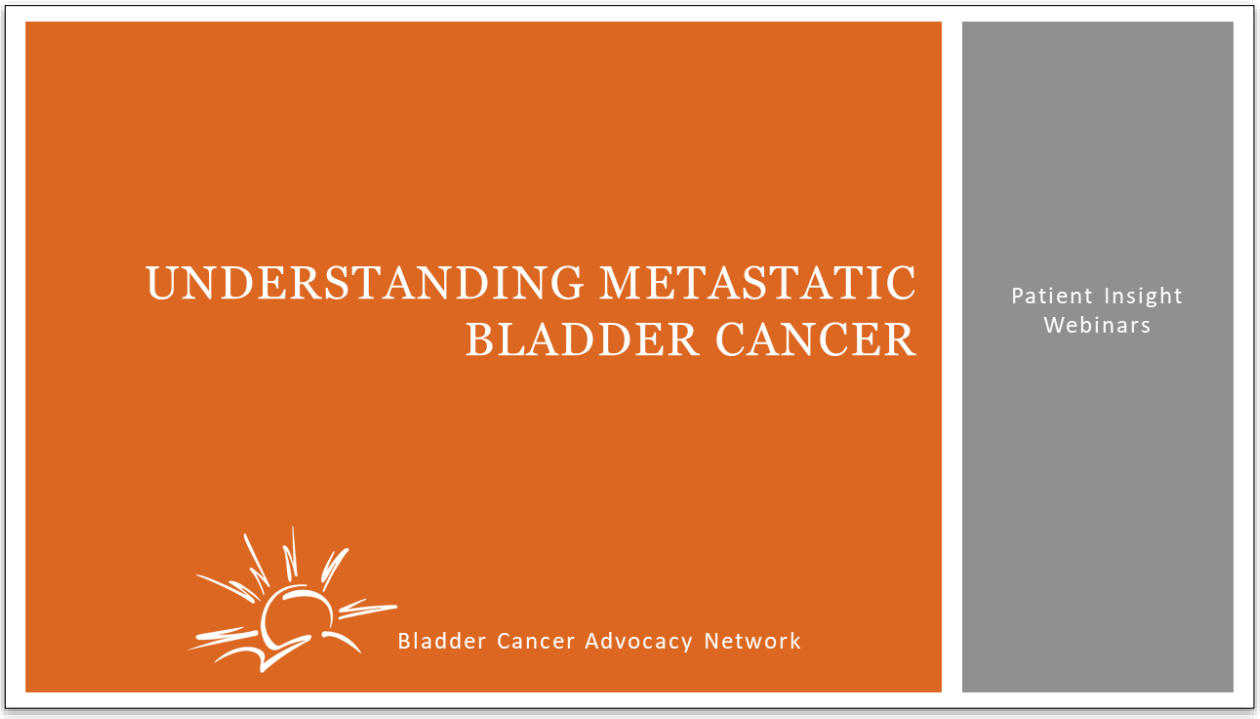
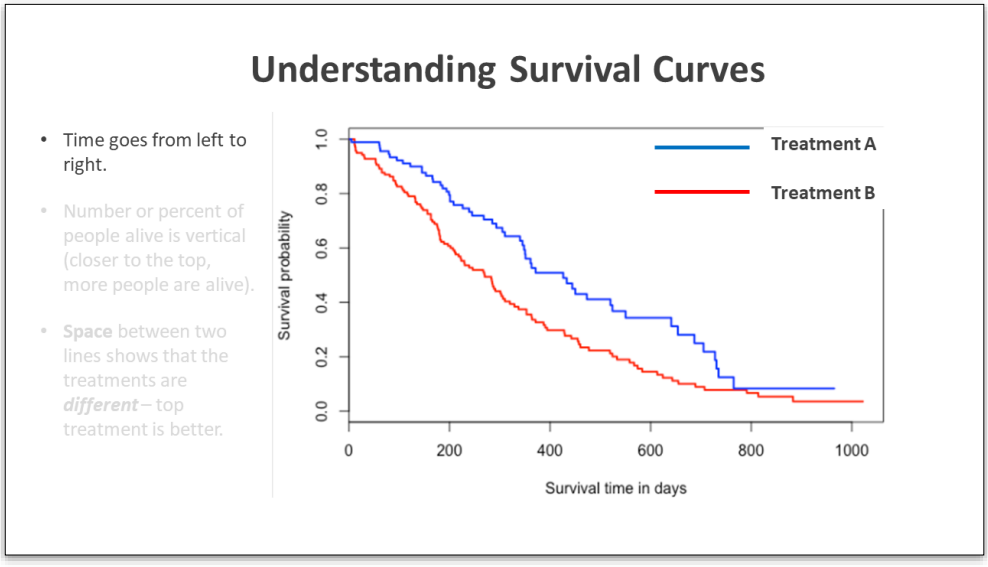


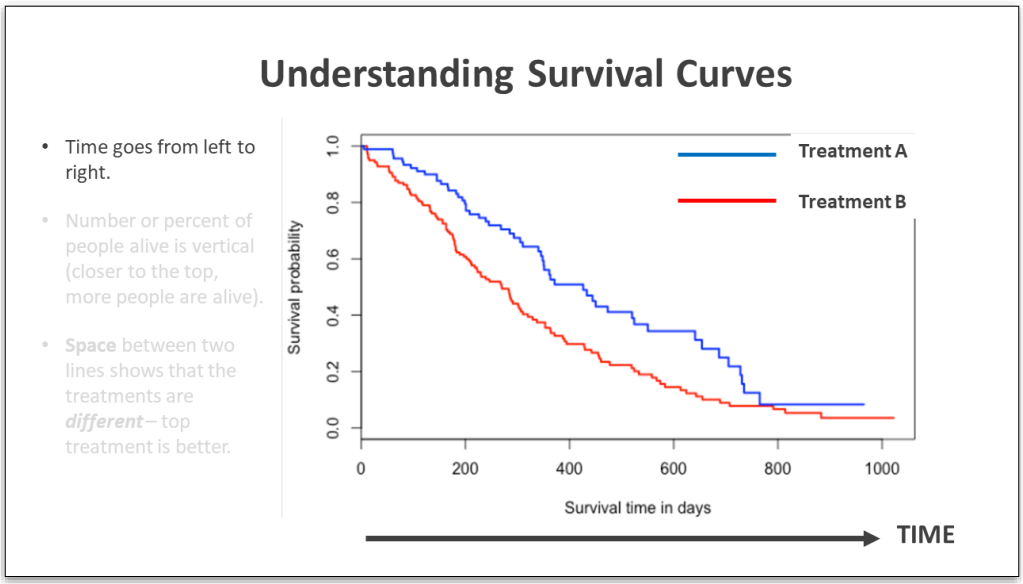
Dr. Morgans:

So as we move on to our treatment portion of this conversation, I want to help everyone make sure that they understand how we look at survival curves. This looks really stressful I assume. As a non-medical person, I can imagine looking at these blue and red lines is very confusing and very stressful. And I'm trying to break it down, because your doctors are going to talk to you about this. And you might look at papers on websites or you might look at meeting information and I want you to be able to have some confidence as you try to work through what we call survival curves. And there are essentially ways that we as doctors, as scientists, as researchers think about how effective a treatment is.We usually, just to start, have two treatments. In this case, in this survival curve, we've got treatment A, we've got treatment B. And we represent each treatment with a color. In this particular diagram, we've got blue for treatment A, we've got red for



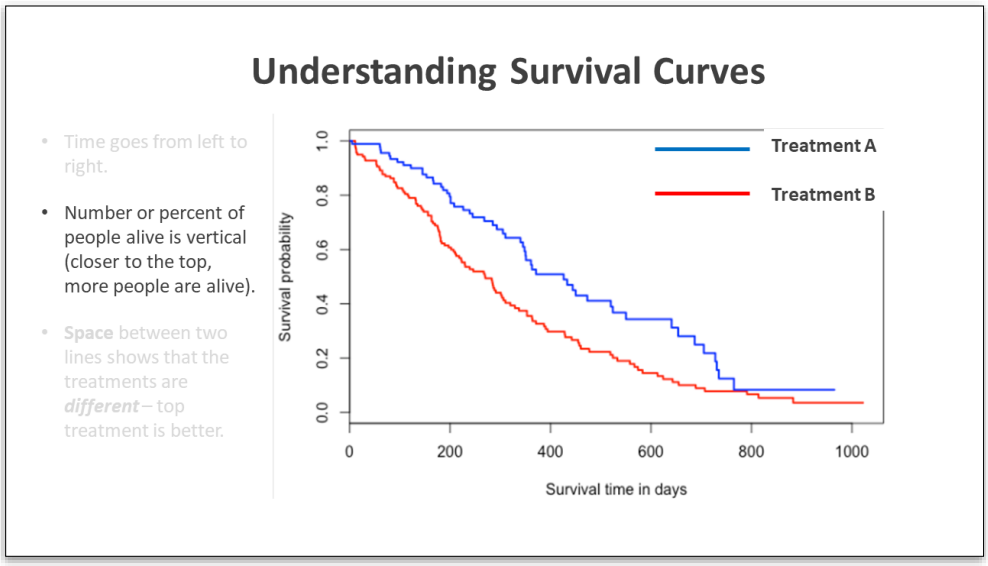
treatment B. And we try to compare these treatments and see which one is going to be the most effective in taking care of our person, whether it's person who's being treated for bladder cancer or breast cancer, prostate cancer or lung cancer, we can compare the effectiveness of these treatments using these curves. And these curves are the data or the output that we get from clinical trials.

So the first step is knowing there are two treatments. One is in blue. In this diagram, it's labeled treatment A. And one is in red, treatment B. The second thing to know is that time, the time on this clinical trial is going to go from left to right. And it's represented on the bottom axis. That 0 to 1000, that's in days. And you can see here, I made a little extra hour here time going from the beginning of the trial on the left to the end of the trial on the right.



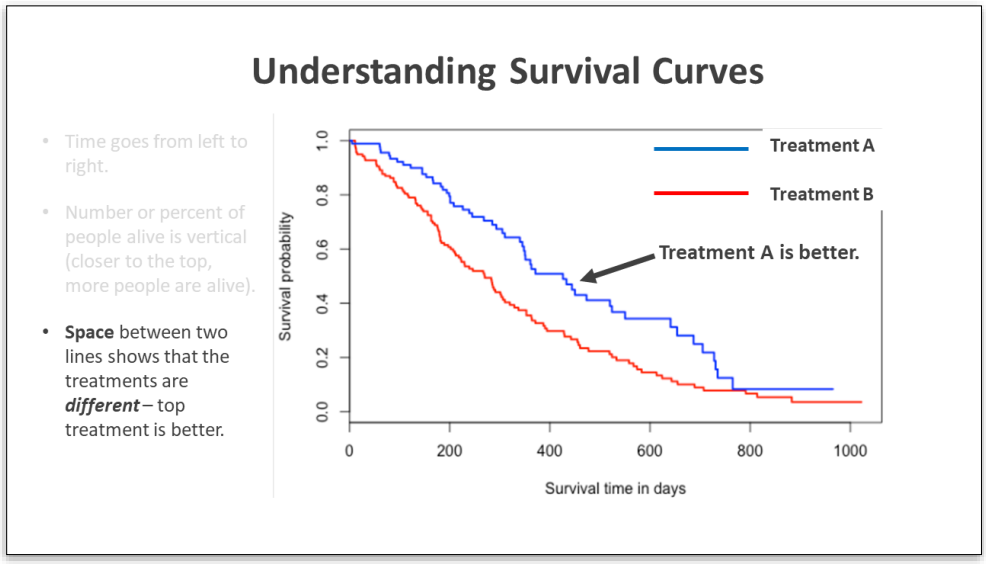
Dr. Morgans:

Now, the next thing to know is we're looking at this is the number of people or the percent of people who are alive in this particular clinical trial are going to be represented on that up and down (vertical) access on the left. And this shows that the higher the curve is, the more people are alive over time.



So if we look at the very beginning, the upper left corner, so even I get confused, the upper left corner, where we see the blue and the red line are overlapping, 100% of people are alive and that's time 0. That's when everyone's starting on this clinical trial, everybody's alive. And over time as we move to the right, people are passing away and other people are surviving, and that the lines both move down, because the percentage of people is moving down.

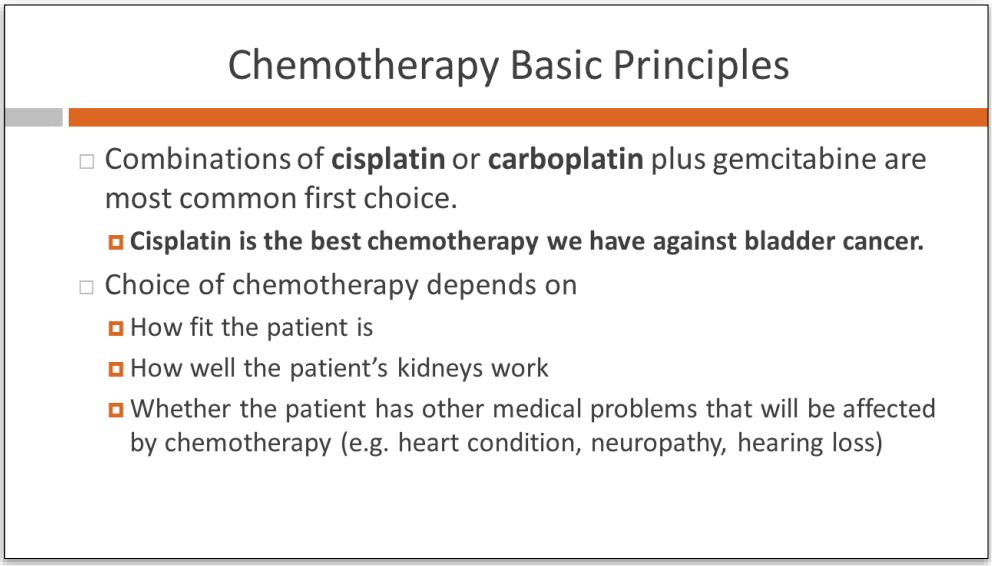
So if we go onto the final thing, the space between these curves is what's going to tell us that there's a difference between treatment A and treatment B. If there's no difference, they're on top of each other, if there's a difference, they separate. And that shows us that one of these treatments is better than the other. Treatment A is better than treatment B here. Treatment A is further, it's higher up, and so that blue line is better. Treatments are going to be better if they're higher up on that graph. So treatment A is better.



So I will show you a couple curves in the following conversation, but I just wanted you to know this because your doctors will talk about improvements in survival, better survival. If you Google it and if you look at papers, you're going to look at pictures like this and just know that the thing that's on the top, regardless of the color, whatever it is, that's better. The thing that's on the bottom is a thing that's not doing as well.

Dr. Morgans:

So chemotherapy. Let's return to this. Let's talk about some basic principles very briefly. And remember, these are things that have been used and have been unchanged essentially since the 1970s. We have not found a better thing than cisplatin at this point in time, though, we have a lot of good candidates and we're trying to replace it. But combinations of cisplatin, that's that thing that was approved in the 1970s or its cousin carboplatin plus gemcitabine, that's the other thing that was approved you saw on the timeline, are the most common first choice for treatment of metastatic, urothelial or bladder cancer. So cisplatin and gemcitabine or carboplatin and gemcitabine are the most common.



Cisplatin is the best chemotherapy we have against bladder cancer that has not changed since the 1970s, which is crazy, I guess, but is maybe opportune that we found a good chemo all the way back in the 70s and we just haven't found something better to unseat it. I would say again, there are multiple candidates on the horizon. We might be able to get rid of this chemotherapy stuff at some point in time, but for now, cisplatin is the thing that is helping us through, it is the most effective thing that we have.

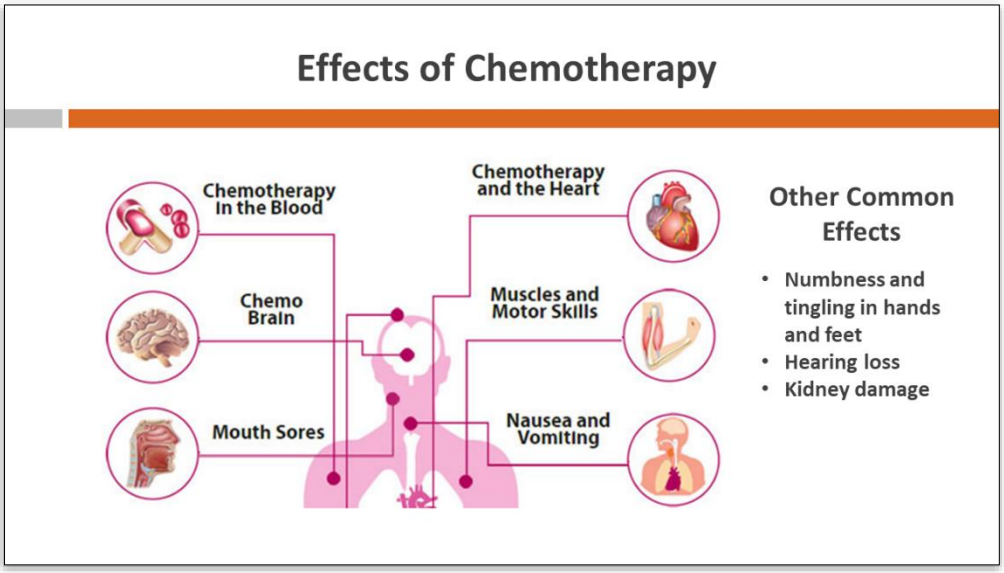
The choice of chemotherapy, whether it's cisplatin or it's cousin carboplatin really depends on a couple things, and they're all related to the patient. How fit the patient is, how strong, how frail, how much vigor that person has versus how weak that person might be. That's really important and is probably the way that we decide between chemotherapy at all or maybe a different pathway, that decision algorithm that I showed you earlier on the way doctors think about it. How well the patients kidneys work, is their creatinine number still at a low level, that helps us choose between cisplatin, which needs really high functioning kidneys that are healthy and happy or carboplatin, which can be given even if the kidneys are not so good, actually, even if the kidneys are not working at all and the patient has to be on dialysis. So that's a decision point.

And whether the patient has other medical problems that might be really negatively affected by cisplatin chemotherapy, whether the person has heart failure or really bad neuropathy, maybe from diabetes, which would be numbness and tingling nerve damage in the fingers, in the toes or even in the ears, so hearing loss, because hearing is a nerve related function. So if there's a lot of nerve damage preexisting, cisplatin could make that worse and we would not want to use that. So those are the main things that we think about when we're trying to choose that chemotherapy. And usually if we can, we try to give someone cisplatin or carboplatin chemotherapy with gemcitabine if we can. For people who are strong enough, and of course, that's not related to anything, that's not a patient's fault or a person's fault, it's just is there your body going to be strong enough to get this chemotherapy, which is tough, which we've already talked about, but is still the backbone of what we try to do for people with metastatic bladder cancer.

Dr. Morgans:

There are lots of effects of chemotherapy. Chemotherapy goes in through a vein. So it's infused a catheter in the vein or sometimes through a port up here in the chest. And it goes through the blood, it goes everywhere the blood flows and it goes into cells of cancer cells and it just destroys them. And that's our goal, that's what we want to do. But it also goes into other cells, cells that are trying to survive by dividing and replicating themselves like blood cells that are just turning over and making new cells all the time or heart cells that can be damaged pretty easily or muscle cells that need to be in a healthy environment to stay well and to grow and to get strong.

So chemotherapy goes into all of those cells. It's not really targeted, it doesn't choose where it goes, it goes everywhere. And because it does that, it can cause low blood counts like white blood cells that protect our bodies from infection or red blood cells that carry oxygen to all of our organs and chemotherapy can damage those and make it harder for our bodies to do the normal things that they do with the blood that they normally have. It can also affect the cells in our mouths and the cells in the GI tract. So again, mouth to anus. And the reason that it can do that is because these cells in our mouths, in our esophagus, in our stomach, in our GI tract, these are all cells that replace themselves on a regular basis. They are only here around with us for a little bit of time and they replace themselves and get new ones, new versions of themselves very, very quickly in terms of a body's life.

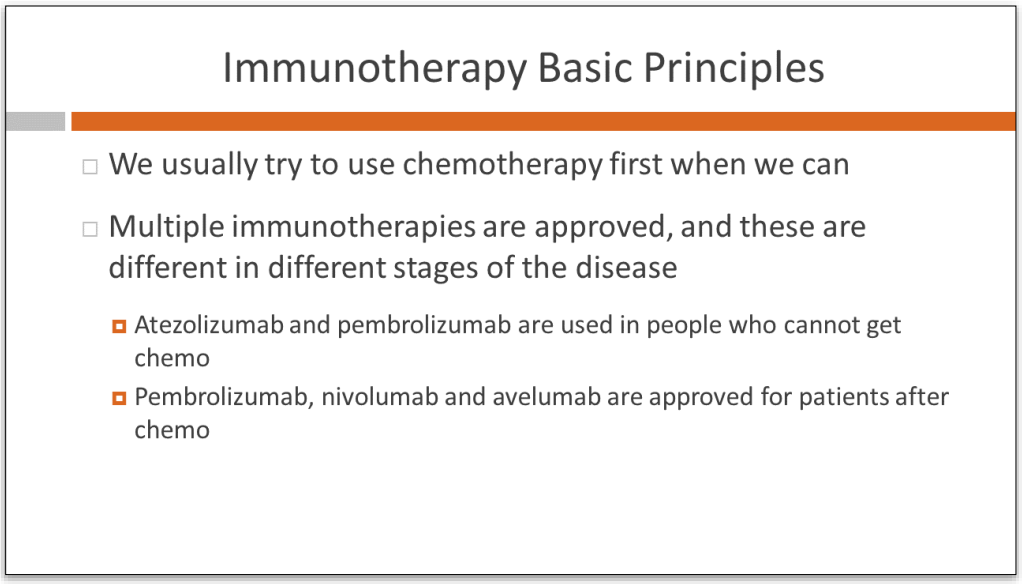


And any cell that's going to turn itself over and make a new one in a short period of time is one that's going to be affected by chemotherapy. So people get mouth sores and they get stomach upset, because those cells get irritated or they do get diarrhea, potentially. Cisplatin in particular can cause neuropathy that I mentioned. So damage the longest nerves in our body. The nerves that go down to the tips of our fingers or the tips of our toes are the ones that are damaged or affected by cisplatin chemotherapy. And so that can cause a numbness or a tingling. It's very strange, I think to people at the beginning. They think, well, it just feels like my fingers fell asleep or my foot fell asleep. And hopefully, that as the body heals after chemotherapy, that should go away, but some degree of that can be more permanent, this numbness you could feel.

And hearing is also a nerve that helps you hear. And that can be affected by cisplatin chemotherapy and cause people to have ringing in the ears or even hearing loss over time. And the most sensitive organs to cisplatin chemotherapy are the kidneys. We get two. We're lucky about that. But they can be really damaged by cisplatin. So really we have to recognize that cisplatin is not targeted, it's the most effective treatment that we have, but it can cause some damage. It's important to recognize that and acknowledge that as we try to keep people safe as we move through.

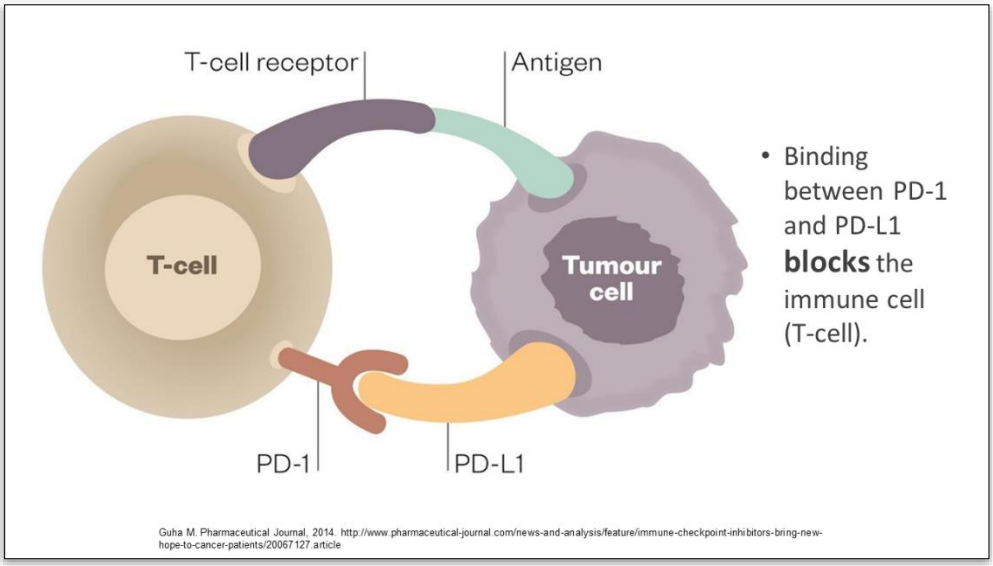
Dr. Morgans:

So anyone who can get chemotherapy, we try to give it to them first. If they can't get chemotherapy, we use something like immunotherapy. And let's go through that. And I have some immunotherapy basic principles. We usually try to use chemotherapy first if we can. But if we can't because a person is not going to be able to get chemotherapy for whatever that reason is, we have the option to use multiple immunotherapies either first or after we've used chemotherapy and it's no longer working for us. And sometimes we're actually using them together, chemotherapy followed by immunotherapy. And I'll show you that information in just a moment. That's probably the most important advance that we've had or one of the most important advances that we've had in metastatic bladder cancer in the last year or so.



So the immunotherapies that we have are atezolizumab and pembrolizumab. You may have heard of Tecentriq or Keytruda. These are the other names for these drugs. And these are the drugs that we use for people who can't get chemo right up front. Or after we've used chemo and the chemos no longer keeping the cancer at bay, we can use things like pembrolizumab, nivolumab or avelumab. And these are for people who have had cancer that's growing this type of bladder or urothelial cancer after we've used chemotherapy.

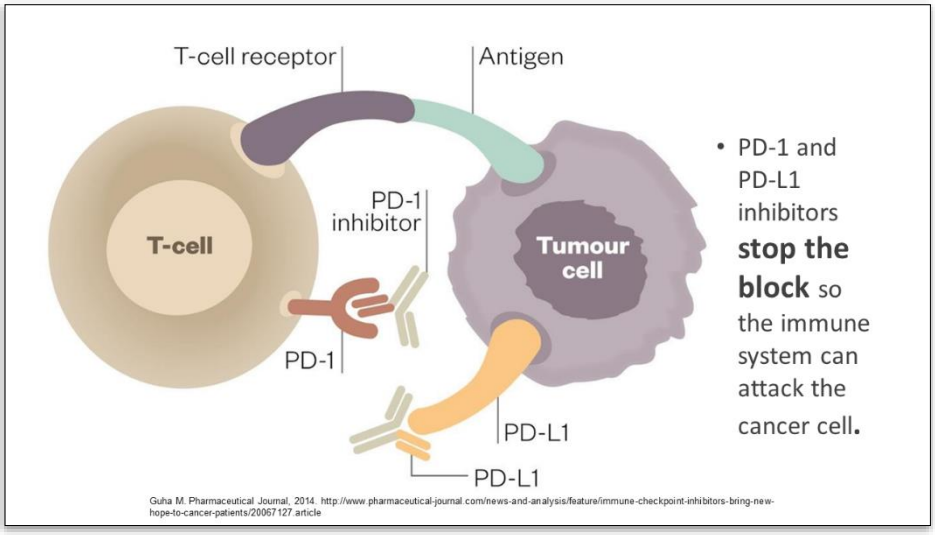
So how does immunotherapy work? I think this is really interesting from a scientist and doctor perspective and was so exciting when we were seeing the development of these treatments back in 2015, 2016 or so. So let's go through this just briefly. So T-cells are a type of white blood cell. These are cells that patrol your body all the time looking for invaders. And these invaders could be things like infections, they could be things like bacteria, something that's not supposed to be there and that we need to get rid of or viruses that we need to get rid of, anything that's not supposed to be there, because it's not part of you and it's not something that



is going through your digestive tract. This is something in your blood, then T-cells are supposed to recognize it.

There's something else that can be in a person that's not supposed to be there, and it's not an infectious disease, it's cancer. Cancer cells start off as your own normal cells, but they go through mutations that make them go rogue and they are no longer part of you. And now they are trying to grow and spread and do whatever they want, but they're not following directions by your body anymore. And that's because they've gotten some mutations that essentially make these cells immortal, live forever, and make them have the ability to potentially spread and cause trouble.

So T-cells, these are the patrollers of our system, can recognize, hey, that cell used to be part of me, but now it's not, now it's doing something it's not supposed to do. And it recognizes that, because it can see that these cells are putting proteins up on their surfaces. What's in this diagram listed as an antigen, it's just a protein that the cell is putting out there to allow it to do something it wasn't supposed to do in the first place. A mutation allowed it to have that antigen or protein out there. And the T-cell can see that's not supposed to be there. But the tumor cell is also putting out this PD-L1 protein, a different protein that is essentially a silence protein.



Dr. Morgans:

So when the T-cell comes in, it uses its T-cell receptor to recognize, hey, there's a weird protein on there, this is not supposed to be here. But it has a second signal, a second protein called a PD-1 protein on that T-cell and the tumor engages with that with its PD-L1 silencer protein and turns the T-cell off. Binding between the PD-1 and the PD-L1 protein combinations block the T-cell, turn it off, put it to sleep, it doesn't know what's going on. So it recognized that, that tumor cell was weird, but it was silenced essentially, put in handcuffs before it could do its work and the tumor cell turned it off.

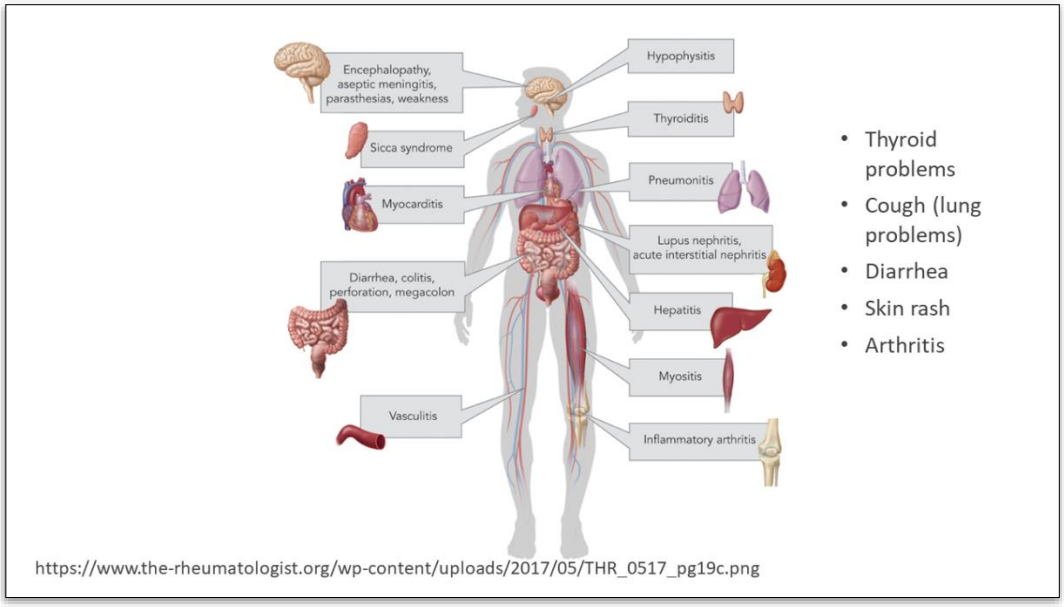
However, PD-1 and PD-L1 treatments, these immunotherapies can come in and stop that engagement between the T-cell and the tumor cell and let that T-cell do its job in getting that tumor cell out of the system. So the T-cell comes in, uses its T-cell receptor, it recognizes that the tumor cell is not supposed to be there, because it's putting proteins, antigens up on its surface that are not right. It comes in, it engages and it's ready to do its job, and before it is silenced by the tumor cells, PD-L1 that turns it off and makes it inactive, makes it go to sleep, the PD-L1 or the PD-1 treatment comes in, blocks that interaction, it stops that blockade of the tumor cell to put the T-cell to sleep. And it lets the immune system recognize that intruder and kill it.

So that was a whole lot of mess, a lot of stuff to think about, but essentially these treatments, these immunotherapies, let the T-cells be the police cells that they're supposed to be, let them recognize the intruders, those cancer cells and let them get them out of there. So as they're doing that, as they're getting that immune system up and attacking those cancer cells, they can also cause side effects. And so

that's what I wanted to mention to make sure we were all aware of. They can cause inflammation. They can cause it anywhere.

Dr. Morgans:

The most common places that they cause it are the thyroid. They can cause a little inflammation here. And sometimes people need to take thyroid medicine to replace thyroid hormone if the thyroid is irritated and it's not doing its job because of the immunotherapy. They can cause inflammation in the lungs that can cause a person to have a bit of cough. And sometimes we need to monitor that or give some steroids to reduce the action of the immune system, turn it down so that people don't feel that cough.

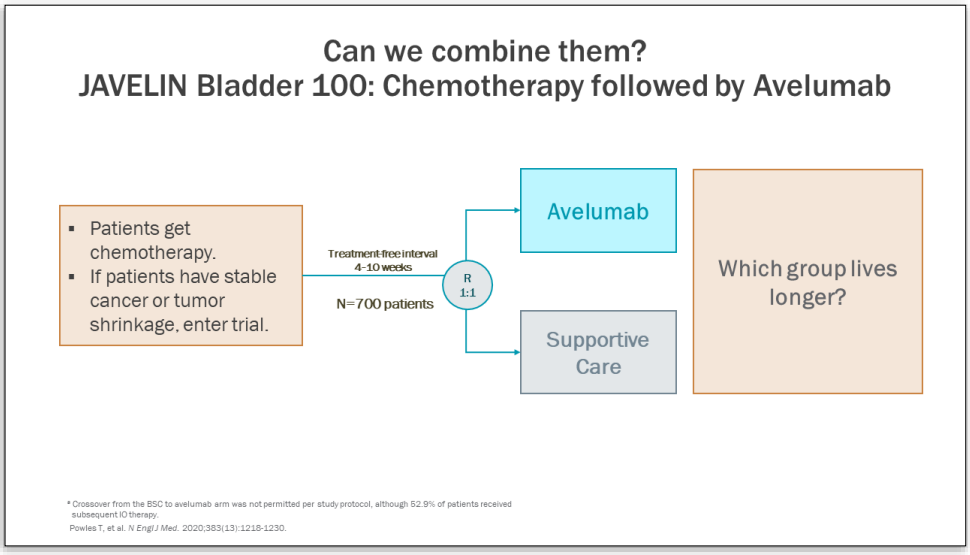


It can cause diarrhea, because it causes inflammation. Immune cells go into the colon and don't allow the colon to absorb water the way it normally would. So extra water in your bowels means diarrhea. So that's something certainly we'd need to be aware of and turn off the immune system so the colon can absorb water and do its job. Again, it can cause inflammation in the skin, immune reactions in the skin, and that causes an itchy rash, which no one likes. And we can use usually a steroid cream to a quiet down the immune system and help keep the treatment going and soothe the rash on the skin. And arthritis. Inflammation in the joints causes arthritis or pain, irritation and swelling in the joints, which is one of the more common things.

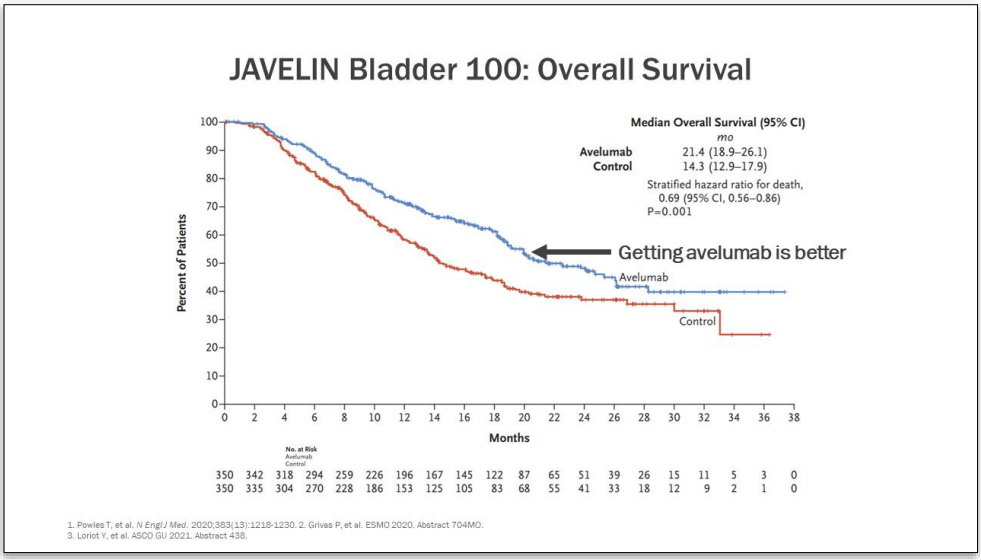
But in reality, the immune system is in the whole body and it can cause effects anywhere in the entire body. So it's important anytime you're on immunotherapy to tell your doctor if you're not feeling well, if there's anything going on, because the doctor can do a number of different tests or physical examination moves to understand what's going on with you and make sure that the immunotherapy is not causing a problem.

Dr. Morgans:

What if we combined chemotherapy and immunotherapy? This is one of the big advances I wanted to tell you about tonight, because this study called the JAVELIN Bladder 100 trial came out in about the last year and a half, and I think was one of the most impressive treatments for metastatic urothelial or bladder cancer that we've had in a long time. So all of the patients in this trial got chemotherapy. And that's one of the reasons that I, as a doctor, want to try to give chemotherapy to people. If there's even a remote possibility, I want to try to help them get through that chemo, because I want to use this JAVELIN approach with my patients.

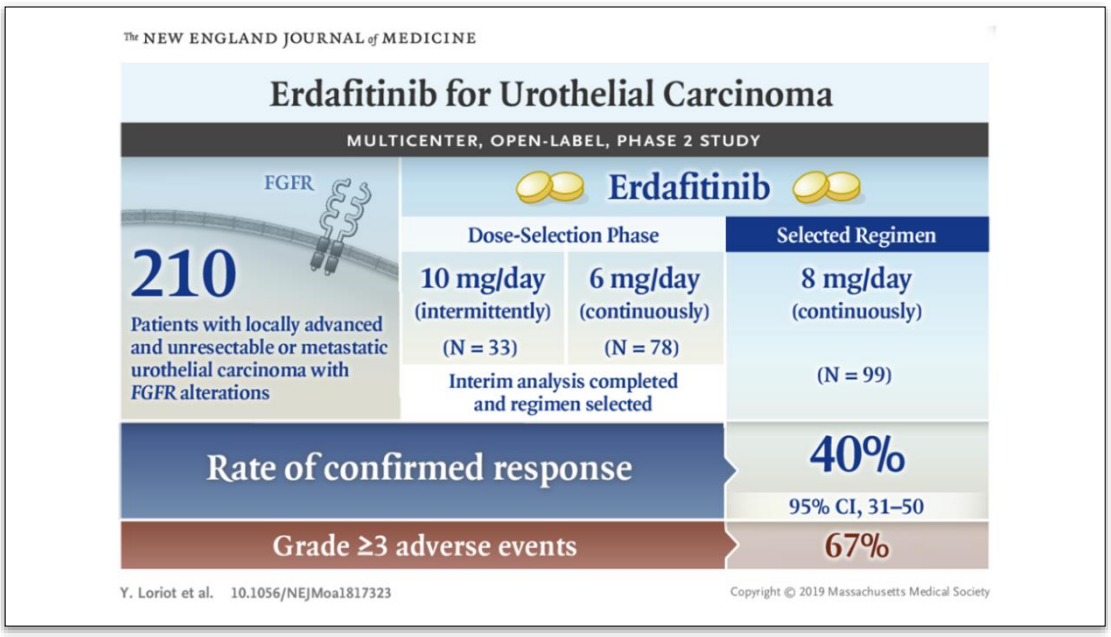


So they all got chemo. And as long as they had cancer, that had been stable, so no growth, no spread. Or if the tumor shrink, they could then get in this trial either avelumab, an immunotherapy every two weeks, or supportive care. So pain control and nutrition management and all the normal things that we do just to support people, but nothing directed against the cancer. And then the trial asked which group lives longer, which has a better survival? Here we have a survival curve. This is why I wanted to go through that with you to help make sure that everyone understood survival curves. And this survival curve is one of the most impressive that I've seen in metastatic bladder cancer in a long time. What it shows is a clear separation of those curves. And that means one treatment's better than the other. And in this case, avelumab, given every two weeks to patients after their chemotherapy help them live on average seven months longer. But it's not about the averages, it's about the tail of the curve and the way that this whole disease trajectory shifts.



So because an individual person is not an average, an individual person could be the tail on the curve, could be the most impressive responder, so this caused a huge separation of curves. It showed that, that treatment with avelumab was really helpful for people after their chemotherapy. And it reduced the risk

of death from urothelial cancer or bladder cancer by about 30%. So really, really impressive. 31% reduction in death, that's huge in this type of cancer. And we can see that around that median time, that 50% time people are living for years, which is really, really impressive as compared to people who only got the chemotherapy, which also those people did pretty well too, but avelumab helped them do even better.

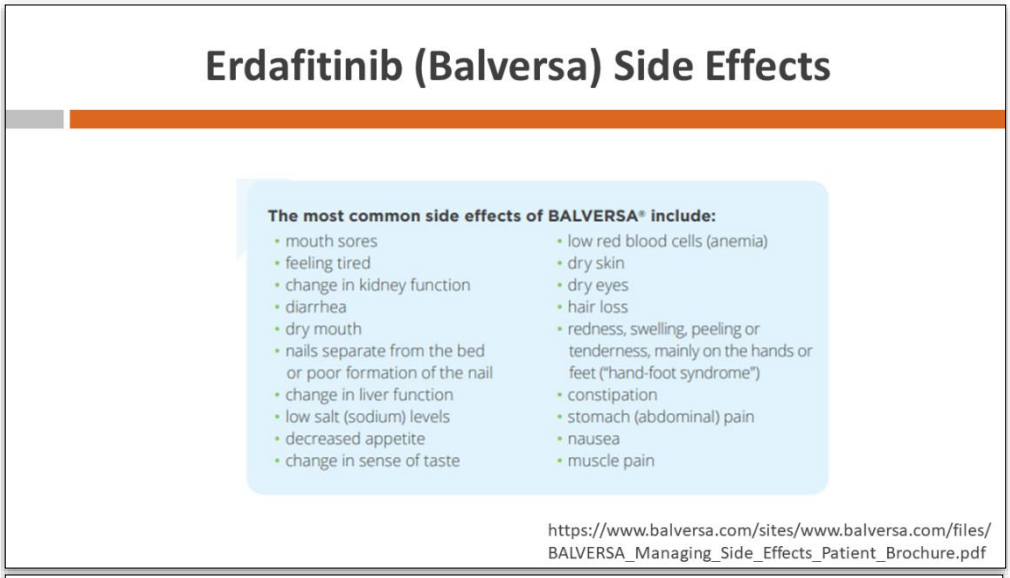


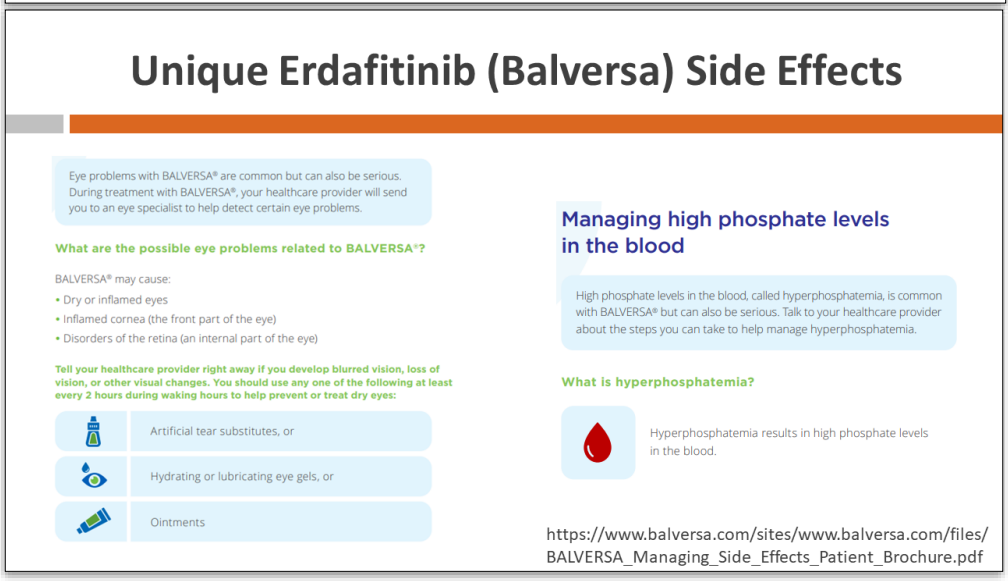
So let's move on a little bit to talk about a couple targeted therapies. And then I want to have some time for discussion. So erdafitinib is a pill. And this is actually a slide that was made for the New England Journal of Medicine, which is one of our top medical journals. This slide was made when the phase two trial, so a clinical trial of a test of erdafitinib was done in patients with urothelial or bladder cancer. They were looking at these pills, this oral therapy, that was targeting FGFR mutations. So these are mutations that we can only find by testing the DNA or the genetic material of the cancer cells. And your doctor knows how to do this testing. And if we do this testing and we find these particular mutations, we can use erdafitinib as a targeted treatment.

Targeted treatments are nice, because they hopefully have most of their effect against the cancer cells that have this genetic mutation, because the person shouldn't have the genetic mutation, only the cancer. Now, of course, they have their own side effects, but the majority of effect is supposed to be against the cancer. And the patients that I've treated with erdafitinib have done well, but we, of course, need to watch out for certain side effects. But this is a drug that was approved just in the last couple of years. It's a targeted treatment for metastatic urothelial cancer only used if we can identify the mutation in cancer cells. So important to talk to your doctor, both doing genetic testing for erdafitinib.

Dr. Morgans:

So there are some quirky side effects. These are the main and major side effects. The most common side effects for erdafitinib also called Balversa, things like mouth sores or feeling tired and sometimes blood count effects. These are very common for many of the things that we do. But for this particular drug, we also have to remember that there can be specific eye effects that are reversible, but we do need to work with an ophthalmologist to make sure that it's safe. And they monitor your vision and make sure that it's safe for you to continue to get this drug. If you do have any vision to changes, we stop the medicine. Typically, those are all reversible, but important to be monitored for the eyes.

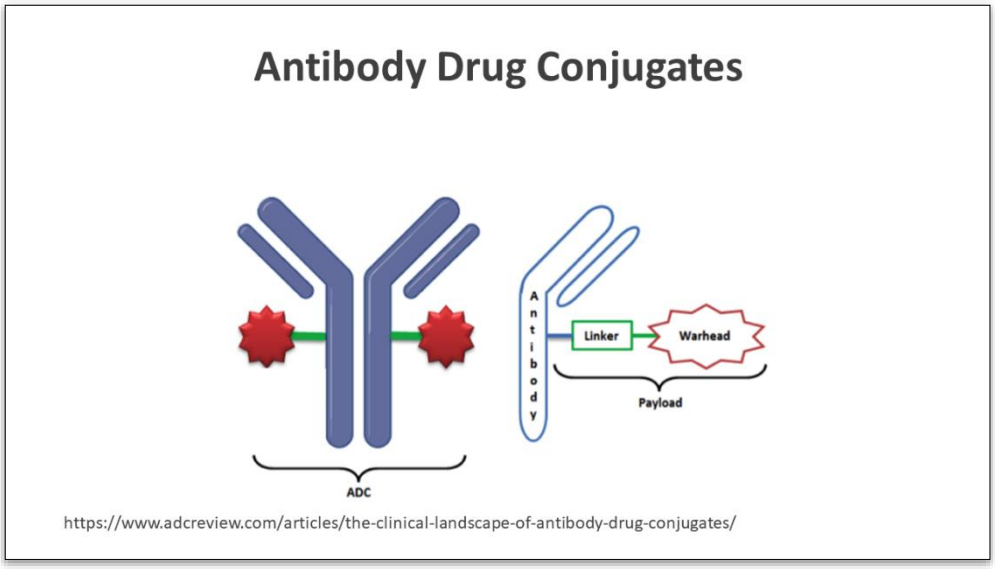




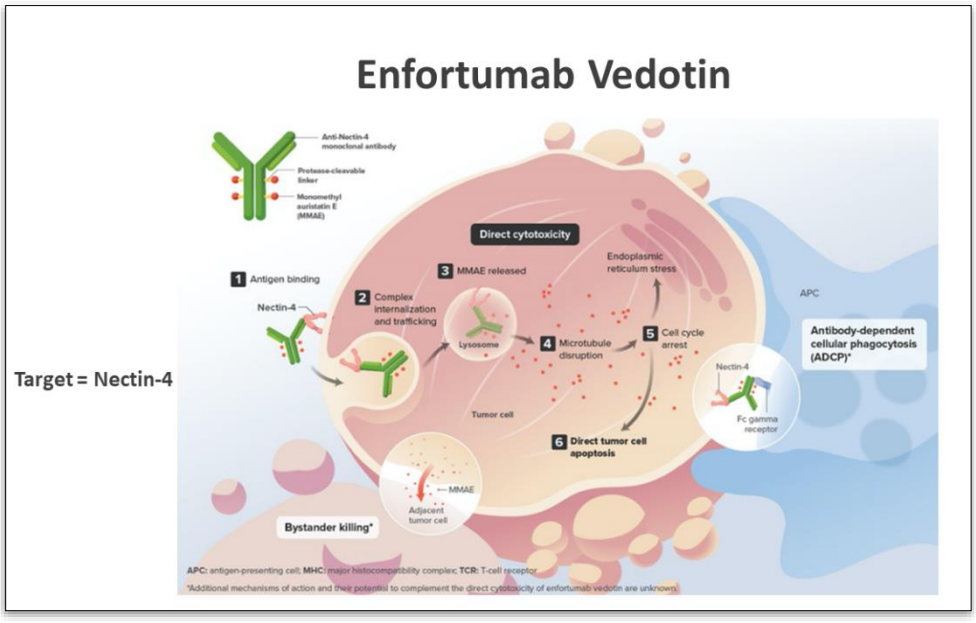
And the other thing that this particular drug can cause that's a little unique is high phosphate levels. And that can be affected by diets. So you usually would do diet changes to lower phosphate. And then also sometimes we can use medicines to lower phosphate two. But these are two unique symptoms or side effects of Balversa or erdafitinib that we just need to be aware of as we move forward and use this targeted treatment, which is highly effective.

Dr. Morgans:

There's a whole other class that I want to mention. It's a targeted treatment that you need to be aware of if you're thinking about metastatic bladder cancer. And this group of therapies is called antibody drug conjugates. Sounds very complex, but let me break it down. So the first part is the antibody part. That's the Y part on this particular picture that you can see. And that why part binds to a very specific protein on a cancer cell, and is targeted to that cancer cell because of the Y, the way that the Y binds. And that is very specific and important. That's one of the most important parts of this drug. Then the antibody drug conjugate has a linker, which is basically just a connector to what they call on this particular diagram a warhead, where it's essentially the treatment, the thing that will kill the cancer cell. And it's indicated by the red, that red warhead or that red floret on this picture.

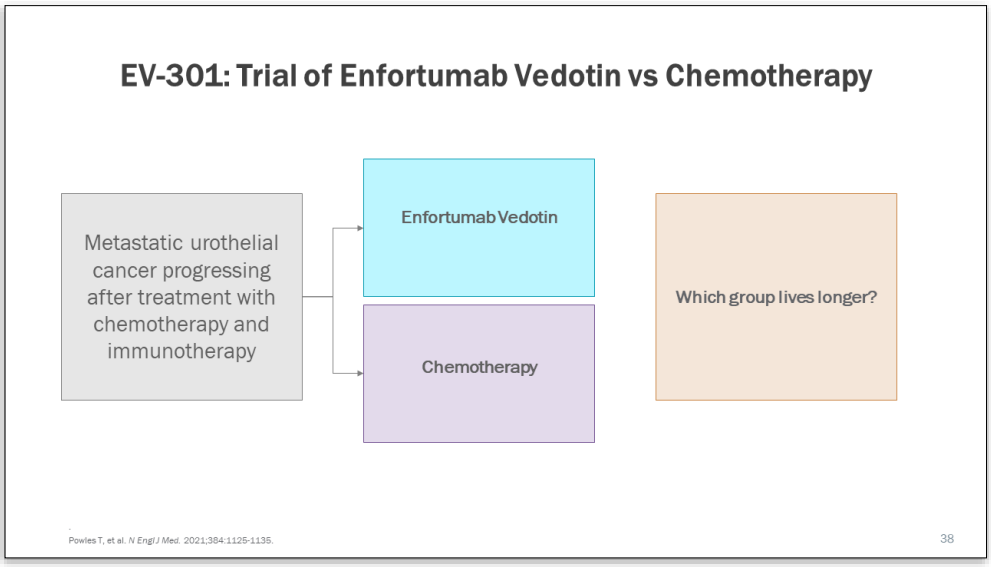


So essentially what this drug approach is, is trying to use its very targeted antibody Y linked to a certain protein that's hopefully mostly just on the cancer cell and deliver it's very potent, either chemotherapy or targeted drug right there and dump all of that toxic stuff right on the cancer cell, kill the cancer cell and leave the rest of the body basically, hopefully untouched. So one of these is enfortumab vedotin, and this is the one that's farther along in development, really effective treatment. And we'll talk about that in just a moment. It's target, it's antibody Y is targeting a particular protein called nectin-4. And you can see in the diagram here, that's an anti nectin-4 antibody. So the Y tries to get to this protein called nectin-4. And when it gets there, it's dumping a really nasty chemo right on top of it called MMAE.

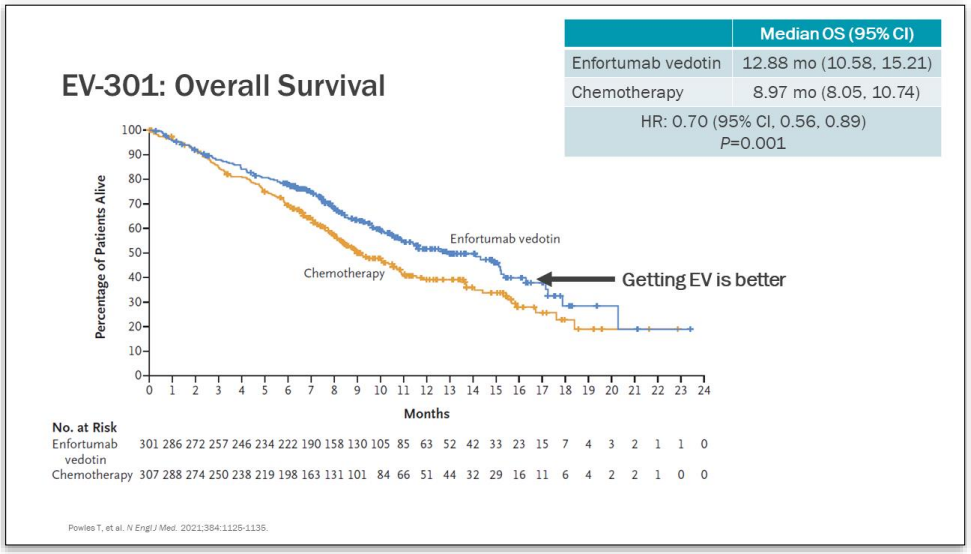


And that chemo is so potent that we would not want to give it to a person without that

targeting, because it can really damage the cells. And it does. And it's really importantly damaging those cancer cells and hopefully not the person. And I've treated many people with this particular treatment and it's highly effective. And people even in their 80s and who have other medical problems, can get this treatment safely. But it's important to be monitored, of course, with a doctor that it's been in advance. I think that's been very transformative in this field.



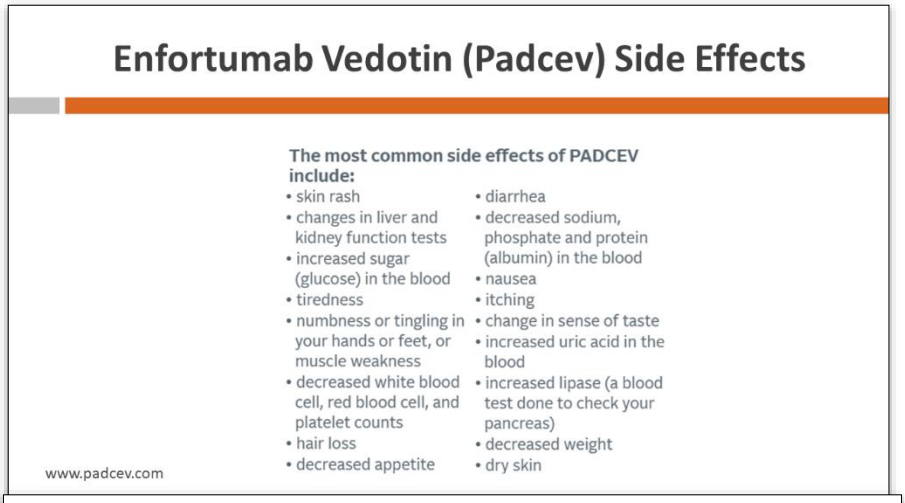
So this is a schematic of a trial that recently has been presented looking at enfortumab vedotin. This included, on the left, you can see people who have metastatic bladder cancer that's growing after chemotherapy and immunotherapy. So the two other treatment approaches that I showed you earlier. And people got either enfortumab vedotin or another different chemotherapy. And the study asks which group lives longer, which group is going to do better. And here we have another survival curve. So we get another test of our ability to read these survival curves. And you could see separation of curves means that one group is doing better. And the group that's doing better is the group that got the enfortumab vedotin by a lot. 30% reduction in death when they were treated with enfortumab vedotin versus a different chemotherapy.

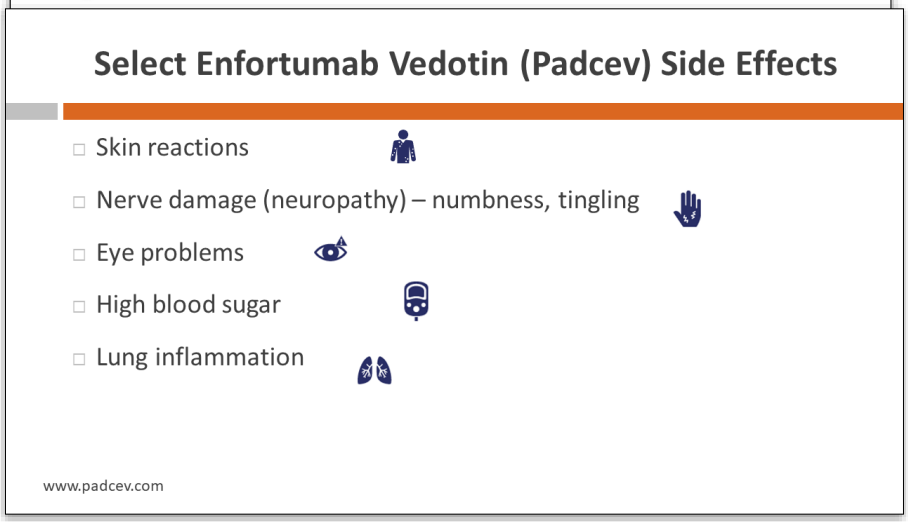


And really this beautiful big separation of curves demonstrates that there's actually nice and strong advantage to that treatment within enfortumab vedotin, that antibody drug conjugate as compared to the older chemotherapy options that we had. And this is, of course, in a group of people who had already had chemotherapy in the past. So it's not the chemos that I've talked about, the cisplatin and a carboplatin, these are different second and third line chemos that we might use if the other chemos no longer are working. But this is really, really important, I think will be something that we think about as we move forward a lot.

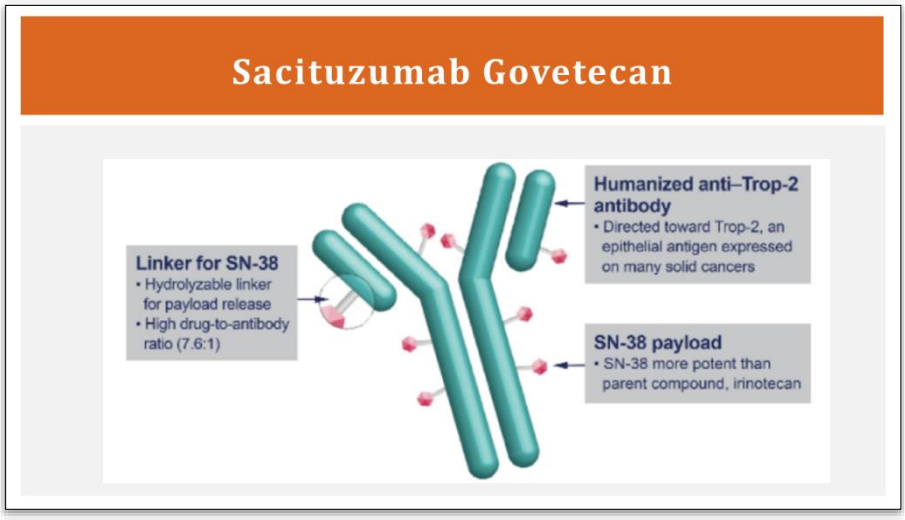
Dr. Morgans:

So enfortumab vedotin is also called Padcev. And some of the most common side effects that, of course, we should review here, include things like skin rash, it can include some high blood sugar and some other complications. But generally these are very similar complications to regular chemotherapy. But the ones I want to mention, just so that we're all aware are some more potent skin reactions that your doctor needs to watch for some pretty significant neuropathy that numbness and tingling in the longest nerves in the body, in the fingers in the toes, sometimes eye problems, though not as commonly as erdafitinib, high blood sugar, which is a unique thing about this and inflammation in the lungs, a little bit of cough. So important that a doctor is monitoring and watching, but generally quite a safe treatment under a doctor's supervision.





And finally, we'll talk about sacituzumab govitecan, another mouthful, but another antibody drug conjugate. This one is targeting against a protein on the cancer cell surface called trop-2. And it hones there and it binds the trop-2 and it dumps something called SN-38, which is something very similar to irinotecan, which is a chemo that we use in some other situations and other cancers. And when that irinotecan is targeted to the cancer and dumped there, it can help people live longer, it could help them feel better. But, of course, it has side effects that we'll talk about in a second. This drug is also approved for patients with breast cancer. So not just used in urothelial carcinoma.



So it's also called Trodelvy. And so these are the side effects that we can think about. Things like diarrhea are some of the more common effects. And that's very common, because irinotecan, we know as a chemotherapy causes that. And so we use antidiarrhea medicines to help resolve that diarrhea. We

can also cause blood count issues, some nausea, but generally people feel okay when they're on this medicine. And again, it's also used for people with breast cancer. So is something that has been tried in other cancer populations and can help people live longer, not just in urothelial carcinoma, but also in breast cancer.

There are multiple other trials that are going on, trials that are looking at things like enfortumab vedotin plus immunotherapy or sacituzumab govitecan plus immunotherapy or different immunotherapy drugs, nivolumab and ipilimumab used together, as well as multiple other approaches. These are just a couple. So it's important, I think for all of us to recognize that even though this is not a disease that we can cure, it's disease that we are attacking from every front and using every bit of technology and brainpower that we have to make a difference and really help people live longer.

So in summary, I know I've talked for a long time, metastatic bladder cancer is less common than non muscle invasive and muscle invasive bladder cancer. That's the earlier stage bladder cancer, and it's not curable, but it is highly treatable. And treatment advances are giving us more options and more hope every single day for patients. And I really appreciate the time that you spent here. And I am looking forward to answering some questions. So thank you. And it looks like Stephanie's back to ask some of those questions.