Stephanie Chisolm:

Thank you so much, Dr. Stewart. That was a phenomenal presentation absolutely. So you mentioned a number of different things. And I know it wasn't just pulling alphabets together in different combinations, but FGFR, nectin-4, HER2, those are all genetic mutations and changes in the genes, right?

Dr. Tyler Stewart:

Well, oftentimes what these are, so some things are genomic mutations, and sometimes they are markers on a cancer cell that are just more frequently seen on that cancer cell than normal tissue. For instance, in FGFR, this is a mutation that happens within the genome of somebody with cancer. And so this is not a normal mutation that we see.

And what we know about it is that 50, 60% of patients who have localized cancers might have one of these. And the patients with advanced disease, probably 15% of patients do. And these therapies that block FGFR can be effective for those who have these genomic alterations.

Meanwhile, for the other ABC word salad stuff that I mentioned, this nectin-4, HER2, Trop-2, what these are, these are little proteins that sit on cancer cell surfaces that are more prevalent on cancer cell surfaces than on normal tissue, and can serve as targets for our targeted therapy. So we can make drugs that seek out these targets and then hook a chemotherapy onto that drug. As soon as it hits that target, releases that chemotherapy, kills some cancer.

Stephanie Chisolm:

So how do you know if you have all of these weird little bits that might be attached to your tumor? Is this something that is standardly done in all institutions? Do they take a look for these things, or is this something that has to be done separately? And maybe if you want to stop your screen share, your picture will show up a little bit bigger, unless you need your slides again.

Dr. Tyler Stewart:

No, I'm all set. Thank you so much.

Stephanie Chisolm:

Okay-

Dr. Tyler Stewart:

Great question-

Stephanie Chisolm:

Really find this out. Yeah.

Dr. Tyler Stewart:

So a couple of things. Some of these things you need to do special testing. Some of them are so ubiquitous that the therapies are likely to work no matter what. So let's take FGFR for example. So for this study, we can actually take somebody's tumor, send it off for analysis, and see if they have one of these genomic mutations.

The other way we can find that out is actually using that same circulating tumor DNA thing that I talked about where we can isolate that cancer DNA in the blood and see if they have one of these mutations present.

So for patients who come to us, we actually do genomic sequencing on all patients with advanced disease. This is not necessarily a mutation that you are born with. It's something oftentimes that is acquired over time, although there are some cancers that are associated with that familial history and some mutations in bladder cancer. That's a very low prevalence, fortunately.

But these are acquired over time. There's nothing that you did, or you didn't eat something that maybe... This is just bad luck that it happens. But when it happens and a cancer is formed, sometimes we can find a target.

For some of these other ones, that enfortumab vedotin and the Trop-2, actually the nectin-4 and Trop-2 are highly expressed on urothelial carcinoma, that we don't actually even test for these. We just use these drugs, and there's not a test that we do first to see if you're more or less likely to respond, at least not right now.

That's a little bit different than one of these tests. So one of these tests, that HER2 one that just came out, that's a drug where we actually stain your cancer. So we take a slide of your tumor, we stain it for something called HER2 to see how much of it is around, because it seems like the more of that HER2 that's around, the more likely that patient is to derive benefit from that drug.

Stephanie Chisolm:

So a lot of these different treatments like the immunotherapies and some of the antibody-drug conjugates, I mean they work really well when they work, but they also have what we call adverse events, or in common terms, they're known as side effects. People know them as side effects. So

what are some of the common things that people should be aware of? And why when you're on some of these treatments, could maybe a touch of diarrhea be more than you think it is?

Dr. Tyler Stewart:

Yeah. So it's a great, great point. Back in the day when we just had chemotherapy, I think people had a real clear idea about what chemotherapy might do. It might make you more at risk for infections, it might give you some nausea, vomiting, diarrhea. Might drop your blood counts, might make you more tired. That is absolutely true.

And the truth about chemotherapy is that those drugs from the... We still use those today, but so many of our supportive therapies are so much better than they were in the 1990s. In drugs that make people feel very, very nauseous, many patients actually do very, very well with the drugs and supportive therapy that we have now. Many patients who might get drugs that should make them very, very nauseous actually do very well on chemotherapy now just because of all the other medicines that we can use.

The new drugs that we have are very different. So first off, immunotherapy works totally different than chemotherapy and the side effects are totally different. So sometimes, what happens with immunotherapy is that your immune system gets revved up, and then it starts attacking parts of your body that you don't want it to.

Now generally speaking, immunotherapy is a very well tolerated drug, and compared to chemotherapy, super well tolerated. But some patients who get immunotherapy can have significant side effects that really affects their quality of life and some can be severe. What I quote is around 20 30% of patients are going to have side effects that they're going to notice. About 10% of patients are going to have something serious where I might have to stop the medicine, and gives you something to dampen down your immune system. About 1% of patients could get very, very sick from this stuff, have to go to the hospital, or something along those lines.

That being said, immunotherapies, if you get one of these, they can work for a long time and provide really Lazarus effects. So certainly it's a great treatment option.

The antibody-drug conjugates are kind of like chemotherapy. They're kind of a mix. And so usually, the side effects are all about what is the chemotherapy that's linked, because a small amount of that drug is going to get released into the blood system and can cause some of those side effects. Sometimes those can make you feel tired, sometimes it can cause some numbness or tingling in your hands, sometimes can give you diarrhea, sometimes it can drop your blood counts.

So really, it's a complicated conversation and certainly one that patients should chat with their doctor about, about really what to expect. But I do want to make it very clear that the side effects are very different. And just because you may have known somebody who's gotten chemotherapy in the past, that doesn't mean that the side effects that that person had is going to be the side effects that you have or that your loved one has when they're receiving one of these new agents.

Stephanie Chisolm:

Yeah, I think there's a whole lot of great big unknowns. And I think that communication, both from the doctor's perspective to explain to patients what could be a possible side effect or adverse

event, but also the patient reminding the doctor, "Hey yeah, I've experienced some of this," because it might be nothing or it might be something, and the doctor can bring out a whole bunch of other tools to help take care of that. So I think it's really important to make sure that that communication is there.

Dr. Tyler Stewart:

So I might just emphasize, so I tell all my patients that I'm pretty good at treating the side effects. I really am, but I treat zero side effects that I don't know about. And so really it's all about that good communication, patients talking to me and let me know what's going on. There are those modifications. I mean, there are just a huge number of things that we can do as long as we know about it.

Stephanie Chisolm:

Absolutely. You have to tell your patients and they have to tell you, because you don't know. So this is really important. There were a couple of good questions that were submitted. Are there trials examining dose de-escalation for patients seeing pathological complete response with treatment by enfortumab vedotin and pembrolizumab?

Dr. Tyler Stewart:

Oh man, I don't know who to ask that. What an amazing question. We are absolutely looking into this. So what an amazing place that we can have a conversation about deescalating therapy for advanced urothelial carcinoma based on how good these drugs work.

But absolutely the answer is yes. We are currently in the works. I actually have a meeting tomorrow about this exact topic, about if somebody does very, very well on therapy, maybe we can drop the enfortumab vedotin and, just keep the immunotherapy going. We don't know the right answer here, but we are actively creating clinical trials that we need to investigate these questions.

These drugs, they have side effects. And if patients do extremely well, do they need to bear more side effects from it? An absolutely wonderful question. The answer is yes.

Stephanie Chisolm:

So we'd love to see more patients being in clinical trials. One of the things that I think is really important since BCAN started in 2005, there have been numerous, as you just saw, numerous advances in the treatment of bladder cancer. And that didn't come just because somebody smart was just thinking up stuff. They had to test it, they had to see if it worked or not, and you need people to do that.

So some people will do a clinical trial and some people will want to be in a clinical trial. And the thing about a clinical trial is it's not just a science experiment, but it's really looking at an investigational medicine and trying to understand how this new treatment is going to act in the real world. Right?

Dr. Tyler Stewart:

That's absolutely right. And just a couple of things about clinical trials, and I think these points are really important, so I'm going to take a second and just emphasize.

So we run clinical trials to ask the question, can we improve on the standard of care right now? Is there something that we can do that is better than what we normally do for patients with a specific cancer? Whether that's a novel treatment, or a change of dose of treatment, or supportive measures, or you name it. The reason to run a clinical trial is to say, "Can we do better and can we prove that one agent is really more effective than another agent?"

We would never open up a clinical trial that we don't think is actually moving the field forward. We would never open up a clinical trial that we weren't totally supportive, that family member, loved one if we were in the situation that we would feel totally comfortable being put on the study.

It's also important to know that you don't have to be involved in the clinical study. This is something that has to be the right thing for you. And you have to feel comfortable with your clinician, the environment, and the study.

And I tell all of my patients that these clinical trials are investigations. And if you don't feel comfortable, don't do it. I'm going to give you the absolute best standard of care therapy. But if your hope is to be part of something that might be the next version of it, then this is the process that we do.

Some people will have a clinical trial that'll have to be randomized to either X or Y therapy. And the reason why I can't give you the Y therapy is that I don't know that that therapy is better. It actually might be more toxic, but the reason why we're doing this study is that we think it might be. And so those are my 2 cents about clinical studies.

Stephanie Chisolm:

Sure. Thank you so much. And I encourage everybody to do that, because you get much closer observation and you have the opportunity to try that new treatment. And also, patients can decide that they don't want to still be in a clinical trial at some point if it becomes too onerous for them. I think that's important.

Dr. Tyler Stewart:

100%.

Stephanie Chisolm:

Okay. Is gemcitabine and docetaxel still effective and still being used?

Dr. Tyler Stewart:

Great. So actually we're moving on to the part of the topic that I didn't talk about too much. So Stephanie, you're asking about patients with non-muscle invasive bladder cancer, where in patients who have BCG... So patients who have non-muscle invasive bladder cancer are usually put into risk categories. And particularly in patients who are high risk, oftentimes we'll give a medicine called BCG into the bladder to prevent cancer from coming on back, because some of these patients have such a high risk of their cancer coming back.

Unfortunately, that BCG medicine may not work and that cancer may come back despite that BCG. One standard treatment approach at that point is actually to just take out that bladder, because that means that the cancer might come back.

There are many new therapies that are currently FDA approved or currently being studied in the space to get rid of that cancer and prevent that bladder from having to be removed.

One of the treatments that we use in the clinic right now is a combination of two chemotherapies, gemcitabine and docetaxel right inside the bladder. And early studies suggest that this can be quite effective. And at UCSD, we oftentimes will think about this for patients who have BCG unresponsive or cancer that comes back after BCG. It is being used. Actually, there's a large study ongoing right now that is looking at whether or not the frontline therapy should either be BCG or Gem/Doce because we think it's so effective. So that study's going on right now, and we're happy to be involved with it.

Particularly with the BCG shortage that is ongoing, if we find that Gem/Doce is maybe just as good or if not better, I think that would be a real boon to our whole society.

Stephanie Chisolm:

So are there any clinical trials that are not treatment related that you know of, but more looking at post-treatment and quality of life aspects?

Dr. Tyler Stewart:

Well actually, we have some of those ongoing as well right now. We have a lot of biomarker studies that we are particularly interested, as I kind of mentioned. So just talking about what we're doing at UC San Diego, which we're really excited.

So we're looking at a lot of studies, seeing if that urine tumor DNA might be able to identify patients who are at high risk of their cancer coming back or may actually be clear of cancer.

So I certainly think that more studies need to be investigated, particularly patients who have non-muscle invasive disease, to see whether or not we can use these urine biomarkers instead of having somebody undergo, for instance, cystoscopy every three months. I think that is a huge quality of life improvement for the vast majority of patients who have non-muscle invasive disease. And quite frankly, some patients may not even come to the doctor because they don't want to undergo such a procedure.

And so having a new method to surveil patients I think is just a huge thing. Also, if you can make the test cost-effective as well, probably saves healthcare dollars in general too.

Stephanie Chisolm:

Absolutely. So treatment is one thing. Can you just briefly touch on how some of these different medications, these different treatment options are also being used as maintenance therapy to make sure that that cancer doesn't come back? Because I know some of these are also being applied in a maintenance sense, where you might not have actual visible disease. Can you talk about maintenance?

Dr. Tyler Stewart:

Yeah. So maintenance is used in a couple of different aspects, and there are a couple of times that we use treatments when somebody doesn't have any clear evidence of disease.

So one time that we use maintenance therapy is in patients who have advanced disease. So let's say you present and your cancer is spread to the liver, lung, bone.

When I give treatment for patients, oftentimes when I think about doing, for instance, chemotherapy. That chemotherapy might cause a significant reduction in the amount of cancer in their body, but at some point that cancer is likely to grow despite that chemotherapy. And oftentimes we'll use immunotherapy as a maintenance drug to keep that cancer down and at bay.

And so early on, we would use a medicine called avelumab as maintenance therapy really to prevent that cancer from coming back. Unfortunately, for some patients, the cancer came back despite that. We would have to be used different treatments.

Now when we're thinking about combination of enfortumab vedotin and pembrolizumab, some patients who get a combination of these two drugs, they might have tremendous responses, but then they might get toxicities that is specifically from that enfortumab, that antibody-drug conjugate, that chemotherapy.

And so even though their cancer might be all gone from the scans, what we might end up doing is stopping that enfortumab vedotin and continuing on that maintenance immunotherapy trying to prevent that cancer from coming on back.

So that's one key aspect, and oftentimes we will do that. We always have to balance from maintenance therapy what we think the real benefit of maintenance therapy is with the risk of the cancer coming on back. And in patients with advanced disease, I think maintenance immunotherapy in all of these settings makes a lot of sense.

The other place where we use therapy despite the fact that we don't know if somebody has cancer left is after somebody has had a curative intense surgery where somebody might be at high risk of the cancer coming back. That's the time when we were talking a little bit about that adjuvant therapy and adjuvant immunotherapy.

This is a time where I think that we are giving immunotherapy to a lot of patients. Some of those patients really should be getting it, and probably there are some patients who may not need it.

And so this is where I think that role of ctDNA, that blood-based cancer marker to see if somebody's cancer is still there. And I'm hoping that that cancer marker might discriminate which patients really do need that adjuvant therapy to prevent the cancer from coming back, versus those who don't need it at all.

Stephanie Chisolm:

Well, one of the things... We're coming up on time, and I think I'm reading the vibe from this Zoom room. But I think you'll all agree with me that with clinicians like Dr. Stewart, who's also a talented researcher, over the last 20 years since BCAN started, there has been a significant change. And the future is very bright for bladder cancer patients because there's so many talented individuals like

Dr. Stewart. And this has been a comprehensive, wonderful overview of the history of the treatments and how it can help. And I thank you so much.

I want to just end with one last question. What do you say would be the single most important message you want our listeners to take away from what you were talking about?

Dr. Tyler Stewart:

Yeah. I would say that bladder cancer has made great advances, particularly over the last 20 years, through a lot of hard work and effort. And I want everyone on this call to know that we are proud of some of the work that is being done, but we are not happy with where we're at, and we are hungry to continue to move the field forward.

We are aiming to cure patients with bladder cancer, every single one. We are moving the field forward. It is not as fast as we want it to be. We want it to be faster. I want it to be faster. You want it to be faster. But we are working real hard. Through support like BCAN's network and through patients and clinical trials, we hope to move the field forward. And I really do see a day coming when we do get to cure every single patient.