Stephanie Chisolm:

Hello and welcome to Advances in Muscle Invasive and Metastatic Bladder Cancer: Past, Present and Future Directions. I begin today's program by thanking the sponsors of our Patient Insight webinar series, Merck and UroGen. Today's topic is about advances in muscle invasive and metastatic bladder cancer, and BCAN started in 2005 when Diane and John Quale were really amazed at how limited the treatment options were back then. So we are now 19 years old. And they really were kind of taken aback by the inadequate research funding to find new ways to treat bladder cancer.

And I'm really happy to say that in the past 10 years or so, the landscape for bladder cancer patients has significantly changed, and I'm really delighted to welcome Dr. Tyler Stewart, a medical oncologist from the University of California San Diego Health, to share an overview of the treatment and research landscape since we started almost 20 years ago.

Dr. Stewart is a genitourinary medical oncologist and researcher. As an assistant professor of medicine at the University of California San Diego, his research focuses on clinical trials, translational studies, and urologic malignancies, with a special focus on bladder and upper tract cancer. He serves as a principal investigator for trials investigating novel therapeutics for advanced and locally advanced urothelial carcinoma, and he also serves as a principal investigator for studies investigating novel biomarkers in plasma and urine to detect minimal residual disease for genitourinary malignancies.

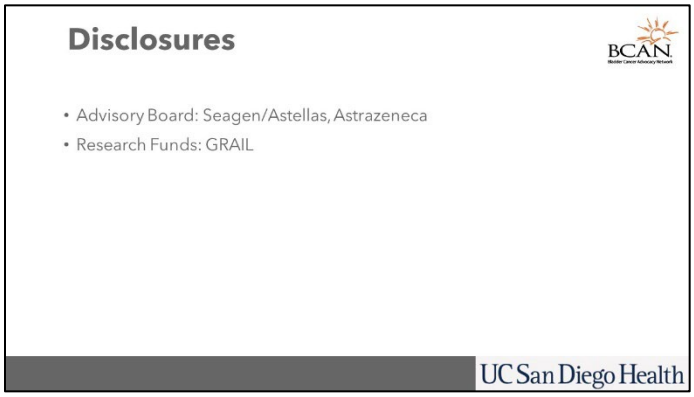
Dr. Stewart has published extensively on urinary malignancies and is an active member of the Alliance for Clinical Trials in Oncology cooperative group. And in addition to that, he currently sits on the NCCN, the National Comprehensive Cancer Network guidelines panel for bladder and penile cancer. I'm now going to turn your attention to Dr. Stewart for his presentation about

advances in bladder cancer. So Dr. Stewart, if you'd like to share your slides, welcome. It's a pleasure to have you here.

Dr. Tyler Stewart:

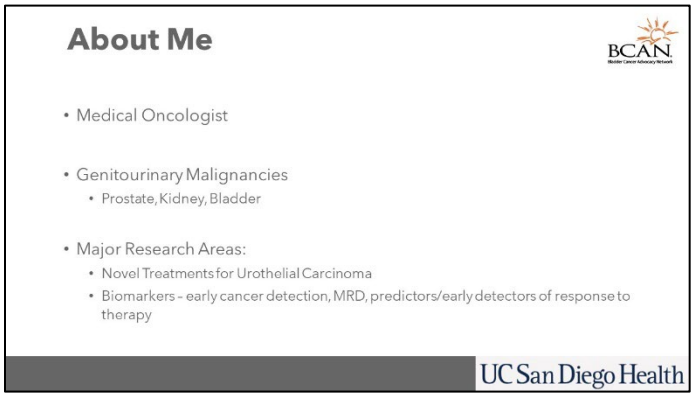
So thanks so much for having me and thanks for the whole BCAN community for coming out to this webinar. Really an honor to be here. As you know, BCAN has been such a great network for patients, and family members, and loved ones of patients with bladder cancer that I really feel honored to be part of this program series. Today I'm going to talk about advances in muscle invasive and metastatic bladder cancer.

Dr. Tyler Stewart:



Here are a couple of disclosures.

Dr. Tyler Stewart:

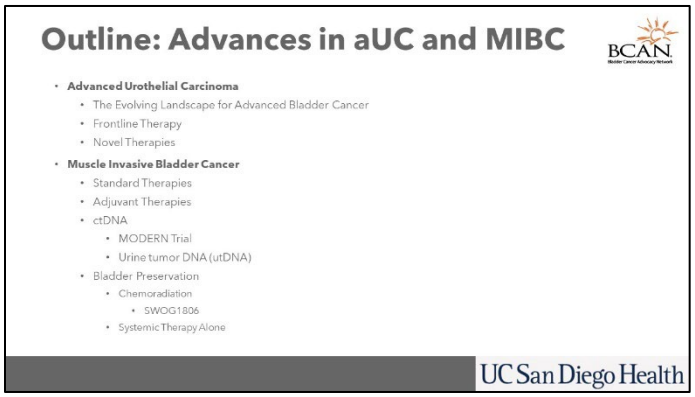


So a little bit about me.

So I am a medical oncologist here at UC San Diego, and I do general urinary malignancies, which means that I treat mostly patients with prostate cancer, kidney cancer, really my specialty and area focus is bladder cancer.

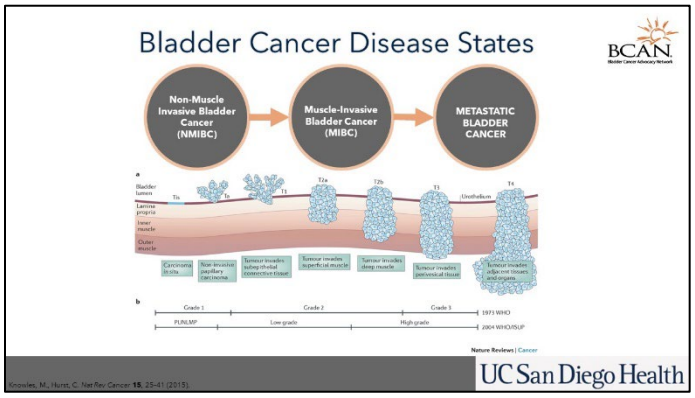
My research is, as you said, Stephanie, in novel treatments for urothelial carcinoma and then biomarkers really for early cancer detection, minimal residual disease and predictors, and early detectors of response for therapy.

Dr. Tyler Stewart:



Today, we're going to talk about two major topics. We're going to talk about advances in advanced urothelial carcinoma and how the treatment has evolved, especially over that year of 2005 since BCAN's inception. And then really the treatment and standard treatment therapy is currently available for patients with muscle invasive bladder cancer, and really where the horizon is going for both of these fields.

Dr. Tyler Stewart:



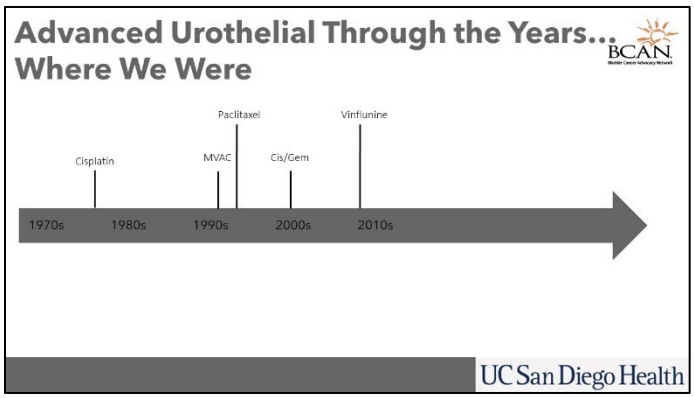
The first thing that you should know is that bladder cancer diseases, we treat these based on the disease state. So for many patients with bladder cancer, these may be very superficial, just really in the lining of the bladder, and nowhere else. And oftentimes, those might be treated with just surgery alone.

Once the disease gets into that muscle layer, it has an ability to then spread through the bloodstream. And so patients who have muscle invasive bladder cancer are at higher risk of the cancer spreading. And we certainly have to think about how we treat those patients a little bit differently than just resecting the tumor. In patients who have metastatic bladder cancer, what this means is the cancer started within the bladder or the upper tract, its upper tract disease, and then unfortunately is spread to another organ. And how we treat all of these is very different.

As a medical oncologist, my major role is to talk to patients about the systemic therapy options. So major providers that cancer bladder cancer include the urologists who do a lot of surgery, and oftentimes in the United States will do the intravesicular therapy. There are radiation doctors who may use radiation to treat bladder cancer, both for localized and metastatic disease.

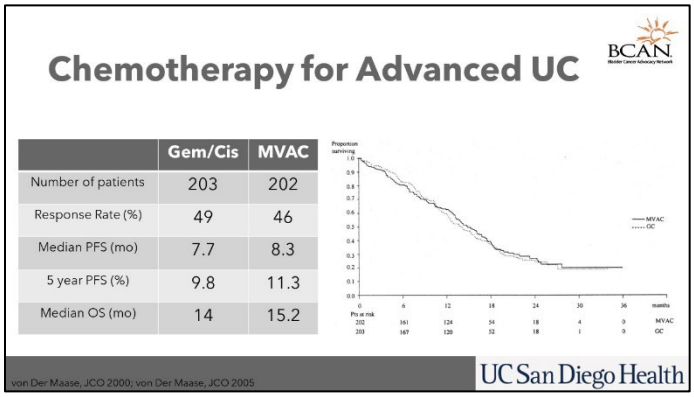
I, as a medical oncologist, specialize in treating patient patients with systemic therapies, which sound like chemotherapy, immunotherapy. And we're going to talk about a lot of these today.

Dr. Tyler Stewart:



Today, I'm excited to talk about where we were and mostly where we are going with advanced urothelial carcinoma. So what you can see here is that we have had chemotherapies throughout the years. And up until really the late 2000 teens, really the only treatments that we had for advanced urothelial carcinoma, meaning cancer that had started in the bladder and spread, was really just chemotherapy. So in the 1970s, we had cisplatin. Then we started combining chemotherapy agents together to treat patients with advanced disease.

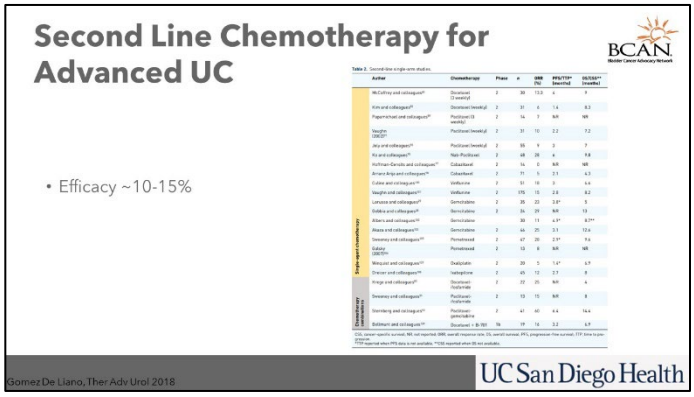
Dr. Tyler Stewart:



When we started out, what we started to do was combine chemotherapies together with really the backbone of using this medicine called cisplatin. And what we found out is that when we combine cisplatin with other agents, patients generally did better than the single agent.

In this study, they looked at two combinations of gemcitabine and cisplatin versus another regimen called MVAC, which is four chemotherapies. The important take-home point of this is that although many patients who have advanced cancer might respond around 50% of patients, oftentimes patients would only respond for the course of seven, eight months. And unfortunately, the vast majority of patients would progress, and ultimately that cancer could be fatal.

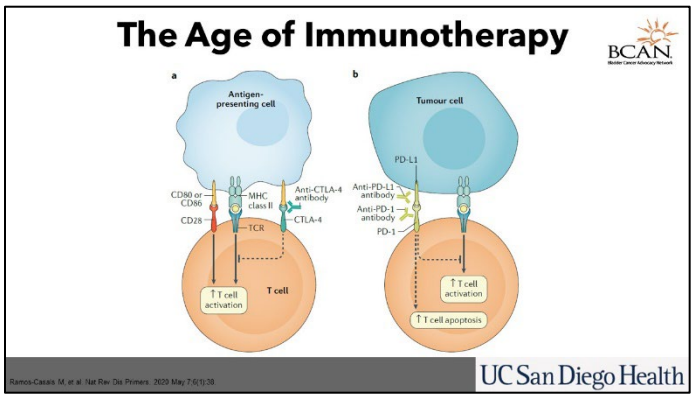
Dr. Tyler Stewart:



When those patients progress on chemotherapy, oftentimes we would think about using a second line chemotherapy agent. So many chemotherapies were studied. Unfortunately, chemotherapy after you've already had chemotherapy doesn't often work very well, with response rates only around 10 to 15%. Some patients may respond quite well to these for a limited amount of time. But what this really told

the field is that we need to do better. We need to find other treatment options other than just standard chemotherapy.

Dr. Tyler Stewart:

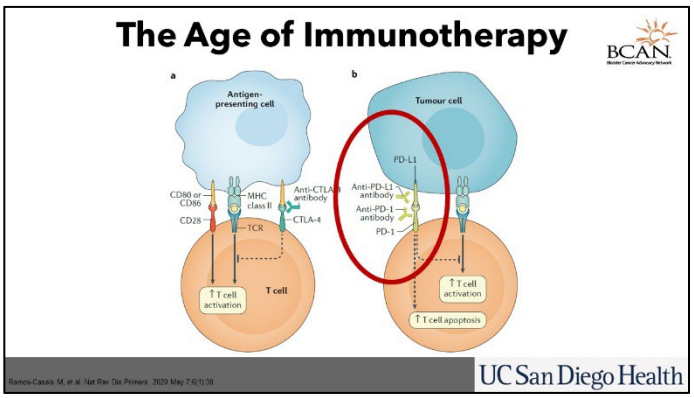


Enter the age of immunotherapy.

So in the 2000s and early 2010s, scientists started learning more about your immune system and how your immune system can attack and kill cancer, but then how cancer can put up camouflage signals called checkpoints, so immune checkpoints.

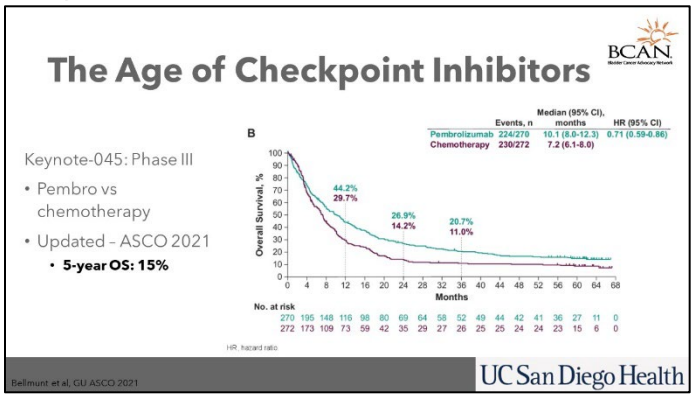
And so researchers started to say to ourselves, "Well, what happens if you get rid of those checkpoints, if you found a way to inhibit the inhibition of the immune system?"

Dr. Tyler Stewart:



The major focus was on this target of anti-PD-1 and anti-PD-L1. This is a signal that stops the immune system from attacking cancer. And so early in the 2000s and 2010s, studies started to come out in multiple cancers looking at these checkpoint inhibitors.

Dr. Tyler Stewart:

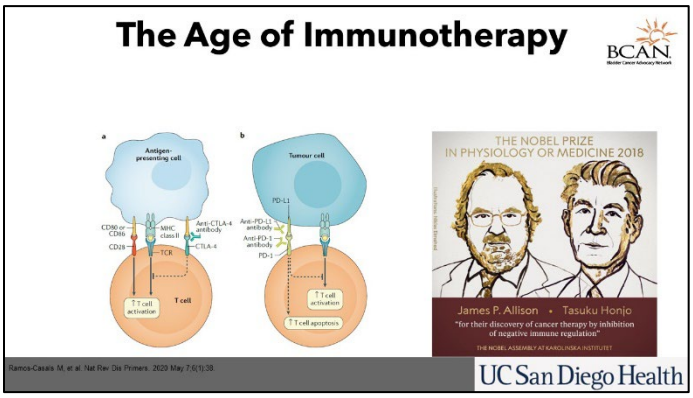


One of these checkpoint inhibitors, it's called pembrolizumab. And when this therapy was looked at for patients who have urothelial carcinoma, it looked like in patients who were treated with pembrolizumab, around 20, 25% of patients can respond to this. And unlike chemotherapy, when you had a response to this, it could last for a long time. In fact,

there have been patients who have been treated with checkpoint inhibitors that are alive many years now without any evidence of disease.

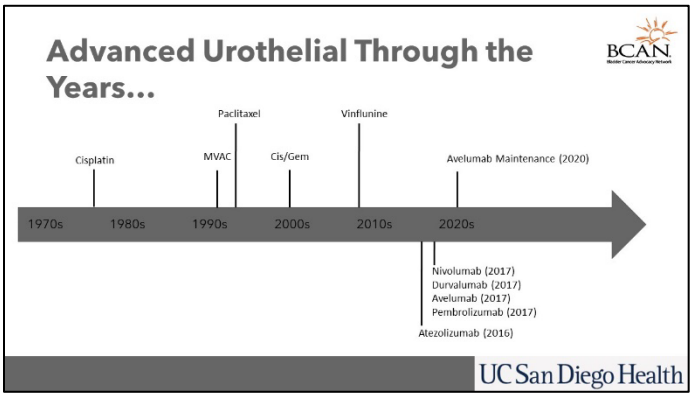
We then did studies looking at these checkpoint inhibitors comparing them to chemotherapy as second-line agents. And trial after trial showed that patients who were treated with checkpoint inhibitors had a response rate around 15, 20 to 25%, and when they responded, could do very well.

Dr. Tyler Stewart:



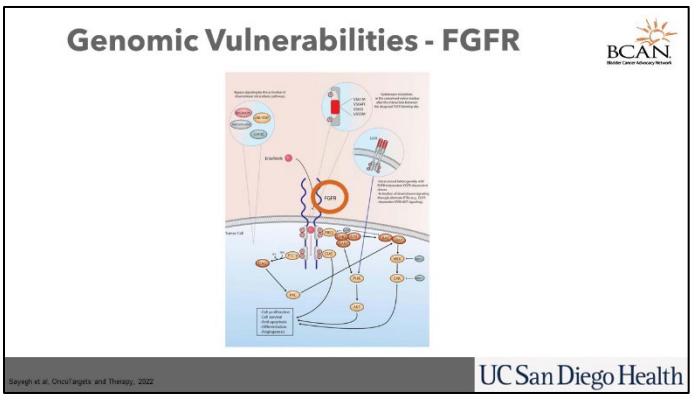
This work led to the two pioneers in this field of winning the Nobel Prize back in 2018 really revolutionizing cancer care. And for patients with bladder cancer, although not everyone responds to this, those who do sometimes can enjoy a very long time on treatment without their cancer progressing.

Dr. Tyler Stewart:



So during this time, at least five different checkpoint inhibitors were actually approved for advanced urothelial carcinoma. Some of those have actually been taken out for other reasons, but this was really the dawn of a new era for urothelial carcinoma.

Dr. Tyler Stewart:

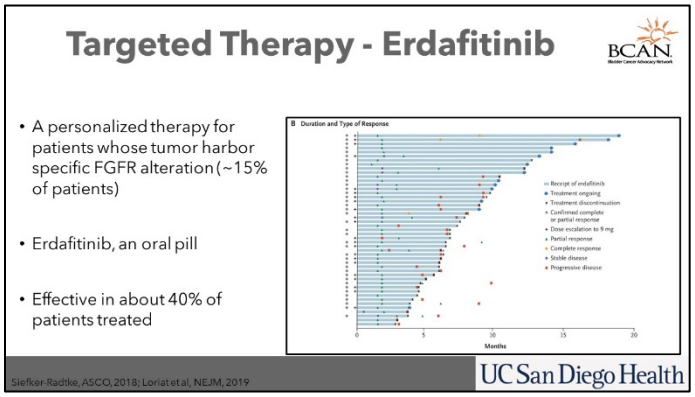


The next big leap for urothelial carcinoma was looking at genomic vulnerabilities. As the field of cancer research has evolved, we are oftentimes looking for how cancers are different than normal cells, and can we find something that's abnormal in a cancer cell where we can find a therapy for that?

And what we know is that patients with bladder cancer and upper tract urothelial carcinoma, they have alterations in something called FGFR. This is the FGFR receptor, oftentimes FGFR2 and 3, really FGFR3 is a major component.

This is very prevalent in patients who have localized disease, but we see mutations in FGFR around 15% of the time in patients with advanced disease. So then the thought was, "Well, in patients who have these alterations in FGFR, which make this receptor constitutively active, kind of always on, can we turn off the switch by adding some therapy that is an FGFR inhibitor?"

Dr. Tyler Stewart:

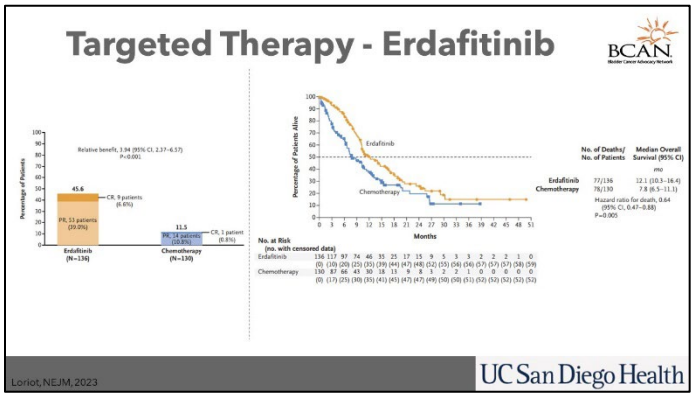


The first of these that really came through in the clinic was a drug called erdafitinib. This is a therapy that blocks FGFR and can work on patients who have FGFR alterations.

In studies and early studies, about 40% of patients who were treated with this, who had an FGFR alteration. Again, that's only around 15% of patients who have one of these. But of those patients who were treated, about 40% saw significant shrinkage.

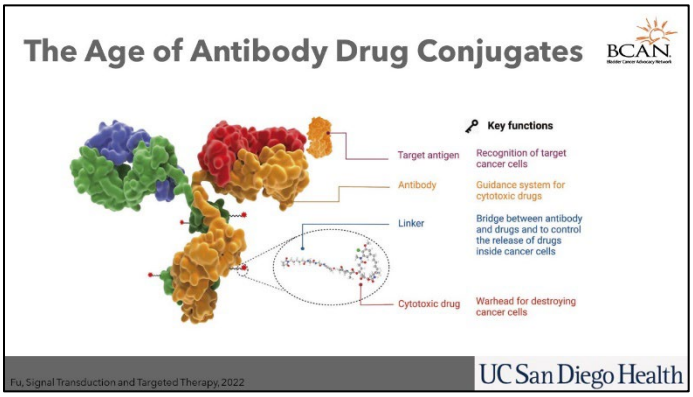
And for some of the patients who were treated with this therapy, which is an oral pill that you take once a day, this is a therapy that sometimes can work for a long time, many months.

Dr. Tyler Stewart:



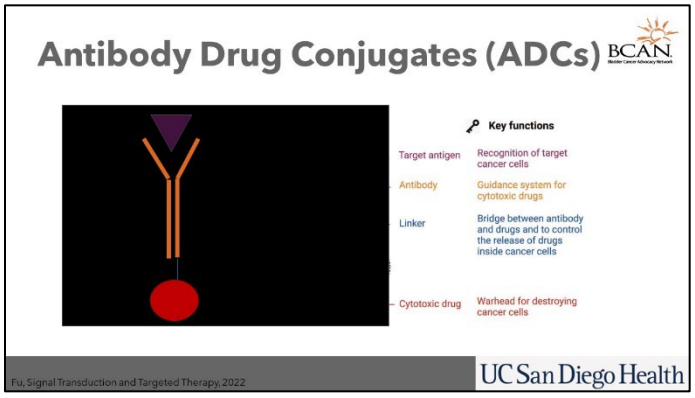
More recently, a trial underwent to compare that therapy versus getting that second line chemotherapy. And really, we saw significantly higher response rates, and patients overall did better, lived longer on this therapy. So like immunotherapy, really moving the field forward from just that second agent chemotherapy. Bringing new therapies, new weapons into our clinic.

Dr. Tyler Stewart:



The next big breakthrough that we've had in advanced urothelial carcinoma is really these antibody-drug conjugates. And these are the newest kid on the block, and we are still in the age of antibody-drug conjugates. Antibody-drug conjugates are this amalgam of ideas that have come together to create a very cool weapon against cancer.

Dr. Tyler Stewart:

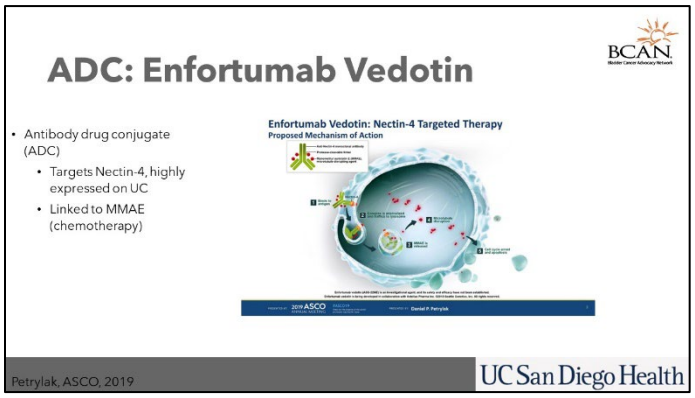


This is how I think about them. So antibody-drug conjugates are just an antibody that recognizes a specific target on cancer cells. It then has a little linker to chemotherapy.

So the idea is that this medicine gets into your system usually by an IV infusion, goes throughout the body. And if it finds an area that is abnormal that signals a cancer cell, it latches onto it, oftentimes will get absorbed into the cell, and then releases its chemotherapy, kind of boom goes the dynamite.

A heat-seeking missile for cancer therapy and antibody-drug conjugates have been studied in many cancers and bladder cancer is not unique. But let's take a look at the data for what therapies have been investigated.

Dr. Tyler Stewart:

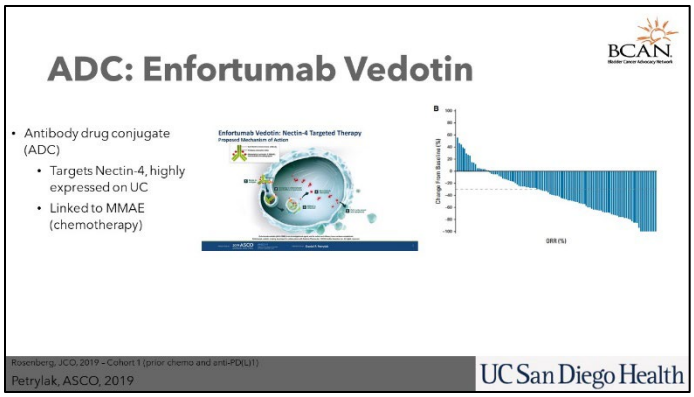


The first of these drugs that really hit the scene was something called enfortumab vedotin. So enfortumab vedotin is an antibody-drug conjugate that targets nectin-4, which is highly expressed on urothelial cancer cells.

The antibody has something called MMAE, which is a type of chemotherapy that's linked onto it. And again, the idea here is the antibody finds this target, this nectin-4

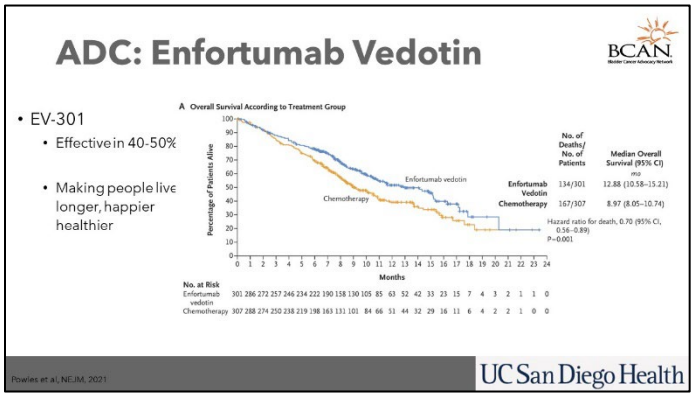
and gets absorbed into the cell. The linker breaks off, and then boom, chemotherapy is released and the cancer cell dies. So it's a great theory, but how did it work out in the clinic?

Dr. Tyler Stewart:



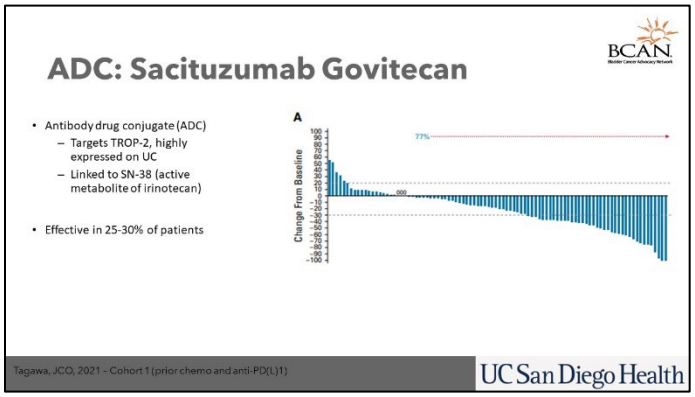
Well, it started to work out really well. When this drug first came on the scene in early phase studies, we saw response rates of around 40 to 50% of patients. Which compared to 10 to 15%, this was really a big breakthrough, and some patients really had these dramatic responses.

Dr. Tyler Stewart:



This drug was also compared against chemotherapy in large randomized studies. And what we found again was that 40 to 50% of patients had significant shrinkage. And compared to chemotherapy alone, patients who received enfortumab vedotin lived longer, happier, healthier lives, which is certainly a great tool to have in our toolkit when we're thinking about treating patients who have advanced urothelial carcinoma.

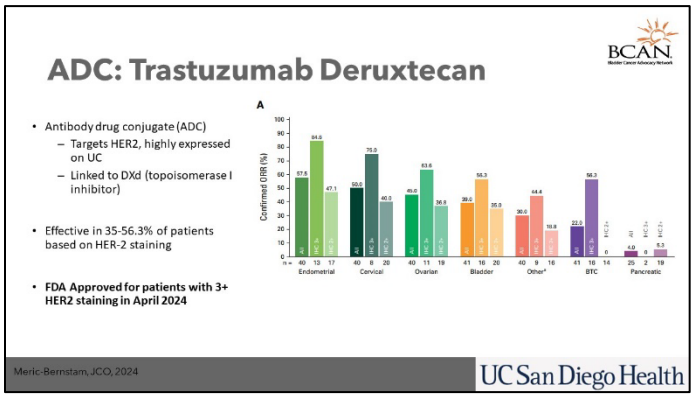
Dr. Tyler Stewart:



Another antibody-drug conjugate that is on the scene, something called sacituzumab govitecan. So similar to enfortumab vedotin, this is an antibody-drug conjugate. But now the target is a little different. It's called Trop-2, and the chemotherapy is a little bit different.

In early phase studies, this has an efficacy rate of shrinking the tumor significantly around 25 to 30% of the time, which looks pretty good in comparison to historic rates of how chemotherapy did. There are ongoing larger studies that are evaluating this versus standard of care.

Dr. Tyler Stewart:

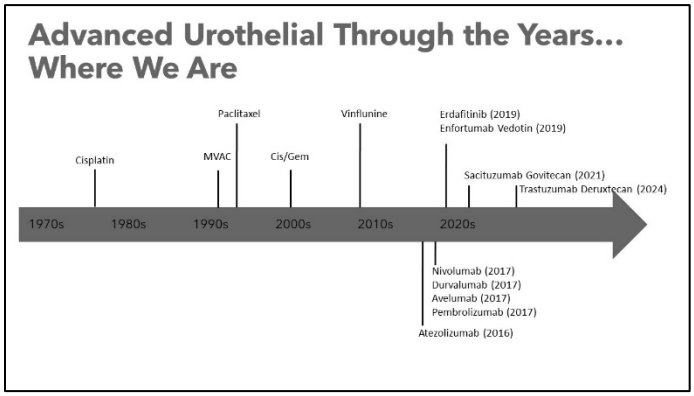


The newest kid on the block is trastuzumab deruxtecan. So similar to the last two, here, our target is HER2 instead of nectin-4 or Trop-2. Now we're targeting something called HER2, which is highly expressed on some urothelial carcinoma.

In this study that was done, which looked at this agent against multiple cancer types, in the patients who have bladder cancer, they looked at patients where their HER2 expression was very high, meaning they had this signal on a lot of their cancer cells. And in patients where the signal was the highest, that three plus range, 56% of the patients responded.

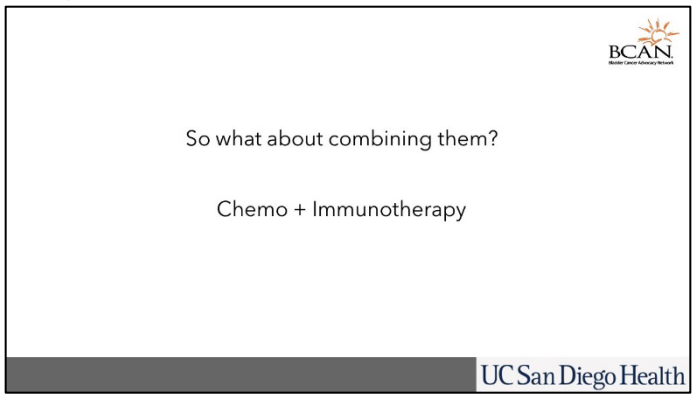
And based on that, just a couple of months ago, the FDA actually approved trastuzumab deruxtecan for many cancers that express HER2 at high rates, including bladder cancer. And now this is in our armamentarium. And now I've been able to treat some patients with this agent.

Dr. Tyler Stewart:



So this is where we were with just immunotherapy, and now we have even more therapies that are at our disposal.

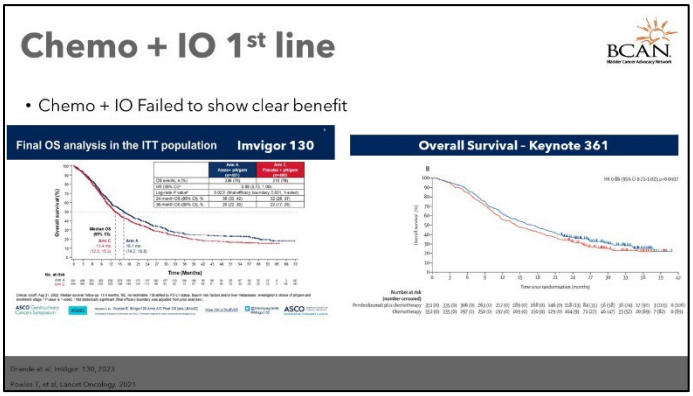
Dr. Tyler Stewart:



When oncologists start seeing drugs that are working pretty well, we start asking ourselves, should we combine these? Can we get a better effect if I add a couple agents together, trying to get rid of all of that cancer? Which is our ultimate goal?

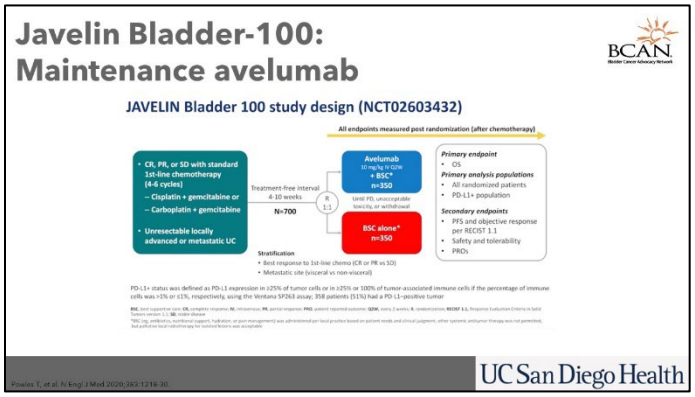
The first thing that we try to do is do something like chemotherapy plus immunotherapy. Well, chemotherapy works sometimes and immunotherapy works sometimes. Let's put them together and see how we do.

Dr. Tyler Stewart:



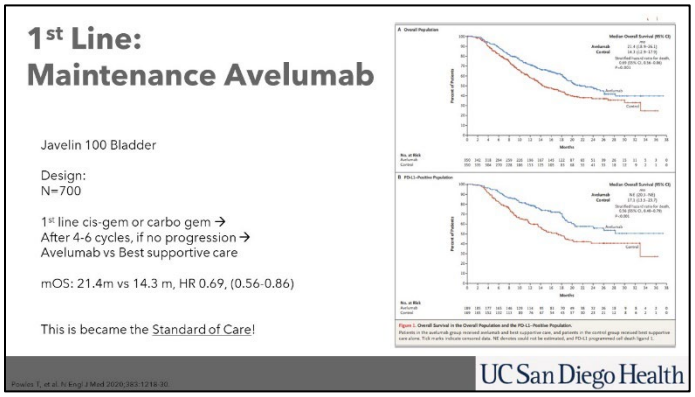
So it turns out that when we started doing this in big studies called IMvigor and Keynote, it didn't seem to work. Compared to chemotherapy, those who got chemotherapy plus immunotherapy didn't seem to be doing especially better, which was a real shock and real disappointment to the field. So then we had a little bit of a different idea.

Dr. Tyler Stewart:



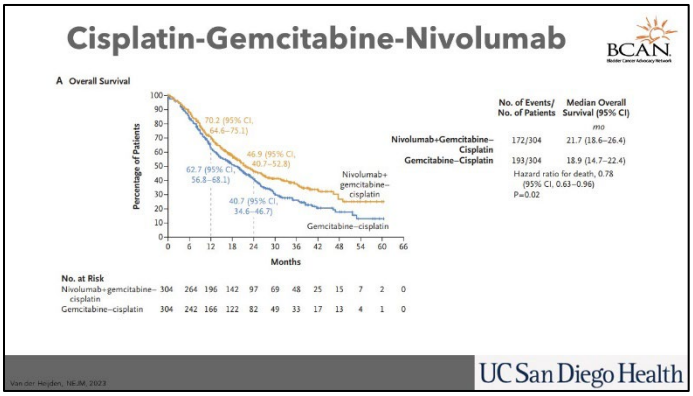
So in the JAVELIN Bladder study, we actually took patients who got chemotherapy, had a response, or at least their cancer didn't seem to be getting worse. And then we randomized to just watching them and waiting until their cancer progressed and then giving them immunotherapy or giving them an immunotherapy right away. And this immunotherapy was called avelumab.

Dr. Tyler Stewart:



In this study, the patients who received avelumab right away instead of waiting until their cancer got worse, did significantly better. And up until last year, this was really the standard of care for how we treat patients with advanced urothelial carcinoma. So chemotherapy, get the cancer under control. And then right away, give them some immunotherapy while they're waiting.

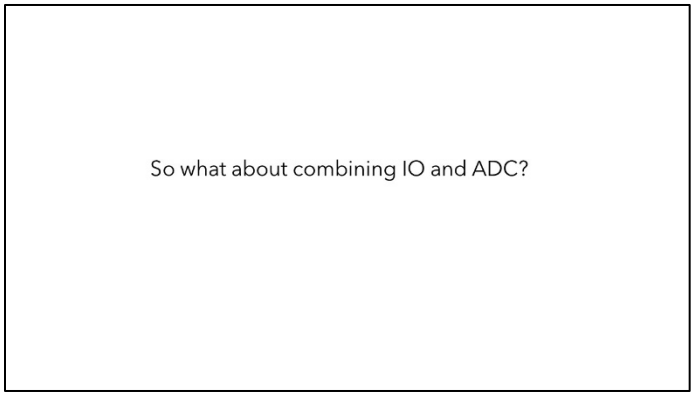
Dr. Tyler Stewart:



More recently, another study came out looking at combination of cisplatin, gemcitabine, and nivolumab, another checkpoint inhibitor, versus cisplatin and gemcitabine alone.

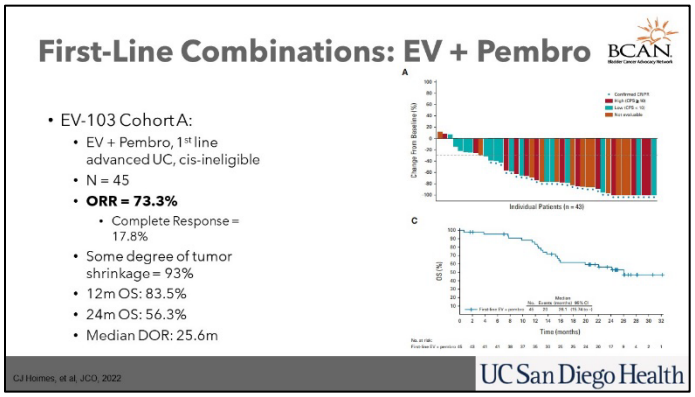
And unlike the first two trials where the combination of chemo plus immunotherapy didn't seem to work, this one seemed to work. Some of us think it's because the chemotherapy agents here were limited to cisplatin instead of another agent called carboplatin. But clearly, patients who were getting cisplatin and gemcitabine, if they got nivolumab as well, those patients seem to be doing much better and lived longer. And as of recently, this triplet combination is approved to treat patients with advanced urothelial carcinoma.

Dr. Tyler Stewart:



But what about those other drugs that we were talking about, those antibody-drug conjugates? What if we combine those with immune therapies? Could we be doing any better? So this was a really sought-after question that we were all interested in.

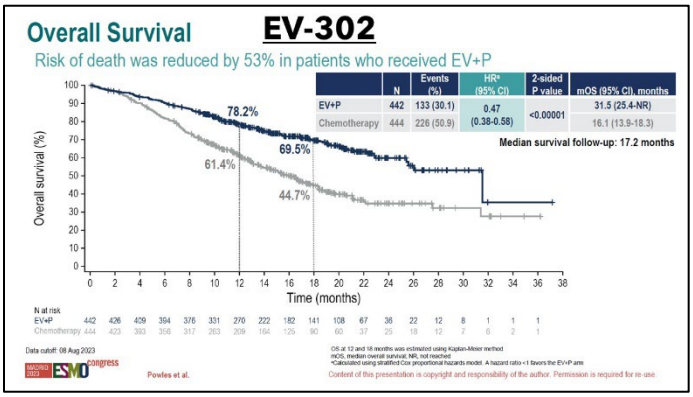
Dr. Tyler Stewart:



So in early studies, what we did is we combined that in drug called enfortumab vedotin and pembrolizumab. And in the original study that was done with 45 patients, what we saw is that when patients got enfortumab vedotin and pembrolizumab, 73% of patients had significant shrinkage, with 18% of patients showing their scans after their treatment showed no evidence of cancer. Now, that doesn't mean that all those patients were

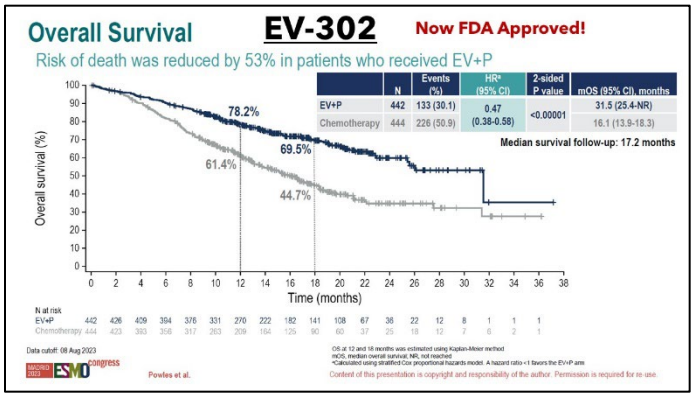
cured of cancer, but this is a huge, huge number. When we saw this, we, who treat patients with bladder cancer, very excited and said, "We have got to study this in bigger numbers."

Dr. Tyler Stewart:



Last year, a major study was released that really changed the landscape for advanced urothelial carcinoma. And this study was called EV-302, where patients were randomized to get chemotherapy or enfortumab vedotin (EV) plus pembrolizumab, the combination that we just looked at. And in this study, the combination of EV plus pembrolizumab, the patients who received this did significantly better, really setting the standard as this is the new frontline treatment for advanced urothelial carcinoma.

Dr. Tyler Stewart:



And as of December of last year, this is now FDA approved, and really my standard treatment for patients who come in and have advanced disease.

I will say as a medical oncologist who treats patients with advanced urothelial carcinoma, I am so happy to see this field move forward. But we are just not done yet. We have so much to do here. So this is a huge leap forward, but we still have a lot of work to do trying to increase the length of survival and really aiming towards cures.