BCAN Patient WEBINAR SERIES

Clinical Trials: Advanced or Metastatic Bladder Cancer

Wednesday June 22nd, 2016

Part II: Current Areas of Research

Presented by

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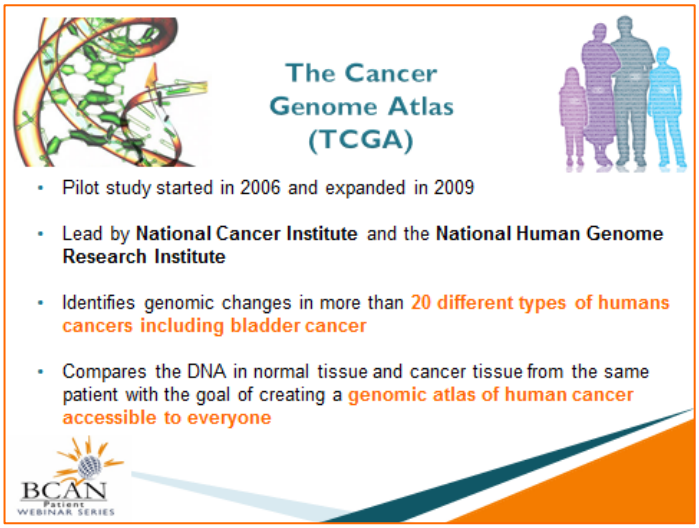
Dr. Apolo served in international committees, including the genitourinary tract of the Education Program Committee and a member of the Scientific Program Committee of the American Society for Clinical Oncology, otherwise known as ASCO. She's a member of the Bladder Cancer Program Committee of the Society of Urologic Oncology and shared the Bladder Cancer Advocacy Network's Think Tank Steering Committee.

***Betsy Plimack, MD, MS** is an Associate Professor of Medical Oncology and the Director of the Genitourinary Clinical Research at Fox Chase Cancer Center in Pennsylvania. She's an expert on the treatment of genitourinary malignancies with a focus on bladder cancer. Her research is directed towards the discovery of novel therapeutic approaches and predictive markers for patients with advanced bladder cancer. Dr. Plimack has extensive clinical experience with immunotherapies, and novel combination therapies. She serves on the National Comprehensive Cancer Network Guidelines Panel for Bladder Cancer, the ASCO GU Program Committee, and the Bladder Cancer Advocacy Network's Think Tank Steering Committee. She's also on the American Joint Committee on Cancer, Kidney/Urinary Tract Expert Panel.*

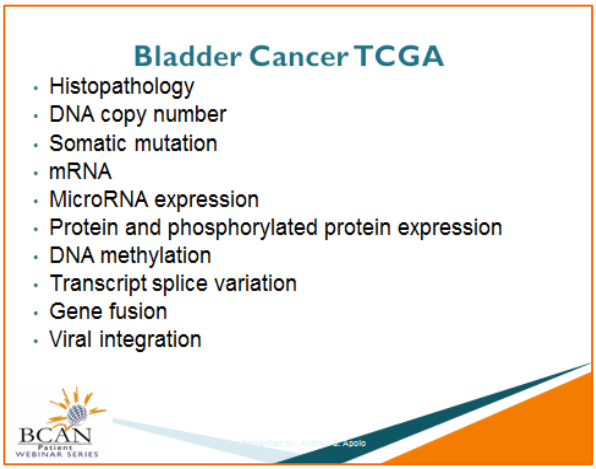
Betsy received her undergraduate degree from Yale University, and completed her MD degree and residency in internal medicine at New York University School of Medicine. She went on to a medical oncology fellowship at MD Anderson Cancer Center, and received a master's in patient-based biologic research from the University of Texas, Graduate School of Biomedical Science.

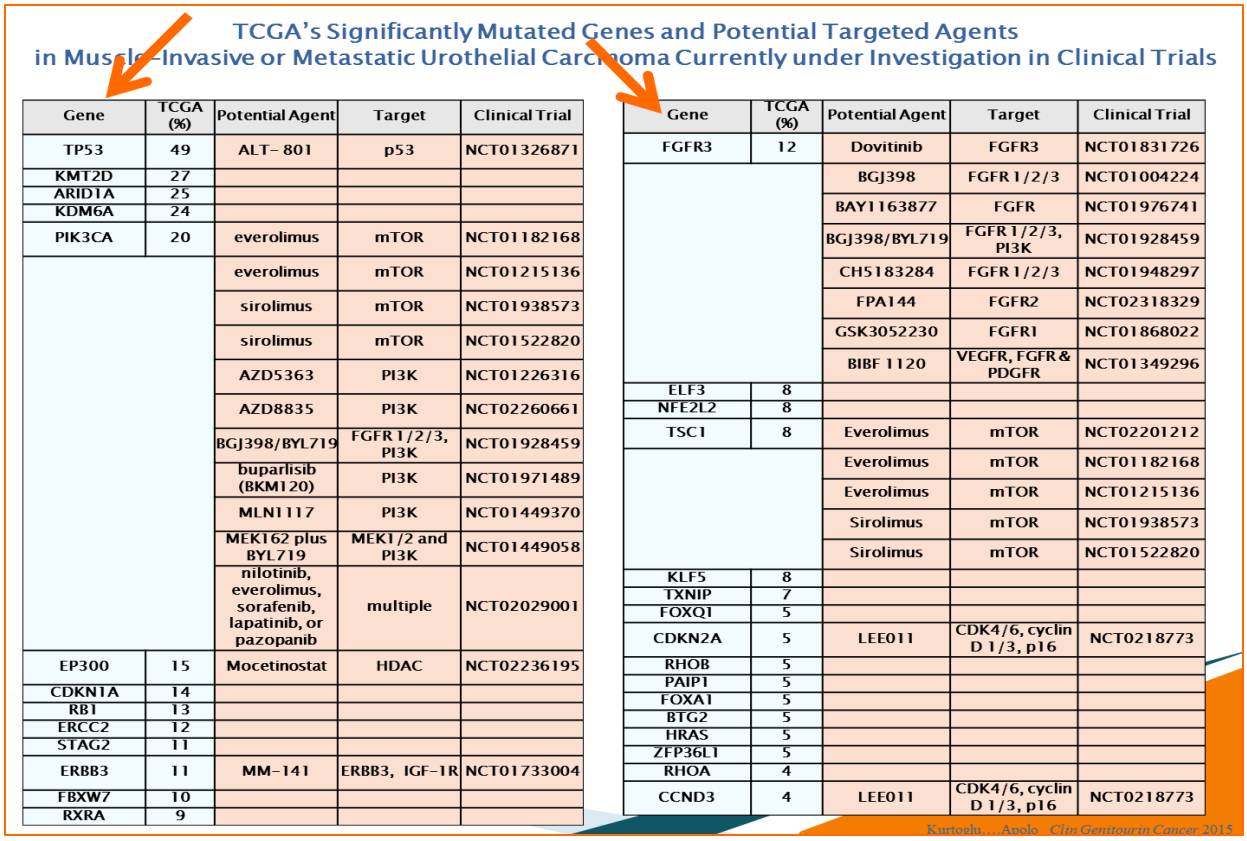
Dr. Andrea Apolo: Targeted therapies, we believe it to be smarter therapy than chemotherapy. Chemotherapy kills rapidly dividing cells, so they're not often targeting something specific. I tell patients a lot of times that chemotherapy is like a bomb. It's very effective, it goes off, it kills off everything around it. Targeted therapy actually targets either specific mutations or specific proteins that are known to be secreted on the surface of the tumor. We call it smarter therapy. I'll talk a little bit about how some of the targeted therapies are personalizing the approach that we have for a lot of the patient care that we do now. In a lot of other tumors, we're using targeted therapy a lot more and we're extrapolating a lot of the data from other tumors to see how effective they are in bladder cancer.



I first wanted to give you a little bit of background in terms of The Cancer Genome Atlas, or the TCGA. You may have heard about the TCGA. It's a very important effort. It was initially started back in 2006 and it was so successful that it was expanded in 2009. It was led by the National Cancer Institute and the National Human Genome Research Institute with a plan to identify genomic changes in more than twenty different types of human cancers, including bladder cancer. It compares the DNA in normal tissue and cancer tissue from the same patient with the goal of creating a genomic atlas available to everybody.

The TCGA looks at the tumor and it looks at the histology, which mean it looks at the cells, it looks at the DNA, it looks at the RNA, it looks at the protein, and really comprehensively describes the tumors that we're seeing in bladder cancer so we can understand a little bit more about what is driving these tumors to show up. What are the mutations that we see that are presented in these tumors?

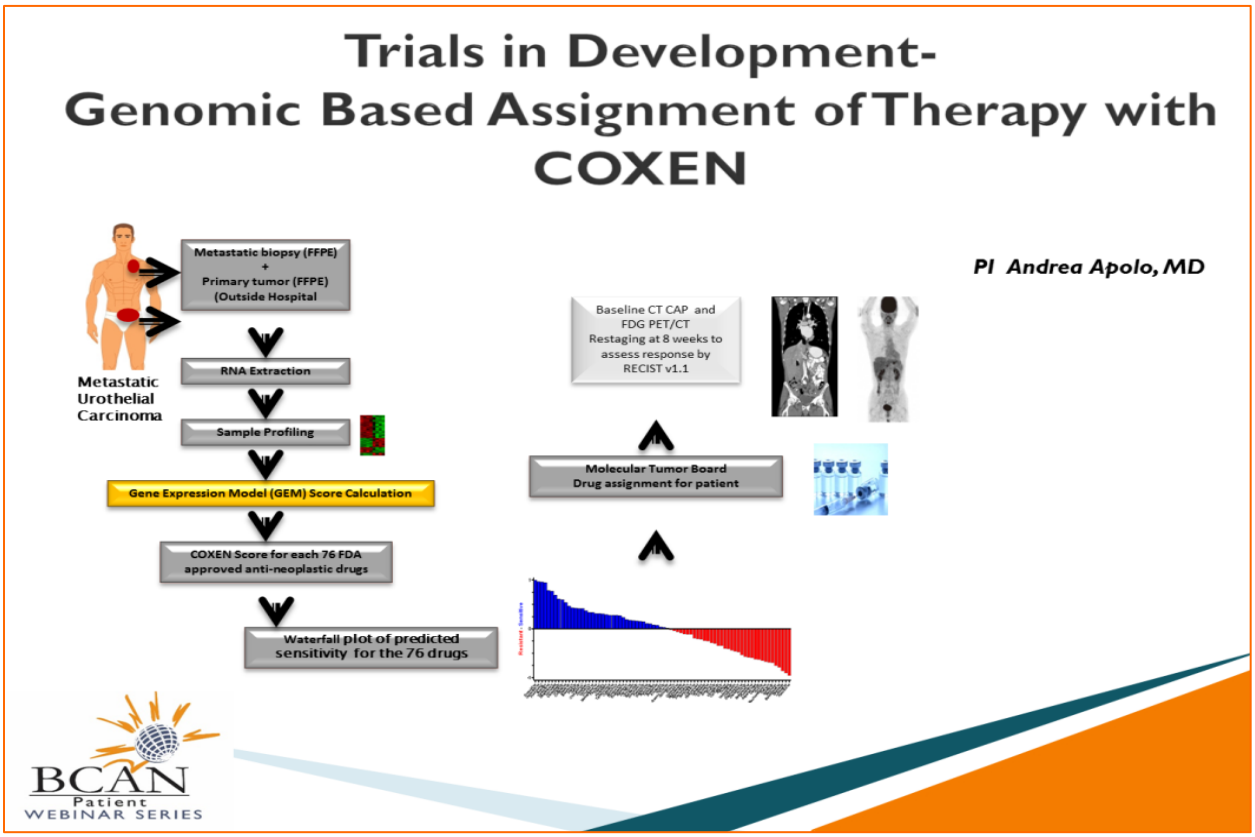




The next slide is actually a little bit busy, but I'll explain to you what they are. The **first column** has the genes that were identified. The TCGA and bladder cancer, they looked at muscle invasive specimens. They identified over thirty genes that seemed to be very important in the development of bladder cancer. The great thing about it is that there are a lot of targets for those genes. There are a lot of therapies that are currently being developed to target those genes and those specific mutations.

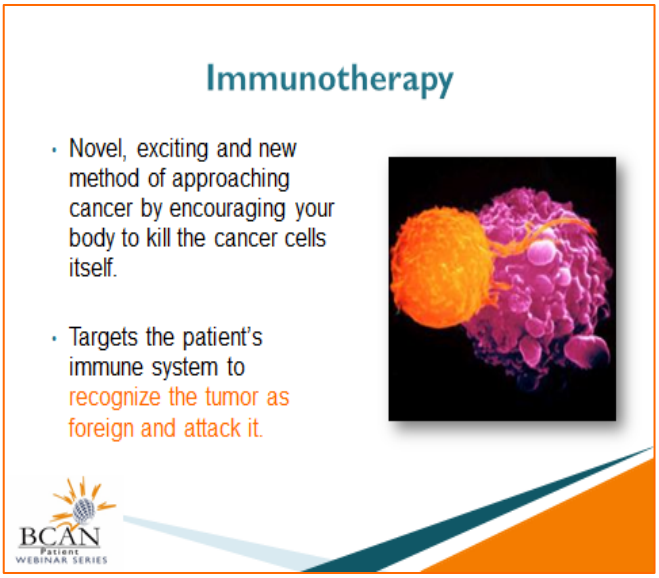
The **last column** is the NCTN or the clinicaltrials.gov number for a lot of these clinical trials just to highlight how many clinical trials are currently ongoing, looking at targeted therapy, targeting specific mutations that were described in the TCGA.

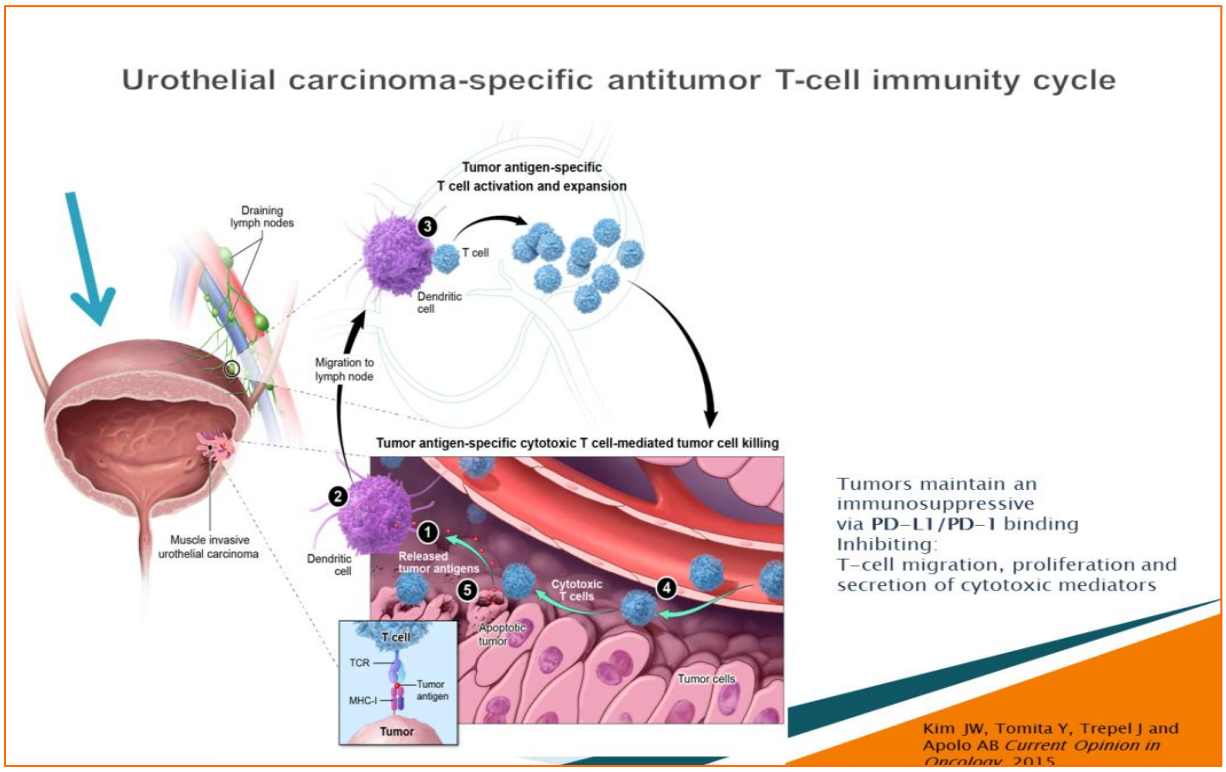
We're also moving to personalizing the treatment that we give patients, specific to their tumor, because although patients may have bladder cancer, some patients respond and some patients don't respond to therapies that we use. Why do some tumors respond versus the other?



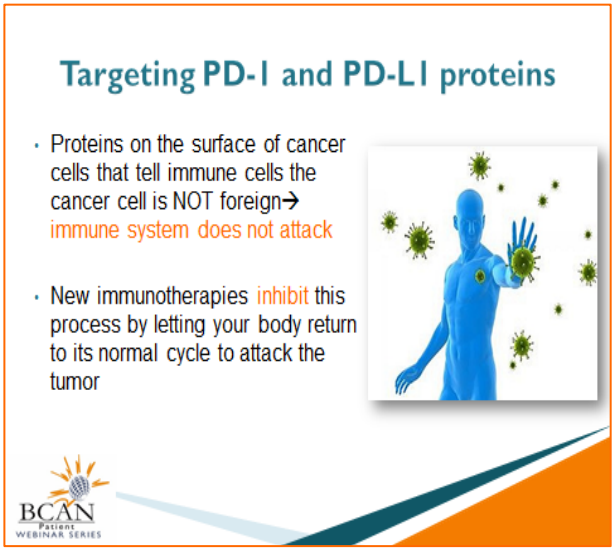
For example, this is a schema of the ideal clinical trial scenario for the personalized approach, where we are taking a biopsy from the patient, then profiling it, similar to the way that it was profiled in the TCGA and looking at the mutations, and then selecting the therapy based on the mutations that the patients have. This is a trial. This is one of the many examples of personalized therapies that are currently going right now testing this approach in bladder cancer and other cancer.

I'm going to move off from targeted therapies to immunotherapies because I think we have a lot to talk about. There's definitely been a lot of excitement on immunotherapy in bladder cancer. Immunotherapy is a completely different approach than the standard approach that we used to have where we targeted the tumor, we tried to kill the tumor, or used targeted therapies that specifically were aimed at the tumor. Immunotherapy is actually, what it's doing, it's aimed at your own immune system to try to make it recognize the tumor as foreign and attack it. It's definitely a very novel mechanism to approaching killing of the tumor using your own immune system. We're not targeting the tumor; we're targeting the immune system.



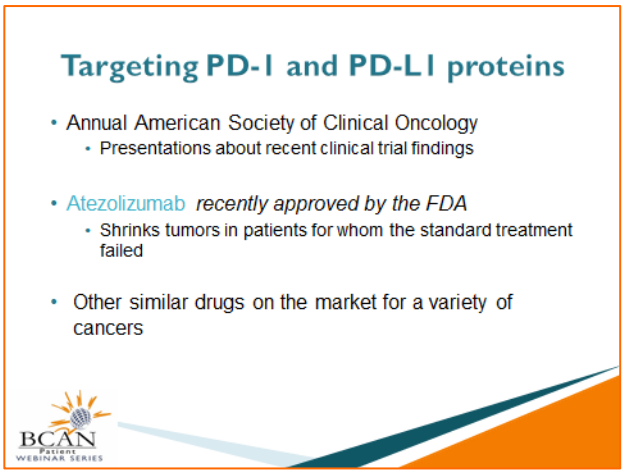


This is a picture explaining the immunity cycle as we see in cancers. On the left slide, it's a bladder. That's a schema of a bladder. If you look at that mass, that's a tumor. That's been magnified right there just to highlight the immunity cycle that is supposed to go on. Your immune system is supposed to recognize the tumor. The tumor secretes these proteins that are called antigens and then the lymphocytes, which are your immune cells, that's the purple cell that you see there, picks it up and says, "Hey. This is foreign", takes it back to the lymph node where the lymph node creates all these other immune cells called T-cells that are specific to that antigen to go back to that tumor site, you can go back, and kill the tumor.



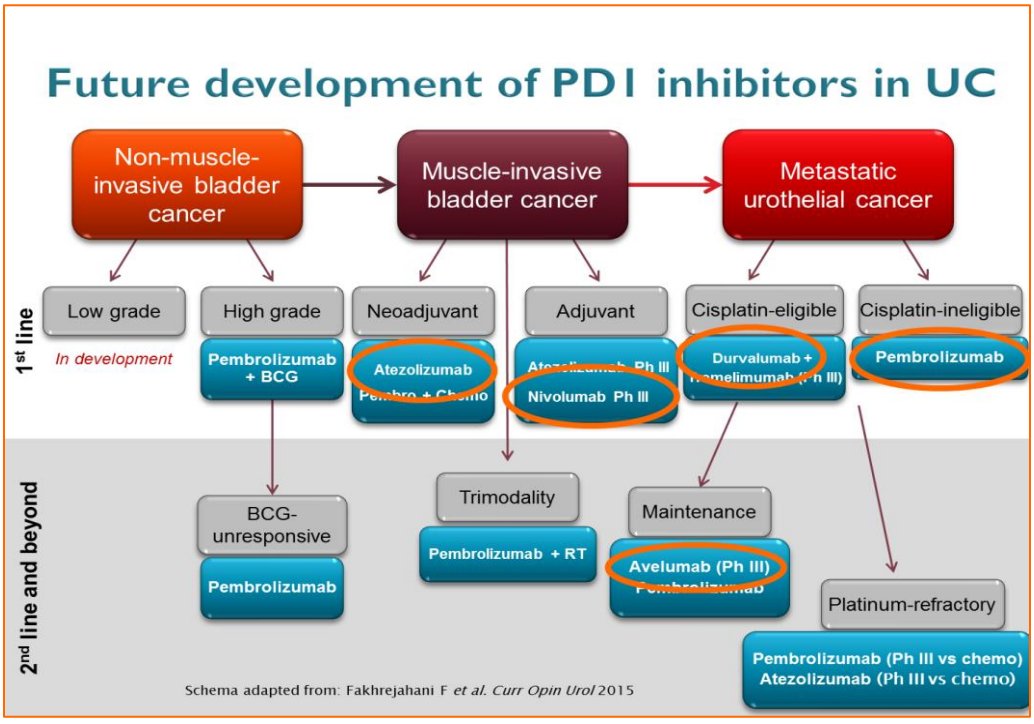
This perfect immunity cycle doesn't happen because the cancer can produce an immunosuppressive environment by a lot of different mechanisms. One of the mechanisms that we're going to talk about is targeting PD-L1 or PD-1, which are proteins that are either on the surface of the immune cells or on the surface of tumor cells and they bind and then the cancer says, "I'm not foreign. I'm actually part of your body", and your immune system doesn't attack it. These new therapies, these new immunotherapies that are PD-1 and PD-L1 targets, are actually inhibiting this natural T-cell immunity cycle that should go on in the body. What the immunotherapies are doing is letting your own body go back to the normal cycle so the tumor can be attacked.

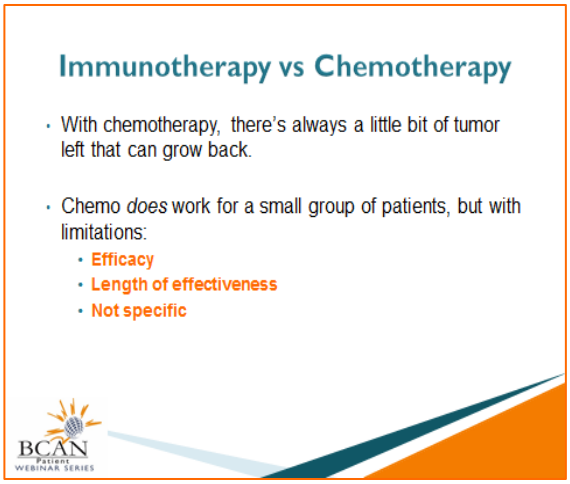
I want to just talk about this year at our medical oncology meeting, at **ASCO**, there were a lot of immunotherapies that were presented, a lot of immunotherapy trials that were presented, and that have shown that they work in bladder cancer. The **Atezolizumab** study was presented last year actually, so we knew about that one. That one had shown that it worked in bladder cancer in terms of shrinking tumors in patients that have already received standard therapy and it didn't work. Other companies have also developed similar drugs, either targeting PD-L or PD-1, to see if they can also have efficacy, specifically in bladder cancer.



These therapies seem to also work just across all cancers, or across many cancers I should say, that have been tested. Initially, the studies were done on melanomas, even tested in kidney cancer, lung cancer, and have subsequently shown that it works and are FDA approved now for other cancer types.

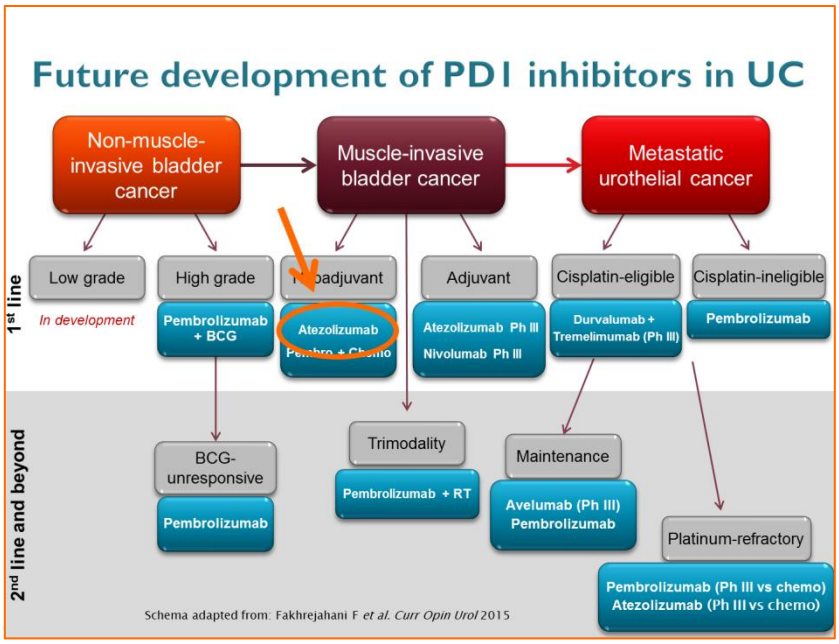
We heard about five agents at ASCO that are checkpoint inhibitors that actually have shown to shrink tumor in bladder cancer patients, and that's **atezolizumab, nivolumab, pembrolizumab, avelumab,** and **durvalumab.** Of course, they have very long and complicated names, but those are the five so far that have all shown activity, and very similar, about 15-25% of the patients have tumor shrinkage. What's really exciting about the shrinkage that we're seeing is that it seems to last a long time, or longer, than we would see with chemotherapy.





That was one of the disappointments in chemotherapy is that we can kill the tumor, we can shrink it, but there's always a little bit left and then it starts growing back again. It seems that with these checkpoint inhibitors the effect lasts longer than we see with chemotherapy. We think it's because of the memory of the immune system. The immune system remembers that these proteins or these tumors are foreign and we should continue to attack them.
A lot of exciting research that was presented at ASCO and we have a lot of exciting drugs that have shown activity in bladder cancer. I think Betsy now will talk a little bit more about what direction we're heading in terms of immunotherapies.

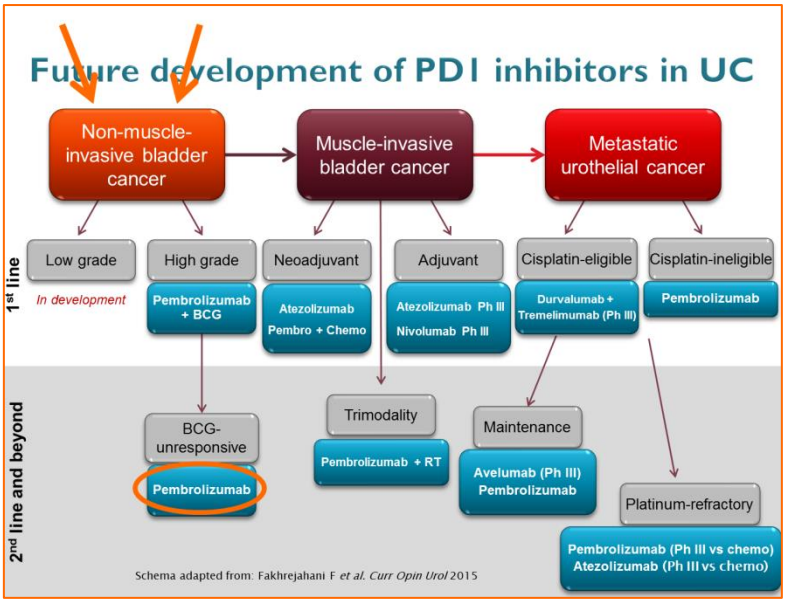
Dr. Besty Plimack: Thanks Andrea. That's a great overview of the immunotherapy. Just to echo Dr. Apolo's comments, this is particularly exciting in the world of bladder cancer, which has ... In patients with bladder cancer that has spread or metastatic, incurable bladder cancer, we've been relying on chemotherapy. Chemotherapy works very well for a small group of patients but has limitations that I think you just head about in terms of how well they work, how long they work, how specific they are. They're not very specific. When we first saw the immunotherapy agents working in our patients with bladder cancer, we got very excited that this is a new approach or a new trajectory.



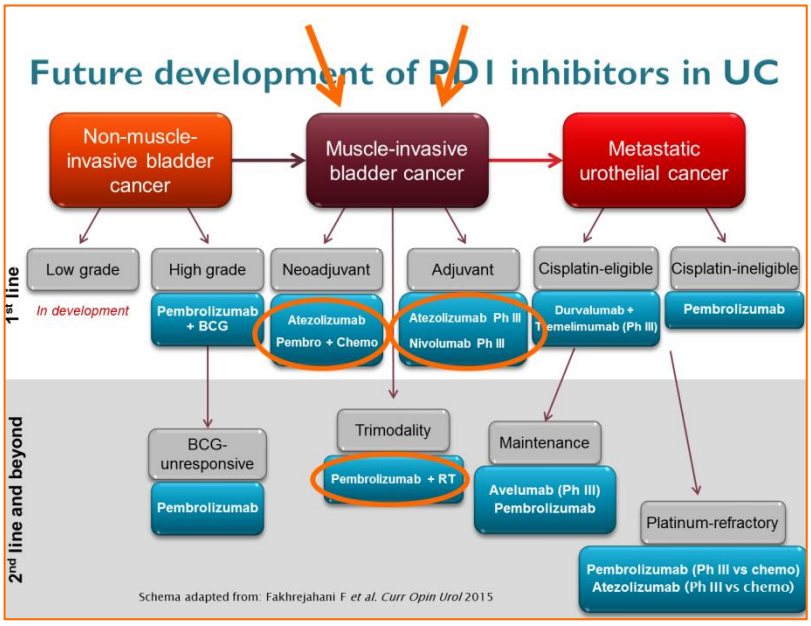
While Dr. Apolo mentioned the five agents currently being tested in bladder cancer, one thing that's important to note is they're really all in the same category. These are all inhibitors of the PD-1 pathway. I know that's a technical term, but they all inhibit the same T-cell tumor interaction, allowing the immune system to recognize and attack the cancer. We're excited that so many companies are interested in testing these in bladder cancer. We're very excited that one of them was just FDA approved, that is **atezolizumab.**

That was approved based on a single-arm study, so there wasn't a direct comparison to chemotherapy. That means that that drug can now be used outside of a clinical trial for patients with bladder cancer that's metastatic or incurable and who have had prior chemotherapy.

Of course, we're still trying to improve. We're not satisfied with just having one agent approved in one setting. We want to learn how well these work and we want to figure out ways to make this group of agents better. The slide that you're looking at now shows the trajectory across bladder cancer stages. **On the left,** the orange box, showing non-muscle invasive bladder cancer. Those are patients who do not necessarily have incurable disease, but in some cases, that disease can live, that cancer can live, and crawl along the surface of the bladder. Even though it doesn't invade, it requires cystoscopies, treatments instilled within the bladder, such as BCG, and sometimes those treatments don't work.

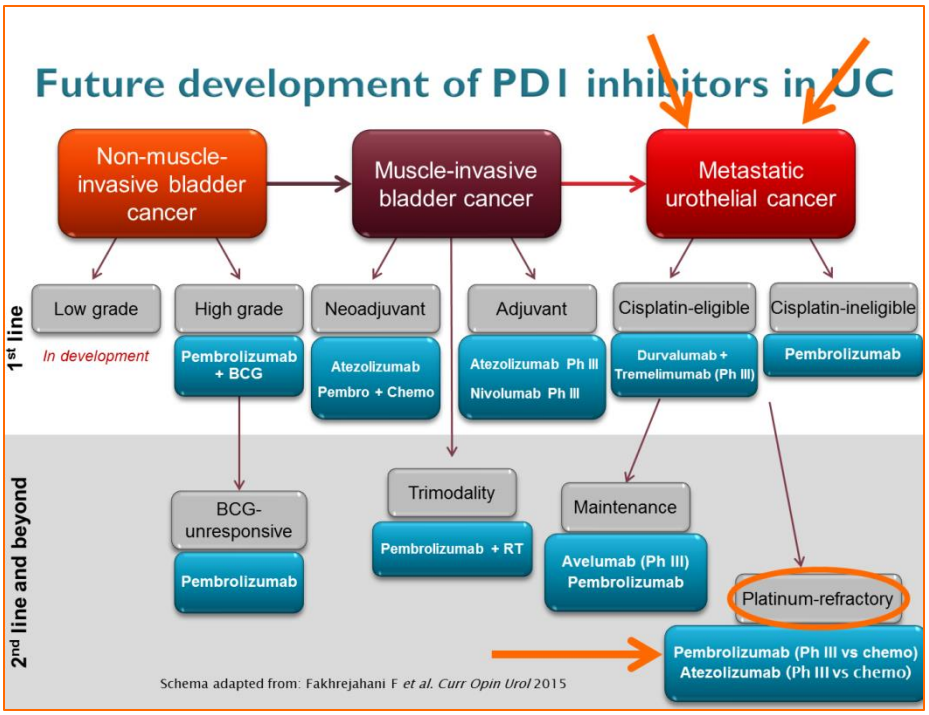


There are clinical trials looking to see if giving, in this case, we're highlighting here the listed trials, **pembrolizumab** in this setting will help improve the response to BCG or, on its own, get rid of the bladder cancer.



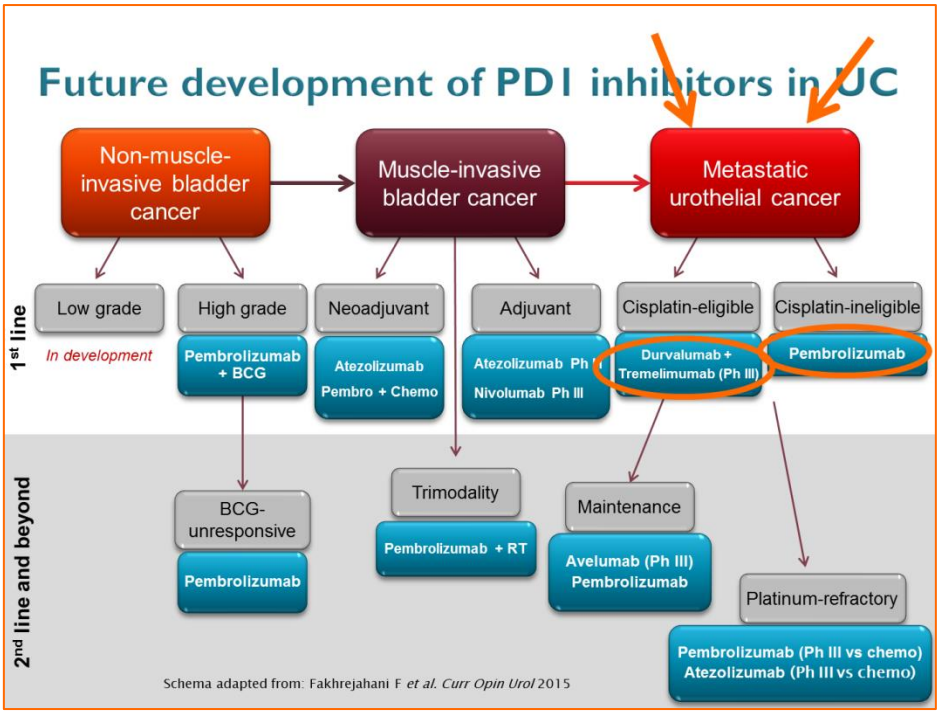
Moving down the trajectory, there's muscle-invasive bladder cancer. That's cancer that's still, as far as we can tell, located in the bladder itself, but the cells have dug down into the muscle, showing that they're on the move and that they are prone to spreading. In that setting, we're still treating with the intent to cure the patient, but we're looking at incorporating immunotherapy along with chemotherapy, either prior to surgical removal of the bladder, prior to or concurrent with radiation, or for patients who've had their bladder removed because of muscle-invasive disease, but are at risk for a recurrent in that setting, which is called the adjuvant setting.

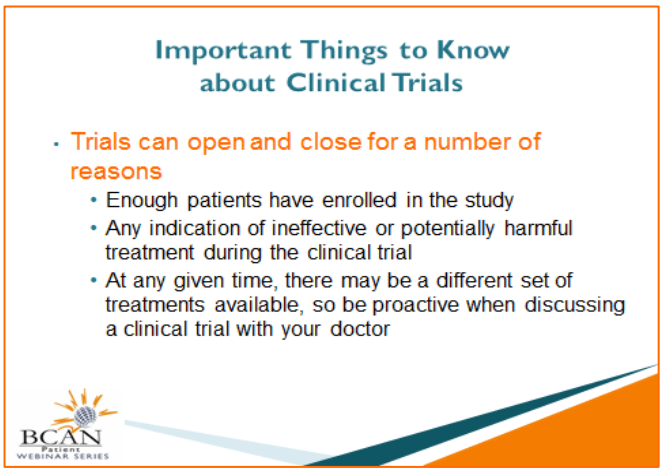
Again, we're looking at **pembrolizumab, nivolumab**, and **atezolizumab** in muscle-invasive bladder cancer in all these settings. Once again, this slide just lists the currently open clinical trials. There are many more that we're working on and that are in development.



Moving on to metastatic urothelial cancer. This is the setting where **atezolizumab** is approved; in fact, it's approved in that bottom box down there on the right, platinum refractory disease. We're still looking to see if atezolizumab is better than chemotherapy, so that phase three trial is on-going, mostly outside of the United States, and it's almost complete. It may be complete as we're speaking today, in terms of approval. That's to really test the findings that we saw in the single-arm phase two that led to its approval to show that it truly is better. **Pembrolizumab**, a similar drug, is also being investigated in a phase three trial in that setting.

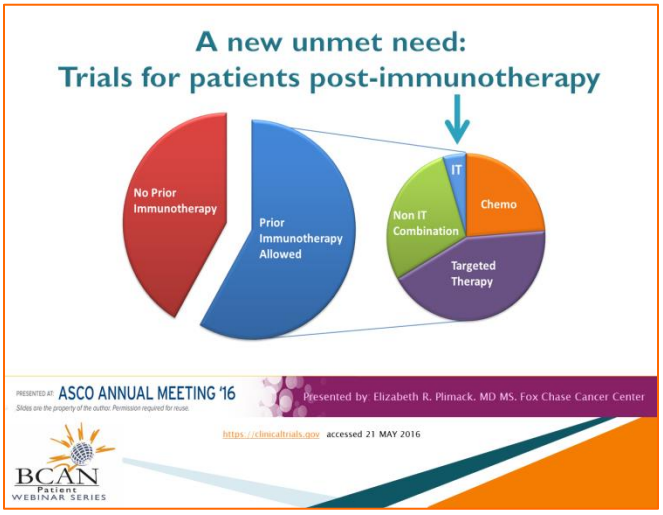
In addition, we're looking sooner to see if giving these agents by themselves in the beginning, before chemotherapy, helps people live longer. Those are the two blue boxes at the top on the right. There's a combination study of **durvalumab plus tremelimumab** as a phase three looking at cisplatin in eligible patients, patients who are healthy enough and whose kidneys work well enough to get strong chemotherapy. There is a trial of **pembrolizumab** in patients for whom cisplatin or strong chemotherapy is not appropriate, and we're looking there to see if those work.





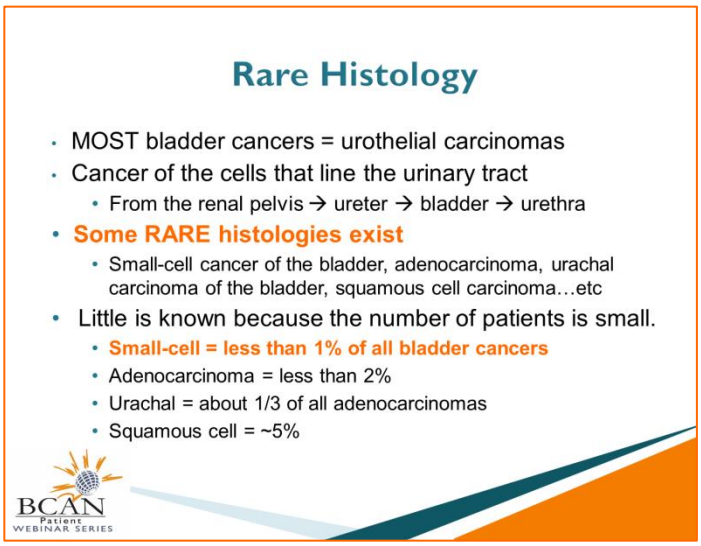
The last trial that we'll mention, this is just focusing on the PD-1 inhibitors, is a set of trials which look at maintenance immunotherapy. These are patients who've had a nice response to their chemotherapy, and then after they've received four or six cycles, chemotherapy is paused and immunotherapy is brought in. The idea is that immunotherapy is gentler than chemotherapy, it can be given for longer, and it may help people live longer by introducing it in this setting. This is just an overview of what we're doing right now.

An important thing to know about clinical trials is that they open and close for a number of reasons. One, once enough patients have enrolled to give an answer to the question being asked, the study will close. Rarely, if there's any indication that the treatment isn't working or that safety is a concern, studies occasionally close for that reason too. They're very carefully monitored. If there's any safety issue that's concerning, it's evaluated critically, so these can close for that reason too. Because of that, at any given time when you're discussing a clinical trial with your doctor, down the road, there may be a whole different set of treatments available. As Dr. Apolo alluded to, while we're very excited about immunotherapy, we're always looking for other mechanisms as well. Those may be offered down the road to patients as clinical trials.

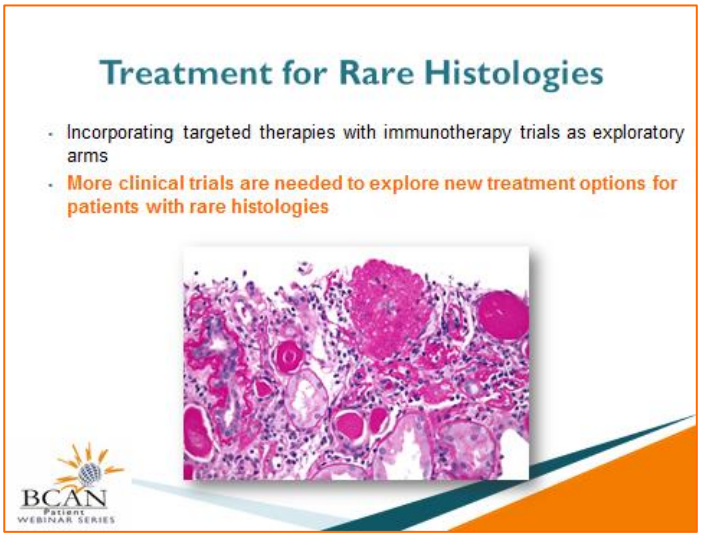


The next slide shows where we are now in terms of open clinical trials. For immunotherapy, if you're looking for an immunotherapy clinical trial, even though there's an approved agent, there's still many trials looking to improve upon what we've done so far. Many are looking at combinations. Among these trials, many do not let prior immunotherapy. If a patient receives one immunotherapy as part of a trial, another immunotherapy trial is likely to not allow that because they're testing a similar mechanism. Among the clinical trials that do allow prior immunotherapy, you'll see that circle on the right, a small piece of that pie is looking at alternative immunotherapeutic approaches, whereas most of the trials for patients who've already received immunotherapy, are looking at other mechanisms. These are targeted therapy, non-immunotherapy combinations, or different chemotherapy approaches.

Dr. Andrea Apolo: I'm going to talk a little bit about rare histology just because we've been talking about bladder cancer, and when we talk about bladder cancer, we really mean urothelial carcinoma, or the cells that line all of the urinary tract, starting from the renal pelvis down to the ureter and the bladder and the urethra. Not all bladder cancers are urothelial carcinomas. There are some rare histologies and I wanted to mention, such as small-cell of the bladder, adenocarcinoma, or urachal carcinoma of the bladder, squamous cell carcinoma of the bladder, just to mention a few. There are efforts on-going to try to incorporate patients with rare tumor histologies into clinical trials.



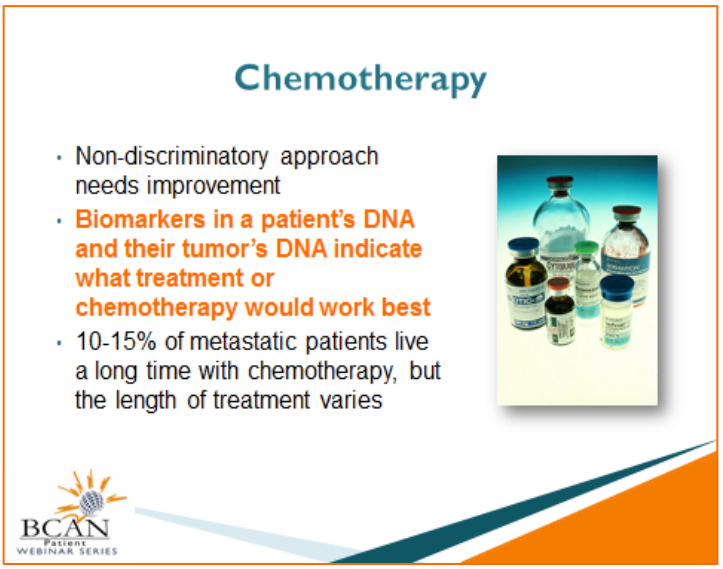
The issue is the numbers. These are small numbers. Small-cell is less than 1% of all bladder cancers. Adeno is about less than 2%. Urachals are about 1/3 of the adenocarcinomas. Squamous cell carcinomas at about 5%. There's just really small numbers in order to have these large trials and ask these questions. What a lot of investigators are doing are looking as to adding them to on-going trials in bladder cancer and just having them as a separate exploratory discovery arm, just to see is there something that's working in standard bladder cancer that may also have an effect in these rare tumor histologies.



A lot of the focus has been on targeted therapies, targeting specific mutations, because a lot of the rare tumors have specific mutations that may be associated with them. They're also now being incorporated into some of the immunotherapy trials as exploratory arms. That's very exciting because if we do see efficacy in these rare tumors, then we can actually open up a trial that would really be a big effort nationally or internationally in order to have a good number of patients to say, "Yes this works" or "This doesn't work". I can have a patient where I have a good effect from a therapy, but that's called anecdotal, that's my experience.

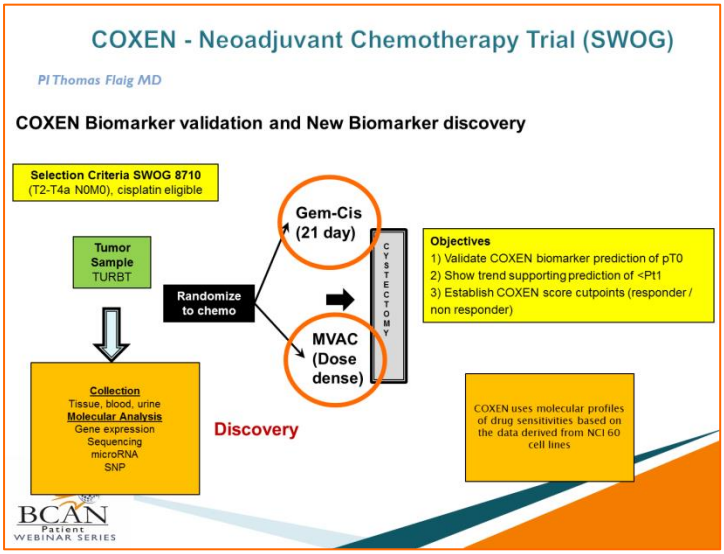
We really would like to have numbers to see in, for example, 100 patients treated with this type of cell type, how many of them do we expect to have a response or tumor shrinkage. There are a lot of efforts to try to incorporate rare histologies into bladder cancer trials. These are not as available, clinical trials are not as available, in rare histologies, but I think more and more clinical trials are incorporating them to try to explore new treatment options because the treatment options have been limited for patients with rare histologies.

Dr. Besty Plimack: I just wanted to say a word about chemotherapy. I think Andrea described it well before, saying it's non-discriminatory approach to attacking the cancer. It kills rapidly dividing cells. I like the analogy that it's like a bomb, it's very effective, but non-specific. I think that being said, we can still be smarter about how we use chemotherapy. We've been looking for what we call biomarkers, or clues, in a patient's tumor DNA, patient's DNA, patient's blood, that may indicate to use that chemotherapy or other treatments may work very well for an individual patient. We do know that a subset of patients, maybe 10 or 15% of patients, with incurable or metastatic disease live for a very long time as the result of chemotherapy being effective at controlling their cancer.



Some of those patients are on various chemotherapeutic agents for many years, but others are on for a period of time and then have chemo breaks or long holidays in between where they're still doing well after chemotherapy. There's a lot of active research looking to figure out which cancers will be the ones that are exquisitely sensitive to chemotherapy, and we don't want to give up on this modality for those patients for whom we know it will benefit. On the next slide, we'll show you an example of a trial that we're looking at to refine how we use chemotherapy. Chemotherapy given before surgery to remove the bladder, we know helps people live years longer and helps increase the chance of cure in any individual patient. We've been giving this to everybody who qualifies, or that's the recommendation in our guidelines. What we'd like to do is understand which patients will have their chance of cure increased by chemotherapy, identify them, and then be able to collectively offer them the right chemotherapy.

This is a clinical trial that's open around the country, as part of the Inter group, looking at patients' tissue samples, which are collected. Patients then go and get standard chemotherapy, either one regimented Gem-Cis, the other is MVAC accelerated. We don't think one is better than the other; we're just looking at both. Then their outcomes are measured. What this trial will do is we'll learn more about how well chemotherapy works in the modern day in this setting, but we're also going to learn, from looking at the biology of each tumor, whether there's a signature or a sign in those tumors that tells us whether or not a patient will respond. This is a real important study that I think we'll learn a lot from and be able to be more specific and strategic in how we apply chemotherapy.



As much as we're always looking for the next new thing, we won't stop looking to develop new drugs, we don't want to give up on the old ones for the patients for whom they'll be helpful, and so chemotherapy falls into that category.

Dr. Andrea Apolo: Combination therapies. Betsy just talked about chemotherapy. Chemotherapy works and it remains the standard of care for our patients. We have found through clinical trials that some targeted therapies also work, and we have found through clinical trials that also immunotherapy works. How about combining these different treatment modalities to see if we can get more efficacy, see if we can get more patients that are having tumor shrinkage? There's a lot of on-going trials now combining immunotherapy with chemotherapy, immunotherapy with targeted therapy, targeted therapy with chemotherapy, or two different targeted therapies together, or two different types of immunotherapies together. There are a lot of efforts right now to try to combine it.

Of course, one of the most important things is safety, making sure that the toxicities are not overlapping and that it's safe to give. That's why they have to be done in the context of a clinical trial.