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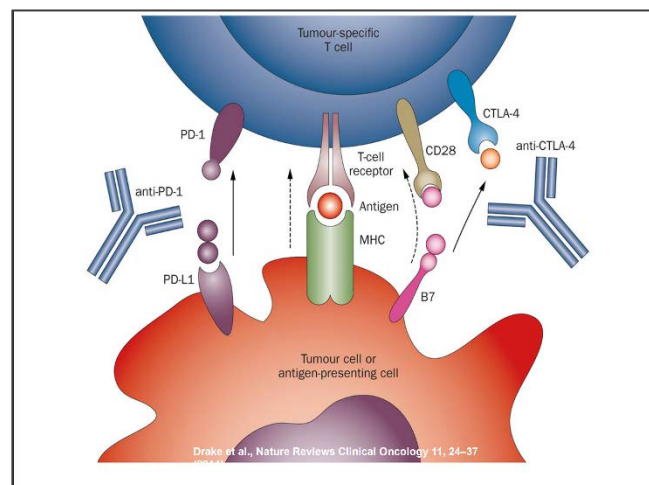


**Dr. Parminder Singh** is a Senior Associate Consultant at the Mayo Clinic in Arizona in medical oncology. He is also a member of the Southwest Oncology Group Genitourinary Committee, playing a very critical role in designing clinical trials in bladder cancer. Dr. Singh is an active clinical trial investigator, conducting clinical trials in genitourinary cancers with a focus on bladder cancer.

**Dr. Singh:** Broadly, I have divided my presentation in three slides. The first slide describes immunotherapy, which is being investigated in patients as a next line of treatment once the BCG stops working. The second slide will show you the clinical trial, which we are conducting through SWOG. My idea to show you that slide is for you to understand how trial dynamics work, how patients are given treatments, and how patients are followed on a trial. Then, to show you what other kinds of trials are available in clinicaltrials.gov website, and all over the nation other trials looking in this space.

I'll start with the first slide, just to give you a slight background. Patients, once the patient's bladder cancer stops to respond to BCG, the next treatment option is having their bladder removed. That is a life-changing event, and Rick is going to talk about patients having bladder surgery. There's a need for us to design new medications, which can reduce this outcome of having your bladder removed. Where there's we give you a medication, and the bladder cancer goes away, and such that you don't need your bladder removed.

In that vein, there are many new medications which are being investigated. One of those is the immunotherapy, which is getting a lot of media with many high-profile people getting their cancers treated with immunotherapy. Just to give you a sense of how this immunotherapy class of drug works. On the screen, you see a blue cell, and a red cell on the lower side. The blue cell is the immune cell of our body, which approaches the red cell, which is the tumor cell. In the tumor cell, you see a center red circle dot, in a cup, which is a green cup which is holding



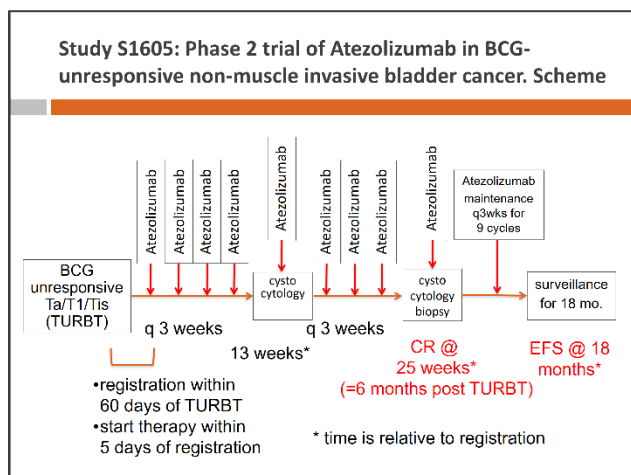
that dot. This red dot is a protein which the tumor cell is presenting to the immune cell, which is a blue cell. Once the immune cell reaches this protein, it recognizes this as a bad actor, and then can destroy this cancer cell.

When this interaction is happening, you see that next to the green cup, there is a purple and a magenta cup, or proteins. These proteins also interact with the immune cell, and give a signal to the immune cell that, "No, please don't destroy me. I am one of your own." This interaction, in technical terms, is called immune checkpoint. Essentially the tumor cell is asking the immune cell not to kill me. This class of drug blocks this interaction. The blue proteins, which you see on both sides, are these new drugs.

These drugs are given intravenously. It goes to the location where the cancer cells are. It binds to these proteins, which are interacting and leading to immune checkpoint, such that this pathway is blocked; and then the immune cell will go ahead and destroy the cancer cell. If this happens, essentially your immune system is getting rid of the cancer, and it can lead to a durable remission where the cancer goes away and never comes back. Essentially, we are making your immune system capable of destroying your cancer.

This class of drug is now approved for bladder cancer patients in advanced disease setting, where they have metastatic disease, and the chemotherapy is not helping them, or they're not a good candidate for strong chemotherapy. These medicines can offer a possibility of durable remission, even in advanced stage settings. At the same time, from our past experience, we know that every stage of cancer is different; and we need to investigate new medication in every stage separately before approving or using it in that disease setting. What it means is that medications are approved in late stage of the disease, which is the advanced stage disease; and now we are conducting clinical trials to see if these medicines help this early stage, which is carcinoma in-situ, or Ta, or T1, as Dr. Svatek showed you on the screen, if these medicines can prevent or eliminate this disease.

This is a clinical trial again, coming from Southwest Oncology Group. This clinical trial is looking at this molecule called Atezolizumab, which you see on the vertical boxes. This medicine is one type of immunotherapy approved for bladder cancer. Patients whose cancer is not responding to BCG, we categorize them into a BCG-unresponsive category. These patients are then enrolled on the clinical trial, and they receive this medication every three weeks.



This flow chart shows you how patient goes through the treatment on the clinical trial, where they receive the medication every three weeks. Then at a 13-week time point they get a cystoscopy, where a urologist will look inside their bladder and see the treatment is helping. If the treatment is not helping, then the patient is asked. They can go and proceed with having their bladder removed, since the medicine is not working, or may even enroll on subsequent clinical trials. If the treatment is helping, they can continue with this treatment to a total of 17

infusions. Then, we follow these patients with frequent cystoscopies to see how long the treatment keeps the bladder cancer away.

Now, there are a few take away points from this slide. Number one is once you go on a clinical trial, you are somehow bound to that institution who is providing you those medications for the duration of the treatment. If clinical trials are clinical tests, then we, as investigators, want to have some degree of rigidity involved where patients are treated similarly who are involved on the trial. They are followed closely at pre-defined time points, so that we can make an assessment if the medicine is working or is not working in that disease setting.

There's always some degree of acceptable limits in terms of time points. For example, the infusions, there are allowable time limits of plus/minus three, four days, or plus/minus a week at the evaluation. But more or less, once you start on a clinical trial, you are bound at that institution for the duration of the treatment; and Rick is going to talk more about what it takes to be on a clinical trial. Then, these trials are very important, because once patient goes on these trials, and we find that these medicines work in this disease setting, that opens up a new option for patients all over the world, to get these medicines and have their bladder preserved, and they may not need radical cystectomies for their cancer.

### Open Studies in BCG Refractory Bladder Cancer in the US

- Intravesical Photodynamic Therapy (PDT) in BCG Refractory High-Risk Non-muscle Invasive Bladder Cancer (NMIBC) Patients; NCT03053635
- Study to Evaluate the Efficacy and Safety Of Intravesical Nanoxel®M In BCG Refractory NMIBC; NCT02982395
- Phase 1/2 Study of ABI-009 in Nonmuscle Invasive Bladder Cancer: NCT02009332
- Pembrolizumab and BCG Solution in Treating Patients With Recurrent Non-Muscle-Invasive Bladder Cancer: NCT02808143
- Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (CGC) in the Treatment Urothelial Carcinoma of the Bladder (CGC): NCT02202772

This is a long list of other clinical trials in the same BCG-unresponsive disease setting, which I picked up from the [clinicaltrials.gov](https://clinicaltrials.gov) website. That is a resource, which is an open resource for anybody. You can log onto that website by typing in [clinicaltrials.gov](https://clinicaltrials.gov), and then search for BCG refractory or unresponsive, and it will show you all clinical trials which are recruiting. In fact, Stephanie can talk more about BCAN website, where this resource is also available, where you can go and look up all these clinical trials. Then, it gives you

information at where all these clinical trials are open in US or nearby your location, and what it takes for you to go there and get enrolled on, if you need to be on that clinical trial.

As you see, there are multiple new medications. The first one shows you the Instiladrin, second is Durvalumab, and third one is looking for a combination of BCG with a new molecule, ALT-803. A variety of drugs, both through immune mechanisms and chemotherapies, which we are evaluating to see if we can reduce the chance of patients getting their bladder removed, if they are not responding to initial BCG. If the patient's cancer is not responding to BCG, then to look for newer options.

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